STUDY OF SOME BIOACTIVE SYNTHETIC HETEROCYCLES

A THESIS SUBMITTED TO THE SAURASHTRA UNIVERSITY

IN THE FACULTY OF SCIENCE

FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

IN

CHEMISTRY

By

VIJAY R. VIRSODIA

UNDER THE GUIDANCE OF

PROF. ANAMIK SHAH

DEPARTMENT OF CHEMISTRY

(DST-FIST Funded & UGC-SAP Sponsored)

SAURASHTRA UNIVERSITY

RAJKOT – 5 (GUJARAT, INDIA)

AUGUST – 2007

STUDY OF SOME BIOACTIVE SYNTHETIC HETEROCYCLES

A THESIS SUBMITTED TO THE

SAURASHTRA UNIVERSITY

IN THE FACULTY OF SCIENCE

FOR THE DEGREE OF

Doctor of Philosophy

IN

CHEMISTRY

By

VIJAY R. VIRSODIA

UNDER THE GUIDANCE OF

PROF. ANAMIK SHAH
DEPARTMENT OF CHEMISTRY
SAURASHTRA UNIVERSITY
RAJKOT – 5 (GUJARAT, INDIA)

AUGUST – 2007

Statement under O.Ph.D.7 of Saurashtra University

The work included in the thesis is done by me under the supervision of Prof. Anamik Shah and the contribution made thereof is my own work.

Date:

Place: ***Vijay R. Virsodia***

Certificate

This is to certify that the present work submitted for the Ph.D. degree of Saurashtra University by Mr. Vijay R. Virsodia has been the result of work carried out under my supervision and is a good contribution in the field of organic chemistry.

Date:

Place: ***Prof. Anamik Shah***

To My Family,

With Love

Acknowledgement

Firstly, I bow my head humbly before the Almighty God for making me capable of completing my Ph.D. Thesis; with his blessings only I have accomplished this huge task.

I express deep sense of gratitude and thankfulness to my guide Professor **Dr. Anamik Shah** who has helped me at each and every point of my research work with patience and enthusiasm. I am much indebted to him for his inspiring guidance, affection, generosity and everlasting enthusiasm throughout the tenure of my research work, without that the Thesis would not have appeared in the present form.

I also thank to Dr. P H Parsania, Professor and Head, Department of Chemistry, Saurashtra University, Rajkot for her encouragement and providing adequate research facilities.

At this juncture I thank my whole family for encouraging me and providing every help to fulfill my task especially my parents, my sister Rimpal and my brother Sumit for their invaluable support and constant motivation during tenure of my work.

I like to mention a special thanks to Dr. Ranjanben Shah and Aditya (chiki) for their kind support in personal matter and making me feel like home.

My heartily thanks to my seniors Dr. Naliapara, Dr. Karia, Dr. Dinesh, Dr. Hrisikesh, Dr. Arun, Dr. Chintan, Dr. Priti, Dr. Kena, Dr. Pravin and Dr. Kuldip for their co-operation and help.

I offer my gratitude to my lab mates Nikhil, Atul, Rupesh, Jitender and Dhaval for their fruitful discussion at various stages. I would like to thank my dear friends Sanjay, Mehul, Jimmy, Vasu, Rushit; and Prema.

I would like to thank my friends Jignesh, Dhiru, Manoj, Satish, Chirag, Akshay, Janak, Hitesh, Bharat, Viren, Dr. Shailesh, Dr. Vrajesh, Dr. Niral, Dr. Mayur, Dr. Vimal, Dr. Vijay, Dr. Dinesh, Dr. Paresh, Dr. Mahesh, Dr. Sunil, Dr. Bhavin, Dr. Shukla, Dr. Shekhda, Dr. Nimisha, Pankaj, Nayan, Samrat, Abhay, Dinesh, Renish, Jagdish, Naval, Raju, Vaibhav, Anchal, Nilay and Jyoti.

I am truly thankful to teaching and non teaching staff of my Department for their kind support. I am profoundly indebted to Department of Chemistry, Saurashtra University for providing me the excellent laboratory facility for accomplishing this work. I express my grateful acknowledgement to Gujarat State Government for Junior research Fellowship which shorted out my financial worries to some extent.

I would like to thank Regional Sophisticated Instrumentation Centre, Chandigarh for ^{1}H NMR analysis; Department of Chemistry for GC-MS and IR facility; Dr. Roberto and Dr. Paolo La Colla, Italy for anti viral screening; and Dr. Cecil Kwong, TAACF, USA for anti tubercular screening.

Vijay Virsodia

Content

General Protocol

1. ^{1}H NMR spectra were recorded on Bruker avance II 400 MHz NMR spectrometer using TMS as an internal reference.

2. Mass spectra were recorded on GC-MS QP-2010 spectrometer.

3. IR spectra were recorded on Schimadzu FR-IR-8400 spectrometer using KBr pellet method.

4. Elemental analysis was carried out on Vario EL III Carlo Erba 1108.

5. Thin layer chromatography was performed on Silica Gel (Merck 60 F_{254}).

6. The chemicals used for the synthesis of compounds were purchased from Spectrochem, Merck, Thomas-baker and SD fine chemical.

7. MPs were taken in open capillary and are uncorrected.

8. Microwave assisted reaction were carried out in QPro-M microwave synthesizer.

Chapter 1

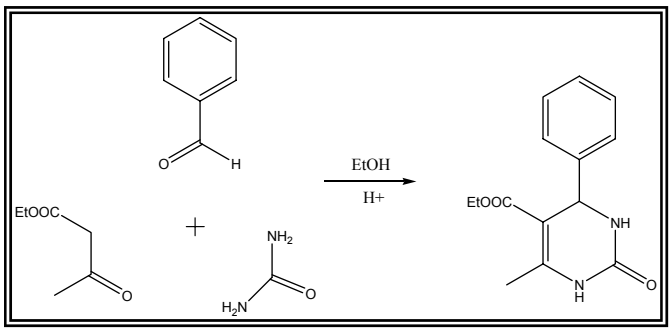
Synthesis and characterization of N-aryl substituted DHPM derivatives by Biginelli reaction

Chapter 1

Synthesis and characterization of N-aryl substituted DHPM derivatives by Biginelli reaction

1.1 Biginelli Reaction

P. Biginelli reported the synthesis of functionalized 3,4-dihydropyrimidin-(1*H*)-ones (DHPMs) via three-component condensation reaction of an aromatic aldehyde, urea, and ethyl acetoacetate. In the past decade, this long-neglected multicomponent reaction has experienced a remarkable revival, mainly due to the interesting pharmacological properties associated with this dihydropyrimidine scaffold[1].



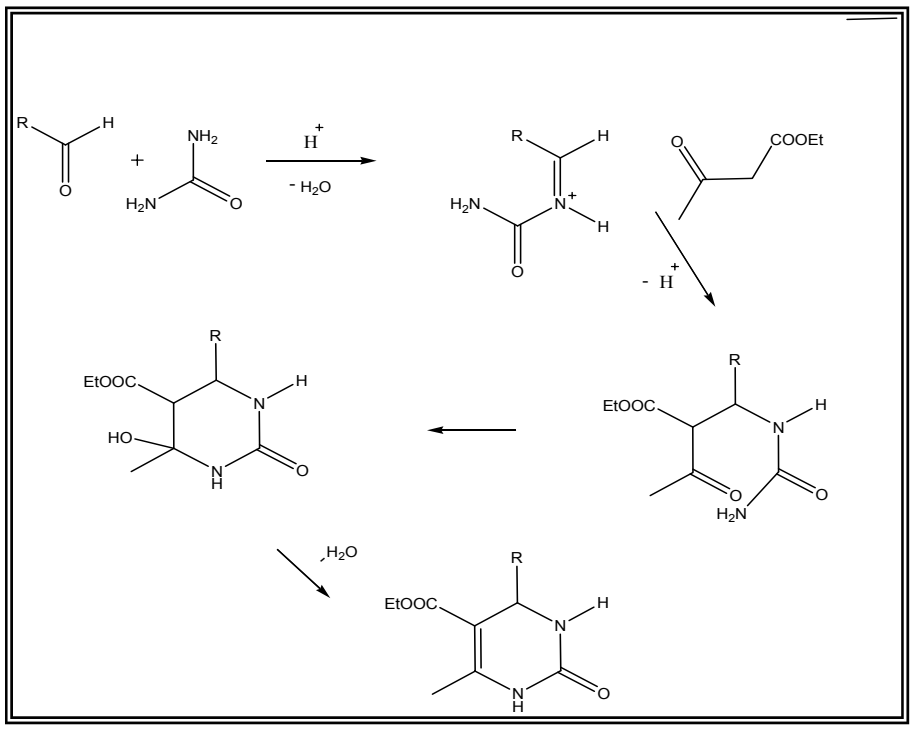
Biginelli Dihydropyrimidine Synthesis

The reaction was carried out by simply heating a mixture of the three components dissolved in ethanol with a catalytic amount of HCl at reflux temperature. The product of this novel one-pot, three-component synthesis that precipitated on cooling of the reaction mixture was identified correctly by Biginelli as 3,4-dihydropyrimidin-2(1*H*)-one. Apart from a series of publications by the late Karl Folkers in the mid 1930s, the "Biginelli reaction" or "Biginelli condensation" as it was henceforth called was largely ignored in the early part of the 20th century. The synthetic potential of this new heterocycle synthesis therefore remained unexplored for quite some time. In the 1970s and 1980s, interest slowly increased, and the scope of the original cyclocondensation reaction was gradually

extended by variation of all three building blocks, allowing access to a large number of multifunctionalized dihydropyrimidines.[2-4]

1.2 Mechanistic Studies of Biginelli Reaction [5-9]

The mechanism of the Biginelli reaction has been the subject of some debate over the past decades. Early work by Folkers and Johnson[3] suggested that bisureide, i.e. the primary bimolecular condensation product of benzaldehyde and urea, is the first



intermediate in this reaction. In 1973, Sweet and Fissekis[5] proposed a different pathway and suggested that carbenium ion, produced by an acid-catalyzed aldol reaction of benzaldehyde with ethyl acetoacetate, is formed in the first and limiting step of the Biginelli condensation. Kappe et al[6] reinvestigated the mechanism in 1997 using $^{1}H/^{13}C$ NMR spectroscopy and trapping experiments and have established that the key step in this sequence involves the acid-catalyzed formation of an *N*-acyliminium ion intermediate from the aldehyde and urea precursors. Interception of the iminium ion by ethyl acetoacetate, presumably through its enol tautomer, produces an open-chain ureide which subsequently cyclizes to hexahydropyrimidine. Acid-catalyzed elimination of water ultimately leads to the final DHPM product. The reaction mechansim can therefore be classified as an α-amidoalkylation, or more specifically as an α-ureidoalkylation. The alternative "carbenium ion mechanism" does not constitute a major pathway; however,

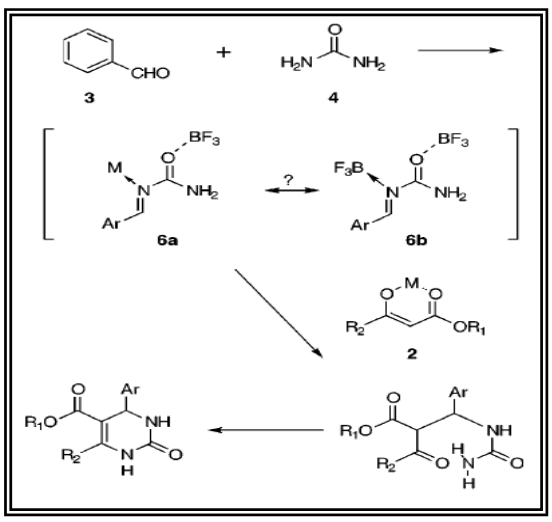
small amounts of enone are sometimes observed as byproduct. Although the highly reactive *N*-acyliminium ion species could not be isolated or directly observed, further evidence for the proposed mechanism was obtained by isolation of intermediates, employing sterically bulky or electron-deficient acetoacetates respectively. The relative stereochemistry in hexahydropyrimidine was established by an X-ray analysis. In fact, a number of hexahydropyrimidines could be synthesized by using perfluorinated 1,3-dicarbonyl compounds or α-keto esters as building blocks in the Biginelli condensation.

1.3 Alternative synthetic routes for better yield, shorter reaction time and to synthesize new analogs

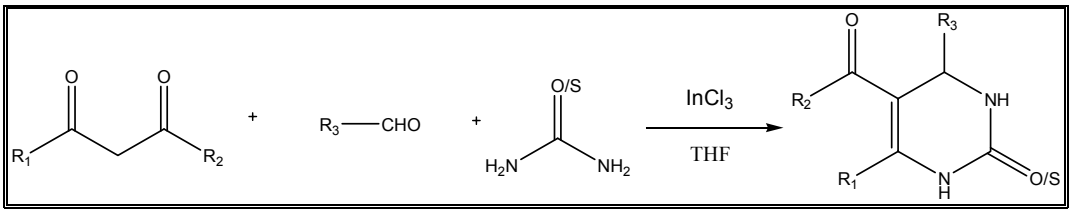
Various modifications have been applied to Biginelli reaction to get better yield and to synthesize biologically active analogs. Different catalysts have been reported to increase the yield of the reaction. Microwave synthesis strategies are also applied to shorten the reaction time. Solid phase synthesis and combinatorial chemistry has made possible to generate library of DHPM analogs.

1.3.1 Catalysts

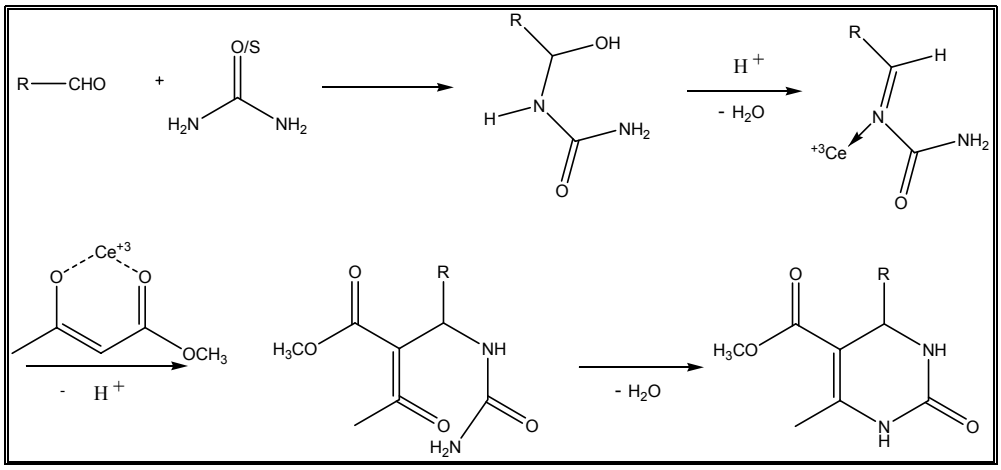
Essa H. Hu et al[10] reported Biginelli reaction catalyzed with trifluoroborane etherate, transition metal salt, and proton source to yield 80-90% Biginelli product. They proposed a mechanism similar to that of Folkers and Johnson[3] and to that of Kappe[5] for the Biginelli reaction wherein formation of acyl imine intermediate formed by reaction of the aldehyde with urea and stabilized by either trifluoroborane or the transition metal, is the key, rate limiting step. Subsequent addition of the α-keto ester enolate, followed by cyclization and dehydration, would afford the dihydropyrimidinone.



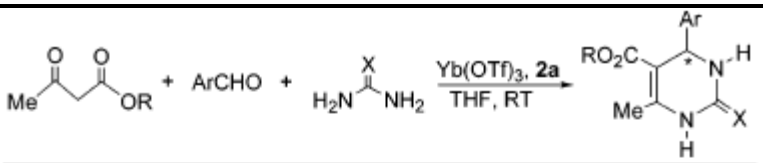
Brindaban C. Ranu et al[11]reported Indium (III) Chloride as an efficient catalyst for Biginelli reaction. A wide range of structurally varied α-dicarbonyl compound, aldehyde and urea were coupled together by this procedure to produce the corresponding dihydropyrimidinones. A variety of substituted aromatic, aliphatic, and heterocyclic aldehydes have been subjected to this condensation very efficiently. Thiourea has been used with similar success to provide the corresponding dihydropyrimidin-2(1H)-thiones.



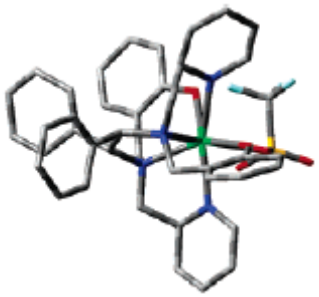
Bose et al[12]used cerium(III) chloride as a catalyst and reported solvent free synthesis of Biginelli compounds using this new catalyst. This procedure provides higher yield, shorter reaction time and simple work up methods. Solvent free reactions using this catalyst gave about 70% yield and reaction time was about 10 hrs. If ethanol is used as solvent, 90% yield was obtained with this catalyst. 25 mol % amount of cerium(III) chloride heptahydrate was found to be sufficient to push the reaction forward. The increased amount did not build further advantage.

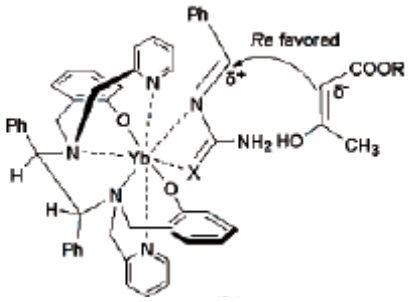


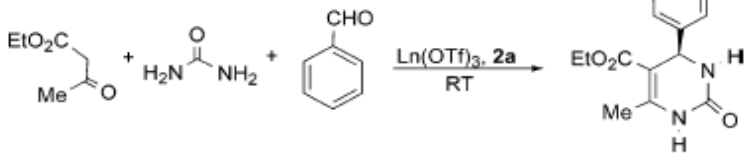
Enantioselective one pot synthesis of Biginelli reaction is reported with use of lanthanide triflates/ytterbium triflates. These catalyst leads to highly enantioselectivity and up to 99% enantioselective Biginelli reaction can be carried out.[13]



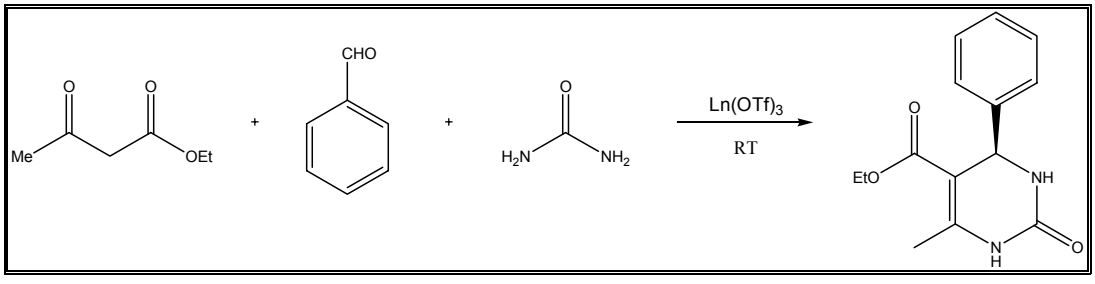
entry	Ar	R	X	yield, %[b]	ee, %[c]	config.
1	C_6H_5	Et	O	87	90	*R*[e]
2	C_6H_5	Et	S	81	99	*R*[e]
3	3-(NO_2)-C_6H_4	^{i}Pr	O	90	>99	*R*[d]
4	3-(NO_2)-C_6H_4	^{i}Pr	S	88	87	*R*[e]
5	3-(F)-C_6H_4	Et	O	80	97	*R*[e]
6	2-(Cl)-C_6H_4	Et	S	73	98	*R*[e]
7	2-(Cl)-C_6H_4	Et	O	78	89	*R*[e]
8	4-(Br)-C_6H_4	Et	O	82	95	*R*[e]
9	3-(OH)-C_6H_4	Et	O	81	91	*R*[e]
10	3-(OH)-C_6H_4	Et	S	80	99	*R*[d]
11	2-(OH)-C_6H_4	Et	O	86	98	*R*[e]
12		Et	O	81	80	*R*[e]
13		Et	O	82	82	*R*[e]
14		Et	O	87	93	*R*[e]



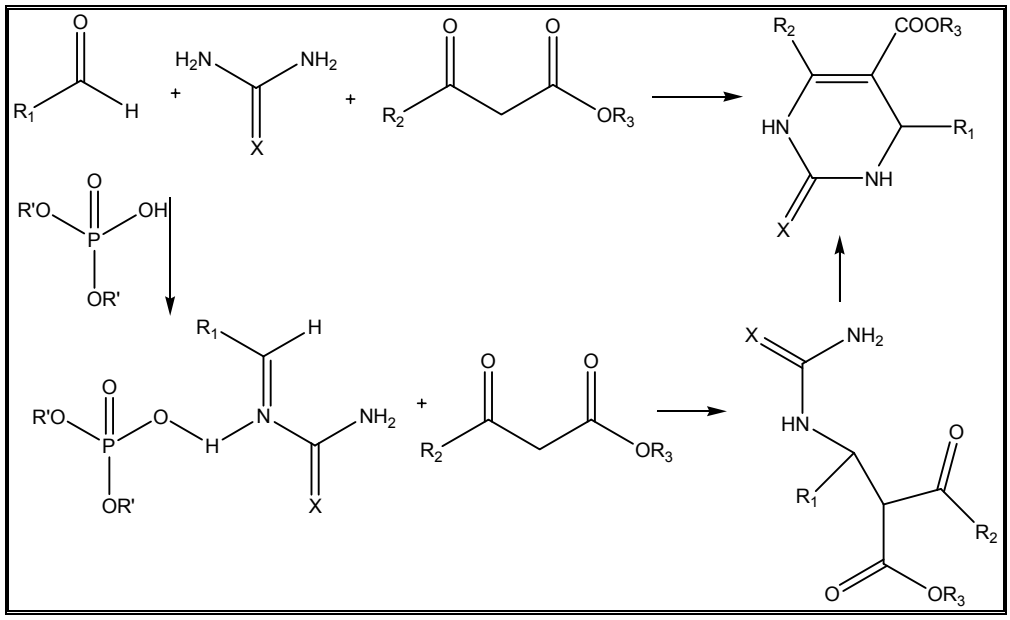




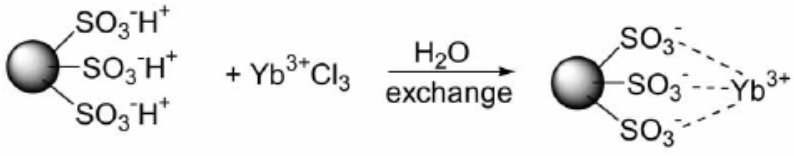
entry	Lewis acid	solvent	yield, %[b]	ee, %[c]	config.[d]
1	$La(OTf)_3$	THF	83	81	R
2	$Sm(OTf)_3$	THF	81	85	R
3	$Yb(OTf)_3$	THF	87	90	R
4	$Yb(OTf)_3$	CH_2Cl_2	80	83	R
5	$Yb(OTf)_3$	CH_3CN	86	82	R
6	$Yb(OTf)_3$	CH_3OH	88	80	R
7	$Yb(OTf)_3$[e]	THF	84	85	R

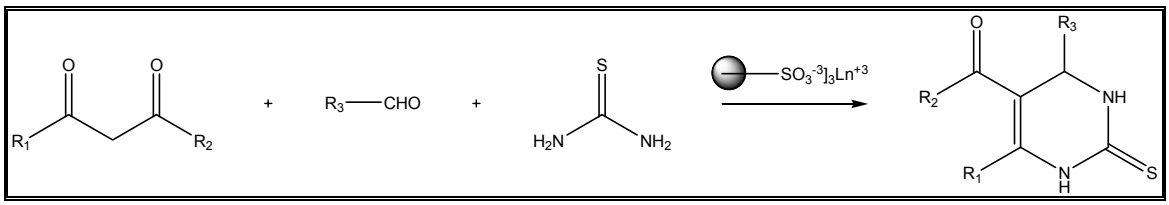


Very recently, chiral phosphoric acid is reported as highly enantioselective catalyst for Biginelli reaction. Reaction is reported in presence of 10 mol % of chiral phosphoric acid to produce desired enantioselective product. This is the first organocatalytic asymmetric Biginelli reaction. The optimal chiral phosphoric acid afforded the reaction in high yields with excellent enantioselectivities of up to 97% ee. A wide variety of substrates, including aldehydes and *α*-keto esters, could be tolerated. This reaction has an advantage of avoiding the contamination of transition metals in the manufacture of the medicinally relevant chiral 3,4-dihydropyrimidin-2-(1*H*)-ones.[14]



Recently Jiang and Chen[15]reported Yb(III)-Resin catalyzed Biginelli reaction under solvent-free conditions.





Heravi et al[16] recently reported synthesis of dihydropyrimidones using 12-molybdophosphoric acid in refluxing acetic acid to catalyze this three-component condensation reaction to afford the corresponding pyrimidinones in good yields.

An improved approach has been found to carry out the Biginelli reaction for the synthesis of 3,4- dihydropyrimidin- 2(1H)-one derivatives. This synthesis was performed in the presence of hydrochloric acid and β-cyclodextrin in ethanol solution. Compared with the classical Biginelli reaction conditions, this new approach has the advantage of excellent yields and short reaction time.[17]

An efficient synthesis of 3,4-dihydropyrimidinones from the aldehyde, β-keto ester and urea in ethanol, using ferric chloride hexahydrate or nickel chloride hexahydrate as the catalyst, is described[18]. Compared with the classical Biginelli reaction conditions, this new method has the advantage of excellent yields (53-97%) and short reaction time (4-5 hours).

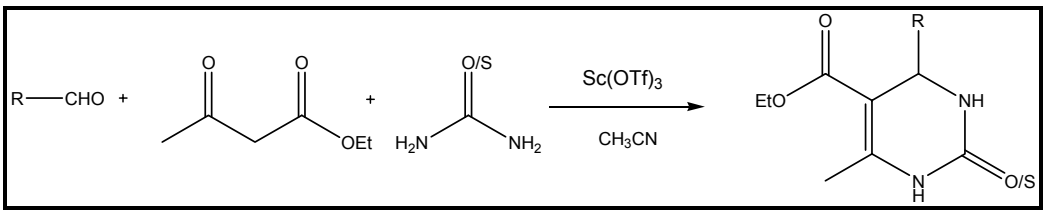
5-Alkoxycarbonyl-4-aryl-3,4-dihydropyrimidin-2-ones are synthesised by the one-pot reactions of aldehydes, β-ketoesters and urea using a catalytic amount of phosphotungstic acid (PTA) in ethanol. The modified Biginelli cyclocondensation not only shortens the reaction period and simplifies the operation, but also improves the yields.[19]

Ruthenium(III) chloride efficiently catalyzes the three-component Biginelli reaction of an aldehyde, a β-keto ester, and urea or thiourea under solvent-free conditions to afford the corresponding 3,4-dihydropyrimidine-2-(1*H*)-ones in excellent yields.[20]

The Biginelli reaction, a one-pot condensation of aldehydes, urea or thiourea, and β-dicarbonyl compounds, is efficiently catalyzed by samarium diiodide. The biologically active dihydropyrimidinones are easily synthesized in moderate to excellent yields under solvent-free conditions.[21]

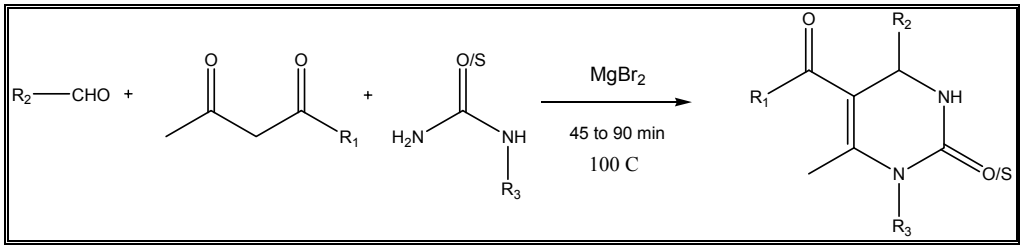
Hydroxyapatite doped with $ZnCl_2$, $CuCl_2$, $NiCl_2$ and $CoCl_2$ efficiently catalyses the three components Biginelli reaction between an aldehyde, ethyl acetoacetate and urea in refluxing toluene to afford the corresponding dihydropyrimidinones in high yields.[22]

Scandium (III)triflate efficiently catalyzes the three-component condensation reaction of an aldehyde, a β-ketoester, and urea in refluxing acetonitrile to afford the corresponding 3,4-dihydropyrimidin-2(1H)-ones in excellent yields. The catalyst can be recovered and reused, making this method friendly and environmentally acceptable.[23]

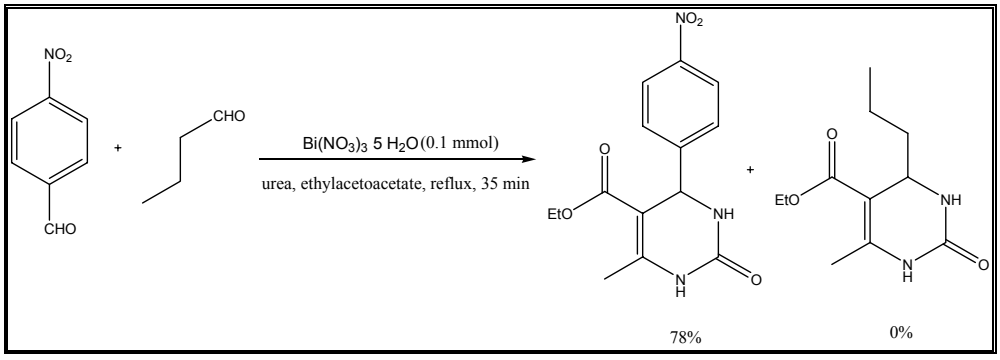


Shailaja et al[24] have demonstrated experimentally a simple and straightforward protocol (combination system of $SnCl_2$–LiCl) which provides dihydropyrimidin-2-one system in high yield and high purity while retaining the simplicity of the Biginelli concept.

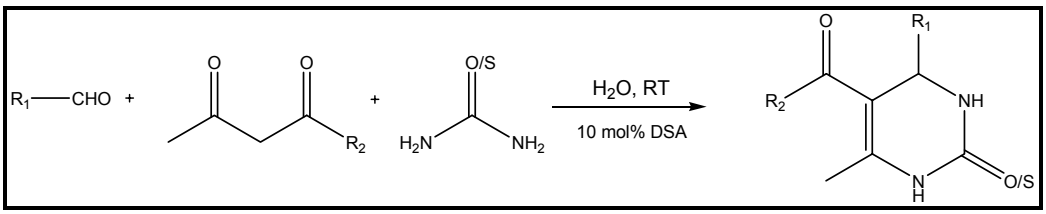
Magnesium bromide efficiently catalyzes the three-component condensation reaction of aldehyde, β-diketone and urea/thiourea under solvent free conditions to afford the corresponding dihydropyrimidinones in high yields and short reaction time.[25]



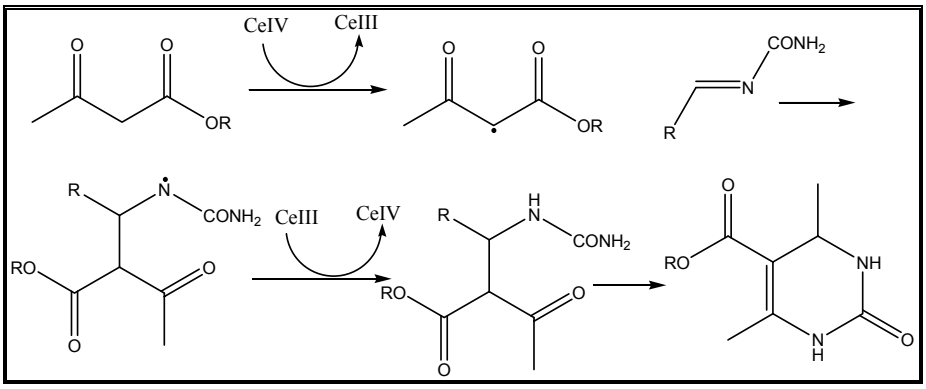
Bismuth nitrate pentahydrate catalyzes the three component condensation reaction of an aromatic aldehyde, urea and a β-ketoester or a β-diketone under solvent-free conditions to afford the corresponding dihydropyrimidinones (DHPMs) in high yields. The method is also effective for the selective condensation of aryl aldehydes in the presence of aliphatic aldehydes.[26]



Sharma et al[27] reported a simple, efficient, mild and green method has been developed for the synthesis of 3,4-dihydropyrimidin-2-ones employing dodecyl sulfonic acid as an excellent surfactant-type Bronsted acid catalyst in aqueous media at room temperature.

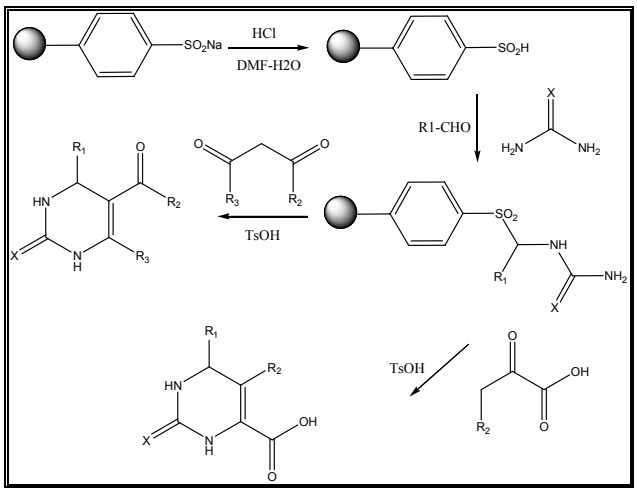


Yadav et al[28] reported that Ceric ammonium nitrate efficiently catalyzes the three component Biginelli reaction in methanol to afford the corresponding dihydropyrimidinones in excellent yields under sonication.

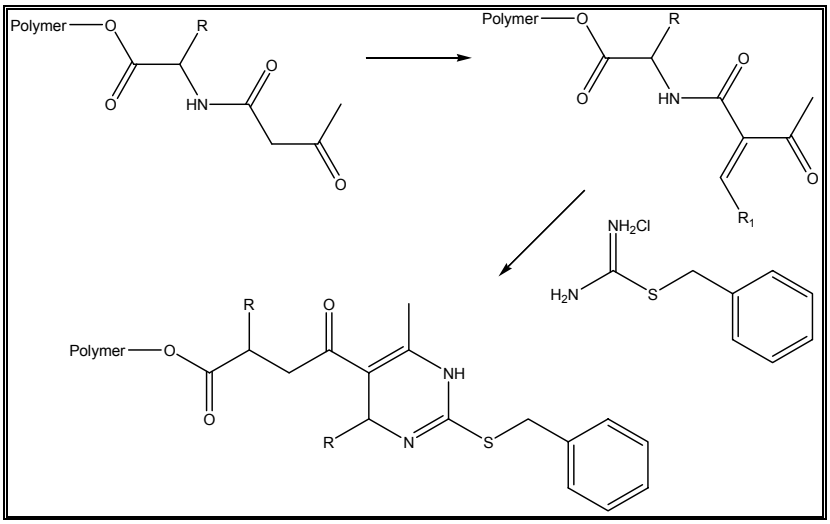


1.3.2 Solid Phase Synthesis

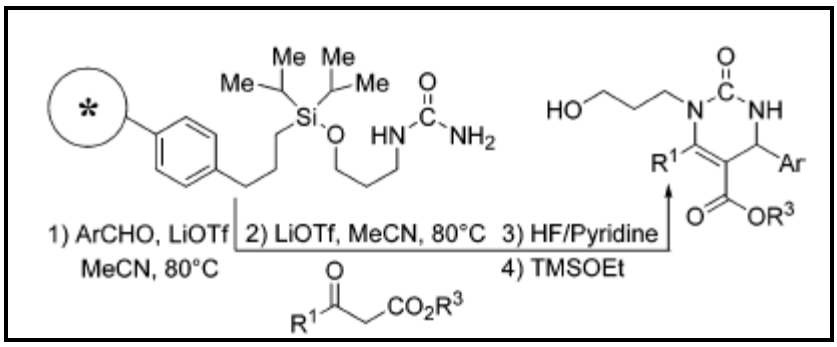
In recent years, various methods have been examined for the synthesis of DHPM on solid phase. Li and Lam[29] describe a convenient traceless solid-phase approach to synthesize3,4-dihydropyrimidine-2-ones. Key steps in the synthesis are (i) sulfinate acidification, (ii) condensation of urea or thiourea with aldehydes and sulfinic acid, and (iii) traceless product release by a one-pot cyclization-dehydration process. Since a variety of reagents can be used in steps (ii) and (iii), the overall strategy appears to be applicable to library generation.



Very recently, Gross et al[30] developed a protocol based on immobilized α-ketoamides to increase the diversity of DHPM. The resulting synthetic protocol proved to be suitable for the preparation of a small library using different building blocks. They found that the expected DHPM derivatives were formed in high purity and yield if aromatic aldehyde- and α-ketoamide building blocks were used. The usage of an aliphatic aldehyde leads to an isomeric DHPM mixture. Purities and yields were not affected if thiourea was used instead of urea.

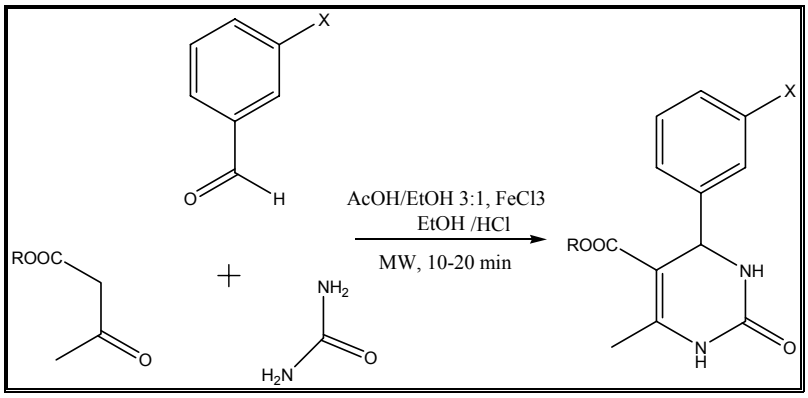


Lusch and Tallarico[31] reported a direct, Lewis acid-catalyzed Biginelli synthesis of 3,4-dihydropyrimidinones on high-capacity polystyrene macrobeads with a polymer *O*-silyl-attached *N*-(3-hydroxypropyl)urea. Resin-urea was first reacted separately with either 4-bromo- or 4-chlorobenzaldehyde or lithium trifluoromethanesulfonate in acetonitrile at 80 °C. After washing, the beads were pooled and reacted with ethyl acetoacetate and lithium trifluoromethanesulfonate in acetonitrile at 80 °C. Formation of only *one* kind of Biginelli product per bead demonstrated the feasibility of a solid-phase non-Atwal two-step split-and-pool synthesis of 3,4-dihydropyrimidinones.



1.3.3 Microwave assisted synthesis

In general, the standard procedure for the Biginelli condensation involves one-pot condensation of the three building blocks in a solvent such as ethanol using a strongly acidic catalyst, that is, hydrochloric acid. One major drawback of this procedure, apart from the long reaction times involving reflux temperatures, are the moderate yields frequently observed when using more complex building blocks. Kappe et al[32] recently described a high yielding and rapid microwave-assisted protocol that allows the synthesis of gram quantities of DHPMs utilizing controlled single-mode microwave irradiation. As the first model reaction for our scale-up experiments, they selected the standard Biginelli cyclocondensation, where in a one-pot process equimolar amounts of benzaldehyde, ethyl acetoacetate, and urea react under Lewis acid (FeCl3) catalysis to the corresponding dihydropyrimidine. Utilizing single-mode microwave irradiation, the reaction can be carried out on a 4.0 mmol scale in AcOH/EtOH 3:1 at 120 °C within 10 min, compared to 3-4 h using conventional thermal heating, providing DHPM in 88% isolated yield and high purity (>98%).



Dihydropyrimidines were synthesised in high yields by one-pot cyclocondensation reaction of aldehydes, acetoacetates and urea using various acid catalysts like Amberlyst-15, Nafion-H, KSF clay and dry acetic acid under microwave irradiation.[33]

The antimony(III) chloride impregnated on alumina efficiently catalyses a one-pot, three-component condensation reaction among an aldehyde, a β-ketoester, and urea or thiourea to afford the corresponding dihydropyrimidinones in good to excellent yields. The reactions are probed in microwave (MW), ultrasonic, and thermal conditions and the best results are found using MW under solvent-free conditions.[34]

Cupric chloride dihydrate catalyzes the three-component Biginelli condensation between an aldehyde, a β-ketoester and urea or thiourea under microwave irradiation in the absence of solvent to yield various substituted 3,4-dihydropyrimidin-2(1*H*)-ones. The reaction is also effective when performed at room temperature in acetonitrile or at 100 °C in a solvent free approach, without any side reactions as observed by Biginelli and others.[35]

The publications by Gupta[36] and Dandia[37] describe 26 examples of microwave-enhanced solution-phase Biginelli reactions employing ethyl acetoacetate, (thio) ureas, and a wide variety of aromatic aldehydes as building blocks. Upon irradiation of the individual reaction mixtures (ethanol, catalytic HCl) in an open glass beaker inside the cavity of a domestic microwave oven the reaction times were reduced from 2–24 hours of conventional heating (80 °C, reflux) to 3–11 minutes under microwave activation (*ca.* 200–300 W). At the same time the yields of DHPMs obtained by the authors were markedly improved compared to those reported earlier using conventional conditions.

Kappe[38] reinvestigated above reactions using a purpose-built commercial microwave reactor with on-line temperature, pressure, and microwave power control. Transformations carried out under microwave heating at atmospheric pressure in ethanol solution show no rate or yield increase when the temperature is identical to conventional thermal heating. In the case of superheating by microwave irradiation at atmospheric pressure the observed yield and rate increase phenomenon are rationalized as a consequence of a thermal (kinetic) effect. Under sealed vessel conditions (20 bar, 180 ºC) the yield of products is decreased and formation of various byproducts observed. The only significant rate and yield enhancements are found when the reaction is performed under “open system” conditions where the solvent is allowed to rapidly evaporate during microwave irradiation. However, the observed rate and yield enhancements in these experiments are a consequence of the solvent-free conditions rather than caused specifically by microwave irradiation. This was confirmed by control experiments of the solvent less Biginelli reaction under microwave and thermal heating.

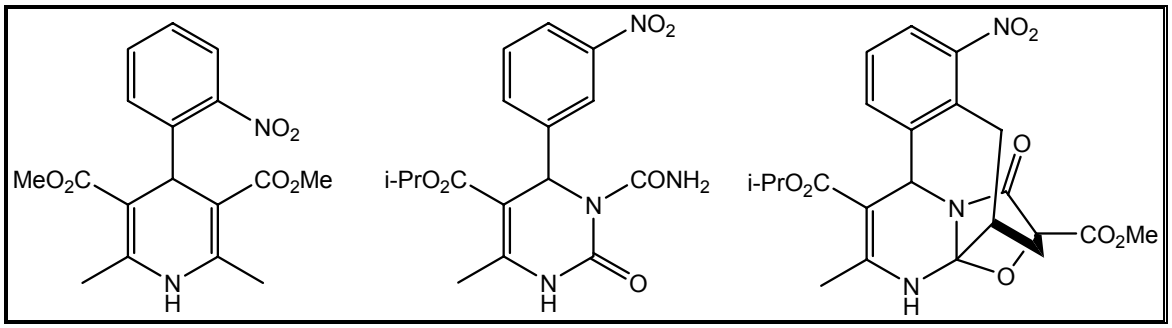
1.3.4 Ionic liquid

Wang et al[39] reported the Biginelli reaction between an aromatic aldehyde, ethyl acetoacetate, and urea - catalyzed by polymer-supported, re-usable, room-temperature ionic liquids (RTIL) - was shown to efficiently proceed in glacial AcOH at 100° to afford the corresponding pyrimidine-5-carboxylates in yields up to 99% within 2 h. The catalyst(s) could be reused at least five times, basically without loss of activity, which makes this transformation not only straight-forward, but also considerably less expensive compared to methods involving classical RTIL catalysts.

1.4 Biologically active dihydropyrimidones

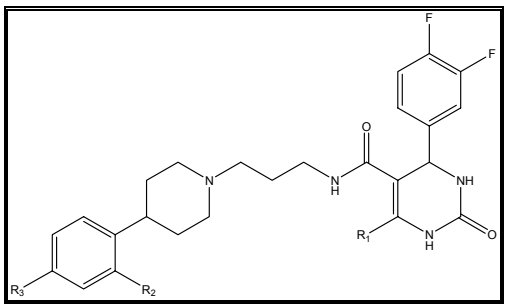
4-Aryl-1,4-dihydropyridines (DHPs, e.g nifedipine,) are the most studied class of organic calcium channel modulators. More than 30 years after the introduction of nifedipine, many DHP analogs have now been synthesized and numerous second-generation commercial products have appeared on the market.[40, 41]

In recent years, interest has also focused on aza-analogs such as dihydropyrimidines (DHPMs) which show a very similar pharmacological profile to classical dihydropyridine calcium channel modulators.[42-49] Over the past few years several lead-compounds were developed that are superior in potency and duration of antihypertensive activity to classical DHP drugs, and compare favorable with second-generation analogs such as amlodipine and nicardipine.[50]



Barrow et al[55] reported *in vitro* and *in vivo* evaluation of dihydropyrimidinone C-5 amides as potent and selective α_{1a} Receptor Antagonists for the treatment of benign prostatic hyperplasia.

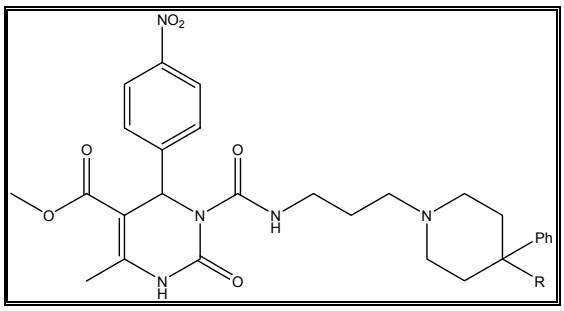
α_1 adrenergic receptors mediate both vascular and lower urinary tract tone, and α_1 receptor antagonists such as terazosin are used to treat both hypertension and benign prostatic hyperplasia (BPH). Recently, three different subtypes of this receptor have been identified, with the α_{1a} receptor being most prevalent in lower urinary tract tissue. 4-aryldihydropyrimidinones attached to an aminopropyl-4-arylpiperidine via a C-5 amide as selective α_{1a} receptor subtype antagonists. In receptor binding assays, these types of compounds generally display *K*i values for the α_{1A} receptor subtype <1 nM while being greater than 100-fold selective versus the α_{1b} and α_{1d} receptor subtypes. Many of these compounds were also evaluated *in vivo* and found to be more potent than terazosin in both a rat model of prostate tone and a dog model of intra-urethral pressure without significantly affecting blood pressure. While many of the compounds tested displayed poor pharmacokinetics, one compound was found to have adequate bioavailability (>20%) and half-life (>6 h) in both rats and dogs. Due to its selectivity for the α_{1a} over the α_{1b} and α_{1d} receptors as well as its favorable pharmacokinetic profile, it has the potential to relieve the symptoms of BPH without eliciting effects on the cardiovascular system.[51-55]



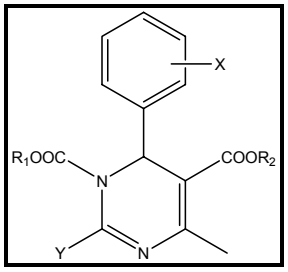
The 4-aryldihydropyrimidinone heterocycle attached to an aminopropyl-4-arylpiperidine via a C-5 amide has proved to be an excellent template for selective α_{1a} receptor subtype antagonists. These types of compounds are exceptionally potent in both cloned receptor binding studies as well as in *in vivo* pharmacodynamic models of prostatic tone.

Compounds exhibited high binding affinity and subtype selectivity for the cloned human α_{1A} receptor. Systematic modifications led to identification of highly potent and subtype-selective compounds with high binding affinity (*K*i =0.2 nM) for α_{1a} receptor and greater than 1500-fold selectivity over α_{1b} and α_{1d} adrenoceptors. The compounds were found to be functional antagonists in human, rat, and dog prostate tissues. They exhibited excellent selectively to inhibit intraurethral pressure (IUP) as compared to lowering diastolic blood

pressure (DBP) in mongrel dogs (*K*b(DBP)/*K*b(IUP))suggesting uroselectivity for α_{1a}-selective compounds.[56]

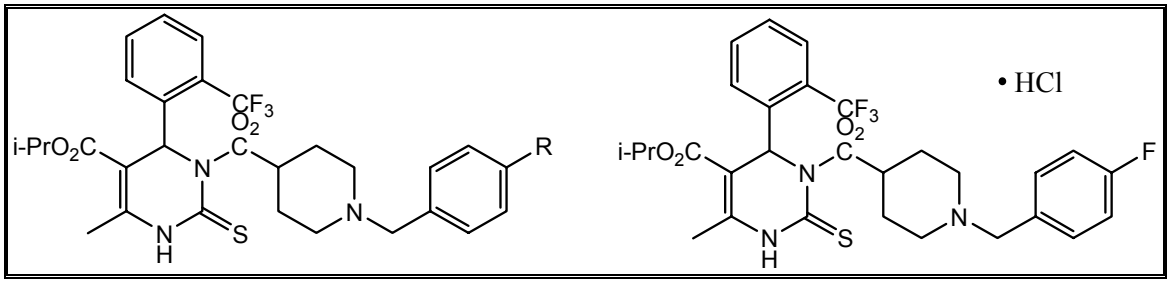


Cho et al[57] reported 3-N-substituted-3,4-dihydropyrimidine and 3-N-substituted-dihydropyrimidin-2(1H)-ones as calcium channel antagonist. Compounds [especially [R_1=$(CH_2)_2$N(benzyl)(2-naphthylmethyl),R_2=i-Pr,X=2-N0_2] and [R'= $(CH_2)_2$N(benzyl) (3,4-dichlorobenzyl),R_2=i-Pr, X=2-NO_2]] exhibited not only more potent and longer lasting vasodilative action but also a hypertensive activity with slow onset as compared with dihydropyridines. Moreover, some dihydropyrimidines [R'=$(CH_2)_2$N(benzyl)(3-phenylpropyl),R_2=CH_2(cyclopropyl),X=2-NO_2] were weaker in blocking atrioventricular conduction in anesthetized open-chest dogs and less toxic than the dihydropyridines.

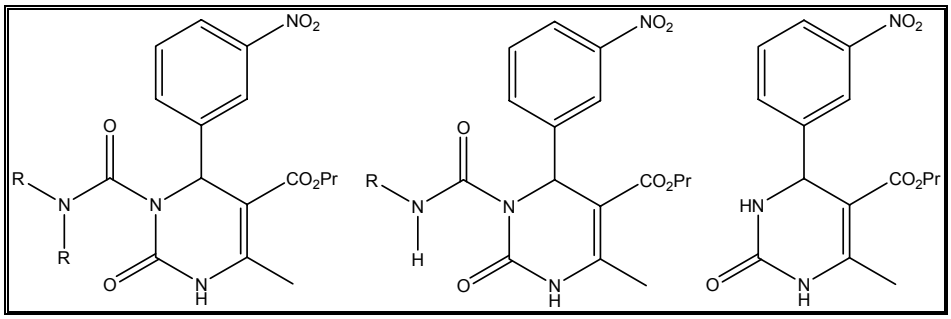


Atwal et al[58] examined a series of novel dihydropyrimidine calcium channel blockers that contain a basic group attached to either C_5 or N_3 of the heterocyclic ring. Structure-activity studies show that l-(phenylmethyl)-4-piperidinyl carbamate moiety at N_3 and sulfur at C_2 are optimal for vmrelaxant activity in vitro and impart potent and long-acting antihypertensive activity *in vivo*. One of the compounds was identified as a lead, and the individual enantiomers were synthesized. Two key steps of the synthesis were (1) the efficient separation of the diastereomeric ureido derivatives and (2) the high-yield transformation of 2-methoxy intermediate to the (p-methoxybenzy1)thio intermediates. Chirality was demonstrated to be a significant determinant of biological activity, with the dihydropyridine receptor recognizing the enamino ester moiety but not the carbamate moiety. Dihydropyrimidine is equipotent to nifidepine and amlodipine *in vitro*. In the spontaneously hypertensive rat, dihydropyrimidine is both more potent and longer acting

than nifidepine and compares most favorably with the long-acting dihydropyridine derivative amlodipine. Dihydropyrimidine has the potential advantage of being a single enantiomer.

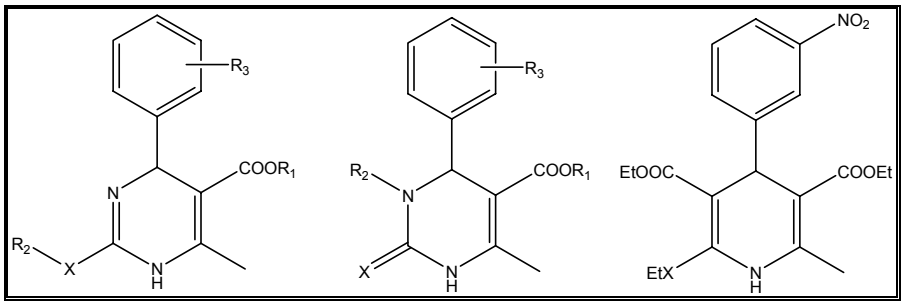


In order to explain the potent antihypertensive activity of the modestly active (ICw = 3.2 pM) dihydropyrimidine calcium channel blocker**,** Atwal et al[59] carried out drug metabolism studies in the rat and found it is metabolized. Two of the metabolites (ICw = 16 nM) and (ICw = 12 nM), were found to be responsible for the antihypertensive activity of compound**.** Potential metabolism *in vivo* precluded interest in pursuing compounds related to it. Structure-activity studies aimed at identifying additional aryl-substituted analogues led to comparable potential *in vivo*, though these compounds were less potent *in vitro*. To investigate the effects of absolute stereochemistry on potency, authors resolved via diastereomeric ureas, prepared by treatment with (R)-α-methylbenzylamine. The results demonstrate that the active R-(-)-enantiomer is both more potent and longer acting than nifedipine as an antihypertensive agent in the SHR. The *in vivo* potency and duration is comparable to the long-acting dihydropyridine amlodipine. The superior oral antihypertensive activity compared to that of previously described carbamates could be explained by its improved oral bioavailability, possibly resulting from increased stability of the urea functionality.

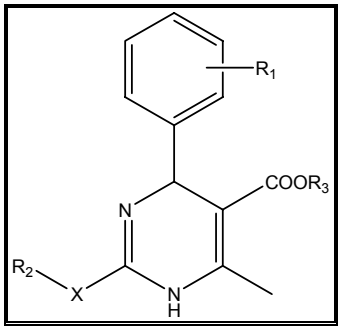


Atwal et al[60] modified the structure of previously described dihydropyrimidine i.e. 3-substituted 1,4-dihydropyrimidines**.** Structure- activity studies using potassium-depolarized rabbit aorta show that ortho,meta-disubstituted aryl derivatives are more

potent than either ortho- or meta-monosubstituted compounds. While vasorelaxant activity was critically dependent on the size of the C_5 ester group, isopropyl ester being the best, a variety of substituents (carbamate, acyl, sulfonyl, alkyl) were tolerated at N_3. The results show dihydropyrimidines are significantly more potent than corresponding 2-heteroalkyl-l,4-dihydropyrimidines and only slightly less potent than similarly substituted 2-heteroalkyl-1-4-dihydropyridines**.** Where as dihydropyridine enantiomen usually show 10-15-fold difference in activity, the enantiomers of dihydropyrimidine show more than a 1000-fold difference in activity. These results strengthen the requirement of an enamino ester for binding to the dihydropyridine receptor and indicate a nonspecific role for the N_3-substituent.



2-Heterosubstituted-4-aryl-l,4-dihydro-6-methyl-5-pyrimidinecarboaxcyildicesters, which lack the potential symmetry of dihydropyridine calcium channel blockers, were prepared and evaluated for biological activity. Biological assays using potassium-depolarized rabbit aorta and radio ligand binding techniques showed that some of these compounds are potent mimics of dihydropyridine calcium channel blockers.[60]



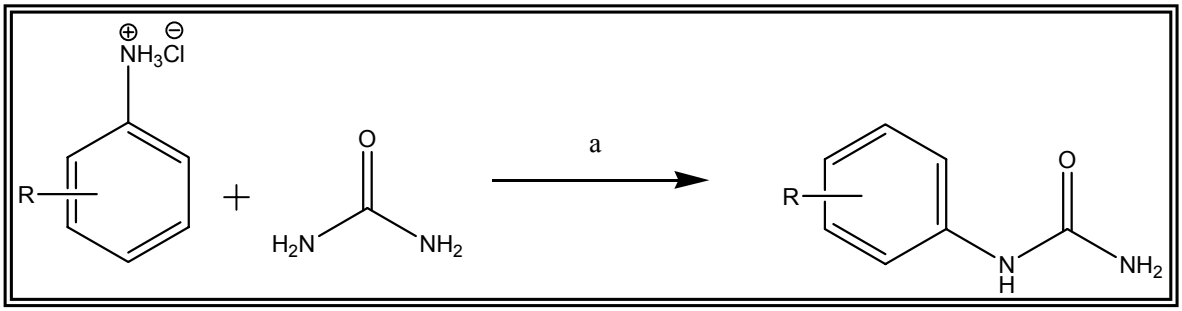
1.5 Current work

Our group is involved in the synthesis of modified 1,4-dihydropyridine and dihydropyrimidine skeleton derivatives for last few years. Introduction of phenyl carbamoyl moiety at C-3 and/or C-5 position in dihydropyridine skeleton has showed diversed activity profile. Very promising results obtained with these modifications to dihydropyridine skeleton. N-phenyl substituted dihydropyridines were also synthesized and it also showed interesting biological profile. Result obtained in dihydropyridine modification, inspired to introduce phenyl carbamoyl moiety at C-5 position of dihydropyrimidine skeleton. This modification to dihydropyrimidine skeleton exhibited moderate biological profile. Moderate anti tubercular activity was observed for these derivatives against *Mycobacterium $H_{37}Rv$.*

Current work describes the synthesis of derivatives with phenyl ring at N_1 of dihydropyrimidine skeleton and phenyl carbamoyl moiety at C-5 position. Reaction schemes are illustrated in Section 1.6. Scheme 1 and 2 displays the synthesis of N-phenyl urea and acetoacetanilides, two building blocks of Biginelli reaction. Different N-phenyl ureas with methyl substations (-Phenyl, -3-methylphenyl, 2,4-dimethylphenyl) were synthesized. Acetoacetanilides were synthesized with different halogen substitutions (4-chloro, 4-flouro, 3-chloro-4-flouro). Scheme 3 is synthesis of N-phenyl substituted DHPM derivatives by reacting N-(phenyl/3-methylphenyl/2,4-dimethyl) urea, (4-chloro, 4-flouro, 3-chloro-4-flouro)acetoacetanilide and aromatic aldehyde. The reaction time was observed 8-12 hours depending on the substitution on substitutions on 4-phenyl and N-phenyl ring. The synthesized compounds are characterized by IR, NMR and Mass spectral analysis and are under screening against *Mycobacterium $H_{37}Rv$* for anti tubercular activity. Physical data of synthesized compounds is reported in Section 1.8 and spectral data is discussed in Section 1.9.

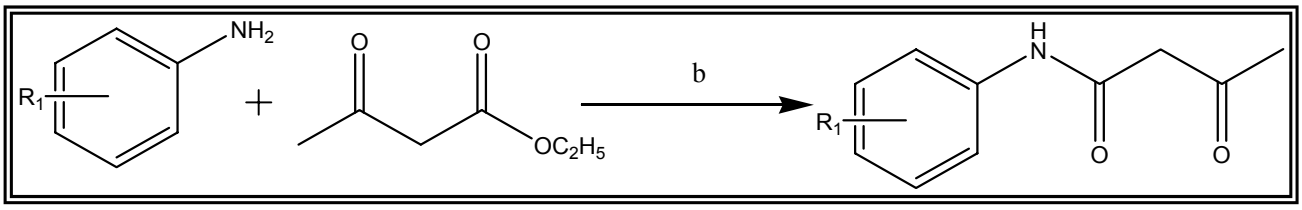
1.6 Reaction Schemes

1.6.1 Scheme 1.



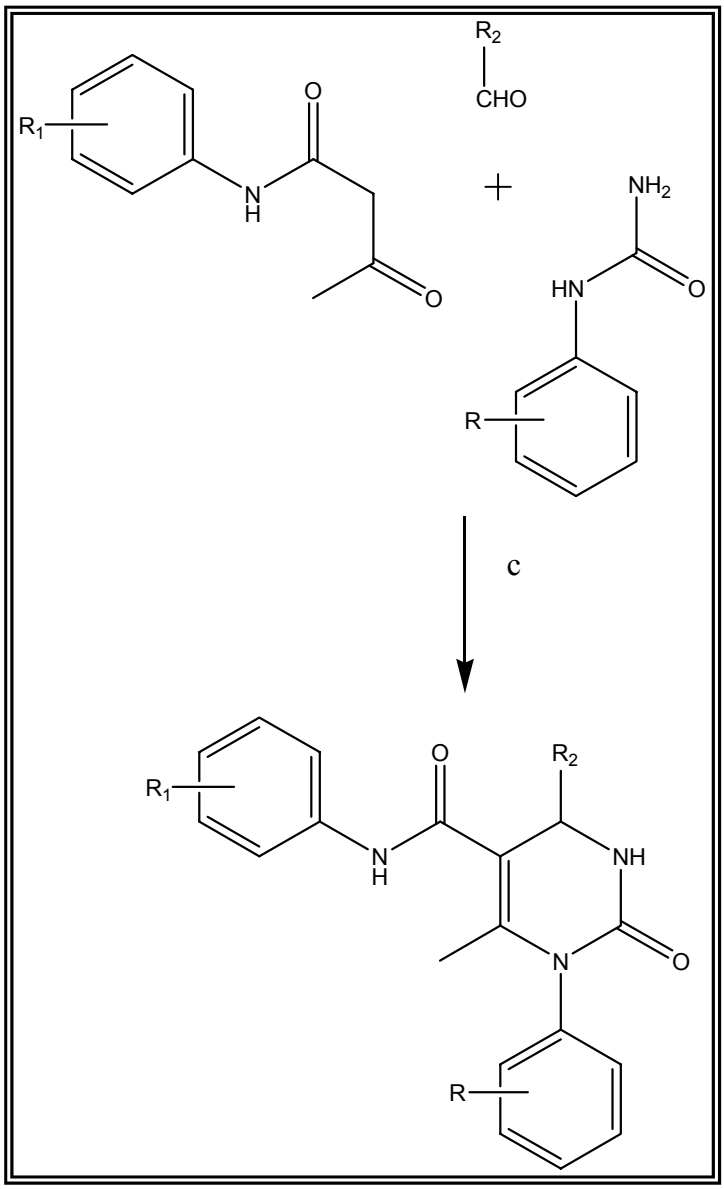
Scheme 1. Reagents and conditions: a = water, glacial acetic acid, con. HCl, reflux.

1.6.2 Scheme 2.



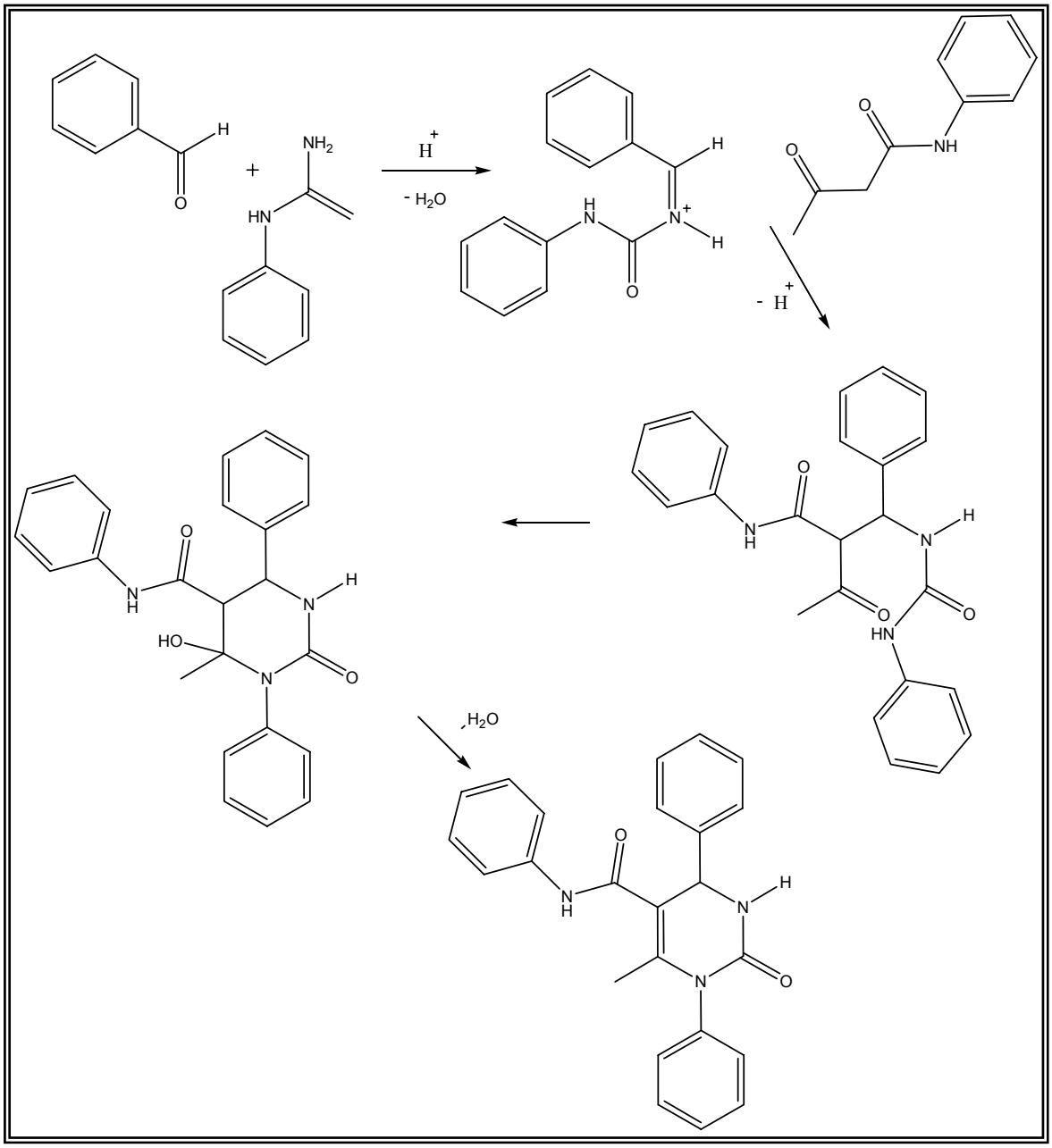
Scheme 2. Reagents and conditions: b = KOH/NaOH, toluene, 115° C.

1.6.3 Scheme 3.



Scheme 3. Reagents and conditions: c = MeOH, con. HCl, reflux.

Reaction Mechanism



1.7 Experimental

1.7.1 N-substitutedphenylurea:

It was prepared according to literature method[a]. Aniline (3-methyl/2,4-dimethylaniline) hydrochloride (0.2M) and urea (0.2M) were dissolved in 100 ml of water. 2 ml of glacial acetic acid and 2 ml of conc. HCl was added to this solution. The reaction mixture was refluxed and white crystals appeared after 30-40 minutes. It was further refluxed for another 30 minutes. The reaction mixture was cooled and filtered. The solid product was taken into 300 ml of water and boiled. It was filtered, and the filtrate was concentrated and allowed to cool. The crystal of phenyl urea was filtered and dried. Similarly, N-(3-methylphenyl)urea and N-(2,4-dimethylphenyl) urea were synthesized. (Physical data is given in Table 1.8.2)

1.7.2 Substituted acetoacetanilide:

It was prepared according to literature method[b]. Substituted aniline (0.1M) and ethyl aceto acetate was refluxed at 110° C in 40 ml of toluene and catalytic amount of KOH/NaOH. The completion of reaction was monitored with thin layer chromatography. After completion of reaction, toluene was distilled out. The residue was cooled at room temperature and was treated with ether. The solid was filtrated and dried. (Physical data is given in Table 1.8.1)

1.7.3 4-(substitutedphenyl)-N-(substitutedphenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxo-1-(substituted phenyl)lpyrimidine-5-carboxamide:

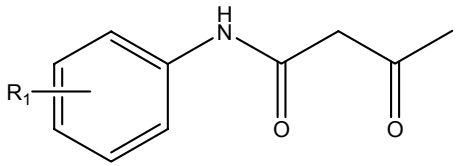
Acetoacetanilide (0.01M), aldehyde (0.01M) and N-phenyl urea (0.015M) were dissolved in methanol and refluxed until clear solution is obtained. Few drops of con HCl was added to reaction mixture and was refluxed for 8-12 hrs. The reaction was monitored with thin layer chromatography and after completion; the reaction mixture was allowed to cool. The solid separated was filtered, washed with hot methanol and dried. The compounds were recrystallized from dimethylformamide. (Physical data is given in Table 1.8.3)

[a] Vogel's text book of practical organic chemistry, 5th Edition, Page no. 965.

[b] [1] Desai, B.; Sureja, D.; Naliapra, Y.; Shah, A.; Saxena, A.; *Bioorg. Med. Chem.* **2001** 9, 1993-98. [2] Kharkar, P.; Desai, B.; Gaveria, H.; Varu, B.; Loriya, R.; Naliapara, Y.; Shah, A.; Kulkarni, V.; *J. Med. Chem.* **2002** 45, 4858-67.

1.8 Physical data tables

1.8.1 Physical data of N-(substituted phenyl)-3-oxobutanamide [compounds 1a-c].

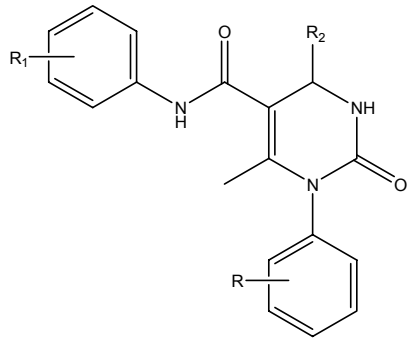


Compound	R_1	MF	MW	MP ºC	Yield	R_f
1a	4-Cl	$C_{10}H_{10}ClNO_2$	211.64	134-35	58	0.64
1b	4-F	$C_{10}H_{10}FNO_2$	195.19	91-92	52	0.69
1c	3-Cl,4-F	$C_{10}H_9ClFNO_2$	229.64	122-24	45	*0.51
1d	H	$C_{10}H_{11}NO_2$	177.20	82-83	64	0.53
1e	2-Cl	$C_{10}H_{10}ClNO_2$	211.64	104-106	57	0.59
1f	2-Me	$C_{11}H_{13}NO_2$	191.22	106-08	58	0.52
1g	2,4-di-Me	$C_{12}H_{15}NO_2$	205.23	92-93	62	0.57
1h	3-Me	$C_{11}H_{13}NO_2$	191.22	112-14	60	0.48

1.8.2 Physical data of N-(substituted phenyl) urea [compounds 2a-c].

Compound	R_1	MF	MW	MP ºC	Yield	R_f
2a	H	$C_7H_8N_2O$	136.15	149-50	55	0.41
2b	3-CH_3	$C_8H_{10}N_2O$	150.18	172-73	65	0.37
2c	2,4-di-CH_3	$C_9H_{12}N_2O$	164.20	156-59	60	0.30

1.8.3 Physical data of 4-(substitutedphenyl)-N-(substitutedphenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxo-1-(substituted phenyl)lpyrimidine-5-carboxamide [compounds 3a-t].



Compound	Code	R	R_1	R_2	MF	MW	MP	Yield	R_f
3a	AKS-121	H	4-Cl	Ph	$C_{24}H_{20}ClN_3O_2$	417.89	208-10	52	0.48
3b	AKS-122	H	4-Cl	4-OH-Ph	$C_{24}H_{19}ClN_4O_4$	462.89	176-77	48	0.53
3c	AKS-123	H	4-Cl	4-Cl-Ph	$C_{24}H_{19}Cl_2N_3O_2$	452.33	188-89	50	0.61
3d	AKS-124	3-CH_3	4-Cl	2-Cl-Ph	$C_{25}H_{21}Cl_2N_3O_2$	466.36	213-14	54	0.45
3e	AKS-125	3-CH_3	4-Cl	2-OH-Ph	$C_{25}H_{22}ClN_3O_3$	447.91	199-201	50	0.49
3f	AKS-126	H	4-Cl	2-OCH_3-Ph	$C_{26}H_{24}ClN_3O_3$	461.94	191-92	50	0.67
3g	AKS-127	3-CH_3	4-Cl	3-NO_2	$C_{25}H_{21}ClN_4O_4$	476.91	214-17	42	0.55

3h	AKS-128	2,4-CH_3	4-Cl	2-Cl-Ph	$C_{26}H_{23}Cl_2N_3O_2$	480.39	168-70	46	0.39
3i	AKS-129	2,4-CH_3	4-Cl	4-Cl-Ph	$C_{26}H_{23}Cl_2N_3O_2$	480.39	195-96	45	0.41
3j	AKS-130	2,4-CH_3	4-Cl	4-NO_2-Ph	$C_{26}H_{23}ClN_4O_4$	490.94	182-83	50	0.56
3k	AKS-131	H	4-F	Ph	$C_{24}H_{20}FN_3O_2$	401.15	218-220	54	0.63
3l	AKS-132	3-CH_3	4-F	2-Cl-Ph	$C_{25}H_{21}ClFN_3O_2$	449.90	204-05	46	0.59
3m	AKS-133	3-CH_3	4-F	4-NO_2-Ph	$C_{25}H_{21}FN_4O_4$	460.46	213-14	42	0.40
3n	AKS-134	2,4-CH_3	4-F	2-Cl-Ph	$C_{26}H_{23}ClFN_3O_2$	463.93	196-98	47	0.58
3o	AKS-135	2,4-CH_3	4-F	4-NO_2-Ph	$C_{26}H_{23}FN_4O_4$	474.48	221-24	40	0.37
3p	AKS-136	3-CH_3	3-Cl, 4-F	2-Cl-Ph	$C_{25}H_{20}Cl_2FN_3O_2$	484.35	172-74	44	0.54
3q	AKS-137	3-CH_3	3-Cl, 4-F	4-NO_2-Ph	$C_{25}H_{20}ClFN_4O_4$	494.90	176-77	42	0.62
3r	AKS-138	2,4-CH_3	3-Cl, 4-F	4-NO_2-Ph	$C_{26}H_{22}ClFN_4O_4$	508.93	185-86	38	0.46
3s	AKS-139	H	3-Cl, 4-F	4-Cl-Ph	$C_{26}H_{22}Cl_2FN_3O_2$	471.24	211-14	43	0.55
3t	AKS-140	H	4-Cl	3-NO_2-Ph	$C_{26}H_{23}ClN_4O_4$	462.77	199-01	50	0.42

TLC solvent system: Compound 1a-c (EA:Hexane) 2:8, *1:9
Compound 2a-c ($CHCl_3$:MeOH) 0.5:9.5
Compound 3a-t (EA:Hexane) 3:7

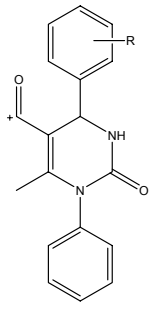
MPs were taken in open capillary and are not corrected

1.9 Spectral discussion

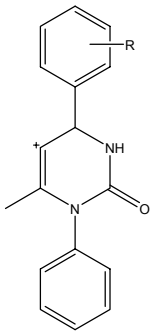
1.9.1 Mass spectral study

Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using Direct Injection Probe technique. The molecular ion peak was found in agreement with molecular weight of the respective compound. Characteristic M^{+2} ion peaks with one-third intensity of molecular ion peak were observed in case of compounds having chlorine atom. The DHPMs having chlorine atom showed this characteristic peak. Fragmentation pattern can be observed to be particular for this kind of compounds and the characteristic peaks obtained for each compound. Various characteristic peaks obtained for each compound in this series can be discussed as below.

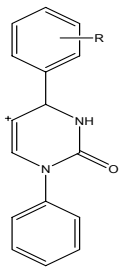
1. Cleavage of bond adjacent to carbonyl group expected to give peak in mass spectrum. Cleave of C-N bond (adjacent bond to C=O bond at carbamoyl side chain at C-5 position) gave intense peak in each spectrum [1].
2. Cleavage of another bond adjacent to C=O group of carbamoyl moiety gives another characteristic peak which is observed in each spectrum of this series [2].
3. Cleavage of –Me group at C-6 position from above fragment gave characteristic peak at m/e value less than 15 [3].
4. Cleavage to both α-bonds to C=O bond of DHPM ring, gives another characteristic peak for this series of compounds [4].
5. Another characteristic peak was observed at 153 m/e [5].



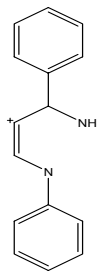
[1]



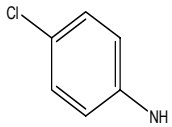
[2]



[3]



[4]



[5]

1.9.2 IR spectral study

Various functional groups present in molecule were identified by characteristic frequency obtained for them. Presence of two carbonyl groups can be confirmed by IR spectra because two carbonyl stretching frequencies were observed for two carbonyl groups present in the moiety. Cyclic C=O group peak was observed between 1690-1720 cm^{-1} while another C=O group (NH-CO-) was observed between 1655-1680 cm^{-1}. Two N-H groups gave peaks between 3210-3380 cm^{-1}. Peaks were identified for aromatic and alkyl group as per their characteristics. In case of compounds having different substations on aromatic ring, characteristic frequencies were observed depending on the functional group present i.e. nitro, hydroxyl, chloro, methoxy etc.

1.9.3 ^{1}H NMR spectral study

Numbers of proton identified from NMR spectrum and their chemical shift (δ ppm) were in agreement of structure of molecule. Methyl protons were observed at 1.3-1.9 δ ppm. Proton on C-4 carbon atom gave singlet at 5.12-5.80 δ ppm. Aromatic protons were observed between 7.2-7.9 δ ppm. J values were calculated to identify ortho and meta coupling. In some cases, aromatic protons were obtained as multiplet.

In spectrum of compound AKS-123, singlet was obtained at 1.81 δ ppm for methyl protons. Proton on C_4 gave singlet in downfield at 5.48 δ ppm. A doublet with J value of 8.52 and 1.96 for two aromatic protons for ortho and meta coupling were observed. Another doublet for two protons was also observed for ortho and meta coupling J values. Doublet for one proton with J value for ortho coupling was obtained. Other aromatic protons were obtained as multiplet.

In spectrum of AKS-122, methyl protons gave singlet at 1.68 δ ppm and C_4 proton singlet was observed at 5.48 δ ppm. Aromatic protons were observed as a doublet for one proton with J value of ortho coupling (8.8), a triplet for three protons with J value of ortho coupling (8.32, 9.87), a doublet for two protons with J value of ortho coupling (8.80) and two multiplet for three and five protons.

In case of compound AKS-139, singlets were observed at 1.71 and 5.38 for methyl and C_4 proton respectively. A doublet with J value of 8.42 for two protons, a triplet with J value of 2.04 for one proton, a doublet with J value of 1.57 for one proton, a doublet with J value of 10.16 for one proton and two multiplets for four protons each were observed.

1.9.4 Elemental analysis

Elemental analysis showed calculated and found percentage values of carbon, hydrogen and nitrogen in support of structure of synthesized compounds. The spectral and elemental analysis data are given below for individual compounds.

Spectral data of synthesized compounds (AKS 121-140)

N*-(4-chlorophenyl)-6-methyl-2-oxo-1,4-diphenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (AKS-121) – IR (cm^{-1}):** 3375, 3288 (-NH-), 3055 (Ar-H), 2988, 2918, 2866 (-Me), 1716 (C=O), 1666 (C=O), 1596, 1491, 1473, 1096 (C-O), 883, 775 (OOP); ***Anal cacld for $C_{24}H_{20}ClN_3O_2$: C 68.98, H 4.82, N 10.06, found: C 69.01, H 4.85, N 10.14.

N*-(4-chlorophenyl)-4-(4-hydroxyphenyl)-6-methyl-2-oxo-1-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (AKS-122) – IR (cm^{-1}):** 3396, 3247 (-NH-), 3085 (Ar-H), 2945, 2903, 2818 (-Me), 1707 (C=O), 1660 (C=O), 1585, 1428, 1447, 1124 (C-O), 894, 754 (OOP); ***^{1}H NMR *(δ ppm):* 1.68 (3H, s), 5.48 (1H, s), 6.53 (1H, d, J=8.8), 6.87 (3H, m), 7.18 (5H, m), 7.32 (3H, t, J=8.32, 9.87), 7.64 (2H, d, J=8.80), 8.35 (1H, s), 9.59 (1H, s); ***Anal cacld*** for $C_{24}H_{19}ClN_4O_4$: C 66.44, H 4.65, N 9.68, found: C 66.48, H 4.70, N 9.75.

N*-(4-chlorophenyl)-4-(4-chlorophenyl)-6-methyl-2-oxo-1-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (AKS-123) – IR (cm^{-1}):** 3412, 3310 (-NH-), 3019 (Ar-H), 2971, 2911, 2853 (-Me), 1702 (C=O), 1674 (C=O), 1555, 1446, 1085 (C-O), 824, 741 (OOP); ***^{1}H NMR *(δ ppm):* 1.81 (3H, s), 5.48 (1H, s), 7.21 (4H, m), 7.34 (2H, d, J=8.52, 1.96), 7.38 (1H, d, J=7.20), 7.43 (4H, m), 7.57 (2H, d, J=8.88, 2.08); ***Anal cacld*** for $C_{24}H_{19}Cl_2N_3O_2$: C 63.73, H 4.23, N 9.29, found: C 63.78, H 4.27, N 9.35.

N*-(4-chlorophenyl)-4-(2-chlorophenyl)-6-methyl-1-(3-methylphenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (AKS-124) – IR (cm^{-1}):** 3347, 3217 (-NH-), 3079 (Ar-H), 2917, 2841 (-Me), 1694 (C=O), 1654 (C=O), 1519, 1460, 1447, 1184 (C-O), 704 (OOP); ***Mass** (m/e)*: 466 (Molecular ion peak), 339 (base peak), 311, 296, 269, 153, 122, 91, 77; ***Anal cacld for $C_{25}H_{21}Cl_2N_3O_2$: C 64.39, H 4.54, N 9.01, found: C 64.36, H 4.51, N 9.06.

N*-(4-chlorophenyl)-4-(2-hydroxyphenyl)-6-methyl-1-(3-methylphenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (AKS-125) – IR (cm^{-1}):** 3481, 3222 (-NH-), 3061 (Ar-H), 2973, 2945, 2811 (-Me), 1701 (C=O), 1678 (C=O), 1503, 1441, 1408, 1056 (C-O), 770 (OOP); ***Anal cacld for $C_{25}H_{22}ClN_3O_3$: C 67.04, H 4.95, N 9.38, found: C 67.08, H 4.91, N 9.45.

N*-(4-chlorophenyl)-4-(2-methoxyphenyl)-6-methyl-2-oxo-1-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (AKS-126) – *IR** *(cm^{-1}):* 3334, 3217 (-NH-), 3107 (Ar-H), 2991, 2957, 2831 (-Me), 1692 (C=O), 1674 (C=O), 1509, 1427, 1128 (C-O), 717(OOP); ***Mass** (m/e)*: 462 (Molecular ion peak), 336, 308, 294, 265, 153, 127, 118 (base peak), 91, 77; ***Anal cacld for $C_{26}H_{24}ClN_3O_3$: C 67.04, H 4.95, N 9.38, found: C 67.09, H 4.96, N 9.44.

N*-(4-chlorophenyl)-4-(3-nitrophenyl)-6-methyl-1-(3-methylphenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (AKS-127) - IR (cm^{-1}):** 3292, 3248 (-NH-), 3101 (Ar-H), 2924, 2870 (-Me), 1701 (C=O), 1658 (C=O), 1525, 1510, 1492 (C=C), 1089, 1010 (C-O), 812, 775 (OOP); ***Anal cacld for $C_{25}H_{21}ClN_4O_4$: C 62.96, H 4.44, N 11.75, found: C 62.89, H 4.49, N 11.82.

N*-(4-chlorophenyl)-4-(2-chlorophenyl)-1-(2,4-dimethylphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (AKS-128) – IR (cm^{-1}):** 3412, 3345 (-NH-), 3120 (Ar-H), 3008, 2922, 2856 (-Me), 1721 (C=O), 1658 (C=O), 1544, 1477, 1055 (C-O), 878, 657 (OOP); ***Anal cacld for $C_{26}H_{23}Cl_2N_3O_2$: C 65.01, H 4.83, N 8.75, found: C 64.97, H 4.85, N 8.81.

***N*-(4-chlorophenyl)-4-(4-chlorophenyl)-1-(2,4-dimethylphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (AKS-129) – IR (cm^{-1}):** 3440, 3207 (-NH-), 3117 (Ar-H), 2944, 2903, 2818(-Me), 1700 (C=O), 1654 (C=O), 1550, 1448, 1427,

1184 (C-O), 647 (OOP); ***Anal cacld*** for $C_{26}H_{23}Cl_2N_3O_2$: C 65.01, H 4.83, N 8.75, found: C 65.07, H 4.81, N 8.83.

N*-(4-chlorophenyl)-4-(4-nitrophenyl)-1-(2,4-dimethylphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (AKS-130) – IR (cm^{-1}):** 3314, 3185 (-NH-), 3104 (Ar-H), 2917, 2924, 2854 (-Me), 1721 (C=O), 1651 (C=O), 1547, 1440, 1418, 1117 (C-O), 841, 681 (OOP); ***Anal cacld for $C_{26}H_{23}ClN_4O_4$: C 63.61, H 4.72, N 11.41, found: C 63.65, H 4.73, N 11.45.

N*-(4-fluorophenyl)-6-methyl-2-oxo-1,4-diphenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (AKS-131) – IR (cm^{-1}):** 3425, 3177 (-NH-), 3021 (Ar-H), 2991, 2955, 2853 (-Me), 1710 (C=O), 1657 (C=O), 1541, 1452, 1407, 1163 (C-O), 942, 752 (OOP); ***Anal cacld for $C_{24}H_{20}FN_3O_2$: C 71.81, H 5.02, N 10.47, found: C 71.75, H 5.06, N 10.54.

N*-(4-fluorophenyl)-4-(2-chlorophenyl)-6-methyl-1-(3-methylphenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (AKS-132) - IR (cm^{-1}):** 3319, 3290 (-NH-), 3037 (Ar-H), 2953, 2916, 2854 (-Me), 1724 (C=O), 1654 (C=O), 1531, 1514, 1491 (C=C), 1095, 1043 (C-O), 767 (OOP); ***Anal cacld for $C_{25}H_{21}ClFN_3O_2$: C 66.74, H 4.70, N 9.34, found: C 66.79, H 4.74, N 9.39.

N*-(4-fluorophenyl)-4-(4-nitrophenyl)-6-methyl-1-(3-methylphenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (AKS-133) – IR (cm^{-1}):** 3318, 3223 (-NH-), 3018 (Ar-H), 2943, 2817 (-Me), 1685 (C=O), 1671 (C=O), 1558, 1433, 1407, 1142 (C-O), 682 (OOP); ***Anal cacld for $C_{25}H_{21}FN_4O_4$: C 65.21, H 4.60, N 12.17, found: C 65.23, H 4.57, N 12.22.

N*-(4-fluorophenyl)-4-(2-chlorophenyl)-1-(2,4-dimethylphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (AKS-134) – IR (cm^{-1}):** 3387, 3247 (-NH-), 3112 (Ar-H), 2954, 2815, 2780 (-Me), 1717 (C=O), 1652 (C=O), 1547, 1441, 1405, 1185 (C-O), 773 (OOP); ***Mass *(m/e)*: 464 (Molecular ion peak), 353 (base peak), 325, 310, 295, 280, 220, 138, 110, 77; ***Anal cacld*** for $C_{26}H_{23}ClFN_3O_2$: C 67.31, H 5.00, N 9.06, found: C 67.28, H 5.04, N 9.14.

***N*-(4-fluorophenyl)-4-(4-nitrophenyl)-1-(2,4-dimethylphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (AKS-135) – IR (cm^{-1}):** 3419, 3219 (-NH-),

3077 (Ar-H), 2916, 2851, 2768 (-Me), 1711 (C=O), 1657 (C=O), 1547, 1417, 1107 (C-O), 748 (OOP); ***Anal cacld*** for $C_{26}H_{23}FN_4O_4$: C 65.81, H 4.89, N 11.81, found: C 65.85, H 4.94, N 11.88.

N*-(3-chloro-4-fluorophenyl)-4-(2-chlorophenyl)-6-methyl-1-(3-methylphenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (AKS-136) – IR (cm^{-1}):** 3337, 3217 (-NH-), 3124(Ar-H), 2951, 2884 (-Me), 1696 (C=O), 1654 (C=O), 1556, 1430, 1411, 1073 (C-O), 814 (OOP); ***Anal cacld for $C_{25}H_{20}Cl_2FN_3O_2$: C 61.99, H 4.16, N 8.68, found: C 62.02, H 4.17, N 8.72.

N*-(3-chloro-4-fluorophenyl)-4-(4-nitrophenyl)-6-methyl-1-(3-methylphenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (AKS-137) – IR (cm^{-1}):** 3423, 3258 (-NH-), 3076 (Ar-H), 2951, 2827, 2780 (-Me), 1714 (C=O), 1665 (C=O), 1552, 1481, 1116 (C-O), 756 (OOP); ***Anal cacld for $C_{25}H_{20}ClFN_4O_4$: C 60.67, H 4.07, N 11.32, found: C 60.68, H 4.05, N 11.37.

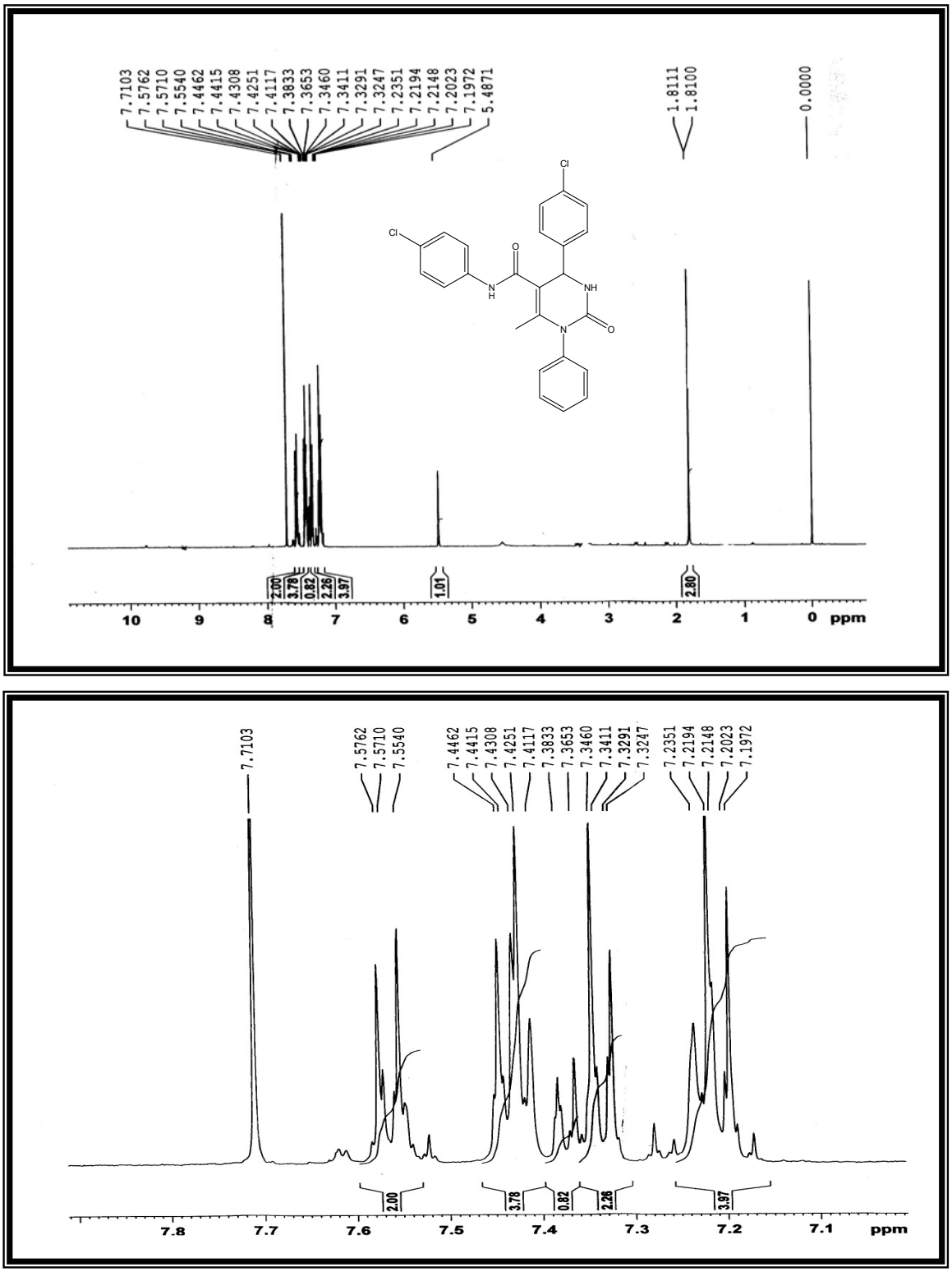
N*-(3-chloro-4-fluorophenyl)-4-(4-nitrophenyl)-1-(2,4-dimethylphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (AKS-138) – IR (cm^{-1}):** 3413, 3285 (-NH-), 3009 (Ar-H), 2912, 2857 (-Me), 1697 (C=O), 1651 (C=O), 1542, 1433, 1410, 1076 (C-O), 648 (OOP); ***Anal cacld for $C_{26}H_{22}ClFN_4O_4$: C 61.36, H 4.36, N 11.01, found: C 61.38, H 4.35, N 11.05.

N*-(3-chloro-4-fluorophenyl)-4-(4-chlorophenyl)-6-methyl-2-oxo-1-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (AKS-139) - IR (cm^{-1}):** 3377, 3286 (-NH-), 3055 (Ar-H), 2949, 2916 (-Me), 1716 (C=O), 1666 (C=O), 1525, 1467 (C=C), 1122, 1093 (C-O), 887, 776 (OOP) ***^{1}H NMR *(δ ppm):* 1.71 (3H, s), 5.38 (1H, s), 6.87 (2H, d, J=8.42), 7.19 (4H, m), 7.28 (4H, m), 7.35 (1H, t, J=2.04), 7.60 (1H, d, J=1.57), 8.05 (1H, d, J=10.16); ***Anal cacld*** for $C_{26}H_{22}Cl_2FN_3O_2$: C 62.66, H 4.45, N 8.43, found: C 62.65, H 4.47, N 8.48.

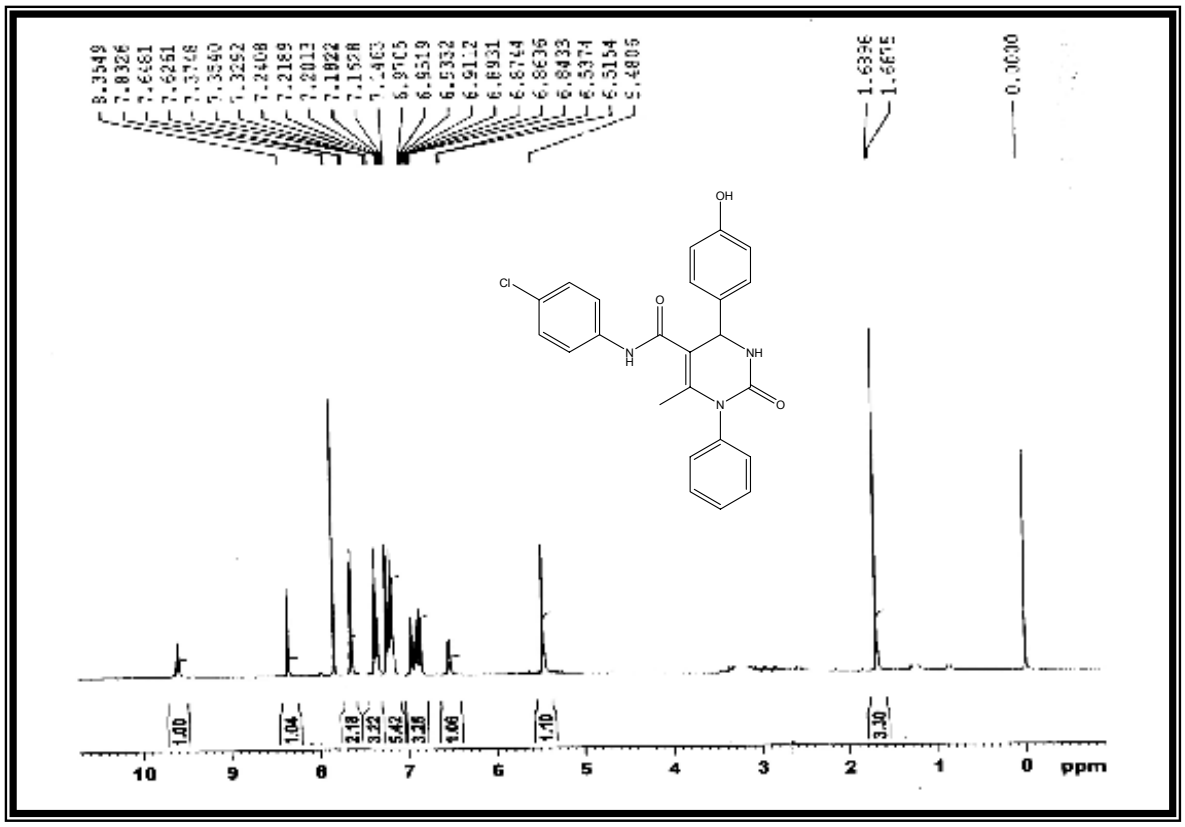
N*-(4-chlorophenyl)-4-(3-nitrophenyl)-6-methyl-2-oxo-1-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (AKS-140) – IR (cm^{-1}):** 3336, 3251 (-NH-), 3094 (Ar-H), 2991, 2843 (-Me), 1708 (C=O), 1662 (C=O), 1547, 1420, 1404, 1163 (C-O), 722 (OOP); ***Mass *(m/e)*: 447 (Molecular ion peak), 321 (base peak), 293, 278, 250,

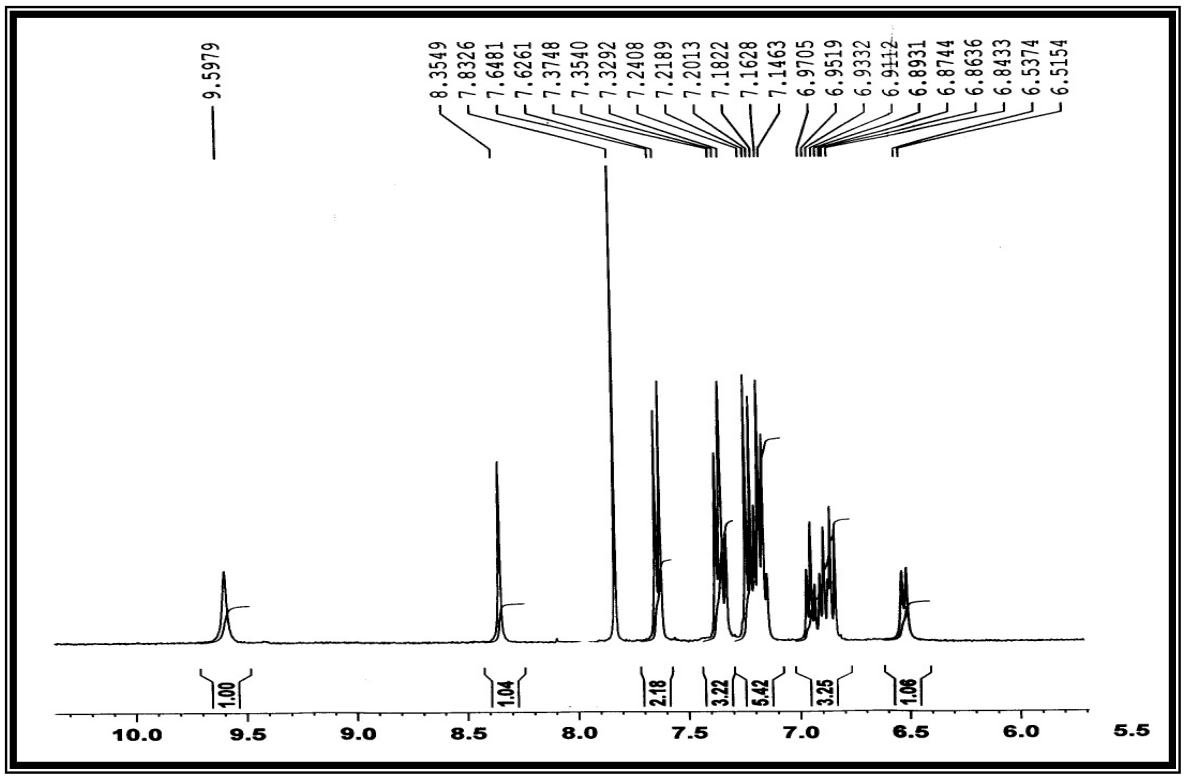
187, 153, 91, 77; ***Anal cacld*** for $C_{26}H_{23}ClN_4O_4$: C 63.61, H 4.72, N 11.41, found: C 63.64, H 4.73, N 11.46.

1.9.5.1 1H NMR spectrum of AKS-123

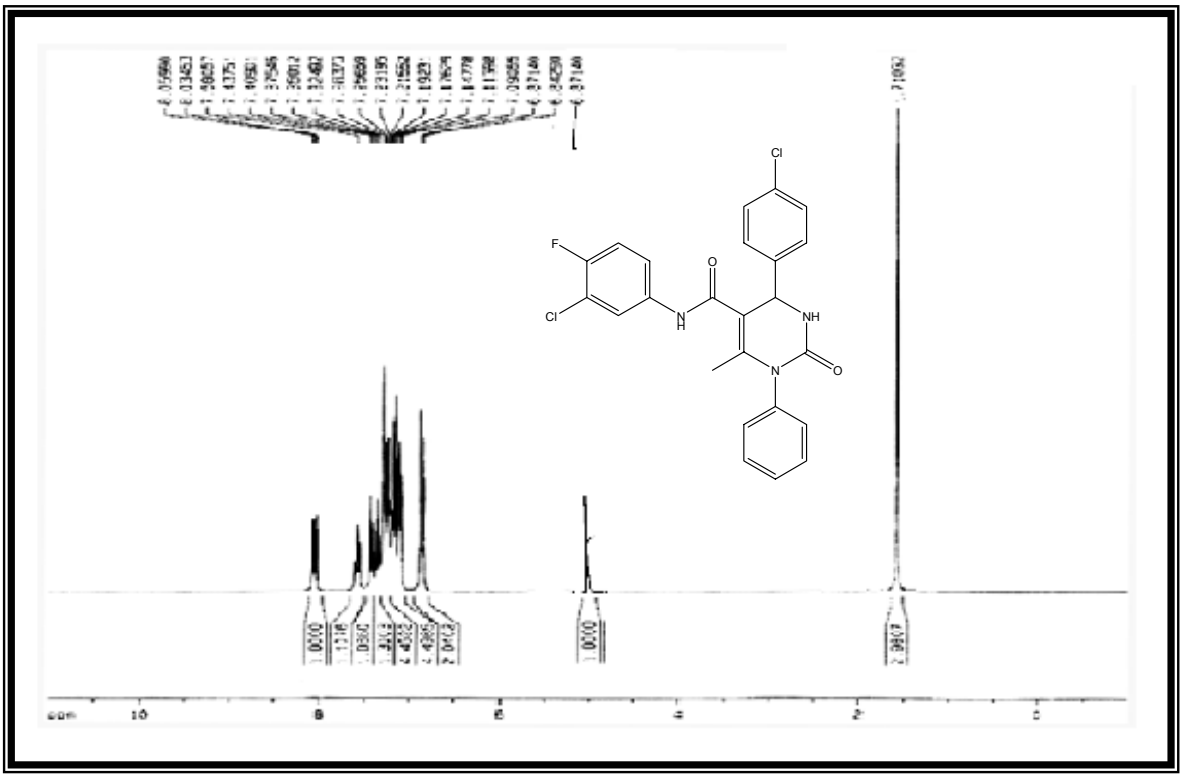


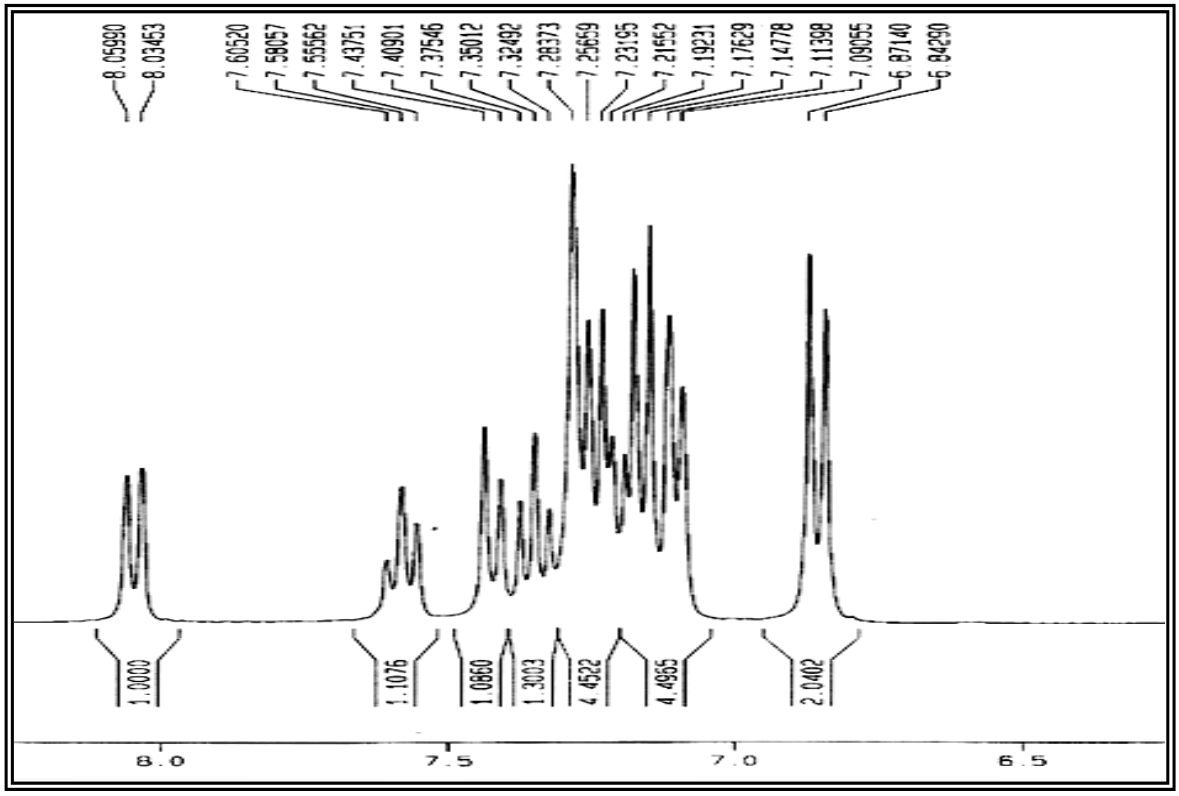
1.9.5.2 1H NMR spectrum of AKS-122



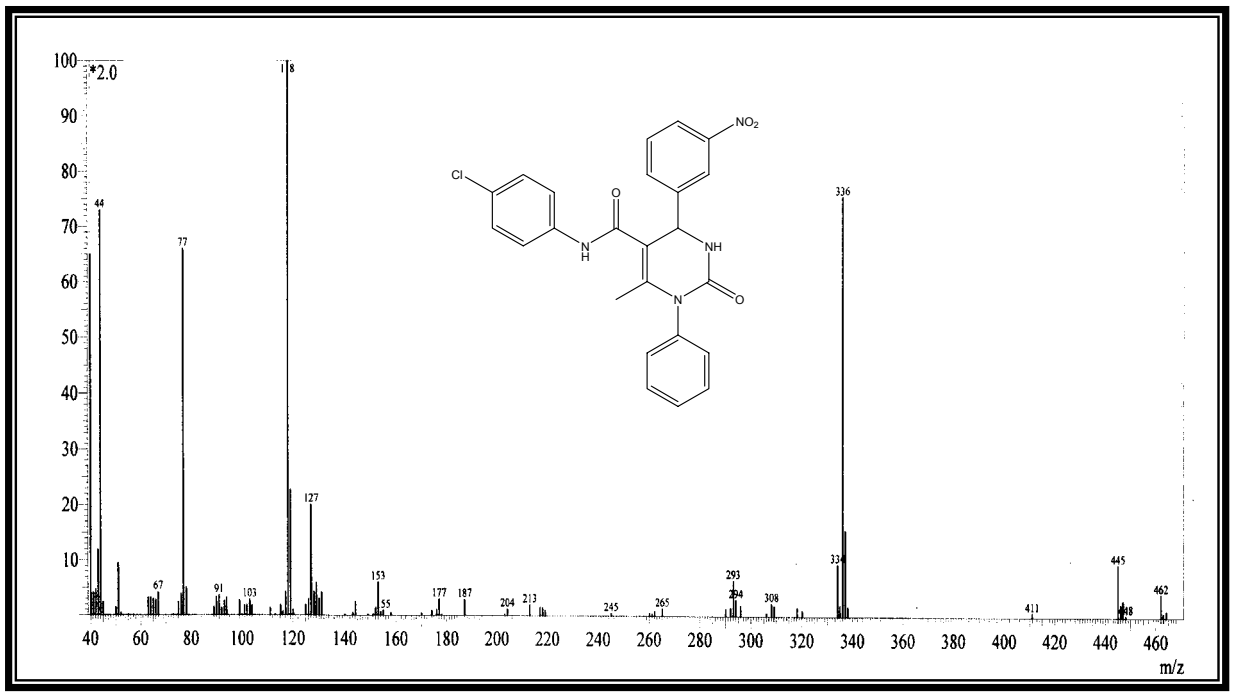


1.9.5.3 1H NMR spectrum of AKS-139

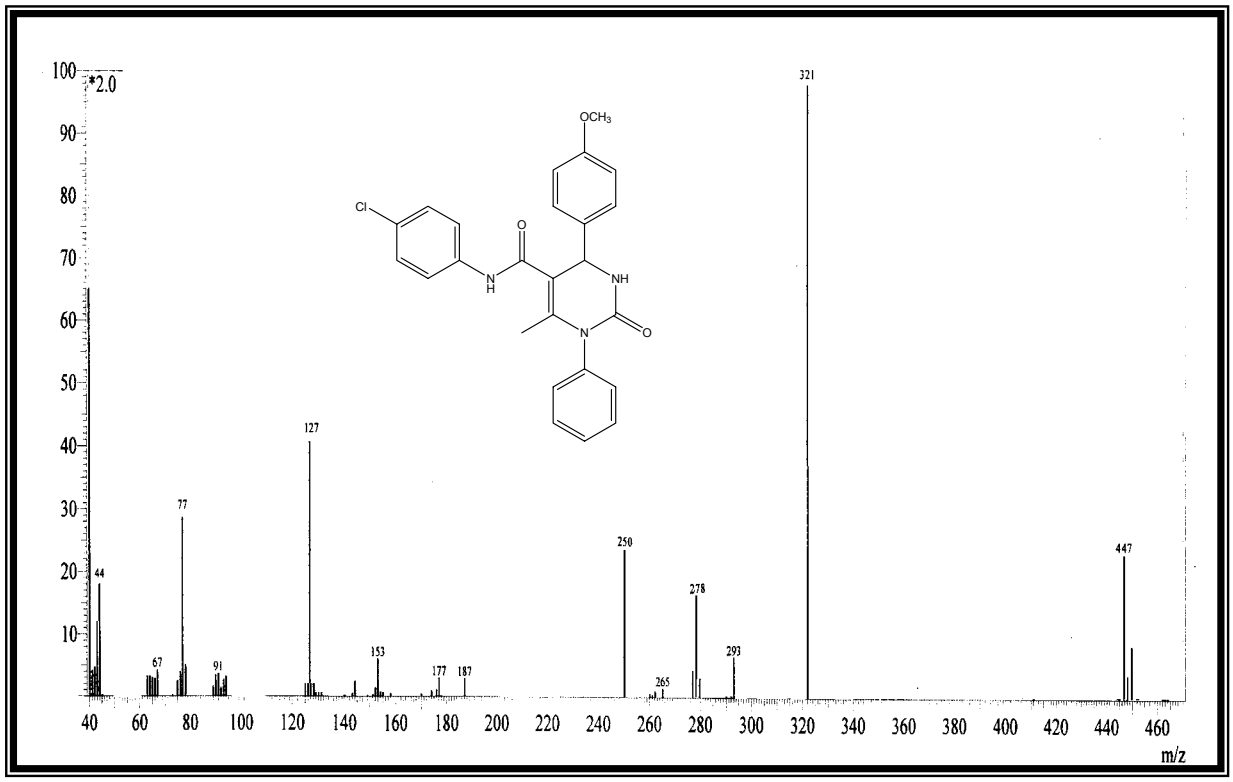




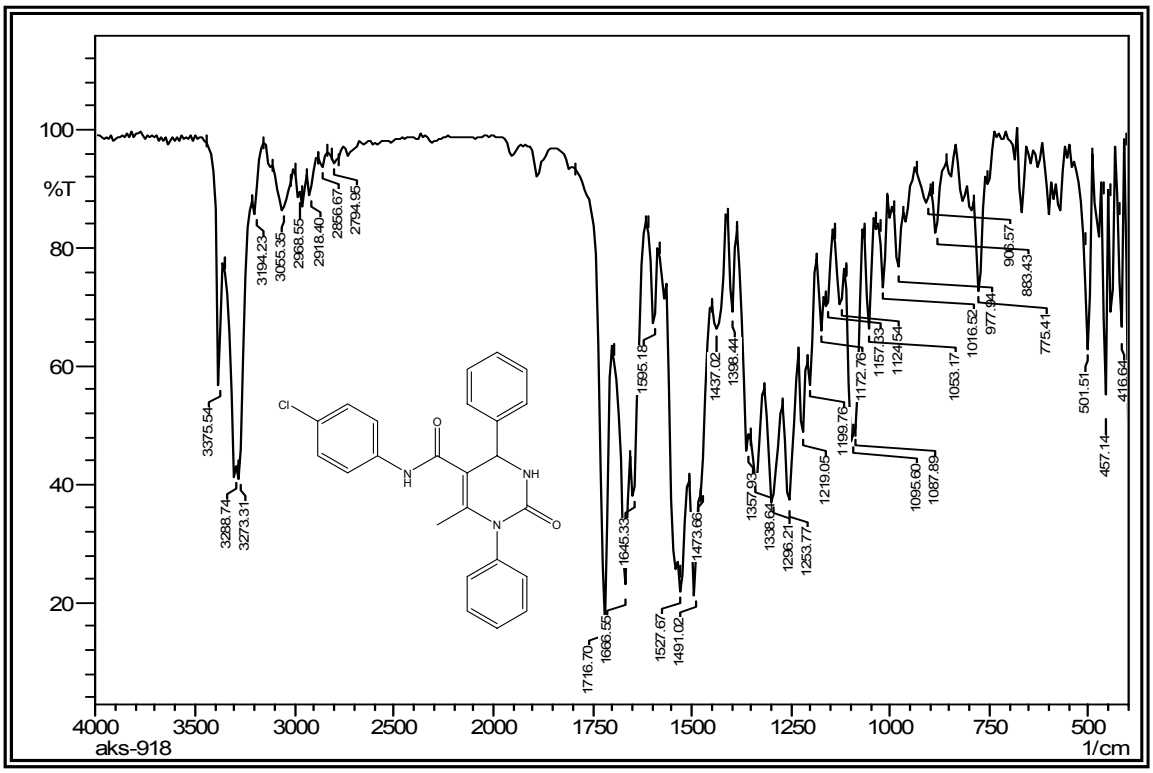
1.9.5.4 Mass Spectrum of AKS - 126



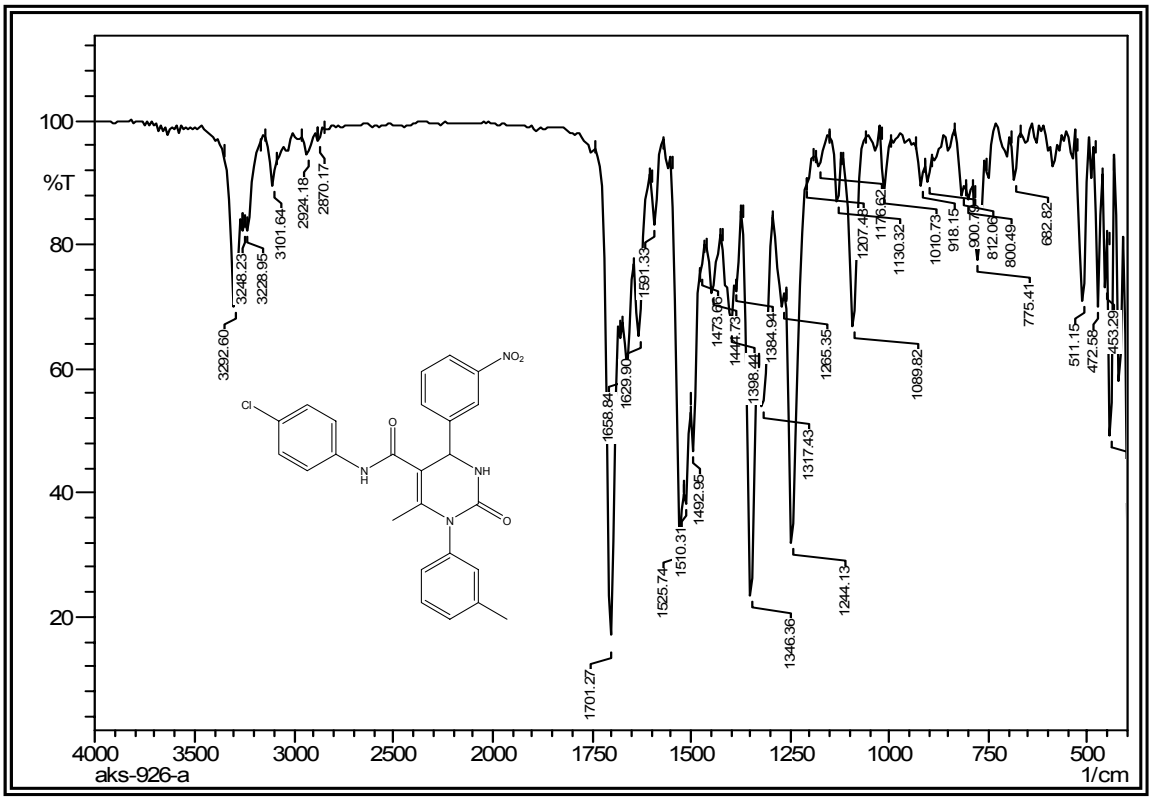
1.9.5.5 Mass spectrum of AKS - 140



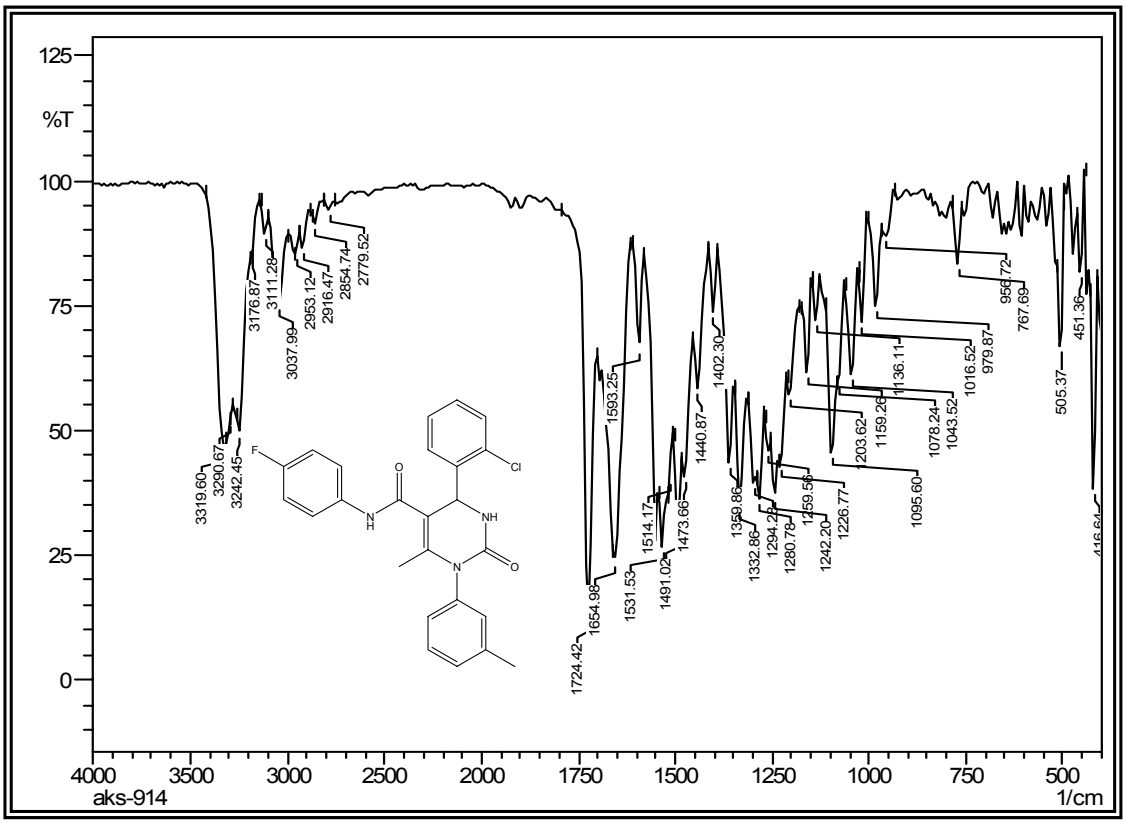
1.9.5.6 IR spectrum of AKS-121



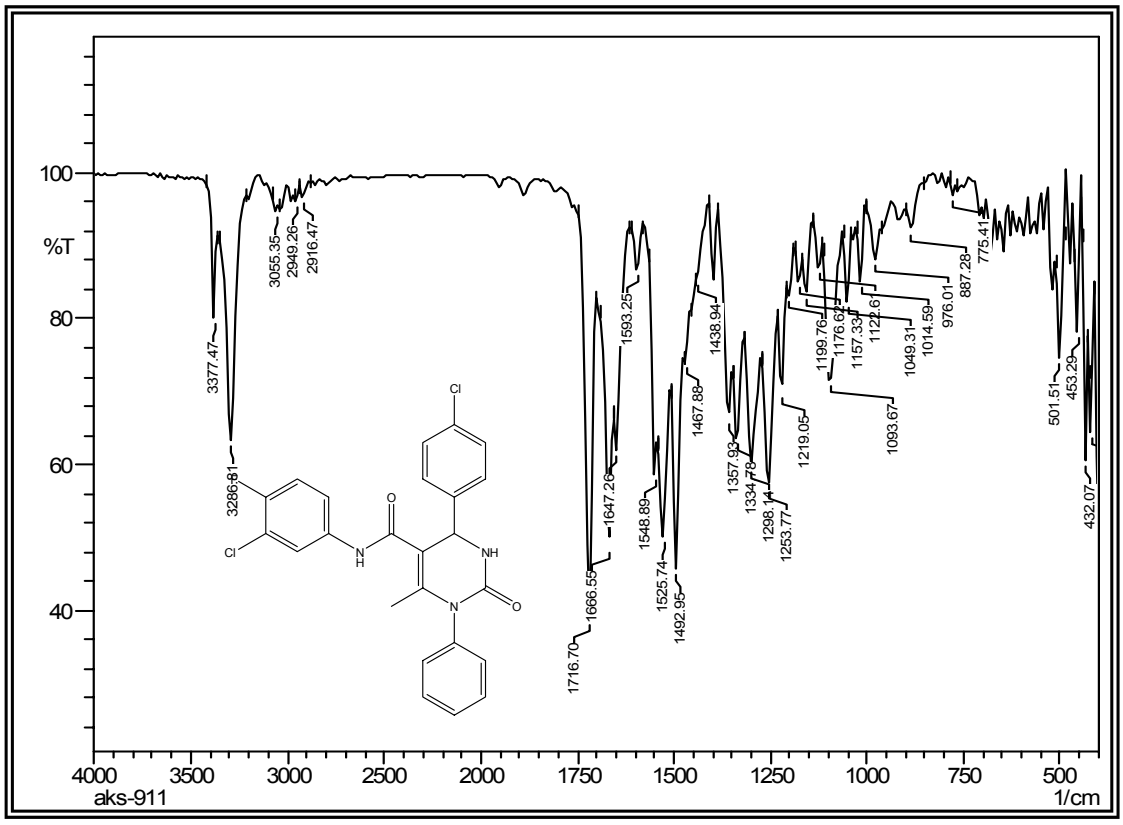
1.9.5.7 IR spectrum of AKS-127



1.9.5.8 IR spectrum of AKS-132



1.9.5.9 IR spectrum of AKS-139



1.10 References

1. Kappe, C. O.; Acc. Chem. Res. **2000**, 33, 879-888.
2. Biginelli, P.; Gazz. Chim. Ital. **1893**, 23, 360-413.
3. Folkers, K.; Johnson, T. B.; J. Am. Chem. Soc. **1933**, 55, 3781-3791.
4. Kappe, C. O.; Tetrahedron **1993**, 49, 6937-6963.
5. Sweet, F. S.; Fissekis, J. D.; J. Am. Chem. Soc. **1973**, 95, 8741-8749.
6. Kappe, C. O.; J. Org. Chem. **1997**, 62, 7201-7204.
7. Hu, E. H.; Sidler, D. R.; Dolling, U.-H.; J. Org. Chem. **1998**, 63, 3454-3457.
8. Kappe, C. O.; Falsone, F.; Fabian, W. M. F.; Belaj, F.; Heterocycles **1999**, 51, 77-84.
9. Saloutin, V. I.; Burgat, Ya. V.; Kuzueva, O. G.; Kappe, C. O.; Chupakhin, O. N.; J. Fluorine Chem. **2000**, 103, 17-23.
10. Hu, E. H.; Sidler, D. R. and Dolling, U.; *J. Org. Chem.* **1998,** *63,* 3454-3457.
11. Ranu, B. C.; Hajra, A. and Jana, U.; *J. Org. Chem.* **2000,** *65,* 6270-6272.
12. Bose, D. S.; Liyakat, F. and Mereyala, H. B.; *J. Org. Chem.* **2003**, *68*, 587-590.
13. Yijun, H; Fengyue, Y.; and Chengjian, Z.; *J. Am. Chem. Soc*. **2005**, 127, 16386-16387.
14. Xiao-Hua Chen,Xiao-Ying Xu, Hua Liu, Lin-Feng Cun, and Liu-Zhu Gong; *J. Am. Chem. Soc*. **2006**, 128, 14802-14803.
15. Zhidong, J. and Ruifang, C.; *Syn Comm* **2005,** 35: 503–509,
16. Majid, M. H.; Khadijeh, B. and Fatemeh, F. B.; *Catalysis Communications*. **2006**, 7(6), 373-376.
17. Zhou, H.; He, M.; Liu, C.; Luo, G.; *Letters in Organic Chemistry* **2006**, 3(3), 225-227.
18. Jun, L., Yinjuan B.; *Synthesis* **2002**: 0466-0470.
19. Jin, Tong-Shou; Xiao,Jin-Chong; Chen,Yan-Xue; Li,Tong-Shuang; *Journal of Chemical Research* **2004**, 3, 190-191.
20. De, S. K.; Gibbs, R. A.; *Synthesis* **2005**: 1748-1750.
21. Xiaoyan Han, Fan Xu, Yiqin Luo, Qi Shen ; Eur. *J. Org. Chem*. **2005**, 8, 1500-1503.
22. Badaoui, H.; Bazi, F.; Sokori, S.; Boulaajaj, S.; Lazrek, H. B.; Sebti, S; *Letters in Organic Chemistry*. **2005**, 2(6), 561-565.
23. De, S. K. and Gibbs, R. A.; *Syn Comm*, **2005** 35: 2645–2651.
24. Shailaja, M.; Manjula, A.; Rao, B. V. and Parvathi, N.; *Syn Comm*, **2004** 34, 1559–1564.
25. Hojatollah Salehi and Qing-Xiang Guo; *Syn Comm*. **2004** 34, 171–179.
26. Khodaei, M. M.; Khosropour, A. R. and Beygzadeh, M.; *Syn Comm*. **2004** 34, 1551–1557.
27. Sharma, S. D.; Gogoi, P. and Konwar, D.; *Green Chem*. **2007**, 9, 153–157.
28. Yadav, J. S.; Reddy, B. V. S.; Reddy, K. B.; Raj, K. S. and Prasad, A. R.; *J. Chem. Soc., Perkin Trans. 1*, **2001**, 1939–1941.
29. Weiwei Li and Yulin Lam; *J. Comb. Chem* **2005**, 7, 721-725.
30. Gross, G. A.; Wurziger, H. and Schober, A.; *J. Comb. Chem* **2006**, 8, 153-155.
31. Lusch, M. J. and Tallarico, J. A.; *Org. Lett.,* **2004,** 6, 19.

32. Stadler, A.; Yousefi, B. H.; Dallinger, D.; Walla, P.; Van der Eycken, E.; Kaval, N. and Kappe, C. O.*; Organic Process Research & Development* **2003**, 7, 707-716
33. Yadav J. S.; Reddy B.V.S.; Reddy E.J.; Ramalingam T.; *Journal of Chemical Research*. **2000**, 7, 354-355.
34. Kapoor, K. K.; Ganai, B. A.; Kumar, S. and Andotra, C. S.; *Can. J. Chem./Rev. can. chim*. **2006** 84(3): 433-437.
35. Gohain, M.; Prajapati, D.; Sandhu; J. S.; *Synlett* **2004**: 0235-0238.
36. Gupta, R.; Gupta, A. K.; Paul S. and Kachroo, P. L.; *Ind. J. Chem.*, **1995**, 34B, 151.
37. Dandia, A.; Saha, M.and Taneja, H.; *J. Fluorine Chem.*, **1998**, 90, 17.
38. Stadler , A. and Kappe, C. O.; *J. Chem. Soc., Perkin Trans. 2* **2000**, 1363–1368
39. Zong-Ting Wang , Shu-Chao Wang , Li-Wen Xu ; *Helvetica Chemica Acta*. **2005**, 88, 986-989.
40. Janis, R. A.; Silver, P. J.; Triggle, D. J. *Adv. Drug Res*. **1987**, *16*, 309.
41. Bossert, F.; Vater, W. *Med. Res. Rev*. **1989**, *9*, 291.
42. Cho, H.; Ueda, M.; Shima, K.; Mizuno, A.; Hayashimatsu, M.; Ohnaka, Y.; Takeuchi, Y.; Hamaguchi, M.; Aisaka, K.; Hidaka, T.; Kawai, M.; Takeda, M.; Ishihara, T.; Funahashi, K.; Satah, F.; Morita, M.; Noguchi, T. *J. Med. Chem*. **1989**, *32*, 2399.
43. Atwal, K.; Rovnyak, G. C.; Schwartz, J.; Moreland, S.; Hedberg, A.; Gougoutas, J. Z.; Malley, M. F.; Floyd, D. M. *J. Med. Chem*. **1990**, *33*, 1510.
44. Atwal, K. S.; Rovnyak, G. C.; Kimball, S. D.; Floyd, D. M.; Moreland, S.; Swanson, B. N.; Gougoutas, J. Z.; Schwartz, J.; Smillie, K. M.; Malley, M. F. *J. Med. Chem*. **1990**, *33*, 2629.
45. Atwal, K. S.; Swanson, B. N.; Unger, S. E.; Floyd, D. M.; Moreland, S.; Hedberg, A.; O´Reilly, B. C. *J. Med. Chem.* **1991**, *34*, 806.
46. Rovnyak, G. C.; Atwal, K. S.; Hedberg, A.; Kimball, S. D.; Moreland, S.; Gougoutas, J. Z.; O´Reilly, B. C.; Schwartz, J.; Malley, M. F. *J. Med. Chem*. **1992**, *35*, 3254.
47. Grover, G. J.; Dzwonczyk, S.; McMullen, D. M.; Normadinam, C. S.; Sleph, P. G.; Moreland, S. J. *J. Cardiovasc. Pharmacol*. **1995**, *26*, 289.
48. Rovnyak, G. C.; Kimball, S. D.; Beyer, B.; Cucinotta, G.; DiMarco, J. D.; Gougoutas, J.; Hedberg, A.; Malley, M.; McCarthy, J. P.; Zhang, R.; Moreland, S. *J. Med. Chem*. **1995**, *38*, 119
49. Triggle, D. J.; Padmanabhan, S. *Chemtracts: Org. Chem.* **1995**, *8*, 191.
50. Birgit Jauk, Tetiana Pernat and C. Oliver Kappe; Molecules **2000**, 5, 227-239.
51. McConnell, J. D.; Bruskewitz, R.; Walsh, P.; Andriole, G.; Lieber, M.; Holtgrewe, H. L.; Albertsen, P.; Roehrborn, C. G.; Nickel, J. C.; Wang, D. Z.; Taylor, A. M.; Waldstreicher, J.; *N. Engl. J. Med.* **1998**, *338*, 557-563.
52. Roehrborn, C. G.; Oesterling, J. E.; Auerbach, S.; Kaplan, S. A.; Lloyd, L. K.; Milam, D. F.; Padley, R. J.; *Urology* **1996**, *47*, 159-168.
53. Heible, J. P.; Bylund, D. B.; Clarke, D. E.; Eikenburg, D. C.; Langer, S. Z.; Lefkowitz, R. J.; Minneman, K. P.; Ruffolo, R. R.; *Pharmacol.Rev*. **1995**, *47*, 267-270.
54. Forray, C.; Bard, J. A.; Wetzel, J. M.; Chiu, G.; Shapiro, E.; Tang, R.; Lepor, H.; Hartig, P. R.; Weinshank, R. L.; Branchek, T. A.; Gluchowski, C.; *Mol.Pharmacol*. **1994**, *45*, 703-708.

55. Barrow, J. C.; Nantermet, P. G.; Selnick, H. G.; Glass, K. L.; Rittle, K. E.; Gilbert, K. F.; Steele, T. G.; Homnick, C. F.; Freidinger, R. M.; Ransom, R. W.; Kling, P.; Reiss, D.; Broten, T. P.; Schorn, T. W.; Chang, R. S. L.; O'Malley, S. S.; Olah, T. V.; Ellis, J. D.; Barrish, A.; Kassahun, K.; Leppert, P.; Nagarathnam, D. and Forray, C.; *J. Med. Chem.* **2000,** *43,* 2703-2718

56. Nagarathnam, D.; Miao, S. W.; Lagu,, B.; Chiu, G.; Fang, J.; Murali Dhar, T. G.; Zhang, J.; Tyagarajan, S.; Marzabadi, M. R.; Zhang, F.; Wong, W. C.; Sun, W.; Tian, D.; Wetzel, J. M.; Forray, C.; Chang, R. S. L.; Broten, T. P.; Ransom, R. W.; Schorn, T. W.; Chen, T. B.; O'Malley, S.; Kling, P.; Schneck, K.; Bendesky, R.; Harrell, C. M.; Vyas, K. P. and Gluchowski, C.; *J. Med. Chem.* **1999,** *42,* 4764-4777.

57. Cho, H.; Ueda, M.; Shima, K.; Mizuno, A.; Hayashimatsu, M.; Ohnaka, Y.; Takeuchi, Y.; Hamaguchi, M.; Aisaka, K.; Hidaka, T.; Kawai, M.; Takeda, M.; Ishihara, T.; Funahashi, T.; Satoh, F.; Morita, M. and Noguchi, T.; *J. Med. Chem.* **1989**, 32, 2399-2406.

58. Rovnyak, G. C.; Atwal, K. S.; Hedberg: A.; Kimball, S. D.; Moreland, S.; Gougoutas, J. Z.; O'Reilly, B. C.; Schwartz, J.; and Malleys; M. F.; *J. Med. Chem*. **1992**,35,3254-3263.

59. Atwal, K. S.; Swanson, B. N.; Unger, S. E.; Floyd, D. M.; Moreland, S.; Hedberg, A. and O'Reilly, B. C.; *J. Med. Chem*. **1991**,34,806-811.

60. Atwal, K. S.; Rovnyak, G. C.; Kimball, S. D.; Floyd, D. M.; Moreland, S.; Swanson, B. N.; Gougoutas, J. Z.; Schwartz, J.; Smillie, K. M. and Malley, M. F.; *J. Med. Chem.* **1990**,33, 2629-2635.

Chapter 2

Synthesis & characterization of 3,5-dihydro-2H-thiazolo[3,2-a]pyrimidines & 2,3,4,6-tetrahydropyrimido [2,1-b][1,3]thiazines

Chapter 2

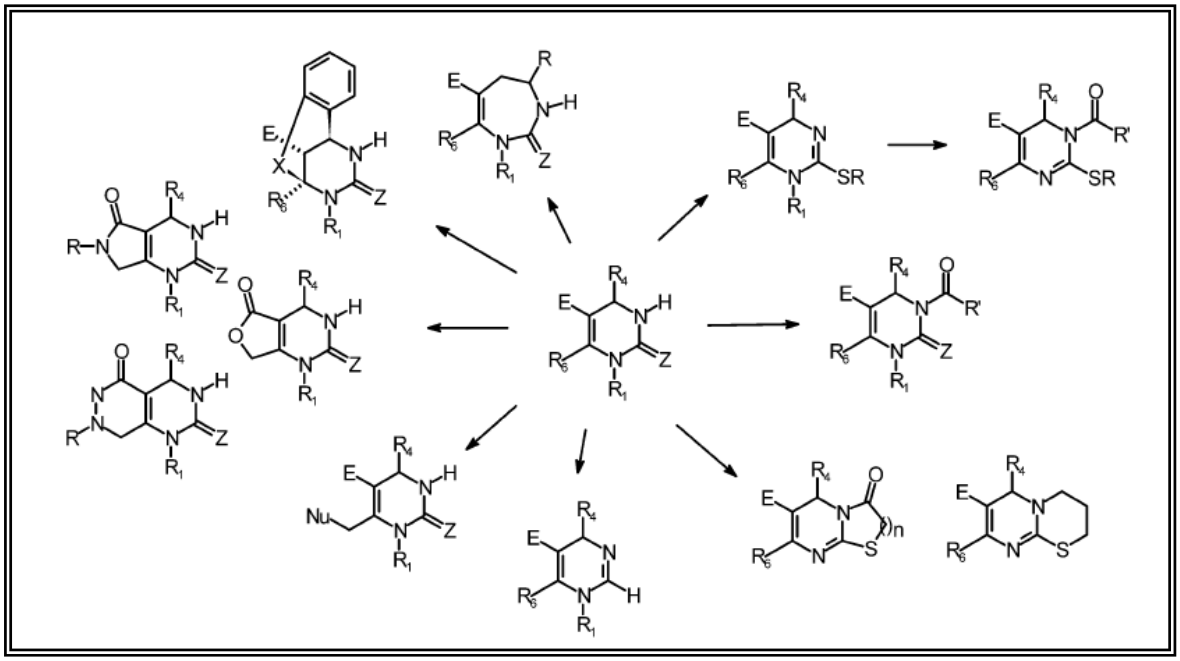
Synthesis & characterization of 3,5-dihydro-2H-thiazolo[3,2-a]pyrimidines & 2,3,4,6-tetrahydropyrimido [2,1-b] [1,3] thiazines

2.1 Scaffold decoration of DHPM ring, methods of synthesis and their biological profile

Importance of DHPM moiety and various modifications applied to Biginelli reaction for better yield, shorter reaction time and synthesis of various analogs is surveyed in detail in Chapter 1. The biological profile of this heterocyclic moiety is briefly reported in the same Chapter.

Biginelli reaction is not only important to synthesize analogs of DHPM ring using different building block as potent bioactive heterocycles, but diversed fused and non-fused heterocycles can be synthesized by careful applications.

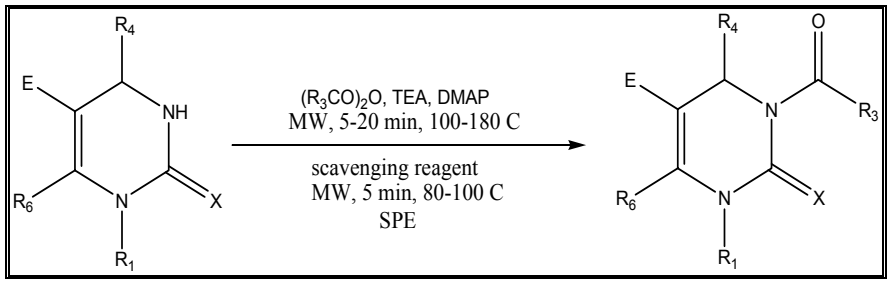
2.1.1 Various scaffolds derived from DHPMs



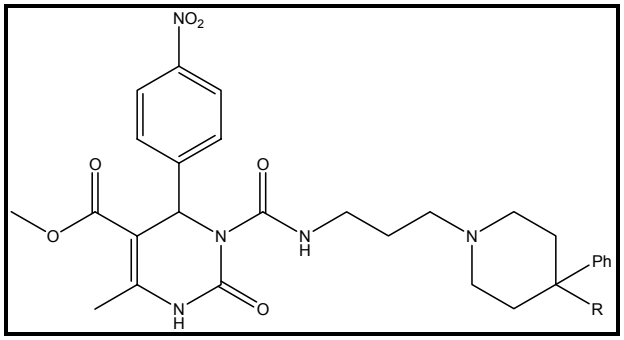
As displayed in above figure, it can be understood that a number of new moieties can be generated from DHPM ring.

2.1.2 N_3-Acylated and C_5-substituted DHPMs and their biological importance

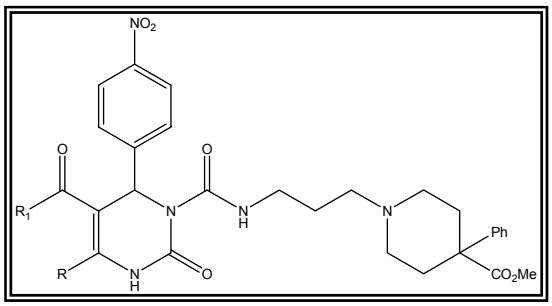
Kappe et al[2] reported that N_3-acylated DHPMs can be rapidly synthesized in a highthroughput fashion by combining microwave-assisted acylations with microwave-assisted scavenging techniques. Scavenging experiments can be carried out employing either supported nucleophilic amine sequestration reagents or water. N-acylated DHPMs are pharmacologically important N-acylation of DHPM can be performed as shown below.

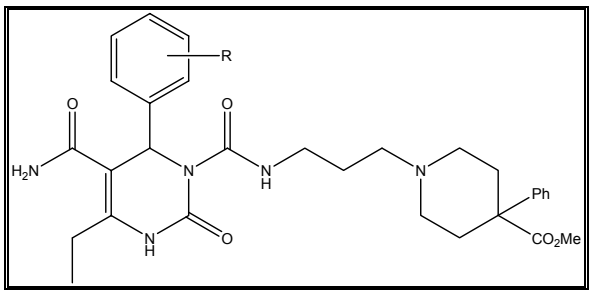


N_3-substituted DHPMs have been identified to possess potent pharmacological profiles, e.g. following compound exhibited high binding affinity and subtype selectivity for the cloned human α_{1a} receptor[3].

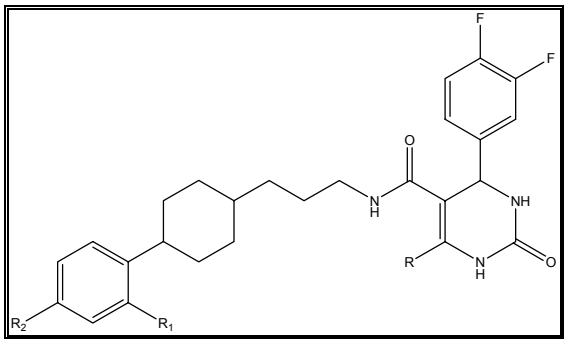


Systematic modifications of above compounds led to identification of highly potent and subtype-selective compounds with high binding affinity (*K*i = 0.2 nM) for α_{1a} receptor and greater than 1500-fold selectivity over α_{1b} and α_{1d} adrenoceptors. The compounds were found to be functional antagonists in human, rat, and dog prostate tissues.



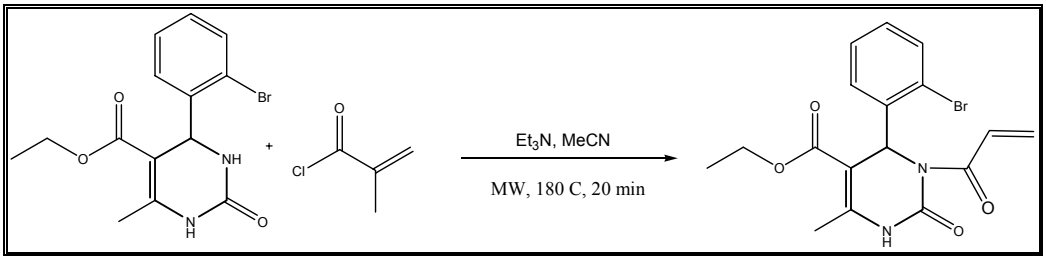


Modifications to the C_5 position also play important role in potency of DHPM ring. 4-aryldihydropyrimidinones attached to an aminopropyl-4-arylpiperidine via a C-$_5$ amide as selective α_{1a} receptor subtype antagonists. In receptor binding assays, these types of compounds generally display *K*i values for the α_{1a} receptor subtype <1 nM while being greater than 100-fold selective versus the α_{1b} and α_{1d} receptor subtypes. Many of these compounds were also evaluated *in vivo* and found to be more potent than terazosin in both a rat model of prostate tone and a dog model of intra-urethral pressure without significantly affecting blood pressure[4].

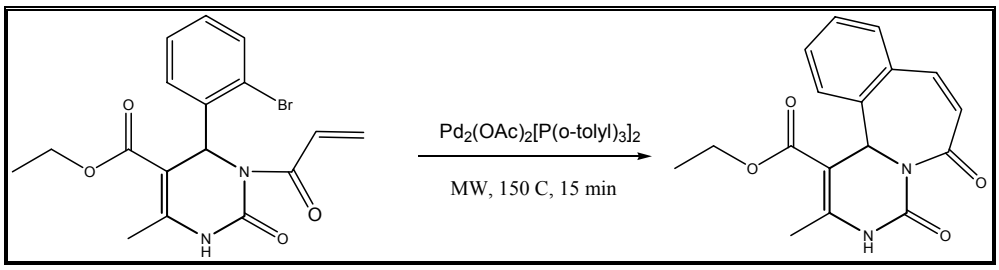


2.1.3 Intramolecular Heck cyclization of DHPMs

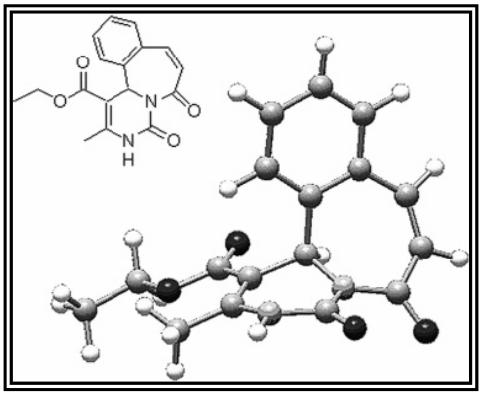
The intramolecular Heck reaction can be observed in DHPM skeleton. The starting material for the intramolecular Heck reaction was prepared by selective N_3-acylation of 4-(*o*-bromophenyl)-dihydropyrimidone with acryloyl chloride[5]



Applying intramolecular Heck reaction, tricyclic ring system can be obtained as shown below.[6]



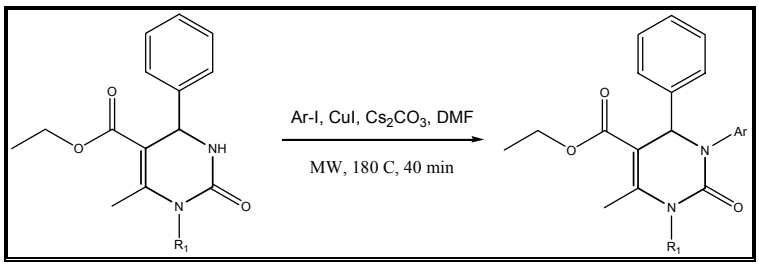
The computational experiments reveal that the formation of a tricyclic ring system did not flatten out the overall geometry. On the contrary, the aryl ring was still locked in a pseudoaxial position, resembling other nonfused 4-aryl-dihydropyrimidines.[7,8] In fact, here, the intramolecular Heck strategy allows locking of the aryl ring in the proposed bioactive, that is, the pseudoaxial orientation.[9]



2.1.4 N_3-Arylation of DHPMs

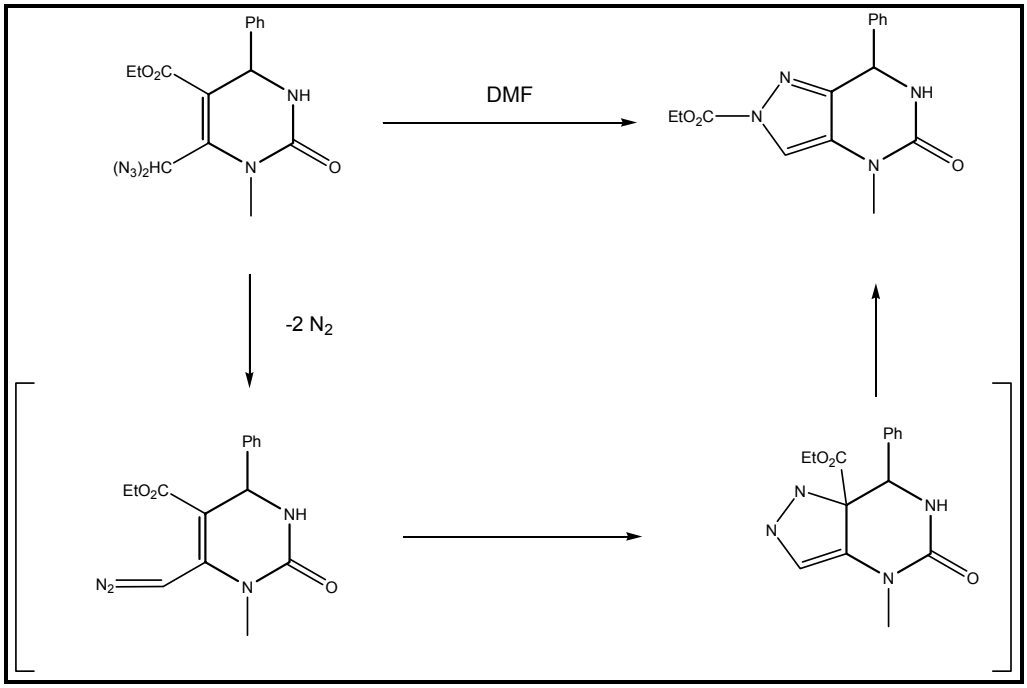
N_3-arylated DHPM analogues cannot be obtained by classical Biginelli condensation strategies involving *N*-arylureas. Here, the corresponding N_1-substituted derivates will be formed exclusively[10,11].

Wannberg et al[11] reported protocol using concentrated mixture of 20 mol % of cuprous iodide as catalyst, 1.5 equiv of cesium carbonate as base, and 5 mol equiv of dimethylformamide as solvent. The reactions were conducted at 180 °C for 40 min with a set of eight differently substituted aryl iodides.

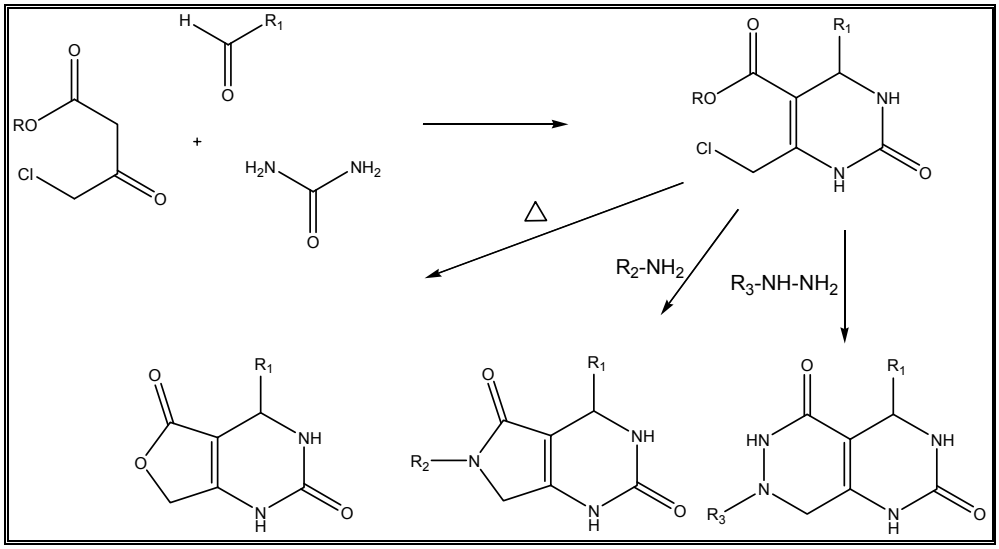


2.1.5 Fused bicyclic systems derived from DHPMs

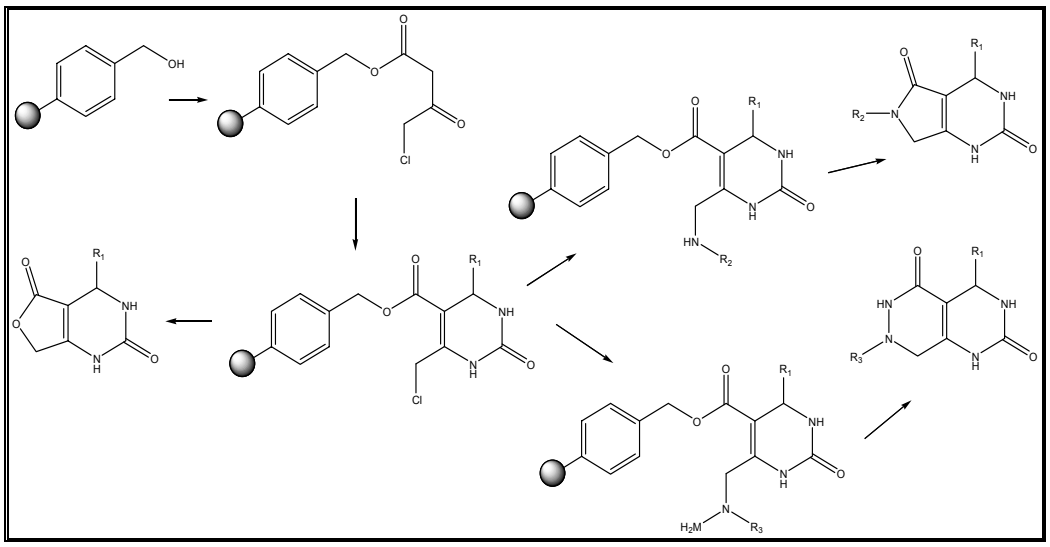
Many bicyclic fused systems can be synthesized from DHPM scaffold. Pyrazolo[4,3-d]pyrimidine derivatives synthesized by reacting sodium azide with N-Methyl, 6-Bromomethyl DHPM. The possible mechanism of this transformation is shown below and involves decomposition of the diazide to vinyl diazo derivative, which undergoes spontaneous 1,5-electrocyclization to 3H-pyrazole. Subsequent migration of the ester substituent from the tetrahedral carbon to N_2 (thermal van Alphen-Hüttel rearrangement) yields pyrazolo[4,3-d]pyrimidine. The structure confirming the position of the ester group at N_2 was established by an X-ray analysis[55].



Use of the 4-chloroacetoacetate building block in a Biginelli-type condensation is very useful to get variety of bicyclic systems. The resulting functionalized DHPM appeared to be an ideal common chemical template for the generation of a variety of interesting bicyclic scaffolds such as furo[3,4-*d*]- pyrimidines, pyrrolo[3,4-*d*]pyrimidines, and pyrimido-[4,5-*d*]pyridazines.



Solid-phase and solution-phase protocols for the synthesis of furo[3,4-*d*]pyrimidines, pyrrolo[3,4-*d*]-pyrimidines, and pyrimido[4,5-*d*]pyridazines are reported. The multistep solid-phase sequence involves the initial high-speed, microwave-promoted acetoacetylation of hydroxymethylpolystyrene resin with methyl 4-chloroacetoacetate. The immobilized 4-chloroacetoacetate precursor was subsequently subjected to three component Biginelli-type condensations employing urea and a variety of aromatic aldehydes. The resulting 6-chloromethyl-functionalized resin-bound dihydropyrimidones served as common chemical platforms for the generation of the desired heterobicyclic scaffolds using three different *traceless cyclative cleavage strategies*. The corresponding furo[3,4-*d*]pyrimidines were obtained by microwave flash heating in a rapid, thermally triggered, cyclative release. Treatment of the chloromethyl dihydropyrimidone intermediates with a variety of primary amines followed by high-temperature microwave heating furnished the anticipated pyrrolo[3,4-*d*]pyrimidine scaffolds via nucleophilic cyclative cleavage. In a similar way, reaction with monosubstituted hydrazines resulted in the formation of pyrimido[4,5-*d*]pyridazines. All compounds were obtained in moderate to good overall yields and purities[56].



2.1.6 Chemistry and biological importance of thaizolo[3,2-a]pyrimidine and pyrimido[2,1-b][1,3]thiazines scaffolds

Preparation of thiazolo[3,2-a]pyrimidine derivatives is very well reported in literature. Two approaches is generally employed for synthesis.

1. Azole approach

Literature survey on synthetic methodology for thiazolo[3,2-a]pyrimidine derivatives can be summarized in Chart 1 & 2 where various methods are illustrated for synthesis of this class of compounds.

Chart 1: Thiazolo[3,2-a]pyrimidine **2** was prepared in 30% yield by the reaction of 2-aminothiazole **1** with ethyl cyanoacetate in a sodium ethoxide/ethanol mixture or using polyphosphoric acid or acetic acid. However, oxothiazolopyrimidine **3** was obtained upon treatment with phosphorous pentoxide and methanesulfonic acid.

The reaction of **1** with ethyl acetoactate at 140-150°C resulted in the formation of compound that was then converted to the Z-isomer upon heating at 250°C and cyclized to give **4**. 2-Aminothiazole **5** cyclized with acetylacetone at 100°C, in the presence of methanesulfonic acid-phosphorus pentoxide or formic acid-phosphorus pentoxide, followed by treatment with 70% perchloric acid, to give the thiazolopyrimidin-4-ium salt **5**. The ester **6** was obtained from 2-aminothiazole **1** with an excess of methyl methanetricarboxylate in 61 % yield. Cyclocondensation of **1** with diethyl

ethoxymethylene malonate in acetic acid followed by hydrolysis of the ester gave **7.** Similarly, 2-aminothiazole **1** reacted with benzylidine in ethanol to give **8**. Stanovink *et al* reported the synthesis of a series of thiazolopyrimidine derivatives upon reacting 2-aminothiazole with a variety of different reagents. Thus, dimethylaminobut- 2-enoate (or pentenoate), reacted with **1** to give thiazolopyrimidines**.**[12-25]

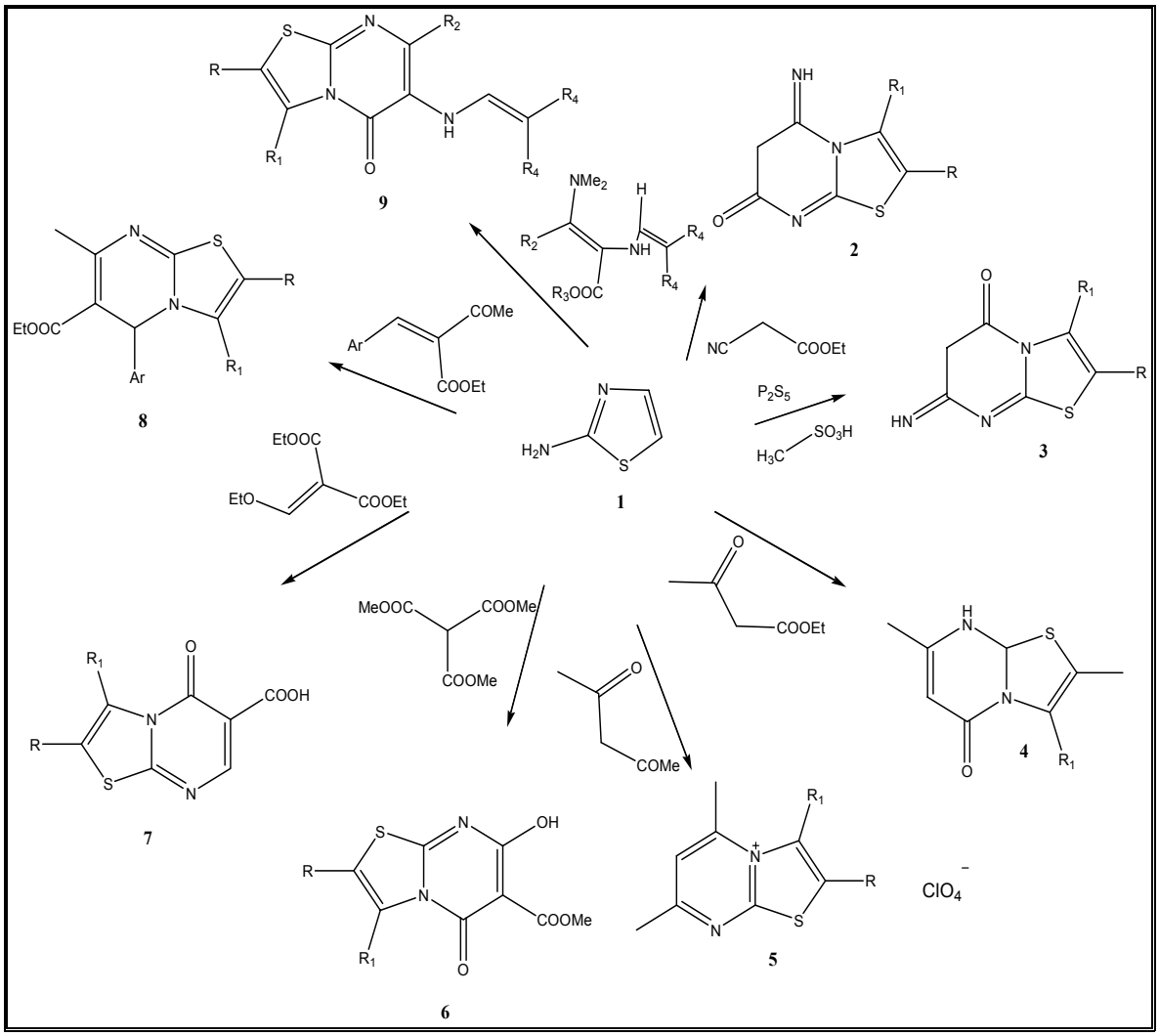


Chart 1

Chart 2: The reaction of 2-aminothiazole **1** with 2-hydropolyfluoroalk-2-enoate in basic medium gave two isomers, 7-oxo **2** and its isomeric 5-0x0 **3.** The structure of both **2** and **3** was established through ^{1}H NMR, ^{19}F NMR and mass spectra[26]**.** 2-Aminothiazole derivatives **,** (R' = **H,** C02Et; R2 = Ph, aryl, Me), reacted with the acetylenic derivative and ester derivative in ethanol and polyphosphoric acid, respectively, to give the isomeric oxothiazolopyrimidine derivatives **4** and **5,** in 5-32% and 8-97 % yield, respectively[27]. Condensation of 2-aminothiazole **1** in absolute ethanol with the sodium salt of ethyl

oximinocyanoacetate gave after acidification (pH 6) with diluted hydrochloric acid, the nitroso derivative **6** in 92% yield[28]. Treatment of the 2-aminothiazaole derivatives **5** with the hydrazone derivatives **gave** the oxothiazolo [3,2-a] pyrimidine derivatives **7.**[29]

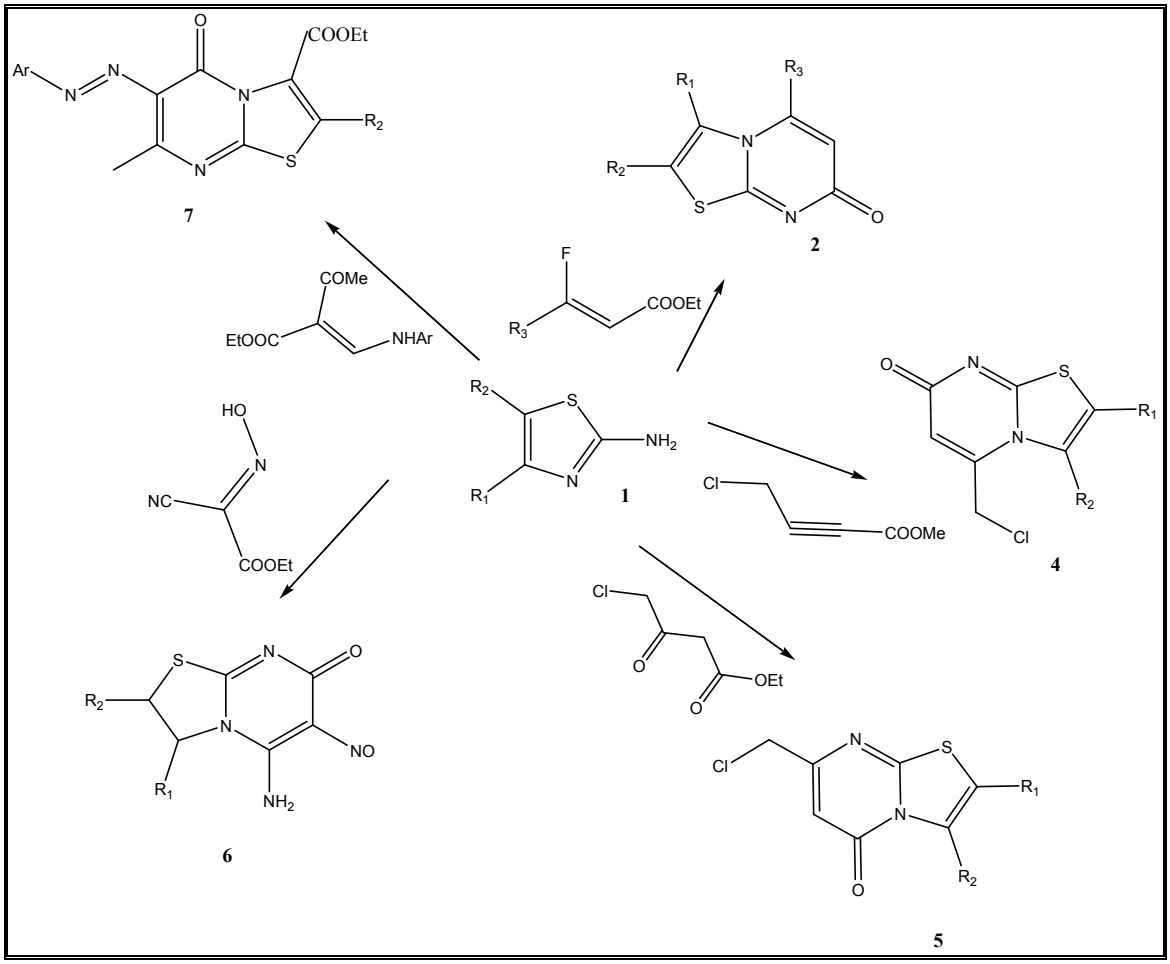
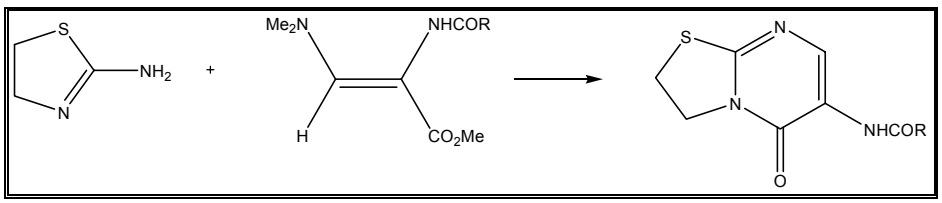
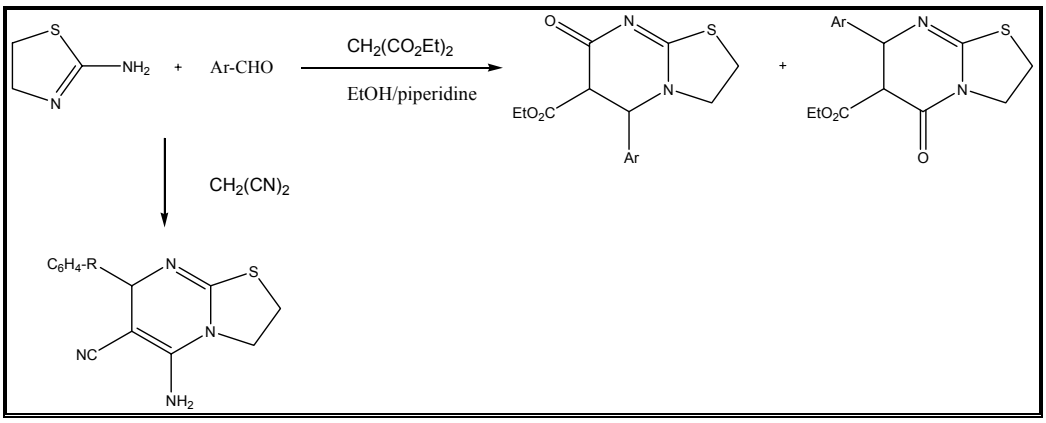


Chart 2

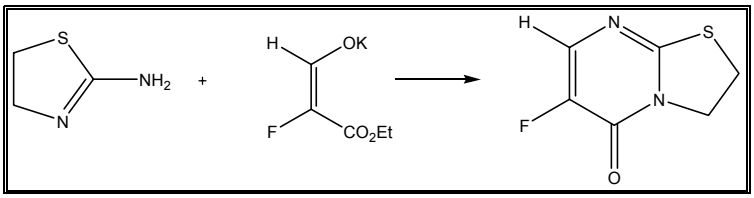
2-Amino-2-thiazoline reacted with 2-acylamino-3-dimethylamino-propenoates in acetic acid to yield 6-acylamino-5-oxo-2,3-dihydro-5-thiazolo[3,2-a]pyrimidines in 73 and 12% yields, respectively[30].



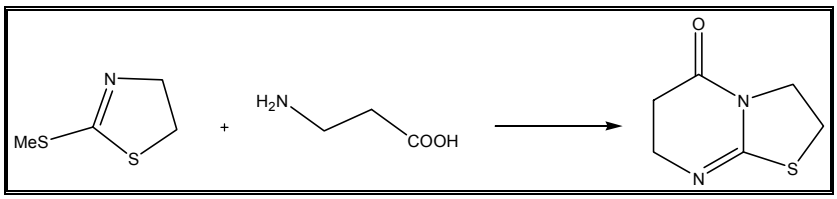
Moreover, 2-amino-2-thiazoline reacted with an aromatic aldehyde and diethyl malonate, to give a mixture of thiazolidino[3,2-a]pyrimidines. Furthermore, malononitrile reacted to give following product.[31-32]



2-Amino-thiazoline reacted with potassium 2-ethoxycarbonyl-2-fluorovinyl alcoholate in a sodium methoxide/methanol mixture to give 6-fluoro-2,3-dihydro-5-oxothiazolo[3,2-a]pyrimidine[33].

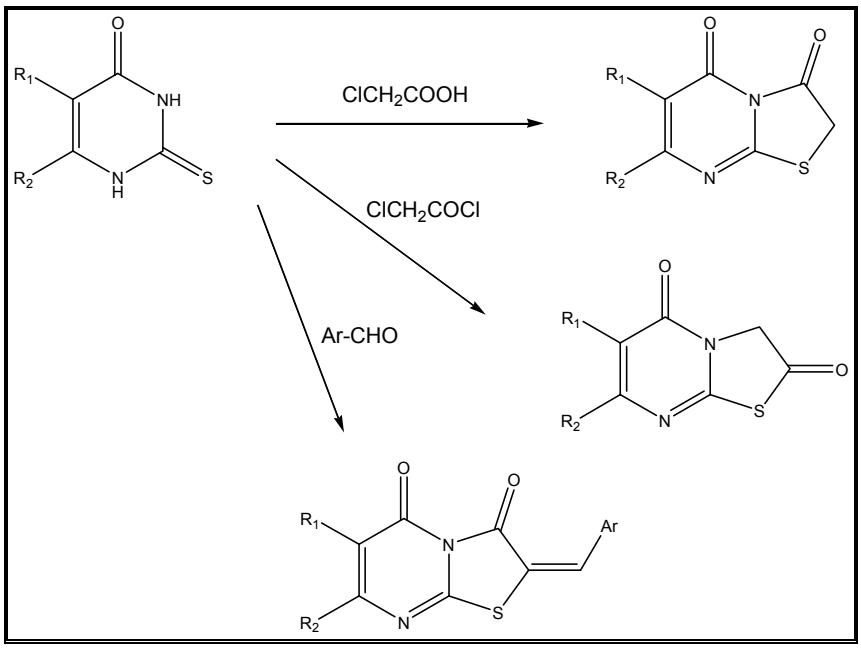


2-(Methylthio)-24hiazoline reacted with /3-alanine to give a 5-oxothiazolo[3,2-a]-pyrimidine derivative in 23% yield[34].

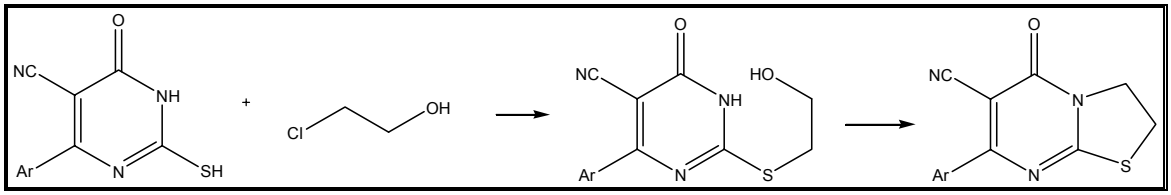


2. Azine approach

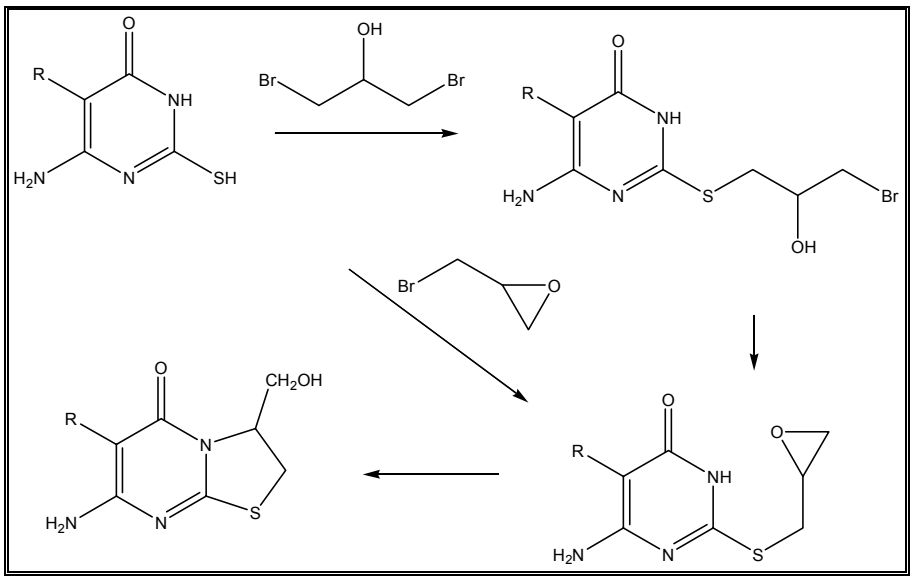
Pyrmidinethione derivatives were alkylated with monochloroacetic acid or chloroacetyl chloride and then cyclized to give thiazolopyrimidine derivatives.[35-48] Thus, pyrimidinethione reacted in dimethylformamide[35] or in an acetic anhydride/pyridine mixture[37] to give thiazolo-pyrimidines**.** Alkylation in the presence of an aromatic aldehyde gave the ylidene. Similarly, pyrimidinethione derivatives reacted with monochloroacetic acid in acetic acid/acetic anhydride/sodium acetate mixture or with chloroacetyl chloride in dry dioxane to give the corresponding thiazolopyrimidines[39,40].



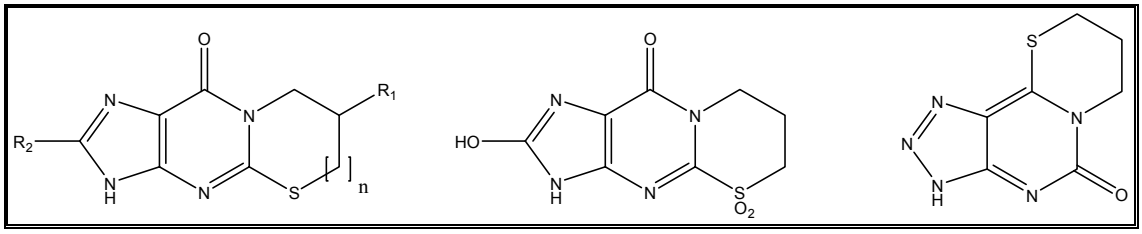
Treatment of mercaptopyrimidine derivative with 2-chloroethanol in dimethylformamide gave the asymmetrical thioether which underwent cyclization on refluxing with a mixture of acetic anhydride-pyridine, to give the oxothiazolopyrimidine[49].



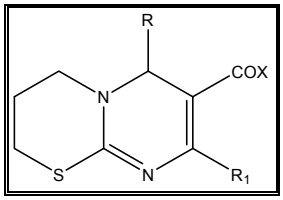
1,3-Dibromopropan-2-ol reacted with mercaptopyrimidine derivative to give product through the non isolated intermediates**.** The same reaction product was obtained by reacting with I-bromomethyloxirane.[50]



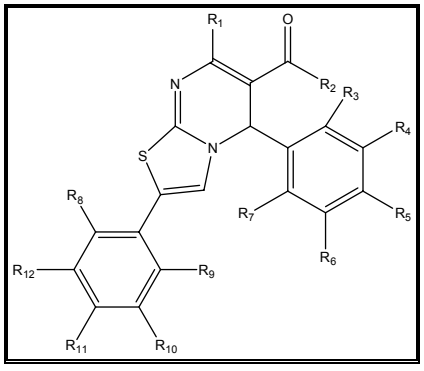
Several derivatives of 4,5-disubstituted imidazole, 2,4,5-trisubstituted pyrimidine, 2-substituted purine, thiazolo[3,2-*a*]purine, [1,3]thiazino[3,2-*a*]purine, thiazolo[2,3-*i*]purine, [1,3]thiazino-[2,3-*i*]purine, and 6-substituted pyrazolo[3,4-*d*]pyrimidine were synthesized and tested as inhibitors of the xanthine oxidase enzyme[51].



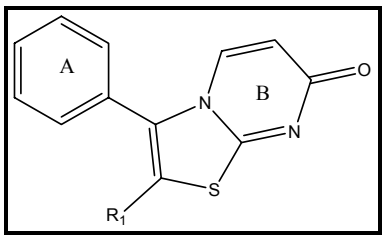
Dihydropyrimidines are now known for calcium channel blockers property. According to the literature, analogous derivatives are anti-inflammatory. Bo´szing and co-workers[52] reported the synthesis of the pyrimidothiazines and assay these compounds for the same profile. Acute anti-inflammatory activity was tested by inhibition of the carrageenan-induced paw edema in rats.



Adam et al[53] filed US patent for phenyl substituted thiazolo pyrimidine derivatives synthesized from DHPM. These compounds and their slats are novel and are distinguished by valuable therapeutic properties. Specifically, it has been found that the compounds of general formula given below are metabotropic glutamate receptor antagonists. These compounds are capable of high affinity binding to group II mGluα receptors.



Compounds displayed by general formulae given below exhibit excellent adenosine α_3 receptor antagonism where A is an optionally substituted benzene ring. B may be substituted and R_1 is optionally substituted cyclic group[54].


A
B
N
N
O
S
R1

2.2 Current work

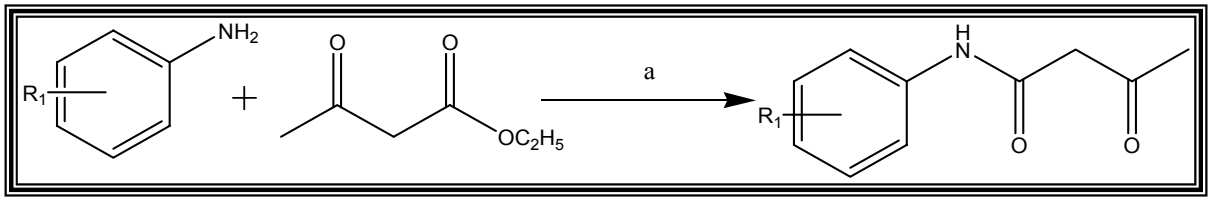
Importance of dihydropyrimidine ring to develop variety of bicyclic systems is briefly surveyed in Section 2.1. N_3-substitution in dihydropyrimidine ring is reported to enhance activity profile. Similarly, substitutions at C_5 position also plays key role in activity profile. Earlier in our lab, phenyl carbomoyl side chain is introduced at C_5 position of dihydropyrimidine ring, but this substitution does not enhance activity profile of dihydropyrimidine ring. Moderate result obtained for this kind of derivatives. To get better activity profile, N-phenyl derivatives with phenyl carbamoyl moiety at C_5 position are synthesized and characterized in Chapter 1.

Thiazolo pyrimidine and pyrimido thiazine are very important bicyclic system in medicinal chemistry. Various synthetic routes have been reported in literature to synthesize these bicyclic systems. Utility of dihydropyrimidine ring to synthesize such bicyclic system can be used to obtain derivatives with phenyl carbamoyl as side chain on pyrimidine ring of bicyclic system.

Dihydropyrimidine ring, substituted with phenyl carbamoyl side chain at C_5 position, was synthesized by reacting acetoacetanilide, thiourea and aldehyde. This dihydropyrimidine ring was reacted with dihalo alkane to get fused bicyclic systems. In synthesis of thiazolo pyrimidine system, 1,2-dibromo ethane was reacted with 2-thiodihydropyrimidine derivatives. Pyrimido-thiazine systems can be synthesized using 1,3-dibromo propane in place of 1,2-dibromo ethane with shorter reaction time and better yields as compared with synthesis of thiazolo pyrimidine systems. Reaction schemes for synthesis of these bicyclic systems are given in Section 2.3. Physical data of synthesized compounds are given in Section 2.5 and spectral data are discussed in Section 2.6.

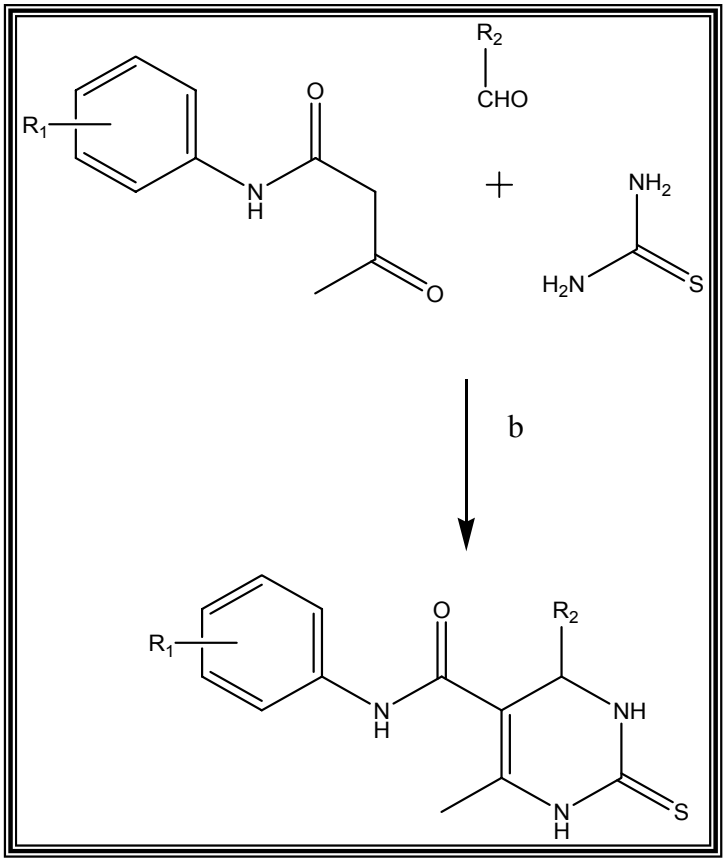
2.3 Reaction Schemes

2.3.1 Scheme 1



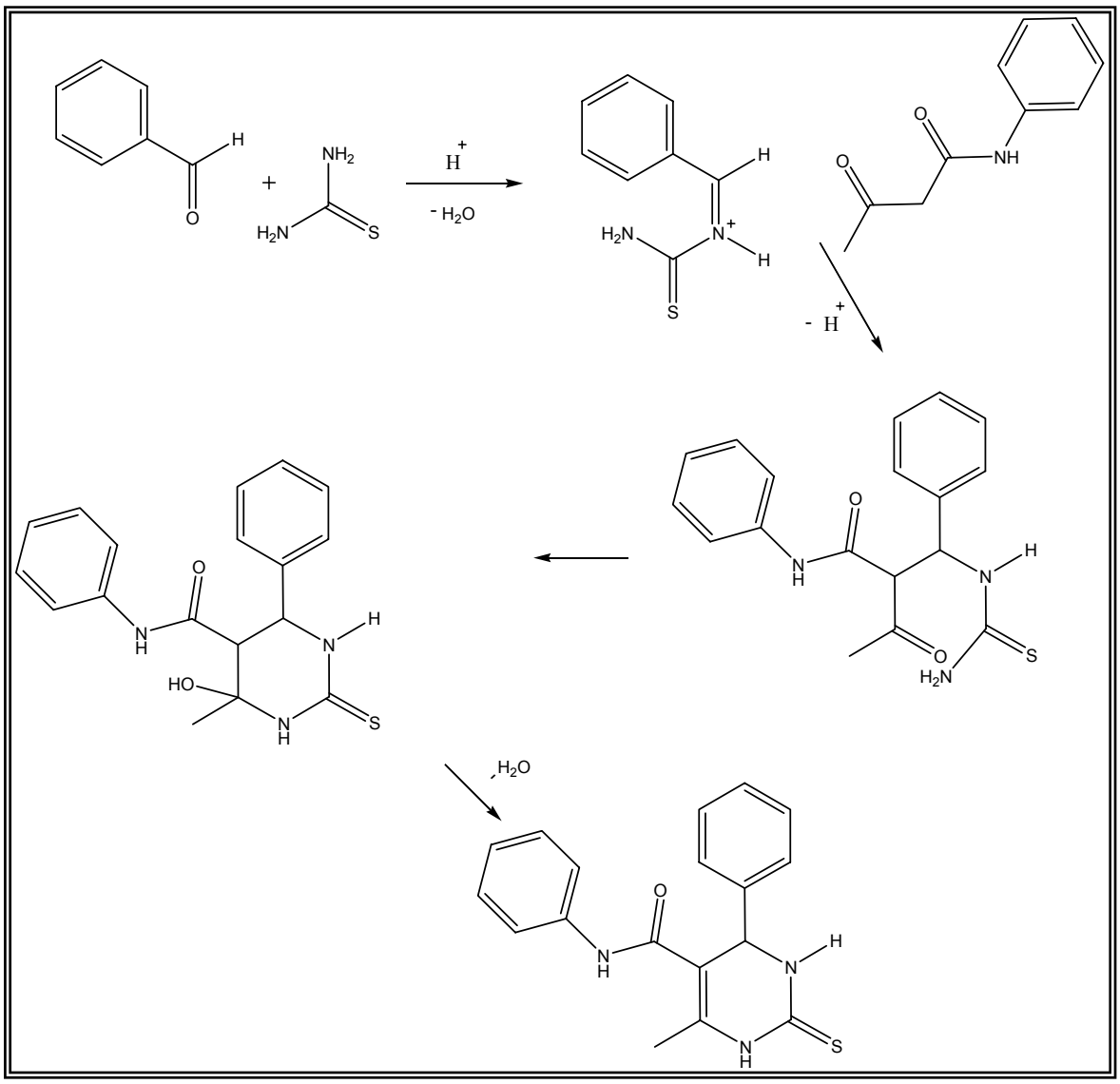
Scheme 1. Reagents and conditions: a = KOH/NaOH, toluene, 115° C.

2.3.2 Scheme 2

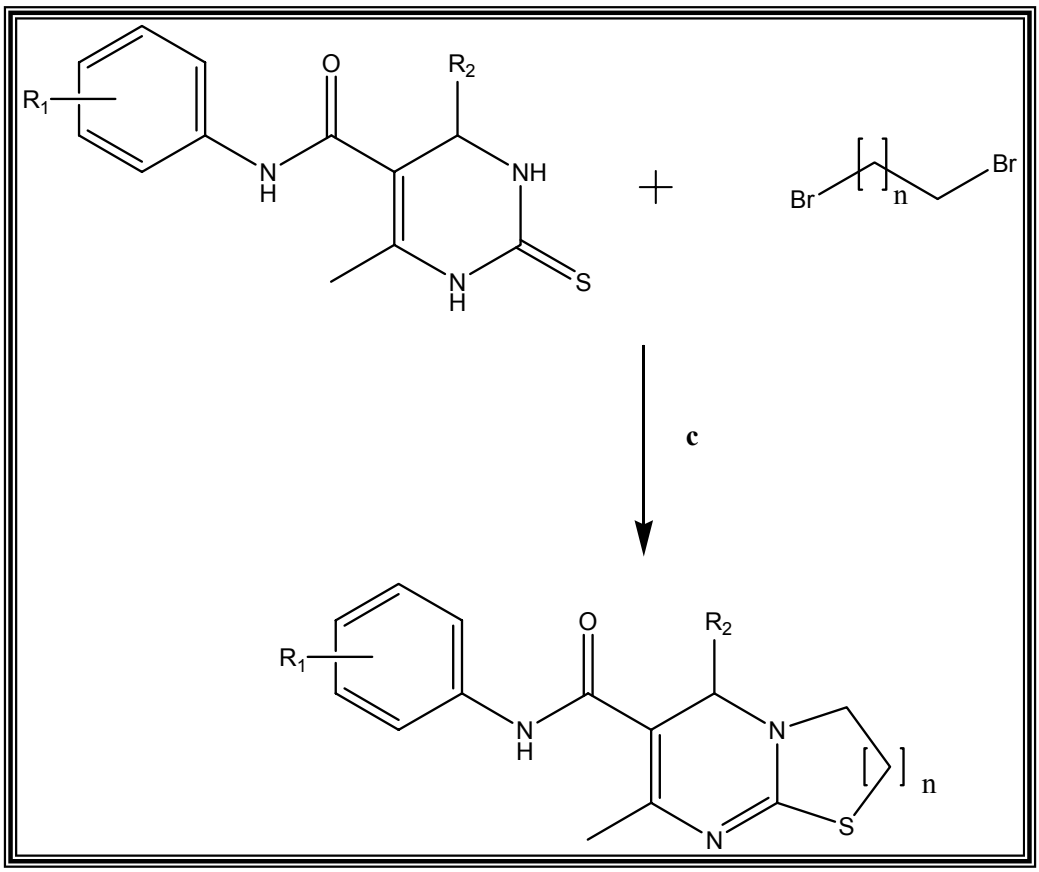


Scheme 2. Reagents and conditions: b = MeOH, con. HCl, reflux.

Reaction Mechanism

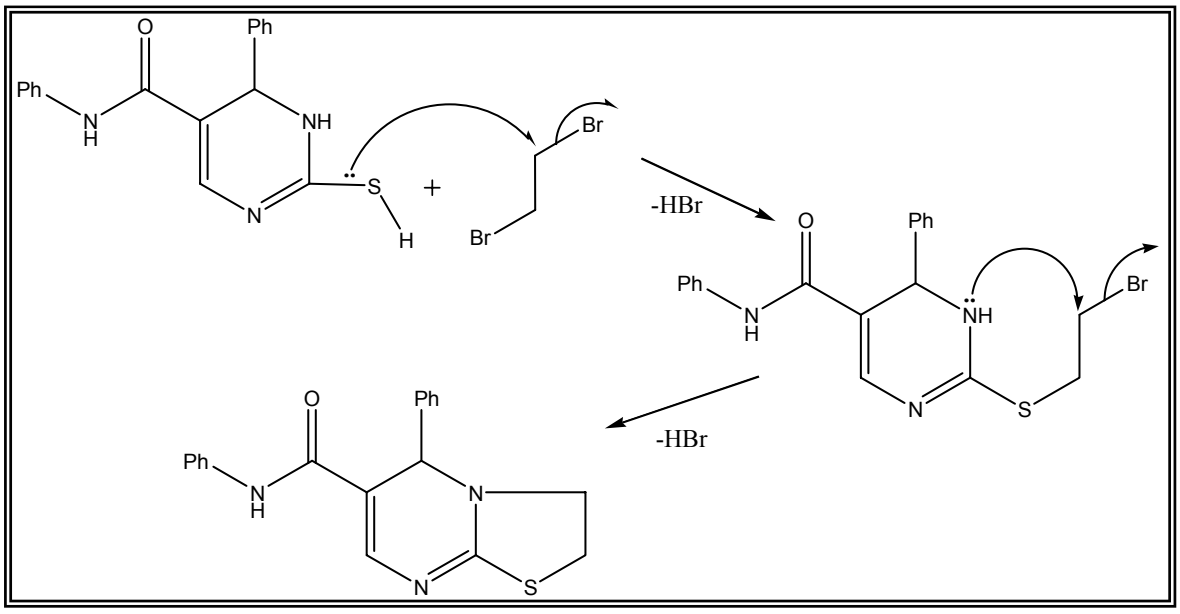


2.3.3 Scheme 3



Scheme 3. Reagents and conditions: c = DMF/CH_3CN, 140 ° C, n = 1-2

Reaction Mechanism



2.4 Experimental

2.4.1 4-chloro/flouro acetoacetanilide

4-chloro/flouro aniline (0.1M) and ethyl aceto acetate was refluxed at 110° C in 40 ml of toluene and catalytic amount of KOH/NaOH. The completion of reaction was monitored with TLC. After completion of reaction, toluene was distilled out. The residue was cooled at room temperature and was treated with ether. The solid was filtrated and dried. (Physical data is given in Chapter 1)

2.4.2 N-(substitutedphenyl)-1,2,3,4-tetrahydro-6-methyl-4-(substitutedphenyl)-2-thioxopyrimidine-5-carboxamide

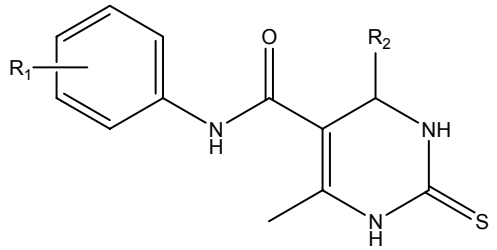
Acetoacetanilide (0.01M), aldehyde (0.01M) and thiourea (0.015M) were dissolved in minimum quantity of methanol. It was heated for 5-10 minutes to get the clear solution. Few drops of con. HCl were added to the reaction mixture as a catalyst. The reaction mixture was then refluxed in water bath for 6-12 hrs. The progress of reaction was monitored by thin layer chromatography. The reaction mixture was allowed to cool at room temperature. The solid separated upon cooling was filtered, washed with hot methanol and dried. Compounds were recrystallized from dimethylformamide. (Physical data are given in Table 2.5.1)

2.4.3 N-(4-chlorophenyl)-3,5,8,8a-tetrahydro-7-methyl-5-phenyl-2H-thiazolo[3,2-a]pyrimidine-6-carboxamide

N-(substitutedphenyl)-1,2,3,4-tetrahydro-6-methyl-4-(substitutedphenyl)-2-thioxopyrimidine-5-carboxamide (2a-p) (0.01M) and dibromo propane (or ethane) (0.015M) were dissolved in DMF and the reaction mixture was refluxed at 140° C for 2-2.5 hrs. The reaction mixture was poured on crushed ice and was extracted with chloroform. The chloroform was removed in vacuum. The residue was dried and recrystallized from dimethylformamide. (Physical data is given in Table 2.5.2)

2.5 Physical data

2.5.1 Physical data of N-(substitutedphenyl)-1,2,3,4-tetrahydro-6-methyl-4-(substitutedphenyl)-2-thioxopyrimidine-5-carboxamide *(compounds 2a-p)*



Compound	Code	R_1	R_2	MF	MW	MP° C	Yield	R_f
2a	AKS- 201	4-Cl	Ph	$C_{18}H_{16}ClN_3OS$	357.89	211-13	55	0.44
2b	AKS- 202	4-Cl	3,4-OCH_3-Ph	$C_{20}H_{20}ClN_3O_3S$	417.95	163-66	49	0.56
2c	AKS- 203	4-Cl	4-NO_2-Ph	$C_{18}H_{15}ClN_4O_3S$	402.89	253-55	52	0.49
2d	AKS- 204	4-Cl	3,4-OH-Ph	$C_{18}H_{16}ClN_3O_3S$	392.89	268-69	46	0.36
2e	AKS- 205	4-Cl	2-OCH_3-Ph	$C_{19}H_{18}ClN_3O_2S$	387.92	189-90	50	0.47

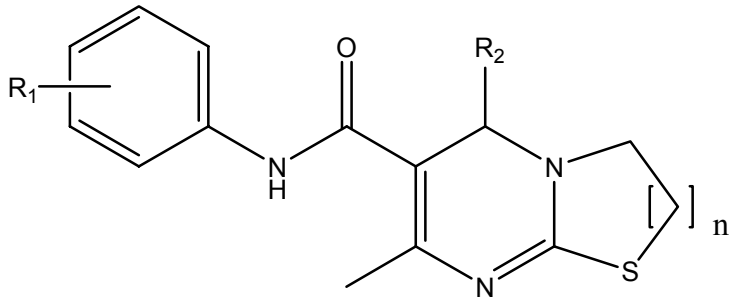
2f	AKS- 206	4-Cl	2-Cl-Ph	$C_{18}H_{15}Cl_2N_3OS$	392.34	204-06	56	0.54
2g	AKS- 207	4-Cl	3-NO_2-Ph	$C_{18}H_{15}ClN_4O_3S$	402.89	244-45	58	0.54
2h	AKS- 208	4-Cl	2-NO_2-Ph	$C_{18}H_{15}ClN_4O_3S$	402.89	201-04	55	0.57
2i	AKS- 209	4-F	2-OH-Ph	$C_{18}H_{16}FN_3O_2S$	357.44	175-78	59	*0.40
2j	AKS- 210	4-F	4-$N(CH_3)_2$-Ph	$C_{20}H_{21}FN_4OS$	387.51	166-67	48	*0.52
2k	AKS- 211	4-F	2-Cl-Ph	$C_{18}H_{15}ClFN_3OS$	375.88	158-59	53	*0.46
2l	AKS- 212	4-F	4-OCH_3-Ph	$C_{19}H_{18}FN_3O_2S$	371.47	196-97	50	*0.48
2m	AKS- 213	3,4-benzo	2-OCH_3-Ph	$C_{23}H_{21}N_3O_2S$	403.53	184-86	56	**0.55
2n	AKS- 214	3,4-benzo	4-$N(CH_3)_2$-Ph	$C_{24}H_{24}N_4OS$	416.58	198-99	48	**0.61
2o	AKS- 215	3,4-benzo	2-Cl-Ph	$C_{22}H_{18}ClN_3OS$	407.95	152-53	59	**0.58
2p	AKS- 216	3,4-benzo	2-OH-Ph	$C_{22}H_{19}N_3O_2S$	389.51	221-22	62	**0.46

TLC solvent system: EA:Hexane 3.5:6.5
*EA:Hexane 3:7
**CH_2Cl_2:MeOH 9.5:0.5

MPs were taken in open capillary and are not corrected

.

2.5.2 Physical data of N-(4-chlorophenyl)-3,5,8,8a-tetrahydro-7-methyl-5-phenyl-2H-thiazolo[3,2-a]pyrimidine-6-carboxamide *(compounds 3a-r)*



Compound	Code	R_1	R_2	MF	MW	MP° C	Yield	R_f
3a	AKS-231	4-Cl	Ph	$C_{20}H_{18}ClN_3OS$	383.89	153-54	68	0.48
3b	AKS-232	4-Cl	3,4-OCH_3-Ph	$C_{22}H_{22}ClN_3O_3S$	443.95	174	66	0.41
3c	AKS-233	4-Cl	4-NO_2-Ph	$C_{20}H_{17}ClN_4O_3S$	428.89	182-85	72	0.54
3d	AKS-234	4-Cl	4-OH-Ph	$C_{20}H_{18}ClN_3O_2S$	399.89	190-91	69	0.49
3e	AKS-235	4-Cl	4-OCH_3-Ph	$C_{21}H_{20}ClN_3O_2S$	413.92	160-62	66	0.62
3f	AKS-236	4-Cl	2-Cl-Ph	$C_{20}H_{17}Cl_2N_3OS$	418.34	177-78	60	0.56

#3g	AKS-237	4-Cl	3-NO_2-Ph	$C_{21}H_{19}ClN_4O_3S$	442.92	214-17	59	0.58
#3h	AKS-238	4-Cl	2-Cl-Ph	$C_{21}H_{19}Cl_2N_3OS$	432.37	168-70	72	0.55
#3i	AKS-239	4-Cl	2-NO_2-Ph	$C_{21}H_{19}ClN_4O_3S$	442.92	190-92	68	0.44
#3j	AKS-240	4-Cl	Ph	$C_{21}H_{20}ClN_3OS$	397.92	144-45	74	0.52
3k	AKS-241	4-F	2-OH-Ph	$C_{20}H_{18}FN_3O_2S$	383.44	183-84	63	0.66
3l	AKS-242	4-F	4-$N(CH_3)_2$-Ph	$C_{22}H_{23}FN_4OS$	410.51	212-14	65	0.43
3m	AKS-243	4-F	2-Cl-Ph	$C_{20}H_{17}ClFN_3OS$	401.88	196-97	62	0.52
3n	AKS-244	4-F	4-NO_2-Ph	$C_{21}H_{20}FN_3O_2S$	397.47	175	69	0.61
3o	AKS-245	3,4-benzo	2-OCH_3-Ph	$C_{25}H_{23}N_3O_2S$	429.53	181	72	*0.48
3p	AKS-246	3,4-benzo	4-$N(CH_3)_2$-Ph	$C_{26}H_{26}N_4OS$	442.58	193-95	74	*0.52
3q	AKS-247	3,4-benzo	2-Cl-Ph	$C_{24}H_{20}ClN_3OS$	433.95	162-63	70	*0.43
3r	AKS-248	3,4-benzo	2-OH-Ph	$C_{24}H_{21}N_3O_2S$	415.51	186-88	72	*0.56

TLC solvent system: EA:Hexane – 4:6, * CH_2Cl_2:MeOH - 9:1 MPs were taken in open capillary and are not corrected

n = 2

2.6 Spectral discussion

2.6.1 *Mass spectral study*

Systematic fragmentation pattern was observed in mass spectral analysis. Peaks for specific fragments were identified in each mass spectrum. Molecular ion peaks observed were in agreement with molecular weight of compounds. Fragmentation pattern can be described as below.

[1] A base peak in each spectrum was obtained because of specific fragmentation in each molecule. Fragment obtained due to cleavage of bond adjacent to carbonyl double bond in the phenyl carbamoyl side chain at C_5 position gave base peak in each spectrum. Base peak obtained at 271, 317, 273, 302 and 300 m/e values in mass spectrum of compound AKS-240, AKS-232, AKS-234, AKS-244 and AKS-242 were due to specific fragmentation pattern for this observed for this series.

[2] The second characteristic peak observed in each spectrum was due to cleave bond adjacent to carbonyl double bond at the other side. Peaks were observed at 243, 289, 245, 274 and 272 m/e values in respective spectrum for these fragments.

[3] Cleavage of methyl group from peak [1] gave another characteristic peak. Peaks were observed at 256, 303, 258 and 285 m/e values for compounds AKS-240, AKS-232, AKS-234 and AKS-242.

[4] Cleavage of bonds adjacent to both N atoms, gives characteristic peaks with respect to ring size (peak at 99 and 115 respectively for n = 1 and 2).

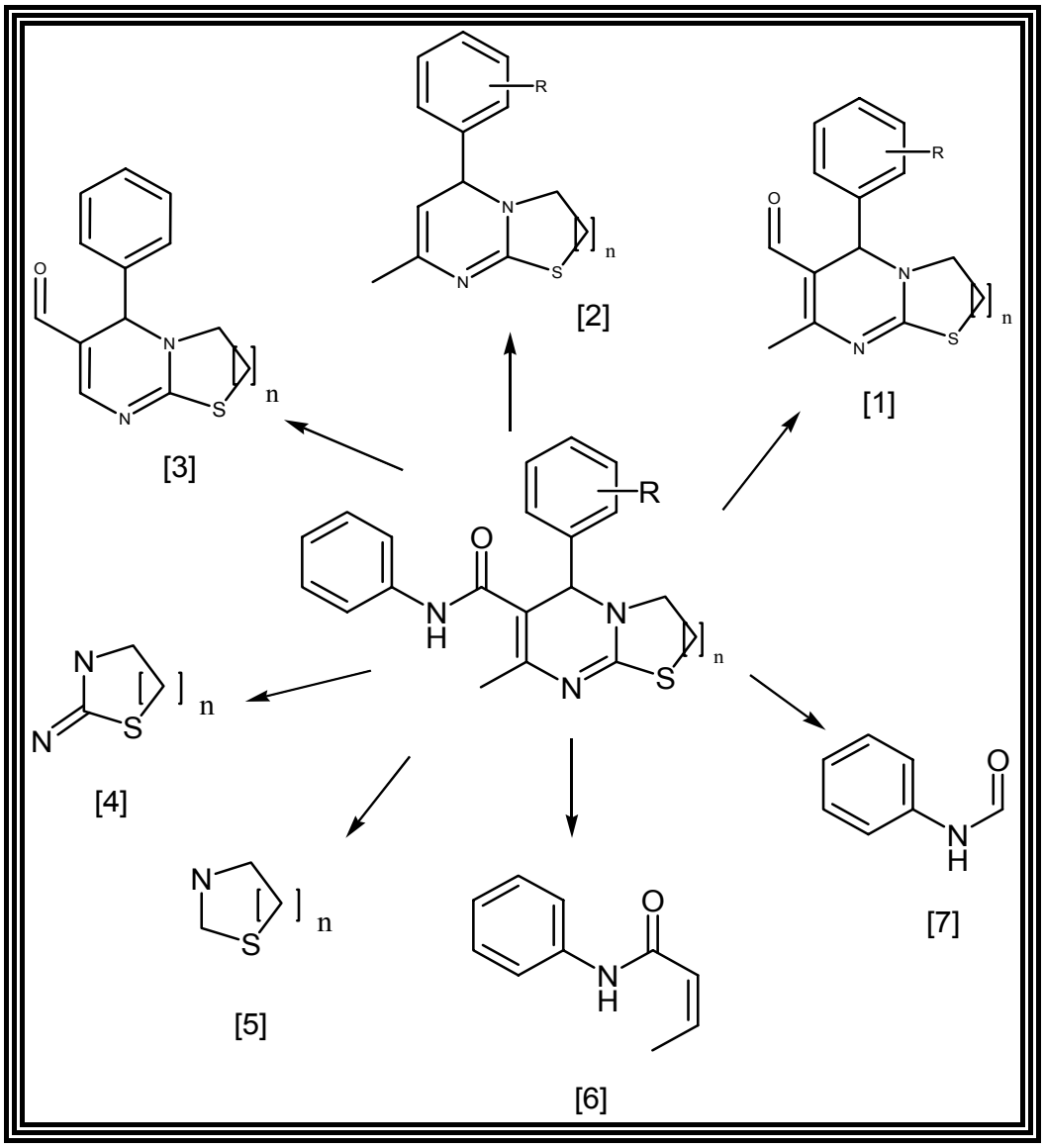
[5] Removal of one N atom from above fragment gave peak at 14 less m/e value.

[6] Peaks were also observed for fragment shown as [6] in figure 1.

[7] Cleavage of bond adjacent to carbonyl double bond gave fragment [7].

Above fragments are shown in the Figure 1 given below.

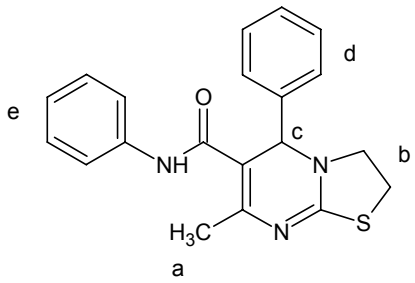
Figure 1. Characteristic fragments observed in mass spectrums



2.6.2 IR spectral study

In IR spectrums, characteristic frequencies were observed for functional group present in the molecule. -NH stretching vibration was observed between 3420-3112 cm^{-1}. Methyl and methylene group gave characteristic peaks between 2980-2815 cm^{-1}. Carbonyl frequency was characterized between 1680-1645 cm^{-1} because of amide carbonyl group. Aromatic ring gave characteristic frequencies for Ar-H, ring –C=C- and out of plane vibration. IR frequencies for each compound are given in spectral data of the compounds.

2.6.3 ^{1}H NMR spectral study



Number of protons and their chemical shifts were found to support the structure of the synthesized compounds. Signal (a) of methyl proton was observed between 2.1-2.4 δ ppm. Protons (-CH_2-) of thiazol and thiazine ring gave double doublet between 3.0-3.8 δ ppm. Signal (c) was observed between 5.2-5.8 δ ppm. Aromatic protons (d, e) were observed between 7-8 δ ppm and J values were found to be according to substitution on phenyl ring.

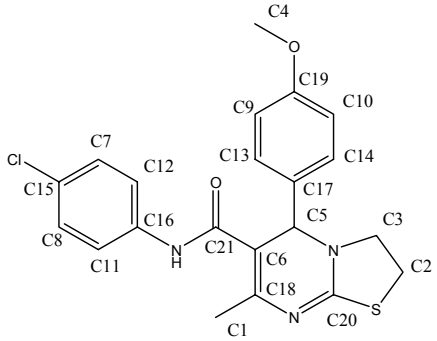
In spectrum of AKS-231, singlet for methyl protons was obtained at 2.23 δ ppm. Four protons of two cyclic –CH_2- of thiazolo ring were observed as multiplet for each proton at 3.11, 3.22, 3.42 and 3.61 δ ppm. C4 proton gave singlet at 5.48 δ ppm. Aromatic protons were obtained as multiplet.

In case of AKS-235, C_6 methyl proton singlet was observed at 2.25, while methoxy proton singlet was obtained at 3.46 δ ppm. Four multiplets were obtained for four cyclic thiazolo protons. C_4 proton was identified at 5.39 δ ppm. A triplet for a proton with J value of 7.96 and another triplet for a proton with 2.11 J value were obtained. A doublet with 7.76 J value for a proton and a double doublet with 8.12 and 2.16 J values were obtained. Other aromatic protons were obtained as multiplet.

In spectrum of AKS-247, a singlet (2.36 δ ppm) for methyl protons, four multiplets for four cyclic thiazolo protons and a singlet (6.13 δ ppm) for C_4 proton were observed. The NMR data along with chemical shifts and respective J values are given in spectral data of compounds.

2.6.4 ^{13}C NMR Spectral study

13C NMR spectrum data for compound AKS-235 is given below. δ ppm values is listed along with corresponding carbon atom number given in bracket and displayed in the structure.



^{13}C δ ppm: 14.73 (C1), 21.25 (C2), 25.08 (C3), 50.39 (C4), 55.93 (C5), 107.86 (C6), 114.39 (C7), 114.61 (C8), 121.17 (C9), 121.24 (C10), 127.56 (C11), 128.97 (C12), 129.36 (C13), 130.06 (C14), 131.88 (C15), 134.26 (C16), 145.00 (C17), 157.02 (C18), 159.43 (C19), 163.79 (C20), 165.78 (C21)

2.6.5 Elemental Analysis

Elemental analysis of the synthesized compounds was found in agreement of calculated % of elements for respective compounds. The spectral and elemental analysis data are given below for individual compound.

Spectral data of synthesized compounds (AKS 231-248)

N*-(4-chlorophenyl)-7-methyl-5-phenyl-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*] pyrimidine-6-carboxamide (AKS-231)** - ***IR *(cm^{-1}):* 3256 (N-H), 3089 (Ar-H), 2914 (-CH_3), 2818 (-CH_2), 1673 (C=O), 1614 (C=C), 1126 (C-O); ***^{1}H NMR*** *(DMSO d6) (δ ppm)*: 2.23 (3H, s), 3.11 (1H, m), 3.22 (1H, m), 3.42 (1H, m), 3.61 (1H, m), 5.48 (1H, s), 7.14 (1H, s), 7.16-7.40 (9H, m); ***Anal cacld*** for $C_{20}H_{18}ClN_3OS$: C 62.57, H 4.73, N 10.95, found: C 62.61, H 4.72, N 10.97.

N*-(4-chlorophenyl)-7-methyl-5-(3,4-dimethoxyphenyl)-2,3-dihydro-5*H*-[1,3] thiazolo[3,2-*a*]pyrimidine-6-carboxamide (AKS-232)** - ***IR *(cm^{-1}):* 3318 (N-H), 3077

(Ar-H), 2922 (-CH_3), 2835 (-CH_2), 1658 (C=O), 1622 (C=C), 1169 (C-O); ***Mass*** *(m/e)*: 443 (molecular ion peak), 428, 317 (base peak), 303, 289, 215, 127, 99; ***Anal cacld*** for $C_{22}H_{22}ClN_3O_3S$: C 59.52, H 4.99, N 9.47, found: C 59.50, H 4.98, N 9.49.

N*-(4-chlorophenyl)-7-methyl-5-(4-nitrophenyl)-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-6-carboxamide (AKS-233)** - ***IR *(cm^{-1}):* 3346 (N-H), 3114 (Ar-H), 2988 (-CH_3), 2857 (-CH_2), 1662 (C=O), 1608 (C=C), 1078 (C-O); ***Anal cacld*** for $C_{20}H_{17}ClN_4O_3S$: C 56.01, H 4.00, N 13.06, found: C 56.03, H 4.02, N 13.09.

N*-(4-chlorophenyl)-7-methyl-5-(4-hydroxyphenyl)-2,3-dihydro-5*H*-[1,3]thiazolo [3,2-*a*]pyrimidine-6-carboxamide (AKS-234)** - ***IR *(cm^{-1}):* 3341 (N-H), 3056 (Ar-H), 2907 (-CH_3), 2823 (-CH_2), 1681 (C=O), 1606 (C=C), 1142 (C-O); ***Mass*** *(m/e)*: 399 (molecular ion peak), 384, 273 (base peak), 245, 127, 99; ***Anal cacld*** for $C_{20}H_{18}ClN_3O_2S$: C 60.07, H 4.54, N 10.51, found: C 60.08, H 4.53, N 10.53.

N*-(4-chlorophenyl)-7-methyl-5-(4-methoxyphenyl)-2,3-dihydro-5*H*-[1,3]thiazolo [3,2-*a*]pyrimidine-6-carboxamide (AKS-235)** - ***IR *(cm^{-1}):* 3273 (N-H), 3051 (Ar-H), 2924 (-CH_3), 2868 (-CH_2), 1662 (C=O), 1639 (C=C), 1107 (C-O); ***^{1}H NMR*** *(DMSO d6) (δ ppm)*: 2.25 (3H, s), 2.93 (1H, m), 3.01 (1H, m), 3.23 (1H, m), 3.41 (1H, m), 3.46 (3H, s), 5.39 (1H, s), 7.23 (2H, m), 7.37 (3H, m), 7.53 (1H, t) (J=7.96), 7.76 (1H, d) (J=7.76), 8.15 (1H, dd)(J=8.12, 2.16), 8.20 (1H, t) (J=2.11); ***^{13}C NMR*** *(δ ppm)*: 14.73, 21.25, 25.08, 50.39, 55.93, 107.86, 114.39, 114.61, 121.17, 121.24, 127.56, 128.97, 129.36, 130.06, 131.88, 134.26, 145.00, 157.02, 159.43, 163.79, 165.78; ***Anal cacld*** for $C_{21}H_{20}ClN_3O_2S$: C 60.94, H 4.87, N 10.15, found: C 60.96, H 4.88, N 10.17.

N*-(4-chlorophenyl)-7-methyl-5-(2-chlorophenyl)-2,3-dihydro-5*H*-[1,3]thiazolo [3,2-*a*]pyrimidine-6-carboxamide (AKS-236)** - ***IR *(cm^{-1}):* 3284 (N-H), 3012 (Ar-H), 2926 (-CH_3), 2878 (-CH_2), 1674 (C=O), 1637 (C=C), 1112 (C-O); ***^{1}H NMR*** *(DMSO d6) (δ ppm)*: 2.21 (3H, s), 3.14 (1H, m, 3.25 (1H, m, 3.44 (1H, m, 3.61 (1H, m, 7.20-7.34 (8H, m); ***Anal cacld*** for $C_{20}H_{17}Cl_2N_3OS$: C 57.42, H 4.10, N 10.04, found: C 57.45, H 4.11, N 10.07.

N*-(4-chlorophenyl)-8-methyl-6-(3-nitrophenyl)-3,4-dihydro-2*H*,6*H*-pyrimido[2,1-*b*][1,3]thiazine-7-carboxamide (AKS-237)** - ***IR *(cm^{-1}):* 3230 (N-H), 3014 (Ar-H), 2988

($-CH_3$), 2816, 2719 ($-CH_2$), 1692 (C=O), 1610 (C=C), 1179 (C-O); ***Anal cacld*** for $C_{21}H_{19}ClN_4O_3S$: C 56.95, H 4.32, N 12.65, found: C 56.98, H 4.31, N 12.67.

N*-(4-chlorophenyl)-8-methyl-6-(2-chlorophenyl)-3,4-dihydro-2*H*,6*H*-pyrimido [2,1-*b*][1,3]thiazine-7-carboxamide (AKS-238)** - ***IR *(cm^{-1}):* 3341 (N-H), 3077 (Ar-H), 2945 ($-CH_3$), 2862 ($-CH_2$), 1652 (C=O), 1616 (C=C), 1171 (C-O); ***Anal cacld*** for $C_{21}H_{19}Cl_2N_3OS$: C 58.34, H 4.43, N 9.72, found: C 58.35, H 4.45, N 9.75.

N*-(4-chlorophenyl)-8-methyl-6-(2-nitrophenyl)-3,4-dihydro-2*H*,6*H*-pyrimido[2,1-*b*][1,3]thiazine-7-carboxamide (AKS-239)** - ***IR *(cm^{-1}):* 3292 (N-H), 3026 (Ar-H), 2941 ($-CH_3$), 2889, 2866 ($-CH_2$), 1689 (C=O), 1643 (C=C), 1091 (C-O); ***Anal cacld*** for $C_{21}H_{19}ClN_4O_3S$: C 56.95, H 4.32, N 12.65, found: C 56.99, H 4.33, N 12.68.

N*-(4-chlorophenyl)-8-methyl-6-phenyl-3,4-dihydro-2*H*,6*H*-pyrimido[2,1-*b*][1,3] thiazine-7-carboxamide (AKS-240)** - ***IR *(cm^{-1}):* 3275 (N-H), 3020 (Ar-H), 2941 ($-CH_3$), 2872, 2820 ($-CH_2$), 1678 (C=O), 1653, 1645 (C=C), 1089 (C-O); ***Mass*** *(m/e)*: 397 (molecular ion peak), 271 (base peak), 243, 167, 115, 100; ***Anal cacld*** for $C_{21}H_{20}ClN_3OS$: C 63.39, H 5.07, N 10.56, found: C 63.44, H 5.10, N 10.60.

N*-(4-fluorophenyl)-5-(2-hydroxyphenyl)-7-methyl-2,3-dihydro-5*H*-[1,3]thiazolo [3,2-*a*]pyrimidine-6-carboxamide (AKS-241)** - ***IR *(cm^{-1}):* 3522 (-OH), 3312 (N-H), 3079 (Ar-H), 2935 ($-CH_3$), 2888, 2845 ($-CH_2$), 1659 (C=O), 1603 (C=C), 1129 (C-O); ***Anal cacld*** for $C_{20}H_{18}FN_3O_2S$: C 62.57, H 4.73, N 10.95, found: C 62.61, H 4.72, N 10.97.

N*-(4-fluorophenyl)-5-(4-dimethylaminophenyl)-7-methyl-2,3-dihydro-5*H*-[1,3] thiazolo[3,2-*a*]pyrimidine-6-carboxamide (AKS-242)** - ***IR *(cm^{-1}):* 3326 (N-H), 3055 (Ar-H), 2947 ($-CH_3$), 2824 ($-CH_2$), 1680 (C=O), 1617 (C=C), 1178 (C-O); ***Mass*** *(m/e)*: 402 (molecular ion peak), 300, 272, 111, 86; ***Anal cacld*** for $C_{22}H_{23}FN_4OS$: C 62.57, H 4.73, N 10.95, found: C 62.61, H 4.72, N 10.97.

N*-(4-fluorophenyl)-5-(2-chlorophenyl)-7-methyl-2,3-dihydro-5*H*-[1,3]thiazolo [3,2-*a*]pyrimidine-6-carboxamide (AKS-243)** - ***IR *(cm^{-1}):* 3346 (N-H), 3082 (Ar-H), 2967 ($-CH_3$), 2866 ($-CH_2$), 1661 (C=O), 1650 (C=C), 1118 (C-O); ***Anal cacld*** for $C_{20}H_{17}ClFN_3OS$: C 62.57, H 4.73, N 10.95, found: C 62.61, H 4.72, N 10.97.

N*-(4-fluorophenyl)-5-(4-nitrophenyl)-7-methyl-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-6-carboxamide (AKS-244)** - ***IR *(cm^{-1}):* 3389 (N-H), 3098 (Ar-H), 2971 (-CH_3), 2856 (-CH_2), 1653 (C=O), 1602 (C=C), 1146 (C-O); ***Mass*** *(m/e)*: 412 (molecular ion peak), 302 (base peak), 256, 243, 115, 86; ***Anal cacld*** for $C_{21}H_{20}FN_3O_2S$: C 62.57, H 4.73, N 10.95, found: C 62.61, H 4.72, N 10.97.

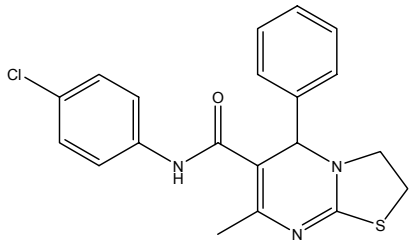
7-methyl-*N*-1-naphthyl-5-(2-methoxyphenyl)-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-6-carboxamide (AKS-245) - ***IR*** *(cm^{-1}):* 3146 (N-H), 3086 (Ar-H), 2924 (-CH_3), 2875 (-CH_2), 1674 (C=O), 1651 (C=C), 1014 (C-O); ***Anal cacld*** for $C_{25}H_{23}N_3O_2S$: C 62.57, H 4.73, N 10.95, found: C 62.61, H 4.72, N 10.97.

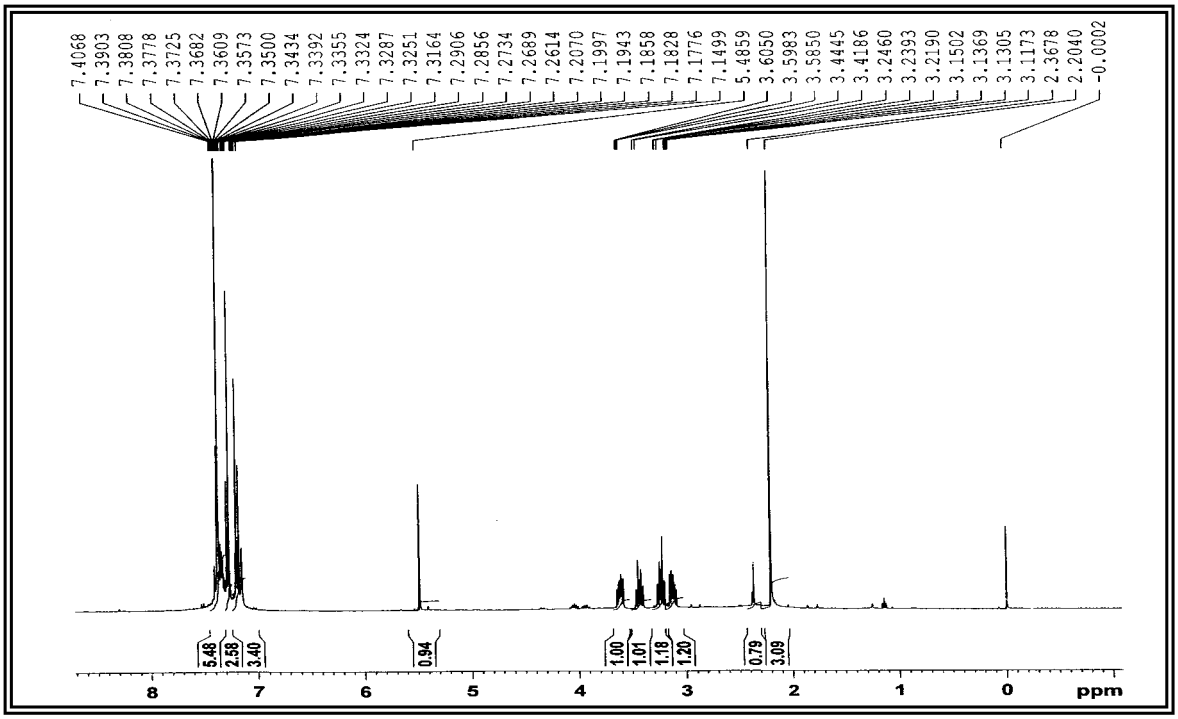
7-methyl-*N*-1-naphthyl-5-(4-dimethylaminophenyl)-2,3-dihydro-5*H*-[1,3]thiazolo [3,2-*a*]pyrimidine-6-carboxamide (AKS-246) - ***IR*** *(cm^{-1}):* 3319 (N-H), 3056 (Ar-H), 2918 (-CH_3), 2814 (-CH_2), 1670 (C=O), 1609 (C=C), 1136 (C-O); ***Anal cacld*** for $C_{26}H_{26}N_4OS$: C 62.57, H 4.73, N 10.95, found: C 62.61, H 4.72, N 10.97.

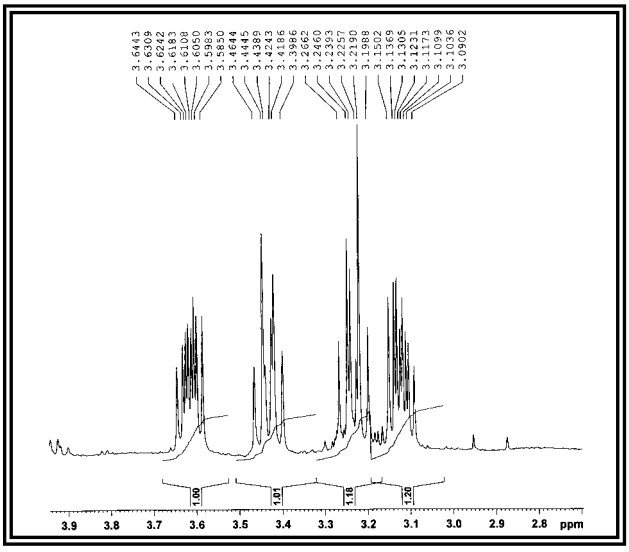
7-methyl-*N*-1-naphthyl-5-(2-chlorophenyl)-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*] pyrimidine-6-carboxamide (AKS-247) - ***IR*** *(cm^{-1}):* 3277 (N-H), 3032 (Ar-H), 2947 (-CH_3), 2877 (-CH_2), 1681 (C=O), 1620 (C=C), 1116 (C-O); ***^{1}H NMR*** *(DMSO d6) (δ ppm)*: 2.36 (3H, s), 3.09 (1H, m), 3.22 (1H, m), 3.40 (1H, m), 3.72 (1H, m), 6.13 (1H, s), 7.16 (1H, s), 7.37 (3H, m), 7.40 (4H, m), 7.64 (2H, dd, J=8.2, 2.1), 7.73 (1H, d, J=7.48), 7.80 (1H, d, J=8.2); ***Anal cacld*** for $C_{24}H_{20}ClN_3OS$: C 62.57, H 4.73, N 10.95, found: C 62.61, H 4.72, N 10.97.

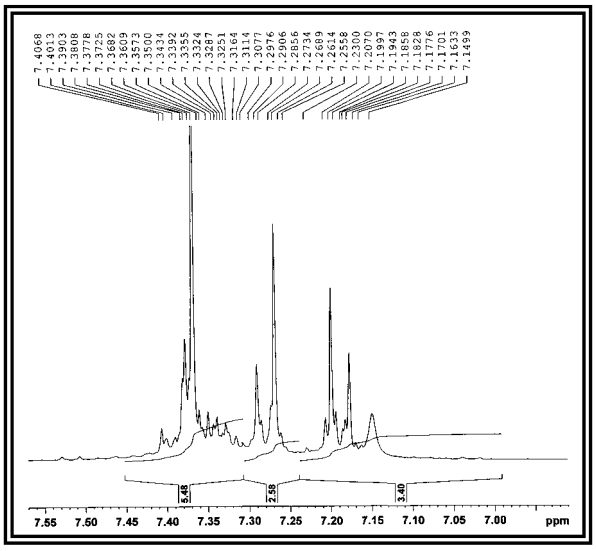
7-methyl-*N*-1-naphthyl-5-(2-hydroxyphenyl)-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-6-carboxamide (AKS-248) - ***IR*** *(cm^{-1}):* 3309 (N-H), 3055 (Ar-H), 2915 (-CH_3), 2811 (-CH_2), 1668 (C=O), 1619 (C=C), 1128 (C-O); ***Anal cacld*** for $C_{24}H_{21}N_3O_2S$: C 62.57, H 4.73, N 10.95, found: C 62.61, H 4.72, N 10.97.

2.6.6.1 ^{1}H NMR spectrum of AKS- 231

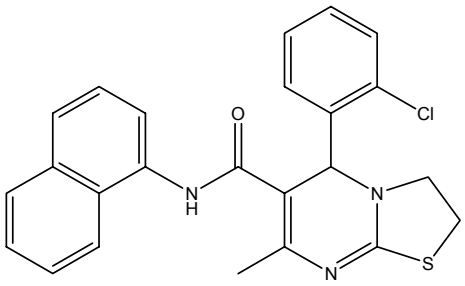


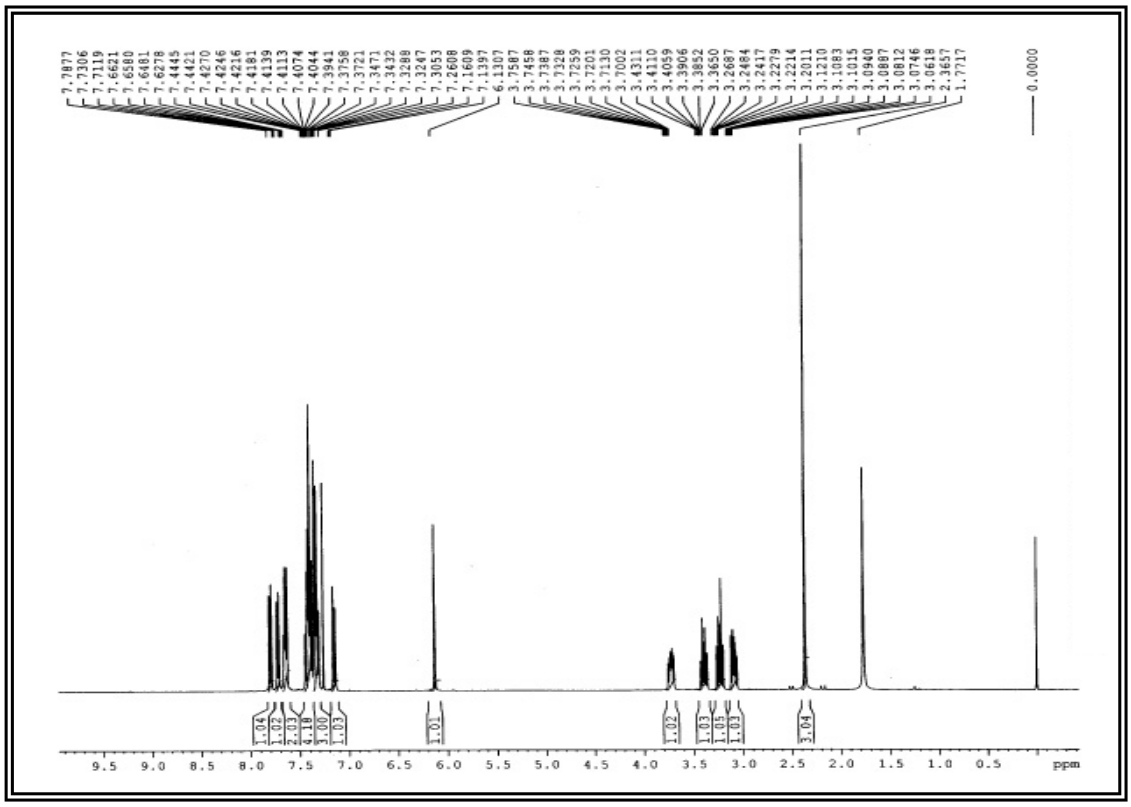


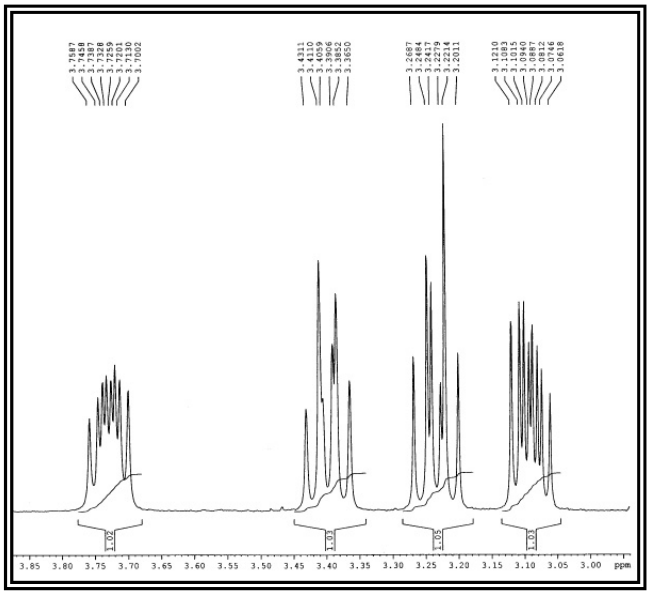


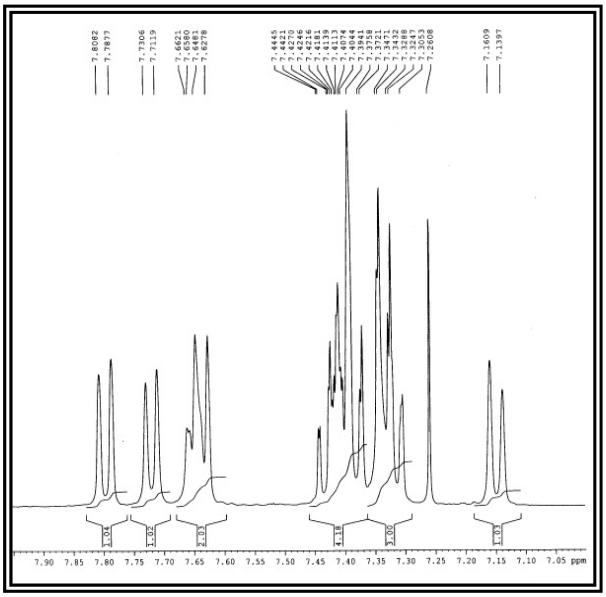


2.6.6.2 ^{1}H NMR spectrum of AKS- 247

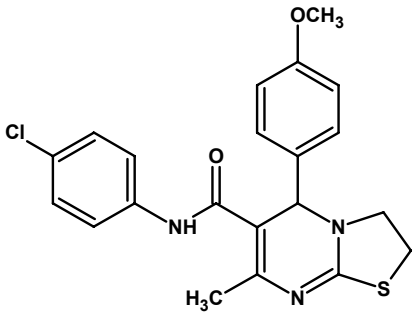


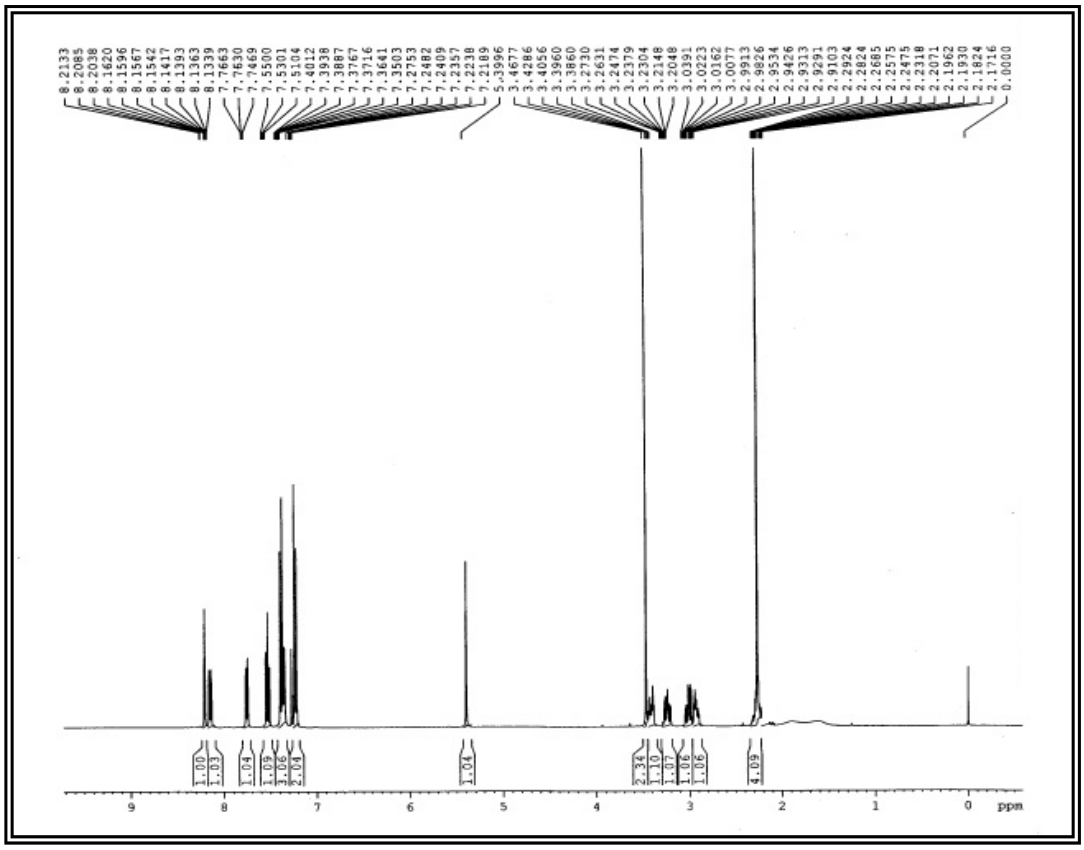


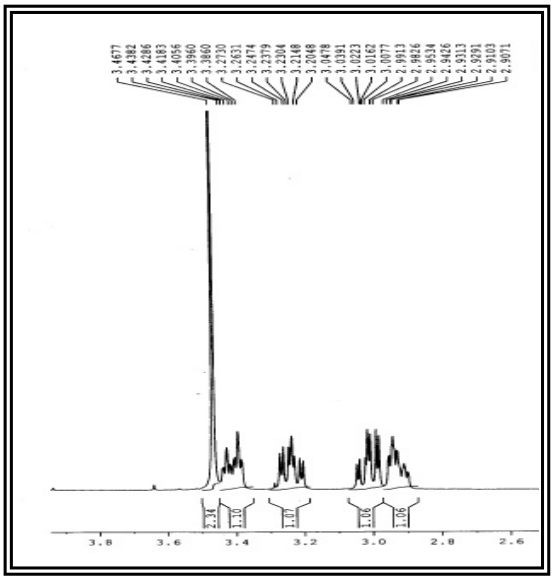


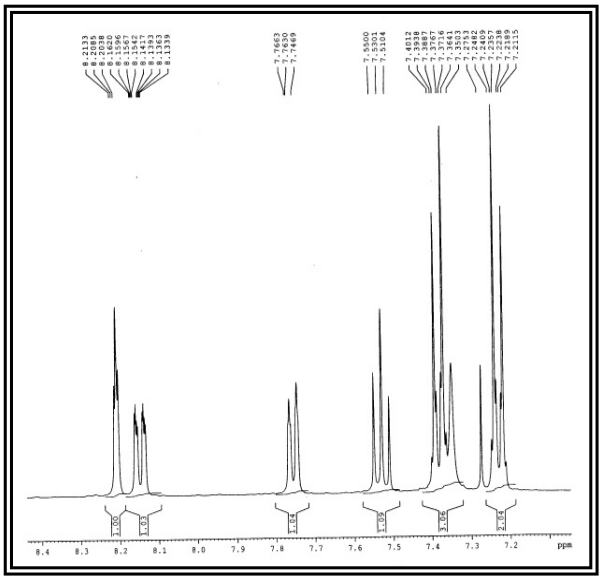


2.6.6.3 ^{1}H NMR spectrum of AKS-235

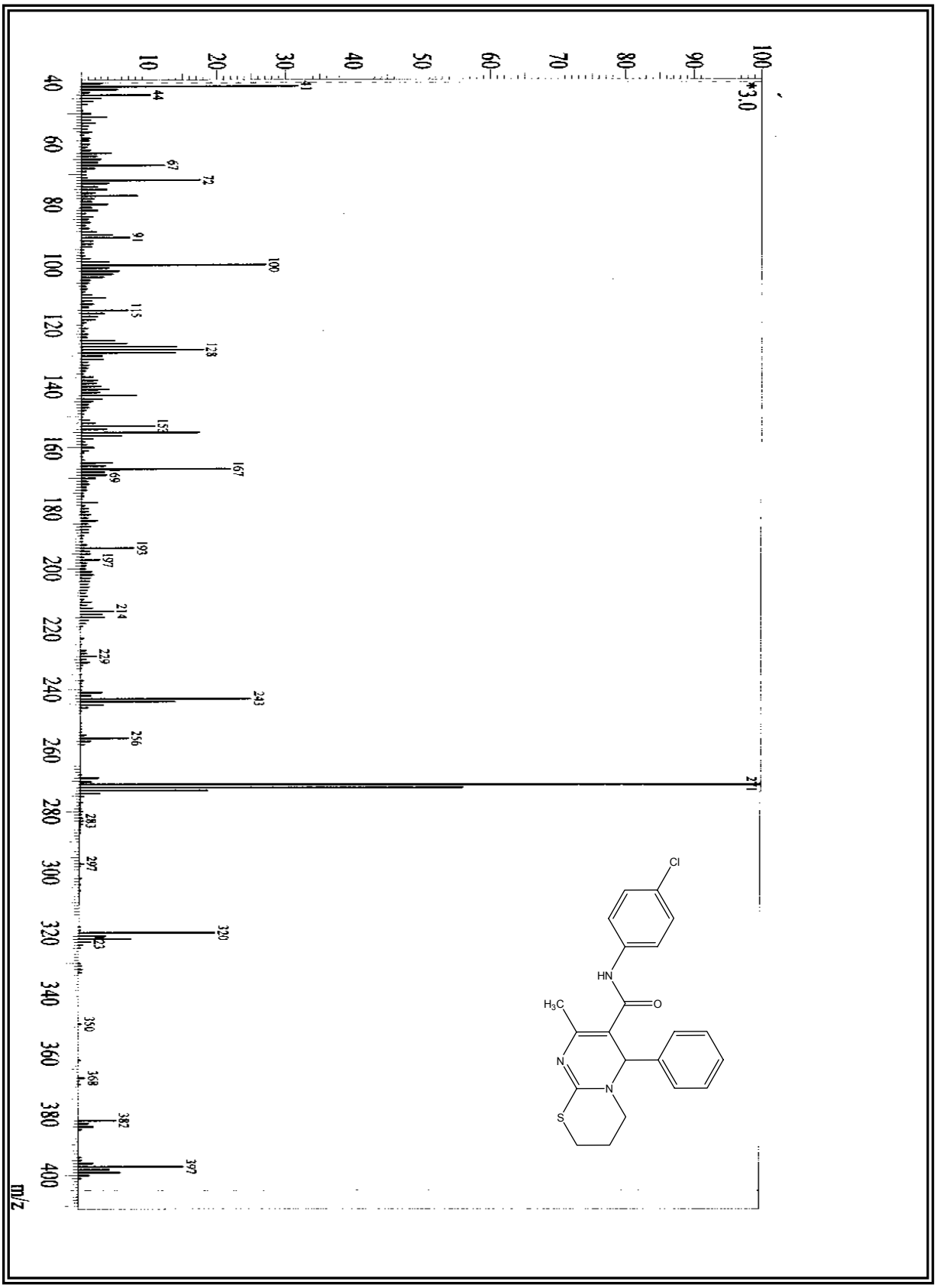




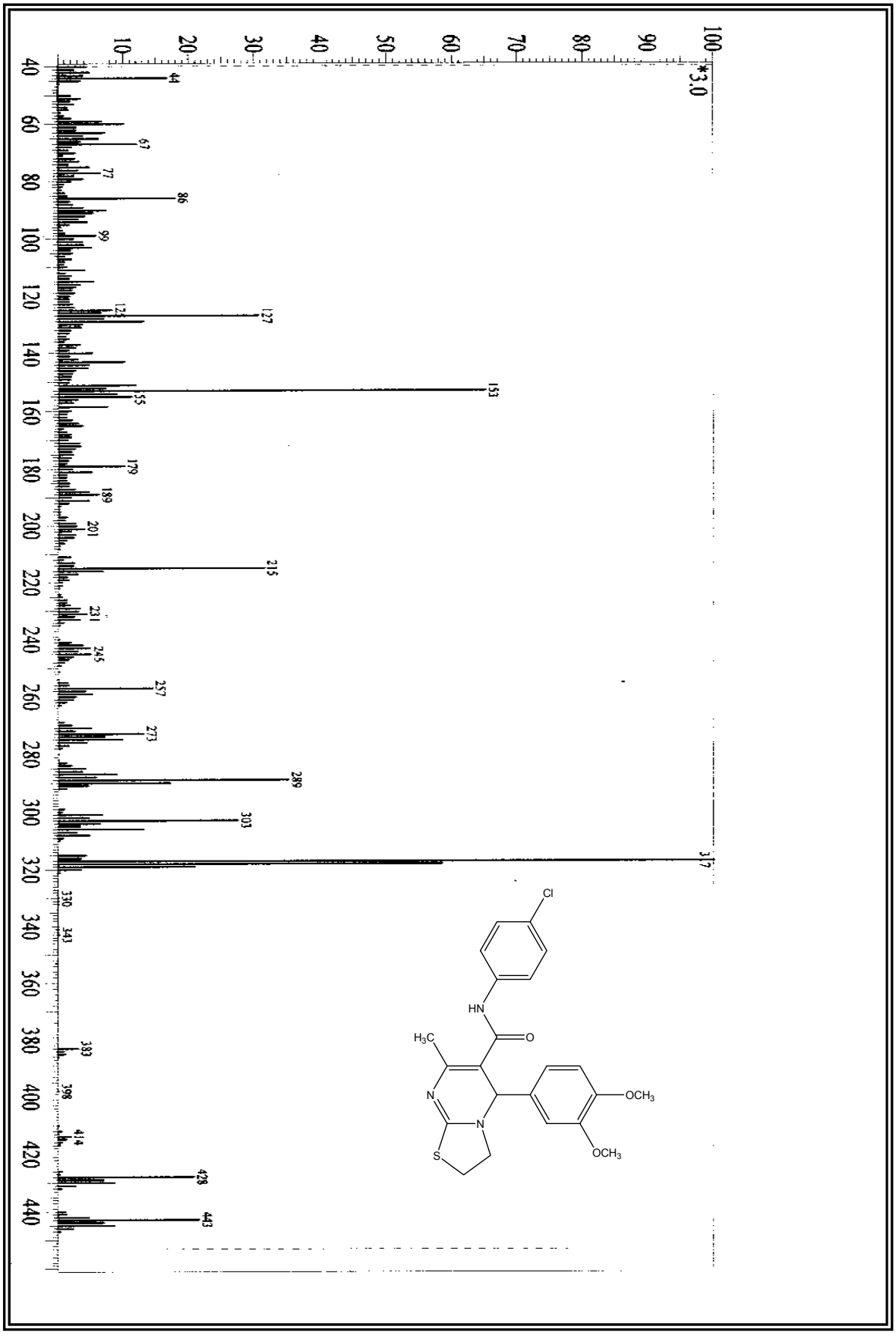




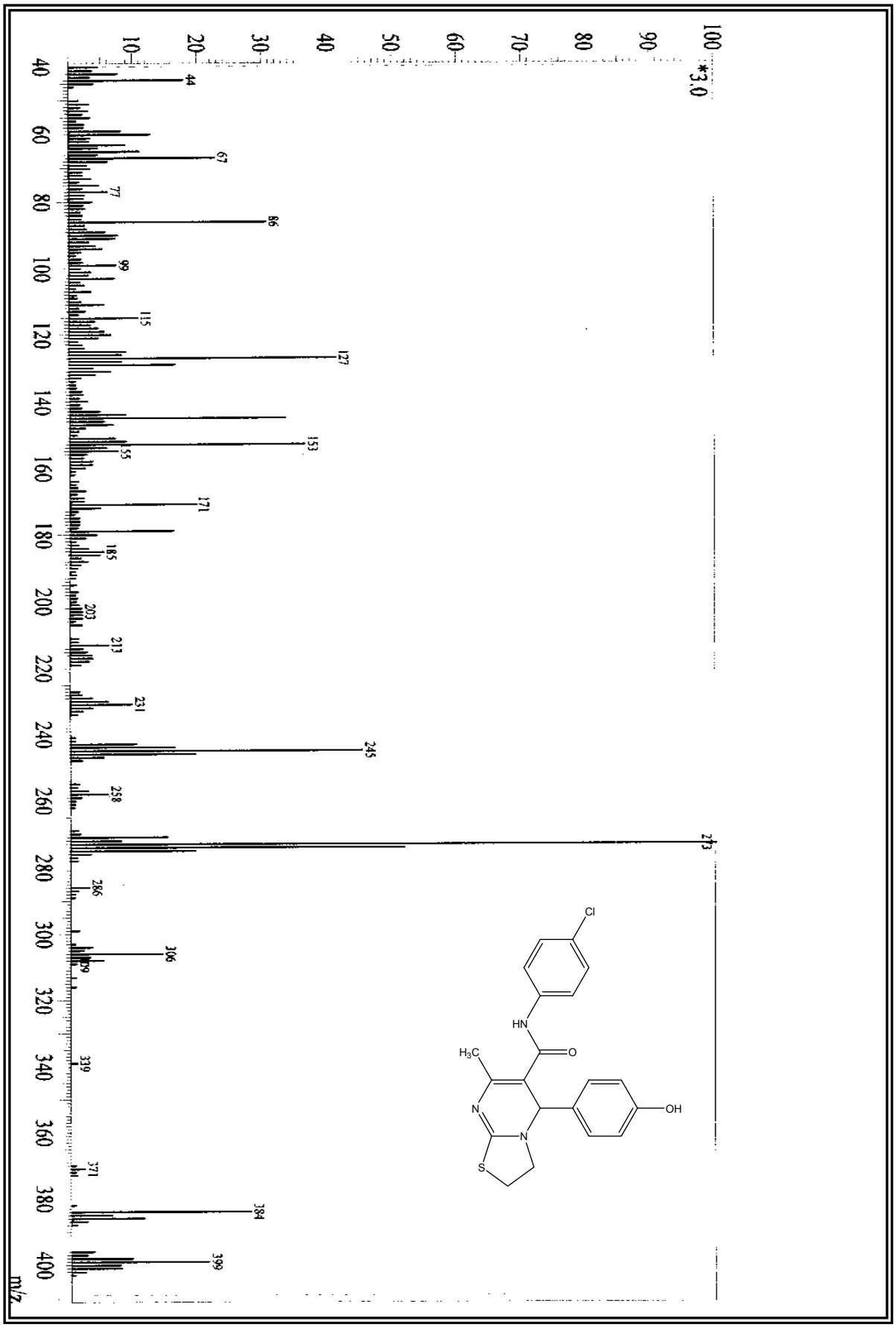
2.6.6.4 Mass spectrum of AKS- 240



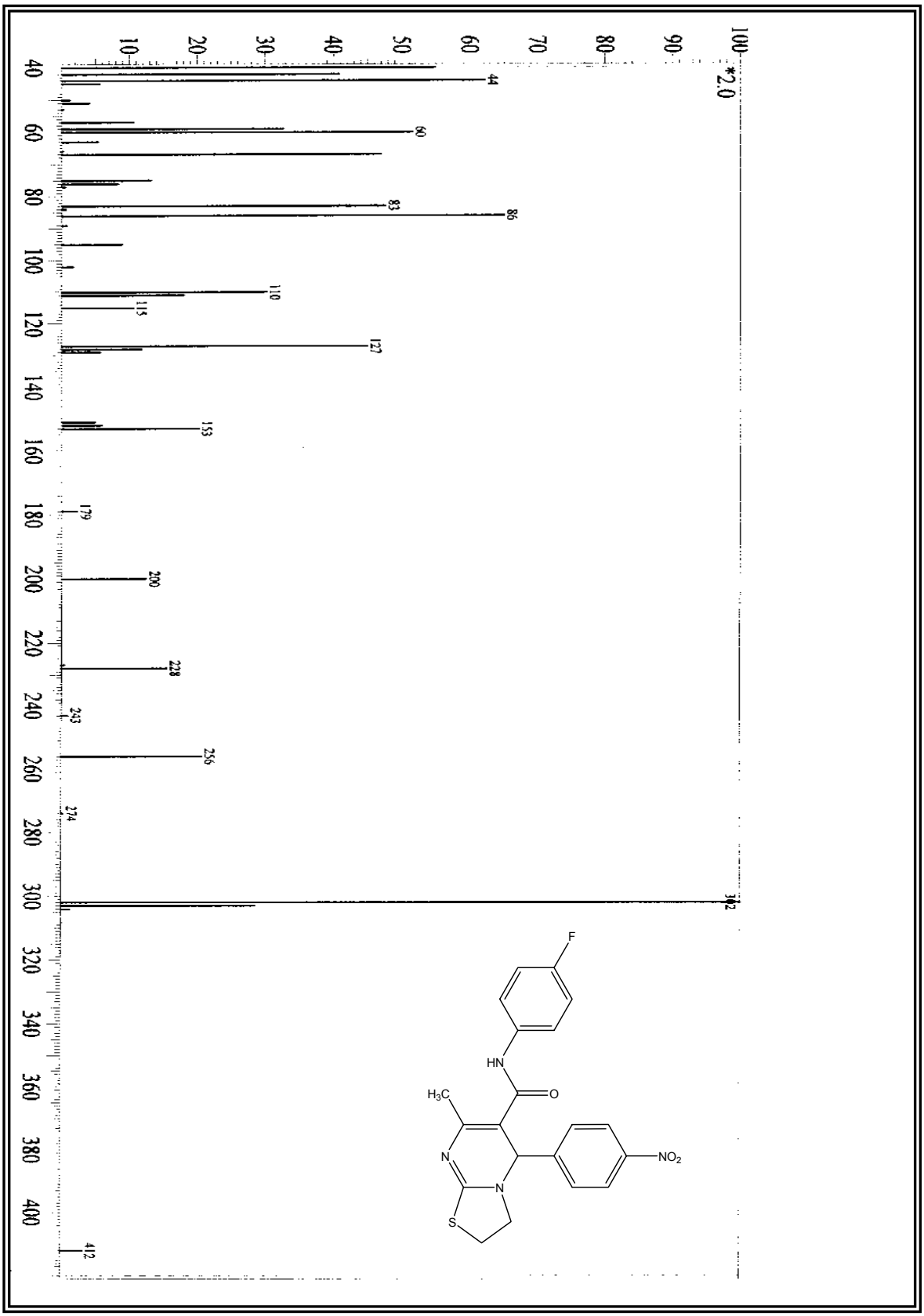
2.6.6.5 Mass spectrum of AKS- 232



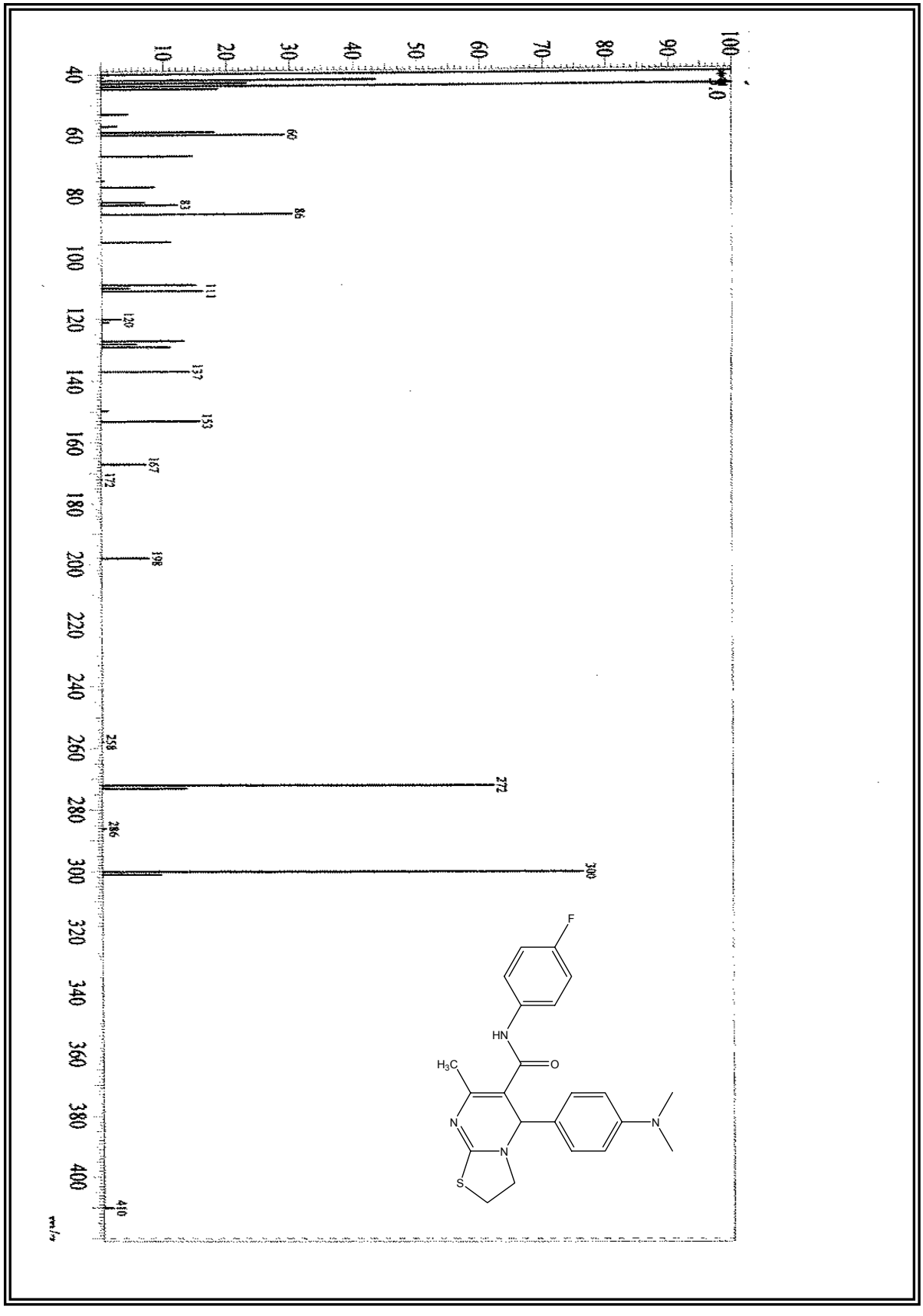
2.6.6.6 Mass spectrum of AKS- 234



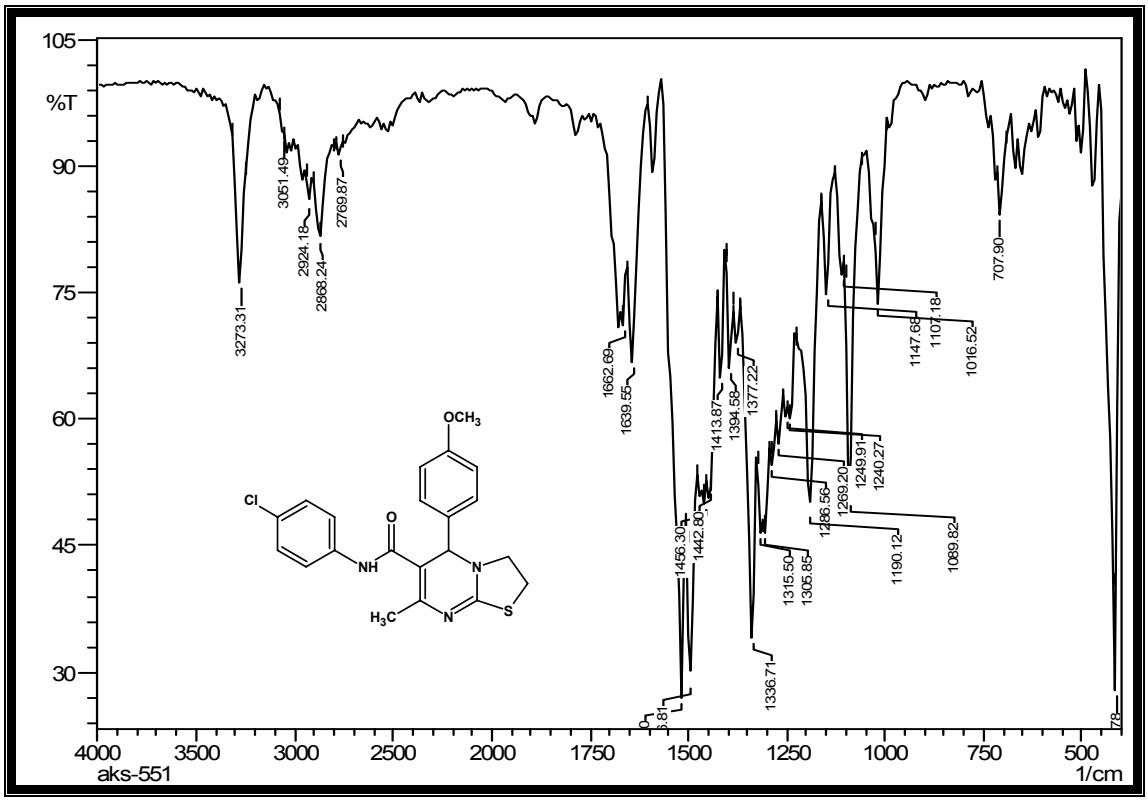
2.6.6.7 Mass spectrum of AKS- 244



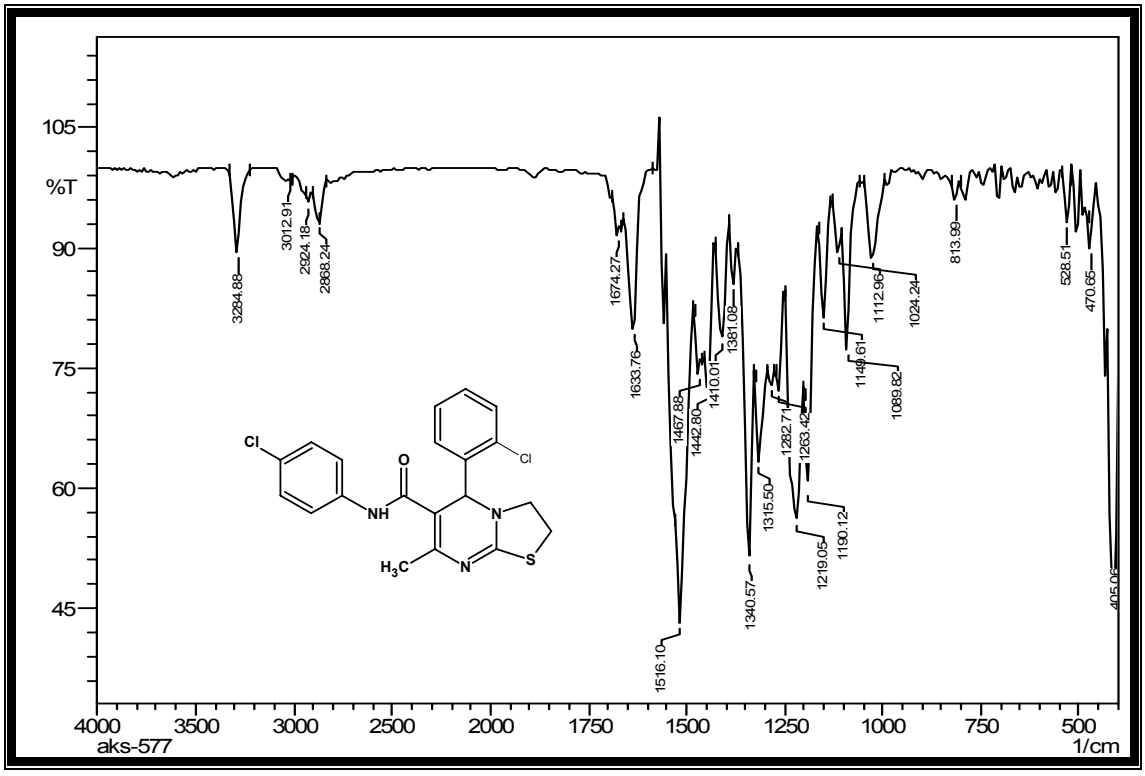
2.6.6.8 Mass spectrum of AKS- 242



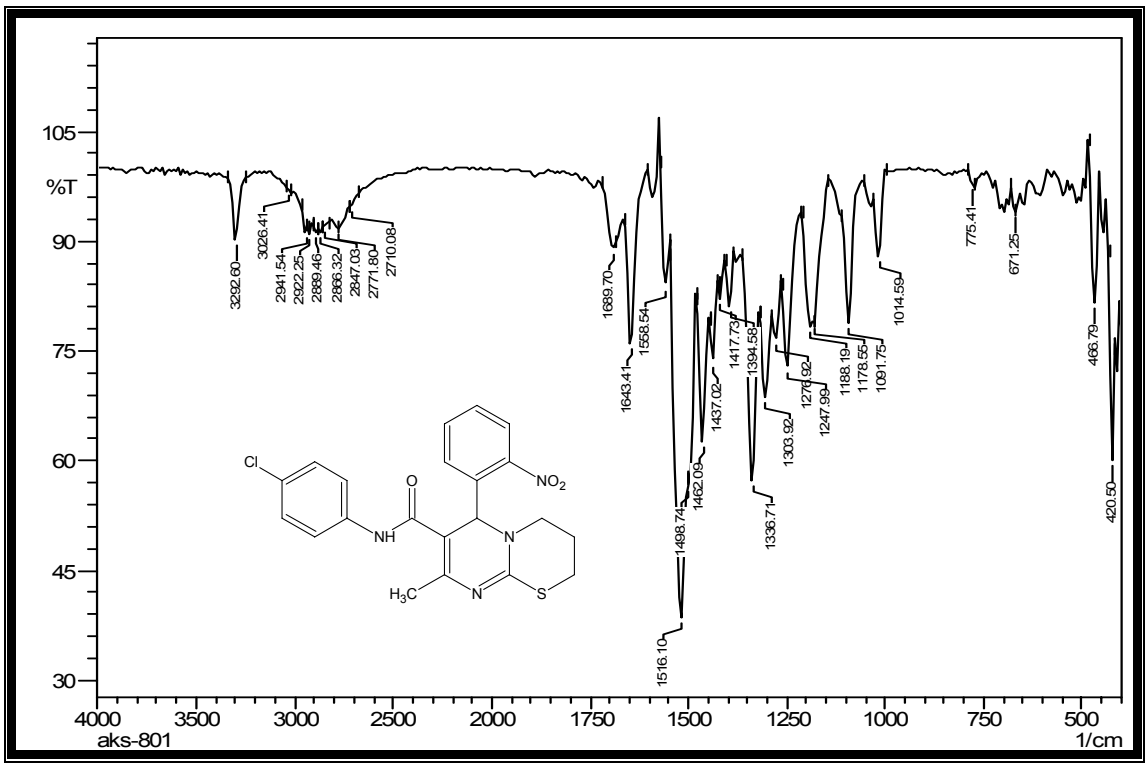
2.6.6.9 IR spectrum of AKS-235



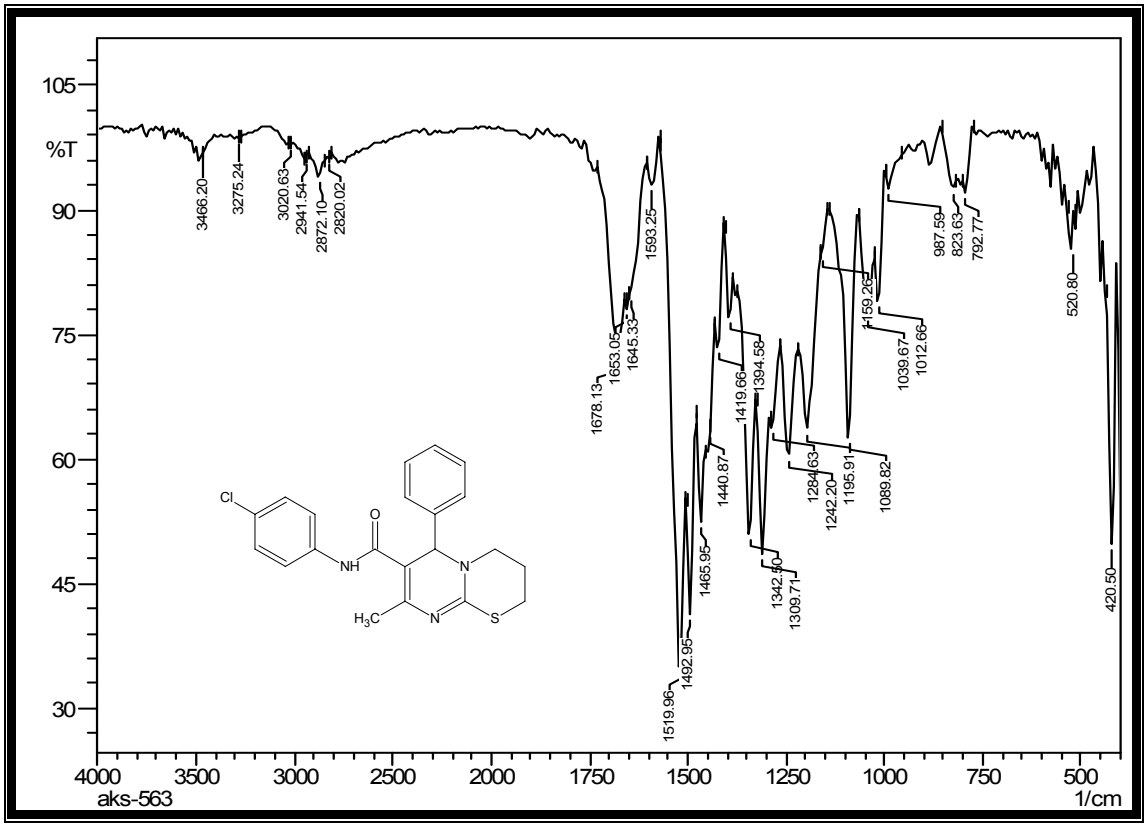
2.6.6.10 IR spectrum of AKS-236



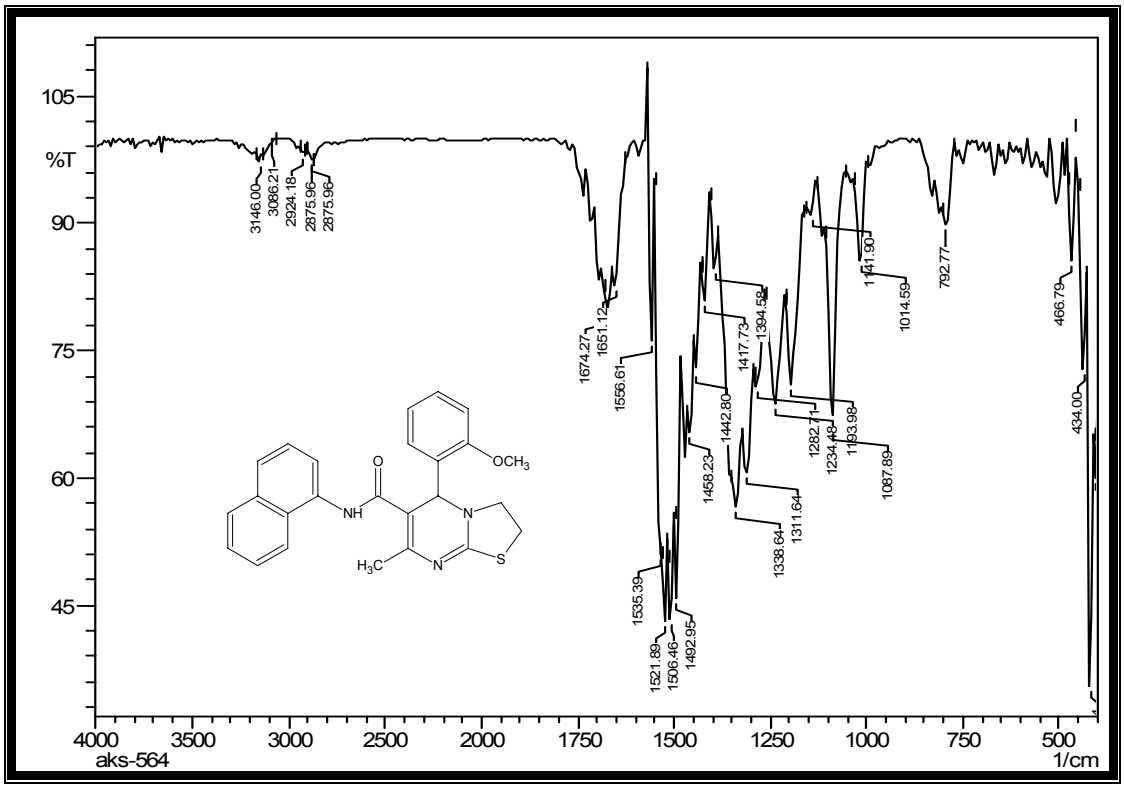
2.6.6.11 IR spectrum of AKS-239



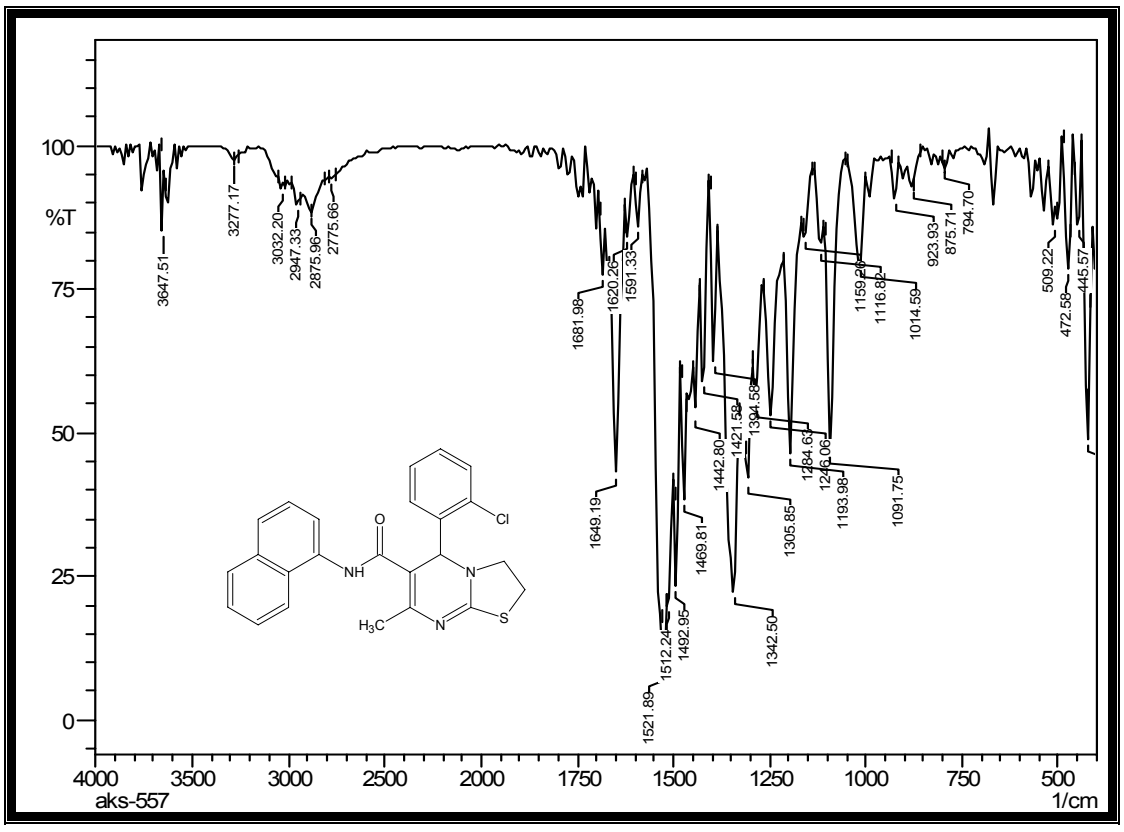
2.6.6.12 IR spectrum of AKS-240



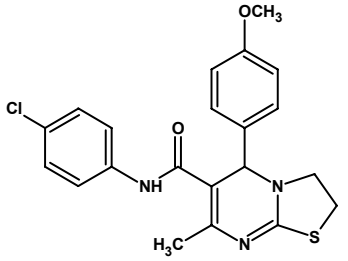
2.6.6.13 IR spectrum of AKS-245

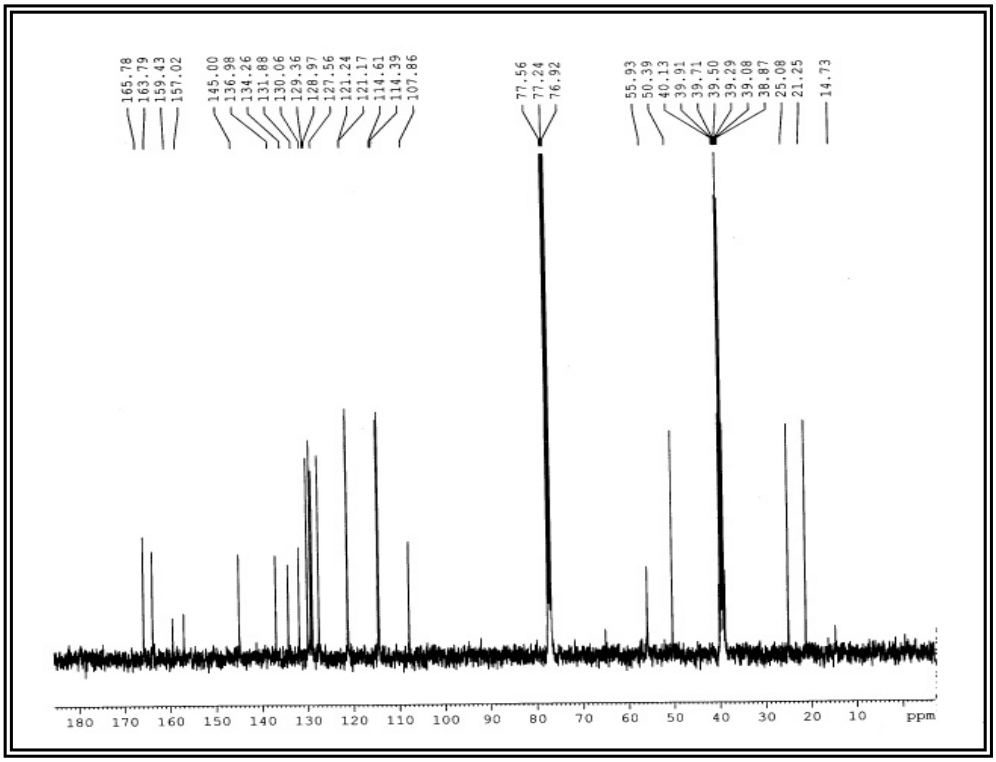


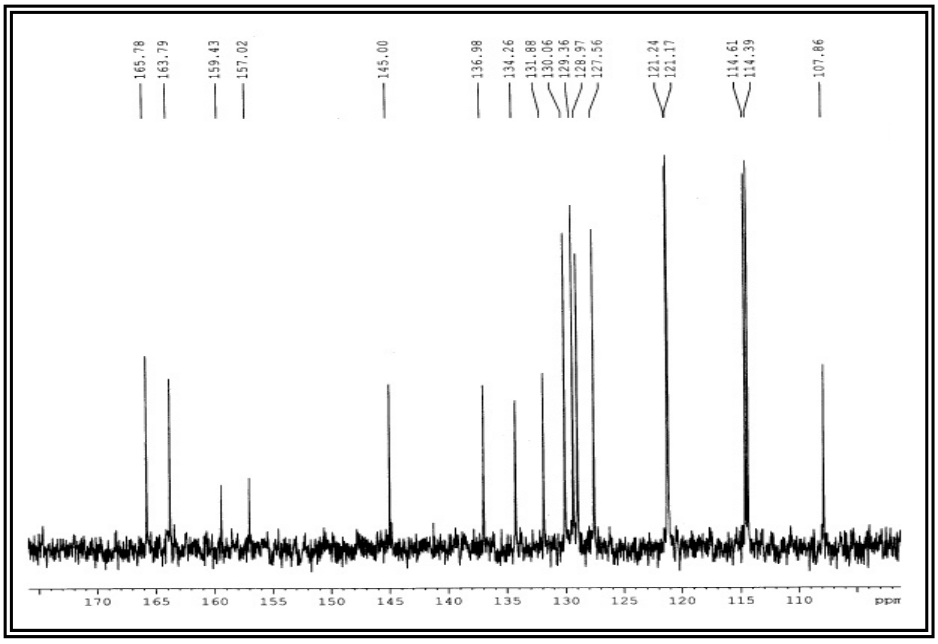
2.6.6.14 IR spectrum of AKS-247



2.6.6.15 ^{13}C NMR spectrum of AKS-235







2.7 References

1. Dallinger, D.; Stadler, A. and Kappe, C. O.; *Pure Appl. Chem.* **2004**, 76, 1017-1024.
2. Dallinger, D.; Gorobets, N. Y. and Kappe, C. O.; *Org. Lett.* **2003**, 5, 1205-1208.
3. Nagarathnam, D.; Miao, S. W.; Lagu, B.; Chiu, G.; Fang, J.; Dhar, T. G. M.; Zhang, J.; Tyagarajan, S.; Marzabadi, M. R.; Zhang, F. Q.; Wong, W. C.; Sun, W. Y.; Tian, D.; Wetzel, J. M.; Forray, C.; Chang, R. S. L.; Broten, T. P.; Ransom, R. W.; Schorn, T. W.; Chen, T. B.; O'Malley, S.; Kling, P.; Schneck, K.; Benedesky, R.; Harrell, C. M.; Vyas, K. P.; Gluchowski, C. *J. Med. Chem*. **1999**, 42, 4764-4777.
4. Barrow, J. C.; Nantermet, P. G.; Selnick, H. G.; Glass, K. L.; Rittle, K. E.; Gilbert, K. F.; Steele, T. G.; Homnick, C, F.; Freidinger, R. M.; Ransom, R. W.; Kling, P.; Reiss, D.; Broten, T. P.; Schorn, T. W.; Chang, R. S. L.; O'Malley, S. S.; Olah, T. V.; Ellis, J. D.; Barrish, A.; Kassahun, K.; Leppert, P.; Nagarathnam, D.; Forray, C. *J. Med. Chem*. **2000**, 43, 2703-2718.
5. Dallinger, D.; Gorobets, N. Y.; Kappe, C. O. *Mol. DiVersity* **2003**, *7*, 229-245.
6. Wannberg, J.; Dallinger, D.; Kappe, O. and Larhed. M.; *J. Comb. Chem.* **2005,** *7,* 574-583.
7. Kappe, C. O.; Fabian, W. M. F.; Semones, M. A. *Tetrahedron* **1997**, *53*, 2803-2816.
8. Kappe, C. O.; Shishkin, O. V.; Uray, G.; Verdino, P. *Tetrahedron* **2000**, *56*, 1859-1862.
9. Rovnyak, G. C.; Kimball, S. D.; Beyer, B.; Cucinotta, G.; DiMarco, J. D.; Gougoutas, J.; Hedberg, A.; Malley, M.; McCarthy, J. P.; Zhang, R.; Moreland, S. *J. Med. Chem.***1995**, *38*, 119-127.
10. Namazi, H.; Mirzaei, Y. R.; Azamat, H. *J. Heterocycl. Chem.***2001**, *38*, 1051-1054.
11. Lewandowski, K.; Murer, P.; Svec, F.; Frechet, J. M. J. *J.Comb. Chem.* **1999**, *1*, 105-112.
12. Tsuji, T.; **1991** *J. Heterocycl. Chem.,* 28, 489.
13. Jacobson, M.A. and Norton, R.; **1997** PCT Int. Appl. *WO 97 33,879*; *Chem. Abstr.,* 127,293241.
14. El-kerdawy, M.M.; Moustafa, M.A.; Gad, L.M. and Badr, S.M.E.; **1993** *Bull Fac. Pharm. (Cairo Univ.),* 31(1), 67; **1994** *Chem. Abstr.,* 121, 57472b.
15. Sharma, S; Khanna, M.S.; Garg, C.P.; Kapoor, R.P.; Kapil A. **1993** *Indian J. Chem.*
16. Takenaka, K. and Tsuji, T.; **1996** *J. Heterocycl. Chem.,* 33, 1367.
17. Kutyrev, A. and Kappe, T.; **1999** *J. Heterocycl. Chem.,* 36, 237.
18. Shridhar, D.R.; Jogibhukta, M. and Krishnan, V.S. **1986** *Indian J. Chem. See. B,* 25B(3), 345.
19. Shioiri, T.; Ninomija, K.and Yamada, S.; **1972** *J. Am. Chem. Soc.,* 94, 6203.
20. Mishina, T.; Tsuda, N.; Inui, A. and Miura, Y. **1987** Jpn. Kokai Tokkyo Koho *JP 62,169,793*; **1988** *Chem. Abstr.,* 108, 56120e.
21. Selic, L.; Grdadolnik, S.G. and Stanovnik, B.; **1997** *Heterocycles***,** 45(12), 2349.
22. Sorsak, G.; Grdadolnik, S.G.and Stanovnik, B.; **1998** *J. Heterocycl. Chem.,* 35, 1275.
23. Selic, L. and Stanovnik, B.; **1997** *J. Heterocycl. Chem.***,** 34, 813.
24. Sorsak, G.; Sinur, A.; Colic, L. and Stanovnik, B.; **1995** *J. Heterocycl. Chem., 32***,** 921.
25. Stanovnik, B.; Bovenkamp, H. Van de; Svete, J.; Hvala, A.; Simonic, I. and Tisher, M.; **1990** *J. Heterocycl. Chem.,* 21, 359.

26. Liu, Y.S. and Uang , W. H.; **1997** *J. Chem. Soc. Perkin Trans.,* 1(6), 981.
27. Janietz, D.; Goldmann, B. and Rudorf, W.D.; **1988** *J. Prakt. Chem.,* 330(4), 607.
28. Giudice, M.R.D.; Borioni, A.; Mustazza, C.; Gatta, F.; and Stanovnik, B.; **1995** *J. Heterocycl. Chem.,* 32, 1725.
29. Metwally, M.A.; Ismaiel, A.M.; Yousif, Y.M.and Eid, F.; *J. Indian Chem. Soc.* **1989** 66,3, 179.
30. Malesic, M.; Krbavcic, A. and Stanovnik, B.; *J. Heterocycl. Chem.* **1997,** 34, 49.
31. Sauter, F.; Frohlich, J.; Chowdhury, A.Z.M.S. and Hametner, C.; *Monatsh. Chem,* **1997,** 128, 503.
32. Giandinoto, S.; Mbagwu, G.O.; Robinson, T.A.; Ferguson, C. and Nunez, J.; *J. Heterocycl. Chem.* **1996** 33, 1839.
33. Melo, S.J. De and Luu-Duc, C.; *J. Chem. Res. (S)* **1992,** 286.
34. Sauter, F.; Frohlich, J.; Chowdhury, A.Z.M.S. and Hametner, C.; *Monatsh. Chem.* **1997,** 128, 503.
35. Abdel-Aziz, S.A.; *Phosphorus. Sulfur Silicon Relat. Elem.,* **1996,** 116, 39.
36. Manhi, M. and Abdel-Fattah, A.M.; *Egypt. J. Pharm.,* **1992** 33, 825; **1994** *Chem. Abstr.,* 121,83254b.
37. Ghorab, M.; Mohamed, Y.A.; Mohamed, S.A. and Ammar, Y.A.; *Phosphorus, Sulfur Silicon Relat. Elem.,* **1996,** 108(1-4), 249.
38. Ghoneim, K.M.; Essawi, M.Y.H.; Mohamed, M.S. and Kamal, A.M.; *Pol. J. Chem.,* **1998,** 72(7), 1173.
39. Mohamoud, M.R.; Soliman A.Y. and Bakeer, H.M.; *Indian J. Chem. Sec. B,* **1990** 29B(9), 830.
40. Champaneri, H.R.; Modi, S.R.; and Naik, H.B.; *Asian J. Chem.,* **1994** 6(3), 737; **1994** *Chem. Abstr.,* 121, 300842.
41. Moustafa, H.Y.; *Indian J. Heterocycl. Chem.,* **1998** 7(4), 273.
42. Salama, M.A.; Mousa, H.H. and Al-Shaikh, M.; *Orient. J. Chem.* **1991** 7(4), 185; **1992** *Chem. Abstr.,* 116**,** 151713.
43. Sharaf, M.A.F.; Abdel Aal, F.A.; Abdel Fattah, A.M. and Khalik, A.M.R.; *J. Chem. Res. (S),* **1996** 354.
44. Tozkoparan, B.; Ertan, M.; Kelicen, P. and Demirdamar, R.; *Farmaco***, 1999** 54(9), 588.
45. Akhtar, M.S.; Seth, M. and Bhaduri, A.P.; *Indian* J. *Chem. Sec. B***, 1987** 26B (6), 556.
46. Salama, M.A.; Mousa, H.H.A.; and El-Essa, S.A.; *Orient. J. Chem.,* **1991** 7(3), 128; **1992** *Chem. Abstr,* 116, 41405t.
47. Abdel-Rahman, R.M.; Fawzy, M. and El-Baz, I.; *Pharmazie***, 1994** 49, 729.
48. Kappe, C.O. and Roschger, P.; *J. Heterocycl. Chem.,* **1989** 26, 55.
49. Abdel-Aziz, S.A.; Allimony, H.A.; El-Shaaer, H.M.; Ali, U.F. and Abdel-Rahman, R.M.; *Phosphorus, Sulfur Silicon Relat. Elem.,* **1996** 113, 67.
50. Pecoran, P.; Rinaldi, M.; Costi, M.P. and Antolini, L.; *J. Heterocycl. Chem.,* **1991** 28, 891.
51. Biagi, G.; Costantini, A.; Costantino, L.; Giorgi, I.; Livi, O.; Pecorari, P.; Rinaldi, M. and Scartoni, V.; *J. Med. Chem.* **1996,** *39,* 2529-2535.
52. Bo´szing, D.; Soha´r, P.; Gigler, G.; Kova´ cs, G. *Eur. J. Med. Chem*. **1996**, *31*, 663.
53. Geo, A.; Sabine, K.; Vincent, M.; Jurgen, W.; *US patent 5958931*, **1999**
54. Shigenori, O.; Naoyuki, K.; Seiji, M.; *US patent 6583146*, **2003**.

55. Kappe, C. O.; Färber, G. *J. Chem. Soc., Perkin Trans.1* **1991**, 1342.

56. Pe´rez, R.; Beryozkina, T.; Zbruyev, O. I.; Haas, W. and Kappe, C. O.; *J. Comb. Chem.* **2002,** *4,* 501-510

Chapter 3

Microwave assisted synthesis of N-(substitutedphenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxo-4-propylpyrimidine-5-carboxamide and thiazolo, thiazino & thiazepino benzimidazole

Chapter 3

Microwave assisted synthesis of N-(substitutedphenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxo-4-propylpyrimidine -5-carboxamide and thiazolo, thiazino & thiazepino benzimidazole

3.1 Biginelli Reaction: problems associated with conventional methods

First chapter deals with synthesis and characterization of DHPMs with N-phenyl substitution and second chapter covers synthesis of bicyclic systems derived from DHPM. Importance of Biginelli reaction is very well described and recent development on this more than hundred year old reaction is also briefly reviewed.

The major limitations of Biginelli reaction are lower yield and longer reaction time. When thiourea is used for synthesis, yield obtained is very low and reaction completion takes longer time. Similar disadvantages are observed when different 1,3-diketone and aldehyde other than aromatic are used for the synthesis of designed molecules. Moreover, product separation and work up also cause problem and needed special techniques. Thus, three main disadvantages are lower yield, longer reaction time and work up in Biginelli reaction when different building blocks are used to synthesize library of compound.

3.2 Microwave Assisted Organic Synthesis

The use of microwave as energy source in organic synthesis for better yield and shorter reaction time has been extensively investigated[1-6]. Most of the early pioneering experiments in MAOS were performed in domestic, sometimes modified, kitchen microwave ovens; the current trend is to use dedicated instruments which have only become available in the last few years for chemical synthesis. The number of publications

related to MAOS has therefore increased dramatically since the late 1990s to a point where it might be assumed that, in a few years, most chemists will probably use microwave energy to heat chemical reactions on a laboratory scale. Not only is direct microwave heating able to reduce chemical reaction times from hours to minutes, but it is also known to reduce side reactions, increase yields, and improve reproducibility. Therefore, many academic and industrial research groups are already using MAOS as a forefront technology for rapid optimization of reactions, for the efficient synthesis of new chemical entities, and for discovering and probing new chemical reactivity. A large numbers of review articles provide extensive coverage of the subject[7-12].

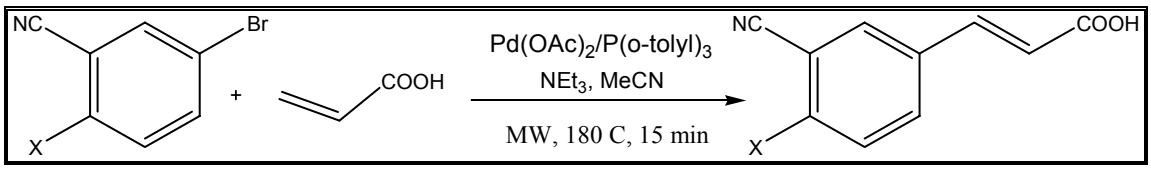
Microwave-enhanced chemistry is based on the efficient heating of materials by "microwave dielectric heating" effects. This phenomenon is dependent on the ability of a specific material (solvent or reagent) to absorb microwave energy and convert it into heat. The electric component of an electromagnetic field causes heating by two main mechanisms: dipolar polarization and ionic conduction. Irradiation of the sample at microwave frequencies results in the dipoles or ions aligning in the applied electric field. As the applied field oscillates, the dipole or ion field attempts to realign itself with the alternating electric field and, in the process, energy is lost in the form of heat through molecular friction and dielectric loss. The amount of heat generated by this process is directly related to the ability of the matrix to align itself with the frequency of the applied field. If the dipole does not have enough time to realign, or reorients too quickly with the applied field, no heating occurs. The allocated frequency of 2.45 GHz used in all commercial systems lies between these two extremes and gives the molecular dipole time to align in the field, but not to follow the alternating field precisely[13-14].

The heating characteristics of a particular material (for example, a solvent) under microwave irradiation conditions are dependent on its dielectric properties. The ability of a specific substance to convert electromagnetic energy into heat at a given frequency and temperature is determined by the so-called loss factor tanδ. This loss factor is expressed as the quotient $\tan\delta = e''/e'$, where e'' is the dielectric loss, which is indicative of the efficiency with which electromagnetic radiation is converted into heat, and e' is the dielectric constant describing the ability of molecules to be polarized by the electric field. A reaction medium with a high tanδ value is required for efficient absorption and, consequently, for rapid heating[15].

Solvent	tanδ	Solvent	tanδ
ethylene glycol	1.350	DMF	0.161
ethanol	0.941	1,2-dichloroethane	0.127
DMSO	0.825	water	0.123
2-propanol	0.799	chlorobenzene	0.101
formic acid	0.722	chloroform	0.091
methanol	0.659	acetonitrile	0.062
nitrobenzene	0.589	ethyl acetate	0.059
1-butanol	0.571	acetone	0.054
2-butanol	0.447	tetrahydrofuran	0.047
1,2-dichlorobenzene	0.280	dichloromethane	0.042
NMP	0.275	toluene	0.040
acetic acid	0.174	hexane	0.020

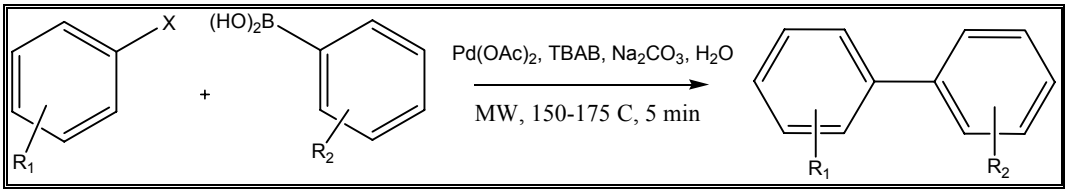
3.2.1 Name reactions

Following scheme shows an example of a standard Heck reaction involving aryl bromides and acrylic acid to furnish the corresponding cinnamic acids. Optimization of the reaction conditions under small-scale (2 mmol) single-mode microwave conditions led to a protocol that employed acetonitrile as the solvent, 1 mol% palladium acetae/p-tolyl phosphine as the catalyst system, and triethylamine as the base. The reaction time was 15 minutes at a reaction temperature of 180ºC.

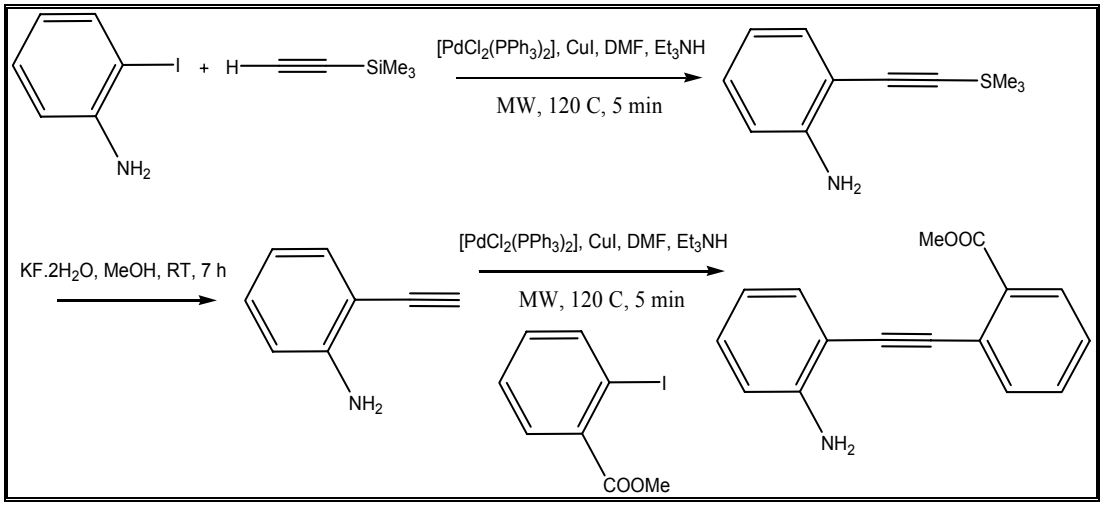


The Suzuki reaction (the palladium-catalyzed cross-coupling of aryl halides with boronic acids) is arguably one of the most versatile and at the same time also one of the most often used cross-coupling reactions in modern organic synthesis. Carrying out high-speed Suzuki reactions under controlled microwave conditions can be considered almost a routine synthetic procedure today, given the enormous literature precedent for this transformation. Recent examples include the use of the Suzuki protocol for the high-speed modification of various heterocyclic scaffolds of pharmacological interest[16-24].

A significant advance in Suzuki chemistry has been the observation that Suzuki couplings can be readily carried out using water as the solvent in conjunction with microwave heating[25-28].

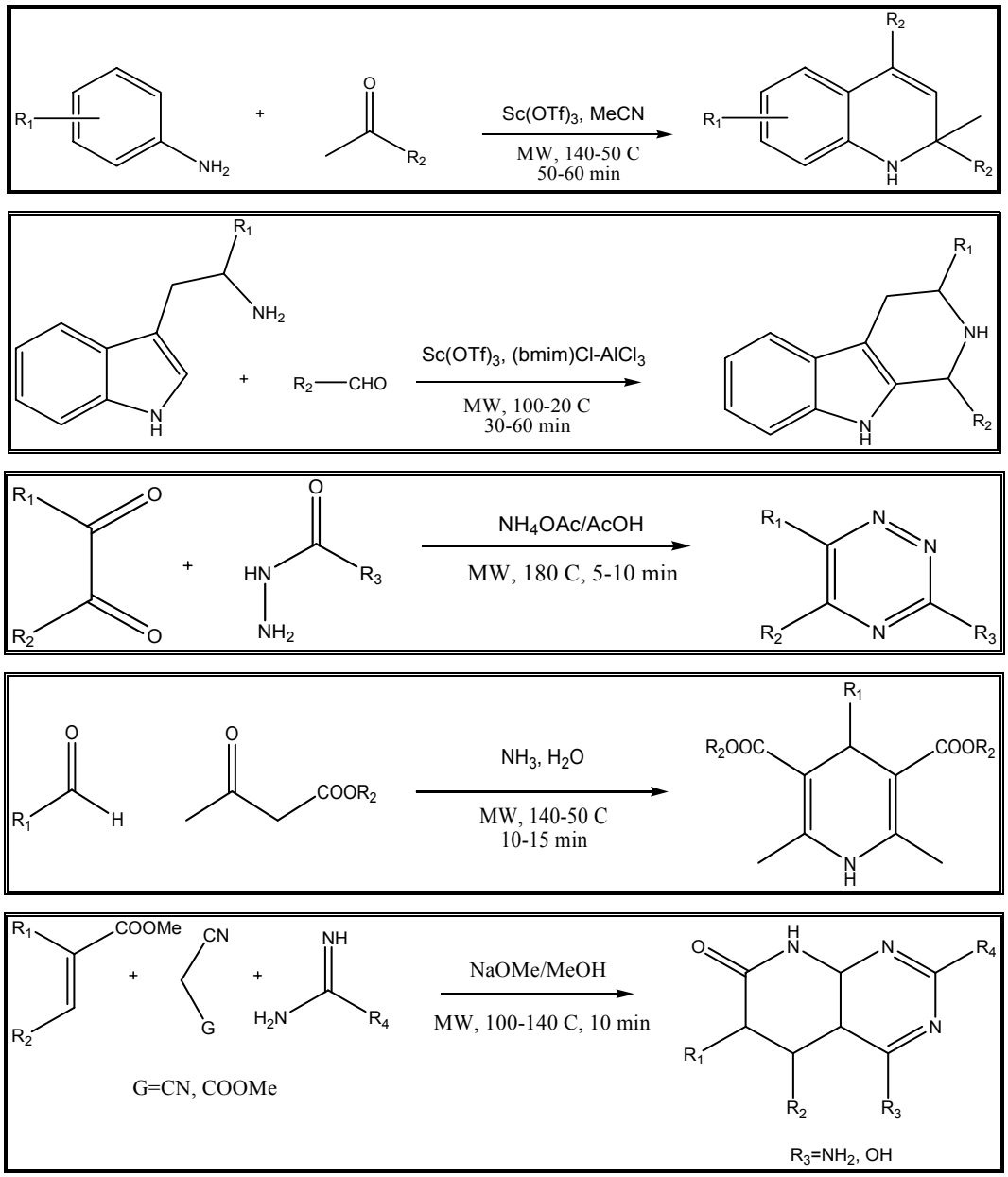


General protocols for microwave-assisted Sonogashira reactions under controlled conditions were first reported in 2001 by ErdMlyi and Gogoll[35-36]. Many more examples can be cited for different name reaction.



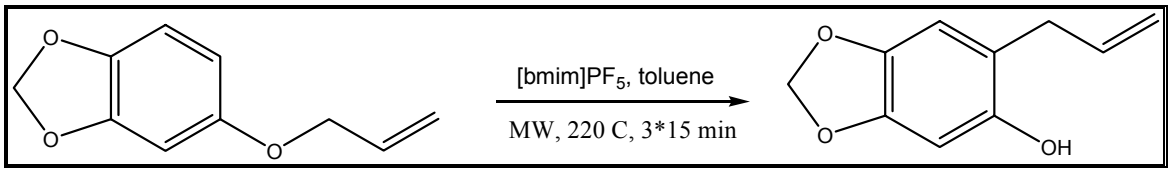
3.2.2 Heterocyclic systems

Various heterocyclic systems can be synthesized in short time with high yield. Heterocyclic systems like dihydroquinolone, triazine, dihydropyridines and other bicyclic systems are reported in literature synthesized using microwave[29-33]. Few examples are shown below.

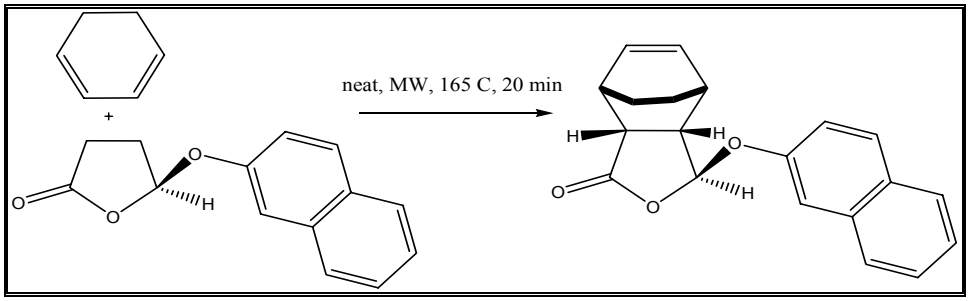


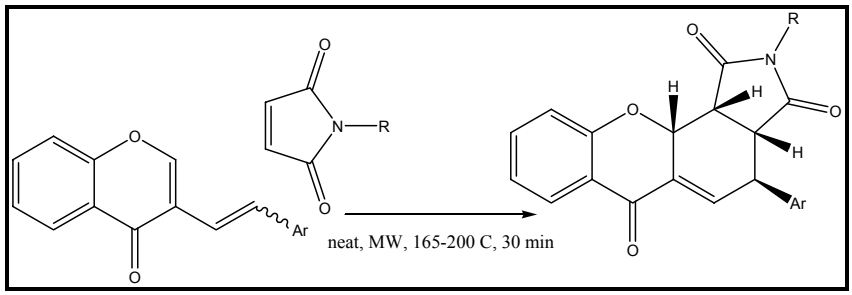
3.2.3 Rearrangements

Ley and co-workers[34] have described the microwave assisted Claisen rearrangement of allyl ether in their synthesis of the natural product carpanone. A 97% yield of the rearranged product could be obtained by three successive 15-minute irradiations at 220 ºC. This is an example of microwave assisted reaction clubbed with ionic liquid.



3.2.4 Cycloaddition reaction

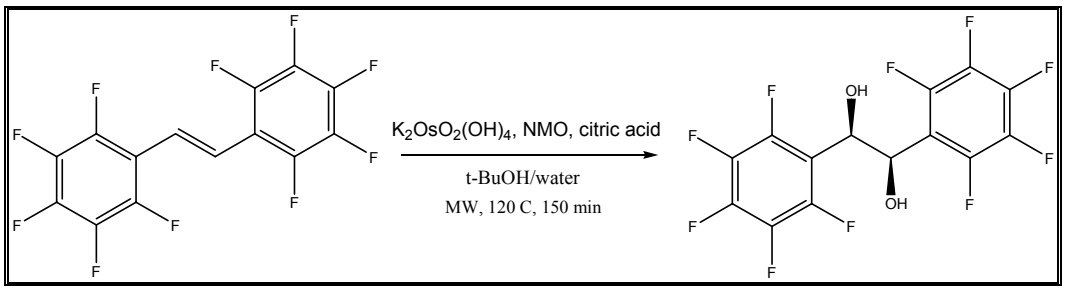




Above scheme display microwave assisted diles alder reaction in neat condition without using any solvent. First process gave 97% yield in 20 min. in second process, diastereomers were obtained.[37-38]

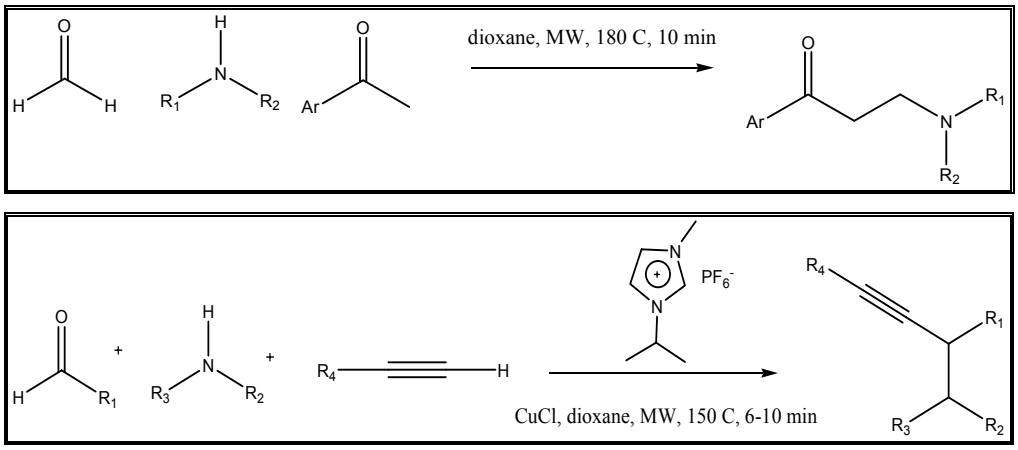
3.2.5 Oxidation

The osmium-catalyzed dihydroxylation reaction, the addition of osmium tetroxide to olefins to produce a vicinal diol, is one of the most selective and reliable organic transformations. Recent work by Sharpless, Fokin, and coworkers[39] has uncovered that electron-deficient olefins can be converted into the corresponding diols much more efficiently when the reaction medium is kept acidic.



3.2.6 Multicomponent Reaction

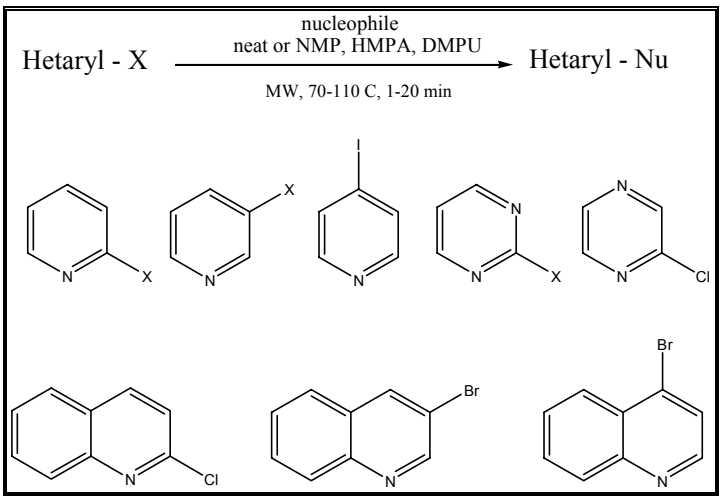
The Mannich reaction has been known since the early 1900s and has since then been one of the most important transformations to produce β-amino ketones. Although the reaction is powerful, it suffers from some disadvantages, such as the need for drastic reaction conditions, long reaction times, and sometimes low yields of products. Luthman and coworkers[40] have reported microwave-assisted Mannich reactions that employed paraformaldehyde as a source of formaldehyde, a secondary amine in the form of its hydrochloride salt, and a substituted acetophenone.



3.2.7 Nucleophilic Aromatic Substitution

A number of publications report efficient nucleophilic aromatic substitutions driven by microwave heating involving either halogen substituted aromatic or heteroaromatic systems. Scheme given below summarizes some heteroaromatic systems and nucleophiles along with the reaction conditions that have been developed by Cherng for microwave-assisted nucleophilic substitution reactions. In general, the microwave-driven processes

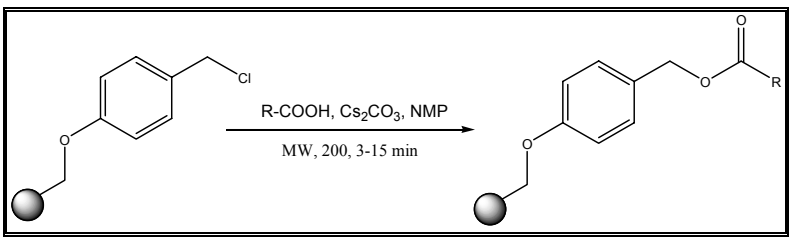
provide significantly higher yields of the desired products in much shorter reaction times[41-45].



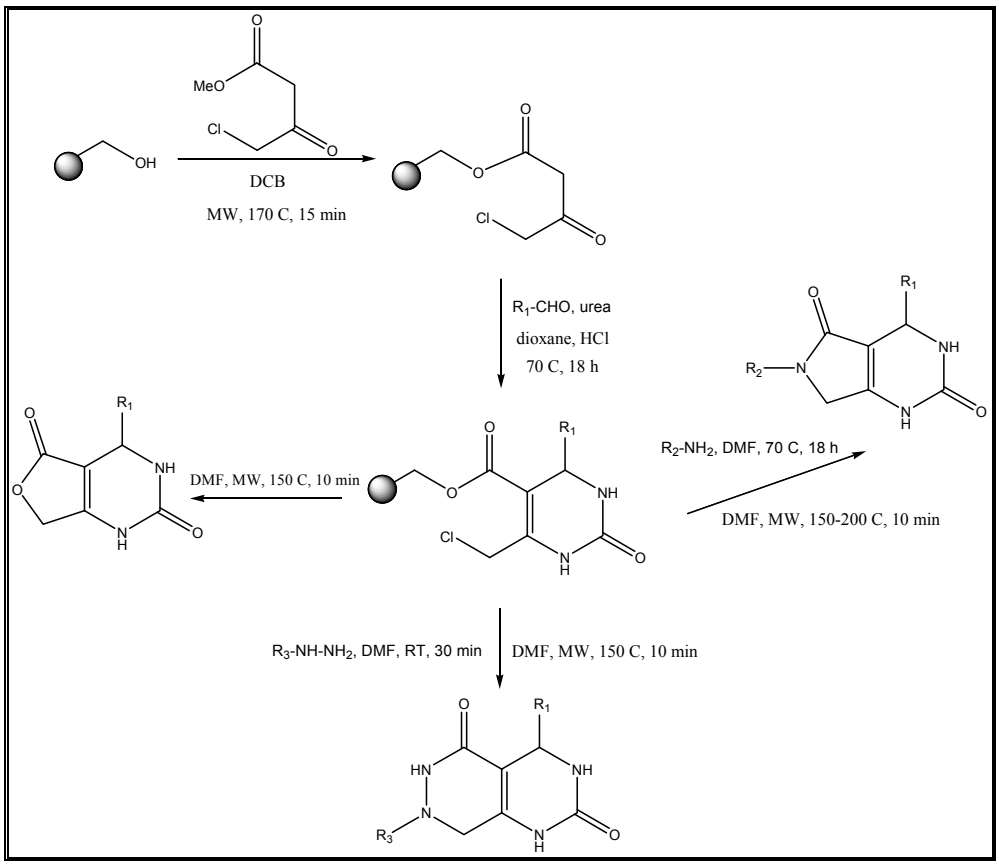
3.2.8 Solid Phase Organic Synthesis

Solid-phase organic synthesis (SPOS) exhibits several advantages compared with classical protocols in solution. Reactions can be accelerated and driven to completion by using a large excess of reagents, as these can easily be removed by filtration and subsequent washing of the solid support. In addition, SPOS can easily be automated by using appropriate robotics and applied to "split-and-mix" strategies, useful for the synthesis of large combinatorial libraries[46-47]

A study published in 2001 demonstrated that high temperature microwave heating (200 8C) can be effectively employed to attach aromatic carboxylic acids to chloromethylated polystyrene resins (Merrifield and Wang) by the cesium carbonate method. Significant rate accelerations and higher loadings were observed when the microwave-assisted protocol was compared to the conventional thermal method. Reaction times were reduced from 12–48 hours with conventional heating at 80 ºC to 3–15 minutes with microwave heating at 200 ºC in NMP in open glass vessels[48-49].



Kappe et al[50] have reported microwave assisted synthesis of bicyclic systems derived from Biginelli DHPM derivatives.


MeO
Cl
OH
DCB
MW, 170 C, 15 min
R1-CHO, urea
dioxane, HCl
70 C, 18 h
R2-NH2, DMF, 70 C, 18 h
DMF, MW, 150-200 C, 10 min
DMF, MW, 150 C, 10 min
R3-NH-NH2, DMF, RT, 30 min
DMF, MW, 150 C, 10 min

3.3 Current work

Work done earlier in our lab on 1,4-dihydropyridine and interesting results obtained for this structural class inspire to modify aza analogs of 1,4-dihydropyridine i.e. dihydropyrimidine. Earlier library of compounds was generated of dihydropyrimidine derivatives with phenyl carbamoyl moiety at C_5 position. Moderate pharmacological profile obtained for this library. In continuation of work, it was planned to develop various modified compounds of this class.

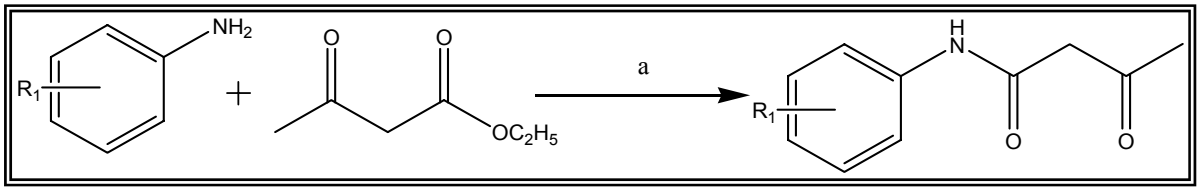
In earlier chapters, synthesis of dihydropyridine derivatives is reported with N-phenyl substitution and phenyl carbamoyl moiety at C_5 position; and bicyclic systems with phenyl carbamoyl moiety at C_5 position. In this chapter, phenyl ring at C_4 position of classical dihydropyrimidine is replaced with aliphatic chain. The current chapter deals with an aliphatic aldehyde (butyraldehyde) as a substrate to obtain a dihydropyrimidine skeleton without phenyl or heteroaryl ring at C_4. The aim of this work was to develop small library of novel DHPM compounds which give diversity from earlier ones. When the reactions carried out by conventional methods, very long reaction time (12-15 hours) and very low yield (10-12%) cause major problem in synthesizing series of compounds with 4-alkyl substitutions.

To overcome these problems, microwave irradiation technique was utilized and higher yields (30-35%) within shorter reaction time (10-15 minutes) were obtained. Different solvent were used (methanol, ethanol, THF, acetonitrile, DMF) but methanol was found to be most suitable. The synthesized compounds were analyzed by IR, NMR and Mass spectral techniques. The physical data is given in Table 3.6.2.

In another scheme, benzimidazole-2-thiol was reacted with dibromo alkanes under microwave irradiation to cyclize the ring fused to imidazole. In conventional method, the reaction time was observed 2.5-3 hours, while under microwave, the reaction completed within 4-7 minutes. The physical data of synthesized compounds are given in Table 3.6.2.

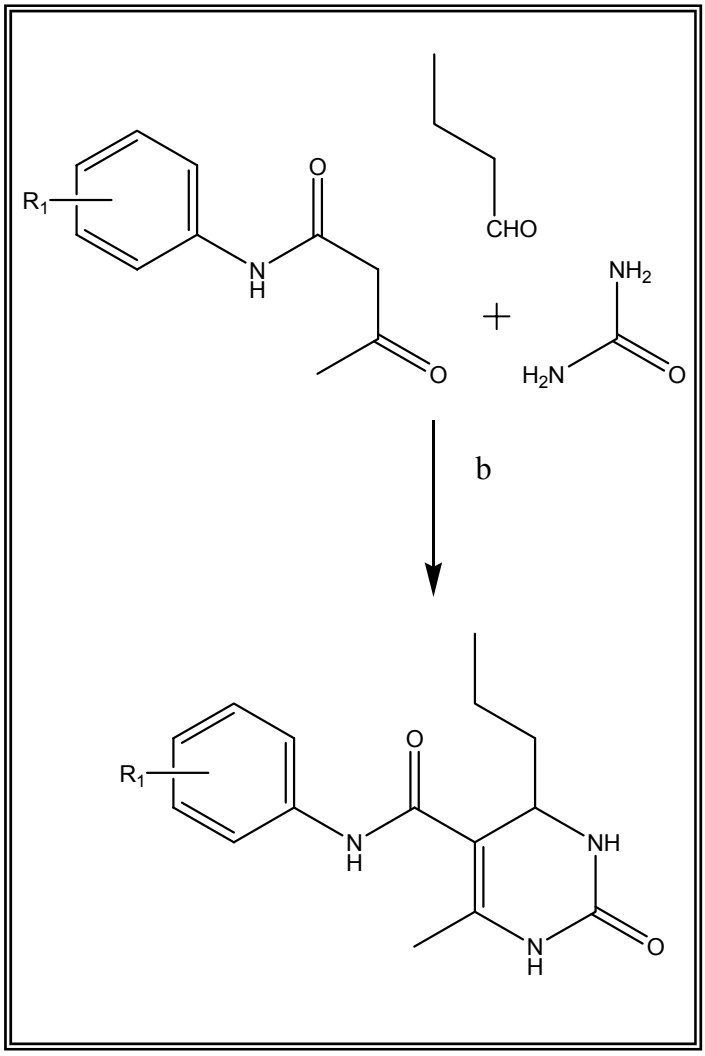
3.4 Reaction Schemes

3.4.1 Scheme 1.



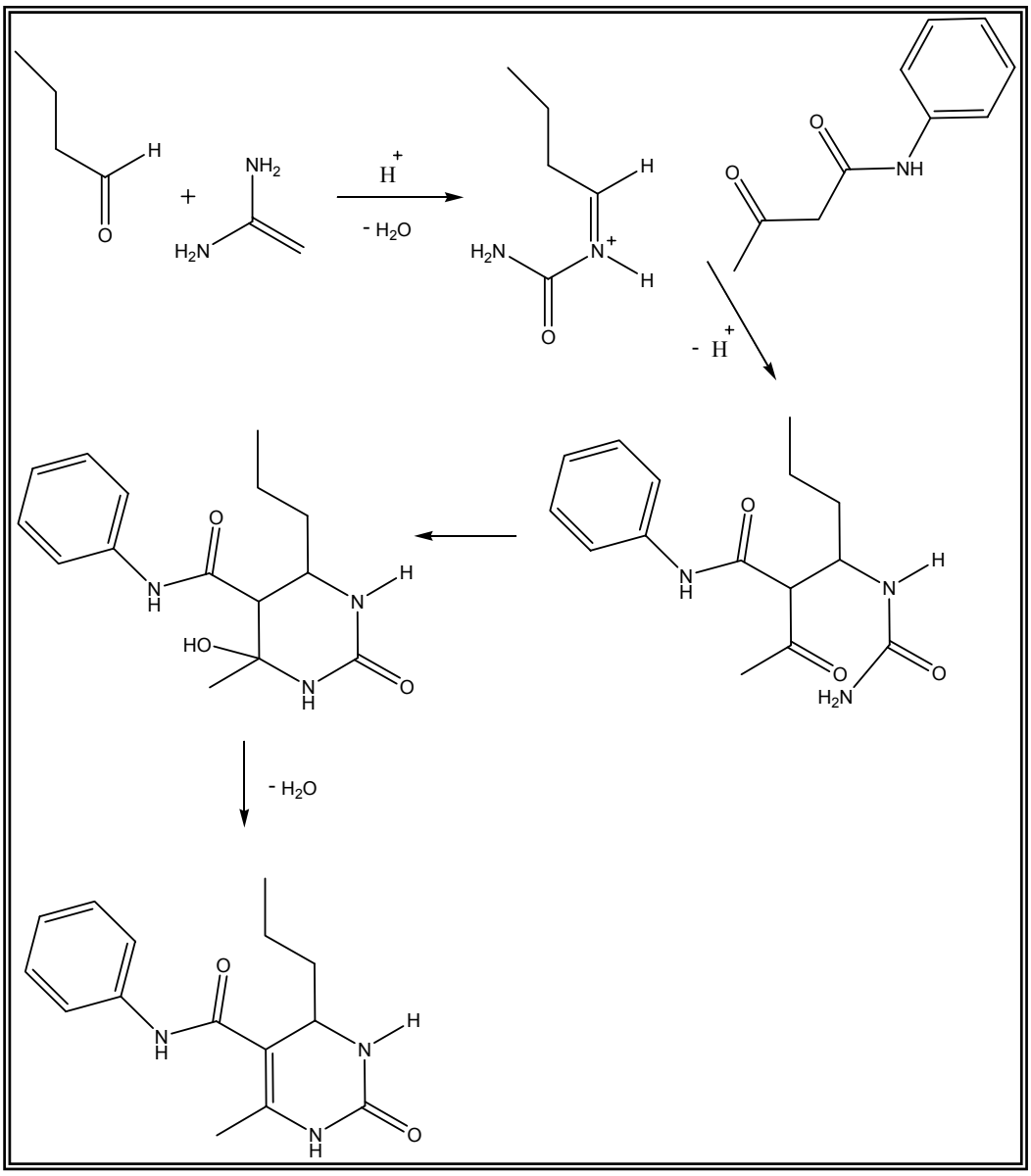
Scheme 1. Reagents and conditions: a = KOH/NaOH, toluene, 115° C.

3.4.2 Scheme 2.

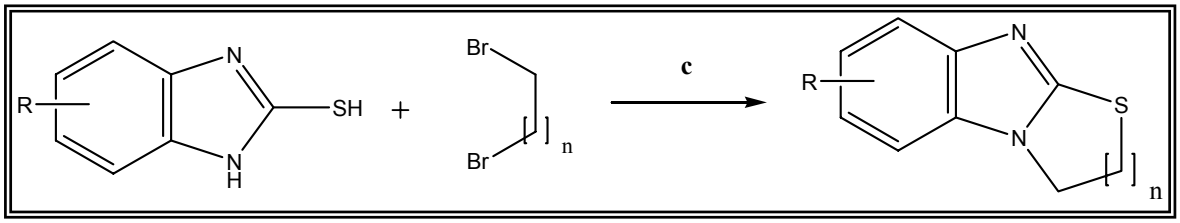


Scheme 2. Reagents and conditions: b = MeOH, con. HCl, MW (200W), 90º C

Reaction Mechanism

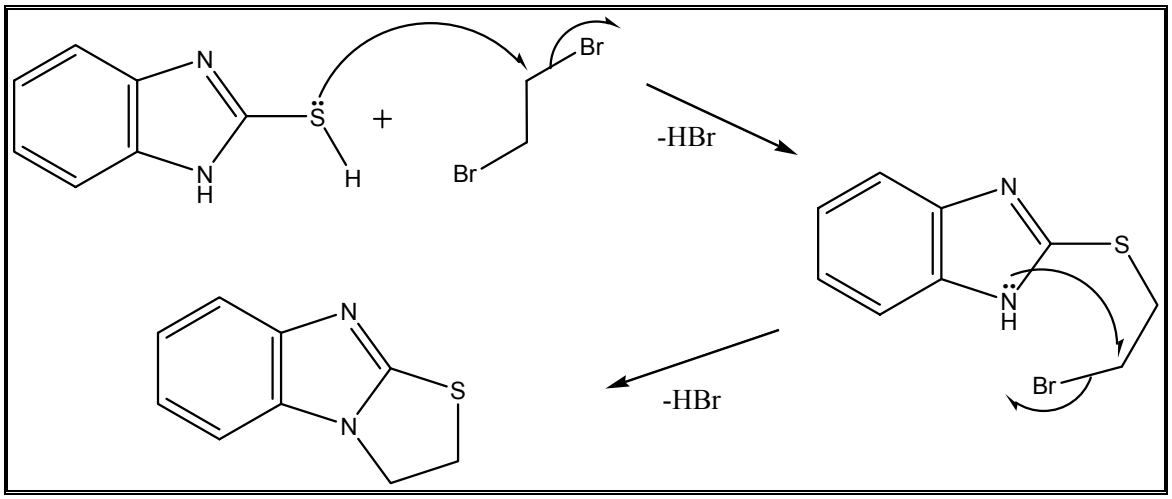


3.4.3 Scheme 3.



Scheme 3. Reagents and conditions: c = DMF, MW (200W), 150º C

Reaction Mechanism



3.5 Experimental

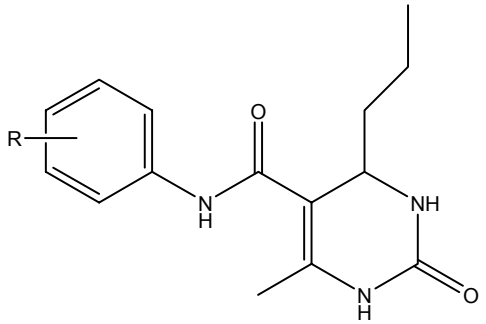
3.5.1 Substituted acetoacetanilide: It was prepared as described in Section 1.7.2, Chapter 1.

3.5.2 N-(substitutedphenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxo-4-propylpyrimidine -5-carboxamide: Substituted acetoacetanilide (0.01M), butyraldehye and urea were dissolved in methanol and few drops of HCl were added. The reaction mixture was irradiated with microwave (200W) at 80° C for 12-15 minutes. The completion of reaction was monitored by thin layer chromatography. The reaction mixture was allowed to stand at room temperature. The solid separated was filtered and recrystallized from dimethylformamide. (Physical data are given in Table 3.6.1)

3.5.3 6-methoxy-2,3-dihydro[1,3]thiazolo[3,2-*a*]benzimidazole: 6-methoxy-1*H*-benzimidazole-2-thiol and dibromo ethane were taken into dimethylformamide and irradiated with microwave (200W) at 150° C for 4-7 minutes. The completion of reaction was monitored with thin layer chromatography. It was extracted with chloroform. The solvent was evaporated and solid was dried and crystallized from dimethylformamide. (Physical data are given in Table 3.6.2)

3. 6 Physical data tables

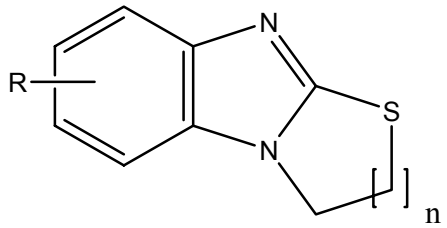
3.6.1 Physical data of N-(substitutedphenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxo-4-propylpyrimidine -5-carboxamide [compounds 2a-o]



Compound	Code	R	MF	MW	Yield	Mp	R_f
2a	AKS-321	H	$C_{15}H_{19}N_3O_2$	273.26	32	170-71	0.41
2b	AKS-322	4-Cl	$C_{15}H_{18}ClN_3O_2$	307.77	36	185-86	0.53
2c	AKS-323	4-F	$C_{15}H_{18}FN_3O_2$	291.24	30	210-11	0.55
2d	AKS-324	3-Cl,4-F	$C_{15}H_{17}ClFN_3O_2$	325.76	28	168-69	0.47
2e	AKS-325	4-Me	$C_{16}H_{21}N_3O_2$	287.35	33	177-79	0.61

2f	AKS-326	2,3-benzo	$C_{19}H_{21}N_3O_2$	323.38	35	160-63	0.58
2g	AKS-327	2-Cl	$C_{15}H_{18}ClN_3O_2$	307.77	36	201-03	0.44
2h	AKS-328	4-NO_2	$C_{15}H_{18}N_4O_4$	318.32	29	213-14	0.50
2i	AKS-329	3-Me	$C_{16}H_{21}N_3O_2$	287.35	32	188-90	0.59
2j	AKS-330	3,4-di-Me	$C_{17}H_{23}N_3O_2$	301.45	34	196-98	0.63
2k	AKS-331	2-Me	$C_{16}H_{21}N_3O_2$	287.35	36	205-08	0.58
2l	AKS-332	2,4-di-Me	$C_{17}H_{23}N_3O_2$	301.45	34	175-77	0.52
2m	AKS-333	2,5-di-Me	$C_{17}H_{23}N_3O_2$	301.45	33	182-83	0.46
2n	AKS-334	3-NO_2	$C_{15}H_{18}N_4O_4$	318.32	26	210-12	0.40
2o	AKS-335	2-CF_3	$C_{18}H_{18}F_3N_3O_2$	341.32	32	200-02	0.61

3.6.2 Physical data [compounds 3a-f]



Compound	Code	R	n	MF	MW	Yield	Mp	R_f
3a	AKS-341	H	1	$C_9H_8N_2S$	176.23	62	177-79	0.46
3b	AKS-342	H	2	$C_{10}H_{10}N_2S$	190.26	68	182-85	0.50
3c	AKS-343	H	3	$C_{11}H_{12}N_2S$	204.29	70	180-83	0.47
3d	AKS-344	6-OMe	1	$C_{10}H_{10}N_2OS$	206.26	65	190-191	0.52
3e	AKS-345	6-OMe	2	$C_{11}H_{12}N_2OS$	220.29	70	205-07	0.58
3f	AKS-346	6-OMe	3	$C_{12}H_{14}N_2OS$	234.31	70	196-98	0.55

TLC solvent system: Compound 2a-o (EA:Hexane) 4:6
Compound 3a-f ($CHCl_3$:MeOH) 0.5:9.5

MPs were taken in open capillary and are not corrected

3.7 Spectral discussion

3.7.1 Mass spectral study

Molecular ion peak was obtained in agreement of molecular weight of the molecules. Specific fragmentation pattern was observed. For example, in mass spectrum of AKS-322, following characteristic peaks were obtained. Similar pattern was observed in other Mass spectra also.

[1] M^{+2} peak was obtained at 309 m/e because of chlorine atom.

[2] Molecular ion peak was obtained at 307 m/e.

[3] Cleavage of alkyl chain at C-4 position gave peak at 264 m/e. [M- (CH_2-CH_2-CH_3)].

[4] Cleavage of α-bond of carbonyl gave base peak at 181 m/e.

[5] Cleavage of other α-bond of carbonyl gave peak at 153 m/e.

3.7.2 IR spectral study

In IR spectrums, characteristic frequencies were observed for functional group present in the molecule. N-H groups are present in DHPM derivatives and characteristic frequencies were observed at 3320-3450 cm^{-1}. Alkyl chain gave characteristic methyl and methylene frequencies. Two carbonyl groups were distinctly observed. Cyclic carbonyl group gave peak at 1680-1710 cm^{-1}, while amide carbonyl group gave peak at lower value (1650-1690 cm^{-1}). Aromatic protons were also identified in specific frequency region for aromatic C-H stretching, aromatic C=C and out of plane bending vibrations.

3.7.3 ^{1}H NMR spectral study

Number of protons and their chemical shifts were found to support the structure of the synthesized compounds. In NMR spectrum of AKS-245, -CH_2- protons were obtained as multiplet between 2.45-4.14 δ ppm. Methoxy protons were identified at 3.84 δ ppm. Three aromatic protons gave two doublets and one double doublet and it can be 1,2,4-trisubstituted aromatic ring signal pattern. Proton on C_3 position gave doublet with J value for meta coupling while, proton on C_6 gave doublet with J value for ortho coupling. A

double doublet was observed for proton on C_5 and because of coupling with ortho and meta protons, respective J values were obtained.

Similar pattern was observed in NMR spectrum of AKS-244. Four protons of two $–CH_2$- group were identified to give two multiplets. Signal at 3.83 can be assigned to methoxy protons. Three aromatic protons, similar to 1,2,4-trisubstituted aromatic ring, gave two doublets and a double doublet as observed in AKS-245.

In NMR spectrum of AKS-334, protons of methyl group at C_6 position gave signal at 1.98, while protons of methyl group of aliphatic chain on C_4 atom observed at 1.74. Protons of two $–CH_2$- groups gave two multiplets at 2.50 and 3.13 ppm. Four aromatic protons (similar to 1,3-substituted aromatic ring) were observed between 6.78 to 7.38 ppm. [i] C_2 proton gave doublet with J value of 2.32 (meta coupling), [ii] C_4 proton observed as double doublet with J value of 2.44, 8.56 (ortho & meta coupling), [iii] C_5 proton gave doublet with J value of 8.72 (ortho coupling), [iv] C6 proton also gave doublet with J value of 8.92 (ortho coupling).

3.7.4 Elemental analysis

Elemental analysis of synthesized compounds was in agreement with calculated values of composition of carbon, hydrogen and nitrogen. Spectral data and elemental analysis data are given below for individual compounds.

Spectral data of synthesized compounds (AKS 321-335, AKS 341-46)

6-Methyl-2-oxo-*N*-phenyl-4-propyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (AKS-321) – *IR* *(cm^{-1}):* 3315, 3227 (N-H), 3070 (Ar-H), 3039, 2924 (alkane), 1701, 1662 (C=O), 1529, 1492, 1475 (C=C), 1313 (C-N), 1080 (C-O), 790 (OOP); ***Anal cacld*** for $C_{15}H_{19}N_3O_2$: C 68.19, H 6.99, N 14.73, found: C 68.24, H 7.04, N 14.81.

N*-(4-Chlorophenyl)-6-methyl-2-oxo-4-propyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (AKS-322) - *IR *(cm^{-1}):* 3370, 3283 (N-H), 3065 (Ar-H), 2974, 2856 (alkane), 1708, 1671 (C=O), 1520, 1476, 1423 (C=C), 1294 (C-N), 1123 (C-O), 807

(OOP); ***Mass*** *(m/e)*:309 (M^{+2}), 307 (molecular ion peak), 264, 181 (base peak), 153, 127, 110, 84, 68; ***Anal cacld*** for $C_{15}H_{18}ClN_3O_2$: C 63.58, H 6.32, N 13.73, found: C 63.62, H 6.35, N 13.78.

N*-(4-Flourophenyl)-6-methyl-2-oxo-4-propyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (AKS-323) - *IR *(cm^{-1}):* 3417, 3218 (N-H), 3055 (Ar-H), 2968, 2843 (alkane), 1692, 1654 (C=O), 1553, 1447, 1417 (C=C), 1297 (C-N), 1079 (C-O), 756 (OOP); ***Mass*** *(m/e)*: 291 (molecular ion peak), 248, 214, 183, 170, 141, 116, 91 (base peak), 77, 65; ***Anal cacld*** for $C_{15}H_{18}FN_3O_2$: C 65.70, H 6.53, N 14.19, found: C 65.76, H 6.55, N 14.25.

N*-(3-Chloro-4-flourophenyl)-6-methyl-2-oxo-4-propyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (AKS-324) – *IR *(cm^{-1}):* 3408, 3316 (N-H), 3028 (Ar-H), 2966, 2811 (alkane), 1688, 1659 (C=O), 1577, 1450, 1423 (C=C), 1278 (C-N), 1069 (C-O), 827 (OOP); ***Anal cacld*** for $C_{15}H_{17}ClFN_3O_2$: C 61.42, H 5.92, N 13.26, found: C 61.48, H 5.97, N 13.33.

6-Methyl-*N*-(4-methylphenyl)-2-oxo-4-propyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (AKS-325) - *IR* *(cm^{-1}):* 3339, 3286 (N-H), 3081 (Ar-H), 2949, 2851 (alkane), 1711, 1663 (C=O), 1517, 1471, 1410 (C=C), 1302 (C-N), 1147 (C-O), 745 (OOP); ***Anal cacld*** for $C_{16}H_{21}N_3O_2$: C 68.69, H 7.21, N 14.30, found: C 68.74, H 7.23, N 14.38.

6-Methyl-*N*-(1-naphthyl)-2-oxo-4-propyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (AKS-326) – *IR* *(cm^{-1}):* 3421, 3292 (N-H), 3018 (Ar-H), 2977, 2847 (alkane), 1690, 1668 (C=O), 1521, 1448, 1413 (C=C), 1311 (C-N), 1059 (C-O), 841 (OOP); ***Anal cacld*** for $C_{19}H_{21}N_3O_2$: C 70.83, H 6.71, N 13.32, found: C 70.90, H 6.76, N 13.41.

N*-(2-Chlorophenyl)-6-methyl-2-oxo-4-propyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (AKS-327) - *IR *(cm^{-1}):* 3362, 3271 (N-H), 3058 (Ar-H), 2945, 2806 (alkane), 1706, 1671 (C=O), 1586, 1480, 1422 (C=C), 1276 (C-N), 1172 (C-O), 757 (OOP); ***Anal cacld*** for $C_{15}H_{18}ClN_3O_2$: C 63.58, H 6.32, N 13.73, found: C 63.64, H 6.36, N 13.79.

N*-(4-Nitrophenyl)-6-methyl-2-oxo-4-propyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (AKS-328) - *IR *(cm^{-1}):* 3310, 3277 (N-H), 3082 (Ar-H), 2924, 2891 (alkane), 1700, 1656 (C=O), 1545, 1473, 1429 (C=C), 1288 (C-N), 1055 (C-O), 811 (OOP); ***Anal cacld*** for $C_{15}H_{18}N_4O_4$: C 62.29, H 6.20, N 16.14, found: C 62.36, H 6.26, N 16.27.

6-Methyl-*N*-(3-methylphenyl)-2-oxo-4-propyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (AKS-329) - *IR* *(cm^{-1}):* 3369, 3296 (N-H), 3061 (Ar-H), 2916, 2817 (alkane), 1685, 1666 (C=O), 1599, 1539, 1491 (C=C), 1317 (C-N), 1087 (C-O), 860 (OOP); ***Mass*** *(m/e)*: 302 (molecular ion peak), 258, 208, 181 (base peak), 153, 121, 105, 84, 68; ***Anal cacld*** for $C_{16}H_{21}N_3O_2$: C 68.69, H 7.21, N 14.30, found: C 68.76, H 7.25, N 14.37.

6-Methyl-*N*-(3,4-dimethylphenyl)-2-oxo-4-propyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (AKS-330) - *IR* *(cm^{-1}):* 3310, 3221 (N-H), 3057 (Ar-H), 2944, 2870 (alkane), 1688, 1672 (C=O), 1543, 1485, 1411 (C=C), 1330 (C-N), 1140 (C-O), 795 (OOP); ***Anal cacld*** for $C_{17}H_{23}N_3O_2$: C 69.16, H 7.40, N 13.91, found: C 69.20, H 7.46, N 14.02.

6-Methyl-*N*-(2-methylphenyl)-2-oxo-4-propyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (AKS-331) - *IR* *(cm^{-1}):* 3330, 3274 (N-H), 3098 (Ar-H), 2905, 2864 (alkane), 1704, 1680 (C=O), 1590, 1523, 1470 (C=C), 1329 (C-N), 1146 (C-O), 831 (OOP); ***Anal cacld*** for $C_{16}H_{21}N_3O_2$: C 68.69, H 7.21, N 14.30, found: C 68.73, H 7.23, N 14.41.

6-Methyl-*N*-(2,4-dimethylphenyl)-2-oxo-4-propyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (AKS-332) - *IR* *(cm^{-1}):* 3431, 3323 (N-H), 3107 (Ar-H), 2981, 2904 (alkane), 1712, 1675 (C=O), 1521, 1473, 1440 (C=C), 1295 (C-N), 1127 (C-O), 740 (OOP); ***Anal cacld*** for $C_{17}H_{23}N_3O_2$: C 69.16, H 7.40, N 13.91, found: C 69.22, H 7.44, N 14.00.

6-Methyl-*N*-(2,5-dimethylphenyl)-2-oxo-4-propyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (AKS-333) - *IR* *(cm^{-1}):* 3300, 3211 (N-H), 3080 (Ar-H), 2966, 2811

(alkane), 1698, 1664 (C=O), 1498, 1453 (C=C), 1258 (C-N), 1071 (C-O), 817 (OOP); ***Anal cacld*** for $C_{17}H_{23}N_3O_2$: C 69.16, H 7.40, N 13.91, found: C 69.24, H 7.47, N 13.98.

N*-(3-Nitrophenyl)-6-methyl-2-oxo-4-propyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (AKS-334) - *IR *(cm^{-1}):* 3327, 3217 (N-H), 3045 (Ar-H), 2961, 2854 (alkane), 1709, 1668 (C=O), 1540, 1479, 1420 (C=C), 1281 (C-N), 1156 (C-O), 719 (OOP); ***^{1}H NMR*** *($CDCl_3$) (δ ppm)*: 1.75 (3H, m), 1.98 (3H, s), 2.50 (2H, m), 3.14 (2H, m), 5.75 (1H, t), 6.79 (1H, dd, J=2.44, 8.56), 7.01 (1H, d, J=2.32), 7.18 (1H, d, J=8.72), 7.38 (1H, d, J=8.92), 8.25 (1H, s), 8.51 (1H, s), 9.03 (1H, s); ***Anal cacld*** for $C_{15}H_{18}N_4O_4$: C 62.29, H 6.20, N 16.14, found: C 62.33, H 6.24, N 16.24.

N*-(2-Trifluorophenyl)-6-methyl-2-oxo-4-propyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (AKS-335) - *IR *(cm^{-1}):* 3429, 3310 (N-H), 3074 (Ar-H), 2945, 2875 (alkane), 1688, 1563 (C=O), 1515, 1497, 1406 (C=C), 1276 (C-N), 1082 (C-O), 852 (OOP); ***Anal cacld*** for $C_{18}H_{18}F_3N_3O_2$: C 61.87, H 5.93, N 12.88, found: C 61.93, H 6.02, N 12.97.

2,3-dihydro[1,3]thiazolo[3,2-*a*]benzimidazole (AKS-341) - *IR* *(cm^{-1}):* 3007 (Ar-H), 2981, 2943, 2743 (alkane), 1597, 1506, 1476, 1420 (C=C), 1325 (C-N), 784 (OOP); ***Anal cacld*** for $C_9H_8N_2S$: C 61.34, H 4.58, N 15.90, found: C 61.41, H 4.56, N 16.03.

3,4-dihydro-2*H*-[1,3]thiazino[3,2-*a*]benzimidazole (AKS-342) - *IR* *(cm^{-1}):* 3088 (Ar-H), 2926, 2855, 2817, 2756 (alkane), 1546, 1503, 1436 (C=C), 1315 (C-N), 801 (OOP); ***Anal cacld*** for $C_{10}H_{10}N_2S$: C 63.13, H 5.30, N 14.72, found: C 63.17, H 5.36, N 14.83.

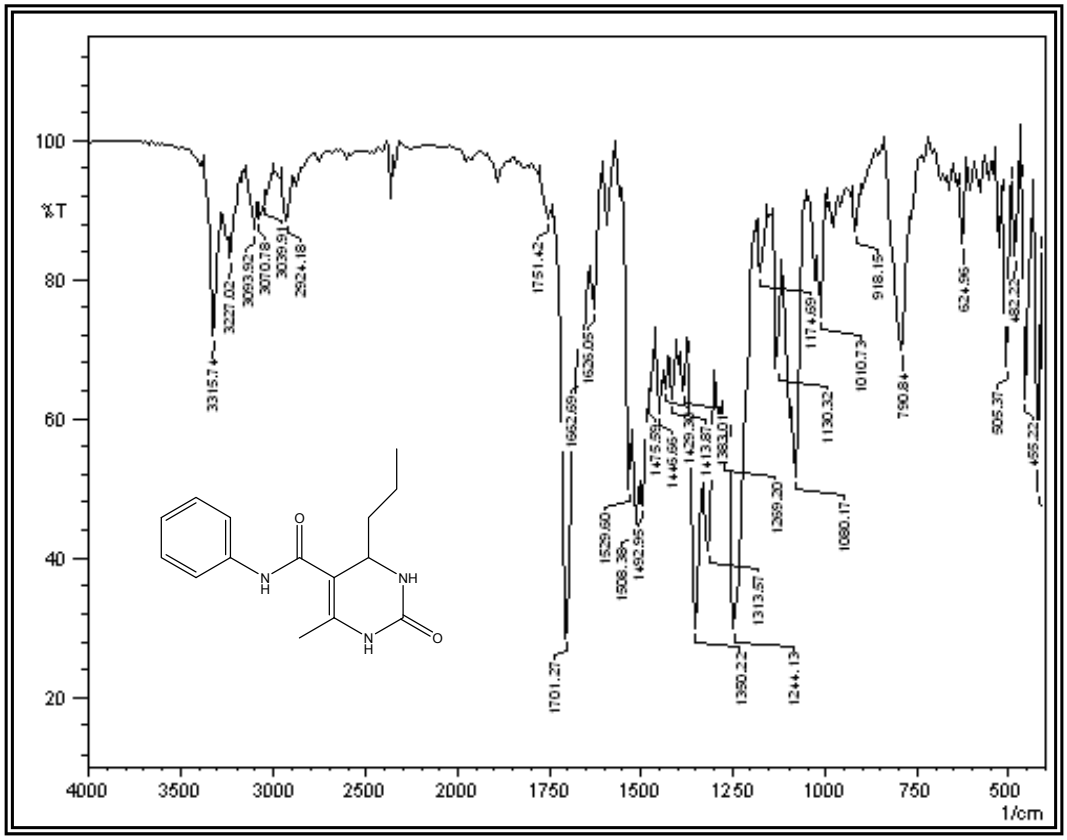
2,3,4,5-tetrahydro[1,3]thiazepino[3,2-*a*]benzimidazole (AKS-343) - *IR* *(cm^{-1}):* 3024 (Ar-H), 2930, 2856, 2830 (alkane), 1543, 1478, 1428 (C=C), 1305 (C-N), 749 (OOP); ***Anal cacld*** for $C_{11}H_{12}N_2S$: C 64.67, H 5.92, N 13.71, found: C 64.74, H 5.89, N 13.84.

6-methoxy-2,3-dihydro[1,3]thiazolo[3,2-*a*]benzimidazole (AKS-344) - *IR* *(cm^{-1}):* 3055 (Ar-H), 2969, 2947, 2850 (alkane), 1604, 1583, 1531, 1494 (C=C), 1348 (C-N), 748 (OOP); ***^{1}H NMR*** *($CDCl_3$ d6) (δ ppm)*: 3.18 (2H, m), 3.83 (3H, s), 4.10 (2H, m), 6.79 (1H, dd, J=2.37, 8.73), 7.06 (1H, d, J=8.72), 7.11 (1H, d, J=2.36); ***Anal cacld*** for $C_{10}H_{10}N_2OS$: C 58.23, H 4.89, N 13.58, found: C 58.18, H 4.93, N 13.69.

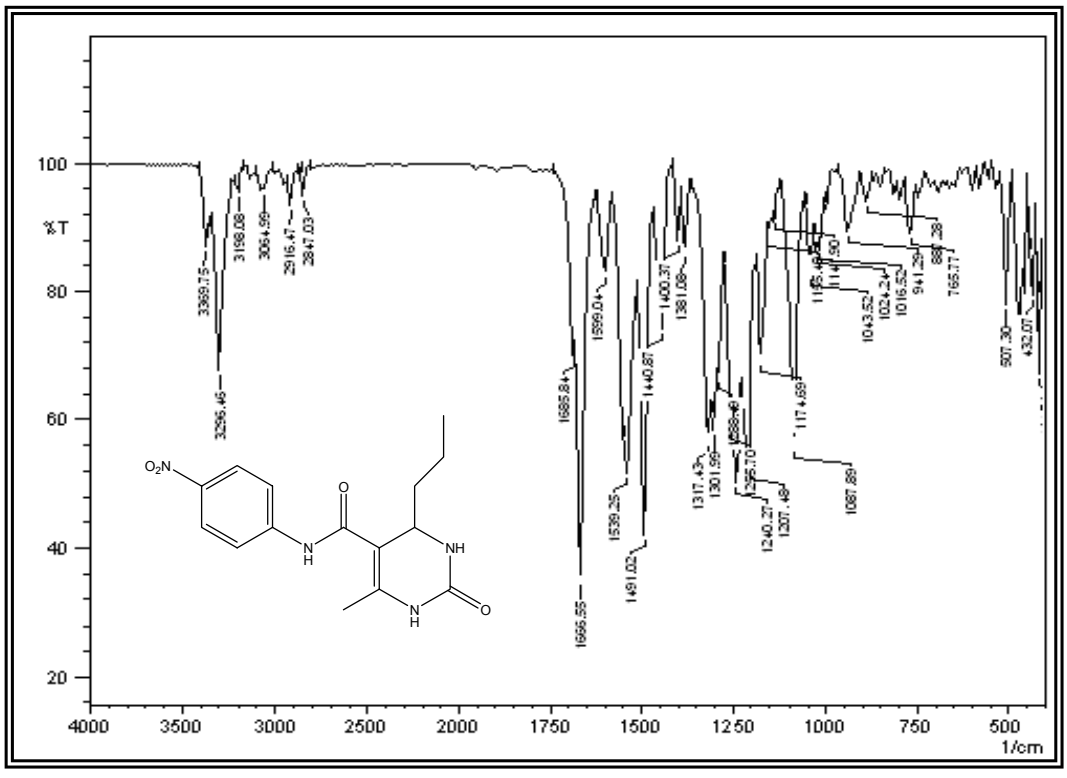
7-methoxy-3,4-dihydro-2*H*-[1,3]thiazino[3,2-*a*]benzimidazole (AKS-345) - *IR* *(cm^{-1}):* 3060 (Ar-H), 2944, 2908, 2859, 2811 (alkane), 1589, 1547, 1486, 1453 (C=C), 1330 (C-N), 711 (OOP); ***^{1}H NMR*** *($CDCl_3$ d6) (δ ppm)*: 2.45 (2H, m), 3.20 (2H, m), 3.84 (3H, s), 4.14 (2H, m), 6.82 (1H, dd, J=2.26, 8.67), 7.09 (1H, d, J=8.68), 7.12 (1H, d, J=2.32); ***Anal cacld*** for $C_{11}H_{12}N_2OS$: C 59.97, H 5.49, N 12.72, found: C 0.07, H 5.53, N 12.76.

8-methoxy-2,3,4,5-tetrahydro[1,3]thiazepino[3,2-*a*]benzimidazole (AKS-346) - *IR* *(cm^{-1}):* 3018 (Ar-H), 2928, 2843, 2769 (alkane), 1537, 1491, 1458 (C=C), 1309 (C-N), 792 (OOP); ***Mass*** *(m/e)*: 220 (molecular ion peak, base peak), 205, 192, 177, 149, 133, 128, 86, 72; ***Anal cacld*** for $C_{12}H_{14}N_2OS$: C 61.51, H 6.02, N 11.96, found: C 61.58, H 5.98, N 12.07.

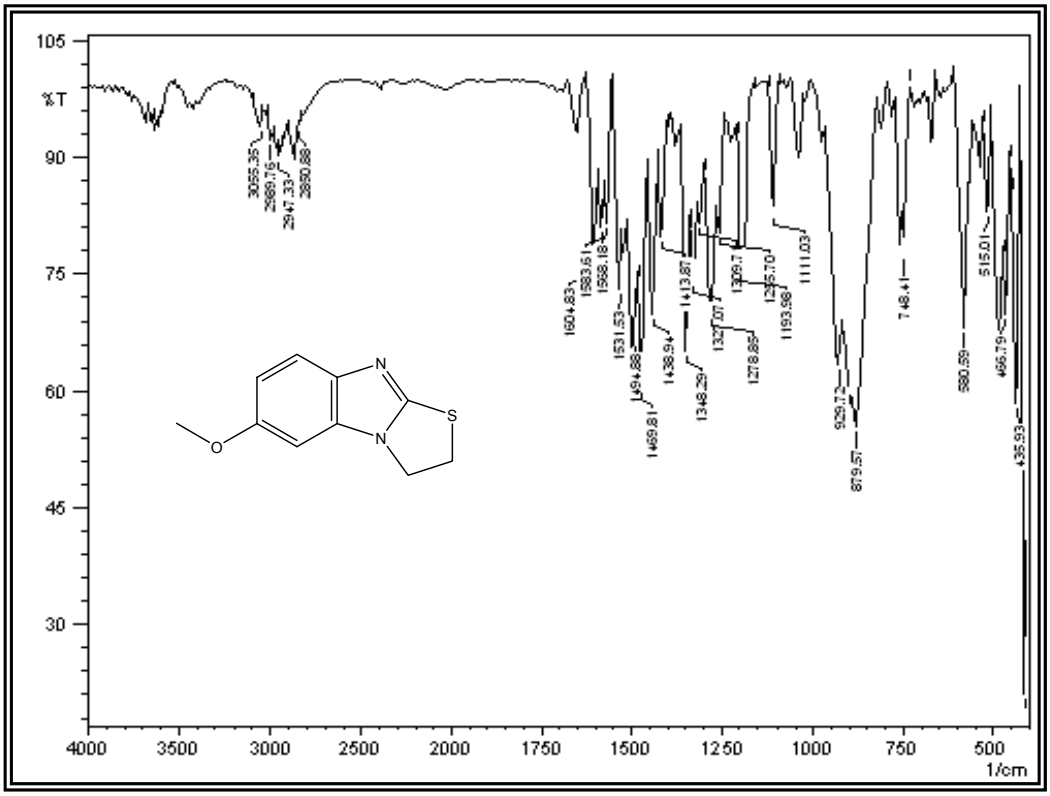
3.7.5.1 IR spectrum of AKS- 321



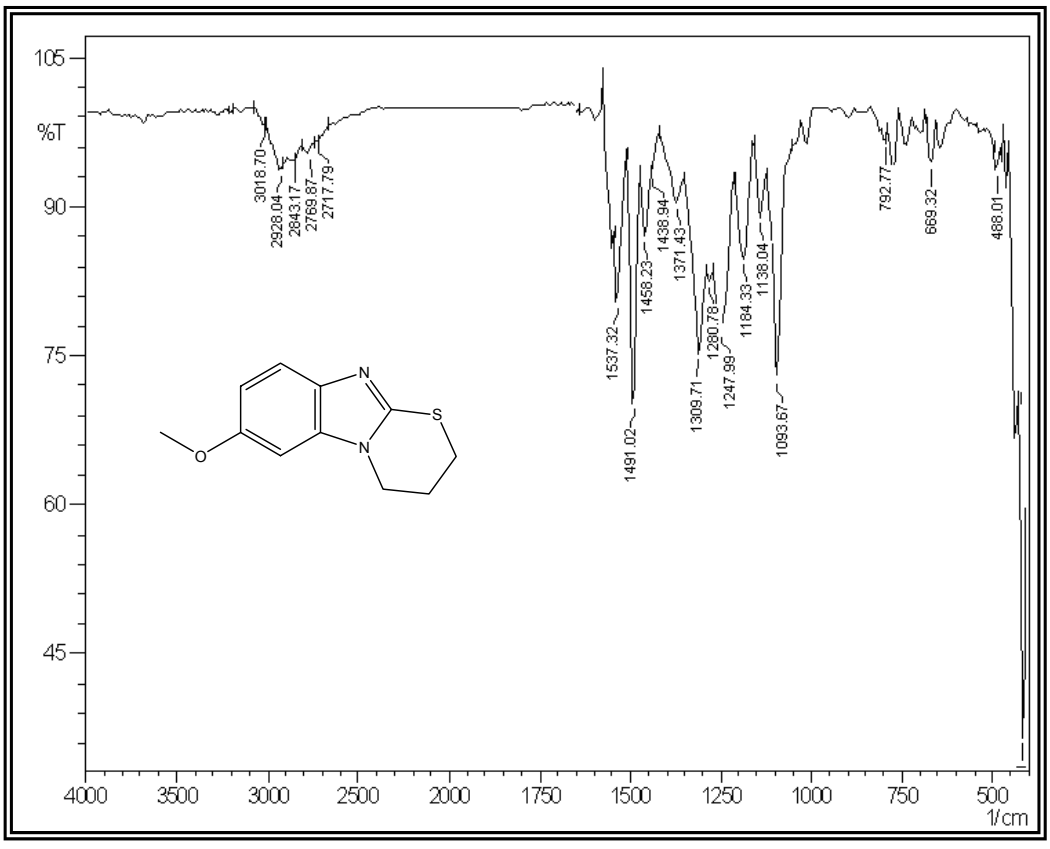
3.7.5.2 IR spectrum of AKS- 328



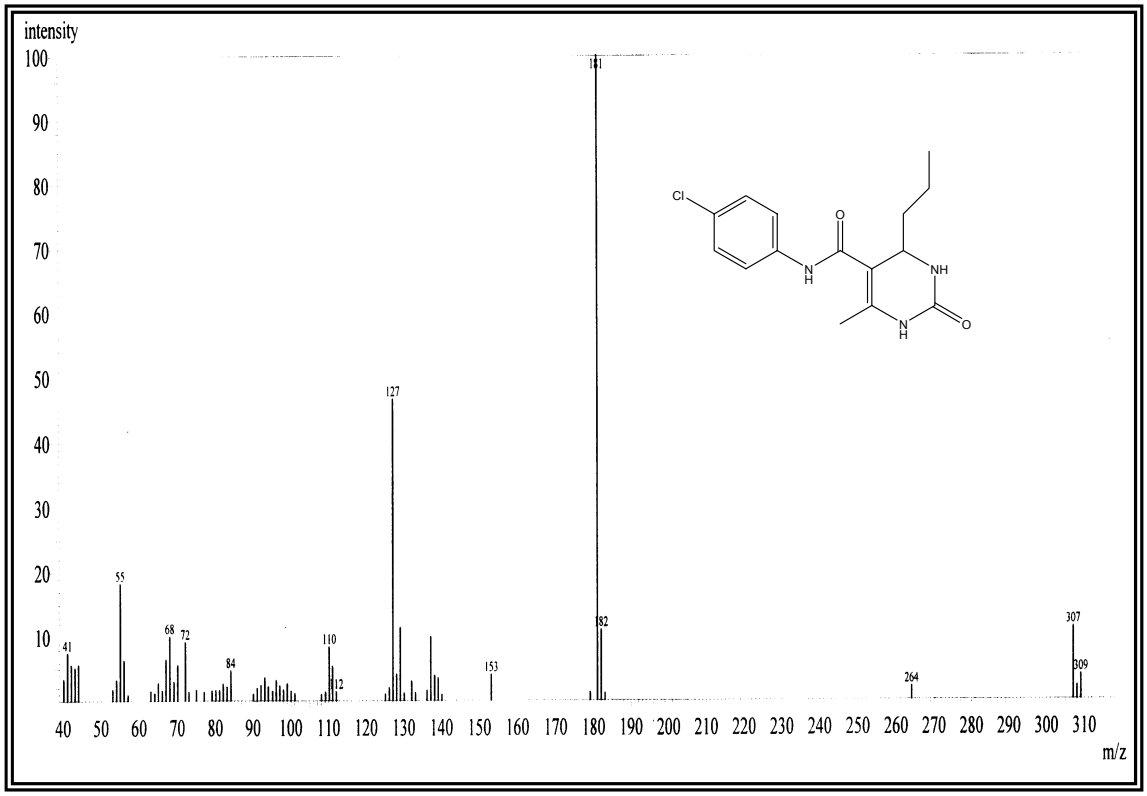
3.7.5.3 IR spectrum of AKS- 344



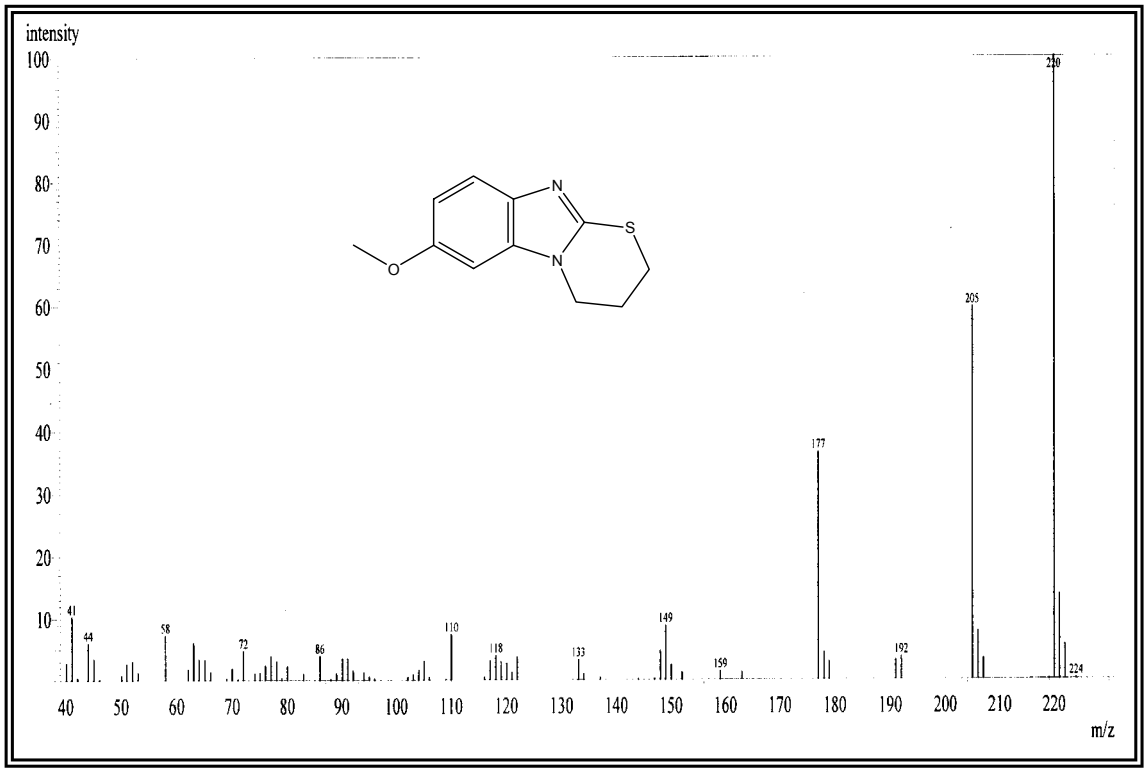
3.7.5.4 IR spectrum of AKS- 346



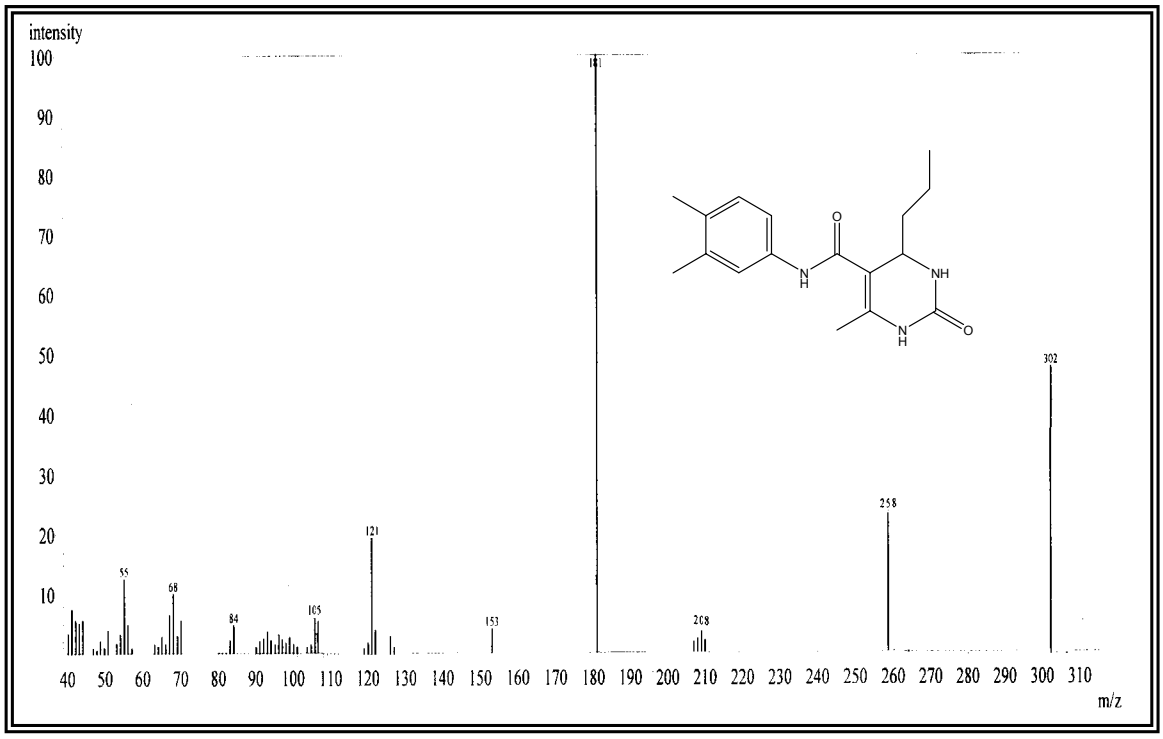
3.7.5.5 Mass spectrum of AKS- 322



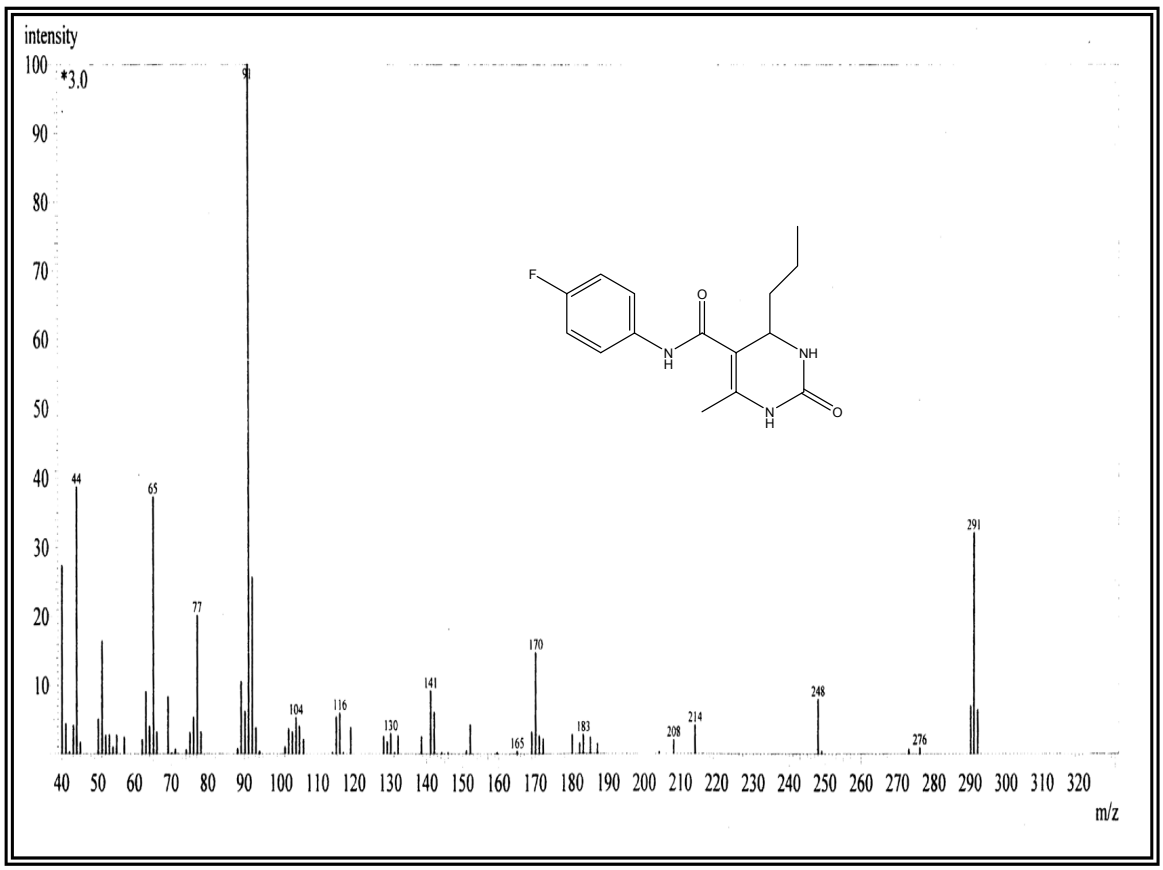
3.7.5.6 Mass spectrum of AKS- 345



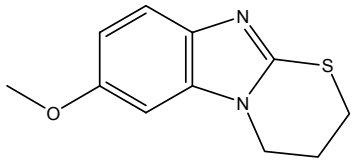
3.7.5.7 Mass spectrum of AKS- 330

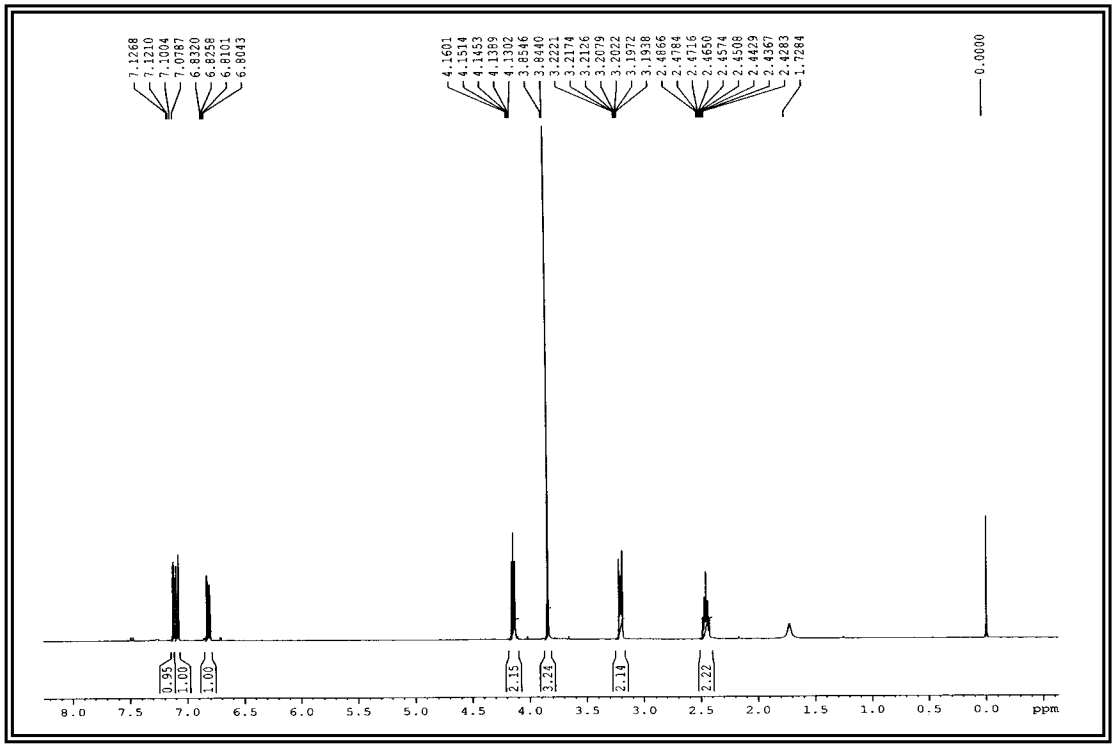


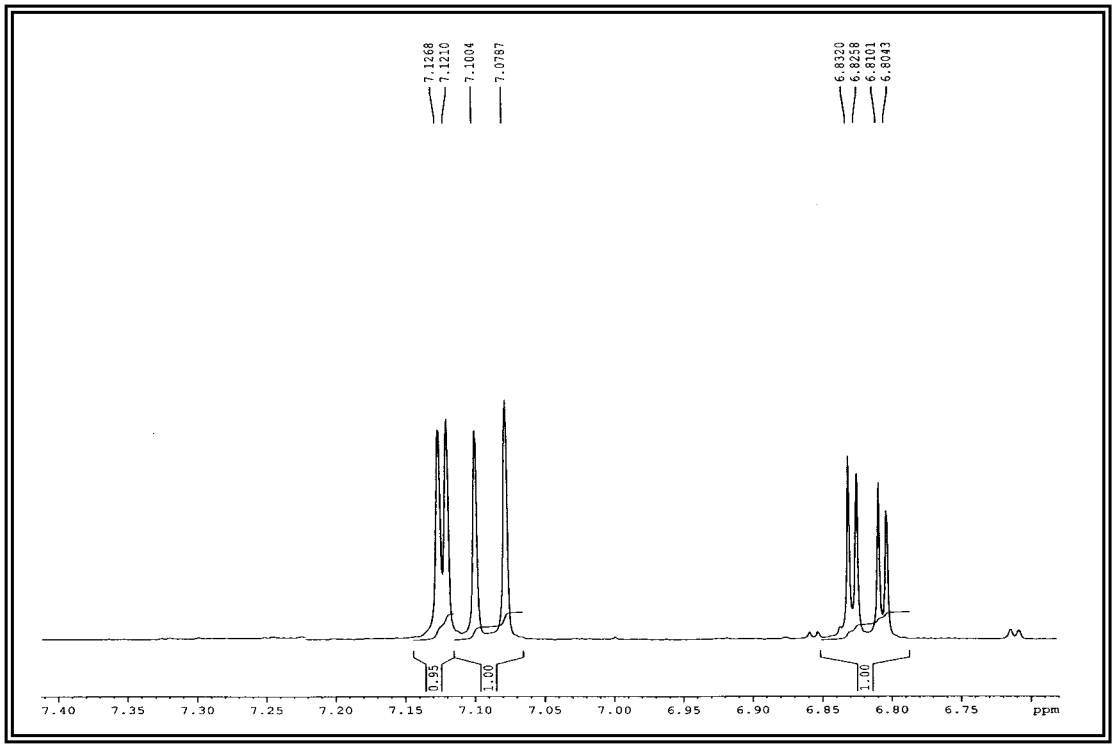
3.7.5.8 Mass spectrum of AKS- 323



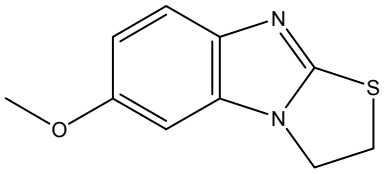
3.7.5.9 ^{1}H NMR spectrum of AKS- 345

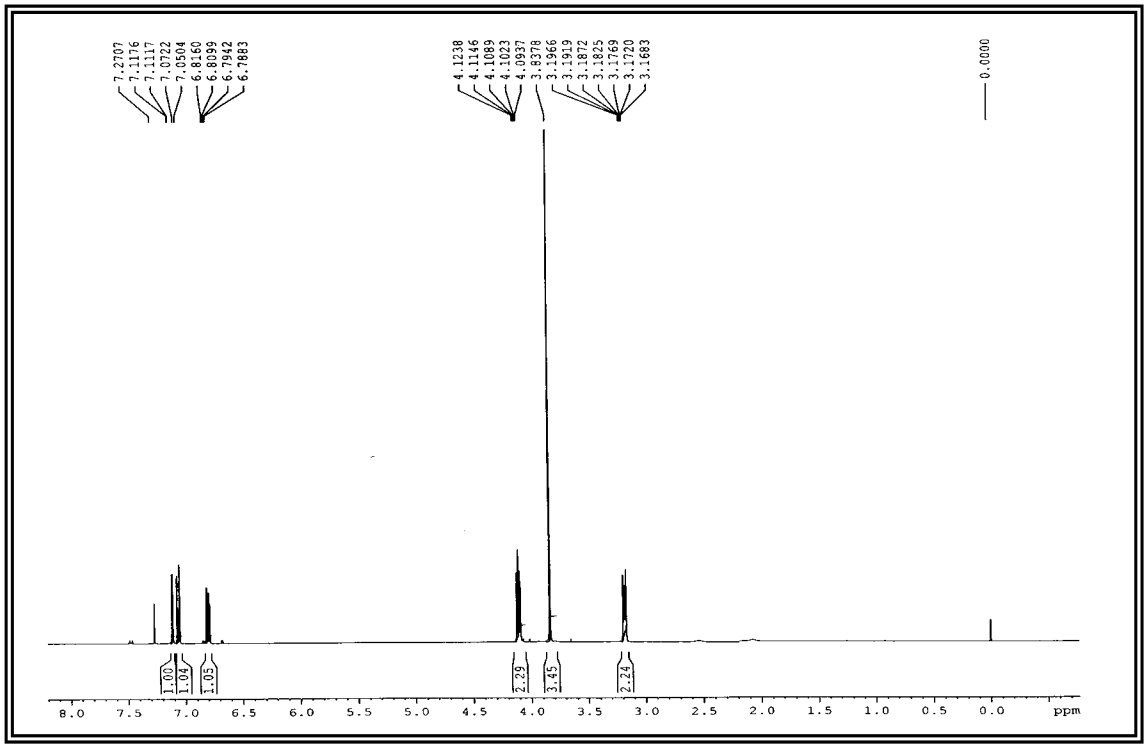


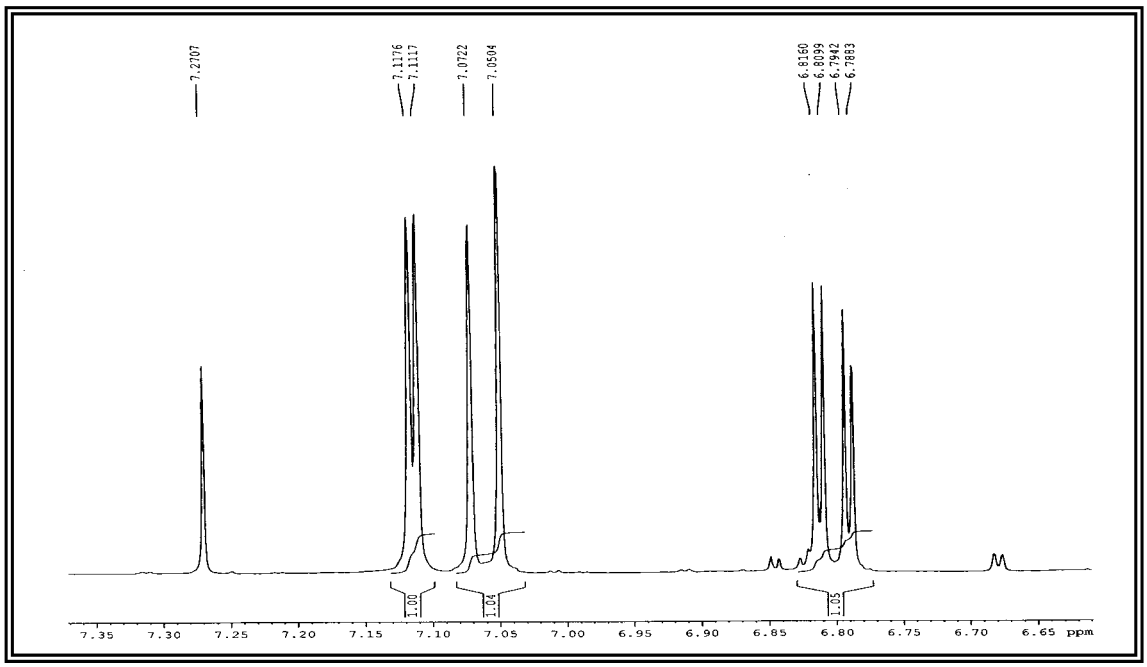




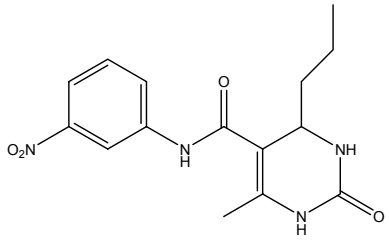
3.7.5.10 ^{1}H NMR spectrum of AKS- 344

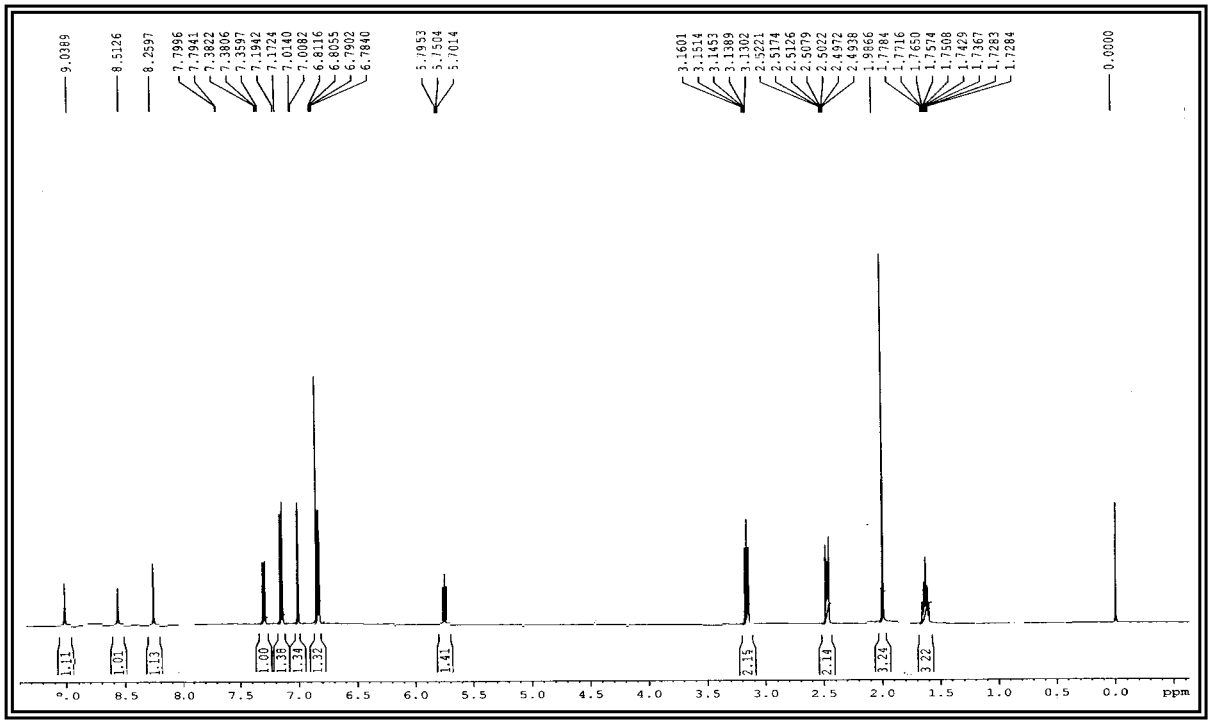


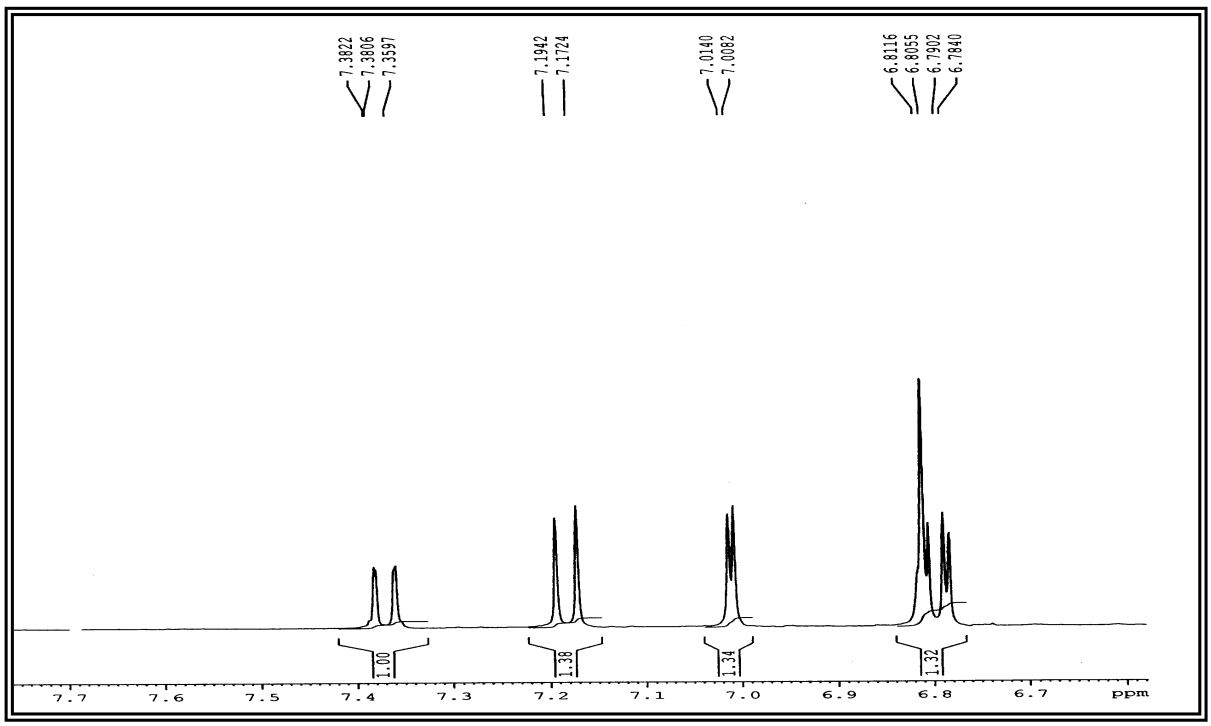




3.7.5.11 ^{1}H NMR spectrum of AKS- 334







3.7 References

1. Westaway, K. C. and Gedye, R. N.; *J. Microwave PowerElectromagn. Energy*, **1995**, 30, 219.
2. Caddick, S.; *Tetrahedron*, **1995**, 51, 10403.
3. Varma, R. S.; *Green Chem.*, **1999**, 1, 43.
4. Lidström, P.; Tieney, J.; Wathey, B.and Westmann, J.; *Tetrahedron*, **2001**, 57, 9225.
5. Larhed, M.; Moberg, Ch. and Hallberg, A.; *Acc. Chem. Res.*, **2002**, 35, 717.
6. Trotzki, R.; Nüchter, M. and Ondruschka, B.; *Green Chem.*, **2003**, 5, 285.
7. Strauss, C. R.; Trainor, R.W.; *Aust. J. Chem*. **1995**, 48, 1665 –1692.
8. Larhed, M.; Moberg, C.; Hallberg, A.; Acc. Chem. Res. **2002**, 35, 717 – 727.
9. Krstenansky, J. L.; Cotterill, I.; *Curr. Opin. Drug Discovery Dev.* **2000,** 3, 454 – 461.
10. Swamy, K. M. K., Yeh, W.B.; Lin, M.J.; Sun, C.M.; *Curr. Med. Chem*. **2003**, 10, 2403 – 2423.
11. Microwaves in Combinatorial and High-Throughput Synthesis (Ed.: Kappe, C. O.), Kluwer, Dordrecht, 2003 (a special issue of *Mol. Diversity* **2003**, 7, pp. 95–307.
12. Online resources on microwave-assisted organic synthesis (MAOS), see: www.maos.net.
13. Baghurst, D. R.; Mingos, D. M. P.; *Chem. Soc. Rev.* **1991**, 20, 1–47.
14. Gabriel, C., Gabriel, S.; Grant, E. H.; Halstead, B. S.; Mingos, D. M. P.; *Chem. Soc. Rev.* **1998**, 27, 213 – 223.
15. Hayes, B. L. ; Microwave Synthesis: Chemistry at the Speed of Light, CEM Publishing, Matthews NC, **2002**.
16. Miyaura, N.; Suzuki, A.; *Chem. Rev.* **1995**, 95, 2457 – 2483.
17. Li, C. J.; *Angew. Chem.* **2003,** 115, 5004 – 5006; *Angew. Chem. Int. Ed.* **2003**, 42, 4856 – 4858.
18. Gong, Y.; He, W.; *Org. Lett.* **2002,** 4, 3803 – 3805.
19. Nuteberg, D.; Schaal, W.; Hamelink, E.; Vrang, L.; Larhed, M.; *J. Comb. Chem*. **2003**, 5, 456 – 464.
20. Miller, S. P.; Morgan, J. B.; Nepveux, F. J.; Morken, J. P. ; *Org. Lett.* **2004**, 6, 131 – 133.
21. Kaval, N.; Bisztray, K.; Dehaen, W.; Kappe C. O.,; Van der -Eycken, E.; *Mol. Diversity* **2003**, 7, 125 – 134.
22. Luo, G.; Chen, L.; Pointdexter, G. S.; *Tetrahedron Lett*. **2002**, 43, 5739 – 5742.
23. Wu, T. Y. H.; Schultz, P. G.; Ding, S.; *Org. Lett*. **2003**, 5, 3587 – 3590.
24. Han, J. W.; Castro, J. C.; Burgess, K.; *Tetrahedron Lett.* **2003**, 44, 9359 – 9362.
25. Leadbeater, N. E.; Marco, M.; *Org. Lett.* **2002**, 4, 2973 – 2976.
26. Leadbeater, N. E.; Marco, M.; *J. Org. Chem*. **2003**, 68, 888 – 892.
27. Leadbeater, N. E.; Marco, M.; *Angew. Chem*. **2003**, 115, 1445 – 1447; *Angew. Chem. Int. Ed*. **2003**, 42, 1407 – 1409.
28. Leadbeater, N. E.; Marco, M.; *J. Org. Chem.* **2003**, 68, 5660 – 5667.
29. Theoclitou, M.-E.; Robinson, L. A.; *Tetrahedron Lett*. **2002**, 43, 3907 – 3910.

30. Hberg, L., Westman, J.; *Synlett* **2001**, 1296 – 1298.
31. Zhao, Z.; Leister, W. H.; Strauss, K. A.; Wisnoski, D. D.; Lindsley, C. W.; *Tetrahedron Lett*. **2003**, 44, 1123 – 1128
32. Lindsley, C. W.; Wisnoski, D. D.; Wang, Y.; Leister, W. H.; Zhao, Z.; *Tetrahedron Lett*. **2003**, 44, 4495 – 4498.
33. Mont, N.; Teixid, J.; Borrell, J. I.; Kappe, C. O.; *Tetrahedron Lett.* **2003**, 44, 5385 – 5388; Mont, N.; Teixid, J.; Borrell, J. I.; Kappe, C. O.; *Mol. Diversity* **2003**, 7, 153 – 159.
34. Baxendale, I. R.; Lee, A.I.; Ley, S. V.; *J. Chem. Soc. Perkin Trans*. **2002**, 1850 – 1857.
35. ErdMlyi, M.; Gogoll, A.; *J. Org. Chem.* **2001**, 66, 4165 – 4169.
36. ErdMlyi, M.; Langer, V.; KarlMn, A.; Gogoll, A.; *New. J. Chem*. **2002**, 26, 834 – 843.
37. Trost, B. M.; Crawley, M. L.; *J. Am. Chem. Soc.* **2002**, 124, 9328 – 9329.
38. Pinto, D. C. G. A.; Silva, A. M. S.; Almeida, L. M. P. M.; Carrillo, J. R.; Waz-Ortiz, A. D.; de la Hoz, A.; Cavaleiro, J. A. S.; *Synlett* **2003**, 1415 – 1418.
39. Dupau, P.; Epple, R.; Thomas, A. A.; Fokin, V. V.; Sharpless, K. B.; *Adv. Synth. Catal*. **2002**, 344, 421 – 433.
40. Lehmann, F.; Pilotti, K. Luthman, *Mol. Diversity* **2003**, 7, 145 – 152.
41. Cherng, Y.J.; *Tetrahedron* **2000**, 56, 8287 – 8289.
42. Brown, G. R.; Foubister, A. J.; Roberts, C. A.; Wells, S. L.; Wood, R.; *Tetrahedron Lett.* **2001**, 42, 3917 – 3919.
43. Cherng, Y.J.; *Tetrahedron* **2002**, 58, 887 – 890.
44. Cherng, Y.J.; *Tetrahedron* **2002**, 58, 1125 – 1129.
45. Cherng, Y.J.; *Tetrahedron* **2002**, 58, 4931 – 4935.
46. Zaragoza, F.; *Organic Synthesis on Solid Phase*, *Wiley-VCH, Weinheim*, **2002**.
47. *Handbook of Combinatorial Chemistry* (Eds.: Nicolaou, K. C.; Hanko, R.; Hartwig, W.), Wiley-VCH, Weinheim, **2002**.
48. Stadler, A.; Kappe, C. O. ; *Eur. J. Org. Chem*. **2001**, 919 – 925.
49. Stadler, A.; Kappe, C. O.; *Tetrahedron* **2001**, 57, 3915 – 3920.
50. Mrez, R. P.; Beryozkina, T.; Zbruyev, O. I.; Haas, W.; Kappe, C. O.; *J. Comb. Chem*. **2002**, 4, 501 – 510.

Chapter 4

Synthesis & characterization of 1,4-dihydropyridine derivatives

Chapter 4

Synthesis & characterization of 1,4-dihydropyridine derivatives

4.1 Biological profile of 1,4-dihydropyridine

Dihydropyridine (DHP) chemistry began in 1882 when Hantzch[1,2] published the synthesis. In its simplest form of the synthesis involves heating an aldehyde 1,3-diketone and ammonia. The reaction almost certainly involves aldol condensation to form the benzylidene derivative as the first step. Conjugated addition of a second mole of 1,3-diketone would then afford the 1,5-diketone. Reaction of the carbonyl group with ammonia will lead to the formation of the dihydropyridine ring.

The DHP nucleus is common to numerous bioactive compounds which include various vasodilator, antihypertensive, bronchodilator, antiatherosclerotic, hepatoprotective, antitumor, antimutagenic, geroprotective, and antidiabetic agents[3-8].

DHPs have found commercial utility as calcium channel blockers, as exemplified by therapeutic agents such as Nifedipine[9], Nitrendipine[10] and Nimodipine[11]. Second-generation calcium antagonists include DHP derivatives with improved bioavailability, tissue selectivity, and/or stability,such as the antihypertensive/antianginal drugs like Elgodipine[12], Furnidipine[13,14], Darodipine[15], Pranidipine[16], Lemildipine[17], Dexniguldipine[18], Lacidipine[19], and Benidipine[20]. Number of DHP calcium agonists has been introduced as potential drug candidates for treatment of congestive heart failure[21, 22].

The key characteristic of calcium channel blockers is their inhibition of entry of calcium ions via a subset of channels, thereby leading to impairment of contraction. There are three main groups of calcium channel blockers, i.e. dihydropyridines, phenylalkylamines and benzothiazepines, typical examples of which are nifedipine, verapamil and diltiazem,

respectively[23-26]. Each has a specific receptor on the calcium channel and a different profile of pharmacological activity. Dihydropyridines have a less negative inotropic effect than phenylalkylamines and benzothiazepines but can sometimes cause reflex tachycardia. Dihydropyridines are able to reduce peripheral resistance, generally without clinically significant cardiodepression.

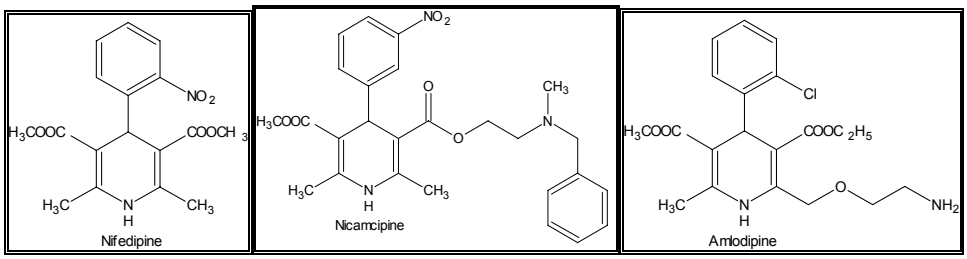
Among DHPs with other types of bioactivity, Cerebrocrast[27] has been recently introduced as a neuroprotectant and cognition enhancer lacking neuronal-specific calcium antagonist properties. In addition, a number of DHPs with platelet antiaggregatory activity have also been discovered[28]. These recent examples highlight the level of ongoing interest toward new DHP derivatives and have prompted us to explore this pharmacophoric scaffold to develope a fertile source of bioactive molecules.

1,4- DHPs possess different pharmacological activities such as antitumor[29], vasodilator[30], coronary vasodilator and cardiopathic[31], antimayocardiac ischemic, antiulcer[32], antiallergic[33], antiinflammatory[34] and antiarrhythmic[35], PAF antagonist[36], Adenosine A3 receptor antagonist[37] and MDR reversal activity[38,39].

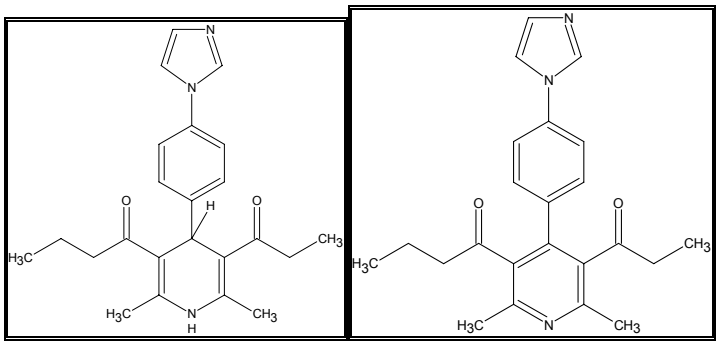
In particular, DHP-CA (calcium channel antagonist DHP) are extensively used for the treatment of hypertension,[40] subarachnoid hemorrhage,[41,42] myocardial infarction[43-46] and stable[47,48] and unstable angina[49,50] even though recently their therapeutic efficacy in myocardial infarction and angina has been questioned[51]. This class of compounds is also under clinical evaluation for the treatment of heart failure[52], ischemic brain damage[53] nephropathies, and atherosclerosis[54].

1,4-Dihydropyridines are now established as heterocycles having numerous applications and having widened scope for its pronounced drug activity like calcium channel antagonism and antihypertensive action. Many other cardiovascular activities are associated with such compounds and they can be presented in the structure as 2,6-dimethyl-3,5-diacetyl or dicarboxylate or dicarbamoyl or many other homoaryl or heteroaryl carbon chain having C_2 to C_8 1,4-dihydropyridines substituted at 4-position.

Some representative Ca^{2+} andtagonists of Dihydropyridine class are as shown below:

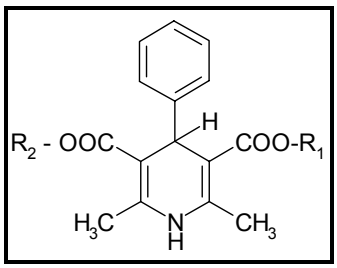


A starting revelation is found recently in which the imidazolyl moiety is linked to the phenyl ring by means of a methylene bridge, the activity tends to decrease. Finally, the replacement of DHP itself by a pyridine ring gives an inactive compound [56].



Cozzy and coworkers[56] have synthesized a series of 4-phenyl-1,4-dihydropyridines bearing imidazol-1-yl or pyridine-3-yl moieties on the phenyl ring, with the aim of combining Ca^{2+} antagonism and thermboxane $A_2(TxA_2)$ synthase inhibition in the same molecules. Some of the compounds showed significant combined activity *in vitro*, while other showed single activity. As far as Ca^{2+} antagonism is concerned, two points deserve comment. First, the SAR, in most cases, does not differ substantially from that reported for classic DHP-CA, even though the potency is lower than that found with the most potent drugs of this class as, for example, reference compound nifedipine. In fact, Ca^{2+} antagonism is dramatically reduced by (a) replacement of DHP by a pyridine ring, (b) substitution of DHP nitrogen N-1 by a methyl group, (c) para substitution on the phenyl ring, and (d) replacement of one ester function by a ketone or carboxy group. All these variations are also detrimental in classic DHP-CA.[57]

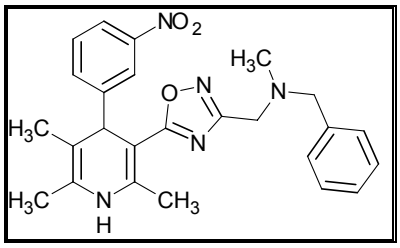
Hernandez-Gallegos and coworkers[58] have synthesized new 1,4-dihydropyridines and evaluated their relaxant ability (rat aorta), antihypertensive activity in spontaneously hypertensive rats and their microsomal oxidation rate (MOR) was determined.



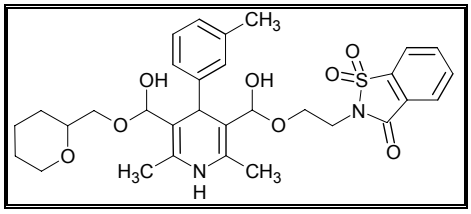
R = 3-NO2, 4-F, 3,5-di-F, 3-Br-4-F.

$R_1 = R_2$= Me, Et, $-CH_2-CF_3$, $-CH_2CH_2-OPh$, $-(CH_2)_2-N(CH_3)-CH_3-Ph$

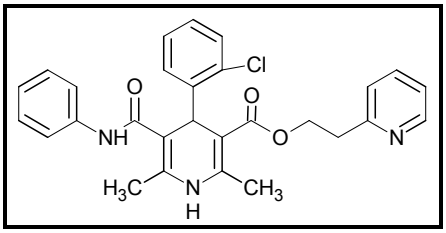
Christiaans and Timmerman[59] studied new molecules like CV-159 for possible variation at 3-position.



Carlos et al[60] reported 1,4-DHPs derivatives with a 1,2-benzothiazol-3-one-1-sulphoxide group, linked through an alkylene bridge to the C_3 carboxylate of the DHP ring, with both vasoconstricting and vasorelaxant properties were obtained. In blocking Ca^{2+} evoked contractions of K^+ depolarized rabbit aortic strips. Many compounds were 10 times more potent than nifedipine. Their vascular versus cardiac selectivity was very pronounced.

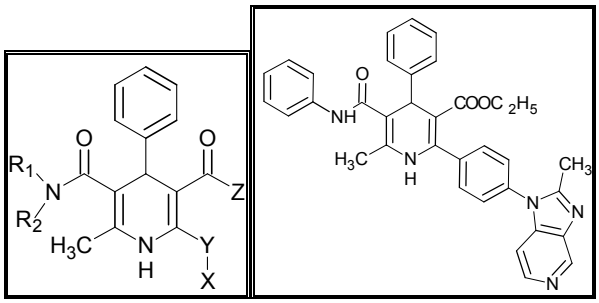


Schramm and coworker[61] have proved that phenyl carbamoyl moiety in dihydorpyridine affords for cardiovascular selective activity.

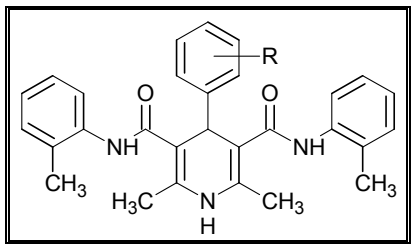


Similarly Kelvin Cooper (Pfitzer , USA) et al[62] found that DHP can be highly selective as platlet activating factor (PAF) antagonist. They found potent compounds and prove that platlet aggregating activity (PAF) exhibits a wide spectrum of biological activities elicited either directly or via the release of other powerful mediator such as Thromboxane A_2 or the Leukotrienes. *In vitro* PAF stimulates the movement and aggregation and the release

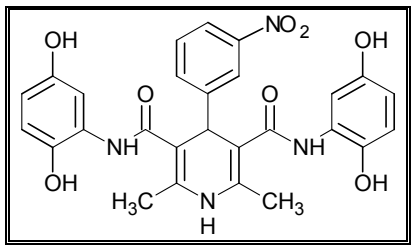
there from of tissue damaging enzymes and oxygen radicals. Accordingly compounds like UK-74505, antagonize the action of PAF and consequently also prevent mediator release by PAF, will have clinical utilities in the treatment of the variety of the allergic, inflammatory and hypersecretory conditions such as asthama, arthritis, rhinitis, bronchitis and utricaria[63] in future.



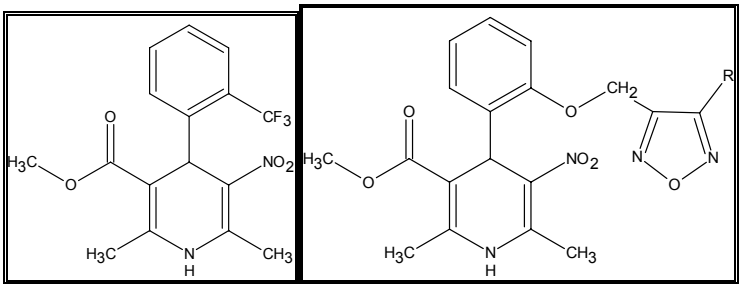
Reddy and coworkers[64] synthesized 4-aryl hetroaryl-2,6-dimethyl-3,5-bis-N-(2-methyl phenyl)carbamoyl-1,4-dihydropyridines through one-pot synthesis using appropriate aromatic aldehydes and liquid ammonia. Pharmacological screening of the new 1,4-dihyropyridines were also carried out for CNS depresant (anticonvulsant and analgesic) and cardiovascular (inotropic and blood pressure) activities by standard methods.



Neamati and coworkers[44] reported that a 1,4-dihydorpyridine NCS-372643 came out with its anti-HIV activity, which has opened up the synthetic as well as pharmacological importance in antiviral area also.



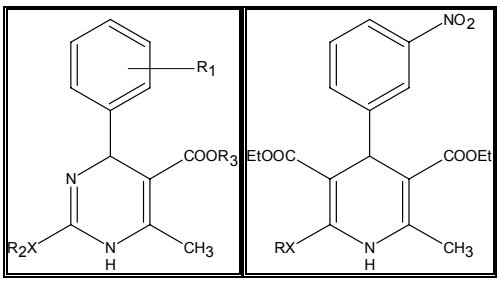
Sonja[66] and group have synthesized a new series of calcium channel agonists structurally related to Bay K8644, containing NO donor furoxans and the related furazans unable to release NO. The racemic mixtures were studied for their action on L-type Ca^{2+} channels expressed in cultured rat insulinoma RINm5F cells. All the products proved to be potent calcium channel agonists



Recent reports show that efonidipine, a dihydropyridine Ca^{2+} antagonist, has blocking action on T-type Ca channels, which may produce favorable actions on cardiovascular systems. However, the effects of other dihydropyridine Ca antagonists on T-type Ca channels have not been investigated yet. Therefore, Furukawa and group[67] have examined the effects of dihydropyridine compounds clinically used for treatment of hypertension on a T-type Ca channel subtype, alpha1G, expressed in Xenopus oocytes. Twelve DHPs (amlodipine, barnidipine, benidipine, cilnidipine, efonidipine, felodipine, manidipine, nicardipine, nifedipine, nilvadipine, nimodipine, nitrendipine) and mibefradil were tested. Cilnidipine, felodipine, nifedipine, nilvadipine, minodipine, and nitrendipine had little effect on the T-type channel. The blocks by drugs at 10 muM were less than 10% at a holding potential of -100 mV. The remaining 6 drugs had blocking action on the T-type channel comparable to that on the L-type channel. These results show that many dihydropyridine Ca^{2+} antagonists have blocking action on the alpha1G channel subtype.

Labedipinedilol-A, a novel dihydropyridine-type calcium antagonist, has been shown to induce hypotension and vasorelaxation. Liou[68] and co-workers have studied to investigate the effect of labedipinedilol-A on vascular function of rat aortic rings and cultured human umbilical vein endothelial cells (HUVECs).

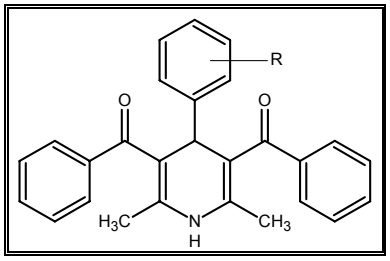
2-Heterosubstituted-4-aryl-l,4-dihydro-6-methyl-5-pyrimidinecarboxylic acid esters, which lack the potential C_3 symmetry of dihydropyridine calcium channel blockers, were evaluated for biological activity. Biological assays using potassium-depolarized rabbit aorta and radioligand binding techniques showed that some of these compounds are potent mimics of dihydropyridine calcium channel blockers. The combination of a branched ester (e.g. isopropyl, sec-butyl) and an alkylthio group (e.g. SMe) was found to be optimal for biological activity[69].


R1
COOR3
N
R2X
N
H
CH3
NO2
EtOOC
COOEt
RX
N
H
CH3

4.2 Current work

In last few years, 1,4-dihydropyridine skeleton is extensively modified in our laboratory and very interesting results are obtained with these modification to various positions of 1,4-dihydropyridine skeleton and can be discussed as below.

3,5-dibenzoyl-1,4-dihydropyridines (BzDHPs) substituted at 4-phenyl ring were synthesized and compared for their cytotoxic activity and multidrug resistance reversing activity in in vitro assay systems. Among fifteen BzDHPs, 2-trifluoromethyl, 2-chloro and 3-chloro derivatives showed the highest cytotoxic activity[70].

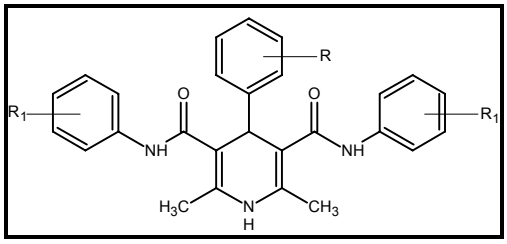


R = 2-CF_3, 3-CF_3, 4-CF_3, 2-Cl, 3-Cl, 4-Cl, 2-NO_2, 3-NO_2, 3-OPh etc.

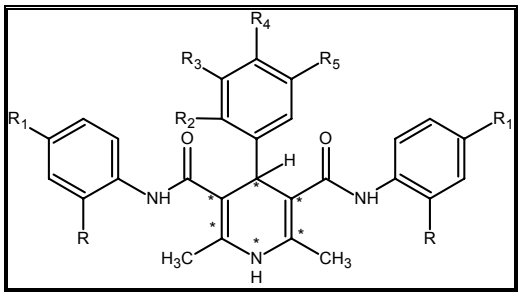
3,5-Dibenzoyl-4-(3-phenoxyphenyl)-1,4-dihydropyridine-2,6-dimethylpyridine, a BzDHP derivative as *mdr* inhibitor, was investigated for cardiac effects in Langendorff-perfused rat heart and compared with nifedipine. It was found that this molecule represent a lead for development of potent DHP *mdr* chemosensitizers devoid of cardiac effect[71].

Dibenzoyl-DHPs, tested for their mdr reversing activity, were found to show one or two orders higher tumor-specific cytotoxic activity against human tumor cell lines than human normal cells[72].

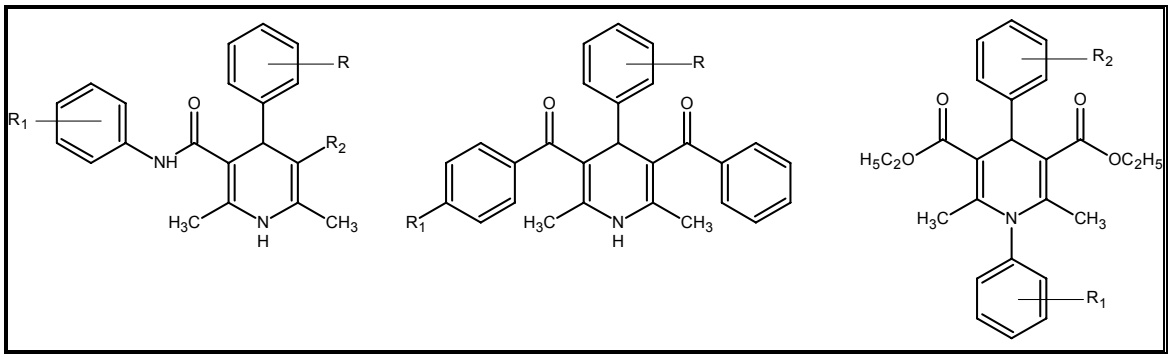
Dihydropyridine derivatives with phenyl carbamoyl side chain on 3 and 5 positions were synthesized and evaluated for their anti-tubercular activity. The results of anti-tubercular activity for dicarbamoyl derivatives were studied for 2D QSAR. The study indicates the presence of bulkier group on 4-phenyl ring contributes for the activity. The electronic influence of substituents at carbamoyl phenyl ring is important for activity[73].



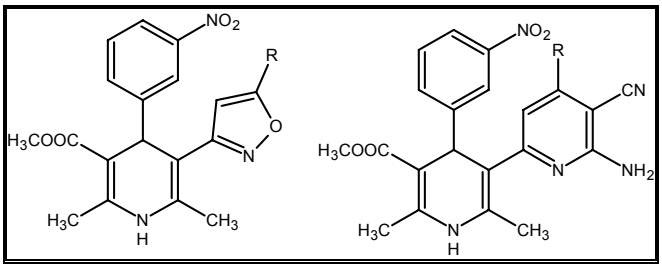
To find out structural requirement of dicarbamoyl DHPs for anti tubercular activity, CoMFA and CoMSIA methods were applied on a set of 33 dicarbamoyl derivatives. The QSAR models reveal the importance of spatial properties and conformational flexibility of side chains for anti tubercular activity[74].



Dihydropyridines with N-phenyl substitution were synthesized and tested for tumor specific cytotoxicity and *mdr* reversal activity to find out the effects of N-phenyl substitution on activity. Asymmetric BzDHPs with different substitution on benzoyl aromatic ring were synthesized and evaluated for tumor specific cytotoxicity. In continuation, dihydropyridines with phenyl carbamoyl side chain on one arm and –CN, -COOEt, -COOMe side chain on other arm were also synthesized and evaluated as mdr reversal dihydropyridines[75].



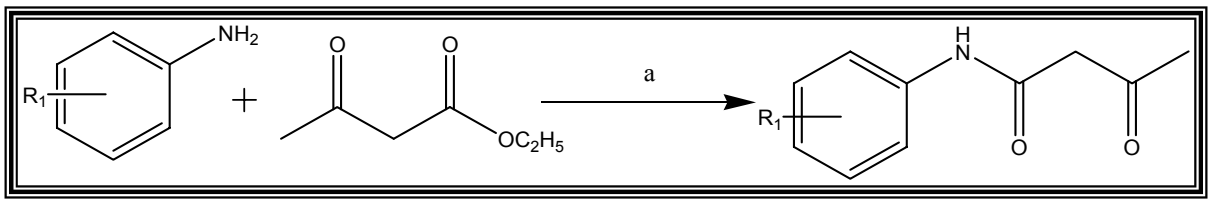
in continuation of skeleton modification, dihydropyridines with heterocyclic systems on side chain were synthesized and evaluated for anti tubercular activity. These derivatives showed moderate activity and it was found that aromatic heterocyclic systems on side chain do not enhance anti tubercular activity[76].



In continuation of work on dihydropyridine skeleton modification, this chapter reports synthesis of symmetrical 1,4-DHPs with naphthyl ring at C3 and C5 positions of DHP; and asymmetrical derivatives with different substituted phenyl carbamoyl side chain. The reaction schemes for synthesis of compounds are given in Section 4.3. The synthesized compounds and their physical data along with Mp and R_f values are given in Section 4.5. The spectral data are discussed in Section 4.6.

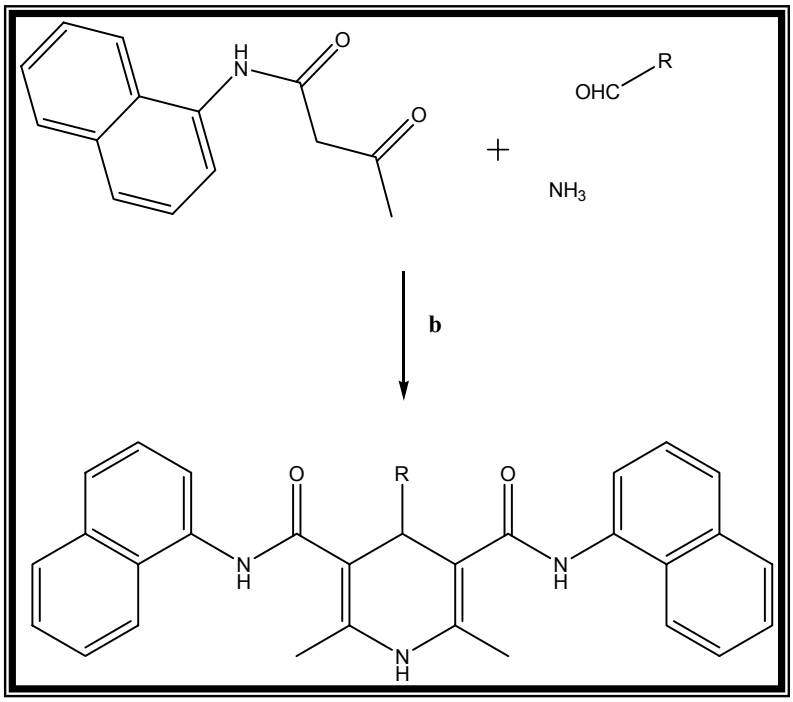
4.3 Reaction Schemes

4.3.1 Scheme 1



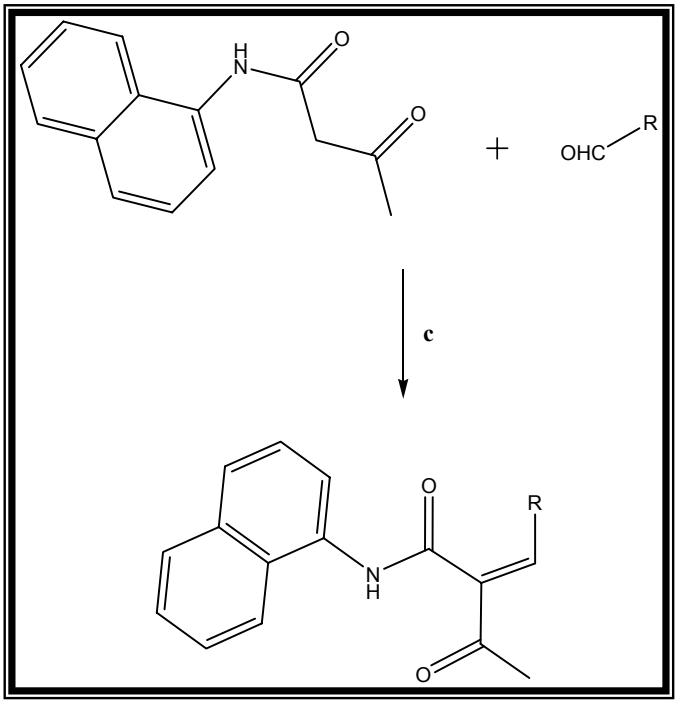
Scheme 1. Reagents and conditions: a = KOH/NaOH, toluene, 115° C.

4.3.2 Scheme 2



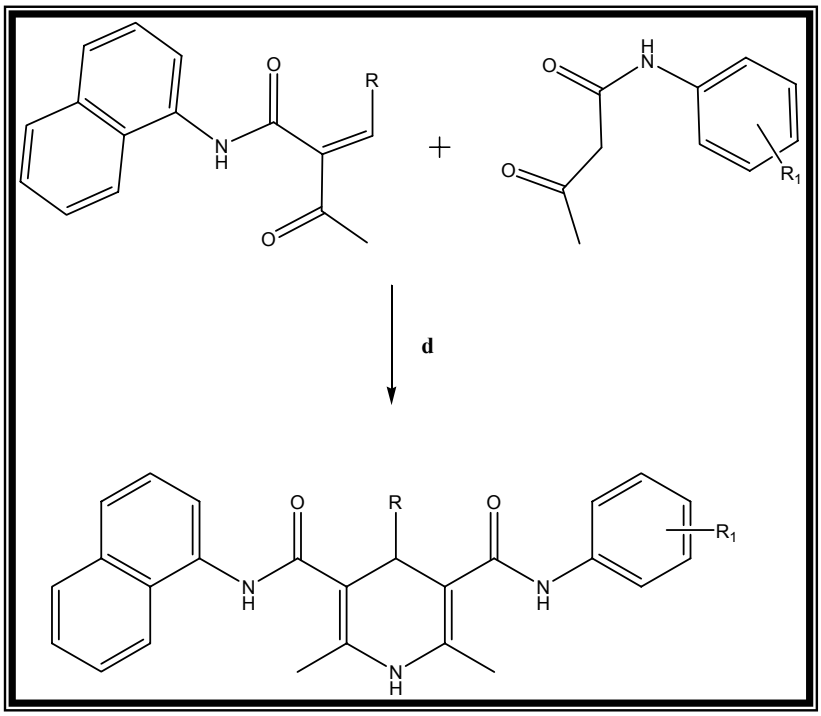
Scheme 2. Reagents and conditions: b = MeOH, reflux.

4.3.3 Scheme 3



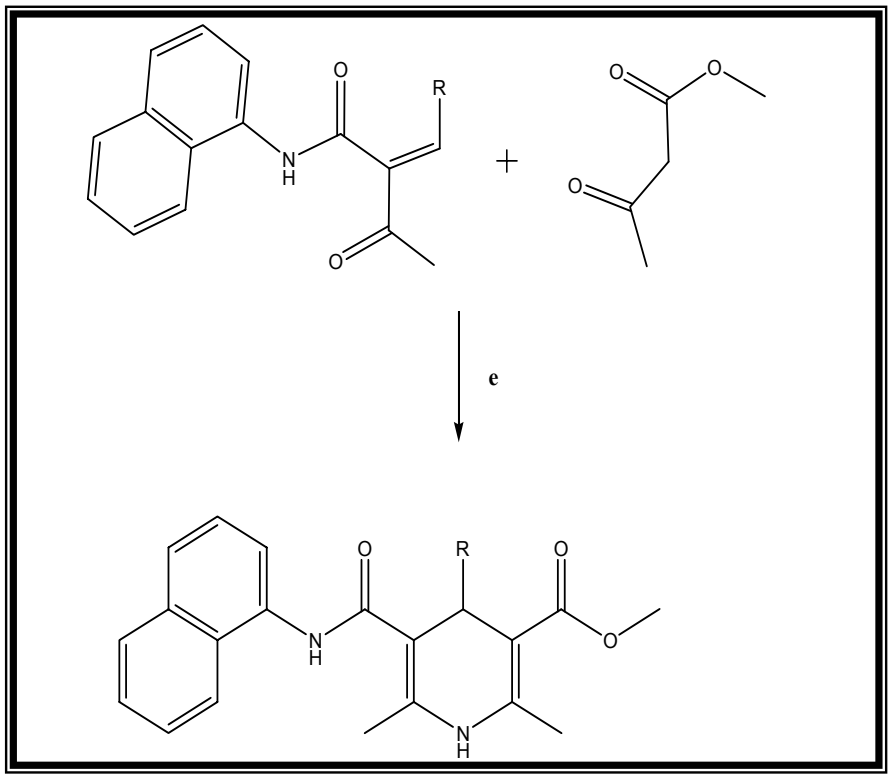
Scheme 3. Reagents and conditions: c = IPA, piperidine, reflux

4.3.4 Scheme 4



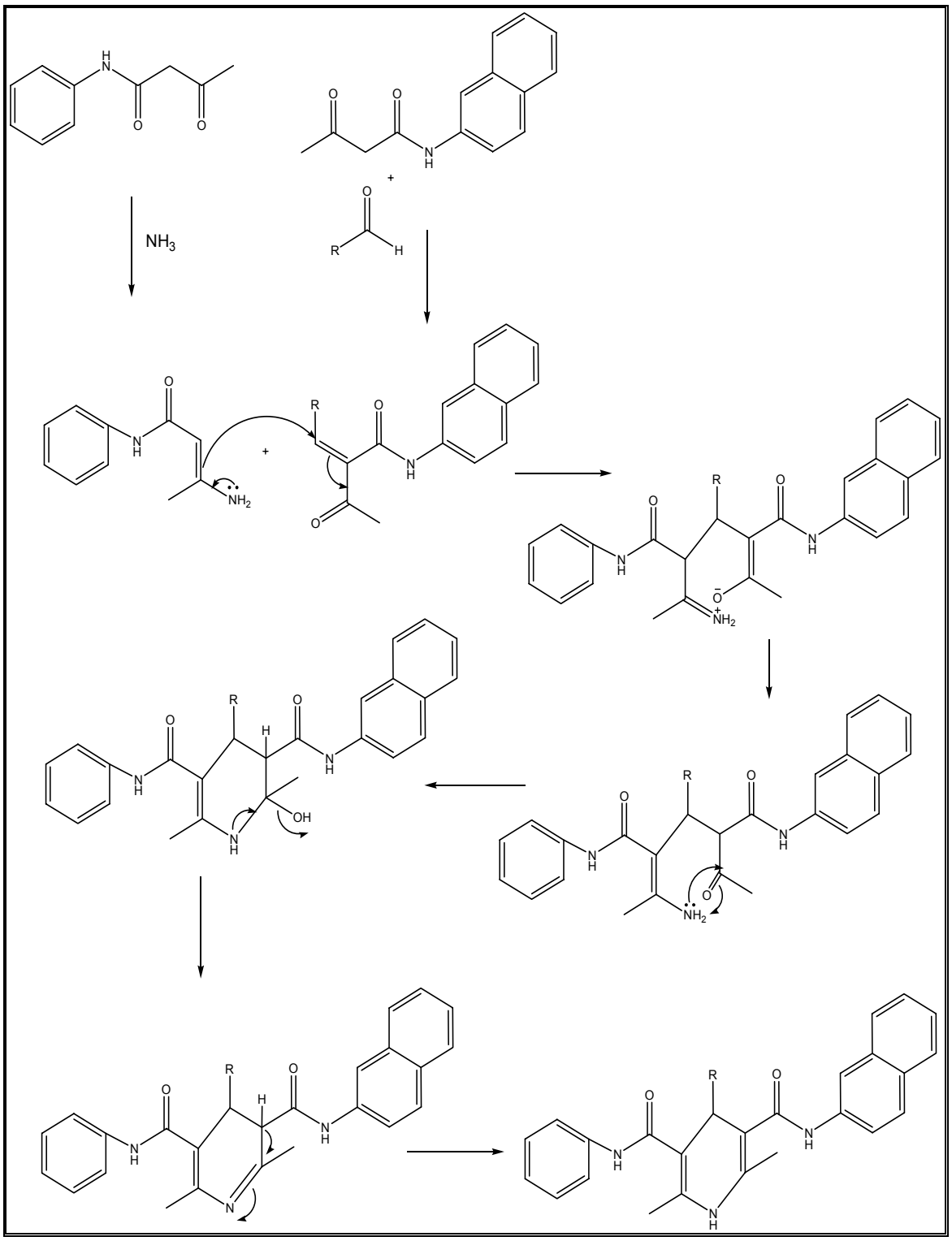
Scheme 4. Reagents and conditions: d = NH_3, MeOH, stirring, 90° C

4.3.5 Scheme 5



Scheme 5. Reagents and conditions: e = NH_3, MeOH, stirring, 90° C

Reaction Mechanism



4.4 Experimental

4.4.1 Substituted acetoacetanilide

Substituted aniline (0.1M) and ethyl aceto acetate was refluxed at 110° C in 40 ml of toluene and catalytic amount of KOH/NaOH. The completion of reaction was monitored with TLC. After completion of reaction, toluene was distilled out. The residue was cooled at room temperature and was treated with ether. The solid was filtrated and dried. (Physical data is given in Table 4.5.1)

4.4.2 2,6-Dimethyl-N,N'-di-(1-naphthyl)-4-(substitutedphenyl)-1,4-dihydropyridine-3,5-dicarboxamide

N-1-Naphthyl-3-oxobutanamide (0.02M) and aldehyde (0.01M) were dissolved in 20 ml of methanol. The rection mixture was stirred and refluxed. Ammonia (1.5 ml) was added dropwise and the reaction mixture was stirred with reflux to complete the reaction. (7-12 hours). The reaction mixture was allowed to cool and solid separated was filtered and washed with methanol. The crude product was crystallized from dimethylformamide. (Physical data is given in Table 4.5.2)

4.4.3 2-(Substitutedbenzylidene)-*N*-1-naphthyl-3-oxobutanamide

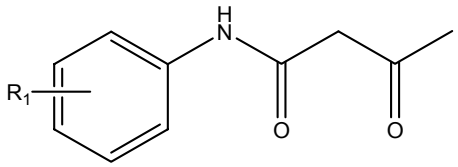
Substituted acetoacetanilide (0.01M) and aromatic aldehyde (0.01M) were taken into 30 ml of isopropyl alcohol. The reaction mixture was stirred for 30 minutes and then, catalytic amount of piperidine was added. The reaction was stirred until the completion of reaction observed by TLC. The reaction mixture was allowed to cool. The solid separated was filtered, washed with isopropyl alcohol and crystallized from methanol.

4.4.4 N-(Substitutedphenyl)-2,6-dimethyl-N'-(1-naphthyl)-4-(substitutedphenyl)-3,5-carbamoyl-1,4-dihydropyridine

2-(Substitutedbenzylidene)-*N*-1-naphthyl-3-oxobutanamide (0.01M) and substituted acetoacetanilide (0.01M) were dissolved in 25 ml of methanol. The reaction mixture was stirred and refluxed at 90° C. Ammonia (2 ml) was added drop wise and the reaction was stirred and refluxed until the completion of reaction (8-12 hours). The reaction mixture was allowed to cool and solid separated was filtered and washed with methanol. The crude product was crystallized from dimethylformamide. (Physical data is given in Table 4.5.3 & 4.5.4)

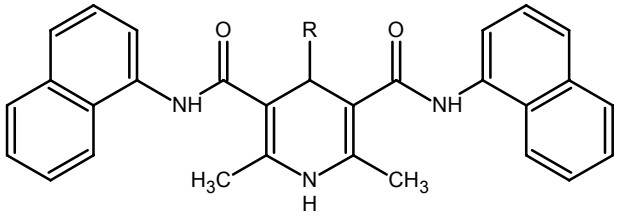
4.5 Physical data

4.5.1 Physical data of N-(substituted phenyl)-3-oxobutanamide [compounds 1a-f]



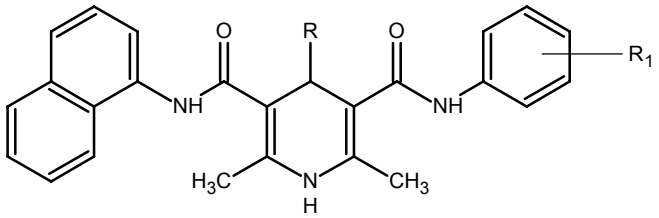
Compound	Code	R_1	MF	MW	Yield	R_f
1a	AKS-401	4-Cl	$C_{10}H_{10}ClNO_2$	211.64	58	0.64
1b	AKS-402	4-F	$C_{10}H_{10}FNO_2$	195.19	52	0.69
1c	AKS-403	3-Cl,4-F	$C_{10}H_9ClFNO_2$	229.64	45	*0.51
1e	AKS-404	4-CH_3	$C_{11}H_{13}NO_2$	191.22	53	0.52
1f	AKS-405	2,3-benzo	$C_{14}H_{13}NO_2$	227.25	57	0.47

4.5.2 Physical data of 2,6-Dimethyl-N,N'-di-(1-naphthyl)-4-(substitutedphenyl)-1,4-dihydropyridine-3,5-dicarboxamide [compounds 2a-e]



Compound	Code	R	MF	MW	MP	Yield	R_f
2a	AKS-411	1-naphthyl	$C_{39}H_{31}N_3O_2$	573.68	234-36	38	0.45
2b	AKS-412	4-NO_2-Ph	$C_{35}H_{28}ClN_3O_2$	558.06	240-41	42	0.53
2c	AKS-413	4-OCH_3-Ph	$C_{36}H_{31}N_3O_3$	553.65	233-36	40	0.42
2d	AKS-414	4-OH-Ph	$C_{35}H_{29}N_3O_3$	539.65	202-04	40	0.62
2e	AKS-415	4-Cl-Ph	$C_{35}H_{28}N_4O_4$	568.62	258-61	32	0.55

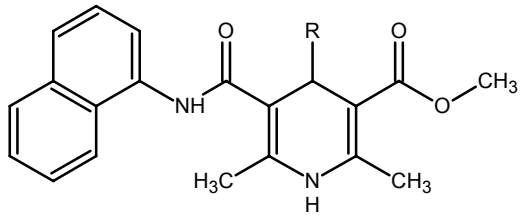
4.5.3 Physical data of N-(Substitutedphenyl)-2,6-dimethyl-N'-(1-naphthyl)-4-(substitutedphenyl)-3,5-carbamoyl-1,4-dihydropyridine [compounds 4a-p]



Compound	Code	R	R_1	MF	MW	MP	Yield	R_f
4a	AKS-431	Ph	4-Cl	$C_{31}H_{26}ClN_3O_2$	508.01	211-13	42	0.47
4b	AKS-432	4-Cl-Ph	4-Cl	$C_{31}H_{25}Cl_2N_3O_2$	542.45	230-31	45	0.51
4c	AKS-433	4-NO_2-Ph	4-Cl	$C_{31}H_{25}ClN_4O_4$	553.00	207-10	38	0.39
4d	AKS-434	4-OCH_3-Ph	4-Cl	$C_{32}H_{28}ClN_3O_3$	538.03	252-55	40	0.43
4e	AKS-435	Ph	4-F	$C_{31}H_{26}FN_3O_2$	491.55	197-99	42	0.55
4f	AKS-436	4-Cl-Ph	4-F	$C_{31}H_{25}ClFN_3O_2$	526.00	204-07	47	0.58
4g	AKS-437	4-NO_2-Ph	4-F	$C_{31}H_{25}FN_4O_4$	536.55	233-34	36	0.62
4h	AKS-438	4-OCH_3-Ph	4-F	$C_{32}H_{28}FN_3O_3$	521.58	184-85	42	0.60

4i	AKS-439	Ph	3-Cl,4-F	$C_{31}H_{25}ClFN_3O_2$	526.00	244-45	46	0.46
4j	AKS-440	4-Cl-Ph	3-Cl,4-F	$C_{31}H_{24}Cl_2FN_3O_2$	560.44	267-69	33	0.50
4k	AKS-441	4-NO_2-Ph	3-Cl,4-F	$C_{31}H_{24}ClFN_4O_4$	570.99	253-56	30	0.43
4l	AKS-442	4-OCH_3-Ph	3-Cl,4-F	$C_{35}H_{27}ClFN_3O_3$	556.02	220-22	38	0.56
4m	AKS-443	Ph	4-CH_3	$C_{32}H_{29}N_3O_2$	487.59	192-93	44	0.61
4n	AKS-444	4-Cl-Ph	4-CH_3	$C_{32}H_{28}ClN_3O_2$	522.03	199-00	40	0.59
4o	AKS-445	4-NO_2-Ph	4-CH_3	$C_{32}H_{28}N_4O_4$	532.58	213-14	45	0.52
4p	AKS-446	4-OCH_3-Ph	4-CH_3	$C_{33}H_{31}N_3O_3$	517.61	204-05	42	0.47

4.5.4 Physical data of methyl 5-(naphthalen-1-ylcarbamoyl)-1,4-dihydro-2,6-dimethyl-4-(substitutedphenyl) pyridine-3-carboxylate [compounds 5a-e]



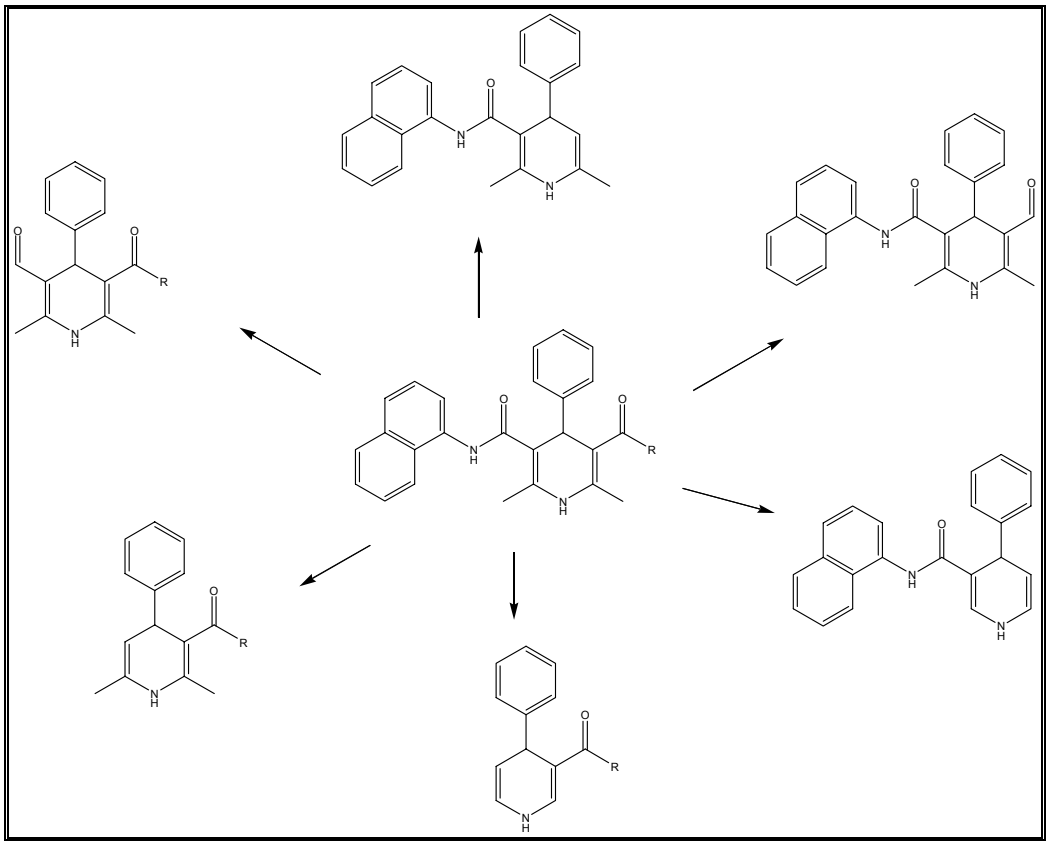
Compound	Code	R	MF	MW	MP	Yield	R_f
5a	AKS-451	Ph	$C_{26}H_{24}N_2O_3$	412.67	188-89	42	0.45
5b	AKS-452	4-Cl-Ph	$C_{26}H_{23}ClN_2O_3$	446.92	208-10	38	0.36
5c	AKS-453	4-OCH_3-Ph	$C_{27}H_{26}N_2O_4$	443.50	165-67	35	0.52
5d	AKS-454	4-NO_2-Ph	$C_{26}H_{23}N_3O_5$	457.47	192-93	40	0.33
5e	AKS-455	4-CH_3-Ph	$C_{27}H_{26}N_2O_3$	426.50	176-79	38	0.47

TLC solvent system: Compound 1a-f (EA:Hexane) 2:8, *1:9
Compound 2a-e (EA:Hexane) 4:6
Compound 4a-p (EA:Hexane) 3:7
Compound 5a-e (EA:Hexane) 4:6
MPs were taken in open capillary and are not corrected

4.6 Spectral discussion

4.6.1 *Mass spectral study*

Molecular ion peak was observed in agreement with molecular weight of compound in mass spectra of synthesized dihydropyridine compounds. Systematic fragmentation pattern was observed in mass spectral analysis. Characteristic peaks for specific fragments were identified in each mass spectrum. Following diagram shows characteristic fragments which gave peak at particular m/e values in mass spectrum. Cleavage of bonds adjacent to carbonyl double bond gave fragments at specific m/e values. In case of compound AKS-446, molecular ion peak was observed at 518 m/e and base peak was obtained at 269 due to cleavage of two C-N bond adjacent to both carbonyl groups. Compound AKS-451 and AKS-453 gave molecular ion peak at 413 and 444 m/e respectively. Following fragmentation pattern was observed in all spectra.



(Mass spectrums of AKS-412, AKS-446, AKS-451, and AKS-453 are given on Page no. 150 & 151)

4.6.2 IR spectral study

In IR spectrums, characteristic frequencies were observed for functional group present in the molecule. Functional groups present in the molecules like –NH-, Ar-H, -Me, C=O, Ar-C=C, C-N, C-O and OOP vibrations were observed in IR spectrum. Secondary amide (N-H) vibrations gave peaks between 3302-3470 cm^{-1}. Characteristic peaks were observed for aromatic ring vibrations (Ar-H, C=C, OOP). In case of dicarbamoyl DHP, two amide carbonyl groups gave two peaks between 1654-1698 cm^{-1}, while DHPs with ester group on side chain gave carbonyl frequency at 1705-1715 cm-1. Methyl groups also gave characteristic peaks between 2900-3100 cm^{-1}. C-N vibrations were observed between 1250-1320 cm^{-1}.

(IR spectrums of AKS-431, AKS-436, AKS-441, and AKS-446 are given on Page no. 146 & 147)

4.6.3 ^{1}H NMR spectral study

Number of protons and their chemical shifts were found to support the structure of the synthesized compounds. In spectrum of compound AKS-411, methyl proton at 2 & 6 position gave singlet for six protons at 2.32 δ ppm. C_4-proton was observed at 5.66 δ ppm. A triplet was observed for four protons at 6 & 7 position of both naphthyl rings at 7.42, while proton at 3rd positions of both naphthyl rings gave triplet for two protons at 7.32. Doublets were obtained at 7.50, 7.57, 7.68 and 8.21 δ ppm for two protons each with 7.16, 8.44, 8.04 and 8.56 J value respectively. Two carabmoyl –NH- protons gave singlet 2H at 9.17 δ ppm.

In case of AKS-413, 6H of two methyl group of DHP gave singlet at 2.83 while methoxy protons gave singlet in downfield at 3.78 δ ppm. C_4 proton singlet was obtained at 5.00 δ ppm. Aromatic protons were obtained 6.97-7.83 δ ppm. A triplet was obtained at 7.26 δ ppm for two protons with J value of 7.00. a double doublet with J value of 2.96 and 9.28 was observed at 7.69 δ ppm. Doublets were obtained at 6.97, 7.16, 7.65 and 7.80 with 8.76, 8.48, 8.72 and 8.16 J value respectively. Two –NH- protons gave singlet at 10.06 δ ppm.

(^{1}H NMR spectrum of AKS-411 and AKS-413 are given on Page no. 148 & 149)

4.6.4 Elemental analysis

Elemental analysis of synthesized compounds was in agreement with calculated values of carbon, hydrogen and nitrogen. The spectral and elemental analysis data of individual compound is given below.

Spectral data of synthesized compounds (AKS 411-415, AKS 431-446 & AKS-451-455)

2,6-Dimethyl-N,N'-di-(1-naphthyl)-4-(1-naphthyl)-1,4-dihydropyridine-3,5-dicarboxamide (AKS-411) – *IR* *(cm^{-1}):* 3457, 3318 (-NH-), 3145 (Ar-H), 3078, 2946 (-Me), 1689, 1676 (C=O), 1633, 1568 (C=C), 1287 (C-N), 1143 (C-O), 834, 766 (OOP); ***^{1}H NMR*** *(DMSO d6) (δ ppm)*: 2.32 (6H, s), 5.66 (1H, s), 7.32 (2H, t, J=7.60, 7.44), 7.42 (4H, t, J=7.68, 7.18), 7.50 (2H, d, J=7.16), 7.57 (2H, d, J=8.44), 7.68 (2H, d, 8.04), 7.77 (5H, m), 7.97 (2H, d), 8.21 (2H, d, J=8.56), 9.17 (2H, s); ***Anal cacld*** for $C_{20}H_{18}ClN_3OS$: C 62.57, H 4.73, N 10.95, found: C 62.61, H 4.72, N 10.97.

2,6-Dimethyl-N,N'-di-(1-naphthyl)-4-(4-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxamide (AKS-412) - *IR* *(cm^{-1}):* 3456, 3384 (-NH-), 3109 (Ar-H), 3057, 2921 (-Me), 1697, 1663 (C=O), 1607, 1552 (C=C), 1308 (C-N), 1181 (C-O), 814 (OOP); ***Mass*** *(m/e):* 566 (molecular ion peak), 424, 397, 382, 367, 312, 281, 255 (base peak), 225, 209, 182, 169, 143, 115, 89, 70; ***Anal cacld*** for $C_{20}H_{18}ClN_3OS$: C 62.57, H 4.73, N 10.95, found: C 62.61, H 4.72, N 10.97.

2,6-Dimethyl-N,N'-di-(1-naphthyl)-4-(4-methoxyphenyl)-1,4-dihydropyridine-3,5-dicarboxamide (AKS-413) - *IR* *(cm^{-1}):* 3474, 3361(-NH-), 3124 (Ar-H), 3027, 2952 (-Me), 1677, 1653 (C=O), 1602, 1582 (C=C), 1260 (C-N), 1164 (C-O), 786 (OOP); ***^{1}H NMR*** *(DMSO d6) (δ ppm)*: 2.83 (6H, s), 3.78 (3H, s), 5.00 (1H, s), 6.97 (2H, d, J=8.76), 7.16 (2H, d, J=8.48), 7.26 (2H, t, J=7.00), 7.42 (4H, m), 7.65 (2H, d, J=8.72), 7.69 (2H, dd, J=2.96, 9.28), 7.80 (2H, d, J=8.16), 7.83 (3H, d), 10.06 (2H, s); ***Anal cacld*** for $C_{20}H_{18}ClN_3OS$: C 62.57, H 4.73, N 10.95, found: C 62.61, H 4.72, N 10.97.

2,6-Dimethyl-N,N'-di-(1-naphthyl)-4-(4-hydroxyphenyl)-1,4-dihydropyridine-3,5-dicarboxamide (AKS-414) - *IR* *(cm^{-1}):* 3386 (-OH-), 3341 (-NH-), 3107 (Ar-H), 3033, 2928 (-Me), 1670, 1654 (C=O), 1600, 1555 (C=C), 1258 (C-N), 1113 (C-O), 814, 725 (OOP); ***Anal cacld*** for $C_{20}H_{18}ClN_3OS$: C 62.57, H 4.73, N 10.95, found: C 62.61, H 4.72, N 10.97.

2,6-Dimethyl-N,N'-di-(1-naphthyl)-4-(4-chlorophenyl)-1,4-dihydropyridine-3,5-dicarboxamide (AKS-415) – *IR* *(cm^{-1}):* 3450, 3368 (-NH-), 3103 (Ar-H), 3055, 2933 (-Me), 1696, 1658 (C=O), 1613, 1577 (C=C), 1310 (C-N), 1086 (C-O), 804(OOP); ***Anal cacld*** for $C_{20}H_{18}ClN_3OS$: C 62.57, H 4.73, N 10.95, found: C 62.61, H 4.72, N 10.97.

N-(4-Chlorophenyl)-2,6-dimethyl-N'-(1-naphthyl)-4-phenyl-3,5-carbamoyl-1,4-dihydropyridine (AKS-431) – *IR* *(cm^{-1}):* 3423, 3313 (-NH-), 3093 (Ar-H), 2925, 2844 (-Me), 1662, 1653 (C=O), 1604, 1533 (C=C), 1290 (C-N), 1114 (C-O), 833, 742 (OOP); ***Anal cacld*** for $C_{31}H_{26}ClN_3O_2$: C 73.29, H 5.16, N 8.27, found: C 73.35, H 5.19, N 8.32.

N-(4-Chlorophenyl)-2,6-dimethyl-N'-(1-naphthyl)-4-(4-chlorophenyl)-3,5-carbamoyl-1,4-dihydropyridine (AKS-432) - *IR* *(cm^{-1}):* 3410, 3372 (-NH-), 3088 (Ar-H), 3015, 2946 (-Me), 1690, 1668 (C=O), 1617, 1562(C=C), 1247 (C-N), 1077 (C-O), 796 (OOP); ***Anal cacld*** for $C_{31}H_{25}Cl_2N_3O_2$: C 68.64, H 4.65, N 7.75, found: C 68.68, H 4.66, N 7.81.

N-(4-Chlorophenyl)-2,6-dimethyl-N'-(1-naphthyl)-4-(4-nitrophenyl)-3,5-carbamoyl-1,4-dihydropyridine (AKS-433) - *IR* *(cm^{-1}):* 3376, 3327 (-NH-), 3110 (Ar-H), 3005, 2955 (-Me), 1672, 1656 (C=O), 1616, 1546 (C=C), 1332 (C-N), 1121 (C-O), 812 (OOP); ***Anal cacld*** for $C_{31}H_{25}ClN_4O_4$: C 67.73, H 4.56, N 10.13, found: C 67.75, H 4.60, N 10.21.

N-(4-Chlorophenyl)-2,6-dimethyl-N'-(1-naphthyl)-4-(4-methoxyphenyl)-3,5-carbamoyl-1,4-dihydropyridine (AKS-434) – *IR* *(cm^{-1}):* 3354, 3286 (-NH-), 3117 (Ar-H), 3050, 2944 (-Me), 1698, 1657 (C=O), 1630, 1525 (C=C), 1290 (C-N), 1167 (C-O), 817, 763 (OOP); ***Anal cacld*** for $C_{32}H_{28}ClN_3O_3$: C 71.43, H 5.25, N 7.81, found: C 71.48, H 5.27, N 7.88.

N-(4-Fluorophenyl)-2,6-dimethyl-N'-(1-naphthyl)-4-phenyl-3,5-carbamoyl-1,4-dihydropyridine (AKS-435) - *IR* *(cm^{-1}):* 3433, 3347 (-NH-), 3104 (Ar-H), 3022, 2952 (-Me), 1679, 1665 (C=O), 1613, 1580 (C=C), 1272 (C-N), 1086 (C-O), 830, 747 (OOP); ***Anal cacld*** for $C_{31}H_{26}FN_3O_2$: C 75.75, H 5.33, N 8.55, found: C 75.79, H 5.35, N 8.61.

N-(4-Fluorophenyl)-2,6-dimethyl-N'-(1-naphthyl)-4-(4-chlorophenyl)-3,5-carbamoyl-1,4-dihydropyridine (AKS-436) – *IR* *(cm^{-1}):* 3410, 3372 (-NH-), 3088 (Ar-H), 3015, 2946 (-Me), 1690, 1668 (C=O), 1617, 1562(C=C), 1247 (C-N), 1077 (C-O), 796 (OOP); ***Anal cacld*** for $C_{31}H_{25}ClFN_3O_2$: C 70.79, H 4.79, N 7.99, found: C 70.75, H 4.79, N 8.06.

N-(4-Fluorophenyl)-2,6-dimethyl-N'-(1-naphthyl)-4-(4-nitrophenyl)-3,5-carbamoyl-1,4-dihydropyridine (AKS-437) - *IR* *(cm^{-1}):* 3431, 3251 (-NH-), 2921, 2853 (-Me), 1681, 1631 (C=O), 1592, 1516 (C=C), 1221 (C-N), 1083 (C-O), 747 (OOP); ***Anal cacld*** for $C_{31}H_{25}FN_4O_4$: C 69.39, H 4.70, N 10.44, found: C 69.44, H 4.73, N 10.51.

N-(4-Fluorophenyl)-2,6-dimethyl-N'-(1-naphthyl)-4-(4-methoxyphenyl)-3,5-carbamoyl-1,4-dihydropyridine (AKS-438) - *IR* *(cm^{-1}):* 3462, 3316 (-NH-), 3118(Ar-H), 3066, 2925 (-Me), 1697, 1670 (C=O), 1630, 1561 (C=C), 1282 (C-N), 1141 (C-O), 801 (OOP); ***Anal cacld*** for $C_{32}H_{28}FN_3O_3$: C 73.69, H 5.41, N 8.06, found: C 73.74, H 5.47, N 8.13.

N-(3-Chloro-4-fluorophenyl)-2,6-dimethyl-N'-(1-naphthyl)-4-phenyl-3,5-carbamoyl-1,4-dihydropyridine (AKS-439) - *IR* *(cm^{-1}):* 3417, 3310 (-NH-), 3144 (Ar-H), 3077, 2945 (-Me), 1688, 1671 (C=O), 1637, 1519 (C=C), 1283(C-N), 1157 (C-O), 755 (OOP); ***Anal cacld*** for $C_{31}H_{25}ClFN_3O_2$: C 70.79, H 4.79, N 7.99, found: C 70.54, H 4.82, N 8.05.

N-(3-Chloro-4-fluorophenyl)-2,6-dimethyl-N'-(1-naphthyl)-4-(4-chlorophenyl)-3,5-carbamoyl-1,4-dihydropyridine (AKS-440) - *IR* *(cm^{-1}):* 3403, 3341 (-NH-), 3111 (Ar-H), 3017, 2904 (-Me), 1690, 1662 (C=O), 1608, 1547 (C=C), 1288 (C-N), 1122 (C-O), 740 (OOP); ***Anal cacld*** for $C_{31}H_{24}Cl_2FN_3O_2$: C 69.82, H 4.76, N 6.78, found: C 69.87, H 4.79, N 6.86.

N-(3-Chloro-4-fluorophenyl)-2,6-dimethyl-N'-(1-naphthyl)-4-(4-nitrophenyl)-3,5-carbamoyl-1,4-dihydropyridine (AKS-441) – *IR* *(cm^{-1}):* 3427, 3244 (-NH-), 3111 (Ar-H), 2926, 2854 (-Me), 1707, 1660 (C=O), 1591, 1518 (C=C), 1295 (C-N), 1186 (C-O), 856, 741 (OOP); ***Anal cacld*** for $C_{31}H_{24}ClFN_4O_4$: C 65.21, H 4.24, N 9.81, found: C C 65.26, H 4.26, N 9.88.

N-(3-Chloro-4-fluorophenyl)-2,6-dimethyl-N'-(1-naphthyl)-4-(4-methoxyphenyl)-3,5-carbamoyl-1,4-dihydropyridine (AKS-442) - *IR* *(cm^{-1}):* 3375, 3263 (-NH-), 3120 (Ar-H), 3053, 2947 (-Me), 1681, 1658 (C=O), 1630, 1547 (C=C), 1250 (C-N), 1137 (C-O), 811 (OOP); ***Anal cacld*** for $C_{35}H_{27}ClFN_3O_3$: C 71.65, H 5.25, N 6.82, found: C 71.67, H 5.28, N 6.89.

N-(4-Methylphenyl)-2,6-dimethyl-N'-(1-naphthyl)-4-phenyl-3,5-carbamoyl-1,4-dihydropyridine (AKS-443) - *IR* *(cm^{-1}):* 3444, 3361 (-NH-), 3107 (Ar-H), 3047, 2991 (-Me), 1677, 1655 (C=O), 1622, 1542 (C=C), 1255 (C-N), 1078 (C-O), 744 (OOP); ***Anal cacld*** for $C_{32}H_{29}N_3O_2$: C 78.17, H 5.89, N 7.44, found: C 78.22, H 5.94, N 7.52.

N-(4-Methylphenyl)-2,6-dimethyl-N'-(1-naphthyl)-4-(4-chlorophenyl)-3,5-carbamoyl-1,4-dihydropyridine (AKS-444) - *IR* *(cm^{-1}):* 3486, 3314 (-NH-), 3140 (Ar-H), 3071, 2913 (-Me), 1695, 1664 (C=O), 1610, 1554 (C=C), 1302 (C-N), 1188 (C-O), 798 (OOP); ***Anal cacld*** for $C_{32}H_{28}ClN_3O_2$: C 74.75, H 5.50, N 7.12, found: C 74.79, H 5.54, N 7.19.

N-(4-Methylphenyl)-2,6-dimethyl-N'-(1-naphthyl)-4-(4-nitrophenyl)-3,5-carbamoyl-1,4-dihydropyridine (AKS-445) - *IR* *(cm^{-1}):* 3417, 3330 (-NH-), 3119 (Ar-H), 3037, 2944 (-Me), 1688, 1653 (C=O), 1612, 1554 (C=C), 1286 (C-N), 1187 (C-O), 815 (OOP); ***Anal cacld*** for $C_{32}H_{28}N_4O_4$: C 73.76, H 5.43, N 8.78, found: C 73.82, H 5.46, N 8.86.

N-(4-Methylphenyl)-2,6-dimethyl-N'-(1-naphthyl)-4-(4-methoxyphenyl)-3,5-carbamoyl-1,4-dihydropyridine (AKS-446) – *IR* *(cm^{-1}):* 3409, 3282 (-NH-), 3022 (Ar-H), 2920 (-Me), 1676, 1652 (C=O), 1598, 1490 (C=C), 1292 (C-N), 1128 (C-O), 875, 752 (OOP); ***Mass*** *(m/e):* 518 (molecular ion peak), 411, 382, 375, 367, 347, 269 (base peak), 210, 183, 143, 116, 89, 63; ***Anal cacld*** for $C_{33}H_{31}N_3O_3$: C 76.70 H 5.92, N 7.16, found: C 76.77 H 5.95, N 7.27.

Methyl-5-(naphthalen-1-ylcarbamoyl)-1,4-dihydro-2,6-dimethyl-4-phenylpyridine-3-carboxylate (AKS-451) – *IR* *(cm^{-1}):* 3512 (-NH-), 3027 (Ar-H), 2918 (-Me), 1708, 1658 (C=O), 1590, 1497 (C=C), 1272 (C-N), 1120 (C-O), 752 (OOP); ***Mass*** *(m/e):* 413 (molecular ion peak), 386, 270, 244, 217, 182, 169, 143, 115, 89, 44 (base peak); ***Anal cacld*** for $C_{26}H_{24}N_2O_3$: C 75.71 H 5.86, N 6.79, found: C 75.78 H 5.90, N 6.87.

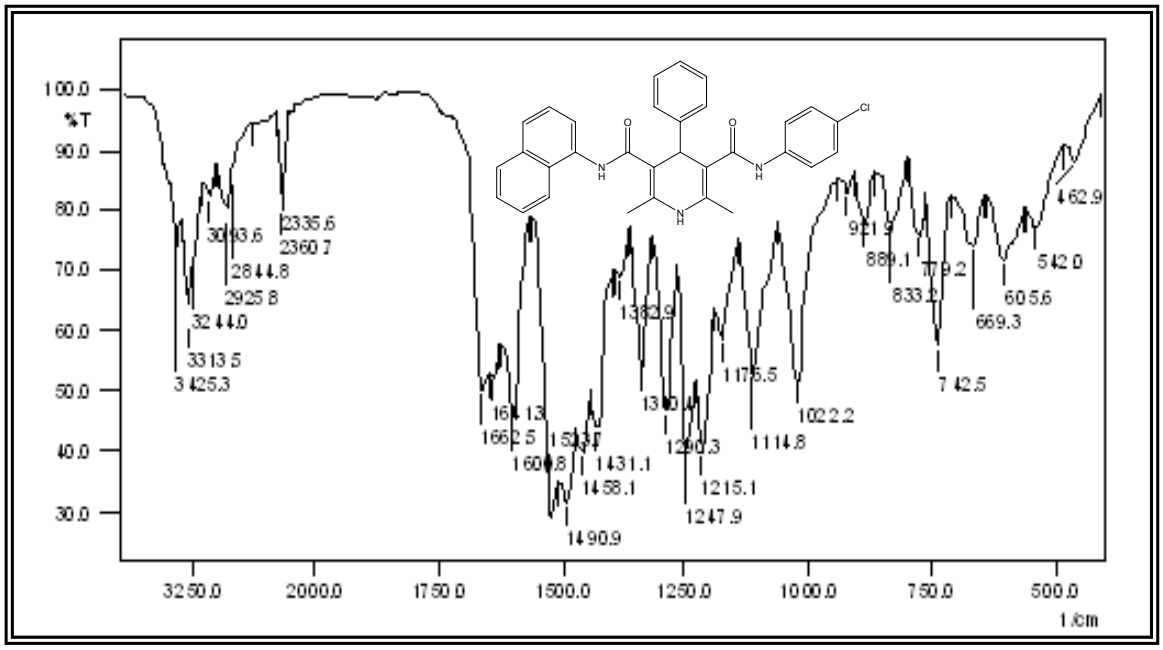
Methyl-5-(naphthalen-1-ylcarbamoyl)-1,4-dihydro-4-(4-chlorophenyl)-2,6-dimethylpyridine-3-carboxylate (AKS-452) – *IR* *(cm^{-1}):* 3378(-NH-), 3102 (Ar-H), 2956 (-Me), 1714, 1656 (C=O), 1522, 1441 (C=C), 1303 (C-N), 1121 (C-O), 875 (OOP); ***Anal cacld*** for $C_{26}H_{23}N_2O_3$: C 69.87 H 5.19, N 7.93, found: C 69.92 H 5.23, N 7.99.

Methyl-5-(naphthalen-1-ylcarbamoyl)-1,4-dihydro-4-(4-methoxyphenyl)-2,6-dimethylpyridine-3-carboxylate (AKS-453) – *IR* *(cm^{-1}):* 3411, 3280 (-NH-), 3029 (Ar-H), 2956 (-Me), 1716, 1651 (C=O), 1598, 1490 (C=C), 1259 (C-N), 1175 (C-O), 851, 748 (OOP); ***Mass*** *(m/e):* 444 (molecular ion peak), 309 (base peak), 280, 275, 252, 236, 223, 188, 169, 121, 108, 89, 71; ***Anal cacld*** for $C_{27}H_{26}N_2O_4$: C 73.28 H 5.92, N 6.33, found: C 73.34 H 5.91, N 6.39.

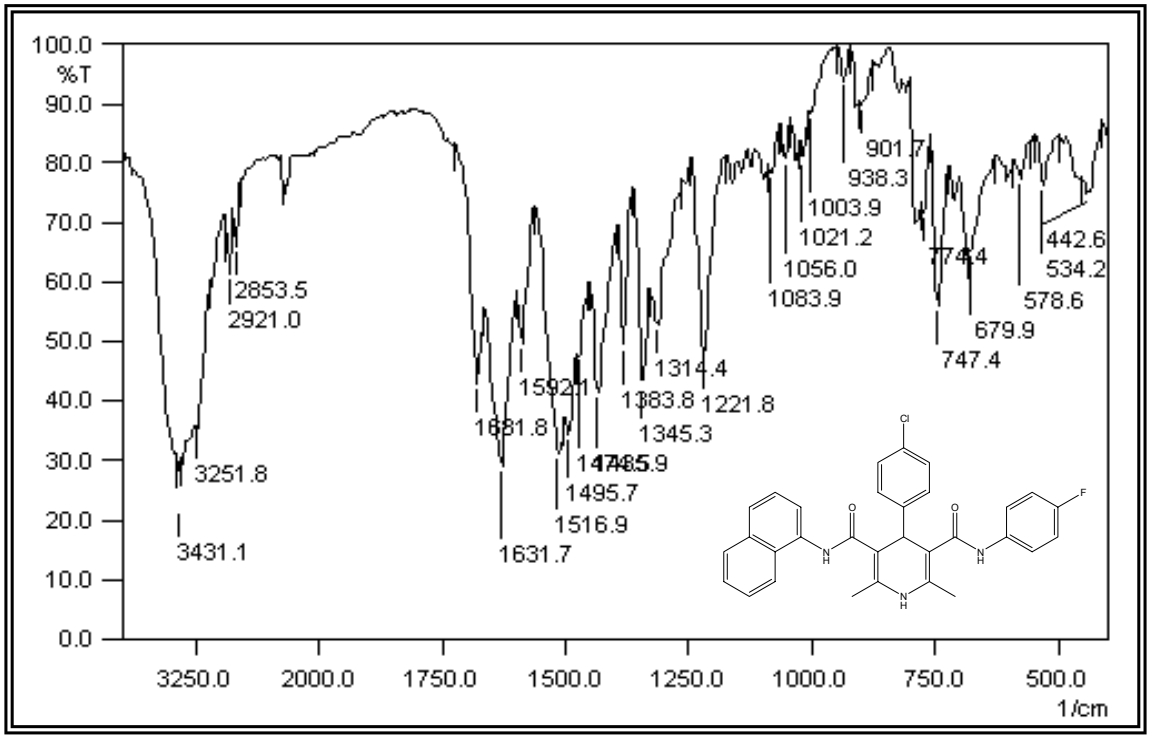
Methyl-5-(naphthalen-1-ylcarbamoyl)-1,4-dihydro-4-(4-nitrophenyl)-2,6-dimethylpyridine-3-carboxylate (AKS-454) – *IR* *(cm^{-1}):* 3396 (-NH-), 3048 (Ar-H), 2920, 2876 (-Me), 1712, 1659 (C=O), 1522, 1423 (C=C), 1262 (C-N), 1177 (C-O), 874, 750 (OOP); ***Anal cacld*** for $C_{26}H_{23}N_3O_5$: C 68.26 H 5.07, N 9.19, found: C 68.29 H 5.10, N 9.25.

Methyl-5-(naphthalen-1-ylcarbamoyl)-1,4-dihydro-4-(4-methylphenyl)-2,6-dimethylpyridine-3-carboxylate (AKS-455) – *IR* *(cm^{-1}):* 3345 (-NH-), 3018 (Ar-H), 2988, 2855 (-Me), 1705, 1656 (C=O), 1555, 1476 (C=C), 1252 (C-N), 1125 (C-O), 806 (OOP); ***Anal cacld*** for $C_{27}H_{26}N_2O_3$: C 76.03 H 6.14, N 6.57, found: C 76.11 H 6.11, N 6.60.

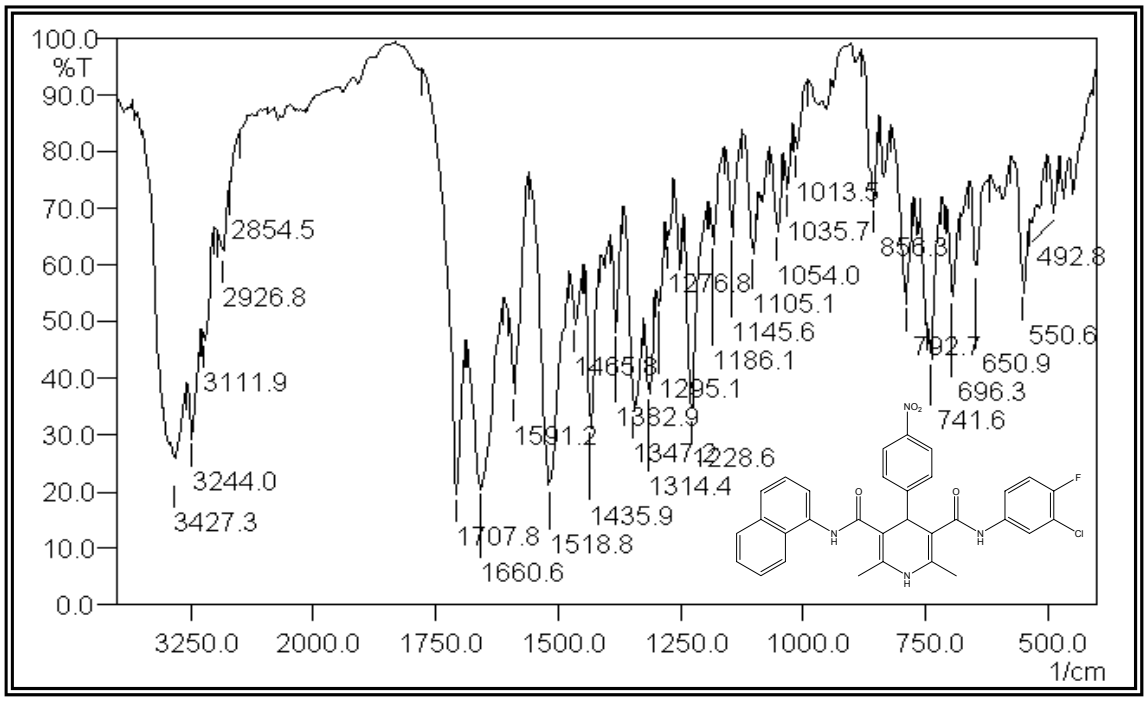
4.6.5.1 IR spectrum of AKS-431



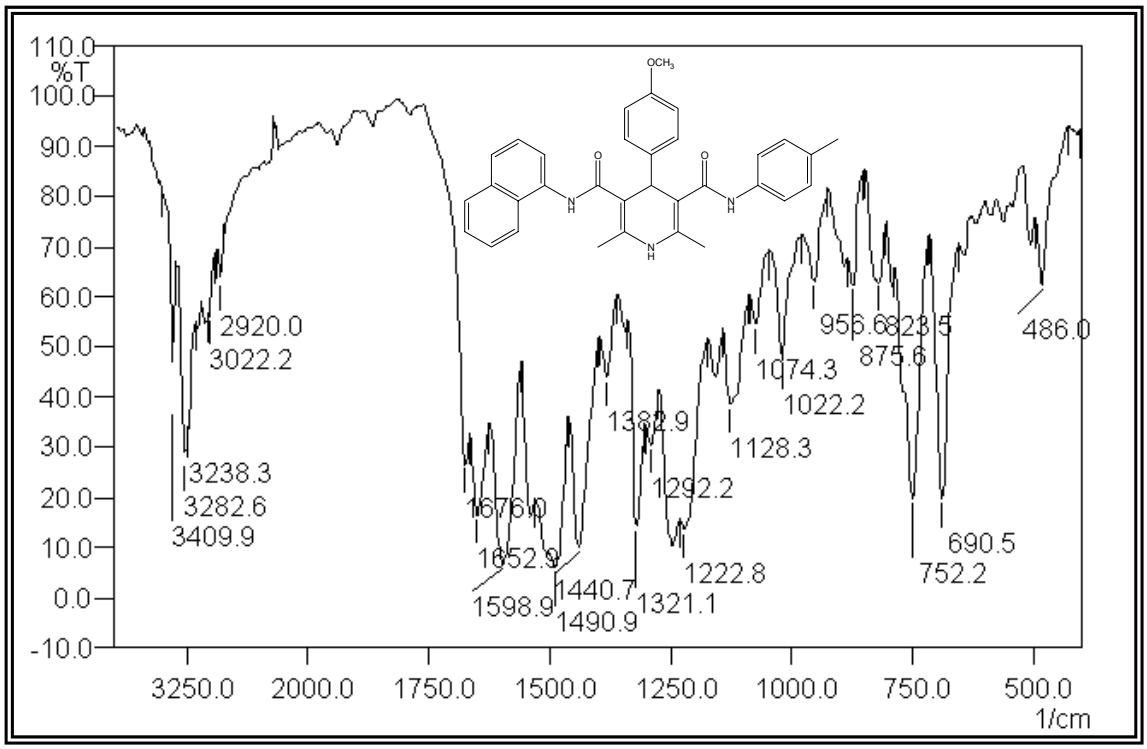
4.6.5.2 IR spectrum of AKS-436



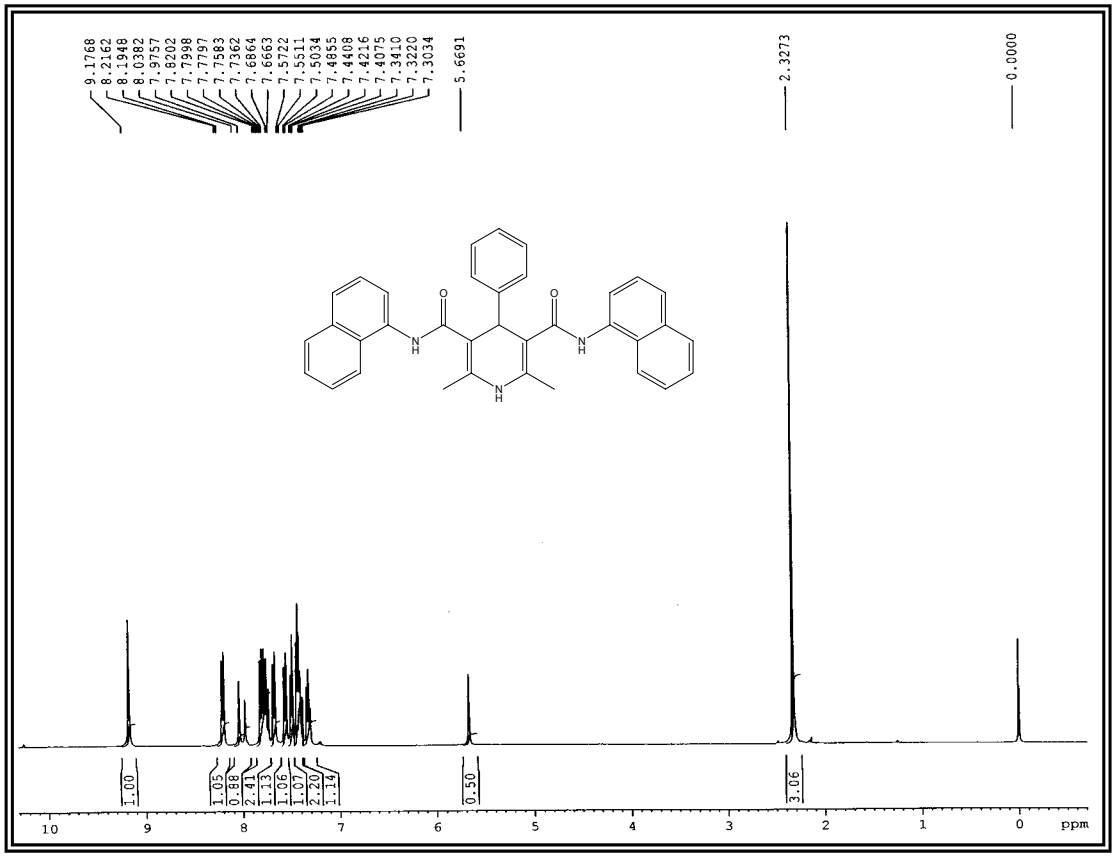
4.6.5.3 IR spectrum of AKS-441

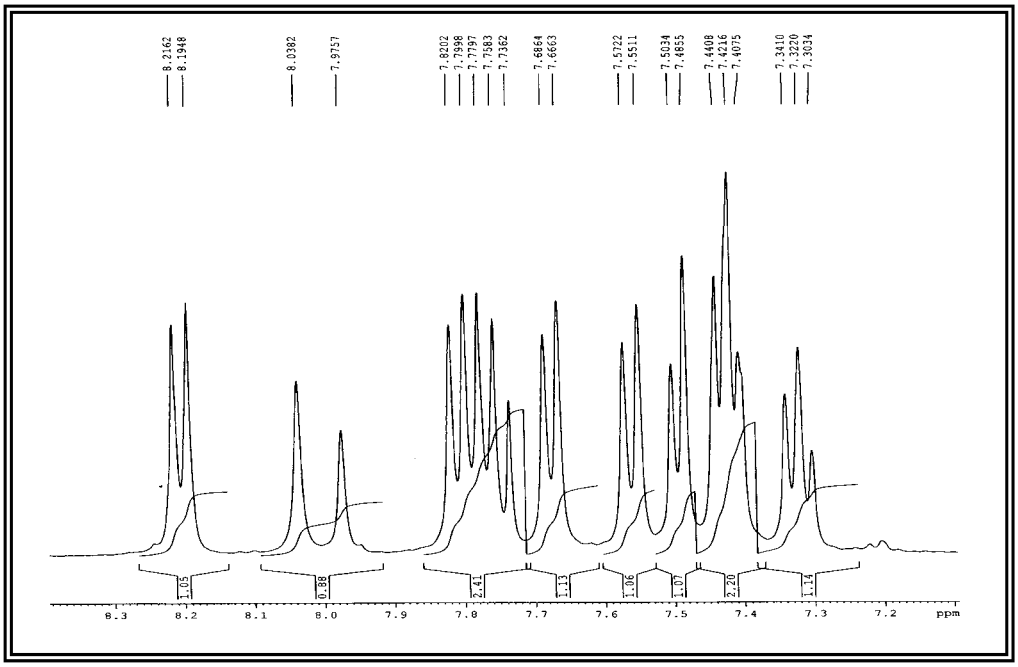


4.6.5.4 IR spectrum of AKS-446

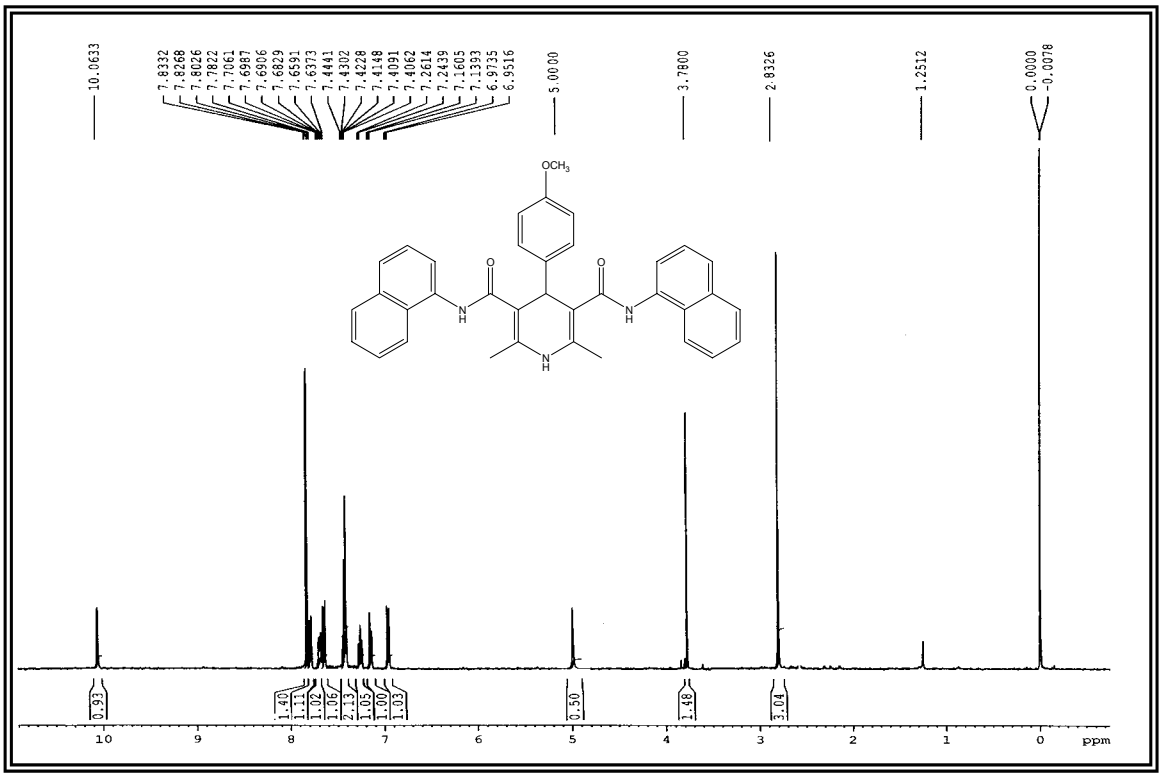


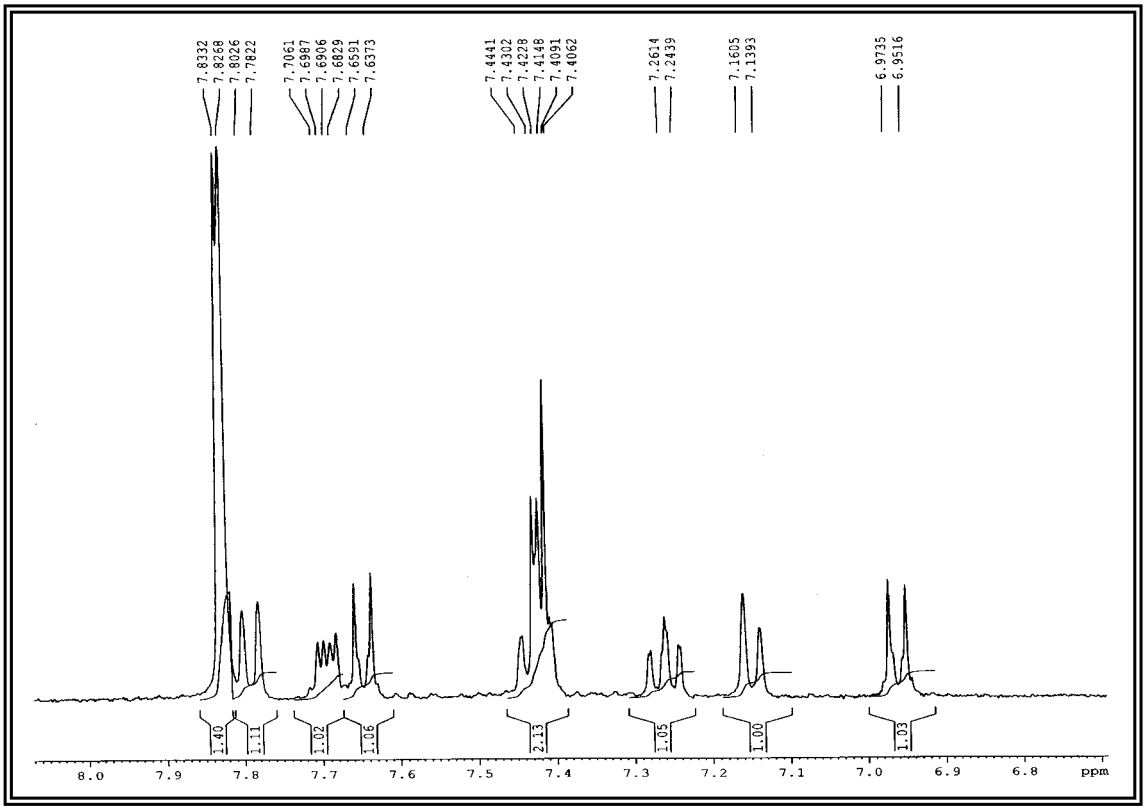
4.6.5.5 ^{1}H NMR spectrum of AKS- 411



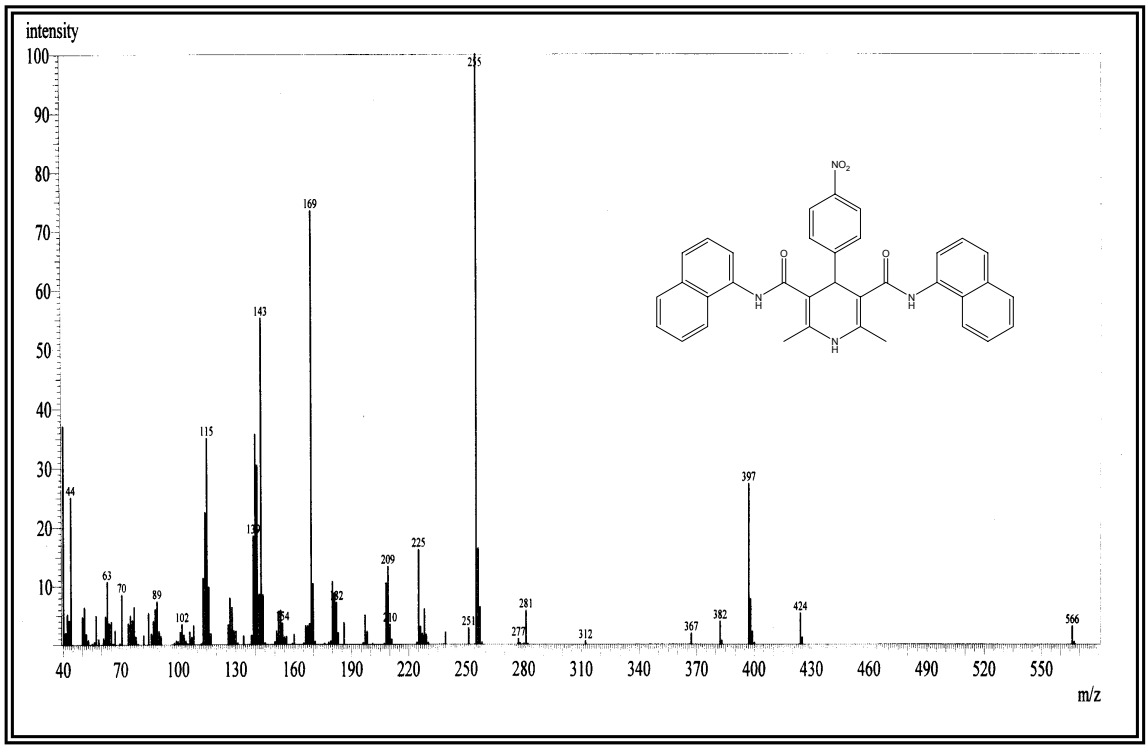


4.6.5.6 ^{1}H NMR spectrum of AKS- 413

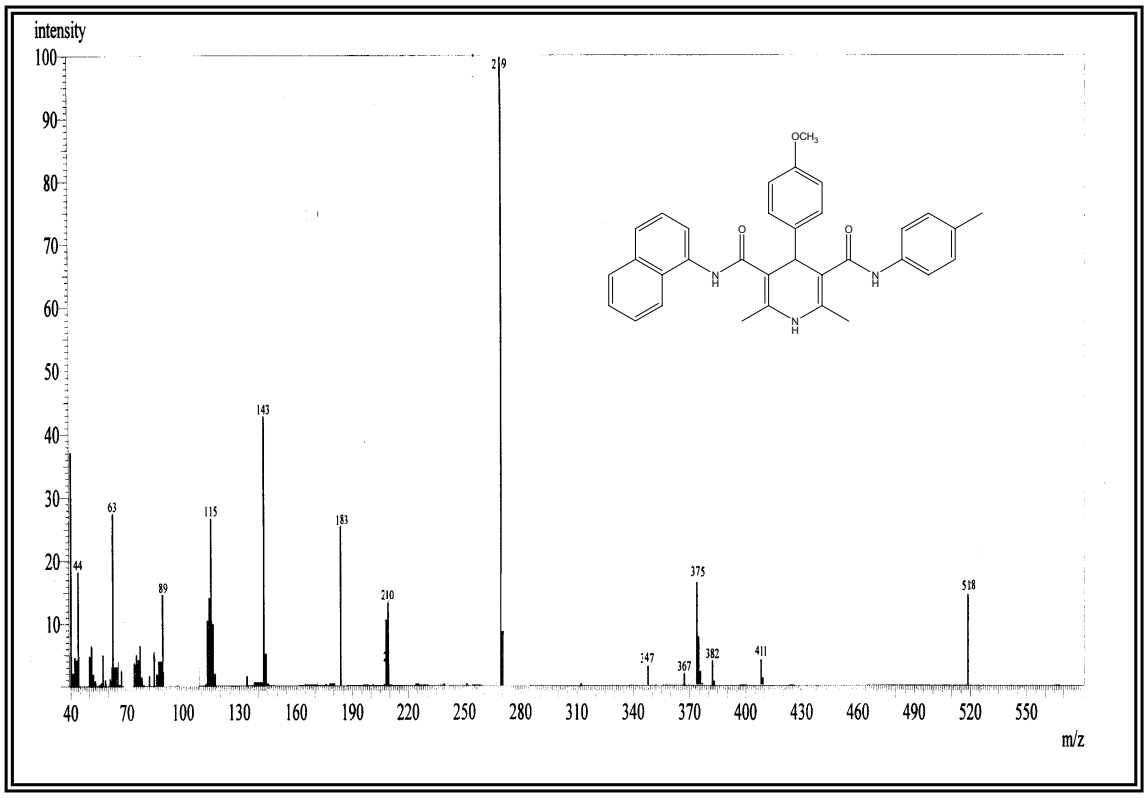




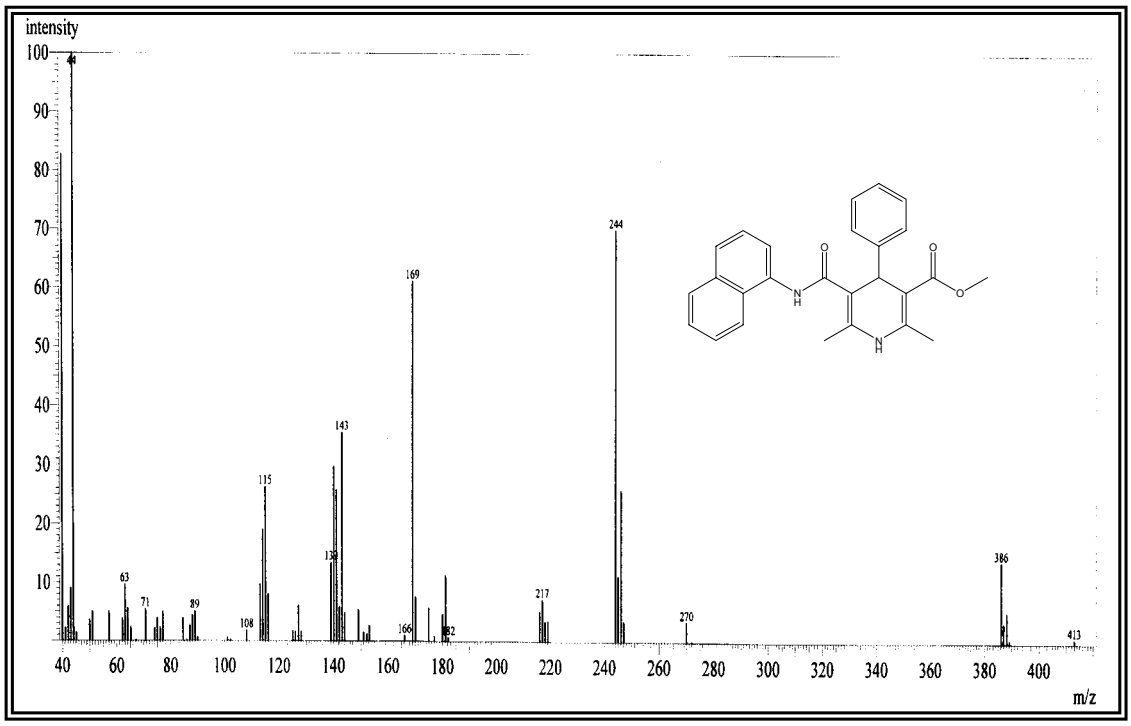
4.6.5.7 Mass spectrum of AKS- 412



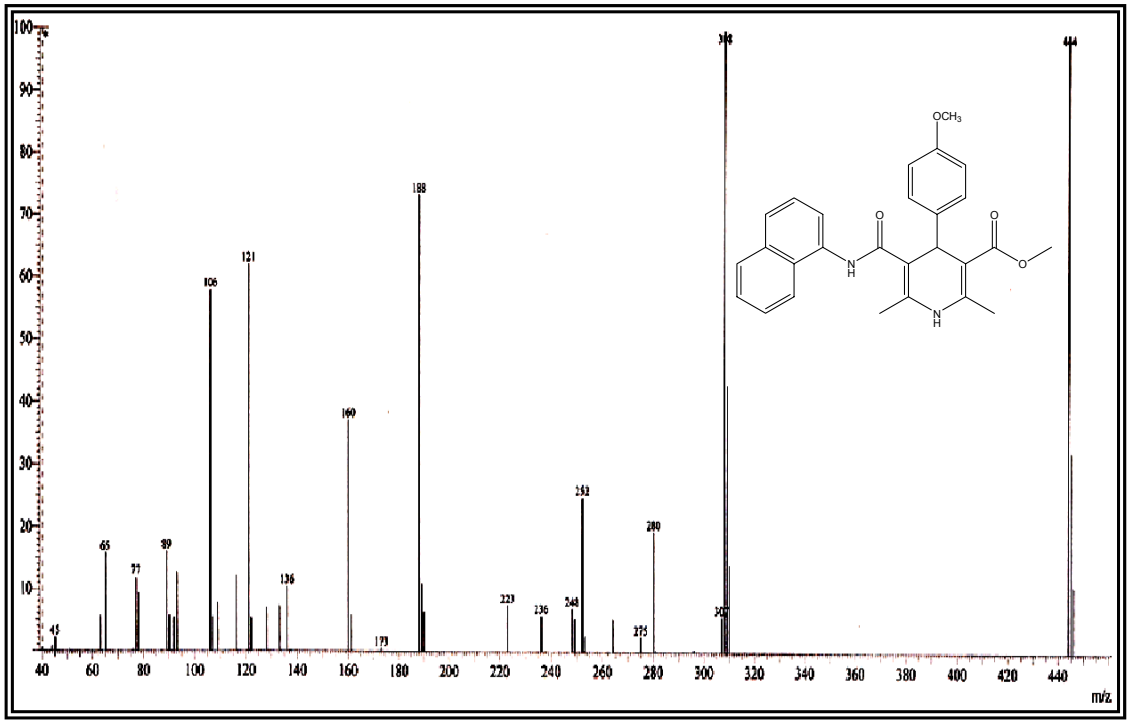
4.6.5.8 Mass spectrum of AKS- 446



4.6.5.9 Mass spectrum of AKS-451



4.6.5.10 Mass spectrum of AKS-453



4.7 References

1. Hantzsch, A., *Justus Liebigs Ann.Chem.,* **1882** 1, 215,.

2. Hantzsch, A., *Ber.,* **1884** 17, 1515.; *Ber*., **1885** 18, 1774, 2579.

3. Godfraind, T.; Miller, R.; Wibo, M.; *Pharmacol. Rev.,* **1986** 38, 321.

4. Janis, R. A.; Silver, P. J.; Triggle, D. J.; *Adv. Drug Res.,* **1987** 16, 309.

5. Sausins, A.; Duburs, G.; *Heterocycles*, **1988** 27, 269.

6. Mager, P. P.; Coburn, R. A.; Solo, A. J.; Triggle, D. J.; Rothe, H.; *Drug Des Discovery*, **1992** 8, 273.

7. Mannhold, R.; Jablonka, B.; Voigdt, W.; Schoenafinger, K.; Schraven, E.; *J. Med. Chem.,* **1992** 27, 229.

8. Gaudio, A. C.; Korolkovas, A.; Takahata, Y.; *J. Pharm. Sci.,* **1994** 83, 1110

9. Bossert, F.; Vater, W.; *U.S. Patent 3,485,847*, Dec 23, **1969**

10. Meyer, V. H.; Bossert, F.; Wehinger, K.; Stoepel, K.; Vater, W.; *Arzneim.-Forsch* **1981** 31, 407.

11. Meyer, V. H.; Bossert, F.; Vater, W.; Stoepel, K.; *U.S. Patent 3,799,934*, **1974**

12. Galiano, A.; *Drugs Fut.,* **1995** 20, 231.

13. Alajarin, R.; Vaquero, J. J.; Alvarez- Builla, J.; Pastor, M.; Sunkel, C.; de Casa-Juana, M. F.; Priego, J.; Statkow, P. R.; Sanz-Aparicio, J.; *Tetrahedron: Asy smetry* **1993** 4, 617.

14. Alajarin, R.; Alvarez-Builla, J.; Vaquero, J. J.; Sunkel, C.; de Casa-Juana, M. F.; Statkow, P. R.; Sanz-Aparicio, J.; Fonseka, I.; *J. Med. Chem.,* **1995** 38, 830.

15. Sannita, W. A.; Busico, S.; Di Bon, G.; Ferrari, A. & Riela, S.; *Int. J. Clin. Pharmacol. Res.,* **1993** 13, 2819.

16. Uehar, Y.; Kawabata, Y.; Ohshima, N.; Hirawa, N.; Takada, S.; Numabe, A.; gata, T.; Goto, A.; Yagi, S.; Omata, M.; *J. Cardiovasc. Pharmacol.,* **1994** 23, 970.

17. Nakagawa, T.; Yamauchi, Y.; Kondo, S.; Fuji, M.; Yokoo, N.; *Jpn. J. Pharmacol. ,* **1994** 64 (Suppl. 1); Abstr. P-260.

18. Boer, R.; Gekeler, V.; *Drugs Fut.,* **1995** 20, 499.

19. Bristolol, J. A.; *Ed. In Annu. Rep. Med. Chem*., **1992** 27, 330.

20. Bristolol, J. A.; *Ed. In Annu. Rep. Med. Chem.,* **1992** 27, 322.

21. Sunkel, C. E.; de Casa-Juana, M. F.; Santos, L.; Garcia, A. G.; Artaljero, C. R.;Vilaroya, M.; Gonzalez-Morales, M. A.; Lopez, M. G.; Cillero, J.; Alonso, S.; Priego, J. G.; *J. Med. Chem*., **1992** 35, 2407.

22. Vo, D.; Matowe, W. C.; Ramesh, M.; Iqbal, M.; Wolowyk, M. W.; Howlett, S. E.; Knaus, E. E.; *J. Med. Chem.,* **1995** 38, 2851.

23. *Therapeutic guidelines, cardiovascular, 3rd ed. Victoria: Therapeutic Guidelines*; **1998**

24. Robertson, R.M.; Robertson D.; *Drugs used for the treatment of myocardial ischemia. In: Hardman JG, Limbird JG, editors. Goodman and Gilman's the pharmacological basis of therapeutics, 9th ed. New York:McGraw-Hill;* p. 759– 78. Chapter 32, **1996.**

25. Calcium channel blocking agents in USP DI. Drug information for the health care professional, 22nd ed. Colorado: Micromedex; p. 727– 42, 2002**.**

26. Antihypertensive drugs. In: Mycek MJ, Harvey R.A. & Chempe PC, editors. Lippincott's illustrated reviews: pharmacology. Pennsylvania: Lippincott Williams & Wilkins; p. 179– 92. Chapter 19, **2000**

27. Klusa,V.; *Drugs Fut.,* **1995** 20, 135.

28. Cooper, K.; Fray, M. J.; Parry, M. J.; *J. Med. Chem.,* **1992** 35, 3115.

29. Zidermane, A.; Duburs, G.; Zilbere, A.; . PSR Zinat. Akad. Vestic 4, 77 **1971**; C.A., **1991** 75,47266,9

30. Wehinger, W. E.; Horst, M.; Andres, K.; Yoshiharu; Ger. Offen; C.A., **1987** 107, 217482.

31. Hachiro, S.; Kunizo, H.; Tadao, S.; Hideyuki, A.; Yoshihsru, D.; *Eur. Patent 197,488.***1986**.; *JP 68,649,* **1985**.; C.A., 106, 328559, **1987.**

32. Yan, Z. M., Dong, Y. M. & Xuebao, Y.; *EP 220, 653, 1987*.; *JP 253,909, 1985*.; C.A., 116, 173968, **1992**

33. Marco, F.; Andrea, Z.; Carmelo, G.; Bermini, M.; *EP 272, 693*; C.A. 109, 190259, **1988**

34. Johnson, R. C.; Taylor, D. J.; Hann Kenneth, V.; Sheng, S.; *U.S. Patent 4,758,669*; C.A. 109, 149366, **1988**

35. Masakatu, H.; Kenichi, K.; Yasuhiko, S.; Masakazu, H.; Osamu, K.; Hiroyoshi, H.; *EP653, 1987*; *JP 235 909,1985;* C.A. 107, 134209. **1987**

36. Cooper K.; Fray M. J.; Parry M. J.; Richardson K.; Steele J.; *J. Med. Chem*. **1992** 35, 3115-3129.

37. Van Rhee A. M.; Jiang J. L.; Melman N.; Olah M. E.; Stiles G. L.; Jacobson K. A.; *J. Med. Chem.,* **1996** 39, 2980-2989.

38. Shah A.; Gaveriya H.; Motohashi N.; Kawase M.; *Anticancer Res.,* **2000** 20, 373.

39. Singer, T. P.; Kearney, E. B.; *Advan. Enzymol*., **1964** 15, 79.

40. Haneeon, L.; *Calcium antagonists: An Overview. Am. Heart J.* **1991** 122, 308-311.

41. Pickard, J. D.; Murray, G. D.; Illingworth, R.; Shaw, M. D. M.; Teasdale, G. M.; Foy, P. M.; Humphrey, P. R. D.; Lang, D. A.; Nelson, R.; Richards, P.; Sinar, J.;Bailey, S.; *Brit.Med. J.,* **1989** 298,636-642.

42. Buchbeit, J. M.; Tremoulet, M.; *Neurosurg.*, **1988** 23,154-167.

43. Loogna, E.; Sylven, C.; Groth, T.; Mogensen, L.; *Eur. Heart J.,* **1986** 6,114-119.

44. SPRINT Study Group. The secondary prevention re-infarction Israeli nifedipine trial (SPRINT) 11: design and methods, results. *Eur. Heart. J.,* **1988** 9 (Suppl. I), 360A.

45. Myocardial Infarction Study Group. Secondary prevention of ischemic heart disease: a long term controlled lidoflazine study. *Acta Cardiol.,* **1979** 34 (Suppl. 24), 7-46.

47. Subramanian,V. B.; *Excerpta Medica (Amsterdam)* , **1983** 97-116.

48. Mueller, H. S.; Chahine,R. A.; *Am. J. Med.,* **1981** 71, 645-657.

49. Antman, E.; Muller, J.; Goldberg, S.; McAlpin, R.; Rubenfire, M.; Tabatznik, B.; Liang, C.-S.; Heupler, F.; Achuff, S.; Reichek, N.; Geltman, E.; Kerin, N. Z.; Neff, R. K.; Braunwald, E. N.; *Engl. J. Med.,* **1980** 302, 1269-1273.

50. Ginsburg, R.; Lamb, I. H.; Schroeder, J. S.; Harrison, M. H.; Harrison, D. C.; *Am. Heart. J.,* **1982** 103,44-48.

51. Held, P. H.; Yueuf, S.; Furberg, C. D.; *Br. Med. J.*, **1989** 299,1187.

52. Reicher-Reiss, H.; Baruch, E.; *Drugs Today*, **1991** 42, 3, 343-364.

53. Gelmere, H. J.; Henneric, N.; *Stroke*, **1990** 21 (SUPPI. IV), 81-IV84.

54. Di Bona, G. F.; Epstein, M.; Mann, J.; Nordlander, M.; *Kidney Int.*, **1991** 41 (Suppl. 36)

55. Triggle, D. J.; *Drugs Today*, **1991** 27, 3, 147-155.

56 Cozzi, P.;German, C.; Domenico, F.; Mauro, G.; Maria M.; Vittorio, P.; Roberto, T.; Fabrizio, V.; Patricia, S.; *J. Med. Chem.*, **1993** 36, 2964-2972.

57. Triggle, D. J.; Langs, D. A.; Janis, R. A.; *Med. Res. Rev.,* **1989** 9, 2, 123-180.

58. Hernandez-Gallegos, Z.; Lehmann, F.; Hong, E.; Posadas, F.; Ernandez-Gallegos, E.; *Eur. J. Med. Chem.,* **1995** 30, 355-364.

59. Christiaans, J.A.M.; *Ph.D. Thesis, Vrij University, Amsterdam, The Netherlands*, **1994**

60. Carlos E.; Sunkel, L.; *J . Med. Chem.* **1992** 35, 2407-2414.

61. Schramm,M.; Towart, R.; *Modulation of Calcicum Channel by Drugs Life Sci.,* **1985** 37, 1843-60

62. Kelvin Cooper. et al, *US Patent 4,935,430*. *EP-A-258033*, *EP-A-266989* **1999.**

63. Christiaans J.A.M.; Timmerman, H.; *Eur. J. Pharm. Sci.* **1996** 4 , 1-22.

64. Swamy, S.K.; Reddy, T.M.; Reddy, V.M.; *J. Pharm. Sci.,* **1998** 60, 2, 102-106.

65. Neamati, N.; Hong, H.; Mazumder, A.; Pommier, Y.; *J. Med. Chem*. **1997** 40, 6, 942-951.

66. Sonja,V.; Barbara, R.; Antonella Di, S.; Roberta, F.; Monica, N.; Emilio, C.; Christian, R.; Nicolas, V.; Alberto, G.; *J. Med. Chem.,* **2004** 47, 10, 2688 -2693.

67. Furukawa T, Nukada T, Miura R, Ooga K, Honda M, Watanabe S, Koganesawa,S. & Isshiki T. J Cardiovasc Pharmacol. 45(3):241-246 (2005)

68. Liou, S.F.; Wu, J.R.; Lai, W.T.; Sheu, S.H.; Chen, I.J.; Yeh, J. L.; *J Cardiovasc Pharmacol*. **2005** 45, 3, 232-240.

69. Karnail, S. A.; George, C .R.; Joseph, S.; Suzanne, M.; Anders, H.; Jack, Z. G.; Mary, F. M.; David, M. F.; *J. Med. Chem.,* **1990** 33, 1510-1515.

70. Kawase, M.; Shah, A; Gaveriya, H.; Motohashi, N.; Sakagami, H.; Varga, A.; Molnar, J.; *Bioorg. Med. Chem.* **2002** 10, 1051-55.

71. Saponara, S.; Ferrara, A.; gorelli, B.; Shah, A.; Kawase, M.; Motohashi, N.; Molnar, J.; Sgaragli, G.; Fusi, F.; *Eur. J. Pharmc.* **2007** 563, 160-63

72. Morshed, S.; Hashimoto, K.; Murotani, Y.; Kawase, M.; Shah, A.; Satoh, K.; Kikuchi, H.; Nishikawa, H.; Maki, J.; Sakagami, H.; *Anticancer Research* **2005** 25, 2033-38.

73. Desai, B.; Sureja, D.; Naliapra, Y.; Shah, A.; Saxena, A.; *Bioorg. Med. Chem.* **2001** 9, 1993-98.

74. Kharkar, P.; Desai, B.; Gaveria, H.; Varu, B.; Loriya, R.; Naliapara, Y.; Shah, A.; Kulkarni, V.; *J. Med. Chem.* **2002** 45, 4858-67.

75. Engi, H.; Sakagami, H.; Kawase, M.; Parecha, A.; Manvar, D.; Kothari, H.; Adlakha, P.; Shah, A.; Motohashi, N.; Ocsovszki, I.; Molnar, J.; *In Vivo* **2006** 20, 637-44.

76. Gaveria, H.; Desia, B.; Vora, V.; Shah, A.; *Indian J. Pharm. Sci.* **2001** 64, 1, 59062.

Chapter 5

Synthesis and characterizations of 3-substituted phenyl-10*H*-[1,2,4] triazolo[4,3-b][1,2,4] triazino [5,6-*b*]indoles

Chapter 5

Synthesis and characterizations of 3-substituted phenyl-10*H*-[1,2,4]triazolo[4,3-b][1,2,4] triazino [5,6-*b*]indoles

Azoles and azines are well known for their diversed biological activities. It is also known that fusion of the heterocyclic nuclei enhances the pharmacological activities more than its parent nucleus. The importance of the indole nucleus is well established in pharmaceutical chemistry as it's corresponding derivatives are used as antipyretic, anticonvulsant, antianalgesic and antidepresant agents[1-3].

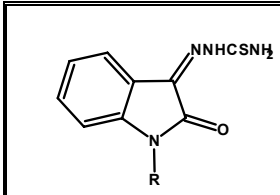
5.1 Pharmacological profile

The antiviral activity of as-triazines[4] and clinical efficacy of methisazone[5] were well documented. The action of isatin-3-thiosemicarbazone is known to have antiviral activity against certain poxviruses[6,7]. The antiviral spectrum of 1-methylisatin-3-thiosemicarbazone, which reportedly extends to adenoviruses, may be rather broader but is still limited to several groups of DNA viruses[8-9]. It was therefore an unexpected finding that these compounds are also active against certain rhinoviruses. J.M.Z.Gladych[10] and co-workers have studied isatin thiosemicarbazone analogues among which two compounds were found to have activity against all rhinovirus strains used so far.

Human rhinovirus (HRV) is a primary cause of mild upper respiratory infection in humans. Although rhinovirus infection, as the "common cold" is known to spread easily throughout human populations, only higher primates are susceptible[11,12]; thus, the virus possesses a narrow host range. This narrow host range is reflected in tissue culture in that the HRV replicates only in cells of primate origin.

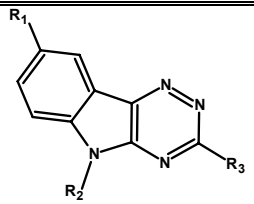
In vitro testing of the 5H-triazino[5,6-b]indoles show a broad spectrum antiviral activity against both DNA and RNA viruses. A notable feature of the series is the wide spread

action against several strains of rhinovirus which is most consistently shown by compounds containing hydroxyalkylamino substituents at C_3.



Isatin-3-thiosemicarbozones

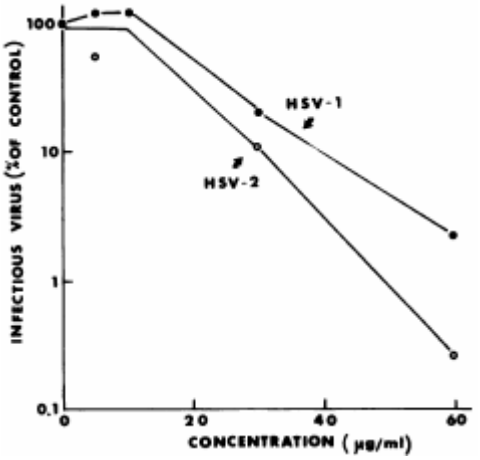
R = CH_3 Methisazone or (1-methylisatin-3-thiosemicarbazone)

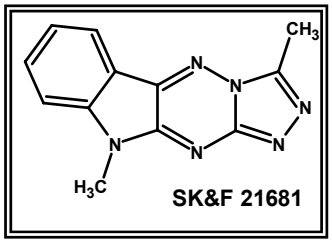


5H-as-triazino[5,6-b]indoles

R_1 = H,Cl, NO_2, Me, Pr, NO, OMe R_2 = H, Me, $C_6H_5(CH_2)_2$, $C_6H_5CH_2$
R_3 = $OH(CH_2)_2NH$, $OH(CH_2)_3NH$, NH_2, Me_2N, Morphonyl, $Me_2CH(CH_2)_2NH$, $Me(CH_2)_{11}NH$, $CH_3(CH_2)_{17}NH$, $OHCH_2CH(OH)CH_2NH$, $OH(CH_2)_4NH$, $MeO(CH_2)_3NH$, $OH(CH_2)_2NH(CH_2)_2NH$, $Me_2N(CH_2)_3NH$, $OH(CH_2)_6NH$ etc.

Isatin-3-thiosemicarbazone exhibits antiviral activity, mainly against poxviruse[13,14]. A group of 3-substituted triazinoindoles, which are structurally related to isatin thiosemicarbazone, inhibit the growth of several rhinoviruses[15,16]. Ehud Katz et al[17]suggested SK&F 21681 (3,10-dimethyl-10-H-s-triazolo[4',3':2,3]-astriazino-[5,6-b]indole) as an inhibitor of the growth of herpes simplex viruses types 1 and 2 at a concentration of 60µg/ml without causing any morphological alterations in BSC1 cells. The DNA synthesis rate of BSC1 affected by 16% between 0.5 to 7 hrs and this inhibition increased upto 33% between 2 to 22 h.p.i.





SK&F 21681

The growth of HSV-1 and HSV-2 in BSC1 cells was followed in the presence of different concentrations of SK&F 21681. It was shown that the highest rate of inhibition occurred at the concentration of 60µg/ml (the upper limit of solubility of this compound in aqueous solution); decreasing the concentration resulted in a parallel loss in the efficiency of the inhibition (Fig. 3). Concentrations of SK&F 21681 lower than 10µg/ml were not active. The results also suggest that the susceptibility of the growth of HSV-2 to this compound

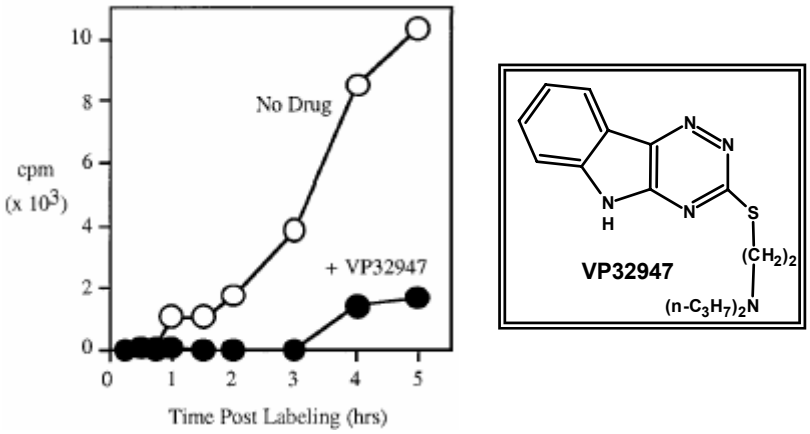
is higher than that of HSV-1 (Fig. 3). When formation of plaques of HSV in the presence of SK&F 21681 (60 p.g/ml) was studied, a remarkable inhibition was observed.

Scott Baginski and co-researchers[18] have reported the discovery of a small molecule inhibitor of pestivirus replication. The compound, designated VP32947, inhibits the replication of bovine viral diarrhea virus (BVDV) in cell culture at a 50% inhibitory concentration of approximately 20nM. VP32947 inhibits both cytopathic and noncytopathic pestiviruses, including isolates of BVDV-1, BVDV-2, border disease virus and classical swine fever virus. However, the compound shows no activity against viruses from unrelated virus groups.

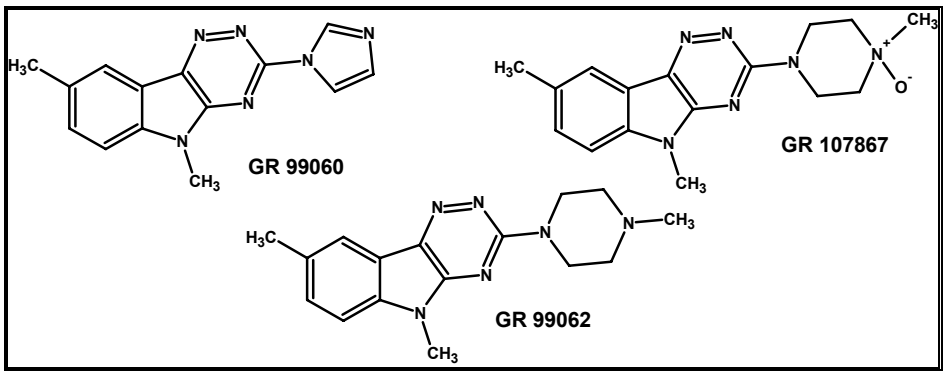
Bovine viral diarrhea virus (BVDV), the prototypic representative of the pestivirus genus, family *Flaviviridae*, is ubiquitous and causes a range of clinical manifestations, including abortion, teratogenesis, respiratory problems, chronic wasting disease, immune system dysfunction, and predisposition to secondary viral and bacterial infections[19]. Certain BVDV strains can cause acute fatal disease with mortality rates of 17–32%[20-22]. BVDV is also able to establish persistent infections in fetuses[23,24]. When born, these persistently infected animals remain viremic throughout life and serve as continuous sources for virus spread in herds. Persistently infected animals may also succumb to fatal mucosal disease on superinfectionwith closely related BVDV strains. Vaccines are used in some countries in an attempt to control pestivirus disease with varying degrees of success[25].

Time of drug addition studies indicated that VP32947 acts after virus adsorption and penetration and before virus assembly and release. Analysis of viral macromolecular synthesis showed VP32947 had no effect on viral protein synthesis or polyprotein processing. The investigation of the effect of VP32947 on viral RNA synthesis indicated when virus-infected cells, treated with actinomycin D(to inhibit cellular RNA synthesis) with or without VP32947 in the cell culture medium. There was a clear inhibition of incorporation of 3H-uridine into viral RNA found in the drug treated culture. Although the drug-free culture showed the time-dependent incorporation of ^{3}H-uridine into viral RNA. When this experiment was performed in the absence of actidomycin D, no change of ^{3}H-uridine uptake in the presence of drug was observed for cellular RNA synthesis, indicating that VP32947 had no obvious effect on uridine uptake by the cells or on

cellular RNA synthesis. These results suggest that VP32947 exerted its antiviral effect at the level of viral RNA synthesis.



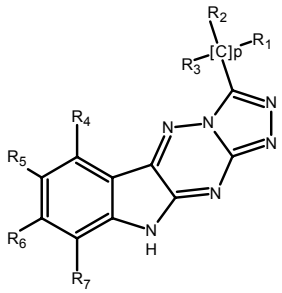
Oonagh Kinsman and co-workers[26] have described GR99060 and GR99062 as representatives of a series of 1,2,4-triazino[5,6-b]indole compounds. This series possessed broad-spectrum antifungal activity in vitro. The MIC ranges of the two compounds were as follows: 0.25 to 4 μg/ml for *Candida albicans*, 0.25 to 16 μg/ml for Candida sp., 1 to 8 μg/ml for *Asperigllus spp.,* and 0.25 to 16 μg/ml for *Cryptococcus neoformans.* GR99062 was metabolized to corresponding N-oxide analogue GR107867 in vitro by a mouse liver microsomal preparation, while GR99060 was stable. GR99060 was efficacious in a murine model of systemic candidiasis by oral or parenteral administration, although no clear dose-response was achieved; suggesting that other factors adversely affected the compound's *in vivo* activity.



GR99060 showed a therapeutic effect in mice with systemic C. *albicans* infections when it was administered by both the oral and subcutaneous routes. Since the levels of the drug in blood after subcutaneous dosing were low, the compound may be released slowly over a longer period of time. In the efficacy test, the dose-response was variable by both routes. Toxicity in infected animals may account for the reduced activity at high doses,

since a lower survival rate was noted in mice that received 100 mg/kg than in those that received lower doses. Variations in bioavailability and possible further metabolism may also account for the lack of good dose-responses. Similarly, in the subacute infection model, the oral route of administration was more effective than the subcutaneous route in reducing kidney counts when a dose of 100 mg/kg was used.

Tomas Vijkovsky et al[27] have patented compounds of formula I and II for treating c-MET related disorders or in another preferred embodiment, the cancer selected from the group consisting breast cancer, lung cancer, prostate cancer, pancreatic cancer, glioma, liver cancer, gastric cancer, throat cancer, melanoma, renal cancer, leucamia, myeloma and sarcoma. The invention deals with a family of novel tetracyclic compounds which exhibits c-MET modulationg activity and have ameliorating effect against disorders related to abnormal c-MET activity.



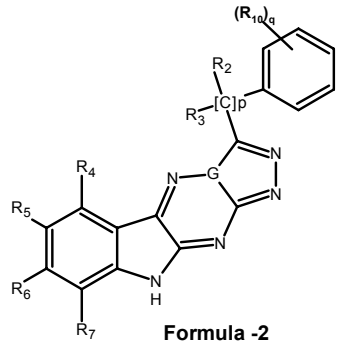
Formula -1

R_1=substituted aryl or heteroaryl group

R_2 & R_3=H, halogen, OH, OR, $N(R)_2$, -CN, -COR, COOR, $CON(R)_2$, CF_3, lower alkyl, cycloalkyl, heterocycle, alkenyl and alkynyl or R_2 & R_3 togather form cycloalkyl or heterocyle

R_4, R_5, R_6 and R_7= H, halogen, OR, $N(R)_2$, -CN, -COR, COOR, $CON(R)_2$, NO_2, $S(O)_nR$ (where n=0,1,2), CF_3,lower alkyl, cycloalkyl, heterocycle, alkenyl, alkynyl or aryl

p=0,1,2,3,4 or 5



Formula -2

R_{10}=OH,OR, COR, COOR, $CON(R)_2$, $N(R)_2$, CN, NO_2, SO_2R, $SO_2N(R)_2$, CF_3, lower alkyl, cycloalkyl, heterocycle, alkenyl or aryl

q=1,2,3,4 or 5 G = C or N

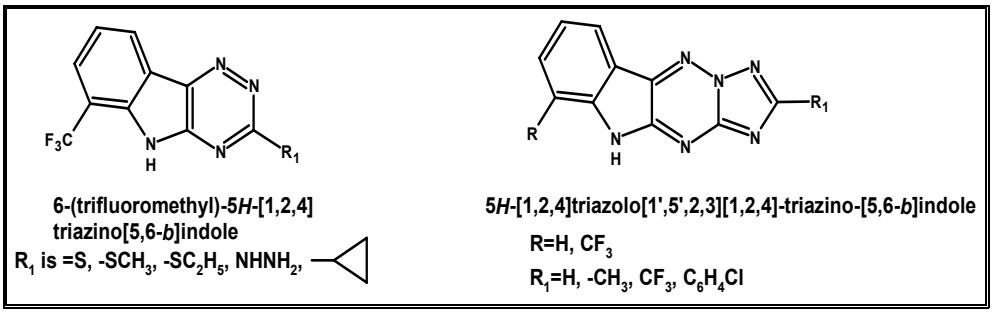
R_2 & R_3=H, halogen, OH, OR, $N(R)_2$, -CN, -COR, COOR, $CON(R)_2$, CF_3, lower alkyl, cycloalkyl, heterocycle, alkenyl and alkynyl or R_2 & R_3 togather form cycloalkyl or heterocyle

R_4, R_5, R_6 and R_7= H, halogen, OR, $N(R)_2$, -CN, -COR, COOR, $CON(R)_2$, NO_2, $S(O)_nR$ (where n=0,1,2), CF_3,lower alkyl, cycloalkyl, heterocycle, alkenyl, alkynyl or aryl

p=0,1,2,3,4 or 5

Joseph Kgokong et al[28] have synthesized the unsubstituted and the 6-trifluoromethyl-1,2,4-triazino[5,6b]indole analogues and evaluated for antimalarial activity *in vitro* against the chloroquine sensitive and chloroquine-resistant strains of P. falciparum. The results have revealed that the CF_3 group tends to lead to an increased in vitro antimalarial

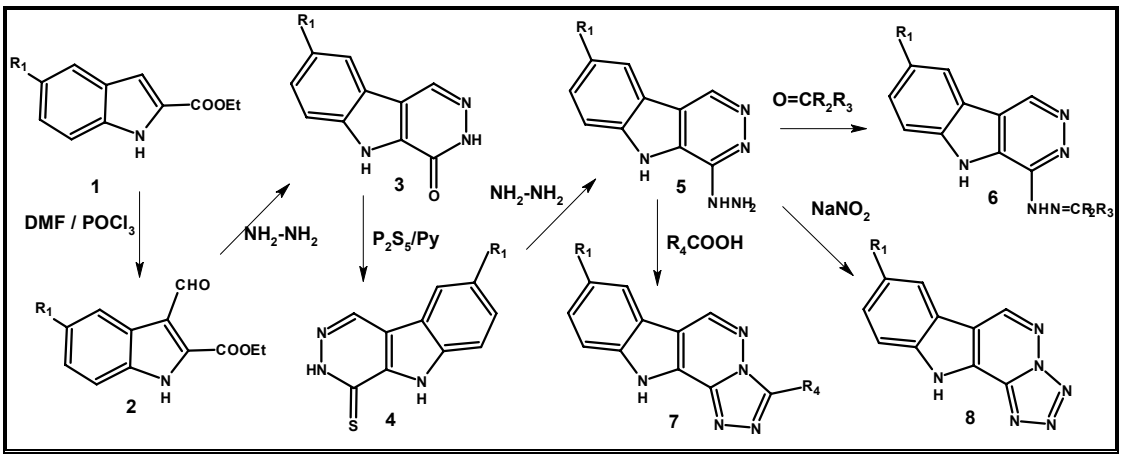
activity of the 1,2,4-triazino[5,6b]indole albeit to a smaller degree in some compounds. Analogues without the trifluoromethyl group, which were evaluated simultaneously, were all devoid of activity even at concentrations as high as 400 μM. The increased activity resulting from the presence of this group could be ascribed to the increased lipophilicity of the compound, as this group is known to be more hydrophobic than even the fluorine atom.[29] In this series, the size of the substituent on the thiol group have no significant effect on in vitro antimalarial activity. Replacement of a thiol group by a hydrazino group in the trifluoromethyl substituted derivatives leads to compounds with half the potency of those with alkyl groups on the thiol group. On the other hand, the activity of the 6-trifluoromethyl-5H-1,2,4-triazolo[1',5',2,3]-1,2,4-triazino[5,6b]indole series was almost identical to those of the 6-trifluoromethyl-1,2,4-triazino[5,6b]indole-3-alkylthiols, with the exception of compound containing the 6-CF_3 and the 3-CH_3 groups. The later exhibited a four fold improvement in activity against the chloroquine-sensitive strains. However, introduction of a second CF_3 particularly at position 3 tends to lead to compounds with diminished antimalarial activity. Further consideration of the structure–activity relationship of compounds in the series without the 6-CF_3 indicates that compound with 3 –CH_3 substitution was the most active against the chloroquine-sensitive strains followed by unsubstituted skeleton. The former exhibited activity against the chloroquine-sensitive strains in the same molar range as chloroquine and mefloquine under identical experimental conditions, while later was the most active



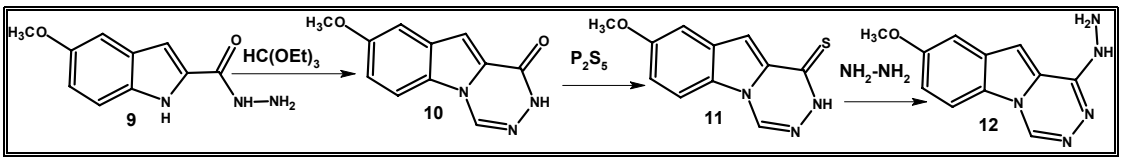
against the chloroquine-resistant strains of P. falciparum. Both –CF_3 and –C_6H_4Cl groups at position 3 without CF_3 at position 6 lead to relatively inactive compounds. The fact that the P. falciparum lactate dehydrogenase (PfLDH)activity can be distinguishable from the host LDH[30] by using the 3-acetyl pyridine adenine dinucleotide analogue of nicotinamide adenine dinucleotide (APAD) has afforded an opportunity for the development of an enzymatic method for the evaluation of antimalarial compounds.[31] The compounds selected for screening against the chloroquine-resistant strain of P. falciparum have shown identical but much higher in vitro activity than against the chloroquine-sensitive

strain, with the exception of compound having no substitution, which has a IC_{50} value of 48.0 μM, which was very close to that of chloroquine (IC_{50} of 277.5 μM) against this strain. The 3-CF_3 substitution did not lead to any improvement on the in vitro antimalarial activity than it did when attached at position 6. The 3,6-bis(trifluoromethyl)-5H- 1,2,4-triazolo-[10,50,2,3]-1,2,4-triazino-[5,6b]indole has a much lower activity against both the chloroquine- sensitive and chloroquine-resistant strains of P.falciparum than the other 6-CF_3 substituted derivatives. As a result of a direct relationship between the level of drug accumulation in the parasite food vacuole and antimalarial drug potency, but no simple relationship between accumulation and either p_{Ka} or lipophilicity,[32-34] it could be inferred that the bulkiness of the molecule conferred by the second CF_3 group will affect the relative membrane permeability of the molecule, leading to reduced drug accumulation within the parasite food vacuole.

Monge A. et al[35] have studied the regulation of the PGI_2/TXA_2 system with antihypertensive effects by synthesizing a series of 4-hydrazino-5H-pyridazino[4,5-b]indole and 4-hydrazinopyridazino[4,5-a]indole derivatives (Scheme-1), structurally related to hydralazine[36] (1-hydrazinophthalazine) and dihydralazine(1,4-dihydrazinophthalazine), peripheral vasodilators used in the treatment of hypertension. The demonstration of selective inhibitory actions of the compounds was determined in concordance with the Gorman mode[37], namely, the inhibition of the second wave of platelet aggregation induced by adenosine 5'-diphosphate (ADP), inhibition of aggregation induced by arachidonic acid (AA), and prostaglandin H, (PGH_2) and prostaglandin H_2(PGH_2) production with AA as aggregating agent with concomitant inhibition of TXA_2 production.



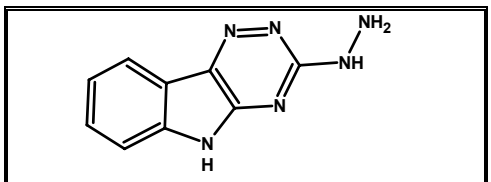
compound	R^1	R^2	R^3	R^4
1a, 2a, 3a, 4a, 5a	CH_3O			
1b, 2b, 3b, 4b, 5b	C_2H_5O			
1c, 2c, 3c, 4c, 5c	$C_6H_5CH_2O$			
1d, 2d, 3d, 5d	HO			
6a	CH_3O	CH_3	CH_3	
6b	CH_3O	C_6H_5	H	
6c	$C_6H_5CH_2O$	C_6H_5	H	
6d	$C_6H_5CH_2O$	$CH_3(CH_2)_2$	H	
7a	CH_3O			H
7b	CH_3O			CH_3
7c	$C_6H_5CH_2O$			H
7d	$C_6H_5CH_2O$			CH_3
8a	CH_3O			
8b	$C_6H_5CH_2O$			



Compounds 3,5, and 10-12 were studied as potential inhibitors of the blood platelet aggregation induced by ADP and/or AA, PGH_2, and adrenaline. Compounds 3c and 5a.HCl were found to be the most potent inhibitors in all of these experiments. These compounds were inhibitors of the *in vitro* platelet aggregation induced by ADP, AA, and PGH, and compound 5a.HCl also inhibited the aggregation induced by adrenaline.

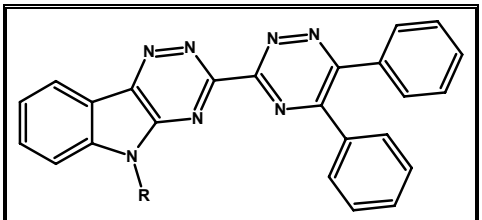
Compounds 3c and 5a-HCl were subsequently studied with ASA as reference as potential inhibitors of thromboxane synthetase in the in vitro blood platelet aggregation induced by AA and in the *ex vivo* blood platelet aggregation induced by ADP and AA. In both types of experiments, 3c and 5a.HCl showed an inhibitory effect on the synthesis of TXB_2 and a stimulation of the synthesis of prostaglandin $E_2(PGE_2)$. Both effects are more significant with 5a-HCl. To a 100 μM concentration, this compound as compared with ASA showed no significant inhibitory effect on the PGI_2 release from rat aortic tissue. The antihypertensive effect of the compounds was measured in spontaneously hypertensive rats (SHR), after intraperitoneal, oral, and intravenous administration to SHR for compounds 3-8, 12 and hydralazine. The introduction of the hydrazino group in the position 4 of the 5H-pyridazino[4,5-b]indole system considerably increased the antihypertensive activity and toxicity. However, compounds 6a and 6b were less active as compared with compound 5. Considering the results together following decreasing order of activity may be stated for compounds 5: hydralazine >/= 5a = 5d >/= 5 (R' = H)>/=5b >> 5c. The results for 5a, 5b, 5d, and hydralazine for a short time after iv administration revealed that decreasing order of activity seems to be 5d > hydralazine = 5a > 5b.

After this, the same group have extended their study with a series of 5H-triazino[5,6-b]indole. Only one compound 3-hydrazino-5H-[1,2,4]triazino [5,6-b] indole hydrochloride was found to be most potent as antihypertensive agent with slighly affecting the cardiac rhythm but did not present any antiaggregative effect.



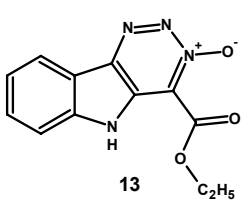
3-hydrazino-5*H*-[1,2,4]triazino[5,6-*b*]indole

Morsy J.M. and Abd el-Monem W.R.[38] have synthesized 3-(5,6-Diphenyl-1,2,4-triazin-3-yl)-5-substituted-1,2,4-triazino[5,6-b]indole derivatives showed pronounced effect on the Cellobiase produced by *Thermomyces lanuginosus* and *Chaetomium thermophilum*.

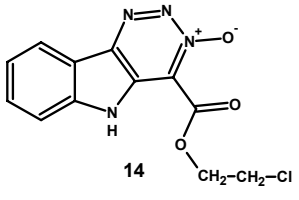


3-(5,6-diphenyl-1,2,4-triazine-3-yl)-5-substituted-1,2,4-triazino[5,6-b]indoles

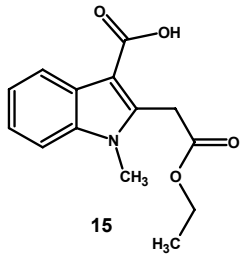
Ethyl 1,2,3-triazino[5,4-b]indole-4-carboxylate N_3-oxide (13) and 2-chloroethyl 1,2,3-triazino-[5,4-b]indole-4-carboxylate N_3-oxide (14) have shown potent platelet antiaggregating and hypotensive activity, and their precursors 2-ethoxy-carbonylmethyl-1-methylindole-3-carboxylic acid (15) and 2-(2-chloroethoxy carbonylmethyl)-1-methylindole-3-carboxylic acid (16) were tested in four strains of *Salmonella typhimurium* (TA98, TA100, TA97 and TA102) using the standard plate incorporation technique. 15 & 16 were not mutagenic whereas 13 was mutagenic to all the strains and 14 was mutagenic to TA97, TA98 and TA100[39].



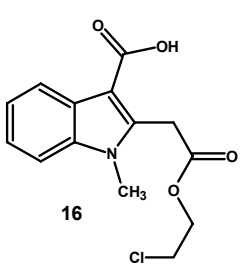
Ethyl-1,2,3-triazino[5,4-b]indole-4-carboxylate N(3)oxide



2-Chloroethyl-1,2,3-triazino[5,4-b] indole-4-carboxylate N(3)oxide

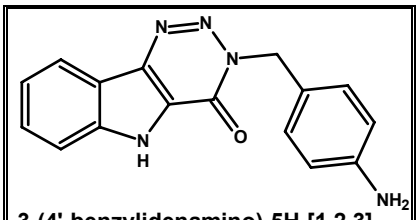


2-Ethoxycarbonyl methyl-1-methyl-indol-3-carboxylic acid

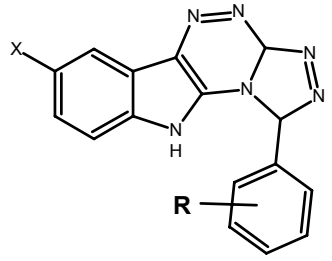


2-Chloroethoxycarbonyl methyl-1-methyl-indol-3-carboxylic acid

In continuation with this, Garcia et al[40] have studied quantitative structure-mutagenic activity relationship of 3-(4'-benzylidenamino)-5H-1,2,30triazin[5,4-b]indole-4-one derivatives. The title compounds were assayed with the Ames test using the *Salmonella typhimurium* strains TA97, TA98, TA100 and TA102. The adaptive least-squares method (ALS method) was used to carry out a quantitative structure-activity relationship (QSAR) analysis. Three equations, based on 10 congeners, were found for strains TA97, TA98 and TA100. The results suggest that lipophilicity of the substituent decreases the mutagenicity of the series.



3-(4'-benzylidenamino)-5H-[1,2,3] triazino[5,4-*b*]indol-4-one

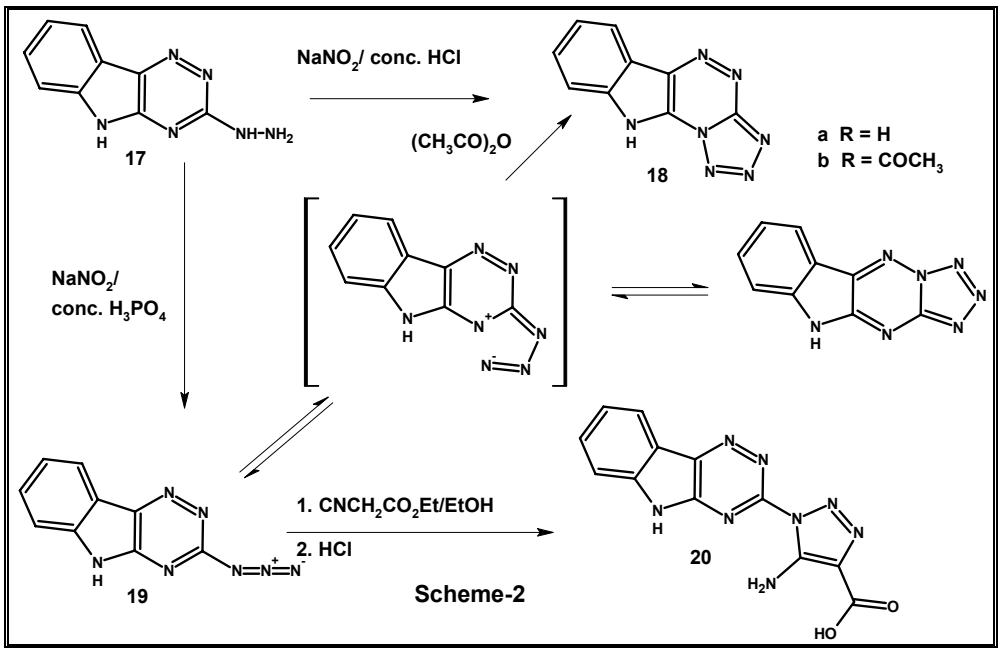


6H-5-aryl-9-halo-1,2,4-triazolo [3' , 4' :3,4]-1,2,4-triazino[5,6-b]-indoles

Holla B.S. et al[41] synthesized a series of 6H-5-aryl-9-halo-1,2,4-triazolo [3' , 4' :3,4]-1,2,4-triazino[5,6-b]-indoles and 5H-1-aryl-5-halo-1,2,4- triazolo [4' ,3' :2,3]-1,2,4-triazino [5,6-b]-indoles. The titled compounds assayed against *B. subtilis, E.coli, P. aeruginosa* and *S.aureus*.

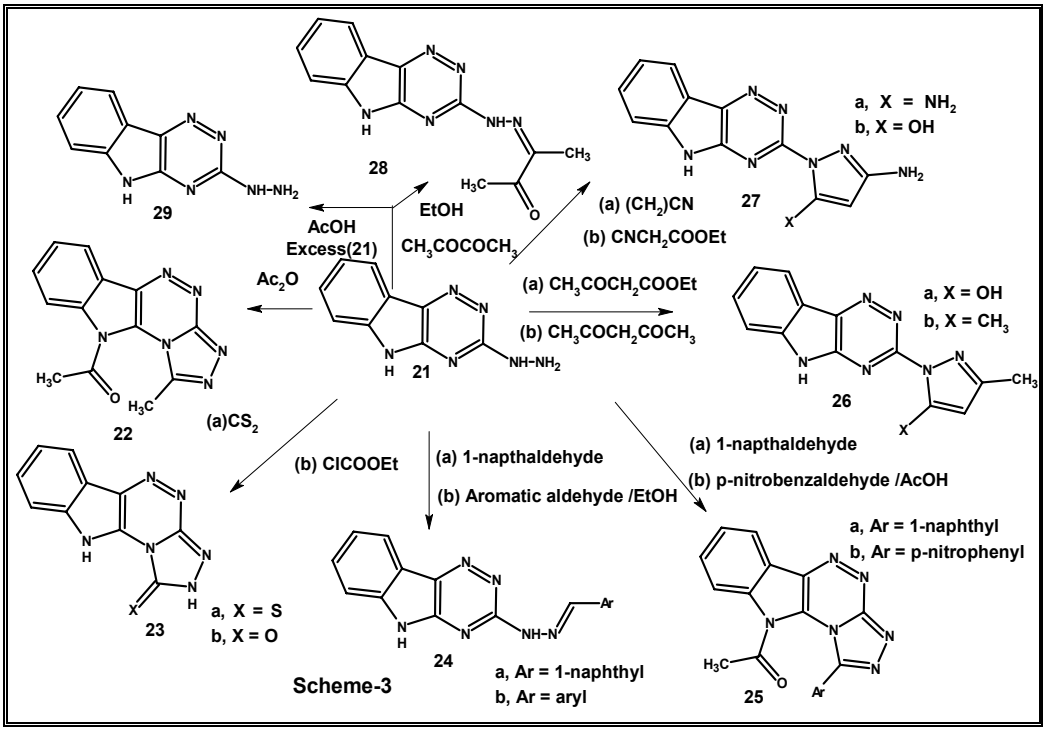
5.2 Synthetic Methodology and Chemistry

Joshi et al[42] reported that the reaction of 3-hydrazino[1,2,4]triazino[5,6-b]indole (17) with nitrous acid (sodium nitrite/PPA) gave 10H-tetrazolo[5',1':3,4][1,2,4]triazino[5,6-b]indole(18), where as reaction of (17) with nitrous acid gave azide(19)[43,44], the structure of the azide was confirmed by its analytical and spectral data. The azide (19) was cyclized to tetrazolo compound (18b) on treatment with acetic anhydride, while cyclization with ethyl cyanoacetate in presence of sodium ethoxide afforded 5-amino-4-carboxy[1,2,3]-triazolyl-[1,2,4]-triazino-[5,6-b]indole (20)[45]. On the other hand, treatment of (17) with sodium nitrite/concentrated hydrochloric acid gave the corresponding tetrazolo compound 18a.



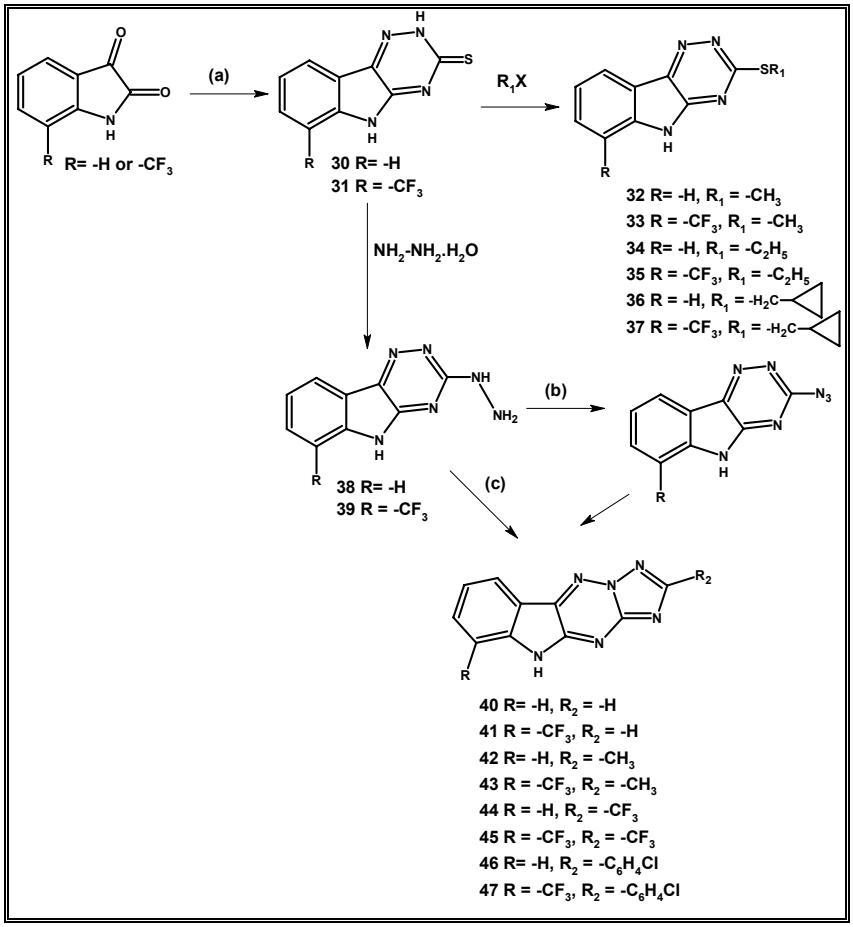
F.F.Abdel-Latif et al[46] have studied reactivity of hydrazino compound (21) toward different condensing cyclization reagents[47](Scheme-3) , found that when (21) treated with acetic anhydride affords the fused triazolo compound (22) namely 10-acetyl-1-methyl-10H-[1,2,4]triazolo[3',4':3,4[-1,2,4]triazino[5,6-b]indole. Refluxing (21) with carbon disulphide produced 1,2-dihydro-10H-[1,2,4]triazolo[3',4':3,4][1,2,4]triazino[5,6-b]indol-1-thione (23a). In the same manner, refluxing (21) with ethyl chloro formate produced 1,2-dihydro-10H-[1,2,4] triazolo[3',4':3,4][1,2,4]triazino[5,6-b]indol-1-one (23b). On the other hand refluxing (21) with 1-napthaldehyde in absolute ethanol produced 1-naphthylidine-(5H-[1,2,4]-triazino[5,6-b]indol-3-yl)hydrazone (24a), where as upon heating in glacial acetic acid gave corresponding triazolo compound, namely 10-acetyl-1-(1-naphthyl)-10H-[1,2,4]triazolo[3',4':3,4] triazino[1,2,4] [5,6-b]indole (25a). Treatment of (21) with benzaldehyde or p-nitrobenzaldehyde in ethanol and/or in glacial acetic acid similarly afforded both benzylidene((5H-[1,2,4]-triazino[5,6-b]indol-3-yl)hydrazone(24b) and 10-acetyl-1-(p-nitrophenyl)-10H-[1,2,4]triazolo[3',4':3,4]triazino[1,2,4] [5,6-b]indole (25b) respectively. Cyclization of (21) with ethyl acetoacetate yielded the pyrazolino compound 3-(5'-hydroxy-3'-methyl-1H-pyrazol-1-yl)-5H-[1,2,4]triazino[5,6-b]indole (26a). Similarly, refluxing (21) with acetyl acetone produced 3(3',5'-dimethyl-1H-pyrazolo-1-yl)-5H-[1,2,4]triazino[5,6-b]indole (26b). Condensation of (21) with malanonitrile resulted 3-(3',5'-diamino-1H-pyrazol-1-yl)-5H-[1,2,4]triazino[5,6-b]indole (27a), while treatment of (21) with ethyl cyanoacetate gave 3-(3'-amino-5'-hydroxy-1H-pyrazol-1-yl)-5H-[1,2,4]triazino[5,6-b]indole (27b).

The reaction of (21) with α-dicarbonyl compounds was assumed to involve one or both carbonyl groups in the condensation. Thus, heating of (21) and diacetyl in ethanol gave only the corresponding mono hydrazone namely 2-(5H-[1,2,4]triazino[5,6-b]indol-3-yl)-hydrazono-3-oxobutane (28). However in the presence of excess of (21) the corresponding 2,3-bis(5H-[1,2,4]triazino[5,6-b]indol-3-yl)hydrazonobutane (29) was formed.. The same result was also obtained if the monohydrazone (28) was heated with excess of hydrazine(21). All the resulting compounds were well characterized by IR and NMR spectral data and elemental analysis.



Joseph Kgokong et al[48] have synthesized a series of unsubstituted and 6-trifluoromethyl-1,2,4- triazino[5,6b]indole and 5H-1,2,4-triazolo[1',5',2,3]-1,2,4-triazino[5,6b]indole derivatives and their chemical structures confirmed by 1H NMR and 13C NMR, elemental, IR and mass spectrophotometric analyses. The synthetic stretegy was to condense Isatin or the 6-trifluoromethyl isatin with thiocarbazide in K_2CO_3 solution to form 1,2,4-triazino-[5,6b]indole-3-thione (30) or 6-trifluoromethyl-1,2,4-triazino-[5,6b]indole-3-thione (31) as show in scheme below. Each of one of these products was alkylated with each of methyl chloride, ethylchloride and chlorocyclopropylmethane to form 3-methylthio- (32), 3-methylthio-6-trifluoromethyl- (33), 3-ethylthio- (34), 3-ethylthio-6-trifluoromethyl-(35) and 3-cyclopropylmethylthio-(36) and 3-cyclopropylmethylthio-6-trifluoromethyl-(37) 1,2,4-triazino-[5,6b]indole derivatives following a known procedure. Refluxing a mixture of 30 or 31 with hydrazine hydrate in

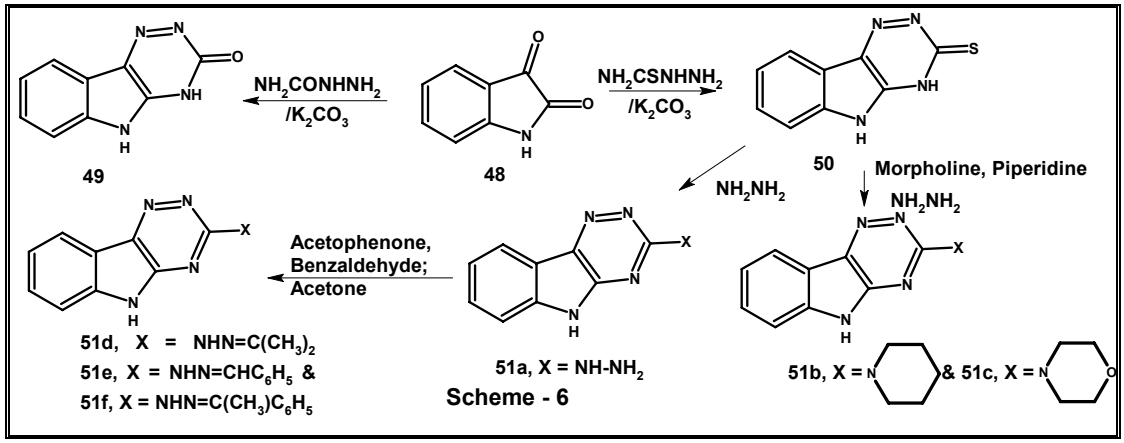
HCl resulted in the formation of 3-hydrazo-1,2,4-triazino-[5,6-b]indole (38) or 3-hydrazo-6-trifluoromethyl-1,2,4-triazino-[5,6b]indole (39), which on reaction with sodium nitrite resulted in the formation of 3-azido derivatives. In the presence of HCl, formic, acetic, trifluoroacetic or chlorobenzoic acid, the hydrazo and azido derivatives cyclize to form fused tetrazole compounds, 5H-1,2,4-triazolo-[1',5',2,3]-1,2,4-triazino-[5,6-b]indole derivatives (40 and 41), 3-methyl- (42 and 43), 3-trifluoromethyl- (44) and 3,6-bis(trifluoromethyl)-(45) and 3-(2-chlorophenyl)- (46 and 47) 5H-1,2,4-triazolo-[1',5',,2,3]-1,2,4-triazino-[5,6-b]indole derivatives.



Tomas Vijkovsky et al[49] have described general procedure for synthesis of 3-(4-hydroxybenzyl-10H-[1,2,4]triazolo[4',3':2,3][1,2,4]triazino[5,6-b]indole derivatives.

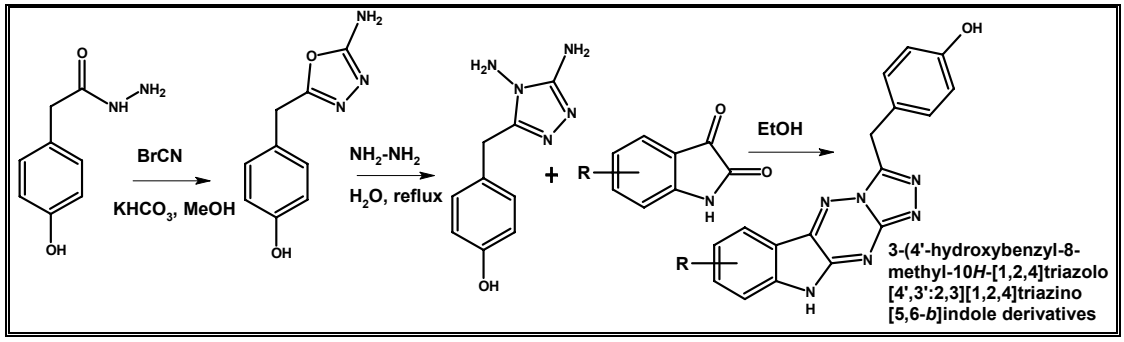
Monge et al[50] have reported a series of 5H-1,2,4-triazino[5,6-b]indole derivatives of type 50 and 51 as per shown in scheme below. The 1,2,4-triazino[5,6-b]indoles (49 & 50) were obtained by cyclization of isatin(48) with semicarbazide or thiosemicarbazide in the presence of potassium carbonate. When a mixture of 50 and hydrazine hydrate was boiled, 90% of 51a was obtained. The compound was characterized as the free base and its monohydrochloride by elemental analysis and spectroscopic data (IR &1H-NMR).

Several other hydrazones, not reported earlier (51d, 51e, and 51f), were prepared by standard methods and also characterized. Upon boiling, solutions of 50 with piperidine and morpholine, compound 51b and 51c were obtained in good yields 80 and 83% respectively.



Scheme - 6

The synthetic approach suggested that p-hydroxyphenyl acetic acid methyl ester was condensed with neat hydrazine-hydrate to afford corresponding hydrazide. The hydrazide was treated with cyanogen bromide in the presence of potassium hydrogen carbonate to yield appropriate 1,3,4-oxadiazole, which on treatment with hydrazine hydrate would converted into 1,2-diamino-1,3,4-triazole derrivative. Condensation of later with substituted isatins afforded the 3-(4-hydroxybenzyl-10H-[1,2,4]triazolo[4',3':2,3][1,2,4]triazino[5,6-b]indole derivatives.



5.3 Current work

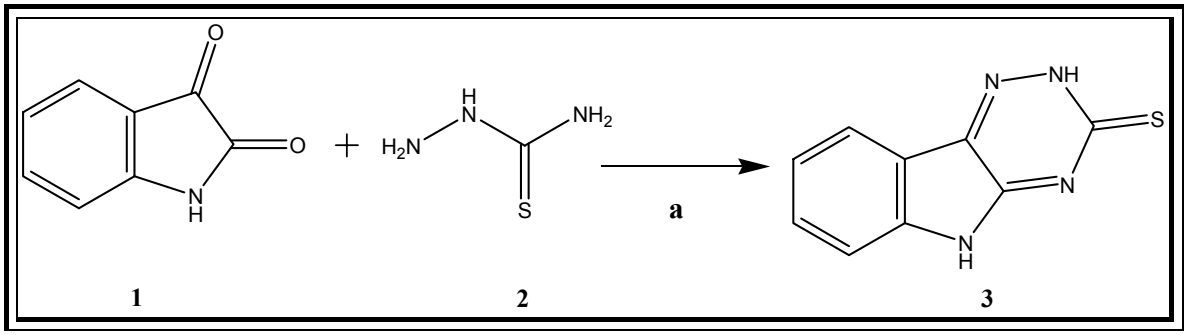
Earlier 1-substituted phenyl-10H-[1,2,4]triazolo[3',4':3,4][1,2,4]triazino[5,6-b]indole derivatives were synthesized in our lab and tested for their antibacterial, anti tubercular and antiviral activity. Some promising results were obtained and few molecules showed potent activity. In continuation of work, linearly fused triazolo-triazino-indloe derivatives are synthesized to find out effect of linear and angular fused derivatives on their biological profile.

Current chapter deals with the synthesis of compounds containing triazolo-triazino-indole fused system. Synthetic methodology is illustrated in reaction Schemes 1-4. First step is the reaction between isatin and thiosemicarbazide. The reaction is carried out in water using potassium carbonate as base. After completion of reaction, acidification of the reaction mixture yielded triazino-indole-3-thione in 78% yield.

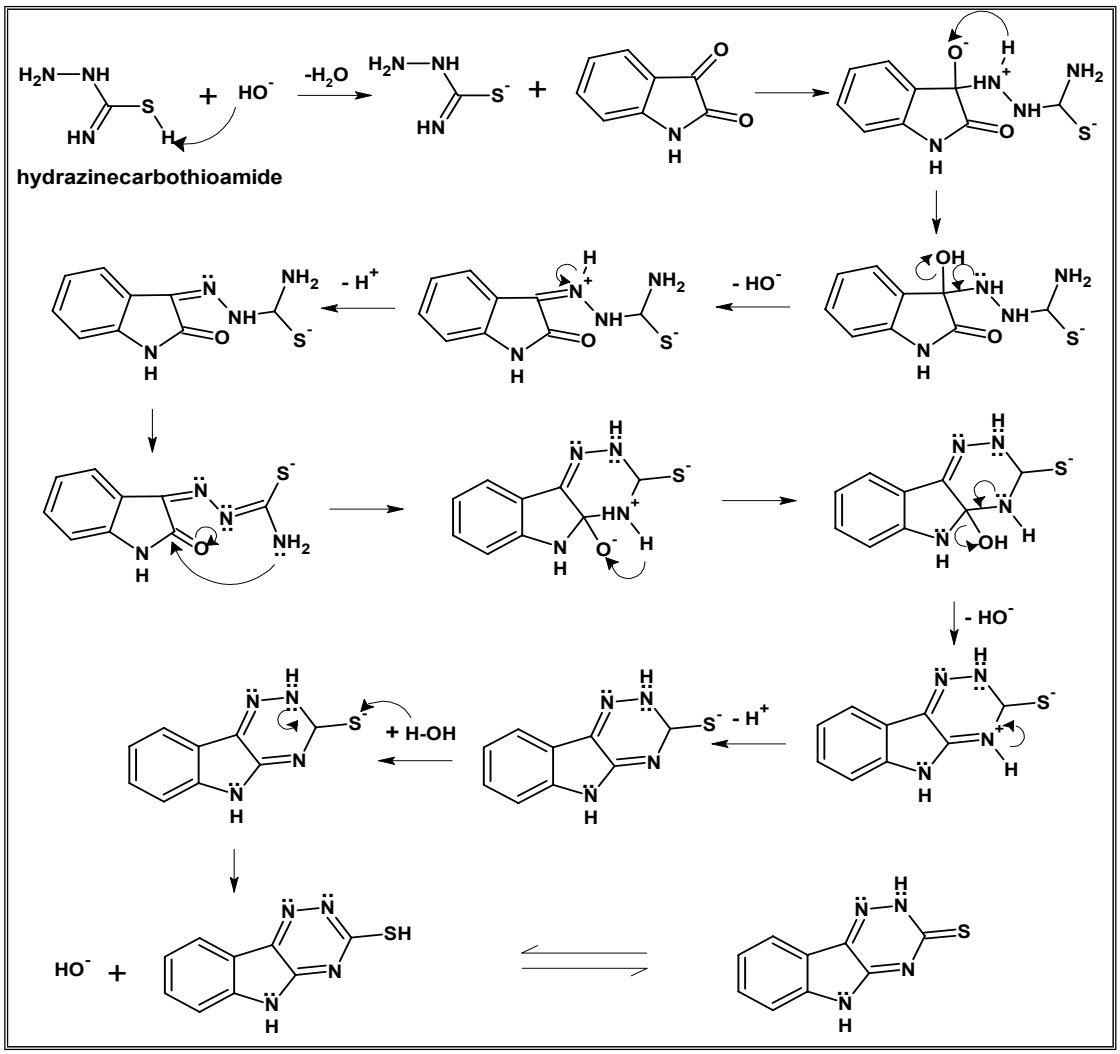
Triazino-indole-3-thione, thus obtained, was reacted with hydrazine hydrate by refluxing for four hours to give hydrazino derivative. It was crystallized from dimethylformamide and the yield of hydrazino compound was 60%. The hydrazino compound and various aldehydes were refluxed in methanol to yield corresponding benzylidine derivative in very good yield (70-80%). The benzylidine derivative was cyclized using bromine and acetic acid to form title compound i.e. triazolo-triazino-indole derivatives. The reaction schemes are given in Section 5.4 and physical data are given in Section 5.6. The spectral characterizations are discussed in Section 5.6.

5.4 Reaction schemes

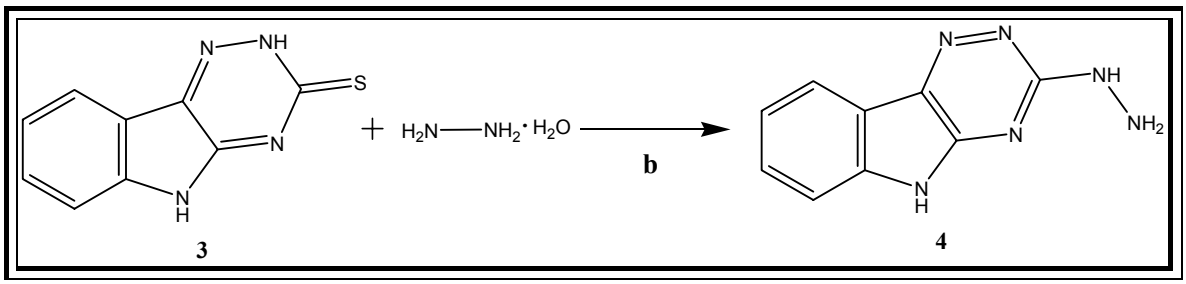
5.4.1 Scheme 1



Scheme 1. Reagents and conditions: a = i) K_2CO_3, H_2O, reflux, 24 hrs. ii) gl. AcOH.

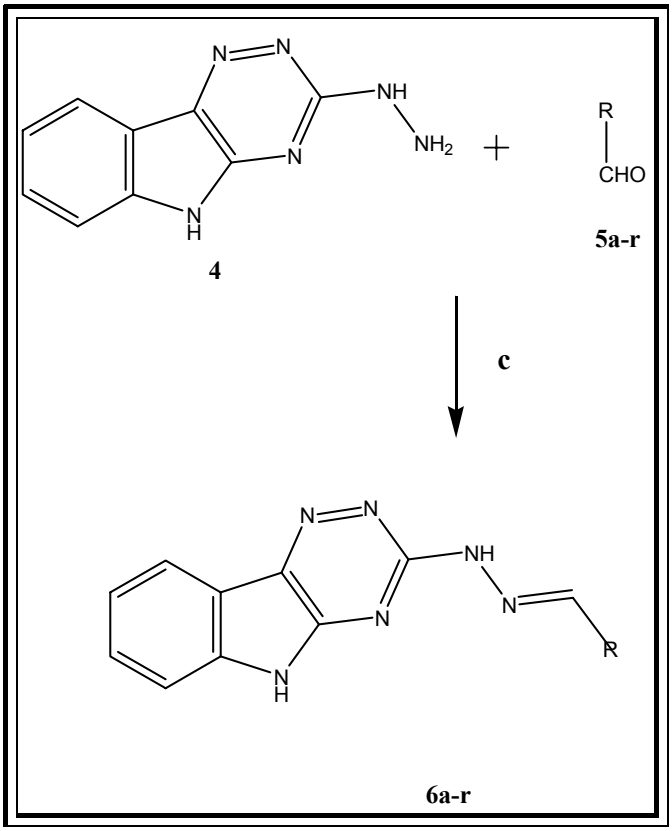


5.4.2 Scheme 2



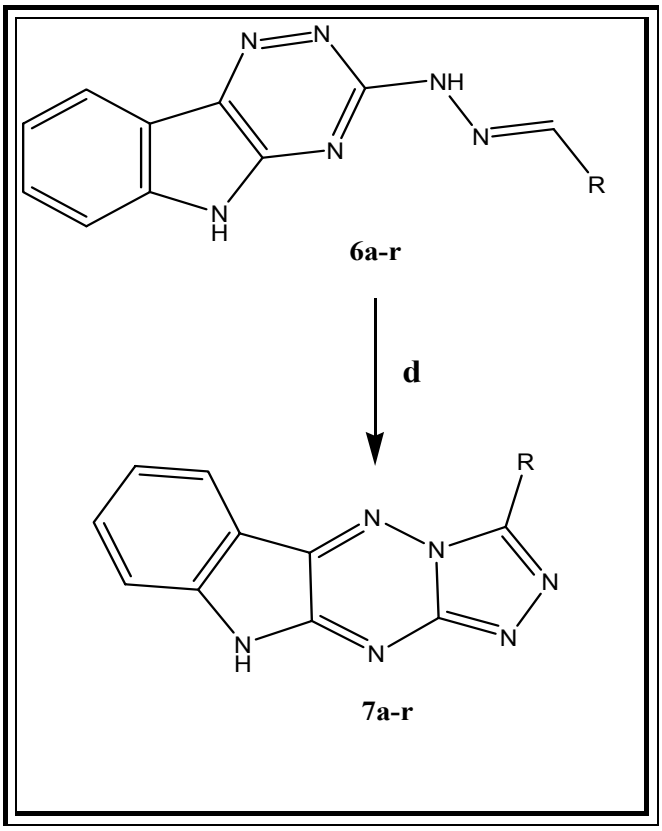
Scheme 2. Reagents and conditions: b = reflux, 4 hrs.

5.4.3 Scheme 3



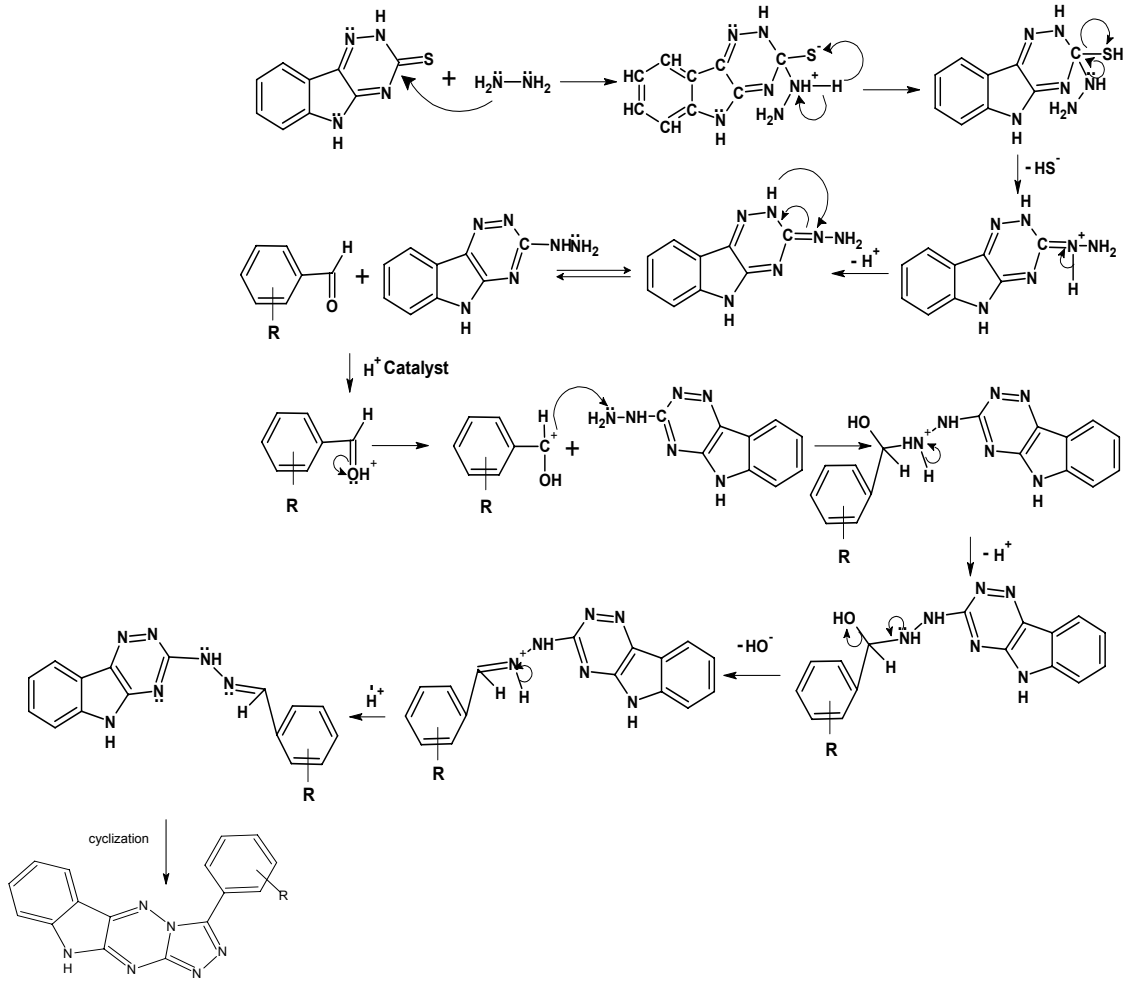
Scheme 3. Reagents and conditions: c = EtOH, gl. AcOH, reflux.

5.4.4 Scheme 4



Scheme 4. Reagents and conditions: d = Br_2, AcOH, stirring.

Reaction Mechanism



5.5 Experimental

5.5.1 Synthesis of 2,5-dihydro-3*H*-[1,2,4]triazino[5,6-*b*]indole-3-thione (3): Isatin (0.1mole), thiosemicarbazidde (0.11mole), potassium carbonate(0.15mole) and distilled water (500ml) were stirred and refluxed for 24 hrs. The mixture was filtered after cooling and acidified with acetic acid. The solid was filtered off, washed with water and dried. Recrystallized from dimethylformamide. Yield 78%, m.p. >300°C.

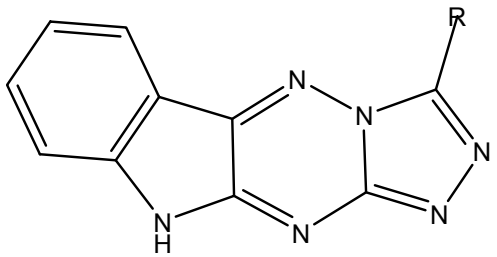
5.5.2 Synthesis of 3-hydrazino-5H-[1,2,4]triazino[5,6-b]indole (4): 2,5-dihydro-3H-[1,2,4]triazino[5,6-b]indole-3-thione (0.01mole) was refluxed with 99% Hydrazine hydrate (15ml) for 4 hrs. Crystals, separated on cooling, were filtered washed with ethanol to afford 1.4gms (71%) Yield. Recrystallized from dimethylformamide. Yield 60% m.p. 275-278°C.

5.5.3 Synthesis of 2-(substitutedbenzylidene)-1-(5H-[1,2,4]triazino[5,6-b]indol-3-yl)hydrazine (6a-r): A mixture of substituted benzaldehyde (0.01mole) and 3-hydrazino-5H-[1,2,4]triazino[5,6-b]indole (0.01mole) with catalytic amount of glacial acetic acid were refluxed in ethanol. On cooling, it gives crystals of corresponding 2-(substitutedbenzylidene)-1-(5H-[1,2,4]triazino[5,6-b]indol-3-yl)hydrazine in good yield (70-80%), which were purified by recrystallization from dimethylsulfoxide.

5.5.4 3-substituted phenyl-10*H*-[1,2,4]triazolo[4,3-b][1,2,4] triazino [5,6-*b*]indole (7a-r): Bromine (0.12mole) in 10 ml of glacial acetic acid was added dropwise to the solution of 2-(substitutedbenzylidene)-1-(5H-[1,2,4]triazino[5,6-b]indol-3-yl)hydrazine (6a-r) (0.01mole) in glacial acetic acid. The reaction mixture was then stirred at ambient temperature for 4-6 hours. Solid was filtered and it was washed with petroleum ether and recrystallized from dimethylsulfoxide. (Physical data is given in Table 5.6.1)

5.6 Physical data

5.5.1 Physical data of 3-(substituted phenyl)-10*H*-[1,2,4]triazolo[4,3-b][1,2,4] triazino [5,6-*b*]indole [compound 7a-r]



Compound	Code	R	MF	MW	Yield	MP	R_f
7a	AKS – 501	Ph	$C_{16}H_{10}N_6$	286.29	63	223-25	0.69
7b	AKS – 502	4-SCH_3-Ph	$C_{17}H_{12}N_6S$	332.38	54	289-90	0.45
7c	AKS – 503	2-Cl-Ph	$C_{16}H_9ClN_6$	320.74	59	261	0.53
7d	AKS – 504	4-OCH_3-Ph	$C_{17}H_{12}N_6O$	316.32	55	238-40	0.58
7e	AKS – 505	3,4- OCH_3-Ph	$C_{18}H_{14}N_6O_2$	346.34	52	251-52	0.66

7f	AKS – 506	4-OH-Ph	$C_{16}H_{10}N_6O$	302.29	53	272-74	0.48*
7g	AKS – 507	4-F-Ph	$C_{16}H_9FN_6$	304.28	56	247	0.55
7h	AKS – 508	3-NO_2-Ph	$C_{16}H_9N_7O_2$	331.29	48	>300	0.49
7i	AKS – 509	3-OH-Ph	$C_{16}H_{10}N_6O$	302.29	45	265-66	0.52*
7j	AKS – 510	4-Cl-Ph	$C_{16}H_9ClN_6$	320.74	54	253-55	0.59
7k	AKS – 511	2,5-OCH_3-Ph	$C_{18}H_{14}N_6O_2$	346.34	56	243-44	0.64
7l	AKS – 512	2-OH-Ph	$C_{16}H_{10}N_6O$	302.29	48	269-70	0.41
7m	AKS – 513	4-CH_3-Ph	$C_{17}H_{12}N_6$	300.32	59	221-22	0.57
7n	AKS – 514	9-anthryl	$C_{24}H_{14}N_6$	386.41	50	188-90	0.68
7o	AKS – 515	4-OH-3-OCH_3-Ph	$C_{17}H_{12}N_6O_2$	332.32	54	233-35	0.44*
7p	AKS – 516	2-NO_2-Ph	$C_{16}H_9N_7O_2$	331.29	43	284-87	0.51
7q	AKS – 517	m-phenoxy-Ph	$C_{22}H_{14}N_6O$	378.39	52	231-32	0.60
7r	AKS – 518	Furfuryl	$C_{14}H_8N_6O$	276.25	56	211-12	0.68

Solvent system for TLC: EA:Hexane – 4:6
*EA:Hexane – 3:7

MPs were taken in open capillary and are uncorrected

5.7 Spectral discussion

5.7.1 Mass spectral study

In mass spectra of synthesized compounds, molecular ion peaks obtained were in agreement with molecular weight of respective compounds. Base peak in each spectrum was observed same because of specific fragment. Intense peak obtained at 157 m/e in each mass spectrum, and was identified as base peak. AKS-507 gave molecular ion peak at 304 and base peak at 157. M^{+2} peak was observed at 323 with 1/3 intensity of molecular ion peak for AKS-510 because of presence of chlorine atom. Similarly, molecular ion peaks were observed at 386 and 378 for AKS-514 and AKS-517. In case of AKS-517, cleavage of phenoxy group (Ar-O bond) gave peaks at 301 and 285. Base peak obtained in each spectrum can be assigned to the fragment generated because of cleavage of two C-N bond of triazine ring.

(Mass spectrum of AKS-507, AKS-510, AKS-514 and AKS-517 are given on Page no. 188 & 189)

5.7.2 IR spectral study

In IR spectrums, characteristic frequencies were observed for functional group present in the molecule. There is absence of carbonyl, hydroxyl and other functional groups in basic skeleton. Cyclic –NH- functionality, aromatic ring and –C=N- groups are present in basic moiety. –NH- group was observed at 3380-3450 cm^{-1}. Characteristic peaks were observed for aromatic ring. (Ar-H, 3010-3140 cm^{-1}), (-C=C-, 1580-1640 cm^{-1}) and (OOP bending, 680-780 cm^{-1}). C=N vibrations gave peak at 1615-1670 cm^{-1}. C-N vibrations were observed at 1210-1270 cm^{-1}. These are the characteristic frequencies observed in each spectrum, while other frequencies were obtained for the functional group present on the 3-phenyl ring. Presence of methyl, methoxy, thiomethyl, hydroxy etc. groups was identified with their characteristic frequencies and is mentioned in the spectral data of individual compound.

(IR spectrum of AKS-513, AKS-511, AKS-504 and AKS-505 are given on Page no. 183 & 184)

5.7.3 ^{1}H NMR spectral study

In NMR spectra of the compounds, number of protons and their chemical shifts were found to support the structure of the synthesized compounds. Aromatic protons were obtained between 6.8-8.2 δ ppm. N-H proton in each spectrum, gave signal in downfield between 12-13 δ ppm.

In NMR spectrum of AKS-504, singlet was observed for three protons of methoxy group on 3-phenyl ring at 4.20 δ ppm. A doublet was obtained for two protons beacuse of coupling with ortho protons (J=8.57). Two protons showed ortho as well as meta coupling, and each give triplet with J values 7.19&1.87 and 8.14&2.16 respectvely. Antoher doublet was observed for one proton with ortho coupling J value (J=8.79). remaining there aromatic protons could not be reoslved and obtained as multiplet. –NH- proton gave signal in downfiled at 13.05 δ ppm.

In case of compound AKS-505, two singlets were observed due to two methoxy group protons at 3.90 and 4.07 δ ppm. Three protons of 3-phenyl ring gave two doublets and a singlet. Two protons on adjacent carbon atoms gave two doublets due to orhto coupling (J= 7.11, 8.31). Two protons of benzenoid part of indole, gave two triplet, while another two proton observed as doublet for each. –NH- proton signal was observed in downfield as in earlier spectrum (12.21 δ ppm).

In case of compound AKS-501, nine aromatic protons were obtained between 7.46-8.48 δ ppm and –NH- proton gave singal at 13.10 δ ppm. The splitting of signals and their J values are given in spectral data of compounds.

(1H NMR spectrum of AKS-505, AKS-501 and AKS-504 are given on Page no. 185, 186 & 187)

5.7.4 Elemental analysis

Percentage values of carbon, hydrogen and nitrogen found in elemental analysis were in agreement with calculated values of elements. The spectral and elemental analysis data are given below for individual compound.

Spectral data of synthesized compounds (AKS 501-518)

3-Phenyl-10*H*-[1,2,4]triazolo[4,3-b][1,2,4] triazino [5,6-*b*]indole (AKS-501) – ***IR*** *(cm^{-1}):* 3378 (N-H), 3106 (Ar-H), 1628 (C=N), 1607, 1581, 1472 (C=C), 1217 (C-N), 881, 749 (OOP); ***^{1}H NMR*** *(DMSO d6) (δ ppm)*: 7.46 (1H, t, J=8.27), 7.59 (1H, d, J=7.63), 7.70 (3H, m), 7.84 (1H, t, J=8.05), 8.31 (1H, d, J=8.52), 8.48 (2H, d, J=7.83), 13.10 (1H, s); ***Anal cacld*** for $C_{16}H_{10}N_6$: C 67.12, H 3.52, N 29.35, found: C 67.18, H 3.53, N 29.42.

3-(4-Methylthiophenyl)-10*H*-[1,2,4]triazolo[4,3-b][1,2,4] triazino [5,6-*b*]indole (AKS-502) - ***IR*** *(cm^{-1}):* 3441 (N-H), 3086 (Ar-H), 2978 (-CH_3), 2577 (S-H), 1644 (C=N), 1586, 1540, 1417 (C=C), 1212 (C-N), 831 (OOP); ***Anal cacld*** for $C_{17}H_{12}N_6S$: C 61.43, H 3.34, N 25.28, found: C 61.47, H 3.35, N 25.33.

3-(2-Chlorophenyl)-10*H*-[1,2,4]triazolo[4,3-b][1,2,4] triazino [5,6-*b*]indole (AKS-503) - 3354 (N-H), 3123 (Ar-H), 1618 (C=N), 1596, 1552, 1431 (C=C), 1256 (C-N), 831, 718 (OOP); ***Anal cacld*** for $C_{16}H_9ClN_6$: C 59.92, H 2.83, N 26.20, found: C 59.90, H 2.85, N 26.26.

3-(4-Methoxyphenyl)-10*H*-[1,2,4]triazolo[4,3-b][1,2,4] triazino [5,6-*b*]indole (AKS-504) - ***IR*** *(cm^{-1}):* 3419 (N-H), 3118 (Ar-H), 3008, 2925 (-CH_3), 1620 (C=N), 1528, 1475 (C=C), 1299 (C-N), 1073 (C-O), 771 (OOP); ***^{1}H NMR*** *(DMSO d6) (δ ppm)*: 4.20 (3H, s), 7.24 (2H, d, J=8.57), 7.47 (1H, t, J=7.19, 1.87), 7.60 (1H, d, J=8.79), 7.84 (1H, t, J=8.14, 2.16), 9.39 (3H, m), 13.05 (1H, s); ***Anal cacld*** for $C_{17}H_{12}N_6O$: C 64.55, H 3.82, N 26.57, found: C 64.50, H 3.81, N 26.63.

3-(3,4-dimethoxyphenyl)-10*H*-[1,2,4]triazolo[4,3-b][1,2,4] triazino [5,6-*b*]indole (AKS-505) - ***IR*** *(cm^{-1}):* 3419 (N-H), 3129 (Ar-H), 2924, 2832 (-CH_3), 1637 (C=N), 1594,

1561, 1460 (C=C), 1256 (C-N), 1159 (C-O), 754 (OOP); ***^{1}H NMR*** *(DMSO d6) (δ ppm)*: 3.90 (3H, s), 4.07 (3H, s), 7.22 (1H, d, J=7.92), 7.34 (1H, t, J=8.53), 7.42 (1H, d, J=7.58), 7.71 (1H, t, J=8.16), 7.92 (1H, s), 8.06 (1H, d, 7.11), 8.25 (1H, d, J=8.31), 12.21 (1H, s); ***Anal cacld*** for $C_{18}H_{14}N_6O_2$: C 62.42, H 4.07, N 24.27, found: C 62.43, H 4.05, N 24.30.

3-(4-Hydroxyphenyl)-10*H*-[1,2,4]triazolo[4,3-b][1,2,4] triazino [5,6-*b*]indole (AKS-506) – 3517 (-OH-), 3346 (N-H), 3078 (Ar-H), 1624 (C=N), 1577, 1551, 1486 (C=C), 1226 (C-N), 806 (OOP); ***Anal cacld*** for $C_{16}H_{10}N_6O$: C 63.57, H 3.33, N 27.80, found: C 63.59, H 3.32, N 27.84.

3-(4-Fluorophenyl)-10*H*-[1,2,4]triazolo[4,3-b][1,2,4] triazino [5,6-*b*]indole (AKS-507) - 3456 (N-H), 3120 (Ar-H), 1609 (C=N), 1581, 1542, 1479 (C=C), 1263 (C-N), 796 (OOP); ***Mass (m/e)*:** 304 (molecular ion peak), 285, 209, 189, 179, 157 (base peak), 143, 127, 77; ***Anal cacld*** for $C_{16}H_9FN_6$: C 63.16, H 2.98, N 27.62, found: C 63.19, H 3.00, N 27.67.

3-(3-Nitrophenyl)-10*H*-[1,2,4]triazolo[4,3-b][1,2,4] triazino [5,6-*b*]indole (AKS-508) - 3443 (N-H), 3115 (Ar-H), 1678 (C=N), 1633, 1561, 1422 (C=C), 1344 (C-NO_2), 1272 (C-N), 817, 773 (OOP); ***Anal cacld*** for $C_{16}H_9N_7O_2$: C 58.01, H 2.74, N 29.60, found: C 58.03, H 2.75, N 29.68.

3-(3-Hydroxyphenyl)-10*H*-[1,2,4]triazolo[4,3-b][1,2,4] triazino [5,6-*b*]indole (AKS-509) - 3502 (-OH-), 3318 (N-H), 3155 (Ar-H), 1617 (C=N), 1602, 1567, 1457 (C=C), 1211 (C-N), 881, 732 (OOP); ***Anal cacld*** for $C_{16}H_{10}N_6O$: C 63.57, H 3.33, N 27.80, found: C 63.60, H 3.36, N 27.90.

3-(4-Chlorophenyl)-10*H*-[1,2,4]triazolo[4,3-b][1,2,4] triazino [5,6-*b*]indole (AKS-510) - 3418 (N-H), 3111 (Ar-H), 1681 (C=N), 1555, 1521, 1464 (C=C), 1207 (C-N), 745 (OOP); ***Mass (m/e)*:** 323 (M^{+2}), 321 (molecular ion peak), 286, 243, 163, 157(base peak), 128, 72; ***Anal cacld*** for $C_{16}H_9ClN_6$: C 59.92, H 2.83, N 26.20, found: C 59.90, H 2.84, N 26.24.

3-(2,5-dimethoxyphenyl)-10*H*-[1,2,4]triazolo[4,3-b][1,2,4] triazino [5,6-*b*]indole (AKS-511) – ***IR*** *(cm^{-1}):* 3404 (N-H), 3130 (Ar-H), 2923, 2854 (-CH_3), 1603 (C=N),

1515, 1480 (C=C), 1261 (C-N), 1190 (C-O), 774 (OOP); ***Anal cacld*** for $C_{18}H_{14}N_6O_2$: C 62.42, H 4.07, N 24.27, found: C 62.45, H 4.08, N 24.31.

3-(2-Hydroxyphenyl)-10*H*-[1,2,4]triazolo[4,3-b][1,2,4] triazino [5,6-*b*]indole (AKS-512) - 3562 (-OH-), 3337 (N-H), 3130 (Ar-H), 1658 (C=N), 1621, 1554, 1467 (C=C), 1273 (C-N), 894, 714 (OOP); ***Anal cacld*** for $C_{16}H_{10}N_6O$: C 63.57, H 3.33, N 27.80, found: C 63.59, H 3.33, N 27.82.

3-(4-Methylphenyl)-10*H*-[1,2,4]triazolo[4,3-b][1,2,4] triazino [5,6-*b*]indole (AKS-513) - ***IR*** *(cm^{-1}):* 3404 (N-H), 3136 (Ar-H), 3025, 2923 (-CH_3), 1650 (C=N), 1600, 1542, 1476 (C=C), 1268 (C-N), 837, 737 (OOP); ***Anal cacld*** for $C_{17}H_{12}N_6$: C 67.99, H 4.03, N 27.98, found: C 68.03, H 4.01, N 28.05.

3-(9-Anthryl)-10*H*-[1,2,4]triazolo[4,3-b][1,2,4] triazino [5,6-*b*]indole (AKS-514) - 3448 (N-H), 3122 (Ar-H), 1666 (C=N), 1628, 1593, 1447 (C=C), 1217 (C-N), 853, 786 (OOP); ***Mass (m/e)*****:** 386 (molecular ion peak), 282, 231, 217, 185, 157 (base peak), 115, 86; ***Anal cacld*** for $C_{24}H_{14}N_6$: C 74.60, H 3.65, N 21.75, found: C 74.63, H 3.66, N 21.80.

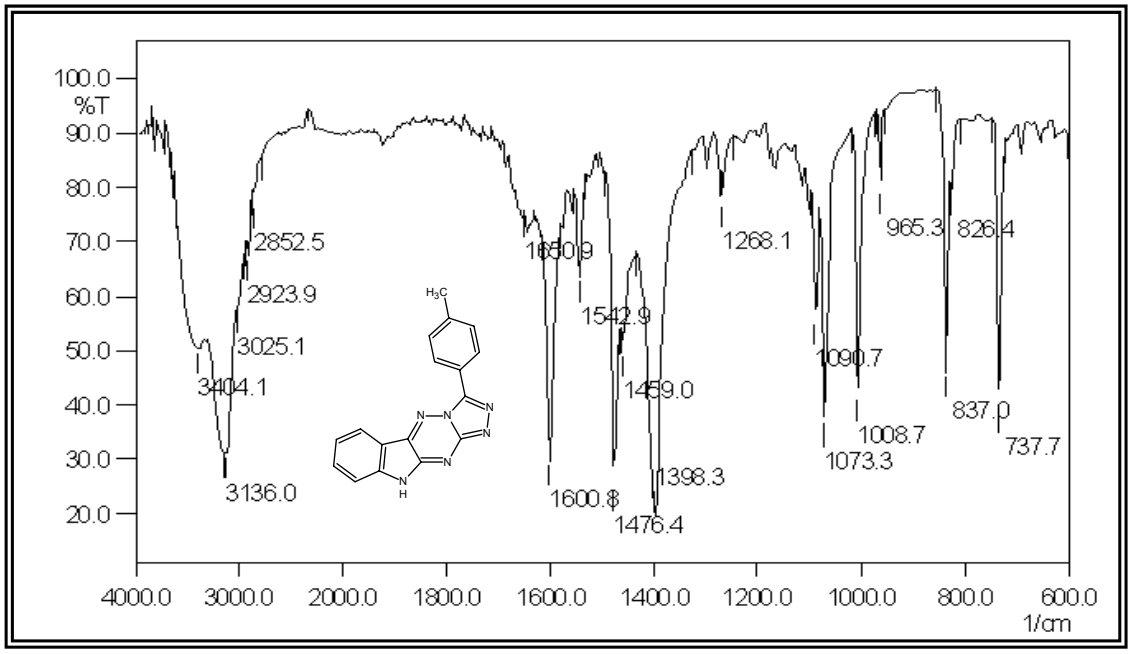
3-(3-Methoxy-4-Hydroxyphenyl)-10*H*-[1,2,4]triazolo[4,3-b][1,2,4] triazino [5,6-*b*]indole (AKS-515) – 3588 (-OH-), 3418 (N-H), 3108 (Ar-H), 3011, 2956 (-CH_3), 1652 (C=N), 1607, 1588, 1461 (C=C), 1260 (C-N), 888, 764 (OOP); ***Anal cacld*** for $C_{17}H_{12}N_6O_2$: C 61.44, H 3.64, N 25.29, found: C 61.47, H 3.66, N 25.34.

3-(2-Nitrophenyl)-10*H*-[1,2,4]triazolo[4,3-b][1,2,4] triazino [5,6-*b*]indole (AKS-516) - 3403 (N-H), 3016 (Ar-H), 1658 (C=N), 1617, 1563, 1420 (C=C), 1348 (C-NO_2), 1223 (C-N), 740 (OOP); ***Anal cacld*** for $C_{16}H_9N_7O_2$: C 58.01, H 2.74, N 29.60, found: C 58.04, H 2.73, N 29.67.

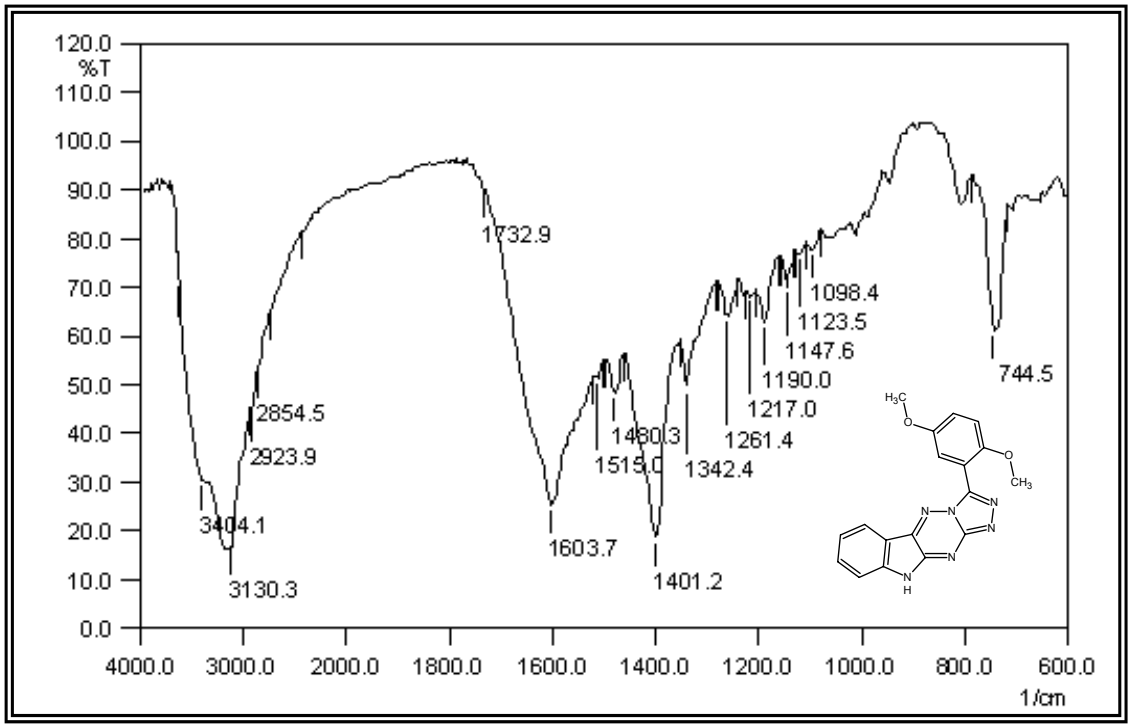
3-(3-Phenoxyphenyl)-10*H*-[1,2,4]triazolo[4,3-b][1,2,4] triazino [5,6-*b*]indole (AKS-517) - 3347 (N-H), 3119 (Ar-H), 1641 (C=N), 1602, 1578, 1433 (C=C), 1210 (C-N), 833, 762 (OOP); ***Mass (m/e)*****:** 378 (molecular ion peak), 301, 285, 189, 157(base peak), 143, 127, 77; ***Anal cacld*** for $C_{22}H_{14}N_6O$: C 69.83, H 3.73, N 22.21, found: C 69.85, H 3.75, N 22.27.

3-(2-Furfuryl)-10*H*-[1,2,4]triazolo[4,3-b][1,2,4] triazino [5,6-*b*]indole (AKS-518) - 3399 (N-H), 3023 (Ar-H), 1655 (C=N), 1621, 1577, 1463 (C=C), 1296(C-O), 1267 (C-N), 810 (OOP); ***Anal cacld*** for $C_{14}H_8N_6O$: C 60.87, H 2.92, N 30.42, found: C 60.90, H 2.94, N 30.49.

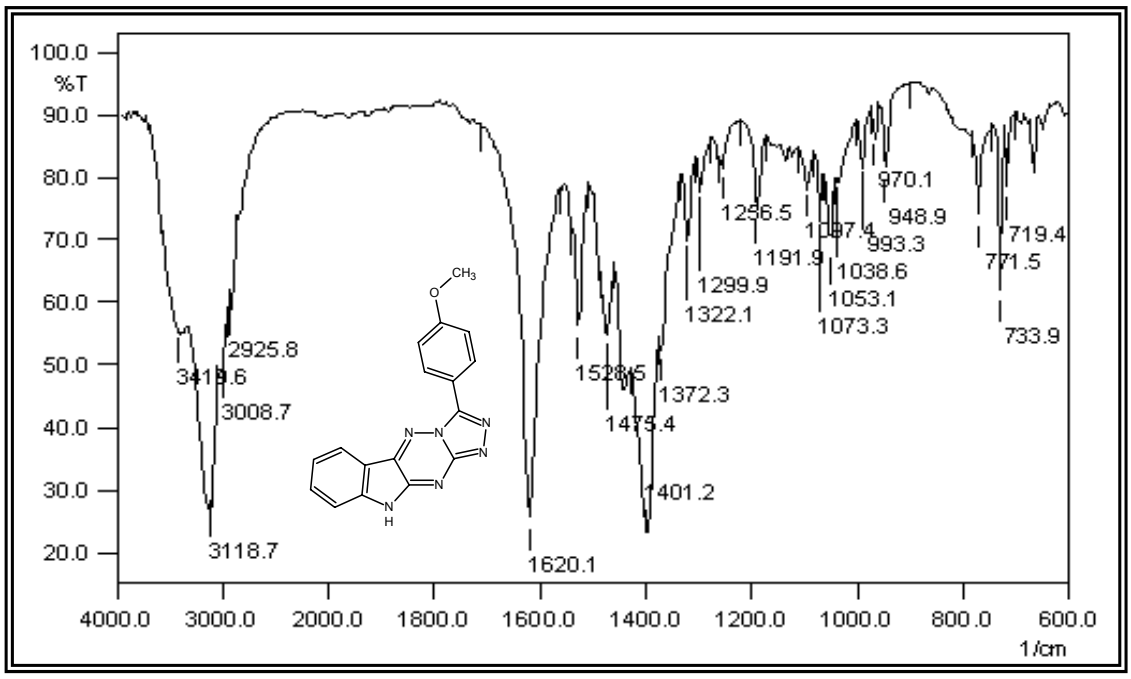
5.7.5.1 IR spectrum of AKS-513



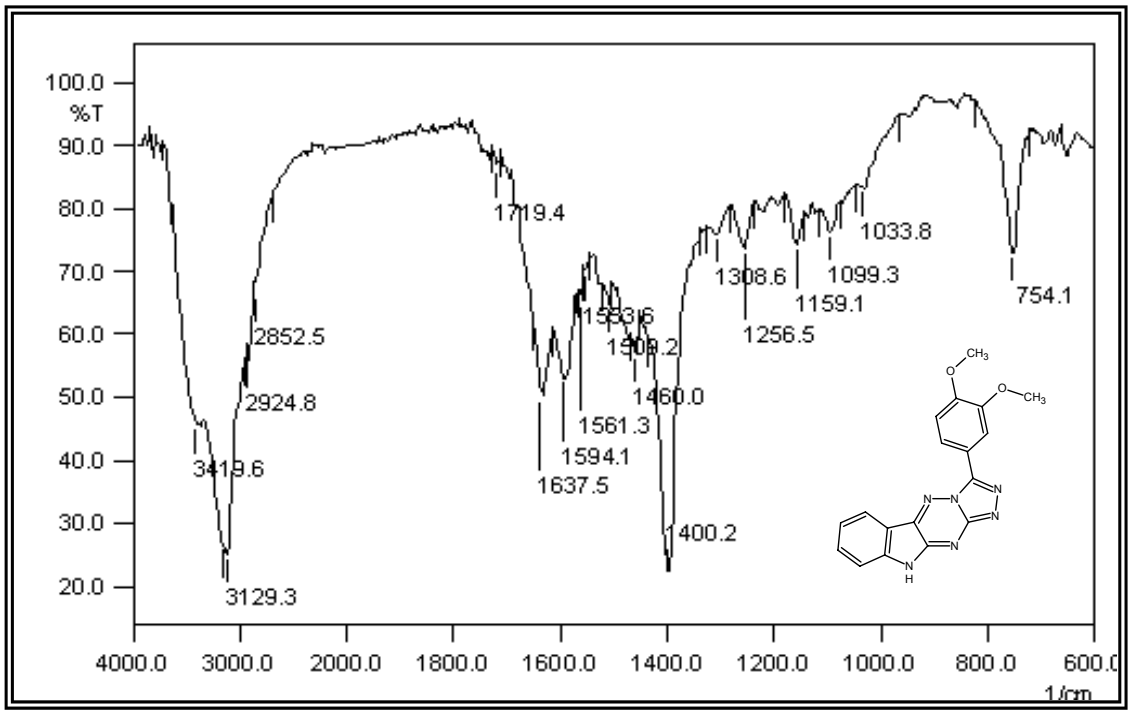
5.7.5.2 IR spectrum of AKS-511



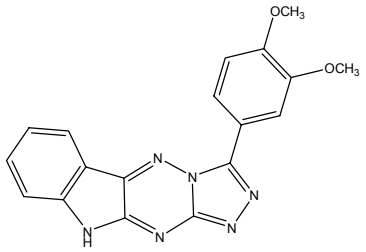
5.7.5.3 IR spectrum of AKS-504

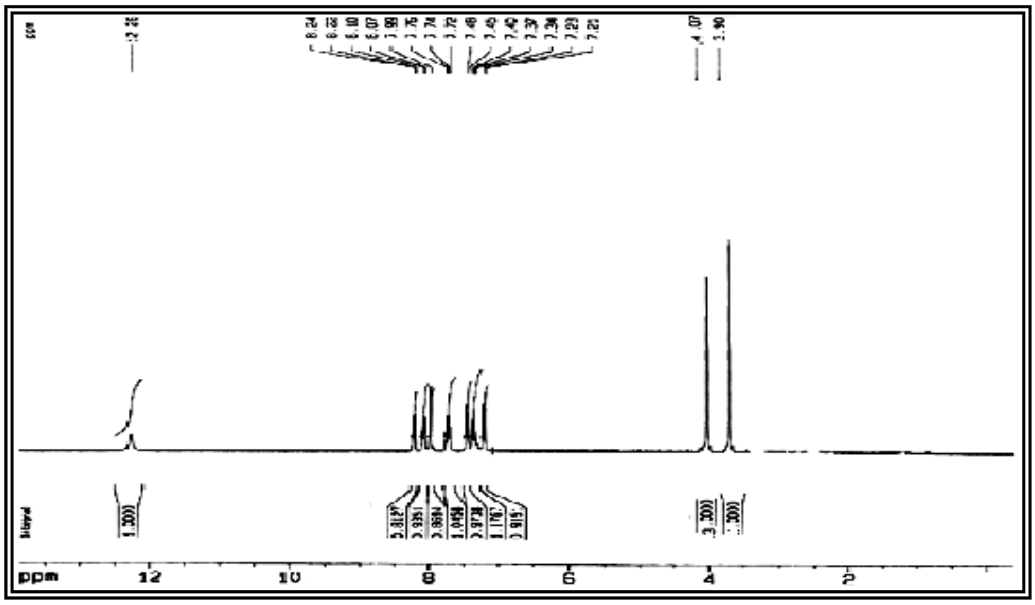


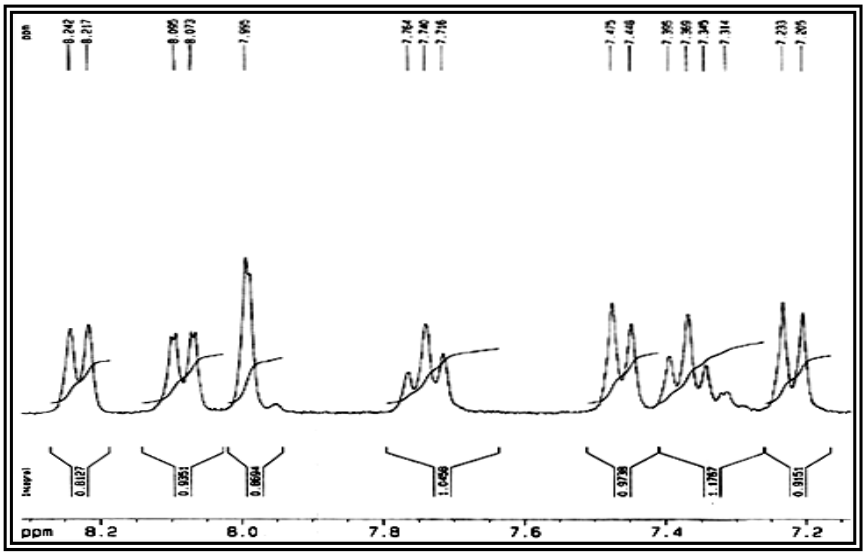
5.7.5.4 IR spectrum of AKS-505



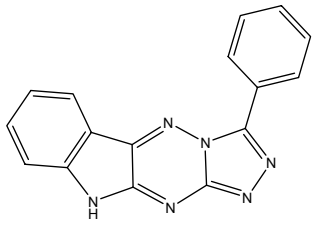
5.7.5.5 ^{1}H NMR spectrum of AKS-505

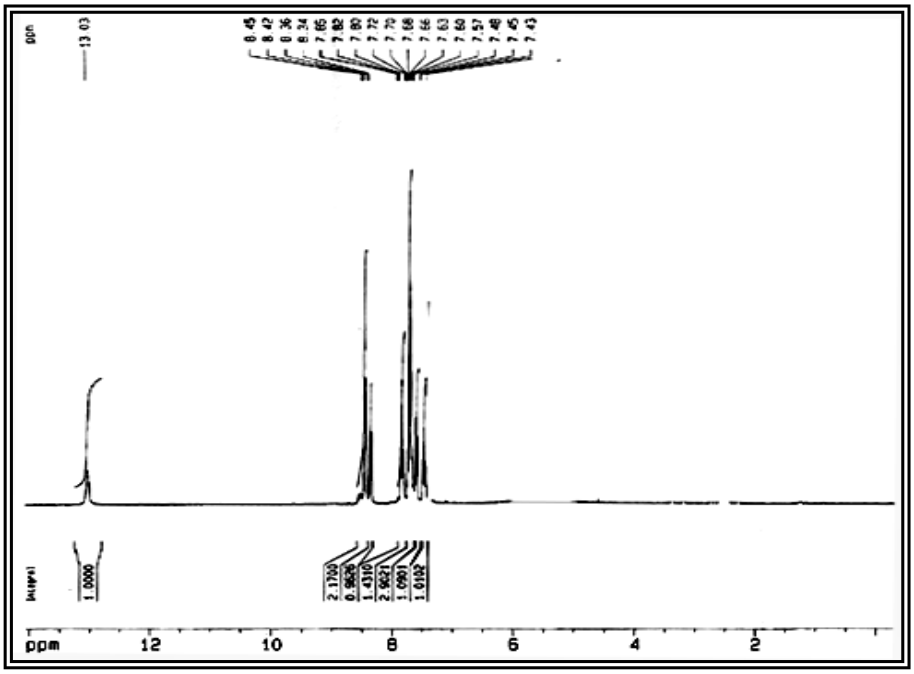


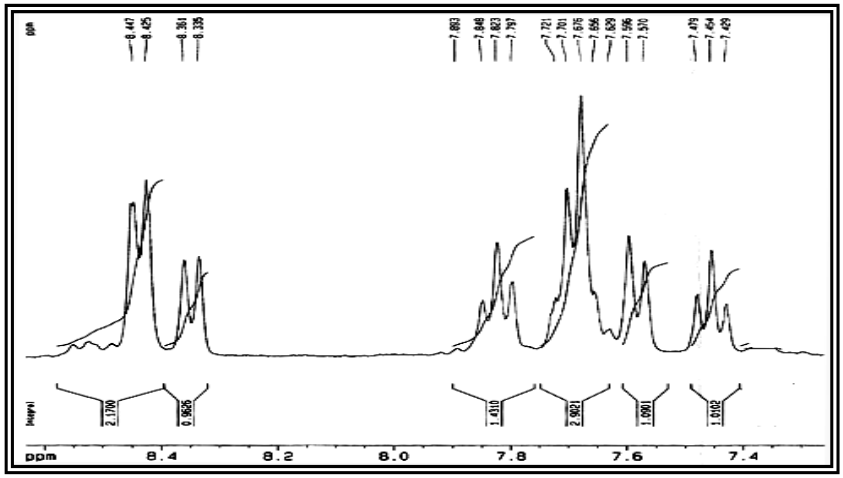




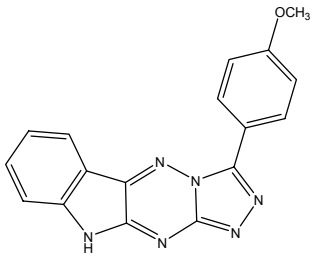
5.7.5.6 ^{1}H NMR spectrum of AKS-501

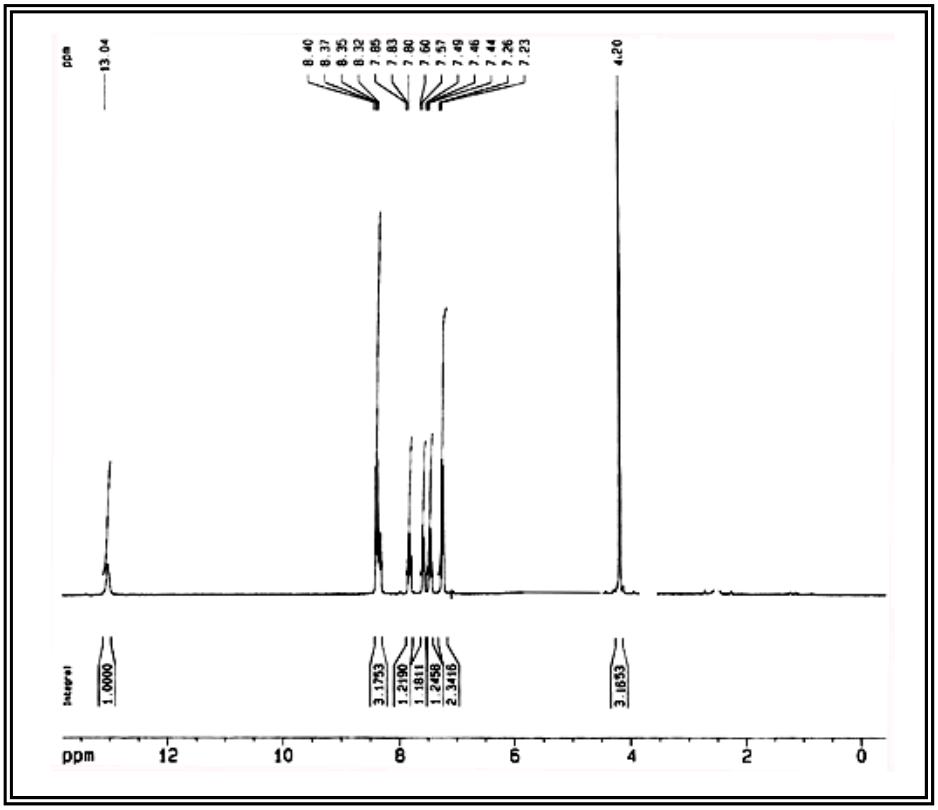


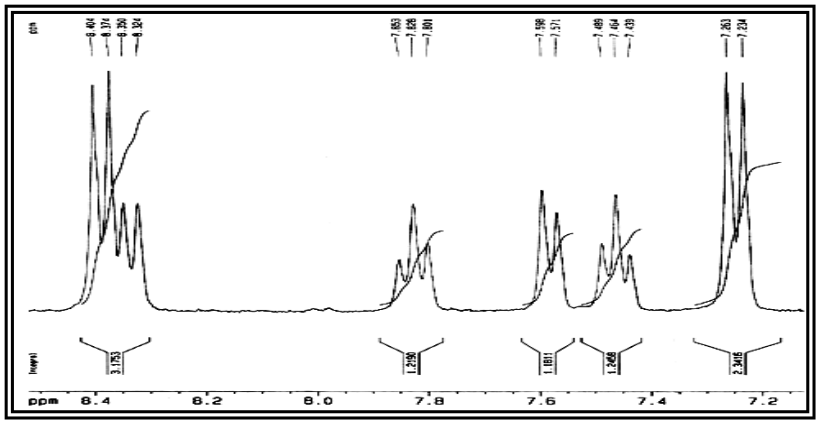




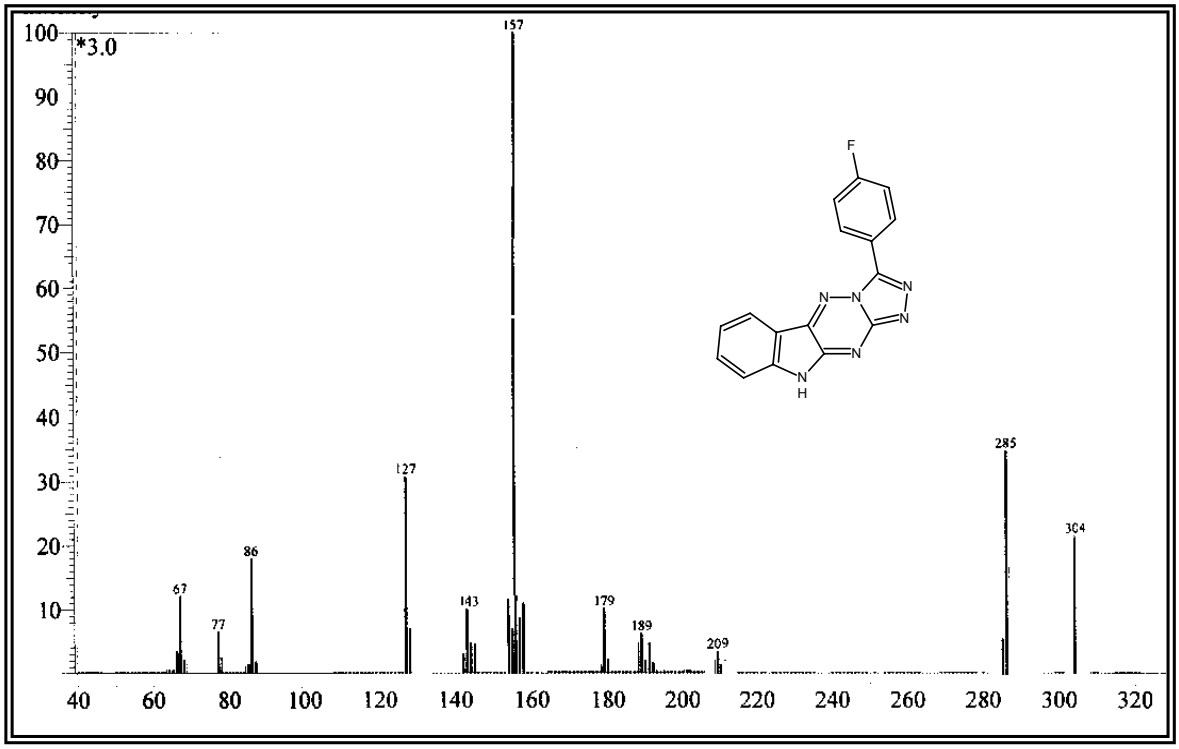
5.7.5.7 ^{1}H NMR spectrum of AKS-504



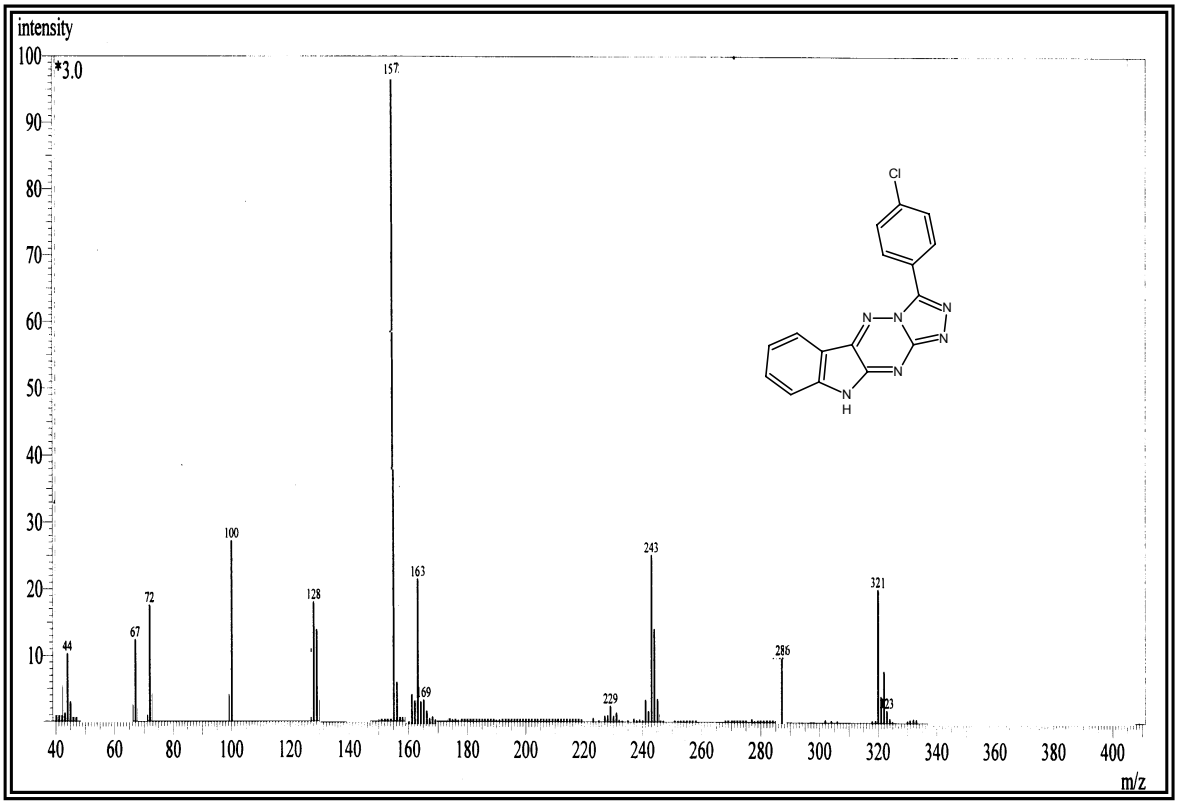




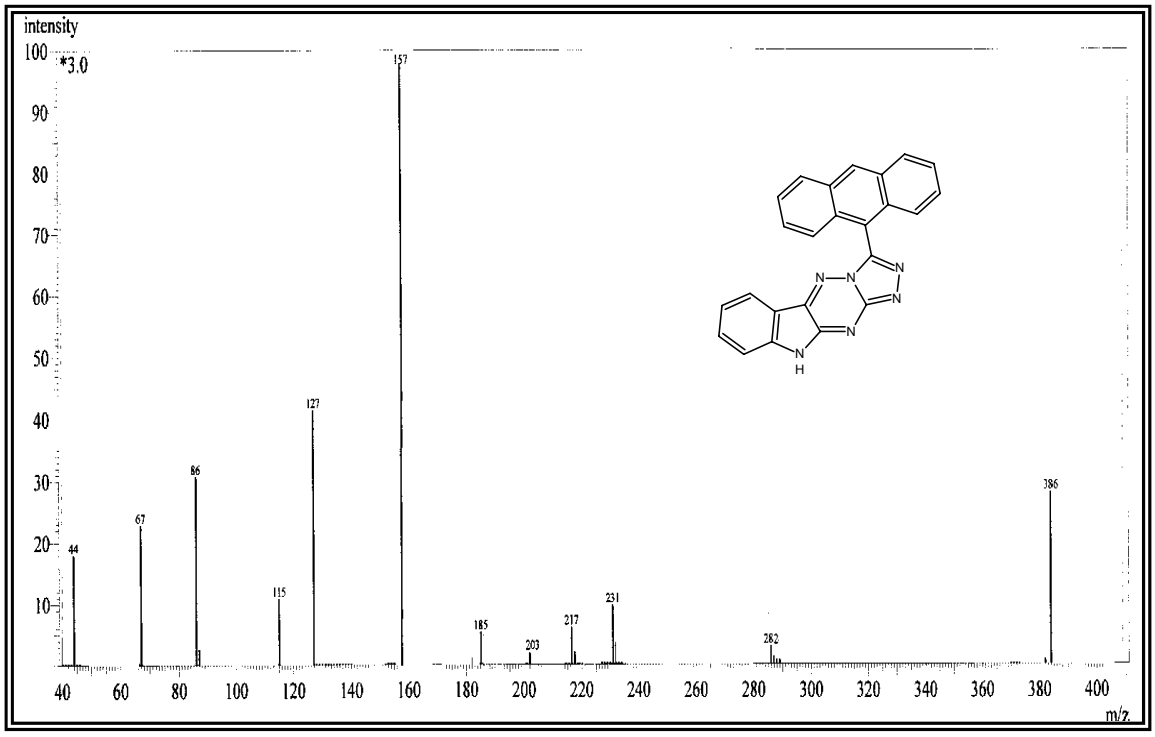
5.7.5.8 Mass spectrum of AKS-507



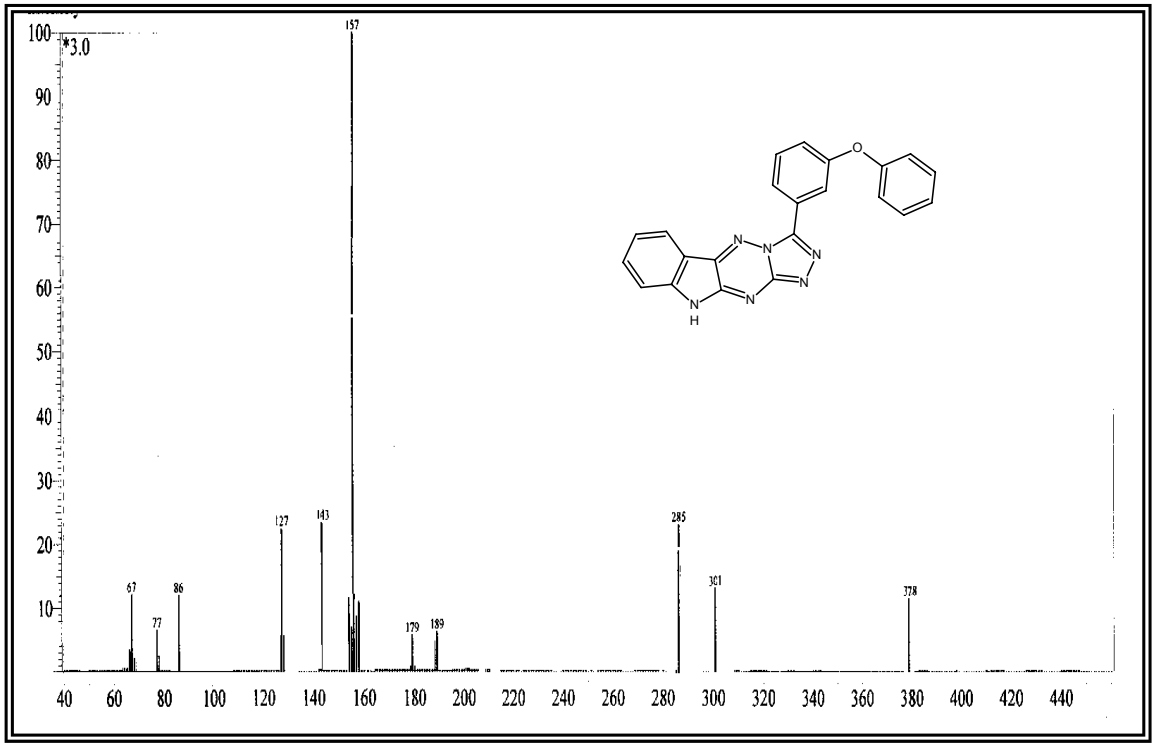
5.7.5.9 Mass spectrum of AKS-510



5.7.5.10 Mass spectrum of AKS-514



5.7.5.11 Mass spectrum of AKS-517



5.8 References

1. Bell, M.; Zalay, A.; Oesterlin, R.; Clemans, S.; Dum, D.; Bradford, J.; Rozitis, J.; *J.Med.Chem*., **1977** 22, 537.

2. Popp, F.; *J.Heterocycl.Chem.*, **1984** 21, 1641.
3. Joshi, K.; Pathak, V.; Jain, S.; *Pharmazie*, **1980** 35, 677.
4. Ueda, T.; Nakata, I.; Zasshi, Y.; **1960** 80, 1068, *Chem.Abst*., **1961** 55,562.
5. Bauer, D.; Sheffield, F.; *Nature*, **1959** 184,1496.
6. Thompson, R.; Minton, A.; Jun, S.; Officer, J.; Hitchings, G.; *J. Immunol.,* **1953** 70, 229.
7. Bauer, D.; Sadler, P.; *Brit. J. Pharmacol. Chemother.*, **1960** 15, 101.
8. D.Bauer, K. Apostolov, *Science*, **154**, 796 (1966).
9. Gladych, J.; Hunt, J.; Jack, D.; Haff, R.; Boyle, J.; Stewart, R.; Ferlauto, R.; *Nature,* **1969** 221, 286.
10. Tyrrell, D.; Bynoe, M.; *Lance t* **1966** 76
11. Dick, E.; *Proc. Soc. Exp.Biol. Med.*, **1968** 127,1079
12. Pinto, C.; Huff, R.; *Nature (London)*, **1969** 224,1310.
13. Bauer, D.; *Chemotherapy of virus diseases*, **1972** 1, 35.
14. Pfau, C.; *Handbook of experim.pharmcol.,* **1982** 61,147.
15. Gladych, J.; Hunt, J.; Jack, D.; Haff, R.; Boyle, J.; Stewart, R.; Ferlauto, R.; *Nature,* **1969** 221, 286.
16. Gwaltney, J.; *J Proc Soc Exp Biol Med*, **1970** 133, 1148.
17. Katz, E.; Margalith, E.; *Antimicrob. Agents Chemother.,* **1984** 25,195.
18. Baginski, S.; Pevear, D.; Seipel, M.; Sun, S.; Benetatos, C.; Chunduru, S.; Rice, C.; Collett, M.; *Proc Natl Acad Sci.,* **2000** 97, 14, 7981.
19. Thiel, H.; Plagemann, P.; Moennig, V.; *Virology*, (Lippincott, Philadelphia), **1996** 1059.
20. Sockett, D.; Bolin, D.; Ridpath, J.; Bolin, S.; *Bovine Viral Diarrhea Virus: A 50 Year Review.* (Cornell University College of Veterinary Medicine,Ithaca, NY), **1996** 207.
21. Corapi, W.; French, T.; Dubovi, E.; *J. Virol*. **1989** 63, 3934.
22. Pellerin, C.; Van den Hurk, J.; Lecomte, J.; Tijssen, P.; *Virology* **1994** 203, 260.
23. Bolin, S.; *Vet. Clin. North Am. Food Anim. Pract*. **1995** 11, 489.
24. Brownlie, J.; Clarke, M.; *Intervirology*, **1993** 35, 51.
25. Van Oirschot, J.; Bruschke, C.; Van Rijn, P.; *Vet. Microbiol*. **1999** 64, 169.
26. Kinsman, O.; Livermore, D.; Smith, C.; *Antimicrob.Agen.Chemother*. **1993** 37, 6, 1243.
27. Vijkovsky, T.; Koenig, M.; Zhang, F.; Cui, J.; *US Patent 7037909*
28. Kgokong, J.; Smith, P.; Matsabisa, G.; *Bioorg. Med.Chem.,* **2005** 13, 2935.
29. Raynes, K.; Stocks, P.; ONeill, P.; Park, B.; Ward, S.; *J. Med. Chem*., **1999** 42, 2747.
30. Menting, J.; Tilley, L.; Deady, L.; Ng, K.; Simpson, R.; Cowman, A.; Foley, M.; *Mol. Biochem.Parasitol.,* **1997** 88, 215.

31. Makler, M.; Ries, J.; Williams, J.; Bancroft, J.; Piper, R.; Gibbs, B.; Hinrichs, D.; D. J. Am. *J. Trop.Med. Hyg.,* **1993** 48, 6, 739.
32. Hawley, S.; Bray, P.; ONeill, P.; Park, B.; Ward, S.; *Biochem. Pharmacol.,* **1996** 52, 723.
33. Egan, T.; Hunter, R.; Kaschula, C.; Marques, H.; Mavuso, W.; *Afr. J. Sci.*, **1998** 94, 1.
34. Constantinidis, I.; Satterlee, J.; *J. Am. Chem. Soc.,* **1988** 110, 927.
35. Monge, A.; Parrado, P.; Font , M.; Fernandez, A.; *J.Med.Chem*., **1987** 30, 1029.
36. Reece, P.; *Med. Res. Rev., I ,* **1981** 73.
37. Gorman, R.; Samuelsson, B.; Kamwell, P.; Paleotti, R.; *Eds.;Raven: New York*, **1980** 417.
38. Morsy, J.; Abd el-Monem, W.; *Boll.Chim.Farm.,* **2001** 140, 2, 83.
39. Lopez-de-Cerain, A.; Garcia , E.; Gullon, A.; Recalde, J.; Monge, A.; *Mutagenesis*, **1990** 5, 4, 307.
40. Garcia, E.; Lopez-de-Cerain , A.; Martinez-Merino, Monge, A.; *Mutat. Res*, **1992** 268, 1, 1.
41. Holla, B.; Shashidhara, N.; Udupa, K.; Poojary, B.; *Ind.J.Heterocycl.Chem.,* **2005** 14, 4, 347.
42. Joshi, K.; Chand, P.; *J.Heterocycl. Chem.,* **1980** 17, 1783.
43. Alcalde, E.; Mendoza, J.; Elguero, J.; *J.Heterocycl.Chem.,* **1974** 11,921.
44. Monga Vega, A.; Aldana, I.; Rabbani, M.; Fernandez-Alvarez, E.; *J.Heterocycl.Chem.,* **1980** 17, 77.
45. Hoover, J.; Day, A.; *J.Am.Chem.Soc.,* 78, 5832
46. Abdel-Latif, F.; Shaker, R.; Mahgoub, S.; Badr, M.; *J.Heterocycl.Chem.,* **1980** 26, 769.
47. Badr, M.; Mahgoub, S.; Fahmey, A.; Abdel-Latif, F.; *Acta.Chim.Hung.,* **1987** 124, 413.
48. Kgokong, J.; Smith, P.; Matsabisa, G.; *Bioorg. Med.Chem.,* **2005** 13, 2935.
49. Diana, G.; Salvador, U.; Zalay, E.; Johnson, R.; Collins, J.; Johnson, W.; Hinshaw, W.; Lorenz, R.; Thielking, W.; Pancic, F.; *J. Med. Chem.,* **1977** 20, 750.
50. Monge, A.; Palop, J.; Ramirez, C.; Font, M.; Fernandez-Alvarez, E.; *Eur.J.Med.Chem*., **1991** 26, 179.

Chapter 6

3D-QSAR study of DHPM derivatives

Chapter 6

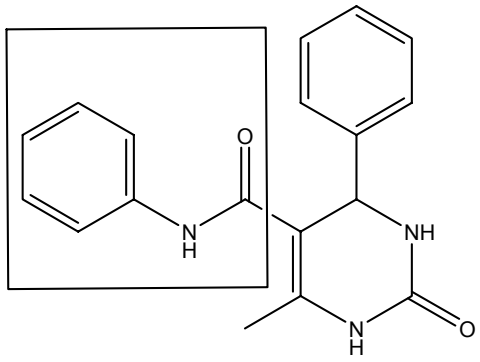
3D-QSAR study of DHPM derivatives

In earlier Chapters (1,2 & 3), synthetic and biological profile of dihydropyrimidinone derivatives has been reviewed in brief. A large number of references is sited for modification of Biginelli multi component reaction by means of catalyst, microwave assisted synthesis and solid phase synthesis. It has been of great interest to develop convenient methods for synthesis of modified dihydropyrimidinone derivatives. Three building blocks of Biginelli reaction (1) 1,3-diketone (2) aldehyde and (3) urea (thiourea) has been widely modified to develop libraries of DHPM derivatives. The biological importance of DHPM skeleton has encouraged developing better synthetic methods for synthesis of modified derivatives for potent biological profiles.

6.1 Efforts from our laboratory

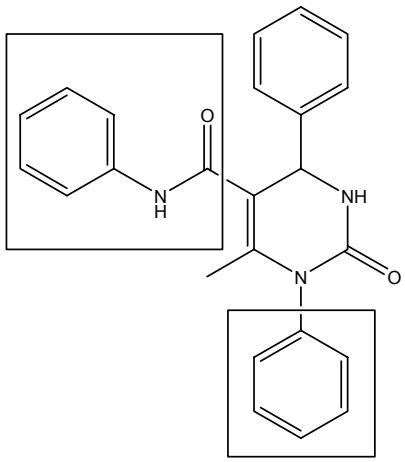
1,4-dihydropyridine skeleton has been extensively modified at 3 and 5 position in our lab where $–COCH_3$ group at 3^{rd} and 5^{th} position replaced with –CO-(substituted)Ph and –CO-NH-(substituted)Ph. This modifications to 1,4-DHPs showed potent anti tubercular activity and 1,4-DHP skeleton can be developed for potent anti tubercular structure class. The results obtained were studied for 2D-QSAR and 3D-QSAR study to find structural requirements for 1,4-DHP skeleton.

Dihydropyrimidinones (DHPMs, aza analogs of 1,4-DHPs) is also very interesting bioactive skeleton. From results obtained in 1,4-DHP modification, we started modifications to DHPM skeleton. Priti, Dinesh and Chintan synthesized DHPMs with –CO-NH-(substituted)Ph moiety at 5^{th} position. These molecules were screened for their anti tubercular activity and showed moderate activity profile.

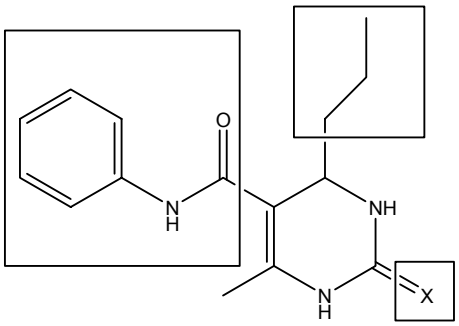


In continuation of work, earlier chapters of thesis deal with the modifications to DHPM skeleton as below.

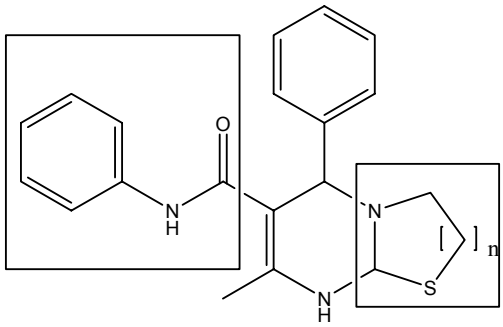
1. (N-Ph with –CO-NH-(substituted)Ph at 5th position)



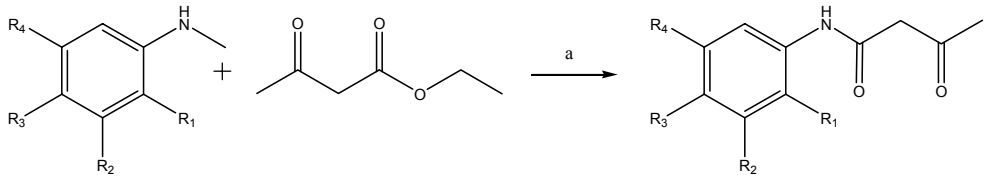
2. (Alkyl chain at 4th position with –CO-NH-(substituted)Ph at 5th position)



3. (Fused system with –CO-NH-(substituted)Ph at 5th position)

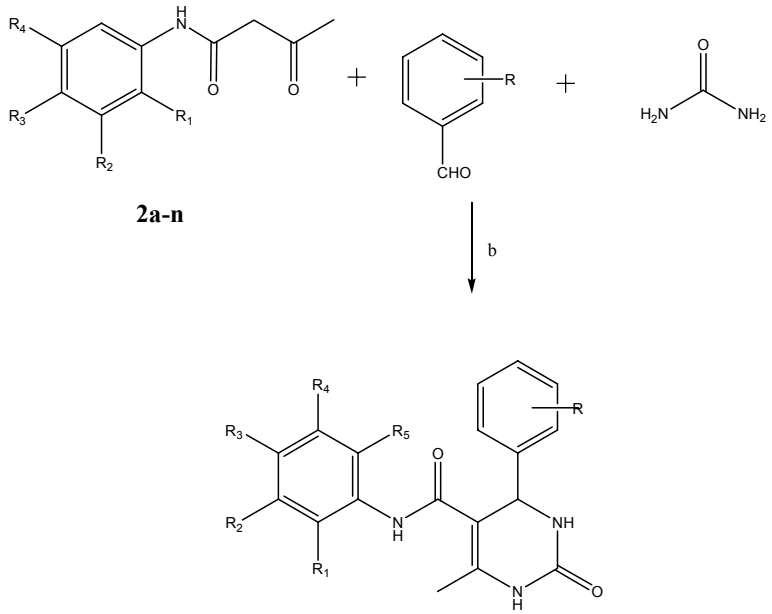


To find out the structural requirements, the results obtained with earlier modification were studied for 3D QSAR. The molecules were synthesized as per Scheme 1 and 2.



1a-n **2a-n**

Scheme 1. **Reagents and conditions: a) NaOH/KOH, toluene, 110º C, 10-15 hours.**



2a-n **3a-n**
4a-p

Scheme 2. Reagents and conditions: b) HCl, methanol, reflux, 5-10 hours.

Table 1. Physical data with anti tubercular activity. (Training set)

Compound	R	R_1	R_2	R_3	R_4	% Inhibition
3a	4-OCH_3	CH_3	H	H	CH_3	2
3b	3-OPh	CH_3	H	H	CH_3	27
3c	3-OPh	CH_3	CH_3	H	H	65
3d	2-NO_2	Cl	H	H	H	11
3e	4-NO_2	CH_3	H	H	CH_3	4
3f	4-Cl	H	H	H	H	6
3g	4-OH	F	H	H	H	18
3h	4-NO_2	Cl	H	H	Cl	18
3i	4-OH	CH_3	H	CH_3	H	12
3j	4-OH	H	NO_2	H	H	2
3k	3-Cl	H	Cl	F	H	48
3l	4-NO_2	F	H	H	H	4
3m	4-NO_2	H	CH_3	CH_3	H	13
3n	4-NO_2	CH_3	H	CH_3	H	12
3o	3-NO_2	Cl	H	H	H	26
3p	3-NO_2	H	Cl	F	H	29
3q	3-NO_2	F	H	H	H	24
3r	3-Cl	H	H	F	H	38
3s	4-NO_2	H	H	OCH_3	H	21
3t	3-NO_2	H	H	Cl	H	29
3u	3-NO_2	H	H	CH_3	H	28
3v	3-NO_2	H	H	F	H	30

Table 2. Physical data with ant tubercular activity (Test set)

Compound	R	R_1	R_2	R_3	R_4	% Inhibition
4a	3-NO_2	CH_3	H	H	H	6
4b	4-Cl	Cl	H	H	H	26
4c	4-NO_2	H	H	Cl	H	9
4d	3-OPh	H	CH_3	CH_3	H	32
4e	4-NO_2	H	H	H	H	25
4f	3-NO_2	H	CH_3	CH_3	H	63
4g	4-NO_2	H	Cl	F	H	22

6.2 QSAR study

6.2.1 Computational Details: The 3D-QSAR techniques of CoMFA and CoMSIA were carried out with *Sybyl 7.1* (Tripos Inc., USA) running on a Pentium IV computer under the Linux Red Hat Enterprise 2.3.1 OS

***6.2.2 Ligand preparation*:** A novel set of N-phenyl-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydro-pyrimidine-5-carboxamide analogs with substituuions on the 4-phenyl and N-phenyl rings were synthesized and screened for anti-tubercular activity (Table 1) was used for the 3D-QSAR study. The dataset was divided into a training set (23 molecules) and a test set (7 molecules) on the basis of chemical and biological diversity using the Tanimoto similarity coefficient.

For the QSAR study, the activity values were transformed as follows

Log activity = -log *c* + *logit* (where *c* is molar concentration = concentration (μg/mL) * 0.001 / (molecular weight); *logit* = log [% inhibition / (100 - % inhibition)]

The molecules were built using the builder module in *Sybyl* 7.1. The crystal structure of methyl-4-(3-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate was used as a template (Figure 1) to built the molecules in the dataset. The template structure of N-phenyl-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydro-pyrimidine-5-carboxamide had the pyrimidine ring in the boat conformation with the 4-phenyl ring in the axial orientation with C_4 atom of the pyrimidine having *S*-configuration. The ligand geometries were optimized by energy minimization using the Powel gradient method with the MMFF94 charges and forcefield, till a gradient of 0.005 kcal/mol/Å was reached while maintaining the template structure rigid.

***6.2.3 Molecular Alignment*:** The molecules of the dataset were aligned by two techniques. First by the atom-fit technique, using atoms common with the crystal structure of methyl-4-(3-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate; this is depicted in Figure 2a. In the second approach, the molecules were aligned by the field-fit technique where the steric and electrostatic fields of the most active molecule in the series were extracted and used for the alignment of the fields of the other molecules (Figure 2b).

***6.2.4 CoMFA and CoMSIA studies*:** CoMFA (Comparative Molecular Field Analysis) and CoMSIA (Comparative Molecular Similarity Indices Analysis)studies were carried out with the default settings for the 3D cubic lattice, the grid spacing, the probe atom, and the energy cutoff.

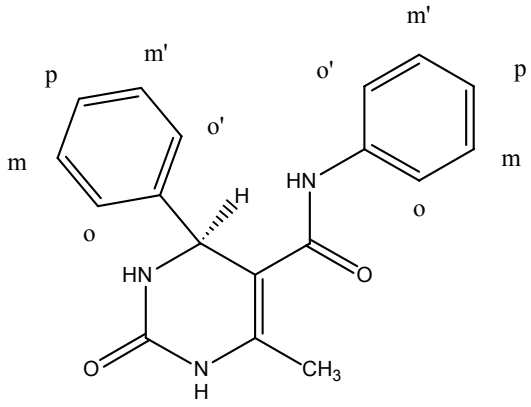
For CoMSIA, five physicochemical properties (steric, electrostatic, hydrophobic, and hydrogen-bond donor and acceptor) were explored, and the attenuation factor was set to the default value of 0.3. The CoMFA and CoMSIA descriptors were used as independent variables and the log activities as the dependent variable in a partial least squares (PLS) regression analysis to derive the 3D-QSAR models. The models were internally evaluated by leave-one-out (LOO) cross-validation. The optimal number of components was determined by the SAMPLS method which was subsequently used to derive the final QSAR models. In addition to the q^2, the conventional correlation coefficient r^2, and standard errors (SE) were also computed. The robustness of the models was gauged by cross validation using leave-group-out (LGO) of 10 groups and bootstrapping carried out with 100 runs. The CoMFA and CoMSIA models were also validated for their predictivity on an external dataset of 7 molecules.

All the molecules have N-phenyl-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydro-pyrimidine-5-carboxamideas the common substructure. The substitutions are at the *ortho*, *meta* and *para* positions of the 4-phenyl and the 5-N-phenyl rings.

The CoMFA and CoMSIA studies were conducted on a training set of 23 molecules which as mentioned earlier were aligned by the atom-fit and field-fit techniques. The molecules predicted by the initial CoMFA models with residuals greater than 0.80 were reintroduced into the dataset with alternate conformations, and the QSAR models regenerated. The correlation coefficients (r^2) of the 3D-QSAR CoMFA and CoMSIA models for the atom-fit technique are excellent with acceptable cross-validated coefficients (q^2) and suitably reliable predicted r^2.

6.2.5 Graphical Analysis

The CoMFA and CoMSIA contour maps were generated using scalar products of coefficients and standard deviation (STDEV*COEFF) set at 80% and 20% for favored and disfavored levels, respectively. The CoMFA and CoMSIA contours are depicted in Figure 3 and 4 respectively. CoMFA exhibits equal steric and electrostatic contribution to the activity while electrostatic and hydrophobicity contributions are seen to be dominated in CoMSIA.



The 3D-QSAR contours are explained with the help of Figure 4. The CoMFA steric fields favor (green contours, Figure 3a) the substitution of bulky groups at the *meta* position of the both 5-N-phenyl and the 4-phenyl moieties, while disfavored steric fields (yellow contours) are seen at the *para* position of the 4-phenyl group, which is also supported by the CoMSIA steric contours (Figure 4a). In addition, disfavored steric CoMSIA contours are also seen at the *meta'*-position of the 5-N-phenyl residue.

The CoMFA electrostatic contours depict that electropositive groups (blue contour, Figure 3b) are favored at *meta* position of the 5-N-phenyl group and the *ortho' meta*, *para* positions of the 4-phenyl group. However, electronegative groups (red contour) at the *meta'*-position of the 4-phenyl moiety are likely to increase the activity. The CoMSIA electrostatic contours (Figure 4b) also favor electropositive groups at the *para* and *ortho'* positions of the 4-phenyl and in addition, electronegative groups at the *para* position of 5-N-phenyl group. The hydrophobic contours of CoMSIA indicate desired and undesired hydrophobic regions around the two phenyl rings. The hydrophobic groups (white contours, Figure 4c) would cause

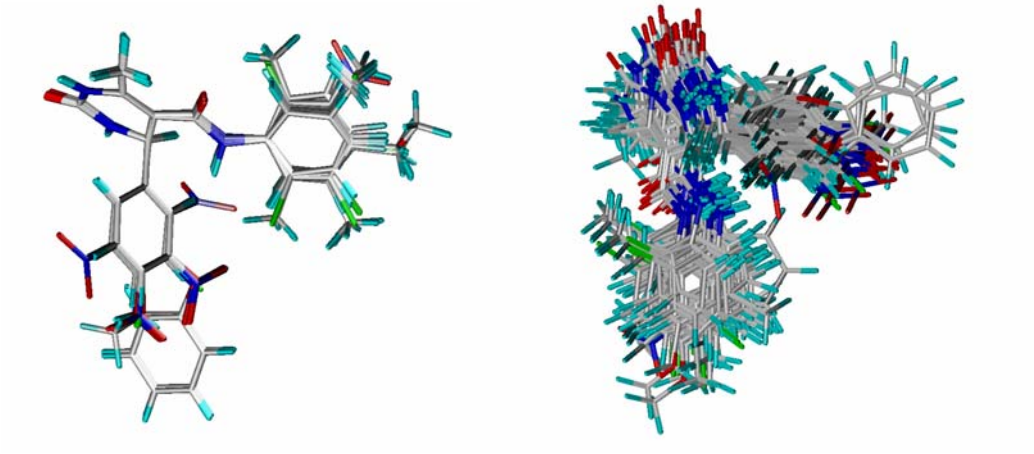


Figure 2a and 2b

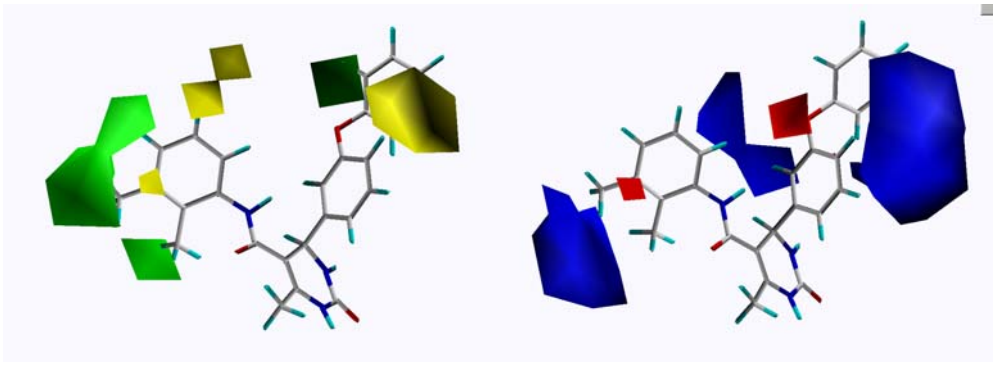


Figure 3a and 3b

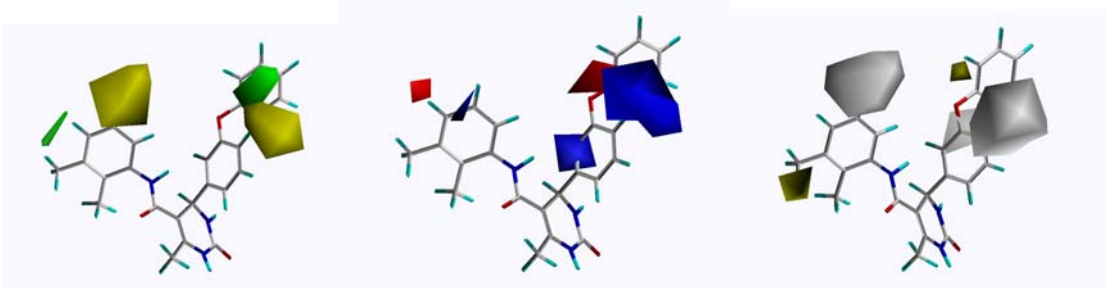


Figure 4a, 4b and 4c

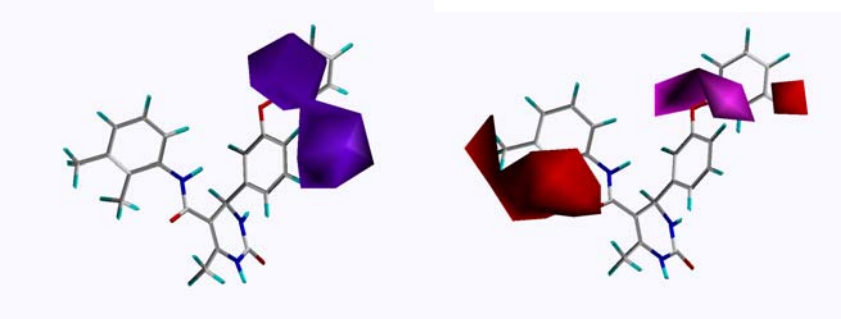
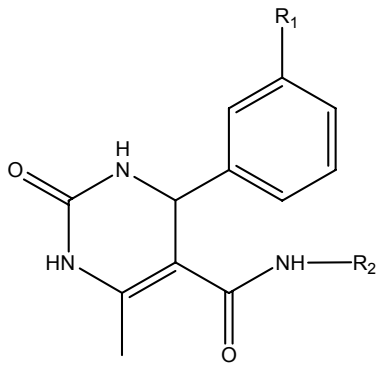


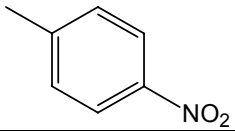
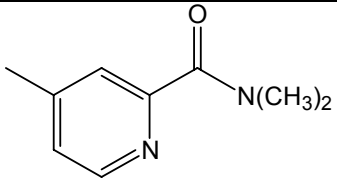
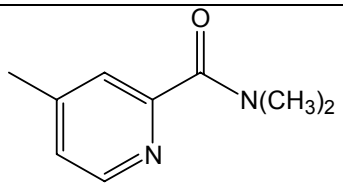
Figure 4d and 4e

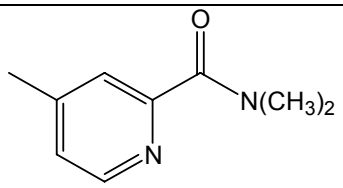
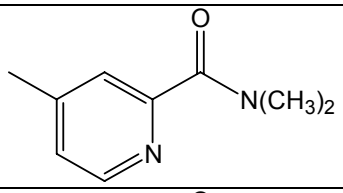
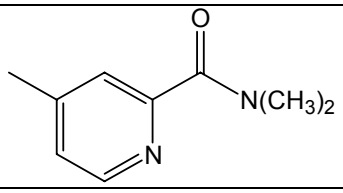
the activity to decrease when placed at on the *meta'* position of 5-N-phenyl ring or the *meta'*, *para* positions of the 4-phenyl; small hydrophobic groups (yellow fields) are accepted at the *meta* position of the 5-N-phenyl ring.

The H-bond donor fields are absent in the CoMSIA model. The disfavored fields of the H-bond acceptor are seen as red contours in Figure 4d, are found in the vicinity of the 5-carboxamide, the *ortho*, and *meta* position of the 5-N-phenyl ring, while the favored magenta contours are found to encapsulate the *para* and *meta'* positions of the 4-phenyl ring.

Table 3. New molecules with improved predicted activity



Sr. No.	**Molecule**	**R_1**	**R_2**	**Predicted Activity (CoMFA)***	**Predicted Activity (CoMSIA)***
1	N001	H		5.36	4.65
2	N002	–OCONHCH$_3$		5.57	4.63
3	N003	–COCH$_3$		5.36	4.55

4	N004	–CN		5.61	4.47
5	N005	$–NHSO_2CH_3$		5.52	4.35
6	N006	$–CF_3$		5.61	4.37

Summary

The work presented in the Thesis entitled "Study of some bioactive synthetic heterocycles" can be summarized as below.

Chapter 1 covers the synthesis of novel dihydropyrimidine derivatives via three component Biginelli reaction between acetoacetanilides, aromatic aldehydes and substituted phenyl urea. Synthesized molecules have phenyl carbamoyl moiety at 5^{th} position and phenyl ring on Nitrogen atom of DHPM skeleton. Acetoacetanilides were prepared from substituted aniline and ethylacetoacetate using NaOH/KOH as catalyst and toluene as solvent. Substituted phenyl ureas were prepared by reacting hydrochloride salt of amines and urea in water. Components of the reaction, thus prepared, were reacted in methanol using catalytic con. HCl. The spectral data is presented to support the structure of synthesized molecules. Twenty dihydropyrimidine derivatives are synthesized and characterized.

In chapter 2, bicyclic systems are synthesized from Biginelli dihydropyrimidine derivatives. DHPM skeleton is very important scaffold to synthesize variety of bicyclic systems. Acetoacetanilides, synthesized as mentioned in chapter 1, were reacted with thiourea and aldehydes. The DHPMs, thus synthesized, were reacted with dibromo alkanes to obtain fused bicyclic systems. The thiazolo-pyrimidine and pyrimido-thiazine systems thus synthesized were studied by NMR, Mass and IR spectroscopy. Total eighteen derivatives are synthesized with phenyl carbamoyl moiety at side chain.

Chapter 3 includes application of microwave in the synthesis of dihydropyrimidone molecules. Acetoacetanilides, butyraldehyde and urea were reacted to yield derivatives with propyl chain at 4^{th} position of DHPM skeleton to find out effects of replacement of phenyl ring with alkyl chain in classical DHPM skeleton with –CONH-Ph side chain. Very low yield was obtained by conventional method (5-10%). The reaction was carried out under microwave irradiation and that lead to increase in the yield of reaction product (30-35%). Benzimidazole-2-thiol was reacted with dihalo alkanes in DMF under microwave and yield bicyclic systems in 65-70%. Spectral data for synthesized

compounds are in support of their structures. Fifteen dihydropyrimidine and six fused bicyclic system from benimidazole-2-thiols are synthesized and characterized.

In chapter 4, synthesis of different 1,4-DHP derivatives, one of most important biologically active scaffold, is reported. A large number of drugs are marketed containing this basic skeleton. These skeleton derivatives are mostly known as calcium channel blockers since long time. Earlier findings from our lab reported these derivatives to possess mdr reversal, anti tubercular and other activity. In continuation of earlier work done, symmetrical and unsymmetrical dihydropyridines are synthesized with naphthyl ring in side chain. Twenty-six DHPs are synthesized and characterized.

Chapter 5 covers a brief literature survey on fused system containing indole system, their synthesis and biological profile. This chapter deals with the synthesis of triazolo-triazine-indole systems starting from isatin and thiosemicarbazide. The subsequent reaction with hydrazine hydrate and aldehydes; and cyclization using bromine/acetic acid yielded title compounds. Synthesis of eighteen compounds and their spectral data are reported.

In the last chapter, efforts made in our lab to modify DHPM skeleton and anti tubercular activity data obtained for them are studied for QSAR to find out structural requirement and to throw light on further modifications to this skeleton. CoMFA and CoMSIA methods are applied and new molecules are designed and predicted to exhibit better activity.

Total 103 compounds are synthesized and characterized in entire work. Synthesized compounds are under anti tubercular and anti viral screening and their results are awaited.

Papers accepted/communicated

1. Microwave-assisted and Zn[L-proline]$_2$ Catalyzed Tandem Cyclization under Solvent Free Condition: Rapid Synthesis of chromeno[4,3-*c*]pyrazol-4-ones
   Atul Manvar, Pravin Bochiya, **Vijay Virsodia**, Rupesh Khunt and Anamik Shah (***Journal of Molecular Catalysis A- Chemical: In Press***)

2. Synthesis, Anti-tubercular activity and 3D-QSAR study of Coumrine-4-acetic acid benzylidenhydrazides
   Atul Manvar**,** Alpesh Malde, Arun Mishra, **Vijay Virsodia**, Hrishikesh Acharya, Evans Coutinho and Anamik Shah (submitted to ***European Journal of Medicinal Chemistry)***

3. Synthesis, screening for antitubercular activity and 3D-QSAR studies of substituted N-phenyl-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydro-pyrimidine-5-carboxamide
   Vijay Virsodia, Raghuvir R. S. Pissurlenkar, Dinesh Manvar, Chintan Dholakia, Priti Adlakha, Anamik Shah and Evans C. Coutinho (submitted to ***European Journal of Medicinal Chemistry)***

4. Synthesis, Anticancer Screening against SW620 colon cancer cell line and 3D-QSAR Studies of *trans*-3-methylene-1-(2,6-dichlorophenyl)-1,3-dihydro-indol-2-one derivatives
   Vijay Virsodia, Mushtaque S. Shaikh, Kuldip Upadhyay, Rajesh Loriya, Denish Karia, Manu Jaggi, Anu T Singh, Anamik Shah, Rama Mukherjee and Evans C. Coutinho (submitted to ***Bioorganic & Medicinal Chemistry Letters)***

5. PEG-400 Promoted and Microwave assisted one pot three-component coupling reactions: Expedient and Rapid synthesis of Hantzsch 1,4-dihydropyridines
   Atul Manvar**,** Dinesh Manvar, **Vijay Virsodia**, Kuldip Upadhyay and Anamik Shah (submitted to ***Bioorganic & Medicinal Chemistry Letters)***

Conference/Seminar participated

- UGC-SAP sponsored national seminar on "New Frontiers in Pharmaceutical Process Chemistry and Related Topics" at Department of Chemistry, Saurashtra University, Rajkot (March 5, 2007)
- "International Conference on Advances in Drug Discovery Research" held by ISCB at Aurangabad, India (24-26 Feb, 2007) *
- National seminar on "Recent Advances in Chemical Science and Approach Towards Green Chemistry" held at Saurashtra University, Rajkot, India (October 17, 2006).
- National seminar on "e-Resources in Chemical Synthesis and Natural Products." Held at Department of Chemistry, Saurashtra university, Rajkot, India (March 2-3, 2006).
- International Conference on "Advance in Organic Chemistry and Chemical Biology" jointly organized by American Chemical Society and Indian Institute of Chemical Technology IICT, Hyderabad, India. (January 16-17, 2006) *
- International conference on "Building Bridges, forging bonds" for 21st Century Organic Chemistry and Chemical Biology, jointly organized by American Chemical Society and National Chemical Laboratory(NCL) at NCL Pune, India(January 5-7, 2006) *
- National workshop on Green Chemistry at Nirma University, India(November-2005)
- Workshop on Nanotechnology: Opportunities and Challenges at Saurashtra University, India(October 17, 2005)

(* paper presented)