SYNTHESIS OF SOME PHARMACOLOGICALLY ACTIVE QUINOXALINE DERIVATIVES AND STUDY ON THE KINETICS OF THE REACTION OF 2-CHLOROQUINOXALINE WITH PHENYLHYDRAZINE

A DISSERTATION

Submitted in partial fulfilment of the requirement for the award of the degree of

MASTER OF TECHNOLOGY

in

ADVANCED CHEMICAL ANALYSIS

By

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CANDIDATE'S DECLARATION

I hereby certify that the work which is being presented in this dissertation entitled **"SYNTHESIS OF SOME PHARMACOLOGICALLY ACTIVE QUINOXALINE DERIVATIVES AND STUDY ON THE KINETICS OF THE REACTION OF 2-CHLOROQUINOXALINE WITH PHENYLHYDRAZINE"** in partial fulfilment of the requirement for the award of the **Degree of Master of Technology in Advanced Chemical Analysis** and submitted to the **Department of Chemistry** of the Institute is an authentic record of my own work carried out during the period from **July 2005 to June 2006** under the supervision **of Dr. G. Bhattacharjee**, Professor, **Department of Chemistry, Indian Institute of Technology, Roorkee, Roorkee.**

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

Sushanta Kumar Mishra

Dated **(SUSHANTA KUMAR MISHRA)**

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

29.06.06

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ABSTRACT

Synthesis of various types of heterocyclic compounds is dominating the field of modern organic and medicinal chemistry. The presence of heterocyclic rings in drugs represents the majority of known pharmaceutical preparations. A number of 2-substituted Quinoxaline derivatives have been synthesized by the reactions of 2-Chloroquinoxaline with various amines by means of microwave enhancement of nucleophilic substitution reaction. The reaction of 2-Chloroquinoxaline with phenylhydrazine in MeOH followed 2^{nd} – order kinetics (1^{st} order in each reactant). The reactions have been carried out at five different temperatures and the various activation parameters have been estimated which are typical of a bimolecular aromatic nucleophilic substitution reaction (SNAr). The kinetics obeyed Hammett and Bronsted LFERs.

ACKNOWLEDGEMENT

I wish to express my deep sense of gratitude to my guide **Dr. G. Bhattacharjee,** Professor, Department of Chemistry, Indian Institute of Technology, Roorkee for his valuable guidance, constant encouragement and whole hearted co-operation in carrying out this study, without which it would not have been possible to complete this dissertation at all.

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

Dated **(SUSHANTA KUMAR MISHRA)**

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NOMENCLATURE

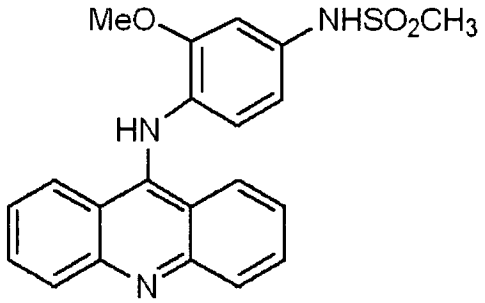
k_o	Pseudo first order rate constant
k_A	Second order rate constant
A	Frequency factor
E_a	Energy of activation
T	Temperature
t	Time in minutes
h	Planck's constant $6.626 \times 10^{-34} JS$
k	Boltzmann constant $1.380 \times 10^{-23} JK^{-1}$
R	Gas constant $8.314 JK^{-1} mol^{-1}$
HBD	Hydrogen bond donor
HBA	Hydrogen bond acceptor

Chapter 1
INTRODUCTION

1. INTRODUCTION

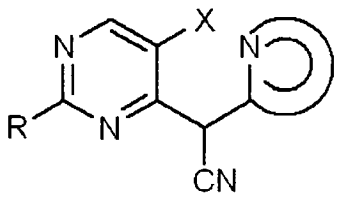
The presence of heterocycles in drugs represents the majority of known pharmaceuticals. For example:-

Anticancer drugs



m-AmSA(m-Amsacrime)

1



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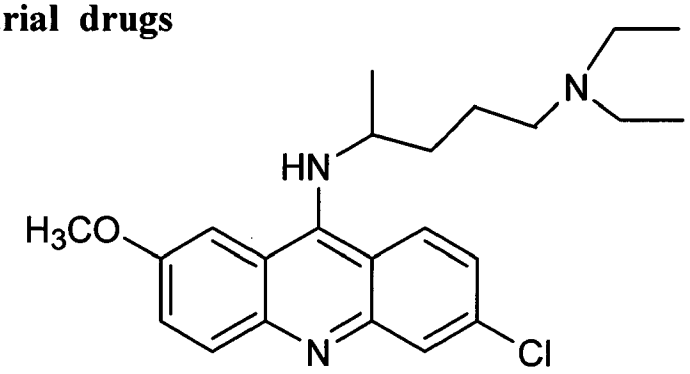
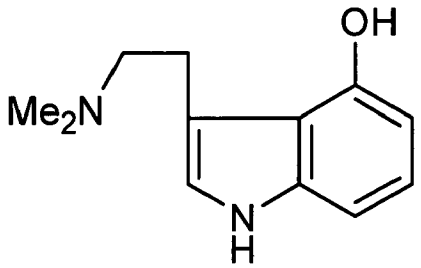
Antimalarial drugs



Quinacrime

3

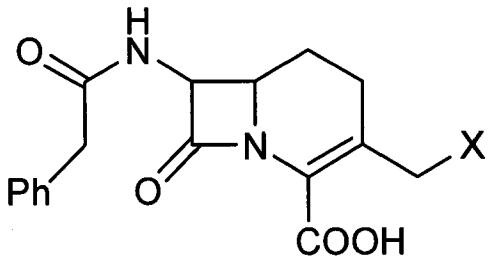
Drugs for psychotic diseases



Psilocin

4

Antibacterial drugs



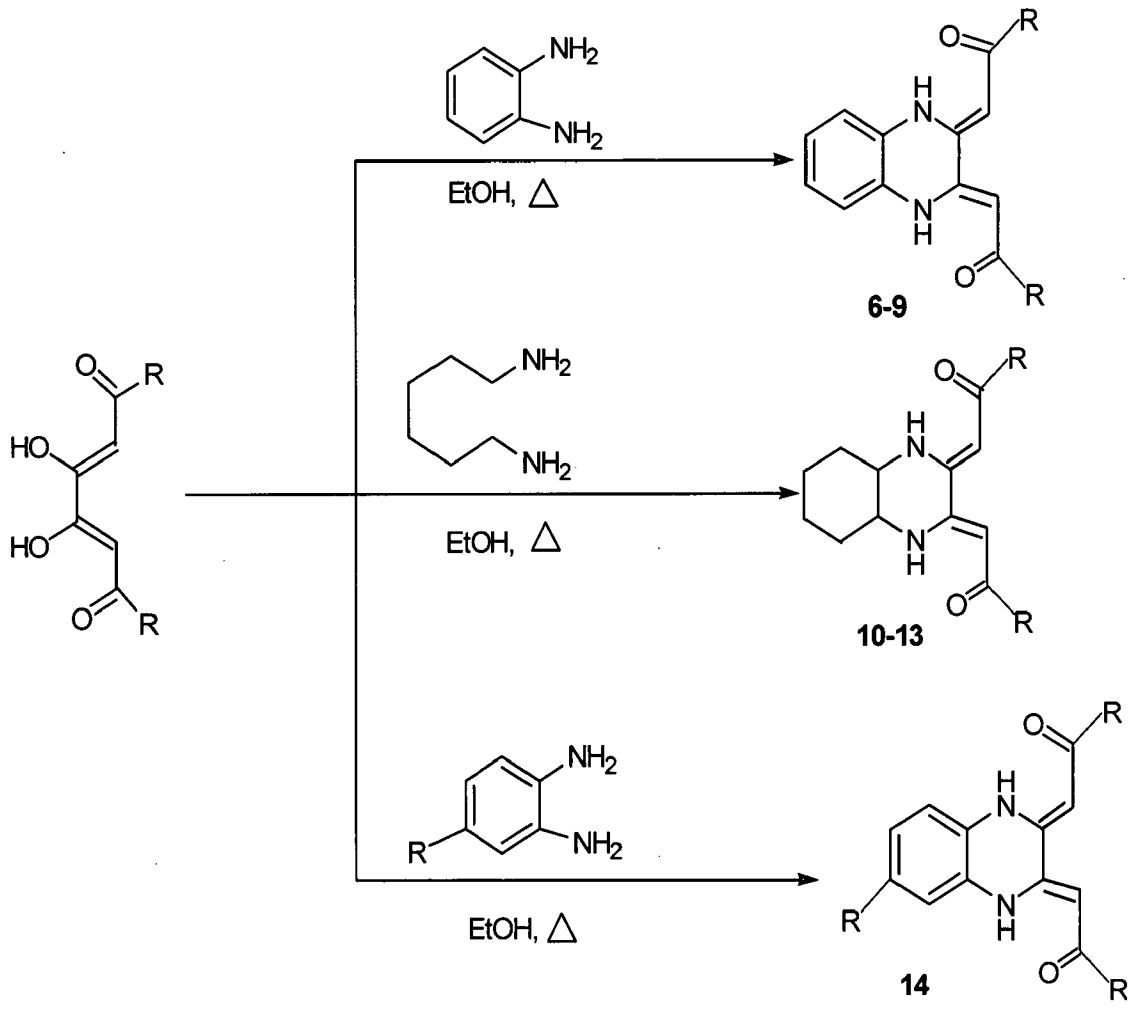
Cephalosporins

5

Therefore different type: of heterocycles have been synthesized. Quinoxaline, also known as benzopyrazine is a heterocyclic compound containing a ring complex, made up of a benzene ring and a pyrazine ring. It is isomeric with Cinnolene and Quinazoline. A derivative of Quinoxaline, Sulfaquinoxaline (4-amino-N-quinoxalin-2-yl-benzenesulfonamide) is used as an anti-infective or anti-protozoan agents and another derivative of Quinoxaline , Echinomycin is used as polypeptide antibiotic agents [1].

The chemistry of the Quinoxaline system continues to attract considerable attention. Quinoxaline containing compounds are physiologically active, Pyridoquinoxaline is anticonvulsant and Imidazoquinoxaline is a receptor antagonist [2]. Certain Quinoxaline-2, 3-diones [1, 2] and Quinoxaline-2-ones were highly potent NMDA receptor antagonists [3]. Quinoxalines are well-known class of compound and selected Quinoxaline derivatives have been described for use in various therapeutic applications [4]. For example, selected 4-N-aroyl-, arylacyl- and arylsulfonyl-3, 4-dihydroquinoxalin-2(1H)-ones were described as anti-inflammatory agents, Dihydroquinoxalin-2(1H)-one-3-carboxamides were described as anti-inflammatory agents in U.S. Pat. No. 3,654,275. In another example, selected pyridinyl-alkyltetrahydro-pyrazino [1, 2-a] quinoxalinone derivatives were described in U.S. Pat. Nos. 4,203,987 and 4,032,639 as antihypertensive and antisecretory agents. Furthermore, 4-N-benzenesulfonyl-3,4-dihydroquinoxalin-2(1H)-one-1-alkyl carboxylic acids were reported as aldose reductase inhibitors in European Patent Application EP 266,102, and selected Quinoxalines were described in U.S. Pat. No. 6,369,057 as therapeutic agents against HIV. However, none of the known Quinoxaline derivatives have been demonstrated to exhibit activity against RNA-dependent RNA polymerases, and especially the RNA polymerase NS5B of HCV. In recent years, polyfunctionalised Quinoxalines have been prepared and studied because of their interesting biological activities and DNA interactive behavior. Some act as anti-diabetic agents, anti-HIV agents, or NMDA receptor antagonists. Others can be used in O- conjugated polymer chemistry

due to their electron withdrawing properties. In addition, the fluorescence characteristics of 5, 8- and 6, 7- dimethoxyquinoxaline [4] and their potential as fluoroionophores have recently been described [5]. Substituted Quinoxaline compounds bear a strong resemblance to well-characterized drugs that bind to DNA by intercalation [7]. In general, three major aspects of the binding of drugs to DNA may be expected to influence their biological activity: (i) mode of interaction with the double helix, (ii) sequence specificity of binding, and (iii) kinetics of association/dissociation.



Scheme 1.1

6: R= Ph
7: R= neo-pentyl
8: R= Pr
9: R= p-Cl-Ph
10:R= Ph; (R,R) (chiral)
11: R= Ph; (R,S)(recemic)
12: R=Pr; (R,S)(recemic)
13:R= p-Cl-Ph;(recemic)
14: R=NO2

Compounds **6-14** of Scheme 1.1 represents attractive model for theoretical and experimental study of intercalators and find medical applications because of the variability in available forms. Moreover, given the current interest in drug targeting to harmful genes through development of molecules that recognize specific DNA sites [8, 9]. It is desired to extend the methodology to the synthesis of pharmacologically important Quinoxalines bearing functional groups at positions 2 and 3 of the Quinoxaline ring. The development of a short and convergent approach to the synthesis provides access to the new Quinoxaline family **6-14** of Scheme 1.1. In this context, efforts have been made to extend the methodology to the synthesis of pharmacologically important Quinoxalines bearing substitution at positions 2. Literature has been reviewed mainly on the heterocycles containing 2- Chloroquinoxaline.

1.1 Kinetics and Reaction Mechanism

In classical terms reaction kinetics refers to measurement of rates of a reaction under appropriate condition. Kinetics provide vital information about the mechanism of a reaction. Knowledge on reaction mechanism helps to optimize yields, correlate and predict reactions.

Kinetics can provide answers on the following:

(i)Why some reactions are fast and others slow?

(ii)Why do the rates of some reactions show temperature dependence?

(iii)How to optimize yields and predict course of a reaction?

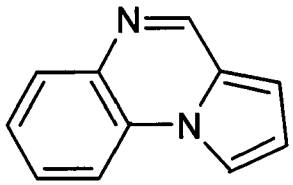
Reaction kinetics is a core subject in chemistry with a link with thermodynamics, statistical mechanics and spectroscopy. Reaction kinetics is crucial in determining organic and inorganic reaction mechanism and is of central importance for atmospheric chemistry.

There are two major aspects of reaction kinetics: a search for fundamental information about the molecular mechanism of elementary reactions and the application of kinetic data to complex chemical system. Many a time, kinetic results do not lead unambiguously to one particular mechanism. In such cases other experimental techniques for characterization of reactive intermediates and transition state is made in conjugation with the kinetic data to pick up the best out of several possible mechanisms. The mechanism of different types of organic reactions such as oxidation, addition, elimination, substitution, molecular rearrangement and various other reactions has been kinetically established.

Chapter 2
LITERATURE SURVEY

2. LITERATURE SURVEY

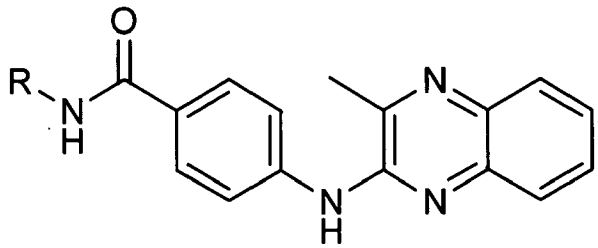
Derivatives of 2-Chloroquinoxaline form an important class of heterocyclic compounds possessing a wide range of biological activities. 3-Benzyl-2-substituted quinoxalines have been synthesized by means of microwave irradiation involving nucleophilic substitution reaction of the corresponding 2-Chloroquinoxaline analogs and substituted amines or hydrazine. Mohga and coworkers [10] have highlighted that the synthesized compounds showed selective inhibitory activity toward MAO-A than MAO-B. In addition, the acute toxicity of the synthesized compounds was determined. Pyrrolo[1,2-a]quinoxaline,Bispyrrolo[1,2-a]quinoxalines, Bispyrido[3,2-e]pyrrolo[1,2-a]pyrazines, and Bispyrrolo[1,2-a]thieno[3,2-e]pyrazines were synthesized from various substituted nitroanilines or nitropyridines .



pyrrolo[1,2-a]quinoxaline

15

Various 3-methyl-2-[4-(substituted amino carbonyl)anilino] Quinoxalines were synthesized from the new key compound 2-[4-(ethoxycarbonyl)anilino]-3-methyl quinoxaline. Refaat et al. [11] have highlighted the anti-malarial activity of the synthesized compound.



3-methyl-2-[4-(substituted amino carbonyl)anilino] quinoxaline

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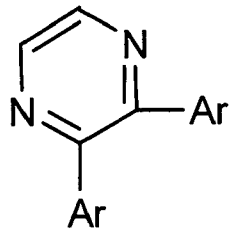
Jochen [12] has reported that Quinoxalines are widely used compounds in electrophysiological studies to separate excitatory and inhibitory neurotransmission mediated by the strychnine-insensitive and strychnine-sensitive glycine receptor (NMDA, GlyR), respectively.

Aviv et al. [13] have reported that Quinoxalines are highly potent and selective inhibitors of the type III receptor tyrosine kinases PDGFR, FLT3, and KIT.

Sergio et al. [14] have synthesized twenty eight compounds which are derivatives of compound (15) bearing various substituents at position 4 that are related to the moieties present in classical and non classical antifolic agents having antiproliferative activity.

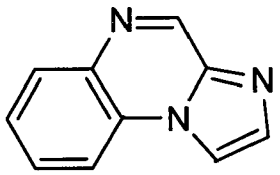
Hui et al. [15] have synthesized twentynine new quinoxaline derivatives evaluated *in vitro* against several parasites (Leishmania donovani, Trypanosoma brucei , and Trichomonas vaginalis).

Sunil et al. [16] have synthesized Several 2, 3-diaryl pyrazines and quinoxalines with 4-sulfamoyl (SO_2NH_2) / methylsulfonyl (SO_2Me-phenyl) pharmacophores and evaluated for their cyclooxygenase (COX-1/COX-2) inhibition activity.



17

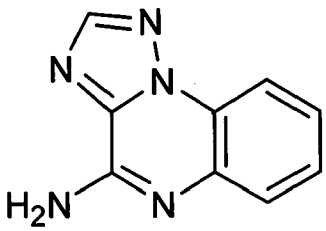
Parra et al. [17] have synthesized a group of imidazo[1,2-a]quinoxalines from Quinoxaline by condensation of an appropriate haloester or intramolecular cyclization of a keto moiety with an intracyclic nitrogen atom. The synthesized compounds have cyclic nucleotide phosphodiesterase inhibitory activity.



imidazo[1,2-a]quinoxaline

18

Antonio et al. [18] have synthesized a new series of 3-alkyl-, 3-trifluoromethyl-, 3-carboxyethyl- and 3-bromomethylquinoxaline-2-ones and 2,3- bis (bromomethyl)quinoxalines bearing Cl, CF_3, morpholine on the benzene ring, found to have antibacterial activities.



4-amino-1,2,4-triazolo[1,5-a]quinoxaline

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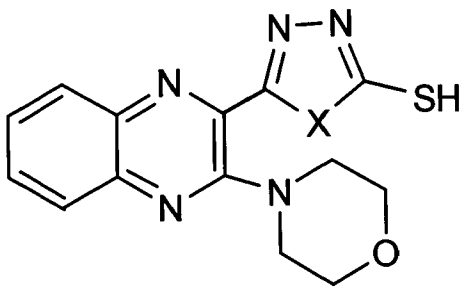
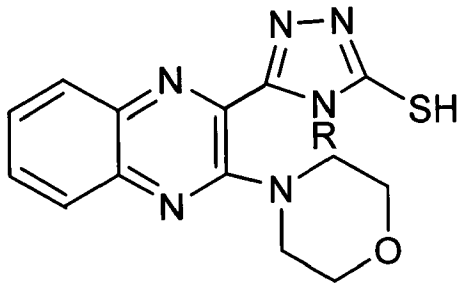
Daniela et al.[19] have synthesized 4-amino-1,2,4-triazolo[1,5-a]quinoxalines bearing ethyl carboxylate group or hydrogen atom at position-2, which act as adenosine receptor antagonists. Rangisetty et al. [20] have synthesized 2-arylaminoquinoxalines by the condensation of 2-Chloroquinoxaline with the appropriate Mannich bases in the presence of HCl. To synthesize the Mannich bases, 4-Acetamidophenol was reacted with formaldehyde and dialkylamine to yield 3-[(dialkylamino) methyl]-4-hydroxyacetanilide, followed by hydrolysis. Antimalarial activities of the new arylaminoquinoxalines were evaluated against the rodent malaria parasite Plasmodium yoelii at a dose of 75mg kg^{-1}.

Tatiana et al. [21] have incorporated Quinoxalines into a hydrophenanthrene and naphthalene skeleton and the synthesized compounds have found to have antiviral activity.

The heterocyclic derivatives of morpholinoquinoxaline **20** (R = Ph,4-MeOC6H4 ; 4-ClC4H4 ; X = O ,S) and **21** were prepared from 2-Chloroquinoxaline-3-carboxylate in 4 steps and were tested for their antibacterial activity.

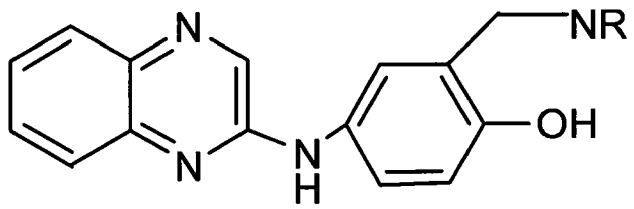


20



21

Patel [22] synthesized various 2-sustituted Quinoxaline derivatives by the reaction of 2-Chloroquinoxaline with amines and the synthesized compounds were evaluated for their *in vitro* growth inhibitory activity against various bacteria and fungi. All 2-Chloroquinoxaline amines exhibited very good antibacterial as well as antifungal activities.



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2.1 Literature survey on kinetics

Patel [55] has mentioned that the reactions of 2-Chloroquinoxaline with anilines in ethanol followed second order kinetics, first order in each reactant. The activation parameters determined, from the rate data at five different temperatures were found to be typical of bimolecular aromatic nucleophilic substitution (S_N^2Ar). The rate data were also correlated in terms of Hammett as well as Bronsted relationships. The rate of the reaction of 2-Chloroquinoxaline with piperidine in dimethyl sulphoxide was measured over a wide range of amine concentrations and at several temperatures. It was found that the order with respect to the nucleophile is close to 1 between 300 and 320 K, but is definitely less at lower and higher temperature. It is suggested that below 300 K an unreactive charge-transfer complex is formed between the reactants which dissociates

at higher temperatures, whereas at temperatures higher than 320 K an unproductive σ-complex is formed, the concentration of which increases with increase in temperature [56].

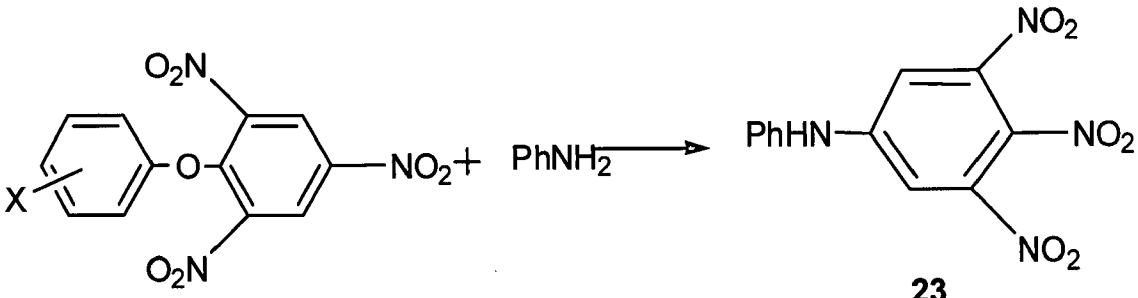
Patel [57] has reported Pseudo-first-order rate constants and activation parameters for the solvolysis of 2-Chloroquinoxaline in various aquo-organic mixtures using methanol, ethanol, and isopropanol as solvents. Excellent linear correlations were found between ln k and the mol fraction of co-solvent and ln [H_2O]. The medium effect on the rates of solvolysis was assessed by Grunwald-Winstein's mY relationship. The estimated values of m (0.55-0.72) and the entropy of activation (148-212 J deg^{-1} mol^{-1}) for the reactions were well in the range for a bimolecular aromatic substitution reaction.

The reactions of 2-Chloroquinoxaline with various aniline derivatives in methanol were measured at four different temperatures .The reactions got accelerated by electron releasing and retarded by electron withdrawing group on aniline showing second order kinetics, first order with respect to both substrate and reagent. The rate data were correlated with both Hammett and Bronsted relations. The activation parameters supported S_N^2Ar mechanism [58]. The reaction of 2-Chloroquinoxaline with anilines in EtOH followed 2^{nd}-order kinetics (1^{st} order in each reactant). The activation parameters determined at five different temperatures were typical of bimolecular aromatic nucleophilic substitution reactions (S_N^2Ar).The kinetics obeyed Hammett and Bronsted LFERs .

2.2 Literature survey on aromatic nucleophilic substitution reactions(S_NAr)

Many papers and reviews on aromatic nucleophilic substitution (SNAr) reactions have appeared concerning steric effect, polar effect, nucleophilicity, solvent effect and structure reactivity correlation. Bernasconi has reported nucleophilic substitution reaction on 2, 4-dinitrobenzene with morpholine in dipolar solvent [23]. Kinetic studies [24] on the reaction of hydroxide ion and piperidine with several 2, 4-dinitrophenyl ethers in 60% dioxane-40% water have been reported. Plots of k_A vs. [piperidine] were linear and those of k_A vs [hydroxide ion] were curvilinear showing base catalysis in both the cases. Reactions of 4-$NO_2C_6H_4F$ with piperidine and methyl derivatives of piperidine in dipolar aprotic solvent (DMSO) did not show any drastic change in the rate pattern compared to those of 2, 4-(NO_2) C6H3F [25]. The reactions of piperidine and 1, 2, 4-$(NO_2)_3C_6H_3$ and 1, 2-$(NO_2)_2C_6H_4$ in benzene have also been investigated [26]. Quantitative yields of 2, 4-dinitro and 2-nitro-1-piperidinobenzene have been obtained respectively. The reaction was first order in both reactant and not catalyzed by acid or base. Addition-elimination mechanism has been suggested for the expulsion of NO_2 from the intermediate. Satisfactory correlation between the rate and equilibrium constant for the formation and decomposition of sigma complex has been reported [27]. An unusual aromatic nucleophilic substitution reaction of acetone-1-naphthalene sulphonylhydrazone with MeLi producing 1-isopropenylnaphthalene has been reported [28]. The reaction of o-bromo-p-chloronitrobenzene and 1, 4-dinitrobenzene with $NaBH_4$ in

DMSO lead to some nitrobenzene that is a proof for the role of hydride Meisenheimer adduct as a reaction intermediate [29]. Rate constants were determined for the reaction of polyfluoropyridine and poly halobenzene with NaOMe in MeOH [30].The reactions showed that 2-F derivatives of pyridine were strongly activating, while in benzene 3-F derivatives were strongly activating and the remaining F-derivatives are slightly deactivating [31]. Banjoko et al. [32] gave new evidence for cyclic transition state mechanism over the dimmer mechanism in non polar aprotic solvents for the reaction. The results were interpreted in terms of a cyclic mechanism involving 4-, 6-, and 8- membered ring in the transition state.



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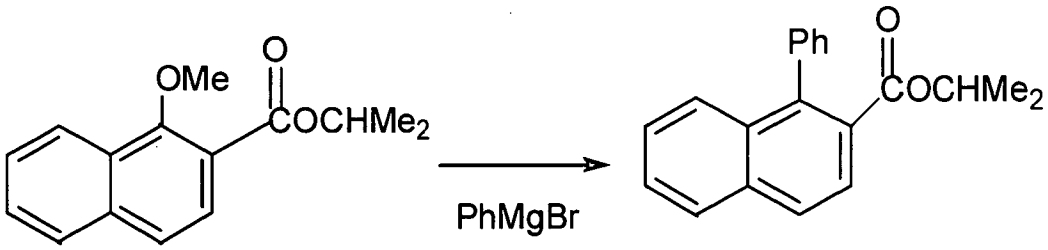
X=o, m and p-NO2

X=2,4-(NO2);3,4-(NO2)2;2,5-(NO2)2and 2,6-(NO2)2

Reactions of 4-(4-methoxyphenylazo)pyrinidium methiodide with primary , secondary , tertiary and aliphatic amines in dipolar aprotic solvent have been reported [33]. A convenient method was presented for the construction of the 1-phenyl naphthyl skeleton via an ester mediated nuceophilic displacement of a



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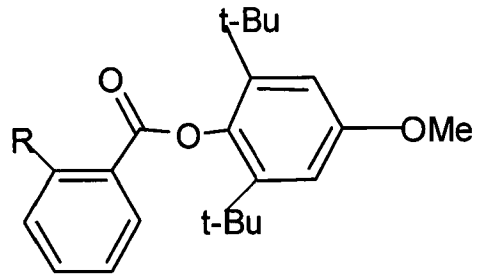
methoxy group from an aromatic nucleus by Grignard nucleophiles.Thus treatment of isopropyl-1-methoxy-2-naphthoate with PhMgBr , afforded 1-phenyl-2-naphthoate ester in good yields. The reaction of methoxide ion with 7-methyl-4-nitrobenzofuroxan has been investigated in MeOH and MeOH:DMSO mixture [34]. Stopped flow Spectophotometry showed two rapid reversible and well-separated processes due to 1:1 interaction. The most rapid reaction due to methoxide ion attack at the unsubstituted position ortho to nitro group resulted in the formation of a 5-methyl sigma adduct. The S_NAr of 1-methoxy-2-sulphonylnaphthalene with aliphatic Grignard reagent gave 1-alkyl-2-sulphonylnaphthalene[35]. Reactions of 2, 6-ditert.butyl-4-methoxyphenylbenzoate with several organolithium and magnesium reagents have been reported [36]. Nucleophilic substitution reactions [37] of 1, 4-dimethoxybenzene and 1, 3, 5-trimethoxybenzene with the anions of 1H-tetrazole-1, 2,



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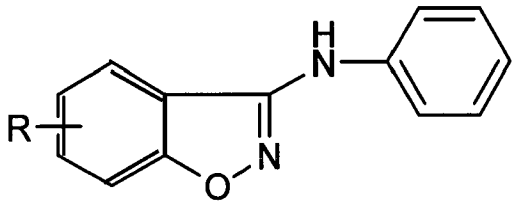
R=Ph,Bu,Me_3C,allyl,$PhCH_2$ and Me_3Si

4-triazole and 5-phenyl-1H-tetrazole have been carried out effectively by paired electrosynthesis. An Efficient three step process for the preparation of secondary 3-amino-1, 2-benzoxazoles(R=H, F, CF3, MeO, 6-NO_2) is described. The key step is the isomerization / cyclization of an ortho halo or nitro amidoxime.The S_NAr reaction is successful with a wide variety of substituents on the aromatic ring, including an electron donating substituent para to the site of attack [38].



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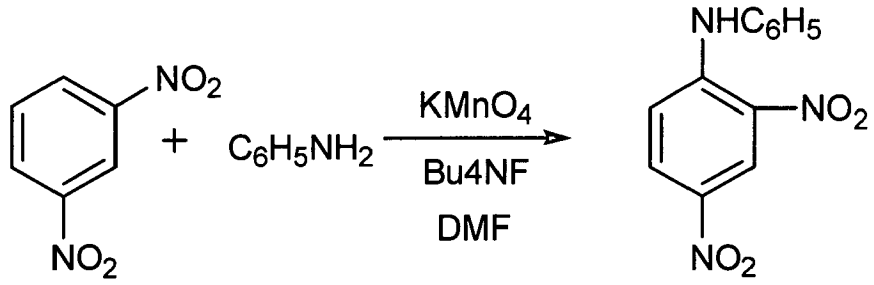
R=H, CF_3, MeO

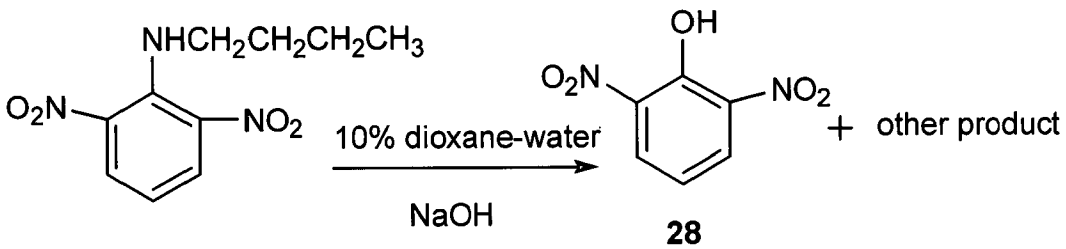
A one pot procedure using aromatic nucleophilic substitution of (η6-fluroarene) tricarbonyl chromium complexes for the synthesis of aryl piperidines in high yield has been reported [39]. The activating ability of sulphonyl group for nucleophilic displacement of methoxy in 2-sulphonyl-substituted -1-methoxynaphthalene by Grignard reagents via a chelation assisted conjugate addition-elimination process has been discussed [40]. The S_NAr between glutathione and 2,4-dinitrochlorobenzene was studied in reverse micellar system (surfactant with a polar head , non polar tail and the organic solvent 2,2,4-trimethylpentane) when the surfactant was positively charged and contained an aromatic ring in the polar head, the second order kinetics were observed. The rate enhancement may be attributed to stabilization of negative Meisenheimer sigma complex by the

positive polar head [41]. Recently [42] work dealing with the structure reactivity relationship in the pyridinolysis of N-methyl-N-aryl carbonyl chlorides in DMSO has been investigated.



27

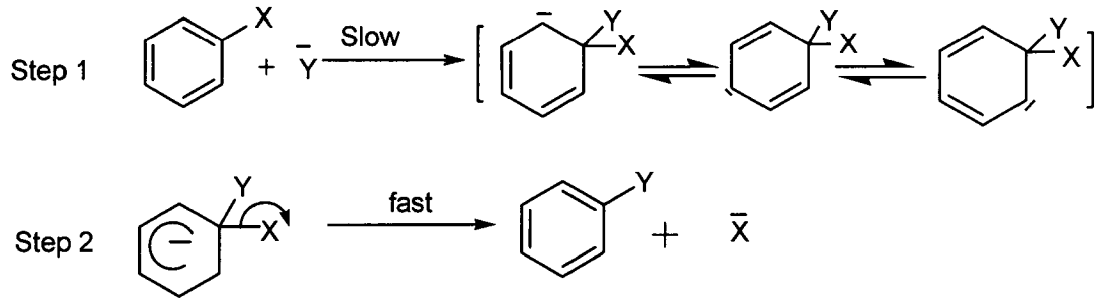
The mechanism for nucleophilic (pyridine) addition to resonance stabilized carbocation has been reported. The regioslective [43] direct coupling of amines, amides and ketones with m-dinitrobenzene, 1-nitronaphthalene and 1,3-dinitronaphthalene through oxidatively activated nucleophilic aromatic substitution of H promoted by fluoride anions are also described. Reactions of m-dinitrobenzene with other nucleophiles like $BuNH_2$, $MeCONH_2$, $PhCONH_2$, MeCOEt, MeCN and Me_2CO have also been reported. A kinetic study [44] on the reaction of n-butyl-2,6-dinitroaniline with NaOH was carried out in 10% 1,4-dioxane-water giving 2,6-dinitrophenol and other products.



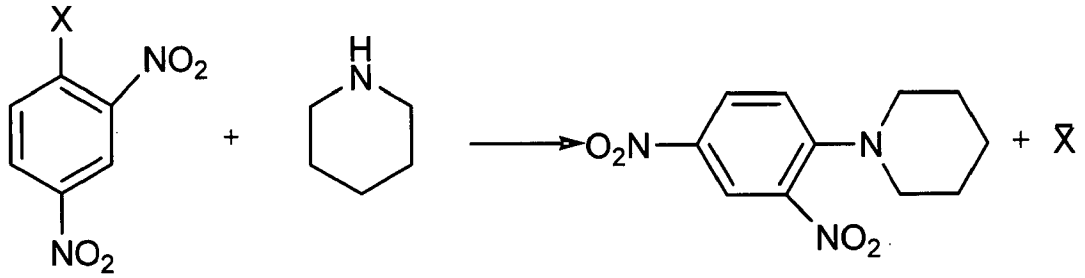
28

The rate constant for the formation of phenol is second order in [OH^-] with formation of a sigma complex.

2.2.1 Mechanism of Nucleophilic aromatic substitution reaction (S_NAr)



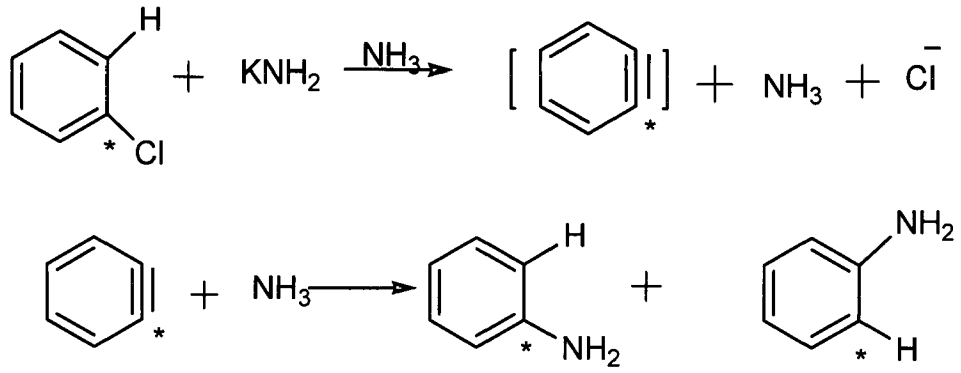
Usually nucleophilic substitution proceeds slowly at an aromatic carbon. However there is exception to this statement. The reaction in an aromatic substrate is largely of four types, (i) reactions activated by electron withdrawing groups, ortho and para to the leaving group; (ii) reactions catalyzed by very strong base and proceeding through aryl intermediate; (iii) reactions initiated by electron donors; and (iv) reactions in which the nitrogen of a diazonium salt is replaced by nucleophile. By far the most important mechanism for nucleophilic aromatic substitution consists of two steps: The first step is usually but not always rate determining, and then in the step 2 the leaving group departs. An example of above mechanism (S_NAr) is given below. A change in the leaving group should not have much effect on the rate of the reaction.



Where X=Cl, Br, SO_2Ph etc. the rate differing by a factor of 5 [45].

2.2.2 Reaction proceeding via benzyne

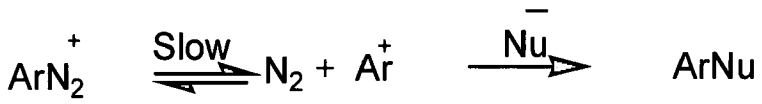
In 1953 Roberts and Coworkers [46] observed that when chlorobenzene-1-^{14}C in the substrate is reacted with KNH_2 in NH_3 , approximately 50% of the ^{14}C in the product is found in 1 and approximately 50% in the position 2. The overall substitution then must go by an elimination –addition mechanism via benzyne as shown below.



Benzyne mechanism is supported by the fact that an aryl halide lacking o-hydrogen do not undergo such reactions. Other workers [47,48] supported this mechanism by isolating benzyne in an organic matrix. Evidence for benzyne mechanism in the reaction of 1,2-dichloro- with metal phosphide and arsenides [49], also in the amido-dehalogination of 4-chloro-3,6-diphenylpyridazine [50] are reported . Substitution only occurred at the ortho position, if both were occupied, the reaction was totally suppressed.

2.2.3 Unimolecular substitution(S_N^1Ar) reaction

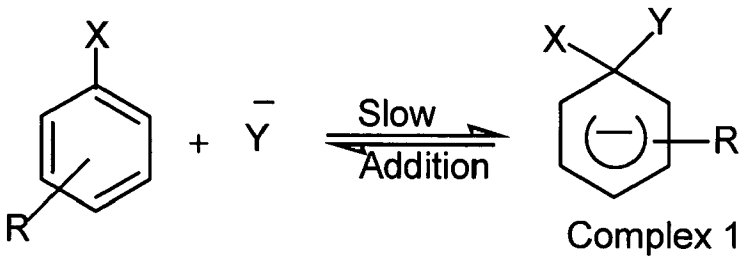
It seems surprising in view of this that only SN_1 reactions with aromatic substrate occur at all, but a number of displacements of nitrogen from diazonium salts do seem to proceed in this manner.

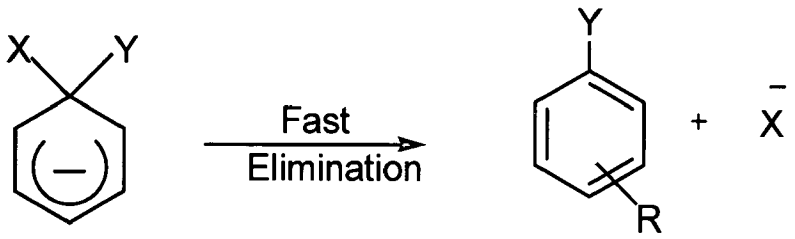


The following have been observed: (i) the reaction is first order in $[ArN_2^+]$ and independent of $[Nu^-]$, (ii) the rate determining step preceeds the product forming step (iii) the reaction is not affected remarkably by solvent (iv) shows very large isotope effect and (v) constituent in the ring influence the reaction rate in an unusual manner.

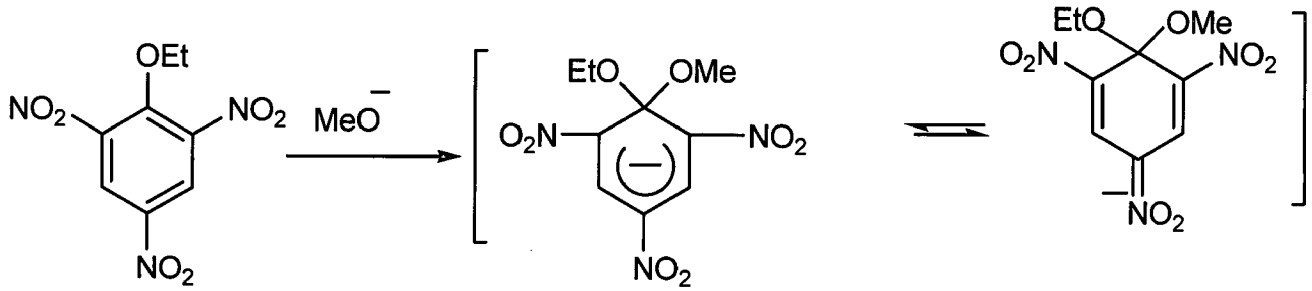
2.2.4 Bimolecular substitution (S_N^2Ar) reaction

In this mechanism, nucleophilic attack on aromatic substrate leads to the formation of a complex 1 from which the leaving group is lost to give the products as both the substrate and nucleophile are involved in the slow step, and a second order kinetics is observed in the uncatalyzed path.





A novel cine-substitution in the reaction of 4-alkoxy-2, 3-dinitroanilines presumably arise from the initial base attack at the 6-position. A kinetic study of the formation of 1, 3-dinitronaphthyl-piperidine by cine-substitution of 2,3-dinitronaphthalene with piperidine in benzene indicates an addition –elimination pathway for this reaction . Isomeric products were reported for the reaction of dimethylamine with bromo-1,4-benzoquinone derivatives, and this was another evidence for the addition-elimination mechanism . The reaction of methoxide ion with ethyl picryl ether gave stable Meisenheimer complex , as shown below,



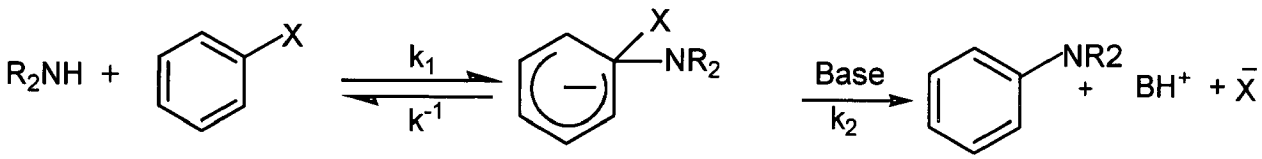
Meisenheimer Complex

Supporting bimolecular substitution mechanism. Indeed most of

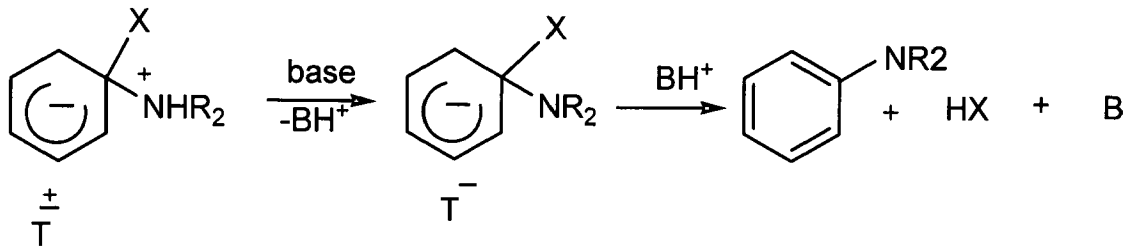
these reactions required some activation by electron-withdrawing groups to stabilize the anionic intermediate.

2.2.5 Aminolysis reaction and base catalysis

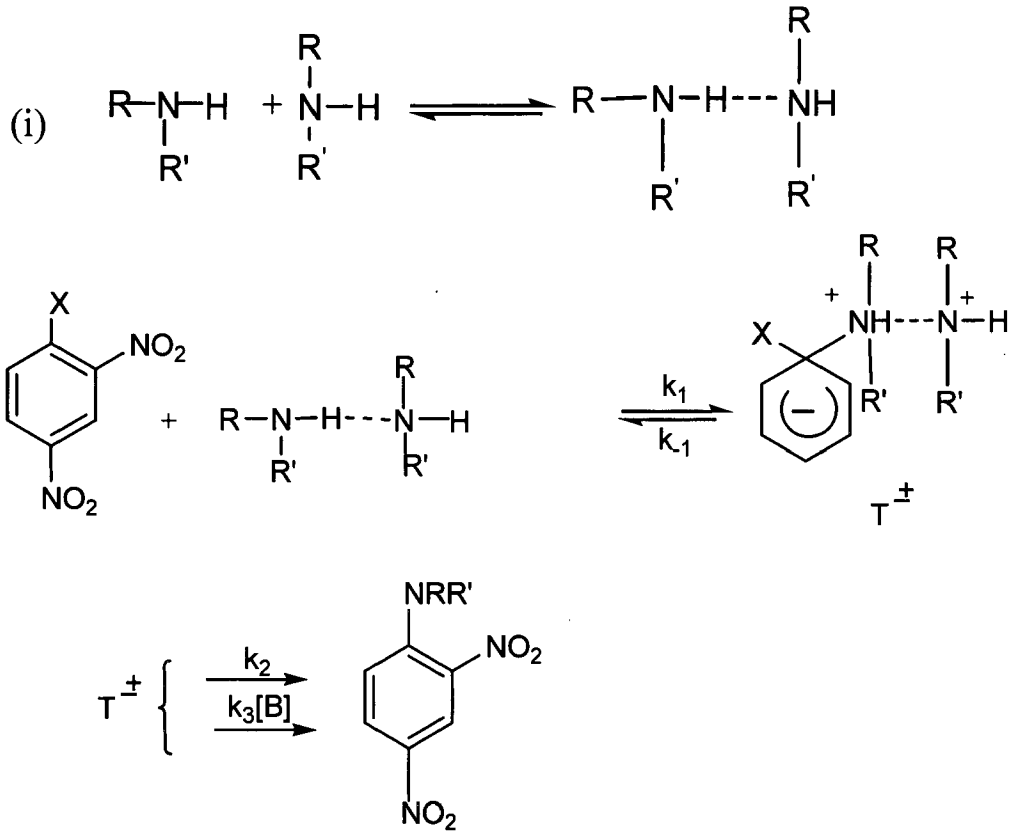
In most of the aromatic nucleophilic substitution reactions investigated, amines have been used as nucleophiles and the reaction termed as aminolysis. Base catalysis was found in those cases where the amines moiety cleaved easily but not X so that k_{-1} is large and step 2 was rate determining. This is an evidence for S_NAr mechanism because it involved two steps.



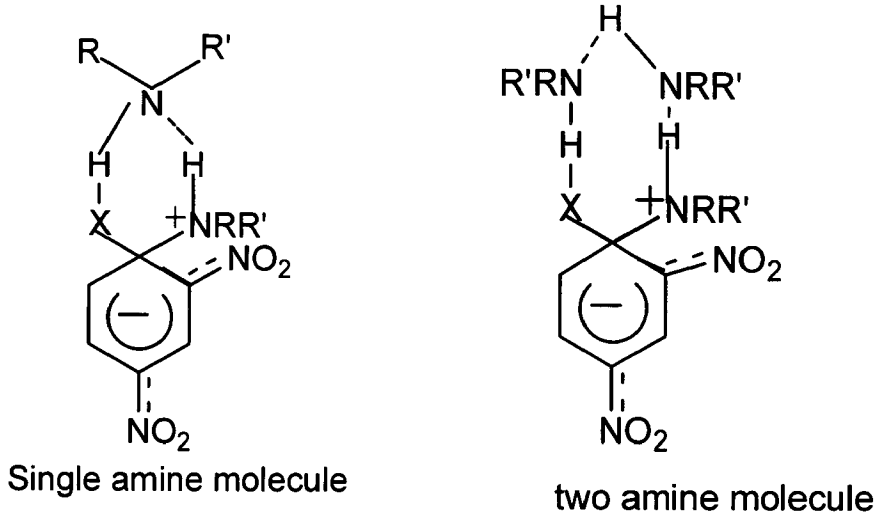
Furthermore, when bases were used as catalysts, catalysis occurred only at low concentration. A plot of the rate against the base concentration showed that small increment of base rapidly increased the rate up to a certain concentration , after which further base addition no longer greatly affected the rate . For protic solvents two proposals have been presented: (i) step 2 consists of two steps, rate determining deprotonation of T^+ followed by rapid loss of X and the base catalyzed the reaction by increasing the rate of deprotonation step,



(ii) The loss of X assisted by BH^+ is the rate determining step. For aprotic solvent two mechanisms have been proposed both based on kinetic evidence. In both the proposals the ordinary S_NAr mechanism operated, but in (i) attacking species involved two molecules of the amines while in (ii) is a cyclic transition state was involved as shown in Scheme 1.2.

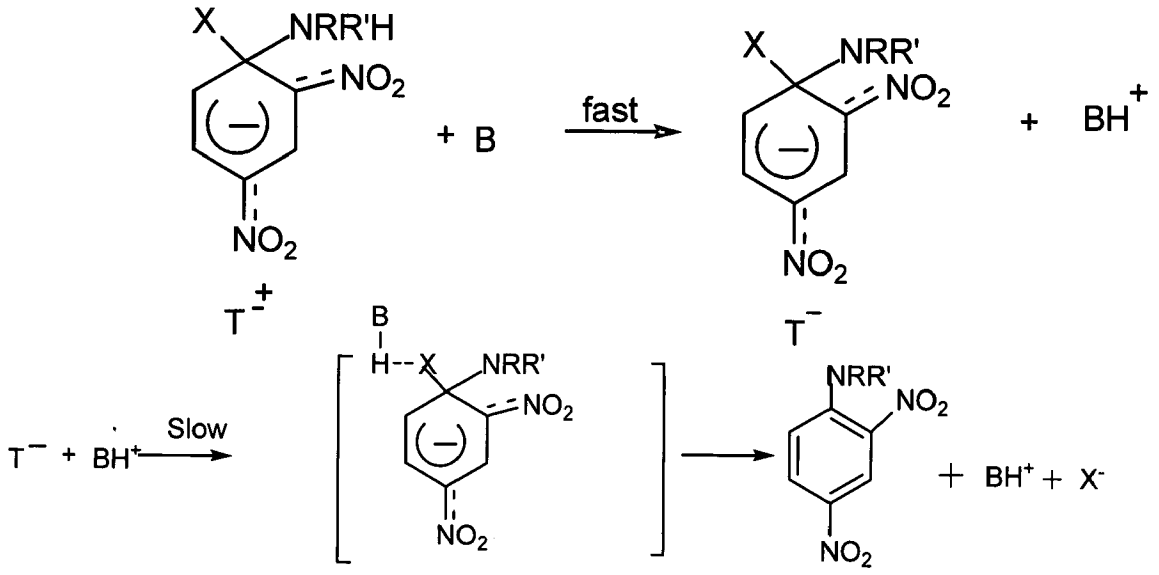


(ii)



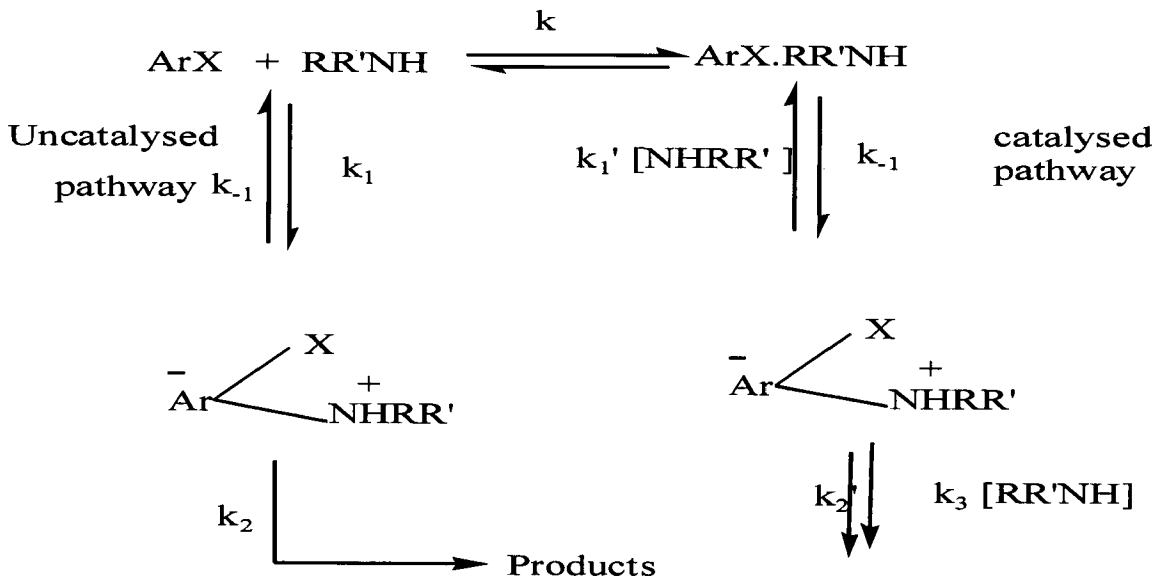
Scheme 1.2

Further evidence for the S_NAr mechanism has been proposed by Bunnett et al. [51] which is the specific base–general acid mechanism in dipolar aprotic solvent. This mechanism involves the formation of a new intermediate T^- by fast deprotonation of zwitterionic intermediate by base followed by slow general acid catalyzed removal of the leaving group as shown in Scheme 1.3.



Scheme 1.3

The above mechanisms have been firmly established and accepted by most of the workers [52] to explain their results. Barnasconi et al. [53] however, pointed out the invalidity of this mechanism for the reaction in a protic solvent. They adopted proton transfer mechanism to interpret base catalysis in protic solvent in which the deprotonation of zwitterionic intermediate $T^{\pm}$ to T^{-} is the rate limiting step followed by the loss of the leaving group at a faster rate . A number of investigations have been made by Forlani et al. [54] proposing the operation of base catalyzed pathway involving the formation of molecular complex due to substrate nucleophile interaction prior to the substitution reaction .The mechanistic details of Forlani's concept involving third order dependence on amine is shown in Scheme 1.4 .



Scheme 1.4

Chapter 3
MATERIALS USED

3. MATERIALS USED

3.1.1 Solvents

Organic solvents used are of high purity unless otherwise cited. MeOH (Merck), Ethyl Acetate (Qualigens),$CHCl_3$ (Rankem),Acetone (Rankem), Petroleum Ether (Merck).

3.1.2 Reagents

Silicagel,60-120 mesh(Qualigens), 2-Chloroquinoxaline (Aldrich), Imidazole(Merck) , Tryptamine (Aldrich), Pyrimidine Aldrich), Thiosemicarbazide(Merck),Sulphacetamide(Rankem),Pyridine (Rankem),Phenylhydrazine (Qualigens).

3.1.3 Equipment used

Shimadzu UV-1601 UV-VIS Recording Spectrophotometer operating in both spectral and kinetic modes. Spectrophotometer was coupled to a PC which allowed absorbance measurement vs. time each 20 second and the multi cell holder was thermostatted to temperature $\pm 0.1^0$C using a 240 A-Shimdzu themostat. NEXUS FT-IR, BRUKER NMR, PERKIN-ELMERGC-MS CLARUS 500, PERFIT M.P. Apparatus, SAMSUNGMicrowave Oven M 197 DL.

Chapter 4
EXPERIMENTAL

4. EXPERIMENTAL

4.1 Synthesis of 1-(Quinoxalin-2-yl)thiosemicarbazide under Microwave irradiation.

2-Chloroquinoxaline (1mmol/100mg) and thiosemicarbazide (1mmol/56mg) were dissolved in methanol to obtain a homogeneous solution, and 2-3 drops of pyridine was added. The resultant mixture was irradiated in a microwave oven at 300W for 10 minutes. The progress of the reaction was monitored using TLC. After completion of the reaction the solvent was distilled off and the product was obtained with 90% yields (119mg). However, when the reaction was carried out at room temperature by condensation of 2-Chloroquinoxaline and thiosemicarbazide and the condensed product was purified by column chromatography over silicagel gave the condensed product **29** with 30% yields (40 mg). The m.p. was found to be 160^0C which is different from 2-chloroquinoxaline (35^0C) and thiosemicabazide (120^0C). U.V. spectrum of the product showed λ_{max} at 347 nm whereas 2-Chloroquinoxaline showed λ_{max} at 319.50 nm and thiosemicabazide at 240.50 nm (Scheme 1.5). ^{1}HNMR (500MHz;DMSO-d_6) (Fig.4.1) showed signals at δ 9.12 (s,1H,Ar) ; 8.49-8.47(d,2H,Ar); 8.04-8.03 (d,2H,Ar);7.79 -7.68 (m,bs,4H,NH). GC-MS of **29** (Fig.4.2) showed M^+ ion peak at m/z (218) . IR spectrum of **29** (Fig.4.3) showed absorption bands at 3408 (NH); 3282&3178 (NH_2), 1617, 1569&1526(Ar), 1656(C=S) cm^{-1}. Spectral data of **29** are in agreement with the structure assigned to it.

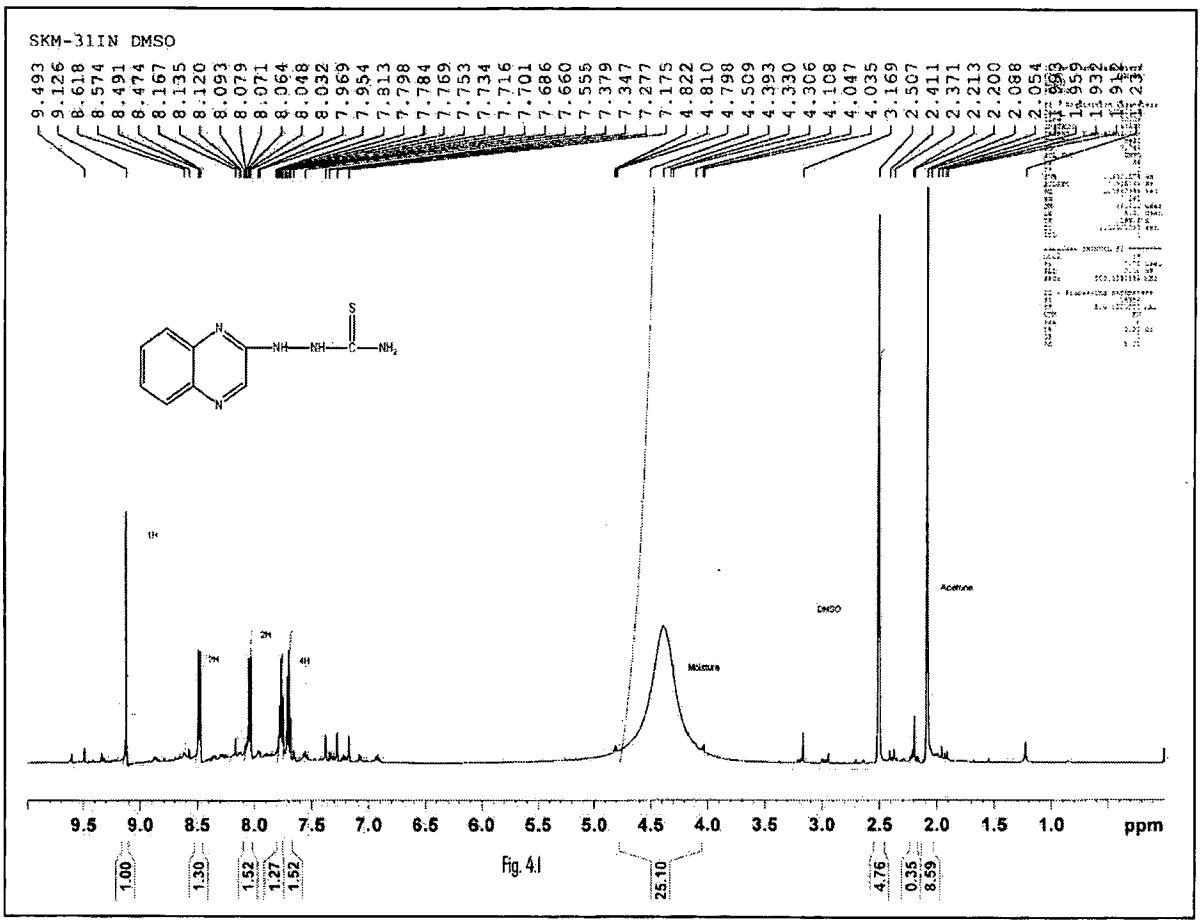


Fig. 4.1

Fig.4.1- ^{1}HNMR Spectrum of 1-(Quinoxalin-2-yl)thiosemicarbazide.

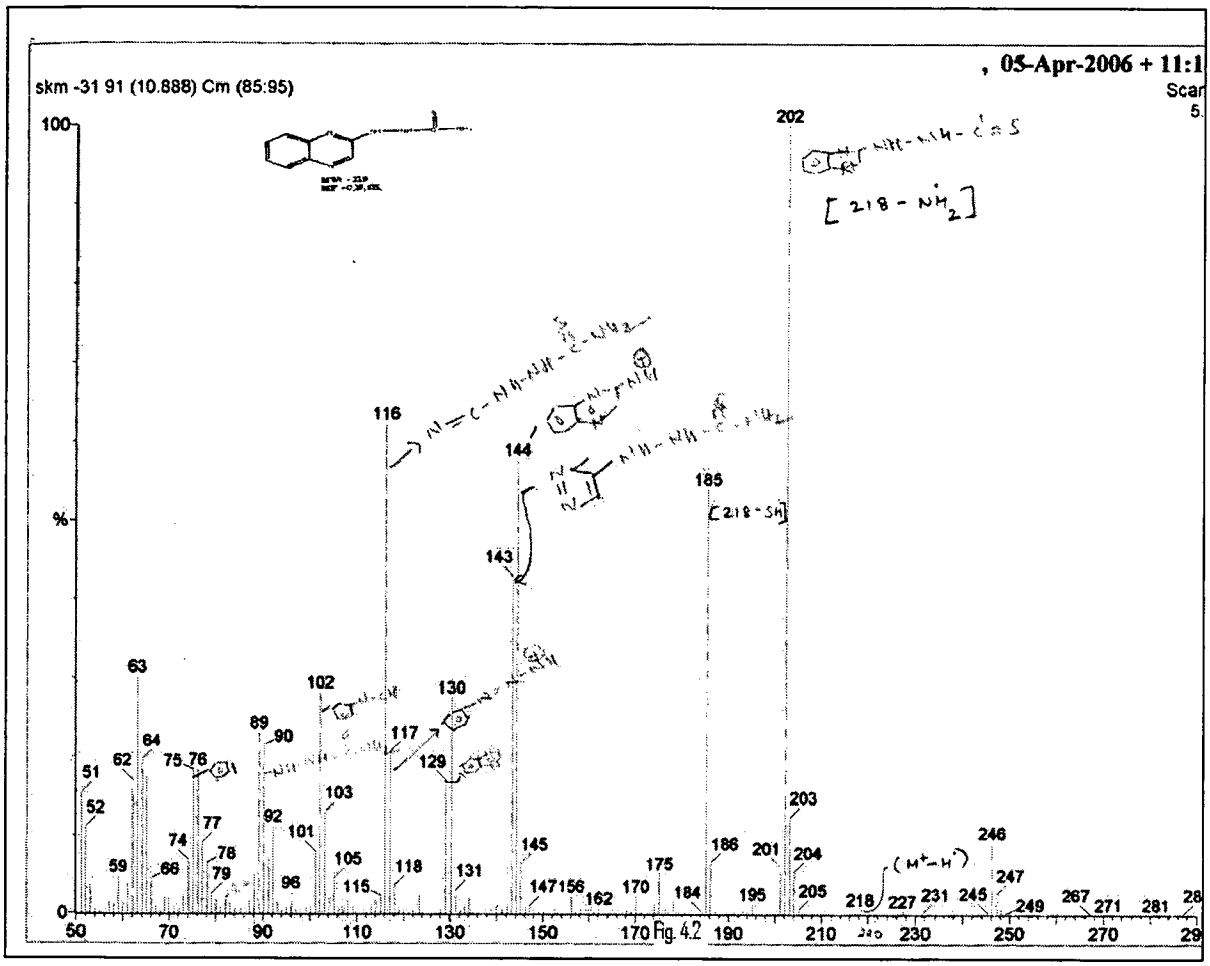


Fig. 4.2- GC-MS Spectrum of 1-(Quinoxalin-2-yl)thiosemicarbazide .

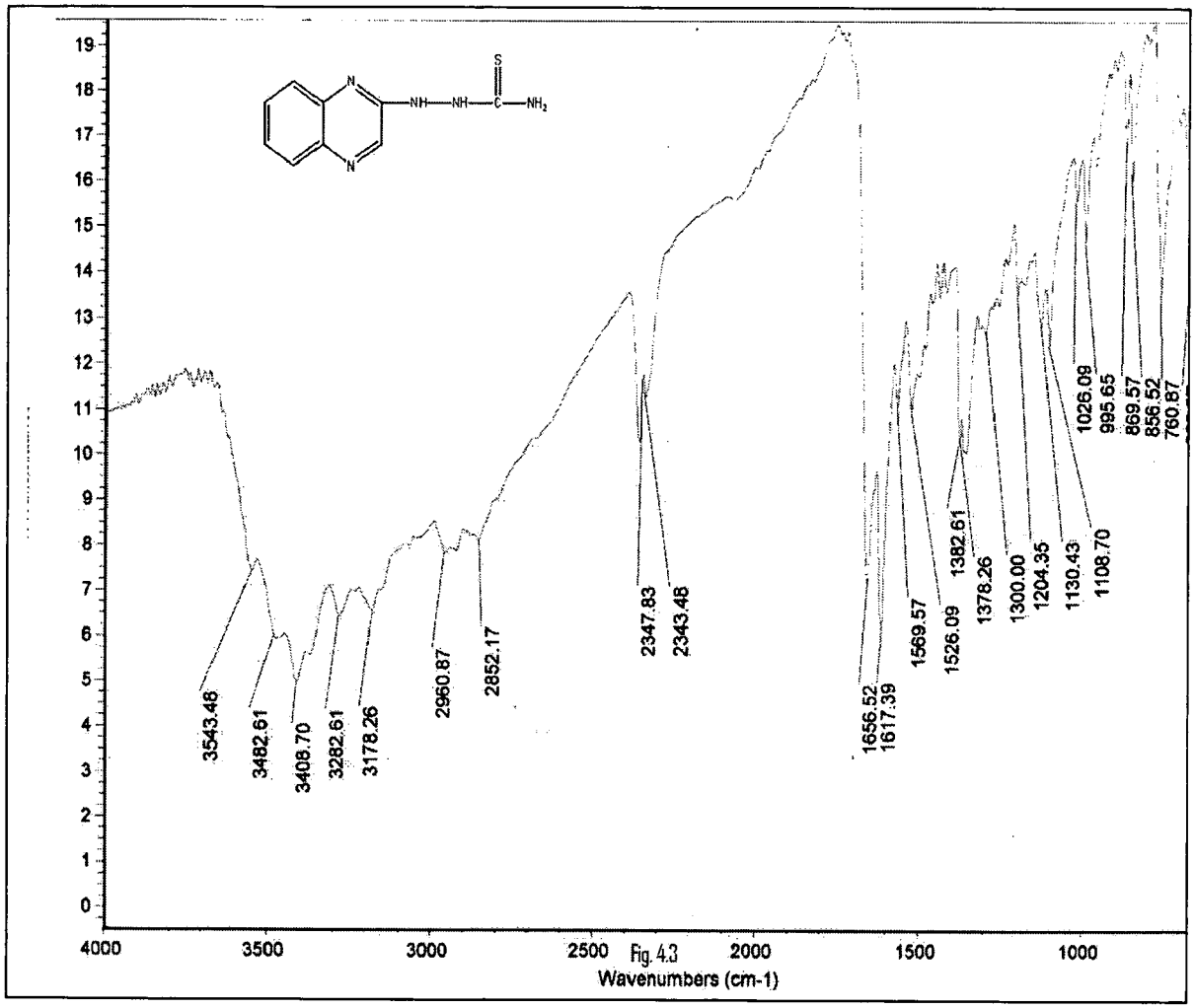
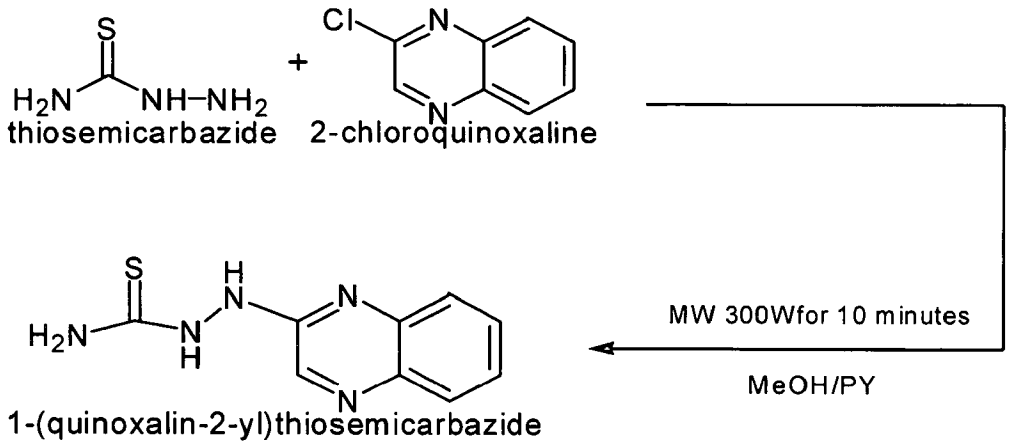


Fig. 4.3

Fig. 4.3- IR Spectrum of 1-(Quinoxalin-2-yl)thiosemicarbazide .



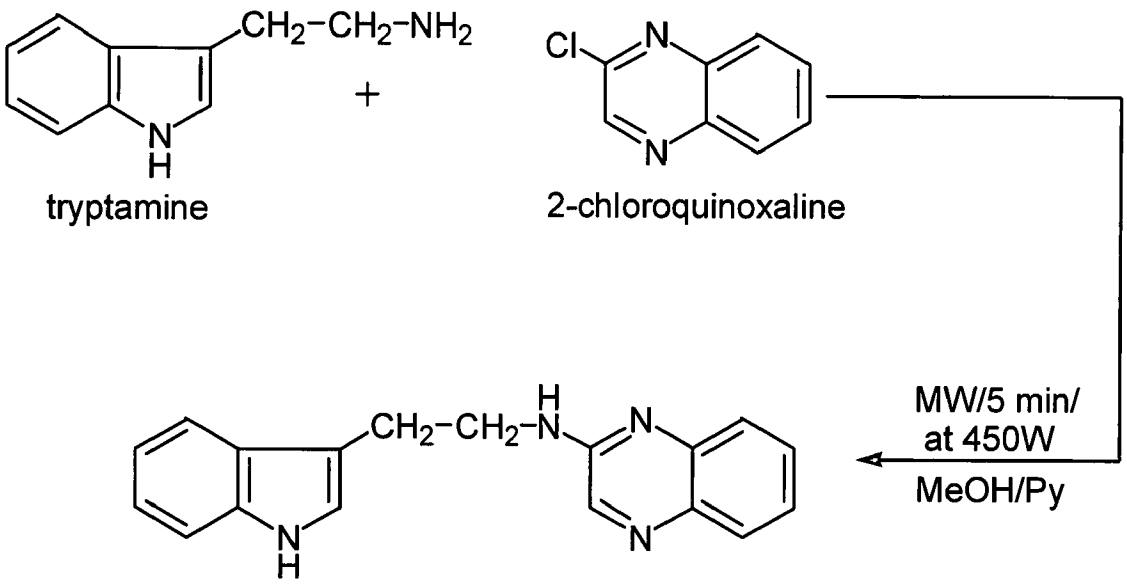
29

Scheme 1.5

4.2 Synthesis of N-[2-(1H-indol-3-yl)ethyl]quinoxalin-2-amine under microwave irradiation.

Equimolar amounts of 2-chloroquinoxaline (200 mg/1mmol) and tryptamine (123mg/1mmol) were dissolved in methanol to obtain a homogeneous solution. Then 2-3 drops of pyridine was added and the resultant mixture was irradiated with microwave at 450W for 5 minutes. The progress of the reaction was monitored using TLC. After completion of the reaction the solvent was distilled off and the product was obtained with 92% yields (320mg). However when the reaction was carried out at room temperature by condensation of 2-chloroquinoxaline and tryptamine and the condensed product was purified by column chromatography over silicagel gave the condensed product **30** with 25% yields (87 mg) (Scheme 1.6). ^{1}HNMR (500MHz;DMSO-d_6) (Fig.4.4) showed signals at δ 10.98 (s,2H,NH) ;7.57-7.55(d,2H,Ar); 7.38-7.36 (d,2H,Ar);7.23

(S,2H,Ar) 7.11-7.08(t,2H,Ar) 7.02-6.99(t,2H,Ar) 3.05-3.04(t,2H,CH_2) 3.01-3.00(t,2H,CH_2). IR spectrum of **30** (Fig 4.5) showed absorption bands at 3290 (NH); 3026 (Ar C-H) 1596, 1501(Ar), 1452(C=N) cm^{-1}. Spectral data of **30** are in agreement with the structure assigned to it.



N-(2-(1H-indol-3-yl)ethyl)quinoxalin-2-amine

Yields(92%)

30

Scheme 1.6

4.3 Synthesis of N-[4-(quinoxalin-2-ylamino)phenylsulphonyl]acetamide under microwave irradiation.

Equimolar amounts of 2-chloroquinoxaline (200mg/1mmol) and sulphacetamide (260mg/1 mmol) were dissolved in methanol and then 2-3 drops of pyridine was added. The resultant mixture was

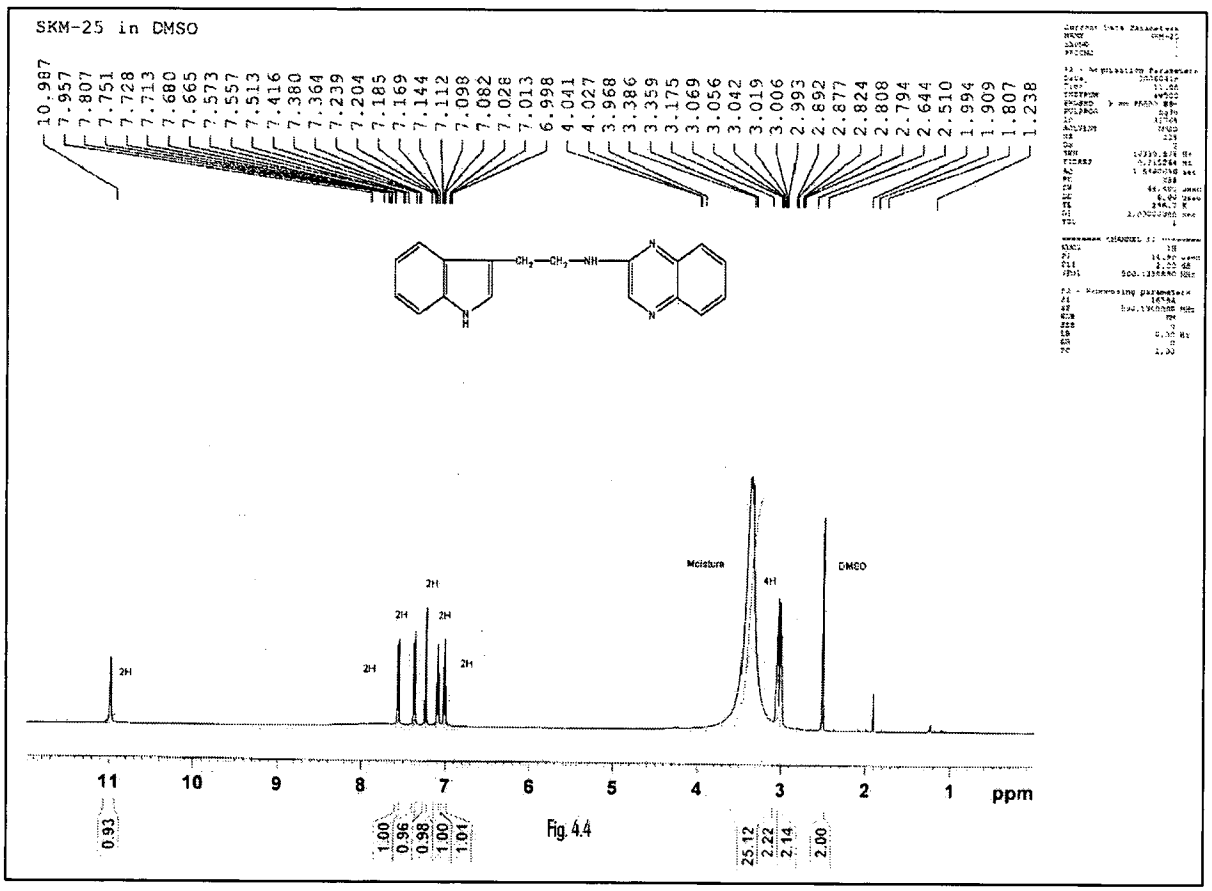


Fig. 4.4

Fig. 4.4- ^{1}HNMR Spectrum of N-[2-(1H-indol-3-yl)ethyl]quinoxalin-2- amine.

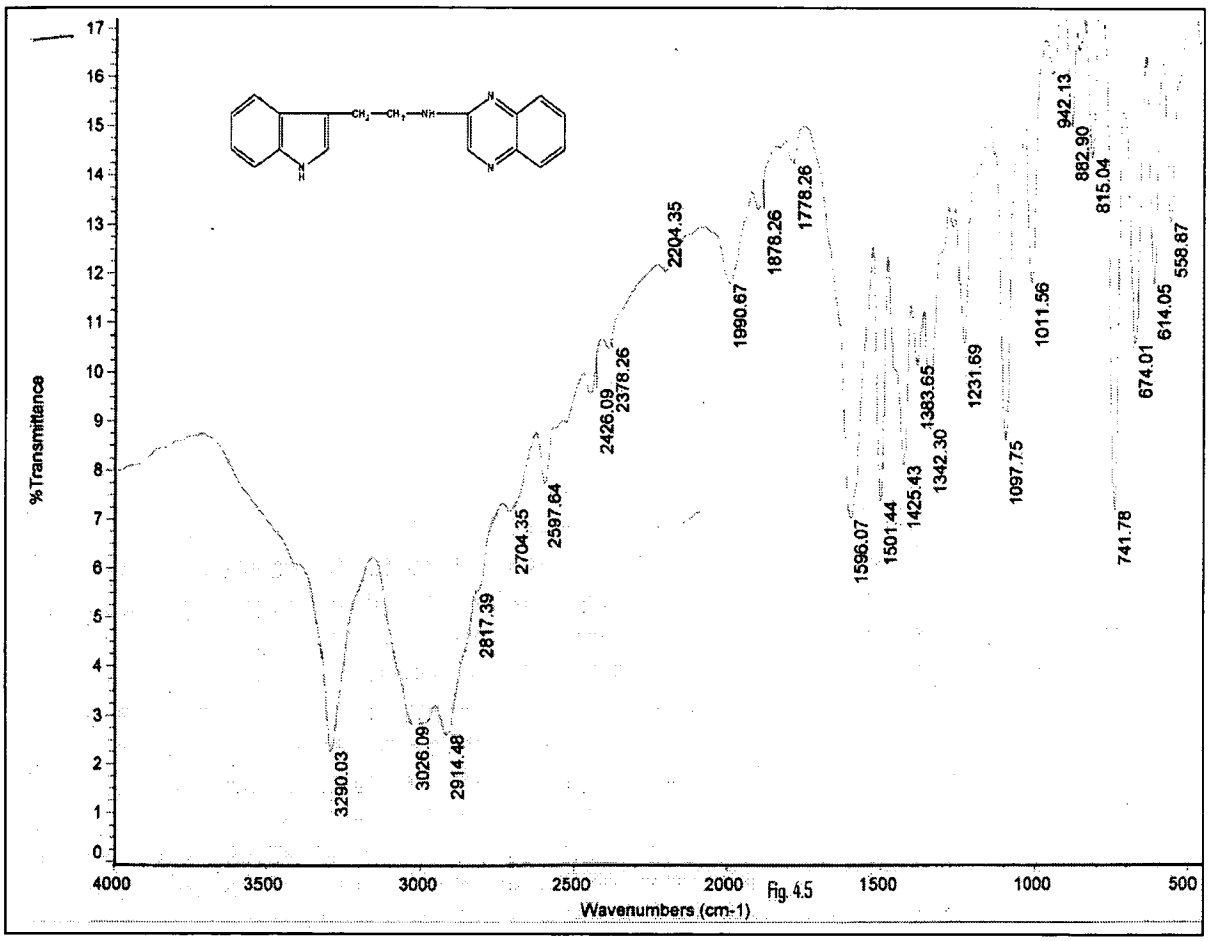
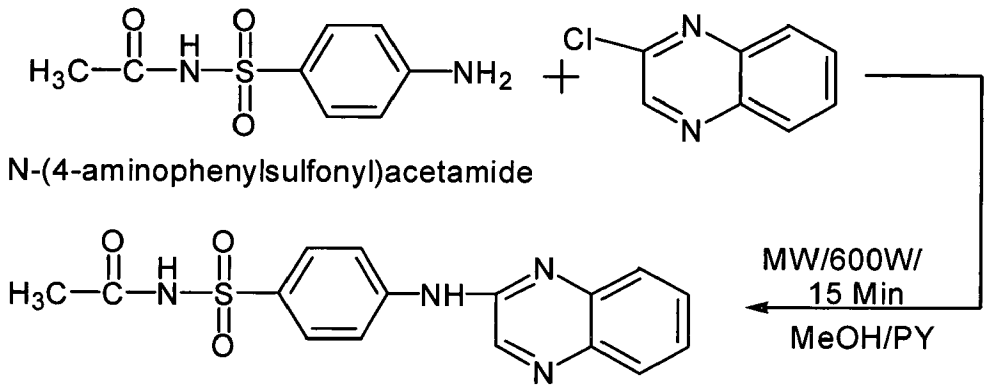


Fig. 4.5

Fig. 4.5- IR Spectrum of N-[2-(1H-indol-3-yl)ethyl]quinoxalin-2- amine.

then irradiated with microwave at 600W for 12 minutes and the progress of the reaction was monitored using TLC. After completion of reaction the solvent was distilled off and the product was recovered with 60% yields (247mg). The m.p. of the product was found to be (180^0C) which is different from 2-chloroquinoxaline (35^0C) and sulphacetamide (150^0C) (Scheme 1.7) ^{1}HNMR(500MHz;DMSO-d_6) (Fig.4.6) showed signals at δ 11.62 (s,1H,NH) ; 7.53-7.52(s,3H,Ar); 6.79-6.77 (s,3H,Ar); 6.13-6.05 (s,3H,Ar); 4.01(s,1H,NH); 1.26(s,3H,-$COCH_3$). GC-MS of **31** (Fig. 4.7) showed M^+ ion peak at m/z (341). IR spectrum of **31** (Fig 4.8) showed absorption bands at 3470,3380 (NH_2); 3110 (NH) 1594,1503(Ar), 1686(C=O); cm^{-1}. Spectral data of **31** are in agreement with the structure assigned to it.



N-(4-aminophenylsulfonyl)acetamide

N-(4-(quinoxalin-2-ylamino)phenylsulfonyl)acetamide

Yields(60%)

31

Scheme 1.7

4.4 Synthesis of 2-(1H-imidazo-1-yl)quinoxaline under microwave irradiation.

Equimolar amounts of 2-chloroquinoxaline (200mg/1mmol) and

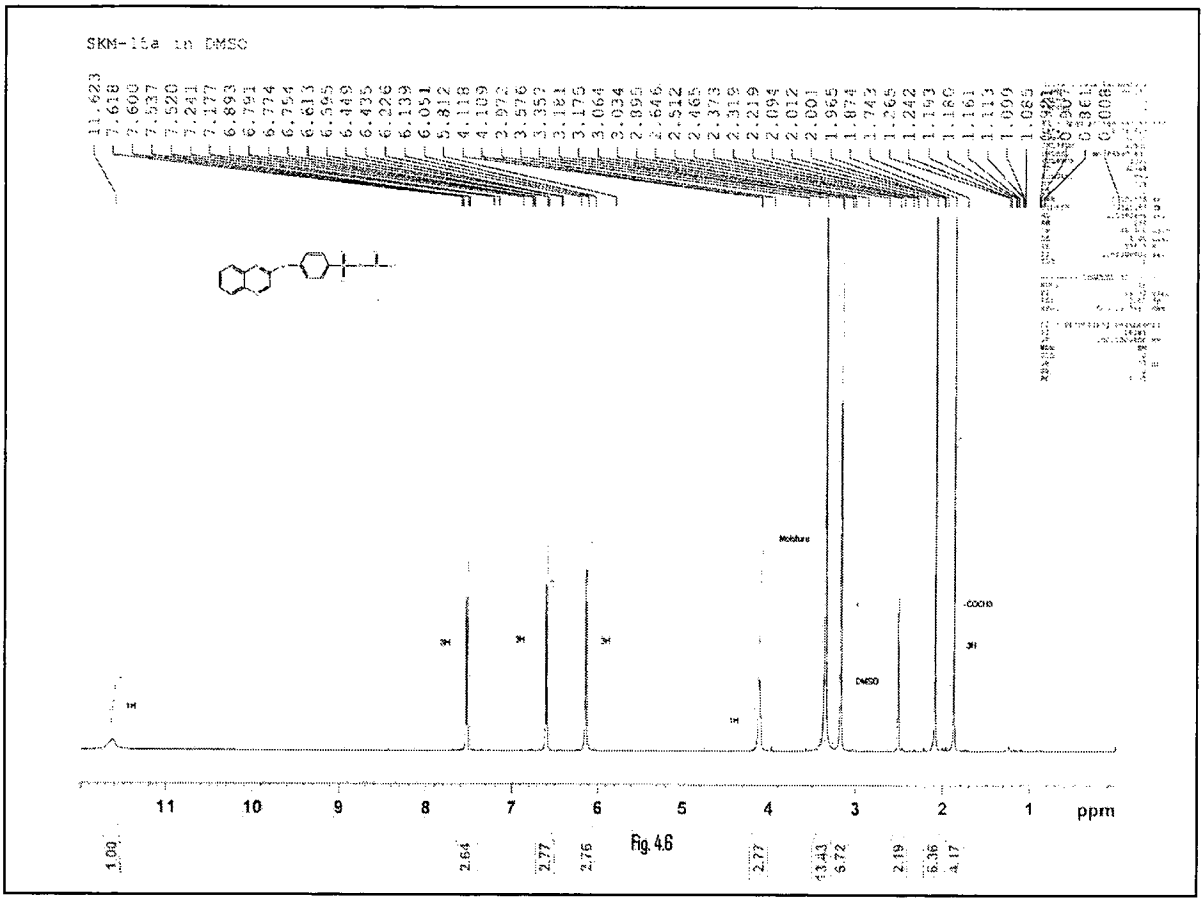


Fig.4.6-^{1}HNMR Spectrum of N-[4-(Quinoxalin-2-ylamino)phenylsulphonyl]acetamide

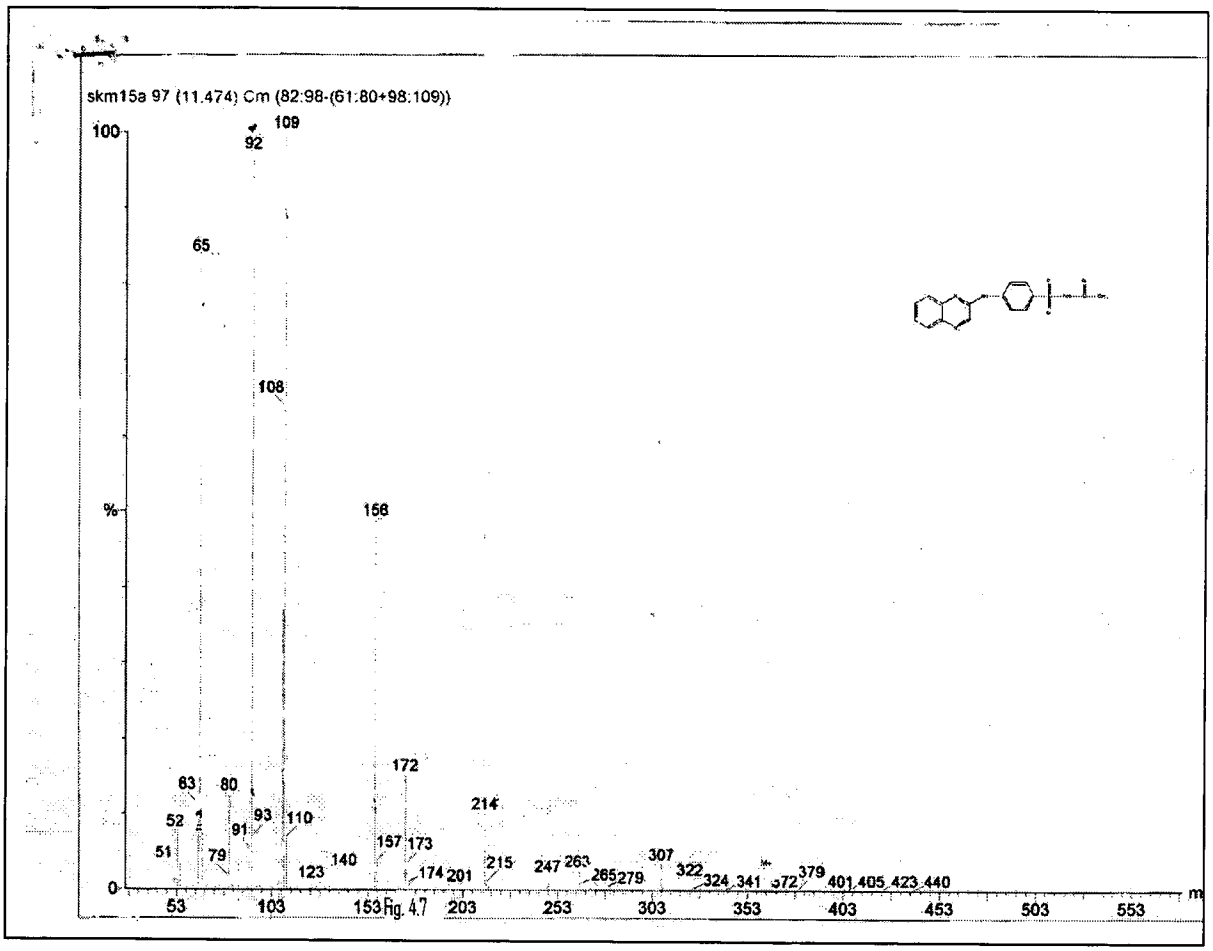


Fig.4.7-GC-MS Spectrum of N-[4-(Quinoxalin-2-yl-amino)phenylsulphonyl]acetamide.

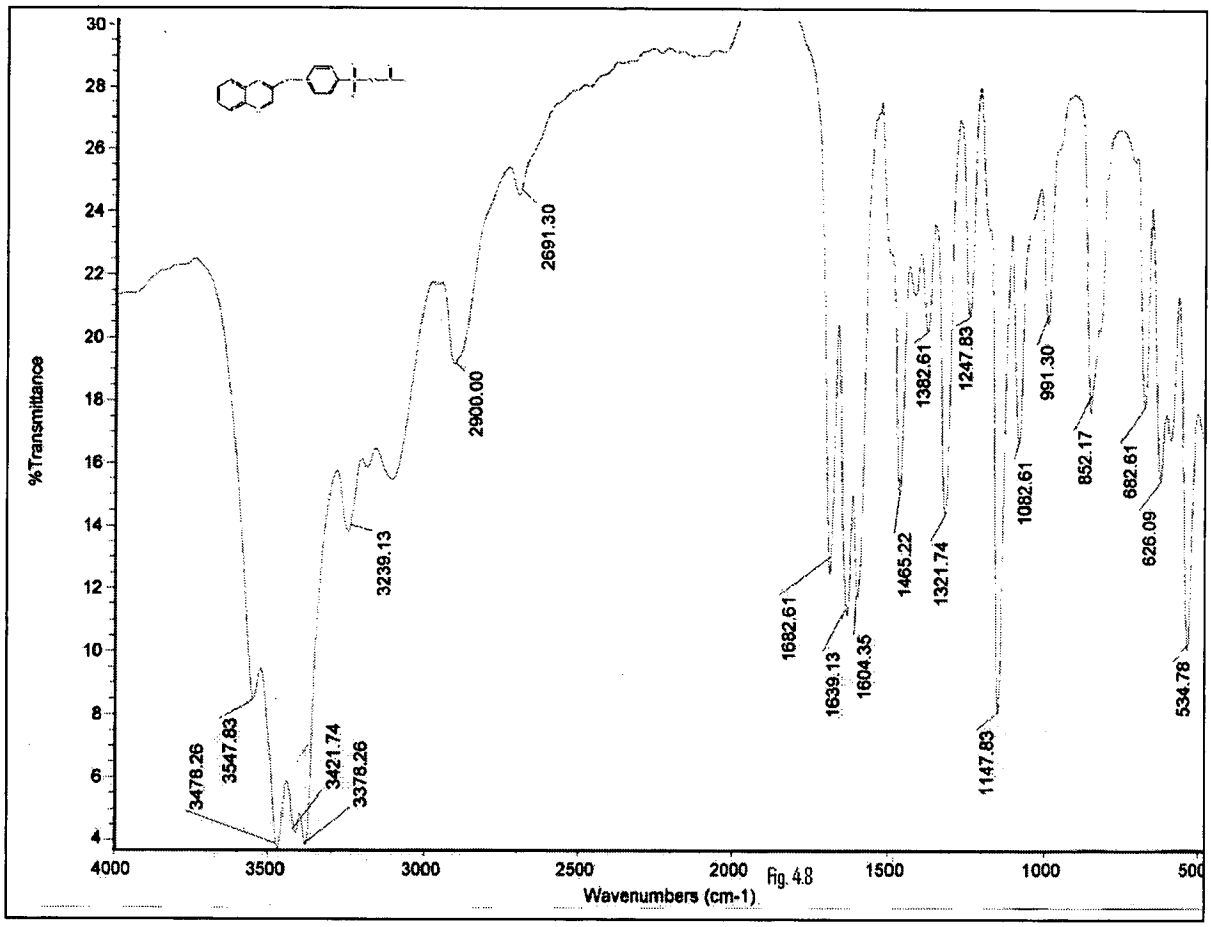
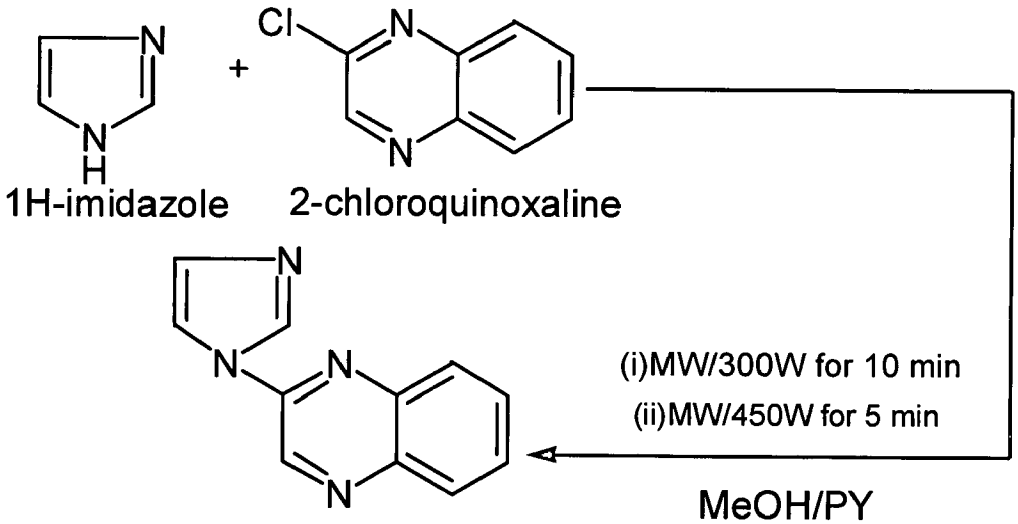


Fig. 4.8

Fig.4.8- IR Spectrum of N-[4-(Quinoxalin-2-yl-amino)phenylsulphonyl]acetamide.

imidazole (83mg/1mmol) were dissolved in methanol and then 2-3 drops of pyridine was added and the resultant mixture was irradiated in a microwave oven at 300W for 10 minutes. It was again irradiated at 450W for another 5 minutes,. The progress of the reaction was monitored using TLC. After completion of the reaction, the solvent was distilled off and the product was isolated with 87% yields (200mg). (Scheme 1.8) ^{1}HNMR(500MHz;DMSO-d_6) (Fig. 4.9) showed signals at δ 9.73 (s,1H,AR) ; 8.84(s,1H,Ar); 8.21 (s,1H,Ar);8.17-8.15 (d,1H,Ar); 8.08-8.06 (d,1H,Ar); 7.94-7.92 (t,1H,Ar) ;7.91-7.86 (t,1H,Ar); 7.25(S,1H,Ar). IR spectrum of **32** (Fig.4.10) showed absorption bands at 1622,1570,1495(Ar), 1429(C=N), 3052(Ar C-H) cm^{-1}. Spectral data of **32** are in agreement with the structure assigned to it.



2-(1H-imidazol-1-yl)quinoxaline
yields (87%)

32

Scheme 1.8

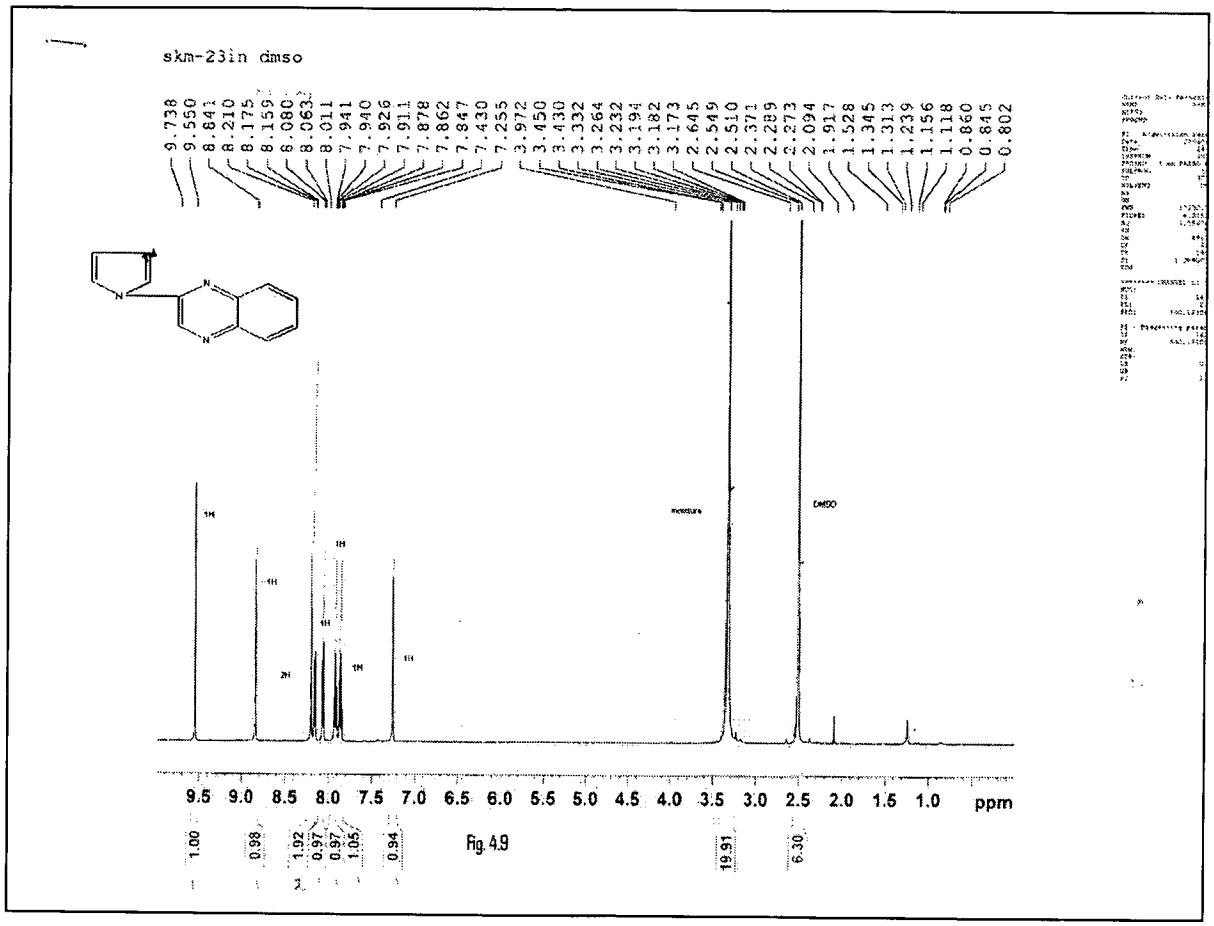


Fig. 4.9- ^{1}HNMR Spectrum of 2-(1H-imidazo-1-yl)quinoxaline .

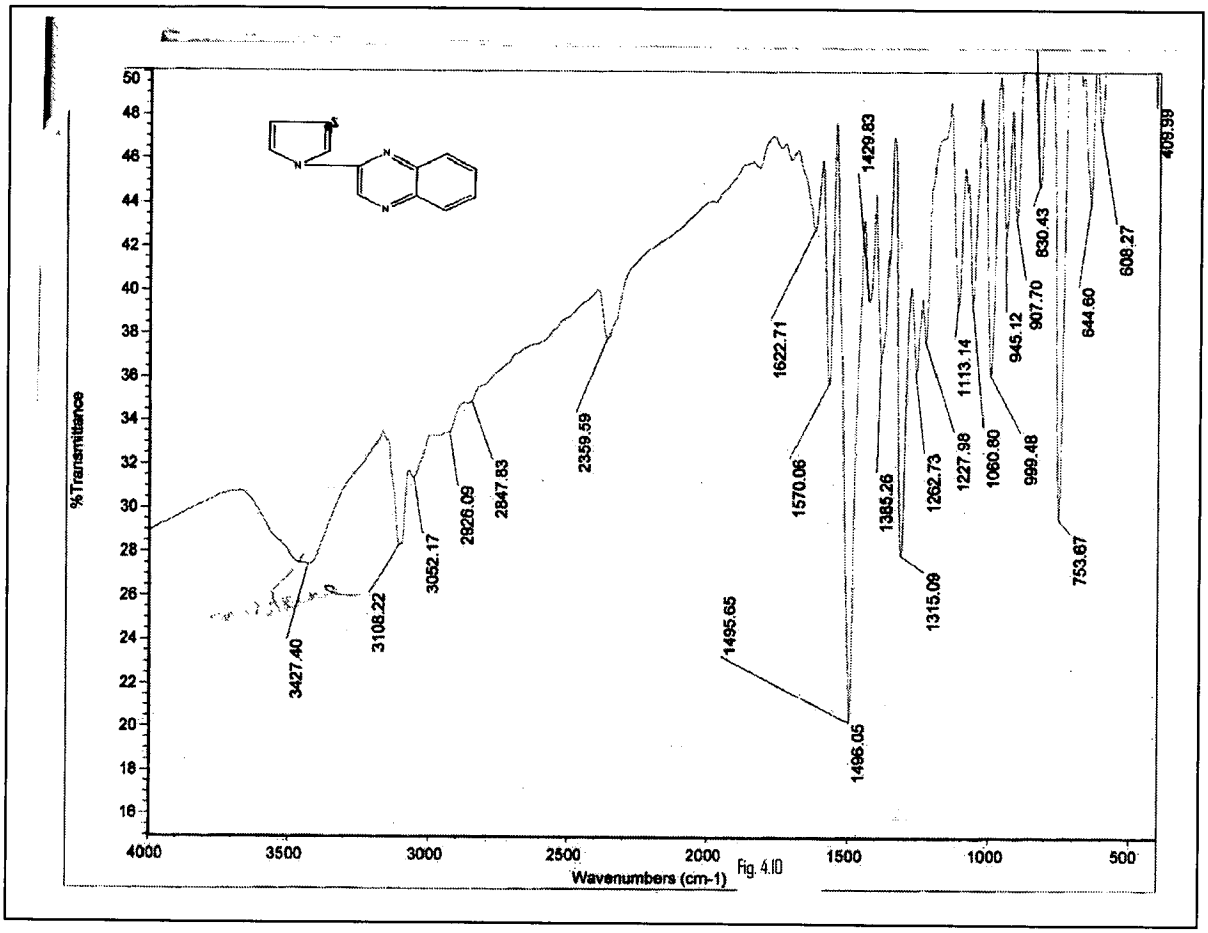
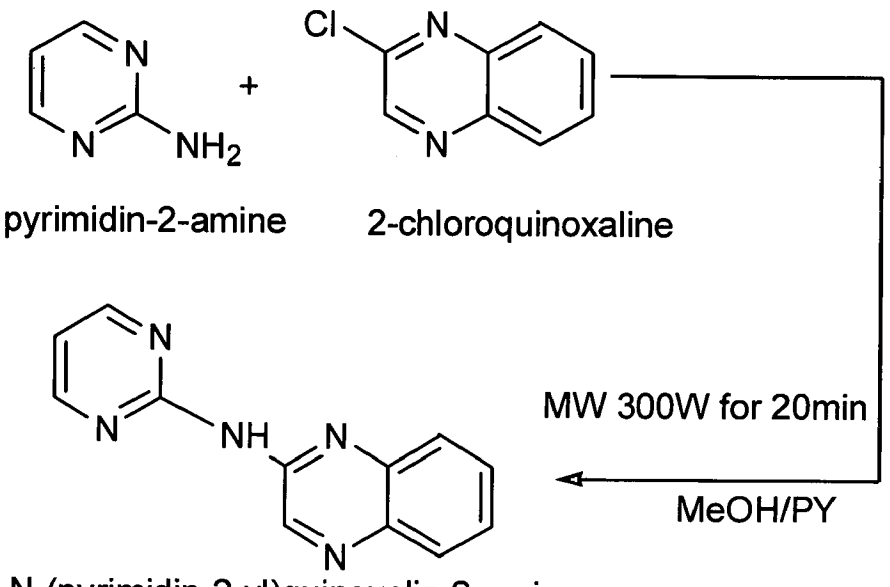


Fig. 4.10- IR Spectrum of 2-(1H-imidazo-1-yl)quinoxaline .

4.5 Synthesis of N-(Pyrimidine-2-yl)quinoxalin-2-amine under microwave irradiation.

Equimolar amounts of 2-chloroquinoxaline (200mg/1mmol) and pyrimidine (116mg/1mmol) were dissolved in methanol and then 2-3 drops of pyridine was added. The resultant mixture was irradiated in a microwave oven at 300W for 10 minutes and the progress of the reaction was monitored using TLC. After completion of the reaction the solvent was distilled off and the product was isolated with 89% yields (239mg) (Scheme 1.9). ^{1}HNMR(500MHz;DMSO-d_6) (Fig.4.11) showed signals at δ 11.80 (s,1H,NH) ; 7.91-7.91-7.90 (d,2H,Ar); 7.55 (s,3H,Ar);7.08 (s,1H,Ar); 6.89(s,1H,Ar);6.36(s,1H,Ar) ; GC-MS of **33** (Fig.4.12) showed M^+ ion peak at m/z (223). IR spectrum of **33** (Fig.4.13) showed absorption bands at 3170(NH); 3065 (Ar C-H); 1647, 1560, 1497 (Ar) cm^{-1}. Spectral data of **33** are in agreement with the structure assigned to it



pyrimidin-2-amine 2-chloroquinoxaline

N-(pyrimidin-2-yl)quinoxalin-2-amine

Yields(89%)

33

Scheme1.9

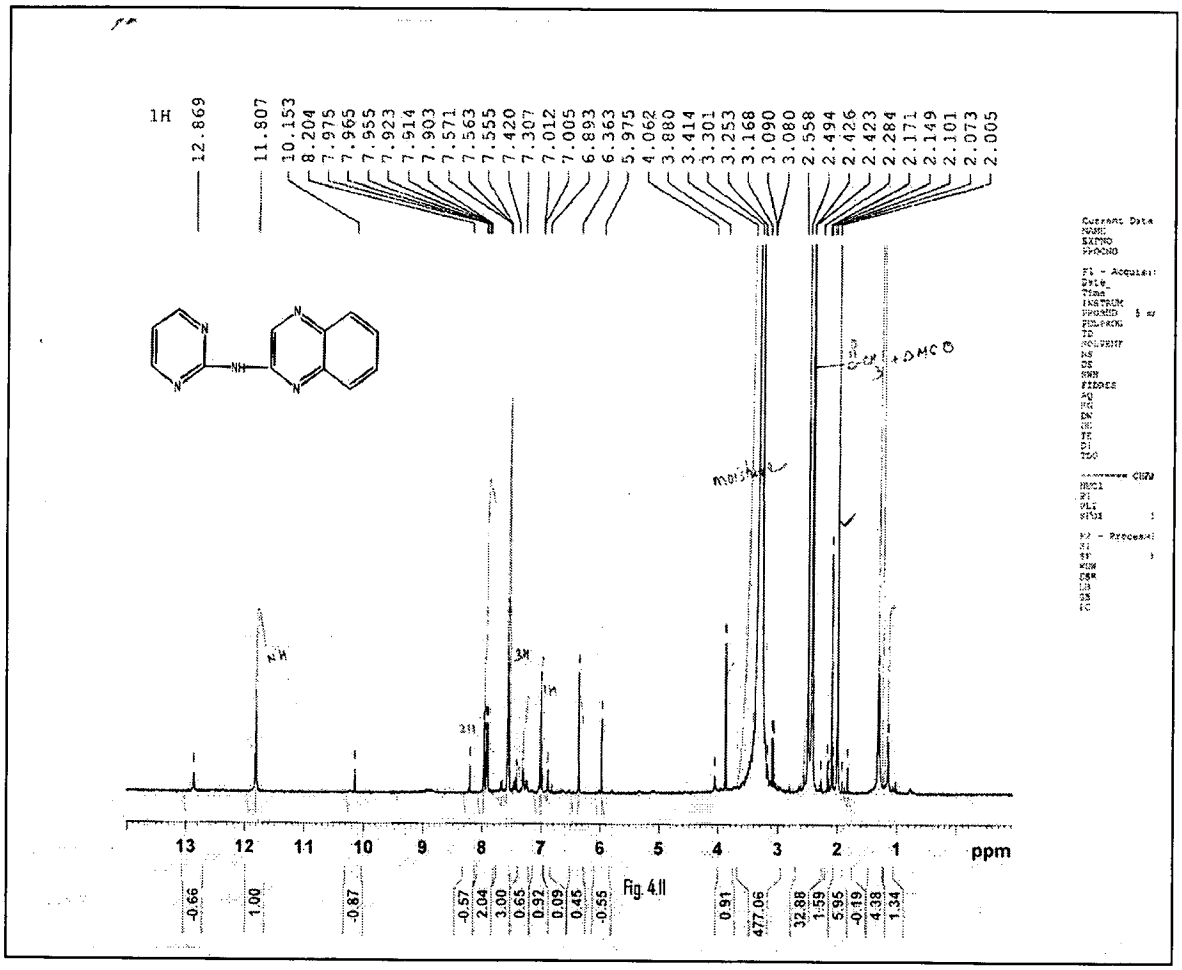


Fig. 4.11

Fig. 4.11- ^{1}HNMR Spectrum of N-(Pyrimidine-2-yl)quinoxalin-2-amine.

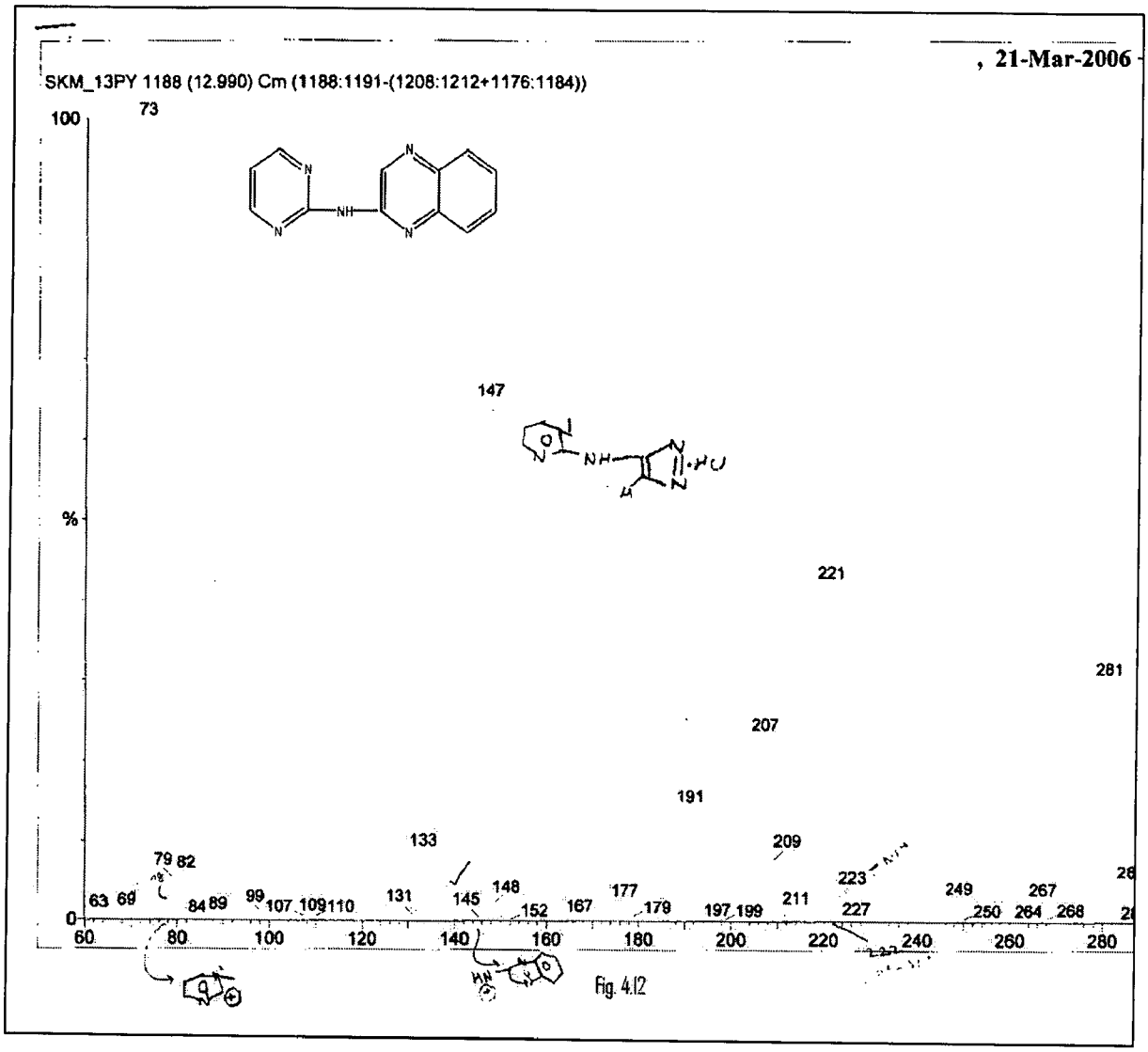


Fig. 4.12- GC-MS Spectrum of N-(Pyrimidine-2-yl)quinoxalin-2-amine.

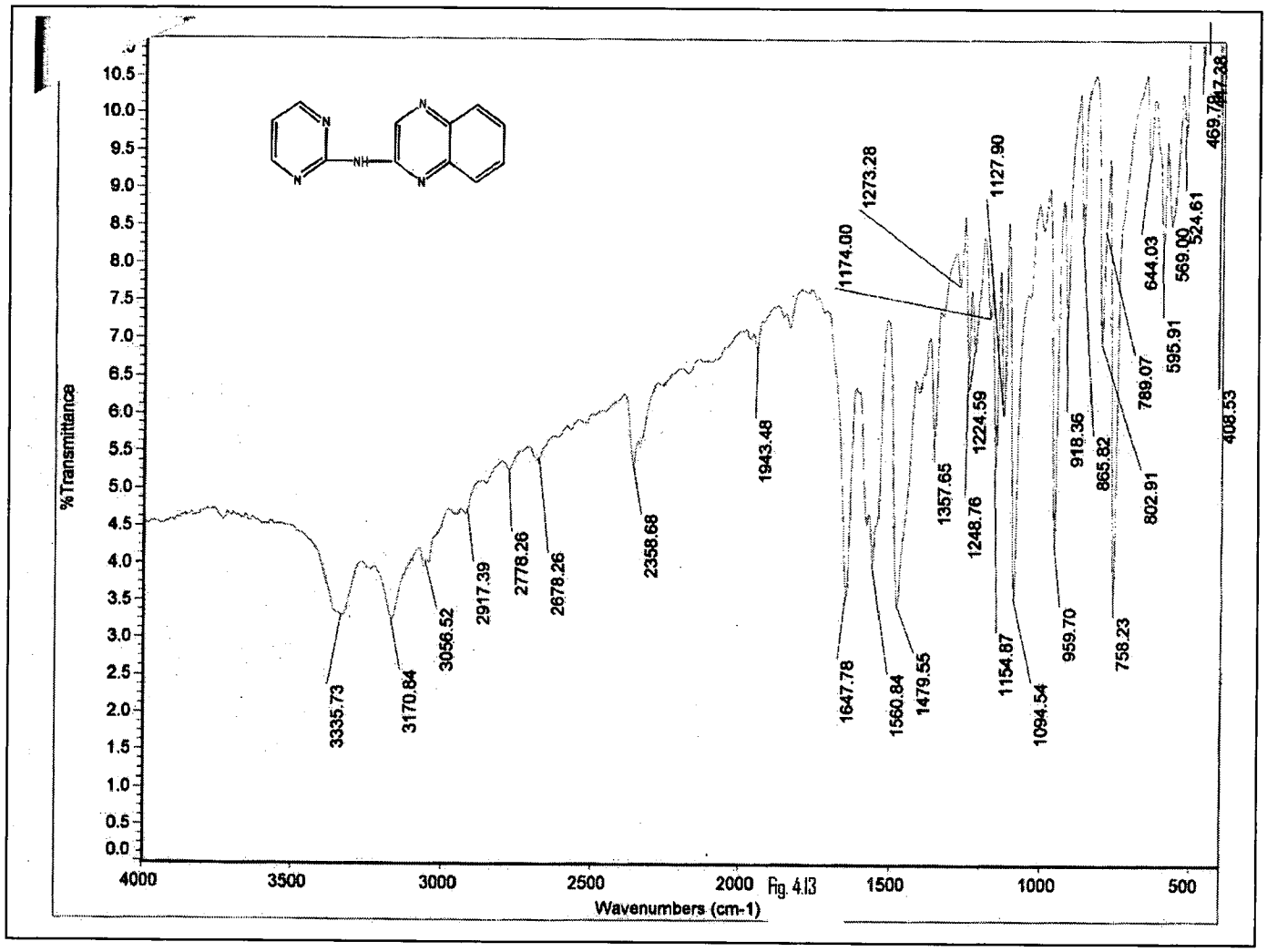


Fig. 4.13- IR Spectrum of N-(Pyrimidine-2-yl)quinoxalin-2-amine.

Chapter 5
KINETICS

5. Kinetics

5.1 Preparation of solutions

Stock solutions of the substrates, nucleophiles were prepared in appropriate solvents and diluted to obtain the desired concentration for the kinetics runs.

5.2 Kinetic procedure

To start a kinetic run, 1 ml stock solution of the substrate was mixed with 9 ml of solution of nucleophile of appropriate concentration for the aminolysis reaction under pseudo-first order conditions. The reaction was followed at the λ_{max} of the product. For example the reaction of 2-chloroquinoxaline with phenylhydrazine followed at 390 nm. The λ_{max} of the product and its observance at an infinity reaction time were constant with the corresponding authentic sample within ± 3-5%. A typical kinetic run for aminolysis of 2-Chloroquinoxaline in MeOH at 26^0C is described below.

Stock solution of 2-Chloroquinoxaline (1.5×10^{-4} mol dm^{-3}) and phenylhydrazine (30×10^{-4} mol dm^{-3}) in MeOH were prepared. 1 ml of the substrate solution was mixed with 9 ml of the nucleophile solution. About 2.7 ml of this reaction mixture was taken in a thermostatted quartz cuvette fitted with cap in the cell compartment of the Spectrophotometer. Thus in the reaction mixture the initial concentration of the substrate was 1.5×10^{-5} mol dm^{-3} and that of phenylhydrazine was 27×10^{-4} mol dm^{-3}. The absorbance of the reaction mixture was recorded at 390 nm after 10 minutes interval up to a period of 3 half lives.

5.3 Treatment of kinetic data

Since all the reactions have been studied under pseudo first order Conditions these obeyed the first order kinetic equation 2.1.

$$k_0 t = 2.303 \log \frac{a}{a-x} \qquad (2.1)$$

Where a is the initial concentration of the substrate, x is the Concentration of the product after time t and k_0 is the pseudo first Order rate constant; a and a-x were determined in terms of Absorbance as $A_\infty - A_0$ and $A_\infty - A_t$ where A_∞, A_t *and* A_0 are the Absorbances at ∞ , t and 0 time respectively. The equation can be Simplified to equation 2.2.

$$\log(A_\infty - A_t) = -\frac{k_0 t}{2.303} + \log(A_\infty - A_0) \qquad (2.2)$$

and k_0 was calculated numerically in EXCEL from linear plot $1 + \log(A_\infty - A_t)$ versus time and the specific second order rate constant k_A, was obtained by dividing k_o by the nucleophile concentration [S]. Duplicate kinetic runs with correlation coefficient of R>0.997 were accepted. Computation for a typical run is shown in Table 5.1 and the fitted plot is shown in Figure 5.1 for the reaction of 2-Chloroquinoxaline with phenylhydrazine in MeOH at 26^0C.

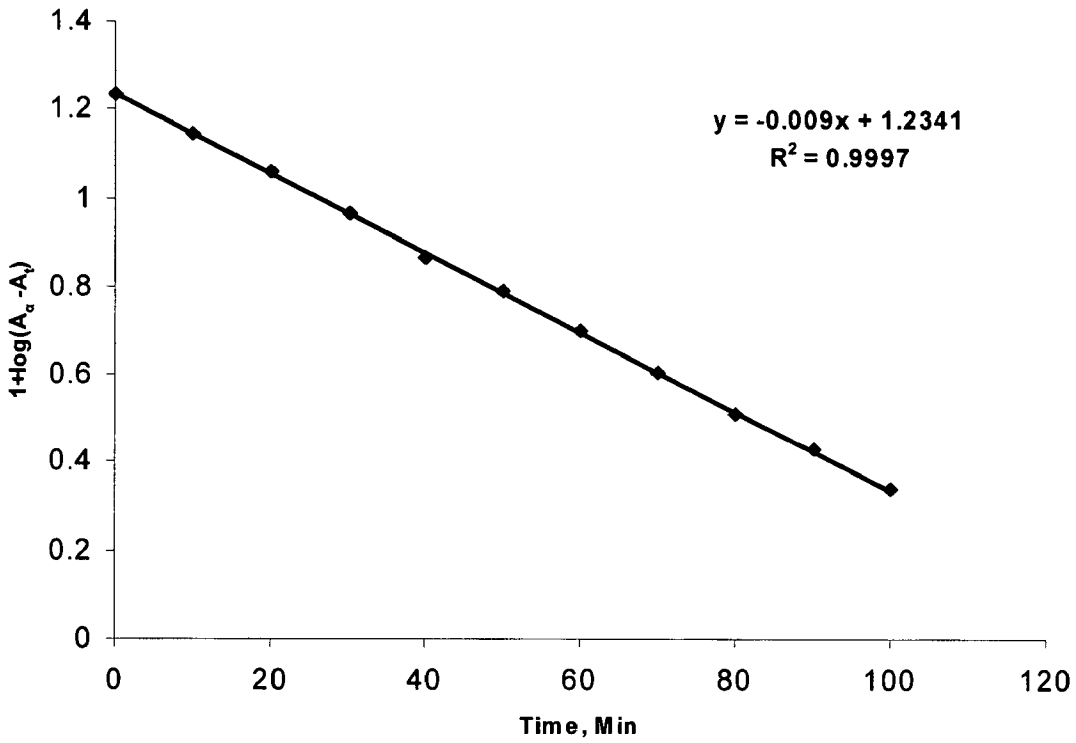


Fig. 5.1:- Plot of $1+\log(A_\alpha - A_t)$ vs. time for the reaction of 2-chloroquinoxaline with phenylhydrazine in MeOH at 26^0C.

Table 5.1:- Computation of a representative kinetic run.
[2-chloroquinoxaline] = 0.00015 mol/dm^3, [phenylhydrazine]= 0.0027 mol/dm^3,Solvent = MeOH, Temperature = 26^0C $A_\infty = 1.863$

Time (min) ,	Abs	$A_\infty - A_t$	$1+\log(A_\infty - A_t)$
0	0.143	1.72	1.236
10	0.47	1.39	1.143
20	0.713	1.15	1.060
30	0.943	0.920	0.963
40	1.127	0.736	0.867
50	1.247	0.616	0.790
60	1.36	0.503	0.702
70	1.46	0.403	0.605
80	1.54	0.323	0.509
90	1.59	0.240	0.43
100	1.64	0.220	0.342

Slope = - 0.009

Intercept =1.2341

R^2 Value = 0.9997

$k_0 = 0.0207 \min^{-1}$

$k_A = 7.68\ dm^3 / Min.Mol$

5.4 Reactions of 2-chloroquinoxaline and phenylhydrazine.

Figure 5.2 shows the absorption spectra of a typical kinetic run in methanol. An isosbestic point at 290 nm has been observed. This indicates the formation of a single reaction product and absence of any stable intermediate during the course of the reaction. The Spectrum was taken at five different temperature keeping the concentration constant in MeOH (Figure 5.3).

Table 5.2 shows the k_0 and k_A values for phenylhydrazine at five different concentrations of phenylhydrazine (10-50×10^{-4} mol/dm^3) at 26^0C and also at five different temperatures 25,30,35, 40 and 45^0C, ([phenylhydrazine] = 27×10^{-4} mol/dm^3) in MeOH .

Figure 5.4 shows the plot of k_0 versus [phenylhydrazine] for the reaction of 2-Chloroquinoxaline with phenylhydrazine in MeOH at 26^0C. And Figure 5.5 shows the plot of second order rate constant,k_A values versus [phenylhydrazine] in MeOH at 26^0C .

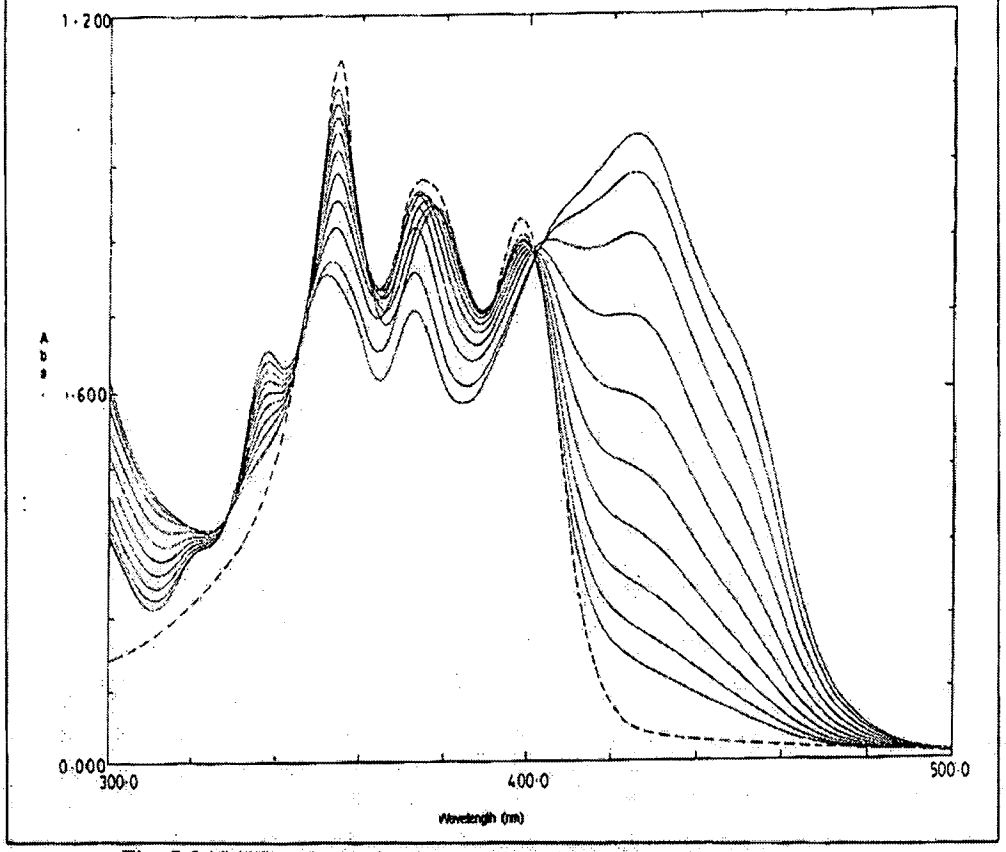
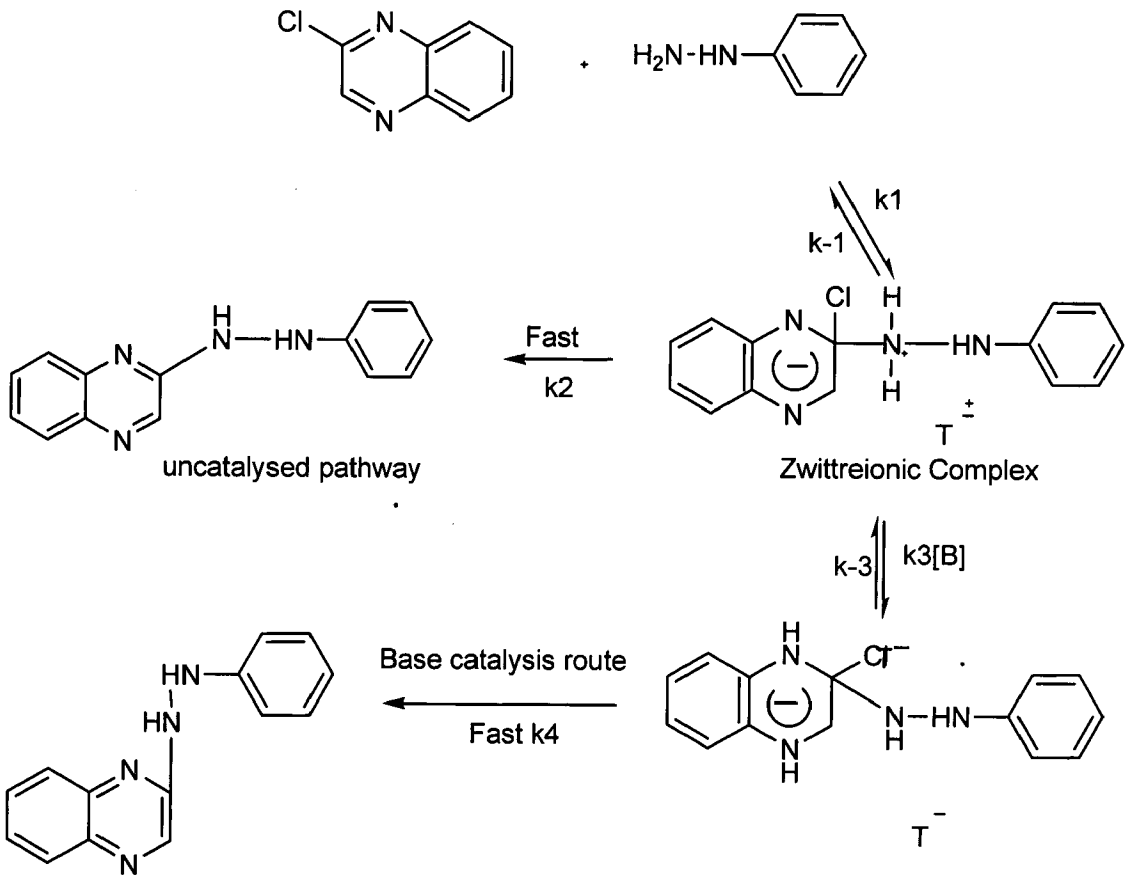


Fig. 5.2 UV-Vis spectra for the reaction of 2-chloroquinoxaline with phenylhydrazine in MeOH at different time intervals.

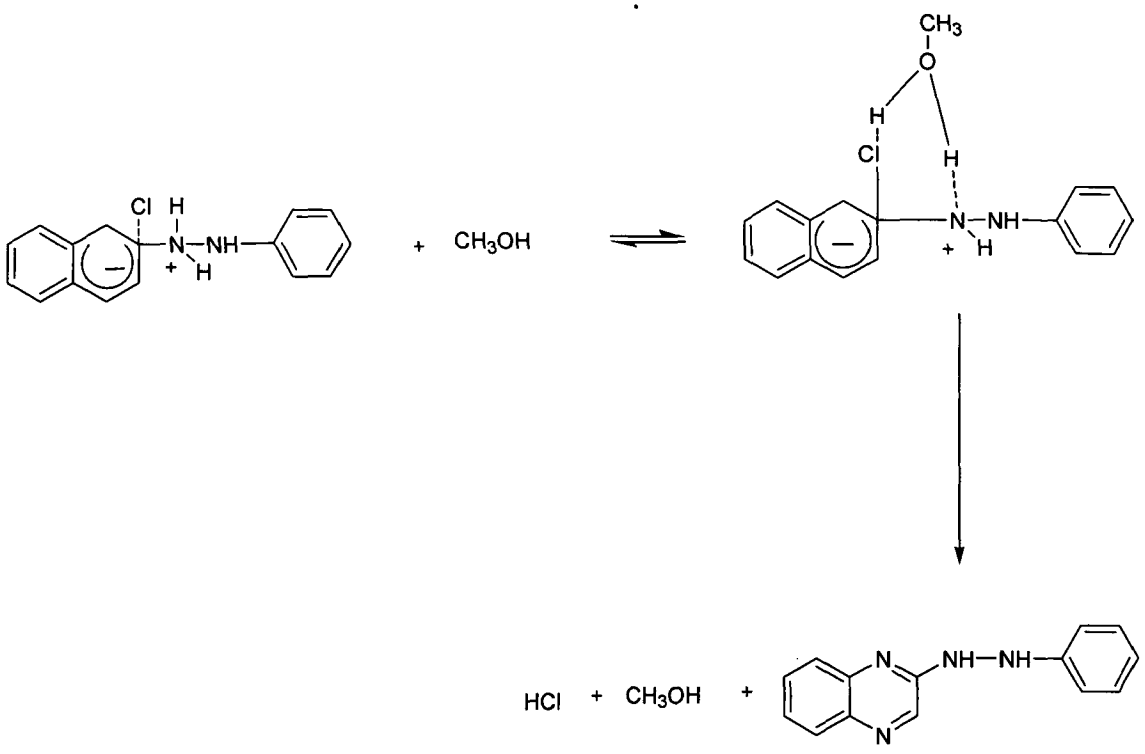
5.5 Concentration effect

In MeOH with increase in the concentration of phenylhydrazine the k_0 also increased. Plots of k_0 vs. [phenylhydrazine] showed linear increase with increase in [phenylhydrazine] .To have more information on the above; k_A was plotted vs. [phenylhydrazine] (Figure 5.5). A linear increase was observed in MeOH. From the above plots, it may concluded that the reaction with phenylhydrazine in MeOH depended upon the concentration of amine. Further the reaction seems to proceed through catalyzed route in MeOH. The mechanistic steps are shown in Scheme 1.10



Scheme 1.10

It seems that MeOH being a hydrogen bond donor solvent, participates in the expulsion of Cl^- from the zwitterionic complex shown in Scheme 1.11.



Scheme 1.11

Table 5.2- Values of pseudo-first order rate constants (k_0) and second order rate constants (k_A) for the reaction of 2-chloroquinoxaline with phenylhydrazine in MeOH. [2-chloroquinoxaline] = 1.5×10^{-4} mol/dm^3 and [phenylhydrazine] = $10\text{-}50\times10^{-4}$ mol/dm^3.

Nu.	$10^{-4}k_0$, min-1,299K (k_A dm^3 mol^{-1} min^{-1})					10^{-4} k_0, min^{-1} (k_A, dm^3 mol^{-1} min^{-1})				
	C1	C2	C3	C4	C5	298K	303K	308K	313K	318K
Phenyl Hydra Zine.	14.2 (2.2)	28.1 (2.3)	40.3 (2.4)	55.8 (2.6)	70.9 (2.8)	40.7 (0.9)	64.2 (1.3)	88.4 (1.8)	112.3 (2.2)	135.8 (2.6)

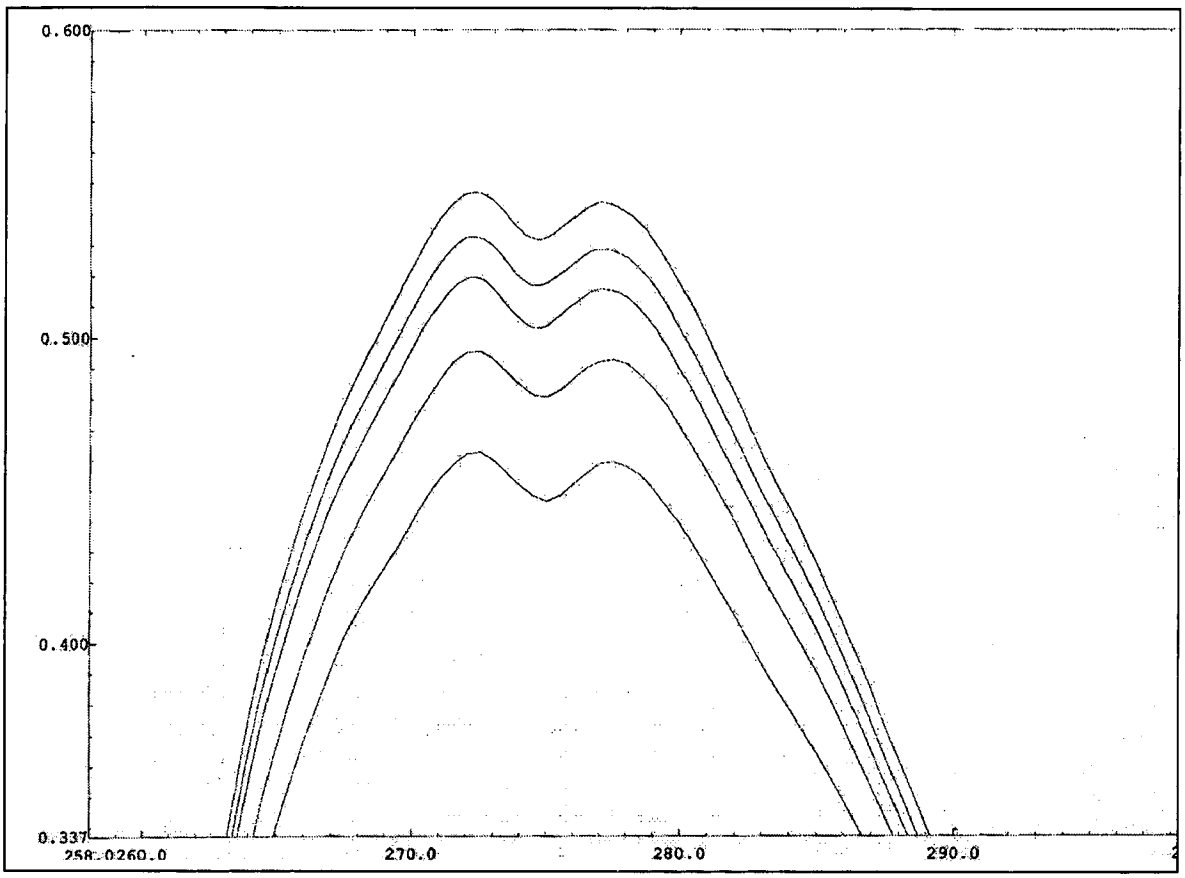


Fig. 5.3- The absorption Spectrum of the reaction of 2-chloroquinoxaline and phenylhydrazine in methanol at five different temperatures .

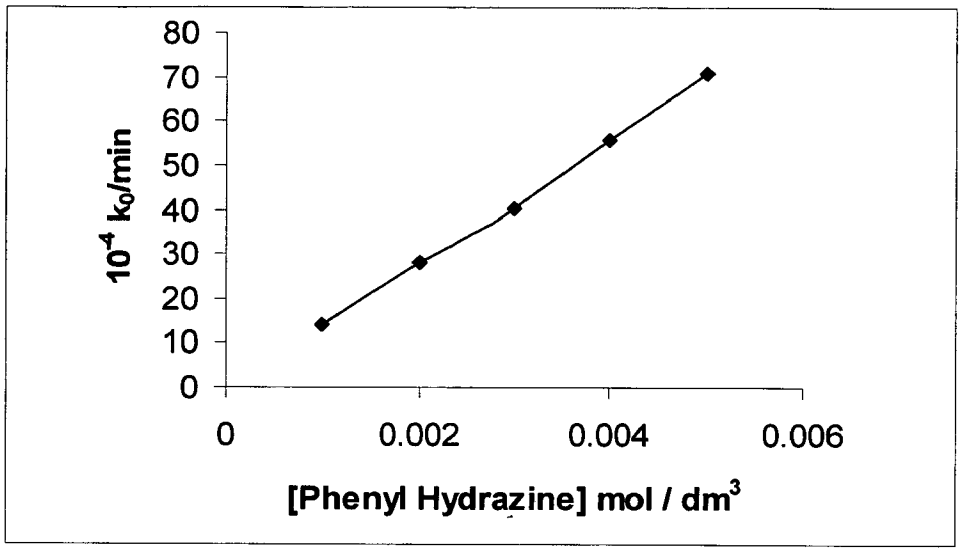


Fig 5.4:- Plots of k_0 vs. [phenylhydrazine] for the reaction of 2-chloroquinoxaline With phenylhydrazine

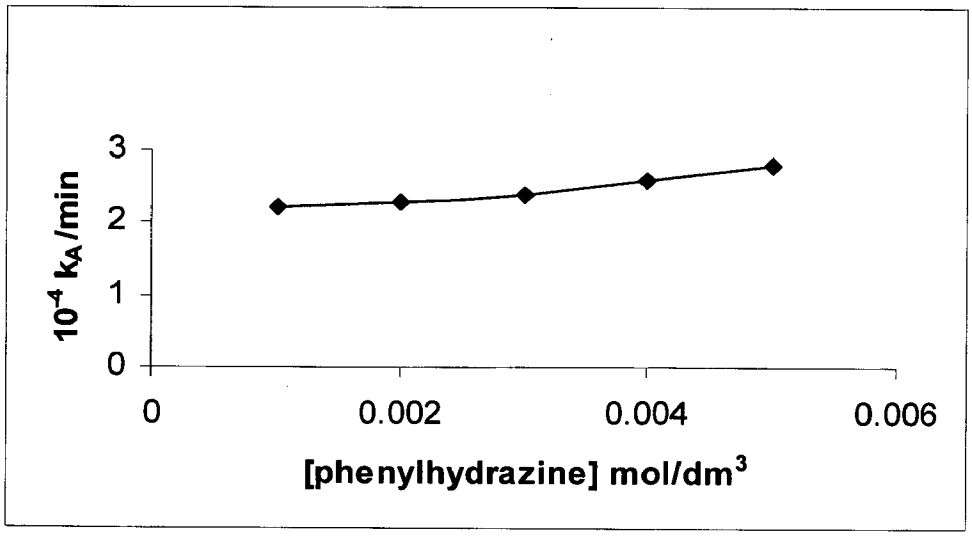


Fig 5.5:- Plots of k_A vs. [phenylhydrazine] for the reaction of 2-chloroquinoxaline with phenylhydrazine.

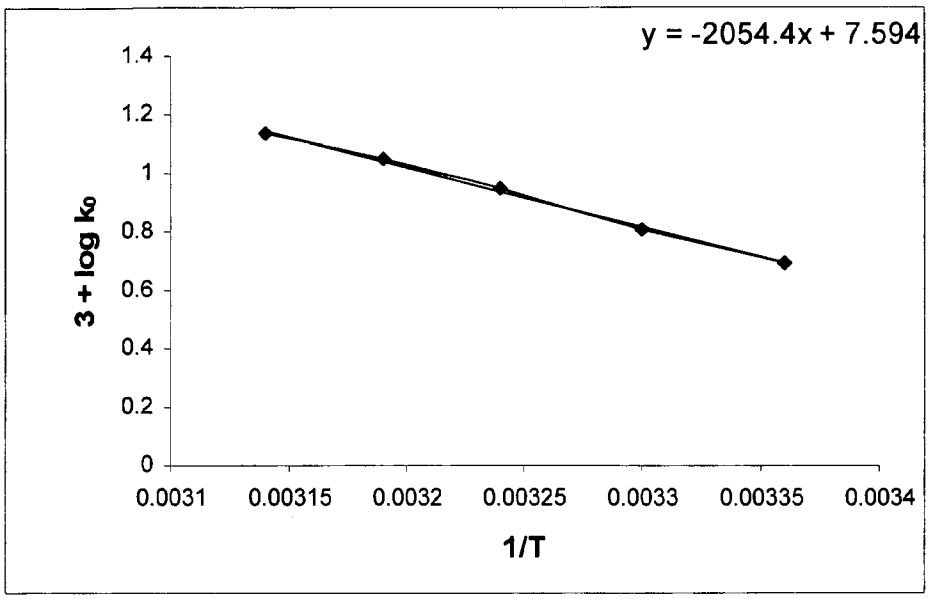


Fig 5.6 :- Arrhenius Plot, 3+ log k_0 vs. 1/T for the reaction of 2-chloroquinoxaline with phenylhydrazine.

5.6 Temperature Effect

The study of activation parameters provide useful information on the nature of the transition state leading to product formation in a reaction. Therefore in order to determine the energy of activation and other activation parameters, the reactions of 2-chloroquinoxaline with phenylhydrazine were carried at five different temperatures in methanol, the results (mean value ± average deviation at four temperature) of which are given in Table 5.3 . The plot of log k_0 vs. $1/T$ was linear. Figure 5.6 is in agreement with the Arrhenius equation which relates rate constant to temperature as in equation 2.3.

$$Log\, k_0 = -E_a / 2.303RT + LogA \qquad (2.3)$$

From the slope and intercept of the plots of log k_0 vs. $1/T$, the activation energy, and the frequency factor, A were calculated. The following equations (2.4-2.8) were used to calculate entropy of activation, ($\Delta S^{\neq}$), free energy of activation, ($\Delta G^{\neq}$) and enthalpy of activation, ($\Delta H^{\neq}$).

$$A = k_0 e^{E_a / RT} \qquad (2.4)$$

$$k_0 = \frac{kT}{h} e^{-E_a/RT} . e^{\Delta S^{\pm}/R} \qquad (2.5)$$

$$k_0 = \frac{k}{h} e^{-\Delta G^{\pm}/RT} \qquad (2.6)$$

$$k_0 = \frac{k}{h} e^{\Delta S^{\pm}/RT} e^{-\Delta G^{\pm}/RT} \qquad (2.7)$$

$$\Delta H^{\pm} = \Delta G^{\pm} + T\Delta S^{\pm} \qquad (2.8)$$

In the above equations k_0, k, h, and R are rate constant, Boltzmann constant, Planck's constant and gas constant respectively. The value of $\Delta H^{\pm}$ is rather low which indicates that solvent has played an important role in the transfer of energy to reactant having energy below the activation barrier enabling them to overcome the barrier The variation of the activation parameters for the S_NAr reaction can be related to carbanion mediated mechanism. Since methanol molecules have strong tendency to participate both as HBD and as

HBA solvent, the formation of hydrogen bonds would produce a decrease in enthalpy and the participating molecules become relatively fixed. In this S_NAr reaction high negative $\Delta S^{\pm}$ values and low $\Delta H^{\pm}$ values have been obtained probably due to minimal interaction between carbanion and its solvation sphere. Therefore hydrogen-bonding ability of solvent methanol regulates the stability of the carbanion intermediate varying the S_NAr rate.

Table- 5.3 -Thermodynamic parameters and frequency factors for the reactions of 2-chloroquinoxaline with phenylhydrazine.

E_a kJmol^{-1}	Log A min^{-1}	$\Delta G^{\pm}$ $kJ\,mol^{-1}$	$-\Delta S^{\pm}$ $J\,mol^{-1}K^{-1}$	$\Delta H^{\pm}$ $kJ\,mol^{-1}$
107.30	7.594	290±0.45	339±0.44	80±0.34

Conclusions

Derivatives of 2-Chloroquinoxaline have important pharmacological activities and play vital role in the synthesis of drugs. Many of the anti malarial drugs, antifungal drugs, anti bacterial drugs, anti HIV agents, anti diabetic agents etc. contain Quinoxaline as residue. A slight change in the substituent attached to the Quinoxaline derivative causes change in biological activity of drugs. Introduction of Quinoxaline in the drugs formulation has induced encouraging results in medicinal Chemistry; Hence synthesis of Quinoxaline derivatives has been undertaken in the dissertation. The rate of formation of various Quinoxaline derivatives and the rate of decomposition of the same play useful role in drug administration. Hence a study on the kinetics of the reaction of 2-Chloroquinoxaline with a suitable amine derivative has been undertaken.

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