SYNTHESIS OF SOME HETEROCYCLIC COMPOUNDS AND THEIR CHARACTERIZATION

A DISSERTATION

Submitted in partial fulfillment of the requirements for the award of the degree of

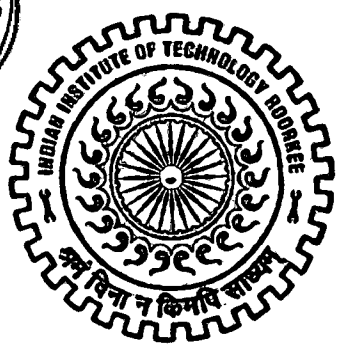
MASTER OF TECHNOLOGY

in

ADVANCED CHEMICAL ANALYSIS

By

VARU RANI



DEPARTMENT OF CHEMISTRY

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CANDIDATE'S DECLARATION

I hereby certify that the work which is being presented in this dissertation entitled **"SYNTHESIS OF SOME HETEROCYCLIC COMPOUNDS AND THEIR CHARACTERIZATION"** in partial fulfillment of the requirement for the award of the **Degree of Masters of Technology in Advanced Chemical Analysis** and submitted to the **Department of Chemistry** of the Institute in an authentic record of my work carried out during the period from **July 2006 to June 2007** under the supervision of **Prof. S. M. Sondhi, Department of Chemistry Indian Institute of Technology, Roorkee**.

I have not submitted the matter embodied in this report for the award of any other degree of this and other Institute.

Varu Rani

Date: 28/6/07 **(VARU RANI)**

CERTIFICATE

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

Date: 28/6/07

Place: Roorkee **(Dr. S. M. Sondhi)**

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Here comes my wholehearted sense of gratitude and immense respect for my in-laws, Dr. Vijay Kumar Singh, my sisters, my brother Mr. V. K. Chauhan and his family.

Countless images flash through my mind when I remember the hard phase of time I had been through and here my husband Mr. Ajay Kumar Singh deserves a special mention, who made the conspicuous contribution in making this ambition of mine a reality.

I am in dearth of words to express my heart felt reverence to my parents who have been the strongest influence in my life. Apart from providing the best available education and poignantly bearing my long absence from home, they have always encouraged me and felt proud of my every achievement.

Finally, I wish to thanks all those whose names have not figured but have helped me during my research work.

Dated 28/6/07

Varu Rani

VARU RANI

ABSTRACT

A number of amidine derivatives were synthesized by condensation of 2-cyanopyridine, 4-cyanopyridine and 2-cyanopyrazine with amines in the presence of sodium methoxide. All the compounds, that is, **III(a-f)**, **IV(a-g)**, and **V(a–d)** were purified by crystallization or by column chromatography. Structures of all the synthesized and purified compounds are supported by correct IR, ^{1}H NMR and mass spectral data reported in **Table 1, 2, 3.**

CONTENTS

LIST OF TABLE

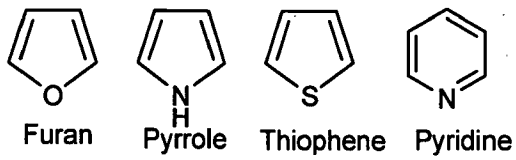
LIST OF SPECTRA

CHAPTER 1

Introduction:

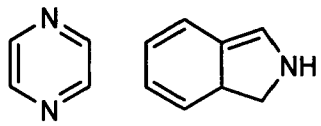
Compounds classified as heterocyclic probably constitute the largest and most varied family of organic compounds. After all, every carbocyclic compound, regardless of structure and functionality, may in principle be converted into a collection of heterocyclic analogs by replacing one or more of the ring carbon atoms with a different element. Even if we restrict our consideration to oxygen, nitrogen and sulphur (the most common heterocyclic elements), the permutations and combinations of such a replacement are numerous.

Cyclic compounds containing one or more heteroatoms (usually O, N, S etc) are called heterocyclic compounds. Some simplest heterocyclic compounds as shown below:



Furan Pyrrole Thiophene Pyridine

1 **2** **3** **4**



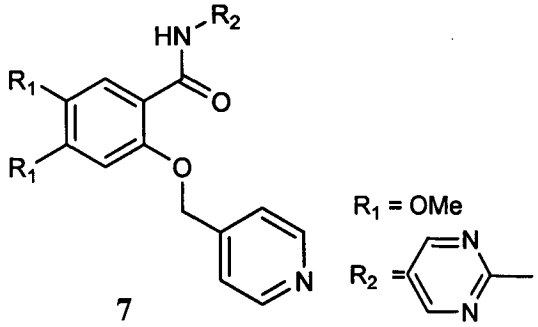
pyrazine 1,7a-dihydro-2H-isoindole

5 **6**

Numerous heterocyclic compounds have been synthesized which show biological activities. Compounds with anti-inflammatory, analgesic, antidegenerative, anticancer, antimicrobial activities had already seen, reported in literature. Most of the drugs heterocyclic compounds are biologically active. Acridine [1], amidines and hydrazones [2,3], pyrimidines and bispyrimidine derivatives [4-8] with anti-inflammatory and analgesic activities are reported in literature. In addition to above-mentioned activities, pyrimidine derivatives possessing antitumour [9], antimicrobial [10], antibacterial [11], antifungal [12] and antiinfective [13] activities have been reported in literature. Hydrazone derivative possesing anti-inflammatory, analgesic [14,15] antipyratic [16],

and antibacterial activities [17].

It is also well known that amides, amidines and combinations of both are present in a variety of antimicrobial, antiparasitic, antihelmintic, antiviral and antitumoural agents.



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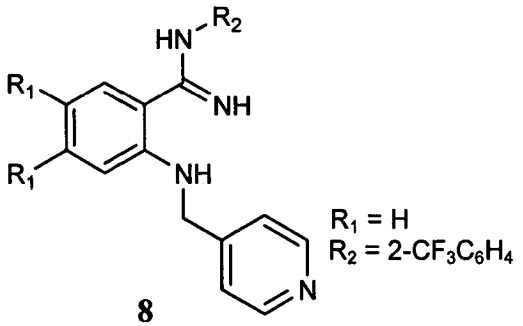

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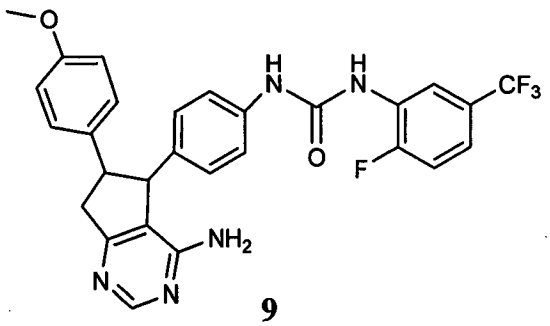


9

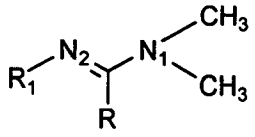
The amidine functionality has been found in many natural products and amidine-containing molecules are found to be a critical part of many biological processes. The amidine moiety is an important pharmacophore in medicinal chemistry and had been intensively investigated. A number of pharmaceutical products for example the fibrinogen receptor antagonist lamifiban, which is currently in clinical development as an injectable antithrombic.

Amidine is a functional group or type of chemical compound that has two amine groups attached to the same carbon atom with one carbon nitrogen double bond

$HN=CR'-NH'_2$

The configuration and molecular dynamics of the compounds with amidine group N=C-N are widely investigated [18]. Amidines contain two different nitrogen atoms: amine (N_1) and imine (N_2) type, however, because of conjugation between the N_2=C double bond

and the lone electron pair at N_1 both carbon-nitrogen bonds exhibit a partial double bond character.



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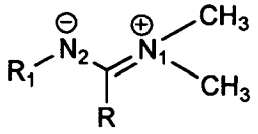

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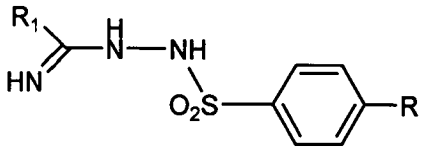
A few amidine derivatives i.e. **12-19** are mentioned below:



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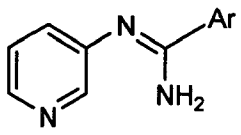

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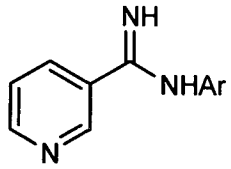

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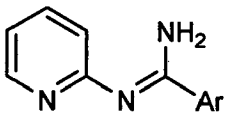

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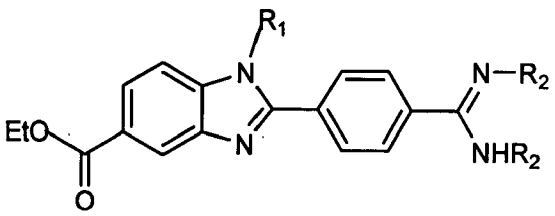
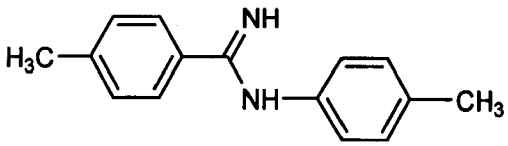


R_1 = H, propyl, benzyl **16**

R_2 = isopropyl, H



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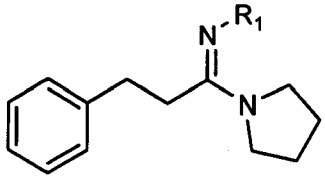
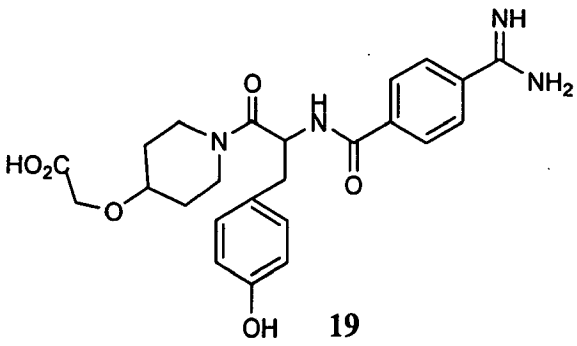


R^1 =Et, Bn **18**



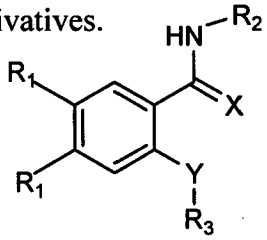
19

Many amidine derivatives possess useful biological activities, which are due to the resemblance of the amidine functionality to the biologically important pyrimidines and

purines systems. Formamidines feature in the biochemical pathways associated with the biosynthesis of imidazoles, purines, and in the catabolism of histidine.

Amidine derivatives possessing anti-degenerative [19], anticancer [20, 21], anti-platelet [22] and antimicrobial [23] activities have been reported in the literature. Amidine derivatives also acting as serine protease inhibitors [24] and nitric oxide synthase inhibitors [25] reported in the literature. Amidines, the nitrogen analogues of carboxylic acids, are structural parts of numerous compounds of biological interest including important medical and biochemical agents. Amidines are also versatile building blocks for the synthesis of various heterocyclic compounds.

The wide-ranging biological activity includes, for example, antiviral activity of some naturally occurring amidines [26] interfering with the reverse transcription process. Distamycin derivatives have also been examined for reverse transcription inhibitory properties. Antibacterial [27], antifungal [28], and antiprotozoal activity have been shown for benzamidine derivatives.

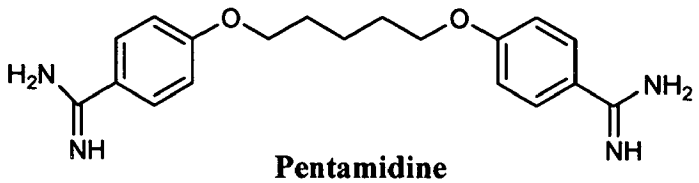


20

X=NH, Y=NH anthranilic amidine
X=NH, Y=O salicylic amidine

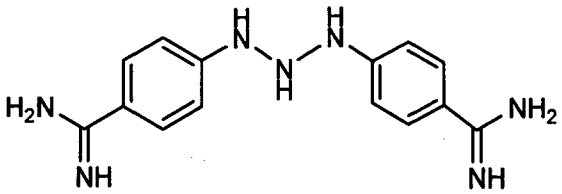
This series benzamidines and benzamides **20** were synthesized as selective inhibitors of vascular endothelial growth factor receptor (VEGFR) tyrosine kinases, and tested for inhibitory activity toward autophosphorylation by the enzyme assay. Selective inhibition of VEGFR-2 tyrosine kinase was observed in the salicylic amide and the anthranilic amidine [29].

Pentamidine **21** and berenil **22** are used in the treatment of pneumonia due to *Pneumocystis carinii.* This is a serious disease in patients receiving immunosuppressive therapy for leukaemia, lymphoma, or transplant rejection. N-substituted heteroaromatic cyanoamidines possess good vasodilating and antibypertensive activity [30] by opening the potassium channel. Pentamidine has been used in leishmaniasis therapy, a dangerous tropical disease, in substitution of arsenic derivatives and in combating collateral infections in AIDS treatment.



Pentamidine

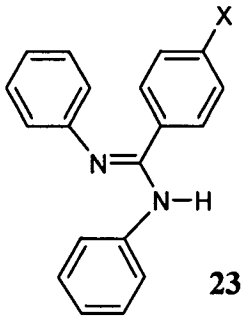
21



Berenil

22

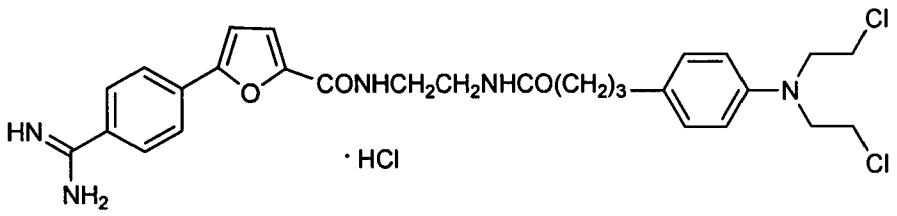
Some amidines are used in the synthesis of various drugs. The structure containing amidine moiety is also used as a drug. Triarylamidines **23** were tested for their ability to inhibit the replication of HIV cells.



X=OCH_3, CH_3, H, Br, Cl and NO_2

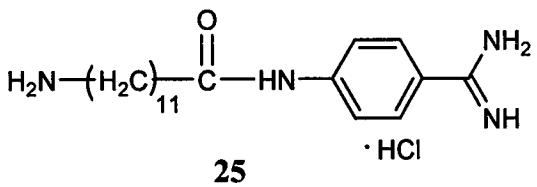
23

Chlorambucil is an alkylating agent commonly used in pharmacotherapy of chronic lymphatic leukaemia, lymphomas as well as ovarian and breast carcinomas. The amidine analogue of chlorambucil **24** evokes stronger cytotoxicity on breast cancer than does the parent drug, chlorambucil [31]. First of all, this analogue appeared to be a more potent inhibitor of collagen synthesis than chlorambucil. Moreover, showed a higher than Chlorambucil potency to inhibit the activity of prolidase, which represents an important factor in the regulation of collagen biosynthesis and cell growth.



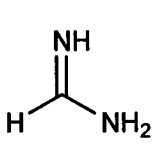
24

It was shown a surface coating with anticoagulant characteristics showing significantly reduced coagulation activation. The synthesis of a monomeric conjugate containing a benzamidine moiety **25** was carried out and its inhibitory activity against human thrombin, the key enzyme of the blood coagulation cascade, was determined using a chromogenic assay. Based on that, low thrombogenic interfaces were prepared by covalent attachment of this low-molecular weight thrombin inhibitor on poly (octadecenealt-maleic anhydride) copolymer thin films and characterized using ellipsometry, XPS and dynamic contact angle measurements. The invitro hemocompatibility tests using freshly drawn human whole blood showed, in agreement with the SEM images, that a PO-MA film modified with a benzamidine moiety using a PEG spacer decreased the activation of coagulation, platelets and the complement system. The decreased protein adsorption, in addition to the specific inhibition of thrombin, effectively enhanced the short-term hemocompatibility characteristics [32].



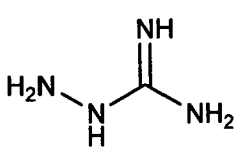
25

Pharmacological modulation of nitric oxide synthase activity has been achieved using structural analogs of arginine **28**. In the present studies, it was demonstrated that the minimal amidine structure required for enzymatic inhibition is formamidine **26** [33].



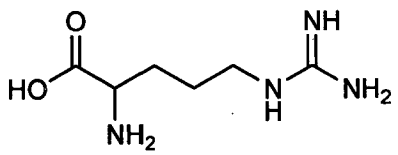
formamidine

26



aminoguanidine

27

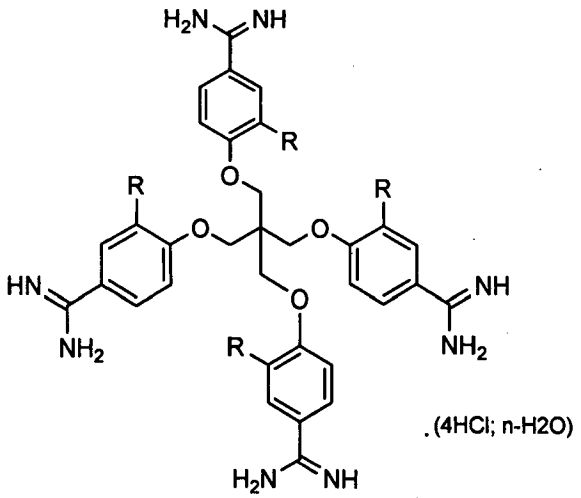


L- arginine

28

Cyclic amidines represent a heterocyclic core of wide pharmacological interest. Among them, dihydroimidazoles and tetrahydropyrimidines are found in many biologically active compounds [34].

In literature it was also described the design and preparation of lecithin microemulsion gels containing the aromatic tetra-benzamidine (TAPP-Br, tetra-p-amidinophenoxy neo-pentane) **29** and the antitumor evaluation of this topical formulation on nude mice xenografted with the highly tumorigenic cell line FH06T l- 1, in comparison to the antitumor activity of TAPP-Br administered by intraperitoneal injections (0.5 mg/injection). After (trans) dermal treatment with 0.1 ml lecithin gels incorporating TAPP-Br (0.2 mg/ml), a reduction of in vivo tumor cell growth was observed. These results could be of great interest with a view to developing a releasing system useful for experimental chemotherapy of tumor lesions occurring at cutaneous or subcutaneous level. The bromo-derivative (TAPP-Br) of tetra-p-amidinophenoxy neo-pentane (TAPP-H) is very active on a variety of cell lines, including breast carcinoma, erythroleukemic, melanoma, B-lymphoid and colon carcinoma cell lines [35].



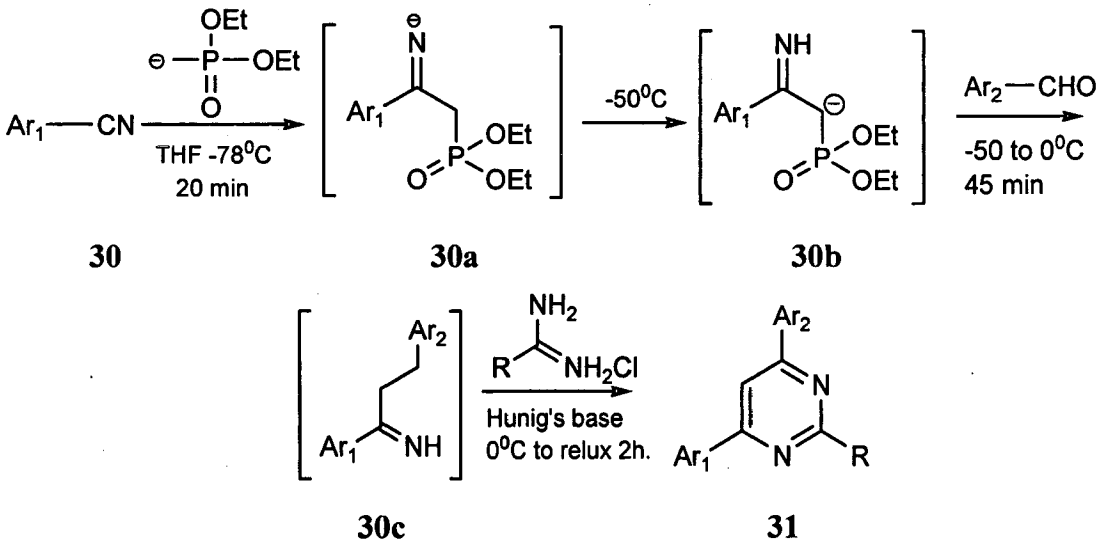
R= H,(TAPP-H); Br,(TAPP-Br) **29**

In Synthesis:

Amidines are much used in synthesis. In some cases for the preparation of acyclic compounds, but mostly for the synthesis of heterocyclic compounds such as aziridines [36], pyrroles [37], oxazoles, oxadiazoles and thiadiazoles, pyridines, pyrimidines [38], imidazoles[39], and triazines[40]. Accordingly, the condensation of amidines with ∝-halo

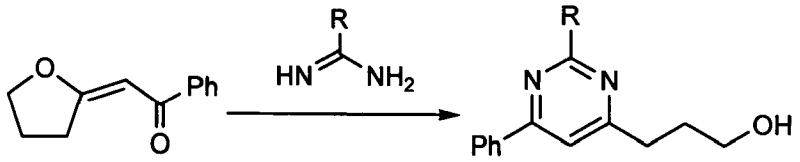
ketones or ∝-hydroxy ketones yields imidazole rings, while heating amidine salts with ethylene diamine yields dihydroimidazoles. Pyrimidine derivatives have also been prepared from amidines using a vast array of ß-dicarbonyl compounds, ß-dinitriles, ß-cyano esters, ß-keto nitriles as well as ∝,ß -unsaturated esters, nitriles and carbonyls. Substituted amidines are useful intermediates in the synthesis of many heterocyclic compounds like ß- lactum imidazole indole and pyrimidine.

A series of polysubstituted pyrimidines were synthesized from in situ generated α,β-unsaturated imines and the corresponding amidine or guanidine derivatives in a convenient one-pot procedure [41]. The described transformations proceed via the initial formation of α,β-unsaturated imines **30c** that undergo nucleophilic attack by a bi-dentate nucleophile (amidine or guanidine). This step is then followed by elimination of ammonia and aromatization to yield the observed polysubstituted pyrimidines **31** Optimized reaction conditions include application of dry THF or dioxane as solvents, as well as thorough temperature control of the reaction mixtures, especially at the earlier stages of reagent addition. This is attributed to the formation of unstable aza-Wittig species **30b** that undergo smooth reaction with aldehydes to result in the reactive imine species **30c.** Addition of polar solvents (DMF, NMP, N-methyl morpholine; 20–50 vol %) to better solubilize amidine or guanidine species did not affect the outcome of the reaction. **Scheme 1.1**



Scheme 1.1

The reaction of 2-alkylidenetetrahydrofurans **32** with amidines (NEt_3, EtOH, reflux) afforded the 2-phenyl-, 2-methyl-, and 2-dimethylamino-4- (3-hydroxypropyl) pyrimidines **33**, which are biologically active compounds [42] **Scheme 1.2**.

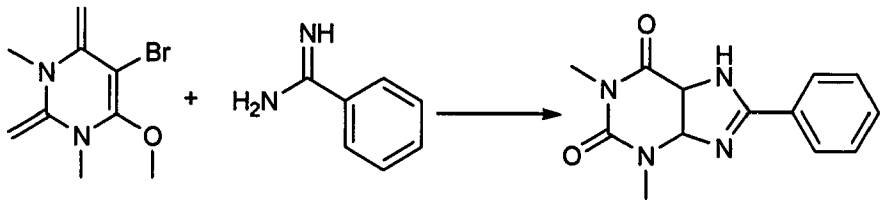


32 **33**

R= alkyl aryl substituents

Scheme 1.2

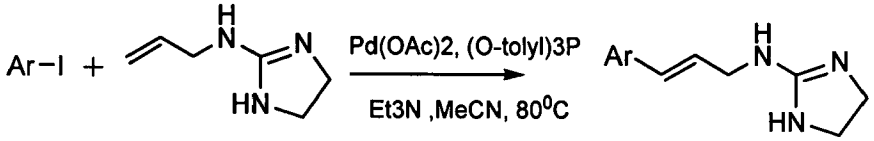
Purines, xanthines, and other fused imidazoles **36** can be prepared from amidines or guanidines, with retrosynthetic disconnection at the ring fusion. Ring closure proceeds using Cu (I), with no special ligands required. The method allows for easy modification of the heterocyclic nucleus and is tolerant of functionality pendant to the ring system [43] **Scheme 1.3**.



34 **35** **36**

Scheme 1.3

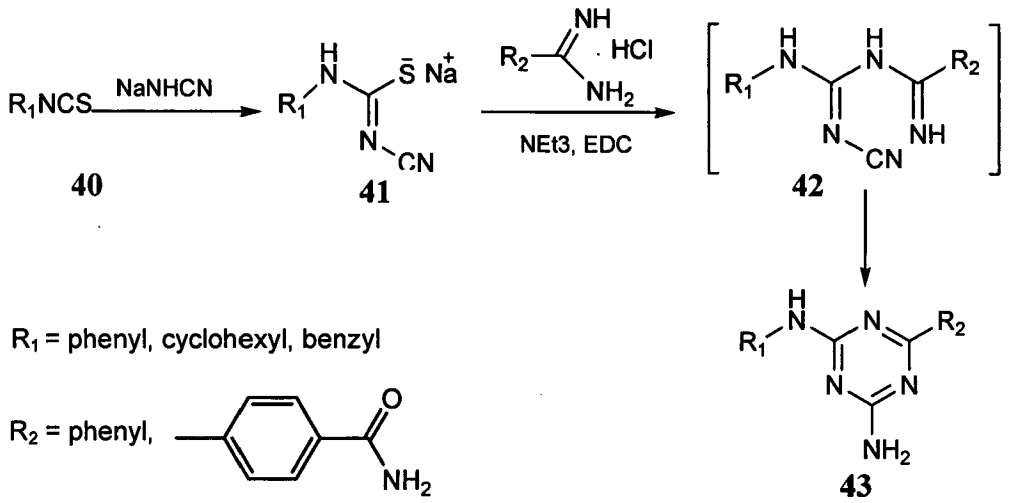
The applicability of Heck methodology to the introduction of unprotected amidines and guanidines was investigated. These were coupled to various simple aryl iodides **37**, and this methodology was then applied to a highly fictionalized 6-iodoquinazolinone substrate **37**, providing an efficient synthesis of a new class of vitronectin receptor antagonists **39** [44] **Scheme 1.4**.



37 **38** **39**

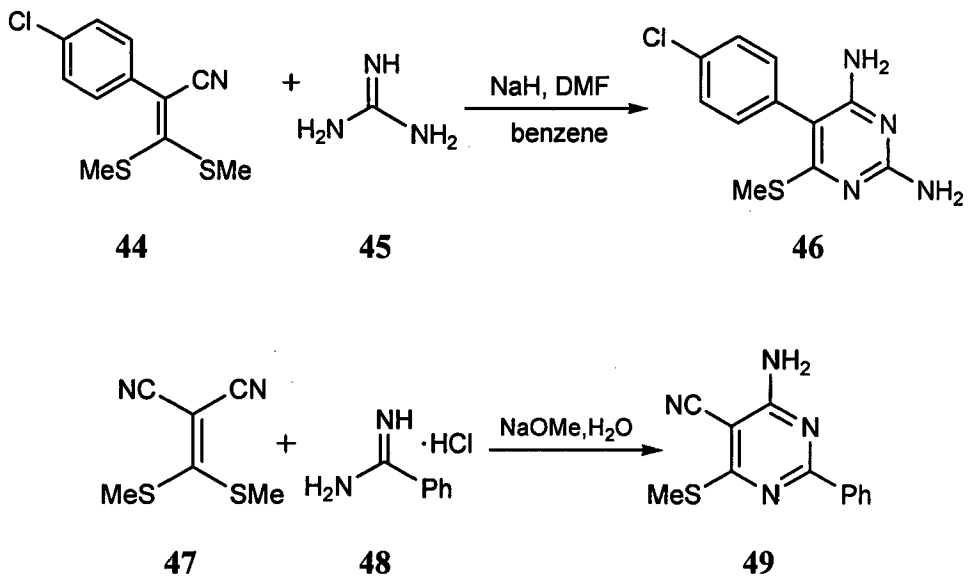
Scheme 1.4

One-pot synthesis of N, 6-disubstituted-1, 3,5-triazine-2, 4- diamines derivatives **43** from isothiocyanates **40** sodium hydrogencyanamide, and with amidines in the presence of (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) is reported [45] **Scheme 1.5**.



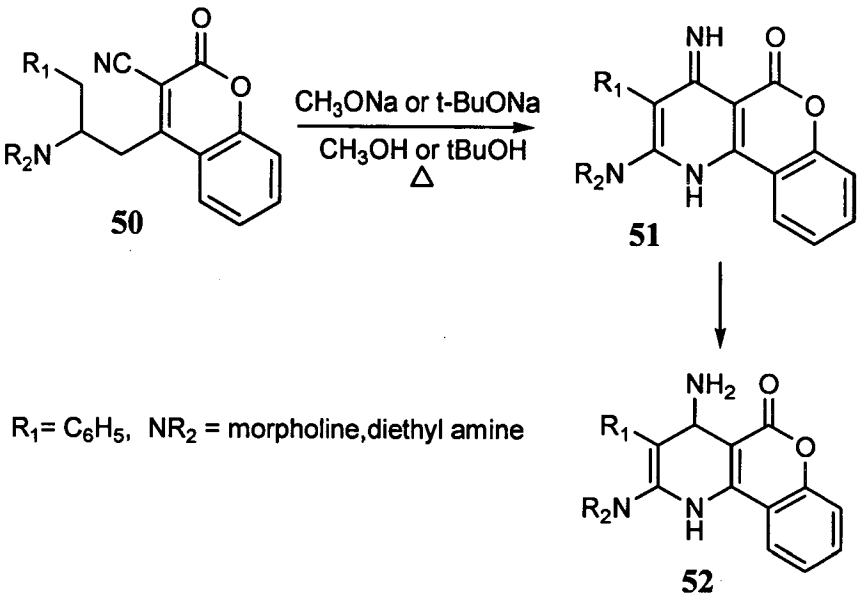
Scheme 1.5

Amidines are also used for the synthesis of the pyrimidine derivative **46.** The preparation of pyrimidine **46** from the ketenedithioacetal **44 (Scheme 1.6)**. The preparation of the cyanopyrimidine **48** from dicyanoketenedimethyldithioacetal **47** has also been reported [46].

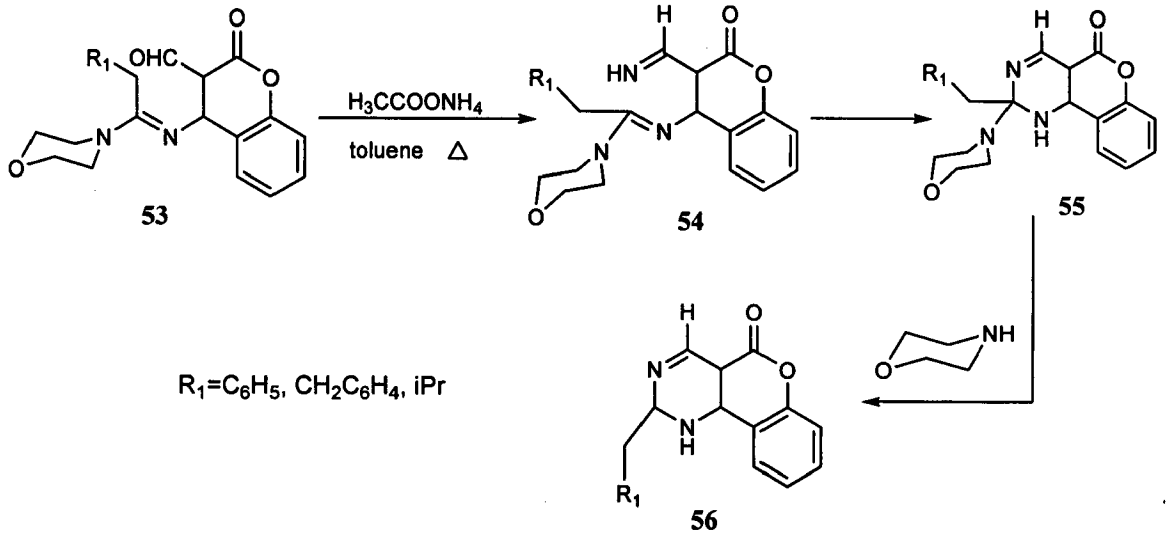


Scheme 1.6

Substituted coumarin amidines are useful building blocks for the preparation of [1] benzopyrano [4,3-b] pyridin-5-one and [1] benzopyrano [4,3-d] pyrimidin-5-one derivatives. The synthesis of [1] benzopyrano [4,3-b] pyridin-5-ones **52** starting from 3-cyanocoumarin **50**, N-functionalized amidines **51** was reported **Scheme 1.7**. The ring-closure reaction mechanism, under basic or acidic media, was proposed. Furthermore, the reaction of 3-formylamidines **53** with ammonium acetate gave good yields of 2-substituted [1] benzopyrano [4,3-d] pyrimidin-5-ones **56** [47] **Scheme 1.8**.



Scheme 1.7



Scheme 1.8

Here we report the synthesis of some amidines from nitriles. Direct reaction of nitriles with amines is difficult so we use sodium methoxide to activate the nitriles. These amidines are prepared by conventional method, refluxing the reaction content for 8 to 15 hours. Some compounds are purified by column chromatography and then they are characterized by melting point, 1H NMR, IR, and GC-MS.

CHAPTER 2

Literature Survey:

The amidine functionality has been found in many natural products [48,49] and amidine containing molecules are found to be a critical part of many biological processes. Substituted amidines are useful intermediates in the synthesis of many heterocyclic compounds. Consequently, a plethora of methods have been developed for the preparation of amidines The most common methods of preparation are from amides, nitriles or thioamides An efficient one step preparation of an amidine by the direct nucleophilic addition of an amine to the parent nitrile is an extremely desirable transformation.

Literature methods include the preparation of

(i) *N*-monosubstituted amidines by

(a)Addition of Grignard or organolithium reagents to carbodiimides or cyanoamides, followed by hydrolysis, and in this approach, a C-C bond is formed

(b) Heating hydrazones in the presence of $NaNH_2$.

(c) Addition of the anions of urea and amines to nitriles.

(d) Addition of amines to nitriles in the presence of $AlCl_3$.

(ii) *N,N*-disubstituted amidines by the reaction of secondary amines with imidic ester salts derived from nitriles in which one C-N bond is formed.

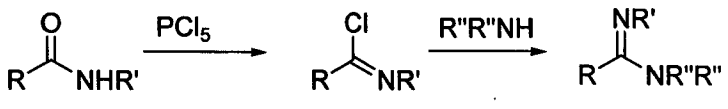
(iii) *N,N'*-disubstituted amidines by the reaction of two moles of an amine with orthoesters, acetals, or thioesters, in which both the C-N bonds are formed, and

(iv) *N,N'*-disubstituted and *N,N,N'*-trisubstituted amidines by imidoylation of amines with imidoyl chlorides.

Some general methods reported in literature are discussed here from the different reactants.

Amidines from Amides or Carboxylic acids:

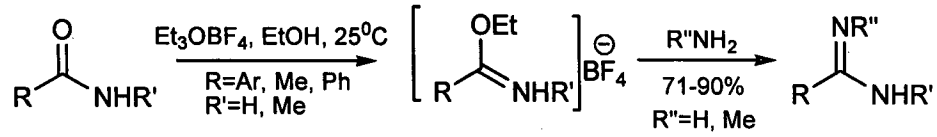
Secondary amides **57** can be converted to imidoyl chlorides **58** with phosphorous pentachloride, which can react with primary or secondary amines to yield amidines **59** **Scheme 2.1**[50]. This method is generally poor for preparing unsubstituted amidines from primary amides but is an excellent general method for preparing di-and tri-substituted amidines. Other reagents such as phosphorous oxychloride or thionyl chloride can be employed in the synthesis of the imidoyl chlorides but usually lower yields are obtained.



57 **58** **59**

Scheme 2.1

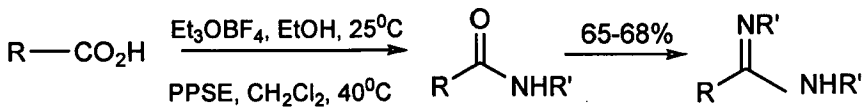
Weintraub showed that secondary amides **60** were *O*-alkylated with triethyloxonium fluoroborate at ambient temperature to yield imidic ester fluoroborates **61** which can be converted to amidines **62** with amines [51].



60 **61** **62**

Scheme 2.2

Kakimoto showed a novel direct synthesis of amidines **65** from carboxylic acids **63** and, amines via intermediate amides **64** using polyphosphoric acid trimethylsilyl ester (PPSE), generated in situ from phosphorous pentoxide and hexamethyldisiloxane, as the condensing agent [52].



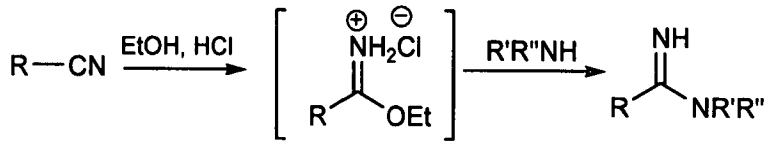
63 **64** **65**

Scheme 2.3

Amidines from Nitriles:

The classical Pinner Reaction, discovered by Klein Pinner in the late 1800s, is probably

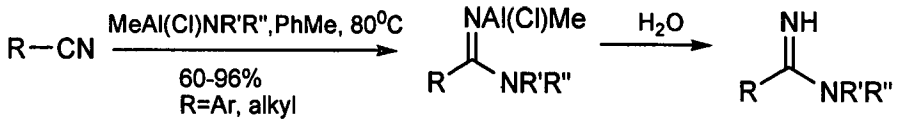
the most commonly used method for the transformation of nitriles to amidines **68** [53] Nitriles **66** are activated to the intermediate imidic ester salts **67** in the presence of alcohol and hydrogen chloride under anhydrous conditions. Imidic ester salts **67** are then reacted with amines, either in situ or after isolation, to generate amidines **68** [54]. The Pinner protocol is the most widely used method for the formation of unsubstituted amidines.



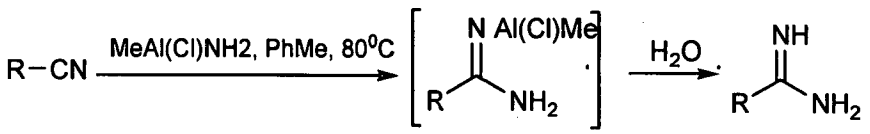
66 **67** **68**

Scheme 2.4

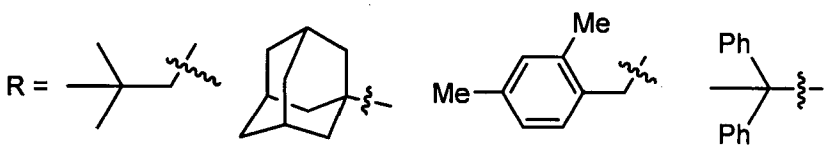
The direct synthesis of amidines from nitriles and amines can only be achieved if nitriles are substituted by electron-withdrawing groups [55]. Unreactive nitriles have been used to prepare amidines in the presence of Lewis acids such as $AlCl_3$ or $ZnCl_2$ at elevated temperatures of 150-200 °C [56]. It has been shown that alkylchloroaluminum amides are useful reagents for the conversion of nitriles to amidines under milder conditions. Garigipati found that addition of alkylchloroaluminum amides, generated conveniently from trimethyl aluminum and ammonium chlorides, to nitriles **69** in warm toluene efficiently afforded the desired amidines **71** in reasonable yields after hydrolysis of aluminum species **70** [57] Moss has demonstrated that reaction with methylchloroaluminum amide readily converted sterically hindered nitriles **(72-75)** to amidines 77 **(Scheme 2.5)** [58].



69 **70** **71**



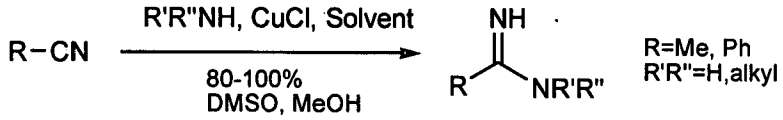
72-75 **76** **77**



72 73 74 75

Scheme 2.5

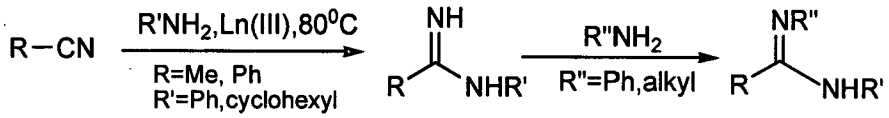
Capdevielle has reported a general preparation of amidines from unactivated nitriles [59]. Stoichiometric copper (I) chloride induced addition of various amines to nitriles **76** provided amidines **77** in excellent yields.



76 **77**

Scheme 2.6

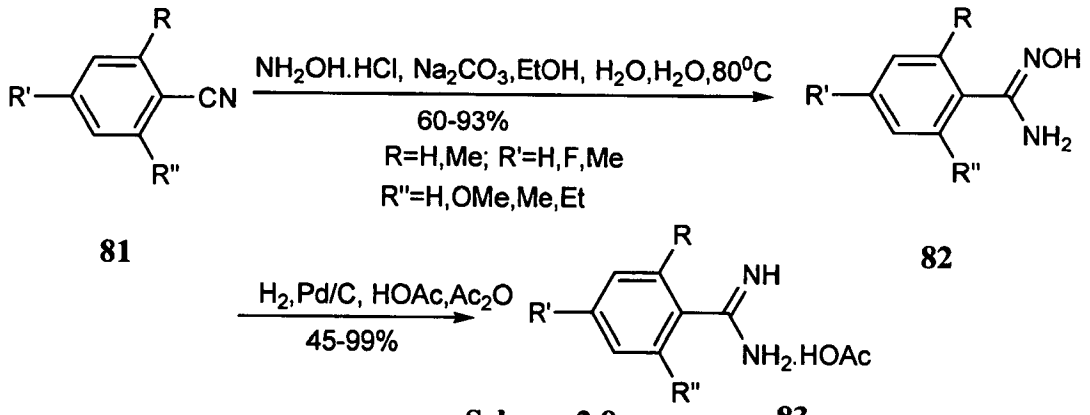
Forsberg has shown catalytic use of Ln (III) ions in the presence of primary amines can be added to unactivated nitriles **78** to give intermediate mono-substituted amidines **79**, which can react with another primary amine to yield di-substituted amidine **80** [60].



78 **79** **80**

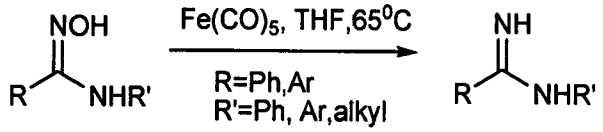
Scheme 2.7

Judkins transformed benzonitriles **81** to intermediate benzamidoximes **82** that were then successfully reduced to benzamidines **83(Scheme 2.8)** via palladium-catalyzed hydrogenolysis in acetic acid/acetic anhydride mixture [61]. Acetic anhydride was found to be a necessary acylating agent in providing useful reaction rates in the hydrogenolysis step. The usual preparation of amidines via thioimidates failed for his specific substrates. Dondoni employed iron pentacarbonyl to the conversion of amidoximes **84**into amidines **85(Scheme 2.9)** via reductive cleavage of the N-O bond [62].



81 **82** **83**

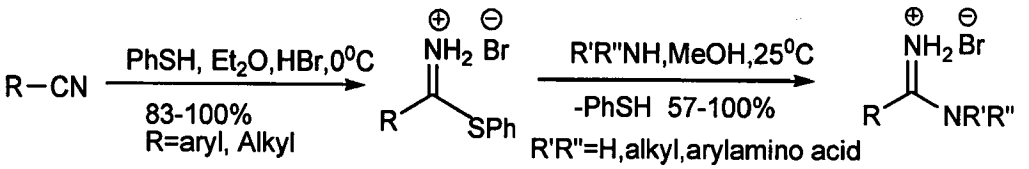
Scheme 2.8



84 **85**

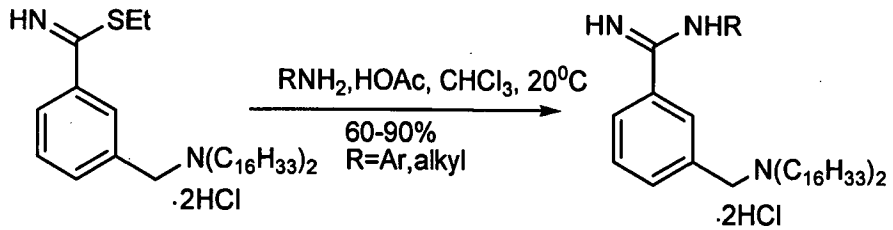
Scheme 2.9

Mioskowski prepared phenylthioimidates **87** from nitriles **86** in the presence of thiophenol and HBr [63] Phenylthioimidates **87** were readily converted to amidine salts **88** in the presence of various amines. Schnur showed that additions of primary amines to ethylthioimidates **89** under acidic conditions provided amidines **90(Scheme 2.11)**[64].



86 **87** **88**

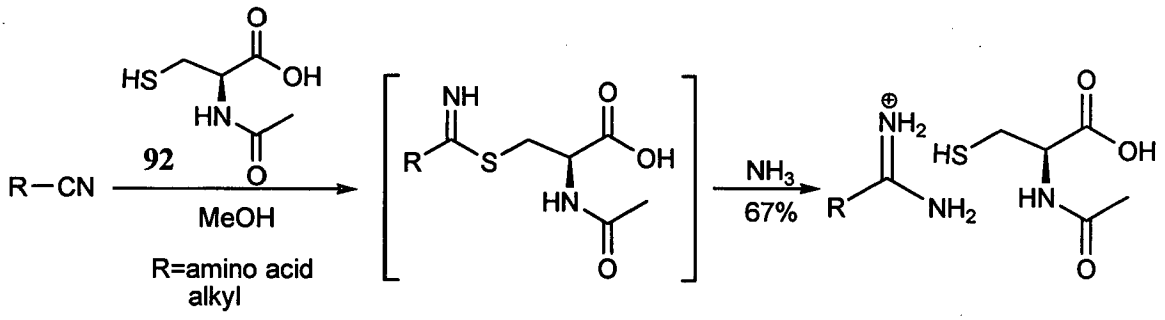
Scheme 2.10



89 **Scheme 2.11** **90**

Reported recently was a mild method for the synthesis of amidines. Schäfer employed the use of *N*-acetylcysteine **92** to transform nitriles **91** to thioimido intermediates **93,** which

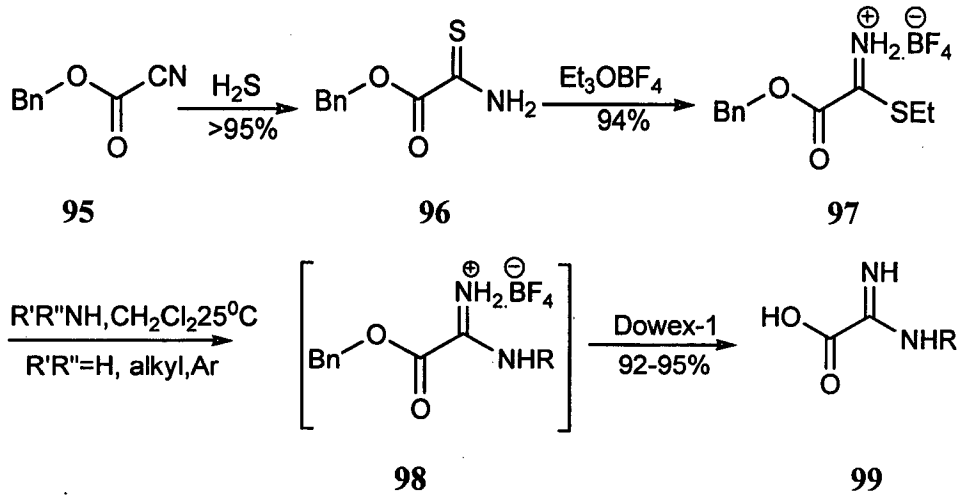
reacted with ammonia to give amidines salts **94(Scheme 2.12)**[65]. The amidines are then isolated as their acetate salts via ion exchange. The author describes procedures for both stoichiometric and catalytic amounts of **92** to be used. This mild method allowed the synthesis of amidines in complex molecules containing acid labile groups, base-sensitive centers of asymmetry and functional groups sensitive to hydrogenation conditions.



91 **93** **94**

Scheme 2.12

Ohno reported an efficient synthesis of amidinoformic acids **99** using benzyl cyanoformate **95** as a synthon. Benzyl cyanoformate was converted to thioamide **96** in the presence of hydrogen sulfide [66]. Thioamide was *S*-alkylated with triethyloxonium tetrafluoroborate to afford thioamidate **97** . Addition of one equivalent of amines to **97** furnished amidinoformic esters **98**, which after hydrolysis with Dowex-1, provided amidinoformic acids **99(Scheme 2.13)**.



95 **96** **97**

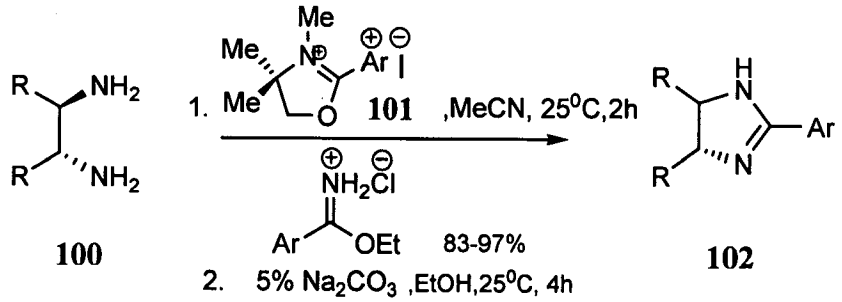
98 **99**

Scheme 2.13

Cyclic Amidines:

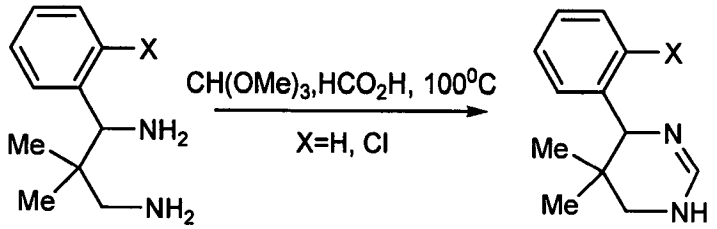
Cyclic optically active amidines are strongly basic compounds, which can serve as

auxiliary compounds for NMR analysis of enantiomeric mixtures of weakly acid compounds or as ligands in catalysts for enantioselective synthesis. Buddrus synthesized enantiopure *C*2-chiral amidines **102** from diamines **100** with D2-oxazolinium salts **101** or imidic ester salts [67] Wynberg synthesized cyclic amidine **104** from diamines **103 with** trimethylorthoformate and formic acid [68].



100 **102**

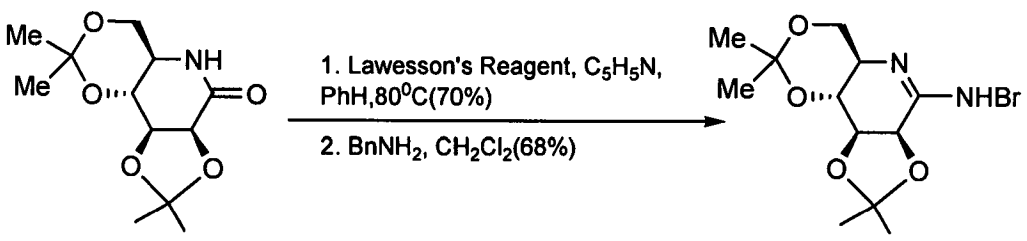
Scheme 2.14



103 **104**

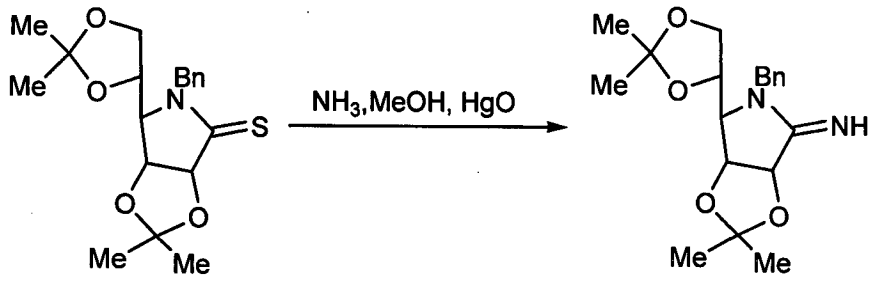
Scheme 2.15

A potent mannosidase amidine inhibitor **106** was prepared from D-mannose based lactam **105** via the intermediate thiolactam, which was reacted with benzylamine [69]. Williams converted thionolactam **107** to amidines **108** in the presence of methanolic ammonia and mercuric oxide [70]. Similarly, Ganem prepared amidines **110(Scheme 2.18)**, derivatives of D-glucose, from thiolactam **109** as part of a study of inhibiting glycosidases [71].

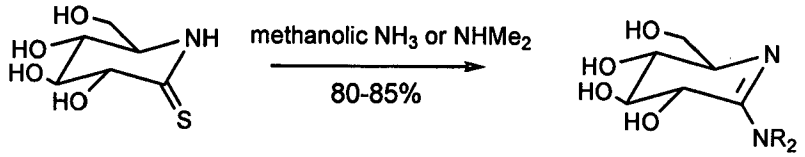


105 **106**

Scheme 2.16



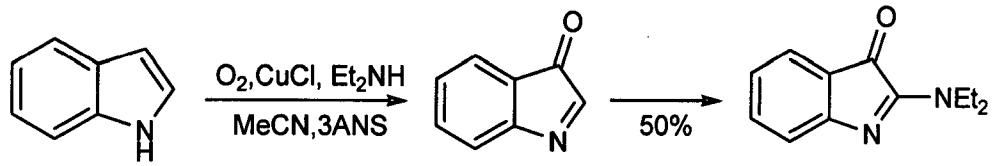
107 **Scheme 2.17** **108**



109 **110** R=H or Me

Scheme 2.18

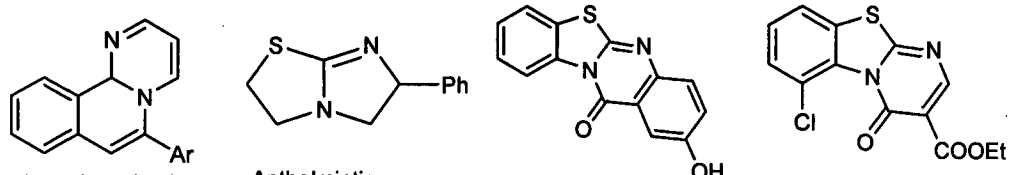
A one-flask synthesis of 2-dialkylamino 3-oxo-3*H*-indoles **113** via 3-oxo-3*H*-indole **112** from oxygen copper-catalyzed oxidation of indole **111** has been reported.



111 **112** **113**

Scheme 2.19

2-Aminobenzothiazoles, 2-aminopyrazine, 1-aminoisoquinoline, 2-cuninonaphthyridines all undergo reaction with formaldehyde and electron rich alkenes such as styrenes, cyclopenta diene, cyclohexadiene and indene to give cyclic amidines **(Scheme 2.20)**, or in the case of the benzothiazoles, cyclic isothioureas. The relationship of the diverse series of skeletons, which are easily prepared, to compounds of known biological activity is emphasized [72].

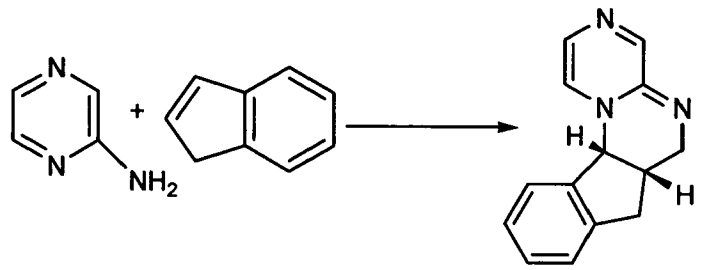


antagonizesplatelet activating factor

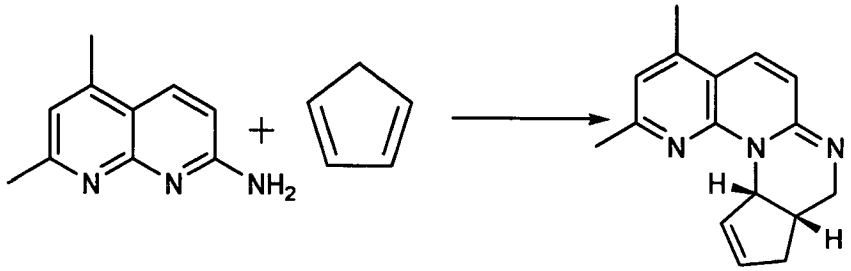
Anthelmintic, anticancer agent

Cytotoxic Agonist for benzodiazepine recepter

114 **115** **116** **117**



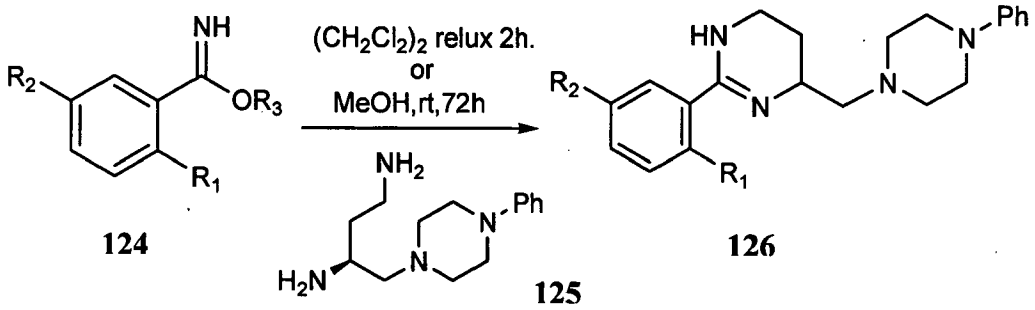
118 119 120



121 122 123

Scheme 2.20

The synthesis of the tetrahydropyrimidine derivatives **126(Scheme 2.21)** was envisioned by reaction of a benzimidate **124** with a suitable 1,3-diamine building block **125**, the pyrimidinone derivative should be prepared by condensation with the appropriate b-alanine equivalent [48].



124 125 126

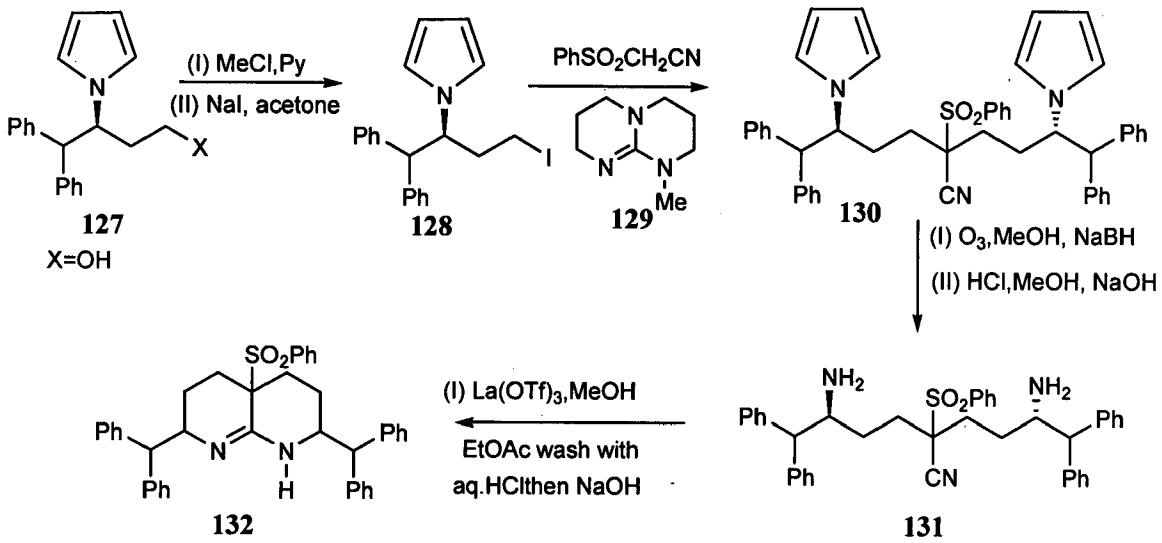
R_1= R_2=H; R_3= CH_3

Scheme 2.21

Bicyclic amidines:

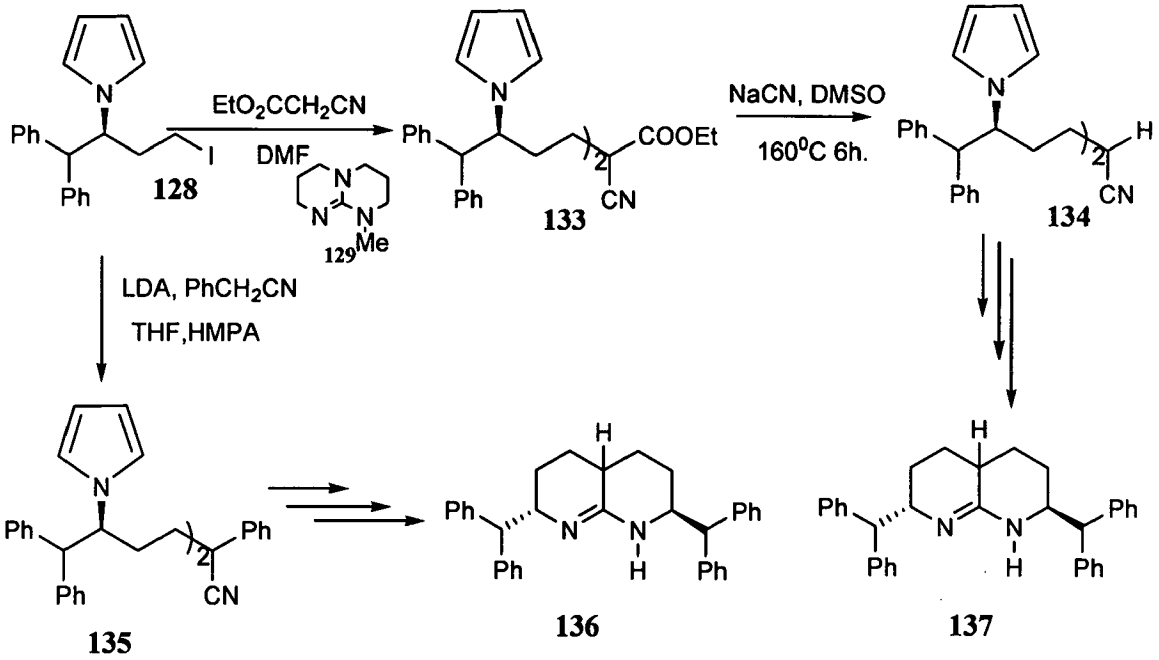
The enantiopure bicyclic amidine bases **132** were synthesized from alcohol, v/a alkylation of the appropriate nitriles [73]. In synthesis of **132** planned to use the pyrrolyl substituent in **127** as a masked amino group, compatible with a nucleofugal leaving group

even under strongly basic conditions. The synthetic pathway to **132** is summarised in **(Scheme 2.22)**. After conversion of **127** to iodide **128** the latter was used to bisalkylate phenylsulphonylacetonitrile, employing the hindered guanidine 7-methyl-1,5,7-triazabicyclo[4.4.0]dec- 5-ene (MTBD) as base. Deprotection of the product **130** gave diamine **131** in 40% overall yield from **127** and **131** might cyclise spontaneously under the deprotection conditions. Although this did not occur, treatment of **131** with lanthanum triflate in methanol gave **132** in an acceptable yield of 65%.



Scheme 2.22

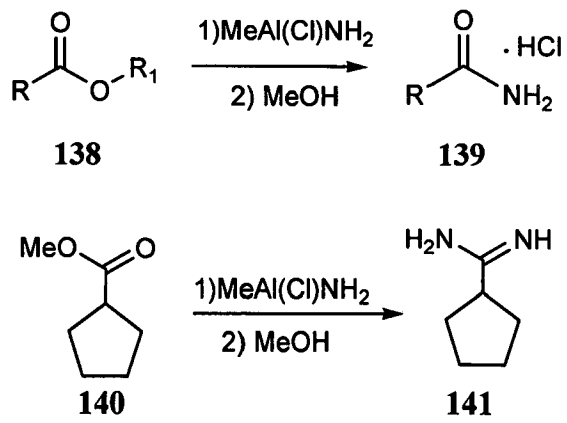
To access enantiopure bicyclic amidines without the electron-withdrawing sulphonyl group, the methodology was extended in two respects. Firstly, as shown in **Scheme 2.23**, the guanidine-catalysed alkylation on ethyl cyanoacetate, giving an intermediate **133** which could be deethoxycarbonylated to nitrile **134**. Unmasking of the amino groups and bicyclisation, as in **(Scheme 2.22)**, gave amidine **137**. Secondly, the bis-alkylation of phenylacetonitrile using LDA [74] as base led to nitrile **135, Scheme 2.23**, which was transformed as before into bicyclic amidine **136**.

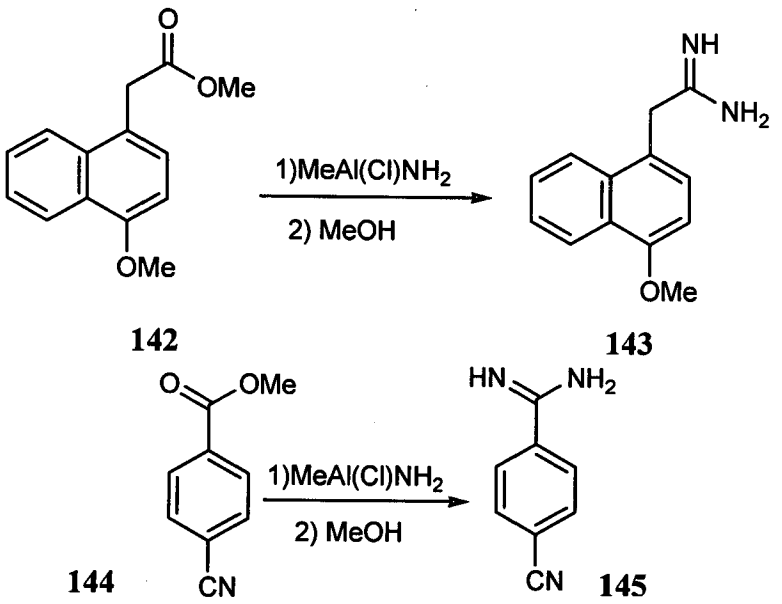


Scheme 2.23

Amidines from esters:

The conversion of esters to amidines with 1–5 equiv. methylchloroaluminium amide followed by hydrolysis of the aluminium complexes with methanol **Scheme 2.24** is reported in literarure. The quenching conditions seem to be crucial for the isolation of amidines or amides, the amides would then be the hydrolysis products of the amidines. This method is useful for the preparation of aromatic, heteroaromatic, and benzylic and aliphatic amidinium hydrochlorides in moderate to high yields [75].



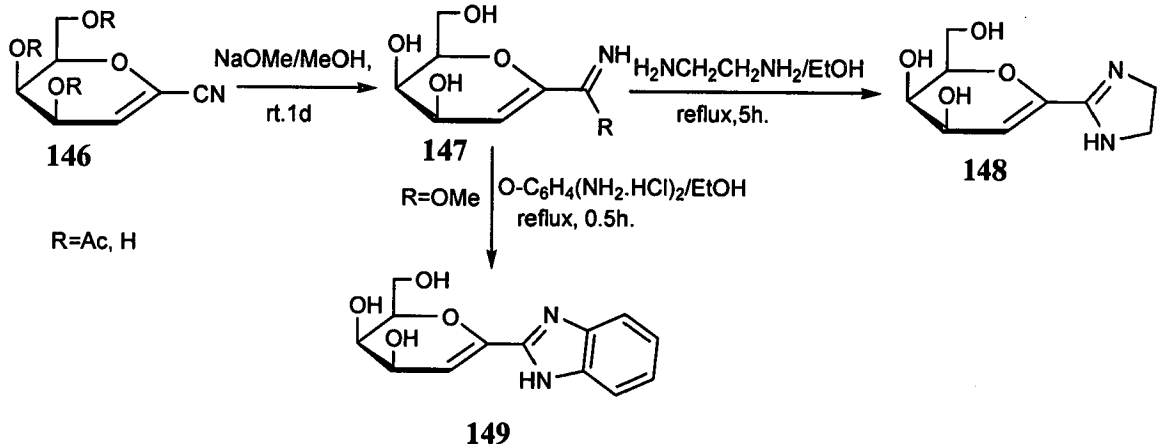


Scheme 2.24

Even nitriles as further substituents are tolerated **144**, in contrast to previous studies, which described the selective transformation of nitriles to amidines in the presence of esters [76].

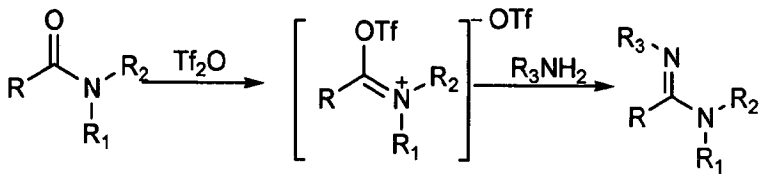
Miscellaneous Amidine Formations:

Some amidines derivatives have also been prepared from 1- cyano –D-glactal **146**. With ethylenediamine, the imidazoline **148** crystallised from the reaction mixture. 1,2 phenylenediamine did not react with **147** but its dihydrochloride gave the benzimidazole **149(Scheme 2.25)**. This reaction, performed under essentially neutral conditions [77].



Scheme 2.25

The synthesis of amidines was also achieved by the addition of amines to amides that were previously activated with trifluoromethanesulfonic anhydride (triflic anhydride) and pyridine **(Scheme 2.26)**. Various disubstituted and trisubstituted amidines were prepared in yields up to 84% [78]. Secondary and tertiary amides can be activated with trifluoromethanesulfonic anhydride (triflic anhydride) to generate the corresponding iminium salts which can further react with ethanol, hydrogen sulfide, ^{18}O-labeled water, aminothiols or 1,1,1 tris(hydroxymethyl)ethane to give the corresponding ethyl esters, thioamides, ^{18}O-labeled amides, thiazolines and cyclic orthoesters, respectively. Dossena and co-workers have also reported similar results using triflic anhydride and 2,6-di-*tert*-butylpyridine for the activation of simple amides (usually DMF and *N,N*-dimethylacetamide) and their subsequent conversion into thioimidates, esters and *O*-alkyl thioesters. They also reported the formation of amidine salts when an amine was added, but only two examples were reported and the yields were moderate (57% and 59%). Then a general protocol is developed to access amidines in high yields from both secondary and tertiary amides based previous findings and using pyridine as the base. The addition of triflic anhydride to a secondary or tertiary amide and pyridine would generate the iminium triflate that should be converted into the amidine upon addition of the appropriate amine.



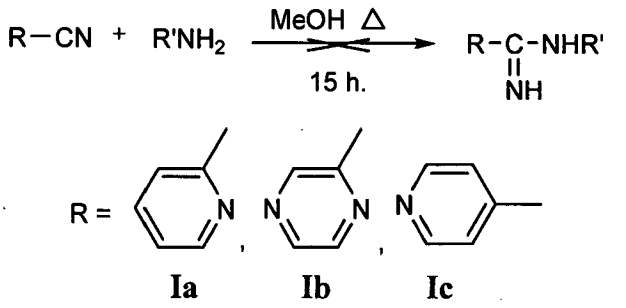
	Amines	
150	Me_2NH	$R_1 = R_2 = Me$
151	$EtNH_2$	$R_1 = H$, $R_2 = Et$
152	$BnNH_2$	$R_1 = H$, $R_2 = Bn$

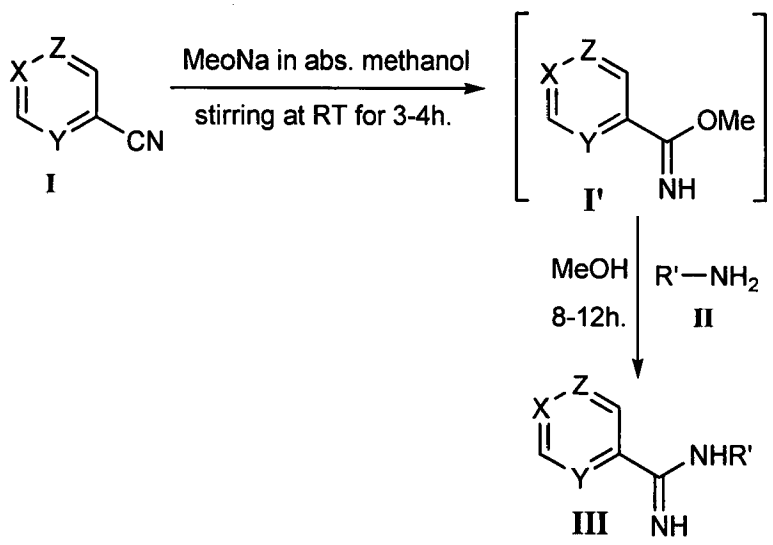
Scheme 2.26

Debenzylation of 5-benzyloxy-l,2,4-oxadiazole **153** would give the corresponding 1,2,4-oxadiazolin-5-one which, under the reaction conditions employed should reduce further to the required amidine **154 (Scheme 2.27)** [79].

Results and Discussion

2-Cyanopyridine, 4-cyanopyridine and 2-cyanopyrazine on refluxing with amines in methanol do not give condensation product **(III, Scheme 3.1)**. 2-Cyanopyridine, 4-cyanopyridine and 2-cyanopyrazine when first treated with catalytic amount of sodium methoxide in dry methanol at room temperature for 3-4 h and then adding amine and allowing the reaction contents to reflux for 8-16 hours, gave condensation products in good yields. Direct condensation of cyanopyridine or cyanopyrazine with amine is an addition reaction, which does not take place, however, in the presence of sodium methoxide an intermediate **(I' Scheme 3.1)** will be formed in situ, which can easily undergo substitution reaction with amine to give condensation products in good yields.





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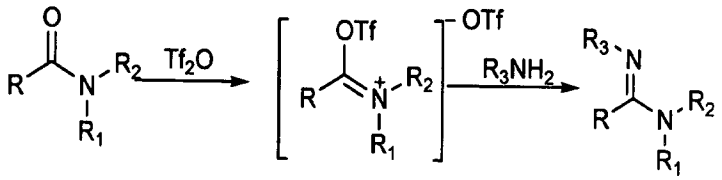


	Amines	
150	Me_2NH	$R_1 = R_2 = Me$
151	$EtNH_2$	$R_1 = H$, $R_2 = Et$
152	$BnNH_2$	$R_1 = H$, $R_2 = Bn$

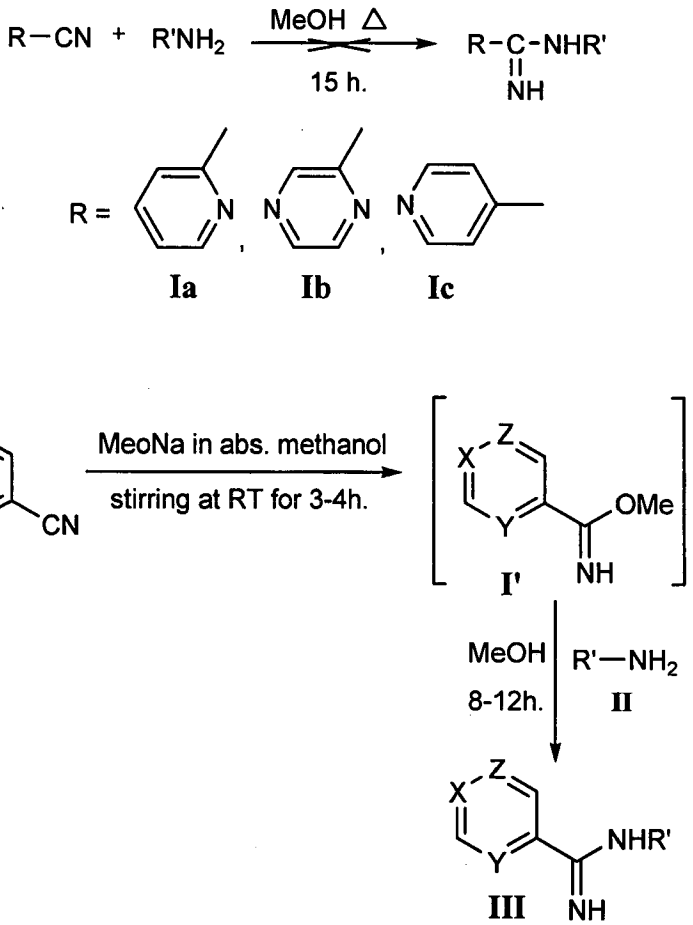
Scheme 2.26

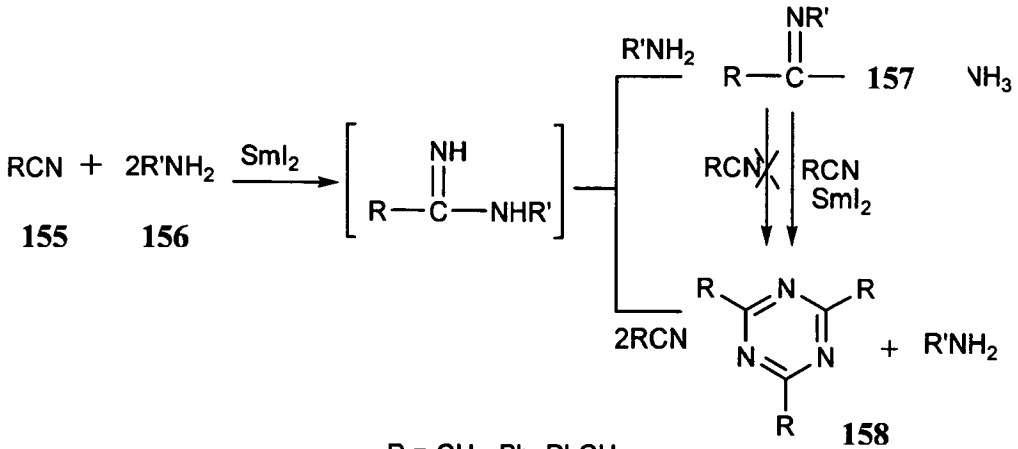
Debenzylation of 5-benzyloxy-l,2,4-oxadiazole **153** would give the corresponding 1,2,4-oxadiazolin-5-one which, under the reaction conditions employed should reduce further to the required amidine **154 (Scheme 2.27)** [79].

CHAPTER 3

Results and Discussion

2-Cyanopyridine, 4-cyanopyridine and 2-cyanopyrazine on refluxing with amines in methanol do not give condensation product **(III, Scheme 3.1)**. 2-Cyanopyridine, 4-cyanopyridine and 2-cyanopyrazine when first treated with catalytic amount of sodium methoxide in dry methanol at room temperature for 3-4 h and then adding amine and allowing the reaction contents to reflux for 8-16 hours, gave condensation products in good yields. Direct condensation of cyanopyridine or cyanopyrazine with amine is an addition reaction, which does not take place, however, in the presence of sodium methoxide an intermediate **(I' Scheme 3.1)** will be formed in situ, which can easily undergo substitution reaction with amine to give condensation products in good yields.





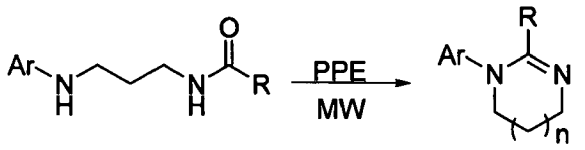
R = CH_3, Ph, $PhCH_2$

R' = n-C_3H_7, n-C_4H_9

Scheme 2.28

Microwave enhanced synthesis of amidines:

A simple and efficient microwave based protocol for the synthesis of heterocyclic amidines by PPE promoted cyclodehydration of N-aryl-N-acylalkylenediamines is reported(**Scheme 2.29**). The method is general for five- to eight-membered heterocycles and affords high yields of the desired products in remarkably short reaction times. Cyclocondensation is one of the most important methods for the synthesis of heterocycles. These reactions usually require long reaction times, high temperatures. Previously polyphosphoric acid esters PPE (ethyl polyphosphate) and PPSE (trimethylsilylpolyphosphate) were used as mild dehydrating agents for the preparation of tetrahydropyrimidines [34]. The main limitation of this procedure is long reaction times resulting in lower yields of the products in some cases. Recently, reactions performed under microwave irradiation proceed in general faster, more cleanly and with better yields than under conventional heating [81,82].



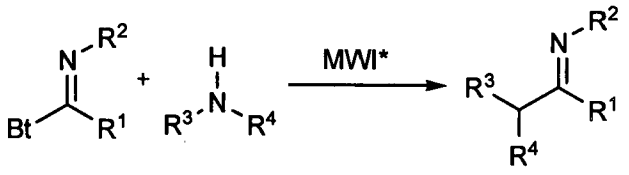
2 **159** **160**

Ar =4-ClC_6H_4, C_6H_5, 4-$CH_2C_6H_4$

R = C_6H_5, C_2H_5, $C(CH_3)_3$

Scheme 2.29

Microwave reactions of primary and secondary amines with imidoylbenzotriazoles gave diversely substituted amidines in 76-94% yields. Different type of amidines can be prepared by this method *N*-monosubstituted amidines N, N-disubstituted amidines N,N'-disubstituted Amidines *N,N'*-disubstituted and *N,N,N'*-trisubstituted amidines(**Scheme 2.30**)[83].



161 **162** **163**

Bn = benzotriazole R^1 = Me, Ph, Bn, 2-furyl

R^2 = Ph, Bn, p-tolyl, cyclohexyl

R^3 = Et, Bn, p-tolyl, cyclohexyl

R^4 = Et, H, Me

Different reaction conditions have been used there for the preparation of different kind of amidines.

Reaction conditions: 1) solvent, HOAc; MW, 120 W; temperature, 120 °C; reaction Time, 10 min.

2)$AlCl_3$ (catalytic amount); solvent, $CHCl_3$; MW, 80 W; Temperature, 80 °C; reaction time, 10 min

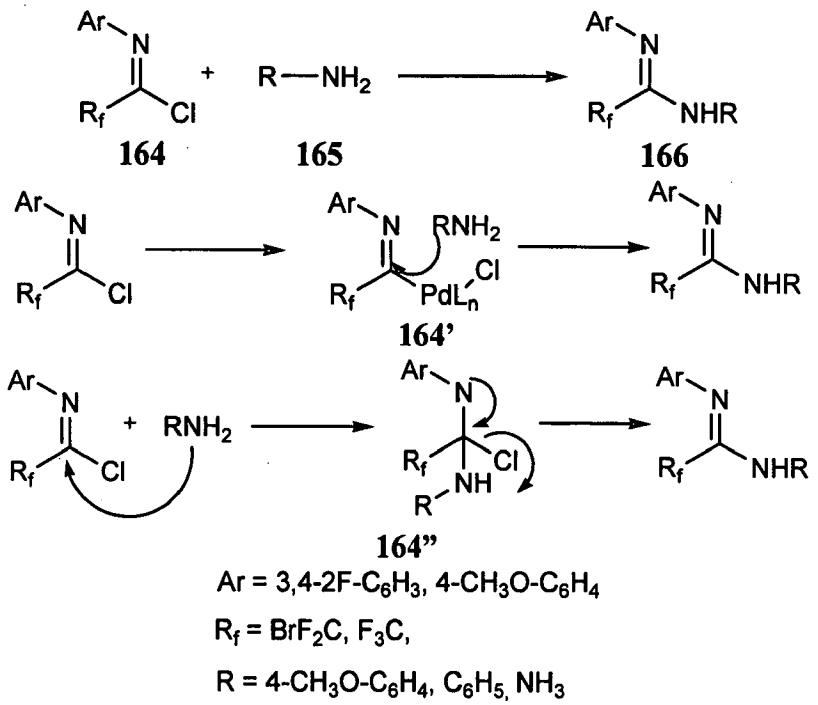
3) HCl salt of amine used;

4)$CHCl_3$; MW, 80 W; temperature, 80 °C; reaction time, 10 min

Scheme 2.30

However there are few reports on the synthesis of fluorinated arylamidines. In the past few years' organofluorine chemistry has returned as an expanding and productive area of research. Furthermore, organofluorine chemicals have found a wide range of applications in medicine and agriculture due, in part, to the unique biological properties imparted by the fluorine. A series of α-fluoro subustituted amidines were synthesized from corresponding fluorinated imidoyl chlorides in good to excellent yields. Different kind of amines have been used to expand this reaction. In these cases the nucleophilic substitution reaction proceeded smoothly to give the corresponding disubstituted

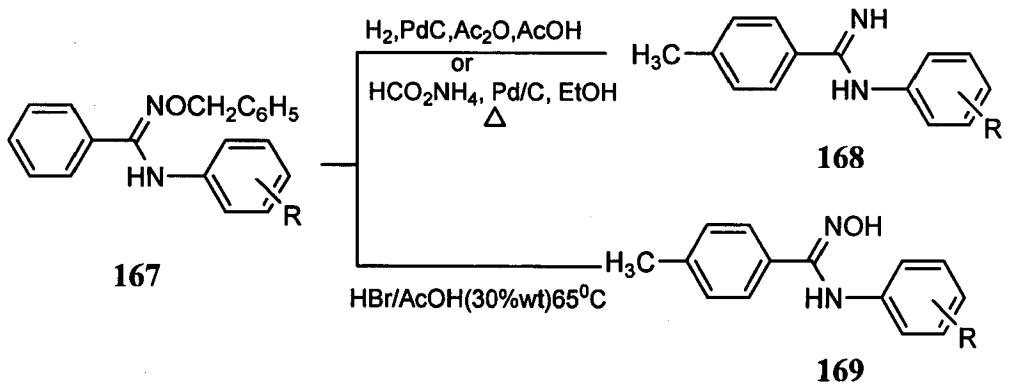
amidines in good to excellent yields. It was interesting to find that different kind of amine had dramatically different reactivity in this transformation. Strong electron-withdrawing groups in N-aryl of imidoyl chlorides would promote the reactions rates, and short reaction time was needed. On the other side, nucleophilic reagent with strong electron-withdrawing groups (NO_2) would prolong the reaction time and the catalyst $PdCl_2(PPh_3)_2$ was needed. Usually, the reactions of aliphatic amine and ammonia with imidoyl chlorides can proceed quickly under room temperature and the reaction could be completed within 5– 30 min while the substitution reactions of aromatic amines needed heating to 80^0C to obtain desired results. Generally speeking, an addition–elimination route was involved in the active amine **(Scheme 2.31)**. But for unreactive amine, a palladium promoted coupling mechanism is more reasonabl [84].



Scheme 2.31

Amidoximes are also of biological interest, as they serve as prodrugs for amidines and certain acyl derivatives are highly active against cytomegalovirus. As an important class of *N*-substituted derivatives, *N*-aryl amidines possess potent activity as well against nitric oxide synthase and various microbial diseases. *N*-Aryl amidines are typically prepared from anilines, either by direct reaction with a thioimidate or, under more forcing conditions with a nitrile. *O*-Benzyl-*N*-arylamidoximes **167** have been regioselectively

deprotected to provide either *N*-aryl amidines **168** or amidoximes **169(Scheme 2.32)**. As a result, the targeted compounds can now be prepared using palladium-catalyzed *N*-arylation chemistry [85].

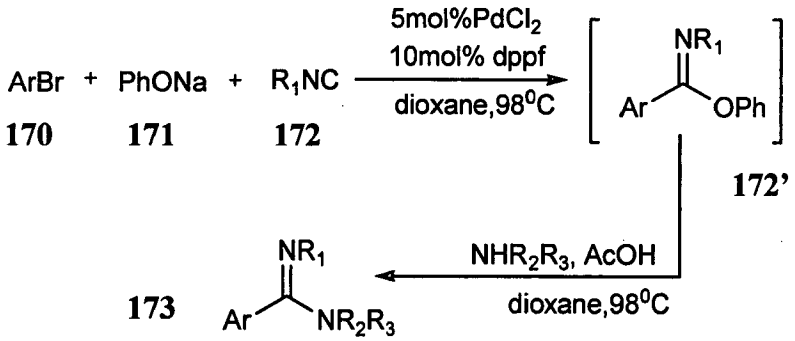


R = H, 4-CF_3, 4-C_6H_5, 3-OCH_3 (for amidines)

R = H, 4-CN, 4-NO_2, 4-C_6H_5, 4-Cl (for amidoxims)

Scheme 2.32

Amidines from aryl halides are also reported in literature. Palladium-catalysed reaction of an aryl bromide **170** with sodium phenoxide and cyclohexyl- or *n*-butyl-isocyanide in dioxane at 98°C for 4 h followed by addition of an amine (5 equiv.) and acetic acid (3 equiv.) and heating for a further 3 h gave the amidines **173** in excellent overall yields. This procedure for the synthesis of amidines via the corresponding imitates **172'**, overcomes the isocyanide component limitations of the direct amidine synthesis. The developed methodologies should find application in the synthesis of valuable intermediates as well as in pharmaceutical discovery [86].



ArX = C_6H_5Br, p-$MeCOC_6H_4Br$, 3-Bromopyridine

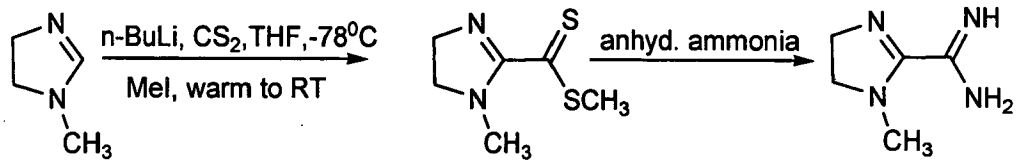
R^2, R^3 = Ph, H; $PhCH_2$,H

R^1NC = BuNC, CyNC

Scheme 2.33

1,1-bis (- diphenylphosphino) ferrocene (dppf, 10 mol%)

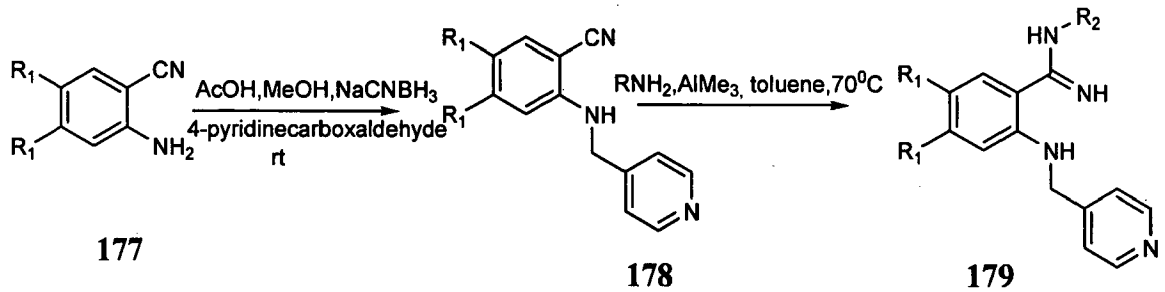
A method was developed for novel amidine synthesis that allows the preparation of heterocyclic amidines that were previously unknown and difficult to prepare by published methods. The route involves the lithiation of heterocycles by the action of n-BuLi followed by reaction with carbon disulfide and trapping with methyl iodide, yielding a dithioate ester. The latter, when heated in 20% methanolic ammonia at 80°C in a sealed tube provides the heterocyclic amidines directly, in good yield. The products are isolated by crystallization of the respective hydrochloride salts **(Scheme 2.34)**[87].



174 **175** **176**

Scheme 2.34

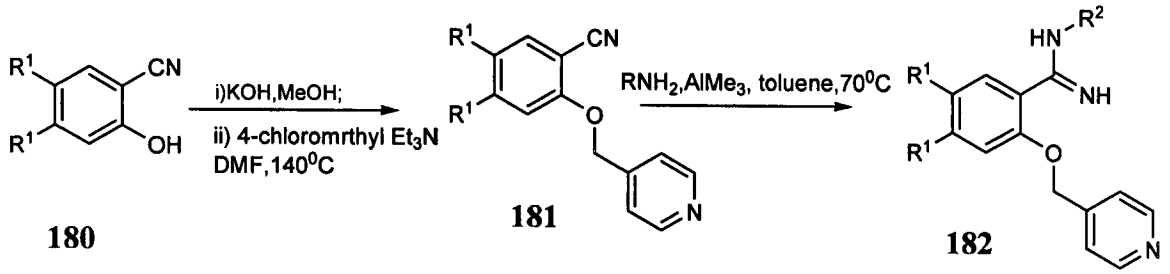
Wenext synthesized the anthranilic and salicylic amidines. The anthranilic amidines **179** **(Scheme 2.35)** were synthesized from2-aminobenzonitrile **177** or 4,5-dimethoxyl-2 aminobenzonitrile. Reductive amination **177** with 4-pyridinecarboxaldehyde proceeded in the presence of $NaCNBH_3$, giving the corresponding benzonitriles **178** in 41% yields. Amidine formation with various amines was promoted by trimethylaluminum to afford the corresponding anthranilic amidines.



177 **178** **179**

Scheme 2.35

Salicylic amidines **182** were also synthesized from 2-hydroxybenzonitrile **180** and 4,5-dimethoxyl-2-hydroxybenzonitrile [29].



R^1 = H, OMe

R^2 = 2-$CF_3C_6H_4$, 4-ClC_6H_4, 2ClC_6H_4

Scheme 2.36

General synthesis of substituted amidines has been also worked out starting from a nitrile compound, an alkyl halide, a Lewis acid and an amine. In this method four steps are involved (1) Formation of a nitrile-Lewis acid complex **184**.

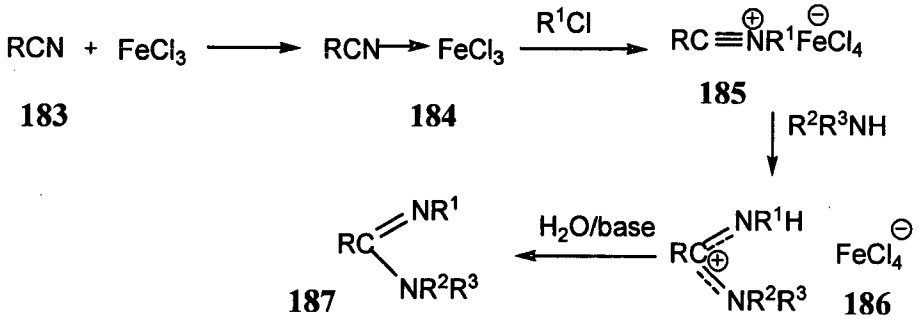
(2) N-Alkylation of this complex **184** with an alkyl halide and formation of a nitrilium salt **185**.

(3) Aminolysis of the nitrilium salt **185** with ammonia, a primary or a secondary aliphatic or aromatic amine to get the amidinium salt **186**.

(4) Neutralization of the amidinium salt with a base yielding the substituted amidine **187**.

In practice, the amidine **187(Scheme 2.37)** is obtained in a one-pot synthesis and none of the intermediates needs to be isolated.

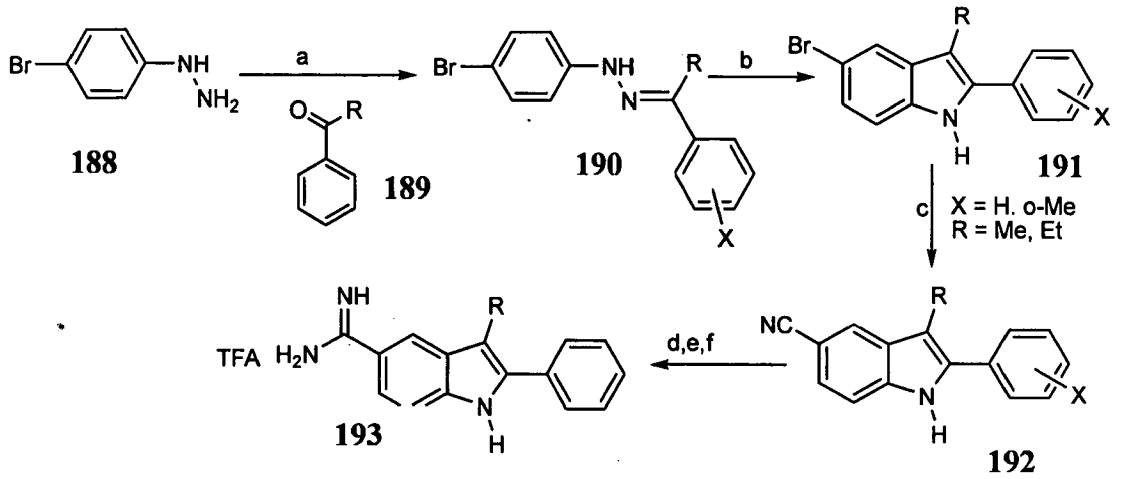
A number of aliphatic or aromatic mono-, di- or tri-substituted amidines containing aliphatic, cycloaliphatic or aromatic substituents shows the generality of the method. The very mild reaction conditions make this process particularly useful for the synthesis of thermal sensitive amidines [88].



Scheme 2.37

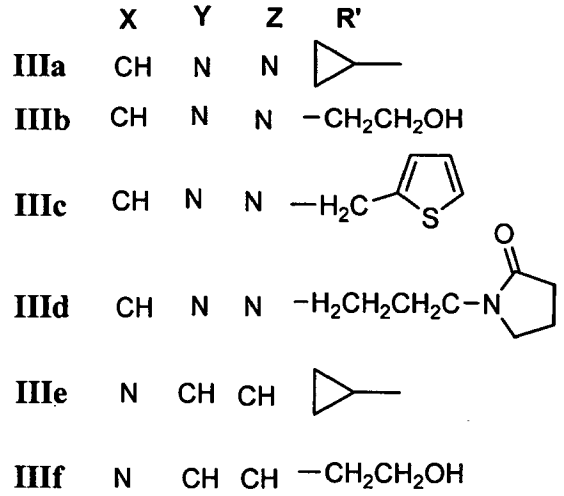
Derivative of 5- amidie indole displays competitive kinetics for the inhibition of human α-thrombin. Two different synthetic strategies were employed to prepare either the 2-

phenyl or the 2-benzyl analogs. The former analogs were prepared as outlined in **(Scheme 2.38)** Hydrazones **190** were prepared from the condensation of hydrazine **188** with the corresponding ketone **189** in refluxing methanol. Polyphosphoric acid was employed to fashion the indole skeleton to give **191**. The nitrile functionality was introduced using cuprous cyanide/quinoline in a sealed tube at 230 °C. The amidine moiety was prepared from the corresponding nitrile *via* a two-step procedure. The intermediate imidoester was prepared by treatment with hydrochloric acid/ethanol, the solvent was removed and the resulting solids treated with saturated ammonia/ethanol to give **193** [89].



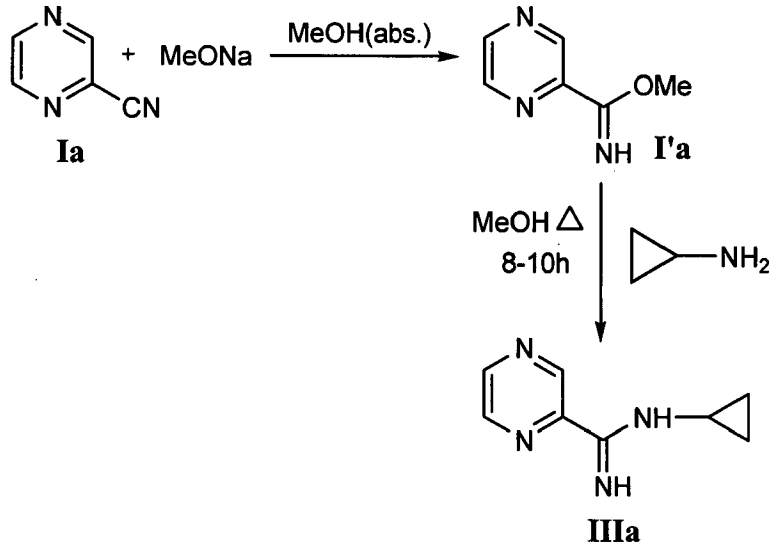
a) MeOH, reflux,10h; b)polyphosphoric acid 120^{0}C 3h.; c) CaCN/quinoline 230^{0}C 1h.
d) HCl/EtOH 0^{0}C to rt, 10h.; e) NH_3/EtOH in a sealed tube, 80^{0}C 24h.; f) preparative HPLC purifucation (CH_3CN/H_2O with 1% TFA

Scheme 2.38



Scheme 3.1

2-cyanopyrazine **Ia** and MeONa was taken in abs. Methanol and the reaction mixture was stirred at room temperature leads to the formation of intermediate **I'a,** after 3-4 hour of stirring, to this in situ generated intermediate, cyclopropyl amine was added. The reaction mixture was refluxed in dry methanol. Crude product obtained was purified by crystallization to give pure product, which was then fully characterized by IR, ^{1}H NMR, and mass spectral data.



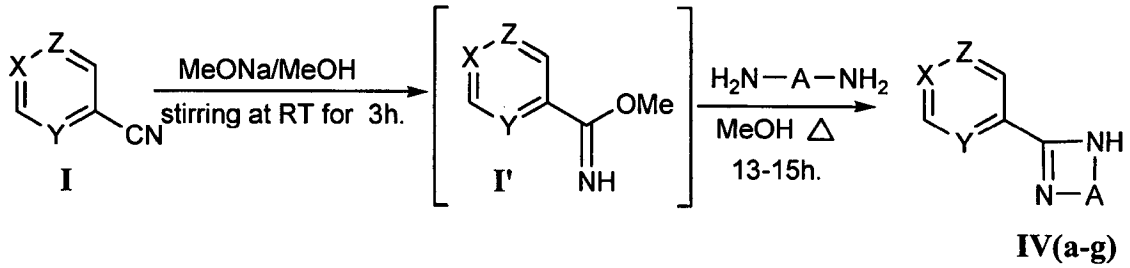
Compounds **III(b-d)** were similarly prepared and had been confirmed by spectral data reported in **Table-1**

Table 1: Spectral data and physical constant of compound III(a-f)

Comp. No.	Solvent of Crystallization	Yield (%)	m.p. (^{0}C)	Spectral Data
IIIa	Diethyl ether +ethyl acetate	35	130(d)	IR (KBr) ν_{max}: 3464(NH), 1621 (C=N), 1568 and 1409(Ar) cm^{-1}. ^1H NMR(60MHz, DMSO-d_6) δ: 4.0(s, 5H), 8.3(s, 2H, Py), 8.9(s, 1H, Py).
IIIb	Diethyl ether	32	101	IR(KBr)ν_{max}:3446(NH), 1635 (C=N), 1556 and 1401(Ar) cm^{-1} GC-MS m/z 148(M^+-H_2O, 78%), 147 ($C_7H_7N_4^+$, 34%), 120 ($C_5H_4N_4^+$, 21%), 119($C_5H_3N_4^+$, 81%), 79($C_4H_3N_2^+$, 100%)
IIIc	Diethyl ether + ethyl acetate	52	150(d)	IR (KBr) ν_{max}: 3433 (NH), 1632 (C=N), 1564 and 1418 (Ar) cm^{-1}. ^1H NMR(60MHz, DMSO-d_6) δ: 4.6(s, 2H), 8.0(s, 2H), 8.9(br signal, 2H), 9.4(s, 2H).
IIId	Diethyl ether	39	65	IR (KBr) ν_{max}: 3433 (NH), 1650 (C=N), 1464 and 1421 (Ar) cm^{-1}. GC-MS m/z 149($C_7H_9N_4^+$, 100%), 135 ($C_6H_7N_4^+$, 58%), 119($C_5H_3N_4^+$, 23%), 98 ($C_5H_8NO^+$, 39%), 79($C_4H_3N_2^+$, 38%). ^1H NMR(60MHz, DMSO-d_6) δ: 2.3(m, 6H), 3.4(m, 6H), 8.7(d, 2H, Py), 9.4(s, 1H, Py)
IIIe	Diethyl ether + ethyl acetate	31	160	IR (KBr) ν_{max}: 3443(NH), 1630 (C=N), 1555 and 1414(Ar) cm^{-1} ^1H NMR(60MHz, DMSO-d_6) δ: 3.6(s,

				5H), 8.0(br signal, 3H), 8.7(br signal, 1H).
IIIf	Diethyl ether	29	115	IR (KBr) ν_{max}: 3451(NH), 1600 (C=N), 1556 and 1457(Ar) cm^{-1}. GC-MS m/z 147(M^+-H_2O, 41%), 146 ($C_8H_9N_3^+$, 30), 119($C_6H_5N^+$, 12%), 118 ($C_6H_4N_3^+$, 100%), 78($C_5H_4N^+$, 29%). ^{1}H NMR(60MHz, DMSO-d_6) δ: 3.9(s, 4H), 7.9(d, 2H), 8.7(d, 2H).

Further when the reactions are carried out with diamines **(Scheme 3.2)**, five and six membered products are obtained by the elimination of ammonia molecule.

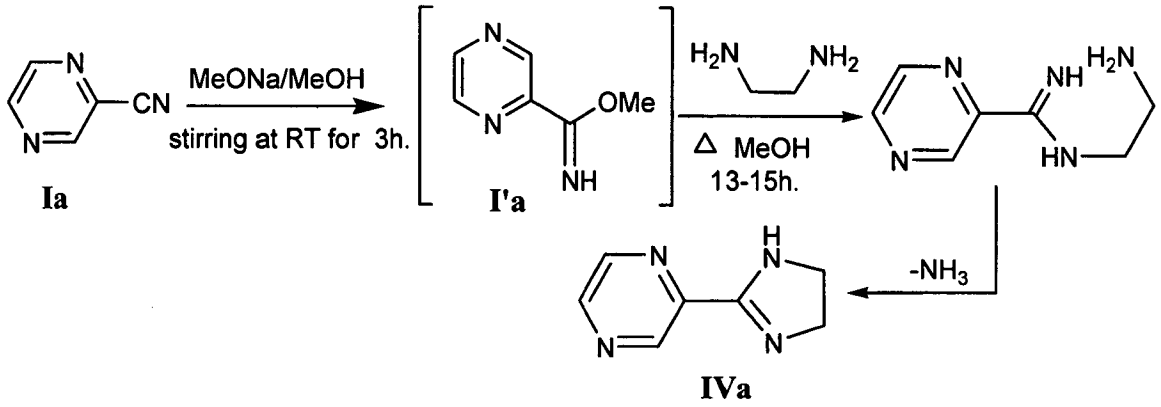


I I' IV(a-g)

	X	Y	Z	A
IVa	CH	N	N	$-(CH_2)_2-$
IVb	CH	N	N	$-(CH_2)_3-$
IVc	CH	N	N	$-H_2C-\underset{\displaystyle H}{\overset{\displaystyle |}{C}}-CH_3$
IVd	N	CH	CH	$-(CH_2)_2-$
IVe	N	CH	CH	$-(CH_2)_3-$
IVf	N	CH	CH	$-H_2C-\underset{\displaystyle H}{\overset{\displaystyle |}{C}}-CH_3$
IVg	CH	N	CH	$-(CH_2)_2-$

Scheme 3.2

When 2-cyano pyrazine **(Ia)** and Sodium methoxide was taken in dry methanol, stirred at room temperature to give intermediate **(I'a)** to this in situ generated intermediate 1,2-diamino ethane was added and this reaction mixture was refluxed in dry methanol. Crude product obtained was purified by crystallization to give pure product **(IVa, Scheme 3.2)**, which was fully characterized by IR, NMR and mass spectral data.



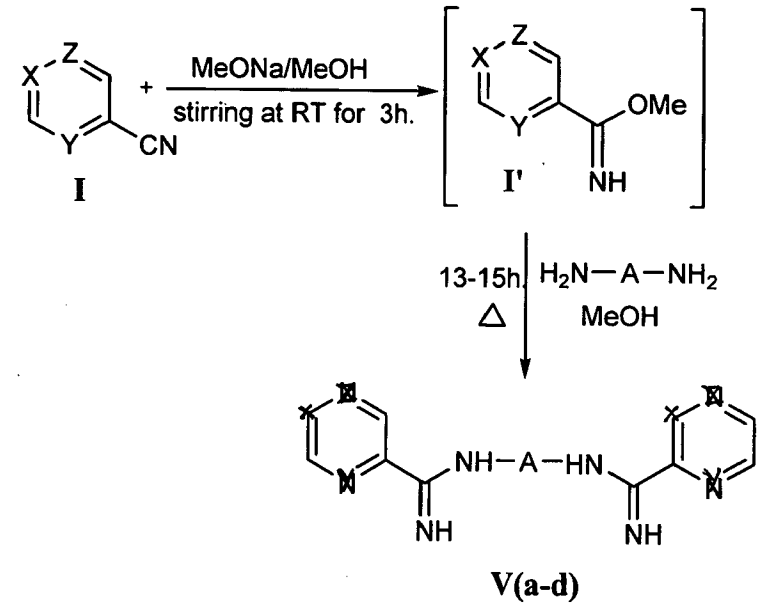
compounds **4(a-g)** were similarly prepared and have been confirmed by spectral data reported in **Table 2**

Table 2: Spectral data and physical constant of compound IV(a-g)

Comp. No.	Solvent of crystallization/ Elution	Yield (%)	m.p. (^{0}C)	Spectral data
IVa	Ethyl acetate + methanol (8:2)*	35	170	IR (KBr) ν_{max}: 3422(NH), 1627 (C=N), 1559 and 1421(Ar) cm^{-1} GC-MS: m/z 148(M^+, 19%), 147(M^+-$H^\bullet$, 62%), 120($C_5H_4N_4^+$, 4%), 119 ($C_5H_3N_4^+$, 13%), 79($C_4H_3N_2^+$, 100%).
IVb	Ethyl acetate + methanol (7:3)*	45	97	IR (KBr) ν_{max}: 3414 and 3361(NH), 1627(C=N), 1567 and 1405(Ar) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.88(m, 2H, -CH_2-), 3.53(t, 4H, -CH_2-NH + -CH_2-N), 8.45(s, 1H Pyr), 8.61(d, 1H Pyr), 9.4(s, 1H Pyr).

				GC-MS m/z 162(M^+, 88%), 161(M^+-$H^\bullet$, 100%), 134($C_6H_6N_4^+$, 10%), 120 ($C_5H_4N_4^+$, 8%), 79($C_4H_3N_2^+$, 81%).
IVc	Ethyl acetate + methanol (8:2)*	33	Hygro-scopic	IR (KBr) ν_{max}: 3432(NH), 1566 and 1426(Ar) cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6), δ: .51(d, 3H, -CH_3-), 2.59(s, 1H, -CH), 3.15(d, 1H, -CH), 3.35(d, 1H, -CH), 8.01(d, 1H Pyr), 8.06(d, 1H Pyr), 8.51(d, 1H Pyr). GC-MS m/z 162(M^+, 43%), 147 ($C_7H_7N_4^+$,100%), 119($C_5H_3N_4^+$, 35%), 79($C_4H_3N_2^+$, 80%).
IVd	Ethyl acetate + diethyl ether	55	98	IR (KBr) ν_{max}: 3482(NH), 1634 (C=N), 1548 and 1401(Ar) cm^{-1} GC-MS m/z 147(M^+, 43%), 146(M^+-$H^\bullet$, 25%), 119($C_6H_5N_3^+$, 12%), 118 ($C_6H_4N_3^+$, 100%), 78($C_5H_4N^+$, 38%).
IVe	Ethyl acetate	57	85	IR (KBr) ν_{max}: 3416(NH), 1624 (C=N), 1562 and 1417(Ar) cm^{-1} ^1H NMR (500 MHz, DMSO-d_6), δ: 1.68(m, 2H, -CH_2-), 3.29(t, 4H, -CH_2-NH + -CH_2-N), 7.56(d, 2H, Py), 8.53(d, 2H, Py). GC-MS m/z 161(M^+, 34%), 160(M^+-$H^\bullet$, 100%), 133($C_7H_7N_3^+$,10%), 118 ($C_6H_4N_3^+$,8%), 78($C_5H_4N^+$, 37%).
IVf	Ethyl acetate + methanol (8:2)*	38	Hygro-scopic	IR (KBr) ν_{max}: 34167 (NH), 1648 (C=N), 1551 and 1415 (Ar) cm^{-1}. GC-MS m/z 161(M^+, 30%), 160(M^+-H ,

				8%), 146($C_8H_8N_3^+$, 100%), 132 ($C_8H_8N_2^+$, 28%), 118($C_6H_4N_3^+$, 84%), 78($C_5H_4N^+$, 41%). ^{1}H NMR(60MHz, $CDCl_3$) δ:1.3(broad signal, 4H), 3.3(broad signal, 2H), 7.9(d, 2H, Pyr), 8.8(d, 2H, Pyr).
IVg	Ethyl acetate + methanol (8:2)*	30	Hygro-scopic	IR (KBr) ν_{max}: 3438(NH), 1617 (C=N), 1568 and 1433(Ar) cm^{-1} GC-MS m/z 147(M^+, 68%), 146(M^+-$H^\bullet$, 28%), 119($C_6H_5N_3^+$, 15%), 118 ($C_6H_4N_3^+$, 53%), 92($C_5H_4N_2^+$, 28%), 78($C_5H_4N^+$, 100%).

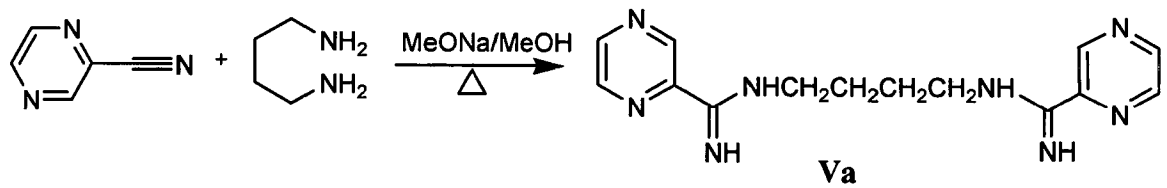


V(a-d)

	X	Y	Z	A
Va	CH	N	N	$-(CH_2)_4-$
Vb	CH	N	N	$-(H_2C)_3-N$ $N-(CH_2)_3-$
Vc	CH	N	N	$-(H_2C)_3-$ $-(CH_3)_3-$
Vd	N	CH	CH	$-(CH_2)_4-$

Scheme 3.3

When the reactions of cyano pyrazine and cyano pyridine were carried out with 1,4-diamino butane, it leads to the formation of dimeric product rather than giving the seven membered ring, which is quite unstable as compared to five and six membered ring.



Va

The reactions were also carried out with more bulky amines, also in that case dimeric products are obtained. Compounds **V(a-d)** are similarly prepared and fully characterized by spectral data, which is reported in **Table 3**.

Table 3: Spectral data and physical constant of compound V(a-d)

Comp. No.	Solvent of crystallization	Yield (%)	m.p. (^{0}C)	Spectral data
Va	Methanol	42	180	IR (KBr) ν_{max}: 3396 and 3305(NH), 1638(C=N), 1596 and 1470(Ar) cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6), δ: 1.75 (s, 4H, 2X-CH_2-NH), 3.26(s, 4H, -CH_2-CH_2-), 6.51(br s, 2H, 2X -NH, exch.), 8.62(s, 2H, Pyr), 8.70(s, 2H, Pyr) 9.32(s, 2H Pyr). GC-MS m/z 175($C_9H_{11}N_4^+$, 85%), 147 ($C_7H_7N_4^+$, 38%), 121($C_5H_5N_4^+$,11%), 119($C_5H_3N_4^+$, 98%),79($C_4H_3N_2^+$,100%).
Vb	Ethyl acetate	83	165	IR (KBr) ν_{max}: 3445(NH), 1644 (C=N), 1413(Ar) cm^{-1}. ^{1}H NMR(60MHz, DMSO-d_6) δ: 2.6(br signal, 8H), 3.4(br signal, 12H), 8.2(s, 2H), 8.7(br signal, 2H), 9.4(br sig, 2H).
Vc	Ethyl acetate	85	135	IR (KBr) ν_{max}: 3450 (NH), 1633 (C=N), 1560 and 1466(Ar) cm^{-1}
Vd	Ethyl acetate	40	96	IR (KBr) ν_{max}: 3415 (NH), 1610 (C=N), 1563 and 1418(Ar) cm^{-1} ^{1}H NMR (500 MHz, DMSO-d_6), δ: 1.70(s, 4H, 2X-CH_2-NH), 3.15(s, 4H, 2X-CH_2-), 7.70(D, 4H, Py), 8.57(t, 4H, Py). GC-MS m/z 174($C_{10}H_{12}N_3^+$, 70%), 160 ($C_9H_{10}N_3^+$, 10%), 146($C_8H_8N_3^+$, 13%), 118($C_6H_4N_3^+$, 100%).

CHAPTER 4

Experimental section:

4.1 CHEMICALS AND SUPPLIERS:

S No.	Chemicals	Suppliers
1.	2-cyanopyrazine	Aldrich
2.	4-cyanopyridine	Aldrich
3.	2-cyanopyridine	Aldrich
4.	1,2-diamino ethane	Aldrich
5.	1,3-diamino propane	Aldrich
6.	1,2-diamino propane	Aldrich
7.	1,4-diamino butane	Aldrich
8.	2-amino ethanol	Aldrich
9.	Cyclopropyl amine	Aldrich
10.	2-thiophene methyl amine	Aldrich
11.	1,4-Bis(3-aminopropyl)piperazine	Aldrich
12.	1-(3-aminopropyl)pyrrolidin-2-one	Aldrich
13.	Diethyl ether	Merck
14.	Ethyl actetate	Qualigens
15.	Methanol	Rankem
16.	Chloroform	Rankem
17.	Petroleum ether	Merck
18.	Silica Gel (60-120 mesh)	Qualigen
19	2,4,8,10-tetraoxaspro[5,5]-undecane-3,9-dipropaneamine	Aldrich

the residue left behind was scratched with diethyl ether and the solid separated out was filtered, give crude product, which was purified by column chromatography over silica gel. Elution with ethyl acetate: chloroform (8:2) removed side products and further elution with ethyl acetate: methanol (8:2) gave pure condensed product.

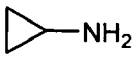
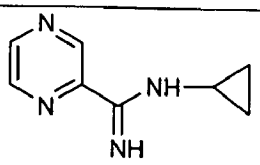
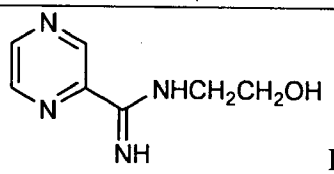
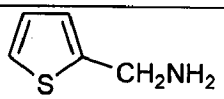
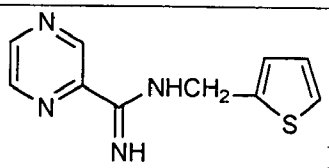
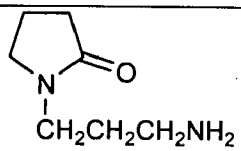
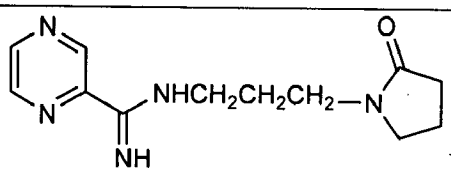
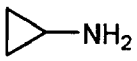
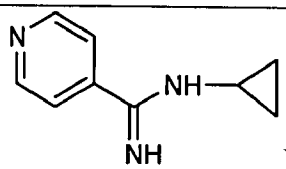
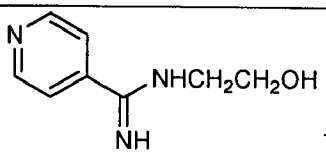
Other compounds **IVa, IV(c-g)** were similarly prepared. Yield, melting point, solvents of crystallization are reported in **Table 2.**

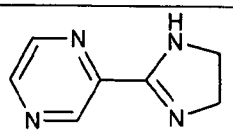
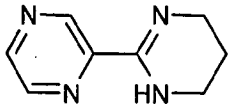
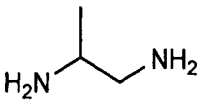
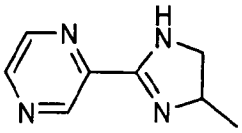
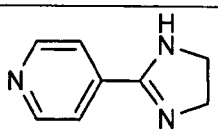
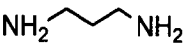
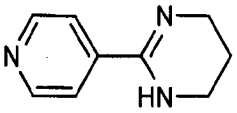
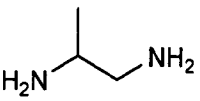
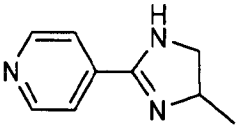
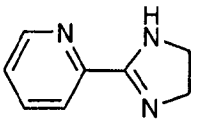
4.3.3 N-(4-(pyrazine-2-carboxamidino)butyl)pyrazine-2-carboxamidine (Va):

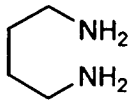
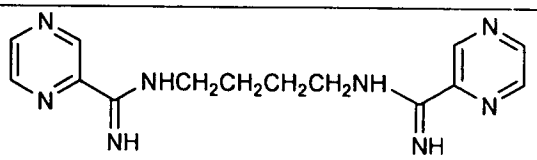
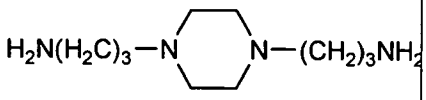
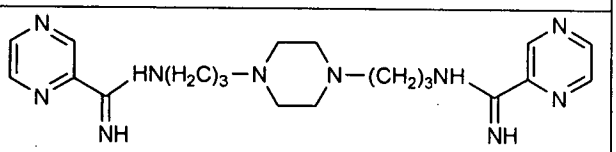
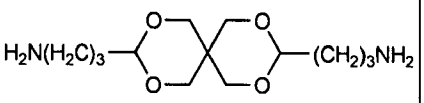
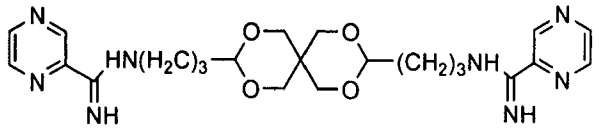
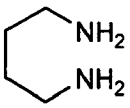
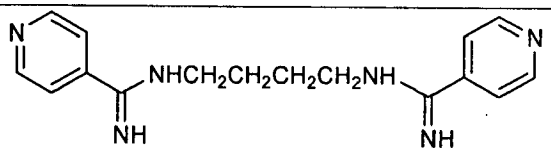
Sodium metal 23 mg was dissolved in 20 ml absolute methanol and was labeled as sodium methoxide solution in methanol. 2-Cyanopyrazine (0.210g; 2 mmol) was dissolved in absolute methanol (8 ml) and to it was added sodium methoxide solution (2.5 ml) prepared above, the reaction contents were stirred at room temperature for 4 h and then 1,4-diamino butane (0.088 g; 1 mmol) was added to it. The reaction content was refluxed for 15h. After the completion of the reaction solvent was removed under reduced pressure and to the residue left behind was scratched with ethyl acetate, the solid separated out was filtered, give pure condensed product.

Other compounds **V(b-d)** were similarly prepared. Yield, melting point, solvents of crystallization are reported in **Table 3.**

Table 4:

S.No.	Amine	Amidines
1		 **IIIa** N-cyclopropylpyrazine-2-carboxamidine
2	$H_2NCH_2CH_2OH$	 **IIIb** N-(2-hydroxyethyl)pyrazine-2 carboxamidine
3		 **IIIc** N-(thiophen-2-ylmethyl)pyrazine-2 carboxamidine
4		 **IIId** N-(3-(2-oxopyrrolidin-1-yl)propyl)pyrazine-2-carboxamidine
5		 **IIIe** N-cyclopropylisonicotinamidine
6	$H_2NCH_2CH_2OH$	 **IIIf** N-(2-hydroxyethyl)isonicotinamidine:

7	$NH_2CH_2CH_2NH_2$	 **IVa** 2-(4,5-dihydro-1H-imidazol-2-yl) pyrazine
8		 **IVb** 2-(1,4,5,6-tetrahydropyrimidin-2-yl) pyrazine
9		 **IVc** 2-(4-methyl-4,5-dihydro-1H-imidazol-2-yl) pyrazine
10	$NH_2CH_2CH_2NH_2$	 **IVd** 4-(4,5-dihydro-1H-imidazol-2-yl) pyridine
11		 **IVe** 2-(pyridin-4-yl)-1,4,5,6-tetrahydropyrimidine
12		 **IVf** 4-(4-methyl-4,5-dihydro-1H-imidazol-2-yl) pyridine
13	$NH_2CH_2CH_2NH_2$	 **IVg** 2-(4,5-dihydro-1H-imidazol-2-yl)pyridine

14		 **Va** N-(4-(pyrazine-2-carboxamidino) butyl) pyrazine-2-carboxamidine
15		 **Vb** N-(3-(4-(3-(pyrazine-2-carboxamidino) propyl)piperazin-1-yl)propyl)pyrazine-2-carboxamidine
16		 **Vc** dimeric amidine of 2,4,8,10-tetraoxaspro [5,5]-undecane-3,9-dipropaneamine
17		 **Vd** N-(4-(isonicotinamidino)butyl) isonicotin amidine

Conclusion:

As we have seen that amidine derivatives show biological activity and are also used in the synthesis of heterocyclic compounds, which also show biological activity. We have synthesized some amidine derivatives starting from nitriles and amines. Direct reaction of nitrile with amine was not possible so we used sodium methoxide in absolute methanol to carry out the reaction for the synthesis of amidines. We have synthesized some monomeric amidines **III(a-f)** using monoamines, some cyclized amidines **IV(a-g)**, and some dimeric amidines **V(a-d)** using nitriles with diamines. These are purified by column chromatography or by crystallization. These all synthesized and purified products are characterized by melting point, IR, ^{1}H NMR, GC-MS.

SPECTRA

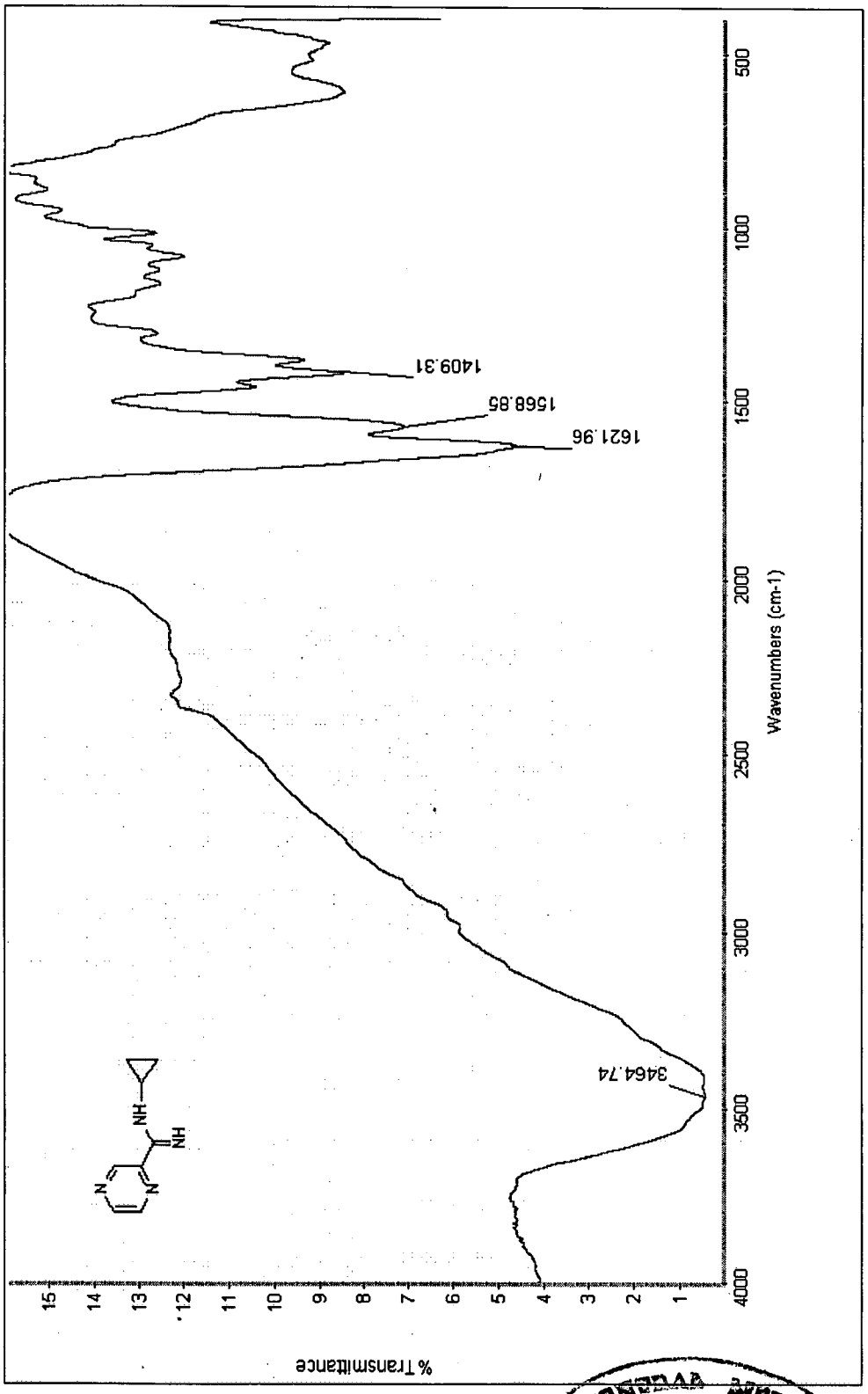


Fig 1

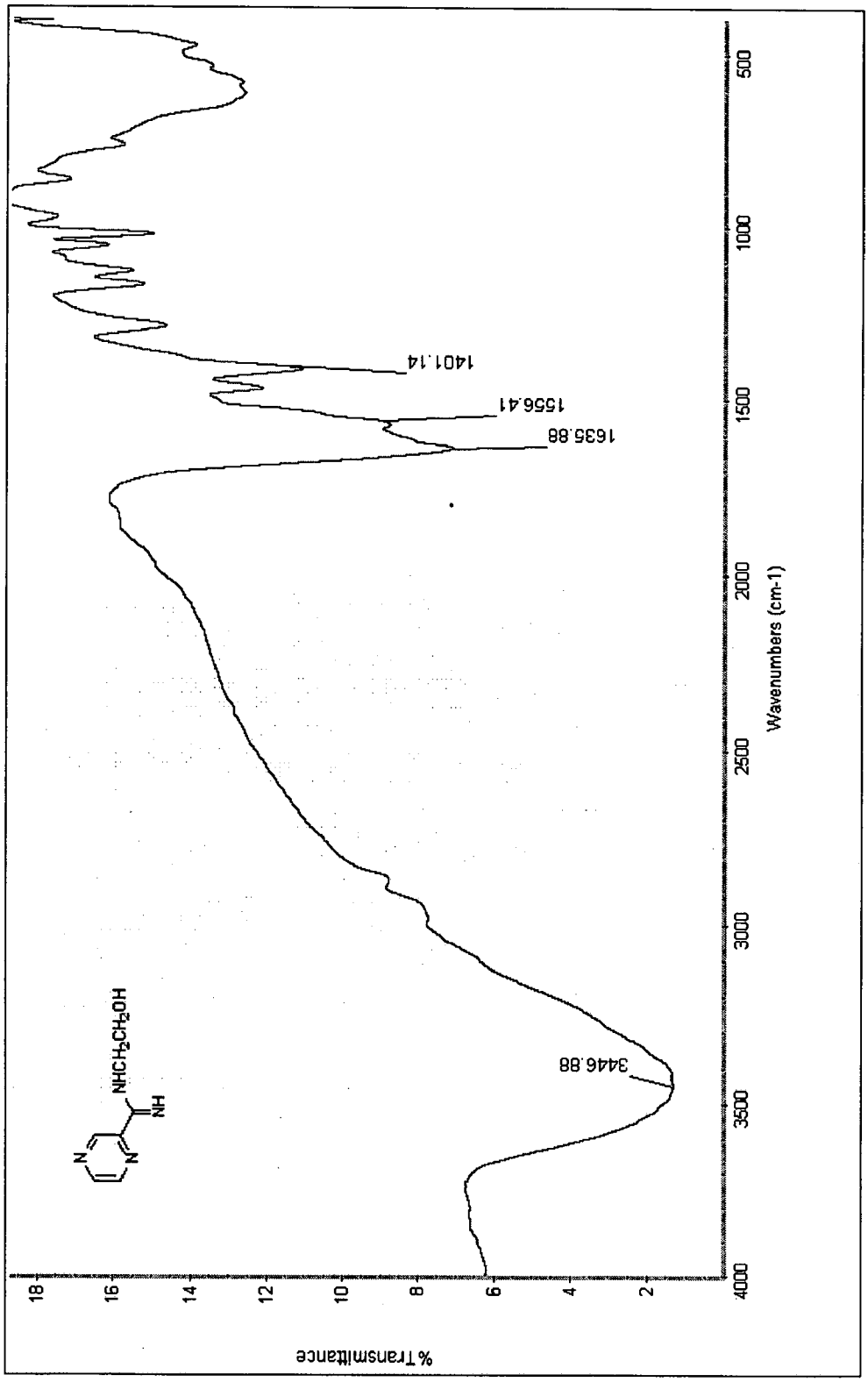

%Transmittance
Wavenumbers (cm-1)
3446.88
1635.88
1556.41
1401.14
NHCH2CH2OH
NH
N
N

Fig. 2

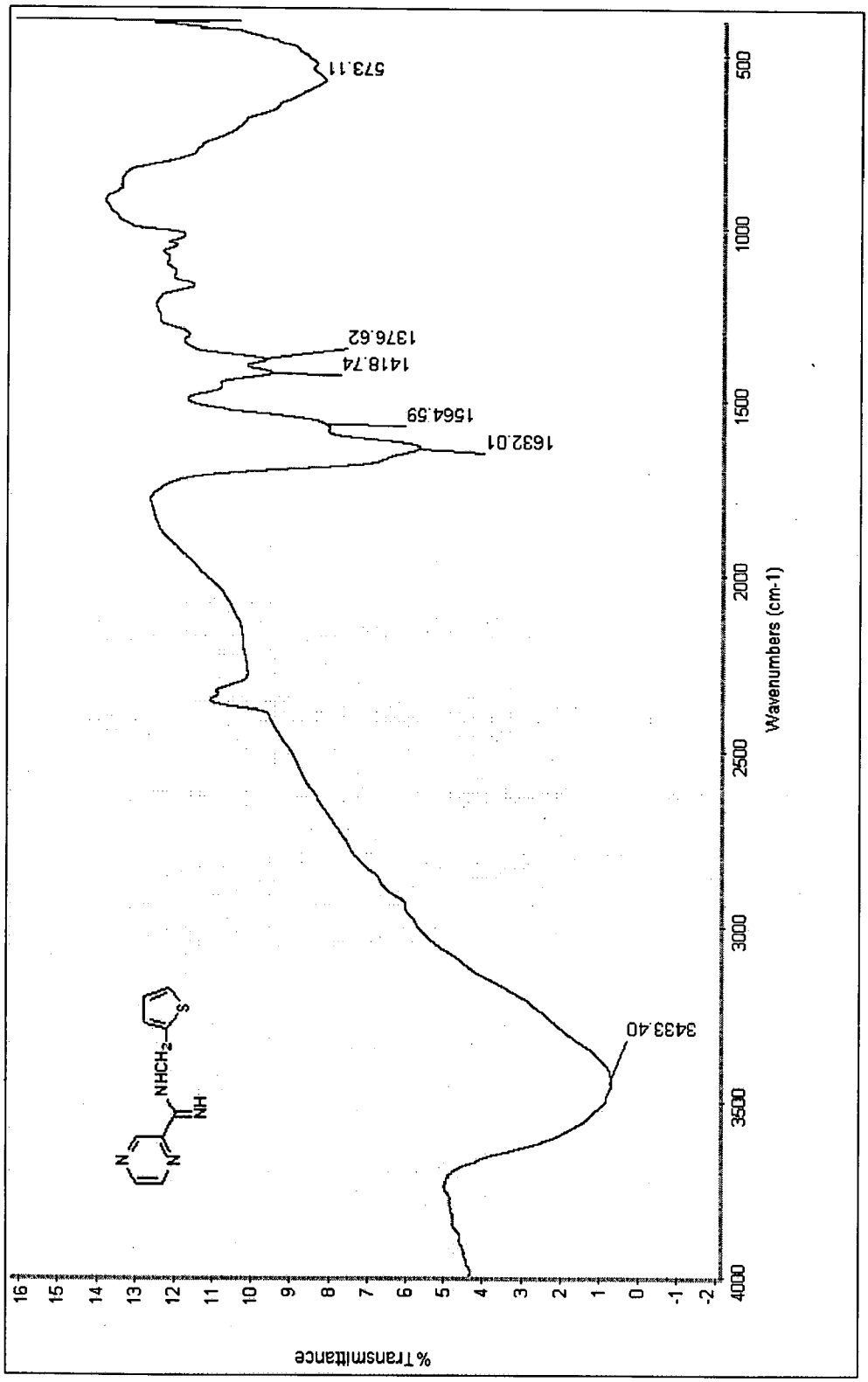

573.11
1376.62
1418.74
1564.59
1632.01
3433.40
Wavenumbers (cm-1)
%Transmittance
NHCH2
NH
S
N
N

Fig. 3

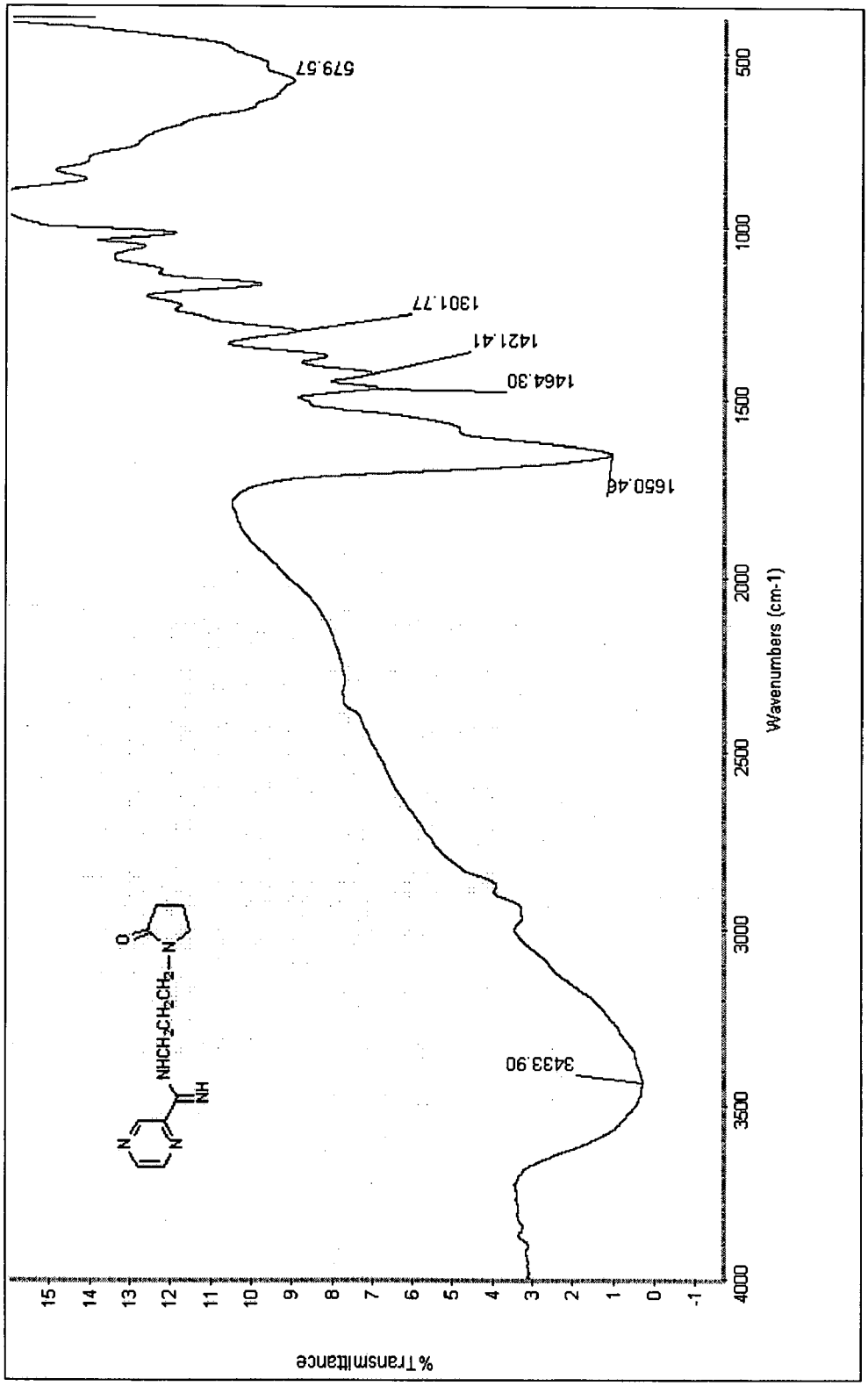

579.57
1301.77
1421.41
1464.30
1650.46
3433.90
Wavenumbers (cm-1)
%Transmittance
NHCH2CH2CH2—N
HN
O
N
N

Fig. 4

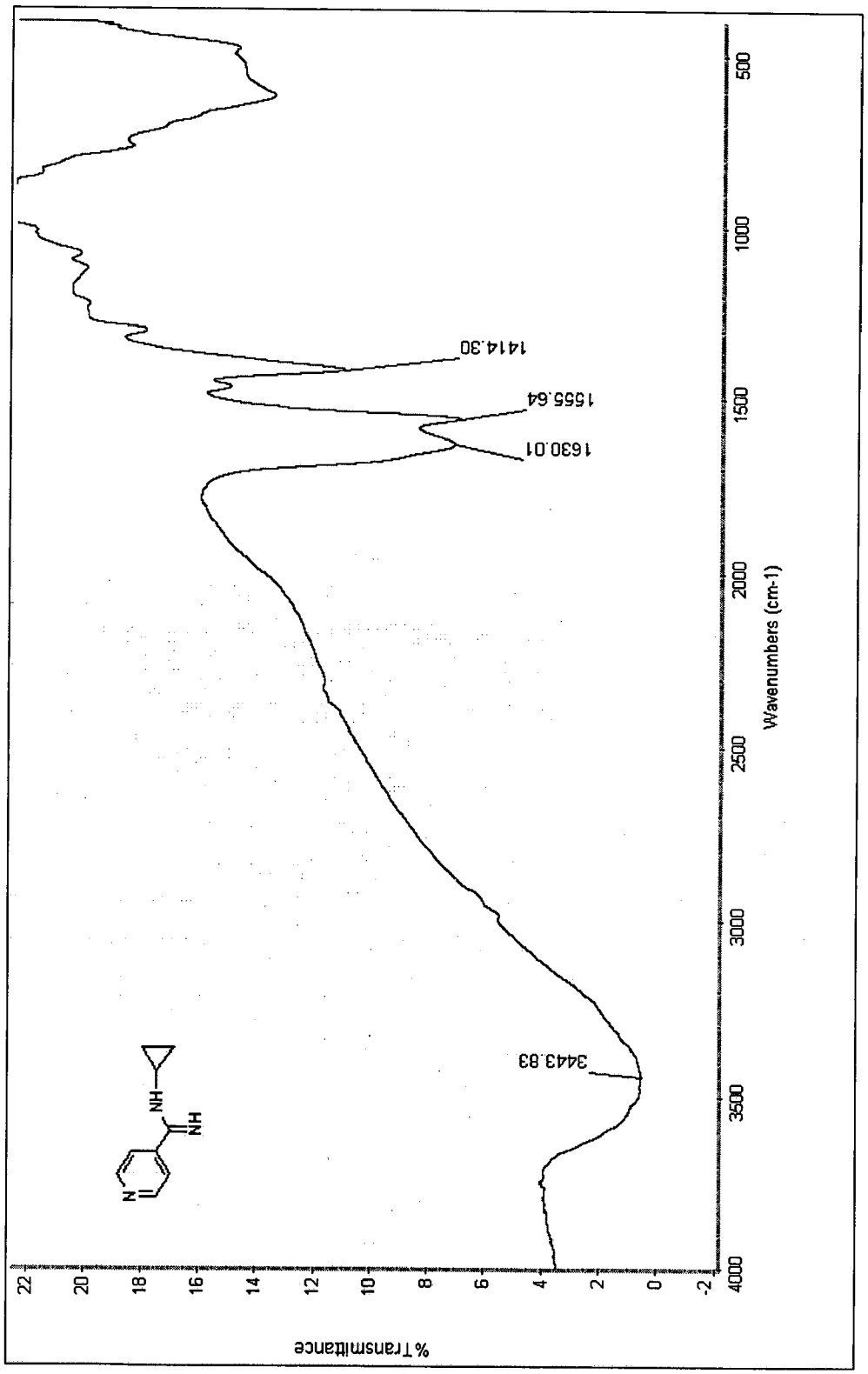

%Transmittance
Wavenumbers (cm-1)
3443.83
1630.01
1555.64
1414.30
NH
HN
N

Fig. 5

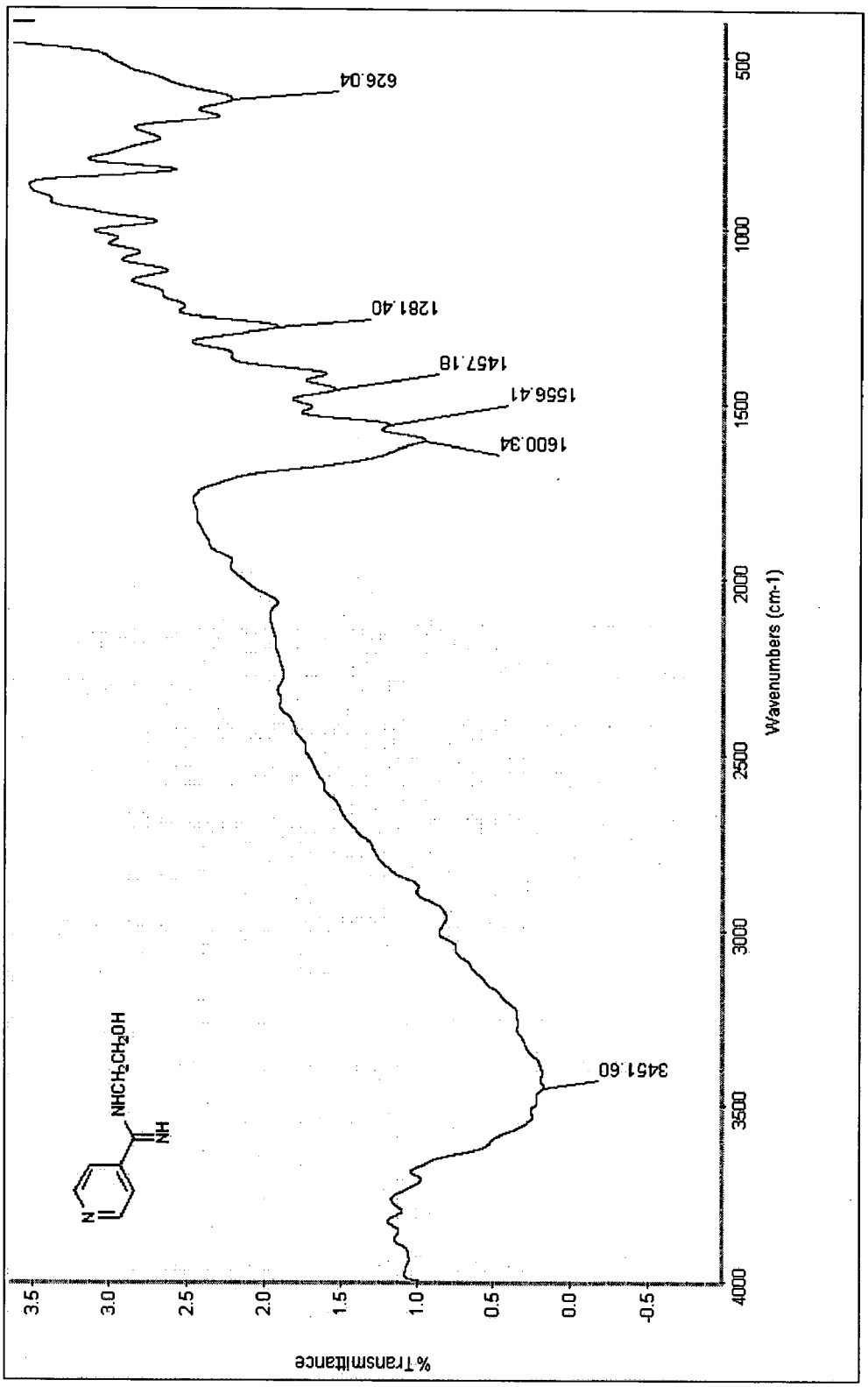

%Transmittance
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
4000
3500
3000
2500
2000
1500
1000
500
Wavenumbers (cm-1)
3451.60
1600.34
1556.41
1457.18
1281.40
626.04
NHCH2CH2OH
NH
N

Fig. 6

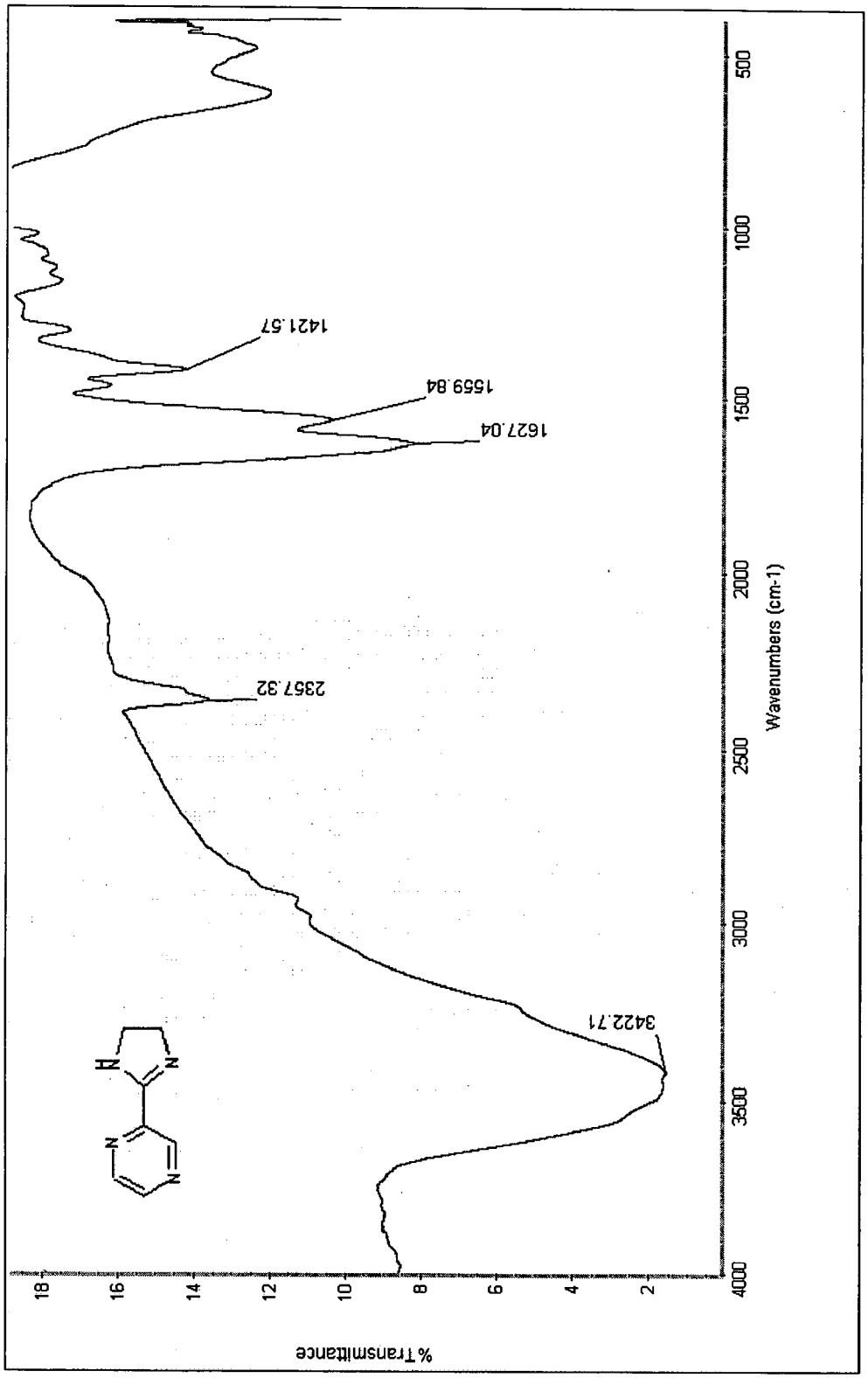

%Transmittance
18
16
14
12
10
8
6
4
2
4000
3500
3000
2500
2000
1500
1000
500
Wavenumbers (cm-1)
3422.71
2357.32
1627.04
1559.84
1421.57
H
N
N
N
N

Fig. 7

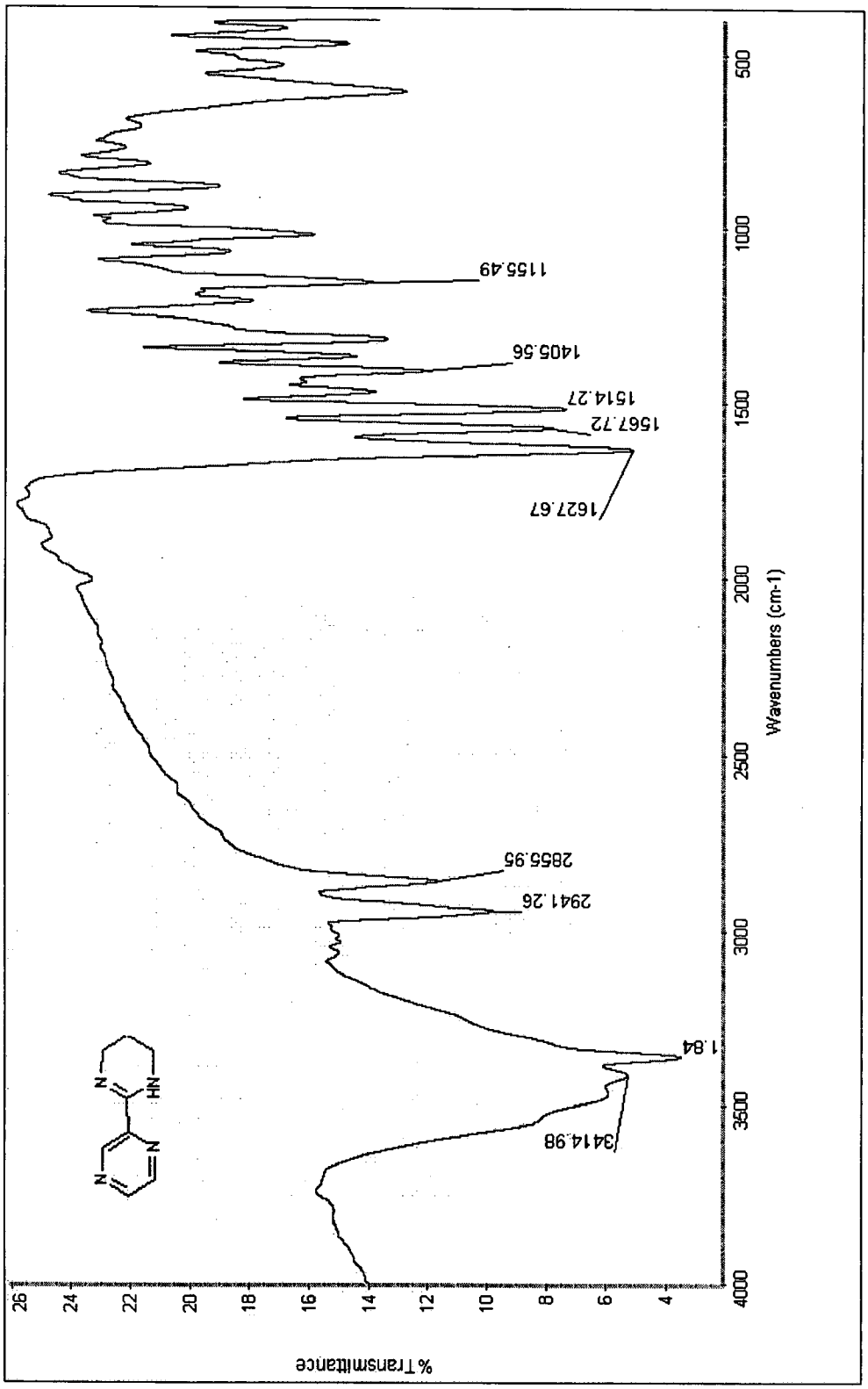

%Transmittance
Wavenumbers (cm-1)
3414.98
2941.26
2855.95
1627.67
1567.72
1514.27
1405.56
1155.49
1.84
HN
N
N

Fig. 8

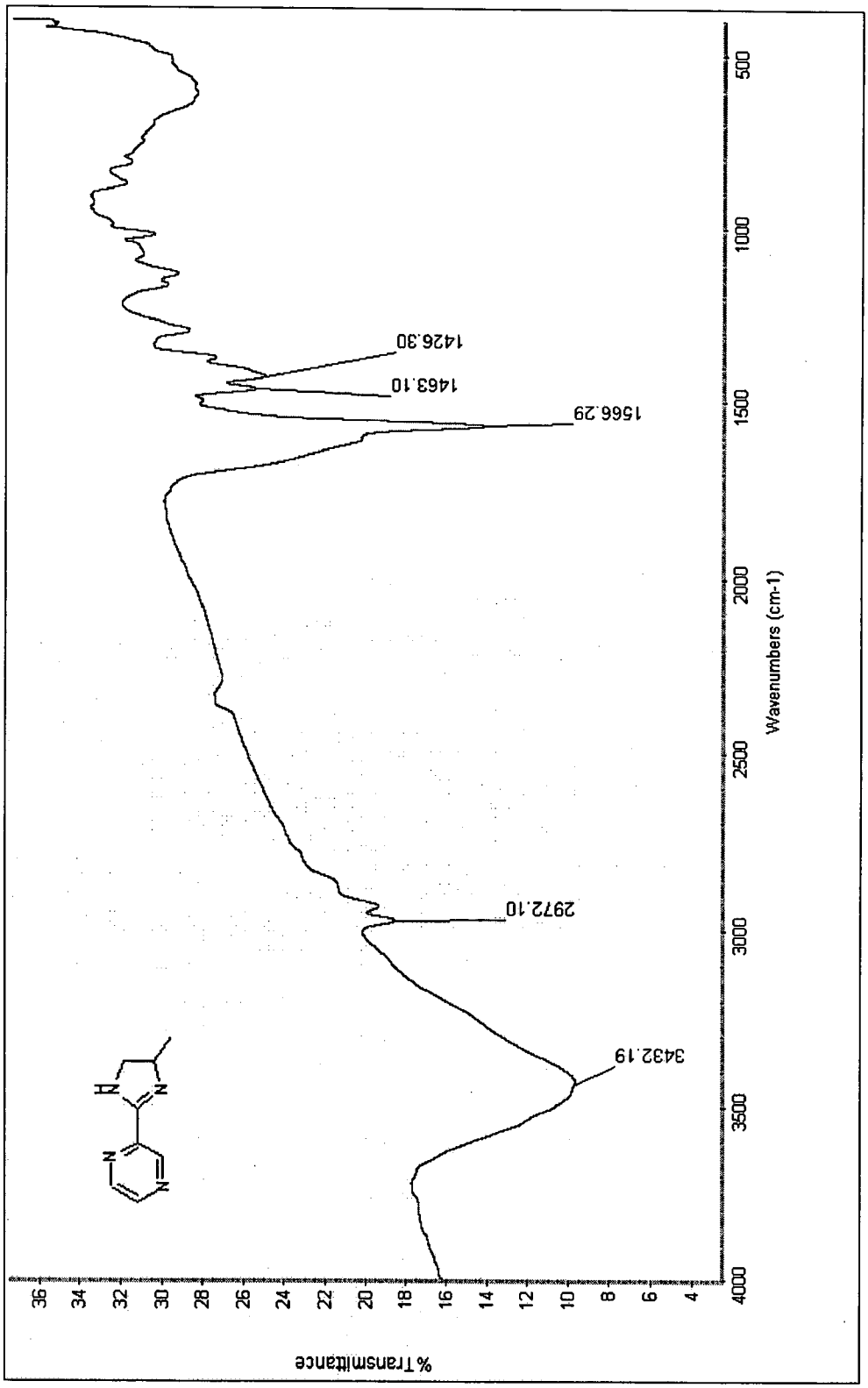

%Transmittance
Wavenumbers (cm-1)
3432.19
2972.10
1566.29
1463.10
1426.30

Fig. 9

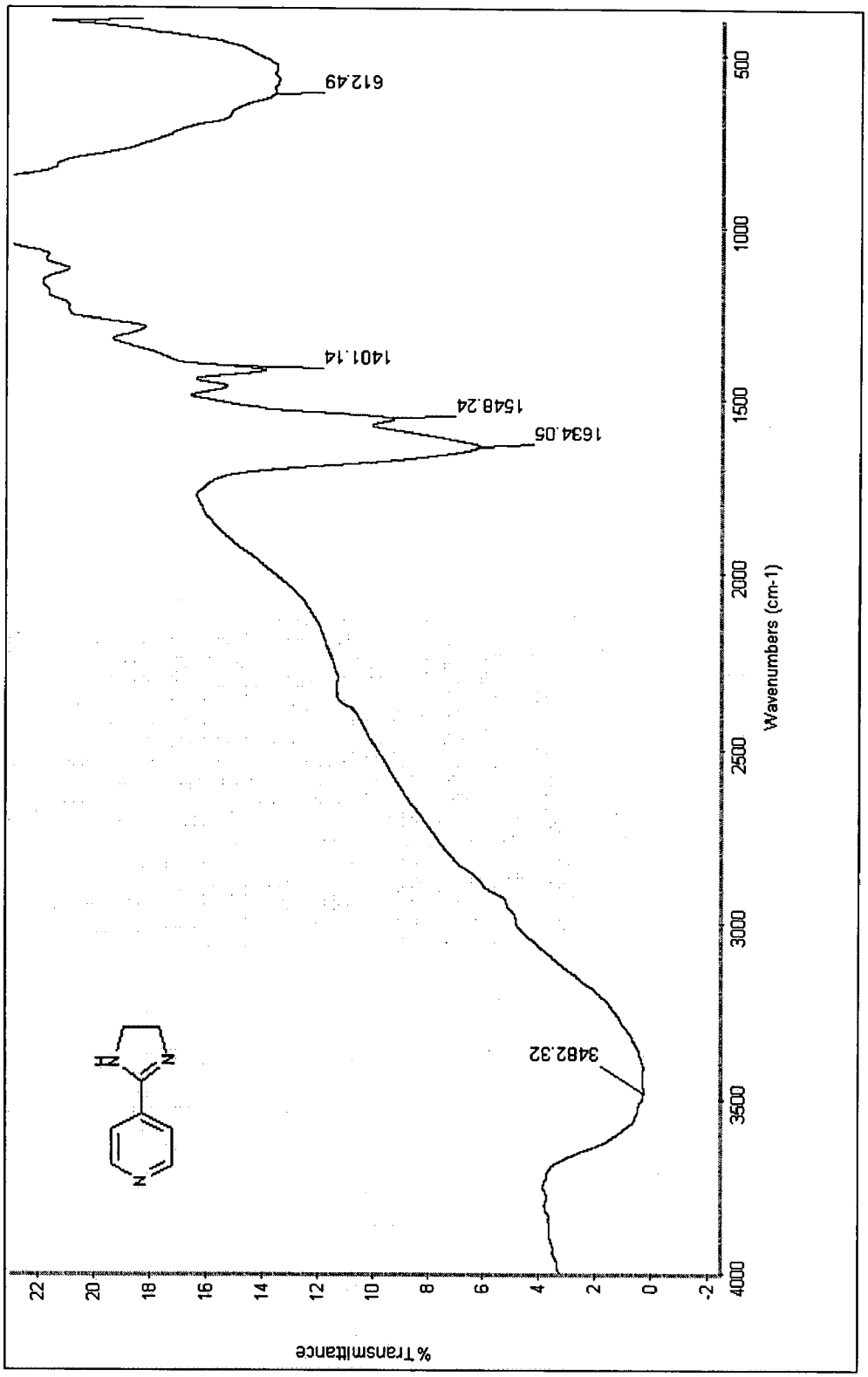

612.49
1401.14
1548.24
1634.05
3482.32
Wavenumbers (cm-1)
%Transmittance

Fig. 10

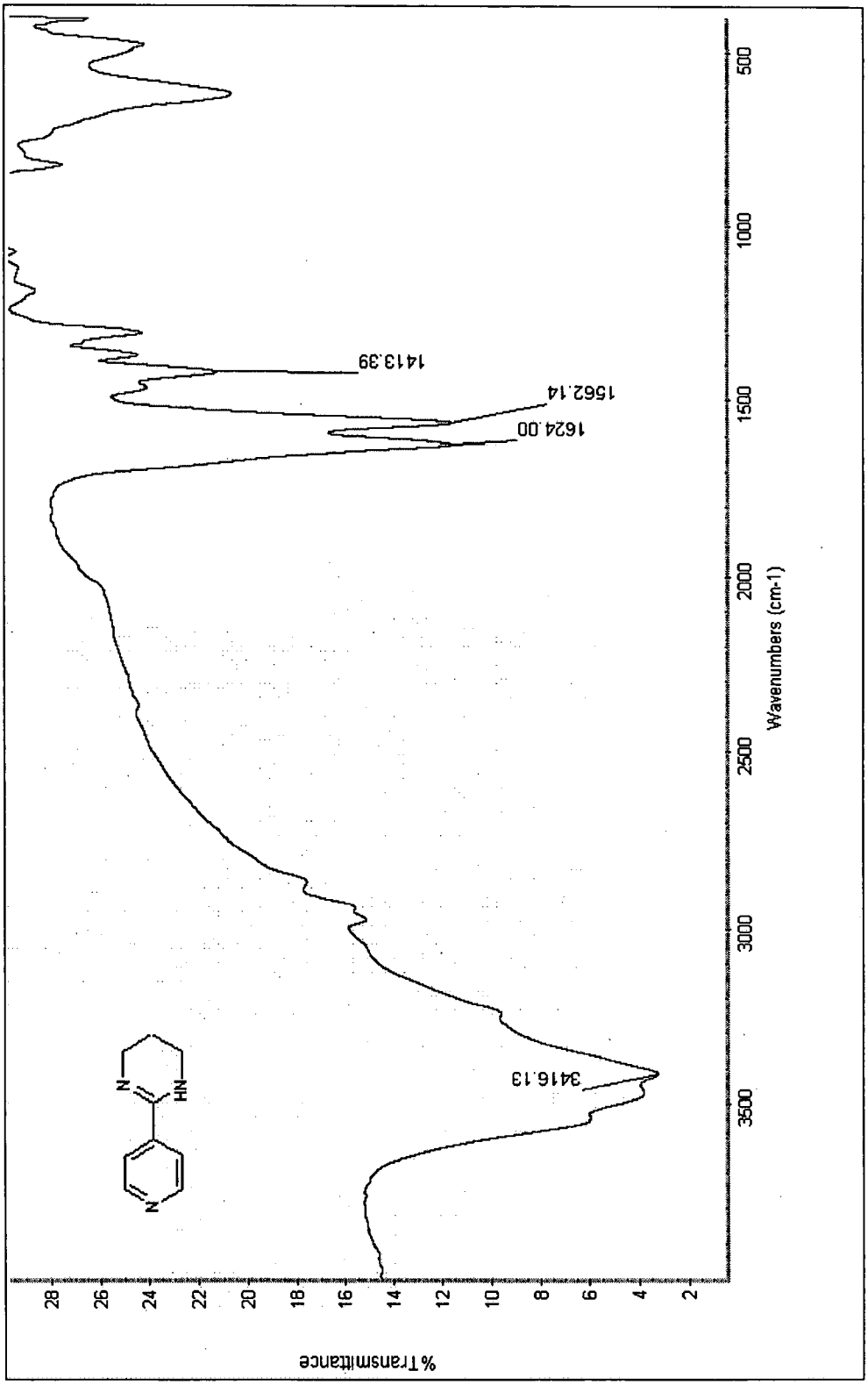

%Transmittance
28
26
24
22
20
18
16
14
12
10
8
6
4
2
Wavenumbers (cm-1)
3500
3000
2500
2000
1500
1000
500
3416.13
1624.00
1562.14
1413.39
N
HN
N

Fig. 11

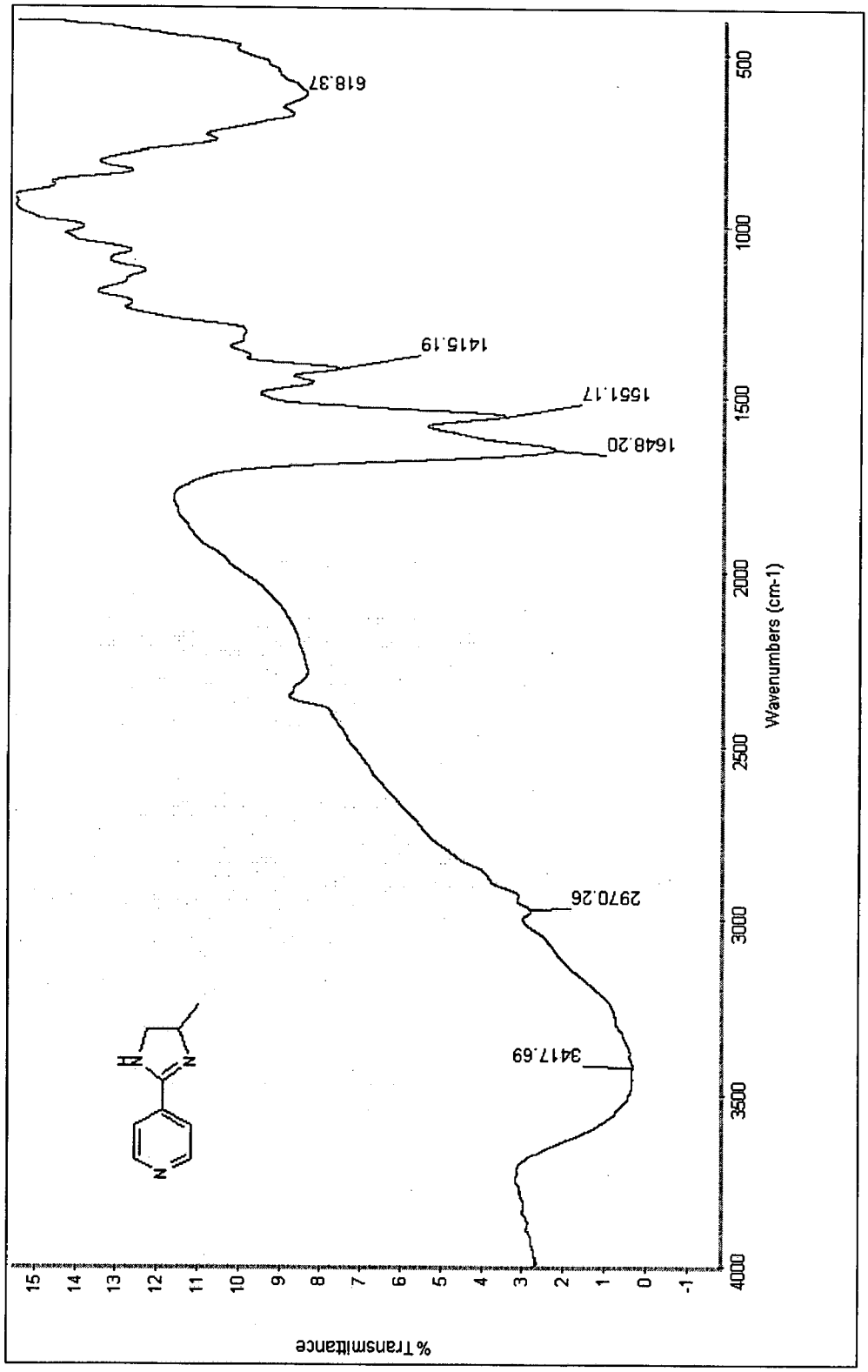

618.37
1415.19
1551.17
1648.20
2970.26
3417.69
Wavenumbers (cm-1)
%Transmittance

Fig. 12

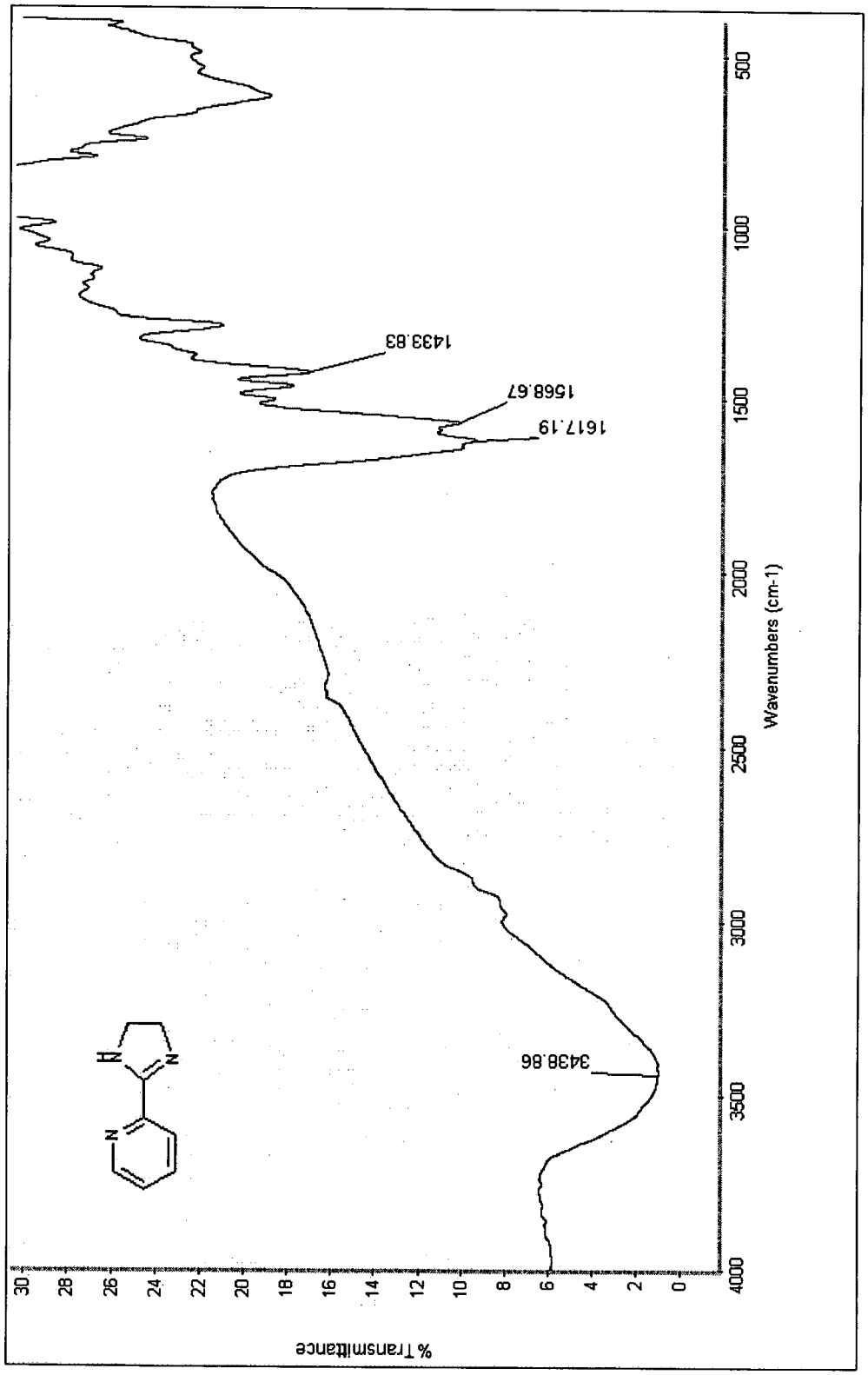

3438.86
1617.19
1568.67
1433.83
% Transmittance
Wavenumbers (cm-1)
4000
3500
3000
2500
2000
1500
1000
500
30
28
26
24
22
20
18
16
14
12
10
8
6
4
2
0
H
N
N

Fig. 13

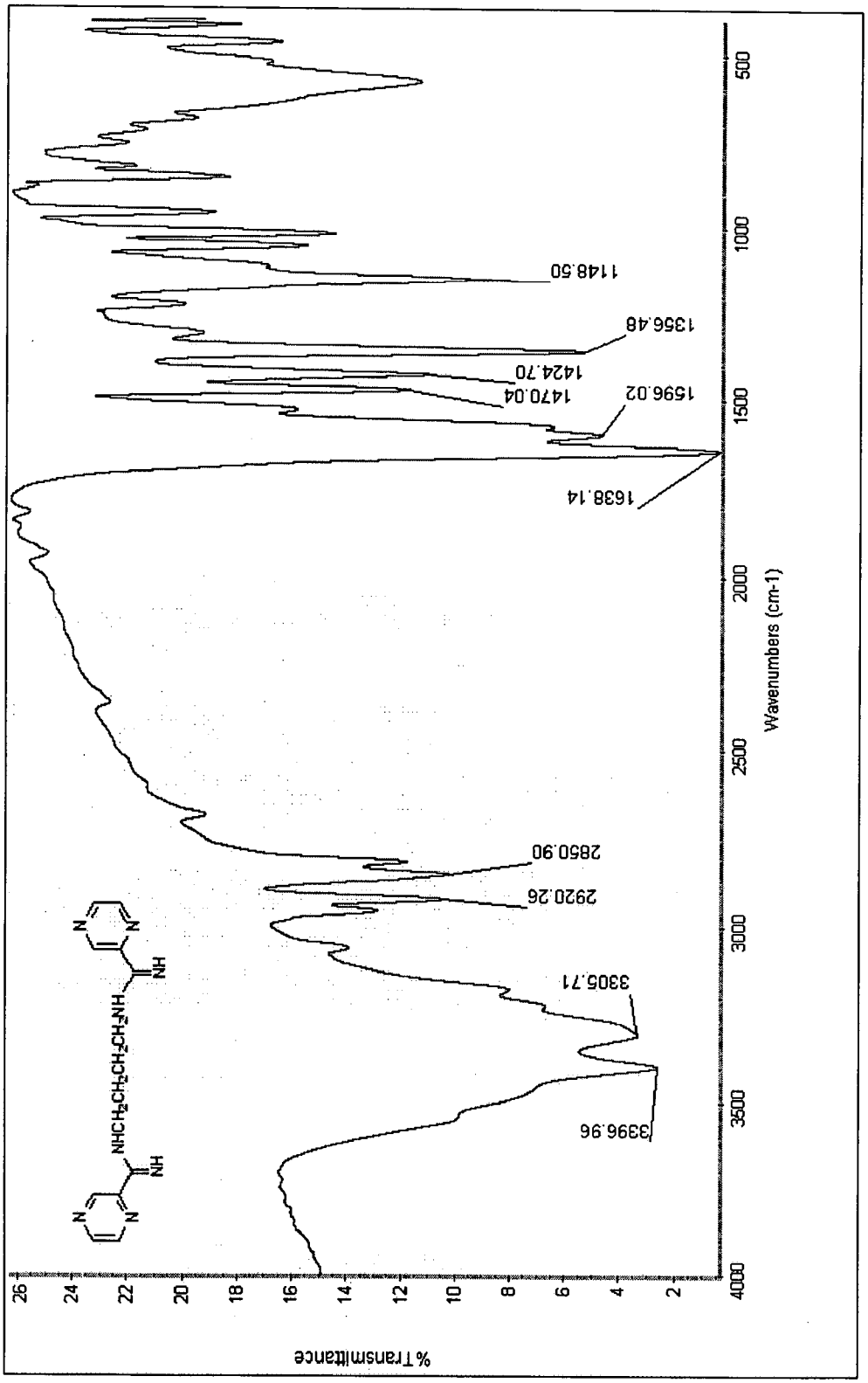

%Transmittance
Wavenumbers (cm-1)
4000
3500
3000
2500
2000
1500
1000
500
26
24
22
20
18
16
14
12
10
8
6
4
2
3396.96
3305.71
2920.26
2850.90
1638.14
1596.02
1470.04
1424.70
1356.48
1148.50
NHCH2CH2CH2CH2NH
NH
NH
N
N
N
N

Fig. 14

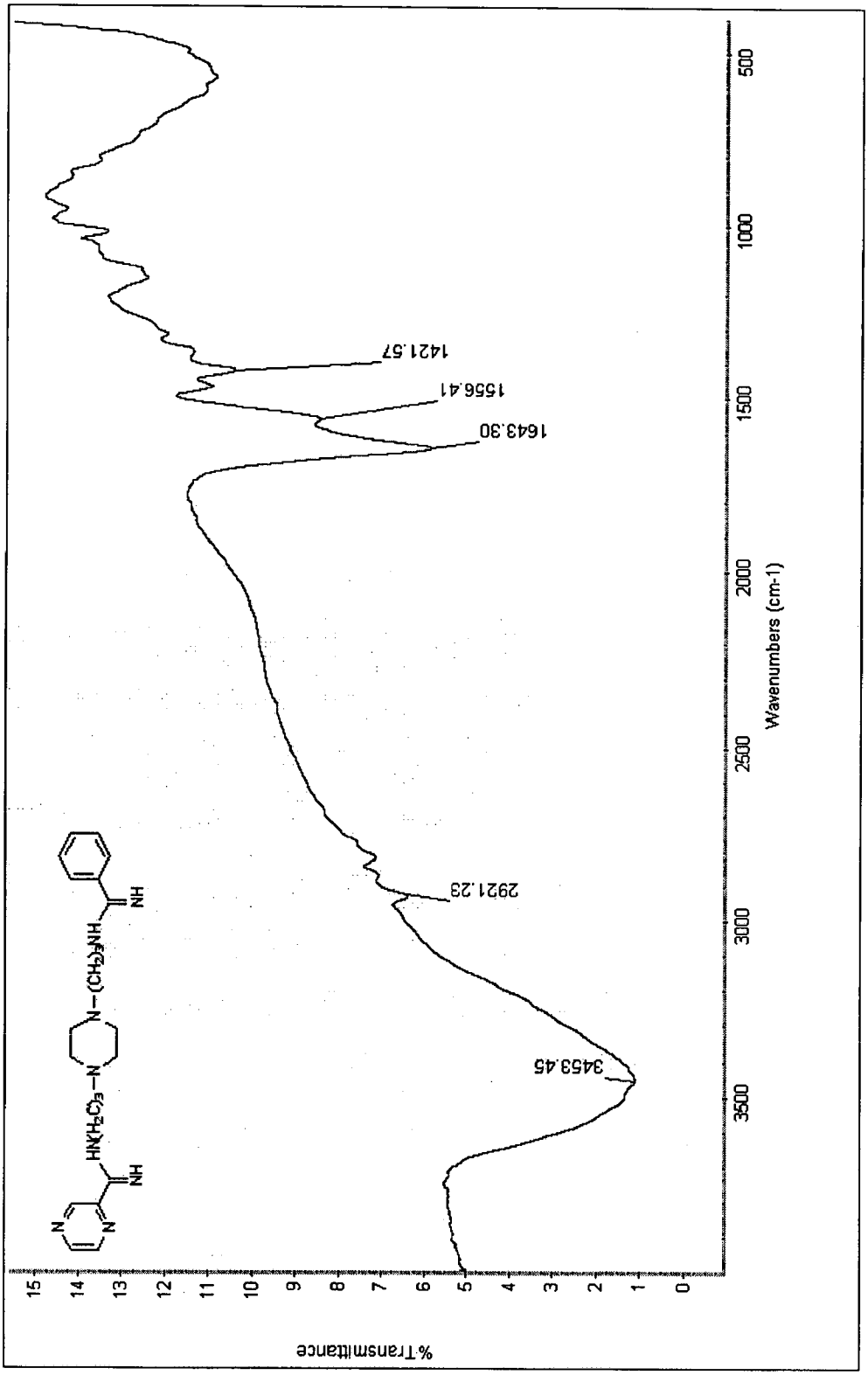

%Transmittance
Wavenumbers (cm-1)
3453.45
2921.28
1643.30
1556.41
1421.57
HN
NH
HN(H2C)3
N
N
N
(CH2)3NH
NH

Fig. 15

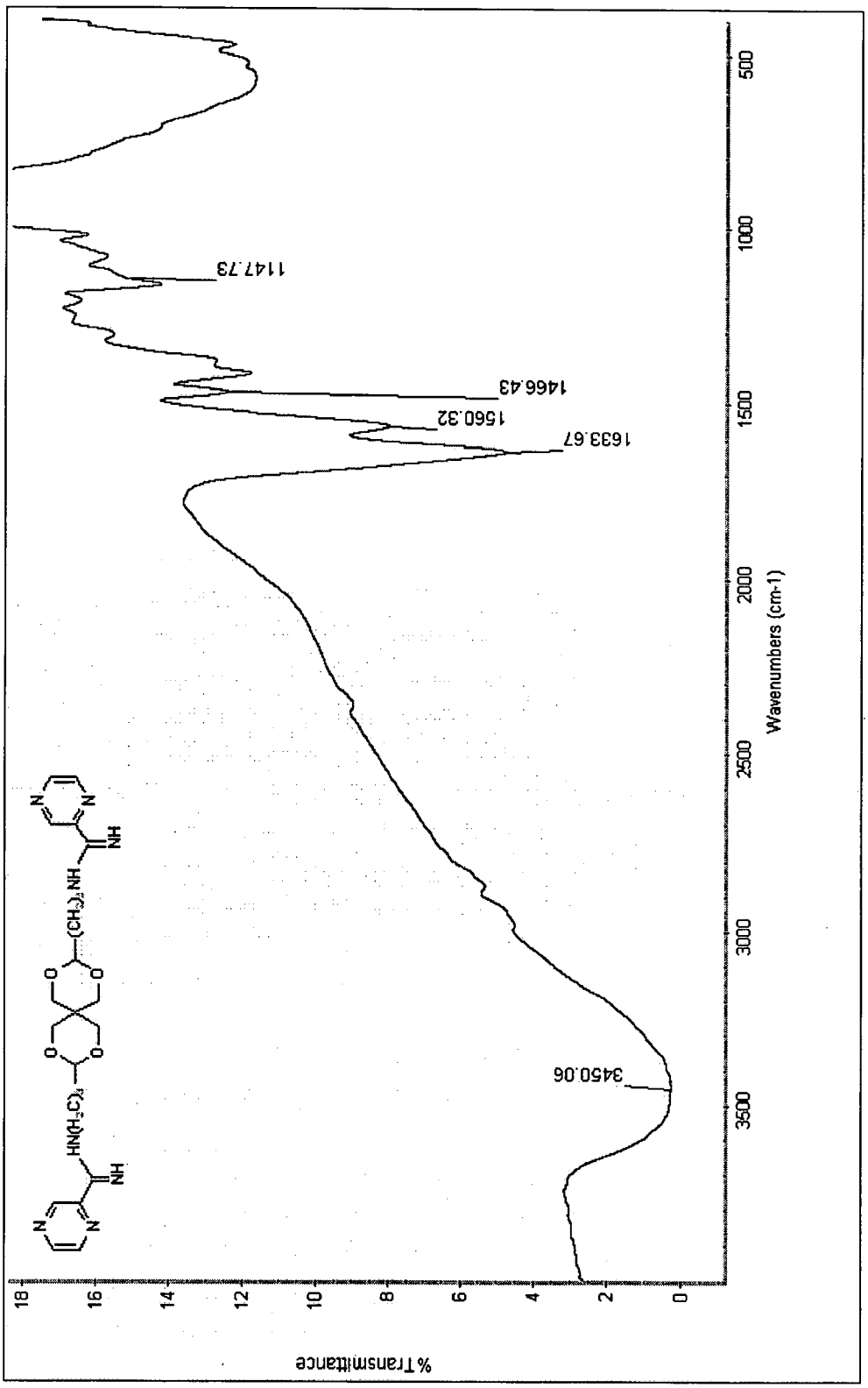

%Transmittance
Wavenumbers (cm-1)
3450.06
1633.67
1560.32
1466.43
1147.73

Fig. 16

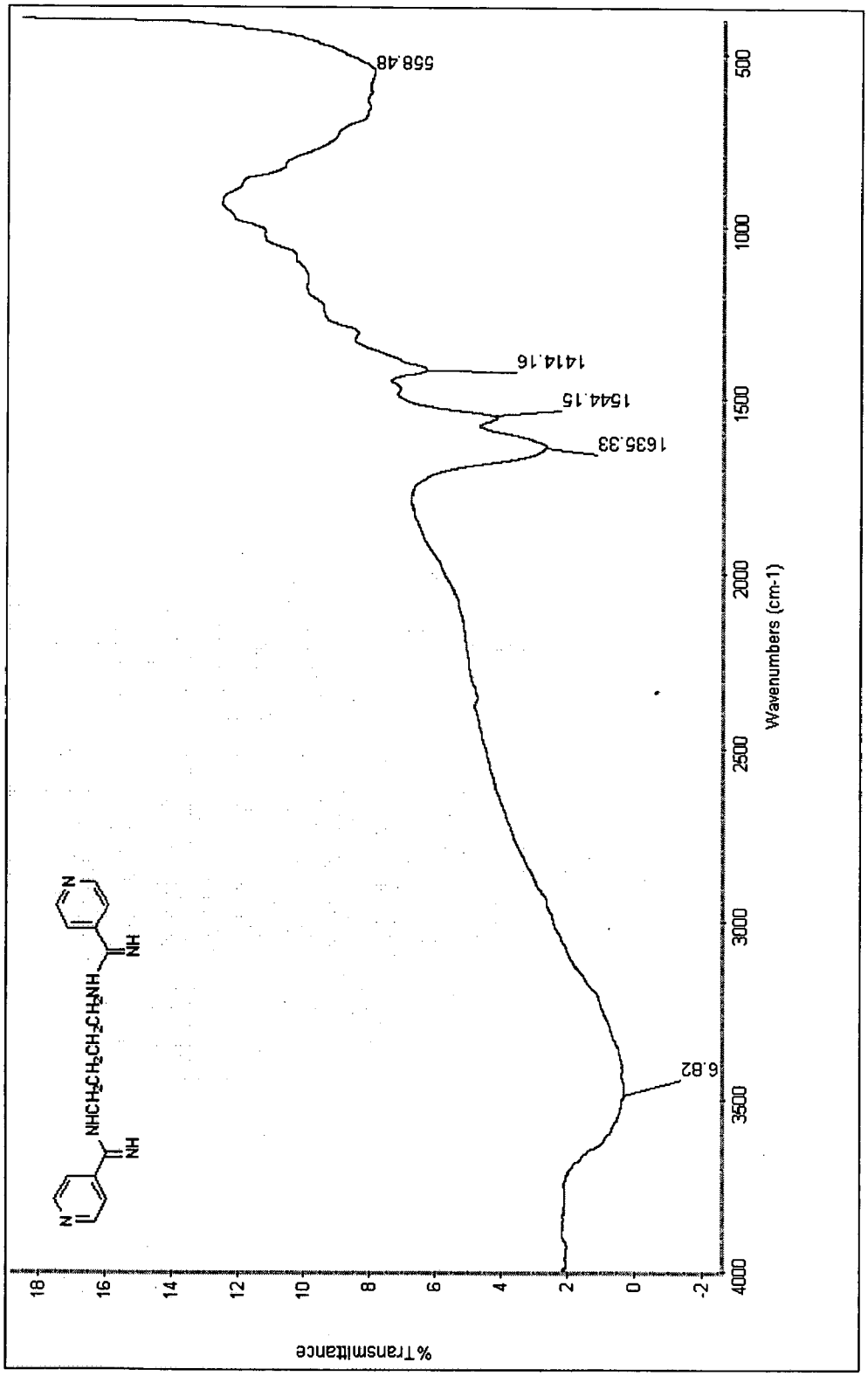

%Transmittance
Wavenumbers (cm-1)
558.48
1414.16
1544.15
1635.33
6.82
NHCH2CH2CH2CH2NH
NH
NH
N
N

Fig. 17

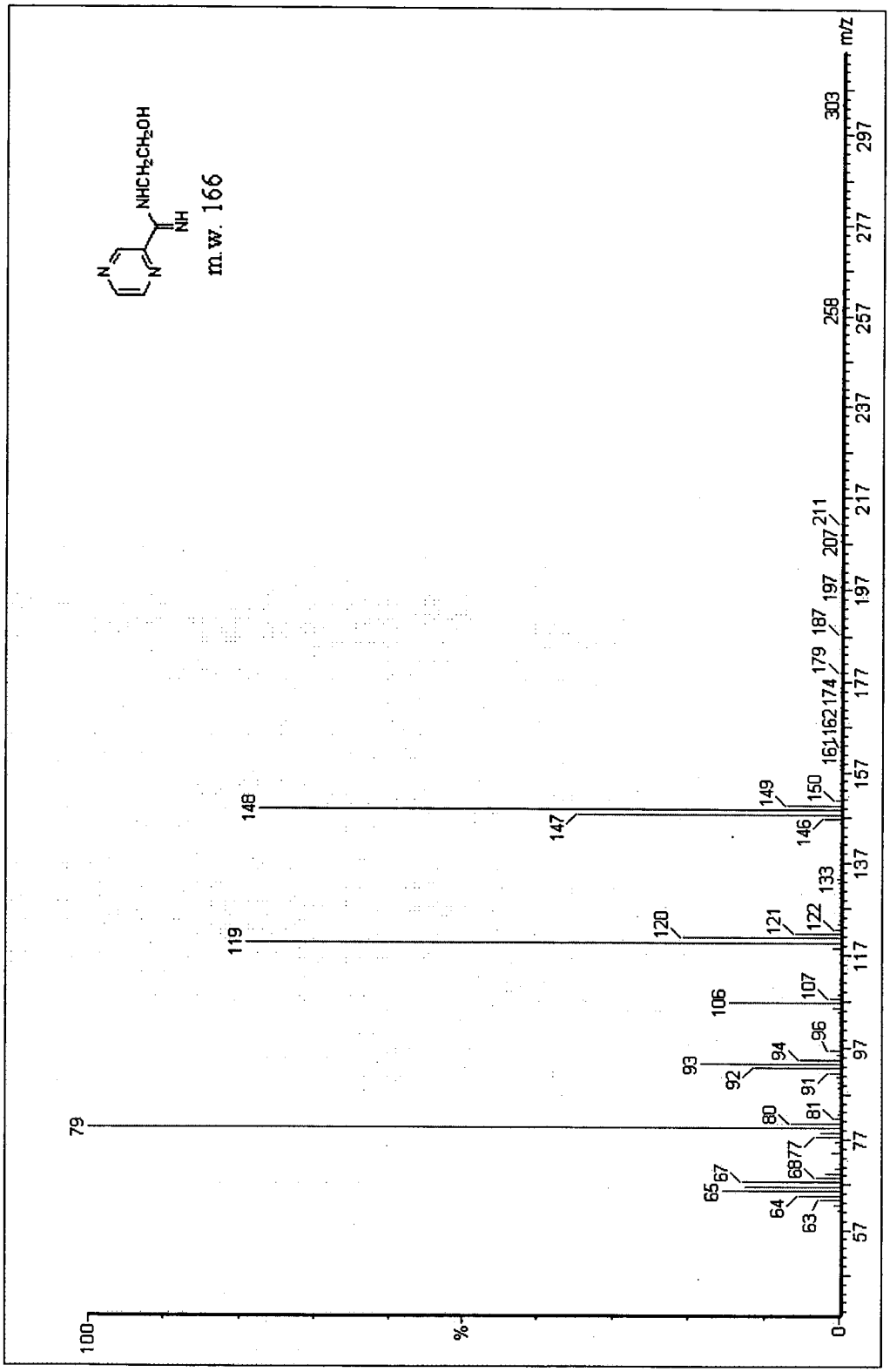

NHCH2CH2OH
NH
m.w. 166
100
%
0
m/z
79
148
147
119
149
150
146
120
121
122
133
106
107
93
94
96
92
91
80
81
65
67
64
68
77
63
57
77
97
117
137
157
177
197
217
237
257
277
297
303
258
211
207
197
187
179
174
162
161

Fig. 18

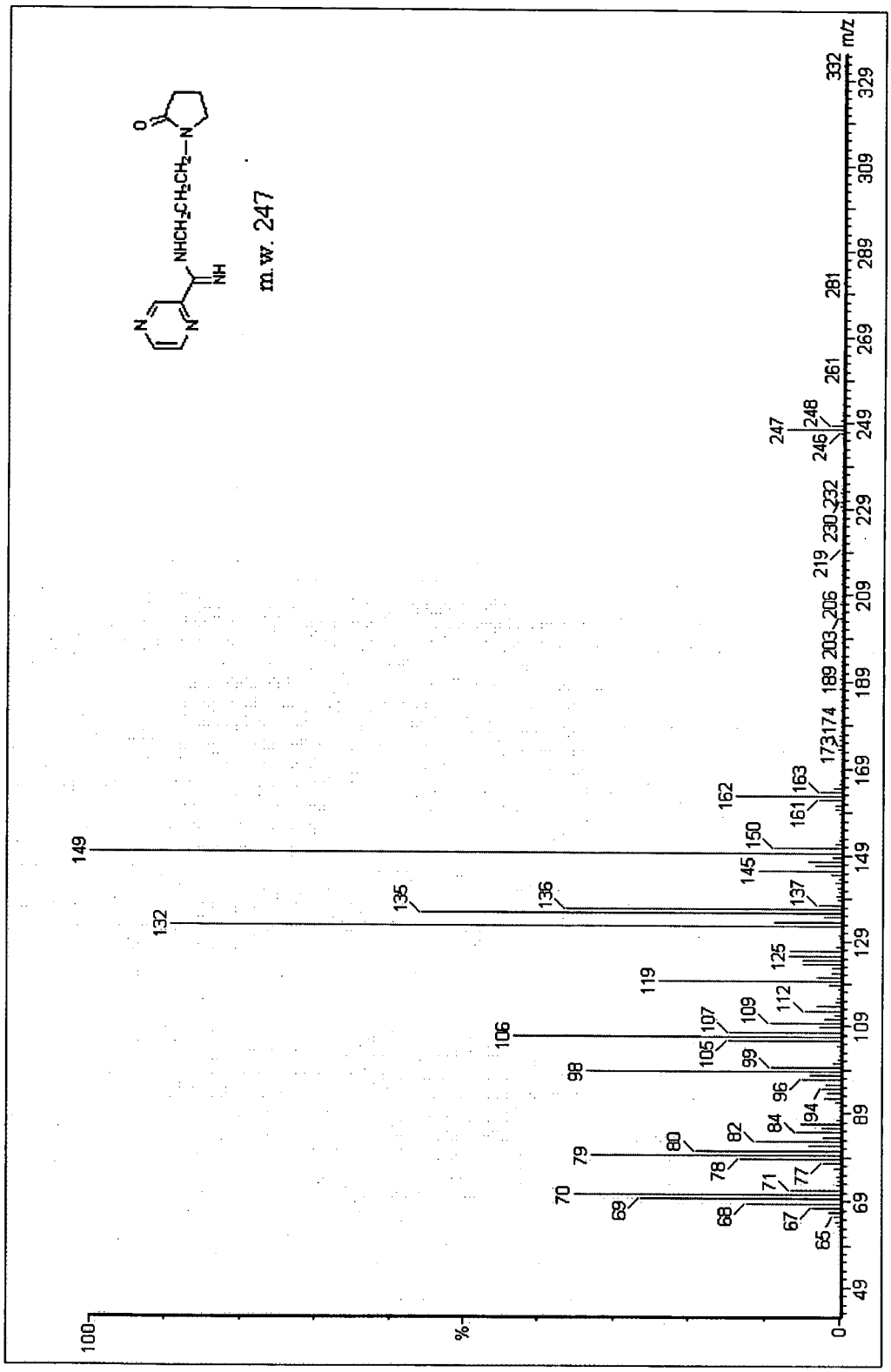

m.w. 247
NHCH2CH2CH2
NH
%
100
0
m/z
49
65
67
68
69
70
71
77
78
79
80
82
84
94
96
98
99
105
106
107
109
112
119
125
129
132
135
136
137
145
149
150
161
162
163
173
174
189
203
206
219
230
232
246
247
248
261
281
289
309
329
332

Fig. 19

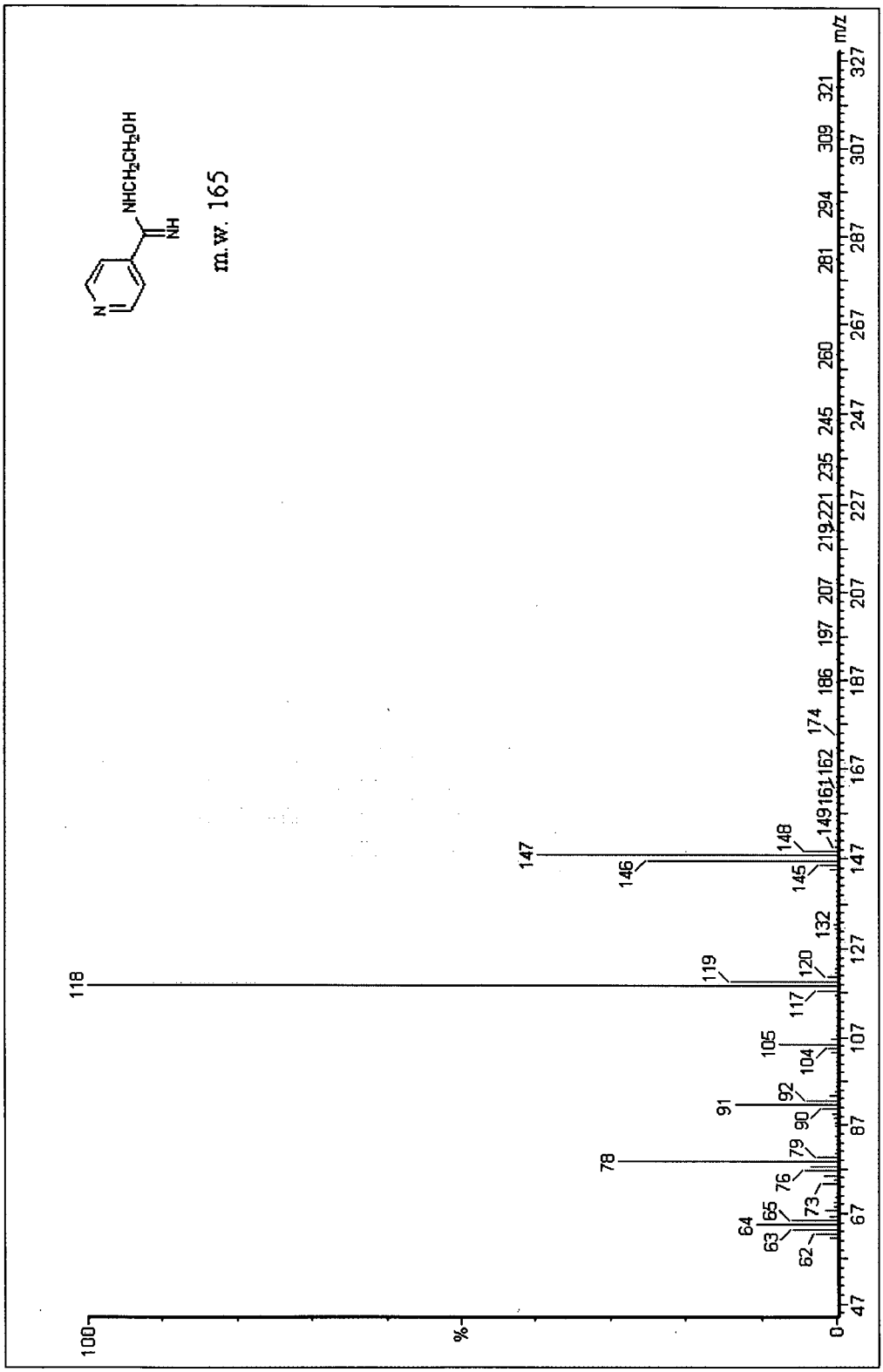

NHCH2CH2OH
NH
N
m.w. 165
100
%
0
m/z
47 62 63 64 65 67 73 76 78 79 87 90 91 92 104 105 107 117 118 119 120 127 132 145 146 147 148 149 161 162 167 174 186 187 197 207 207 219 221 227 235 245 247 260 267 281 287 294 307 309 321 327

Fig. 20

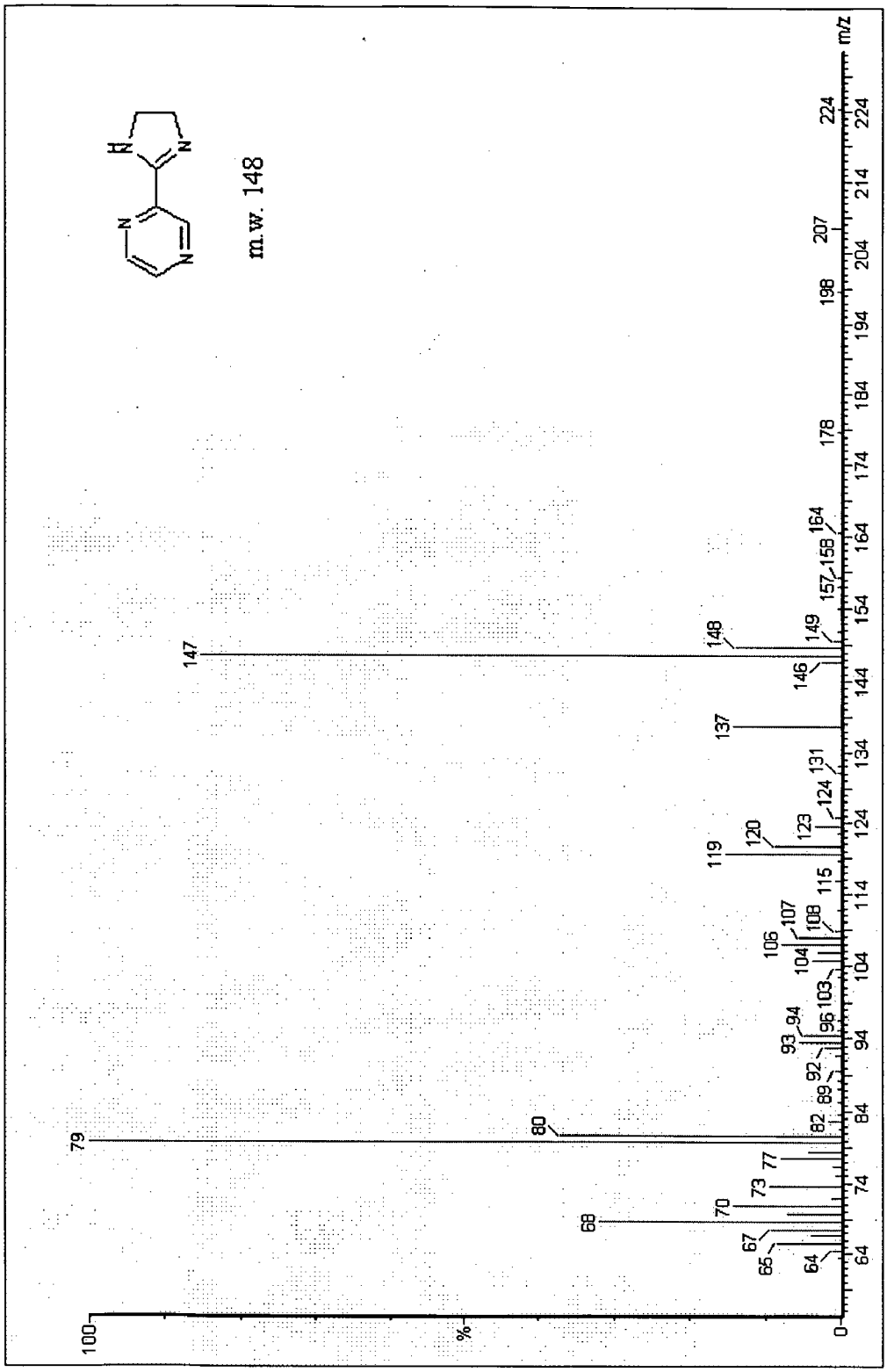

m.w. 148
100
%
0
m/z
79
80
147
148
149
68
70
73
77
82
89
92
93
94
96
103
104
106
107
108
115
119
120
123
124
131
137
146
157
158
164
64
65
67
74
84
94
104
114
124
134
144
154
164
174
178
184
194
198
204
207
214
224

Fig. 21

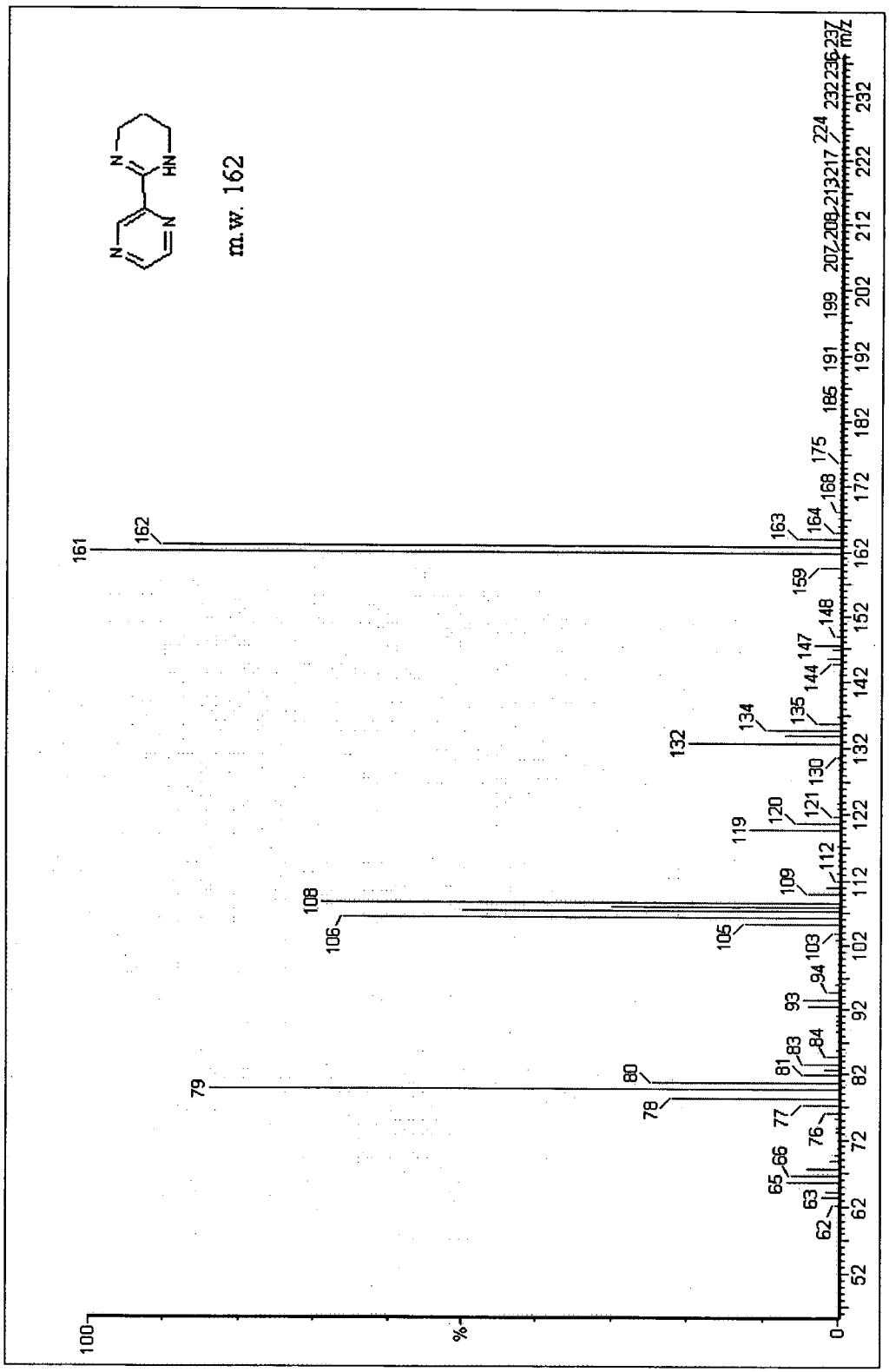

m.w. 162
100
%
0
m/z
52
62
72
82
92
102
112
122
132
142
152
162
172
182
192
202
212
222
232
237

Fig. 22

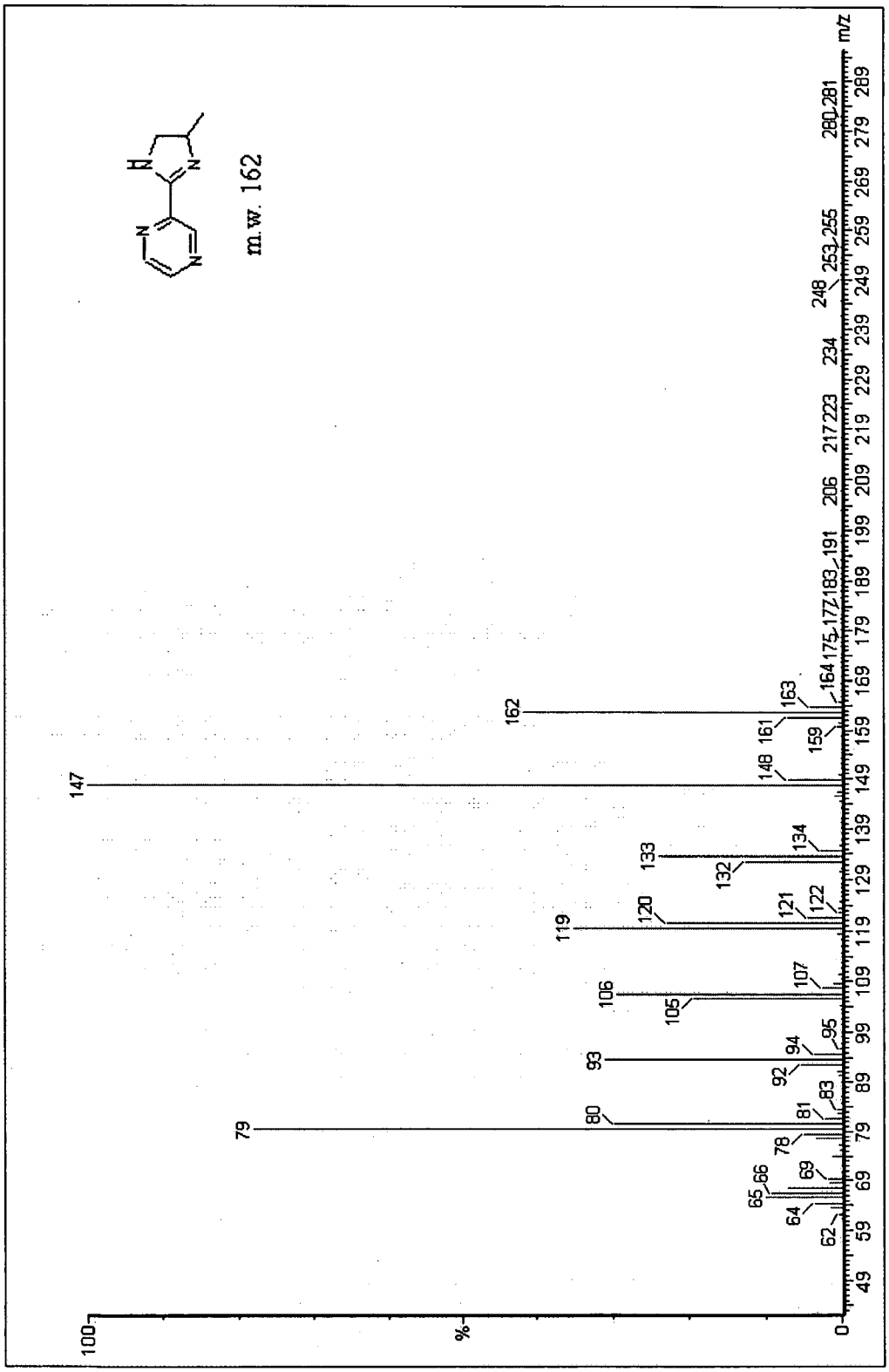

m.w. 162
100
%
0
m/z
147
162
79
119
106
93
105
133
132
134
120
121
122
107
95
94
92
80
81
83
78
69
66
65
64
62
148
161
163
164
159
175
172
183
191
206
217
223
234
248
253
255
280
281

Fig. 23

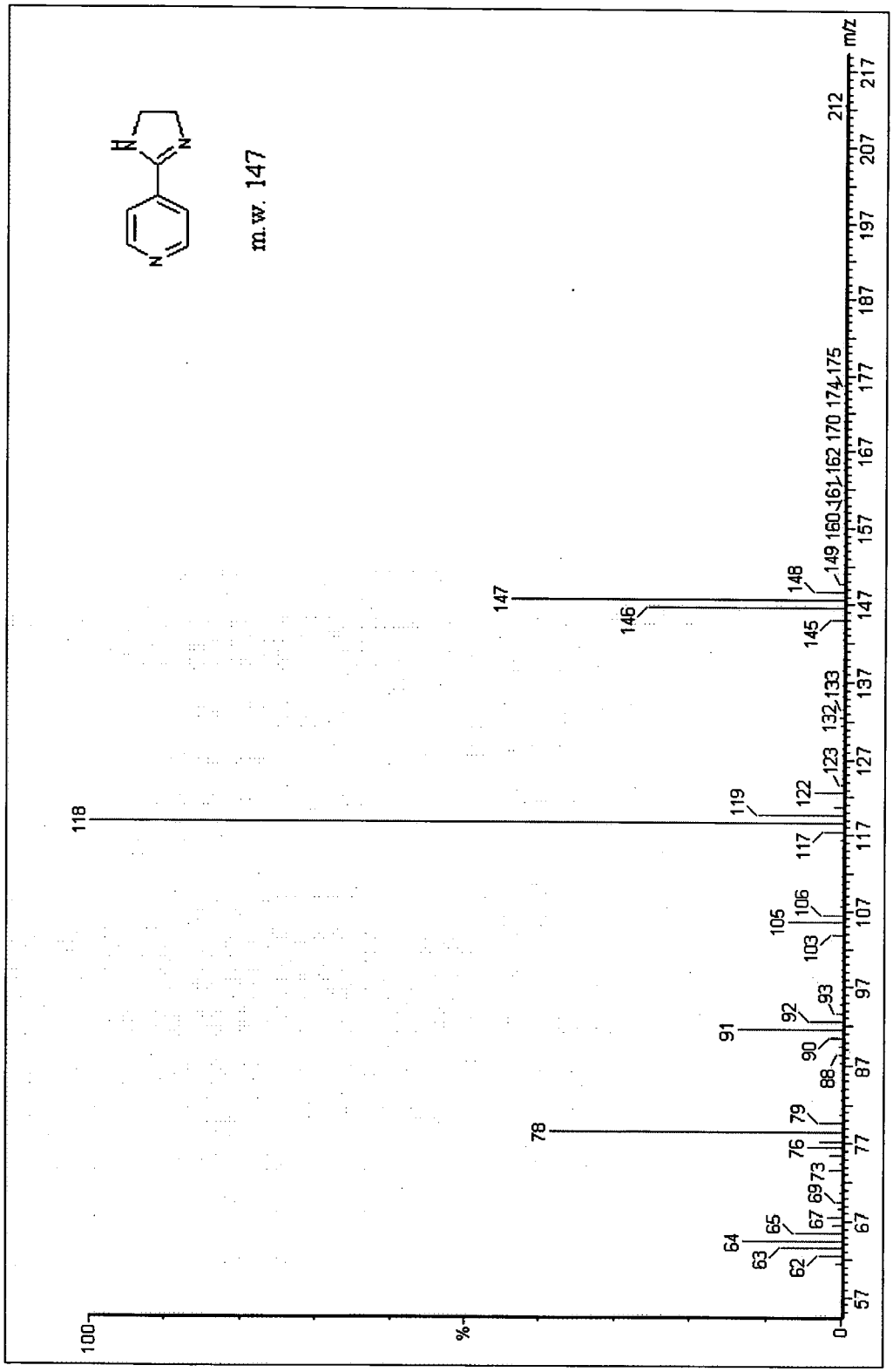

m.w. 147
100
%
0
m/z
57
62
63
64
65
67
69
73
76
77
78
79
87
88
90
91
92
93
97
103
105
106
107
117
118
119
122
123
127
132
133
137
145
146
147
148
149
157
160
161
162
167
170
174
175
177
187
197
207
212
217

Fig. 24

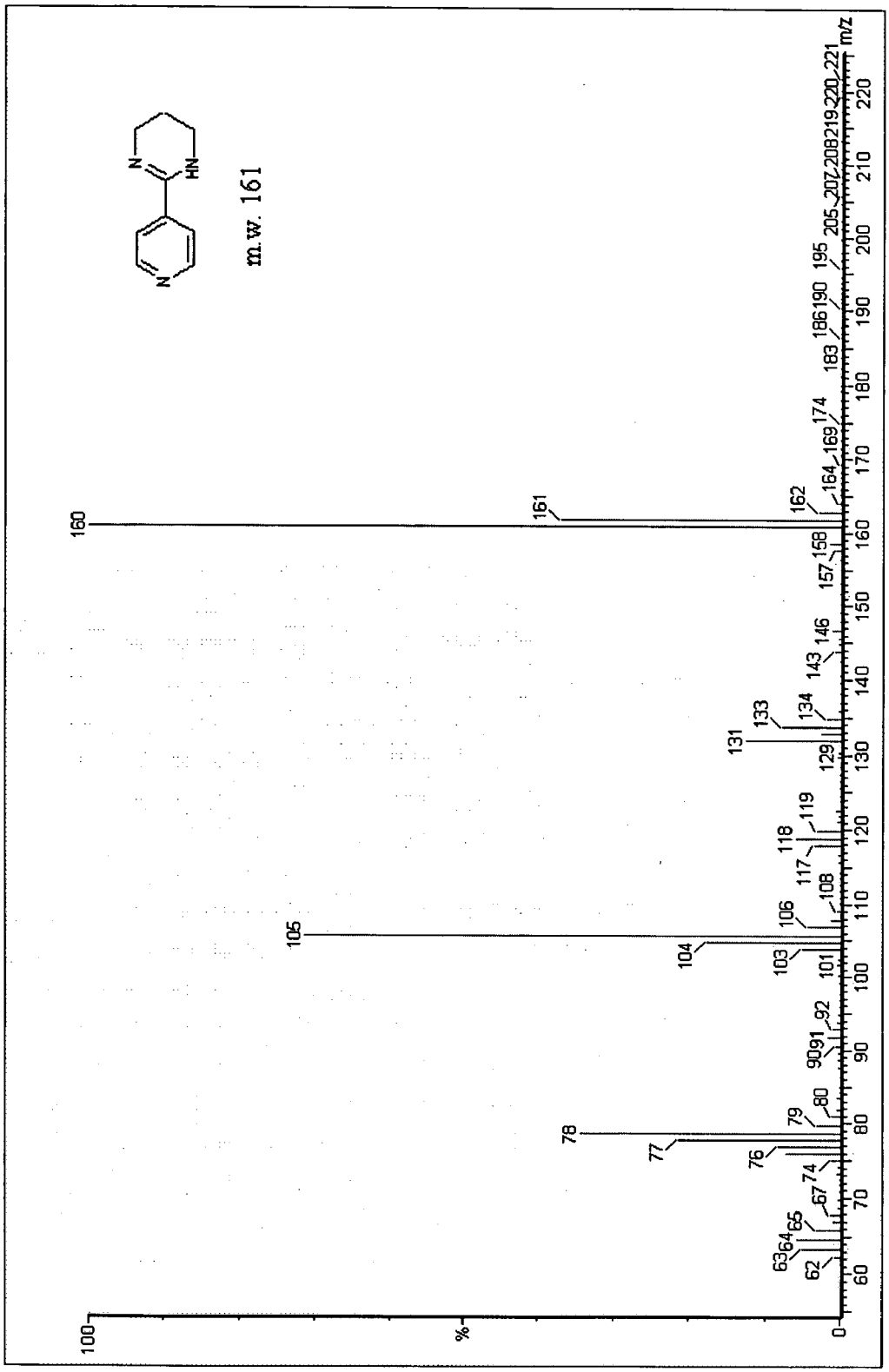

m.w. 161
100
%
0
m/z
160
161
162
105
104
78
77
76
79
131
133
129
134
143
146
157
158
164
169
174
183
186
190
195
205
207
208
219
220
221

FIg. 25

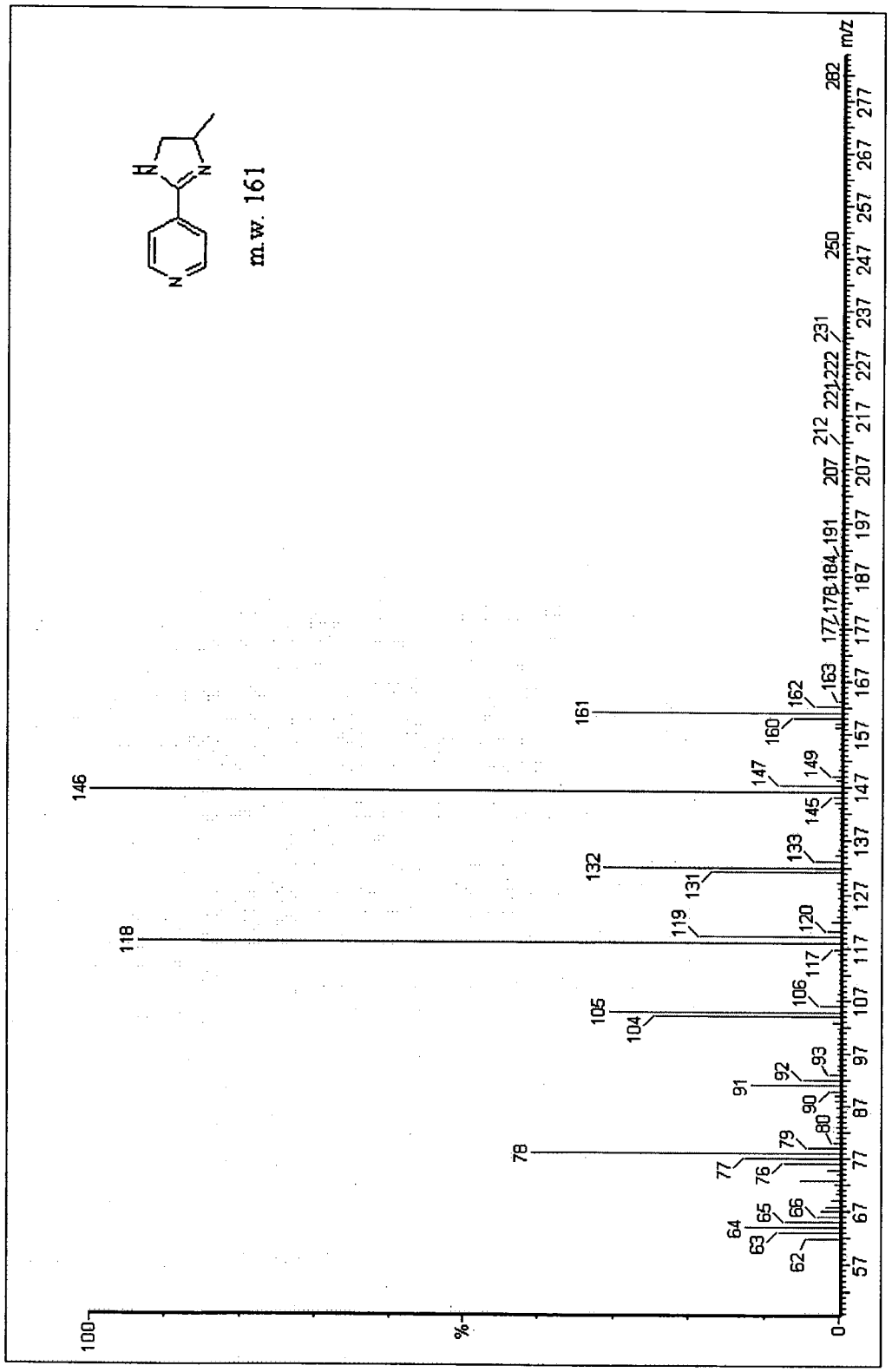

m.w. 161
100
%
0
m/z
282
277
267
257
250
247
237
231
227
222
221
217
212
207
207
197
191
187
184
178
177
177
172
167
163
162
160
157
149
147
147
145
137
133
132
131
127
120
119
118
117
117
107
106
105
104
97
93
92
91
90
87
80
79
78
77
76
67
66
65
64
63
62
57

Fig. 26

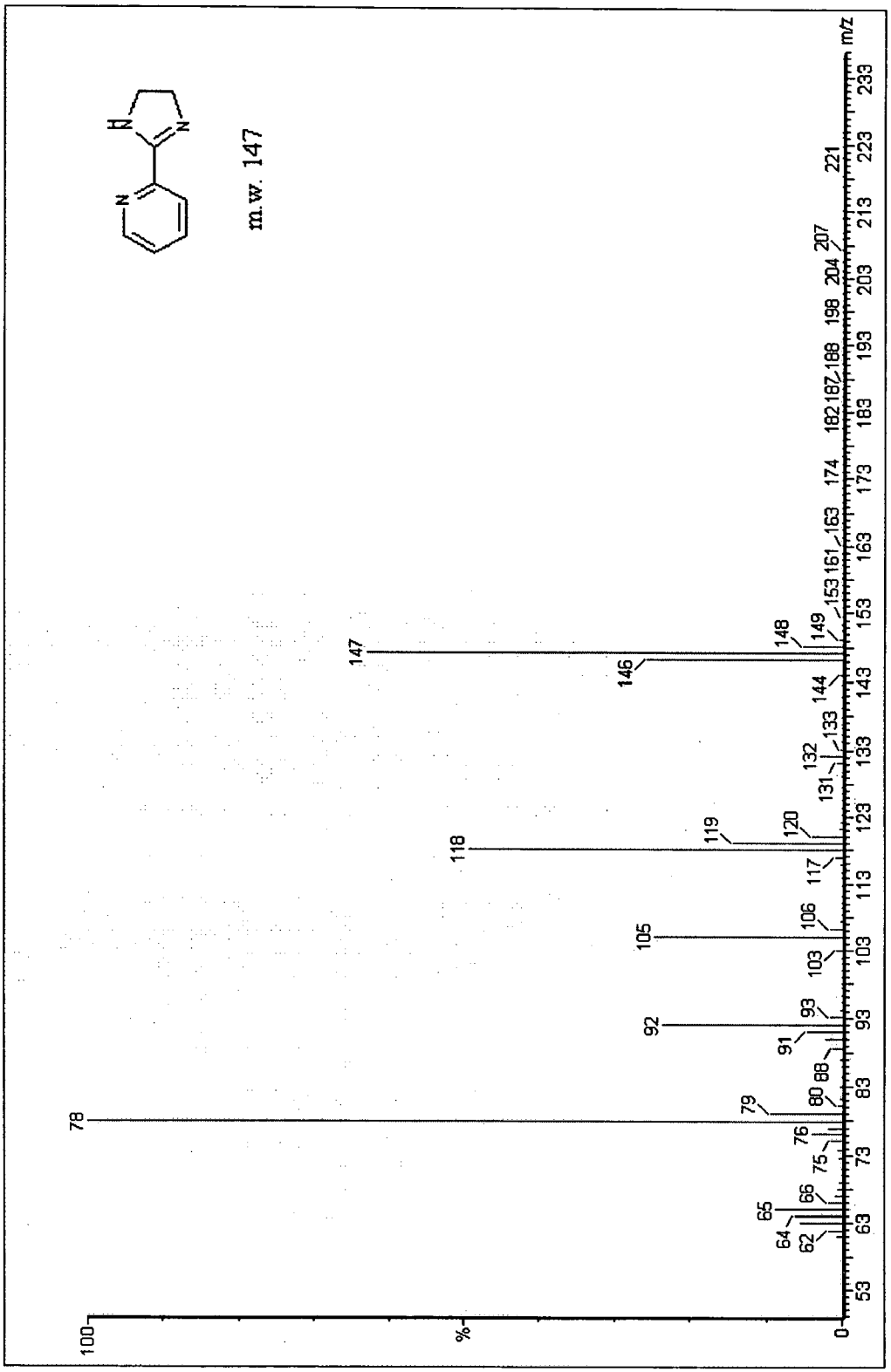

m.w. 147
100
%
0
m/z
78
147
146
148
118
119
105
92
79
91
93
65
64
62
66
76
75
80
88
103
106
117
120
131
132
133
144
149
153
161
163
174
182
187
188
198
204
207
221
233

Fig. 27

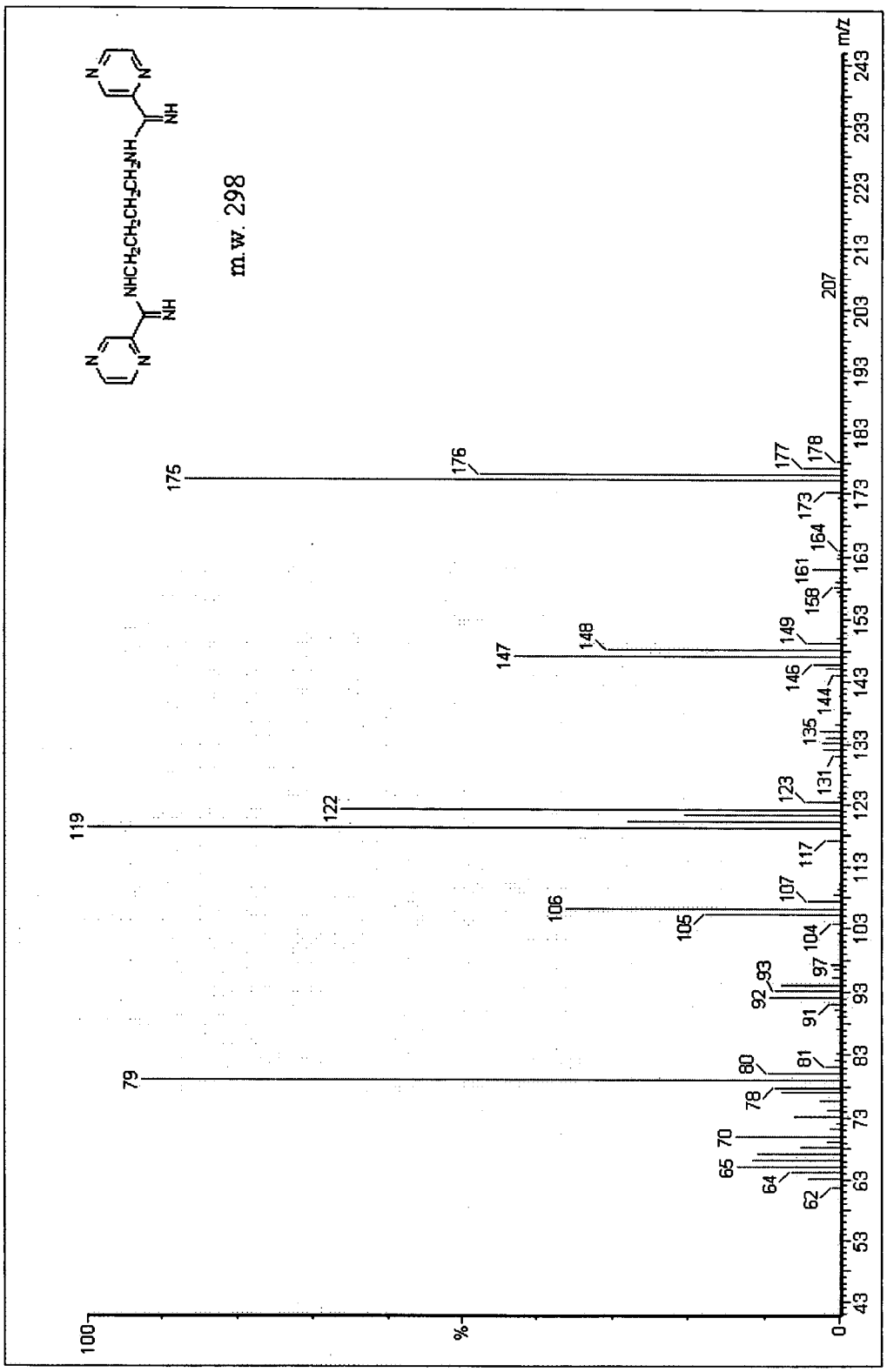

m.w. 298
NHCH2CH2CH2CH2NH
NH
NH
N
N
N
N
100
%
0
m/z
43
53
63
73
83
93
103
113
123
133
143
153
163
173
183
193
203
213
223
233
243
62
64
65
70
78
79
80
81
91
92
93
97
104
105
106
107
117
119
122
123
131
135
144
146
147
148
149
158
161
164
173
175
176
177
178
207

Fig. 28

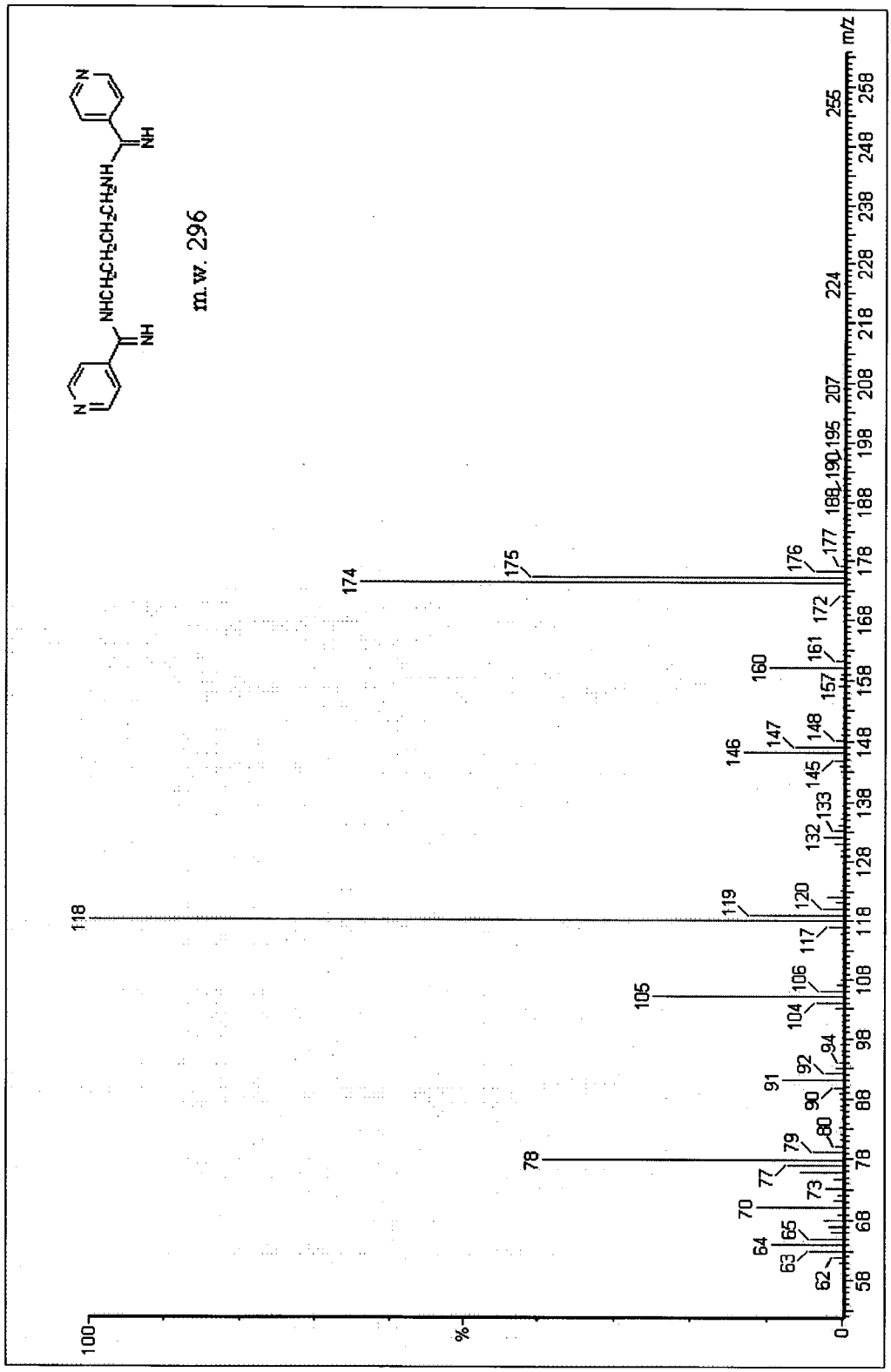

m.w. 296
NHCH2CH2CH2CH2NH
NH
NH
N
N
100
%
0
m/z
118
174
175
176
105
78
79
91
119
120
146
147
148
160
161
172
255

Fig. 29

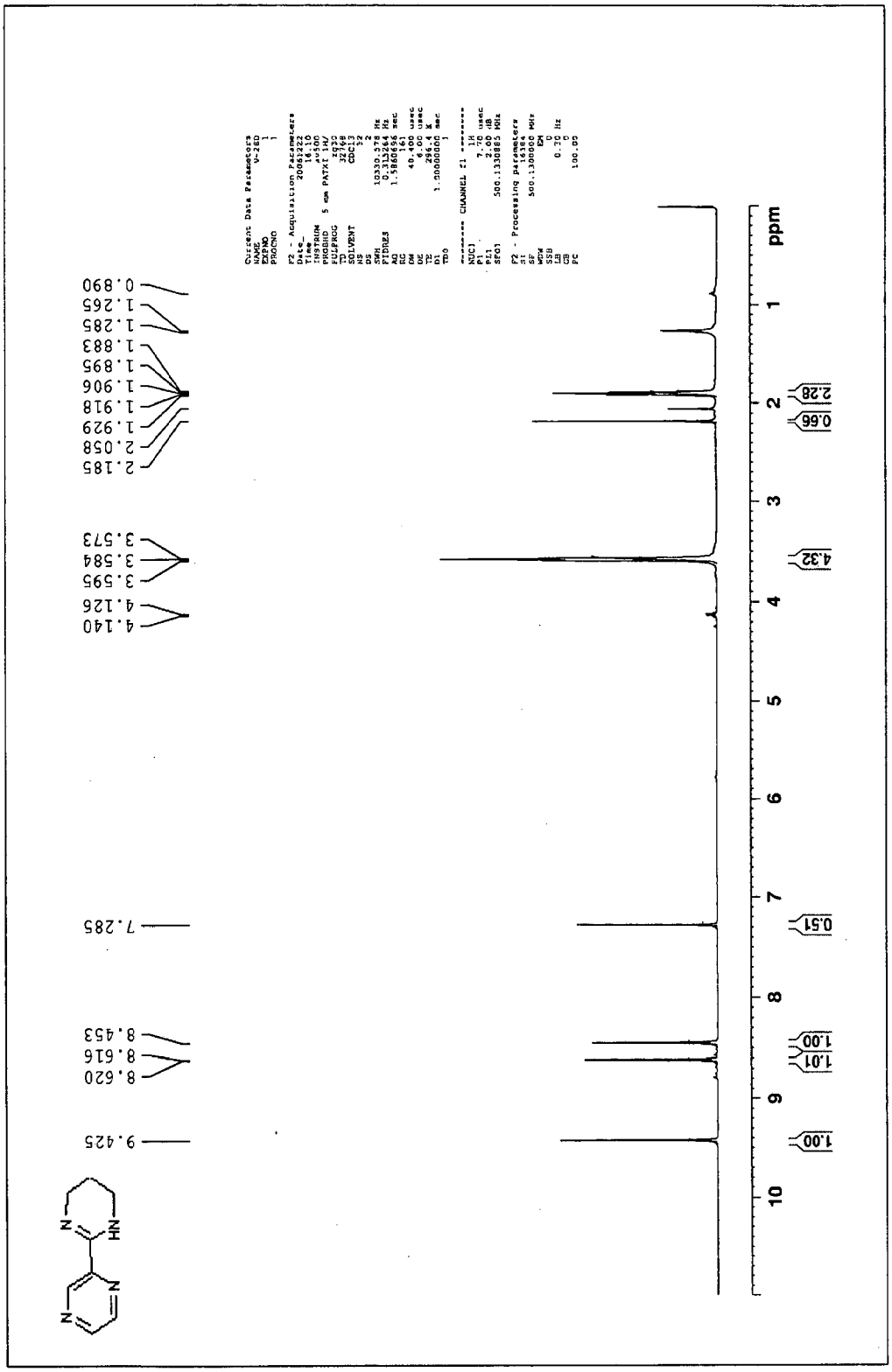

0.890
1.265
1.285
1.883
1.895
1.906
1.918
1.929
2.058
2.185
3.573
3.584
3.595
4.126
4.140
7.285
8.453
8.616
8.620
9.425
ppm
1
2
3
4
5
6
7
8
9
10
2.28
0.66
4.32
0.51
1.00
1.01
1.00
N
NH
N
N

Fig. 30

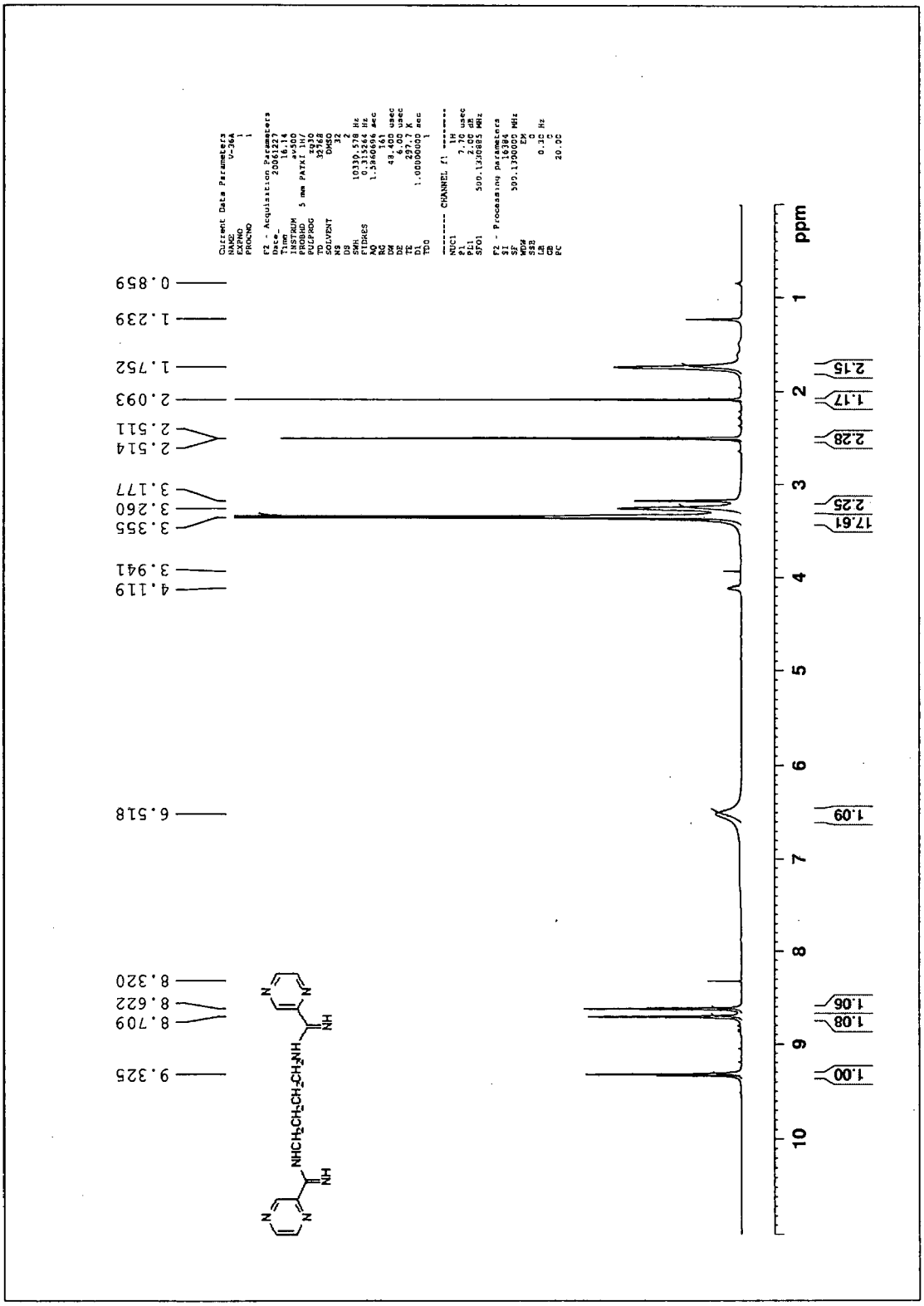

0.859
1.239
1.752
2.093
2.511
2.514
3.177
3.260
3.355
3.941
4.119
6.518
8.320
8.622
8.709
9.325
NHCH2CH2CH2NH
HN
HN
N
N
N
N
ppm
1
2
3
4
5
6
7
8
9
10
2.15
1.17
2.28
2.25
17.61
1.09
1.06
1.08
1.00

Fig. 31

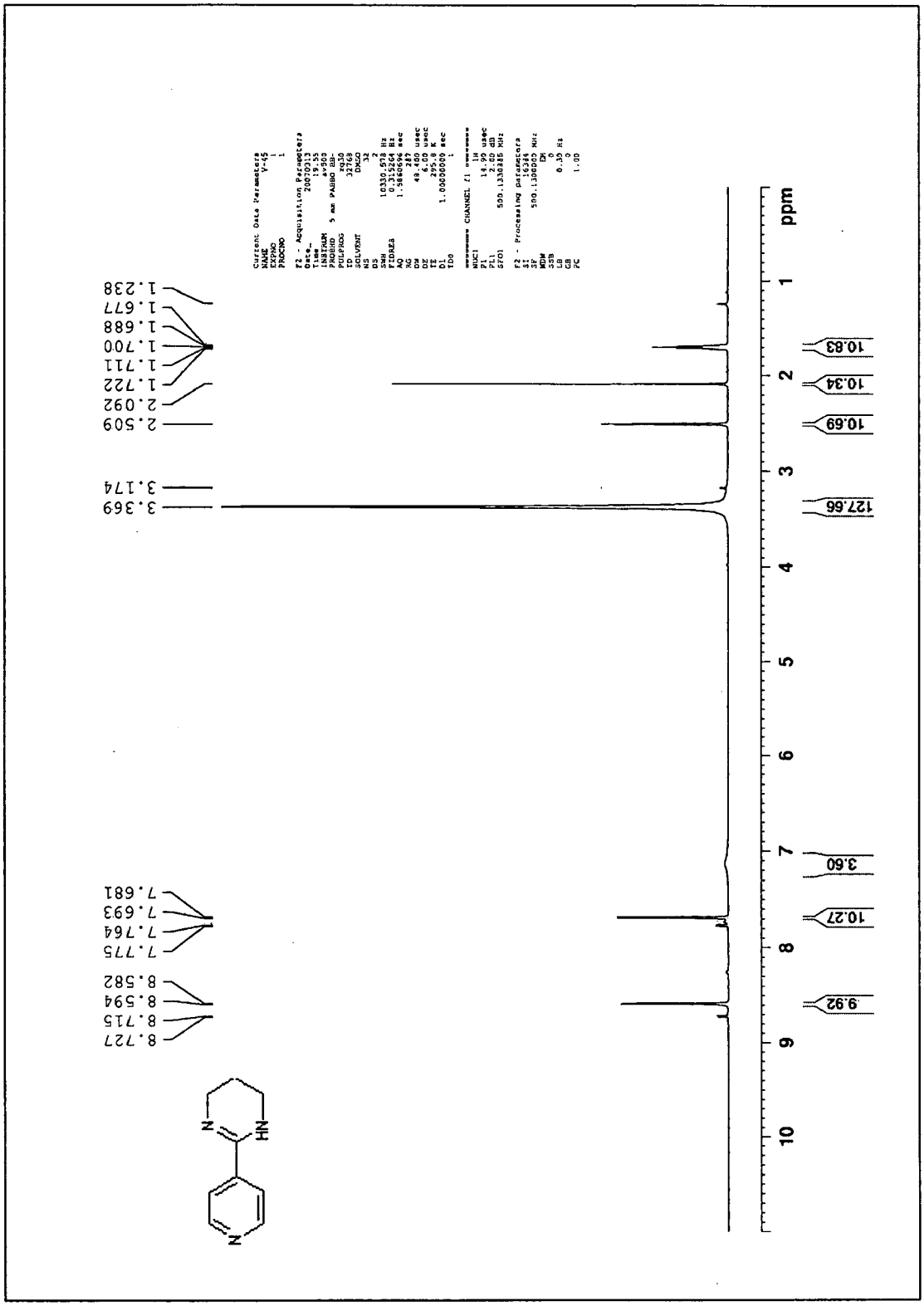

1.238
1.677
1.688
1.700
1.711
1.722
2.092
2.509
3.174
3.369
7.681
7.693
7.764
7.775
8.582
8.594
8.715
8.727
10.83
10.34
10.69
127.66
3.60
10.27
9.92
ppm
1
2
3
4
5
6
7
8
9
10
N
HN
N

Fig. 32

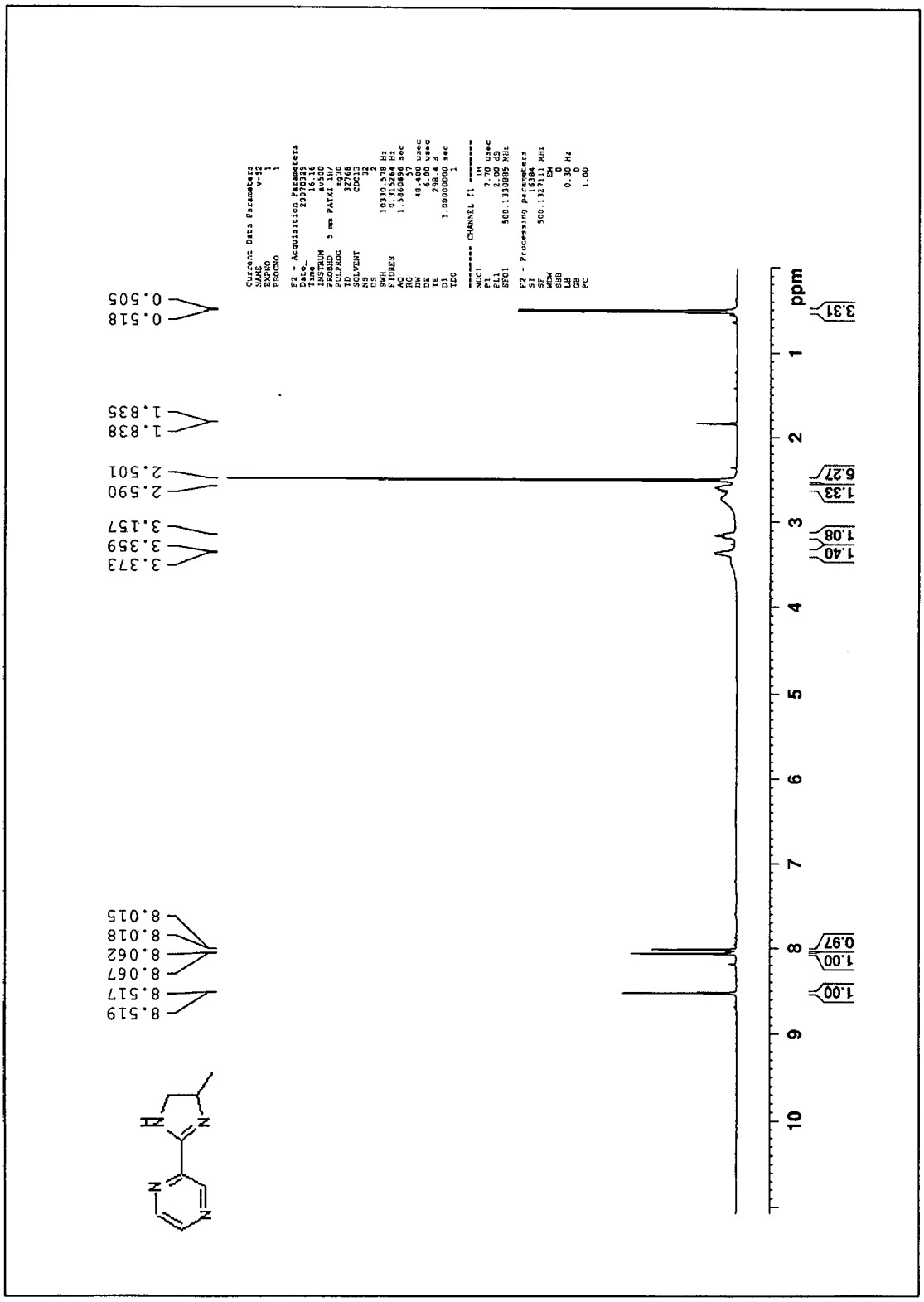

8.519
8.517
8.067
8.062
8.018
8.015
3.373
3.359
3.157
2.590
2.501
1.838
1.835
0.518
0.505
ppm
3.31
1.00
0.97
1.00
1.08
1.40
1.33
6.27

Fig. 33

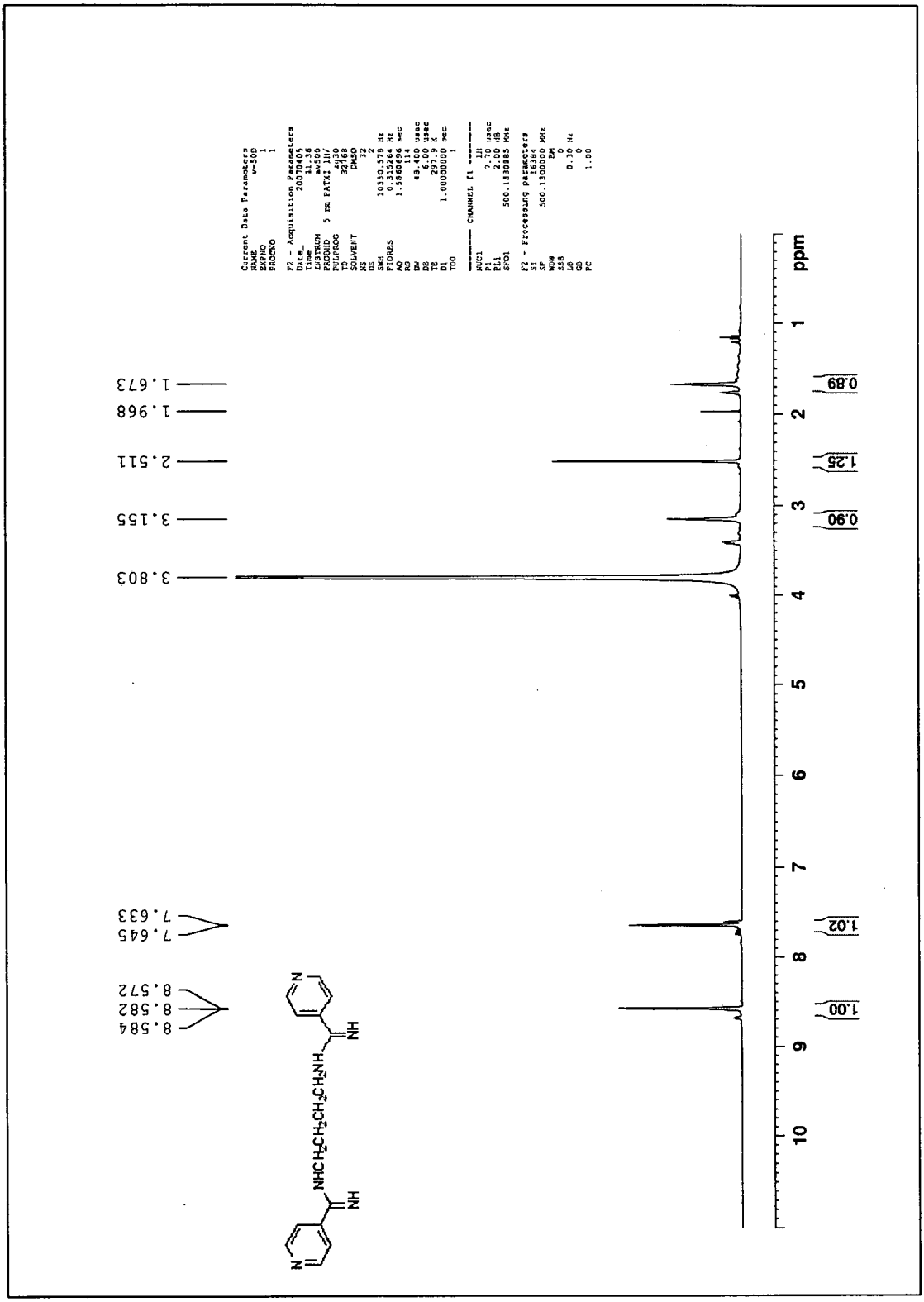

1.673
1.968
2.511
3.155
3.803
7.633
7.645
8.572
8.582
8.584
NHCH2CH2CH2NH
HN
NH
N
ppm
0.89
1.25
0.90
1.02
1.00

Fig. 34

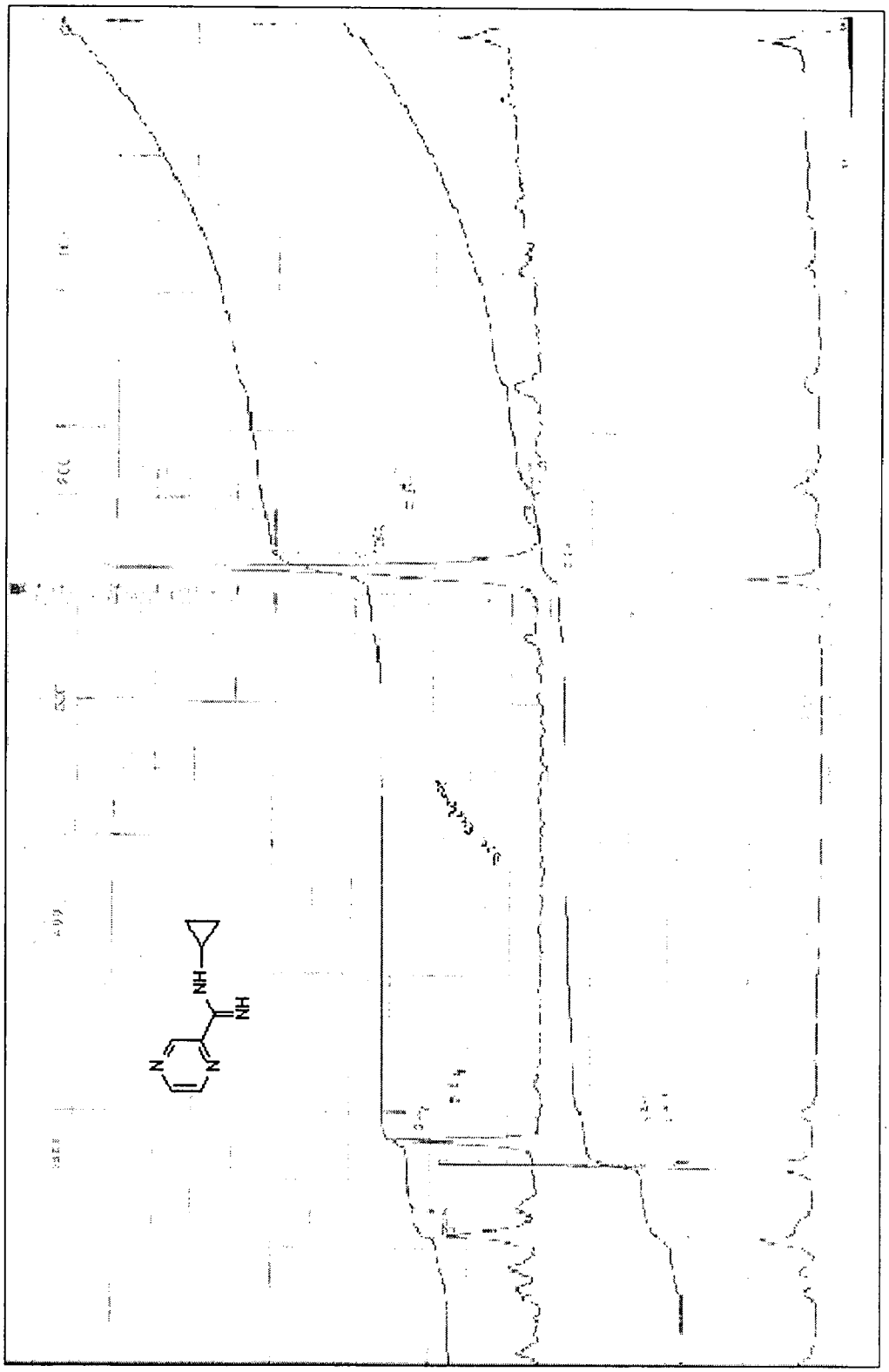


Fig. 35

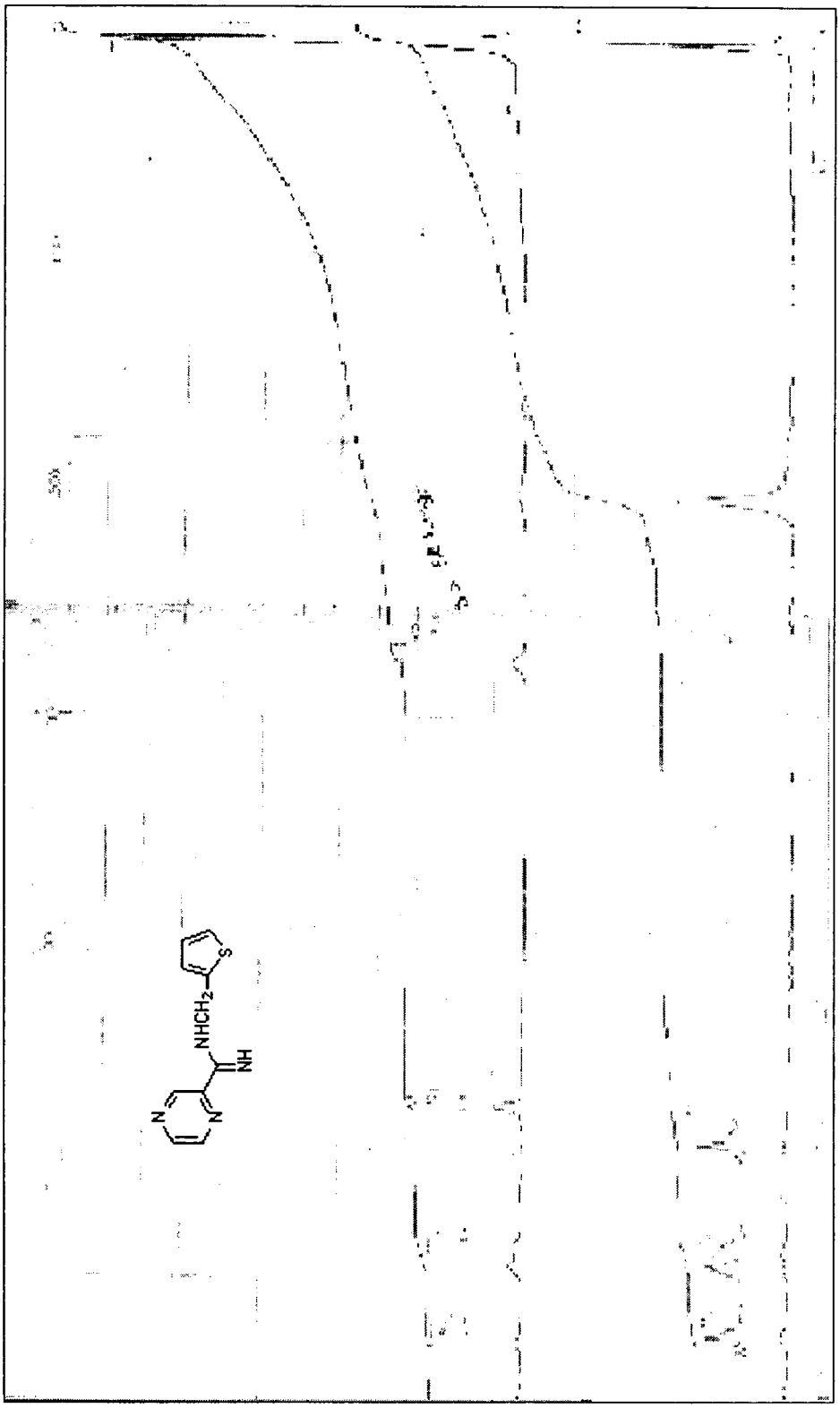


Fig. 36

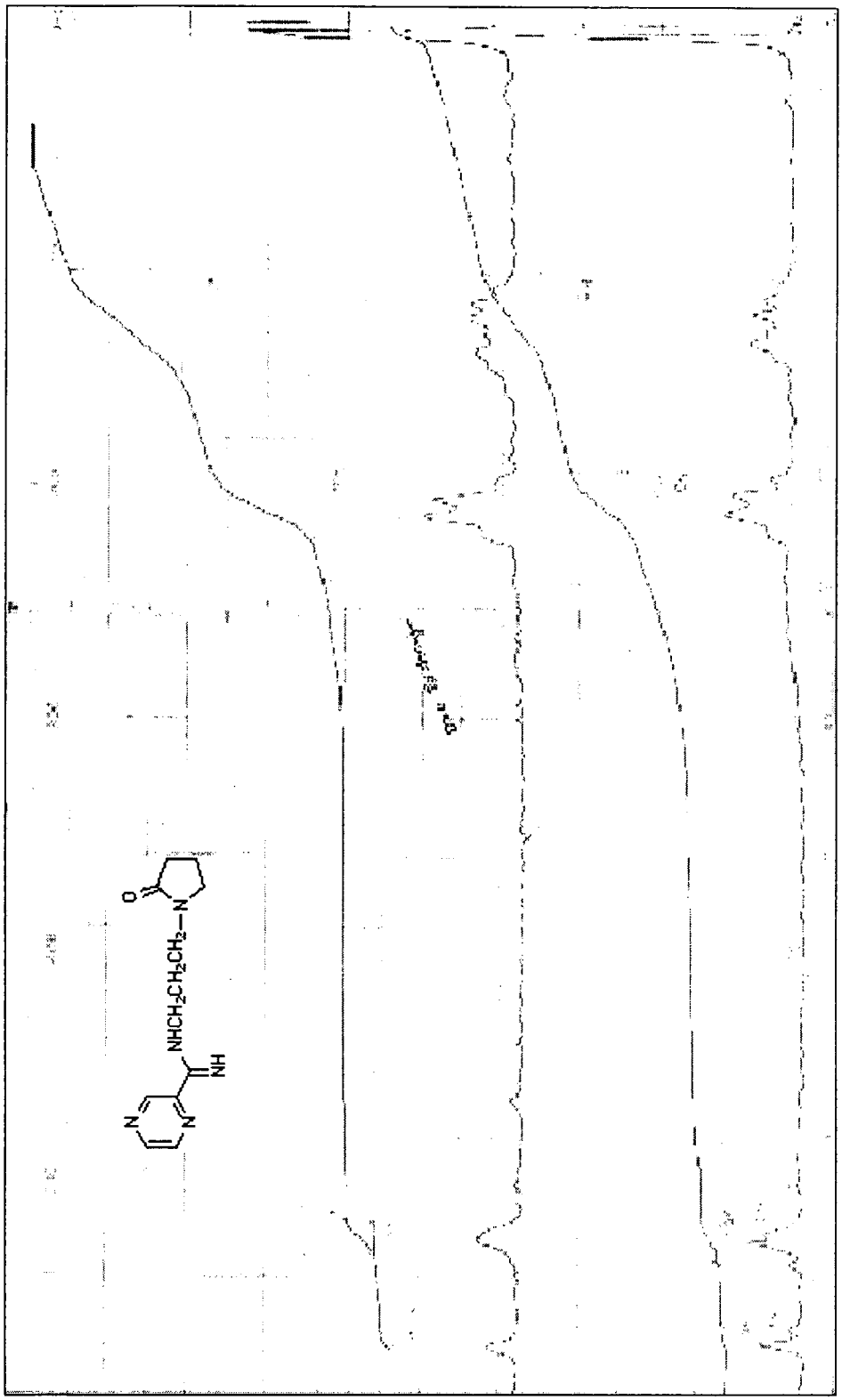


Fig. 37

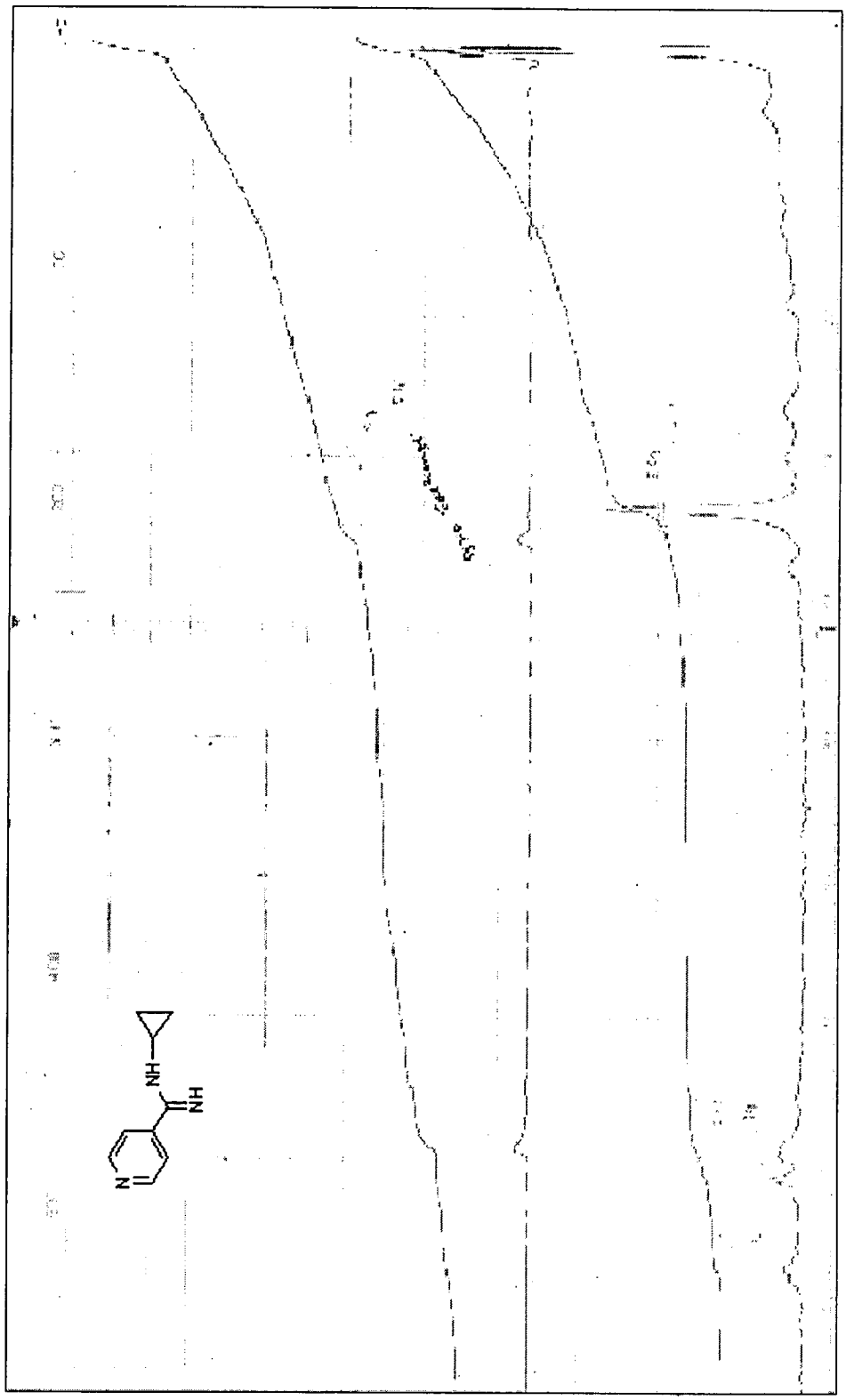


Fig. 38

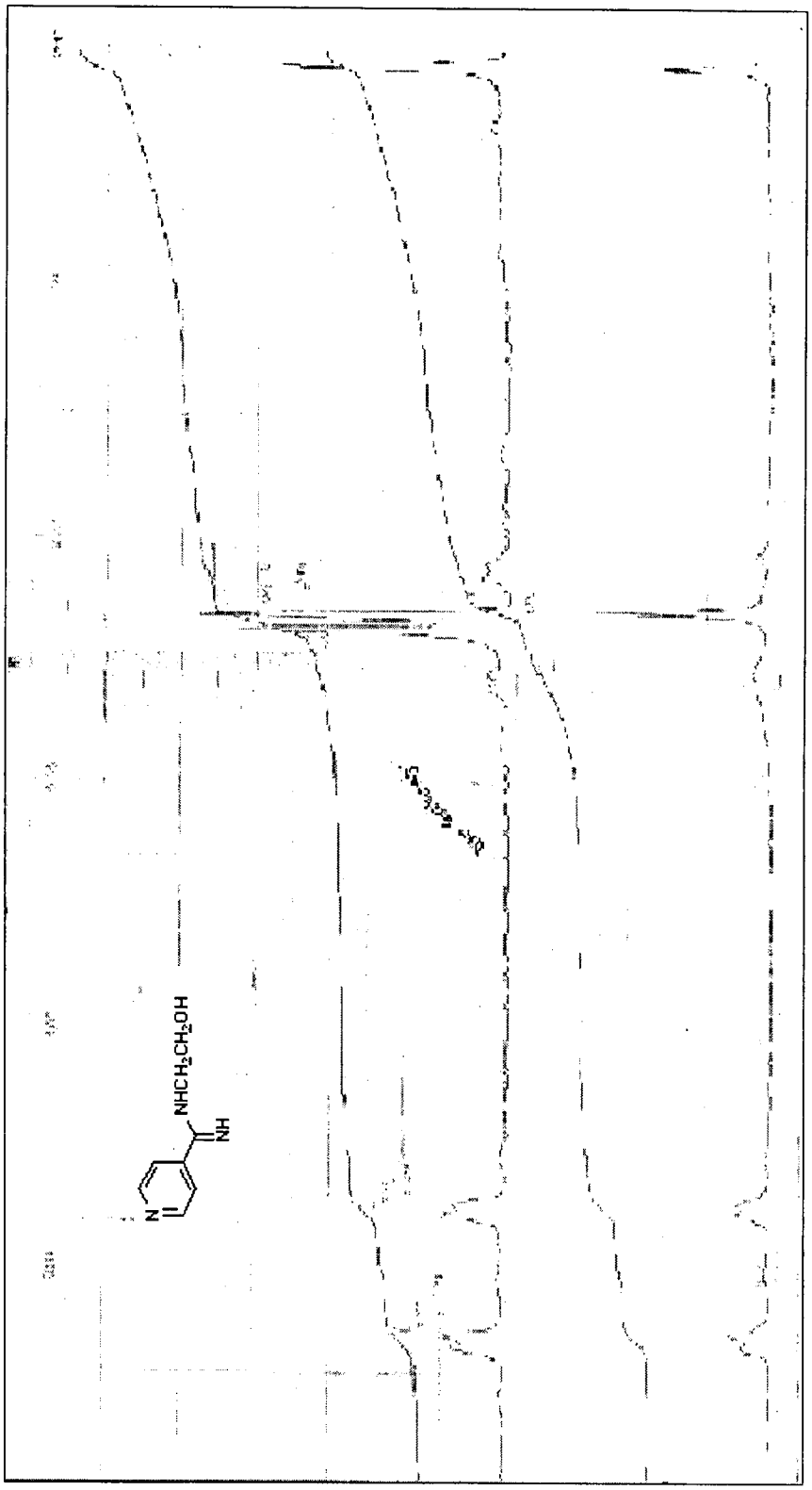


Fig. 39

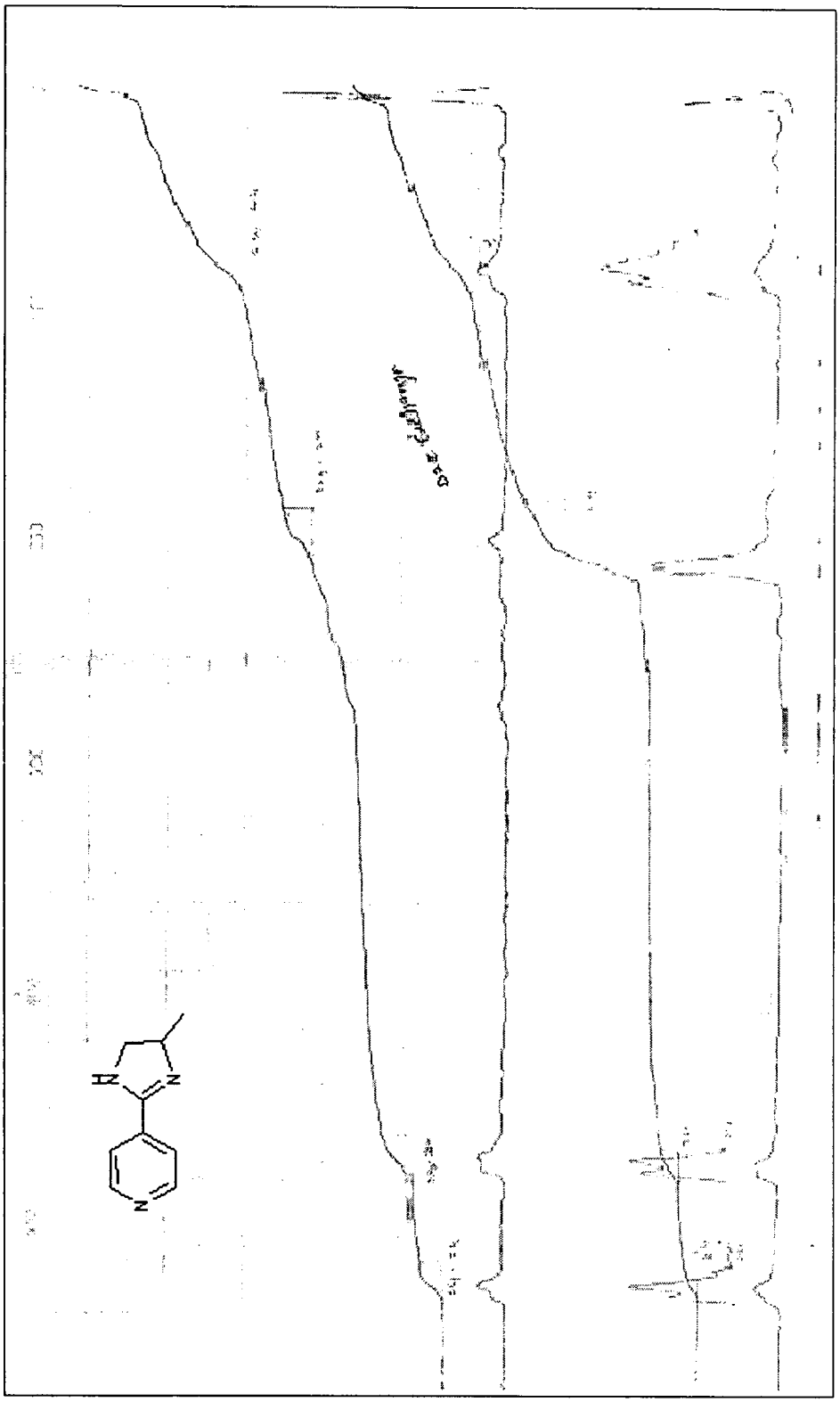


Fig. 40

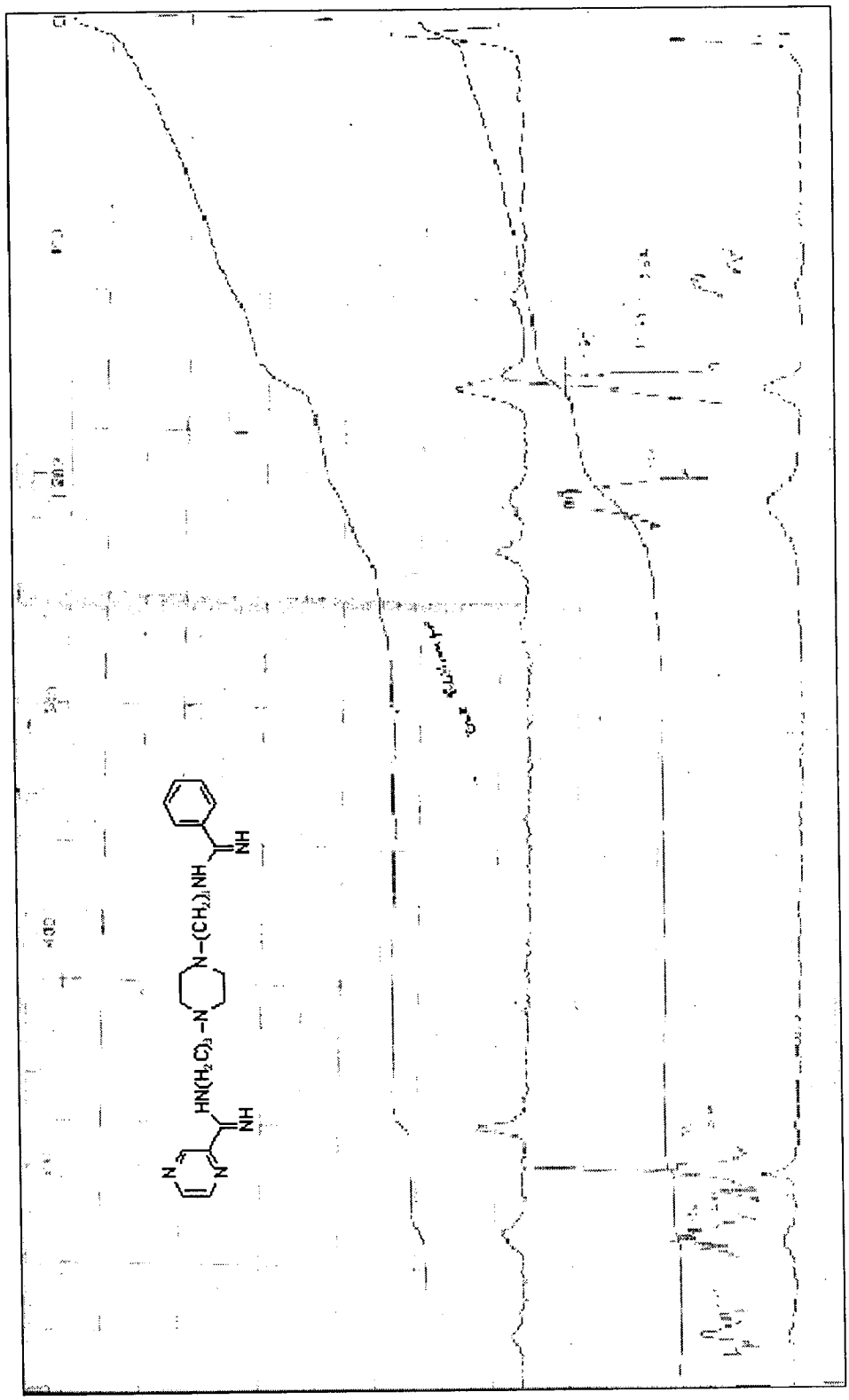


Fig. 41

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