# SYNTHESIS OF HETEROCYCLIC COMPOUNDS OF BIOLOGICAL INTEREST

**Ph. D. THESIS**

**by**

**SANDEEP KUMAR**

**DEPARTMENT OF CHEMISTRY**
**INDIAN INSTITUTE OF TECHNOLOGY ROORKEE**
**ROORKEE- 247 667 (INDIA)**
**JULY, 2013**

# SYNTHESIS OF HETEROCYCLIC COMPOUNDS OF BIOLOGICAL INTEREST

**A THESIS**

***Submitted in partial fulfilment of the***

***requirements for the award of the degree***

***of***

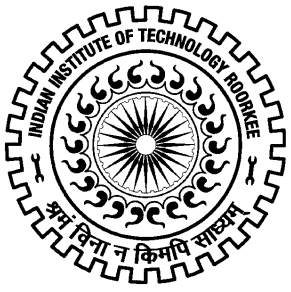
**DOCTOR OF PHILOSOPHY**

***in***

**CHEMISTRY**

***by***

**SANDEEP KUMAR**

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## CANDIDATE'S DECLARATION

I hereby certify that the work which is being presented in the thesis entitled "**SYNTHESIS OF HETEROCYCLIC COMPOUNDS OF BIOLOGICAL INTEREST"** in partial fulfilment of the requirements for the award of the Degree of **Doctor of Philosophy** and submitted in the **Department of Chemistry** of the Indian Institute of Technology Roorkee, Roorkee is an authentic record of my own work carried out during a period from **January, 2009 to July, 2013** under the supervision of **Dr. S. M. Sondhi**, Professor, Department of Chemistry, Indian Institute of Technology Roorkee, Roorkee.

The matter presented in the thesis has not been submitted by me for the award of any other degree of this or any other Institute.

**(SANDEEP KUMAR)**

This is to certify that the above statement made by the candidate is correct to the best of my knowledge.

(S. M. SONDHI)
Dated: July, 2013 Supervisor

The Ph.D. Viva-Voce examination of **Mr. Sandeep Kumar**, Research Scholar, has been held on . . . . . .

Signature of Supervisor Chairman, SRC External Examiner

Head of the Department/Chairman,ODC

# Abstract

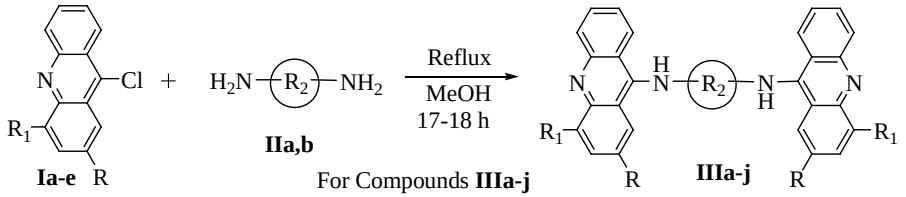
For human beings inflammatory diseases and cancer continue to be serious health problems. A number of anti-inflammatory drugs and a few anticancer drugs are available in the market. At present anti-inflammatory drugs available have serious side effects such as gastric ulcer, kidney damage & heart failure *etc*. Need for safer anti-inflammatory drugs and more anticancer drugs exist. There is an urgent need to identify new potent anti-inflammatory and anticancer molecules which can be developed as anti-inflammatory and anticancer drugs. Efforts have been made by us in this direction, which is described in this thesis. For the sake of clarity, the work embodied in thesis is divided into five chapters.

## First Chapter :

**General introduction:** In part Ia of this this chapter recent work on the use of microwave technology in organic synthesis reported in literature is summarized. In part Ib recent work reported in literature on the synthesis, anti-inflammatory and anticancer activities of **acridine, bisacridine, pyrazole, oxadiazole, isoindole, pyrrolopyrazine, amidine, azomethine, benzimidazole and piperazine** derivatives is summarized.

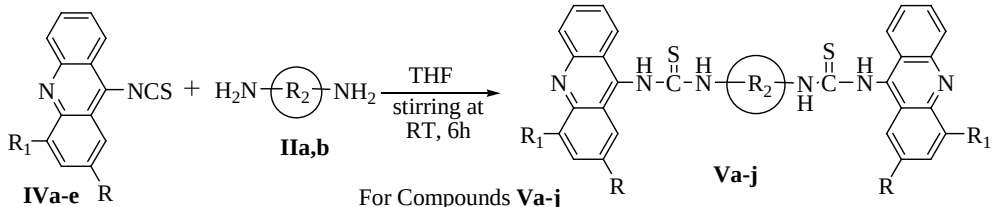
All the new compounds synthesized and reported in the following chapters were charaterized by IR, $^{1}H$ NMR, $^{13}C$ NMR, Mass (GC-MS, APCI-MS) spectroscopy and elemantal analysis.

**Second Chapter**: In this chapter synthesis of bisacridine derivatives **IIIa-j** and **Va-j** by following reaction Scheme 2.1 & 2.2 is discussed.




| | R | $R_1$ | $R_2$ |
|---|---|---|---|
| **IIIa** | H | H | $-(CH_2)_3$-piperazine-$(CH_2)_3-$ |
| **IIIb** | $CH_3$ | H | $-(CH_2)_3$-piperazine-$(CH_2)_3-$ |
| **IIIc** | $OCH_3$ | H | $-(CH_2)_3$-piperazine-$(CH_2)_3-$ |
| **IIId** | H | $CH_3$ | $-(CH_2)_3$-piperazine-$(CH_2)_3-$ |
| **IIIe** | H | $OCH_3$ | $-(CH_2)_3$-piperazine-$(CH_2)_3-$ |
| **IIIf** | H | H | $-(CH_2)_3$-dioxane-$(CH_2)_3-$ |
| **IIIg** | $CH_3$ | H | $-(CH_2)_3$-dioxane-$(CH_2)_3-$ |
| **IIIh** | $OCH_3$ | H | $-(CH_2)_3$-dioxane-$(CH_2)_3-$ |
| **IIIi** | H | $CH_3$ | $-(CH_2)_3$-dioxane-$(CH_2)_3-$ |
| **IIIj** | H | $OCH_3$ | $-(CH_2)_3$-dioxane-$(CH_2)_3-$ |

Scheme:-2.1 Synthesis of bisacridine derivatives **IIIa-j**

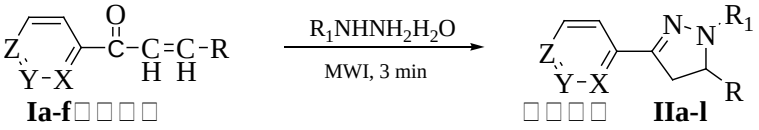



| | R | $R_1$ | $R_2$ |
|---|---|---|---|
| **Va** | H | H | $-(CH_2)_3$-piperazine-$(CH_2)_3-$ |
| **Vb** | $CH_3$ | H | $-(CH_2)_3$-piperazine-$(CH_2)_3-$ |
| **Vc** | $OCH_3$ | H | $-(CH_2)_3$-piperazine-$(CH_2)_3-$ |
| **Vd** | H | $CH_3$ | $-(CH_2)_3$-piperazine-$(CH_2)_3-$ |
| **Ve** | H | $OCH_3$ | $-(CH_2)_3$-piperazine-$(CH_2)_3-$ |
| **Vf** | H | H | $-(CH_2)_3$-dioxane-$(CH_2)_3-$ |
| **Vg** | $CH_3$ | H | $-(CH_2)_3$-dioxane-$(CH_2)_3-$ |
| **Vh** | $OCH_3$ | H | $-(CH_2)_3$-dioxane-$(CH_2)_3-$ |
| **Vi** | H | $CH_3$ | $-(CH_2)_3$-dioxane-$(CH_2)_3-$ |
| **Vj** | H | $OCH_3$ | $-(CH_2)_3$-dioxane-$(CH_2)_3-$ |

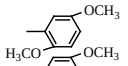
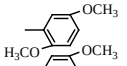
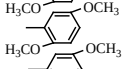
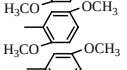
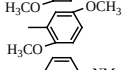
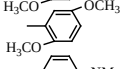
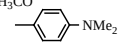
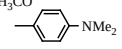
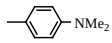
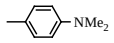
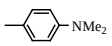
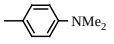
Scheme:-2.2 Synthesis of bisacridine derivatives **Va-j**

Compounds **IIIa-j** and **Va-j** were screened for anti-inflammatory activity at 50mg/kg p.o. Compound **IIIg** exhibited 41% anti-inflammatory activity whereas standard drug ibuprofen exhibited 39% activity at 50 mg/kg p.o. Anticancer activity evaluation against five human cancer cell lines i.e. lung (NCI H-522), ovary (PA-1), breast (T47D), colon (HCT-15) and liver (HepG2) at a concentration of $1\times 10^{-5}$M, indicate that compound **IIIh** possess good anticancer activity i.e. 76%, 81%, 86% and 67% against first four cancer cell lines whereas compound **IIIa** exhibited good anticancer activity i.e. 50% against liver (HepG-2) cancer cell line.

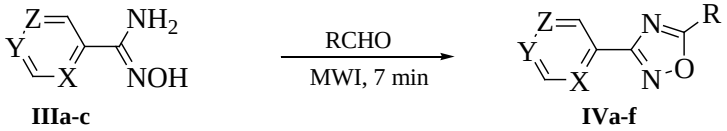
**Third Chapter**: In this chapter synthesis of pyrazole derivatives i.e. **IIa-j** (Scheme 3.1) and oxadiazole derivatives i.e. **IVa-f** (Scheme 3.2) using microwave irradiation technique is described.




**Ia-f** **IIa-l**

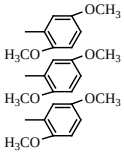
| | X | Y | Z | R | $R_1$ | | X | Y | Z | R | $R_1$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **IIa** | N | CH | CH |  | H | **IIg** | N | CH | CH |  | Ph |
| **IIb** | CH | N | CH |  | H | **IIh** | CH | N | CH |  | Ph |
| **IIc** | CH | CH | N |  | H | **IIi** | CH | CH | N |  | Ph |
| **IId** | N | CH | CH |  | H | **IIj** | N | CH | CH |  | Ph |
| **IIe** | CH | N | CH |  | H | **IIk** | CH | N | CH |  | Ph |
| **IIf** | CH | CH | N |  | H | **III** | CH | CH | N |  | Ph |

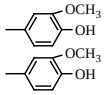
Scheme-3.1: Synthesis of pyrazole derivatives




**IIIa-c** **IVa-f**

| | X | Y | Z |
|---|---|---|---|
| **IIIa** | N | CH | CH |
| **IIIb** | CH | N | CH |
| **IIIc** | N | CH | N |

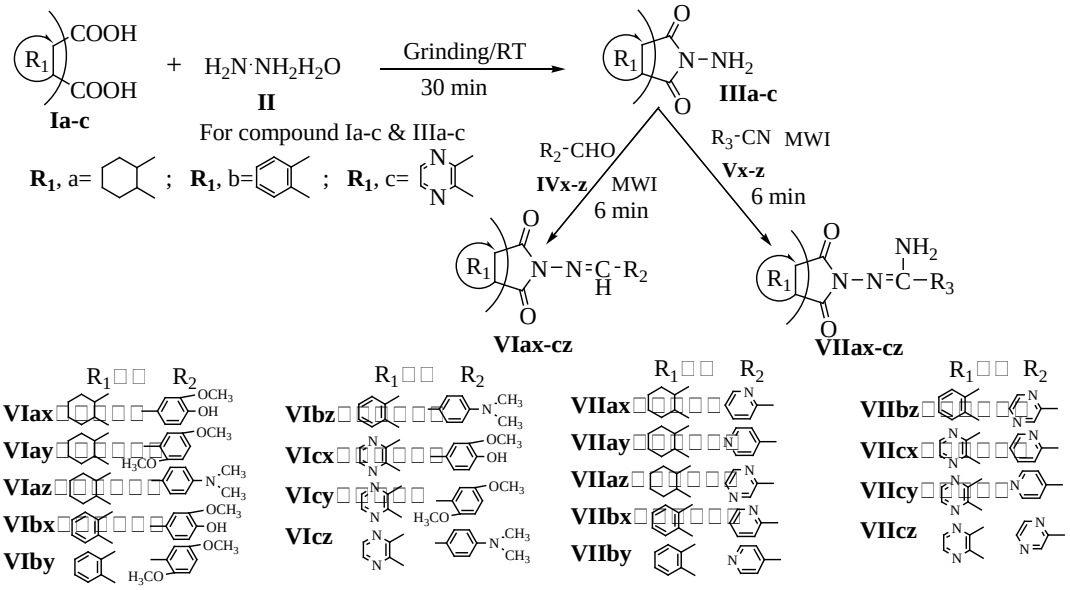
| | X | Y | Z | R |
|---|---|---|---|---|
| **IVa** | N | CH | CH |  |
| **IVb** | CH | N | CH | |
| **IVc** | N | CH | N | |

| | X | Y | Z | R |
|---|---|---|---|---|
| **IVd** | N | CH | CH |  |
| **IVe** | CH | N | CH | |
| **IVf** | N | CH | N | |

Scheme-3.2: Synthesis of oxadiazole derivatives

Pyrazole and oxadiazole derivatives **(IIa-l**, **IVa-f)** were screened for anti-inflammatory activity at 50mg/kg p.o. and for anticancer activity against five human cancer cell lines (mentioned in chapter-2) at a concentration of $1\times 10^{-5}$M. Compound **IIj** and **IVh** exhibited 35% anti-inflammatory activity as compared to ibuprofen which showed 39% activity at 50 mg/kg p.o. Compound **IVd** exhibited 48% and 39% anticancer activity against lung (NCI H-522) & liver (HepG2) and compound **IIj** show 41% anticancer activity against breast (T47D) cancer cell lines.

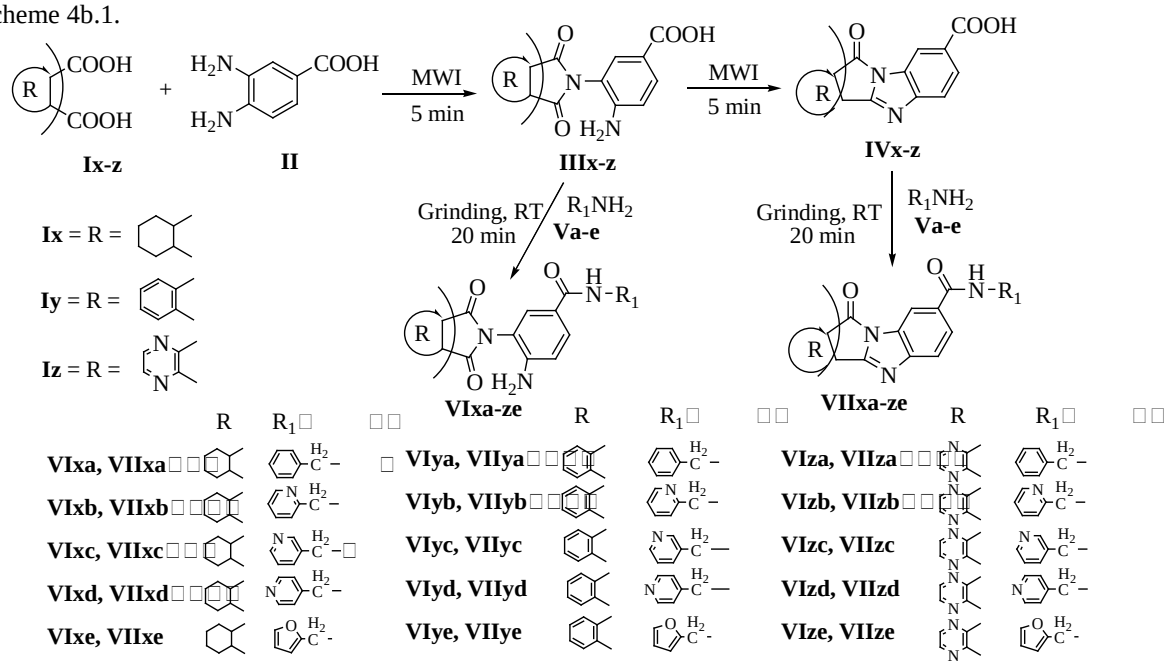
**Fourth Chapter**: It is divided into two parts i.e. 4a and 4b. Part 4a: deals with the synthesis of azomethine (**VIax-cz**) and amidine (**VIIax-cz**) derivatives of isoindole (**IIIa, b**) and pyrrolopyrazine (**IIIc**) by following reaction Scheme 4a.1.




Scheme 4a.1 Synthesis of azomethine & amidine derivatives of isoindole & pyrrolopyrazine **IIIa-c**, **VIax-cz** & **VIIax-cz**.

Azomethine derivatives i.e. (**VIax-cz**) and amidine derivatives (**VIIax-cz**) were screened for anti-inflammatory activity at 50mg/kg p.o. and for anticancer activity against five human cancer cell lines i.e. breast (T47D), lung (NCI H-522), colon (HCT-15), ovary (PA-1) and liver (HepG2) at a concentration of $1\times 10^{-5}$M. Compound **VIIcx** exhibited good anti-inflammatory activity i.e. 35% as compared to standard drug ibuprofen which showed 39% activity at 50 mg/kg p.o.. Compounds **VIbz**, **VIIcx**, **VIIcz** (breast T47D), **VIbz**, **VIcy** (lung NCI H-522), **VIbx**, **VIIbz** (colon HCT-15), **VIbz** (ovary PA-1) and **VIbx**, **VIcz** (liver HepG-2) exhibited good anticancer activity.

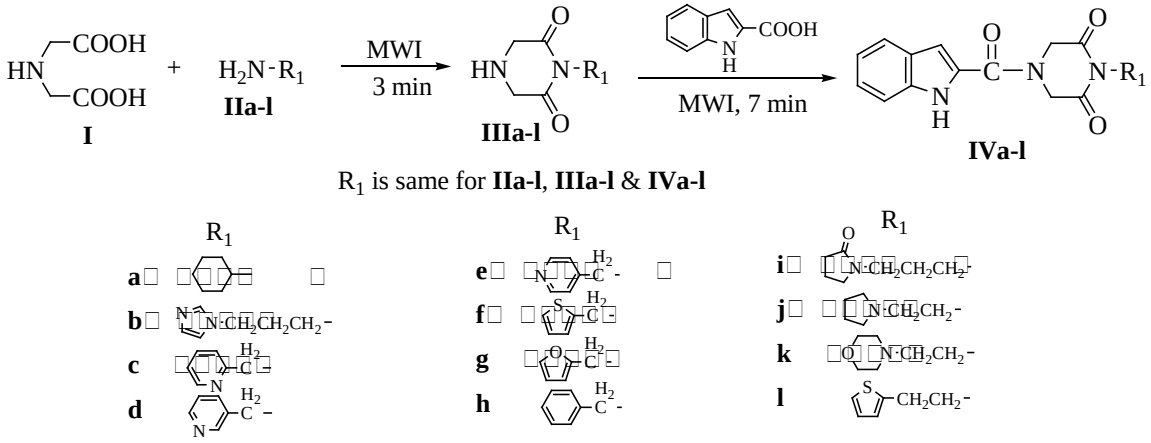
Part 4b: deals with the synthesis of isoindole, pyrrolopyrazine, benzimidazoisoindole and benzimidazopyrrolopyrazine derivatives i.e. **IIIx-z**, **IVx-z**; **VIxa-ze** and **VIIxa-ze** by following reaction Scheme 4b.1.



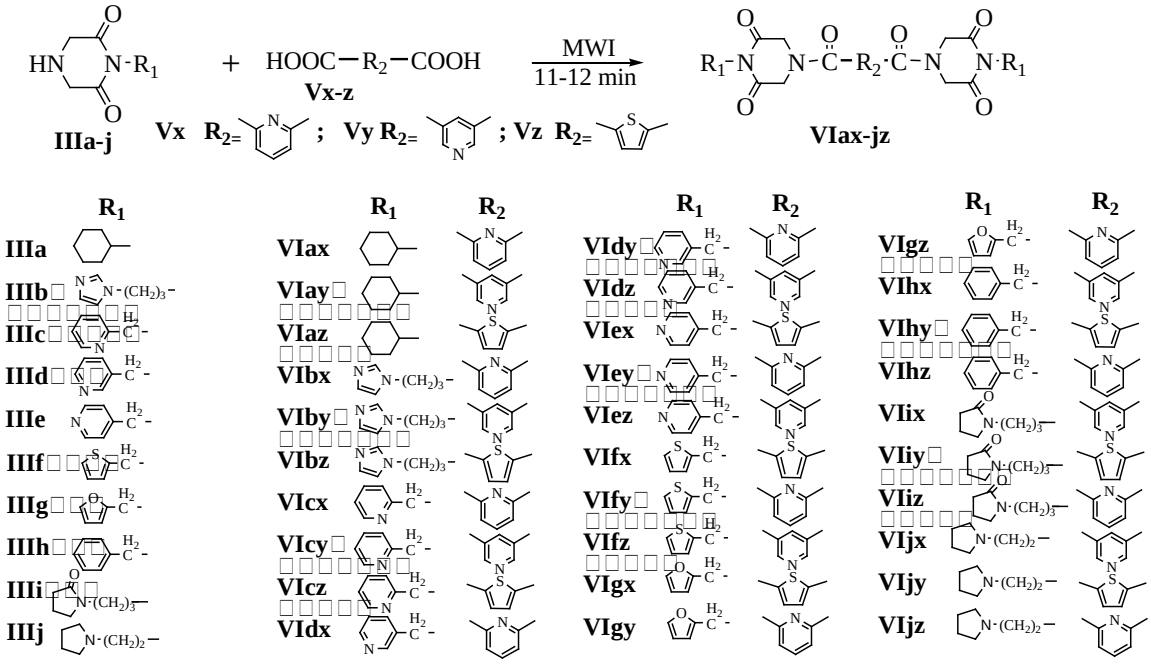

Scheme 4b.1 Synthesis of compounds **IIIx-z, IVx-z, VIxa-ze, VIIxa-ze.**

Compounds **VIyc** and **VIIzd** exhibited good anti-inflammatory activity i.e. 34% and 37% as compared to standard drug ibuprofen which showed 39% activity at 50 mg/kg p.o. Compounds **VIzc**, **VIIzd** (lung NCI H-522), **VIye**, **VIIxd**, **VIIyd**, **VIIzc**, **VIIzd** (colon HCT-15), **VIxc**, **VIIzc** (ovary PA-1), **VIxc**, **VIyb**, **VIzc** (liver Hep G-2) exhibited good anticancer activity.

**Fifth Chapter**: contains microwave assisted synthesis of piperazine-2,6-dione (**IIIa-l**) and 4-(1H-indole-2 carbonyl)piperazine-2,6-dione (**IVa-l**) derivatives by following reaction scheme 5.1. It also contain synthesis of bis piperazine-2,6-dione derivatives (**VIax-jz**) by following reaction scheme 5.2.




**Scheme 5.1** Synthesis of piperazine-2,6-dione **(IIIa-l)** and 4-(1H-indole-2-carbonyl) piperazine-2,6-dione **(IVa-l)** derivatives.




**Scheme 5.2** Synthesis of heterocyclic compounds **VIax-VIjz**

Compounds **IIIa-l** and **IVa-l** and **VIax-jz** were screened for anti-inflammatory activity at 50mg/kg p.o. and for anticancer activity against five human cancer cell lines i.e. breast (T47D), lung (NCI H-522), colon (HCT-15), ovary (PA-1) and liver (HepG2) at a concentration of $1\times 10^{-5}$M. Biological evaluation reveals that compounds **VIbx** and **VIex** possess anti-inflammatory activity 43% and 39% respectively, which is comparable or better than ibuprofen (a standard drug) which exhibited 39% activity at 50 mg/kg p.o. Compounds **VIax** exhibited anticancer activity 28% against breast (T47D); **VIay** 39% against lung (NCI H-522); **IIIj** 49% against colon (HCT-15); **IVe** 42% against ovary (PA-1) and **IIIh, IVf** 46%, 45% respectively against liver (HepG2) cancer cell lines. All these compounds exhibited moderate to good anticancer activity against the cell lines mentioned above.

**Conclusion:** In this thesis synthesis, characterization, anti-inflammatory and anticancer activity evaluation of more than one hundred forty compounds is reported. Compounds **IIIg** (Chapter 2), **VIbx**, **VIex**, **VIcx**, **VIdx**, **IVe** (Chapter 5) and **VIIzd** (Chapter 4b) exhibited anti-inflammatory activity comparable or better than standard drug ibuprofen. Compounds **IIIh**, **IIIi** (Chapter 2) against lung (NCI H-522); **IIIf**, **IIIh**, **IIIi**, **IIIf** (Chapter 2) against ovary (PA-1); **IIIh** (Chapter 2) against breast (T47D); **IIIh** (Chapter 2) against colon (HCT-15) and **IIIa** (Chapter 2), **VIxc** (Chapter 4b), **IIIh**, **IVf** (Chapter 5) against liver (HepG2) exhibited good anticancer activity against various cancer cell lines mentioned above. One compound **IIIh** (Chapter 2) exhibited good anticancer activity against all the cancer cell lines screened except one i.e. liver (HepG2) cancer cell line. Compounds which exhibited good anti-inflammatory and anticancer activities can be candidate for further studies. From the work reported in this thesis three research papers have been published and three are under review in various international journals.

**********

# ACKNOWLEDGEMENTS

First and foremost I humbly and politely bow my head to **Almighty**, Who bestowed upon me an opportunity to accomplish this work and gave me ample vision and strength to understand and grasp very minutely the happening on this earth.

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I am highly grateful to Prof. Ravi Bhushan (former Head) and Prof. Anil Kumar, present Head, Department of Chemistry, IIT Roorkee, for providing me all the necessary facilities and support for pursuing my research work. I wish to acknowledge Mr. Abdul Haq and Mr. Madan Pal for their technical assistance and also to Mr. Babu Ram, Mr. Tilak Ram and Mr. Ramesh for their help.

I sincerely thanks Prof. Ritu Barthwal, coordinator, Central NMR Facility and technical staff of Chemistry Department, Indian Institute of Technology Roorkee for various spectral and analytical results. My thanks are due to Dr. Partha Roy, Associate Professor, Department of Biotechnology, Indian Institute of Technology Roorkee, Roorkee for biological activity results, and helpful discussions.

With great pleasure I would like to thank my labmates Surbhi, Anuj and Naresh for their cooperation and pleasant company in the lab. I would like to thank my seniors Dr. Jaiveer Singh and Dr. Reshma Rani for their co-operation, suggestions, congenial company, and numerous forms of assistance.

Friendship is a wonderful thing and is vitally important for personal growth and success. Today I recall all my friends Dr. Parkash, Dr. Anand, Sanjay, Manohar, Raman, Sudhir, Anoop, Gaurav and Shakti for their help and support.

I cannot express my heartly feelings in words towards my loving wife, **Monika** who has always been there for me in every situation. Without her encouragement and constant support, I could not have finished this thesis. She is always there to talk about my ideas, to proofread and mark up my papers and chapters, and to ask me good questions to help me think through my problems. Words fail me to express my regards to my In-laws for their love and immeasurable affection that provided the foundation for this work.

Last but not the least; with deepest gratitude, I would like to thank my family. The constant inspiration and guidance kept me focused and motivated. I am grateful to my Papa, **Sh. Des Raj** for giving me the life I ever dreamed. I can't express my gratitude for my mummy **Smt. Laxmi Devi** in words, whose unconditional love has been my greatest strength. I would also like to extend my sincere thanks to my loving sister **Renu** and brother in law **Virender** for their confidence in me and their constant support to make this journey so congenial and easy. I thank them for their memorable concern, affection and constant care. I am also thankful to Shiristi, Vansh & Akshit for giving me happiness with their cute smile. I am lucky to have such a nice family and I wish to have the same in all my births.

The financial assistance provided by Ministry of Human Resource & Development (MHRD), New Delhi, made my research work very smooth and prompt, is gratefully acknowledged.

**Dated: July 2013** **(Sandeep Kumar)**

## LIST OF PUBLICATIONS

**Research papers published/communicated & presented**

1. Synthesis anti-inflammatory and anticancer activity evaluation of some pyrazole and oxadiazole derivatives
   Sham M. Sondhi, **Sandeep Kumar**, Nikhil Kumar, Partha Roy
   **Med Chem Res, 21, 3043–3052 (2012).** Chapter-3
   (Springer Publication)

2. Synthesis of bis-acridine derivatives exhibiting anticancer and anti-inflammatory activity
   Sham M. Sondhi, **Sandeep Kumar**, Reshma Rani, Ajanta Chakraborty, Partha Roy
   **Journal of Heterocyclic Chemistry, 50, 252-260 (2013)**. Chapter-2
   (Wiley & Sons Publication)

3. Efficient synthesis of piperazine-2,6-dione and 4-(1H-indole-2-carbon yl)piperazine-2,6-dione derivatives and their evaluation for anticancer activity
   **Sandeep Kumar**, Nikhil Kumar, Partha Roy, Sham M. Sondhi
   **Med Chem Res, 10.1007/s00044-012-0438-7.** Chapter-5
   (Springer Publication)

4. Synthesis anti-inflammatory and anticancer activity evaluation of isoindole, pyrrolopyrazine, benzimidazoisoindole and benzimidazopyrrolopyrazine derivatives
   **Sandeep Kumar**, Nikhil Kumar, Partha Roy, Sham M. Sondhi
   **Molecular diversity,** (Submitted after Revision) Chapter-4b
   (Springer Publication)

5. Efficient synthesis of heterocyclic compounds derived from 2,6-dioxopiperazine derivatives and their evaluation for anti-inflammatory and anticancer activities
   **Sandeep Kumar**, Nikhil Kumar, Partha Roy, Sham M. Sondhi
   **Journal of Heterocyclic Chemistry,** (Under Review) Chapter-5
   (Wiley & Sons Publication)

6. Synthesis of azomethine & amidine derivatives of isoindole and pyrrolopyrazine and their evaluation for anti-inflammatory and anticancer activities
   **Sandeep Kumar**, Nikhil Kumar, Partha Roy Sham M. Sondhi
   (Communicated) Chapter-4a

7. Synthesis of bis acridine derivatives and their evaluation for anti-inflammatory activity
   **Sandeep kumar**, Sham M Sondhi, Surbhi Arya, Partha Roy
   **National Synposium on Emerging Trends in Chemistry (NSETC-10),** Punjabi University, Patiala, Feb 15-16, 2010**. (PS-100).**

8. Synthesis, anti-inflammatory activity evaluation of isoindole and benzimidazole derivatives
   **Sandeep Kumar**, Surbhi Arya, Partha Roy, Sham M. Sondhi
   **International conference on Chemistry Frontier & Challenges,** Department of Chemistry, Aligarh Muslim University, Aligarh, India, March, 2-3, 2013**, (ID-264).**

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## LIST OF ABBREVIATIONS

| | |
|---|---|
| APCI-MS | Atmospheric-pressure chemical ionization |
| ASIC3 | Acid Sensing Ion Channel-3 |
| COX | Cyclooxygenase |
| COX-1 | Cyclooxygenase-1 |
| COX-2 | Cyclooxygenase-2 |
| CB1 | Cannaboid receptor 1 |
| CB2 | Cannaboid receptor 2 |
| CCK2 receptor | Cholecystokinin receptor |
| CDK1 | Cyclin-dependent kinase 1 |
| CDK5 | Cyclin-dependent kinase 5 |
| CSCPK | Cancer Stem Cell Pathway Kinase |
| CXCR2 receptor | CXC Chemokine receptor |
| CEM | Leukemia Cell |
| DBU | 1,8-Diazabicycloundec-7-ene |
| DIC | Diisopropyl carbodiimide |
| DMF | Dimethylformamide |
| FTIR | Fourier transform infrared spectroscopy |
| GI | Growth inhibition potency |
| HWB COX-2 | Human whole blood cyclooxygenas-2 |
| GC-MS | Gas-chromatography mass spectrometry |
| H DAC | Histone deacetylases |
| $IC_{50}$ | Concentration for 50% inhibition |

| | |
|---|---|
| JAK-1 | Janus kinase 1 |
| LPS | Lipopolysacchride |
| L1210 | Mouse lymphocytic leukemia cells |
| MWI | Microwave irradiation |
| MMP | Matrix metals proteinase |
| NSAIDs | Nonsteroidal anti-inflammatory drugs |
| nM | Nanomolar |
| NMR | Nuclear magnetic resonance |
| $P_{38}$αMAP Kinase | $P_{38}$ mitogen activated protein Kinase |
| $PGH_2$ | Prostaglendin $H_2$ |
| PKB | Protein kinase B |
| PDE4 | Phosphodiesterase enzyme 4 |
| PGE2 | Prostaglandin E2 |
| p-TsOH | p-Toluenesulfonic acid |
| ROCK protein kinase | Rho-associated coiled-coil protein kinase |
| Syk | Spleen tyrosine kinase |
| TNF-α | Tumor necrosis factor alpha |
| µM | Micromolar |

# CONTENTS

# Chapter 1

## General Introduction

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***1a Synthesis***

***1b Heterocyclic compounds as anti-inflammatory and anticancer agents***

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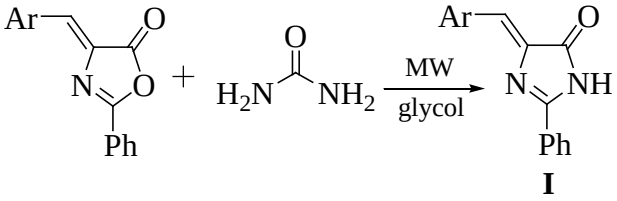
# *General Introduction*

## *1a Synthesis*:

First organic compound urea was synthesized by Friedrich Wohler in 1828 by evaporating aqueous solution of ammonium cyanate. Since then a number of organic compounds have been synthesized. In modern drug discovery and development, synthesis of heterocyclic molecules [1-10] continue to be an area of interest to the scientists. For rapid synthesis of heterocyclic compounds with or without use of solvent and in high yields, microwave assisted reactions are quite useful. In the following few pages we will summarize some of the recent work reported in literature.

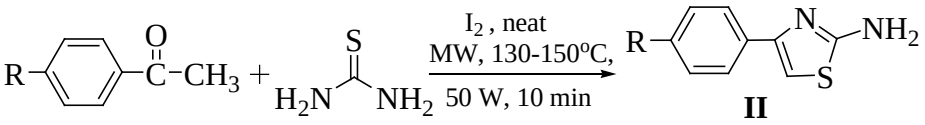
4-Arylidene-2-phenyl-1H-imidazol-5(4H)-ones **I** was synthesized in high yield [11] by following reaction scheme mentioned below. Caceres-Castillo *et. al.* [12]




**I**

[Ar=$C_6H_5$, 2-$ClC_6H_4$, 4-$ClC_6H_4$, 3-$BrC_6H_4$, 4-$BrC_6H_4$, 3-$NO_2C_6H_4$, 4-$NO_2C_6H_4$, 2,3-$(CH_3O)_2C_6H_3$, 3,4-$(CH_3O)_2C_6H_3$, 3,4,5-$(CH_3O)_3C_6H_2$, 3,4-$OCH_2$-$OC_6H_3$, 4-$(CH_3)_2NC_6H_4$, Thiophen-2-yl]

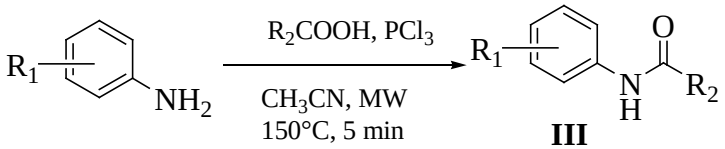
synthesized 2-amino-4-arylthiazoles **II** by condensation of p-substituted acetaphenones with thiourea and iodine under solvent free conditions. Phosphorus trichloride mediated




**II**

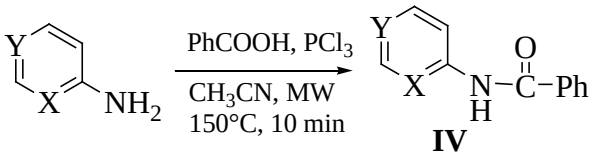
[R= H, $CH_3$, $OCH_3$, OH, $NH_2$, Cl, Br, $NO_2$]

and microwave assisted several amide derivatives **III**, **IV** have been synthesized and reported in literature [13]. A series of 2-hydrazolyl-4-thiazolidinone derivatives **V** have




**III**

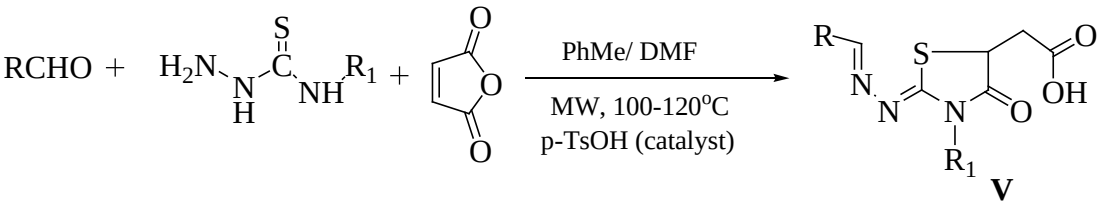
[$R_1$=$NO_2$, $CF_3$;
$R_2$= aryl, alkyl, heteroaryl]




**IV**

been synthesized as mentioned below [14] using p-TsOH as catalyst in 45% to 82% yield.

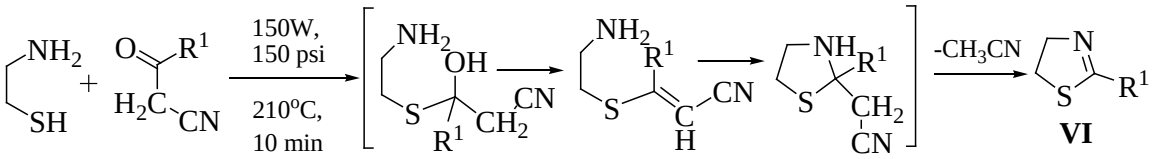
2-Thiazoline derivatives **VI** have been synthesized by reaction of aryl ketonitriles with




**V**

[$R_1$= H, R= Ph, p-N(Me)$_2$-Ph, o-F-Ph, p-OBut-Ph, p-$NO_2$-Ph, p-Cl-Ph, p-MeO-Ph, $CH(Me)_2$, $-CH_2-CH_2$-Ph]

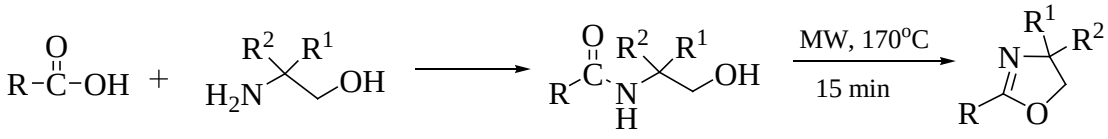
cysteamine by using microwave at 210ºC temperature in 10 min by following reaction scheme mentioned below [15]. Sharma *et. al.* [16] synthesized 2-oxazoline derivatives




**VI**

$R^1$ are various substituents

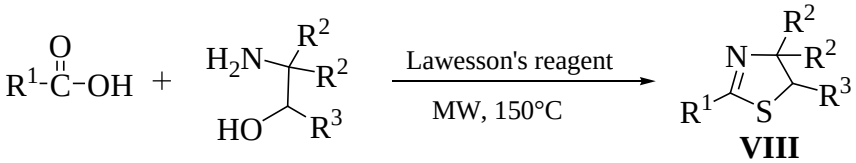
**VII** in 70-85% yields by following reaction scheme mentioned below. 2-Thiazoline derivatives **VIII** have been synthesized using Lawesson's reagent. The role of




**VII**

[R= various substituents; $R^1$ =$R^2$ =H; $R^1$ =$R^2$ =$CH_3$; $R^1$ =$R^2$ =$CH_2OH$]

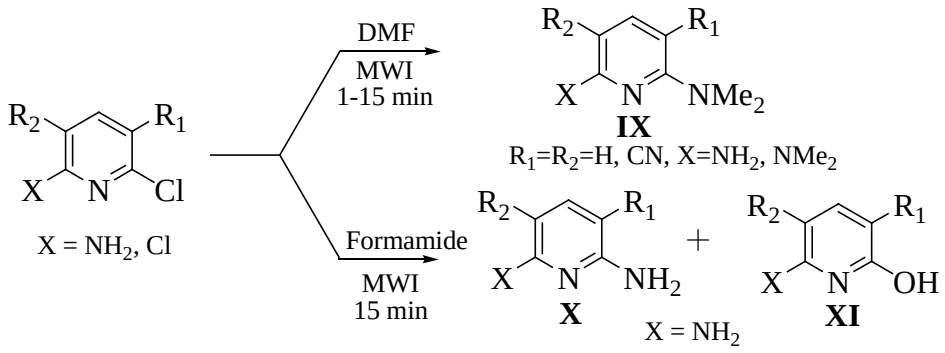
Lawesson's reagent is to transform the 1,2-amino alcohol into 1,2-aminothiol and also activate its [17] reaction with carboxylic acid. Microwave assisted amination of 2-



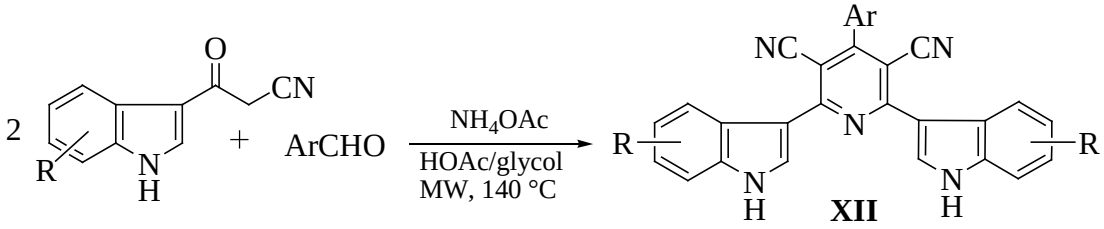

**VIII**

[$R^1$= various substituents; $R^2$ =$R^3$ =H; $R^2$ =$CH_3$, $R^3$ =H; $R^2$ =H; $R^3$ =Ph]

chloropyridine derivatives to give corresponding amino derivatives **IX** & **X** have been

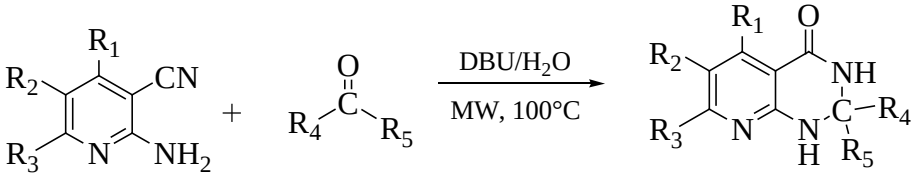



achieved by using amide solvents [18]. A series of bis(3´-indolyl)pyridine derivatives **XII** have been synthesized [19] via a one pot multi-component reaction using microwave irradiation. Yang *et. al.* [20] synthesized 2,3-dihydropyrido[2,3-d]pyrimidin-4(1H)-ones



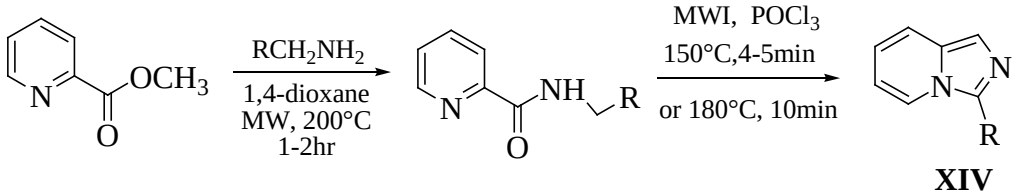

**[a-l**: R=H; Ar= 4-ClPh; Ph; 2-ClPh; 2-BrPh; 4-$CH_3$Ph; 4-$CH_3$OPh; 3-$NO_2$Ph; 4-$NO_2$Ph; 4-HO-Ph; 3,4-$OCH_2OC_6H_3$; 4-OH,3-$OCH_3C_6H_3$; 2-thienyl; **m-p**:Ar= 4-ClPh; R=2-Ph; 4-$CH_3$; 5-$CH_3$; 7-$CH_3$]

**XIII** in good yields by using DBU as catalyst in aqueous medium and microwave irradiation. A series of 3-substituted imidazo[1,5-a]pyridines **XIVa-m** have been



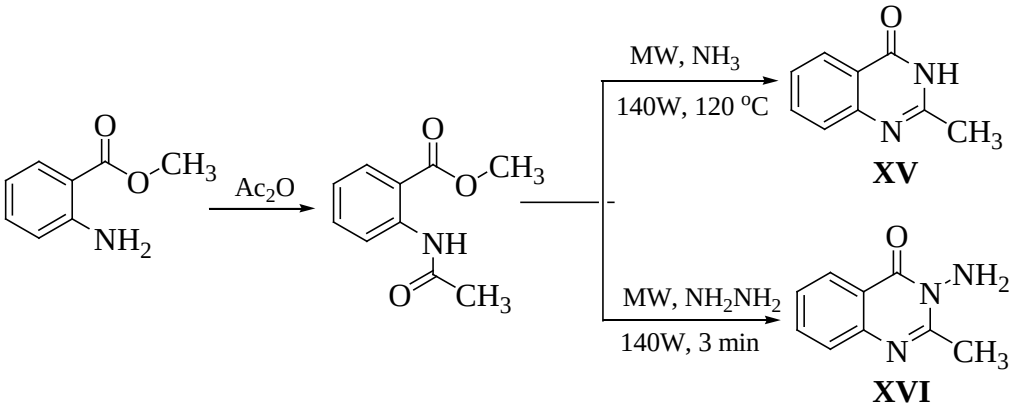

[$R_1$, $R_2$, $R_3$, $R_4$, & $R_5$ are various substituents]

synthesized by Arvapalli *et. al.* [21] in two step reaction by following reaction scheme outlined below. 2-Methyl-3(H)-4-quinazolinone **XV** and 2-methyl-3-amino-4-



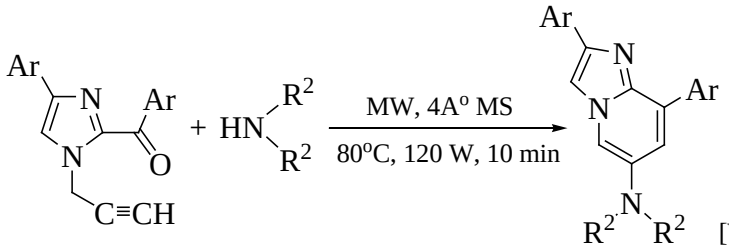

[R=Ph, 4-$CF_3$Ph, 4-CNPh, 4-Cl-Ph, 2-OMePh, 4-F-Ph, 4-OMePh, 4-$NMe_2$Ph, $CO_2C_2H_5$, 3,4-methylenedioxy-Ph, 4-pyridyl,CN, $CH(OMe)_2$]

quinazolinone **XVI** has been synthesized [22] by reaction of ammonia and hydrazine hydrate with methyl-2-acetamidobenzoate in 63% & 78% yield respectively. Nagaraj *et.*




**XV** **XVI**

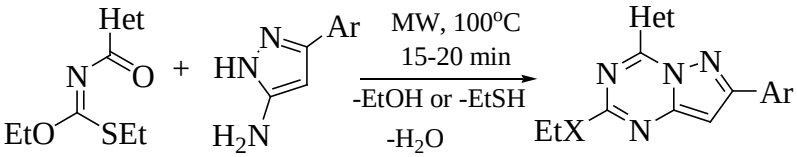
*al.* [23] synthesized 2,8-diaryl-6-amino-imidazo[1,2-a]pyridine **XVII** by condensation of 2-aroyl-4-aryl-1-prop-2-ynyl-1H-imidazoles with secondary amines under microwave




[Where Ar and $R^2$ are various substituents]

**XVII**

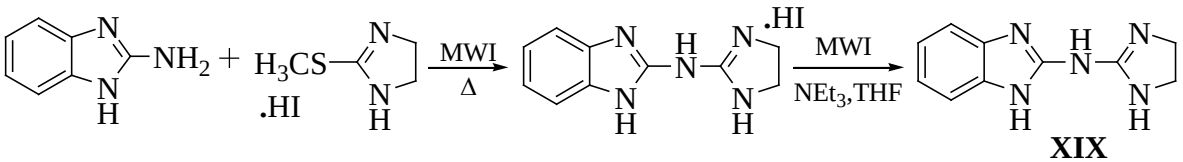
irradiation condition. Microwave irradiation technique is being used to synthesize a series of 4-hetaryl substituted pyrazolo[1,5-a][1,3,5]triazines **XVIII** under solvent free conditio-




[Het=2-furyl; Het=2-thienyl; Ar=4-$ClC_6H_4$, 4-$CH_3C_6H_4$, Ph; X=O, S]

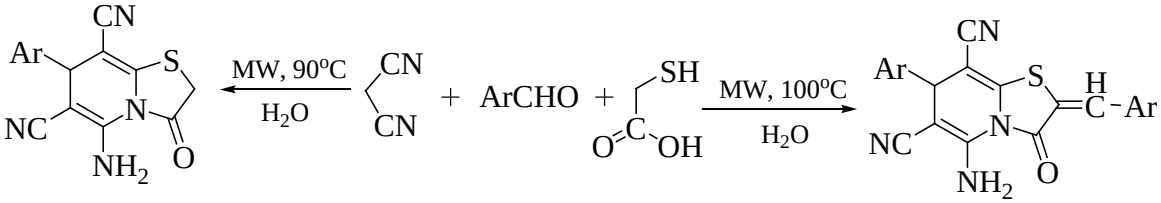
**XVIII**

ns [24]. N-(1H-imidazoline-2-yl)-1H-benzimidazol-2-amine **XIX** have been synthesized [25] in excellent yield using microwave irradiation technique. Shi *et. al.* [26] reported a




**XIX**

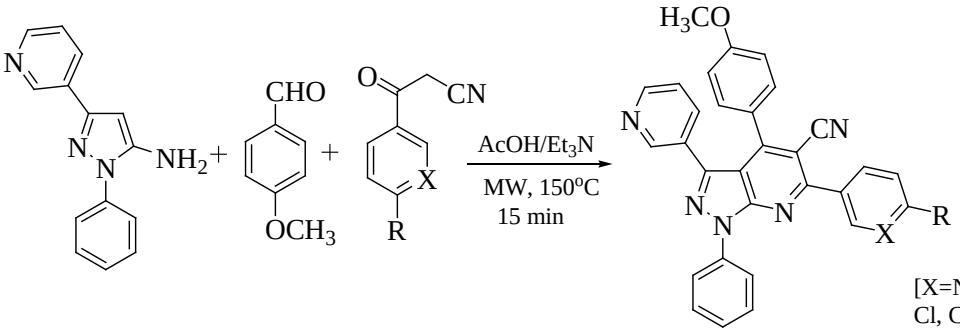
chemoselective synthesis of thiazolo[3,2-*a*]pyridine derivatives **XX**, **XXI** by following reaction scheme mentioned below. Pyrazolo[3,4-b]pyridine derivatives **XXII**, **XXIII**




**XX** **XXI**

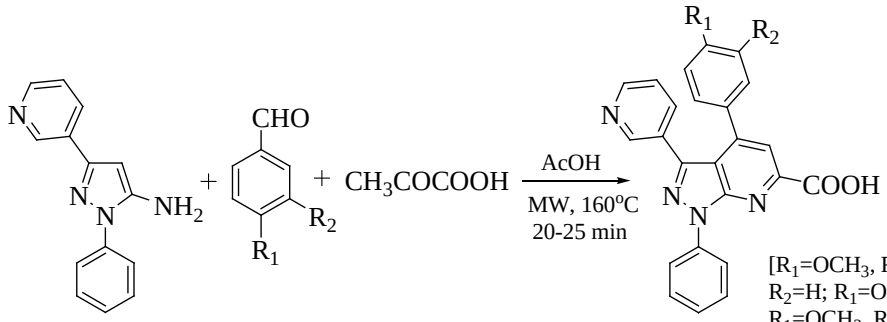
[Ar= 4-$FC_6H_4$, 4-$BrC_6H_4$, 4-$ClC_6H_4$, 2,4-$Cl_2C_6H_3$,4-$CH_3OC_6H_4$, 2-thienyl, Ph, 3,4-$OCH_2O$-$C_6H_3$, $CH_3C_6H_4$, 4-$NO_2C_6H_4$, 3-$NO_2C_6H_4$,4-OH,3-$NO_2C_6H_3$]

possessing anti-tumor and antimicrobial activities have been synthesized [27] following reaction scheme mentioned below. Alen *et. al.* [28] synthesized pyrazino[1,2-a]




[X=N, R=H, X=CH, R=H, Cl, $CH_3$, F, $NO_2$]

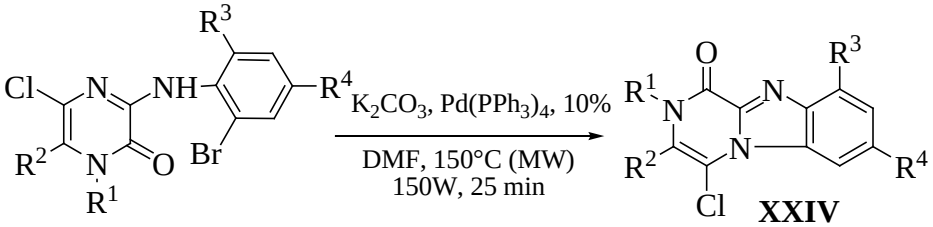
**XXII**




[$R_1$=$OCH_3$, $R_2$=H; $R_1$=$R_2$=H; $R_1$=$NEt_2$, $R_2$=H; $R_1$=OH, $R_2$=H; $R_1$=Br, $R_2$=H; $R_1$=$OCH_3$, $R_2$=$OCH_3$, $R_1$=$NMe_2$, $R_2$=H]

**XXIII**

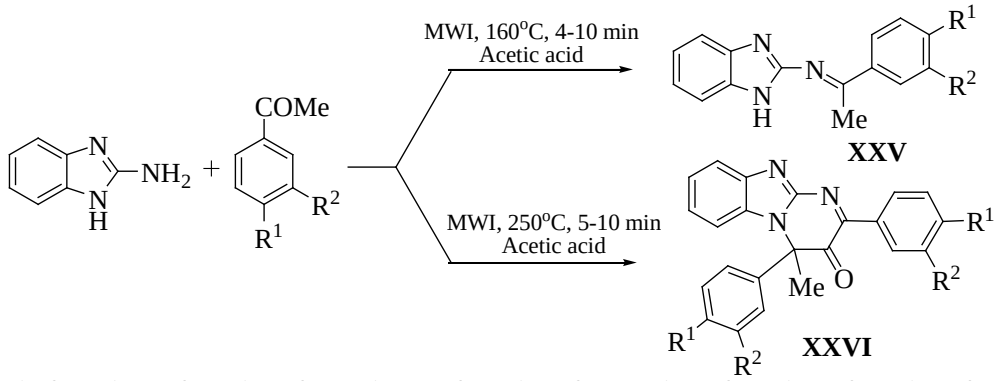
benzimidazol-1(2H)ones **XXIV** in good to moderate yields by using microwave irradiation technique. Benzimidazole Schiff bases **XXV** & pyrimido[1,2-a]benzimidazol-




**XXIV**

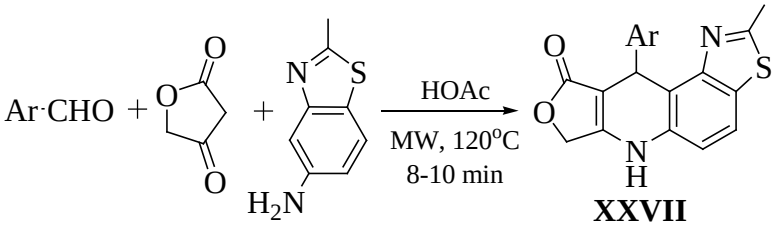
[$R^1$= p-methoxy benzyl, Ph; $R^2$=H, Me, Ph; $R^3$= H, Me,F, Cl; $R^4$=H, $CF_3$, CN, Me, $OCF_3$, F, H]

3(4H)-ones **XXVI** possessing cytotoxicity have been synthesized [29] by following reaction scheme mentioned below. 4-Aza-podophyllotoxin analogs **XXVII** possessing




[$R^1$=$R^2$=H; $R^1$=Me, $R^2$=H; $R^1$=H, $R^2$=Me; $R^1$=OMe, $R^2$=H; $R^1$=H, $R^2$=OMe; $R^1$=Cl, $R^2$=H; $R^1$=Br, $R^2$=H; $R^1$=H, $R^2$=Br; $R^1$, $R^2$=(-CH=)$_4$]

cytotoxicity to three carcinoma cell lines i.e. M14, MCF7, SW1116 have been synthesized by microwave-assisted multicomponent reactions and reported in lit. [30]



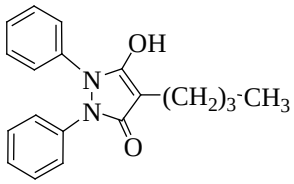

[Ar = 4-$FC_6H_4$, 4-$ClC_6H_4$, 4-$BrC_6H_4$, 3-$NO_2C_6H_4$, $C_6H_5$, 4-$CH_3C_6H_4$, 4-$OCH_3C_6H_4$, 2,4-$Cl_2C_6H_3$, 4-OH-3-$NO_2C_6H_3$, 3,4,5-$(OCH_3)_3C_6H_2$, Thien-2-yl]

In the above few pages we have summarized some of the recent references reported in literature regarding use of microwave irradiation technique in the synthesis of a variety of heterocyclic compounds. Microwave irradiation technique has helped in synthesizing various heterocyclic compounds [31] in high yields, high purity and in a short reaction time.

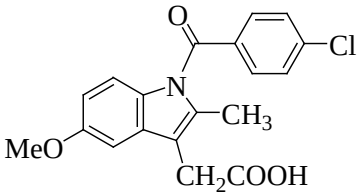
## *1b. Heterocyclic compounds as anti-inflammatory and anticancer agents:*

Inflammatory diseases and cancer continue to be a major health problem for mankind. Various drugs [32, 33] *i.e.* phenylbutazone **XXVIII**, indomethacin **XXIX**, piroxicam **XXX**, valdecoxib **XXXI**, celecoxib **XXXII**, rofecoxib **XXXIII**, 6-

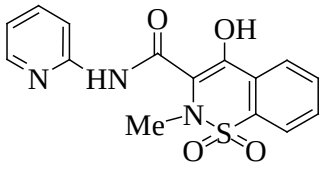
mercaptopurine **XXXIV**, 5-fluorouracil **XXXV**, floxuridine **XXXVI**, dacarbazine **XXXVII** used for the treatment of inflammatory diseases and cancer are heterocyclic



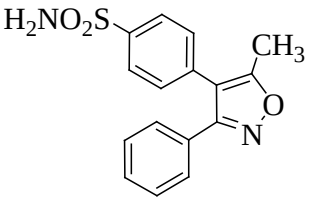

**XXVIII**
Phenylbutazone



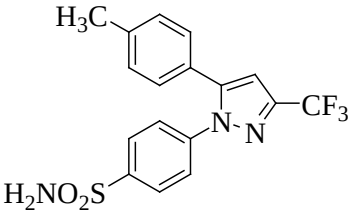

**XXIX**
Indomethacin



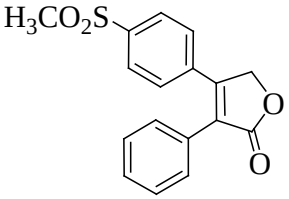

**XXX**
Piroxicam



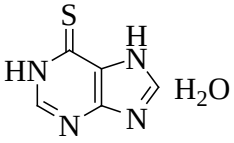

**XXXI**
Valdecoxib



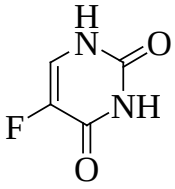

**XXXII**
Celecoxib



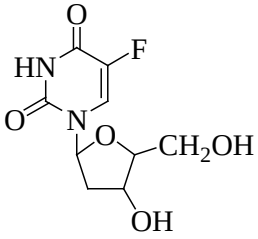

**XXXIII**
Rofecoxib



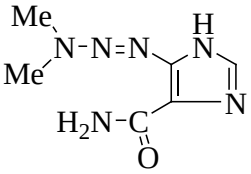

**XXXIV**
6-Mercaptopurine




**XXXV**
5-Fluorouracil




**XXXVI**
Floxuridine




**XXXVII**
Dacarbazine

molecules. Use of various drugs for the treatment of above said diseases is associated with serious side effects and hence cannot be used continuously for long period of time. One strategy to overcome these health problems is to synthesize new molecules, in search of potent compounds, which can be developed as safer drugs. For the researchers interested in the area of drug discovery, synthesis of heterocyclic molecules [34-39] their identification by modern instrumental techniques [40, 41] and evaluation for biological activities [42-46] is an interesting area of research.

Inflammation is a protective attempt by the organism to remove the harmful responses as well as initiate the healing process for the tissue. Non steroidal anti-inflammatory drugs (NSAIDs) are used to treat a wide variety of diseases, including inflammation, cancers, cardiovascular diseases, diabetes, Alzheimer's and Parkinson's diseases [47]. The anti-inflammatory effect of NSAIDs arise from their interaction with enzyme COX while other biological effects of these drugs are COX independent [48]. Although NSAIDs-COX interaction has been well characterized, the molecular mechanisms for their COX-independent activities are still not clear. NSAIDs show their effect by inhibiting cyclooxygenase (COX) enzyme, existing in two major isoform COX-1 and COX-2. COX-1 is considered to be expressed in most of the tissue where as COX-2 is induced with inflammation. Both COX-1 and COX-2 enzyme catalyzed arachidonic acid to produce prostaglandin $H_2$ ($PGH_2$). A number of enzymes further metabolized this $PGH_2$ into bioactive lipids (prostanoids), including prostacyclin, thromboxane $A_2$ and prostaglandins $D_2$, $E_2$ and $F_2$ which influence immune, cardiovascular, GI, renovascular, pulmonary, central nervous system, and reproductive system [49]. Clear role of COX-metabolites in fever, pain and inflammation make COX enzyme a target for the treatment of these diseases. Traditional NSAIDs such as indomethacin, aspirin, diclofenac, ibuprofen, and naproxen inhibit both isoform of COX. If these drugs do not inhibit COX-2, they do not act as anti-inflammatory, antipyretic or analgesic agent. However when used to inhibit COX-2 these drugs also inhibit COX-1, which is associated with gastrointestinal side effect [50]. From above observation selective COX-2 inhibitors came into existence. This selective action provides the benefits of reducing inflammation without irritating the stomach [51]. Selective COX-2 inhibitor drugs *i.e.* celecoxib,

valdecoxib and rofecoxib inhibit COX-2 but not COX-1 and thus have anti-inflammatory properties but no gastrointestinal side effects.

Another aspect of anti-inflammatory drugs which came to the attention of academic research, biomedical industry and medical professionals is that a close relationship between infection-inflammation and cancer exist [52]. Various case studies reported [53, 54] that a regular intake of NSAIDs produced highly significant composite risk reductions of 43% for colon cancer, 25% for breast cancer, 28% for lung cancer and 27% for prostate cancer. It is also reported that daily use of selective COX-2 inhibitor, either rofecoxib or celecoxib significantly reduced the risk for each of these malignancies. The evidence is compelling that anti-inflammatory agents with selective or nonselective activity against COX-2 have strong potential for the chemoprevention of cancers of breast, prostate, colon and lung. In case of COX-2 selective NSAIDs, the cardiovascular protective effects of non selective NSAIDs are lost [55, 56]. COX-2 selective inhibitor rofecoxib was withdrawn from the market by Merck because of the concern about increased risk of heart attack and stroke associated with long term high dose usage [57]. From above discussion it is clear that selective or non selective NSAIDs cannot be used continuously for long time and hence there is an urgent need to develop safer anti-inflammatory drugs.

In order to get safer alternative of these drugs wide range of heterocyclic molecules are synthesized and screened for anti-inflammatory and anticancer activities all over the world, which is evident from the large number of papers/patents published every year. We have also made some efforts in this direction which we will describe in this thesis.

In the following pages of this **chapter** recent literature on the following types of heterocyclic molecules will be discussed.

1b.1 Acridine and bisacridine derivatives

1b.2 Pyrazole and oxadiazole derivatives

1b.3 Isoindole and pyrrolopyrazine derivatives

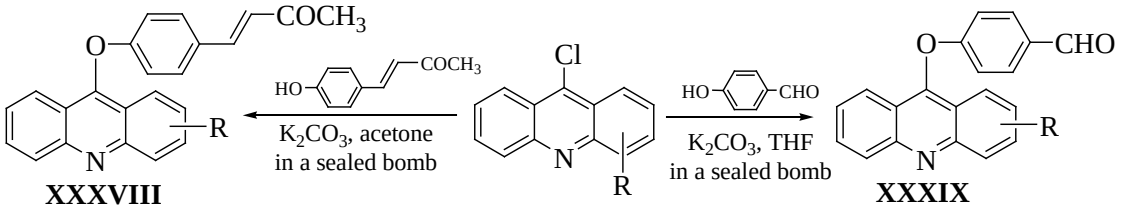
1b.4 Amidine and azomethine derivatives.

1b.5 Benzimidazole and piperazine derivatives.

## 1b.1 Acridine and bisacridine derivatives

### *1b.1.1 As anti-inflammatory agents:*

9-Phenoxyacridine derivatives **XXXVIII** & **XXXIX** have been synthesized [58] by following reaction scheme mentioned below. These acridine derivatives have inhibiting effects on the activation of mast cells, neutrophils and macrophages and hence showed potent anti-inflammatory activity. Chen *et. al.* [59] synthesized several



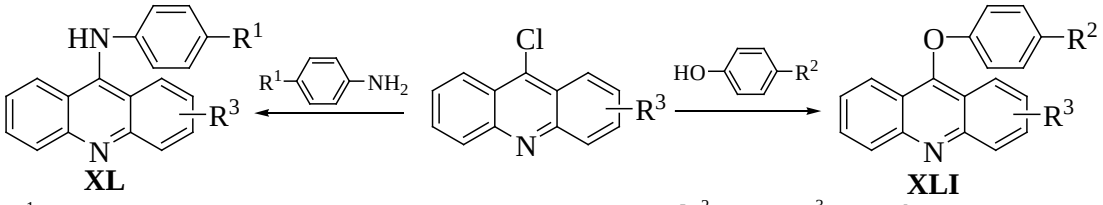

**XXXVIII**

[a, R=H; b, R=4-OMe; c, R=2-OMe
d, R=2-OMe; 6-Cl; e, R=2-Cl]

**XXXIX**

[a,R=H;b,R=4-OMe;c,R=2-OMe
d, R=2-OMe; 6-Cl; e, R=2-Cl]

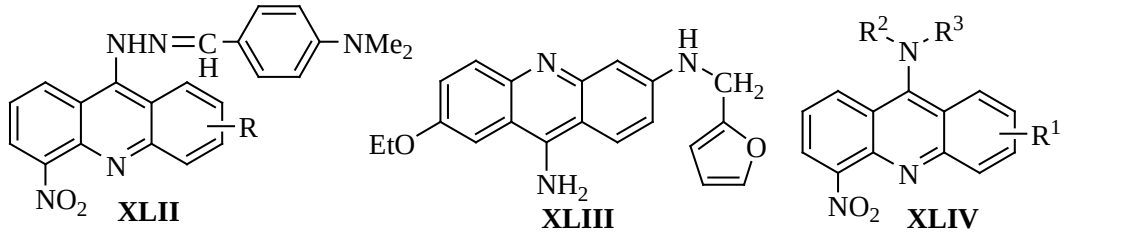
9-anilinoacridines **XL** and 9-phenoxyacridines **XLI** by the reaction of 9-chloroacridines with appropriate anilines and phenols respectively as mentioned below. These acridines are reported to have the potential to be novel anti-inflammatory agents with no significant cytotoxicity. Several 9-[[4-(dimethyl amino)benzylidene]hydrazino]-5-nitroacridines **XLII** which exhibited moderate anti-inflammatory activity have been synthesized and reported in literature [60]. Usefulness of acridine derivatives **XLIII** in the treatment of



**XL** [$R^1$ = MeCO, HON:CMe, MeON:CMe, $MeCOCH_2O$; $R^3$ =H]

**XLI** [$R^2$ =MeCO, $R^3$ =H, 2-Cl, 2-MeO, 4-MeO; $R^2$ =CHO, $R^3$=H; $R^2$=(E)-MeCOCH:CH, $R^3$=H]

autoimmunity, inflammation, allergy, asthma, graft rejection, cancer and immunodeficiency are disclosed in an international patent [61]. 9-Amino-5-nitroacridine

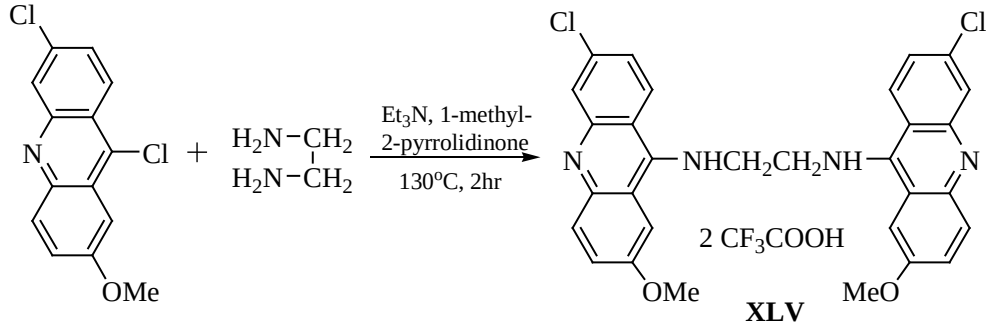


**XLII** [R = H; 1-,2-,4-Me; 1-,2-,3-,4-OMe;2-,4-Br; 2-, 4-Cl; etc.]

**XLIII**

**XLIV** [Where $R^1$, $R^2$ and $R^3$ are various substituents]

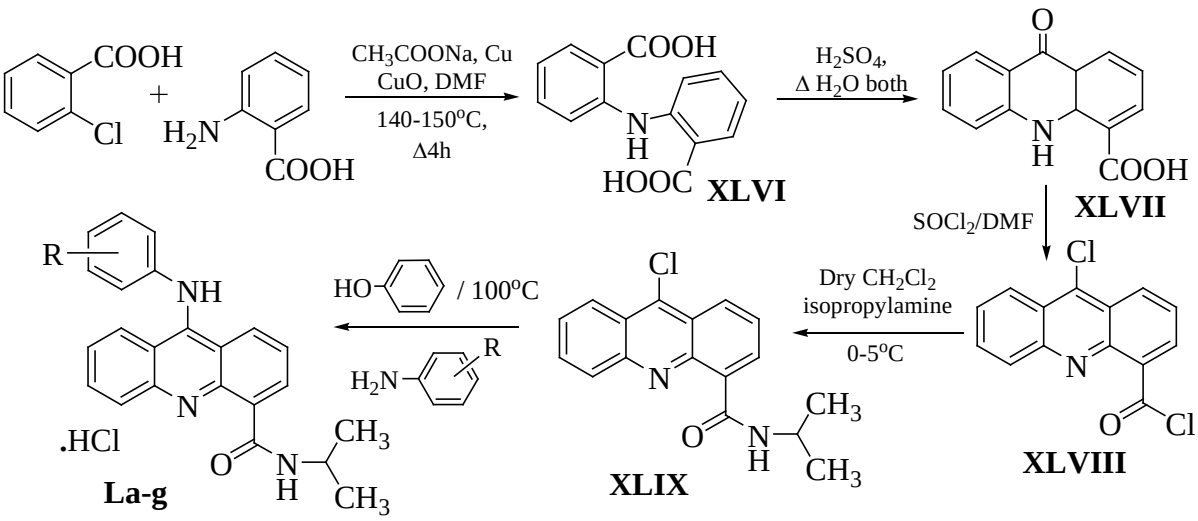
derivatives **XLIV** have been synthesized and reported in literature [62]. These derivatives were screened for bacteriostatic, fungicidal, anti-inflammatory and analgesic activities. Bondinell *et. al*. [63] synthesized N,N'-bis(6-chloro-2-methoxy-9-acridinyl)-1,2-ethane diamine bis(trifluoroacetate) **XLV** by condensing 6,9-dichloro-2-methoxyacridine with ethylene diamine. Compound **XLV** showed anti-inflammatory and antiviral activities.



**XLV**

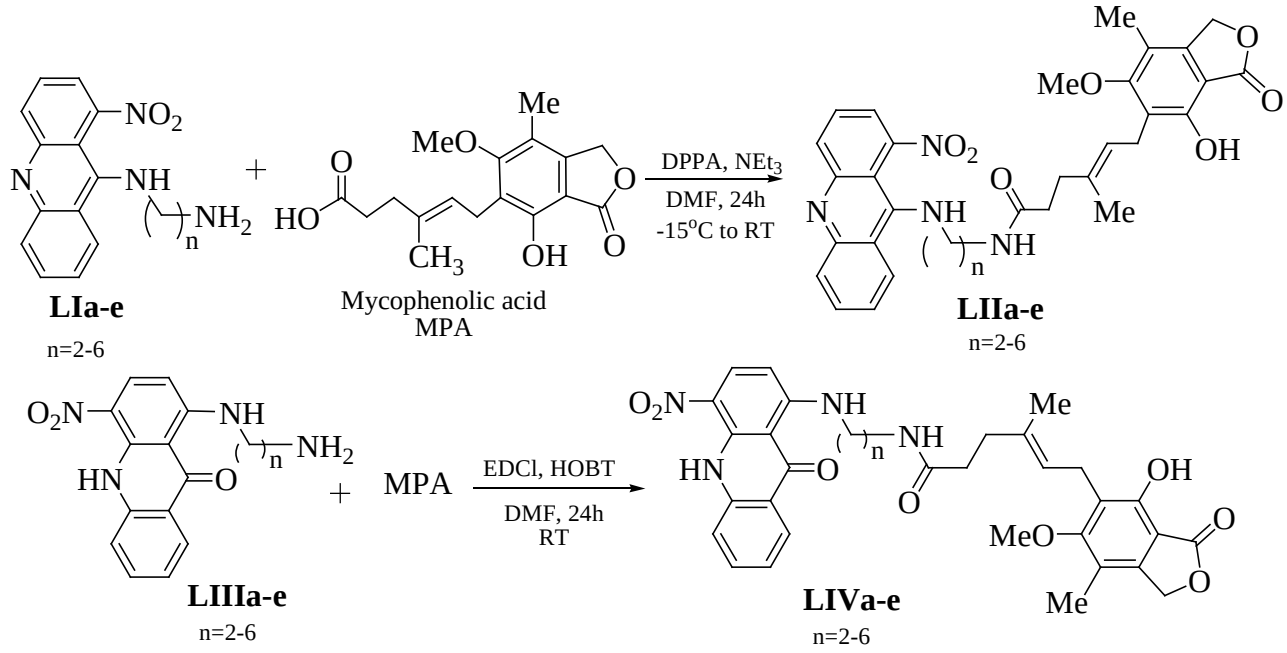
***1b.1.2 As anticancer agents:***

9-Aminoacridine-4-carboxamide derivatives **L** have been synthesized [64] by following reaction scheme mentioned below. Compounds **Lb** and **Le** exhibited anticancer activity against cervical cancer (HeLa) cell line and lung cancer (A-549) cell line respectively. Malachowska-Ugarte *et. al.* [65] synthesized conjugates of mycophenolic

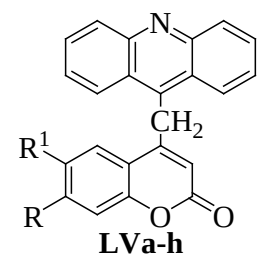



[R= a, 3'-$CF_3$; b, 4'-COOH; c, 4'-$OCH_3$; d, 2'-COOH; e, 3'-Cl; f, 4'-Cl; g, 4'-$CH_3$]

acid and 1-nitro acridine derivatives **LIa-e** and 4-nitroacridone derivatives **LIIIa-e** i.e. compounds **LIIa-e** and **LIVa-e** by following reaction sequence mentioned below. These compounds exhibited good anticancer activity against various leukemia cell lines i.e.

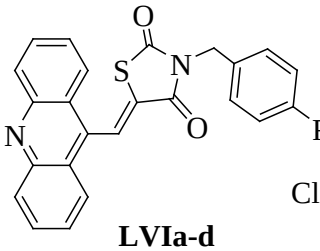



Jurkat, Molt-4, HL-60, CCRF-CEM, L1210. Several acridine derivatives **LVa-h** have been synthesized and screened for antimicrobial and anticancer activities [66]. Compounds **LVe** and **LVg** exhibited good anticancer activity against cancer cell line HL-60 with $IC_{50}$ values 27.53 & 28.72 µM. A series of 5-acridin-9-ylmethylene-3-benzyl-



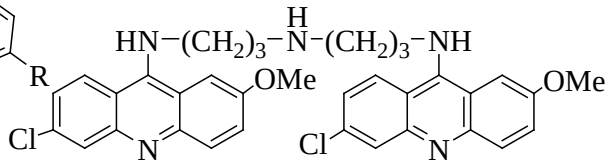
**LVa-h**

[a, R=H, $R^1$=H; e, R=Cl,$R^1$=H;
b, R=$NO_2$, $R^1$=H; f, R=OH, $R^1$=H;
c, R=$CH_3$, $R^1$=H; g, R=H, $R^1$=Cl;
d, R=H, $R^1$=Me; h, R=H, $R^1$=OH]



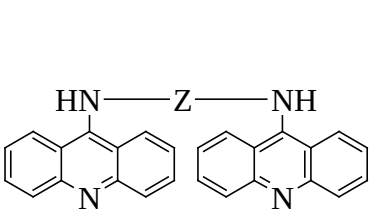
**LVIa-d**

[a, R=$CH_3$; b, R=Br;
c, R=Cl; d, R=F]



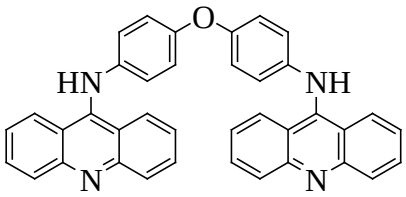
**LVII**

thiazolidine-2,4-diones **LVIa-d** have been synthesized [67, 68] and screened for cytotoxic activity on cancer and normal cells. These compounds exhibited high cytotoxicity on colon carcinoma and glioblastoma tumor cell lines. Wang *et. al.* [69] synthesized linker modified triamine linked acridine dimers and evaluated them for cytotoxicity in vitro and in vivo. Compound **LVII** exhibited potent solid tumor inhibition (COLO-205) in vivo. Different salts of **LVII** to increase its solubility have also been prepared and studied for antitumor activity [70]. Two international patents [71, 72] and one U.S. patent [73] reported synthesis of bis acridine derivatives **LVIII**, **LIX** and **LX**

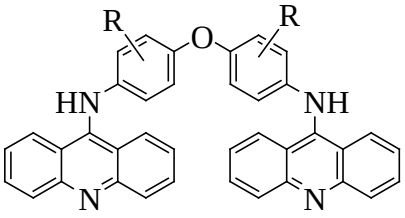


**LVIII**

[Z= linear arrangement of ≥ 2 aromatic rings linked in a 1,4 or 1,3-manner]



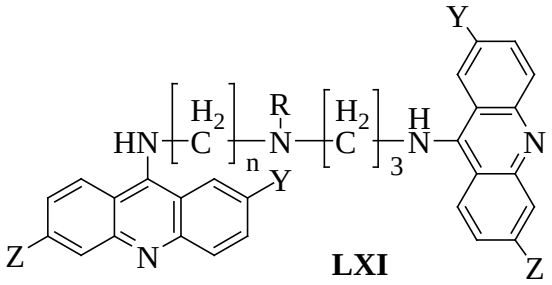
**LIX**



**LX**

[Where R = independently, amide, amino, azido, nitro, hydroxy, hydroxymethyl, carboxy, cyano, sulfinyl, aryl, heteroaryl, alkenyl, alkyl, alkylene, cycloalkyl, cycloalkenyl, heterocycle, spirocycle, alkoxy, halo etc.]

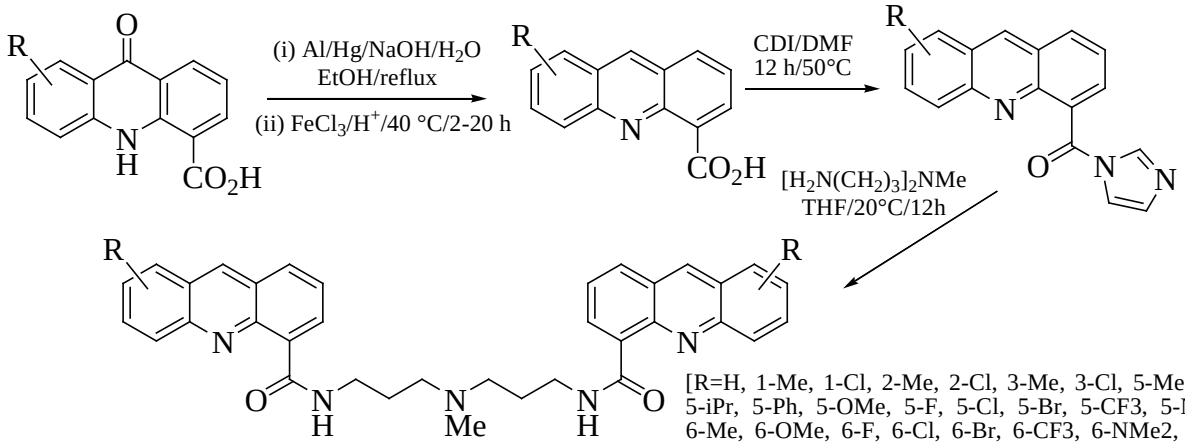
respectively. These compounds are reported to be useful in the treatment of cancer. Synthesis and usefulness of novel polyamine-linked acridine dimers **LXI** as potential anticancer agents is disclosed in a U.S. patent [74]. Thus compound **LXI** [R=H, n=3, Z=Cl, Y=MeO, X=O] exhibited $IC_{50}$ value of 0.04-4.94 µg/mL against HA22T.



**LXI**

[Where n = 3-6; X = 0-5; Z = H, F, Cl, Br, I; Y = H, OH, OC 1-4 alkyl; A = OAc, $OCOCF_3$; $OSO_2Me$, halo; R = C1-10 hydroxyalkyl, C1-10 polyhydroxyalkyl, C1-10 aminoalkyl etc.]

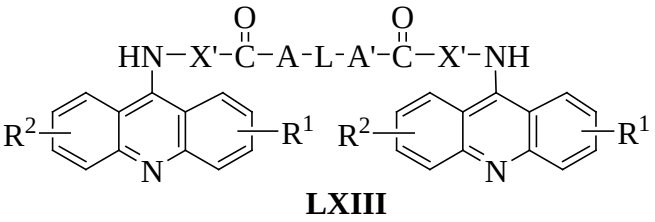
Gamage *et. al.* [75] synthesized bis(acridine-4-carboxamides) **LXII** by following reaction scheme mentioned below. These compounds are potent topoisomerage inhibitors.



**LXII**

[R=H, 1-Me, 1-Cl, 2-Me, 2-Cl, 3-Me, 3-Cl, 5-Me, 5-Et, 5-iPr, 5-Ph, 5-OMe, 5-F, 5-Cl, 5-Br, 5-CF3, 5-NMe2, 6-Me, 6-OMe, 6-F, 6-Cl, 6-Br, 6-CF3, 6-NMe2, 7-Me, 7-Et, 7-iPr, 7-tBu, 7-Ph, 7-OMe, 7-F, 7-Cl, 7-Br, 7-NMe2, 8-Me, 8-Cl, 5,7-diMe, 5,8-diMe, 1,5-diMe, 5-Me, 8-Cl, 1-Cl, 5-Me]

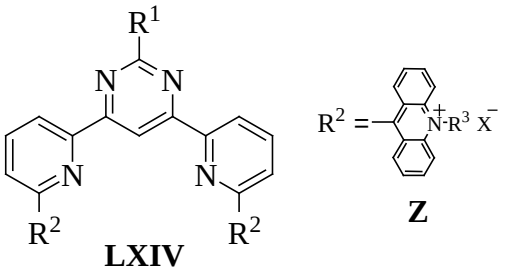
Fifty one aminoacridine derivatives **LXIII** have been synthesized and reported [76] in an international patent. Some of these compounds exhibited anticancer activity better



**LXIII**

[Where $R^1$, $R^2$ are H, EWG, EDG; X is $-CH_2$-aryl, $-CH_2$-heteroaryl, aryl, heteroaryl, benzoquinone, or polycyclic arom. quinone, which may be substituted by EWG or EDG; X' is aryl or heteroaryl, which may be substituted by EWG or EDG; A, A' are NH or O; L is an (un)substituted alkylene chain that may be non-adjacently interrupted by one or more N atoms or by a phenylene group]

than anticancer drug amsacrine. A Canadian patent [77] describe synthesis of 4,6-bis[6-(acridin-9-yl)pyridin-2-yl] pyrimidines **LXIV**. These compounds are reported to be useful in the treatment of cancers and related diseases. Lorente *et. al.* [78] synthesized a series of bisacridine derivatives **LXVa-d** containing rigid aromatic linking chains. These derivatives were studied for their DNA interaction and in vitro cytotoxicity against

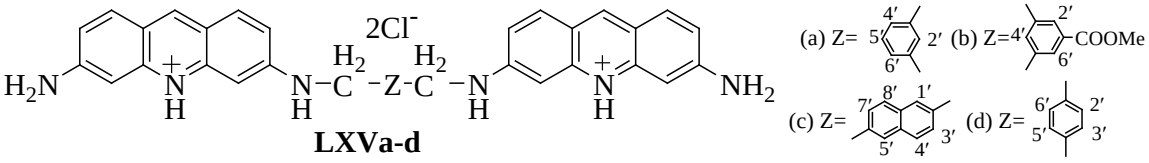


**LXIV**

**Z**

[$R^1$ is H, alkyl, aryl, cycloalkyl, etc.; each $R^2$ is formula Z or one $R^2$ is formula Z and one $R^2$ is 9-acridinyl; $R^3$ is alkyl, hydrophilic and hydrophobic substituent; X- is triflate, chloride, bromide, iodide, nitrate and sulfate; pharmaceutically acceptable salts, solvates, esters, amides, hydrates, and protected forms thereof]

HT-29 human carcinoma cells. $IC_{50}$ values of these compounds were found to be 8.9, 9.7, 17 and 26 µM.

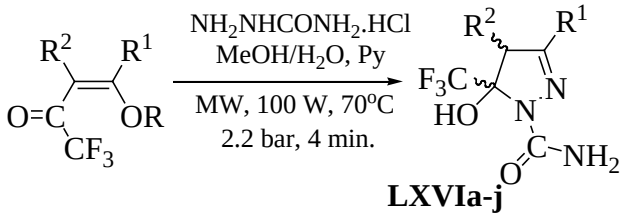


**LXVa-d**

## 1b.2 Pyrazole and oxadiazole derivatives

### *1b.2.1 As anti-inflammatory agents:*

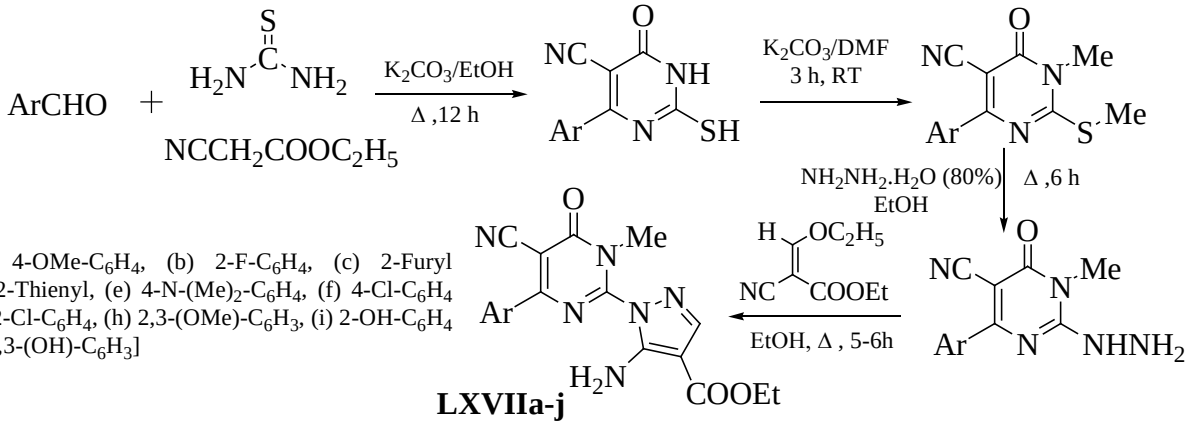
A series of 5-trifluoromethyl-4,5-dihydro-1H-pyrazole derivatives **LXVIa-j** have been synthesized using microwave irradiation technique, as mentioned below [79].



**LXVIa-j**

| | R | $R^1$ | $R^2$ | | R | $R^1$ | $R^2$ |
|---|---|---|---|---|---|---|---|
| a | Et | H | H | f | Me | Bu | H |
| b | Me | Me | H | g | Me | t-Bu | H |
| c | Me | Et | H | h | Me | Ph | H |
| d | Me | Pr | H | i | Me | 4-Br-Ph | H |
| e | Me | i-Pr | H | j | Et | H | Me |

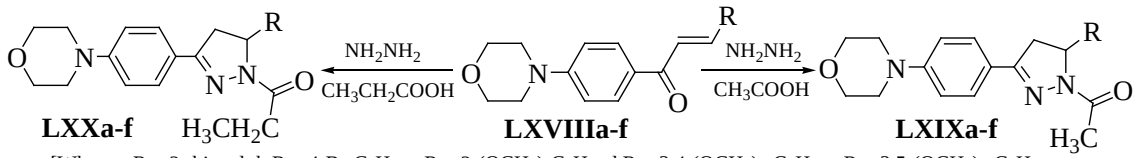
Compounds **LXVIc** & **LXVIj** exhibited good anti-inflammatory activity. Ramesh and Bhalgat [80] synthesized dihydropyrimidinyl pyrazole derivatives **LXVII** by following



[(a) 4-OMe-$C_6H_4$, (b) 2-F-$C_6H_4$, (c) 2-Furyl (d) 2-Thienyl, (e) 4-N-$(Me)_2$-$C_6H_4$, (f) 4-Cl-$C_6H_4$ (g) 2-Cl-$C_6H_4$, (h) 2,3-(OMe)-$C_6H_3$, (i) 2-OH-$C_6H_4$ (j) 2,3-(OH)-$C_6H_3$]

**LXVIIa-j**

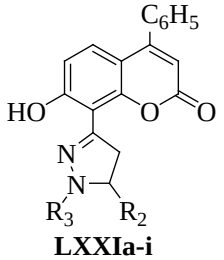
reaction scheme mentioned below. These compounds **LXVIIa-j** exhibited moderate to potent in vitro anti-inflammatory, antioxidant, antibacterial, antifungal and anthelmintic activity. A series of acetyl/propenyl pyrazolines carrying morpholinophenyl moiety **LXIXa-f** and **LXXa-f** have been synthesized and reported in literature [81]. Compounds **LXIXc** and **LXXd** exhibited good anti-inflammatory activity. Benzopyranone bearing



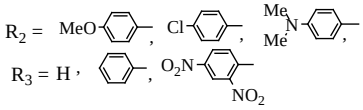

**LXXa-f** **LXVIIIa-f** **LXIXa-f**

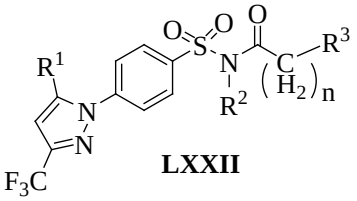
[Where a R = 2-thienyl; b R = 4-Br-$C_6H_4$; c R = 2-$(OCH_3)$-$C_6H_4$; d R = 3,4-$(OCH_3)_2$-$C_6H_3$; e R = 3,5-$(OCH_3)_2$-$C_6H_3$; f R = 3,4,5-$(OCH_3)_3$-$C_6H_2$]

pyrazole derivatives **LXXI** exhibiting anti-inflammatory, analgesic and antipyretic activity have been synthesized and reported in literature [82]. Out of several compounds synthesized compounds **LXXIb**, **e, d, i** exhibited significant anti-inflammatory activity. Amino sulfonyl containing pyrazole derivatives **LXXII** useful for treating fever, pain,



**LXXIa-i**

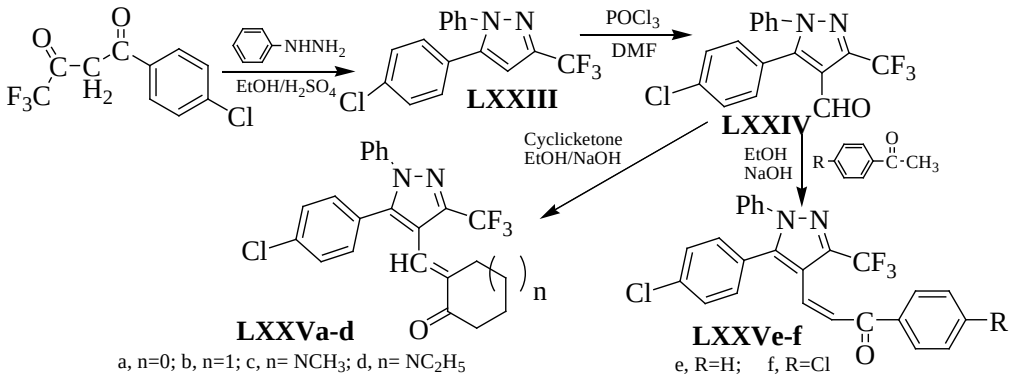




**LXXII**

[Wherein n = 1-6; $R^1$ = (cyclo)alkyl, heterocyclyl, halo, nitro, alkyl, alkoxy, (un)substituted Ph, naphthyl, or heteroaryl; $R^2$= H; $R^3$= H or COOH] or pharmaceutically acceptable salts]

inflammation or neoplasm is disclosed in a Chinese patent [83]. El-sayed *et. al.* [84] synthesized 1,5-diphenyl pyrazole derivatives by following reaction scheme mentioned




**LXXIII** **LXXIV**

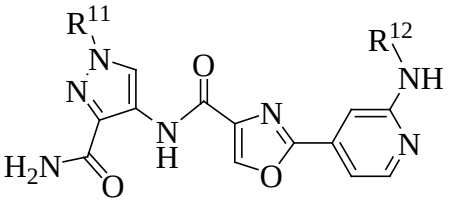
**LXXVa-d**

a, n=0; b, n=1; c, n= $NCH_3$; d, n= $NC_2H_5$

**LXXVe-f**

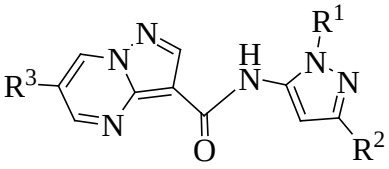
e, R=H; f, R=Cl

below. Compounds **LXXIV**, **LXXVa** and **LXXVd** exhibited selective COX-2 inhibitory activity. In a Japanese patent synthesis and usefulness of 4-amino-1-methyl-1H-pyrazole-3-carboxamide **LXXVI** for the treatment of inflammatory diseases and autoimmune disease is described [85]. Usefulness of amidopyrazole compounds **LXXVII** in the treatment of cancer, hyperplasia, inflammation, immune disorder and pyrazolylisoxazoles



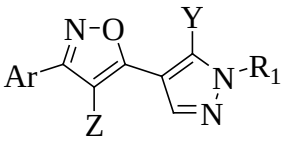
**LXXVI**

[$R^{11}$= pyridine-3yl
$R^{12}$= -$CH_2CF_3$]



**LXXVII**

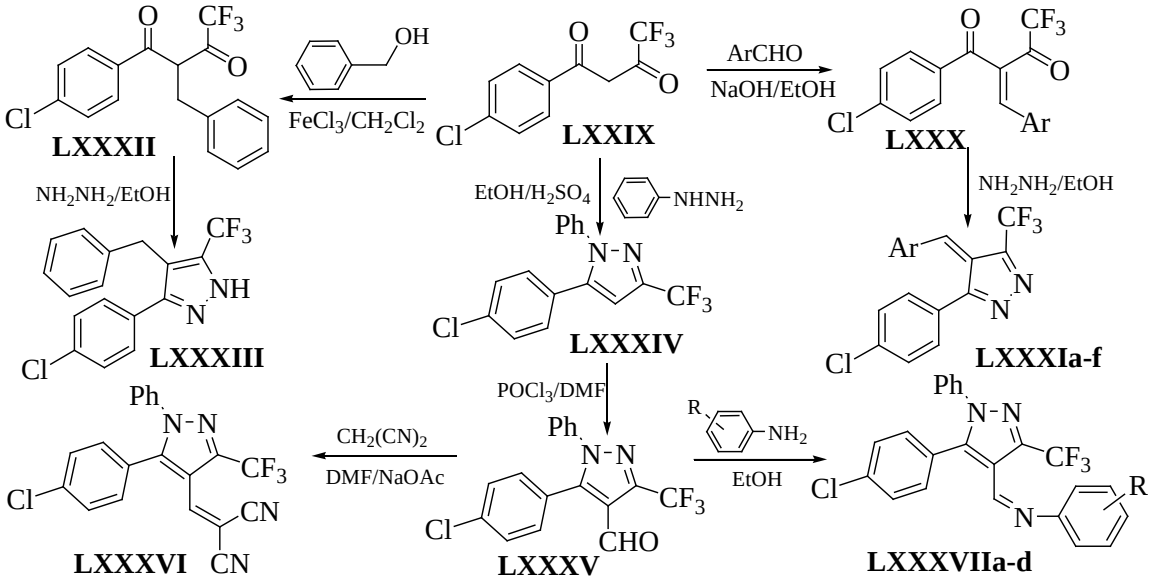
[Where $R^1$ = aryl, heteroaryl, hetero cyclyl, etc.$R^2$=aryl, heteroaryl, cyclo alkyl, etc.$R^3$=halo, CN, O, OH, etc.]



**LXXVIII**

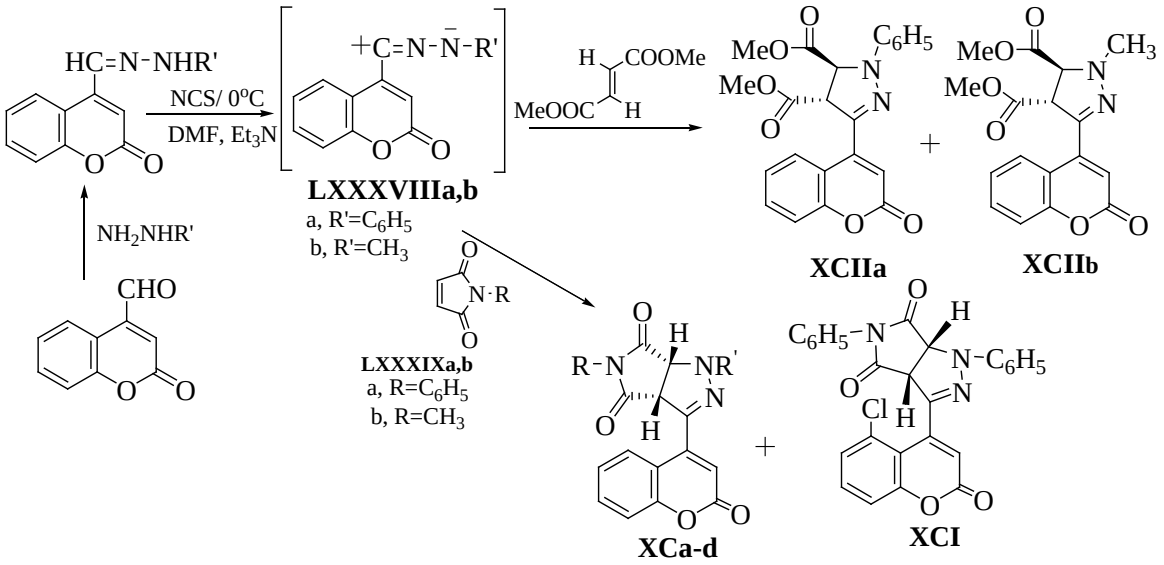
[Where $R^1$ = (un)substituted (hetero)aryl, cycloalkyl, heterocyclyl,alkyl; Ar=(un)sub stituted (hetero)aryl, cycloalkyl, heterocyclyl; Z=(un)substituted (hetero)aryl, cycloalkyl, heterocyclyl; Y=H, halo, (un)substituted halo alkyl, alkoxycarbonyl or pharmaceutically acceptable salts]

**LXXVIII** in the treatment of autoimmune disorder and inflammation is disclosed in two international patents [86, 87]. Several diaryl pyrazole derivatives **LXXXI**, **LXXXIII**, **LXXXIV**, **LXXXV**, **LXXXVI** and triaryl pyrazole derivatives **LXXXVII** have been synthesized by following reaction scheme mentioned below [88]. COX-1/COX-2



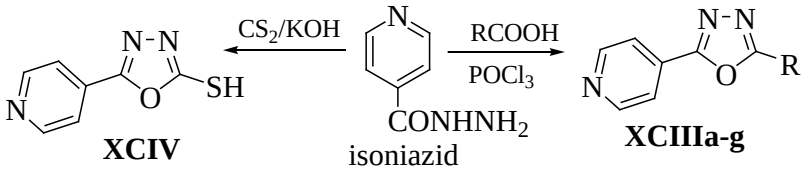
[Where LXXXIa-f: a, Ar= 2-hydroxyphenyl; b, Ar= 4-hydroxyphenyl; c, Ar= 4-methoxyphenyl; d, Ar= 3,4-dimethoxy phenyl; e, Ar= 3-nitrophenyl; f, Ar= 2-furyl; LXXXIa-d: a, R= 4-Br; b, R = 2-Cl; c, R= 4-$NO_2$; d, R= 3,5-di$CF_3$]

inhibition ability of **LXXXIa-f**, **LXXXIII**, **LXXXVI** and **LXXXVIIa-d** was evaluated using in vitro COX inhibition assay. COX-2 selectivity of **LXXXVIId** was comparable with reference drug celecoxib. Emmanuel-Giota *et. al.* [89] synthesized a series of 3-(coumarin-4-yl)dihydropyrazoles by following reaction scheme mentioned below.



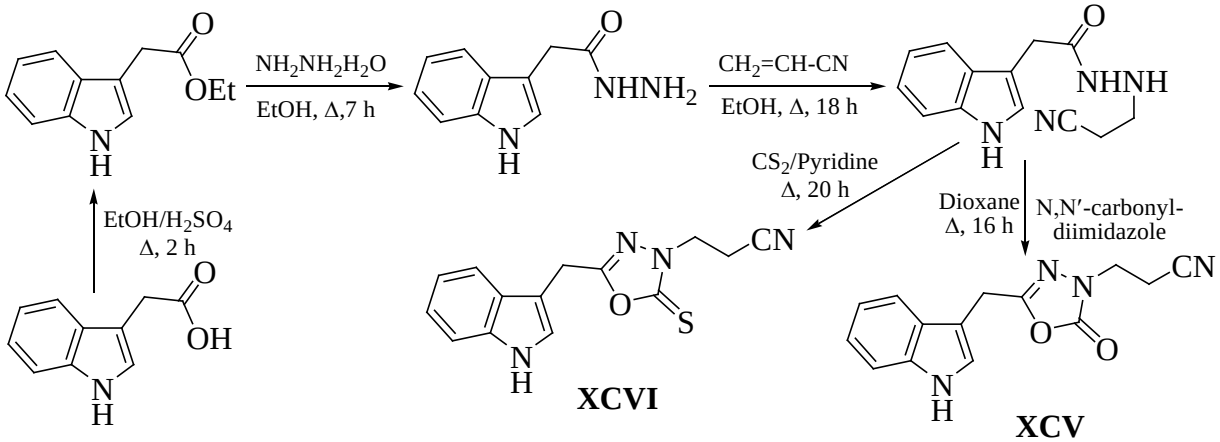

[XCa: R=R'=$C_6H_5$; XCb: R=$C_6H_5$, R'=$CH_3$; XCc: R=$CH_3$, R'= $C_6H_5$; XCd: R=R'=$CH_3$]

All these compounds were screened in vivo as anti-inflammatory agents in the rat carrageenan paw edema assay. Compound **XCIIa** exhibited good anti-inflammatory activity and this may be lead molecule for further structural modification. Gilani *et. al.* [90] synthesized 1,3,4-oxadiazole **XCIIIa-g** & **XCIV** by following reaction scheme mentioned below. These compounds i.e. **XCIIIa-g** & **XCIV** were screened for anti-inflammatory activity. Compounds **XCIIIa** and **XCIIIc** exhibited good anti-inflammatory activity. 3-[5-(1H-indol-3-yl-methyl)-2-oxo-[1,3,4]oxadiazol-3-yl]propio

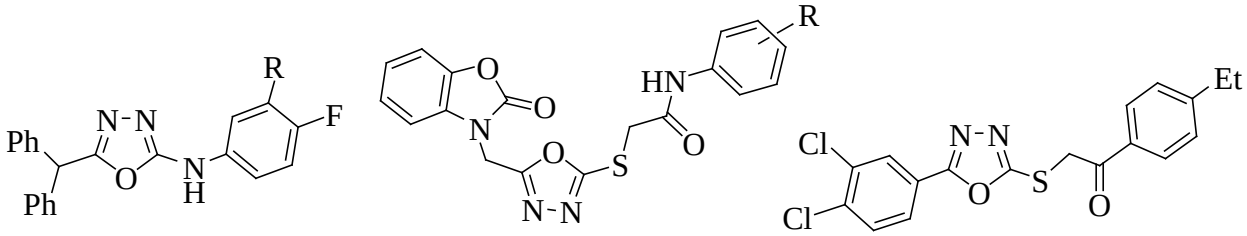



[(a) R = $C_6H_5$; (b) R = 2-Cl-$C_6H_4$; (c) R = 2,4-$C_6H_3Cl_2$; (d) R = 2-$C_6H_4CH_3$; (e) R = 2-$C_6H_4OCOCH_3$; (f) R = $OC_6H_5$; (g) R = 4-$C_6H_4NO_2$]

nitrile **XCV** and 3-[5-(1H-indol-3-yl-methyl)-2-thioxo-[1,3,4]oxadiazol-3-yl]propionitrile **XCVI** have been synthesized [91] and screened for anti-inflammatory activity. At a dose of 10mg/kg p.o. these compounds exhibited 70% and 57% activity compared to activity




shown by indomethacin. Amir *et. al.* [92], Li *et. al.* [93] and Koksal *et. al.* [94] synthesized oxadiazole derivatives **XCVIIa,b**; **XCVIIIa-n** and **XCIX** and screened them for anti-inflammatory activity. Compounds **XCVIIa,b** were moderately more active than ibuprofen, **XCVIIIa-n** were inactive and **XCIX** exhibited anti-inflammatory activity comparable to indomethacin at a dose of 100mg/kg p.o. A series of S-Substituted

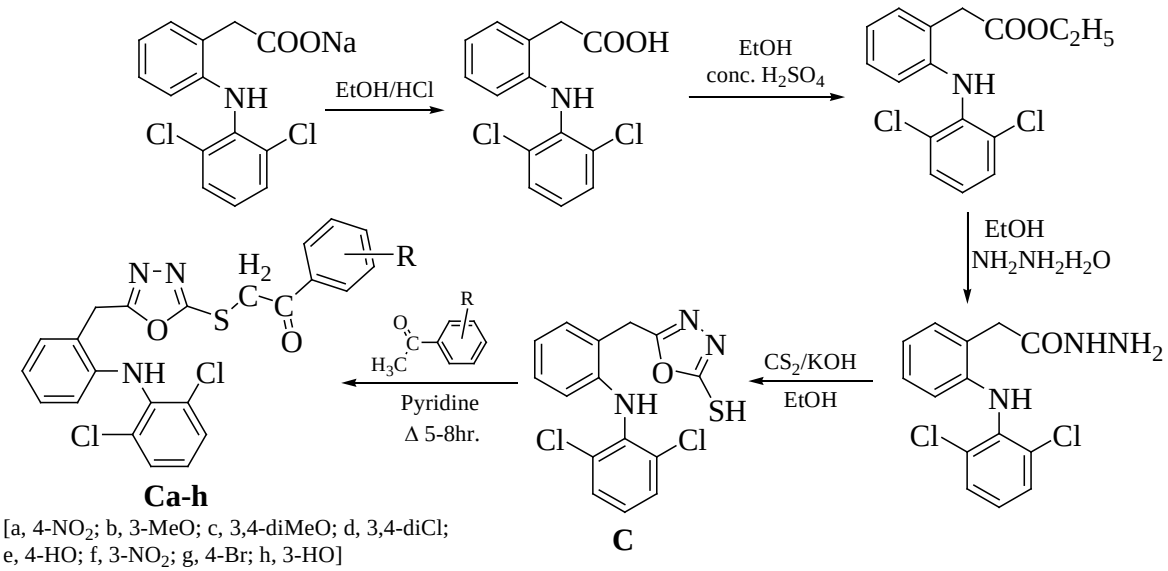


**XCVII**
[a, R=H; b, R=Cl]

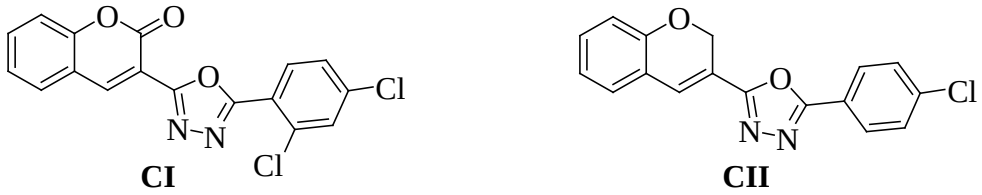
**XCVIIIa-n**
[R = H, 2-Me, 3-Me, 4-Me, 4-MeO, 2-Br, 4-Br, 4-F, 2-Cl, 3-Cl, 4-Cl, 2-$NO_2$, 3-$NO_2$, 4-$NO_2$]

**XCIX**

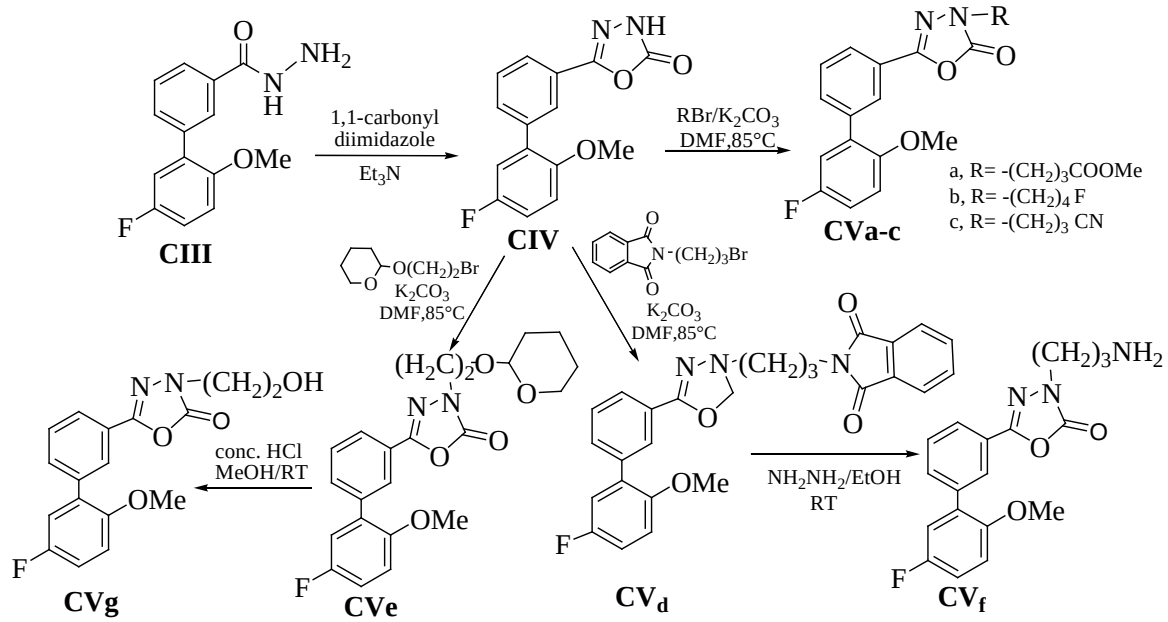
phenacyl-1,3,4-oxadiazole-2-thiol **Ca-h** have been synthesized [95] by following reaction scheme mentioned below. These compounds were screened for anti-inflammatory activity. Compounds **Cb**, **c**, **e** and **g** exhibited anti-inflammatory activity comparable standard drug dichlofenac. 2,5-disubstituted 1,3,4-oxadiazole **CI** & **CII** exhibiting 89%



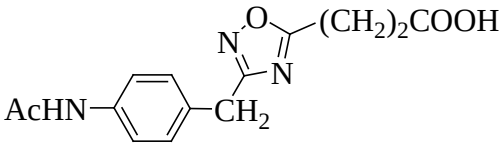

and 86% inhibition of edema induced by carrageenan have been synthesized and reported



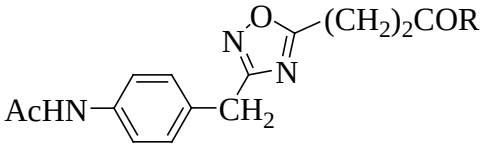

in literature [96]. Several oxadiazole derivatives have been synthesized [97] by following reaction scheme mentioned below. Compounds **CIV** and **CVa-g** were screened for anti-



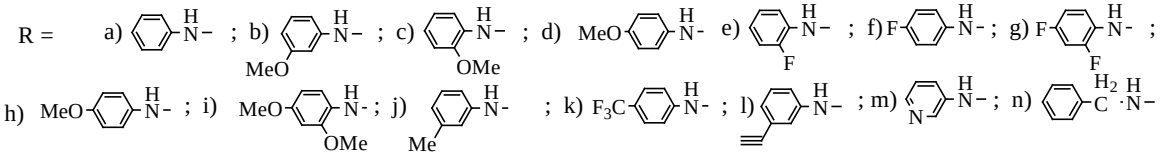
Inflammatory activity using carrageenan induced paw edema assay. Anti-inflammatory activity comparable to diclofenac was exhibited by **CVa-c**. Farooqui *et. al.* [98] synthesized 3-(4-acetamido-benzyl)-5-substituted-1,2,4-oxadiazoles **CVI**, **CVIIa-n** and screened them for anti-inflammatory activity. Compounds **CVI**, **CVIIc, e, f, i, l, m** and **n** exhibited anti-inflammatory activity better than reference drug dichlofenac sodium. In an international patent [99] usefulness of oxadiazole derivatives **CVIII** for the treatment of



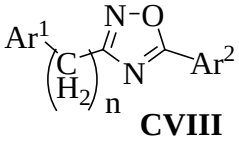
**CVI**



**CVIIa-n**



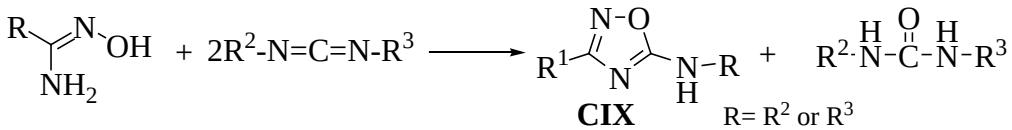
diseases or disorders related to the cholinergic system of the central nervous system (CNS), the peripheral nervous system (PNS), smooth muscle contraction, inflammation,



**CVIII**

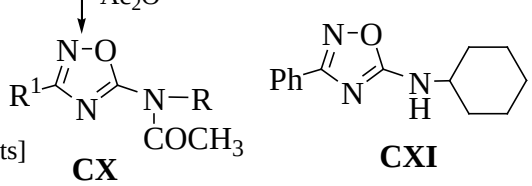
[n= 0, 3; $Ar^1$=(un)substituted monocyclic carbocycle and (un)substituted monocyclic heterocycle; $Ar^2$=(un)substituted arom. monocyclic heterocycle; and their isomers, mixts. of isomers, N-oxides, prodrugs, and pharmaceutically acceptable salts]

pain etc. is described. Ispikoudi *et. al.* [100] synthesized 5-amino-substituted 1,2,4-oxadiazole derivatives **CIX**, **CX** and **CXI** by following reaction sequence mentioned below. In all thirty four compounds have been synthesized and some selected compounds



**CIX**

R= $R^2$ or $R^3$

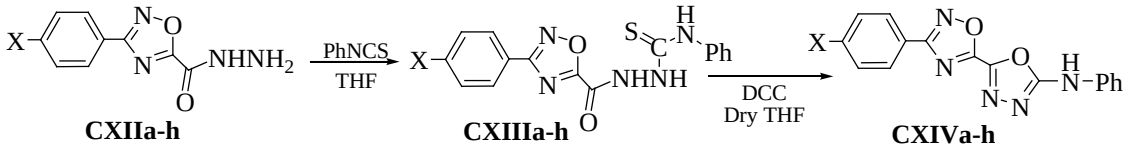


[where R & $R^1$ are various substituents]

**CX**

**CXI**

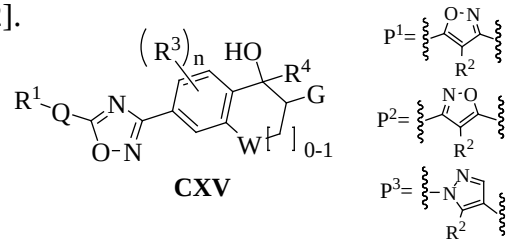
were screened for in vivo anti-inflammatory activity. Compounds **CXI** exhibited significant anti-inflammatory activity. A series of $N^1$-[3-(4-substituted-aryl)-1,2,4-oxadiazol-5-yl carbonyl]-$N^4$-phenyl thiosemicarbazides **CXIII** and another series of 5-[3-(4-substituted-aryl)-1,2,4-oxadiazol-5-yl]-2-(N-phenylamino)-1,3,4-oxadiazoles **CXIV** have been synthesized [101] by following reaction scheme mentioned below. Compounds **CXIIIa-h** and **CXIVa-h** were screened for anti-inflammatory activity using carrageenan




**CXIIa-h** **CXIIIa-h** **CXIVa-h**

[a, X=H; b, X=$CH_3$; c, X=F; d, X=Cl; e, X=Br; f, X=$OCH_3$; g, X=$NO_2$; h, X=OH]

induced edema assay. Compounds **CXIIIa-h** exhibited low level whereas **CXIVa-h** exhibited moderate level activity. Synthesis and usefulness of 5-[3-phenyl-4-(trifluoromethyl)isoxazol-5-yl]-1,2,4-oxadiazole derivatives **CXV** in the treatment of autoimmune and chronic inflammatory diseases is disclosed in an international patent [102].

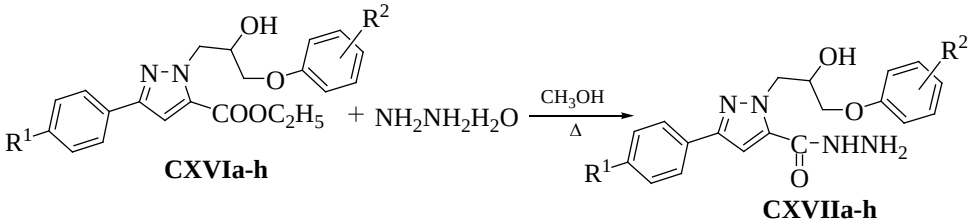



**CXV**

[W = $CH_2$ or O; Q = $P^1$, $P^2$ or $P^3$, wherein $R^2$ = C1-6 alkyl, C1-3 fluoroalkyl, C3-7 cycloalkyl, etc.; $R^1$ = C3-6 alkyl, (un)substituted C3-7 cycloalkyl, (un)substituted Ph, etc.; n = 0, 1 or 2; $R^3$ = independently C1-3 alkyl, F, Cl, etc.; $R^4$ = H or $CH_3$; G = NRaRa, NH(CRxRx)1-3C(O)ORa, NH(CRxRx)1-4OH, etc., wherein Ra = independently H, C1-4 alkyl, or C1-3 hydroxyalkyl, Rx = independently H, OH, F, etc.; or a pharmacetically acceptable salt thereof]

### *1b.2.2 As anticancer agents*

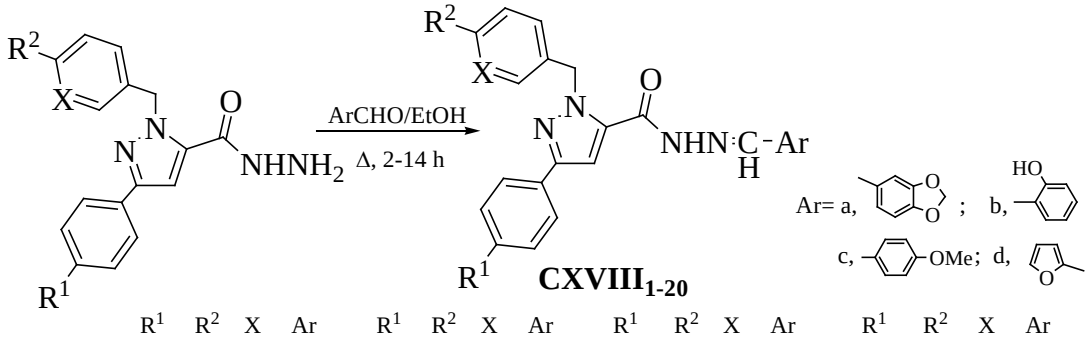
Fan *et. al.* [103] synthesized 1-(2′-hydroxy-3′-aroxypropyl)-3-aryl-1H-pyrazole-5-carbohydrazide derivatives **CXVIIa-h** by following reaction scheme mentioned below.




**CXVIa-h** **CXVIIa-h**

[a: $R^1$= H, $R^2$= p-Cl; b:$R^1$=H,$R^2$=p-$NO_2$; c: $R^1$= H, $R^2$= o-$OCH_3$; d: $R^1$= p-Cl, $R^2$= p-Cl; e: $R^1$=p-Cl, $R^2$= p-$NO_2$; f: $R^1$= p-Cl, $R^2$= o-$OCH_3$; g: $R^1$= p-$OCH_3$, $R^2$= p-Cl; h: $R^1$= p-$OCH_3$, $R^2$= o-$OCH_3$]

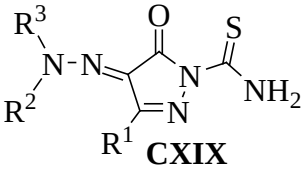
All these compounds **CXVIIa-h** inhibit the growth of A549 cells in dosage and time dependent manners. A series of 1-arylmethyl-3-aryl-1H-pyrazole-5-carbohydrazide hydrazone derivatives **CXVIII$_{1\text{-}20}$** have been synthesized [104] and screened for A549




**CXVIII$_{1\text{-}20}$**

| | $R^1$ | $R^2$ | X | Ar | | $R^1$ | $R^2$ | X | Ar | | $R^1$ | $R^2$ | X | Ar | | $R^1$ | $R^2$ | X | Ar |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Cl | H | C | a | 6 | H | Cl | N | d | 11 | OMe | Cl | N | a | 16 | H | t-Bu | C | b |
| 2 | Cl | H | C | d | 7 | Cl | Cl | N | a | 12 | OMe | Cl | N | b | 17 | Cl | H | C | b |
| 3 | H | Cl | N | a | 8 | Cl | Cl | N | b | 13 | OMe | Cl | N | c | 18 | Cl | t-Bu | C | b |
| 4 | H | Cl | N | b | 9 | Cl | Cl | N | c | 14 | OMe | Cl | N | d | 19 | OMe | H | C | b |
| 5 | H | Cl | N | c | 10 | Cl | Cl | N | d | 15 | H | H | C | b | 20 | OMe | t-Bu | C | b |

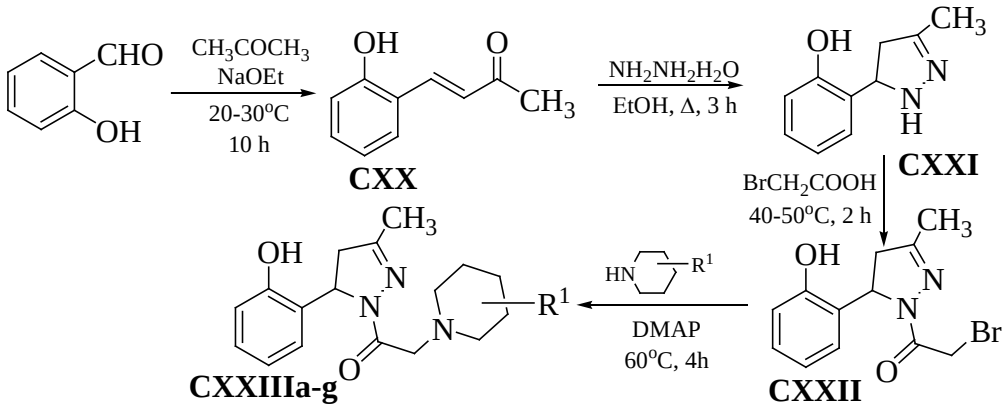
lung cancer cells inhibition activity. All the compounds show inhibitory effects on the growth of A549 cells but compounds **CXVIII$_8$** & **CXVIII$_{18}$** were found to be most active with $IC_{50}$ value 3.68 & 3.33 μM. Usefulness of pyrazole derivatives **CXIX** for the



**CXIX**

[$R^1$ = (un)substituted monocyclic carbocyclyl or alkyl; $R^2$, $R^3$ = H, (un)substituted heterocyclyl, etc.]

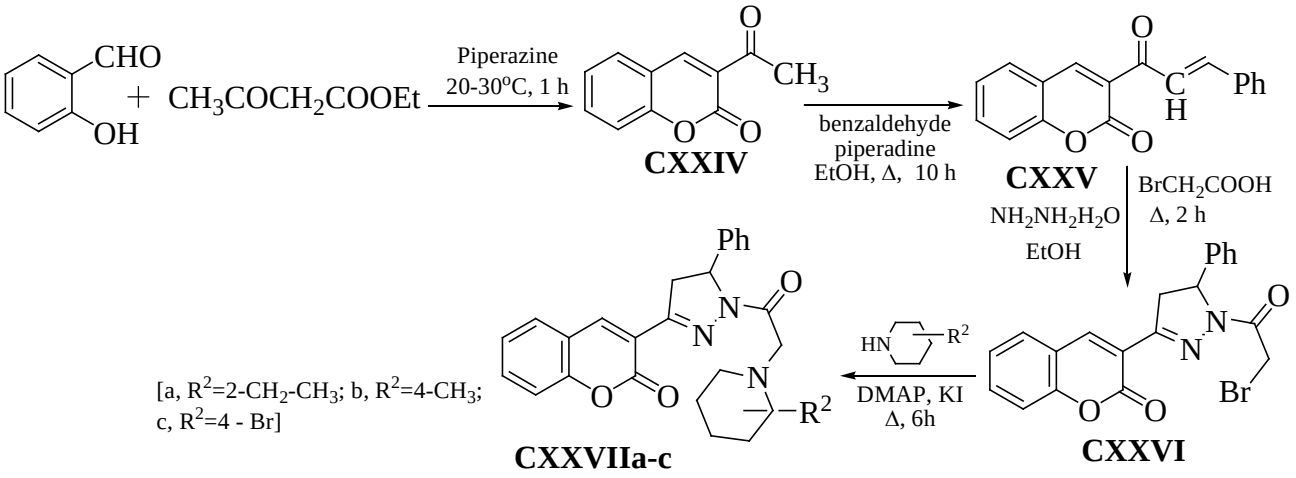
treatment of pain, fever, inflammation and cancer have been disclosed in an international patent [105]. A series of 5-phenyl-N-piperidine ethanone-4, 5-dihydropyrazole derivatives **CXXIIIa-g** and **CXXVIIa-c** have been synthesized by following reaction



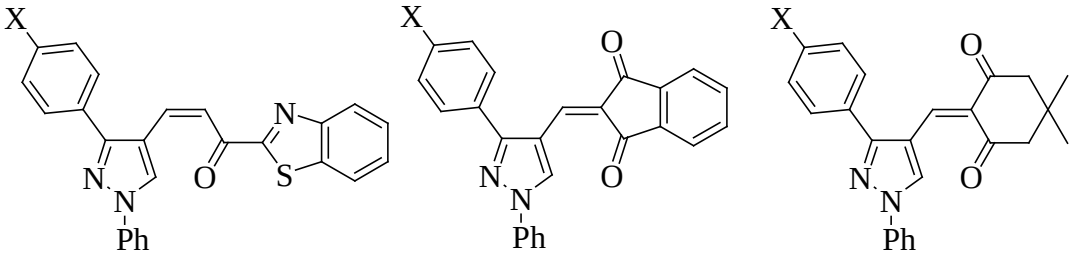

**CXX** **CXXI** **CXXII** **CXXIIIa-g**

[a: $R^1$=4 -OH; b, $R^1$=2-$CH_3$; c, $R^1$=2-$CH_2$-$CH_3$; d, $R^1$=4-$CH_3$; e, $R^1$=2-$CONH_2$; f, $R^1$=4-$CF_3$; g, $R^1$=2-$NO_2$]

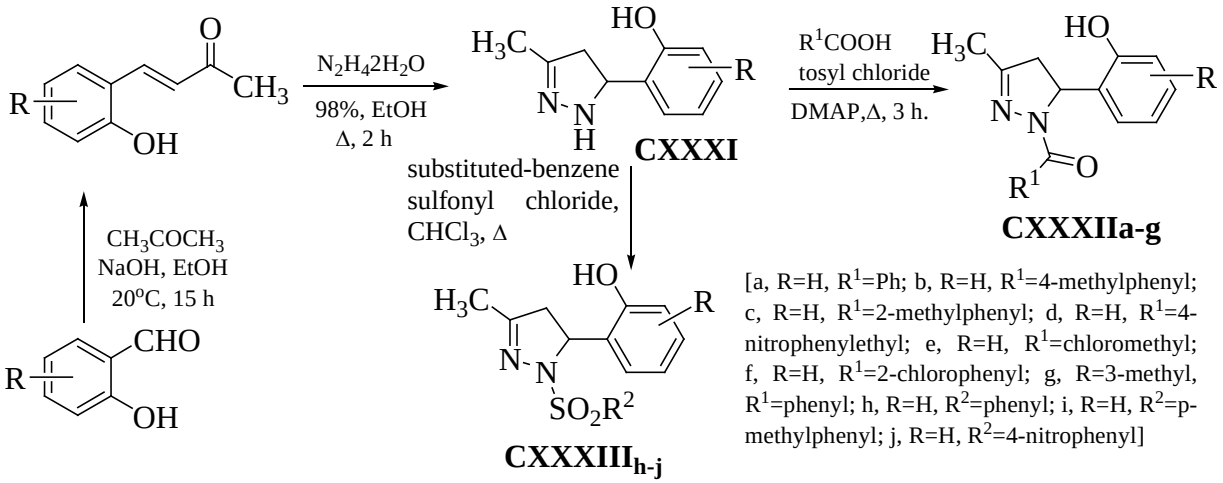
sequence mentioned below [106]. Bioassay of these compounds **CXXIIIa-g** & **CXXVIIa-c** demonstrated that compounds **CXXIIId&f** and **CXXVIIa&b** exhibited high




antiproliferative activities against SGC-7901, MGC-803 and Bcap-37cell lines. Several pyrazole derivatives **CXXVIII**, **CXXIX** and **CXXX** exhibiting potential cytotoxicity against human cancer cell lines MCF-7(breast), HEPG2(liver) and HCT-116(colorectal) have been synthesized and reported in literature [107]. Liu *et. al.* [108] synthesized N-




phenyl-acetyl (sulfonyl)-4,5-dihydropyrazole derivatives **CXXXIIa-g** & **CXXXIIIh-j** and screened them for antitumor activity against human gastric cell (SGC-7901), liver (Hep-G2) and prostate (PC-3) cancer cell lines. Compound **CXXXIIa** exhibited high activity with $IC_{50}$ values of 21.23±0.99, 29.43±0.32 and 30.89±1.07 µM respectively. Aryl-2H-pyrazole derivatives **CXXXIVa-u** have been synthesized [109] and screened for telomerase, human gastric cancer cell (SGC-7901) and human melanoma cell B16-F10



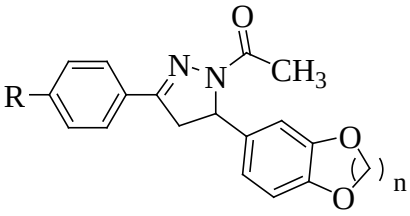

**CXXXI**

**CXXXIIa-g**

**CXXXIII$_{h-j}$**

[a, R=H, $R^1$=Ph; b, R=H, $R^1$=4-methylphenyl; c, R=H, $R^1$=2-methylphenyl; d, R=H, $R^1$=4-nitrophenylethyl; e, R=H, $R^1$=chloromethyl; f, R=H, $R^1$=2-chlorophenyl; g, R=3-methyl, $R^1$=phenyl; h, R=H, $R^2$=phenyl; i, R=H, $R^2$=p-methylphenyl; j, R=H, $R^2$=4-nitrophenyl]

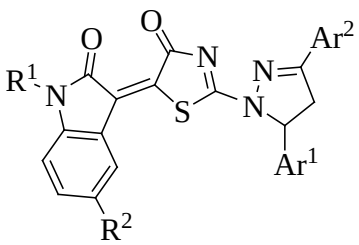
inhibition activity. Compound **CXXXIV$_f$** exhibited potent inhibitory activity against telomerase with $IC_{50}$ value of 0.9 µM and high activity against SGC-7901 and B16-F10



| | n | R | | n | R | | n | R | | n | R | | n | R | | n | R |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| a, | 1 | H; | b, | 1 | F; | c, | 1 | Cl; | d, | 1 | Br; | e, | 1 | $CH_3$; | f, | 1 | $OCH_3$; |
| g, | 1 | $NO_2$; | h, | 2 | H; | i, | 2 | F; | j, | 2 | Cl; | k, | 2 | Br; | l, | 2 | $CH_3$; |
| m, | 2 | $OCH_3$; | n, | 2 | $NO_2$; | o, | 3 | H; | p, | 3 | F; | q, | 3 | Cl; | r, | 3 | Br; |
| s, | 3 | $CH_3$; | t, | 3 | $OCH_3$; | u, | 3 | $NO_2$ | | | | | | | | | |

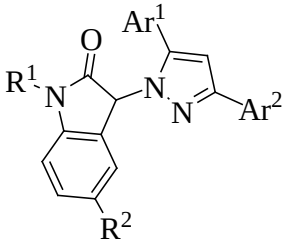
**CXXXIVa-u**

with $IC_{50}$ values 18.07 and 5.34 µM. Synthesis of 3-[2-(3,5-diaryl-4,5-dihydropyrazol-1-yl)-4-oxo-4,5-dihydro-1,3-thiazol-5-ylidene]-2,3-dihydro-1H-indol-2-ones **CXXXV$_{1-23}$** and 3-(3,5-diarylpyrazol-1-yl)-2,3-dihydro-1H-indol-2-one **CXXXVI$_{24-39}$** and their in vitro anticancer activity screening is reported in literature [110]. Most active compound was found to be **CXXXV$_{10}$** with mean $GI_{50}$ and TGI values 0.071 µM & 0.76 µM, respectively. Compound **CXXXV$_{10}$** demonstrated the highest antiproliferative influence



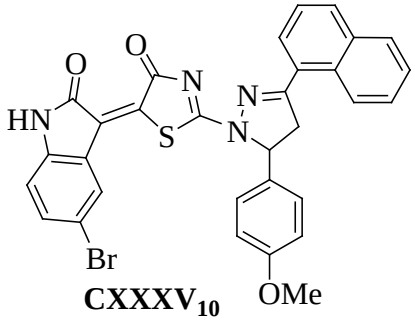
**CXXXV$_{1-23}$**

[where $R^1$, $R^2$ and $Ar^1$ & $Ar^2$ are various substituents]



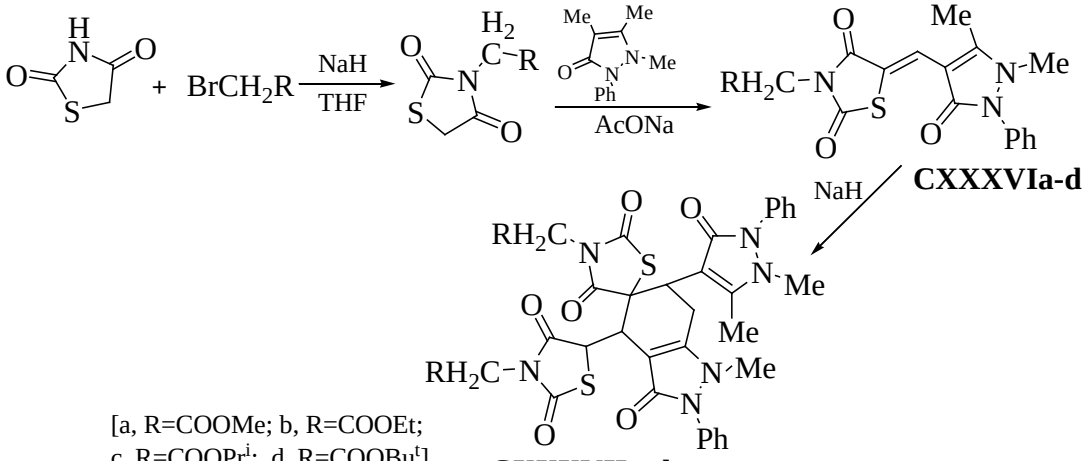
**CXXXV$_{24-39}$**

[where $R^1$, $R^2$ and $Ar^1$ & $Ar^2$ are various substituents]



**CXXXV$_{10}$**

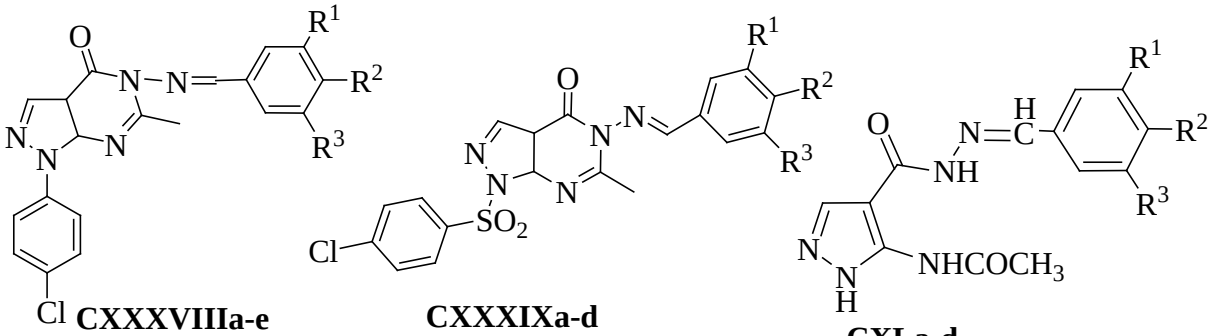
on the non-small-cell lung cancer cell line HOP-92 ($GI_{50}$ < 0.01 μM), colon cancer line HCT-116 ($GI_{50}$ = 0.018 μM), CNS cancer cell line SNB-75 ($GI_{50}$ = 0.0159 μM), ovarian cancer cell line NCI/ADR-RES ($GI_{50}$=0.0169 μM), and renal cancer cell line RXF 393 ($GI_{50}$ = 0.0197 μM). Nishida *et. al.* [111] synthesized thiazolidine derivatives containing pyrazole ring i.e. compounds **CXXXVI** and **CXXXVII** by following reaction scheme mentioned below. Compounds **CXXXVIa-d** & **CXXXVIIa-d** were screened for growth




**CXXXVIa-d**

**CXXXVIIa-d**

inhibitory activity in A549 lung cancer, B16F10 murine melanoma, and HeLa human uterine carcinoma cells. Compound **CXXXVIc** exhibited inhibitory effect of B16F10 cells with ($IC_{50}$ = 27 μM). New series of pyrazolo[3,4-d]pyrimidines **CXXXVIIIa-e**, **CXXXIXa-d** and pyrazole hydrazones **CXLa-d** have been synthesized and screened



**CXXXVIIIa-e**

[a, $R^1$ =$R^2$ = $R^3$ = H
b, $R^1$ = H, $R^2$= $OCH_3$, $R^3$ = H
c, $R^1$ = $OCH_3$, $R^2$= OH,$R^3$ = H
d, $R^1$ = $OCH_3$, $R^2$ = $OCH_3$, $R^3$ = H
e, $R^1$ =$R^2$ = $R^3$ = $OCH_3$]

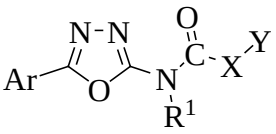
**CXXXIXa-d**

[a, $R^1$ =$R^2$ = $R^3$ = H
b, $R^1$ = H, $R^2$= $OCH_3$, $R^3$ = H
c, $R^1$ = $OCH_3$, $R^2$ = $OCH_3$, $R^3$ = H
e, $R^1$ =$R^2$ = $R^3$ = $OCH_3$]

**CXLa-d**

[a, $R^1$ =$R^2$ = $R^3$ = H
b, $R^1$ = H, $R^2$= $OCH_3$, $R^3$ = H
c, $R^1$ = $OCH_3$, $R^2$ = $OCH_3$, $R^3$ = H
e, $R^1$ =$R^2$ = $R^3$ = $OCH_3$]

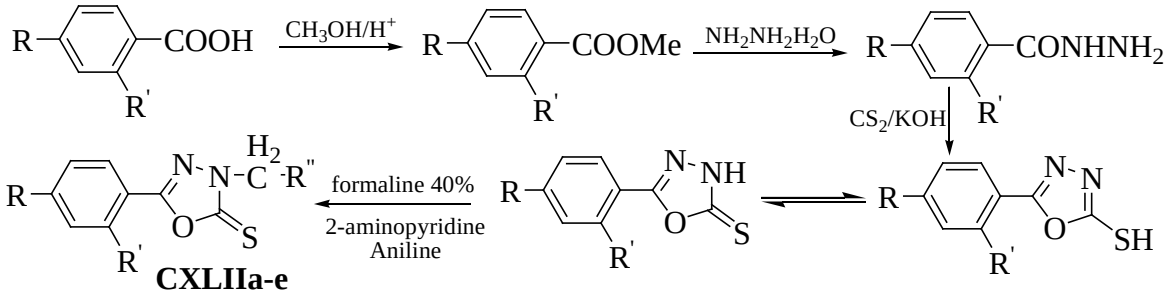
[112] for their anticancer activity against human breast adenocarcinoma MCF-7 cell line. Compound **CXXXVIIIe** exhibited better potency to the reference drug cisplatin with $IC_{50}$=7.60 and 13.29 µM respectively. In an international patent usefulness of 1,3,4-oxadiazole-3-carboxamide **CXLI** as an anticancer agent is disclosed [113]. A series of



**CXLI**

[$R^1$ = H, (substituted) alkyl; Ar = arom. group meeting specific requirements; X = (substituted) arom. group meeting specifi requirements; Y = (substituted) aryl, arom. hetero cycle, dioxaborolanyl; X-Y = diaryl group] or a pharmacol. acceptable salt]

3,5-disubstituted 1,3,4- oxadiazole derivatives have been synthesized [114] by following reaction scheme mentioned below. On screening for tumor formation inhibition activity compounds **CXLIIa-e** showed 60.8, 56.5, 52.2, 73.9 and 56.5% tumor formation inhibition activity at a dose of 50 mg/kg body weight, whereas standard drug 5-fluorouracil exhibited 93% inhibition at 20 mg/kg body weight. Ravindra *et. al.* [115]

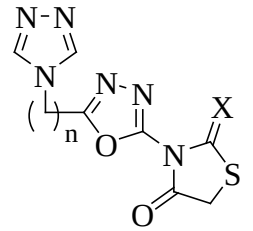



**CXLIIa-e**

a, R=$NO_2$, R'=H, R"= ; b, R=$NO_2$, R'=H, R"= ; c, R=Cl, R'=Cl, R"=

d, R=OH, R'=H, R"= ; c, R=$CH_3$, R'=H, R"=

synthesized oxadiazole derivatives **CXLIII** which are reported to exhibit antitumor activity. A series of 1,3,4-oxadiazole derivatives based on benzisoselenazolone **CXLV**

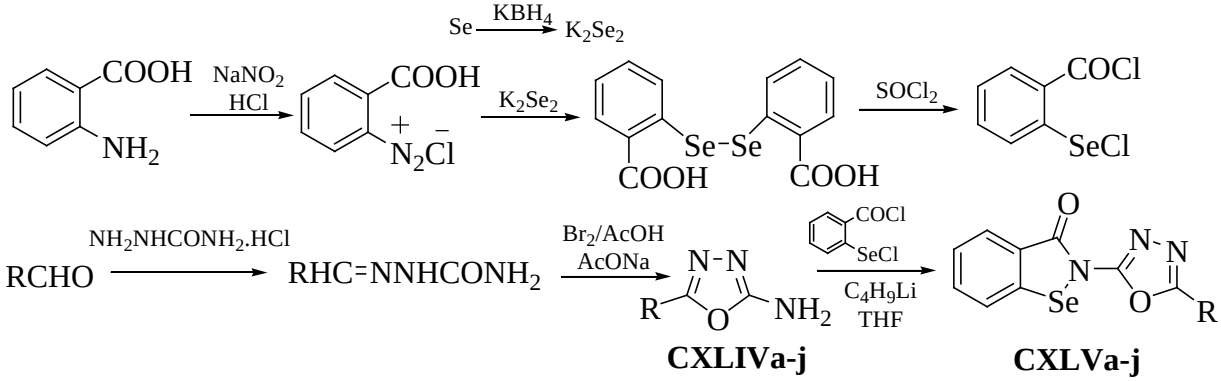


**CXLIII**

[X = A, B (wherein $R^1$, $R^2$ = H, alkyl, alkoxy, etc.), n = 1-3]

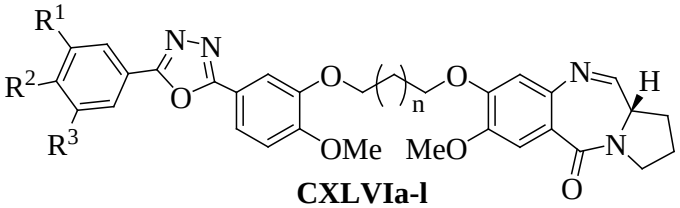
A= B=

have been synthesized [116] by following reaction scheme mentioned below. Compounds **CXLVa-j** were screened against three human cancer cell lines i.e. SSMC-7721 (liver




[a R=Ph; b, R=2-F-Ph; c R=4-F-Ph; d, R=4-Cl-Ph; e, R=4-Br-Ph; f, R=4-$CH_3$-Ph; g, R=4-(i-$C_3H_7$)-Ph, h, R=4-$OCH_3$-Ph; i, R=3,4,5-$(OCH_3)_3$-Ph; j, R=4-$NO_2$-Ph]

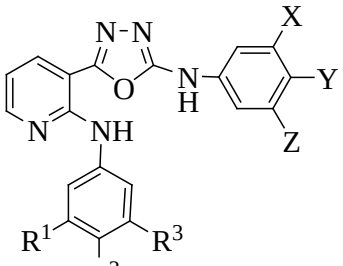
cancer cell), MCF-7 (breast cancer cell) & A-549 (lung cancer cell). Compounds **CXLVd** and **CXLVi** showed significant anticancer activities against MCF-7 cell with $IC_{50}$ values of 1.07 & 1.76 µM respectively. Compound **CXLVd** exhibited $IC_{50}$ value 4.46 µM against SSMC-7721 cells. Kamal *et. al.* [117] synthesized 2,5-diaryloxadiazole–pyrrolobenzodiazepine conjugates **CXLVIa-l** and screened them against eleven cancer cell lines i.e. A-549 (lung cancer), Gurav (lung cancer) HOP62 (lung cancer), MCF-7 (breast cancer), Zr-75-1 (breast cancer), A-2780 (ovarian cancer), DWD (oral cancer), KB (oral cancer), colo205 (colon cancer), PC-3 (prostate cancer) and SiHa (cervix cancer). Compounds **CXLVIa, d, i** and **l** exhibited significant anticancer activity. Several 2-anilinonicotinyl linked 1,3,4-oxadiazole derivatives **CXLVII** have been synthesized and reported in literature [118]. On screening for anticancer activity against five human cancer cell lines i.e. MDA-MB-231 (breast adenocarcinoma), HepG-2 (liver cancer), A-549 (lung adenocarcinoma), HeLa (cervix cancer) and DU-145 (prostate cancer). Compound **CXLVIIm** showed potent antitumor activity against all the cell line tested. A



**CXLVIa-l**

n=1-3

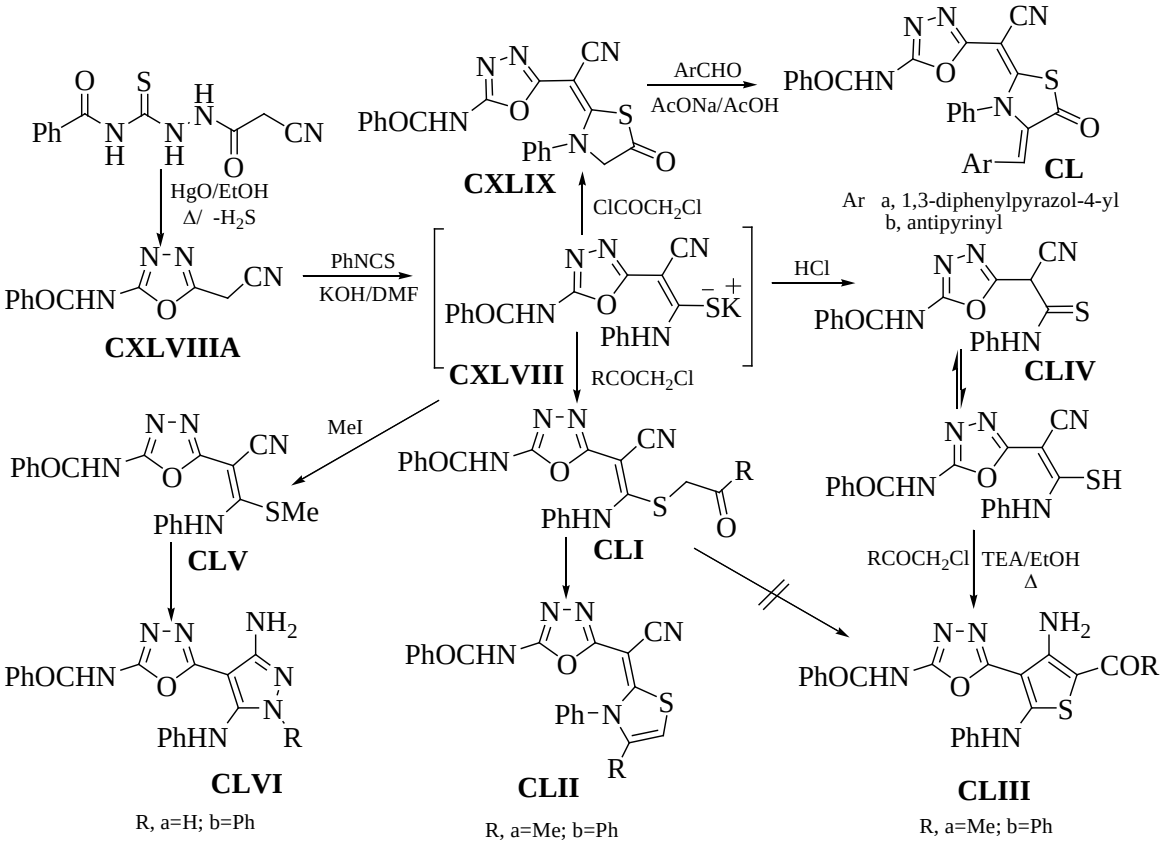
| | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|
| a-c; | H | F | H |
| d-f; | H | $CF_3$ | H |
| g-i; | $OCH_3$; | $OCH_3$ | $OCH_3$ |
| j-l; | H | $OCH_3$ | $OCH_3$ |

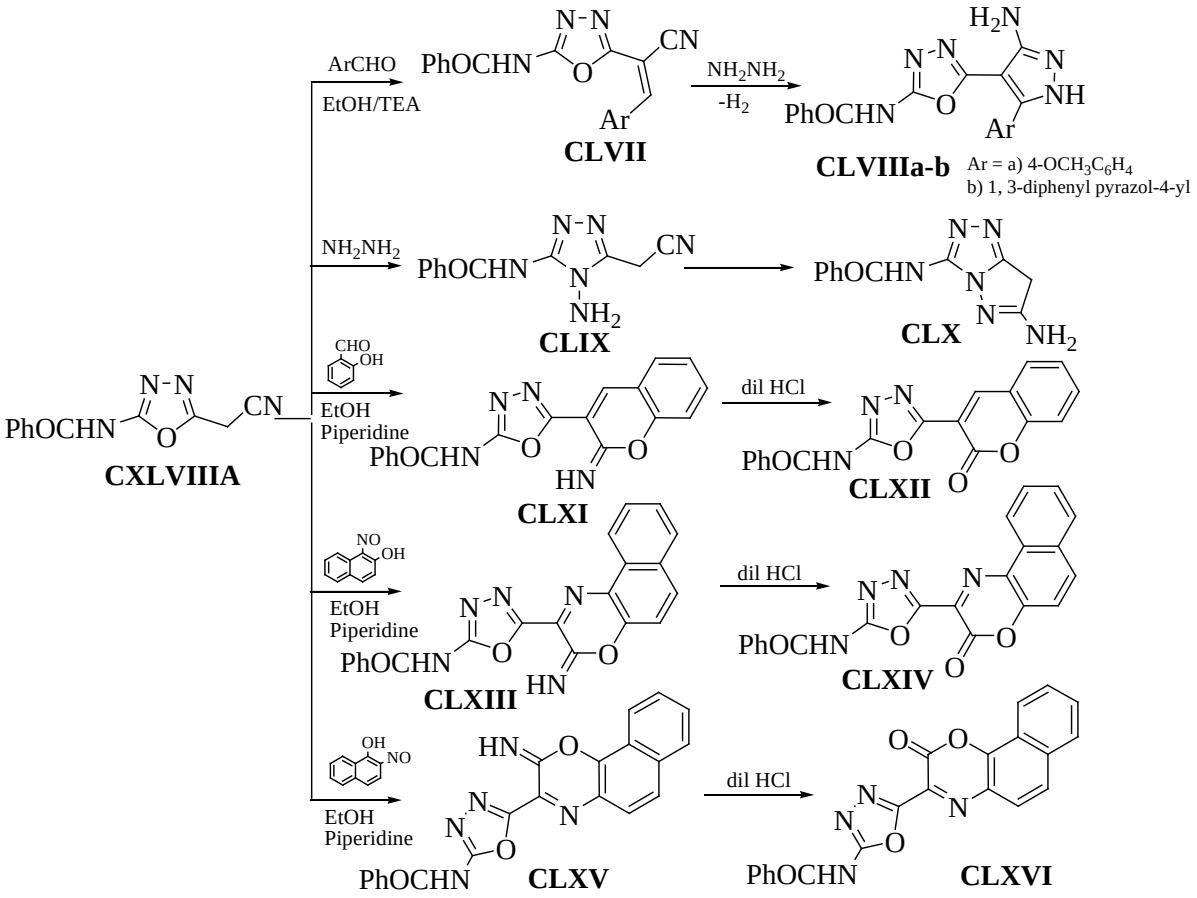


**CXLVIIa-m**

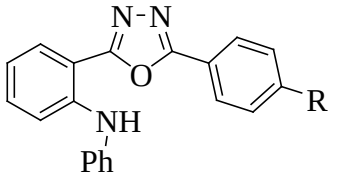
| | $R^1$ | $R^2$ | $R^3$ | X | Y | Z | | $R^1$ | $R^2$ | $R^3$ | X | Y | Z |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| a | H | F | H | H | Cl | H | h | F | F | F | H | Cl | H |
| b | H | F | H | H | $NO_2$ | H | i | F | F | F | H | $NO_2$ | H |
| c | H | F | H | $OCH_3$ | $OCH_3$ | $OCH_3$ | j | $OCH_3$ | $OCH_3$ | $OCH_3$ | H | H | H |
| d | H | Cl | H | H | H | H | k | $OCH_3$ | $OCH_3$ | $OCH_3$ | H | Cl | H |
| e | H | Cl | H | H | Cl | H | l | $OCH_3$ | $OCH_3$ | $OCH_3$ | H | $NO_2$ | H |
| f | H | Cl | H | $OCH_3$ | $OCH_3$ | $OCH_3$ | m | $OCH_3$ | $OCH_3$ | $OCH_3$ | $OCH_3$ | $OCH_3$ | $OCH_3$ |
| g | F | F | F | H | H | H | | | | | | | |

number of 1,3,4-oxadiazole base heterocycles have been synthesized for following reaction scheme mentioned below [119]. All the compounds were screened for potential antitumor and cyotoxic actives against four human cancer cell lines i.e. HepG2, WI-38, VERO and MCF-7. Compounds **CXLVIIIA**, **CLIIa**, **CLVIa**, **CLVIIb** and **CLXII**



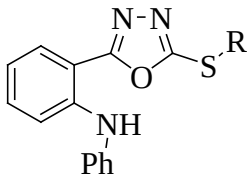



exhibited promising in vitro antitumor activities. Abdel Rahman D. E. [120] synthesized 2,5-disubstituted-1,3,4-oxadiazole **CLXVIIa-c**, 3-substituted aminomethyl-5-substituted-1,3,4-oxadiazole-2(3H)-thione **CLXIXa-m** and 2-substituted thio-5-substituted-1,3,4-oxadiazole **CLXVIIIa, b** and screened them for anticancer activity against HT-29 and MCF-7 cancer cell lines. Compounds **CLXVIIa-c**, **CLXVIIIa, CLXIXf**, exhibited potent cytotoxicity ($IC_{50}$ 1.3-2.0 µM) and selectivity against HT-29 cancer cell line. A number of hybrid heterocyclic compounds **CLXXa-t** have been synthesized [121] by



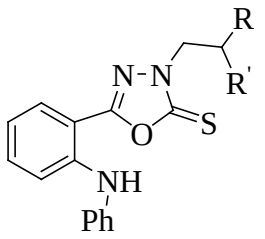
[a, R=H; b, R=Cl; c, R=$OCH_3$]

**CLXVII**



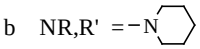
[a, R=$C_2H_5$; b, -$CH_2C_6H_5$]

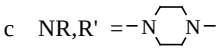
**CLXVIII**

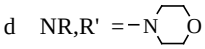


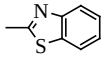
**CLXIXa-m**

a R,R' = $-C_2H_5$

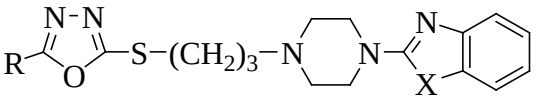
b NR,R' = 

c NR,R' = 

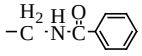
d NR,R' = 

| | R | R' |
|---|---|---|
| e | H, | $-C_6H_5$ (p) |
| f | H, | $-C_6H_4CH_3$ (p) |
| g | H, | $-C_6H_4COCH_3$ (p) |
| h | H, | $-C_6H_4F$ (p) |
| i | H, | $-C_6H_4CI$ (p) |
| j | H, | $-C_6H_4Br$ (p) |
| k | H, | $-C_6H_4OCH_3$ (p) |
| l | H, | $-C_6H_4SO_2NH_2$ (p) |
| m | H |  |

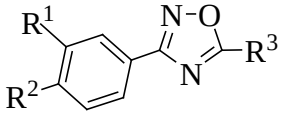
coupling piperazinyl benzothiazole/benzoxazole derivatives with 1,3,4-oxadiazole-2-thiol. All these compounds were screened for anticancer activity against five human cancer cell lines i.e. MCF-7 (breast), HeLa (cervical), HepG2 (liver), A431 (skin) and A549 (lung). Compounds **CLXXj** & **CLXXt** exhibited $IC_{50}$ value 36.9 & 55.9 µM



**CLXXa-t** X= O, S a-j X=O k-t X=S

| | R | | R |
|---|---|---|---|
| a,k | $-C_6H_4OMe$(p) | f,p | $-C_6H_4Br$(p) |
| b,l | $-C_6H_4NO_2$(p) | g,q | $-C_6H_4(CMe_3)$(p) |
| c,m | $-C_6H_4CH_3$(p) | h,r | $-C_6H_4OH$(p) |
| d,n | $-C_6H_4Cl$(p) | i,s | $-C_6H_5$ |
| e,o | $-C_6H_4F$(p) | j,t |  |

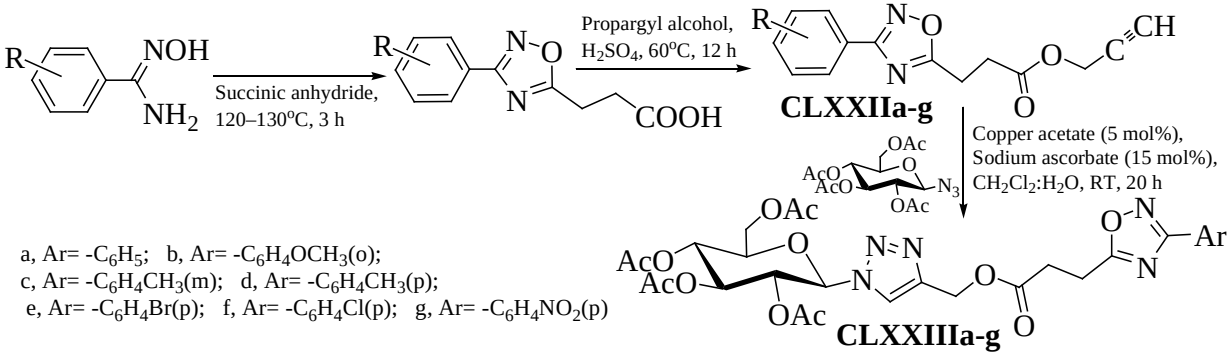
against A431 cancer cell line. 3,5-Disubstituted-1,2,4-oxadiazole derivatives **CLXXIa-p** have been synthesized and reported in literature [122]. These compounds were screened for various human cancer cell lines i.e. prostate (PC-3, DU145 & LnCaP), breast (MCF-7



**CLXXIa-p**

| | $R^1$ | $R^2$ | $R^3$ | | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|---|---|---|---|
| a | H | H | 4-$FC_6H_4$ | h | $OC_5H_9$ | $OCH_3$ | Pyridin-4-yl |
| b | H | H | Pyridin-4-yl | i | $OC_5H_9$ | $OCH_3$ | Pyridin-3-yl |
| c | $OCH_3$ | OBn | Pyridin-4-yl | j | $OC_5H_9$ | $OCH_3$ | (Indol-3-yl)methyl |
| d | $OC_5H_9$ | $OCH_3$ | $C_6H_5$ | k | $OC_5H_9$ | $OCH_3$ | $CH_2COCH_3$ |
| e | $OC_5H_9$ | $OCH_3$ | 4-$FC_6H_4$ | l | OH | $OCH_3$ | 4-$FC_6H_4$ |
| f | $OC_5H_9$ | $OCH_3$ | 4-$ClC_6H_4$ | n | $OC_5H_9$ | $OCH_3$ | Pyrrolidin-2-yl |
| g | $OC_5H_9$ | $OCH_3$ | 4-$HOC_6H_4$ | p | $OC_5H_9$ | $OCH_3$ | Piperidin-4-yl |

and MDA-231), colon (HCT-116), and pancreas (PaCa2). Compounds **CLXXIf, h, j** and **k** exhibited specificity towards pancreatic and **CLXXIn** towards prostate cancer cell line. $IC_{50}$ value of compound **CLXXIp** against prostate cancer cell lines was found to be 10 µM. dos Anjos *et. al.* [123] synthesized glycosyl–triazole linked 1,2,4-oxadiazole derivatives **CLXXIII** by following reaction scheme mentioned below. All these compound i.e.

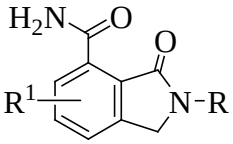



**CLXXIIIa-g** were screened for anticancer activity against two cancer cell lines i.e. NCI-H292 (lung carcinoma) and HEp-2 (larynx carcinoma). These compounds exhibited weak cytotoxic activity.

## 1b.3 Isoindole and pyrrolopyrazine derivatives

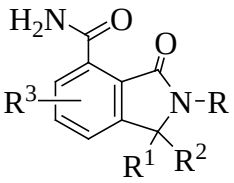
### *1b.3.1 As anti-inflammatory agents:*

Usefulness of 3-oxo-2,3-dihydro-1H-isoindole-4-carboxamides **CLXXIV** and **CLXXV** for the treatment of cancer, cardiovascular diseases, central nervous system injury and different forms of inflammation is described in international patents [124,125].



**CLXXIV**

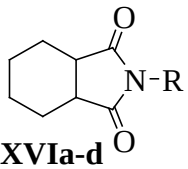
[R = alkyl, alkenyl, alkynyl (each group substituted with one or more substituents selected from either $NR^3R^4$, Oalkyl, $CO_2$ alkyl and $CONR^aR^b$; wherein $R^a$, $R^b$ = alkenyl, alkynyl, etc.; or $NR^aR^b$ = (un)substituted heterocyclyl); $R^1$ = H, halo, CN, $NO_2$, etc.; $R^3$, $R^4$ = H, alkenyl, alkynyl, etc.; or $NR^3R^4$ = (un)substituted heterocyclyl]



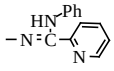
**CLXXV**

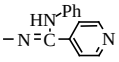
[R = alkyl, alkenyl, cycloalkyl, etc.; $R^1$, $R^2$ = H, alkyl, cycloalkyl, etc.; $R^3$ = H, halo, CN, etc.]

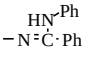
Modzelewska-Banachiewicz *et. al.* [126] synthesized isoindole derivatives **CLXXVIa-d** and predicted their biological effects by using predication of activity spectra for substances (PASS) program. Anti-inflammatory, analgesic, antibacterial and antiviral

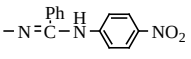


**CLXXVIa-d**

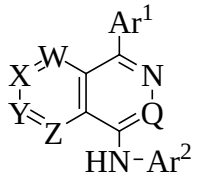
a, R= 

b, R= 

c, R= 

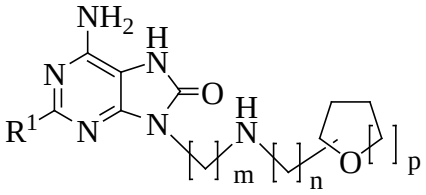
d, R= 

activities were also determined experimentally. Anand *et. al.* [127] synthesized phthalazine derivatives **CLXXVII** which are JAK-1 inhibitors and hence useful for treating cancer, inflammatory disorders and autoimmune diseases. In an international patent synthesis of purine derivatives **CLXXVIII** which are inducers of human interferon



**CLXXVII**

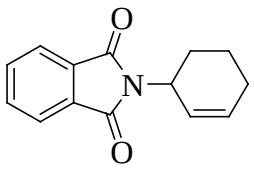
[$Ar^1$ = (un)substituted Ph, fused to a 5- to 6-membered heterocyclyl, heterocyclyl, or heteroaryl; $Ar^2$ = (un)substituted phenyl; Q = C(H) or N; W = C(H) or N; X = C(H) or N; Y = C(H) or N; Z = C(H) or N]



**CLXXVIII**

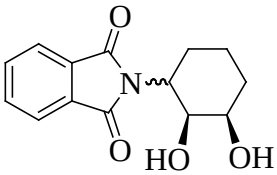
[$R^1$ is C1-6alkylamino, or C1-6alkoxy; m is 3-5; n is 0-3; p is 1 or 2 and salts thereof]

and hence useful in the treatment of allergic diseases, inflammatory conditions, infectious diseases and cancer are disclosed [128]. 2-Cyclohex-2-enylisoindole-1,3-dione on oxidation gave rac-2-[(1R,2S,3R)-2,3-dihydroxycyclohexyl]-1H-isoindole-1,3(2H)-dione **CLXXX** which is used in the treatment of various diseases such as cancer,



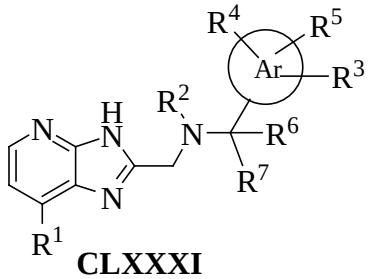
**CLXXIX**

sodium metaperiodate, cesium(III) chloride heptahydrate in acetonitrile, Et acetate, and water under nitrogen at 0°C in the presence of ruthenium(III) chloride.



**CLXXX**

inflammation, kidney disease, pain etc. [129]. In a Chinese patent [130] synthesis of imidazopyridines of formula **CLXXXI** and their pharmaceutically acceptable salts, esters, prodrugs or hydrates which can be used for the treatment or prevention of $CXCR_4$

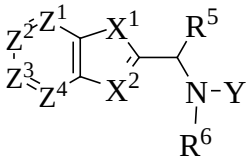


**CLXXXI**

[Ar is C6-12 aryl and five- to twelve-membered heteroaryl; $R^1$ is H, (un)substituted amino, or piperazinyl; $R^2$ is H, C1-6 (halo)alkyl, C3-10 cycloalkyl, C2-6 alkenyl, C2-6 alkynyl, C6-10 arylamino, etc.; $R^3$-$R^5$ are independently H, nitro, hydroxy, halo, cyano, trifluoromethyl, (un) substituted C1-6 alkyl, (un)substituted C1-6 alkoxy, (un)substituted C2-6 alkenyl, (un)substituted C2-6 alkynyl, (un)substituted C3-8 cycloalkyl, etc.; $R^6$ and $R^7$ are independently H, C1-3 alkyl, or C2-3 alkenyl; $R^3R^6$ may be taken together with the atoms attached to form C3-8 alkylene; and their pharmaceutically acceptable salts, esters, prodrugs or hydrates thereof]

receptor activation related diseases such as HIV infection, rheumatoid arthritis, inflammation or cancer is described. Synthesis of heterocyclic compounds **CLXXXII**

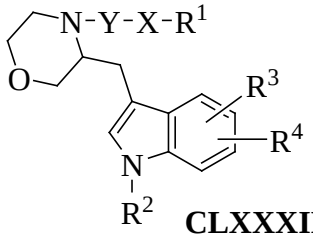
which are selective inhibitors of the p110 delta isoform of PI3K and can be used in the treatment of inflammation, immune diseases and cancers is reported in a U.S. patent



**CLXXXII**

[$Z^1$=$CR^1$, N; $Z^2$ =$CR^2$, N; $Z^3$ =$CR^3$, N; $Z^4$ =$CR^4$, N; none, one or two of $Z^{1-4}$ are N; where (i) $X^1$ = $NR^{10}$ and $X^2$ = N, (ii) $X^1$ = S and $X^2$ = $CR^{11}$, (iii) $X^1$ = O and $X^2$ = $CR^{11}$, or (iv) $X^1$ = $NR^{10}$ and $X^2$ = $CR^{11}$; or $Z^1$ and $X^1$, wherein $X^1$ = N, form an (un)substituted 5-7 membered heteroaryl or heterocyclyl; $R^5$, $R^6$ = independently H, (un)substituted alk(en/yn)yl; or $R^5CNR^6$ = (un)substituted 5-6 membered heteroaryl or heterocyclyl; $R^{1-4}$ = independently H, F, Cl, CN, $NH_2$, (un)substituted heteroaryl, etc.; Y =(un) substituted heteroaryl or heterocyclyl; or $R^6NY$ =(un)substituted 5-6 membered heteroaryl or heterocyclyl; $R^{10}$ = H, (un)substituted aryl, carbocyclyl; $R^{11}$ = H, I, Br, (un)substituted (hetero)aryl, etc]

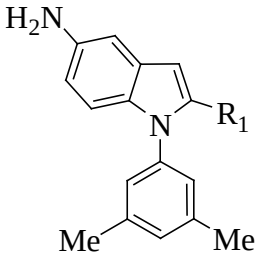
[131]. Ali *et. al.* [132] reported synthesis of indolylmethyl-morpholine derivatives **CLXXXIII** which are kinase inhibitors. These compounds can be used in the treatment



**CLXXXIII**

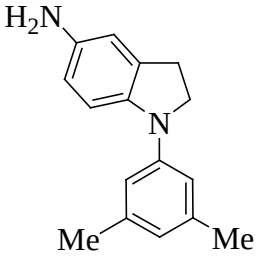
[X = O, $NR^5$, or a covalent bond; Y = C(O), $SO_2$; $R^1$ = alkyl, cycloalkyl, aryl, etc.; $R^2$ = H, alkyl; $R^3$, $R^4$ = H, halo, CN, $NO_2$, etc.; $R^5$ = H or alkyl]

of inflammatory, autoimmune, cardiovascular, neurodegenerative diseases etc. A series of substituted indoline & indole derivatives have been synthesized and their COX-1 and COX-2 inhibitory activity determined [133]. Out of 48 compounds screened following seven compounds are reported to exhibit preferential COX-1 inhibitory activity over



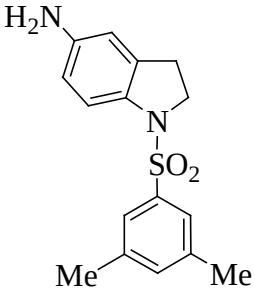
**CLXXXIVa,b**

| | $R_1$ | COX-1/COX-2 |
|---|---|---|
| a, | H | 99.3/40.5 |
| b, | $CH_3$ | 87.3/14.7 |



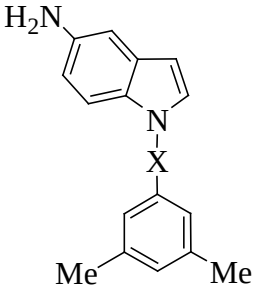
**CLXXXV**

COX-1/COX-2
89.5 /44.9



**CLXXXVI**

COX-1/COX-2
72.0/12.3

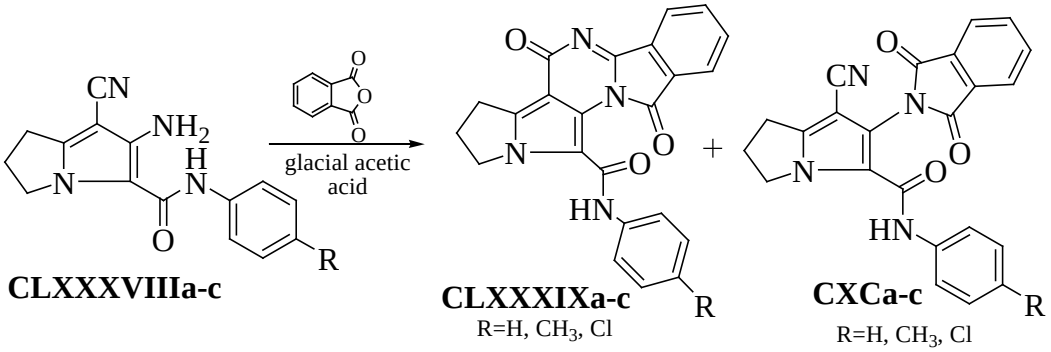


**CLXXXVIIa-c**

| | X | COX-1/COX-2 |
|---|---|---|
| a, | $CH_2$ | 83.0/22.5 |
| b, | CO | 88.1/13.8 |
| b, | $SO_2$ | 77.8/34.1 |

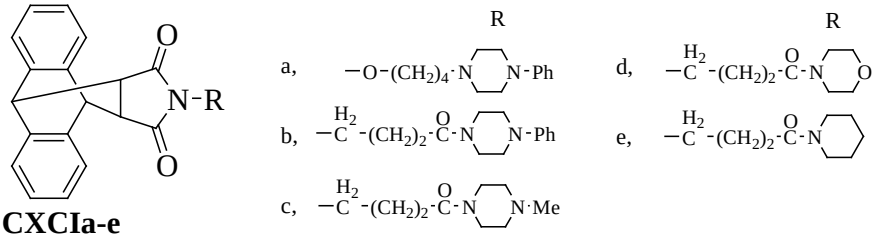
COX-2. These compounds are useful leads for the development of drugs to treat COX associated diseases such as inflammatory diseases and cancer.

Pyrrolizinopyrimidoisoindole derivatives **CLXXXIXa-c** and isoindolinylpyrrolizine derivatives **CXCa-c** have been synthesized [134] by following reaction scheme mentioned below. These compounds exhibited moderate anti-inflammatory activity.



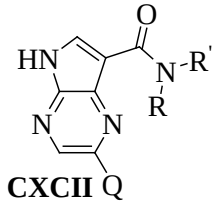

**CLXXXVIIIa-c** **CLXXXIXa-c** R=H, $CH_3$, Cl

Abu-Hashem & Gouda [135] synthesized several new 3a,4,9,9a-tetrahydro-4,9-benzenobenz[f]isoindole-1,3-diones and screened them for anti-inflammatory and



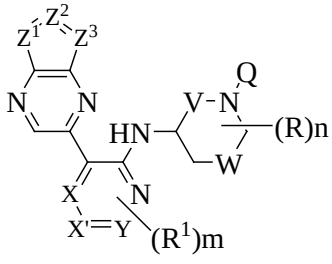

**CXCIa-e**

analgesic activities. Compounds **CXCIa-e** exhibited good anti-inflammatory and analgesic activities. A number of patents [136-144] have disclosed JAK and SYK inhibition activities of various pyrrolopyrazine derivatives **CXCII-CC** respectively.



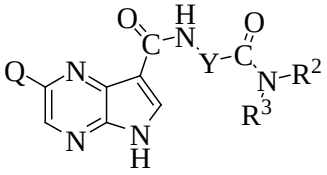
**CXCII**

[R is H; R' is lower alkoxy and (un)substituted alkyl; RR' can be taken together to form (un)substituted heterocycloalkyl; Q is (un)substituted bicyclic heteroaryl; and pharmaceuti cally acceptable salts thereof]



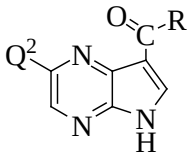
**CXCIII**

[R is lower alkyl, lower haloalkyl, lower alkoxy, lower hydroxy alkyl,OH and halo; n is 0 and 1; $Z^1$ is CH, NH and S; $Z^2$ is CH and N; $Z^3$ is $CR^2$, N and NH and derivs.; $R^1$ is halo, CN, lower alkyl, cycloalkyl,heterocycloalkyl, etc.; m is 0 and 1; $R^2$ is H, lower alkyl, cycloalkyl, CN, lower cyanoalkyl, and halo; X and Y are independently CH, $CR^1$and N; X' is absent, CH, $CR^1$ and N; Q is H, lower alkylsulfonyl, lower alkylcarbonyl, lower alkyl, etc; V is $CH_2$ and $CH_2CH_2$; W is absent,$CH_2$, and $CH_2CH_2$; dashed line is single or double bond, provided that the bonds between $Z^1$ and $Z^2$, and $Z^2$ and $Z^3$ are both both single bond or both double bonds at the same time; and pharmaceutically acceptable salts thereof]



**CXCIV**

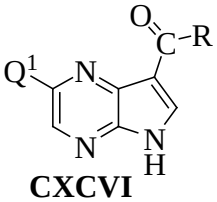
[Y = $C(R^1)_2$-$(C(R^1)_2)$m; m = 0-1; $R^1$ =H, lower alkyl, lower alkoxy, Ph, benzyl, heteroaryl, cycloalkyl, heterocycloalkyl, cycloalkyl, etc.; $R^2$=H, lower alkyl, lower haloalkyl, lower alkoxy, lower hydroxyalkyl, cyano lower alkyl, cycloalkyl, hetero cycloalkyl, etc.; $R^3$ = H, lower alkyl, lower haloalkyl,lower alkoxy, lower hydroxy alkyl, cyano lower alkyl, etc.;Q=H, halogen, hydroxy, cyano, lower alkyl, lower alk enyl, lower alkynyl, cycloalkyl, Ph, cycloalkenyl, heterocycloalkyl, heteroaryl, etc]



**CXCV**

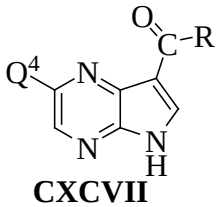
[R = $R^1$-$R^4$; $R^1$ = (un)substituted alkyl, alkoxy, Ph, etc.; $R^2$ = (un) substituted $NH_2$; $R^3$ =C(O)$R^{3a}$ (wherein $R^{3a}$ =alkyl, alkoxy, Ph, etc.); $R^4$=(un) substituted OH; $Q^2$=(un)substituted cycloalkyl, cycloalkenyl, heterocycloalkyl, heteroaryl]

These compounds are reported to be useful for the treatment of auto-immune and inflammatory diseases. Hanney *et. al.* [145] synthesized pyrrolopyrazine and indole



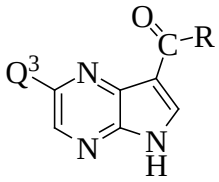
**CXCVI**

[R=$R^1$-$R^4$; $R^1$=(un)substituted alkyl, alkoxy, Ph, etc.; $R^2$=(un) substituted $NH_2$; $R^3$= C(O)$R^{3a}$ (wherein $R^{3a}$=alkyl, alkoxy, Ph, etc.); $R^4$=(un)substituted OH; $Q^1$=(un)substituted Ph, indolyl, benzodioxinyl, etc.]



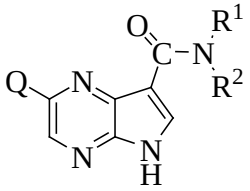
**CXCVII**

[R=$R^1$-$R^4$; $R^1$=(un)substituted alkyl, alkoxy, Ph, etc.; $R^2$=(un)substituted $NH_2$; $R^3$=C(O)$R^{3a}$ (wherein $R^{3a}$= alkyl, alkoxy, Ph, etc.); $R^4$=(un)substituted OH; $Q^4$= H, OH, CN, halo, alkyl, etc.]



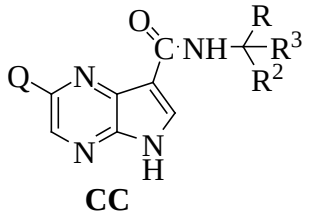
**CXCVIII**

[R=$R^1$-$R^4$;$R^1$=(un)substituted alkyl, alkoxy, Ph, etc.; $R^2$= (un)substituted $NH_2$;$R^3$=C(O)$R^{3a}$ (wherein $R^{3a}$=alkyl, alkoxy, Ph, etc.); $R^4$=(un)substituted OH; $Q^3$=O$Q^{3a}$, S$Q^{3a}$, C(O)$Q^{3a}$, etc. (wherein $Q^{3a}$ = H, alkyl, haloalkyl, etc]



**CXCIX**

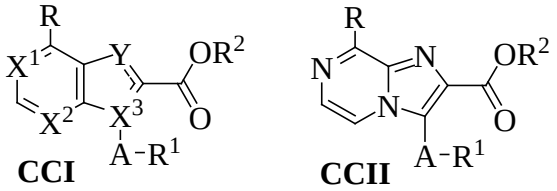
[$R^1$ is H and OH; $R^2$ is (un)substituted Ph, (un)substituted hetero cycloalkyl, (un)substituted heteroaryl, etc.; Q is (un)substituted heterocycloalkyl, (un)substituted cycloalkyl, (un)substituted cyclo alkenyl, etc.; and pharmaceutically acceptable salts thereof]



**CC**

[R is H, CN, lower alkyl, (un)substituted cycloalkyl, (un)substituted heteroaryl, etc.; $R^2$ is H, OH, lower alkyl, and lower haloalkyl; $R^3$ is H, OH, CN, (un)substituted lower alkyl, (un)substituted lower alkoxy, etc.; Q is (un)substituted heterocycloalkyl, (un)substituted cycloalkyl, (un)substituted biaryl, etc.; and pharmaceutically acceptable salts thereof]

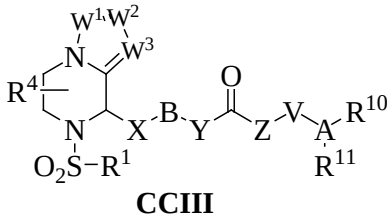
derivatives **CCI** & **CCII** which are tropomyosin-related kinase (Trk) family protein kinase inhibitors and hence useful in the treatment of inflammation, pain, cancer, restenosis, atherosclerosis, psoriasis etc. In an international patent [146] synthesis of sulfonylated tetrahydroazolopyrazines **CCIII** as bradykinin 1 receptor modulators and



**CCI** **CCII**

[$X^1$ =N, N(O), $CR^3$; $X^2$, $X^3$, Y = N or CH; R = H, halo, (un)substituted (hetero)aryl; $R^1$ = H, $(CH_2)_n$aryl, $(CH_2)_n$ heteroaryl (aryl and heteroaryl are optionally substituted); $R^2$ = H or alkyl; $R^3$ = alkyl, alkenyl, O, etc.; n = 0-4]

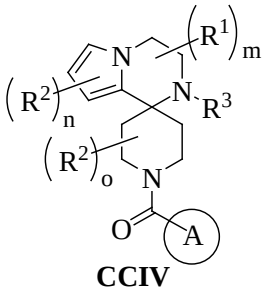
hence useful in the treatment of pain, respiratory tract and neurol. diseases, inflammatory bowel diseases, skin inflammations, rheumatic diseases, obesity etc is disclosed.



**CCIII**

[X=($CR^{2a}R^{2b}$)m; m=1-2; Y=($CR^{3a}R^{3b}$)n; n=0-2; B=a bond,$CR^{6a}R^{6b}$, $NR^7$, O with the proviso that if n=0, then B is not $NR^7$; $W^{1-3}$=independently $CR^5$, N with the proviso that at least one of $W^{1-3}$is $CR^5$;$R^1$=(hetero)aryl, $CH(aryl)_2$, etc.; $R^{2a}$, $R^{2b}$, $R^{3a}$, $R^{3b}$, $R^{6a}$,$R^{6b}$=independently H, F, Cl, OH, cycloalkyl, aryl, etc and/or $CR^{2a}R^{2b}$ and/or$CR^{3a}R^{3b}$=C:O; R=0-4 substituents independently selected from F, Cl, OH,alkyl, etc; and/or two adjacent substituents out of the 0-4 substituents $R^4$ form an anellated aryl or heteroaryl; $R^5$=H, alkyl, halo, CN, $CF_3$; $R^7$=H, (hetero)aryl bound by a alk(en /yn)ylene group, etc.; Z=($NR^8$)p; V=($CR^{9a}R^{9b}$)q; p=0-1; q=0-3; $R^8$=H,alkyl, heteroaryl, etc; $CR^{9a}$, $R^{9b}$=independently H, F, OH, cycloalkyl, etc; A=N, CH with the proviso that if p=1 & q=0 then A=CH and if p=0 then q=0 and A=N; $AR^{10}R^{11}$=spirocyclyl, cyclyl]

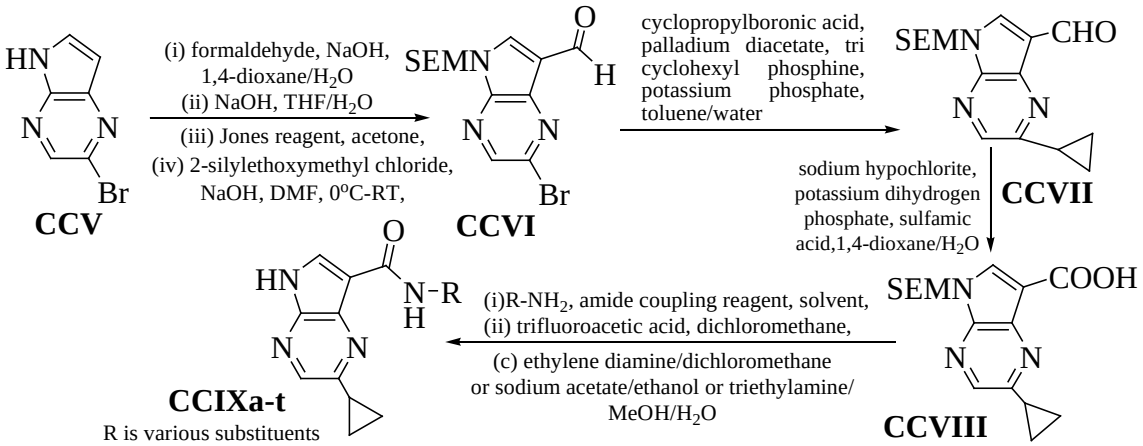
Synthesis of pyrrolopyrazine-spirocyclic piperidine amides **CCIV** which are inhibitors of ion channels and hence useful in treating or lessening the severity in a subject of acute, chronic, neuropathic or inflammatory pain, arthritis, migraine etc is reported in literat-



**CCIV**

[$R^1$=group A, $C_{3-8}$cycloalkyl, halo, cyano, $NR^8SO_2R^8$, $SO_2R^8$, $SR^8$, $SOR^8$, $NR^8COR^8$, $NR^8CO_2R^8$, $CON(R^8)_2$, $SO_2N(R^8)_2$, or heterocycloalkyl, or two $R^1$ taken together form an oxo group, or a 3- to 7-membered fused cycloalkyl ring, or a 3- to 7-membered spirocyclic ring; group A=H, $C_{1-8}$ alkyl, $CF_3$, or a straight chain, bran ched, or cyclic ($C_{1-8}$)-$R^9$ (wherein up to two $CH_2$ units may be replaced with O, CO, S, SO, $SO_2$ or $NR^8$); $R^2$= group A, halo, $C_{1-8}$ haloalkyl, cyano, OH, $SO_2R^8$, $SR^8$, $SOR^8$, $COR^8$, $CO_2R^8$, $CON(R^8)_2$, $SO_2N(R^8)_2$, $CF_3$, or $CHF_2$; $R^3$=group A, $C_{3-8}$ cycloalkyl, $CO_2R^8$, $COR^8$, COH, $CON(R^8)_2$, $CF_3$, $CH_2CF_3$, or $CH_2CHF_2$; $R^4$=H, $C_{1-8}$ alkyl, halo, $C_{3-8}$ cycloalkyl (wherein up to two $CH_2$ units may be replaced by O, CO, S, SO, $SO_2$, or $NR^8$), or 2 $R^4$ taken together form a fused 3- to 7-membered cycloalkyl ring; $R^8$=group A, $CF_3$, $C_{3-8}$ cycloalkyl, fluoroalkyl, aryl, or heteroaryl, or 2 $R^8$ taken together with the atoms to which they are attached form a ring; $R^9$ is H, $CF_3$, $CO_2R$, OH, aryl, heteroaryl, $C_{3-8}$ cycloalkyl, heterocycloalkyl, $N(R)_2$, NRCOR, $CON(R)_2$, cyano, halo, or $SO_2R$; R=H, $C_{1-8}$ alkyl, aryl, heteroaryl, $C_{3-8}$ cycloalkyl, or heterocycloalkyl; A=(un)substituted aryl, heteroaryl or heterocyclic; m, o = 0-4; n = 0-3; o is an integer]

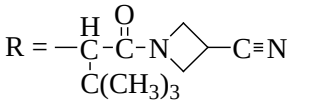
ure [147]. Soth *et. al.* [148] synthesized 3-amido-5-cyclopropylpyrrolopyrazines **CCIX**




**CCV** **CCVI** **CCVII** **CCVIII**

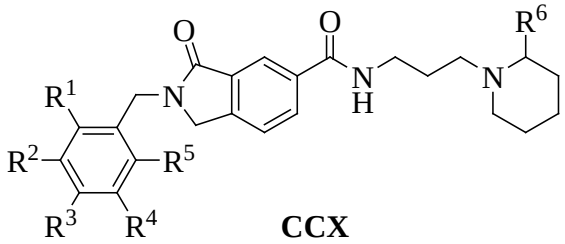
**CCIXa-t**
R is various substituents

by the following reaction scheme mentioned below. Out of several compounds **CCIXa-t** synthesized and screened for JAK kinase inhibition activity. Compound **CCIX**

(  ) was found to be potent with reasonable kinome selectivity, including selectivity for JAK3 vs JAK1 and good biopharmaceutical properties.

***1b.3.2 As anticancer agents*:-**

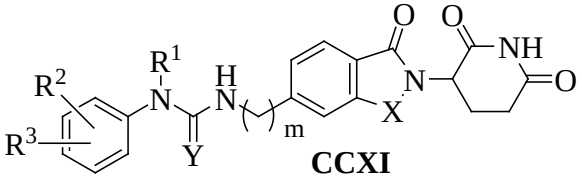
Isoindolinone derivatives **CCX** useful for the prevention or treatment of hypertension, cancer, epilepsy or neuropathic pain is disclosed in a US patent [149].



**CCX**

[I; $R^1$-$R^5$ represent independently a hydrogen atom, a halogen atom, a C1-6 alkoxy, a C1-6 alkyl, a C1-6 haloalkyl, a nitro, a cyano or a hydroxy; and $R^6$ repre sents a hydrogen atom, a C1-6 alkyl, or an aryl] or pharmaceutically acceptable salts thereof]

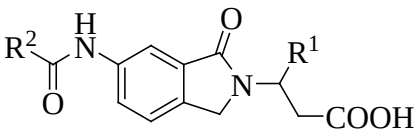
Muller *et. al.* [150] synthesized isoindoline derivatives **CCXI** which are useful in treating cancer and other diseases. Usefulness of 1,3-dihydro-1-oxo-2H- isoindole derivatives



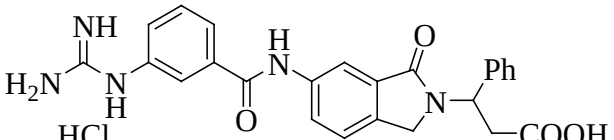
**CCXI**

[X=C(O), $CH_2$; Y=O, N(CN), NH; m=0-3;$R^1$=H, alkyl; $R^2$=H, $NO_2$, alkyl, etc.; $R^3$=H, halo, $NO_2$]

**CCXII** in the treatment of neoplasm metastasis, tumor growth, solid tumor growth, angiogenesis, retinopathy, macular degeneration, osteoporosis, arthritis, smooth muscle cell migration and atherosclerosis is reported in literature [151]. Compound **CXXIII** at 10 μM exhibited 52.9% inhibition against binding M21 melanoma cancer cells to



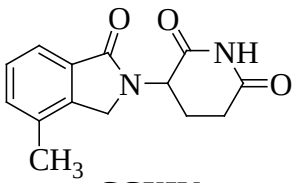
**CCXII**



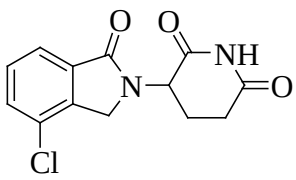
**CCXIII**

[wherein $R^1$=H, Ph, 2-furyl, 2-thienyl, 3-pyridyl, 4-pyridyl, 3,4-methylenedioxophenyl, 2,3-methylenedioxophenyl, etc.; $R^2$=$H_2NC(:NH)NH(CH_2)n$, $H_2NC(:NH)NHC_6H_4$, etc.; n = 1-3 or pharmaceutically acceptable salts thereof]

fibronectin. Several isosteric analogs of lenalidomide and pomalidomide have been synthesized [152] and screened for antiproliferative activity against the Namalwa

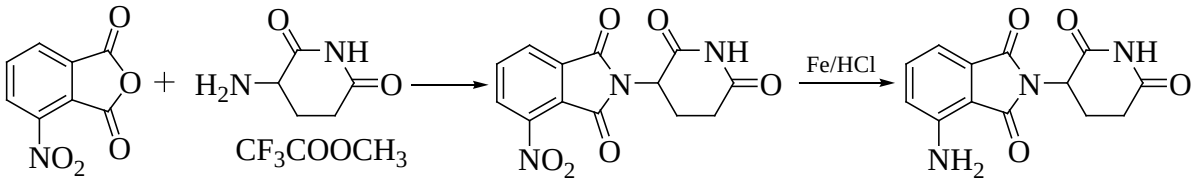


**CCXIV**



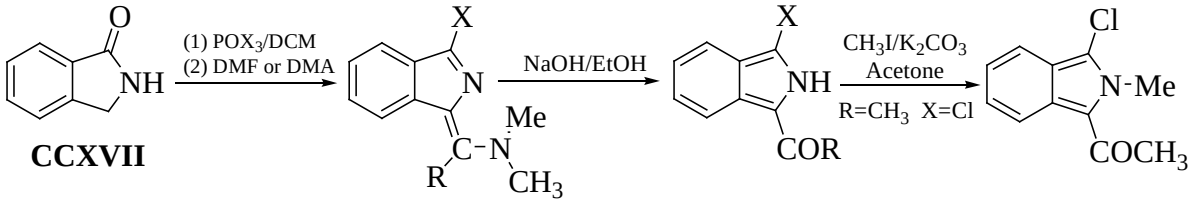
**CCXV**

lymphoma cell line. Compounds **CCXIV** and **CCXV** exhibited potent inhibition with $IC_{50}$ value 0.013 and 0.067 µM. A pathway for synthesis of antitumor agent



**CCXVI**

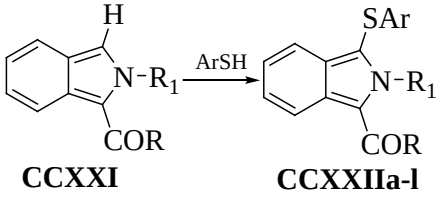
pomalidomide **CCXVI** is reported by Tang *et. al.* [153]. Diana *et. al.* [154] synthesized a number of isoindole derivatives by following reaction scheme mentioned below.



**CCXVII** **CCXVIIIa-c** **CCXIXa-c** **CCXX**

a, R=H X=Cl
b, R=$CH_3$ X=Cl
c, R=H X=Br

a, R=H X=Cl
b, R=$CH_3$ X=Cl
c, R=H X=Br

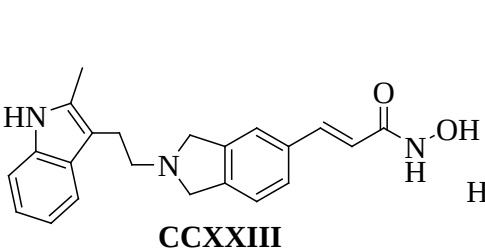


**CCXXI** **CCXXIIa-l**

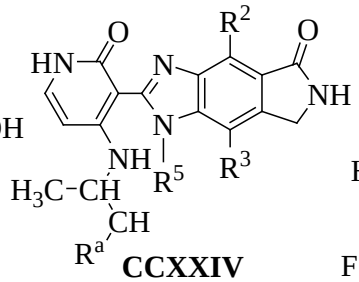
a, R=$R_1$=H, Ar=$C_6H_5$
b, R=$R_1$=H, Ar=$C_6H_4$-4-$OCH_3$
c, R=$R_1$=H, Ar=$C_6H_4$-4-$CH_3$
d, R=$R_1$=H, Ar=$C_6H_4$-3-$OCH_3$
e, R=$CH_3$, $R_1$=H; Ar=$C_6H_5$
f, R=$CH_3$, $R_1$=H; Ar=$C_6H_4$-4-$OCH_3$
g, R=$CH_3$, $R_1$=H; Ar=$C_6H_4$-4-$CH_3$
h, R=$CH_3$, $R_1$=H; Ar=$C_6H_4$-3-$OCH_3$
i, R=$R_1$=$CH_3$, Ar=$C_6H_5$
j, R=$R_1$=$CH_3$, Ar=$C_6H_4$-4-$OCH_3$
k, R=$R_1$=$CH_3$, Ar=$C_6H_4$-4-$CH_3$
l, R=$R_1$=$CH_3$, Ar=$C_6H_4$-3-$OCH_3$

Compound **CCXXIIa,b,e,f,i** were screened for a group of 60 cancer cell lines at a dose conc. of $10^{-5}$ M. Two compounds **CCXXIIb** and **CCXXIIf** on further evaluation show $GI_{50}$ values from micromolar to submicromolar concentrations against all the cell lines investigated. Out of several isoindoline derivatives synthesized [155] and screened for anti-proliferative activity against human colon cancer cell line HCT116, compound

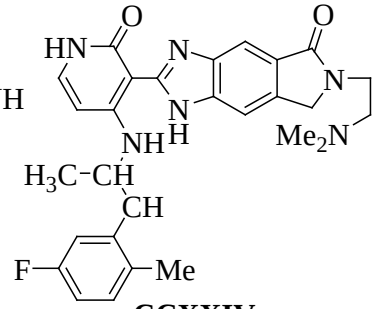
**CCXXIII** exhibited $IC_{50}$ 0.042 µM and was found to be most active among all the compounds synthesized. Usefulness of imidazo[4,5-f]isoindole derivatives **CCXXIV** as tyrosine kinase inhibitors and hence useful for treating cancer is disclosed in a US patent



**CCXXIII**



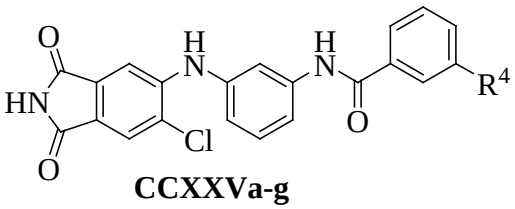
**CCXXIV**



**$CCXXIV_A$**

[wherein $R^a$ is optionally substituted aryl or heteroaryl; $R^2$ and $R^3$ are each independently hydrogen, lower alkyl, lower alkoxy, halogen, cyano, lower alkylamino or dilower alkylamino; and $R^5$ is hydrogen, lower alkyl, lower alkoxy, halogen, cyano, lower alkylamino or dilower alkylamino]

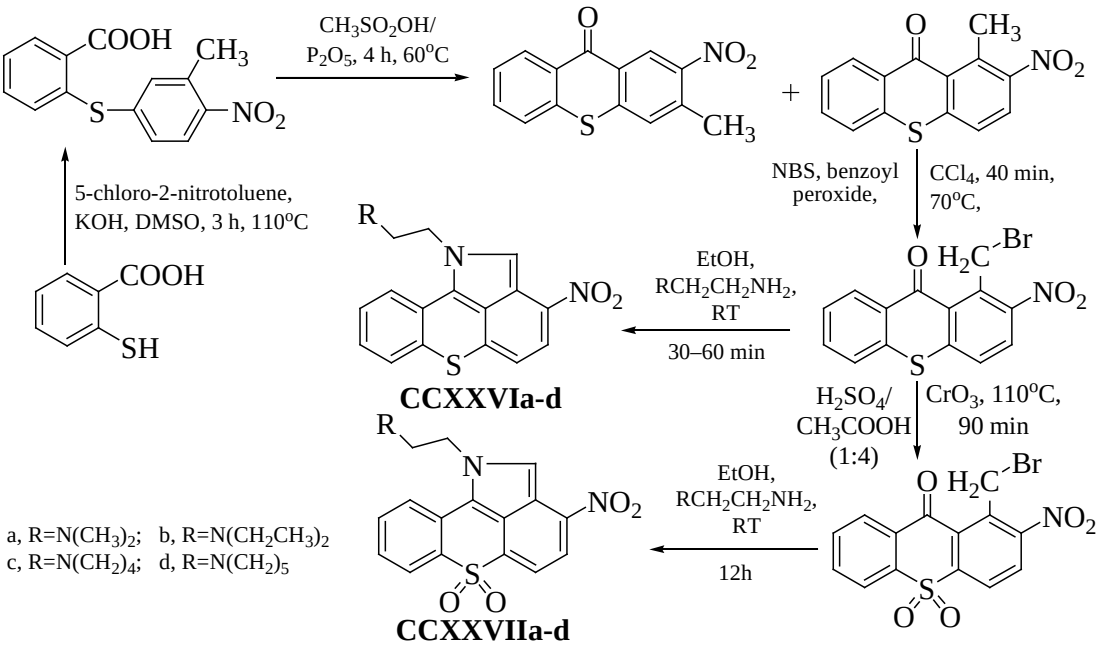
[156]. Compound **$CCXXIV_A$** exhibited $IC_{50}$ values of 66-95 nM against $BaF_3$ cells expressing anaplastic lymphoma kinase (ALK) mutants that confer resistance to Crizotinib. Wang *et. al.* [157] synthesized isoindoline-1,3-dione derivatives **CCXXVa-g** which are B-Raf inhibitors and hence useful in the treatment of cancer. B-Raf $IC_{50}$ for



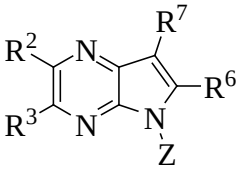
**CCXXVa-g**

a, $R^4$=Cl; b, $R^4$=Br; c, $R^4$=I
d, $R^4$=$CF_3$; e, $R^4$=$OCF_3$; f, $R^4$=CN

**CCXXVa-g** is reported to be 0.117, 0.035, 0.008, 0.010, 0.006 and 0.297 µM respectively. A number of benzothiopyrano[4,3,2-cd]isoindole amino derivatives **CCXXVI**, **CCXXVII** have been synthesized [158] by following reaction scheme mentioned below. These compounds are reported to possess good cytotoxicity in a low µM range against HCT-116, MES-SA and MES-SA/Dx cancer cell line. In a European patent [159] usefulness of pyrrolo[2,3-b]pyrazines **CCXXVIII** as kinase inhibitors and hence useful in the treatment or prevention of neurodegenerative disorders such as Alzheimer's and Parkinson's disease and proliferative disorders is described. Compound

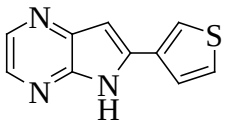



**CCXXIX** inhibited CDK1/cyclin B, CDK5/p25 and GSK-3α/β with $IC_{50}$ values of 2.30 μM, 1.00 μM and 0.80 μM respectively. Usefulness of pyrrolopyrazines **CCXXX** and



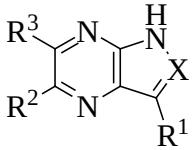
**CCXXVIII**

[wherein $R^2$ and $R^3$=independently H or (un)substituted alkyl; $R^6$=(un)substituted aryl or (aryl)cycloalkyl; $R^7$=H, alkyl, halo (alkyl), propenyl, cycloalkylmethyl, or arylmethyl; Z=H or $CH_3$]



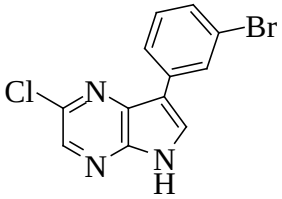
**CCXXIX**

pyrazolopyrazines which are inhibitors of protein kinases and hence useful in the treatment of cancer is reported in literature [160]. Compound **CCXXXI** inhibit Aurora protein kinases and its Ki value is less than 200 nM. Ibrahim *et. al.* [161] synthesized



**CCXXX**

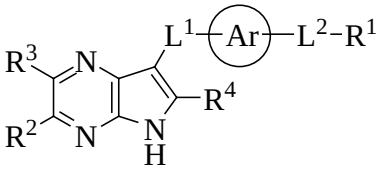
[X = CH, N; $R^1$=aryl, 5-14 membered heteroaryl; $R^2$, $R^3$=H, halo, CN, etc]



**CCXXXI**

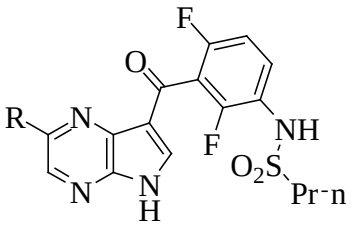
pyrrolopyrazine derivatives **CCXXXII** which are Raf kinase modulators and hence useful in the treatment of diseases and conditions related with activity of Raf protein

kinases, including ovarian, thyroid and colorectal cancer, melanoma, cholangiocarcinoma, pain or polycystic kidney disease. Compound **CCXXXIIIa** exhibited $IC_{50}$ value less than 10 µM in A-Raf, B-Raf, B-Raf V600E and C- Raf assays



**CCXXXII**

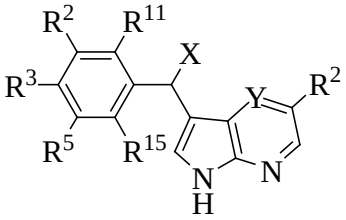
[wherein Ar=(un)substituted Ph, pyridinyl, pyrimidinyl, etc.; $L^1$=O, S, CO, etc.; $L^2$=(un)substituted -amino-CO-, -amino-CS-, -amino-$SO_2$-, etc.; $R^1$ = (un)substituted alkyl, alkynyl, aryl, etc.; $R^2$, $R^3$=independently H, F, (un)substituted alkyl, etc.; $R^4$=H, halo, (un)substituted alkyl, etc.; and salts, prodrugs, tautomers, stereoisomers thereof]



**CCXXXIIIa, b**

[a, R=H,
b, R=1-methylpyrazol-4-yl]

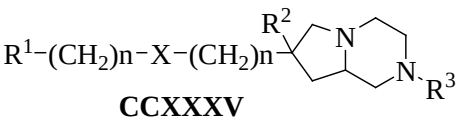
and **CCXXXIIIb** exhibited $IC_{50}$ value less than 10 µM in Kdr and Src assays. In an international patent synthesis of pyrrolo[2,3-b]pyridines and pyrrolo[2,3-b]pyrazines **CCXXXIV** and their usefulness in the treatment of cancer is disclosed [162]. Pyrrolo



**CCXXXIV**

[wherein X is OH, C1-3 alkyl and C1-3 alkoxy; Y is CH and N; $R^{11}$-$R^{15}$ are independently H, halo, CN, (un)substituted C1-6 alkyl, $CF_3$, $OCF_3$, (un)substituted -$OC_{0-6}$ alkyl, (un)substituted -$SO_{0-2}$-$C_{1-6}$ alkyl, (un)subs tituted -$SO_2$($C_{0-6}$ alkyl)CO($C_{0-6}$ alkyl), (un)substituted -N($C_{0-6}$ alkyl) CO($C_{0-6}$ alkyl), etc.; $R^2$ is H, halo, CN, $CF_3$, $NO_2$, (un)substituted $C_{0-6}$ alkyl, (un)substituted $C_{2-6}$ alkenyl, (un)substituted $C_{2-6}$ alkynyl, (un) substituted $C_{3-6}$ (hetero)cycloalkyl-$C_{0-6}$ alkyl, (un)substituted aryl-$C_{0-6}$ alkyl, etc.; and their pharmaceutically acceptable salts thereof]

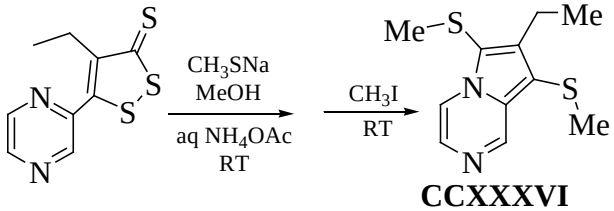
[1,2-a]pyrazine derivatives **CCXXXV** capable of enhancing or inhibiting serotonergic neurotransmission and hence useful for the treatment of headache, anxiety, depression, post-traumatic stress disorders, neurodegenerative disorders, prostatic cancer, drug addictions have been synthesized and disclosed in a Japanese patent [163]. Cancer



**CCXXXV**

[$R^1$=Ph, naphthyl, benzoxazolonyl, indolyl, indolonyl, benzimidazolinyl, quinolyl, furyl, benzofuryl, thienyl, benzothienyl, oxazolinyl, benzoxazolyl; $R^2$=H, C1-6 alkyl; $R^3$=Ph, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl; $R^4$, $R^5$=H, C1-6 alkyl; $R^1$-$R^3$ may be substituted with 1-4 F, C, Br, iodo, cyano, $NO_2$, thiocyano, $SR^4$, $SOR^4$, $SO_2R^4$, $NHSOR^4$, C1-6 alkoxy, $NR^4R^5$, $NR^4COR^5$, $CONR^4R^5$, Ph, $COR^4$, $CO_2R^4$, C1-6 (halo)alkyl, C3-6 cycloalkyl, $OCF_3$; X = O, S, SO, $SO_2$, $NR^4$, CO, CH(OH), $CHR^4$, OCO, $CO_2$, $NR^4CO$, $CONR^4$; m=0, 1; n = 0, 1, 2]

chemopreventive agent oltipraz [164, 165] in animal models and clinical studies get metabolized to 7-methyl-6,8-bis(methylthio)pyrrolo[1,2-a]pyrazine; 7-methyl-8-(methylsulfinyl)-6-(methylthio)pyrrolo[1,2-a]pyrazine and 7-methyl-6,8-bis(methyl sulfinyl)pyrrolo[1,2-a]pyrazine to a large extent. In view of above 7-ethyl-6,8-bis(methylthio)pyrrolo[1,2-a]pyrazine **CCXXXVI** is synthesized by following reaction sequence mentioned below. Compound **CCXXXVI** have ability to prevent the induction of hypoxia-inducible factor-1 (HIF-1)α which may result from inhibition of HIF-1α *de novo* synthesis and hence act as antitumor agent.

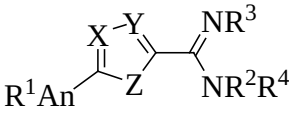



**CCXXXVI**

**1b.4 Amidine and azomethine derivatives**

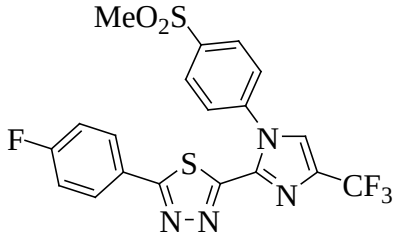
***1b.4.1 As anti-inflammatory agents:***

Azolylamidines derivatives **CCXXXVII** exhibiting COX-2 inhibition activity and hence useful in the treatment of inflammation is disclosed in a U.S. patent [166]. Thus compound **CCXXXVIII** inhibited COX-2 by 98% at 10nM concentration. Banner *et. al.*



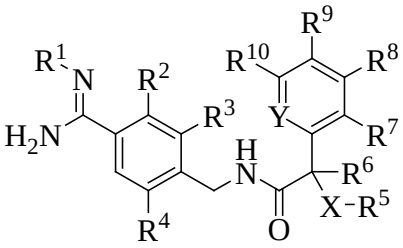

**CCXXXVII**

[X, Y=C, N; Z=N, O, S; $R^1$, $R^2$=(substituted) aryl, heteroaryl; $R^3$, $R^4$=H, alkyl; $R^3R^4$=atoms to form a (substituted) ring; A = $CH_2$, $NR^5$, O, S; $R^5$=H, alkyl; n = 0, 1]




**CCXXXVIII**

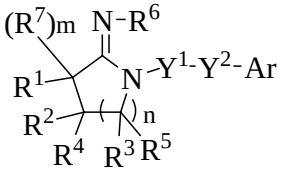
[167] synthesized N-(carbamimidoylbenzyl)benzeneacetamides and pyridineacetamides **CCXXXIX** which are reported to be useful in the treatment of deep vein thrombosis, pulmonary embolism, unstable angina pectoris, cardiac infarction, stroke due to atrial



**CCXXXIX**

[X = O, S, $NR^{12}$, $SO_2$; Y=N, $CR^{11}$; $R^1$=H, OH, $NH_2$, or (un)substituted (aryl) alkoxycarbonyl, aryloxycarbamoyl, alkanoyl, arylcarbonyl; $R^2$-$R^4$=independently H, halo, OH, carboxyalkylamino, carbamoylalkylamino, hydroxycycloalkyloxy, (hetero)aryl(oxy), (hetero)aryl(alkyl)amino, etc.; $R^5$=(cyclo)alkyl; or if X = O or $NR^{12}$, $R^5$ may be H; $R^6$=H, (fluoro)alkyl; $R^7$-$R^{11}$=independently H, OH, halo, $NO_2$, CHO, or (un)substituted amino, fluoroalkyl, alkoxy, (hetero)aryl(oxy), heterocyclyl alkyl, carbamoyl, cycloalkyl(alkoxy), etc.; or $R^8$ and $R^9$ or $R^8$ and $R^7$ are bound to each other to form a ring together with the C's to which they are attached; $R^{12}$=H, alkyl(carbonyl); and pharmaceutically acceptable salts thereof]

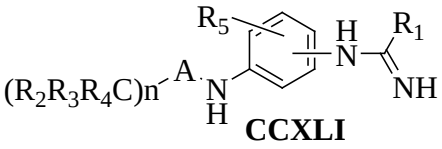
fibrillation, inflammation, arteriosclerosis and/or tumors. Synthesis of cyclic amidine derivatives **CCXL** useful as platelet aggregation inhibitors and proliferation inhibitors of smooth muscle cell and for the treatment of cerebral infarction, heart disease, hypertension, inflammation, rheumatism, asthma etc is described in an international



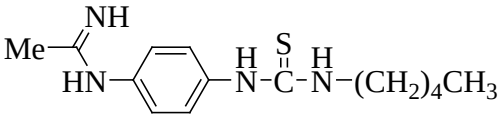
**CCXL**

[$R^1$-$R^5$, $R^7$=H, cyano, halo, $C_{1-6}$ alkyl, alkylidene, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, acyl,$CO_2H$, $CONH_2$, $C_{1-6}$ alkoxycarbonyl, $C_{1-6}$ alkylaminocarbonyl, HO, $C_{1-6}$ alkoxy,$C_{3-8}$ cycloalkoxy, $NH_2$, $C_{1-6}$ alky lamino, $C_{3-8}$ cycloalkylamino, acylamino, sulfonylamino, sulfonyl, sulfamoyl, $C_{3-8}$ cycloalkyl, 5 to 14-membered arom. or nonarom. heterocyclyl, $C_{6-14}$ arom. cyclic hydrocarbyl; m = 0,1; or $R^2$ and $R^4$ are linked to each other to form a 5 or 6-membered ring contg. 1-5 atoms selected from C, N, and O; or $R^4$ and $R^5$ together form a single bond; $R^6$=H, $C_{1-6}$ alkyl, acyl, $CONH_2$, HO, $C_{1-6}$ alkoxy, $C_{1-6}$ alkoxycarbonyloxy, $C_{3-8}$ cycloalkyl, optionally acyloxy-substituted $C_{1-6}$ alkoxycarbonyl, (un)substit uted $C_{6-14}$ arom. cyclic hydrocarbyl or 5 to 14-membered arom. heterocyclyl; n = 1,2; $Y^1$ = $(CH_2)_z$ (wherein z=an integer of 1-3), $CH_2CO$, SO, $SO_2$, CO, each (un)substituted CH, $CH_2$, NH, CONH, or $SO_2NH$; $Y^2$=a single bond, O, N, $(CH_2)_z$, SO, SO, $SO_2$, each (un)substituted CH, $CH_2$, or C(:NOH); Ar = H, (un)substituted Ph or 5 to 14-membered arom. heterocyclyl]

patent [168]. Benzamidine derivatives **CCXLI** exhibiting anti-inflammatory and immuno suppressive activity is synthesized and reported in literature [169]. Thus compound **CCXLII** inhibited NO production in rabbit joint chondrocytes with $IC_{50}$=6.6 μM. A



**CCXLI**

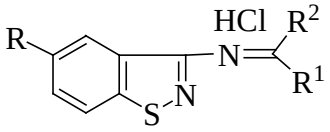


**CCXLII**

[A = carboxamide, thiocarboxamide, carbonyl; $R_1$=alkyl, amino, optionally substituted with $NO_2$ or Me $R_2$=H, alkyl, MeO, EtO, PrO, mono-, bi- or tricyclic cycloalkyl having 5-12 C atoms, adamantyl, aryl, naphthyl, heterocyclyl optionally substituted with Me, MeO, OH, amino, halo; $R_3$, $R_4$=H, alkyl; $R_5$=1-2 of H, Me, MeO, OH; n = 0-6; the amidine groups is in the para or meta position relative to the ANH group]

number of amidinobenzisothiazole derivatives **CCXLIII** have been synthesized [170] and evaluated for the prevention of cartilage destruction in articular disease. All these

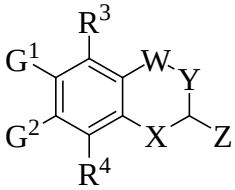
compounds in the presence of IL-1β blocked the cartilage breakdown with different behaviour. The antidegenerative activity is more evident in human cartilage. Makovec *et.*



**CCXLIII**

[R=H, Me; $R^1$= H, Me, Ph, -CH=$CH_2$, 2-pyridyl; $R^2$= $NH_2$, $NMe_2$]

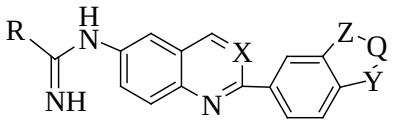
*al.* [171] synthesized heterocyclic amidine derivatives **CCXLIV** which inhibit nitrogen oxide (NO) production and hence useful as anti-inflammatory and analgesic agents.



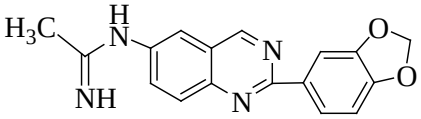
**CCXLIV**

[$G^1$ and $G^2$=H, halogen, OH, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ alkyl, and an amidino substituent, provided that only one of the two substituents $G^1$ or $G^2$ is an amidino substituent; W, Y and X combine to form 9- or 10- membered bi cyclic heteroarom. derivs. contg. up to 2 hetero atoms in the same ring; Z= aryl or heteroaryl group, a linear or branched $C_1$-$C_6$ alkyl or alkenyl chain, a $C_1$-$C_4$ alkyl-aryl group or a $C_1$-$C_4$ alkyl-heteroaryl group; and $R^3$ and $R^4$= H, halogen, OH, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ alkenyl, or $C_1$-$C_4$ alkyl]

Amidine derivatives of 2-heteroaryl-quinazolines and quinolines **CCXLV** and **CCXLVI** exhibiting analgesic and anti-inflammatory activity have been synthesized and disclosed in an international patent [172]. These compounds are not acting through inhibition of



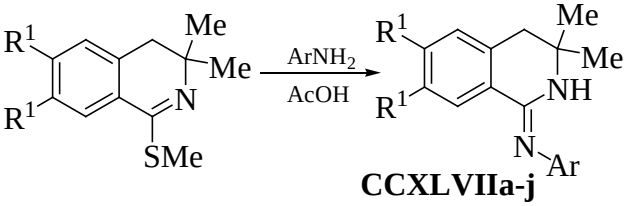
**CCXLV**



**CCXLVI**

[X = CH or N; Y and Z independently = O, S, $SO_2$, $CH_2$, etc.; Q independently = -$CH_2$-, -CH=, -$CH_2CH_2$-, etc., provided the combination of Y, Z, and Q give rise to benzocondensed hexaat. or pentaat. heterocycle; R independently = (un)substituted alkyl, cycloalkyl]

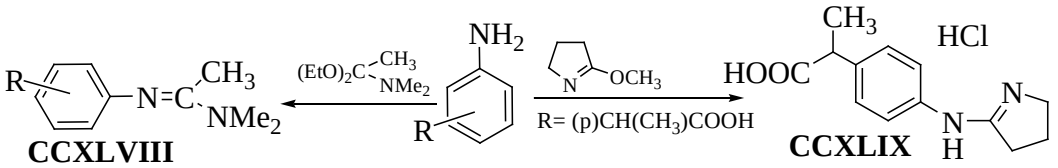
COX or NOS enzymes but are effective in inhibiting inflammatory cytokine production induced by inflammatory stimuli. Glushkov *et. al.* [173] synthesized amidine derivatives of 3,4-dihydroisoquinoline **CCXLVIIa-j** by following reaction scheme mentioned below. Anti-inflammatory activity exhibited by **CCXLVIIa** and **CCXLVIIi** is better than



**CCXLVIIa-j**

[a, $R^1$=H, Ar=Ph; b, $R^1$=H, Ar=3,4-$F_2C_6H_3$; c, $R^1$ = $OCH_3$, Ar = 2,4-$Cl_2C_6H_3$; d, $R^1$ = $CH_3$, Ar = 2-$BrC_6H_4$; e, $R^1$=H, Ar = p-$H_2NSO_2C_6H_4$; f, $R^1$= $OCH_3$, Ar=p-$H_2NSO_2C_6H_4$; g, $R^1$=$OCH_3$, Ar=2-thiazolyl; h, $R^1$=$CH_3$, Ar = 2-thiazolyl; i, $R^1$=$OCH_3$, Ar = 4-phenyl-2-thiazolyl; j, $R^1$= H, Ar=1,2,4-triazol-4-yl]

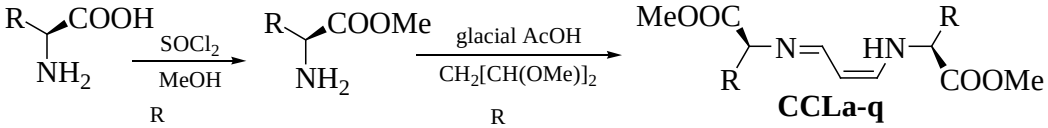
standard drug diclofenac sodium. A number of amidine derivatives **CCXLVIII**, **CCXLIX** have been synthesized [174] by following reaction scheme mentioned below.



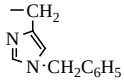

**CCXLVIII** **CCXLIX**

[R= a: 4-OH, b: 3-OH, c: 4-$OCH_3$, d: 4-COOH, e: 4-$COOC_2H_5$; f: 4-$CH_2COOH$, g: 4-$CH_2COOC_2H_5$, h: -$CH(CH_3)COOH$, i: 4-$CH(CH_3)COOC_2H_5$ ]

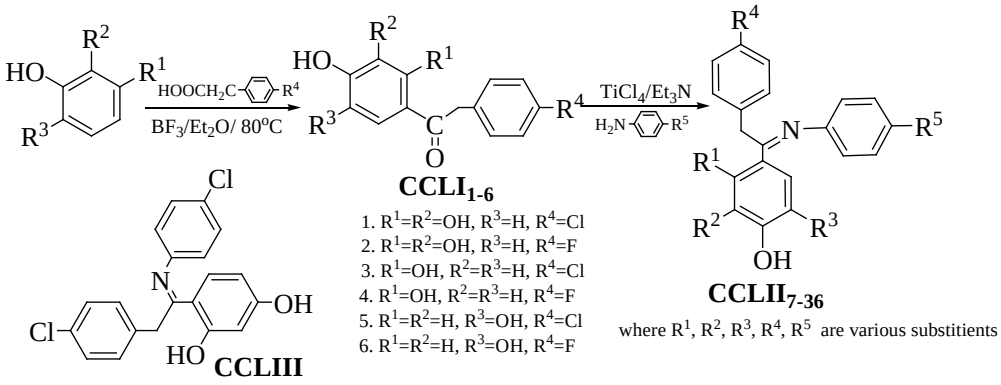
These compounds on screening for anti-inflammatory activity did not show any advantage over reference drug ibuprofen. A novel target for the treatment of chronic pain is Acid-Sensing ion Channel-3 (ASIC3). A number of amidine derivatives which are ASIC-3 inhibitors and hence can be useful in the treatment of chronic pain have been synthesized and reported in literature [175, 176]. Zhou *et. al.* [177] synthesized novel Schiff's bases **CCL** by the following reaction scheme mentioned below. These Schiff's base exhibit desirable anti-inflammatory activity on xylene-induced ear edema mouse



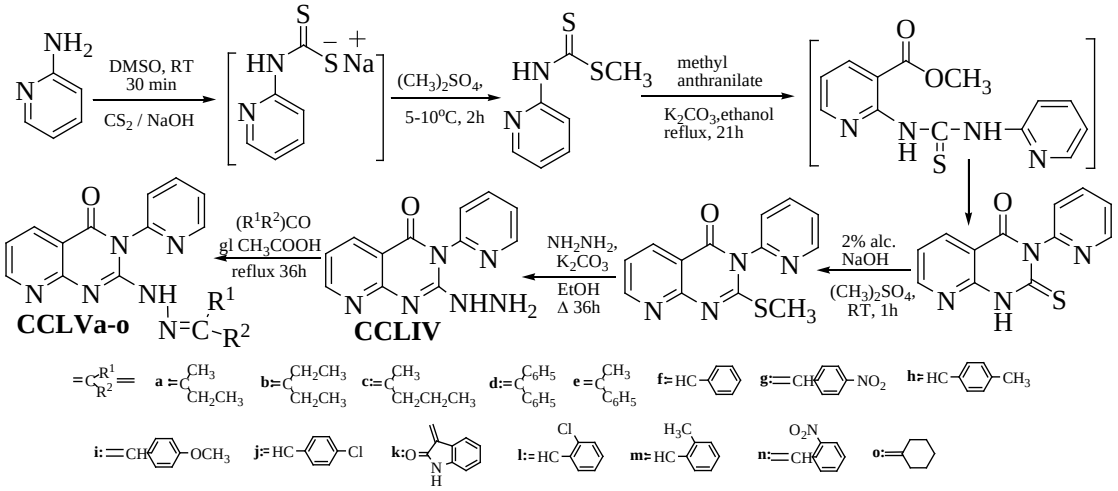

**CCLa-q**

| | R |
|---|---|
| a, | $-CH_3$ |
| b | $-(CH_2)_3NHC(NH)NHNO_2$ |
| c | $-CH_2SCH_2C_6H_4-CH_3$-p |
| d | $-CH_2CO_2CH_3$ |
| e | H |
| f | $-CH_2CH_2CO_2CH_3$ |
| g |  |
| h, | $—(CH_2)_4NHCOOCH_2C_6H_5$ |
| i | $-CH(CH_3)CH_2CH_3$ |
| j | $-CH_2CH(CH_3)_2$ |
| k | $-CH_2CH_2SCH_3$ |
| l | $-CH_2C_6H_5$ |
| m | $-CH_2OCH_2C_6H_5$ |
| n | $-CH(CH_3)OCH_2C_6H_5$ |
| o | $-CH(CH_3)_2$ |
| p |  |
| q | $-CH_2C_6H_4-OH$-p |

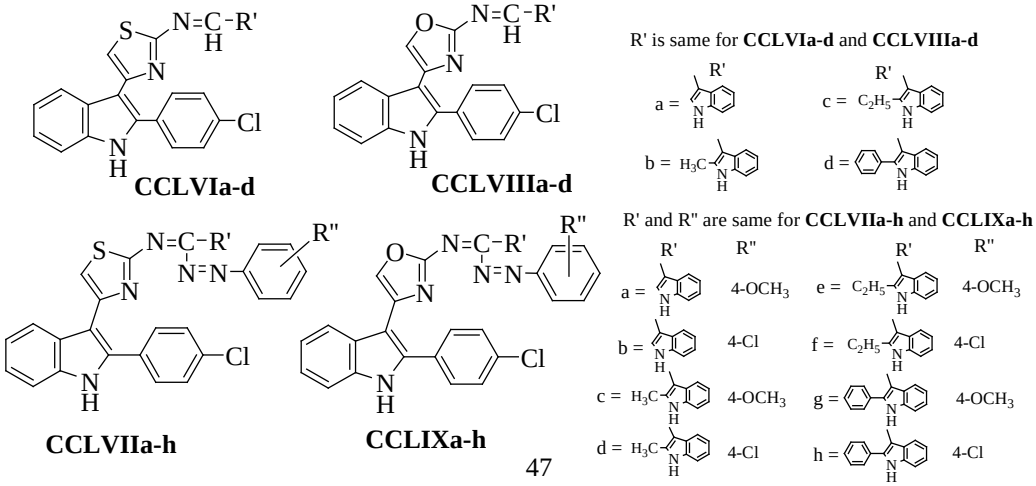
model 20 µmol/kg and hence useful to treat chronic pain from inflammation. A number of Schiff's bases have been synthesized [178] by following reaction sequence mentioned below. Out of several compounds synthesized and screened as FabH inhibitors and as anti-inflammatory agents, compound **CCLIII** was able to reduce the ECE-induced IL-8 production in gastric mucosal cells significantly. On the bases of biological data and molecular docking compound **CCLIII** is a potential FabH inhibitor and anti-



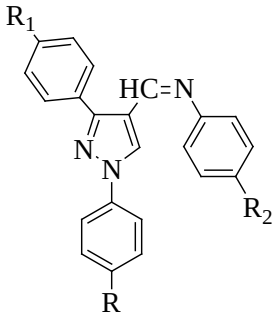

inflammatory agent. A new series of 3-(2-pyridyl)-2-substitued-quinazolin-4(3*H*)ones **CCLVa-o** have been synthesized by following reaction scheme mentioned below [179].




Anti-inflammatory activity screening of compounds **CCLVa-o** showed that compound **CCLVb** possess anti-inflammatory activity better than standard drug diclofenac at a dose of 10 or 20 mg/kg *p.o.*. A number of thiazolylindole and oxazolylindole based Schiff's bases **CCLVI**, **CCLVII**, **CCLVIII**, **CCLIX** have been synthesized [180] and screened



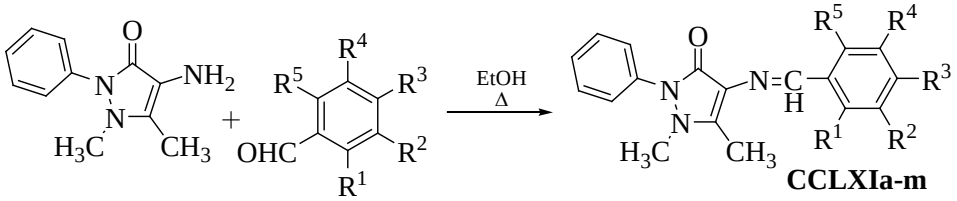
for anti-inflammatory activity. Out of all the compounds screened, compound **CCLVIb** exhibited better anti-inflammatory activity and lower ulcerogenic activity than refrence drug phenylbutazone. Ragab *et. al.* [181] synthesized several azomethine compounds **CCLXa-l** and screened them for anti-inflammatory and analgesic activity. Compound **CCLXe** exhibited anti-inflammatory and analgesic activity better than reference drug



**CCLXa-l**

| | R | $R_1$ | $R_2$ | | R | $R_1$ | $R_2$ |
|---|---|---|---|---|---|---|---|
| a | Cl | $CH_3$ | H | g | $SO_2NH_2$ | $CH_3$ | H |
| b | Cl | $CH_3$ | $OCH_3$ | h | $SO_2NH_2$ | $CH_3$ | $OCH_3$ |
| c | Cl | $CH_3$ | Cl | i | $SO_2NH_2$ | $CH_3$ | Cl |
| d | Cl | $OCH_3$ | H | j | $SO_2NH_2$ | $OCH_3$ | H |
| e | Cl | $OCH_3$ | $OCH_3$ | k | $SO_2NH_2$ | $OCH_3$ | $OCH_3$ |
| f | Cl | $OCH_3$ | Cl | l | $SO_2NH_2$ | $OCH_3$ | Cl |

phenylbutazone. A number of Schiff's base analogues of **CCLXIa-m** of 4-amino-1,5-dimethyl-2-phenyl pyrazol-3-one have been synthesized [182] by following reaction scheme mentioned below. Compound **CCLXIf** significantly reduced NO production and

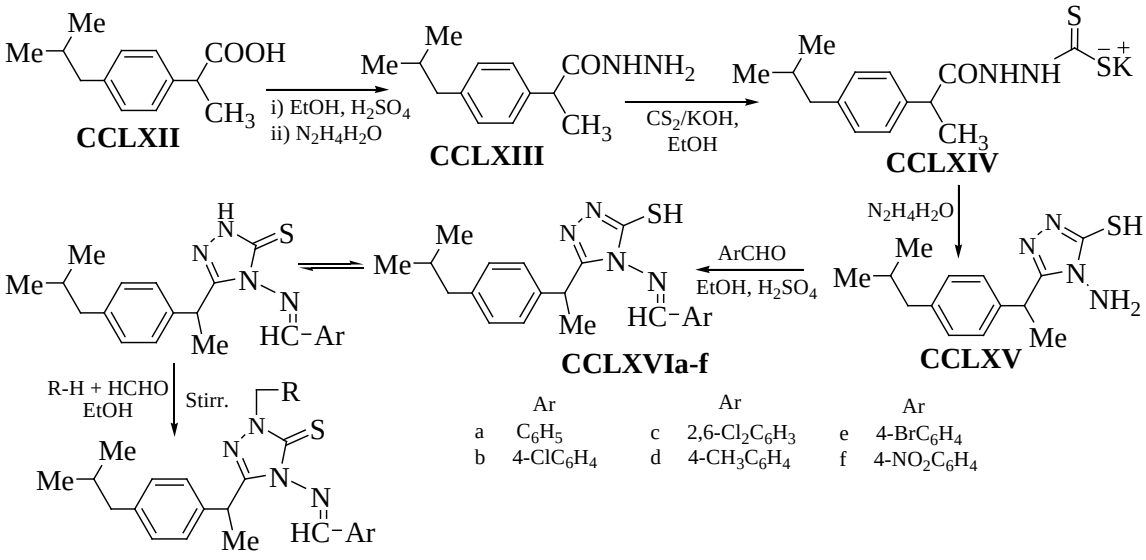


**CCLXIa-m**

| | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ | | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| a | H | H | H | H | H | h | H | OMe | OMe | H | H |
| b | H | H | Cl | H | H | i | OH | H | OH | H | H |
| c | H | H | $NMe_2$ | H | H | j | OMe | H | OMe | H | H |
| d | H | H | OH | H | H | k | OH | H | OH | H | OH |
| e | H | H | OMe | H | H | l | H | OMe | OH | OMe | H |
| f | H | OH | OH | H | H | m | H | Me | OMe | H | H |
| g | H | OMe | OH | H | H | | | | | | |

inhibited LPS-stimulated iNOS and COX-2 mRNA levels in a dose dependent manner and exhibited promising anti-inflammatory activity. A number of Schiff's bases **CCLXVIa-f** and **CCLXVIIa-n** containing ibuprofen moiety have been synthesized [183]

by following reaction scheme mentioned below. All these compounds were screened for anti-inflammatory and analgesic activities. Compounds **CCLXVIe**, **CCLXVIIb, k,l**



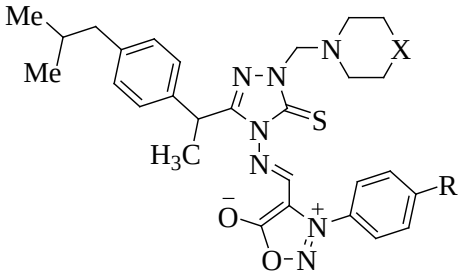

| | Ar |
|---|---|
| a | $C_6H_5$ |
| b | 4-$ClC_6H_4$ |

| | Ar |
|---|---|
| c | 2,6-$Cl_2C_6H_3$ |
| d | 4-$CH_3C_6H_4$ |

| | Ar |
|---|---|
| e | 4-$BrC_6H_4$ |
| f | 4-$NO_2C_6H_4$ |

| | Ar | R |
|---|---|---|
| a | $C_6H_5$ | Morpholine |
| b | 4-$ClC_6H_4$ | Morpholine |
| c | 4-$ClC_6H_4$ | 1-Methylpiperazine |
| d | 2,6-$Cl_2C_6H_3$ | Morpholine |
| e | 2,6-$Cl_2C_6H_3$ | 1-Phenylpiperazine |
| f | 4-$CH_3C_6H_4$ | Morpholine |
| g | 4-$CH_3C_6H_4$ | 1-Methylpiperazine |
| h | 4-$CH_3C_6H_4$ | Diphenylamine |
| i | 4-$CH_3C_6H_4$ | 1-Phenylpiperazine |
| j | 4-$BrC_6H_4$ | Diphenylamine |
| k | 4-$NO_2C_6H_4$ | Morpholine |
| l | 4-$NO_2C_6H_4$ | 1-Methylpiperazine |
| m | 4-$NO_2C_6H_4$ | Diphenylamine |
| n | 4-$NO_2C_6H_4$ | 1-Ethylpiperazine |

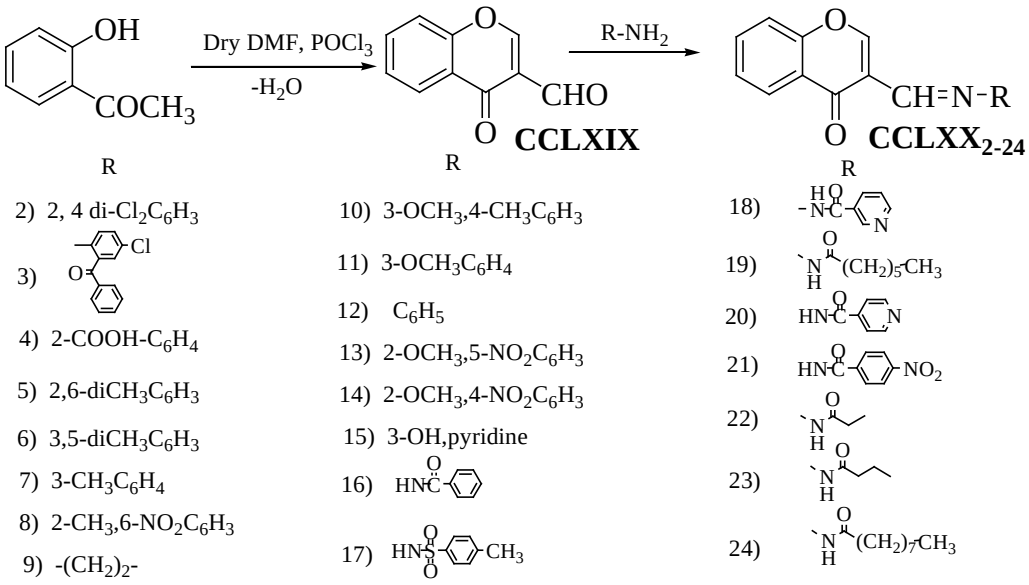
exhibited anti-inflammatory activity better then ibuprofen and diclofenac. Chandra *et. al.* [184] synthesized Schiff's bases containing syndone **CCLXVIIIa-k** and screened them



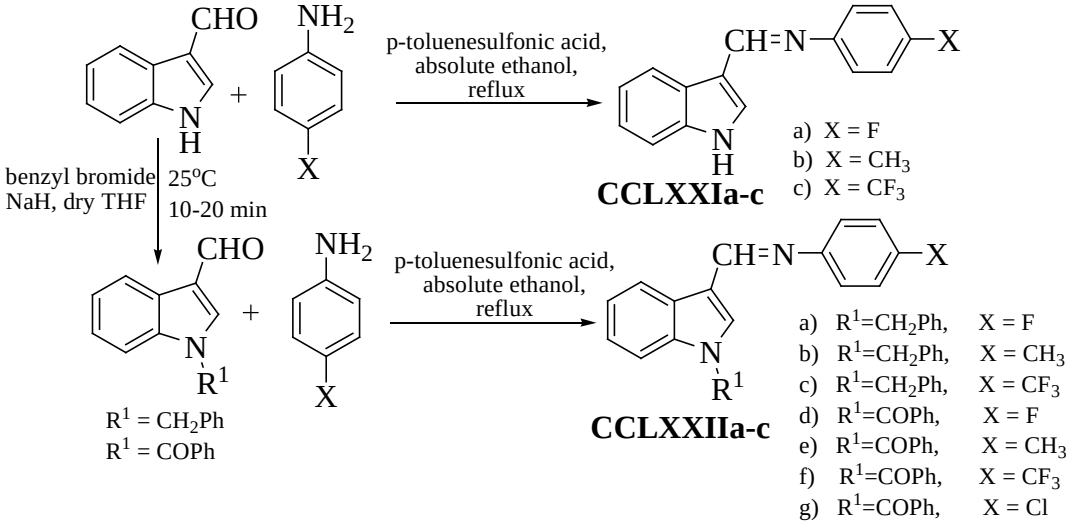

**CCLXVIIIa-k**

| | | |
|---|---|---|
| a | R=H | X=O |
| b | R=H | X=$CH_2$ |
| c | R=H | X=$NCH_3$ |
| d | R=H | X=$NC_2H_5$ |
| e | R=H | X=$NC_6H_5$ |
| f | R=$CH_3$ | X=O |
| g | R=$CH_3$ | X=$CH_2$ |
| h | R=$CH_3$ | X=$NCH_3$ |
| i | R=$CH_3$ | X=$NC_6H_5$ |
| j | R=$OCH_3$ | X=O |
| k | R=$OCH_3$ | X=$CH_2$ |

for anti-inflammatory and analgesic activities. Compounds **CCLXVIIIb** and **CCLXVIIIf** exhibited anti-inflammatory activity comparable to indomethacin. A number of chromone Schiff's bases **$CCLXX_{1\text{-}23}$** have been synthesized [185] by following reaction scheme mentioned below. All these compounds **$CCLXX_{2\text{-}24}$** were screened for anti-inflammatory activity. Compound **$CCLXX_{23}$** exhibited anti-inflammatory activity better than aspirin.



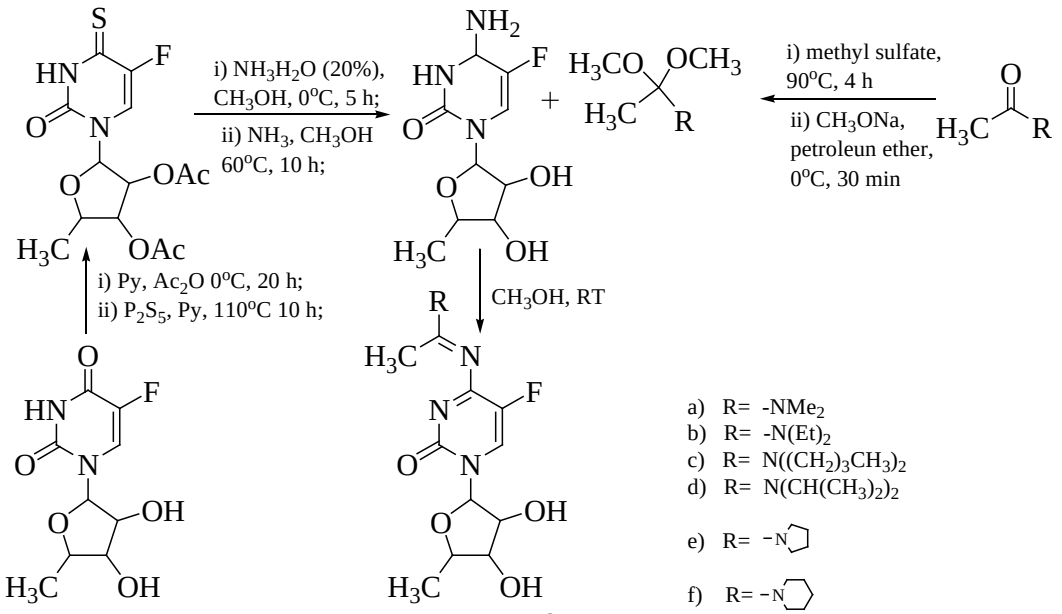

N-1 and C-3 substituted indole Schiff's bases **CCLXXIa-c** and **CCLXXIIa-g** have been synthesized [186] by following reaction sequence mentioned below. These compounds




were screened for inhibition activity of COX-1 and COX-2. Compound **CCLXXIIf** is selective COX-2 inhibitor in contrast to reference drug indomethacin which is a potent COX-1 inhibitor.

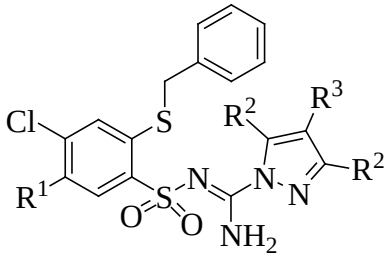
### *1b.4.2 As anticancer agents*:-

A number of amidine derivatives of doxifluridine **CCLXXIII** have been synthesized [187] by following reaction scheme mentioned below. Compound




**CCLXXIIIa-f**

**CCLXXIIIe** exhibited $IC_{50}$ value of 3.2 µM/L against A549 cells and is 16 times more potent than 5-Fu. A series of N´-(2-benzylthio-4-chlorobenzenesulfonyl)-1H-pyrazole-1-amidines **CCLXXIVa-n** exhibiting antitumor activity against leukemia, non-small cell, lung cancer, colon cancer, CNS cancer, melanoma, ovarian cancer, renal cancer, prostate



$R^1$= Me, 5-Ph-1,3,4-oxadiazole-2-yl, 5-(4-Cl-Ph)-1,3,4-oxadiazole-2-yl, 5-Ph-1,3,4-thiadiazole-2-yl, 5-(4-Cl-Ph)-1,3,4-thiadiazole-2-yl,

$R^2$= H, Me, Ph

$R^3$= H, Me, $(CH_2)_2COOEt$

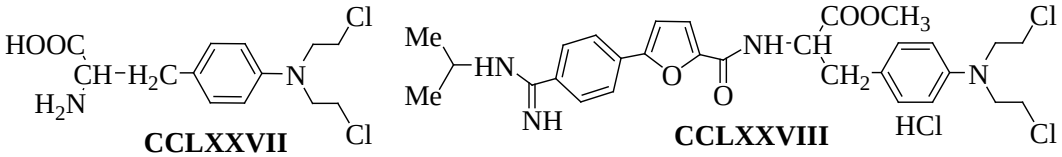
**CCLXXIVa-n**

cancer, breast cancer cell lines is reported in literature [188]. Usefulness of azole-amidines **CCLXXV**, **CCLXXVI** as modulators of indoleamine 2,3-dioxygenase and hence useful in the treatment of cancer, viral infection etc is disclosed in an international

**CCLXXV** **CCLXXVI**

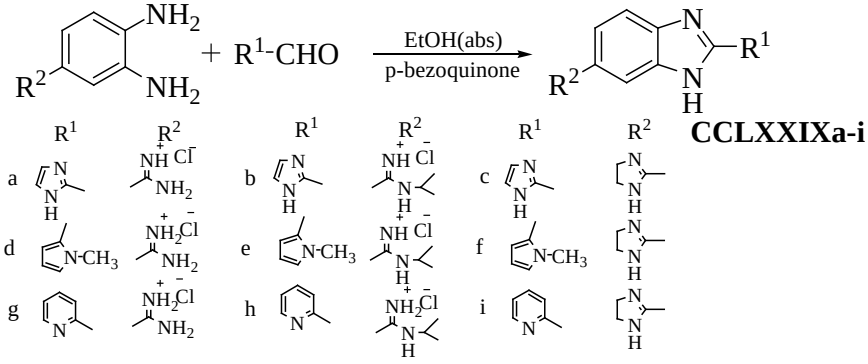
[T=O, S or NH; U, V, W=N or CH; L=bond, alkylene, alkenylene, etc.; A=aryl, cycloalkyl, heteroaryl, etc.; R=H C(O)$R^2$, C(O)$OR^3$, etc.; $R^1$=H or alkyl; $R^2$, $R^3$=H, alkyl, aryl, etc.; further details on T, U, V, and W are given]

patent [189]. Novel amidine analogs of melphalan are synthesized and reported in



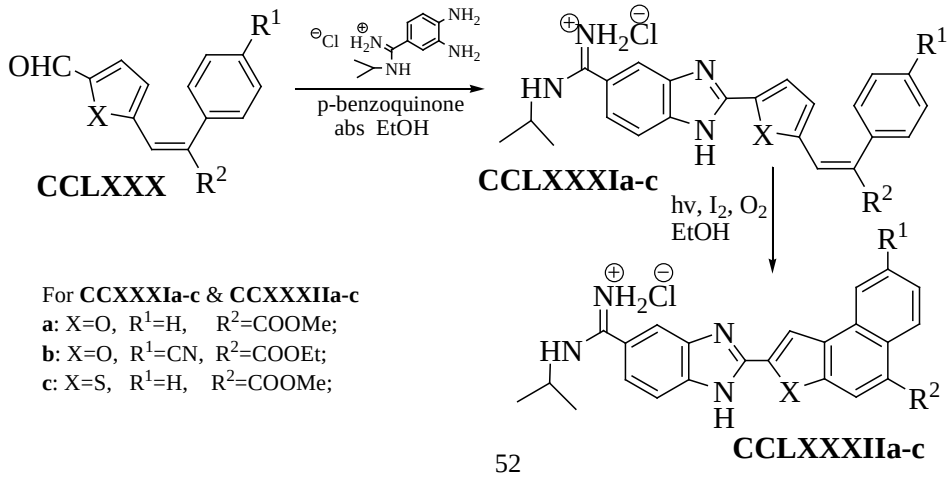
**CCLXXVII** **CCLXXVIII**

literature [190]. Amidine analog **CCLXXVIII** was found to be more cytotoxic than melphalan **CCLXXVII**. Starcevic *et. al.* [191] synthesized 2-substituted-5-amidino-benzimidazoles **CCLXXIXa-i** by following reaction scheme mentioned below. All these compounds were screened for antiviral and antitumor activities. Compounds **CCLXXIXa**



**CCLXXIXa-i**

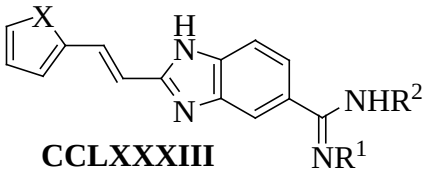
and **CCLXXIXb** exhibited good antitumor activity. Several amidino substituted benzimidazole derivatives **CCLXXXIa-c** and **CCLXXXIIa-c** have been synthesized and reported in literature [192]. Compounds **CCLXXXIa-c** and **CCLXXXIIa-c** exhibited antitumor activity against MCF-7 tumor cell lines and **CCLXXXIc** and **CCLXXXIIa-c** exhibited noticeable selectivity in regards to normal fibroblasts (WI 38). A number of



**CCLXXX** **CCLXXXIa-c** **CCLXXXIIa-c**

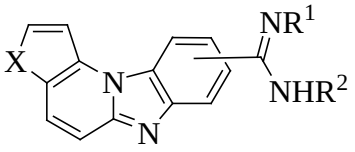
For **CCXXXIa-c** & **CCXXXIIa-c**
**a**: X=O, $R^1$=H, $R^2$=COOMe;
**b**: X=O, $R^1$=CN, $R^2$=COOEt;
**c**: X=S, $R^1$=H, $R^2$=COOMe;

bicyclic and tetracyclic amidino derivatives **CCLXXXIII** and **CCLXXXIV** have been synthesized [193]. DNA and RNA binding study and antitumor activity evaluation revealed that compounds bearing thiophene ring are more active than furan containing



**CCLXXXIII**

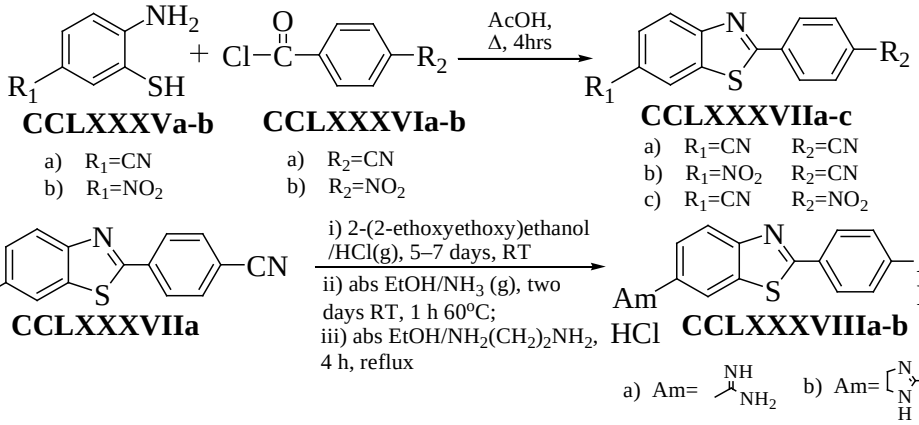
[X=O, S; $R^1$=H,$R^2$=H, $Me_2CH$, cyclohexhyl 4-morpholinyl; $R^1R^2$=$CH_2CH_2$]



**CCLXXXIV**

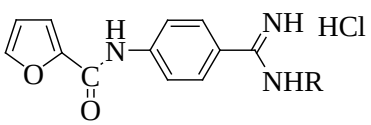
[X=S, O; $R^1R^2$= -$CH_2CH_2$-]

analogous. Several amidino and bis amidino derivatives have been synthesized [194] by following reaction scheme mentioned below. All amidino and bis amidino derivatives



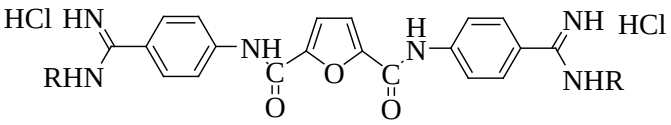

screened for antitumor activity against MOLT-4, HCT-116, SW-620, MCF-7 and H 460 cell lines. Except compound **CCLXXXVIIIa** all other compounds exhibited good tumor cell growth inhibitory activity and cytotoxcity. Compound **CCXCa** exhibited selectivity towards MCF-7 and H 460 cells. Jarak *et. al.* [195] synthesized several amidine and

bis amidine derivatives **CCXCIII-CCXCVI** and screened them against several human



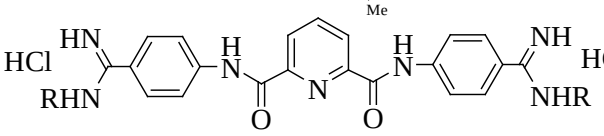
**CCXCIIIa,b**

a) R=H b) R= 



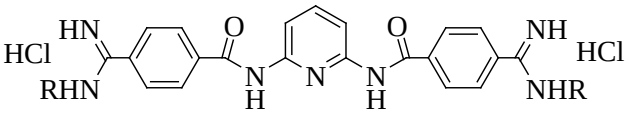
**CCXCIVa,b**

a) R=H b) R= 



**CCXCVa,b**

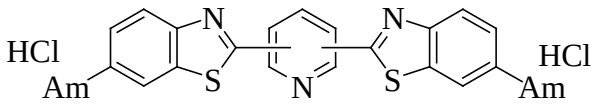
a) R=H b) R= 



**CCXCVIa,b**

a) R=H b) R= 

cancer cell lines. Compound **CCXCIVb** exhibited good antiproliferative activity against SW620 cell line ($IC_{50}$ 4µM). Bis amidine derivatives **CCXCVIIa-k** and **CCXCVIII** have been synthesized [196] and reported in literature. All these compounds were screened for MCF-7, SK-BR-3, SW620, MiaPaCa-2, BJ and HeLa cancer cell lines. Compound **CCXCVIIb** exhibited $IC_{50}$ 0.2 and 0.02 µM against SW-620 and BJ fibrobla-



**CCXCVIIa-k**

a) =  , Am= 

b) =  , Am= 

c) =  , Am= 

d) =  , Am= 

e) =  , Am= 

f) =  , Am= 

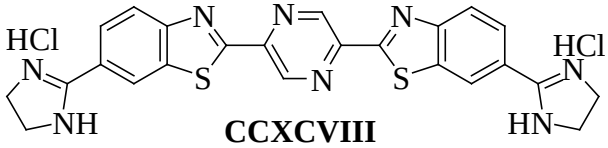
g) =  , Am= 

h) =  , Am= 

i) =  , Am= 

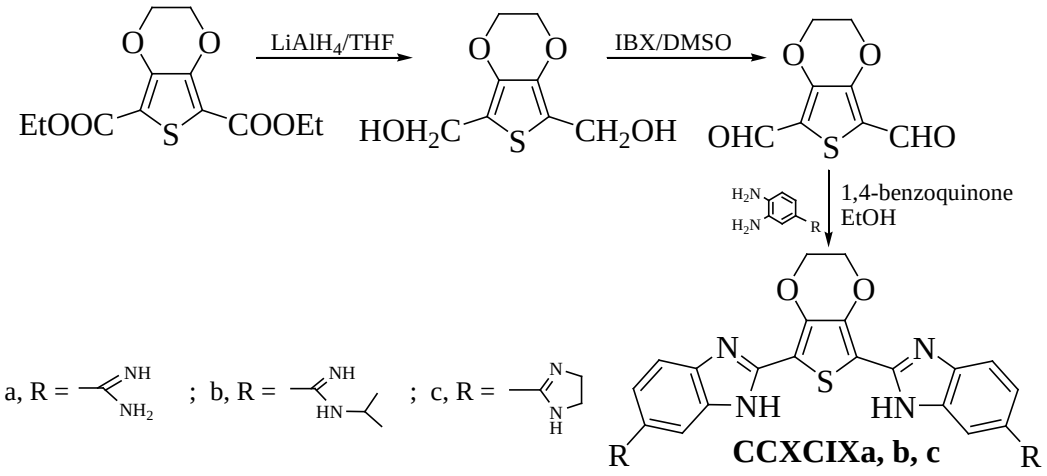
j) =  , Am= 

k) =  , Am= 

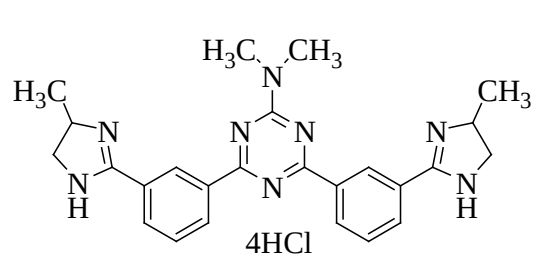


**CCXCVIII**

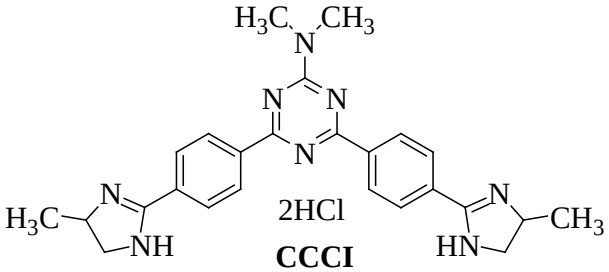
sts cell lines. Bisbenzimidazole amidines **CCXCIXa, b, c** were synthesized [197] by following reaction scheme mentioned below. These compounds exhibited moderate to strong antiproliferative effect towards a panel of eight carcinoma cell lines. Out of several polycationic compounds [198] screened for potential antitumor activity by NCI's in vitro



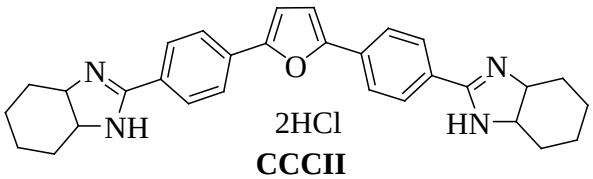

testing, compounds **CCC**, **CCCI**, **CCCII** and **CCCIII** exhibited $GI_{50}$ values of 1.9, 2.4, 1.9 and 15 μM respectively. However compound **CCCIII** possessed cytotoxic activity in nanomolar range against several cancer cell lines: CCRF-CEM, HL-60 (TB), MOLT-4, NCI-H522, COLO 205 and SF-268. Probable mode of action for anticancer activity is



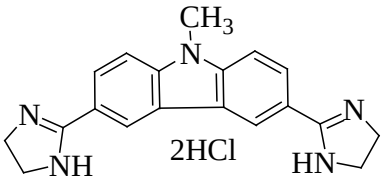

**CCC**




**CCCI**

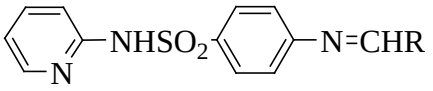



**CCCII**

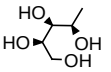


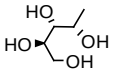

**CCCIII**

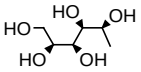
DNA minor groove binding. Several sulfonamide Schiff's bases **CCCIVa-c** and **CCCVa-e** have been synthesized [199] & some representative compounds were screened for antitumor activity against MCF-7 and HELA tumor cell lines. Compounds **CCCIVb** and **CCCVa, CCCVe** exhibited $IC_{50}$ values better than standard drug doxorubicin. In a

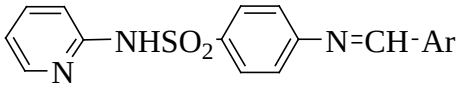


**CCCIVa-c**

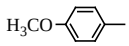
R= (a) 

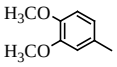
R= (b) 

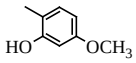
R= (c) 

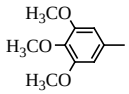


**CCCVa-e**

Ar = (a) 

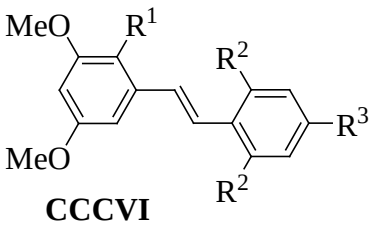
(b) 

(c) 

(d) 

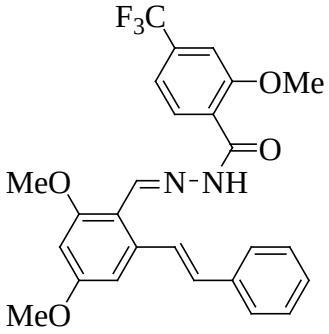
(e) 

Chinese patent Schiff's base and hydrazone derivatives **CCCVI** and **CCCVII** useful as antitumor, antioxidative and antibacterial agents is described [200]. A number of



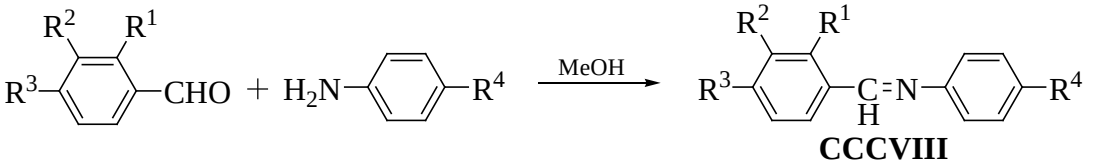
**CCCVI**

$R^1$ = Schiff base or benzoyl hydrazone
$R^2$ = H or Cl
$R^3$ = H or $NO_2$]



**CCCVII**

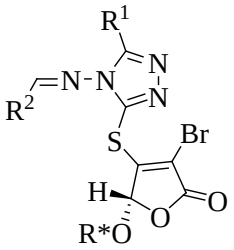
hydroxyl substituted Schiff's bases **CCCVIIIa-h** have been synthesized [201] by following reaction scheme mentioned below. Antiproliferative activity of **CCCVIIIa-h**



**CCCVIII**

| | $R^1$ | $R^2$ | $R^3$ | $R^4$ | | $R^1$ | $R^2$ | $R^3$ | $R^4$ | | $R^1$ | $R^2$ | $R^3$ | $R^4$ | | $R^1$ | $R^2$ | $R^3$ | $R^4$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| a | OH | H | H | H | c | H | H | H | OH | e | H | H | OH | $OCH_3$ | g | H | OH | OH | H |
| b | H | H | OH | H | d | H | $OCH_3$ | OH | H | f | H | H | OH | OH | h | H | OH | OH | OH |

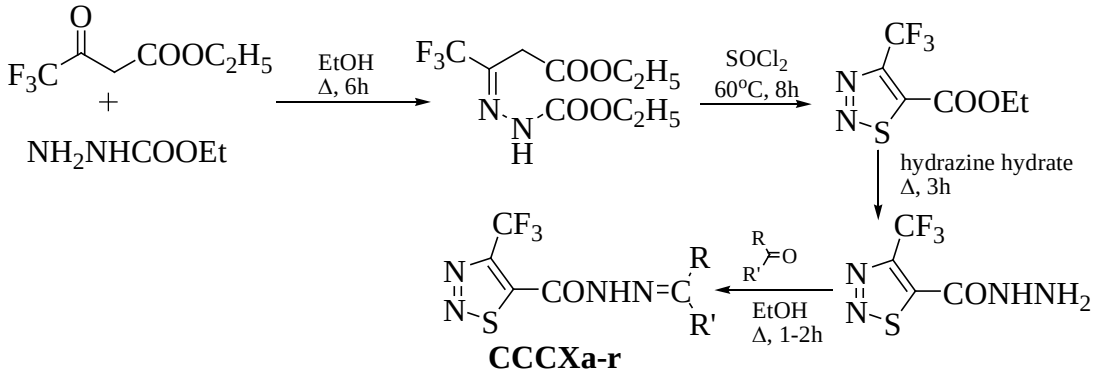
against HepG2 cell was determined and compounds **CCCVIIIg,h** exhibited antiproliferative activity comparable to that of VP-16 (etoposide). Li *et. al.* [202] synthesized chiral 1,2,4-triazole Schiff bases **CCCIXa-l** and screened them for in vitro anticancer activity against HeLa cell line. $IC_{50}$ value of **CCCIXl** was found to be 1.8 µM as compared to reference drug cisplatin which exhibited $IC_{50}$ value 2.6 µM. A series of 4-trifluoromethyl-(1,2,3)-thiadiazolo-5-carboxylic acid hydrazide Schiff's bases **CCCX**



| | $R^*$ | $R^1$ | $R^2$ | | $R^*$ | $R^1$ | $R^2$ |
|---|---|---|---|---|---|---|---|
| a | 1-menthyl | $C_6H_5$ | 4-Cl-$C_6H_4$ | g | 1-menthyl | $CH_3$ | 4-Cl-$C_6H_4$ |
| b | 1-menthyl | 4-$CH_3O$-$C_6H_4$ | 4-Cl-$C_6H_4$ | h | 1-menthyl | 4-OH-$C_6H_4$ | 4-$CH_3O$-$C_6H_4$ |
| c | 1-menthyl | $C_6H_5$ | 4-$O_2N$-$C_6H_4$ | i | 1-menthyl | $C_6H_5$ | 4-OH-$C_6H_4$ |
| d | 1-menthyl | 4-$CH_3O$-$C_6H_4$ | 4-$O_2N$-$C_6H_4$ | j | bornyl | $C_6H_5$ | 4-Cl-$C_6H_4$ |
| e | 1-menthyl | $C_6H_5$ | 2-furanl | k | bornyl | 4-OH-$C_6H_4$ | 4-$CH_3O$-$C_6H_4$ |
| f | 1-menthyl | 4-$CH_3O$-$C_6H_4$ | 2-furanl | l | bornyl | $CH_3$ | 2-OH-$C_6H_4$ |

**CCCIXa-l**

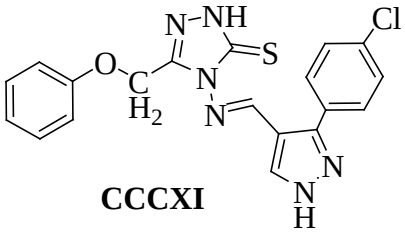
have been synthesized [203] by following reaction scheme mentioned below. All the compounds were screened for cytotoxic activity against breast carcinoma cells MDA-MB 231 (aggressive) and MCF-7 (non-aggressive). Doxorubicin was used as reference drug. None of the compound exhibited cytotoxic activity comparable to doxorubicin. Out of



**CCCXa-r**

| | R | R' | | R | R' | | R | R' |
|---|---|---|---|---|---|---|---|---|
| a | H | $C_6H_5$ | g | H | 4-OH-$C_6H_4$ | m | $CH_3$ | 2,4-Br2-$C_6H_3$ |
| b | H | 4-F-$C_6H_4$ | h | H | 4-OMe-$C_6H_4$ | n | $CH_3$ | Pyridine-2-yl |
| c | H | 4-Cl-$C_6H_4$ | i | H | Furan-2-yl | o | $CH_3$ | $CH_3$ |
| d | H | 4-Br-$C_6H_4$ | j | H | Thiophene-2-yl | p | (R, R'=)-$CH_2(CH_2)_2CH_2$- | |
| e | H | 4-$NO_2$-$C_6H_4$ | k | $CH_3$ | $C_6H_5$ | q | (R, R'=)-$CH_2(CH_2)_3CH_2$- | |
| f | H | 4-$N(Me)_2$-$C_6H_4$ | l | $CH_3$ | 4-$NO_2$-$C_6H_4$ | r | (R, R'=)-$CH_2(CH_2)_4CH_2$- | |

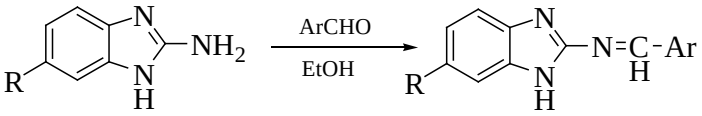
several new Schiff's bases and Mannich bases synthesized [204] and screened for cytotoxic activity against HepG2 cell line, compound **CCCXI** exhibited $IC_{50}$ value of



**CCCXI**

0.018 g/l which is comparable to the standard drug doxorubicin. Hranjec *et. al.* [205] synthesized benzimidazole substituted Schiff's bases **CCCXIII** by following reaction

scheme mentioned below. All these Schiff's bases were screened for cancer cell lines



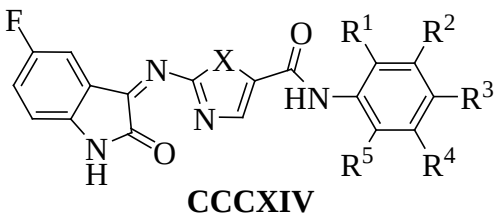

**CCCXIIa-d** **CCCXIIIa-n**

| | R |
|---|---|
| a | CN |
| b | $CH_3$ |
| c | $NO_2$ |
| d | H |

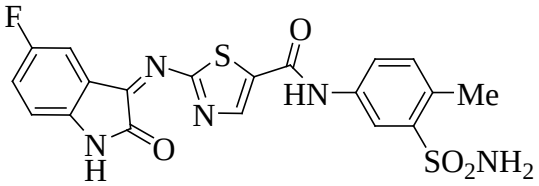
| | R | Ar |
|---|---|---|
| a | H | pyridyl |
| b | H | 1-methylpyrrolyl |
| c | CN | furyl |
| d | $CH_3$ | furyl |
| e | CN | thienyl |
| f | $CH_3$ | thienyl |
| g | $NO_2$ | thienyl |

| | R | Ar |
|---|---|---|
| h | CN | 4-$N(Me)_2$-phenyl |
| i | $CH_3$ | 4-$N(Me)_2$-phenyl |
| j | $NO_2$ | 4-$N(Me)_2$-phenyl |
| k | CN | 2-HO-4-$N(Et)_2$-phenyl |
| l | $CH_3$ | 2-HO-4-$N(Et)_2$-phenyl |
| m | $NO_2$ | 2-HO-4-$N(Et)_2$-phenyl |
| n | H | 2-HO-4-$N(Et)_2$-phenyl |

HeLa, MCF-7, SW-620, MiaPaCa-2 and normal human fibroblasts WI38. Compounds **CCCXIIIk** and **CCCXIIIl** exerted strongest non specific antiproliferative effect on all the cell lines but these compounds are highly cytotoxic on human fibroblasts. Usefulness of Schiff bases **CCCXIV** for the treatment of tumor, diabetes, mellitus, dermatitis, or rheumatic arthritis is described in a Chinese patent [206]. Thus compound **CCCXV** exhibited $IC_{50}$ value of 4.5, 3.1, and 7.1 µM against human MDA-MB-435, HT-29 and BGC-823 cancer cell lines respectively. A series of pyranothiazole-Schiff's bases



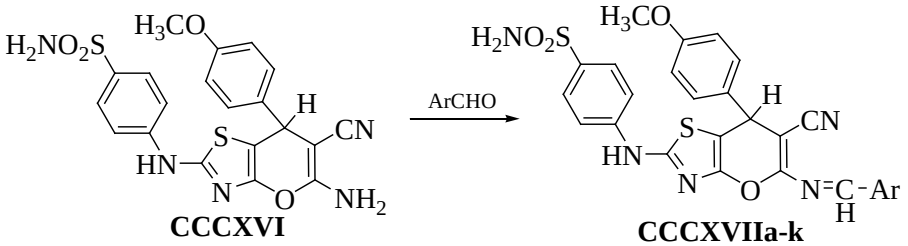
**CCCXIV**



**CCCXV**

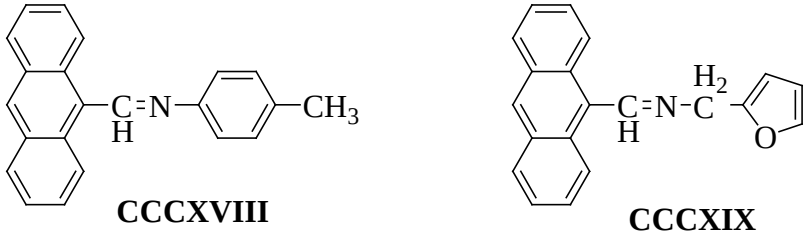
[$R^1$-$R^5$ = independently halo, aminosulfonyl, nitro, H, (un)substituted alkyl, or alkoxy; X = S or NH, pharmaceutically acceptable salts, or solvates thereof]

**CCCXVIIa-k** have been synthesized [207] by following reaction scheme mentioned below. All these compounds were screened against human breast cancer cell line MCF-7. Compounds **CCCXVI** and **CCCXVIIb-d, g** exhibited $IC_{50}$ value 27.51, 10.25, 9.55, 9.39 and 9.70 µM respectively as compared to reference drug doxorubicin having $IC_{50}$ 32.00



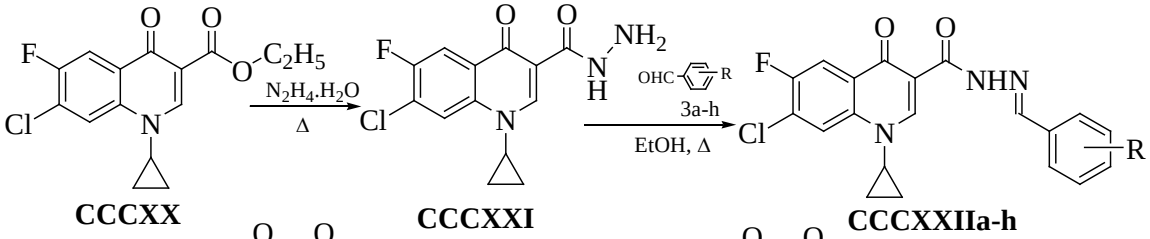

| | Ar | | Ar | | Ar | | Ar |
|---|---|---|---|---|---|---|---|
| a | $C_6H_5$ | d | 3-($C_6H_4$)Br | g | 4-($C_6H_4$)$NO_2$ | j | 4-($C_6H_4$)OH |
| b | 2-($C_6H_4$)Cl | e | 4-($C_6H_4$)F | h | 4-($C_6H_4$)$N(CH_3)_2$ | k | piperonyl |
| c | 4-($C_6H_4$)Cl | f | 2,4-($C_6H_3$)$Cl_2$ | i | CH=CH-$C_6H_5$ | | |

µM. Anthracene derived Schiff's bases **CCCXVIII** and **CCCXIX** exhibited potent antiproliferative activity against colon carcinoma cell line HT-29 and HBL-100 & HT-29




**CCCXVIII** **CCCXIX**

tumor cell lines respectively [208]. Several mono and bis Schiff bases **CCCXXIVa-h** and **CCCXXIIa-h** have been synthesized [209] and screened for antitumor activity against




**CCCXX** **CCCXXI** **CCCXXIIa-h**

**CCCXXIII** **CCCXXIVa-h**

R is same for **CCCXXIIa-h** & **CCCXXIVa-h**

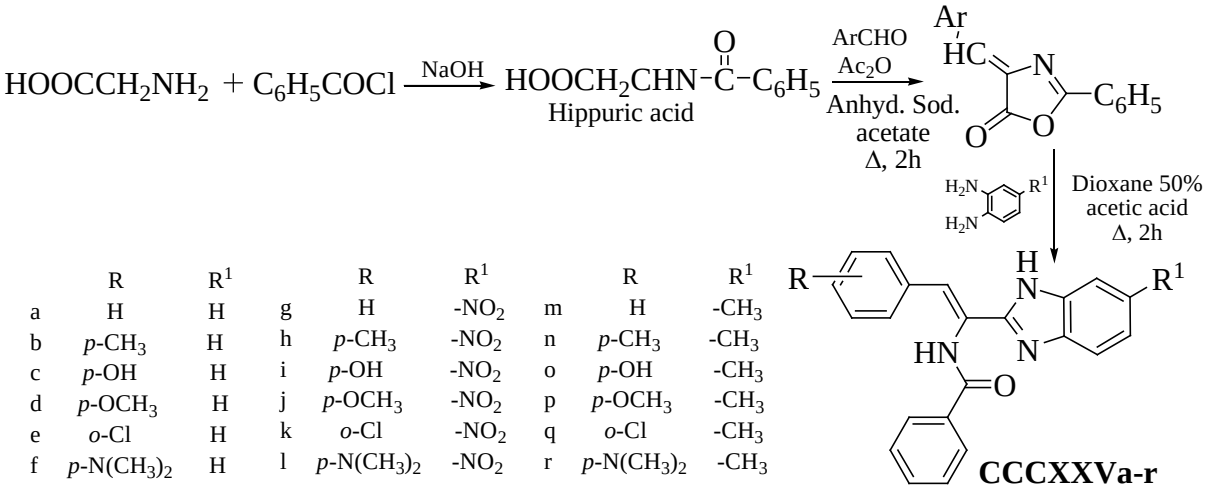
| | R | | R | | R | | R |
|---|---|---|---|---|---|---|---|
| a | H | b | OH | c | 4-$CH_3O$ | d | 3, 4-$OCH_2O$ |
| e | 3,4,5-$(CH_3O)_3$ | f | 3-OH-4-$CH_3O$ | g | 4-F | h | 4-$NO_2$ |

CHO (Chinese hamster ovary), HL-60 (human leukemia) and L1210 (murine leukemia) cells. Both mono & bis Schiff's bases have $IC_{50}$ value with in 25.0 µmol. Activity of bis Schiff bases **CCCXXIIa-h** against L1210 is better than mono Schiff's bases **CCCXXIVa-h.**

## 1b.5 Benzimidazole and piperazine derivatives

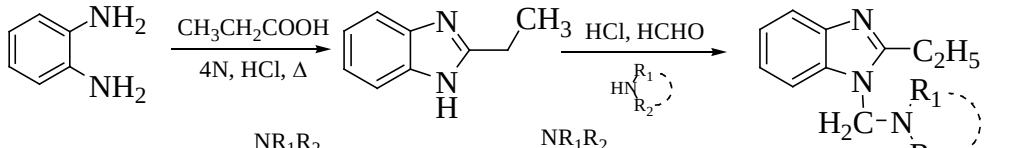
### *1b.5.1 As anti-inflammatory agents:*

Several benzimidazole derivatives **CCCXXVa-r** have been synthesized [210] by following reaction scheme mentioned below. Anti-inflammatory activity evaluation of these compounds show that compounds **CCCXXVb** and **CCCXXVk** are almost



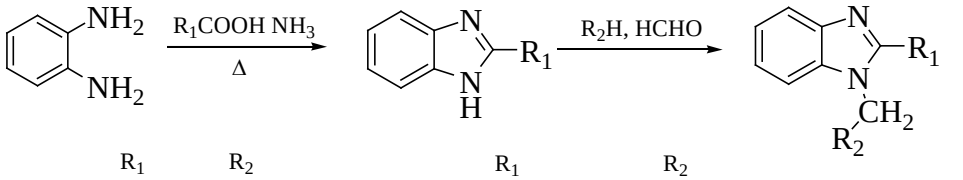

| | R | $R^1$ | | R | $R^1$ | | R | $R^1$ |
|---|---|---|---|---|---|---|---|---|
| a | H | H | g | H | $-NO_2$ | m | H | $-CH_3$ |
| b | *p*-$CH_3$ | H | h | *p*-$CH_3$ | $-NO_2$ | n | *p*-$CH_3$ | $-CH_3$ |
| c | *p*-OH | H | i | *p*-OH | $-NO_2$ | o | *p*-OH | $-CH_3$ |
| d | *p*-$OCH_3$ | H | j | *p*-$OCH_3$ | $-NO_2$ | p | *p*-$OCH_3$ | $-CH_3$ |
| e | *o*-Cl | H | k | *o*-Cl | $-NO_2$ | q | *o*-Cl | $-CH_3$ |
| f | *p*-$N(CH_3)_2$ | H | l | *p*-$N(CH_3)_2$ | $-NO_2$ | r | *p*-$N(CH_3)_2$ | $-CH_3$ |

equipotent to refrenence drug indomethacin. Mariappan *et. al.* [211] synthesized benzimidazole derivatives **CCCXXVIa-j** by following reaction scheme mentioned below and screened them for anti-inflammatory activity. All these compounds exhibited




| | $NR_1R_2$ | | $NR_1R_2$ |
|---|---|---|---|
| a | diethylamino | f | 3-chiloroanilino |
| b | piperidino | g | 2,3-dichiloroanilino |
| c | morpholino | h | 3,4-dichiloroanilino |
| d | diethanolamino | i | 4-fluroanilino |
| e | 2-chiloroanilino | j | 4-bromoanilino |

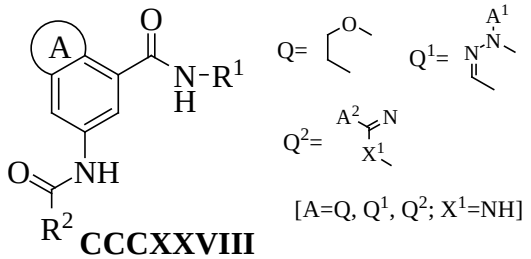
moderate anti-inflammatory activity. Several benzimidazole derivatives **CCCXXVIIa-f** have been synthesized [212] and screened for anti-inflammatory activity. Compound **CCCXXVIIf** exhibited anti-inflammatory activity comparable to reference drug dichlofenac. In an international patent [213] synthesis of benzimidazole-3 carboxamide, 2,3- dihydrobenzofuran-7-carboxamide, indazole-7-carboxamide, and 1,3-benzoxazole-4-




| | $R_1$ | $R_2$ | | $R_1$ | $R_2$ |
|---|---|---|---|---|---|
| a | H | $-N(Me)_2$ | d | -CH=CH-Ph | $-N(Et)_2$ |
| b | H | $-N(Et)_2$ | e | -CH=CH-Ph | $-N$ |
| c | $CH_3$ | $-N(C_6H_5)_2$ | f | -CH=CH-Ph | $-N$O |

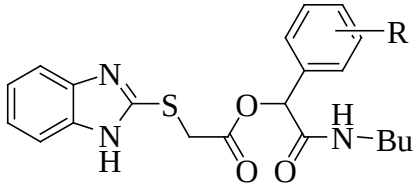
**CCCXXVIIa-f**

carboxamide derivatives **CCCXXVIII** useful in the treatment of rheumatoid arthritis, osteoarthritis, low back pain, overactive bladder, malignancy, neurodegenerative disease etc is described. Synthesis of benzimidazole derivatives **CCCXXIXa,b** possessing potent




**CCCXXVIII**

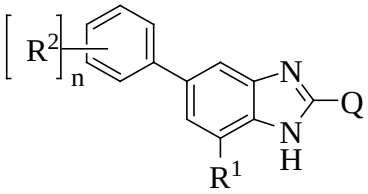
[A=Q, $Q^1$, $Q^2$; $X^1$=NH]




**CCCXXIX**

[a, R= 2-Cl, b, R= 4-Cl]

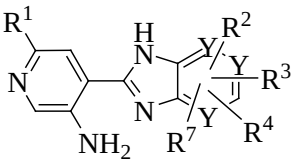
anti-inflammatory activity is reported in literature [214]. In a US patent synthesis of benzimidazole derivatives **CCCXXX** useful for the treatment of inflammatory pain, inflammatory hyperalgesia, cardiovascular disease etc is disclosed [215]. Calderini




**CCCXXX**

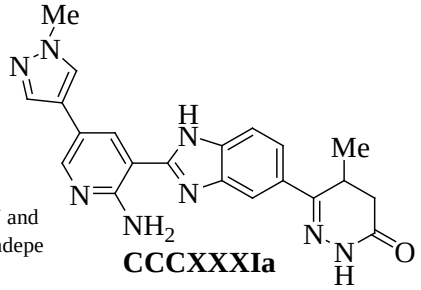
[$R^1$ = H, Cl, Me, $CF_3$; n = 0-2; $R^2$ = independently at each occurrence F, alkyl, alkoxy, etc.; Q = substituted furan-3-yl, isoxazol-5-yl, 2-methyl-6, 6-spirocyclohexyl-2,4,5,6-tetrahydrocyclopentapyrazol-3-yl, 2,6,6-trime thyl-2,4,5,6-tetrahydrocyclopentapyrazol-3-yl, etc.]

*et. al.* [216] synthesized aminopyridine benzimidazole and imidazopyridine derivatives **CCCXXXI** which are PDK1 inhibitors and hence useful in the treatment of inflammatory diseases. $IC_{50}$ value of **CCCXXXIa** for PDK-1 inhibitory activity was found to be in the range of 1nM to 10µM. Benzimidazole derivatives **CCCXXXIa** which are COT Kinase inhibitors and hence useful in the treatment of inflammation, cancer and other diseases is



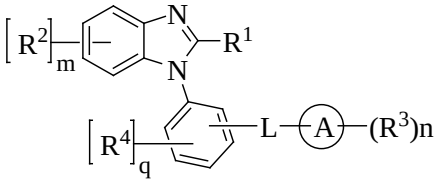
**CCCXXXI**

[$R^1$ is (un)substituted (un)satd. heterocycle; each Y is independently N and C, provided that no more than two of Y are N; $R^2$, $R^3$, $R^4$ and $R^7$ are indepe ndently H, halo, $NO_2$, CN, etc.; and pharmaceutically acceptable salts]



**CCCXXXIa**

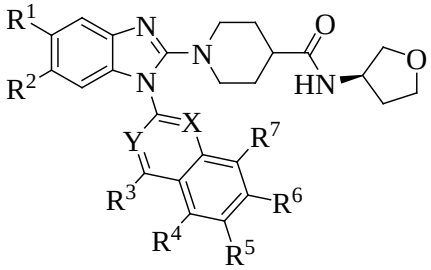
synthesized and reported in literature [217]. In an international patent synthesis of piperidinyl benzimidazole derivatives **CCCXXXIII** is described [218]. These



**CCCXXXII**

[A is $C_{6-14}$aryl, 5-14 membered heteroaryl or 3-15 membered heterocyclyl; L is a bond, O or C(O); $R^{2a}$ is -COOH, (un)sub stituted $C_{6-14}$ aryl, etc.; $R^{2b}$ is hydrogen, halogen, nitro, etc.; $R^3$, at each occurrence,is independently halogen, cyano, hydr oxy, etc.; $R^4$, at each occurrence,is independently halogen, cyano, hydroxy or (un)substituted $C_{1-8}$-alkyl; n = 0-5; q = 0-4 or pharmaceutically acceptable salts thereof]

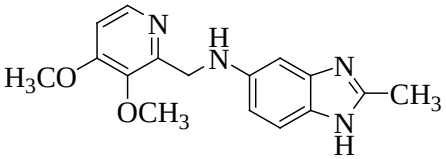
derivatives are mPGEs-1 inhibitors and hence are useful for the treatment of inflammatory diseases, pain auto immune disease, breathing disorders, fever, cancer, inflammation related anorexia over active bladder etc. A number of benzimidazole



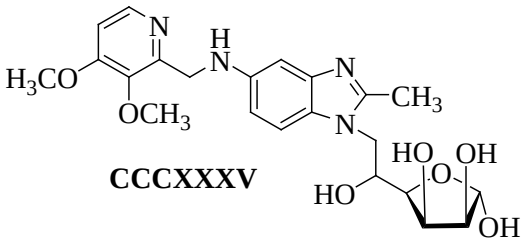
**CCCXXXIII**

[$R^1$ and $R^2$ independently = Me and chlorine; $R^{3-7}$ independently = H, fluorine, chlorine, or alkyl; X = N or CH; Y = N or CH, and their pharmaceutically acceptable salts]

derivatives have been synthesized [219] and screened for anti-inflammatory activity. Compounds **CCCXXXIV** and **CCCXXXV** exhibited anti-inflammatory activity comparable to diclofenac. Anti-inflammatory activity of **CCCXXXIV** and **CCCXXXV** is not only free from any side effects on the gastric mucosa but also showed significant

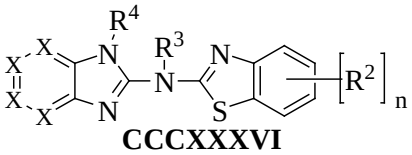


**CCCXXXIV**

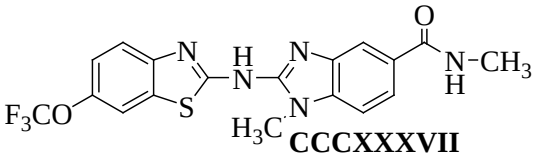


**CCCXXXV**

anti ulcerogenic activity. In a US patent synthesis [220] of benzimidazole derivatives **CCCXXXVI** as HMOX1 modulator and hence useful for the treatment of inflammatory diseases is described. Compound **CCCXXXVII** exhibited HMOX1 modulatory activity



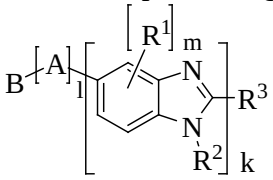
**CCCXXXVI**



**CCCXXXVII**

[one of X is C-L-G and the remaining X are independently N and $CR^1$; G is H, (un)substituted $C_{1-8}$ alkyl, (un)substituted $C_{3-10}$ cycloalkyl, etc.; L is CONH and derivs., $SO_2$, CO, etc.; $R^1$ is H, halo, (un)substituted Ph, etc.; each $R^2$ is independen tly halo, (un)substituted $C_{1-6}$ alkyl, (un)substituted $C_{3-10}$ cycloalkyl, etc.; $R^3$ is H, (un)substituted $C_{1-6}$ alkyl and (un)substi tuted $C_{1-6}$ alkylene-$C_{3-10}$ cycloalkyl; $R^4$ is (un)substituted $C_{1-6}$ alkyl and (un)substituted $C_{1-6}$ alkylene-$C_{3-10}$]

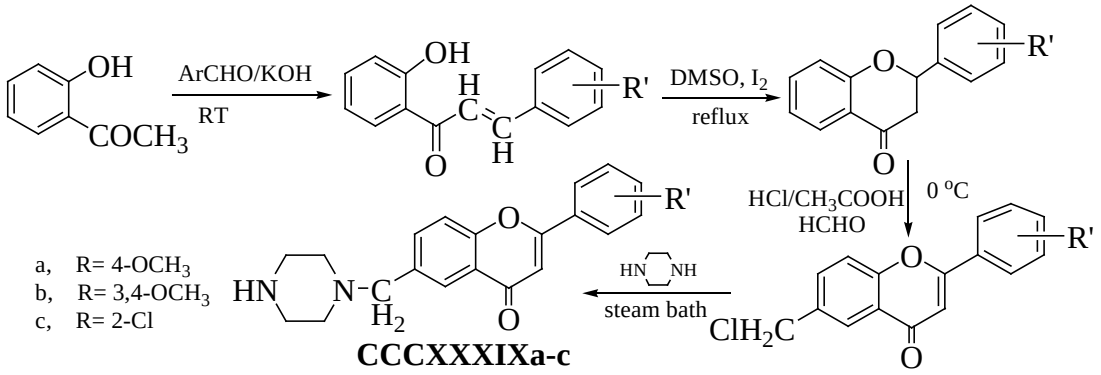
which is 19.37 fold induction at 5 µM. Usefulness of benzimidazole derivatives **CCCXXXVIII** for preventing or treating an inflammatory diseases is disclosed in an



**CCCXXXVIII**

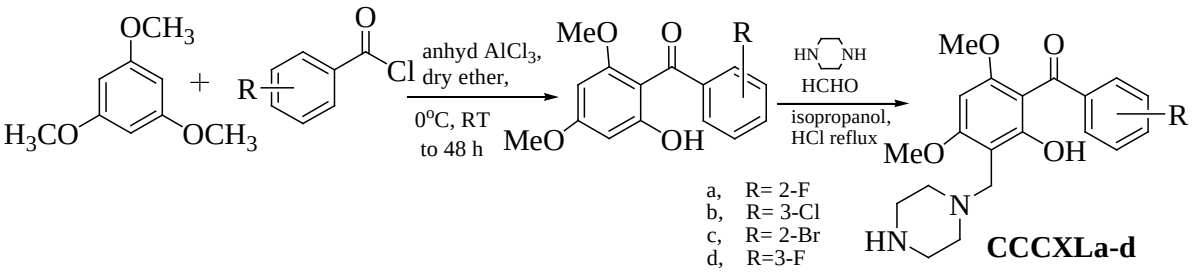
[A = phenylene, NHC(O), C(O)NH, etc.; B = (un)substituted alkyl, aryl, heteroaryl, etc.; k = 0-1; l = 0-1; m = 0-3; $R^1$ = halo, alkyl, alkoxy, $CO_2H$; $R^2$ = H, alkyl; $R^3$ = (un)substituted $NH_2$, aryl, heteroaryl]

international patent [221]. Hasan *et. al.* [222] synthesized 6-piperazino-2-aryl-1-benzopyran-4-one derivatives **CCCXXXIX** by the following reaction scheme mentioned

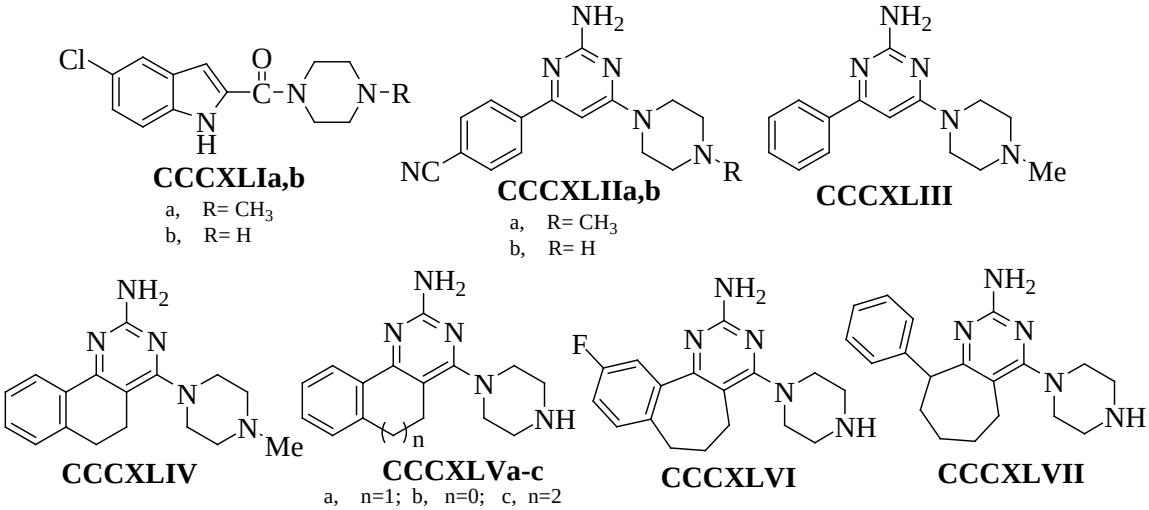



**CCCXXXIXa-c**

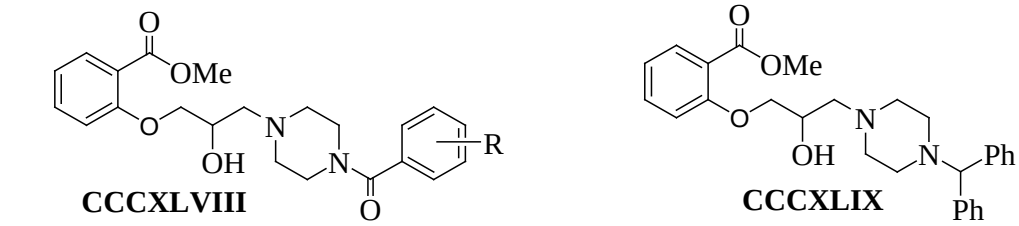
below. All these compounds exhibited good anti-inflammatory activity. Several benzophenone derivatives **CCCXLa-d** containing piperazine moiety have been synthesized [223] and screened for inhibition of pro-inflammatory cytokines, TNF-α and IL-6. Compound **CCCXLd** exhibited good TNF-α (54%) and IL-6 (97%) inhibition activity at 10 µM concentration. A number of piperazine containing heterocyclic



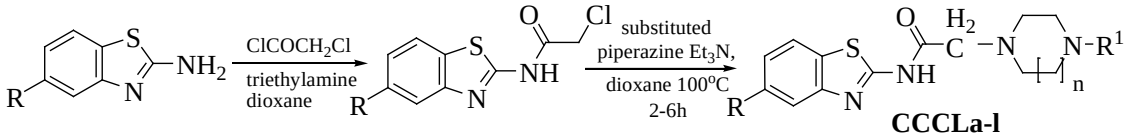

compounds **CCCXLI-CCCXLVII** possessing good in vivo anti-inflammatory activity have been synthesized and reported in literature [224]. In a Chinese patent [225]




synthesis of methyl salicylate-piperazine derivatives **CCCXLVIII** useful as anti-inflammatory agents is disclosed, thus compound **CCCXLIX** exhibited 89.29%



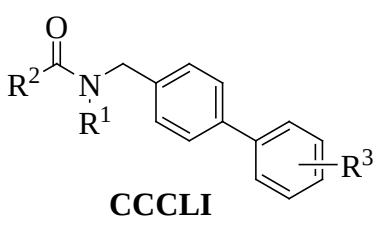

inhibition activity. Raghavendra *et. al.* [226] synthesized N-(benzo[d]thiazol-2-yl)-2-(piperazin-1-yl)acetamide derivatives **CCCLa-l** by following reaction scheme mentioned below. Anti-inflammatory activity screening reveals that compound **CCCLa** possess promising activity. Usefulness of biphenyl derivatives **CCCLI** for the treatment of dermatitis, allergy and inflammation is described in an international patent [227].



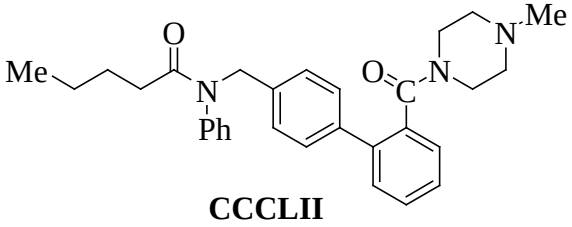

**CCCLa-l**

| | R | $R^1$ | n | | R | $R^1$ | n | | R | $R^1$ | n | | R | $R^1$ | n |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| a | H | H | 1 | d | H | $C_6H_5$ | 1 | g | $OCH_3$ | H | 2 | j | $NO_2$ | $C_2H_5$ | 1 |
| b | H | $C_2H_5$ | 1 | e | $OCH_3$ | H | 1 | h | $OCH_3$ | $C_6H_5$ | 1 | k | $NO_2$ | H | 2 |
| c | H | H | 2 | f | $OCH_3$ | $C_2H_5$ | 1 | i | $NO_2$ | H | 1 | l | $NO_2$ | $C_6H_5$ | 1 |

Compound **CCCLII** promote phagocytic action, suppress chemotaxis of macrophages and have anti-inflammatory activity. Out of several piperazine derivatives synthesized



**CCCLI**

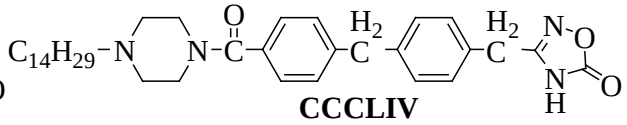


**CCCLII**

[$R^1$ = Ph or halo-substituted phenyl; $R^2$ = alkyl; $R^3$ = heteroaryl or -CO-A; A = OH, alkyl or (un)substituted heteroaryl; or pharmaceutically acceptable salts therof]

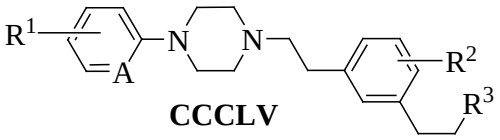
[228] and screened for anti-inflammatory activity, compounds **CCCLIII** & **CCCLIV** exhibited anti-inflammatory activity comparable to indomethacin. Synthesis of

**CCCLIII**



**CCCLIV**

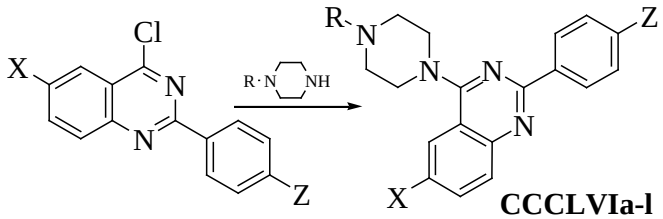
phenyl-alkyl-piperazines **CCCLV** useful for treating joint pain and inflammation is described in an international patent [229]. 2-(4-Substituted- phenyl)-4-(4-substituted



**CCCLV**

[$R^1$, $R^2$ = independently H, halo, alkyl, haloalkyl, perfluoroalkyl, alkoxy, perfluoroalkoxy; $R^3$ = alkyl; A = :CH, :N]

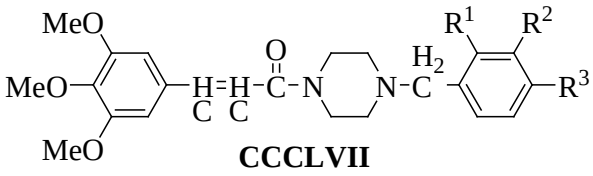
piperazino)-6-substituted quinazoline derivatives **CCCLVIa-l** have been synthesized [230] by following reaction scheme mentioned below. On screening for anti-



**CCCLVIa-l**

| | X | Z | R | | X | Z | R |
|---|---|---|---|---|---|---|---|
| a | H | H | Me | g | H | Cl | Me |
| b | H | H | Ph | h | H | Cl | Ph |
| c | Br | H | Me | i | Br | Cl | Me |
| d | Br | H | Ph | j | Br | Cl | Ph |
| e | I | H | Me | k | I | Cl | Me |
| f | I | H | Ph | l | I | Cl | Ph |

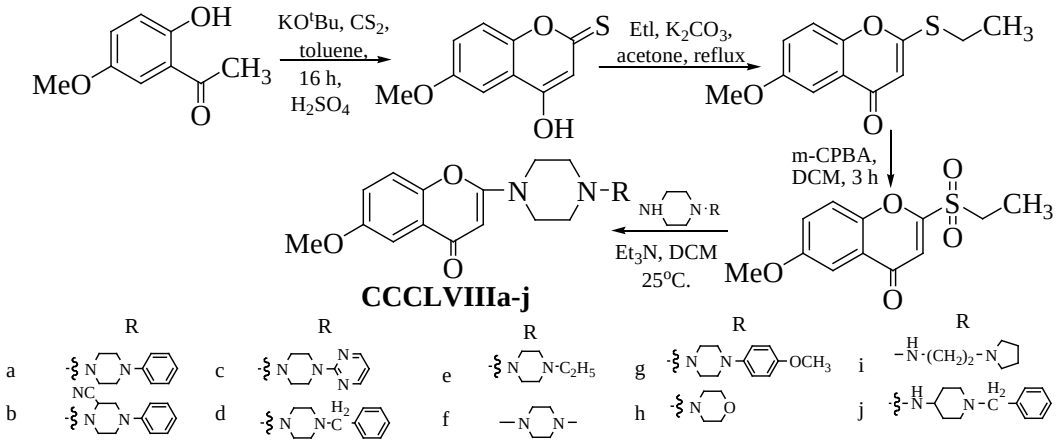
inflammatory activity compound **CCCLVIb** exhibited anti-inflammatory activity comparable to indomethacin. Synthesis of 1-sinapinoyl-4-benzylpiperazine derivatives **CCCLVII** and their usefulness as radical scavengers & anti-inflammatory agents

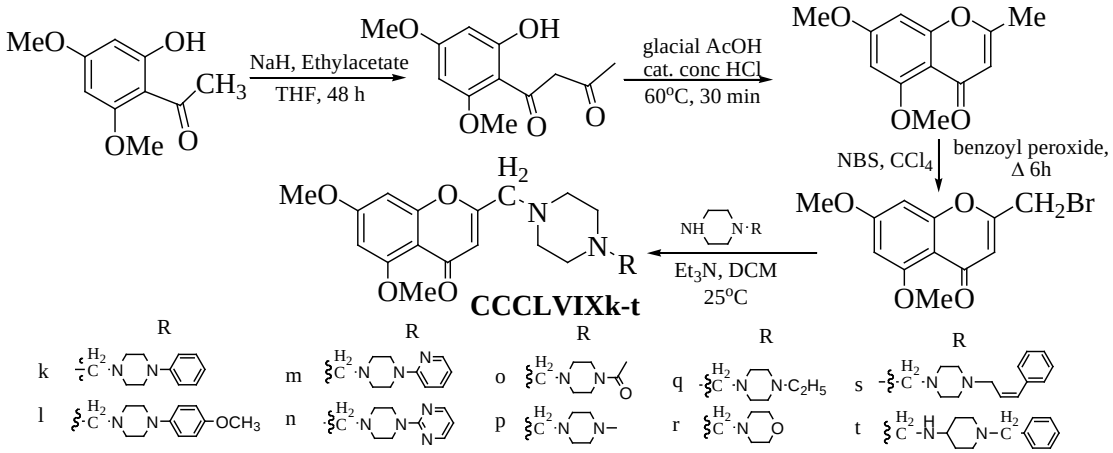



**CCCLVII**

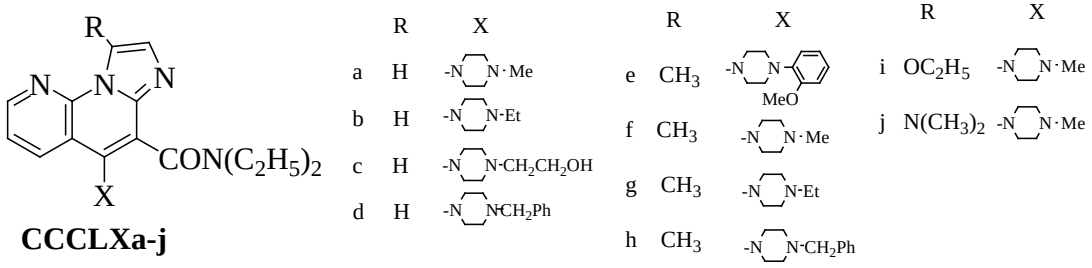
[$R^1$ = H, alkyl, alkoxy, or halogen;
$R^2$ = H, alkyl, alkoxy, or halogen;
$R^3$ = H, alkyl, alkoxy, or halogen]

is disclosed in a Chinese patent [231]. Hatnapure *et. al.* [232] synthesized two series of piperazine derivatives of flavone by following reaction scheme mentioned below. All these compound i.e. **CCCLVIIIa-j** and **CCCLIXk-t** were screened for pro-



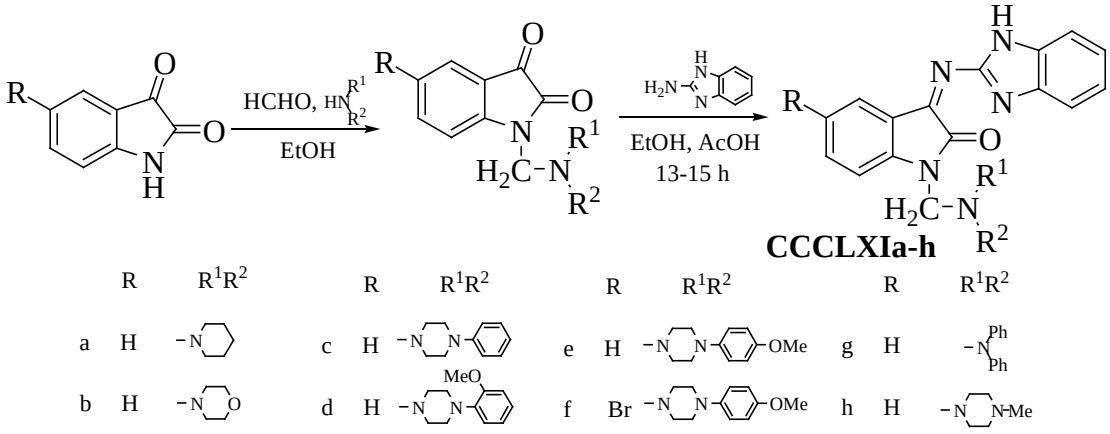



inflammatory cytokines (TNF-α and IL-6) activity. Compounds **CCCLVIIIc, g, h** and **CCCLIXl**,**m,n,r** exhibited promising anti-inflammatory activity (up to 65-87% TNF-α and 70-93% IL-6 inhibitory activity) at 10 μM concentration whereas dexamethasone (71% TNF-α and 84% IL-6 inhibitory activity) at 1 μM concentration. Several naphthyridine derivatives with piperazine moiety as substituent **CCCLXa-j** have been synthesized [233] and screened for anti-inflammatory activity. Compounds **CCCLXd,e,i** exhibited moderate anti-inflammatory activity whereas other derivatives were found to be inactive.



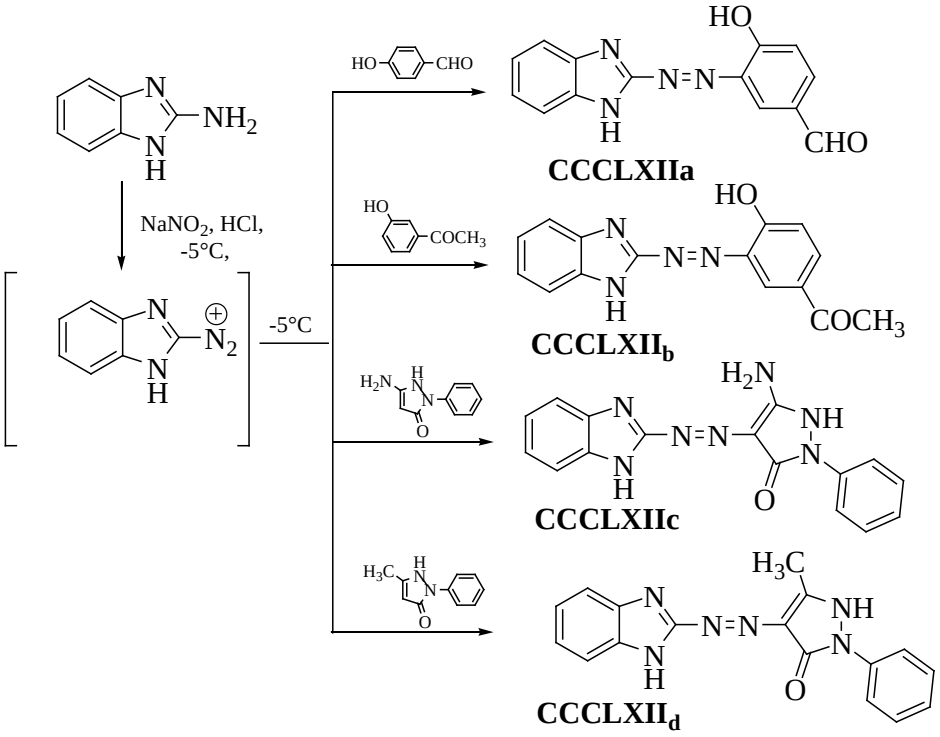

***1b.5.2 As anticancer agents*:-**

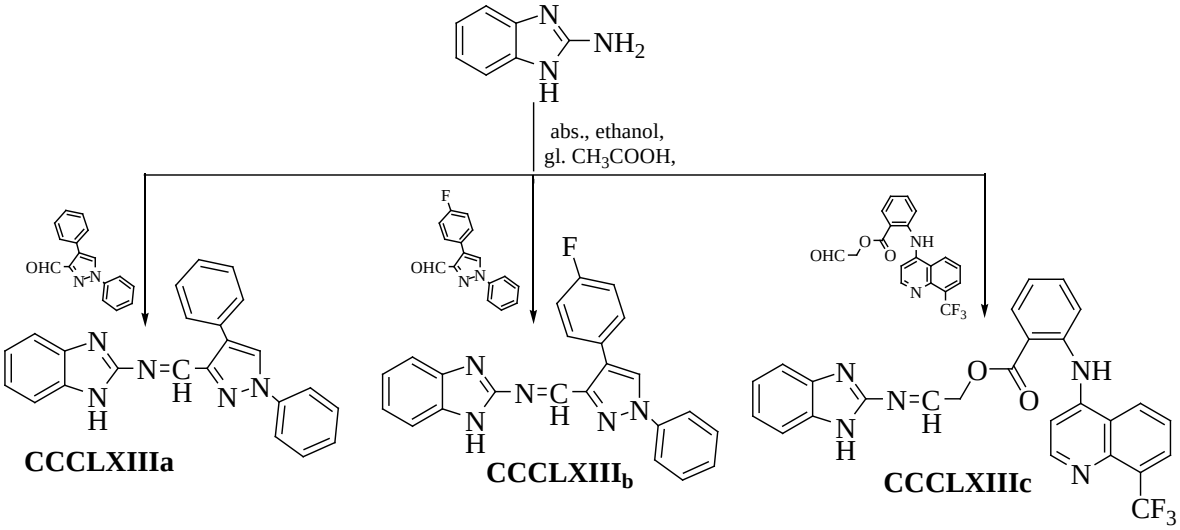
A number of benzimidazole derivatives **CCCLXIa-h** have been synthesized [234] by following reaction scheme mentioned below. Compounds **CCCLXIa,b,c,d,e,j** were

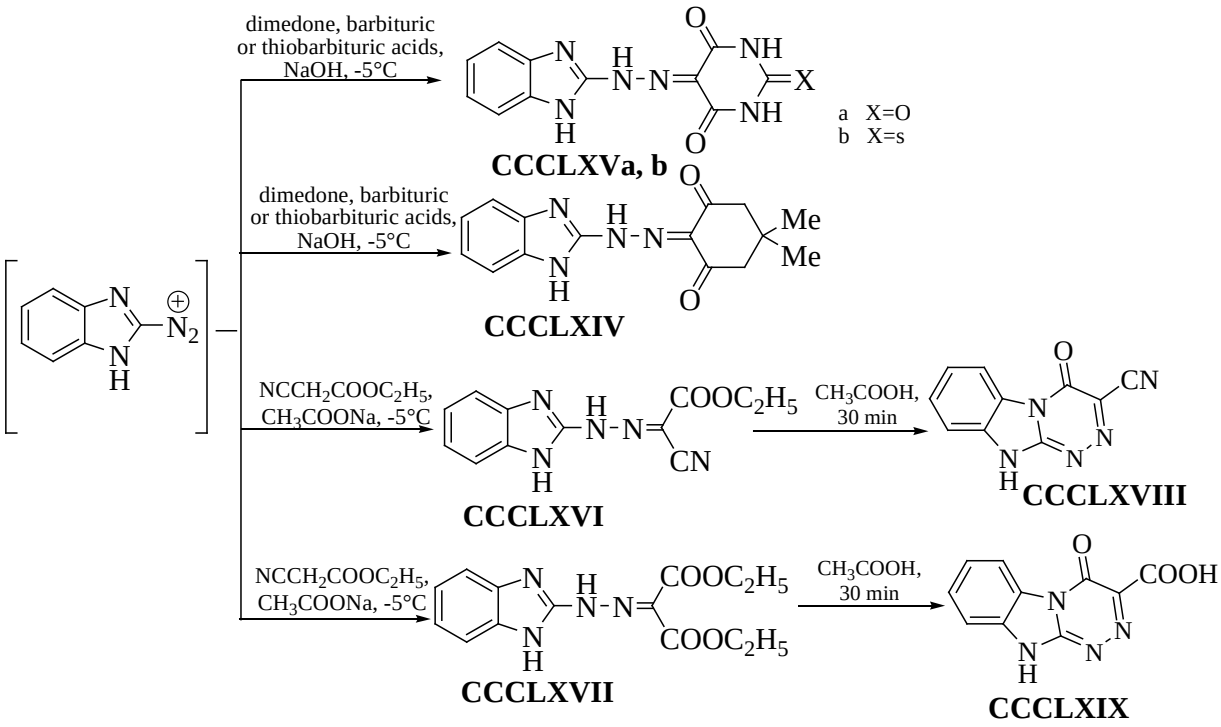



screened for cytotoxic activity against human breast cancer line MCF-7. All these compounds exhibited moderate cytotoxic activity. Several new benzimidazole derivatives

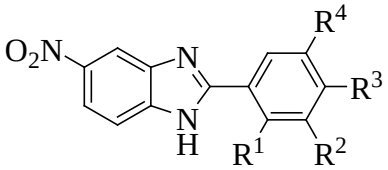
**CCCLXII-CCCLXIX** synthesized [235] by following reaction scheme mentioned below. All these compounds were screened for cytotoxic activity against human breast cancer cell line HeLa and $IC_{50}$ values were determined. Compounds **CCCLXIIc, CCCLXIIIb,c, CCCLXIV, CCCLXVa,b** exhibited cytotoxic activity better than doxorubicin. Romero-castro *et. al.* [236] synthesized six benzimidazole derivatives





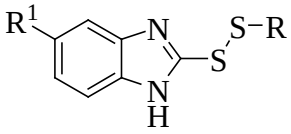

**CCCLXXa-f** and screened them for cytotoxic activity against seven human neoplastic cell lines i.e.K562, HL60, MCF7, MDA-231, A549, HT29 and KB. Compound **CCCLXXf** exhibited $IC_{50}$ of 28nm against the A549 cell line and is most active of all the



**CCCLXXa-f**

| | $R^1$ | $R^2$ | $R^3$ | $R^4$ |
|---|---|---|---|---|
| a | -H | -H | -H | -H |
| b | $-NO_2$ | -H | -H | -H |
| c | -H | $-NO_2$ | -H | -H |
| d | -H | -H | $-NO_2$ | -H |
| e | -H | $-NO_2$ | -H | $-NO_2$ |
| f | -H | $-NO_2$ | -Cl | -H |

compounds i.e. **CCCLXXa-f**. In a Chinese patent [237] disulfide containing benzimidazole derivatives **CCCLXXIa-f** useful in the treatment of colon cancer or

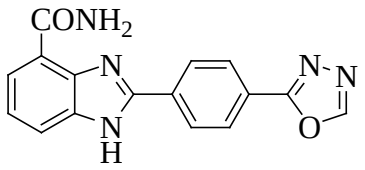


**CCCLXXIa-f**

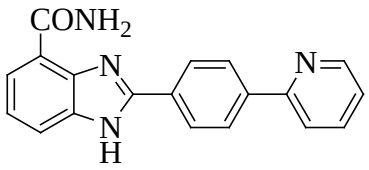
| | R | $R^1$ |
|---|---|---|
| a | $C_2H_5$ | H |
| b | $C_2H_5$ | $CH_3$ |
| c | $C_2H_5$ | $NO_2$ |
| d | $CH_3(CH_2)_3$- | H |
| e | $CH_3(CH_2)_3$- | $CH_3$ |
| f | $CH_3(CH_2)_3$- | $NO_2$ |

lymph cancer is disclosed. Out of several benzimidazole derivatives synthesized [238] and evaluated for their poly (ADP-ribose) polymerase-1 (PARP-1) inhibition activity

compounds **CCCLXXII** and **CCCLXIII** exhibited $EC_{50}$ 3.7 and 7.8 nM respectively. These compounds also exhibited potent oral in vivo efficacy in potentiating the cytotoxic

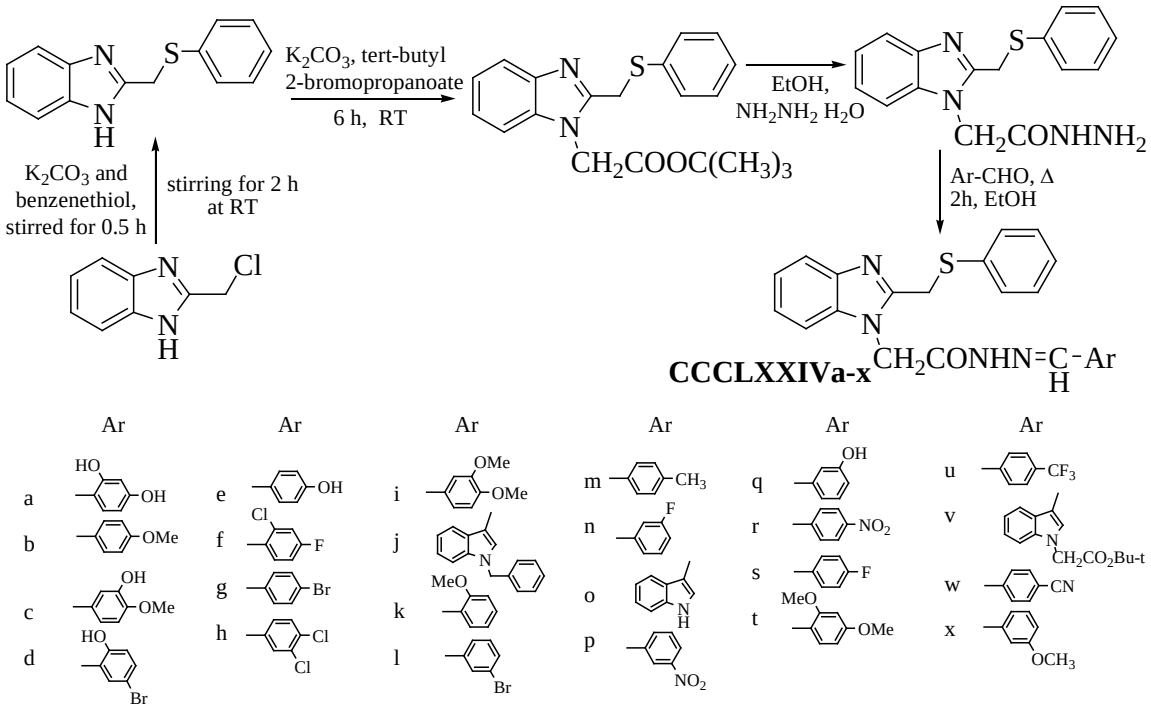


**CCCLXXII**



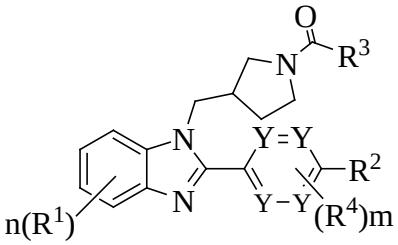
**CCCLXXIII**

agent temozolomide in B16F10 murine melanoma model. A large number of benzimidazole derivatives **CCCLXXIVa-x** have been synthesized [239] by following reaction scheme mentioned below. All these compounds were screened for five human cancer cell lines i.e. A549, HCT116, HepG2, PC-9 and A375. Compound **CCCLXXIVd**

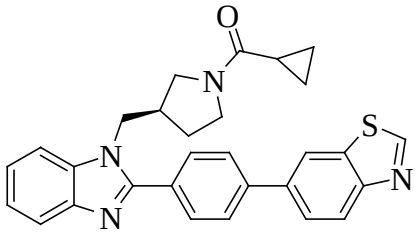



exhibited excellent anticancer activity against various cancer cell lines tested ($IC_{50}$ 4–17 μM), compared with 5-FU and SU11248. Bonham *et. al.* [240] synthesized aziridinyl fused pyrrolo[1,2-a]benzimidazoles and screened them for anticancer activity against breast cancer cell lines i.e. MCF-7 and HCC1937. Usefulness of benzimidazole

derivatives **CCCLXXV** in the treatment of cancer is described in an international patent [241]. Thus compound **CCCLXXVI** exhibited $pIC_{50}$ value of 7.26 when evaluated for



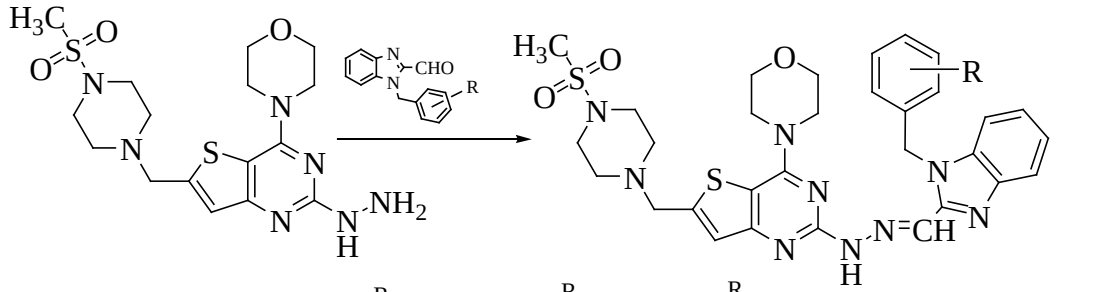
**CCCLXXV**



**CCCLXXVI**

[$R^1$ is independently halo, $C_{1-6}$ alkyl, alkoxy, CN, etc.; $R^2$ is (un)substituted aryl and (un)substituted heteroaryl; $R^3$ is amino, alkylamino, dialkylamino, etc.; each $R^4$ is $C_{1-6}$ alkyl, alkoxy, OH and halo; each Y is independently C and N; n is 0 to 4; m is 0 to 4; provided that at least two Y are C; and pharmaceutically acceptable salts thereof]

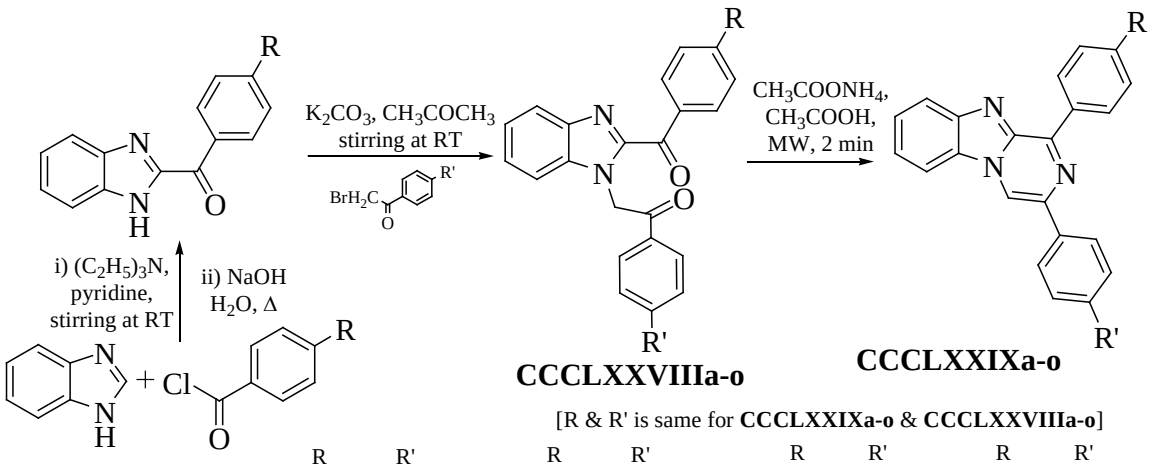
their fatty acid synthase inhibitory activity. Benzimidazole derivatives **CCCLXXVIIa-h** have been synthesized [242] by following reaction scheme mentioned below. All these



| | R | | R | | R | | R |
|---|---|---|---|---|---|---|---|
| a | 3,4-dichloro | b | 4-tert-butyl | c | 4-methyl | d | 2,3-dichloro |
| e | 2-chlorol | f | H | g | 4-chloro | h | 3-chloro |

**CCCLXXVIIa-h**

compounds i.e. **CCCLXXVIIa-h** were screened for anticancer activity against H460, HT-29, MDA-MB-231 cancer cell lines and compounds **CCCLXXVII f, g** exhibited good anticancer activity against all the three cell lines. 1,3-diarylpyrazino[1,2-a] benzimidazoles derivatives **CCCLXXIXa-o** have been synthesized [243] by following reaction sequence mentioned below. Compounds **CCCLXVIIIa-e,h-j,m,o**; **CCCLXXIXa-f, j** & **l** were screened for anticancer activity against sixty human tumor cell lines by NCI. Compounds **CCCLXXVIIIc,h** exhibited good anticancer activity. Gellis *et.al*. [244] synthesized benzimidazole-4,7-diones **CCCLXXXa,b; CCCLXXXIa-**

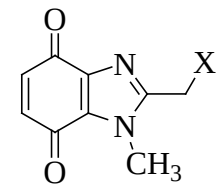



**CCCLXXVIIIa-o** **CCCLXXIXa-o**

[R & R' is same for **CCCLXXIXa-o** & **CCCLXXVIIIa-o**]

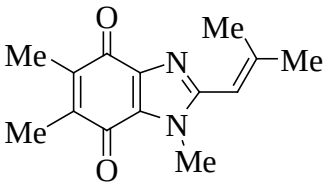
| | R | R' | | R | R' | | R | R' | | R | R' |
|---|---|---|---|---|---|---|---|---|---|---|---|
| a | H | H | e | H | Cl | i | $OCH_3$ | F | m | Cl | $OCH_3$ |
| b | H | $CH_3$ | f | $OCH_3$ | H | j | $OCH_3$ | Cl | n | Cl | F |
| c | H | $OCH_3$ | g | $OCH_3$ | $CH_3$ | k | Cl | H | o | Cl | Cl |
| d | H | F | h | $OCH_3$ | $OCH_3$ | l | Cl | $CH_3$ | | | |

**h CCCLXXXII** and **CCCLXXXIII** as bioreductive anticancer agents. All these compounds were screened for anticancer activity against T47D (breast), A549 (lung) and

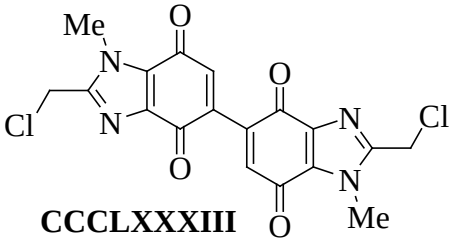


**CCCLXXXa,b**

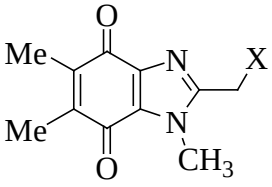
a, X= Cl
b, X= Br



**CCCLXXXII**

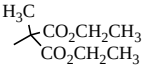
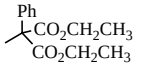


**CCCLXXXIII**

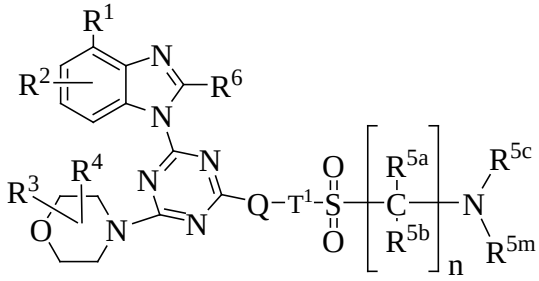


**CCCLXXXIa-h**

| | X |
|---|---|
| a | -Cl |
| b | $-SO_2$-Ph |
| c | $-SO_2-C_4H_9$ |
| d |  |
| e |  |

| | X |
|---|---|
| f |  |
| g |  |
| h |  |

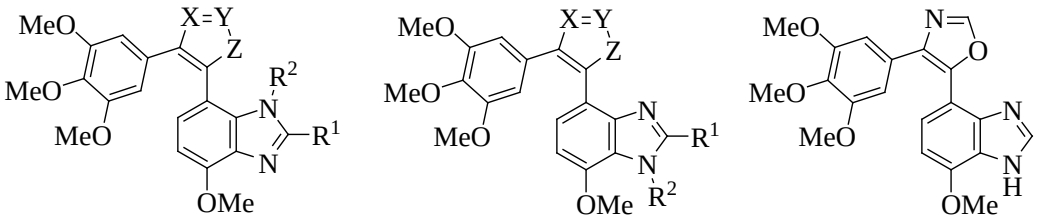
HT-29 (colon) cancer cell lines. Compound **CCCLXXXIII** exhibited cytotoxicity comparable to that of mitomycin C. 1,3,5-Triazinyl-benzimidazole sulphonamides **CCCLXXXIV** useful in the treatment of cancer therapy is synthesized and reported in



**CCCLXXXIV**

[$R^1$ and $R^2$ = independently H, CN, halo, nitro, (cyclo)alkyl, alkenyl, alkynyl, (hetero)aryl, aralkyl, heterocyclyl, etc.; $R^3$ and $R^4$ = indepen dently H, alkyl, or $R^3$ and $R^4$ together = a bond, (hetero)alkylene, or (hetero)alkenylene; $R^{5a}$ and $R^{5b}$ = independently H, halo, (cyclo)alkyl, alkenyl, alkynyl, (hetero)aryl, aralkyl, or heterocyclyl; $R^{5c}$ and $R^{5m}$ = H, (cyclo)alkyl, alkenyl, alkynyl, (hetero)aryl, aralkyl, or heterocyclyl; $R^6$ = H or alkyl; Q = cycloalkylene, arylene, heteroarylene, or heterocyclylene; $T^1$ = a bond or (un)substituted NH; n = 1-5) and their enantiomers, mixt. of enantiomers and diastereomers, isotopic variants, acceptable salts, solvates, hydrates, prodrugs, or compns.]

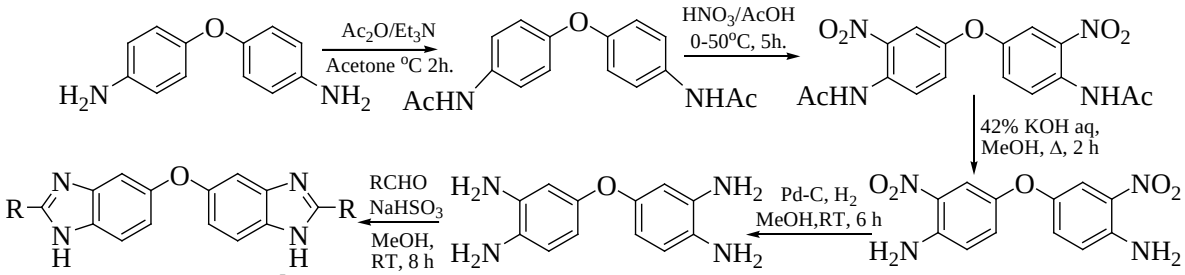
literature [245]. Synthesis of benzimidazole derivatives **CCCLXXXV** and



**CCCLXXXV** **CCCLXXXVI** **CCCLXXXVII**

[X to Z independently=CH, C(O), N, O, or S; $R^1$=H, $CF_3$, $CCl_3$, OH, or halo, etc.; $R^2$=(un)substituted alkyl, alkoxy, or cycloalkyl, etc.]

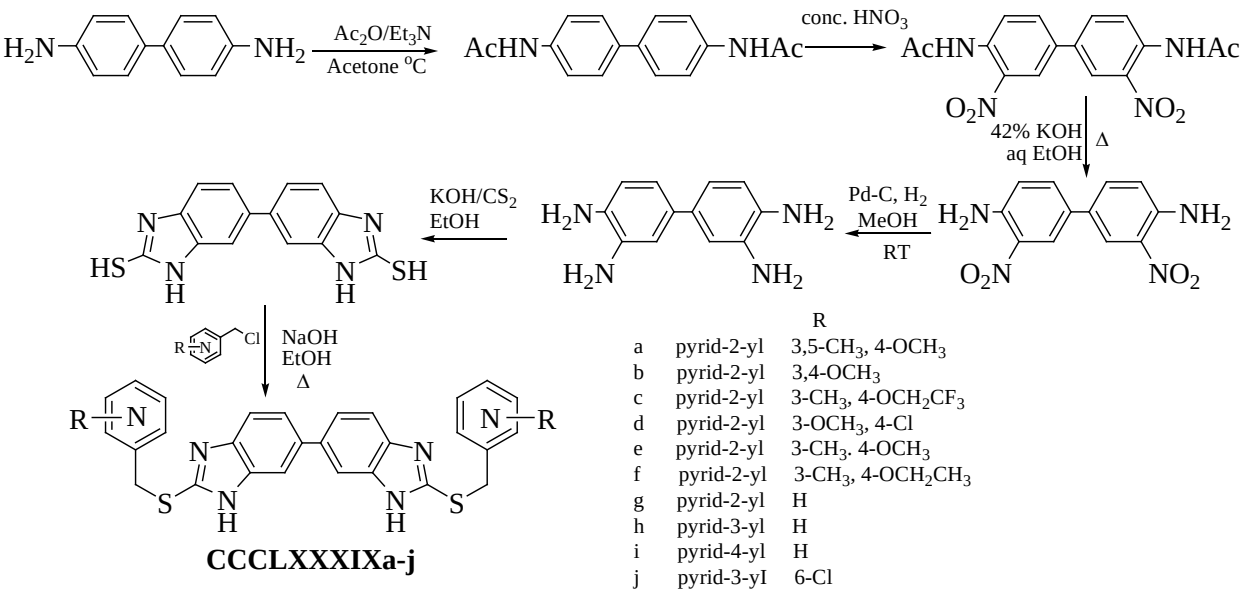
**CCCLXXXVI** for the treatment of tumor is described in a Chinese patent [246]. Compound **CCCLXXXVII** gave $IC_{50}$ value of $2.52x10^{-8}$ mol/L for inhibition of MCF-7. Wang *et. al.* [247] synthesized bis-benzimidazole derivatives **CCCLXXXVIIIa-h** by following reaction scheme mentioned below. All these bis-benzimidazole derivatives



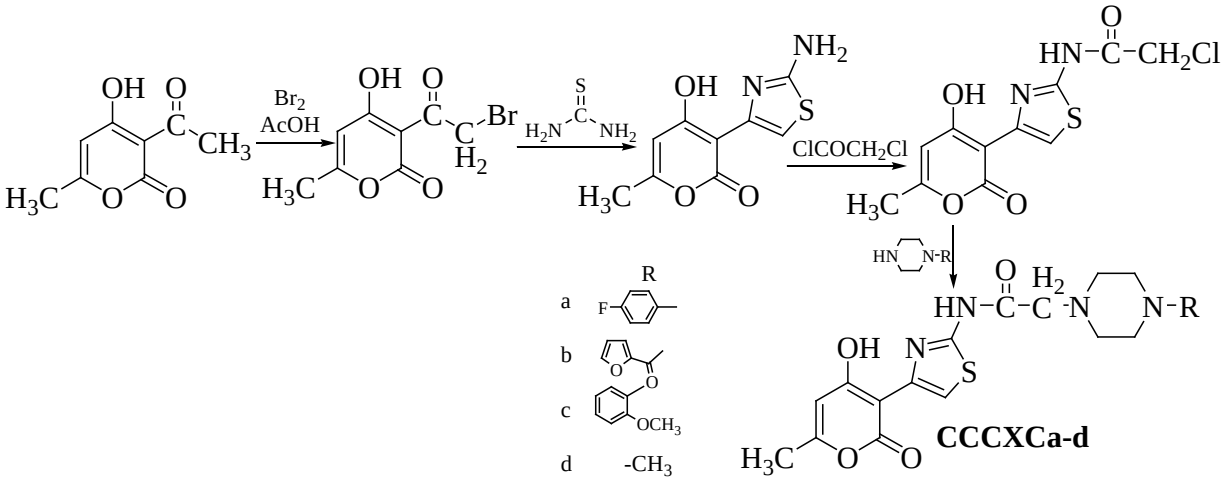
**CCCLXXXVIIIa-h**

| | R | | R | | R | | R |
|---|---|---|---|---|---|---|---|
| a | 4-$OCH_3$, phenyl | b | 3, 5-$OCH_3$, phenyl | c | 3, 4, 5-$OCH_3$, phenyl | d | 3-$OCH_3$, 4-OH, phenyl |
| e | phenyl | f | 4-Br, phenyl | g | 2, 4-Cl, phenyl | h | 4-F, phenyl |

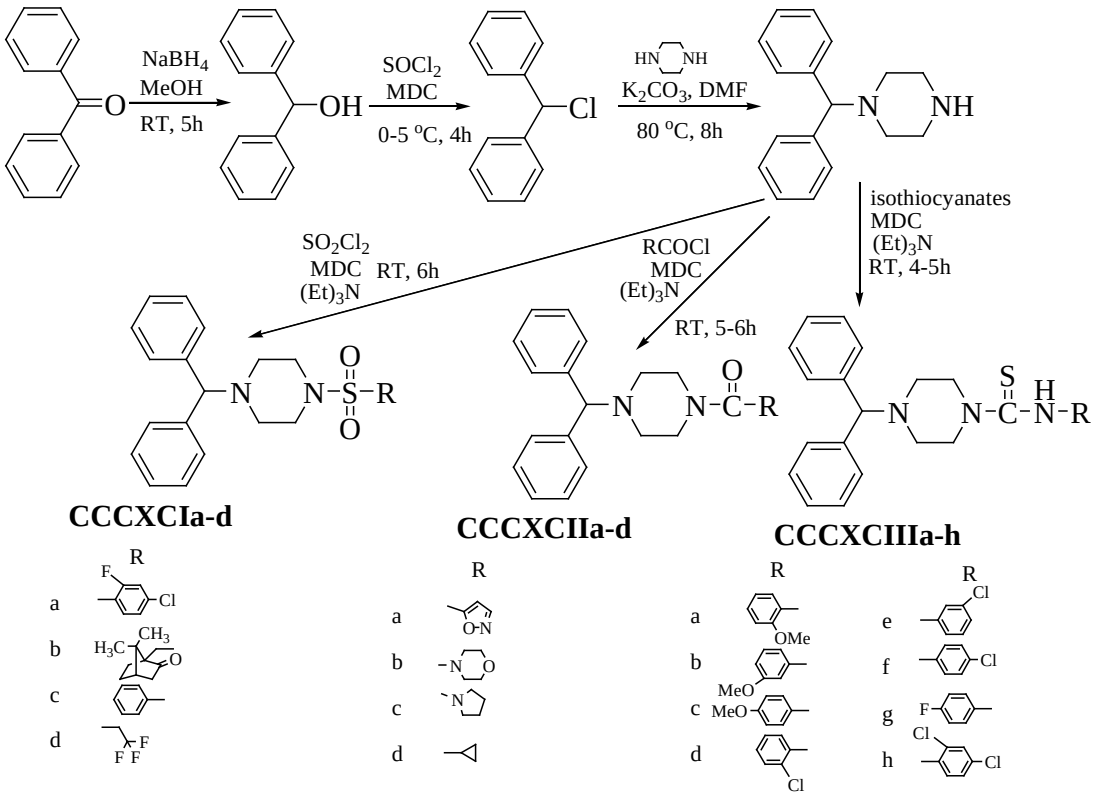
were screened for antitumor activity against HeLa, HL60 and U937 cancer cell lines. Compound **CCCLXXXVIIIa** exhibited good antitumor activity. Symmetrical bis-benzimidazole derivatives **CCCLXXXIXa-j** have been synthesized [248] by following reaction sequence mentioned below. On screening for cytotoxic activity against SKOV-3, HeLa and BGC-823 cell lines, compounds **CCCLXXXIXa** and **CCCLXXXIXi** exhibited good cytotoxic activity against SKOV-3 cell line. A number of piperazine derivatives **CCCXCa-d** have been synthesized [249] by following reaction scheme



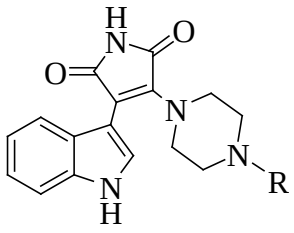

mentioned below. These compounds were screened for anticancer activity against Ehrlich Ascites Carcinoma cells and compound **CCCXCc** exhibited good anticancer activity.




Kumar *et. al.* [250] synthesized 1-benzhydrylpiperazine derivatives **CCCXCIa-d**, **CCCXCIIa-d** and **CCCXCIIIa-h** by following reaction sequence mentioned below. All these compounds were screened for antiproliferative activity against one normal cell (NF-103 skin fibroblast cells) and four human cancer cell lines MCF-7, HepG-2, HeLa and HT-29. These compounds did not exhibit potent antiproliferative activity. Synthesis of

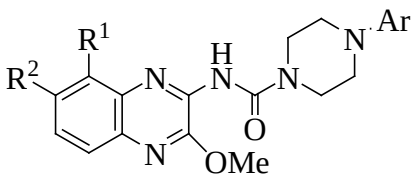



piperazine derivatives **CCCXCIV** useful as antitumor agents is disclosed in a Chinese patent [251]. A number of piperazine derivatives **CCCXCV$_{1\text{-}29}$** have been synthesized [252] and screened for anticancer activity against fourteen human cancer cell lines. Compound **CCCXCV$_{13}$** exhibited more potent effect than paclitaxel, doxorubicin,



[R =Me, -$CH_2CH_2OH$, Ph–C(=O)– ]

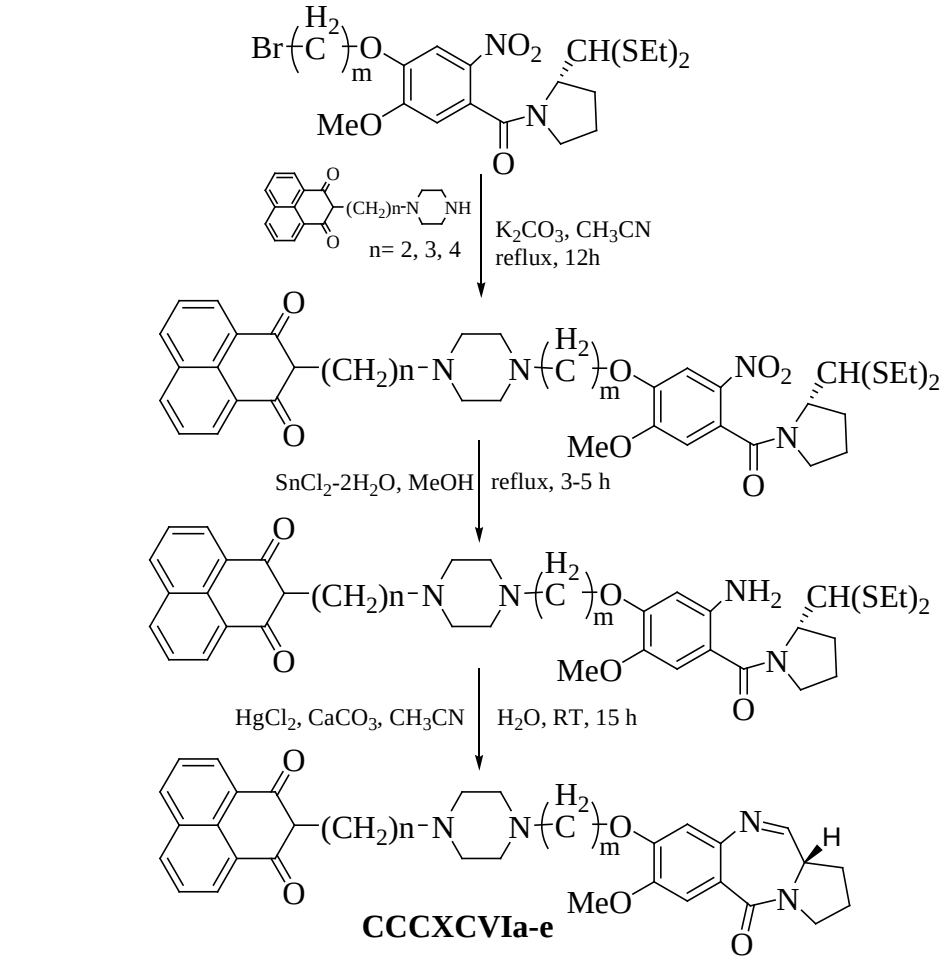
**CCCXCIV**



**CCCXCV$_{1\text{-}29}$**

| | $R^1$ | $R^2$ | Ar |
|---|---|---|---|
| 1 | F | H | 3,5-Dimethoxyphenyl |
| 2 | F | H | 3.5-Dimethylphenyl |
| 3 | Cl | H | 3,5-Dimethoxyphenyl |
| 4 | Cl | H | 3.5-Dimethylphenyl |
| 5 | Me | H | 3,5-Dimethoxyphenyl |
| 6 | Me | H | 3.5-Dimethylphenyl |
| 7 | MeO | H | 3,5-Dimethoxyphenyl |
| 8 | MeO | H | 3.5-Dimethylphenyl |
| 9 | H | F | Phenyl |
| 10 | H | F | 2-Methoxyphenyl |
| 11 | H | F | 3-Methoxyphenyl |
| 12 | H | F | 4-Methoxyphenyl |
| 13 | H | F | 3,5-Dimethoxyphenyl |
| 14 | H | F | 3,4,5-Trimethoxyphenyl |
| 15 | H | F | 2-Methylphenyl |
| 16 | H | F | 3-Methylphenyl |
| 17 | H | F | 2,6-Dimethylphenyl |
| 18 | H | F | 3,5-Dimethylphenyl |
| 19 | H | F | 2-Fluorophenyl |
| 20 | H | F | 4-Fluorophenyl |
| 21 | H | F | 2-Chlorophenyl |
| 22 | H | F | 3-Chlorophenyl |
| 23 | H | F | 4-Chlorophenyl |
| 24 | H | Cl | 3,5-Dimethoxyphenyl |
| 25 | H | Cl | 3,5-Dimethylphenyl |
| 26 | H | Me | 3,5-Dimethoxyphenyl |
| 27 | H | Me | 3,5-Dimethylphenyl |
| 28 | H | OMe | 3,5-Dimethylphenyl |
| 29 | H | H | 3,5-Dimethylphenyl |

cisplatin, gemcitabine or 5-fluorouracil in cancer cells. Kamal *et. al.* synthesized several piperazine linked derivatives and screened them for antitumor activity against various cancer cell lines [253,254]. Thus pyrrolobenzodiazepine-naphthalimide conjugates **CCCXCVI** have been synthesized [255] by following reaction sequence mentioned below. Compounds **CCCXCVIa,b,c** were screened for anticancer activity against seven

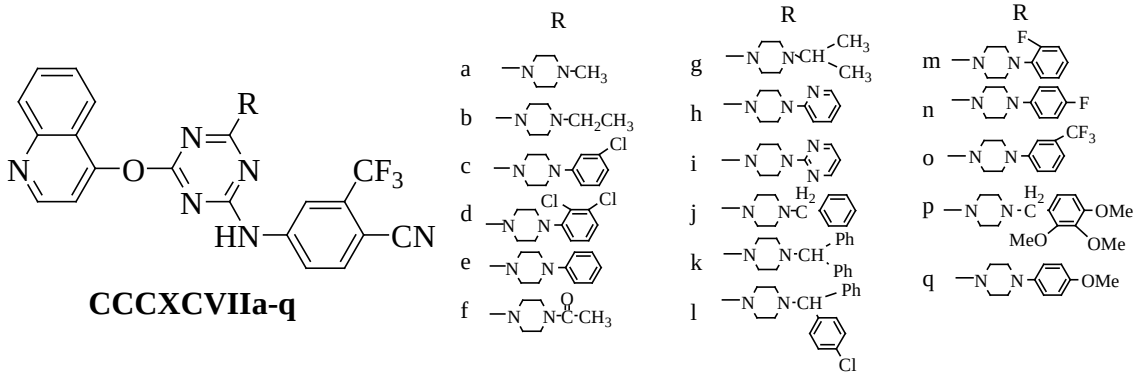



**CCCXCVIa-e**

| | n | m | | n | m | | n | m | | n | m | | n | m |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| a | 2 | 2 | b | 2 | 3 | c | 2 | 4 | d | 3 | 3 | e | 4 | 4 |

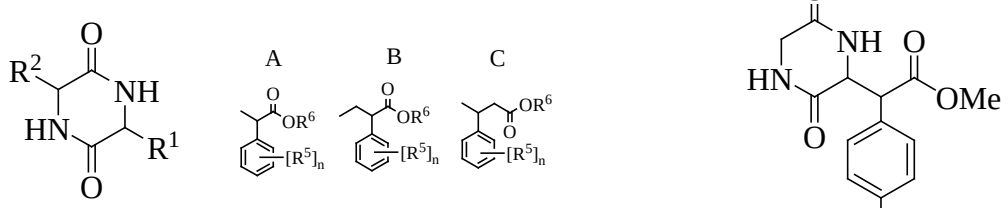
human cancer cell lines i.e. Hop62 (lung), SiHa (cervix), MCF7 and ZR-75-1 (breast), Colo205 (colon), PC-3 (prostate), and A2780 (ovarian). Compound **CCCXCVIa** exhibited cytotoxicity against A 2780, PC3 and SiHa cell lines with $IC_{50}$ values 0.5 to 1.0 μM. A number of s-triazine derivatives containing piperazine moiety **CCCXCVIIa-q**

have been synthesized [256] and some representative molecules i.e. **CCCXCVIId,f,l,m,n,o,p,q** were screened for anticancer activity against human prostate cancer cell line DU-145. Compound **CCCXCVIIo** was found to be markedly active.




**CCCXCVIIa-q**

In an international patent [257] synthesis of diketopiperazines derivatives. **CCCXCVIII** useful in the treatment of an angiogenic disease or condition, treatment of cancer and precancerous conditions, treatment of a fibrotic disorder, a viral infection etc is disclosed. Thus diketopiperazines **CCCXCIX** inhibited proliferation of STTG astrocytoma and AU565 cancer cells and inhibited the Akt phosphorylation in AU565 breast cancer and



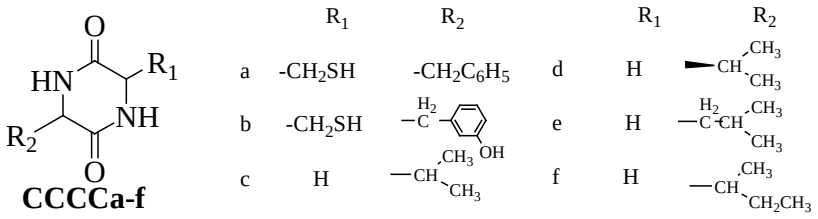

**CCCXCVIII**




**CCCXCIX**

[$R^1$ = a side chain of an amino acid, $CH_2CH_2CH_2$ or $CH_2CH(OH)CH_2$ and together with the adjacent ring nitrogen forms proline or hydroxyproline, a deriv. of a side chain of an amino acid wherein the derivatized chain has: (i) an $NH_2$replaced by $NHR^3$, $N(R^3)_2$; (ii) an SH replaced by $SSCH_2CH(NH_2)CO_2H$; (iii) a $CH_2$ replaceed by a CH(Me) or CH(OH), etc.; $R^3$=(un)substituted alkyl, cycloalkyl, heterocycloalkyl, (hetero)aryl, alkylaryl, arylalkyl; $R^2$ = A, B, C; $R^5$ = independently (hetero)aryl, alkyl, acyl, halo, etc.; n = 0-5; $R^6$ = alkyl, lower alkyl], their pharmaceutically-acceptable salts or prodrugs]

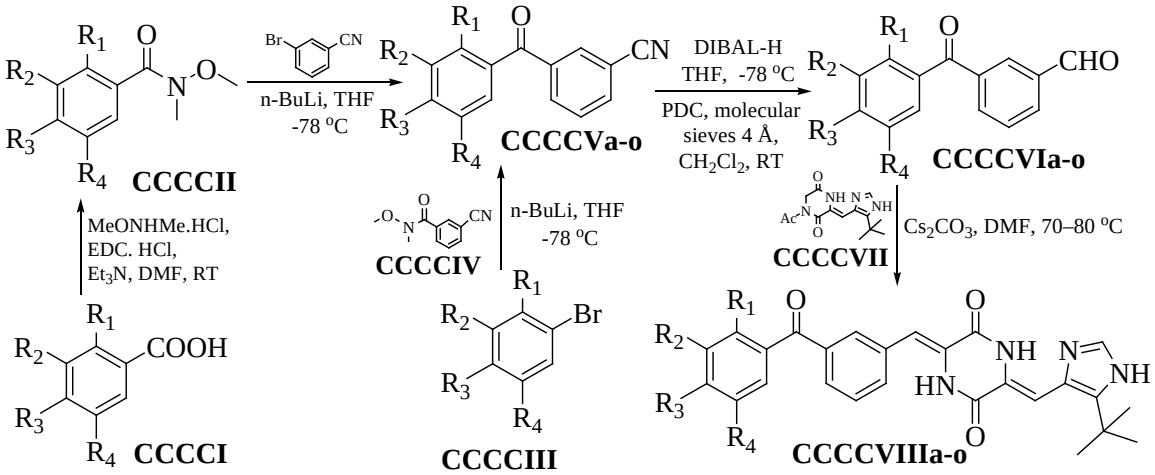
WM-266-4 melanoma cells. Diketopiperazines derivatives **CCCCa-f** have been synthesized [258] and screened for anticancer activity against three human cancer lines i.e. HT-29, HeLa and MCF-7. Compound **CCCCb** caused maximum inhibition in growth of HeLa cancer cells and near equivalent activity against HT-29 & MCF-7 cells whereas



| | $R_1$ | $R_2$ | | $R_1$ | $R_2$ |
|---|---|---|---|---|---|
| a | $-CH_2SH$ | $-CH_2C_6H_5$ | d | H | $-CH(CH_3)_2$ |
| b | $-CH_2SH$ | $-CH_2C_6H_4OH$ | e | H | $-CH_2CH(CH_3)_2$ |
| c | H | $-CH(CH_3)_2$ | f | H | $-CH(CH_3)CH_2CH_3$ |

**CCCCa-f**

other compounds i.e. **CCCCa,c-f** were not as effective as **CCCCb**. Yamazaki *et. al.* [259,260] synthesized benzophenone-bearing diketopiperazine derivatives **CCCCVIIIa-o** by following reaction scheme mentioned below. All these compounds were screened for cytotoxic activity against HT-29 cells. Compounds **CCCCVIIIi** and **CCCCVIIIj** exhibited $IC_{50}$ value of 0.6 and 0.5 nM.




| | $R_1$ | $R_2$ | $R_3$ | $R_4$ |
|---|---|---|---|---|
| a | OMe | H | H | H |
| b | H | OMe | H | H |
| c | H | H | OMe | H |
| d | OMe | OMe | H | H |
| e | OMe | H | OMe | H |

| | $R_1$ | $R_2$ | $R_3$ | $R_4$ |
|---|---|---|---|---|
| f | H | OMe | OMe | H |
| g | H | OMe | OMe | OMe |
| h | F | H | H | H |
| i | H | F | H | H |
| j | H | H | F | H |

| | $R_1$ | $R_2$ | $R_3$ | $R_4$ |
|---|---|---|---|---|
| k | Cl | H | H | H |
| l | H | Cl | H | H |
| m | H | H | Cl | H |
| n | H | H | Br | H |
| o | H | H | $CF_3$ | H |

In this chapter we have summarized the recent work reported in literature on the use of microwave technology in organic synthesis; synthesis of acridine & bis acridine; pyrazole & oxadiazole; isoindole & pyrrolopyrazine; amidine & azomethine; benzimidazole & piperazine derivatives and their evaluation for anti-inflammatory, anticancer and other biological activities.

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# Chapter *2*

***Synthesis anti-inflammatory and anticancer activity evaluation of bisacridine derivatives***

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# 2.1 Introduction

Acridine and bisacridine derivatives are well known for their broad range of pharmaceutically relevant properties. Recent work reported in literature on acridine and bisacridine derivatives exhibiting anti-inflammatory and anticancer activities have been summarized in chapter-1. Apart from anti-inflammatory and anticancer activities, these compounds are reported to possess fungicidal [1, 2], antiparasitic [3], antimicrobial [4, 5], antitubercular [6, 7], antibacterial [8, 9], antimalarial [10, 11], antiviral [12, 13] and antialzheimer and antiprion [14] activities.

In continuation of our efforts towards [15, 16], in search of potent molecules possessing anti-inflammatory and anticancer activities, we have synthesized two series of bis-acridine derivatives in which two bioactive acridine heterocycles are tethered *via* a flexible linker. These bis-acridine derivatives have been screened for anti-inflammatory and anticancer activities, which we will describe in this chapter.

## 2.2 Results and discussion

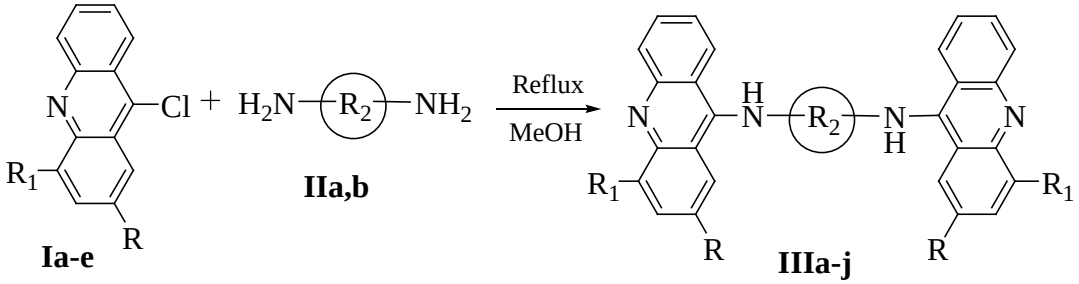
### 2.2.1 *Chemistry:*

9-Chloro-2,4-(un)substituted acridines (**Ia-e**; Scheme 2.1) [17, 18] and 9-isothiocyanato-2,4-(un)substituted acridines (**IVa-e**; Scheme 2.2) [19] were synthesized by following reaction procedure reported in literature and used for the synthesis of bis acridine heterocycles.

9-Chloroacridine (**Ia**; Scheme 2.1) and 3-(4-(3-aminopropyl)piperazin-1-yl)propan-1-amine (**IIa**; Scheme 2.1) were dissolved in methanol and refluxed for 17 hours and then solvent was removed under reduced pressure. The solid residue left behind was treated with 10% cold aqueous sodium bicarbonate solution and then

washed with cold water. Solid so obtained was air dried to give crude condensed product, which was further purified by column chromatography over silica gel to give pure product **IIIa** *i.e.* *N*-(3-(4-(3-(acridin-9-ylamino)propyl)piperazin-1-yl)propyl)acridin-9-amine (Scheme 2.1) in 43% yield. IR spectrum of **IIIa** depicted absorption signal at 3434 $cm^{-1}$, which is attributed to NH functional group and strong absorption signals at 1632, 1589, 1530 $cm^{-1}$ correspond to aromatic region of acridinyl moiety. ($^1$H NMR data is interpreted by following numbering of **IIIa** and **IIIf** as mentioned in Figure 2.1) $^1$H NMR (500 MHz, $D_2O$) (Figure 2.2) of compound **IIIa** exhibited signals at $\delta$ 2.028-2.057 (t, 4H, J= 7 Hz, 2×$CH_2$, $C^2$, $C^{11}$), 2.622-2.651 (m, 12H, 6×$CH_2$, $C^3$, $C^5$, $C^6$, $C^8$, $C^9$, $C^{10}$), 3.964-3.992 (t, 4H, J= 7 Hz, 2×$CH_2$, $C^1$, $C^{12}$), 7.381-7.411 (t, 4H, J= 7.5 Hz, Ar), 7.474-7.491 (d, 4H, J= 9 Hz, Ar), 7.775-7.806 (m, 4H, Ar), 8.077-8.095 (d, 4H, J= 9 Hz, Ar). $^{13}$C NMR (125 MHz, DMSO-$d_6$) (Figure 2.3) data of **IIIa** exhibited signals at $\delta$: 30.855 (2C), 40.562 (4C), 53.089 (2C), 56.373 (4C), 113.418 (4C), 122.041 (4C), 123.767 (4C), 129.143 (4C), 130.360 (4C), 149.279 (2C) and 150.609 (2C). APCI-MS: (Figure 2.4) of **IIIa** exhibited $MH^+$ ion peak at *m/z* 555.40 (100%). Elemental analysis Calculated for $C_{36}H_{38}N_6$: C, 77.98; H, 6.86; N, 15.16; Found C, 77.63; H, 6.70; N, 15.30. Spectral and analytical data of **IIIa** fully support the structure assigned to it.

Similarly condensation of 9-chloro-2-methylacridine (**Ib**), 9-chloro-2-methoxyacridine (**Ic**), 9-chloro-4-methylacridine (**Id**) and 9-chloro-4-methoxyacridine (**Ie**) with 3-(4-(3-aminopropyl)piperazin-1-yl)propan-1-amine (**IIa**; Scheme 2.1) gave corresponding condensation products **IIIb-e** (Scheme 2.1). All these condensation products **IIIb-e** were purified by column chromatography over silica gel. Spectral and analytical data of compounds **IIIa-e** reported in Table 2.1 fully support the structures assigned to them.




**Ia-e** **IIa,b** **IIIa-j**

| | R | $R_1$ |
|---|---|---|
| **Ia** | H | H |
| **Ib** | $CH_3$ | H |
| **Ic** | $OCH_3$ | H |
| **Id** | H | $CH_3$ |
| **Ie** | H | $OCH_3$ |

**IIa** $-(CH_2)_3-N\square N-(CH_2)_3-$

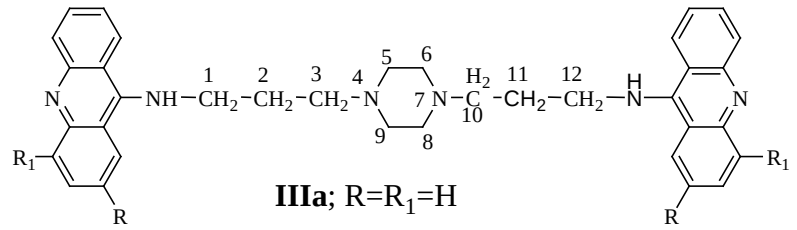
**IIb** $-(CH_2)_3-\square(O)_2-\square(O)_2-(CH_2)_3-$

For Compounds **IIIa-j**

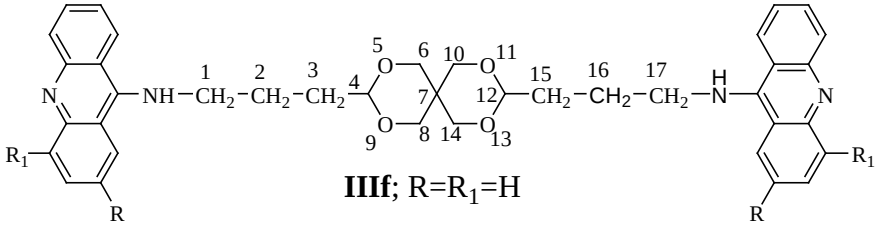
| | R | $R_1$ | $R_2$ |
|---|---|---|---|
| **IIIa** | H | H | $-(CH_2)_3-N\square N-(CH_2)_3-$ |
| **IIIb** | $CH_3$ | H | $-(CH_2)_3-N\square N-(CH_2)_3-$ |
| **IIIc** | $OCH_3$ | H | $-(CH_2)_3-N\square N-(CH_2)_3-$ |
| **IIId** | H | $CH_3$ | $-(CH_2)_3-N\square N-(CH_2)_3-$ |
| **IIIe** | H | $OCH_3$ | $-(CH_2)_3-N\square N-(CH_2)_3-$ |

| | R | $R_1$ | $R_2$ |
|---|---|---|---|
| **IIIf** | H | H | $-(CH_2)_3-\square(O)_2-\square(O)_2-(CH_2)_3-$ |
| **IIIg** | $CH_3$ | H | $-(CH_2)_3-\square(O)_2-\square(O)_2-(CH_2)_3-$ |
| **IIIh** | $OCH_3$ | H | $-(CH_2)_3-\square(O)_2-\square(O)_2-(CH_2)_3-$ |
| **IIIi** | H | $CH_3$ | $-(CH_2)_3-\square(O)_2-\square(O)_2-(CH_2)_3-$ |
| **IIIj** | H | $OCH_3$ | $-(CH_2)_3-\square(O)_2-\square(O)_2-(CH_2)_3-$ |

Scheme:-2.1 Synthesis of acridine derivatives **IIIa-j**

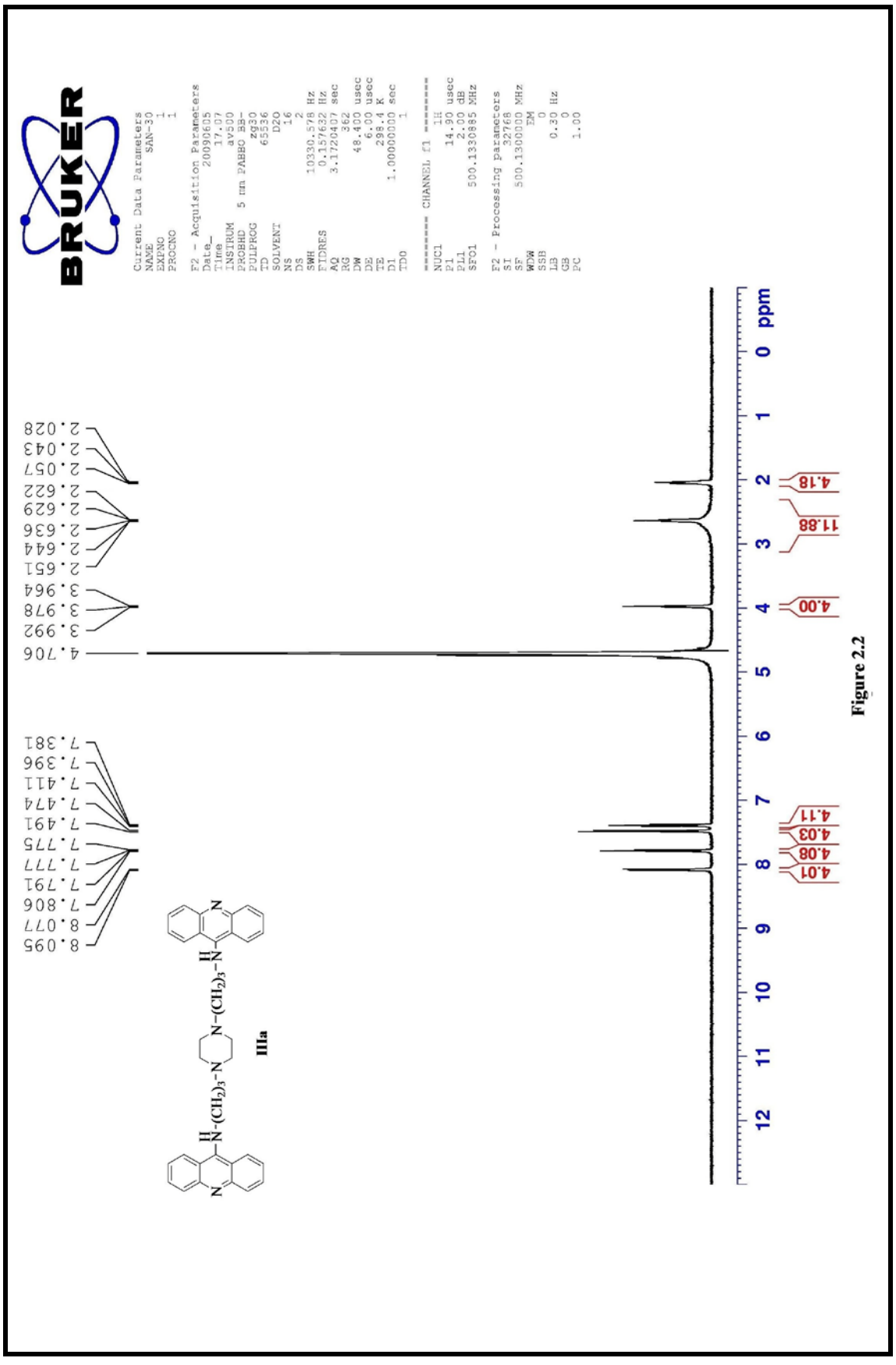


**IIIa**; $R=R_1=H$



**IIIf**; $R=R_1=H$

Figure:-2.1 Numbering of **IIIa** and **IIIf** for interpretation of $^1H$ NMR data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PROCNO 1
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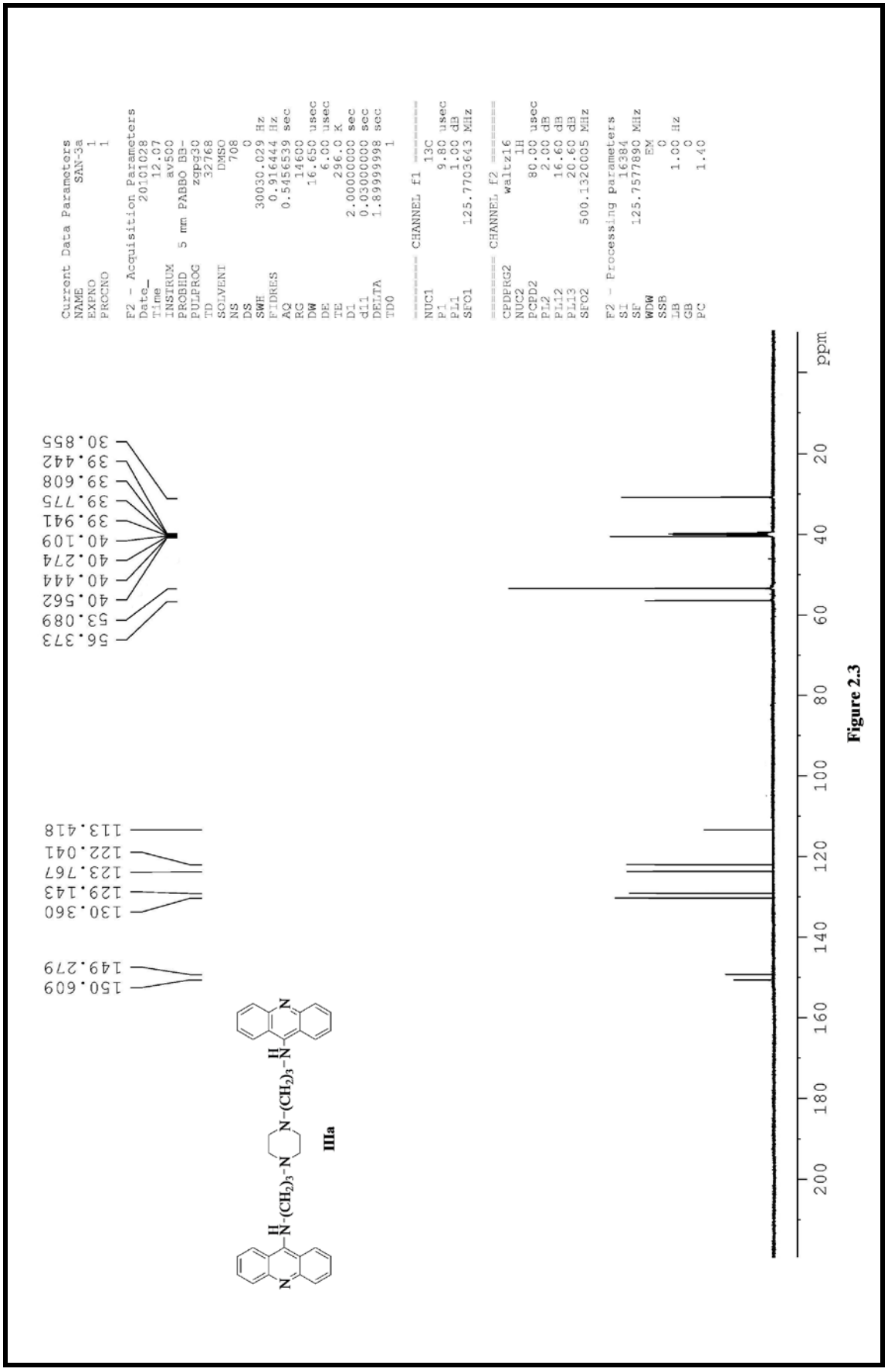
PULPROG zg30
TD 65536
SOLVENT D2O
NS 16
DS 2
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1720407 sec
RG 362
DW 48.400 usec
DE 6.00 usec
TE 298.4 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 14.90 usec
PL1 2.00 dB
SFO1 500.1330885 MHz
F2 - Processing parameters
SI 32768
SF 500.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
8.095
8.077
7.806
7.791
7.777
7.775
7.491
7.474
7.411
7.396
7.381
4.706
3.992
3.978
3.964
2.651
2.644
2.636
2.629
2.622
2.057
2.043
2.028
IIIa
4.01
4.08
4.03
4.11
4.00
11.88
4.18
ppm

Figure 2.2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PROCNO 1
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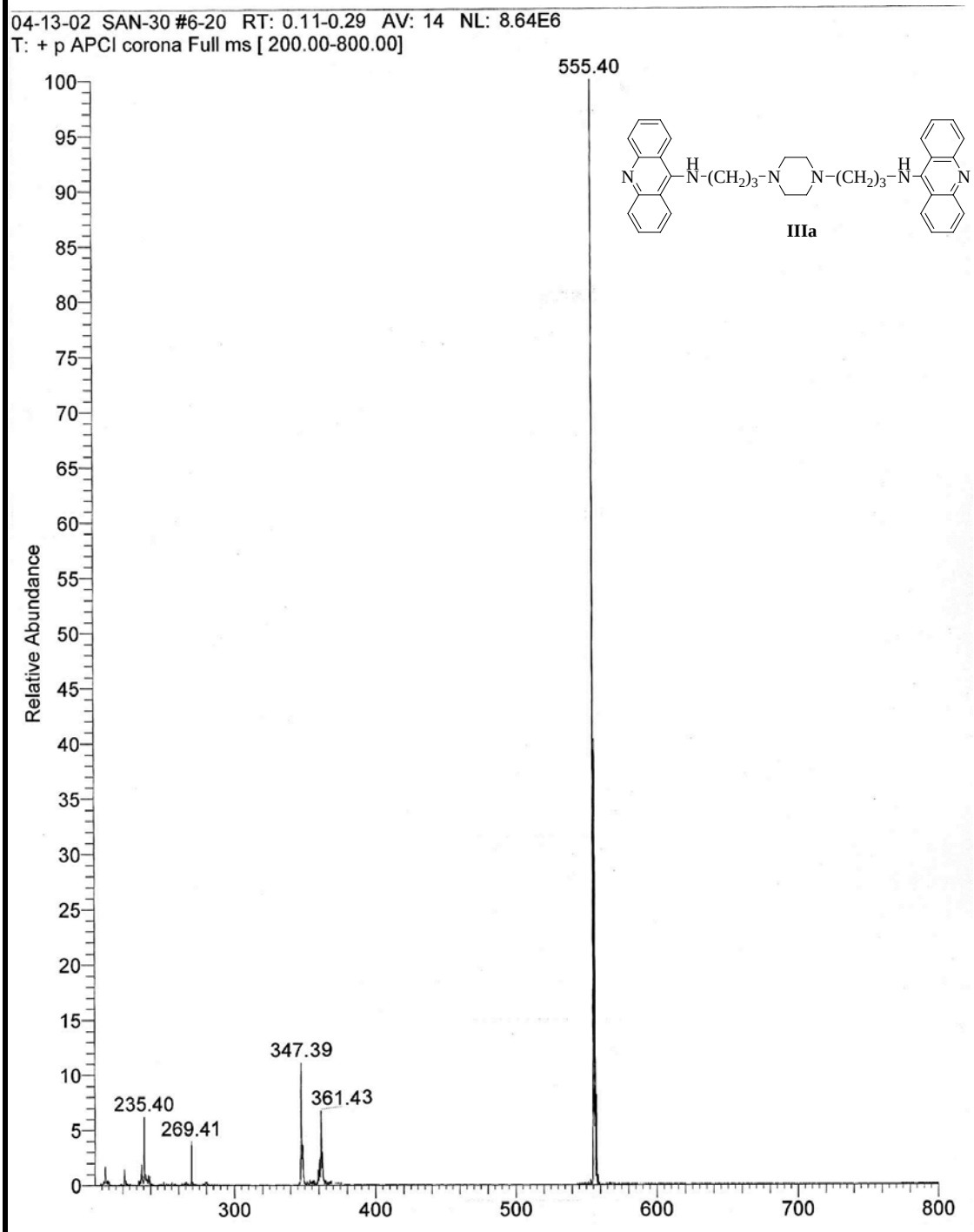
TD 32768
SOLVENT DMSO
NS 708
DS 0
SWH 30030.029 Hz
FIDRES 0.916444 Hz
AQ 0.5456539 sec
RG 14600
DW 16.650 usec
DE 6.00 usec
TE 296.0 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 9.80 usec
PL1 1.00 dB
SFO1 125.7703643 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 2.00 dB
PL12 16.60 dB
PL13 20.60 dB
SFO2 500.1320005 MHz
F2 - Processing parameters
SI 16384
SF 125.7577890 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
56.373
53.089
40.562
40.444
40.274
40.109
39.941
39.775
39.608
39.442
30.855
150.609
149.279
130.360
129.143
123.767
122.041
113.418
IIIa
200
180
160
140
120
100
80
60
40
20
ppm

**Figure 2.3**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T: + p APCI corona Full ms [ 200.00-800.00]
555.40
347.39
361.43
235.40
269.41
Relative Abundance
IIIa

**Figure 2.4**

Condensation of 9-chloroacridine **Ia** with diamine **IIb** i.e. 2,4,8,10-tetraoxaspiro[5,5]undecane-3,9-dipropane amine on refluxing in methanol for 18 hour gave condensed product **IIIf**, which was purified by column chromatography over silica gel to give pure product **IIIf** *i.e.* acridin-9-yl-[3-(9-{3-[(acridin-9-ylamino)]-propyl}-2,4,8,10-tetraoxa-spiro[5,5]undec-3-yl)-propyl]-amine(Scheme 2.1) in 42% yield. IR spectrum of **IIIf** exhibited absorption signal at 3374 $cm^{-1}$ (NH) functional group and strong absorption signals at 1629, 1560, 1515 $cm^{-1}$ correspond to aromatic region. Although interpreting $^{1}H$ NMR data of **IIIf**, peak positions were assigned with the help of $^{1}H$ NMR of starting material, that is **IIb** and similar compounds reported in literature [20]. It is considered that dioxane ring starting with $C_4$ is in the plane and dioxane ring starting with $C_{12}$ is out of plane. $^{1}H$ NMR (500 MHz, DMSO-$d_6$) data of **IIIf** depicted signals at $\delta$ 1.656-1.679 (m, 4H, 2×$CH_2$, $C^2$, $C^{16}$), 1.960-1.989 (m, 4H, 2×$CH_2$, $C^3$, $C^{15}$), 3.145-3.165 (t, 2H, J= 5 Hz, $C^{10a}$, $C^{14a}$), 3.522-3.546 (t, 4H, J= 6 Hz, 2×$CH_2$, $C^1$, $C^{17}$), 3.716-3.739 (d, 1H, J= 11.5 Hz, CH, $C^4$), 4.096 (s ,4H, $C^6$, $C^8$), 4.164-4.186 (d, 1H, J= 11 Hz, CH, $C^{12}$), 4.482-4.542 (m, 2H, $C^{10b}$, $C^{14b}$), 7.530-7.549 (d, 4H, J= 9.5 Hz Ar), 7.904-8.024 (m, 8H, Ar), 8.575-8.708 (bs, 4H, Ar), 9.829 (s, 1H, NH exch), 9.877 (s, 1H, NH exch). $^{13}C$ NMR (125 MHz, DMSO-$d_6$) data of **IIIf** exhibited signals at $\delta$: 27.183, 32.151, 32.326, 41.476, 69.423, 69.946, 102.158, 113.705, 122.671, 124.013, 129.574, 131.070, 149.426, and 151.102 which satisfy the carbon skelton of compound **IIIf**. APCI-MS of **IIIf** exhibited $MH^+$ ion peak at *m/z* 629.53 (100%). Elemental analysis Calculated for $C_{39}H_{40}N_4O_4$: C, 74.52; H, 6.37; N, 8.92%. Found C, 74.13; H, 6.20; N, 8.81%. Spectral and analytical data of **IIIf** fully support the structure assigned to it.

**Table 2.1: Physical constants and spectral data of bis-acridine derivatives IIIa-j**

| Comp no | Solvent of cryst./elution | m.p. ºC | Yield % | IR (KBr) $cm^{-1}$, $^1H$ (500MHz) & $^{13}C$ (125MHz) NMR ($D_2O$, DMSO-$d_6$, $CD_3OD$), $\delta$ J(Hz), APCI-MS (*m/z*; relt int %) |
|---|---|---|---|---|
| **1** | **2** | **3** | **4** | **5** |
| **IIIa** | $CHCl_3$:MeOH (7:3) | >300 | 43 | IR 3434 (NH), 1632, 1589, 1530 and 1472 (Ar) $cm^{-1}$. $^1H$ NMR (500MHz, $D_2O$) $\delta$ : 2.028-2.057 (t, 4H, J= 7 Hz, 2×$CH_2$, $C^2$, $C^{11}$), 2.622-2.651 (m, 12H, 6×$CH_2$, $C^3$, $C^5$, $C^6$, $C^8$, $C^9$, $C^{10}$), 3.964-3.992 (t, 4H, J= 7 Hz, 2×$CH_2$, $C^1$, $C^{12}$), 7.381-7.411 (t, 4H, J= 7.5 Hz, Ar), 7.474-7.491 (d, 4H, J= 9 Hz, Ar), 7.775-7.806 (m, 4H, Ar), 8.077-8.095 (d, 4H, J= 9 Hz, Ar). $^{13}C$ NMR (125MHz, DMSO-$d_6$) $\delta$: 30.8, 40.5, 53.0, 56.3, 113.4, 122.0, 123.7, 129.1, 130.3, 149.2 and 150.6 APCI-MS: *m/z* 555.40, ($MH^+$, 100%). Anal. Calcd for $C_{36}H_{38}N_6$: C, 77.98; H, 6.86; N, 15.16%. Found C, 77.63; H, 6.70; N, 15.30%. |
| **IIIb** | $CHCl_3$:MeOH (8:2) | >300 | 48 | IR 3412(NH), 1626, 1590, 1531 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, $CD_3OD$) $\delta$: 2.077-2.102 (t, 4H, J= 6.5 Hz, 2×$CH_2$, $C^2$, $C^{11}$), 2.488-2.632 (s+bs, 18H, 2×$CH_3$, 6×$CH_2$, $C^3$, $C^5$, $C^6$, $C^8$, $C^9$, $C^{10}$), 4.238-4.264 (t, 4H, J= 6.5 Hz, 2×$CH_2$, $C^1$, $C^{12}$), 7.496-7.526 (t, 2H, J= 7.5 Hz, Ar), 7.714-7.731 (d, 2H, J= 8.5 Hz, Ar), 7.730-7.803 (t, 4H, J= 7.5 Hz, Ar), 7.890-7.920 (t, 2H, J= 7.5 Hz, Ar), 8.252 (s, 2H, Ar), 8.463-8.480 (d, 2H, J= 8.5 Hz, Ar). $^{13}C$ NMR (125MHz, DMSO-$d_6$) $\delta$: 18.7, 30.7, 40.5, 53.1, 56.3, 113.4, 114.2, 122.0, 123.7, 124.4, 126.1, 127.1, 129.1, 130.3, 134.0, 148.7, 149.1 and 150.6. APCI-MS: *m/z* 583.40, ($MH^+$, 100%). Anal. Calcd for $C_{38}H_{42}N_6$: C, 78.35; H, 7.22; N, 14.43%. Found C, 78.70; H, 7.34; N, 14.20%. |
| **IIIc** | $CHCl_3$:MeOH (8:2) | >300 | 43 | IR 3414(NH), 1587, 1571, 1529, (Ar)$cm^{-1}$. $^1H$ NMR (500 MHz, $D_2O$) $\delta$ : 1.894 (bs, 4H, 2×$CH_2$, $C^2$, $C^{11}$), 2.462 (bs, 12H, 6×$CH_2$, $C^3$, $C^5$, $C^6$, $C^8$, $C^9$, $C^{10}$), 3.77 (s, 10H, 2×$OCH_3$, 2×$CH_2$, $C^1$, $C^{12}$), 6.874 (s, 2H, Ar), 7.182-7.221 (m, 5H, Ar), 7.273- |

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| | | | | 7.290 (d, 2H, J= 8.5 Hz, Ar), 7.592-7.652 (m, 3H, Ar), 7.802-7.787 (d, 2H, J= 7.5 Hz, Ar). $^{13}$C NMR (125MHz, DMSO-$d_6$) $\delta$: 30.7, 40.5, 53.1, 56.2, 57.7, 113.0, 114.2, 121.9, 123.8, 125.1, 126.0, 127.0, 128.8, 131.0, 147.7, 149.1, 150.5 and 154.7. APCI-MS: *m/z* 615.47, ($MH^+$, 100%). Anal. Calcd for $C_{38}H_{42}N_6O_2$: C, 74.26; H, 6.84; N, 13.68%. Found C, 73.92; H, 6.64; N, 13.41%. |
| **IIId** | $CHCl_3$:MeOH (8:2) | >300 | 41 | IR 3412(NH), 1590, 1531 (Ar) $cm^{-1}$. $^1$H NMR (500 MHz, $D_2O$) $\delta$ : 1.938-1.964 (t, 4H, J= 6.5 Hz, 2×$CH_2$, $C^2$, $C^{11}$), 2.275 (s, 6H, 2×$CH_3$), 2.549-2.574 (m, 12H, 6×$CH_2$, $C^3$, $C^5$, $C^6$, $C^8$, $C^9$, $C^{10}$), 3.779-3.804 (t, 4H, J= 6.5 Hz, 2×$CH_2$, $C^1$, $C^{12}$), 7.146-7.177 (t, 2H, J= 7.5 Hz, Ar), 7.303-7.333 (t, 2H, J= 7.5 Hz, Ar), 7.478-7.492 (d, 2H, J= 7 Hz, Ar), 7.528-7.545 (d, 2H, J= 8.5 Hz, Ar), 7.660-7.676 (d, 2H, J= 8 Hz, Ar), 7.708-7.738 (t, 2H, J= 7.5 Hz, Ar), 7.879-7.895 (d, 2H, J= 8 Hz, Ar). $^{13}$C NMR (125MHz, DMSO-$d_6$) $\delta$ : 19.1, 31.4, 41.5, 54.1, 57.1, 113.4, 114.2, 122.1, 123.7, 124.5, 126.7, 127.1, 128.9, 130.3, 134.0, 148.7, 149.1 and 150.6. APCI-MS: *m/z* 583.40, ($MH^+$, 100%). Anal. Calcd for $C_{38}H_{42}N_6$: C, 78.35; H, 7.22; N, 14.43%. Found C, 78.55; H, 7.12; N, 14.18%. |
| **IIIe** | $CHCl_3$:MeOH (8.5:1.5) | >300 | 47 | IR 3384(NH), 1580, 1535, 1478 (Ar) $cm^{-1}$. $^1$H NMR (500 MHz, $D_2O$) $\delta$ : 1.967 (bs, 4H, 2×$CH_2$, $C^2$, $C^{11}$), 2.768(bs, 12H, 6×$CH_2$, $C^3$, $C^5$, $C^6$, $C^8$, $C^9$, $C^{10}$), 3.695 (bs, 4H, 2×$CH_2$ ,$C^1$, $C^{12}$), 3.805 (s, 6H, 2×$OCH_3$), 6.977 (s, 2H, Ar), 7.102 (s, 2H, Ar), 7.268 (s, 4H, Ar), 7.370-7.390 (d, 2H, J= 10 Hz, Ar), 7.66-7.69 (t, 2H, J= 7.5 Hz, Ar), 7.771 (s, 2H, Ar). $^{13}$C NMR (125MHz, DMSO-$d_6$) $\delta$ : 30.4, 40.5, 53.1, 56.3, 57.7, 112.6, 114.0, 122.2, 123.9, 125.1, 126.1, 127.0, 128.8, 131.1, 147.7, 149.1, 150.7 and 154.5. APCI-MS: *m/z* 615.40, ($MH^+$, 100%). Anal. Calcd for $C_{38}H_{42}N_6O_2$: C, 74.26; H, 6.84; N, 13.68%. Found C, 74.47; H, 6.79; N, 13.82%. |

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| **IIIf** | $CHCl_3$:MeOH (8:2) | >300 | 42 | IR 3374(NH), 1560, 1515 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$) $\delta$ : 1.656-1.679 (m, 4H, 2×$CH_2$, $C^2$, $C^{16}$), 1.960-1.989 (m, 4H, 2×$CH_2$, $C^3$, $C^{15}$), 3.145-3.165 (t, 2H, J= 5 Hz, $C^{10a}$, $C^{14a}$), 3.522-3.546 (t, 4H, J= 6 Hz, 2×$CH_2$, $C^1$, $C^{17}$), 3.716-3.739 (d, 1H, J= 11.5 Hz, CH, $C^4$), 4.096 (s ,4H, $C^6$, $C^8$), 4.164-4.186 (d, 1H, J= 11 Hz CH, $C^{12}$), 4.482-4.542 (m, 2H, $C^{10b}$, $C^{14b}$), 7.53-7.549 (d, 4H, J= 9.5 Hz Ar), 7.904-8.024 (m, 8H, Ar), 8.575-8.708 (bs, 4H, Ar), 9.829 (s, 1H, NH exch), 9.877 (s, 1H, NH exch). $^{13}C$ NMR (125MHz, DMSO-$d_6$) $\delta$ : 27.1, 32.1, 32.3, 41.4, 69.4, 69.9, 102.1, 113.7, 122.6, 124.0, 129.5, 131.1, 149.4 and 151.1. APCI-MS: *m/z* 629.53, ($MH^+$, 100%). Anal. Calcd for $C_{39}H_{40}N_4O_4$: C, 74.52; H, 6.37; N, 8.92%. Found C, 74.13; H, 6.20; N, 8.81%. |
| **IIIg** | $CHCl_3$:MeOH (8:2) | >300 | 43 | IR 3414 (NH), 1587, 1529, 1463 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$+$D_2O$) $\delta$ : 1.644-1.684 (m, 4H, 2×$CH_2$, $C^2$, $C^{16}$), 1.983-1.919 (m, 4H, 2×$CH_2$, $C^3$, $C^{15}$), 2.524 (s, 6H, 2×$CH_3$), 3.301-3.324 (d, 2H, J= 11.5 Hz, $C^{10a}$, $C^{14a}$), 3.457-3.502 (m, 4H, 2×$CH_2$, $C^1$, $C^{17}$), 4.046-4.075 (m, 4H, 2×$CH_2$, $C^6$, $C^8$), 4.106-4.128 (t, 2H, J= 5.5 Hz, $C^4$, $C^{12}$), 4.501-4.520 (t, 2H, J= 5 Hz, $C^{10b}$, $C^{14b}$), 7.508-7.538 (t, 2H, J= 7.5 Hz, Ar), 7.877-7.812 (m, 4H, Ar), 7.896-7.969 ( m, 4H, Ar), 8.386 (bs, 2H, Ar), 8.517 (bs, 2H, Ar). $^{13}C$ NMR (125MHz, DMSO-$d_6$) $\delta$ 18.9, 27.1, 32.3, 32.7, 41.5, 69.5, 69.9, 102.2, 114.0, 114.9, 122.5, 123.9, 124.9, 126.7, 127.7, 129.5, 130.7, 134.2, 148.9, 149.7 and 151.2. APCI-MS: *m/z* 657.60, ($MH^+$, 100%). Anal. Calcd for $C_{41}H_{44}N_4O_4$: C, 75.00; H, 6.70; N, 8.54%. Found C, 75.39; H, 6.41; N, 8.26%. |
| **IIIh** | $CHCl_3$:MeOH (8:2) | >300 | 39 | IR 3387(NH), 1593, 1539, 1463 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$+$D_2O$) $\delta$ : 1.600-1.639 (m, 4H, 2×$CH_2$, $C^2$, $C^{16}$), 1.896-1.939 (m, 4H, 2×$CH_2$, $C^3$, $C^{15}$), 3.293-3.316 (d, 2H, J= 11.5 Hz, $C^{10a}$, $C^{14a}$), 3.447-3.494 (m, 4H, 2×$CH_2$, $C^1$, $C^{17}$), 3.925 (s, 6H, 2×$OCH_3$), 4.042-4.070 (m, |

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| | | | | 4H, 2×$CH_2$, $C^6$, $C^8$), 4.093-4.118 (t, 2H, J= 6.5 Hz, $C^4$, $C^{12}$), 4.508-4.528 (t, 2H, J= 5 Hz, $C^{10b}$, $C^{14b}$),7.486-7.517 (t, 2H, J= 7.5 Hz, Ar), 7.645-7.669 (dd, 2H, J= 2.5 & 9.5 Hz, Ar), 7.792-7.851 (m, 6H, Ar), 7.886-7.917 (t, 2H, J= 7.5 Hz, Ar), 8.409-8.426 (d, 2H, J= 8.5 Hz, Ar). $^{13}$C NMR (125MHz, DMSO-$d_6$) $\delta$ : 32.4, 32.7, 41.7, 57.1, 69.6, 70.2, 103.1, 113.4, 114.5, 121.9, 122.3, 124.2, 125.8, 126.6, 127.7, 129.3, 131.8, 147.9, 149.7, 151.3 and 155.5. APCI-MS: *m/z* 689.40, ($MH^+$, 100%). Anal. Calcd for $C_{41}H_{44}N_4O_6$: C, 71.51; H, 6.40; N, 8.14%. Found C, 71.89; H, 6.81; N, 8.60%. |
| **IIIi** | $CHCl_3$:MeOH (8:2) | >300 | 36 | IR 3419(NH), 1589, 1533 (Ar) $cm^{-1}$. $^1$H NMR (500 MHz, DMSO-$d_6$+$D_2O$) $\delta$ : 1.642-1.666 (m, 4H, 2×$CH_2$, $C^2$, $C^{16}$), 1.954-1.982 (m, 4H, 2×$CH_2$, $C^3$, $C^{15}$), 2.731 (s, 6H, 2×$CH_3$), 3.175-3.184 (d, 2H, J= 4.5 Hz, $C^{10a}$, $C^{14a}$), 3.515-3.550 (m, 4H, 2×$CH_2$, $C^1$, $C^{17}$), 4.072 (bs, 4H, 2×$CH_2$, $C^6$, $C^8$), 4.183-4.204 (t, 2H, J= 5 Hz, $C^4$, $C^{12}$), 4.523-4.542 (t, 2H, J= 5 Hz, $C^{10b}$, $C^{14b}$), 7.450-7.481 (t, 2H, J= 7.5 Hz, Ar), 7.558-7.571 (t, 2H, J= 7.5 Hz, Ar), 7.831-7.844 (d, 2H, J= 6.5 Hz, Ar), 7.963-7.992 (t, 2H, J= 7.5 Hz, Ar), 8.303-8.320 (d, J= 8.5 Hz, 2H, Ar), 8.471 (s, 2H, Ar), 8.558 (s, 2H, Ar). $^{13}$C NMR (125MHz, DMSO-$d_6$) $\delta$ : 19.1, 27.1, 32.4, 32.7, 41.7, 69.5, 69.8, 102.5, 113.8, 114.5, 122.6, 124.1, 124.8, 126.9, 127.7, 129.4, 130.9, 134.7, 149.1, 149.8 and 151.3. APCI-MS: *m/z* 657.53, ($MH^+$, 100%). Anal. Calcd for $C_{41}H_{44}N_4O_4$: C, 75.00; H, 6.70; N, 8.54%. Found C, 75.46; H, 6.96; N, 8.79%. |
| **IIIj** | $CHCl_3$:MeOH (8:2) | >300 | 38 | IR 3419(NH), 1576, 1536, 1474 (Ar) $cm^{-1}$. $^1$H NMR (500 MHz, DMSO-$d_6$+$D_2O$) $\delta$ : 1.609-1.647(m, 4H, 2×$CH_2$, $C^2$, $C^{16}$), 1.901-1.959 (m, 4H, 2×$CH_2$, $C^3$, $C^{15}$), 3.313-3.336 (d, 2H, J= 11.5 Hz, $C^{10a}$, $C^{14a}$), 3.447-3.494 (m, 4H, 2×$CH_2$, $C^1$, $C^{17}$), 4.023-4.051 (m, 4H, 2×$CH_2$, $C^6$, $C^8$), 4.071 (s, 6H, 2×$OCH_3$), 4.130-4.152 (t, 2H, J=5.5 Hz, $C^4$, $C^{12}$), 4.527-4.546 (t, 2H, J= 5 |

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| | | | | Hz, $C^{10b}$, $C^{14b}$), 7.443-7.546 (m, 6H, Ar), 7.910-7.941 (t, 2H, J= 7.5 Hz, Ar), 8.000-8.015(d, 2H, J= 7.5 Hz, Ar), 8.150-8.187 (d, 2H, J= 8.5 Hz, Ar), 8.441-8.457 (d, 2H, J= 8 Hz, Ar). $^{13}$C NMR (125MHz, DMSO-$d_6$) $\delta$ : 27.2, 32.2, 32.6, 41.8, 57.2, 69.4, 69.8, 102.5, 113.6, 114.3, 122.7, 124.3, 125.7, 126.5, 127.7, 129.3, 131.2, 147.9, 149.5, 151.1 and 155.1. APCI-MS: *m/z* 689.53 ($MH^+$, 100%). Anal. Calcd for $C_{41}H_{44}N_4O_6$: C, 71.51; H, 6.40; N, 8.14%. Found C, 71.94; H, 6.14; N, 8.49%. |

Similarly condensation of acridines **Ib-e** with **IIb** gave corresponding condensation products **IIIg, IIIh, IIIi** and **IIIj** (Scheme 2.1). All these condensation products i.e. **IIIg-i** were purified by column chromatography over silica gel. Spectral and analytical data of **IIIg-i** reported in Table 2.1 fully support the structures assigned to them.

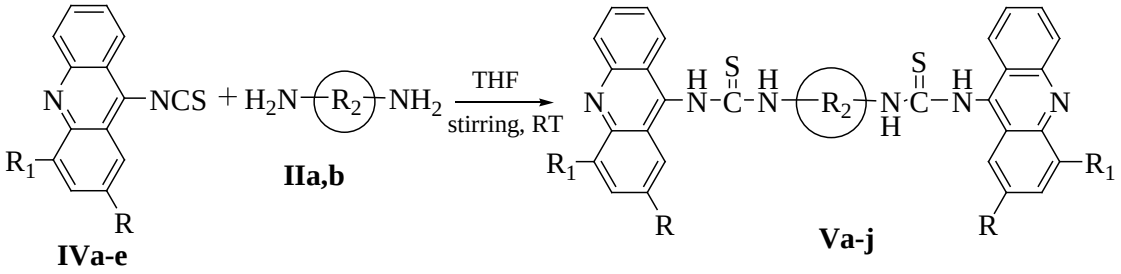
9-Isothiocyanatoacridine (**IVa**; Scheme 2.2) and 3-(4-(3-amino propyl)piperazin-1-yl)propan-1-amine (**IIa**; Scheme 2.2) were dissolved in THF (10 ml) separately and mixed together with constant stirring and allowed to stand at room temperature. After standing for 2 hour solid started separating out which was further allowed to stand for 6 hours and the reaction contents were filtered. Solid residue so obtained was purified by column chromatography over silica gel to give pure product **Va** *i.e.* 1-(3-(4-(3-(9-acridinylamine)methanethioamido propyl)piperazin-1-yl) propyl)-3-(acridin-9-yl)thiourea (**Va**; Scheme 2.2) in 37% yield. IR spectrum of **Va** give absorption signal at 3425 and 1621 $cm^{-1}$ which are due to NH and C=S functional groups respectively and strong absorption signals at 1586 $cm^{-1}$ and 1523 $cm^{-1}$ arise due to aromatic region of acridinyl moiety. $^1$H NMR (500MHz, DMSO-$d_6$+$D_2O$) (Figure 2.5) data of **Va** exhibited signals at $\delta$: 1.454 (bs, 2H, $C^{2a}$, $C^{11a}$),

1.642-1.675 (m, 2H, $C^{2b}$, $C^{11b}$), 2.018-2.192 (m, 12H, 6×$CH_2$, $C^3$, $C^5$, $C^6$, $C^8$, $C^9$, $C^{10}$), 3.052 (bs, 2H, $C^{1a}$, $C^{12a}$), 3.508-3.519 (d, 2H, J= 5.5 Hz, $C^{1b}$, $C^{12b}$), 7.074-7.168 (m, 4H, Ar), 7.343-7.415 (m, 4H, Ar), 7.524-7.623 (m, 4H, Ar), 8.104-8.136 (m, 4H, Ar), $^{13}$C NMR (125MHz, DMSO-$d_6$) (Figure 2.6) data of **Va** exhibited signals at $\delta$: 30.745, 40.442, 52.749, 56.308, 112.418, 123.551, 124.747, 130.143, 131.161, 149.009, 151.109 and 176.967. APCI-MS: (Figure 2.7) of **Va** exhibited $MH^+$ ion peak at *m/z* 673.39 (100%). Elemental analysis Calculated for $C_{38}H_{40}N_8S_2$: C, 67.86; H, 5.95; N, 16.67; S, 9.52%. Found C, 67.47; H, 6.19; N, 16.89; S, 9.50%. Spectral and analytical data of **Va** is in full agreement with the structure assigned to it.

Similarly condensation of 9-isothiocyanatoacridine (**IVa**), 9-isothiocyanato-2-methylacridine (**IVb**), 9-isothiocyanato-2-methoxyacridine (**IVc**), 9-isothiocyanato-4-methylacridine (**IVd**) and 9-isothiocyanato-4-methoxyacridine (**IVe**) with 3-(4-(3-aminopropyl)piperazin-1-yl)propan-1-amine **IIa** and 2,4,8,10-tetraoxaspiro[5,5] undecane-3,9-dipropane amine **IIb** gave corresponding condensation products **Va-j** (Scheme 2.2). All these compounds were purified by column chromatography over silica gel. Spectral and analytical data of **Va-j** reported in Table 2.2 fully support the structures assigned to them.

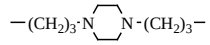
### 2.2.2 Biological results and discussion

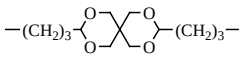
Anti-inflammatory activity [21] evaluation of **IIIa-j** and **Va-j** was carried out using carrageenan induced paw oedema assay and results are summarized in the **Table 2.3**. A look at the **Table 2.3** indicates that out of these compounds *i.e.* **IIIa-j** and **Va-j** compound **IIIg** exhibited interesting *i.e.* 41% anti-inflammatory activity, whereas most commonly used standard drug ibuprofen exhibited 39% anti-inflammatory activity at 50 mg/kg *p.o.* As mentioned in chapter one [Ref 52-54] a



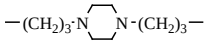
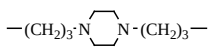
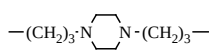
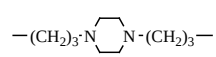
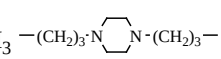

| | R | $R_1$ |
|---|---|---|
| **IVa** | H | H |
| **IVb** | $CH_3$ | H |
| **IVc** | $OCH_3$ | H |
| **IVd** | H | $CH_3$ |
| **IVe** | H | $OCH_3$ |

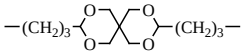
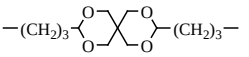
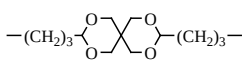
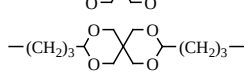
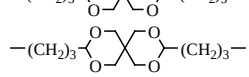
**$R_2$**

**IIa** 

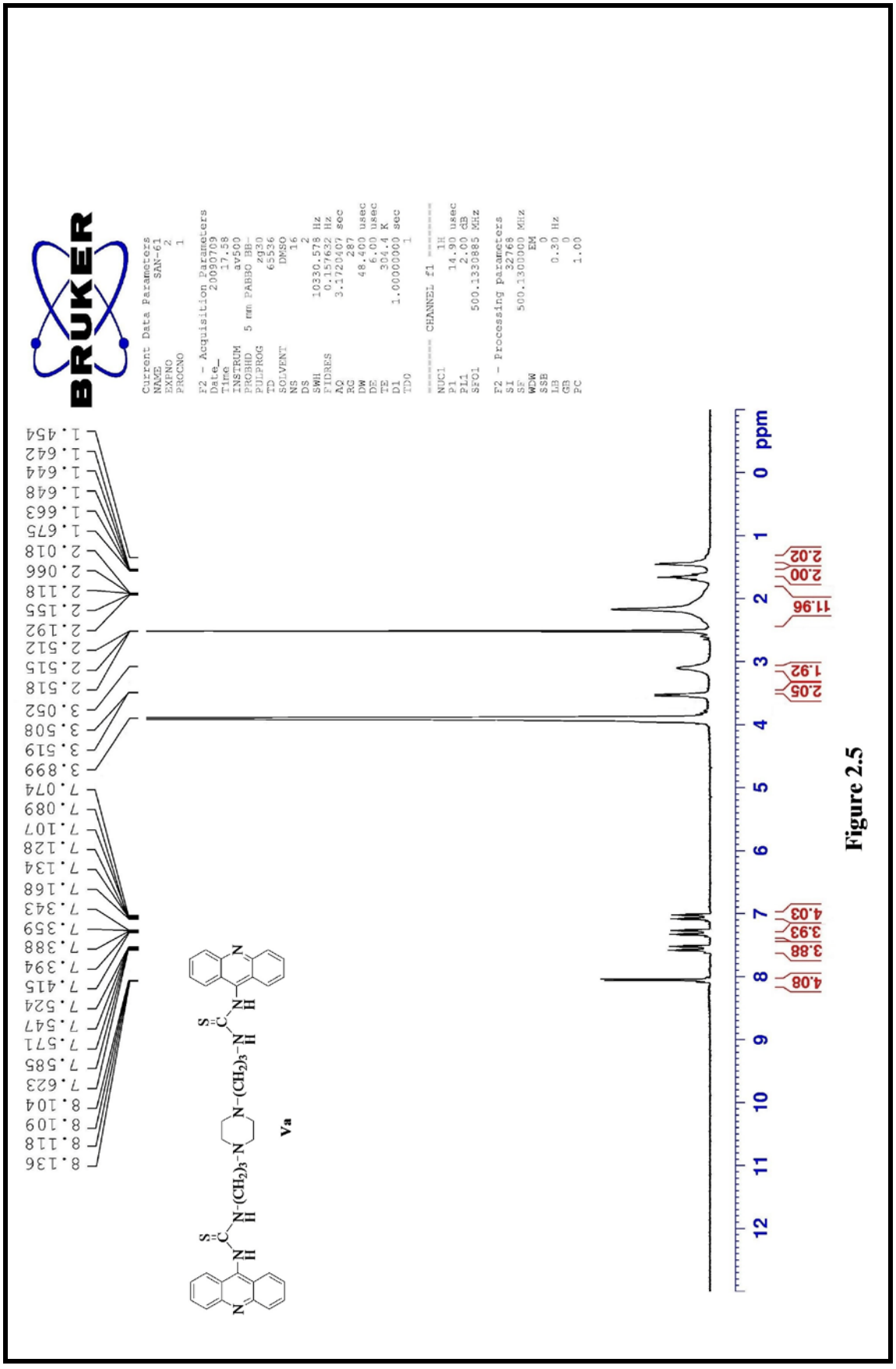
**IIb** 

For Compounds **Va-j**

| | R | $R_1$ | $R_2$ |
|---|---|---|---|
| **Va** | H | H |  |
| **Vb** | $CH_3$ | H |  |
| **Vc** | $OCH_3$ | H |  |
| **Vd** | H | $CH_3$ |  |
| **Ve** | H | $OCH_3$ |  |

| | R | $R_1$ | $R_2$ |
|---|---|---|---|
| **Vf** | H | H |  |
| **Vg** | $CH_3$ | H |  |
| **Vh** | $OCH_3$ | H |  |
| **Vi** | H | $CH_3$ |  |
| **Vj** | H | $OCH_3$ |  |

Scheme:-2.2 Synthesis of acridine derivatives **Va-j**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PROCNO 1
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DS 2
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FIDRES 0.157632 Hz
AQ 3.1720407 sec
RG 287
DW 48.400 usec
DE 6.00 usec
TE 304.4 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 14.90 usec
PL1 2.00 dB
SFO1 500.1330885 MHz
F2 - Processing parameters
SI 32768
SF 500.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
Va
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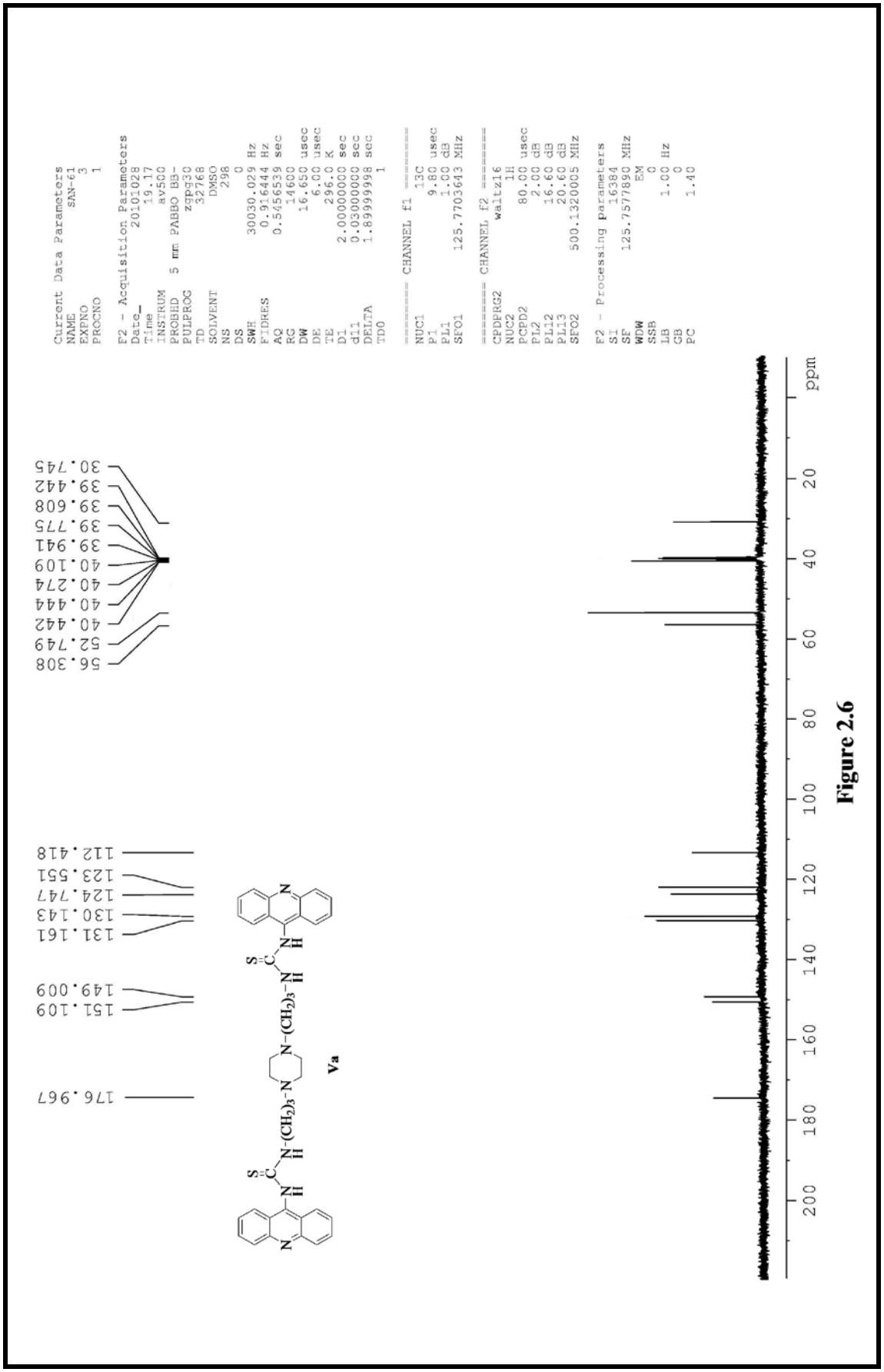
2.02
2.00
4.08
3.88
3.93
4.03

**Figure 2.5**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FIDRES 0.916444 Hz
AQ 0.5456539 sec
RG 14600
DW 16.650 usec
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d11 0.03000000 sec
DELTA 1.89999998 sec
TD0 1
CHANNEL f1
NUC1 13C
P1 9.80 usec
PL1 1.00 dB
SFO1 125.7703643 MHz
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 2.00 dB
PL12 16.60 dB
PL13 20.60 dB
SFO2 500.1320005 MHz
F2 - Processing parameters
SI 16384
SF 125.7577890 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
56.308
52.749
40.442
40.444
40.274
40.109
39.941
39.775
39.608
39.442
30.745
176.967
151.109
149.009
131.161
130.143
124.747
123.551
112.418
Va
ppm
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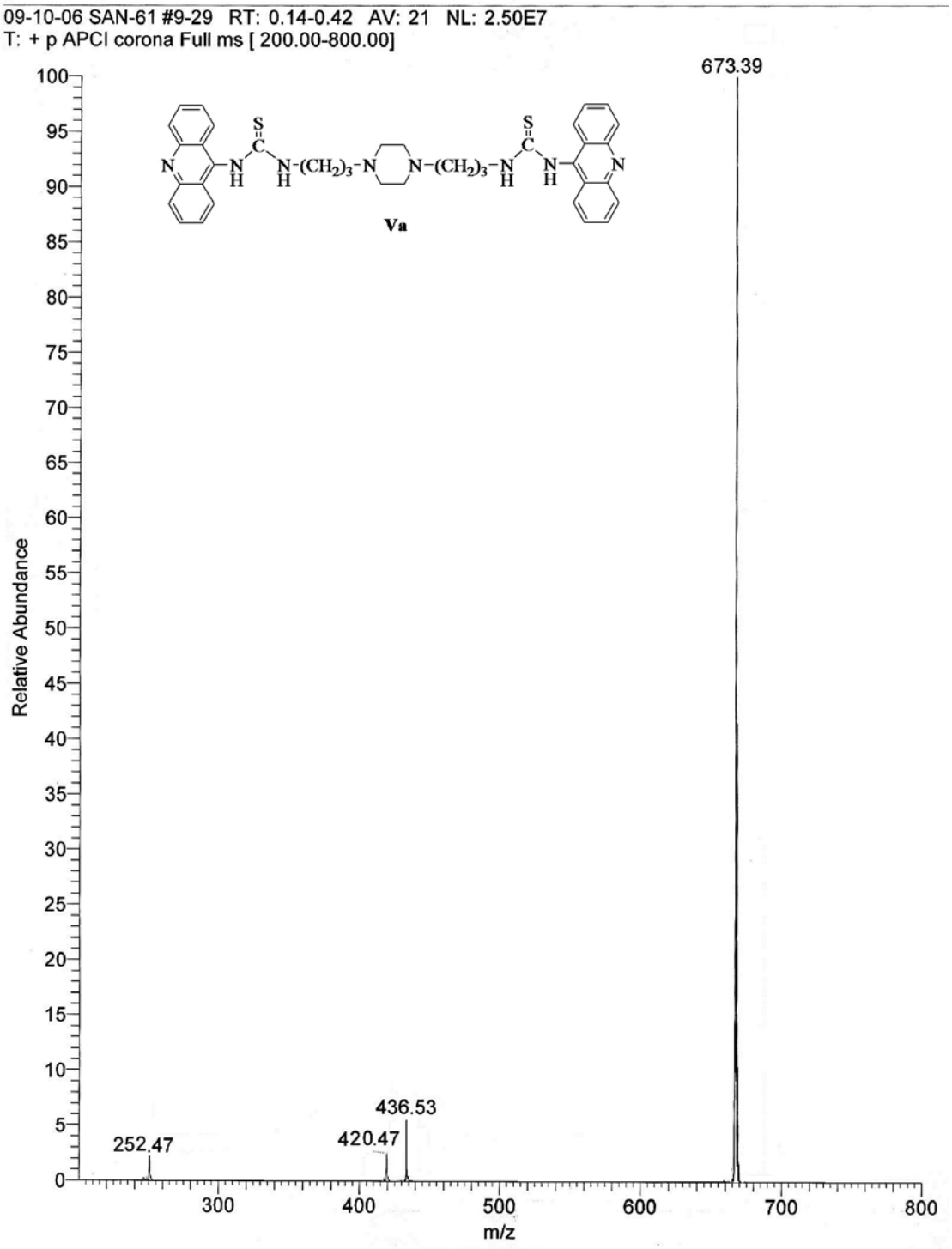
160
140
120
100
80
60
40
20

**Figure 2.6**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420.47
252.47
Relative Abundance
m/z
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
300
400
500
600
700
800

Va

**Figure 2.7**

**Table 2.2: Physical constants and spectral data of acridine derivatives Va-j.**

| Comp no | Solvent of cryst./elution | m.p. ºC | Yield % | IR (KBr) $cm^{-1}$, $^1H$ (500MHz) & $^{13}C$ (125MHz) NMR (DMSO-$d_6$,$D_2O$), $\delta$ J(Hz), APCI-MS (*m/z*; relt int %) |
|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 |
| **Va** | $CHCl_3$:MeOH (8:2) | >300 | 37 | IR 3425 (NH), 1586, 1523, 1462 (Ar) $cm^{-1}$. $^1H$ NMR (500MHz, DMSO-$d_6$+$D_2O$) $\delta$ : 1.454 (bs, 2H, $C^{2a}$, $C^{11a}$), 1.642-1.675 (m, 2H, $C^{2b}$, $C^{11b}$), 2.018-2.192 (m, 12H, 6×$CH_2$, $C^3$, $C^5$, $C^6$, $C^8$, $C^9$, $C^{10}$), 3.052 (bs, 2H, $C^{1a}$, $C^{12a}$), 3.508-3.519 (d, 2H, J= 5.5 Hz, $C^{1b}$, $C^{12b}$), 7.074-7.168 (m, 4H, Ar), 7.343-7.415 (m, 4H, Ar), 7.524-7.623 (m, 4H, Ar), 8.104-8.136 (m, 4H, Ar). $^{13}C$ NMR (125MHz, DMSO-$d_6$) $\delta$: 30.7, 40.4, 52.7, 56.3, 112.4, 123.5, 124.7, 130.1, 131.1, 149.0, 151.1 and 176.9. APCI-MS: *m/z* 673.39, ($MH^+$, 100%). Anal. Calcd for $C_{38}H_{40}N_8S_2$: C, 67.86; H, 5.95; N, 16.67; S, 9.52%. Found C, 67.47; H, 6.19; N, 16.89; S, 9.50%. |
| **Vb** | $CHCl_3$:MeOH (8:2) | >300 | 39 | IR 3439 (NH), 1572, 1523, 1460 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$+$D_2O$) $\delta$ : 1.622-1.646 (m, 4H, 2×$CH_2$, $C^2$, $C^{11}$), 2.074-2.175 (m, 12H, 6×$CH_2$, $C^3$, $C^5$, $C^6$, $C^8$, $C^9$, $C^{10}$), 2.620 (s, 6H, 2×$CH_3$), 3.313 (bs, 4H, 2×$CH_2$, $C^1$, $C^{12}$), 7.134 (bs, 2H, Ar), 7.243 (bs, 2H, Ar), 7.474-7.486 (d, 2H, J= 6 Hz, Ar), 7.609-7.636 (t, 2H, J= 7 Hz, Ar), 7.890-7.901 (d, 2H, J= 5.5 Hz, Ar), 7.938-7.955 (d, 2H, J= 8.5 Hz, Ar), 8.055-8.072 (d, 2H, J= 8.5 Hz, Ar). $^{13}C$ NMR (125MHz, DMSO-$d_6$) $\delta$ : 17.9, 30.5, 41.0, 52.3, 56.0, 113.4, 114.5, 122.0, 123.7, 124.7, 126.1, 127.1, 130.0, 131.1, 135.1, 148.5, 149.3, 151.1 and 177.1. APCI-MS: *m/z* 701.22, ($MH^+$, 47%). Anal. Calcd for $C_{40}H_{44}N_8S_2$: C, 68.57; H, 6.29; N, 16; S, 9.14%. Found C, 68.84; H, 6.53; N, 15.87; S, 9.49%. |
| **Vc** | $CHCl_3$:MeOH (8:2) | >300 | 40 | IR 3414 (NH), 1584, 1520, 1465 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$+$D_2O$) $\delta$ : 1.606-1.617 (m, 4H, 2×$CH_2$, |

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| | | | | $C^{2}$, $C^{11}$), 2.039-2.155 (m, 12H, 6×$CH_2$, $C^{3}$, $C^{5}$, $C^{6}$, $C^{8}$, $C^{9}$, $C^{10}$), 3.158-3.196 (m, 2H, $C^{1a}$, $C^{12a}$), 3.355-3.517 (m, 2H, $C^{1b}$,$C^{12b}$), 3.901 (s, 6H, 2×$OCH_3$), 7.101-7.181 (m, 6H, Ar), 7.570-7.599 (t, 2H, J= 7.5 Hz, Ar), 7.685-7.702 (d, 2H, J= 8.5 Hz, Ar), 7.828 (bs, 2H, Ar), 8.091-8.108 (d, 2H, J= 8.5 Hz, Ar), $^{13}$C NMR (125MHz, DMSO-$d_6$) $\delta$ : 31.1, 40.5, 52.1, 56.2, 57.1, 113.1, 114.2, 120.7, 122.8, 125.1, 125.9, 126.8, 128.8, 131.0, 147.3, 149.5, 150.2, 154.7 and 178.0. APCI-MS: *m/z*: 733.23, ($MH^+$, 57%). Anal. Calcd for $C_{40}H_{44}N_8O_2S_2$: C, 65.57; H, 6.01; N, 15.3; S, 8.74%. Found C, 65.89; H, 6.47; N, 15.68; S, 8.49%. |
| **Vd** | $CHCl_3$:MeOH (8:2) | >300 | 41 | IR 3426 (NH), 1586, 1522, 1463 (Ar) $cm^{-1}$. $^1$H NMR (500 MHz, DMSO-$d_6$+$D_2O$) $\delta$: 1.609-1.633 (m, 4H, 2×$CH_2$, $C^{2}$, $C^{11}$), 2.162 (bs, 12H, 6×$CH_2$, $C^{3}$, $C^{5}$, $C^{6}$, $C^{8}$, $C^{9}$, $C^{10}$), 2.607 (s, 6H, 2×$CH_3$), 3.281-3.352 (bs, 4H, 2×$CH_2$, $C^{1}$, $C^{12}$), 7.121 (bs, 2H, Ar), 7.229 (bs, 2H, Ar), 7.461-7.473 (d, 2H, J= 6 Hz, Ar), 7.596-7.623 (t, 2H, J= 7 Hz, Ar), 7.877-7.888 (d, 2H, J= 5.5 Hz, Ar), 7.925-7.942 (d, 2H, J= 8.5 Hz, Ar), 8.059-8.042 (d, 2H, J= 8.5 Hz, Ar). $^{13}$C NMR (125MHz, DMSO-$d_6$) $\delta$ : 17.9, 30.6, 40.7, 52.5, 56.5, 113.7, 114.9, 122.4, 124.1, 125.2, 126.5, 126.6, 127.6, 178.2, 130.4, 131.4, 135.7, 149.2, 149.9 and 151.7. APCI-MS: *m/z*: 701.26, ($MH^+$, 84%). Anal. Calcd for $C_{40}H_{44}N_8S_2$: C, 68.57; H, 6.29; N, 16.00; S, 9.14%. Found C, 68.11; H, 6.74; N, 16.00; S, 9.31%. |
| **Ve** | $CHCl_3$:MeOH (8:2) | >300 | 33 | IR 3432 (NH), 1540, 1505, 1477 (Ar) $cm^{-1}$. $^1$H NMR (500 MHz, DMSO-$d_6$+$D_2O$) $\delta$: 1.599-1.644 (m, 4H, 2×$CH_2$, $C^{2}$, $C^{11}$), 2.074-2.121 (m, 12H, 6×$CH_2$, $C^{3}$, $C^{5}$, $C^{6}$, $C^{8}$, $C^{9}$, $C^{10}$), 3.369 (bs, 4H, 2×$CH_2$, $C^{1}$, $C^{12}$), 3.808 (s, 6H, 2×$OCH_3$), 7.251-7.397 (m, 6H, Ar), 7.702-7.803 (m, 6H, Ar), 8.035-8.051 (d, 2H, J= 8 Hz, Ar). $^{13}$C NMR (125MHz, DMSO-$d_6$) $\delta$: 31.2, 40.9, 53.3, 56.1, 56.9, 112.7, |

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| | | | | 114.2, 122.3, 123.9, 125.6, 126.7, 127.5, 129.1, 131.5, 148.2, 149.6, 152.0, 155.5 and 179.2. APCI-MS: *m/z* 733.22, ($MH^+$, 32%). Anal. Calcd for $C_{40}H_{44}N_8O_2S_2$: C, 65.57; H, 6.01; N, 15.30; S, 8.74%. Found C, 65.39; H, 6.00; N, 14.98; S, 8.64%. |
| **Vf** | $CHCl_3$:MeOH (8:2) | >300 | 37 | IR 3421 (NH), 1590, 1525, 1471 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$+$D_2O$) $\delta$ : 1.615-1.628 (m, 4H, 4×$CH_2$, $C^2$, $C^{16}$), 1.646-1.673 (m, 4H, 4×$CH_2$, $C^3$, $C^{15}$), 3.328-3.351 (m, 6H, $C^1$, $C^{17}$, $C^{10a}$, $C^{14a}$), 3.514-3.563 (m, 4H, 2×$CH_2$, $C^6$, $C^8$), 4.263-4.284 (t, 2H, J= 5 Hz, $C^4$, $C^{12}$), 4.526-4.543 (t, 2H, J= 4.5 Hz, $C^{10b}$, $C^{14b}$), 7.187-7.217 (t, 4H, J= 7.5 Hz, Ar), 7.582-7.612 (t, 4H, J= 7.5 Hz, Ar), 7.699-7.762 (m, 4H, Ar), 8.052-8.069 (d, 4H, J= 8.5 Hz, Ar). $^{13}C$ NMR (125MHz, DMSO-$d_6$) $\delta$: 27.4, 32.2, 32.4, 41.8, 69.8, 70.1, 103.2, 112.8, 123.7, 125.2, 130.6, 131.7, 149.4, 151.6 and 177.3. APCI-MS: *m/z* 747.32, ($MH^+$, 23%). Anal. Calcd for $C_{41}H_{42}N_6O_4S_2$: C, 65.95; H, 5.63; N, 11.26; S, 8.57%. Found C, 65.87; H, 5.43; N, 11.19; S, 8.43%. |
| **Vg** | $CHCl_3$:MeOH (8:2) | >300 | 39 | IR 3425 (NH), 1578, 1525, 1464 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$+$D_2O$) $\delta$ : 1.619-1.629 (m, 4H, 4×$CH_2$, $C^2$, $C^{16}$), 1.644-1.675 (m, 4H, 4×$CH_2$, $C^3$, $C^{15}$), 2.611 (s, 6H, 2×$CH_3$), 3.152-3.357 (m, 6H, 2×$CH_2$, $C^1$, $C^{17}$, $C^{10a}$, $C^{14a}$), 3.514-3.579 (m, 4H, 2×$CH_2$, $C^6$, $C^8$), 4.261-4.287 (t, 2H, J= 6.5 Hz, $C^4$, $C^{12}$), 4.531-4.548 (t, 2H, J= 4.5 Hz, $C^{10b}$, $C^{14b}$), 7.187-7.217 (t, 4H, J= 7.5 Hz, Ar), 7.290-7.762 (m, 4H, Ar), 7.582-7.612 (t, 4H, J= 7.5 Hz, Ar), 8.052-8.069 (d, 4H, J= 8.5 Hz, Ar). $^{13}C$ NMR (125MHz, DMSO-$d_6$) $\delta$: 18.9, 27.3, 32.1, 32.3, 41.6, 69.7, 69.9, 102.5, 113.4, 114.7, 122.1, 123.7, 124.8, 125.4, 126.3, 127.4, 130.1, 135.5, 149.0, 149.7, 151.5 and 178.1. APCI-MS: *m/z* 775.43, ($MH^+$, 8%). Anal. Calcd for $C_{43}H_{46}N_6O_4S_2$: C, 66.67; H, 5.94; N,10.85; S, 8.27%. Found C, 66.94; |

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| | | | | H, 5.62; N, 11.20; S, 8.61%. |
| **Vh** | $CHCl_3$:MeOH (8:2) | >300 | 38 | IR 3425 (NH), 1573, 1529, 1479 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$+$D_2O$) $\delta$ : 1.575-1.679 (m, 4H, 2×$CH_2$, $C^2$, $C^{16}$), 1.908-1.984 (m, 4H, 2×$CH_2$, $C^3$, $C^{15}$), 3.499-3.554 (m, 6H, $C^1$, $C^{17}$, $C^{10a}$, $C^{14a}$), 3.908 (s, 6H, 2×$OCH_3$), 4.051-4.081 (m, 4H, 2×$CH_2$, $C^6$, $C^8$), 4.181-4.202 (t, 2H, J= 5.5 Hz, $C^4$, $C^{12}$), 4.530-4.555 (t, 2H, J= 6.5 Hz, $C^{10b}$, $C^{14b}$), 7.525-7.551 (m, 4H, Ar), 7.901-7.995 (m, 8H, Ar), 8.321-8.575 (m, 2H, Ar). $^{13}C$ NMR (125MHz, DMSO-$d_6$) $\delta$: 27.1, 32.0, 32.1, 41.7, 56.5, 69.6, 69.8, 112.7, 114.2, 122.4, 123.9, 125.6, 126.7, 127.5, 129.1, 131.5, 148.2, 149.6, 152.3, 155.5 and 179.2. APCI-MS: *m/z* 808.35, ($MH^+$+1, 21%). Anal. Calcd for $C_{43}H_{46}N_6O_6S_2$: C, 64.00; H, 5.75; N, 10.41; S, 7.95%. Found C, 64.29; H, 5.42; N, 10.97; S, 8.14%. |
| **Vi** | $CHCl_3$:MeOH (8:2) | >300 | 37 | IR 3425 (NH), 1586, 1523, 1462 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$+$D_2O$) $\delta$ : 1.559-1.616 (m, 4H, 2×$CH_2$, $C^2$, $C^{16}$), 1.628-1.655 (m, 4H, 2×$CH_2$, $C^3$, $C^{15}$), 2.593 (s, 6H, 2×$CH_3$), 3.273-3.497 (m, 10H, $C^6$, $C^8$, $C^1$, $C^{17}$, $C^{10a}$, $C^{14a}$), 4.246-4.267 (t, 2H, J= 5.5 Hz, $C^4$, $C^{12}$), 4.487 (bs, 2H, $C^{10b}$, $C^{14b}$), 7.139 (bs, 2H, Ar), 7.231 (bs, 2H, Ar), 7.489 (bs, 2H, Ar), 7.628 (bs, 2H, Ar), 7.830-7.942 (d, 2H, J= 6 Hz, Ar), 8.041-8.057 (d, 2H, J= 8 Hz, Ar). $^{13}C$ NMR (125MHz, DMSO-$d_6$) $\delta$: 18.8, 27.1, 32.0, 32.1, 41.5, 69.6, 69.8, 102.2, 114.1, 114.7, 122.7, 124.0, 125.3, 126.7, 127.5, 130.3, 131.5, 136.3, 149.6, 150.3, 151.9 and 178.4. APCI-MS: *m/z* 775.42, ($MH^+$, 12%). Anal. Calcd for $C_{43}H_{46}N_6O_4S_2$: C, 66.67; H, 5.94; N, 10.85; S, 8.27%. Found C, 66.98; H, 5.42; N, 10.97; S, 8.20%. |
| **Vj** | $CHCl_3$:MeOH (8:2) | >300 | 39 | IR 3425 (NH), 1565, 1538, 1483 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$+$D_2O$) $\delta$: 1.632-1.681 (m, 4H, 2×$CH_2$, $C^2$, $C^{16}$), 1.962-1.991 (m, 4H, 2×$CH_2$, $C^3$, $C^{15}$), 3.522-3.546 (m, 6H, $C^1$, $C^{17}$, $C^{10a}$, $C^{14a}$), |

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| | | | | 3.912 (s, 6H, 2×$OCH_3$), 4.091-4.102 (m, 4H, 2×$CH_2$, $C^6$, $C^8$), 4.168-4.189 (t, 2H, J= 5 Hz, $C^4$, $C^{12}$), 4.525-4.545 (t, 2H, J= 5 Hz, $C^{10b}$, $C^{14b}$), 7.524-7.558 (m, 4H, Ar), 7.900-7.994 (m, 8H, Ar), 8.322-8.576 (m, 2H, Ar). $^{13}$C NMR (125MHz, DMSO-$d_6$) $\delta$: 27.2, 32.0, 32.2, 41.5, 56.2, 69.6, 69.8, 112.7, 114.1, 122.4, 123.9, 125.2, 126.7, 127.5, 129.4, 131.5, 148.1, 149.7, 152.3, 155.5 and 179.0. APCI-MS: *m/z* 808.48, ($MH^+$+1, 43%). Anal. Calcd for $C_{43}H_{46}N_6O_6S_2$: C, 64.00; H, 5.75; N, 10.41; S, 7.95%. Found C, 64.10; H, 5.81; N, 10.69; S, 8.07%. |

close relationship between infection-inflammation and cancer exist, in view of this information newly synthesized compounds were also screened for anticancer activity.

*In vitro* anticancer activity [22, 23] evaluation of compounds **IIIa-j** and **Va-j** was carried out against five human cancer cell lines consisting of lung (NCI H-522), ovary (PA1), breast (T47D), colon (HCT-15) and liver (HepG2). Percentage (%) growth inhibition of compounds **IIIa-j** and **Va-j** against various cancer cell lines was determined at a concentration of 10µM and graphical representations of these results are summarized in Figure 2.8 and Figure 2.9 respectively.

From Figure 2.8, it is evident that bis-acridine derivatives **IIIa-j** are more effective than standard drugs (ST1= Adriamycin, ST2= Mitomycin C) for ovary (PA1) and lung (NCI H-522) cancer cell lines which are shown in blue and red colours in Figure 2.8. For breast cancer cell line only, two compounds **IIIb** and **IIIh** exhibited good anticancer activity *i.e.* 63% and 86% respectively while others showed moderate anticancer activity. In case of colon cancer cell line compound **IIIh** and for liver cancer cell line compound **IIIa** showed good anticancer activity while others did not show significant activity. Out of compounds **IIIa-j**, compound **IIIh** exhibited

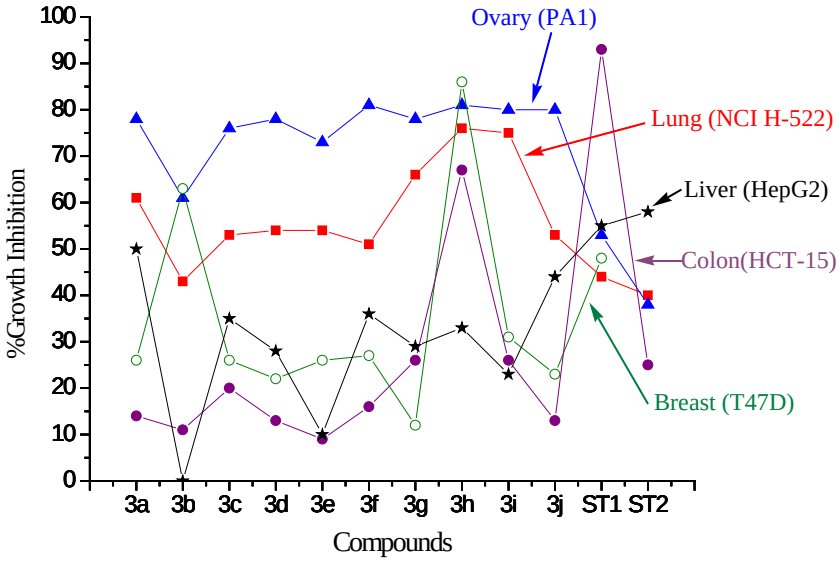


Figure:-2.8 Graphical representation of anticancer activity of compounds **IIIa-j** and ST1 (adriamycin) & ST2 (mitomycin C) against five human cancer cell lines.

good anticancer activity against four human cancer cell lines *i.e.* lung (NCI H-522), ovary (PA1), breast (T47D) and colon (HCT-15). In this series, bis-acridines **IIIa-j**, compounds having flexible linker i.e. 2,4,8,10-tetraoxaspiro[5,5]undecane-3,9-dipropyl (**IIIf-j**) exhibited better anticancer activity than those having 1,4-dipropylpiperazine as flexible linkage *i.e.* (**IIIa-e**).

In second series (compounds **Va-j)**, compound **Vg** exhibited good anticancer activity against breast cancer cell line while all other compounds exhibited moderate activity. For liver cancer cell line only two compounds **Vc** and **Ve** showed moderate

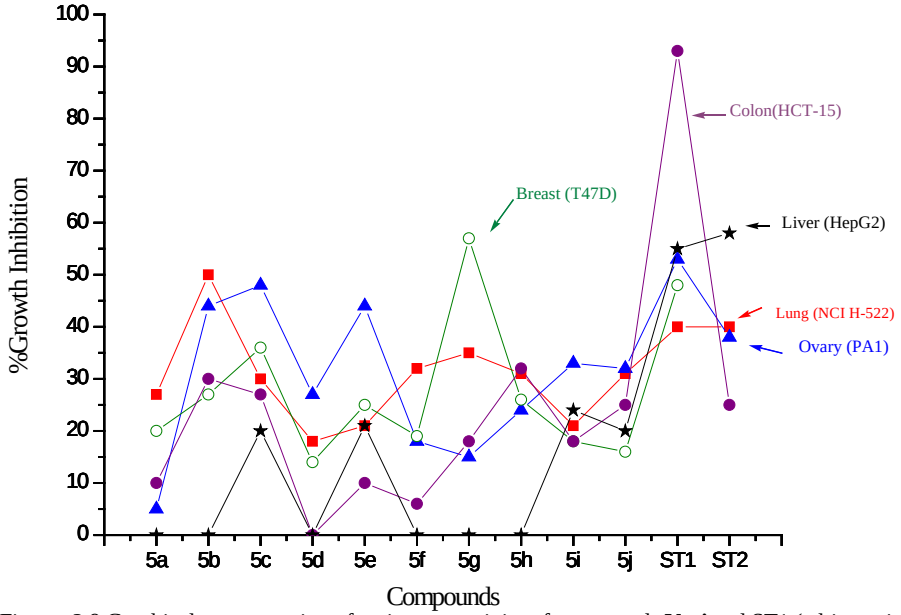


Figure:-2.9 Graphical representation of anticancer activity of compounds **Va-j** and ST1 (adriamycin) & ST2 (mitomycin C) against five human cancer cell lines.

**Table-2.3** Anti-inflammatory** and *in vitro* anticancer** activity of compounds **IIIa-j & Va-j**.

| Compd. No. | Anti-inflammatory activity (%) at 50mg/kg p.o. | Anticancer activity at a concentration of $1\times10^{-5}$ M | | | | |
|---|---|---|---|---|---|---|
| | | Lung NCI H-522 | Ovary PA1 | Breast T47D | Colon HCT-15 | Liver HepG2 |
| IIIa | 16 | 61 | 78 | 26 | 14 | 50 |
| IIIb | 17 | 43 | 61 | 63 | 11 | 00 |
| IIIc | 00 | 53 | 76 | 26 | 20 | 35 |
| IIId | 07 | 54 | 78 | 22 | 13 | 28 |
| IIIe | 13 | 54 | 73 | 26 | 09 | 10 |
| IIIf | 19 | 51 | 81 | 27 | 16 | 36 |
| **IIIg** | **41** | 66 | 78 | 12 | 26 | 29 |
| **IIIh** | 24 | **76** | **81** | **86** | **67** | 33 |
| IIIi | 00 | 75 | 80 | 31 | 26 | 23 |
| IIIj | 24 | 53 | 80 | 23 | 13 | 44 |
| Va | 08 | 27 | 05 | 20 | 10 | 00 |
| Vb | 34 | 50 | 44 | 27 | 30 | 00 |
| Vc | 34 | 30 | 48 | 36 | 27 | 20 |
| Vd | 09 | 18 | 27 | 14 | 00 | 00 |
| Ve | 09 | 21 | 44 | 25 | 10 | 21 |
| Vf | 00 | 32 | 18 | 19 | 16 | 00 |
| Vg | 28 | 35 | 15 | 57 | 09 | 00 |
| Vh | 10 | 31 | 24 | 26 | 06 | 00 |
| Vi | 15 | 21 | 33 | 18 | 18 | 24 |
| Vj | 21 | 31 | 32 | 16 | 32 | 02 |
| Ibuprofen | 39 | - | - | - | - | - |
| Adriamycin | - | 44 | - | 48 | 93 | 55 |
| Mito-C | - | 40 | 48 | - | 25 | 58 |
| Paclitaxel | - | 51 | - | 65 | - | 75 |
| 5-FU | - | 00 | 39 | 00 | 29 | 29 |

** We are thankful to Dr. Partha Roy, Department of Biotechnology, Indian Institute of Technology Roorkee, Roorkee for these results.

activity while other compounds are inactive. From Figure-2.9 it can be concluded that compounds **Vf-j** exhibited better anticancer activity than **Va-e**. In compounds **Vf-j** two acridine moieties are tethered *via* a flexible linker 2,4,8,10-tetraoxaspiro[5,5]undecane-3,9-dipropyl and in compounds **Va-e** two acridine moieties are tethered *via* a flexible linker 1,4-dipropylpiperazine. All the data of anticancer activity against five human cancer cell lines *i.e.* lung (NCI H-522), ovary (PA1), breast (T47D), colon (HCT-15) and liver (HepG2) is summarized in **Table-2.3**. From the activity data of two series of compounds it can be concluded that 2,4,8,10-tetraoxaspiro[5,5]undecane-3,9-dipropyl is a better flexible linker than 1,4-dipropylpiperazine.

It is concluded that acridine derivatives **IIIa-j** exhibited better anticancer and anti-inflammatory activity as compared to **Va-j**. This may be due to the fact that in case of **IIIa-j** both acridine moieties may be able to interact with DNA more effectively as compared to in case of **Va-j** where acridine moieties are far apart of each other and this may hinder their effective interaction with DNA.

## 2.3 Experimental

### *2.3.1 General*

Melting points (mp) were determined on a JSGW apparatus and are uncorrected. IR spectra were recorded using a Perkin Elmer 1600 FT spectrometer. $^{1}H$ and $^{13}C$ NMR spectra were recorded on a Bruker WH-500 spectrometer at a *ca* 5-15% (*w/v*) solution in DMSO-$d_6$, $CH_3OD$ and $D_2O$. APCI mass was recorded using Finnigan Mat LCQ Mass Spectrometer. Elemental analysis was carried out on a Vario EL III elementor. Thin layer chromatography (TLC) was performed on silica gel G for TLC (Merck) and spots were visualized by iodine vapour or by irradiation with ultraviolet light (short wave length, 254nm). Column chromatography was performed

by using Qualigen's silica gel for column chromatography (60-120 mesh). Physical constants, spectral data and elemental analysis of compounds **IIIa-j** and **Va-j** are reported in Table-2.1 and Table 2.2 respectively.

**2.3.2 Synthesis of 9-chloro-2,4-(un)substituted acridines (Ia-e):-**

These acridines were synthesized by following reaction procedure reported in literature [17, 18].

**2.3.3 Synthesis of 9-isothiocyanato-2,4-(un)substituted acridines (IVa-e):-**

These acridines were synthesized by following reaction procedure reported in literature [19].

**2.3.4 General procedure for condensation of 9-chloro-2,4-(un)substituted acridines (Ia-e) with various amines (IIa,b)**

2.3.4.1 N-(3-(4-(3-(acridin-9-ylamino)propyl)piperazin-1-yl)propyl)acridin-9-amine **(IIIa)**

9-Chloroacridine (200 mg, 0.92 mmol) was taken in methanol (20 mL) and to it was added 3-(4-(3-aminopropyl)piperazin-1-yl) propan-1-amine (90 mg, 0.45 mmol). Reaction contents were heated under reflux for 17 hours. Solvent was removed under reduced pressure and the residue left behind was treated with 10 % cold aq sodium bicarbonate solution (5 ml), then washed with cold water to give crude product, which was purified by column chromatography over silica gel to give pure product **IIIa.** Solvent of elution: $CHCl_3$: MeOH (7:3, $R_f$ =0.6); Yield: 238mg (43%).

Similarly other acridine derivatives i.e. 2-methyl-N-(3-(4-(3-(2-methylacridin-9-ylamino)propyl)piperazin-1-yl)propyl)acridin-9-amine **(IIIb),** 2-methoxy-N-(3-(4-(3-(2-methoxyacridin-9-ylamino)propyl)piperazin-1-yl)propyl)acridin-9-amine **(IIIc)**, 4-methyl-N-(3-(4-(3-(4-methylacridin-9-ylamino)propyl)piperazin-1-l)propyl)acridin-

9-amine **(IIId)**, 4-methoxy-N-(3-(4-(3-(4-methoxyacridin-9-ylamino)propyl)piperazin -1-yl) propyl) acridin-9-amine **(IIIe),** (acridin-9-yl)-[3-(9-{3-[(acridin-9-ylamino)]-propyl}-2,4,8,10-tetraoxa-spiro[5,5]undec-3-yl)-propyl]-amine **(IIIf),** (2-methyl-acridin-9-yl)-[3-(9-{3-[(2-methyl-acridin-9-ylamino)]-propyl}-2,4,8,10-tetraoxa-spiro [5,5]undec-3-yl)-propyl]-amine **(IIIg),** (2-methoxy-acridin-9-yl)-[3-(9-{3-[(2-methoxy-acridin-9-ylamino)]-propyl}-2,4,8,10-tetraoxa-spiro[5,5]undec-3-yl)-prop yl]-amine **(IIIh),** (4-methyl-acridin-9-yl)-[3-(9-{3-[(4-methyl-acridin-9-yl amino)]-propyl}-2,4,8,10-tetraoxa-spiro[5,5]undec-3-yl)-propyl]-amine **(IIIi)**, (4-methoxy-acridin-9-yl)-[3-(9-{3-[(4-methoxy-acridin-9-ylamino)]-propyl}-2,4,8,10-tetraoxa-spiro[5,5] undec-3-yl)-propyl]-amine **(IIIj)** were synthesized and reported in Table 2.1.

**2.3.5 General procedure for condensation of 9-isothiocyanato-2-4-(un)substituted acridines (IVa-e) with diamines (IIa, b)**

2.3.5.1 1-(3-(4-(3-(9-Acridinylamine)methanethioamidopropyl)piperazin-1-yl)propyl)-3-(acridin-9-yl)thiourea **(Va)**

9-Isothiocyanatoacridine (300 mg, 1.27 mmol) and 3-(4-(3-aminopropyl)piperazin-1-yl)propan-1-amine (127 mg, 0.63 mmol) were dissolved separately in THF (10 mL) and mixed together with constant stirring and allowed to stand at room temperature for 6 hours. Solid product separated out was filtered and purified by column chromatography over silica gel to give pure product **Va.** Solvent of elution: $CHCl_3$: MeOH (8:2, $R_f$ =0.6); Yield: 248 mg (37%).

Similarly other acridine derivatives **Va-j** i.e. 1-(3-(4-(3-(9-acridinyl amine)methanethioamidopropyl)piperazin-1-yl)propyl)-3-(acridin-9-yl) thiourea **(Va),** 1-(3-(4-(3-(2-methyl-9-acridinylamine)methanethioamidopropyl)piperazin-1-yl) propyl)-3-(2-methylacridin-9-yl)thiourea **(Vb)**, 1-(3-(4-(3-(2-methoxy-9-acridinyl

amine)methanethioamidopropyl)piperazin-1-yl)propyl)-3-(2-methoxyacridin-9-yl) thiourea **(Vc)**, 1-(3-(4-(3-(4-methyl-9-acridinylamine)methanethioamidopropyl) piperazin-1-yl)propyl)-3-(4-methylacridin-9-yl)thiourea **(Vd)**, 1-(3-(4-(3-(4-methoxy-9-acridinylamine)methanethioamidopropyl)piperazin-1-yl)propyl)-3-(4-methoxy acridin-9-yl)thiourea **(Ve),** 1-(3-(9-(3-(9-acridinylamine)methanethioamidopropyl) 2,4,8,10-tetraoxa-spiro[5.5]undecane-3-yl)propyl)-3-(acridin-9-yl) thiourea **(Vf)**, 1-(3-(9-(3-(2-methyl-9-acridinylamine)methanethioamidopropyl)-2,4,8,10-tetraoxa-spiro [5.5]undecane-3-yl)propyl)-3-(2-methylacridin-9-yl)thiourea **(Vg),** 1-(3-(9-(3-(2-methoxy-9-acridinylamine)methanethioamidopropyl)2,4,8,10-tetraoxa-spiro[5.5] undecane-3-yl)propyl)-3-(2-methoxyacridin-9-yl)thiourea **(Vh)**, 1-(3-(9-(3-(4-methyl-9-acridinylamine)methanethioamidopropyl)2,4,8,10-tetraoxa-spiro[5.5] undecane-3-yl)propyl)-3-(4-methylacridin-9-yl)thiourea **(Vi),** 1-(3-(9-(3-(4-methoxy-9-acridinyl amine)methane thioamidopropyl)2,4,8,10-tetraoxa-spiro[5.5]undecane-3-yl)propyl)-3-(4-methoxyacridin-9-yl)thiourea **(Vj)** were synthesized and reported in Table 2.2.

### 2.3.6 Anti-inflammatory activity evaluation [21]

Paw oedema inhibition test was used on albino rats of Charles Foster by adopting the method of Winter *et al.* [21]. Groups of five animals of both sexes (body weight 120-160g), excluding pregnant females, were given a dose of test compound. Thirty minute later, 0.20 mL of 1% freshly prepared carrageenan suspension in 0.9% NaCl solution was injected subcutaneously into the planter aponeurosis of the hind paw and the volume was measured by a water plethysmometer apparatus and then measured again 1-3h later. The mean increase of paw volume at each interval was compared with that of control group (five rats treated with carrageenan but not with test compound) at the same intervals and percent inhibition value calculated by the formula given below.

$$\% \text{ anti-inflammatory activity} = [1-D_t/D_c]\times 100$$

$D_t$ and $D_c$ are paw volumes of oedema in tested and control groups, respectively. Compounds **IIIa-j** and V**a-j** were screened for anti-inflammatory activity and results are summarized in **Table 2.3**.

### 2.3.7 *In vitro* cytotoxicity against human cancer cell lines [22, 23]

The human cancer cell lines procured from National Cancer Institute, Frederick, U. S. A. were used in present study. Cells were grown in tissue culture flasks in complete growth medium (RPMI-1640 medium with 2 mM glutamine, pH 7.4 supplemented with 10% fetal bovine serum, 100 µg/mL streptomycin and 100 units/mL penicillin) in a carbon dioxide incubator ($37^oC$, 5% $CO_2$, 90% RH). The cells at subconfluent stage were harvested from the flask by treatment with trypsin (0.05% in PBS (pH 7.4) containing 0.02% EDTA). Cells with viability of more than 98%, as determined by trypan blue exclusion, were used for determination of cytotoxicity. The cell suspension of $1\times10^5$ cells/mL was prepared in complete growth medium.

Stock $4\times10^{-2}$ M compound solutions were prepared in DMSO. The stock solutions were serially diluted with complete growth medium containing 50µg/mL of gentamycin to obtaine working test solution of required concentrations.

*In vitro* cytotoxicity against various human cancer cell lines was determined (Monks *et. al.*) [22] using 96-well tissue culture plates. The 100 µL of cell suspension was added to each well of the 96-well tissue culture plates. The cells were allowed to grow in $CO_2$ incubator ($37^oC$, 5% $CO_2$, 90% RH) for 24 hours. The test materials in complete growth medium (100 µL) were added after 24 hours incubation to the wells containing cell suspension. The plates were further incubated for 48 hours ($37\ ^oC$ in an atmosphere of 5% $CO_2$ and 90% relative humidity) in a carbon dioxide incubator

after addition of test material and then the cell growth was stopped by gently layering trichloroacetic acid (50% TCA, 50 µL) on top of the medium in all the wells. The plates were incubated at 4$^{o}$C for one hour to fix the cells attached to the bottom of the wells. The liquid of all the wells was gently pipetted out and discarded. The plates were washed five times with distilled water to remove TCA, growth medium low molecular weight metabolites, serum proteins *etc*. and air dried. Cell growth was measured by staining with sulforhodamine B dye (Skehan *et. al*.) [23]. The adsorbed dye was dissolved in Tris-HCl Buffer (100 µL, 0.01M, pH 10.4) and plates were gently stirred for 10 minutes on a mechanical stirrer. The optical density (OD) was recorded on ELISA reader at 540nm.

Compounds **IIIa-j** and **Va-j** were screened for anticancer activity and results are summarized in Table 2.3.

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# Chapter *3*

***Synthesis, anti-inflammatory and anticancer activity evaluation of pyrazole and oxadiazole derivatives***

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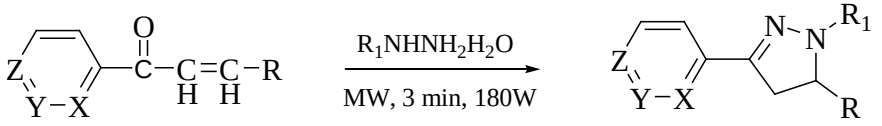
# 3.1 Introduction

Pyrazole and oxadiazole derivatives form an important class of compounds possessing wide range of biological activities [1, 2]. Recent work reported in literature on pyrazole and oxadiazole derivatives exhibiting anti-inflammatory and anticancer activities have been summarized in chapter-1. Apart from anti-inflammatory and anticancer activities, these compounds are also reported to exhibit antiviral [3, 4], antiasthmatic [5, 6], antimalarial [7-10], antimicrobial [11-17] and antibacterial [18, 19] activities. Motivated by wide range of biological activities exhibited by pyrazole and oxadiazole derivatives and in continuation of our efforts in search of potent anti-inflammatory and anticancer agents [20, 21] we have synthesized a number of pyrazole and oxadiazole derivatives and screened them for anti-inflammatory and anticancer activities, which we will describe in this chapter.

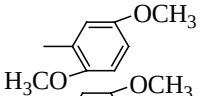
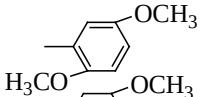
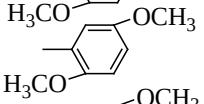
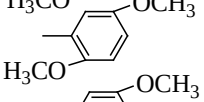
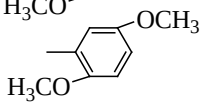
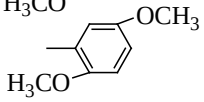
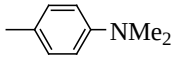
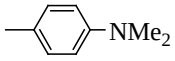
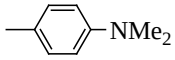
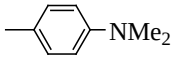
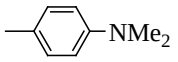
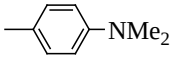
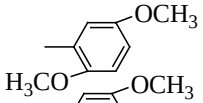
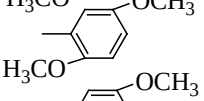
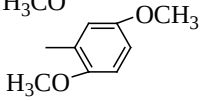
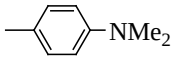
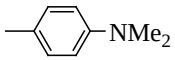
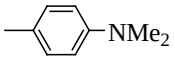
## 3.2 Results and discussion

### 3.2.1 *Chemistry:*

Chalcone derivatives **Ia-f** (Scheme 3.1) were synthesized by condensation of 2-acetyl pyridine, 3-acetyl pyridine, 4-acetyl pyridine with 2,5-dimethoxybenzaldehyde and 4-(dimethylamino) benzaldehyde as reported in literature [22, 23]. 3-(2,5-dimethoxyphenyl)-1-(pyridin-2-yl)prop-2-en-1-one (**Ia**; Scheme 3.1) on condensation with hydrazine hydrate under microwave irradiation for 3 minutes and at a power level of 180 Watt gave condensation product **IIa** (Scheme 3.1). This product was purified by




**Ia-f** **IIa-l**

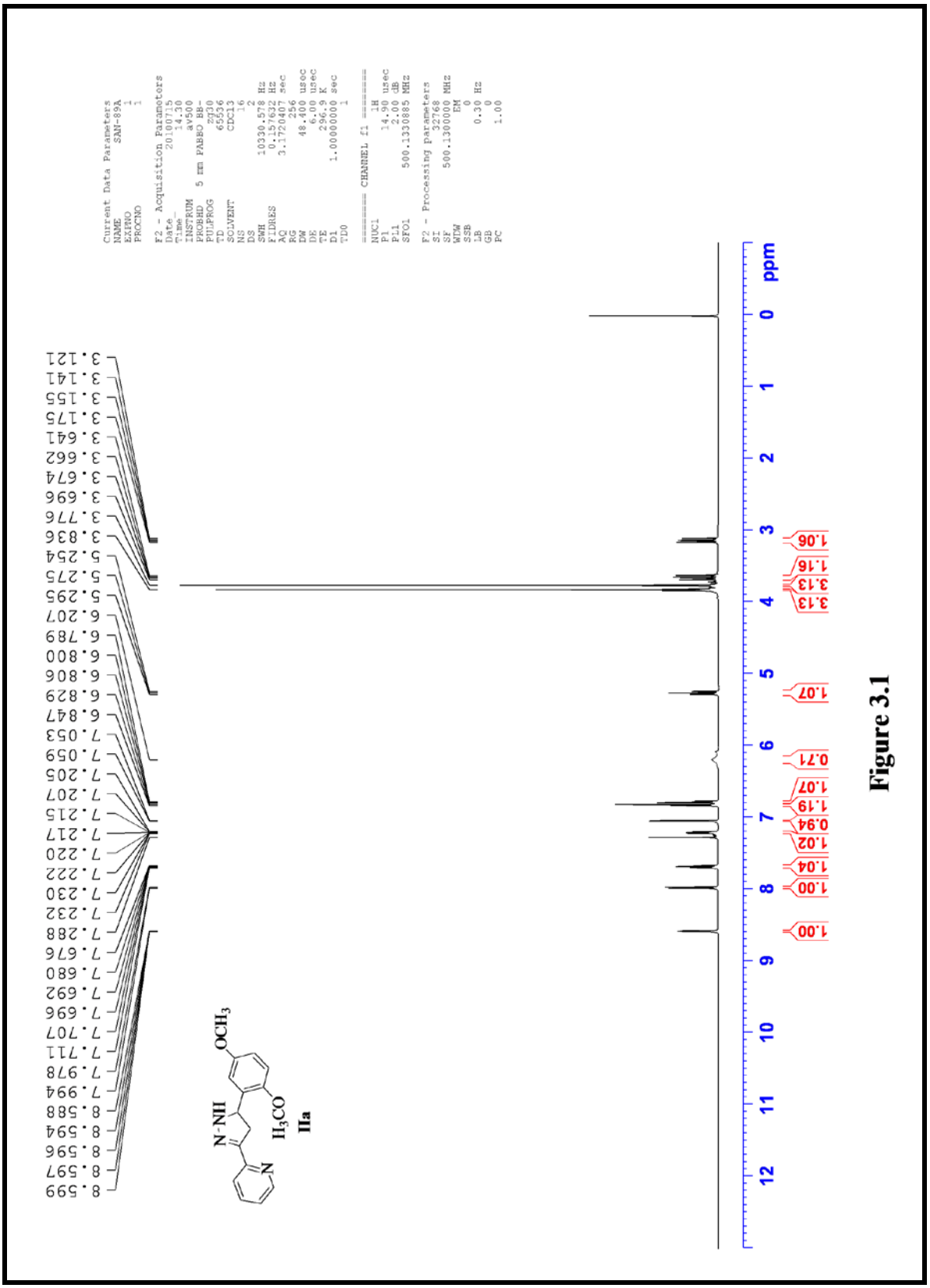
| | X | Y | Z | R | X | Y | Z | R | $R_1$ |
|---|---|---|---|---|---|---|---|---|---|
| **Ia** | N | CH | CH |  | **IIa** | N | CH | CH |  | H |
| **Ib** | CH | N | CH |  | **IIb** | CH | N | CH |  | H |
| **Ic** | CH | CH | N |  | **IIc** | CH | CH | N |  | H |
| **Id** | N | CH | CH |  | **IId** | N | CH | CH |  | H |
| **Ie** | CH | N | CH |  | **IIe** | CH | N | CH |  | H |
| **If** | CH | CH | N |  | **IIf** | CH | CH | N |  | H |
| | | | | | **IIg** | N | CH | CH |  | Ph |
| | | | | | **IIh** | CH | N | CH |  | Ph |
| | | | | | **IIi** | CH | CH | N |  | Ph |
| | | | | | **IIj** | N | CH | CH |  | Ph |
| | | | | | **IIk** | CH | N | CH |  | Ph |
| | | | | | **IIl** | CH | CH | N |  | Ph |

Scheme-3.1: Synthesis of pyrazole derivatives

crystallization from chloroform to give pure 2-[5-(2,5-dimethoxyphenyl)-4,5-dihydro-1H-pyrazol-3yl] pyridine (**IIa**; Scheme 3.1) in good yield. IR spectrum of **IIa** shows absorption signal at 3140 $cm^{-1}$ which is attributed to NH functional group and strong absorption signals at 1587, 1489 $cm^{-1}$ correspond to aromatic region. $^{1}H$ NMR (500 MHz, $CDCl_3$) (Figure 3.1) of compound **IIa** exhibited signals at $\delta$ : 3.121-3.175 (dd, 1H, J= 10 & 17 Hz, one H of $CH_2$), 3.641-3.696 (dd, 1H, J= 10 & 17 Hz, one H of $CH_2$), 3.776 (s, 3H, $OCH_3$), 3.836 (s, 3H, $OCH_3$), 5.254-5.295 (t, 1H, J= 10 Hz, CH), 6.207 (bs, 1H, NH), 6.789-6.806 (m, 1H, Ar), 6.829-6.847 (d, 1H,J= 9 Hz, Ar), 7.053-7.059 (d, 1H, J= 3 Hz, Ar), 7.205-7.232 (m, 1H, Ar), 7.676-7.711 (m, 1H, Ar), 7.978-7.994 (d, 1H, J= 8 Hz, Ar), 8.588-8.599 (m, 1H, Ar). $^{13}C$ NMR (125MHz, $CDCl_3$) (Figure 3.2) data of **IIa** exhibited signals at $\delta$ : 43.122, 49.681, 55.593, 55.944, 111.335, 111.776, 113.034, 113.376, 114.300, 120.041, 122.467, 136.708, 148.164, 148.394, 150.945 and 153.438. GC-MS spectrum (*m/z*; relt. int. %) (Figure 3.3) of **IIa** gave $M^{+\bullet}$ ion peak at *m/z* 283 (3%). In addition to $M^{+\bullet}$ ion peak GCMS of **IIa** shows some other prominent ion peaks which can arise through its fragmentation. The fragmentation pattern of **IIa** is outlined in chart 3.1. Elemental analysis Calculated for $C_{16}H_{17}N_3O_2$: C, 67.83; H, 6.05; N, 14.83% Found C, 67.55; H, 6.12; N, 14.78%. Spectral data and elemental analysis of **IIa** fully support the structure assigned to it.

Similarly chalcone derivatives **Ib-f** (Scheme 3.1) on condensation with hydrazine hydrate gave corresponding products **IIb-f** (Scheme 3.1). Physical constants, spectral and analytical data of **IIb-f** reported in Table-3.1 is in full agreement with structures assigned to them.

Condensation of 3-(2,5-dimethoxyphenyl)-1-(pyridin-2-yl)prop-2-en-1-one (**Ia**;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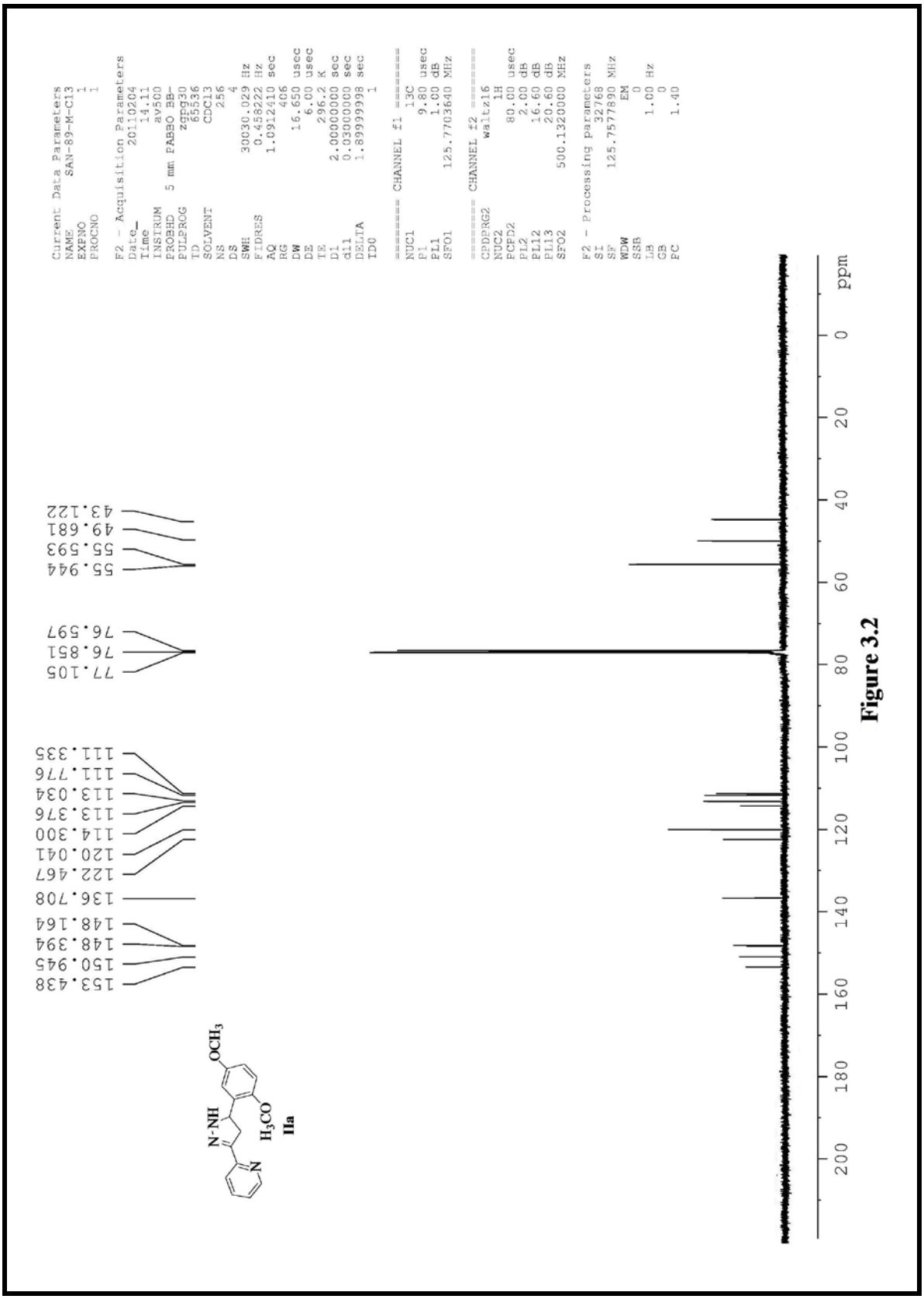
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20100715
Time 14.30
INSTRUM av500
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1720407 sec
RG 256
DW 48.400 usec
DE 6.00 usec
TE 296.9 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 14.00 usec
PL1 2.00 dB
SFO1 500.1330885 MHz
F2 - Processing parameters
SI 32768
SF 500.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
3.121
3.141
3.155
3.175
3.641
3.662
3.674
3.696
3.776
3.836
5.254
5.275
5.295
6.207
6.789
6.800
6.806
6.829
6.847
7.053
7.059
7.205
7.207
7.215
7.217
7.220
7.222
7.230
7.232
7.288
7.676
7.680
7.692
7.696
7.707
7.711
7.978
7.994
8.588
8.594
8.596
8.597
8.599
N-NH
OCH3
H3CO
N
IIa
ppm
1.00
1.00
1.04
1.02
0.94
1.19
1.07
0.71
1.07
3.13
3.13
1.16
1.06

**Figure 3.1**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PROCNO 1
F2 - Acquisition Parameters
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Time 14.11
INSTRUM av500
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 256
DS 4
SWH 30030.029 Hz
FIDRES 0.458222 Hz
AQ 1.0912410 sec
RG 406
DW 16.650 usec
DE 6.00 usec
TE 296.2 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 9.80 usec
PL1 1.00 dB
SFO1 125.7703640 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 2.00 dB
PL12 16.60 dB
PL13 20.60 dB
SFO2 500.1320000 MHz
F2 - Processing parameters
SI 32768
SF 125.7577890 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
153.438
150.945
148.394
148.164
136.708
122.467
120.041
114.300
113.376
113.034
111.776
111.335
77.105
76.851
76.597
55.944
55.593
49.681
43.122
N-NH
N
OCH3
H3CO
IIa
200
180
160
140
120
100
80
60
40
20
0
ppm

**Figure 3.2**

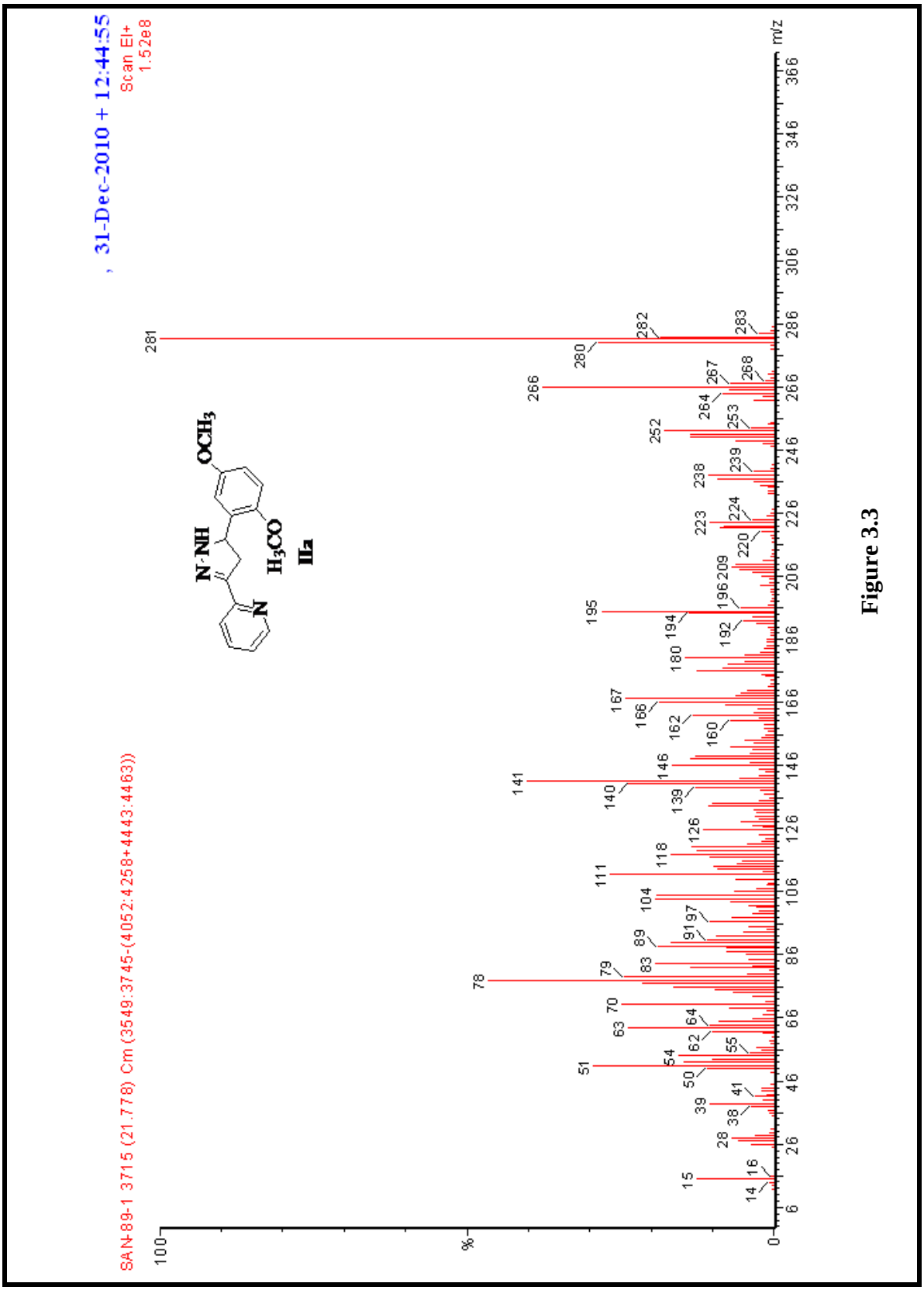

SAN-89-1 3715 (21.778) Cm (3549:3745-(4052:4258+4443:4463))
, 31-Dec-2010 + 12:44:55
Scan EI+
1.52e8
100
%
0
m/z
N-NH
N
H3CO
OCH3
IIa

**Figure 3.3**

**Fragmentation pattern of IIa**

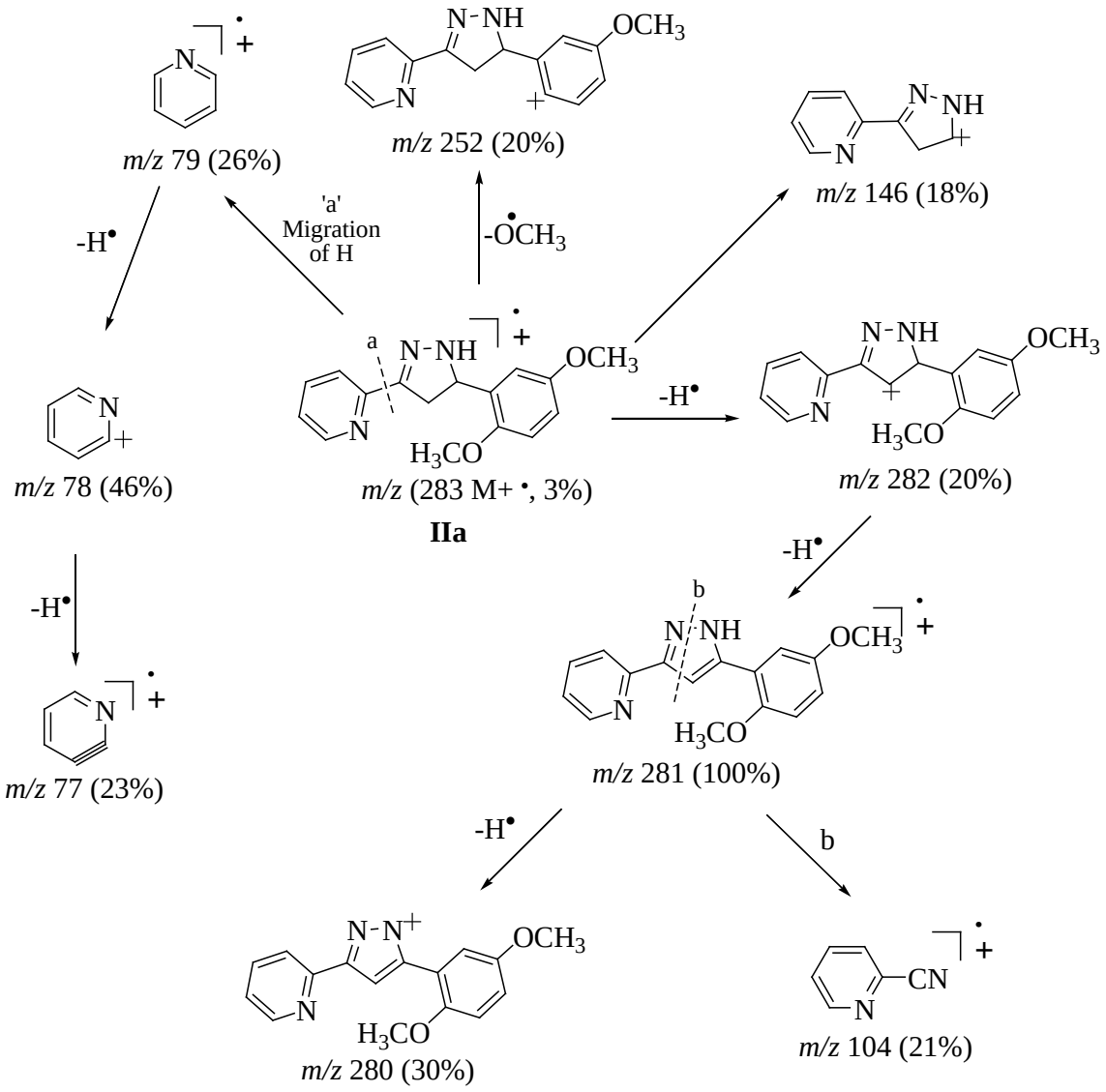


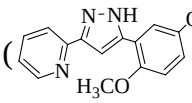
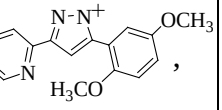
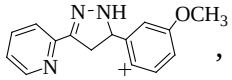
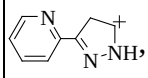
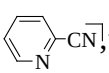

**Chart 3.1**

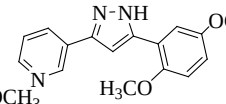
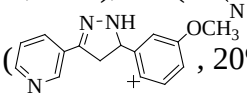
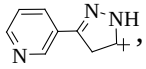
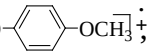
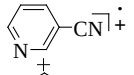
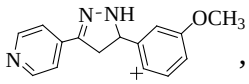
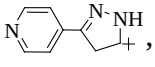
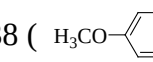
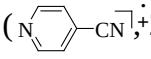
Scheme 3.1) with phenyl hydrazine in equimolar ratio, under microwave irradiation for 3 minutes (power level 450 Watt) gave condensation product **IIg**, which was crystallized from chloroform: MeOH (8:2) to give pure 2-[5-(2,5-dimethoxyphenyl)-1-phenyl-4,5-dihydro-1H-pyrazol-3yl] pyridine (**IIg**; Scheme 3.1) in good yield. IR spectrum of **IIg** shows absorption signal at 3382 $cm^{-1}$ which is attributed to NH functional group and strong absorption at 1601, 1485 $cm^{-1}$ correspond to aromatic region. $^{1}H$ NMR (500 MHz, $CDCl_3$) of compound **IIg** exhibited signals at $\delta$ : 3.200-3.250 (dd, 1H, J= 7 & 18 Hz, one H of $CH_2$), 3.645 (s, 3H, $CH_3$), 3.922 (s, 3H, $CH_3$), 3.979-4.041 (dd, 1H, J= 13 & 18.5 Hz, one H of $CH_2$), 5.630-5.668 (dd, 1H, J= 6.5 & 12.5 Hz, CH), 6.707-6.713 (d, 1H, J= 3 Hz, Ar), 6.744-6.768 (m, 1H, Ar), 6.818-6.847 (t, 1H, J= 9.5 Hz, Ar), 6.878-6.887 (d, 1H, J= 4.5 Hz, Ar), 7.077-7.099 (m, 2H, Ar), 7.148-7.243 (m, 3H, Ar), 7.691-7.725 (m, 1H, Ar), 8.139-8.161 (m, 1H, Ar), 8.550-8.557 (m, 1H, Ar), $^{13}C$ NMR (125MHz, $CDCl_3$) data of **IIg** exhibited signals at $\delta$ : 43.681, 49.699, 55.593, 55.944, 111.741, 112.301, 112.780, 112.919, 123.559, 127.118, 128.909, 129.107, 129.928, 133.005, 148.345, 149.307, 152.075, 152.878, 154.304 and 155.455. GC-MS spectrum (*m/z*; relt. int. %) of **IIg** gave $M^{+\bullet}$ ion peak at *m/z* 359 (5%). Elemental analysis Calculated for $C_{22}H_{21}N_3O_2$: C, 73.52; H, 5.89; N, 11.69%. Found C, 73.68; H, 5.76; N, 11.78%. Spectral data and elemental analysis of **IIg** fully support the structure assigned to it.

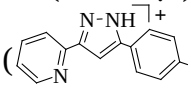
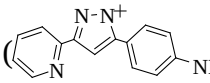
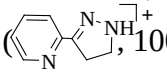
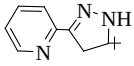
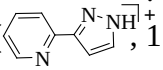
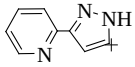
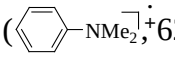
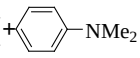
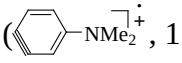
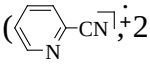
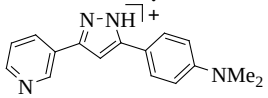
Similarly condensation of **Ib-f** (Scheme 3.1) with phenyl hydrazine gave corresponding condensation products **IIh-l** (Scheme 3.1) respectivaly. Physical constants, spectral and analytical data of compounds **IIg-l** reported in Table-3.1 fully support the structures assigned to them.

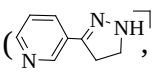
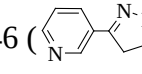
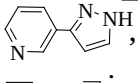
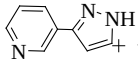
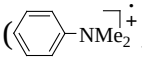
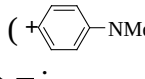
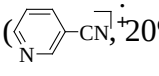
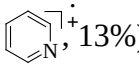
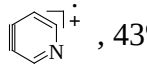
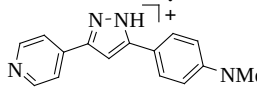
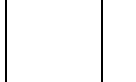
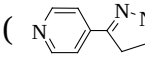
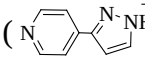
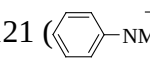
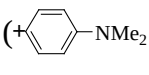
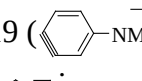
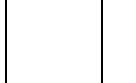
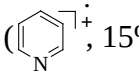
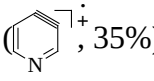
N′-Hydroxypicolinamidine, (**IIIa**, Scheme 3.2), N′-hydroxy-isonicotinamidine

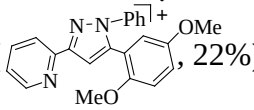
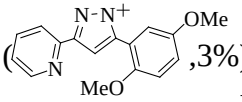
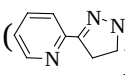
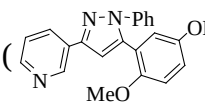
**Table 3.1: Physical constants and spectral data of pyrazole (IIa-l) and oxadiazole derivatives (IVa-f)**

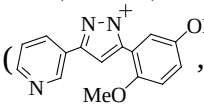
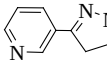
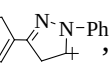
| Comp no | Solvent of cryst./elution | m.p. ºC | Yield % | IR (KBr) $cm^{-1}$, $^1H$ (500MHz) & $^{13}C$ (125MHz) NMR ($CDCl_3$, DMSO-$d_6$), $\delta$ J(Hz), GC-MS (*m/z*; relt int %) |
|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 |
| **IIa** | $CHCl_3$ | 114 | 83 | IR 3140 (NH) 1587, 1489 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ : 3.121-3.175 (dd, 1H, J= 10 & 17 Hz, one H of $CH_2$), 3.641-3.696 (dd, 1H, J= 10 & 17 Hz, one H of $CH_2$), 3.776 (s, 3H, $OCH_3$), 3.836 (s, 3H, $OCH_3$), 5.254-5.295 (t, 1H, J= 10 Hz, CH), 6.207 (bs, 1H, NH), 6.789-6.806 (m, 1H, Ar), 6.829-6.847 (d, 1H, J= 9 Hz, Ar), 7.053-7.059 (d, 1H, J= 3 Hz, Ar), 7.205-7.232 (m, 1H, Ar), 7.676-7.711 (m, 1H, Ar), 7.978-7.994 (d, 1H, J= 8 Hz, Ar), 8.588-8.599 (m, 1H, Ar). $^{13}C$ NMR (125MHz, $CDCl_3$) $\delta$ : 43.1, 49.6, 55.5, 55.9, 111.3, 111.7, 113.0, 113.3, 114.3, 120.0, 122.4, 136.7, 148.1, 148.3, 150.9 and 153.4. GC-MS: : *m/z* 283 ($M^{+\bullet}$, 3%), 282 ($M^{+\bullet}$-H, 20%), 281 (  , 100%), 280 (  , 30%), 252 (  , 20%), 146 (  , 18%), 104 (  , 21%), 79 (  , 26%), 78 (  , 46%), 77 (  , 23%). Anal. Calcd for $C_{16}H_{17}N_3O_2$: C, 67.83; H, 6.05; N, 14.83%. Found C, 67.55; H, 6.12; N, 14.78%. |
| **IIb** | $CHCl_3$ | 118 | 84 | IR 3314(NH), 1587, 1487 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, MHz, $CDCl_3$) $\delta$: 3.094-3.147 (dd, 1H, J= 9.5 & 16.5 Hz, one H of $CH_2$), 3.613-3.668 (dd, 1H, J= 10.5 & 16.5 Hz, one H of $CH_2$), 3.748 (s, 3H, $OCH_3$), 3.809 (s, 3H, $OCH_3$), 5.226-5.267 (t, 1H, J= 10.5 Hz, CH), 6.179 (bs, 1H, NH), 6.755-6.819 (m, 2H, Ar), 7.025-7.031 (d, 1H, J= 3 Hz, Ar), 7.117-7.214 (m, 1H, Ar), 7.649-7.683 (m, 1H, Ar), 7.950-7.966 (d, 1H, J= 8 Hz, Ar), 8.560-8.570 (m, 1H, Ar). $^{13}C$ NMR (125MHz, $CDCl_3$) $\delta$ : 43.3, 49.8, 55.8, 56.1, 111.4, 111.9, 113.4, 114.4, |

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| | | | | 120.1, 122.6, 136.8, 148.3, 148.5, 151.0 and 153.7. GC-MS: *m/z* 283, ($M^{+\bullet}$, 20%), 282 ($M^{+\bullet}$- H, 24%), 281(  , 1%), 252 (  , 20%), 146 (  , 100%), 138 (  ; 11%), 104 (  , 16%), 79 (  , 20%), 78 (  , 25%), 77 (  , 22%). Anal. Calcd for $C_{16}H_{17}N_3O_2$: C, 67.83; H, 6.05; N, 14.83%. Found C, 67.64; H, 6.09; N, 14.79%. |
| **IIc** | $CHCl_3$ | 115 | 82 | IR 3412(NH), 1590, 1531 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ : 3.095-3.148 (dd, 1H, J= 9.5 & 16.5 Hz, one H of $CH_2$), 3.614-3.669 (dd, 1H, J= 10.5 & 17 Hz, one H of $CH_2$), 3.749 (s, 3H, $CH_3$), 3.810 (s, 3H, $CH_3$), 5.228-5.268 (t, 1H, J= 10 Hz, CH), 6.167 (bs, 1H, NH), 6.762-6.780 (m, 1H, Ar), 6.803-6.820 (d, 1H, J= 8.5 Hz, Ar), 7.026-7.032 (d, 1H, J= 3 Hz, Ar), 7.658-7.669 (d, 2H, J= 5.5 Hz, Ar), 8.348-8.360 (d, 2H, J= 6 Hz, Ar), $^{13}C$ NMR (125MHz, $CDCl_3$) $\delta$ : 43.4, 49.9, 55.7, 56.1, 111.4, 111.9, 113.1, 113.5, 114.4, 120.2, 122.7, 136.9, 148.3, 149.0, 151.1 and 153.8. GC-MS: *m/z* 283 ($M^{+\bullet}$, 20%), 282 ($M^{+\bullet}$- H, 22%), 252 (  , 20%), 146 (  , 100%), 138 (  , 10%), 104 (  ;20%), 79 (  , 19%), 78 (  , 30%), 77 (  , 18%). Anal. Calcd for $C_{16}H_{17}N_3O_2$: C, 67.83; H, 6.05; N, 14.83%. Found C, 67.77; H, 6.09; N, 14.89%. |
| **IId** | $CHCl_3$ | 121 | 81 | IR 3414(NH), 1587, 1490 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, MHz, $CDCl_3$) $\delta$: 2.900 (s, 6H, 2×$CH_3$), 3.212-3.263 (dd, 1H, J= 8 & 17.5 Hz, |

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| | | | | one H of $CH_2$), 3.535-3.591 (dd, 1H, J= 11 & 17 Hz, one H of $CH_2$), 4.876-4.914 (t, 1H, J= 10 Hz, CH), 6.050 (bs, 1H, NH), 6.594-6.612 (d, 3H, J= 9 Hz, Ar), 7.213-7.227 (d, 2H, J= 7 Hz, Ar), 7.652-7.691 (m, 1H, Ar), 7.951-7.967 (d, 1H, J= 8 Hz, Ar), 8.560-8.570 (d, 1H, J= 5 Hz, Ar). $^{13}$C NMR (125MHz, $CDCl_3$) $\delta$ : 40.5, 50.6, 112.8, 112.9, 123.6, 127.1, 128.9, 129.9, 133.0, 147.2, 148.3, 149.3, 150.4 and 154.5. GC-MS: *m/z* 266 ($M^{+\bullet}$, 90%), 265 ($M^{+\bullet}$-H, 87%), 264 (  , 12%), 263 (  , 7%), 147 (  , 100%), 146 (  , 90%), 145 (  , 15%), 144 (  , 12%), 121 (  , 62 %), 120 (  , 42%), 119 (  , 15%), 104 (  , 21%), 79 (  , 15%), 78 (  , 35%), 77 (  , 38%). Anal. Calcd for $C_{16}H_{18}N_4$: C, 72.15; H, 6.81; N, 21.04%. Found C, 72.29; H, 6.84; N, 21.11%. |
| **IIe** | $CHCl_3$ | 119 | 80 | IR 3316 (NH), 1591, 1569, 1488 $cm^{-1}$. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$: 2.931 (s, 6H, 2×$CH_3$), 3.214-3.264 (dd, 1H, J= 8 & 17 Hz, one H of $CH_2$), 3.537-3.592 (dd, 1H, J= 10.5 & 17 Hz, one H of $CH_2$), 4.877-4.915 (t, 1H, J= 10 Hz, CH), 6.051 (bs, 1H, NH), 6.688-6.712 (m, 2H, Ar), 7.183-7.232 (m, 3H, Ar), 7.658-7.692 (m, 1H, Ar), 7.952-7.968 (d, 1H, J= 8 Hz, Ar), 8.562-8.571 (d, 1H, J= 4.5 Hz, Ar). $^{13}$C NMR (125MHz, $CDCl_3$) $\delta$ : 40.4, 50.5, 111.6, 112.2, 112.7, 123.4, 126.9, 128.8, 129.8, 132.9, 147.1, 148.2, 149.2, 150.3 and 155.4. GC-MS: *m/z* 266 ($M^{+\bullet}$, 85%), 265 ($M^{+\bullet}$-H, 70%), 264 (  , 7%), |

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| | | | | 147 (  , 100%), 146 (  , 90%), 145 (  , 13%), 144 (  , 11%), 121 (  , 55%), 120 (  , 40%), 104 (  , 20%), 79 (  , 13%), 78 (, 29%), 77 (  , 43%). Anal. Calcd for $C_{16}H_{18}N_4$: C, 72.15; H, 6.81; N, 21.04% Found C, 72.25; H, 6.83; N, 21.08%. |
| **IIf** | $CHCl_3$ | 128 | 81 | IR 3384(NH), 1639, 1580, 1535, 1478 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, 2.930 (s, 6H, 2×$CH_3$), 3.216-3.266 (dd, 1H, J= 8 & 17 Hz, one H of $CH_2$), 3.541-3.596 (dd, 1H, J= 10.5 & 17 Hz, one H of $CH_2$), 4.879-4.918 (q, 1H, J= 7 & 10 Hz, CH), 6.147 (bs, 1H, NH), 6.690-6.715 (d, 2H, J= 12 Hz, Ar), 7.184-7.213 (dd, 2H, J= 1.5 & 8 Hz, Ar), 7.657-7.668 (d, 2H, J= 5.5 Hz, Ar), 8.349-8.361 (d, 2H, J= 6.5 Hz, Ar). $^{13}C$ NMR (125MHz, $CDCl_3$) $\delta$ : 40.2, 50.4, 111.5, 112.5, 123.3, 126.9, 128.6, 129.7, 132.7, 148.1, 149.0, 149.6, 150.1 and 154.2. GC-MS: *m/z* 266 ($M^{+\bullet}$, 90%), 265 ($M^{+\bullet}$-H, 81%), 264 (  , 7%), 147 (  , 100%), 146 (  , 92%), 145 (  , 12%), 121 (  , 62%), 120 (  , 41%), 119 (  , 16%), 104 (  , 19%), 79 (  , 15%), 78 (, 29%), 77 (  , 35%). Anal. Calcd for $C_{16}H_{18}N_4$: C, 72.15; H, 6.81; N, 21.04%. Found C, 72.31; H, 6.78; N, 21.07%. |
| **IIg** | $CHCl_3$:MeOH (8:2) | 173 | 77 | IR 3382(NH), 1601, 1485 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ : 3.200-3.250 (dd, 1H, |

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| | | | | J= 7 & 18 Hz, one H of $CH_2$), 3.645 (s, 3H, $CH_3$), 3.922 (s, 3H, $CH_3$), 3.979-4.041 (dd, 1H, J= 13 & 18.5 Hz, one H of $CH_2$), 5.630-5.668 (dd, 1H, J= 6.5 & 12.5 Hz, CH), 6.707-6.713 (d, 1H, J= 3 Hz, Ar), 6.744-6.768 (m, 1H, Ar), 6.818-6.847 (t, 1H, J= 9.5 Hz, Ar), 6.878-6.887 (d, 1H, J= 4.5 Hz, Ar), 7.077-7.099 (m, 2H, Ar), 7.148-7.243 (m, 3H, Ar), 7.691-7.725 (m, 1H, Ar), 8.139-8.161 (m, 1H, Ar), 8.550-8.557 (m, 1H, Ar). $^{13}$C NMR (125MHz, $CDCl_3$) $\delta$ : 43.7, 49.7, 55.6, 56.7, 111.7, 112.3, 112.8, 123.6, 127.1, 128.9, 129.1, 129.9, 133.0, 148.3, 149.3, 152.1, 152.9, 154.3 and 155.5. GC-MS: *m/z* 359 ($M^{+\bullet}$, 5%), 358 ($M^{+\bullet}$-H, 6%), 357 (  , 22%), 328 (*m/z* 359-$OCH_3$, 16%), 326 (*m/z* 357-$OCH_3$, 10%), 280 (  ,3%), 222 (  , 10%), 79 (  , 22%), 78 (  , 23%), 77 (  , 42%).<br><br>Anal. Calcd for $C_{22}H_{21}N_3O_2$: C, 73.52; H, 5.89; N, 11.69. Found C, 73.68; H, 5.76; N, 11.78%. |
| **IIh** | $CHCl_3$:MeOH (8:2) | 183 | 81 | IR 3444 (NH), 1625, 1575, 1524, 1497 (Ar) $cm^{-1}$. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ : 3.17-3.22 (dd, 1H, J= 10 & 20 Hz, one H of $CH_2$), 3.61 (s, 3H, $CH_3$), 3.88 (s, 3H, $CH_3$), 3.95-4.01 (dd, 1H, J= 15 & 20 Hz, one H of $CH_2$), 5.58-5.63 (dd, 1H, J= 10 & 20 Hz, CH), 6.68-6.69 (d, 1H, J= 5 Hz, Ar), 6.72-6.74 (m, 1H, Ar), 6.79-6.82 (t, 1H, J= 7.5 Hz, Ar), 6.84-6.86 (d, 1H, J= 10 Hz, Ar), 7.07-7.09 (m, 2H, Ar), 7.18-7.22 (m, 2H, Ar), 7.66-7.67 (d, 1H, J= 5 Hz, Ar), 8.35-8.36 (d, 1H, J= 5 Hz, Ar), 8.53-8.55 (t, 2H, J= 5 Hz, Ar). $^{13}$C NMR (125MHz, $CDCl_3$) $\delta$ : 43.8, 49.7, 55.5, 56.8, 111.9, 112.2, 112.9, 115.4, 123.8, 127.5, 129.0, 129.9, 131.1, 133.0, 148.2, 149.3, 152.1, 152.9, 154.3 and 155.4. GC-MS: *m/z* 359 ($M^{+\bullet}$, 5%), 358 ($M^{+\bullet}$-H, 20%), 357 (  , 71%), 328(*m/z* 359- $OCH_3$ |

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| | | | | 52%), 326 (*m/z* 357-$OCH_3$, 35%), 280 (  , 13%), 222 (  , 25%), 79 (  , 51%), 78 (  , 52%), 77 (  , 100%). Anal. Calcd for $C_{22}H_{21}N_3O_2$: C, 73.52; H, 5.89; N, 11.69%. Found C, 73.62; H, 5.82; N, 11.74%. |
| **IIi** | $CHCl_3$:MeOH (8:2) | 187 | 77 | IR 3429 (NH), 1628, 1585, 1509 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ : 3.18-3.22 (dd, 1H, J= 5 & 10 Hz, one H of $CH_2$), 3.61 (s, 3H, $CH_3$), 3.88 (s, 3H, $CH_3$), 3.95-4.01 (dd, 1H, J= 15 & 20 Hz, one H of $CH_2$), 5.60-5.64 (dd, 1H, J= 10 & 15 Hz, CH), 6.68-6.69 (d, 1H, J= 5 Hz, Ar), 6.72-6.74 (m, 1H, Ar), 6.79-6.82 (t, 1H, J= 7.5 Hz, Ar), 6.84-6.86 (d, 1H, J= 10 Hz, Ar), 7.07-7.09 (m, 2H, Ar), 7.18-7.22 (m, 2H, Ar), 7.66-7.67 (d, 2H, J= 5 Hz, Ar), 8.35-8.36 (d, 2H, J= 5 Hz, Ar). $^{13}C$ NMR (125MHz, $CDCl_3$) $\delta$ : 44.1, 49.6, 55.3, 56.7, 111.7, 112.3, 112.8, 112.9, 123.8, 127.7, 129.0, 129.8, 133.0, 149.3, 152.2, 152.9, 154.4 and 155.4. GC-MS: *m/z* 359, ($M^{+\bullet}$, 20%), 358 ($M^{+\bullet}$-H, 5%), 328 ($M^{+\bullet}$- $OCH_3$, 3%), 222 (  , 100%), 78 (  , 21%), 77 (  , 32%). Anal. Calcd for $C_{22}H_{21}N_3O_2$: C, 73.52; H, 5.89; N, 11.69%. Found C, 73.49; H, 5.85; N, 11.62%. |
| **IIj** | $CHCl_3$:MeOH (8:2) | 183 | 79 | IR 3315 (NH), 1587, 1487, 1442 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ : 2.968 (s, 6H, 2×$CH_3$), 3.070-3.118 (dd, 1H, J= 7 & 17 Hz, one H of $CH_2$), 3.792-3.852 (dd, 1H, J= 12.5 & 17 Hz, one H of $CH_2$), 5.342-5.381 (dd, 1H, J= 7 & 12.5 Hz, CH), 6.826-6.839 (t, 1H, J= 3 Hz, Ar), 6.956-6.973 (d, 2H, J= 8.5 Hz, Ar), 7.062-7.081 (dd, 2H, J= 1 & 7.5 Hz, Ar), 7.165-7.217 (m, 4H, Ar), 7.542-7.569 (m, 1H, Ar), 8.295-8.323 (m, 1H, Ar), 8.533-8.546 (dd, 1H, J= 1.5 & 5 Hz, Ar), 8.859-8.862 |

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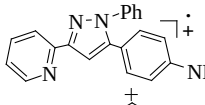
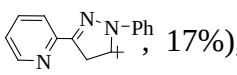
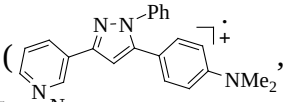
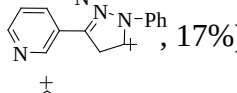
| | | | | (d, 1H, J= 1.5 Hz, Ar). $^{13}$C NMR (125MHz, $CDCl_3$) $\delta$ : 40.6, 42.8, 50.5, 111.7, 113.1, 113.4, 119.4, 123.5, 126.6, 128.8, 130.7, 132.8, 143.2, 144.2, 146.2, 148.3, 149.7, 152.1 and 156.3. GC-MS: *m/z* 342, ($M^{+\bullet}$, 60%), 341 ($M^{+\bullet}$-H, 26%), 340 (  , 30%), 222 (  , 17%), 78 (  , 11%), 77 (  , 45%). Anal. Calcd for $C_{22}H_{22}N_4$: C, 77.16; H, 6.48; N, 16.36%. Found C, 77.27; H, 6.44; N, 16.41%. |
| **IIk** | $CHCl_3$:MeOH (8:2) | 191 | 76 | IR 3386 (NH), 1622, 1595, 1495 (Ar) $cm^{-1}$. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ : 2.92 (s, 6H, 2×$CH_3$), 3.09-3.13 (dd, 1H, J= 5 & 15 Hz, one H of $CH_2$), 3.74-3.79 (dd, 1H, J= 5 & 15 Hz, one H of $CH_2$), 5.24-5.28 (dd, 1H, J= 5 & 10 Hz, CH), 6.70-6.72 (m, 2H, Ar), 6.78-6.81 (m, 1H, Ar), 7.09-7.11 (m, 2H, Ar), 7.15-7.20 (m, 4H, Ar), 7.66-7.67 (d, 1H, J= 5 Hz, Ar), 8.35-8.36 (d, 1H, J= 5 Hz, Ar), 8.53-8.55 (t, 2H, J= 5 Hz, Ar), $^{13}$C NMR (125MHz, $CDCl_3$) $\delta$ : 40.6, 42.8, 50.5, 113.0, 113.1, 119.4, 123.5, 126.6, 128.8, 129.2, 130.7, 132.8, 143.2, 144.2, 146.2, 148.3, 149.7, 153.2 and 155.3. GC-MS: *m/z* 342 ($M^+$, 55%), 341 ($M^+$- H, 32%), 340 (  , 35%), 222 (  , 17%), 78 (  , 11%), 77 (  , 44%). Anal. Calcd for $C_{22}H_{22}N_4$: C, 77.16; H, 6.48; N, 16.36 Found C, 77.23; H, 6.49; N, 16.44. |
| **IIl** | $CHCl_3$:MeOH (8:2) | 197 | 76 | IR 3387(NH), 1632, 1593, 1539 (Ar) $cm^{-1}$. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ : 2.92 (s, 6H, 2×$CH_3$), 3.08-3.13 (dd, 1H, J= 5 & 20 Hz, one H of $CH_2$), 3.75-3.79 (dd, 1H, J= 10 & 15 Hz, one H of $CH_2$), 5.24-5.28 (dd, 1H, J= 5 & 10 Hz, CH), 6.70-6.72 (m, 2H, Ar), 6.78-6.81 (t, |

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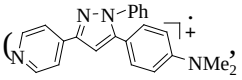
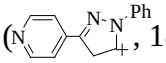
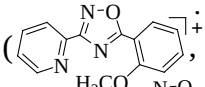
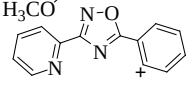
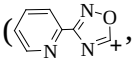
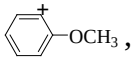
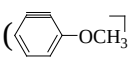
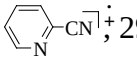
| | | | | 1H, J=7.5 Hz, Ar), 7.09-7.11 (m, 2H, Ar), 7.15-7.20 (m, 4H, Ar), 7.66-7.67 (d, 2H, J= 5 Hz, Ar), 8.35-8.36 (d, 2H, J= 5 Hz, Ar). $^{13}$C NMR (125MHz, $CDCl_3$) $\delta$ : 40.8, 42.9, 50.6, 112.8, 113.6, 119.6, 123.7, 126.8, 129.9, 130.8, 132.9, 143.4, 146.3, 148.4, 149.8, 152.5 and 155.8. GC-MS: *m/z* 342 ($M^{+\bullet}$, 58%), 341 ($M^{+\bullet}$-H, 28%), 340 (  , 30%), 222 (  , 18%), 78 (  , 11%), 77 (  , 45%). Anal. Calcd for $C_{22}H_{22}N_4$: C, 77.16; H, 6.48; N, 16.36%. Found C, 77.11; H, 6.51; N, 16.34%. |
| **IVa** | MeOH | 211 | 77 | IR 1587, 1489, (Ar) $cm^{-1}$. $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ : 3.748 (s, 3H, $OCH_3$), 3.869 (s, 3H, $OCH_3$), 7.164-7.194 (q, 2H, J= 3.5 & 5.5 Hz, Ar), 7.247-7.272 (dd, 1H, J= 3 & 9 Hz, Ar), 7.723-7.750 (m, 1H, Ar), 8.015-8.072 (m, 2H, Ar), 8.747-8.758 (dd, 1H, J= 1 & 4.5 Hz, Ar). $^{13}$C NMR (125MHz, $CDCl_3$) $\delta$ : 55.6, 56.0, 110.3, 113.2, 117.1, 123.3, 124.7, 126.9,128.4, 133.8, 136.9, 150.9, 153.4, 156.4 and 156.5. GC-MS: *m/z* 283 ($M^{+\bullet}$ , 18%), 253 (  , 10%), 252 ($M^{+\bullet}$-$OCH_3$, 17%), 222 (  , 10%), 147 (  , 20%), 146 (  , 31%), 136 (  , 22%),107 (  , 5%), 106 (  , 14%), 104 (  , 29%), 78(  , 100%), 77 (  , 27%), 76 (107-$OCH_3$,10%). Anal. Calcd for $C_{15}H_{13}N_3O_3$: C, 63.60; H, 4.60; N, 15.19%. Found C, 63.67; H, 4.69; N, 14.89%. |
| **IVb** | MeOH | 237 | 77 | IR 2921 ($CH_3$), 1585, 1462 (Ar) $cm^{-1}$. $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ : 3.751 (s, 3H, $OCH_3$), 3.873 (s, 3H, $OCH_3$), 7.169-7.203 (q, 2H, J= 3.5 & 8 Hz, Ar), 7.255-7.280 (q, 1H, J= 3.5 & |

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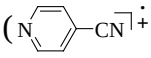
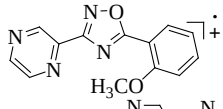
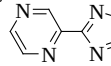
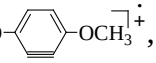
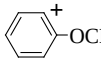
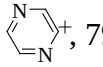
| | | | | 9.5 Hz, Ar), 7.865-7.876 (d, 2H, J= 6 Hz, Ar), 8.839-8.851 (d, 2H, J= 6 Hz, Ar). $^{13}$C NMR (125MHz, $CDCl_3$) $\delta$ : 56.7, 57.0, 111.2, 114.2, 117.2, 121.3, 124.3, 125.7, 126.1, 151.6, 154.4, 156.4 and 157.5. GC-MS: *m/z* 283 ($M^+$ , 88%), 282 ($M^{+\bullet}$-H, 3%), 252 ($M^{+\bullet}$-$OCH_3$ , 7%), 104 (  , 8%), 78 (  , 36%), 77 (  , 45%). Anal. Calcd for $C_{15}H_{13}N_3O_3$: C, 63.60; H, 4.60; N, 15.19%. Found C, 63.54; H, 4.67; N, 14.97%. |
| **IVc** | MeOH | 196 | 78 | IR 1575, 1447 (Ar) $cm^{-1}$. $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ : 3.749 (s, 3H, $OCH_3$), 3.877 (s, 3H, $OCH_3$), 7.165-7.195 (q, 2H, J= 3.5 & 5.5 Hz, Ar), 7.247-7.272 (q, 1H, J= 3 & 9 Hz, Ar), 8.864-8.871 (t, 1H, J= 2 Hz, Ar), 8.970-8.975 (d, 1H, J= 2.5 Hz, Ar), 9.225-9.228 (d, 1H, J= 1.5 Hz, Ar). $^{13}$C NMR (125MHz, $CDCl_3$) $\delta$ : 55.7, 56.0, 110.3, 113.2, 115.2, 123.3, 124.7, 130.9, 145.4, 147.3, 148.2, 153.4, 155.4 and 156.6. GC-MS: *m/z* 284 ($M^{+\bullet}$, 54%), 283 ($M^{+\bullet}$-H, 5%), 254 (  , 9%), 253 ($M^+$-$OCH_3$ , 6%), 148 (  , 47%), 136 (  , 19%), 107 (  , 100%), 79 (  , 79%). Anal. Calcd for $C_{14}H_{12}N_4O_3$: C, 59.15; H, 4.23; N, 19.71%. Found C, 59.28; H, 4.19; N, 19.67%. |
| **IVd** | MeOH | 247 | 79 | IR 3425 (OH), 1626, 1578, 1525 (Ar) $cm^{-1}$. $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ : 3.843 (s, 3H, $OCH_3$), 6.954-6.970 (d, 1H, J= 8 Hz, Ar), 7.387-7.415 (t, 1H, J= 12.5 Hz, Ar), 7.428-7.430 (d, 1H, J= 1 Hz, Ar), 7.723-7.750 (m, 1H, Ar), 8.015-8.072 (m, 2H, Ar), 8.747-8.758 (dd, 1H, J= 1 & 4.5 Hz, Ar), 10.254 (bs, 1H, OH). $^{13}$C NMR (125MHz, $CDCl_3$) $\delta$ : 55.9, 108.7, 114.3, 116.9, 126.9, 127.3, 128.4, 129.6, |

| 1 | 2 | 3 | 4 | 5 |
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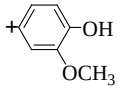
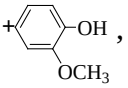
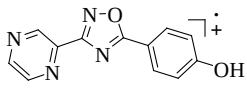
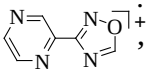
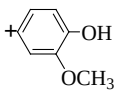
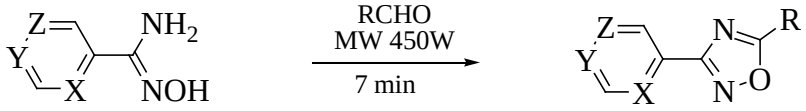
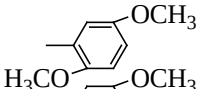
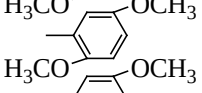
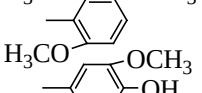
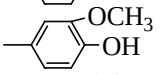
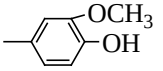
| | | | | 133.7, 136.9, 147.1, 150.9, 151.7, 156.8. GC-MS: *m/z* 269 ($M^{+\bullet}$, 55%), 123 (  , 19%), 78 (  , 20%). Anal. Calcd for $C_{14}H_{11}N_3O_3$: C, 62.45; H, 4.09; N, 15.65%. Found C, 62.41; H, 4.15; N, 15.69%. |
| **IVe** | MeOH | 253 | 81 | IR 3425 (OH), 1578, 1525 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$) $\delta$ : 3.837 (s, 3H, $OCH_3$), 6.948-6.965 (d, 1H, J= 8.5 Hz, Ar), 7.382-7.385 (d, 1H, J= 1.5 Hz, Ar), 7.407-7.427 (dd, 1H, J= 2 & 8 Hz, Ar), 7.860-7.872 (dd, 2H, J= 1.5 & 4.5 Hz, Ar), 8.837-8.849 (dd, 2H, J= 1.5 & 4 Hz, Ar), 10.245 (bs, 1H, OH). $^{13}C$ NMR (125MHz, $CDCl_3$) $\delta$ : 55.9, 108.7, 114.4, 116.2, 120.4, 125.2, 127.4, 129.6, 147.2, 150.5, 151.8 and 156.8. GC-MS: *m/z* 269, ($M^{+\bullet}$ ,60%), 123 (  , 20%), 78 (  , 22%), 77 (  , 10%). Anal. Calcd for $C_{14}H_{11}N_3O_3$: C, 62.45; H, 4.09; N, 15.65%. Found C, 62.48; H, 4.10; N, 15.67%. |
| **IVf** | MeOH | 235 | 77 | IR 3312 (OH), 1612, 1590, 1532, (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$) $\delta$ : 3.840 (s, 3H, $OCH_3$), 6.953-6.969 (d, 1H, J= 8 Hz, Ar), 7.386 (s, 1H, Ar), 7.411-7.430 (dd, 1H, J= 1.5 & 8 Hz, Ar), 8.864-8.871 (t, 1H, J= 2 Hz, Ar), 8.970-8.975 (d, 1H, J= 2.5 Hz, Ar), 9.225-9.228 (d, 1H, J= 1.5 Hz, Ar), 10.253 (bs, 1H, OH). $^{13}C$ NMR (125MHz, $CDCl_3$) $\delta$ : 55.9, 108.7, 114.3, 115.1, 127.3, 129.6, 130.8, 145.3, 147.1, 147.2, 148.1, 151.6 and 156.8. GC-MS: *m/z* 270, ($M^{+\bullet}$ 10%), 240(  , 6%), 148 (  , 53), 123 (  , 5%), 79 (  , 11%). Anal. Calcd for $C_{13}H_{10}N_4O_3$: C, 57.78; H, 3.73; N, 20.73%. Found C, 57.72; H, 3.76; N, 20.67%. |

(**IIIb**, Scheme 3.2) and N′-hydroxy-pyrazine-2-carboxamidine (**IIIc**, Scheme 3.2) have been synthesized by following reaction procedure reported in literature [24]. Equimolar ratio of N′-hydroxypicolinamidine (**IIIa**, Scheme 3.2) and 2,5-dimethoxybenzaldehyde were mixed together thoroughly and subjected to microwave irradiation at a power level of 450 Watt for 3 minutes. TLC of reaction mixture showed the presence of starting materials, so the reaction contents were further irradiated for 4 minutes and progress of reaction was monitored by TLC, which showed absence of starting materials. From this observation it is inferred that irradiation for 3+4 minutes is required for completion of reaction to give condensation product **IVa**. Compound **IVa** was further purified by crystallization from methanol to give pure 2-[5-(2,5-dimethoxyphenyl)-[1,2,4] oxadiazol-3-yl] pyridine (**IVa**, Scheme 3.2) in good yield.

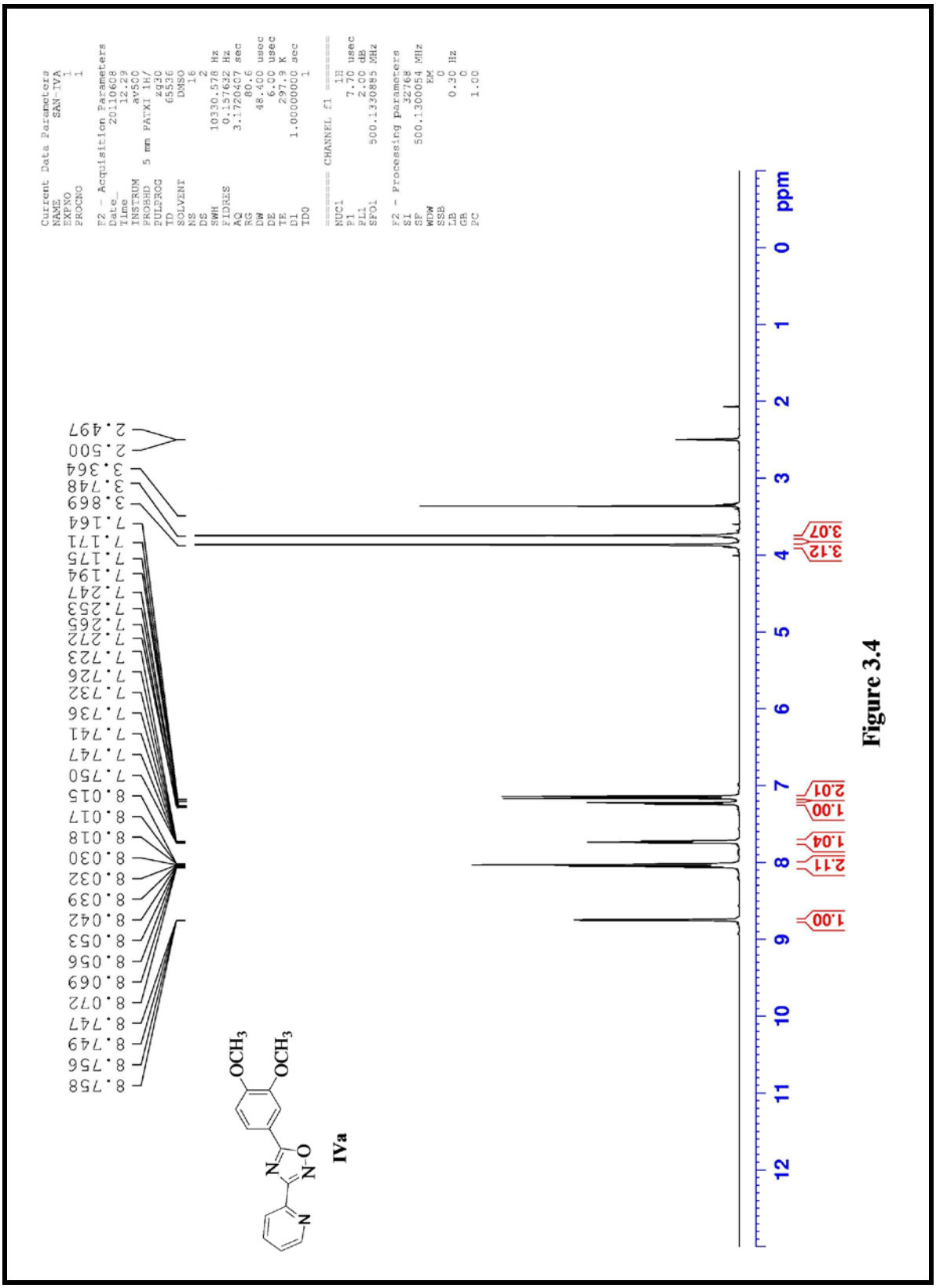
IR spectrum of **IVa** shows absorption signal at 1587, 1489 $cm^{-1}$ correspond to aromatic region. $^{1}H$ NMR (500 MHz, DMSO-$d_6$) (Figure 3.4) of compound **IVa** exhibited signals at $\delta$ : 3.748 (s, 3H, $OCH_3$), 3.869 (s, 3H, $OCH_3$), 7.164-7.194 (q, 2H, J= 3.5 & 5.5 Hz, Ar), 7.247-7.272 (dd, 1H, J= 3 & 9 Hz, Ar), 7.723-7.750 (m, 1H, Ar), 8.015-8.072 (m, 2H, Ar), 8.747-8.758 (dd, 1H, J= 1 & 4.5 Hz, Ar). $^{13}C$ NMR (125MHz, $CDCl_3$) (Figure 3.5) data of **IVa** exhibited signals at $\delta$ : 55.640, 56.006, 110.281, 113.219, 117.079, 123.254, 124.676, 126.872, 128.428, 133.767, 136.971, 150.991, 153.376, 156.431 and 156.537. GC-MS spectrum (*m/z*; relt. int. %) (Figure 3.6) of **IVa** gave $M^{+\bullet}$ ion peak at *m/z* 283 (18%). In addition to $M^{+\bullet}$ ion peak GCMS of **IVa** shows some other prominent ion peaks which can arise through its fragmentation. The fragmentation pattern of **IVa** is outlined in chart 3.2. Elemental analysis Calculated for




**IIIa-c** **IVa-f**

| | X | Y | Z | | X | Y | Z | R |
|---|---|---|---|---|---|---|---|---|
| **IIIa** | N | CH | CH | **IVa** | N | CH | CH |  |
| **IIIb** | CH | N | CH | **IVb** | CH | N | CH |  |
| **IIIc** | N | CH | N | **IVc** | N | CH | N |  |
| | | | | **IVd** | N | CH | CH |  |
| | | | | **IVe** | CH | N | CH |  |
| | | | | **IVf** | N | CH | N |  |

Scheme-3.2: Synthesis of oxadiazole derivatives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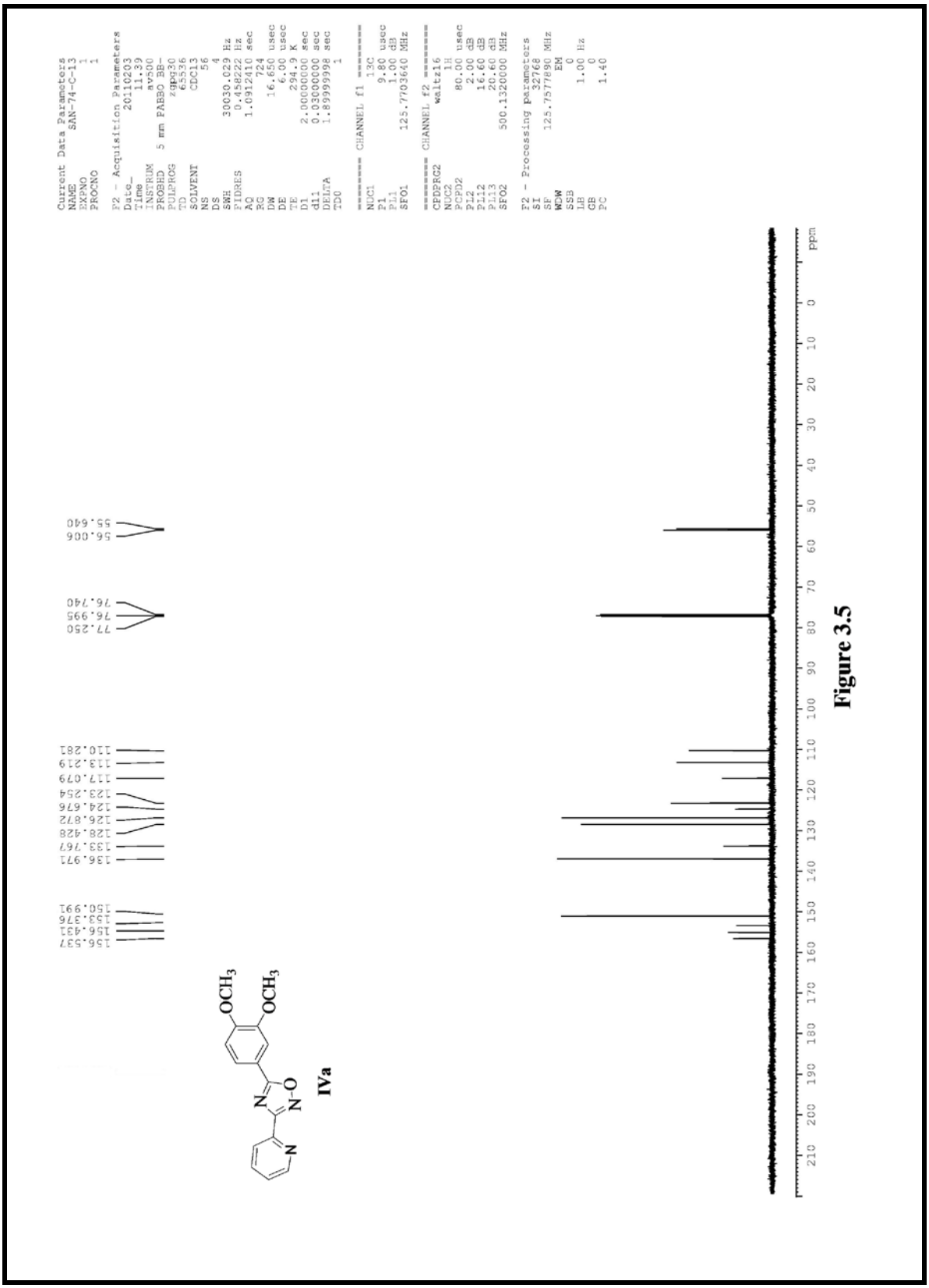
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20110608
Time 12.29
INSTRUM av500
PROBHD 5 mm PATXI 1H/
PULPROG zg30
TD 65536
SOLVENT DMSO
NS 16
DS 2
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1720407 sec
RG 80.6
DW 48.400 usec
DE 6.00 usec
TE 297.9 K
D1 1.00000000 sec
TD0 1
CHANNEL f1
NUC1 1H
P1 7.70 usec
PL1 2.00 dB
SFO1 500.1330885 MHz
F2 - Processing parameters
SI 32768
SF 500.1300054 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
8.758
8.756
8.749
8.747
8.072
8.069
8.056
8.053
8.042
8.039
8.032
8.030
8.018
8.017
8.015
7.750
7.747
7.741
7.736
7.732
7.726
7.723
7.272
7.265
7.253
7.247
7.194
7.175
7.171
7.164
3.869
3.748
3.364
2.500
2.497
1.00
2.11
1.04
1.00
2.01
3.12
3.07
ppm
IVa

**Figure 3.4**


Current Data Parameters
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EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20110203
Time 11.39
INSTRUM av500
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 56
DS 4
SWH 30030.029 Hz
FIDRES 0.458222 Hz
AQ 1.0912410 sec
RG 724
DW 16.650 usec
DE 6.00 usec
TE 294.9 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 9.80 usec
PL1 1.00 dB
SFO1 125.7703640 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 2.00 dB
PL12 16.60 dB
PL13 20.60 dB
SFO2 500.1320000 MHz
F2 - Processing parameters
SI 32768
SF 125.7577890 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
156.537
156.431
153.376
150.991
136.971
133.767
128.428
126.872
124.676
123.254
117.079
113.219
110.281
77.250
76.995
76.740
56.006
55.640
OCH3
OCH3
N
O
N
N
IVa
ppm

**Figure 3.5**

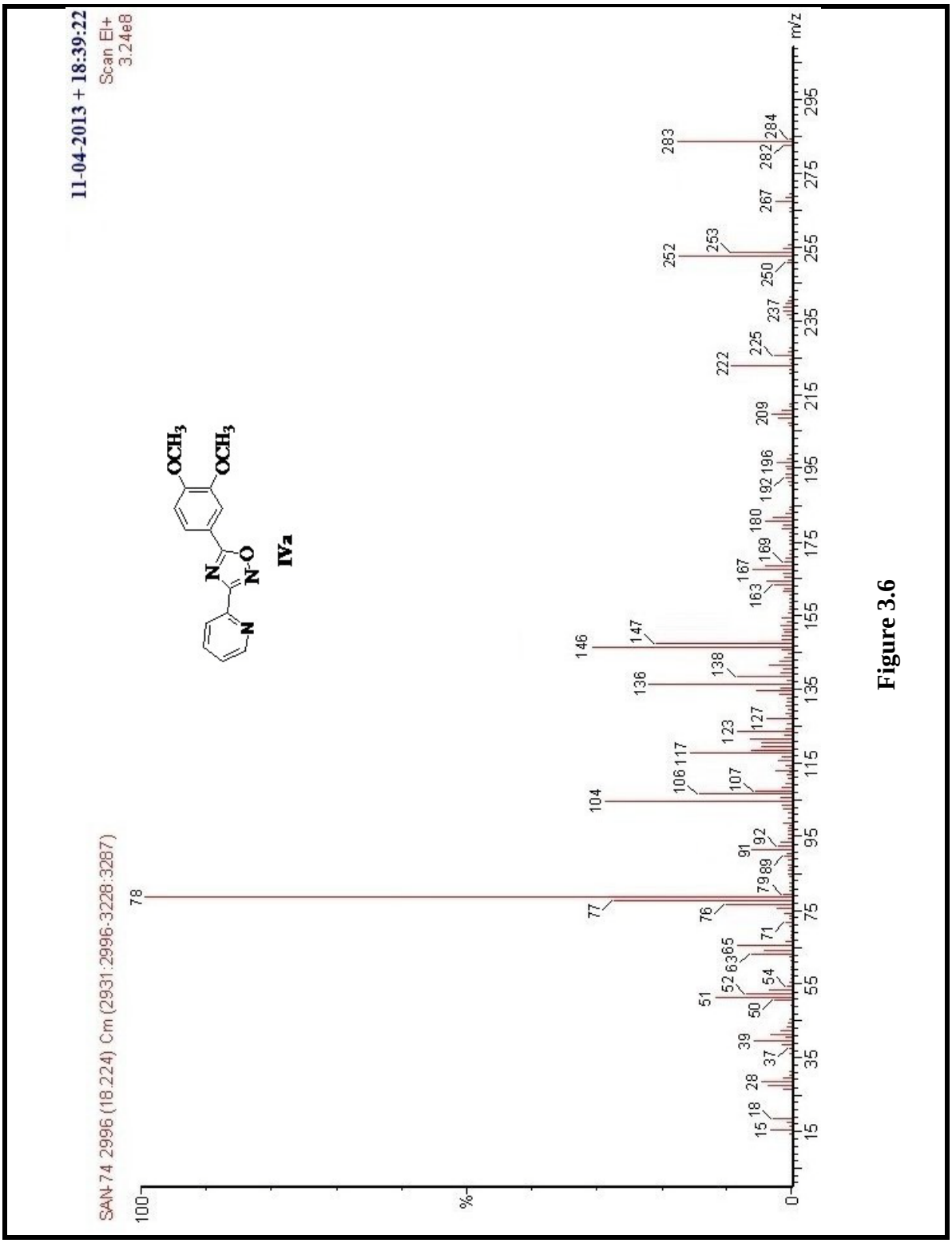
11-04-2013 + 18:39:22
Scan EI+
3.24e8
SAN-74 2996 (18.224) Cm (2931:2996-3228:3287)
OCH3
OCH3
N
N-O
IVa
%
m/z

**Figure 3.6**

**Fragmentation pattern of IVa**

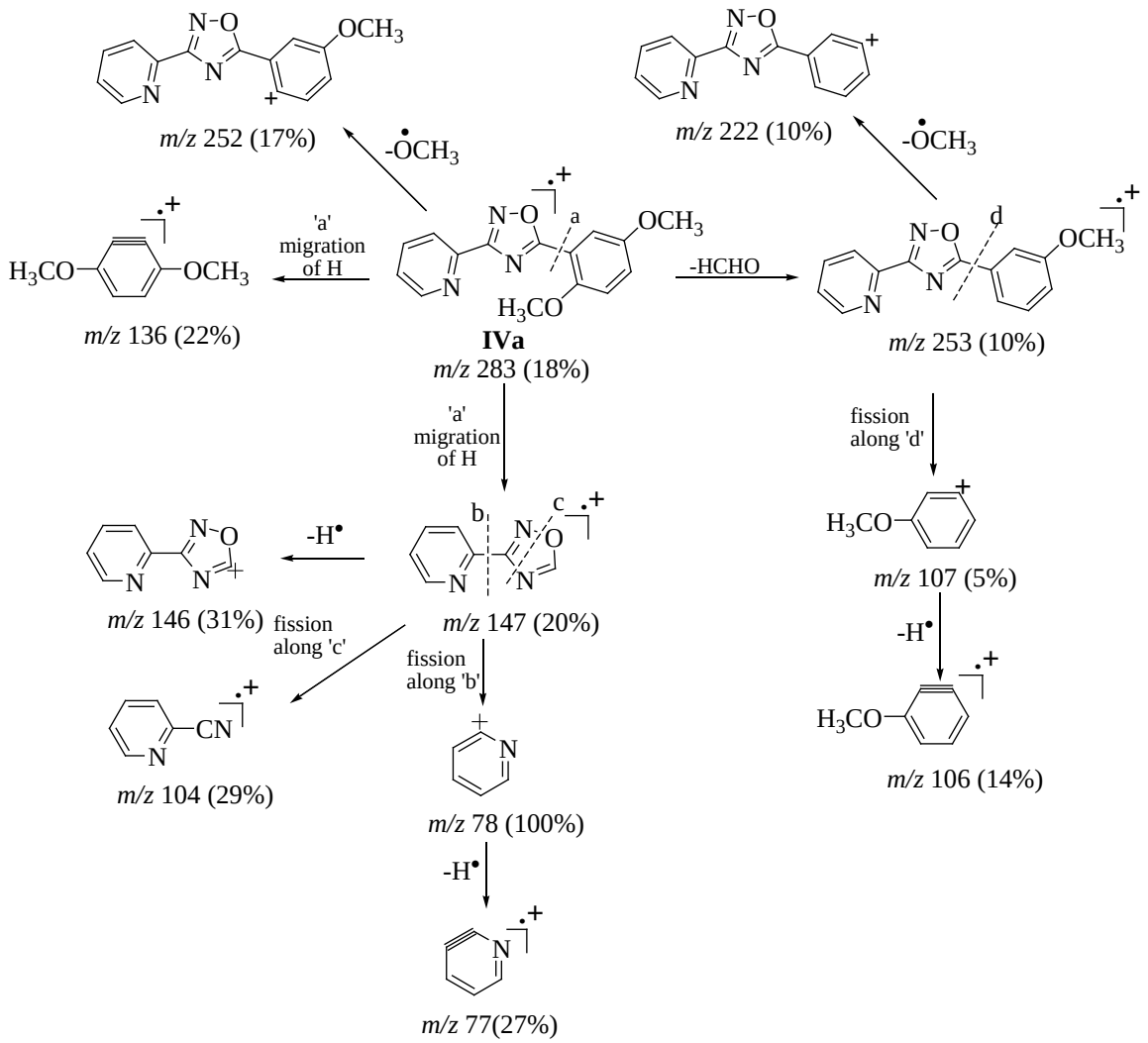


**Chart 3.2**

$C_{15}H_{13}N_3O_3$: C, 63.60; H, 4.60; N, 15.19%. Found C, 63.67; H, 4.69; N, 14.89%. Spectral data and elemental analysis of **IVa** is in full agreement with the structure assigned to it.

Similarly condensation of **IIIb** and **IIIc** with 2,5-dimethoxybenzaldehyde and **IIIa**, **b**, **c** with 3-methoxy-4-hydroxy benzaldehyde gave **IVb**, **c** and **IVd-f** (Scheme -3.2) respectively. Physical constants and spectral data of **IVa-f** reported in Table-3.1 fully support the structures assigned to them.

All the compounds were also prepared by using microwave reactor model CEM DISCOVER No 908010. Reaction temperature for **IIa-f**, **IIg-l** and **IVa-f** was 85, 110 & 160°C and irradiation time was 3 min, 5 min and 5 min respectively.

**3.2.2 Biological results and discussion**

Anti-inflammatory activity [21; Chapter 2] evaluation of **IIa-l** and **IVa-f** was carried out using carrageenan induced paw oedema assay and results are summarized in the Table 3.2. A look at the Table 3.2 indicates that compounds **IIj, IIk and IVb** exhibited 35, 34 and 35% anti-inflammatory activity respectively, whereas standard drug ibuprofen exhibited 39% anti-inflammatory activity at 50mg/kg *p.o*.

*In vitro* anticancer activity [22, 23; Chapter 2] evaluation of compounds **IIa-l** and **IVa-f** was carried out against five human cancer cell lines consisting of lung (NCI H-522), ovary (PA1), breast (T47D), colon (HCT-15) and liver (HepG2). Percentage (%) growth inhibition of compounds **IIa-l** and **IVa-f** against various cancer cell lines was determined at a concentration of 10µM and results are summarized in Table-3.2. Graphical representations of these results are shown in Figure 3.7 and Figure 3.8 respectively. Compounds **IIa**, **c**, **j** exhibited good anticancer activity against four cancer cell lines i.e. lung (NCI H-522), breast (T47D), colon (HCT-15), liver (HepG2) and **IVd**

Table-**3.2** Anti-inflammatory** and *in vitro* anticancer activity** of compounds **IIa-l** and **IVa-f**

| Compd. No. | Anti-inflammatory activity (%) at 50 mg/kg p.o. | Anticancer activity at a concentration of $1\times10^{-5}$ M | | | | |
|---|---|---|---|---|---|---|
| | | Lung | Ovary | Breast | Colon | Liver |
| | | NCI H-522 | PA1 | T47D | HCT-15 | HepG2 |
| **IIa** | 15 | **28** | 25 | **26** | **10** | **23** |
| **IIb** | 15 | 40 | 31 | 13 | 04 | 34 |
| **IIc** | 13 | **24** | 24 | **19** | **28** | **34** |
| **IId** | 18 | 34 | 21 | 03 | 05 | 29 |
| **IIe** | 22 | 25 | 36 | 15 | 06 | 35 |
| **IIf** | 00 | 28 | 26 | 21 | 03 | 29 |
| **IIg** | 27 | 16 | 18 | 12 | 09 | 20 |
| **IIh** | 24 | 32 | 32 | 22 | 07 | 26 |
| **IIi** | 18 | 29 | 31 | 37 | 05 | 32 |
| **IIj** | **35** | **26** | 16 | **41** | **12** | **24** |
| **IIk** | **34** | 20 | 20 | 33 | 01 | 32 |
| **IIl** | 32 | 32 | 24 | 07 | 06 | 35 |
| **IVa** | 28 | 23 | 25 | 37 | 05 | 33 |
| **IVb** | **35** | 10 | 19 | 25 | 02 | 27 |
| **IVc** | 11 | 23 | 26 | 41 | 07 | 17 |
| **IVd** | 24 | **48** | 30 | **33** | 03 | **39** |
| **IVe** | 14 | 25 | 32 | 34 | 05 | 13 |
| **IVf** | 26 | 20 | 20 | 35 | 01 | 20 |
| Ibuprofen | 39 | - | - | - | - | - |
| *CYC-PHO | - | 04 | 04 | 18 | 05 | 14 |
| *CYC-HEXI | - | 13 | 51 | 09 | 03 | 05 |
| *5-FU | | 24 | 10 | 05 | 08 | 18 |

*CYC-PHO Cyclophospamide; *CYC-HEXI Cycloheximide; *5-FU 5-Flurouracil;

** We are thankful to Dr. Partha Roy, Department of Biotechnology, Indian Institute of Technology Roorkee, Roorkee for these results.

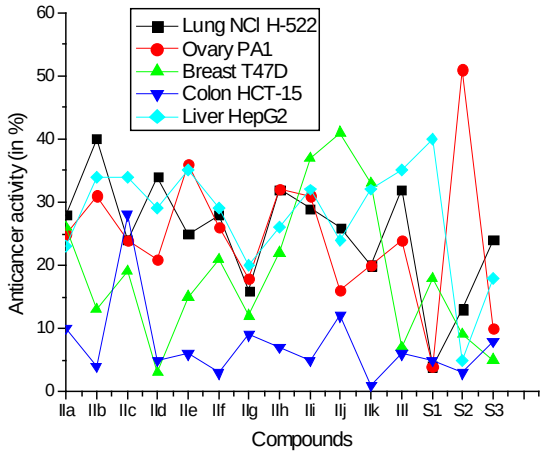


Figure:-3.7 Graphical representation of anticancer activity of compounds **IIa-l** and S1 (CYC-PHO), S2 (CYC-HEXI C) & S3 (5-FU) against five human cancer cell lines.

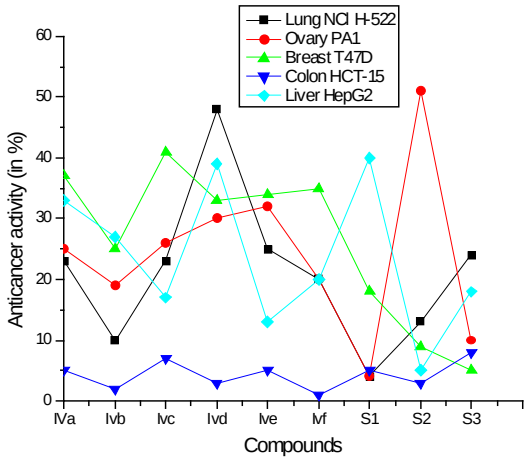


Figure:-3.8 Graphical representation of anticancer activity of compounds **IVa-j** and S1 (CYC-PHO), S2 (CYC-HEXI C) & S3 (5-FU) against five human cancer cell lines.

against three cancer cell lines i.e. lung (NCI H-522), breast (T47D), liver (HepG2).

## 3.3 Experimental

### *3.3.1 General*

Microwave oven model M197DL (Samsung) and microwave reactor model CEM DISCOVER model NO 908010 were used for microwave irradiation. Melting points (mp) were determined on a JSGW apparatus and are uncorrected. IR spectra were recorded using a Perkin Elmer 1600 FT spectrometer. $^{1}H$ and $^{13}C$ NMR spectra were recorded on a Bruker WH-500 spectrometer at a *ca* 5-15% (*w/v*) solution in DMSO-$d_6$,

$CDCl_3$ and $D_2O$. GC-MS was recorded on Perkin Elmer Clarus 500 gas chromatograph where built in MS detector was used. Elemental analysis was carried out on a Vario EL III elementor. Thin layer chromatography (TLC) was performed on silica gel G for TLC (Merck) and spots were visualized by iodine vapour or by irradiation with ultraviolet light (short wave length, 254nm). Physical constants, spectral data and elemental analysis of compounds **IIa-l** and **IVa-f** are reported in Table-3.1.

### 3.3.2 Synthesis of chalcone derivatives Ia-f.

Chalcone derivatives 3-(2,5-dimethoxyphenyl)-1-(pyridin-2-yl)prop-2-en-1-one (**Ia**), 3-(2,5-dimethoxyphenyl)-1-(pyridin-3-yl)prop-2-en-1-one (**Ib**), 3-(2,5-dimethoxy phenyl)-1-(pyridin-4-yl)prop-2-en-1-one (**Ic**), 3-(4-(dimethylamino)phenyl)-1-(pyridin-2-yl)prop-2-en-1-one (**Id**), 3-(4-(dimethylamino)phenyl)-1-(pyridin-3-yl)prop-2-en-1-one (**Ie**) and 3-(4-(dimethylamino)phenyl)-1-(pyridin-4-yl)prop-2-en-1-one (**If**) were synthesized by following reaction procedure reported in literature [22, 23].

### 3.3.3 General procedure for synthesis of pyrazole derivatives IIa-l.

3.3.3.1 Synthesis of 2-[5-(2,5-dimethoxyphenyl)-4,5-dihydro-1H-pyrazol-3-yl]-pyridine (**IIa**)

(i) 3-(2,5-Dimethoxyphenyl)-1-(pyridin-2-yl)prop-2-en-1-one (0.269 g; 1 mmol) and hydrazine hydrated (0.060 g;1.2 mmol) were mixed together to make a homogeneous mixture and then this reaction mixture was subjected to microwave irradiation for 3 minutes at a power level of 180W. Progress of reaction was monitored by TLC. TLC of reaction mixture showed formation of a new product and absence of starting materials. This crude product was crystallized from chloroform to give pure product **IIa**. Yield 234 mg (83%).

(ii) 3-(2,5-Dimethoxyphenyl)-1-(pyridin-2-yl)prop-2-en-1-one (0.269 g; 1 mmol) and hydrazine hydrated (0.060 g;1.2 mmol) were mixed together to make a homogeneous mixture. This homogeneous mixture was subjected to microwave irradiation at 85°C for 3 minutes. TLC of reaction mixture show absence of starting materials. Crude product so obtained was purified by crystallization from chloroform to give pure product **IIa**. Yield 240 mg (85%).

Similarly other pyrazole derivatives **IIb-l** i.e. 3-[5-(2,5-dimethoxyphenyl)-4,5-dihydro-1H-pyrazol-3-yl]-pyridine (**IIb**), 4-[5-(2,5-dimethoxyphenyl)-4,5-dihydro-1H-pyrazol-3-yl]-pyridine (**IIc**), N,N-dimethyl-4[3-(pyridin-2-yl)-4,5-dihydro-1H-pyrazol-5-yl] benzenamine (**IId**), N,N-dimethyl-4[3-(pyridin-3-yl)-4,5-dihydro-1H-pyrazol-5-yl] benzenamine (**IIe**), N,N-dimethyl-4[3-(pyridin-4-yl)-4,5-dihydro-1H-pyrazol-5-yl] benzenamine (**IIf**), 2-[5-(2,5-dimethoxyphenyl)-1-phenyl-4,5-dihydro-1H-pyrazol-3-yl]-pyridine (**IIg**)*, 3-[5-(2,5-dimethoxyphenyl)-1-phenyl-4,5-dihydro-1H-pyrazol-3-yl]-pyridine (**IIh**)*, 4-[5-(2,5-dimethoxyphenyl)-1-phenyl-4,5-dihydro-1H-pyrazol-3-yl]-pyridine (**IIi**)*, N, N-dimethyl-4[1-phenyl-3-(pyridin-2-yl)-4,5-dihydro-1H-pyrazol-5-yl] benzenamine (**IIj**)*, N,N-dimethyl-4[1-phenyl-3-(pyridin-3-yl)-4,5-dihydro-1H-pyrazol-5-yl] benzenamine (**IIk**)* and N,N-dimethyl-4[1-phenyl-3-(pyridin-4-yl)-4,5-dihydro-1H-pyrazol-5-yl] benzenamine **(IIl**)* were synthesized and reported in Table 3.1.

* For compounds **IIg-l** in method-(i) power level used was 450 watt.

* For compounds **IIg-l** in method-(ii) temperature used was 110ºC.

### 3.3.4 Synthesis of IIIa-c.

N′-Hydroxypicolinamidine, (**IIIa**), N′-hydroxy-isonicotinamidine (**IIIb**) and N′-hydroxy-pyrazine-2-carboxamidine (**IIIc**) were synthesized by following reaction procedure reported in literature [24].

### 3.3.5 General procedure for synthesis of oxadiazole derivatives (IVa-f)

3.3.5.1 Synthesis of 2-[5-(2,5-dimethoxyphenyl)-[1,2,4]oxadiazol-3-yl]-pyridine (**IVa**)

(i) N′-Hydroxypicolinamidine (**IIIa**, Scheme 3.2), (0.269 g; 1 mmol) and 2,5-dimethoxybenzaldehyde (0.060 g; 1.2 mmol) were mixed together to give a homogeneous mixture and then this reaction mixture was subjected to microwave irradiation for 3 minutes at a power level of 450 Watt. TLC of reaction mixture showed the presence of starting materials so reaction contents were further irradiated for 4 minutes and progress of reaction was monitored by TLC, which showed absence of starting materials. From this observation it is inferred that irradiation for 3+4 minutes is required for completion of reaction to give condensation product **IVa**. Compound **IVa** was further purified by crystallization from methanol to give pure 2-[5-(2,5-dimethoxyphenyl)-[1,2,4] oxadiazol-3-yl] pyridine (**IVa**, Scheme 3.2). Yield 218 mg (77%).

(ii) N′-Hydroxypicolinamidine (**IIIa**, Scheme 3.2), (0.269 g; 1 mmol) and 2,5-dimethoxybenzaldehyde (0.060 g;1.2 mmol) were mixed together to make a homogeneous mixture. This homogeneous mixture was subjected to microwave irradiation at 160°C for 5 min. TLC of reaction mixture show absence of starting materials. This crude product was crystallized from methanol to give pure product **IVa**. Yield 212 mg (75%).

Similarly other oxadiazole derivatives **IVb-f** i.e. 4-[5-(2,5-dimethoxyphenyl)-[1,2,4]oxadiazol-3-yl]-pyridine (**IVb**), 2-[5-(2,5-dimethoxyphenyl)-[1,2,4]oxadiazol-3-yl]-pyrazine (**IVc**), 2-methoxy-4-[3-(pyridin-2-yl)-[1,2,4]oxadiazol-5-yl]-phenol (**IVd**), 2-methoxy-4-[3-(pyridin-4-yl)-[1,2,4]oxadiazol-5-yl]-phenol (**IVe**) and 2-methoxy-4-[3-(pyrazin-2-yl)-[1,2,4]oxadiazol-5-yl]-phenol (**IVf**) were synthesized and reported in Table 3.1.

### 3.3.6 Anti-inflammatory activity [21; Chapter-2]

Anti-inflammatory activity evaluation was carried out by following procedure described in chapter-2 of this thesis.

### 3.3.7 In vitro cytotoxicity against human cancer cell lines [22, 23; Chapter-2]

In vitro cytotoxicity against human cancer cell lines was carried out by following procedure described in chapter-2 of this thesis.

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# Chapter *4*

*4a Synthesis anti-inflammatory and anticancer activity evaluation of azomethine and amidine derivatives of isoindole and pyrrolopyrazine*

*4b Synthesis anti-inflammatory and anticancer activity evaluation of isoindole, pyrrolopyrazine, benzimidazo-isoindole and benzimidazopyrrolopyrazine derivatives*

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***4a Synthesis anti-inflammatory and anticancer activity evaluation of azomethine and amidine derivatives of isoindole and pyrrolopyrazine***

## 4a.1 Introduction

Synthesis of heterocyclic molecules which can be easily prepared and exhibit good biological activities is an interesting area of research. Recent work reported in literature on isoindole, pyrrolopyrazine, amidine and azomethine derivatives exhibiting anti-inflammatory and anticancer activities is summarized in chapter-1. In addition to anti-inflammatory and anticancer activities, isoindole & pyrrolopyrazine derivatives are also reported to possess antibacterial [1-3] and HIV-I integrase inhibition activity [4-6]. Isoindole derivatives exhibiting antiasthmatic [7], antimicrobial [8], antimalarial [9], antiplasmodial [10], anticonvulsant [11], antifungal [12] and pyrrolopyrazine derivatives exhibiting antiarrhythmic activity [13] is also known in literature. Azomethine and amidine derivatives possessing antimalarial [14, 15], antiparasitic [16-18], antimicrobial [19-21], antibacterial [22-24] and antifungal [25, 26] activities are also reported in literature.

Wide range of biological activities exhibited by isoindole, pyrrolopyrazine, azomethine and amidine derivatives and our efforts in search of biological active molecules [27, 28] tempted us to synthesize amidine and azomethine derivatives of isoindole and pyrrolopyrazine. Some more complex molecules i.e. benzimidazoisoindole and benzimidazopyrrolopyrazine derivatives have also been synthesized. For the sake of clarity this chapter is divided into two parts i.e. part-a & part-b. In part-a synthesis, anti-inflammatory and anticancer activity evaluation of azomethine and amidine derivatives of isoindole and pyrrolopyrazine will be described.

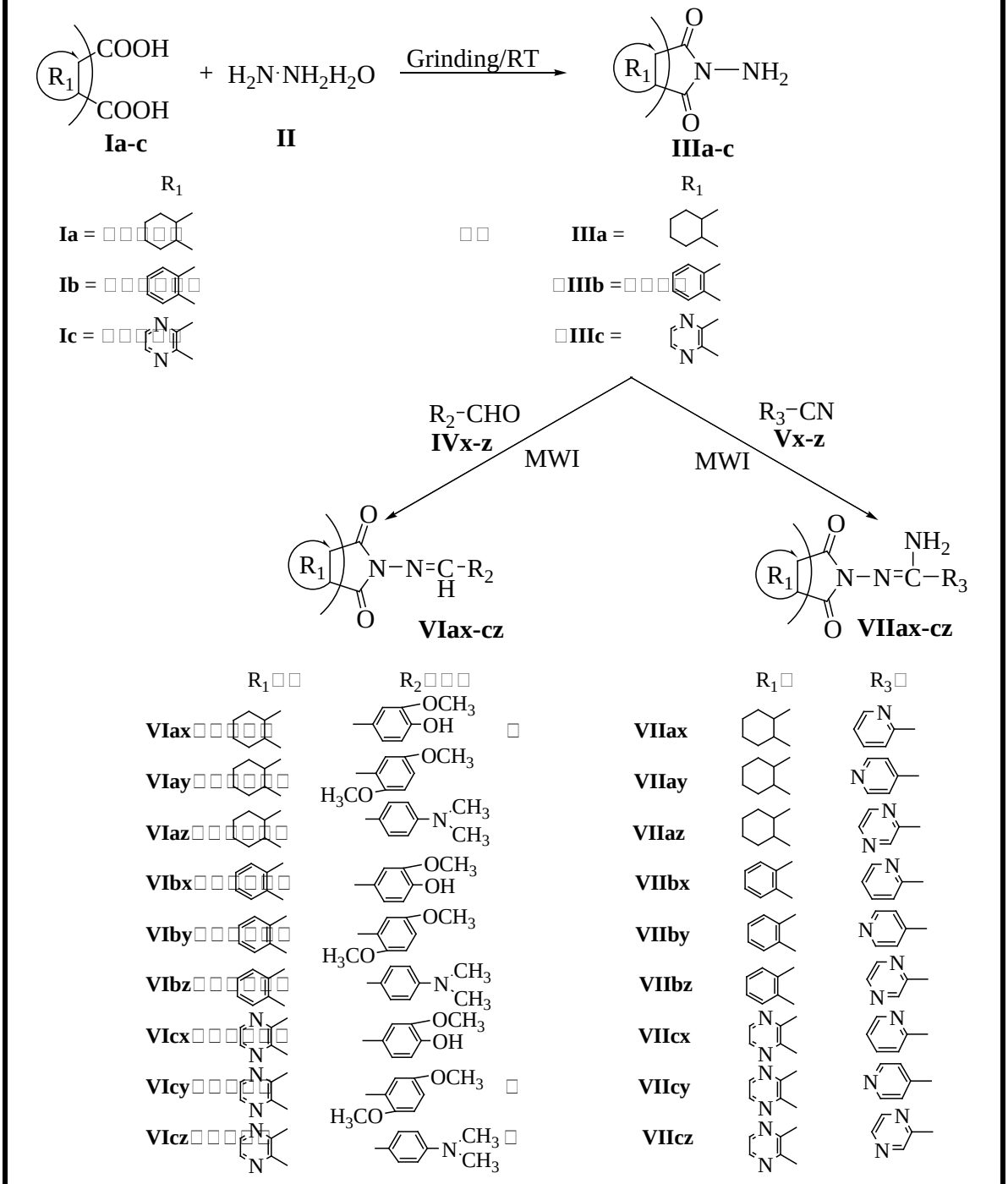
**Part-a**

## 4a.2 Results and discussion

### 4a.2.1 *Chemistry:*

Reported methods for the synthesis of 2-aminohexahydro-2H-isoindole-1,3-dione (**IIIa**) [29, 30] and N-aminophthalimide (**IIIb**) [29, 31] involve two step synthesis & refluxing in a solvent. We have synthesized 2-aminohexahydro-2H-isoindole-1,3-dione (**IIIa**; Scheme 4a.1), N-aminophthalimide (**IIIb**; Scheme 4a.1) and 6-amino-6H-pyrrolo[3,4-b]pyrazine-5,7-dione (**IIIc**; Scheme 4a.1) by simple grinding a mixture of corresponding dicarboxylic acids (**Ia-c**; Scheme 4a.1) and hydrazine hydrate (1 : 1.2 mole ratio) for 30 minutes at room temperature. Crude products so obtained were purified by crystallization from methanol to give pure products **IIIa-c** (Scheme 4a.1) in good yields. Spectral data and elemental analysis of **IIIa-c** reported in experimental section fully support the structures assigned to them.

Condensation of 2-aminohexahydro-2H-isoindole-1,3-dione **IIIa** with 4-hydroxy-3-methoxybenzaldehyde **IVx** was carried out by dissolving both of them in 1:1 molar ratio in methanol and then adding silica gel to this reaction solution & removing the solvent under vacuum to give both of the reactants adsorbed on silica gel. This silica gel was irradiated for six minutes at 600 watt. TLC showed that reaction is complete. In another experiment silica gel adsorbed with both of the reactants was irradiated at 120ºC for six minutes. TLC showed that reaction is complete. Crude products were obtained from both the reactions by shaking irradiated silica gel with methanol for 10 minutes and removing the solvent under vacuum. Both the crude products were purified by

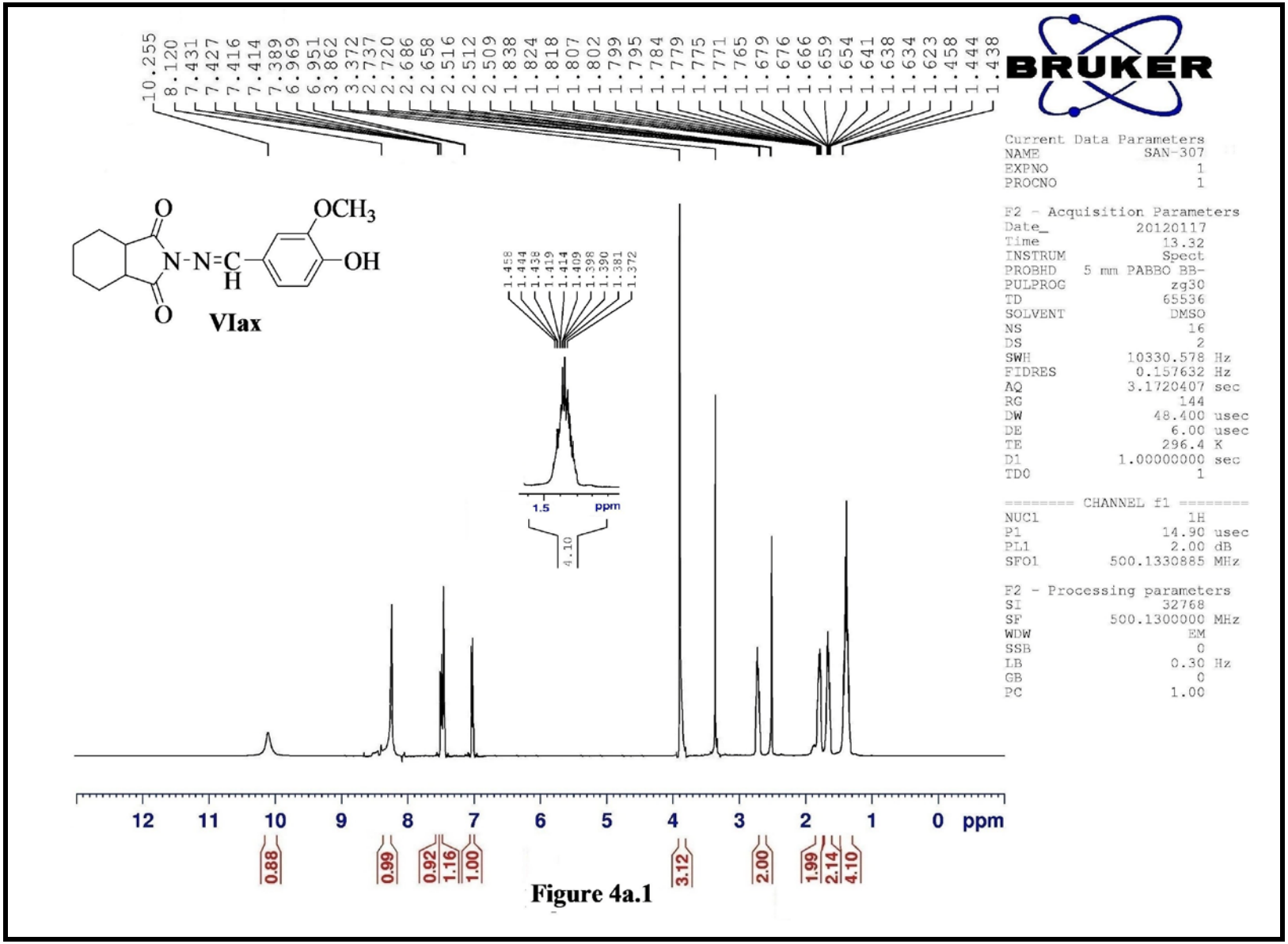



Scheme 4a.1 Synthesis of azomethine & amidine derivatives of isoindole & pyrrolopyrazine i.e. **IIIa-c**, **VIax-cz** & **VIIax-cz**.

crystallization from methanol to give 83% and 81% yield of pure product 2-(4-hydroxy-3-methoxybenzylideneamino)-hexahydro-2H-isoindole-1,3-dione (**VIax**, Scheme 4a.1). IR spectrum of **VIax** shows absorption bands at 1675 (>C=O), 1657 (>C=N-), 1536, 1506 (Ar) $cm^{-1}$. $^{1}H$ NMR (500 MHz, DMSO-$d_6$) (Figure 4a.1) of **VIax** show signals at δ: 1.372-1.458 (m, 4H, 2×$CH_2$), 1.623-1.679 (m, 2H, $CH_2$), 1.765-1.838 (m, 2H, $CH_2$), 2.658-2.737 (m, 2H, CH+CH), 3.862 (s, 3H, $CH_3$), 6.951-6.969 (d, 1H, J=9Hz, Ar,), 7.389-7.431 (m, 2H, Ar), 8.120 (s, 1H, Ar), 10.255 (bs, 1H, OH, exch). $^{13}C$ NMR (125 MHz, DMSO-$d_6$) (Figure 4a.2) δ: 25.139, 26.949, 39.042, 55.907, 102.140, 108.020, 109.141, 131.415, 143.425, 150.021, 151.998, 178.148. GC-MS (*m/z*; relt. int. %) (Figure 4a.3) of **VIax** gave $M^{+\bullet}$ ion peak at *m/z* 302 ($M^{+\bullet}$, 33%). In addition to $M^{+\bullet}$ ion peak GCMS of **VIax** shows some other prominent peaks which can arise through its fragmentation. The fragmentation pattern of **VIax** is outlined in chart 4a.1. Elemental analysis Calculated for $C_{16}H_{18}N_2O_4$: C, 63.57; H, 5.96; N, 9.27 Found: C, 63.66; H, 6.05; N, 9.39%. Spectral and analytical data of **VIax** fully support the structure assigned to it.

Similarly condensation of **IIIb,c** with 4-hydroxy-3-methoxybenzaldehyde (**IVx**) and **IIIa-c** with 2,5-dimethoxybenzaldehyde (**IVy**) & 4-(dimethylamino)benzaldehyde (**IVz**) gave corresponding azomethine derivatives **VIay-cz** (Scheme 4a.1) in good yield. Physical constants, spectral and analytical data of **VIay-cz** reported in Table-4a.1 is in full agreement with structures assigned to them.

Condensation of 2-cyanopyridine (**Vx**), 4-cyanopyridine (**Vy**), 2-cyanopyrazine (**Vz**) with **IIIa-c** to give amidine derivatives **VIIax-cz** (Scheme 4a.1), was carried out in a similar way as mentioned above. Silica gel adsorbed with both the reactants in 1:1 molar ratio was irradiated for 6 minutes at 850 watt or alternatively at 135ºC for 6 minutes.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7.427
7.416
7.414
7.389
6.969
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3.862
3.372
2.737
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2.686
2.658
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1.679
1.676
1.666
1.659
1.654
1.641
1.638
1.634
1.623
1.458
1.444
1.438
BRUKER
OCH3
N-N=C
H
OH
O
O
O
VIax
1.458
1.444
1.438
1.419
1.414
1.409
1.398
1.390
1.381
1.372
1.5
ppm
4.10
Current Data Parameters
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EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
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Time 13.32
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PULPROG zg30
TD 65536
SOLVENT DMSO
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DS 2
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1720407 sec
RG 144
DW 48.400 usec
DE 6.00 usec
TE 296.4 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 14.90 usec
PL1 2.00 dB
SFO1 500.1330885 MHz
F2 - Processing parameters
SI 32768
SF 500.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
12
11
10
9
8
7
6
5
4
3
2
1
0 ppm
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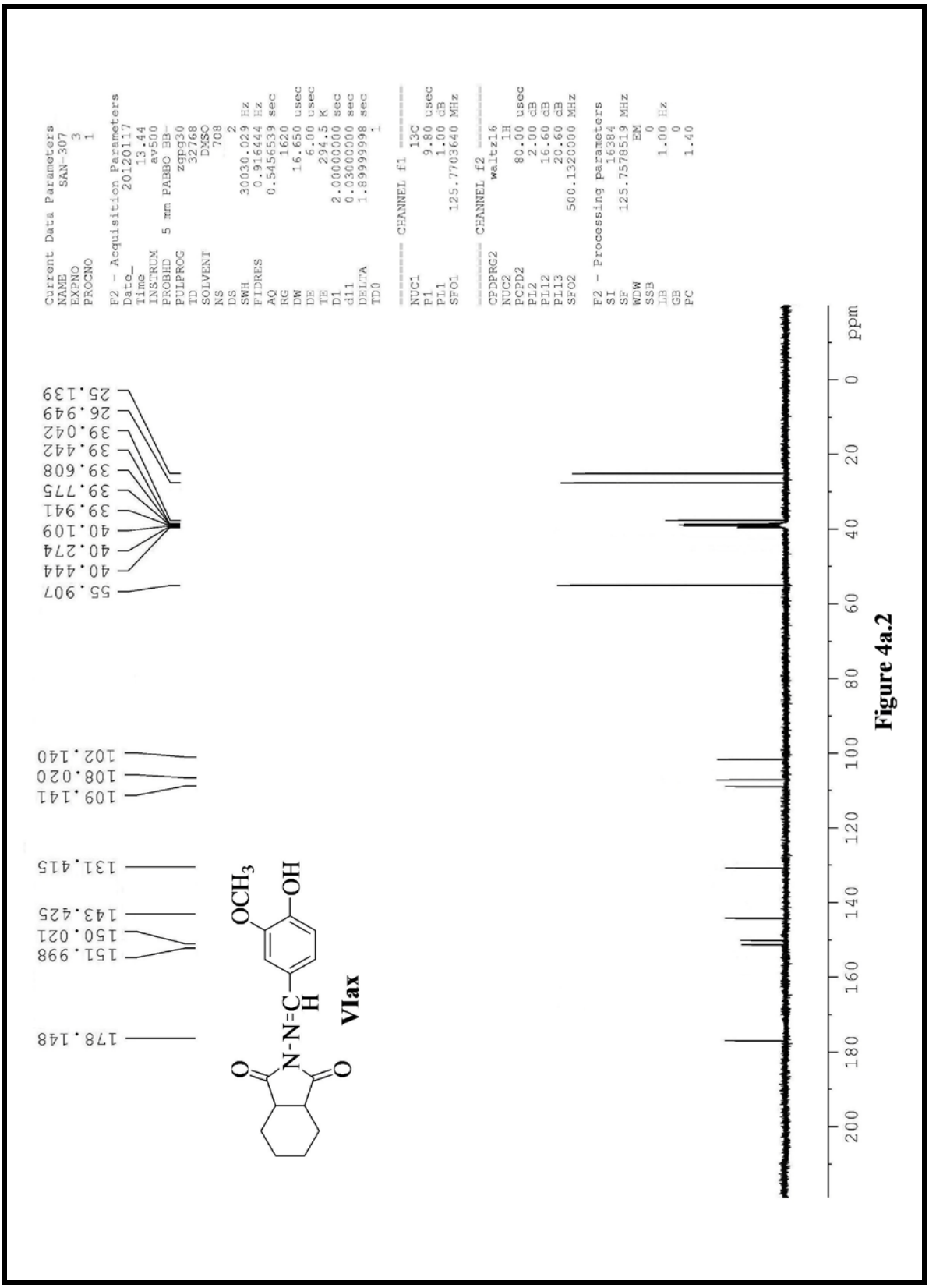
0.92
1.16
1.00
3.12
2.00
1.99
2.14
4.10

**Figure 4a.1**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d11 0.03000000 sec
DELTA 1.89999998 sec
TD0 1
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PL1 1.00 dB
SFO1 125.7703640 MHz
CHANNEL f2
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PL2 2.00 dB
PL12 16.60 dB
PL13 20.60 dB
SFO2 500.1320000 MHz
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SF 125.7578519 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
55.907
40.444
40.274
40.109
39.941
39.775
39.608
39.442
39.042
26.949
25.139
109.141
108.020
102.140
131.415
143.425
150.021
151.998
178.148
OCH3
OH
N-N=C
H
O
O
O
VIax
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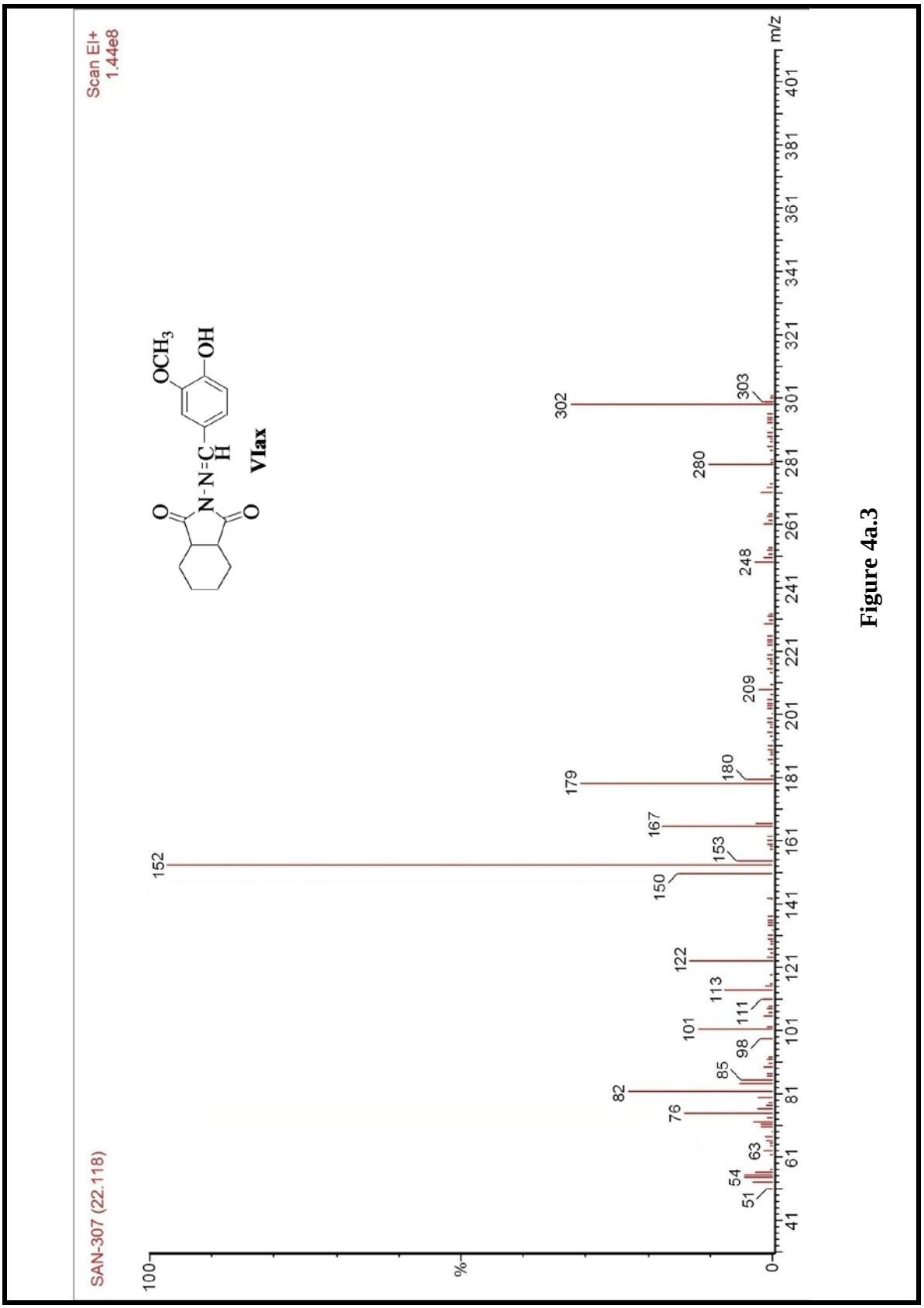
160
140
120
100
80
60
40
20
0
ppm

**Figure 4a.2**


Scan EI+
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SAN-307 (22.118)
100
%
0
m/z
41
51
54
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63
76
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82
85
98
101
111
113
121
122
141
150
152
153
161
167
179
180
181
201
209
221
241
248
261
280
281
301
302
303
321
341
361
381
401
OCH3
OH
N
N
H
O
O
VIax

**Figure 4a.3**

**Fragmentation pattern of VIax**

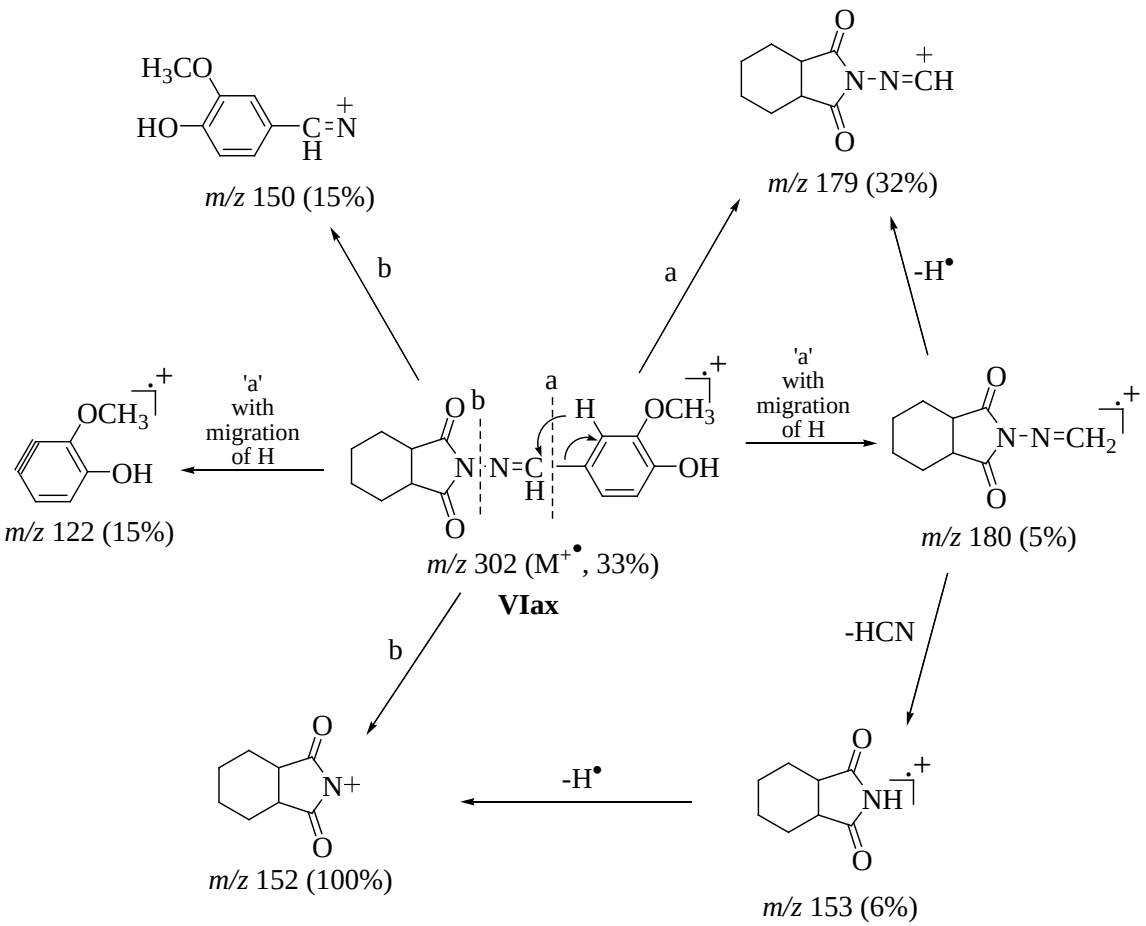
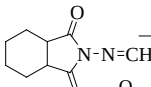
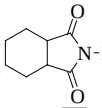
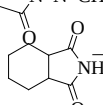
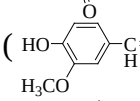
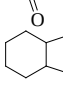
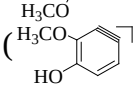
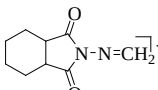
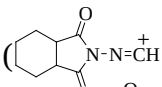
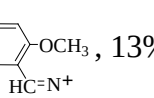
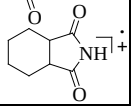
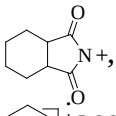
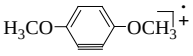
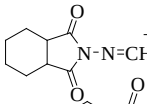
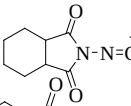
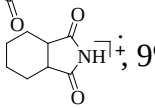
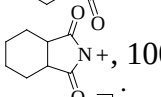
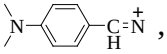
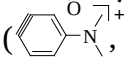
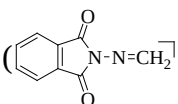
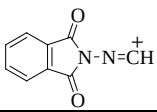
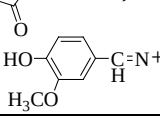



**Chart 4a.1**

**Table 4a.1: Physical constants and spectral data of compounds VIax-cz and VIIax-cz.**

| Comp no | Solvent of cryst./elution | m.p. °C | Yield % | IR (KBr) $cm^{-1}$, $^1H$ (500MHz) & $^{13}C$ (125MHz) NMR (DMSO-$d_6$), $\delta$ J(Hz), GC-MS (*m/z*; relt int %) |
|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 |
| **VIax** | MeOH | 161 | 81 | IR 1675 (>C=O), 1657 (>C=N-), 1536, 1506 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$) δ: 1.372-1.458 (m, 4H, 2×$CH_2$), 1.623-1.679 (m, 2H, $CH_2$), 1.765-1.838 (m, 2H, $CH_2$), 2.658-2.737 (m, 2H, CH+CH), 3.862 (s, 3H, $CH_3$), 6.951-6.969 (d, 1H, J=9 Hz, Ar), 7.389-7.431 (m, 2H, Ar), 8.120 (s, 1H, Ar), 10.255 (bs, 1H, OH, exch). $^{13}C$ NMR (125 MHz, DMSO-$d_6$) δ: 25.1, 26.9, 39.0, 55.9, 102.1, 108.0, 109.1, 131.4, 143.4, 150.0, 151.9 and 178.1. GC-MS: *m/z* 303($M^{+\bullet}$+1, 2%), 302 ($M^{+\bullet}$, 33%), 180 (  , 5%), 179 (  , 32%), 153(  , 6%), 152 (  , 100%), 150 (  , 15%), 122 (  , 15%). Anal. Calcd for $C_{16}H_{18}N_2O_4$: C, 63.57; H, 5.96; N, 9.27%. Found: C, 63.66; H, 6.05; N, 9.39%. |
| **VIay** | MeOH | 174 | 77 | IR 1688 (>C=O), 1635 (>C=N-), 1594, 1497 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$) δ: 1.355-1.444 (m, 4H, 2×$CH_2$), 1.622-1.688 (m, 2H, $CH_2$), 1.761-1.837 (m, 2H, $CH_2$), 2.645-2.752 (m, 2H, CH+CH), 3.743 (s, 3H, $OCH_3$), 3.872 (s, 3H, $OCH_3$), 7.163-7.195 (m, 2H, Ar), 7.245-7.276 (m, 1H, Ar), 8.135 (s, 1H, Ar). $^{13}C$ NMR (125 MHz, DMSO-$d_6$) δ: 25.1, 26.7, 39.0, 55.0, 55.9, 114.0, 115.1, 117.1, 117.7, 143.3, 152.1, 153.8 and 178.1. GC-MS: *m/z* 317 ($M^{+\bullet}$+1, 1%), 316 ($M^{+\bullet}$ 26%), 180 (  , 4%), 179 (  , 20%), 164 (  , 13%), 153 (  ) |

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| | | | | , 3%), 152 (  , 100%), 136 (  , 25%), 82 (  , 30%). Anal. Calcd for $C_{17}H_{20}N_2O_4$: C, 64.55; H, 6.32; N, 8.86%. Found: C, 64.63; H, 6.41; N, 8.97%. |
| **VIaz** | MeOH | 146 | 83 | IR 1679 (>C=O), 1657 (>C=N-), 1533, 1476, 1453 $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$) δ: 1.374-1.446 (m, 4H, 2×$CH_2$), 1.625-1.681 (m, 2H, $CH_2$), 1.765-1.842 (m, 2H, $CH_2$), 2.640-2.737 (m, 2H, CH+CH), 2.972 (s, 6H, 2×$CH_3$), 6.686-6.704 (d, 2H, J=9 Hz, Ar), 7.355-7.373 (d, 2H, J= 9Hz, Ar), 8.123 (s, 1H, Ar). $^{13}C$ NMR (125 MHz, DMSO-$d_6$) δ: 25.1, 26.6, 39.0, 40.9, 114.7, 123.5, 130.2, 143.3, 151.5 and 178.0. GC-MS: *m/z* 300($M^{+\bullet}$+1, 1%), 299 ($M^{+\bullet}$, 44%),180 (  , 8%), 179 (  , 25%), 153 (  , 9%), 152 (  , 100%), 147 (  , 11%), 119 (  , 13%), 82 ( , 17%). Anal. Calcd for $C_{17}H_{21}N_3O_2$: C, 68.22; H, 7.02; N, 14.04%. Found: C, 68.29; H, 7.11; N, 14.09%. |
| **VIbx** | MeOH | 234 | 88 | IR 3377 (OH), 1683 (>C=O), 1664 (>C=N-), 1612, 1477 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$) δ: 3.802 (s, 3H, $OCH_3$), 6.953-6.969 (d, 1H, J=8 Hz, Ar), 7.386-7.430 (m, 2H, Ar), 7.586-7.612 (m, 2H, Ar), 7.659-7.692 (m, 2H, Ar), 8.122 (s, 1H, Ar), 10.253 (bs, 1H, OH, exch). $^{13}C$ NMR (125 MHz, DMSO-$d_6$) δ: 55.9, 102.8, 108.1, 109.2, 127.6, 132.0, 132.8, 143.0, 153.0, 154.3, 156.7 and 168.7. GC-MS: *m/z* 297($M^{+\bullet}$+1, 1%), 296 ($M^{+\bullet}$, 22%), 174 (  , 2%), 173 (  , 10%), 150 (  , 9%), |

| 1 | 2 | 3 | 4 | 5 |
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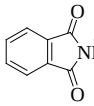
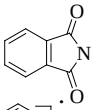
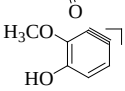
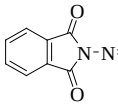
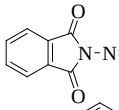
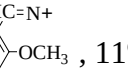
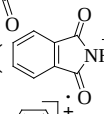
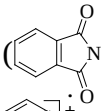
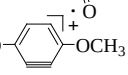
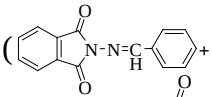
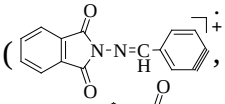
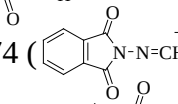
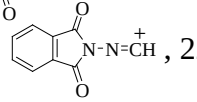
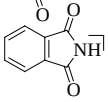
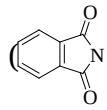
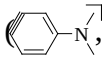
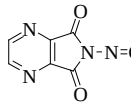
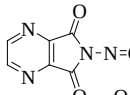
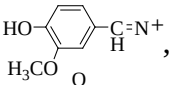
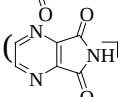
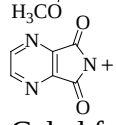
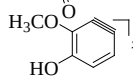
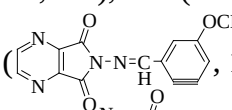
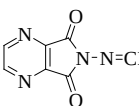
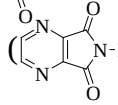
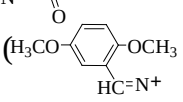
| | | | | 147 (  , 13%), 146 (  , 100%), 122 (  , 19%), 76 (  , 12%). Anal. Calcd for $C_{16}H_{12}N_2O_4$: C, 64.86; H, 4.05; N, 9.46%. Found: C, 64.95; H, 4.12; N, 9.57%. |
| **VIby** | MeOH | 276 | 82 | IR 1682 (>C=O), 1665 (>C=N-), 1610, 1510, 1476 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$) δ: 3.749 (s, 3H, $OCH_3$), 3.877 (s, 3H, $OCH_3$), 7.166-7.197 (m, 2H, Ar), 7.246-7.277 (m, 1H, Ar), 7.588-7.615 (m, 2H, Ar), 7.656-7.689 (m, 2H, Ar), 8.138 (s, 1H, Ar). $^{13}C$ NMR (125 MHz, DMSO-$d_6$) δ: 55.0, 55.8, 114.2, 115.3, 117.1, 117.9, 127.6, 132.0, 132.8, 143.1, 152.5, 153.2 and 168.3. GC-MS: *m/z* 311 ($M^{+\bullet}$+1, 1%), 310 ($M^{+\bullet}$, 35%), 174 (  , 3%), 173 (  , 23%), 164 (  , 11%), 147 (  , 11%), 146 (  , 100%), 136 (  , 10%), 76 (  , 18%). Anal. Calcd for $C_{17}H_{14}N_2O_4$: C, 65.81; H, 4.52; N, 9.03%. Found: C, 65.96; H, 4.58; N, 9.15%. |
| **VIbz** | MeOH | 224 | 83 | IR 1684 (>C=O), 1669 (>C=N-), 1611, 1576, 1543, 1508, 1478 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$) δ: 2.974 (s, 6H, 2×$CH_3$), 6.686-6.704 (d, 2H, J=9 Hz, Ar), 7.355-7.373 (d, 2H, J=9 Hz, Ar), 7.585-7.610 (m, 2H, Ar), 7.655-7.686 (m, 2H, Ar), 8.121 (s, 1H, Ar). $^{13}C$ NMR (125 MHz, DMSO-$d_6$) δ: 40.9, 114.2, 124.1, 127.3, 130.0, 132.0, 132.9, 143.0, 151.5 and 167.8. GC-MS: *m/z* 294 ($M^{+\bullet}$+1, 1%), 293 ($M^{+\bullet}$, 53%), 249 (  , 6%), 248 (  , 28%), 174 (  , 2%), 173(  , 22%), 147 (  , 3%), |

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| | | | | 146 (  , 100%), 119 (  , 6%), 76(  , 15%). Anal. Calcd for $C_{17}H_{15}N_3O_2$: C, 69.62; H, 5.12; N, 14.33%. Found: C, 69.73; H, 5.19; N, 14.47%. |
| **VIcx** | MeOH | 256 | 85 | IR 1687 (>C=O), 1672 (>C=N-), 1608, 1593, 1498 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$) δ: 3.840 (s, 3H, $OCH_3$), 6.953-6.969 (d, 1H, J=8 Hz, Ar), 7.386-7.430 (m, 2H, Ar), 8.122 (s, 1H, Ar), 8.864 (s, 2H, Ar), 10.253 (bs, 1H, OH, exch). $^{13}C$ NMR (125 MHz, DMSO-$d_6$) δ: 55.9, 102.1, 108.3, 109.0, 131.0, 142.4, 143.7, 145.9, 153.0, 155.9 and 168.0. GC-MS: *m/z* 299($M^{+\bullet}$+1, 1%),298 ($M^{+\bullet}$, 53%), 176(  , 10%), 175 (  , 22%), 150 (  , 2%), 149 (  , 10%), 148 (  , 100%), 122 (  ,13%). Anal. Calcd for $C_{14}H_{10}N_4O_4$: C, 56.37; H, 3.35; N, 18.79%. Found: C, 56.49; H, 3.44; N, 18.73%. |
| **VIcy** | MeOH | 273 | 81 | IR 1698 (>C=O), 1668 (>C=N-), 1536, 1506 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$) δ: 3.749 (s, 3H, $OCH_3$), 3.877 (s, 3H, $OCH_3$), 7.263-7.295 (m, 2H, Ar), 7.345-7.376 (m, 1H, Ar), 8.125 (s, 1H, Ar), 8.867 (s, 2H, Ar). $^{13}C$ NMR (125 MHz, DMSO-$d_6$) δ: 55.1, 55.9, 114.3, 115.1, 117.0, 117.8, 143.1, 143.8, 145.7, 152.5, 153.3 and 167.8. GC-MS: *m/z* 313 ($M^{+\bullet}$+1, 1%), 312 ($M^{+\bullet}$, 32%), 280 (  , 13%), 176 (  , 5%), 175 (  , 32%), 164 (  , |

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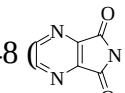
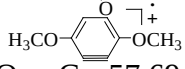
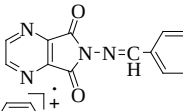
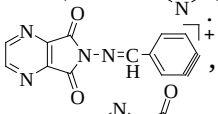
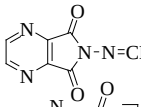
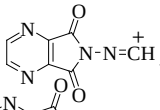
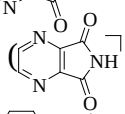
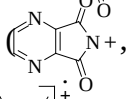
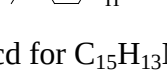
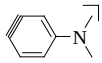
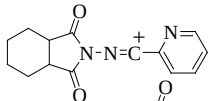
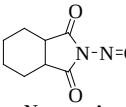
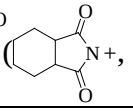
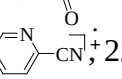
| | | | | ,18%), 149 (  , 3%), 148 (  , 100%), 136 (  , 11%). Anal. Calcd for $C_{15}H_{12}N_4O_4$: C, 57.69; H, 3.85; N, 17.95%. Found: C, 57.57; H, 3.83; N, 17.89%. |
| **VIcz** | MeOH | 243 | 86 | IR 1678 (>C=O), 1660 (>C=N-), 1537, 1506 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$) δ: 2.966 (s, 6H, 2×$CH_3$), 6.688-6.706 (d, 2H, J=9 Hz, Ar), 7.365-7.383 (d, 2H, J=9 Hz, Ar), 8.123 (s, 1H, Ar), 8.870 (s, 2H, Ar). $^{13}C$ NMR (125 MHz, DMSO-$d_6$) δ: 40.8, 114.1, 123.3, 130.0, 143.0, 143.9, 145.0, 151.4 and 167.9. GC-MS: *m/z* 296($M^{+\bullet}$+1, 1%),295 ($M^{+\bullet}$, 53%), 251(  , 12%), 250 (  , 8%), 176 (  , 9%), 175 (  , 30%), 149 (  , 10%), 148 (  , 100%), 147(  , 3%). 119 (  , 6%). Anal. Calcd for $C_{15}H_{13}N_5O_2$: C, 61.01; H, 4.41; N, 23.73%. Found: C, 61.12; H, 4.49; N, 23.81%. |
| **VIIax** | MeOH | 104 | 73 | IR 3403 ($NH_2$), 1684 (>C=O), 1647 (>C=N-), 1565, 1476 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$) δ: 1.374-1.446 (m, 4H, 2×$CH_2$), 1.626-1.679 (m, 2H, $CH_2$), 1.764-1.830 (m, 2H, $CH_2$), 2.666-2.739 (m, 2H, CH+CH), 6.762 (bs, 2H, $NH_2$, exch), 7.726-7.736 (m, 1H, Ar), 8.013-8.074 (m, 2H, Ar,), 8.745-8.756 (d, 1H, J= 5.5 Hz, Ar). $^{13}C$ NMR (125 MHz, DMSO-$d_6$) δ: 25.0, 26.9, 39.0, 120.0, 125.1, 136.4, 149.4, 154.0, 155.9 and 178.2. GC-MS: *m/z* 273 ($M^{+\bullet}$+1, 1%), 272 ($M^{+\bullet}$, 19%), 256(  , 72%), 179 (  , 12%), 152 (  , 100%), 104 (  , 22%), |

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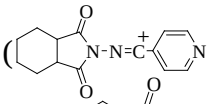
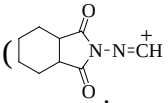
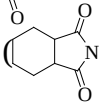
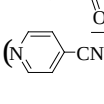
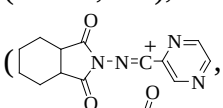
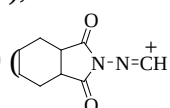
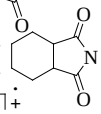
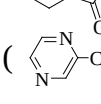
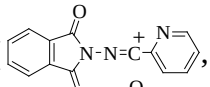
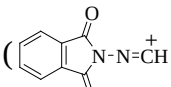
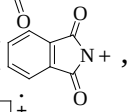
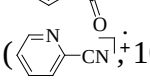
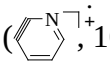
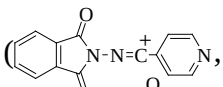
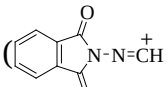
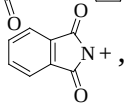
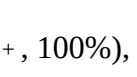
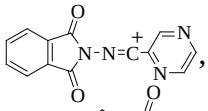
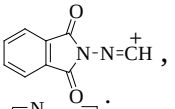
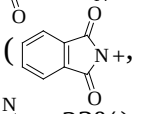
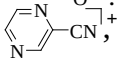
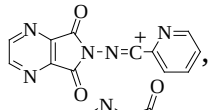
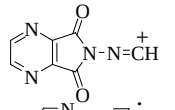
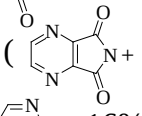
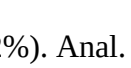
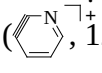
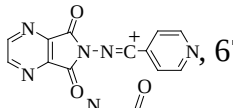
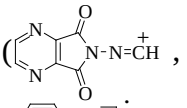
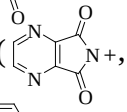
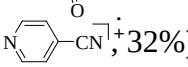
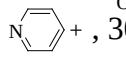
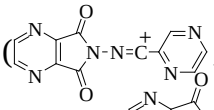
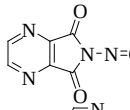
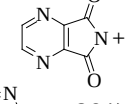
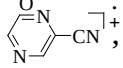
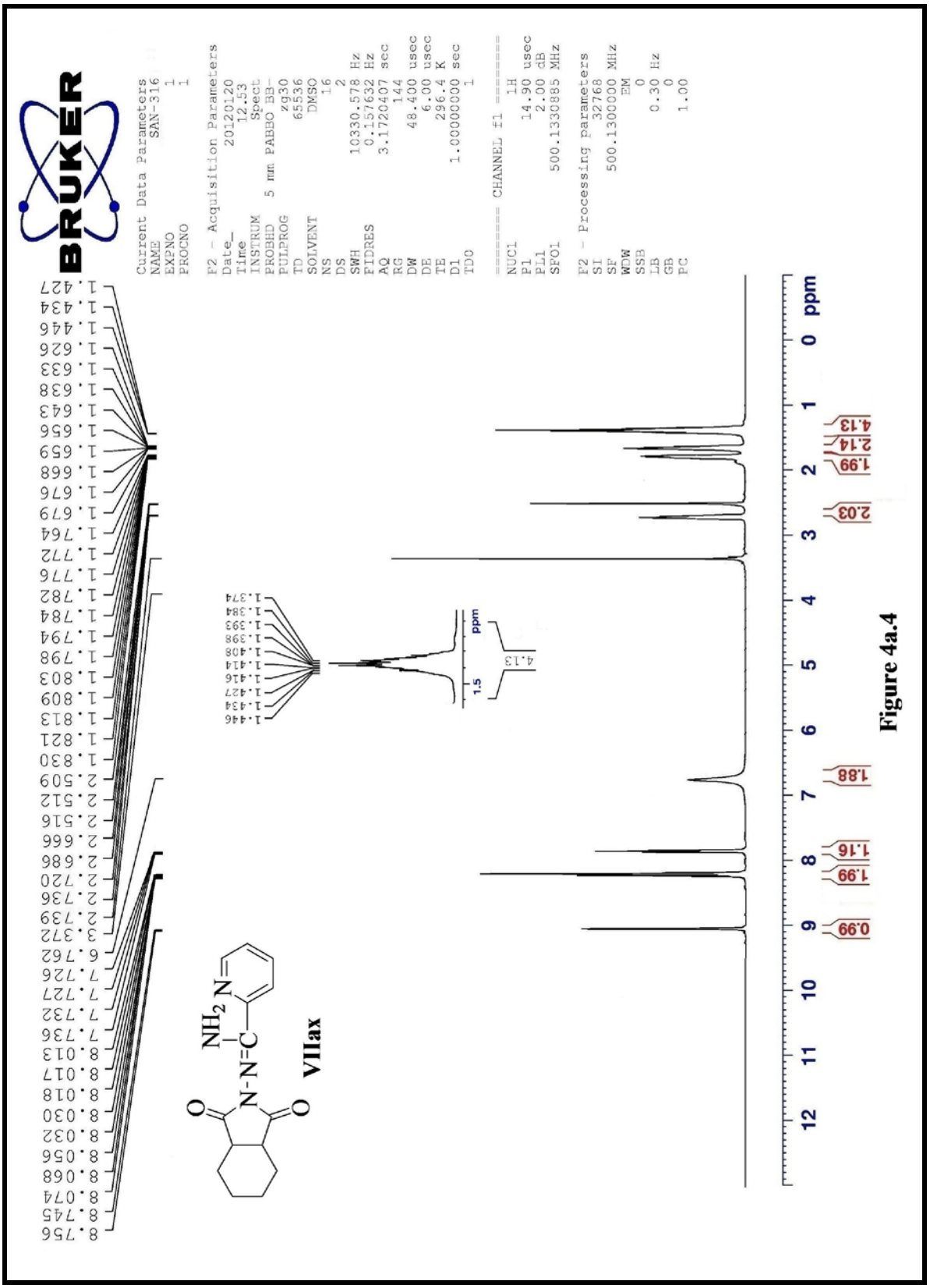
| | | | | 82 (  , 13%), 78 (, 30%), 77 (, 23%).<br><br>Anal. Calcd for $C_{14}H_{16}N_4O_2$: C, 61.76; H, 5.88; N, 20.59%. Found: C, 61.81; H, 5.96; N, 20.72%. |
| **VIIay** | MeOH | 195 | 73 | IR 3288 ($NH_2$), 1697 (>C=O), 1663 (>C=N-), 1599, 1545, 1502 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$) δ: 1.370-1.442 (m, 4H, 2×$CH_2$), 1.623-1.675 (m, 2H, $CH_2$), 1.765-1.832 (m, 2H, $CH_2$), 2.657-2.766 (m, 2H, CH+CH), 6.758 (bs, 2H, $NH_2$, exch), 7.977-7.995 (d, 2H, J= 9Hz, Ar), 8.555-8.573 (d, 2H, J= 9Hz, Ar). $^{13}C$ NMR (125 MHz, DMSO-$d_6$) δ: 25.0, 26.9, 39.0, 121.4, 133.6, 149.1, 162.0 and 178.1. GC-MS: *m/z* 273 ($M^{+\bullet}$+1, 1%), 272 ($M^{+\bullet}$, 8%),<br>256 (  , 31%), 179 (  ,<br>8%), 152 (  , 100%), 104 (  , 14%),<br>82 (  , 19%), 78 (  , 23%), 77 (  ,<br><br>9%). Anal. Calcd for $C_{14}H_{16}N_4O_2$: C, 61.76; H, 5.88; N, 20.59%. Found: C, 61.84; H, 5.97; N, 20.63%. |
| **VIIaz** | MeOH | 109 | 72 | IR 3264 ($NH_2$), 1684 (>C=O), 1644 (>C=N-), 1513, 1484 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$) δ: 1.369-1.448 (m, 4H, 2×$CH_2$), 1.625-1.680 (m, 2H, $CH_2$), 1.765-1.831 (m, 2H, $CH_2$), 2.666-2.719 (m, 2H, CH+CH), 6.680 (bs, 2H, $NH_2$, exch), 8.862-8.870 (t, 1H, J= 2Hz, Ar), 8.973-8.977 (d, 1H, J= 2Hz, Ar), 9.221-9.225 (d, 1H, J= 2Hz, Ar). $^{13}C$ NMR (125 MHz, DMSO-$d_6$) δ: 25.1, 26.8, 39.0, 141.2, 143.3, 144.4, 145.5, 155.5 and 178.1. GC-MS: *m/z* 274 ($M^{+\bullet}$+1, 1%), 273 ($M^{+\bullet}$, 13%), 257<br>(  , 61%), 179 (  , 18%),<br>152 (  , 100%), 105 (  , 12%), 82<br>(  , 21%), 79 (  , 22%), 78 (, 16%). |

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| | | | | Anal. Calcd for $C_{13}H_{15}N_5O_2$: C, 57.14; H, 5.49; N, 25.64%. Found: C, 57.25; H, 5.58; N, 25.69%. |
| **VIIbx** | MeOH | 227 | 78 | IR 3424 ($NH_2$), 1685 (>C=O), 1645 (>C=N-), 1522, 1492 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$) δ: 6.676 (bs, 2H, $NH_2$, exch), 7.586-7.612 (m, 2H, Ar), 7.659-7.692 (m, 2H, Ar), 7.723-7.750 (m, 1H, Ar), 8.015-8.072 (m, 2H, Ar), 8.747-8.758 (q, 1H, J=1 & 4.5 Hz, Ar). $^{13}C$ NMR (125 MHz, DMSO-$d_6$) δ: 120.9, 125.7, 127.2, 131.7, 132.0, 136.1, 149.0, 154.2, 155.9 and 167.3. GC-MS: *m/z* 267 ($M^{+\bullet}$+1, 1%), 266 ($M^{+\bullet}$, 12%), 250 (  , 69%), 173 (  , 6%), 146 (  , 100%), 104 (  , 10%), 78 (  , 16%), 77 (  , 25%). Anal. Calcd for $C_{14}H_{10}N_4O_2$: C, 63.15; H, 3.76; N, 21.05%. Found: C, 63.28; H, 3.86; N, 21.12%. |
| **VIIby** | MeOH | 263 | 80 | IR 3283 ($NH_2$), 1686 (>C=O), 1656 (>C=N-), 1519, 1456 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$) δ: 6.689 (bs, 2H, $NH_2$, exch), 7.589-7.612 (m, 2H, Ar), 7.657-7.692 (m, 2H, Ar), 7.976-7.994 (d, 2H, J= 9Hz, Ar), 8.556-8.574 (d, 2H, J= 9Hz, Ar). $^{13}C$ NMR (125 MHz, DMSO-$d_6$) δ: 121.1, 127.6, 131.9, 132.9, 136.7, 149.5, 162.8 and 168.0. GC-MS: *m/z* 267 ($M^{+\bullet}$+1, 1%), 266 ($M^{+\bullet}$, 12%), 250 (  , 60%), 173 (  , 17%), 146 (  , 100%), 104 (  , 10%), 78 (  , 15%), 77 (  , 24%). Anal. Calcd for $C_{14}H_{10}N_4O_2$: C, 63.15; H, 3.76; N, 21.05%. Found: C, 63.27; H, 3.83; N, 21.16%. |
| **VIIbz** | MeOH | 226 | 76 | IR 3368 ($NH_2$), 1688 (>C=O), 1643 (>C=N-), 1584, 1554, 1497 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, |

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| | | | | DMSO-$d_6$) δ: 6.688 (bs, 2H, $NH_2$, exch), 7.586-7.613 (m, 2H, Ar), 7.655-7.693 (m, 2H, Ar), 8.864-8.872 (t, 1H, J= 2Hz, Ar), 8.970-8.975 (d, 1H, J= 2.5Hz, Ar), 9.225-9.228 (d, 1H, J= 1.5Hz, Ar). $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ: 127.2, 132.0, 132.8, 141.2, 143.1, 144.1, 145.2, 155.9 and 168.0. GC-MS: *m/z* 268 ($M^{+\bullet}$+1, 1%), 267($M^{+\bullet}$, 10%), 251(  , 69%), 173 (  , 15%), 146 (  , 100%), 105 (  , 14%), 79 (  , 23%), 78 (  , 34%). Anal. Calcd for $C_{13}H_9N_5O_2$: C, 58.43; H, 3.37; N, 26.21%. Found: C, 58.59; H, 3.43; N, 26.35%. |
| **VIIcx** | MeOH | 219 | 77 | IR 3267 ($NH_2$), 1684 (>C=O), 1647 (>C=N-), 1519, 1449 (Ar) $cm^{-1}$. $^1$H NMR (500 MHz, DMSO-$d_6$) δ: 6.669 (bs, 2H, $NH_2$, exch), 7.722-7.752 (m, 1H, Ar), 8.012-8.077 (m, 2H, Ar,), 8.747-8.758 (q, 1H, J= 1 & 4.5 Hz, Ar), 8.866 (s, 2H, Ar). $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ: 120.7, 125.2, 136.7, 143.3, 145.7, 149.4, 154.2, 155.8 and 167.6. GC-MS: *m/z* 269 ($M^{+\bullet}$+1, 1%), 268 ($M^{+\bullet}$, 10%), 252 (  , 55%), 175 (  , 9%), 148 (  , 100%), 104 (  , 22%), 78 (  , 16%), 77 (  , 12%). Anal. Calcd for $C_{12}H_8N_6O_2$: C, 53.73; H, 2.98; N, 31.34%. Found: C, 53.64; H, 3.05; N, 31.41%. |
| **VIIcy** | MeOH | 249 | 80 | IR 3241 ($NH_2$), 1678 (>C=O), 1644 (>C=N-), 1582, 1512, 1474 (Ar) $cm^{-1}$. $^1$H NMR (500 MHz, DMSO-$d_6$) δ: 6.699 (bs, 2H, $NH_2$, exch), 7.977-7.995 (d, 2H, J= 9Hz, Ar), 8.552-8.570 (d, 2H, J= 9Hz, Ar), 8.883 (s, 2H, Ar). $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ: 121.2, 136.7, 143.8, 145.6, 149.2, 162.3 and 167.9. GC-MS: *m/z* 269 ($M^{+\bullet}$+1, 1%), 268 ($M^{+\bullet}$, 15%), 252 ( |

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| | | | |  , 67%), 175 (  , 8%), 148 (  , 100%), 104 (  , 32%), 78 (  , 30%), 77 (, 12%). Anal. Calcd for $C_{12}H_8N_6O_2$: C, 53.73; H, 2.98; N, 31.34%. Found: C, 53.81; H, 3.04; N, 31.39%. |
| **VIIcz** | MeOH | 224 | 76 | IR 3361 ($NH_2$), 1688 (>C=O), 1649 (>C=N-), 1572, 1512 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$) δ: 6.687 (bs, 2H, $NH_2$, exch), 8.864-8.872 (t, 3H, J= 2Hz, Ar,), 8.972-8.976 (d, 1H, J= 2Hz, Ar), 9.232-9.237 (d, 1H, J= 2.5Hz, Ar). $^{13}C$ NMR (125 MHz, DMSO-$d_6$) δ: 141.2, 143.0, 143.8, 144.5, 145.7, 146.0, 155.0 and 168.0. GC-MS: *m/z* 270($M^{+\bullet}$+1, 1%), 269 ($M^{+\bullet}$, 9%), 253 (  , 73%), 175 (  , 17%), 148 (  , 100%), 105 (  , 37%), 79 (  , 29%), 78 (  , 24%). Anal. Calcd for $C_{11}H_7N_7O_2$: C, 49.07; H, 2.60; N, 36.43%. Found: C, 49.16; H, 2.66; N, 36.39% |

TLC in both the cases showed that reaction is complete. Microwave irradiated silica gel was shaken with methanol for 10 minutes and then filtered. Removal of the solvent from the filtrate gave crude amidine derivative, which was purified by crystallization from methanol. Yields from both the experiments are comparable. IR spectrum of **VIIax** shows absorption signals at 3403 ($NH_2$), 1684 (>C=O), 1647 (>C=N-), 1565, 1476 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$) (Figure 4a.4) of **VIIax** exhibited signals at δ: 1.374-1.446 (m, 4H, 2×$CH_2$), 1.626-1.679 (m, 2H, $CH_2$), 1.764-1.830 (m, 2H, $CH_2$), 2.666-2.739 (m, 2H, CH+CH), 6.762 (bs, 2H, $NH_2$, exch), 7.726-7.753 (m, 1H, Ar),


BRUKER
Current Data Parameters
NAME SAN-316
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20120120
Time 12.53
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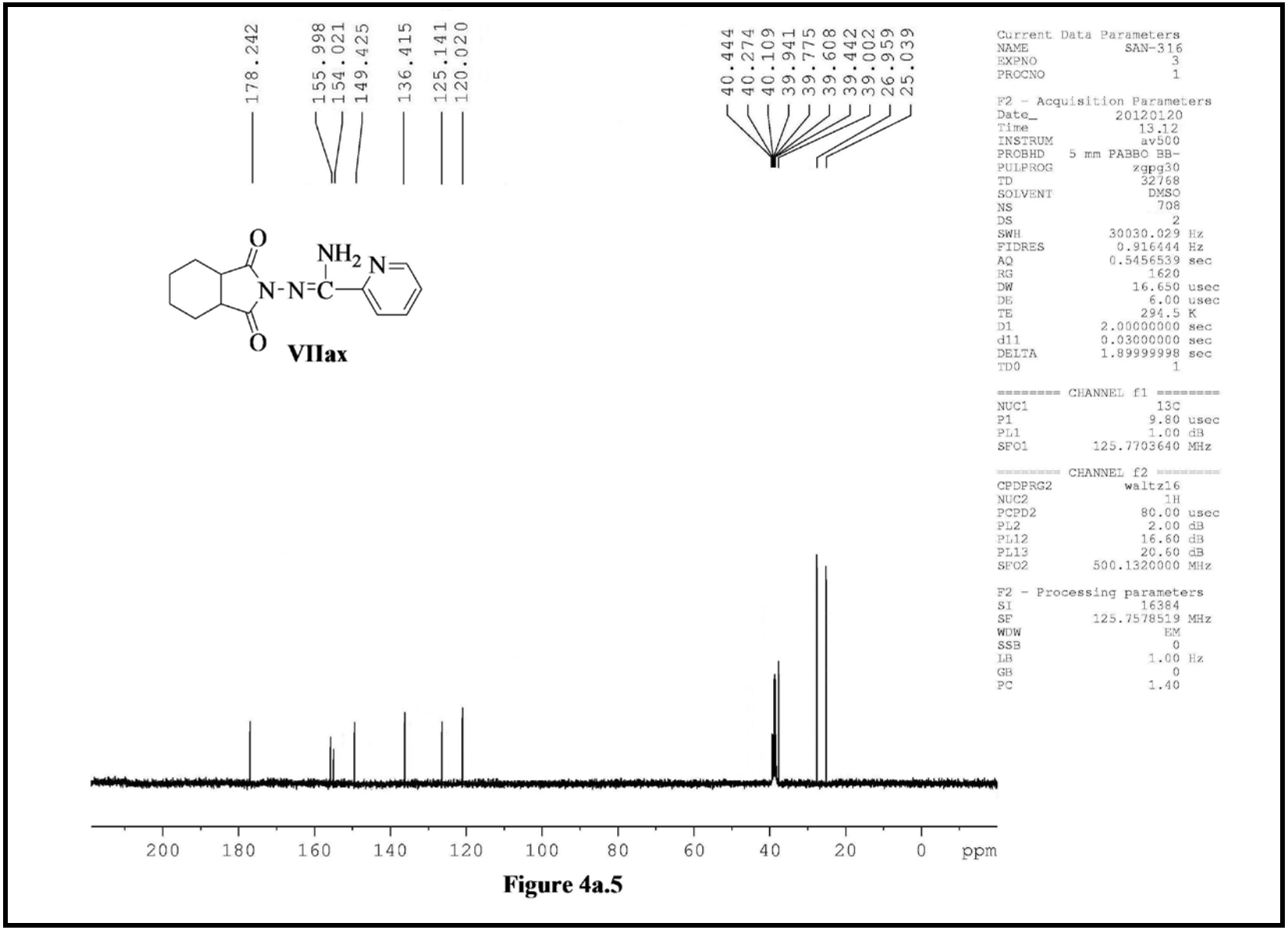
PULPROG zg30
TD 65536
SOLVENT DMSO
NS 16
DS 2
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1720407 sec
RG 144
DW 48.400 usec
DE 6.00 usec
TE 296.4 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 14.90 usec
PL1 2.00 dB
SFO1 500.1330885 MHz
F2 - Processing parameters
SI 32768
SF 500.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
VIIax
Figure 4a.4

8.013-8.074 (m, 2H, Ar,), 8.745-8.756 (d, 1H, J= 5.5Hz, Ar). $^{13}$C NMR (125 MHz, DMSO-$d_6$) (Figure 4a.5) δ: 25.039, 26.959, 39.002, 120.020, 125.141, 136.415, 149.425, 154.021, 155.998, 178.242. GC-MS spectrum (*m/z*; relt. int. %) (Figure 4a.6) of **VIIax** gave $M^{+\bullet}$+1 and $M^{+\bullet}$ ion peaks at *m/z* 273 ($M^{+\bullet}$+1, 1%), 272 ($M^{+\bullet}$, 19%). In addition to $M^{+\bullet}$ ion peak GCMS of **VIIax** shows some other prominent ion peaks which can arise through its fragmentation. The fragmentation pattern of **VIIax** is outlined in chart 4a.2. Elemental analysis Calculated for $C_{14}H_{16}N_4O_2$: C, 61.76; H, 5.88; N, 20.59%. Found: C, 61.81; H, 5.96; N, 20.72%. Spectral data and elemental analysis of **VIIax** fully support the structure assigned to it. Physical constants, spectral and analytical data of **VIIax-cz** reported in Table-4a.1 is in agreement with structures assigned to them.

**4a.2.2 Biological results and discussion**

Compounds **VIax-cz** and **VIIax-cz** (Scheme 4a.1) were screened for anti-inflammatory activity [21; Chapter 2] using carrageenan induced paw oedema assay and results are summarized in Table 4a.2. Compound **VIIcx** exhibited good anti-inflammatory activity i.e. 35% at 50 mg/kg p.o. as compared to ibuprofen which showed 39% activity at 50 mg/kg p.o..

Compounds **VIax-cz** and **VIIax-cz** were screened *in vitro* for anticancer activity [32] against five human cancer cell lines i.e. breast (T47D), lung (NCl H-522), colon (HCT-15), ovary (PA-1) and liver (HepG-2) at a concentration of $1\times10^{-5}$ M and results are summarized in Table 4a.2. Compounds **VIbz**, **VIIcx**, **VIIcz** (breast T47D), **VIbz**, **VIcy** (lung NCI H-522), **VIbx**, **VIIbz** (colon HCT-15), **VIbz** (ovary PA-1) and **VIbx**, **VIcz** (liver HepG-2) exhibited good anticancer activity against various cancer cell lines mentioned above. Compounds **VIbx**, **VIbz**, **VIcy**, **VIcz**, **VIIbz**, **VIIcx** and **VIIcz** which


178.242
155.998
154.021
149.425
136.415
125.141
120.020
40.444
40.274
40.109
39.941
39.775
39.608
39.442
39.002
26.959
25.039
VIIax
Current Data Parameters
NAME SAN-316
EXPNO 3
PROCNO 1
F2 - Acquisition Parameters
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Time 13.12
INSTRUM av500
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 32768
SOLVENT DMSO
NS 708
DS 2
SWH 30030.029 Hz
FIDRES 0.916444 Hz
AQ 0.5456539 sec
RG 1620
DW 16.650 usec
DE 6.00 usec
TE 294.5 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 9.80 usec
PL1 1.00 dB
SFO1 125.7703640 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 2.00 dB
PL12 16.60 dB
PL13 20.60 dB
SFO2 500.1320000 MHz
F2 - Processing parameters
SI 16384
SF 125.7578519 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
200
180
160
140
120
100
80
60
40
20
0
ppm

**Figure 4a.5**

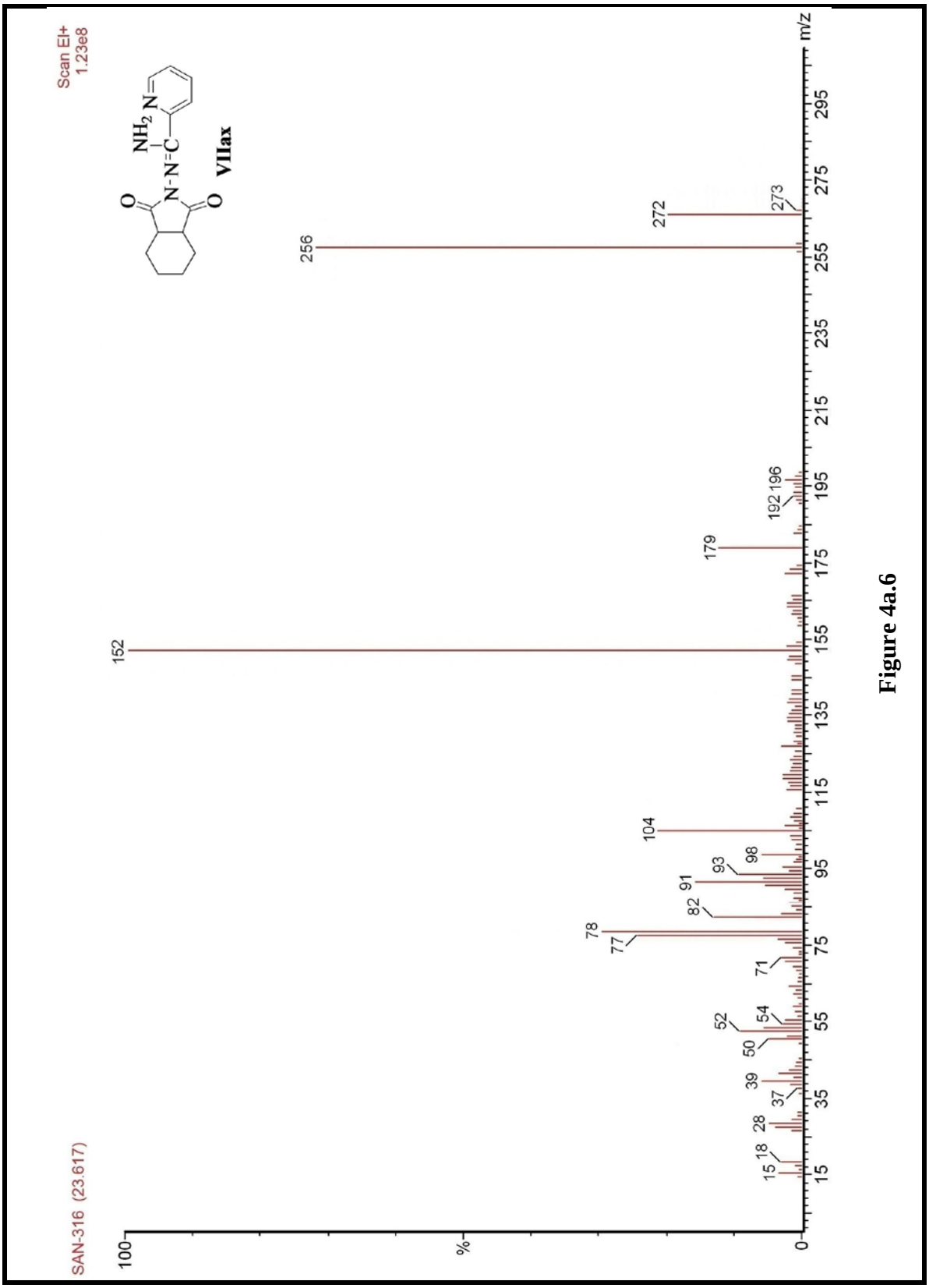

Scan EI+
1.23e8
SAN-316 (23.617)
VIIax
100
%
0
m/z
15
18
28
37
39
50
52
54
71
77
78
82
91
93
98
104
152
179
192
196
256
272
273
15
35
55
75
95
115
135
155
175
195
215
235
255
275
295

**Figure 4a.6**

**Fragmentation pattern of VIIax**

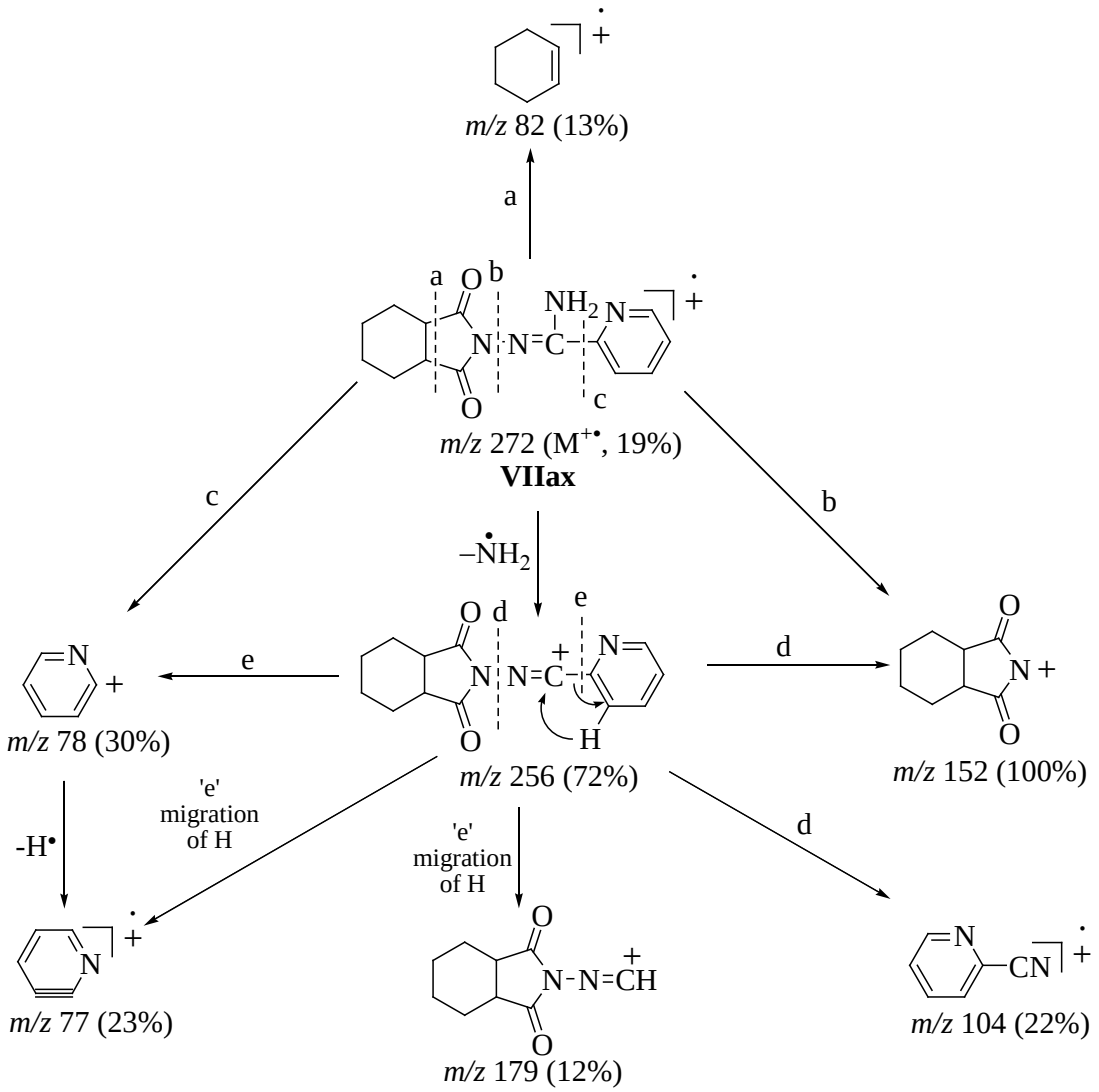



**Chart 4a.2**

Table-4a.2 Anti-inflammatory** and *in vitro* anticancer activity** of azomethine & amidine derivatives of isoindole & pyrrolopyrazine i.e. **VIax-cz** and **VIIax-cz.**

| Compd. No. | Anti-inflammatory activity (%) at 50 mg/kg p.o. | *Anticancer activity at a concentration of $1\times10^{-5}$ M | | | | |
|---|---|---|---|---|---|---|
| | | Breast T47D | Lung NCI H-522 | Colon HCT-15 | Ovary PA1 | Liver HepG2 |
| **VIax** | 09 | 22 | 16 | 19 | 18 | 21 |
| **VIay** | 06 | 14 | 12 | 19 | 21 | 23 |
| **VIaz** | 32 | 15 | 14 | 10 | 09 | 17 |
| **VIbx** | 22 | 34 | 25 | **38** | 31 | **35** |
| **VIby** | 24 | 24 | 05 | 04 | 19 | 14 |
| **VIbz** | 18 | **35** | **40** | 25 | **36** | 24 |
| **VIcx** | 26 | 13 | 10 | 05 | 11 | 19 |
| **VIcy** | 14 | 25 | **37** | 16 | 29 | 25 |
| **VIcz** | 29 | 11 | 28 | 18 | 16 | **39** |
| **VIIax** | 17 | 13 | 28 | 23 | 11 | 19 |
| **VIIay** | 20 | 14 | 25 | 05 | 21 | 17 |
| **VIIaz** | 17 | 15 | 20 | 01 | 25 | 20 |
| **VIIbx** | 17 | 17 | 16 | 29 | 19 | 24 |
| **VIIby** | 23 | 13 | 11 | 24 | 18 | 32 |
| **VIIbz** | 20 | 27 | 22 | **36** | 14 | 30 |
| **VIIcx** | **35** | **37** | 33 | 05 | 30 | 13 |
| **VIIcy** | 12 | 25 | 10 | 12 | 19 | 27 |
| **VIIcz** | 14 | **41** | 23 | 07 | 26 | 17 |
| Ibuprofen | 39 | - | - | - | - | - |
| *5-FU | - | 18 | 24 | 20 | 21 | 18 |
| *CYC-PHO | - | 16 | 15 | 13 | 30 | 26 |
| *CYC-HEXI | | 26 | 11 | 12 | 15 | 18 |

*Compounds tested in triplicate, data expressed as mean value of three independent experiments.
[a]5-FU 5-Fluorouracil; [b]CYC-PHO Cyclophosphamide; [c]CYC-HEXI Cycloheximide;
Bold values represent compounds showing good anti-inflammatory and good anticancer activity.
** We are thankful to Dr. Partha Roy, Department of Biotechnology, Indian Institute of Technology-Roorkee, Roorkee for this data.

exhibited good anticancer activity were further studied and their $IC_{50}$ values for various cancer cell lines and normal cell (COS-1) was determined and reported in Table 4a.3.

Compound **VIIcx** showed good anti-inflammatory activity whereas other compounds showed moderate to low anti-inflammatory activity, it may be due to the fact that structure of compound **VIIcx** can effectively interact with the targets both from electronic and stereochemical point of view and hence exhibited good anti-inflammatory activity.

Compounds derived from **IIIa** i.e. **VIax-az** and **VIIax-az** did not show good anticancer activity whereas compounds derived from **IIIb** (**VIbx**, **VIbz**, **VIIbz**) and **IIIc** (**VIcy**, **VIcz**, **VIIcx**, **VIIcz**) exhibited good anticancer activity. From this observation it may be concluded that aromatic (**IIIb**) or heteroaromatic (**IIIc**) ring in place of cyclohexyl (**IIIa**) ring made the structures of these molecules suitable for interaction with the cancerous cell both from stereochemical and electronic point of view and hence exhibited good anticancer activity.

## 4a.3 Experimental

### *4a.3.1 General*

Microwave reactor Anton Paar (monowave 300) and microwave oven model M197DL (Samsung) were used for microwave irradiation. Melting points (mp) were determined on a JSGW apparatus and are uncorrected. IR spectra were recorded using a Perkin Elmer 1600 FT spectrometer. $^{1}H$ and $^{13}C$ NMR spectra were recorded on a Bruker WH-500 spectrometer at a *ca* 5-15% (*w/v*) solution in deuterated solvent (TMS as internal standard). GC-MS was recorded on Perkin Elmer Clarus 500 gas chromatograph where built in MS detector was used. Elemental analysis was carried out on a Vario EL

Table 4a.3 $IC_{50}$ values[a,*] of *in vitro* anticancer** active compounds.

| Comp No | $IC_{50}$ (µM) | | | | | |
|---|---|---|---|---|---|---|
| | Breast T47D | Lung NCI H-522 | Colon HCT-15 | Ovary PA-1 | Liver HepG-2 | Normal cell COS-1 |
| **VIbx** | 13.55±2.54 | 22.43±1.84 | **12.78±3.13** | 18.02±2.71 | **14.06±3.39** | 123.76±3.98 |
| **VIbz** | **15.32±2.78** | **11.33±3.11** | 23.32±4.03 | **15.67±2.35** | 24.64±2.74 | 117.97±2.56 |
| **VIcy** | 21.13±4.31 | **16.11±2.65** | 34.73±1.93 | 21.07±4.27 | 23.78±1.46 | 109.77±1.99 |
| **VIcz** | 38.92±3.91 | 19.13±3.14 | 26.32±2.34 | 31.26±1.74 | **12.33±2.07** | 132.44±4.11 |
| **VIIbz** | 20.21±2.08 | 28.34±2.56 | **14.07±2.54** | 37.66±3.31 | 15.46±4.04 | 128.46±2.18 |
| **VIIcx** | **13.22±1.74** | 15.16±1.91 | 67.63±3.75 | 16.88±4.13 | 38.39±2.78 | 116.51±2.37 |
| **VIIcz** | **11.23±2.98** | 25.08±3.41 | 65.47±2.44 | 23.68±2.66 | 28.77±3.33 | 110.25±3.25 |
| [b]**5-FU** | 51.8±2.34 | 56.76±3.4 | 45.01±1.45 | 39.5±4.32 | 29.87±1.82 | 110±8.98 |
| [c]**CYC-PHO** | 70.1±2.32 | 67.9±3.09 | 74.32±4.98 | 64.12±5.43 | 55.3±3.59 | 125.43±9.24 |
| [d]**CYC-HEXI** | 65.13±7.31 | 60.1±5.34 | 54.13±4.65 | 40.6±2.09 | 57.12±4.65 | 128.31±7.89 |

[a]50% growth inhibition as determined by MTT assay (24hr drug exposure)

*Compounds tested in triplicate, data expressed as mean value ± SD of three independent experiments.

[b]5-FU 5-Fluorouracil; [c]CYC-PHO Cyclophosphamide; [d]CYC-HEXI Cycloheximide;

** We are thankful to Dr. Partha Roy, Department of Biotechnology, Indian Institute of Technology-Roorkee, Roorkee for this data.

III elementor. Thin layer chromatography (TLC) was performed on silica gel G for TLC (Merck) and spots were visualized by iodine vapors or by irradiation with ultraviolet light (254nm). Compounds **VIax-cz** and **VIIax-cz** were purified by crystallization from methanol. Physical constants, spectral data and elemental analysis of **VIax-cz** and **VIIax-cz** are reported in Table-4a.1.

### 4a.3.2 General procedure for synthesis of isoindole and pyrazine derivatives (IIIa-c)

#### 4a.3.2.1 Synthesis of 2-amino-hexahydro-2H-isoindole-1,3-dione (**IIIa**)

Cis-cyclohexane-1,2-dicarboxylic acid (0.344 g; 2.0 mmol) and hydrazine hydrate (0.12 ml; 2.4 mmol) were grinded together in a small mortar with a pestle for 30 minutes. TLC of the reaction mixture on silica gel using ethyl acetate: methanol (7:3) as mobile phase exhibited that the reaction is complete. The crude product so obtained was purified by crystallization from methanol to give pure product 2-amino-hexahydro-2H-isoindole-1,3-dione (**IIIa**; scheme 4a.1). Yield 272 mg (82%). mp: 63-65ºC (lit [29, 30] mp 60-62ºC). IR (KBr) $\nu_{max}$: 3288 ($NH_2$), 1687 (>C=O) $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$) δ: 1.362-1.444 (m, 4H, 2×$CH_2$), 1.622-1.679 (m, 2H, $CH_2$), 1.765-1.828 (m, 2H, $CH_2$), 2.666-2.751 (m, 2H, CH+CH), 6.008 (bs, 2H, $NH_2$, exch). $^{13}C$ NMR (125 MHz, DMSO-$d_6$) δ: 25.008, 26.789, 38.949, 178.148. GC-MS: *m/z* 169 ($M^{+\bullet}$+1, 1%), 168 ($M^{+\bullet}$, 15%), 152 ($M^{+\bullet}$-$\dot{N}H_2$, 100%). Elemental analysis Calculated for $C_8H_{12}N_2O_2$: C 57.14, H 7.14, N 16.67%. Found: C 57.29, H 7.23. N 16.78%.

Similarly, compounds **IIIb** and **IIIc** were synthesized.

#### 4a.3.2.2 2-Aminoisoindoline-1,3-dione (**IIIb**)

Yield: 77%. mp: 202-205ºC (lit [29, 31] mp 200-205ºC). IR (KBr) $\nu_{max}$: 3377 ($NH_2$), 1669 (>C=O), 1476 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$) δ: 6.093 (s, 2H,

$NH_2$, exch), 7.582-7.616 (m, 2H, Ar), 7.653-7.689 (m, 2H, Ar). $^{13}C$ NMR (125 MHz, DMSO-$d_6$) δ: 127.277, 132.703, 160.139, 167.666. GC-MS: *m/z* 163 ($M^{\bullet+}$+1, 1%), 162 ($M^{+\bullet}$, 38%), 146 ($M^{+\bullet}$-$\dot{N}H_2$; 100%), 76 (  , 14%). Elemental analysis Calculated for $C_8H_6N_2O_2$: C 59.26, H 3.70, N 17.28%. Found: C 59.41, H 3.81, N 17.42%.

**4a.3.2.3** 6-Amino-6H-pyrrolo[3,4-b]pyrazine-5,7-dione (**IIIc**)

Yield: 77%. mp: 218ºC. IR (KBr) $\nu_{max}$: 3315 ($NH_2$), 1679 (>C=O), 1536, 1507 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$) δ: 6.044 (s, 2H, $NH_2$, exch), 8.868 (s, 2H, Ar). $^{13}C$ NMR (125 MHz, DMSO-$d_6$) δ: 143.482, 145.941, 168.007. GC-MS: *m/z* 165 ($M^{\bullet+}$+1, 1%), 164 ($M^{+\bullet}$, 46%), 148 ($M^{+\bullet}$-$\dot{N}H_2$; 100%). Elemental analysis Calculated for $C_6H_4N_4O_2$: C 43.90, H 2.44, N 34.14%. Found: C 43.99, H 2.40, N 34.02%.

**4a.3.3 General procedure for synthesis of azomethine derivatives (VIax-cz)**

4a.3.3.1 Synthesis of 2-(4-hydroxy-3-methoxybenzylideneamino)-hexahydro-2H-isoindole-1,3-dione (**VIax**)

(i) 2-Amino-hexahydro-2H-isoindole-1,3-dione (0.168 g, 1 mmol) (**IIIa**; Scheme 4a.1) and 4-hydroxy-3-methoxybenzaldehyde (0.152 g; 1 mmol) were dissolved in methanol (5ml). To this solution silica gel (5g, 60-120 mesh) was added and then solvent was removed under vacuum to give dry silica gel adsorbed with the above said reactants. This silica gel was subjected to microwave irradiation at 600 W for 6 minutes. A small portion of above silica gel was shaken with methanol (5ml) and filtered. Filtrate was reduced to one milliliter (1 ml) and was checked for progress of the reaction. TLC of this reaction solution over silica gel using ethyl acetate: methanol (4:1) as mobile phase showed absence of starting materials and hence completion of reaction. Total amount of microwave irradiated silica gel was shaken with methanol (20ml) for 10 minutes and then

filtered. Silica gel on filter paper was further washed with methanol (2×10ml). Solvent from the combined filtrate was removed under vacuum to give crude product **VIax**. This crude product was purified by crystallization from methanol to give pure 2-(4-hydroxy-3-methoxybenzylideneamino)-hexahydro-2H-isoindole-1,3-dione (**VIax**). Yield 0.250 g (83%).

(ii) Alternatively reactant adsorbed silica gel was irradiated at 120ºC for 6 min and work up was done as mentioned above to give pure condensed product **VIax**. Yield 0.244 g (81%). Yield of condensed product **VIax** by both the methods is comparable.

Similarly other azomethine derivatives **VIay-cz** i.e. 2-(2,5-dimethoxy benzylideneamino)-hexahydro-2H-isoindole-1,3-dione (**VIay**), 2-(4-(dimethylamino) benzylideneamino)-hexahydro-2H-isoindole-1,3-dione (**VIaz**) [33], 2-(4-hydroxy-3-methoxybenzylideneamino)isoindoline-1,3-dione (**VIbx**), 2-(2,5-dimethoxybenzylidene amino)isoindoline-1,3-dione (**VIby**), 2-(4-(dimethylamino)benzylideneamino)isoindoline -1,3-dione (**VIbz**) [34], 6-(4-hydroxy-3-methoxybenzylideneamino)-6H-pyrrolo[3,4-b] pyrazine-5,7-dione (**VIcx**), 6-(2,5-dimethoxybenzylideneamino)-6H-pyrrolo[3,4-b] pyrazine-5,7-dione (**VIcy**) and 6-(4-(dimethylamino)benzylideneamino)-6H-pyrrolo[3,4-b] pyrazine-5,7-dione (**VIcz**) were synthesized and reported in Table 4a.1.

### 4a.3.4 General procedure for synthesis of amidine derivatives (VIIax-cz)

4a.3.4.1 Synthesis of N'-(1,3-dioxo-hexahydro-1H-isoindol-2(3H)-yl)picolin amidine (**VIIax**)

(i) 2-Amino-hexahydro-2H-isoindole-1,3-dione (**IIIa;** Scheme 4a.1) (0.168 g, 1 mmol) and 2-cyanopyridine (**Va;** Scheme 4a.1) (0.104 g; 1 mmol) were dissolved in methanol (5ml). To this solution silica gel (5g, 60-120 mesh) was added and then solvent was removed under reduced pressure to give reactant adsorbed silica gel. This silica gel

was subjected to microwave irradiation at 850 W for 6 minutes. A small portion of microwave irradiated silica gel was shaken with methanol (5ml) for 10 minutes and then filtered. Solvent of reaction mixture was reduced to one milliliter. TLC of this reaction mixture on silica gel using ethyl acetate: methanol (3:2) as mobile phase showed absence of starting materials and hence reaction is complete. Total amount of microwave irradiated silica gel was shaken with methanol (20ml) for 10 minutes and then filtered. Silica gel on the filter paper was washed with methanol (2×10ml). Solvent from the total filtrate was removed under reduced pressure to give crude product **VIIax** (Scheme 4a.1). Crude product so obtained was purified by crystallization from methanol to give pure product N'-(1,3-dioxo-hexahydro-1H-isoindol-2(3H)-yl)picolinamidine (**VIIax**) Yield 0.198 g (73%).

(ii) Alternatively above reactant adsorbed silica gel was irradiated at 135ºC for 6 minutes and work up of reaction mixture as mentioned above gave crude product **VIIax**, which was purified by crystallization from methanol to give pure N'-(1,3-dioxo-hexahydro-1H-isoindol-2(3H)-yl)picolinamidine (**VIIax**) Yield 0.210 g (74%). Yield of condensed product **VIIax** by both the methods is comparable.

Similarly other amidine derivatives **VIIay-cz** i.e. N'-(1,3-dioxo-hexahydro-1H-isoindol-2(3H)-yl)isonicotinamidine (**VIIay**), N'-(1,3-dioxo-hexahydro-1H-isoindol-2(3H)-yl)pyrazine-2-carboxamidine (**VIIaz**), N'-(1,3-dioxoisoindolin-2-yl)picolinamidine (**VIIbx**), N'-(1,3-dioxoisoindolin-2-yl)isonicotinamidine (**VIIby**), N'-(1,3-dioxoiso indolin-2-yl)pyrazine-2-carboxamidine (**VIIbz**), N'-(5,7-dioxo-5H-pyrrolo[3,4-b]pyrazin-6(7H)-yl)picolinamidine (**VIIcx**), N'-(5,7-dioxo-5H-pyrrolo[3,4-b]pyrazin-6(7H)-yl)

isonicotin amidine (**VIIcy**) and N'-(5,7-dioxo-5H-pyrrolo[3,4-b]pyrazin-6(7H)-yl)pyrazine-2-carbox amidine (**VIIcz**) were synthesized and reported in Table 4a.1.

### 4a.3.5 Anti-inflammatory activity [21; Chapter-2]

Anti-inflammatory activity evaluation was carried out by following procedure described in chapter-2 of this thesis.

### 4a.3.6 In vitro cytotoxicity against human cancer cell lines [32]

Human breast (T47D), colon (HCT-15), lung (NCI-H522), liver (HepG-2) and ovary (PA-1) cancer cell lines were obtained from National Center for Cell Science (NCCS), Pune, India. Cells were grown in tissue culture flask in complete growth medium (RPMI-1640 medium with 2 mM glutamine, pH 7.4 supplemented with 10% fetal bovine serum, 100µg/ml streptomycin and 100 units/ml penicillin) in a carbon dioxide incubator (37$^{o}$C, 5% $CO_2$, 90% RH). All cell culture reagents were from GIBCO (Invitrogen, USA). Penicillin, streptomycin, MTT (3-(4,5-dimethyl-2-thiazolyl)2,5diphenyl-2H tetrazoliumbromide), cell culture grade DMSO, 5 Fluorouracil (5-FU), Cyclophosphamide and Actidione (cycloheximide) were from Himedia (Mumbai, India).

MTT assay was carried out as described previously [32]. In brief, $5 \times 10^3$ cells in 200 µl of medium were seeded in 96-well plates (Griener, Germany). Serial dilutions of compound initially ranging from 0-100 µM in DMSO were added to the monolayer. The final DMSO concentration for all dilutions was 0.1% which was used as vehicle control. The cultures were assayed after 24 h by the addition of 50 µl of 5 mg/ml MTT and incubating for another 4 h at 37°C. The MTT-containing medium was aspirated and 200 µl of DMSO (Himedia, Mumbai, India) and 25 µl of Sorensen glycine buffer (0.1 M

glycine and 0.1 M NaCl, pH 10.5) were added to lyse the cells and solubilize the water insoluble formazone. Absorbance of the lysates was determined on a Fluostar optima (BMG Labtech, Germany) microplate reader at 570 nm.

The percentage inhibition was calculated as:

$$\frac{\text{Mean OD of vehicle treated cells (negative control)} - \text{Mean OD of treated cells}}{\text{Mean OD of vehicle treated cells (negative control)}} \times 100$$

The $IC_{50}$ values were calculated using graph pad prism, version 5.02 software (Graph Pad Software Inc., CA, USA).

**********

**Part-b**

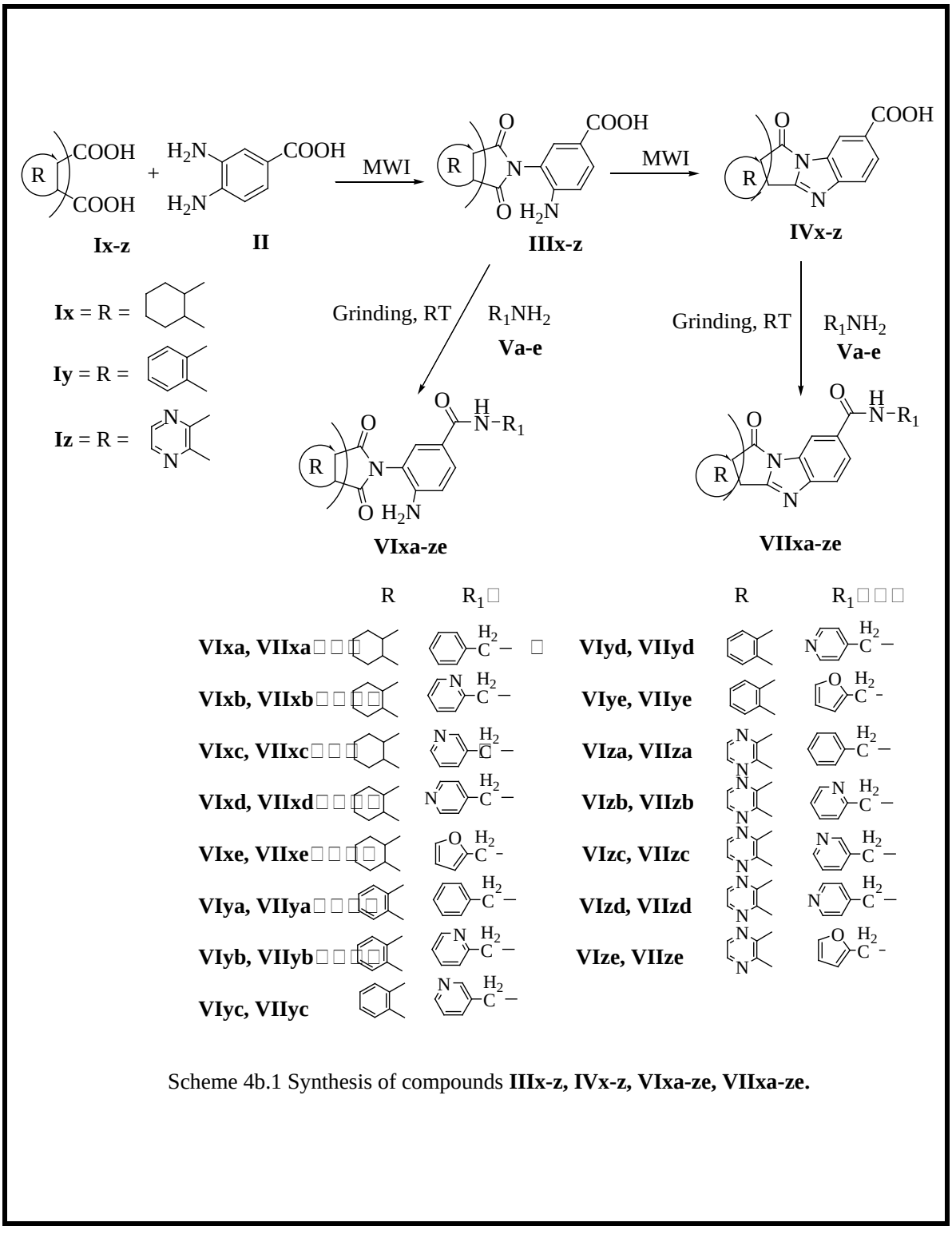
# 4b.1 Introduction

Recent work reported in literature on benzimidazole derivatives exhibiting anti-inflammatory and anticancer activities is summarized in chapter-1 of this thesis. Benzimidazole derivatives exhibiting antimalarial [35], antibacterial [36], antimicrobial [37, 38], antifungal [39], antitubercular [40], antiparasitic [41] and antiviral [42-44] activities are also known in literature. Various biological activities shown by isoindole and pyrrolopyrazine derivatives is already mentioned in part-a of this chapter. In continuation of our efforts in search of biologically active molecules [45, 46] we have synthesized some more complex derivatives of isoindole and pyrrolopyrazine and also tetracyclic heterocyclic molecules i.e. benzimidazoisoindole and benzimidazopyrrolopyrazine derivatives and screened them for anti-inflammatory and anticancer activities which we will describe in this chapter of the thesis.

## 4b.2 Results and discussion

### 4b.2.1 *Chemistry:*

Cis-1,2-cyclohexane dicarboxylic acid (**Ix;** Scheme 4b.1) and 3, 4-diaminobenzoic acid (**II**; Scheme 4b.1) were mixed in 1:1 molar ratio and this reaction mixture was subjected to microwave irradiation [47] at 600 Watt for 3 minutes and progress of reaction was monitored by TLC on silica gel. TLC of reaction mixture showed presence of starting materials; hence this reaction mixture was further irradiated at 600 Watt for 2 minutes. TLC of the reaction mixture showed absence of starting materials and hence reaction is complete. Crude product so obtained was purified by



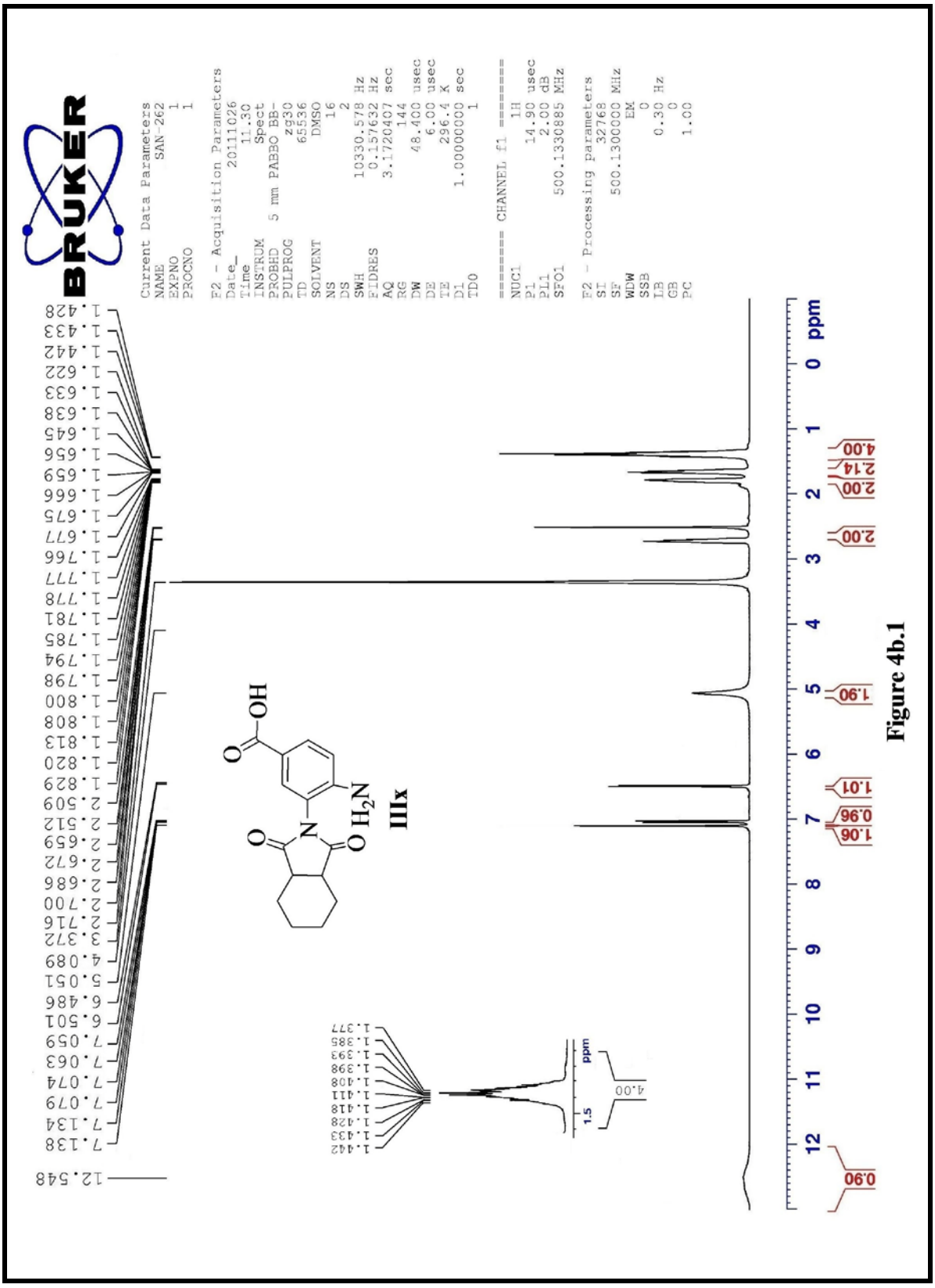

Scheme 4b.1 Synthesis of compounds **IIIx-z, IVx-z, VIxa-ze, VIIxa-ze.**

crystallization from methanol to give pure product 4-amino-3-(1, 3-dioxo-hexahydro-1H-isoindol-2(3H)-yl) benzoic acid (**IIIx;** Scheme 4b.1) in 86% yield.

Alternatively above reaction mixture was subjected to microwave irradiation at 90ºC for 5 minutes and TLC of the reaction mixture showed completion of reaction. Crude product so obtained was purified by crystallization from methanol to give pure product **IIIx** (Scheme 4b.1) in 84% yield. $^1$H NMR (500 MHz, DMSO-$d_6$) (Figure 4b.1) of **IIIx** show signals at δ: 1.377-1.442 (m, 4H, 2×$CH_2$), 1.622-1.677 (m, 2H, $CH_2$), 1.766-1.829 (m, 2H, $CH_2$), 2.659-2.716 (m, 2H, CH+CH), 5.051 (bs, 2H, $NH_2$, exch), 6.486-6.501 (d, 1H, J= 7.5 Hz, Ar), 7.059-7.079 (dd, 1H, J= 2.5 & 7.5 Hz, Ar), 7.134-7.138 (d, 1H, J = 2 Hz, Ar), 12.548 (bs, 1H, COOH, exch). In 3, 4-diaminobenzoic acid there are two amino groups on aromatic ring, one –$NH_2$ is meta to –COOH group and other is para to –COOH group. Amino group meta to –COOH group is more nucleophilic than amino group para to –COOH group and hence will undergo condensation reaction first to give product **IIIx** (Scheme 4b.1). Our results are in agreement with the observations of Cul *et. al.* [48] and our own results reported earlier [49].

In order to further support the structure assigned to **IIIx**, NOE (Nuclear Overhauser Effect) experiments were carried out. Irradiation of –$NH_2$ at δ 5.051 showed correlation with aromatic proton at δ 6.486-6.501 (d, 1H, J= 7.5 Hz, Ar) (Figure 4b.2), whereas irradiation of aromatic proton at δ 6.486-6.501 showed correlation with one aromatic proton δ 7.059-7.079 (dd, 1H, J= 2.5 & 7.5 Hz, Ar) and one –$NH_2$ group at δ 5.051 (bs, 2H, –$NH_2$, exch) (Figure 4b.3). From these NOE experiments it is clear that –$NH_2$ group meta to –COOH group react first to give product **IIIx** (Scheme 4b.1).

IR spectrum of **IIIx** shows absorption bands at 3293 ($NH_2$), 1680 (>C=O), 1621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TE 296.4 K
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TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 14.90 usec
PL1 2.00 dB
SFO1 500.1330885 MHz
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SSB 0
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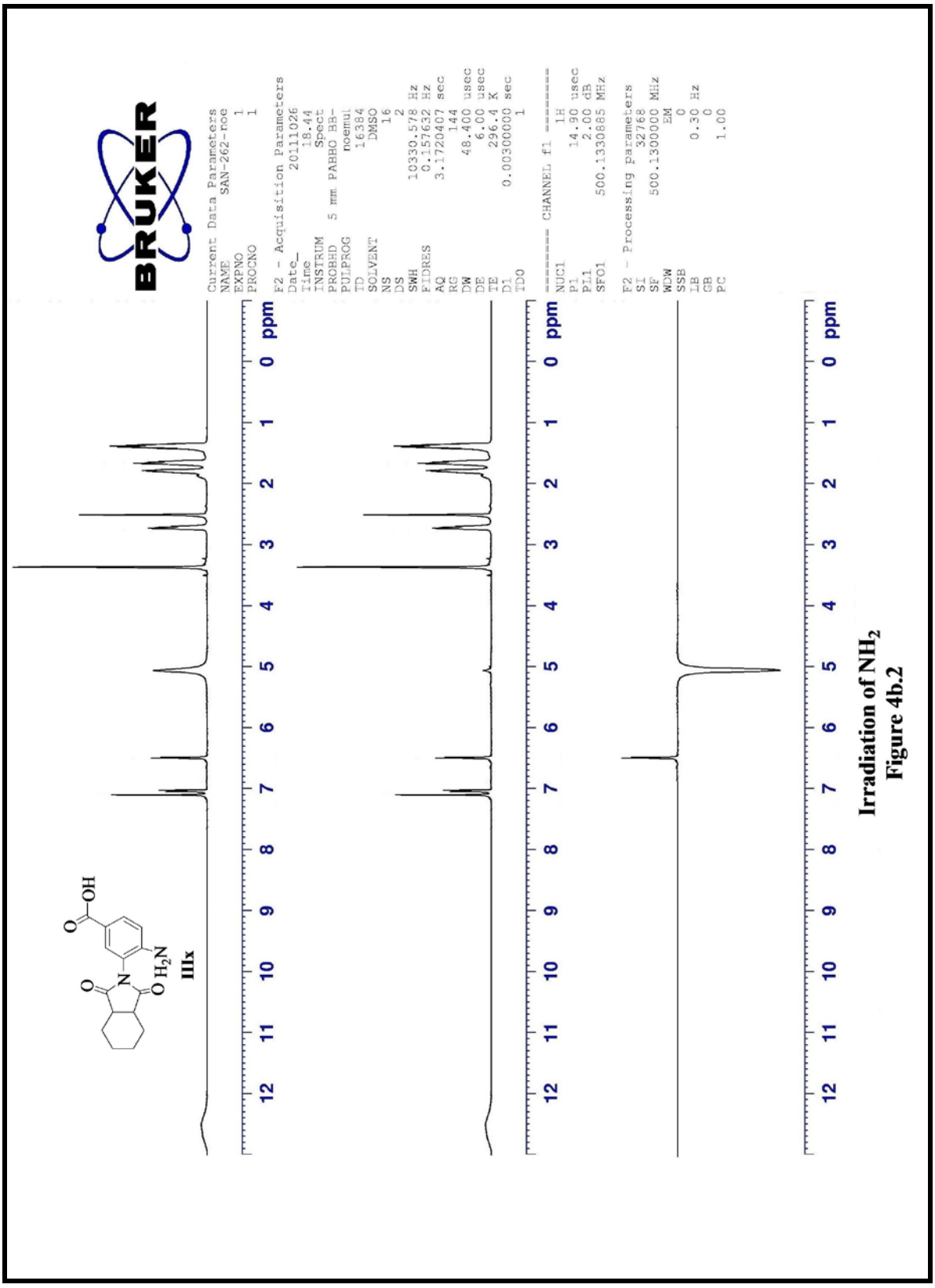
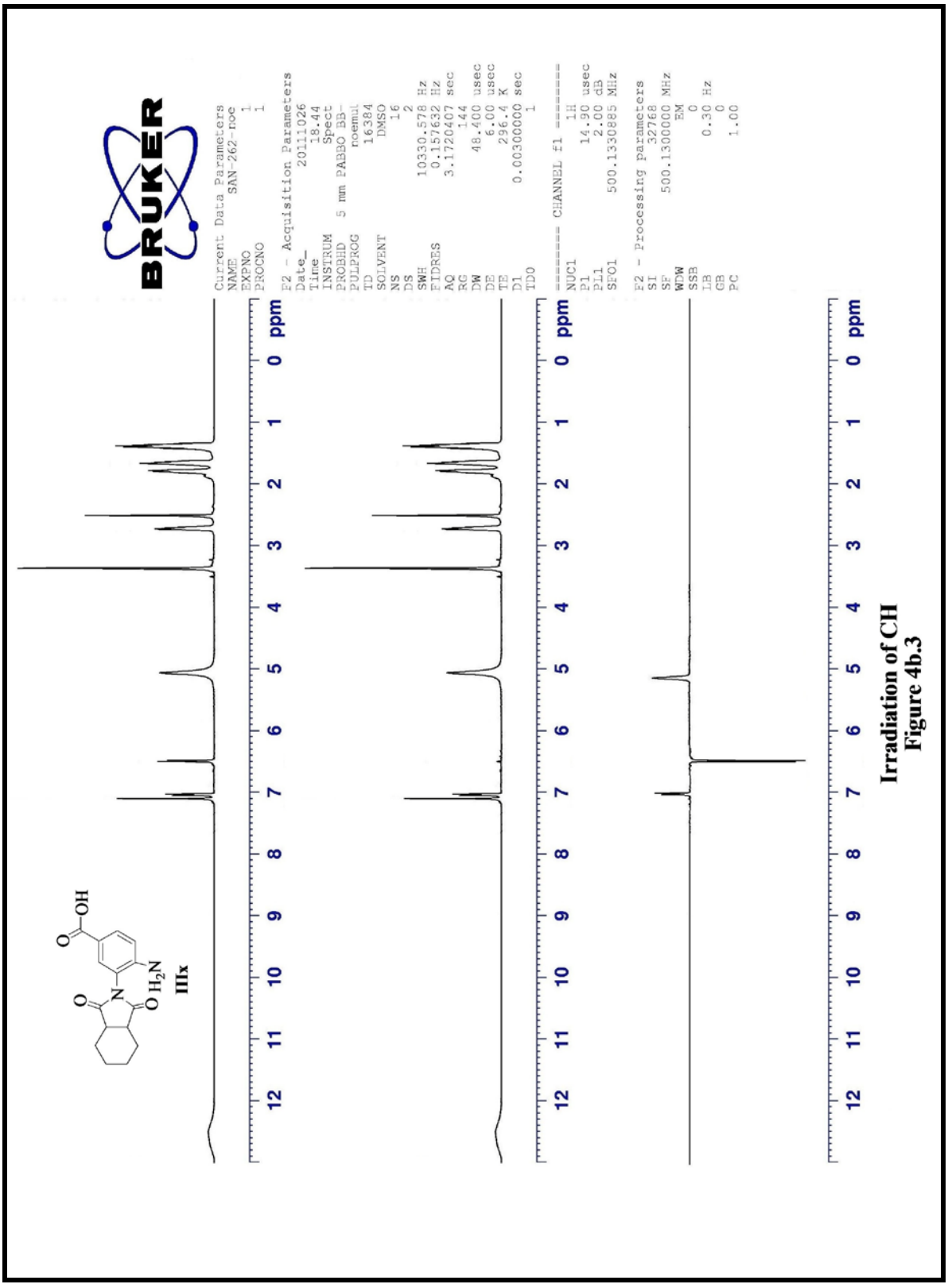
IIIx
ppm
Figure 4b.1




**Irradiation of $NH_2$**

**Figure 4b.2**




**Irradiation of CH**
**Figure 4b.3**

( —C(=O)-N-C(=O)— ), 1529, 1426 (Ar) $cm^{-1}$. $^{13}C$ NMR (125 MHz, DMSO-$d_6$) (Figure 4b.4) δ: 24.265, 26.653, 37.942, 44.390, 116.127, 120.128, 121.941, 126.109, 129.141, 145.207, 169.143 and 175.109. APCI-MS (Figure 4b.5) show the $MH^+$ ion peak at *m/z* 289.20 (100%). Elemental analysis Calculated for $C_{15}H_{16}N_2O_4$: C, 62.50; H, 5.55; N, 9.72%. Found: C, 62.58; H, 5.64; N, 9.81%. Spectral and analytical data of **IIIx** fully support the structure assigned to it.

Similarly condensation of phthalic acid (**Iy)**, pyrazine-2, 3-dicarboxylic acid (**Iz**) with 3, 4-diaminobenzoic acid (**II**) gave corresponding condensation products **IIIy** and **IIIz** (Scheme 4b.1) respectively in good yields. Spectral (IR, $^1H$ NMR, NOE, $^{13}C$ NMR, APCI-MS) & analytical data of **IIIy** and **IIIz** reported in Table 4b.1 fully support the structures assigned to them.

4-Amino-3-(1, 3-dioxo-hexahydro-1H-isoindol-2(3H)-yl) benzoic acid (**IIIx;** Scheme 4b.1) was irradiated at 850 Watt for 5 minutes. TLC of reaction contents over silica gel showed absence of starting material. Crude product so obtained was purified by crystallization from methanol to give pure tetracyclic product **IVx** in 82% yield. Alternatively compound **IIIx** was irradiated for 5 minutes at 130ºC. TLC of reaction contents showed absence of starting material. Crude product so obtained was crystallized from methanol to give pure tetracyclic compound i.e. 8-(1, 2, 3, 4, 4a, 11a hexahydro-11-oxobenzimidazo [2, 1-a]isoindol)-oicacid (**IVx;** Scheme 4b.1) in 81% yield.

IR spectrum of **IVx** shows absorption bands at 1684 (>C=O), 1624 ( —C(=O)-N— ), 1513 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$) (Figure 4b.6) δ: 1.372-1.458 (m, 4H, 2×$CH_2$), 1.623-1.679 (m, 2H, $CH_2$), 1.765-1.838 (m, 2H, $CH_2$), 2.649-2.737 (m, 2H,

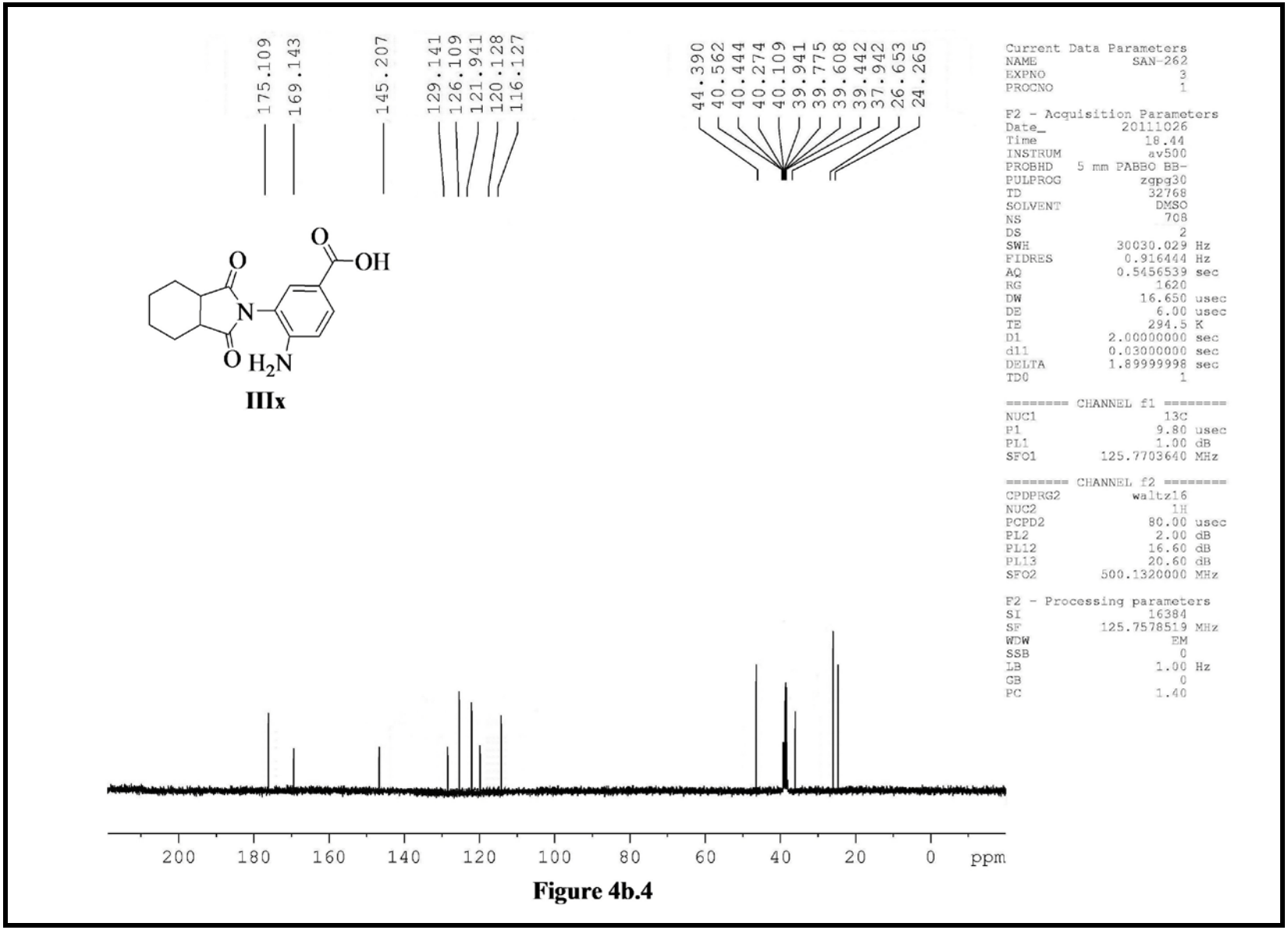

175.109
169.143
145.207
129.141
126.109
121.941
120.128
116.127
44.390
40.562
40.444
40.274
40.109
39.941
39.775
39.608
39.442
37.942
26.653
24.265
O
O
OH
N
O
H2N
IIIx
Current Data Parameters
NAME SAN-262
EXPNO 3
PROCNO 1
F2 - Acquisition Parameters
Date_ 20111026
Time 18.44
INSTRUM av500
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 32768
SOLVENT DMSO
NS 708
DS 2
SWH 30030.029 Hz
FIDRES 0.916444 Hz
AQ 0.5456539 sec
RG 1620
DW 16.650 usec
DE 6.00 usec
TE 294.5 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 9.80 usec
PL1 1.00 dB
SFO1 125.7703640 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 2.00 dB
PL12 16.60 dB
PL13 20.60 dB
SFO2 500.1320000 MHz
F2 - Processing parameters
SI 16384
SF 125.7578519 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
200
180
160
140
120
100
80
60
40
20
0
ppm

**Figure 4b.4**

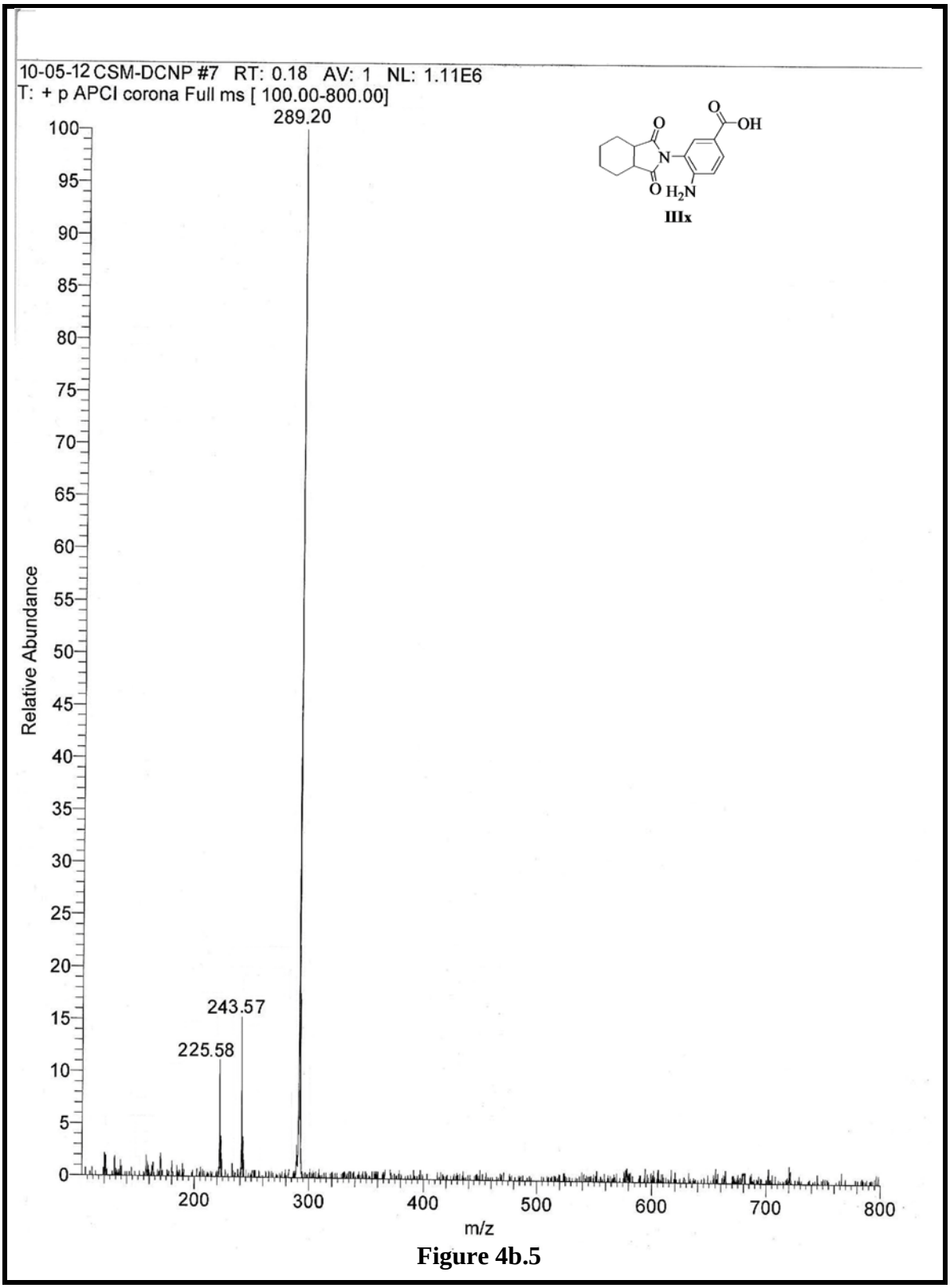
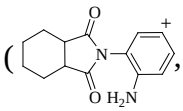
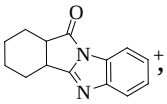
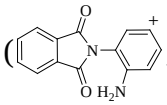
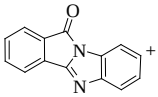
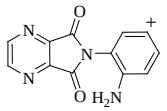
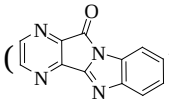
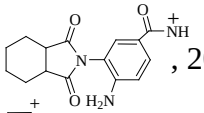
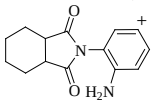
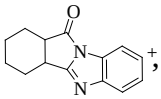
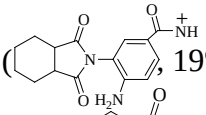
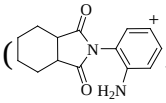
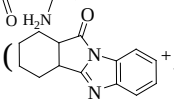

10-05-12 CSM-DCNP #7 RT: 0.18 AV: 1 NL: 1.11E6
T: + p APCI corona Full ms [ 100.00-800.00]
289.20
243.57
225.58
Relative Abundance
m/z
IIIx

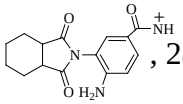
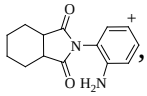
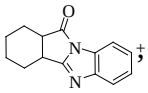
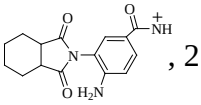
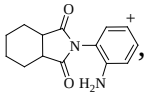
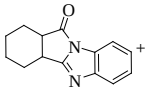
**Figure 4b.5**

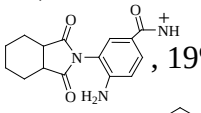
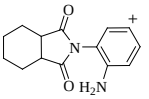
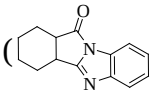
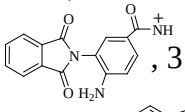
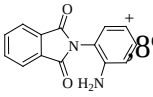
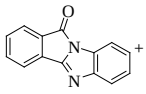
**Table 4b.1: Physical constants and spectral data of compounds IIIx-z and VIxa-ze.**

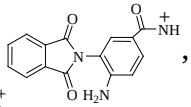
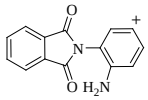
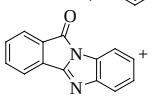
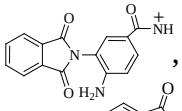
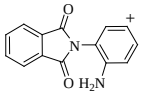
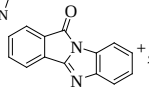
| Comp no | Solvent of cryst./elution | m.p. ºC | Yield % | IR (KBr) $cm^{-1}$, $^1H$ (500MHz) & $^{13}C$ (125MHz) NMR (DMSO-$d_6$), $\delta$ J(Hz), APCI-MS (*m/z*; relt int %) |
|---|---|---|---|---|
| **1** | **2** | **3** | **4** | **5** |
| **IIIx** | MeOH | 234 | 84 | IR 3293 ($NH_2$), 1680 (>C=O), 1621 (  ), 1529, 1426 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$) δ: 1.377-1.442 (m, 4H, 2×$CH_2$), 1.622-1.677 (m, 2H, $CH_2$), 1.766-1.829 (m, 2H, $CH_2$), 2.659-2.716 (m, 2H, CH+CH), 5.051 (bs, 2H, $NH_2$, exch), 6.486-6.501 (d, 1H, J= 7.5 Hz Ar), 7.059-7.079 (dd, 1H, J= 2.5 & 7.5 Hz, Ar), 7.134-7.138 (d, 1H, J = 2 Hz, Ar), 12.548 (bs, 1H, COOH, exch). NOE (500 MHz, DMSO-$d_6$) Irradiation of –$NH_2$ at δ 5.051 showed correlation with aromatic proton at δ 6.486-6.501 (d, 1H, J= 7.5 Hz, Ar), whereas irradiation of aromatic proton at δ 6.486-6.501 showed correlation with one aromatic proton δ 7.059-7.079 (dd, 1H, J= 2.5 & 7.5 Hz, Ar) and one –$NH_2$ group at δ 5.051 (bs, 2H, –$NH_2$, exch). $^{13}C$ NMR (125 MHz, DMSO-$d_6$) δ: 24.2, 26.6, 37.9, 44.3, 116.1, 120.1, 121.9, 126.1, 129.1, 145.2, 169.1 and 175.1. APCI-MS: *m/z* 289.20 ($MH^+$, 100%), 243.57 (  , 15%), 225.58 (  ; 11%), Anal. Calcd for $C_{15}H_{16}N_2O_4$: C, 62.50; H, 5.55; N, 9.72%. Found: C, 62.58; H, 5.64; N, 9.81%. |
| **IIIy** | MeOH | 187 | 86 | IR 3377 ($NH_2$), 1682 (>C=O), 1669 (  ), 1612, 1477 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$) δ: 5.198 (bs, 2H, $NH_2$, exch), 6.485-6.501 (d, 1H, J = 8 Hz, Ar), 7.059-7.079 (dd, 1H, J = 2 & 8 Hz, Ar), 7.132-7.135 (d, 1H, J = 1.5 Hz, Ar), 7.586-7.612 (m, 2H, Ar), 7.659-7.692 (m, 2H, Ar), 12.676 (bs, 1H, COOH, exch). NOE (500 MHz, DMSO-$d_6$) Irradiation of –$NH_2$ at δ 5.198 showed correlation with aromatic proton at δ 6.485-6.501 (d, 1H, J = 8 Hz, Ar), whereas irradiation of aromatic proton at δ 6.485-6.501 showed correlation with one aromatic proton δ 7.059-7.079 (dd, 1H, J= 2 & 8 Hz, Ar) and one |

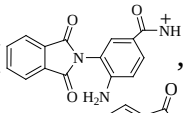
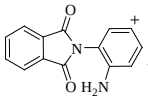
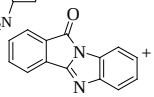
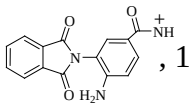
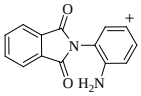
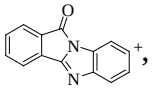
| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| | | | | -$NH_2$ group at δ 5.198 (bs, 2H, –$NH_2$, exch). $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ: 116.7, 120.6, 121.8, 125.1, 126.4, 127.1, 132.0, 133.2, 147.6, 167.2 and 170.1. APCI-MS: *m/z* 283.33 ($MH^+$, 100%), 237.19 (  , 14%), 219.23 (  , 7%). Anal. Calcd for $C_{15}H_{10}N_2O_4$: C, 63.83; H, 3.57; N, 9.92 %. Found: C, 63.77; H, 3.53; N, 9.87%. |
| **IIIz** | MeOH | 247 | 88 | IR 3215 ($NH_2$), 1698 (>C=O), 1619 ( —C(=O)-N-C(=O)—), 1536 (Ar) cm$^{-1}$. $^1$H NMR (500 MHz, DMSO-$d_6$) δ: 5.198 (bs, 2H, $NH_2$, exch), 6.486-6.501 (d, 1H, J = 7.5 Hz, Ar), 7.059-7.079 (dd, 1H, J = 2 & 8 Hz, Ar), 7.132-7.136 (d, 1H, J = 2 Hz, Ar), 8.726 (s, 2H, Ar), 12.635 (bs, 1H, COOH, exch). NOE (500 MHz, DMSO-$d_6$) Irradiation of –$NH_2$ at δ 5.198 showed correlation with aromatic proton at δ 6.486-6.501 (d, 1H, J= 7.5 Hz, Ar), whereas irradiation of aromatic proton at δ 6.486-6.501 showed correlation with one aromatic proton δ 7.059-7.079 (dd, 1H, J= 2.5 & 7.5 Hz, Ar) and one –$NH_2$ group at δ 5.198 (bs, 2H, –$NH_2$, exch). $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ: 116.0, 120.5, 122.3, 126.3, 129.6, 143.0, 146.2, 147.8, 163.4 and 169.1. APCI-MS: *m/z* 285.74 ($MH^+$, 100%), 239.27 (  , 19%), 221.12 (  , 8 %) Anal. Calcd for $C_{13}H_8N_4O_4$: C, 54.93; H, 2.84; N, 19.71%. Found: C, 54.84; H, 2.88; N, 19.77%. |
| **VIxa** | MeOH | 276 | 86 | IR 3218 ($NH_2$), 1695, 1676, 1612 (>C=O), 1478 (Ar) cm$^{-1}$. $^1$H NMR (500 MHz, DMSO-$d_6$) δ: 1.377-1.445 (m, 4H, 2×$CH_2$), 1.623-1.679 (m, 2H, $CH_2$), 1.763-1.829 (m, 2H, $CH_2$), 2.657-2.718 (m, 2H, CH+CH), 4.089 (s, 2H, $CH_2$), 5.051 (bs, 2H, $NH_2$, exch), 6.486-6.500 (d, 1H, J= 7.0 Hz, Ar), 7.059-7.079 (dd, 1H, J= 2.5 & 8 Hz, Ar), 7.134-7.138 (d, 1H, J = 2.0 Hz, Ar), 7.279-7.341 (m, 5H, Ar), 8.136 (s, 1H, NH, |

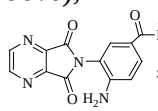
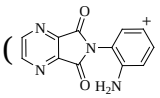
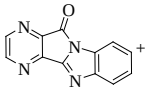
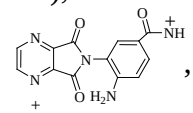
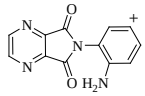
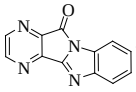
| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| | | | | exch). $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ: 24.2, 26.6, 37.9, 44.3, 116.2, 118.4, 123.6, 124.7, 126.1, 127.9, 128.1, 129.1, 141.1, 145.2, 167.1 and 174.7. APCI-MS: *m/z* 378.65 ($MH^+$, 100%), 286.20 (  , 20%), 243.50 (  , 11%), 225.58 (  , 7 %). Anal. Calcd for $C_{22}H_{23}N_3O_3$: C, 70.02; H, 6.10; N, 11.14%. Found: C, 70.32; H, 6.29; N, 11.34%. |
| **VIxb** | MeOH | 285 | 89 | IR 3399 ($NH_2$), 1678, 1623 (>C=O), 1530, 1426 (Ar) $cm^{-1}$. $^1$H NMR (500 MHz, DMSO-$d_6$) δ: : 1.378-1.446 (m, 4H, 2×$CH_2$), 1.622-1.678 (m, 2H, $CH_2$), 1.764-1.830 (m, 2H, $CH_2$), 2.661-2.716 (m, 2H, CH+CH), 4.086 (s, 2H, $CH_2$), 5.051 (bs, 2H, $NH_2$, exch), 6.484-6.500 (d, 1H, J = 8 Hz, Ar), 7.059-7.079 (dd, 1H, J = 2.5 & 8.5 Hz, Ar), 7.134-7.138 (d, 1H, J = 2 Hz, Ar), 7.225-7.261 (q, 1H, J = 8 & 10 Hz, Ar), 7.388-7.415 (d, 1H, Ar), 7.752-7.802 (dt, 1H, J = 2.5 & 9.5 Hz, Ar), 8.132 (s, 1H, NH, exch), 8.452-8.468 (d, 1H, J = 8 Hz, Ar,). $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ: 24.1, 26.1, 37.6, 49.3, 116.2, 118.7, 120.6, 123.2, 124.2, 125.5, 129.1, 136.1, 145.1, 148.6, 156.2, 167.2 and 174.4. APCI-MS: *m/z* 379.77 ($MH^+$, 100%), 286.52 (  , 19%), 243.28 (  , 15%), 225.22 (  , 12 %). Anal. Calcd for $C_{21}H_{22}N_4O_3$: C, 66.66; H, 5.82; N, 14.81%. Found: C, 66.53; H, 5.97; N, 14.99%. |
| **VIxc** | MeOH | 281 | 91 | IR 3317 ($NH_2$), 1680, 1615 (>C=O), 1533 (Ar) $cm^{-1}$. $^1$H NMR (500 MHz, DMSO-$d_6$) δ: 1.378-1.446 (m, 4H, 2×$CH_2$), 1.622-1.678 (m, 2H, $CH_2$), 1.763-1.828 (m, 2H, $CH_2$), 2.659-2.739 (m, 2H, CH+CH), 4.072 (s, 2H, $CH_2$), 5.051 (bs, 2H, $NH_2$, exch), 6.488-6.504 (d, 1H, J = 8 Hz, |

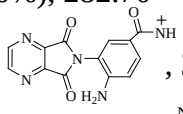
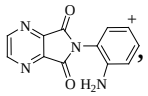
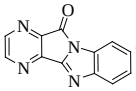
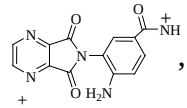
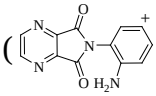
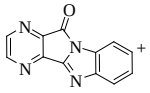
| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| | | | | Ar), 7.068-7.084 (dd, 1H, J=2 & 6 Hz, Ar), 7.134-7.139 (d, 1H, J = 2.5 Hz, Ar), 7.236-7.268 (dt, 1H, J = 2 & 6 Hz, Ar), 7.843-7.859 (d, 1H, J= 8Hz, Ar), 8.125 (s, 1H, NH, exch), 8.325-8.414 (m, 2H, Ar). $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ: 24.1, 26.2, 37.7, 46.4, 116.2, 118.7, 123.6, 124.2, 125.2, 130.5, 134.1, 135.1, 145.1, 147.6, 150.2, 167.5 and 174.4. APCI-MS: *m/z* 379.65 ($MH^+$, 100%), 286.36 (  , 28%), 243.78 (  , 13%), 225.17 (  ; 8%). Anal. Calcd for $C_{21}H_{22}N_4O_3$: C, 66.66; H, 5.82; N, 14.81%. Found: C, 66.74; H, 5.75; N, 14.64%. |
| **VIxd** | MeOH | >300 | 96 | IR 3388 ($NH_2$), 1668, 1654 (>C=O), 1593, 1495 (Ar) $cm^{-1}$. $^1$H NMR (500 MHz, DMSO-$d_6$) δ: 1.374-1.446 (m, 4H, 2×$CH_2$), 1.625-1.681 (m, 2H, $CH_2$), 1.765-1.828 (m, 2H, $CH_2$), 2.640-2.737 (m, 2H, CH+CH), 4.085 (s, 2H, $CH_2$), 5.055 (bs, 2H, $NH_2$, exch), 6.486-6.502 (d, 1H, J = 8 Hz, Ar), 7.059-7.079 (dd, 1H, J=2 & 8 Hz, Ar), 7.133-7.136 (d, 1H, J = 1.5 Hz, Ar), 7.327-7.343 (d, 2H, J= 8Hz, Ar), 8.135 (s, 1H, NH, exch), 8.357-8.373 (d, 2H, J=8 Hz, Ar).$^{13}$C NMR (125 MHz, DMSO-$d_6$) δ: 24.6, 26.2, 37.9, 44.4, 116.1, 118.6, 123.6, 124.0, 124.9, 125.4, 129.1, 145.9, 147.6, 149.7, 167.9 and 174.4. APCI-MS: *m/z* 379.39 ($MH^+$, 100%), 286.34 (  , 27%), 243.66 (  , 13%), 225.15 (  , 9 %). Anal. Calcd for $C_{21}H_{22}N_4O_3$: C, 66.66; H, 5.82; N, 14.81%. Found: C, 66.55; H, 5.99; N, 14.92%. |
| **VIxe** | MeOH | 271 | 90 | IR 3313 ($NH_2$), 1679, 1617 (>C=O), 1533 (Ar) $cm^{-1}$. $^1$H NMR (500 MHz, DMSO-$d_6$) δ: 1.381-1.448 (m, 4H, 2×$CH_2$), 1.623-1.678 (m, 2H, $CH_2$), 1.763-1.842 (m, 2H, $CH_2$), 2.639-2.736 |

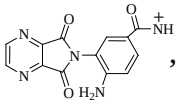
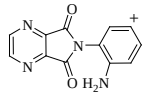
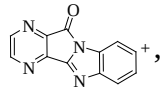
| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| | | | | (m, 2H, CH+CH), 4.083 (s, 2H, $CH_2$), 5.053 (bs, 2H, $NH_2$, exch), 6.181-6.211 (t, 1H, J = 7.5 Hz, Ar), 6.485-6.501 (d, 1H, J = 8 Hz, Ar), 6.726-6.742 (d, 1H, J = 8 Hz, Ar), 7.044-7.060 (d, 1H, J= 8 Hz, Ar), 7.133-7.138 (d, 1H, J = 2.5 Hz, Ar), 7.330-7.346 (d, 1H, J= 8Hz, Ar), 8.142 (s, 1H, NH, exch). $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ: 24.6, 26.2, 37.9, 38.9, 106.9, 110.1, 116.9, 118.4, 123.9, 125.5, 129.1, 142.9, 145.6, 148.6, 167.6 and 174.0. APCI-MS: *m/z* 368.88 ($MH^+$, 100%), 268.29 (  , 19%), 243.61 (  , 11%), 225.40 (  , 7 %). Anal. Calcd for $C_{20}H_{21}N_3O_4$: C, 65.39; H, 5.72; N, 11.44%. Found: C, 65.29; H, 5.60; N, 11.63%. |
| **VIya** | MeOH | 267 | 93 | IR 3380 ($NH_2$), 1680, 1667 (>C=O), 1611 (Ar) $cm^{-1}$. $^1$H NMR (500 MHz, DMSO-$d_6$) δ: 4.089 (s, 2H, $CH_2$), 5.169 (bs, 2H, $NH_2$, exch), 6.485-6.502 (d, 1H, J = 8.5 Hz, Ar), 7.058-7.079 (dd, 1H, J = 2.5 & 8.5 Hz, Ar), 7.134-7.138 (d, 1H, J = 2 Hz, Ar), 7.232-7.397 (m, 5H, Ar), 7.587-7.614 (m, 2H, Ar), 7.658-7.693 (m, 2H, Ar), 8.127 (s, 1H, NH, exch). $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ: 46.9, 118.4, 119.7, 121.8, 123.1, 124.9, 125.1, 126.4, 127.1, 128.7, 132.0, 133.2, 144.4, 146.6, 166.2 and 168.0. APCI-MS: *m/z* 372.33 ($MH^+$, 100%), 280.33 (  , 31%), 237.13 (  ,8%), 219.20 (  , 4 %). Anal. Calcd for $C_{22}H_{17}N_3O_3$: C, 71.15; H, 4.58; N, 11.32%. Found: C, 71.28; H, 4.65; N, 11.59%. |
| **VIyb** | MeOH | 283 | 94 | IR 3424 ($NH_2$), 1685 (>C=O), 1594, 1492 (Ar) $cm^{-1}$. $^1$H NMR (500 MHz, DMSO-$d_6$) δ: 4.089 (s, 2H, $CH_2$), 5.189 (bs, 2H, $NH_2$, exch), 6.486-6.502 (d, 1H, J = 8 Hz, Ar), 7.059-7.079 (dd, 1H, J = 2 & 8 Hz, Ar), 7.135-7.138 (d, 1H, J = 1.5 Hz, Ar), 7.228-7.308 (q, 1H, J= 6 & 8 Hz, Ar), |

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| | | | | 7.387-7.413 (d, 1H, J= 13Hz, Ar), 7.588-7.616 (m, 2H, Ar), 7.659-7.685 (m, 2H, Ar), 7.687-7.799 (dt, 1H, J = 2 & 8 Hz, Ar), 8.127 (s, 1H, NH, exch), 8.452-8.462 (d, 1H, J = 5 Hz, Ar). $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ: 47.3, 118.5, 119.9, 120.8, 123.1, 123.9, 125.5, 126.2, 127.2, 131.7, 132.0, 134.5, 144.8, 148.6, 156.7, 166.0 and 168.3. APCI-MS: *m/z* 373.22 ($MH^+$, 100%), 280.33 (  , 22%), 237.13 (  , 12%), 219.20 (  , 3%). Anal. Calcd for $C_{21}H_{16}N_4O_3$: C, 67.74; H, 4.30; N, 15.05%. Found: C, 67.45; H, 4.37; N, 15.16%. |
| **VIyc** | MeOH | 274 | 96 | IR 3318 ($NH_2$), 1680, 1619 (>C=O), 1538 (Ar) $cm^{-1}$. $^1$H NMR (500 MHz, DMSO-$d_6$) δ: 4.074 (s, 2H, $CH_2$), 5.181 (bs, 2H, $NH_2$, exch), 6.484-6.500 (d, 1H, J = 8 Hz, Ar), 7.058-7.078 (dd, 1H, J = 2 & 8 Hz, Ar), 7.133-7.137 (d, 1H, J = 2Hz, Ar), 7.328-7.364 (dt, 1H, J = 2 & 8 Hz, Ar), 7.587-7.614 (m, 2H, Ar), 7.659-7.687 (m, 2H, Ar), 7.840-7.856 (d, 1H, J = 8 Hz, Ar), 8.127 (s, 1H, NH, exch), 8.325-8.412 (m, 2H, Ar). $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ: 47.3, 116.5, 119.9, 123.1, 123.9, 124.5, 126.2, 127.2, 131.7, 132.0, 134.5, 135.5, 144.8, 148.6, 150.7, 166.0 and 167.3. APCI-MS: *m/z* 373.28 ($MH^+$, 100%), 280.55 (  , 29%), 237.17 (  , 8%), 219.52(  , 3 %). Anal. Calcd for $C_{21}H_{16}N_4O_3$: C, 67.74; H, 4.30; N, 15.05%. Found: C, 67.81; H, 4.36; N, 15.23%. |
| **VIyd** | MeOH | >300 | 96 | IR 3375 ($NH_2$), 1698, 1619 (>C=O), 1536 (Ar) $cm^{-1}$. $^1$H NMR (500 MHz, DMSO-$d_6$) δ: 4.089 (s, 2H, $CH_2$), 5.099 (bs, 2H, $NH_2$, exch), 6.485-6.501 (d, 1H, J = 8 Hz, Ar), 7.060-7.080 (dd, 1H, J = 2 & 8 Hz, Ar), 7.133-7.137 (d, 1H, J = 2Hz, |

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| | | | | Ar), 7.323-7.340 (d, 2H, J = 8.5 Hz, Ar), 7.588-7.606 (m, 2H, Ar), 7.616-7.687 (m, 2H, Ar), 8.162 (s, 1H, NH, exch), 8.457-8.474 (d, 2H, J = 8.5 Hz, Ar). $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ: 46.4, 116.5, 118.7, 123.9, 124.9, 127.5, 128.1, 129.2, 131.5, 132.1, 145.1, 147.3, 148.9, 166.0 and 167.4. APCI-MS: *m/z* 373.85 ($MH^+$, 100%), 280.46 (  , 15%), 237.53 (  , 9%), 219.37 (  , 3%). Anal. Calcd for $C_{21}H_{16}N_4O_3$: C, 67.74; H, 4.30; N, 15.05%. Found: C, 67.63; H, 4.29; N, 15.11%. |
| **VIye** | MeOH | 262 | 92 | IR 3378 ($NH_2$), 1682, 1619 (>C=O), 1535 (Ar) $cm^{-1}$. $^1$H NMR (500 MHz, DMSO-$d_6$) δ: 4.074 (s, 2H, $CH_2$), 5.193 (bs, 2H, $NH_2$, exch), 6.182-6.212 (t, 1H, J = 8 Hz, Ar), 6.486-6.501 (d, 1H, J = 7.5 Hz, Ar), 6.731-6.748 (d, 1H, J = 8.5 Hz, Ar), 7.060-7.076 (d, 1H, J = 8 Hz, Ar), 7.134-7.137 (d, 1H, J = 1.5 Hz, Ar), 7.333-7.349 (d, 1H, J = 8 Hz, Ar), 7.588-7.605 (m, 2H, Ar), 7.615-7.687 (m, 2H, Ar), 8.115 (s, 1H, NH, exch). $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ: 38.0, 106.2, 110.5, 116.7, 118.7, 123.2, 124.9, 126.0, 127.5, 131.5, 132.3, 142.4, 145.3, 148.9, 166.2 and 167.3. APCI-MS: *m/z* 362.22 ($MH^+$, 100%), 280.33 (  , 15%), 237.13 (  , 6%), 219.20 (  , 3 %). Anal. Calcd for $C_{20}H_{15}N_3O_4$: C, 66.48; H, 4.15; N, 11.63%. Found: C, 66.59; H, 4.21; N, 11.89%. |
| **VIza** | MeOH | 289 | 92 | IR 3317 ($NH_2$), 1692, 1619 (>C=O), 1536 (Ar) $cm^{-1}$. $^1$H NMR (500 MHz, DMSO-$d_6$) δ: 4.092 (s, 2H, $CH_2$), 5.051 (bs, 2H, $NH_2$, exch), 6.486-6.501 (d, 1H, J = 7.5 Hz, Ar), 7.059-7.079 (dd, 1H, J = 2.5 & 8 Hz, Ar), 7.134-7.138 (d, 1H, J = 2Hz, Ar), 7.279-7.340 (m, 5H, Ar), 8.130 (s, 1H, NH, exch), 8.704 (s, 2H, Ar). $^{13}$C NMR (125 |

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| | | | | MHz, DMSO-$d_6$) δ: 44.3, 116.0, 118.1, 123.5, 124.3, 125.1, 126.3, 127.8, 128.0, 141.8, 143.0, 145.7, 146.7, 164.2 and 168.0. APCI-MS: *m/z* 374.53 ($MH^+$, 100%), 282.13 (  , 31%), 239.20 (  , 13%), 221.19 (  , 8%). Anal. Calcd for $C_{20}H_{15}N_5O_3$: C, 64.34; H, 4.02; N, 18.76%. Found: C, 64.23; H, 4.19; N, 18.88%. |
| **VIzb** | MeOH | >300 | 93 | IR 3363 ($NH_2$), 1689, 1612 (>C=O), 1520, 1487 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$) δ: 4.085 (s, 2H, $CH_2$), 5.193 (bs, 2H, $NH_2$, exch), 6.486-6.502 (d, 1H, J = 8 Hz, Ar), 7.058-7.078 (dd, 1H, J=2 & 8 Hz, Ar), 7.134-7.138 (d, 1H, J = 2 Hz, Ar), 7.266-7.302 (q, 1H, J=8 & 10 Hz, Ar), 7.388-7.415 (d, 1H, J = 13.5 Hz, Ar), 7.752-7.801 (dt, 1H, J = 2 & 8.5 Hz, Ar), 8.122 (s, 1H, NH, exch), 8.453-8.469 (d, 1H, J=8 Hz, Ar), 8.776 (s, 2H, Ar). $^{13}C$ NMR (125 MHz, DMSO-$d_6$) δ: 49.1, 116.7, 118.3, 120.5, 123.3, 124.1, 125.1, 127.3, 136.8, 143.7, 145.0, 145.8, 148.1, 156.3, 164.2 and 167.7. APCI-MS: *m/z* 375.43 ($MH^+$, 100%), 282.23 (  , 26%), 239.21 (  , 15%), 221.12 (  , 9 %). Anal. Calcd for $C_{19}H_{14}N_6O_3$: C, 60.96; H, 3.74; N, 22.45%. Found: C, 60.84; H, 3.92; N, 22.53%. |
| **VIzc** | MeOH | >300 | 94 | IR 3283 ($NH_2$), 1666, 1616 (>C=O), 1519 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$) δ: 4.097 (s, 2H, $CH_2$), 5.183 (bs, 2H, $NH_2$, exch), 6.483-6.499 (d, 1H, J = 8 Hz, Ar), 7.060-7.080 (dd, 1H, J=2 & 8.5 Hz, Ar), 7.135-7.139 (d, 1H, J = 2 Hz, Ar), 7.329-7.365 (dt, 1H, J = 2 & 8 Hz, Ar), 7.843-7.859 (d, 1H, J= 8Hz, Ar), 8.125 (s, 1H, NH, exch), 8.325-8.414 (m, 2H, Ar), 8.778 (s, 2H, Ar). $^{13}C$ NMR (125 MHz, DMSO-$d_6$) δ: |

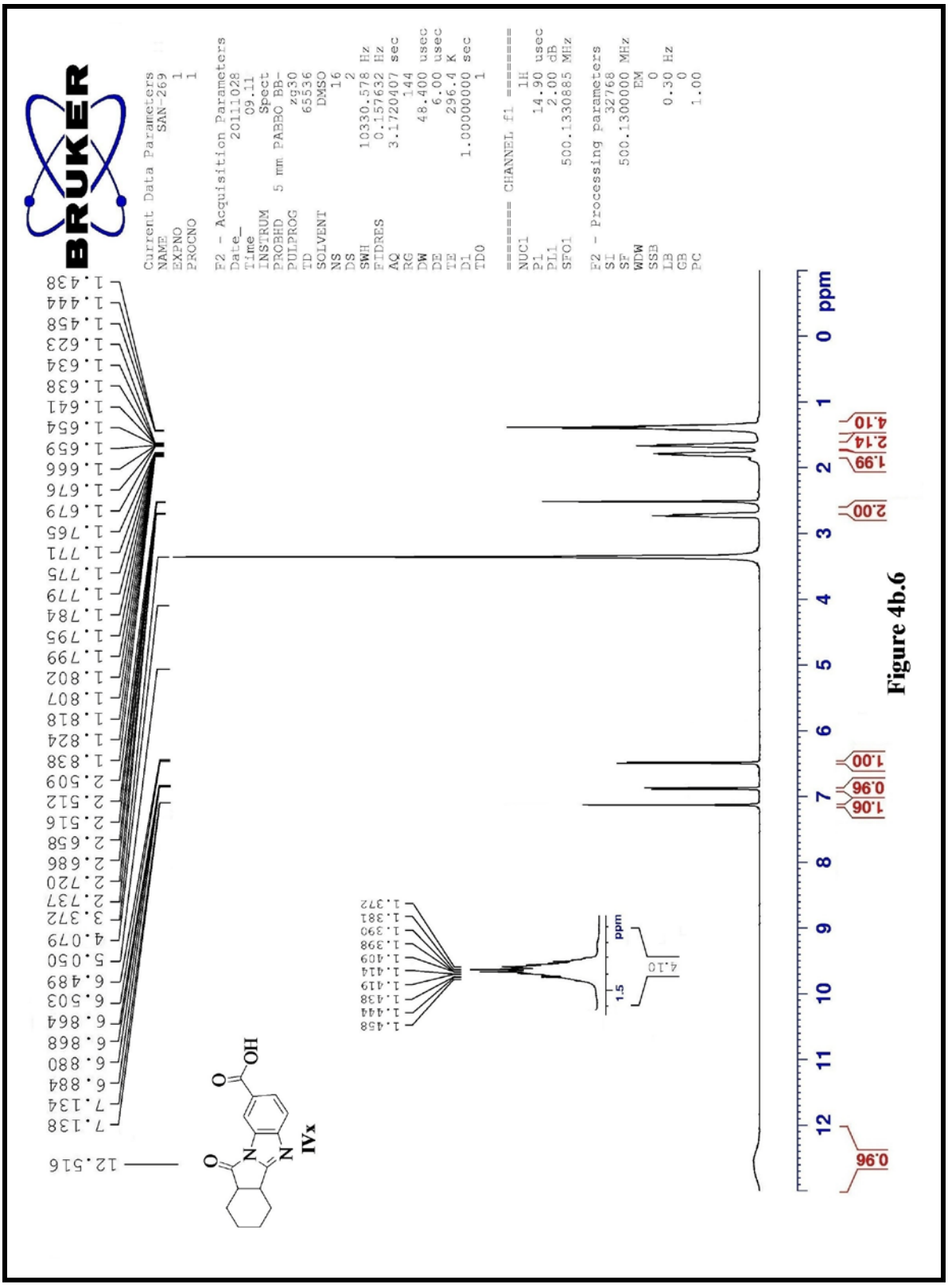
| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| | | | | 46.9, 116.1, 118.2, 123.1, 124.3, 125.1, 127.2, 134.3, 135.8, 143.4, 145.3, 146.3, 147.4, 150.3, 163.9 and 167.3. APCI-MS: *m/z* 375.65 ($MH^+$, 100%), 282.70 (  , 33%), 239.22 (  , 15%), 221.78 (  , 11 %). Anal. Calcd for $C_{19}H_{14}N_6O_3$: C, 60.96; H, 3.74; N, 22.45%. Found: C, 60.83; H, 3.81; N, 22.33%. |
| **VIzd** | MeOH | >300 | 96 | IR 3368 ($NH_2$), 1688, 1653 (>C=O), 1594, 1497 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$) δ: 4.075 (s, 2H, $CH_2$), 5.099 (bs, 2H, $NH_2$, exch), 6.487-6.503 (d, 1H, J = 8 Hz, Ar), 7.060-7.080 (dd, 1H, J=2.5 & 8.5 Hz, Ar), 7.134-7.138 (d, 1H, J = 2 Hz, Ar), 7.327-7.343 (d, 2H, J= 8Hz, Ar), 8.134 (s, 1H, NH, exch), 8.458-8.474 (d, 2H, J=8 Hz, Ar), 8.788 (s, 2H, Ar). $^{13}C$ NMR (125 MHz, DMSO-$d_6$) δ: 44.6, 116.5, 118.3, 123.1, 124.3, 125.1, 126.8, 144.7, 145.1, 146.3, 147.3, 149.1, 163.8 and 167.4. APCI-MS: *m/z* 375.65 ($MH^+$, 100%), 282.70 (  , 33%), 239.20 (  , 16%), 221.78 (  , 11 %), Anal. Calcd for $C_{19}H_{14}N_6O_3$: C, 60.96; H, 3.74; N, 22.45%. Found: C, 60.86; H, 3.73; N, 22.37%. |
| **VIze** | MeOH | 286 | 93 | IR 3231 ($NH_2$), 1678, 1624 (>C=O), 1512 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$) δ: 4.085 (s, 2H, $CH_2$), 5.195 (bs, 2H, $NH_2$, exch), 6.182-6.212 (t, 1H, J = 7.5 Hz, Ar), 6.485-6.501 (d, 1H, J = 8 Hz, Ar), 6.730-6.746 (d, 1H, J = 8 Hz, Ar), 7.064-7.080 (dd, 1H, J= 8 Hz, Ar), 7.135-7.138 (d, 1H, J = 1.5 Hz, Ar), 7.330-7.346 (d, 1H, J= 8Hz, Ar), 8.128 (s, 1H, NH, exch), 8.782 (s, 2H, Ar). $^{13}C$ NMR (125 MHz, DMSO-$d_6$) δ: 38.5, 106.4, 110.3, 116.2, 118.3, 123.1, 124.1, 126.1, 142.7, 144.1, 145.1, 146.3, 148.1, 163.8 and 167.4. APCI-MS: |

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| | | | | *m/z* 364.48 ($MH^+$, 100%), 282.30 (  , 33%), 239.07 (  , 15%), 221.27 (  , 12 %). Anal. Calcd for $C_{18}H_{13}N_5O_4$: C, 59.50; H, 3.58; N, 19.28%. Found: C, 59.63; H, 3.67; N, 19.37%. |

CH+CH), 6.489-6.503 (d, 1H, J= 7 Hz, Ar), 6.864-6.884 (dd, 1H, J =2 & 8 Hz, Ar), 7.134-7.138 (d, 1H, J= 2 Hz, Ar), 12.516 (bs, 1H, COOH, exch). $^{13}$C NMR (125 MHz, DMSO-$d_6$) (Figure 4b.7) δ: 24.105, 25.074, 26.644, 30.303, 30.826, 41.279, 115.777, 119.221, 125.274, 126.619, 130.125, 141.133, 144.949, 169.988, 198.274. APCI-MS (Figure 4b.8) shows $MH^+$ ion peak at *m/z* 271.36 (100%). Elemental analysis Calculated for $C_{15}H_{14}N_2O_3$: C, 66.66; H, 5.18; N, 10.37%. Found: C, 66.75; H, 5.27; N, 10.43%. Spectral and analytical data of **IVx** is in full agreement with the structure assigned to it.

Similarly compounds **IIIy** and **IIIz** (Scheme 4b.1) were converted to **IVy** & **IVz** respectively in quantitative yields. Spectral & analytical data of **IVy** & **IVz** reported in Table 4b.2 fully support the structures assigned to them.

Condensation of 4-amino-3-(1,3-dioxo-hexahydro-1H-isoindol-2(3H)-yl)benzoic acid (**IIIx**) with benzyl amine (**Va;** Scheme 4b.1) was carried out by grinding [50] both of them in equimolar ratio in a small mortar with a pestle for 20 minutes. Thin layer chromatography (TLC) of reaction mixture showed completion of reaction. Crude product so obtained was crystallized from methanol to give pure product 4-amino-N-benzyl-3-(1, 3-dioxo-hexahydro-1H-isoindol-2(3H)-yl) benzamide (**VIxa**; Scheme 4b.1) in 86% yield. IR spectrum of **VIxa** shows absorption bands at IR 3218 ($NH_2$), 1695,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PROCNO 1
F2 - Acquisition Parameters
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Time 09.11
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PULPROG zg30
TD 65536
SOLVENT DMSO
NS 16
DS 2
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1720407 sec
RG 144
DW 48.400 usec
DE 6.00 usec
TE 296.4 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 14.90 usec
PL1 2.00 dB
SFO1 500.1330885 MHz
F2 - Processing parameters
SI 32768
SF 500.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
12.516
7.138
7.134
6.884
6.880
6.868
6.864
6.503
6.489
5.050
4.079
3.372
2.737
2.720
2.686
2.658
2.516
2.512
2.509
1.838
1.824
1.818
1.807
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1.634
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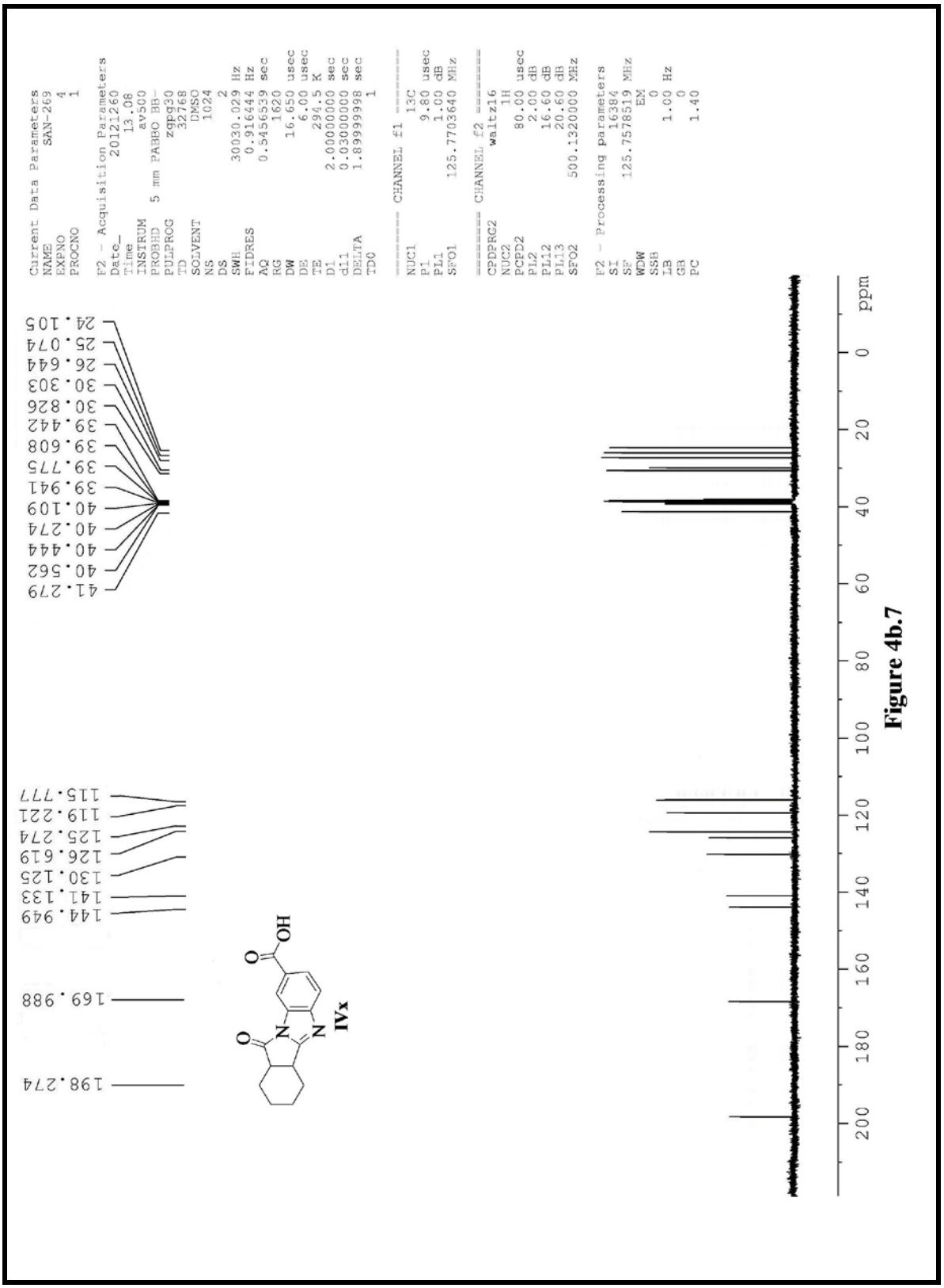
1.419
1.414
1.409
1.398
1.390
1.381
1.372
4.10
1.5
ppm
IVx
OH
O
N
N
O
0.96
4.10
2.14
1.99
2.00
1.06
0.96
1.00
ppm
0 1 2 3 4 5 6 7 8 9 10 11 12

**Figure 4b.6**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PULPROG zgpg30
TD 32768
SOLVENT DMSO
NS 1024
DS 2
SWH 30030.029 Hz
FIDRES 0.916444 Hz
AQ 0.5456539 sec
RG 1620
DW 16.650 usec
DE 6.00 usec
TE 294.5 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
TD0 1
CHANNEL f1
NUC1 13C
P1 9.80 usec
PL1 1.00 dB
SFO1 125.7703640 MHz
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 2.00 dB
PL12 16.60 dB
PL13 20.60 dB
SFO2 500.1320000 MHz
F2 - Processing parameters
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SF 125.7578519 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
41.279
40.562
40.444
40.274
40.109
39.941
39.775
39.608
39.442
30.826
30.303
26.644
25.074
24.105
198.274
169.988
144.949
141.133
130.125
126.619
125.274
119.221
115.777
IVx
ppm

**Figure 4b.7**

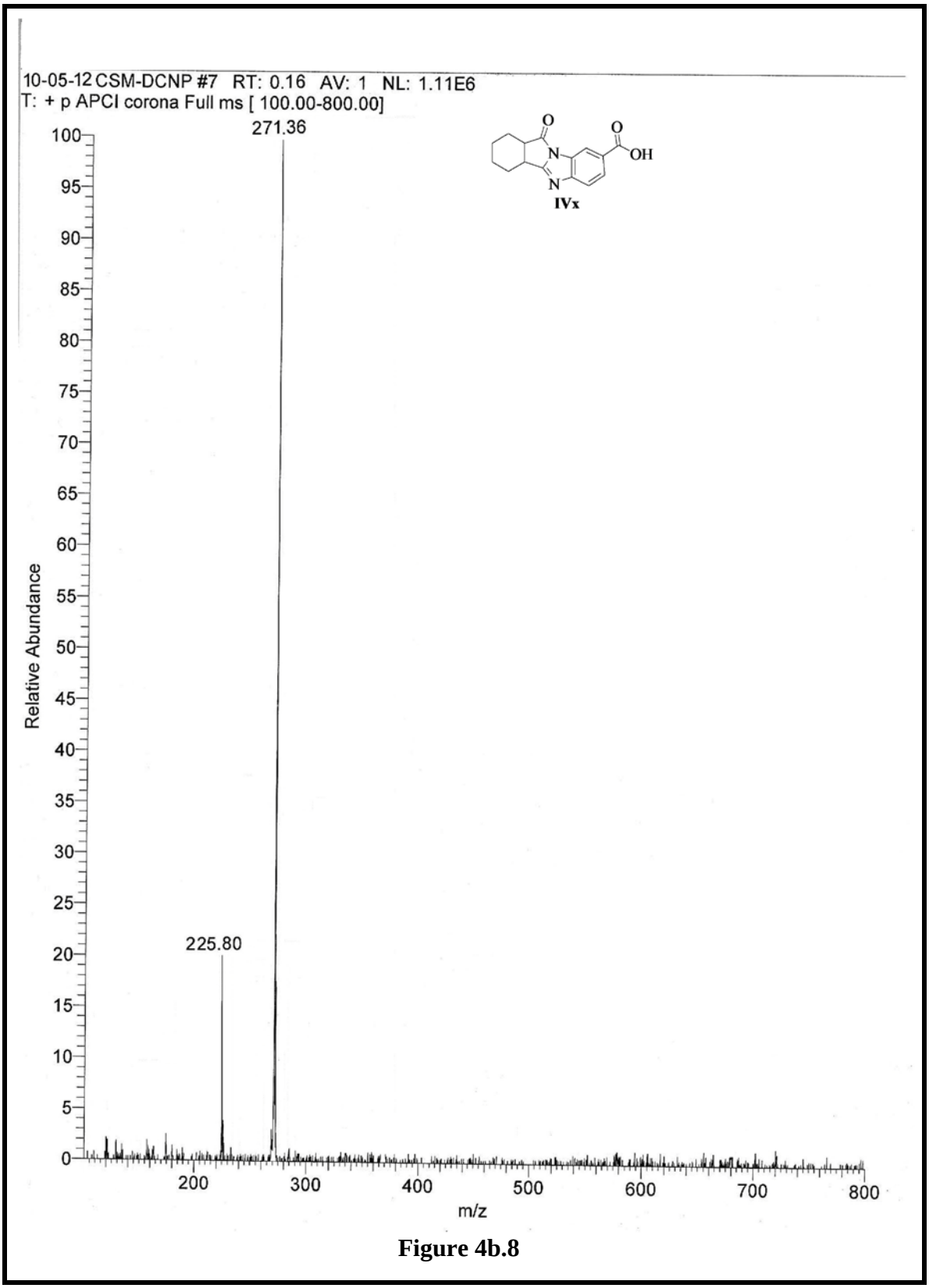
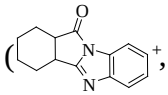
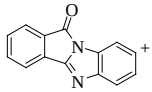
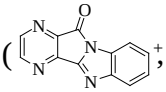
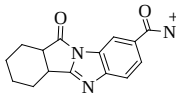
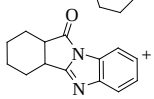
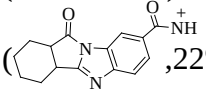
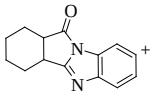
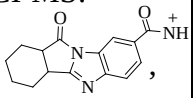
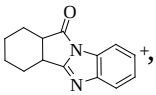

10-05-12 CSM-DCNP #7 RT: 0.16 AV: 1 NL: 1.11E6
T: + p APCI corona Full ms [ 100.00-800.00]
271.36
225.80
IVx
Relative Abundance
m/z
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
200
300
400
500
600
700
800

**Figure 4b.8**

**Table 4b.2: Physical constants and spectral data of compounds IVx-z and VIIxa-ze.**

| Comp no | Solvent of cryst./elution | m.p. ºC | Yield % | IR (KBr) $cm^{-1}$, $^1H$ (500MHz) & $^{13}C$ (125MHz) NMR (DMSO-$d_6$), $\delta$ J(Hz), APCI-MS (*m/z*; relt int %) |
|---|---|---|---|---|
| **1** | **2** | **3** | **4** | **5** |
| **IVx** | MeOH | >300 | 81 | IR 1684(>C=O), 1624(—C(=O)-N—), 1513 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$) δ: 1.372-1.458 (m, 4H, 2×$CH_2$), 1.623-1.679 (m, 2H, $CH_2$), 1.765-1.838 (m, 2H, $CH_2$), 2.649-2.737 (m, 2H, CH+CH), 6.489-6.503 (d, 1H, J= 7 Hz, Ar), 6.864-6.884 (dd, 1H, J =2 & 8 Hz, Ar), 7.134-7.138 (d, 1H, J= 2 Hz, Ar), 12.516 (bs, 1H, COOH, exch). $^{13}C$ NMR (125 MHz, DMSO-$d_6$) δ: 24.1, 25.0, 26.6, 30.3, 30.8, 41.2, 115.7, 119.2, 125.2, 126.6, 130.1, 141.1, 144.9, 169.9 and 198.2. APCI-MS: *m/z* 271.36 ($MH^+$, 100%), 225.80 (  , 21%), Anal. Calcd for $C_{15}H_{14}N_2O_3$: C, 66.66; H, 5.18; N, 10.37%. Found: C, 66.75; H, 5.27; N, 10.43%. |
| **IVy** | MeOH | >300 | 85 | IR 1686 (>C=O), 1616 ( —C(=O)-N— ), 1519 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$) δ: 6.485-6.500 (d, 1H J = 7.5 Hz, Ar), 6.854-6.874 (dd, 1H J = 2 & 8 Hz, Ar), 7.134-7.139 (d, 1H, J = 2.5 Hz, Ar), 7.578-7.619 (m, 1H, Ar), 7.658-7.695 (m, 2H, Ar), 7.840-7.856 (d, 1H, J = 8 Hz, Ar), 12.586 (bs, 1H, COOH, exch). $^{13}C$ NMR (125 MHz, DMSO-$d_6$) δ: 115.2, 119.1, 125.2, 126.8, 128.9, 129.2, 130.2, 131.7, 135.0, 135.9, 137.0, 141.3, 144.1, 169.5 and 190.2. APCI-MS: *m/z* 265.86 ($MH^+$, 100%), 219.21 (  , 21%). Anal. Calcd for $C_{15}H_8N_2O_3$: C, 68.18; H, 3.05; N, 10.60%. Found: C, 68.35; H, 3.43; N, 10.80%. |
| **IVz** | MeOH | >300 | 82 | IR 1683 (>C=O), 1612 (—C(=O)-N—), 1534 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$) δ: 6.485-6.500 (d, 1H, J= 7.5 Hz, Ar), 6.854-6.874 (dd, 1H, J =2 & 8 Hz, Ar), 7.134-7.139 (d, 1H, J= 2.5 Hz, Ar), 8.734 (s, 2H, Ar), 12.548 (bs, 1H, |

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| | | | | COOH, exch). $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ: 115.3, 119.1, 125.3, 126.5, 131.8, 141.0, 142.2, 144.0, 147.7, 148.4, 149.2, 169.9 and 190.0. APCI-MS: *m/z* 267.63 ($MH^+$, 100%), 221.13 (  ; 13%). Anal. Calcd for $C_{13}H_6N_4O_3$: C, 58.65; H, 2.27; N, 21.05%. Found: C, 58.54; H, 2.31; N, 21.14%. |
| **VIIxa** | MeOH | >300 | 89 | IR 3288 (NH), 1697, 1635 (>C=O), 1515 (Ar) $cm^{-1}$. $^1$H NMR (500 MHz, DMSO-$d_6$) δ: 1.374-1.455 (m, 4H, 2×$CH_2$), 1.623-1.678 (m, 2H, $CH_2$), 1.764-1.823 (m, 2H, $CH_2$), 2.658-2.738 (m, 2H, CH+CH), 4.089 (s, 2H, $CH_2$), 6.489-6.503 (d, 1H, J = 7 Hz, Ar), 6.864-6.884 (dd, 1H, J=2 & 8 Hz, Ar), 7.134-7.138 (d, 1H, J = 2 Hz, Ar), 7.287-7.354 (m, 5H, Ar), 8.135 (s, 1H, NH, exch). $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ: 24.2, 25.0, 26.6, 30.0, 30.8, 41.3, 44.4, 115.2, 116.4, 122.6, 126.7, 127.1, 127.9, 128.2, 130.9, 141.1, 142.1, 143.2, 167.8 and 198.7. APCI-MS: *m/z* 360.87 ($MH^+$, 100%), 268.24(  , 19%), 225.69 (  , 11%), Anal. Calcd for $C_{22}H_{21}N_3O_2$: C, 73.52; H, 5.89; N, 11.69%. Found: C, 73.64; H, 5.83; N, 11.78%. |
| **VIIxb** | MeOH | >300 | 93 | IR 3289 (NH), 1668, 1636 (>C=O), 1515 (Ar) $cm^{-1}$. $^1$H NMR (500 MHz, DMSO-$d_6$) δ: 1.374-1.446 (m, 4H, 2×$CH_2$), 1.626-1.679 (m, 2H, $CH_2$), 1.765-1.823 (m, 2H, $CH_2$), 2.643-2.739 (m, 2H, CH+CH), 4.089 (s, 2H, $CH_2$), 6.497-6.513 (d, 1H, J = 8 Hz, Ar), 6.854-6.874 (dd, 1H, J=2 & 8 Hz, Ar), 7.133-7.139 (d, 1H, J = 3 Hz, Ar), 7.233-7.418 (m, 2H, Ar), 7.743-7.779 (m, 1H, Ar), 8.138 (s, 1H, NH, exch), 8.450-8.466 (d, 1H, J = 8 Hz, Ar). $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ: 24.2, 25.0, 26.6, 30.0, 30.8, 41.3, 49.0, 115.2, 116.1, 120.1, 122.4, 124.3, 128.0, 130.2, 136.0, 141.6, 142.3, 149.2, |

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| | | | | 156.5, 167.8 and 198.9. APCI-MS: *m/z* 361.69 ($MH^+$, 100%),268.29 (  ,22%), 225.69 (  , 14%). Anal. Calcd for $C_{21}H_{20}N_4O_2$: C, 70.00; H, 5.55; N, 15.55%. Found: C, 69.87; H, 5.50; N, 15.64%. |
| **VIIxc** | MeOH | >300 | 87 | IR 3268 (NH), 1682, 1622 (>C=O), 1532, 1422 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$) δ: 1.355-1.444 (m, 4H, 2×$CH_2$), 1.622-1.688 (m, 2H, $CH_2$), 1.761-1.837 (m, 2H, $CH_2$), 2.645-2.752 (m, 2H, CH+CH), 4.082 (s, 2H, $CH_2$), 6.493-6.509 (d, 1H, J = 8 Hz, Ar), 6.849-6.869 (dd, 1H, J=2 & 8 Hz, Ar), 7.134-7.138 (d, 1H, J = 2 Hz, Ar), 7.333-7.369 (dt, 1H, J=2 & 8 Hz, Ar), 7.842-7.858 (d, 1H, J = 8 Hz, Ar), 8.140 (s, 1H, NH, exch), 8.321-8.414 (m, 2H, Ar). $^{13}C$ NMR (125 MHz, DMSO-$d_6$) δ: 24.1, 25.1, 26.7, 30.1, 30.8, 41.3, 44.3, 115.1, 116.5, 122.1, 124.5, 127.3, 130.5, 134.1, 135.8, 141.7, 142.1, 147.2, 150.7, 167.3 and 198.7. APCI-MS: *m/z* 361.55 ($MH^+$, 100%), 268.45 (  , 18%), 225.62(  , 14%). Anal. Calcd for $C_{21}H_{20}N_4O_2$: C, 70.00; H, 5.55; N, 15.55%. Found: C, 69.86; H, 5.64; N, 15.67%. |
| **VIIxd** | MeOH | >300 | 95 | IR 3296 (NH), 1680, 1623 (>C=O), 1532, 1425 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$) δ: 1.374-1.446 (m, 4H, 2×$CH_2$), 1.625-1.681 (m, 2H, $CH_2$), 1.765-1.842 (m, 2H, $CH_2$), 2.640-2.737 (m, 2H, CH+CH), 4.099 (s, 2H, $CH_2$), 6.487-6.503 (d, 1H, J = 8 Hz, Ar), 6.844-6.864 (dd, 1H, J=2 & 8 Hz, Ar), 7.134-7.137 (d, 1H, J = 1.5 Hz, Ar), 7.327-7.343 (d, 2H, J = 8 Hz, Ar), 8.122 (s, 1H, NH, exch), 8.435-8.451 (d, 2H, J = 8 Hz, Ar). $^{13}C$ NMR (125 MHz, DMSO-$d_6$) δ: 24.2, 25.1, 26.1, 30.0, 30.9, 41.3, 44.7, 115.5, 116.1, 122.1, 124.3, 127.3, 130.5, 140.7, |

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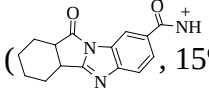
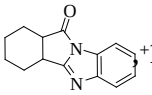
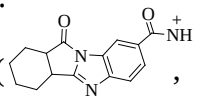
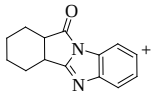
| | | | | 142.4, 147.1, 149.7, 167.2 and 198.7. APCI-MS: *m/z* 361.35 ($MH^+$, 100%), 268.45 (  , 15%), 225.72 (  , 10%). Anal. Calcd for $C_{21}H_{20}N_4O_2$: C, 70.00; H, 5.55; N, 15.55%. Found: C, 69.87; H, 5.63; N, 15.44%. |
| **VIIxe** | MeOH | >300 | 88 | IR 3201 (NH), 1688, 1670 (>C=O), 1612, 1478 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$) δ: 1.374-1.446 (m, 4H, 2×$CH_2$), 1.626-1.679 (m, 2H, $CH_2$), 1.764-1.830 (m, 2H, $CH_2$), 2.661-2.716 (m, 2H, CH+CH), 4.082 (s, 2H, $CH_2$), 6.182-6.212 (t, 1H, J = 7.5 Hz, Ar), 6.484-6.500 (d, 1H, J = 8 Hz, Ar), 6.730-6.747 (d, 1H, J= 8.5 Hz, Ar), 6.863-6.879 (d, 1H, J = 8 Hz, Ar), 7.134-7.138 (d, 1H, J = 2 Hz, Ar), 7.330-7.346 (d, 1H, J = 8 Hz, Ar), 8.129 (s, 1H, NH, exch). $^{13}C$ NMR (125 MHz, DMSO-$d_6$) δ: 24.2, 25.3, 26.0, 30.0, 30.9, 38.2, 41.3, 106.5, 110.1, 115.5, 116.1, 122.3, 128.3, 130.8, 141.8, 142.4, 143.1, 148.7, 167.1 and 199.0. APCI-MS: *m/z* 350.69 ($MH^+$, 100%), 268.38 (  , 22%), 225.02 (  , 11%), Anal. Calcd for $C_{20}H_{19}N_3O_3$: C, 68.76; H, 5.48; N, 12.03%. Found: C, 68.87; H, 5.53; N, 12.15%. |
| **VIIya** | MeOH | >300 | 93 | IR 3267 (NH), 1684, 1623 (>C=O), 1519 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$) δ: 4.089 (s, 2H, $CH_2$), 6.486-6.501 (d, 1H, J = 7.5 Hz, Ar), 6.854-6.874 (dd, 1H, J = 2 & 8 Hz, Ar), 7.134-7.138 (d, 1H, J = 2 Hz, Ar), 7.279-7.340 (m, 5H, Ar), 7.579-7.619 (m, 1H, Ar), 7.659-7.695 (m, 2H, Ar), 7.842-7.858 (d, 1H, J = 8 Hz, Ar), 8.136 (s, 1H, NH, exch). $^{13}C$ NMR (125 MHz, DMSO-$d_6$) δ: 44.7, 115.1, 116.1, 122.2, 126.1, 127.0, 127.9, 128.1, 128.9, 129.2, 130.8, 131.7, 135.1, 135.9, 137.0, 141.4, 142.1, 142.9, |

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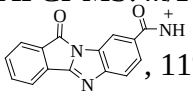
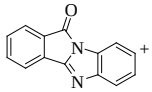
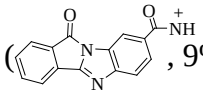
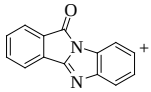
| | | | | 167.5 and 190.1. APCI-MS: *m/z* 354.82 ($MH^+$, 100%) , 262.63 (  , 11%), 219.23 (  , 14%). Anal. Calcd for $C_{22}H_{15}N_3O_2$: C, 74.78; H, 4.25; N, 11.89%. Found: C, 74.71; H, 4.31; N, 11.96%. |
| **VIIyb** | MeOH | >300 | 94 | IR 3241 (NH), 1678, 1644 (>C=O), 1582, 1512, 1474 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$) δ: 4.087 (s, 2H, $CH_2$), 6.484-6.500 (d, 1H, J = 8 Hz, Ar), 6.829-6.865 (m, 1H, Ar), 7.134-7.138 (d, 1H, J = 2 Hz, Ar), 7.266-7.413 (m, 2H, Ar), 7.587-7.605 (m, 1H, Ar), 7.614-7.685 (m, 2H, Ar), 7.733-7.749 (d, 1H, J = 8 Hz, Ar), 7.755-7.798 (dt, 1H, J=1.5 & 8 Hz, Ar), 8.122 (s, 1H, NH, exch), 8.451-8.467 (d, 1H, J = 8 Hz, Ar). $^{13}C$ NMR (125 MHz, DMSO-$d_6$) δ: 49.0, 115.2, 116.8, 120.2, 122.1, 124.0, 128.0, 128.9, 129.2, 130.2, 131.0, 135.0, 135.7, 136.1, 138.0, 141.4, 142.1, 148.2, 156.0, 167.5 and 190.1. APCI-MS: *m/z* 355.35 ($MH^+$, 100%), 262.15 (  , 9%), 219.27 (  , 16%). Anal. Calcd for $C_{21}H_{14}N_4O_2$: C, 71.18; H, 3.98; N, 15.81%. Found: C, 71.29; H, 3.94; N, 15.90%. |
| **VIIyc** | MeOH | >300 | 91 | IR 3369 (NH), 1680, 1613 (>C=O), 1512 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$) δ: 4.089 (s, 2H, $CH_2$), 6.488-6.503 (d, 1H, J = 7.5 Hz, Ar), 6.848-6.868 (dd, 1H, J= 2 & 8 Hz, Ar), 7.134-7.137 (d, 1H, J = 1.5 Hz, Ar), 7.347-7.387 (dt, 1H, J= 2 & 9 Hz, Ar), 7.587-7.605 (m, 1H, Ar), 7.614-7.677 (m, 2H, Ar), 7.759-7.775 (d, 1H, J = 8 Hz, Ar), 7.840-7.856 (d, 1H, J= 8 Hz, Ar), 8.127 (s, 1H, NH, exch), 8.324-8.413 (m, 2H, Ar). $^{13}C$ NMR (125 MHz, DMSO-$d_6$) δ: 44.2, 115.0, 116.8, 122.2, 124.1, 127.1, 128.0, 129.2, 130.2, 131.1, 134.0, 135.1, 135.8, 136.1, 137.0, 141.1, 142.3, 147.0, 150.1, 167.9 and |

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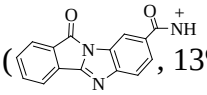
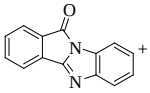
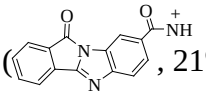
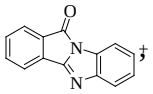
| | | | | 190.4. APCI-MS: *m/z* 355.12 ($MH^+$, 100%), 262.15 (  , 13%), 219.16 (  , 10%), Anal. Calcd for $C_{21}H_{14}N_4O_2$: C, 71.18; H, 3.98; N, 15.81%. Found: C, 71.28; H, 3.95; N, 15.93%. |
| **VIIyd** | MeOH | >300 | 96 | IR 3361 (NH), 1678, 1615 (>C=O), 1512 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$) δ: 4.094 (s, 2H, $CH_2$), 6.487-6.503 (d, 1H, J = 8 Hz, Ar), 6.847-6.867 (dd, 1H, J= 1.5 & 8 Hz, Ar), 7.134-7.137 (d, 1H, J = 1.5 Hz, Ar), 7.323-7.340 (d, 2H, J = 8.5 Hz, Ar), 7.589- 7.616 (m, 1H, Ar), 7.659-7.685 (m, 2H, Ar), 7.818-7.836 (d, 1H, J= 9 Hz, Ar), 8.118 (s, 1H, NH, exch), 8.457-8.473 (d, 2H, J = 8 Hz, Ar). $^{13}C$ NMR (125 MHz, DMSO-$d_6$) δ: 44.0, 115.6, 116.5, 122.2, 124.1, 127.5, 128.3, 129.2, 130.0, 131.1, 135.0, 135.9, 137.0, 141.1, 142.9, 147.4, 150.0, 167.5 and 190.4. APCI-MS: *m/z* 355.18 ($MH^+$, 100%), 262.30 (  , 21%), 219.46 (  , 8%). Anal. Calcd for $C_{21}H_{14}N_4O_2$: C, 71.18; H, 3.98; N, 15.81%. Found: C, 71.31; H, 3.94; N, 15.76%. |
| **VIIye** | MeOH | >300 | 93 | IR 3312 (NH), 1697, 1653 (>C=O), 1594, 1497 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$) δ: 4.086 (s, 2H, $CH_2$), 6.181-6.212 (t, 1H, J = 7.5 Hz, Ar), 6.484-6.500 (d, 1H, J = 8 Hz, Ar), 6.730-6.747 (d, 1H, J = 8.5 Hz, Ar), 6.863-6.879 (d, 1H, J= 8 Hz, Ar), 7.134-7.137 (d, 1H, J = 1.5 Hz, Ar), 7.330-7.347 (d, 1H, J = 8.5 Hz, Ar), 7.587-7.614 (m, 1H, Ar), 7.659-7.685 (m, 2H, Ar), 7.801-7.817 (d, 1H, J= 8 Hz, Ar), 8.124 (s, 1H, NH, exch). $^{13}C$ NMR (125 MHz, DMSO-$d_6$) δ: 38.3, 105.9, 110.6, 115.5, 116.7, 122.8, 127.5, 128.9, 129.1, 130.0, 131.4, 135.8, 136.3, 137.0, 142.7, 143.4, 145.4, 148.8, 168.0 and 190.2. APCI-MS: *m/z* 344.84 ($MH^+$, 100%),262.70 |

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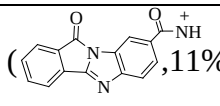
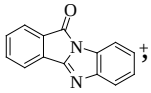
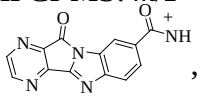
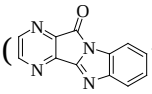
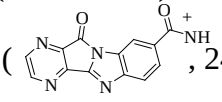
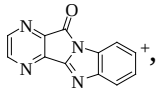
| | | | | (  ,11%), 219.67 (  ; 8%).<br>Anal. Calcd for $C_{20}H_{13}N_3O_3$: C, 69.97; H, 3.78; N, 12.24%. Found: C, 69.87; H, 3.87; N, 12.32%. |
| **VIIza** | MeOH | >300 | 91 | IR 3309 (NH), 1683, 1612 (>C=O), 1544, 1513 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$) δ: 4.086 (s, 2H, $CH_2$), 6.486-6.501 (d, 1H, J = 7.5 Hz, Ar), 6.855-6.875 (dd, 1H, J=2.5 & 8 Hz, Ar), 7.135-7.139 (d, 1H, J = 2 Hz, Ar), 7.279-7.342 (m, 5H, Ar), 8.222 (s, 1H, NH, exch), 8.840 (s, 2H, Ar). $^{13}C$ NMR (125 MHz, DMSO-$d_6$) δ: 44.3, 115.1, 116.0, 122.1, 126.5, 127.3, 127.9, 128.3, 130.8, 140.0, 141.8, 142.4, 143.0, 147.7, 148.7, 149.2, 168.0 and 191.0. APCI-MS: *m/z* 356.53 ($MH^+$, 100%), 264.28 (  , 31%), 221.13 (  , 8%), Anal. Calcd for $C_{20}H_{13}N_5O_2$: C, 67.60; H, 3.66; N, 19.71%. Found: C, 67.49; H, 3.64; N, 19.79%. |
| **VIIzb** | MeOH | >300 | 90 | IR 3404 (NH), 1664, 1614 (>C=O), 1476 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$) δ: 4.099 (s, 2H, $CH_2$), 6.484-6.499 (d, 1H, J = 7.5 Hz, Ar), 7.060-7.078 (dd, 1H, J=2.5 & 7 Hz, Ar), 7.134-7.139 (d, 1H, J = 2.5 Hz, Ar), 7.225-7.261 (q, 1H, J=8 & 10 Hz, Ar), 7.388-7.413 (d, 1H, J=12.5 Ar), 7.749-7.799 (dt, 1H, J=1.5 & 8.5 Hz, Ar), 8.120 (s, 1H, NH, exch), 8.450-8.466 (d, 1H, J = 8 Hz, Ar), 8.846 (s, 2H, Ar). $^{13}C$ NMR (125 MHz, DMSO-$d_6$) δ: 49.2, 115.1, 116.0, 121,3, 123.1, 124.5, 128.3, 130.1, 136.3, 140.8, 141.0, 142.8, 147.4, 148.0, 148.7, 150.7, 156.2, 168.0 and 191.0. APCI-MS: *m/z* 357.83 ($MH^+$, 100%), 264.24 (  , 24%), 221.03 (  , 8%), Anal. Calcd for $C_{19}H_{12}N_6O_2$: C, 64.04; H, 3.37; N, 23.59%. Found: C, 64.15; H, 3.43; N, |

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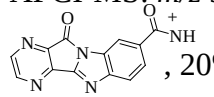
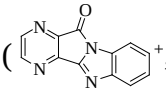
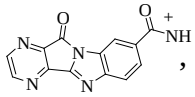
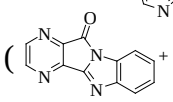
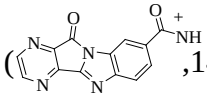
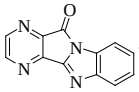
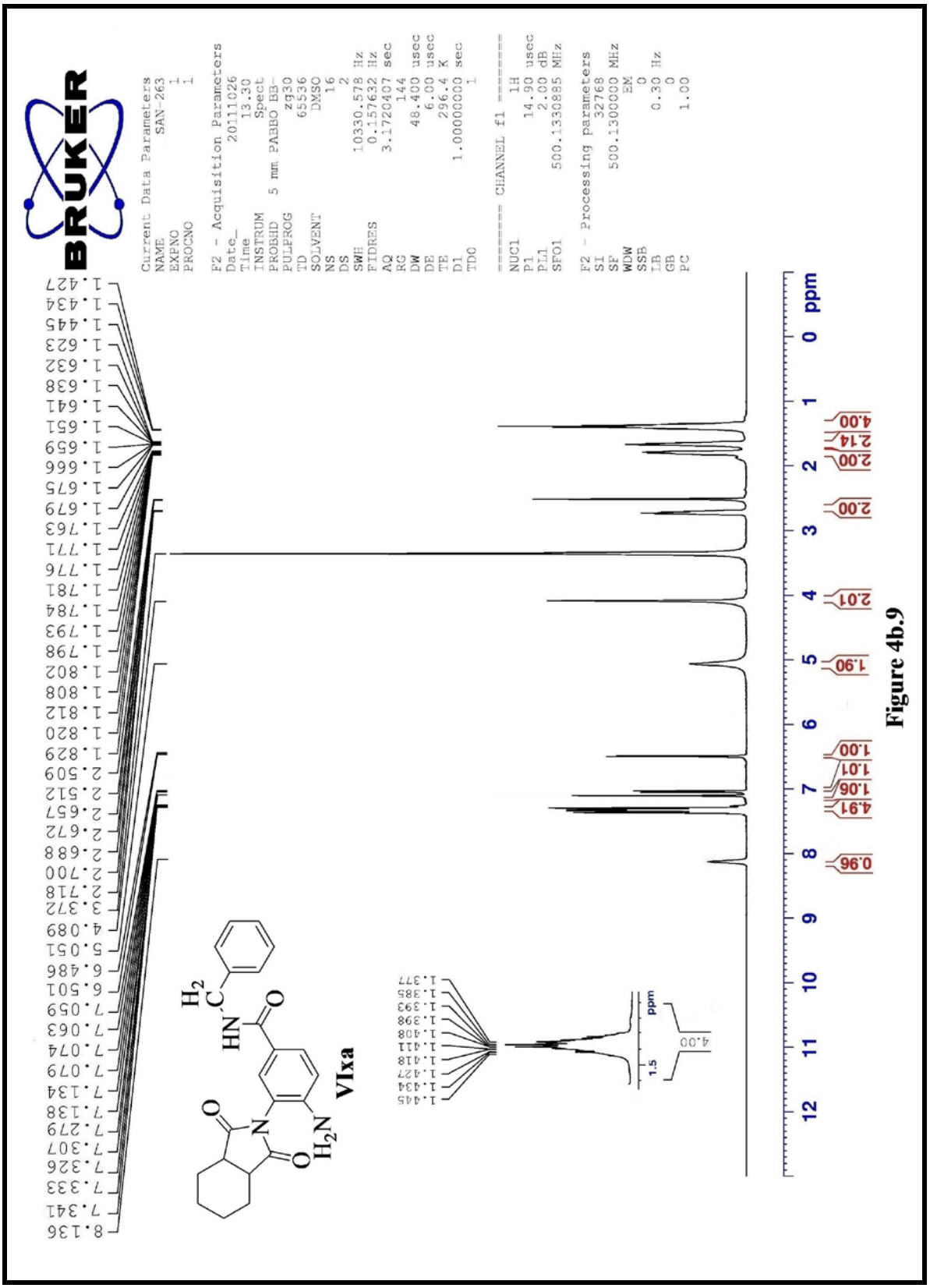
|---|---|---|---|---|
| | | | | 23.67%. |
| **VIIzc** | MeOH | >300 | 88 | IR 3293 (NH), 1666, 1613 (>C=O), 1474 (Ar) $cm^{-1}$. $^{1}H$ NMR (500 MHz, DMSO-$d_6$) δ: 4.082 (s, 2H, $CH_2$), 6.486-6.503 (d, 1H, J = 8.5 Hz, Ar), 6.849-6.869 (dd, 1H, J=2 & 8 Hz, Ar), 7.132-7.137 (d, 1H, J = 2.5 Hz, Ar), 7.339-7.375 (dt, 1H, J=2 & 8 Hz, Ar), 7.842-7.858 (d, 1H, J = 8 Hz, Ar), 8.128 (s, 1H, NH, exch), 8.324-8.413(m, 2H, Ar), 8.875 (s, 2H, Ar). $^{13}C$ NMR (125 MHz, DMSO-$d_6$) δ: 44.7, 115.1, 116.0, 122.3, 123.1, 127.5, 131.3, 134.1, 135.3, 140.8, 141.0, 142.8, 147.0, 147.9, 148.7, 149.5, 150.2, 167.0 and 190.4. APCI-MS: *m/z* 357.60 ($MH^+$, 100%), 264.58 (  , 20%), 221.53 (  , 11%). Anal. Calcd for $C_{19}H_{12}N_6O_2$: C, 64.04; H, 3.37; N, 23.59%. Found: C, 64.35; H, 3.54; N, 23.72%. |
| **VIIzd** | MeOH | >300 | 96 | IR 3288 (NH), 1670 (>C=O), 1596, 1532, 1422, (Ar) $cm^{-1}$. $^{1}H$ NMR (500 MHz, DMSO-$d_6$) δ: 4.103 (s, 2H, $CH_2$), 6.487-6.503 (d, 1H, J = 8 Hz, Ar), 6.847-6.867 (dd, 1H, J=2 & 8 Hz, Ar), 7.133-7.137 (d, 1H, J = 2 Hz, Ar), 7.334-7.350 (d, 2H, J = 8 Hz, Ar), 8.122 (s, 1H, NH, exch), 8.431-8.447 (d, 2H, J = 8 Hz, Ar), 8.912 (s, 2H, Ar). $^{13}C$ NMR (125 MHz, DMSO-$d_6$) δ: 44.1, 115.1, 116.0, 122.9, 124.1, 128.9, 131.9, 141.8, 142.0, 142.8, 147.0, 147.9, 148.7, 149.4, 150.1, 167.4 and 190.1. APCI-MS: *m/z* 357.29 ($MH^+$, 100%), 264.29 (  , 18%), 221.09 (  , 8%), Anal. Calcd for $C_{19}H_{12}N_6O_2$: C, 64.04; H, 3.37; N, 23.59%. Found: C, 64.41; H, 3.12; N, 23.73%. |
| **VIIze** | MeOH | >300 | 91 | IR 3317 (NH), 1682, 1619 (>C=O), 1536 (Ar) $cm^{-1}$. $^{1}H$ NMR (500 MHz, DMSO-$d_6$) δ: 4.101 |

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| | | | | (s, 2H, $CH_2$), 6.182-6.213 (t, 1H, J = 7.5 Hz, Ar), 6.484-6.500 (d, 1H, J = 8 Hz, Ar), 6.731-6.746 (d, 1H, J= 7.5 Hz, Ar), 6.862-6.878 (d, 1H, J = 8 Hz, Ar), 7.134-7.139 (d, 1H, J = 2.5 Hz, Ar), 7.330-7.346 (d, 1H, J = 8 Hz, Ar), 8.133 (s, 1H, NH, exch), 8.888 (s, 2H, Ar). $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ: 38.7, 106.2, 110.1, 115.0, 116.9, 123.1, 128.9, 130.9, 141.8, 142.0, 142.8, 143.9, 147.0, 148.4, 149.1, 150.0, 167.4 and 190.1. APCI-MS: *m/z* 346.80 ($MH^+$, 100%), 264.35 (  ,14%), 221.59 (  , 7%). Anal. Calcd for $C_{18}H_{11}N_5O_3$: C, 62.61; H, 3.18; N, 20.29%. Found: C, 62.72; H, 3.26; N, 20.37%. |

1676, 1612 (>C=O), 1478 (Ar) $cm^{-1}$. $^1$H NMR (500 MHz, DMSO-$d_6$) (Figure 4b.9) δ: 1.377-1.445 (m, 4H, 2×$CH_2$), 1.623-1.679 (m, 2H, $CH_2$), 1.763-1.829 (m, 2H, $CH_2$), 2.657-2.718 (m, 2H, CH+CH), 4.089 (s, 2H, $CH_2$), 5.051 (bs, 2H, $NH_2$, exch), 6.486-6.500 (d, 1H, J= 7.0 Hz, Ar), 7.059-7.079 (dd, 1H, J= 2.5 & 8 Hz, Ar), 7.134-7.138 (d, 1H, J = 2.0 Hz, Ar), 7.279-7.341 (m, 5H, Ar), 8.136 (s, 1H, NH, exch). $^{13}$C NMR (125 MHz, DMSO-$d_6$) (Figure 4b.10) δ: 24.265, 26.653, 37.942, 44.390, 116.208, 118.442, 123.608, 124.775, 126.109, 127.941, 128.141, 129.109, 141.108, 145.207, 167.143, 174.749. APCI-MS (Fig 4b.11) show $MH^+$ ion peak at *m/z* 378.65 (100%). Elemental analysis Calculated for $C_{22}H_{23}N_3O_3$: C, 70.02; H, 6.10; N, 11.14%. Found: C, 70.32; H, 6.29; N, 11.34%. Spectral and analytical data of **VIxa** fully support the structure assigned to it.

Similarly condensation of **IIIx**, **IIIy** and **IIIz** with benzyl amine (**Va**), pyridin-2-ylmethanamine (**Vb**), pyridin-3-ylmethanamine (**Vc**), pyridin-4-ylmethanamine (**Vd**) and furan-2-ylmethanamine (**Ve**) gave corresponding condensation products **VIxa-ze**


BRUKER
Current Data Parameters
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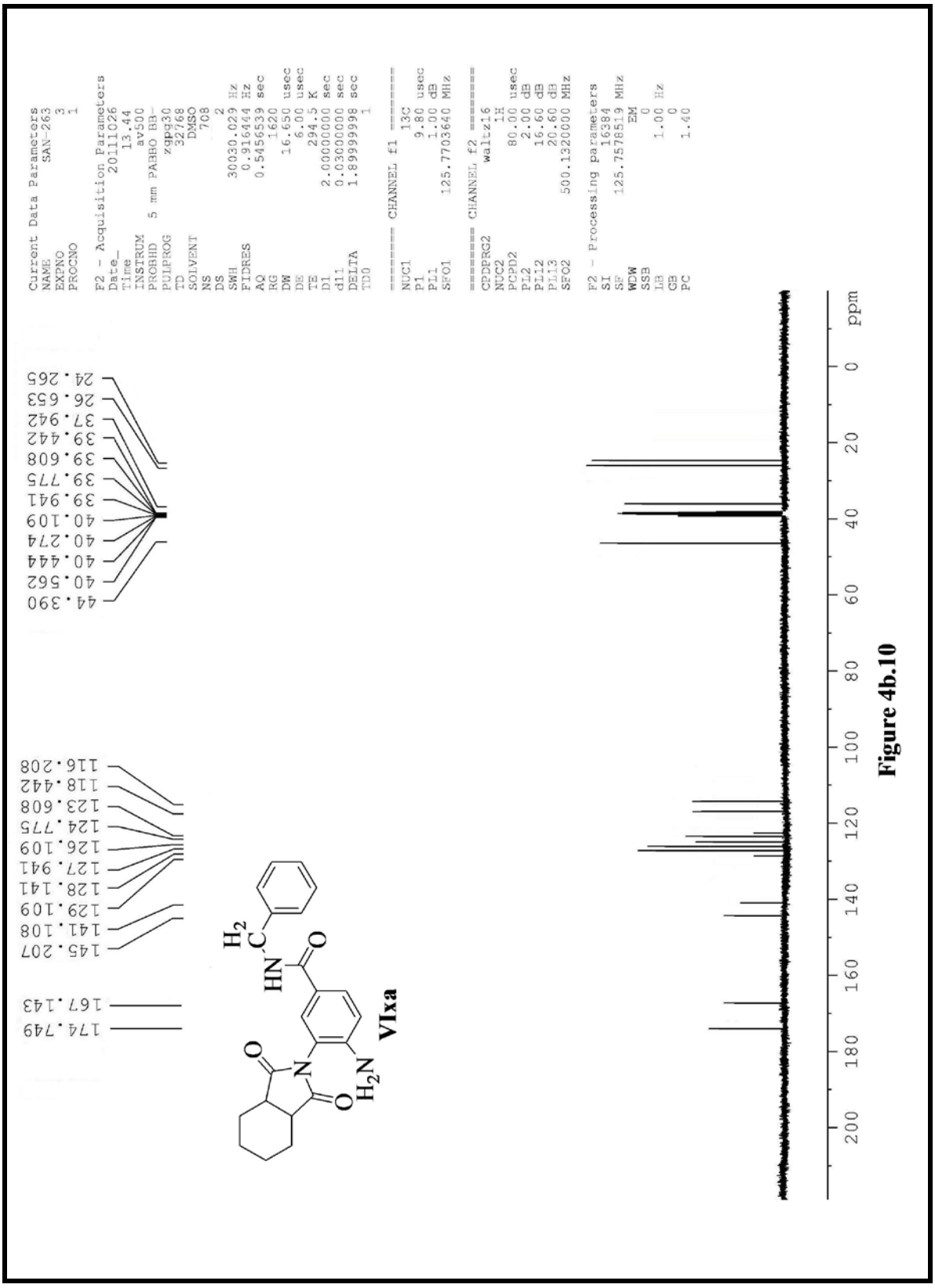
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20111026
Time 13.30
INSTRUM Spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 65536
SOLVENT DMSO
NS 16
DS 2
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1720407 sec
RG 144
DW 48.400 usec
DE 6.00 usec
TE 296.4 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 14.90 usec
PL1 2.00 dB
SFO1 500.1330885 MHz
F2 - Processing parameters
SI 32768
SF 500.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
VIxa
ppm
4.00
1.5
0.96
4.91
1.06
1.01
1.00
1.90
2.01
2.00
2.00
2.14
4.00

**Figure 4b.9**


Current Data Parameters
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PROCNO 1
F2 - Acquisition Parameters
Date_ 20111026
Time 13.44
INSTRUM av500
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 32768
SOLVENT DMSO
NS 768
DS 2
SWH 30030.029 Hz
FIDRES 0.916444 Hz
AQ 0.5456539 sec
RG 1620
DW 16.650 usec
DE 6.00 usec
TE 294.5 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 9.80 usec
PL1 1.00 dB
SFO1 125.7703640 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 2.00 dB
PL12 16.60 dB
PL13 20.60 dB
SFO2 500.1320000 MHz
F2 - Processing parameters
SI 16384
SF 125.7578519 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
174.749
167.143
145.207
141.108
129.109
128.141
127.941
126.109
124.775
123.608
118.442
116.208
44.390
40.562
40.444
40.274
40.109
39.941
39.775
39.608
39.442
37.942
26.653
24.265
VIxa
200
180
160
140
120
100
80
60
40
20
0
ppm

**Figure 4b.10**

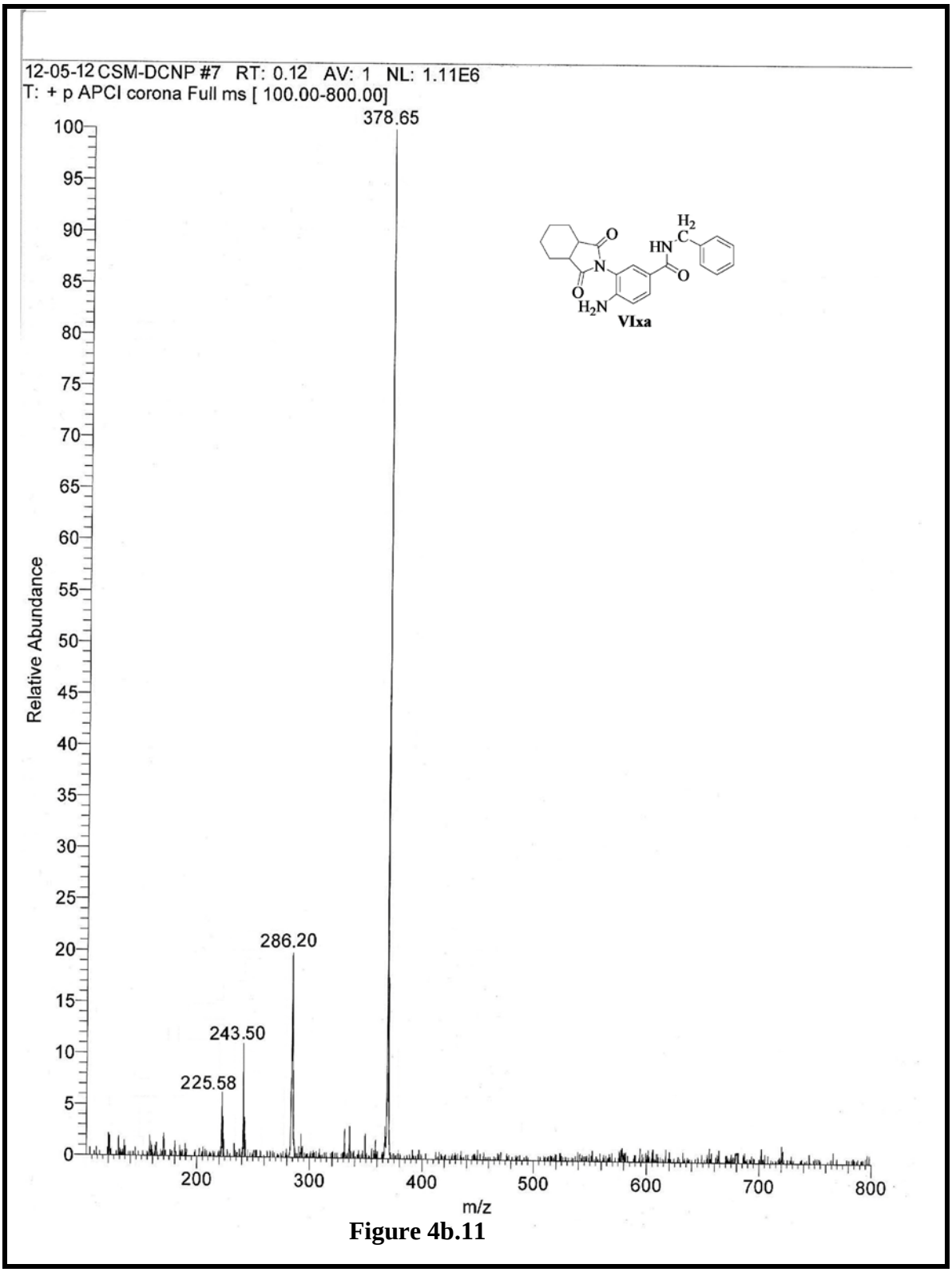

12-05-12 CSM-DCNP #7 RT: 0.12 AV: 1 NL: 1.11E6
T: + p APCI corona Full ms [ 100.00-800.00]
378.65
286.20
243.50
225.58
Relative Abundance
m/z
VIxa

**Figure 4b.11**

(Scheme 4b.1) in excellent yields. Physical constants, spectral data and elemental analysis of **VIxa-ze** reported in Table 4b.1 are in full agreement with the structures assigned to them.

Condensation of 8-(1, 2, 3, 4, 4a, 11a hexahydro-11-oxobenzimidazo [2, 1-a] isoindol)-oic acid (**IVx**; Scheme 4b.1) with benzyl amine (**Va**) was carried out by grinding both of them in equimolar ratio in a small mortar with a pestle for 20 minutes. Thin layer chromatography of the reaction mixture indicated completion of reaction. Crude product so obtained was purified by crystallization from methanol to give pure product N-benzyl-8-(1, 2, 3, 4, 4a, 11a hexahydro-11-oxobenzimidazo [2, 1-a] isoindol)-amide (**VIIxa**) in 89% yield. IR spectrum of **VIIxa** shows absorption bands at 3288 (NH), 1697, 1635 (>C=O), 1515 (Ar) $cm^{-1}$. $^{1}H$ NMR (500 MHz, DMSO-$d_6$) (Figure 4b.12) δ: 1.374-1.455 (m, 4H, 2×$CH_2$), 1.623-1.678 (m, 2H, $CH_2$), 1.764-1.823 (m, 2H, $CH_2$), 2.658-2.738 (m, 2H, CH+CH), 4.089 (s, 2H, $CH_2$), 6.489-6.503 (d, 1H, J = 7 Hz, Ar), 6.864-6.884 (dd, 1H, J=2 & 8 Hz, Ar), 7.134-7.138 (d, 1H, J = 2 Hz, Ar), 7.287-7.354 (m, 5H, Ar), 8.135 (s, 1H, NH, exch). $^{13}C$ NMR (125 MHz, DMSO-$d_6$) (Figure 4b.13) δ: 24.215, 25.080, 26.657, 30.052, 30.804, 41.390, 44.424, 115.208, 116.442, 122.608, 126.775, 127.109, 127.941, 128.274, 130.941, 141.109, 142.108, 143.227, 167.898 and 198.749. APCI-MS (Figure 4b.14) show $MH^+$ ion peak at *m/z* 360.87 (100%). Elemental analysis Calculated for $C_{22}H_{21}N_3O_2$: C, 73.52; H, 5.89; N, 11.69%. Found: C, 73.64; H, 5.83; N, 11.78%. Spectral and analytical data of **VIIxa** fully support the structure assigned to it.

Similarly condensation of **IVx**, **IVy** and **IVz** with benzyl amine (**Va**), pyridin-2-ylmethanamine (**Vb**), pyridin-3-ylmethanamine (**Vc**), pyridin-4-ylmethanamine (**Vd**) and

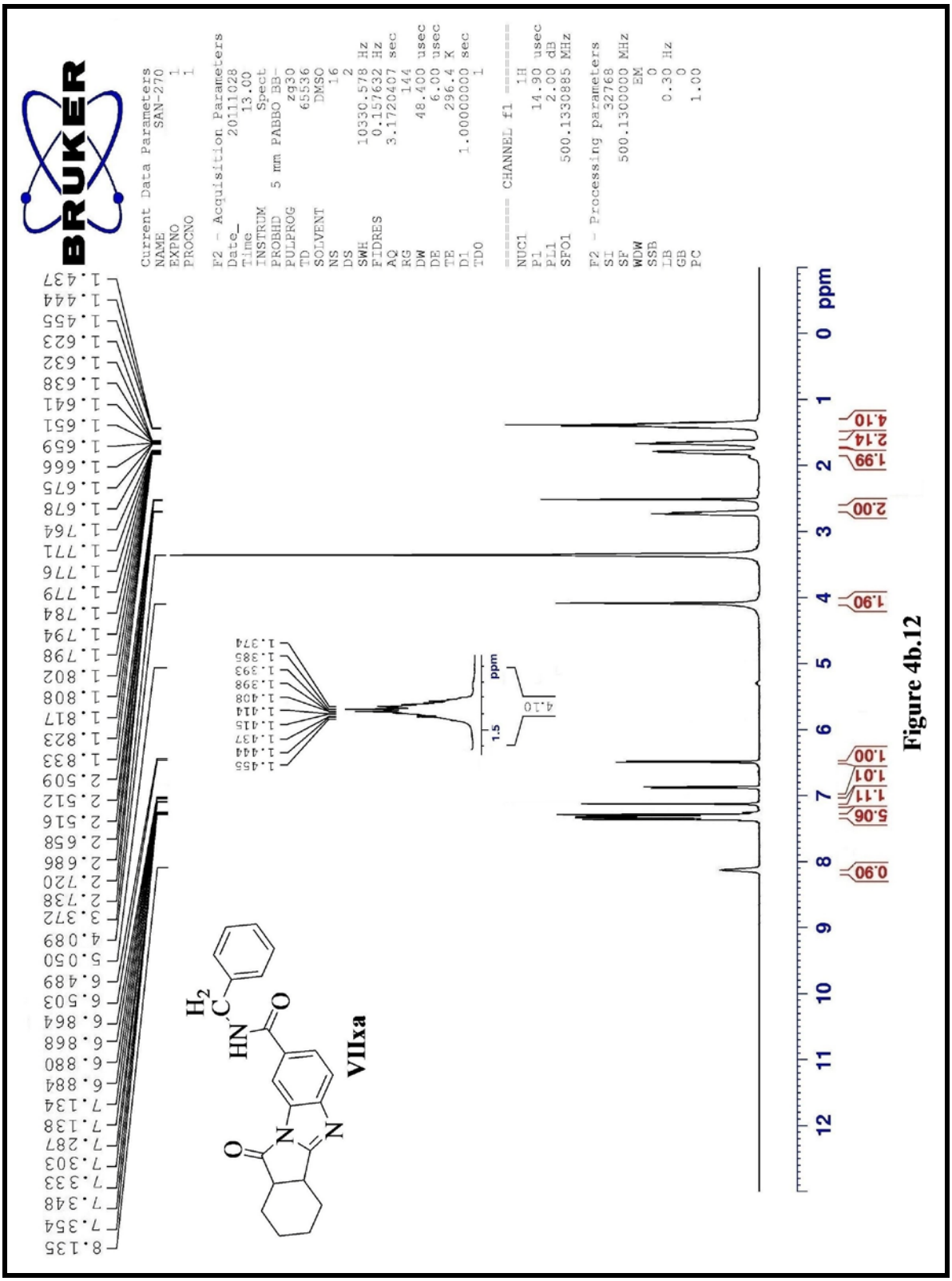
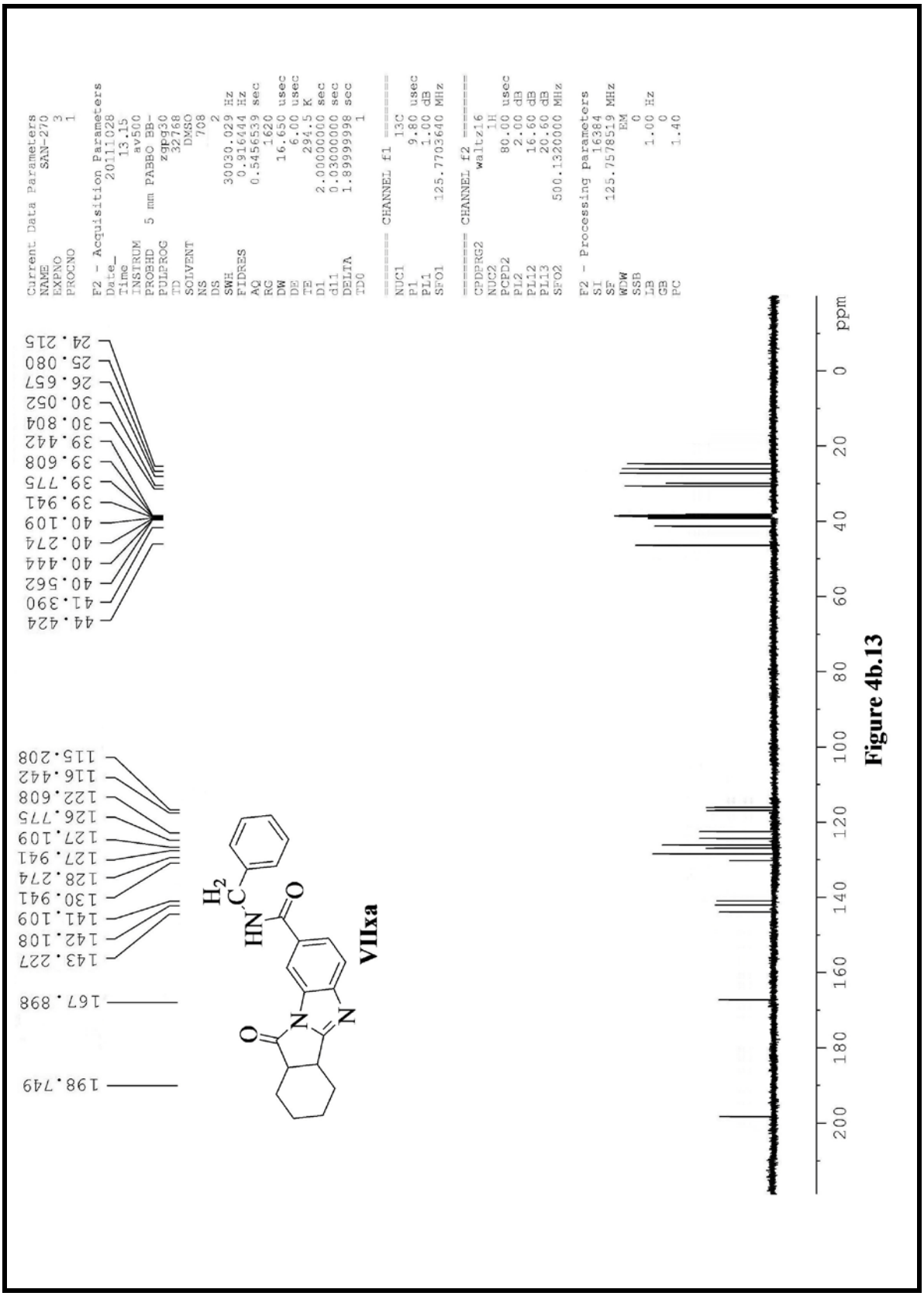



Figure 4b.12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EXPNO 3
PROCNO 1
F2 - Acquisition Parameters
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Time 13.15
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PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 32768
SOLVENT DMSO
NS 708
DS 2
SWH 30030.029 Hz
FIDRES 0.916444 Hz
AQ 0.5456539 sec
RG 1620
DW 16.650 usec
DE 6.00 usec
TE 294.5 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
TD0 1
CHANNEL f1
NUC1 13C
P1 9.80 usec
PL1 1.00 dB
SFO1 125.7703640 MHz
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 2.00 dB
PL12 16.60 dB
PL13 20.60 dB
SFO2 500.1320000 MHz
F2 - Processing parameters
SI 16384
SF 125.7578519 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
24.215
25.080
26.657
30.052
30.804
39.442
39.608
39.775
39.941
40.109
40.274
40.444
40.562
41.390
44.424
115.208
116.442
122.608
126.775
127.109
127.941
128.274
130.941
141.109
142.108
143.227
167.898
198.749
VIIxa
200
180
160
140
120
100
80
60
40
20
0
ppm

**Figure 4b.13**

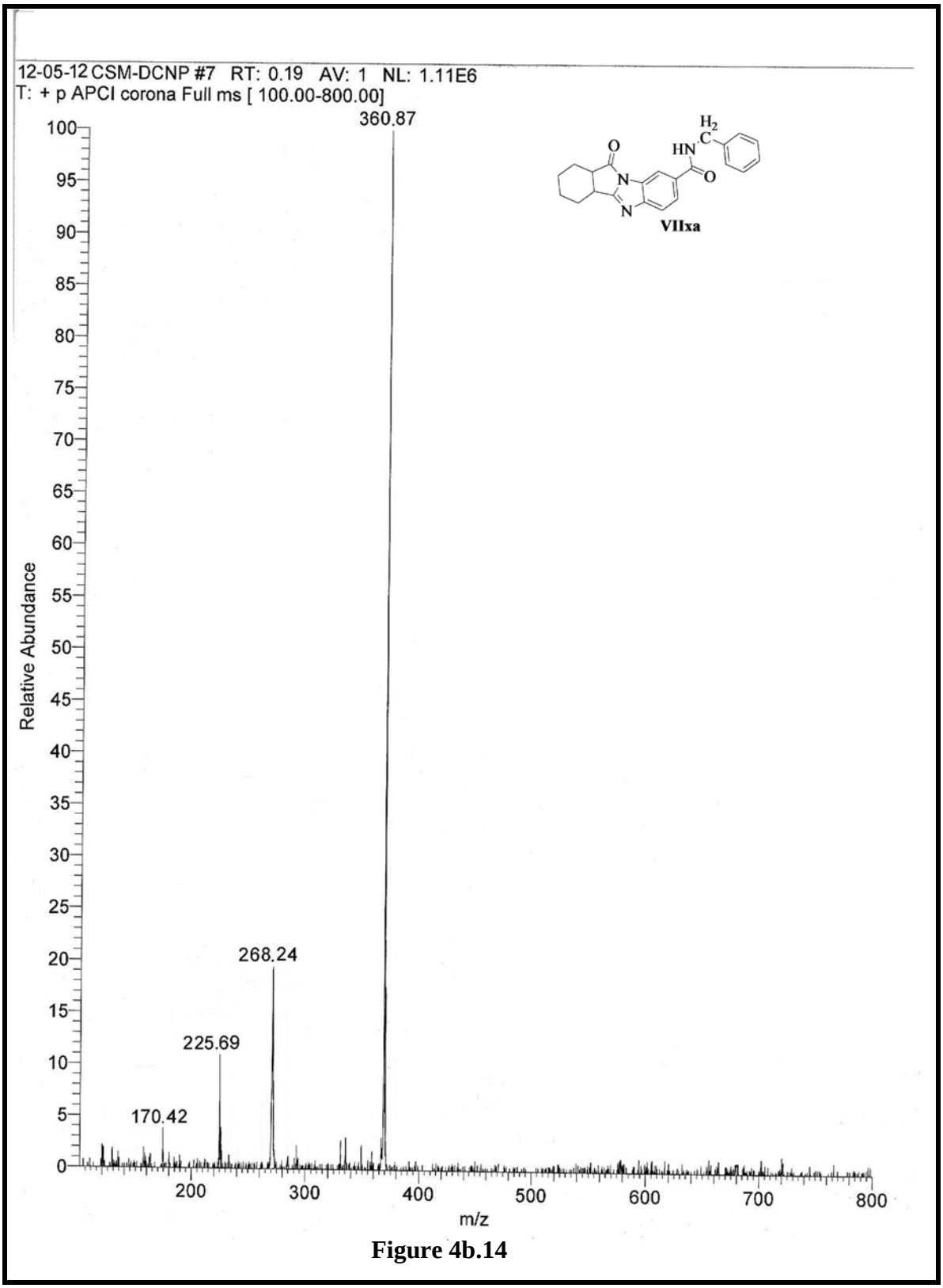
12-05-12 CSM-DCNP #7 RT: 0.19 AV: 1 NL: 1.11E6
T: + p APCI corona Full ms [ 100.00-800.00]
360.87
268.24
225.69
170.42
Relative Abundance
m/z
VIIxa

**Figure 4b.14**

furan-2-ylmethanamine (**Ve**) gave the corresponding condensation products **VIIxa-ze** (Scheme 4b.1) in excellent yields. Physical constants, spectral data and elemental analysis reported in Table 4b.2 fully support the structures assigned to them.

**4b.2.2 Biological results and discussion**

Fully characterized and purified compounds **IIIx-z**, **IVx-z**, **VIxa-ze** and **VIIxa-ze** were screened for anti-inflammatory activity [21; Chapter 2] using carrageenan induced paw oedema assay and results are summarized in Table 4b.3. A look at Table 4b.3 indicates that compounds **VIyc** and **VIIzd** exhibited good anti-inflammatory activity i.e. 34% and 37% respectively at 50 mg/kg p.o. as compared to ibuprofen which showed 39% activity at 50 mg/kg p.o.

Compounds **IIIx-z**, **IVx-z**, **VIxa-ze** and **VIIxa-ze** were screened *in vitro* for anticancer activity [32] against five human cancer cell lines i.e. breast (T47D), lung (NCl H-522), colon (HCT-15), ovary (PA-1) and liver (HepG-2) in concentration of $1\times10^{-5}$ M and results are summarized in Table 4b.3. A look at Table 4b.3 indicates that compounds **VIzc**, **VIIzd** (lung NCI H-522), **VIye**, **VIIxd**, **VIIyd**, **VIIzc**, **VIIzd** (colon HCT-15), **VIxc**, **VIzc** (ovary PA-1), **VIxc**, **VIyb**, **VIzc** (liver Hep G-2) exhibited good anticancer activity against various cancer cell lines mentioned above. Compounds **VIxc**, **VIyb**, **VIye**, **VIzc, VIIxd**, **VIIyd**, **VIIzc** and **VIIzd** which showed good anticancer activity were further studied and their $IC_{50}$ values for various cancer cell lines and normal cell lines (COS-1) was determined and reported in Table 4b.4.

Anti-inflammatory activity of isoindole and pyrrolopyrazine derivatives reported in literature are comparable to ibuprofen [51, 52] whereas isoindole derivatives reported in this thesis are also comparable to ibuprofen but pyrrolopyrazine derivatives are less

Table-4b.3 Anti-inflammatory** and *in vitro* anticancer** activity of compounds **IIIx-z, IVx-z, VIxa-ze, VIIxa-ze**

| Compd. No. | Anti-inflammatory activity (%) at 50 mg/kg p.o. | [a]Anticancer activity at a concentration of $1\times10^{-5}$ M | | | | |
|---|---|---|---|---|---|---|
| | | Breast T47D | Lung NCI H-522 | Colon HCT-15 | Ovary PA1 | Liver HepG2 |
| **1** | 2 | **3** | **4** | **5** | **6** | **7** |
| **IIIx** | 12 | 09 | 16 | 16 | 06 | 29 |
| **IIIy** | 18 | 20 | 30 | 27 | 15 | 25 |
| **IIIz** | 18 | 24 | 04 | 18 | 10 | 03 |
| **IVx** | 18 | 11 | 18 | 15 | 19 | 13 |
| **IVy** | 18 | NT | NT | NT | NT | NT |
| **IVz** | 15 | 29 | 13 | 23 | 27 | 08 |
| **VIxa** | 21 | 32 | 29 | 18 | 23 | 07 |
| **VIxb** | 27 | 14 | 10 | 09 | 05 | 07 |
| **VIxc** | 24 | 04 | 23 | 19 | **32** | **47** |
| **VIxd** | 22 | 22 | 14 | 23 | 08 | 20 |
| **VIxe** | 18 | 08 | 16 | 21 | 14 | 20 |
| **VIya** | 27 | 11 | 21 | 18 | 25 | 32 |
| **VIyb** | 28 | 09 | 29 | 06 | 17 | **37** |
| **VIyc** | **34** | 07 | 25 | 23 | 13 | 12 |
| **VIyd** | 30 | 02 | 16 | 20 | 12 | 19 |
| **VIye** | 21 | 08 | 18 | **41** | 27 | 23 |
| **VIza** | 21 | 15 | 22 | 24 | 08 | 31 |
| **VIzb** | 23 | 15 | 16 | 01 | 17 | 26 |
| **VIzc** | 24 | 02 | **32** | 03 | 11 | **33** |

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| **VIzd** | 26 | 19 | 28 | 22 | 01 | 27 |
| **VIze** | 21 | 14 | 25 | 09 | 09 | 19 |
| **VIIxa** | 15 | 06 | 14 | 10 | 24 | 20 |
| **VIIxb** | 21 | 19 | 15 | 28 | 25 | 19 |
| **VIIxc** | 24 | 13 | 05 | 20 | 06 | 03 |
| **VIIxd** | 24 | 17 | 20 | **37** | 26 | 30 |
| **VIIxe** | 18 | 22 | 18 | 20 | 08 | 27 |
| **VIIya** | 31 | 22 | 07 | 27 | 20 | 07 |
| **VIIyb** | 24 | 13 | 19 | 24 | 10 | 26 |
| **VIIyc** | 29 | 19 | 13 | 06 | 08 | 11 |
| **VIIyd** | 32 | 11 | 04 | **35** | 25 | 03 |
| **VIIye** | 21 | 18 | 21 | 27 | 11 | 30 |
| **VIIza** | 22 | 09 | 28 | 23 | 13 | 19 |
| **VIIzb** | 23 | 23 | 18 | 10 | 12 | 15 |
| **VIIzc** | 33 | 04 | 25 | **35** | **33** | 27 |
| **VIIzd** | **37** | 09 | **33** | **30** | 13 | 25 |
| **VIIze** | 27 | 21 | 08 | 20 | 09 | 11 |
| Ibuprofen | 39 | - | - | - | - | - |
| [b]5-FU | - | 18 | 28 | 26 | 25 | 31 |
| [b]CYC-PHO | - | 29 | 11 | 11 | 22 | 31 |
| [c]CYC-HEXI | - | 21 | 17 | 09 | 36 | 32 |

[a] Compounds tested in triplicate, data expressed as mean value of three independent experiments.
[b] 5-FU 5-Fluorouracil; [c] CYC-PHO Cyclophosphamide; [d] CYC-HEXI Cycloheximide.
Bold values represent compounds showing good anticancer activity. NT Not Tested.
[**] We are thankful to Dr. Partha Roy, Department of Biotechnology, Indian Institute of Technology-Roorkee, Roorkee for these results.

**Table 4b.4** $IC_{50}$ values[a, b] of *in vitro* anticancer activity** of active compounds.

| Comp No | $IC_{50}$ (μM) | | | | | |
|---|---|---|---|---|---|---|
| | Breast T47D | Lung NCI H-522 | Colon HCT-15 | Ovary PA-1 | Liver HepG-2 | Normal cell COS-1 |
| **VIxc** | 93.15±4.78 | 24.44±3.61 | 24.29±2.81 | **17.83±2.39** | **09.11±1.77** | 117.53±3.66 |
| **VIyb** | 47.78±3.72 | 17.24±2.45 | 84.78±3.23 | 28.33±3.04 | **12±1.67** | 119.67±3.37 |
| **VIye** | 57.32±4.51 | 31.33±3.75 | **11.17±2.05** | 17.35±2.34 | 20.14±3.49 | 105.81±3.08 |
| **VIzc** | 89.97±4.98 | **16.43±2.32** | 103.8±4.14 | 43.66±3.73 | **4.56±1.95** | 129.67±4.67 |
| **VIIxd** | 31.77±3.25 | 29.21±2.24 | **13.17±1.87** | 18.22±1.72 | 14.33±2.09 | 130.76±5.07 |
| **VIIyd** | 39.21±1.46 | 89.54±2.11 | **13.02±2.32** | 19.08±2.76 | 97±3.12 | 121.29±2.28 |
| **VIIzc** | 86.58±2.33 | 23.27±1.59 | **16.16±1.98** | **17.01±2.09** | 19.64±2.22 | 122.48±1.98 |
| **VIIzd** | 51.33±2.58 | **16.66±1.34** | **19.11±3.79** | 41.88±2.62 | 24.51±2.66 | 125.59±2.34 |
| **[c]5-FU** | 51.8±2.34 | 56.76±3.4 | 45.01±1.45 | 39.5±4.32 | 29.87±1.82 | 110±8.98 |
| **[d]CYC-PHO** | 70.1±2.32 | 67.9±3.09 | 74.32±4.98 | 64.12±5.43 | 55.3±3.59 | 125.43±9.24 |
| **[e]CYC-*HEXI*** | 65.13±7.31 | 60.1±5.34 | 54.13±4.65 | 40.6±2.09 | 57.12±4.65 | 128.31±7.89 |

[a]50% growth inhibition as determined by MTT assay (24hr drug exposure).
[b]Compounds tested in triplicate, data expressed as mean value ± SD of three independent experiments.
[c]5-FU 5-Fluorouracil.
[d]CYC-PHO Cyclophosphamide.
[e]CYC-HEXI Cycloheximide.
** We are thankful to Dr. Partha Roy, Department of Biotechnology, Indian Institute of Technology-Roorkee, Roorkee for these results.

active than ibuprofen. A comparison between bicyclic and tetracyclic systems reported in this thesis show compounds **IIIz**, **VIxa**, **VIxb**, **VIyb**, **VIyc**, **VIyd** showed better anti-inflammatory activity than corresponding tertacyclic systems whereas in case of **IIIx**, **VIya**, **VIzc**, **VIzd**, **VIze** corresponding tetracyclic systems are more active.

Anticancer activity of isoindole derivatives against HepG-2 cancer cell line reported in this thesis is better than reported in literature [53] but in case of NCI-H522, HCT-15 and T47D cancer cell lines anticancer activity reported in literature [54] is better than reported in this thesis. Anticancer activity of pyrrolopyrazine against NCI-H522 reported in this thesis is better than reported in literature [55]. A comparison between bicyclic and tetracyclic systems reported in this thesis show that compounds **VIxc**, **VIyb**, **VIye** exhibit better anticancer activity than corresponding tetracyclic systems whereas compounds **VIIxd**, **VIIyd** and **VIIzd** exhibit better anticancer activity than corresponding bicyclic systems. In case of **VIzc** and **VIIzc** both bicyclic and tetracyclic compounds were found to be active.

Cyclization of **IIIx-z** to **IVx-z** (Scheme 4b.1) did not make much difference in their anti-inflammatory or anticancer activity (Table 4b.3). However coupling of **IIIy** with pyridin-3-ylmethanamine and **IVz** with pyridin-4-ylmethanamine to give corresponding coupled products **VIyc** & **VIIzd** (Scheme 4b.1) proved beneficial for anti-inflammatory activity (Table 4b.3). Although other compounds reported in Table 4b.3 are also similar with number of heteroatom present in them for interaction with the target but above mentioned molecules i.e. **VIyc** & **VIIzd** are having structures which can effectively interact with the targets both from electronic & stereochemical point of view and hence showed good anti-inflammatory activity.

Coupling of **IIIx**, **IIIz**, **IVz** with pyridin-3-ylmethanamine; **IVx**, **IVy**, **IVz** with pyridin-4-ylmethanamine and **IIIy** with pyridin-2-ylmethanamine & furan-2-ylmethan amine to give **VIxc**, **VIzc**, **VIIzc**, **VIIxd**, **VIIyd**, **VIIzd**, **VIyb** & **VIye** (Scheme 4b.1) proved beneficial for anticancer activity (Table 4b.3, Table 4b.4).

## 4b.3 Experimental

### *4b.3.1 General*

Microwave reactor model CEM DISCOVER model NO 908010 and microwave oven model M197DL (Samsung) were used for microwave irradiation. Melting points (mp) were determined on a JSGW apparatus and are uncorrected. IR spectra were recorded using a Perkin Elmer 1600 FT spectrometer. $^{1}H$ and $^{13}C$ NMR spectra were recorded on a Bruker WH-500 spectrometer at a *ca* 5-15% (*w/v*) solution in deuterated solvent (TMS as internal standard). APCI mass was recorded using Finnigan Mat LCQ Mass Spectrometer. Elemental analysis was carried out on a Vario EL III elementor. Thin layer chromatography (TLC) was performed on silica gel G for TLC (Merck) and spots were visualized by iodine vapor or by irradiation with ultraviolet light (254nm). Compounds were purified by crystallization from methanol. Physical constants, spectral data and elemental analysis of **IIIx-z, VIxa-ze** and **IVx-z, VIIxa-ze** are reported in Table-4b.1 and 4b.2 respectively.

### 4b.3.2 General procedure for synthesis of isoindole, pyrrolopyrazine derivatives (IIIx-z)

4b.3.2.1 Synthesis of 4-amino-3-(1, 3-dioxo-hexahydro-1H-isoindol-2(3H)-yl) benzoic acid (**IIIx**)

Cis-1,2-cyclohexane dicarboxylic acid (0.172 g; 1.0 mmol) (**Ix**; Scheme 4b.1) and 3,4-diaminobenzoic acid (0.152 g; 1.0 mmol) (**III**; Scheme 4b.1) were mixed thoroughly and this reaction mixture was subjected to microwave irradiation at 600 Watt for 3 minutes and then progress of reaction was monitored by TLC on silica gel using ethyl acetate: methanol (2:3) as mobile phase. TLC indicated presence of starting materials. This reaction mixture was again irradiated for 2 minutes (600 watt) and TLC was performed which showed absence of starting materials and hence reaction is complete. Crude product so obtained was purified by crystallization from methanol to give pure 4-amino-3-(1, 3-dioxo-hexahydro-1H-isoindol-2(3H)-yl) benzoic acid (**IIIx**). Yield 0.248 g (86%).

Alternatively a mixture of Cis-1,2-cyclohexane dicarboxylic acid (0.172 g; 1.0 mmol) (**Ix**; Scheme 4b.1) and 3, 4-diaminobenzoic acid (0.152 g; 1.0 mmol) (**II**; Scheme 4b.1) were mixed thoroughly and this reaction mixture was subjected to microwave irradiation at 90$^{o}$C for 5 min. TLC of this reaction mixture on silica gel using ethyl acetate: methanol (2:3) as mobile phase showed absence of starting materials, hence the reaction is complete. This crude product was crystallized from methanol to give pure condensed product 4-amino-3-(1, 3-dioxo-hexahydro-1H-isoindol-2(3H)-yl) benzoic acid (**IIIx**). Yield 0.241 g (84%). Similarly other derivatives i.e. 4-amino-3-(1, 3-dioxoisoindolin-2-yl) benzoic acid (**IIIy**) and 4-amino-3-(5, 7-dioxo-5H-pyrrolo [3, 4-b] pyrazin-6(7H)-yl) benzoic acid (**IIIz**) were synthesized and reported in Table 4b.1.

### 4b.3.3 General procedure for synthesis of benzimidazoisoindole and benzimidazopyrrolopyrazine derivatives (IVx-z)

4b.3.3.1 Synthesis of 8-(1, 2, 3, 4, 4a, 11a hexahydro-11-oxobenzimidazo [2, 1-a] isoindol)-oicacid (**IVx**)

4-Amino-3-(1,3-dioxo-hexahydro-1H-isoindol-2(3H)-yl)benzoic acid (0.288 g; 1.0 mmol) (**IIIx**; Scheme 4b.1) was irradiated at 850 Watt for 5 minutes and then progress of reaction was monitored by TLC on silica gel using ethyl acetate: methanol (2:3) as mobile phase. TLC indicated absence of starting material and hence reaction is complete. Crude product so obtained was purified by crystallization from methanol to give pure cyclized product i.e. 8-(1, 2, 3, 4, 4a, 11a hexahydro-11-oxobenzimidazo [2, 1-a] isoindol)-oicacid (**IVx**; Scheme 4b.1). Yield 0.221 g (82%).

Alternatively the above compound was subjected to microwave irradiation at 130ºC for 5 min. TLC of this reaction mixture on silica gel using ethyl acetate: methanol (2:3) as mobile phase showed absence of starting material. Crude product so obtained was crystallized from methanol to give pure cyclized product **IVx** (Scheme 4b.1). Yield 0.218 g (81%). Similarly other derivatives i.e. 8-(11H, 11-oxobenzimidazo [2, 1-a] isoindol)-oicacid (**IVy**) and 8-(11H,11-oxobenz[4',5']imidazo[1',2:1,2] pyrrolo[3,4-b]pyr azin)-oicacid (**IVz**) were synthesized and reported in Table 4b.2.

### 4b.3.4 General procedure for synthesis of isoindole and pyrrolopyrazine derivatives (VIxa-ze)

4b.3.4.1 Synthesis of 4-amino-N-benzyl-3-(1, 3-dioxo-hexahydro-1H-isoindol-2(3H)-yl) benzamide (**VIxa**)

4-Amino-3-(1, 3-dioxo-hexahydro-1H-isoindol-2(3H)-yl) benzoic acid (0.288 g; 1.0 mmol) (**IIIx**; Scheme 4b.1) and benzyl amine (0.107 g; 1.0 mmol) (**Va**; Scheme 4b.1) were grinded together in a small mortar with a pestle for 20 minutes. TLC of the reaction

mixture on silica gel using ethyl acetate: methanol (2:3) mobile phase exhibited that the reaction is complete. The crude product so obtained was purified by crystallization from methanol to give pure product 4-amino-N-benzyl-3-(1, 3-dioxo-hexahydro-1H-isoindol-2(3H)-yl) benzamide (**VIxa;** Scheme 4b.1). Yield 0.324 g (86%). Similarly other derivatives (**VIxb-ze**) i.e. 4-amino-3-(1, 3-dioxo-hexahydro-1H-isoindol-2(3H)-yl)-N-(pyridin-2-ylmethyl) benzamide (**VIxb**), 4-amino-3-(1, 3-dioxo-hexahydro-1H-isoindol-2(3H)-yl)-N-(pyridin-3-ylmethyl) benzamide (**VIxc**), 4-amino-3-(1, 3-dioxo-hexahydro-1H-isoindol-2(3H)-yl)-N-(pyridin-4-ylmethyl) benzamide (**VIxd**), 4-amino-3-(1,3-dioxo-hexahydro-1H-isoindol-2(3H)-yl)-N-(furan-2-ylmethyl) benzamide (**VIxe**), 4-amino-N-benzyl-3-(1, 3-dioxoisoindolin-2-yl) benzamide (**VIya**), 4-amino-3-(1, 3-dioxoisoindolin-2-yl)-N-(pyridin-2-ylmethyl) benzamide (**VIyb**), 4-amino-3-(1, 3-dioxoisoindolin -2-yl)-N-(pyridin-3-ylmethyl) benzamide (**VIyc**), 4-amino-3-(1,3-dioxoisoin dolin-2-yl)-N-(pyridin-4-ylmethyl) benzamide (**VIyd**), 4-amino-3-(1, 3-dioxoisoindolin-2-yl)-N-(furan-2-ylmethyl) benzamide (**VIye**), 4-amino-N-benzyl-3-(5, 7-dioxo-5H-pyrrolo [3, 4-b] pyrazin-6(7H)-yl) benzamide (**VIza**), 4-amino-3-(5, 7-dioxo-5H-pyrrolo [3, 4-b] pyrazin-6(7H)-yl)-N-(pyridin-2-ylmethyl) benzamide (**VIzb**), 4-amino-3-(5, 7-dioxo-5H-pyrrolo [3, 4-b] pyrazin-6(7H)-yl)-N-(pyridin-3-ylmethyl) benzamide (**VIzc**), 4-amino-3-(5, 7-dioxo-5H-pyrrolo [3, 4-b] pyrazin-6(7H)-yl)-N-(pyridin-4-ylmethyl) benzamide (**VIzd**) and 4-amino-3-(5, 7-dioxo-5H-pyrrolo [3, 4-b] pyrazin-6(7H)-yl)-N-(furan-2-ylmethyl) benzamide (**VIze**) were synthesized and reported in Table 4b.1.

### 4b.3.5 General procedure for synthesis of benzimidazoisoindole and benzimidazopyrrolopyrazine derivatives (VIIxa-ze)

4b.3.5.1 Synthesis of N-benzyl-8-(1, 2, 3, 4, 4a, 11a hexahydro-11-oxobenz imidazo [2, 1-a] isoindol)-amide (**VIIxa**)

8-(1, 2, 3, 4, 4a, 11a Hexahydrobenzimidazo [2, 1-a] isoindol-11-one)-oicacid (0.270 g; 1.0 mmol) (**IVx**; Scheme 4b.1) and benzyl amine (0.107 g; 1.0 mmol) (**Va**; Scheme 4b.1) were grinded together in a small mortar with a pestle for 20 minutes. TLC of the reaction mixture on silica gel using ethyl acetate: methanol (2:3) mobile phase indicated completion of the reaction. The crude product so obtained was purified by crystallization from methanol to give pure product N-benzyl-8-(1, 2, 3, 4, 4a, 11a hexahydro-11-oxobenzimidazo [2, 1-a] isoindol)-amide (**VIIxa;** Scheme 4b.1). Yield 0.319 g (89%). Similarly other derivatives (**VIIxb-ze**) i.e. N-pyridin-2-ylmethyl-8-(1, 2, 3, 4, 4a, 11a hexahydro-11-oxobenzimidazo [2, 1-a] isoindol)-amide (**VIIxb**), N-pyridin-3-ylmethyl-8-(1, 2, 3, 4, 4a, 11a hexahydro-11-oxobenzimidazo [2, 1-a] isoindol)-amide (**VIIxc**), N-pyridin-4-ylmethyl-8-(1, 2, 3, 4, 4a, 11a hexahydro-11-oxobenzimidazo [2, 1-a] isoindol)-amide (**VIIxd**), N-furan-2-ylmethyl-8-(1, 2, 3, 4, 4a, 11a hexahydro-11-oxobenzimidazo [2, 1-a] isoindol)-amide (**VIIxe**), N-benzyl-8-(11H,11-oxobenzimidazo[2,1-a]isoindol)-amide (**VIIya**), N-pyridin-2-ylmethyl-8-(11H,11-oxobenzimid azo[2, 1-a] isoindol)-amide (**VIIyb**), N-pyridin-3-ylmethyl-8-(11H,11-oxobenzimidazo[2,1-a]isoindol)-amide (**VIIyc**), N-pyridin-4-ylmethyl-8-(11H,11-oxobenzimidazo[2, 1-a] isoindol)-amide (**VIIyd**), N-furan-2-ylmethyl-8-(11H,11-oxobenz imidazo [2, 1-a] isoindol)-amide (**VIIye**), N-benzyl-8-(11H,11-oxobenz[4',5']imidazo [1',2:1,2]pyrrolo[3,4-b]pyrazin)-amide (**VIIza**), N-pyridin-2-ylmethyl-8-(11H,11-oxobenz [4',5']imidazo[1',2:1,2]pyrrolo[3,4-b]pyrazin)-amide (**VIIzb**), N-pyridin-3-ylmethyl-8-(11H,11-oxobenz[4',5']imidazo[1',2:1,2]pyrrolo[3,4-

b]pyrazin)-amide (**VIIzc**), N-pyridin-4-ylmethyl-8-(11H,11-oxobenzo[4',5']imidazo [1',2:1,2] pyrrolo[3,4-b]pyrazin)-amide (**VIIzd**) and N-furan-2-ylmethyl-8-(11H,11-oxobenzo[4',5']imidazo [1',2:1,2]pyrrolo[3,4-b]pyrazin)-amide (**VIIze**) were synthesized and reported in Table 4b.2.

### 4b.3.6 Anti-inflammatory activity [21; Chapter-2]

Anti-inflammatory activity evaluation was carried out by following procedure described in chapter-2 of this thesis.

### 4b.3.7 In vitro cytotoxicity against human cancer cell lines [32; Chapter-4a]

In vitro cytotoxicity against human cancer cell lines was carried out by following procedure described in chapter-4a of this thesis.

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# Chapter *5*

***Synthesis anti-inflammatory and anticancer activity evaluation of piperazine-2,6-dione, 4-(1H-indole-2-carbonyl)piperazine-2,6-dione and bis piperazinedione derivatives***

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# 5.1 Introduction

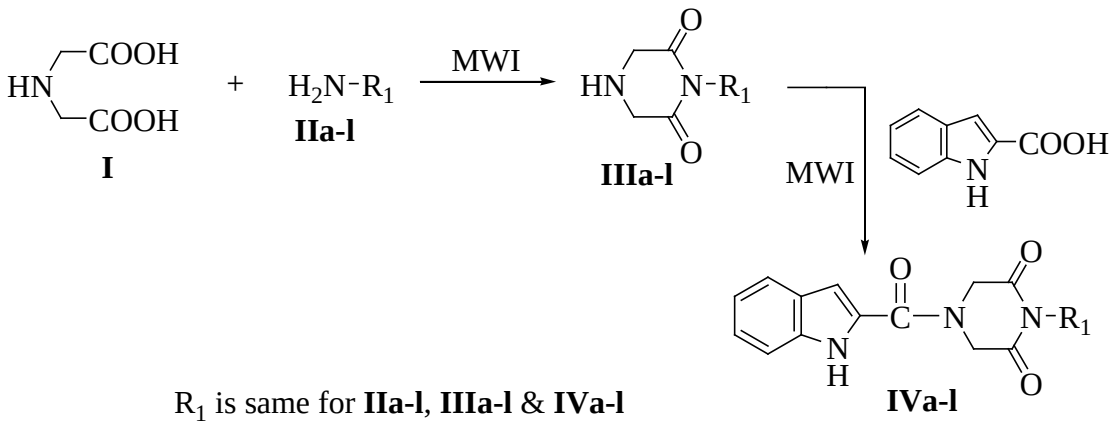
Piperazine derivatives form an important class of heterocyclic compounds due to their biological activities and have attracted attention of the researchers working in the area of medicinal chemistry [1-5]. Recent work reported in literature on piperazine derivatives exhibiting anti-inflammatory and anticancer activity is summarized in chapter-1 of this thesis. Piperazine derivatives exhibiting antiviral [6], antifungal [7-9], antibacterial [10, 11], antiaggregatory [12], antileishmanial [13, 14], antimalarial [15], antiplasmodial [16], antidepressant [17] and antimicrobial [18] activities are reported in literature. Apart from above mentioned activities piperazine derivatives also act as plasminogen activator inhibitor-1 (PAI-1) [19], thrombin inhibitor [20] and topoisomerase-II inhibitors [21].

Wide range of biological activities exhibited by piperazine derivatives and our efforts in search of biological active molecules [22, 23] tempted us to synthesize new piperazine derivatives. Several new piperazine derivatives have been synthesized and screened for anti-inflammatory and anticancer activity, which will be described in this chapter.

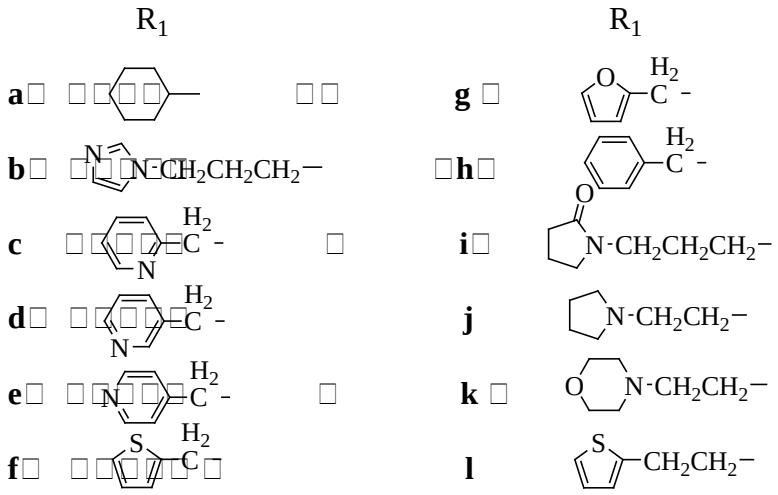
## 5.2 Results and discussion

### 5.2.1 *Chemistry:*

Iminodiacetic acid (**I**; Scheme 5.1) and cyclohexanamine (**IIa**; Scheme 5.1) were mixed in equimolar proportion and then subjected to microwave irradiation at 85°C for 3 min. TLC of reaction mixture showed completion of reaction. Crude product, so




$R_1$ is same for **IIa-l**, **IIIa-l** & **IVa-l**

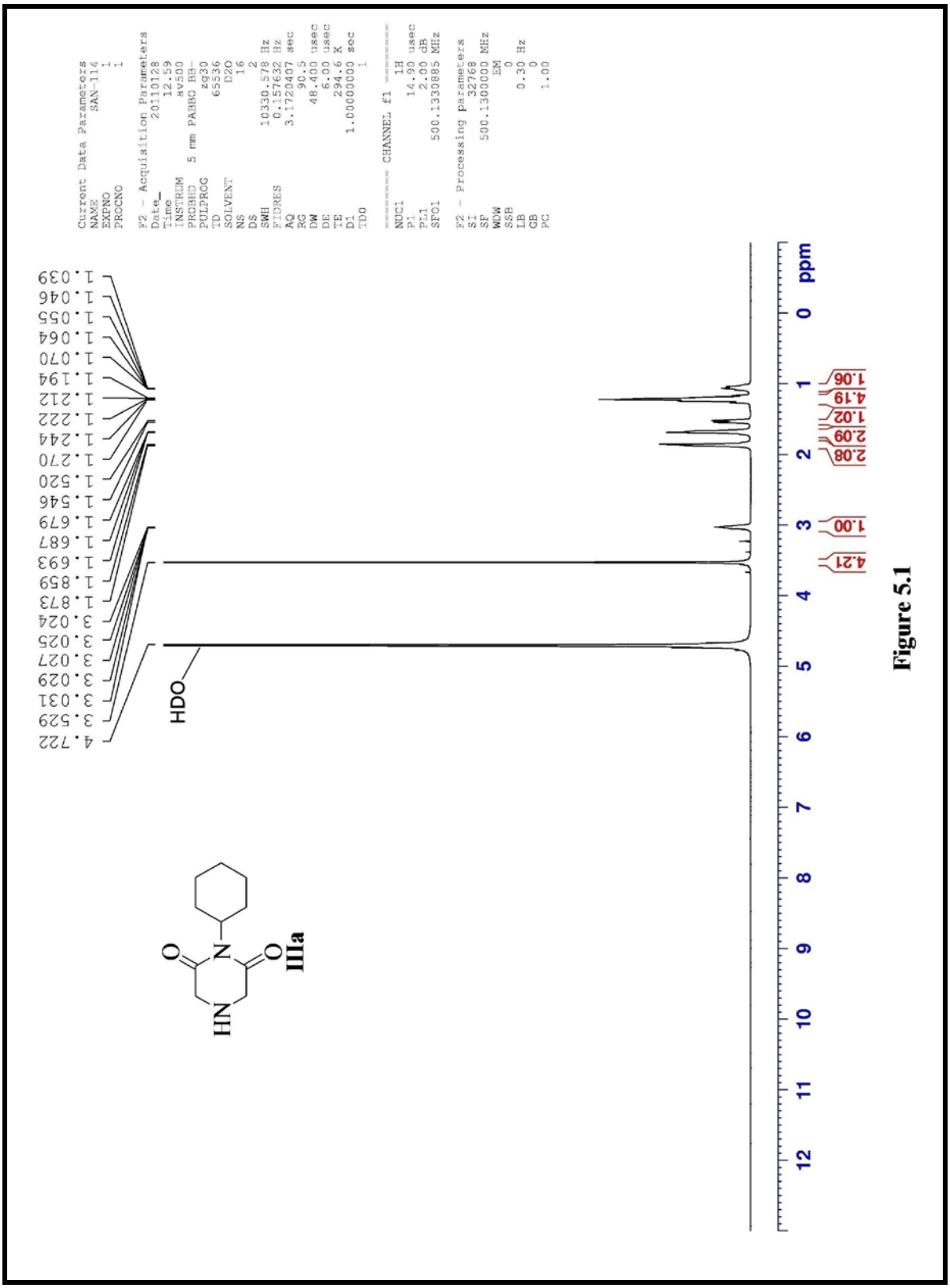



**Scheme 5.1** Synthesis of piperazine-2,6-dione **(IIIa-l)** and 4-(1H-indole-2-carbonyl) piperazine-2,6-dione **(IVa-l)** derivatives.

obtained, was purified by crystallization from methanol to get 1-cyclohexyl-piperazine-2,6-dione (**IIIa**; Scheme 5.1) in 89% yield.

In another experiment the above reaction mixture was subjected to microwave irradiation for 3 min at a power level of 300 W. TLC of reaction mixture showed that the reaction is complete. Crude product, so obtained, was crystallized from methanol to get pure product **IIIa** in 87% yield. Yields of product **IIIa** obtained by the above two methods are comparable. IR spectrum of **IIIa** exhibit absorption bands at 3146 (NH), 1669 (>C=O) $cm^{-1}$. $^{1}H$ NMR (500 MHz, $D_2O$) (Figure 5.1) $\delta$: 1.039-1.070 (m, 1H, one H of $CH_2$), 1.194-1.270 (m, 4H, 2×$CH_2$), 1.520-1.546 (d, 1H, J= 13 Hz, one H of $CH_2$), 1.679-1.693 (t, 2H, J= 7 Hz, $CH_2$), 1.859-1.873 (d, 2H, J=7 Hz, $CH_2$), 3.024-3.031 (m, 1H, >CH-N-), 3.529 (s, 4H, 2×$CH_2$). $^{13}C$ NMR (125MHz, $D_2O$) (Figure 5.2) $\delta$: 23.649, 24.139, 30.165, 48.790, 50.153 and 171.090. GC-MS spectrum (*m/z*; relt. int. %) (Figure 5.3) of **IIIa** gave $M^{+\bullet}$ ion peak at *m/z* 196 (53%). Elemental analysis Calculated for $C_{10}H_{16}N_2O_2$: C 61.20, H 8.22, N 14.27%. Found C 61.47, H 8.18, N 14.35%. Spectral and analytical data of **IIIa** fully support the structure assigned to it.

Similarly, condensation of 1-(3-aminopropyl)imidazole **(IIb)**, pyridin-2-ylmethanamine **(IIc)**, pyridin-3-ylmethanamine **(IId)**, pyridin-4-ylmethanamine **(IIe)**, thiophen-2-ylmethanamine **(IIf)**, furan-2-ylmethanamine **(IIg)**, benzylamine **(IIh)**, 1-(3-aminopropyl) pyrrolidin-2-one **(IIi),** 2-(pyrrolidin-1-yl)ethanamine **(IIj),** 2-morpholinoethanamine **(IIk)** and 2-(thiophen-2-yl)ethanamine **(III)** (**IIb-l**; Scheme 5.1) with iminodiacetic acid (**I**; Scheme 5.1) gave the corresponding piperazine-2,6-dione derivatives **IIIb-l** (Scheme 5.1) in quantitative yields. Physical constants, spectral and analytical data of compounds **IIIb-l** reported in Table 5.1 are in agreement with the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PULPROG zg30
TD 65536
SOLVENT D2O
NS 16
DS 2
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1720407 sec
RG 90.5
DW 48.400 usec
DE 6.00 usec
TE 294.6 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 14.90 usec
PL1 2.00 dB
SFO1 500.1330885 MHz
F2 - Processing parameters
SI 32768
SF 500.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
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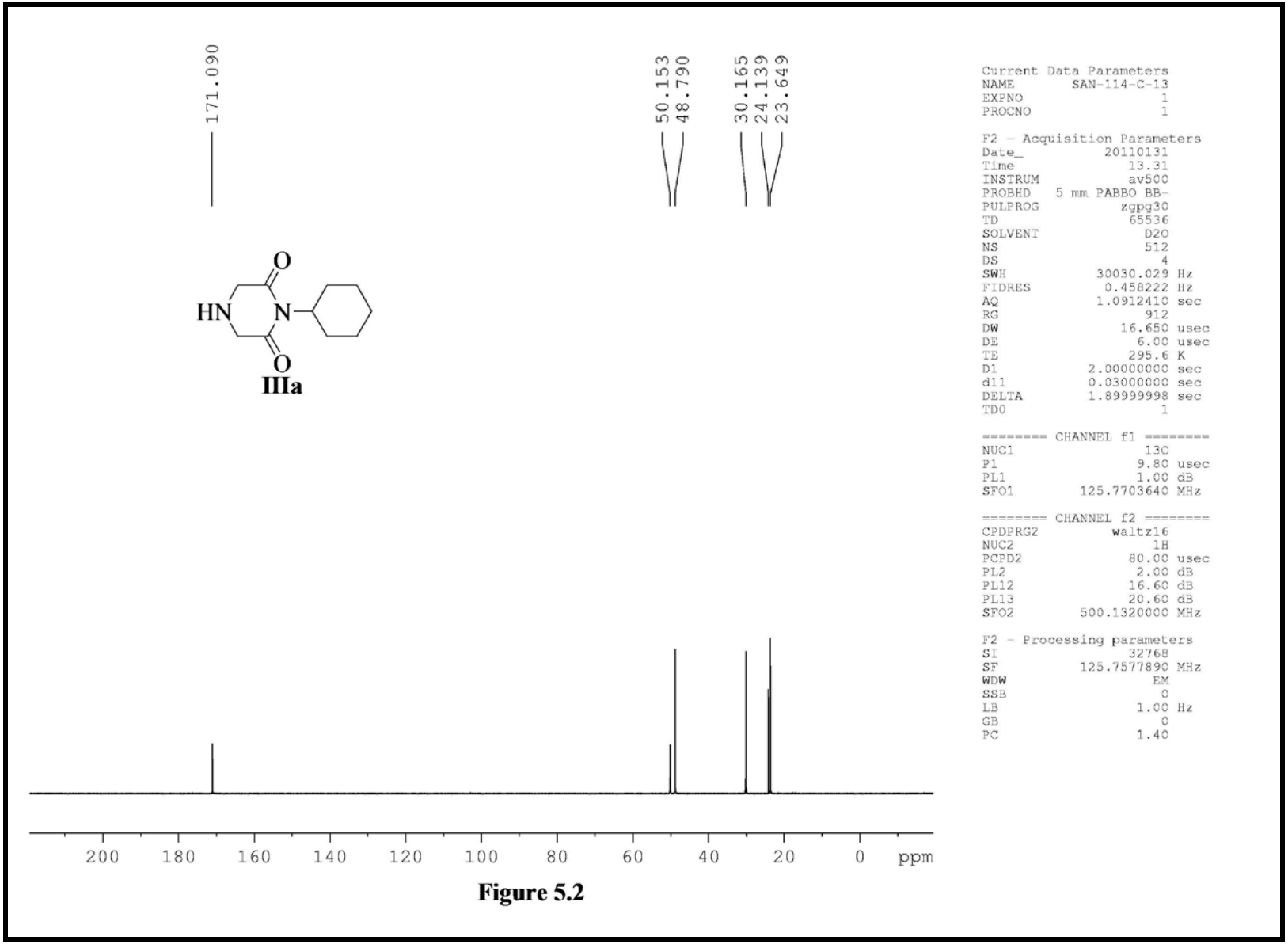
3.529
3.031
3.029
3.027
3.025
3.024
1.873
1.859
1.693
1.687
1.679
1.546
1.520
1.270
1.244
1.222
1.212
1.194
1.070
1.064
1.055
1.046
1.039
HDO
IIIa
4.21
1.00
2.08
2.09
1.02
4.19
1.06
ppm

**Figure 5.1**

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PROCNO 1

F2 - Acquisition Parameters
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PULPROG zgpg30
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SOLVENT D2O
NS 512
DS 4
SWH 30030.029 Hz
FIDRES 0.458222 Hz
AQ 1.0912410 sec
RG 912
DW 16.650 usec
DE 6.00 usec
TE 295.6 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
TD0 1

======== CHANNEL f1 ========
NUC1 13C
P1 9.80 usec
PL1 1.00 dB
SFO1 125.7703640 MHz

======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 2.00 dB
PL12 16.60 dB
PL13 20.60 dB
SFO2 500.1320000 MHz

F2 - Processing parameters
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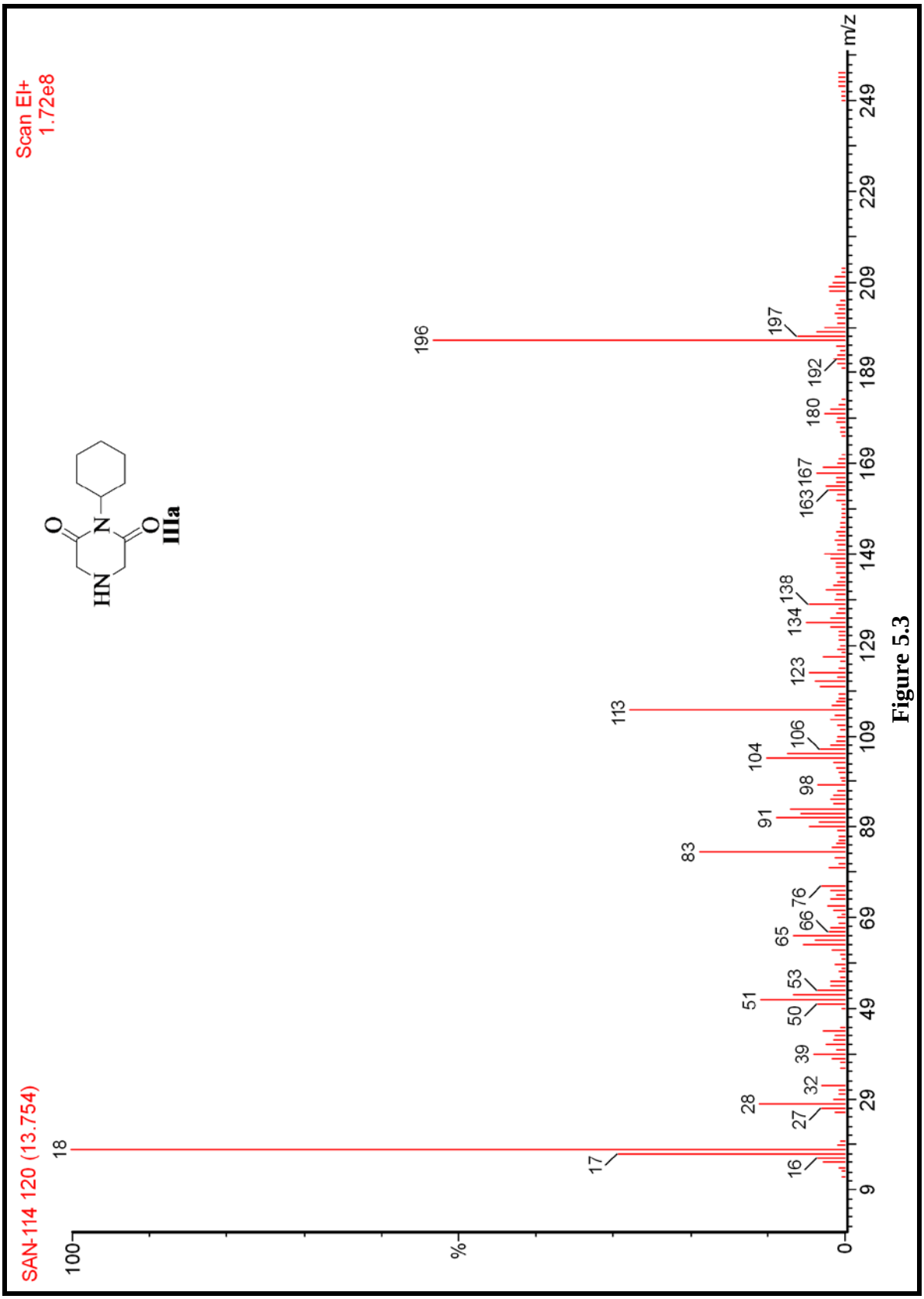
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

**Figure 5.2**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Scan EI+
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100
%
0
m/z
9
29
49
69
89
109
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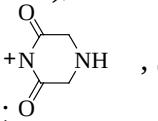
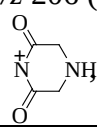
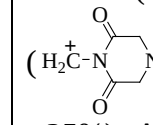
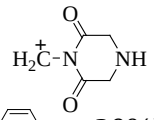
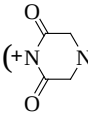
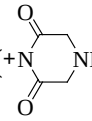
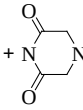
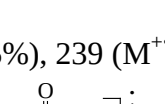
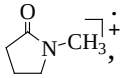
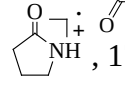
169
189
209
229
249
18
17
16
28
27
32
39
51
50
53
65
66
76
83
91
98
104
106
113
123
134
138
163
167
180
192
196
197
O
N
O
HN
IIIa

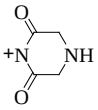
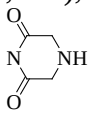
**Figure 5.3**

**Table 5.1: Physical constants and spectral data of piperazine-2,6-dione derivatives IIIa-l.**

| Comp no | Solvent of cryst./elution | m.p. °C | Yield % | IR (KBr) $cm^{-1}$, $^1H$ (500MHz) & $^{13}C$ (125MHz) NMR ($D_2O$), $\delta$ J(Hz), GC-MS (*m/z*; relt int %) |
|---|---|---|---|---|
| **1** | **2** | **3** | **4** | **5** |
| **IIIa** | MeOH | 118 | 85 | IR 3146 (NH), 1669 (>C=O) $cm^{-1}$. $^1H$ NMR (500 MHz, $D_2O$) $\delta$: 1.039-1.070 (m, 1H, one H of $CH_2$), 1.194-1.270 (m, 4H, 2×$CH_2$), 1.520-1.546 (d, 1H, J= 13 Hz, one H of $CH_2$), 1.679-1.693 (t, 2H, J= 7 Hz, $CH_2$), 1.859-1.873 (d, 2H, J=7 Hz, $CH_2$), 3.024-3.031 (m, 1H, >CH-N-), 3.529 (s, 4H, 2×$CH_2$), $^{13}C$ NMR (125MHz, $D_2O$) $\delta$: 23.6, 24.1, 30.2, 48.8, 50.1 and 171.1. GC-MS: *m/z* 197 ($M^{+\bullet}$+1, 10%), 196 ($M^{+\bullet}$, 53%), 113 (  , 30%), 83 (  , 22%), 18 ($H_2O^{+}$ 100%). Anal. Calcd for $C_{10}H_{16}N_2O_2$: C 61.20, H 8.22, N 14.27%. Found C 61.47, H 8.18, N 14.35%. |
| **IIIb** | MeOH | 114 | 91 | IR 3470 (NH), 1674 (>C=O) $cm^{-1}$. $^1H$ NMR (500 MHz, $D_2O$) $\delta$: 2.011-2.140 (m, 2H, $CH_2$), 2.781-2.813 (t, 2H, J=7.5Hz, $CH_2$), 3.461 (s, 4H, 2×$CH_2$), 3.983-4.010 (t, 2H, J=6.5Hz, $CH_2$,), 6.909 (s, 1H, Ar), 7.050 (s, 1H, Ar), 7.628 (s, 1H, Ar), $^{13}C$ NMR (125MHz, $D_2O$) $\delta$: 28.0, 36.5, 43.9, 48.9, 120.0, 127.3, 137.5 and 171.3. GC-MS: *m/z* 223 ($M^{+\bullet}$+1, 5%), 222 ($M^{+\bullet}$, 30%). Anal. Calcd for $C_{10}H_{14}N_4O_2$: C 54.04, H 6.35, N 25.21%. Found C 54.13, H 6.30, N 25.27%. |
| **IIIc** | MeOH | 142 | 94 | IR 3500 (NH), 1673 (>C=O), 1473(Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, $D_2O$) $\delta$: 3.524 (s, 4H, 2×$CH_2$), 4.215 (s, 2H, $CH_2$), 7.329-7.354 (q, 1H, J= 5 Hz & 7 Hz, Ar), 7.377-7.393 (d, 1H, J= 8Hz, Ar), 7.779-7.798 (m, 1H, Ar), 8.450-8.460 (d, 1H, J= 5 Hz, Ar). $^{13}C$ NMR (125MHz, $D_2O$) $\delta$: 43.2, 48.9, 123.2, 124.1, 138.5, 149.1, 151.4 and 171.2. GC-MS: *m/z* 206 ($M^{+}$+1, 5%), 205 ($M^{+}$, 50%),113 (  22%), 78(  |

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| | | | | , 25%). Anal. Calcd for $C_{10}H_{11}N_3O_2$: C 58.53,H 5.40, N 20.48%. Found C 58.69, H 5.47, N 20.54%. |
| **IIId** | MeOH | 128 | 92 | IR 3500 (NH), 1682 (>C=O), 1474 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, $D_2O$) $\delta$: 3.502 (s, 4H, 2× $CH_2$), 4.092 (s, 2H, $CH_2$), 7.382-7.406 (t, 1H, Ar), 7.812-7.827 (d, 1H, J= 7.5 Hz, Ar), 8.425-8.432 (d, 1H, J=3.5 Hz, Ar), 8.457 (s, 1H, Ar), $^{13}C$ NMR (125MHz, $D_2O$) $\delta$: 43.0, 48.1, 123.2, 134.1, 135.5, 149.9, 151.2 and 171.2. GC-MS: *m/z* 206 ($M^{+\bullet}$+1, 6%), 205 ($M^{+\bullet}$, 65%), 127 (, 4%), 113(  , 24%),78 (  , 25%). Anal. Calcd for $C_{10}H_{11}N_3O_2$: C 58.53, H 5.40, N 20.48%. Found C 58.71, H 5.45, N 20.55%. |
| **IIIe** | MeOH | 133 | 90 | IR 3500 (NH), 1662(>C=O), 1474 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, $D_2O$) $\delta$: 3.533 (s, 4H, 2× $CH_2$), 4.116 (s, 2H, $CH_2$), 7.370 (s, 2H, Ar), 8.464 (s, 2H, Ar), $^{13}C$ NMR (125MHz, $D_2O$) $\delta$: 43.0, 48.1, 123.2, 143.3, 149.9 and 171.2. GC-MS: *m/z* 206 ($M^{+\bullet}$+1, 6%), 205 ($M^{+\bullet}$, 53%), 127 (  , 5%), 113 (  , 22%), 78 (  , 20%). Anal. Calcd for $C_{10}H_{11}N_3O_2$: C 58.53, H 5.40, N 20.48%. Found C 58.69, H 5.44, N 20.57%. |
| **IIIf** | MeOH | 130 | 87 | IR 3427(NH), 1651(>C=O), 1464 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, $D_2O$) $\delta$: 3.454-3.468 (q, 4H, J= 4Hz & 5Hz, 2× $CH_2$,), 4.230-4.236 (d, 2H, J= 3Hz, $CH_2$), 6.934-6.954(q, 1H, J=2Hz & 5Hz, Ar), 7.076 (s, 1H, Ar), 7.348-7.361 (t, 1H, J= 3Hz, Ar). $^{13}C$ NMR (125MHz, $D_2O$) $\delta$: 37.3, 48.9, 127.6, 127.7, 129.3, 134.0 and 171.3. GC-MS: *m/z* 211 ($M^{+\bullet}$+1, 6%), 210 ($M^{+\bullet}$, 35%), 113 (  , 25%), 83 (  , 20%). Anal. Calcd for $C_9H_{10}N_2O_2S$: C 51.41, H 4.79, N |

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| | | | | 13.32, S 15.25%. Found C 51.47, H 4.82, N 13.38, S 15.31%. |
| **IIIg** | MeOH | 122 | 96 | IR 3420 (NH), 1652 (>C=O), 1593 (Ar) $cm^{-1}$. $^{1}H$ NMR (500 MHz, $D_2O$) $\delta$: 3.478 (s, 4H, 2× $CH_2$), 4.070 (s, 2H, $CH_2$), 6.331-6.337 (t, 1H, Ar), 6.403-6.409 (d, 1H, J= 3Hz, Ar), 7.424-7.425 (d, 1H, J= 0.5 Hz, Ar). $^{13}C$ NMR (125MHz, $D_2O$) $\delta$: 35.5, 48.9, 110.7, 110.8, 144.2, 146.1 and 171.0. GC-MS: *m/z* 195 ($M^{+\bullet}$+1, 8%), 194 ($M^{+\bullet}$, 50%), 113 (  , 25%). Anal. Calcd for $C_9H_{10}N_2O_3$: C 55.67, H 5.19, N 14.43%. Found C 55.75, H 5.23, N 14.37%. |
| **IIIh** | MeOH | 122 | 86 | IR 3461 (NH), 1669 (>C=O), 1591, 1506 (Ar) $cm^{-1}$. $^{1}H$ NMR (500 MHz, $D_2O$) $\delta$ : 3.446 (s, 4H, 2× $CH_2$), 4.009 (s, 2H, $CH_2$), 7.295-7.305 (d, 5H, J= 5 Hz, Ar). $^{13}C$ NMR (125MHz, $D_2O$) $\delta$ (ppm): 42.9, 48.8, 128.7, 129.0, 132.5 and 171.2. GC-MS: *m/z* 205 ($M^{+\bullet}$+1, 1%), 204 ($M^{+\bullet}$, 49%). Anal. Calcd for $C_{11}H_{12}N_2O_2$: C 64.69; H 5.92; N 13.72%. Found: C 64.49; H 5.72; N 13.82%. |
| **IIIi** | MeOH | 109 | 94 | IR 3432 (NH), 1668, 1626 (>C=O) $cm^{-1}$. $^{1}H$ NMR (500 MHz, $D_2O$) $\delta$: 1.806-1.835 (t, 2H, J=7.5Hz, $CH_2$), 1.928-1.958 (t, 2H, J=7.5Hz, $CH_2$), 2.316-2.349 (t, 2H, J=8.5Hz, $CH_2$), 2.854-2.884 (t, 2H, J=7.5Hz, $CH_2$), 3.246-3.273 (t, 2H, J=6.5Hz, $CH_2$), 3.384-3.413 (t, 2H, J= 7Hz, 2× $CH_2$), 3.550 (s, 4H, 2× $CH_2$). $^{13}C$ NMR (125MHz, $D_2O$) $\delta$: 18.2, 24.4, 30.8, 36.8, 39.4, 47.9, 48.8, 171.1 and 178.7. GC-MS: *m/z* 240 ($M^{+\bullet}$+1, 5%), 239 ($M^{+\bullet}$, 35%), 113 (  , 25%), 99 (  , 17%), 85 (  , 17%).<br><br>Anal. Calcd for $C_{11}H_{17}N_3O_3$: C 55.22, H 7.16, N 17.56%. Found C 55.29, H 7.11, N 17.63%. |
| **IIIj** | MeOH | 117 | 89 | IR 3440 (NH), 1678 (>C=O) $cm^{-1}$. $^{1}H$ NMR (500MHz, $D_2O$) $\delta$: 1.859(s, 4H, 2× $CH_2$), 3.003- |

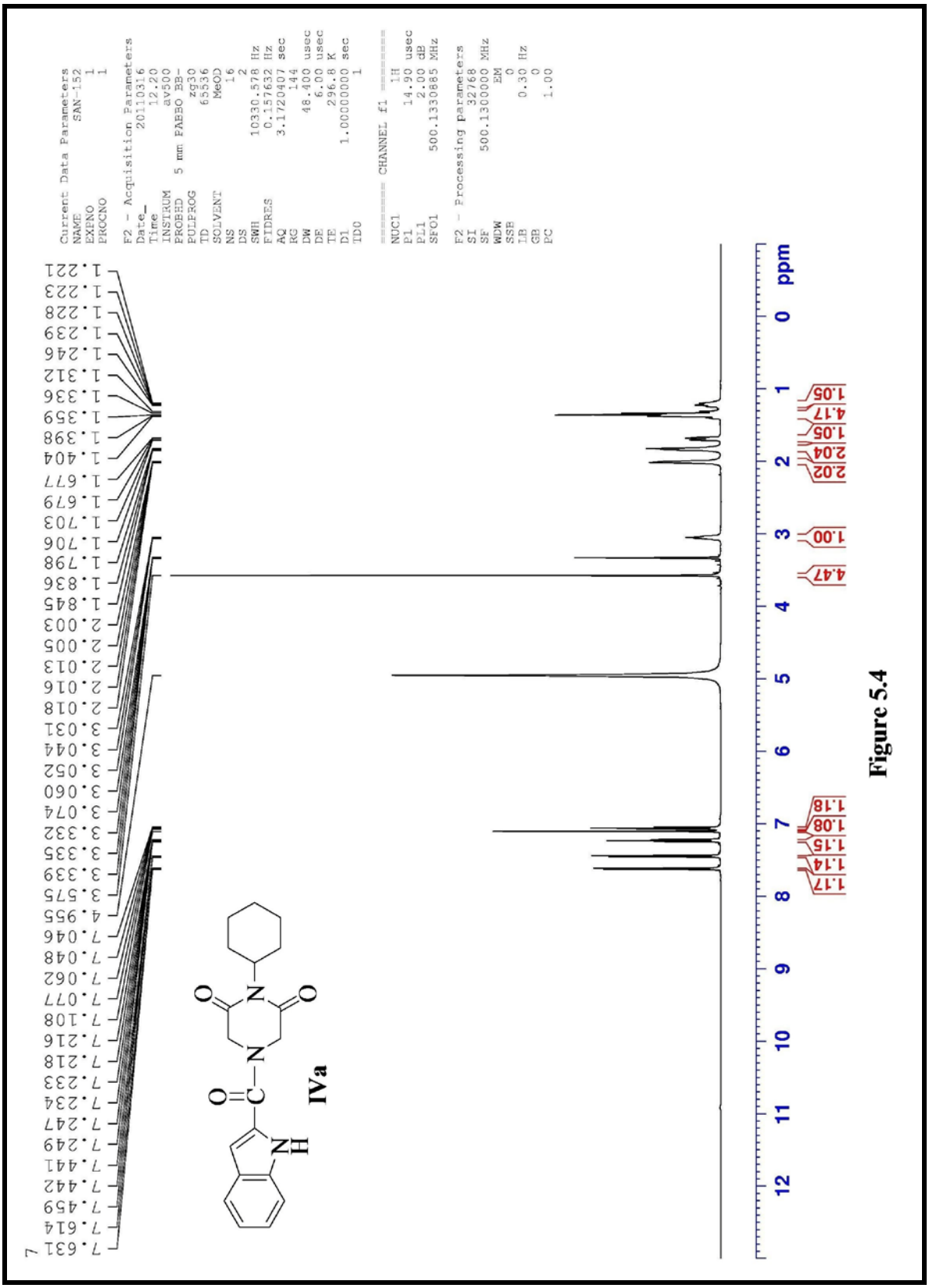
| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| | | | | 3.072 (m, 8H, 4× $CH_2$), 3.493 (s, 4H, 2× $CH_2$). $^{13}$C NMR (125MHz, $D_2O$) $\delta$: 22.5, 36.5, 48.9, 53.7, 55.9 and 171.4. GC-MS: *m/z* 212 ($M^{+\bullet}$+1, 5%), 211 ($M^{+\bullet}$, 30%), 113 (  , 25%). Anal. Calcd for $C_{10}H_{17}N_3O_2$: C 56.85, H 8.11, N 19.89%. Found C 56.96, H 8.14, N 19.76%. |
| **IIIk** | MeOH | 123 | 93 | IR 3500 (NH), 1686 (>C=O) $cm^{-1}$. $^1$H NMR (500 MHz, $D_2O$) $\delta$: 2.509 (s, 4H, 2× $CH_2$), 2.624 (t, 2H, J= 5 Hz, $CH_2$), 3.052 (t, 2H, J= 5 Hz, $CH_2$), 3.522 (s, 4H, 2×$CH_2$), 3.641-3.659 (t, 4H, J= 4.5 Hz, 2×$CH_2$). $^{13}$C NMR (125MHz, $D_2O$) $\delta$: 35.5, 48.9, 52.4, 54.1, 66.0 and 171.3. GC-MS: *m/z* 228 ($M^{+\bullet}$+1, 8%), 227 ($M^{+\bullet}$, 45%), 18 ( $H_2\dot{O}^+$ , 100%). Anal. Calcd for $C_{10}H_{17}N_3O_3$: C 52.85, H 7.54, N 18.49%. Found C 52.78, H 7.59, N 18.60%. |
| **IIIl** | MeOH | 136 | 87 | IR 3450 (NH), 1669, 1647 (>C=O), 1,613 (Ar) $cm^{-1}$. $^1$H NMR (500 MHz, $D_2O$) $\delta$: 3.113-3.139 (t, 2H, J= 6.5Hz, $CH_2$), 3.180-3.206 (t, 2H, J= 6.5 Hz, $CH_2$), 3.521(s, 4H, 2× $CH_2$), 6.916-6.946 (m, 2H, Ar), 7.257-7.267 (d, 1H, J= 5Hz, Ar). $^{13}$C NMR (125MHz, $D_2O$) $\delta$: 26.9, 40.7, 48.9, 125.3, 126.6, 127.5, 138.5 and 171.5. GC-MS: *m/z* 225 ($M^{+\bullet}$+1, 9%), 224 ($M^{+\bullet}$, 50%), 113 (  , 30%), 83(  , 20%). Anal. Calcd for $C_{10}H_{12}N_2O_2S$: C 53.55, H 5.39,N 12.49, S 14.30%. Found C 53.51, H 5.41, N 12.54, S 14.36%. |

structures assigned to them.

1-Cyclohexyl-piperazine-2,6-dione (**IIIa**; Scheme 5.1) and 1H-indole-2-carboxylic acid were mixed in equimolar proportion and subjected to microwave irradiation at 150°C for 7 min. TLC of the reaction mixture showed absence of the starting materials. Crude product so obtained was purified by crystallization from

methanol to get pure product 1-cyclohexyl-4-(1H-indole-2-carbonyl)-piperazine-2,6-dione (**IVa**; Scheme 5.1) in 86% yield.

In another experiment the above reaction mixture was subjected to microwave irradiation at a power level of 850 W for 4 min. TLC of the reaction mixture showed absence of the starting materials. Crude product so obtained was purified by crystallization from methanol to get pure product **IVa** in 82% yield. Yields of product **IVa** obtained from the above two methods are comparable. IR spectrum of **IVa** shows absorption bands at 3403 (NH), 1702 (>C=O), 1519 (Ar) $cm^{-1}$. $^{1}H$ NMR (500 MHz, $CD_3OD$) (Figure 5.4) $\delta$: 1.221-1.246 (q, 1H, J=3.5Hz & 9 Hz, one H of $CH_2$), 1.312-1.404 (m, 4H, 2×$CH_2$), 1.677-1.706 (dd, 1H, J=1.5Hz & 13.5 Hz, one H of $CH_2$), 1.798-1.845 (m, 2H, $CH_2$), 2.003-2.018 (m, 2H, $CH_2$), 3.031-3.074 (m, 1H, CH), 3.575 (s, 4H, 2×$CH_2$), 7.046-7.077 (m, 1H, Ar), 7.108 (s, 1H, Ar), 7.216-7.249 (dt, 1H, J= 1 & 8 Hz, Ar), 7.441-7.459 (d, 1H, J= 8.5 Hz, Ar), 7.614-7.631 (d, 1H, J= 8.5 Hz, Ar). $^{13}C$ NMR (125MHz, $CD_3OD$) (Figure 5.5) $\delta$: 25.376, 25.916, 31.970, 50.424, 51.488, 108.052, 113.089, 120.961, 122.889, 125.180, 128.993, 131.673, 138.618, 166.923 and 171.161. GC-MS (*m/z*; relt. int. %) (Figure 5.6) of **IVa** gave $M^{+\bullet}$ ion peak at *m/z* 339 ($M^{+\bullet}$, 26%). Elemental analysis Calculated for $C_{19}H_{21}N_3O_3$: C 67.24, H 6.24, N 12.38%. Found C 67.11, H 6.31, N 12.44%. Spectral and analytical data of **IVa** fully support the structure assigned to it. Similarly condensation of piperazine-2,6-dione derivatives **IIIb-l** (Scheme 5.1) with 1H-indole-2-carboxylic acid gave the corresponding 4-(1H-indole-2-carbonyl)piperazine-2,6-dione derivatives **IVb-l** (Scheme 5.1) in quantitative yields. Physical constants, spectral and analytical data of **IVa-l** reported in the Table 5.2 fully support the structures assigned to them.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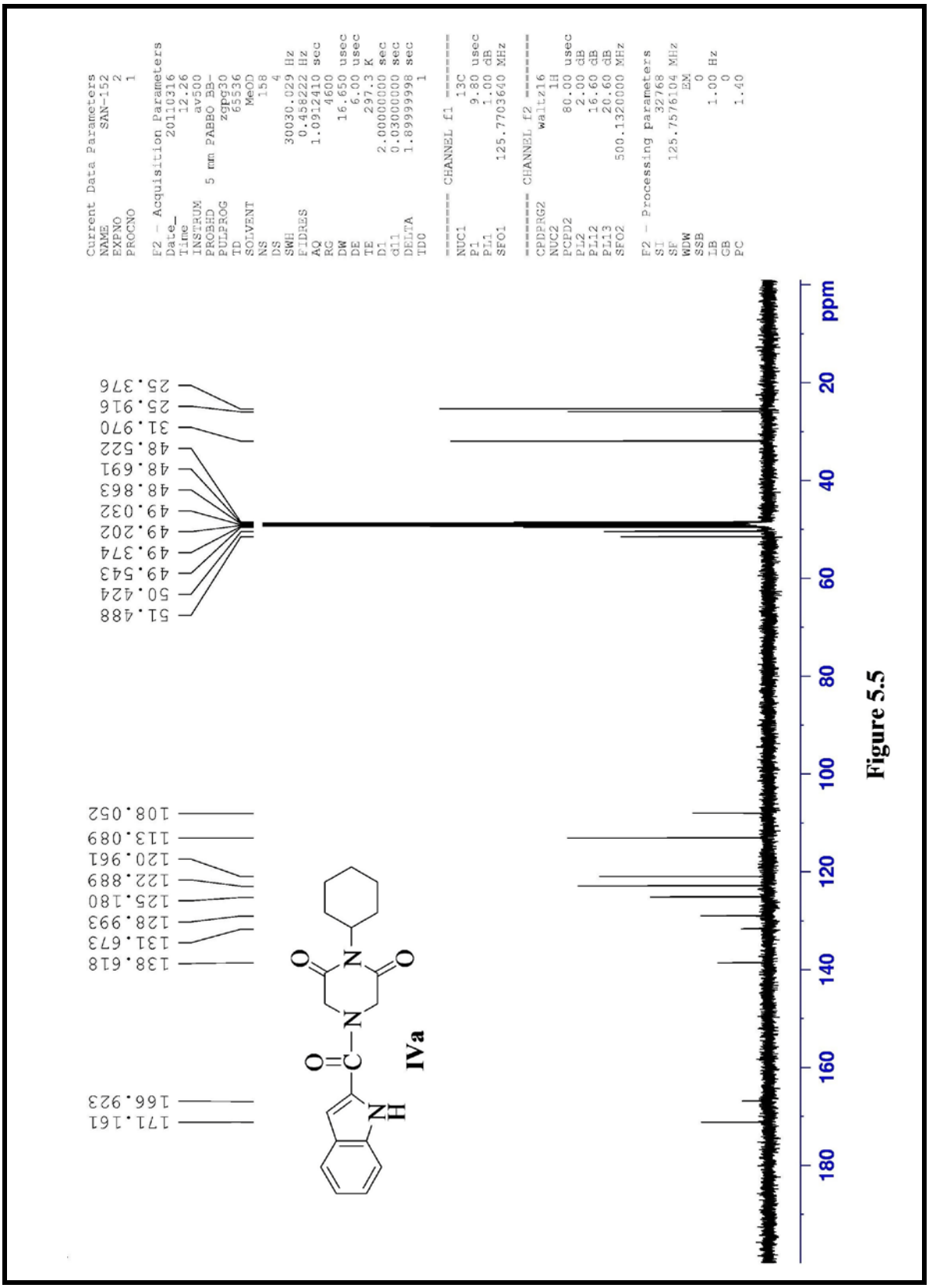
1.08
1.18
Figure 5.4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DE 6.00 usec
TE 297.3 K
D1 2.00000000 sec
d11 0.03000000 sec
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TD0 1
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PL1 1.00 dB
SFO1 125.7703640 MHz
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NUC2 1H
PCPD2 80.00 usec
PL2 2.00 dB
PL12 16.60 dB
PL13 20.60 dB
SFO2 500.1320000 MHz
F2 - Processing parameters
SI 32768
SF 125.7576104 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
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49.374
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128.993
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122.889
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120
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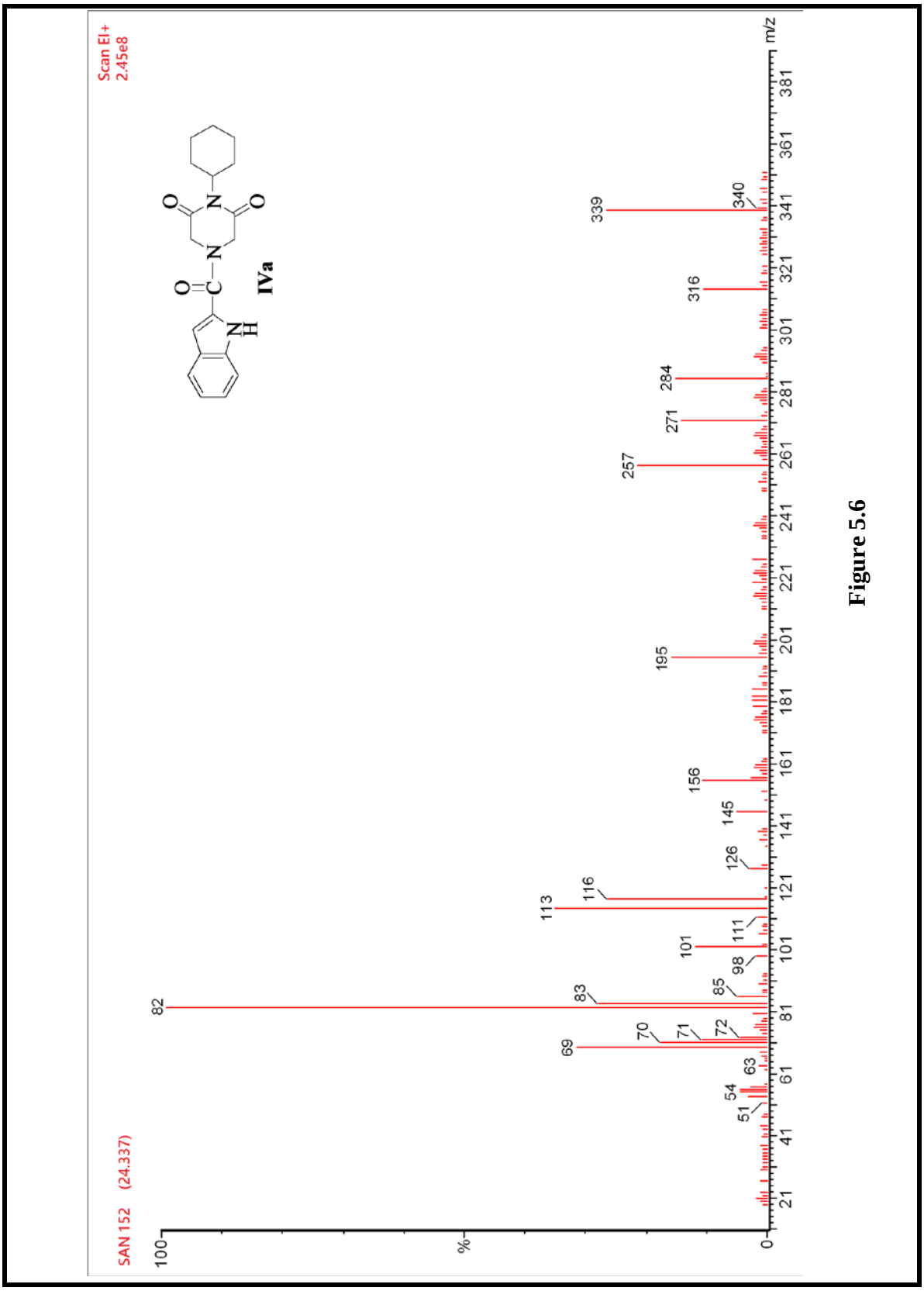
80
60
40
20

Figure 5.5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316
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340
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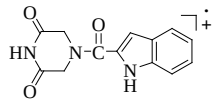
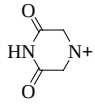
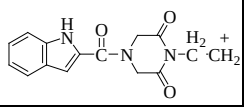
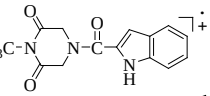
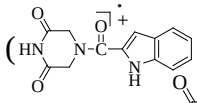
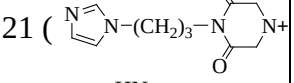
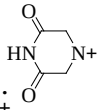
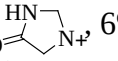
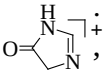
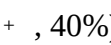
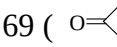
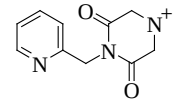
63
54
51
21
41
61
81
101
121
141
161
181
201
221
241
261
281
301
321
341
361
381

**Figure 5.6**

**Table 5.2: Physical constants and spectral data of 4-(1H-indole-2-carbonyl) piperazine-2,6-dione derivatives IVa-l.**

| Comp no | Solvent of cryst./elution | m.p. °C | Yield % | IR (KBr) $cm^{-1}$, $^1H$ (500MHz) & $^{13}C$ (125MHz) NMR ($CD_3OD$, DMSO-$d_6$, $D_2O$), $\delta$ J(Hz), GC-MS (*m/z*; relt int %) |
|---|---|---|---|---|
| **1** | **2** | **3** | **4** | **5** |
| **IVa** | MeOH | 280 | 80 | IR 3403 (NH), 1702 (>C=O), 1519 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, $CD_3OD$) $\delta$: 1.221-1.246 (q, 1H, J=3.5Hz & 9 Hz, one H of $CH_2$), 1.312-1.404 (m, 4H, 2×$CH_2$), 1.677-1.706 (dd, 1H, J=1.5Hz & 13.5 Hz, one H of $CH_2$), 1.798-1.845 (m, 2H, $CH_2$), 2.003-2.018 (m, 2H, $CH_2$), 3.031-3.074 (m, 1H, CH), 3.575 (s, 4H, 2×$CH_2$), 7.046-7.077 (m, 1H, Ar), 7.108 (s, 1H, Ar), 7.216-7.249 (dt, 1H, J= 1 & 8 Hz, Ar), 7.441-7.459 (d, 1H, J= 8.5 Hz, Ar), 7.614-7.631 (d, 1H, J= 8.5 Hz, Ar). $^{13}C$ NMR (125MHz, $CD_3OD$) $\delta$: 25.4, 25.9, 31.9, 50.4, 51.5, 108.0, 113.1, 120.9, 122.9, 125.2, 128.9, 131.7, 138.6, 166.9 and 171.2. GC-MS: *m/z* 340 ($M^{+\bullet}$+1, 1%), 339 ($M^{+\bullet}$, 26%), 257 (  , 22%), 113(  , 35%), 83 (  , 29%), 82 (  , 100%). Anal. Calcd for $C_{19}H_{21}N_3O_3$: C 67.24, H 6.24, N 12.38%. Found C 67.11, H 6.31, N 12.44%. |
| **IVb** | MeOH | >300 | 86 | IR 3470 (NH), 1694, 1635 (>C=O), 1515 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, $CD_3OD$) $\delta$: 2.130-2.188 (m, 2H, $CH_2$), 2.900-2.930 (t, 2H, J= 7.5Hz, $CH_2$), 3.582 (s, 4H, 2× $CH_2$), 4.079-4.159 (t, 2H, J=7Hz, $CH_2$), 7.040-7.085 (m, 3H, Ar), 7.188-7.235 (m, 2H, Ar), 7.434-7.450 (d, 1H, J= 8Hz, Ar), 7.593-7.609 (d, 1H, J= 8Hz, Ar), 7.813 (s, 1H, Ar). $^{13}C$ NMR (125MHz, $CD_3OD$) $\delta$: 30.0, 37.9, 45.2, 50.4, 106.9, 113.0, 120.7, 120.8, 122.7, 124.7, 128.6, 129.2, 133.8, 138.3, 138.3, 168.6 and 171.4. GC-MS: *m/z* 366 ($M^{+\bullet}$+1, 5%), 365 ($M^{+\bullet}$, 20%), 284(  |

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| | | | | , 11%), 271 (  ,8%), 257 (  ,20%), 221 (  ,6%), 113 (  ,20%), 85 (  , 6%), 84 (  , 32%), 82(  ,12%), 70 (  , 40%), 69 (  ,57%). Anal. Calcd for $C_{19}H_{19}N_5O_3$: C 62.46, H 5.24, N 19.17%. Found C 62.62, H 5.19, N 19.35%. |
| **IVc** | MeOH | >300 | 88 | IR 3470 (NH), 1692 (>C=O), 1528 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, $CD_3OD$) $\delta$: 3.511(s, 4H,2×$CH_2$), 4.289 (s, 2H, $CH_2$), 7.067-7.083 (m, 1H, Ar), 7.118-7.120 (d, 1H, J=1Hz ), 7.223-7.256 (m, 1H, Ar), 7.375-7.400 (m, 1H, Ar), 7.440-7.458 (dd, 2H, J= 1Hz & 8.5Hz, Ar), 7.617-7.634 (d, 1H, J= 8.5 Hz, Ar), 7.827-7.862 (m, 1H, Ar), 8.622-8.632 (d, 1H, J= 5Hz, Ar). $^{13}C$ NMR (125MHz, $CD_3OD$) $\delta$: 44.1, 50.4, 108.4, 113.1, 121.0, 122.9, 123.5, 124.7, 125.3, 128.9, 130.9, 138.6, 138.7, 150.5, 153.8, 166.4 and 171.1. GC- MS: *m/z* 349($M^{+\bullet}$+1, 7%), 348 ($M^{+\bullet}$, 35%), 204 (  , 50%). Anal. Calcd for $C_{19}H_{16}N_4O_3$: C 65.51, H 4.63, N 16.08%. Found C 65.69, H 4.70, N 16.31%. |
| **IVd** | MeOH | 276 | 82 | IR 3444 (NH), 1691, 1624 (>C=O), 1511 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO+$D_2O$) $\delta$: 3.590 (s, 4H, 2×$CH_2$), 3.917 (s, 2H, $CH_2$), 6.358 (s, 1H, Ar), 6.589-6.619 (t, 1H, J= 7.5 Hz, Ar), 6.719-6.749 (t, 1H, J= 7.5 Hz, Ar), 7.021-7.041 (m, 2H, Ar), 7.166-7.182 (d, 1H, J= 8.0Hz, Ar), 7.507-7.522 (d, 1H, J=7.5 Hz, Ar), 8.133-8.140 (d, 1H, J= 3.5 Hz, Ar), 8.267-8.270 (d, 1H, J= 1.5Hz, Ar). $^{13}C$ NMR (125MHz, DMSO +$D_2O$) $\delta$: 40.7, 48.9, 103.2, 111.9, 118.9, 120.9, 122.2, 123.7, 127.5, 133.4, 135.6, |

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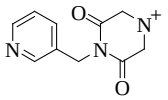
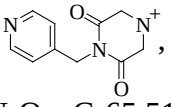
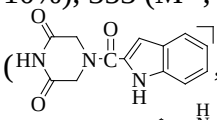
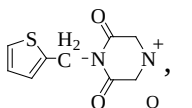
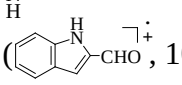
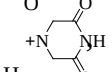
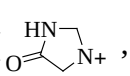
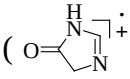
| | | | | 136.3, 136.5, 148.5, 149.1, 166.4, and 172.1. GC-MS: *m/z* 349 ($M^{+\bullet}$+1, 6%), 348 ($M^{+\bullet}$, 30%), 204 (  , 30%). Anal. Calcd for $C_{19}H_{16}N_4O_3$: C 65.51, H 4.63, N 16.08%. Found C 65.72, H 4.57, N 16.27%. |
| **IVe** | MeOH | >300 | 86 | IR 3452 (NH), 1684, 1624 (>C=O), 1515 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO+$D_2O$) $\delta$: 3.505 (s, 4H, 2×$CH_2$), 3.982 (s, 2H, $CH_2$), 6.750 (s, 1H, Ar), 6.955-6.985 (t, 1H, J= 7.5 Hz, Ar), 7.090-7.120 (t, 1H, J= 7.5 Hz, Ar), 7.549-7.372 (m, 4H, Ar), 8.534-8.545 (d, 2H, J= 5Hz, Ar). $^{13}C$ NMR (125MHz, DMSO+$D_2O$) $\delta$: 41.7, 48.1, 103.5, 111.9, 119.1, 121.1, 122.4, 123.1, 127.4, 135.6, 135.8, 145.6, 149.2, 166.7 and 171.9, GC-MS: *m/z* 349 ($M^{+\bullet}$+1, 5%), 348 ($M^{+\bullet}$, 50%), 204 (  , 40%). Anal. Calcd for $C_{19}H_{16}N_4O_3$: C 65.51, H 4.63, N 16.08%. Found C 65.69, H 4.69, N 16.01%. |
| **IVf** | MeOH | >300 | 85 | IR 3390 (NH), 1683(>C=O), 1476 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, $D_2O$) $\delta$: 3.524 (s, 4H, 2×$CH_2$), 4.182 (s, 2H, $CH_2$), 6.918-6.988 (m, 2H, Ar), 7.046-7.077 (t, 1H, J=7.5Hz, Ar), 7.108 (s, 1H, Ar), 7.217-7.248 (dt, 1H, J=1Hz & 7.5 Hz, Ar), 7.257-7.267 (d, 1H, J= 5Hz, Ar), 7.443-7.460 (d, 1H, J= 8.5Hz, Ar), 7.615-7.632 (d, 1H, J= 8.5Hz, Ar). $^{13}C$ NMR (125MHz, $CD_3OD$) $\delta$: 40.9, 48.1, 108.2, 113.1, 120.9, 122.9, 125.2, 127.6, 127.7, 128.9, 129.3, 131.3, 134.1, 138.7, 166.7 and 171.2. GC-MS: *m/z* 354 ($M^{+\bullet}$+1, 10%), 353 ($M^{+\bullet}$, 78%), 257 (  , 25%), 209 (  , 8%), 145 (  , 10%), 113 (  25%), 85 (  , 7%), 84 (  , |

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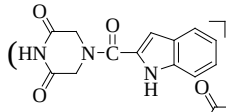
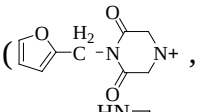
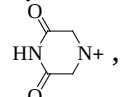
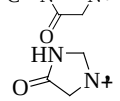
| | | | | 32%), 70 (  , 40%), 69 (  , 100%), Anal. Calcd for $C_{18}H_{15}N_3O_3S$; C 61.18, H 4.28, N 11.89%. Found C 61.39, H 4.21, N 12.07%. |
| **IVg** | MeOH | 281 | 87 | IR 3450 (NH), 1692 (>C=O), 1536 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, $CD_3OD$) $\delta$: 3.568 (s, 4H, 2×$CH_2$), 4.183 (s, 2H, $CH_2$), 6.468-6.479 (q, 1H, J= 2 & 3.5 Hz, Ar), 6.554-6.561 (d, 1H, J= 3.5 Hz, Ar), 7.048-7.080 (m, 1H, Ar), 7.109-7.110 (d, 1H, J= 0.5Hz, Ar), 7.221-7.252 (m, 1H, Ar), 7.439-7.458 (dd, 1H, J= 1Hz & 8.5Hz, Ar), 7.596-7.632 (m, 2H, Ar). $^{13}C$ NMR (125MHz, $CD_3OD$) $\delta$: 36.8, 50.4, 108.2, 111.7, 111.9, 113.1, 120.9, 122.9, 125.2, 128.9, 131.3, 138.7, 145.3, 148.3, 166.7 and 171.2. GC-MS: *m/z* 338 ($M^{+\bullet}$+1, 8%), 337($M^{+\bullet}$, 30%), 257 (  , 16%), 193 (  , 30%), 113 (  , 18%), 85 (  , 6%), 84 (  , 75%), 70 (  , 58%), 69 (  , 70%). Anal. Calcd for $C_{18}H_{15}N_3O_4$: C 64.09, H 4.48, N 12.46%. Found C 64.34, H 4.55, N 12.34%. |
| **IVh** | MeOH | 290 | 87 | IR 3408 (NH), 1706, 1666 (>C=O), 1616 & 1532 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, $D_2O$) $\delta$: 3.440 (s, 4H, 2×$CH_2$), 4.007 (s, 2H, $CH_2$), 7.044-7.088 (m, 1H, Ar), 7.108 (s, 1H, Ar), 7.218-7.255 (m, 1H, Ar), 7.295-7.324 (m, 5H, Ar), 7.442-7.460 (dd, 1H, J= 0.5 & 8.5Hz, Ar), 7.615-7.630 (d, 1H, J= 7.5Hz, Ar). $^{13}C$ NMR (125MHz, $D_2O$) $\delta$: 40.9, 50.0, 108.9, 112.1, 120.0, 122.3, 123.8, 124.8, 125.9, 128.3, 131.0, 138.6, 141.7, 147.6, 165.7 and 170.2. GC-MS: *m/z* 348 ($M^{+\bullet}$+1 ,1%), 347 ($M^{+\bullet}$, 23%), |

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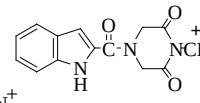
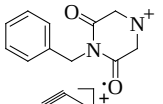
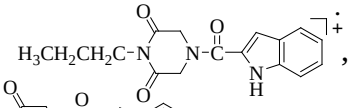
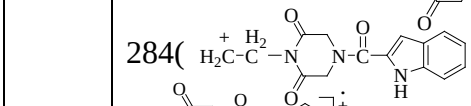
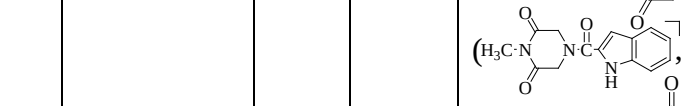
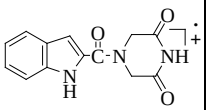
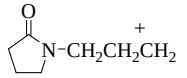
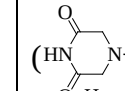
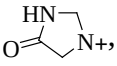
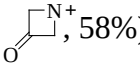
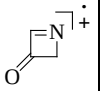
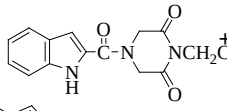
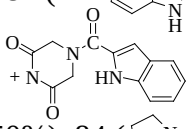
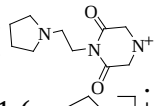
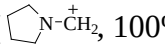
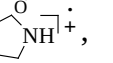
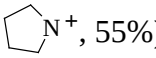
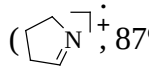
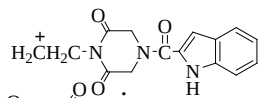
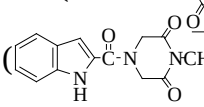
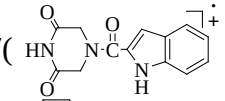
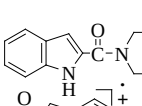
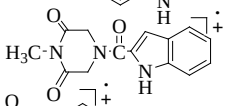
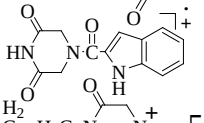
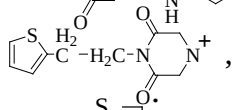
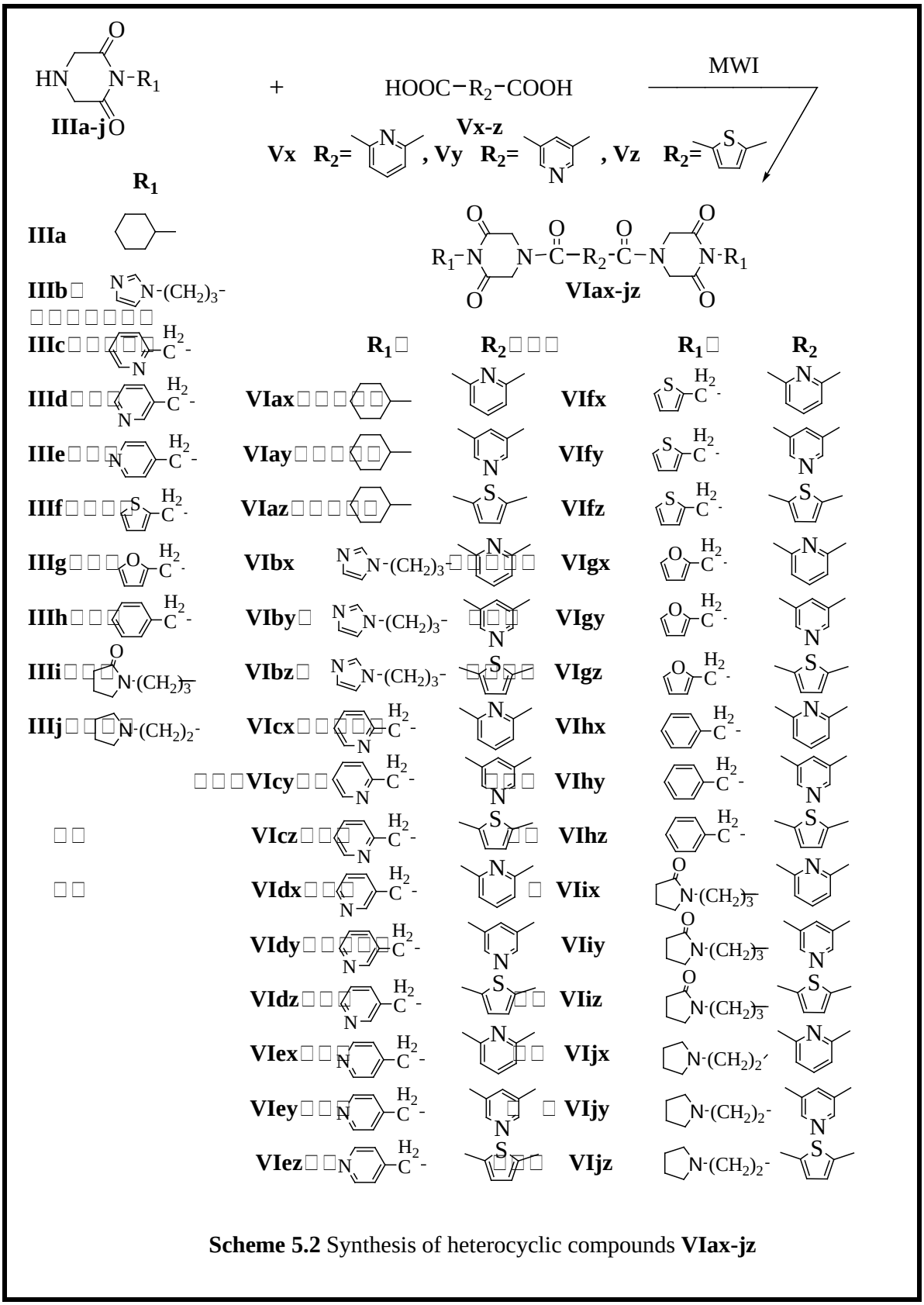
| | | | | 270 (  , 22%), 203 (  , 34%), 77 (  ,100%), 76 (  , 24%). Anal. Calcd for $C_{20}H_{17}N_3O_3$: C 69.16, H 4.89, N, 12.10%. Found 69.64, H 4.81, N, 12.21%. |
| **IVi** | MeOH | >300 | 83 | IR 3426 (NH), 1702 (>C=O), 1591 & 1532 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, $CD_3OD$) $\delta$: 1.888-1.917 (m, 2H, $CH_2$), 2.057-2.072 (m, 2H, $CH_2$), 2.387-2.419 (t, 2H, J= 8Hz, $CH_2$), 2.911-2.941 (t, 2H, J= 7.5Hz, $CH_2$), 3.369-3.396 (t, 2H, J= 7Hz, $CH_2$), 3.448-3.477 (t, 2H, 7.5Hz, Ar), 3.583 (s, 4H, 2× $CH_2$), 7.056-7.086 (m, 1H, Ar), 7.127 (s, 1H, Ar), 7.229-7.261 (dt, 1H, J= 0.5Hz & 7.0Hz Ar), 7.447-7.465 (dd, 1H, J= 1Hz & 8.5Hz, Ar), 7.624-7.640 (d, 1H, J= 8Hz, Ar). $^{13}C$ NMR (125MHz, $CD_3OD$) $\delta$: 18.8, 26.2, 31.8, 38.0, 40.4, 50.3, 54.6, 108.4, 113.1, 121.1, 122.9, 125.4, 128.9, 138.7, 171.2, 178.6 and 209.8. GC-MS: *m/z* 383 ($M^{+\bullet}$+1, 7%), 382 ($M^{+\bullet}$, 25%), 299 (  , 5%), 284(  , 10%), 271 (  ,10% ), 257(  , 22%), 126 (  , 5%), 113 (  , 18%), 85 (  , 5%), 84 ( ; 60%), 70 (  , 58%), 69 (  ,70%). Anal. Calcd for $C_{20}H_{22}N_4O_4$: C 62.82, H 5.80, N 14.65%. Found C 62.98, H 5.87, N 14.49%. |
| **IVj** | MeOH | 276 | 83 | IR 3450 (NH), 1691, 1624 (>C=O), 1541 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, $CD_3OD$) $\delta$: 2.528 (s, 4H, 2× $CH_2$), 2.628-2.652 (t, 2H, J= 6Hz, $CH_2$), 3.064-3.088 (q, 2H, J= 6Hz & |

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| | | | | 7Hz, $CH_2$), 3.601 (s, 4H, 2× $CH_2$), 3.711-3.730 (t, 4H, J= 5 Hz, 2× $CH_2$), 7.058-7.090 (dt, 1H, 1Hz & 8.5Hz, Ar), 7.138-7.139 (d, 1H, J= 0.5Hz, Ar), 7.233-7.266 (m, 1H, Ar), 7.449-7.467 (dd, 1H, J= 1Hz & 8.5Hz, Ar), 7.626-7.643 (d, 1H, J= 8.5Hz, Ar). $^{13}$C NMR (125MHz, $CD_3OD$) $\delta$: 36.9, 50.3, 54.4, 56.0, 67.7, 108.6, 113.2, 121.1, 123.0, 125.5, 128.9, 130.5, 138.8, 166.1 and 171.2. GC-MS: *m/z* 355 ($M^{+\bullet}$+1, 7%), 354 ($M^{+\bullet}$, 25%), 284 (  , 10%), 256 (  , 12%), 210 (  , 50%), 84 (  , 100%), 71 (  , 25%), 70 (  , 55%), 69 (  , 87% ).<br><br>Anal. Calcd for $C_{19}H_{22}N_4O_3$: C 64.39, H 6.26, N 15.81%. Found C 64.51, H 6.32, N 15.97%. |
| **IVk** | MeOH | >300 | 81 | IR 3426 (NH), 1706 (>C=O), 1594 & 1523 (Ar) $cm^{-1}$. $^1$H NMR (500 MHz, $CD_3OD$) $\delta$: 2.509 (s, 4H, 2×$CH_2$), 2.610-2.638 (t, 2H, J= 7Hz, $CH_2$), 3.038-3.066 (t, 2H, J= 7Hz, $CH_2$), 3.522 (s, 4H, 2×$CH_2$), 3.641-3.659 (t, 4H, J= 4.5 Hz, 2×$CH_2$), 7.045-7.076 (t, 1H, J= 7.5 Hz, Ar), 7.107 (s, 1H, Ar), 7.217-7.250 (dt, 1H, J= 1 & 7.5 Hz, Ar), 7.442-7.460 (d, 1H, J= 9Hz, Ar), 7.615-7.632 (d, 1H, J= 8.5Hz, Ar). $^{13}$C NMR (125MHz, DMSO+$D_2O$) $\delta$: 24.1, 37.4, 50.3, 53.2, 55.1, 108.0, 113.1, 121.0, 122.9, 125.2, 128.9, 131.7, 138.6, 167.3, and 171.7. GC-MS: *m/z* 371 ($M^{+\bullet}$+1,10%), 370 ($M^{+\bullet}$, 50%), 284 (  , 11%), 271 (  , 11%), 257(  , 16%), 85 (  , 5%), 84 (, 35%).<br><br>Anal. Calcd for $C_{19}H_{22}N_4O_4$: C 61.61, H |

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| | | | | 5.99, N, 15.13%. Found C 61.79, H 5.88, N 15.32%. |
| **IVl** | MeOH | >300 | 83 | IR 3403 (NH), 1701 (>C=O), 1615 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, $CD_3OD$) $\delta$: 3.114-3.140 (t, 2H, J= 6.5 Hz, $CH_2$), 3.181-3.207 (t, 2H, J= 6.5Hz, $CH_2$), 3.522 (s, 4H, 2×$CH_2$), 6.917-6.947 (m, 2H, Ar), 7.046-7.077 (t, 1H, J= 7.5 Hz, Ar), 7.108 (s, 1H, Ar), 7.216-7.249 (dt, 1H, J= 1Hz & 8 Hz, Ar), 7.257-7.267 (d, 1H, J= 5Hz, Ar), 7.441-7.459 (d, 1H, J= 8.5Hz, Ar), 7.614-7.631 (d, 1H, J= 8.5Hz, Ar). $^{13}C$ NMR (125MHz, DMSO+$D_2O$) $\delta$: 26.9, 40.7, 48.1, 108.2, 113.1, 120.9, 122.9, 125.2, 127.6, 127.7, 128.9, 129.3, 131.3, 134.1, 138.7, 166.7 and 171.2. GC-MS: *m/z* 368 ($M^{+\bullet}$+1, 10%), 367 ($M^{+\bullet}$, 55%), 284 (  , 12%), 271 (  , 11%), 257 (  , 16%), 223 (  , 5%), 113 (  ,18%), 84 (  , 32%). Anal. Calcd for $C_{19}H_{17}N_3O_3S$: C 62.11,H 4.66, N 11.44%. Found C 62.28, H 4.71, N 11.35%. |

Various piperazine-2,6-diones (**IIIa-j**; Scheme 5.2) were condensed with 2,6-pyridine dicarboxylic acid (**Vx**), 3,5-pyridine dicarboxylic acid (**Vy**) and 2,5-thiophene dicarboxylic acid (**Vz**) under microwave irradiation to give corresponding condensation products (**VIax-jz**; Scheme 5.2) in good yields. Thus 1-cyclohexylpiperazine-2,6-dione (**IIIa**; Scheme 5.2) and 2,6-pyridine dicarboxylic acid (**Vx**; Scheme 5.2) were mixed together thoroughly in a molar ratio of 2:1 respectively. This reaction mixture was subjected to microwave irradiation at 850 W for three min and then progress of the

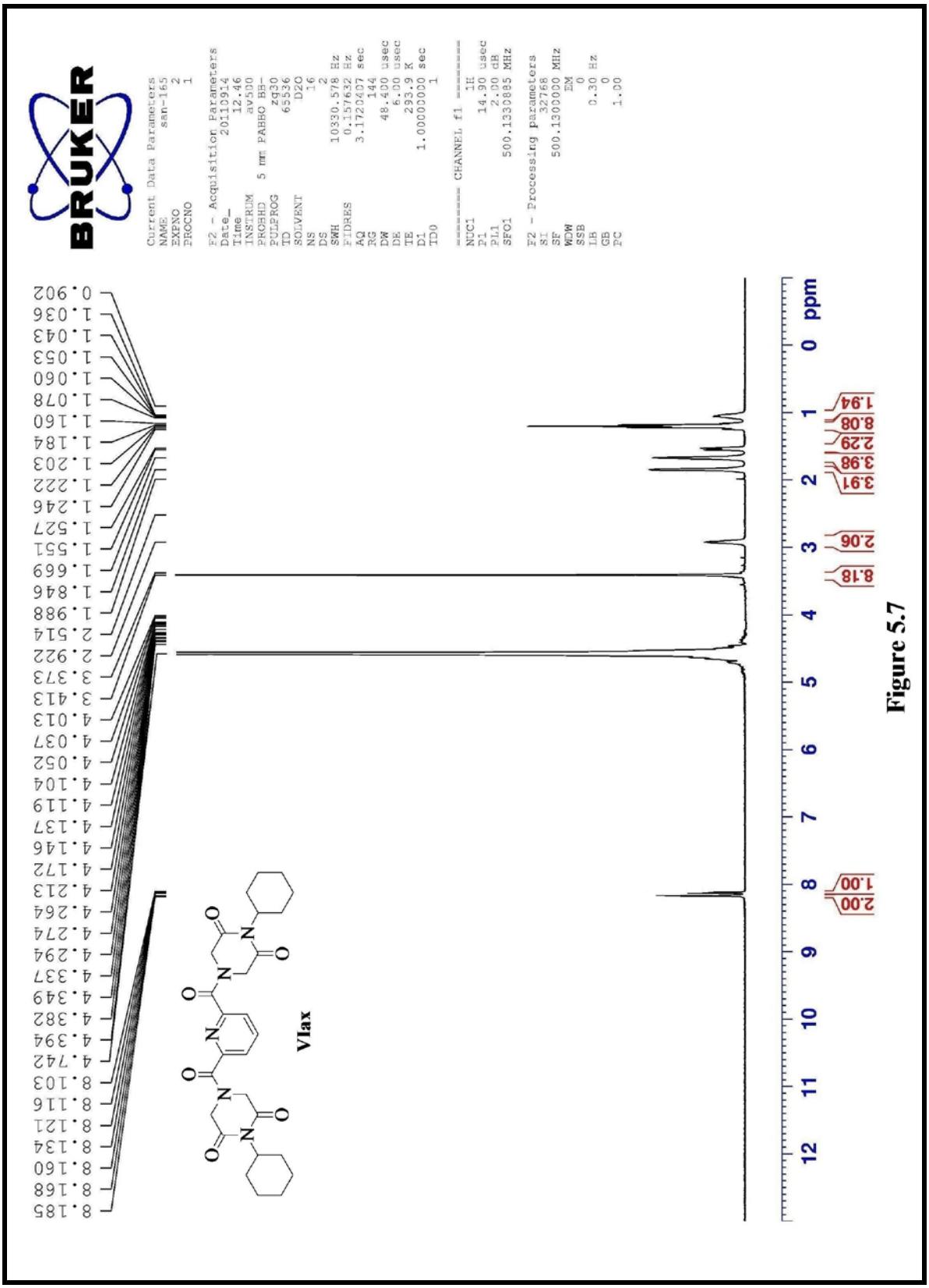



**Scheme 5.2** Synthesis of heterocyclic compounds **VIax-jz**

reaction was monitored by TLC on silica gel using ethyl acetate: methanol (2:3) as solvent of elution. TLC indicated presence of starting materials. This reaction mixture was again irradiated for three min (850 W) and TLC was performed, which indicated presence of starting materials. This reaction mixture was again irradiated for five min and TLC was performed. This time TLC indicated absence of starting materials and hence reaction was complete. The crude product so obtained was purified by crystallization from methanol to give pure product 2,6-bis-(1-cyclohexyl-2,6-dioxopiperazine-4-carbonyl) pyridine (**VIax**; Scheme 5.2) in 81% yield.

Alternatively a mixture of 1-cyclohexylpiperazine-2,6-dione (**IIIa**; Scheme 5.2) and 2,6-pyridine dicarboxylic acid (**Vx**; Scheme 5.2) in a molar ratio of 2:1 were mixed thoroughly and subjected to microwave irradiation at 150ºC for 12 min. TLC of this reaction mixture on silica gel using ethyl acetate: methanol (2:3) as mobile phase showed absence of starting materials. This crude product was crystallized from methanol to give pure condensed product **VIax** (Scheme 5.2) in 83% yield.

Reaction products obtained from both the methods was found to be same as monitored by TLC and co-TLC. Both the methods gave quantitative yield of the condensed product. IR spectrum of **VIax** show absorption bands at 1682 & 1669 (>C=O), 1612 & 1477 (Ar) $cm^{-1}$. $^{1}H$ NMR (500 MHz, $D_2O$) (Figure 5.7) δ: 1.036-1.078 (m, 2H), 1.160-1.246 (m, 8H), 1.527-1.551 (d, 2H, J = 12 Hz), 1.669 (s, 4H), 1.846 (s, 4H), 2.922 (s, 2H), 3.413 (s, 8H, 4×$CH_2$), 8.103-8.134 (q, 1H, J = 6.5 & 9.0 Hz, Ar), 8.168-8.185 (d, 2H, J = 8.5 Hz, Ar). $^{13}C$ NMR (125 MHz, $D_2O$) (Figure 5.8) δ: 23.581, 24.244, 30.015, 48.054, 49.182, 126.760, 139.464, 148.681, 166.293 and 168.039. GC-MS (*m/z*; relt. int. %) (Figure 5.9) of **VIax** gave $M^{+\bullet}$ ion peak at *m/z* 523 (76%). In addition to $M^{+\bullet}$ ion peak


BRUKER
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DS 2
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FIDRES 0.157632 Hz
AQ 3.1720407 sec
RG 144
DW 48.400 usec
DE 6.00 usec
TE 293.9 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 14.90 usec
PL1 2.00 dB
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SI 32768
SF 500.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
8.185
8.168
8.160
8.134
8.121
8.116
8.103
4.742
4.394
4.382
4.349
4.337
4.294
4.274
4.264
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4.172
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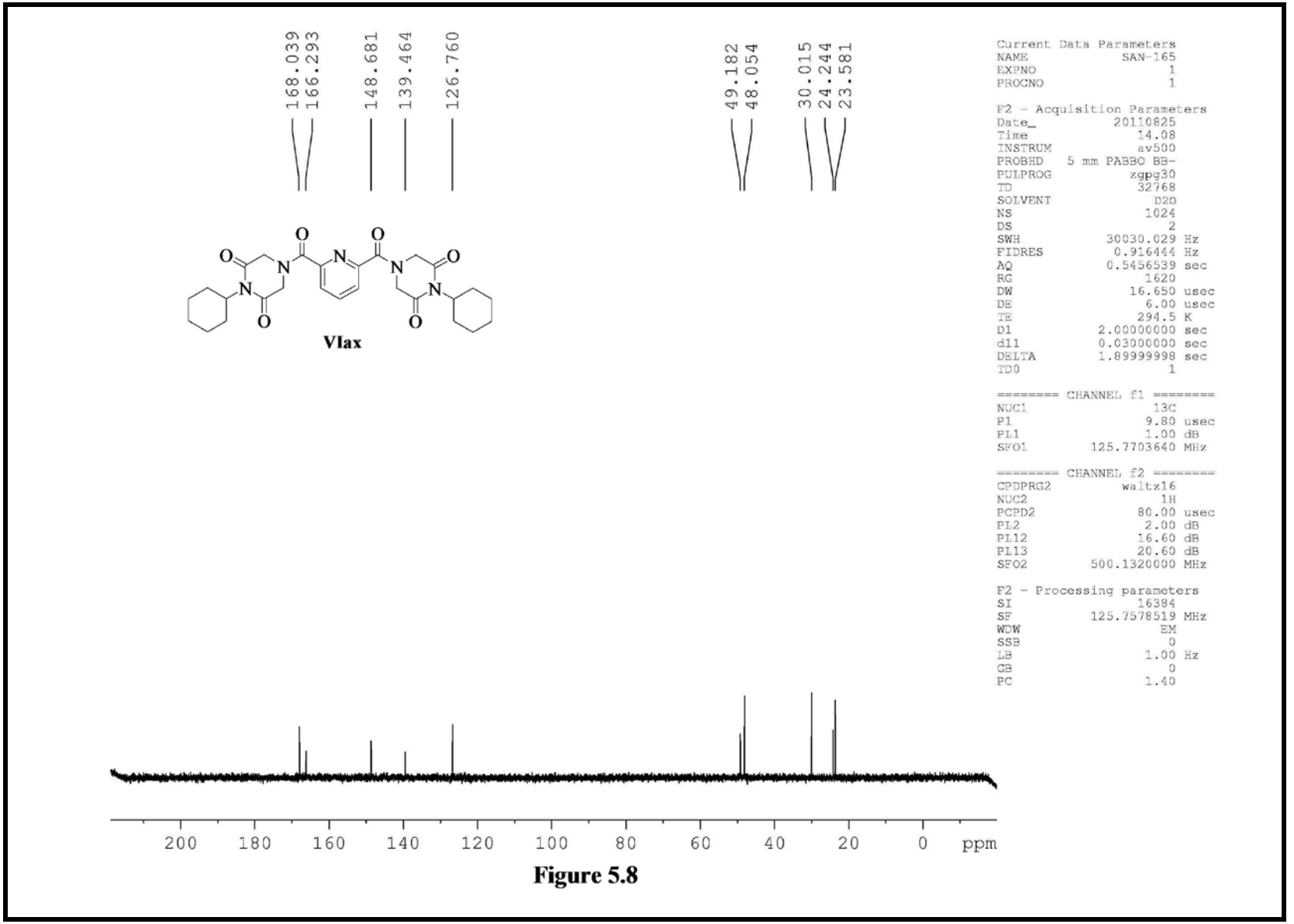
1.551
1.527
1.246
1.222
1.203
1.184
1.160
1.078
1.060
1.053
1.043
1.036
0.902
2.00
1.00
8.18
2.06
3.91
3.98
2.29
8.08
1.94
12 11 10 9 8 7 6 5 4 3 2 1 0 ppm
VIax

**Figure 5.7**

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PROCNO                      1

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SWH               30030.029 Hz
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AQ                0.5456539 sec
RG                     1620
DW                  16.650 usec
DE                   6.00 usec
TE                   294.5 K
D1              2.00000000 sec
d11             0.03000000 sec
DELTA           1.89999998 sec
TD0                        1

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PL1                   1.00 dB
SFO1           125.7703640 MHz

======== CHANNEL f2 ========
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PL2                   2.00 dB
PL12                 16.60 dB
PL13                 20.60 dB
SFO2           500.1320000 MHz

F2 - Processing parameters
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GB                           0
PC                    1.40
```

**Figure 5.8**

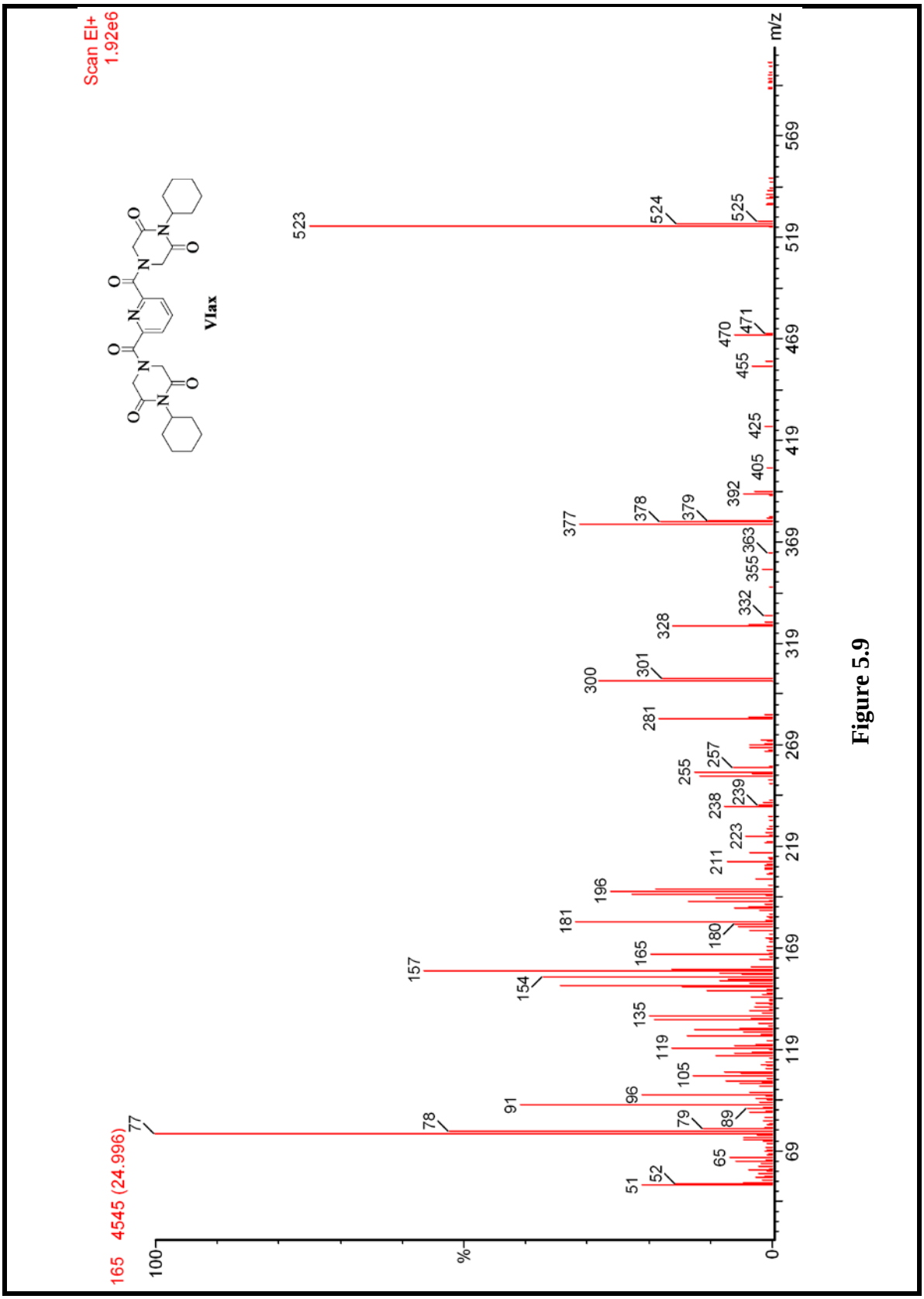

Scan EI+
1.92e6
VIax
165 4545 (24.996)
100
%
0
m/z
69
119
169
219
269
319
369
419
469
519
569
77
78
79
89
91
96
105
119
135
154
157
165
180
181
196
211
223
238
239
255
257
281
300
301
328
332
355
363
377
378
379
392
405
425
455
470
471
523
524
525

**Figure 5.9**

GCMS of **VIax** shows some other prominent peaks, which can arise through its fragmentation. The fragmentation pattern of **VIax** is outlined in chart 5.1. Elemental analysis Calculated for $C_{27}H_{33}N_5O_6$: C 61.95; H 6.30; N, 13.38%. Found: C 62.07; H 6.41; N, 13.32%. Spectral and analytical data of **VIax** fully support the structure assigned to it.

Similarly by following both the methods, compounds **VIay-jz** (Scheme 5.2) were synthesized. All these compounds were purified by crystallization from methanol. Spectral (IR, $^1$H NMR, $^{13}$C NMR, GC-MS or APCI-MS) and analytical data of **VIay-jz** (Scheme 5.2) reported in Table 5.3 is in agreement with the structures assigned to them.

**5.2.2 Biological results and discussion**

Fully characterized and purified compounds **IIIa-l, IVa-l** (Scheme 5.1) and **VIax-jz** (Scheme 5.2) were screened for anti-inflammatory activity [21, Chapter-2] using carrageenan induced paw oedema assay and results are summarized in Table 5.4 and 5.5. A look at Table 5.4 and 5.5 indicates that compounds **IVe, VIbx, VIcx, VIdx** and **VIex** exhibited good anti-inflammatory activity i.e. 37%, 43%, 38%, 38% and 39% respectively at 50 mg/kg p.o. as compared to ibuprofen which showed 39% activity at 50 mg/kg p.o..

Compounds **IVe, VIbx, VIcx, VIdx** and **VIex** which are heterocyclic molecules derived from **IIIe, IIIb, IIIc** and **IIId** exhibited good anti-inflammatory activity as compared to their parent molecules and thus coupling with 1H-indole-2-carboxylic acid in case of **IVe** and with 2,6-pyridine dicarboxylic acid in case of **VIbx, VIcx, VIdx** and **VIex** with **IIIe; IIIb, IIIc, IIId** and **IIIe** respectively proved beneficial.

**Fragmentation pattern of VIax**

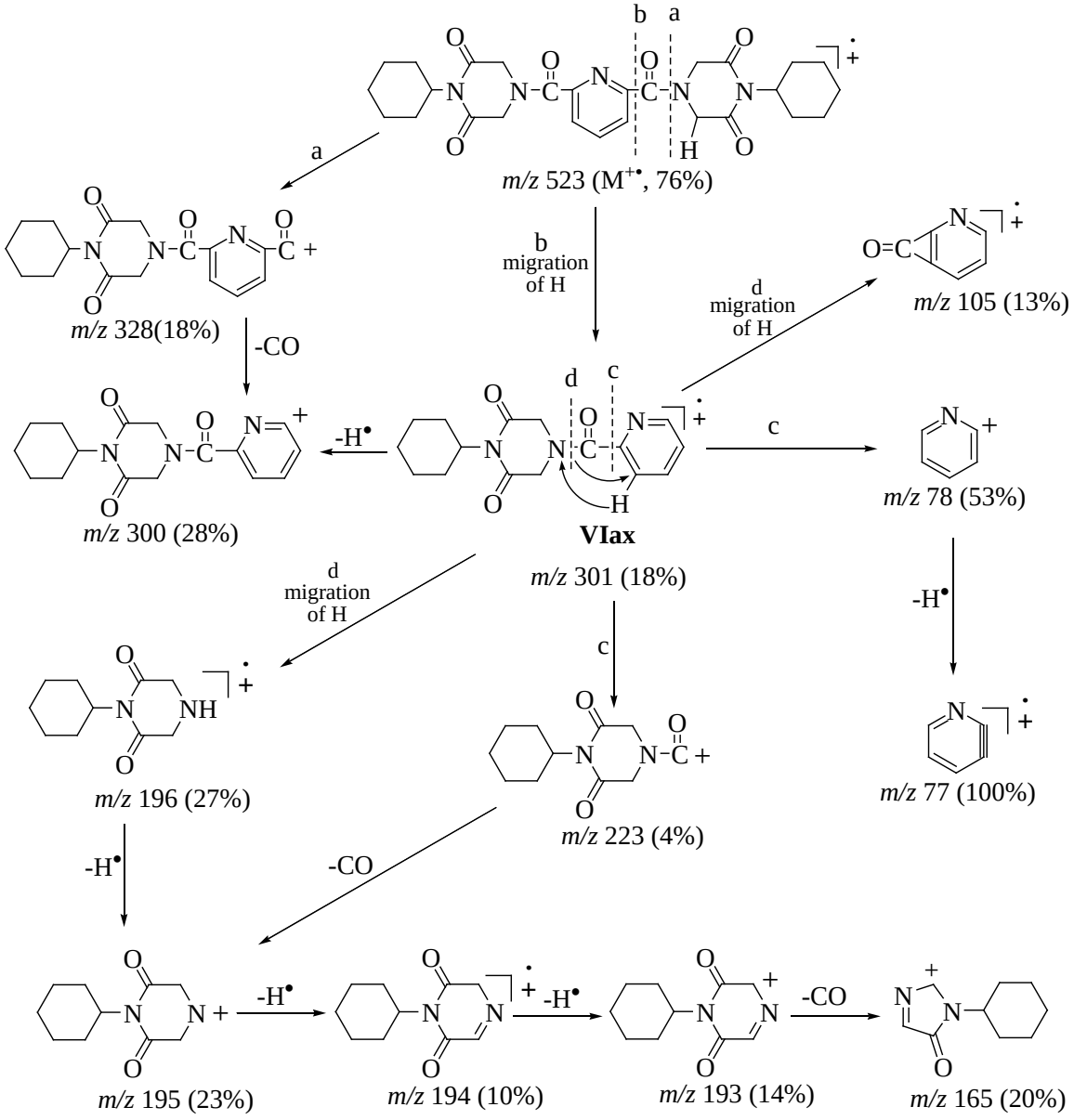
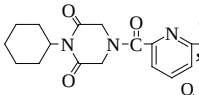
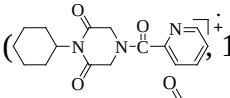
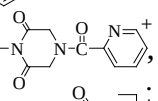
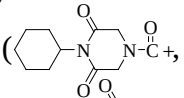
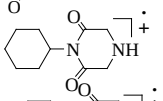
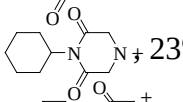
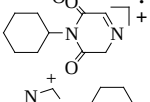
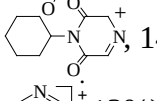
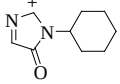
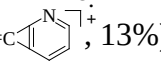
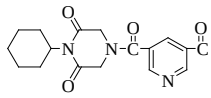
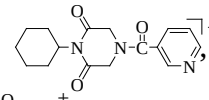
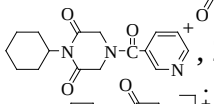
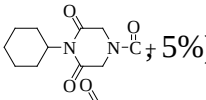
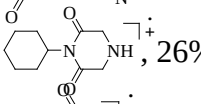
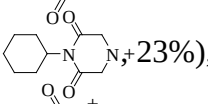
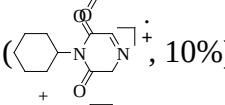
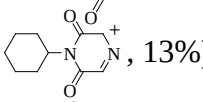
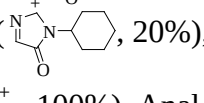
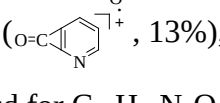
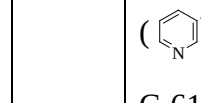
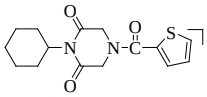
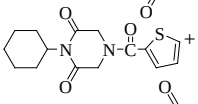
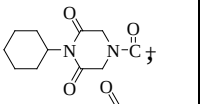
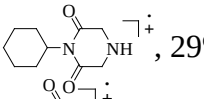
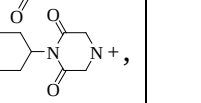
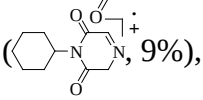
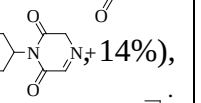
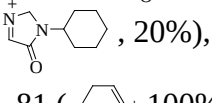
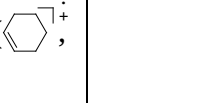
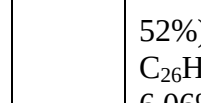
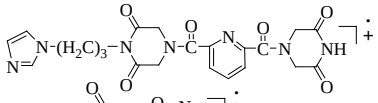
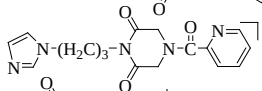
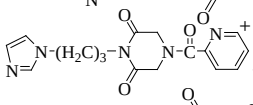
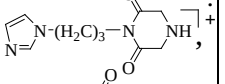
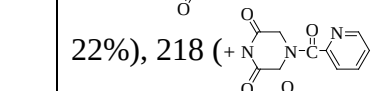
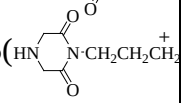
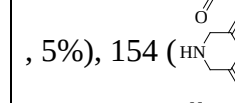
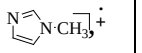
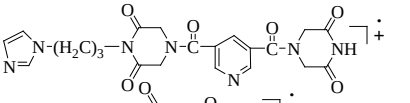
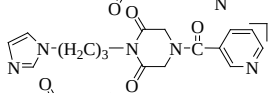
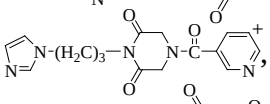
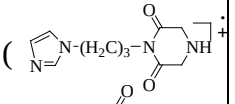
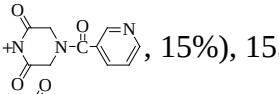
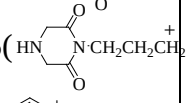
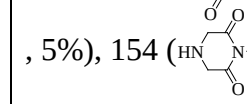


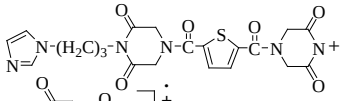
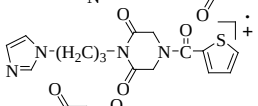
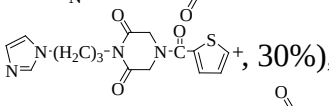
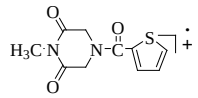
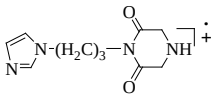
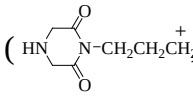
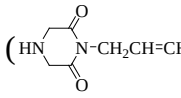
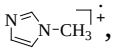
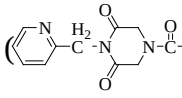
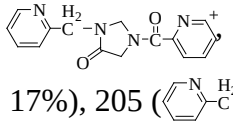
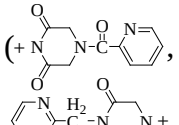
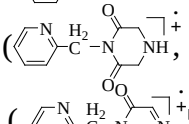
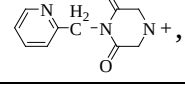
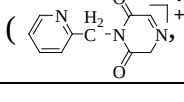

**Chart 5.1**

**Table 5.3: Physical constants and spectral data of heterocyclic compounds VIax-jz.**

| Comp no | Solvent of cryst./elution | m.p. °C | Yield % | IR (KBr) $cm^{-1}$, $^1H$ (500MHz) & $^{13}C$ (125MHz) NMR ($D_2O$), $\delta$ J(Hz), GC-MS/APCI-MS (*m/z*; relt int %) |
|---|---|---|---|---|
| **1** | **2** | **3** | **4** | **5** |
| **VIax** | MeOH | >300 | 81 | IR 1682, 1669 (>C=O), 1612, 1477 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, $D_2O$) δ : 1.036-1.078 (m, 2H), 1.160-1.246 (m, 8H), 1.527-1.551 (d, 2H, J = 12 Hz), 1.669 (s, 4H), 1.846 (s, 4H), 2.922 (s, 2H), 3.413 (s, 8H, 4×$CH_2$), 8.103-8.134 (q, 1H, J = 6.5 & 9.0 Hz, Ar), 8.168-8.185 (d, 2H, J = 8.5 Hz, Ar). $^{13}C$ NMR (125 MHz, $D_2O$) δ: 23.5, 24.2, 30.0, 48.0, 49.1, 126.7, 139.4, 148.6, 166.2 and 168.0. GC-MS : *m/z* 523 ($M^{+\bullet}$, 76%), 328 (  , 18%), 301 (  , 18%), 300 (  , 28%), 223 (  , 4%), 196 (  , 27%), 195 (  , 23%),194 (  , 10%), 193 (  , 14 %),165 (  , 20%), 105 (  , 13%), 78 (  , 53%), 77 (  , 100%). Anal. Calcd for $C_{27}H_{33}N_5O_6$: C 61.95; H 6.30; N 13.38%. Found: C 62.07; H 6.41; N 13.32%. |
| **VIay** | MeOH | >300 | 78 | IR 1694 (>C=O), 1590, 1497 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, $D_2O$) δ : 1.032-1.081 (m, 2H), 1.162-1.248 (m, 8H, 4×$CH_2$), 1.525-1.550 (d, J = 12.5 Hz, 2H), 1.742 (s, 4H, 2×$CH_2$), 1.849 (s, 4H, 2×$CH_2$), 2.925 (s, 2H, CH+CH), 3.415 (s, 8H, 4×$CH_2$), 8.604 (s, 1H, Ar), 9.242 (s, 2H, Ar). $^{13}C$ NMR (125 MHz, $D_2O$) δ : 23.5, 24.2, 30.0, 48.0, 49.0, 126.5, 144.2, 152.0, 166.5 and 168.2. GC- MS: *m/z* 523 ($M^{+\bullet}$, 50%), 328 (  , 16%), |

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| | | | | 301 (  , 12%), 300 (  , 23%), 223 (  , 5%), 196 (  , 26%), 195 (  , 23%), 194 (  , 10%), 193 (  , 13%), 165 (  , 20%), 105 (  , 13%), 78 (  , 100%). Anal. Calcd for $C_{27}H_{33}N_5O_6$: C 61.94; H 6.35; N 13.38%. Found: C 61.82; H 6.39; N 13.43%. |
| **VIaz** | MeOH | >300 | 81 | IR 1680, 1667 (>C=O), 1611 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, $D_2O$) δ : 1.030-1.079 (m, 2H), 1.162-1.248 (m, 8H), 1.526-1.551 (d, 2H, J = 12.5 Hz), 1.738 (s, 4H), 1.848 (s, 4H), 2.923 (s, 2H), 3.415 (s, 8H, 4×$CH_2$), 7.568 (s, 2H, Ar). $^{13}C$ NMR (125 MHz, $D_2O$) δ : 23.5, 24.2, 29.9, 48.0, 49.0, 131.9, 141.8, 163.4 and 168.1. GC-MS: *m/z* 528 ($M^{+\bullet}$, 49%), 306 (  , 46%) 305 (  , 56%), 223(  , 5%), 196 (  , 29%), 195 (  , 23%), 194 (  , 9%), 193 (  , 14%), 165 (  , 20%), 83 ( , 5%), 82 (  , 52%), 81 (  , 100%). Anal. Calcd for $C_{26}H_{32}N_4O_6S$: C 59.09; H 6.06; N 10.60; S 6.06%. Found: C 59.19; H 6.15; N 10.53; S 6.11%. |
| **VIbx** | MeOH | >300 | 76 | IR 1692 (>C=O), 1619, 1536 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, $D_2O$) δ : 1.985-2.043 (m, 4H, 2×$CH_2$), 2.781-2.813 (t, 4H, J = 8.0 Hz, 2×$CH_2$), 3.461 (s, 8H, 4×$CH_2$), 3.983-4.010 (t, 4H, J = 6.5 Hz, 2×$CH_2$), 6.909 (s, 2H, Ar), 7.050 |

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| | | | | (s, 2H, Ar), 7.628 (s, 2H, Ar), 8.103-8.183 (m, 3H, Ar). $^{13}$C NMR (125 MHz, $D_2O$) δ : 27.1, 35.7, 46.6, 48.7, 119.8, 121.3, 130.8, 134.3, 139.3, 144.0, 165.9 and 168.7. GC-MS: *m/z* 575 ($M^{+\bullet}$, 18%), 467(  , 10%), 327 (  ,16%), 326 (  , 33%), 222 (  , 22%), 218 (  , 15%), 155(  , 5%), 154 (  ; 38%), 82 (  , 46%), 78 (  , 100%), 67 (  ,35%). Anal.<br><br>Calcd for $C_{27}H_{29}N_9O_6$: C 56.34; H 5.04; N 21.91%. Found C 56.45; H 5.11; N 21.82%. |
| **VIby** | MeOH | >300 | 74 | IR 1698 (>C=O), 1610, 1536 (Ar) $cm^{-1}$. $^1$H NMR (500 MHz, $D_2O$) δ : 2.004-2.067 (m, 4H, 2×$CH_2$), 2.782-2.814 (t, 4H, J = 8 Hz, 2×$CH_2$), 3.782 (s, 8H, 4×$CH_2$), 3.983-4.011 (t, 4H, J = 7 Hz, 2×$CH_2$), 6.909 (s, 2H, Ar), 7.050 (s, 2H, Ar), 7.628(s, 2H, Ar), 8.658 (s, 1H, Ar), 9.209 (s, 2H, Ar). $^{13}$C NMR (125 MHz, $D_2O$) δ : 28.1, 35.4, 46.5, 49.0, 119.8, 121.9, 131.0, 134.9, 140.3, 144.0, 165.5 and 168.7. GC-MS *m/z* 575 ($M^{+\bullet}$, 38%), 467 (  , 10%), 327 (  , 16%), 326 (  , 40%), 222 (  , 23%), 218 (  , 15%), 155(  , 5%), 154 (  ,31%), 78 (  , 100%), 67 (  ; 35%). Anal. Calcd for $C_{27}H_{29}N_9O_6$: C 56.34; H 5.04; N 21.91%. Found C 56.47; H 5.13; N 21.78%. |

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| **VIbz** | MeOH | >300 | 74 | IR 1693 (>C=O), 1619, 1538 (Ar) $cm^{-1}$. $^{1}H$ NMR (500 MHz, $D_2O$) δ : 1.986-2.041 (m, 4H, 2×$CH_2$), 2.782-2.814 (t, 4H, J = 8.0 Hz, 2×$CH_2$), 3.472 (s, 8H, 4×$CH_2$), 3.983-4.010 (t, 4H, J = 6.5 Hz, 2×$CH_2$), 6.909 (s, 2H, Ar), 7.050 (s, 2H, Ar), 7.478 (s, 2H, Ar), 7.628 (s, 2H, Ar). $^{13}C$ NMR (125 MHz, $D_2O$) δ : 27.1, 35.3, 46.6, 48.1, 119.3, 120.9, 130.9, 134.2, 144.2, 165.4 and 168.6. GC-MS: *m/z* 580 ($M^{+\bullet}$, 21%), 471 (  , 6%), 332 (  , 9%), 331 (  , 30%), 238 (  , 8%), 222 (  , 27%), 155 (  , 4%), 154 (  , 37%), 82 (  , 100%), 67 (, 35%). Anal.<br><br>Calcd for $C_{26}H_{28}N_8O_6S$: C 53.78; H 4.86; N 19.31%. Found C 53.93; H 4.91; N 19.39%. |
| **VIcx** | MeOH | >300 | 81 | IR 1695, 1636 (>C=O), 1514 (Ar) $cm^{-1}$. $^{1}H$ NMR (500 MHz, $D_2O$) δ: 3.348 (s, 8H, 4×$CH_2$), 4.168 (s, 4H, 2×$CH_2$), 7.363-7.388 (t, 2H, J = 6 Hz, Ar), 7.433-7.448 (d, 2H, J = 7.5 Hz, Ar), 7.803-7.834 (t, 2 H, J = 7.5 Hz, Ar), 8.041-8.072 (t, 1H, J = 7.5 Hz, Ar), 8.111-8.126 (d, 2H, J = 7.5 Hz, Ar), 8.558-8.566 (d, 2H, J = 4 Hz, Ar). $^{13}C$ NMR (125 MHz, $D_2O$) δ: 42.4, 48.3, 122.4, 123.4, 126.1, 137.3, 138.8, 148.8, 149.9, 152.7, 167.0 and 168.3. GC-MS: *m/z* 541 ($M^{+\bullet}$, 25%), 310 (  , 9%), 309 (, 28%), 281 (  , 19%), 218 (  , 17%), 205 (  , 8%), 204 (  , 21%), 203 (  , 5%), 105 |

| 1 | 2 | 3 | 4 | 5 |
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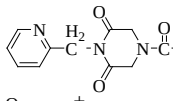
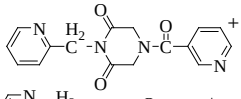
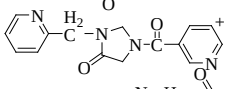
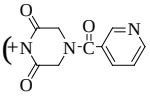
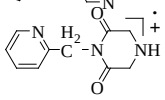
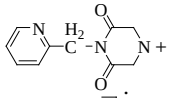
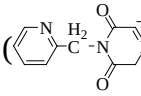
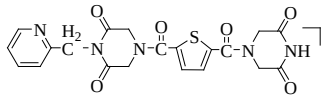
| | | | | (, 13%), 78 (, 100%). Anal. Calcd for $C_{27}H_{23}N_7O_6$: C 59.89; H 4.28; N 18.11%. Found C 59.76; H 4.32; N 18.17%. |
| **VIcy** | MeOH | >300 | 78 | IR 1696 (>C=O), 1513 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz; $D_2O$) δ : 3.348 (s, 8H, 4×$CH_2$), 4.177 (s, 4H, 2×$CH_2$), 7.364-7.389 (t, 2H, J = 6 Hz, Ar), 7.433-7.448 (d, 2H, J = 7.5 Hz, Ar), 7.800-7.831 (t, 2H, J = 7.5 Hz, Ar), 8.111-8.126 (d, 2H, J = 7.5 Hz, Ar), 8.666 (s, 1H, Ar), 9.208 (s, 2H, Ar). $^{13}C$ NMR (125 MHz, $D_2O$) δ : 42.2, 48.3, 122.4, 123.4, 126.1, 137.0, 138.0, 147.9, 149.0, 153.1, 167.2 and 168.3. GC-MS *m/z* 541 ($M^{+\bullet}$, 33%), 310 (  , 2%), 309 (  , 22%), 281 (  , 18%), 218 (  , 16%), 205 (  , 7%), 204 (  , 20%), 203 (  , 5%), 105 (  , 13%), 78 (  , 100%). Anal. Calcd for $C_{27}H_{23}N_7O_6$: C 59.89; H 4.28; N 18.11%. Found C 59.97; H 4.31; N 18.16%. |
| **VIcz** | MeOH | >300 | 79 | IR 1697, 1635 (>C=O), 1515 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, $D_2O$) δ: 3.357 (s, 8H, 4×$CH_2$), 4.005 (s, 4H, 2×$CH_2$), 7.363-7.387 (t, 2H, J = 5.5 Hz, Ar), 7.400-7.415 (d, 2H, J = 7.5 Hz, Ar), 7.542 (s, 2H, Ar), 7.799-7.828 (t, 2H, J = 7.5 Hz, Ar), 8.546-8.555 (d, 2H, J = 4.5 Hz, Ar). $^{13}C$ NMR (125 MHz, $D_2O$) δ: 42.6, 48.1, 122.4, 123.5, 131.9, 137.4, 142.0, 148.9, 152.1, 163.9 and 168.5. GC- MS: *m/z* 546 ($M^{+\bullet}$, 19%), 455 (  , 3%), |

| 1 | 2 | 3 | 4 | 5 |
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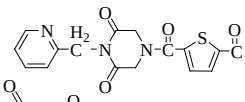
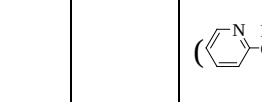
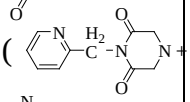
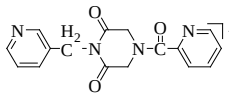
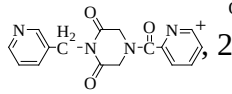
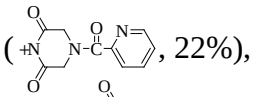
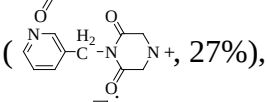
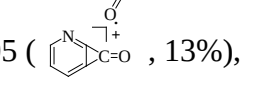
| | | | | 342 (  , 10%), 314 (  ; 9%), 313 (  , 24%), 205 (  , 7%), 204 (  , 23%), 203 (  , 5%), 78 (  , 100%). Anal. Calcd for $C_{26}H_{22}N_6O_6S$: C 57.14; H 4.03; N 15.38%. Found C 57.26; H 4.11; N 15.32%. |
| **VIdx** | MeOH | >300 | 83 | IR 1698 (>C=O), 1514 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, $D_2O$) δ: 3.502 (s, 8H, 4×$CH_2$), 4.092 (s, 4H, 2×$CH_2$), 7.382-7.406 (t, 2H, Ar), 7.812-7.827 (d, 2H, J = 7.5 Hz, Ar), 8.103-8.183 (m, 3H, Ar), 8.425-8.457 (t, 4H, Ar). $^{13}C$ NMR (125 MHz, $D_2O$) δ: 40.8, 48.0, 122.4, 123.3, 126.3, 132.6, 139.1, 142.9, 149.0, 149.2, 166.9 and 168.3. GC- MS: *m/z* 541 ($M^{+\bullet}$, 32%), 310 (  , 9%), 309 (  , 25%), 281 (  , 24%), 218 (  , 22%), 205 (  , 7%), 204 (  , 27%), 203 (  , 5%), 105 (  , 13%), 78 (  , 100%). Anal. Calcd for $C_{27}H_{23}N_7O_6$: C 59.89; H 4.25; N 18.11%. Found C 59.97; H 4.25; N 18.17%. |
| **VIdy** | MeOH | >300 | 78 | IR 1699 (>C=O), 1514 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz; $D_2O$) δ : 3.292 (s, 8H, 4×$CH_2$), 4.636 (s, 4H, 2×$CH_2$), 7.382-7.406 (t, 2H, Ar), 7.812-7.827 (d, 2H, J = 7.5 Hz, Ar), 8.425-8.457 (t, 4H, Ar), 8.625 (s, 1H, Ar), 9.202 (s, 2H, Ar). $^{13}C$ NMR (125 MHz, $D_2O$) δ: 41.3, 48.7, 122.4, 123.7, 126.5, 132.6, 139.3, 142.9, 149.1, 150.2, 167.0 and 168.7. GC-MS *m/z* 541 ($M^{+\bullet}$,23%), 310 |

| 1 | 2 | 3 | 4 | 5 |
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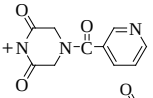
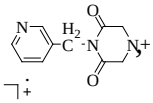
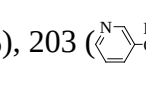
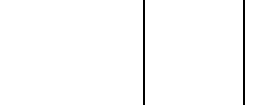
| | | | | (, 4%), 309 (, 20%), 281 (, 20%), 218 (  , 29%), 205 (; 7%), 204 (  , 27%), 203 (, 4%),105 (  ; 13%), 78 (  , 100%). Anal. Calcd for $C_{27}H_{23}N_7O_6$: C 59.89; H 4.28; N 18.11%. Found C 60.02; H 4.23; N 18.19%. |
| **VIdz** | MeOH | >300 | 78 | IR 1695, 1637 (>C=O), 1514 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, $D_2O$) δ: 3.502 (s, 8H, 4×$CH_2$), 4.092 (s, 4H, 2×$CH_2$), 7.381-7.407 (t, 2H, Ar), 7.568 (s, 2H, Ar), 7.813-7.828 (d, 2H, J = 7.5 Hz, Ar), 8.425-8.457 (t, 4H, Ar). $^{13}C$ NMR (125 MHz, $D_2O$) δ: 40.8, 48.5, 122.4, 123.9, 126.3, 132.0, 139.5, 142.9, 149.0, 166.2 and 168.3. GC-MS: *m/z* 546 ($M^{+\bullet}$, 27%), 455 (  , 3%), 342 (, 10%), 314 (, 9%), 313 (; 30%), 205 (, 7%), 204 (, 29%), 203 (, 5%), 78 (, 100%).<br>Anal. Calcd for $C_{26}H_{22}N_6O_6S$: C 57.14; H 4.03; N 15.38%. Found C 57.27; H 4.09; N 15.32%. |
| **VIex** | MeOH | >300 | 81 | IR 1698, 1643 (>C=O), 1514 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, $D_2O$) δ: 3.533 (s, 8H, 4×$CH_2$), 4.116 (s, 4H, 2×$CH_2$), 7.370 (s, 4H, Ar), 8.103-8.183 (m, 3H, Ar), 8.432 (s, 4H, Ar). $^{13}C$ NMR (125 MHz, $D_2O$) δ: 39.6, 48.1, 123.9, 126.4, 129.6, 137.5, 139.1, 149.3, 167.0 and 168.4. GC-MS: *m/z* 541 ($M^{+\bullet}$, 37%), 310 (, 9%), 309 (, |

| 1 | 2 | 3 | 4 | 5 |
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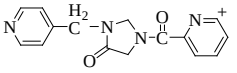
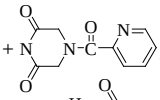
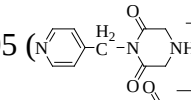
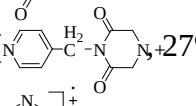
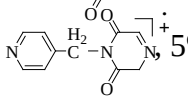
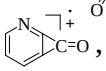
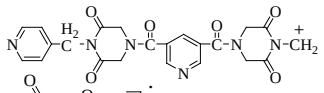
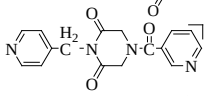
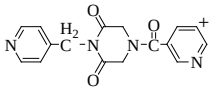
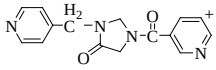
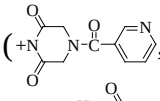
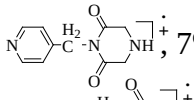
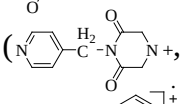
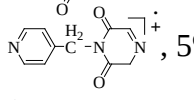
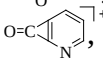
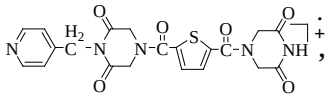
| | | | | 24%), 281 (  , 24%), 218(  , 24%), 205 (  , 9%), 204 (  , 27%), 203 (  , 5%), 105(  , 14%), 78 (  , 100%). Anal.<br><br>Calcd for $C_{27}H_{23}N_7O_6$: C 59.89; H 4.28; N 18.11%. Found C 59.79; H 4.21; N 18.17%. |
| **VIey** | MeOH | >300 | 76 | IR 1696, 1645 (>C=O), 1515 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz; $D_2O$) δ : 3.533 (s, 8H, 4×$CH_2$), 4.116 (s, 4H, 2×$CH_2$), 7.370 (s, 4H, Ar), 8.214 (s, 1H, Ar), 8.464 (s, 4H, Ar), 9.599 (s, 2H, Ar). $^{13}C$ NMR (125 MHz, $D_2O$) δ: 39.1, 48.1, 123.7, 126.4, 129.6, 137.5, 139.1, 151.0, 167.6 and 168.4. GC-MS: *m/z* 541 ($M^{+\bullet}$, 30%),<br><br>463 (  , 6%), 310 (  , 9%), 309 (  , 29%), 281 (  , 24%), 218 (  , 17%), 205 (  , 7%), 204 (  , 32%), 203 (  , 5%), 105 (  , 13%), 78(  , 100%). Anal.<br><br>Calcd for $C_{27}H_{23}N_7O_6$: C 59.89; H 4.28; N 18.11%. Found C 59.73; H 4.23; N 18.02%. |
| **VIez** | MeOH | >300 | 76 | IR 1698, 1641 (>C=O), 1513 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, $D_2O$) δ: 3.533 (s, 8H, 4×$CH_2$), 4.116 (s, 4H, 2×$CH_2$), 7.370 (s, 4H, Ar), 7.542 (s, 2H, Ar), 8.464 (s, 4H, Ar). $^{13}C$ NMR (125 MHz, $D_2O$) δ: 39.7, 48.4, 126.3, 129.4, 137.4, 139.1, 149.4, 163.7 and 168.3. GC-MS: *m/z* 546 ($M^{+\bullet}$, 26%), 455<br><br>(  , 3%), 342 |

| 1 | 2 | 3 | 4 | 5 |
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| | | | | (, 8%), 314 (, 8%), 313 (, 17%), 205 (, 7%), 204 (, 32%), 203(, 5%), 78 (, 100%).<br>Anal. Calcd for $C_{26}H_{22}N_6O_6S$: C 57.14; H 4.03; N 15.38%. Found C 57.28; H 4.10; N 15.43%. |
| **VIfx** | MeOH | >300 | 74 | IR 1700 (>C=O), 1615, 1478 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, $D_2O$) δ: 3.625 (s, 8H, 4×$CH_2$), 4.319 (s, 4H, 2×$CH_2$), 6.544-6.653 (q, 2H, J = 1.5 & 3.0 Hz, Ar), 6.617-6.623 (d, 2H, J = 3 Hz, Ar), 7.153-7.157 (d, 2H, J = 2.5 Hz, Ar), 8.289-8.304 (d, 2H, J = 7.5 Hz, Ar), 8.545-8.580 (t, 1H, J = 8.5 Hz, Ar). $^{13}C$ NMR (125 MHz, $D_2O$) δ: 34.1, 48.5, 122.4, 122.9, 126.5, 139.4, 143.6, 146.6, 148.6, 166.6 and 168.4. GC-MS: *m/z* 551 ($M^{+\bullet}$, 22%), 454 (, 10%), 342 (, 10%), 315 (, 17%), 314 (, 33%) 210 (, 7%), 209 (, 13%), 208 (, 7%), 181 (, 36%), 180 (, 6%), 98 (, 36%), 82 (, 46%), 78 (, 100%). Anal. Calcd for $C_{25}H_{21}N_5O_6S_2$: C 54.44; H 3.81; N 12.70%. Found C 54.61; H 3.89; N 12.63%. |
| **VIfy** | MeOH | >300 | 73 | IR 1697, 1653 (>C=O), 1594, 1497 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz; $D_2O$) δ : 3.563 (s, 8H, 4×$CH_2$), 4.304 (s, 4H, 2×$CH_2$), 6.545-6.654 (q, 2H, J = 1.5 & 3.0 Hz, Ar), 6.617-6.623 (d, 2H, J = 3 Hz, Ar), 7.160-7.165 (d, 2H, J = 2.5 Hz, Ar), 8.599 (s, 1H, Ar), 9.289 (s, 2H, Ar). |

| 1 | 2 | 3 | 4 | 5 |
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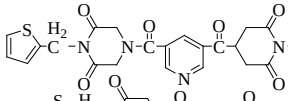
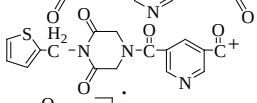
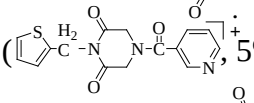
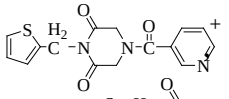
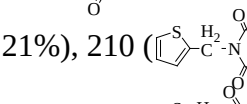
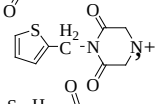
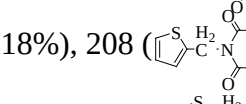
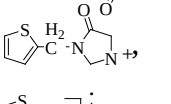
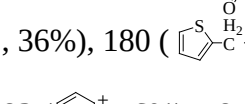
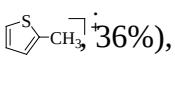
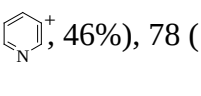
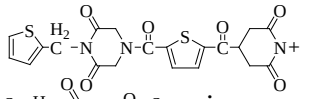
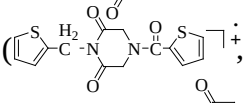
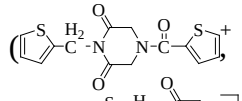
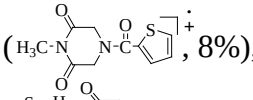
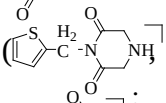
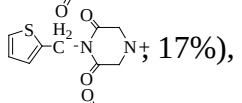
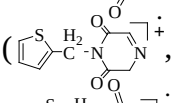
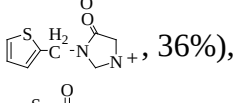
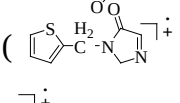
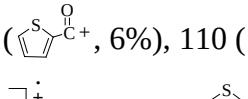
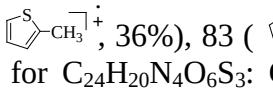
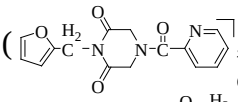
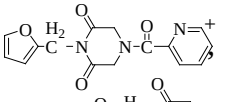
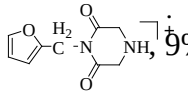
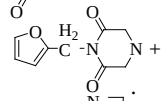
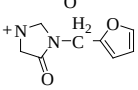
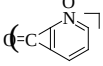
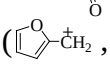
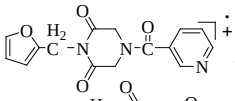
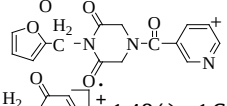
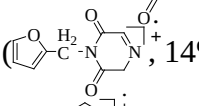
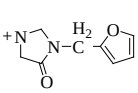
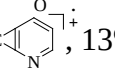
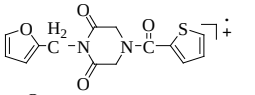
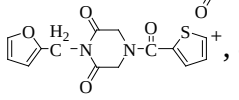
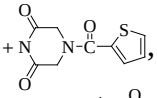
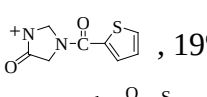
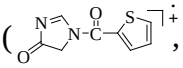
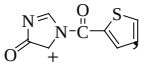
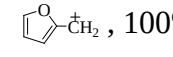
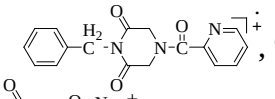
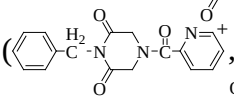
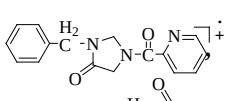
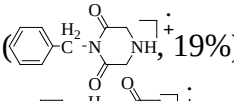
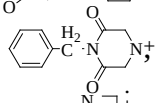
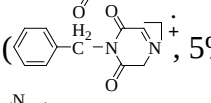
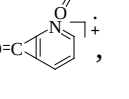
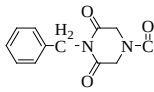
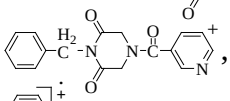
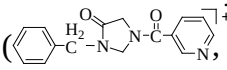
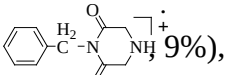
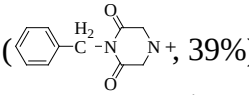
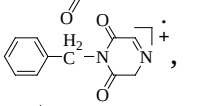
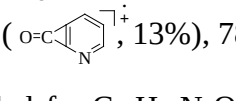
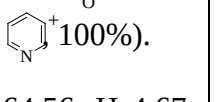
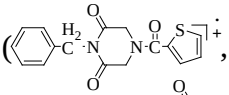
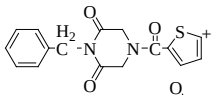
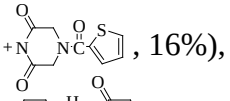
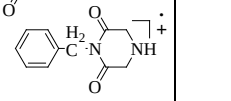
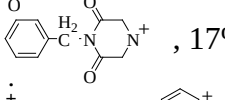
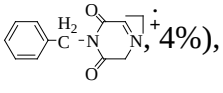
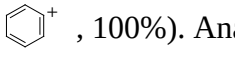
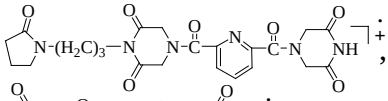
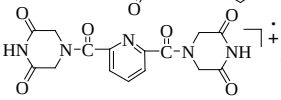
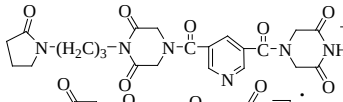
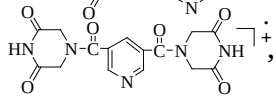
| | | | | $^{13}$C NMR (125 MHz, $D_2O$) δ: 34.2, 48.1, 122.5, 122.9, 126.4, 139.6, 143.5, 146.1, 148.6, 167.6 and 168.4.GC-MS: *m/z* 551 ($M^{+\bullet}$, 30%), 454 (  , 11%), 342 (  , 10%), 315 (  , 5%), 314 (  21%), 210 (  , 7%), 209 (  , 18%), 208 (  , 4%), 181 (  , 36%), 180 (  , 6%), 98 (  , 36%), 83 (  , 46%), 78 (  , 100%). Anal. Calcd for $C_{25}H_{21}N_5O_6S_2$: C 54.44; H 3.81; N 12.70%. Found C 54.31; H 3.79; N 12.82%. |
| **VIfz** | MeOH | >300 | 75 | IR 1702 (>C=O), 1612, 1519 (Ar) $cm^{-1}$. $^1$H NMR (500 MHz, $D_2O$) δ: 3.458 (s, 8H, 4×$CH_2$), 4.236 (s, 4H, 2×$CH_2$), 6.934-6.965 (m, 2H, Ar), 7.349-7.362 (t, 2H, J= 3.0 Hz, Ar), 7.366 (s, 2H, Ar), 7.523 (s, 2H, Ar). $^{13}$C NMR (125 MHz, $D_2O$) δ: 34.8, 48.5, 120.9, 121.5, 122.4, 122.9, 126.5, 130.4, 166.6 and 168.4. GC-MS: *m/z* 556 ($M^{+\bullet}$, 30%), 459 (  , 10%), 320 (  , 14%), 319 (  , 29%), 238 (  , 8%), 210 (  , 7%), 209 (  , 17%), 208 (  , 7%), 181 (  , 36%), 180 (  , 7%), 111 (  , 6%), 110 (  , 17%), 98 (  , 36%), 83 (  , 100%). Anal. Calcd for $C_{24}H_{20}N_4O_6S_3$: C 51.79; H 3.59; N 10.07%. Found C 51.89; H 3.57; N 10.18%. |

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| **VIgx** | MeOH | >300 | 76 | IR 1701 (>C=O), 1613, 1476 (Ar) $cm^{-1}$. $^{1}H$ NMR (500 MHz, $D_2O$) δ: 3.620 (s, 8H, 4×$CH_2$), 4.305 (s, 4H, 2×$CH_2$), 6.343-6.353 (q, 2H, J = 2 & 3.5 Hz, Ar), 6.417-6.423 (d, 2H, J = 3 Hz, Ar), 7.433-7.438 (d, 2H, J = 2.5 Hz, Ar), 8.289-8.304 (d, 2H, J = 7.5 Hz, Ar), 8.545-8.580 (t, 1H, J = 8.5 Hz, Ar). $^{13}C$ NMR (125 MHz, $D_2O$) δ: 34.8, 48.1, 110.4, 110.9, 126.5, 139.4, 143.6, 146.6, 149.0, 166.8 and 168.4. GC-MS: *m/z* 519 ($M^{+\bullet}$, 55%), 299 (  , 9%), 298 (  , 28%), 194 (  , 9%), 193(  , 14%), 165 (  , 20%), 105 (  , 13%), 81 (  , 46%), 78 (  , 52%), 77 (, 100%), 67 (  , 37%). Anal. Calcd for $C_{25}H_{21}N_5O_8$: C 57.80; H 4.05; N 13.48%. Found: C 57.71; H 4.11; N 13.41%. |
| **VIgy** | MeOH | >300 | 75 | IR 1700 (>C=O), 1614, 1476 (Ar) $cm^{-1}$.$^{1}H$ NMR (500 MHz; $D_2O$) *δ* : 3.618 (s, 8H, 4×$CH_2$), 4.495 (s, 4H, 2×$CH_2$), 6.343-6.353 (q, 2H, J = 1.5 & 3.0 Hz, Ar), 6.418-6.424 (d, 2H, J = 3 Hz, Ar), 7.434-7.439 (d, 2H, J = 2.5 Hz, Ar), 8.604 (s, 1H, Ar), 9.242 (s, 2H, Ar). $^{13}C$ NMR (125 MHz, $D_2O$) *δ*: 34.8, 48.1, 110.4, 110.9, 126.5, 140.1, 144.2, 146.1, 150.0, 166.8 and 168.4. GC- MS *m/z* 519 ($M^{+\bullet}$, 33%), 299 (  , 4%), 298 (  , 24%), 193 192 (  , 14%), 165 (  , 20%), 105 (  , 13%), 78 (  , 100%), 67 (  , 35%). Anal. Calcd for $C_{25}H_{21}N_5O_8$: C 57.80; H 4.07; N 13.48%. Found: C 57.93; H 4.12; N 13.55%. |

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| **VIgz** | MeOH | >300 | 77 | IR 1700 (>C=O), 1613, 1475, (Ar) $cm^{-1}$. $^{1}H$ NMR (500 MHz, $D_2O$) δ: 3.478 (s, 8H, 4×$CH_2$), 4.070 (s, 4H, 2×$CH_2$), 6.331-6.337 (t, 1H, J = 1.5 Hz, Ar), 6.403-6.409 (d, 1H, J = 3 Hz, Ar,), 7.424-7.429 (d, 2H, J = 2.5 Hz, Ar), 7.554 (s, 4H, Ar). $^{13}C$ NMR (125 MHz, $D_2O$) δ: 34.8, 47.9, 110.6, 110.9, 132.3, 141.6, 143.7, 146.2, 164.1 and 168.6. GC- MS: *m/z* 524 ($M^{+\bullet}$, 41%), 304 (  , 38%), 303 (  , 48%), 223 (  , 5%), 195 (  , 19%). 194 (  , 5%), 193 (  , 39%), 82 (  , 52%), 81 (  , 100%), 67 (  , 60%). Anal. Calcd for $C_{24}H_{20}N_4O_8S$: C 54.96; H 3.81; N 10.68%. Found: C 54.87; H 3.87; N 10.62%. |
| **VIhx** | MeOH | >300 | 79 | IR 1653 (>C=O), 1594, 1497 (Ar) $cm^{-1}$. $^{1}H$ NMR (500 MHz, $D_2O$) δ: 3.446 (s, 8H, 4×$CH_2$), 4.009 (s, 4H, 2×$CH_2$), 7.295-7.305 (d, 10H, J = 5 Hz, Ar), 8.100-8.134 (m, 1H, Ar), 8.169-8.184 (d, 2H, J = 7.5 Hz, Ar). $^{13}C$ NMR (125 MHz, $D_2O$) δ: 43.3, 49.0, 123.1, 124.1, 133.3, 138.4, 144.2, 149.2, 151.5, 167.0 and 171.3. GC-MS: *m/z* 539 ($M^{+\bullet}$, 40%), 309 (  , 9%), 308 (  , 28%), 281 (  , 18%), 204 (  , 19%), 203 (  , 26%), 202 (  , 5%), 105 (  , 13%), 78 (, 52%), 77 (, 100%). Anal. Calcd for $C_{29}H_{25}N_5O_6$: C 64.56; H 4.67; N 12.98%. Found C 64.67; H 4.64; N 12.91%. |

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| **VIhy** | MeOH | >300 | 73 | IR 1655 (>C=O), 1594, 1497 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, $D_2O$) δ: 3.556 (s, 8H, 4×$CH_2$), 4.009 (s, 4H, 2×$CH_2$), 7.295-7.305 (d, 10H, J = 5 Hz, Ar), 8.625 (s, 1H, Ar), 9.202 (s, 2H, Ar). $^{13}C$ NMR (125 MHz, $D_2O$) δ: 43.9, 49.2, 123.1, 124.1, 133.2, 137.4, 144.2, 150.0, 151.8, 168.0 and 170.6. GC- MS: *m/z* 539 ($M^{+\bullet}$, 31%), 309 (  ,  , 9%), 308 (, 39%), 281 (  , 19%), 204 (  , 9%), 203 (  , 39%), 202 (  , 5%), 105 (  , 13%), 78 (  , 100%).<br><br>Anal. Calcd for $C_{29}H_{25}N_5O_6$: C 64.56; H 4.67; N 12.98%. Found C 64.48; H 4.72; N 12.88%. |
| **VIhz** | MeOH | >300 | 74 | IR 1685 (>C=O), 1594, 1492 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, $D_2O$) δ: 3.447 (s, 8H, 4×$CH_2$), 4.008 (s, 4H, 2×$CH_2$), 7.296-7.306 (d, 10H, J = 5 Hz, Ar), 7.698 (s, 2H, Ar). $^{13}C$ NMR (125 MHz, $D_2O$) δ: 42.1, 48.1, 127.1, 132.0, 133.2, 138.2, 141.8, 147.8, 163.6 and 168.2. GC-MS: *m/z* 544 ($M^{+\bullet}$, 24%), 314 (  , 9%), 313 (  , 28%), 223 (  , 16%), 204 (  , 7%), 203 (  , 17%), 202 (  , 4%), 77 (  , 100%). Anal.<br><br>Calcd for $C_{28}H_{24}N_4O_6S$: C 61.75; H 4.44; N 10.29%. Found C 61.66; H 4.47; N 10.32%. |
| **VIix** | MeOH | >300 | 76 | IR 1700 (>C=O), 1596, 1532, (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, $D_2O$) δ: 1.874-1.933 (m, 4H, 2×$CH_2$), 2.042-2.073 (t, 4H, J = 7.5 Hz, 2×$CH_2$), 2.386-2.418 (t, 4H, J = 8 Hz, 2×$CH_2$), 2.910-2.940 (t, 4H, J = 7.5 Hz, 2×$CH_2$), 3.369- |

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| | | | | 3.396 (t, 4H, J = 6.5 Hz, 2×$CH_2$), 3.449-3-478 (t, 4H, J = 7.5 Hz, 2×$CH_2$), 3.586 (s, 8H, 4×$CH_2$), 8.103-8.185 (m, 3H, Ar). $^{13}$C NMR (125 MHz, $D_2O$) δ: 18.8, 26.2, 31.1, 38.0, 40.4, 48.1, 130.9, 134.2, 144.2, 165.4, 168.6 and 173.1. APCI-MS: *m/z* 610.53 ($MH^+$, 100%), 484.63 (  , 14%), 359.23 (  , 11%). Anal. Calcd for $C_{29}H_{35}N_7O_8$: C 57.13; H 5.79; N 16.08%. Found C 57.28; H 5.74; N 16.21%. |
| **VIiy** | MeOH | >300 | 74 | IR 1689 (>C=O), 1612, 1487 (Ar) $cm^{-1}$. $^1$H NMR (500 MHz; $D_2O$) *δ* : 1.874-1.931 (m, 4H, 2×$CH_2$), 2.043-2.073 (t, 4H, J = 7.5 Hz, 2×$CH_2$), 2.386-2.418 (t, 4H, J = 8 Hz, 2×$CH_2$), 2.911-2.941 (t, 4H, J = 7.5 Hz, 2×$CH_2$), 3.369-3.396 (t, 4H, J = 6.5 Hz, 2×$CH_2$), 3.449-3.478 (t, 4H, J = 7.5 Hz, 2×$CH_2$), 3.599 (s, 8H, 4×$CH_2$), 8.605 (s, 1H, Ar), 9.124 (s, 2H, Ar). $^{13}$C NMR (125 MHz, $D_2O$) *δ*: 18.4, 26.2, 31.2, 38.0, 40.8, 48.9, 130.2, 134.4, 148.7, 165.7, 168.2 and 174.1. APCI-MS: *m/z* 610.83 ($MH^+$, 100%), 484.14 (  , 24%), 359.25 (  , 19%). Anal. Calcd for $C_{29}H_{35}N_7O_8$: C 57.13; H 5.74; N 16.08%. Found C 57.26; H 5.83; N 16.19%. |
| **VIiz** | MeOH | >300 | 72 | IR 1702 (>C=O), 1591, 1532 (Ar) $cm^{-1}$. $^1$H NMR (500 MHz, $D_2O$) δ: 1.790-1.851 (m, 4H, 2×$CH_2$), 1.928-1.958 (t, 4H, J = 7.5 Hz, 2×$CH_2$), 2.316-2.349 (t, 4H, J = 8 Hz, 2×$CH_2$), 2.854-2.884 (t, 4H, J = 7.5 Hz, 2×$CH_2$), 3.246-3.273 (t, 4H, J = 6.5 Hz, 2×$CH_2$), 3.384-3.413 (t, 4H, J = 7 Hz, 2×$CH_2$), 3.550 (s, 8H, 4×$CH_2$), 7.568 (s, 2H, Ar). $^{13}$C NMR (125 MHz, $D_2O$) δ: 18.1, 26.2, 31.1, 38.0, 40.9, 49.0, 130.2, 134.1, 165.4, 168.2 and 173.4. APCI-MS: *m/z* 615.76 ($MH^+$, 100%), |

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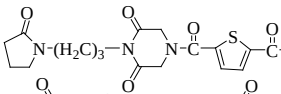
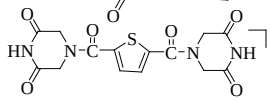
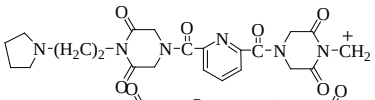
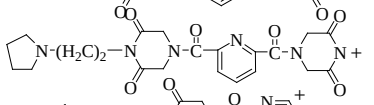
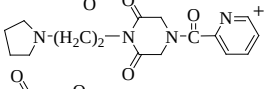
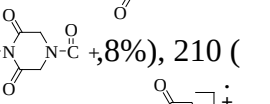
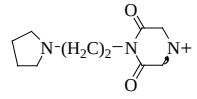
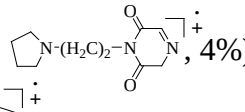
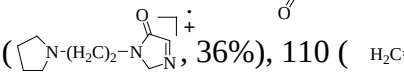
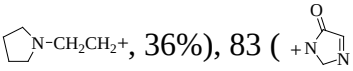
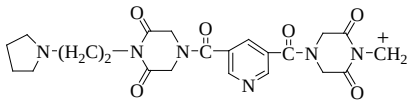
|---|---|---|---|---|
| | | | | 489.64 (  , 14%), 364.70 (  , 11%). Anal. Calcd for $C_{28}H_{34}N_6O_8S$: C 54.72; H 5.54; N 13.68%. Found C 54.86; H 5.63; N 13.75%. |
| **VIjx** | MeOH | >300 | 76 | IR 1683, 1671 (>C=O), 1612, 1478, (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, $D_2O$) δ: 8.103-8.186 (m, 3H, Ar), 3.493 (s, 8H, 4×$CH_2$), 3.003-3.072 (m, 16H, 8×$CH_2$), 1.859 (s, 8H, 4×$CH_2$). $^{13}C$ NMR (125 MHz, $D_2O$) δ: 171.4, 168.6, 164.4, 144.2, 134.2, 130.9, 53.9, 53.5, 48.9, 36.2 and 22.4. GC-MS: *m/z* 553 ($M^{+\bullet}$, 27%), 469 (  , 8%), 455 (  , 10%), 315 (  , 11%), 238 (  ,8%), 210 (  19%), 209 (  , 4%), 181 (  , 36%), 110 ( , 17%), 98 (  , 36%), 83 (  , 100%). Anal. Calcd for $C_{27}H_{35}N_7O_6$: C 58.58; H 6.37; N 17.71%. Found C 58.69; H 6.31; N 17.79%. |
| **VIjy** | MeOH | >300 | 73 | IR 1695, 1676 (>C=O), 1621, 1478 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz; $D_2O$) *δ* : 1.799 (s, 8H, 4×$CH_2$), 3.005-3.074 (m, 16H, 8×$CH_2$), 3.594 (s, 8H, 4×$CH_2$), 8.635(s, 1H, Ar), 9.268 (s, 2H, Ar). $^{13}C$ NMR (125 MHz, $D_2O$) *δ*: 23.0, 36.6, 49.2, 53.6, 54.1, 131.2, 134.2, 144.7, 164.4, 168.4 and 171.5. GC-MS *m/z* 553 ($M^{+\bullet}$, 36%), 469 (  , 7%), 455 |

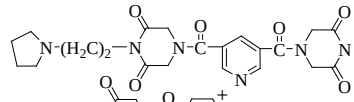
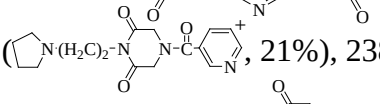
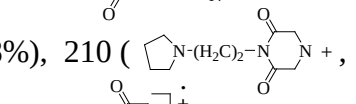
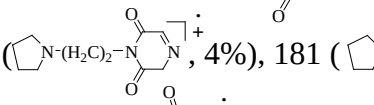
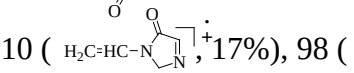
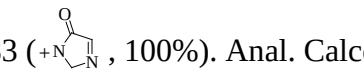
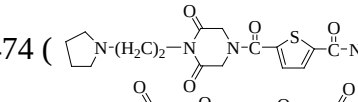
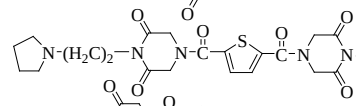
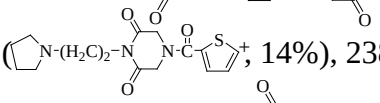
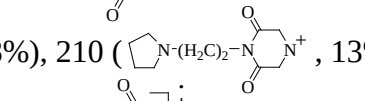
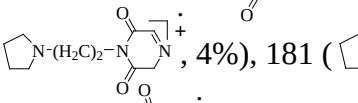
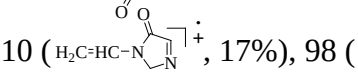
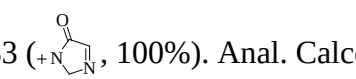
| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| **VIjz** | MeOH | >300 | 73 | (  , 9%), 315 (  , 21%), 238 ( , 8%), 210 (  , 19%), 209 (  , 4%), 181 ( , 36%), 110 (  , 17%), 98 (  , 36%), 83 ( , 100%). Anal. Calcd for $C_{27}H_{35}N_7O_6$: C 58.58; H 6.33; N 17.71%. Found C 58.44; H 6.43; N 17.65%. |
| | | | | IR 1691 (>C=O), 1624, 1512 (Ar) $cm^{-1}$. $^1H$ NMR (500 MHz, $D_2O$) δ: 1.872 (s, 8H, 4×$CH_2$), 3.005-3.092 (m, 16H, 8×$CH_2$), 3.493 (s, 8H, 4×$CH_2$), 7.572 (s, 2H, Ar). $^{13}C$ NMR (125 MHz, $D_2O$) δ: 22.5, 36.2, 48.9, 53.6, 53.9, 130.2, 134.1, 164.4, 168.2 and 171.4. GC-MS: *m/z* 558 ($M^{+\bullet}$, 30%), 474 (  , 8%), 460 (  , 2%), 320 (  , 14%), 238 ( , 8%), 210 (  , 13%), 209 (  , 4%), 181 ( , 36%) 110 (  , 17%), 98 (  , 36%), 83 ( , 100%). Anal. Calcd for $C_{26}H_{34}N_6O_6S$: C 55.91; H 6.09; N 15.05%. Found C 55.77; H 6.19; N 15.13%. |

Table-5.4 Anti-inflammatory** and *in vitro* anticancer** activity of compounds **IIIa-l** and **IVa-l**

| Compd. No. | Anti-inflammatory activity (%) at 50 mg/kg p.o. | Anticancer activity[a] at a concentration of $1\times10^{-5}$ M | | | | |
|---|---|---|---|---|---|---|
| | | Breast T47D | Lung NCI H-522 | Colon HCT-15 | Ovary PA1 | Liver HepG2 |
| **1** | 2 | **3** | **4** | **5** | **6** | **7** |
| **IIIa** | 12 | 15 | 11 | 07 | 24 | 38 |
| **IIIb** | 18 | 08 | 08 | 32 | 23 | 13 |
| **IIIc** | 25 | 16 | 08 | 01 | 17 | 31 |
| **IIId** | 24 | 08 | 04 | 20 | 20 | 21 |
| **IIIe** | 27 | 04 | 08 | 33 | 27 | 25 |
| **IIIf** | 16 | 08 | 15 | 04 | 18 | 29 |
| **IIIg** | 07 | 04 | 07 | 30 | 26 | 21 |
| **IIIh** | 10 | 15 | 16 | 03 | 22 | **46** |
| **IIIi** | 07 | 21 | 21 | 19 | 25 | 40 |
| **IIIj** | 21 | 01 | 00 | **49** | 26 | 18 |
| **IIIk** | 11 | 01 | 09 | 04 | 37 | 38 |
| **IIIl** | 10 | 16 | 21 | 25 | 15 | 24 |
| **IVa** | 16 | 07 | 06 | 30 | 40 | 25 |
| **IVb** | 24 | 00 | 00 | 07 | 17 | 34 |
| **IVc** | 34 | 20 | 19 | 02 | 23 | 34 |
| **IVd** | 30 | 12 | 04 | 14 | 13 | 17 |
| **IVe** | **37** | 21 | 05 | 38 | **42** | 20 |
| **IVf** | 15 | 06 | 00 | 15 | 24 | **45** |
| **IVg** | 21 | 21 | 15 | 24 | 23 | 36 |
| **IVh** | 15 | 10 | 14 | 12 | 16 | 11 |



**Contd…**

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| **IVi** | 21 | 14 | 08 | 27 | 08 | 11 |
| **IVj** | 19 | 16 | **31** | 17 | 29 | 30 |
| **IVk** | 27 | 16 | 08 | 07 | 18 | 03 |
| **IVl** | **36** | 09 | 14 | 04 | 11 | 19 |
| Ibuprofen | 39 | - | - | - | - | - |
| [b]FU | - | 15 | 13 | 19 | 22 | 32 |
| [b]CYC-PHO | - | 09 | 11 | 04 | 12 | 18 |
| [c]CYC-HEXI | - | 11 | 09 | 16 | 34 | 18 |

[a] Compounds tested in triplicate, data expressed as mean value of three independent experiments.

[b] 5-FU 5-Fluorouracil.

[c] CYC-PHO Cyclophosphamide.

[d] CYC-HEXI Cycloheximide.

Bold values represent compounds showing good anticancer activity.

[**] We are thankful to Dr. Partha Roy, Department of Biotechnology, Indian Institute of Technology-Roorkee, Roorkee for these results.

Table-5.5 Anti-inflammatory** and *in vitro* anticancer** activity of compounds **VIax-jz**

| Compd. No. | Anti-inflammatory activity (%) at 50 mg/kg p.o. | Anticancer activity at a concentration of $1\times10^{-5}$ M | | | | |
|---|---|---|---|---|---|---|
| | | Breast T47D | Lung NCI H-522 | Colon HCT-15 | Ovary PA1 | Liver HepG2 |
| **1** | 2 | **3** | **4** | **5** | **6** | **7** |
| **VIax** | 17 | 28 | 25 | 04 | 21 | 07 |
| **VIay** | 13 | 02 | **39** | 08 | 28 | **36** |
| **VIaz** | 16 | 19 | 26 | **33** | 25 | **36** |
| **VIbx** | **43** | 17 | 15 | 26 | 34 | 11 |
| **VIby** | 19 | 19 | 14 | 12 | 16 | 03 |
| **VIbz** | 13 | 06 | 29 | 31 | 10 | 01 |
| **VIcx** | **38** | 20 | 15 | 10 | 21 | 13 |
| **VIcy** | 32 | 16 | 28 | 18 | 15 | 25 |
| **VIcz** | 33 | 27 | 24 | 27 | 13 | **35** |
| **VIdx** | **38** | 06 | 32 | **35** | 17 | 19 |
| **VIdy** | 31 | 14 | 32 | 24 | 20 | 16 |
| **VIdz** | 34 | 15 | 13 | 24 | 18 | 07 |
| **VIex** | **39** | 11 | 20 | 40 | 20 | 13 |
| **VIey** | 14 | 11 | 19 | 26 | 13 | 07 |
| **VIez** | 34 | 17 | 29 | **30** | 02 | **33** |
| **VIfx** | 07 | 10 | 31 | **36** | 05 | 31 |
| **VIfy** | 15 | 19 | 15 | 26 | 12 | 17 |
| **VIfz** | 06 | NT | NT | NT | NT | NT |
| **VIgx** | 17 | 14 | 26 | 12 | 20 | **35** |



**Contd…**

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| **VIgy** | 30 | 01 | 18 | 16 | 16 | 29 |
| **VIgz** | 14 | 01 | 09 | 21 | 13 | 13 |
| **VIhx** | 00 | 09 | 16 | 16 | 06 | 29 |
| **VIhy** | 32 | 11 | 23 | 12 | 08 | 17 |
| **VIhz** | 06 | 06 | 15 | **33** | 01 | 32 |
| **VIix** | 20 | 11 | 23 | 07 | 11 | 10 |
| **VIiy** | 27 | 09 | 06 | 12 | 03 | 10 |
| **VIiz** | 08 | 05 | 15 | 16 | 19 | 07 |
| **VIjx** | 05 | 12 | 07 | 12 | 11 | 11 |
| **VIjy** | 35 | 11 | 05 | 03 | 10 | 06 |
| **VIjz** | 00 | 06 | 01 | 02 | 10 | 12 |
| Ibuprofen | 39 | - | - | - | - | - |
| [b]5-FU | - | 18 | 24 | 20 | 21 | 18 |
| [b]CYC-PHO | - | 16 | 15 | 13 | 30 | 26 |
| [c]CYC-HEXI | - | 26 | 11 | 12 | 15 | 18 |

[a] Compounds tested in triplicate, data expressed as mean value of three independent experiments.
[b] 5-FU 5-Fluorouracil.
[c] CYC-PHO Cyclophosphamide.
[d] CYC-HEXI Cycloheximide.
Bold values represent compounds showing good anticancer activity.
NT Not Tested.
[**] We are thankful to Dr. Partha Roy, Department of Biotechnology, Indian Institute of Technology-Roorkee, Roorkee for these results.

Piperazine-2,6-dione derivatives **IIIa-l** (Scheme 5.1), 4-(1H-indole-2-carbonyl)-piperazine-2,6-dione derivatives **IVa-l** (Scheme 5.1) and heterocyclic molecules derived from 2,6-dioxopiperazine derivatives i.e. **VIax-jz** (Scheme 5.2) were screened in vitro for anticancer activity [32, Chapter 4a] against five human cancer cell lines i.e. breast (T47D), lung (NCl H-522), colon (HCT-15), ovary (PA-1) and liver (HepG-2) at a concentration of $1\times10^{-5}$ M and results are summarized in Table 5.4 and 5.5. A look at Table 5.4 and 5.5 indicate that the compounds **VIax** breast (T47D), **VIay** lung (NCl H-522), **IIIj** colon (HCT-15), **IVe** ovary (PA-1) and **IIIh, IVf** liver (HepG-2) exhibited good anticancer activities against various cancer cell lines mentioned above.

## 5.3 Experimental

### *5.3.1 General*

Microwave reactor model CEM DISCOVER model NO 908010 and microwave oven model M197DL (Samsung) were used for microwave irradiation. Melting points (mp) were determined on a JSGW apparatus and are uncorrected. IR spectra were recorded using a Perkin Elmer 1600 FT spectrometer. $^{1}$H and $^{13}$C NMR spectra were recorded on a Bruker WH-500 spectrometer at a *ca* 5-15% (*w/v*) solution in deuterated solvent (TMS as internal standard). GCMS was recorded on Perkin Elmer Clarus 500 gas chromatograph where built in MS detector was used. APCI mass was recorded using Finnigan Mat LCQ Mass Spectrometer. Elemental analysis was carried out on a Vario EL III elementor. Thin layer chromatography (TLC) was performed on silica gel G for TLC (Merck) and spots were visualized by iodine vapors or by irradiation with ultraviolet light (254nm). Compounds **IIIa-l, IVa-l** and **VIax-jz** were purified by crystallization from

methanol. Physical constants, spectral data and elemental analysis of **IIIa-l, IVa-l** and **VIax-jz** are reported in Table 5.1, 5.2 and 5.3 respectively.

### 5.3.2 General procedure for synthesis of piperazine-2,6-dione derivatives IIIa-l

5.3.2.1 Synthesis of 1-cyclohexylpiperazine-2,6-dione (**IIIa**)

(i) Iminodiacetic acid **I** (0.133 g; 1 mmol) and cyclohexanamine (0.100 g; 1 mmol) were mixed thoroughly to form a homogeneous mixture. This mixture was subjected to microwave irradiation at 85°C for 3 min. TLC of the reaction mixture on silica gel using ethyl acetate/methanol (1:1) as mobile phase showed absence of starting materials. Crude product so obtained was purified by crystallization from methanol to get pure product **IIIa** in quantitative yield (84%).

(ii) Above experiment was also performed by irradiating homogeneous mixture at a power level of 300W for 3 min. Completion of the reaction was checked by TLC on silica gel using ethyl acetate/methanol (1:1) as mobile phase. Crude product so obtained was purified by crystallization from methanol to get pure product **IIIa** in quantitative yield (85%). Yields of product **IIIa** obtained by method (i) and (ii) are comparable.

Similarly other piperazine derivatives **(IIIb-l)** i.e. 1-(3-imidazol-1-yl-propyl)-piperazine-2,6-dione (**IIIb**), 1-(pyridin-2-ylmethyl)piperazine-2,6-dione (**IIIc**), 1-(pyridin-3-ylmethyl)piperazine-2,6-dione (**IIId**), 1-(pyridin-4-ylmethyl)piperazine-2,6-dione (**IIIe**), 1-thiophen-2-ylmethyl-piperazine-2,6-dione (**IIIf**), 1-furan-2-ylmethyl-piperazine-2,6-dione (**IIIg**), 1-benzylpiperazine 2,6-dione (**IIIh**), 1-[3-(2-oxo-pyrrolidin-1-yl)-propyl]-piperazine-2,6-dione (**IIIi**), 1-(2-pyrrolidin-1-yl-ethyl)-piperazine-2,6-dione (**IIIj**), 1-(2-morpholino ethyl)piperazine-2,6-dione (**IIIk**) and 1-(2-thiophen-2-yl-ethyl)-piperazine-2,6-dione (**IIIl**) were synthesized and reported in Table 5.1.

### 5.3.3 General procedure for synthesis of 4-(1H-indole-2-carbonyl)piperazine-2,6-dione derivatives IVa-l

5.3.3.1 Synthesis of 1-cyclohexyl-4-(1H-indole-2-carbonyl)piperazine-2,6-dione (**IVa**)

(i) Cyclohexylpiperazine-2,6-dione **IIIa** (0.196 g; 1mmol) and 1H-indole-2-carboxylic acid (0.161 g;1mmol) were mixed thoroughly to form a homogeneous mixture. This reaction mixture was subjected to microwave irradiation at 150°C for 7 min. TLC of the reaction mixture on silica gel using ethyl acetate/methanol (1:1) as mobile phase showed absence of starting materials. Crude product so obtained was crystallized from methanol to get pure product **IVa** in quantitative yield (82%).

(ii) The above experiment was also performed by irradiating the homogeneous mixture for 4 min at a power level of 850 W. Completion of the reaction was checked by TLC on silica gel using ethyl acetate/methanol (1:1) as mobile phase. Crude product so obtained was crystallized from methanol to get pure product **IVa** in quantitative yield (80%). Yields of product **IVa** obtained by method (i) and (ii) are comparable.

Similarly other piperazine derivatives **(IVb-l)** i.e. 1-(3-(1H-imidazol-1-yl)propyl)-4-(1H-indole-2-carbonyl)-piperazine-2,6-dione (**IVb**), 4-(1H-indole-2-carbonyl)-1-pyridin-2-ylmethyl piperazine-2,6-dione (**IVc**), 4-(1H-indole-2-carbonyl)-1-pyridin-3-ylmethyl piperazine-2,6-dione (**IVd**), 4-(1H-indole-2-carbonyl)-1-pyridin-4-ylmethylpiperazine-2,6-dione (**IVe**), 4-(1H-indole-2-carbonyl)-1-(thiophen-2-ylmethyl)piperazine -2,6-dione (**IVf**), 1-(furan-2-ylmethyl)-4-(1H-indole-2-carbonyl)-piperazine-2,6-dione (**IVg**), 1-benzyl-4-(1H-indol-2-yl)piperazine-2,6-dione (**IVh**), 4-(1H-indole-2-carbonyl)-1-[3-(2-oxo pyrrolidin-1-yl)-propyl]-piperazine-2,6-dione (**IVi**),

4-(1H-indole-2-carbonyl)-1-(2-pyrrolidin-1-yl-ethyl)-piperazine-2,6-dione (**IVj**), 4-(1H-indole-2-carbonyl)-1-2-morpholinoethylpiperazine-2,6-dione (**IVk**) and 4-(1H-indole-2-carbonyl)-1-(2-(thiophen-2-yl)ethyl)piperazine-2,6-dione (**IVl**) were synthesized and reported in Table 5.2.

### 5.3.4 Synthesis of heterocyclic molecules derived from 2,6-dioxopiperazine derivatives (VIax-jz)

5.3.4.1 Synthesis of 2,6-bis-(1-cyclohexyl-2,6-dioxopiperazine-4-carbonyl)-pyridine **(VIax)**

(i) 1-Cyclohexylpiperazine-2,6-dione (0.206 g; 1.0 mmol) (**IIIa**; Scheme 5.2) and 2,6-pyridine dicarboxylic acid (0.084 g; 0.50 mmol) (**Vx**; Scheme 5.2) were mixed together thoroughly in a molar ratio of 2:1 respectively. This reaction mixture was subjected to microwave irradiation at 850 Watt for three min and then progress of reaction was monitored by TLC on silica gel using ethyl acetate: methanol (2:3) as solvent of elution. TLC indicated presence of starting materials. This reaction mixture was again irradiated for three min (850 W) and TLC was performed, which indicated presence of starting materials. This reaction mixture was again irradiated for five min and TLC was performed. This time TLC indicated absence of starting materials and hence reaction was complete. The crude product so obtained was purified by crystallization from methanol to give pure product 2,6-bis-(1-cyclohexyl-2,6-dioxopiperazine-4-carbonyl)-pyridine (**VIax**; Scheme 5.2) in 83% yield (218 mg).

(ii) Alternatively a mixture of 1-cyclohexylpiperazine-2,6-dione (0.206 g; 1.0 mmol) (**IIIa**; Scheme 5.2) and 2,6-pyridine dicarboxylic acid (0.084 g; 0.50 mmol) (**Vx**; Scheme 5.2) in a molar ratio of 2:1 were mixed thoroughly and subjected to microwave

irradiation at 150ºC for 12 min. TLC of this reaction mixture on silica gel using ethyl acetate: methanol (2:3) as mobile phase showed absence of starting materials. This crude product was crystallized from methanol to give pure condensed product **VIax** in 81% yield (212 mg). Yields of product **VIax** obtained by method (i) & (ii) are comparable.

Similarly other piperazine derivatives **(VIay-jz)** i.e. 3,5-bis-(1-cyclohexyl-2,6-dioxopiperazine-4-carbonyl)-pyridine **(VIay),** 2,5-bis-(1-cyclo hexyl-2,6-dioxopiperazine-4-carbonyl)-thiophene **(VIaz),** 2,6-bis-(1-(3-(1-1H-imidazolyl) propyl)-2,6-dioxopiperazine-4-carbonyl)-pyridine **(VIbx),** 3,5-bis-(1-(3-(1-1H-imidazolyl)-propyl)-2,6-dioxopiperazine-4-carbonyl)-pyridine **(VIby),** 2,5-bis-(1-(3-(1-1H-imidazol yl)-propyl)-2,6-dioxopiperazine-4-carbonyl)-thiophene **(VIbz),** 2,6-bis-(1-(2-pyridyl methyl)-2,6-dioxopiperazine-4-carbonyl)-pyridine **(VIcx),** 3,5-bis-(1-(2-pyridylmethyl)-2,6-dioxopiperazine-4-carbonyl)-pyridine **(VIcy),** 2,5-bis-(1-(2-pyridylmethyl)-2,6-dioxopiperazine-4-carbonyl)-thiophene **(VIcz),** 2,6-bis-(1-(3-pyridylmethyl)-2,6-dioxo piperazine-4-carbonyl)-pyridine **(VIdx),** 3,5-bis-(1-(3-pyridylmethyl)-2,6-dioxopiperazine-4-carbonyl)-pyridine **(VIdy),** 2,5-bis-(1-(3-pyridyl methyl)-2,6-dioxopiperazine-4-carbonyl)-thiophene **(VIdz),** 2,6-bis-(1-(4-pyridylmethyl)-2,6-dioxopiperazine-4-carbonyl)-pyridine **(VIex),** 3,5-bis-(1-(4-pyridylmethyl)-2,6-dioxopiperazine-4-carbonyl)-pyridine **(VIey),** 2,5-bis-(1-(4-pyridylmethyl)-2,6-dioxopiperazine-4-carbonyl)-thiophene **(VIez),** 2,6-bis-(1-(2-thienylmethyl)-2,6-dioxopiperazine-4-carbonyl)-pyridine **(VIfx),** 3,5-bis-(1-(2-thienylmethyl)-2,6-dioxopiperazine-4-carbonyl)-pyridine **(VIfy),** 2,5-bis-(1-(2-thienylmethyl)-2,6-dioxopiperazine-4-carbonyl)-thiophene **(VIfz),** 2,6-bis-(1-(2-furylmethyl)-2,6-dioxopiperazine-4-carbonyl)-pyridine **(VIgx),** 3,5-bis-(1-(2-furylmethyl)-2,6-dioxopiperazine-4-carbonyl)-pyridine **(VIgy),** 2,5-bis-(1-(2-

furylmethyl)-2,6-dioxopiperazine-4-carbonyl)-thiophene **(VIgz),** 2,6-bis-(1-benzyl-2,6-dioxopiperazine-4-carbonyl)-pyridine **(VIhx),** 3,5-bis-(1-benzyl-2,6-dioxopiperazine-4-carbonyl)-pyridine **(VIhy),** 2,5-bis-(1-benzyl-2,6-dioxopiperazine-4-carbonyl)-thiophene **(VIhz),** 2,6-bis-(1-(3-(2-oxopyrrolidin-1-yl)-propyl)-2,6-dioxo piperazine-4-carbonyl)-pyridine **(VIix),** 3,5-bis-(1-(3-(2-oxopyrrolidin-1-yl)-propyl)-2,6-dioxopiperazine-4-carbonyl)-pyridine **(VIiy),** 2,5-bis-(1-(3-(2-oxopyrrolidin-1-yl)-propyl)-2,6-dioxopiperazine-4-carbonyl)-thiophene **(VIiz),** 2,6-bis-(1-(2-(pyrrolidin-1-yl)-ethyl)-2,6-dioxopiperazine-4-carbonyl)-pyridine **(VIjx),** 3,5-bis-(1-(2-(pyrrolidin-1-yl)-ethyl)-2,6-dioxopiperazine-4-carbonyl)-pyridine **(VIjy),** 2,5-bis-(1-(2-(pyrrolidin-1-yl)-ethyl)-2,6-dioxopiperazine-4-carbonyl)-thiophene **(VIjz)** were synthesized and reported in Table 5.3.

### 3.3.5 Anti-inflammatory activity [21; Chapter-2]

Anti-inflammatory activity evaluation was carried out by following procedure described in chapter-2 of this thesis.

### 3.3.6 In vitro cytotoxicity against human cancer cell lines [32; Chapter-4a]

In vitro cytotoxicity against human cancer cell lines was carried out by following procedure described in chapter 4a of this thesis.

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