SYNTHESIS OF SUBSTITUTED PYRIMIDINE DERIVATIVES AND RELATED HETEROCYCLES

BY

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DEPARTMENT OF CHEMISTRY
SCHOOL OF PHYSICAL SCIENCES

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SUBMITTED IN FULFILLMENT OF THE REQUIREMENT FOR THE
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IN CHEMISTRY

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NORTH EASTERN HILL UNIVERSITY
Permanent Campus, Shillong – 793 022 (Meghalaya)

DECLARATION

I, Mr **Tovishe Phucho,** hereby declare that the subject matter of the thesis entitled ***"Synthesis of substituted pyrimidine derivatives and related heterocycles"*** is the record of work done by me and the content of this thesis did not form the basis of the award of any previous degree to me or to anybody else to the best of my knowledge and that the thesis has not been submitted by me for any research degree in any other University/Institution

This is being submitted to the North-Eastern Hill University for the degree of Doctor of Philosophy in Chemistry.

Place: Shillong

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CERTIFICATE

This is to certify that the thesis entitled "***Synthesis of substituted pyrimidine derivatives and related heterocycles***" Submitted by Mr **Tovishe Phucho** for the degree of Doctor of Philosophy of North-Eastern Hill University, Shillong embodies the record of original investigation carried out by him under my supervision. He has been duly registered and the thesis presented is worthy of being considered for the Ph. D degree in Chemistry.

The work described in this thesis is original and has not been submitted for any other degree or diploma in this or any other University.

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Dedicated

to

my

Beloved

Father

(Late) ***Ivulho Phucho***

and

Mother

(Late) ***Imelho Phucho***

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Above all, I thank the Almighty God who abides with me throughout my life.

Date: 25 July

Place: Shillong

Tovishe Phucho

Preface

The contents of this thesis entitled "**Synthesis of substituted pyrimidine derivatives and related heterocycles**" have been divided into five chapters based on the results of experimental works performed during the complete course of the research period. The introductory chapter (Chapter I) of the thesis presents an overview of different aspects of Heterocyclic chemistry and their importance in various fields. Also, the application of microwave irradiation in the synthesis of heterocyclic compounds has been highlighted.

Chapter (II) describes the synthesis of pyrimidine derivatives starting from enolisable ketones (substituted acetophenones or cyclohexanones) and aromatic aldehydes through the use of readily available *p*-TsOH or sodium tertiary butoxide as reaction mediator. The results of the conventional process and the microwave irradiation process for the synthesis of pyrimidine derivatives are also included.

Chapter (III) demonstrates the comparative studies between conventional and microwave synthesis of 1,2,4-triazines starting from amides, 1,2-dicarbonyl compounds and hydrazine hydrate in presence of base. The regioisomeric synthesis of 1,2,4-triazines from unsymmetrical diketones due to the difference in reactivity of the two carbonyl groups is highlighted.

Chapter (IV) illustrates green, solvent free synthesis of 3-substituted-quinazolin-4(3*H*)-one using silica supported potassium carbonate. This chapter describes a convenient route for the synthesis of 3-substituted-quinazolin-4(3*H*)-one starting from methyl anthranilate, orthoester and substituted amines (both aromatic and aliphatic amines).

Chapter (V) focuses on the green synthesis of bis-benzoxazines and bis-benzothiazines. A variety of bis-oxazines and bis-thiazines having aliphatic linkages between two monomers have been successfully synthesized keeping in view the importance of green chemistry.

Each chapter constitutes sub-sections, describing introduction, reviews, results and discussions of the present work, experimental section and spectral data along with the reference spectra of the respective titled compounds. The references of the published work of the present investigation are cited at the end of the respective chapter.

My curriculum vitae followed by the list of publications are attached at the end.

Contents

Chapter I

Introduction to Heterocycles and application of microwave in organic synthesis

1.1. Introduction to Heterocyclic Chemistry

Heterocyclic compounds are cyclic compounds with at least two different atoms in the ring as ring atoms or member of the ring. If at least one ring atom is a C-atom, then the molecule is organic heterocyclic compound otherwise it is an inorganic heterocycle. In organic heterocycles, all the atoms which are not carbon are called heteroatoms. The most commonly found heteroatoms are **nitrogen**, **oxygen** and **sulfur**; however all elements except alkali metals can act as a ring atom.

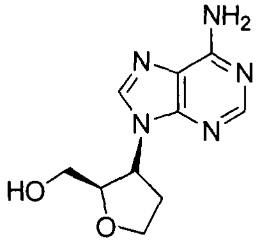
Besides type, the ring size is dependent on the number of atoms per ring. The smallest possible is a three membered ring, whereas the most abundant and stable are the five and six membered heterocycles. There is no upper limit as far as the size of the ring is concerned; there exist seven-, eight-, nine- and larger membered heterocycles. Because of the flexibility in their structures, they can behave as bases as well as acids and also take part in a wide range of chemical reactions.

1.2. Heterocycles and their Importance

Heterocyclic chemistry comprises of at least half of all organic chemistry worldwide, it is one of the broadest and most complex branches of organic chemistry. The widespread use of heterocyclic compound is due to the fact that their structures can be subtly manipulated to achieve a required modification in function.

Heterocyclic units such as pyrimidine, quinazoline, triazine, benzoxazine and their analogues are of special interest due to their important biological activities. An important approach for the synthesis of these types of compounds involves application of annelation methods, which is the construction of cyclic compounds from open chain precursors.

Heterocyclic compounds have a wide range of applications: they are predominant among the types of compounds used as pharmaceuticals,[1] agrochemicals and veterinary products. They are used as optical brightening agents, as anti-oxidants, as corrosion inhibitors and as additives with variety of other functions. Many dyestuff and pigments have heterocyclic structures.[2] For example derivatives of dideoxynucleoside (**1** and **2**) analogs were found to be potent anti-AIDS drugs.[3] Nitroimidazoles such as metronidazoles (**3**) and dimetridazoles (**4**) are widely used in veterinary medicine.[4]



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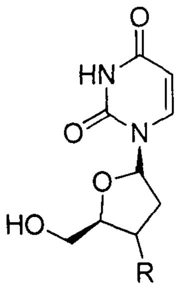

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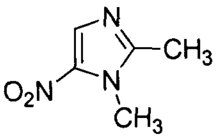

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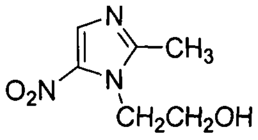

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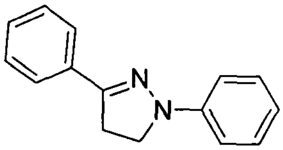
Nitrogen containing heterocycles such as diaryl-pyrazoline[5] (**5**) and 3,7-ditriazolocoumarin (**6**) derived from azidocoumarin are reported as optical brightening agents.[6]



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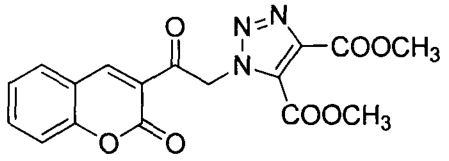

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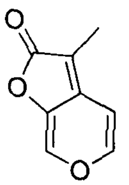
Karrikins (**7**), an oxygen containing hetrocyclic compound, is a novel class of naturally occurring plant growth regulator that promotes seed germination among a diverse range of species. This key germination stimulant, from smoke, was first isolated and identified by Flematti *et al*,[7] as 3-methyl-2*H*-furo[2,3-*c*]pyran-2-one (**8**), now termed as karrikinolide.[8] This naturally occuring germination stimulant and its derivative displays activity in a variety of species at concentrations as low as one parts-per-billion.[9] It has been revealed that at least five other analogues are present in smoke leading to the collective name 'karrikins'.[10]



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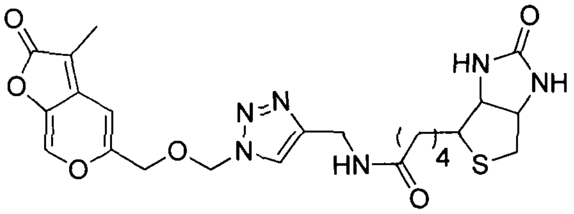

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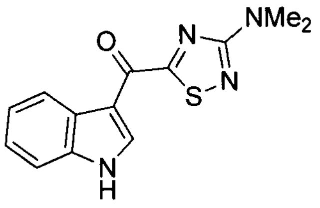
Multi-hetero atom heterocycles are comparatively rare in nature, dendrodoine (**9**), a cytotoxic substance from a marine tunicate, is an example. However in medicinal chemistry they are of considerable significance. Alprazolam (**10**) is a major drug for the treatment of anxiety, acetazolamide (**11**) is an inhibitor of the enzyme carbonic anhydrase and is used principally for the treatment of glaucoma, and fluconazole (**12**) is an anti-fungal agent. Dendrodoine, alprazolam, acetazolamide and fluconazole analogues of the pyrimidine nucleosides have been extensively studied: 5-Azacytidine (**13**) is anti-leukemic and ribavirin (**14**), an anti-viral agent, is used in the treatment of lung infections in infants.



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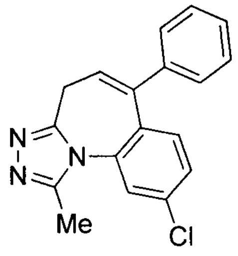

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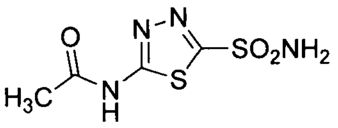

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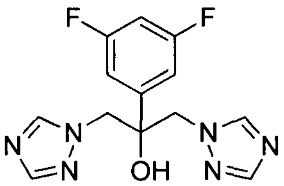

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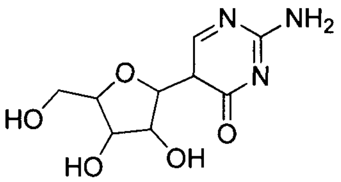

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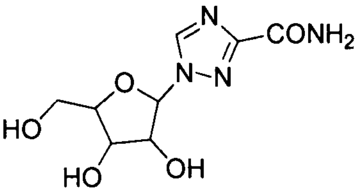

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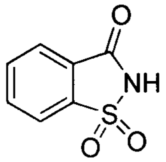
1,2-Benzisothiazolin-3(2*H*)-one-1,1-dioxide (**15**) is saccharin, the well known sweetening agent. Omeprazole (**16**), a gastric proton-pump inhibitor, is an anti-ulcerative and risperidone (**17**) is used in the treatment of schizophrenia.



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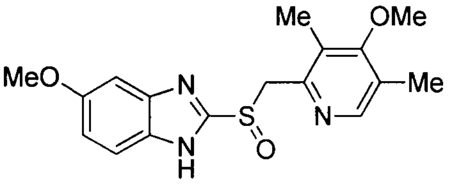

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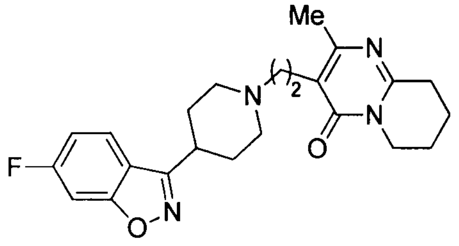

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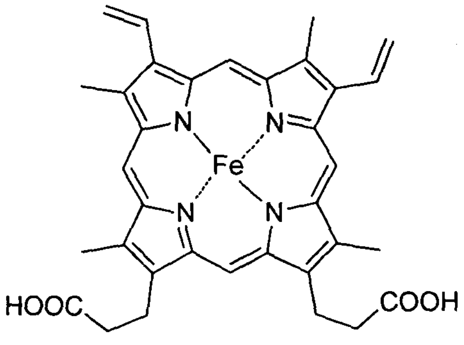
N-heterocycles form the basic skeleton of many biologically important classes of natural products such as anti-biotics, vitamins (vitamin B_{12} *i.e.*, cyanocobalamine), marine products, animal toxins and fungal metabolites. Porphyrin rings form the basic skeleton of life supporting system, for example, the heme (**18**) found in haemoglobin and myoglobin which is responsible for transport of oxygen and green coloring pigment chlorophyll (**19**) in plants contains a heterocyclic porphyrin system. Indigo blue (**20**), a dyestuff of plant origin, used for dying clothes is also a nitrogen containing heterocyclic compound.[11]



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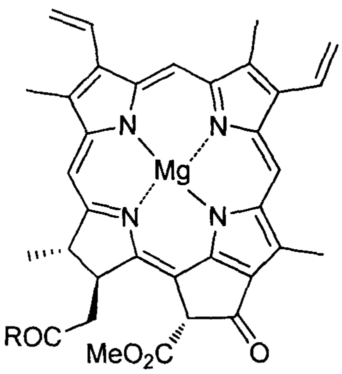

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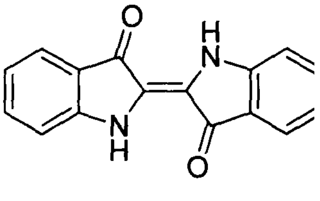

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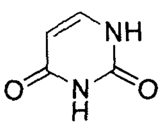
1.3. Pyrimidine based heterocyclic compounds

Pyrimidine derivatives are well known for their role in biological chemistry. Out of the five major bases in nucleic acids, three are pyrimidine derivatives which comprises of Cytosine (**21**) found in deoxyribonucleic acid (DNA) and ribonucleic acid (RNA), uracil (**22**) in RNA and thymine (**23**) in DNA. Because of their involvement as bases in DNA and RNA, they have become very important in the world of synthetic organic chemistry.



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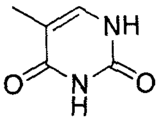

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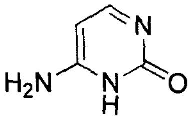

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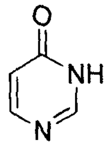

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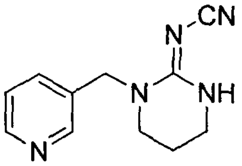
Physiochemical techniques have shown that 2- and 4-hydroxy pyrimidines are predominantly in the oxo forms. The former as **23** and the latter in ortho-quinonoid structure **24** in preference to its para-quinonoid isomer.[12] In dihydroxy derivatives, such as uracil, the dioxo form 2,4-(1*H*,3*H*)-pyrimidindione is the predominant form and in the trihydroxy pyrimidine, barbituric acid, the 2,4,6-(1*H*,3*H*,5*H*)-pyrimidinetrione form is predominant.[13]

Pyrimidine and its derivatives have been found to be of minimal toxicity to men, domesticated animals and fishes, and selectively display remarkable control on pests. A few examples of such molecules, their preparations and the uses of such compounds are described below:



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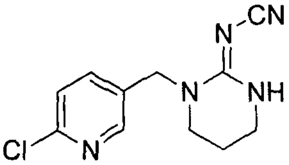

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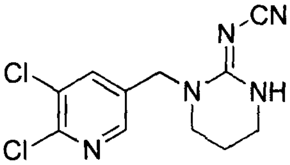

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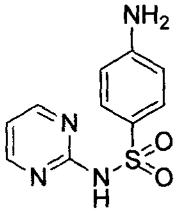
Several pyrimidine derivatives have been developed as chemotherapeutic agents and have been found to possess wide range of pharmaceutical applications. Pyrimidine derivatives of sulfa drugs, such as sulfadiazine, sulfamerazine and sulfadimidine are superior to many other sulfonamides and are used in some acute urinary tract (UT) infections, cerebrospinal meningitis and for patients allergic to pencillins, sulfonamide–trimethoprim combinations are used extensively for opportunistic infections in patients with AIDS.[14] Sulfadiazine **(28)** is a sulfonamide antibiotic which is used for treatment of different kinds of bacterial infections, like those of the brain, ears and urinary tract. sulfamerzine **(29)** and sulfadimidine **(30)** possess good water solubility and therefore carry minimum risk of kidney damage, which makes them safe even for patients with impaired renal functions. Sulfadoxine[15] **(31)**, a short and intermediate acting sulfonamide with a half-life of 7–9 days is used for malarial prophylaxis. Sulfisomidine **(32)** with a half-life of 7 hours is used as a combination sulfa therapy in veterinary medicine.[16] Flucytosine **(33)** is a synthetic fluorinated pyrimidine anti-fungal drug that was first synthesized as a cytosine analog for use as an anti-neoplastic compound.[17] Pyrimethamine **(34)** is an anti-parasitic medicine used to treat and prevent malaria. This medicine is also used to treat the infection of toxoplasmosis.[18] The chemotherapy agent fluorouracil **(35)** is a drug which has been in use against cancer for about 40 years and acts in several ways, but principally as a thymidylate synthase inhibitor. Interrupting the action of this enzyme blocks synthesis of the pyrimidine-thymidine, which is a nucleotide required for DNA replication.[19] Silver sulfadiazine has an anti-bacterial property which is used as cream on burns, including chemical burns and tropical burns. It prevents the growth of a wide array of bacteria as well as yeast on the damaged skin.[20]



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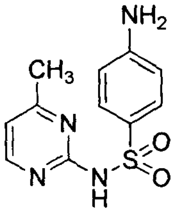

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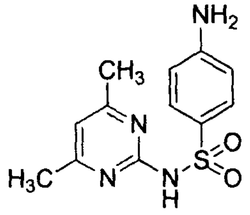

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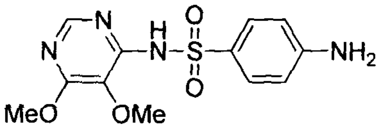

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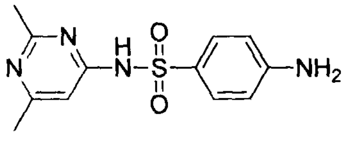

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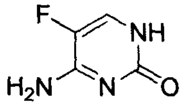

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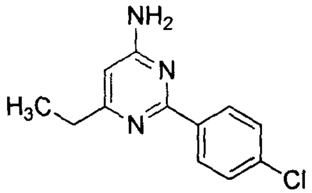

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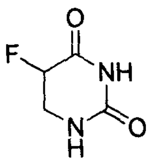

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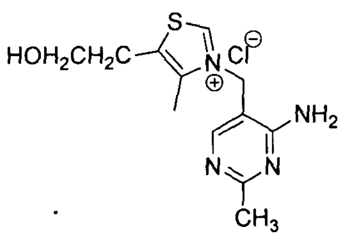
The pyrimidine ring is found in vitamins like thiamine (**36**), riboflavin (**37**) and folic acid (**38**).[21] Barbitonel (**39**), the first barbiturate hypnotic sedative and anti-convulsant is a pyrimidine derivative.[22]



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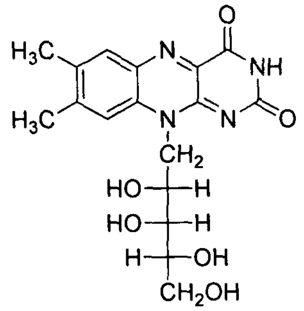

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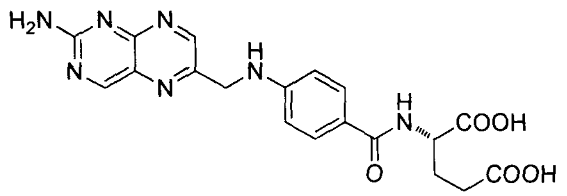

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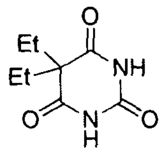

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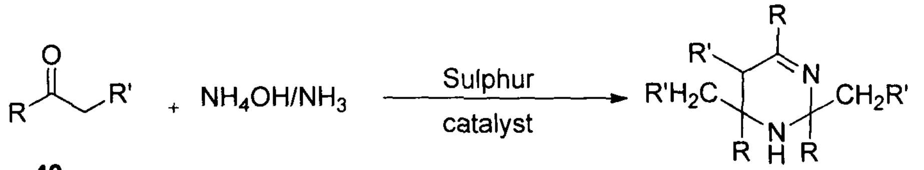
Bernardus and co-workers[23] have reported the synthesis of substituted pyrimidines (**42**) and their derivatives which were found to be useful as bactericides, biocides, anti-oxidants, oxygen-scavengers and as corrosion inhibitors

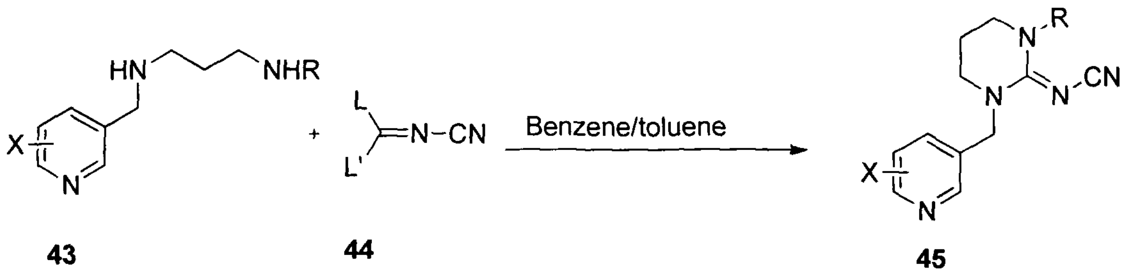


40 **41** **42**

R, R' = Alkry or aryl

Scheme-1

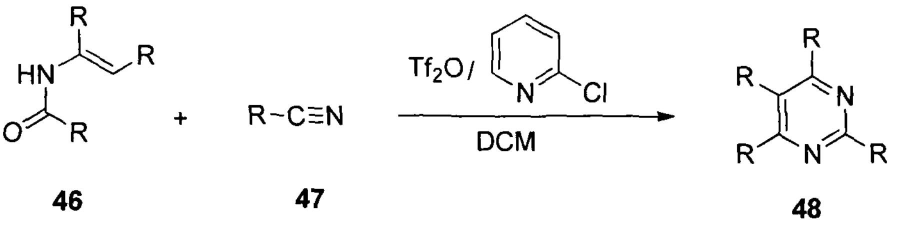
Laurenz Gsell[24] has reported the synthesis of substituted pyridyl methyl cyanoiminotetrahydropyrimidine (**45**) by the section of compounds having the structures **43** and **44** in appropriate solvents as shown in **Scheme-2**.



R= H or alkyl groups,
X= Halide
L=L' are leaving groups such as $-SCH_3$, $-OCH_3$, $-OC_6H_5$

Scheme-2

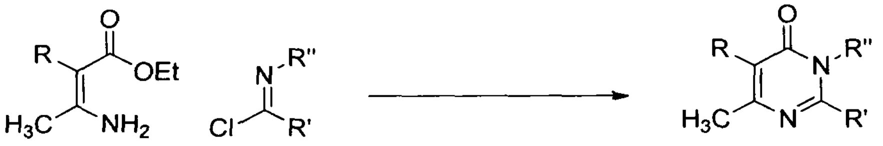
These compounds were found to be useful in controlling insects and pests of rice crops, while being well tolerated by plants and having low toxicity to warm blooded animals. *N*-vinyl and *N*-aryl amides can be converted into various pyrimidine and quinazoline derivatives which involves amide activation with 2-chloropyridine and trifluoromethanesulfonic anhydride (Tf_2O) followed by nitrile addition into a single-step conversion of the reactive intermediate and cycloisomerization[25] **(Scheme-3)**.



R = Alkyl, aryl or H

Scheme-3

Staskun and Stephen[26] have reported the synthesis of 3-alkyl-4-oxo-dihydro pyrimidine (**51**) by reacting 2-alkyl-β-aminocrotonic esters (**49**) with imidoyl chlorides (**50**).

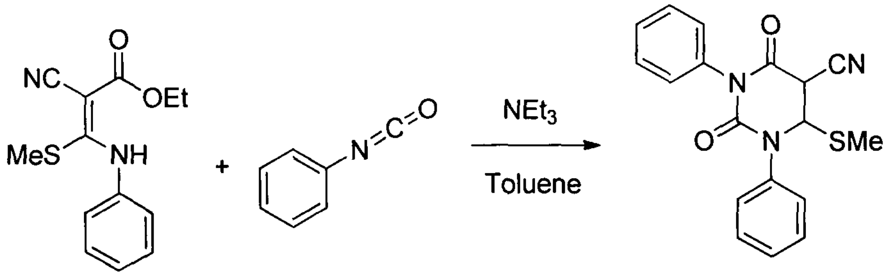


49 **50** **51**

R = Alkyl,
R' = Aryl
R'' = Aryl, Ethyl

Scheme-4

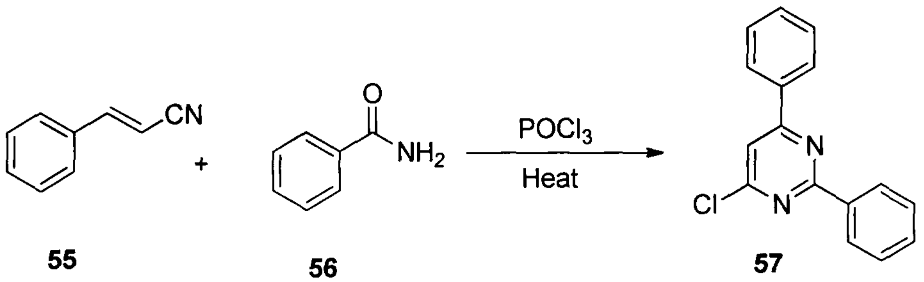
Phenyl isocyanate (**53**) reacts with the ethyl-3-phenyl-aminoacrylate (**52**) and triethylamine as a base to form 4-methyl-thio-2,6-dioxo-1,3,4,5-tetrahydropyrimidine-5-carbonitrile[27] (**54**) (**Scheme-5**).



52 **53** **54**

Scheme-5

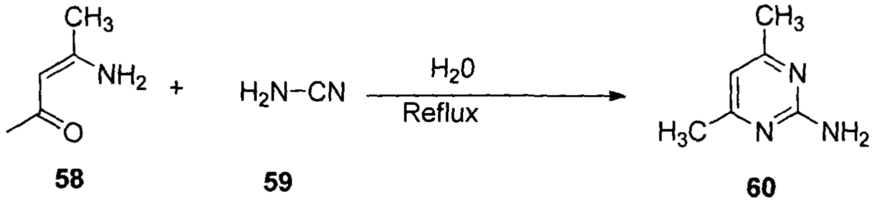
Cinnamonitrile (**55**) reacts with benzamide (**56**) in the presence of phosphorous oxychloride to give 6-chloro-2,4-diphenylpyrimidine (**57**) (**Scheme-6**).[28]



55 **56** **57**

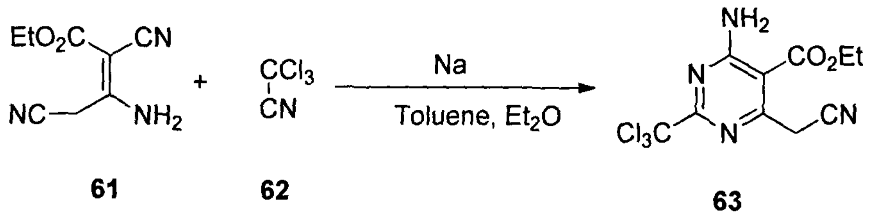
Scheme-6

Cyanamide (**59**) reacts with 4-aminopent-3-en-2-one (**58**) and substituted derivatives in aqueous solution to form the 2-aminopyrimidine (**60**)[29] in high yield (**Scheme-7**).



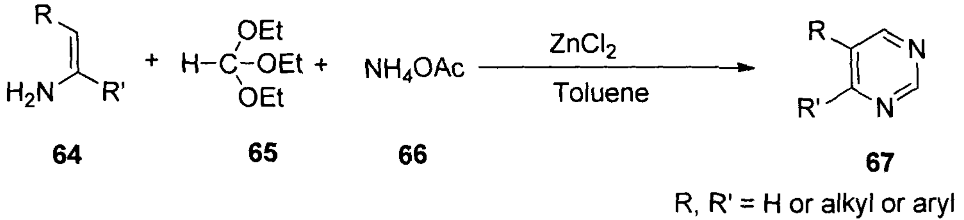
Scheme-7

Ethyl-3-amino-2,4-dicyanocrotonate (**61**) as its sodium salt reacts with 2,2,2-trichloroacetonitrile (**62**), while the amino nitrogen initiates the reaction by addition to the cyano group of the acetonitrile eventually forming **63**.[30]



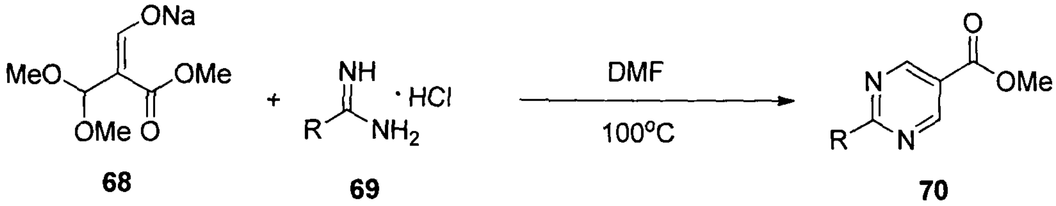
Scheme-8

Sasada and co-workers[31] have reported the synthesis of various 4,5-disubstituted pyrimidine derivatives (**67**) in a single step from functionalized enamines (**64**), triethyl orthoformate (**65**), and ammonium acetate (**66**) using $ZnCl_2$ as a catalyst (**Scheme-9**). This procedure can also be successfully applied to the efficient synthesis of mono- and disubstituted pyrimidine derivatives, using methyl ketone derivatives instead of enamines.



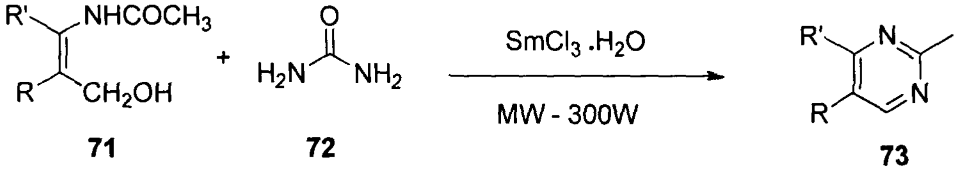
Scheme-9

The sodium salt of 3,3-dimethoxy-2-methoxycarbonylpropen-1-ol (**68**) has been found to react with a variety of amidinium salts (**69**) to afford the corresponding 2-substituted pyrimidine-5-carboxylic esters (**70**).[32]



Scheme-10

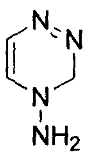
A novel and efficient synthesis of pyrimidine derivatives (**73**) from β-formyl enamide (**71**) involves samarium chloride catalysed cyclisation of β-formyl enamides using urea (**72**) as a source of ammonia under microwave irradiation[33] (**Scheme-11**).



Scheme-11

1.4. Triazine based heterocyclic compounds

Derivatives of triazine are very well known and available in large quantities as they are amongst the oldest known heterocycles. Three types of triazine are known namely 1,2,3-triazine, 1,2,4-triazine and 1,3,5-triazine. Derivatives of triazines are biochemically active compounds, for example 4-amino-1,2,4-triazines (**74**), 4-amino-6-tert-butyl-3-(methylmercapto)-1,2,4-triazinone (**75**) and derivatives of 1,2,3-triazines (**76**) are the most known and widely used herbicides.



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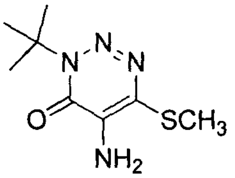

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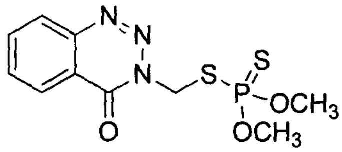
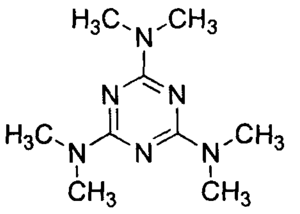


76

Owing to the high biochemical activities of these compounds, tests have been carried out with the aim of controlling numerous insects or fungal diseases by these substances or to test their toxicities to insects or animals such as ball worm,[34a] moths,[34b] leafhopper,[34c] mites,[34d] leafworms,[34e] caterpillers,[34f] etc.

Some 1,3,5-triazines also display important biological properties,[35] for example hexamethylmelamine (HMM) (**77**) and 2-amino- 4-morphlino-*s*-triazine (**78**) are used clinically due to their anti-tumor properties to treat lung, breast and ovarian cancer, respectively.[36] Hydroxymethylpentamethylmelamine (HMPMM, **79**) is also the hydroxylated metabolite which corresponds to the major active form of HMM. For the similar general structure **80**, anti-tumor activity in human cancer and murine leukemia cell lines were observed.[37] The 1,3,5-triazine (**81**) presents potential use as siderophore (microbial iron shelter) mediated drug[38] and the general structure **82** presents potent corticotrophin releasing factor receptor antagonist activity.[39] The compounds of type **83** show potent activity against leukotriene C4 (LTC4) antagonist, which possess a protective effect on HCl.ethanol-induced gastric lesions.[40] Several other 1,3,5-triazine substituted polyamines present a good in-vitro activity against the protozoan parasite *Trypanosoma brucei*, the causative organism of human african trypanosomasis.[41]



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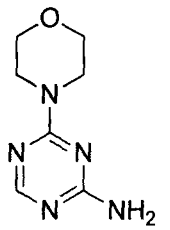

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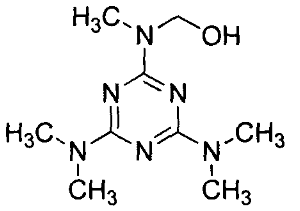

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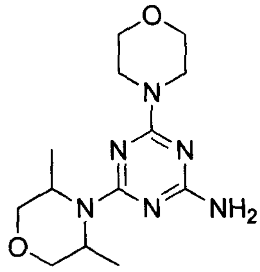

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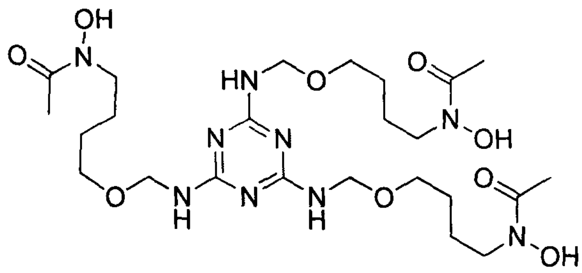

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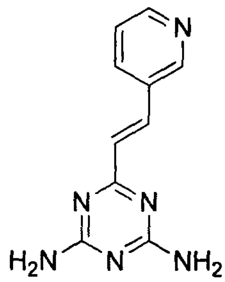

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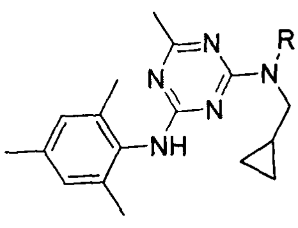
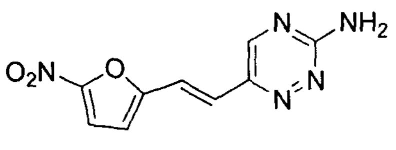


R= H or alkyl

83

Another group of biochemically active 1,2,4-triazines are 6-(5-nitrofuryl)-substituted 1,2,4-triazines, especially 3-amino-6-[(5-nitro-2-furyl)-ninyl]-[1,2,4]-triazines (**84**). These compounds have been tested for their pharmacological, anti-bacterial and tuberculostatic activity.[42] *N*-methyl derivatives of pyrimido[5,4*e*] [1,2,4]triazine-5,7-dione are the naturally occurring anti-biotics fervenulin (**85**), toxoflavin (**86**) and reumycin (**87**), the related anti-biotic being 2,6,8-trimethyl pyrimido[5,4*e*] [1,2,4]triazine-3,5,7-trione (**88**).[43] Lamotrigine (**89**) is used for the treatment of epilepsy.



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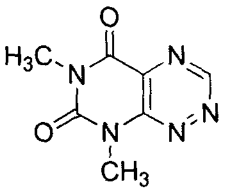

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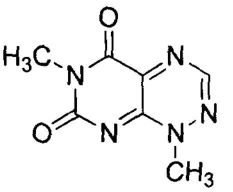

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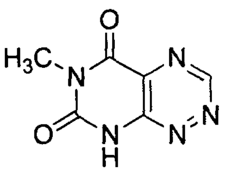

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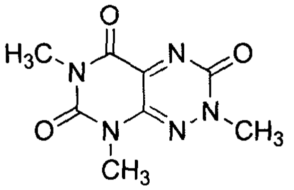

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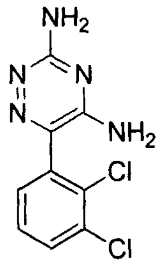
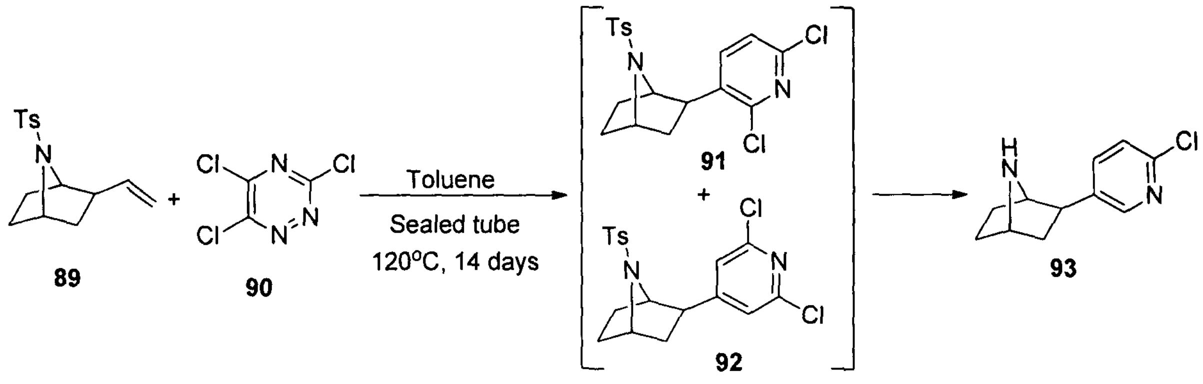


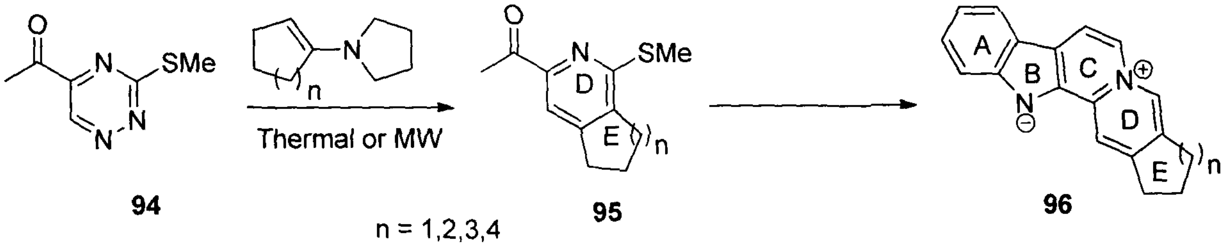
89

Triazines have been utilized in the total synthesis of natural products. Armstrong *et al*,[44] used 3,5,6-trichloro-1,2,4-triazine (**89**) to synthesize (±)-epibatidine (**93**) (**Scheme-12**). However, the approach was abandoned due to the poor selectivity in the aza-Diels–Alder reaction and the anticipated difficulty in the selective removal of the extra chlorine from **92**. The authors did note the utility of this approach as a convenient means of varying the heteroaromatic portion of epibatidine in analogue synthesis.



Scheme-12

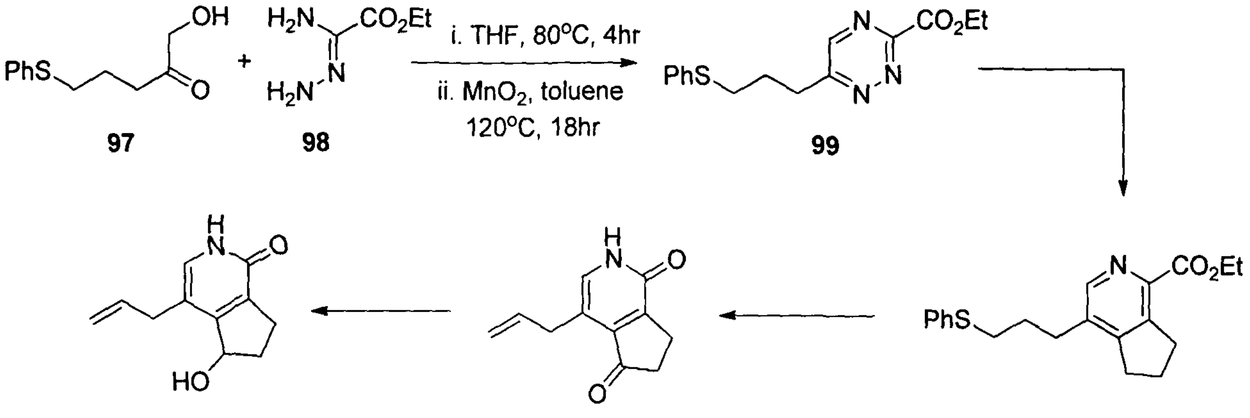
Construction of the D/E-ring system **95** of semipervirine (**96**) from the aza-Diels–Alder reaction of a 1,2,4-triazine (**94**) was reported by Lipinska.[45] The divergency afforded by the methodology also allows the easy synthesis of analogues containing different E-rings **96** (**Scheme-13**).



94 **95** **96**

Scheme-13

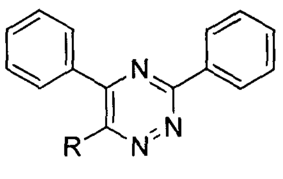
Taylor and co-workers have exploited the aza-Diels–Alder reaction of 1,2,4-triazine (**99**) in the synthesis of the Louisianin family of alkaloids,[46] the 3,6-disubstituted-1,2,4-triazine (**99**) is prepared regioselectively using tandem oxidation process (TOP) methodology[47] (**Scheme 14**), then converted into the key pyridine (**100**) using the improved methodology developed for the aza-Diels–Alder reaction with enamines.[48] This common pyridine intermediate **100** is then converted into the Louisianins: firstly, into Louisianin-A (**101**) in six steps, from which stereocontrolled reduction furnishes essentially enantiopure Louisianin-B (**102**).



97 **98** **99** **102** **101** **100**

Scheme-14

Many triazines form complexes with metal ions and can be used for their determination. Thus, 3-and /or 5-(2-pyridyl)-substituted 1,2,4-triazines (**103**) can be used for determination of iron(II), cobalt(II), nickel(II) and copper(II) ions. Thallium and palladium ions can be analysed by 5,6-diphenyl-1,2,4-triazine-3-thione (**104**), while osmium can be determined by 3-thioxo-1,2,4 triazin-5-one (**105**) and 3,5-dithioxo-1,2,4-triazine-6-carboxylates (**106**). Pyrimido [4',5':5,6][1,2,4]triazino[4,3-*e*] indazole (**107**) and derivatives of benzotriazine-7-carboxylic acid-1-oxide (**108**) are used as dyes.[49]



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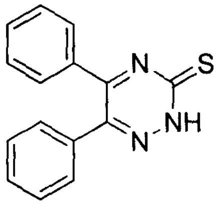

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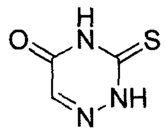

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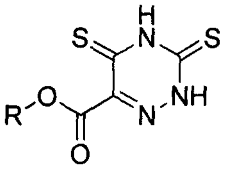

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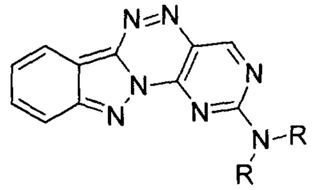

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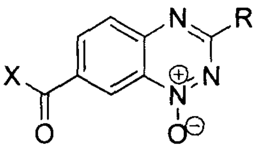
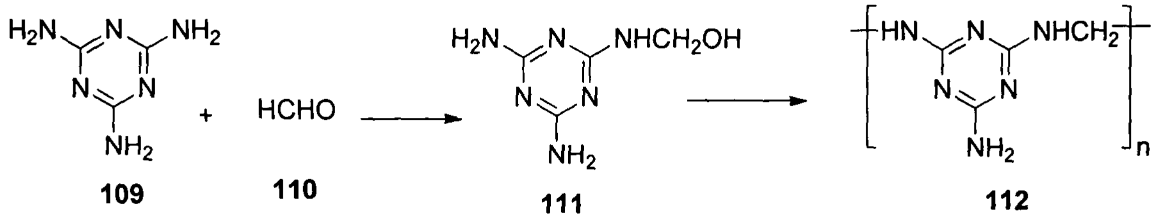


108

R = alkyl, aryl

X= halides

Melamine (**109**), on condensation with formaldehyde (**110**) produces the melamine resins (**112**) which are well known in kitchen utensils and is an important industrial intermediate.

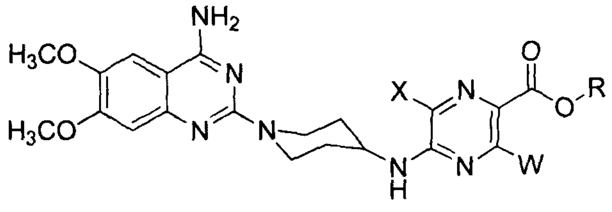


Scheme-15

1.5. Quinazoline based heterocyclic compounds

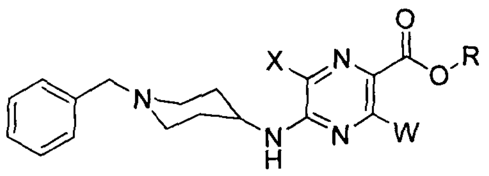
Quinazolines are important class of heterocyclic compounds which are also known as fused pyrimidines. A large number of natural and unnatural quinazoline skeletons with a variety of substituents have been prepared *via* several synthetic strategies because of their pharmacological properties,[50a] *e.g.*, protein tyrosine kinase inhibitory, cholecystokinin inhibitory, anti-microbial, anti-convulsant, sedative, hypotensive, anti-depressant, anti-inflammatory and anti-allergy properties. Some of these compounds also have interesting biological properties[50b] such as anti-malarial activity, biofungicide and diuretic properties.

Pei-Pei Kung and co-workers[51] have reported the antibacterial activity of a series of quinazolinone containing compounds **113** where upon replacement of the quinazoline fragment with either tertiary butyl anhydride, hydrogen or benzyl functionalities like **114** resulted in similar loss of its activity. Therefore, the presence of quinazolinone moiety in the reported series of compounds displayed improved broad-spectrum anti-bacterial activity against a variety of bacterial strains which was tested for its ability to cure a systemic *K. pneumonia* infection in the mouse.[52]



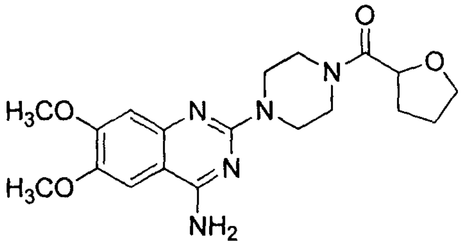
113

X,W = alkyl, Halide,etc
R = Alkyl, aryl



114

Terazosin (**115**) and doxazosin (**116**) are nonselective α_1-antagonists, which show significant effects on lowering blood pressure at the doses required to block the contraction of prostate caused by an α_1 agonist in the dog model.[53]



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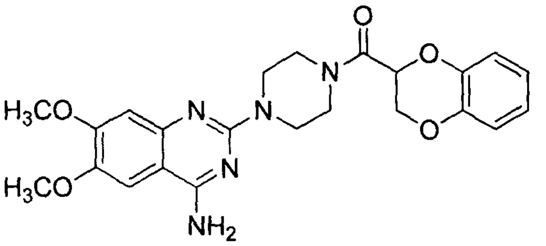
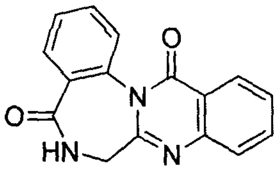


116

Wei Zhang and co-workers isolated sclerotigenin (**117**) from the sclerotia of *Penicillium sclerotigenum* which shows a promising anti-insectant activity.[54a] It is the simplest member of the benzodiazepine–quinazolinone natural alkaloid family. Other members in this family such as circumdatins-C (**118**) isolated from terrestrial fungus *Aspergillus ochraceus*[54b] and benzomalvins-A (**119**) isolated from fungus *Penicillium species* also possess interesting biological activities.[54c]



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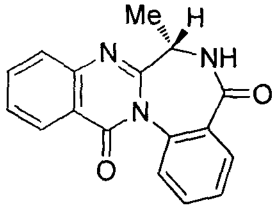

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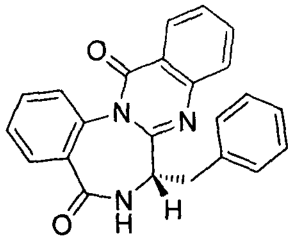
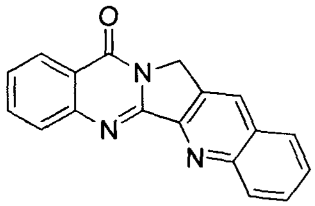


119

The quinazolinone alkaloid, luotonin-A (**120**), has attracted the attention of chemists and pharmacists worldwide, because it is strikingly reminiscent of the cytotoxic alkaloid, camptothecin, the derivatives of which are clinically useful anti-cancer agents. Cagir *et al*,[55] recently reported the importance of these findings by demonstrating that, despite the lack of A-ring functionality, luotonin A stabilizes human DNA topoisomerase I-dependent cytotoxicity in intact cells. Leutonin-F (**121**) is also another class of quinazolinone known for its anti-tumor activity isolated from *Peganum nigellastrum* by Mhaske and Argade.[56]



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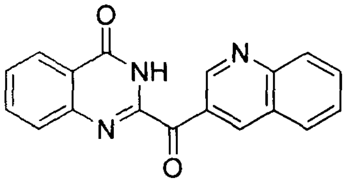
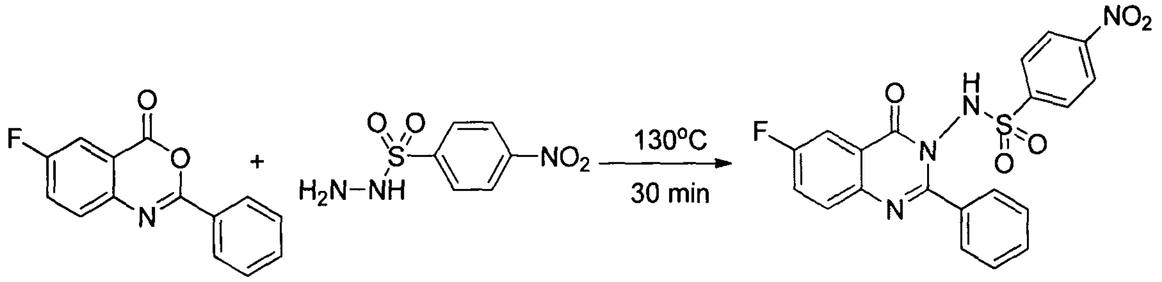


121

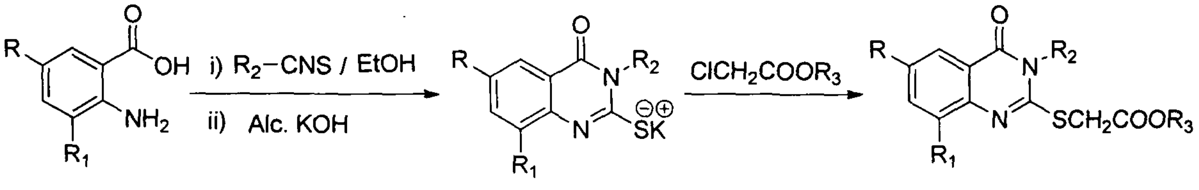
Yuefen Zhou and co-workers[57] have reported a series of 3-sufonamide-substituted quinazolinone derivatives (**124**) which are known to possess various anti-infective agents.



122 **123** **124**

Scheme-16

Waheb *et al*,[58] have reported a new series of 3-substituted (methyl, ethyl or phenyl)-quinazolin-4(3*H*)-one derivatives (**127**) which were synthesized through the condensation reaction of their potassium salts with methyl, ethyl and phenylisocyanate. The synthesized derivatives **127** were evaluated for anti-convulsant activity which showed the highest anti-convulsant activity at low doses (50–100 mg kg^{-1}), whereas at doses over 100 mg kg^{-1} they showed a stimulant effect on the central nervous system that even potentiated the effect of the convulsive agent, pentylenetetrazole, in mice. A series of halogenated derivatives, 3-methyl, 3-ethyl and 3-phenyl-6-mono and 6,8-disubstituted-quinazolin-4(3*H*)-one derivatives were also synthesized and evaluated for anti-convulsant activity.

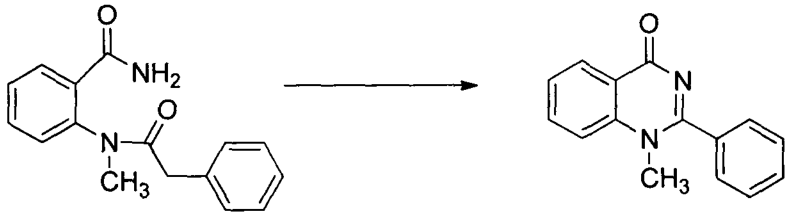


125 **126** **127**

R/R1 = H, Br, Cl
R_2 = CH3, C_2H_5, C_6H_5
R_3 = H, Ar, Cyclohexyl

Scheme-17

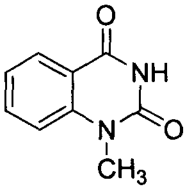
Quinazoline alkaloid are found in atleast six botanical families of which rutaceae are the most important. Thus arborine (**129**) was isolated from *Glyosmis arborea* which also can be synthetically obtained by thermal cyclisation of phenylacetyl derivatives of *N*-methylanthranilamide (**128**).[59]



128 **129**

Scheme-18

The same plant material yielded three related alkaloids, glycosmicine (**130**), glycorine (**131**), and glycosminine (**132**).[60]



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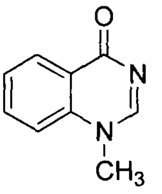

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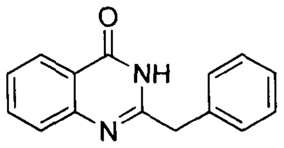
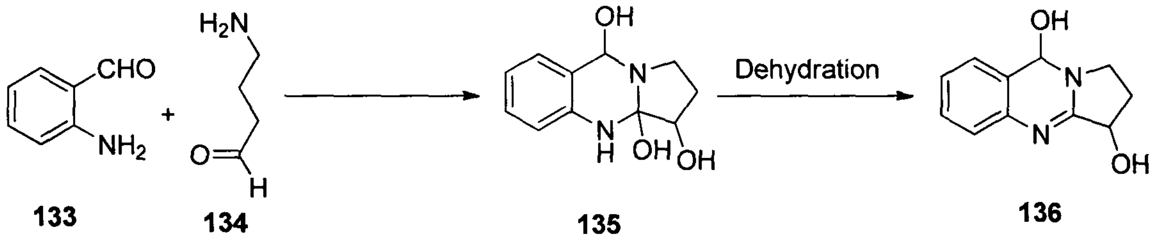


132

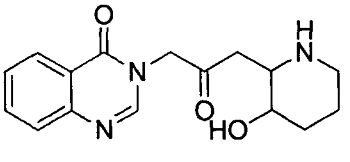
Similary, the alkaloid vasicine (**136**) which has bronchodilatory activity can be isolated from *Adhatoda vasica*. Leonard and Martell[61] reported the synthesis of vasicine by simple route from aminobezaldehyde (**133**) and 4-amino-2-hydroxybutyraldehyde (**134**) followed by dehydration of tricyclic intermediate (**135**).



Scheme-19

The anti-malarial quinazoline alkaloid febrifugine (**137**) and isofebrifugine (**138**) which are far better than quinine were isoalated from *Dichroa februga.*[62a] A group of researchers from China have isolated the interesting new quinazolinone-quinolizidine dimer, A neodichroine (**142**), which was isolated as a crystalline solid[62b] as the principal component from extracts of the leaves of *Dichroa febrifuga*.

There are several alkaloids which have both quinazoline and indole nuclei. Evodiamine (**139**) and rutaecarpine (**141**) were both isolated from the seeds of *Evodia rutaecarpa*. They also occur in *Xantoxylem rhetsa*, which in addition yielded rhetsinine (**140**).[63]



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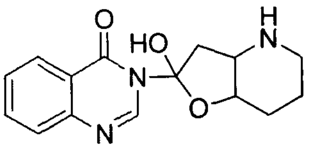

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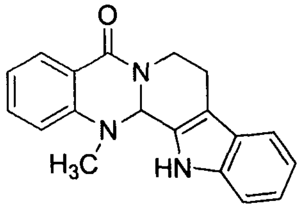

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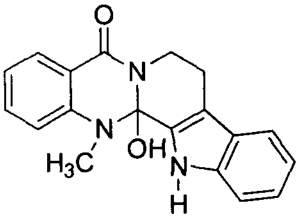

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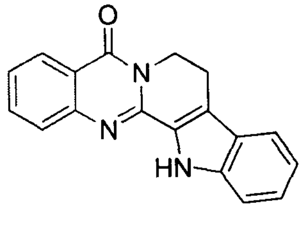

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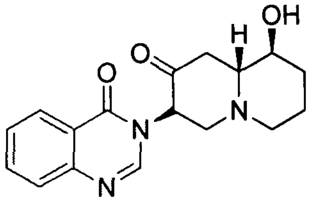
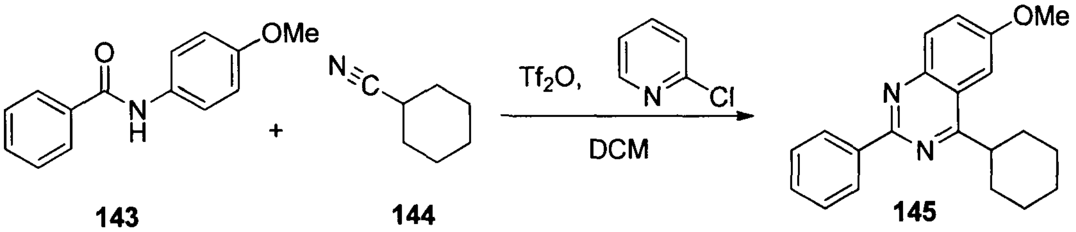


142

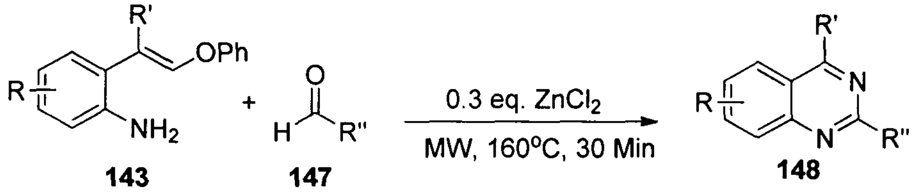
Owing to the vast application of quinazolinone, many synthetic methods have been reported, out of which a few synthetic route to quinazolines are described below:

Movassaghi and Hill[64] have reported a novel synthetic method of quinazoline derivatives (**145**) by reaction of certain amides with carbonitriles under electrophilic activation of the amide with 2-chloropyridine and trifluoromethanesulfonic anhydride (Tf_2O).



Scheme-20

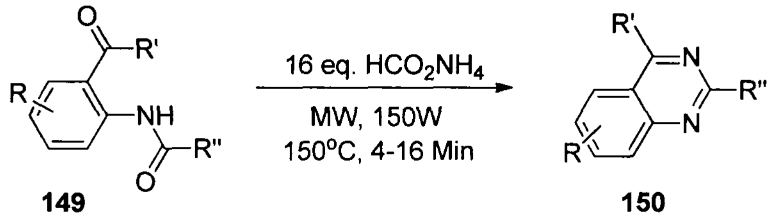
Microwave-promoted reactions of *O*-phenyl oximes (**146**) with aldehydes (**147**) in the presence of $ZnCl_2$ give quinazolines (**148**) in good yield. This convenient freeradical-based synthesis worked well with alkyl, aryl and heterocyclic aldehydes and for a variety of substituents in the benzenic part of the molecule.



R= Me, H
R' = Alky, H
R'' = Aryl, alkyl

Scheme-21

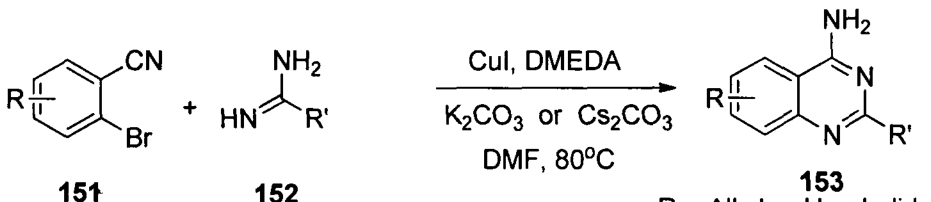
Another microwave assisted reaction of quinazoline was reported by Ferrini and co-workers[65] where a photochemically induced Fries rearrangement of anilides gave several *ortho*-aminoacylbenzene derivatives which undergoes rapid microwave-assisted cyclization to 2,4-disubstituted quinazolines and benzoquinazolines in the presence of ammonium formate.[66]



R= H, Cl, alkyl
R= alkyl or alkoxy
R = Aryl or alkyl

Scheme-22

Quinazoline can also be synthesized from substituted 2-bromo-benzonitriles (**151**) which on reaction with amidines or guanidines allow an economical and practical synthesis of 4-aminoquinazoline and 2,4-diaminoquinazoline derivatives (**153**).[67]

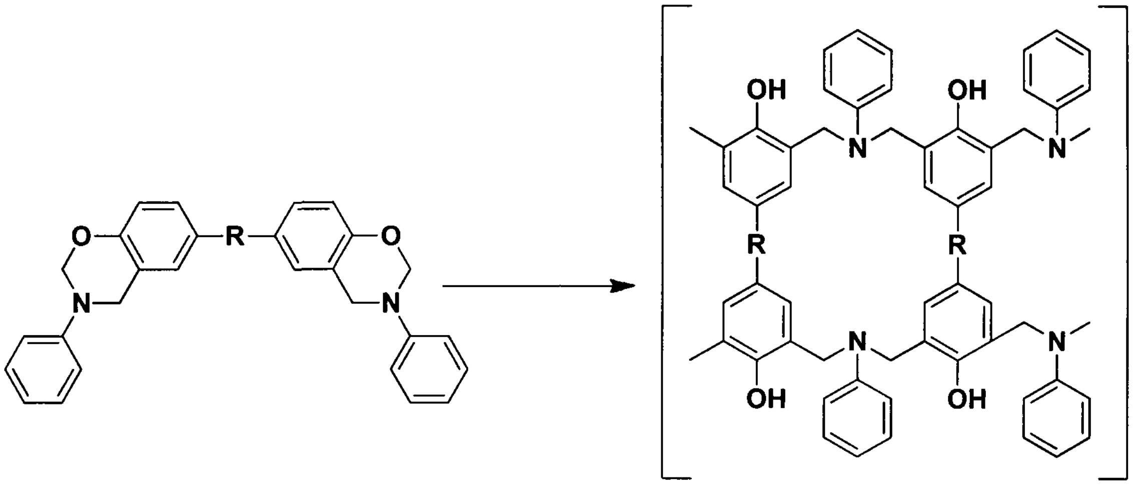


R = Alkyl or H or halides
R' = Alkyl

Scheme-23

1.6. Benzoxazine and benzothiazine based heterocyclic compounds

Benzoxazine and Benzothiazine are fused heterocyclic compounds of oxazine and thiazine moiety respectively. Their rings are stable at room temperature for a long period of time and start to homo-polymerize to high molecular weight oligomer or polymer at elevated temperatures. They are used as thermoset resins which complement the broad line of multifunctional epoxies, cyanate esters and bismaleimides. They exhibit excellent performance properties including, flame retardance, dimensional stability, low water absorption, low dielectric constant, temperature resistance, thermal and mechanical properties and offer many advantages for formulating halogen-free systems to be used in producing composites, coatings, adhesives and encapsulants. Benzoxazine thermoset resins (**155**), when heated, homopolymerize to form a rigid polymer that can be used for manufacturing products such as high-temperature composites and electronic components.



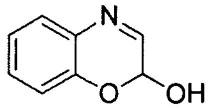
154 **155**

Scheme-24

Various glycosides of the 2-hydroxy-(2*H*)-1,4-benzoxazine (**156**) skeletons have been found to occur in graminous plants such as maize, wheat, rye, and rice and act as plant resistance factors against microbial diseases and insects.[68]

Inhibition of HIV-1 (human immunodeficiency virus type 1) reverse transcriptase by nucleosides such as zidovudine or azidothymidine (AZT), zalcitabine (DDC), didanosine (DDI), stavudine (D4T) and lamivudine (3TC) is a proven therapy for delaying the progression to AIDS. However, the rapid viral mutation to resistant strains requires the development of new therapeutic agents.[69] The recent developments of both protease inhibitors and non-nucleoside reverse transcriptase inhibitors offer hope of effective treatment, especially when co-administered.[70a] Efavirenz (**157**) is a non-nucleoside reverse transcriptase inhibitor that shows high potency against a variety of HIV-1 mutant strains[70b] and is currently undergoing clinical studies.[70c]

1,3-benzoxazines are used as an important intermediate in the development of anti-microbial, anti-viral, and anti-fungal drugs.[71] 2-Morpholino chromones are structurally similar to 2-morpholino benzoxazines (**158**) and have been reported to exhibit potent antiplatelet properties.[72]



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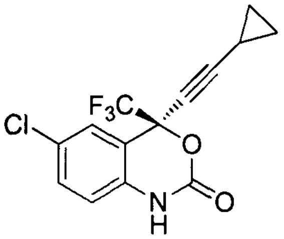

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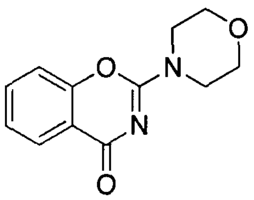
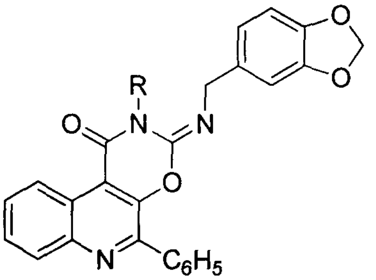


158

The mono- and bisoxazines derived from naphthalene have been reported to possess anti-malarial activity.[73a] Similar activity was found in some quinoline bis-oxazines (**159**).[73b] The removal of one of the oxazine rings from various quinoline-bis-oxazines, however, caused an almost complete loss of activity. Similar dihydro-l,3-oxazines have recently been reported to have a strong cytotoxic effect on tumor cells, especially in low concentration.[73c] The secondary ring of cephalosporin antibiotics consists of a 2,3-dihydro-(6*H*)-1,3-thiazine ring (**160**).



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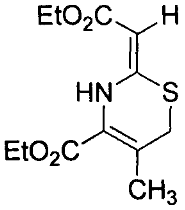
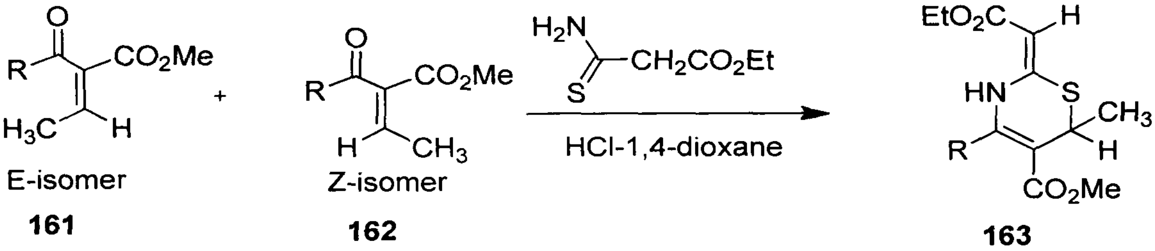


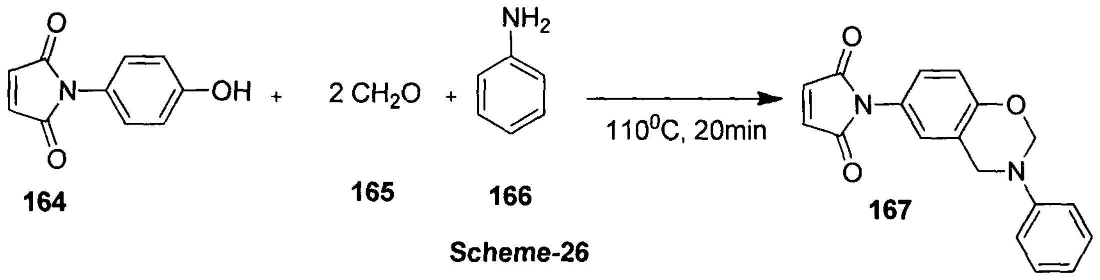
160

Synthesis of the dihydrothiazines (**163**) originally began with preparation of the corresponding α,β-unsaturated keto esters (**161** and **162**) by the procedure of Lenhert.[74a] However, a modification of a procedure by Knoevenagel[74b] was later shown to be less time consuming. Condensation of ethoxycarbonylthioacetamide with the α,β-unsaturated keto esters using anhydrous hydrogen chloride in 1,4-dioxane,[74c] gave the expected dihydrothiazines in 71–77% yield.

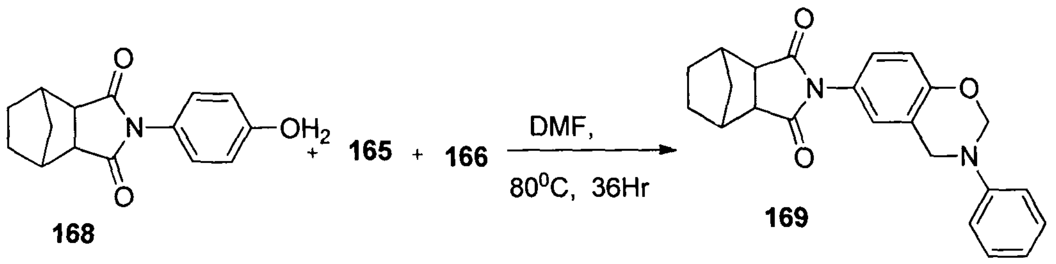


Scheme-25

By taking advantage of the molecular design flexibility of benzoxazine chemistry, thermal and thermo-oxidative stability of polybenzoxazines has been improved by adding functional groups on the amine and/or phenol. Shen and Ishida[75a] developed polyfunctional naphthoxazines and benzophenone-based benzoxazines to improve thermal stability by increasing the number of aromatic groups per repeat unit. This resulted in glass transition temperatures above 300^{0}C and char yield of 67% for some of the compounds; Low and Ishida[75b] studied the thermal and thermo-oxidative degradation of polybenxozazines, using thermogravimetric analysis–Fourier transform infrared spectroscopy (TGA–FTIR), and gas chromatography–mass spectrometry (GC–MS), and concluded that there are three stages in the thermal degradation of bisphenol-based polybenzoxazines. Evaporation of amine moiety first occurs below 300°C and between 300 and 400^{0}C, the degradation of the schiff base occurs. Finally above 400°C, the evaporation of phenolic moiety was observed. This observation gave rise to the postulation that if amine evaporation was reduced, the char yield can be greatly increased. H. Ishida and S. Ohba synthesised and characterized maleimide and norbornene functionalized benzoxazines as shown in **Scheme-26** and **Scheme-27**.[75c]

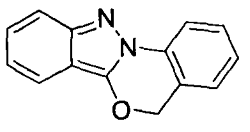


Scheme-26



Scheme-27

The indazolobenzoxazine ring system (**170**) is a rare heterocycle comprising of benzo-1,3-oxazine (**171**) and 2*H*-indazole (**172**) substructures.



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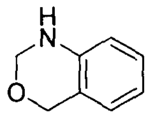

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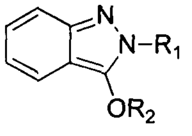
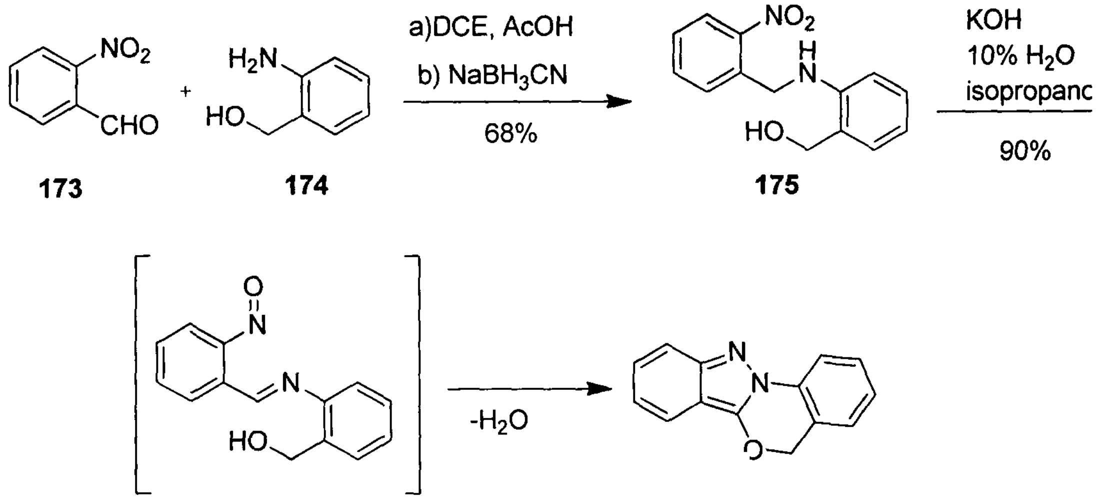


172

Benzo-1,3-oxazines are also known to be biologically active, demonstrating anti-anginal activity,[76a] anti-hypertensive affects[76b] and potency as anti-rheumatic agents.[76c] Thus, it is envisioned that indazolobenzoxazines, which contain both the indazole and benzoxazine moieties, may afford unique biological activities. Jeffrey D. Butler and co-workers provided the synthesis of the parent [5*H*]-indazolo[3,2-*b*]benzo[*d*]-1,3-oxazine (**177**) system, which culminated in the preparation of a novel library focused on this heterocycle.[77]



I.7. General characteristics and applications of microwaves in organic synthesis.

I.7.1 Advent of Microwaves

A remarkable device for generating fixed-frequency microwaves, called magnetron,[78] was designed by Randall and Booth at the University of Birmingham. A magnetron is a vacuum device which converts DC electrical energy into microwaves. In early days, it was recognized that microwaves could heat water in a dramatic fashion. Domestic and commercial appliances for heating and cooking of food began to appear in the 1950s. In 1947, the appliance called "Radarange" appeared on the market; it was intended for food processing. In 1955, Tappan introduced the first microwave oven, but the widespread use of domestic microwave ovens occurred during the 1970s and 1980s. The first application of microwave irradiation in chemical synthesis was published in 1986.[79]

Microwave irradiation is an electromagnetic irradiation in the frequency range of 0.3 to 300 GHz. All domestic kitchen microwave ovens and all dedicated microwave reactors for chemical synthesis operate at a frequency of 2.45 GHz (which corresponds to a wavelength of 12.24 cm) to avoid interference with telecommunication and cellular phone frequencies.

Microwave irradiation is becoming an increasingly popular method of heating samples in the laboratory[80] which led scientists to investigate the mechanism of microwave dielectric heating and to identify the advantages of the technique for chemical synthesis.[81] During recent years, microwaves have been extensively used for carrying out chemical reactions and have become a useful non-conventional energy source for performing organic synthesis.[82] This is supported by a great number of publications in recent years, because it offers a clean, cheap and convenient method of heating which often results in higher yields and shorter reaction times. The first recorded application of microwave (MW) energy in organic synthesis is the aqueous emulsion polymerization of butyl acrylate, acrylic acid and metacrylic acid using pulsed electromagnetic radiation. The start of the rapid growth of microwave-assisted procedures in organic synthesis was ignited in 1986 by pioneering papers by Gedye and co-workers[83a] and Giguere and co-workers.[83b] During the last two decades, the activity in this new technique has experienced exponential growth and has been extensively reviewed.[84] Kappe and Dallinger have reported the impact of microwaves on drug discovery. Even microwave-assisted reactions under solvent-free conditions promoted the synthesis of Zincke's salt and its conversion to chiral pyridinium salts in water[85] and microwave-assisted organic transformations using benign reaction media have also been reported.[10,11] Moreover, Varma and co-workers have reported the drug discovery by using aqueous microwave chemistry.[86]

Organic transformations take place by either of the two ways- **Conventional heating and Microwave heating.** In conventional heating, reactants are slowly activated by a conventional external heat source. Heat is driven into the substance, passing first through the walls of the vessel in order to reach the solvent and the reactants. This is a slow and inefficient method for transferring energy into the reacting system. Whereas in microwave heating, microwave couple directly with the molecules of the entire reaction mixture, leading to a rapid rise in the temperature. Since the process is not limited by the thermal conductivity of the vessel, the result is an instantaneous localized superheating of any substance that will respond to either dipole rotation or ionic conductivity.

The conduction mechanism leads to the much stronger interaction of ions with electric field due to the generation of heat. The ions will move under the influence of an electric field, resulting in expenditure of energy due to an increased collision rate, converting kinetic energy into heat. The heat generated by both mechanisms adds up resulting in a higher final temperature. The main benefits of microwave heating are:[87]

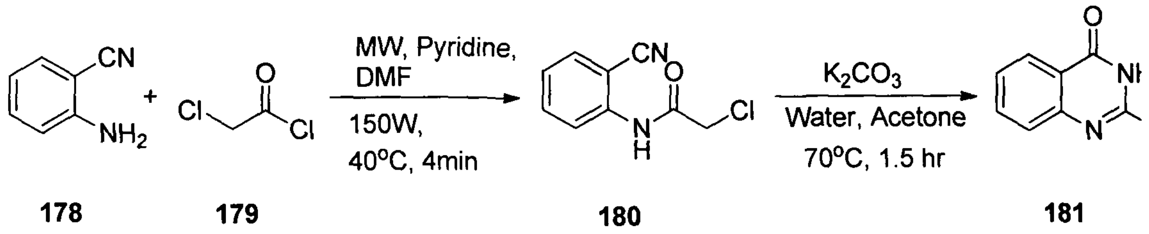
- very fast heating;
- absence of inertia;
- ease of use, i.e. power regulation is easy with an instantaneous "on and off" control;
- better homogeneity in temperature with quick transfer of energy into the whole mass without superficial heating;
- the selective heating of the polar molecules.

Since the ability of a molecule to couple with the microwave radiation is a function of its molecular polarisability (i.e. a function of its dipole moment), only polar molecules interact with microwave energy. As a guide, compounds with high dielectric constants such as water, ethanol, acetonitrile, *N,N*-dimethylformamide (DMF), acetic acid, chloroform, dichloromethane, acetone, ethylene glycol etc., tend to heat rapidly under microwave irradiation, while less polar substances, such as aromatic and aliphatic hydrocarbons or compounds with no net dipole moment, such as carbon dioxide, carbon tetrachloride, diethyl ether etc. as well as highly ordered crystalline substances, are poorly absorbing. Thus, polar molecules in a non-polar solvent would absorb energy, but not the solvent or the reaction vessel, if it is made of teflon ($\mu = 2.1$ at 22 °C) or ceramic or even pyrex (μ= 4.5–6.0). Sometimes it is possible to use mixtures comprising microwave active reactants and microwave inactive solvents. It has also been suggested that if microwave energy is absorbed by the solvent and not by the substrate, only modest rate increase will result relative to those observed with conventional energy. If, on the other hand, the microwave energy is absorbed selectively by a reactant, by a complex or by an intermediate during the rate determining step, then large rate increase will result.

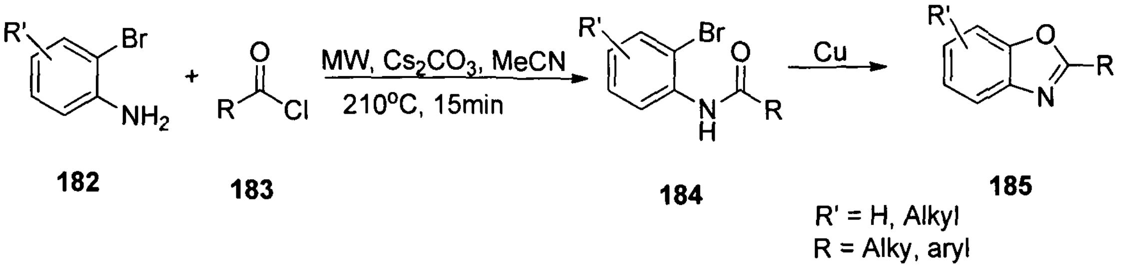
A microwave heating technique is preferred over conventional heating because microwave assisted organic syntheses can lead to a large decrease in reaction time and to an enhancement of conversion and selectivity, compared to conventional heating.[88] These microwave effects could be attributed to the characteristic heating modes of the microwaves, caused by the interaction of oscillating electromagnetic fields with the assemblies of the polar molecules, expressed as dielectric loss, leading to the unusual phenomenon called superheating[89a] or hot spots.[89b] Instantaneous heat release at the molecular level favourably induce certain thermal reactions taking place through a polar charge transfer or polar transition state as is often observed in photo-induced chemical reactions.

The microwave-assisted organic reactions can be carried out using solvents as well as in solvent-free conditions. Some of the microwave assisted reactions for the synthesis of heterocycles are cited below:

Vanelle and co-workers [90] have reported a microwave assisted green synthesis of quinazoline derivatives (**181**) possessing anti-cancer activity. The products were obtained *via* an SNR1 reaction.

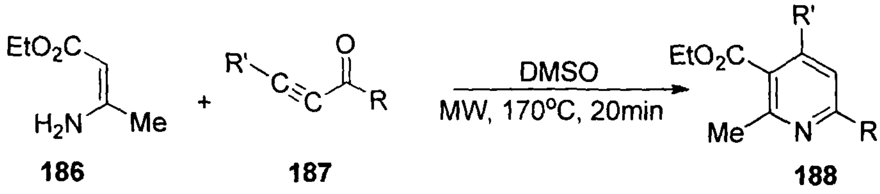


Batey carried out a copper catalyzed one-pot synthesis of benzoxazoles **185** using bromoanilines (**182**) and acyl halides (**183**) in the presence of a base and solvent giving intermediates which finally gave pure benzoxazoles (21–97% isolated yields), exhibiting a broad range of biological activities. They can also be used as precursors in the synthesis of drugs. Similarly, syntheses of benzoxazoles have also been carried out.[91]



Scheme-30

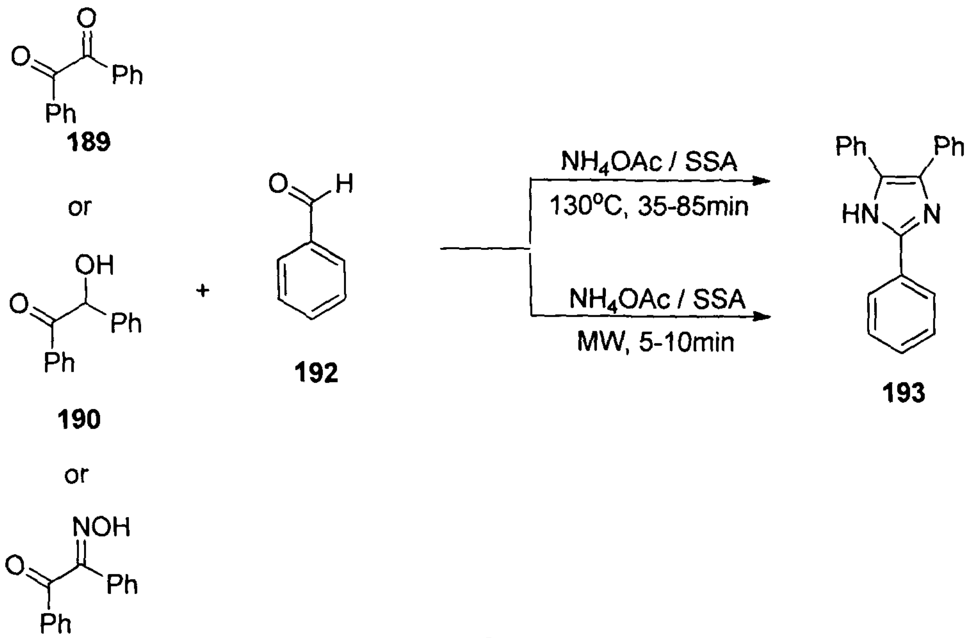
Bagley *et al*, have developed a microwave assisted modification of this heteroannulation method, which is best conducted in DMSO at 170°C for 20 minutes, and provided the desired pyridine derivatives (**188**) in 24–94% yield (**Scheme-31**).[92]



R = H, Et, Ph
R' = Alkyl, aryl

Scheme-31

Shaabani and co-workers[93] have reported a silica-supported sulphuric acid-promoted one-pot synthesis of trisubstituted imidazoles (**193**). Comparative studies between conventional and microwave irradiation indicates that products were obtained in excellent yields under microwave irradiation.



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Scheme-32

1.8. References

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Chapter II

Synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones and 3, 4, 5, 6, 7, 8-hexahydroquinazolin-2(1*H*)-ones *via* three component cyclocondensation#

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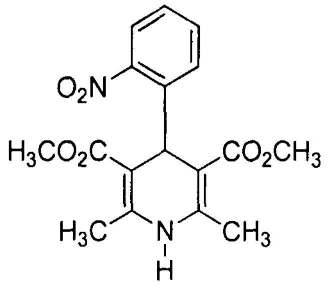
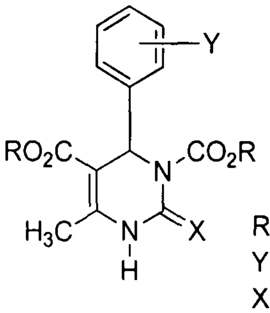
II.1. Introduction

Pyrimidinones or Dihydropyrimidinones (DHPM) are important class of heterocyclic compounds which have received considerable attention in recent years and have emerged as target molecules due to their attractive application in different field. DHPMs and their derivatives are of interest because of their pharmacological properties, like protein tyrosine kinase inhibitory, cholecystokinin inhibitory, anti-microbial, anticonvulsant, sedative, hypotensive, anti-depressant, anti-inflammatory, and anti-allergy properties. Some of these compounds also have interesting biological properties such as anti-malarial, anti-cancer, biofungicide and diuretic properties.[1]

4-aryl-1,4-dihydropyridines (DHPs) of the nifedipine type[2] (*e.g.*, **1**) were first introduced into clinical medicine in 1975 and are still the most potent group of calcium channel modulators available for the treatment of cardiovascular diseases.[3] Dihydropyrimidines of type **2** show a very similar pharmacological profile and in recent years, several related compounds (**2**) were developed that are equal in potency and duration of anti-hypertensive activity to classical and second-generation dihydropyridine drugs.



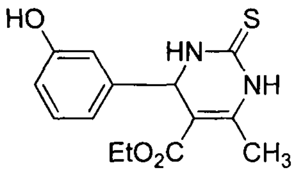
1



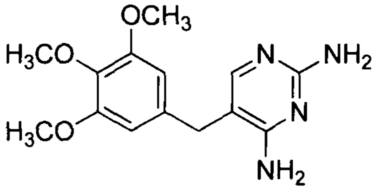
R= Alkyl,
Y= NO_2, CF_3
X= O, S, NH

2

The scope of this pharmacophore has been further widened with the identification of 4-(3-hydroxyphenyl)-2-thione derivative (**3**) called monastrol[4] as a novel cellpermeable molecule for the development of new anti-cancer drugs. Monastrol (**3**) has been identified as a compound that specifically affects the cell-division (mitosis) by a new mechanism which does not involve tubulin targeting. It has been established that the activity of **3** consists of the specific and reversible inhibition of the motility of the mitotic kinesis, a motor protein required for spindle bipolarity. Trimethoprim (**4**) is a type of drug with a pyrimidine core which attacks the folic acid metabolism of bacteria and is often used as anti-bacterial agents.[5]

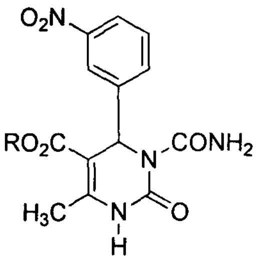


3

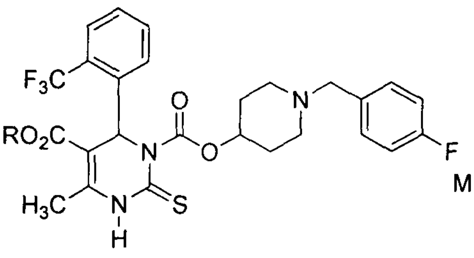


4

Recently, appropriately functionalized DHPMs which are the aza-analogs of classical Hantzsch 1,4-dihydropyridine calcium channel modulators, SQ 32926 (**5**) and *SQ 32547* (**6**) [6] were reported to be effective orally as active anti-hypertensive agents and the related compound of the type 7 are known to possess α_{la} adrenoceptor-selective antagonists.[7]

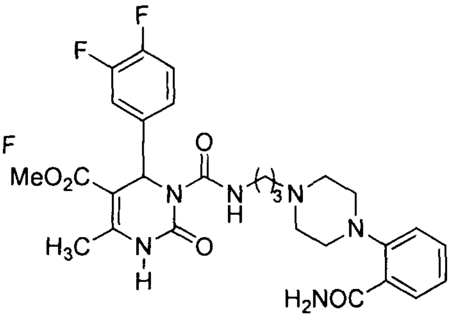


5



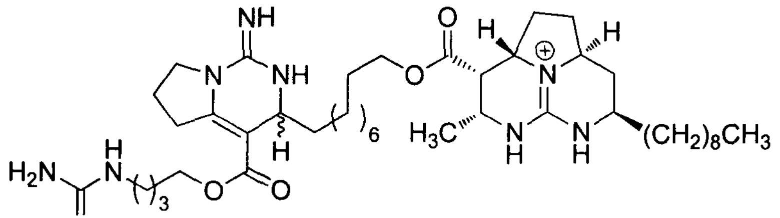
R= Isopropyl

6



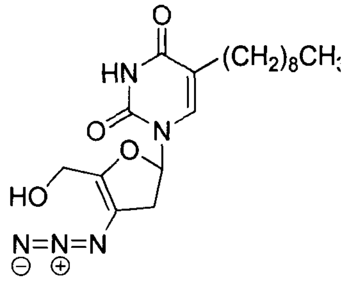
7

Several alkaloids containing the dihydropyrimidine core unit have been isolated from marine sources, which exhibit interesting biological properties. Most notably, among these are the batzelladine alkaloids-A (**8**) and batzelladine alkaloids-B (**9**), which inhibit the binding of HIV envelope protein gp-120 to human CD4 cells and are potential new leads for AIDS.[8] 3'-azido-2'-deoxythymidine (AZT) (**10**) is perhaps the best known among the drugs designed to interfere with retroviral DNA synthesis.[9] AZT is taken up by the T-lymphocyte cells and are particularly susceptible to human immunodeficiency virus (HIV), the retrovirus that causes AIDS. Once in the cell, AZT is converted to AZT-triphosphate. The retroviral enzyme (reverse transcriptase) that catalyzes DNA formation from RNA binds AZT-triphosphate more tightly than it binds dTTP. Therefore, AZT is added to the growing DNA chain and no additional nucleotides can be added to the chain and DNA synthesis comes to a sudden halt.



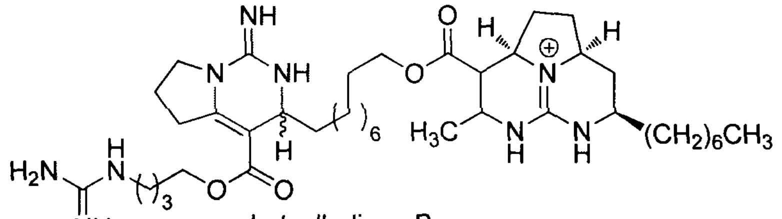
batzelladines-A

8



3'-azido-2'-deoxythymidine

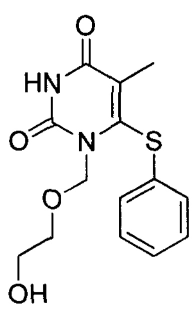
10



batzelladines-B

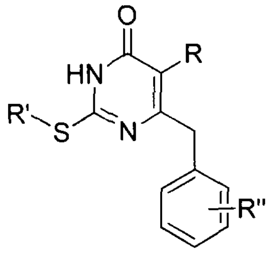
9

The best strategy for AIDS treatment involves a combination therapy using inhibitors of reverse transcriptase and protease. However, the emergence of HIV-1 strains resistant to these drugs and their cytotoxicity requires the synthesis of new ant-iviral drugs, as well as the development of newer strategies and viral targets. In the last few years, 6-substitued pyrimidines, as for example 1-[(2-hydroxyethyl)methyl]-6-(phenylthio)thymine (HEPT),[10] 3,4-dihydro-2-alkoxy-6-benzyl-4-oxopyrimidines (DABOs),[11] and diarylpyrimidine analogues (DAPY)[12] are reported to show a potent and selective activity against reverse transcriptase of human immunodeficiency virus type-1 (HIV-1).



HEPT

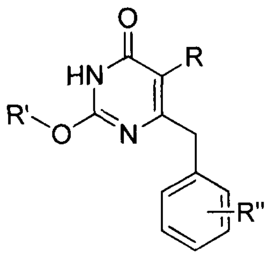
11



S-DABOs

12

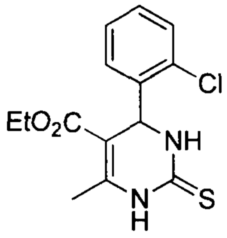
R= Alkyl
R'= Alkyl, aryl
R''= Alkyl, Alkoxy



DABOs

13

As early as 1930, the derivatives of dihydropyrimidine such as **13** were patented by Hentrich and co-workers[13] as an agent for the protection of wool against moths. The same compound was also reported to possess cardiovascular activity by Ertan et al.[14] Other DHPMs such as **14**[15] and **15**[16] having cardiovascular activity were also reported.



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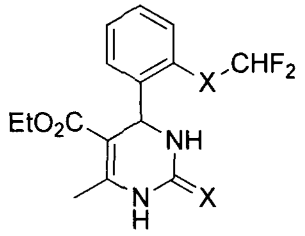
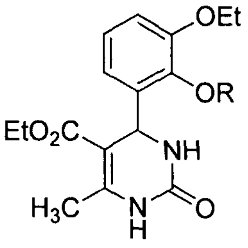


X= O, S

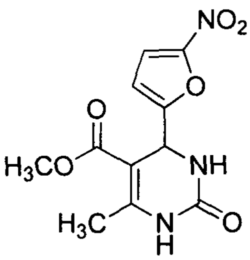
15



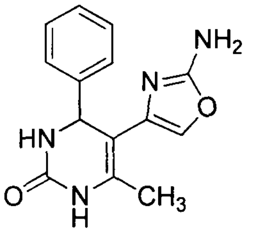
R = 2,3,4,6-tetra-O-acetyl
-D-glucopyranosyl

16

Much interest have been focused on the biological properties of Biginelli compounds, which eventually leads to the development of nitractin (**17**), which has excellent activity against the viruses of the trachoma group.[17] The same compound **17** also exhibits modest anti-bacterial activity. The anti-bacterial and anti-fungal activity of DHPMs were reported by Chorghade and coworkers,[18] where derivative of pyrimidine such as 5-(2-aminothiazol-4-yl)-3,4-dihydro-4-phenylpyrimidne-2(1*H*)-one (**18**) showed activity against *S. aureus*, *K. pneumonae* and *C. albicans*. Patel *et al*,[19] have reported that compound **19** showed excellent anti-bacterial activity against *E. coli* and *B. subtillis* comparable to that of streptomycin.



17



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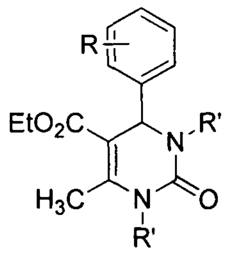
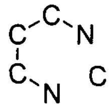


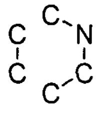
R= H, OH, OMe
R'= Morpholine
19

II.2. Synthetic studies on pyrimidine derivatives

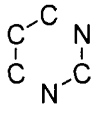
Pyrimidine does not normally serve as a starting point for the preparation of substituted pyrimidine. These compounds are generally prepared by five types of ring synthesis (A, B, C, D and E) according to the nature of the fragments which combine together to form the pyrimidine nucleus.[20]



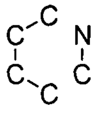
A



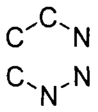
B



C



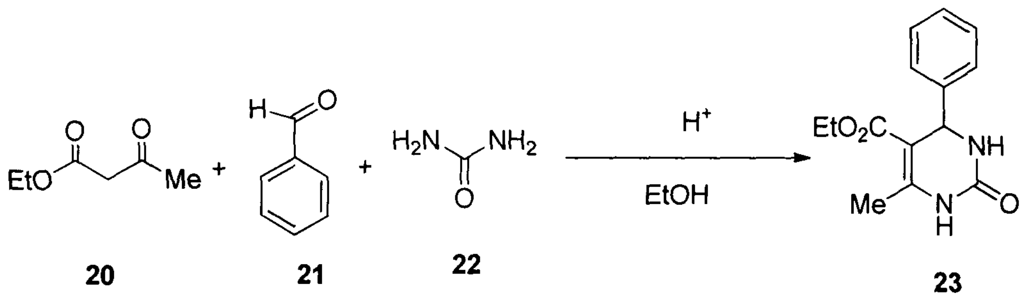
D



E

The first synthesis of dihydropyrimidinones, the most explored derivative of pyrimidine was reported by Biginelli[21] in 1893, however, the synthetic potential of this heterocyclic synthesis remained unexplored for quite some time. In the 1970's, interest gradually increased and the scope of the original cyclocondensation reaction shown in **Scheme-1** was gradually extended by variation of all the building blocks, allowing access to a large number of multifunctionalized dihydropyrimidines of type **11**. Since the late 1980's, a tremendous increase in activity has again occurred, as evident by the growing number of publications and patents on the subject. This is mainly due to the fact that the multifunctionalized dihydropyrimidine scaffold (Biginelli compounds) represents a heterocyclic system of remarkable pharmacological efficiency. Since then, several reviews on synthesis and chemical properties of pyrimidinones have been reported. The search for new and efficient methods for the synthesis of pure compounds has been an active area of research in organic synthesis. From a modern point of view, Biginelli protocol is obviously very attractive for combinatorial chemistry and has been rarely used for parallel synthesis, Hence a new avenue could be connected with an elaboration of catalytic procedures.

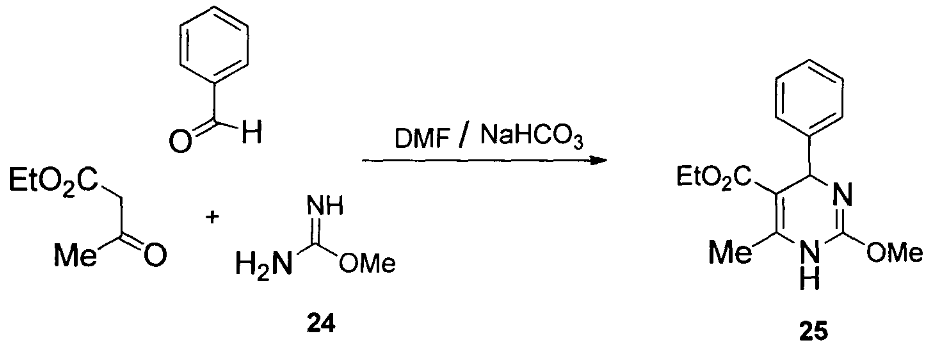
P. Bigenelli reported the acid catalyzed cyclo-condensation reaction of ethyl acetoacetate (**20**), benzaldehyde (**21**), and urea (**22**). The reaction was carried out by simply heating a mixture of the three components dissolved in ethanol with a catalytic amount of hydrochloric acid at reflux temperature. The product of this novel one-pot, three components synthesis that precipitated on cooling of the reaction mixture was identified as 3,4-dihydropyrimidin-2(1*H)*-one (**23**) and this reaction is known as "Biginelli reaction", or "Biginelli Condensation", or as "Biginelli dihydropyrimidine synthesis".[21]



Scheme-1. Classical biginelli synthesis of DHPMs

Since then a number of improved variants employing new reagents, catalysts, methodologies and techniques have emerged. Numerous synthetic methods for the preparation of these compounds have been reported using $InCl_3$,[22] lanthanide triflate,[23] $BF_3.OEt_2$,[24] PPE,[25a] KSF clay,[25b] $LaCl_3$,[26] H_2SO_4,[27] ceric ammonium nitrate (CAN),[28] $Mn(OAc)_2$,[29] ion-exchange resin,[30] $InBr_3$,[31] $FeCl_3$,[32] $CdCl_2$,[33]1-butyl-3-methyl imidazolium tetrafluoroborate,[34] ytterbium triflates,[35] $SiO_2/NaHSO_4$,[36] $BiCl_3$,[37] $LiClO_4$,[38] $ZrCl_4$,[39] $Cu(OTf)_2$,[40] $Bi(OTf)_3$,[41] LiBr,[42] NH_4Cl,[43] $SnCl_2.2H_2O$,[44a] $AlCl_3/KI$,[44b] $CoCl_2$ /$MnCl_2$,[44c] $AlCl_3/AlBr_3$,[44d] P_2O_5,[45] $BiOClO_4.xH_2O$,[46]$CaCl_2$,[47a] 1,3-dibromo-5,4-dimethylhydantoin,[47b] zinc tetrafluoroborate,[47c] ZnI_2, $MgSO_4$ and CH_3COOH.[47d]

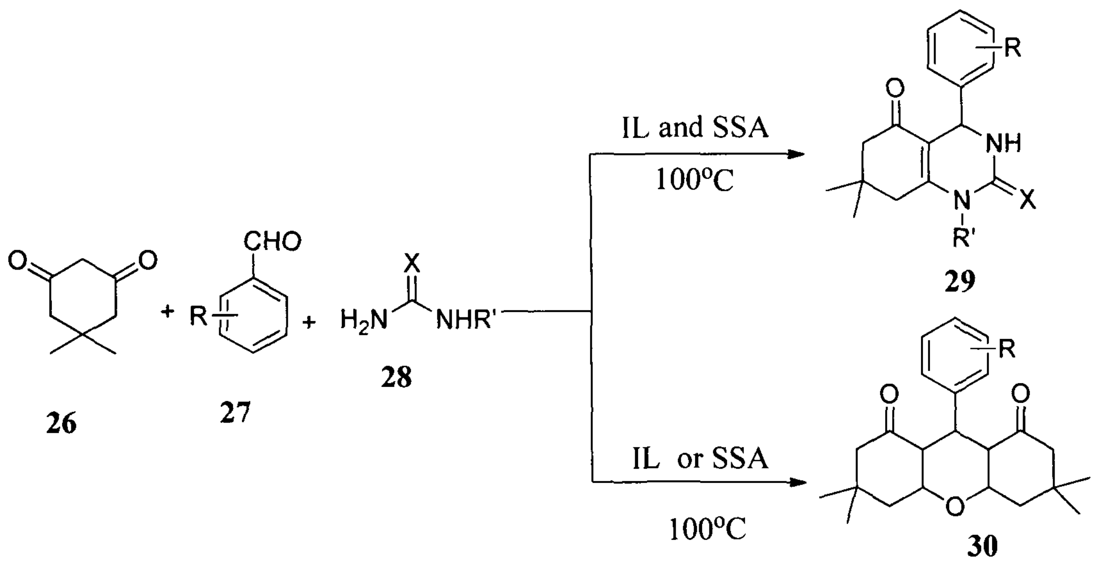
C. O. Kappe reported the synthesis of 2-methoxy-1,4-dihydropyrimidines (**25**) which was obtained by condensation of ethylacetoacetate, *O*-methyl isourea (**24**) and an appropriate aldehyde.[48]



Scheme-2

Recently, for novel Biginelli-like scaffold syntheses,[49a] the use of common open-chain β-dicarbonyl compounds have been extended to cyclic β-diketones,[49b] β-ketolactones,[49c] cyclic β-diesters[49d] or β-diamides,[49e-g] benzocyclic ketones and α–ketoacids,[49g]

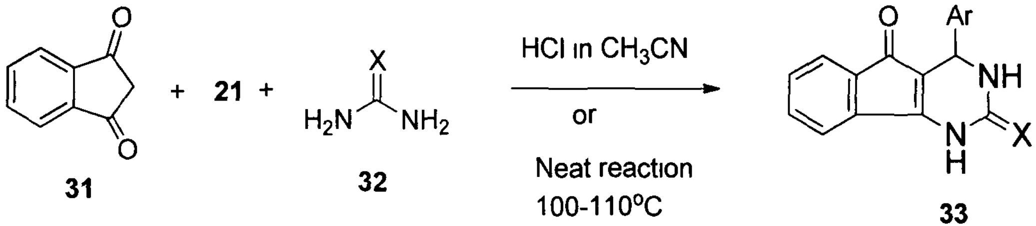
Shaabani *et al*,[50] have reported the use of silica sulfuric acid (SSA) and 1-butyl-3-methylimidazolium bromide, [bmim]Br as an ionic liquid (IL) for the synthesis of biginelli type compounds **29** from 5,5-dimethyl-1,3-cyclohexanedione (**26**) aromatic aldehydes (**27**) and urea or *N*-methylurea or thiourea (**28**). Interestingly, they have pointed out that in the presence of only one of the two species, SSA or IL, the reaction proceeds in a different way giving rise to different products **30**. According to them, in the presence of both SSA and IL there is a formation of *N*-acylium intermediate which is accelerated and stabilized leading to the formation of product **29**. However, in the presence of only one species, the dione carbonyl oxygen is protonated preferably which tautomerize to take the latter pathway.



R' = Methyl
R= Alkyl, alkoxy, halides
X=O,S

Scheme-3

The above reaction (**Scheme-3**) is the modification of the earlier report of Perumal *et al,*[44f] where hydrochloric acid in acetonitrile was used instead of ionic liquid in SSA and the use of indane-1,3-dione (**31**) gives 4-aryl-indeno-[1,2-*d*] pyrimidine (**33**) where it was found that solvent-free and catalyst-free reaction at 100-110°C gave better yield than those catalysed by hydrochloric acid.

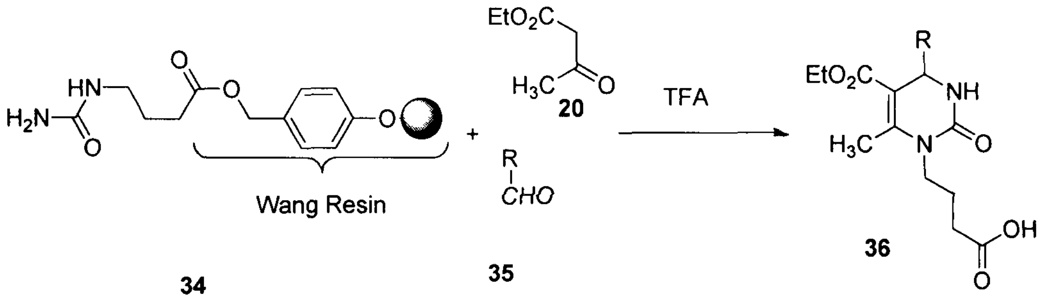


X = O, S
Ar = Aryl

Scheme-4

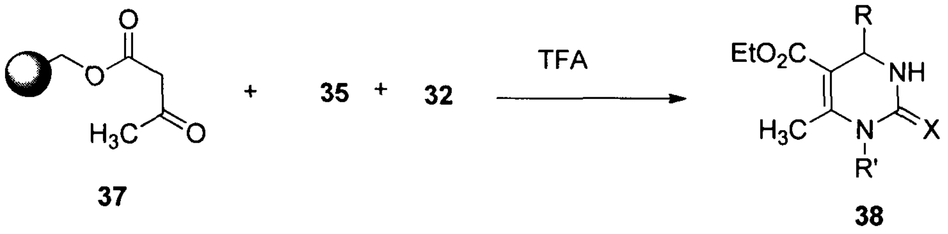
Kappe and Stadler reported the automated microwave-assisted synthesis of dihydropyrimidines utilizing $Yb(OTf)_3$.[51] They prepared a forty-eight compounds library within a time span of twelve hours which involves a variety of aldehydes, *N*-substituted ureas and carbon acids. Solid-phase synthesis provided another method for accessing a diverse collection of dihydropyrimidines. The use of a large excess of reagents in solid-phase synthesis resulted in high yield products. Also, non-resin bound by-products formed could be easily washed away, eliminating the need for further purification. A variety of polymer-supported building blocks have been explored, including attachment of the linker to the urea and β-keto ester components. Wipf and Cunningham provided the first example of a solid-phase Biginelli reaction using a resin bound urea **(34)** **(Scheme-5)**.[52] Formation of the dihydropyrimidine and cleavage from the resin with TFA produced the *N*-1 substituted products **36**.

The scope of the solid-phase application by using a β-keto ester immobilized reagent **37** **(Scheme-6)** was explored.[53] This strategy yielded 5-carboxylic acid dihydropyrimidines (**38**) upon cleavage from the resin, as well as *N*-1 unsubstituted compounds. In another application, Kappe utilized a polymer bound thiouronium salt (**39**)[54] (**Scheme**-7). After completion of the Biginelli reaction, the resin bound dihydropyrimidines (**40**) was cleaved under different conditions to yield dihydropyrimidines (**41**), thiopyrimidines (**43**) or 2-iminodihydropyrimidines (**42**). These solid-phase methods allow for the synthesis of diverse dihydropyrimidines in high yield and purity with a potential for automation.



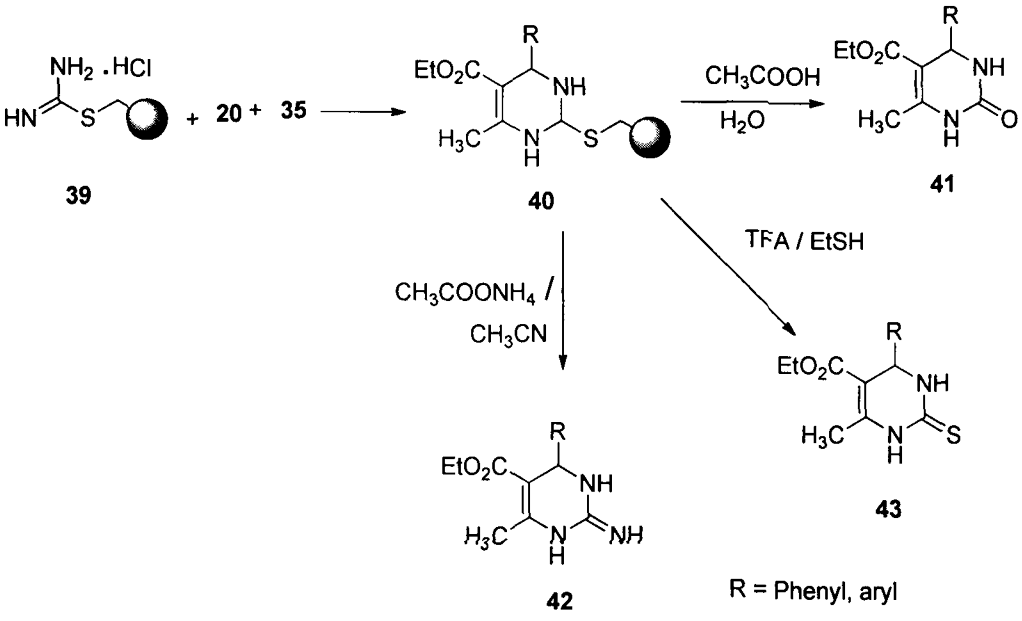
R = Phenyl, aryl

Scheme-5



R = Phenyl, aryl

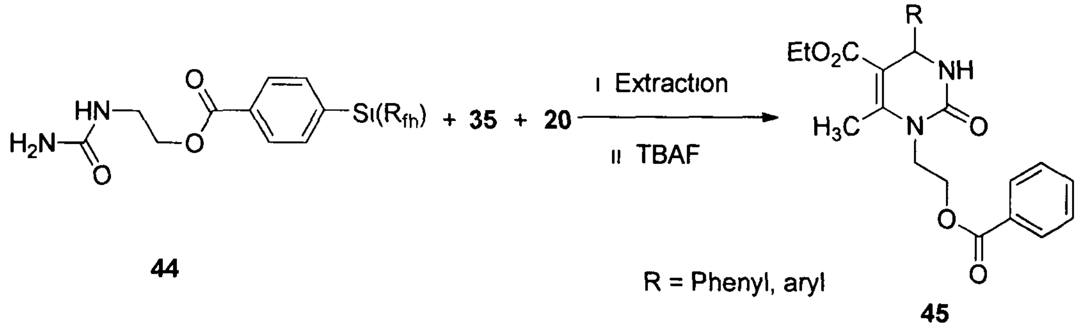
Scheme-6



R = Phenyl, aryl

Scheme-7

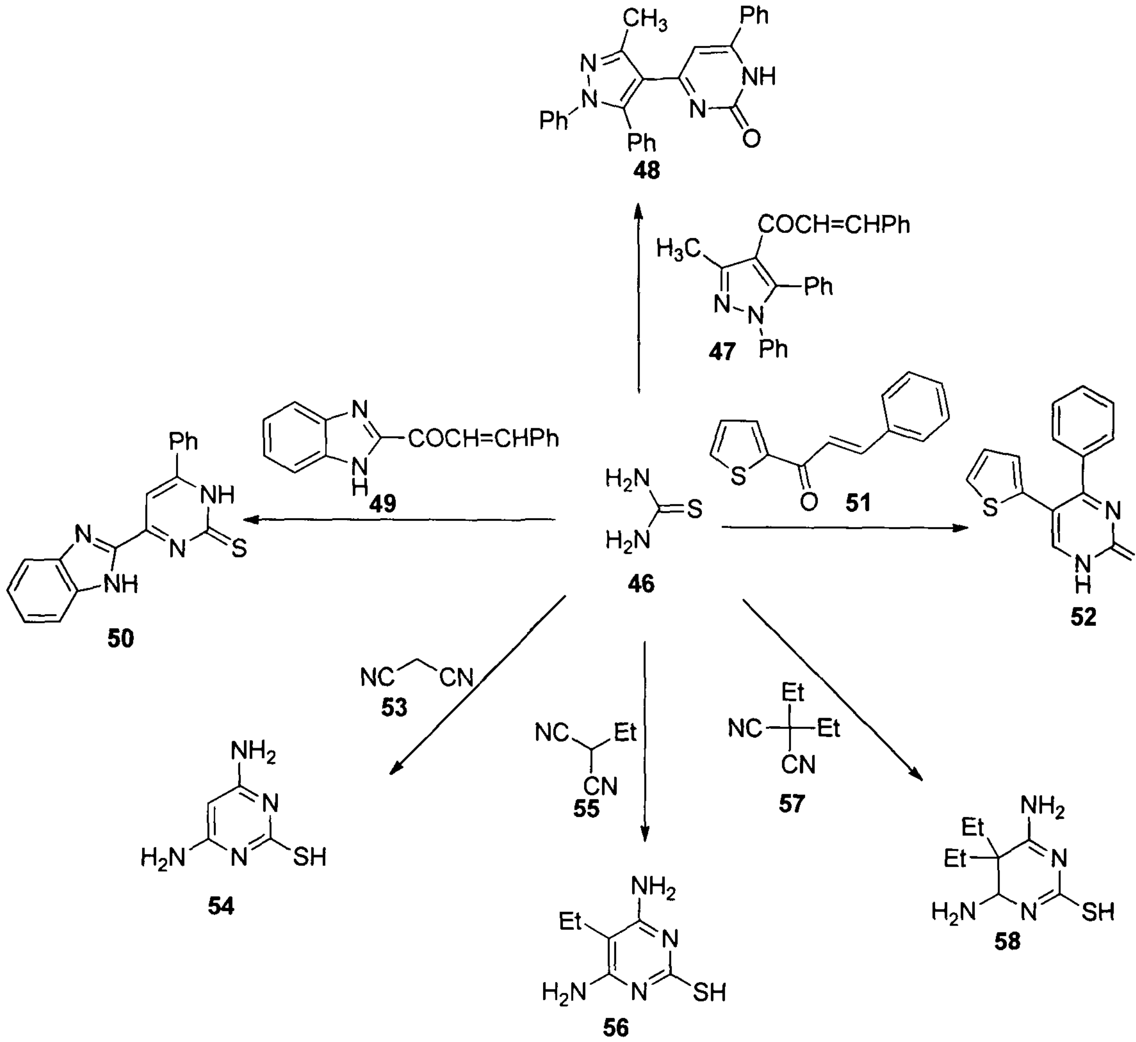
Curran and co-workers[55] adapted fluorous-phase chemistry towards the synthesis of dihydropyrimidines. These strategies are based on the high ability of fluorinated compounds mixed with the fluorinated solvents. The reaction mixture was purified by a liquid-liquid extraction method since the by-products were not soluble in the fluorinated solvent. Curran has prepared fluorinated ureas (**44**), which underwent the Biginelli reaction and were cleanly extracted into fluorinated hexanes. Desilylation affords *N*-1 substituted dihydropyrimidines (**45**). The yields for the fluorous-phase reaction are comparable to reactions performed under standard Biginelli reaction conditions (**Scheme-6**). However, the fluorous methodology required the synthesis of fluorinated ureas and the use of expensive fluorinated solvents.



Scheme-8

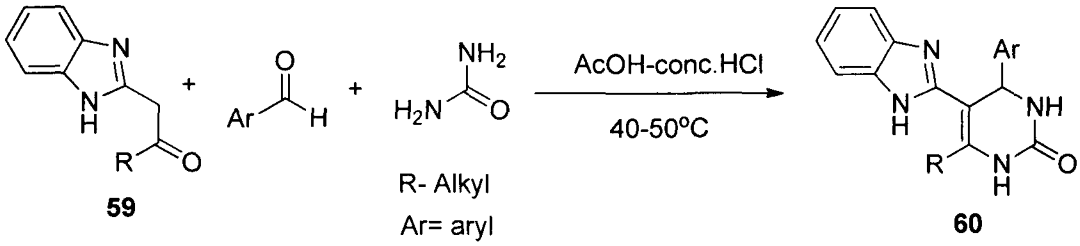
In many of the reported reactions, thiourea (**46**) serves as the starting material for the synthesis of pyrimidine thione. Variety of heterocyclic chalcones were used in the synthesis of pyrimidine with heterocyclic moiety at 4 or 6 position, thus the use of 4-cinnamoyl-3-methyl-1,5-diphenylpyrazole (**47**), 2-cinnamoylbenzimidazole (**49**) and benzal-α-acetothienone (**51**), afforded pyrimidine-2-thione **48, 50, 52** respectively.[56]

Thiourea reacts with malononitriles (**53**) to give 4,6-diamino-2-mercaptopyrimidine (**54**), ethylmalononitrile (**55**) and diethyl malononitrile, (**57**) gives 5-ethyl and 5,5-diethyl, derivatives **56** and **58**.[57]



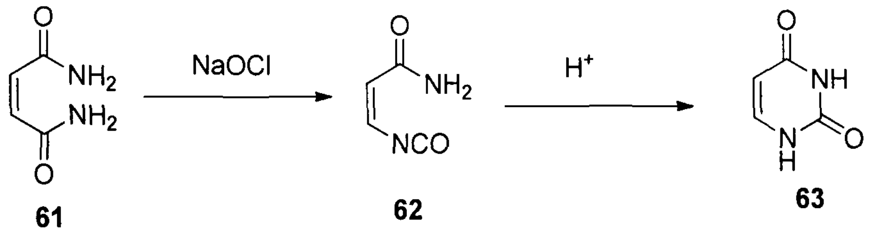
Scheme-9

Dzvinchuk and co-workers,[58] have reported the synthesis of pyrimidone derivatives from cyclocondensation of 2-phenacylbenzimidazole (**59**) with aldehydes and urea which leads to the formation of previously unknown 4-aryl-5-(2-benzimidazolyl)-2-oxo-1,2,3,4-tetrahydro-6-phenylpyrimidines (**60**).



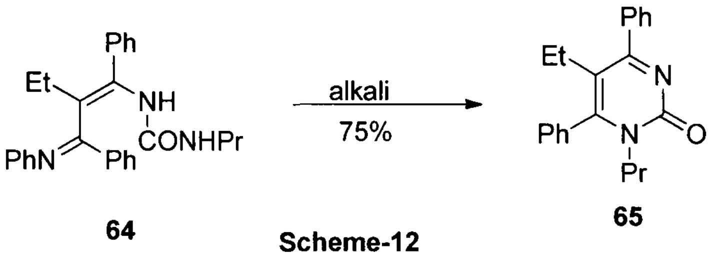
Scheme-10

Barluenga and co-workers[59] have reported the synthesis of pyrimidine derivatives by reacting appropriate diamides (**61**) with NaOCl which undergoes Hoffmann type degradation via the formation of an isocyanate intermediate **62** followed by cyclization to give pyrimidinedione (**63**).



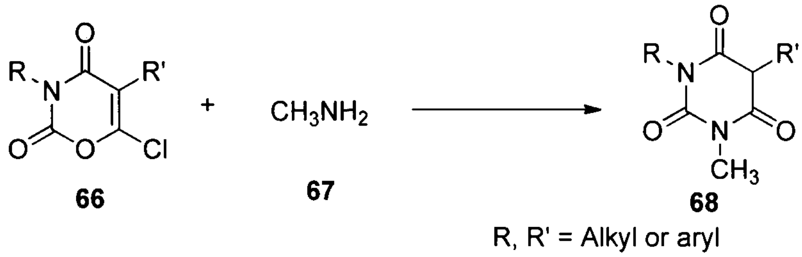
Scheme-11

The formation of 4,6-diphenyl-1-propyl-2(1*H*) pyrimidinone (**65**) from propylurido substrate was reported by Nishio and Omote in 1984.[60] The uriedo nitrogen in the propylurido substrate **64** was made nucleophilic by carrying out the reaction under alkaline conditions which upon cyclization gives the desired product.



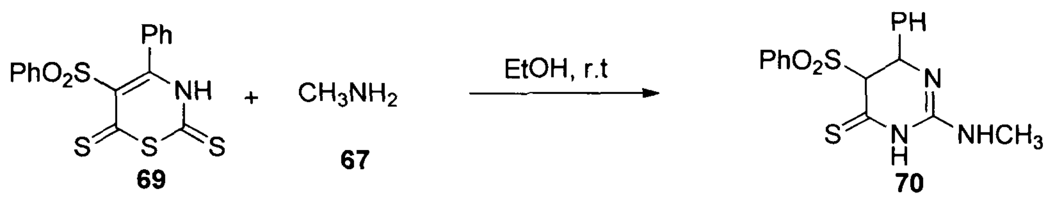
Scheme-12

Derivatives of pyrimidine can also be synthesized from other heterocyclic compounds such as thiazine, oxazine, oxazoles etc., by ring transformation method. Aminolysis of 6-chloro-1,3-oxazine-2,4-diones (**66**) with primary aliphatic amines such as methyl amine (**67**) gave 1,3-dimethylbarbituric acid (**68**).[61]



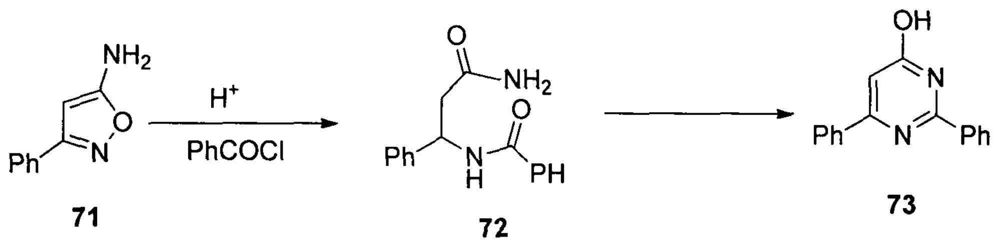
Scheme-13

Pyrimidine formation from thiazine (**Schme-14**) involves a Dimroth like rearrangement of thiazinamine, an aminolytic displacement of the ring sulphur atom or combination of both where an aqueous ethanol in methylamine converts 4-phenyl-5-phenylsulfonyl-(2*H*)-1,3-thiazine-2,6(3*H*)-dithione (**69**) into pyrimidine (**70**) by displacement of the ring sulfur and a nucleophilic substitution of the thioxo sulfur in the 2-position.[62]



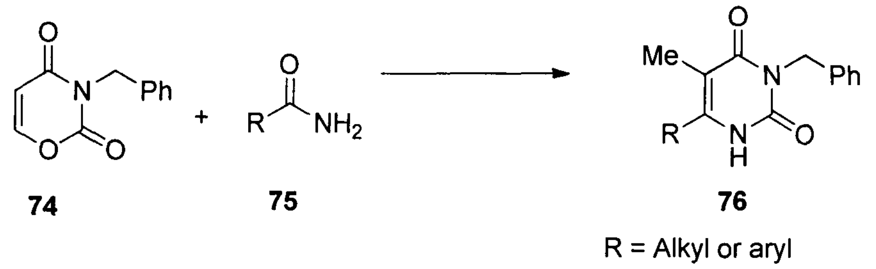
Scheme-14

Hydrogenation of 5-amino-3-phenylisoxazole (**71**) to **72**, followed by cyclization in warm aqueous alkali gives 4-hydroxy-2,6-phenylpyrimidine (**73**).[63]



Scheme-15

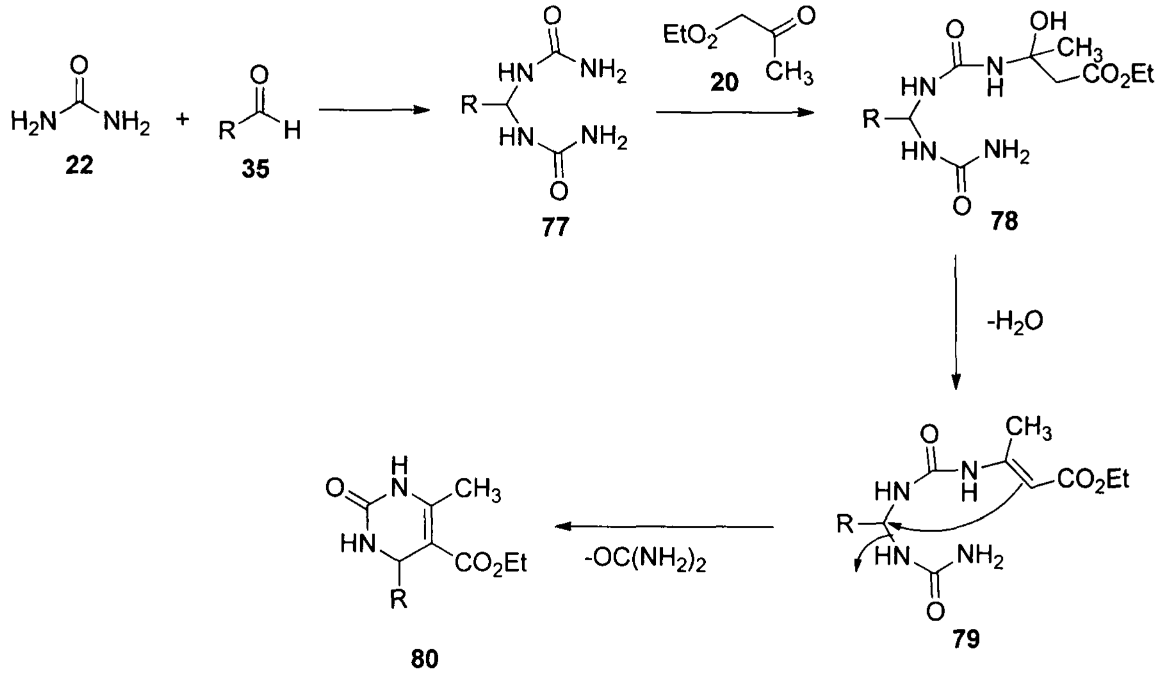
The reaction of 1,3-oxazine (**74**) with amides or thioamides (**75**) resulted in ring transformation affording 6-alkyl and 6-aryl-5-acetyl-3-benzyluracil derivative **76**.[64]



Scheme-16

II.3. Mechanistic studies

Forty years after Biginelli's initial report, the first mechanism for the synthesis of DHPMs (Biginelli reaction) were conducted by Folkers and Johnson in 1933.[65a] Reaction dependence on acid catalysis was experimentally established.



Scheme-17

Four possible combinations of the three reaction components were examined for the generation of dihydropyrimidine (**80**) (**Scheme-17**):

A. the intermolecular reaction between benzaldehyde, ethyl acetoacetate and urea,

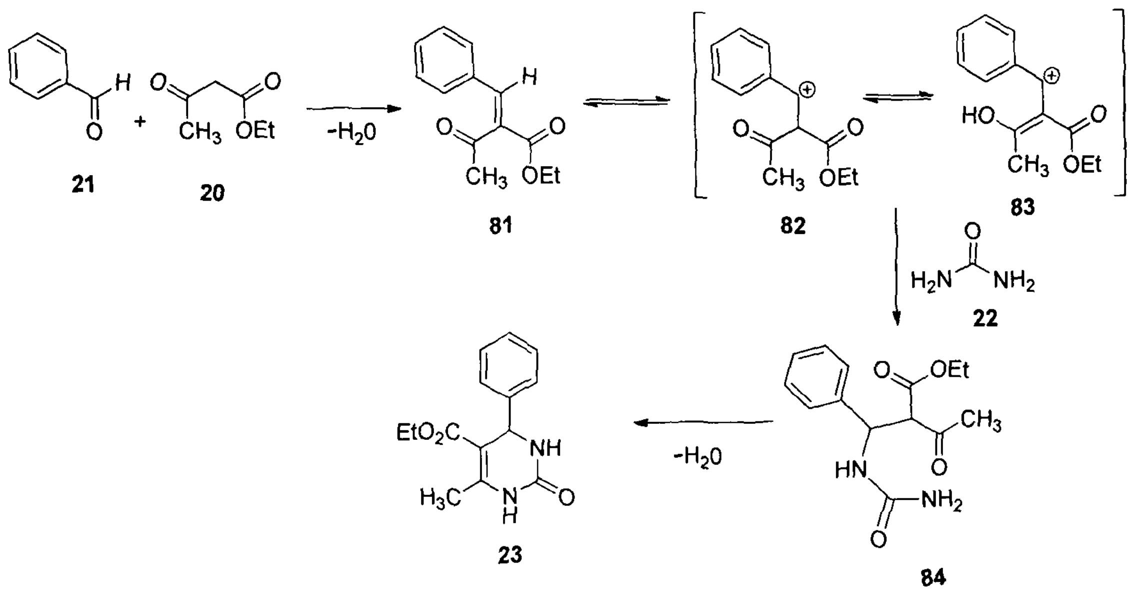
B. the combination of ethyl acetoacetate and benzal bisurea,

C. the reaction of benzaldehyde and ethyl β-carbamidocrotonate and

D. the reaction of ethyl α-benzalacetoacetate and urea.

Folkers and Johnson based their mechanistic conclusions on the reaction yields and visual observations. They proposed that the simultaneous combination of the three components in **A** was improbable. **D** was ruled out on the basis of the low reaction yields (2%). In contrast, **B** and **C** gave high yields of 80%. The authors noted that **B** may undergo fragmentation of the benzal-bisurea, regenerating the three reaction components, which may then form the product by another pathway. Further, the authors posit that the β-carbamidocrotonate in **C** hydrolyzes to the original three reaction components. Therefore, they concluded that **80** is likely to be formed from the cyclization of **79**, which was generated from either **B** or **C**. Folker's suggestion was confirmed by Mamaev and Dubovenko[65b] who showed that bis-ureides such as **77** readily reacted with β-dicarbonyl compounds **20** to afford DHPMs. Recently, Valverde and colleagues have reported that in a modified Biginelli procedure with polymer-bound acetoacetate, the *bis*-ureides initially precipitated from the reaction mixture and eventually are converted to DHPMs upon longer reaction time.[65c]

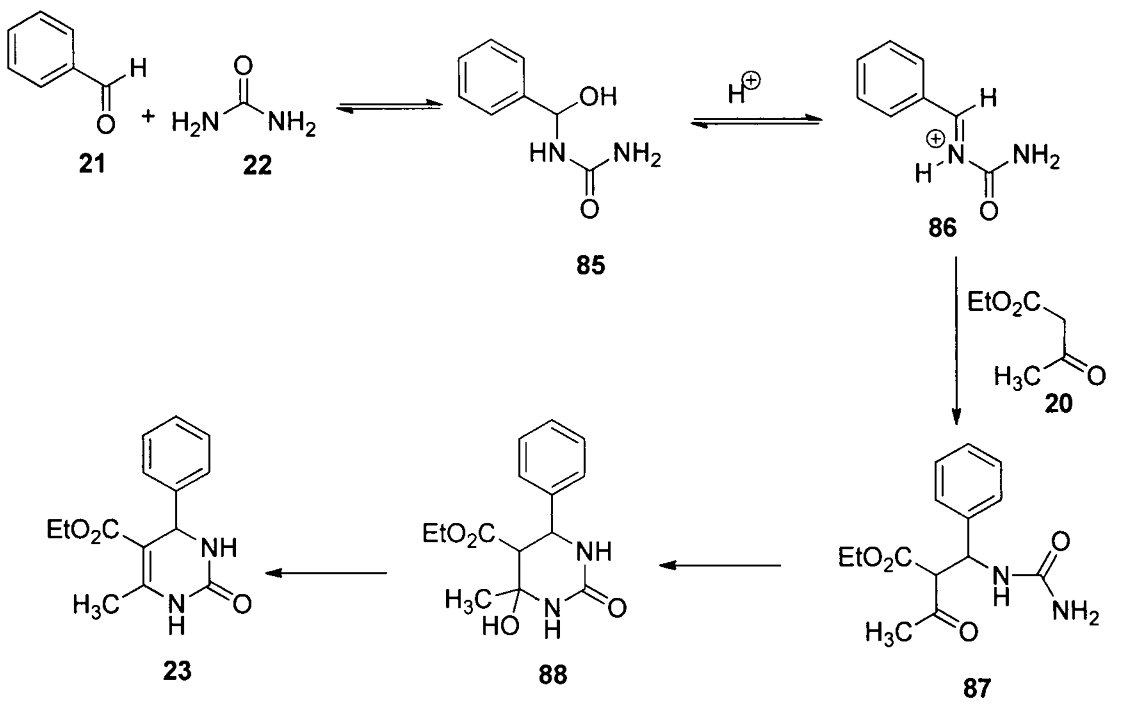
Again in 1973, a second mechanistic proposal was suggested by Sweet and Fissekis, forty years after Folker's pioneering work.[66]



Scheme-18. Sweet and Fissekis Mechanism

The proposal involved an aldol condensation between benzaldeyde and ethyl acetoacetate to form a stabilized carbenium ion (**82** and **83**) derived from either aldol intermediate or from enone 37. Trapping with *N*-methylurea gave **84**, which cyclized to form **23** (**Scheme-18**). The observation that, independently prepared **81** reacted with urea under acidic conditions to generate **23** provided evidence in support of this mechanism.

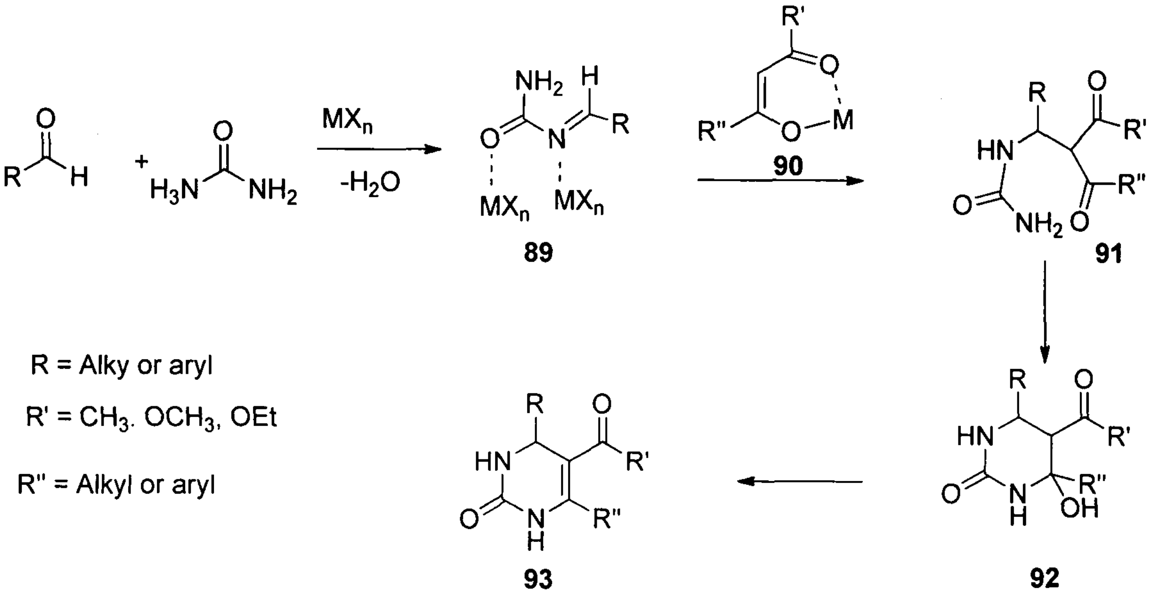
The plausible mechanism for the acid-catalyzed condensation was finally postulated and definitively proved in 1997 by Kappe.[67] The key step involves the formation of *N*-acyliminium ion (**86**) following the ureidoalkylation to form the open-chain ureide (**87**) which undergoes cyclization to the hexahydropyrimidine (**88**) and subsequent elimination of water leads to the final DHPM (**23**) (**Scheme-19**).



Scheme-19. Kappe Mechanism

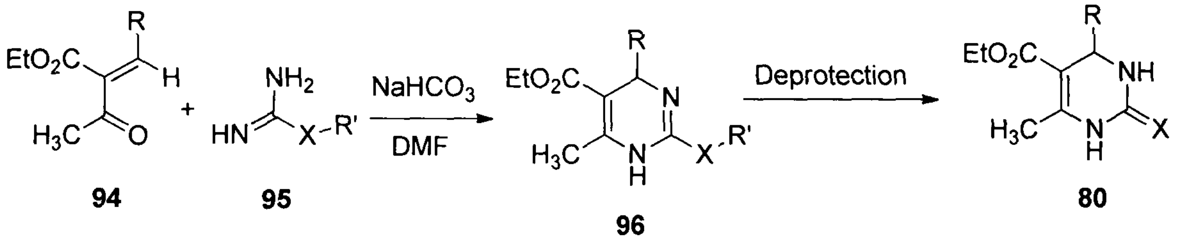
Kappe further explored the mechanism of the Biginelli reaction using NMR spectroscopy and trapping experiments. He proposed the formation of *N*-acyliminium (**86**) from benzaldehyde and urea *via* an unobservable (^{1}H NMR) hemiaminal (**85**) (**Scheme-19**). Interception of **86** with the enol tautomer of ethyl acetoacetate gave **87**, the precursor to dihydropyrimidine (**23**). Kappe suggested that the first step, formation of **85**, is rate limiting, thus preventing the observation of intermediates **86** and **87** by NMR. Kappe's proposal is currently the accepted mechanism for the Biginelli reaction.

The "carbenium ion mechanism" suggested by Sweet and Fissekis does not play any significant role, being a side reaction which gives aldol by-products like **81**.[66] However, the mechanism proposed by Kappe can take place only in highly acidic media when Bronsted acids (or precursors which release a protic acid, i.e., in spite of hydrolysis) were employed as catalysts, but in the case of Lewis acids there is no reaction. Generally, the formation of acyl imine intermediates (**89**) coordinated with Lewis acid either via a nitrogen atom lone pair or both the *O*- & *N*-atom pairs is supposed to be the key and rate-limiting step of the reaction. Next, the addition of a β-keto ester enolate (**90**) followed by cyclodehydration of open-chain ureide (**91**) would afford target DHPMs. Note that this mechanism does not fit all reported cases and cannot be realized when catalysts such as TEBA,[68] ionic liquids,[69] graphite[70] or baker's yeast [71] are employed.



Scheme-20. lewis acid catalysed reaction

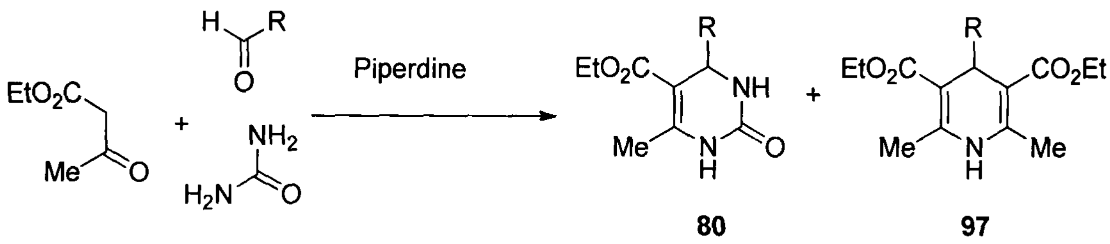
Another reliable approach to Biginelli compounds (**80**) was reported in 1987 by K. Atwal and co-workers[72] (**Scheme-21**). In the first step an unsaturated ketoester is condensed with a suitable protected urea or thiourea derivative (**95**) in the presence of sodium bicarbonate. The reaction presumably proceeds through a Michael addition pathway and affords dihydropyrimidines (**96**). Deprotection with HCl or trifluoroacetic acid/ethanol leads to the desired Biginelli compounds in high overall yield. Although this method requires prior synthesis of the unsaturated ketoesters (**94**), its reliability and broad applicability makes it an attractive alternative to the standard Biginelli condensation. It should be noted that this approach requires basic media in the first stage.



R = Aromatic or aliphatic
R' = H or -CH_3

Scheme-21. Atwal modification.

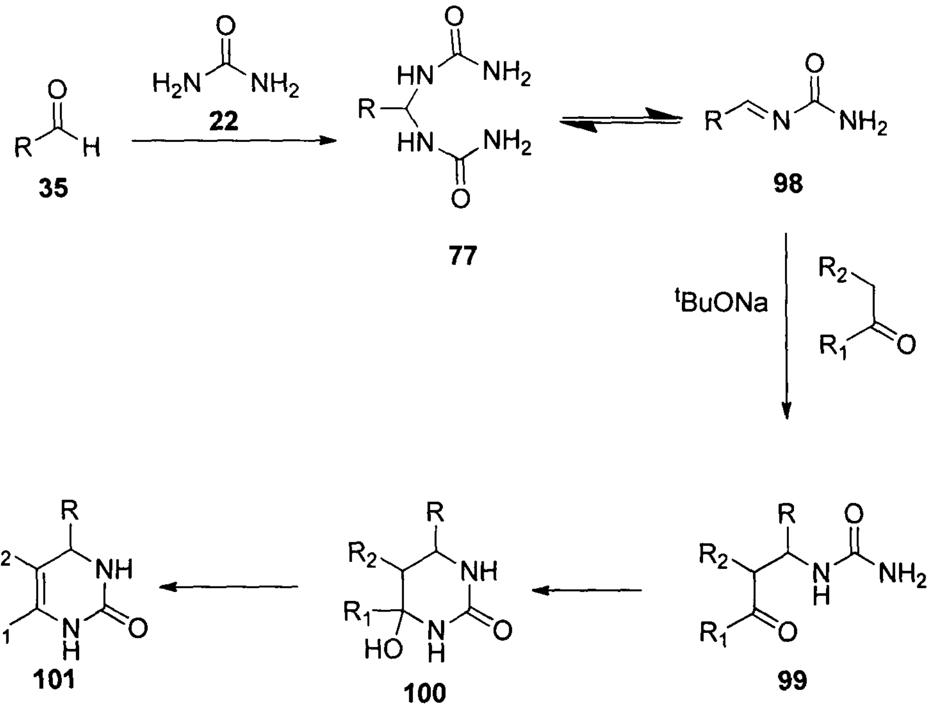
Finally, base-catalyzed approach to the synthesis of DHPMs was developed by Bakibaev and Filimonov[73] (**Scheme-22**). They found that piperidine can promote the reaction to afford corresponding DHPMs along with, Hantzsch 1,4-dihydropyridines (**97**) as by-products and presumably the latter were formed in spite of the decomposition of urea, releasing ammonia.



R = Alkyl or aryl

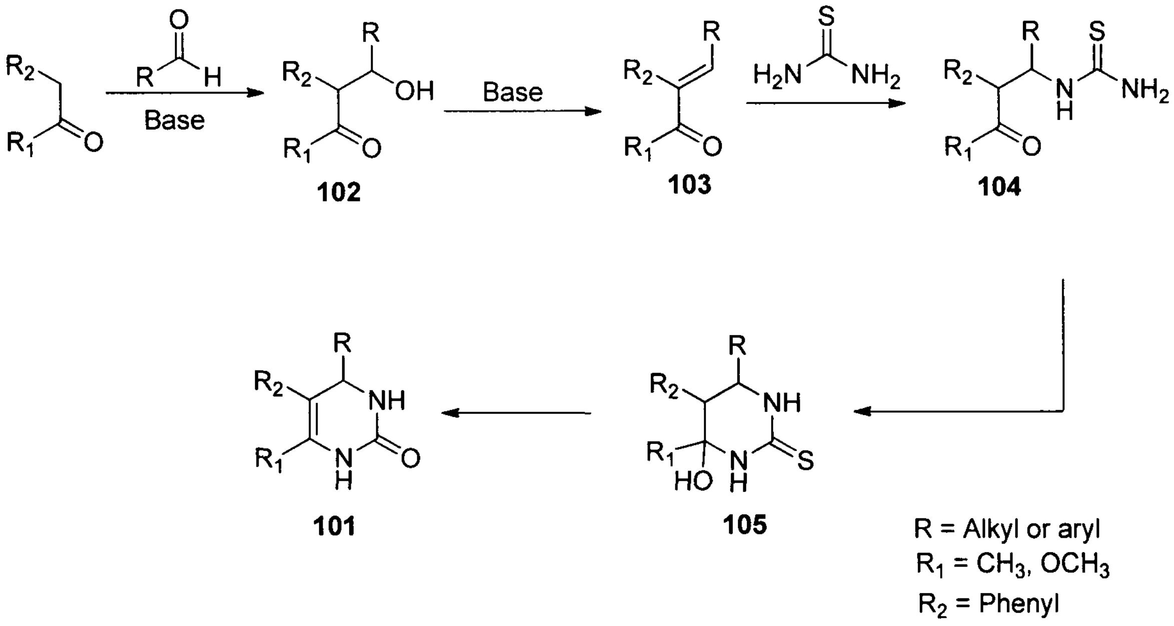
Scheme-22

The first Bronsted base mediated one-pot Biginelli-type reaction for the synthesis of dihydropyrimidinones was reported by Shen *et al*,[74] and reported that the Biginelli-type reaction using urea and thiourea proceeds through two totally different pathways. According to their observations, two plausible reaction mechanisms were proposed for the Bronsted base-mediated reaction.



R = Alkyl or aryl
$R_1 = CH_3, OCH_3$
R_2 =Phenyl

Scheme-23a. Mechanism using urea as substrate



R = Alkyl or aryl
$R_1 = CH_3, OCH_3$
R_2 = Phenyl

Scheme-23b. Mechanism using thiourea as substrate

When urea is used as substrate, the reaction is proposed to initiate *via* the formation of an equilibrium mixture of intermediates **77** and **98**. When compound **22** is present, it reacts with either intermediate **77** or **98** to generate compound **99**. Compound **99** further cyclizes under base catalysis and finally afford the desired product **101** upon elimination of the hydroxyl group. The reaction using thiourea (**Scheme-23b**) is initiated by the aldol condensation of aldehyde with acetophenone, followed by elimination of the resulting hydroxyl group to give enone (**103**). Subsequent base-catalyzed Aza-Michael addition of thiourea to enone (**103**) leads to the formation of Michael adducts (**104**). Finally, 1,2-addition of amino group (-NH_2) to the carbonyl group followed by *in situ* elimination of the hydroxyl group affords the desired product **101**.

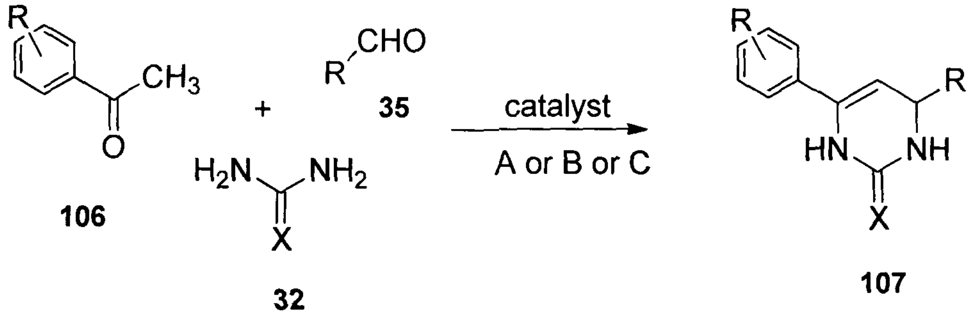
II.4. Results and discussions

Our literature survey reveals that in almost all the reported methods, DHPMs have been synthesized, whereby diketones or ketoesters were used as starting materials and the reactions were carried out in acidic medium or in presence of acid catalysts. We have developed a convenient route for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones or thiones (**107**) (**Scheme-24**) and 3,4,5,6,7,8-hexahydroquinazolin-2(1*H*)-one or thiones (**109**) (**Scheme-25**) starting from enolisable ketones (substituted acetophenones or cyclohexanone) and aromatic aldehydes. The one pot synthesis of the titled compound is achieved *via* chalcone formation, which is generated *in situ* by the condensation of ketones with aromatic aldehydes in presence of sodium tertiary butoxide or *p*-toluenesulfonic acid (PTSA) followed by the cyclisation with urea or thiourea to give the products (**Table I** and **II**). The reaction was also carried out under Microwave irradiation without using solvent. The results of the conventional process and the MWI process were compared which revealed that the latter process gave a comparatively higher yield in a shorter reaction time (**Table III**).

Solvent free reactions[74] in fine chemical synthesis are of increasing interest to synthetic organic chemists and industrialists. The development of solvent-free synthesis using microwave irradiation (MWI) technique has contributed significantly to the eco-friendly synthesis due to the increasing environmental consciousness worldwide. In continuation with our investigations on the methodology of green synthesis, we report herein a three-component cyclocondensation of acetophenone, aldehyde and urea /thiourea to synthesise pyrimidinone derivatives using inexpensive *p*-toluenesulfonic acid as catalyst under solvent-free condition and microwave irradiation, which is an efficient and environmentally friendly method. In all of the studied examples, the reaction proceeded smoothly; aromatic aldehydes having either electron-withdrawing or electron-releasing substituents reacted efficiently to give very good to excellent yields of the desired dihydropyrimidinones. Besides compound **107a, 107b, 107c** and **107d** which are known compounds, all other compounds **107(e-y)** and **109(a-h)** are new compounds, to the best of our knowledge. The analytical and spectral data of the known compounds are compared with the reported values.

In both the acid catalysed and base catalysed reactions, the product is expected to form *via* enone (**103**) intermediate which is in contrast to the mechanism proposed by Shen and co-workers[74] where the use of urea and thiourea as substarte proceeds through different pathways. When the three reactants *i.e*, ketone, aldehyde and urea are taken in the ratio 1:1:1, the yield are low as compared to the reactant ratio of 1:1:1.5. Therefore in all the reaction the urea or thiourea is taken in 50% excess than aldehyde and ketone. Excess of urea/thiourea and *p*-toluenesulfonic acid (*p*-TsOH) as well as sodium tertiary butoxide can be easily removed from the crude product by washing with water during work-up as they are water soluble.

In summary, this procedure discloses a rapid and simple protocol for the pyrimidinone synthesis through the use of readily available *p*-TsOH or sodium tertiary butoxide as reaction mediator. The excellent yields with short reaction time, makes this method better than many existing ones.

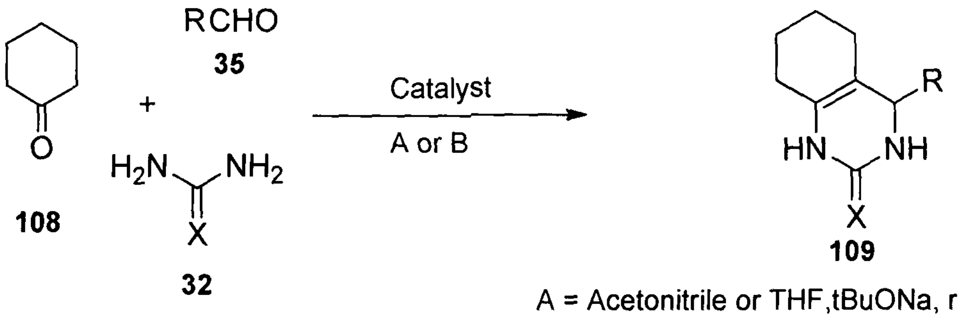


A = Acetonitrile or THF,tBuONa, refluxed

B = MWI, tBuONa, Solvent free.

C = MWI, PTSA, Solvent free

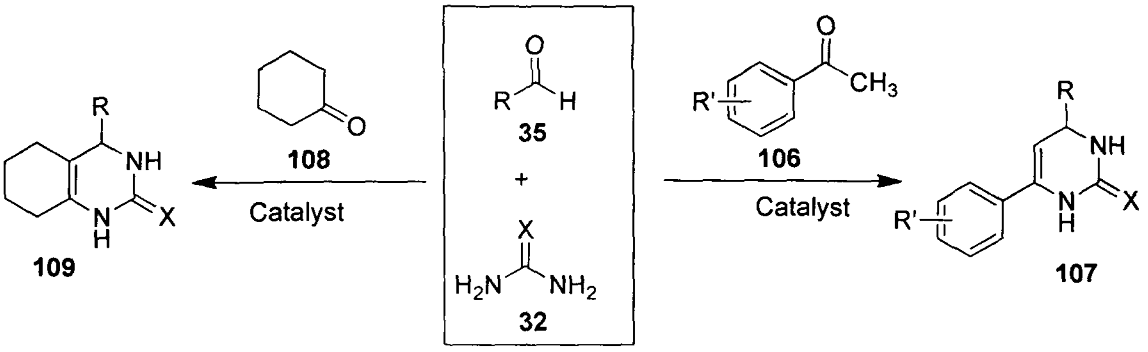
Scheme-24



A = Acetonitrile or THF,tBuONa, refluxed

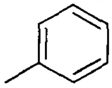
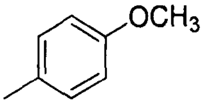
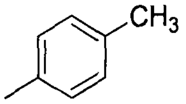
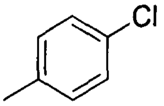
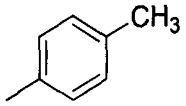
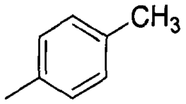
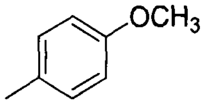
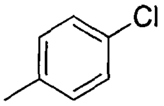
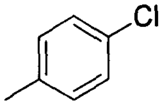
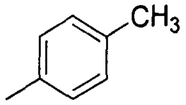
B = MWI, tBuONa, Solvent free.

Scheme - 25



Scheme-26

Table-I: Preparation of 4,6-disubstituted-3,4-dihydropyrimidin-2(1*H*)-ones

R	R'	X	Product	Yield (%)
	H	O	**107 a**	76
	H	O	**107 b**	82
	H	O	**107c**	79
	H	O	**107d**	68
	4-CH3	O	**107e**	81
	4-OCH3	O	**107f**	76
	4-Cl	O	**107g**	69
	4-CH3	O	**107h**	68
	4-OCH3	O	**107i**	68
	4-OCH3	O	**107j**	80

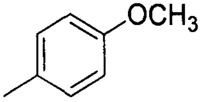
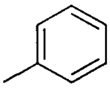
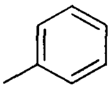
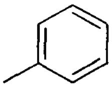
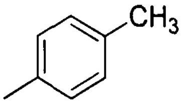
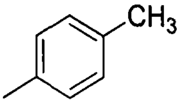
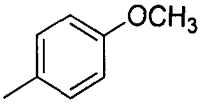
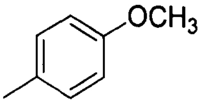
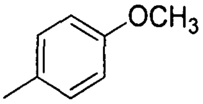
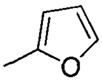
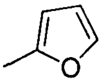
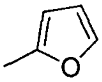
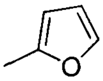
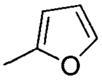
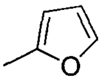
R	R'	X	Product	Yield (%)
	4-OCH3	O	**107k**	74
	H	S	**107l**	73
	4-CH3	S	**107m**	66
	4-OCH3	S	**107n**	68
	H	S	**107o**	74
	4-OCH3	S	**107p**	76
	H	S	**107q**	78
	4-CH3	S	**107r**	76
	4-Cl	S	**107s**	68
	H	O	**107t**	71
	4-CH3	O	**107u**	67
	4-OCH3	O	**107v**	69
	4-CH3	S	**107w**	65
	4-OCH3	S	**107x**	67
	H	S	**107y**	68

Table-II: Preparation of 3,4,5,6,7,8-hexahydroquinazolin-2(1*H*)-ones

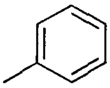
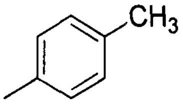
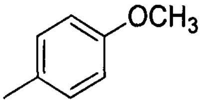
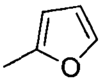
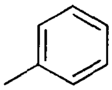
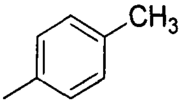
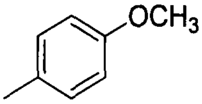
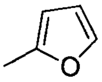
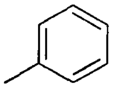
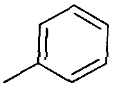
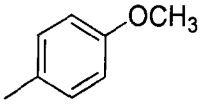
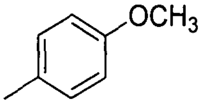
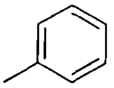
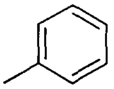
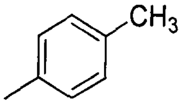
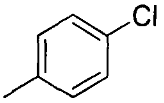
R	X	Product	Yield %
	O	**109a**	75
	O	**109b**	64
	O	**109c**	71
	O	**109d**	65
	S	**109e**	69
	S	**109f**	64
	S	**109g**	68
	S	**109h**	70

Table-III: Comparison between Conventional and MWI process

Product	Reaction Time		Yield (%)	
	Conventional heating (Hours)	Microwave heating (Seconds)	Conventional Heating	Microwave heating
107a	4	180	76	83
107l	4.5	180	73	81
107n	6	240	68	80
107q	6	240	65	78
107y	5	180	67	80
109f	6	240	65	72
109h	6	240	68	75

Table IV. List of the title compound synthesized using acidic catalyst (PTSA) with reaction time and yields.

Entry	**R**	**R_1**	**X**	**Reaction Time (Min)**	**Yield (%)[a]**
107a		H	O	7	76
107l		H	S	7	69
107b		H	O	5	67
107q		H	S	5	65
107f		4-OCH_3	O	5	72
107n		4-OCH_3	S	5	65
107c		H	O	6.5	67
107j		H	O	6	63

[a] refer to isolated yields.

II.5. Experimental Section

Melting points were determined in open capillary tubes and are uncorrected. Infrared spectra were recorded on a BOMEM DA-8 FTIR instrument and the frequencies are expressed in cm.$^{-1}$ ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance II-400 spectrometer using $CDCl_3$ as the solvent. Chemical shifts are reported in ppm downfield from internal tetramethylsilane and are given on the δ scale. Mass spectral data were obtained with a JEOL D-300 (EI) mass spectrometer. Elemental analyses were carried out on a Heraeus CHN-O-Rapid analyzer. Microwave reactions were carried out in a CEM Discover Benchmate microwave digester. All compounds give satisfactory elemental analyses within ± 0.4% of the theoretical values. All reactions were monitored by TLC using precoated aluminum sheets (silica gel 60 F_{254} 0.2 mm thicknesses) and developed in an iodine chamber or under UVGL-15 mineral light 254 lamp. Column chromatographic separations were carried out using ACME silica gel (60–120 mesh).

General Procedure

A. Conventional Method

To a well stirred solution of sodium tertiarybutoxide (1 g) in acetonitrile or THF, ketone (1mmol) was added, followed by aldehyde (1mmol). The mixture was stirred for about 5 minutes and then Urea/ Thiourea (1.5mmol) in ethanol was added and the mixture was refluxed for about three to six hours till the reaction was completed (monitored by TLC). The mixture was then cooled to room temperature and poured into water with continuous stirring when the solid product separated out. The crude solid product was purified by repeated recrystallisation from alcohol or by column chromatography using dichloromethane/methanol as eleunt, to give the pure products. (**Table I** and **II**).

B. Microwave method

A mixture of ketone (1mmol), aldehyde (1mmol), urea/thiourea (1.5mmol) and sodium tertiary butoxide (1g) was grounded thoroughly and irradiated in a microwave digester at 300 W and 100°C for about 3 to 4 minutes at an interval of 30 seconds. After the completion of the reaction, (monitored by TLC) the reaction mixture was cooled to room temperature and water was added with stirring when the solid product precipitated out which was then filtered. The crude product was washed with water followed by hexane. It was purified by recrystallisation from alcohol or by column chromatography using dichloromethane/methanol as eleunt to give the pure products in good to excellent yields.

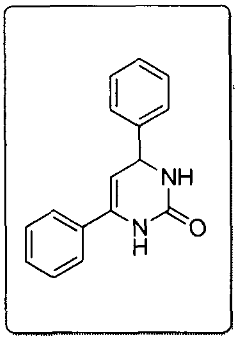
C. Microwave method using PTSA as catalyst.

To a mixture of acetophenone (1 mmol), aldehyde (1 mmol) and urea/thiourea (1.5 mmol), a catalytic amount of *p*-toluenesulfonic acid was added and grounded thoroughly. The mixture was then subjected to Microwave Irradiation in Microwave Digester at 100°C, 200 watts and a pressure of 5 bar for the specified time **(Table-IV)**. After completion of the reaction (monitored by TLC), the reaction mixture was treated with water to remove the catalyst and the unreacted urea/thiourea and was extracted with ethylacetate (3 x 5 mL). The combined extract were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure to give the crude product which was purified by recrystallisation from alcohol mixture or by column chromatography using dichloromethane/methanol as an eluent.

All the products were characterised by melting point, ^{1}HNMR, ^{13}CNMR, IR, Mass spectra and CHN analysis.

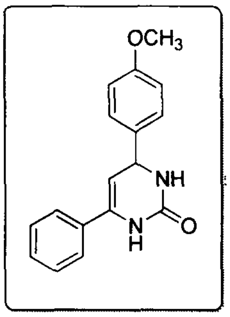
Spectral and analytical data:

4,6-diphenyl-3,4-dihydropyrimidin-2(1*H*)-one (107a):



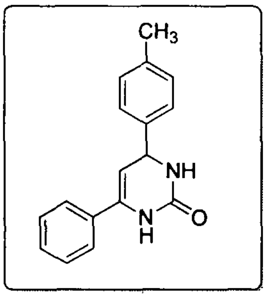
Mp 240-242°C (lit.[44e] mp 245-246°C); IR (KBr, cm^{-1}): 3283, 2032, 1672, 1600, 1447; ^{1}H NMR (CDCl$_3$): δ 5.11 (d, 1H, CH), 5.46 (d, 1H, CH), 7.10–8.02 (m, 10H, ArH), 9.15 (s, 1H, NH), 9.31 (s, 1H, NH); ^{13}C NMR (CDCl$_3$): δ 52.91, 98.55, 125.68, 126.01, 126.98, 127.00, 127.71, 127.99, 132.31, 141.27, 135.61, 168.97; Mass: m/z 250 [M$^+$]; Anal. Calcd for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19; Found: C, 76.42; H, 5.33; N, 11.27%.

4-(4-methoxyphenyl)-6-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (107b):



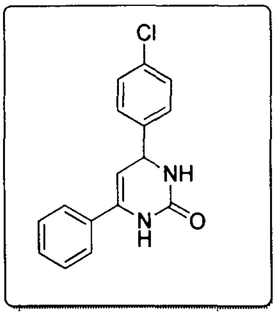
Mp 252-254°C (lit.[47d] mp 259-261°C); IR (KBr, cm^{-1}): 3348, 2932, 1654, 1535, 1421; ^{1}H NMR (CDCl$_3$): δ 3.69 (s, 3H, OCH$_3$), 5.27 (d, 1H, CH), 5.89 (d, 1H, CH), 7.17-7.85 (m, 9H, ArH), 8.07 (s, 1H, NH), 9.25 (s, 1H, NH); ^{13}C NMR (CDCl$_3$): δ 52.47, 57.83, 115.23, 118.32, 126.43, 127.81, 129.38, 130.81, 131.21, 134.81, 145.92, 163.18; Mass: m/z 280 [M$^+$]; Anal. Calcd. For $C_{17}H_{16}N_2O$; C, 72.84; H, 5.75; N, 9.99; Found: C, 72.82; H, 5.78; N, 10.02%.

6-phenyl-4-(*p*-tolyl)-3,4-dihydropyrimidin-2(1*H*)-one (107c):



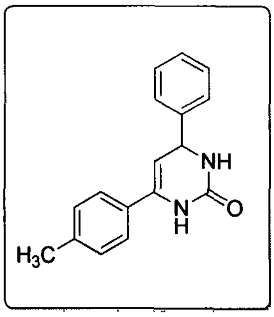
Mp 243-245°C (lit.[47d] mp 248-250°C); IR (KBr, cm^{-1}): 3232, 2915, 1637, 1589, 1416 ; ^{1}H NMR (CDCl$_3$): δ 2.54 (s, 3H, CH$_3$), 5.45 (d, 1H, CH), 5.63 (d, 1H, CH), 7.08–7.88 (m, 9H, ArH), 8.56 (s, 1H, NH), 9.21 (s, 1H, NH); ^{13}C NMR (CDCl$_3$): δ 23.87, 58.11, 98.23, 120.81, 124.91, 126.81, 127.00, 127.86, 128.23, 129.17, 133.20, 139.80, 159.76; Mass: m/z 264 [M$^+$]; Anal. Calcd for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60; Found: C, 77.33; H, 5.89; N, 10.58%.

4-(4-chlorophenyl)-6-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (107d):



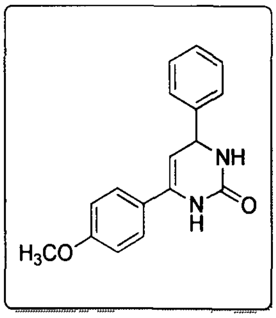
Mp 266–268°C (lit.[44d] mp 267-269°C); IR (KBr, cm^{-1}): 3224, 2937, 1678, 1568; ^{1}H NMR (CDCl$_3$): δ 5.17 (d, 1H, CH), 5.65 (d, 1H, CH), 7.30–7.71 (m, 9H, ArH), 8.18 (s, 1H, NH), 9.54(s, 1H, NH); ^{13}C NMR (CDCl$_3$): δ 55.21, 56.43, 97.44, 126.34, 127.89, 128.54, 129.14, 130.21, 136.74, 138.32, 141.42, 150.35; Mass: m/z 284 [M$^+$]; Anal. Calcd for $C_{16}H_{13}N_2OCl$: C, 67.49; H, 4.60; N, 9.84; Found: C, 67.34; H, 4.52; N, 9.92%.

4-phenyl-6-(*p*-tolyl)-3,4-dihydropyrimidin-2(1*H*)-one (107e):



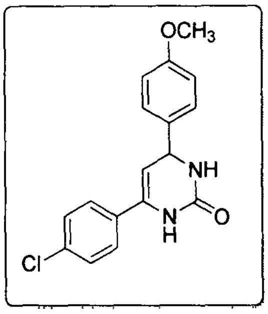
Mp 202-203°C; IR (KBr, cm^{-1}): 3266, 2951, 1617; ^{1}H NMR (CDCl$_3$): δ 2.38 (s, 3H, CH$_3$), 5.67 (d, 1H, CH), 5.91 (d, 1H, CH), 7.14–7.39 (m, 9H, ArH), 8.75 (s, 1H, NH), 9.08(s, 1H, NH); ^{13}C NMR (CDCl$_3$): δ 21.82, 55.89, 97.67, 125.33, 126.38, 127.65, 128.82, 129.06, 135.22, 136.49, 137.23, 143.75, 150.28; Mass: m/z 264 [M$^+$]; Anal. Calcd for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60; Found: C, 77.07; H, 6.25; N, 10.42%.

(6-(4-methoxyphenyl)-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (107f):



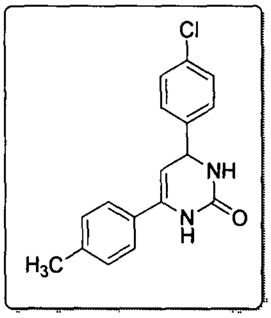
Mp 210-213°C; IR (KBr, cm^{-1}): 3243, 2932, 1611; ^{1}H NMR (CDCl$_3$): δ 3.75 (s, 3H, OCH$_3$), 5.59 (d, 1H, CH), 5.88 (d, 1H, CH), 6.98–7.41 (m, 9H, ArH), 8.59 (s, 1H, NH), 9.27(s, 1H, NH); ^{13}C NMR (CDCl$_3$): δ 54.84, 55.64, 97.42, 121.25, 126.12, 127.09, 128.61, 129.77, 13.62, 136.67, 143.45, 150.56, 159.71; Mass: m/z 281 [M$^+$]; Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99; Found: C, 72.60; H, 5.85; N, 9.78%.

6-(4-chlorophenyl)-4-(4-methoxyphenyl)-3,4-dihydropyrimidin-2(*1H*)-one (107g):



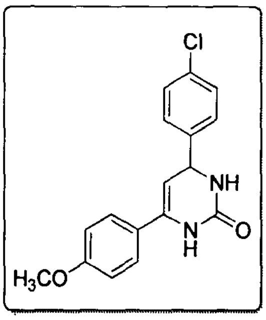
Mp 260-262°C; IR (KBr, cm^{-1}): 3241, 2978, 1597, 1434; ^{1}H NMR (CDCl$_3$): δ 3.77 (s, 3H, OCH$_3$), 5.33 (d, 1H, CH), 5.74 (d, 1H, CH), 6.91–7.52 (m, 8H, ArH), 8.13 (s, 1H, NH), 9.45(s, 1H, NH); ^{13}C NMR (CDCl$_3$): δ 55.12, 56.23, 97.55, 114.34, 120.89, 125.65, 128.76, 133.32, 135.93, 136.86, 137.35, 150.45, 158.78; Mass: m/z 314 [M$^+$]; Anal. Calcd for C$_{17}$H$_{15}$N$_2$O$_2$Cl: C, 64.87; H, 4.80; N, 8.90; Found: C, 64.65; H, 4.89; N, 8.74%.

4-(4-chlorophenyl)-6-(*p*-tolyl)-3,4-dihydropyrimidin-2(1*H*)-one (107h):



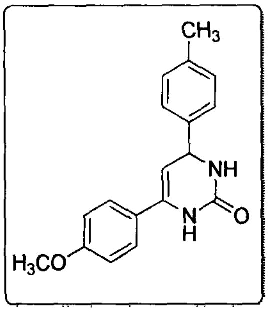
Mp 251-252°C; IR (KBr, cm^{-1}): 3312, 3013, 1611, 1454; ^{1}H NMR (CDCl$_3$): δ 2.48 (s, 3H, CH$_3$), 5.44 (d, 1H, CH), 5.92 (d, 1H, CH), 7.15–7.57 (m, 8H, ArH), 8.09 (s, 1H, NH), 9.38 (s, 1H, NH); ^{13}C NMR (CDCl$_3$): δ 22.18, 55.93, 97.32, 126.84, 127.63, 128.53, 129.09, 132.40, 135.09, 136.67, 138.12, 141.78, 150.65; Mass: m/z 298 [M$^+$]; Anal. Calcd for C$_{17}$H$_{15}$N$_2$O$_2$Cl: C, 68.34; H, 5.06; N,,9.38; Found: C, 68.20; H, 5.16; N, 9.58%.

4-(4-chlorophenyl)-6-(4-methoxyphenyl)-3,4-dihydropyrimidin-2(1*H*)-one (107i):



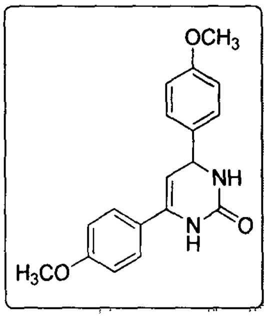
Mp 263-265°C; IR (KBr, cm^{-1}): 3286, 2934, 1621, 1453; ^{1}H NMR (CDCl$_3$): δ 3.82 (s, 3H, OCH$_3$), 5.21 (d, 1H, CH), 5.84 (d, 1H, CH), 6.98–7.45 (m, 8H, ArH), 8.26 (s, 1H, NH), 9.57(s, 1H, NH); ^{13}C NMR (CDCl$_3$): δ 54.22, 56.43, 97.32, 121.69, 126.19, 128.76, 129.84, 130.92, 132.14, 136.06, 141.65, 150.39, 159.73; Mass: m/z 314 [M$^+$]; Anal. Calcd for C$_{17}$H$_{15}$N$_2$O$_2$Cl: C, 64.87; H, 4.80; N, 8.90; Found: C, 64.71; H, 4.54; N, 8.83%.

6-(4-methoxyphenyl)-4-(*p*-tolyl)-3,4-dihydropyrimidin-2(1*H*)-one (107j):



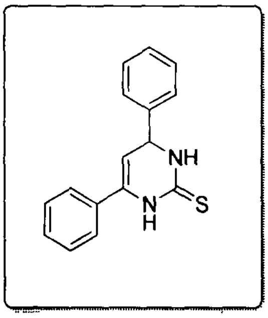
Mp 247-249°C; IR (KBr, cm^{-1}): 3245, 3002, 1637; ^{1}H NMR ($CDCl_3$): δ 2.32 (s, 3H, CH_3), 3.87 (s, 3H, OCH_3), 5.42 (d, 1H, CH), 5.80 (d, 1H, CH), 6.96–7.58 (m, 8H, ArH), 8.61 (s, 1H, NH), 9.15 (s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 22.95, 55.86, 57.17, 97.30, 121.86, 126.10, 128.12, 129.81, 130.25, 136.73, 137.38, 140.27, 150.28, 159.17; Mass: m/z 294 [M^+]; Anal. Calcd for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52; Found: C, 73.57; H, 6.30; N, 9.20%.

4,6-bis(4-methoxyphenyl)-3,4-dihydropyrimidin-2(1*H*)-one (107k):



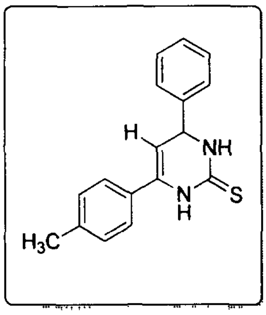
Mp 229–231 °C; IR (KBr, cm^{-1}): 3311, 2948, 1613, 1543; ^{1}H NMR ($CDCl_3$): δ 3.76 (s, 6H, OCH), 5.13 (d, 1H, CH), 5.65 (d, 1H, CH) 6.87–7.41(m, 8H, ArH), 8.23 (s, 1H, NH), 9.61(s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 55.09, 56.32, 97.55, 114.32, 121.44, 125.91, 129.74, 135.84, 130.31, 135.72, 136.83, 150.45, 158.05, 159.44; Mass: m/z 310 [M^+]; Anal. Calcd for $C_{16}H_{13}N_2OCl$: C, 69.66; H, 5.85; N, 9.03; Found: C, 69.53; H, 5.75; N, 9.43%.

4,6-diphenyl-3,4-dihydropyrimidine-2(1*H*)-thione (107l):



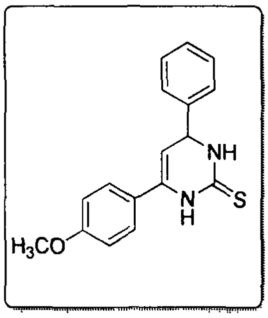
Mp 205-207°C; IR (KBr, cm^{-1}): 3307, 3075, 1673, 1602, 1554; ^{1}H NMR ($CDCl_3$): δ 5.48 (s, 1H), 5.89 (s, 1H), 7.00-7.87 (m, 10H ArH), 8.03 (s, 1H), 8.72 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 54.71, 95.37, 125.61, 126.52, 127.30, 128.50, 129.31, 130.50, 135.31, 137.42, 150.23, 163.33; Mass: m/z 266 [M^+]; Anal. Calcd. For $C_{16}H_{14}N_2S$; C, 72.15; H, 5.30; N, 10.52; Found: C, 72.20; H, 5.37; N, 10.47%.

4-phenyl-6-(*p*-tolyl)-3,4-dihydropyrimidine-2(1*H*)-thione (107m):



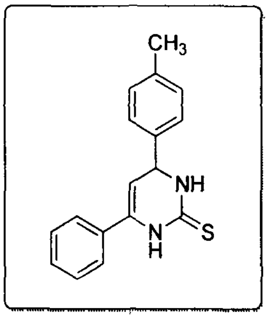
Mp 195-197°C ; IR (KBr, cm^{-1}): 3256, 2967, 1632,; ^1H NMR ($CDCl_3$): δ 2.41 (s, 3H, CH_3), 4.69 (d, 1H, CH), 6.12 (d, 1H, CH), 7.18–7.44 (m, 9H, ArH), 8.08 (s, 1H, NH), 9.12 (s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 21.65, 58.19, 95.82, 126.52, 127.76, 128.74, 129.33, 135.54, 136.51, 137.43, 143.23, 150.22, 160.13; Mass: m/z 280 [M^+]; Anal. Calcd for $C_{17}H_{16}N_2S$: C, 72.82; H, 5.75; N, 9.99; Found: C, 72.65; H, 5.83; N, 9.73%.

6-(4-methoxyphenyl)-4-phenyl-3,4-dihydropyrimidine-2(1*H*)-thione (107n):



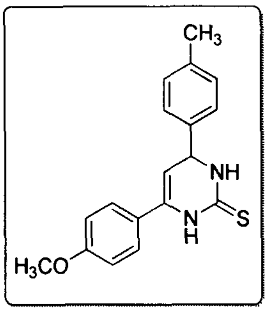
Mp 203-204°C; IR (KBr, cm^{-1}): 3307, 3007, 1626, 1574; ^1H NMR ($CDCl_3$): δ 3.45 (s, 3H, OCH_3), 5.23 (d, 1H, CH), 5.78 (d, 1H, CH), 7.34-7.98 (m, 9H, ArH), 8.16 (s, 1H, NH), 9.22 (s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 54.87, 57.81, 96.31, 117.21, 123.82, 126.84, 127.18, 128.63, 129.66, 130.67, 137.82, 150.58, 177.38; Mass: m/z 296 [M^+]; Anal. Calcd. For $C_{17}H_{16}N_2OS$: C, 68.89; H, 5.44; N, 9.45; Found: C, 68.86; H, 5.39; N, 9.31%.

6-phenyl-4-(*p*-tolyl)-3,4-dihydropyrimidine-2(1*H*)-thione (107o):



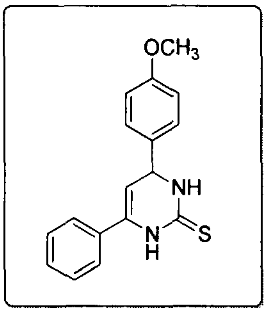
Mp 197-198°C; IR (KBr, cm^{-1}): 3255, 2956, 1687, 1543, 1416; ^1H NMR ($CDCl_3$): δ 2.65 (s, 3H, CH_3), 5.31 (d, 1H, CH), 5.78 (d, 1H, CH), 7.11-7.72 (m, 9H, ArH), 8.24 (s, 1H, NH), 9.38 (s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 22.37, 60.61, 95.44, 125.23, 126.87, 127.21, 128.34, 128.96, 129.23, 135.74, 139.88, 149.63, 159.76; Mass: m/z 280 [M^+]; Anal. Calcd for $C_{17}H_{16}N_2S$: C, 72.82; H, 5.75; N, 9.99; Found: C, 72.91; H, 5.45; N, 9.72%.

6-(4-methoxyphenyl)-4-(*p*-tolyl)-3,4-dihydropyrimidine-2(1*H*)-thione (107p):



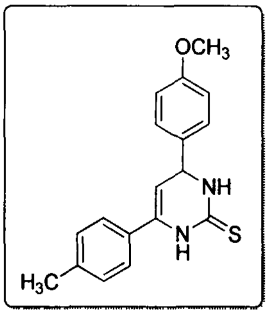
Mp 118-119°C; IR (KBr, cm^{-1}): 3233, 1982, 1632; ^{1}H NMR ($CDCl_3$): δ 2.37 (s, 3H, CH_3), 3.93 (s, 3H, OCH_3), 4.76 (d, 1H, CH), 5.96 (d, 1H, CH), 6.89–7.45 (m, 8H, ArH), 8.74 (s, 1H, NH), 9.21 (s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 22.41, 55.21, 60.43, 95.76, 121.54, 126.72, 128.53, 129.33, 130.39, 136.81, 140.64, 149.38, 159.17, 167.45; Mass: m/z 311 [M$^+$]; Anal. Calcd for $C_{18}H_{18}N_2O_2$: C, 69.65; H, 5.84; N, 9.02; Found: C, 69.53; H, 5.75 N, 9.31%.

4-(4-methoxyphenyl)-6-phenyl-3,4-dihydropyrimidine-2(1*H*)-thione (107q):



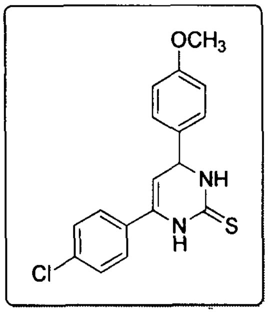
Mp 227-229°C; IR (KBr, cm^{-1}): 3332, 2971, 1644, 1581; ^{1}H NMR ($CDCl_3$): δ 3.45 (s, 3H, OCH_3), 5.17 (d, 1H, CH), 5.74 (d, 1H, CH), 7.21-7.96 (m, 9H, ArH), 8.21 (s, 1H, NH), 9.15 (s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 54.46, 60.82, 117.13, 120.62, 125.76, 129.74, 130.68, 131.41, 132.22, 134.31, 145.42, 165.71. Mass: m/z 296 [M$^+$]; Anal. Calcd. For $C_{17}H_{16}N_2OS$: C, 68.89; H, 5.44; N, 9.45; Found:C, 68.65; H, 5.54; N, 9.37%.

4-(4-methoxyphenyl)-6-(p-tolyl)-3,4-dihydropyrimidine-2(1*H*)-thione (107r):



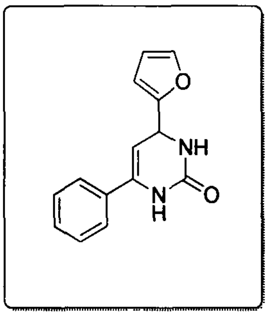
Mp 116-117°C; IR (KBr, cm^{-1}): 3242, 1923, 1611; ^{1}H NMR ($CDCl_3$): δ 2.37 (s, 3H, CH_3), 3.93 (s, 3H, OCH_3), 4.76 (d, 1H, CH), 5.96 (d, 1H, CH), 6.89–7.45 (m, 8H, ArH), 8.74 (s, 1H, NH), 9.21 (s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 22.41, 55.21, 60.43, 95.76, 121.54, 126.72, 128.53, 129.33, 130.39, 136.81, 140.64, 149.38, 159.17, 167.45; Mass: m/z 311 [M$^+$]; Anal. Calcd for $C_{18}H_{18}N_2O_2$: C, 69.65; H, 5.84; N, 9.02; Found: C, 69.53; H, 5.75 N, 9.31%.

6-(4-chlorophenyl)-4-(4-methoxyphenyl)-3,4-dihydropyrimidine-2(1*H*)-thione(107s):



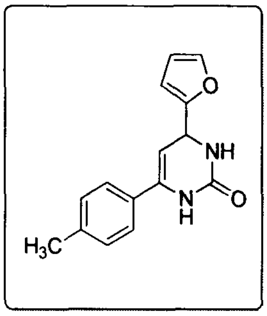
Mp 241-243°C; IR (KBr, cm^{-1}): 3252, 2964, 1523, 1456; ^1H NMR ($CDCl_3$): δ 3.65 (s, 3H, OCH_3), 4.67 (d, 1H, CH), 6.03 (d, 1H, CH), 6.97–7.43 (m, 8H, ArH), 8.24 (s, 1H, NH), 9.67 (s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 55.82, 60.73, 95.22, 117.53, 120.54, 125.76, 128.23, 133.87, 135.11, 136.49, 149.15, 159.45, 167.39; Mass: m/z 332 [M^+]; Anal. Calcd for $C_{17}H_{15}N_2OSCl$: C, 61.72; H, 4.57; N, 8.47; Found: C, 61.54; H, 4.61; N, 8.71%.

4-(furan-2-yl)-6-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (107t):



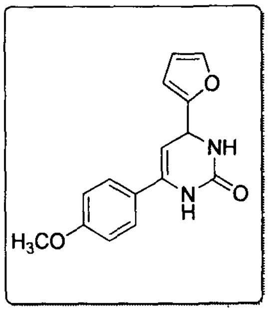
Mp 224-225°C ; IR (KBr, cm^{-1}): 3247, 2931, 1612, 1473; ^1H NMR ($CDCl_3$): δ 5.06 (d, 1H, CH), 5.53 (d, 1H, CH), 6.26 (d, 1H, CH), 6.46 (d, 1H, CH), 7.33–7.71 (m, 6H, ArH), 8.34 (s, 1H, NH), 9.13 (s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 56.82, 97.52, 106.23, 110.64, 126.41, 127.39, 128.65, 136.67, 138.01, 142.19, 150.75, 152.23; Mass: m/z 240 [M^+]; Anal. Calcd for $C_{14}H_{12}N_2O_2$: C, 69.99; H, 5.03; N, 11.66; Found: C, 69.84; H, 5.15; N, 11.40%.

4-(furan-2-yl)-6-(*p*-tolyl)-3,4-dihydropyrimidin-2(1*H*)-one (107u):



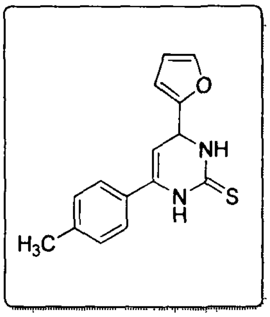
Mp 226-28°C; IR (KBr, cm^{-1}): 3237, 2953, 1624, 1466; ^1H NMR ($CDCl_3$): δ 2.37 (s, 3H, CH_3), 5.11 (d, 1H, CH), 5.63 (d, 1H, CH), 6.12 (d, 1H, CH), 6.51 (d, 1H, CH), 7.18–7.53 (m, 5H, ArH), 8.27 (s, 1H, NH), 9.09 (s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 21.46, 56.54, 97.82, 106.52, 110.48, 126.36, 127.72, 128.93, 136.42, 138.23, 142.27, 150.44, 152.51; Mass: m/z 240 [M^+]; Anal. Calcd for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02; Found: C, 70.93; H, 5.63; N, 11.21%.

4-(furan-2-yl)-6-(4-methoxyphenyl)-3,4-dihydropyrimidin-2(1*H*)-one (107v):



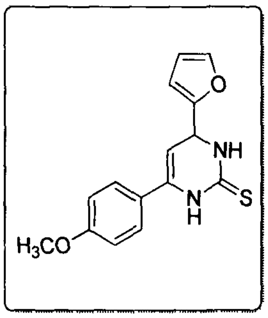
Mp 253-255°C ; IR (KBr, cm^{-1}): 3213, 2987, 1639; ^1H NMR ($CDCl_3$): δ 3.76 (s, 3H, OCH_3), 5.23 (d, 1H, CH), 5.57 (d, 1H, CH), 6.22 (d, 1H, CH), 6.54 (d, 1H, CH), 7.21–7.60 (m, 5H, ArH), 8.34 (s, 1H, NH), 9.18 (s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 54.26, 56.67, 97.64, 106.62, 110.28, 126.58, 127.21, 128.65, 136.73, 138.95, 142.66, 150.31, 152.58; Mass: m/z 270 [M^+]; Anal. Calcd for $C_{15}H_{14}N_2O_3$: C, 66.66; H, 5.22; N, 10.36; Found: C, 66.43; H, 5.32; N, 10.53%.

4-(furan-2-yl)-6-(*p*-tolyl)-3,4-dihydropyrimidine-2(1*H*)-thione (107w):



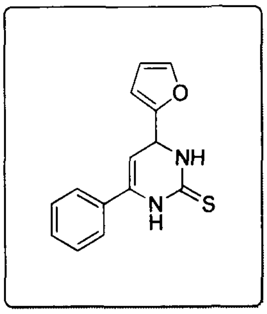
Mp 211-213°C ; IR (KBr, cm^{-1}): 3234, 2937, 1653, 1442; ^1H NMR ($CDCl_3$): δ 2.30 (s, 3H, CH_3), 4.83 (d, 1H, CH), 5.95 (d, 1H, CH), 6.17 (d, 1H, CH), 6.57 (d, 1H, CH), 7.22–7.65 (m, 5H, ArH), 8.32 (s, 1H, NH), 9.23 (s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 22.23, 57.94, 95.02, 106.44, 110.40, 128.47, 129.82, 135.93, 137.73, 142.65, 149.50, 152.28, 167.11; Mass: m/z 270 [M^+]; Anal. Calcd for $C_{15}H_{14}N_2OS$: C, 66.64; H, 5.22; N, 10.36; Found: C, 66.54; H, 5.34; N, 10.51%.

4-(furan-2-yl)-6-(4-methoxyphenyl)-3,4-dihydropyrimidine-2(1*H*)-thione (107x):



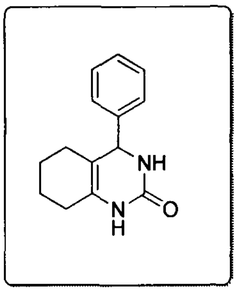
Mp 242-245°C ; IR (KBr, cm^{-1}): 3266, 2972, 1651; ^1H NMR ($CDCl_3$): δ 3.85 (s, 3H, OCH_3), 5.01 (d, 1H, CH), 5.65 (d, 1H, CH), 6.28 (d, 1H, CH), 6.49 (d, 1H, CH), 7.13–7.53 (m, 5H, ArH), 8.40 (s, 1H, NH), 9.31 (s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 55.63, 60.32, 95.74, 107.63, 110.61, 121.78, 129.90, 130.25, 142.36, 148.82, 142.66, 152.63, 156.28, 168.31; Mass: m/z 286 [M^+]; Anal. Calcd for $C_{15}H_{14}N_2O_2S$: C, 62.92; H, 4.93; N, 9.78; Found: C, 62.82; H, 4.71; N, 9.84%.

4-(furan-2-yl)-6-phenyl-3,4-dihydropyrimidine-2(1*H*)-thione (107y):



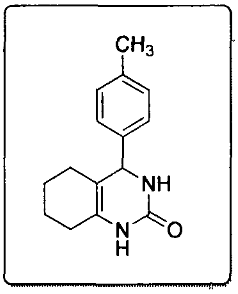
Mp 207-209°C ; IR (KBr, cm^{-1}): 3258, 2963, 1643, 1472; ^1H NMR ($CDCl_3$): δ 4.96 (d, 1H, CH), 5.68 (d, 1H, CH), 6.31 (d, 1H, CH), 6.63 (d, 1H, CH), 7.45–7.69 (m, 6H, ArH), 8.48 (s, 1H, NH), 9.32 (s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 58.73, 95.37, 106.79, 110.39, 126.54, 127.82, 128.57, 136.55, 138.76, 142.08, 150.28, 164.60; Mass: m/z 256 $[M^+]$; Anal. Calcd for $C_{14}H_{12}N_2OS$: C, 65.60; H, 4.72; N, 10.93; Found: C, 65.78; H, 4.85; N, 10.75%.

4-phenyl-3,4,5,6,7,8-hexahydroquinazolin-2(*1H*)-one (109a):



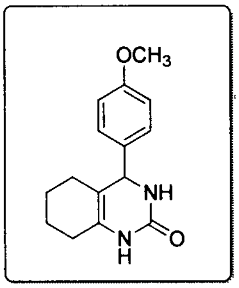
Mp 163-165°C; IR (KBr, cm^{-1}): 3313, 3023, 1673, 1546; ^1H NMR ($CDCl_3$): δ 1.68-1.75 (m, 4H, CH_2), 1.96 (m, 4H, CH_2), 5.63 (s, 1H, CH), 7.21-7.37 (m, 5H, ArH), 8.21 (s, 1H, NH), 9.35 (s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 20.56, 22.54, 23.91, 28.39, 63.62, 116.48, 126.17, 127.53, 128.91, 131.38, 141.62, 150.74; Mass: m/z 228 $[M^+]$; Anal. Calcd for $C_{14}H_{16}N_2O$; C, 73.66; H, 7.06; N, 12.27; Found: C, 73.82; H, 7.31; N, 12.43%.

4-(*p*-tolyl)-3,4,5,6,7,8-hexahydroquinazolin-2(1*H*)-one (109b):



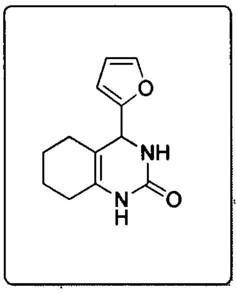
Mp 184-186°C; IR (KBr, cm^{-1}): 3372, 3022, 1664, 1524; ^1H NMR ($CDCl_3$): δ 1.71 (m, 4H, CH_2), 1.98 (m, 4H, CH_2), 3.26 (s, 3H, CH_3), 5.63 (s, 1H, CH), 7.10-7.23 (m, 4H, ArH),7.89 (s, 1H, NH), 9.34 (s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 20.38, 21.74, 22.45, 23.52, 28.59, 63.27, 116.84, 126.19, 128.65, 131.73, 136.22, 138.76, 150.42; Mass: m/z 242 $[M^+]$; Anal. Calcd for $C_{15}H_{18}N_2O$; C, 74.35; H, 7.49; N, 11.56; Found: C, 74.52; H, 7.64; N, 11.73%.

4-(4-methoxyphenyl)-3,4,5,6,7,8-hexahydroquinazolin-2(1*H*)-one (109c):



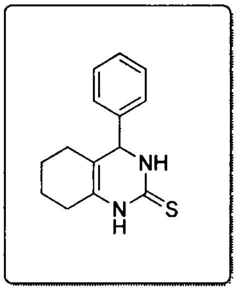
Mp 210-213°C; IR (KBr, cm^{-1}): 3356, 3038, 1671, 1547; ^1H NMR ($CDCl_3$): δ 1.74 (m, 4H, CH_2), 1.98 (m, 4H, CH_2), 3.79 (s, 3H, OCH_3), 5.61 (s, 1H, CH), 6.89-7.09 (m, 4H, ArH),7.88 (s, 1H, NH), 9.23 (s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 20.75, 22.12, 23.07, 28.67, 55.82, 63.82, 114.21, 116.25, 125.85, 131.59, 134.60, 150.28, 158.72; Mass: m/z 258 [M^+]; Anal. Calcd for $C_{15}H_{18}N_2O_2$; C, 69.74; H, 7.02; N, 10.84; Found: C, 69.53; H, 7.23; N, 10.61 %.

4-(furan-2-yl)-3,4,5,6,7,8-hexahydroquinazolin-2(1*H*)-one (109d):



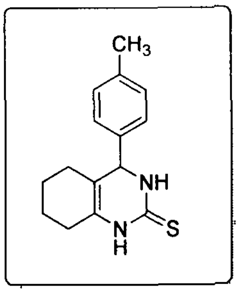
Mp 190-191°C; IR (KBr, cm^{-1}): 3312, 3061, 1645, 1537; ^1H NMR ($CDCl_3$): δ 1.69 (m, 4H, CH_2), 1.90 (m, 4H,CH_2), 5.80 (s, 1H, CH), 6.23 (d, 1H, CH), 6.50 (t, 1H, CH), 7.63 (d, 1H, CH), 8.21 (s, 1H, NH), 9.31 (s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 19.64, 20.63, 22.09, 27.42, 58.06, 106.53, 110.64, 116.85, 131.42, 142.67, 150.35, 152.36; Mass: m/z 218 [M^+]; Anal. Calcd for $C_{12}H_{14}N_2O_2$; C, 66.04; H, 6.47; N, 12.84; Found: C, 66.21; H, 6.62; N, 12.73%.

4-phenyl-3,4,5,6,7,8-hexahydroquinazoline-2(1*H*)-thione (109e):



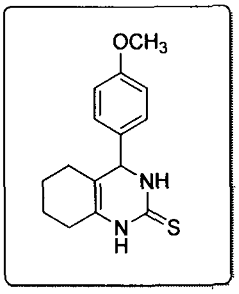
Mp 150-153°C; IR (KBr, cm^{-1}): 3342, 2996, 1617, 1528; ^1H NMR ($CDCl_3$): δ 1.70 (m, 4H, CH_2), 2.01 (m, 4H,CH_2), 4.61 (s, 1H, CH), 7.19-7.32 (m, 5H, ArH), 8.35 (s, 1H, NH), 9.12(s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 21.53, 22.04, 23.31, 29.50, 68.12, 114.66, 126.41, 127.17, 128.53, 141.46, 144.37, 158.74; Mass: m/z 244 [M^+]; Anal. Calcd for $C_{14}H_{16}N_2S$; C, 68.81; H, 6.60; N, 11.46; Found: C, 68.95; H, 6.45; N, 11.33%.

4-(*p*-tolyl)-3,4,5,6,7,8-hexahydroquinazoline-2(1*H*)-thione (109f):



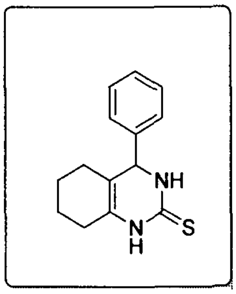
Mp 184-186°C; IR (KBr, cm^{-1}): 3372, 3022, 1664, 1524; ^{1}H NMR ($CDCl_3$): δ 1.73 (m, 4H, CH_2), 1.87 (m, 4H, CH_2), 3.32 (s, 3H, CH_3), 4.56 (s, 1H, CH), 7.11-7.19 (m, 4H, ArH),7.97 (s, 1H, NH), 9.07 (s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 20.53, 21.55, 22.65, 23.03, 29.19, 66.97, 114.94, 126.74, 128.82, 136.43, 138.32, 144.63, 159.61; Mass: m/z 258 [M$^+$]; Anal. Calcd for $C_{15}H_{18}N_2S$; C, 69.73; H, 7.02; N, 10.84; Found: C, 69.82; H, 7.23; N, 10.91%.

4-(4-methoxy Phenyl)-3,4,5,6,7,8-hexahydroquinazolin-2(1*H*)-thione (109g):

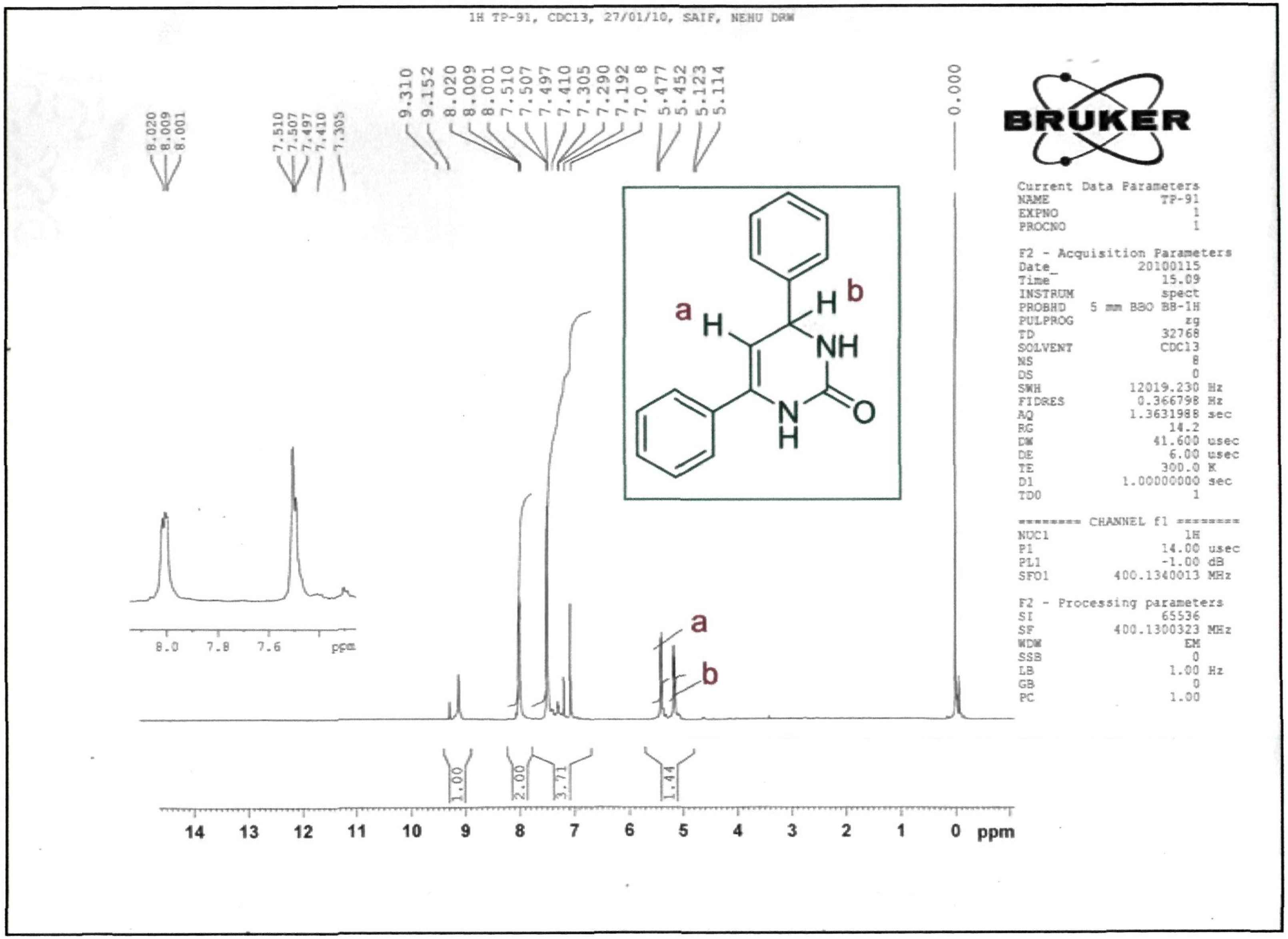


Mp 197-199°C; IR (KBr, cm^{-1}): 3342, 3016, 1652, 1534, 1213; ^{1}H NMR ($CDCl_3$): δ 1.68 (m, 4H,CH_2), 1.96 (m, 4H, -CH2-), 3.89 (s, 3H, OCH3), 5.82 (s, 1H, CH), 6.96-7.10 (m, 4H, ArH),7.98 (s, 1H, NH), 9.47 (s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 21.85, 22.37, 23.32, 29.21, 55.33, 66.32, 114.95, 115.10, 125.73, 134.63, 144.61, 156.31, 168.44; Mass: m/z 274 [M$^+$]; Anal. Calcd for $C_{15}H_{18}N_2OS$; C, 65.66; H, 6.61; N, 10.21; Found: C, 65.62; H, 6.65; N, 10.23%.

4-(furan-2-yl)-3,4,5,6,7,8-hexahydroquinazoline-2(1*H*)-thione (109h):



Mp 169-170°C; IR (KBr, cm^{-1}): 3334, 3072, 1634, 1556; ^{1}H NMR ($CDCl_3$): δ 1.72 (m, 4H, CH_2), 1.95 (m, 4H, CH2), 4.85 (s, 1H, CH), 6.28 (d, 1H, CH), 6.43 (t, 1H, CH), 7.67 (d, 1H, CH), 8.42 (s,1H, NH), 9.25 (s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 19.73, 21.54, 22.17, 28.39, 64.18, 106.25, 110.44, 114.59, 142.57, 144.38, 152.71, 161.29; Mass: m/z 234 [M$^+$]; Anal. Calcd for $C_{12}H_{14}N_2OS$; C, 61.51; H, 6.02; N, 11.96; Found: C, 61.63; H, 6.23; N, 11.79%.



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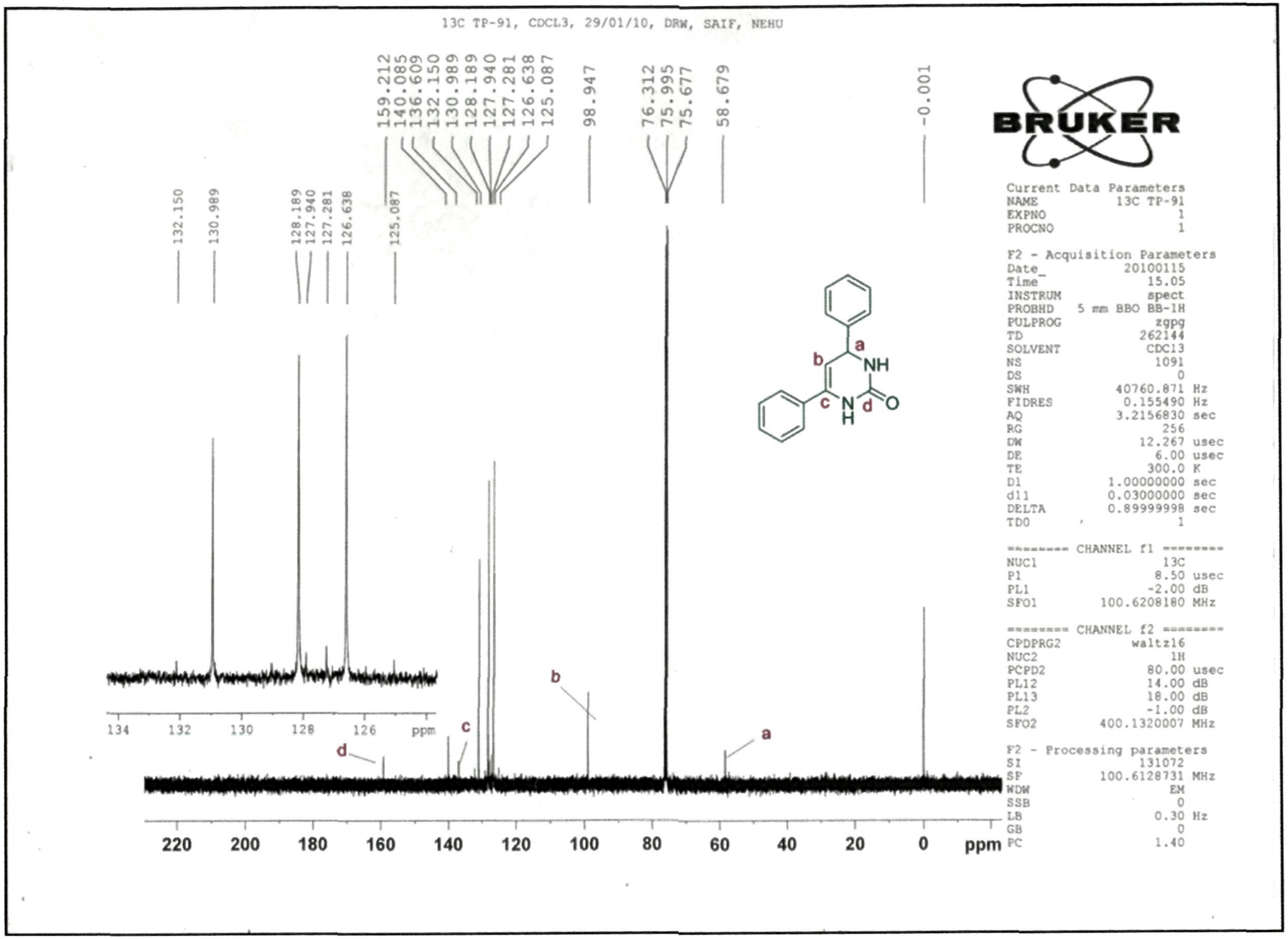

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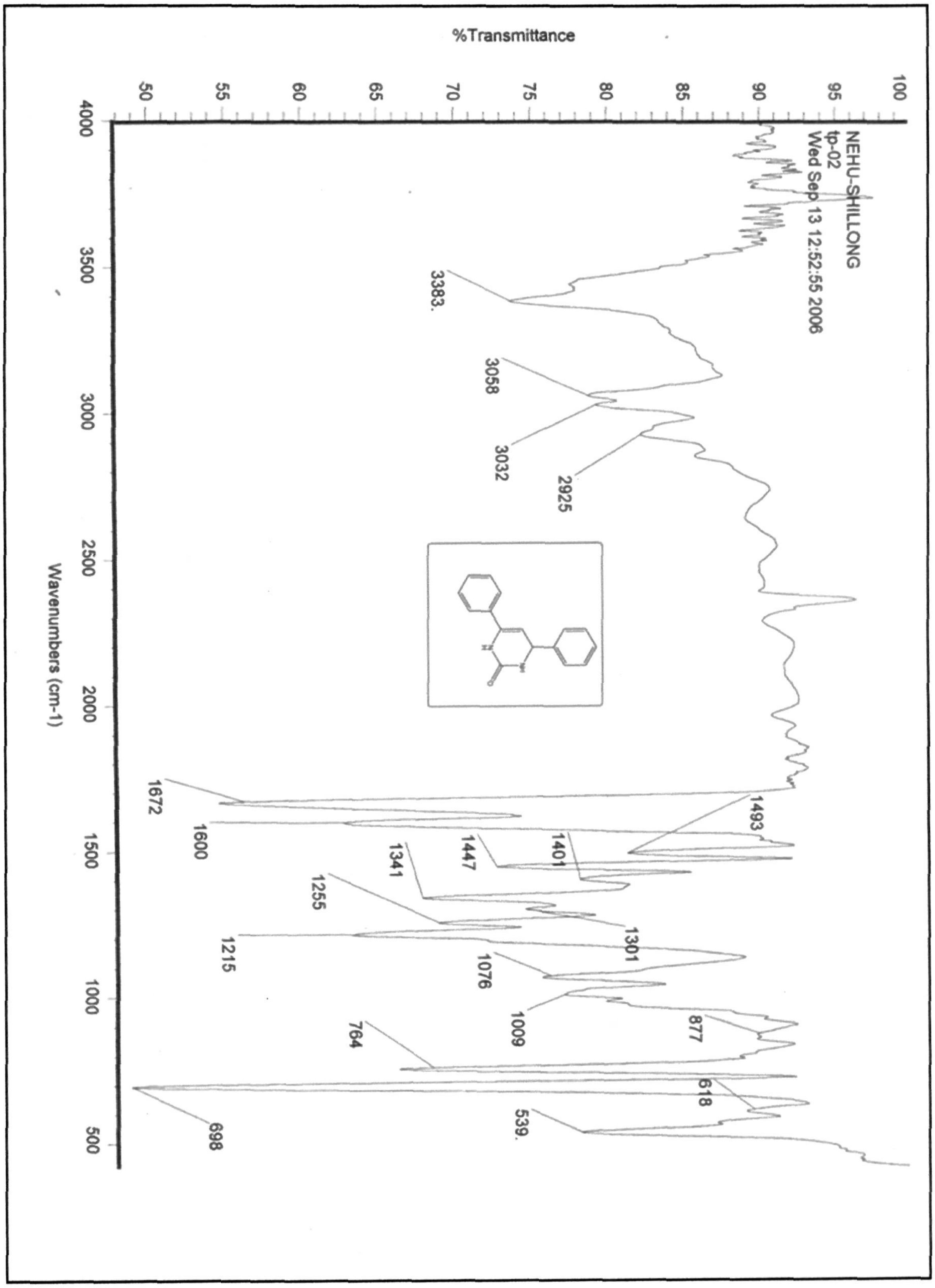
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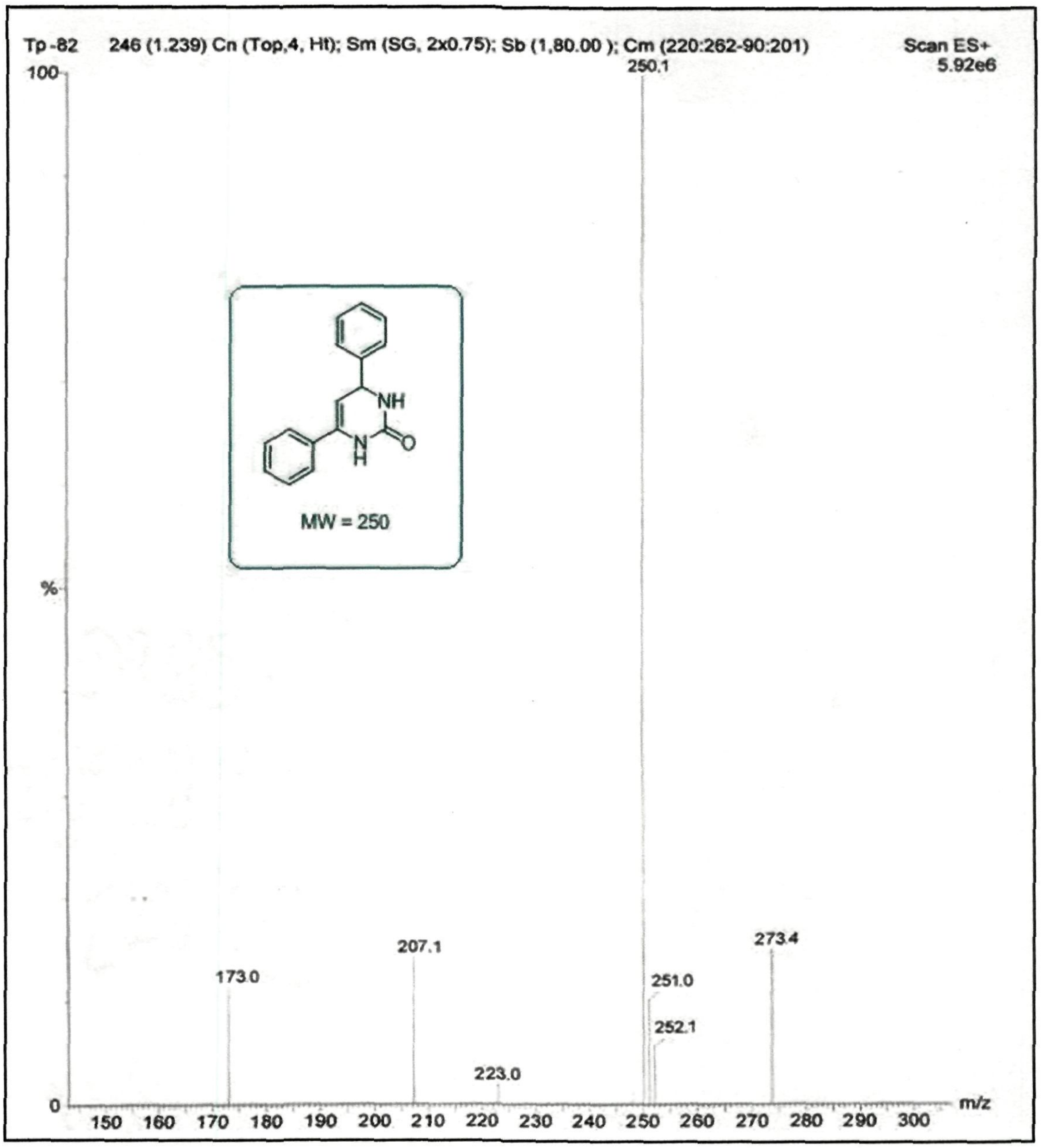
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II.6. References

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Chapter III

Novel one pot synthesis of substituted 1,2,4-triazines under microwave irradiation.[#]

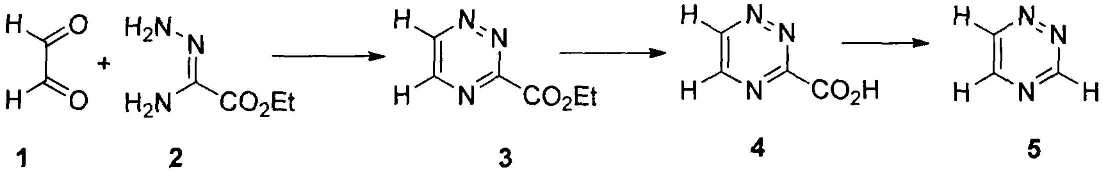
[#]The work described in this chapter has been published:

(i). *Arkivoc,* **2008**, (xv), 79.

III.1. Introduction

1,2,4-triazines and their derivatives have been widely studied in terms of their synthetic methodologies and reactivity since some of these derivatives were reported to have promising biological activities.[1] The synthesis of 1,2,4-triazines and their derivatives are well documented[2] and their methods of preparation are manifold and varied. Triazines are common pharmacophores, making them pervasive in both the pharmaceutical and agrochemical arenas. Furthermore, the electronic properties of the 1,2,4-triazine hetero-aromatic ring impart distinct chemical properties that impact both the reactivity and synthetic approaches to this ring system.

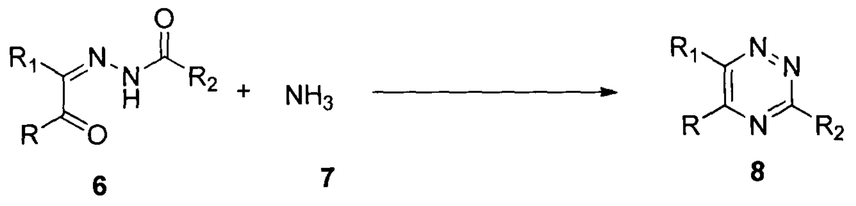
The first synthesis of the parent compound of the 1,2,4-triazine (**5**) series was reported by Paudler and Barton[3] in 1966. They synthesized this compound in 40% yield through decarboxylation of 1,2,4-triazine-3-carboxylic acid (**4**) which was prepared by the reaction of glyoxal (**1**) with ethyl oxalamidrazonate (**2**) and saponification of the formed ethyl 1,2,4-triazine-3-carboxylate **3**. **(Scheme-1)**



Scheme-1

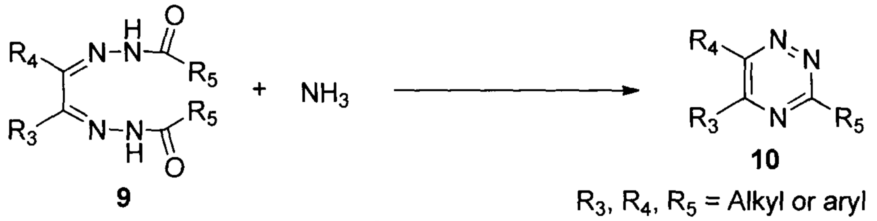
Metze *et al*,[4] and also Hasselquist[5] synthesized 1,2,4-triazine by cyclization of the acylhydrazone (**6**) of 1,2-dicarbonyl compound with ammonia (**Scheme-2**). They have reported that monohydrazones of aromatic 1,2-diketone react with formamide to give 5,6-

diaryl-1,2,4-triazine but the aliphatic monohydrazone do not react with formamide to give the cyclised product. 1,2-bisacylhydrazone (**9**) can also be transformed to 1,2,4-triazine by reaction with ammonia (**Scheme-3**).[6]



R, R_1, R_2 = Alkyl or aryl

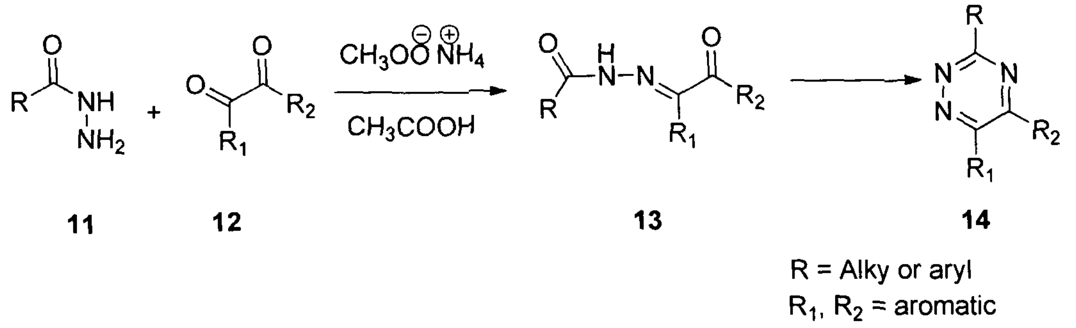
Scheme-2



R_3, R_4, R_5 = Alkyl or aryl

Scheme-3

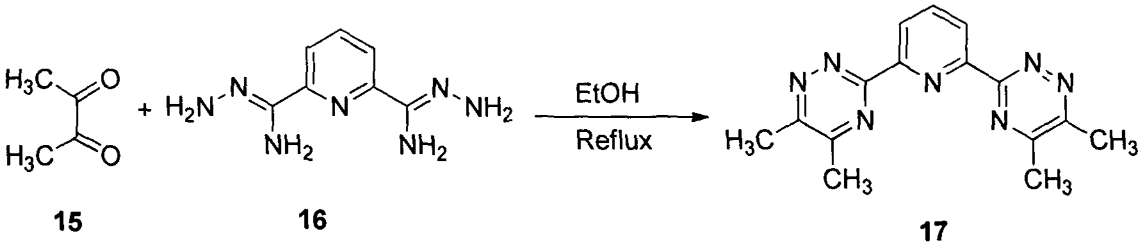
By replacing ammonia with ammonium acetate, Laakso and co-workers[7] synthesized 1,2,4-triazine by condensing acylhydrazide (**11**) with α-diketone in acetic acid containing ammonium acetate. The reaction proceeded *via* monoacylhydrazone intermediate which cyclised to give substituted-1,2,4-triazine (**14**).



Scheme-4

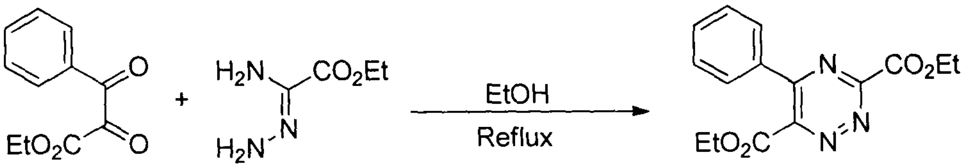
The above procedure was modified by Rostamizadeh and Sadeghi[8] where the reaction was carried out on the surface of silica gel in the presence of triethylamine under microwave irradiation. However when the reaction is done in the Bronsted acidic ionic liquid, 1-*n*-Butylimidazolium tetrafluoroborate ([Hbim]BF_4), better yield was obtained.[9]

Hudson *et al,*[10] have extended Metze's procedure and prepared bis(triazinyl)pyridines (**17**) for the extraction of americium(III) (**Scheme-5**).



Scheme-5

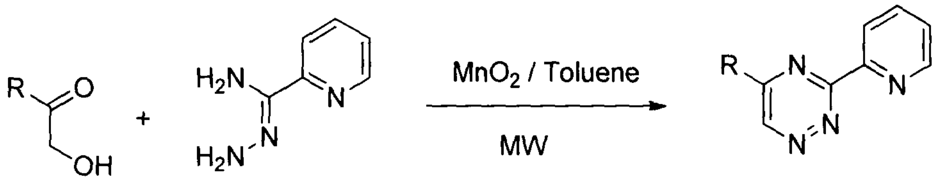
Stanforth's group has extended this concept to tricarbonyl substrates[11] allowing the synthesis of carboxy-substituted 1,2,4-triazines (**20**) (**Scheme-6**). The same group then developed an analogous methodology, which allows the use of α,β-diketoester equivalents in the preparation of 1,2,4-triazines, presumably *via* an intermediate tricarbonyl species.



18 **19** **20**

Scheme-6

Taylor and co-workers[12] have developed a methodology which allows the utilisation of α-hydroxyketones (**21**) in a one-pot tandem oxidation process (TOP), in which the α-ketoaldehyde is generated and trapped *in situ* using manganese dioxide as catalyst in toluene (**Scheme-7**).

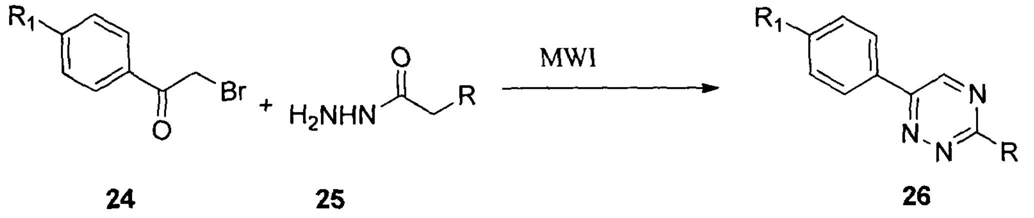


21 **22** **23**

R = Alkyl or aryl or heteroaryl

Scheme-7

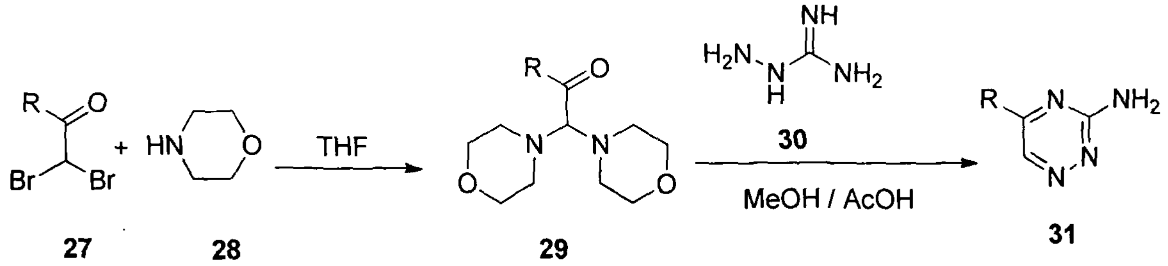
An environmentally benign, solventless synthesis of 1,2,4-triazines using microwave was reported by Kidwai and co-workers where hydrazides (**25**) on reaction with phenacyl bromide/4-chloro phenacyl bromide/4-aminophenacyl bromide (**24**) yielded 1,2,4-triazines (**26**) (**Scheme-8**). Results showed that neutral alumina is the best support in terms of yield and time for the synthesis of 1,2,4-triazines.[13]



R = Heteoaryl or alkyl or O-aryl
R = *Cl* or NH_2

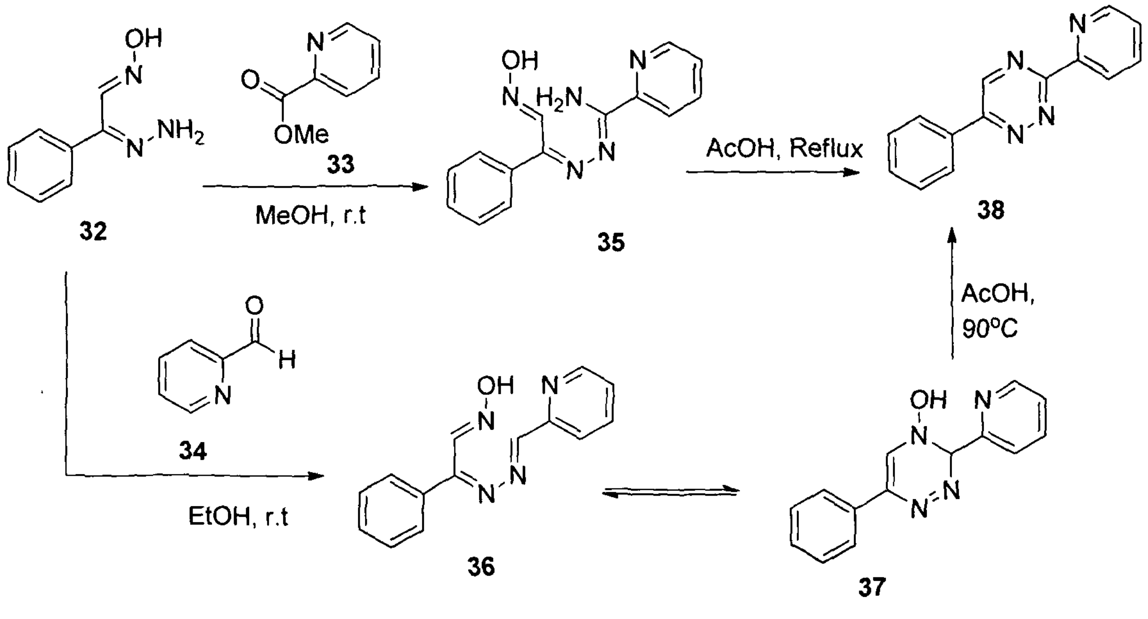
Scheme-8

Nucleophilic displacement of readily available α,α,-dibromoketones (**27**) with excess of morpholine (**28**) gave the corresponding ketoaminals (**29**) which upon condensation with aminoguanidine (**30**) in MeOH in the presence of AcOH afforded 5-substituted-3-amino-1,2,4-triazines (**31**) in 95% yield regioselectivity and 45-76% isolated yield.[14]



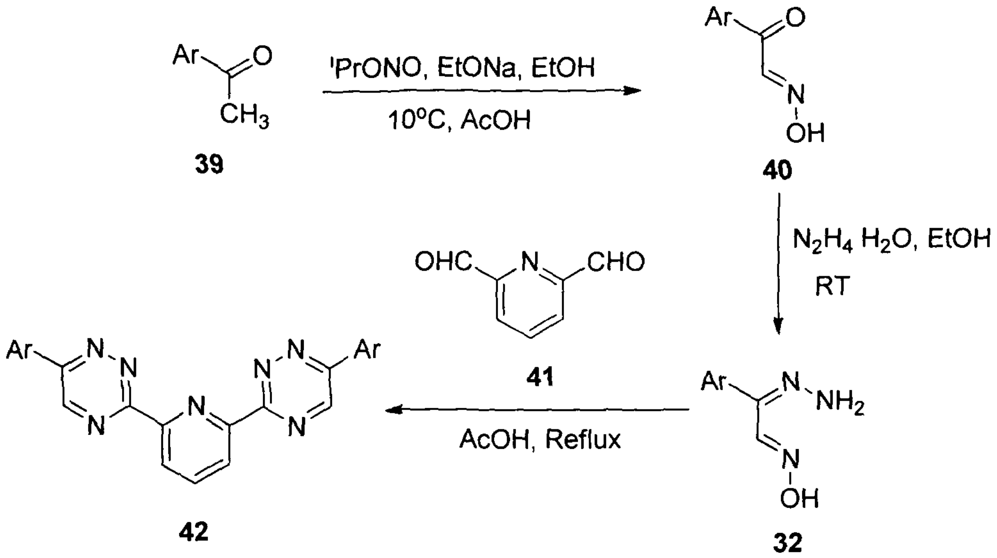
Scheme-9

The Kozhevnikov and group[15] has utilised hydrazones of type **32** in a direct synthesis of 3,6-disubstituted-1,2,4-triazines (**38**) from methoxyimidates (**33**) (**Scheme-10**). This group has also extended the scope of the condensation of hydrazones with aldehydes **34** to allow direct access to 3,6-disubstituted-1,2,4-triazines (**38**) (**Scheme-9**), though this is limited to 2- and 4-pyridinecarboxaldehydes (or related benzopyridines).



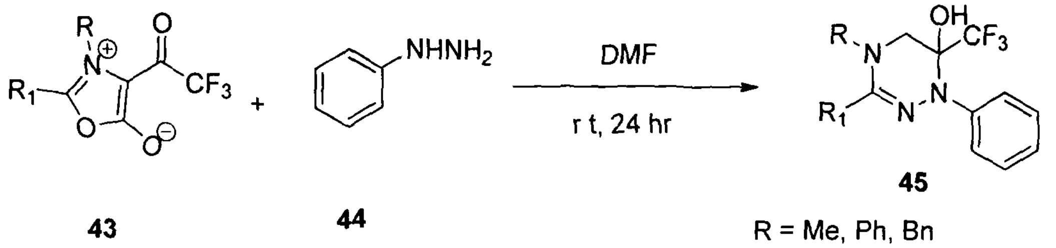
Scheme-10

They also have devised a new method for the synthesis of 2,6-bis(6- aryl-1,2,4-triazin-3-yl)pyridines (**42**),[16] starting from readily available acylarenes (**38**) bearing various substituents on the aryl moiety, for example, bromine, methyl, methoxy or nitro groups. Nitrosation of **38** yielded the corresponding 1-aryl-2-oximino-1-ethanones (**40**) after which treatment with hydrazine hydrate resulted in the formation of 1-aryl-1-hydrazono-2-oximinoethanes (**32**). Condensation of hydrazones **32** with pyridine- 2,6-dicarboxaldehyde (**41**) followed by dehydration of the intermediates (4-hydroxy-3,4-dihydro-1,2,4-triazines) by briefly refluxing in acetic acid gave the bistriazinylpyridines (**42**). The aryl substituents of the starting ketones (**39**) appear at position 6 of the 1,2,4-triazines not position 5, as in typical 1,2,4-triazine synthesis from arylglyoxals.[17]



Scheme-11

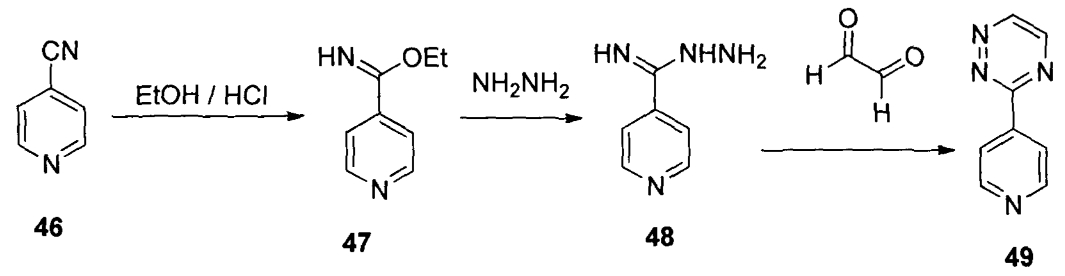
Kawase and Koiwai have developed an unusual ring-transformation methodology for the synthesis of trifluoromethyl-substituted-1,2,4-triazine derivatives (**45**).[18] Mesoionic 4-trifluoroacetyl-1,3-oxazolium-5-olates (**43**) are reacted with phenylhydrazine to give 1,4,5,6-tetrahydro-1,2,4-triazin-6-ols (**Scheme-12**), 3-hydroxypyrazoles or pyrazolones depending on the solvent.



R = Me, Ph, Bn
R$_1$ = Ph, Me, 4-MeOC$_6$H$_4$

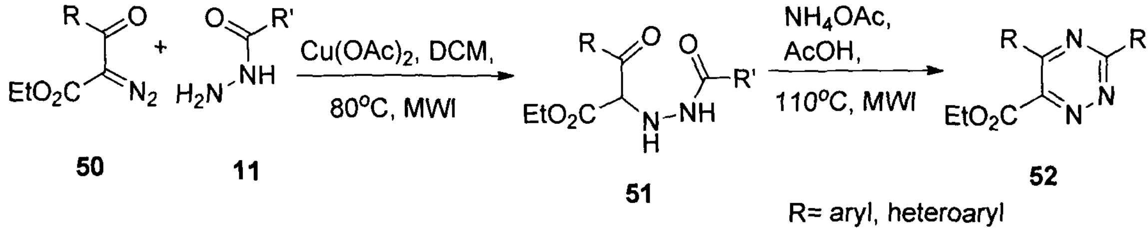
Scheme-12

Lee and co workers[19] have reported the synthesis of substituted 1,2,4-triazines from amidrazone (**48**) formed from imidoester (**47**), which was prepared by reaction of cyanopyridine (**46**) with ethanol and HCl gas. This amidrazone reacted with glyoxal to form 3-(pyridyl)-1,2,4-triazine (**49**).



Scheme-13

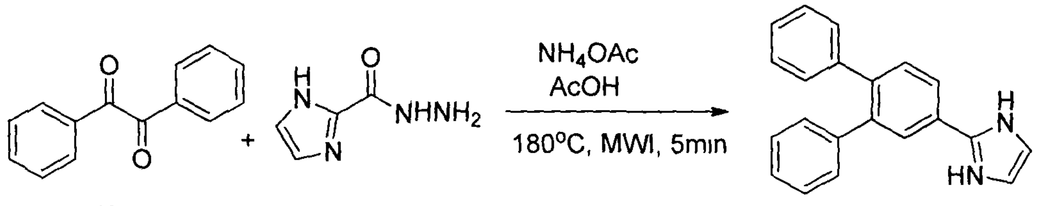
The most recent development in the synthesis of 1,2,4-triazines has been made by the Moody group.[20] In this work, hydrazides (**11**) are reacted with copper carbenes derived from the corresponding α-diazo-β-ketoesters (**50**). Condensation of intermediate **51** with ammonium acetate furnishes the trisubstituted-1,2,4-triazines (47) (**Scheme-14**).



R= aryl, heteroaryl
R' = Me or 4-FC$_6$H$_4$

Scheme-14

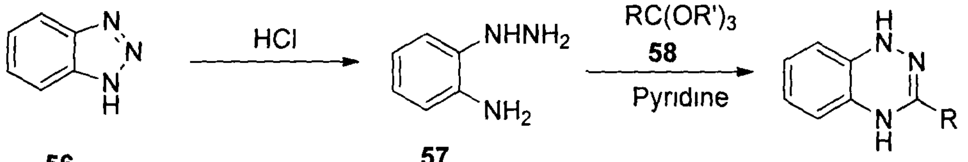
Zhao and coworkers[21] have broadened the synthetic scope of trisubstituted-1,2,4-triazines (55) by applying dry media microwave assisted reaction condition and also the comparative studies in terms of yield and reaction time have been reported.



53 **54** **55**

Scheme-15

Benzotriazole (**56**) can be converted to dihydrobenzo-1,2,4-triazine (**59**). The reaction involves the ring opening of benzotriazole which undergoes reductive ring expansion to 2-aminophenylhydrazine (**57**) by reduction in HCl. **57** condensed with suitable orthoester (**58**) to give the derivatives of benzo-1,2,4-triazine (**59**). This procedure is the most convenient way to prepare derivatives of benzo-1,2,4-triazine.

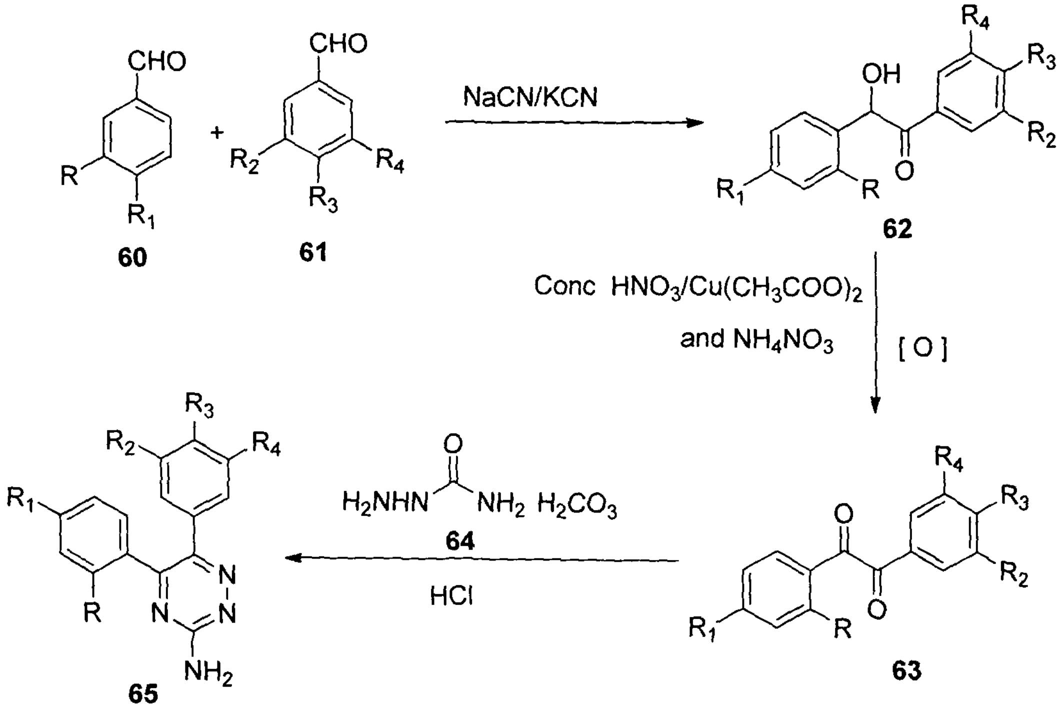


56 **57** **59**

R = H, -CH$_3$ or Et

Scheme-16

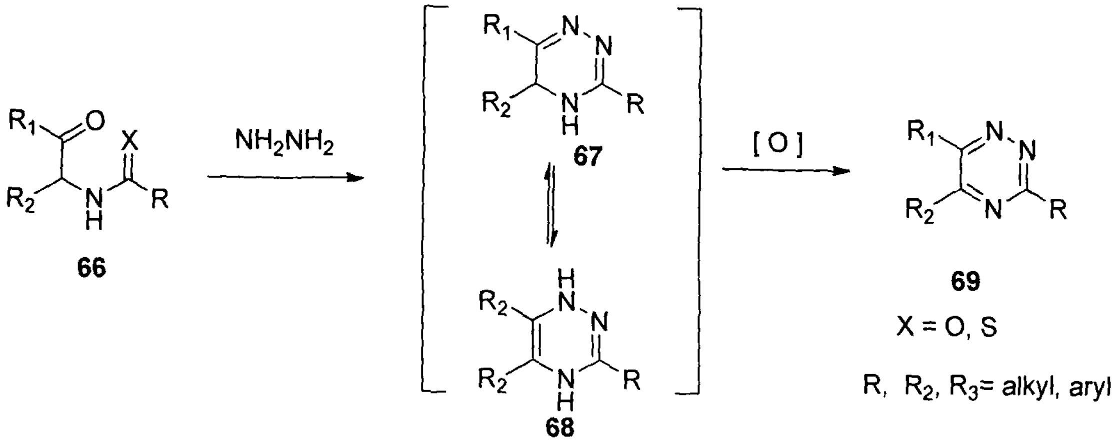
Kumar and co-workers[22] have reported the synthesis of 5,6-bisaryl-1,2,4-triazines (**62**) *via* benzoin condensation using KCN or NaCN as a catalyst. Condensation of aldehyde (**60** and **61**) yield compound **62** which undergoes further oxidation in presence of concentrated HNO$_3$ to give benzil (**63**). Substituted benzyl (**63**) derivatives on condensation with aminoguanidine bicarbonate (**64**) gave corresponding 5,6-bis aryl-1,2,4-triazines (**65**).



R, R_1, R_2, R_3, R_4 = H or Alkyl

Scheme-17

Cyclization of 2-(acylamino)-ketones or 2-[(thioacyl)amino]-ketone (**66**) with hydrazine yields dihydro-1,2,4-triazines (**67**) or its tautomer (**68**). Oxidation of **67** or **68** gives corresponding derivatives of 1,2,4-triazines (**69**).[23]

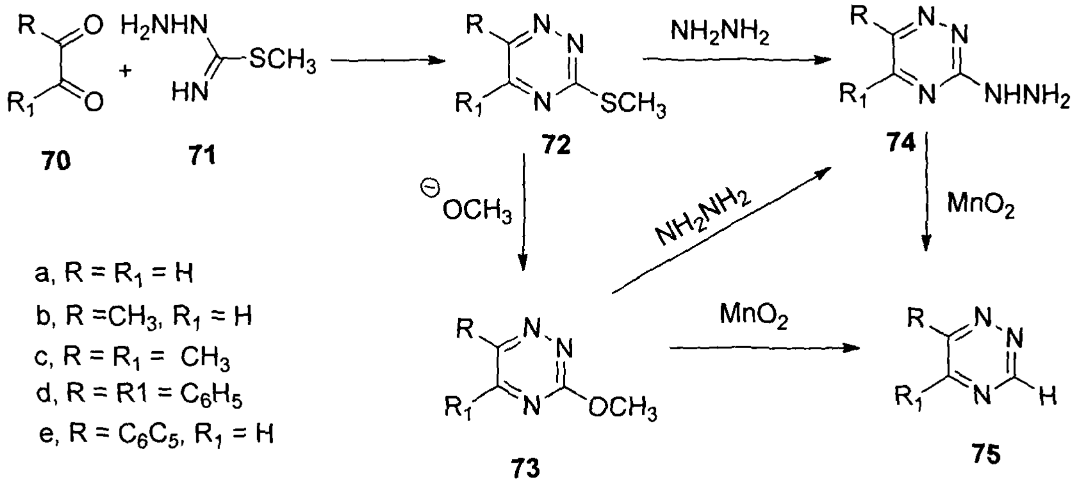


X = O, S

R, R_2, R_3= alkyl, aryl

Scheme-18

A convenient synthesis of 1, 2, 4-triazines from *S*-methyl thiosemicarbazide was reported by Paudler.[24] The condensation of *S*-methyl thiosemicarbazide (**71**) with glyoxal (**70a**) or other α,β-dicarbonyl compounds (**70b-e**) readily affords the 3-methylthio derivatives of 1, 2, 4-triazines (**72**). These substances were readily converted to their 3-hydrazino derivatives (**74**) by treatment with hydrazine and were conveniently oxidized with active manganese dioxide to the appropriate 1, 2, 4-triazines (**74**).



Scheme-19

Unfortunately, the formation of the 3-hydrazino-1,2,4-triazines (**74a**) from **72** was a low yield transformation. However, this shortcoming was overcomed by first converting the 3-methylthio-1,2,4-triazines (**72a**) to its methoxy derivative (**73a**) which was then converted to the 3-hydrazino-1, 2, 4-triazines (**74a**) in high yield. **73** was readily oxidized to the parent compound **74a** by means of activated manganese dioxide. These transformations are delineated in **Scheme-19**.

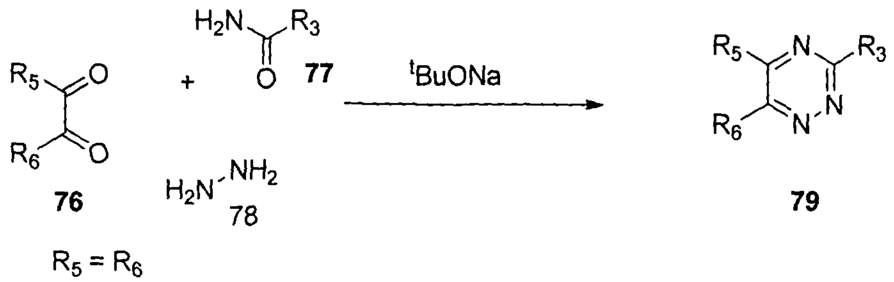
III.2. Results and discussions

Various methods for the preparation of 1,2,4-triazines have been reported abundantly in the literature, but to the best of our knowledge 1,2,4-triazines have not been prepared starting from 1,2-dicarbonyl compounds and amides. This principle was based on our earlier work of synthesis of trisubstituted pyridazines by the condensation of 1,2-diketones with acetophenone in the presence of base, followed by cyclisation with hydrazine hydrate[25] because when ketone containing enolisable proton was replaced by an amide, our required triazines were obtained. Hence we describe here the synthesis of 1,2,4-triazines starting from amides and 1,2-dicarbonyl compounds and hydrazine hydrate in the presence of base.

The novelty of this procedure lies in the fact that the whole reaction sequence is carried out by the stepwise addition of the reagents at the completion of each step without isolating the intermediates as they are formed. Thus, the one pot synthesis of the title compound was achieved *via* the *N*-(2-oxo-1,2-disubstituted-ethylidene)-amide intermediate, which was generated *in situ* by the condensation of amides with 1, 2-dicarbonyl compounds in presence of base. As reported earlier with unsymmetrical diketones,[25] a mixture of two possible isomers[26] is obtained. However, there is predominance of one over the other. This is due to the difference in reactivity of the two carbonyl groups where the more electrophilic carbonyl is reacted first. With 1-phenyl-1, 2-propanedione, a mixture of regioisomeric triazines is obtained.[27]

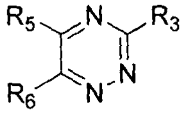
Lee and coworkers[28] have shown similar reactions where both 6,6'- and 6,5'-*bis*-1,2,4-triazinyls were obtained as major and minor products respectively.

In general, amides like formamide, acetamide and benzamide when condensed with aromatic 1,2-diketones formed a jelly mass, which is the condensed product. The condensed product can be cyclised to stable 1,2,4-substituted triazines by treatment with hydrazine hydrate. In all these cases solid products were obtained. The reaction was also carried out under microwave irradiation without using solvent. The results of the conventional process and the microwave irradiation process were compared which revealed that the latter process gave a comparatively higher yield in a shorter reaction time (**Table-I**).



Scheme-20

Table 1: Preparation of 3, 5, 6-trisubstituted 1, 2, 4-triazines.

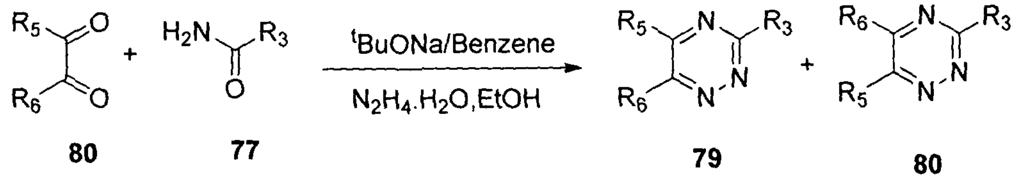


79 (a-r)

Products	**R_3**	**R_5**	**R_6**	**Time**		**Yields (%)**	
				Conv (Hrs)	**MWI (Sec)**	**Conv**	**MWI**
79a	H	C_6H_5	C_6H_5	3	180	56	60
79b	CH_3	C_6H_5	C_6H_5	4	240	78	80
79c	C_6H_5	C_6H_5	C_6H_5	4	240	61	67
79d	H	4-OMeC_6H_4	C_6H_5	5	300	64	67
79e	CH_3	4-OMeC_6H_4	C_6H_5	6	360	57	62
79f	C_6H_5	C_6H_5	4-OMeC_6H_4	5	300	65	70
79g	H	4-ClC_6H_4	C_6H_5	3	180	60	68
79h	CH_3	4-ClC_6H_4	C_6H_5	4	240	61	67
79i	C_6H_5	4-ClC_6H_4	C_6H_5	5	300	72	77
79j	H	Furyl	Furyl	5	300	57	63
79k	CH_3	Furyl	Furyl	6	360	61	69
79l	C_6H_5	Furyl	Furyl	5	300	58	65
79m	H	CH_3	CH_3	5	300	41	52
79n	CH_3	CH_3	CH_3	6	360	42	50
79o	C_6H_5	CH_3	CH_3	5	300	37	43
79p	H	Pyridyl	Pyridyl	6	360	43	49
79q	CH_3	Pyridyl	Pyridyl	5	300	45	42
79r	C_6H_5	Pyridyl	pyridyl	5	300	51	61

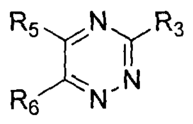
Conv = Conventional heating procedure

MWI = Microwave irradiation

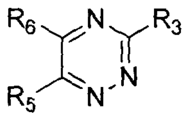


Scheme-21

Table 2: Preparation of Regioisomeric di- and tri-substituted 1,2,4-triazines



79(s-v)



80(s-v)

Products	R_5	R_6	R_3	Yields (%)	Mp(°C)
79s	CH_3	C_6H_5	H	25	89-90
80s	C_6H_5	CH_3	H	13	91-93
79t	CH_3	C_6H_5	C_6H_5	27	113-115
80t	C_6H_5	CH_3	C_6H_5	15	110-112
79u	H	4-MeC_6H_4	C_6H_5	29	128-130
80u	4-MeC_6H_4	H	C_6H_5	12	118-121
79v	C_6H_5	4-$Me_2NC_6H_4$	H	33	170-172
80v	4-$Me_2NC_6H_4$	C_6H_5	H	17	165-167

III.3. Experimental Section

Microwave reactions were carried out in a CEM Discover Benchmate microwave digester. Melting points are uncorrected. Infrared spectra were recorded on a BOMEM DA-8 FTIR instrument and the frequencies are expressed in cm^{-1}. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance II-400 spectrometer using $CDCl_3$ as the solvent. Chemical shifts are reported in ppm downfield from internal tetramethylsilane and are given on the δ scale. Mass spectral data were obtained with a JEOL D-300 (EI) mass spectrometer. Elemental analyses were carried out on a Heraeus CHN-O-Rapid analyzer. All compounds give satisfactory elemental analyses within ± 0.4% of the theoretical values.

All reactions were monitored by TLC using precoated aluminum sheets (silica gel 60 F_{254} 0.2 mm thicknesses) and developed in an iodine chamber or under UVGL-15 mineral light 254 lamp. Column chromatographic separations were carried out using ACME silica gel (60–120 mesh).

General procedure for the synthesis of di-and tri-substituted-1, 2, 4-triazines:

A. Conventional Method

To a well stirred solution of sodium tertiary-butoxide (0.01 moles) in dry benzene, or THF at room temperature, a solution of 0.01 moles of amide (formamide, acetamide and benzamide) in benzene was added, followed by the addition of the 1,2-diketone (biacetyl, benzil, *p*-methoxy benzil, furil, pyridil) (0.01 moles). A solid, jelly-like mass was formed immediately due to the formation of the but-2-ene-1,4-dicarbonyl system. 10 ml of EtOH was added to dissolve the solid mass. Hydrazine hydrate was then added and the reaction mixture was further stirred at room temperature. After the reaction was completed (monitored by TLC), the product was extracted with benzene, dried over anhydrous Na_2SO_4 and the solvent distilled off. After keeping in the fridge for four hours or more, a crystalline solid was formed which was purified by repeated recrystallisation from EtOH or by column chromatography using ethylacetate/hexane as the eluent.

B. Microwave Method

A mixture of diketone (1 mmol), amide (1 mmol), hydrazine hydrate (1.5 mmol) and sodium tertiary-butoxide (1 g) was ground thoroughly and irradiated in a microwave digester at 450 W at 100°C for about 3 to 6 minutes at an interval of 30 seconds. During the irradiation, the solid melted and a sticky crude product was formed upon cooling. It was washed repeatedly with H_2O and then with hexane and finally dissolved in boiling EtOH, which afforded crystalline solid upon cooling. It was further purified by repeated recrystallisation (EtOH) or by column chromatography to give the pure products in good to excellent yield.

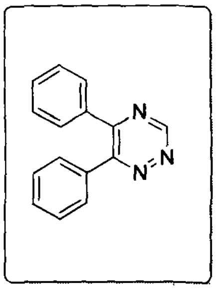
All the products were characterised by melting point, NMR, IR, Mass spectra and CHN analysis.

Preparation of regioisomeric 1, 2, 4-triazines:

To a well stirred solution of sodium tertiary-butoxide (0.01 moles) in benzene, amide (benzamide and formamide) was added, followed by 1, 2-dicarbonyl compound (0.01 moles). Stirring was continued until a jelly-like liquid was formed. 10 ml of EtOH was added to dissolve the jelly reaction mixture. Then 2 ml of hydrazine hydrate was added and the solution heated at reflux for 2.5 hours. Evaporation of the solvent under reduced pressure afforded a reddish brown liquid, which was poured into H_2O and extracted with CH_2Cl_2 (3 x 100 mL), washed with $NaHCO_3$ solution and dried with Na_2SO_4. Evaporation of the solvent under reduced pressure afforded reddish brown oil which contained the regioisomeric triazines. Column chromatography on silica gel and elution with 1:1 CH_2Cl_2/hexane afforded an initial fraction, **79(s-v)** in about 24-33% yield as solid products. Further elution with the same solvent afforded the second fraction, **80(s-v)** in about 13-17% yield (**Table-II**).

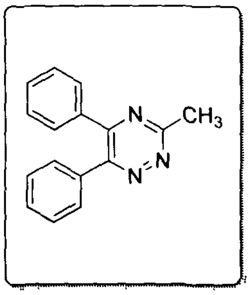
Spectroscopic and analytical data.

5,6-diphenyl-1,2,4-triazine (79a):



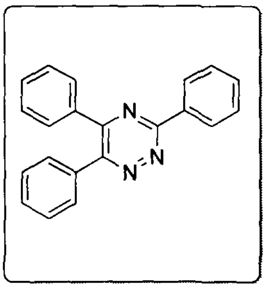
Mp 112-113°C; IR (KBr, cm^{-1}): 3060, 1620, 1585, 1485, 1440, 1405; ^{1}H NMR (CDCl$_3$): δ 7.25-7.94 (m, 10H); 9.60 (s, 1H); ^{13}C NMR (CDCl$_3$): δ 125.0, 126.4, 127.2, 127.9, 129.4, 130.1, 131.2, 136.1, 155.8, 157.0, 161.2; Mass: m/z 233 [M$^+$]; Anal. Calcd. for $C_{15}H_{11}N_3$: C, 77.25; H, 4.72; N, 18.02; Found: C, 77.41; H, 4.86; N, 17.87%.

5,6-diphenyl-3-methyl-1,2,4-triazine (79b):



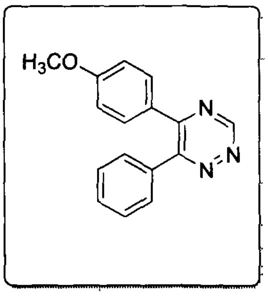
Mp 91-93°C; IR (KBr, cm^{-1}): 3061, 2921, 1577, 1488, 1445, 1393; ^{1}H NMR (CDCl$_3$): δ 2.42 (s, 3H), 7.24-7.51 (m, 7H), 7.80-8.11 (m, 3H); ^{13}C NMR (CDCl$_3$): δ 21.4, 124.8, 126.9, 128.7, 128.9, 129.0, 129.2, 129.7, 130.1, 136.9, 156.4, 157.6, 159.9; Mass: m/z 247 [M$^+$]; Anal. Calcd. for $C_{16}H_{13}N_3$: C, 77.73; H, 5.26; N, 17.00, Found: C, 77.84; H, 5.15; N, 16.83%.

3,5,6-triphenyl-1,2,4-triazine (79c):



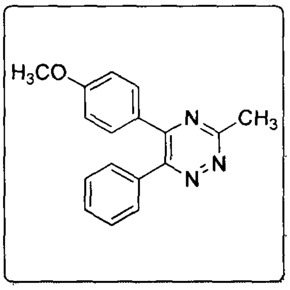
Mp 144-115°C; IR (KBr, cm^{-1}): 2978, 1672, 1477, 1414; ^{1}H NMR (CDCl$_3$): δ 7.27-7.38 (m, 11H), 7.51-7.56(m, 2H), 8.21 (d, 2H); ^{13}C NMR (CDCl$_3$): δ 124.5, 126.6, 127.6, 128.2, 128.3, 128.5, 129.5, 129.6, 135.4, 135.9, 136.5, 139.2, 157.2, 157.7, 159.2; Mass: m/z 309 [M$^+$]; Anal. Calcd. for $C_{21}H_{15}N_3$: C, 81.55; H, 4.85; N, 13.59; Found: C, 81.43; H 4.63; N, 13.50%.

5-anisyl-6-phenyl-1,2,4-triazine (79d):



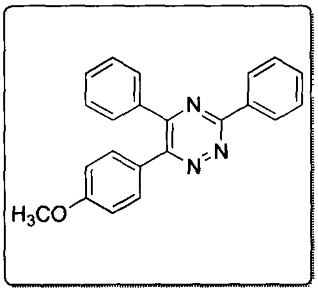
Mp 167-169°C; IR (KBr, cm^{-1}): 3023, 2961, 1608, 1568, 1480; ^{1}H NMR (CDCl$_3$): δ 3.83 (s, 3H), 7.24-8.03 (m, 9H), 9.55 (s, 1H); ^{13}C NMR (CDCl$_3$): δ 50.8, 124.3, 126.9, 127.3, 128.7, 129.3, 131.2, 134.3, 135.8 153.4, 156.1, 161.8; Mass: m/z 263 [M$^+$]; Anal. Calcd. for $C_{16}H_{13}N_3O$: C, 73.00; H, 4.94; N, 15.96; Found: C, 72.90; H, 4.85; N, 16.00%.

5-anisyl-3-methyl-6-phenyl-1,2,4-triazine (79e):



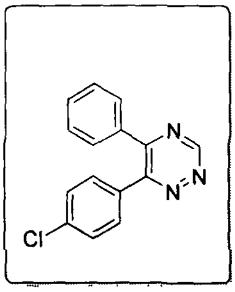
Mp 135-137°C; IR (KBr, cm^{-1}): 3041, 2930, 1625, 1560, 1482, 1431; ^{1}H NMR ($CDCl_3$): δ 2.60 (s, 3H), 3.85 (s, 3H), 7.3-8.0 (m, 9H); ^{13}C NMR ($CDCl_3$): δ 28.0, 50.3, 125.3, 127.0, 127.9, 128.7, 129.4, 131.1, 131.3,136.1, 138.1, 154.3, 158.1, 160.2; Mass: m/z 277 [M$^+$]; Anal. Calcd. for $C_{17}H_{15}N_3O$: C, 73.64; H, 5.41; N, 15.16; Found: C, 73.84; H, 5.33; N, 15.00%.

6-anisyl-3,5-diphenyl-1,2,4-triazine (79f):



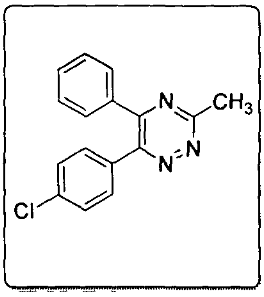
Mp 152-153°C; IR (KBr, cm^{-1}): 3061, 2941, 1618, 1570, 1480; ^{1}H NMR ($CDCl_3$): δ 3.84 (s, 3H), 7.31-7.80 (m, 12H), 8.10-8.25 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 50.5, 125.7, 126.0, 126.4, 127.0, 127.8, 128.6,129.3, 129.7, 130.4, 131.0, 132.4, 135.7, 155.1, 156.4, 160.3; Mass: m/z 339 [M$^+$]; Anal. Calcd. for $C_{22}H_{17}N_3O$, C, 77.87; H, 5.01; N, 12.38; Found: C, 77.70; H, 4.89; N, 12.10%.

6-(p-chlorophenyl)-5-phenyl-1,2,4-triazine (79g):



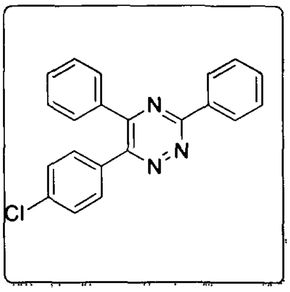
Mp 118-120°C; IR (KBr, cm^{-1}): 3040, 1610, 1568,1460,1405; ^1H NMR ($CDCl_3$): δ 7.3-8.0 (m, 9H), 9.72 *(s, 1H)*; ^{13}C *NMR* *($CDCl_3$): δ 125.6, 126.0, 127.5,* 128.2, 129.7, 132.7, 134.0, 135.6, 154.3, 156.1,162.0; Mass: m/z 267 [M^+]; Anal. Calcd. for $C_{15}H_{10}N_3Cl$: C 67.28, H 3.73, N 15.70; Found: C, 67.12; H, 3.84; N, 15.61%.

3-methyl-6-(p-chlorophenyl)-5-phenyl-1,2,4-triazine (79h):



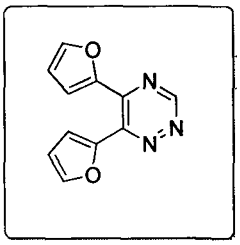
Mp 120-122°C; IR (KBr, cm^{-1}): 3050, 2940, 1622, 1591, 1505, 1450; ^1H NMR ($CDCl_3$): δ 2.68 (s, 1H), 7.31-8.04 (m, 9H); ^{13}C NMR ($CDCl_3$): δ 29.8, 125.9, 127.0, 127.9, 128.6, 130.8, 131.8, 133.0, 134.7, 154.0, 155.6, 162.1; Mass: m/z 233 [M^+]; Anal. Calcd. for $C_{16}H_{12}N_3Cl$: C, 68.20; H, 4.26; N, 14.92; Found: C, 68.45; H, 4.30; N, 14.81%.

3,5-diphenyl-6-(p-chlorophenyl)-1,2,4-triazine (79i):



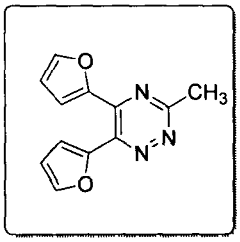
Mp 108-109°C; IR (KBr, cm^{-1}): 3045, 1630, 1592, 1500, 1470; ^1H NMR ($CDCl_3$): δ 7.29-7.96 (m, 12H), 8.07-8.22 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 125.3, 126.5, 127.2, 127.6, 128.0, 128.6, 129.0, 129.7, 131.8, 132.1, 133.2, 134.1, 155.4, 157.0, 161.9; Mass: m/z 343 [M^+]; Anal. Calcd. for $C_{21}H_{14}N_3Cl$: C, 73.36; H, 4.07; N, 12.22; Found: C, 73.44; H, 4.20; N, 12.12.

5,6-difuryl-1,2,4-triazine (79j):



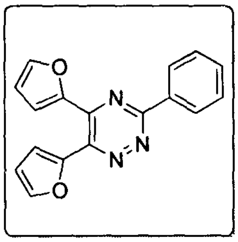
Mp 95-97°C; IR (KBr, cm^{-1}): 2978, 1624, 1477, 1415, 1074; ^1H NMR ($CDCl_3$): δ 6.24-6.61 (m, 6H), 9.71 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 112.1, 113.3, 116.1, 120.0, 123.1, 124.3, 154.1, 158.0, 160.3; Mass: m/z 213 [M^+]; Anal. Calcd. for $C_{11}H_7N_3O_2$: C, 61.97; H, 3.28; N, 19.72; Found: C, 62.08; H, 3.20; N, 19.50%.

5,6-difuryl-3-methyl-1,2,4-triazine (79k):



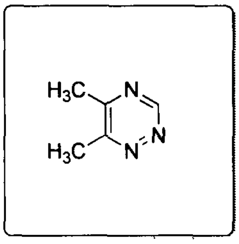
Mp 143-145°C; IR (KBr, cm^{-1}): 3002, 2924, 1620, 1495, 1415, 1033; ^{1}H NMR (CDCl$_3$): δ 2.61 (s, 3H), 6.26-8.05 (m, 6H); ^{13}C NMR (CDCl$_3$): δ 27.9, 112.1, 112.6, 113.0, 114.3, 116.7, 120.6, 124.0, 125.3, 154.1, 158.9, 160.0; Mass: m/z 227 [M$^+$]; Anal. Calcd. for $C_{12}H_9N_3O_2$: C, 63.43, H, 3.96, N, 18.50, Found: C, 63.57; H, 3.84; N, 18.38%.

5,6-difuryl-3-phenyl-1,2,4-triazine (79l):



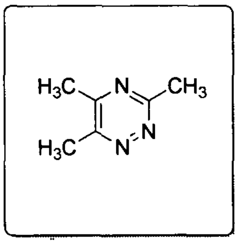
Mp 162-165°C; IR (KBr, cm^{-1}): 3010, 1631, 1505, 1430, 1035; ^{1}H NMR (CDCl$_3$): δ 6.25-6.75 (m, 6H), 7.71-8.01 (m, 5H); ^{13}C NMR (CDCl$_3$): δ 112.0, 112.8, 113.6, 114.3, 115.0, 115.7, 117.1, 120.6, 129.0, 130.1, 132.6, 134.3, 153.6, 154.1, 161.2; Mass: m/z 289 [M$^+$]; Anal. Calcd. for $C_{17}H_{11}N_3O_2$: C, 70.58, H, 3.80, N, 14.53; Found: C, 70.74; H, 3.71; N, 14.62%.

5,6-dimethyl-1,2,4-triazine (79m):



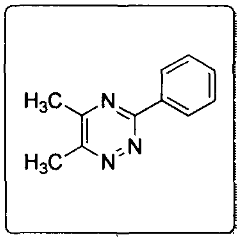
Mp 46-48°C; IR (KBr, cm^{-1}): 2931, 2919, 1511, 1483; ^1H NMR ($CDCl_3$): δ 2.37 (s, 3H), 2.41 (s, 3H), 9.75 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 19.9, 21.3, 156.9, 159.9, 160.2. Mass: m/z 109 [M^+]; Anal. Calcd. for $C_5H_7N_3$, C, 55.04; H, 6.42; N, 38.53; Found: C, 55.10; H, 6.45; N, 38.42%.

3,5,6-trimethyl-1,2,4-triazine (79n):



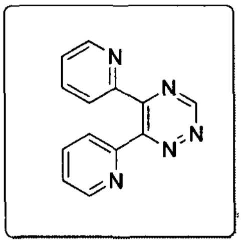
Mp 95-97°C; IR (KBr, cm^{-1}): 2925, 2911, 1520, 1495; ^1H NMR ($CDCl_3$): δ 2.35-2.40 (m, 6H), 2.42 (s, 3H), ^{13}C NMR ($CDCl_3$): δ 20.1, 20.6, 21.4, 157.1, 158.9, 161.3. Mass: m/z 123[M^+]; Anal. Calcd. for $C_6H_9N_3$, C, 58.53; H, 7.31; N, 34.14; Found: C, 58.55; H, 7.34; N, 34.00%.

3-phenyl-5,6-dimethyl-1,2,4-triazine (79o):



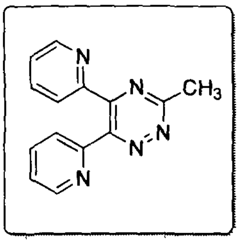
Mp 80-82°C; IR (KBr, cm^{-1}): 3020, 2918, 1610, 1508, 1494; ^{1}H NMR ($CDCl_3$): δ 2.34-2.39 (m, 6H), 7.76-7.81 (m, 5H), ^{13}C NMR ($CDCl_3$): δ 20.3, 21.1 , 126.1, 128.0, 128.8, 129.4, 130.1, 158.0, 159.4, 162.1. Mass: m/z 185 [M$^+$]; Anal. Calcd. for $C_{11}H_{11}N_3$, C, 71.35; H, 5.94; N, 22.70; Found: C, 71.48; H, 5.90; N, 22.62%.

5,6-dipyridyl-1,2,4-triazine (79p):



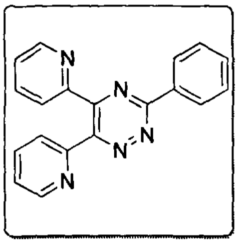
Mp 121-123°C; IR (KBr, cm^{-1}): 1605, 1508, 1495, 1410; ^{1}H NMR ($CDCl_3$): δ 8.9-9.38 (m, 4H), 9.51-9.63 (m, 4H), 9.73 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 158.0, 158.7, 159.8, 160.0, 161.0, 161.5, 162.8, 163.0, 163.8, 164.0, 164.9, 165.4, 166.3, Mass: m/z 235 [M$^+$]; Anal. Calcd. for $C_{13}H_9N_5$, C, 66.38; H, 3.82; N, 29.78; Found: C, 66.45; H, 3.89; N, 29.69%.

3-methyl-5,6-dipyridyl-1,2,4-triazine (79q):



Mp 127-129°C; IR (KBr, cm^{-1}): 1612, 1501, 1485, 1413; ^1H NMR ($CDCl_3$): δ 2.32 (s, 3H), 9.01-9.45 (m, 4H), 9.49-9.60 (m, 4H), 9.73 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 160.3, 160.9, 161.1, 161.5, 162.2, 162.9, 164.0, 164.7, 165.1, Mass: m/z 249 [M^+]; Anal. Calcd. for $C_{14}H_{11}N_5$, C, 67.46; H, 4.41; N, 28.11; Found: C, 67.37; H, 4.50; N, 28.20%.

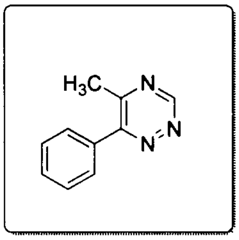
3-phenyl-5,6-dipyridyl-1,2,4-triazine (79r):



Mp 163-165°C; IR (KBr, cm^{-1}): 3040, 1620, 1504, 1490; ^1H NMR ($CDCl_3$): δ 8.31-8.68 (m,5H), 8.95-9.37 (m, 4H), 9.41-9.56 (m, 4H), ^{13}C NMR ($CDCl_3$): δ 131.6, 134.1, 137.0, 141.1, 157.4, 158.0, 158.5, 159.2, 159.8, 160.0, 161.0, 161.9, 164.0, 164.7, 165.7, 166.0, 166.4; Mass: m/z 311 [M^+]; Anal. Calcd. for $C_{19}H_{13}N_5$, C, 73.31; H, 4.18; N, 22.50; Found: C, 73.24; H, 4.11; N, 22.41%.

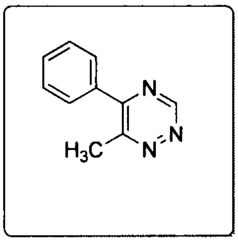
Spectroscopic and analytical data: Unsymmetrical Diketones:

5-methyl-6-phenyl-1,2,4-triazine (79s):



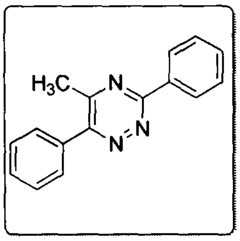
Mp 89-90°C; IR (KBr, cm^{-1}): 3046, 1610, 1590, 1515, 1480, 1455, 1405; ^{1}H NMR (CDCl$_3$): δ 2.64 (s, 3H); 7.64-8.16 (m, 5H); 9.80 (s,1H); ^{13}C NMR (CDCl$_3$): δ 124.6, 125.2, 129.0, 131.4, 133.6, 135.4, 158.0, 159.2, 161.5; Mass: m/z 171 [M$^+$]; Anal. Calcd. for $C_{10}H_9N_3$: C, 70.17; H, 5.26; N, 24.56; Found: C, 70.22; H, 5.29; N, 24.67%.

5-phenyl-6-methyl-1,2,4-triazine (80s):



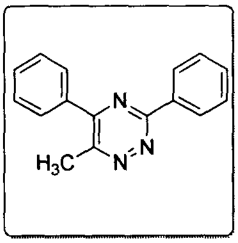
Mp 91-93°C; IR (KBr, cm^{-1}): 3041, 1605, 1595, 1500, 1495; ^{1}H NMR (CDCl$_3$): δ 2.70 (s, 3H), 7.71-8.20 (m, 5H); 9.81 (s, 1H); ^{13}C NMR (CDCl$_3$): δ 29.8, 124.2, 125.0, 128.8, 130.9, 133.4, 135.0, 158.7, 159.8, 162.0; Mass: m/z 171 [M$^+$]; Anal. Calcd. for $C_{10}H_9N_3$: C, 70.17; H, 5.26; N, 24.56; Found: C, 70.27; H, 5.34; N, 24.62%.

3,6-diphenyl-5-methyl-1,2,4-triazine (79t):



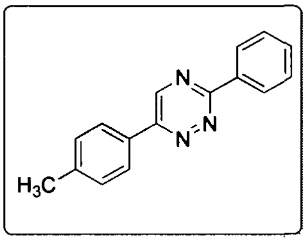
Mp 113-115°C; IR (KBr, cm^{-1}): 3050, 1605, 1590, 1510, 1450; ^{1}H NMR (CDCl$_3$): δ 2.65 (s, 3H), 7.70 - 8.30 (m, 10H); ^{13}C NMR (CDCl$_3$): δ 27.0, 124.8, 128.2, 128.6, 130.1, 131.1, 134.0, 135.7, 137.0, 157.6, 158.4, 162.4; Mass: m/z 247 [M$^+$]; Anal. Calcd. for $C_{16}H_{13}N_3$: C, 77.73; H, 5.26; N, 17.00; Found: C, 77.85; H, 5.40; N, 17.09%.

3,5-diphenyl-6-methyl-1,2,4-triazine (80t):



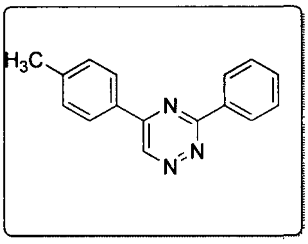
Mp 110-112°C; IR (KBr, cm^{-1}): 3054, 1602, 1595, 1505, 1480; ^{1}H NMR (CDCl$_3$): δ 2.78 (s, 3H); 7.80 - 8.43 (m, 10H); ^{13}C NMR (CDCl$_3$): δ 29.2, 124.5, 127.9, 128.3, 129.6, 130.8, 133.8, 135.6, 136.3, 156.8, 158.0, 162.2; Mass: m/z 247 [M$^+$]; Anal. Calcd. for $C_{16}H_{13}N_3$: C, 77.73; H, 5.26; N, 17.00; Found: C, 77.80; H, 5.46; N, 17.15%.

6-(p-methylphenyl)-3-phenyl-1,2,4-triazine (79u):



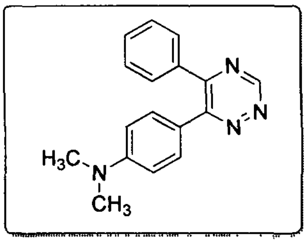
Mp 128-130°C; IR (KBr, cm^{-1}): 3030, 1605, 1595, 1457; ^1H NMR ($CDCl_3$): δ 2.65 (s, 3H), 7.13-8.09 (m, 9H), 8.72(s, 1H); ^{13}C NMR ($CDCl_3$): δ 29.0, 125.8, 129.2, 131.6, 133.1, 136.1, 138.0, 139.7, 112.0, 157.6, 159.4, 160.4; Mass: m/z 247 [M^+]; Anal. Calcd. for $C_{16}H_{13}N_3$: C, 77.71; H, 5.30; N, 16.99; Found: C, 77.72; H, 5.29; N, 17.03%.

5-(p-methylphenyl)-3-phenyl-1,2,4-triazine (80u):



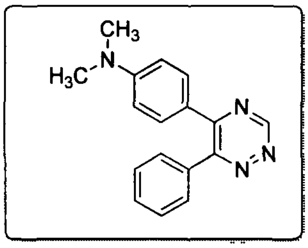
Mp 118-121°C; IR (KBr, cm^{-1}): 3035, 1615, 1590, 1450; ^1H NMR ($CDCl_3$): δ 2.65 (s,3H), 7.78-8.50 (m, 9H), 9.24(s, 1H); ^{13}C NMR ($CDCl_3$): δ 28.0, 125.8, 129.2, 131.6, 133.1, 136.1, 138.0, 139.7, 112.0, 157.6, 159.4, 160.4; Mass: m/z 247 [M^+]; Anal. Calcd. for $C_{16}H_{13}N_3$: C, 77.71; H, 5.30; N, 16.99; Found: C, 77.73; H, 5.35; N, 17.02%.

6-*p*-(*N*,*N*-dimethylamino)phenyl-5-phenyl-1,2,4-triazine (79v):

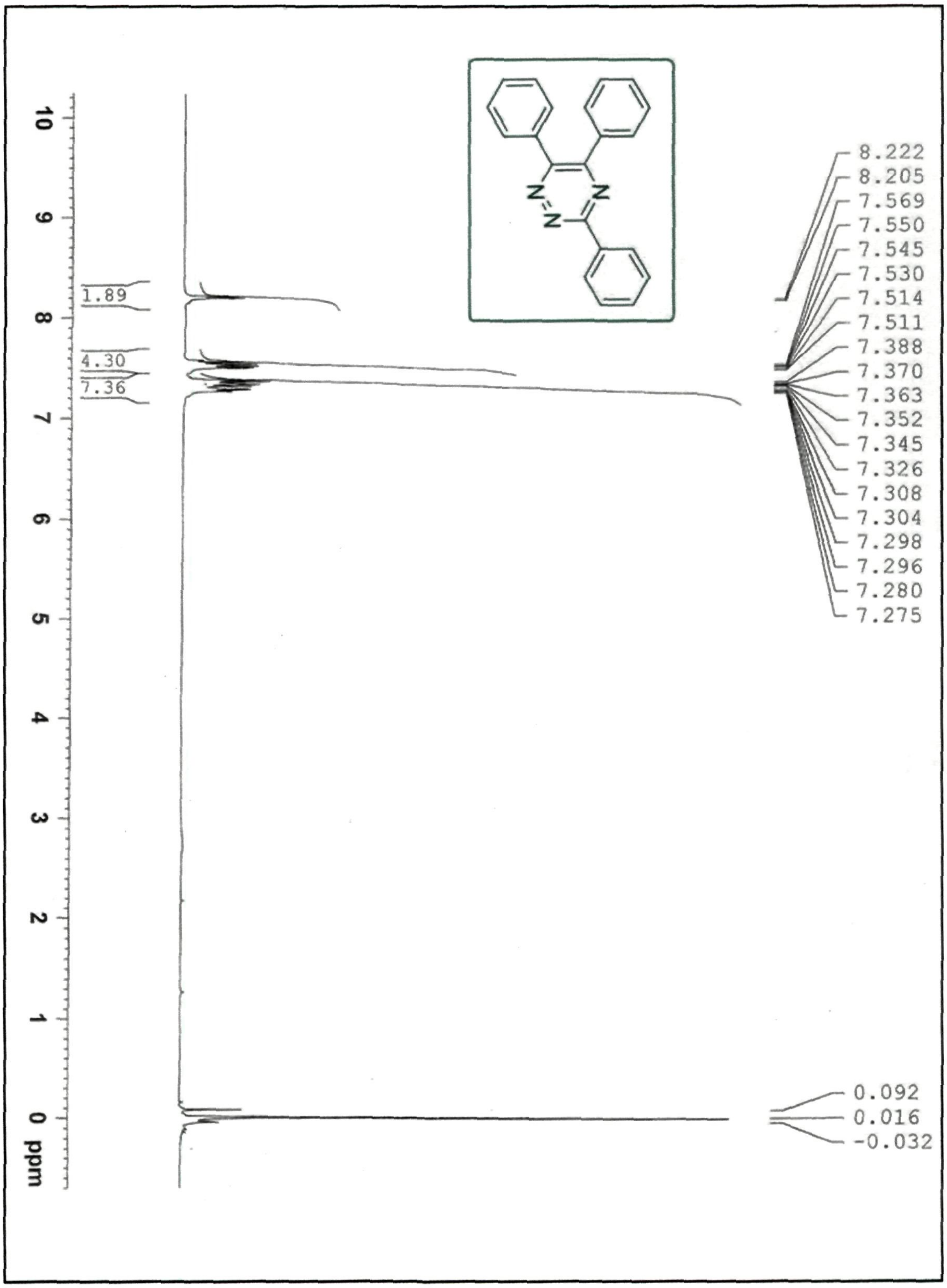


Mp 170-172°C; IR (KBr, cm^{-1}): 3049, 1623, 1545, 1555; ^{1}H NMR (CDCl$_3$): δ 2.80 (s, 6H), 7.37-8.23 (m, 9H), 9.70(s, 1H); ^{13}C NMR (CDCl$_3$): δ 40.3, 122.8, 123.2, 127.2, 131.1, 137.1, 139.0, 141.7, 150.0, 155.8, 158.5, 159.0; Mass: m/z 276 [M$^+$]; Anal. Calcd. for $C_{17}H_{16}N_4$: C, 73.89; H, 5.84; N, 20.27; Found: C, 73.87; H, 5.83; N, 20.25%.

5-*p*-(*N*,*N*-dimethylamino)phenyl-6-phenyl-1,2,4-triazine(80v):



Mp 165-167°C; IR (KBr, cm^{-1}): 3043, 1611, 1584; ^{1}H NMR (CDCl$_3$): δ 2.82 (s, 6H), 7.01-8.13 (m, 9H)), 9.85(s, 1H); ^{13}C NMR (CDCl$_3$): δ 39.3, 120.8, 122.2, 126.2, 133.1, 136.1, 138.0, 139.7, 112.0, 155.8, 158.5, 159.0; Mass: m/z 276 [M$^+$]; Anal. Calcd. for $C_{17}H_{16}N_4$: C, 73.89; H, 5.84; N, 20.27; Found: C, 73.88; H, 5.86; N, 20.29%.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7.550
7.545
7.530
7.514
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7.388
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7.345
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7.296
7.280
7.275
0.092
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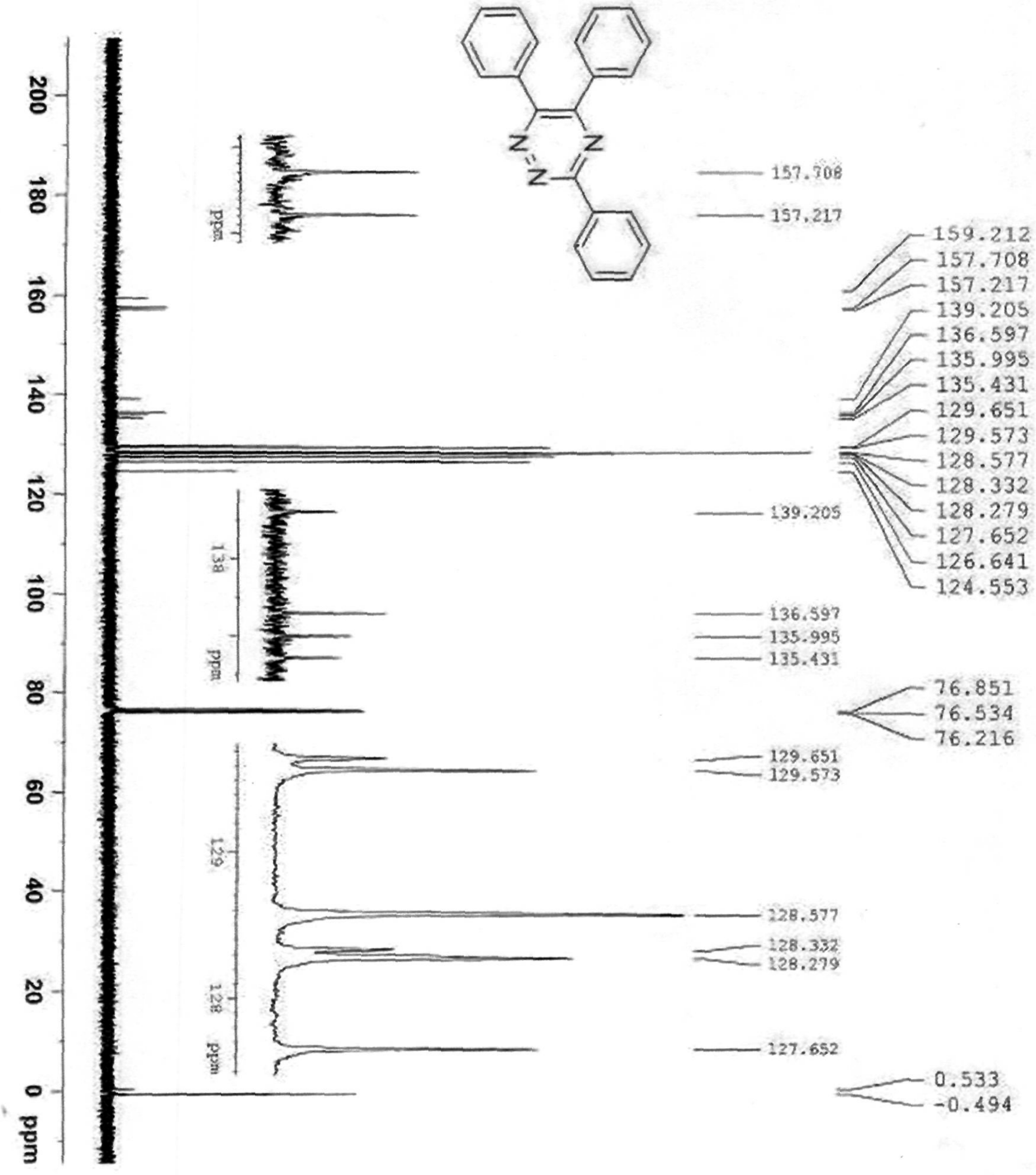
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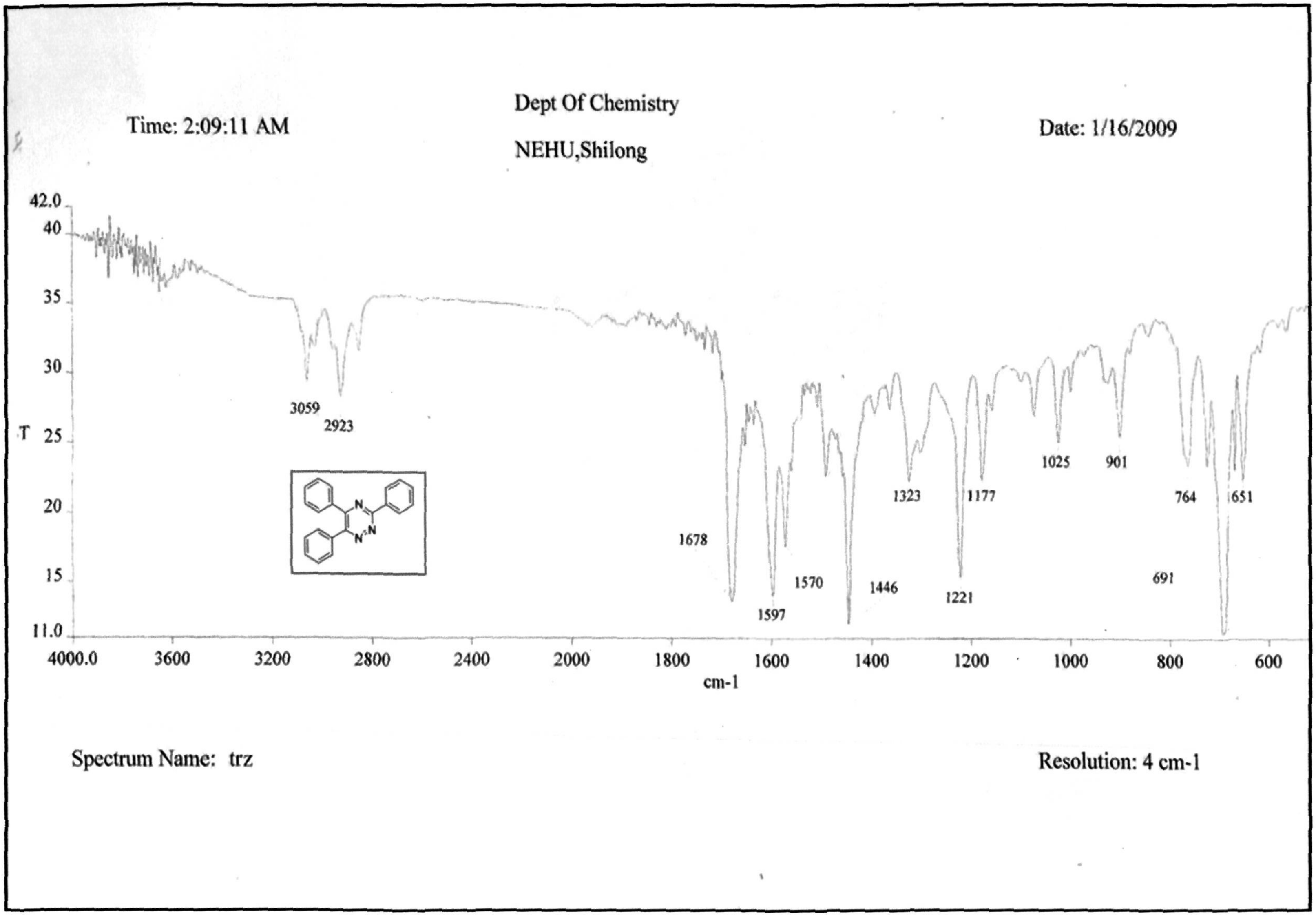

Dept Of Chemistry

NEHU,Shilong

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Date: 1/16/2009

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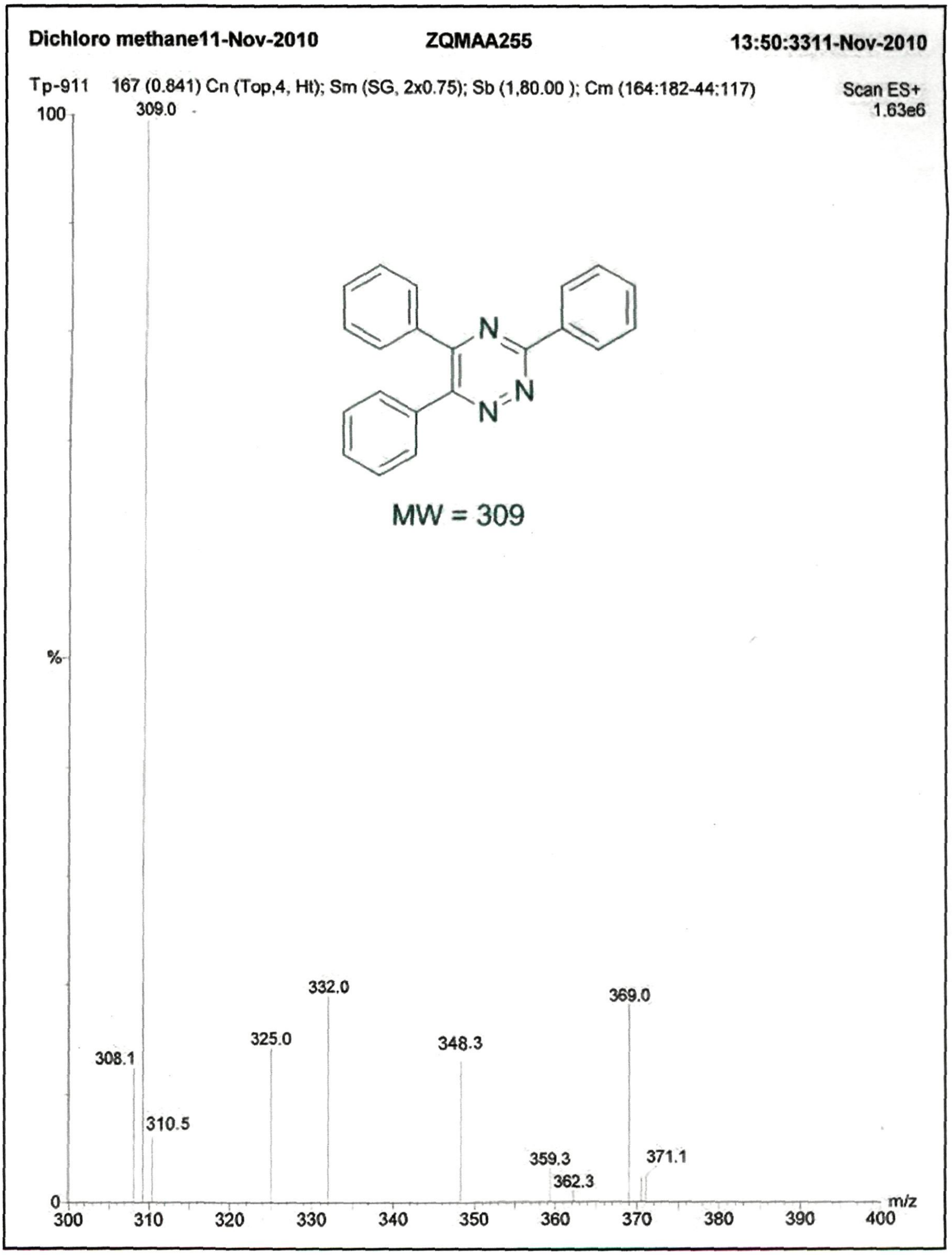
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m/z
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N
N
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III.4. References:

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Chapter IV

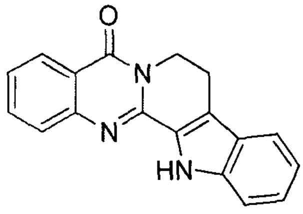
Microwave assisted synthesis of 3-substituted quinazolin-4(3*H*)-one using silica supported potassium carbonate

IV.1. Introduction

Quinazolinones or keto-quinazolines are the most important compounds of quinazoline system. Depending on the position of the keto or oxo group, these compounds may be classified into two types: 2-(1*H*)-quinazolinones or 1,2-dihydro-2-oxoquinazolines and 4(3*H*)-quinazolinones or 3,4-dihydro-oxoquinazolones. These systems exhibit lactam-lactim tautomerism and undergo hydroxyl group replacement reaction.

Quinazolinones are often high melting crystalline solids, insoluble in water and in most organic solvents but soluble in aqueous alkali. They are generally insoluble in dilute acids but are sometimes soluble in concentrated acids. Simple 4(3*H*)-quinazolinones, although insoluble in dilute acids, are soluble in 6N hydrochloric acid. 4(3*H*)-quinazolinones form stable monohydrochlorides, chloroplatinates, chloroaurates and picrates[1] and their metal salts of silver, mercury, zinc, copper, sodium and potassium.[2]

Recent attention has been focused much on the derivatives of quinazolinones, especially in view of their potential pharmalogical and biological activities, such as anti-parasitic, anti-tumor,[3a] anti-bacterial,[3b] anti-fungal,[3c,d] anti-inflammatory,[3e] anti-viral,[3f] potential anti-convulsants,[3g] anti-coccidial activity[3h] and as Tyrosine Kinase Inhibitors.[3i,j] Quinazolinone moieties are also found in several naturally occurring bioactive alkaloids such as rutaecarpine (**1**),[4] Anacine (**2**),[5] fiscalin,[6] sclerotigenin,[7] circumdatin,[8] benzomalvin,[9] etc. Hence, at the present time, approximately 50 quinazolinone derivatives with a wide variety of biological activities are available for clinical use.



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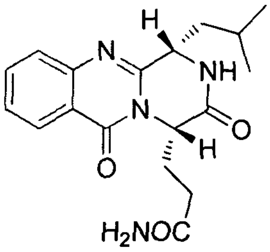
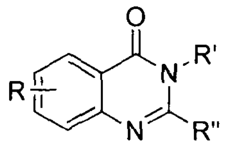


2

3*H*-quinazolin-4-one (**3**) is a frequently encountered unit in natural products such as *l*-vasicinone (**4**),[10] chrysogine (**5**)[11] and drugs[12] such as methaqualone (**6**),[13] febrifugine (**7**) and isofebrifugine (**8**). The latter two compounds are potent but toxic anti-malaria drugs, the stereochemistry of which have recently been revised.[14] Molecules based on quinazoline and quinazolinone exhibit a multitude of interesting pharmacological activities.[15]



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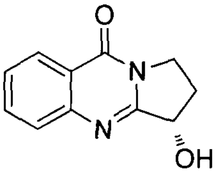

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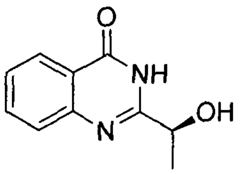

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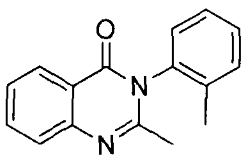

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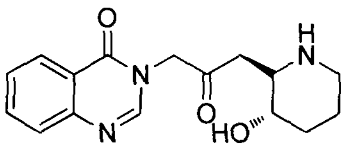

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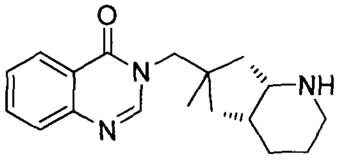

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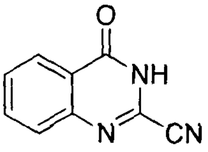
IV.2. Synthetic studies on quinazolinone derivatives.

The first quinazolinone was synthesized[16] in the late 1860s from anthranilic acid and cyanogens to give 2-cyanoquinazolinone (**9**). Interest in the medicinal chemistry of quinazolinone derivatives was stimulated in the early 1950s with the elucidation of a quinazolinone alkaloid, 3-[β-keto-γ-(3-hydroxy-2-piperidyl)-propyl]-4-quinazolone [febrifugine (**7**)], from an asian plant *Dichroa febrifuga*, which is an ingredient of a traditional Chinese herbal remedy, effective against malaria.



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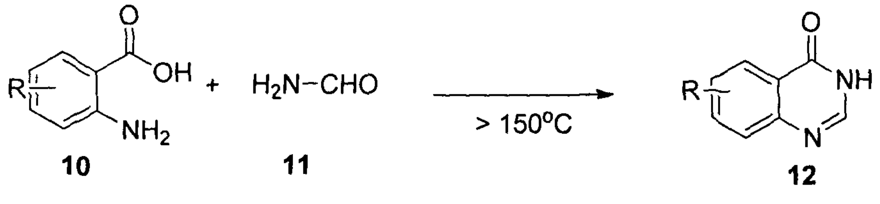
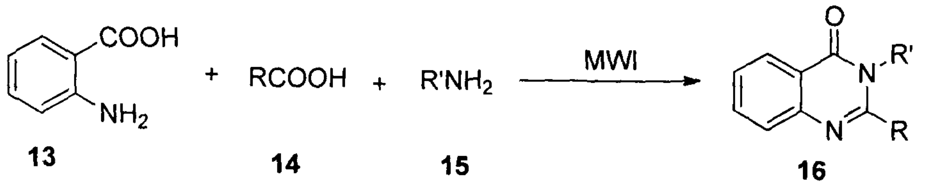
In 1895, Niementowski reported the synthesis of 4-quinazolinones, which involved a cyclocondensation of anthranilic acid or substituted anthranilic acid and amides at temperatures not exceeding 150°C.[18]



Scheme-1

In a search to speed up the aspect of drug-discovery processes, the Niementowski synthesis of the quinazolinone core has been extended to the synthesis of 3-substituted-4(3*H*)quinazolinones in an attempt to improve its yield and applicability.[19a] The amides or amidines generally used in the Niementowski reaction were replaced by formic acid or carboxylic acid (**14**) and primary aromatic or heteroaromatic amines (**15**), which afforded 3-substituted-4(3*H*)quinazolinones instead of the corresponding 2-substituted derivatives.

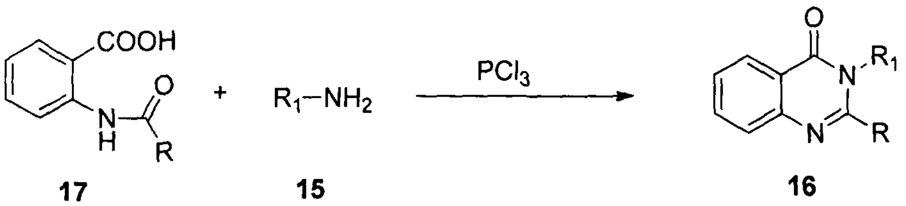
s



R , R' = Alkyl or aryl

Scheme-2

Grimmel modified the former synthesis by heating *N*-acetylanthranilic acids (**17**) with anilines (**15**) in toluene or xylene in the presence of condensing agents such as phosphorus trichloride, phosphorus oxychloride or thionyl chloride[19b] to yield substituted quinazolones (**16**). This procedure was successful when aromatic amines, aralkyl amines, aliphatic amines or arylhydrazines were used, however, with α-naphthylamine, allylamine, 2-amino-pyridine and 2-amino-6-ethoxybenzothiazole, it failed to yield quinazolones under the conditions of the experiments employed and in each case the starting material *N*-acetylanthranilic acid was recovered almost quantitatively.

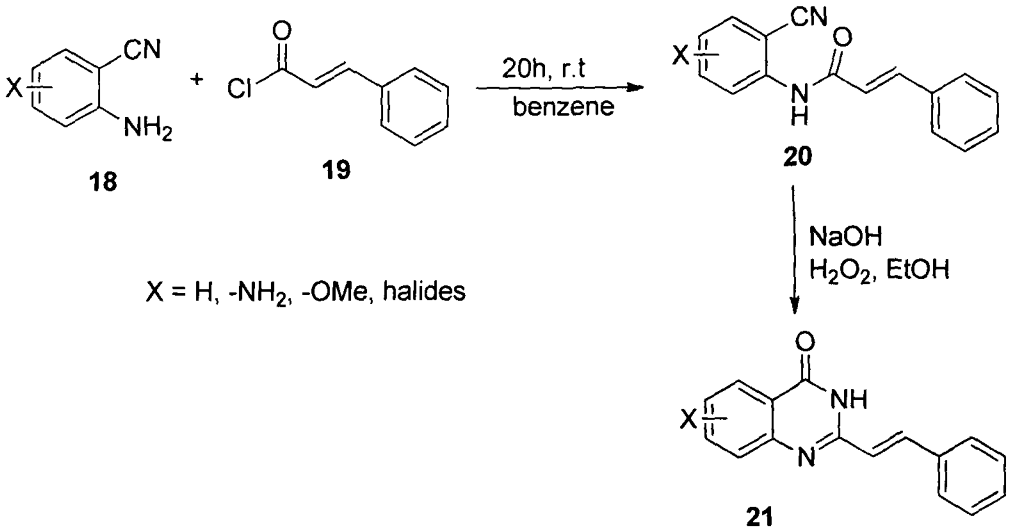


R = Alky or aryl

R_1 = Alkyl, aryl, heteroaryl, aralkyl, arylhydrazine

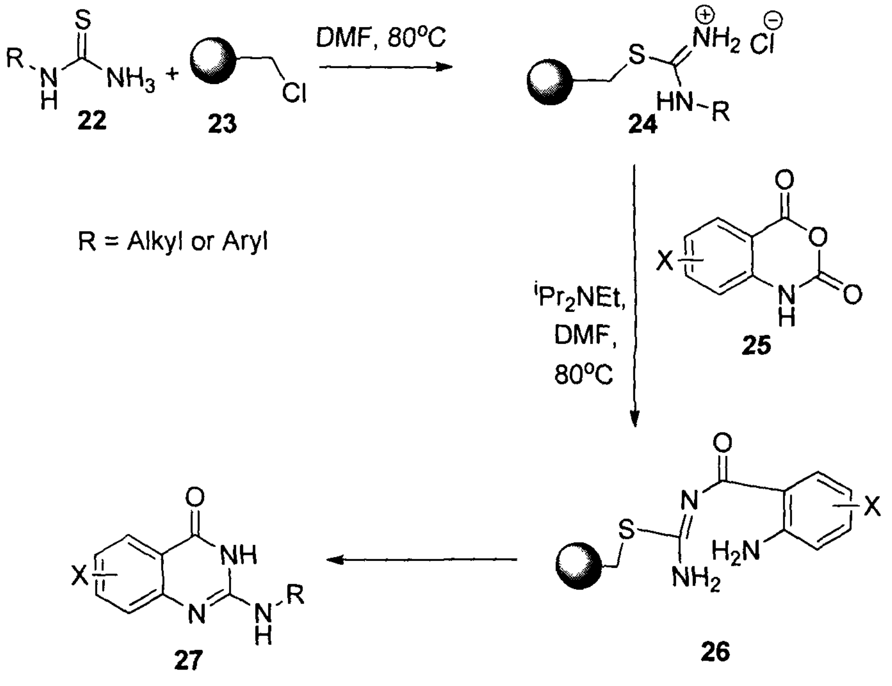
Scheme-3

The most common procedure for the synthesis of quinazolinone involves amidation of 2-aminobenzonitrile (**18**), anthranilic acid (**13**) and 2-aminobenzamide. For example, the reaction of 2-aminobenzonitrile with 3-phenyl-acryloyl chloride followed by oxidative ring closure under basic conditions produced 2-styryl-4(3*H*)-quinazolinone (**21**) in 29% yield (**Scheme-4**).[20] In most cases, the amide intermediates **20** can be isolated in good yields. The overall yields to these 2-styryl-quinazolinones (**21**), however, varied between 4% and 61%.



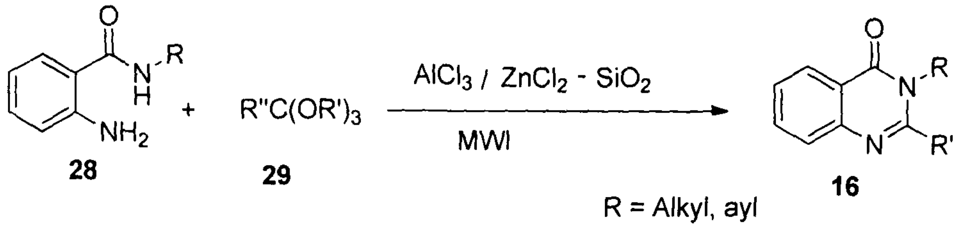
Scheme-4

However, a search for a more reliable and suitable drug is always fascinating and challenging. Therefore, a number of synthetic methods for the preparation of substituted 4-quinazolinones have been described *via* alternate pathways such as reaction of thioureas with isatoic anhydride (**25**).[21] Thiourea or *N*-substituted thiourea (**22**) is loaded to a chloromethylated polystyrene resin (**23**) in DMF at 80°C to form the polymer-bound isothiourea (**24**) which then react with isatoic anhydride (**25**) in DMF in the presence of diisopropylethylamine to afford 2-amino-4(3*H*)-quinazolinones (**27**). The products were formed *via* acylation of the polymer-bound isothiourea by isatoic anhydride , followed by cleavage of the resulting product *via* an intramolecular cyclization.



Scheme-5

The synthesis of mono- and disubstituted (3*H*)-quinazolin-4-ones under solvent free conditions by using microwave irradiation was reported by Babiri and co-workers.[22] Where 2-aminobenzamides (**28**) and orthoesters (**29**) were mixed with $AlCl_3/ZnCl_2$ supported on silica gel and subjected to microwave irradiation, the corresponding substituted (3*H*)-quinazolin-4-ones (**16**) were obtained in good yields .



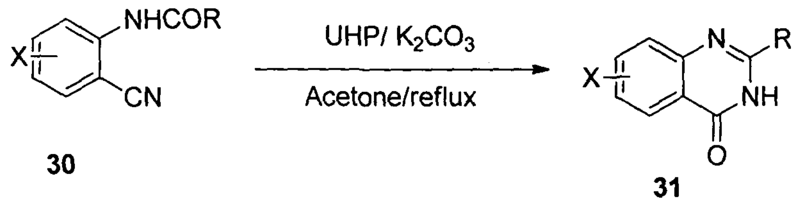
R = Alkyl, ayl

R' = Me or Et

R" =H, alkyl or aryl

Scheme-6

Bandgar[23a] have reported the use of urea–hydrogen peroxide (UHP) adduct which is a mild, safe and non-hazardous oxidising agent, with potassium carbonate for the synthesis of quinazolin-4-(3*H*)-ones (**31**) from suitably functionalized *o*-amidobenzonitriles (**30**). This methodology was also used to synthesise 2-hydroxymethylquinazolin- 4(3*H*)-one in good yields by Batvetsias.[23b]



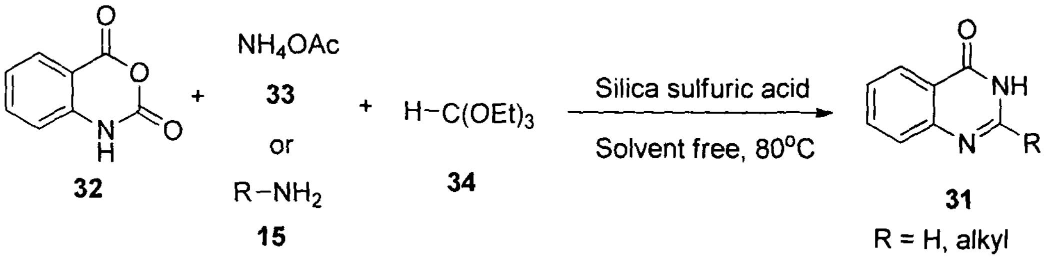
X= Br, H, NO_2

R = Aryl. alkyl

Scheme-7

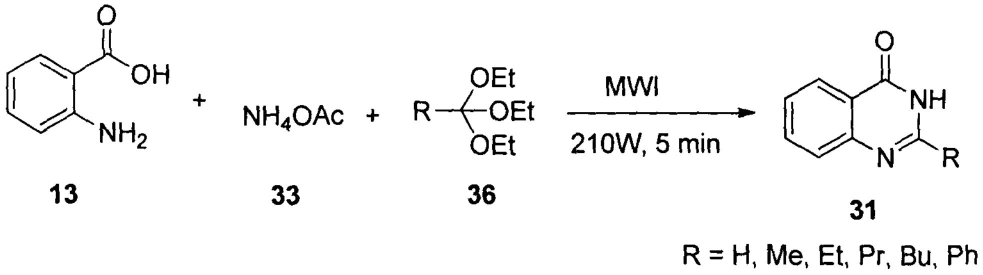
Isatoic anhydride (**32**) also serves as a source for the synthesis of quinazolinone. Quinazolin-4(3*H*)-one derivatives (**31**) were synthesized successfully *via* a one-pot, three component reaction of isatoic anhydride and an orthoester (**34**) with ammonium acetate (**33**) or a primary amine catalyzed by silica sulfuric acid under solvent-free conditions.

This is the first report on the synthesis of 2-substituted quinazolin-4(3*H*)-ones by this procedure.[24]



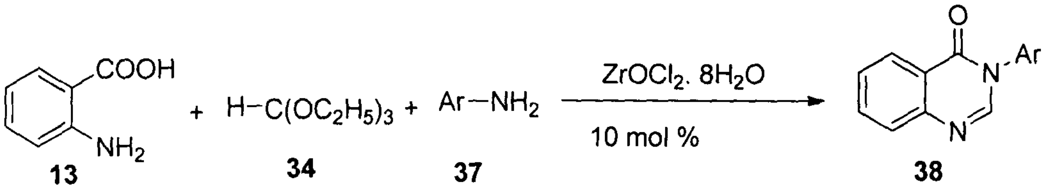
Scheme-8

The above procedure (**Scheme-7**) is the modification of Rad-Moghadam and Mohseni method[25] where anthranilic acid was replaced by isatoic anhydride. The latter protocol involves the condensation of anthranilic acid (**13**), ammonium acetate (**33**) and the orthoesters (**36**), which gives access to the 2-substituted-4(3*H*)-quinazolinone under microwave irradiation.



Scheme-9

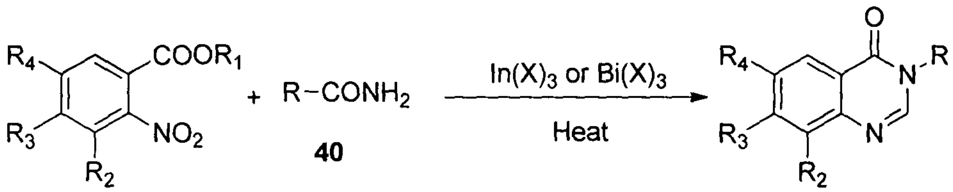
Shinde and co-workers[26] recently reported a route to 3-substituted quinazolin-4(3*H*)-ones using zirconyl(IV)chloride as catalyst, where anthranilic acid (**13**), aniline (**37**), and triethyl orthoformate (**34**) were allowed to react in various solvents like THF, acetonitrile and ethanol etc. Among the results obtained, use of 10 mol% $ZrOCl_2$ in ethanol–water gave the best yield (98%) for the synthesis of quinazolin-4(3*H*)-ones and the use of environmentally benign solvent, such as water, has got very much importance in Green Chemistry. The methodology was extended for the synthesis of an array of quinazolin-4(3*H*)-ones **(38)** using different anilines.



Ar = Ph, Substituted Ph

Scheme-10

Intermolecular reductive *N*-heterocyclization of 2-nitrobenzoic acid (**39**) and its acid derivatives with formamide or amides (**40**) were catalyzed by indium(III) or bismuth(III) salts to yield 4(3*H*)-quinazolinones in one-pot and was reported by Negrete *et al,*[27] The transformation was compatible with indium(III)chloride and triflate salts, as well as bismuth(III) acetate but did not occur with the acetates of Zn^{+2}, Fe^{+3}, Sc^{+3}, Yb^{+3}, and Ni^{+2}. A full equivalent of In(III) or Bi(III) salt was required for the complete conversion. The transformation did not proceed in the absence of the salt even after extended heating.



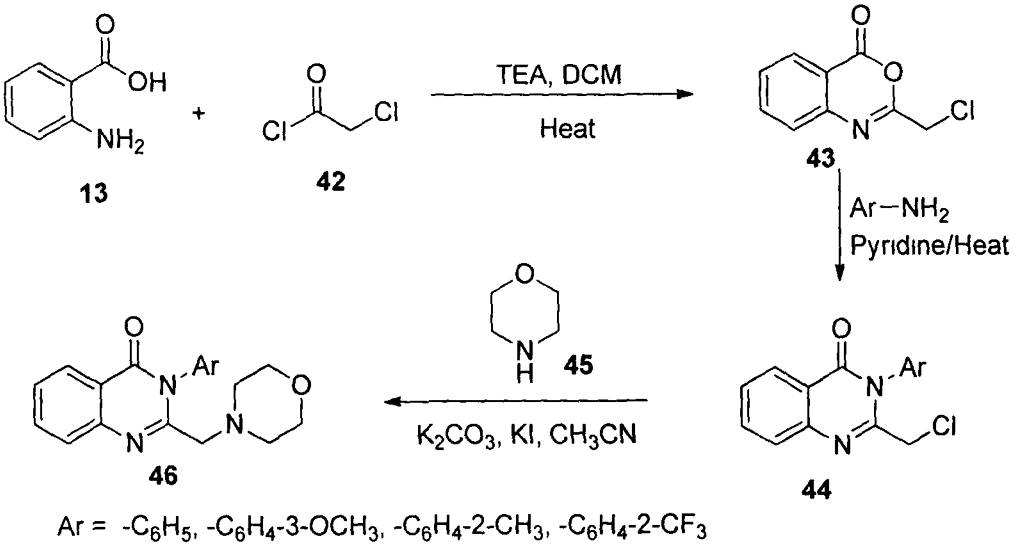
39

R=H, CH_3
R_1 = Bn or Me
R_2, R_3, R_4 = H, OMe, OBn, Cl, SMe

41

Scheme-11

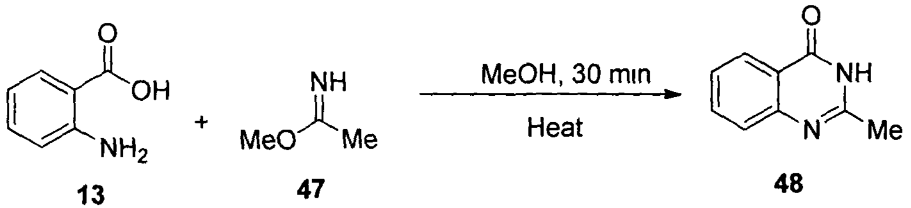
Thatipally and group[27b] have reported the use of polyethylene glycol (PEG-400), an efficient reaction medium for the preparation of quinazolinone derivatives containing nitrogen cyclic ring systems. Anthranilic acid (**13**) was treated with chloroacetyl chloride (**42**) in presence of triethylamine (TEA) in dichloromethane at room temperature to obtain previously reported 2-chloromethyl benzo[*d*][1,3]oxazin-4-one (**43**). The latter on treatment with aniline in refluxing pyridine for 5-6 hrs, followed by simple processing resulted in the formation of 2-(chloromethyl)-3-(3- substituted phenyl) quinazolin-4(3*H*)-one (**44**). The reaction of **44** with morpholine (**45**), K_2CO_3 and KI under refluxing acetonitrile for 90-120 min. resulted in the formation of 2-morpholin-4-yl-methyl-3-phenyl-3*H*-quinazolin-4-one (**46**) (**Scheme-12**).



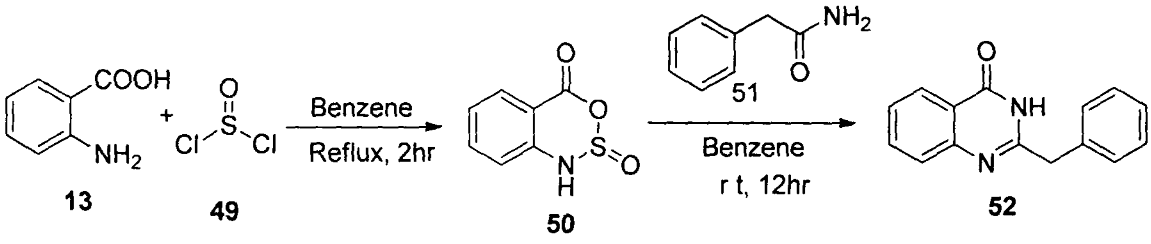
Ar = $-C_6H_5$, $-C_6H_4$-3-OCH_3, $-C_6H_4$-2-CH_3, $-C_6H_4$-2-CF_3

Scheme-12

2-methyl-4(3*H*)-quinazolinone (**48**) was isolated from a culture of the microorganism *Bacillus cereus*[29a] and has been prepared synthetically before its isolation.[29b] Recently, it was synthesized by Connolly and Guiry.[30] In their general approach to the synthesis of this type of alkaloids, a straightforward condensation between anthranilic acid (**13**) and various imidates in boiling methanol produced a range of 2-substituted quinazolin-4(3*H*)-ones, *e g.,* condensation with the imidate (**47**) produced the alkaloid **48** (**Scheme-13**). A more efficient one-pot approach to this type of moiety was provided by Kametani *et al,*[31] in which a natural product, glycosminine (**52**), has been synthesized starting from anthranilic acid *via* a sulfonamide anhydride (**50**) (**Scheme-14**).

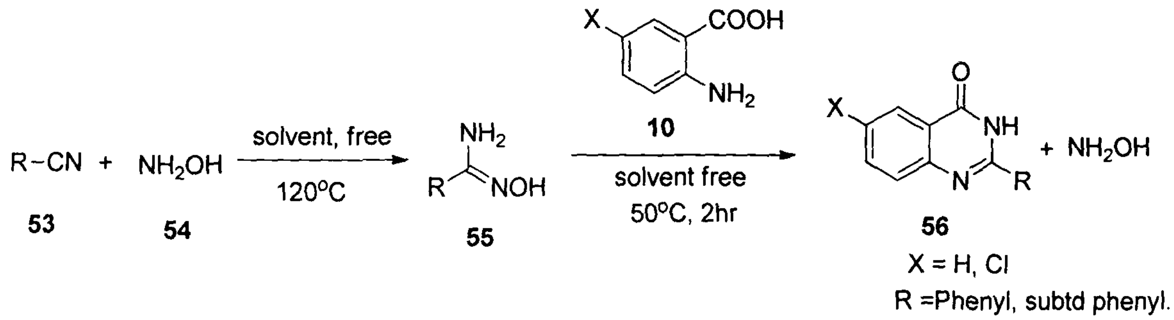


Scheme-12



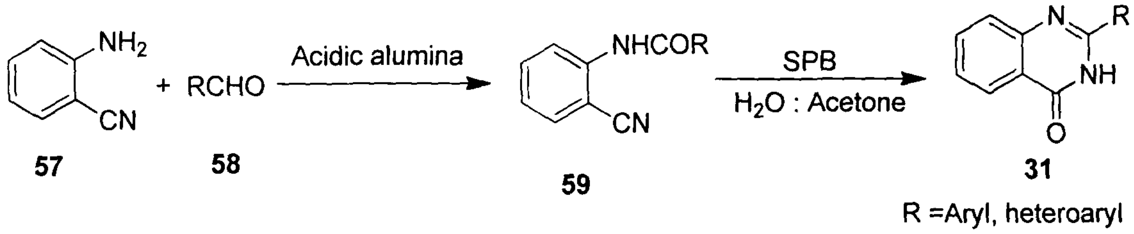
Scheme-14

A novel one-pot synthesis of 4(3*H*)-quinazolinone from nitrile and hydroxyl amine was reported by Adib and co-workers.[32] Nitrile (**53**) and hydroxylamine (**54**) was heated under solvent free condition which produces amidoxine (**55**) *in situ*, further condensation with anthranilic acid (**13**) produces 4(3*H*)-quinazolinone derivative (**36**) in excellent yield. However, when the reaction was performed by heating a mixture of nitrile, hydroxylamine and anthranilic acid in one-pot procedure, the yield is much lower.



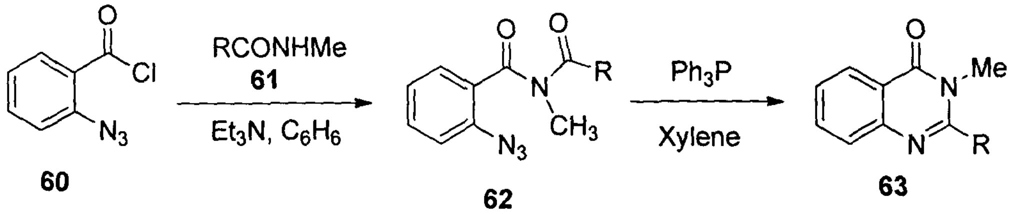
Scheme-15

Acidic alumina and sodium perborate (SPB) can also be used as a catalyst for the synthesis of 4(3*H*)-quinazolinone. 2-aminobenzonitrile (**57**) on reacting with aromatic or heteroaromatic aldehyde in acidic alumina produces the intermediate *N*-(2-cyano-phenyl)-acetaminde which on further reaction in acetone-water mixture in presence of sodium perborate cyclises to give 2-substituted-4(3*H*)-quinazolinone (**31**).[33]



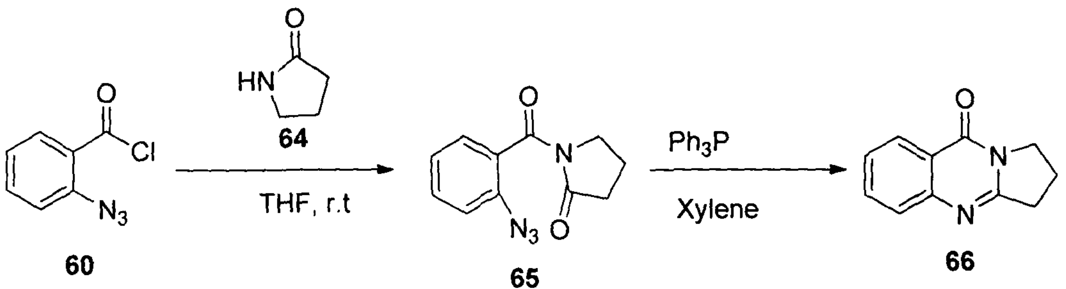
Scheme-16

Acylation of *N*-methylamides (**61**) with 2-azidobenzoyl chloride (**60**) (readily available from 2-azidobenzoic acid) forms imides (**62**), which upon treatment with triphenylphosphine (TPP) in the course of consecutive Staudinger reaction/intramolecular aza-Wittig reaction quantitatively gives 3-methylquinazolin-4(3*H*)-ones (**63**) (**Scheme 17a**).[34] Application of this method to pyrrolidinone (**64**) provides a facile synthesis of deoxyvacisinone (**66**).[35] Cyclization proceeds more rapidly with tributylphosphine (TBP) than with TPP in accordance with the general reactivity trend; however, steric effects should also be considered as an important factor in these aza-Wittig reactions. This method has been generalized for the quinazolinone annelation of lactams.[36] A successful application is the short synthesis of rutecarpine **11**, an alkaloid of *Evodia rutaecarpa*, from 2,3,4,9-tetrahydro-1*H*-β-carbolin-1-one *via* 2-azidobenzoyl derivative (**65**). Among several known syntheses of **11**, this is the most facile one.



R= Me, cyclopropyl, styryl

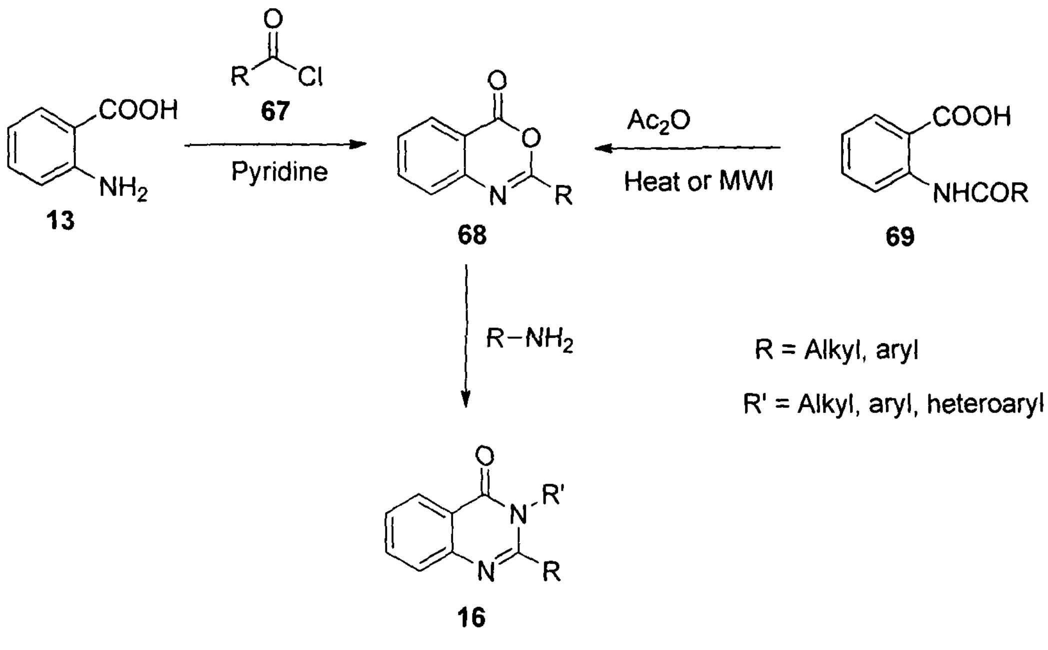
Scheme-17a



Deoxyvasicinone

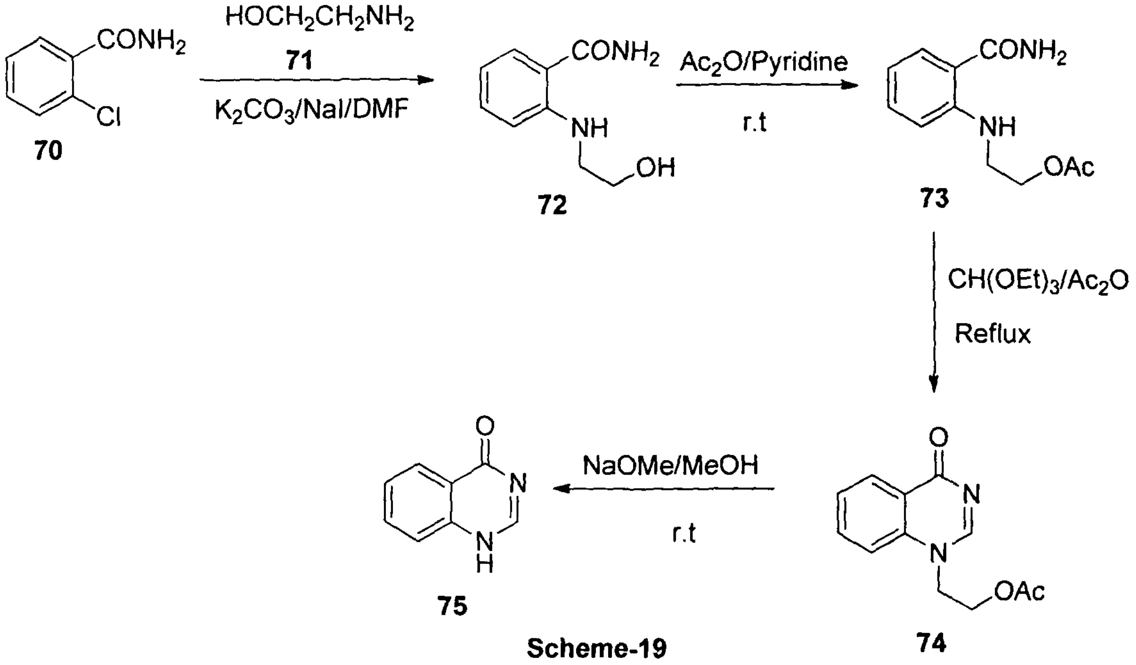
Scheme-17b

Benzoxazin-4-one (**68**) also serves as an important intermediate for the synthesis of quinazolinone. Cyclodehydration of 2-benzamidobenzoic acid (**69**) with excess of acetic anhydride under anhydrous conditions and removal of excess acetic anhydride under reduced pressure gave benzoxazin-4-one (**68**). The alternate procedure is from the reaction of anthranilic acid and benzoyl chloride in pyridine by maintaining the temperature near 0-5°C. Benzoxazin-4-one on further reaction with aliphatic or aromatic primary amines gives substituted quinazolin-4(3*H*)-ones (**16**).[37]



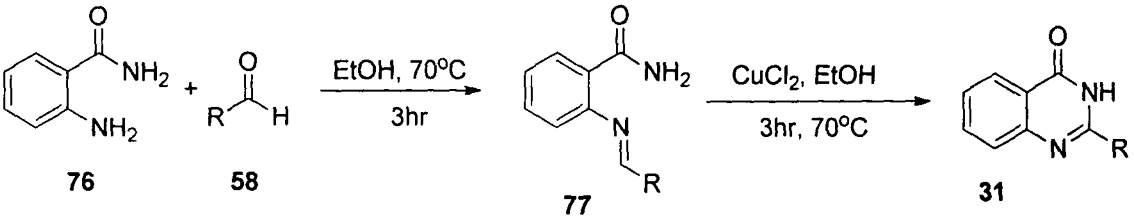
Scheme-18

Reisch and co-workers[38] have reported the synthesis of quinazolinone from *o*-Chlorobenzamide (**70**). The starting reactant, *o*-chlorobenzamide is first converted to l-(2-hydroxyethyl)-4(1*H*)-quinazolinone by reacting with ethanolamine (**71**). The anthranilamide derivative (**72**), which was prepared by Ullmann condensation of the above two compounds, was *O*-acetylated and treated with triethylorthoformate and acetic anhydride to produce the 4(1*H*)- quinazolinone derivatives (**74**). De-acetylation of the acetate with sodium methoxide yielded the desired 4(1*H*)-quinazolinone (**75**) (**Scheme-19**).



Scheme-19

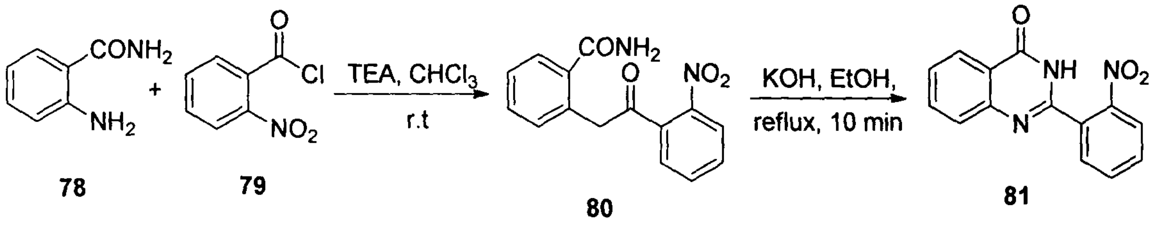
The use of anthranilamide (**76**) for the synthesis of quuinazolinone has been reported by various chemists. Abdel-Jalil *et al,*[39a] reported that the condensation of anthranilamide (**76**) with aryl, alkyl and heteroaryl aldehydes (**58**) in refluxing ethanol in the presence of $CuCl_2$ generates a Schiff base intermediate **77**, which is in turn, converted into the 2-substituted quinazolinones (**31**) in excellent yields (**Scheme-20**). In a one-pot procedure, the aldehyde, anthranilamide and 3 equiv. of $CuCl_2$ are refluxed in ethanol for 2–3 hours. After purification by chromatography, the 2-substituted quinazolinones (**31**) are isolated in 71–88% yield. Although, 2-substituted-4-quinazolinone nucleus has been similarly synthesized *via* condensation of anthranilamides with aldehydes followed by oxidation reaction using $NaHSO_3$[39b] or DDQ[39c] in good yields. This method has the advantage of the low temperature needed to achieve complete conversion of the anthranilamide to the quinazolinone derivatives.



R =Aryl, alkyl and heteroaryl

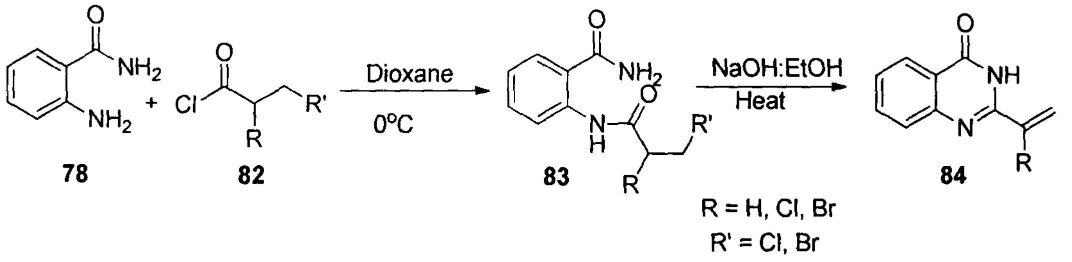
Scheme-20

The amidation of anthranilamide (**78**) using 2-nitrobenzoyl chloride (**79**) and triethylamine (TEA) gives the amide intermediate (**80**), which can be converted to 2-(2-nitrophenyl)-3-quinazolin-4-one (**81**) by ring closure of **80** under basic conditions, using potassium hydroxide in ethanol. 2-(2-nitrophenyl)-quinazolin-4(3*H*)-one is an important intermediate for the synthesis of highly functionalized glycol-conjugated quinazolino[4,3-*b*]quinazolinone molecule.[40]

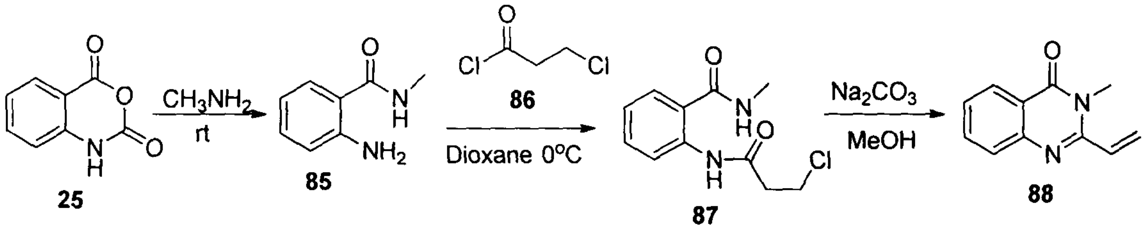


Scheme-21

Anthranilamide (**78**) can be converted to 2-(3-chloropropionylamino)-benzamide (**84**) by reacting with 3-chloropropionyl chloride (**82**). Cyclisation and dehydrohalogenation of **83** with sodium hydroxide in aqueous ethanol gives the substituted vinylquinazolinones (**84**). The *N*-substituted anthranilamide was prepared similarly from isatoic anhydride (**25**) and methylamine in water, the corresponding anthranilamide was treated with 3-chloropropionyl chloride (**86**) to yield 2-(3-chloropropionylamino)-*N*-methyl-benzamide (**87**) which underwent cyclisation in refluxing 0.5 M $Na_2CO_3(aq)$ containing 10% MeOH to 2,3-disubstituted quinazolinone (**88**).[41]

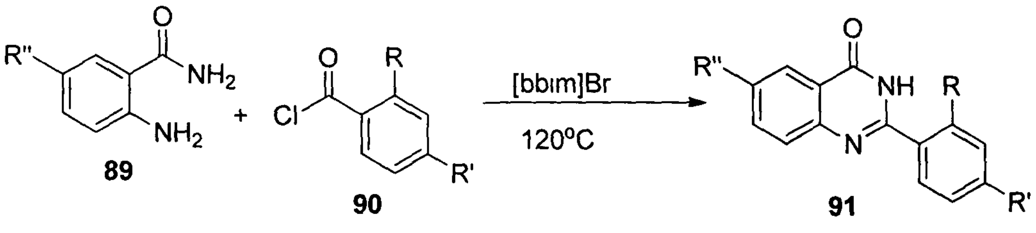


Scheme-22

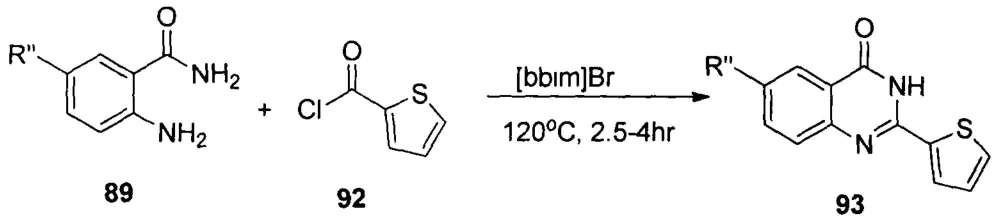


Scheme-23

Srinivasan and co-workers[42] have reported one-pot synthesis of 2-aryl-4(3*H*)-quinazolinone using ionic liquid, 1,3-di-nbutylimidazolium bromide ([bbim]Br) as a reaction medium as well as a promoter. A variety of benzoyl chlorides (**90**) and thiophene-2-carbonyl chloride **92** were condensed with 2-amino benzamide (**89**) and 2-amino-5-chlorobenzamide (R"=Cl), respectively, in the ionic liquid (IL) 1,3-di-n-butylimidazolium bromide ([bbim]Br) at 120°C to afford 2-aryl-4(3*H*)-quinazolinones. A typical reaction of 2-amino benzamide (**89**) with benzoyl chloride (**90**) was carried out in the ionic liquid, ([bbim]Br), at ambient conditions to form 2-phenyl-4(3*H*)-quinazolinone (**91**). However, at room temperature, reaction stops with the formation of 2-(*N*-benzoylamino) benzamide and does not proceed further to afford the 2-phenyl-4(3*H*)-quinazolinone even in trace amounts. Consequently, the reaction was carried out at higher temperatures and the optimum results were obtained at 120°C (92%). The non-volatile IL can be efficiently recovered and reused, and the process does not require any additional catalyst.

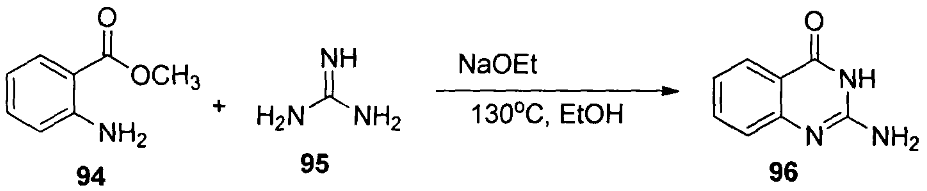


Scheme-24



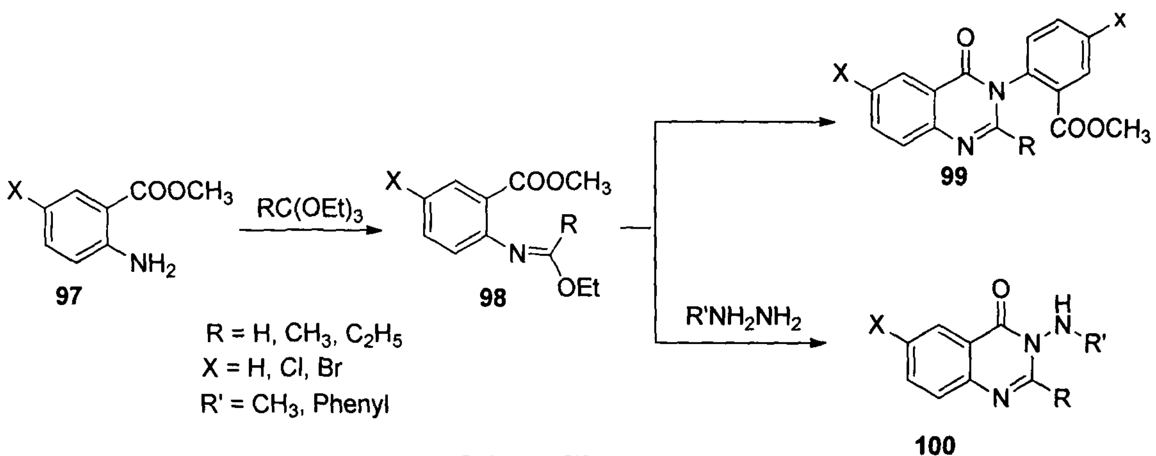
Scheme-25

The amino-quinazolin-4(3*H*)-one (**96**) was developed by Hess *et al.*[43] It was prepared in moderate yield from the corresponding methyl anthranilate (**94**) with excess guanidine (**95**) in the presence of sodium ethoxide in ethanol (**Scheme-26**).



Scheme-26

When excess of methylanthranilate (**97**) is used in the reaction, 3-(2-carbomethoxy-4-phenyl)-4-(3*H*)-quinazolinone (**99**) is formed *via* *N*-(2-carbomethoxyphenyl) imidate esters (**98**).[44a] These esters were prepared by premixing the ortho ester and anthranilate, followed by reflux and by periodic addition of the anthranilate ester to refluxing ortho ester. Treatment of the imidate esters with hydrazine, methylhydrazine and phenylhydrazine resulted in the formation of quinazolinones (**100**) as the sole product,[44b] however, condensation of it with a second molecule of anthranilate ester does occur even in a fairly dilute solution. Larger yields of quinazolinone (**99**) can be achieved with smaller orthoformate/anthranilate ratio. Imidate esters derived from triethyl orthoacetate and triethyl orthopropionate were obtained in excellent yields even with reactant ratios as low as 1:3.



Scheme-27

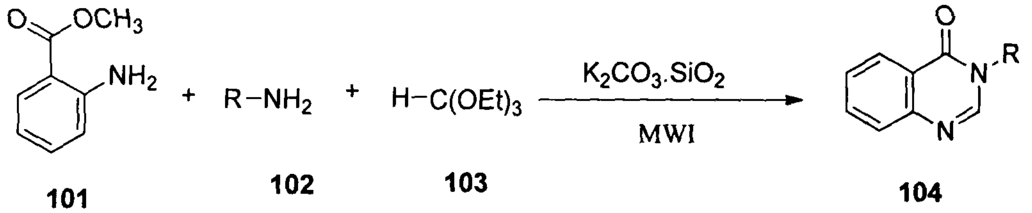
Numerous catalyts also have been employed for the preparation of these compounds such as using alumina supported-$CeCl_3/.7H_2O$–NaI,[45a] lanthanum(III) nitrate hexahydrate or *p*-toluenesulfonic acid,[45b] $Bi(TFA)_3$–[nbp]$FeCl_4$,[45c] $ZnCl_2$,[45d] and heteropolyacids.[45e]

IV.3. Results and discussions:

The replacement of current chemical processing techniques with more environmentally benign alternatives is an increasingly attractive subject. The increasing environmental consciousness throughout the world has put a pressing need to develop an alternate synthetic approach for biologically and synthetically important compounds. This requires a new approach, which will reduce the material and energy intensity of chemical processes and products, minimize or eliminate the dispersion of harmful chemicals in the environment in a way that enhances the industrially benign approach and meets the challenges of green chemistry.

The development of microwave assisted reaction had a profound impact on organic synthesis which require the use of high dielectric solvents such as dimethyl sulfoxide and dimethylformamide or on solid support where the organic compounds are adsorbed on the surface of the inorganic oxides such as alumina, silica and clay. However, microwave assisted solution phase reaction is confined only to low pressure and the use of special vessels and sealed containers and therefore, the use of solid support solvent-free microwave assisted reaction has a better scope which provides an opportunity to work with open vessels thus avoiding the risk of high pressure formation.

According to our literature survey, the environmental friendly syntheses of quinazolinones using solid supports are not well documented. Most of the procedures for the synthesis of quinazolinones employ the derivatives of anthranilic acid and alkoyl/acyl halide where the second condensed ring is closed through the synthesis of benzoxazinone which on further reaction with amine gives quinazolinone. In order to avoid the use of toxic reagents, we have replaced the anthranilic acid with alkyl anthranilate and acyl chloride with orthoester. In conjunction with our ongoing synthesis of heterocyclic systems[24] from readily available non-toxic starting materials, we herein report the synthesis of the derivatives of quinazolinones using potassium carbonate-silica as solid support.

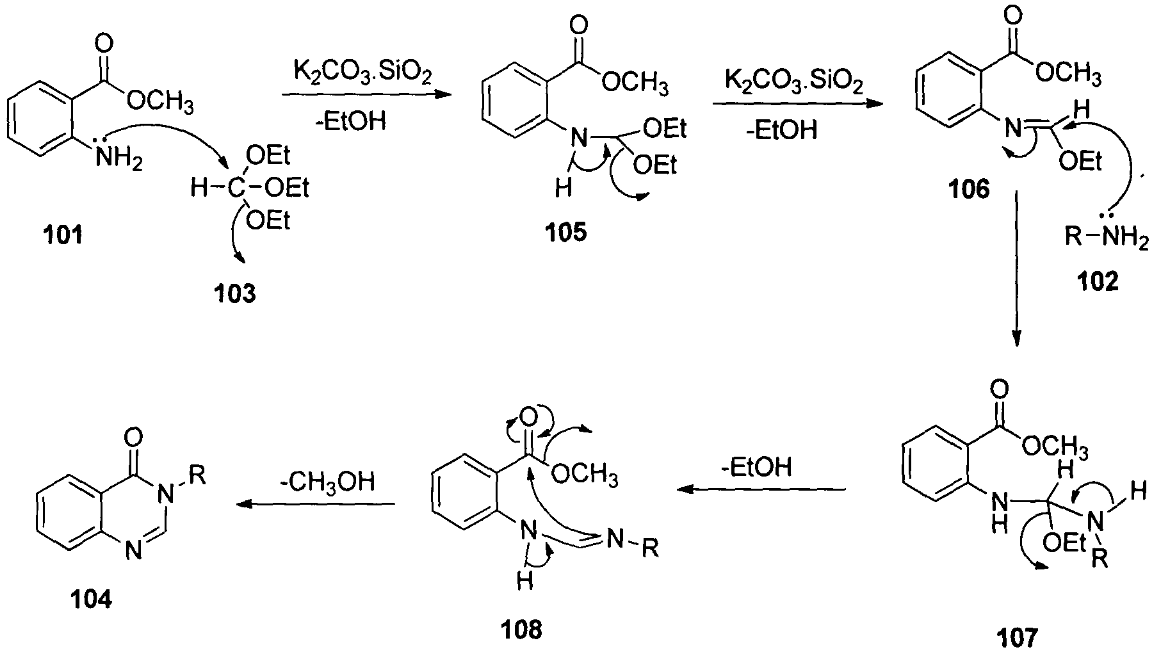


Scheme-29

Potassium carbonate-solid support reaction have been reported in many organic transformations and heterocyclic synthesis.[25] Therefore, in order to broaden the scope of quinazolinone chemistry we have applied the same principle for the synthesis of quinazolinone which gives satisfactory results. We have developed a convenient route for the synthesis of 3-substituted-quinazolin-4(3*H*)-one (**Scheme-28**) starting from methyl anthranilate (**101**), orthoester (**103**) and substituted amines (**102**) (both aromatic and aliphatic amine).

The one-pot synthesis of the title compound is achieved by cyclocondensation, which may involve the intermediate imidic ester **105** (**Scheme-28**). Then, the imidic ester may be very prone to react with an amine, thus leading to the amidine intermediate **108** which is generated *in situ* by the condensation of amino group from anthranilate with ortho ester in presence of potassium carbonate, followed by the cyclisation with aliphatic or aromatic amine to give the products in good to excellent yields (**Table-I**). In some cases the crude product was contaminated with some starting materials and some side reaction, which could be easily removed by recrystallisation or by column chromatography.

A very interesting feature of solid supported catalysts is that the catalyst is usually prepared in bulk amount for using in due course of the reaction. However, prior to use, it has to be activated which is usually done by heating it at 120°C. After successful completion of the reaction (TLC), the catalyst was recovered by filtering the reaction in vacuum pump and repeatedly washed with ethyl acetate. All the compounds prepared were confirmed from ^{1}H NMR, ^{13}C NMR, Mass and elemental analyses and were obtained in good purity. In case of some compounds showing impurities in the ^{1}H NMR, re-column chromatography was performed. It has been found that almost all the title compounds were not very polar and posed no serious difficulties during purification.



Scheme-28. Proposed mechanism for the formation of the title compound

*IV.4.*Experimental Section

Microwave reactions were carried out in a CEM Discover Benchmate microwave digester. Melting points were determined in open capillary tubes and are uncorrected. Infrared spectra were recorded on a BOMEM DA-8 FTIR instrument and the frequencies are expressed in cm^{-1}. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance II-400 spectrometer using $CDCl_3$ as the solvent. Chemical shifts are reported in ppm downfield from internal tetramethylsilane and are given on the δ scale. Mass spectral data were obtained with a JEOL D-300 (EI) mass spectrometer. Elemental analyses were carried out on a Heraeus CHN-O-Rapid analyzer. All compounds give satisfactory elemental analyses within ± 0.4% of the theoretical values. All reactions were monitored by TLC using precoated aluminum sheets (silica gel 60 F_{254} 0.2 mm thicknesses) and developed in an iodine chamber or under UVGL-15 mineral light 254 lamp. Column chromatographic separations were carried out using ACME silica gel (60–120 mesh).

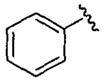
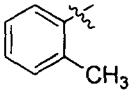
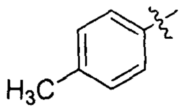
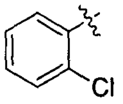
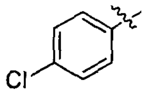
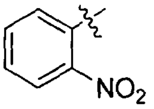
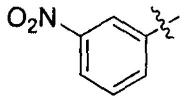
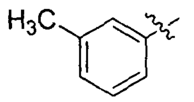
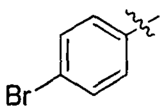
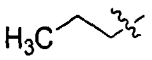
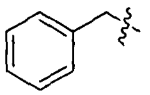
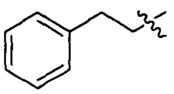
Preparation of the SiO_2 supported K_2CO_3.

To a solution of 4.14 g (0.03 mol) of K_2CO_3 in 20 mL of water in a 100-mL beaker containing a magnetic bar, 10 g of SiO_2 (column chromatographic grade, 60 Å, 200-400 mesh) was added. The mixture was stirred for 20 min and then gently heated on a hot plate, with intermittent swirling, until a free-flowing white solid was obtained. The catalyst was further dried by placing the beaker in an oven maintained at 120 °C for at least 24 hours prior to use.

General procedure for microwave assisted synthesis of Quinazolinones (104a-l).

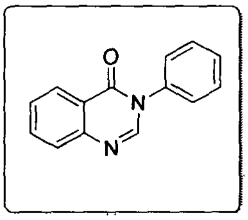
A mixture of the anthranilate ester (1 mmol), triethyl orthoformate (1 mmol) and amine (1 mmol) was mixed thoroughly with 100 mg of $K_2CO_2.SiO_2$ and was irradiated in a microwave digester at 100^0C at 5–10 bar, 80–120 W, for specified time as given in the **Table-I** without the use of solvent. After the reaction was completed (monitored by TLC) the resultant mixture was extracted with ethyl acetate. The combined organic extracts were concentrated on a rotary evaporator and the resulting residue was column-chromatographed with hexane/ethyl acetate as an eluent to afford pure compound.

Table-I

Product	R	Yield (%)	Reaction time(sec)	Mp(°C)
104a		85	300	137-139[16]
104b		83	330	139-140[22]
104c		85	330	144-145[16]
104d		78	420	136-138[22]
104e		75	390	180-181[16]
104f		70	390	154-155[22]
104g		73	290	154-155[22]
104h		90	330	137-138[22]
104i		88	330	186
104j		86	300	82-83
104k		90	360	118–119
104l		85	360	123-124

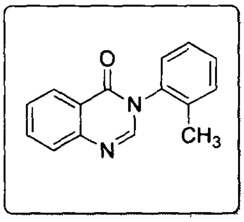
Spectroscopic and Analytical Data:

3-phenylquinazolin-4(3*H*)-one (104a):



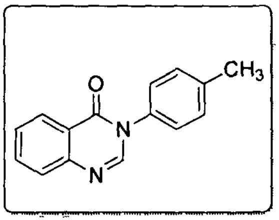
Mp: 137-139°C; IR (KBr, cm^{-1}): 1689, 1633, 1454; ^1H NMR ($CDCl_3$): δ 8.35 (s, 1H), 8.07 (s, 1H), 7.73-7.61 (m, 3H), 7.49-7.33 (m, 4H), 7.21 (t, 1H); ^{13}C NMR ($CDCl_3$): δ 122.1, 126.5, 126.8, , 127.3, 128.7, , 129.4, 131.3, 133.7, 137.2, 147.1, 148.3, 161.0; Mass: m/z: 222 [M^+]. Anal. Calcd. for $C_{14}H_{12}N_2O$: 75.66; H, 4.54; N, 12.60; Found: 75.37; H, 4.63; N, 12.41 %.

3-(2-methylphenyl)-4(3*H*)-quinazolinone (104b):



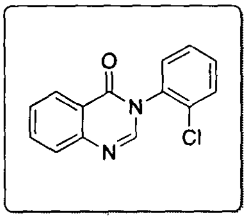
Mp: 139-140°C; IR (KBr, cm^{-1}): 1690, 1597, 1462; ^1H NMR ($CDCl_3$): δ 8.37 (s, 1H), 8.12 (d, 1H), 7.71-7.63 (m, 3H), 7.11-7.37 (m, 4H), 2.45 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 18.7, 122.7, 126. 2, 126.7, 125.2, 127.1, 128. 2, 129.4, 130.7, 133. 6, 134. 4, 135.2, 146. 6, 147.7, 160. 3; Mass: m/z: 236.2 [M^+], 237.2. Anal. Calcd. for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86; Found: C, 76.55; H, 5.32; N, 11.64%.

3-(4-methylphenyl)-4(3*H*)-quinazolinone (104c):



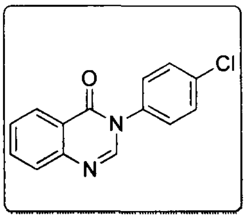
Mp: 144-145°C; IR (KBr, cm^{-1}) : 2923, 1690, 1600, 1471; ^1H NMR ($CDCl_3$): δ 8.30 (s, 1H), 8.05 (d, 1H), 7.69-7.76 (m, 3H), 7.19-7.50 (m,4H), 2.34 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 20.1, 121.3, 125.7, 126.1, 128.1, 129.5, 133.0, 133.4, 134.7, 136.3, 146.2, 147.1, 159.6; Mass: m/z: 237 [M^++1]. Anal. Calcd. for $C_{15}H_{12}N_2O$: C 76.25; H, 5.12; N, 11.86; Found: C, 76.32; H, 5.18; N,11.70%.

3-(2-chlorophenyl)quinazolin-4(3*H*)-one (104d):



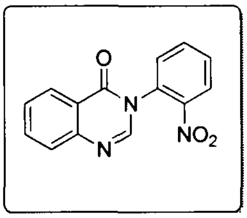
Mp: 1136-138°C; IR (KBr, cm^{-1}): 1693, 1607, 1467; ^1H NMR ($CDCl_3$): δ 8.33 (s, 1H), 8.02 (d, 1H), 7.59-7.75 (m, 5H), 7.33 (t,1H) , 7.15 (t, 1H); ^{13}C NMR ($CDCl_3$): δ 121.9, 125.1, 126.3, 127.1, 129.5, 130.6, 131.0, 131.8, 132.4, 134.3, 135.8, 147.3, 148.5, 160.7; Mass: m/z: 256 [M^+]. Anal. Calcd. for $C_{14}H_9ClN_2O$: C, 65.51; H, 3.53; N, 10.91; Found: C, 65.32; H, 3.43; N, 10.75%.

3-(4-chlorophenyl)quinazolin-4(3*H*)-one (104e):



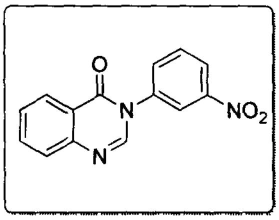
Mp: 180-181°C; IR (KBr, cm^{-1}) : 1693, 1607, 1447; ^1H NMR ($CDCl_3$): δ 8.39 (s, 1H), 8.08 (d, 1H), 7.64-7.72 (m, 3H), 7.42 (d, 2H) , 7.38 (d, 2H); ^{13}C NMR ($CDCl_3$): δ 120.7, 126.2, 126.9, 127.5, 129.2, 130.8, 133.0, 133.8, 135.7, 147.1, 147.8, 160.9; Mass: m/z: 257 [M^++1]. Anal. Calcd. for $C_{14}H_9ClN_2O$: C, 65.51; H, 3.53; N, 10.91; Found: C, 65.42; H, 3.62; N, 10.84%.

3-(2-nitrophenyl)quinazolin-4(3*H*)-one (104f):



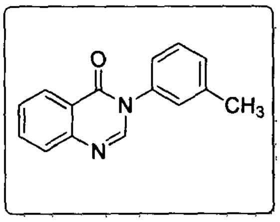
Mp: 154-155°C; IR (KBr, cm^{-1}): 1676, 1601, 1487; ^1H NMR ($CDCl_3$): δ 8.45 (s, 1H), 8.20 (d, 1H), 8.09 (d, 1H), 8.01 (d, 1H), 7.63-7.79 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 120.7, 122.4, 125.3, 125.9, 126.6, 127.1, 127.8, 133.3, 134.3, 136.6, 142.6, 147.3, 148.2, 160.7; Mass: m/z: 267 [M^+]. Anal. Calcd. for $C_{14}H_9N_3O_3$: C, 62.92; H, 3.39; N, 15.72; Found: C, 62.73; H, 3.52; N, 15.85%.

3-(3-nitrophenyl)quinazolin-4(3*H*)-one (104g):



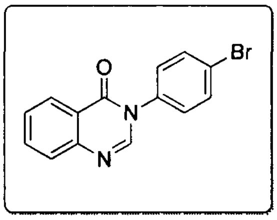
Mp: 154-155°C; IR (KBr, cm^{-1}): 1688, 1605, 1493; ^{1}H NMR ($CDCl_3$): δ 8.77 (s, 1H), 8.12 (d, 1H), 8.00 (d, 1H), 7.65-7.82 (m, 5H), 7.43 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 120.0, 120.8, 121.4, 126.3, 126.8, 127.2, 129.6, 132.9, 133.5, 134.6, 147.1, 147.8, 148.7, 160.4; Mass: m/z: 267 [M^{+}]. Anal. Calcd. for $C_{14}H_9N_3O_3$ are: C, 62.92; H, 3.39; N, 15.72; Found: C, 62.67; H, 3.23; N, 15.79%.

3-(4-methylphenyl)-4(3*H*)-quinazolinone (104h):



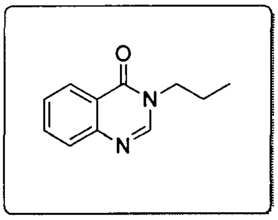
Mp: 137-138°C; IR (KBr, cm^{-1}): 1698, 1584, 1465; ^{1}H NMR ($CDCl_3$): δ 8.10 (d, 1H), 7.64-7.72 (m, 3H), 7.50.(s, 1H), 7.02-7.21 (m, 3H), 6.78 (s, 1H), 2.41 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 22.7, 120.3, 124.7, 125.1, 126.2, 126.8, 127.3, 128.6, 129.5, 133.1, 134.3, 138.6, 147.2, 148.5, 159.9; Mass: m/z: 236 [M^{+}]. Anal. Calcd. for $C_{15}H_{12}N_2O$ are: C, 76.25; H, 5.12; N, 11.86; Found: C, 76.42; H, 5.37; N, 11.96%.

3-(4-bromophenyl)quinazolin-4(3*H*)-one (104i):



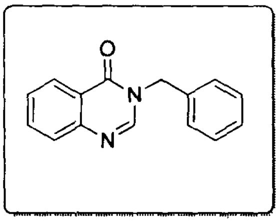
Mp: 137-138°C; IR (KBr, cm^{-1}): 1698, 1603, 1444; ^1H NMR ($CDCl_3$): δ 8.73 (d, 2H), 8.05 (d, 1H), 7.58-7.70 (m, 5H), 7.45 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 120.3, 122.6, 125.9, 126.7, 127.3, 128.7, 130.7, 133.6, 136.8, 147.5, 148.3, 160.3; Mass: m/z: 301 [M^++1]. Anal. Calcd. for $C_{14}H_9BrN_2O$ are: C, 55.84; H, 3.01; N, 9.30; Found: C, 55.92; H, 3.22; N, 9.17%.

3-propylquinazolin-4(3*H*)-one (104j):



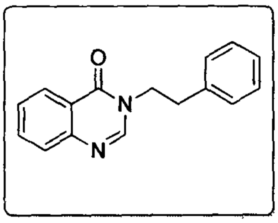
Mp: 137-138°C; IR (KBr, cm^{-1}): 1674, 1612, 1453; ^1H NMR ($CDCl_3$): δ 8.34 (s, 1H), 7.98 (d, 1H), 7.64-7.73 (m, 3H), 4.23 (t, 2H), 1.63-1.69 (m, 2H), 1.03 (t, 3H); ^{13}C NMR ($CDCl_3$): δ 15.3, 21.6, 50.3, 121.1, 126.7, 127.1, 128.7, 133.6, 147.7, 148.5, 161.3; Mass: m/z: 188 [M^+]. Anal. Calcd. for $C_{14}H_9BrN_2O$ are: C, 70.19; H, 6.43; N, 14.88; Found: C, 70.42; H, 6.32; N, 14.75%.

3-benzylquinazolin-4(3*H*)-one (104k):

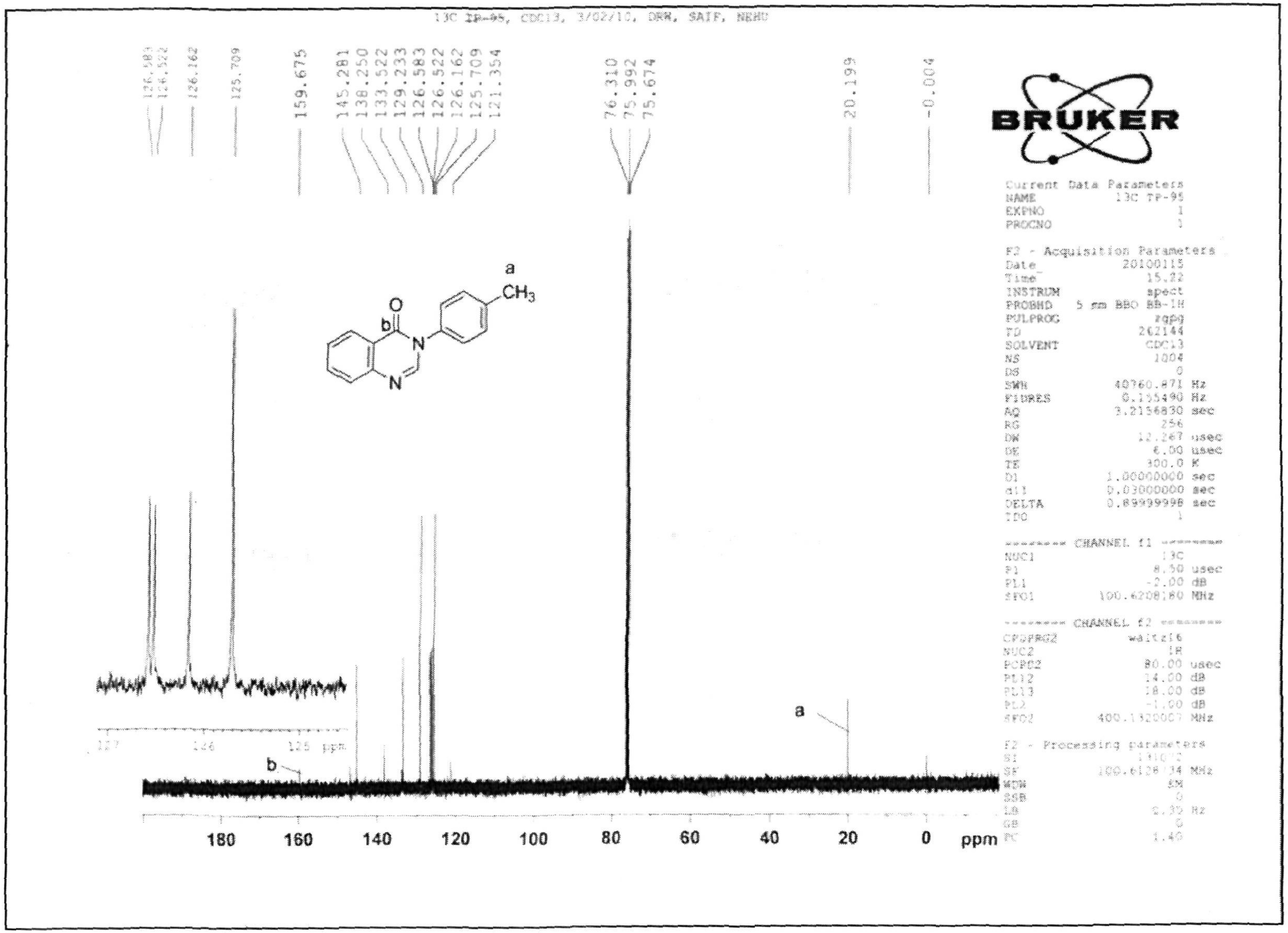


Mp: 137-138°C; IR (KBr, cm^{-1}): 1693, 1608, 1462; ^1H NMR ($CDCl_3$): δ 8.26 (s, 1H), 8.08 (d, 1H), 7.69-7.77 (m, 3H), 7.24-7.38 (m, 5H), 5.47 (s,2H); ^{13}C NMR ($CDCl_3$): δ 52.5, 120.3, 125.6, 126.0, 126.7, 127.1, 127.7, 128.9, 133.5, 136.6, 147.9, 148.7, 161.7; Mass: m/z: 236 [M^+]. Anal. Calcd. for $C_{14}H_9BrN_2O$ are: C, 76.25; H, 5.12; N, 11.86; Found: C, 76.53; H, 5.22; N, 11.65%.

3-phenethylquinazolin-4(3*H*)-one (104l):



Mp: 137-138°C; IR (KBr, cm^{-1}): 1686, 1611, 1455; ^1H NMR ($CDCl_3$): δ 8.30 (s, 1H), 8.12 (d, 1H), 7.61-7.74 (m, 3H), 7.30-7.43 (m, 5H), 3.41 (t,2H), 2.49(t,2H) ^{13}C NMR ($CDCl_3$): δ 41.3, 51.6, 121.1, 125.8, 126.3, 126.9, 127.3, 127.8, 128.6, 133.7, 139.4, 147.6, 148.3, 161.5; Mass: m/z : 250 [M^+]. Anal. Calcd. for $C_{14}H_9BrN_2O$ are: C, 76.78; H, 5.64; N, 11.19; Found: C, 76.67; H, 5.36; N, 11.37%.



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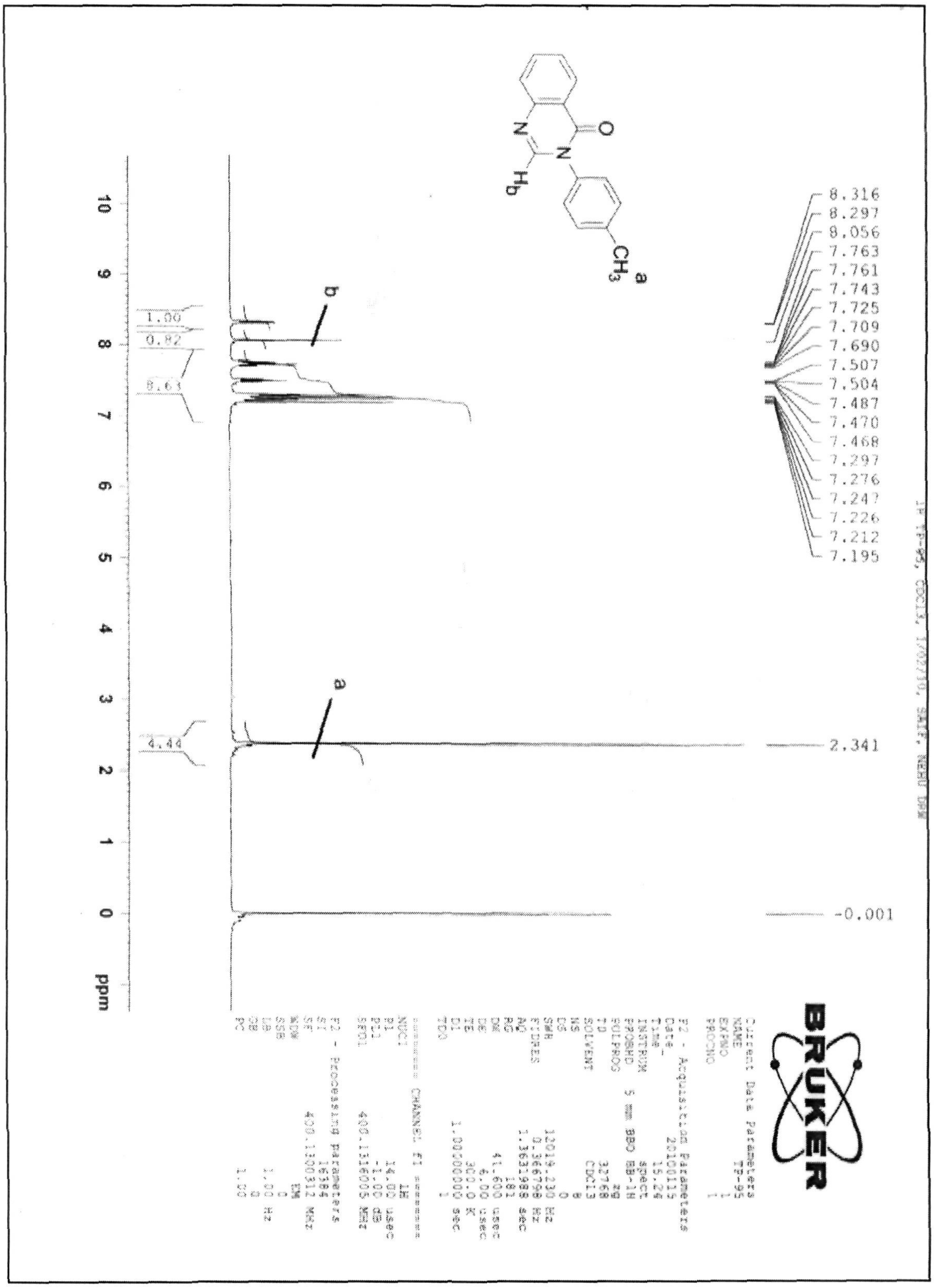
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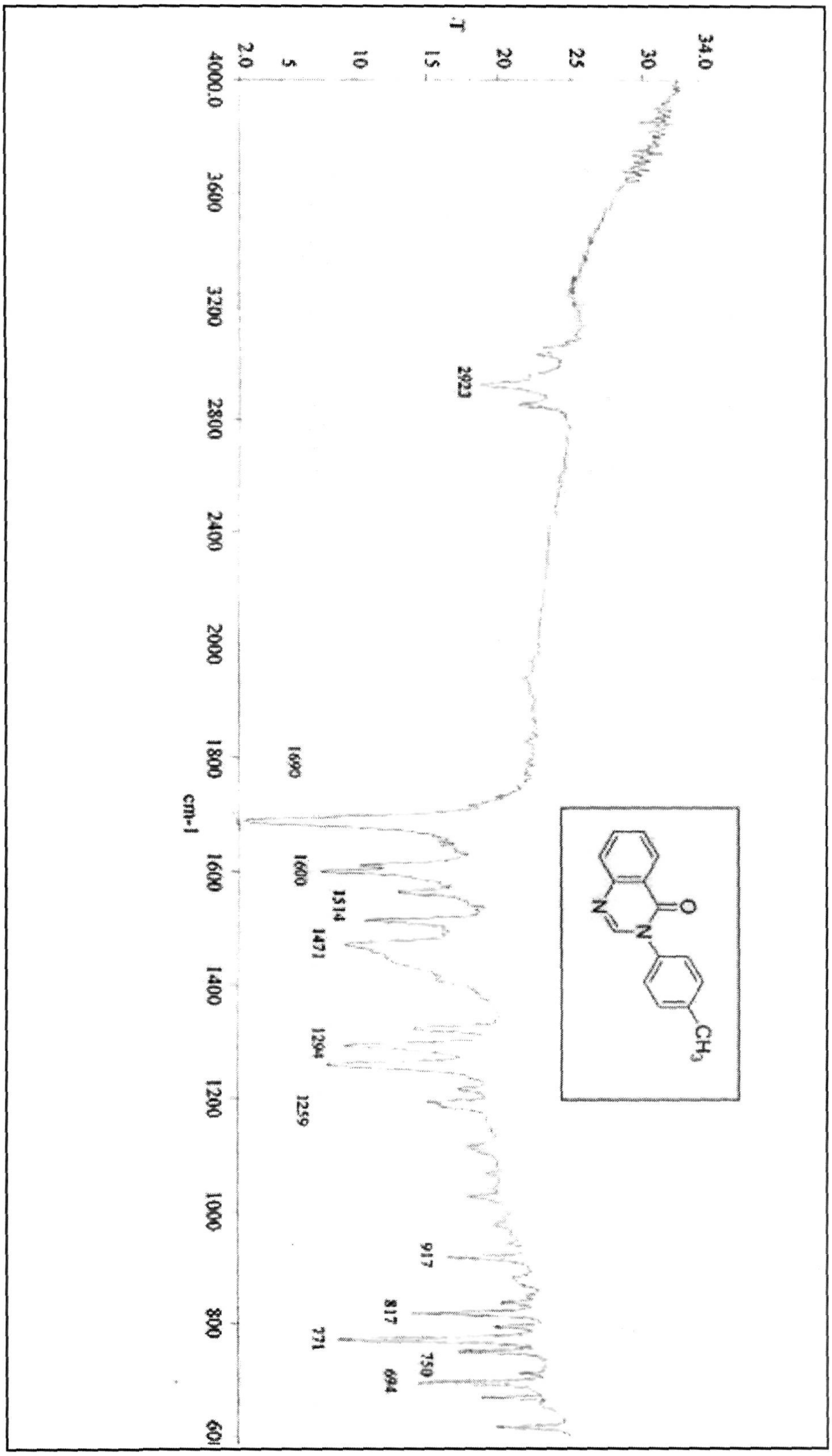
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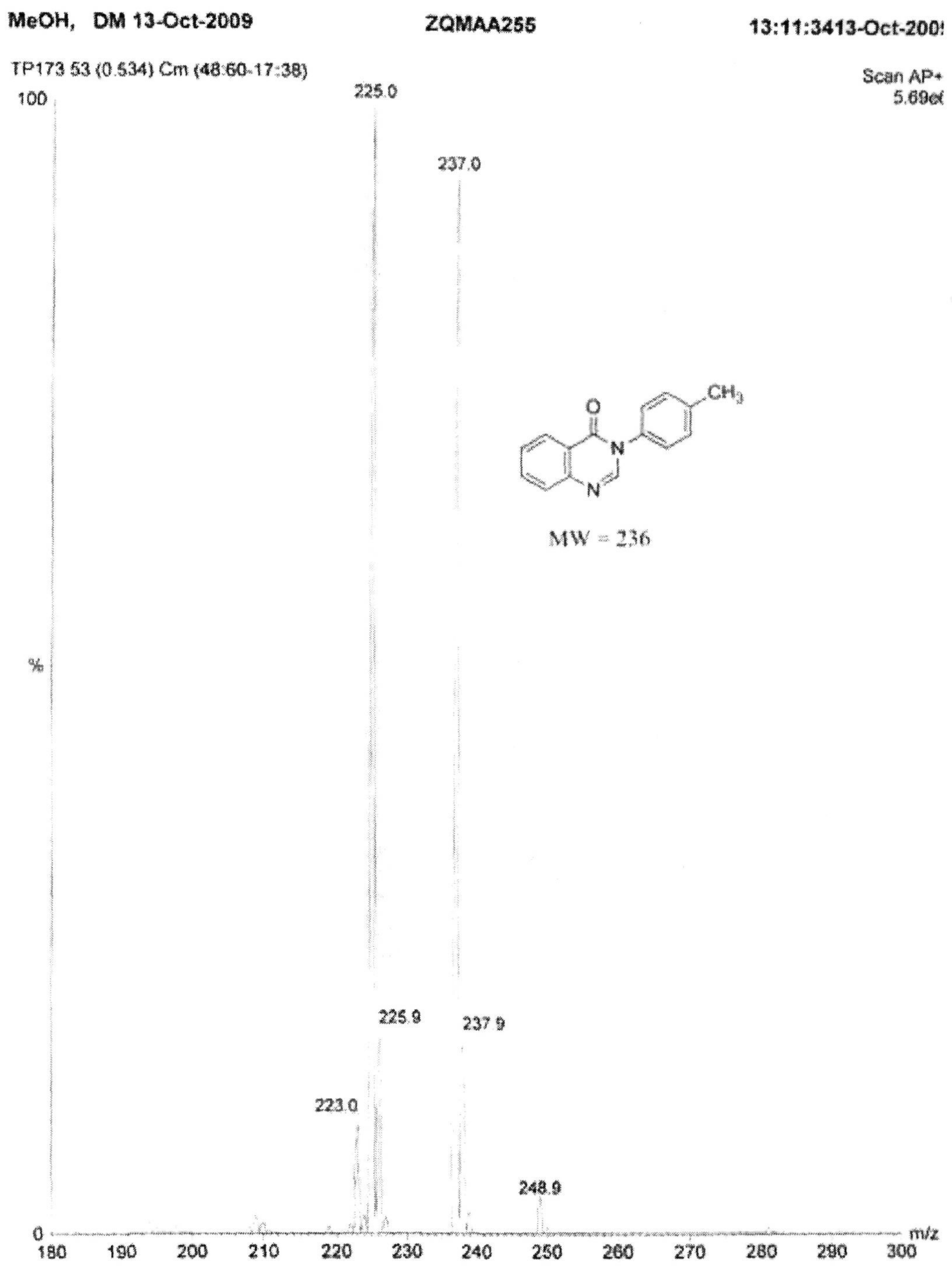
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IV.5. References.

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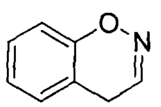
Chapter V

Green and efficient synthesis of bis-benzoxazines and bis-benzothiazines.

V.1. Introduction

Development of novel synthetic methods for the construction of new analogs of bioactive heterocyclic compounds represents a major challenge in synthetic organic and medicinal chemistry. Oxazines are heterocycles containing *O* and *N* hetero atoms in a cyclic ring system. Depending upon the position of the *O*- and *N*-atoms, they may be classified as 1,2-, 1,3- or 1,4-oxazines (**1, 2, 3**). When a benzo/naptho group is attached to the oxazine moiety, it is referred to as benzoxazine/napthoxazine *e.g.*, 4*H*-benzo[*e*][1,2]oxazine (**1**), 4*H*-benzo[*e*][1,3]oxazine (**2**), 2*H*-benzo[*b*][1,4]oxazine (**3**). They are all important bioactive compounds and heterocycles containing the oxazine nucleus and found to possess a wide range of biological applications.[1]



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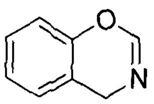

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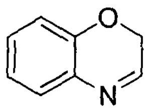
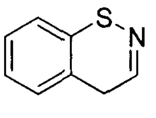


3

The Mannich reaction has been widely used[2] to introduce oxazines into a variety of organic compounds. The Mannich reaction involving phenols, formalin and primary amines has been used as a convenient source for a variety of compounds. The interest on 1,3-oxazine molecules have recently increased, mainly due to compounds containing dihydro-1,3-oxazine ring system which exhibited a wide spectrum of pharmacological activities such as anti-tumor,[3a,b] anti-bacterial,[3c,d] anti-HIV[3e,f] and anti-malarial agents[3g] and their versatility as synthetic intermediates.[3h] This has been the prime driving force for the synthesis of various compounds incorporating the 1,3-oxazine moiety. In addition, naphthoxazine derivatives have exhibited therapeutic potential for the treatment of Parkinson's disease.[4]

Despite the fact that substituted 1,3-thiazines have been known for more than 100 years and constitute the structural basis of several biologically active substances of both natural and synthetic origin, methods for the synthesis of these heterocyclic systems have not been sufficiently well developed. Various benzothiazine derivatives are known to possess a versatile range of biological activities and have been synthesized continuously since the very first synthesis by Abe *et al*,[5] Among these, 1,2-benzothiazine-3-carboxamide-1,1-dioxides such as piroxicam,[6a] ampiroxicam[6b] and meloxicam[6c] are familiar for their analgesic and anti-inflammatory activities and are being used worldwide as non-steroidal anti-inflammatory drugs (NSAIDs). Some of the 3,4-dihydro-1,2-benzothiazine-3-carboxylate-1,1-dioxide α-ketomide and P(2)–P(3) peptide mimetic aldehyde compounds act as potent calpain I inhibitors,[7] while 1,2-benzothiazin-3-yl-quinazolin-4(3*H*)-ones possess anti-bacterial properties.[8]



1,2-thiazine

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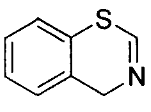

1,3-thiazine

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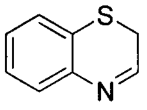
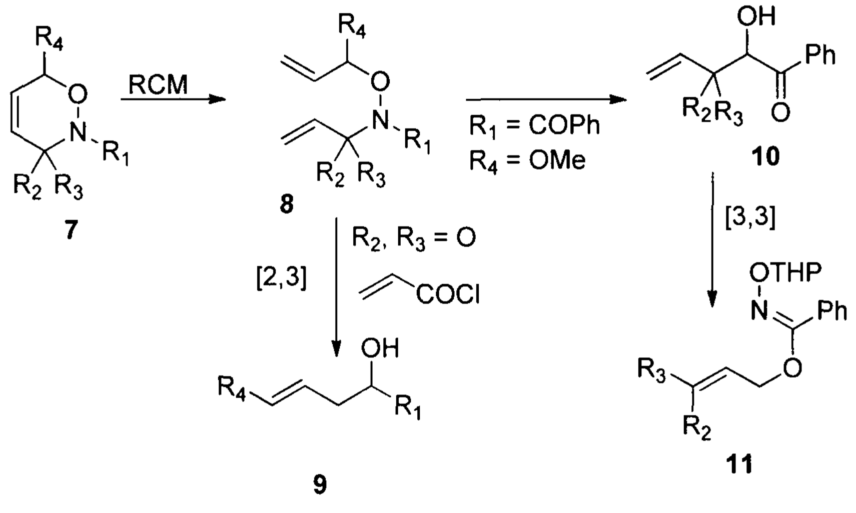


1,4-thiazine

6

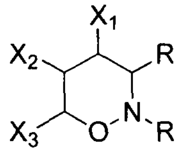
V.2. Synthetic reports on 1, 2-oxazines and 1,2-thiazines:

Desmurs *et al*,[9] provided various pathways for the synthesis of 1,2-oxazines involving [2,3]- or [3,3]-sigmatropic rearrangement to elaborate the dienic compounds and a ring closing metathesis (RCM) to build the heterocycles. Oxazines of type **7** were seen as arising from an RCM applied to *N,O*-substituted unsaturated hydroxylamines of type **8** which could be synthesized following two strategies depending on their substitution pattern. A [2,3]-sigmatropic rearrangement of allylic hydroxylamines of type **9** induced by the presence of acryloyl chloride could provide access to monosubstituted hydroxylamines of type **8**. The formation of mixed acetals of allylic hydroxamic acids of type **10**, which could be obtained by a [3,3]-sigmatropic rearrangement of benzimidoates of type **11**, was proposed for preparing mono- or disubstituted oxazines (**Scheme-1**).



Scheme-1

A wide variety of methods to enable the efficient and stereoselective synthesis of 1,2-oxazine derivatives, in particular of the polyhydroxylated tetrahydro-2*H*-1,2-oxazines (**12**), have been developed.[10] In contrast to the various syntheses and applications of oxygen-substituted 1,2-oxazines, the related 5,6-dihydro-4*H*-1,2-oxazines (**13**) have gained less attention.[11]



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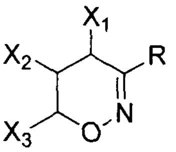
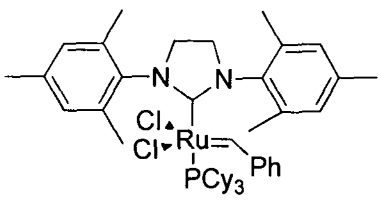


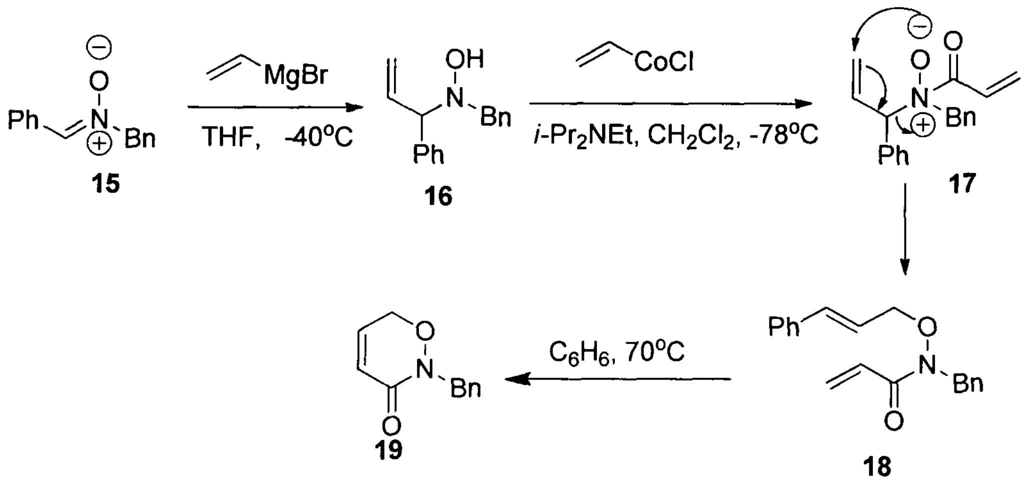
13

X_1, X_2 = OH, OR
X_3 = H, alkyl, aryl
R = H or substituent



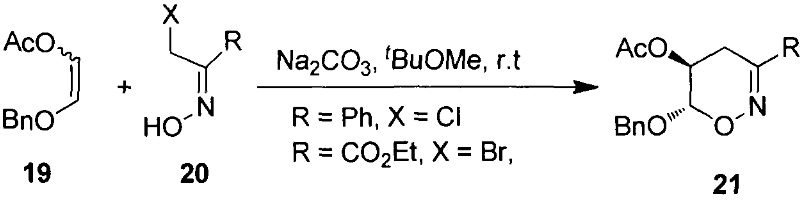
14

The formation of (**19**) was ascribed to a [2,3]-sigmatropic rearrangement (related to the Meisenheimer rearrangement)[12] of the intermediate *N*-acryloyl-*N*-oxide (**17**) generated by treatment of **16** with acryloyl chloride in the presence of Hunig's base (i-Pr_2NEt). The [1,2]oxazin-3-one (**19**) was finally obtained in 92% yield when an RCM reaction catalyzed by Grubbs' catalyst (**14**) was applied to **18** (**Scheme-2**).



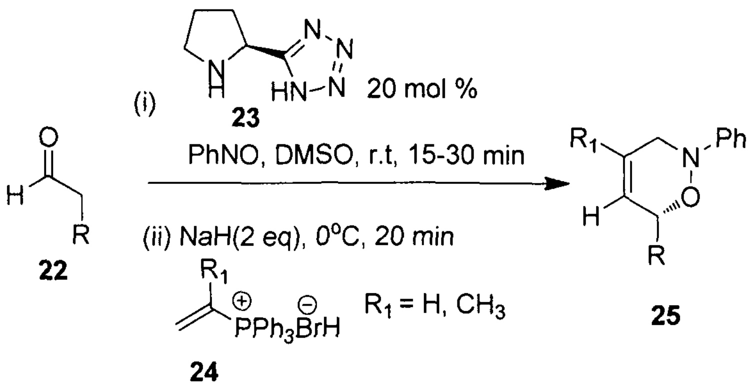
Scheme-2

The synthesis of stereo defined oxygen-substituted dihydro-4*H*-1,2-oxazines (type **21**), mainly through the employment of 6*H*-1,2-oxazines as ideal precursors[13] and their subsequent transformations into synthetically useful amino alcohols and pyrrolidine derivatives have been described (**Scheme-3**).

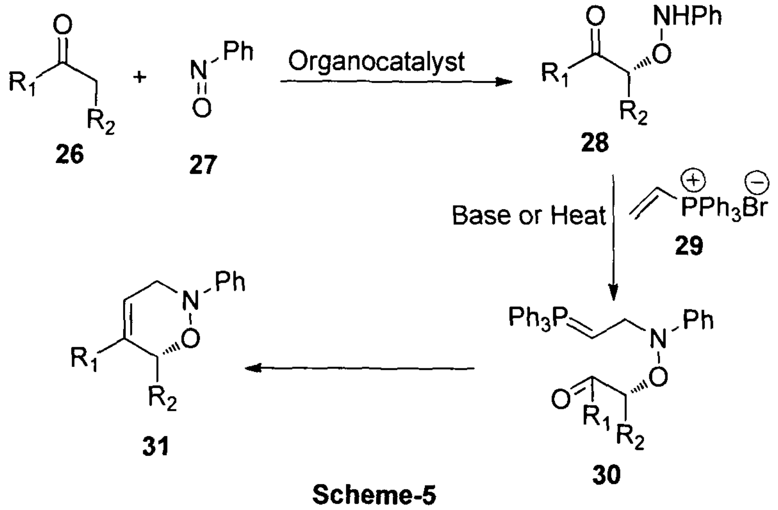


Scheme-3

Ley and co-workers[14] have recently demonstrated an efficient new route to chiral dihydro-1,2-oxazines from commercially available achiral aldehydes with excellent enantioselectivity using pyrrolidinyl-tetrazole (**23**) as an organocatalyst in a tandem reaction sequence (**Scheme-4**).[15] The transformation involves an asymmetric organocatalytic α-oxyamination[16] with nitrosobenzene and the catalyst, using conditions similar to those developed by Zhong,[16a] to afford an intermediate which undergoes conjugate addition to a vinyl phosphonium salt. The resulting ylide cyclises to the dihydro-1,2-oxazine *via* an intramolecular Wittig process (**Scheme-5**).

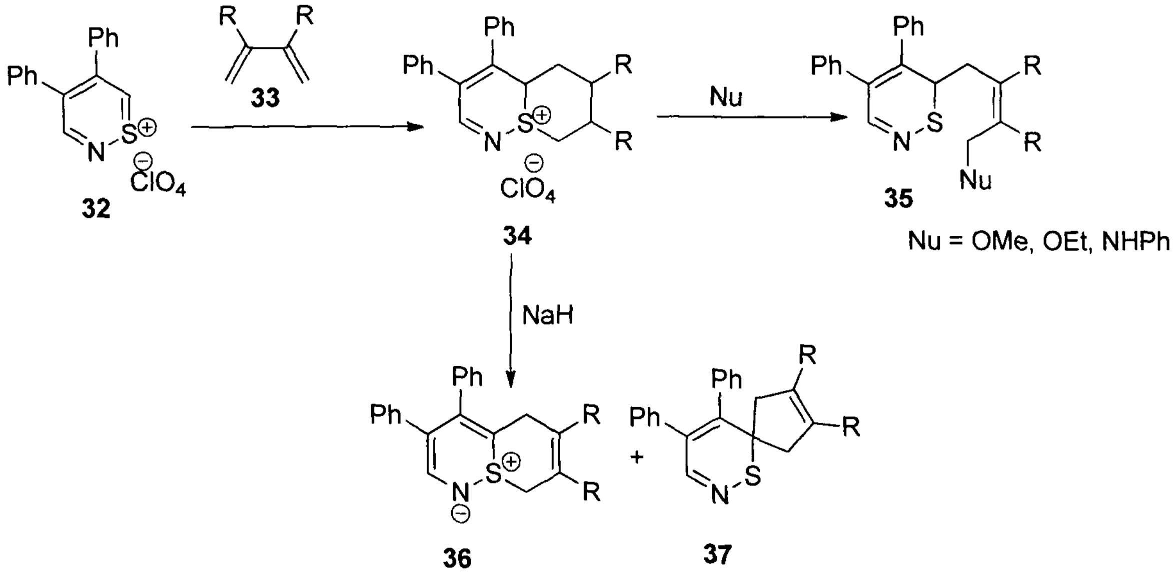


Scheme-4



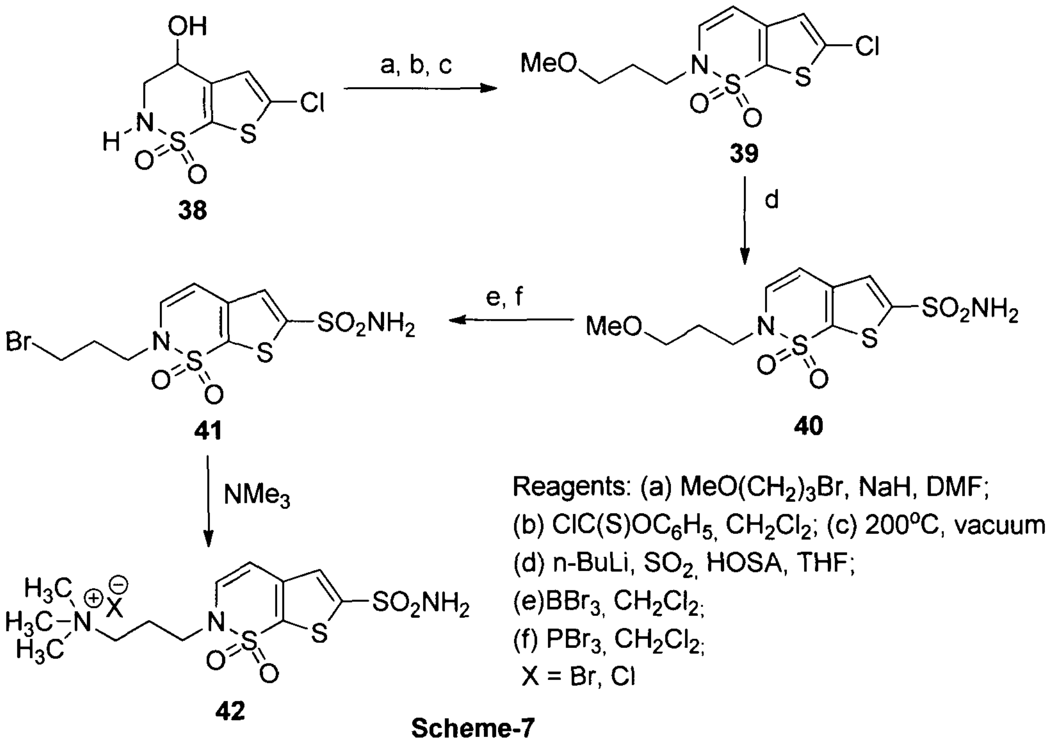
Scheme-5

Much attention has been paid to hetero Diels–Alder reactions as powerful tools for the construction of heterocyclic compounds.[17] Shimizu *et al*,[18] have reported the unique [2^++4]-type polar cycloadditions across the N=S^+ bond of tricyclic dibenzo[*c*,*e*]-[1,2]thiazinylium salt (**32**) with 1,3-butadienes (**33**).[19] Furthermore, they have also succeeded in the synthesis of monocyclic 4,5-diphenyl-1,2-thiazinylium salt (**36**), which provided several 1,2-thiazines having novel biological activities;[20] however, the reactions with 1,3-butadienes underwent the [2^++4] cycloaddition across the C=S^+ bond of the 1,2-thiazinylium salt, not across the N=S^+ bond, to give 1,6-(2-buteno)-6*H*-1,2-thiazinylium salts exclusively[21] (**Scheme-6**).



Scheme-6

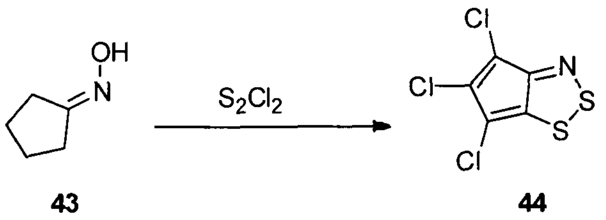
Thieno[3,2-*e*]-1,2-thiazine-6-sulfonamide-1,1-dioxides (**42**), which have a quaternary ammonium moiety incorporated into their structures, were synthesized by Liao and co-workers.[22] All of the quaternary ammonium salts prepared are potent inhibitors of both human carbonic anhydrase-II and recombinant human carbonic anhydrase-IV; they are significantly more potent as inhibitors of these carbonic anhydrase isozymes than the previously reported inhibitor quaternary ammonium homo sulfanilamide.



Reagents: (a) $MeO(CH_2)_3Br$, NaH, DMF;
(b) $ClC(S)OC_6H_5$, CH_2Cl_2; (c) 200°C, vacuum;
(d) n-BuLi, SO_2, HOSA, THF;
(e) BBr_3, CH_2Cl_2;
(f) PBr_3, CH_2Cl_2;
X = Br, Cl

Scheme-7

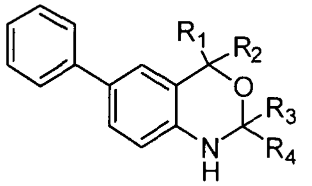
Torroba *et al*,[23] demonstrated an extensive transformation of the oximes of simple saturated ketones with S_2Cl_2 into fully unsaturated and chlorinated heteroaromatic systems.[24] Thus cyclopentanone oxime (**43**) gave the deep violet 10π pseudoazulene 4,5,6-trichlorocyclopenta-1,2,3-dithiazole (**44**) with S_2Cl_2 and Hünig's base ($EtNPr^i_2$) in THF at 4°C; the addition of NCS supplemented the spontaneous chlorination–dehydrochlorination–chlorination sequence and improved the yield of **44**.



Scheme-8

V.3. Synthetic reports on 1,3-oxazines and 1,3-thiazines:

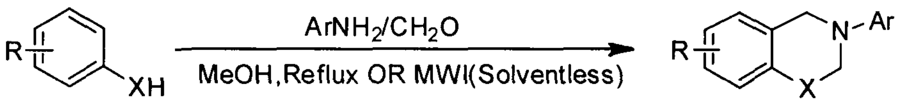
Novel 6-aryl benzoxazines (**45**) were prepared by Zhang *et al,*[25] and examined them as progesterone receptor modulators. Compound with 2,4,4-trimethyl-1,4-dihydro-2*H*-benzo[*d*][1,3]-oxazine core were found to be most potent Progesterone receptor (PR) agonist.



$R_1, R_2 = CH_3$
$R_3 = CH_3, CF_3, CH(CH_3)_2$
$R_4 = H, CH_3$

45

Synthesis of various substituted [1,3]-oxazines (**47**) and [1,3]-thiazines (**47**) (**Scheme 6**) and their relative comparison with microwave assisted synthesis have been reported from our laboratory which were relatively monomers.[26]

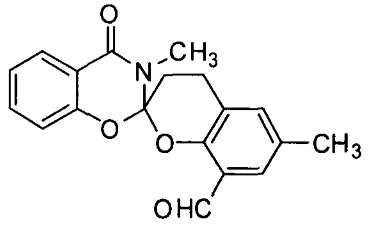


46 **47**

X= O, S
Ar = aryl

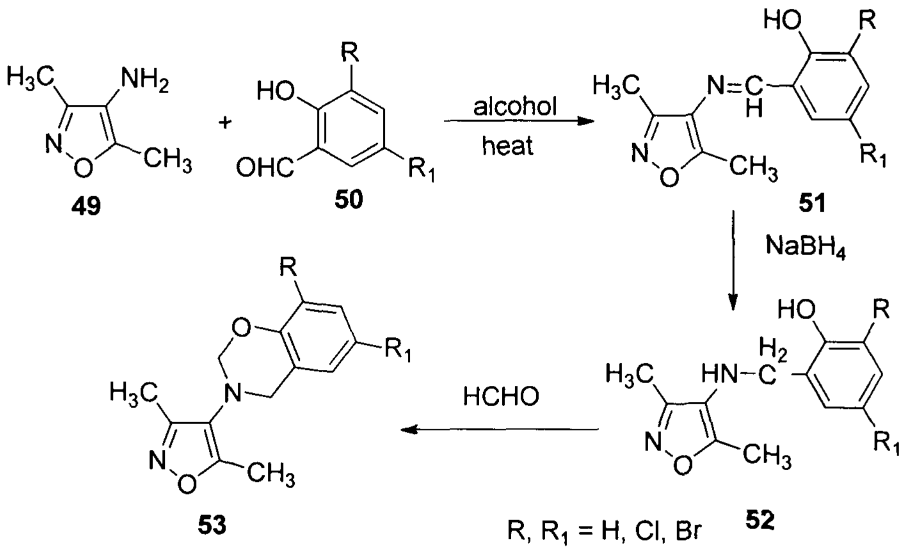
Scheme-9

S. M. Aldoshina *et al,*[27] synthesized 8′-formyl-3,6′-dimethyl-4-oxospiro (3,4-dihydro-2*H*-1,3-benzoxazine-2′,2-[2*H*]chromene) (**48**) based on 2,6-diformyl-4-methylphenol, examined its photochromic properties in solutions and in the solid state (in polydispersed films prepared by vacuum deposition on to glass or quartz supports) and established its crystal structure. The presence of the formyl substituent in compound **48** will allow one to prepare new SP bearing various π-acceptor substituents and study their influence on the photochromic properties. To summarize, synthesis of the spiropyran of the benzoxazine series bearing the formyl group, which exhibits photochromic properties in the solid phase have been successful.[28]



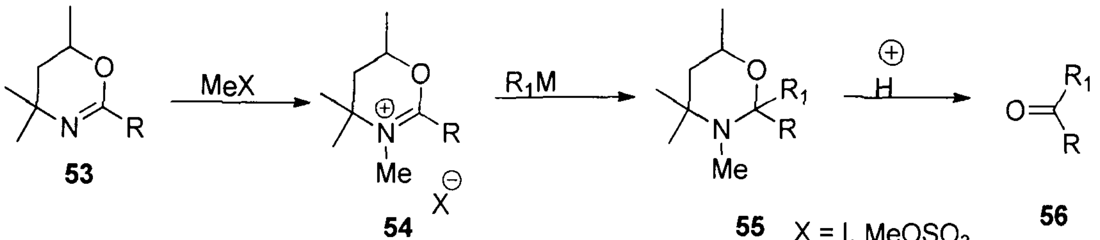
48

Compounds bearing the isoxazole moiety are endowed with various types of pharmacological activities.[29] Literature survey revealed that when one biodynamic heterocyclic system was coupled with another, a molecule with enhanced biological activity[30] was produced. The chemistry of these linked bi-heterocycles has been the fascinating field of investigation in medicinal chemistry as they have been found to exhibit enhanced biological profile.[31] Synthesis as well as investigation of the activity of compounds in which isoxazole moiety has been linked with benzoxazine nucleus as well as a report on the anti-microbial activity of 3-(3,5-dimethyl-isoxazol-4-yl)-3,4-dihydro-2*H*-benzo[*e*][1,3]-oxazines (**53**) have been reported by Reddy *et al*,[32] (**Scheme-7**).



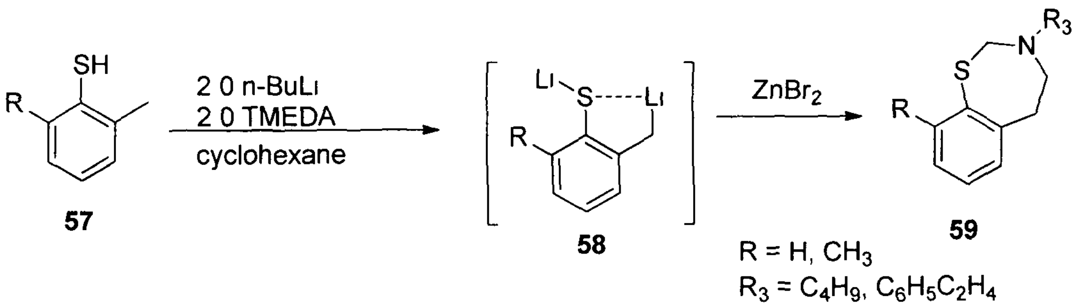
Scheme -10

It was recently demonstrated that the dihydro-1,3-oxazine ring is inert to organometallics[33a] and that, this property afforded a novel protecting group against such reagents. It appeared that the facile elaboration of the 2-alkyl substituent in dihydro-1,3-oxazines by use of strong bases (*e.g.*, butyllithium) and alkyl halides would provide considerable scope in constructing various ketones if the C=N link in the oxazine could be induced to add an appropriate organometallic. Various attempts to increase the reactivity of the C=N bond towards nucleophillic reagents (RMgX, RLi) by the use of BF_3, R_3B or Et_3Al failed to provide the adduct in any appreciable amount. The desired result was finally realized by addition of methyl iodide to **14** followed by introduction of the organometallic which was allowed to react at room temperature (**Scheme-11**).

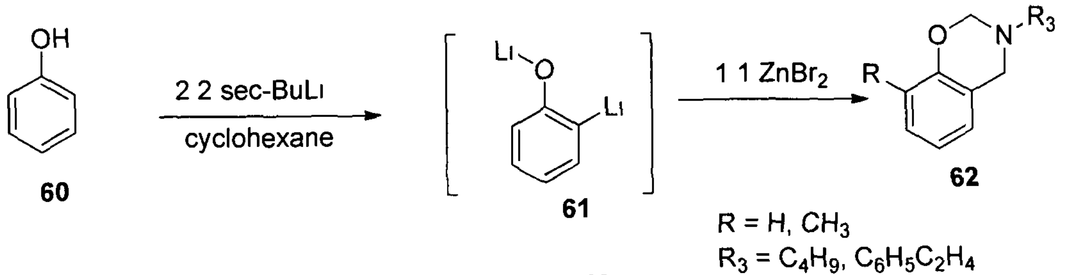


Scheme-11

Synthesis of 3,4-dihydro-2*H*-1,3-benzothiazines **(59)** by Directed Ortho-Lithiation of thiophenols have been reported by Katritzky *et al,*[34] **(Scheme-13)**.

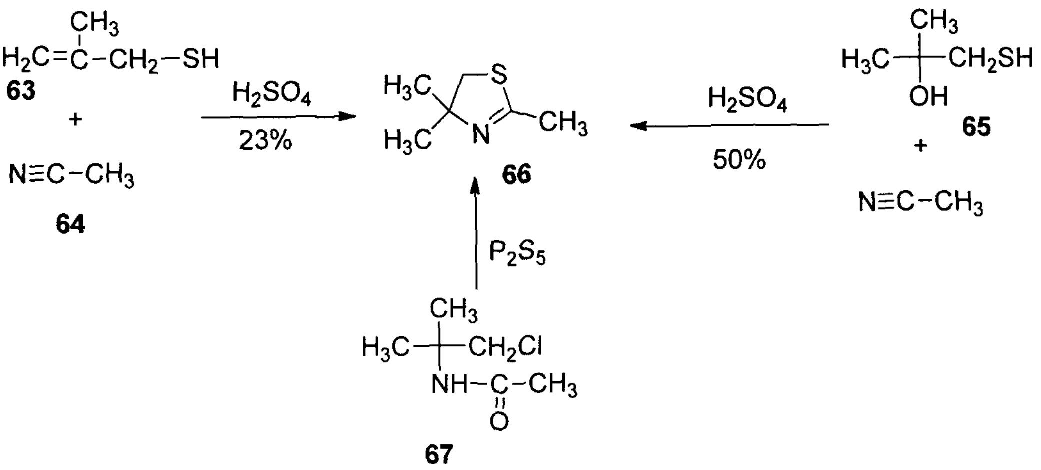


Scheme-12



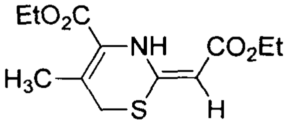
Scheme-13

Albert. I. Rieyers[35] reported that addition of 2-methyl-2-hydroxypropanethiol **(65)** to a cold solution of acetonitrile in concentrated sulfuric acid leads to the formation of 2,4,4-trimethyl-2-thiazoline **(66)** in about 50% yield **(Scheme-14)**.



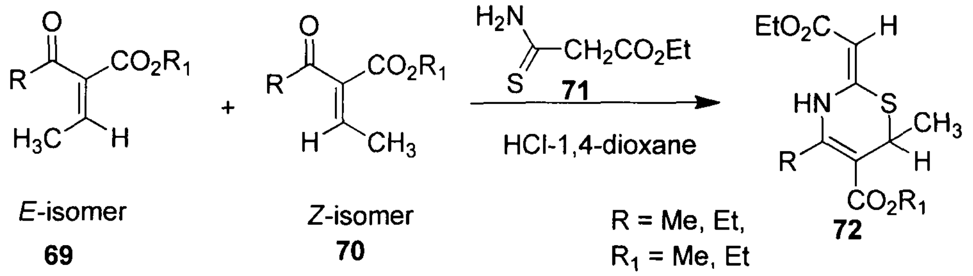
Scheme-14

The secondary ring of cephalosporin antibiotics consists of a 2,3-dihydro-6*H*-1,3-thiazine ring **(68)**.



68

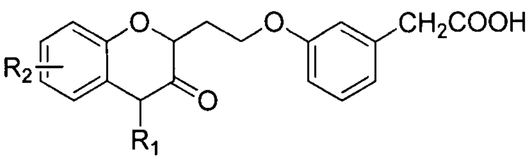
Hitchcock *et al,*[36a] demonstrated the synthesis of the dihydrothiazines **(72)** originally began with preparation of the corresponding α,β-unsaturated keto esters **(69)** by the procedure of Lenhert.[36b] However, a modification of a procedure by Knoevenagel[36c] was later shown to be less time consuming. Condensation of ethoxycarbonylthioacetamide **(71)** with the α,β-unsaturated keto esters **(69)** using anhydrous hydrogen chloride in 1,4-dioxane gave the expected dihydrothiazines **(72)** in yields of 71–77%.



Scheme-15

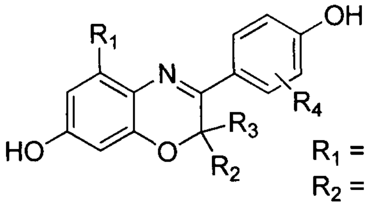
V.4. Synthetic reports on 1, 4-oxazines and 1,4-thiazines:

A series of benzoxazinones (**73**) were synthesized as perixisome proliferator activated receptor (PPAR) agonists by Rybczynski *et al.*[37a] The compounds were tested as functional agonists in the induction of the P2 gene in preadipocytes. A series of 3-aryl-7-hydroxy benzoxazine analogues (**74**) have been prepared and evaluated as ligands for the two estrogen receptor subtypes (ERα and ERβ) by Yang *et al.*[37b]



R_1 = 3ClBn, 4-CH_3Bn, 3,4-$Cl_2Ph(CH_2)_2$
R_2 = H, 7-F, 7-CH_3

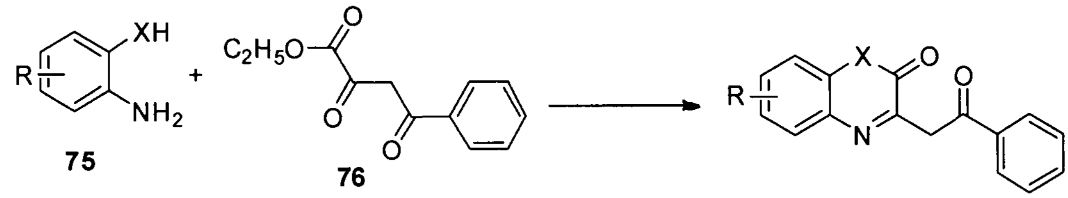
73



R_1 = H, OH, CH_3
R_2 = H, CH_3, C_2H_5
R_3 = H, CH_3, CH_2CH_2
R_4 = H, Br

74

T. Inagaki *et al*,[38] have also synthesized 1,4-benzoxazines by condensation of ethyl benzoylpyruvates (**76**) with *o*-phenylenediammine (**75**), *o*-aminophenol and some of their derivatives gave the corresponding 3-phenacyl-2-(1*H*)-quinoxalinones and 3-phenacyl-2*H*-1,4-benzoxazin-2-ones (**77**).

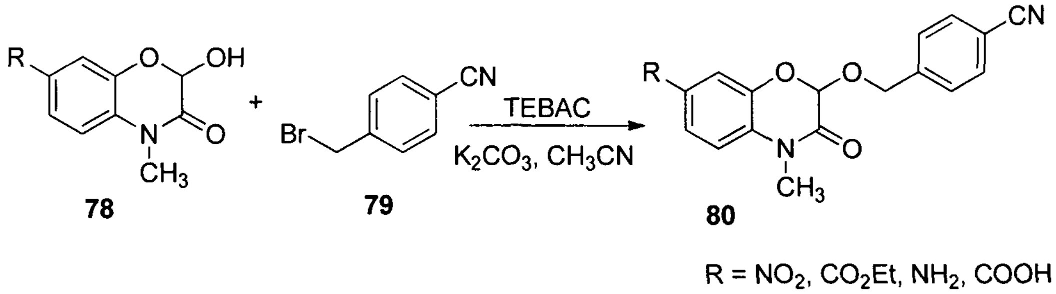


75 **76** **77**

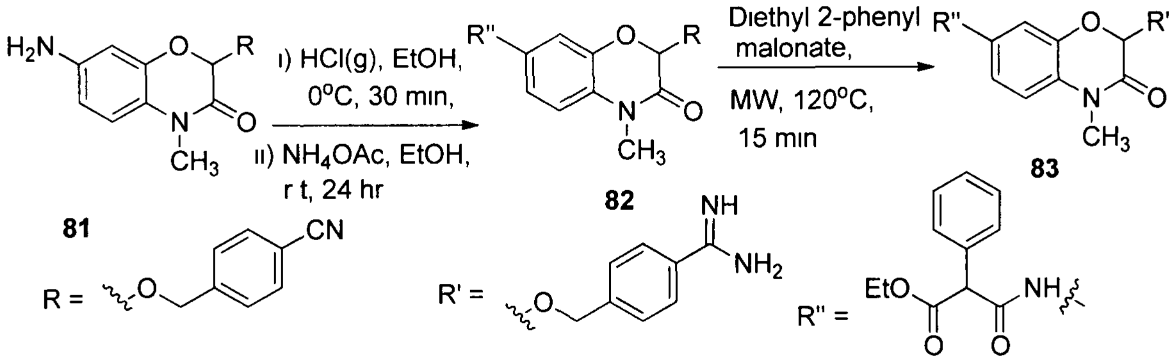
X = NH, O
R = H, CH_3, 4-Cl, benzo

Scheme-16

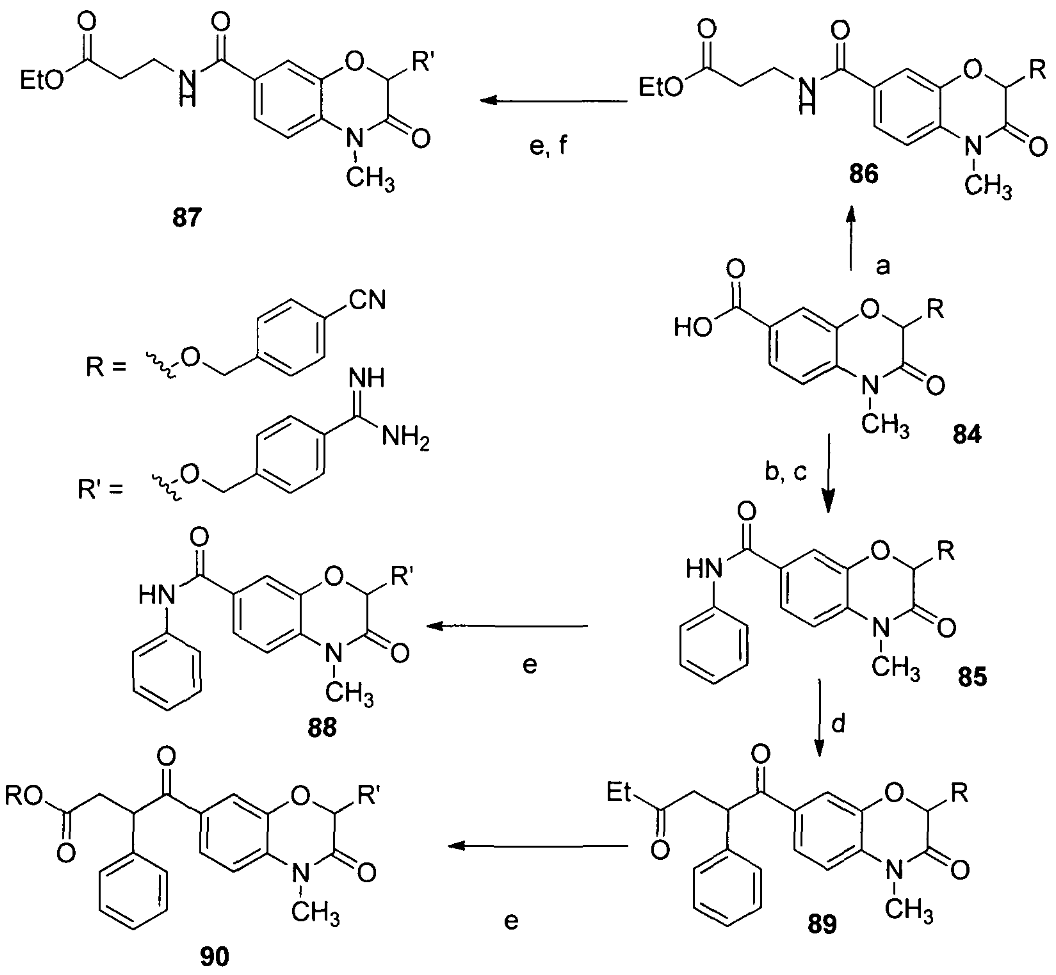
D. Kikelj *et al*,[39] reported at length on the design, synthesis and *in vitro* biological activity of novel 3,4-dihydro-2*H*-1,4-benzoxazine derivatives that act both as thrombin inhibitors and GPIIb/IIIa receptor antagonists and possess a well balanced submicromolar potency against both targets. Compounds containing the 2*H*-1,4-benzoxazin-3(4*H*)-one scaffold were synthesized as depicted in **Scheme-17** to **Scheme-19**.



Scheme-17



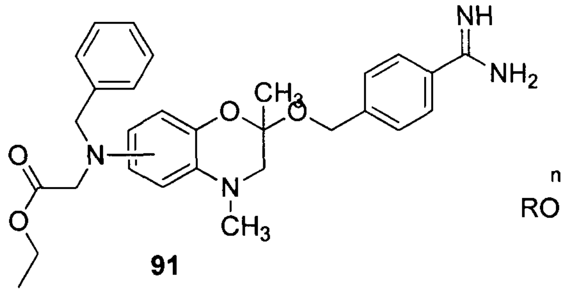
Scheme-18



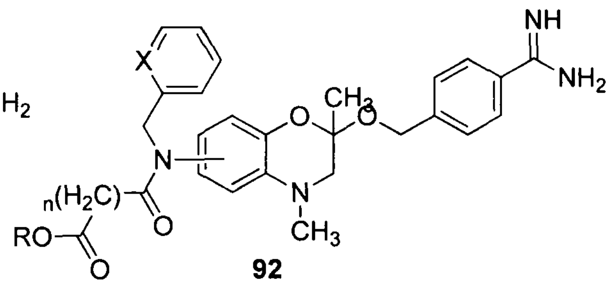
a) Ethyl 3-aminopropanoate, EDC, HOBt, DMF, r t, overnight
b) $SOCl_2$, CH_2Cl_2, Reflux, 4 hr
c) aniline, Et_3N, DMF, overnight
d) $BrCH_2COOEt$, BTEAC, K_2CO_3, CH_3CN, 60°C, 24 hr
e) HCl(g), EtOH, 0°C, 30 min,r t, 48 hr, then NH_4OAc, EtOH, r t, 48 hr
f) 1 5 M NaOH, H_2O, EtOH, r t, 6 hr

Scheme-19

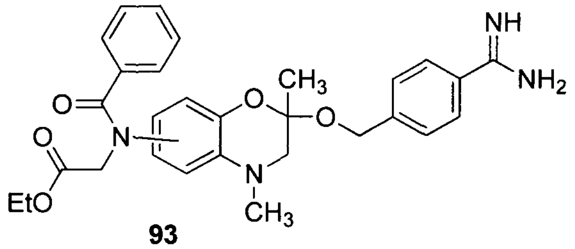
Compounds **91**, **92**, and **93** which have the most potent and well balanced dual anti-thrombotic activity, close to the nanomolar range, can serve as lead compounds for the next generation of dual anti-thrombotic agents, making use of established binding modes and structure-activity relationships.



91

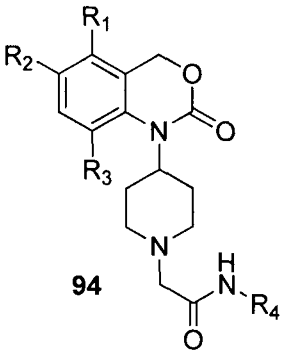


92



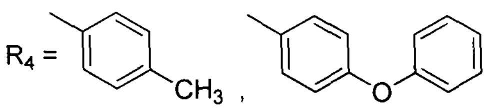
93

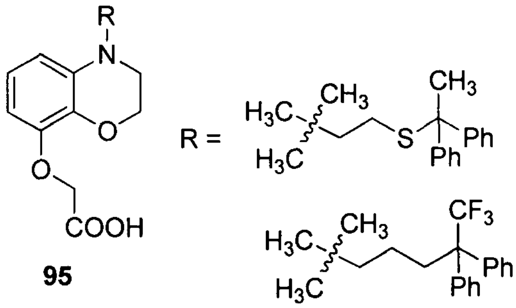
Deswal *et al,*[40] have established the quatitative structure-activity relationship (QSAR) for 30 benzoxazinone **(94)** derivatives acting as neuropeptide YY5 receptor antagonists. Ohno *et al,*[41] reported the synthesis of a novel series of 3, 4-dihydro-2*H*-benzo [1, 4]oxazine- 8-yl-oxyacetic acid derivatives **(95)**. The compounds were screened to block the TXA2 receptor and found as a novel treatment in the anti-thrombotic and the cardiovascular fields avoiding hypotensive side effects. Kern *et al,*[42] previously reported 6-aryl benzoxazine-2-ones **(96)** as PR modulators. In continuation of this work, they examined the specific absorption rate (SAR) of new 6-aryl amino benzoxazinones and found the compounds with benzoxazine-2-thione core as PR antagonists. Powell *et al,*[43] reported the design and synthesis of a series of 6-(2,4-diaminopyrimidinyl)-1,4-benzoxazin-3-ones **(97)** as orally bioavailable small molecule inhibitors as rennin. Compounds with a 2-methyl-2-aryl substitution pattern exhibit potent rennin inhibition and good permeability-solubility and metabolic stability.



94

R_1, R_2 = H, Cl
R_3 = H, CH_3, OCH_3





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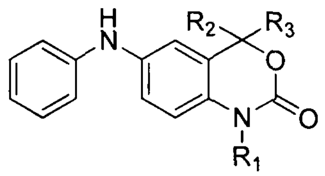
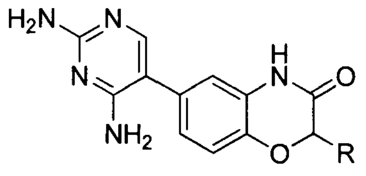


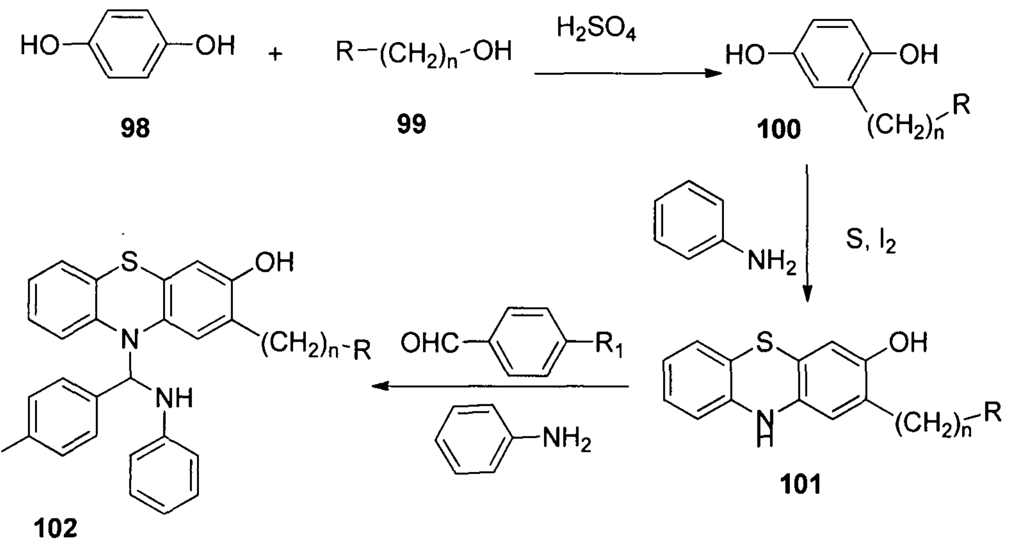
R_1, R_2 = H, CH_3, C_2H_5
96 R_3 = CH_3, C_2H_5, Thien-2-yl



R = CH_3, C_2H_5, C_4H_9

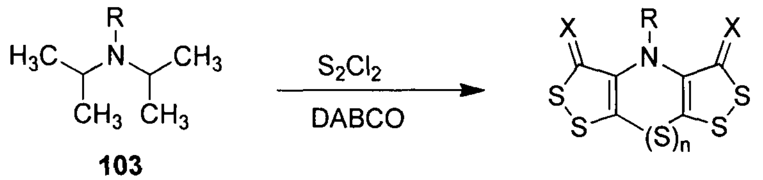
97

Besides having diverse types of bioactive properties like anti-convulsant, anti-parkinsonian and anti-histaminic characters,[44] new vistas of phenothiazine derivatives are being explored now a days.[45] Several phenothiazine derivatives have been reported to possess anti-viral and anti-parasitic properties.[46a,b] They have also been registered as effective agents against prion diseases.[46c] Their effectiveness is controlled upto a greater extent by substituents present on the nucleus. S. K. Saxena and V. K. Pandey[46d] synthesized some new substituted phenothiazines to test their activity against viruses (**Scheme 20**).



Scheme-20

Torroba *et al,*[47] reported a one-pot reaction of the corresponding *N*-alkyldiisopropylamines and disulfur dichloride for the preparation of long-chain or branched-chain *N*-alkyl bisdithiolothiazines (**Scheme-21**), constituting a very short and convenient preparative method in some instances starting from all commercial reagents. These heterocycles, containing the 1,2-dithiole-3-thione moiety could be further functionalized by its cycloaddition with different dienophiles and 1,3-dipolar reagents.



103

R = Et, Me, CH_2Ph, $(CH_2)_2Cl$
$(CH_2)_2SPh$, $(CH_2)_2CO_2H$

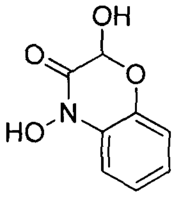
X = O, S
n = 0, 1

104

Scheme-21

V.5. Synthetic reports on bis-oxazines and bis-thiazines.

Our main focus in this paper is on bis-1,3-oxazines and bis-1,3-thiazines. Among the 1,3-oxazines also, there is a vast difference of functional as well as structural diversity patterns. Thorough literature survey revealed that the compounds containing dihydro-1,3-oxazine ring system exhibited a wide spectrum of pharmacological activities and ever since the first isolation of 2, 4-dihydroxy-2*H*-1, 4-benzoxazin-3(4*H*)-one (DIBOA) **(105)** and 4-dihydroxy-7-methoxy-(2*H*)-1,4-benzoxazin-3(4*H*)-one (DIMBOA) **(106)**, benzoxazine derivatives have attracted the attention of phytochemists.



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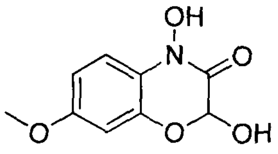


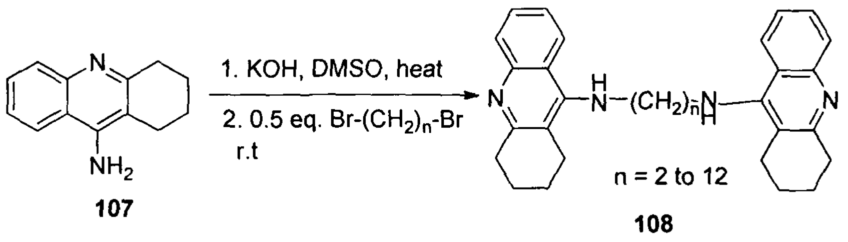
106

These have been studied intensively as important heterocyclic systems for the synthesis of biologically active compounds ranging from herbicides and fungicides to therapeutically usable drugs. A literature survey identified several benzoxazine derivatives in the development phase as potential new drugs. The versatility of the benzoxazine skeleton, in addition to its relative chemical simplicity and accessibility, make these chemicals amongst the most promising sources of bioactive compounds. This has led to the discovery of a wide variety of compounds that are of high interest from the point of view of anti-microbial, anti-mycobacterial, anti-diabetic and anti-depressant effects among others. They can polymerize *via* a ring-opening addition reaction without by-products and exhibit near-zero shrinkage or even a slight expansion upon curing.

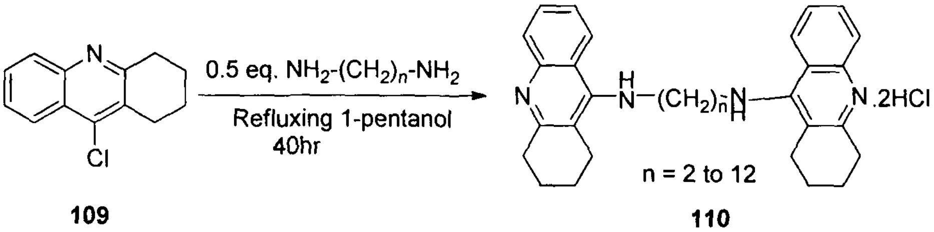
Several properties of polybenzoxazines can be superior to those of the conventional phenolic polymer. In the curing process of multifunctional benzoxazine based precursors, no volatiles are evolved so that there is a small volume change in fabrication. There is also greater flexibility in designing monomers for benzoxazines. Therefore, in the last decade, researchers have paid more and more attention to them. As a result, many kinds of benzoxazine monomers including both mono-benzoxazines and bi-benzoxazines have been synthesized.[48]

It has been reported in literature that bis-compounds sometimes exhibit better properties than their corresponding monomers. Our literature survey at this stage revealed that synthetic study of bis-heterocyclic compounds have become an important field of research for finding new biologically active molecules. Recent reports have revealed that bis-heterocyclic compounds possess important pesticidal properties[49] and also anti-bacterial properties.[50] It is also evident from one of the reports that bis-heterocyclic compounds possess better anti-malarial activity than their monomer units, they are also known to possess anti-proliferative and anti-tumor activities.[51] Following these reports, we envisaged that molecules with two benzoxazine/benzothiazine rings linked through flexible aliphatic chains or through rigid aromatic chains could have enhanced biological activities.

P. R. Carlier and co-workers have also reported[52] the synthesis and evaluation of alkylene-linked dimers of tacarine (9-amino-1,2,3,4-tetrahydroacridine, **107**). The reaction of tacarine with dibromo alkanes gave the desired bis-product in low yields (epecially when n = 2 to n = 6). To overcome this difficulty, Carlier and co-workers explored reaction of 9-chloro-1,2,3,4-tetrahydroacridine with diamines. This method was found to be successful and the optimum temperature proved to be refluxing 1-pentanol at atmospheric pressure for 40 hours (**Scheme-22**).



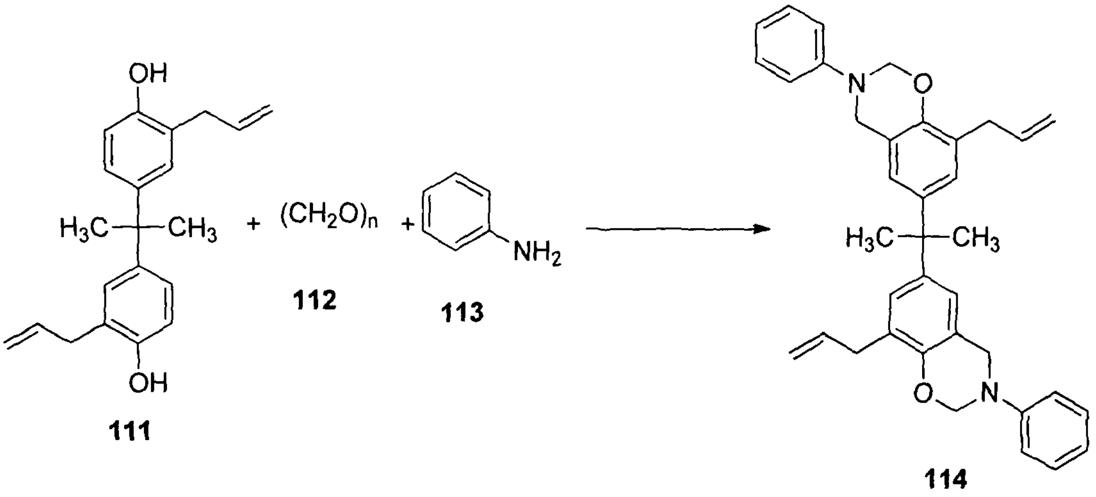
Scheme-22a



Scheme-22b

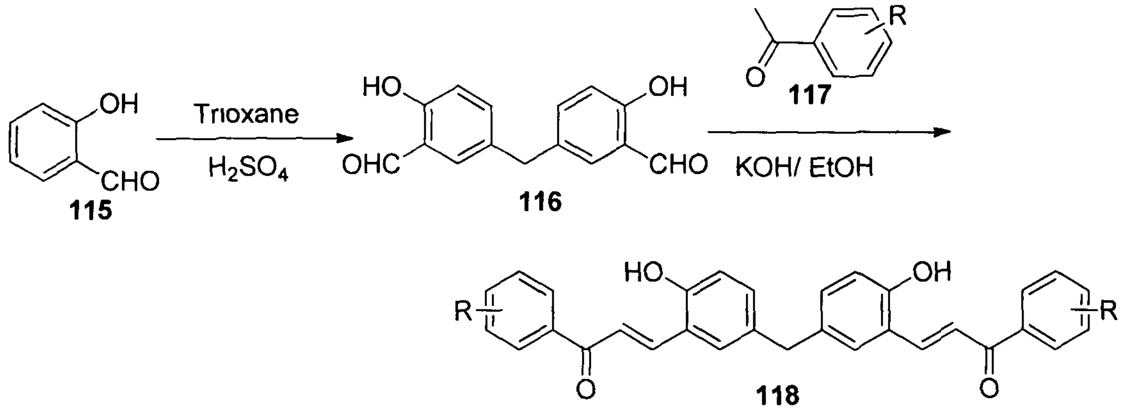
These dimeric compounds (**108**) particularly the heptylene-linked tacarine dimer was found to be 149 fold more potent and 250 fold more selective for acetylcholinesterase (AchE) than tacarine. This dimer also exhibited 24 fold reversing scopolamine-induced memory impairments and thus could be a promising drug candidate for palliative treatment of senile dementia of the Alzheimer's disease.

Polybenzoxazines have evinced significant interest as a class of high performance polymer. These novel materials gain attention because of low volumetric shrinkage upon curing, minimal moisture absorption, excellent resistance to chemicals and UV light and high Tg. They are also promising because of their tremendous flexibility in molecular design and well-balanced thermal and mechanical properties. An effective approach for the performance improvement is the synthesis of novel high performance polybenzoxazines from benzoxazine monomers containing additional polymerisable groups such as phenyl, ethynyl, nitrile, propargyl, allyl, etc. To enhance the thermal characteristics, Ninan *et al,*[53] synthesized a bis-benzoxazine monomer with additional polymerisable allyl groups substituted on the active ortho sites of bisphenol-A (**Scheme-23**). The composition, structure, cyclic ratio and polymer structure of a diallyl di-benzoxazine prepared by suspension method were studied.[54]



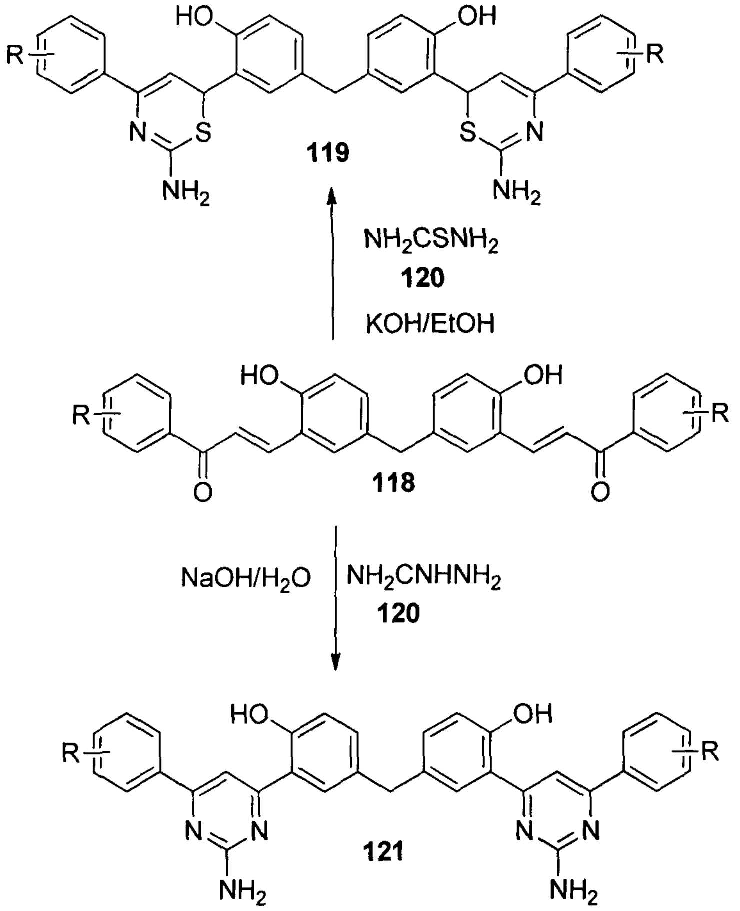
Scheme-23

Besides, monofunctional benzoxazines are hard to produce casting samples to test their physical and mechanical properties, so that it is necessary to study the difunctional benzoxazines combinating synthetic reaction, thermally activated polymerization, structure and property together. A series of novel bis-chalcones (**118**) were prepared by A. Nagaraj and C. Sanjeeva Reddy[55] by the reaction of 5,5'-methylene-bis-salicylaldehyde (**116**) with various acetophenones and subsequent treatment of **118** with thiourea or guanidine resulted to the corresponding bis-thiazines or bis-pyrimidines in good yields.



R = H, 4-OMe, 4-Cl

Scheme-24



R = H, 4-OMe, 4-Cl

Scheme-25

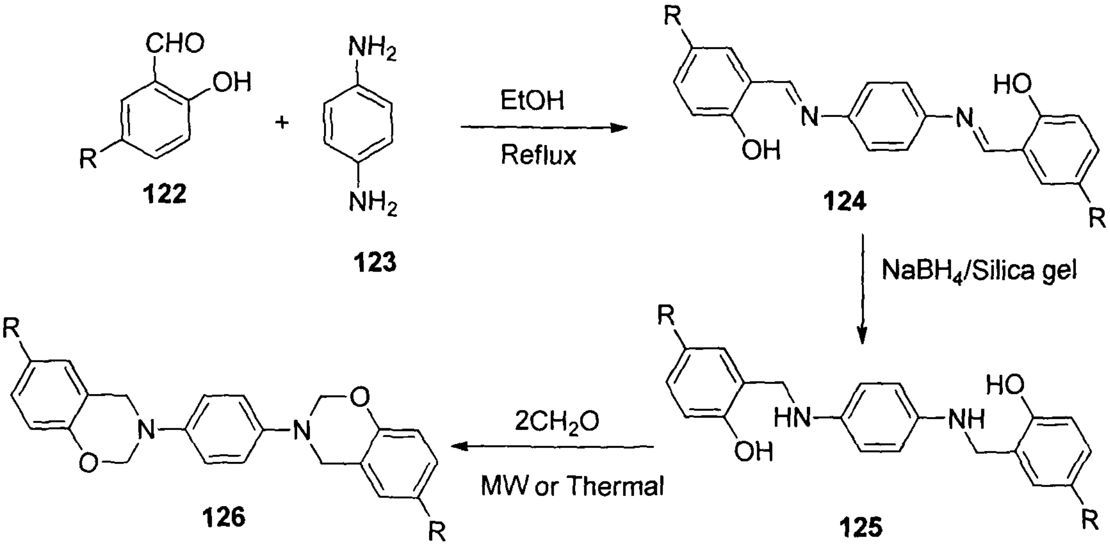
Although little information is available regarding bis-benzoxazines, they are an interesting class of compounds as key precursors leading to nitrogen atom-containing heterocycles as well as skeletons in biologically related molecules. Due to their broad spectrum of biological activities, they are an interesting class of compounds for further structural modifications.

Bis-benzoxazines exhibit various biological activities including anti-bacterial, anti-tumor and plant growth regulative properties. Polybenzoxazines have been used for the preparation of resins by ring opening reactions. The popular method of synthesizing benzoxazine is the Mannich reaction involving the condensation of phenol, formaldehyde and primary amine. Bis-benzoxazine monomers containing phenylphosphine oxide have been synthesized from phosphorous containing bisphenol compounds, primary amine and formaldehyde.[56]

Hence, there is enough scope to explore new oxazine and thiazine derivatives for biological activities. In this connection, the present paper describes the synthetic study of a series of bis-oxazine and bis-thiazine derivatives (**118, 119** etc.), two oxazine/thiazine monomers connected by aliphatic alkyl linkers through an eco-friendly Mannich type condensation–cyclization reaction of phenols or naphthol with formaldehyde and primary amines in water under reflux and its relative comparison with microwave irradiation method.

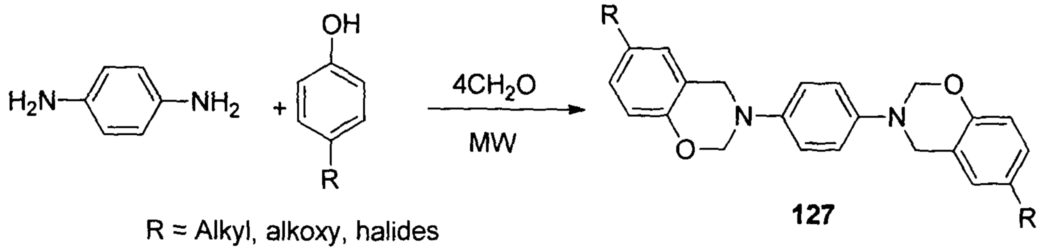
Synthetic approaches for 3,4-dihydro-2*H*-1,3-benzothiazines includes (i) condensation of 4,5-dimethoxy-2-mercaptobenzylammonium chloride with an aromatic aldehyde in the presence of potassium carbonate[57] and (ii) cycloaddition of benzothiete with corresponding substituted imines.[58] Benzoxazine thermoset resins, when heated, homopolymerize to form a rigid polymer that can be used for manufacturing products such as high-temperature composites and electronic components.

Synthesis of oxazine and thiazine monomers has been reported extensively but bis-oxazines have not been well documented. R. Manikannan and S. Muthusubramanian[56] have successfully described the synthesis of symmetrical bis-benzoxazines using microwave irradiation as well as the possibility of a multicomponent approach for the synthesis of the target molecule (**Scheme-26** and **Scheme-27**).



R= H, $C(CH_3)_3$, $CH(CH_3)_2$, $C(C_2H_5)(CH_3)_2$, $C(C_6H_5)(CH_3)_2$, C_2H_5, CH_3

Scheme-26



R = Alkyl, alkoxy, halides

Scheme-27

V.6. Results and discussions

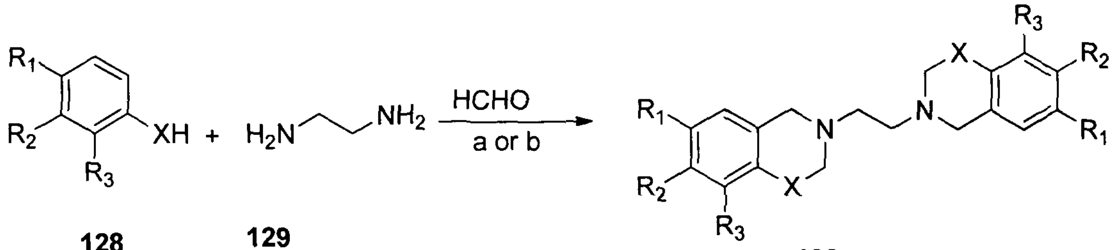
Dihydro-l,3-oxazines have been reported to have a strong cytotoxic effect on tumor cells, especially in low concentration. Many reports on the synthesis of 3,4-dihydro-2*H*-1,3-benzoxazines describe (i) Mannich condensation of phenol and a primary amine with formaldehyde,[26,59] (ii) condensation of *o*-hydroxybenzylamine with an aldehyde,[60] (iii) rearrangement reactions of 2-(allyloxy)benzylamine with H_2/CO in the presence of rhodium catalysts,[61] (iv) condensation of a 4-substituted phenol with 1,3,5-trimethyl-hexahydro-triazine in the presence of oxalyl chloride,[62] (v) reaction of 1-(bromomethyl)-2 (chloromethoxy)benzene with primary amines,[63] (vi) dehydration of *N*-(2-hydroxybenzyl)-3-aminopropanoic acid in the presence of sulfuric acid[64] and (vii) by ortho lithiation.[34]

The synthesis of various 3,4-dihydro-2*H*-benzo[*e*]-2,3-dihydro-1*H*-naphtho[1,2-*e*]-, 3,4-dihydro-2*H*-naphtho[2,1-*e*][1,3]oxazines and 1,2-bis[3,4-dihydrobenzo[*e*][1,3]oxazin-3(4*H*)-yl]ethanes involves one-pot condensation–cyclization reaction of phenols or naphthol with formaldehyde and primary amines. Various methods have been reported[65] for the synthesis of dihydro-1,3-oxazines including the reaction under neat conditions.[66] However, many of these processes have several disadvantages such as the need for a prolonged reaction time, high temperature, use of volatile and toxic organic solvents and occurrence of side products. Thus, the development of simple, efficient and green procedure for the synthesis of these molecules is highly desirable.

In view of this, it has been planned to synthesize a new set of heterocyclic compounds with benzoxazine unit. With a vast number of suitable starting compounds available, multifunctional amine-based bis-benzoxazines and bis-benzothiazines have tremendous untapped potential in the area of tailoring molecular structure for specific applications. A solventless, melt-state reaction is typically the synthetic procedure of choice for the preparation of benzoxazine monomers, primarily due to its simplicity and its purity of products. However, the high reactivity of the linear aliphatic diamines produced an unusually high concentration of oligomeric species during synthesis *via* the solventless protocol. In an effort to minimize the generation of oligomers, synthesis was conducted with the reactants diluted in water (2ml/mmol). A variety of bis-oxazines and bis-thiazines having aliphatic linkages between two monomers have been successfully synthesized keeping in view the importance of green chemistry (**Scheme-28** and **Scheme-29**).

The structures of the linear aliphatic diamine-based benzoxazines were confirmed by NMR, FTIR and Mass spectroscopy. Each ^1H NMR spectrum showed two singlet peaks, centered at approximately 3.9 and 4.8 ppm, which are consistent with the formation of a benzoxazine ring, in case of ethylene linkage, $-CH_2-$ peak comes around 2.9 ppm as singlet. The Mannich bridge protons of open oxazine rings are typically located at approximately 3.7 ppm, which was confirmed for these compounds in other reported work.[67] The absence of any proton peaks in this region indicates that the alcohol washes were successful in separating any oligomeric species from the monomers. Integration analysis of the proton peaks shows the closed-ring content of each compound to be better than 98%. It is especially important to make sure that the compounds synthesized have high purity for polymerization kinetic study as the typical phenolic impurity as either the original phenolic compound used for the synthesis or polybenzoxazine oligomers, both act as the cationic initiators for benzoxazine polymerization. Thus, the accuracy of the study is adversely affected.

As would be expected, the infrared spectra of the benzoxazine monomers are nearly identical for all of the different diamine chain lengths. There are a number of infrared bands in the spectra, which can be used to verify the formation of oxazine rings in each product. While not shown, the presence of the benzoxazine ring aromatic ether is confirmed using absorbance peaks at 1043 and 1208 cm^{-1}, due to the C-O-C symmetric and asymmetric stretching modes respectively.[68] The absorbances at 771 cm^{-1} were used to show the presence of the expected ortho-substituted benzene rings, while the peaks at 857 and 930 cm^{-1} are used to confirm the presence of benzene with an attached oxazine ring. Also noteworthy is the complete lack of bands from free or hydrogen-bonded hydroxyl groups in the higher frequency region of each spectrum. The absence of hydroxyl groups shows that the reaction optimization and purification has successfully eliminated any unreacted phenol and oligomeric species.



128 **129** **130**

X= O,S

R_1 = H, CH_3, OMe, C_6H_5

R_2 = H, CH_3, OCH_3, C_6H_5

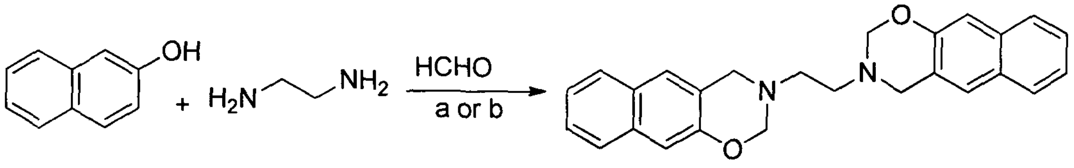
R_3 = H, CH_3, OMe

Conditions for reactions

(a) MWI, 2-5min,Solventless

(b) H_2O, 100^0C, 1-2hr

Scheme-28



131 **129** **132**

Conditions for reactions

(a) MWI, 2-5min,Solventless

(b) H_2O, 100^0C, 1-2hr

Scheme-29

Table-I: Reaction time and yield under different conditions for Compounds (**130a-j** and **132**).

Compound					**Microwave Irradiation**		**Conventional Heating**	
Products	**R_1**	**R_2**	**R_3**	**X**	**Yield (%)**	**Reaction time (sec)**	**Yield (%)**	**Reaction time (hr)**
130a	H	H	H	O	78	180	63	2
130b	H	H	CH_3	O	76	180	58	2
130c	CH_3	H	H	O	75	180	62	2
130d	H	CH_3	H	O	78	180	60	2
130e	C_6H_5	H	H	O	75	180	59	2
130f	H	C_6H_5	H	O	76	180	61	2
130g	H	H	OCH_3	O	76	180	58	2
130h	H	H	H	S	80	120	65	1
130i	OCH_3	H	H	S	82	120	68	1
130j	H	OCH_3	H	S	79	120	65	1
132	---	----	H	O	78	180	60	2

These bis-compounds have been found to exhibit high melting points as compared to their monomers.[26] All of them are solids and the compounds containing naphthalene ring are found to be very good crystals due to the presence of the naphthalene group. The results from **Table-1** show that reactions which were conventionally reported took long hours to complete and when the same reaction was performed under microwave irradiation, there is a drastic change in the time taken for the reaction to complete. The yields are also increased upto a favourable extent thereby, confirming the advantages of microwave reactions which are fast becoming as the most convenient and easy means of carrying out reactions.

V. 7. Experimental Section

Microwave reactions were carried out in a CEM Discover Benchmate microwave digester. Melting points are recorded in open capillary tubes and are uncorrected. Infrared spectra were recorded on a BOMEM DA-8 FTIR instrument and the frequencies are expressed in cm^{-1}. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance II-400 spectrometer using $CDCl_3$ as the solvent. Chemical shifts are reported in ppm downfield from internal tetramethylsilane and are given on the δ scale. Mass spectral data were obtained with a JEOL D-300 (EI) mass spectrometer. Elemental analyses were carried out on a Heraeus CHN-O-Rapid analyzer. All compounds give satisfactory elemental analyses within ± 0.4% of the theoretical values. All reactions were monitored by TLC using precoated aluminum sheets (silica gel 60 F_{254} 0.2 mm thicknesses) and developed in an iodine chamber or under UVGL-15 mineral light 254 lamp. Column chromatographic separations were carried out using ACME silica gel (60–120 mesh).

Procedure for the preparation of the title compound (130-130j) in conventional method:

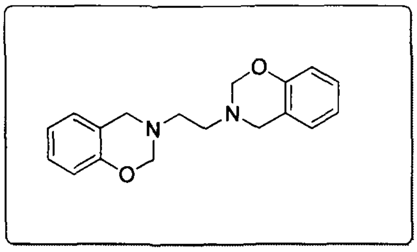
To a solution of **128** or **131** (5 mmol) in water (10 ml), formaldehyde (37% by wt.) (20 mmol) was added. A thick milky precipitate was formed. After 15 mins, diamine **(129)** (10 mmol) was added and the reaction mixture refluxed for 1-2 hrs. After the reaction was completed (as monitored by TLC), the crude compound was extracted with ethyl acetate and purified by column chromatography using ethyl acetate/hexane as an eluent or by repeated recrystallisation from hot ethanol.

Procedure for the preparation of the title compound (130a-j and 132) in microwave method:

To a mixture of **128** or **131** (5 mmol), formaldehyde (37% by wt.) (20 mmol) and **129** (10 mmol) was added and the reaction mixture was irradiated at 5 bar, 100 W, 100°C for the specific time mentioned in **Table-1**. After the reaction was completed (as monitored by TLC), the crude compound was extracted with ethyl acetate and purified by column chromatography using ethyl acetate/hexane or by repeated recrystallisation from hot ethanol.

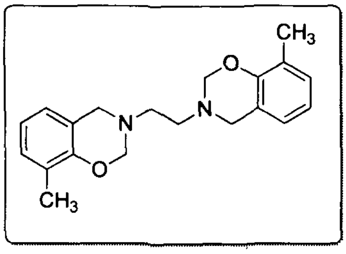
Spectral and analytical data of the compounds

1,2-bis(2*H*-benzo[*e*][1,3]oxazin-3(4*H*)-yl)ethane (130a):



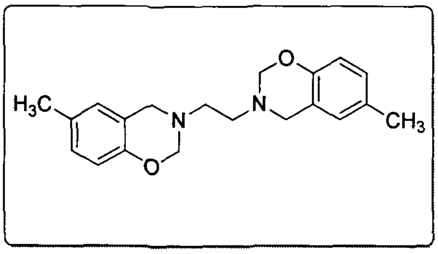
Mp: 107-109°C; IR (KBr, cm^{-1}): 2923, 2817, 1250, 1000, 938, 859, 800; ^1H NMR ($CDCl_3$): δ 2.97 (s, 4H, -CH_2-), 3.96 (s, 4H, CH_2), 4.83 (s, 4H, N-CH_2-O), 6.78-7.15 (m, 8H, ArH); ^{13}C NMR ($CDCl_3$): δ 49.55, 50.38, 84.24, 115.45, 120.53, 126.93, 128.32, 128.65, 158.12; Mass: m/z 297 [M^++1]; Anal. Calcd for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9.45; Found: C, 72.88; H, 6.67; N, 9.54%.

1,2-bis(8-methyl-2H-benzo[e][1,3]oxazin-3(4H)-yl)ethane (130b):



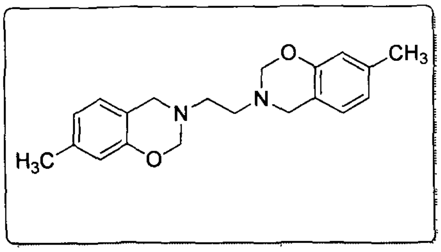
Mp: 108-110°C; IR (KBr, cm^{-1}): 2945, 2853, 1208, 1043, 930, 857, 771; ^1H NMR ($CDCl_3$): δ 2.10 (s, 6H, CH_3), 2.93 (s, 4H, -CH_2-), 3.99 (s, 4H, CH_2), 4.87 (s, 4H, N-CH_2-O), 6.68-7.18 (m, 6H, ArH); ^{13}C NMR ($CDCl_3$): δ 14.57, 48.33, 49.42, 81.56, 118.00, 118.96, 124.00, 124.58, 127.90, 151.07; Mass: m/z 325 [M^++1]; Anal. Calcd for $C_{20}H_{24}N_2O_2$: C, 74.04; H, 7.46; N, 8.64; Found: C, 74.16; H, 7.37; N, 8.71%.

1,2-bis(6-methyl-2*H*-benzo[*e*][1,3]oxazin-3(4*H*)-yl)ethane (130c):



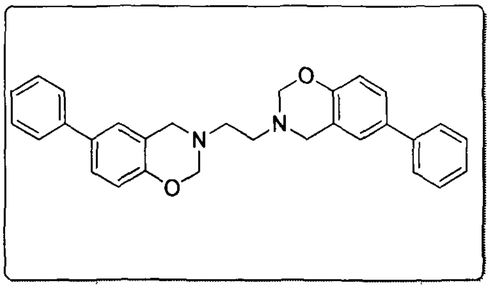
Mp: 109-111°C; IR (KBr, cm^{-1}): 2936, 2862, 1200, 1100, 990, 900, 791; ^1H NMR ($CDCl_3$): δ 2.27 (s, 6H, CH_3), 2.98 (s, 4H, -CH_2-), 3.98 (s, 4H, CH_2), 4.86 (s, 4H, N-CH_2-O), 6.73-7.07 (m, 6H, ArH); ^{13}C NMR ($CDCl_3$): δ 17.85, 49.13, 50.85, 82.58, 115.70, 119.43, 126.32, 130.71, 131.42, 153.95; Mass: m/z 325 [M^++1]; Anal. Calcd for $C_{20}H_{24}N_2O_2$: C, 74.04; H, 7.46; N, 8.64; Found: C, 74.07; H, 7.52; N, 8.58%.

1,2-bis(7-methyl-2*H*-benzo[*e*][1,3]oxazin-3(4*H*)-yl)ethane (130d):



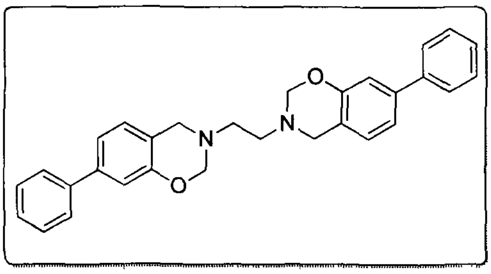
Mp: 107-109°C; IR (KBr, cm^{-1}): 2962, 2847, 1280, 1090, 989, 875, 790; ^{1}H NMR (CDCl$_3$): δ 2.22 (s, 6H, CH$_3$), 2.96 (s, 4H, -CH$_2$-), 3.87 (s, 4H, CH$_2$), 4.93 (s, 4H, N-CH$_2$-O), 6.73-6.97 (m, 6H, ArH); ^{13}C NMR (CDCl$_3$): δ 18.32, 49.03, 51.37, 82.11, 117.42, 121.61, 122.51, 128.92, 135.31, 156.23; Mass: m/z 324 [M$^+$]; Anal. Calcd for $C_{20}H_{24}N_2O_2$; C, 74.04; H, 7.46; N, 8.64; Found: C, 74.11; H, 7.40; N, 8.54%.

1,2-bis(6-phenyl-2*H*-benzo[*e*][1,3]oxazin-3(4*H*)-yl)ethane (130e):



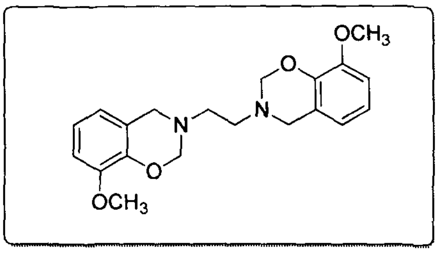
Mp: 102-103°C; IR (KBr, cm^{-1}): 3011, 2894, 1250, 1100, 950, 890, 810; ^{1}H NMR (CDCl$_3$): δ 2.95 (s, 4H, -CH$_2$-), 3.96 (s, 4H, CH$_2$), 4.98 (s, 4H, N-CH$_2$-O), 6.98-7.46 (m, 16H, ArH); ^{13}C NMR (CDCl$_3$): δ 50.33, 52.71, 83.46, 120.17, 121.32, 126.73, 127.35, 128.65, 129.11, 129.96, 134.82, 137.49, 154.44; Mass: m/z 449 [M$^+$+1]; Anal. Calcd for $C_{30}H_{28}N_2O_2$: C, 80.33; H, 6.29; N, 6.25; Found: C, 80.41; H, 6.37; N, 6.18%.

1,2-bis(7-phenyl-2*H*-benzo[*e*][1,3]oxazin-3(4*H*)-yl)ethane (130f):



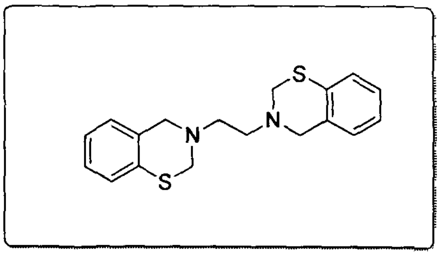
Mp: 101-103°C; IR (KBr, cm^{-1}): 2996, 2888, 1230, 1117, 960, 861, 791; ^{1}H NMR (CDCl$_3$): δ 2.95 (s, 4H, -CH$_2$-), 3.96 (s, 4H, CH$_2$), 4.86 (s, 4H, N-CH$_2$-O), 6.97-7.42 (m, 16H, ArH); ^{13}C NMR (CDCl$_3$): δ 51.23, 52.55, 83.74, 112.38, 118.32, 125.57, 127.61, 128.05, 129.21, 130.19, 139.94, 143.85, 156.28; Mass: m/z 448 [M$^+$]; Anal. Calcd for $C_{30}H_{28}N_2O_2$: C, 80.33; H, 6.29; N, 6.25; Found: C, 80.38; H, 6.21; N, 6.30%.

1,2-bis(8-methoxy-2*H*-benzo[*e*][1,3]oxazin-3(4*H*)-yl)ethane (130g):



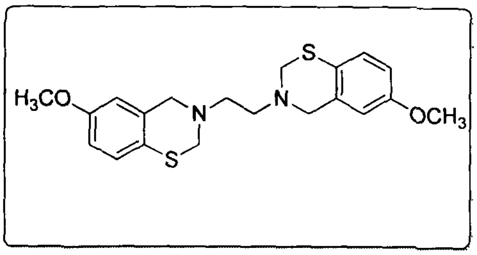
Mp: 106-108°C; IR (KBr, cm^{-1}): 2948, 2822, 1209, 1025, 925, 870, 717; ^{1}H NMR (CDCl$_3$): δ 2.91 (s, 4H, -CH$_2$-), 3.96 (s, 4H, CH$_2$), 3.87 (s, 6H, OCH$_3$), 4.88 (s, 4H, N-CH$_2$-O), 6.86-7.02 (m, 6H, ArH); ^{13}C NMR (CDCl$_3$): δ 50.23, 51.85, 56.07, 83.47, 104.23, 104.65, 107.48, 130.16, 156.28, 157.85; Mass: m/z 356 [M$^+$]; Anal. Calcd for $C_{20}H_{24}N_2O_2$: C, 67.40; H, 6.79; N, 7.86; Found: C, 67.51; H, 6.84; N, 7.73%.

1,2-bis(2*H*-benzo[*e*][1,3]thiazin-3(4*H*)-yl)ethane (130h):



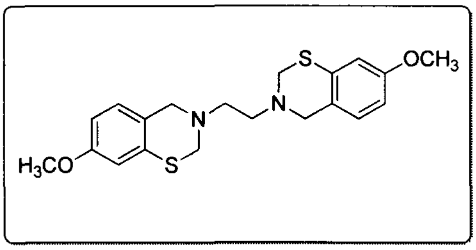
Mp: 98-99°C; IR (KBr, cm^{-1}): 2948, 2822, 1210, 1090, 980, 890, 810 ; ^{1}H NMR (CDCl$_3$): δ 2.92 (s, 4H, -CH$_2$-), 3.74 (s, 4H, CH$_2$), 4.03 (s, 4H, N-CH$_2$-S), 7.06-7.31 (m, 8H, ArH); ^{13}C NMR (CDCl$_3$): δ 50.32, 58.47, 62.18, 126.31, 127.43, 128.04, 128.32, 130.86, 137.29; Mass: m/z 328 [M$^+$]; Anal. Calcd for $C_{18}H_{20}N_2S_2$: C, 65.81; H, 6.14; N, 8.53; Found: C, 65.73; H, 6.28; N, 8.41%.

1,2-bis(6-methoxy-2*H*-benzo[*e*][1,3]thiazin-3(4*H*)-yl)ethane (130i):



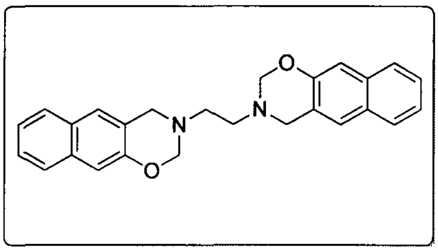
Mp: 95-98°C; IR (KBr, cm^{-1}): 2985, 2864, 1220, 1101, 990, 815, 791 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 2.93 (s, 4H, -CH$_2$-), 3.73 (s, 4H, CH$_2$), 3.95 (s, 6H, OCH$_3$), 4.98 (s, 4H, N-CH$_2$-S), 6.98-7.22 (m, 6H, ArH); ^{13}C NMR (CDCl$_3$): δ 51.43, 54.15, 61.53, 63.11, 113.45, 114.09, 124.57, 127.42, 132.65, 156.83; Mass: m/z 388 [M$^+$]; Anal. Calcd for $C_{20}H_{24}N_2O_2S_2$: C, 61.82; H, 6.23; N, 7.21; Found: C, 61.75; H, 6.14; N, 7.30%.

1,2-bis(7-methoxy-2*H*-benzo[*e*][1,3]thiazin-3(4*H*)-yl)ethane (130j):

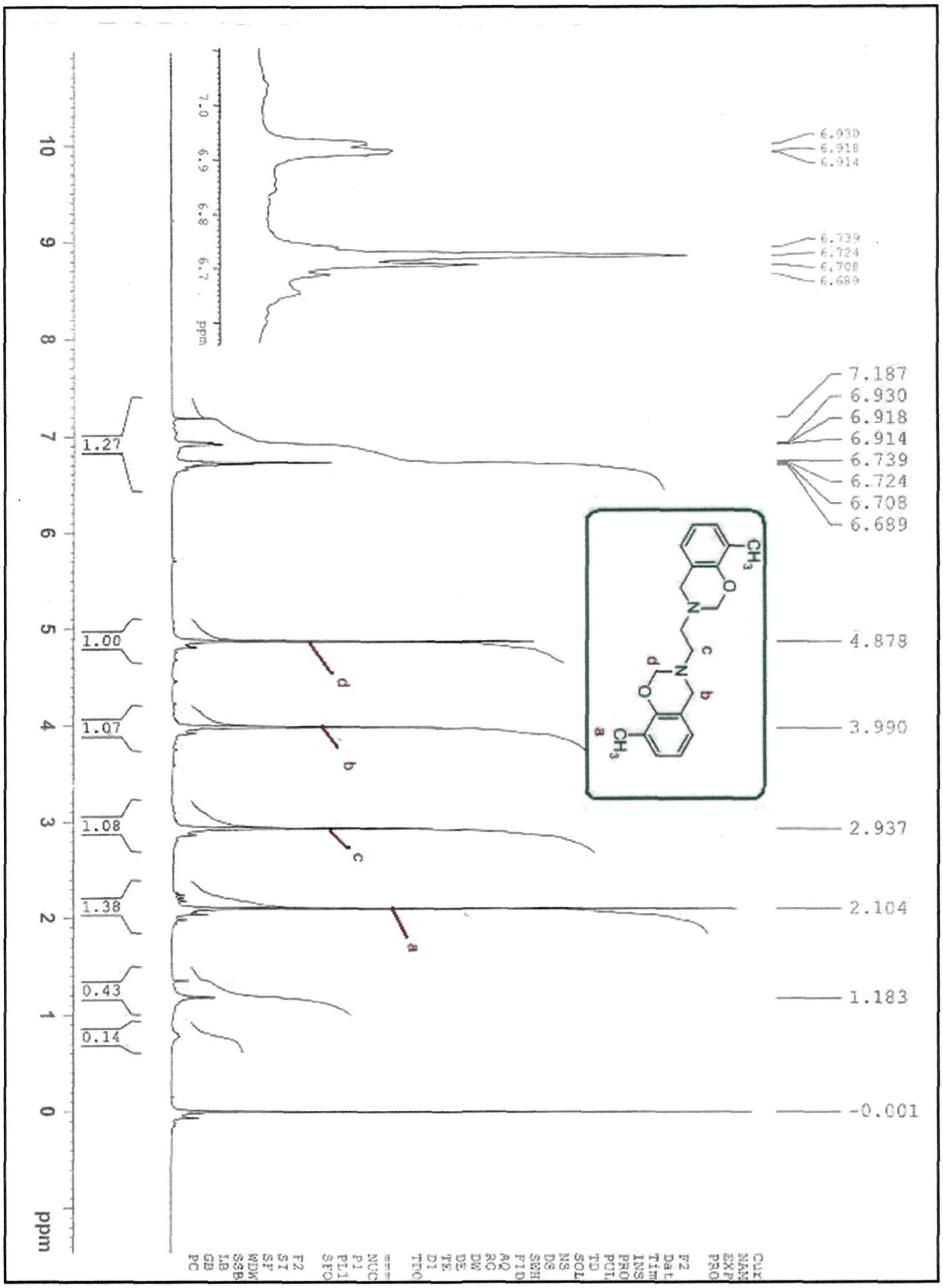


Mp: 99-102°C; IR (KBr, cm^{-1}): 2977, 2859, 1205, 1041, 935, 860, 765; ^{1}H NMR (CDCl$_3$): δ 2.92 (s, 4H, -CH$_2$-), 3.78 (s, 4H, CH$_2$), 3.91 (s, 6H, OCH$_3$), 4.03 (s, 4H, N-CH$_2$-S), 6.79-7.01 (m, 6H, ArH); ^{13}C NMR (CDCl$_3$): δ 51.38, 55.12, 61.58, 62.85, 109.96, 110.94, 125.09, 130.64, 132.75, 157.68; Mass: m/z 389 [M$^+$+1]; Anal. Calcd for $C_{20}H_{24}N_2O_2S_2$: C, 61.82; H, 6.23; N, 7.21; Found: C, 61.72; H, 6.34; N, 7.17%.

1,2-bis(2*H*-naphtho[2,3-*e*][1,3]oxazin-3(4*H*)-yl)ethane (132):



Mp: 108-110°C; IR (KBr, cm^{-1}): 2967, 2851, 1210, 1061, 993, 875, 792; ^{1}H NMR (CDCl$_3$): δ 2.93 (s, 4H, -CH$_2$-), 3.99 (s, 4H, CH$_2$), 5.03 (s, 4H, N-CH$_2$-O), 7.35-7.81 (m, 12H, ArH); ^{13}C NMR (CDCl$_3$): δ 50.92, , 52.33, 83.17, 107.48, 122.52, 125.74, 126.28, 127.54, 128.36, 128.96, 129.42, 132.66,157.43; Mass: m/z 396 [M$^+$]; Anal. Calcd for $C_{26}H_{24}N_2O_2$: C, 78.76; H, 6.10; N, 7.07; Found: C, 78.83; H, 6.22; N, 7.15%.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9
8
7
6
5
4
3
2
1
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1.27
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1.07
1.08
1.38
0.43
0.14
7.0
6.9
6.8
6.7
ppm
6.930
6.918
6.914
6.739
6.724
6.708
6.689
7.187
6.930
6.918
6.914
6.739
6.724
6.708
6.689
4.878
3.990
2.937
2.104
1.183
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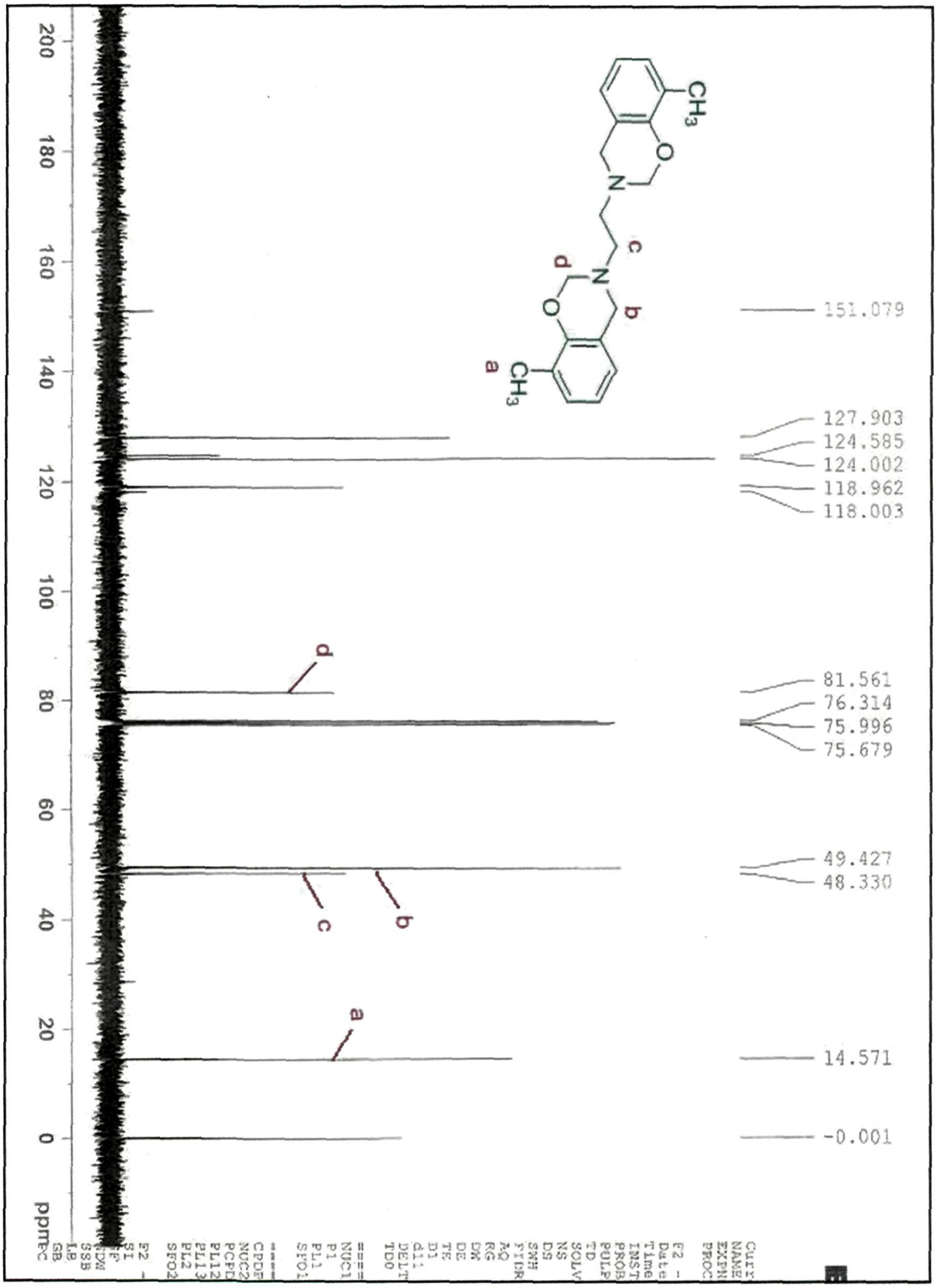
b
c
a
CH3
O
N
c
d
b
a
CH3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d
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118.003
81.561
76.314
75.996
75.679
49.427
48.330
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b
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40
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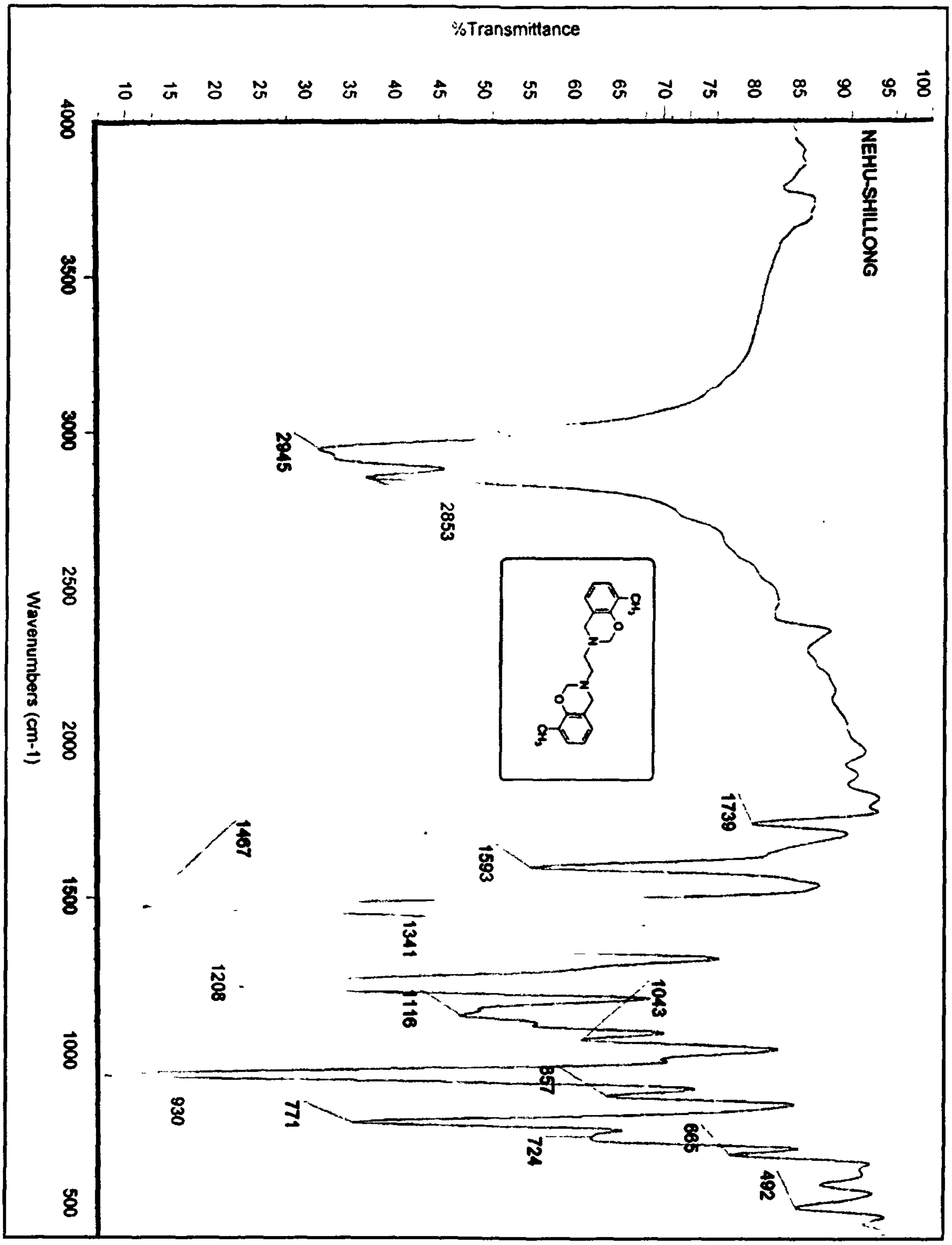
0
ppm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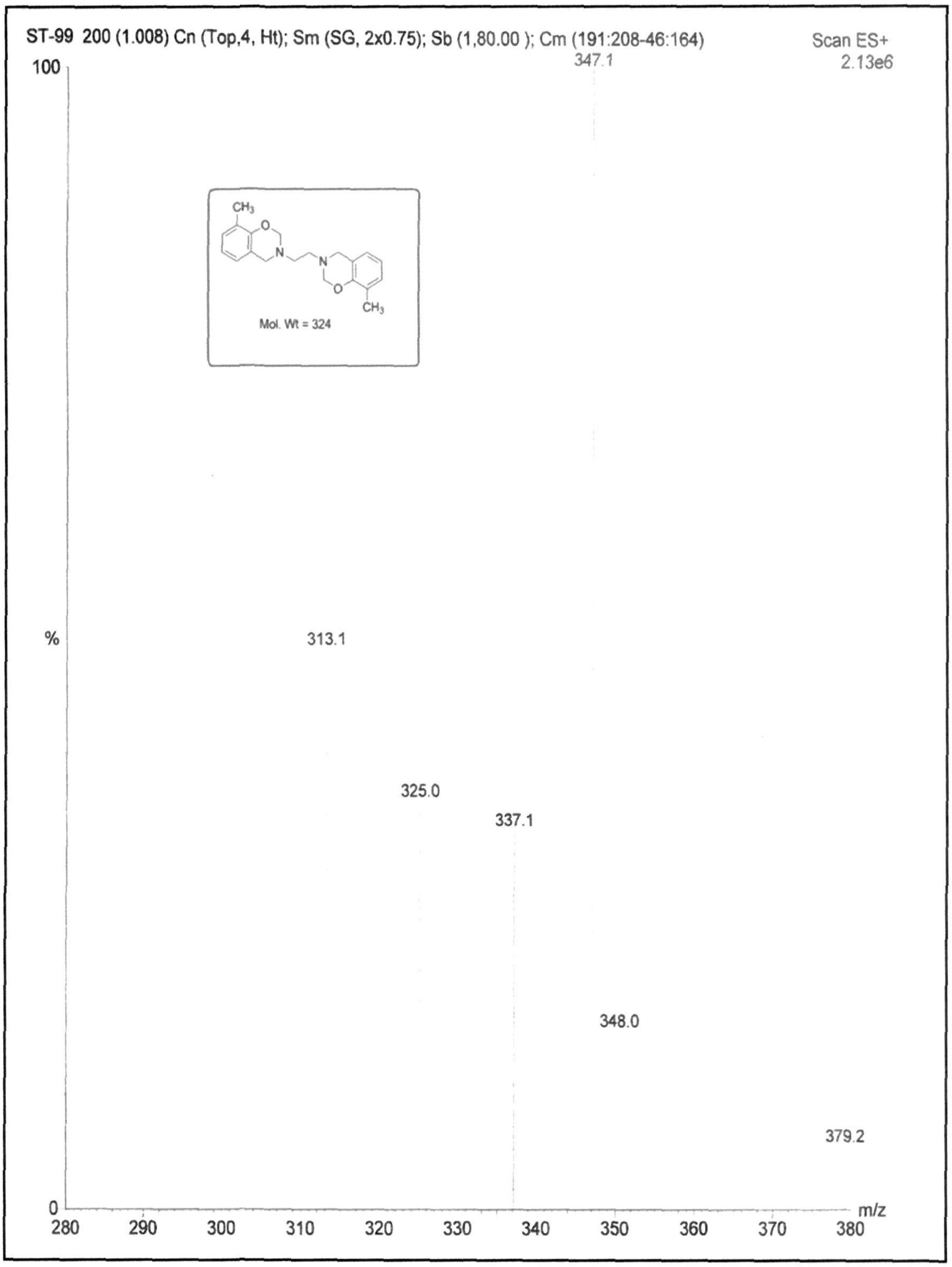
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
NEHU-SHILLONG
2945
2853
1739
1593
1467
1341
1208
1116
1043
857
930
771
724
665
492
CH3
O
N
N
O
CH3
4000
3500
3000
2500
2000
1500
1000
500
Wavenumbers (cm-1)



V.8. REFERENCES:

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LIST OF PUBLICATIONS

1. **Novel one pot synthesis of substituted 1, 2, 4-triazines**
   I. T. Phucho, A. Nongpiur, S Tumtin, R. Nongrum, B. Myrboh and R. L. Nongkhlaw. *Arkivoc,* **2008**, *(xv),* 79.

2. **Recent progress in the chemistry of dihydropyrimidinones**
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3. **One Pot Synthesis of [1,3]-Oxazine and [1,3]-Thiazine Derivatives Under Thermal and Microwave Conditions**
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4. **Synthesis of 3,4-dihydropyrimidine-2(1*H*)-ones/thiones via three component cyclocondensation.**
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5. **Microwave assisted synthesis of 6-methyl-1,2,3,4-tetrahydro-*N*-aryl-2-oxo-4-arylpyrimidine-5-carboxamide and 3, 4-dihydropyrimidin-2(*1H*)-ones under solvent free conditions.**
   I. T. Phucho, S. Tumtin, A. Nongpiur, R. Nongrum and R. L. Nongkhlaw, ***J. Chem. Pharm. Res.***, **2010**, *2(3),* 214-222.

6. **Microwave assisted synthesis of 3-substituted 4(3*H*)-quinazolinone using silica supported potassium carbonate.**
   I. T. Phucho, S. Tumtin, A. Nongpiur, R. Nongrum, R.L. Nongkhlaw
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