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CINNOLINE DERIVATIVES OF MEDICINAL SIGNIFICANCE: SYNTHESIS AND QSAR INSIGHTS

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ABSTRACT

The present study deals with the synthesis and infrared (IR) identification of various heterocyclic and azo compounds using efficient and eco-friendly methodologies. Benzothiazine derivatives were successfully synthesized using a sonication technique, which significantly reduced reaction time and improved yield compared to conventional methods. The use of ultrasonic irradiation demonstrated advantages such as enhanced reaction efficiency, mild conditions, and reduced solvent consumption.

Azo dyes containing pyrazole moieties were synthesized through diazotization followed by coupling reactions, incorporating biologically active heterocyclic systems into the dye structure. The formation of azo dyes was achieved under controlled temperature and pH conditions, ensuring the stability of diazonium salts and effective coupling with suitable aromatic compounds. Additionally, azo chiral dyes were prepared to introduce optical activity, expanding their potential applications in advanced materials and asymmetric synthesis.

The synthesized compounds were characterized using IR spectroscopy, which confirmed the presence of key functional groups. Characteristic absorption bands corresponding to azo (–N=N–), C=N, aromatic C=C, N–H, and C–S groups validated the successful formation of the target molecules. Overall, the study highlights the importance of green synthesis techniques and spectroscopic analysis in developing novel compounds with potential pharmaceutical and industrial applications.

INTRODUCTION

1.1 The major stream of investigation that encompasses biologically active compounds has led to the discovery and synthesis of excellent therapeutic agents. The spectacular achievement of man lies in the fact that, many of the deadly diseases which threatened the very existence of human race, right from the early civilization, have been nearly brought under control and some of them have been completely eradicated. He is now engaged in his pursuit to resolve the biological intricacies woven around the mysterious and unconquered diseases like cancer and AIDS which have eluded human wisdom. The scientific quest for a suitable drug to combat such diseases still remain unanswered.

Though in certain areas of investigation, he has not achieved remarkable success, his spirit has not dampened his restless and persistent efforts to find a solution to such problems and thereby create a better and healthy world to live in, continue unabated. It is a matter of pride that, with rapid advancement in science and technology, medicinal chemistry has made profound progress in the last few decades. Literature survey reveals that, heterocyclic compounds have acquired importance not only in the medicinal world but also in the field of agrochemicals. So, for as chemotherapy is concerned, they have unequivocally qualified as lifesaving drugs.

In view of the general observation that, the pharmacological activities are invariably associated with a large variety of heterocyclic compounds, during the present investigation, we focussed our attention on certain class of heterocyclic compounds which have wide spectrum of biological activities. 1 Owing to the importance and established physiological activities of these compounds, we were encouraged to synthesise and investigate compouds of comparable structures. Thus, the basis of our research programme was centered around the fact that, certain structural units present in known biologically active compounds are also found in other naturally occurring compounds of similar properties.

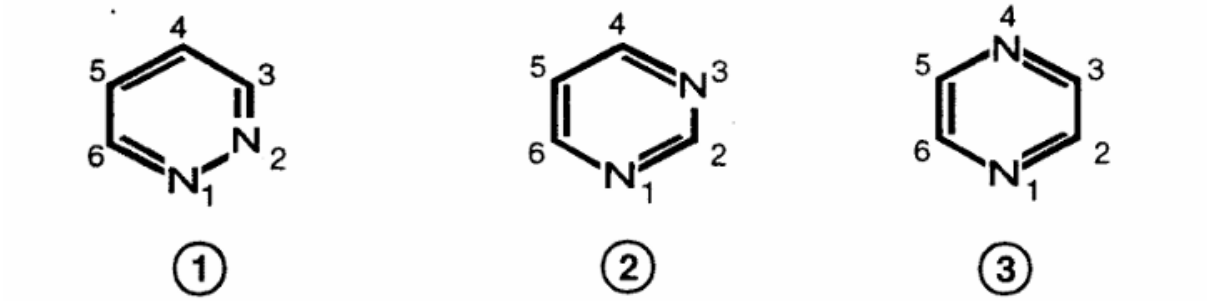
Further, by affecting structural variation, the relationship in respect of chemical structure and biological activity could be better explored. It is well established that slight alterations in the structure of certain compounds are able to bring about drastic changes in biological activity 1. Several physico-chemical parameters are said to be associated with this phenomenon. Both steric and electronic factors are claimed to be prime determinants in the variation of biological activity 2‘4.

The close association of pyrimidine nucleus with biologically important compounds like nucleic acids, vitamins, coenzymes and a wide variety of drugs has drawn the attention of a number of workers. Condensed pyrimidine systems have been extensively investigated. Although much work has been done on condensed pyrimidine with furan 5, thiophene 6, oxazole 7, pyrazole 8, isothiazole 9, pyridine 10, pyrazine 11, indole 12 etc., there is only one report 13 concerning cinnolinopyrimidine in which cinnoline heterocycle is fused to a pyrimidine ring.

During the present investigation, we planned the synthetic sequence of reactions leading to the preparation of compounds wherein the cinnoline nucleus is fused with other heterocycles like pyrazoles, oxazines and mercaptopyrimidines with a view to evaluate them for biological activity.

1.2 THEORETICAL AND STRUCTURAL STUDIES OF CINNOLINNES

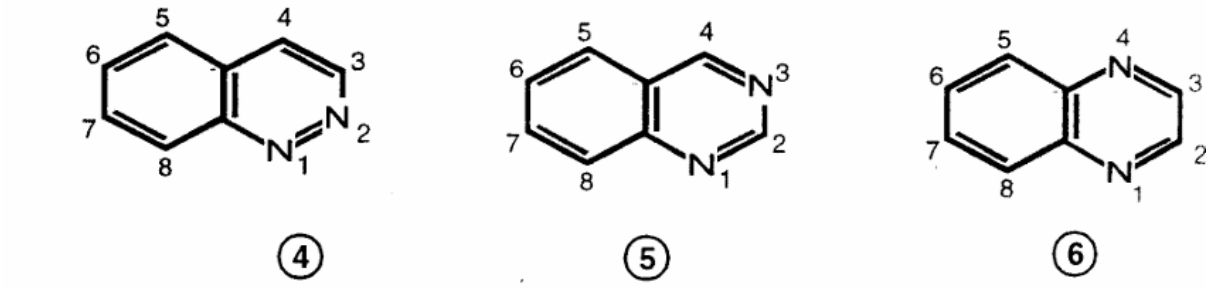
Six membered heterocyclic compounds containing two nitrogen atoms in the ring are called diazines. Depending on the position of the two nitrogen atoms in the ring, they are named as 1,2-1,3- and 1,4-diazines or pyridazine (1), pyrimidine (2) and pyrazine (3) respectively.



These three dinitrogen heterocyclic ring systems and their numberings are as follows: When benzene ring is fused to the 5,6-positions of the above diazines, they are known as cinnoline (4), quinazoline (5) and quinoxaline (6) respectively.

1.3 SYNTHESIS OF CINNOLINES: The different methods employed for the synthesis of cinnolines are briefly discussed below:

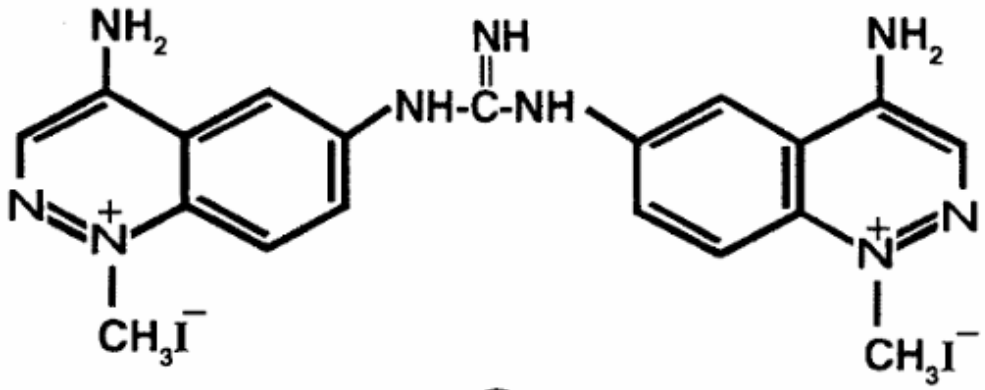
1) Von Richter's Synthesis
2) Busch and Klett's Synthesis
3) Widman-Stoermer's synthesis
4) Borsche's Synthesis



1.4 BIOLOGICAL IMPORTANCE OF CINNOLINES

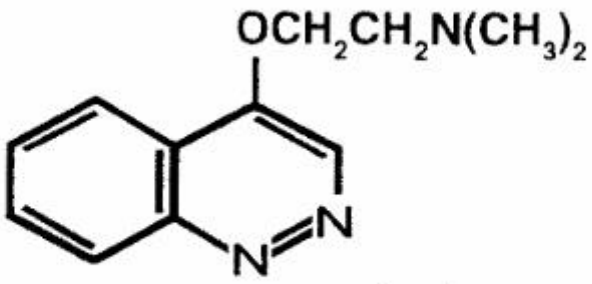
Though no cinnoline occurs in nature, it is observed that considerable chemotherapeutic activity is associated with cinnoline derivatives. Busch and Rast 14 reported that, the parent compound cinnoline showed antimicrobial activity against E-Coli.

Kenford et al 15 have prepared various quaternary salts of aminocinnolines in order to simplify the phenanthridine quaternary salts and at the same time retaining their trypanocidal activity and screened them against Trvpanosma and Spirochete infections in mice. It was found that bis-(4-amino-6-cinnolyl) guanidinedimethiodide (7) had a chemotherapeutic index of the same order of antrycide methyl sulphate and compound 7 has been designated as "L528"



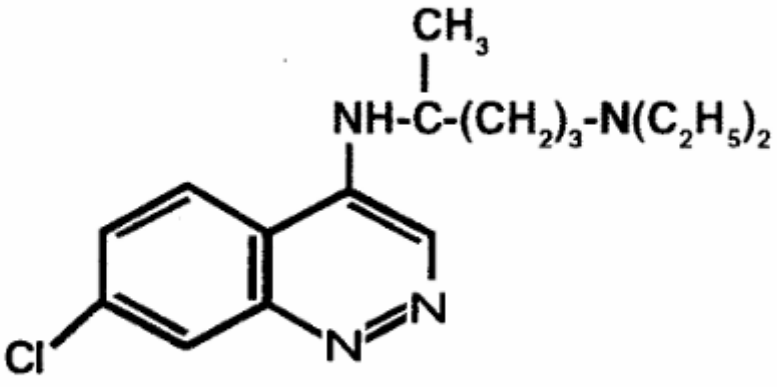
(7)

A number of pyridyl cinnoline quaternary salts have been reported as trypanocidal agents. 16'18 Castle and Onda 19 have prepared a series of substituted esters, ethers and amides for pharmacological screening and tested them for stimulatory activity in rats. Amongst the ethers tested, 4-dimethylaminoethoxy cinnoiine (8) showed slight CNS stimulatory activity in rats.



(8)

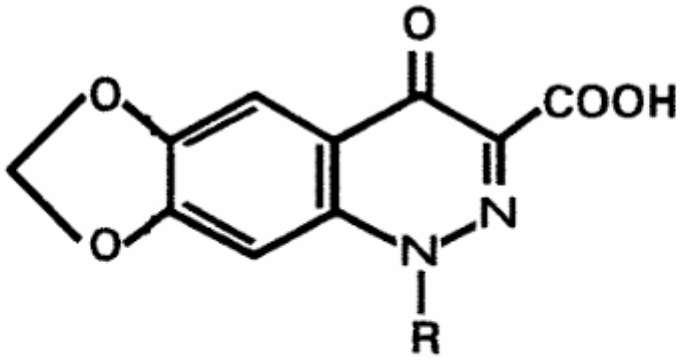
Taylor et al 20 have reported the preparation of poly-methylenedicinnolinium salts and these compounds have been described as antimicrobial and antiparasitic agents. A variety of 4-dialkylaminoalkylcinnolines have been prepared by condensing an appropriate 4-phenoxycinnoline with an aliphatic amine at about 130°21. These aminocinnolines have been tested for antimalarial activity against Plasmodium aallinaceum in chicks and these compounds showed better activity. Two of them were also tested against other malarial strains and the most effective compound was 7-chloro-4(4-diethylamino-1-methylethylamino) cinnoline (9) which is the cinnoline analogue of chloroquine 22.



(9)

Cinnoline carbonitriles have been synthesised 23 by the reactions of 4-methylsulphonylcinnoline or 4-cyanocinnoline with alkali metal cyanides. These compounds have been reported as bactericides.

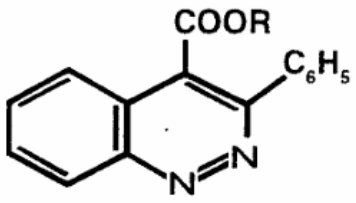
Ansley 24 prepared a number of 1-alkyl-6,7-methylenedioxy-4(1H)-oxocinnolin- 3-carboxylic acids (10). Compounds of the type 10 and their salts were found to be active against Mycoplasma galliceptium. Escherichia coli. Salmonella Dublin. Vibrio coli. Eruvina amvlovora and Xantiomonas phaseoli.



(10)

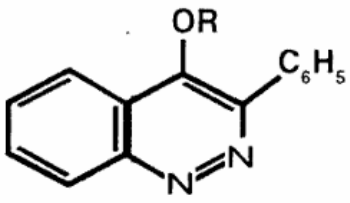
R= CH_3, CH_2-CH_2-CH_3, CH $(CH_3)_2$, CH_2-CH_2OH and CH_2-CH=CH_2

A number of substituted cinnolylsulphones have been prepared by the oxidation of the corresponding sulphides with potassium permanganate. These compounds have been reported as useful bactericides 25. Lowrie 26'31 prepared a large number of 3-phenylcinnolines, such as dialkylamino alkyl esters of 3-phenylcinnolin-4-carboxylic acids (11), 3-phenyl-4- dialkylminoalkoxycinnolines (12), dialkylaminoalkylaminoamides (13), 3-phenyl-4 dialkylaminoalkylcinnolines (14), 3-phenyl-4-aminocinnolines (15) and piperazine amides of 3-phenylcinnolin-4-carboxylic acids (16) and subjected them for pharmacological screening.



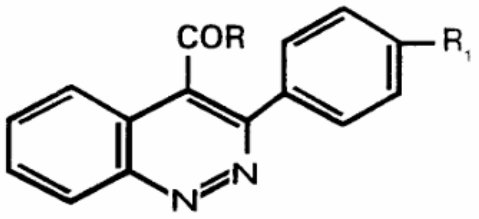
(11)

R=$CH_2.CH_2.CH_2.N(CH_3)_2$



(12)

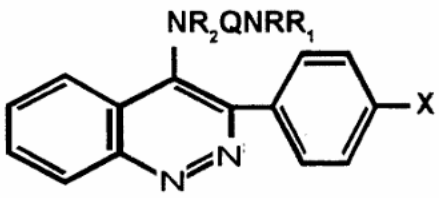
R=$CH_2.CH_2.N(C_2H_5)_2$ and $CH_2.CH_2.CH_2.N(CH_3)_2$



(13)

R= OH, Cl, CH_3 and $NH.CH_2.CH_2.N(CH_3)_2$

R_1=H, Cl or OCH_3



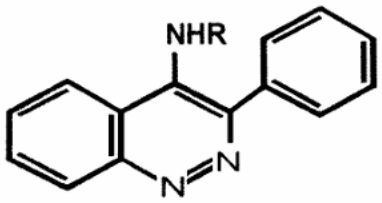
(14)

X = H, Cl,

R = R_1 = CH_3

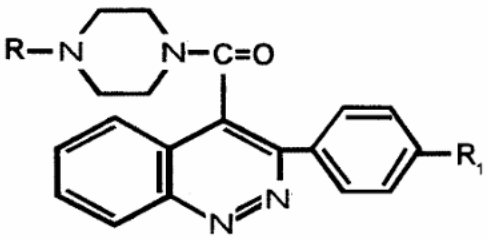
R_2=H

Q=$(CH_2)_3$



(15)

R = $CH_2.C_6H_5$, $CH_2.CH_2.C_6H_5$, $CH_2.CH_2OCH_3$ and CH_2OH



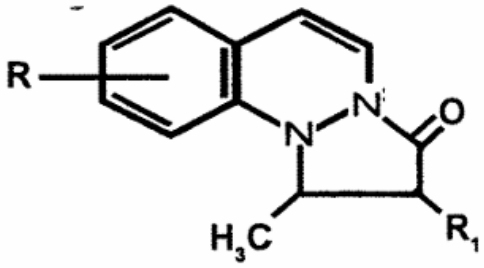
(16)

R = H, C_2H_5, $CH_2.CH_2OH$ and $CH_2.CH_2.CH_2OH$

R_1= H or OCH_3

Compounds 11 to 16 have been reported to possess hypotensive, antiulcer antifungal, antiprotozoal, anti-inflammatory, central nervous system depressant and antibiotic activity against various organisms. They also inhibited the growth of Diplococcus pneumonia. Tetrahvmena qeleii. Chlorella vulgaris. Candida albicans and the germination of seeds of Trifolium.

Theodor and associates 32 have reported the preparation of 1,2-malonyl-1,2- dihydrocinnolines (17).



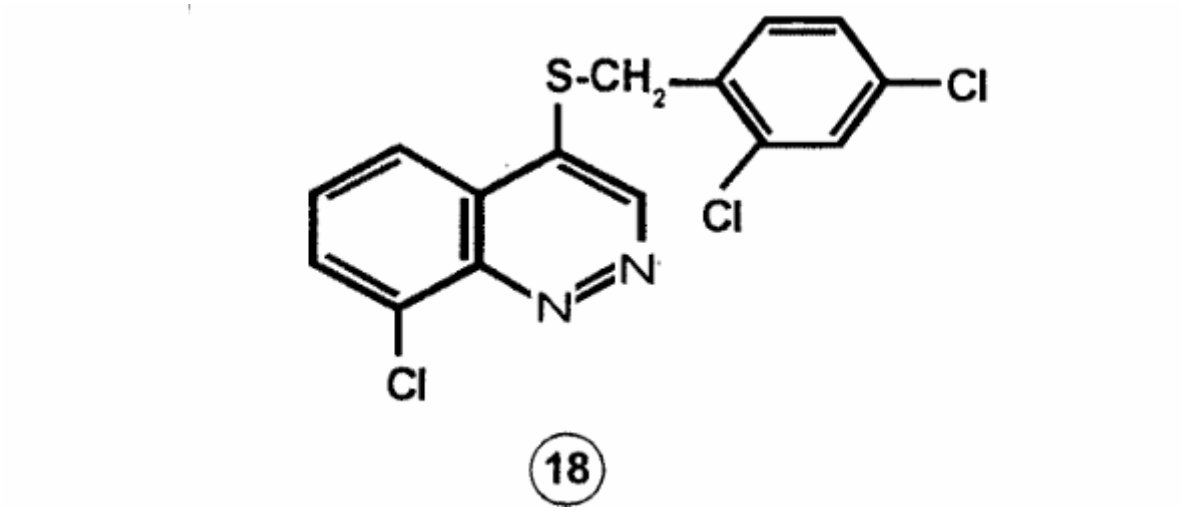
17

$R = C_6H_5$, p-$CH_3.C_6H_4$

$R_1 = CH_2.CH_2.CH_3$ and

$CH_2(CH_2)_2CH_3$

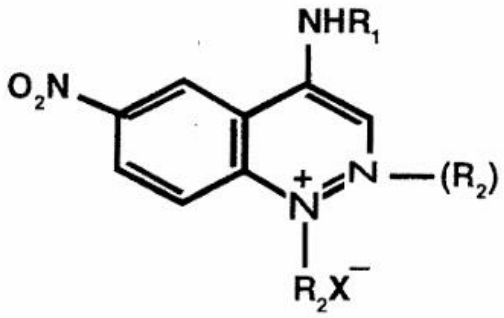
Compounds of the type 17 have been reported to possess anti-inflammatory, antipyretic and analgesic activities. Castle 33 prepared a number of compounds containing pyridazinecinnoline and imidazopyridazine and tested them against tumor cells in-vivo and in-vitro Among the several cinnolines prepared and tested, seven cinnolines showed remarkable activity against certain types of tumor cells. The 8-chloro-4-(2 4-dichlorobenzylthio) cinnoline (18) showed the highest activity against both SA-180 and CA-755 tumor cells in-vivo.



18

The antileukemic activity of 6-mercaptopurine prompted the synthesis of mercaptocinnolines and related compounds by Castle et al 34. They have prepared 4-mercaptodnnoline, 6,7-dimethoxy-4-mercaptocinnoline and a number of alkyl and heterocyclic derivatives, with a view to subject them for a antitumor activity.

Castle et al 3536 have prepared a-(co-dialkylaminoalkyl)-a-phenyl-4- cinnolinacetonitriles and related compounds with a view to screen them to pharmacological activities. Several 4-amino and 4-(substituted amino)-6-nitrocinnoline quaternary salts (19) were prepared by Barber et al 37, and tested them for trypanocidal activity primarily against Trypanosoma congelense. None of the derivatives showed considerable activity although several compounds of the type 19 were active at near toxic doses.



R_1 = H, CH_3 and $CH_2.CH_2.CH_3$

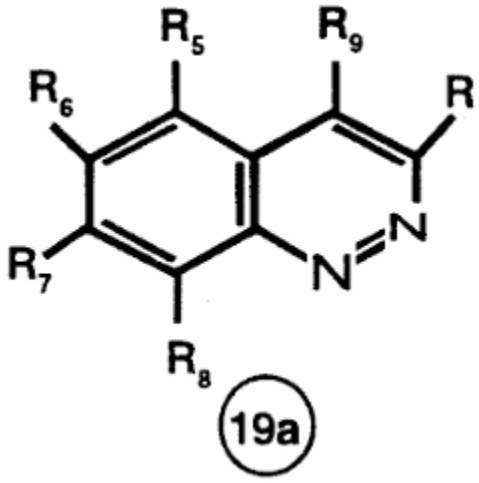
R_2 = CH_3 and C_2H_5

X = I

19

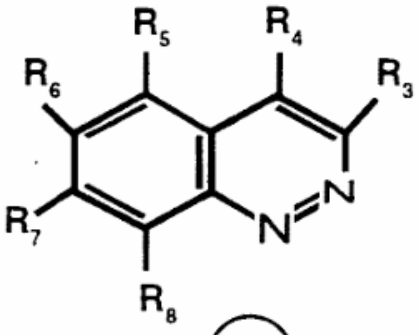
Lunt and coworkers 38 have prepared 4-substituted aminocinnoline analogues of chloroquine together with several substituted a, a>-di(cinnolin-4-yl-amino) alkanes and their diquaternary salts and subjected them for antiprotozoal activity. None of the compounds showed any useful level of activity.

A Japanese patent 39 has reported the synthesis of cinnoline derivatives of the type 19a and were found to be useful central nervous system agents, e.g. anxiolytics.



19a

R=CONR1R2 [Except (R1 =R2 =H), (halo)alkenyl, alkenyl, alkynyl, (un)substituted alkyl, aryl, and aralkyl, 4,5-dihydrothiazol-2-ylor-NR1R2=N-containing. heterocyclyl], COaR1, COCR3R (R3,R4 = H, alkyl), Rs-R8=H, halo, OH, N02 cyanoalkenyl, (un) substituted NH2, alkenyl (oxy), (un) substituted alkyl or arylhalo, alkenyl, and R9=(un) substituted NH2 or OH Resch 40 prepared a number of substituted cinnolincarboxamides(19b) as sedatives and tranquilizers.



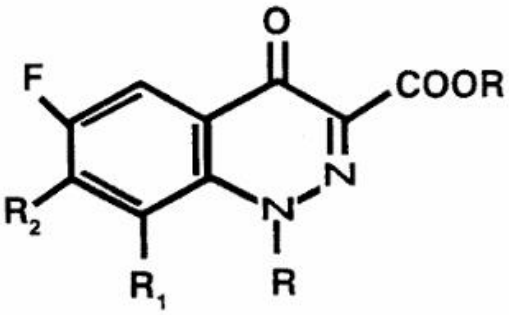
19b

R_3 = aminocarbonyl, alkoxycarbonyl and acyl,

R_4 = amino, hydroxy, alkoxy and acyloxy,

R_5-R_8 = H, alkyl, substituted alkyl, alkenyl, cycloalkyl, aryl, substituted aryl, alkoxy, alkenyloxy, hydroxy, nitro,cyano and amino.

Miyamoto et al 41 have synthesised various substituted fluorocinnolines of the type 19c and tested them for anti-bacterial activity.

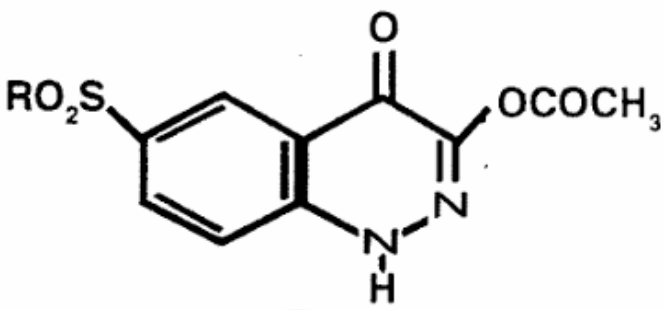


19c

R = CH_3, C_2H_5

R_1 = H, F, and R_2 = $N(CH_3)_2$, morpholino, 1-piperazinyl and 1-pyrrolidinyl

Antibacterial activities of these compounds were evaluated and compared with cinoxacin and norfloxacin. Some compounds showed better activity than cinoxacin but less than norfloxacin. Abbady et al 42 have synthesised cinnoline derivatives of the type 20 containing a sulphone group and were screened for antibacterial and antifungal activity. They observed that the introduction of sulphone group in the cinnoline ring enhances the bactericidal and decreases the fungicidal activities



20

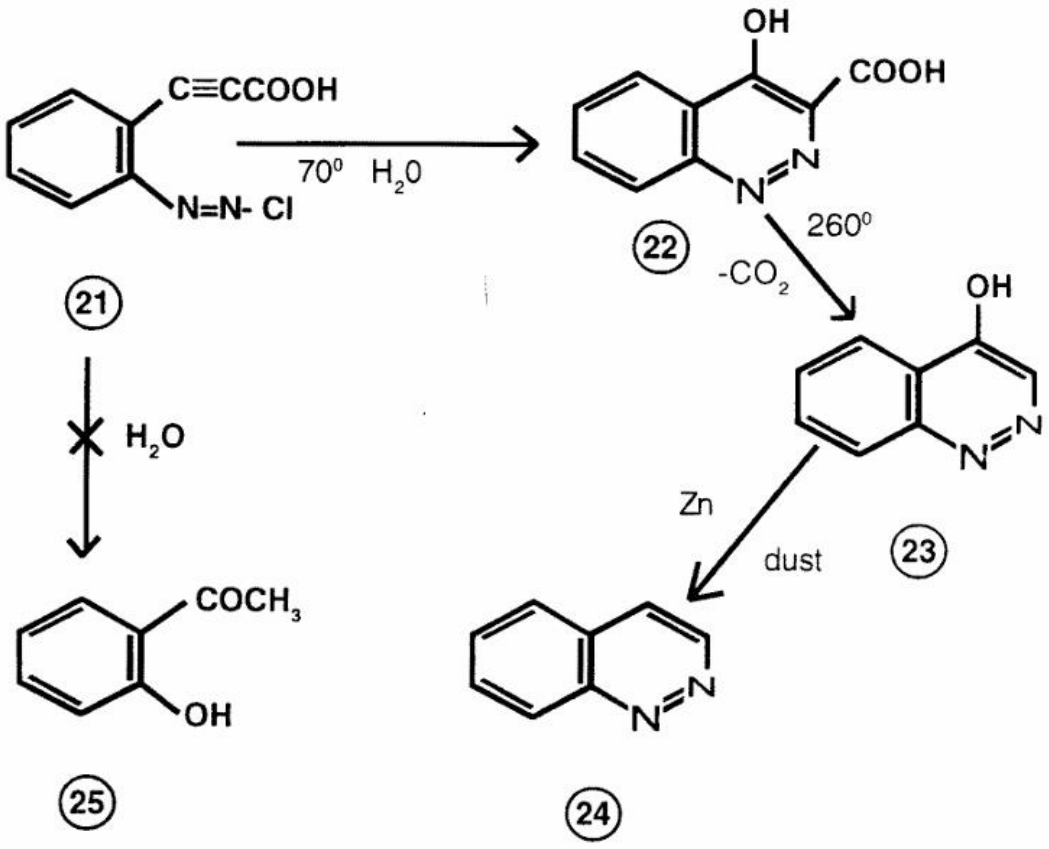
R= OH, NH_2, piperidino, C_6H_5NH, 2-pyridylamino

The foregoing data reveate that, cinnoline derivatives are known to possess varied biodynamic properties. When such a biodynamic molecule is fused to other heterocycle such as pyrimidine it is expected to yield a tricyclic heterocycle with enhanced pharmacological activily.

1.5 SYNTHESIS OF CINNOLINES

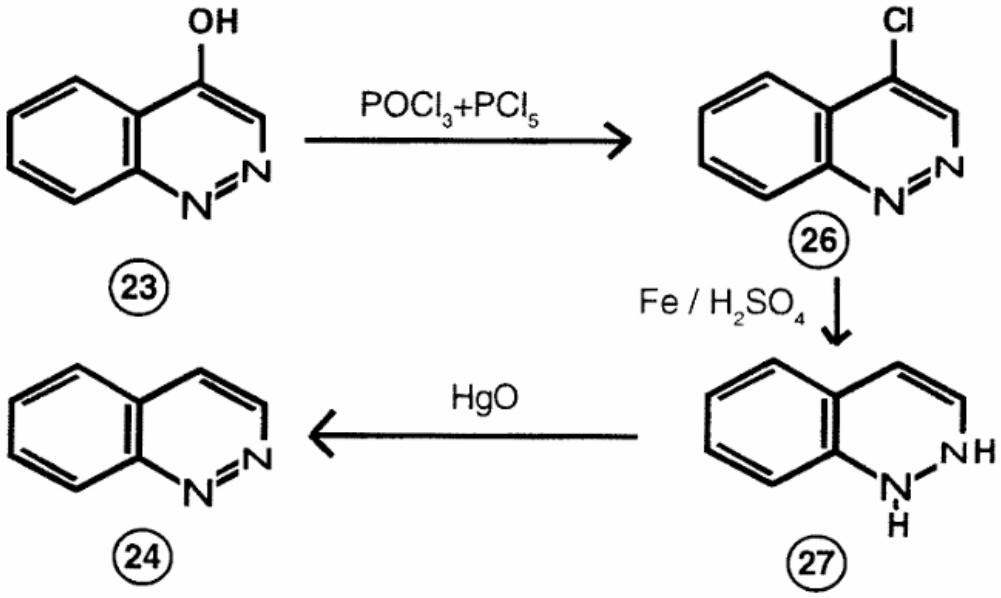
The different methods employed for the synthesis of cinnolines are briefly discussed below: **Von Richter's Synthesis:**

Till now cinnoline derivatives have not been detected in nature. The formation of dinitrogen heterocyclic system was first observed by Richter 43 in 1883, in the course of his unsuccessful attempts to prepare o-hydroxy acetophenone (25) by heating the diazonium chloride of o-aminophenylpropiolic acid (21) with water. The resulting hydroxy acid 22, on decarboxylation yielded the compound 23 which on subsequent heating with zinc dust gave the new heterocyclic compound cinnoline (24). The sequence of reactions is shown below:

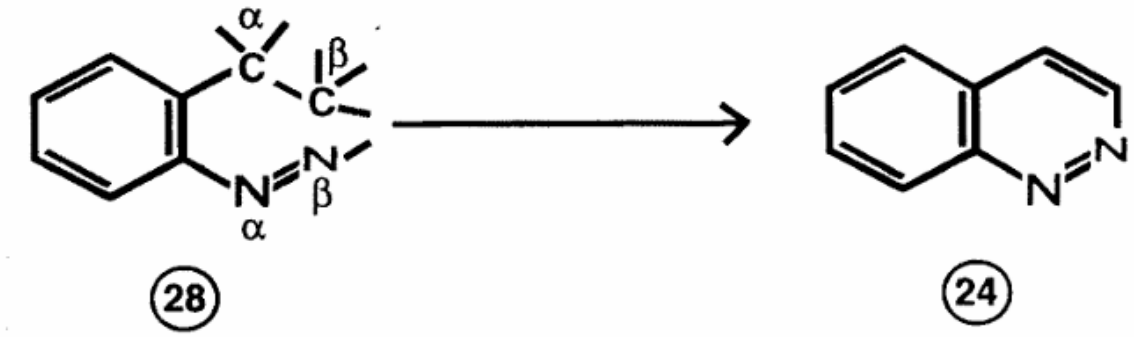


1.6 Busch and Klett's Synthesis:

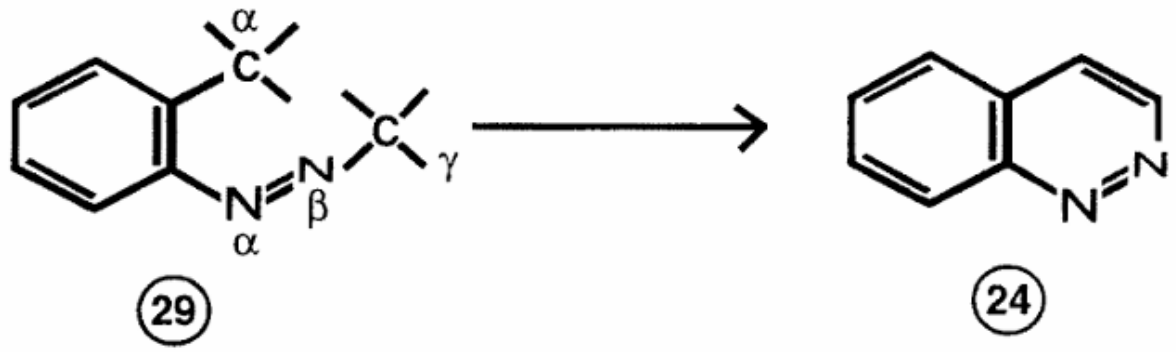
Although Von Richter could not obtain 4-hydroxycinnoline (23) in a sufficiently pure condition for the determination of its physical properties and elemental analysis, he called this new heterocyclic system cinnoline in analogy with quinoline. Pure cinnoline was first obtained by Busch and Klett 44 in 1892 by converting 4-hydroxycinnoline (23) obtained by Von Richter's method to 4-chlorocinnoline (26) with a mixture of phosphorous oxychloride and phosphorous pentachloride, followed by the reduction of the latter with iron and sulfuric acid. The resulting 1,2-dihydrocinnoline {27) was finally oxidised to cinnoline (24) with mercuric oxide.



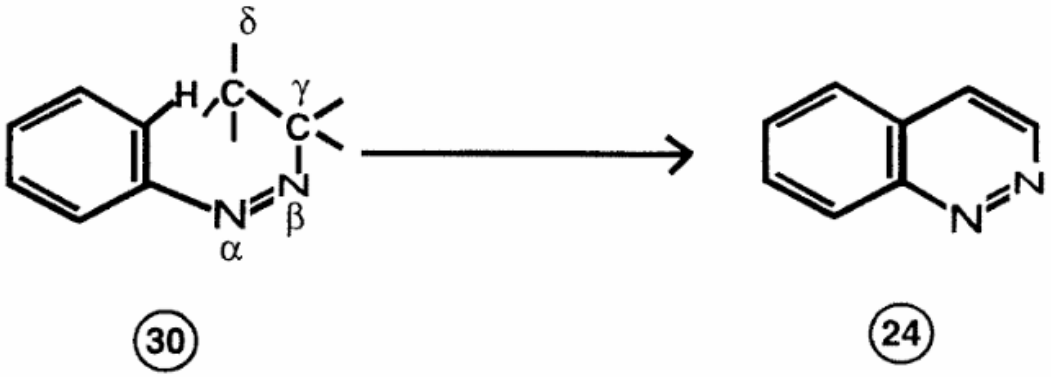
Three main approaches have been explored for the synthesis of cinnolines. The first approach makes use of the condensation between the p-nitrogen atom of a chain of two nitrogen atoms and the p-carbon atom of a chain of two or more carbon atoms, these chains being oriented in the ortho positions of the benzene ring as shown in 28.



in the second approach, the chain of two nitrogen atoms is increased by one carbon atom which condenses with the a-carbon atom of a second chain in the ortho position as in 29 to build up the heterocyclic ring cinnoline (24).

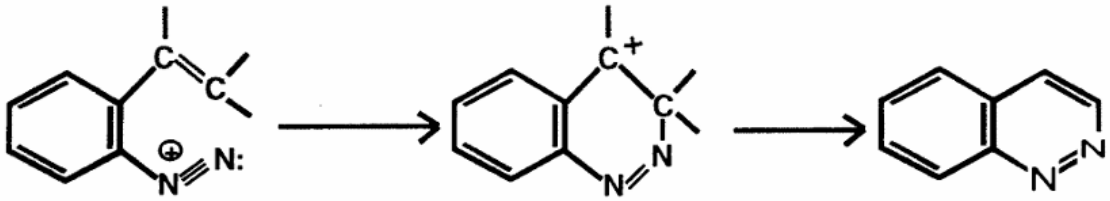


In the third approach, the 5-carbon atom of a chain containing two nitrogen and two carbon atoms react with the hydrogen in the ortho position of the aromatic ring (30) to yield cinnoline (24).



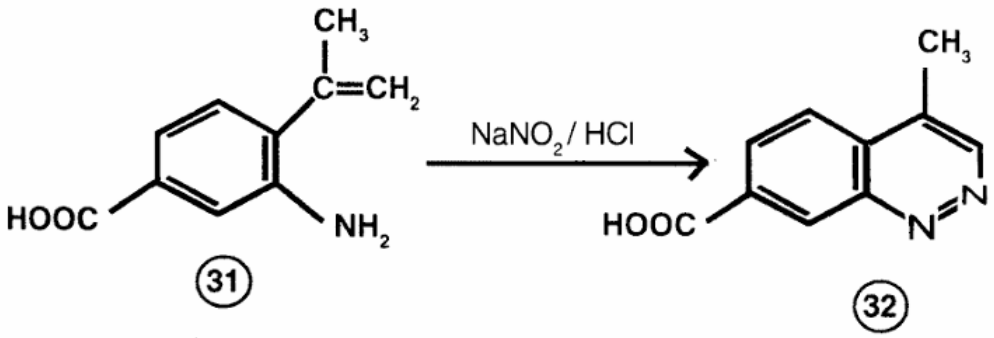
30 24

Possible mechanism of the three synthetic approaches to cinnoline have been put forth by various workers ^ although not supported by experimental evidences. The first two approaches are believed to possess a common feature of the electrophilic attack of the p-nitrogen on the p-carbon of the carbon-carbon centre of unsaturation.



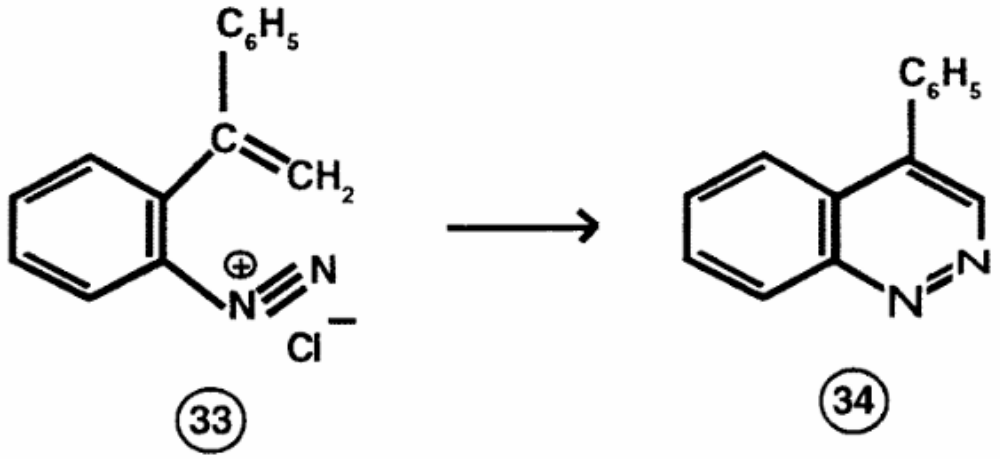
1.7 Widman-Stoermer's synthesis:

Widman 4849 observed that, on keeping a diazotised solution of 3-amino-4- isopropenylbenzoic acid {31) at room temperature, a product was formed which was identified as 4-methylcinnolin-7-carboxylic acid (32)



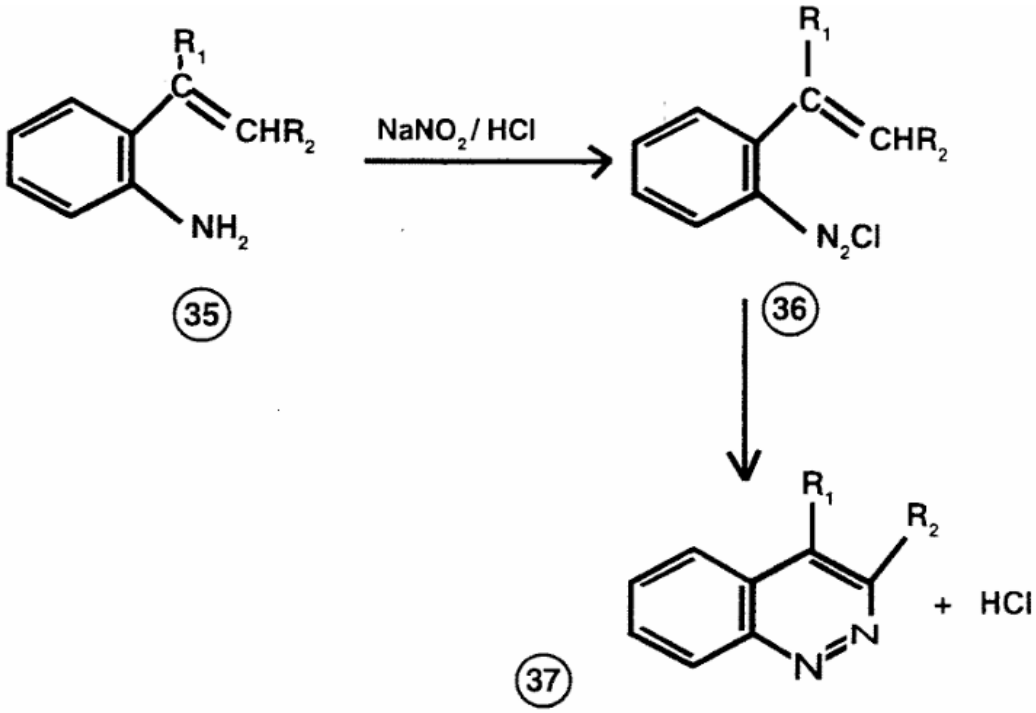
31 32

This method was later exhaustively studied by Stoermer et al 5051, who have synthesised various cinnolines substituted at 4-position starting from a suitable o-aminophenylethylenes. In general, this method can be represented by the following reaction.



33 34

This reaction was further extended by Simpson et al 4546-52-56 for the synthesis of various substituted cinnolines. Investigations on the scope of this reaction 53-55-57 has shown that, it proceeds successfully when R1 is aryl or methyl group and R2 is alkyl, aryl or arylalkyl group, but it fails if R1 is hydrogen or carboxyl and R2 is pyridyl group.

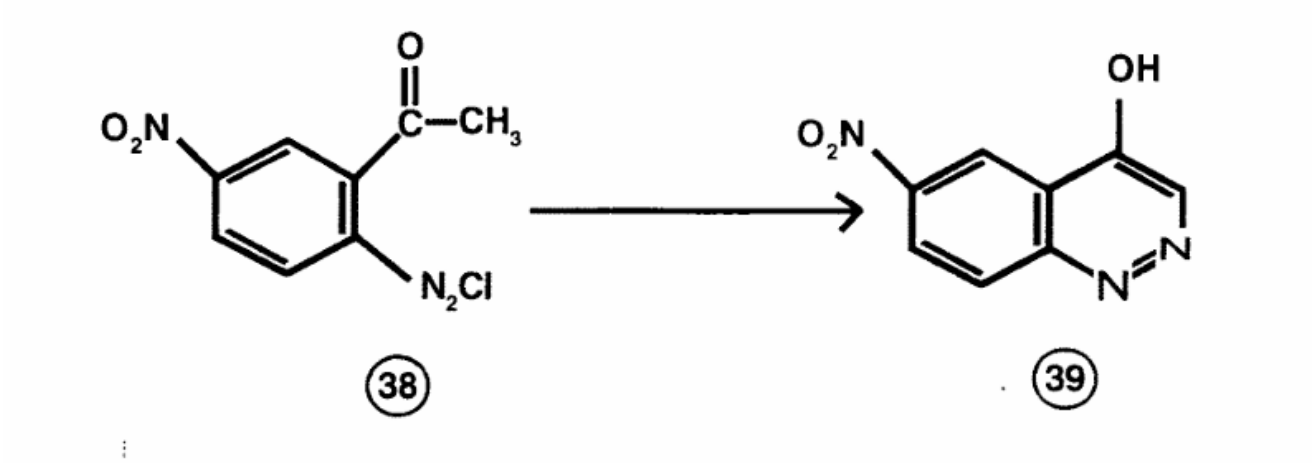


35 36 37

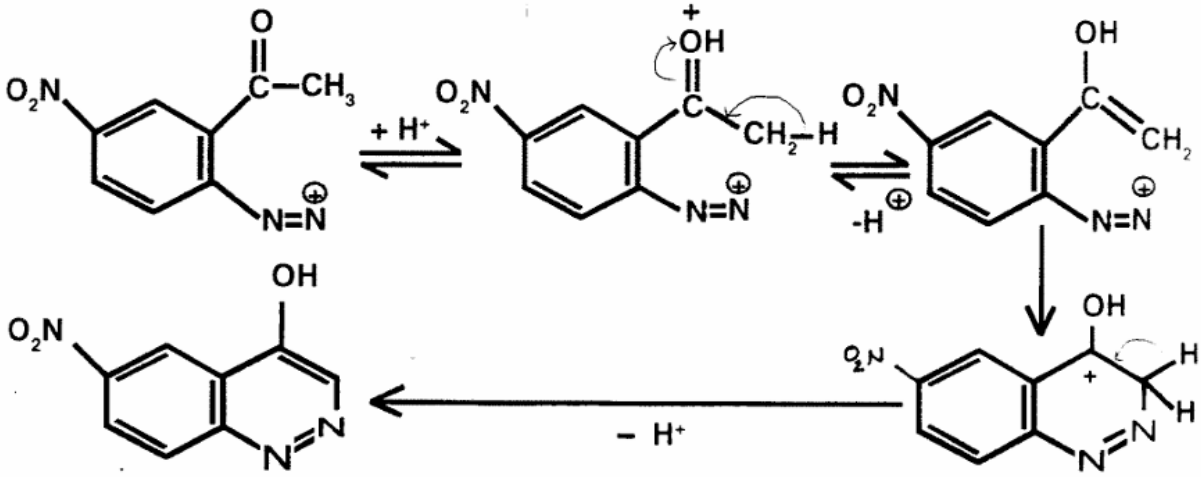
The reaction is usually very rapid and seemingly independent of the geometrical configuration of the group around the ethylenic linkage. It was concluded from these results 5558 that, the ring closure is more or less ionic in character and that it is induced by the polarisation of the diazonium salt.

1.8 Borsche's Synthesis:

Borsche and Herbert 59 in 1941 found that, a solution of diazotised 2-amino- 5-nitroacetophenone (38) when allowed to stand at room temperature, slowly cyclised to yield 6-nitro-4-hydroxycinnoline (39).



Mechanism of Borsche's Synthesis :

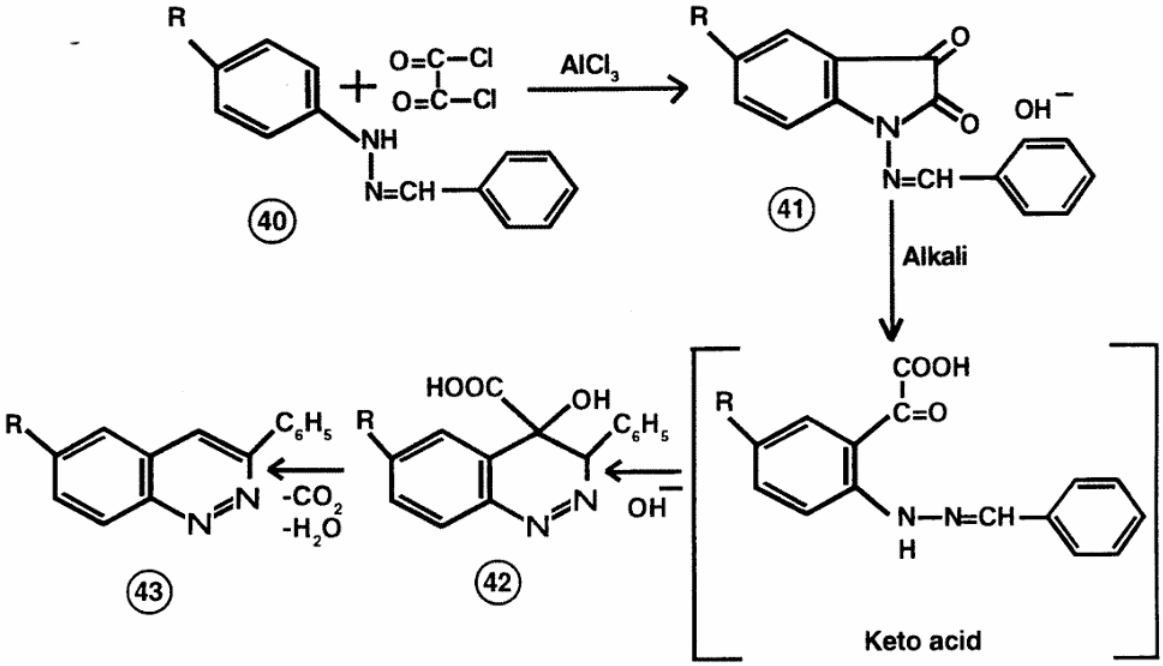


This method has been found to be of general applicability for the synthesis of 4-hydroxycinnoiines substituted at various positions, starting from a suitable o-aminoacetophenone. Cinnoline formation is considered to take place through acid catalysed enolisation of the carbonyl group of the acetophenone derivative. The cyclisation is facilitated by the electrophilic character of the diazonium group. The cyclisation to form the cinnoline ring in this method is slower than that in Widman-Stoermer's method, but is facilitated by electron withdrawing groups in the m-position to the acetyl group. In this reaction heating is avoided to prevent the formation of phenol by the decomposition of the diazonium salt. The presence of hydrochloric acid assists ring closure but can lead to the replacement of nitro group by chlorine 60.

1.9 Stolle-Becker's Synthesis:

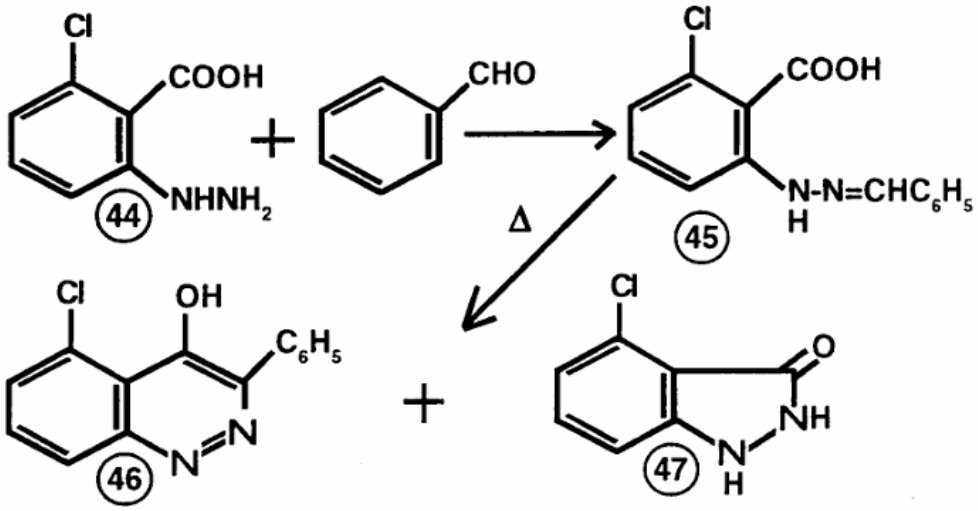
Stolle and Becker 61 in 1924 reported that, N-substituted derivatives (41) obtained through the reaction between substituted phenylhydrazones (40) and oxalyl chlorides, gave 3-phenylcinnolin-4-carboxylic acid (42) on treatment with alkali. These on decarboxylation gave the corresponding 3-pheny! Cinnolines (43). The reaction evidently proceeds through the opening of the heterocyclic ring of the isatin derivative to the

intermediate keto acid containing the structural requirements of the second approach for the synthesis of cinnolines.



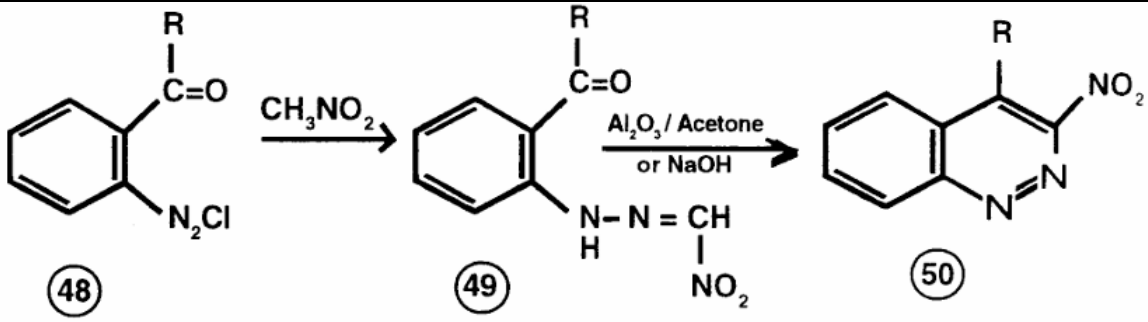
1.10 Pfannstiehl-Janecke's Synthesis:

Another method for the synthesis of cinnolines based on the second approach was reported by Pfannstiehl and Janecke 64 in which, the phenylhydrazone (45) prepared by condensing benzaldehyde with 6-chloro-2-hydrazine benzoic acid (44) gave two products on heating, one of which was 5-chloro-3-phenyl-4-hydroxycinnoline (46) and the other was 4-chloroindazolone (47). The sequence of reactions is as follows:



1.11 Baumgarten's synthesis:

This method is of general applicability for the synthesis of cinnolines based on the second approach developed by Baumgarten et al 66, in 1954. In this method, the required intermediate 49 obtained by the action of nitromethane on o-formyl benzene diazonium chloride(48), undergoes cyclisation in aqueous alkali or with a suspension of alumina in acetone to yield the corresponding 4-substituted-3- nitrocinnolines (50)

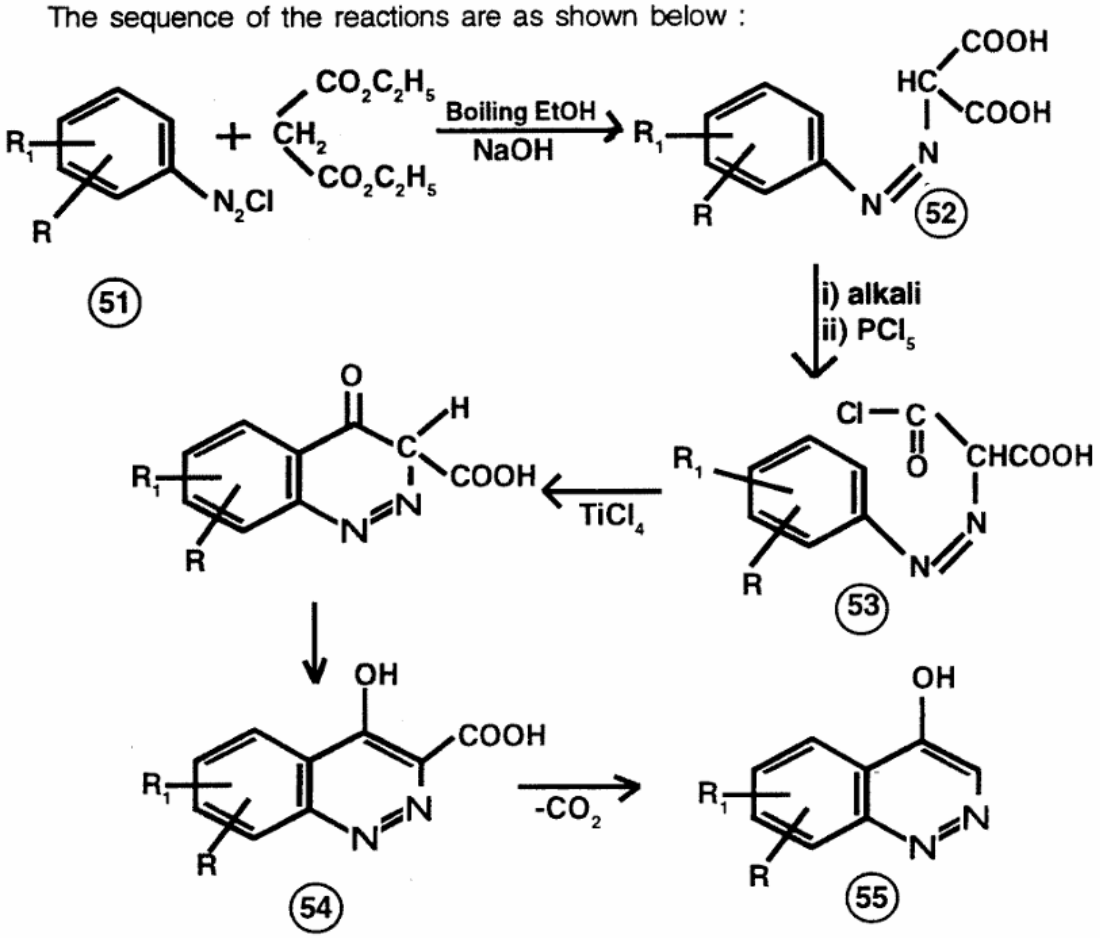


R= H,CH_3 ,OH

1.12 Barber's Synthesis:

This synthetic approach to the cinnoline ring system was first described in a British patent by Barber et al 68 in the preparation of intermediates useful for the preparation of compounds having pharmacological properties. The details of this method were described in a subsequent publication by Barber et al 69. In this method, the appropriate intermediate 52 was obtained by the condensation of a suitable benzene diazonium chloride 51 with diethylmalonate and the subsequent hydrolysis of the resulting product, followed by conversion to the acid chloride 53. The acid chloride 53 on treatment with titanium tetrachloride, underwent cyclisation to yield 4-hydroxycinno! in-3-carboxyiic acids (54) which could thermally be decarboxylated at 205-215° to 4-hydroxycinnoline(55)

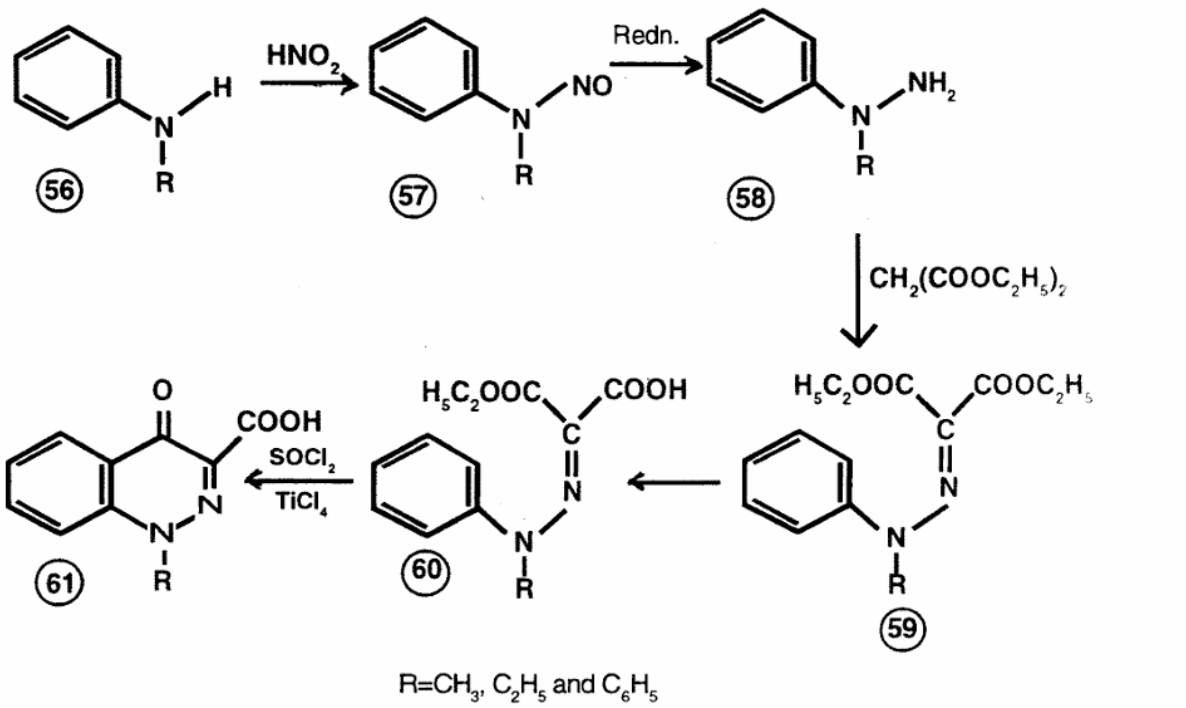
The sequence of the reactions are as shown below :



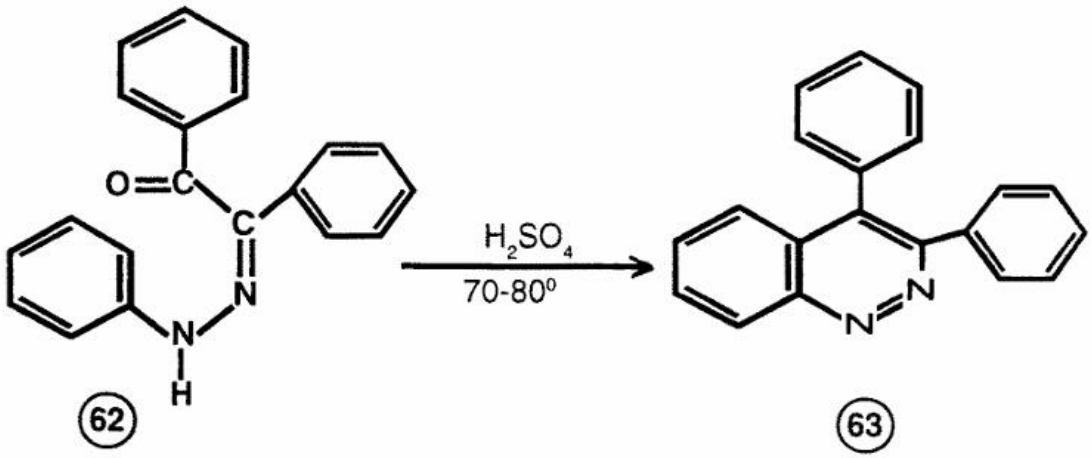
R=4-OH, 4-$OCH_3C_6H_5$, 4-OCH_3, 4-NHAc, 4-$NHCOOC_2H_5$, 3-Cl, 4-Br and 4-NO_2

R_1=H, 3-Cl, 4-Cl, 5-Cl and 4-CH_3

A modification of this method for the synthesis of N-alkyl and N-aryl-4- cinnolines have been described by Barber et al 70'71. In this method, N-substituted anilines (56) were first converted to their nitroso derivatives which however failed to condense with diethylmalonate. These were then reduced to the corresponding a-substituted phenylhydrazones (58) and then condensed with diethylmalonate to obtain the diesters (59). The monoesters (60) obtained by partial hydrolysis of 22 diesters were then converted to the acid chlorides and finally cyclised with titanium tetrachloride to 4-cinnolinone derivatives (61).



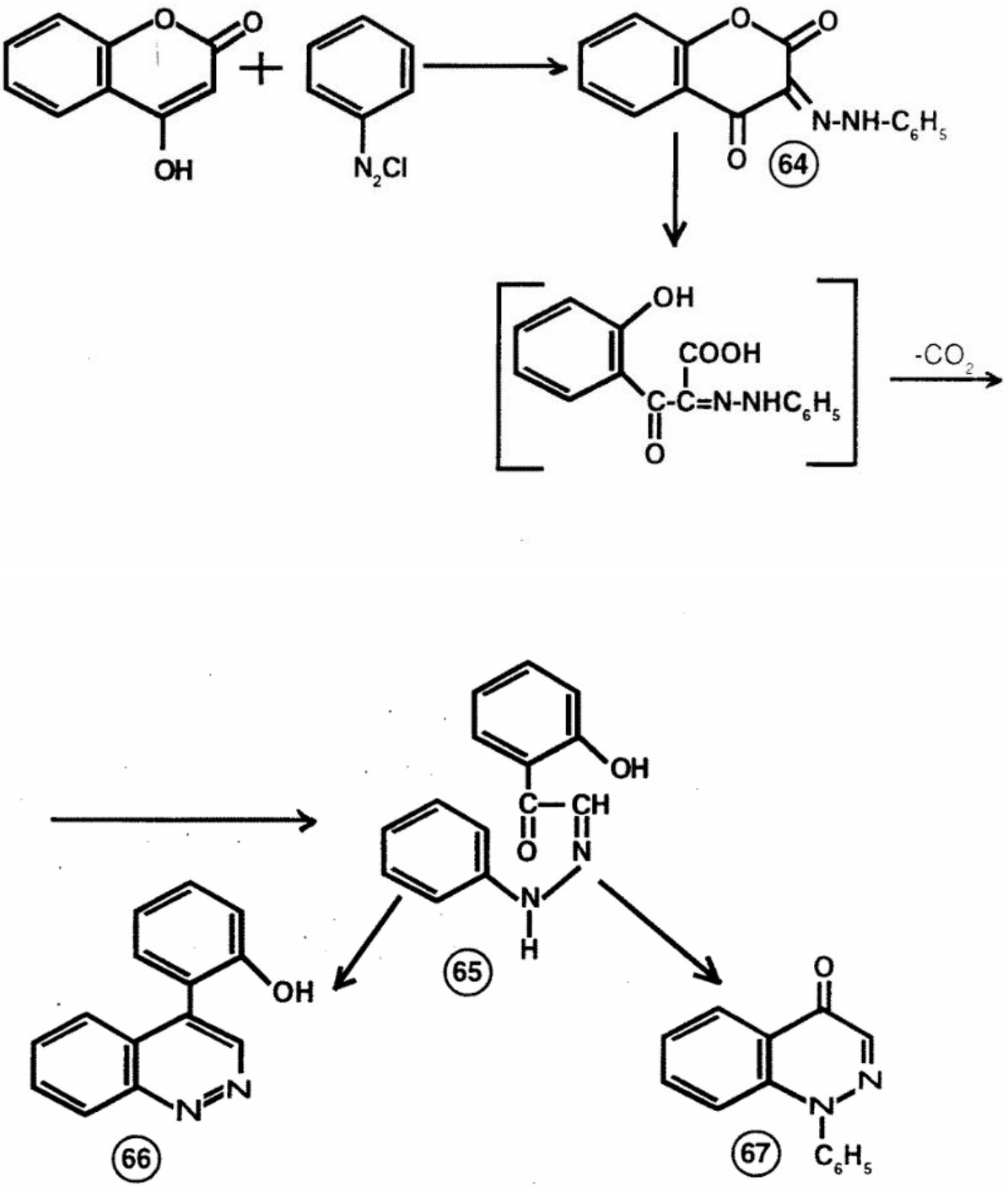
1.13 Moore's Synthesis: CH_(COOC H) H C OOC COOC H 5 2 ∨ 2 s k Moore 72 synthesised 3,4-diphenylcinnoline in good yields by cyclising benzilmonophenylhydrazone (62) with sulfuric acid. Repeatation of this procedure under slightly different conditions, however gave low yields of cinnoline (63) and considerable quantities of a sulphonated product



1.14 Bhat and Bose's Synthesis:

Bhat and Bose 7475 were however successful to bring about the cyclisation of o-hydroxyphenylglyoxal-2-phenylhydrazine (65) by the action of anhydrous aluminium chloride at elevated temperature. In the absence of any solvent, the resulting products were considered to be 1 -phenylcinnolin-4-one 74 (67), but later investigations showed them to be 4-(o-hydroxyphenyl) cinnoline (66)7S. The intermediate o-

hydroxyphenylglyoxal-2-phenylhydrazone (65) was prepared by condensing 4-hydroxycoumarin with benzenediazoniumchloride under slightly alkaline conditions and opening up of the lactone ring of the resulting diketochromon-3-phenylhydrazone (64) with simultaneous decarboxylation



CHAPTER 2

2.LITERATURE REVIEW

1. Anticancer investigations are the dominant recent theme. Several reviews and primary studies in 2020–2025 highlight cinnoline and related benzodiazine scaffolds (cinnoline, phthalazine, quinazoline) as promising anticancer leads.
2. Targeted kinase/PI3K inhibitors and SAR work. Medicinal-chemistry programs used cinnoline cores to make PI3K and other kinase inhibitors with cell-based antiproliferative readouts.
3. Green and efficient synthesis methods (microwave, one-pot, Pd-catalysis) gained traction. There are multiple Elsevier reports describing microwave-assisted, catalyst-free, or Pd-catalysed routes to heavily substituted cinnolines for rapid library generation.
4. Diversity of biological activities beyond cancer. Antimicrobial, anti-inflammatory and enzyme-inhibitory (e.g., aldose reductase, carbonic anhydrase) activities keep appearing, though fewer high-impact clinical leads so far.
5. Recent advances on anticancer activity of benzodiazine derivatives — review (2025). — overview of cinnoline/phthalazine/quinazoline anticancer work.
6. Discovery of cinnoline derivatives as potent PI3K inhibitors — research article (2021) — medicinal chemistry, biochemical & cellular data.
7. Densely functionalized cinnolines: controlled microwave-assisted synthesis — methodology + biological testing (2020). — microwave routes for polyfunctionalized cinnolines with antiproliferative data.
8. One-pot synthesis and negative-ion mass spectrometric study of substituted cinnolines — (2015) — atom-efficient routes to highly substituted cinnolines.
9. Synthesis, crystal structure and spectroscopic properties of substituted cinnoline derivatives — (2017) — structural and spectroscopic characterization with notes on activity.
10. Discovery of cinnoline derivatives as potent PI3K inhibitors — C. Tian et al., 2021. Medicinal-chemistry program that developed cinnoline PI3K inhibitors with enzymatic and cellular activity data.
11. Densely functionalized cinnolines: Controlled microwave-assisted synthesis — M. H. Nazmy et al., 2020. One-pot/microwave routes to polyfunctionalized cinnolines with antiproliferative testing.
12. Synthesis and anticancer activity of cinnoline sulphonamides and 4-heterocyclic derivatives — J. R. Yerrabelly et al., 2024. Cross-coupling approaches to cinnoline sulphonamides and in-vitro anticancer screening.
13. An Overview of Diverse Biological Activities of Cinnoline Analogues — (review), 2025. Recent review summarizing antimicrobial, anti-inflammatory, anticancer and other activities for cinnoline scaffolds.
14. Synthesis and in vitro characterization of cinnoline and benzimidazole PDE10A inhibitors — H. Yang et al., 2015. Developed cinnoline analogues as candidate PET radiopharmaceuticals / PDE10A inhibitors.
15. One-pot synthesis and negative-ion mass spectrometric investigation of a densely functionalized cinnoline — D. J. Lambert et al., 2015. One-pot route and MS characterization for densely substituted cinnolines.

16. Synthesis of Indazolo[2,1-a] Cinnolines via Rh (III) catalysis — W. Hou et al., 2019. Rh (III)-catalyzed tandem C–H annulation to make indazolo-cinnoline scaffolds.
17. Synthesis, crystal structure and spectroscopic properties of substituted cinnoline derivatives — Y. Yuan et al., 2017. Structural and spectroscopic characterization of novel tricyclic cinnoline derivatives.
18. Synthesis and antibacterial activity of novel cinnoline–isoxazole hybrids — M. B. Bommagani et al., 2021. Designed cinnoline/isoxazole hybrids with antibacterial evaluation.
19. Substituted dibenzo cinnolines: topoisomerase I targeting & cytotoxicity — Y. Yu et al., 2003 (often cited by later work). Early study linking dibenzo-cinnolines to topoisomerase I inhibition and cytotoxicity (useful SAR background).
20. Consequent Construction of C–C and C–N Bonds via Pd-catalysed Dual C–H Activation: Synthesis of Benzo[c]cinnoline Derivatives — (Organometallics entry / related summary), 2021. Pd-catalysed cascade annulation producing benzo[c]cinnolines — modern C–H activation strategy.
21. Copper-catalysed cascade cyclization of arylsulfonylhydrazones: Regioselective synthesis of functionalized cinnolines — (reported in Organic Letters / cited in ScienceDirect summaries). Copper cascade approaches used for regioselective cinnoline construction.
22. Facile one-pot protocols and green methods for polyfunctional cinnolines — (several method papers summarized across ScienceDirect 2015–2022). Trend papers showing microwave, metal-free, and tandem approaches for rapid library generation.
23. Synthesis of cinnoline 1,2-dioxide — I. Suzuki et al., (older method) — foundational synthetic transformation often referenced for oxy-derivatives and N-oxide chemistry.
24. Pyrazolo[4,3-c] cinnoline derivatives: synthesis and anti-inflammatory/antibacterial evaluation — R. K. Tonk et al., 2012 (useful scaffold extension cited by later Elsevier work). Shows cinnoline-fused heterocycles with biological activity.
25. Synthesis of azobenzo cinnolines and study of dye properties — O. NalcıoGlu et al., 2021. Cinnoline-based dyes and chromophores — material/optical applications.
26. Practical synthesis of benzo[c]cinnoline-N, N′-dioxides and N-oxides — Paradisi et al., 1993 (classic method still cited by modern papers for oxidation/derivatization steps).
27. Therapeutic potential of the cinnoline core — Mini-Review / trend summary — (discussed in Mini-Reviews in Medicinal Chemistry and related Elsevier sources). Overview of cinnoline as a medicinal scaffold.
28. Substrate-directed C–H activation for synthesis of benzo[c]cinnolines — (Org. Lett / related reports summarized on ScienceDirect 2015–2021). Modern direct functionalization strategies enabling regioselective cinnoline construction.
29. Recent review: anticancer activity of benzodiazine derivatives (phthalazine, cinnoline, quinazoline) — 2025 review summarizing the last decade's anticancer wor k on benzodiazine scaffolds. Useful for SAR and gap identification.

CHAPTER 3

PLAN OF WORK:

3.1 In present research, we planned the synthetic sequence of reactions leading to the preparation of compounds wherein the cinnoline nucleus is fused with other heterocycles like pyrazoles, oxazines and mercaptopyrimidines with a view to evaluate them for biological activity.

Cinnoline and its derivatives belong to the class of nitrogen-containing heteroaromatic compounds that are of great interest in medicinal and synthetic chemistry.

1. Cinnoline – Parent Compound

Structure: Cinnoline is a bicyclic heteroaromatic compound consisting of a benzene ring fused with a pyridazine ring (a six-membered ring containing two adjacent nitrogen atoms).

Molecular formula: $C_8H_6N_2$

Systematic name: 1,2-Benzodiazine

Appearance: It is a pale-yellow crystalline solid

3.2 EXPERIMENTAL WORK

1)THEORETICAL, STRUCTURAL STUDIES AND IR IDENTIFICATION OF OXAZINES

2) THEORETICAL, STRUCTURAL STUDIES AND IR IDENTIFICATION OF PYRAZOLES

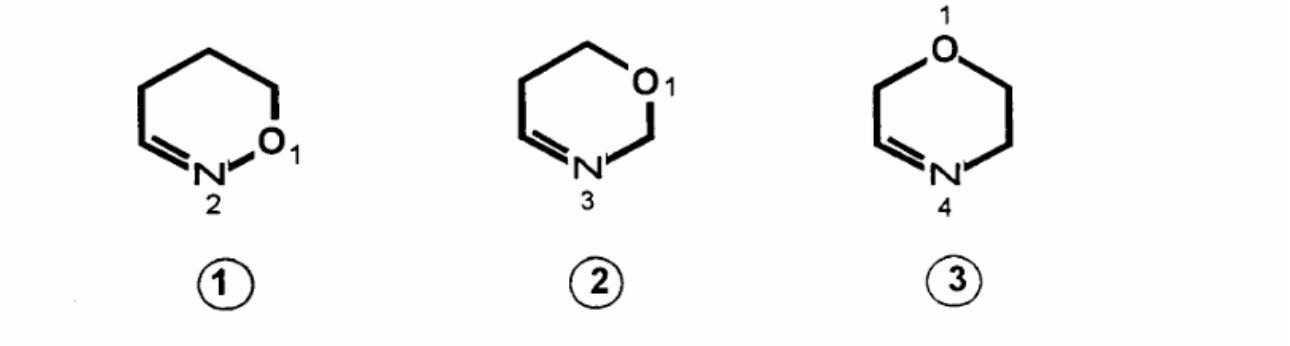
3)THEORETICAL, STRUCTURAL STUDIES AND IR IDENTIFICATION OF FLUOROQUINOLONES

CHAPTER 4

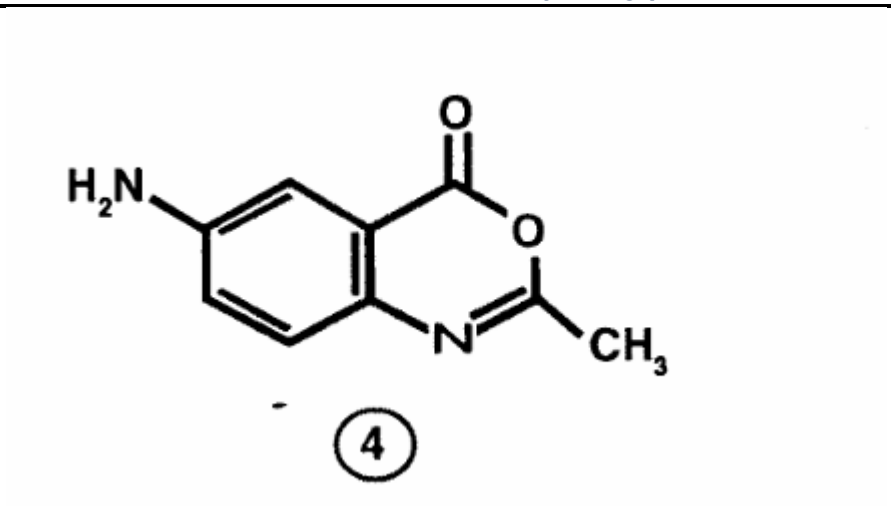
EXPERIMENTAL WORK

4.1 THEORETICAL, STRUCTURAL STUDIES AND IR IDENTIFICATION OF OXAZINES

These are the heterocyclic compounds containing one nitrogen and one oxygen atom. There are three isomeric oxazines present, which are 1,2-(1) 1.3- (2) and 1,4-(3). Morpholine (tetrahydro 1,4-oxazine) and phenoxazine are the important class of oxazine compounds.



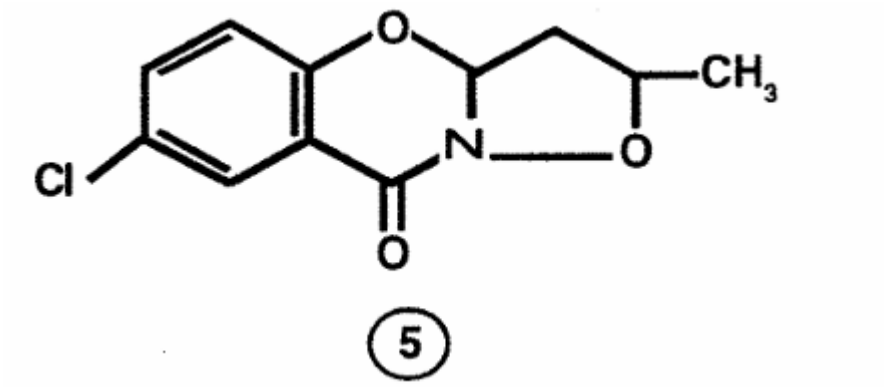
Morpholine finds its use as solvent and also finds its application as derivative of many drugs making the molecule more lipophilic, although as such it is not effective as a drug. The phenoxazines are the parent substances for number of dye intermediates. The sulphur analogs of phenoxazines are found to exert biological activities. Among them, the most important ones are phenothiazine class of compounds.



4

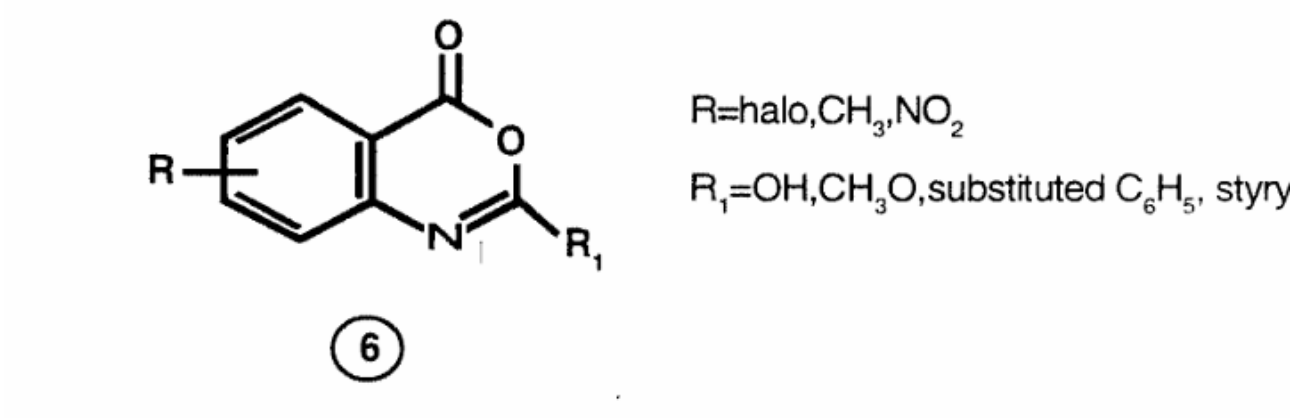
It is evident from the literature survey that, generally oxygen containing compounds are not too toxic, in comparison to sulphur containing compounds. Therefore, during the present study cinnoline moiety was combined with 1,3- oxazines to see whether they can enhance the biological activities, on account of the fact that these types of compounds are already well known for their diverse biological action.

4.2 BIOLOGICALLY ACTIVE OXAZINES 7-Chloro-2-methyl-3,3a-dihydro-2H, 9H-isoxazolo[3,2-b] (3,1) benzoxazin-9- one (5) was synthesised by Stiefel 1. This compound lowered the concentration of uric acid in blood serum from 4.9±0.32 mg / 100 ml to 2.25 ± 0.21 mg / 100 ml at dosage of 1.0 to 2.0 gm / day



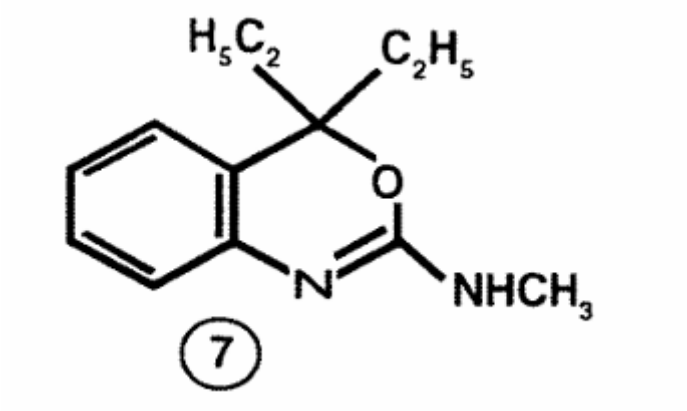
5

Hisamitsu Pharmaceutical Co. 2 has reported the synthesis of various 3,1- benzoxazine derivatives (6) which showed antiallergic, anti-inflammatory and analgesic activities.



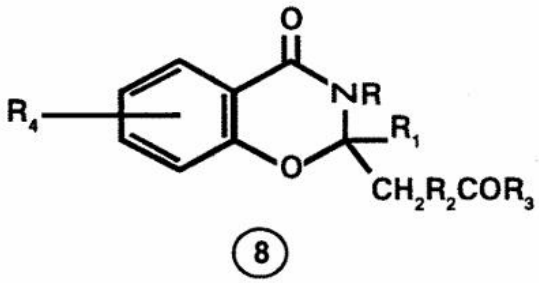
6

Cardiovascular properties of 2-aminomethyl 4,4-diethyl-3,1-benzoxazine (7) was reported by Zagorevaski et al 3. This compound and their salts were useful as antiarrhythmic agents



7

Santeen Pharmaceutical Co. Ltd 4 has reported various benzoxazine acetic acid derivatives^) as antipyretic, analgesic and anti-inflammatory agents with less gastrointestinal leision.



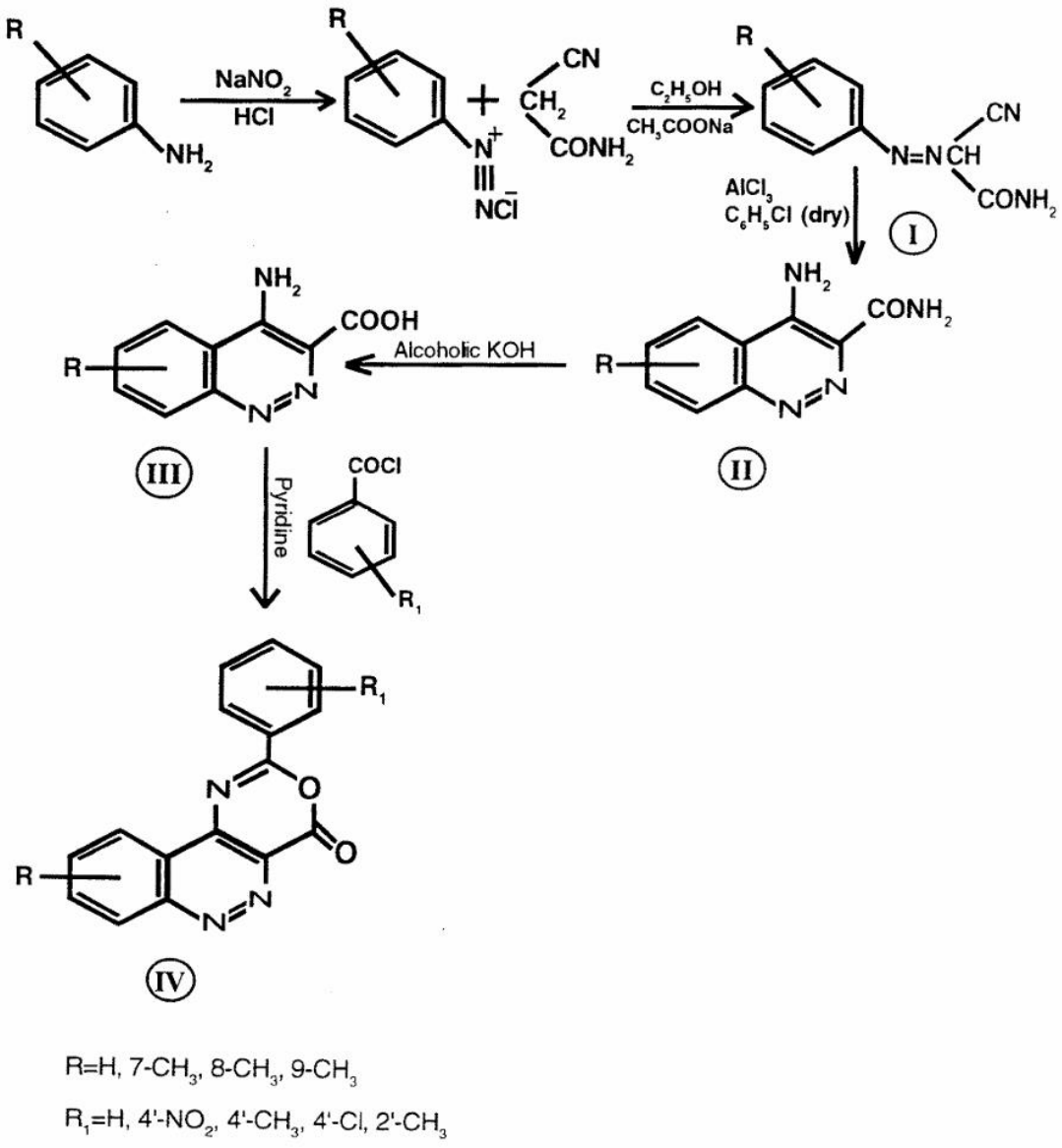
8

R=H, alkyl, substituted-C_6H_5,
substituted aralkyl.
R_1, R_2= H, alkyl
R_3=OH, alkoxy, NH_2, alkylamino,
substituted phenyl amino
R_4=H, alkyl, alkoxy, NO_2, NH_2, alkylamino,
acylamino, halo

4.3 PRESENT WORK

In view of the important biological properties associated with oxazines, -during the present investigation, we thought of synthesising fused oxazinocinnoline derivatives with a view to possess enhanced pharmacological activities. The required arylhydrazone(cyano)acetamide 46 (I) was prepared by the reaction between diazonium salts of substituted anilines and active methylene compounds such as cyanoacetamide, through Japp Kiingemann reaction 47. Arylhrazono(cyano)acetamide in the E form undergoes intramolecular Friedel Crafts reaction in chlorobenzene in presence of anhydrous aluminium trichloride to form 4-amino-3-cinnolincarboxamide (n)48. 4-Amino-3-cinnolincarboxamide (II) was hydrolysed in alcoholic potassium hydroxide to produce 4-amino-3-cinnolincarboxylicacid (III). 4-Amino-3- cinnolincarboxylic acid (III) is an important synthon for the synthesis of oxazine derivatives. Reaction of 4-amino-3-cinnolincarboxylic acid (III) with substituted benzoyl chloride in anhydrous pyridine afforded 2(substituted aryl)-3,1-oxazino [5,4-c] cinnolin-4-ones (IV) as shown in scheme 1.

SCHEME - 1 :



R=H, 7-CH_3, 8-CH_3, 9-CH_3

R_1=H, 4'-NO_2, 4'-CH_3, 4'-Cl, 2'-CH_3

4.4 RESULTS AND DISCUSSION

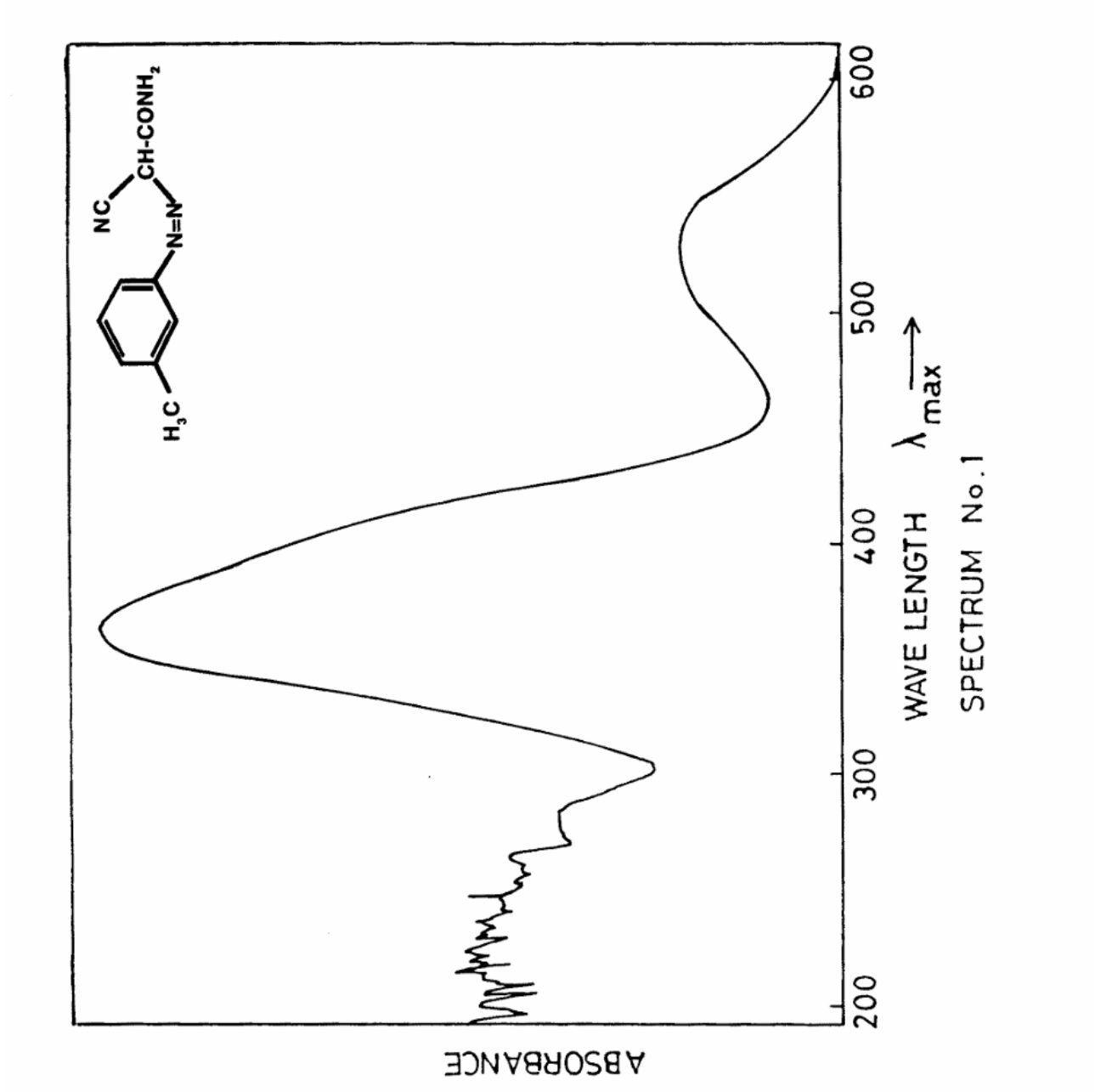
Structures of the compounds synthesised in the present investigation have been established on the basis of their UV and IR. In the following section spectral studies of some selected new compounds have been dealt with.

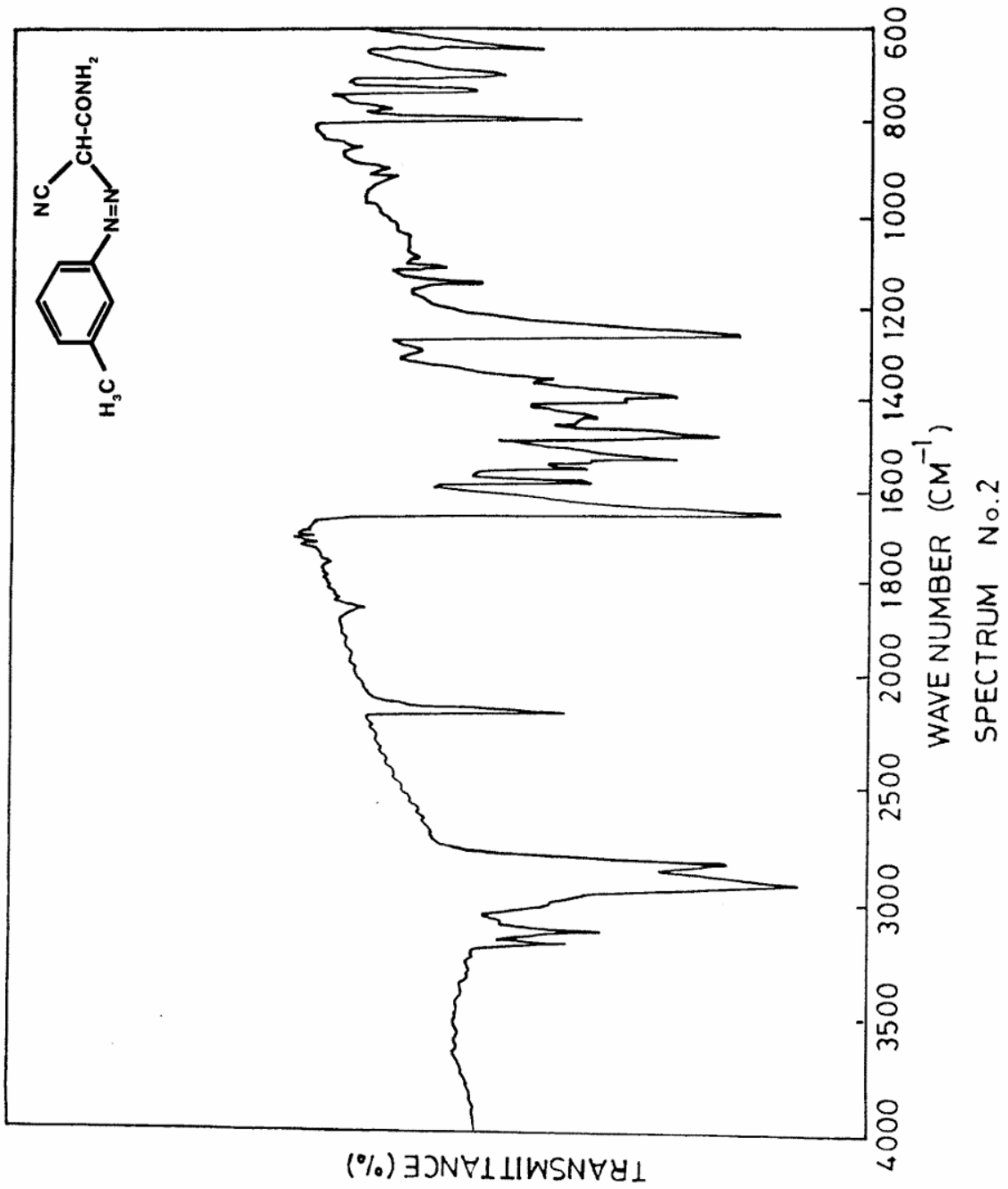
Arylhydrazone(cyano)acetamide shows X max at 340 nm in the UV absorption (Spect No.1) which is characteristic of all the aromatic arylhydrazone(cyano)acetamides.

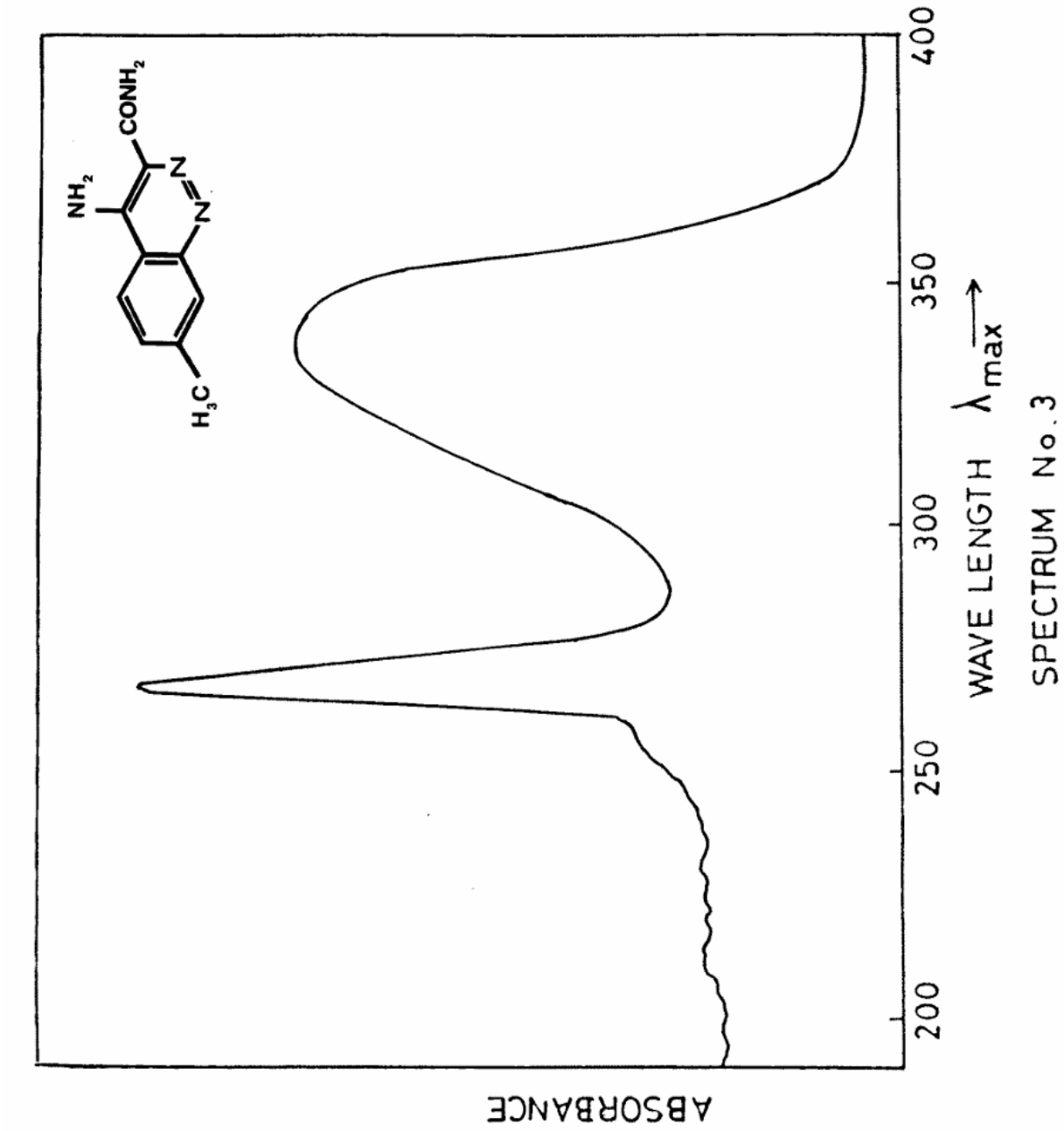
The IR spectrum of this compound (Spect No.2) shows characteristic absorption band for -NH2 of amide with a small shoulder in the region 3150 cm and a sharp peak at 2212 cm'1 indicating -C=N stretching vibrations. It also exhibited the characteristic sharp band at 1660 cm-1 due to amide caroonyi stretching vibrations.

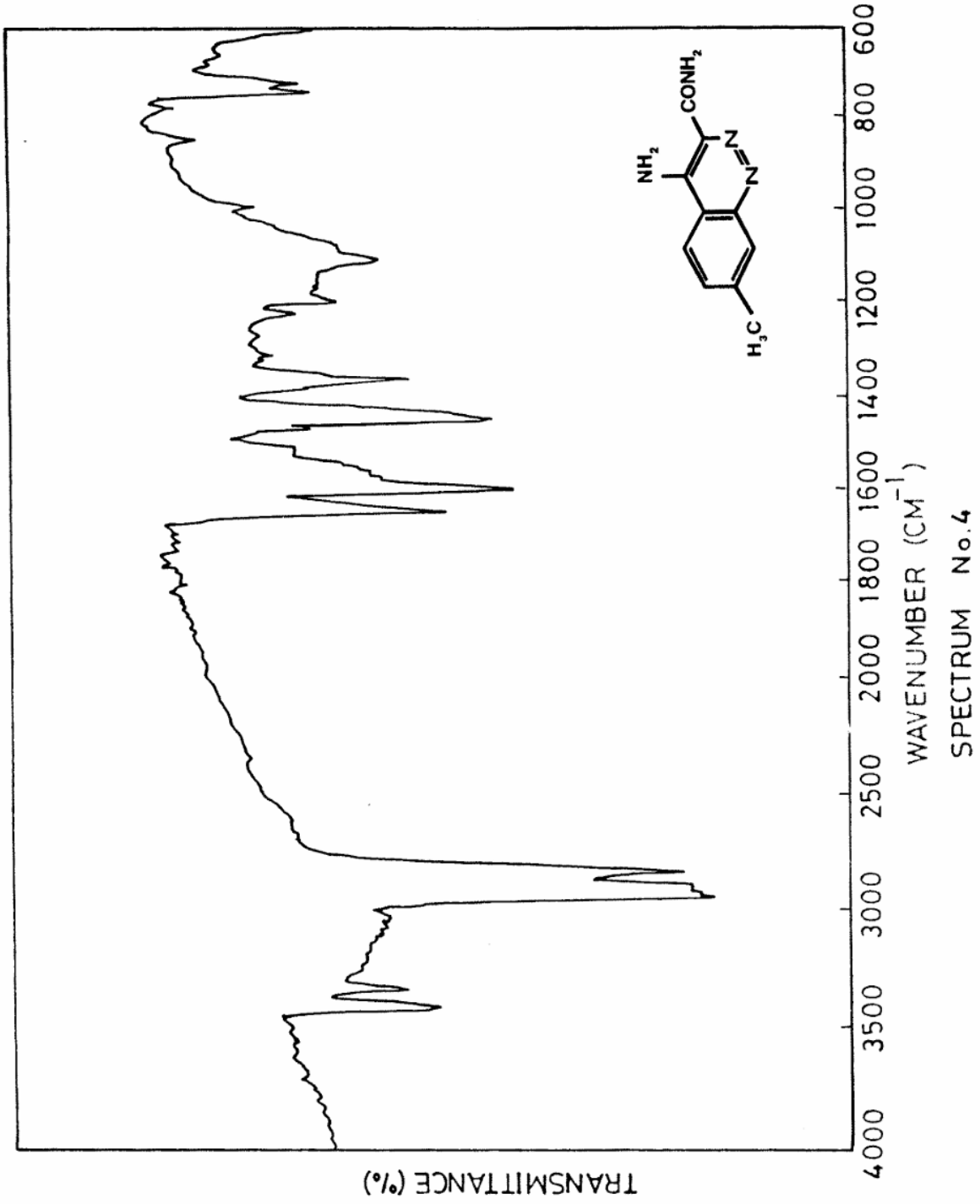
4-Amino-3-cinnolincarboxamide formed from the corresponding arylhydrazono (cyano)acetamide was clearly indicated by its UV and IR spectra. The 4-amino-3-cinnolincarboxamide (Spect No.3) shows X max at 266 and X max 340 nm confirming that the cyclisation has taken place. The IR spectrum of this compound (Spect No.4) shows characteristic absorption bands at 3440 cm ana 3315 cm'1 arising from the asymmetric and symmetric stretching vibrations of the two amino groups. Since amines have a very strong tendency to self-associate by hydrogen bonding, the band positions have been shifted to the lower frequency region. It is further observed that, a characteristic sharp band at 1660 cm1 is due 64 to amide carbonyl stretching vibrations. As a consequence of mesomeric effect, this amide carbonyl group has less double bond character and hence it appears at lower frequency.

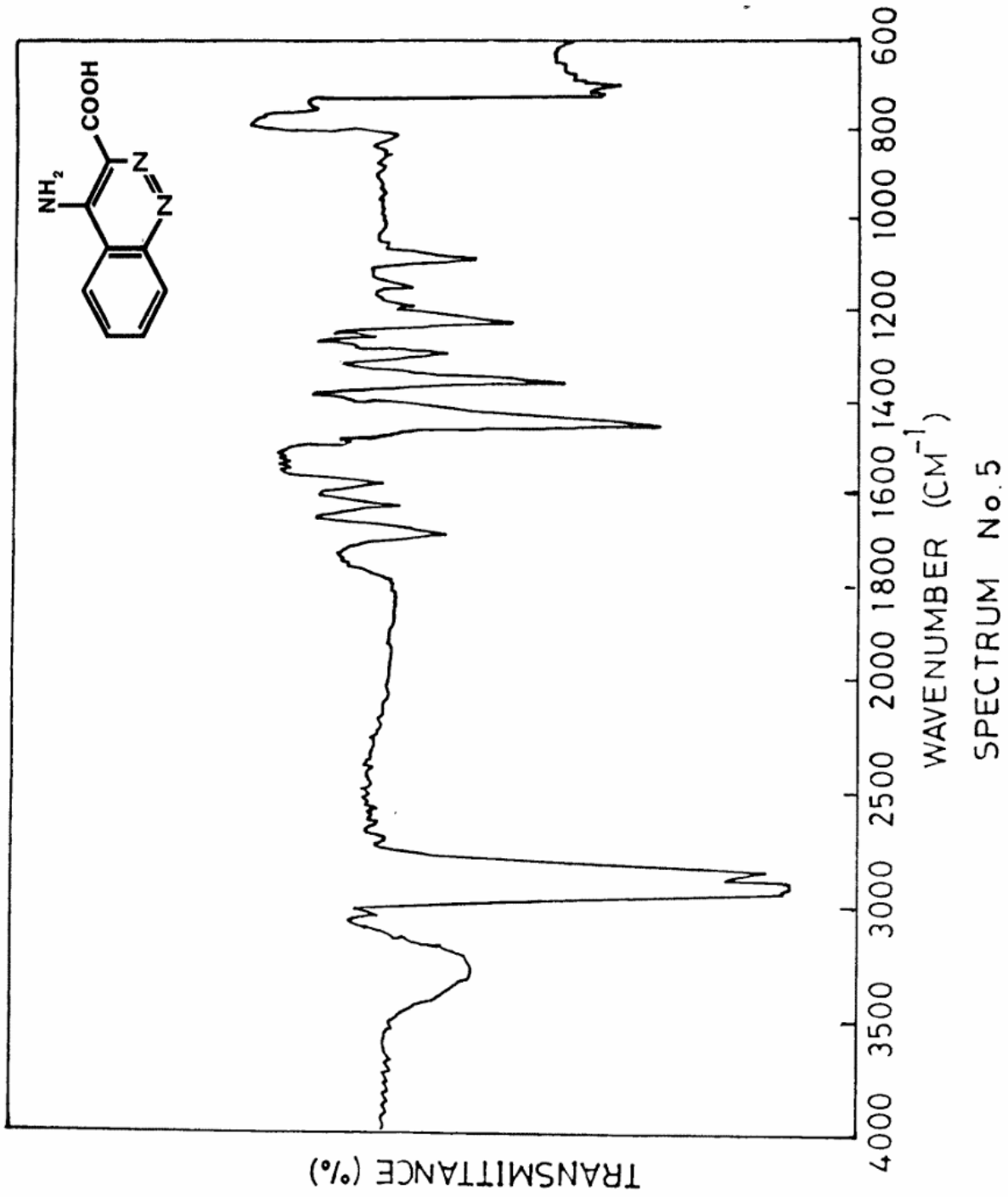
The IR spectra of 2-phenyl-3,1-oxazino[5,4-c] cinnolin-4-one and 2-(p-tolyl)- 3,1-oxazino[5,4-c] cinnolin-4-one (Spect. Nos. 8 and 9) gave intense absorption bands at 1760 cm'1 for carbonyl stretching of lactone and 1640 cm-1 for >C=N stretching vibrations.

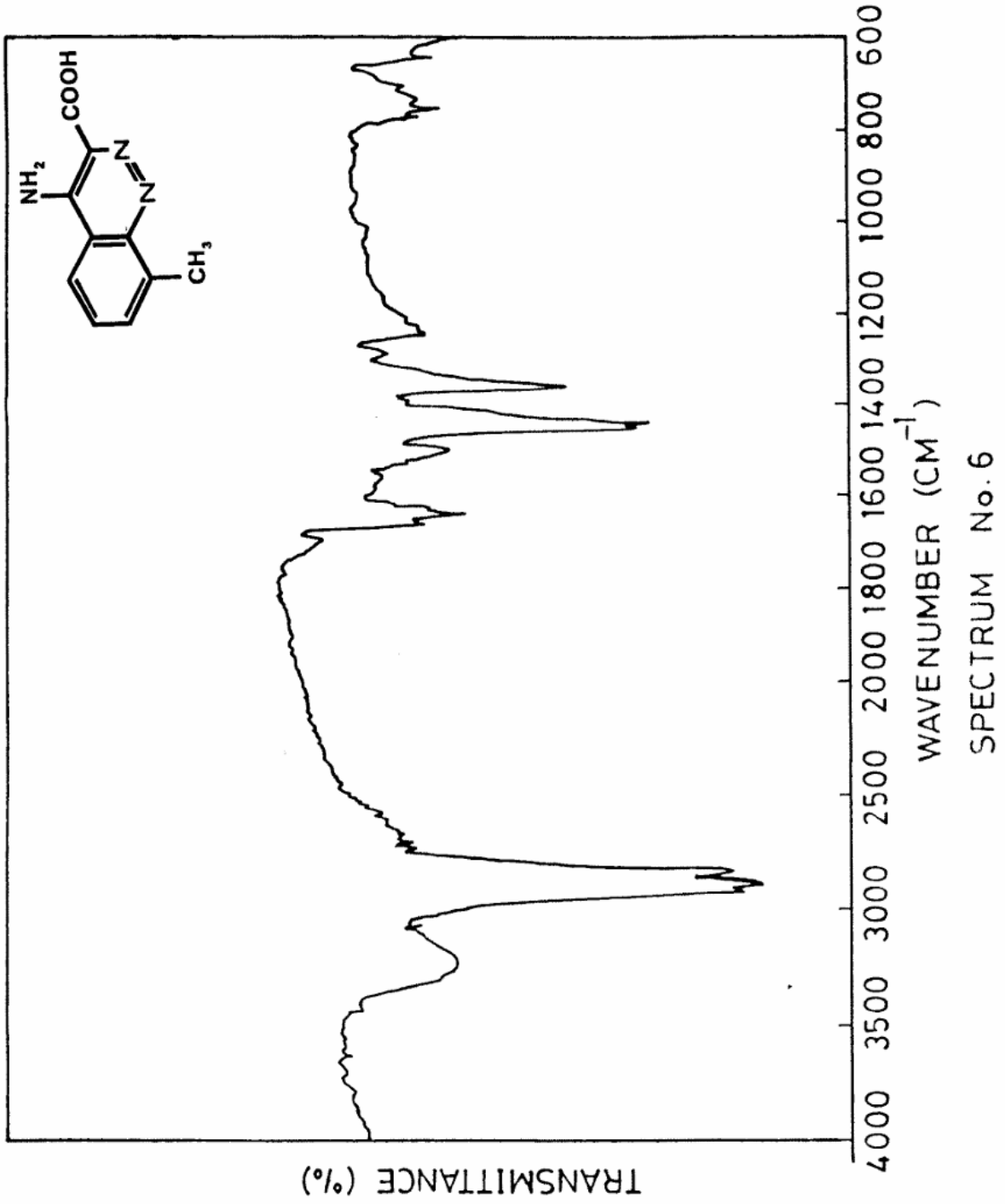


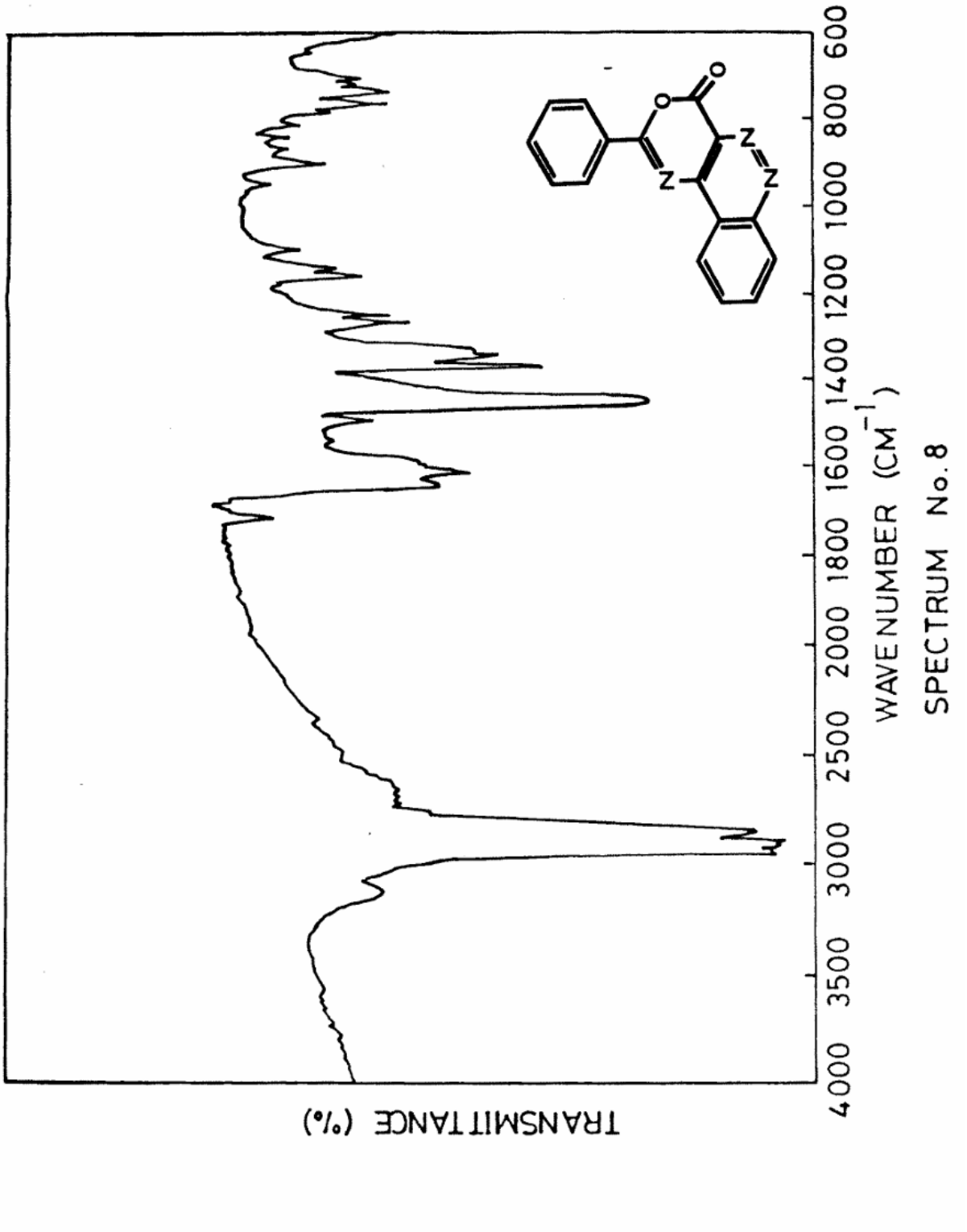

NC
CH-CONH2
N=N
H3C
TRANSMITTANCE (%)
4000 3500 3000 2500 2000 1800 1600 1400 1200 1000 800 600
WAVE NUMBER (CM-1)
SPECTRUM No.2

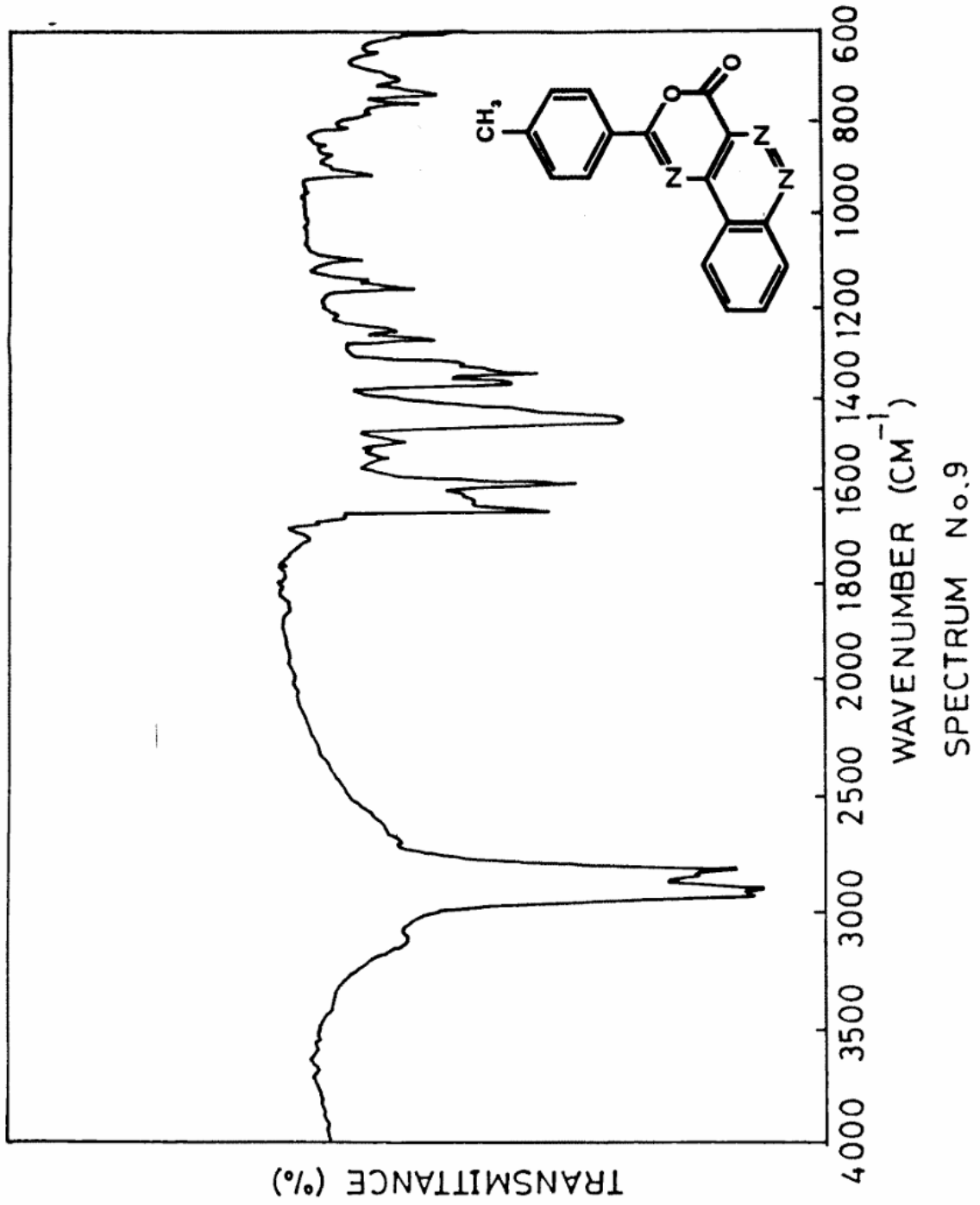

CONH2
NH2
N
N
H3C
ABSORBANCE
200
250
300
350
400
WAVE LENGTH λmax
SPECTRUM No. 3


TRANSMITTANCE (%)
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
WAVENUMBER (CM^{-1})
SPECTRUM No.4
$CONH_2$
NH_2
N
N
H_3C


COOH
NH2
N
N
TRANSMITTANCE (%)
4000 3500 3000 2500 2000 1800 1600 1400 1200 1000 800 600
WAVENUMBER (CM-1)
SPECTRUM No.5


COOH
N
N
NH2
CH3
TRANSMITTANCE (%)
4000 3500 3000 2500 2000 1800 1600 1400 1200 1000 800 600
WAVENUMBER (CM-1)
SPECTRUM No.6


TRANSMITTANCE (%)
4000 3500 3000 2500 2000 1800 1600 1400 1200 1000 800 600
WAVE NUMBER (CM^{-1})
SPECTRUM No. 8
O
O
N
N

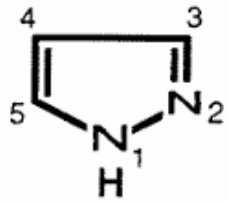

TRANSMITTANCE (%)
4000 3500 3000 2500 2000 1800 1600 1400 1200 1000 800 600
WAVENUMBER (CM⁻¹)
SPECTRUM No.9
CH3
O
O
N
N
N

EXPERIMENTAL WORK

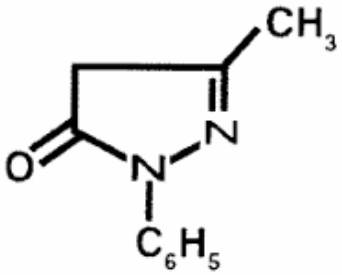
5.1 THEORETICAL, STRUCTURAL STUDIES AND IR IDENTIFICATION OF PYRAZOLES

Pyrazoles and its derivatives have exhibited a wide range of pharmacological activities such as sedatives, cholinesterase inhibitors, bacteriostatic, bactericides, fungicides including bleaching, luminescent and fluorescent properties 16 and also as anaesthetics 78. The chemistry of pyrazoles has been reviewed by Jacobs and Kost et al 10.

The pyrazole ring system (1) consists of a doubly unsaturated five membered ring containing two adjacent nitrogen atoms. Knorr 1112 first synthesised 1-phenyl-3-methyl-5-pyrazolone (2) by the reaction of ethyl acetoacetate with phenylhydrazine. Knorr13 introduced the name pyrazole for these compounds to denote that the nucleus was derived from pyrrole by replacement of a carbon by nitrogen.



(1)

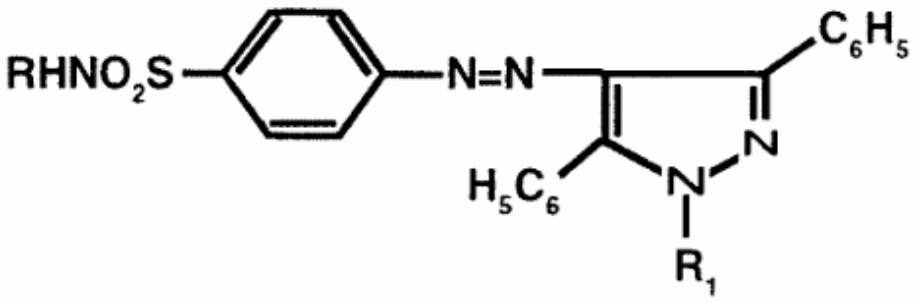


(2)

5.2 PYRAZOLES OF PHARMACOLOGICAL INTEREST

A survey of literature indicates that various substituted pyrazole compounds have been the basis of numerous dyes and intermediates in medicines 14.

3,5-Diaryl-4{substituted sulfonamidobenzeneazo) pyrazole derivatives prepared by Mutreja et ai 15 were found to be antimicrobial against E aureus and E coh- Among the compounds synthesised, compounds 3 and 4 showed better activity.



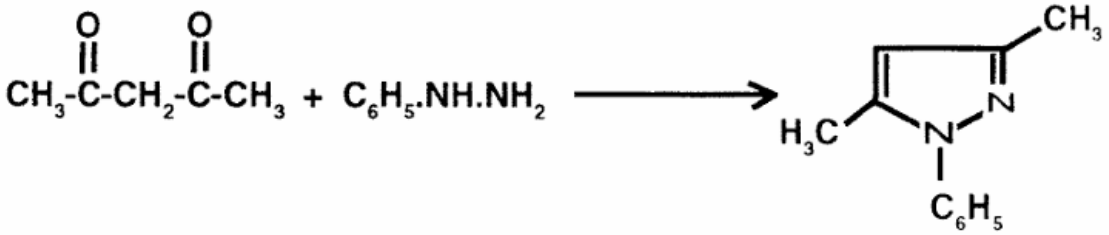
	R1	R
3	Pyrimidyl	H
4	4,6(CH3)2pyrimidyl	C6H5

5.3 RING SYNTHESIS

Three general methods of synthesis of this ring system (1) have been described by Jacobs et al.

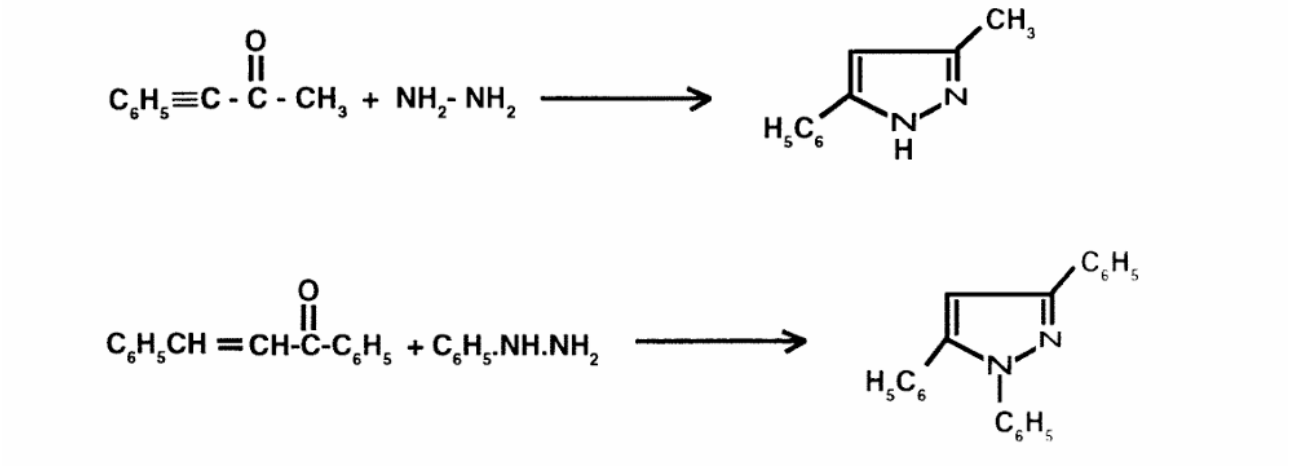
Method- I:

The reaction of hydrazine or its derivatives such as aryi or alkylhydrazines, semi carbazides or aminoguanidines with 1,3-dicarbonyl compounds led to the formation of corresponding pyrazoles



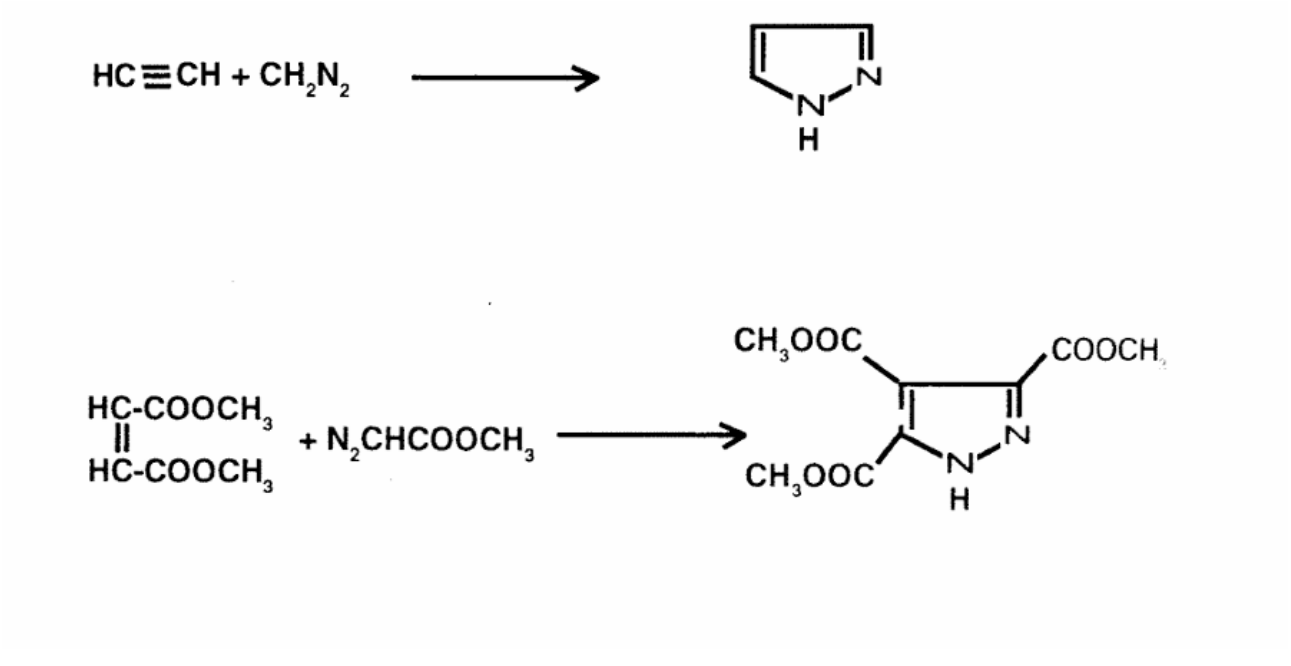
Method - II:

By the reaction of hydrazine's with a, (5-unsaturated carbonyl compounds, pyrazoles and pyrazolidines were obtained from the corresponding a, (3-acetylenic or ethylenic acids or acid derivatives



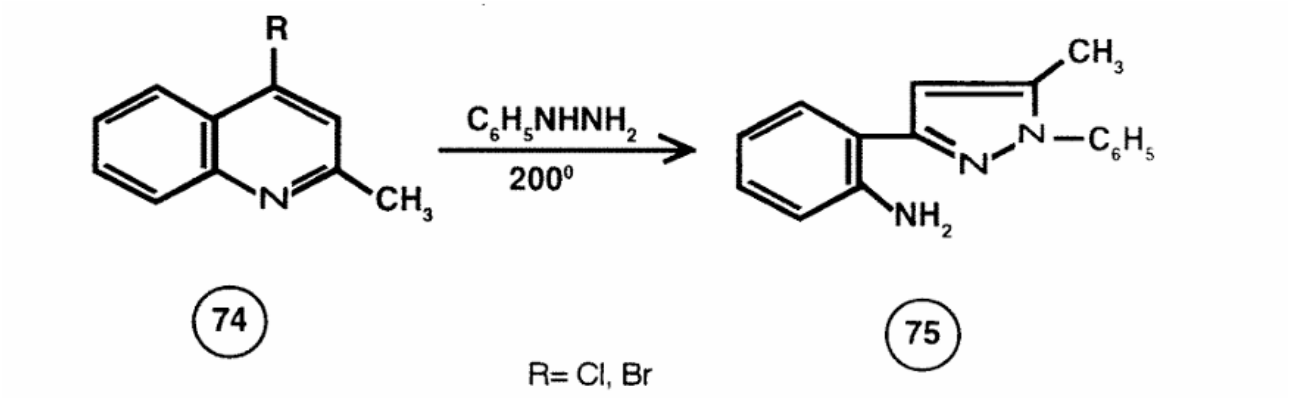
Method-Ill:

The reaction of aliphatic diazo compound such as diazomethane or diazo acetic ester with acetylenes or olefins gave the corresponding pyrazoles.

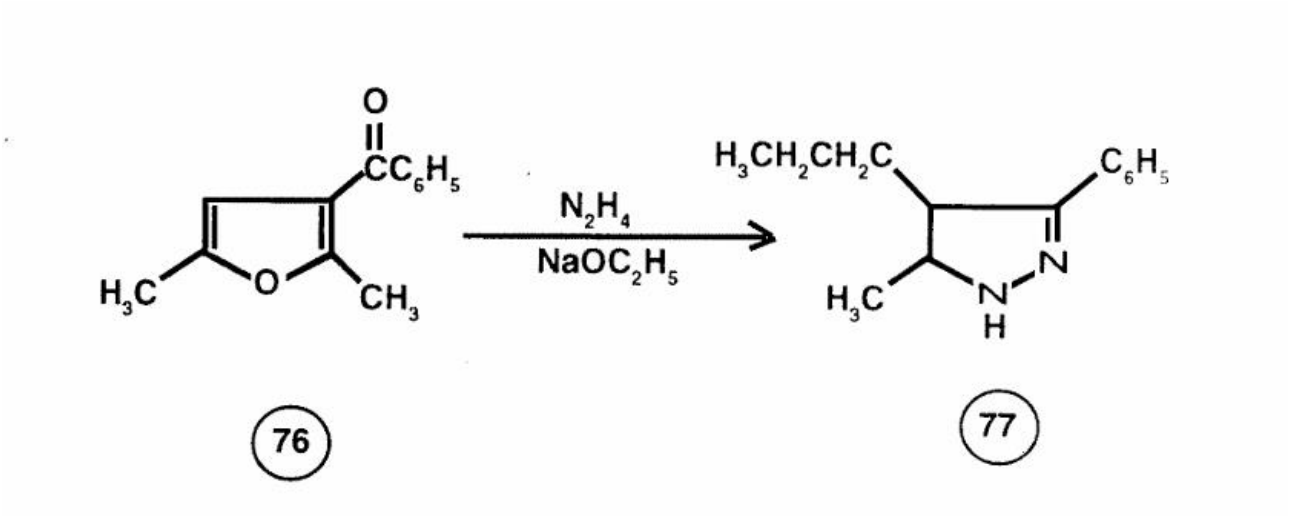


5.4 Pyrazoles from ring transformation reactions:

Nitrogen containing heterocyclic compounds such as quinolin-4-ones and 4-chioro and 4-bromoquinoIines (74) when treated with phenyl hydrazine undergo rupture of the heterocyclic ring with subsequent conversion to pyrazoles 75 under drastic conditions.

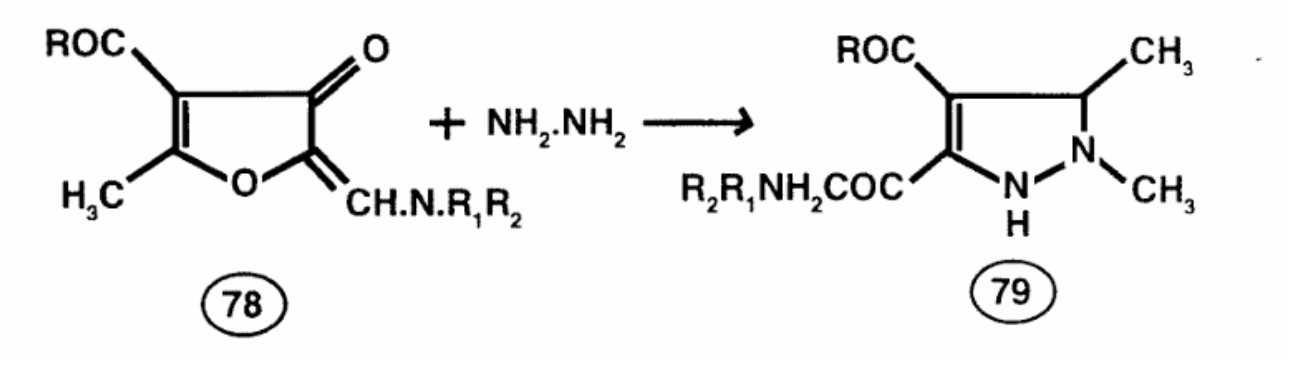


The presence of a carbonyl substituent in the (3-position of furans is essential for the cleavage of this ring 65. 3-Benzoyl-2,5-dimethylfuran undergoes both conversion to pyrazole 77 and Wolf-Kishner reduction of the side chain, when reacted with hydrazine hydrate.



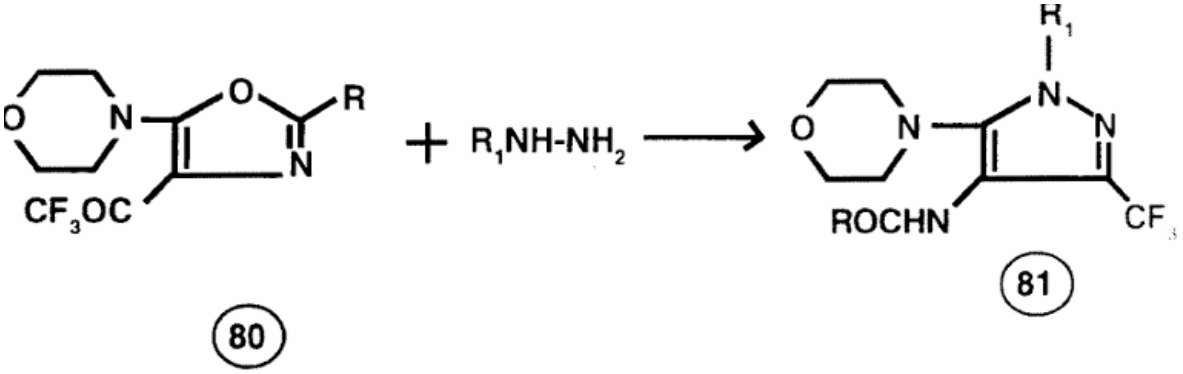
76 77

Cantegrel et al 67 have reported the reaction of substituted furanones with hydrazine hydrate to yield pyrazoles.



78 79

Clerin et al 68 have described the reactions of oxazole's with hydrazine to give Pyrazoles 81 by the nucleophilic attack at C5 followed by ring opening and recyclization



80 81

R=C_6H_5, CF_3, p-$NO_2.C_6H_5$; R_1 = H, CH_3, C_6H_5

From the literature it is obvious that pyrazole nucleus has been associated with diverse biological activities. Amongst various pharmacological activities exhibited by pyrazole derivatives; antipyretic, anti-inflammatory, analgesic, insecticidal and antidiabetic properties are noteworthy.

5.5 PRESENT WORK

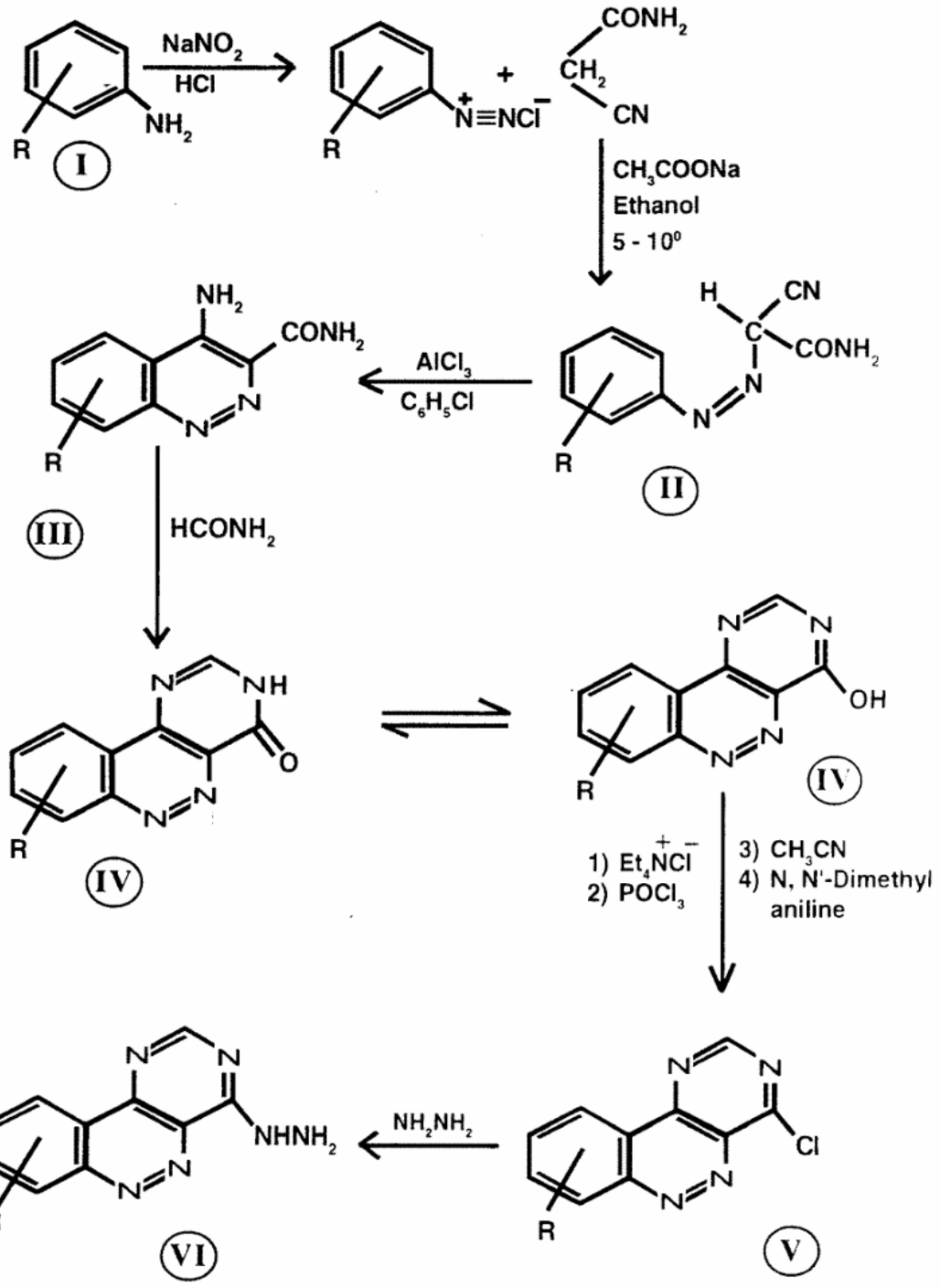
In view of the different pharmacological properties associated with the pyrazole derivatives, our present investigation aims at synthesising various substituted 4-pyBazolylpyrimido[5,4-c] cinnolines. These were obtained by the reaction of substituted-4-hydrazinopyrimido[5,4-c] cinnolines with 2,4-pentadione. S-bismethylethylenecyanoacetate, S-bismethylethylenecyanoacetamide and S-bismethylethylenemalanonitrile in ethanol. The newly synthesised compounds were screened for their biological activities.

The convenient starting material arylhydrazone(cyano)acetamide (II) were prepared by the reaction between diazonium salts of substituted anilines (I) and active methylene compound such as cyanoacetamide through the Japp-Klingemann reaction. Arylhydrazono(cyano)acetamide in the E-form undergoes intramolecular Friedel-Crafts reaction in chlorobenzene in presence of anhydrous AICI3 to form 4-amino-3-cinnofincarboxamides (IEI).

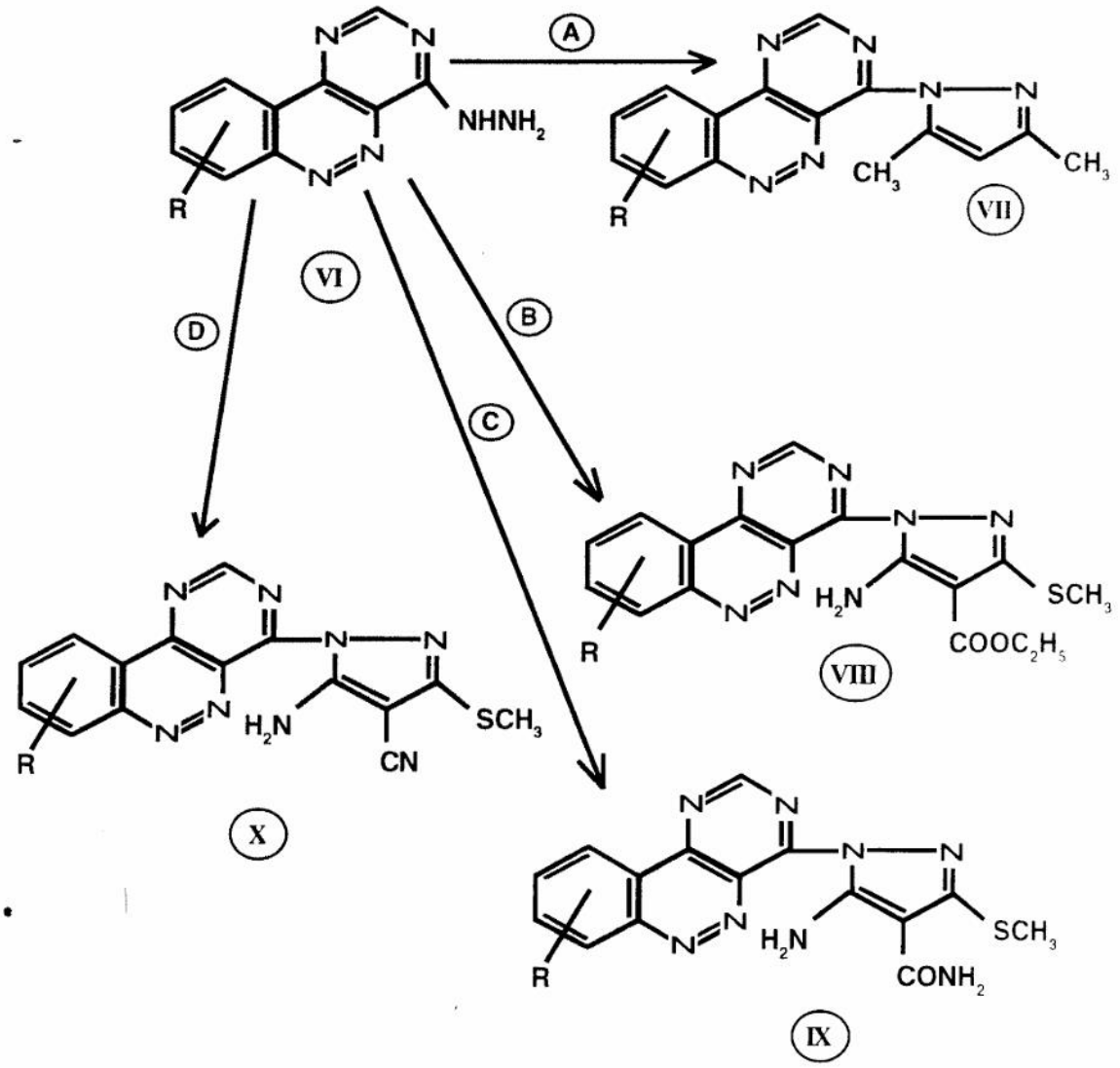
4-amino-3-cinnolincarboxamides(m) were converted to pyrimido[5,4-c] cinnohn- 4-ones (IV) by refluxing them with excess of formamide or formic acid and acetic acid mixture for one hour.

The hydroxyl group of pyrimido[5,4-c] cinnolin-4-ones cannot be readily replaced by chlorine atom by treatment with little more than one equivalent c* phosphrousoxychloride. The reaction with POCI3 and PCI5 mixture also could not yield 4-chloropyrimido[5,4-c] cinnolines. However, 4-chioropyrimido[5,4-c] cinnolines' 104 were obtained by treating compound IV with POCI3 in presence of a phase transfer catalyst like tetraethylammonium chloride in presence of acetonitrile and dimethylaniline, a method reported by Robins and Uzansk.

SCHEME- 2 :


NaNO2
HCl
NH2
R
I
+
N≡NCl
CONH2
CH2
CN
CH3COONa
Ethanol
5 - 10°
H
CN
C
CONH2
N
N
R
II
AlCl3
C6H5Cl
NH2
CONH2
N
N
R
III
HCONH2
N
NH
O
R
IV
N
N
OH
N
N
R
IV
1) Et4NCl
2) POCl3
3) CH3CN
4) N, N'-Dimethyl aniline
N
N
Cl
N
N
R
V
NH2NH2
N
N
NHNH2
N
N
R
VI

SCHEME- 2 (Continued)



A = 2,4-pentadione

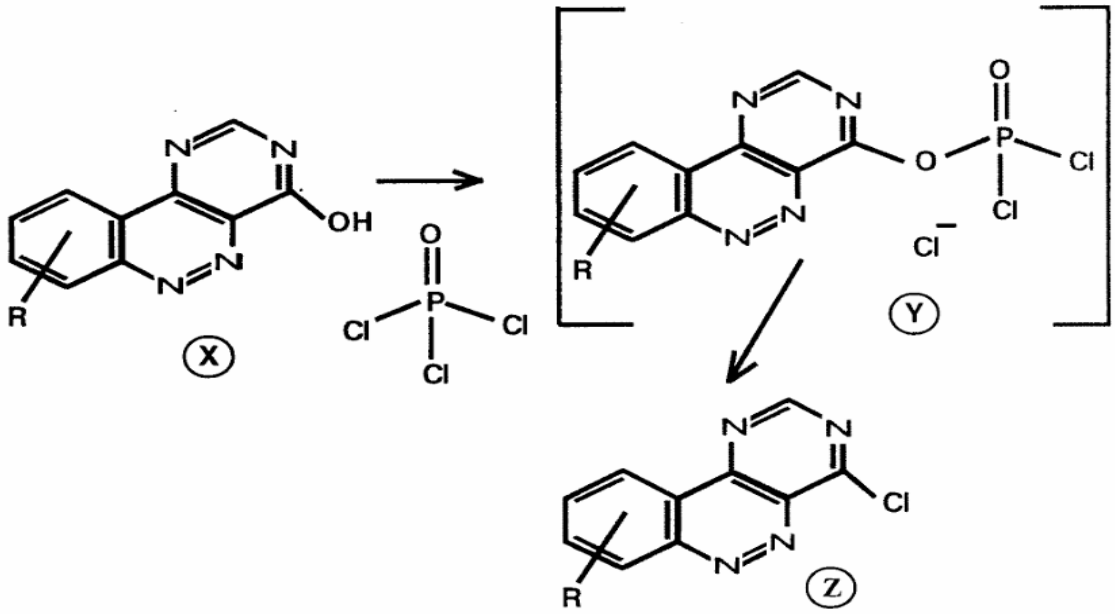
B = S-bismethylethylenecyanoacetate

C = S-bismethylethylenecyanoacetamide

D = S-bismethylethylenemalanonitrile

R= 8-CH_3, 9-CH_3

Mechanism of the reaction :



The phosphorylation of (X) gave the aromatic phosphorodichloride intermediate(Y) followed by the attack of chloride anion at C-4 of (X) to give (Y) and dichlorophosphate. A higher concentration of external chloride anion favours conversion of Y to Z.

4-Chloropyrimido[5,4-c]cinnolines(V), thus obtained are valuable intermediates for preparing a large number of pyrimido[5,4-c]cinnoline derivatives, since chlorine atom at the C_4 position is highly reactive and can be displaced by nucleophilic reagents.

The 4-chloropyrimido[5,4-c] cinnolines(V) so obtained were converted to 4- hydrazinopyrimido [5,4-c] cinnolines (VI) by refluxing with hydrazine hydrate (98%) in ethanol for 2 hours on a steam bath, then cooled, filtered and recrystallised from dimethylformamide. Different substituted pyrazoles were prepared by taking the 4- hydrazinopyrimido[5,4-c] cinnolines (VI) by refluxing them with 2,4-pentadione, 5-bismethylethylenecyanoacetamide, S-bismethylethylenemalanonitrile and S-bismethylethylenecyanoacetate for 5-6 hours. The reaction mixtures were then evaporated to half the volume and cooled. The solid separated after cooling was collected by Alteration, dried and recrystallised from acetic acid.

5.6 RESULTS AND DISCUSSION

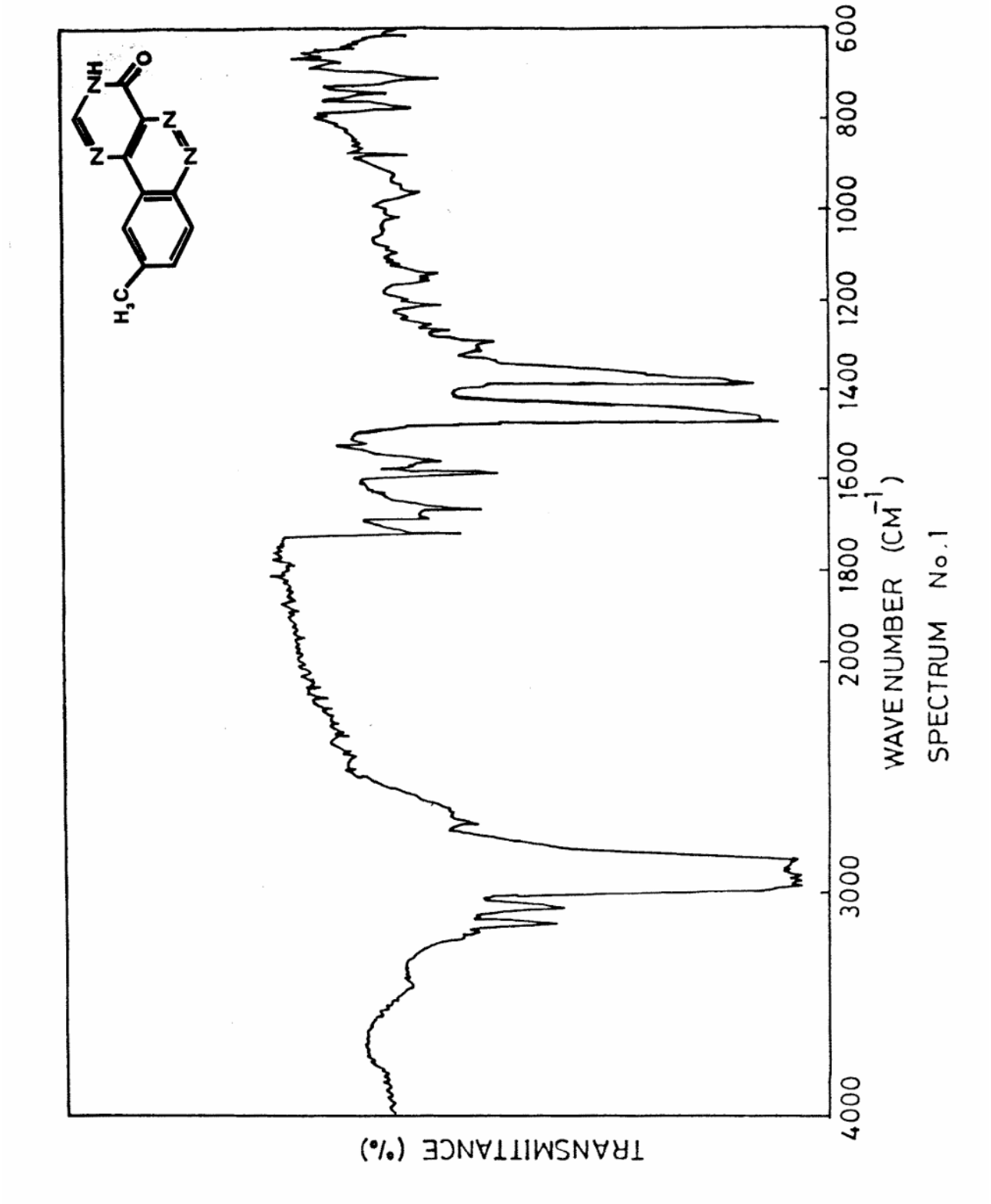
The structures of compounds prepared during the present investigations have been established on the basis of their UV, IR and PMR spectral studies' the following section spectral studies of some selected new compounds have been dealt with.

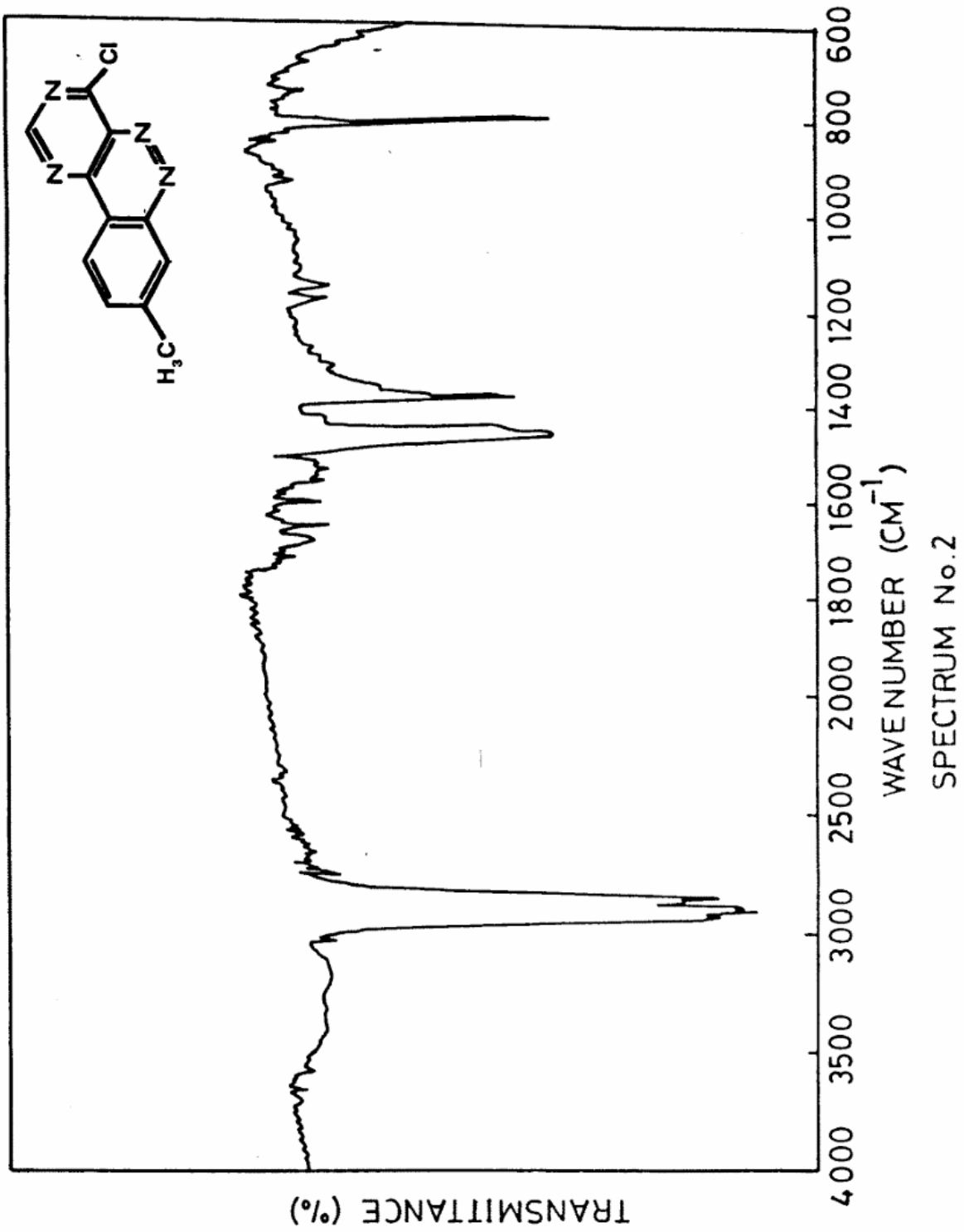
Pyrimido[5,4-c] cinnoiin-4-ones were obtained from 4-amino-3-cinnolm carboxamides. The IR spectrum of 9-methyl-pyrimido[5,4-c] cinnolin-4-one (Sped. No. 1) displayed a weak band at 3130 cm1 due to >NH stretching and the bands due to -NH2 were absent indicating the cyclisation of carboxamide. It has been further supported by the shifting of carbonyl band (>C=0) from lower to higher frequency range and it exhibited a band at 1720 cm1 due to >C=0 stretching.

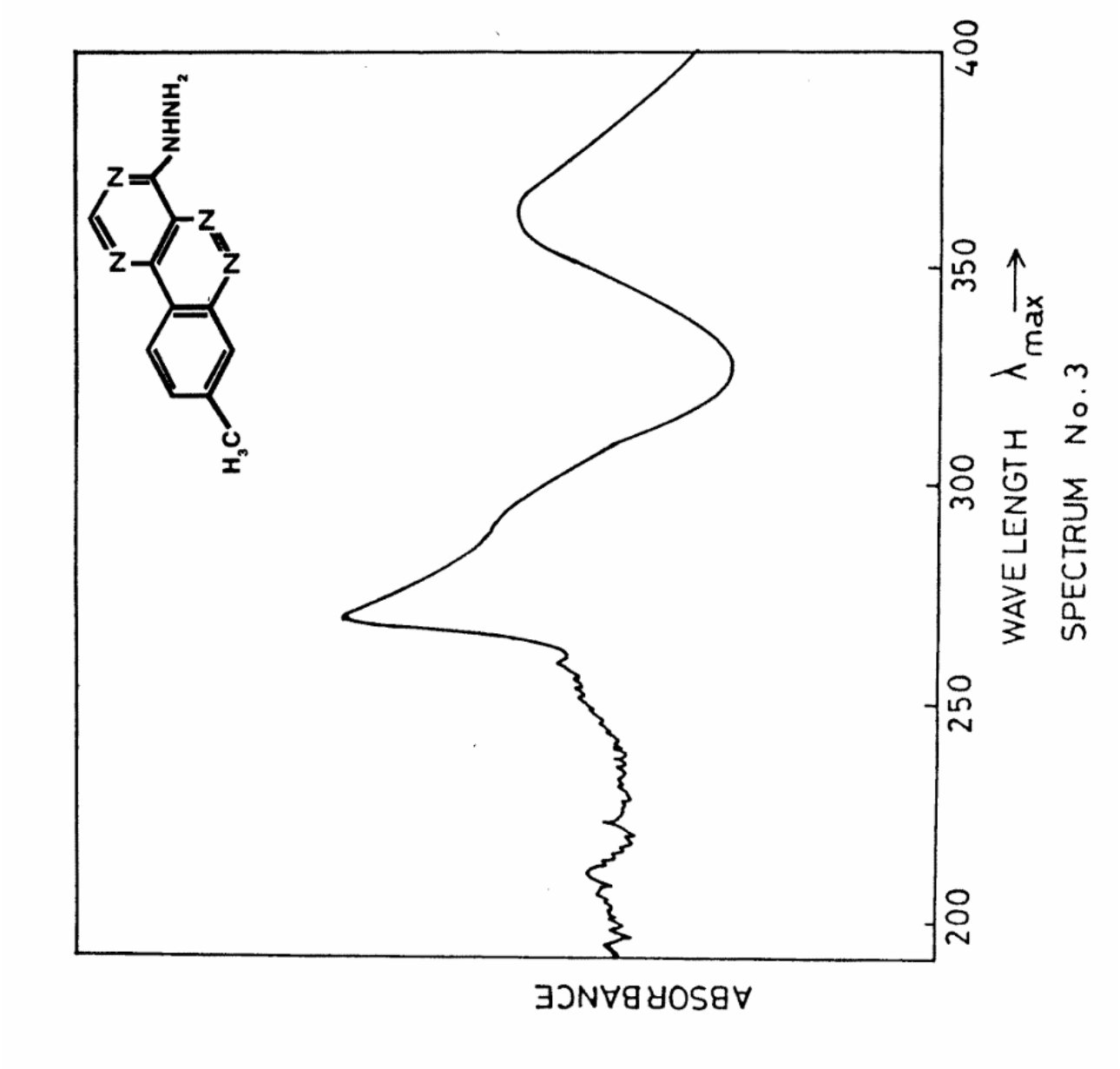
In the IR spectrum (Sped. No. 2) of 4-Chloropyrimido- [5,4-c] cinnoline. the absence of a characteristic band in the range of 3500 - 3100 crrr1 due to >NH group indicated the formation of a chloro compound. The additional support for this has been deduced by the presence of a sharp band at 720 crrr1 due to =C-Ci stretching vibrations.

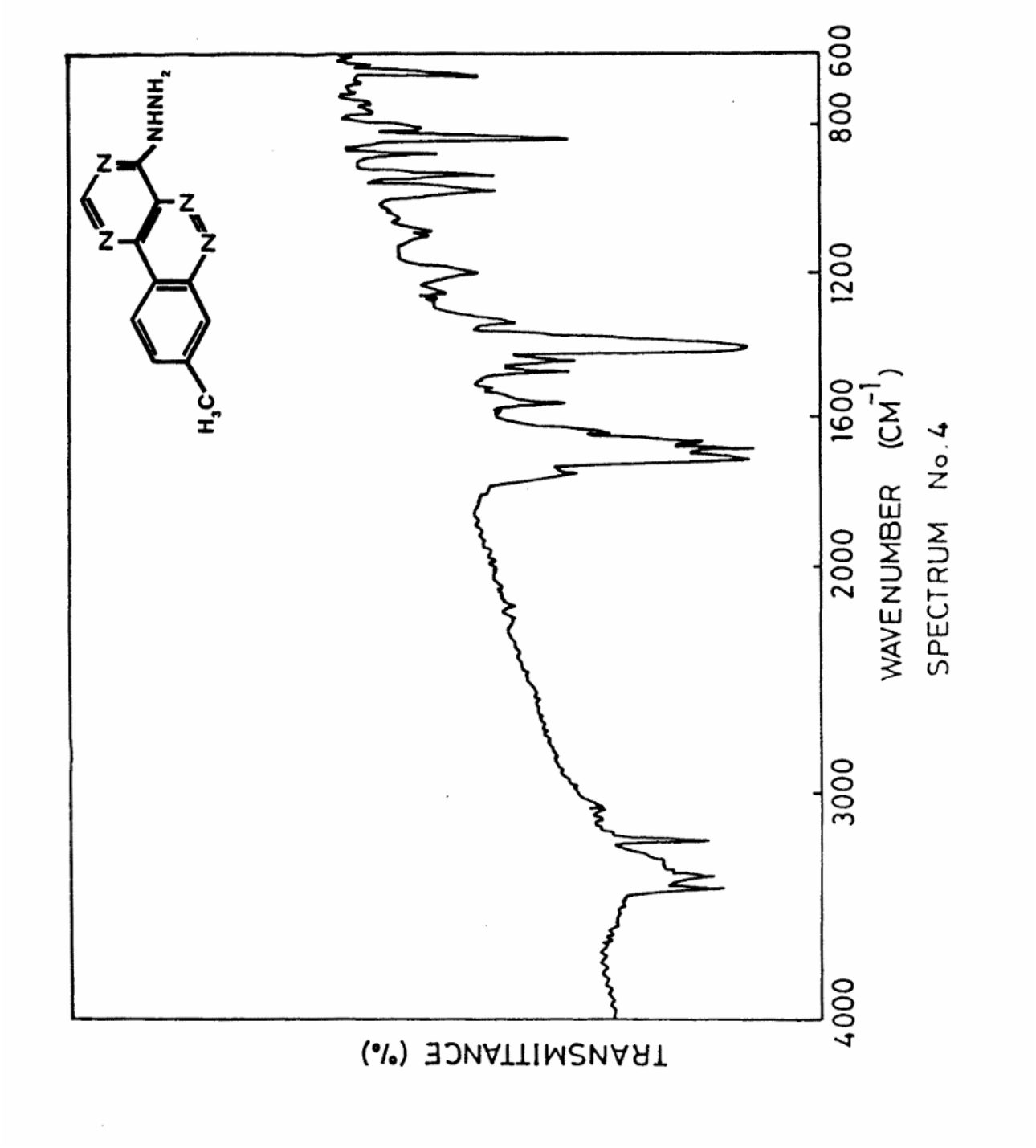
The UV spectrum (Spect. No. 3) of 4-hydrazino-8-methylpyrimido [5.4-c] cinnoline showed an intense band at X max 270 nm and X max 360 nm which may be attributed to -C=C-C=N- chromophore. The IR Spectrum (Spect. No. 4; of this compound showed characteristic bands at 3100 cm'1 and 3310 crrr1 due to -NH-NH2 group.

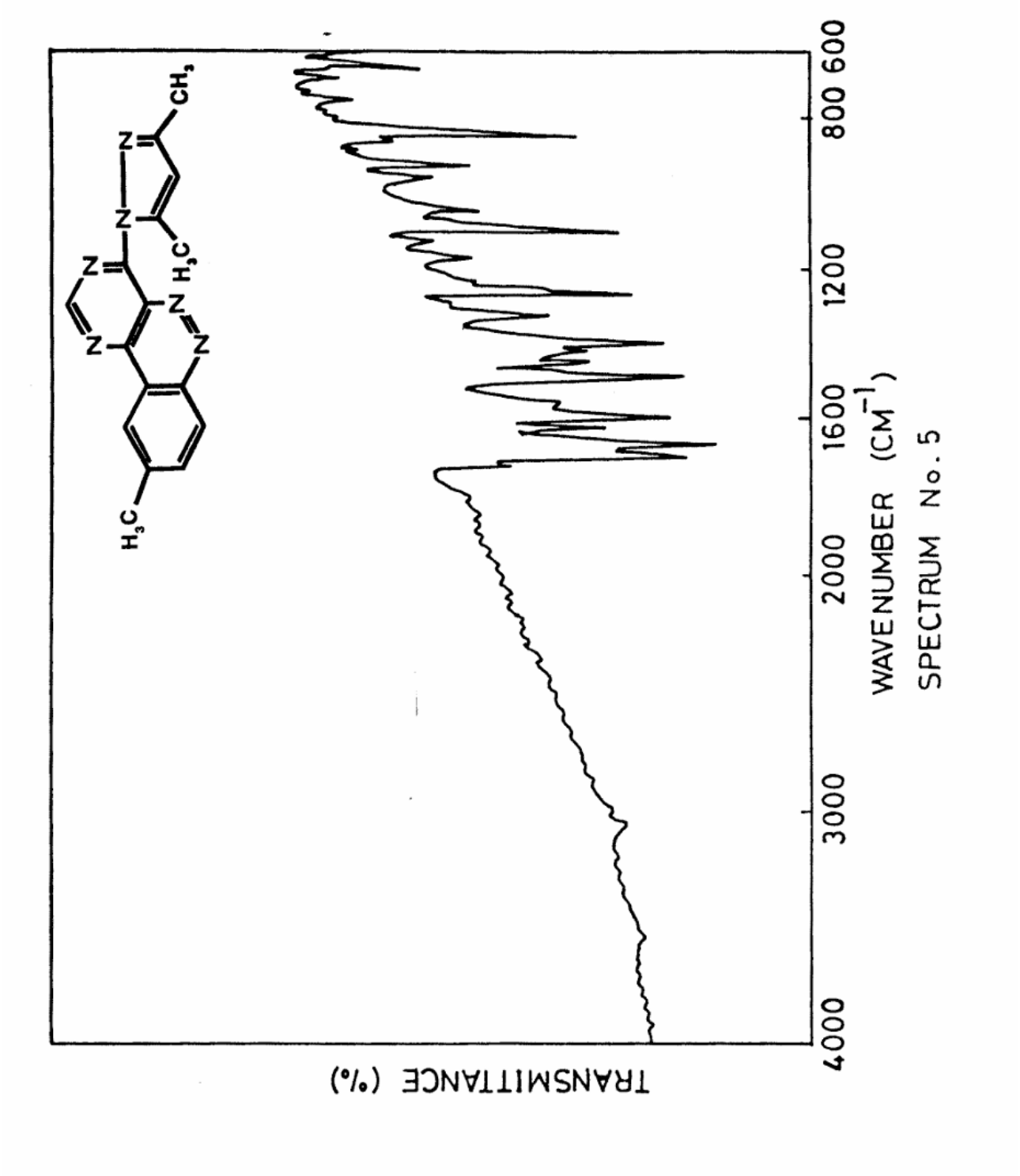
The absence of an absorption band in the range of 3400 cnrr1 to 3200 cnr1 due >NH group in the IR spectrum (Spect. No. 5) of 9-methyl-4(3',5'-dimethyl- 1-pyrazolyl) pyrimidinone indicates the presence of a cyclised pyrazole moiety.

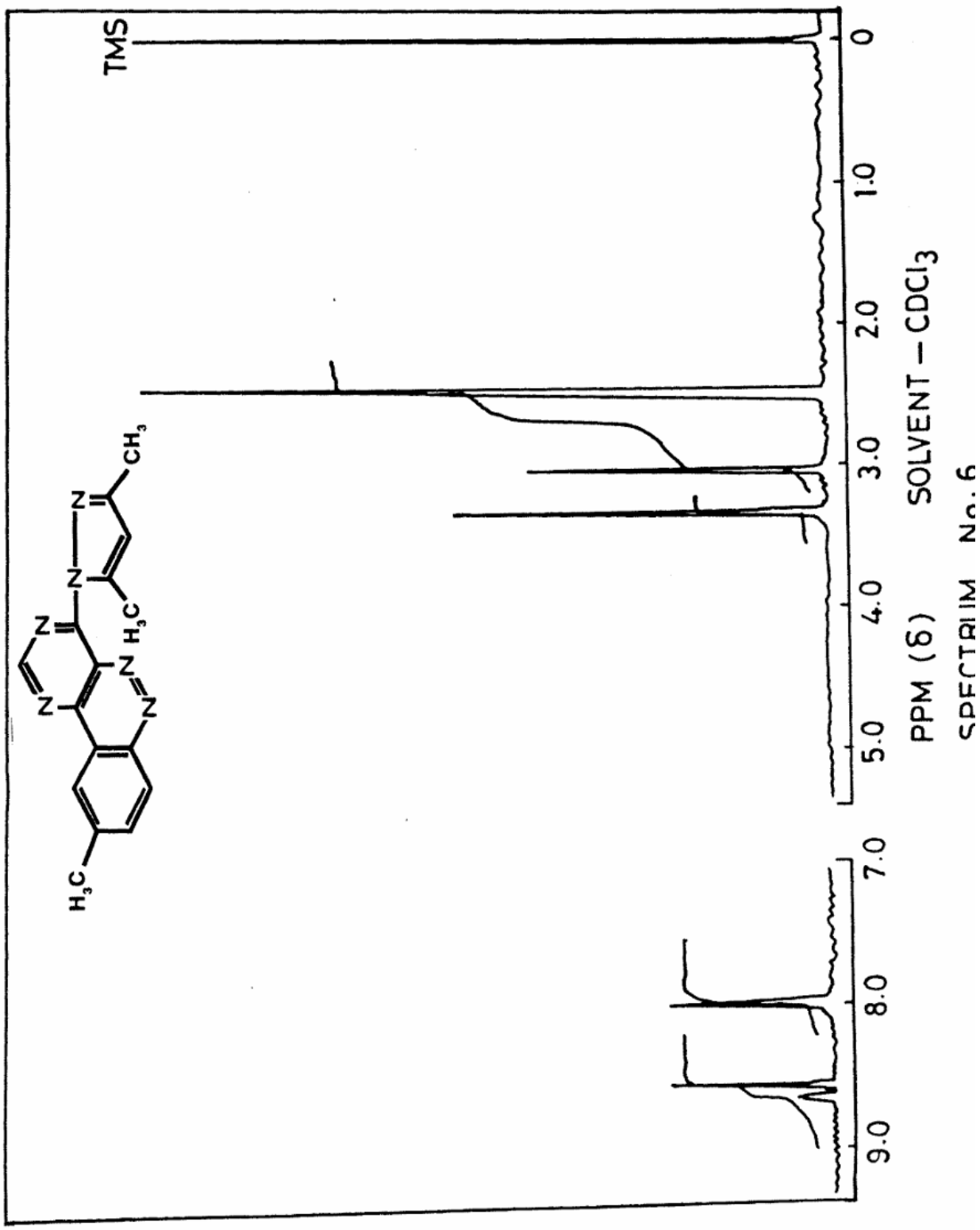

TRANSMITTANCE (%)
4000
3000
2000
1800
1600
1400
1200
1000
800
600
WAVE NUMBER (CM⁻¹)
SPECTRUM No.1
NH
O
N
N
N
N
H3C


Cl
N
N
N
N
H_3C
TRANSMITTANCE (%)
4000 3500 3000 2500 2000 1800 1600 1400 1200 1000 800 600
WAVENUMBER (CM^{-1})
SPECTRUM No.2


NHNH2
N
N
N
N
H3C
ABSORBANCE
200
250
300
350
400
WAVE LENGTH λmax
SPECTRUM No. 3


NHNH2
N
N
N
N
H3C
TRANSMITTANCE (%)
4000
3000
2000
1600
1200
800 600
WAVENUMBER (CM-1)
SPECTRUM No.4


TRANSMITTANCE (%)
4000
3000
2000
1600
1200
800 600
WAVENUMBER (CM^{-1})
SPECTRUM No. 5
CH$_3$
H$_3$C
H$_3$C


TMS
0
1.0
2.0
3.0
4.0
5.0
7.0
8.0
9.0
PPM (δ)
SOLVENT — $CDCl_3$
CH_3
H_3C
H_3C
N

EXPERIMENTAL WORK

6.1 THEORETICAL, STRUCTURAL STUDIES AND IR IDENTIFICATION OF FLUOROQUINOLONES

6.2 Fluoroquinolones as antibacterial agents:

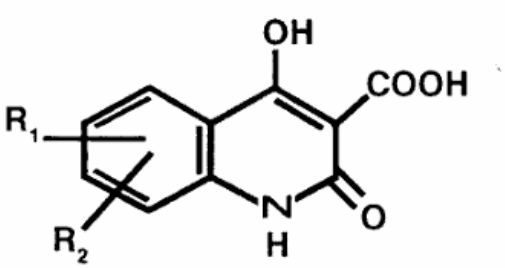
Norfloxacin is an orally absorbed fluoroquinolone antibacterial agent with fluorine at position 6 and a piperazine ring at position 7. These changes have resulted in a marked enhancement (compared with that of the earlier quinolones) in in-vitro antibacterial activity, specifically the antibacterial spectrum of norfloxacin includes Pseudomonas aeruginosa as well as enteric pathogens. Norfloxacin is also active against both penicillin susceptible and penicillin resistant strains of Neisseria gonorrhoea. Relative to its activity against Gram-positive bacteria, norfloxacin is somewhat less active against Gram-positive cocci. In general, the Staphylococci are more susceptible to this drug than Streptococci. The mechanism of action of norfloxacin involves inhibition of subunit of the important enzyme DNA gyrase, which is essential for DNA replication. Plasmid-mediated resistance to the fluoroquinolones is not encountered. Further, although some cross-resistance within the fluoroquinolone class has occurred, there is little cross-resistance between norfloxacin and the antibiotics of other class.

6.2 Classification:

With a view to study new antibacterial agents, Lesher and associates prepared a number of 1,8-naphthyridine carboxylic acid derivatives. Nalidixic acid was considered the outstanding compound in this series. As in Fig. 1, it has a bicyclic, heteroaromatic system made up of a carboxylic acid ring (A) ana a substituted pyridine nucleus (B) with nitrogen atoms at position 1 and 8. The prototype naphthyridine antibacterial, nalidixic acid has pronounced activity against Gram-negative bacteria (excluding P. aeruginosa) and relatively modest activity against Gram-positive organisms. Thus in 1962, this agent was introduced in the United States for the treatment of urinary tract infections.

6.3 BIOLOGICALLY ACTIVE FLUOROQUINOLONES

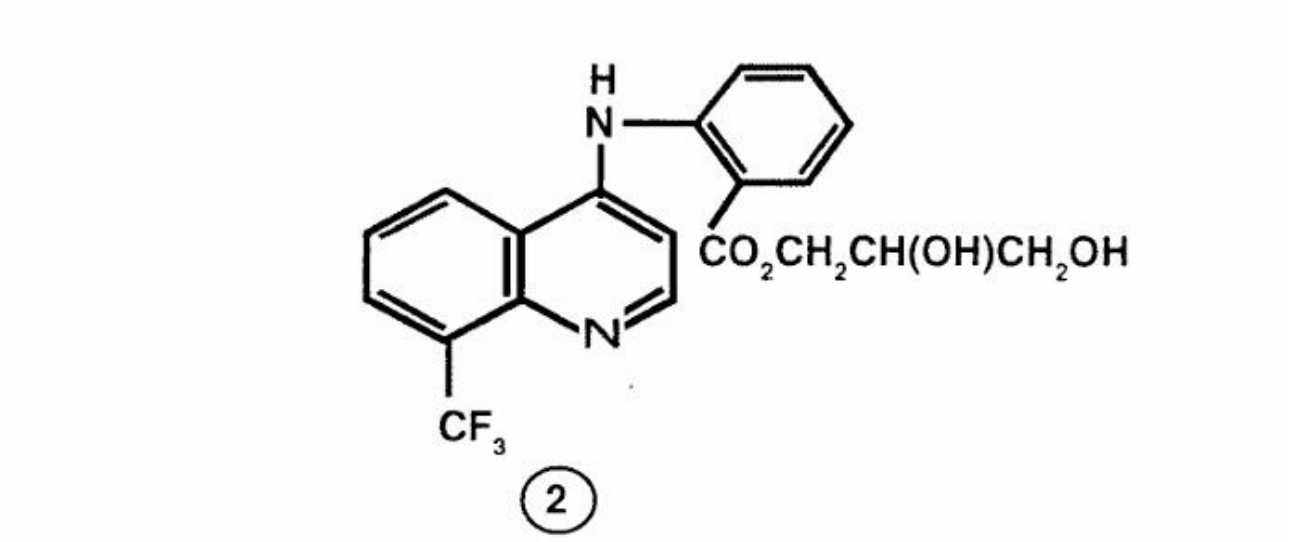
Hardtman 1 has synthesised various 4-hydroxy-2-quinolone-3-carboxylicacids (1) and tested them for prophylaxis of allergic asthama.



R_1=R_2 = halogen, C_{1-4} alkyl, C_{1-4} alkoxy

(1)

Andreoli et al.2 have prepared N-[8-(trifluoromethyl)-4-quinolyl] anthranilate (2) and found that it was more active analgesic with higher gastric tolerance than indomethacin or acetyl salicylic acid.



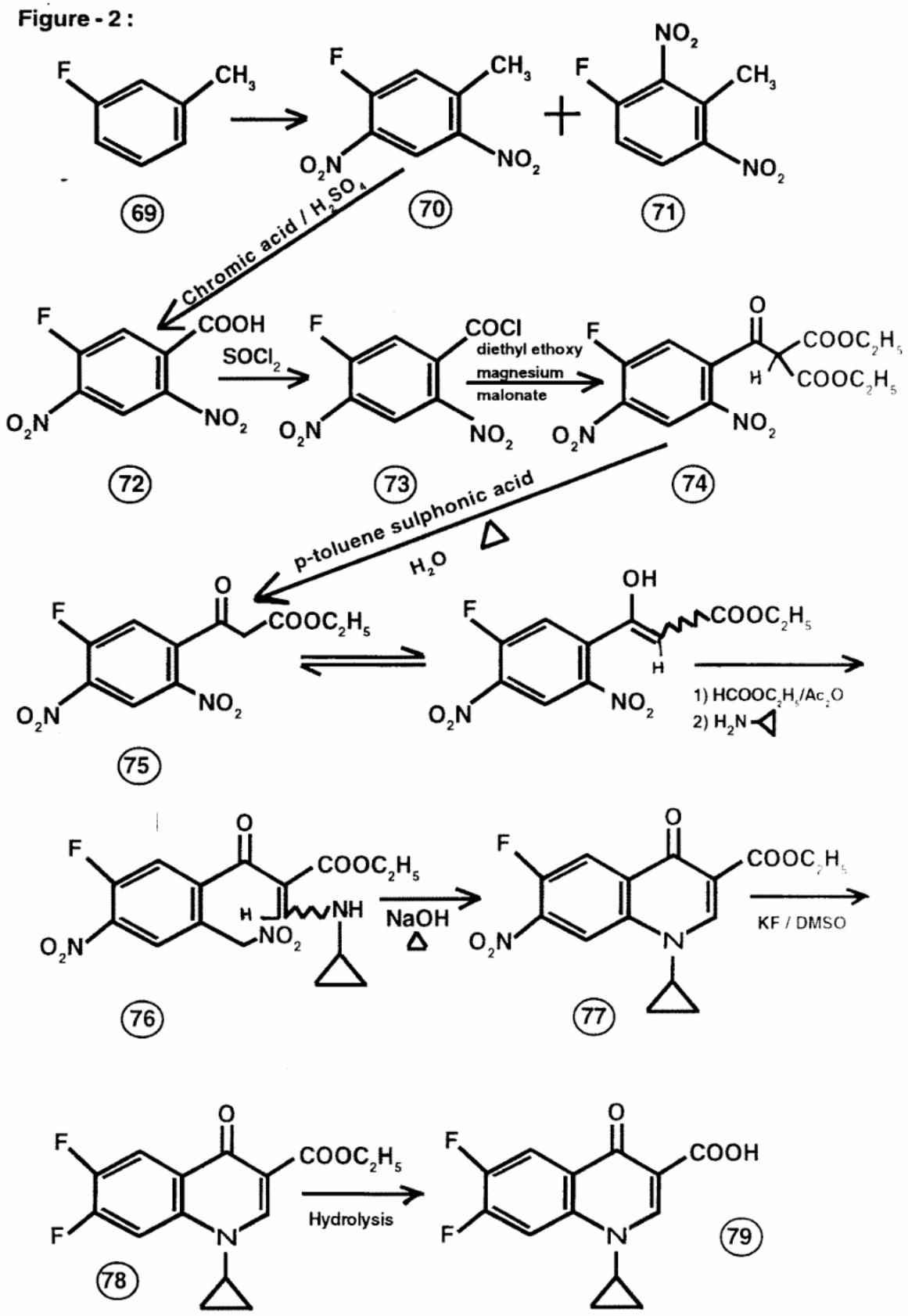
2

6.4 SYNTHESIS OF FLUOROQUINOLONECARBOXYLIC ACIDS

A number of methods have been reported in the literature 11°-122 for the synthesis of fluoroquinolone carboxylic acids. Some of the important methods are outlined below:

Method-1 : Heroshi et.al.118 have described the synthesis of 1-cyclopropyl-6,7-difluoro- 1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (79). (Fig.-2) starting from m-fluor toluene: m-Fluprednidene (69) was nitrated with a mixture of nitric acid and sulphuric acid to give a mixture of 5-fluoro-2,4-dinitrotoluene (70) and 3-fluoro-2 6- dinitro toluene (71). The compound 70 was separated from the mixture by fractional crystallization with isopropyl ether and oxidised to benzoic acid derivative 72 with chromic acid in sulphuric acid which when treated with thionyl chloride gave compound 73. This was treated with diethylethoxymagnesium malonate in tetrahydrofuran to yield benzoyl malonate derivative 74 and this was heated with p-toluene sulphonic acid in water to give (3-ketoester 75 which exists in keto-enoi forms in solution. Compound 76 was cyclised by heating with sodium hydroxide in a mixture of tetrahydrofuran and toluene to give the quinoline 77. which when heated with potassium fluoride in dimethyisulfoxide gave 78 wherein nitro group was replaced by fluorine atom. The ester 78 was subjected to acid hydrolysis to yield 79.

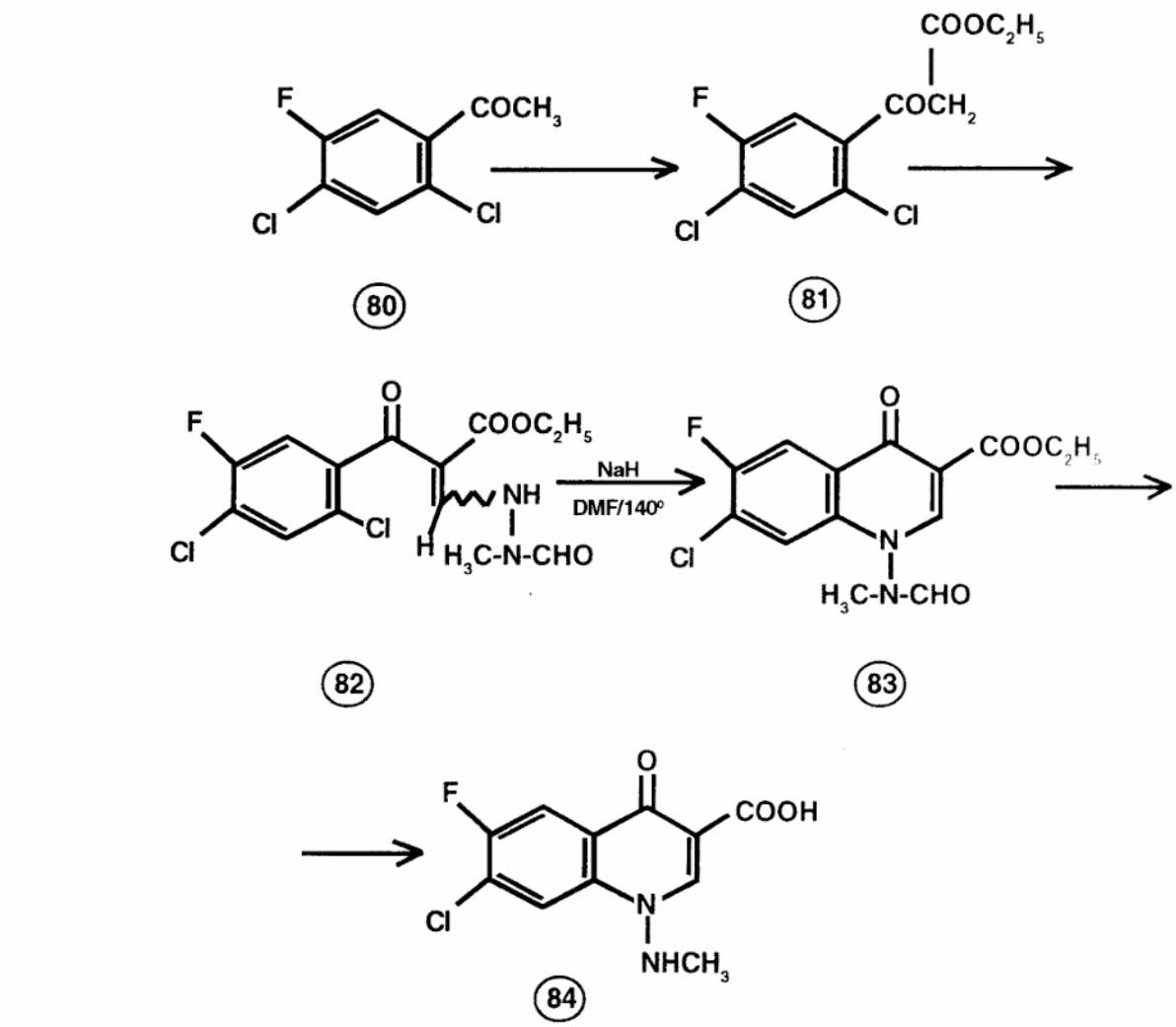
Figure - 2 :



Method-2:

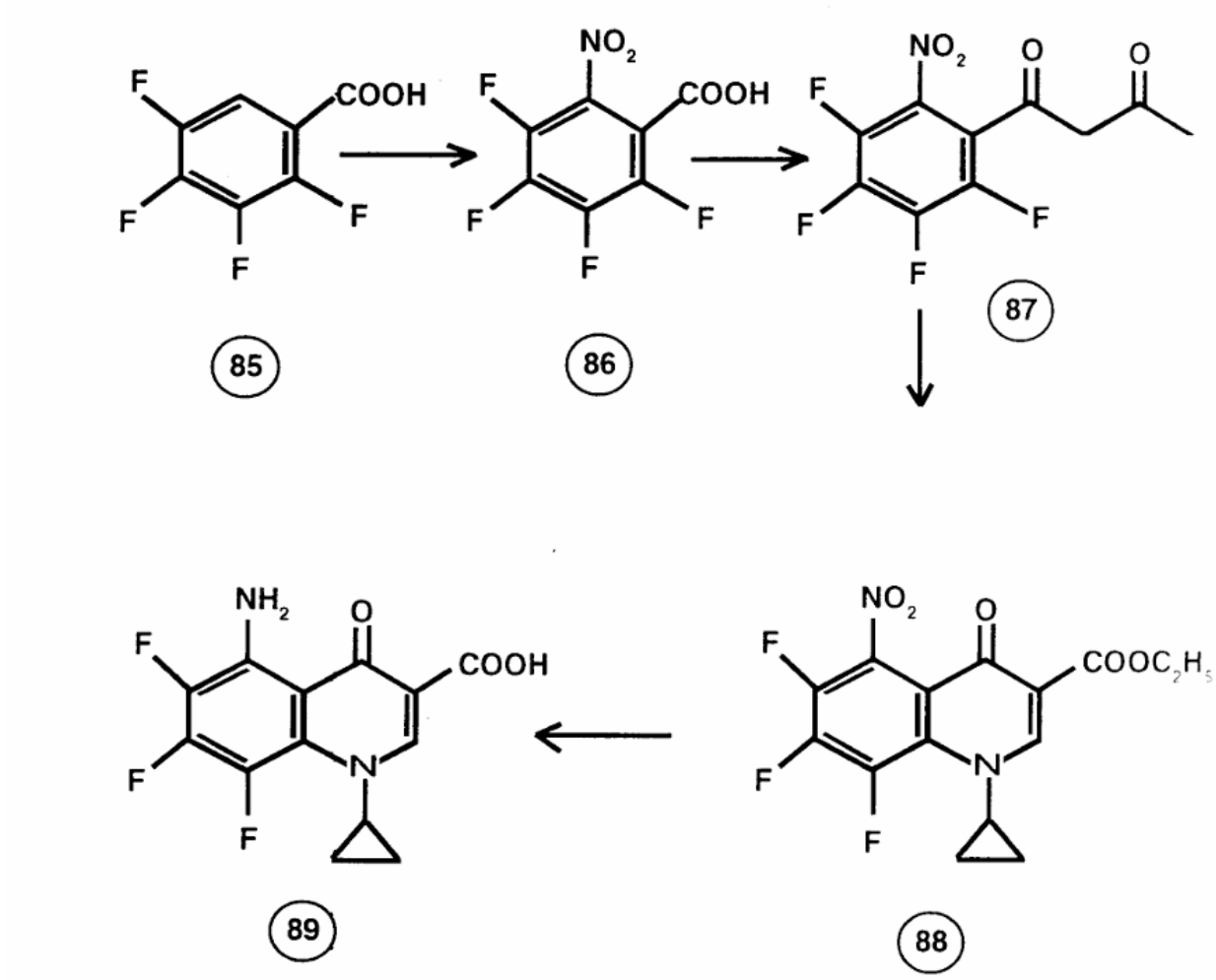
Chu 119 has prepared fluoroquinolin-3-carboxylic acid derivative starting from 2,4-dichloro-5-fluoro-acetophenone (80). Compound 80 was condensed with two molar equivalents of sodium hydroxide in diethyl carbonate to give 2,4-dichloro-5- fluor benzoylacetate (81), and this was treated with triethyl orthoformate in acetone and slight excess of N-formyl-N-methylhydrazine in methylene chloride at room temperature to give

82. Compound 82 was cyciised with sodium hydride in DMF at 140° to yield 83, which was hydrolysed with 0.35 N HCI in acetonitrile to give 84.



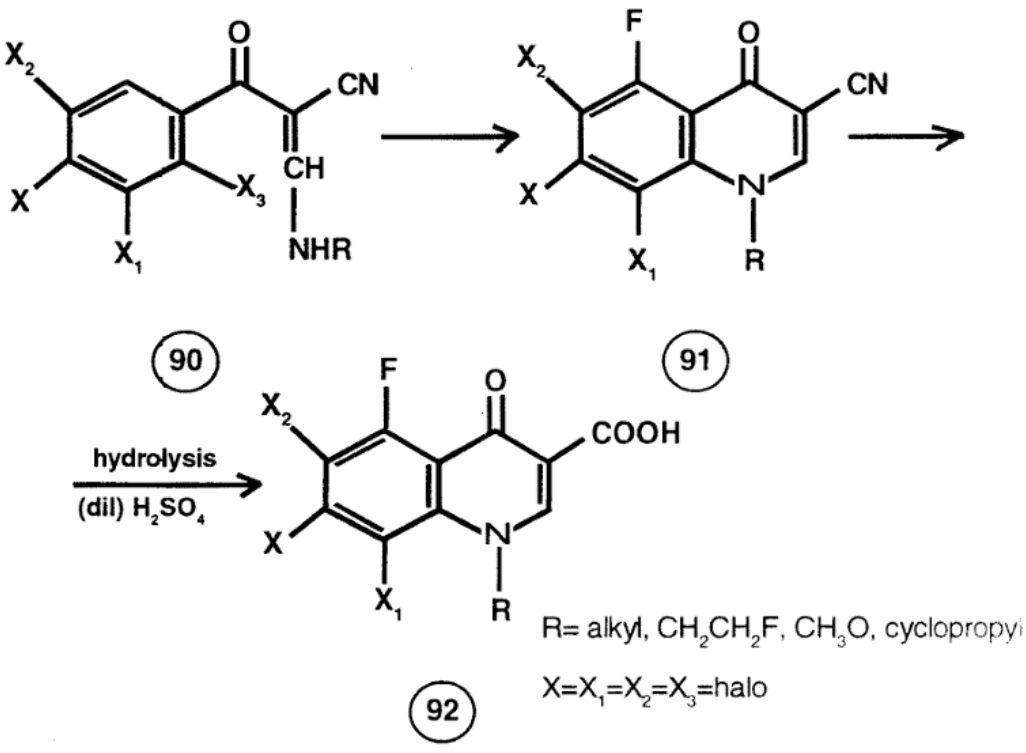
Method-3:

John et.ai 120 have synthesised fluoroquinolin-3-carboxylic acid from 2,3,4,5- tetrafluoro benzoic acid (85): Compound 85 was treated with sulphuric acid and nitric acid at room temperature to give nitroderivative 86. Compound 86 was treated with COCI2, H2CCI2, DMF and malonic ester to give ketoester (87), which was treated with CH(OC2H5)3, (CH3CO)20, C3H5NH2, t-BuOK and t-BuOH to give 88. Compound 88 was subjected to reduction in presence of raney nickel, which on subsequent acid hydrolysis resulted in the formation of 89



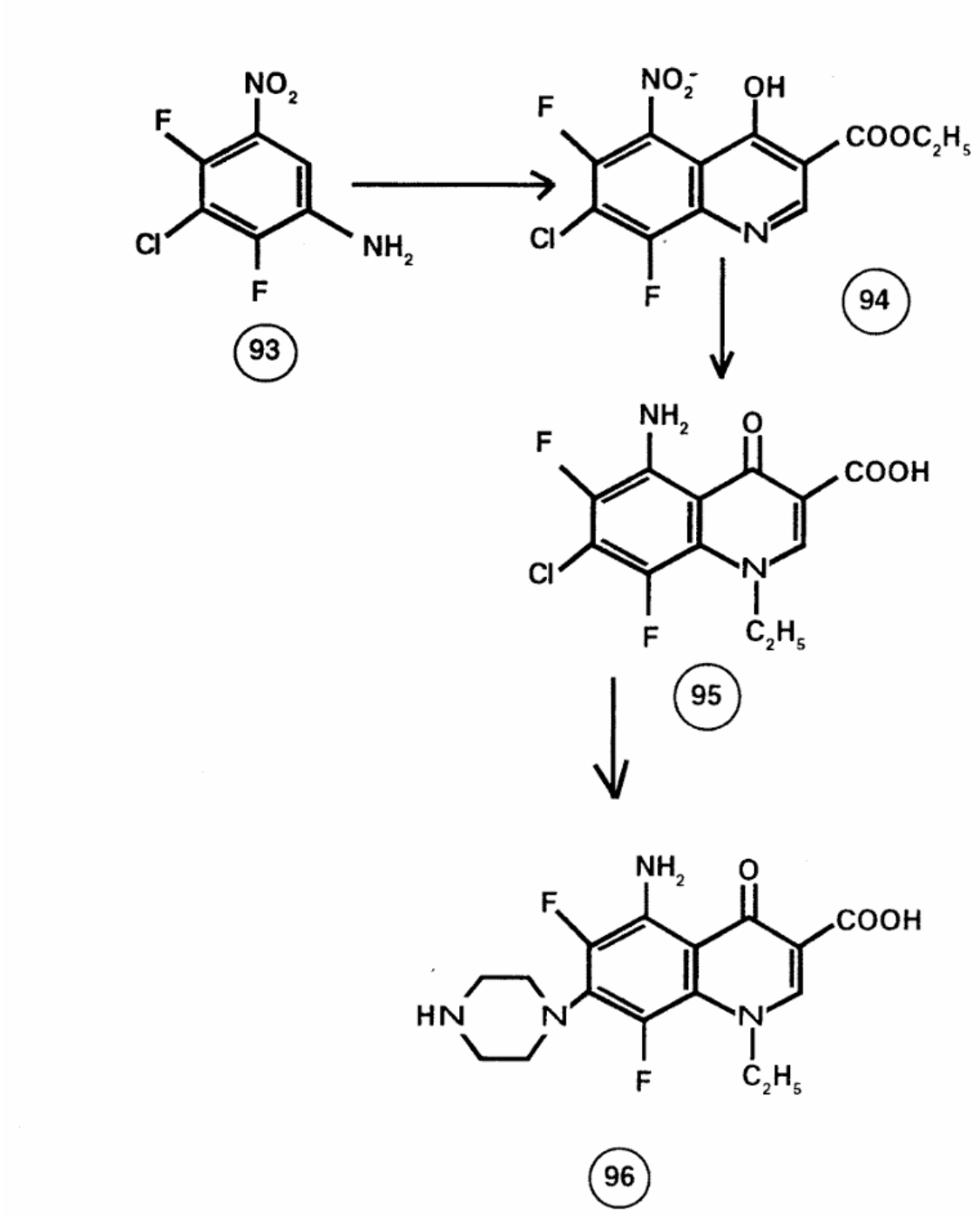
Method-4:

Grohe 121 has reported the synthesis of fluoroquinolone carboxylic acids by the cyclocondensation of benzoylacrylonitriles (90) to give 91, which on hydrolysis gave 92



Method-5:

Tanabe Seiyaku Co.Ltd.122 has reported the synthesis of 1-ethyl-5-amino-6.8- difluoro-7-piperazinyl-1,4-dihydro-4-oxoquinolin-3-carboxylic acid (96) by toe condensation of 2,4-difluoro-3-chloro-5-nitroaniline (93) with diethylethoxymethyiene malonate, followed by cyclisation to give 94. N-gthylation of 94 and subsequent reduction and hydrolysis afforded the quinolincarboxylic acid derivative 95, which when heated with piperazine in DMSO gave compound 96.

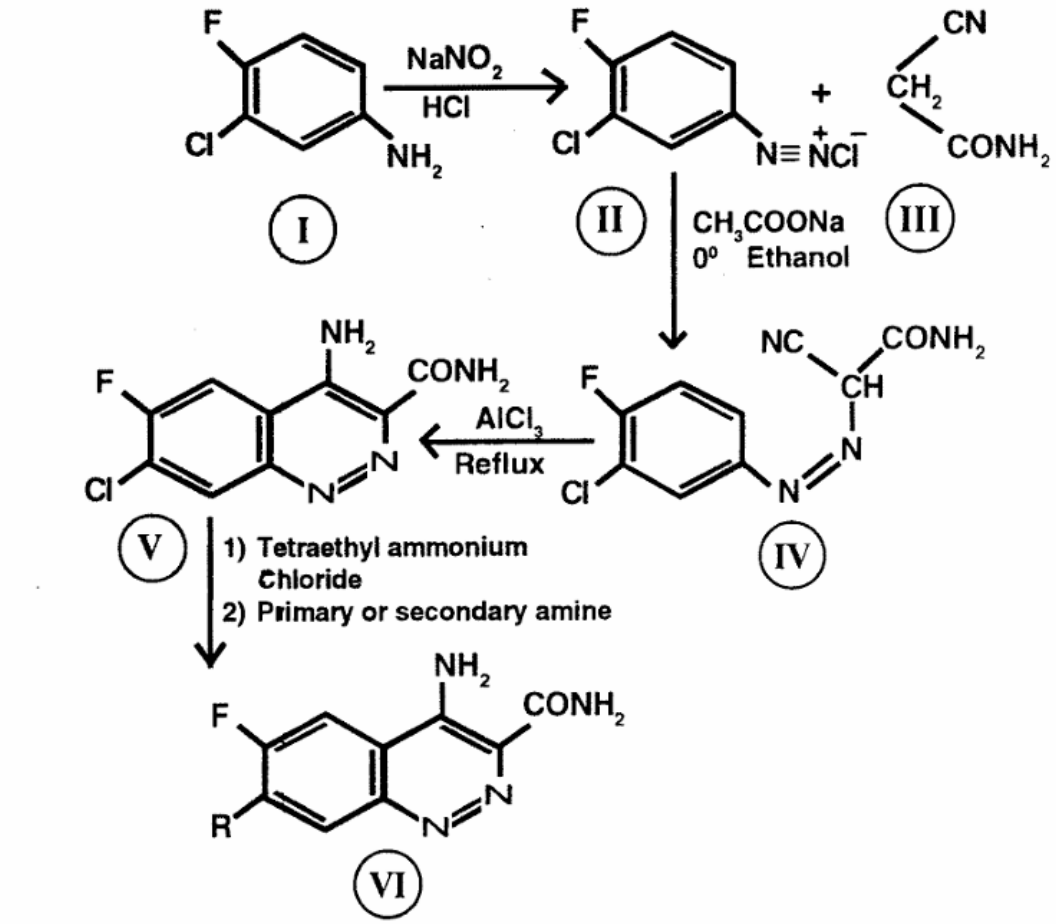


6.5 PRESENT WORK

In view of the foregoing discussion of various biological activities associated with the quinoline derivatives containing fluorine as one of the substituents, we were encouraged to undertake the synthesis of some cinnoline derivatives containing fluorine, couched in different way, the analogues of norfloxacin. In the present chapter we embarked upon the synthesis of a number of fluoroquinolone derivatives. Further, the compounds synthesised have been screened for antibacterial and anti-inflammatory activities. The required precursor fluorochloroarylhydrazono(cyano)acetamide (IV) was prepared by the interaction of diazonium salt of the 3-chloro-4-fluoroaniline (II) with active methylene compound such as cyan acetamide (III), under the Japp- Klingemann reaction conditions

Fluorochloroarylhydrazono(cyano)acetamide (IV) in the E-form easily underwent intramolecular Fridel-Crafts reaction in chlorobenzene and in presence of anhydrous aluminium chloride to form 4-amino-6-fluoro-7-chloro-cinnolin -3-carboxamide(V). 4-Amino-6-fluoro-7N-substituted-cinnolin-3-carboxamides (VI) were prepared from 4-amino-6-fluoro-7-chloro-cinnolin-3-carboxamide (V) by refluxing it with appropriate amine using phase transfer catalyst such as tetraethylammomum chloride in dioxane solvent. The steps involved in the synthesis of 4-amino-6-fluoro-7N-substitutea- cinnolin-3-carboxamides (VI) are given in scheme-3

Scheme-3 :



R=NHC_6H_5, 4'-$NO_2.C_6H_4NH$, 3'-$NO_2.C_6H_4NH$, 2'-$OCH_3.C_6H_4NH$, 3'-$OCH_3.C_6H_4NH$, 4'-$CH_3.C_6H_4NH$, 2'-$Cl.C_6H_4NH$, 3'-$Cl.C_6H_4NH$, 4'-$Cl.C_6H_4NH$, piperazinyl and piperdinyl

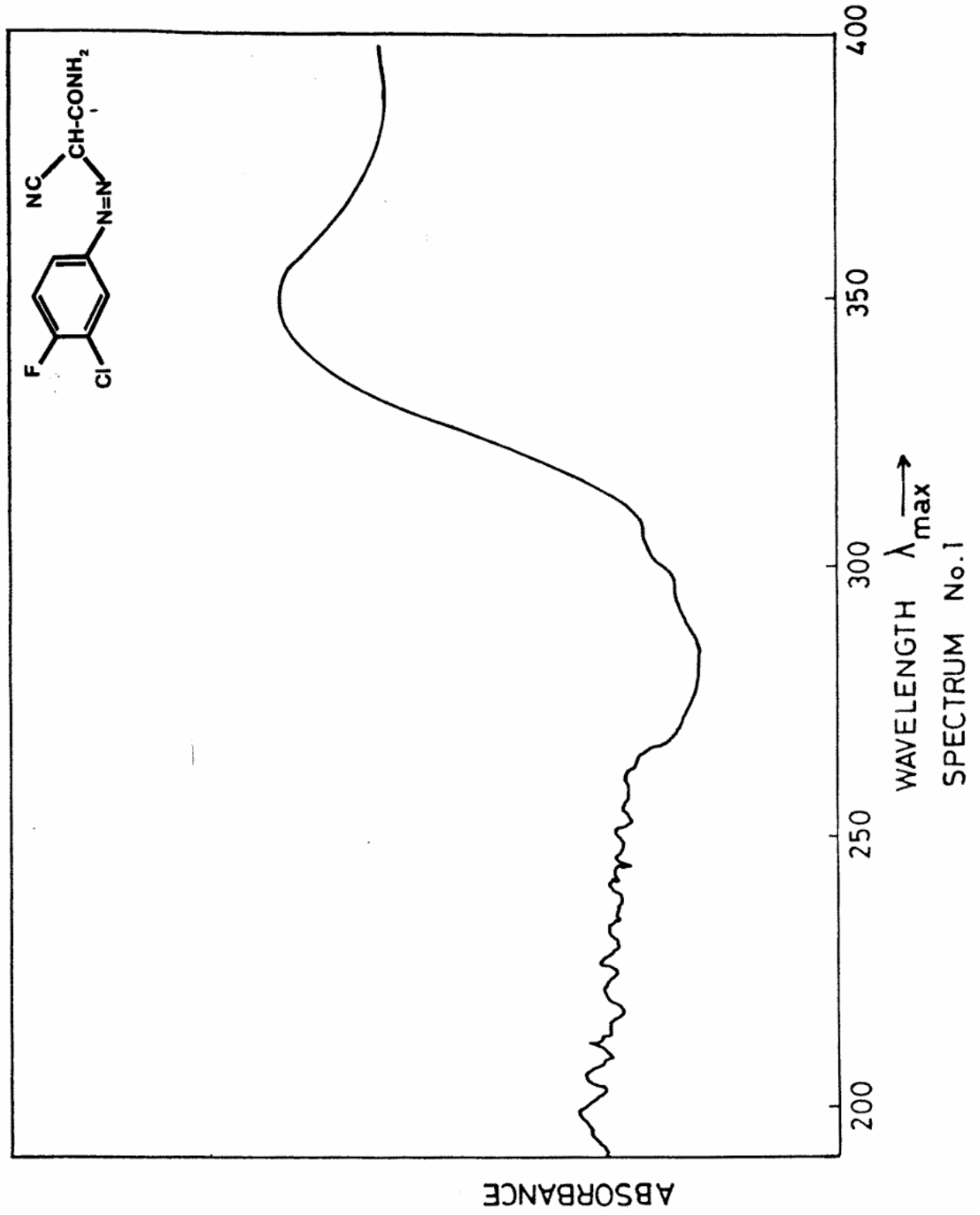
The phase transfer catalysed reactions proceed by the interfacial mechanism proposed by Makossa 126 in which dehalogenation takes place at the interface. Several solvents such as methylene chloride, benzene, paraxylene, acetonitrile and 1,4-dioxane were investigated as reaction medium. This has been attributed to factors such as polarity and hydrophobicity of the organic phase which can be expected to influence the surface activity of quaternary salts. We obtained maximum yield by using tetraethyiammoniumchloride as a phase transfer catalyst and 1,4-dioxane as a solvent.

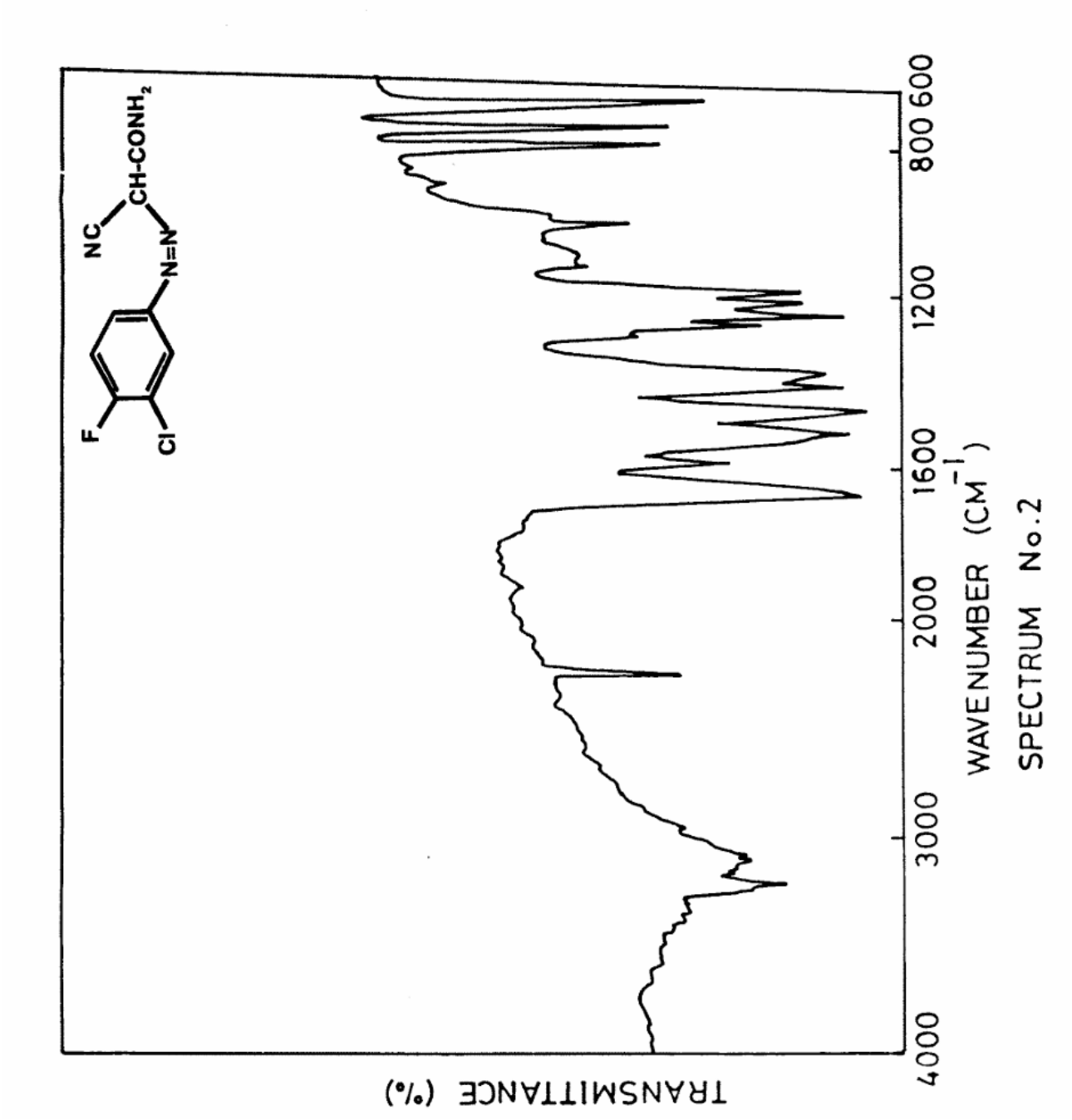
6.6 RESULTS AND DISCUSSION

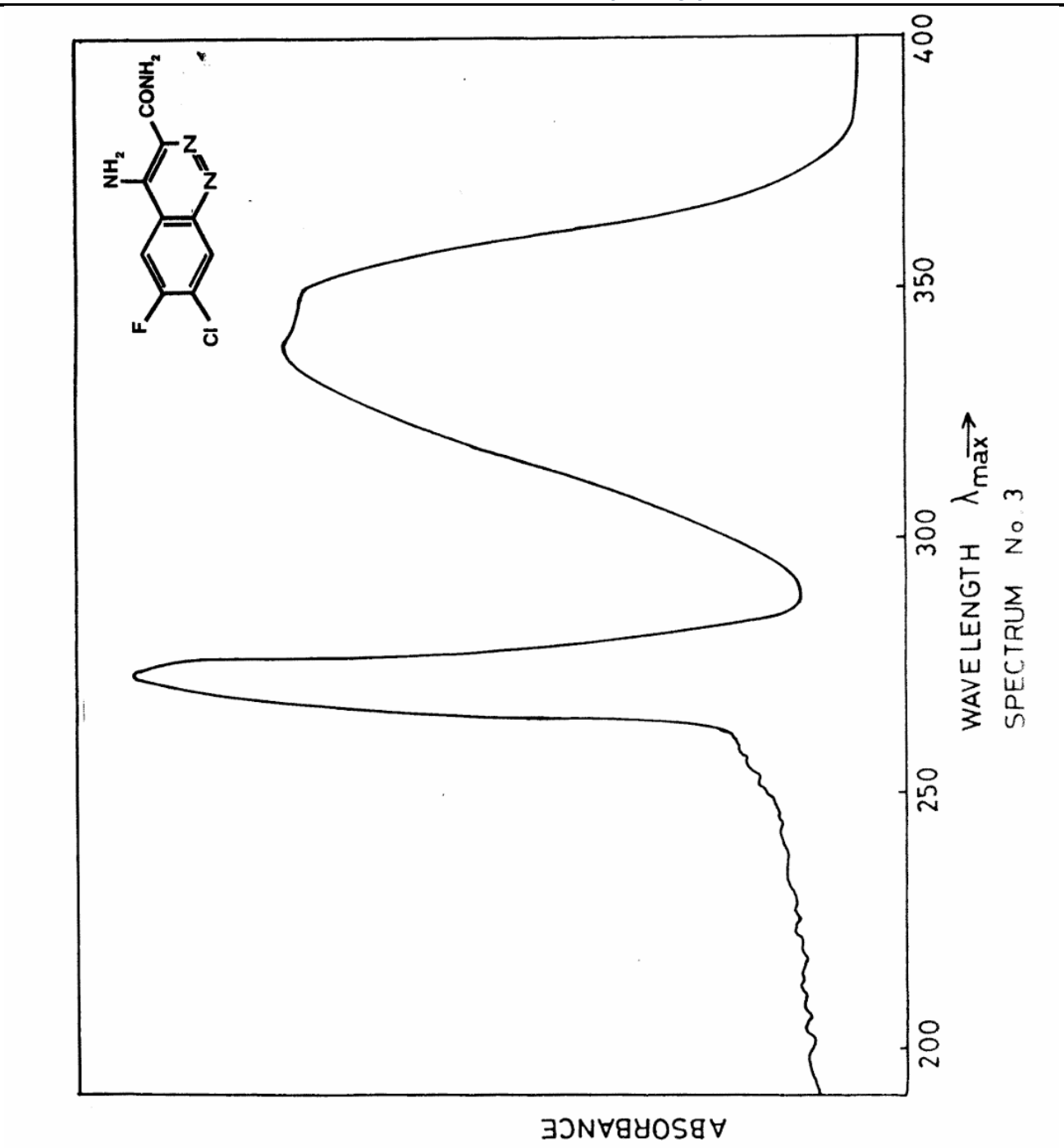
Structures of the compounds synthesised during the present investigation have been established authentically by their UV, IR, PMR and Mass spectral data. In the following section spectral studies of some selected new compounds have been dealt with. 3-Chloro-4-fluroarylhydrazono(cyano)acetamide has shown absorption band at X max 340 nm in its UV spectrum (Spect. No. 1). It exhibited characteristic absorption bands at 3214 crrr1 (NH2 of CONH). 2212 cm-1 (-C=N), 1488 cm'1 (-N=N-), 1263 crrr1 (=C-F) and 762 Cnrr1 (=C-CI) in its IR spectrum (Spect. No. 2).

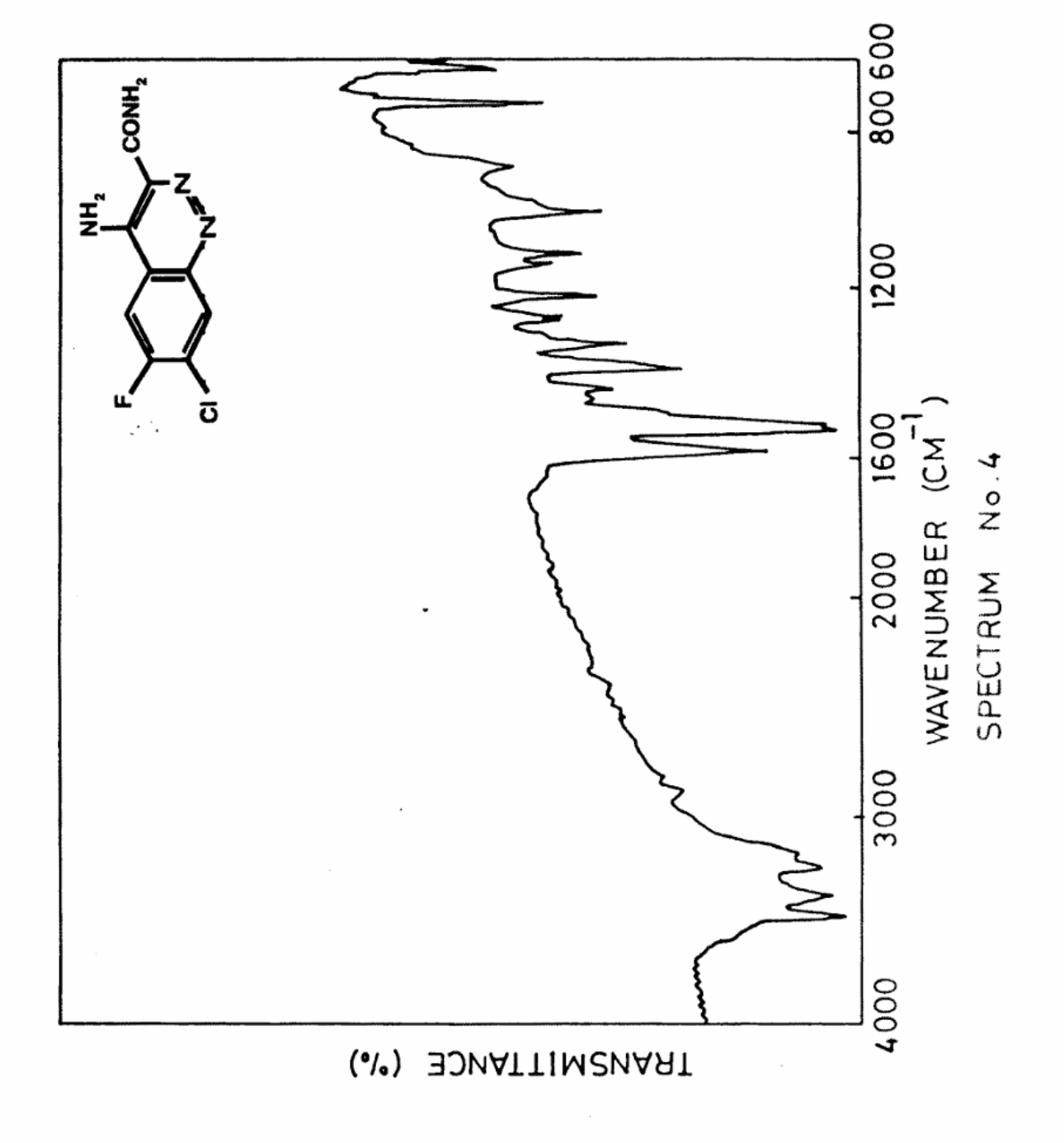
UV spectrum of 4-amino-7-chloro-6-fluoro-cinnolin-3-carboxamide (Spect. No.3) showed strong absorption bands at X max 288 nm and X max 338 nm. This bathochromic shift clearly indicates formation of 4-amino-7-chloro-6-fluoro- cinnolin-3-carboxam ide.

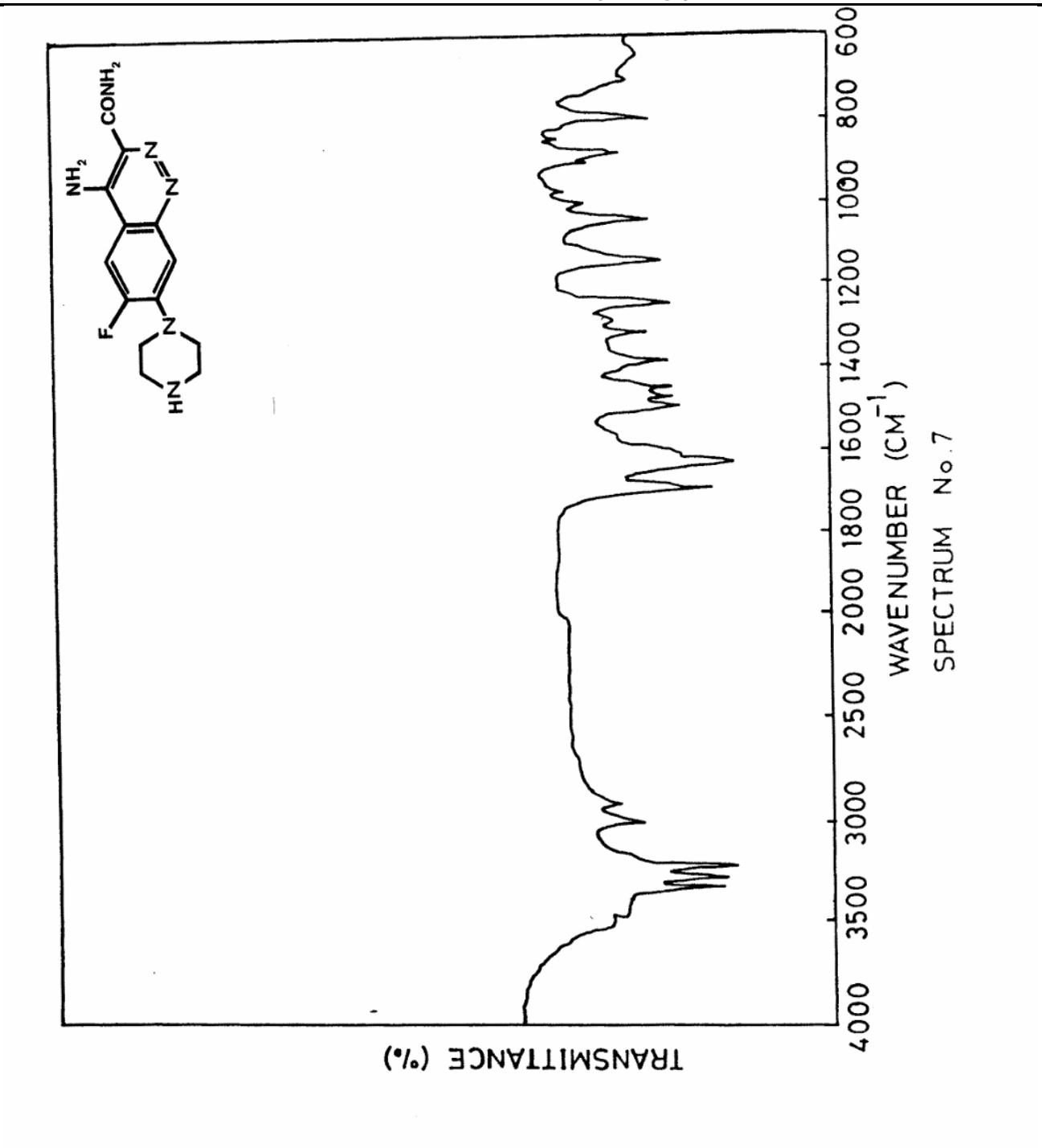
Formation of 4-amino-7-chloro-6-fluoro-cinnolin-3-carboxamide from the corresponding 3-chloro-4-fluoroarylhydrazono(cyano)acetamide is clearly indicated by its IR spectrum (Spect. No. 4). It shows characteristic absorption bands at 3400 cm1 and 3280 cm-1 arising from the asymmetric and symmetric stretching vibrations due to -NH2 group. Further, the presence of a broad band with a small shoulder in the region 3180 cnr1 indicates the presence of amide-NH., group. Since amides have a strong tendency to self-associate by hydrogen bonding, the band positions have been shifted to lower frequency region. It is observed that me 164 spectra shows characteristic sharp band at 1600 cm -1 due to >C=0 stretching vibrations, as a consequence of mesomeric effect. This amide carbonyl group has less double bond character and hence it has appeared at lower frequency.


NC
CH-CONH2
N=N
F
Cl
400
350
300
250
200
WAVELENGTH λmax
SPECTRUM No. 1
ABSORBANCE


NC
CH-CONH2
N=N
F
Cl
TRANSMITTANCE (%)
4000
3000
2000
1600
1200
800 600
WAVENUMBER (CM-1)
SPECTRUM No.2


CONH2
NH2
N
N
F
Cl
ABSORBANCE
200
250
300
350
400
WAVELENGTH λmax
SPECTRUM No. 3


CONH2
NH2
N
N
F
Cl
TRANSMITTANCE (%)
4000
3000
2000
1600
1200
800 600
WAVENUMBER (CM-1)
SPECTRUM No.4


CONH2
NH2
F
HN
TRANSMITTANCE (%)
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
WAVENUMBER (CM-1)
SPECTRUM No.7

CHAPTER 5

RESULT AND DISCUSSION

5.1 Fluoroquinolones

Theoretical and Structural Aspects

Fluoroquinolones are synthetic antibacterial agents derived from the quinolone nucleus. Their structure consists of a bicyclic ring system with a fluorine atom at position C-6, which enhances antimicrobial activity. Substitution at C-7 (usually piperazine ring) improves pharmacokinetic properties.

The general structure includes:

- Carboxylic acid group at C-3
- Keto group at C-4
- Fluorine atom at C-6

These features are crucial for **DNA gyrase inhibition**, which is the primary mechanism of action.

IR Spectral Identification

Characteristic IR peaks observed:

- **O–H (Carboxylic acid):** 2500–3300 cm^{-1} (broad)
- **C=O (Carboxyl group):** ~1700–1725 cm^{-1}
- **C=O (Ketone):** ~1620–1680 cm^{-1}
- **C–F stretching:** 1000–1400 cm^{-1}
- **C–N stretching:** 1200–1350 cm^{-1}

These peaks confirm the presence of functional groups responsible for biological activity.

5.2 Pyrazoles

Theoretical and Structural Aspects

Pyrazoles are five-membered heterocyclic compounds containing two adjacent nitrogen atoms (N–N). They exhibit aromaticity due to delocalized π-electrons.

General structural features:

- Two nitrogen atoms at positions 1 and 2
- Substitution possible at C-3, C-4, and C-5

- Planar aromatic ring system

Pyrazoles are widely used in **anti-inflammatory, antimicrobial, and anticancer drugs**.

IR Spectral Identification

Characteristic peaks:

- **N–H stretching:** 3100–3500 cm^{-1}
- **C=N stretching:** ~1550–1650 cm^{-1}
- **N–N stretching:** ~1000–1250 cm^{-1}
- **C–H (aromatic):** ~3000–3100 cm^{-1}

These confirm the heterocyclic nitrogen-containing structure.

5.3 Oxazines

Theoretical and Structural Aspects

Oxazines are six-membered heterocycles containing one oxygen and one nitrogen atom. They exist in different isomeric forms such as 1,2-oxazine, 1,3-oxazine, and 1,4-oxazine.

Key structural features:

- Heterocyclic ring with O and N atoms
- Aromatic or partially saturated nature
- Substituents influence biological and chemical properties

Oxazines are important in **dyes, pharmaceuticals, and CNS-active agents**.

IR Spectral Identification

Characteristic peaks:

- **C–O–C stretching:** 1000–1300 cm^{-1}
- **C=N stretching:** ~1600–1650 cm^{-1}
- **C–N stretching:** 1200–1350 cm^{-1}
- **Aromatic C–H stretching:** ~3000–3100 cm^{-1}

These peaks validate the presence of oxygen and nitrogen within the ring.

Discussion

The structural analysis confirms that all three classes—fluoroquinolones, pyrazoles, and oxazines—are **heterocyclic compounds with distinct functional groups** responsible for their pharmacological activities.

- **Fluoroquinolones:** Characterized by **fluorine substitution and keto-acid groups**, crucial for antibacterial action.
- **Pyrazoles:** Defined by **N–N heterocyclic system**, contributing to diverse biological effects.
- **Oxazines:** Identified by **O and N heteroatoms in a six-membered ring**, important in medicinal chemistry.

IR spectroscopy proved to be a **reliable and rapid technique** for identifying these compounds through their characteristic functional group vibrations. The observed peaks matched well with theoretical values, confirming successful synthesis and structural integrity.

CHAPTER 6

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