“DEVELOPMENT OF NOVEL METHODS FOR THE SYNTHESIS OF *N*-SUBSTITUTED 3,4-DIHYDRO-2*H*-BENZO[1,4]OXAZINE [BENZOMORPHOLINE], SUBSTITUTED 7-METHYL-6,7-DIHYDRO-5*H*-PYRROLO[2,3-*d*]PYRIMIDIN-2-OL, PYRIDAZINES AND RELATED HETEROCYCLIC MOLECULES”

By

PUSHPAK MIZAR

ABSTRACT

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE

OF

DOCTOR OF PHILOSOPHY

IN

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TO

NORTH EASTERN HILL UNIVERSITY

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MEGHALAYA

INDIA

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ABSTRACT

The work presented in the thesis entitled "Development of novel methods for the Synthesis of *N*-sibstituted 3,4-dihydro-2*H*-benzo[1,4]oxazine [benzomorpholine], substituted 7-methyl-6,7-dihydro-5*H*-pyrrollo[2,3-*d*]pyrimidin-2-ol, pyridazines and related Heterocyclic molecules;" has aimed to explore the chemistry of heterocyclic molecules. The work mainly consist of synthetic methodology towards the synthesis of the above heterocycles. The effect of the reaction condition and mechanism involved have also been discussed.

The thesis is divided into six chapters. The salient features are described below:

A brief introduction on organic compounds in general and heterocyclic compounds in particular are presented in **CHAPTER I**

This chapter gives an insight into the development of organic chemistry from its early years. Early examples of organic reactions and applications were serendipitous, such as Perkin's accidental discovery of Perkin's mauve. However, from the 20th century, the progress of organic chemistry has allowed for the synthesis of specifically selected compounds or even molecules designed with specific properties, as in drug design. Pharmaceutical benefits have been substantial, for example cholesterol-related compounds have opened ways to synthesis of complex human hormones and their modified derivatives. Since the start of the 20th century, complexity of total syntheses has been increasing, with examples such as lysergic acid and vitamin B12. Today's targets feature tens of stereogenic centers that must be synthesized correctly with asymmetric synthesis.

In the biological world the heterocyclic compounds are everywhere. Carbohydrates are heterocyclic, so are chlorophyll and heme, which make leaves green and blood red and bring life to plants and animals. Heterocycles form the site of reaction in many enzymes and

coenzymes. Heredity comes down, ultimately, to the particular sequence of the attachment of a half-dozen heterocyclic rings in the long chains of nucleic acid.

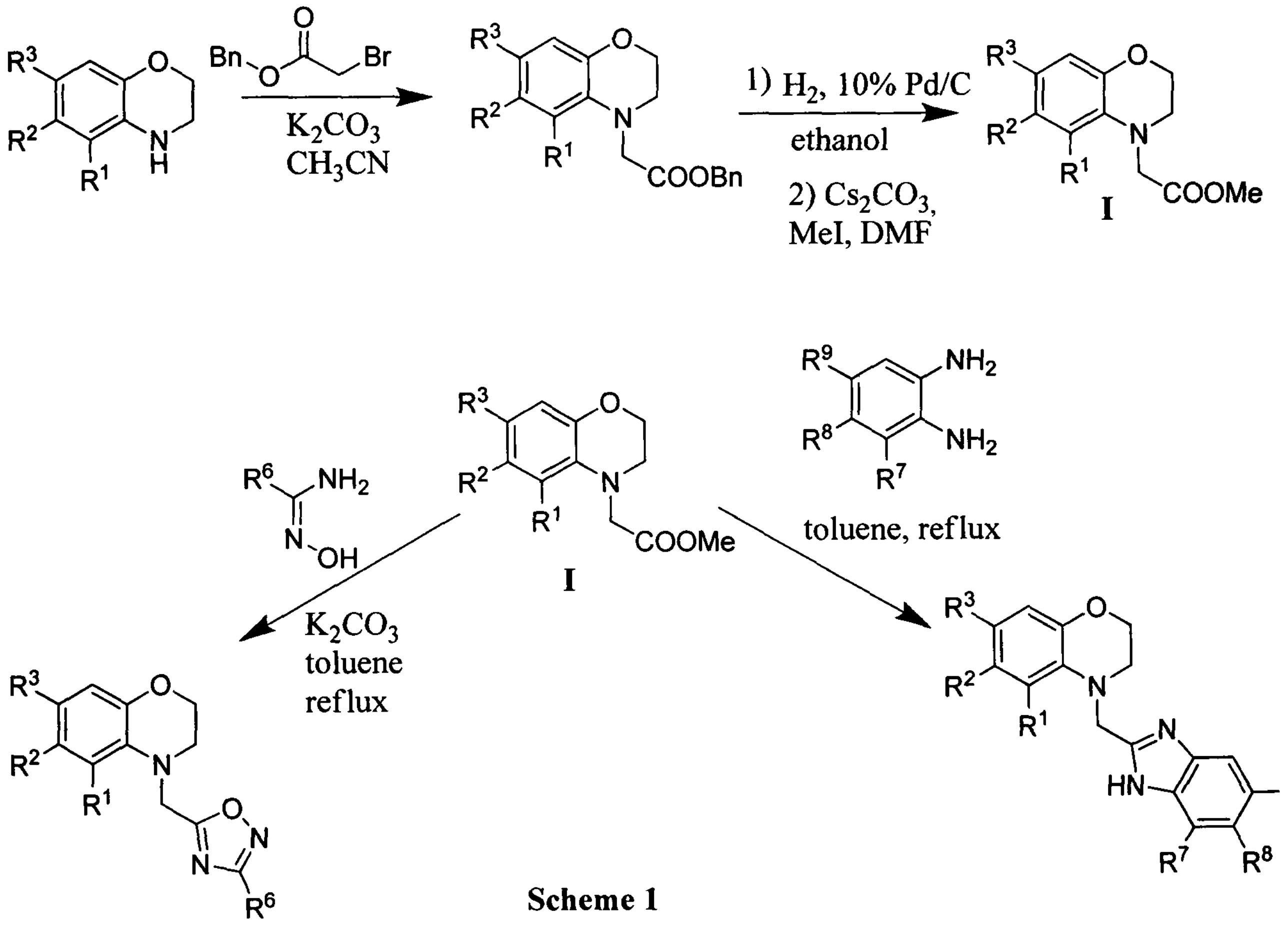
Heterocyclic unit such as 1,4-benzoxazine, pyridazines, fused pyrimidines, fused pyridines and their analogues are of special interest in pharmacology, due to their important biological activities. The importance of heterocyclic molecules in natural product chemistry and pharmacology constantly drives the search for new methods for their construction. An important approach for the synthesis of these types of compounds involve application of annelation methods, this is construction of cyclic compounds from open chain precursors

CHAPTER II

This chapter describes a novel and a versatile method for "Synthesis of substituted 4-(3-alkyl-1,2,4-oxadiazol-5-ylmethyl)-3,4-dihydro-2*H*-1,4-benzoxazines and 4-(1*H*-benzimidazol-2-ylmethyl)-3,4-dihydro-2*H*-1,4-benzoxazines." The 1,4-benzoxazine structure is an integral part of several naturally occurring substances. For example, various glycosides of the 2-hydroxy-2*H*-1,4-benzoxazine-3(4*H*) skeletons have been found to occur in gramineous plants such as maize, wheat, rye, rice etc and have been suggested to act as plant resistance factors against microbial diseases and insects. The 1,4-benzoxazine moiety is also found in various antibiotics such as C-1027.

1,4-benzoxazine were synthesized by reacting of 2-aminophenol (45mmol) and 1,2-dibromoethane (1.2 equiv) in the presence of K_2CO_3 (3 equiv) in dry DMF at 125 °C. This method was extended to the synthesis of various *N*-substituted 3,4-dihydro-2*H*-1,4-benzoxazines. The investigation was further extended to the synthesis of substituted 4-(3-alkyl-1,2,4-oxadiazol-5-ylmethyl)-3,4-dihydro-2*H*-1,4-benzoxazines and 4-(1*H*-

benzimidazol-2-ylmethyl)-3,4-dihydro -2*H*-1,4-benzoxazines as shown in Scheme **1** utilising (2,3-dihydro-2*H*-1,4-benzoxazin-4-yl)acetic acid methyl ester. *N*-Alkylation using benzyl bromoacetate was followed by de-benzylation to yield the corresponding acid. The acid was then converted into the methyl ester using MeI in the presence of Cs_2CO_3 since normal esterification did not yield any product. The methyl ester served as a good precursor for the synthesis of thiazole, imidazole and benzimidazole rings attached to the benzoxazine moiety.

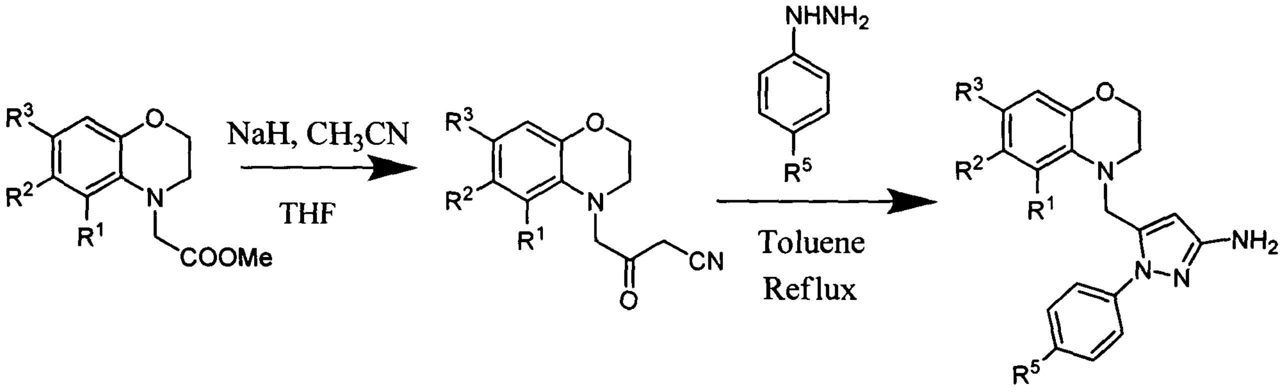


Scheme 1

CHAPTER III

This chapter deals with the synthesis of "Synthesis of Substituted 4-(5-alkyl-thiazol-2-ylmethyl)-3,4-dihydro-2*H*-1,4-benzoxazines and 5-(2,3-dihydro-1,4-benzoxazin-4-ylmethyl)-4-methyl-1-phenyl-1*H*-pyrazol-3-ylamine." The pyrazole and thiazole ring systems are common structural motifs in a number of biologically active molecules. Thiazole ring systems originate in nature as a consequence of peptide modification containing cysteine side chain residue and are the product of cyclodehydration and redox reactions. The synthesis of pyrazole and amino thiazole derivatives are well documented and their methods of preparation are manifold and varied. Our literature survey revealed that benzoxazines bearing pyrazole and thiazole rings on the *N*-atom have not been reported inspite of the fact that these two heterocyclic systems played an important role in drug development.

For our investigation we aimed at synthesizing *N*-substituted benzoxazine derivatives of biological interest, we wanted to introduce different heterocyclic ring systems on the *N*-atom of the benzoxazines. The synthesis of 3,4-Dihydro-1,4-2*H*-benzoxazine was carried out from 2-aminophenols and 1,2-dibromoethane using K_2CO_3 in DMF which was then subjected to *N*-substitution using alkyl bromide. Subsequent de-benzylation and esterification yielded (2,3-dihydro-1,4-benzoxazin-4-yl)-acetic acid methyl ester **I**. Thus, the synthesis of 4-(5-alkyl-thiazol-2-ylmethyl)-3,4-dihydro-2*H*-1,4-benzoxazines and 5-(2,3-dihydro-1,4-benzoxazin-4-ylmethyl)-4-methyl-1-phenyl-1*H*-pyrazol-3-ylamine starting from (2,3-dihydro-1,4-benzoxazin-4-yl)-acetic acid methyl ester was achieved (scheme **2**).

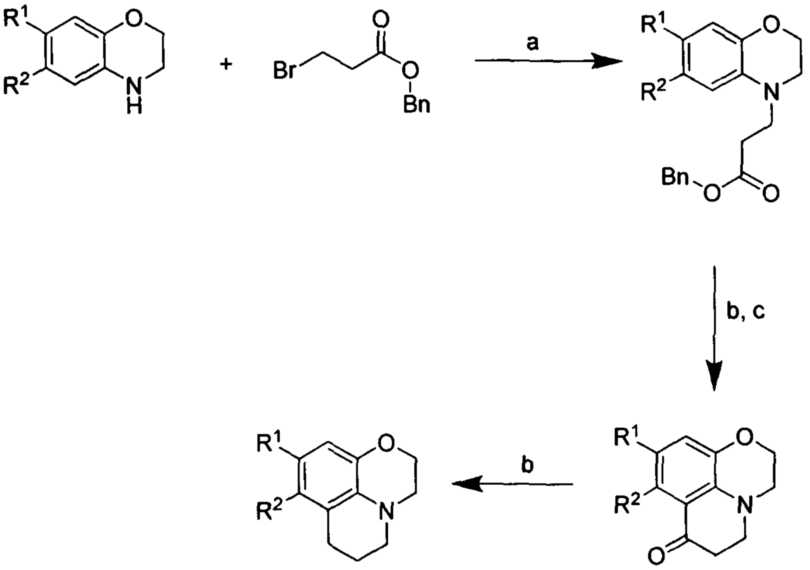


Scheme 2

CHAPTER IV

Chapter iv describe a novel method for the "Synthesis of 2,3-dihydro-6*H*-1-oxa-3a-aza-phenalene and their benzo/hetero fused analogue." Numerous methods for the synthesis of substituted 2*H*-1,4-benzoxazine and their corresponding benzo/hetero-fused derivatives have been developed, the search for new and efficient synthetic routes for these classes of compounds continues to attract a lot of attention. The present work describes two general methods for the synthesis of 2,3-dihydro-6*H*-1-oxa-3a-aza-phenalene, one involving the general *N*-alkylation of the benzoxazines with benzyl propanoate and subsequent reduction and cyclisation. The other by reaction of benzoxaxine and α-oxoketene dithio-acetal to give the *S,N*-acetal which when reacted with Vilsmeier reagent provides a versatile route to highly functionalized 2*H*-1,4-benzoxazine and their benzo- and hetero-fused analogues.

The use of α-oxoketene dithio-acetals in the synthesis of various heterocyclic molecules is well documented in the literature. However, there is no report about its uses in the synthesis of tricyclic analogs of benzoxazines. We report herein a simple procedure for the synthesis of this class of compounds starting from benzoxazine and α-oxoketene dithio-acetals. Benzoxaxine when treated with aryl-oxoketene dithioacetal in presence of *n*-BuLi in THF gave the aryl-oxoketene-*N*,*S*-2*H*-1,4 benzoxazinoacetal by displacement of one of the methyl thiol groups of (Scheme 3). Vilsmeier cyclisation of afforded the tricyclic analogue which on subsequent reduction using Raney-Ni yielded the final product.



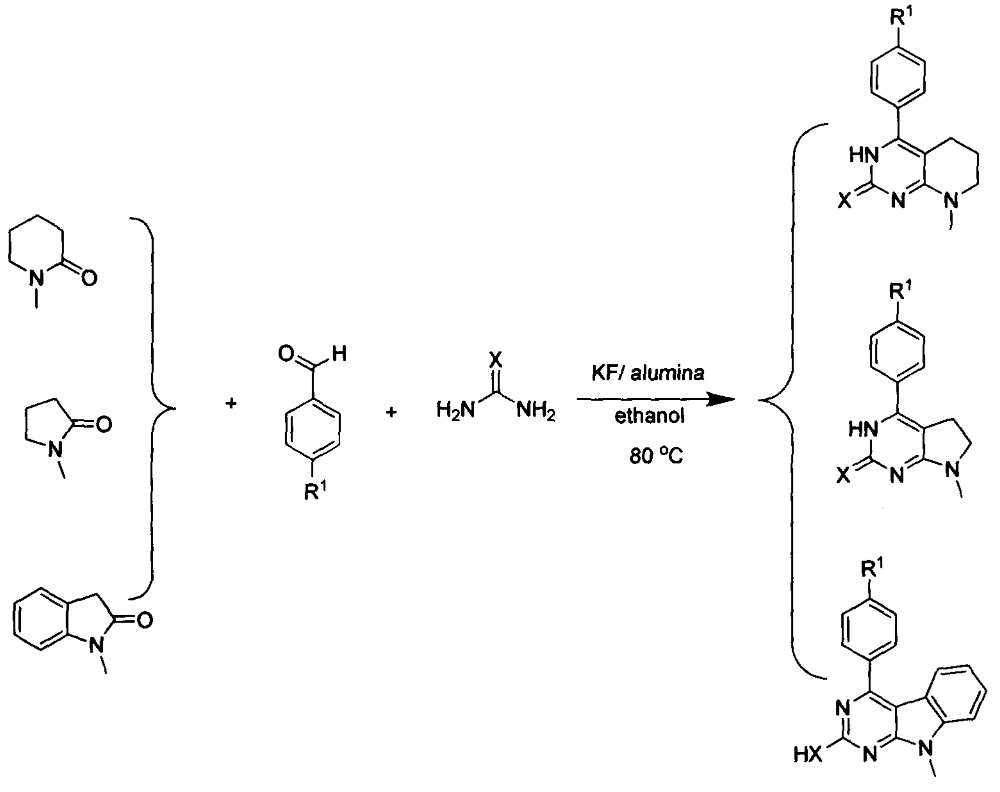
(a) K_2CO_3 DMF reflux; (b) H_2, Pd/C 10%, ethanol; (c) trifluoroacetic acid anhydride, CH_2Cl_2

Scheme 3

CHAPTER V

This chapter describes a “Three-component synthesis of 5:6 and 6:6 fused pyrimidines using KF-Alumina as a catalyst.” Inorganic solid supports as catalysts have been used increasingly in recent years for the synthesis of various biologically active molecules. Among these inorganic solid supports, potassium fluoride coated with alumina (KF-alumina) has been used as a versatile reagent for various reactions such as the Knoevenagel condensation, the

Henry reaction, the Darzens reaction, the Wittig reaction, the Bignelli reaction and alkylation and elimination reactions. In this chapter, we report a simple three-component synthesis of 5:6 fused[*d*]pyrimidines such as pyrazolo[3,4-*d*]pyrimidines, pyrrolo[2,3-*d*]pyrimidines as well as 6:6 fused systems such as pyrido[2,3-*d*]pyrimidines (scheme **4**).

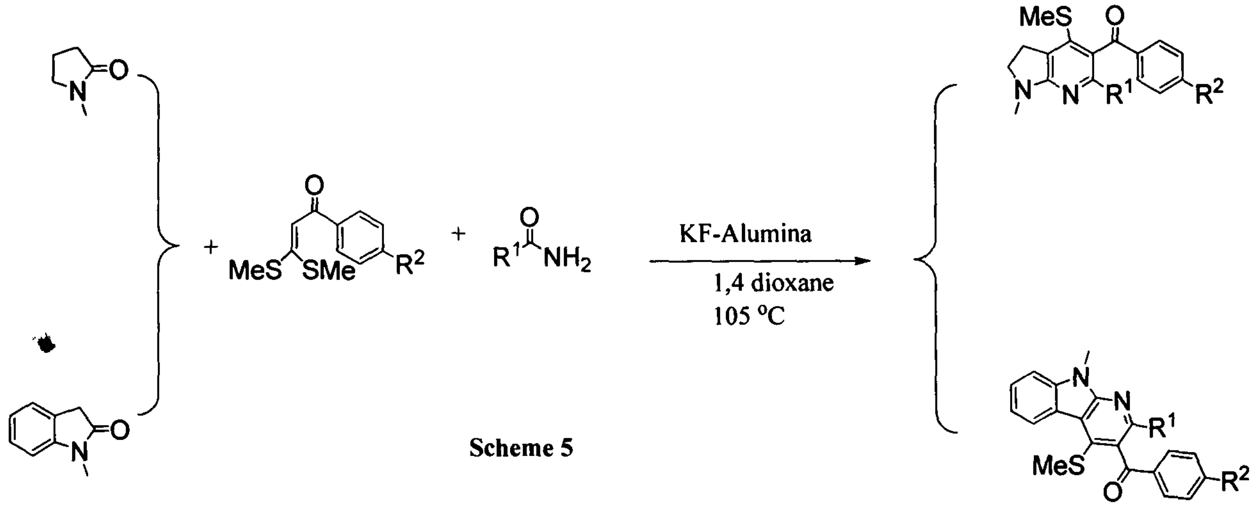


Scheme 4

CHAPTER VI

This chapter describes "a facile, three-component method for the synthesis of substituted fused pyrimidines, pyridines, pyridazines and quinolines; catalysed by KF-Alumina." The drive for more environmentally friendly procedures and the need for increased efficiency have led to an explosive growth in the fields of both multi-component organic synthesis and in the uses of solid support reagents such as KF-Alumina. This versatile reagent was originally introduced in 1979 by Ando *et al* as a useful reagent for inducing alkylation reactions. KF-Alumina is strongly basic in nature and because of this nature it has replaced organic bases in number of reactions.

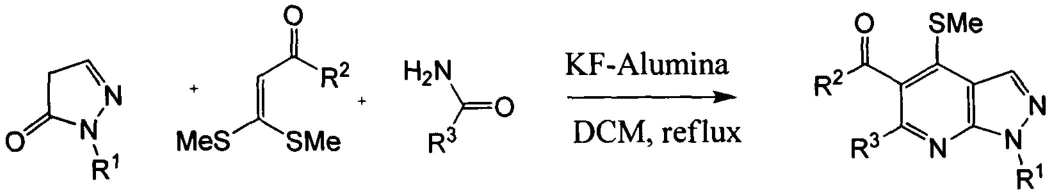
As a part of our ongoing work to explore the utilities of KF-Alumina catalyzed three-component reactions, we wish to report herein it's utilities in the synthesis of 5,6,7-trisubstituted-3,4-dihydro-1,3-dimethylpyrido[*2,3-d*]pyrimidin-2(1*H*)-one, 4,5,6-trisubstituted-2,3-dihydro-1-methyl-1*H*-pyrrolo[*2,3-b*]pyridine, substituted 9-methyl-9*H*-pyrido[*2,3-b*]indole and substituted 5,6,7,8-tetrahydroquinoline (scheme 5). These classes of compounds show wide range of biological activities, such as antifolate activity, antibacterial activity, tyrosine kinase activity, antimicrobial activity, anticonvulsants activity



Scheme 5

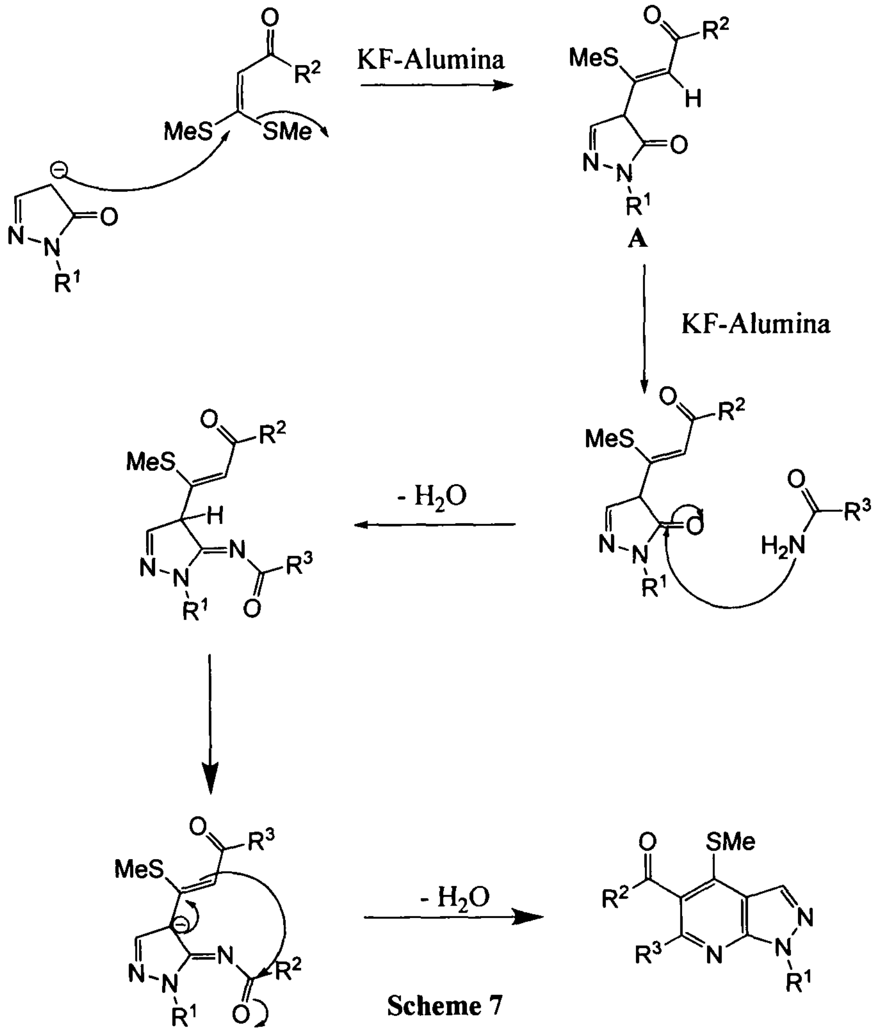
CHAPTER VII

This chapter describes "Synthetic studies on KF-alumina catalysed reaction of substituted and unsubstituted aryl-oxoketene dithioacetals and 1*H*-pyrazone-5(4*H*)-one: a convenient synthesis of pyrazolo[*3,4-b*]pyridine and pyrazolo[*1,5-a*]pyrimidine." The functionalized pyrazolo[*3,4-b*]pyridine and pyrazolo[*1,5-a*]pyrimidine are attractive compounds for drug discovery since many of these scaffolds exhibit excellent biological activities, therefore the development of simple methodologies for the synthesis of these highly functionalized derivatives is highly challenging in organic synthesis. To address this challenge, the development of multi-component reaction method for the synthesis of these derivatives is of great interest owing to its high efficiency and selectivity. Although there are a wide range of methods available for the synthesis of pyrazolo[*1,5-a*] pyrimidines and pyrazolo [*3,4-b*] pyridines, very few of these procedures provide a simple method that could yield compounds with more structural diversities. In this paper, we report a successful multi-component procedure for the synthesis of 1,4,5,6 tetrasubstituted pyrazolo[*3,4-b*] pyridine and a semi-conventional method for the synthesis of 5,6,7 trisubstituted pyrazolo[*1,5-a*] pyrimidines. The principal advantages, scope and limitations of the method are discussed in this chapter. The general method to prepare (1,4,6 tri-substituted-1*H*-pyrazolo[*3,4-b*]pyridi-6-yl) (aryl) methanone involves a three component reaction between 1-substituted-1*H*-pyrazone-5(4*H*)-one, substituted aryl-oxoketene dithioacetals and alkyl amides in presence of KF-Alumina. The reaction presumably involves Michael addition and condensation to yield the desired products. These reaction were attempted in range of solvents such as DMA, acetonitrile, DMF, THF and 1,4 dioxane (Scheme **6**).



Scheme **6**

A plausible mechanism for the formation of the product is outlined in Scheme 7. The reaction was initiated by the Michael addition reaction to give an intermediate **A** which further condensed with substituted amide by abstraction of α-proton to give the desired products. This may be concluded from the fact that when condensation of 1-methyl-pyrazol-5(4*H*)-one and 3,3-bis(methylthio)-1-phenylprop-2-en-1-one was carried out, 1-methyl-4-((*Z*)-1-(methylthio)-3-oxo-3-phenylprop-1-enyl)-pyrazol-5(4*H*)-one was isolated which on further treatment with acetamide afforded the desired product, thereby indicating that Michael addition is the first step in the three-component reaction.



Scheme 7

REFERENCES:

1. ELLIS,G.P.,*Synthesis of fused Heterocycles*, John Wiley and Sons Ltd, 1987 pp 55-57
2. (a) Hietala, P. K.; Virtanen, A. I. *Acta Chem. Scand.* **1960**, *14*, 502-506. (b) Coults, R. T.; Hindmarsh, K. W. *Can. J. Pharm. Sci.* **1966**, 11-17. (c) Chatterjee, A.; Basa, S. C. *Chem. Ind.* **1969**, *11*, 328-332. (d) Hofman, J.; Hofmanova, O. *Eur. J. Biochem.* **1969**, *8*, 109-112. (e) Nagao, T.; Otsuka, H.; Kohda, H.; Sato, T.; Yamasaki, K. *Phytochemistry* **1985**, *24*, 2959-2962. (f) Otsuka, H.; Hirai, Y.; Nagao, T.; Yamasaki, K. *J. Nat. Prod.* **1988**, *51*, 74-79. (g) Neimeyer, H. M. *Phytochemistry* **1988**, *27*, 3349-3353. (I) Lyans, P. C.; Hipskind, H. D.; Wood, K. V.; Nicholson, R. L. *J. Agric. Food Chem.* **1988**, *36*, 57-63. (j) Chatterjee, A.; Sharma, N. J. Banerji, J.; Basa,S. C. *Ind. J. Chem., Sect. B.* **1990**, *29*, 132-135. (k) Ozden, S.; Ozden, T.;Attila, I.; Kucukislamoglu, M.; Okatan, A. *J. Chromatogr.* **1992**, *609*, 402-405. (l) Hartenstein, H.; Sicker, D. *Phytochemistry* **1994**, 827. (m) Hartenstein, H.; Klein, J.; Sicker, D. *Indian J. Heterocycl. Chem.* **1993**, *2*, 151-157.
3. Fukuda, T.; Setoguchi, M.; Inaba, K.; Shoji, H.; Tahara, T. *Eur. J. Pharmacol.* **1991**, *196*, 299-307.
4. Empfield, J. R.; Russell, K. Potassium Channel Openers. In *Ann. Rep. Med. Chem.*; 1995; Chapter 9, Vol. 30, p 81-89.
5. Kotha, S.; Bindra, V.; Kuki, A. *Heterocycles.* **1994**, *38*, 5-12.
6. Lhoste, P.; Massacret, M.; Sinou, D. *Bull. Soc. Chim. Fr.* **1997**, *134*, 343-348.
7. Kajino, M.; Shibouta, Y.; Nishikawa, K.; Meguro, K. *Chem. Pharm. Bull.* **1991**, *39*, 2896-2901.
8. Guillaumet, G.; Loubinoux, B.; Coudert, G. *Tetrahedron Lett.* **1978**, *26*, 2287-2290.

9. Coudert, G.; Guillaumet, G.; Loubinoux, B. *Synthesis* **1979**, 541-549.

10. (a) Bartsch, H.; Kropp, W.; Pailer, M. *Monatsch. Chem.* **1979**, *110*, 267-273. (b). Bartsch, H.; Ofner, M.; Schwarz, O.; Thomann, W. *Heterocycles.* **1984**, *22*, 2789-2793.

    1. Combs, D W. Rampulla, M. S. Bell, S. C. Klaubert, D. H. Tobia, A. J. Falotico, R. Haertlein, B. Lakas-Weiss, C. Moore; J. B. *J.Med. Chem.* **1990**, *33*, 380.

    2. Bourlot, A. S. Sa´nchez, I. Dureng, G. Guillaumet, G. Massingham, R. Monteil, A. Winslow, E. Pujol,. M. D. and Me´rour, Jean-Yves. *J. Med. Chem.* 1998, *41*, 3142.

11. Touzeau, F. Arrault, A. Guillaumet, G. Scalbert, E. Pfeiffer, B. Rettori, M. Renard, P. and Me´rour; J. *J. Med. Chem.* **2003**, *46*, 1962.

12. Thompson, A.M.; Bridges, A.J.; Fry, D.W.; Kraker, A.J.; Denny, W.A. *J. Med. Chem.***1995**, *38*, 3780-3788.

13. Bredereck, H.; Gompper, R.; Schuh, H. G.; Theilig, G. *Angew. Chem.* **1959**, *71*, 753-760.

14. Monge, A.; Martinez-Merino, V.; Sanmartin, C.; Fernandez, F.J.; Ochoa, M.C.; Berllver, C.; Artigas, P.; Fernandez-Alvarez, E. *Eur. J. Med. Chem.* **1989**, *24*, 209-211.

15. Matsunaga, T.; Tohda, Y.; Ariga, M. *J. Chem. Soc., Perkin Trans. 1* **2000**, 27-34.

“DEVELOPMENT OF NOVEL METHODS FOR THE SYNTHESIS OF *N*-SUBSTITUTED 3,4-DIHYDRO-2*H*-BENZO[1,4]OXAZINE [BENZOMORPHOLINE], SUBSTITUTED 7-METHYL-6,7-DIHYDRO-5*H*-PYRROLO[2,3-*d*]PYRIMIDIN-2-OL, PYRIDAZINES AND RELATED HETEROCYCLIC MOLECULES”

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DEPARTMENT OF CHEMISTRY
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DECLARATION

I hereby, declare that the thesis entitled "Development of novel methods for the synthesis of *N*-substituted 3,4-dihydro-2*H*-benzo[1,4]oxazine [benzomorpholine], substituted 7-methyl-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-2-ol, pyridazines and related Heterocyclic molecules" is the result of the work carried out by me under the supervision of Prof. B. Myrboh, Department of Chemistry, School of Physical Sciences, North-Eastern Hill University, Shillong for the award of Doctor of Philosophy in Chemistry. The contents of the thesis did not form the basis of the award of any previous degree to me or to anybody else. The work presented in the thesis is original and the outcome of some useful results has been published in the international journals.

To the best of my knowledge the thesis has not been submitted for any degree to this university or any other university.

29th May '09

Pushpak Mizar
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CERTIFICATE

This is to certify that the research work presented in the thesis entitled "Development of novel methods for the synthesis of *N*-substituted 3,4-dihydro-2*H*-benzo[1,4]oxazine [benzomorpholine], substituted 7-methyl-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-2-ol, pyridazines and related Heterocyclic molecules" is carried out by **Mr Pushpak Mizar** under my supervision in the Department of Chemistry, School of Physical Sciences, North-Eastern Hill University, Shillong. The work embodied in the thesis does not form the basis for the award of any previous degree, diploma, fellowship or any other similar title and that it represents entirely an independent work on the part of the candidate.

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DEDICATED

TO

MY PARENTS,

BROTHER & SISTERS

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I take this opportunity to express my profound regards to my **parents, brother** and **sister's** who shared the joys and distress and gave me the courage and inspiration to stride into the realm of synthetic organic research.

Above all I give all thanks and glory to **God** for strengthening me now and always

Dated: 29th May'09

PUSHPAK MIZAR

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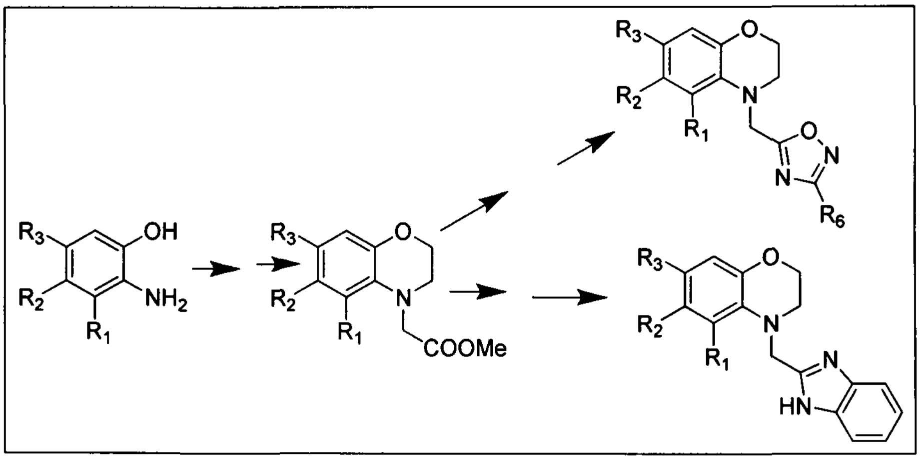
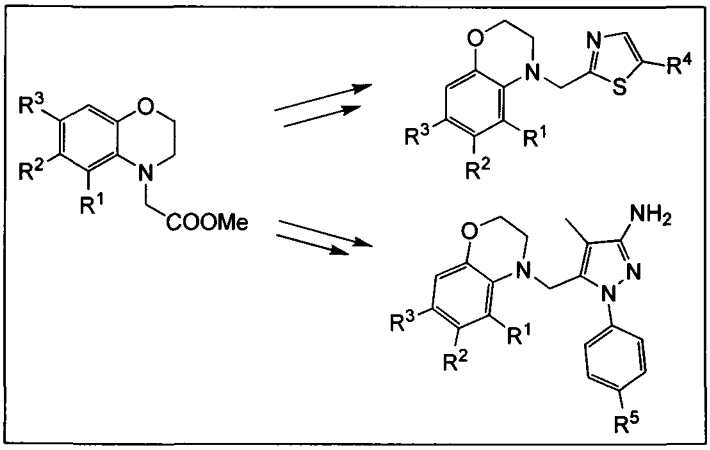
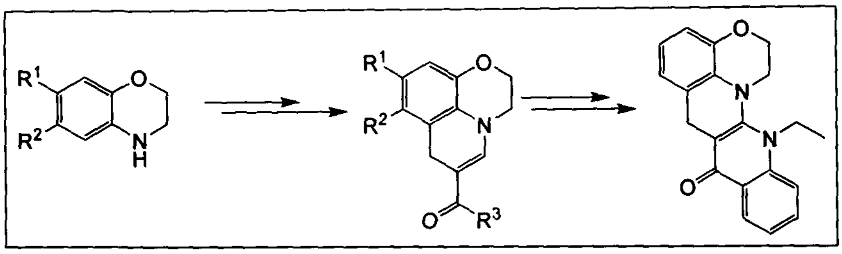




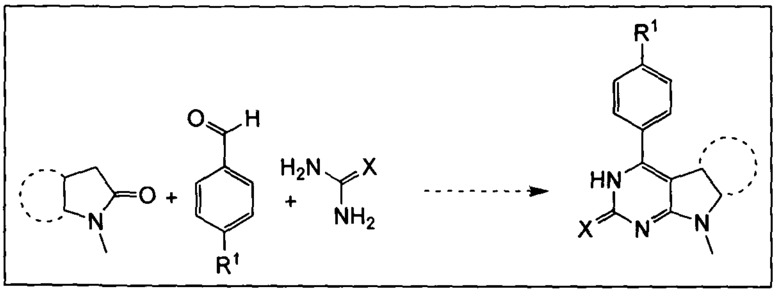
❖ CHAPTER IV 53 - 76

Synthesis of 2,3-dihydro-6*H*-1-oxa-3a-aza-phenalene and their benzo/hetero fused analogue.



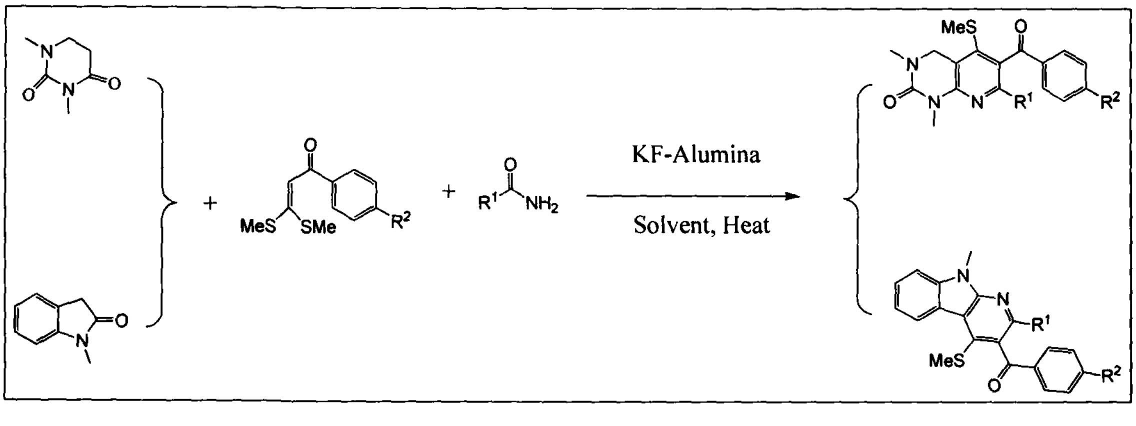
❖ CHAPTER V 77 - 95

Three-component synthesis of 5:6 and 6:6 fused pyrimidines using KF-alumina as a catalyst.



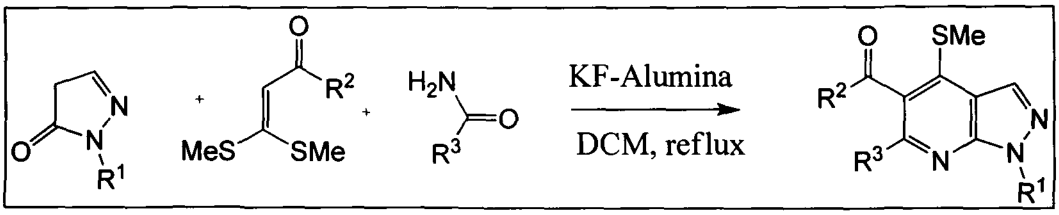
❖ CHAPTER VI 96 - 123

A facile, three-component method for the synthesis of substituted fused pyrimidines, pyridines, pyridazines and quinolines; catalysed by KF-alumina



❖ CHAPTER VII 124 - 146

Synthetic studies on KF-alumina catalysed reaction of substituted and unsubstituted aryl-oxoketene dithioacetals and 1*H*-pyrazone-5(4*H*)-one: a convenient synthesis of pyrazolo[*3,4-b*]pyridine and pyrazolo[*1,5-a*]pyrimidine.



❖ LIST OF PUBLICATION

PREFACE

The thesis consist of seven chapters which describes the development of novel methods for the synthesis of *N*-substituted 3,4-dihydro-2*H*-benzo[1,4]oxazine [benzomorpholine], substituted 7-methyl-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-2-ol, pyridazines and related heterocyclic molecules. Heterocycles forms the basic skeleton of many biologically important classes of natural products such as antibiotics, vitamins, marine products, animal toxins and fungal metabolites. Porphyrin rings form the basic skeleton of life supporting systems such as Haemoglobin, chlorophyll, Vitamin B_{12} etc. Heterocyclic unit such as 1,4-benzoxazine, pyridazines, fused pyrimidines and their analogues are of special interest in pharmacology, due to their important biological activities. The importance of heterocyclic molecules in natural product chemistry and pharmacology constantly drives the search for new methods for their synthesis. An important approach for the synthesis of these types of compounds involves application of annelation methods; that is construction of cyclic compounds from open chain precursors. The work highlighted here describe a novel synthetic methods for the synthesis of 1,4-benzoxazine and related *N*-substituted product starting from simple open chain precursors. It further describes a multi-component method for the synthesis of pyridazines, fused pyrimidines and related heterocyclic molecules.

The first chapter deals with the general introduction of organic compounds. In the second chapter the synthesis of substituted 4-(3-alkyl-1,2,4-oxadiazol-5-ylmethyl)-3,4-dihydro-2*H*-1,4-benzoxazines and 4-(1*H*-benzimidazol-2-ylmethyl)-3,4-dihydro-2*H*-1,4-benzoxazines is discussed.

The third chapter deals with the synthesis of substituted 4-(5-alkyl-thiazol-2-ylmethyl)-3,4-dihydro-2*H*-1,4-benzoxazines and 5-(2,3-dihydro-1,4-benzoxazin-4-ylmethyl)-4-methyl-1-

phenyl-1*H*-pyrazol-3-ylamine. In the fourth chapter the synthesis of 2,3-dihydro-6*H*-1-oxa-3a-aza-phenalene and their benzo/hetero fused analogue is discussed. The advantage of our methods is that, it is able to incorporated large degree of structural as well as substituent diversities into the benzomorpholine ring system.

The fifth chapter describes a three-component synthesis of 5:6 and 6:6 fused pyrimidines using KF-alumina as a catalyst. The drive for more environmentally friendly procedures and the need *for increased efficiency have led to an explosive growth in the fields of both multi-component* organic synthesis and in the uses of solid support reagents such as KF-Alumina. This versatile reagent was originally introduced in 1979 by Ando *et al* as a useful reagent for inducing alkylation reactions. KF-alumina is strongly basic in nature and because of this nature it has replaced organic bases in number of reactions.

The sixth chapter deals with the development of a facile, three-component method for the synthesis of substituted fused pyrimidines, pyridines, pyridazines and quinolines; catalysed by KF-Alumina. Synthetic studies on KF-alumina catalysed reaction of substituted and unsubstituted aryl-oxoketene dithioacetals and 1*H*-pyrazone-5(4*H*)-one: a convenient synthesis of pyrazolo[*3,4-b*]pyridine and pyrazolo[*1,5-a*]pyrimidine is discussed in the last chapter.

Each chapter is framed into Introduction, Results and discussions and Experimental section. The entire documentation in this thesis is supported by appropriate references at the end of each chapter.

CHAPTER I

“GENERAL INTRODUCTION ON ORGANIC COMPOUNDS”

The chemistry of heterocyclic compounds constitutes one of the broadest and most complex branches of organic chemistry. It is equally interesting for its theoretical implications, for the diversity of its synthetic procedures and for the physiological and industrial significance of heterocyclic compounds. At the very beginning of the nineteenth century chemists generally thought that compounds from living organisms were too complicated in structure to be capable of artificial synthesis from non-living things, and that a 'vital force' or vitalism conferred the characteristics of living beings on this form of matter. They named these compounds 'organic', and preferred to direct their investigations toward inorganic materials that seemed more promising.

Organic chemistry received a boost when it was realized that these compounds could be treated in ways similar to inorganic compounds and could be created in the laboratory by means other than 'vital force'. Around 1816 Michel Chevreul started a study of soaps made from various fats and alkali. He separated the different acids that, in combination with the alkali, produced the soap. Since these were all individual compounds, he demonstrated that it was possible to make a chemical change in various fats (which traditionally come from organic sources), producing new compounds, without 'vital force'. In 1828 Friedrich Wöhler first manufactured the organic chemical urea (carbamide), a constituent of urine, from the inorganic ammonium cyanate NH_4OCN, in what is now called the Wöhler synthesis. Although Wöhler was, at this time as well as afterwards, cautious about claiming that he had thereby destroyed the theory of vital force, most have looked to this event as the turning point.

A great next step was when in 1856 William Henry Perkin, while trying to manufacture quinine, again accidentally came to manufacture the organic dye now called Perkin's mauve, which by generating a huge amount of money greatly increased interest in organic chemistry. Another step was the laboratory preparation of DDT by Othmer Zeidler in 1874, but the insecticide properties of this compound were not discovered until much later.

The crucial breakthrough for the theory of organic chemistry was the concept of chemical structure, developed independently and simultaneously by Friedrich August Kekule and Archibald Scott Couper in 1858. Both men suggested that tetravalent carbon atoms could link to each other to form a carbon lattice, and that the detailed patterns of atomic bonding could be discerned by skillful interpretations of appropriate chemical reactions.

The history of organic chemistry continued with the discovery of petroleum and its separation into fractions according to boiling ranges. The conversion of different compound types or individual compounds by various chemical processes created the petroleum chemistry leading to the birth of the petrochemical industry, which successfully manufactured artificial rubbers, the various organic adhesives, the property-modifying petroleum additives, and plastics.

The pharmaceutical industry began in the last decade of the 19th century when acetylsalicylic acid (more commonly referred to as aspirin) manufacture was started in Germany by Bayer. The first time a drug was systematically improved was with arsphenamine (Salvarsan). Numerous derivatives of the dangerously toxic atoxyl were systematically synthesized and tested by Paul Ehrlich and his group, and the compound with best effectiveness and toxicity characteristics was selected for production.

Early examples of organic reactions and applications were serendipitous, such as Perkin's accidental discovery of Perkin's mauve. However, from the 20th century, the progress of organic chemistry allowed for synthesis of specifically selected compounds or even molecules designed with specific properties, as in drug design. The process of finding new synthesis routes for a given compound is called total synthesis. Total synthesis of complex natural compounds started with urea, increased in complexity to glucose and terpineol, and in 1907, total synthesis was commercialized the first time by Gustaf Komppa with camphor. Pharmaceutical benefits have been substantial, for example cholesterol-related compounds have opened ways to synthesis of complex human hormones and their modified derivatives. Since the start of the 20th century, complexity of total syntheses has been increasing, with examples such as lysergic acid and vitamin B12. Today's targets feature tens of stereogenic centers that must be synthesized correctly with asymmetric synthesis.

In the biological world the heterocyclic compounds are everywhere. Carbohydrates are heterocyclic, so are chlorophyll and heme, which make leaves green and blood red and bring life to plants and animals. Heterocycles form the site of reaction in many enzymes and coenzymes. Heredity comes down, ultimately, to the particular sequence of the attachment of a half-dozen heterocyclic rings in the long chains of nucleic acid.

Synthetic organic chemistry is an applied science as it borders engineering, the "design, analysis, and/or construction of works for practical purposes". Organic synthesis of a novel compound is a problem solving task, where a synthesis is designed for a target molecule by selecting optimal reactions from optimal starting materials. Complex compounds can have tens of reaction steps that sequentially build the desired molecule. The synthesis proceeds by utilizing the reactivity of the functional groups in the molecule. For example, a carbonyl compound can be used as a nucleophile by converting it into an enolate, or as an electrophile; the combination of the two is called the aldol reaction. Designing practically useful syntheses always requires conducting the actual synthesis in the laboratory. The scientific practice of creating novel synthetic routes for complex molecules is called total synthesis.

There are several strategies to design a synthesis. The modern method of retrosynthesis, developed by E.J. Corey, starts with the target molecule and splices it to pieces according to known reactions. The pieces, or the proposed precursors, receive the same treatment, until available and ideally inexpensive starting materials are reached. Then, the retrosynthesis is written in the opposite direction to give the synthesis. A "synthetic tree" can be constructed, because each compound and also each precursor have multiple syntheses.

Heterocyclic unit such as 1,4-benzoxazine, pyridazines, fused pyrimidines, fused pyridines and their analogues are of special interest in pharmacology, due to their important biological activities. The importance of heterocyclic molecules in natural product chemistry and pharmacology constantly drives the search for new methods for their construction. An important approach for the synthesis of these types of compounds involve application of annelation methods, this is construction of cyclic compounds from open chain precursors.

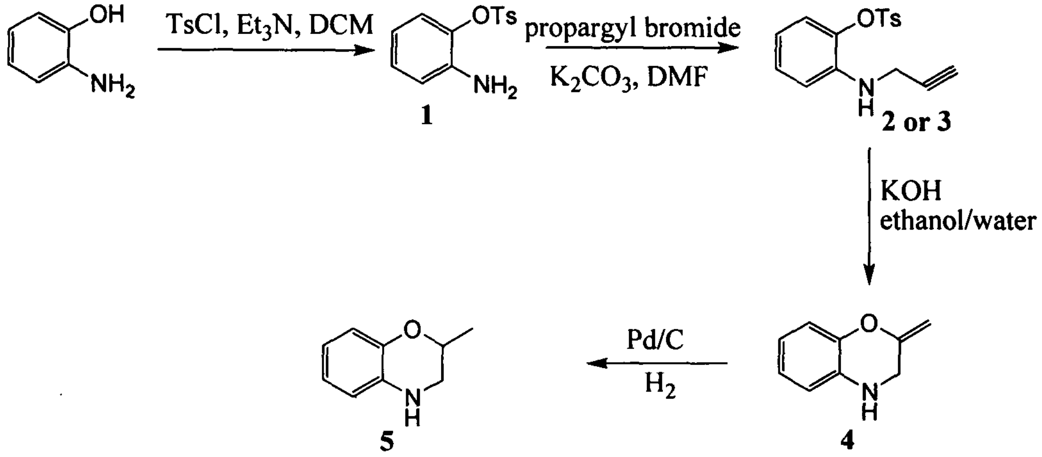
CHAPTER II

"Synthesis of substituted 4-(3-alkyl-1,2,4-oxadiazol-5-ylmethyl)-3,4-dihydro-2*H*-1,4-benzoxazines and 4-(1*H*-benzimidazol-2-ylmethyl)-3,4-dihydro-2*H*-1,4-benzoxazines."

INTRODUCTION

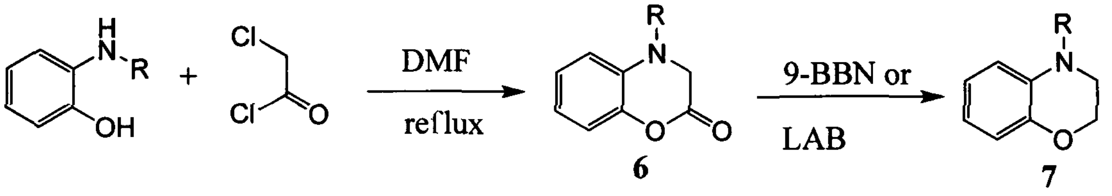
The 1,4-benzoxazine[1] structure is an integral part of several naturally occurring substances. For example, various glycosides of the 2-hydroxy-2*H*-1,4-benzoxazine-3(4*H*) skeletons have been found to occur in gramineous plants such as maize, wheat, rye, rice etc and have been suggested to act as plant resistance factors against microbial diseases and insects.[2] The 1,4-benzoxazine moiety is also found in various antibiotics such as C-1027.[3]

Our literature survey reveals that number of methods have been developed for the synthesis of 1,4-benzoxazines, however each of these methods involved a reduction step. 1,4-benzoxazine can be synthesized starting from o-amino phenol which was *O*-tosylated with *p*-toluenesulfonyl chloride in presence of triethylamine in dichloromethane [4]. *O*-tosylated product **1** was then propargylated with propargyl bromide in the presence of K_2CO_3 in DMF to yield compound 2-(*N*-Prop-2'-ynyl) aminophenyl tosylate **2** was then benzylated or alkylated to 2-[*N*-alkyl(or benzyl)-*N*-prop-2'-ynyl]aminophenyl tosylate **3**, which on further treatment with with KOH in ethanol/water for 8-10 h cyclised to obtain the (Z)-2-alkyllidene-4-alkyl(benzyl)-3,4-dihydro-2*H*-1,4-benzoxazine **4** which on hydrogenation with Pd/C to yield 3 alkylidene 3,4-dihydro-2*H*-benzo-1,4-oxazine **5** (Scheme **1**).



Scheme 1

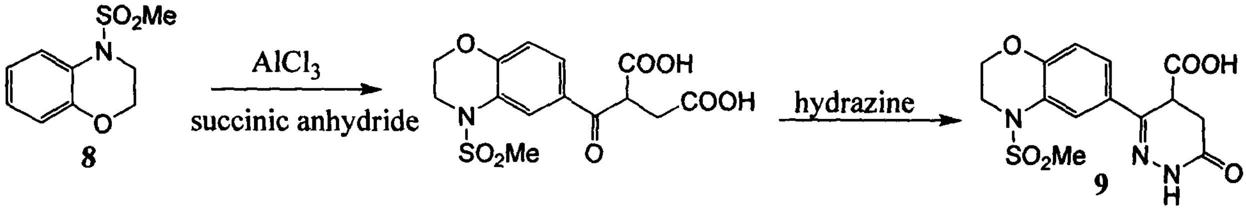
Bakthan Singaram and co-worker modified the multi step method to simple two-step method in which they reacted o-amino phenol with 2-chloroacetyl chloride in DMF to yield 3,4-dihydro-4-alkylbenzo-1,4-oxazin-2-one **6** which was further reduced with 9-Borabicyclo[3,3,1]nonane (9-BBN) or Lithium aminoborohydrides (LAB) to yield 3,4-dihydro-4-methyl-2*H*-benzo-1,4-oxazine **7** (Scheme **2**)



Scheme 2

Various benzoxazine derivatives have been shown to have interesting pharmacological properties. Thus, nazasetran hydrochloride (Y-25130), *N*-(1-azabicyclo[2.2.2]oct-3-yl)-6-chloro-3,4-dihydro-4-methyl-3-oxo-2*H*-1,4-benzoxazine-8-carboxamide hydrochloride, a highly potent 5-HT3 receptor antagonist, has been reported as an antirheumatic agent and as a cure for severe nausea and vomiting induced by chemotherapy in cancer patients.[4] Several 3,4-dihydro-2*H*-1,4-benzoxazine derivatives have been reported to be potassium channel openers (PCOs) in vascular smooth muscle.[5] Benzoxazino-rifamycin KRM-1648 has been shown to have *in vitro* and *in vivo* activities against *Mycobacterium tuberculosis*.[6] Recently, a number of methotrexate derivatives incorporating the benzoxazine moiety have been synthesized which were found to be potent and safe candidates as antirheumatic agents.[7] Benzoxazine derivatives have also been used as intermediates for the synthesis of other heterocyclic structures of biological importance.[8,9]

Donald W. Combs[13a] synthesized 6-[4-substituted-3,4-dihydro-1,4(2*H*)-benzoxazin-6-yl]-2-subsituted-pyridazin-3-ones **9** which was evaluated for pronounced cardiovascular activity. **9** was synthesized by Friedel-Crafts acylation of 3,4-dihydro-4-(methyl-sulfonyl)-1,4(2*H*)-benzoxazine **8** with succinic anhydride and aluminium chloride to obtain ketoacid which was treated with hydrazine to afford **9** (Scheme **3**).

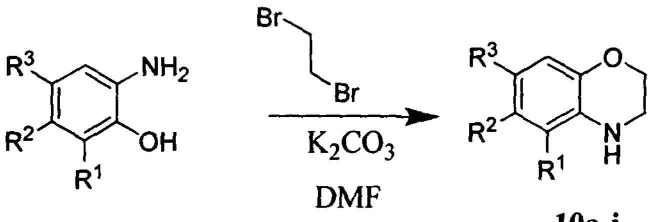


Scheme 3

RESULTS AND DISCUSSIONS:

Due to their biological activity, the synthesis of benzoxazine derivatives has recently attracted increasing attention. Our literature survey reveals that several methods for the synthesis of 1,4-benzoxazine derivatives have been reported.[10-13] However, most of the methods reported targeted the synthesis of specific benzoxazines and lacked generality. Moreover some of the routes involved reduction of 4*H*-benzoxazin-3-ones which requires costly reagents and has to be performed carefully. We report here a simple and general route for the synthesis of various 1,4-benzoxazines and *N*-substituted derivatives.

The reaction of 2-aminophenol (45 mmol) with 1,2-dibromoethane (1.2 equiv) in the presence of K_2CO_3 (3 equiv) in dry DMF at 125 °C proceeded smoothly and provided an 82% yield of **10a**. Other solvents such as acetone and DCM were found to be far less effective. The presence of dry K_2CO_3 is crucial for high yield of the product as it neutralizes the by product i.e. HBr. Increasing the amount of DMF resulted in a lower yield. This process was generalised to synthesise various substituted 3,4-dihydro-2*H*-1,4-benzoxazines as shown in Table **1**. The time taken for the completion of the reaction was between 12-16 h; the amount of K_2CO_3 used ranged from 3-4 equivalents depending upon the nature of substitutent. The 2-aminophenol with alkyl substituents were found to proceed with lower equivalence of K_2CO_3 as compared to halogen substituents.



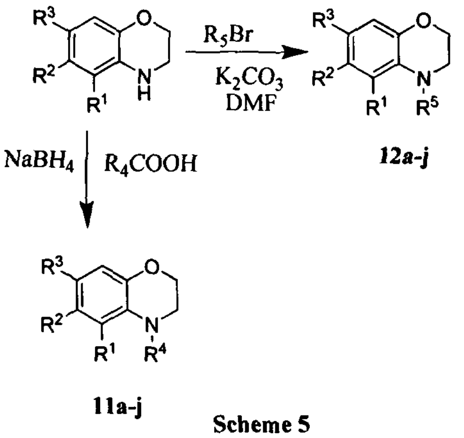
10a-j

Scheme 4

Table 1: Substituted 3,4-dihydro-2*H*-1,4-benzoxazines

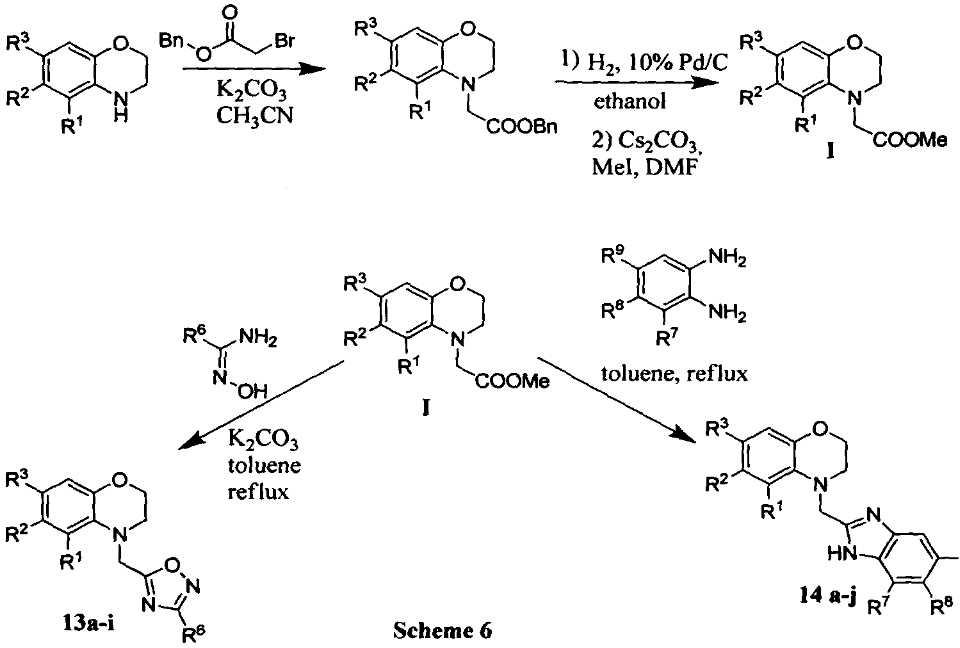
Product(**10**)	R^1	R^2	R^3
a	H	H	H
b	CH_3	H	H
c	H	CH_3	H
d	H	H	CH_3
e	H	Cl	H
f	H	OCH_3	H
g	H	F	H
h	H	CF_3	H
i	H	$CH_2OC_2H_5$	H
j	H	CH_2OH	H

This method was extended to the synthesis of various *N*-substituted 3,4-dihydro-2*H*-1,4-benzoxazines following the routes shown in Scheme **5**. Most of the substitution reactions proceeded readily with high yields. The reduction route was found to be highly exothermic and required cooling. The reaction was found to proceed cleanly with about 89%~91% yield of the product. These processes provided versatile routes for the synthesis of various *N*-substituted 3, 4-dihydro-2*H*-1,4-benzoxazines as shown in Table **2**. In the reductive aminations, a solvent was required only in the reactions involving benzoic acid, substituted furan-2-carboxylic acid, pyrazine-2-carboxylic acid and thiadiazole-5-carboxylic acid, however the quantity of the solvent used was minimal. This reductive route was followed for those alkyl bromides which did not undergo substitution reactions.



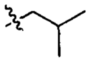
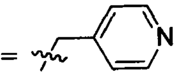
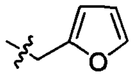
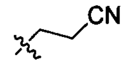
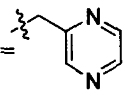
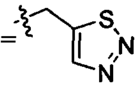
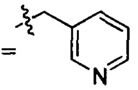
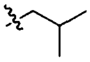
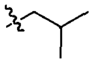
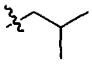
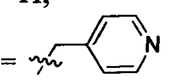
Scheme 5

The investigation was further extended to the synthesis of substituted 4-(3-alkyl-1,2,4-oxadiazol-5-ylmethyl)-3,4-dihydro-2*H*-1,4-benzoxazines **13a-i** and 4-(1*H*-benzimidazol-2-ylmethyl)-3,4-dihydro-2*H*-1,4-benzoxazines **14a-j** as shown in Scheme **6** utilising (2,3-dihydro-2*H*-1,4-benzoxazin-4-yl)acetic acid methyl ester. *N*-Alkylation using benzyl bromoacetate was followed by de-benzylation to yield the corresponding acid. The acid was then converted into the methyl ester using MeI in the presence of Cs_2CO_3 since normal esterification did not yield any product. The methyl ester served as a good precursor for the synthesis of thiazole, imidazole and benzimidazole rings attached to the benzoxazine moiety. For compounds **13a-i** the methyl ester derivatives were refluxed in toluene with amidoximes in the presence of K_2CO_3 to give the desired products in 40%-53% yields. For the synthesis of **14a-j** substituted *ortho*-phenyl-ene- diamines were refluxed in toluene with the methyl ester in 56%~65%; a catalytic amount of I_2 enhanced the rate and increased the overall yield of these reactions.



Scheme 6

Table 2: *N*-substituted 3,4-dihydro-2*H*-1,4-benzoxazines. (** acids were dissolved in THF)

Entry	Product(**11a-j**)**	Product(**12 a-j**)	Product(**13a-i**)	Product(**14a-j**)	Yields(%)
a	R_1=H, R_2=H, R_3=H, R_4=Et	R_1=H, R_2=H, R_3=H, R_5= 	R_1=H, R_2=H, R_3=H, R_6=Me	R_1=H, R_2=H, R_3=H, R_7=H, R_8=H, R_9=H	**11a**=83 **12a**=81 **13a**=52 **14a**=61
b	R_1=H, R_2=H, R_3=H, R_4=Me	R_1=H, R_2=H, R_3=H, R_5= 	R_1=H, R_2=H, R_3=H, R_6=Et	R_1=H, R_2=H, R_3=H, R_7=H, R_8=F, R_9=H	**11b**=80 **12b**=71 **13b**=50 **14b**=64
c	R_1=H, R_2=H, R_3=H, R_4= 	R_1=H, R_2=H, R_3=H, R_5= 	R_1=H, R_2=H, R_3=H, R_6=Ph	R_1=H, R_2=H, R_3=H, R_7=H, R_8=Me, R_9=H	**11c**=81 **12c**=75 **13c**=48 **14c**=62
d	R_1=H, R_2=H, R_3=H, R_4= 	R_1=H, R_2=H, R_3=H, R_5=CH_2COOBn	R_1=Me, R_2=H, R_3=H, R_6=Ph	R_1=Me, R_2=H, R_3=H, R_7=Me, R_8=Me, R_9=H	**11d**=68 **12d**=78 **13d**=49 **14d**=63
e	R_1=H, R_2=H, R_3=H, R_4=CH_2Ph	R_1=H, R_2=H, R_3=H, R_5=C_3H_7	R_1=H, R_2=H, R_3=Me, R_6=Me	R_1=H, R_2=H, R_3=H, R_7=H, R_8=Cl, R_9=Cl	**11e**=78 **12e**=74 **13e**=51 **14e**=56
f	R_1=H, R_2=H, R_3=H, R_4= 	R_1=H, R_2=H, R_3=H, R_5= 	R_1=H, R_2=H, R_3=H, R_6=Et	R_1=H, R_2=H, R_3=H, R_7=Me, R_8=Me, R_9=H	**11f**=71 **12f**=69 **13f**=53 **14f**=62
g	R_1=Me, R_2=H, R_3=H, R_4=Et	R_1=Me, R_2=H, R_5=  R_3=H,	R_1=H, R_2=Me, R_3=H, R_6=Et	R_1=H, R_2=H, R_3=Me, R_7=H, R_8=Cl, R_9=Cl	**11g**=89 **12g**=72 **13g**=49 **14g**=57
h	R_1=H, R_2=Me, R_3=H, R_4=Et	R_1=H, R_2=Me, R_3=H, R_5= 	R_1=H, R_2=H, R_3=Me, R_6=Me	R_1=H, R_2=Me, R_3=H, R_7=H, R_8=Cl, R_9=Cl	**11h**=82, **12h**=71, **13h**=47, **14h**=59.
i	R_1=H, R_2=H, R_3=Me, R_4=Et	R_1=H, R_2=H, R_3=Me, R_5= 	R_1=H, R_2=H, R_3=Me, R_6=Et	R_1=H, R_2=H, R_3=Me, R_7=H, R_8=Cl, R_9=Cl	**11i**=80, **12i**=70, **13i**=46, **14i**=58.
j	R_1=Me, R_2=H, R_3=H, R_4= Me	R_1=Me, R_2=H, R_3=H, R_5= 		R_1=Me, R_2=H, R_3=H, R_7=H, R_8=F, R_9=H	**11j**=81, **12j**=65, **14j**=60.

EXPERIMENTAL:

Melting points were obtained on a Thomas Hoover capillary melting point apparatus and are uncorrected. Carbon, hydrogen and nitrogen analysis were performed with a Perkin-Elmer 2400 series II instrument. IR spectra in BOMEM DA-8 FT-IR spectrophotometer. The ^1H and ^{13}C NMR spectra were recorded on a Bruker AMX 400 spectrometer using $CDCl_3$ or DMSO-d_6 as the solvent. Chemical shifts are reported in ppm from internal tetramethylsilane and are given on the δ scale. The following abbreviations are used to describe peak patterns when appropriate: s = singlet, d = doublet, t = triplet, m = multiplet. Positive-ion and negative-ion electrospray ionization (ESI) mass spectra were measured on an ion trap analyzer Esquire 3000 (Bruker Daltonics).

All reactions were monitored by TLC on glass plates coated with silica gel (ACME's) containing 13% calcium sulphate as binder and visualization of compounds was accomplished by exposure to iodine vapour or by spraying acidic potassium permanganate solution or 2% ninhydrin solution. Column chromatography was carried out using ACME's silica gel.

Chemicals, reagents and solvents:

Dry solvents were obtained by distillation under N_2 atomsphere with appropriate dehydrating agents. The commercial available chemicals were used without further purification.

General procedure for the preparation of 3,4-dihydro-2*H*-1,4-benzoxazines

To a suspension of 2-aminophenol (46 mmol) and potassium carbonate (229. mmol) in dry DMF (40 ml), 1,2-dibromoethane (69 mmol) was added. The mixture was heated at 125 °C for 15 h. After cooling, the mixture was treated with crushed ice and then extracted with ethyl acetate. The organic extracts were dried over Na_2SO_4 and evaporated. The residue was purified by chromatograph on a silica gel column using ethyl acetate and hexane (1:10) as *the eluent.*

3,4-dihydro-2*H*-1,4-benzoxazines 10a:

Reddish oil (73% yields); IR (film) v cm^{-1} 3385 (NH). ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm 3.25 (d, 2H, *J* = *2.7* Hz), 4.07 (t, 2H, *J* = *8.6* Hz), 5.69 (s, 1H), 6.46–6.65 (m, 4H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) 60.2 (NCH_2), 73.1 (OCH_2), 112.8, 116.8, 117.3, 119.5, 140.1, 130.2. *m/z* = 136.21. Calc for C_8H_9NO; C, 71.09; H, 6.71; N, 10.36%; found C, 72.12; H, 6.69; N, 10.31%.

3,4-dihydro-5-methyl-2*H*-1,4-benzoxazine 10b:

Reddish oil; IR (film) v cm^{-1} 3353 (NH). ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm 2.37, 3.41 (d, 2H, *J* = *2.7* Hz), 4.12 (t, 2H, *J* = *8.1* Hz), 5.62 (s, 1H), 6.56-6.61 (m, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) 16.2, 59.2 (NCH_2), 74.5 (OCH_2), 112.8, 117.3, 120.5, 137.2, 141.7. *m/z* = 150.21.Calc for $C_9H_{11}NO$; C, 72.46; H, 7.43; N, 9.39%; found C, 72.47; H, 7.39; N, 9.36%.

3,4-dihydro-6-methyl-2*H*-1,4-benzoxazine 10c:

Reddish oil; IR (film) v cm^{-1} 3362 (NH). ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm 2.39, 3.40 (d, 2H, *J* = *2.9* Hz), 4.13 (t, 2H, *J* = *8.4* Hz), 5.69 (s, 1H), 6.34 (s, 1H), 6.42-6.45 (d, 1H, *J* = *7.3* Hz), 6.56-6.59 (d, 1H, *J* = *7.3* Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) 25.1, 59.7 (NCH_2), 73.4 (OCH_2), 113.1, 116.8, 118.3, 130.2. 137.9, 140.1, *m/z* = 150.16. Calc. for $C_9H_{11}NO$; C, 72.46; H, 7.43; N, 9.39%; found C, 72.47; H, 7.39; N, 9.36%.

3,4-dihydro-7-methyl-2*H*-1,4-benzoxazine 10d:

Reddish oil; IR (film) ν cm^{-1} 3367 (NH). ^1H NMR (DMSO-d_6, 400 MHz) δ ppm 2.31, 3.41 (d, 2H, *J* = *2.7* Hz), 4.21 (t, 2H, *J* = *8.5* Hz), 5.71 (s, 1H), 6.56 (s, 1H), 6.41-6.45 (d, 1H, *J* = *7.1* Hz), 6.61-6.63 (d, 1H, *J* = *7.1* Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) 25.5, 59.2 (NCH_2), 73.8 (OCH_2), 113.9, 114.8, 120.9, 128.1, 135.9, 142.1, *m/z* = 150.16. Calc for $C_9H_{11}NO$; C, 72.46; H, 7.43; N, 9.39%; found C, 72.47; H, 7.39; N, 9.36%.

6-chloro-3,4-dihydro-2*H*-1,4-benzoxazine 10e:

Brownish oil; IR (film) ν cm^{-1} 3378 (NH). ^1H NMR (DMSO-d_6, 400 MHz) δ ppm 3.41 (d, 2H, *J* = *2.7* Hz), 4.20 (t, 2H, *J* = *8.0* Hz), 5.68 (s, 1H), 6.36 (s, 1H), 6.51-6.55 (d, 1H, *J* = *7.0* Hz), 6.61-6.64 (d, 1H, *J* = *7.0* Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) 59.7 (NCH_2), 76.1 (OCH_2), 114.9, 116.8, 117.9, 127.6, 139.1, 140.6, *m/z* = 170.56. Calc for C_8H_8ClNO. C, 56.65; H, 4.75; N, 8.26%. found C, 56.67; H, 4.71; N, 8.22%.

3,4-dihydro-6-methoxy-2*H*-1,4-benzoxazine 10f:

Reddish oil; IR (film) ν cm^{-1} 3371(NH). ^1H NMR (DMSO-d_6, 400 MHz) δ ppm 3.43 (d, 2H, *J* = *2.6* Hz), 3.75 (s, 3H), 4.25 (t, 2H, *J* = *8.3* Hz), 5.71 (s, 1H), 6.16 (s, 1H), 6.21-6.25 (d, 1H, *J* = *7.1* Hz), 6.51-6.54 (d, 1H, *J* = *7.1* Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) 59.4 (NCH_2), 60.1, 76.2 (OCH_2), 98.8, 103.8, 116.9, 134.6, 139.8, 154.1, *m/z* = 166.16. Calc for $C_9H_{11}NO_2$; C, 65.44; H, 6.71; N, 8.48%; found C, 65.41; H, 6.74; N, 8.42%.

6-fluoro-3,4-dihydro-2*H*-1,4-benzoxazine 10g:

Dark Red oil; IR (film) ν cm^{-1} 3361 (NH). ^1H NMR (DMSO-d_6, 400 MHz) δ ppm 3.49 (d, 2H, *J* = *2.3* Hz), 4.28 (t, 2H, *J* = *8.1* Hz), 5.70 (s, 1H), 6.06 (s, 1H), 6.20-6.24 (d, 1H, *J* =

7.0 Hz), 6.61-6.64 (d, 1H, *J* = *7.0* Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) 59.0 (NCH_2), 76.4 (OCH_2), 102.8, 104.9, 117.9, 137.6, 140.8, 156.1. *m/z* = 153.16. Calc for C_8H_8FNO; C, 62.74; H, 5.26; N, 9.15%; found C, 62.77; H, 5.29; N, 9.17%.

6-(trifluoromethyl)-3,4-dihydro-2*H*-1,4-benzoxazine 10h:

Dark Reddish oil; IR (film) ν cm^{-1} 3368 (NH). ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm 3.45 (d, 2H, *J* = *2.0* Hz), 4.20 (t, 2H, *J* = *8.5* Hz), 5.67 (s, 1H), 6.56 (s, 1H), 6.50-6.52 (d, 1H, *J* = *7.2* Hz), 6.69-6.71 (d, 1H, *J* = *7.2* Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) 58.7 (NCH_2), 76.1 (OCH_2), 110.8, 114.9, 116.9, 123.6, 125.7, 138.8, 145.2. *m/z* = 203.16. Calc for $C_9H_8F_3NO$. C, 53.21; H, 3.97; N, 6.89%; found C, 53.18; H, 3.99; N, 6.87%.

6-(ethoxymethyl)-3,4-dihydro-2*H*-1,4-benzoxazine 10i:

Oil; IR (film) ν cm^{-1} 3357 (NH). ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm .18 (t, 3H, *J* = *14.2* Hz), 3.30 (q, 2H, *J* = *8.7* Hz), 3.45 (d, 2H, *J* = *2.2* Hz), 4.21 (t, 2H, *J* = *8.0* Hz), 4.65 (s, 1H), 5.67 (s, 1H), 6.36 (s, 1H), 6.48-6.50 (d, 1H, *J* = *7.1* Hz), 6.60-6.62 (d, 1H, *J* = *7.1* Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) 15.8, 58.1 (NCH_2), 68.72, 75.2, 76.2 (OCH_2), 112.7, 115.9, 117.2, 130.2, 138.9, 141.7. *m/z* = 193.16. Calc for $C_{11}H_{15}NO_2$. C, 68.37; H, 7.82; N, 7.25%; found C, 68.39; H, 7.85; N, 7.27%.

(3,4-dihydro-2*H*-1,4-benzoxazin-6-yl)methanol 10j:

Blackish oil; IR (film) ν cm^{-1} 3353 (NH) 3456 (OH). ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm 3.49 (d, 2H, *J* = *2.5* Hz), 3.65 (s, 1H), 4.25 (t, 2H, *J* = *8.2* Hz), 4.81 (s, 2H), 5.67 (s, 1H), 6.36 (s, 1H), 6.43-6.45 (d, 1H, *J* = *7.0* Hz), 6.59-6.61 (d, 1H, *J* = *7.0* Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) 58.1 (NCH_2), 69.2, 76.7 (OCH_2), 112.5, 115.9, 116.9, 133.9, 138.9, 141.2. *m/z* = 165.06. Calc for $C_9H_{11}NO_2$; C, 65.44; H, 6.71; N, 8.48%; found C, 65.41; H, 6.73; N, 8.50 %.

General method for the preparation of *N*-alkylated 3,4-dihydro-2*H*-1,4-benzoxazines 11a-j by reduction:

To a solution of the acid (mmol) and 3,4-dihydro-2*H*-1,4-benzoxazines (7mmol), $NaBH_4$ (73 mmol) was added slowly at 0 °C. The reaction was highly exothermic and care was taken to maintain the temperature around 0-5 °C. The reaction was stirred for 2-3 h. On completion, the mixture was neutralized using NaOH and extracted with ethyl acetate. The organic layer, was dried and evaporated. The residue was chromatographed on silica gel column using ethyl acetate and hexane as an eluent to obtain the desired product in high yield.

4-ethyl-3,4-dihydro-2*H*-1,4-benzoxazine 11a:

Reddish oil; IR (film) showed the absence of NH stretching. ^1H NMR ($CDCl_3$, 400 MHz) δ ppm 1.18 (t, 3H, *J* = *14.2* Hz), 3.30 (q, 2H, *J* = *8.7* Hz), 3.34 (t, 2H, *J* = *14.1* Hz), 4.24–4.26 (t, 2H, *J* = *8.8* Hz), 6.6–6.84 (m, 4H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 14.5, 49.5, 59.1, 72.3, 112.9, 116.9, 117.1, 122.1, 130.1, 143.6. *m/z* = 164.1. Calcd for $C_{10}H_{13}NO$ is C, 73.59; H, 8.03; N, 8.58%; found: C, 73.12; H, 8.09; N, 8.6%.

3,4-dihydro-4-methyl-2*H*-1,4-benzoxazine 11b:

Reddish oil; IR (film) showed the absence of NH stretching. ^1H NMR ($CDCl_3$, 400 MHz) δ ppm 2.92 (s, 3H), 3.36 (t, 2H, *J* = *14.2* Hz), 4.25 (t, 2H, *J* = *8.6* Hz), 6.72–6.84 (m, 4H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 39.4, 59.7, 72.8, 114.9, 116.9, 119.1, 122.1, 142.1, 144.6. *m/z* = 148.1. Calcd for $C_9H_{11}NO$ is C, 72.46; H, 7.43; N, 9.39%; found: C, 72.49; H, 7.40; N, 9.42%.

4-((furan-2-yl)methyl)-3,4-dihydro-2*H*-1,4-benzoxazine 11c:

Solid; IR (KBr) showed the absence of NH stretching. ^{1}H NMR (CDCl$_3$, 400 MHz) δ ppm 3.86 (t, 2H, *J* = *14.1* Hz), 4.21 (t, 2H, *J* = *8.0* Hz), 4.61 (s, 2H), 6.12 (d, 1H, *J* = *7.5* Hz), 6.23-6.27 (m, 1H), 6.52–6.64 (m, 4H, ArH), 7.33 (d, 1H, *J* = *7.5* Hz). ^{13}C NMR (CDCl$_3$, 100 MHz) δ ppm 59.3, 61.2, 72.1, 107.9, 110.9, 114.7, 115.9, 119.1, 122.1, 142.3, 143.1, 144.6, 149.1. *m/z* = 215.1. Calcd for $C_{13}H_{13}NO_2$ is C, 72.54; H, 6.09; N, 6.51%; found: C, 72.51; H, 6.13; N, 6.54%.

3,4-dihydro-4-((pyrazin-2-yl)methyl)-2*H*-1,4-benzoxazine 11d:

Solid; IR (KBr) ν cm^{-1} 1730. ^{1}H NMR (CDCl$_3$, 400 MHz) δ ppm 3.81 (t, 2H, *J* = *14.0* Hz), 4.22 (t, 2H, *J* = *8.1* Hz), 4.75 (s, 2H), 6.50–6.61 (m, 4H, ArH), 8.41 (d, 1H, *J* = *7.2* Hz), 8.53 (d, 1H, *J* = *7.1* Hz), 8.62 (s, 1H). ^{13}C NMR (CDCl$_3$, 100 MHz) δ ppm 46.1, 59.2, 74.2, 115.1, 115.9, 118.9, 122.5, 141.7, 142.5, 143.9, 144.6, 145.1, 149.2. *m/z* = 227.21. Calcd for $C_{13}H_{13}N_3O$ is C, 68.70; H, 5.77; N, 18.49%; found: C, 68.72; H, 5.79; N, 18.52%.

4-benzyl-3,4-dihydro-2*H*-1,4-benzoxazine 11e:

Solid IR (KBr) ν cm^{-1} 1660. ^{1}H NMR (CDCl$_3$, 400 MHz) δ ppm 3.74 (t, 2H, *J* = *14.1* Hz), 4.19 (t, 2H, *J* = *8.2* Hz), 4.72 (s, 2H), 6.50–6.61 (m, 4H, ArH), 7.09-7.12(m, 5H, ArH). ^{13}C NMR (CDCl$_3$, 100 MHz); δ ppm 54.1, 60.2, 74.1, 114.1, 115.3, 118.2, 121.9, 127.2, 128.5, 129.7, 136.7, 142.5, 144.6. *m/z* = 225.29. Calcd for $C_{15}H_{15}NO$ is C, 79.97; H, 6.71; N, 6.22%; found: C, 79.80; H, 6.74; N, 6.25%.

4-((1,2,3-thiadiazol-5-yl)methyl)-3,4-dihydro-2*H*-1,4-benzoxazine 11f:

Solid IR (KBr) ν cm^{-1} 1721 ^{1}H NMR (CDCl$_3$, 400 MHz) δ ppm 3.71 (t, 2H, *J* = *14.0* Hz), 4.21 (t, 2H, *J* = *8.1* Hz), 4.67 (s, 2H), 6.50–6.61 (m, 4H, ArH), 8.21(s, 1H, ArH). ^{13}C NMR (CDCl$_3$, 100 MHz); δ ppm 56.2, 60.2, 74.1, 114.3, 115.7, 118.2, 121.6, 142.5, 144.6, 146.2, 147.6. *m/z* = 233.19. Calcd for $C_{11}H_{11}N_3OS$ is C, 56.63; H, 4.75; N, 18.01%; found: C, 56.67; H, 4.79; N, 18.05%.

4-ethyl-3,4-dihydro-5-methyl-2*H*-1,4-benzoxazine 11g:

Reddish oil IR (film) showed the absence of NH stretching. ^1H NMR ($CDCl_3$, 400 MHz) δ ppm 1.17 (t, 3H, *J = 14.0* Hz), 2.37 (s, 3H), 3.32 (q, 2H, *J = 8.5* Hz), 3.36 (t, 2H, *J = 14.2* Hz), 4.24–4.26 (t, 2H, *J = 8.2* Hz), 6.58–6.64 (m, 3H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz); δ ppm 14.1, 17.3, 49.5, 59.9, 72.7, 112.9, 118.9, 122.1, 127.3, 131.1, 143.1. *m/z* = 164.1. Calcd for $C_{11}H_{15}NO$ is C, 74.54; H, 8.53; N, 7.90%; found: C, 74.50; H, 8.56; N, 7.93%.

4-ethyl-3,4-dihydro-6-methyl-2*H*-1,4-benzoxazine 11h:

Reddish oil IR (film) showed the absence of NH stretching. ^1H NMR ($CDCl_3$, 400 MHz) δ ppm 1.12 (t, 3H, *J = 14.1* Hz), 2.37 (s, 3H), 3.35 (q, 2H, *J = 8.1* Hz), 3.39 (t, 2H, *J = 14.1* Hz), 4.26 (t, 2H, *J = 8.0* Hz), 6.32 (s, 1H, ArH), 6.37 (d, 1H, *J = 7.5* Hz), 6.56 (d, 1H, *J = 7.5* Hz). ^{13}C NMR ($CDCl_3$, 100MHz); δ ppm 14.3, 24.9, 47.9, 59.9, 73.7, 114.9, 115.7, 120.1, 131.0, 139.9, 145.1. *m/z* = 177.12. Calcd for $C_{11}H_{15}NO$ is C, 74.54; H, 8.53; N, 7.90%; found: C, 74.51; H, 8.52; N, 7.93%.

4-ethyl-3,4-dihydro-7-methyl-2*H*-1,4-benzoxazine 11i:

Reddish oil IR (film) showed the absence of NH stretching. ^1H NMR ($CDCl_3$, 400 MHz) δ ppm 1.17 (t, 3H, *J = 14.0* Hz), 2.32 (s, 3H), 3.38 (q, 2H, *J = 8.2* Hz), 3.34 (t, 2H, *J = 14.3* Hz), 4.28 (t, 2H, *J = 8.1* Hz), 6.41 (s, 1H, ArH), 6.47 (d, 1H, *J = 7.2* Hz), 6.57 (d, 1H, *J = 7.2* Hz). ^{13}C NMR ($CDCl_3$, 100MHz); δ ppm 14.1, 24.4, 46.7, 59.5, 73.9, 113.9, 114.7, 121.2, 128.3, 140.9, 142.1. *m/z* = 177.21. Calcd for $C_{11}H_{15}NO$ is C, 74.54; H, 8.53; N, 7.90%; found: C, 74.51; H, 8.52; N, 7.93%.

3,4-dihydro-4,5-dimethyl-2*H*-1,4-benzoxazine 11j:

Reddish oil IR (film) showed the absence of NH stretching. ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 2.31 (s, 3H), 2.95 (s, 3H), 3.34 (t, 2H, J = *14.2* Hz), 4.22 (t, 2H, J = *8.6* Hz), 6.52–6.64 (m, 3H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 16.2, 39.2, 59.9, 72.6, 112.9, 118.9, 121.8, 128.2, 131.1, 142.1. *m/z* =163.2. Calcd for $C_{10}H_{13}NO$ is C, 73.59; H, 8.03; N, 8.58%; found: C, 73.61; H, 8.05; N, 8.59%.

General method for the preparation of *N*-alkylated 3,4-dihydro-2*H*-1,4-benzoxazines 12 by alkylation:

The amine **10** (6 mmol) and dry K_2CO_3 (15 mmol) were dissolved in dry DMF (15 ml) then an alkyl halide (8.6mmol) was added. The reaction mixture was stirred at room temperature overnight. After the completion of the reaction (TLC monitoring) crushed ice was added and product extracted using ethyl acetate. The combined organic extract were dried (Na_2SO_4) and concentrated. The crude product was purified over silica gel eluting with ethyl acetate and hexane (1:20) to obtain the desired product.

3,4-dihydro-4-isobutyl-2*H*-1,4-benzoxazine 12a:

Reddish oil IR (film) showed the absence of NH stretching.^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 0.98 (d, 6H, J = *6.6* Hz), 1.62–1.67 (m, 1H), 1.77–1.82 (m, 2H), 3.46 (t, 2H, J = *14.1* Hz), 4.26 (t, 2H, J = *8.1* Hz), 6.5–6.84 (m, 4H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 20.3, 28.1, 59.1, 65.8, 72.3, 112.9, 116.9, 117.1, 122.1, 130.1, 143.6. MS (CI) *m/z* = 190.13. Calcd for $C_{12}H_{17}NO$ is C, 75.35; H, 8.96; N, 7.32%; found: C, 75.12; H, 9.01; N, 7.31%.

3,4-dihydro-4-((pyridin-4-yl)methyl)-2*H*-1,4-benzoxazine 12b:

Reddish oil; IR (film) showed the absence of NH stretching.^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm), 3.41 (t, 2H, J = *14.2* Hz), 4.23 (t, 2H, J = *8.0* Hz), 6.75–6.81 (m, 4H, ArH). 7.42(d, 2H, J = *7.1* Hz), 8.51 (d, 2H, J = *7.1* Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm, 52.9, 59.6, 72.7, 114.9, 115.1, 119.1, 121.7, 124.6, 141.1, 144.1, 146.8, 150.1; MS (CI) *m/z* = 190.13. Calcd for $C_{14}H_{14}N_2O$ is C, 74.31; H, 6.24; N, 12.38%; found: C, 74.34; H, 6.27; N, 12.34%.

3-(2,3-dihydro-1,4-benzoxazin-4-yl)propanenitrile 12c:

Oil IR (film) showed the absence of NH stretching. ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm, 2.71 (t, 2H, J = *9.3* Hz), 3.31 (t, 2H, J = *9.5* Hz), 3.42 (t, 2H, J = *14.0* Hz), 4.21 (t, 2H, J = *8.0* Hz), 6.72–6.80 (m, 4H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm, 15.7, 51.9, 59.2, 72.5, 113.7, 115.3, 117.4, 119.3, 121.5, 142.5, 144.8. MS (CI) *m/z* = 188.07. Calcd for $C_{11}H_{12}N_2O$ is C, 70.19; H, 6.43; N, 14.88%; found: C, 70.15; H, 6.41; N, 14.86%.

benzyl 2-(2,3-dihydro-1,4-benzoxazin-4-yl)acetate 12d:

Solid; IR (KBr) ν cm^{-1} 1678. ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 3.47 (t, 2H, J = *14.1*Hz), 4.26 (t, 2H, J = *8.2* Hz), 4.35 (s, 2H), 5.31 (s, 2H), 6.74–6.82 (m, 4H, ArH), 7.13-7.21 (m, 5H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm, 57.9, 59.1, 67.8, 73.5, 114.2, 115.1, 118.2, 121.3, 126.7, 127.3, 129.8, 140.5, 142.2, 144.7; MS (CI) *m/z* = 283.09. Calcd for $C_{17}H_{17}NO_3$ is C, 72.07; H, 6.05; N, 4.94%; found: C, 72.10; H, 6.02; N, 4.92%.

3,4-dihydro-4-propyl-2*H*-1,4-benzoxazine 12e:

Reddish oil; IR (film) showed the absence of NH stretching. ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 1.08 (d, 6H, J = *6.2* Hz), 1.60–1.65 (m, 2H), 2.92 (m, 2H), 3.42 (t, 2H, J = *14.1* Hz), 4.29 (t, 2H, J = *8.2* Hz), 6.75–6.84 (m, 4H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 12.3, 20.3, 59.1, 65.8, 72.3, 114.9, 116.9, 117.1, 121.7, 141.1, 143.6. MS (CI) *m/z* = 190.13. Calcd for $C_{11}H_{15}NO$ is C, 74.54; H, 8.53; N, 7.90%; found: C, 74.57; H, 8.56; N, 7.96%.

3,4-dihydro-4-((pyridin-3-yl)methyl)-2*H*-1,4-benzoxazine 12f:

Reddish oil; IR (film) showed the absence of NH stretching. ^{1}H NMR (CDCl$_3$, 400 MHz) δ ppm), 3.45 (t, 2H, *J* = *14.2* Hz), 4.27 (t, 2H, *J* = *8.0* Hz), 6.72–6.83 (m, 4H, ArH). 7.92-8.11 (m, 3H, ArH), 8.53 (s, 1H,). ^{13}C NMR (CDCl$_3$, 100 MHz) δ ppm, 53.9, 59.3, 72.5, 114.8, 115.2, 119.0, 121.7, 123.6, 134.5, 135.3, 142.1, 144.1, 146.8, 150.5. MS (CI) *m/z* = 190.09. Calcd for $C_{14}H_{14}N_2O$ is C, 74.31; H, 6.24; N, 12.38%; found: C, 74.34; H, 6.25; N, 12.35%.

3,4-dihydro-4-isobutyl-5-methyl-2*H*-1,4-benzoxazine 12g:

Reddish oil; IR (film) showed the absence of NH stretching. ^{1}H NMR (CDCl$_3$, 400 MHz) δ ppm 0.97 (d, 6H, *J* = *6.5* Hz), 1.63–1.66 (m, 1H), 1.76–1.81 (m, 2H), 2.32 (s, 3H), 3.47 (t, 2H, *J* = *14.0* Hz), 4.29 (t, 2H, *J* = *8.0* Hz), 6.65–6.74 (m, 3H, ArH). ^{13}C NMR (CDCl$_3$, 100 MHz) δ ppm 16.5, 20.6, 28.4, 59.6, 65.4, 72.5, 112.9, 117.1, 122.1, 128.3, 130.5, 143.7. MS (CI) *m/z* = 205.12. Calcd for $C_{13}H_{19}NO$ is C, 76.06; H, 9.33; N, 6.82%; found: C, 76.05; H, 9.31; N, 6.85%.

3,4-dihydro-4-isobutyl-6-methyl-2*H*-1,4-benzoxazine 12h:

Reddish oil; IR (film) showed the absence of NH stretching. ^{1}H NMR (CDCl$_3$, 400 MHz) δ ppm 0.99 (d, 6H, *J* = *6.4* Hz), 1.64–1.67 (m, 1H), 1.77–1.81 (m, 2H), 2.37 (s, 3H), 3.48 (t, 2H, *J* = *14.1* Hz), 4.29 (t, 2H, *J* = *8.5* Hz), 6.31 (s, 1H, ArH), 6.65(d, 1H, *J* = *7.1* Hz), 6.77 (d, 1H, *J* = *7.1* Hz). ^{13}C NMR (CDCl$_3$, 100 MHz) δ ppm, 20.5, 24.5, 28.2, 59.8, 65.4, 72.8, 114.9, 115.9, 117.1, 130.9, 139.6, 144.7. MS (CI) *m/z* = 205.12. Calcd for $C_{13}H_{19}NO$ is C, 76.06; H, 9.33; N, 6.82%; found: C, 76.09; H, 9.35; N, 6.85%.

3,4-dihydro-4-isobutyl-7-methyl-2*H*-1,4-benzoxazine 12i:

Reddish oil; IR (film) showed the absence of NH stretching. ^{1}H NMR (CDCl$_3$, 400 MHz) δ ppm 0.97 (d, 6H, *J* = *6.4* Hz), 1.65–1.67 (m, 1H), 1.71–1.81 (m, 2H), 2.37 (s, 3H), 3.48 (t, 2H, J = *14.1* Hz), 4.29 (t, 2H, J = *8.5* Hz), 6.51 (s, 1H, ArH), 6.55 (d, 1H, J = *7.1* Hz), 6.67 (d, 1H, J = *7.1* Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm, 20.5, 24.5, 28.2, 59.8, 65.4, 72.8, 114.9, 115.9, 117.1, 130.9, 141.6, 144.7. MS (CI) *m/z* = 205.12. Calcd for $C_{13}H_{19}NO$ is C, 76.06; H, 9.33; N, 6.82%; found: C, 76.09; H, 9.35; N, 6.85%.

3,4-dihydro-5-methyl-4-((pyridin-4-yl)methyl)-2*H*-1,4-benzoxazine 12j:

Reddish oil; IR (film) showed the absence of NH stretching. ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm), 3.41 (t, 2H, J = *14.2* Hz), 4.23 (t, 2H, J = *8.0* Hz), 6.75–6.81 (m, 4H, ArH). 7.42(d, 2H, J = *7.1* Hz), 8.51 (d, 2H, J = *7.1* Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm, 52.9, 59.6, 72.7, 114.9, 115.1, 119.1, 121.7, 124.6, 141.1, 144.1, 146.8, 150.1. MS (CI) *m/z* = 240.13. Calcd for $C_{15}H_{16}N_2O$ is C, 74.97; H, 6.71; N, 11.66%; found: C, 74.99; H, 6.74; N, 11.68%.

General procedure for the preparation of 2,3-dihydro-1,4-benzoxazin-4-yl)-acetic acid methyl ester I:

To a suspension of Pd/C (0.35 mmol) in ethanol was added **12d** (3.5 mmol), H_2 gas was purged through the solution and the reaction mixture stirred at r.t for 3h. The reaction mixture after completion was filtered through celite. The filtrate was then evaporated to yield a solid mass. To the solution of the crude (5.17 mmol) in DMF was added MeI (5.7 mmol) and Cs_2CO_3 (10.3 mmol) and stirred at r.t for 2h. The reaction upon completion was filtered and the residue washed with ethyl acetate. The combined organic layer was washed with ice-cold water and brine, dried over Na_2SO_4 and evaporated to yield a crude product which was purified by column chromatography using ethyl acetate and hexane (1:10) as an eluent to yield the desired product **I**. Solid; IR (KBr) ν cm^{-1} 1710. ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 3.41 (t, 2H, J = *14.2* Hz), 3.61 (s, 3H), 4.23 (t, 2H, J = *8.0* Hz), 4.38 (s, 2H), 6.75–6.81 (m, 4H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 50.9, 58.3, 59.6, 72.7, 114.9, 115.1, 119.1, 121.7, 142.1, 144.1, 167.1. MS (CI) m/z = 207.23. Calcd for $C_{11}H_{13}NO_3$ is C, 63.76; H, 6.32; N, 6.76%; found: C, 63.72; H, 6.34; N, 6.78%.

General procedure for the preparation of 4-(3-alkyl-1,2,4-oxadiazol-5-ylmethyl)-3,4-dihydro-2*H*-1,4-benzoxazines 13a-j:

To solution of (2,3-dihydro-1,4-benzoxazin-4-yl)-acetic acid methyl ester (4.8 mmol) in toluene was added *N*-hydroxy alkyl amidine (5.28 mmol) and K_2CO_3 (10.08 mmol), the reaction mixture was refluxed for 6-7 h. The reaction upon completion was evaporated in vacuum to yield the crude product which was purified using ethyl acetate: hexane as an eluent to yield the desired products.

3,4-dihydro-4-((3-methyl-1,2,4-oxadiazol-5-yl)methyl)-2*H*-1,4-benzoxazine 13a:

Solid; IR (KBr) ν cm^{-1} 1685 (NH). ^1H NMR (DMSO-d_6, 400 MHz) δ ppm 2.37 (s, 3H), 3.23(d, 2H, J = *2.5* Hz), 4.12 (t, 2H, J = *8.1* Hz), 4.67 (s, 2H), 6.56–6.67 (m, 4H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) 18.9, 60.1 (NCH_2), 73.1 (OCH_2), 114.9, 116.8, 119.5, 122.7, 129.8, 142.1, 144.7, 167.5. *m/z* = 231.21. Calc for $C_{12}H_{13}N_3O_2$ C, 62.33; H, 5.67; N, 18.17 %; found C, 62.35; H, 5.63; N, 18.15%.

4-((3-ethyl-1,2,4-oxadiazol-5-yl)methyl)-3,4-dihydro-2*H*-1,4-benzoxazine 13b:

Solid; IR (KBr) ν cm^{-1} 1679. ^1H NMR ($CDCl_3$, 400 MHz) δ ppm 1.20 (t, 3H, J = *14.1* Hz), 3.21 (q, 2H, J = *8.2* Hz), 3.43 (t, 2H, J = *14.1* Hz), 4.27 (t, 2H, J = *8.3* Hz), 4.76 (s, 2H), 6.76–6.84 (m, 4H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz); δ ppm 14.1, 28.9, 54.7, 59.1, 72.3, 113.9, 115.9, 118.1, 121.4, 137.1, 142.6, 144.7, 169.8. *m/z* = 245.12. Calcd for $C_{13}H_{15}N_3O_2$ is C, 63.66; H, 6.16; N, 17.13%; found: C, 63.67; H, 6.18; N, 17.15%.

3,4-dihydro-4-((3-phenyl-1,2,4-oxadiazol-5-yl)methyl)-2*H*-1,4-benzoxazine 13c:

Solid; IR (KBr) ν cm^{-1} 1667. ^{1}H NMR (CDCl$_3$, 400 MHz) δ ppm 3.74 (t, 2H, *J* = *14.1* Hz), 4.19 (t, 2H, *J* = *8.2* Hz), 4.76 (s, 2H), 6.57–6.67 (m, 4H, ArH), 7.29-7.32(m, 5H, ArH). ^{13}C NMR (CDCl$_3$, 100 MHz); δ ppm 56.1, 60.7, 74.8, 114.6, 115.9, 118.2, 121.9, 127.2, 128.5, 129.7, 136.7, 142.5, 144.6, 154.7, 167.8. *m/z* = 293.13. Calcd for $C_{17}H_{15}N_3O_2$ is C, 69.61; H, 5.15; N, 14.33%; found: C, 69.64; H, 5.17; N, 14.35%.

3,4-dihydro-5-methyl-4-((3-phenyl-1,2,4-oxadiazol-5-yl)methyl)-2*H*-1,4-benzoxazine 13d:

Solid; IR (KBr) ν cm^{-1} 1657. ^{1}H NMR (CDCl$_3$, 400 MHz) δ ppm 2.65 (s, 3H), 3.73 (t, 2H, *J* = *14.2* Hz), 4.23 (t, 2H, *J* = *8.4* Hz), 4.71 (s, 2H), 6.47–6.56 (m, 3H, ArH), 7.21-7.30 (m, 5H, ArH). ^{13}C NMR (CDCl$_3$, 100 MHz); δ ppm 17.4, 56.9, 60.3, 74.3, 112.6, 118.2, 121.9, 127.2, 127.8, 128.5, 129.7, 130.2, 130.9, 136.7, 142.5, 167.8. *m/z* = 307.13. Calcd for $C_{18}H_{17}N_3O_2$ is C C, 70.34; H, 5.58; N, 13.67%; found: C, 70.31; H, 5.55; N, 13.62%.

3,4-dihydro-5-methyl-4-((3-methyl-1,2,4-oxadiazol-5-yl)methyl)-2*H*-1,4-benzoxazine 13e:

Solid; IR (KBr) ν cm^{-1} 1679 (NH). ^{1}H NMR (DMSO-*d*$_6$, 400 MHz) δ ppm 2.34 (s, 3H), 2.39 (s, 3H), 3.25 (t, 2H, *J* = *3.0* Hz), 4.17 (t, 2H, *J* = *8.0* Hz), 4.65 (s, 2H), 6.60–6.67 (m, 3H, ArH).^{13}C NMR (CDCl$_3$, 100 MHz) 16.3, 18.7, 56.7, 60.4 (NCH$_2$), 73.3 (OCH$_2$), 112.9, 119.5, 122.7, 127.6, 130.8, 137.9, 142.1, 161.5. *m/z* = 245.16. Calc for $C_{13}H_{15}N_3O_2$ C, 63.66; H, 6.16; N, 17.13 %; found C, 63.68; H, 6.17; N, 17.15 %.

4-((3-ethyl-1,2,4-oxadiazol-5-yl)methyl)-3,4-dihydro-5-methyl-2*H*-1,4-benzoxazine 13f:

Solid; IR (KBr) ν cm^{-1} 1669. ^{1}H NMR (CDCl$_3$, 400 MHz) δ ppm 1.19 (t, 3H, *J* = *14.1* Hz), 2.34 (s, 3H), 3.23 (q, 2H, *J* = *8.1* Hz), 3.45 (t, 2H, *J* = *14.2* Hz), 4.25 (t, 2H, *J* = *8.2* Hz), 4.71 (s, 2H), 6.75–6.81 (m, 3H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz); δ ppm 14.1, 16.7, 28.9, 56.7, 59.3, 72.3, 112.9, 118.1, 121.4, 127.9, 131.2, 137.1, 142.6, 167.8. *m/z* = 259.17. Calcd for $C_{14}H_{17}N_3O_2$ is C, 64.85; H, 6.61; N, 16.20%; found: C, 64.88; H, 6.64; N, 16.24%.

4-((3-ethyl-1,2,4-oxadiazol-5-yl)methyl)-3,4-dihydro-6-methyl-2*H*-1,4-benzoxazine 13g:

Solid; IR (KBr) ν cm^{-1} 1671. ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 1.17 (t, 3H, *J* = *14.0* Hz), 2.36 (s, 3H), 3.19 (q, 2H, *J* = *8.0* Hz), 3.42 (t, 2H, *J* = *14.1* Hz), 4.25 (t, 2H, *J* = *8.1* Hz), 4.70 (s, 2H), 6.48 (s, 1H, ArH), 6.54 (d, 1H, *J* = *7.2* Hz), 6.71 (d, 1H, *J* = *7.2* Hz). ^{13}C NMR ($CDCl_3$, 100 MHz); δ ppm 14.1, 24.7, 28.7, 56.6, 59.9, 72.5, 114.9, 115.7, 119.6, 130.6, 137.1, 139.7, 145.6, 168.8. *m/z* = 259.13. Calcd for $C_{14}H_{17}N_3O_2$ is C, 64.85; H, 6.61; N, 16.20%; found: C, 64.89; H, 6.67; N, 16.26%.

3,4-dihydro-7-methyl-4-((3-methyl-1,2,4-oxadiazol-5-yl)methyl)-2*H*-1,4-benzoxazine 13h:

Solid; IR (KBr) ν cm^{-1} 1672 (NH). ^{1}H NMR (DMSO-*d$_6$*, 400 MHz) δ ppm 2.32 (s, 3H), 2.37 (s, 3H), 3.25 (t, 2H, *J* = *3.0 Hz*), 4.25 (t, 2H, *J* = *8.1 Hz*), 4.69 (s, 2H), 6.49 (s, 1H, ArH), 6.51 (d, 1H, *J* = *7.5 Hz*), 6.62 (d, 1H, *J* = *7.5 Hz*). ^{13}C NMR ($CDCl_3$, 100 MHz) 17.9, 24.7, 56.4, 60.1 (NCH_2), 73.7 (OCH_2), 113.9, 114.6, 121.7, 128.8, 138.7, 141.9, 142.1, 161.5. *m/z* = 245.13. Calc for $C_{13}H_{15}N_3O_2$ C, 63.66; H, 6.16; N, 17.13 %; found C, 63.68; H, 6.19; N, 17.18 %.

4-((3-ethyl-1,2,4-oxadiazol-5-yl)methyl)-3,4-dihydro-7-methyl-2H-1,4-benzoxazine 13i:

Solid; IR (KBr) ν cm^{-1} 1663. ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 1.14 (t, 3H, *J* = *14.1 Hz*), 2.30 (s, 3H), 3.21 (q, 2H, *J* = *8.2 Hz*), 3.45 (t, 2H, *J* = *14.6 Hz*), 4.28 (t, 2H, *J* = *8.1 Hz*), 4.73 (s, 2H), 6.49 (s, 1H, ArH), 6.55 (d, 1H, *J* = *7.2 Hz*), 6.65 (d, 1H, *J* = *7.2 Hz*). ^{13}C NMR ($CDCl_3$, 100MHz); δ ppm 14.5, 25.1, 28.9, 55.7, 59.9, 72.5, 113.7, 114.8, 120.7, 128.5, , 139.1, 142.6, 143.1, 169.3. *m/z* = 259.21. Calcd for $C_{14}H_{17}N_3O_2$ is C, 64.85; H, 6.61; N, 16.20%; found: C, 64.81; H, 6.60; N, 16.26%.

General procedure for the preparation of 4-(1*H*-benzimidazol-2-ylmethyl)-3,4-dihydro-2*H*-1,4-benzoxazines 14a-j:

To solution of 2,3-dihydro-1,4-benzoxazin-4-yl)-acetic acid methyl ester (4.8 mmol) in toluene was added substituted *o*-phenylene diamine (5.28 mmol), the reaction mixture was refluxed for 12 hs. The reaction upon completion was evaporated in vacuum to yield the crude product which was purified using ethyl acetate: hexane as an eluent to yield the desired products.

4-((1*H*-benzoimidazol-2-yl)methyl)-3,4-dihydro-2*H*-1,4-benzoxazine 14a:

Solid; IR (KBr) ν cm^{-1} 1625. ^1H NMR ($CDCl_3$, 400 MHz) δ ppm 3.56 (t, 2H, J = *14.1* Hz), 4.24 (t, 2H, J = *8.8* Hz), 4.73 (s, 2H), 6.76–6.84 (m, 4H, ArH), 7.23 (d, 2H, J = *7.2* Hz), 7.42 (d, 2H, J = *7.2* Hz), 11.76 (bs, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz); δ ppm 54.1, 59.3, 72.1, 114.3, 115.3, 116.5, 117.1, 119.1, 122.1, 123.9, 139.1, 141.5, 142.9, 144.9. *m/z* = 265.13. Calcd for $C_{16}H_{15}N_3O$ is C, 72.43; H, 5.70; N, 15.84%; found: C, 72.44; H, 5.75; N, 15.89%.

4-((6-fluoro-1*H*-benzoimidazol-2-yl)methyl)-3,4-dihydro-2*H*-1,4-benzoxazine 14b:

Solid; IR (KBr) ν cm^{-1} 1630. ^1H NMR ($CDCl_3$, 400 MHz) δ ppm 3.52 (t, 2H, J = *14.1* Hz), 4.22 (t, 2H, J = *8.8* Hz), 4.79 (s, 2H), 6.72–6.80 (m, 4H, ArH), 6.97 (d, 1H, J = *7.0* Hz), 7.31 (s, 1H, ArH), 7.51 (d, 1H, J = 7.0 Hz), 11.94 (bs, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz); δ ppm 54.5, 59.1, 72.3, 103.5, 110.6, 114.9, 115.9, 117.1, 119.1, 122.1, 135.1, 140.2, 141.9, 142.9, 145.9, 157.6. *m/z* = 283.1. Calcd for $C_{16}H_{14}FN_3O$ is C, 67.83; H, 4.98; N, 14.83%; found: C, 67.87; H, 54.03; N, 14.87%.

3,4-dihydro-4-((6-methyl-1*H*-benzoimidazol-2-yl)methyl)-2*H*-1,4-benzoxazine 14c:

Solid; IR (KBr) ν cm^{-1} 1612. ^1H NMR ($CDCl_3$, 400 MHz) δ ppm 2.23 (s, 3H), 3.51 (t, 2H, *J* = *14.0* Hz), 4.27 (t, 2H, *J* = *8.1* Hz), 4.75 (s, 2H), 6.62–6.70 (m, 4H, ArH), 7.07 (d, 1H, *J* = *7.1* Hz), 7.34 (s, 1H, ArH), 7.52 (d, 1H, *J* = *7.1* Hz), 11.64 (bs, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz); δ ppm 55.1, 60.2, 73.7, 114.9, 115.3, 115.9, 116.2, 117.1, 119.3, 121.7, 131.7, 135.1, 138.9, 141.5, 142.9, 145.9, *m/z* = 279.43. Calcd for $C_{17}H_{17}N_3O$ is C, 73.10; H, 6.13; N, 15.04%; found: C, 73.13; H, 6.17; N, 15.08%.

3,4-dihydro-5-methyl-4-((6,7-dimethyl-1*H*-benzoimidazol-2-yl)methyl)-2*H*-1,4-benzoxazine 14d:

Solid; IR (KBr) ν cm^{-1} 1609. ^1H NMR ($CDCl_3$, 400 MHz) δ ppm 2.23 (s, 3H), 2.31 (s, 6H), 3.54 (t, 2H, *J* = *14.1* Hz), 4.29 (t, 2H, *J* = *8.0* Hz), 4.71 (s, 2H), 6.61–6.67 (m, 3H, ArH), 6.97 (d, 1H, *J* = *7.2* Hz), 7.32 (d, 1H, *J* = *7.2* Hz), 11.60 (bs, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 12.3, 16.3, 17.5, 56.2, 60.1, 72.7, 111.9, 112.6, 119.1, 121.9, 124.7, 125.3, 127.9, 130.4, 131.7, 135.8, 138.9, 141.5, 142.9. *m/z* = 307.33. Calcd for $C_{19}H_{21}N_3O$ is C, 74.24; H, 6.89; N, 13.67%; found: C, 74.20; H, 6.96; N, 13.71%.

4-((5,6-dichloro-1*H*-benzoimidazol-2-yl)methyl)-3,4-dihydro-2*H*-1,4-benzoxazine 14e:

Solid; IR (KBr) ν cm^{-1} 1643. ^1H NMR ($CDCl_3$, 400 MHz) δ ppm 3.57 (t, 2H, *J* = *14.0* Hz), 4.29 (t, 2H, *J* = *8.7* Hz), 4.79 (s, 2H), 6.71–6.80 (m, 4H, ArH), 7.62 (s, 2H, ArH), 11.96 (bs, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 55.7, 59.4, 72.7, 114.7, 115.8, 117.5, 118.6, 122.3, 127.8, 139.1, 141.9, 142.9, 144.9. *m/z* = 333.11. Calcd for $C_{16}H_{13}Cl_2N_3O$ is C, 57.50; H, 3.92; N, 12.57%; found: C, 57.55; H, 3.98; N, 12.51%.

3,4-dihydro-4-((6,7-dimethyl-1*H*-benzoimidazol-2-yl)methyl)-2H-1,4-benzoxazine 14f:

Solid IR (KBr) ν cm^{-1} 1606. ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 2.34 (s, 6H), 3.52 (t, 2H, *J* = *14.0* Hz), 4.31 (t, 2H, *J* = *8.1* Hz), 4.70 (s, 2H), 6.64–6.71 (m, 4H, ArH), 6.92 (d, 1H, *J* = *7.1* Hz), 7.33 (d, 1H, *J* = *7.1* Hz), 11.56 (bs, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz); δ ppm 12.2, 17.3, 56.4, 60.2, 72.9, 112.5, 114.9, 115.6, 118.8, 121.6, 124.7, 125.1, 130.6, 134.7, 139.2, 141.3, 142.7, 144.7. *m/z* = 293.21. Calcd for $C_{18}H_{19}N_3O$ is C, 73.69; H, 6.53; N, 14.32%; found: C, 73.72; H, 6.51; N, 14.36%.

4-((5,6-dichloro-1*H*-benzoimidazol-2-yl)methyl)-3,4-dihydro-5-methyl-2*H*-1,4-benzoxazine 14g:

Solid; IR (KBr) ν cm^{-1} 1637. ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 2.26 (s, 3H), 3.59 (t, 2H, *J* = *14.3* Hz), 4.31 (t, 2H, *J* = *8.1* Hz), 4.71 (s, 2H), 6.67–6.73 (m, 3H, ArH), 7.60 (s, 2H, ArH), 11.81 (bs, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz); δ ppm 17.2, 56.1, 59.9, 73.6, 112.1, 117.3, 118.9, 122.3, 127.5, 128.7, 130.7, 139.4, 141.3, 142.4. *m/z* = 347.02. Calcd for $C_{17}H_{15}Cl_2N_3O$ is C, 58.63; H, 4.34; N, 12.07%; found: C, 58.65; H, 4.37; N, 12.09%.

4-((5,6-dichloro-1*H*-benzoimidazol-2-yl)methyl)-3,4-dihydro-6-methyl-2*H*-1,4-benzoxazine 14h:

Solid; IR (KBr) ν cm^{-1} 1639. ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 2.31 (s, 3H), 3.54 (t, 2H, *J* = *14.2 Hz*), 4.30 (t, 2H, *J* = *8.2 Hz*), 4.73 (s, 2H), 6.47 (s, 1H, ArH), 6.51 (d, 1H, *J* = *7.5 Hz*), 6.64 (d, 1H, *J* = *7.5 Hz*), 7.57 (s, 2H, ArH), 11.77 (bs, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz); δ ppm 23.8, 56.3, 59.7, 73.3, 114.3, 115.3, 117.1, 119.2, 130.5, 137.8, 139.2, 141.5, 144.6. *m/z* =347.05. Calcd for $C_{17}H_{15}Cl_2N_3O$ is C, 58.63; H, 4.34; N, 12.07%; found: C, 58.67; H, 4.30; N, 12.01%.

4-((5,6-dichloro-1*H*-benzoimidazol-2-yl)methyl)-3,4-dihydro-7-methyl-2*H*-1,4-benzoxazine 14i:

Solid; IR (KBr) ν cm^{-1} 1635. ^{1}H NMR (CDCl$_3$, 400 MHz) δ ppm 2.33 (s, 3H), 3.52 (t, 2H, *J* = *14.0* Hz), 4.32 (t, 2H, *J* = *8.1* Hz), 4.69 (s, 2H), 6.49 (s, 1H, ArH), 6.45 (d, 1H, *J* = *7.2* Hz), 6.61 (d, 1H, *J* = *7.2* Hz), 7.59 (s, 2H, ArH), 11.74 (bs, 1H). ^{13}C NMR (CDCl$_3$, 100 MHz) δ ppm 24.0, 56.1, 59.2, 73.1, 114.0, 114.9, 117.5, 120.2, 128.5, 129.2, 138.8, 140.2, 141.7, 143.0. *m/z* =347.12. Calcd for $C_{17}H_{15}Cl_2N_3O$ is C, 58.63; H, 4.34; N, 12.07%; found: C, 58.60; H, 4.32; N, 12.05%.

4-((6-fluoro-1*H*-benzoimidazol-2-yl)methyl)-3,4-dihydro-5-methyl-2*H*-1,4-benzoxazine 14j:

Solid; IR (KBr) ν cm^{-1} 1623. ^{1}H NMR (CDCl$_3$, 400 MHz) δ ppm 2.31 (s, 3H), 3.54 (t, 2H, *J* = *14.0* Hz), 4.27 (t, 2H, *J* = *8.3* Hz), 4.73 (s, 2H), 6.57–6.62 (m, 3H, ArH), 6.98 (d, 1H, *J* = *7.1* Hz), 7.32 (s, 1H, ArH), 7.53 (d, 1H, *J* = *7.1* Hz), 11.91 (bs, 1H). ^{13}C NMR (CDCl$_3$, 100 MHz); δ ppm 17.5, 54.7, 59.6, 72.7, 103.1, 109.7, 112.9, 115.9, 118.6, 121.7, 127.5, 130.2, 135.3, 140.2, 141.9, 142.9, 157.7. *m/z* = 297.11. Calcd for $C_{17}H_{16}FN_3O$ is C, 68.67; H, 5.42; N, 14.13%; found: C, 68.69; H, 5.46; N, 14.18%.

REFERENCES:

1. ELLIS,G.P. *Synthesis of fused Heterocycles*, John Wiley and Sons Ltd, 1987 pp 55-57
2. (a) Hietala, P. K.; Virtanen, A. I. *Acta Chem. Scand.* **1960**, *14*, 502-506. (b) Coults, R. T.; Hindmarsh, K. W. *Can. J. Pharm. Sci.* **1966**, 11-17. (c) Chatterjee, A.; Basa, S. C. *Chem. Ind.* **1969**, *11*, 328-332. (d) Hofman, J.; Hofmanova, O. *Eur. J. Biochem.* **1969**, *8*, 109-112. (e) Nagao, T.; Otsuka, H.; Kohda, H.; Sato, T.; Yamasaki, K. *Phytochemistry* **1985**, *24*, 2959-2962. (f) Otsuka, H.; Hirai, Y.; Nagao, T.; Yamasaki, K. *J. Nat. Prod.* **1988**, *51*, 74-79. (g) Neimeyer, H. M. *Phytochemistry* **1988**, *27*, 3349-3353. (I) Lyans, P. C.; Hipskind, H. D.; Wood, K. V.; Nicholson, R. L. *J. Agric. Food Chem.* **1988**, *36*, 57-63. (j) Chatterjee, A.; Sharma, N. J. Banerji, J.; Basa,S. C. *Ind. J. Chem., Sect. B.* **1990**, *29*, 132-135. (k) Ozden, S.; Ozden, T.;Attila, I.; Kucukislamoglu, M.; Okatan, A. *J. Chromatogr.* **1992**, *609*, 402-405. (l) Hartenstein, H.; Sicker, D. *Phytochemistry* **1994**, 827-832. (m) Hartenstein, H.; Klein, J.; Sicker, D. *Indian J. Heterocycl. Chem.* **1993**, *2*, 151-157.
3. Matzanke N.; Lowe W.; Perachon S.; Sokoloff P.; Schwartz J.-C.; Stark H. *Eur. J. Med. Chem.*, **1999**, 34, 791-798.
4. Fukuda, T.; Setoguchi, M.; Inaba, K.; Shoji, H.; Tahara, T. *Eur. J. Pharmacol.* **1991**, *196*, 299-307.
5. Empfield, J. R.; Russell, K. Potassium Channel Openers. In *Ann. Rep. Med. Chem.*; 1995; Chapter 9, Vol. 30, p 81-89.
6. Hirata, T.; Saito, H.; Tomioka, H.; Sato, K.; Jidoi, J.; Hosoe, K.; Hidaka, T. *Antimicrob. Agents Chemother.* **1995**, *39*, 2295-2301.

7. Matsuoka, H.; Ohi, N.; Mihara, M.; Suzuki, H.; Miyamoto, K.; Maruyama, N.; Tsuji, K.; Kato, N.; Akimoto, T.; Takeda, Y.; Yano, K.;Kuroki, T. *J. Med. Chem.* **1997**, *40*, 105-109.

8. (a) Hayakawa, I.; Atarashi, S.; Yokohama, S.; Imamura, M.; Sakano, K.; Furukawa, M. *Antimicrob. Agents Chemother.* **1986**, *29*, 163-167. (b) Atarashi, S.; Yokohama, S.; Yamazaki, U.; Sakano, K.; Imamura, M.; Hayakawa, I. *Chem. Pharm. Bull.* **1987**, *35*, 1896-1901. (c) Mitscher, L. A.; Gharma, P. N.; Chu, D. T. W.; Shen, L. L.; Pernet, A.G. *J. Med. Chem.* **1987**, *30*, 2283-2287. (d) Atarashi, S.; Tsurumi, H.; Fujiwara, T.; Hayakawa, I. *J. Heterocycl. Chem.* **1991**, *28*, 329-331.

9. Kosemura, S.; Yamamura, S.; Anai, T.; Hasegawa, K. *Tetrahedron Lett.* **1994**, *35*, 8221-8224.

10. Largeron, M.; Lockhart, B.; Pfeiffer, B.; Fleury, M. B. *J. Med. Chem.* **1999**, *42*, 5043-5052.

11. Michihiro, O., Ryoji, H., Masatumi, I. and Hiroshi,U. *PT CT Intl appl .Wo* **2004,** 52, 871-882.

12. Touzeau, F.; Arrault, A.; Guillaumet, G.; Scalbert, E.; Pfeiffer, B.; Rettori, M.-C.; Renard, P.; Merour, J.-Y. *J. Med. Chem.* **2003**, 46, 1962-1979

13. (a) Combs, D. W.; Rampulla, S. C.; Bell, S. C.; Klaubert, D. H.; Tobia,A. J.; Falotico, R.; Haertlein, B.; Lakas-Weiss, C.; Moor, J. B., *J. Med. Chem.***1990**, *33*, 380-386. (b) . Iakovou, K.; Kazanis, M.; Vavayannis, A.; Bruni, G.; Romeo, M.R.; Massarelli, P.; Teramoto, S.; Fujiki, H.; Mori, T. *Eur. J. Med. Chem.* **1999**, *34*, 903-917.

CHAPTER III

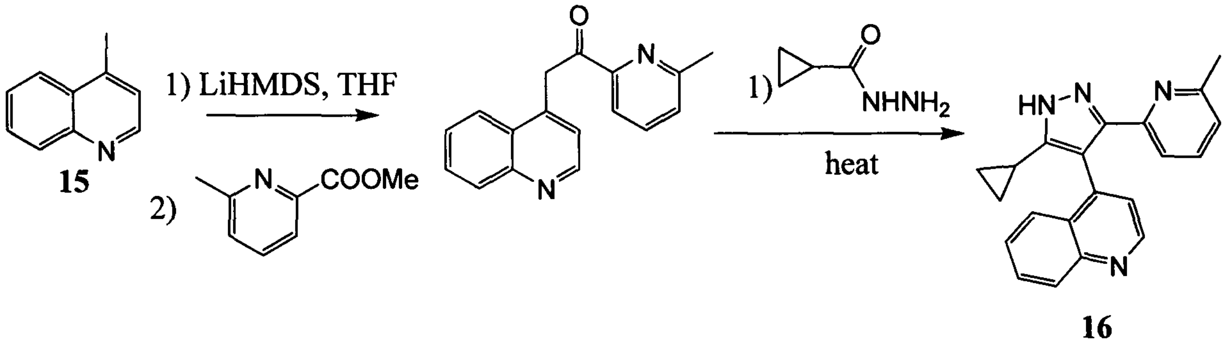
“Synthesis of Substituted 4-(5-alkyl-thiazol-2-ylmethyl)-3,4-dihydro-2*H*-1,4-benzoxazines and 5-(2,3-dihydro-1,4-benzoxazin-4-ylmethyl)-4-methyl-1-phenyl-1*H*-pyrazol-3-ylamine.”

INTRODUCTION

Benzoxazines have been used as intermediates in the synthesis of many heterocyclic structures of biological importance. These derivatives have been shown to be selective serotonin reuptake inhibitors. They have also shown activities towards 5-HT$_{1A}$ receptor while the 1,4-benzoxazine imidazole derivatives have shown *in vivo* activities against a murine experimental model of candidiasis. Some of the benzoxazines were most effective in promoting HUVEC apoptosis and inhibiting A549 cell proliferation.[1-4] Some of the *N*-substituted benzoxazines have been reported to cure thrombi related diseases, for instance platelet aggregation, thrombosis, myocardial infarction[5] etc. While derivatives of benzomorpholine have been incorporated to show hypotensive/anti-hypertensive effectiveness,[6] as well as potential dopamine D$_3$ receptor ligands and inhibitions of cardiac phosphodiestrase (PDE) fraction *in vitro* and for positive inotropic activity *in vivo.*[7] They also tend to inhibit oxidative stress mediated neuronal degeneration in neuronal cell cultures.[8,9]

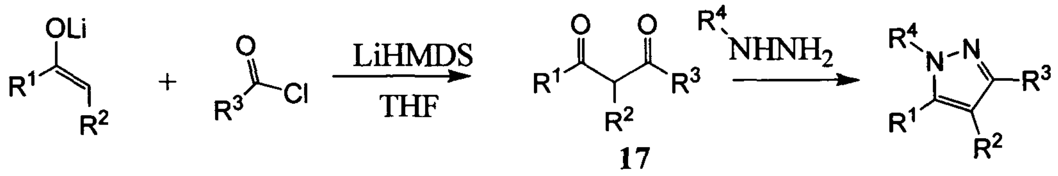
The pyrazole and thiazole ring systems are common structural motifs in a number of biologically active molecules. Thiazole ring systems originate in nature as a consequence of peptide modification containing cysteine side chain residue and are the product of cyclodehydration and redox reactions. More recently, extensive studies have been focused on aryl pyrazoles for exhibiting cyclooxygenase-2 (COX-2) and non-nucleoside HIV-1 reverse transcriptase inhibitory properties. This structure has found applications in drug development for the treatment of allergies, hypertension, schizophrenia, inflammation, bacterial and HIV7 infections. Aminothiazoles are known to be ligands of estrogen receptors as well as a novel class of adenosine receptor antagonists whereas other analogues are used as fungicides, inhibiting in vivo growth of Xanthomonas and as an ingredient of herbicides or as schistosomicidal and anti helmintic drugs.[10-15]

The synthesis of pyrazole and amino thiazole derivatives are well documented and their methods of preparation are manifold and varied. Sawyer and coworkers[10c] reported a very interesting procedure for the synthesis of substituted pyrazole from Lepidine **15**. Lepidine was deprotonated and condensed with an appropriate picolinic ester to provide the intermediate ketone, which was then treated directly with DMF dimethyl acetal and hydrazine to provide final product **16** (Scheme 7).



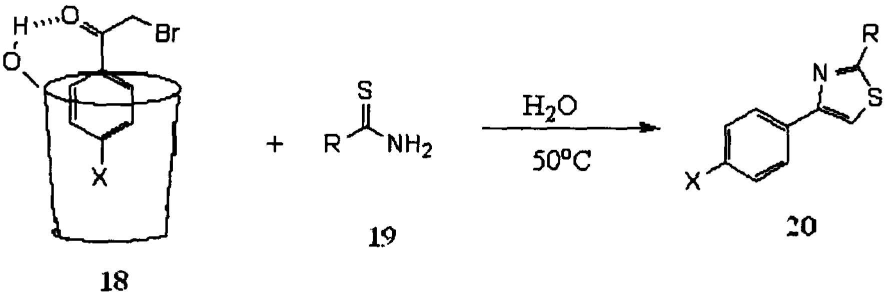
Scheme 7

1,3-diketones are the most common reagent for the synthesis of pyrazoles which was aptly demonstrated by Heller and coworker.[12] They reported a rapid and a general one-pot method for the synthesis of Pyrazoles using 1,3-diketones **17** which were synthesized directly from ketones and acid chlorides and were then converted in-situ into pyrazoles by the addition of hydrazine (Scheme **8**).



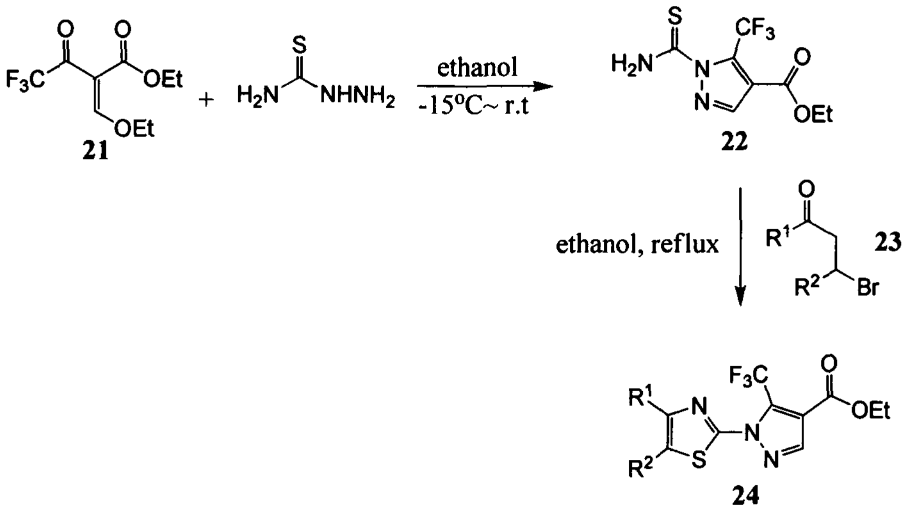
Scheme 8

Amongst various methodologies reported for the synthesis of thiazoles, solid supported synthesis have been widely used to generate small organic molecule libraries and solution phase preparation of 2-amino-thiazole combinatorial libraries have been reported in DMF as well as in 1,4-dioxane. Roa and coworkers[11] reported the aqueous phase synthesis of thiazoles and aminothiazoles in the presence of β-cyclodextrin (Scheme **9**). Reaction were carried out by the in situ formation of the β-cyclodextrin complex of the phenacyl bromide **18** in water followed by the addition of thioamide or thiourea **19** to give the corresponding thiazole or aminothiazole **20** respectively.



Scheme 9

Tice and co-workers[13] designed and synthesized library of 1-(2-thiazolyl)-5-(trifluoromethyl)pyrazole-4-carboxamides (scheme **10**). Ethyl 2-ethoxymethylene-3-oxo-4,4,4-trifluorobutanoate **21** was condensed with thiosemicarbazide in ethanol at -15°C to room temperature to obtain ethyl 1-thiocarbonyl-5-trifluoromethyl-1*H*-pyrazole-4-carboxylate **22** which was reacted with bromomethyl ethyl ketone **23** in refluxing ethanol to obtain ethyl 5-(trifluoromethyl)-1-(4,5-dialkylthiazol-2-yl)-1*H*-pyrazole-4-carboxylate **24**.



Scheme 10

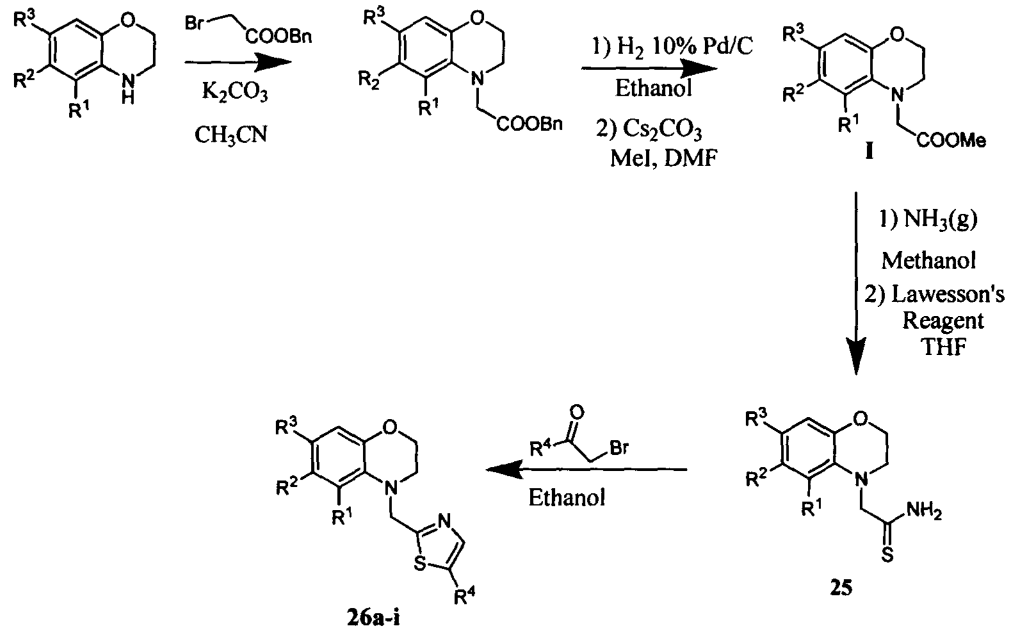
Our literature survey revealed that benzoxazines bearing pyrazole and thiazole rings on the *N*-atom have not been reported inspite of the fact that these two heterocyclic systems played an important role in drug development.

RESULTS AND DISCUSSIONS:

For our investigation we aimed at synthesizing *N*-substituted benzoxazine derivatives of biological interest, we wanted to introduce different heterocyclic ring systems on the *N*-atom of the benzoxazines..

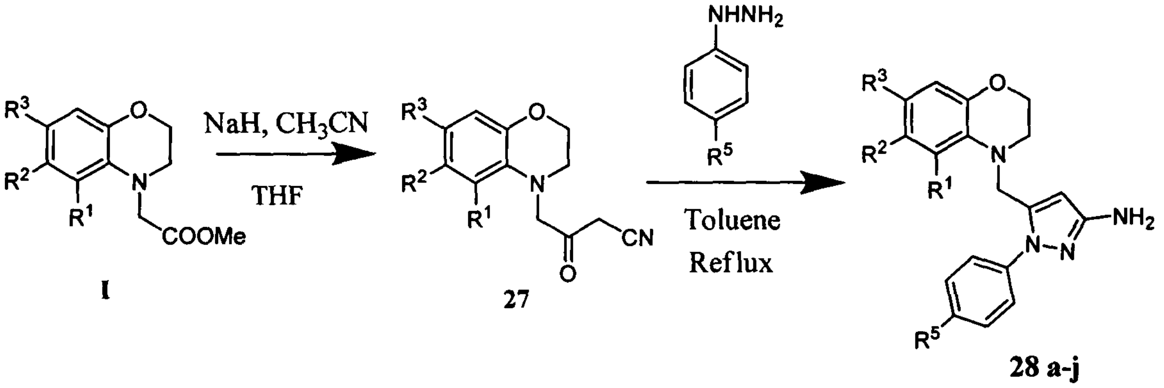
The synthesis of 3,4-Dihydro-1,4-2*H*-benzoxazine was carried out from 2-aminophenols and 1,2-dibromoethane using K_2CO_3 in DMF which was then subjected to *N*-substitution using alkyl bromide. Subsequent de-benzylation and esterification yielded (2,3-dihydro-1,4-benzoxazin-4-yl)-acetic acid methyl ester **I.**[16] Thus, the synthesis of 4-(5-alkyl-thiazol-2-ylmethyl)-3,4-dihydro-2*H*-1,4-benzoxazines and 5-(2,3-dihydro-1,4-benzoxazin-4-ylmethyl)-4-methyl-1-phenyl-1*H*-pyrazol-3-ylamine starting from (2,3-dihydro-1,4-benzoxazin-4-yl)-acetic acid methyl ester was achieved.

The compounds **26a-i** (Table **3**) were prepared by first converting the methyl ester derivatives to amide derivatives by passing NH_3 (g) through the solution of **25** at 0~5 °C and then to the corresponding thioamides using Lawesson's reagent (Scheme **11**). Further treatment with 1-Bromo-alkan-2-one in ethanol gave the desired products in about 53~64% yields.



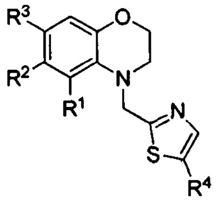
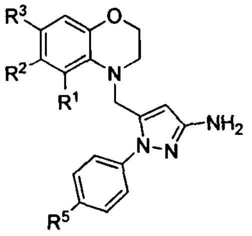
Scheme 11

The compounds **28a-j** (Table 3) was prepared by first converting the methyl ester derivatives to the corresponding butyronitrile derivatives using NaH and acetonitrile. Further treatment with phenyl hydrazine yielded the desired products in 41~62% yields (Scheme 12). Catalytic amounts of KF increased the rate of the reaction and hence the yield.



Scheme 12

Table 3: Preparation of *N*-substituted 3,4-dihydro-2*H*-1,4-benzoxazines

Entry	Product(**26a-i**) 	Yield **26a-i** (%)	Product(**28a-j**) 	Yield **28a-j** (%)
a	R^1=H, R^2=H, R^3=H R^4=Me	64	R^1=H, R^2=H, R^3=H, R^5=H	59
b	R^1=H, R^2=H, R^3=H R^4=CH_2CH_3	61	R^1=H, R^2=H, R^3=H, R^5=Me	57
c	R^1=H, R^2=H, R^3=Me, R^4=Me	53	R^1=Me, R^2=H, R^3=H, R^5=H	59
d	R^1=H, R^2=H, R^3=Me, R^4=CH_2CH_3	54	R^1=H, R^2= Me, R^3=H, R^5=H	61
e	R^1=H,R^2=Me,R^3=H, R^4=CH_2CH_3	61	R^1=H, R^2=F, R^3=H, R^5=H	62
f	R^1=Me, R^2=H, R^3=H, R^4=CH_2CH_3	57	R^1=H, R^2=CF_3, R^3=H, R^5=H	45
g	R^1=H, R^2=H, R^3=H, R^4=Ph	58	R^1=H, R^2=Cl, R^3=H, R^5=Me	41
h	R^1=H, R^2=Me, R^3=H R^4=Ph	62	R^1=H, R^2=Me, R^3=H, R^5=Me	47
i	R^1=Me, R^2=H, R^3=H R^4=Ph	62	R^1=H, R^2=F, R^3=H, R^5=Me	46
j			R^1=H, R^2=H, R^3=Me, R^5=H	61

EXPERIMENTAL:

Melting points were obtained on a Thomas Hoover capillary melting point apparatus and are uncorrected. Carbon, hydrogen and nitrogen analysis were performed with a Perkin-Elmer 2400 series II instrument. IR spectra in BOMEM DA-8 FT-IR spectrophotometer. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AMX 400 spectrometer using $CDCl_3$ or DMSO-d_6 as the solvent. Chemical shifts are reported in ppm from internal tetramethylsilane and are given on the δ scale. The following abbreviations are used to describe peak patterns when appropriate: s = singlet, d = doublet, t = triplet, m = multiplet. Positive-ion and negative-ion electrospray ionization (ESI) mass spectra were measured on an ion trap analyzer Esquire 3000 (Bruker Daltonics).

All reactions were monitored by TLC on glass plates coated with silica gel (ACME's) containing 13% calcium sulphate as binder and visualization of compounds was accomplished by exposure to iodine vapour or by spraying acidic potassium permanganate solution or 2% ninhydrin solution. Column chromatography was carried out using ACME's silica gel.

Chemicals, reagents and solvents:

Dry solvents were obtained by distillation under N_2 atomsphere with appropriate dehydrating agents. The commercial available chemicals were used without further purification.

General procedure for the synthesis of substituted 4-(5-alkyl-thiazol-2-ylmethyl)-3,4-dihydro-2*H*-1,4-benzoxazine:

The methyl ester derivative (**I**) was first dissolved in methanol, the reaction mixture was cooled in ice and NH_3 gas was passed through it for 10 min. The reaction mixture was stirred overnight at R.T.; resulting in separation of dirty white solids which was separated by filtration to yield the amide derivative. The crude product was washed with hexane to *yield the pure product.* IR *(KBr)* v cm^{-1} *3330 (m) and 3050 (m)* ($CONH_2$). H^1 NMR (DMSO-d_6, 400 MHz) δ ppm 3.3 (t, 2H, J = *14.1* Hz), 4.07 (s, 2H,), 4.32 (t, 2H, J = *9.1* Hz), 6.24 (b, 2H), 6.46~6.5 (m, 4H). Calc. for $C_{10}H_{12}N_2O_2$ C, 62.49; H, 6.29; N, 14.57 %; observed were C, 62.50; H, 6.28; N, 14.56 %.

The amide derivative was then dissolved in Dry THF and treated with Lawesson's reagent (0.5eq) and stirred overnight under N_2 atm. The reaction upon completion was evaporated in vacuum and extracted with ethylacetate. The complete organic extract was dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography using ethyl acetate and hexane (1:10) as an eluent to yield the desired product. IR (KBr) v cm^{-1} 1175. The 2-(2,3-Dihydro-1,4-benzoxazin-4-yl)-thioacetamide was then refluxed with 1-bromo butan-2-one in ethanol, the reaction was monitored using TLC. The reaction upon completion was evaporated in vacuum and extracted with DCM. The complete organic extract was dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography using ethyl acetate and hexane (1:20) as an eluent to yield the desired product

4-((5-ethylthiazol-2-yl)methyl)-3,4-dihydro-2*H*-1,4-benzoxazine 26b:

IR (KBr) ν cm^{-1} 1725 (C=N stretching). ^1H NMR ($CDCl_3$, 400 MHz) δ ppm 1.17 (t, 3H, *J* =14.2 Hz), 3.3~3.31 (q, 2H, *J* = *8.6* Hz), 3.82 (t, 2H, *J* =*14.3* Hz), 4.27 (t, 2H, *J* = *8.9* Hz), 5.72 (s, 2H), 6.46~6.65 (m, 4H), 7.04 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 15.6, 22.8, 57.6, 60.2 (NCH_2), 73.1 (OCH_2), 112.8, 116.8, 117.3, 119.5, 130.2, 133.4, 140.1, 141.3, 166.1. *m/z* = 261.26. Calc. for $C_{14}H_{16}N_2OS$ C, 64.58; H, 6.19; N, 10.76 %; observed were C, 64.60; H, 6.18; N, 10.75 %.

3,4-dihydro-4-((5-methylthiazol-2-yl)methyl)-2*H*-1,4-benzoxazine 26a:

IR (KBr) ν cm^{-1} 1720 (C=N stretching). ^1H NMR ($CDCl_3$, 400 MHz) δ ppm 2.37 (s, 3H), 3.81 (t, 2H, *J* =*14.3* Hz), 4.22 (t, 2H, *J* =*8.9* Hz), 4.72 (s, 2H), 6.46~6.65 (m, 4H, ArH), 7.23 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 14.2, 58.6, 60.2 (NCH_2), 73.1 (OCH_2), 113.8, 115.8, 118.3, 120.5, 130.6, 133.7, 140.1, 143.3, 165.4. *m/z* = 247.26. Calc. for $C_{13}H_{14}N_2OS$ C, 63.39; H, 5.73; N, 11.37 %; observed were C, 63.41; H, 5.75; N, 11.36 %.

3,4-dihydro-7-methyl-4-((5-methylthiazol-2-yl)methyl)-2*H*-1,4-benzoxazine 26c:

IR (KBr) ν cm^{-1} 1722 (C=N stretching) ^1H NMR ($CDCl_3$, 400 MHz) δ ppm 2.32 (s, 3H), 2.47 (s, 3H), 3.84 (t, 2H, *J* =*12.3* Hz), 4.22 (t, 2H, *J* =*9.1* Hz), 4.76 (s, 2H), 6.46~6.65 (m, 3H, ArH), 7.31 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 14.5, 21.7, 58.4, 60.2 (NCH_2), 74.1 (OCH_2), 113.5, 115.9, 121.5, 127.1, 127.8, 133.7, 140.1, 143.3, 165.0. *m/z* = 247. Calc. for $C_{14}H_{16}N_2OS$ C, 64.58; H, 6.19; N, 10.76 %; observed were C, 64.60; H, 6.20; N, 10.75 %.

4-((5-ethylthiazol-2-yl)methyl)-3,4-dihydro-7-methyl-2*H*-benzoxazine 26d:

IR (KBr) ν cm^{-1} 1721 (C=N stretching). ^1H NMR ($CDCl_3$, 400 MHz) δ ppm 1.18 (t, 3H, *J* =14.1 Hz), 2.31 (s, 3H), 3.29~3.39 (q, 2H, *J* =*8.7* Hz), 3.82 (t, 2H, *J* =*14.3* Hz), 4.27 (t, 2H, *J =14.1* Hz), 5.69 (s, 2H), 6.41(s, 1H), 6.38 (d, 1H, *J =7.2* Hz), 6.47 (d, 1H, *J =7.2* Hz), 7.11 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 15.5, 21.9, 22.7, 57.7, 60.1 (NCH_2), 73.3 (OCH_2), 112.8, 113.3, 119.9, 127.1, 130.4, 133.5, 140.2, 141.4, 166.1. *m/z* = 274.26. Calc. for $C_{15}H_{18}N_2OS$ C, 65.66; H, 6.61; N, 10.21 %; observed were C, 65.64; H, 6.60; N, 10.22 %.

4-((5-ethylthiazol-2-yl)methyl)-3,4-dihydro-6-methyl-2*H*-1,4-benzoxazine 26e:

IR (KBr) ν cm^{-1} 1718 (C=N stretching). ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 1.15 (t, 3H, *J =14* Hz), 3.29~3.33 (q, 2H, *J =8.7* Hz), 3.80 (t, 2H, *J =14.2* Hz), 4.26 (t, 2H, *J =14* Hz), 5.69 (s, 2H), 6.51~6.60 (m, 4H), 7.15 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 15.7, 22.9, 57.4, 60.2 (NCH_2), 73.4 (OCH_2), 113.1, 114.3, 118.9, 120.5, 130.9, 133.9, 140.6, 141.9, 166.3. *m/z* = 261.10. Calc. for $C_{14}H_{16}N_2OS$ C, 64.58; H, 6.19; N, 10.76 %; observed were C, 64.60; H, 6.18; N, 10.74 %.

4-((5-ethylthiazol-2-yl)methyl)-3,4-dihydro-5-methyl-2*H*-1,4-benzoxazine 26f:

IR (KBr) ν cm^{-1} 1719 (C=N stretching). ^{1}H NMR ($CDCl_3$, 100 MHz) δ ppm 1.15 (t, 3H, *J* =14.1 Hz), 2.30 (s, 3H), 3.34~3.39 (q, 2H, *J =8.9 Hz*), 3.84 (t, 2H, *J =14.2 Hz*), 4.29 (t, 2H, *J =14.0 Hz*), 5.70 (s, 2H), 6.41~ 6.47 (m, 3H), 7.16 (s, 1H). ^{13}C NMR ($CDCl_3$, 400 MHz) δ ppm 15.5, 16.9, 22.5, 57.5, 60.2 (NCH_2), 73.6 (OCH_2), 112.8, 119.9, 120.7, 127.1, 130.4, 130.9, 133.5, 141.4, 165.8. *m/z* = 275.12. Calc. for $C_{15}H_{18}N_2OS$ C, 65.66; H, 6.61; N, 10.21 %; observed were C, 65.64; H, 6.62; N, 10.20 %.

3,4-dihydro-4-((5-phenylthiazol-2-yl)methyl)-2*H*-1,4-benzoxazine 26g:

IR (KBr) ν cm^{-1} 1720 (C=N stretching). ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 3.84 (t, 2H, *J =14.0 Hz*), 4.20 (t, 2H, *J =9.0 Hz*), 4.76 (s, 2H), 6.46~6.65 (m, 4H, ArH), 7.23~7.32 (m, 5H, ArH), 8.21 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 14.5, 21.7, 58.4, 60.2 (NCH_2), 74.1 (OCH_2), 113.5, 115.9, 121.5, 127.1, 127.8, 133.7, 140.1, 143.3, 165.0. *m/z* = 247. Calc. for $C_{14}H_{16}N_2OS$ C, 64.58; H, 6.19; N, 10.76 %; observed were C, 64.61; H, 6.21; N, 10.75 %.

3,4-dihydro-6-methyl-4-((5-phenylthiazol-2-yl)methyl)-2*H*-1,4-benzoxazine 26h:

IR (KBr) ν cm^{-1} 1722 (C=N stretching) ^1H NMR ($CDCl_3$, 400 MHz) δ ppm 2.34 (s, 3H), 3.80 (t, 2H, *J =14* Hz), 4.32 (t, 2H, *J =14.1* Hz), 5.76 (s, 2H), 6.33 (s, 1H), 6.39 (d, 1H, *J =7.8* Hz), 6.47 (d, 1H, *J =7.8* Hz), 7.39~7.45 (m, 5H), 7.89 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 23.5, 57.9, 60.7 (NCH_2), 73.9 (OCH_2), 112.8, 114.9, 118.7, 126.1, 128.2, 129.1, 130.3, 135.7, 133.5, 141.4, 142.8, 147.3, 166.8, *m/z* = 322.11. Calc. for $C_{19}H_{18}N_2OS$ C, 70.78; H, 5.63; N, 8.69 %; observed were C, 70.77; H, 5.61; N, 8.68 %.

3,4-dihydro-5-methyl-4-((5-phenylthiazol-2-yl)methyl)-2*H*-1,4-benzoxazine 26i:

IR (KBr) ν cm^{-1} 1715 (C=N stretching) ^1H NMR ($CDCl_3$, 400 MHz) δ ppm 2.31 (s, 3H), 3.82 (t, 2H, *J =14* Hz), 4.31 (t, 2H, *J =14.1* Hz), 5.79 (s, 2H), 6.43~6.49 (m, 3H), 7.36~7.42 (m, 5H), 7.91(s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 15.5, 57.9, 60.7 (NCH_2), 73.9 (OCH_2), 112.8, 119.9, 120.7, 126.1, 127.1, 128.2, 129.1, 130.9, 135.4, 133.5, 141.4, 147.3, 166.8, *m/z* = 322.12. Calc. for $C_{19}H_{18}N_2OS$ C, 70.78; H, 5.63; N, 8.69 %; observed were C, 70.76; H, 5.62; N, 8.70 %.

General procedure for the synthesis of 5-(2,3-dihydro-1,4-benzoxazin-4-ylmethyl)-4-methyl-1-phenyl-1*H*-pyrazol-3-ylamine:

It involves the synthesis of butyronitrile derivative from the methyl ester (**1**) using acetonitrile (1.5 eq) and NaH (1.5 eq) in THF under N_2 atmosphere. The NaH was dissolved in THF and acetonitrile was added drop wise at 0 °C. The reaction mixture was allowed to stir at R.T for ½ h and followed by drop wise addition of (**I**) solution in THF at 0 °C. The reaction was then stirred at r.t for 3h. The reaction upon completion, the solvent was evaporated and work-up using ethyl acetate, the complete organic extracts were dried over Na_2SO_4 and evaporated to yield the crude product which was purified by column chromatography using ethyl acetate and hexane (1:20). IR (KBr) ν cm^{-1} 2242 (CN stretching). ^1H NMR ($CDCl_3$, 400 MHz) δ ppm 3.61 (s, 2H), 3.82~3.86 (m, 2H), 4.24~4.26 (m, 2H), 4.56 (s, 2H), 6.75~6.84 (m, 4H). Calc. for $C_{12}H_{12}N_2O_2$ C, 66.65; H, 5.59; N, 12.96 %; observed were C, 66.64; H, 5.60; N, 12.94 %. The butyronitrile derivative was then refluxed with substituted phenyl hydrazine (1.2 eq) for 4~5 hrs. The reaction upon completion was evaporated in vacuum and worked-up using DCM. The complete organic was dried over Na_2SO_4 and evaporated to yield the crude product which was purified by column chromatography using Methanol and DCM (1:50) as an eluent.

3,4-dihydro-4-((1-phenyl-1*H*-pyrazol-5-yl)methyl)-2*H*-1,4-benzoxazine 28a:

IR (KBr) ν cm^{-1} 3420 (NH_2 stretching). ^1H NMR (DMSO-d_6, 400 MHz), δ ppm 3.84~3-86 (t, 2H, $J = 14$ Hz), 4.25~4.27 (t, 2H, $J = 8.9$ Hz), 5.56 (s, 2H), 6.4~6.84 (m, 4H) 7.3~7.5 (m, 5H) 7.9 (s, 1H) 8.2 (b, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 50.1, 60.2 (NCH_2), 73.1 (OCH_2), 94.8, 112.8, 116.8, 117.3, 118.8, 119.5, 126.5, 129.1, 130.2, 135.6, 139.8, 141.1, 164.3. *m/z* = 307. Calc. for $C_{18}H_{18}N_4O$; C, 70.57; H, 5.92; N, 18.29 %; observed were C, 70.59; H, 5.91; N, 18.3 %.

3,4-dihydro-4-((1-p-tolyl-1*H*-pyrazol-5-yl)methyl)-2*H*-1,4-benzoxazine 28b:

IR (KBr) ν cm^{-1} 3412 (NH_2 stretching). ^1HNMR (DMSO-d_6, 400 MHz), δ ppm 2.36 (s, 3H), 3.86 (t, 2H, $J = 14$ Hz), 4.27 (t, 2H, $J = 8.9$ Hz), 5.42 (s, 2H), 6.35 (s, 1H), 6.48~6.64 (m, 4H) 7.35~7.51 (m, 4H, ArH), 8.12 (b, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 21.2, 50.2, 59.2 (NCH_2), 74.1 (OCH_2), 94.8, 113.8, 115.8, 117.9, 118.3, 121.5, 129.5, 130.8, 135.2, 136.1, 136.9, 143.1, 164.1. *m/z* = 321. Calc. for $C_{19}H_{20}N_4O$ C, 71.23; H, 6.29; N, 17.49 %; observed were C, 71.25; H, 6.31; N, 17.51 %.

3,4-dihydro-5-methyl-4-((1-phenyl-1*H*-pyrazol-5-yl)methyl)-2*H*-1,4-benzoxazine 28c:

IR (KBr) ν cm^{-1} 3412 (NH stretching). ^{1}H NMR (DMSO-d_6, 400 MHz), δ ppm 2.42 (s, 3H), 3.81 (t, 2H, *J = 9.8* Hz), 4.20 (t, 2H, *J = 9.0* Hz), 5.22 (s, 2H), 6.31 (s, 1H), 6.40~6.44 (m, 3H) 7.31~7.45 (m, 5H, ArH), 7.02 (b, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 13.2, 50.4, 59.6 (NCH_2), 73.9 (OCH_2), 94.9, 112.8, 118.0, 118.6, 121.8, 126.2, 129.2, 131.1, 136.1, 136.9, 139.9, 143.1, 163.8. *m/z* = 319. Calc. for $C_{19}H_{20}N_4O$ C, 71.23; H, 6.29; N, 17.49 %; observed were C, 71.24; H, 6.30; N, 17.48 %.

3,4-dihydro-6-methyl-4-((1-phenyl-1*H*-pyrazol-5-yl)methyl)-2*H*-1,4-benzoxazine 28d:

IR (KBr) ν cm^{-1} 3421 (NH stretching). ^{1}H NMR (DMSO-d_6, 400 MHz), δ ppm 2.47 (s, 3H), 3.85 (t, 2H, *J = 9.5* Hz), 4.23 (t, 2H, *J = 9.1* Hz), 5.27 (s, 2H), 6.39 (s, 1H), 6.41 (s, 1H), 6.47 (d, 1H, *J = 7.2* Hz), 6.52 (d, 1H, *J = 7.2* Hz), 7.31~7.45 (m, 5H, ArH), 7.06 (b, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 23.2, 32.3, 59.3 (NCH_2), 74.1 (OCH_2), 92.9, 113.8, 114.5, 115.1, 118.6, 126.2, 129.2, 130.1, 136.1, 137.9, 139.9, 143.1, 160.8. *m/z* = 320.16 Calc. for $C_{19}H_{20}N_4O$ C, 71.23; H, 6.29; N, 17.49 %; observed were C, 71.22; H, 6.30; N, 17.47 %.

6-fluoro-3,4-dihydro-4-((1-phenyl-1*H*-pyrazol-5-yl)methyl)-2*H*-1,4-benzoxazine 28e:

IR (KBr) ν cm^{-1} 3420 (NH stretching). ^{1}H NMR (DMSO-d_6, 400 MHz), δ ppm 2.45 (s, 3H), 3.82 (t, 2H, *J = 9.5* Hz), 4.21 (t, 2H, *J = 9.1* Hz), 5.25 (s, 2H), 6.38 (s, 1H), 6.40 (s, 1H), 6.44 (d, 1H, *J*=7.1 Hz), 6.50 (d, 1H, *J*=7.1 Hz), 7.33~7.45 (m, 5H, ArH), 7.03 (b, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 32.9, 59.4 (NCH_2), 74.2 (OCH_2), 92.9, 103.7, 105.8, 116.1, 118.6, 126.2, 129.2, 136.1, 137.9, 138.9, 146.1, 154.1, 160.8. *m/z* = 324.16 Calc. for $C_{18}H_{17}FN_4O$ C, 66.65; H, 5.28; N, 17.27 %; observed were C, 66.63; H, 5.30; N, 17.26 %.

6-(trifluoromethyl)-3,4-dihydro-4-((1-phenyl-1*H*-pyrazol-5-yl)methyl)-2*H*-1,4-benzoxazine 28f:

IR (KBr) ν cm^{-1} 3427 (NH stretching). ^1H NMR (DMSO-d_6, 400 MHz), δ ppm 3.86 (t, 2H, *J* = *9.1* Hz), 4.24 (t, 2H, *J* = *9.2* Hz), 5.28 (s, 2H), 6.41 (s, 1H), 6.74 (s, 1H), 6.79 (d, 1H, *J* = *7.0* Hz), 6.85 (d, 1H, *J* = *7.0* Hz), 7.36~7.45 (m, 5H, ArH), 7.23 (b, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 33.1, 59.5 (NCH_2), 74.4 (OCH_2), 93.2, 110.5, 115.1, 116.0, 120.8, 124.1, 125.9, 129.2, 136.1, 137.9, 138.9, 144.1, 146.1, 160.8. *m/z* = 374.26. Calc. for $C_{19}H_{17}F_3N_4O$ C, 60.96; H, 4.58; N, 14.97 %; observed were C, 60.97; H, 4.60; N, 14.96 %.

6-chloro-3,4-dihydro-4-((1-p-tolyl-1*H*-pyrazol-5-yl)methyl)-2*H*-1,4-benzoxazine 28g:

IR (KBr) ν cm^{-1} 3439 (NH stretching). ^1H NMR (DMSO-d_6, 400 MHz), δ ppm 2.31 (s, 3H), 3.85 (t, 2H, *J* = *9.0* Hz), 4.21 (t, 2H, *J* = *9.1* Hz), 5.30 (s, 2H), 6.39 (s, 1H), 6.54 (s, 1H), 6.69 (d, 1H, *J* = *7.2* Hz), 6.75 (d, 1H, *J* = *7.2* Hz), 7.45 (d, 2H, *J* = *7.1* Hz), 7.48 (d, 2H, *J* = *7.1* Hz), 7.18 (bs, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 24.1, 33.5, 59.8 (NCH_2), 74.1 (OCH_2), 93.7, 115.1, 116.0, 119.2, 120.8, 125.9, 129.2, 136.1, 137.2, 139.9, 144.1, 145.2, 160.8. *m/z* = 354.16. Calc. for $C_{19}H_{19}ClN_4O$ C, 64.31; H, 5.40; N, 15.79 %; observed were C, 64.30; H, 5.41; N, 15.80 %.

3,4-dihydro-6-methyl-4-((1-p-tolyl-1*H*-pyrazol-5-yl)methyl)-2*H*-1,4-benzoxazine 28h:

IR (KBr) ν cm^{-1} 3424 (NH stretching). ^1H NMR (DMSO-d_6, 400 MHz), δ ppm 2.31 (s, 3H), 2.35 (s, 3H), 3.80 (t, 2H, *J* = *9.0* Hz), 4.23 (t, 2H, *J* = *9.0* Hz), 5.31 (s, 2H), 6.35 (s, 1H), 6.44 (s, 1H), 6.51 (d, 1H, *J* = *7.1* Hz), 6.59 (d, 1H, *J* =*7.1* Hz), 7.42 (d, 2H, *J* = *7.0* Hz), 7.49 (d, 2H, *J* = *7.0* Hz), 7.21 (b, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 24.1, 33.5, 59.8

(NCH_2), 74.1 (OCH_2), 93.7, 114.5, 115.5, 119.7, 120.8, 129.2, 130.3, 136.1, 137.2, 139.1, 144.1, 145.1, 160.8. *m/z* = 335.16 Calc. for $C_{20}H_{22}N_4O$ C, 71.83; H, 6.63; N, 16.75 %; observed were C, 71.82; H, 6.62; N, 16.77 %.

6-fluoro-3,4-dihydro-4-((1-p-tolyl-1*H*-pyrazol-5-yl)methyl)-2*H*-1,4-benzoxazine 28i:

IR (KBr) ν cm^{-1} 3429 (NH stretching). ^1H NMR (DMSO-d_6, 400 MHz), δ ppm 2.32 (s, 3H), 3.82 (t, 2H, *J* = *9.0* Hz), 4.24 (t, 2H, *J* = *9.0* Hz), 5.32 (s, 2H), 6.41 (s, 1H), 6.56 (s, 1H), 6.70 (d, 1H, *J* = *7.0* Hz), 6.75 (d, 1H, *J* = *7.0* Hz), 7.45 (d, 2H, *J* = *7.1* Hz), 7.48 (d, 2H, *J* = *7.1* Hz), 7.23 (bs, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 24.3, 33.7, 59.9 (NCH_2), 74.5 (OCH_2), 93.4, 115.1, 116.0, 119.2, 120.8, 125.9, 129.2, 136.1, 137.2, 139.9, 145.1, 144.1, 160.8. *m/z* = 339.16 Calc. for $C_{19}H_{19}FN_4O$ C, 67.44; H, 5.66; F, 5.61; N, 16.56 %; observed were C, 67.43; H, 5.60; N, 16.58 %.

3,4-dihydro-6-methyl-4-((1-phenyl-1*H*-pyrazol-5-yl)methyl)-2*H*-benzoxazine 28j:

IR (KBr) ν cm^{-1} 3422 (NH stretching) ^1H NMR (DMSO-d_6, 400 MHz), δ ppm 2.45 (s, 3H), 3.85 (t, 2H, *J* =*9.0* Hz), 4.28 (t, 2H, *J* =*9.1* Hz), 5.32 (s, 2H), 6.37 (s, 1H), 6.41 (s, 1H), 6.47 (d, 1H, *J* =*7.1* Hz), 6.52 (d, 1H, *J* =*7.1* Hz), 7.36~7.45 (m, 5H, ArH), 7.16 (br, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 23.6, 32.6, 59.5 (NCH_2), 74.3 (OCH_2), 92.5, 113.9, 114.5, 115.1, 118.6, 126.2, 129.2, 130.1, 136.1, 137.9, 139.9, 143.1, 160.8. *m/z* = 321.21 Calc. for $C_{19}H_{20}N_4O$ C, 71.23; H, 6.29 %; N, 17.49; observed were C, 71.22; H, 6.30; N, 17.47 %.

REFERENCES:

1. Baxter, E. W.; Reitz, A. B. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 763-767.
2. Kotha, S.; Bindra, V.; Kuki, A. *Heterocycles.* **1994**, *38*, 5-12.
3. Lhoste, P.; Massacret, M.; Sinou, D. *Bull. Soc. Chim. Fr.* **1997**, *134*, 343-348.
4. Kajino, M.; Shibouta, Y.; Nishikawa, K.; Meguro, K. *Chem. Pharm. Bull.* **1991**, *39*, 2896-2901.
5. Guillaumet, G.; Loubinoux, B.; Coudert, G. *Tetrahedron Lett.* **1978**, *26*, 2287-2290.
6. Coudert, G.; Guillaumet, G.; Loubinoux, B. *Synthesis* **1979**, 541-549.
7. (a) Bartsch, H.; Kropp, W.; Pailer, M. *Monatsch. Chem.* **1979**, *110*, 267-273. (b). Bartsch, H.; Ofner, M.; Schwarz, O.; Thomann, W. *Heterocycles.* **1984**, *22*, 2789-2793.
8. (a) Kundu, N. G.; Chaudhuri, G.; Upadhyay, A. *J. Org. Chem.* **2001**, *66*, 20-25. (b).Banzatti, C.; Heidempergher, F.; Melloni P. *J. Heterocycl. Chem.* **1993**, *20*, 259-264.
9. Bourlot, A. S.; Sanchez, I.; Dureng, G.; Guillaumet, G.; Massingham, R.; Monteil, A.; Winslow, E.; Pujol, M. D.; Me'rour, J. Y. *J. Med. Chem.* **1998**, *41*, 3142-3150.
10. (a) Lewis. J. R. *Natural Prod. Rep* **1999**, *16*, 389-395 (b) Roy, R. S.; Gehsing, A. M.; Milne, J. C.; Belsaw, P. J; Walsh, C. *J. Natural Prod Rep.* **1999**, *16*, 249 (c) Swager, K. D.; Hess. *Tetrahedron. Lett.* **2005**, *46*, 5953-5955.
11. Rao, V. N.; Biju, A. T.; Kishore, M.; and Suresh, E.; *Org Letters.* **2006**, *8*, 2213-2219.
12. Stefen, T. H.; Swaminathan, R. N. *Org letters.* **2006**, *8*, 2675-2679.

13. Tice. T.; Cheng, G.; and Youhong, H. *J. Comb. Chem.* **2006**, *8*, 286-290.

14. Kost, A. N.; Grand, G.; *Adv. Heterocycl. Chem.* **1966**, *6*, 347-353.

15. Huang, J. H.; Choi, H. S.; Lee, D. H.; Yoo, S.; Gong, Y. D. *J. Comb. Chem.* **2005**, *7*, 136-141.

16. Mizar. P., Myrboh. B. *Tetrahedron Lett.* **2006.** *47*, 7823-7826.

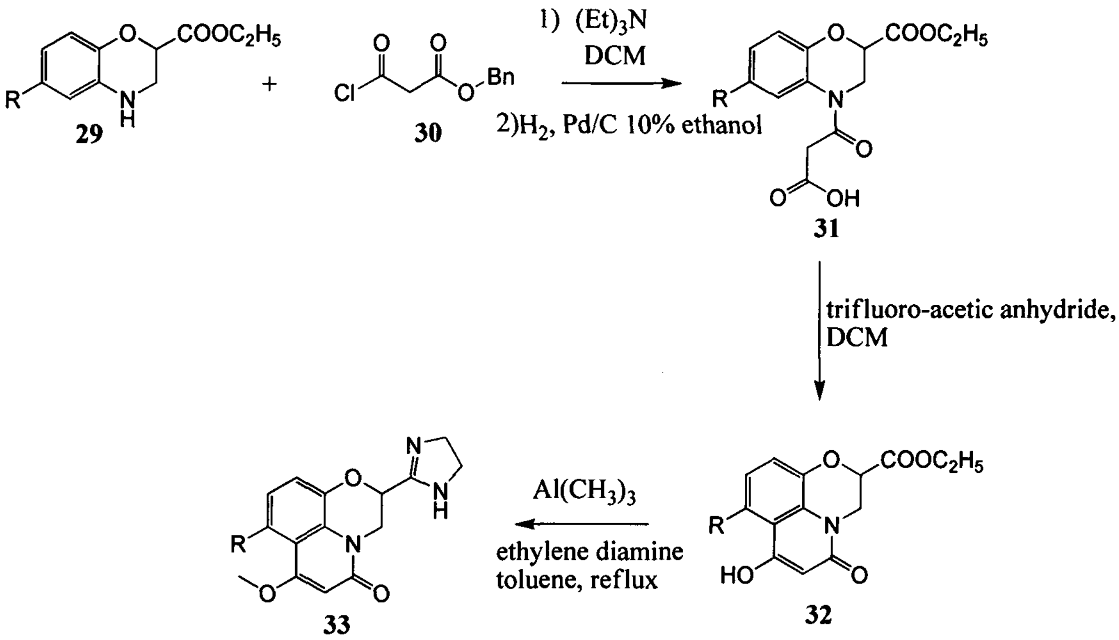
CHAPTER IV

“Synthesis of 2,3-dihydro-6*H*-1-oxa-3a-aza-phenalene and their benzo/hetero fused analogue.”

INTRODUCTION:

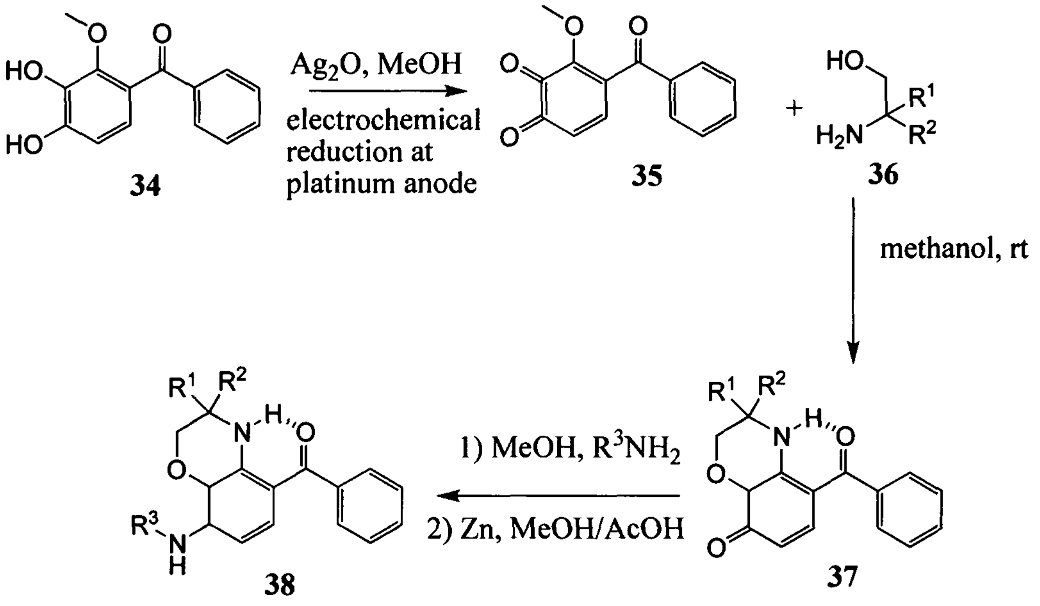
The 2*H*-1,4-benzoxazine derivatives have been extensively used as precursors for the synthesis of a variety of biologically active compounds. They have shown to be long-acting positive inotropes and peripheral vasodilator[1] with potential intracellular calcium activity.[2] Tricyclic analogues with a fused additional ring on the nitrogen atom of the benzoxazine moiety have been prepared and evaluated for their cardiovascular effects and as potential antihypertensive agents. Recently Jean-Yves Me´rour and coworkers[3] have used the benzoxazine framework for the synthesis of number of imidazolinic derivatives which showed pronounced cardiovascular effects on both blood pressure and heart rate either after ip or po administration. Among them, 6-Fluoro-2-(4,5-dihydro-1*H*-imidazol-2-yl)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazine, was considered to be a potential antihypertensive agent.[3] Some tricylic benzoxazines are synthetic analogues of antibacterial fluoroquinolones, exemplified by norfloxacin and ciprofloxacin.[4-7]

Jean-Yves Me´rour and coworkers[2] synthesized tricyclic imidazolinic 3,4-dihydro-2*H*-1,4-benzoxazine derivatives by reacting benzyl 3-chloro-3-oxopropanoate **29** with substituted 3,4-dihydro-2*H*-1,4-benzoxazine **30** to afford the corresponding amide **31** which were cyclised into **32** using trifluoro-acetic acid anhydride using dichloromethane as the solvent. The enol form of the ketone was *O*-methylated using methyl tosylate to afford **33** (Scheme **13**).



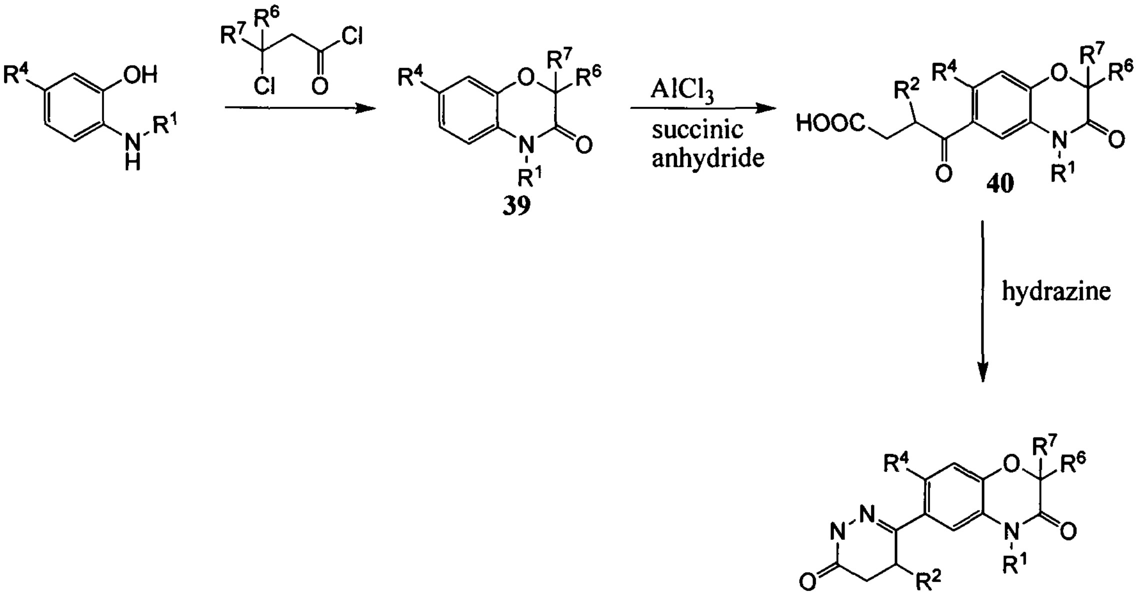
Scheme 13

Maurice-Bernard Fleury[8] synthesized 8-amino-1,4-benzoxazine derivatives (Scheme **14**) using (3,4-dihydroxy-2-methoxyphenyl)(phenyl)methanone **34** which was oxidized using Ag_2O in methanol or electrochemical oxidation at a platinium anode (*E= +0.4 V vs sce*) at rt to yield 3,4-quinone **35**. **35** was further treated with **36** in methanol a r.t to yield 1,4-benzoxazine-8-one derivatives **37** which is further treated with amines and on reduction with Zinc in methanol and acetic acid to yield the final product **38**.



Scheme 14

J. B Moore and co-worker[9c] employed the Friedel-Crafts acylation to synthesize 6-benzoxazinylpyridazin-3-ones **41**. A Friedel-Crafts acylation of 3,4-dihydro-4-(methyl-sulfonyl)-1,4(2H)-benzoxazine **39** with succinic anhydride and aluminium chloride gave oxobutyric acid **40** which on cyclization with hydrazine yield the final product **41** (Scheme **15**).

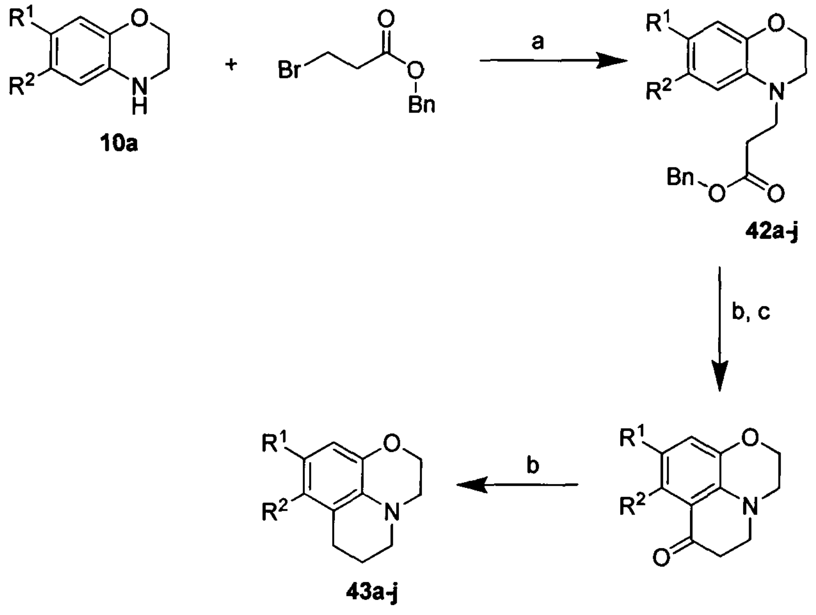


Scheme 15

Although numerous methods for the synthesis of substituted 2*H*-1,4-benzoxazine and their corresponding benzo/hetero-fused derivatives have been developed, the search for new and efficient synthetic routes for these classes of compounds continues to attract a lot of attention. The present work describes two general methods for the synthesis of 2,3-dihydro-6*H*-1-oxa-3a-aza-phenalene, one involving the general *N*-alkylation of the benzoxazines with benzyl propanoate and subsequent reduction and cyclisation. The other by reaction of benzoxaxine and α-oxoketene dithio-acetal to give the *S*,*N*-acetal which when reacted with Vilsmeier reagent provides a versatile route to highly functionalized 2*H*-1,4-benzoxazine and their benzo- and hetero-fused analogues.[11-13]

RESULTS AND DISCUSSIONS:

As part of our earlier work aimed at synthesizing benzoxazine derivatives of biological interest;[14] we wanted to develop new and simpler routes for the synthesis benzo/hetero fused analogues. The first step employed was the *N*-alkylation of benzoxaxine **10a** with 3-bromo-propionic acid benzyl ester in presence of K_2CO_3 to obtain 3-(6,7-Dialkyl-2,3-dihydro-benzo[1,4]oxazin-4-yl)-propionic acid benzyl ester **42a-j**. When the intermediates **42a-j** were subjected to reduction and subsequent cyclisation using trifluoroacetic anhydride in dichloromethane at room temperature to give the desired products **43a-j** (Scheme **16**).

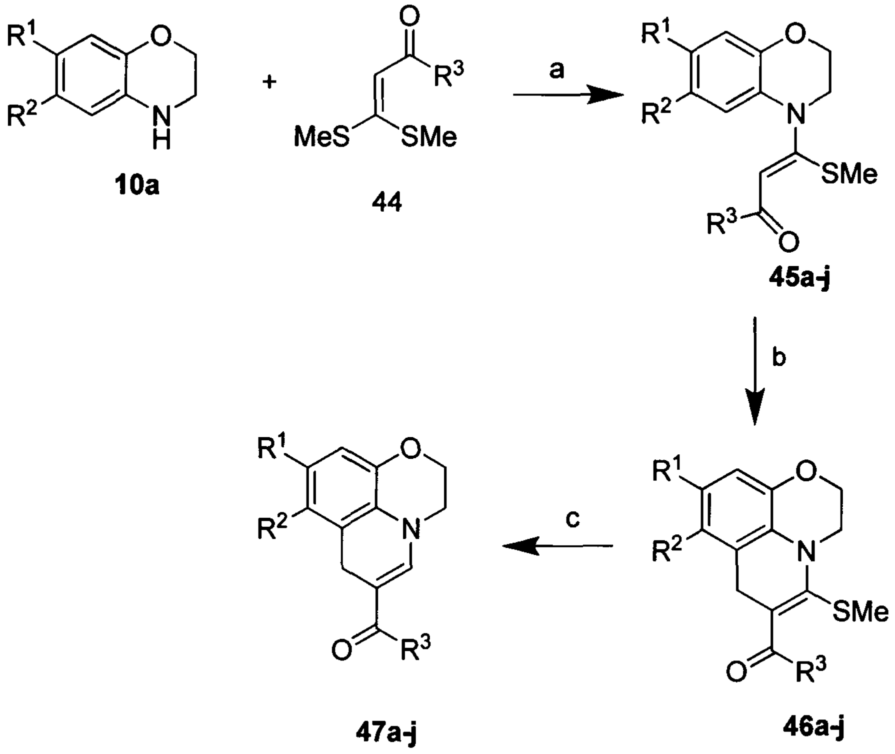


(a) K_2CO_3 DMF reflux; (b) H_2, Pd/C 10%, ethanol; (c) trifluoroacetic acid anhydride, CH_2Cl_2

Scheme 16

The use of α-oxoketene dithio-acetals in the synthesis of various heterocyclic molecules is well documented in the literature. However, there is no report about its uses in the synthesis of tricyclic analogs of benzoxazines. We report herein a simple procedure for the synthesis of this class of compounds starting from benzoxazine and α-oxoketene dithio-acetals.

Benzoxaxine **10a** when treated with aryl-oxoketene dithioacetal **44** in presence of *n*-BuLi in THF[14] gave the aryl-oxoketene-*N*,*S*-2*H*-1,4 benzoxazinoacetal **45** by displacement of one of the methyl thiol groups of **44** (Scheme **16**). Vilsmeier cyclisation of **45a-j** afforded the tricyclic analogue **46a-j** which on subsequent reduction using Raney-Ni yielded the final products **47a-j** (Table 4).



(a) n BuLi / THF; (b) $POCl_3$, DMF, 80°C; (c) Raney Ni/ ethanol/ heat

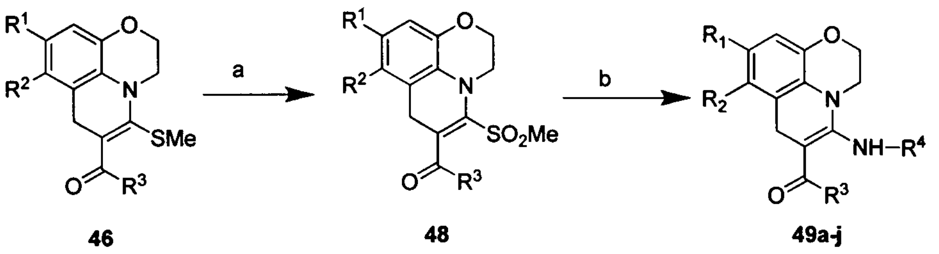
Scheme 17

Table 4 Substituted 2,3-dihydro-6*H*-1-oxa-3a-aza-phenalene

Entry	Product(**43**)	Yield%(**43**)	Product (**46**)	Yield%(**46**)
a	R^1= H, R^2 =H	82	R^1= H, R^2 =H, R^3= Ph	90
b	R^1= CH_3, R^2 =H	84	R^1= H, R^2 =OCH_3, R^3= Ph	81
c	R^1= CH_3, R^2 = CH_3	86	R^1= OCH_3, R^2 = H, R^3= Ph	82
d	R^1= OCH_3, R^2 =H	56	R^1= CH_3, R^2 = H, R^3= 2-BrPh	65
e	R^1= H, R^2 = OCH_3	49	R^1= CH_3, R^2 = CH_3, R^3= Ph	50
f	R^1= OCF_3, R^2 =H	41	R^1= CF_3, R^2 = H, R^3= Ph	72
g	R^1= Cl, R^2 =H	46	R^1= Cl, R^2 = H, R^3= Ph	75
h	R^1= F, R^2 =H	40	R^1= F, R^2 = H, R^3= Ph	68
i	R^1= CH_2OH, R^2 =H	42	R^1= CH_2OH, R^2 = H, R^3= Ph	85
j	R^1= OCH_3, R^2 =CH_3	50	R^1= H, R^2 = H, R^3= 2-BrPh	82

It was observed that the yields of the products in the second method varied significantly with the nature of the substituent. The presence of a methoxy or a hydroxyl group in the aromatic ring system significantly increases the yield as compared to an alkyl substituent. Thus for obtaining an alkyl substituted product the procedure shown in scheme **16** was preferred.

The 2-methylthiol group in 2,3-dihydro-6*H*-1-oxa-3a-aza-phenalene **46a** was oxidized with *m*-chloroperbenzoic acid to afford the corresponding 2-(methylsulfonyl) of 2,3-dihydro-6*H*-1-oxa-3a-aza-phenalene **48** (Scheme **18**) which on further treatment with *n*-butylamine yielded the desired products **49a-j**. This process provided a simple and general route for the synthesis of highly functionalized tricyclic analogues of benzoxazine. The reaction proceeded under mild conditions when an alkyl amine was used; however for aryl amine groups more drastic conditions were necessary. Here again the yield varied with the bulkiness of the substituent (Table **5**).



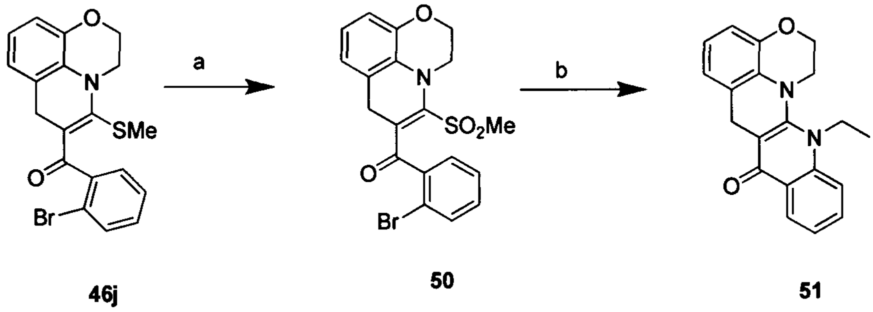
(a) *m*-CPBA/DCM, 0°C to RT; (b)R^4H/heat

Scheme 18

Table 5: Highly substituted 2,3-dihydro-6*H*-1-oxa-3a-aza-phenalene

Entry (49)	R^1	R^2	R^3	R^4	Yield %
a	H	H	Ph	Ph	82
b	H	H	2-Br Ph	Ph	75
c	H	H	Ph	n-butyl	85
d	Cl	H	Ph	Ph	70
e	H	H	Ph	$PhCH_2$	72
f	H	H	2-BrPh	n-butyl	70
g	Cl	H	2-Br Ph	Ph	80
h	OCH_3	H	2-Br Ph	Ph	68
i	OCH_3	H	Ph	Ph	65
j	H	CH_3	Ph	Ph	67

Interestingly when **46j** was treated with ethyl amine in presence of $Pd(dppf)Cl_2$ and K_2CO_3 under Microwave, the reaction did not undergo simple substitution but further coupled to yield the cyclised product **51** (65%) as shown in (Scheme **19**).



(a) *m*-CPBA/DCM, 0°C to RT; (b) $Pd(dppf)Cl_2$, K_2CO_3, $NH_2CH_2CH_3$, MW

Scheme 19

EXPERIMENTAL:

Melting points were obtained on a Thomas Hoover capillary melting point apparatus and are uncorrected. Carbon, hydrogen and nitrogen analysis were performed with a Perkin-Elmer 2400 series II instrument. IR spectra in BOMEM DA-8 FT-IR spectrophotometer. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AMX 400 spectrometer using $CDCl_3$ or DMSO-d_6 as the solvent. Chemical shifts are reported in ppm from internal tetramethylsilane and are given on the δ scale. The following abbreviations are used to describe peak patterns when appropriate: s = singlet, d = doublet, t = triplet, m = multiplet. Positive-ion and negative-ion electrospray ionization (ESI) mass spectra were measured on an ion trap analyzer Esquire 3000 (Bruker Daltonics).

All reactions were monitored by TLC on glass plates coated with silica gel (ACME's) containing 13% calcium sulphate as binder and visualization of compounds was accomplished by exposure to iodine vapour or by spraying acidic potassium permanganate solution or 2% ninhydrin solution. Column chromatography was carried out using ACME's silica gel.

Chemicals, reagents and solvents:

Dry solvents were obtained by distillation under N_2 atomsphere with appropriate dehydrating agents. The commercial available chemicals were used without further purification.

General procedure for the preparation of 2,3,4,6-tetrahydro-6*H*-oxa-3a-aza-phenalene: 3,4-dihydro-2*H*-benzoxazine **10a** (7 mmol) and dry K_2CO_3 (15 mmol) were dissolved in dry DMF (15 ml), followed by benzyl 3-bromopropanoate (8.6 mmol). The reaction mixture was stirred overnight at room temperature. After completion of the reaction (monitored by TLC), crushed ice was added and the product extracted with ethyl acetate. The combined organic extract was dried over Na_2SO_4, concentrated and purified by passing over silica gel and eluting with ethyl acetate/hexane (1:15) to obtain the pure product. The *N*-substituted product (3.4 mmol) was then dissolved in ethanol (15 ml) containing Pd/C 10% (0.3 mmol) and the mixture stirred under 1 atm. of H_2 for 4 h. It was then filtered under pressure and the filtrate evaporated to give brownish oil. IR (film) ν (cm^{-1}) 3540 (ν_{OH}). This was dissolved in dichloroethane and cooled to 0 °C. To the cooled solution trifluoroacetic anhydride (9 mmol) was added and the reaction mixture stirred overnight at room temperature. The p^H of the reaction mixture was adjusted to 9~10 by addition of 4N NaOH. The reaction mixture was extracted with ethyl acetate and the organic layer washed with water, brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent yielded the crude product which was further purified by column chromatography using silica gel as the solid phase and DCM as the mobile phase. The product was further subjected to reduction following the method described above to yield the final product

2,3,4,6-tetrahydro-6*H*-oxa-3a-aza-phenalene 43a:

Yield 82 %; oil; IR (film) absence of ν $_{NH}$ stretching. ^1H NMR ($CDCl_3$, 400 MHz) δ ppm 1.95 (m, 3H), 2.79 (t, 2H, $J = 6.5$ Hz), 3.08 (t, 2H, $J = 6$ Hz), 3.94 (t, 2H, $J = 5$ Hz), 4.31 (t, 2H, $J = 4.5$ Hz), 6.48~6.54 (m, 3H, ArH). ^{13}C NMR ($CDCl_3$, 100MHz) 30.1, 34.5, 58.7, 60.2 (NCH_2), 73.1 (OCH_2), 112.8, 116.8, 117.3, 119.5, 140.1, 130.2. MS (ESI) *m/z* =

176.21. Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99%; found: C, 75.42; H, 7.49; N, 8.01%.

8-Methyl-2,3,5,6-tetrahydro-4*H*-1-oxa-3a-aza-phenalene 43b:

Yield 84%; oil IR (film) absence of ν_{NH} stretching. ^1H NMR ($CDCl_3$, 400 MHz) δ ppm 1.90 (m, 3H), 2.21 (s, 3H), 2.61 (t, 2H, *J* = *6.2* Hz), 3.25 (t, 2H, *J* = *6.4* Hz), 3.61 (t, 2H, *J* = *5.7 Hz*), 4.24 (t, 2H, *J* = *4.9* Hz), 6.41 (s, 1H, ArH), 6.55 (s, 1H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz); 20.1, 25.9, 30.6, 53.1, 61.1 (NCH_2), 73.6 (OCH_2), 112.3, 121.1, 123.2, 127.1, 129.1, 142.5. MS (ESI) *m/z* = 190.52. Calcd for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40%; found: C, 76.21; H, 8.09; N, 7.41%.

8,9-dimethyl-2,3,5,6-tetrahydro-4*H*-1-oxa-3a-aza-phenalene 43c:

Yield 86 %; oil IR (film) absence of ν_{NH} stretching. ^1H NMR ($CDCl_3$, 400 MHz) δ ppm 1.87 (m, 3H), 2.28 (s, 6H), 2.72 (t, 2H, *J* = *6.4* Hz), 3.17 (t, 2H, *J* = 6.7 Hz), 3.60 (t, 2H, *J* = *5.3* Hz), 4.21 (t, 2H, *J* = *4.7* Hz), 6.54 (s, 1H, ArH). ^{13}C NMR ($CDCl_3$, 100MHz); 12.4, 19.5, 21.1, 24.5, 46.6, 60.2 (NCH_2), 73.9 (OCH_2), 112.5, 121.9, 125.2, 127.1, 128.5, 140.1. MS (ESI) *m/z* = 204.12. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89%; found: C, 76.86; H, 8.48; N, 6.85%.

8-Methoxy-2,3,5,6-tetrahydro-4*H*-1-oxa-3a-aza-phenalene 43d:

Yield 56%; oil. IR (film) absence of ν_{NH} stretching. ^1H NMR ($CDCl_3$, 400 MHz) δ ppm 1.91 (m, 3H), 2.65 (t, 2H, *J* = *6.4* Hz), 3.26 (t, 2H, *J* = *6.2* Hz), 3.41 (s, 3H), 3.75 (t, 2H, *J* = *5.5* Hz), 4.19 (t, 2H, *J* = *4.5* Hz), 6.21 (s, 1H, ArH), 6.35 (s, 1H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz); 20.5, 31.1, 50.5, 56.5, 60.7 (NCH_2), 73.6 (OCH_2), 99.7, 105.8, 121.1, 126.1, 140.5, 149.3. MS (ESI) *m/z* = 206.1. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82%. found: C, 70.21; H, 7.39; N, 6.76%.

9-Methoxy-2,3,5,6-tetrahydro-4*H*-1-oxa-3a-aza-phenalene 43e:

Yield 49 %; oil. IR (film) absence of ν $_{NH}$ stretching. ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 1.96 (m, 3H), 2.72 (t, 2H, *J* = *6.8* Hz), 3.31 (t, 2H, *J* = *6.7* Hz), 3.54 (s, 3H), 3.79 (t, 2H, *J* = *6.5 Hz*), 4.22 (t, 2H, *J* = *5.5* Hz), 6.25 (d, 1H, *J* = *7.1* Hz), 6.54 (d, 1H, *J* = *7.1* Hz). ^{13}C NMR ($CDCl_3$, 100 MHz); 20.1, 26.1, 50.2, 56.9, 60.5 (NCH_2), 73.1 (OCH_2), 104.9, 110.1, 114.5, 131.1, 134.5, 149.9. MS (ESI) *m/z* = 206.12. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82%. found: C, 70.26; H, 7.43; N, 6.78%.

8-trifluoromethoxy-2,3,5,6-tetrahydro-4*H*-1-oxa-3a-aza-phenalene 43f:

Yield 41%; oil IR (film) absence of ν $_{NH}$ stretching. ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 1.89 (m, 3H), 2.64 (t, 2H, *J* = *6.0* Hz), 3.29 (t, 2H, *J* = *6.3* Hz), 3.73 (t, 2H, *J* = *5.7* Hz), 4.26 (t, 2H, *J* = *5.0* Hz), 6.15 (s, 1H, ArH), 6.32 (s, 1H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz); 19.7, 29.6, 52.7, 60.7 (NCH_2), 72.9 (OCH_2), 98.7, 105.1, 121.7, 122.9, 126.1, 143.1, 151.2. MS (ESI) *m/z* = 260.02. Calcd for $C_{12}H_{12}F_3NO_2$: C, 55.60; H, 4.67; N, 5.40%; found: C, 55.65; H, 4. 73; N, 5.45%.

8-Chloro-2,3,5,6-tetrahydro-4*H*-1-oxa-3a-aza-phenalene 43g:

yield 46%; oil. IR (film) absence of ν $_{NH}$ stretching. ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 2.01 (m, 3H), 2.61 (t, 2H, *J* = 6.0 Hz), 3.27 (t, 2H, *J* = 6.2 Hz), 3.86 (t, 2H, *J* = 5.5 Hz), 4.22 (t, 2H, *J* = *4.5* Hz), 7.11 (s, 1H, ArH), 7.36 (s, 1H, ArH). ^{13}C NMR ($CDCl_3$, 100MHz); 23.0, 30.9, 53.2, 61.1 (NCH_2), 73.5 (OCH_2), 113.1, 119.9, 121.9, 124.1, 129.5, 141.2. MS (ESI) *m/z* = 210.5 Calcd for $C_{11}H_{12}ClNO$: C, 63.01; H, 5.77; N, 6.68%. found: C, 63.06; H, 5.82; N, 6.75%.

8-fluoro-2,3,5,6-tetrahydro-4*H*-1-oxa-3a-aza-phenalene 43h:

Yield 40%; oil. IR (film) absence of ν $_{NH}$ stretching. ^{1}H NMR (CDCl$_3$, 400 MHz) δ ppm 2.05 (m, 3H), 2.63 (t, 2H, *J* = *6.4* Hz), 3.32 (t, 2H, *J* = *6.7* Hz), 3.79 (t, 2H, *J* = *6.0* Hz), 4.27 (t, 2H, *J* = *5.7* Hz), 6.54 (s, 1H, ArH), 6.67 (s, 1H, ArH). ^{13}C NMR (CDCl$_3$, 100MHz); 22.6, 31.2, 53.7, 61.4 (NCH$_2$), 73.5 (OCH$_2$), 101.3, 108.1, 123.9, 125.7, 143.7, 152.8. MS (ESI) *m/z* = 194.05 Calcd for $C_{11}H_{12}FNO$: C, 68.38; H, 6.26; N, 7.25%; found: C, 68.43; H, 6.20; N, 7.29%.

(2,3,4,6-tetrahydro-6*H*-oxa-3a-aza-phenalene) methanol 43i:

Yield 42%; oil. IR (film) absence of ν $_{NH}$ stretching. ^{1}H NMR (CDCl$_3$, 400 MHz) δ ppm 1.97 (m, 3H), 2.67 (t, 2H, *J* = *6.8* Hz), 3.39 (t, 2H, *J* = *6.9* Hz), 3.72 (t, 2H, *J* = *6.2* Hz), 4.23 (t, 2H, *J* = *5.9* Hz), 4.62 (s, 2H), 5.21 (s, OH), 6.59 (s, 1H, ArH), 6.72 (s, 1H, ArH). ^{13}C NMR (CDCl$_3$, 100 MHz); 21.9, 30.7, 50.1, 60.9 (NCH$_2$), 67.7, 72.8 (OCH$_2$), 110.7, 121.3, 123.5, 129.6, 132.5, 143.2. MS (ESI) *m/z* = 206.10 Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82%; found: C, 70.26; H, 7.42; N, 6.87%.

8-methoxy-9-methyl-2,3,5,6-tetrahydro-4*H*-1-oxa-3a-aza-phenalene 43j:

Yield 50 %; oil. IR (film) absence of ν $_{NH}$ stretching. ^{1}H NMR (CDCl$_3$, 400 MHz) δ ppm 1.88 (m, 3H), 2.28 (s,3H), 2.59 (t, 2H, *J* = *6.7* Hz), 3.39 (t, 2H, *J* = *6.1* Hz), 3.62 (s, 3H), 3.81 (t, 2H, *J* = *5.9* Hz), 4.23 (t, 2H, *J* = *5.9* Hz), 6.22 (s, 1H, ArH). ^{13}C NMR (CDCl$_3$, 100MHz); 9.7, 20.7, 26.7, 51.2, 56.1, 60.1 (NCH$_2$), 73.0 (OCH$_2$), 98.9, 115.3, 122.8, 124.6, 140.9, 149.1. MS (ESI) *m/z* = 206.1. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39%; found: C, 71.16; H, 7.87; N, 6.45%.

General procedure for the preparation of 3-(2,3-Dihydro-benzo[1,4]oxazin-4-yl)-3-methylsulfanyl-1-phenyl-propenone:

To a solution of 3,4-dihydro-2*H*-1,4-benzoxazines(7 mmol) in dry THF (30 ml) was added *n*-BuLi (9 mmol) drop wise under nitrogen atmosphere at -78 °C, it was then allowed to attain room temperature and further stirred for 30 mins. To the reaction mixture a solution of the phenyl oxoketene-*S,S*-acetal (**44**) (5 mmol) in dry THF (25 ml) was added at 0 °C, stirred at room temperature for 1 h and refluxed. The reaction mixture was then cooled, quenched with saturated NH_4Cl solution, evaporated in vacuum and extracted with $CHCl_3$. The combined organic extract was dried over Na_2SO_4 and evaporated to give a solid mass which was purified by column chromatography over silica gel using hexanes-EtOAc (6:1) as eluent to yield the pure product 82%;

3-(2,3-Dihydro-benzo[*1,4*]oxazin-4-yl)-3-methylsulfanyl-1-phenyl-propenone 45a:

IR (KBr), ν (cm^{-1}). 2925, 1614. ^1H NMR ($CDCl_3$, 400 MHz) δ ppm 2.45 (s, 3H), 3.25(t, 2H, *J* = *7.7* Hz), 4.07 (t, 2H, *J* = *8.6* Hz), 5.89 (s, 1H), 6.46–6.65 (m, 4H, ArH), 7.42~7.54 (m, 5H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz); 12.6 (SCH_3), 60.2 (NCH_2), 73.1 (OCH_2), 87.1, 112.8, 116.8, 117.3, 119.5, 129.1, 130.2, 130.2, 134.3, 137.0, 140.1, 166.7, 187.8. MS (ESI) *m/z* = 310.41. Calcd for $C_{18}H_{17}NO_2S$: C, 69.43; H, 5.50; N, 4.50%; found: C, 69.52; H, 5.49; N, 4.51%.

3-(6-Methoxy-2,3-dihydro-benzo[1,4]oxazin-4-yl)-3-methylsulfanyl-1-phenyl-propenone 45b:

Yellowish solid. Yield 78%; IR (KBr), ν (cm^{-1}). 1627. ^1H NMR ($CDCl_3$, 400 MHz) δ ppm 2.41 (s, 3H), 3.31(t, 2H, *J* = *7.5* Hz), 3.51 (s, 3H), 4.05 (t, 2H, *J* = *6.7* Hz), 5.75 (s, 1H), 5.92(s, H), 6.15 (d, 1H, *J* = *8.5* Hz), 6.56 (d, 1H, *J* = *8.5* Hz) 7.62~7.84 (m, 5H, ArH). ^{13}C

NMR ($CDCl_3$, 100 MHz); 12.7 (SCH_3), 59.9 (NCH_2), 61.5, 73.6 (OCH_2), 89.2, 96.5, 102.7, 116.5, 128.7, 130.4, 132.7, 133.5, 134.1, 137.3, 152.1, 165.9, 188.2. MS (ESI) *m/z* = 342.32. Calcd for $C_{19}H_{19}NO_3S$: C, 66.84; H, 5.61; N, 4.10%; found: C, 66.82; H, 5.59; N, 4.12%.

1-(2-Bromo-phenyl)-3-(2,3-dihydro-benzo[1,4]oxazin-4-yl)-3-methylsulfanyl-propenone 45j: solid. Yield 77 %; IR (KBr), ν (cm^{-1}). 1645. ^1H NMR ($CDCl_3$, 400 MHz) δ ppm 2.46 (s, 3H), 3.2(t, 2H, *J* = *7.2* Hz), 4.11 (t, 2H, *J* = *7.1* Hz), 5.95 (s, 1H), 5.92(s, H), 6.51~6.67 (m, 4H, ArH) 7.32~7.41 (m, 5H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz); 12.9 (SCH_3), 60.4 (NCH_2), 73.8 (OCH_2), 90.2, 114.7, 116.1, 118.2, 120.6, 121.9, 128.1, 130.1, 131.4, 132.5, 136.9, 139.4, 141.1, 164.9, 188.6. MS (ESI) *m/z* = 389.15. Calcd for $C_{18}H_{16}BrNO_2S$: C, 55.39; H, 4.13; N, 3.59%; found: C, 55.42; H, 4.15; N, 3.56%.

General procedure for the preparation of (4-Methylsulfanyl-2,3-dihydro-6*H*-1-oxa-3a-aza-phenalen-5-yl)-phenyl-methanone:

To a solution of **45a** (3 mmol) in DMF was added drop wise a solution of Vilsmeier reagent at 0 °C [prepared from $POCl_3$ (5 mmol) and DMF (5 mmol) at 0-5 °C] under nitrogen atmosphere and stirred for 4 h at r.t. The reaction mixture was then heated at 90 °C for 3 h. The reaction mixture was poured into ice cold saturated $NaHCO_3$ solution (20 ml), and extracted with chloroform (2x25ml). The combined organic extract was dried over Na_2SO_4, and then evaporated under reduced pressure. The pure product was obtained by column chromatography over silica gel using hexane-EtOAc as eluent (4.1).

(4-Methylsulfanyl-2,3-dihydro-6*H*-1-oxa-3a-aza-phenalen-5-yl)-phenyl-methanone 46a: (Yield 90 %); ^1H NMR ($CDCl_3$, 400 MHz) δ ppm 2.34 (s, 3H), 3.21 (s, 2H), 3.35(t, 2H, *J* = *6. Hz*), 4.07 (t, 2H, *J* = *5.6* Hz), 6.46–6.65 (m, 3H, ArH), 7.42~7.54 (m, 5H, ArH).^{13}C NMR ($CDCl_3$, 100 MHz); 12.1 (SCH_3), 27.9, 60.1 (NCH_2), 73.5 (OCH_2), 96.1, 112.5, 116.3, 117.1, 119.2, 129.8, 130.5, 130.2, 134.3, 137.0, 140.1, 156.7, 186.8. MS (ESI) *m/z* = 322.21. Calcd for $C_{19}H_{17}NO_2S$: C, 70.56; H, 5.30; N, 4.33%; found: C, 70.60; H, 5.35; N, 4.31%.

(3,7-dihydro-8-methoxy-5-(methylthio)-2*H*-[1,4]oxazino[2,3,4-*ij*]quinolin-6-yl)(phenyl)methanone 46b:

Yellowish solid. Yield 81%; IR (KBr), ν (cm^{-1}). 1629. ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 2.34 (s, 3H), 3.35(s, 2H), 3.65 (s, 3H), 3.43 (t, 2H, *J* = *5.9* Hz), 4.12 (t, 2H, *J* = *6.3 Hz*), 6.11 (d, 1H, *J* = *8.1* Hz), 6.34 (d, 1H, *J* = *8.1* Hz) 7.52~7.76 (m, 5H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz); 12.7 (SCH_3), 18.7, 56.2, 59.9 (NCH_2), 73.6 (OCH_2), 89.2, 96.5, 102.7, 116.5, 128.7, 130.4, 132.7, 133.5, 134.1, 137.3, 152.1, 165.9, 189.3. MS (ESI) m/z = 354.12. Calcd for $C_{20}H_{19}NO_3S$: C, 67.97; H, 5.42; N, 3.96 %; found: C, 68.06; H, 5.49; N, 4.05 %.

(8-Methoxy-4-methylsulfanyl-2,3-dihydro-6*H*-1-oxa-3a-aza-phenalen-5-yl)-phenyl-methanone 46c:

Dirty yellow solid. Yield 82 %, ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 2.35 (s, 3H), 3.19(s, 2H), 3.41(t, 2H, *J* = *6.2* Hz), 3.56 (s, 3H), 4.16 (t, 2H, *J* =*5.9* Hz), 5.76 (s, 1H, ArH), 6.03 (s, 1H, ArH), 7.42~7.51 (m, 5H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz); 12.5 (SCH_3), 28.7, 54.9, 60.1 (NCH_2), 73.5 (OCH_2), 95.9, 98.1, 104.8, 122.7, 128.4, 129.1, 132.9, 134.8, 138.1, 141.4, 149.1, 158.9, 180.6. MS (ESI) *m/z* = 354.1. Calcd for $C_{20}H_{19}NO_3S$: C, 67.97; H, 5.42; N, 3.96%; found: C, 67.94; H, 5.40; N, 3.98%.

(4-bromophenyl)(3,7-dihydro-8-methyl-5-(methylthio)-2*H*-[1,4]oxazino[2,3,4-*ij*] quinolin-6-yl)methanone 46d:

(Yield 65 %); ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 2.25 (s, 3H), 2.31 (s, 3H), 3.28 (s, 2H), 3.45 (t, 2H, *J* = *6.3* Hz), 4.25 (t, 2H, *J* = *5.6* Hz), 6.26(d, 1H, *J* = *9.1* Hz), 6.34 (d, 1H, *J* =

9.1 Hz), 7.34 (d, 2H, *J* = *14.1* Hz), 7.45 (d, 2H, *J* = *14.1* Hz). ^{13}C NMR (CDCl$_3$, 100 MHz); 12.1 (SCH$_3$), 17.5, 25.9, 59.1 (NCH$_2$), 73.1 (OCH$_2$), 96.1, 112.5, 116.3, 117.1, 119.2, 129.8, 130.5, 130.2, 131.7, 132.3, 137.0, 140.1, 155.7, 187.8. MS (ESI) m/z = 417.01. Calcd for $C_{20}H_{18}BrNO_2S$: C, 57.70; H, 4.36; N, 3.36 %; found: C, 57.62; H, 4.30; N, 3.42 %.

(3,7-dihydro-8,9-dimethyl-5-(methylthio)-2*H*-[1,4]oxazino[2,3,4-*ij*]quinolin-6-yl)(phenyl) methanone 46e

Yellowish solid. Yield 50%; IR (KBr), ν (cm^{-1}). 1645. ^{1}H NMR (CDCl$_3$, 400 MHz) δ ppm 2.32 (s, 3H), 2.41(s, 3H), 3.30 (s, 2H), 3.49 (t, 2H, *J* = *5.3* Hz), 4.12 (t, 2H, *J* = *6.9* Hz), 6.13 (s, 1H), 7.56~7.82 (m, 5H, ArH). ^{13}C NMR (CDCl$_3$, 100 MHz); 11.5, 12.9 (SCH$_3$), 18.7, 20.7, 56.2, 59.4 (NCH$_2$), 73.2 (OCH$_2$), 89.2, 96.5, 116.5, 128.7, 130.4, 132.7, 133.5, 134.1, 137.3, 152.1, 165.9, 189.9. MS (ESI) m/z = 352.06. Calcd for $C_{21}H_{21}NO_2S$: C, 71.76; H, 6.02; N, 3.99 %; found: C, 71.83; H, 5.95; N, 4.07 %.

(8-(trifluoromethyl)-3,7-dihydro-5-(methylthio)-2*H*-[1,4]oxazino[2,3,4-*ij*]quinolin-6-yl)(phenyl) methanone 46f:

(Yield 72 %); ^{1}H NMR (CDCl$_3$, 400 MHz) δ ppm 2.20 (s, 3H), 3.23 (s, 2H), 3.51 (t, 2H, *J* = *6.7* Hz), 4.29 (t, 2H, *J* = *5.9* Hz), 6.29(d, 1H, *J* = *9.0* Hz), 6.54 (d, 1H, *J* = *9.0* Hz), 7.44-7.65 (m, 5H, ArH). ^{13}C NMR (CDCl$_3$, 100 MHz); 12.7 (SCH$_3$), 25.9, 59.6 (NCH$_2$), 73.8 (OCH$_2$), 96.1, 112.5, 115.3, 117.9, 119.6, 129.8, 130.5, 130.2, 131.7, 132.3, 137.0, 140.1, 155.7, 190.8. MS (ESI) m/z = 392.06. Calcd for $C_{20}H_{16}F_3NO_2S$: C, 61.37; H, 4.12; N, 3.58 %; found: C, 61.43; H, 4.19; N, 3.67 %.

(8-chloro-3,7-dihydro-5-(methylthio)-2*H*-[1,4]oxazino[2,3,4-*ij*]quinolin-6-yl)(phenyl) methanone 46g:

(Yield 75 %); ^{1}H NMR (CDCl$_3$, 400 MHz) δ ppm 2.23 (s, 3H), 3.0 (s, 2H), 3.56 (t, 2H, *J* = *5.7* Hz), 4.22 (t, 2H, *J* = *5.5* Hz), 6.32 (d, 1H, *J* = *9.3* Hz), 6.49 (d, 1H, *J* = *9.3* Hz), 7.42-7.75 (m, 5H, ArH). ^{13}C NMR (CDCl$_3$, 100 MHz); 122 (SCH$_3$), 25.0, 59.1 (NCH$_2$), 73.3 (OCH$_2$), 96.9, 112.5, 115.3, 117.9, 119.6, 129.8, 130.5, 130.2, 131.7, 132.3, 137.0, 140.1, 155.3, 189.8. MS (ESI) m/z = 359.01. Calcd for $C_{19}H_{16}ClNO_2S$: C, 63.77; H, 4.51; N, 3.91 %; found: C, 63.85; H, 4.64; N, 3.97 %.

(8-Fluoro-4-methylsulfanyl-2,3-dihydro-6*H*-1-oxa-3a-aza-phenalen-5-yl)-phenyl-methanone 46h:

Solid. Yield 68%; ^{1}H NMR (CDCl$_3$, 400 MHz) δ ppm 2.31 (s, 3H), 3.26(s, 2H), 3.45(t, 2H, *J* = *6.5* Hz*)*, 4.21 (t, 2H, *J* =*7.1* Hz), 6.15 (s, 1H, ArH), 6.21 (s, 1H, ArH), 7.21~7.42 (m, 5H, ArH). ^{13}C NMR (CDCl$_3$, 100 MHz); 12.8 (SCH$_3$), 28.9, 60.3 (NCH$_2$), 73.8 (OCH$_2$), 96.7, 100.9, 107.8, 124.7, 128.9, 129.2, 134.1, 136.9, 138.2, 142.1, 150.1, 158.6, 189.8. MS (ESI) *m/z* = 340.52 Calcd for $C_{19}H_{16}FNO_2S$: C, 66.84; H, 4.72; N, 4.10%; found: C, 66.87; H, 4.73; N, 4.13%.

(3,7-dihydro-8-(hydroxymethyl)-5-(methylthio)-2*H*-[1,4]oxazino[2,3,4-*ij*]quinolin-6-yl) (phenyl)methanone 46i:

Yellowish solid. Yield 85 %; IR (KBr), ν (cm^{-1}). 3425, 1629. ^{1}H NMR (CDCl$_3$, 400 MHz) δ ppm 2.27 (s, 3H), 3.22 (s, 2H), 4.62 (s, 2H), 3.41 (t, 2H, *J* = *6.2* Hz), 4.23 (t, 2H, *J* = *6.8 Hz*), 6.21 (d, 1H, *J* = *8.7* Hz), 6.30 (d, 1H, *J* = *8.7* Hz) 7.54~7.70 (m, 5H, ArH). ^{13}C NMR (CDCl$_3$, 100 MHz); 13.6 (SCH$_3$), 19.8, 60.2, 59.3 (NCH$_2$), 73.4 (OCH$_2$), 96.5, 112.7, 116.5, 120.8, 128.7, 130.4, 132.7, 133.5, 134.1, 137.3, 152.1, 165.9, 189.7. MS (ESI) m/z = 354.04. Calcd for $C_{20}H_{19}NO_3S$: C, 67.97; H, 5.42; N, 3.96 %; found: C, 68.09; H, 5.53; N, 4.09 %.

(4-bromophenyl)(3,7-dihydro-5-(methylthio)-2*H*-[1,4]oxazino[2,3,4-*ij*]quinolin-6-yl) methanone 46j

(Yield 82 %); ^{1}H NMR (CDCl$_3$, 400 MHz) δ ppm 2.29 (s, 3H), 3.22 (s, 2H), 3.40 (t, 2H, *J* = *6.0* Hz), 4.21 (t, 2H, *J* = *5.5* Hz), 6.30-6.41 (m, 3H, ArH), 7.45 (d, 2H, *J* = *14.2* Hz), 7.56 (d, 2H, *J* = *14.2* Hz). ^{13}C NMR (CDCl$_3$, 100 MHz); 12.7 (SCH$_3$), 26.9, 59.5 (NCH$_2$), 73.8 (OCH$_2$), 96.1, 112.5, 117.1, 119.2, 129.8, 130.5, 130.2, 131.7, 132.3, 137.0, 140.1, 155.5, 189.2. MS (ESI) m/z = 401.21. Calcd for $C_{19}H_{16}BrNO_2S$: C, 56.72; H, 4.01; N, 3.48 %; found: C, 56.79; H, 4.13; N, 3.54 %.

General procedure for the preparation (8-Chloro-2,3-dihydro-6*H*-1-oxa-3a-aza-phenalen-5-yl)-phenyl-methanone:

Reduction using Raney-Ni. To a solution of **46g** (6.4 mmol) in ethanol was added Raney-Ni (3 times by weight) and the suspension refluxed for 2 h. The reaction mixture was then cooled and filtered through sintered funnel. The residue washed with ethanol (3 x 10 ml) and the filtrate evaporated to give **47g** which was further purified by column chromatography over silica gel using EtOAc-Hexane (1:10) as eluent.

(8-Chloro-2,3-dihydro-6*H*-1-oxa-3a-aza-phenalen-5-yl)-phenyl-methanone 47g:

1.99 g (Yield 87 %); ^{1}H NMR (CDCl$_3$, 400 MHz) δ ppm 3.15 (s, 3H), 3.41 (t, 2H, *J* = *6* Hz), 4.03 (t, 2H, *J* = *7.1* Hz), 3.41(s, 3H), 4.05 (t, 2H, *J* = *5.5* Hz), 6.15 (s, 1H, ArH), 6.21 (s, 1H, ArH). 6.54 (s, 1H), 7.32~7.45 (m, 5H, ArH). ^{13}C NMR (CDCl$_3$, 100 MHz) 31.5, 61.7 (NCH$_2$), 73.8 (OCH$_2$), 111.9, 113.6, 119.5, 120.1, 127.3, 127.8, 128.1, 129.1, 132.1, 135.2, 136.3, 141.1, 165.3. MS (ESI) *m/z* = 312.82.Calcd for $C_{18}H_{14}ClNO_2$: C, 69.35; H, 4.53; N, 4.49%; found: C, 69.41; H, 4.59; N, 4.42%.

General procedure for the preparation of 2-(methylsulfonyl) of 2,3-dihydro-6*H*-1-oxa-3a-aza-phenalene 48:

To a solution of **46j** (2.5 mmol) in dry DCM (30 ml) was added a solution of *m*-CPBA (5.0 mmol) dropwise over a period of 15 min and stirred at r.t for 3 h. The reaction mixture was then neutralized with saturated $NaHCO_3$ (2x25 ml) and washed with brine, dried over anhydrous $NaSO_4$ and evaporated to yield the crude product which was purified by column chromatography using EtOAc-Hexane (1:20) as eluent. 0.892g (Yield 80 %);_ ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 3.21 (s, 2H), 3.34 (s, 3H), 3.45(t, 2H, *J = 6.3 Hz*), 4.14 (t, 2H, *J = 6.7 Hz*), 6.56–6.65 (m, 3H, ArH), 7.39~7.64 (m, 5H, ArH).. ^{13}C NMR ($CDCl_3$, 100 MHz); 27.9, 38.5, 59.1 (NCH_2), 74.9 (OCH_2), 95.9, 112.8, 118.3, 120.6, 121.9, 122.8, 128.7, 131.2, 132.6, 136.5, 138.9, 140.1, 141.5, 160.3, 191.1. MS (ESI) m/z = 435.31. Calcd for $C_{19}H_{16}BrNO_4S$: C, 52.54; H, 3.71; N, 3.23%; found: C, 52.57; H, 3.73; N, 3.21%.

General procedure for the preparation 4-phenylamino-2,3-dihydro-6*H*-1-oxa-3a-aza-phenalene 49a:

A solution of **48a** (3 mmol) and *n*-butyl amine (15 mmol) was refluxed for 6 h in dry THF (Toluene for Aryl amine). The reaction mixture was cooled and THF evaporated off to yield a yellow solid which was further purified by column chromatography on silica gel using EtOAc-Hexane (1:2) as an eluent. 0.87g (Yield 82%); IR (KBr), ν (cm^{-1}), 3316, 1342. ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm 3.16 (s, 2H), 3.54 (t, 2H, *J* = *6.5* Hz), 4.21 (t, 2H, *J* = *6.4* Hz), 6.35~6.42 (m, 3H, ArH), 6.62 (b, 1H), 6.98~7.14 (m, 4H, ArH), 7.42~7.54 (m, 4H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz); 26.1, 58.6 (NCH_2), 75.4 (OCH_2), 82.9, 111.5, 115.9, 117.3, 119.3, 121.3, 123.1, 128.9, 129.2, 130.1, 135.2, 138.7, 140.9, 141.8, 144.8, 156.3, 190.5. MS (ESI) m/z = 367.41. Calcd for $C_{24}H_{20}N_2O_2$: C, 78.24; H, 5.47; N, 7.60%; found: C, 78.21; H, 5.50; N, 7.61%.

The rest of the substituent **49b-49j** were analysed with the help of IR spectroscopy only.

General procedure for the preparation 13-ethyl-1,2,7,13-tetrahydro-3-oxa-13,13b-diaza-benzo-naphthacen-8-one 51:

(2-Bromo-phenyl)-(4-methanesulfonyl-2,3-dihydro-6*H*-1-oxa-3a-aza-phenalen-5-yl)-methanone (**50**) (2.3 mmol) was taken in a 25 ml container which was then sealed with septum and purged with N_2. K_2CO_3 (5.75 mmol), and Pd(dppf)Cl_2 (0.23 mmol) were introduced and the reaction mixture was again purged with N_2. It was then heated in the microwave synthesizer for 10 min at 100 °C and allowed to cool to room temperature. The content of the vessel was filtered through celite and washed with CH_2Cl_2 (3 x 5 ml). The combined organic extracts was further washed with saturated aqueous $NaHCO_3$ and evaporated to yield the crude product (**11**) which was purified by column chromatography using EtOAc-Hexane (1:5) as an eluent. 0.65g (Yield 65 %); IR (KBr) 1712 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ ppm 1.09 (t, 3H, $J = 3.6$ Hz), 2.98 (q, 2H, $J = 3.5$ Hz), 3.18 (s, 2H), 3.54 (t, 2H, $J = 6.5$ Hz), 4.21 (t, 2H, $J = 6.4$ Hz), 6.48~6.54 (m, 3H, ArH), 7.12~7.34 (m, 4H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) 13.1, 26.2, 44.5, 55.2 (NCH_2), 74.1 (OCH_2), 84.1, 111.4, 112.4, 117.1, 117.9, 120.5, 121.3, 122.4, 129.2, 130.4, 135.6, 142.1, 144.6, 155.2, 179.6. MS (ESI) *m/z* = 317.41. Calcd for $C_{20}H_{18}N_2O_2$: C, 75.45; H, 5.70; N, 8.80%; found: C, 75.42; H, 5.69; N, 8.81%.

REFERENCES:

1. Combs, D W. Rampulla, M. S. Bell, S. C. Klaubert, D. H. Tobia, A. J. Falotico, R. Haertlein, B. Lakas-Weiss, C. Moore; J. B. *J.Med. Chem.* **1990**, *33*, 380-385.
2. Bourlot, A. S. Sa′nchez, I. Dureng, G. Guillaumet, G. Massingham, R. Monteil, A. Winslow, E. Pujol,. M. D. and Me′rour, Jean-Yves. *J. Med. Chem.* 1998, *41*, 3142-3146.
3. Touzeau, F. Arrault, A. Guillaumet, G. Scalbert, E. Pfeiffer, B. Rettori, M. Renard, P. and Me′rour; J. *J. Med. Chem.* **2003**, *46*, 1962-1969.
4. Chu, D. T. W.; Maleczka, R. E., Jr. *J. Heterocycl. Chem.* **1987**, *24*, 453-458.
5. Chu, D. T. W.; Hallas, R.; Clement, J. J.; Alder, J.; McDonald, E.; Plattner, J. J. *Drugs Exp. Clin. Res.* **1992**, *18*, 275-279.
6. Chu, D. T. W.; Hallas, R.; Tanaka, S. K.; Alder, J.; Balli, D.; Plattner, J. J. *Drugs Exp. Clin. Res.* **1994**, *20*, 177-182.
7. Besson, T.; Joseph, B.; Moreau, P.; Viaud, M. C.; Coudert, G.;Guillaumet, G. *Heterocycles* **1992**, *34*, 273-279.
8. Petigara, R. B.; Yale, H. L. Novel Polycyclic *J. Heterocycl. Chem.* **1971**, *8*, 455-459.
9. Reviews: (a) Junjappa, H.; Ila, H.; Asokan, C. V. *Tetrahedron* **1990**, *46*, 5423-5428, Tetrahedron Report No. 278. (b) Dieter, R. K. *Tetrahedron* **1986**, *42*, 3029-3034, *Tetrahedron Report No. 202.* (c) Moore, J. B., Tominaga, Y. *J. Heterocycl. Chem.* **1989**, *26*, 1167-1172. (d) Ila, H.; Junjappa, H.; Mohanata, P. K. *Progress in Heterocyclic Chemistry*; Gribble, G. W., Gilchrist, T. L., Eds.; Pergamon: New York, **2001**; *Vol. 13*, Chapter 1, 1-12.

10. (a) Barun, O.; Mohanta, P. K.; Ila, H.; Junjappa, H. *Synlett* **2000**, 653-656. (b) Barun, O.; Ila, H.; Junjappa, H.; Singh, O. M. *J. Org.Chem.* **2000,** *65*, 1583-1586. (c) Reddy, K. R.; Basaveswara Rao; Ila, H.; Junjappa, H. *Synth. Commun.* **1996**, *26*, 4157-4165. (d) Reddy, K. R.; Ila, H.; Junjappa, H. *Synthesis* **1995**, 929-934. (e) Gupta, A. K.; Reddy, K. R.; Ila, H.; Junjappa, H. *J. Chem. Soc.*, *Perkin Trans. 1* **1995**, 1725-1730.
11. (a) Syam Kumar, U. K.; Ila, H.; Junjappa, H. *Org. Lett.* **2001**, *3*, 4193-4197. (b) Barun, O.; Chakrabarty, S.; Ila, H.; Junjappa, H. *J. Org.Chem.* **2001**, *66*, 4457-4464. (c) Basaveswara Rao, M. V.; Suresh, J. R.; Kumar, A.; Ila, H.; Junjappa, H. *J. Indian Chem. Soc.* **1997**, *74*, 955-962.
12. Singh, O. M.; Junjappa, H.; Ila, H. *J. Chem. Soc.*, *Perkin Trans.1* **1997**, 3561-3567.
13. (a)P. K. Mahata, C. Venkatesh, U. K. Syam Kumar, H. Ila, and H. Junjappa *J. Org. Chem.* **2003,** *68*, 3966-3969. (b)Singh, O.M.; Junjappa, H.; Ila, H. *J. Chem. Soc. Perkin Trans. 1* **1997**, 3561-3565.
14. Mizar, P.; and Myrboh, B. *Tetrahedron Lett.* **2006,** *46*, 7823-7825.

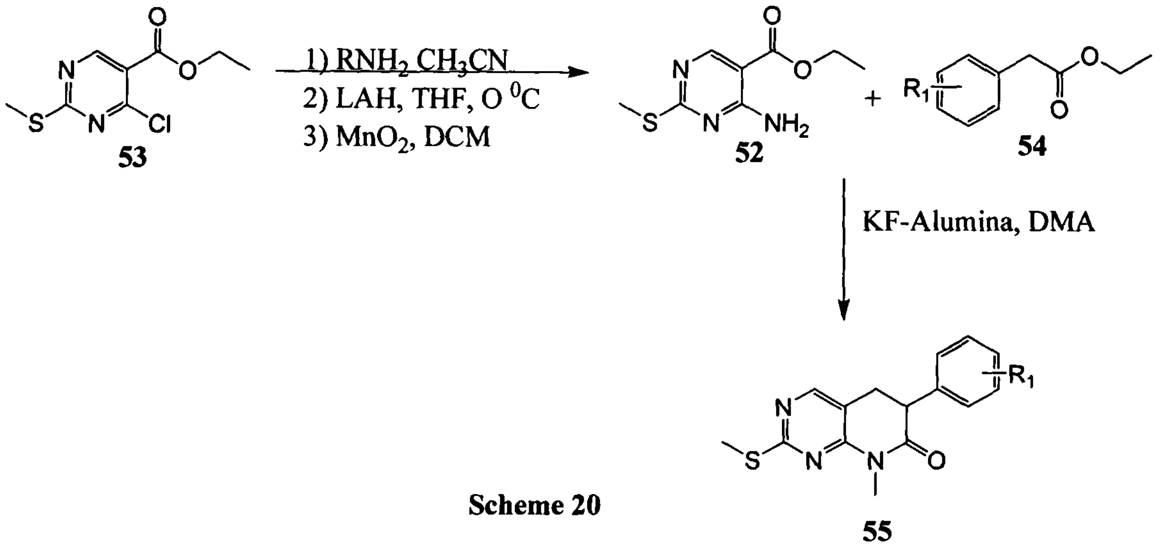
CHAPTER V

“Three-component synthesis of 5:6 and 6:6 fused pyrimidines using KF-alumina as a catalyst.”

INTRODUCTION:

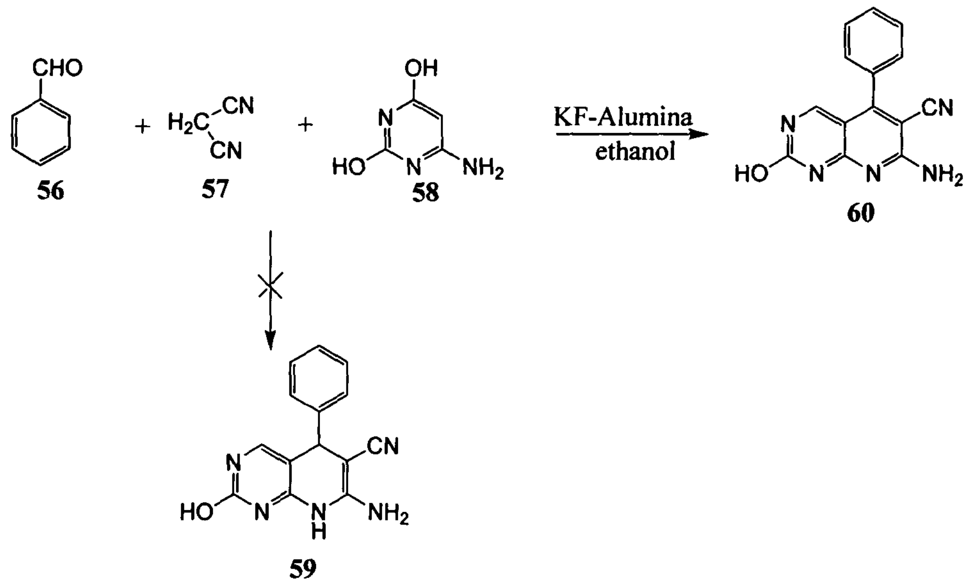
Inorganic solid supports as catalysts have been used increasingly in recent years for the synthesis of various biologically active molecules. Among these inorganic solid supports, potassium fluoride coated with alumina (KF-alumina) has been used as a versatile reagent for various reactions such as the Knoevenagel condensation, [1] the Henry reaction, [2] the Darzens reaction, [3] the Wittig reaction, [4] the Bignelli reaction [5] and alkylation [6] and elimination [7] reactions. In this article, we report a simple three-component synthesis of 5:6 fused[*d*]pyrimidines such as pyrazolo[3,4-*d*]pyrimidines, [8] pyrrolo[2,3-*d*]pyrimidines [9] as well as 6:6 fused systems such as pyrido[2,3-*d*]pyrimidines. [10] These heterocycles represent the aglycons of the more common bicyclic nucleosides many of which have been shown to possess a variety of biological activities, such as inhibitors of epidermal growth factor receptor (EGF-R) protein tyrosine kinases and their potential as a treatment for proliferate diseases involving mitogenic signaling from the EGF-R.[11] The derivatives of pyrrolo[2,3-*d*]pyrimidines have also been evaluated for their anti-tumor activities.

During our literature survey we found that quite a good amount of research has been carried out which described the synthetic utility and reaction of KF-alumina. Blass[12] and co-workers described a facile, KF-alumina mediated method for the synthesis of functionalized pyrido[*2,3-d*]pyrimidin-7(*8H*)-ones. The initial primidine aldehyde was prepared from pyrimidine ester **53** using a three step process. Nucleophilic displacement of the 4-*Cl* substituent with the desired primary amine is followed by the sequential lithium aluminum hydride reduction. Subsequent manganese dioxide oxidation provides the necessary aminopyrimidine aldehyde **52**. Cyclization of **52** to the final product in the presence of KF-alumina using dimethyl acetamide as solvent **55** (Scheme **20**).



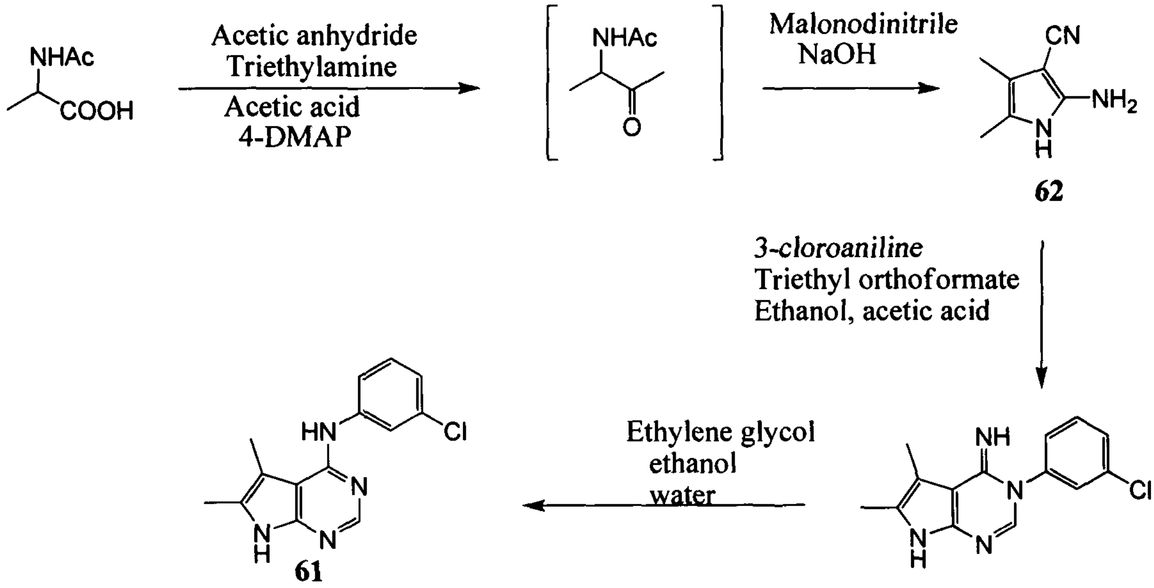
Scheme 20

Wang[13] and co-worker described a one-pot KF-Alumina catalyzed synthesis of Pyrido[*2,3-d*]pyrimidine derivatives. It was noted that when the arylaldehyde **56**, malononitrile **57** and 4-amino-2,6-dihydroxypyrido[*2,3-d*]pyrimidine **58** were treated with KF-Alumina in ethyl alcohol at 80°C, the 1,4-dihydropyrido[*2,3-d*]pyrimidine derivatives **59** were not detected at all, instead, pyrido[*2,3-d*]pyrimidine derivatives **60** were obtained (Scheme **21**).



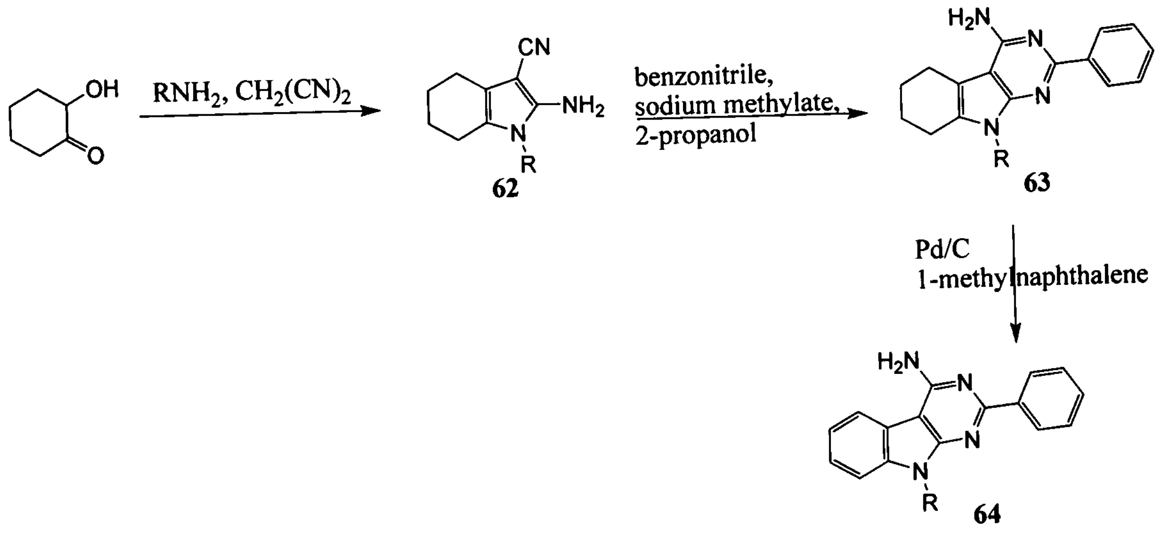
Scheme 21

Reports of pyrrolo[2,3-*d*]pyrimidine derivatives and their synthesis are abundant in the literature. In general, it is favorable to synthesize the pyrrole ring first and to subsequently build up the pyrimidine ring even though the opposite strategy has been applied as well. Fisher and co-worker[6e] synthesized pyrrolo[*2,3-d*]pyrimidine **61** using 2-amino-3-cyano-4,5-dimethylpyrrole **62** as an intermediate (Scheme **22**).



Scheme 22

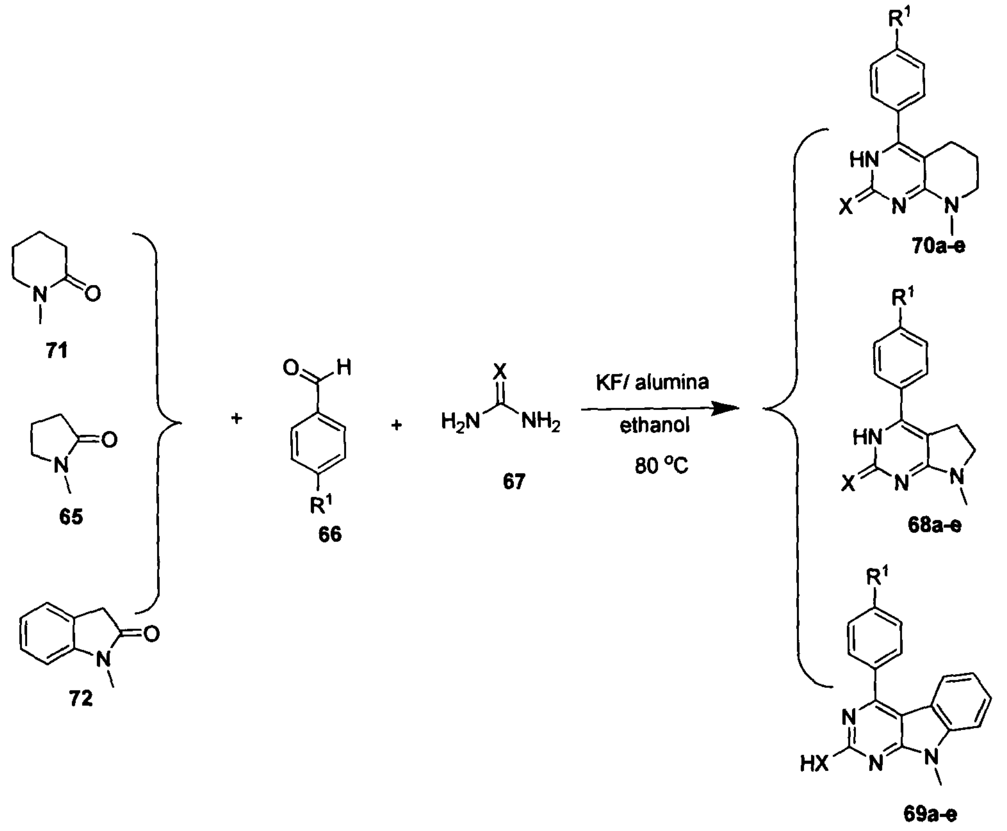
Möller[14a] and co-workers synthesized pyrimido[*4,5-b*]indole derivatives **64** and evaluated its activities as an A$_1$-Adonosine receptor antagonist. *N*-substituted 2-aminotetrahydroindole-3-carbonitriles **62** were obtained in a one-pot reaction developed by Eger et al.[14b] Hydroxycyclohexanone was condensed with an arylalkylamines in the presence of *p*-toluenesulfonic acid. Subsequent base-catalyzed cyclization with malononitrile yielded the desired product. Reaction of **62** with benzonitrile and sodium methylate in 2-propanol yielded the 2-phenyltetrahydropyrimido[*4,5-d*]indolamine derivatives **63**. Dehydration of the tetrahydroindoles **63** to obtain the desired aromatic indole derivatives **64** was achieved catalytically with Pd/C at high temperatures (Scheme **23**).


OH
O
RNH₂, CH₂(CN)₂
CN
NH₂
N
R
62
benzonitrile,
sodium methylate,
2-propanol
H₂N
N
N
N
R
63
Pd/C
1-methylnaphthalene
H₂N
N
N
N
R
64

Scheme 23

RESULTS AND DISCUSSIONS:

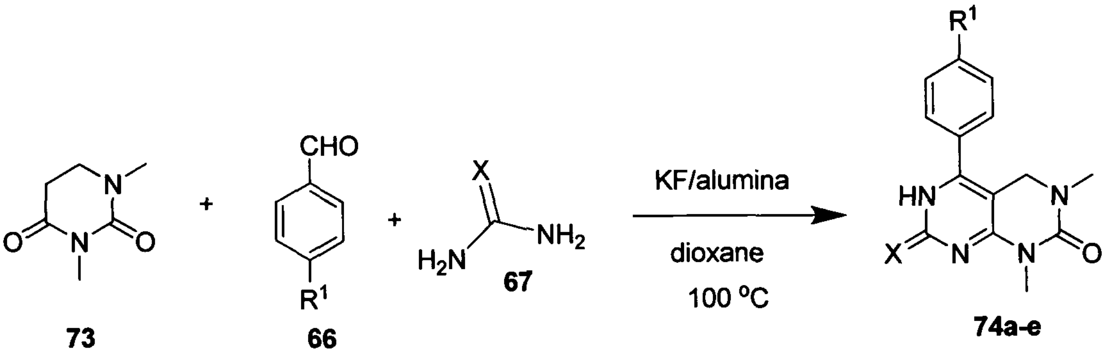
Even though methods for the synthesis of pyrrolo[2,3-*d*]pyrimidine derivatives are widely reported in the literature. However, none of the synthetic procedures reported provides a general route for the synthesis of the three types of fused pyrimidines described here. Thus as part of our ongoing research on the development of new synthetic methods, we found that when 1-methyl-1*H*-pyrrol-2(3*H*)-one **65**, arylaldehydes **66** and urea/guanidine **67** were treated with KF-alumina in ethyl alcohol at 80 °C for 3-5 h, we obtained pyrrolo[2,3-*d*]pyrimidine derivatives **68a-e** in good yield (Scheme **24**). Evidently, a sequence of reactions involving condensation, Michael addition and intramolecular cyclisation took place, in that order, during formation of the product. This may be concluded from the fact that when condensation of 1-methyl-1*H*-pyrrol-2(3*H*)-one and benzaldehyde was carried out, 3-benzylidene-1-methyl-1*H*-pyrrol-2(3*H*)-one was isolated as the product thereby indicating that a condensation reaction is the first step in this three-component reaction.



Scheme 24

In order to demonstrate the efficiency and the applicability of the method, the reaction of a series of arylaldehydes with **71** or **72** was carried out to give the corresponding products **69a-e** and **70a-e** in good yields under same reaction conditions (Table **6**).

The scope of the reaction was also demonstrated by the synthesis of 7-pyrimido[4,5-*d*]pyrimidin-2-ones using 1,3-dimethyl-dihydropyrimidine-2,4-dione **73** as the starting material; the reaction proceeded at 100 °C in presence of KF-alumina as catalyst in dioxane to yield the desired products in moderate yield **74a-e** Scheme **25**.



Scheme 25

The product was also obtained in good yield when an alkyl or an electron donating group was attached to the aromatic ring of **66**. Furthermore, the reaction shown in Scheme **25** proceeded only when dioxane was used as the solvent. The yield of this reaction was improved partially when a few drops of acetic acid were added.

Table 6: Substituted fused pyrimidines

Entry	R^1	X	Yield (%)	Entry	R^1	X	Yield (%)
68a	H	O	86	**69a**	H	NH	87
68b	CH_3	O	76	**69b**	CH_3	O	78
68c	NH_2	O	70	**69c**	NH_2	NH	76
68d	NO_2	NH	81	**69d**	NO_2	O	68
68e	CH_3	NH	92	**69e**	H	O	75
70a	H	NH	77	**74a**	OH	O	50
70b	CH_3	O	81	**74b**	CH_3	O	59
70c	NH_2	NH	83	**74c**	NH_2	O	55
70d	NO_2	O	60	**74d**	NO_2	NH	54
70e	CH_3	NH	66	**74e**	NO_2	O	60

In conclusion, we have developed a convenient method for the synthesis of 5:6 and 6:6 fused pyrimidine derivatives through a three-component reaction catalyzed by KF-alumina having wide applicability, thus providing a general method for the synthesis of potentially biologically active heterocycles.

EXPERIMENTAL:

Melting points were obtained on a Thomas Hoover capillary melting point apparatus and are uncorrected. Carbon, hydrogen and nitrogen analysis were performed with a Perkin-Elmer 2400 series II instrument. IR spectra in BOMEM DA-8 FT-IR spectrophotometer. The ^1H and ^{13}C NMR spectra were recorded on a Bruker AMX 400 spectrometer using $CDCl_3$ or DMSO-d_6 as the solvent. Chemical shifts are reported in ppm from internal tetramethylsilane and are given on the δ scale. The following abbreviations are used to *describe peak patterns when appropriate:* s = *singlet,* d = *doublet,* t = *triplet,* m = *multiplet.* Positive-ion and negative-ion electrospray ionization (ESI) mass spectra were measured on an ion trap analyzer Esquire 3000 (Bruker Daltonics).

All reactions were monitored by TLC on glass plates coated with silica gel (ACME's) containing 13% calcium sulphate as binder and visualization of compounds was accomplished by exposure to iodine vapour or by spraying acidic potassium permanganate solution or 2% ninhydrin solution. Column chromatography was carried out using ACME's silica gel.

Chemicals, reagents and solvents:

Dry solvents were obtained by distillation under N_2 atomsphere with appropriate dehydrating agents. The commercial available chemicals were used without further purification.

General procedure for the preparation of pyrrolo[2, 3-*d*]pyrimidine derivatives:

A dry 100 mL flask was charged with benzaldehyde **66** (8 mmol), urea **67** (8 mmol), 1-methylpyrrolidin-2-one **65** (8 mmol), KF/Al_2O_3 (1 g), and EtOH (30 mL). The mixture was stirred at 80 ^{O}C for 5–8 h. The reaction, after completion (monitored by TLC), was cooled to room temperature, the solvent was evaporated in vacuum and the crude product was purified by silica gel column chromatography using CH_2Cl_2 and methanol (9:1) as eluent to obtain an off- white solid

6,7-dihydro-7-methyl-4-phenyl-3*H*-pyrrolo[*2,3-d*]pyrimidin-2(5*H*)-one 68a.

M.p = 254-256 °C. IR (KBr) 1782 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ ppm 2.01 (t, J = *7.2* Hz, 2H) , 2.52 (s, 3H, CH_3), 2.61 (t, J = *7.2* Hz, 2H), 7.23-7.31 (m, 5H, aromatic), 11.26 (br.s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm $CDCl_3$ 30.5, 36.4, 57.5, 107.1, 126.5, 127.7, 129.1, 134.2, 135.1, 156.5, 160.3. *m/z* = 228.12 (M+1). CHN calculated for $C_{13}H_{13}N_3O$: C, 69.20; H, 5.77; N, 18.49%, observed: C, 69.21; H, 5.71; N, 18.52%.

6,7-dihydro-7-methyl-4-p-tolyl-3*H*-pyrrolo[*2,3-d*]pyrimidin-2(5*H*)-one 68b:

M.p = 261-262 °C. IR (KBr) 3423, 1776 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ ppm 2.01 (t, J = *7.1* Hz, 2H), 2.27 (s, 3H), 2.50 (s, 3H, CH_3), 2.62 (t, J = *7.1* Hz, 2H), 7.12 (d, 2H, J = *7.0* Hz), 7.26 (d, 2H, J = *7.0* Hz), 11.31 (br.s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm $CDCl_3$ 23.7, 31.2, 35.9, 57.8, 108.2, 126.2, 129.9, 132.2, 134.8, 138.7, 157.1, 165.7. *m/z* = 242.11 (M+1). CHN calculated for $C_{14}H_{15}N_3O$: C; 69.69; H, 6.27; N, 17.41%. Observed: C, 69.73, H, 6.29; N, 17.46%.

4-(4-aminophenyl)-6,7-dihydro-7-methyl-3*H*-pyrrolo[*2,3-d*]pyrimidin-2(5*H*)-one 68c:

M.p = 269-270 °C. IR (KBr) 1785 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ ppm 1.99 (t, J = *7.0* Hz, 2H), 2.46 (s, 3H, CH_3), 2.66 (t, J = *7.0* Hz, 2H), 5.46 (br.s, 2H, NH), 6.67 (d, 2H, J

= *7.5* Hz), 7.09 (d, 2H, *J* = *7.5* Hz), 11.29 (br.s, 1H, NH); ^{13}C NMR (CDCl$_3$, 100 MHz) δ ppm CDCl$_3$ 30.8, 34.7, 57.9, 108.5, 117.1, 124.7, 127.9, 134.6, 148.2, 157.4, 165.2. *m/z* = 243.13 (M+1). CHN calculated for $C_{13}H_{14}N_4O$: C, 64.45; H, 5.82; N, 23.13%, observed: C, 64.41; H, 5.77; N, 23.16%.

6,7-dihydro-7-methyl-4-(4-nitrophenyl)-5*H*-pyrrolo[*2,3-d*]pyrimidin-2-amine 68d:

M.p = 256-257 °C. IR (KBr) 3421, 1467 cm^{-1}. ^{1}H NMR (DMSO-*d$_6$*, 400 MHz) δ ppm 2.42 (s, 3H, CH$_3$), 2.59 (t, *J* = *6.3* Hz, 2H), 3.16 (t, *J* = *6.3* Hz, 2H), 6.71 (br.s, 2H, NH), 7.73 (d, 2H, *J* = *7.0* Hz), 8.02 (d, 2H, *J* = *7.0* Hz); ^{13}C NMR (CDCl$_3$, 100 MHz) δ ppm CDCl$_3$ 22.3, 37.1, 56.8, 110.5, 121.4, 128.7, 139.4, 148.9, 158.9, 164.5, 170.3. *m/z* = 272.07 (M+1). CHN calculated for $C_{13}H_{13}N_5O_2$: C, 57.56; H, 4.83; N, 25.82%, observed: C, 57.51; H, 4.80; N, 25.78%.

6,7-dihydro-7-methyl-4-p-tolyl-5*H*-pyrrolo[*2,3-d*]pyrimidin-2-amine 68e:

M.p = 243-245 °C. IR (KBr) 3412, 1459 cm^{-1}. ^{1}H NMR (DMSO-*d$_6$*, 400 MHz) δ ppm 2.19 (s, 3H), 2.32 (s, 3H, CH$_3$), 2.52 (t, *J* = *6.0* Hz, 2H), 3.11 (t, *J* = *6.0* Hz, 2H), 6.67 (br.s, 2H, NH), 7.21 (d, 2H, *J* = *7.4* Hz), 7.42 (d, 2H, *J* = *7.4* Hz); ^{13}C NMR (CDCl$_3$, 100 MHz) δ ppm CDCl$_3$ 21.9, 24.7, 37.9, 56.5, 110.1, 127.9, 129.2, 129.7, 138.8, 159.4, 165.1, 170.9. *m/z* = 241.17 (M+1). CHN calculated for $C_{14}H_{16}N_4$: C, 69.97; H, 6.71; N, 23.32%, observed: C, 69.92; H, 6.67; N, 23.27%.

General procedure for the preparation of pyrido[*2,3-d*]pyrimidine derivatives:

A dry 100 mL flask was charged with benzaldehyde **66** (8.8 mmol), urea **67** (8.8 mmol), 1-methylpiperidin-2-one **71** (8.8 mmol), KF-alumina (1 g), and EtOH (30 mL). The mixture was stirred at 80 ^{O}C for 5–8 h. The reaction, after completion (monitored by TLC), was cooled to room temperature, the solvent was evaporated in vacuum and the crude product was purified by silica gel column chromatography using CH_2Cl_2 and methanol (9:1) as eluent to obtain an off- white solid

5,6,7,8-tetrahydro-8-methyl-4-phenylpyrido[*2,3-d*]pyrimidin-2-amine 70a:

IR (KBr) 3432 cm^{-1}. M.p > 300 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm 1.77 (m, 2H), 2.17 (t, J = *5.7* Hz, 2H), 2.43 (s, 3H, CH_3), 2.96 (t, J = *5.7* Hz, 2H), 6.98 (br.s, 2H, NH) 7.32-7.47 (m, 5H, aromatic),; ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 20.9, 23.6, 38.6, 49.9, 108.7, 127.6, 128.5, 129.9, 133.6, 159.9, 164.6, 171.3. *m/z* = 241.12 (M+1). CHN calculated for $C_{14}H_{16}N_4$: C, 69.97; H, 6.71; N, 23.32%, observed: C, 70.02; H, 6.74; N, 23.31%.

5,6,7,8-tetrahydro-8-methyl-4-p-tolylpyrido[*2,3-d*]pyrimidin-2(3*H*)-one 70b:

IR (KBr) 1778 cm^{-1}. M.p > 300 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm 1.42 (m, 2H), 1.91 (t, J = *7.1* Hz, 2H), 2.37 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 2.56 (t, J = 7.1 Hz, 2H), 7.02-7.21 (m, 4H, aromatic), 11.15 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 21.7, 24.3, 25.1, 35.1, 45.7, 105.6, 126.1, 128.7, 130.9, 133.2, 137.7, 156.2, 159.6. *m/z* = 256.14 (M+1). CHN calculated for $C_{15}H_{17}N_3O$: C, 70.56; H, 6.71; N, 16.46%, observed: C, 70.65; H, 6.68; N, 16.56%.

4-(4-aminophenyl)-5,6,7,8-tetrahydro-8-methylpyrido[*2,3-d*]pyrimidin-2-amine 70c:

IR (KBr) 3452 cm^{-1}. M.p > 300 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm 1.82 (m, 2H), 2.40 (s, 3H, CH_3), 2.47 (t, J = *5.2* Hz, 2H), 3.01 (t, J = *5.2* Hz, 2H), 5.63 (br.s, 2H), 6.61 (d, 2H, J = *7.0* Hz), 6.95 (br.s, 2H, NH), 7.17 (d, 2H, J = *7.0* Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 20.1, 23.2, 38.9, 50.9, 110.8, 116.4, 122.9, 129.1, 148.2, 160.4, 165.8, 172.0. *m/z* = 256.16 (M+1). CHN calculated for $C_{14}H_{17}N_5$: C, 65.86; H, 6.71; N, 27.43%, observed: C, 65.91; H, 6.65; N, 27.58%.

5,6,7,8-tetrahydro-8-methyl-4-(4-nitrophenyl)pyrido[*2,3-d*]pyrimidin-2(3*H*)-one 70d:

IR (KBr) 1761 cm^{-1}. M.p > 300 °C. ^1H NMR (DMSO-d_6, 400 MHz) δ ppm 1.47 (m, 2H), 1.99 (t, *J* = *7.0* Hz, 2H), 2.40 (s, 3H, CH_3), 2.59 (t, *J* = *7.0* Hz, 2H), 7.62 (d, 2H, *J* = *7.9* Hz), 8.07 (d, 2H, *J* = *7.9* Hz), 11.23 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 22.4, 24.0, 35.9, 46.3, 106.3, 121.7, 127.7, 133.9, 139.7, 146.9, 156.8, 160.3. *m/z* = 287.11 (M+1). CHN calculated for $C_{14}H_{14}N_4O_3$: C, 58.73; H, 4.93; N, 19.57%, observed: C, 58.79; H, 4.99; N, 19.63%.

5,6,7,8-tetrahydro-8-methyl-4-p-tolylpyrido[*2,3-d*]pyrimidin-2-amine 70e:

IR (KBr) 3421 cm^{-1}. M.p > 300 °C. ^1H NMR (DMSO-d_6, 400 MHz) δ ppm 1.81 (m, 2H), 2.23 (t, *J* = *5.9 Hz*, 2H), 2.29 (s, 3H), 2.40 (s, 3H, CH_3), 2.91 (t, *J* = *5.9* Hz, 2H), 6.93 (br.s, 2H, NH) 7.16 (d, 2H, *J* = *9.1* Hz), 7.27 (d, 2H, *J* = *9.1* Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 20.1, 22.9, 24.1, 38.9, 50.6, 109.9, 127.9, 129.9, 139.7, 138.6, 160.5, 165.9, 172.7. *m/z* = 255.16 (M+1). CHN calculated for $C_{15}H_{18}N_4$: C, 70.84; H, 7.13; N, 22.03%, observed: C, 70.89; H, 7.19; N, 22.07%.

General procedure for the preparation of pyrimido[4,5-b]indole derivatives:

A dry 100 mL flask was charged with benzaldehyde **66** (6.8 mmol), urea **67** (6.8 mmol), 1-methylindolin-2-one **72** (6.8 mmol), KF-alumina (1 g), and EtOH (30 mL). The mixture was stirred at 80 °C for 5–8 h. The reaction, after completion (monitored by TLC), was cooled to room temperature, the solvent was evaporated in vacuum and the crude product was purified by silica gel column chromatography using CH_2Cl_2 and methanol (9:1) as eluent to obtain an off- white solid

9-methyl-4-phenyl-3*H*-pyrimido[*4,5-b*]indol-2(9*H*)-one 69a:

IR (KBr) 3423 cm^{-1}. M.p > 300 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm 3.65 (s, 3H, CH_3), 6.15 (s, 2H, NH_2) 7.21 (dd, *J* = 7.0 Hz, 1H), 7.24-7.30 (m, 4H, aromatic), 7.32 ~ 7.35 (m, 2H, aromatic), 7.44 (d, *J* = 7.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 44.6, 102.4, 111.3, 119.1, 120.5, 122.5, 127.6, 127.9, 128.5, 129.1, 131.8, 133.5, 136.7, 162.7, 163.7. *m/z* = 275.13. CHN calculated for $C_{17}H_{14}N_4$: C, 74.43; H, 5.14; N, 20.42%, observed C, 74.53; H, 5.184; N, 20.62%.

9-methyl-4-p-tolyl-3*H*-pyrimido[*4,5-b*]indol-2(9*H*)-one 69b:

IR (KBr) 1721 cm^{-1}. M.p > 300 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm 2.26 (s, 3H), 2.79 (s, 3H, CH_3), 6.77 ~ 6.84 (m, 4H, aromatic), 7.12 (d, *J* = 7.2 Hz, 2H), 7.31 (d, *J* = 7.2 Hz, 2H), 11.27 (br.s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 24.3, 31.4, 101.9, 113.2, 114.9, 117.6, 125.9, 127.5, 128.4, 129.2, 131.9, 135.3, 137.9, 149.5, 156.7, 167.1. *m/z* = 290.12. CHN calculated for $C_{18}H_{15}N_3O$: C, 74.72; H, 5.23; N, 14.52%, observed C, 74.79; H, 5.29; N, 14.58%.

4-(4-aminophenyl)-9-methyl-9*H*-pyrimido[*4,5-b*]indol-2-amine 69c:

IR (KBr) 3432 cm^{-1}. M.p > 300 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm 3.48 (s, 3H, CH_3), 6.12 (br.s, 2H), 6.65 (d, *J* = 7.2 Hz, 1H), 6.97 (br.s, 2H), 7.21 ~ 7.27 (m, 4H, aromatic), 7.32 (d, *J* = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 45.2, 102.5, 112.1, 116.7, 119.9, 120.5, 122.4, 123.5, 127.7, 128.6, 131.7, 137.6, 149.2, 162.7, 163.2. *m/z* = 290.14. CHN calculated for $C_{17}H_{15}N_5$: C, 70.57; H, 5.23; N, 24.21%, observed C, 70.62; H, 5.27; N, 24.28%.

9-methyl-4-(4-nitrophenyl)-3*H*-pyrimido[*4,5-b*]indol-2(9*H*)-one 69d:

IR (KBr) 1745 cm^{-1}. M.p > 300 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm 2.77 (s, 3H, CH$_3$), 6.82 ~ 6.92 (m, 4H, aromatic), 7.56 (d, *J* = *7.0* Hz, 2H), 8.11 (d, *J* = *7.0* Hz, 2H), 11.32 (br.s, 1H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ ppm 30.4, 103.9, 113.6, 114.5, 117.7, 121.5, 126.3, 127.5, 128.2, 135.8, 139.9, 147.4, 149.6, 156.1, 167.9. *m/z* = 321.08. CHN calculated for $C_{17}H_{12}N_4O_3$: C, 63.75; H, 3.78; N, 17.49%, observed C, 63.79; H, 3.83; N, 17.54%.

9-methyl-4-phenyl-3*H*-pyrimido[4,5-b]indol-2(9*H*)-one 69e:

IR (KBr) 1732 cm^{-1}. M.p > 300 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm 2.86 (s, 3H, CH$_3$), 6.61 (d, *J* = *7.5* Hz, 1H), 6.72 ~ 6.85 (m, 2H, aromatic), 7.17 ~ 7.24 (m, 4H, aromatic), 7.29 (d, *J* = *7.5* Hz, 2H), 11.23 (br.s, 1H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ ppm 31.4, 104.9, 112.7, 115.2, 117.8, 119.1, 125.8, 126.7, 127.9, 128.4, 129.2, 134.7, 137.2, 156.7, 168.2. *m/z* = 276.11. CHN calculated for $C_{17}H_{13}N_3O$: C, 74.17; H, 4.76; N, 15.26%, observed C, 74.11; H, 4.81; N, 15.29%

General procedure for the preparation of pyrimido[4,5-*b*]indole derivatives:

A dry 100 mL flask was charged with benzaldehyde **66** (7 mmol), urea **67** (7 mmol), dihydro-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione **73** (7 mmol), KF-alumina (1 g), and EtOH (30 mL). The mixture was stirred at 80 °C for 5–8 h. The reaction, after completion (monitored by TLC), was cooled to room temperature, the solvent was evaporated in vacuum and the crude product was purified by silica gel column chromatography using CH_2Cl_2 and methanol (9:1) as eluent to obtain an off- white solid.

7-amino-3,4-dihydro-5-(4-hydroxyphenyl)-1,3-dimethylpyrimido[*4,5-d*]pyrimidin-2(1*H*)-one 74a:

IR (KBr) 1675 cm^{-1}. M.p = 252-253 °C. ^{1}H NMR (DMSO-*d$_6$*, 400 MHz) δ ppm 2.41 (s, 3H, CH_3) 2.68 (s, 6H, CH_3), 3.92 (s, 2H, CH_2), 7.01 (d, *J* = 7.0 Hz, 2H, aromatic), 7.15 (d, *J* = 7.2 Hz, 2H, aromatic), 11.36 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 24.6, 29.7, 38.0, 46.5, 103.6, 126.2, 128.5, 131.6, 134.1, 138.2, 154.9, 156.4, 158.6. *m/z* = 283.13 (M-1). CHN calculated for $C_{15}H_{16}N_4O_2$: C, 63.37; H, 5.67; N, 19.71%, observed: C, 63.47; H, 5.77; N, 19.61%.

3,4-dihydro-1,3-dimethyl-5-p-tolylpyrimido[*4,5-d*]pyrimidine-2,7(1*H*,6*H*)-dione 74b:

IR (KBr) 1665, 3375 cm^{-1}. M.p = 265-266 °C ^{1}H NMR (DMSO-*d$_6$*, 400 MHz) δ ppm 2.31 (s, 3H), 2.69 (s, 6H, CH_3), 3.87 (s, 2H, CH_2), 7.12 (d, *J* = *7.5* Hz, 2H, aromatic), 7.23 (d, *J* = *7.5* Hz, 2H, aromatic), 11.43 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 24.2, 29.5, 36.8, 46.2, 102.1, 126.2, 129.5, 131.6, 133.7, 136.9, 155.2, 156.1, 158.2. *m/z* = 285.13 (M+1). CHN calculated for $C_{15}H_{16}N_4O_2$: C, 63.37; H, 5.67; N, 19.71%, observed C, 63.42; H, 5.63; N, 19.78%.

5-(4-aminophenyl)-3,4-dihydro-1,3-dimethylpyrimido[*4,5-d*]pyrimidine-2,7(1*H*,6*H*)-dione 74 c:

IR (KBr) 1687, 3378 cm^{-1}. M.p = 262-263 °C ^{1}H NMR (DMSO-*d$_6$*, 400 MHz) δ ppm 2.72 (s, 6H, CH_3), 3.81 (s, 2H, CH_2), 5.98 (br.s, 2H), 6.54 (d, *J* = *7.2* Hz, 2H, aromatic), 7.12 (d, *J* = *7.2* Hz, 2H, aromatic), 11.31 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 29.2, 37.1, 46.8, 103.6, 117.5, 124.9, 127.7, 133.1, 147.2, 155.2, 156.7, 158.9. *m/z* = 286.11 (M+1). CHN calculated for $C_{14}H_{15}N_5O_2$: C, 58.94; H, 5.30; N, 24.55%, observed C, 59.03; H, 5.37; N, 24.59%.

7-amino-3,4-dihydro-1,3-dimethyl-5-(4-nitrophenyl)pyrimido[*4,5-d*]pyrimidin-2(1*H*)-one 74d:

IR (KBr) 1671, 3341 cm^{-1}. M.p = 266-267 °C ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm 2.78 (s, 6H, CH_3), 4.41 (s, 2H, CH_2), 6.68 (br.s, 2H), 7.76 (d, J = *7.0* Hz, 2H, aromatic), 8.31 (d, J = *7.0* Hz, 2H, aromatic); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 32.1, 36.2, 43.9, 104.5, 120.8, 127.4, 137.9, 149.4, 152.7, 160.3, 167.8, 170.3. m/z = 315.12 (M+1). CHN calculated for $C_{14}H_{14}N_6O_3$: C, 53.50; H, 4.49; N, 26.74%, observed C, 53.55; H, 4.51; N, 26.79%.

3,4-dihydro-1,3-dimethyl-5-(4-nitrophenyl)pyrimido[*4,5-d*]pyrimidine-2,7(1*H*,6*H*)-dione 74e:

IR (KBr) 1680, 3385 cm^{-1}. M.p = 257-258 °C ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm 2.67 (s, 6H, CH_3), 3.95 (s, 2H, CH_2), 7.56 (d, J = 7.0 Hz, 2H, aromatic), 8.18 (d, J = 7.2 Hz, 2H, aromatic), 11.57 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 29.7, 36.9, 46.5, 102.6, 120.9, 126.9, 134.1, 140.3, 147.5, 155.7, 156.2, 159.1. m/z = 316.10 (M+1). CHN calculated for $C_{14}H_{13}N_5O_4$: C, 53.33; H, 4.16; N, 22.21%, observed C, 53.43; H, 4.26; N, 22.11%.

REFERENCES.

1. Thompson, A.M.; Bridges, A.J.; Fry, D.W.; Kraker, A.J.; Denny, W.A. *J. Med. Chem.* **1995**, *38*, 3780-3788.
2. Bredereck, H.; Gompper, R.; Schuh, H. G.; Theilig, G. *Angew. Chem.* **1959**, *71*, 753-760.
3. Monge, A.; Martinez-Merino, V.; Sanmartin, C.; Fernandez, F.J.; Ochoa, M.C.; Berllver, C.; Artigas, P.; Fernandez-Alvarez, E. *Eur. J. Med. Chem.* **1989**, *24*, 209-211.
4. Matsunaga, T.; Tohda, Y.; Ariga, M. *J. Chem. Soc., Perkin Trans. 1* **2000**, 27-34.
5. (a) Trapini, G.; Franco, M.; Latrofa, A.; Ricciardi, L.;Carotti, A.; Serra, M.; Sanna, E.; Biggio, G.; Liso, G. *J. Med. Chem.* **1999**, *42*, 3934-3941; (b) Lober, S.; Hubner, H.; Gmeneir, P. *Bioorg. Med. Chem. Lett.* **1999**, *42*, 3934-3940; (c) Rival, Y.; Grassy, G.; Michel, G. *Chem. Pharm. Bull.* **1992**, *40*, 1170-1178; (d) Lyon, M.; Kercker, T. *Org. Lett.* **2004**, *26*, 4989-4994; (e) Jaramillo, C.; Carretero, C.; de Diego, E.; Hamoduchi, C.; del Prado, M.; Roldan, J. L.; Sanchez-Martinez, C. *Tetrahedron Lett.* **2002**, *43*, 9051-9056; (f) Kaminski, J. J.; Wallmark, B.; Briving, C.; Andersson, B. M. *J. Med. Chem.* **1991**, *34*, 533-542; (g) Georges, G.;Vercauteren, D. P.; Vanderveken, D. J.; Horion, R.;Evrard, G. H.; Durant, F. V.; George, P.; Wick, A. *Eur. J.Med. Chem.* **1993**, *28*, 323-332.
6. (a) Bristow, N. W.; Charlton, P. T.; Peak, D. A.; Short, W.F. *J. Chem. Soc.* **1954**, 616–629; (b) Tadeka, K.; Shudo, K.; Okamoto, T.; Kousuge, T. *Chem. Pharm. Bull.* **1978**, *26*, 2924; (c) Knott, E. B. *J. Chem. Soc.* **1956**, 1360-1365; (d) Sugiura, S.; Akoi, H. K.; Inouf, S.; Goto, T. Yakukagaku Zasshi **1970**, *90*, 436-442; (e) Fisher, G.,

Saint-Ruf, G.; Loukakou, B.; Zousi, C. *J. Heterocycl. Chem.* **1981**, *18*, 1565–1570; (f) Ohta, M.; Masaki, M. *Bull. Chem. Soc. Jpn.* **1960**, *37*, 1392-1399.

7. D. J. Brown, "The Pyrimidines", 1st ed., Wiley, N.Y., **1962**, p. 19-105.
8. Bystryakova, I.D.; Burova, I.A.; Chelysheva, G.M.; Zhilinkova, S.V.; Smirnova, N.M.; Safonova, T.S. *Khim-Farm. Zh.* **1991**, *25*, 31-37.
9. Deyanov, A.B.; Niyazov, R.K.; Nazmetdinov, F.Y.; Syropyatov, B.Y.; Kolla, V.E.; Konshin, M.E. *Khim-Farm. Zh.* **1991**, *25*, 26-32.
10. (a) Jourdan, F.; Laduree, D.; Robba, M. *J. Heterocycl. Chem.* **1994**, *31*, 305-312. (b) Anderson, E. L.; Casey, J. E.; Greene, L. C.; Lafferty, J. J.; Reiff, H. E. *J. Med. Chem.* **1964**, *7*, 259-268. (c) Russell, P. B.; Hitchings, J. H. *J. Am.Chem. Soc.* **1951**, *73*, 3763-3770. (d) Bruni, F.; Selleri,S.; Costanzo, A.; Guerrini, G.; Casilli, M. L.; Giusti, L. *J.Heterocycl. Chem.* **1995**, *32*, 291-298. (e) Barlin, G. B.; Kotecka, B.; Rieckmann, K. H. *Aust. J. Chem.* **1996**, *49*, 647-650. (f) Selleri, S.; Bruni, F.; Costanzo, A.; Guerrini, G.; Casilli, M. L. *Farmaco* **1995**, *50*, 679-688.
11. Girgis, N.S.; Michael, M.A.; Smee, D.F.; Alaghamandan, H.A.; Robins, R.K.; et al. *J. Med. Chem.* **1990**, *33*, 2750–2755.
12. Blass, B.E.; Coburn, K.; Fairweather, N.; Sabat, M.; West, L. *Tetrahedron. Lett.* **2006**, *47*, 3177-3180.
13. Wang, X.; Zeng, Z.; Shi, D.; Wei, X.; Zong, Z. *Synthetic Communication.* **2004**, *34*, 4331-4338.
14. (a)Müller, C.E.; Geis, U.; Grahner, B.; Lanzner, W.; Eger, K. *J. Med. Chem.* **1996**, *39*, 2482-2491. (b) Eger, K.; Lanzer,Pfahl, J. G.; Folkers, G.; Roth, H.J. *J.Heterocylc. Chem.* **1987**, *24*, 425-470.

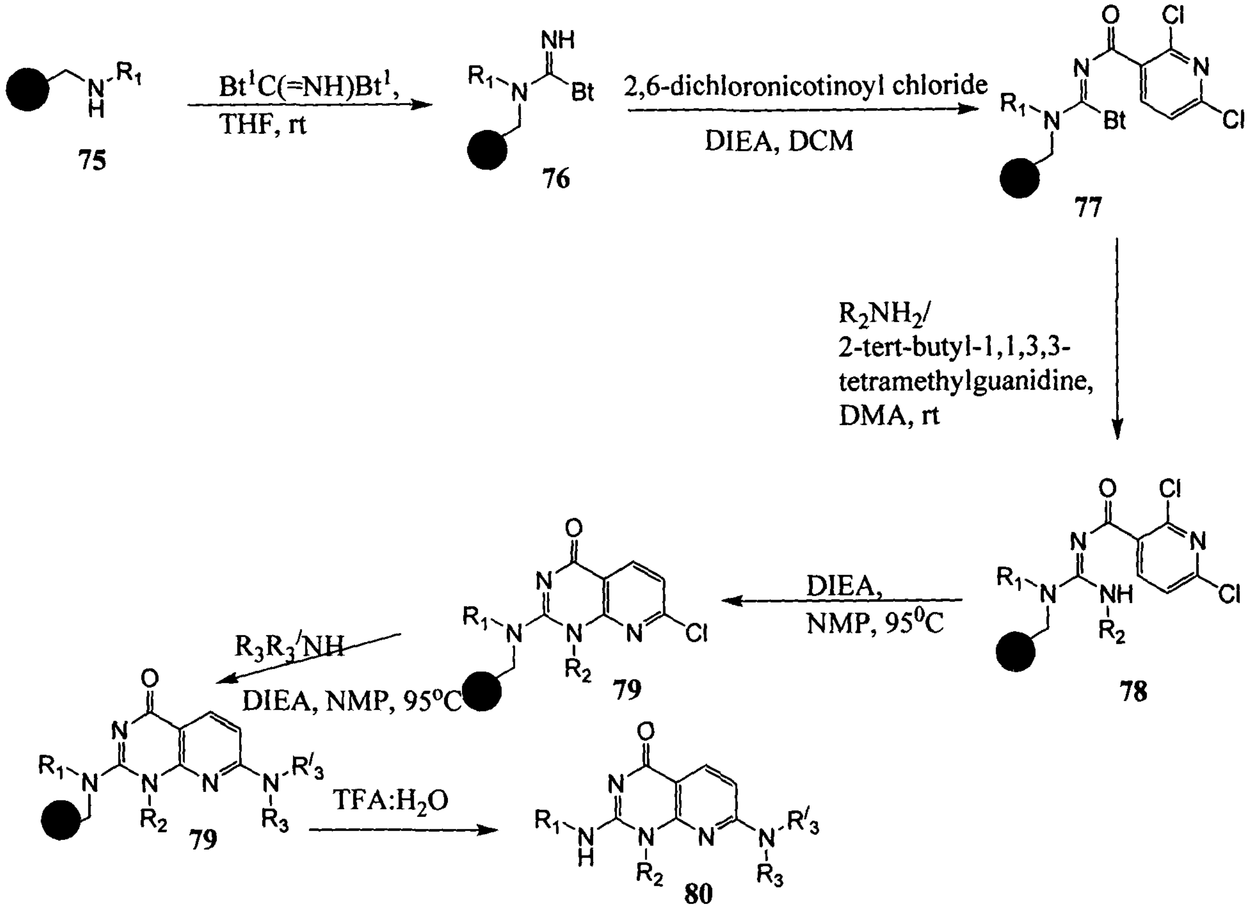
CHAPTER VI

A facile, three-component method for the synthesis of substituted fused pyrimidines, pyridines, pyridazines and quinolines; catalysed by KF-alumina

INTRODUCTION:

The drive for more environmentally friendly procedures and the need for increased efficiency have led to an explosive growth in the fields of both multi-component organic synthesis and in the uses of solid support reagents such as KF-alumina. This versatile reagent was originally introduced in 1979 by Ando *et al* as a useful reagent for inducing alkylation reactions.[1] KF-Alumina is strongly basic in nature and because of this nature it has replaced organic bases in number of reactions such as selective *N*-alkylation of amides,[2] epoxidations,[3] diazotizations,[4] the Sonagashira couplings,[5] the Suzuki couplings,[6] the Biginelli reaction,[7] the Knoevenagel reactions,[8] and Horner-Emmons Chemistry.[9]

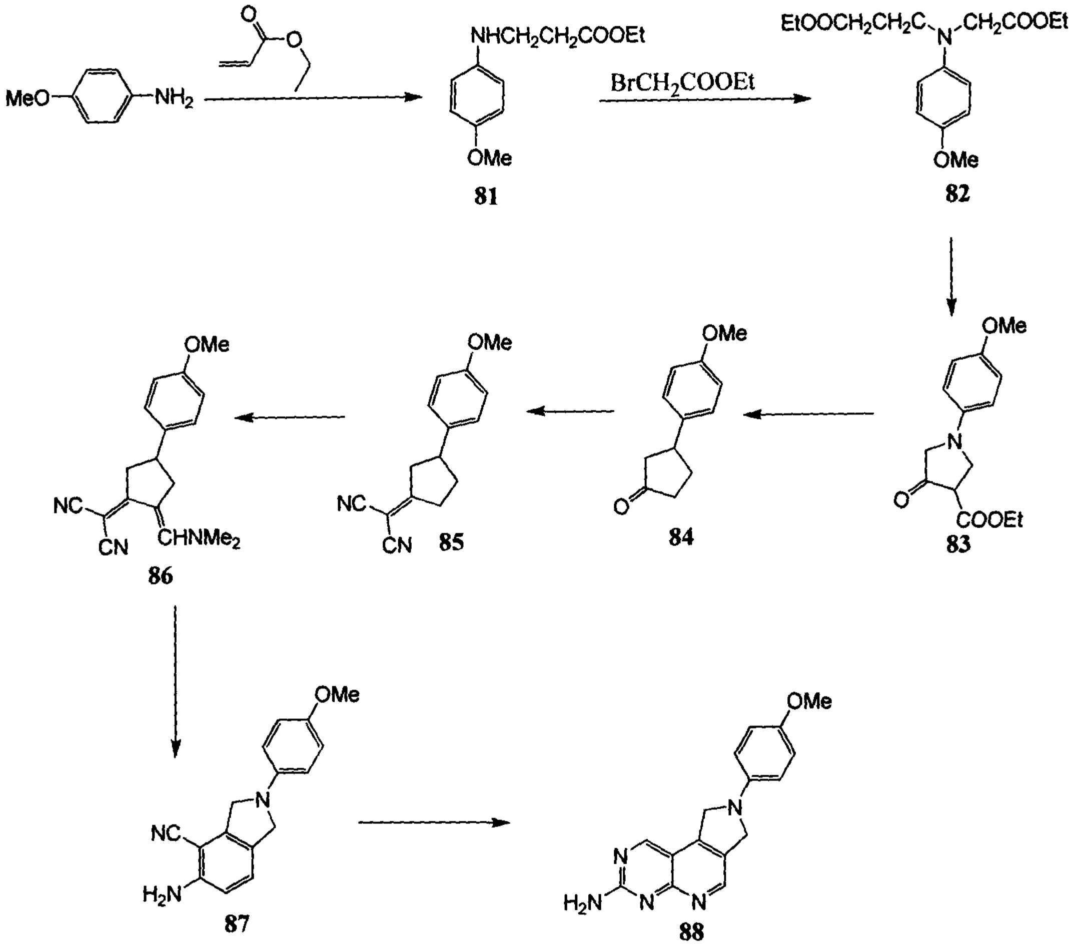
Our literature survey reveals that a number of methods have been developed for the synthesis pyrido[*2,3-d*]pyrimidines. Schell[10] and co-worker devised a versatile solid-phase synthesis of pyrido[*2,3-d*]pyrimidines. The overall synthetic strategy for the synthesis of di- and trisubstituted 1*H*-pyrido[2,3-*d*]pyrimidin-4-ones is outlined in Scheme **26**. Resin-bound secondary amines **75**, generated by the standard solid-phase reductive amination protocol ($NaBH(OAc)_3$/1% AcOH/DMF) from commercially available FMP-resin, were reacted with a solution of di(benzotriazolyl) methanimine in THF to give resin **76**. Resin **76** was acylated with 2,6-dichloronicotinoyl chloride using a variant of our previously described protocol to obtain resin **77**. 2-*tert*butyl-1,1,3,3-tetramethylguanidine (Barton's base) proved to be most efficient for the formation of resin **78**, in terms of both yield and selectivity for benzotriazole displacement. The reaction proceeds at room temperature and no chlorine displacement could be detected. Subsequent cyclization takes place at 95 °C, with DIEA in NMP, giving the best results for cyclized resin **79**. The displacement of the second chlorine by a primary or secondary amine was achieved with DIEA as base at the same temperature. Cleavage of resin **80** with TFA gave the desired trisubstituted 1*H*-pyrido[2,3-*d*]pyrimidin-4-ones (**80**) as TFA salts in good yields and with high purity.



Scheme 26

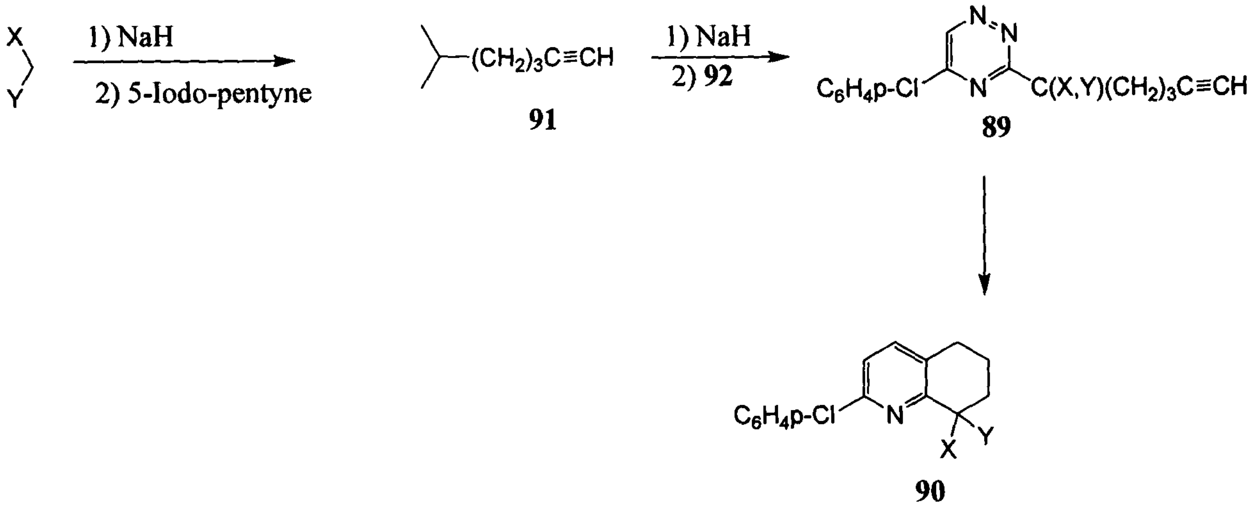
Su[11] and co-worker synthesized pyrido[2,3-*d*]pyrimidines **88** by reacting *p*-anisidine and ethyl acrylate, which gave the addition product ethyl *N*-(4-methoxyphenyl)-β-aminopropionate **81** (Scheme 27). After treatment of **81** with ethyl bromoacetate, the product, ethyl *N*-[β-(ethoxycarbonyl)- ethyl]-*N*-(4-methoxyphenyl)glycinate (**81**), was converted into 1-(4-methoxyphenyl)-4-(ethoxycarbonyl)pyrrolidin-one (**82**) by an intramolecular Dieckmann reaction. Hydrolysis of ester **82** and decarboxylation of the product to 1-(4-methoxyphenyl)pyrrolidin-3-one **83** were performed in situ with 6 N HCl at 100 °C (bath temperature). The bath had to be removed promptly after evolution of CO_2

ceased because **83** was unstable, undergoing decomposition upon prolonged heating. The conditions required for these reactions were rather strict. At higher temperatures, the product decomposed rapidly. At lower temperatures, the reactions proceeded much more slowly, which led to decomposition of **83**. Knoevenagel condensation of **83** with malononitrile also required caution since the dicyanomethylene product **84** polymerized readily in solution even at room temperature. Among several reactions attempted to convert **85** into a (potential) 4-formyl intermediate such as **86**, the best result was obtained when **83** was lithiated with lithium diisopropylamide in THF at -65 °C followed by treatment with (dimethylamino)-methylene dichloride. When **86** was treated with NH_3/MeOH in a sealed container at 150 °C, 6-amino-7-cyano-2,3-dihydropyrrolo-[*3,4-c*]pyridine (**87**) was obtained. Condensation of **87** with *N,N*-dimethylguanidine in DMF at 120°C for 3 days afforded the desired 2,4-diamino-N^6-(4-methoxyphenyl)-6,7-dihydropyrrolo[*3,4-c*]pyrido-[*2,3-d*]pyrimidine (**88**) in high yield.



Scheme 27

Taylor[12] and co-workers demonstrated a very efficient method for the synthesis of 5,6,7,8-Tetrahydroquinoline **90** via an intramolecular Diels-Alder Reactions of 1,2,4-Triazines **89**. Reaction of the anions of a series of active methylene compounds with 4-iodo-l-butynes yielded the alkynes **91**, which were then converted to their anions and treated with 3-(methylsulfonyl)-l,2,4-triazines **92** to yield the desired Diels-Alder precursors **89** (Scheme **28**). As expected, the rate of cycloaddition **89** was substantially slower due to the longer chain linking diene and dienophile. However, yields of products from these cyclizations were excellent, and this method represents a simple approach to 5,6,7,8-tetrahydroquinolines **(90)**.

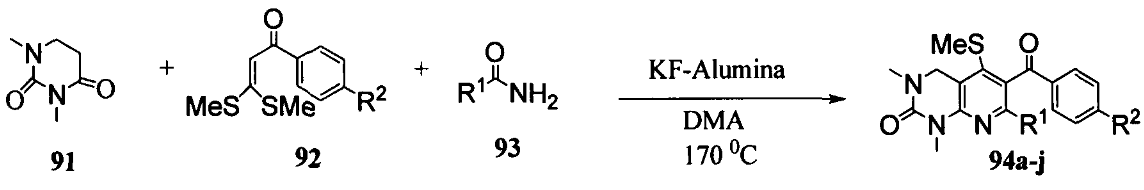

X
Y
1) NaH
2) 5-Iodo-pentyne
(CH2)3C≡CH
91
1) NaH
2) 92
N
N
N
C6H4p-Cl
C(X,Y)(CH2)3C≡CH
89
C6H4p-Cl
N
X
Y
90

Scheme 28

RESULTS AND DISCUSIONS:

As a part of our ongoing work to explore the utilities of KF-alumina catalyzed three-component reactions,[13] we wish to report herein it's utilities in the synthesis of 5,6,7-trisubstituted-3,4-dihydro-1,3-dimethylpyrido[*2,3-d*]pyrimidin-2(1*H*)-one **94a-j**, 4,5,6-trisubstituted-2,3-dihydro-1-methyl-1*H*-pyrrolo[*2,3-b*]pyridine **97a-j**, substituted 9-methyl-9*H*-pyrido[*2,3-b*]indole **98a-j** and substituted 5,6,7,8-tetrahydroquinoline **100a-f**. These classes of compounds show wide range of biological activities, such as antifolate activity, antibacterial activity, tyrosine kinase activity, antimicrobial activity, anticonvulsants activity.[14-15]

Our primary method to prepare **94a-j** involves three component reaction between 1,3-dimethyl dihydropyrimidine-2,4-dione **91**, substituted aryl-oxoketene dithioacetal **92** and alkyl/aryl amides **93** in presence of KF-Alumina. The reaction presumably involves Michael Addition and condensation sequentially to yield the desired products. These reactions were attempted in range of solvents such as DCM, acetonitrile, DMF, THF, and 1,4-dioxane. However, the desired products were obtained in DMA (dimethyl acetamide) at 170 °C (Scheme-29). In all other solvents, either no reaction occurred or the results were a complex mixture of products. All the reactions studied took between 7-12 h for completion. The reaction time increased when steric demands of the reactant **93** increases (Table 7)

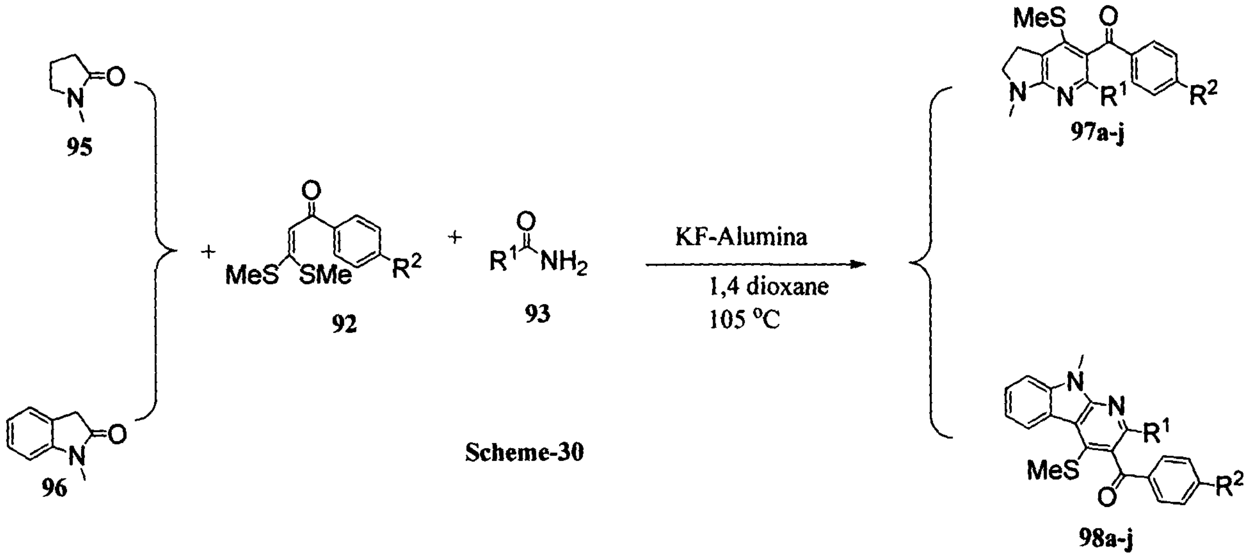


Scheme-29

Table 7: Substituted fused pyridines

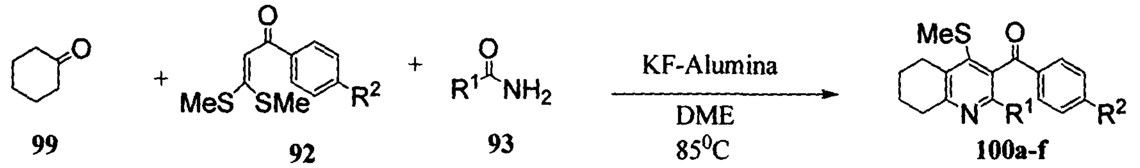
Entry	R^1	R^2	Yield (%)	Entry	R^1	R^2	Yield (%)
94a	CH_3	H	67	**97f**	C_6H_5	H	58
94b	CH_3	NO_2	71	**97g**	C_6H_5	NO_2	62
94c	CH_3	Br	57	**97h**	C_6H_5	Br	49
94d	CH_3	Cl	76	**97i**	C_6H_5	Cl	44
94e	CH_3	F	68	**97j**	C_6H_5	NH_2	40
94f	C_6H_5	H	54	**98a**	CH_3	H	78
94g	C_6H_5	NO_2	53	**98b**	CH_3	NO_2	71
94h	C_6H_5	Br	60	**98c**	CH_3	Br	72
94i	C_6H_5	Cl	61	**98d**	CH_3	Cl	56
94j	C_6H_5	NH_2	51	**98e**	CH_3	F	57
97a	CH_3	H	61	**98f**	C_6H_5	H	46
97b	CH_3	NO_2	67	**98g**	C_6H_5	NO_2	58
97c	CH_3	Br	73	**98h**	C_6H_5	Br	45
97d	CH_3	Cl	77	**98i**	C_6H_5	Cl	50
97e	CH_3	F	70	**98j**	C_6H_5	NH_2	40

The feasibility of this synthetic methodology was further demonstrated by the synthesis of **97a-j** and **98a-j** using 1-methyl-1*H*-pyrrol-2(3*H*)-one **95** or 1-methylindolin-2-one **96**, substituted aryl-oxoketene dithioacetal **92** and alkyl/aryl amides **93**. It was observed that the reaction carried out in 1,4-dioxane at 105 °C provided the desired product in moderate yield (Scheme **30**).[14–15]



Scheme-30

The versatility of this method was again shown by the synthesis of **100a-j** starting from cyclohexanone **99**, substituted aryl-oxoketene dithioacetal **92** and alkyl/aryl amides **93** in presence of KF-Alumina to yield the desired products (Scheme **31**). The reactions were found to be solvent dependent and proceeded only in DME (Dimethoxy ethane) at 85 °C (Table **8**).

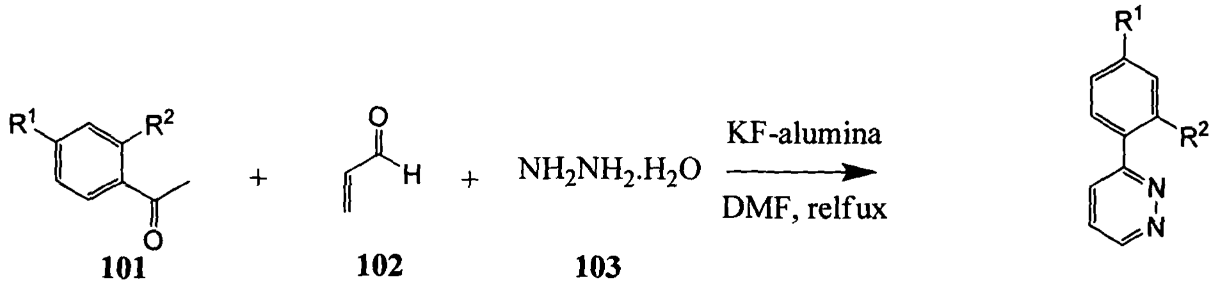


Scheme-31

Table 8: Substituted quinolines and pyridazines

Entry	R^1	R^2	Yield (%)	Entry	R^1	R^2	Yield (%)
100a	CH_3	Cl	79	**104a**	H	Br	62
100b	CH_3	NO_2	77	**104b**	Br	H	76
100c	CH_3	H	70	**104c**	Cl	H	79
100d	C_6H_5	F	65	**104d**	H	H	80
100e	C_6H_5	NH_2	54	**104e**	NO_2	H	83
100f	C_6H_5	Br	62	**104f**	Br	Br	72

This method was further used for the synthesis of 4-substituted pyridazines **104a-f** using substituted acetophenone **101**, acrylaldehyde **102** and hydrazine hydrate using KF-alumina as a catalyst. (Scheme **32**)



104a-f

Scheme 32

In conclusion, efficient methods for the synthesis of biologically active scaffolds were developed using the solid phase reagent, KF-Alumina.

EXPERIMENTAL:

Melting points were obtained on a Thomas Hoover capillary melting point apparatus and are uncorrected. Carbon, hydrogen and nitrogen analysis were performed with a Perkin-Elmer 2400 series II instrument. IR spectra in BOMEM DA-8 FT-IR spectrophotometer. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AMX 400 spectrometer using $CDCl_3$ or DMSO-d_6 as the solvent. Chemical shifts are reported in ppm from internal tetramethylsilane and are given on the δ scale. The following abbreviations are used to describe peak patterns when appropriate: s = singlet, d = doublet, t = triplet, m = multiplet. Positive-ion and negative-ion electrospray ionization (ESI) mass spectra were measured on an ion trap analyzer Esquire 3000 (Bruker Daltonics).

All reactions were monitored by TLC on glass plates coated with silica gel (ACME's) containing 13% calcium sulphate as binder and visualization of compounds was accomplished by exposure to iodine vapour or by spraying acidic potassium permanganate solution or 2% ninhydrin solution. Column chromatography was carried out using ACME's silica gel.

Chemicals, reagents and solvents:

Dry solvents were obtained by distillation under N_2 atomsphere with appropriate dehydrating agents. The commercial available chemicals were used without further purification.

General procedure for the preparation 6-(5,6,7-trisubstituted-3,4-dihydro-1,3-dimethylpyrido[*2,3-d*]pyrimidin-2(1*H*)-one)(subsitutedphenyl)methanone:

A dry 100 mL flask was charged with 3,3-bis(methylthio)-1-phenylprop-2-en-1-one **92** (4.5 mmol), acetamides **93** (4.9 mmol), 1,3-dimethyl dihydropyrimidine-2,4-dione **91** (4.9 mmol), KF-alumina (1 g), and DMA (15 mL). The mixture was stirred at 170 °C for 10 h. The reaction after completion (monitored by TLC), was cooled to room temperature, the solvent was evaporated in vacuum, and the crude product was purified by silica gel column chromatography using $CHCl_3$ as eluent to obtain **94a-j.**

6-(3,4-dihydro-1,3,7-trimethyl5-(methylthio)pyrido[*2,3-d*]pyrimidin-2(1*H*)-one)(p-phenyl) methanone 94a:

Mp = 224~226 °C. IR (KBr) ν cm^{-1} 1685, 1630 and 1592; ^1H NMR ($CDCl_3$, 400 MHz) δ ppm 2.43 (s, 3H), 2.55 (s, 3H), 2.78 (s, 3H), 3.31 (s, 3H), 4.57 (s, 2H), 7.45~7.62 (m, 5H, aromatic), ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 15.8, 18.5, 33.2, 37.1, 45.7, 110.9, 117.8, 128.5, 129.6, 133.1, 135.0, 148.9, 151.7, 158.5, 163.2, 195.1. MS (CI) *m/z* = 342.11 (M+1). Calcd for $C_{18}H_{19}N_3O_2S$: C, 63.32; H, 5.61; N, 12.31%. Found: C, 63.31; H, 5.62; N, 12.30%.

6-(3,4-dihydro-1,3,7-trimethyl-5-(methylthio)pyrido[*2,3-d*]pyrimidin-2(1*H*)-one)(p-nitrophenyl) methanone 94b:

Mp = 239~240 °C. IR (KBr) ν cm^{-1} 1690, 1636; ^1H NMR ($CDCl_3$, 400 MHz) δ ppm 2.41 (s, 3H), 2.56 (s, 3H), 2.84 (s, 3H), 3.36 (s, 3H), 4.59 (s, 2H), 8.22 (d, 2H, *J* = *8.6* Hz), 8.36 (d, 2H, *J* = *8.6* Hz), ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 15.3, 17.9, 33.7, 37.7, 46.8, 112.5, 117.3, 121.9, 131.3, 140.9, 149.8, 152.5, 154.2, 160.1, 166.7, 195.7. MS (CI) *m/z* = 387.13

(M+1). Calcd for $C_{18}H_{18}N_4O_4S$: C, 55.95; H, 4.70; N, 14.50%. Found: C, 55.99; H, 4.74; N, 14.57%.

6-(3,4-dihydro-1,3,7-trimethyl-5-(methylthio)pyrido[*2,3-d*]pyrimidin-2(1*H*)-one)(p-bromophenyl) methanone 94c:

Mp = 230~231 °C. IR (KBr) ν cm^{-1} 1681, 1624 and 1598; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 2.40 (s, 3H), 2.56 (s, 3H), 2.74 (s, 3H), 3.34 (s, 3H), 4.52 (s, 2H), 7.56 (d, 2H, *J* = *7.9* Hz), 7.68 (d, 2H, *J* = *7.9* Hz), ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 15.5, 18.0, 33.6, 37.7, 45.6, 111.6, 117.9, 127.9, 129.9, 131.8, 134.9, 148.9, 153.9, 155.9, 160.2, 166.7, 195.9. MS (CI) *m/z* = 421.03 (M+1). Calcd for $C_{18}H_{18}BrN_3O_2S$: C, 51.43; H, 4.32; N, 10.00%. Found: C, 51.48; H, 4.39; N, 10.07%.

6-(3,4-dihydro-1,3,7-trimethyl-5-(methylthio)pyrido[*2,3-d*]pyrimidin-2(1*H*)-one)(p-chlorophenyl) methanone 94d:

Mp = 229~230 °C. IR (KBr) ν cm^{-1} 1686, 1626; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 2.41 (s, 3H), 2.56 (s, 3H), 2.84 (s, 3H), 3.36 (s, 3H), 4.61 (s, 2H), 7.42 (d, 2H, *J* = *8.1* Hz), 7.66 (d, 2H, *J* = *8.1* Hz), ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 15.8, 17.3, 32.9, 37.3, 45.9, 111.9, 117.9, 128.9, 131.9, 133.8, 138.4, 152.8, 153.8, 161.1, 166.9, 196.0. MS (CI) *m/z* = 387.13 (M+1). Calcd for $C_{18}H_{18}ClN_3O_2S$: C, 57.52; H, 4.83; N, 11.18%. Found: C, 57.57; H, 4.81; N, 11.28%.

6-(3,4-dihydro-1,3,7-trimethyl-5-(methylthio)pyrido[*2,3-d*]pyrimidin-2(1*H*)-one)(p-fluorophenyl) methanone 94e:

Mp = 234~235 °C. IR (KBr) ν cm^{-1} 1691, 1629; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 2.48 (s, 3H), 2.61 (s, 3H), 2.88 (s, 3H), 3.32 (s, 3H), 4.63 (s, 2H), 7.22 (d, 2H, *J* = *7.5* Hz), 7.71 (d, 2H, *J* = *7.5* Hz), ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 15.2, 17.9, 32.7, 37.7, 45.6, 112.7, 115.7, 118.2, 129.7, 131.7, 153.7, 154.7, 161.6, 166.1, 167.4, 196.3. MS (CI) *m/z* = 360.10 (M+1). Calcd for $C_{18}H_{18}FN_3O_2S$: C, 60.15; H, 5.05; N, 11.69%. Found: C, 60.15; H, 5.05; N, 11.69%.

6-(3,4-dihydro-1,3-dimethyl-7-phenyl-5-(methylthio)pyrido[*2,3-d*]pyrimidin-2(1*H*)-one)(p-phenyl) methanone 94f:

Mp = 240~241 °C. IR (KBr) ν cm^{-1} 1684, 1629; ^1H NMR ($CDCl_3$, 400 MHz) δ ppm 2.37 (s, 3H), 2.80 (s, 3H), 3.35 (s, 3H), 4.50 (s, 2H), 7.46~7.67 (m, 10H, aromatic); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 15.9, 32.9, 37.7, 45.9, 111.3, 116.5, 126.9, 127.3, 128.7, 129.1, 129.9, 132.6, 134.9, 136.9, 148.9, 153.2, 155.9, 166.7, 195.5. MS (CI) *m/z* = 402.15 (M-1). Calcd for $C_{23}H_{21}N_3O_2S$: C, 68.46; H, 5.25; N, 10.41%. Found: C, 68.47; H, 5.29; N, 10.47%.

6-(3,4-dihydro-1,3-dimethyl-7-phenyl-5-(methylthio)pyrido[*2,3-d*]pyrimidin-2(1*H*)-one)(p-nitrophenyl) methanone 94g:

Mp = 247~248 °C. IR (KBr) ν cm^{-1} 1692, 1625; ^1H NMR ($CDCl_3$, 400 MHz) δ ppm 2.45 (s, 3H), 2.82 (s, 3H), 3.39 (s, 3H), 4.57 (s, 2H), 7.36~7.53 (m, 5H, aromatic), 8.02 (d, *J* = *8.1* Hz, 2H), 8.19 (d, *J* = *8.1* Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 15.2, 33.3, 37.4, 45.7, 111.2, 116.8, 121.1, 127.0, 129.5, 130.9, 136.5, 141.3, 148.7, 152.2, 153.7, 155.8, 165.7, 196.3. MS (CI) *m/z* = 447.15 (M-1). Calcd for $C_{23}H_{20}N_4O_4S$: C, 61.59; H, 4.49; N, 12.49%. Found: C, 61.54; H, 4.51; N, 12.54%.

6-(3,4-dihydro-1,3-dimethyl-7-phenyl-5-(methylthio)pyrido[*2,3-d*]pyrimidin-2(1*H*)-one)(p-bromophenyl) methanone 94h:

Mp = 243~245 °C. IR (KBr) ν cm^{-1} 1689, 1622 and 1585; ^1H NMR ($CDCl_3$, 400 MHz) δ ppm 2.41 (s, 3H), 2.82 (s, 3H), 3.37 (s, 3H), 4.53 (s, 2H), 7.16~7.47 (m, 5H, aromatic), 7.81

(d, J = *8.5 Hz*, 2H), 7.90 (d, J = *8.5 Hz*, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 15.7, 33.1, 37.2, 45.3, 110.5, 116.1, 126.8, 127.5, 128.1, 129.9, 130.5, 131.3, 133.9, 135.6, 148.1, 152.7, 156.5, 164.1, 195.7. MS (CI) *m/z* = 481.35 (M-1). Calcd for $C_{23}H_{20}BrN_3O_2S$: C, 57.27; H, 4.18; N, 8.71%. Found: C, 57.29; H, 4.19; N, 8.70%.

6-(3,4-dihydro-1,3-dimethyl-6-p-chlorophenyl-7-phenyl-5-(methylthio)pyrido[*2,3-d*]pyrimidin-2(1*H*)-one)(p-chlorophenyl) methanone 94i:

Mp = 241~242 °C. IR (KBr) ν cm^{-1} 1691, 1626 and 1588; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 2.40 (s, 3H), 2.82 (s, 3H), 3.36 (s, 3H), 4.58 (s, 2H), 7.34~7.41 (m, 5H, aromatic), 7.51 (d, J = *7.5* Hz, 2H), 7.70 (d, J =*7.5* Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 15.7, 33.1, 37.2, 45.3, 110.5, 116.1, 126.8, 127.5, 128.1, 129.9, 130.5, 131.3, 133.9, 135.6, 148.1, 152.7, 156.5, 164.1, 195.7. MS (CI) *m/z* = 439.05 (M+1). Calcd for $C_{23}H_{20}ClN_3O_2S$: C, 63.08; H, 4.60; N, 9.59%. Found: C, 63.03; H, 4.66; N, 9.54%.

General procedure for the preparation 4,5,6-trisubstituted-2,3-dihydro-1-methyl-1*H*-pyrrolo[*2,3-b*]pyridine-5-yl)(substitutedphenyl) methanone 97a-j:

A dry 100 mL flask was charged with 1-methylpyrrolidin-2-one **95** (10.1 mmol), acetamides **93** (11.1 mmol), 3,3-bis(methylthio)-1-phenylprop-2-en-1-one **92** (11.1 mmol), KF-alumina (1 g), and 1,4-dioxane (15 mL). The mixture was stirred at 108 °C for 12 h. The reaction after completion (monitored by TLC), was cooled to room temperature, the solvent was evaporated in vacuum, and the crude product was purified by silica gel column chromatography using $CHCl_3$ as eluent to obtain **97a-j.**

(2,3-dihydro-1,6-dimethyl-4-(methylthio)-1*H*-pyrrolo[*2,3-b*]pyridin-5-yl)(phenyl) methanone 97a:

Mp = 165~167 °C. IR (KBr) ν cm^{-1} 1654; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 2.48 (s, 3H), 2.56 (s, 3H), 2.72 (s, 3H), 2.79 (t, *J* = *3.3* Hz, 2H), 3.42 (t, *J* = *3.3* Hz, 2H), 7.54~7.64 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 15.4, 17.9, 20.8, 37.9, 55.1, 116.9, 117.7, 128.7, 129.8, 132.7, 134.6, 152.9, 159.7, 164.1, 192.3. MS (CI) *m/z* = 299.12 (M+1). Calcd for $C_{17}H_{18}N_2OS$: C, 68.42; H, 6.08; N, 9.39%. Found: C, 68.45; H, 6.05; N, 9.44%.

(2,3-dihydro-1,6-dimethyl-4-(methylthio)-1*H*-pyrrolo[*2,3-b*]pyridin-5-yl)(4-nitrophenyl) methanone 97b:

Mp = 177~178 °C. IR (KBr) ν cm^{-1} 1667; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 2.53 (s, 3H), 2.63 (s, 3H), 2.79 (s, 3H), 2.82 (t, *J* = *3.1* Hz, 2H), 3.45 (t, *J* = *3.1* Hz, 2H), 7.93 (d, *J* = *8.3* Hz, 2H), 8.12 (d, *J* = *8.3* Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 15.9, 18.5, 21.3, 38.2, 55.7, 116.8, 117.8, 121.6, 130.6, 131.5, 133.8, 152.6, 158.3, 163.5, 193.1. MS (CI) *m/z* = 344.15 (M+1). Calcd for $C_{17}H_{17}N_3O_3S$: C, 59.46; H, 4.99; N, 12.24%. Found: C, 59.48; H, 4.96; N, 12.27%.

(4-bromophenyl)(2,3-dihydro-1,6-dimethyl-4-(methylthio)-1*H*-pyrrolo[*2,3-b*]pyridin-5-yl) methanone 97c:

Mp = 171~172 °C. IR (KBr) ν cm^{-1} 1662; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 2.52 (s, 3H), 2.61 (s, 3H), 2.77 (s, 3H), 2.80 (t, *J* = *3.1* Hz, 2H), 3.43 (t, *J* = *3.1* Hz, 2H), 7.53 (d, *J* = *7.8* Hz, 2H), 7.70 (d, *J* = *7.8* Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 15.4, 17.9, 20.7, 37.8, 55.5, 117.1, 117.9, 127.6, 130.5, 131.2, 134.6, 152.9, 159.7, 164.2, 193.6. MS (CI) *m/z* = 377.08 (M+1). Calcd for $C_{17}H_{17}BrN_2OS$: C, 54.12; H, 4.54; N, 7.42%. Found: 54.16; H, 4.59; N, 7.48%.

(4-chlorophenyl)(2,3-dihydro-1,6-dimethyl-4-(methylthio)-1*H*-pyrrolo[*2,3-b*]pyridin-5-yl) methanone 97d:

Mp = 170~172 °C. IR (KBr) ν cm^{-1} 1667; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 2.53 (s, 3H), 2.63 (s, 3H), 2.79 (s, 3H), 2.82 (t, *J* = *3.1* Hz, 2H), 3.44 (t, *J* = *3.1* Hz, 2H), 7.37 (d, *J* = *7.5* Hz, 2H), 7.45 (d, *J* = *7.5* Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 15.4, 17.9, 20.7, 37.8, 55.5, 117.1, 117.9, 127.6, 130.5, 131.2, 134.6, 152.9, 159.7, 164.2, 193.6. MS (CI) *m/z* = 333.05 (M+1). Calcd for $C_{17}H_{17}ClN_2OS$: C, 61.34; H, 5.15; N, 8.42%. Found: C, 61.39; H, 5.18; N, 8.36%.

(4-fluorophenyl)(2,3-dihydro-1,6-dimethyl-4-(methylthio)-1*H*-pyrrolo[*2,3-b*]pyridin-5-yl) methanone 97e:

Mp = 167~168 °C. IR (KBr) ν cm^{-1} 1658; ^{1} H NMR ($CDCl_3$, 400 MHz) δ ppm 2.46 (s, 3H), 2.58 (s, 3H), 2.73 (s, 3H), 2.83 (t, *J* = *3.6* Hz, 2H), 3.41 (t, *J* = *3.6* Hz, 2H), 7.08 (d, *J* = *7.1* Hz, 2H), 7.21 (d, *J* = *7.1* Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 15.7, 17.8, 20.3, 37.2, 55.1, 115.1, 116.8, 117.4, 130.2, 131.4, 134.6, 152.4, 159.9, 164.5, 166.7, 193.1. MS (CI) *m/z* = 317.15 (M+1). Calcd for $C_{17}H_{17}FN_2OS$: C, 64.53; F, 6.00; N, 8.85%. Found: C, 64.58; F, 6.05; N, 8.80%.

(2,3-dihydro-1-methyl-4-(methylthio)-6-phenyl-1*H*-pyrrolo[*2,3-b*]pyridin-5-yl)(phenyl) methanone 97f:

Mp = 182~183 °C. IR (KBr) ν cm^{-1} 1680; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 2.47 (s, 3H), 2.71 (s, 3H), 2.82 (t, *J* = *3.2* Hz, 2H), 3.44 (t, *J* = *3.2* Hz, 2H), 7.41~ 7.67 (m, 10H, aromatic); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 15.3, 21.4, 37.3, 53.0, 116.1, 117.9, 119.5, 125.6, 126.7, 128.4, 129.8, 135.1, 136.8, 146.9, 153.1, 164.8, 194.3. MS (CI) *m/z* = 361.11

(M+1). Calcd for $C_{22}H_{20}N_2OS$: C, 73.30; H, 5.59; N, 7.77%. Found: C, 73.25; H, 5.52; N, 7.84%.

(2,3-dihydro-1-methyl-4-(methylthio)-6-phenyl-1*H*-pyrrolo[*2,3-b*]pyridin-5-yl)(4-nitrophenyl) methanone 97g:

Mp = 189~191 °C. IR (KBr) ν cm^{-1} 1683; ^1H NMR ($CDCl_3$, 400 MHz) δ ppm 2.50 (s, 3H), 2.75 (s, 3H), 2.87 (t, *J* = *2.9* Hz, 2H), 3.48 (t, *J* = *2.9* Hz, 2H), 7.45~ 7.89 (m, 5H, aromatic), 7.97 (d, *J* = *7.8* Hz, 2H), 8.02 (d, *J* = *7.8* Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 15.7, 21.2, 37.9, 53.2, 116.1, 116.9, 119.5, 125.6, 126.7, 128.4, 129.8, 135.1, 140.3, 146.7, 150.3, 153.1, 165.8, 194.7. MS (CI) *m/z* = 404.15 (M-1). Calcd for $C_{22}H_{19}N_3O_3S$: C, 65.17; H, 4.72; N, 10.36%. Found: C, 65.19; H, 4.74; N, 10.36%.

(4-bromophenyl)(2,3-dihydro-1-methyl-4-(methylthio)-6-phenyl-1*H*-pyrrolo[*2,3-b*]pyridin-5-yl) methanone 97h:

Mp = 185~186 °C. IR (KBr) ν cm^{-1} 1678; ^1H NMR ($CDCl_3$, 400 MHz) δ ppm 2.47 (s, 3H), 2.72 (s, 3H), 2.83 (t, *J* = *3.3* Hz, 2H), 3.45 (t, *J* = *3.3* Hz, 2H), 7.21~ 7.44 (m, 5H, aromatic), 7.67 (d, *J* = *7.2* Hz, 2H), 7.71 (d, *J* = *7.2* Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 15.3, 21.5, 37.3, 53.7, 116.6, 117.5, 125.5, 126.7, 127.3, 128.9, 130.8, 131.5, 135.1, 137.4, 146.5, 153.1, 165.8, 194.1. MS (CI) *m/z* = 440.35 (M+1). Calcd for $C_{22}H_{19}BrN_2OS$: C, 60.14; H, 4.36; N, 6.38%. Found: C, 60.19; H, 4.39; N, 6.43%.

(4-aminophenyl)(2,3-dihydro-1-methyl-4-(methylthio)-6-phenyl-1*H*-pyrrolo[*2,3-b*]pyridin-5-yl) methanone 97j:

Mp = 188~189 °C. IR (KBr) ν cm^{-1} 3356, 1672; ^1H NMR ($CDCl_3$, 400 MHz) δ ppm 2.43 (s, 3H), 2.69 (s, 3H), 2.81 (t, *J* = *3.1* Hz, 2H), 3.40 (t, *J* = *3.1* Hz, 2H), 5.67 (br.s, 2H), 7.26~ 7.41 (m, 5H, aromatic), 6.81 (d, *J* = *7.1* Hz, 2H), 7.56 (d, *J* = *7.1* Hz, 2H); ^{13}C NMR

($CDCl_3$, 100 MHz) δ ppm 15.7, 20.9, 37.0, 53.1, 115.9, 116.6, 117.5, 125.9, 126.3, 127.1, 128.9, 130.9, 135.8, 146.5, 152.6, 154.9, 165.2, 194.5. MS (CI) *m/z* = 374.45 (M-1). Calcd for $C_{22}H_{21}N_3OS$: C, 70.37; H, 5.64; N, 11.19%. Found: C, 70.33; H, 5.69; N, 11.21%.

General procedure for the preparation 4,5,6-trisubstituted-2,3-dihydro-1-methyl-1*H*-pyrrolo[*2,3-b*]pyridine-5-yl)(substitutedphenyl) methanone 98a-j:

A dry 100 mL flask was charged with 1-methylindolin-2-one **96** (6.8 mmol), acetamides **93** (7.5 mmol), 3,3-bis(methylthio)-1-phenylprop-2-en-1-one **92** (7.5 mmol), KF-alumina (1 g), and 1,4-dioxane (15 mL). The mixture was stirred at 108 °C for 14 h. The reaction after completion (monitored by TLC), was cooled to room temperature, the solvent was evaporated in vacuum, and the crude product was purified by silica gel column chromatography using $CHCl_3$ as eluent to obtain **98a-j.**

(2,9-dimethyl-4-(methylthio)-9*H*-pyrido[2,3-b]indol-3-yl)(phenyl)methanone 98a:

Mp = 261~263 °C. IR (KBr) ν cm^{-1} 1632; ^1H NMR ($CDCl_3$, 400 MHz) δ ppm 2.51 (s, 3H), 2.63 (s, 3H), 3.70 (s, 3H), 7.29~7.72 (m, 9H, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 15.5, 17.9, 44.3, 112.5, 115.8, 118.9, 119.3, 119.9, 120.3, 120.9, 122.8, 127.9, 129.5, 132.3, 134.6, 142.3, 145.6, 151.6, 193.9. MS (CI) *m/z* = 347.10 (M+1). Calcd for $C_{21}H_{18}N_2OS$: C, 72.80; H, 5.24; N, 8.09%. Found: C, 72.86; H, 5.18; N, 8.04%.

(2,9-dimethyl-4-(methylthio)-9*H*-pyrido[*2,3-b*]indol-3-yl)(4-nitrophenyl) methanone 98b:

Mp = 269~271 °C. IR (KBr) ν cm^{-1} 1654; ^1H NMR ($CDCl_3$, 400 MHz) δ ppm 2.59 (s, 3H), 2.67 (s, 3H), 3.80 (s, 3H), 7.26~7.31 (m, 4H, aromatic), 8.02 (d, *J* = 7.5 Hz, 2H), 8.21 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 16.3, 18.5, 43.3, 112.6, 115.0, 119.1, 119.9, 120.3, 120.9, 121.6, 121.8, 130.8, 140.7, 142.5, 150.5, 151.9, 152.8, 193.9. MS (CI) *m/z* = 392.12 (M+1). Calcd for $C_{21}H_{17}N_3O_3S$: C, 64.43; H, 4.38; N, 10.73%; Found: C, 64.49; H, 4.31; N, 10.78%.

(4-bromophenyl)(2,9-dimethyl-4-(methylthio)-9*H*-pyrido[*2,3-b*]indol-3-yl)methanone 98c:

Mp = 265~267 °C. IR (KBr) ν cm^{-1} 1648; ^1H NMR ($CDCl_3$, 400 MHz) δ ppm 2.56 (s, 3H), 2.62 (s, 3H), 3.76 (s, 3H), 7.23~7.32 (m, 4H, aromatic), 7.66 (d, *J* = *7.2* Hz, 2H), 7.79 (d, *J* = *7.2* Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 15.8, 18.2, 43.7, 112.9, 115.3, 118.6, 119.3, 119.9, 120.3, 121.6, 126.9, 130.6, 131.3, 133.6, 140.3, 144.6, 150.1, 151.9, 194.5. MS (CI) *m/z* = 426.12 (M+1). Calcd for $C_{21}H_{17}BrN_2OS$: C, 59.30; H, 4.03; N, 6.59%. Found: C, 59.29; H, 4.04; N, 6.61%.

(4-chlorophenyl)(2,9-dimethyl-4-(methylthio)-9*H*-pyrido[*2,3-b*]indol-3-yl)methanone 98d:

Mp = 263~264 °C. IR (KBr) ν cm^{-1} 1654; ^1H NMR ($CDCl_3$, 400 MHz) δ ppm 2.52 (s, 3H), 2.64 (s, 3H), 3.73 (s, 3H), 7.19~7.22 (m, 4H, aromatic), 7.53 (d, *J* = *7.5* Hz, 2H), 7.71 (d, *J* = *7.5* Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 15.3, 17.7, 43.4, 112.5, 115.3, 118.6, 119.3, 119.9, 120.3, 121.6, 126.9, 130.6, 131.3, 133.6, 140.3, 144.6, 150.1, 151.9, 193.9. MS (CI) *m/z* = 382.08 (M+1). Calcd for $C_{21}H_{17}ClN_2OS$: C, 66.22; H, 4.50; N, 7.35%. Found: C, 66.26; H, 4.55; N, 7.37%.

(4-fluorophenyl)(2,9-dimethyl-4-(methylthio)-9*H*-pyrido[*2,3-b*]indol-3-yl)methanone 98e:

Mp = 261~262 °C. IR (KBr) ν cm^{-1} 1658; ^1H NMR ($CDCl_3$, 400 MHz) δ ppm 2.53 (s, 3H), 2.64 (s, 3H), 3.84 (s, 3H), 7.21~7.27 (m, 4H, aromatic), 7.35 (d, *J* = *7.0* Hz, 2H), 7.91 (d, *J* = *7.0* Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 15.9, 18.1, 42.9, 112.6, 115.0, 119.1, 119.9, 120.3, 120.9, 121.6, 121.8, 130.8, 140.7, 142.5, 150.5, 151.9, 166.2, 194.3. MS (CI) *m/z* = 365.10 (M+1). Calcd for $C_{21}H_{17}FN_2OS$: C, 69.21; H, 4.70; N, 7.69%. Found: C, 69.26; H, 4.75; N, 7.72%.

(9-methyl-4-(methylthio)-2-phenyl-9*H*-pyrido[*2,3-b*]indol-3-yl)(phenyl)methanone 98f:

Mp = 285~286 °C. IR (KBr) ν cm^{-1} 1635; ^1H NMR ($CDCl_3$, 400 MHz) δ ppm 2.53 (s, 3H), 3.61 (s, 3H), 7.19~7.84 (m, 14H, aromatic); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 15.0, 44.5, 112.9, 114.5, 118.8, 119.8, 120.5, 121.1, 122.3, 126.6, 128.1, 129.2, 129.9, 132.1, 133.5, 136.3, 138.5, 142.4, 146.6, 151.0, 152.3, 195.7. MS (CI) *m/z* = 409.10 (M+1). Calcd for $C_{26}H_{20}N_2OS$: C, 76.44; H, 4.93; N, 6.86%. Found: C, 76.40; H, 4.85; N, 6.92%.

(9-methyl-4-(methylthio)-2-phenyl-9*H*-pyrido[*2,3-b*]indol-3-yl)(4-nitrophenyl) methanone 98g:

Mp = 289~290 °C. IR (KBr) ν cm^{-1} 1636; ^1H NMR ($CDCl_3$, 400 MHz) δ ppm 2.54 (s, 3H), 3.68 (s, 3H), 7.21~7.26 (m, 4H, aromatic), 7.54~7.63 (m, 5H, aromatic), 8.01 (d, *J* = *7.7* Hz, 2H), 8.30 (d, *J* = *7.7* Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 15.7, 44.3, 111.6, 115.2, 117.9, 119.2, 120.2, 121.5, 122.6, 127.2, 128.4, 129.7, 130.3, 132.1, 133.8, 136.7, 138.9, 142.7, 146.9, 151.2, 153.5, 194.8. MS (CI) *m/z* = 452.11 (M-1). Calcd for $C_{26}H_{19}N_3O_3S$: C, 68.86; H, 4.22; N, 9.27%. Found: C, 68.91; H, 4.29; N, 9.32%.

(4-bromophenyl)(9-methyl-4-(methylthio)-2-phenyl-9*H*-pyrido[*2,3-b*]indol-3-yl) methanone 98h:

Mp = 286~288 °C. IR (KBr) ν cm^{-1} 1636; ^1H NMR ($CDCl_3$, 400 MHz) δ ppm 2.48 (s, 3H), 3.62 (s, 3H), 7.18~7.25 (m, 4H, aromatic), 7.42~7.46 (m, 5H, aromatic), 7.61 (d, *J* = *7.2* Hz, 2H), 7.72 (d, *J* = *7.2* Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 15.3, 44.1, 111.9, 115.0, 118.5, 119.6, 120.8, 121.9, 122.6, 127.2, 128.4, 129.7, 130.3, 132.1, 133.8, 136.7, 138.9, 142.7, 146.9, 150.2, 152.8, 195.4. MS (CI) *m/z* = 485.04 (M-1). Calcd for $C_{26}H_{19}BrN_2OS$: C, 64.07; H, 3.93; N, 5.75%. Found: C, 64.02; H, 3.98; N, 5.79%.

(4-chlorophenyl)(9-methyl-4-(methylthio)-2-phenyl-9*H*-pyrido[*2,3-b*]indol-3-yl) methanone 98i:

Mp = 293~295 °C. IR (KBr) ν cm^{-1} 1640; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 2.51 (s, 3H), 3.65 (s, 3H), 7.19~7.27 (m, 4H, aromatic), 7.31~7.38 (m, 3H, aromatic), 7.51 (d, *J* = *7.2* Hz, 2H), 7.81 (d, *J* = *7.2* Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 15.3, 44.7, 110.9, 114.5, 118.8, 119.8, 120.5, 121.1, 122.3, 126.6, 128.1, 129.2, 129.9, 132.1, 133.8, 136.7, 138.9, 142.7, 146.9, 151.2, 153.9, 195.7. MS (CI) *m/z* = 444.12 (M+1). Calcd for $C_{26}H_{19}ClN_2OS$: C, 70.50; H, 4.32; N, 6.32%. Found: C, 70.48; H, 4.33; N, 6.34%.

General procedure for the preparation (5,6,7,8-tetrahydro-2-alkyl-4-(methylthio) quinolin-3-yl)(substituted phenyl)methanone 100a-f:

A dry 100 mL flask was charged with cyclohexanone **99** (6.8 mmol), alkyl amides **93** (7.5 mmol), 3,3-bis(methylthio)-1-phenylprop-2-en-1-one **92** (7.5 mmol), KF-Alumina (1 g), and 1,4-dioxane (15 mL). The mixture was stirred at 108 °C for 14 h. The reaction after completion (monitored by TLC), was cooled to room temperature, the solvent was evaporated in vacuum, and the crude product was purified by silica gel column chromatography using $CHCl_3$ as eluent to obtain **100a-f.**

(4-chlorophenyl)(5,6,7,8-tetrahydro-2-methyl-4-(methylthio)quinolin-3-yl)methanone 100a:

Mp = 156~158 °C. IR (KBr) ν cm^{-1} 1640; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 1.73~1.74 (m, 4H), 2.53 (s, 3H), 2.57 (s, 3H), 2.60 (t, *J* = *3.4* Hz, 2H), 2.98 (t, *J* = *3.3* Hz, 2H), 7.41 (d, *J* = *7.4* Hz, 2H), 7.78 (d, *J* = *7.4* Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 15.7, 18.9, 22.4, 22.9, 24.3, 29.4, 126.9, 129.5, 130.1, 130.9, 133.6, 138.5, 152.9, 159.6, 162.3, 196.6. MS (CI) *m/z* = 330.08 (M-1). Calcd for $C_{18}H_{18}ClNOS$: C, 65.15; H, 5.47; N, 4.22%. Found: C, 65.19; H, 5.50; N, 4.28%.

(5,6,7,8-tetrahydro-2-methyl-4-(methylthio)quinolin-3-yl)(4-nitrophenyl) methanone 100b:

Mp = 157~158 °C. IR (KBr) ν cm^{-1} 1634; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 1.75~1.77 (m, 4H), 2.54 (s, 3H), 2.58 (s, 3H), 2.62 (t, *J* = *3.6* Hz, 2H), 2.99 (t, *J* = *3.5* Hz, 2H), 8.04 (d, *J* = *7.2* Hz, 2H), 8.23 (d, *J* = *7.2* Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 15.8, 18.9, 22.4, 22.9, 24.3, 29.4, 121.9, 126.5, 130.2, 130.9, 141.6, 150.5, 152.9, 159.6, 162.3, 196.6. MS (CI) *m/z* = 343.12 (M+1). Calcd for $C_{18}H_{18}N_2O_3S$: C, 63.14; H, 5.30; N, 8.18%. Found: C, 63.19; H, 5.35; N, 8.15%.

(5,6,7,8-tetrahydro-2-methyl-4-(methylthio)quinolin-3-yl)(phenyl)methanone 100c:

Mp = 150~151 °C. IR (KBr) ν cm^{-1} 1637; H^1 NMR ($CDCl_3$, 400 MHz) δ ppm 1.68~1.72 (m, 4H), 2.49 (s, 3H), 2.50 (s, 3H), 2.54 (t, *J* = *3.3* Hz, 2H), 2.92 (t, *J* = *3.3* Hz, 2H), 7.45~7.78 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 15.7, 18.9, 22.4, 22.9, 24.3, 29.4, 126.9, 128.5, 129.1, 130.9, 133.6, 135.5, 152.9, 159.6, 162.3, 196.6. MS (CI) m/z = 296.12 (M-1). Calcd for $C_{18}H_{19}NOS$: C, 72.69; H, 6.44; N, 4.71%. Found: C, 72.64; H, 6.47; N, 4.75%.

(4-fluorophenyl)(5,6,7,8-tetrahydro-4-(methylthio)-2-phenylquinolin-3-yl)methanone 100d:

Mp = 153~155 °C. IR (KBr) ν cm^{-1} 1645; H^1 NMR ($CDCl_3$, 400 MHz) δ ppm 1.71~1.72 (m, 4H), 2.51 (s, 3H), 2.57 (t, *J* = *3.1* Hz, 2H), 2.96 (t, *J* = *2.9* Hz, 2H), 7.21 (d, *J* = *7.3* Hz, 2H), 7.32 ~ 7.36 (m, 3H, aromatic), 7.82 (d, *J* = *7.3* Hz, 2H), 8.12 (d, *J* = *7.8* Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 15.4, 22.1, 22.7, 24.1, 29.6, 114.7, 124.9, 126.9, 127.9, 129.1, 129.5, 130.1, 130.9, 135.6, 148.5, 152.9, 159.6, 164.3, 193.6. MS (CI) m/z = 376.11 (M-1). Calcd for $C_{23}H_{20}FNOS$: C, 73.18; H, 5.34; N, 3.71%. Found: C, 73.19; H, 5.33; N, 3.70%.

(4-bromophenyl)(5,6,7,8-tetrahydro-4-(methylthio)-2-phenylquinolin-3-yl)methanone 100f:

Mp = 150~152 °C. IR (KBr) ν cm^{-1} 1642; ^1H NMR ($CDCl_3$, 400 MHz) δ ppm 1.70~1.72 (m, 4H), 2.52 (s, 3H), 2.59 (t, *J* = *3.4* Hz, 2H), 2.97 (t, *J* = *3.3* Hz, 2H), 7.21 (d, *J* = *7.2* Hz, 2H), 7.35 ~ 7.38 (m, 4H, aromatic), 7.82 (d, *J* = *7.2* Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 15.4, 22.1, 22.7, 24.1, 29.6, 114.7, 124.9, 126.9, 127.9, 129.1, 129.5, 130.1, 130.9, 135.6, 148.5, 152.9, 159.6, 164.3, 193.6. MS (CI) *m/z* = 439.04 (M+1). Calcd for $C_{23}H_{20}BrNOS$: C, 63.02; H, 4.60; N, 3.20%. Found: C, 63.07; H, 4.66; N, 3.26%.

General procedure for the preparation (substituted phenyl)pyridazine 104a-f:

A dry 100 mL flask was charged with substituted acetophenone **101** (8.3 mmol), acrylaldehyde **102** (9.1 mmol), hydrazine hydrate **103** (9.5 mmol), KF-alumina (1 g), and DMF (10 mL). The mixture was refluxed for 6 h. The reaction after completion (monitored by TLC), was cooled to room temperature, the solvent was evaporated in vacuum, and the crude product was purified by silica gel column chromatography using $CHCl_3$ as eluent to obtain **104a-f.**

3-(2-bromophenyl)pyridazine 104a:

Light yellow crystals; mp = 195~197 °C. IR (KBr) ν cm^{-1} 3021, 1614, 1512, 1485; ^1H NMR ($CDCl_3$, 400 MHz) δ ppm 7.25 ~ 7.28 (m, 4H, aromatic), 7.27 (m, 1H), 7.80 (d, *J* = *9.3* Hz, 1H), 8.21 (d, *J* = *8.1* Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 121.3, 124.9, 127.2, 128.4, 129.6, 130.4, 132.3, 138.9, 148.5, 160.9. MS (CI) *m/z* = 234.02 (M-1). Calcd for $C_{10}H_7BrN_2$: C, 51.09; H, 3.00; N, 11.92%. Found: C, 51.17; H, 3.07; N, 12.02%.

3-(4-bromophenyl)pyridazine 104b:

Light yellow crystals; mp = 197~199 °C. IR (KBr) ν cm^{-1} 3073, 1611, 1478; ^{1}H NMR (CDCl$_3$, 400 MHz) δ ppm 7.24 (m, 1H), 7.32 (d, 2H, J = *7.8* Hz), 7.51 (d, 2H, J = *7.8* Hz), 7.78 (d, J = *9.0* Hz, 1H), 8.17 (d, J = *8.3* Hz, 1H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ ppm 122.6, 125.4, 127.9, 129.3, 131.8, 132.7, 147.9, 161.5. MS (CI) *m/z* = 234.09 (M-1). Calcd for $C_{10}H_7BrN_2$: C, 51.09; H, 3.00; N, 11.92%. Found: C, 50.99; H, 2.87; N, 11.82%.

3-(4-chlorophenyl)pyridazine 104c:

Brown solid; mp = 164~166 °C. IR (KBr) ν cm^{-1} 3080, 1631, 1476; ^{1}H NMR (CDCl$_3$, 400 MHz) δ ppm 7.14 (m, 1H), 7.27 (d, 2H, J = *7.1* Hz), 7.36 (d, 2H, J = *7.1* Hz), 7.82 (d, J = *9.9* Hz, 1H), 8.23 (d, J = *8.0* Hz, 1H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ ppm 123.9, 127.2, 128.4, 129.3, 131.5, 134.7, 148.3, 161.0. MS (CI) *m/z* = 191.03 (M+1). Calcd for $C_{10}H_7ClN_2$: C, 63.01; H, 3.70; N, 14.70%. Found: C, 62.92; H, 3.78; N, 14.59%.

3-phenylpyridazine 104d:

White crystals; mp = 132~135 °C. IR (KBr) ν cm^{-1} 3014, 1611, 1522, 1492; ^{1}H NMR (CDCl$_3$, 400 MHz) δ ppm 7.20 ~ 7.32 (m, 4H, aromatic), 7.12 (m, 1H), 7.73 (d, J = *14.1* Hz, 1H), 8.16 (d, J = *9.8* Hz, 1H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ ppm 124.5, 126.7, 127.8, 128.4, 129.6, 133.9, 147.9, 162.3. MS (CI) *m/z* = 234.02 (M-1). Calcd for $C_{10}H_7BrN_2$: C, 51.09; H, 3.00; N, 11.92%. Found: C, 51.17; H, 3.07; N, 12.02%.

3-(4-nitrophenyl)pyridazine 104e:

Dark Brown solid; mp = 156~158 °C. IR (KBr) ν cm^{-1} 3075, 1618, 1472; ^{1}H NMR (CDCl$_3$, 400 MHz) δ ppm 7.31 (m, 1H), 7.69 (d, 2H, J = *14.5* Hz), 8.26 (d, 2H, J = *14.5* Hz), 7.80 (d, J = *7.9* Hz, 1H), 8.18 (d, J = *8.2* Hz, 1H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ ppm 120.4, 124.7, 127.1, 128.9, 139.3, 146.7, 148.6, 161.9. MS (CI) *m/z* = 202.06 (M+1). Calcd for $C_{10}H_7N_3O_2$: C, 59.70; H, 3.51; N, 20.89%. Found: C, 59.63; H, 3.42; N, 20.99%.

3-(2,4-dibromophenyl)pyridazine 104f:

Yellow crystals; mp = 252~255 °C. IR (KBr) ν cm^{-1} 3080, 1623, 1478; ^1H NMR ($CDCl_3$, 400 MHz) δ ppm 7.35 (m, 1H), 7.12 (d, 2H, *J* = 7.5 Hz), 7.34 (d, 2H, *J* = 7.5 Hz), 7.57(s, 1H, aromatic), 7.70 (d, *J* = 7.0 Hz, 1H), 8.22 (d, *J* = 8.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 121.7, 124.3, 125.7, 127.9, 130.7, 131.8, 134.7, 139.0, 146.9, 160.8. MS (CI) *m/z* = 314.81 (M+1). Calcd for $C_{10}H_6Br_2N_2$: C, 38.25; H, 1.93; N, 8.92%. Found: C, 38.31; H, 1.81; N, 8.99%.

REFERENCES:

1. Yamawaki, J.; Ando, T. *Chem. Lett.* **1979**, 755-758.
2. Yamawaki, J.; Ando, T.; Hanafusa, T. *Chem. Lett.* **1981**, 1143-1146.
3. (a) Fraile, J. M.; Garcia, J. I.; Matoral, J. A.; Figueras, F. *Tetrahedron Lett.* **1996**, *37*, 5995-5996; (b) Yadav, V. K.; Kapoor, K. K. *Tetrahedron* **1996**, *52*, 3659-3668.
4. Alloum, B. A.; Villemin, D. *Synth. Commun.* **1989**, *19*, 2567-2571.
5. Kabalka, G. W.; Wang, L.; Namboodiri, V.; Pagni, R. M. *Tetrahedron Lett.* **2000**, *41*, 5151-5154.
6. Kabalka, G. W.; Pagni, R. M.; Hair, C. M. *Org. Lett.* **1999**, *1*, 1423-1425.
7. (a) Biginelli, P. *Ber.* **1891**, *24*, 1317-1345; (b) Biginelli, P. *Ber.* **1893**, *26*, 447-521; (c) Zaugg, H. E.; Martin, W. B. *Org. React.* **1965**, *14*, 88-95; (d) Kappe, C. O. *Tetrahedron* **1993**, *49*, 6937-6963; (e) Svetlık, J.; Veizerova, L.; Kettmann, V. *Tetrahedron Lett.* **2008**, *49*, 3520-3523; (f) Suzuki, I.; Iwata, Y.; Takeda, K. *Tetrahedron Lett.* **2008**, *49*, 3238-3241.
8. Nakano, Y.; Shi, W.; Nishii, Y.; Igarashi, M. *J. Heterocycl. Chem.* **1999**, *36*, 33-40.
9. Boullet, F. T.; Villemin, D.; Ricard, M.; Moison, H.; Foucaud, A. *Tetrahedron* **1985**, *41*, 1259-1266.
10. Schell, P.. Richards, M. P. Hanson, K. Berk, S. C. Makara, G. M. *J. Comb. Chem.* **2005**, *7*, 96-98.
11. Su, T. and Watanabe, K. A. *J. Org. Chem.* **1989**, *54*, 224-228.
12. Taylor, E. C. Macor, J. E. and French, L. G. *J. Org. Chem.* **1991**, *56*, 1812-1816
13. Mizar, P.; Myrboh, B. *Tetrahedron Lett.* **2008**, *49*, 5283-5285.

14. (a) Unangst, P. C.; Connor, D. T.; Cetenko, W. A.; Sorenson, R. J.; Kostlan, C. R.; Sircar, J. C.; Wright, D. C.; Schrier, D. J.; Dyer,R. D. *J. Med. Chem.***1994**, *37*, 322-327. (b) Collins, P. W.; Dajani, E. Z.; Pappo, R.; Gasiecki, A. F.; Bianchi, R. G.; Woods, E. M. *J. Med. Chem.* **1983**, *26*, 786-793.

15. (a) Shishoo, C. J.; Devani, M. B.; Karverkar, M. D.; Ullas, G. V.; Ananthan, S.; Bhadti, V. S.; Patel, R. B.; Gandhi, T. P. *Indian J. Chem.* **1982**, *21B*, 666-669. (b) Haulihan, W. J.; Eberle, M. K. US Patent 3,642,814, *Chem. Abstr.* **1972**, *76*, 140839-140840. (c) Bindra, J. S. US Patent 4,085,213; *Chem. Abstr.* **1978**, *89*, 1975824-1975825. (d) Hiedo, K.; Yasuo, M. Japan Patent 5577, 1959; *Chem. Abstr.* **1960**, *54*, 14280-14281. (e) Hiedo, K.; Yasuo, M. Japan Patent 17236, 1959; *Chem. Abstr.* **1961**, *55*, 17664-17665. (f) Shishoo, C. J.; Jain, S. K. *J. Heterocycl. Chem.* **1992**, *29*, 883-885. (g) Chain, L. K.; Wei, H. S.; Khun, H. M. Tai-wan yao Hsuch Tsa chih 1986, 38, 2428; *Chem. Abstr.* **1998**, *108*, 94490-94491. (h) Franco, G.; Maria, L.; Guiueseppe, P. *J. Heterocycl. Chem.* **1989**, *26*, 613-616. (i) Hand, E. S.; Backer, D. C. *Can. J. Chem.* **1984**, *62*, 2570-2574.

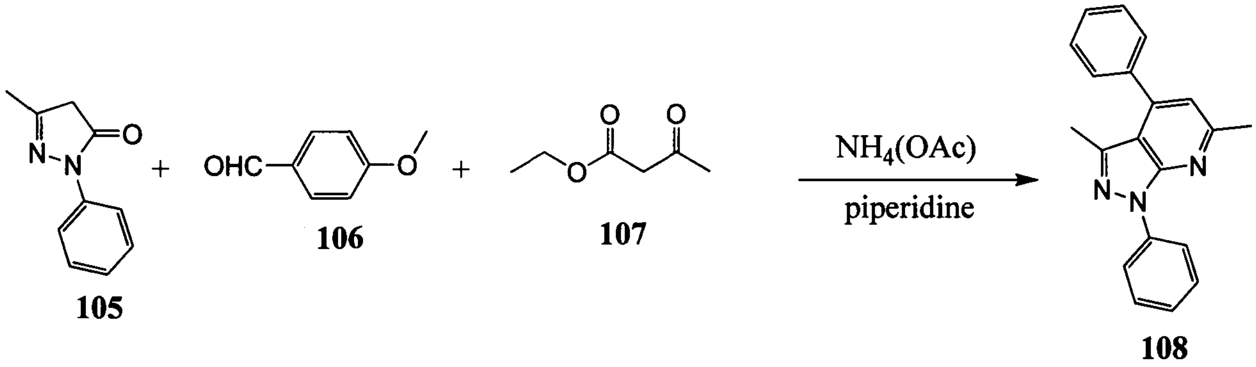
CHAPTER VII

Synthetic studies on KF-alumina catalysed reaction of substituted and unsubstituted aryl-oxoketene dithioacetals and 1*H*-pyrazone-5(4*H*)-one: a convenient synthesis of pyrazolo[*3,4-b*]pyridine and pyrazolo[*1,5-a*]pyrimidine

INTRODUCTION

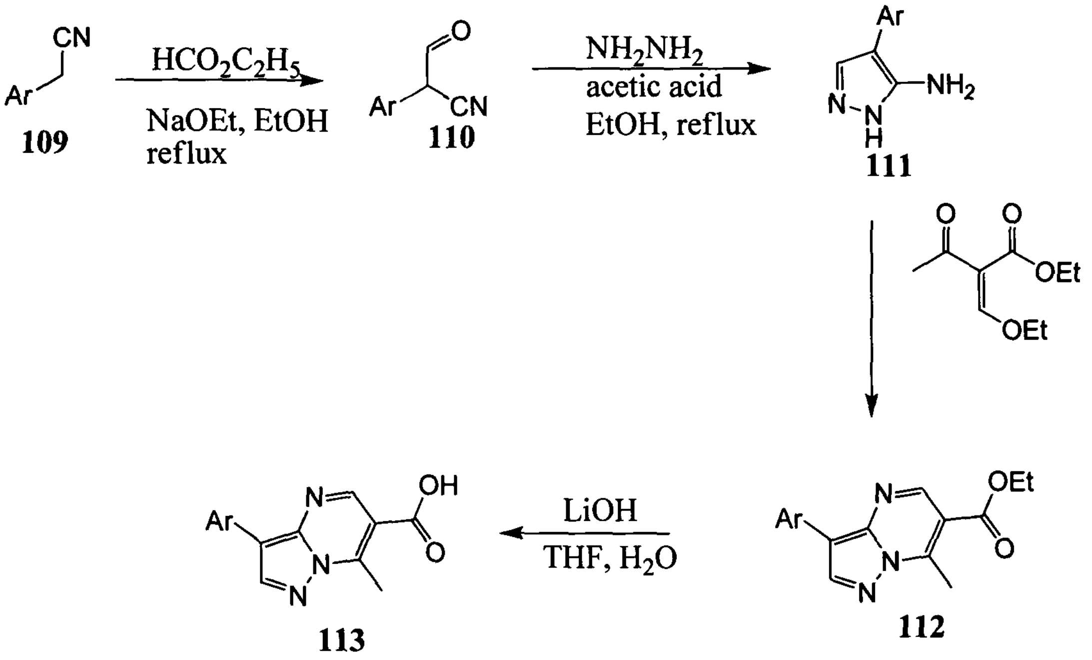
The functionalized pyrazolo[*3,4-b*]pyridine and pyrazolo[*1,5-a*]pyrimidine are attractive compounds for drug discovery since many of these scaffolds exhibit excellent biological activities. For example pyrazolo[*3,4-b*]pyridine derivatives have been evaluated for various biological applications ranging from being good vasodilators to hypotensive, anti-inflammatory, analgesics and antipyretic agents.[1] The pyrazolo[*1,5-a*] pyrimidines structural motif are found in a large number of pharmaceutical agents which exhibit diverse range of physiological activities such as antiepileptic agents,[2] anxiolytics,[3] anti depressants[4] and as agents for treatment of sleep disorders [5] and oncolytics.[6]

Sayed[7] and co-worker described a one-pot method for the preparation of pyrazolo[*3,4-b*]pyridine by reaction of 2-(2,4-dinitrophenyl)-5-methyl-2,4-dihydro-3*H*-pyrazol-3-one **105**, p-methoxybenzaldehyde **106**, ethyl acetoacetate **107** in presence of ammonium acetate and few drops of piperidine to abtain 1-(2,4-dinitrophenyl)-4-(4-methoxyphenyl)-3,6-dimethyl-1*H*-pyrazolo[*3,4-b*]pyridine **108** (Scheme 33)



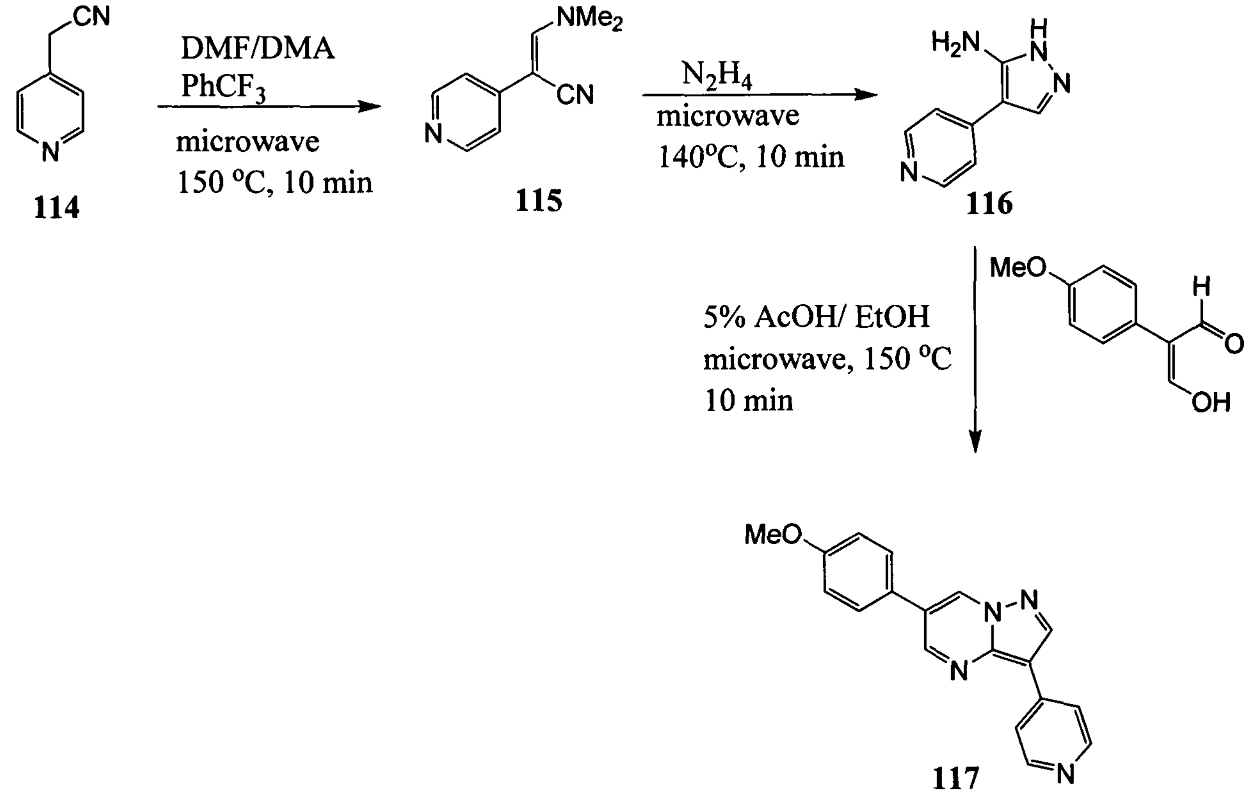
Scheme 33

Gregg and co-worker[8] devised a synthetic route to generate pyrazolo[*1,5-a*]pyrimidines with an aryl aubstitution at the 3-position and a methyl group in the 7-position. Specifically, aryl-substituted acetonitriles **109** were treated with ethylformate in toluene in the presence of sodium methoxide to give the corresponding α-formyl-arylacetonitriles **110** which were further treated with hydrazine and glacial acetic acid yielded 4-aryl-2*H*-pyrazol-3-ylamines **111**. On treatment of **111** with 2-ethoxymethylene-3-oxobutyrate which acted as the dielectrophile for the pyrimidine ring-formation **112** which on saponification afforded acids **113** (Scheme 34).



Scheme 34

Lindsley[9] and co-worker reported microwave-assisted protocols for the expedited synthesis of pyrazolo[*1,5-a*]pyrimidines. The nitrile **114** was heated at 160 °C in DMF/DMA to afford complete conversion to **115** in 10 min to deliver 5-amino-4-pyridylpyrazole **116. 116** was further treated with malondialdehyde in presence of 5% AcOH/ EtOH at 150 °C for 10 min to yield pyrazolo[*1,5-a*]pyrimidine **117** (Scheme 35).



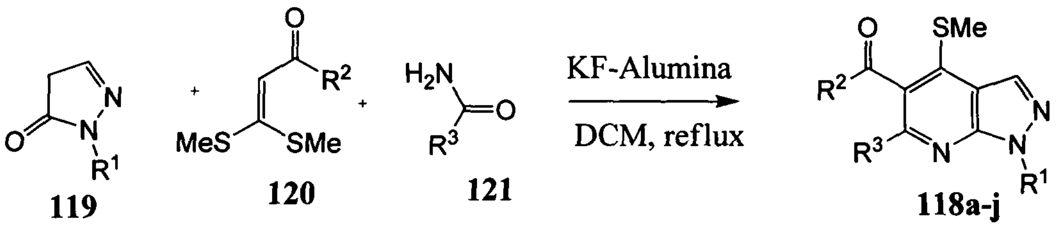
Scheme 35

Therefore the development of simple methodologies for the synthesis of these highly functionalized derivatives is highly challenging in organic synthesis.

RESULTS AND DISCUSSIONS:

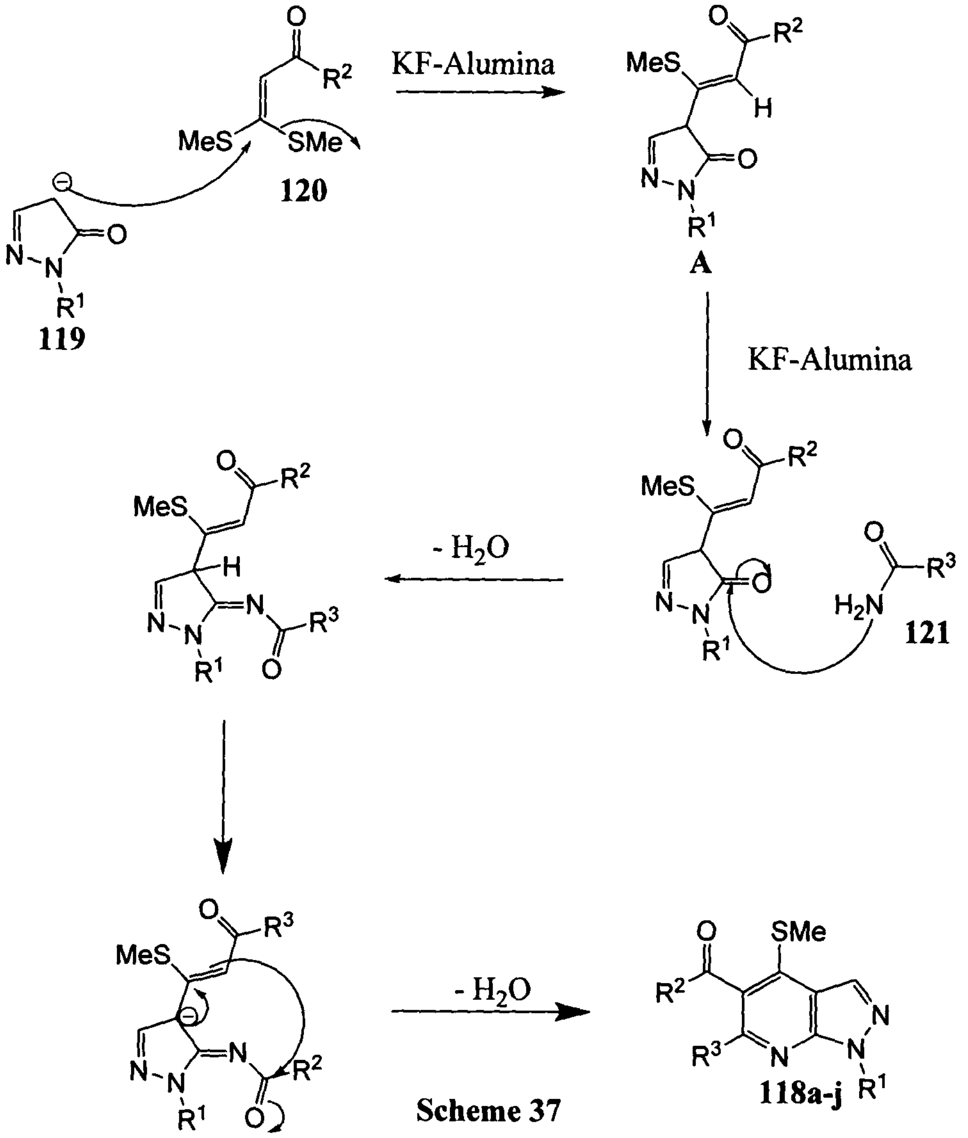
To address this challenge, the development of multi-component reaction method for the synthesis of these derivatives is of great interest owing to its high efficiency and selectivity. Although there are a wide range of methods available for the synthesis of pyrazolo[*1,5-a*] pyrimidines[9] and pyrazolo [*3,4-b*] pyridines,[10] very few of these procedures provide a simple method that could yield compounds with more structural diversities. In this chapter, we report a successful multi-component procedure for the synthesis of 1,4,5,6 tetrasubstituted pyrazolo[*3,4-b*]pyridine and a semi-conventional method for the synthesis of 5,6,7 trisubstituted pyrazolo[*1,5-a*] pyrimidines. The principal advantages, scope and limitations of the method are discussed.

The general method to prepare (1,4,6 tri-substituted-1*H*-pyrazolo[*3,4-b*]pyridi-6-yl) (aryl) methanone **118a-j** involves a three component reaction between 1-substituted-1*H*-pyrazone-5(4*H*)-one **119**, substituted aryl-oxoketene dithioacetals **120** and alkyl amides **121** in presence of KF-Alumina. The reaction presumably involves Michael addition and condensation to yield the desired products. These reaction were attempted in range of solvents such as DMA, acetonitrile, DMF, THF and 1,4 dioxane. However, the desired products were obtained in DCM under refluxing conditions. The reactions studied took between 8-16 h for completion (Scheme **36**). The reaction time increased when the steric demands of the reactant **1** increase (Table **9**).



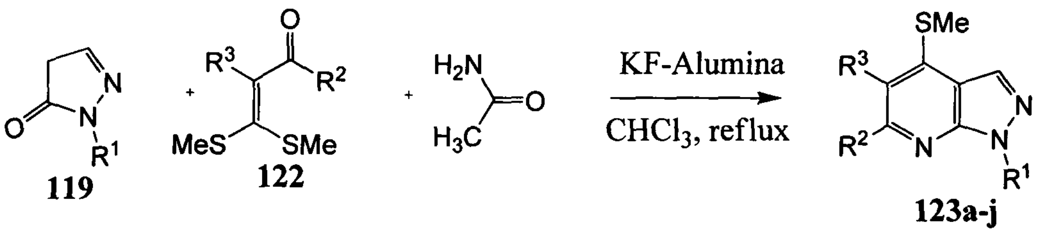
Scheme 36

A plausible mechanism for the formation of **118a-j** is outlined in Scheme 37. The reaction was initiated by the Michael addition reaction between **119** and **120** to give an intermediate **A** which further condensed with **121** by abstraction of α-proton to give the desired products. This may be concluded from the fact that when condensation of 1-methyl-pyrazol-5(4*H*)-one and 3,3-bis(methylthio)-1-phenylprop-2-en-1-one was carried out, 1-methyl-4-((*Z*)-1-(methylthio)-3-oxo-3-phenylprop-1-enyl)-pyrazol-5(4*H*)-one was isolated which on further treatment with acetamide afforded the desired product **118a**, thereby indicating that Michael addition is the first step in the three-component reaction.

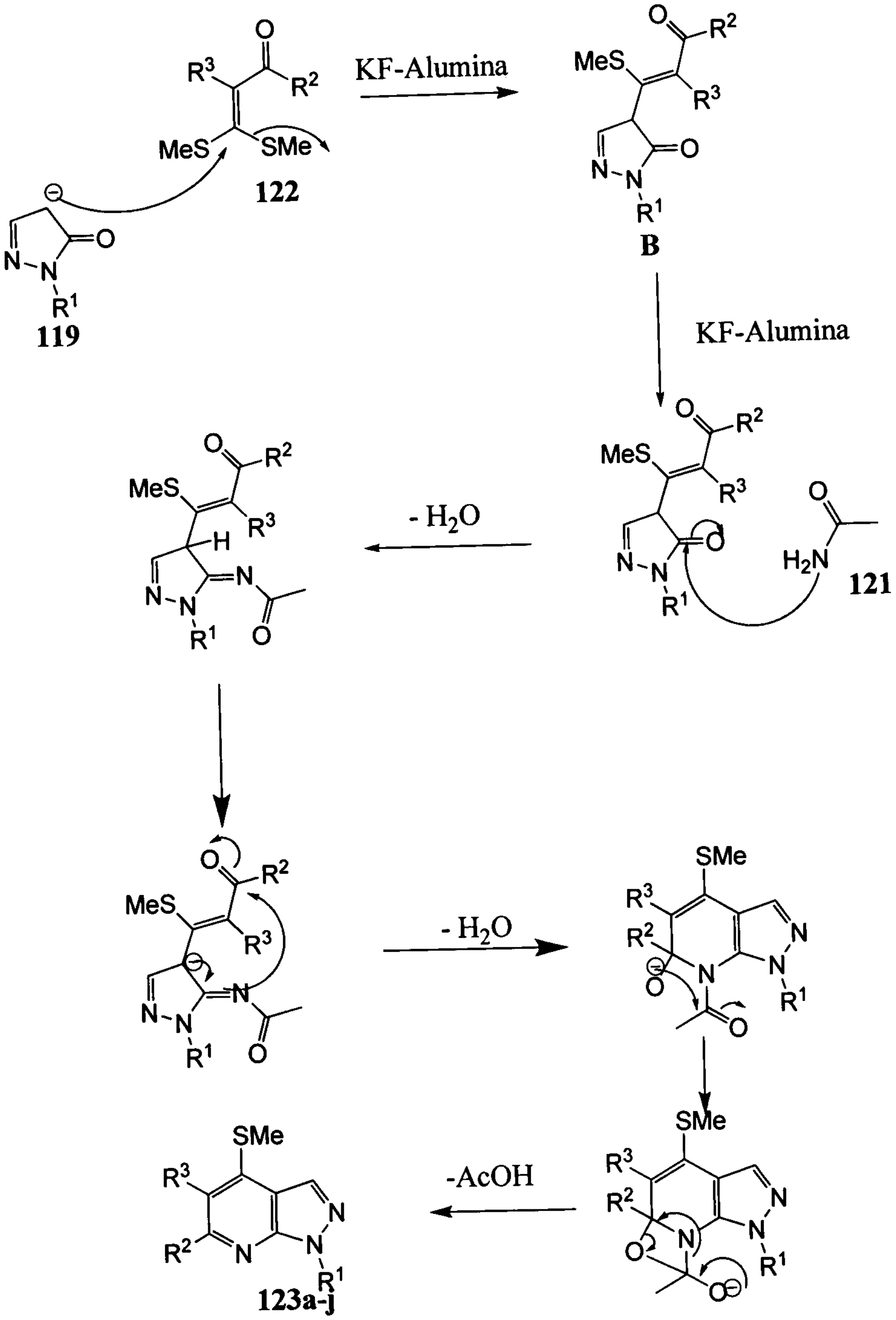


Scheme 37

In order to study whether a similar type of reaction occurred if the α-proton of aryl oxoketene dithioacetals was unavailable, we carried out three component reaction of **119**, α-substituted aryl oxo ketene dithioacetals **122** and acetamide in presence of KF-alumina. Interesting it was observed that the product obtained was 1,4,5,6 tetrasubstituted pyrazolo[*3,4-b*]pyridine (Scheme **38**). The reaction presumably involves a Michael addition reaction to give 1,5 dicarbonyl (Scheme **39**) which further underwent condensation with acetamide to yield **123a-j** (Table.**9**) The reactions were found to be solvent dependent and proceeded only in $CHCl_3$ under refluxing condition. The reactions studied took between 12-24 h for completion.

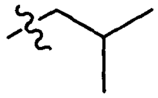
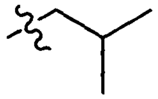
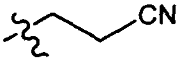
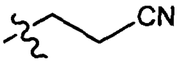
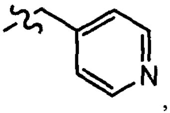
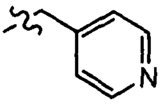
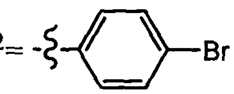
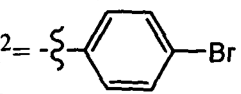
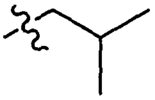
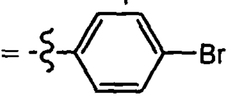
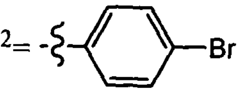
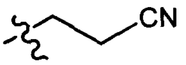
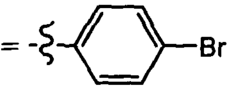
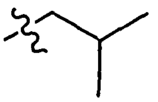
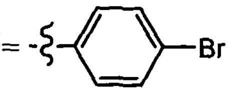


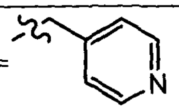
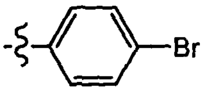
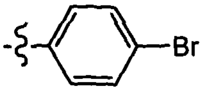
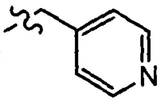
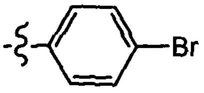
Scheme 38



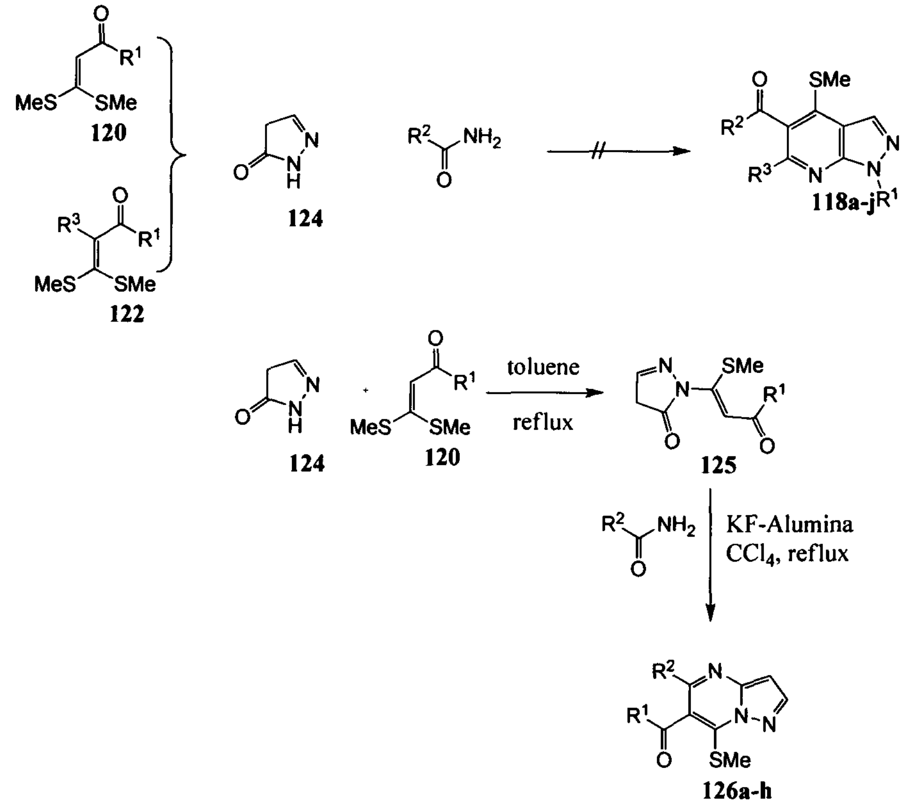
Scheme 39

Table 9: Substituted fused pyridine and pyrimidines

Entry	Product (**118a-j**)	Product (**123a-j**)	Product (**126a-j**)	Yields (%)
a	R^1 = CH$_3$, R^2 = C$_6$H$_5$ R^3 = CH$_3$	R^1 = CH$_3$, R^2 =C$_6$H$_5$, R^3 = CH$_3$	R^1 = C$_6$H$_5$ R^2 = CH$_3$	**118a** = 80 **123a** = 83 **126a** = 78
b	R^1 = C$_2$H$_5$, R^2 = C$_6$H$_5$ R^3 = CH$_3$	R^1 = C$_2$H$_5$, R^2 = C$_6$H$_5$ R^3 = CH$_3$	R^1 = p-Cl-C$_6$H$_5$ R^2 = CH$_3$	**118b** = 82 **123b** = 80 **126b** = 82
c	R^1=  R^2 = C$_6$H$_5$ R^3 = CH$_3$	R^1=  R^2 = C$_6$H$_5$ R^3 = CH$_3$	R^1 = p-NO$_2$-C$_6$H$_5$ R^2 = CH$_3$	**118c** = 81 **123c** = 73 **126c** = 88
d	R^1=  R^2 = C$_6$H$_5$ R^3 = CH$_3$	R^1=  R^2 = C$_6$H$_5$ R^3 = CH$_3$	R^1 = p-Br-C$_6$H$_5$ R^2 = CH$_3$,	**118d** = 83 **123d** = 75 **126d** = 85
e	R^1=  R^2 = C$_6$H$_5$ R^3 = CH$_3$	R^1=  R^2 = C$_6$H$_5$ R^3 = CH$_3$	R^1 = C$_6$H$_5$ R^2 = C$_2$H$_5$,	**118e** = 80 **123e** = 77 **126e** = 79
f	R^1 = CH$_3$, R^2=  R^3 = C$_2$H$_5$	R^1 = CH$_3$, R^2=  R^3 = C$_2$H$_5$	R^1 = p-Cl-C$_6$H$_5$ R^2 = C$_2$H$_5$,	**118f** = 81 **123f** = 73 **126f** = 81
g	R^1=  R^2=  R^3 = CH$_3$	R^1 =, C$_2$H$_5$ R^2=  R^3 = C$_2$H$_5$	R^1 = p-NO$_2$-C$_6$H$_5$ R^2 = C$_2$H$_5$,	**118g** = 79 **123g** = 77 **126g** = 81
h	R^1=  R^2=  R^3 = CH$_3$	R^1=  R^2=  R^3 = C$_2$H$_5$	R^1 = p-Br-C$_6$H$_5$ R^2 = C$_2$H$_5$,	**118h** = 78 **123h** = 67 **126h** = 83

i	R^1=  R^2=  $R^3 = C_2H_5$	R^1=  R^2=  $R^3 = C_2H_5$	**118i** = 80 **123i** = 79
j	$R^1 = CH_3$, $R^2 = C_6H_5$ $R^3 = C_2H_5$	R^1=  R^2=  $R^3 = C_2H_5$	**118j** = 85 **123j** = 73

It was further observed that three-component reaction between 1*H*-pyrrol-2(3*H*)-one **124**, aryl oxoketene dithioacetal or α-substituted aryl oxo ketene dithioacetals **122** with acetamide yielded a complex mixture of products. However, when **124** was refluxed with **120** in toluene an addition product **125** was obtained, which when further refluxed with **121** in CCl_4 yielded 5,7,6 trisubstituted pyrazolo[*1,5-a*] pyrimidines **126a-h**[11] (Scheme **40**)



Scheme 40

In conclusion, we have developed efficient procedures for the synthesis of biologically active scaffolds by using a three component KF-alumina catalysed reaction

EXPERIMENTAL:

Melting points were obtained on a Thomas Hoover capillary melting point apparatus and are uncorrected. Carbon, hydrogen and nitrogen analysis were performed with a Perkin-Elmer 2400 series II instrument. IR spectra in BOMEM DA-8 FT-IR spectrophotometer. The ^1H and ^{13}C NMR spectra were recorded on a Bruker AMX 400 spectrometer using $CDCl_3$ or DMSO-d_6 as the solvent. Chemical shifts are reported in ppm from internal tetramethylsilane and are given on the δ scale. The following abbreviations are used to describe peak patterns when appropriate: s = singlet, d = doublet, t = triplet, m = multiplet. Positive-ion and negative-ion electrospray ionization (ESI) mass spectra were measured on an ion trap analyzer Esquire 3000 (Bruker Daltonics).

All reactions were monitored by TLC on glass plates coated with silica gel (ACME's) containing 13% calcium sulphate as binder and visualization of compounds was accomplished by exposure to iodine vapour or by spraying acidic potassium permanganate solution or 2% ninhydrin solution. Column chromatography was carried out using ACME's silica gel.

Chemicals, reagents and solvents:

Dry solvents were obtained by distillation under N_2 atomsphere with appropriate dehydrating agents. The commercial available chemicals were used without further purification.

Synthesis of (1,6-dimethyl-4-(methylthio)-1*H*-pyrazolo[*3,4-b*]pyridin-5-yl)(phenyl) methanone:

A dry 100 mL flask was charged with 3,3-bis(methylthio)-1-phenylprop-2-en-1-one **120** (9.9 mmol), acetamides **121** (9 mmol), 1-ethyl-1*H*-pyrrol-2(3*H*)-one **119** (9 mmol), KF-alumina (1 g), and DCM (10 mL). The mixture was refluxed for 8–16 h. The reaction after completion (monitored by TLC), was cooled to room temperature, the solvent was evaporated in vacuum, and the crude product was purified by silica gel column chromatography using methanol-DCM (1:20) as eluent to obtain

118a: m.p. 201-202 °C; IR (KBr) ν cm^{-1} 1680, 1631 and 1596; ^1H NMR ($CDCl_3$, 400 MHz) δ ppm 2.36 (s, 3H), 2.56 (s, 3H), 3.67 (s, 3H), 7.51~7.76 (m, 5H, aromatic), 7.95 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 14.9, 18.2, 45.7, 108.1, 127.9, 128.6, 129.9, 132.7, 134.8, 135.9, 151.2, 154.7, 163.4, 195.5. MS (CI) *m/z* = 298.06 (M+1). Anal. Calcd for $C_{16}H_{15}N_3OS$: C, 64.62; H, 5.08; N, 14.13%. Found: C, 64.60; H, 5.02; N, 14.17%.

118b: m.p. 204-205 °C; IR (KBr) ν cm^{-1} 1685, 1630 and 1592; ^1H NMR ($CDCl_3$, 400 MHz) δ ppm 1.27 (t, 3H, J = *14.1* Hz), 2.32 (s, 3H), 2.58 (s, 3H), 3.47 (q, 2H, J = *8.5* Hz), 7.62~7.73 (m, 5H, aromatic), 8.05 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 13.2, 14.7, 18.5, 53.1, 107.6, 127.7, 128.1, 129.1, 132.1, 134.6, 135.7, 150.6, 153.5, 162.9, 195.1. MS (CI) *m/z* = 312.10 (M+1). Anal. Calcd for $C_{17}H_{17}N_3OS$: C, 65.57; H, 5.50; N, 13.49%. Found: C, 65.55; H, 5.52; N, 13.51%.

118c: m.p. 205-206 °C; IR (KBr) ν cm^{-1} 1672, 1634 and 1597; ^1H NMR ($CDCl_3$, 400 MHz) δ ppm 0.99 (d, 6H, J = *6.7* Hz), 1.63–1.68 (m, 1H), 2.36 (s, 3H), 2.51 (s, 3H), 3.61 (d, 2H, J = *7.1* Hz), 7.57~7.71 (m, 5H, aromatic), 7.98 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 13.9, 19.2, 21.3, 27.5, 61.5, 106.9, 128.0, 128.7, 129.5, 132.7, 133.9, 135.9, 151.8, 154.7, 164.7, 194.7. MS (CI) *m/z* = 340.15 (M+1). Anal. Calcd for $C_{19}H_{21}N_3OS$: C, 67.23; H, 6.24; N, 12.38%. Found: C, 67.29; H, 6.28; N, 12.45%.

118d: m.p. 215-217 °C; IR (KBr) ν cm^{-1} 1685, 1630 and 1592; ^1H NMR ($CDCl_3$, 400 MHz) δ ppm 2.31 (s, 3H), 2.49 (s,3H), 2.80 (t, 2H, *J* = *14.1* Hz), 3.96 (t, 2H, *J* = *14.2* Hz), 7.49~7.75 (m, 5H), 8.03 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 13.6, 14.6, 18.4, 52.1, 106.9, 118.2, 127.8, 128.5, 129.1, 130.6, 134.7, 135.6, 150.9, 154.7, 163.2, 195.3. MS (CI) *m/z* = 337.24 (M+1). Anal. Calcd for $C_{18}H_{16}N_4OS$: C, 64.26; H, 4.79; N, 16.65%. Found C, 64.23; H, 4.75; N, 16.68%.

118e: m.p. 208-209 °C; IR (KBr) ν cm^{-1} 1679, 1636 and 1587; ^1H NMR ($CDCl_3$, 400 MHz) δ ppm 2.31 (s, 3H), 2.56 (s, 3H), 4.89 (s, 2H), 7.31 (d, 2H, *J* = *9.1* Hz), 7.58~7.75 (m, 5H, aromatic), 7.83 (s, 1H), 8.27 (d, 2H, *J* = *9.1* Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) 14.1, 18.9, 62.5, 106.3, 123.5, 128.1, 128.9, 129.2, 132.9, 134.3, 135.2, 148.6, 151.6, 154.6, 164.8, 195.8. MS (CI) *m/z* = 375.10 (M+1). Anal. Calcd for $C_{21}H_{18}N_4OS$: C, 67.36; H, 4.85; N, 14.96%. Found: C, 67.39; H, 4.89; N, 15.07%.

118f: m.p. 213-215 °C; IR (KBr) ν cm^{-1} 1687, 1635 and 1590; ^1H NMR ($CDCl_3$, 400 MHz) δ ppm 2.41 (s, 3H), 2.58 (s, 3H), 3.87 (s, 3H), 7.65 (d, 2H, *J* = *8.5* Hz), 7.81 (d, 2H, *J* = *8.5* Hz), 7.91 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 14.1, 19.6, 45.1, 107.9, 126.4, 128.9, 130.5, 131.9, 134.5, 135.6, 150.7, 154.1, 164.1, 196.7. MS (CI) *m/z* = 375.05 (M-1). Anal. Calcd for $C_{16}H_{14}BrN_3OS$: C, 51.07; H, 3.75; N, 11.17%. Found: C, 51.01; H, 3.79; N, 11.23%.

118g: m.p. 221-223 °C; IR (KBr) ν cm^{-1} 1675, 1630 and 1592; ^1H NMR ($CDCl_3$, 400 MHz) δ ppm 0.97 (d, 6H, *J* = *6.2* Hz), 1.64–1.69 (m, 1H), 2.34 (s, 3H), 2.59 (s, 3H), 3.72 (d, 2H, *J* = *7.0* Hz), 7.54 (d, 2H, *J* = *8.2* Hz), 7.69 (d, 2H, *J* = *8.2* Hz), 8.07 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 14.6, 18.6, 20.9, 27.1, 61.0, 106.2, 127.3, 128.6, 131.1, 132.0, 134.2, 135.3, 152.1, 154.3, 164.2, 195.3. MS (CI) *m/z* = 417.05 (M-1). Anal. Calcd for $C_{19}H_{20}BrN_3OS$: C, 54.55; H, 4.82; N, 10.04%. Found: C, 54.62; H, 4.89; N, 10. 12%.

118h: m.p. 191-193 °C; IR (KBr) ν cm^{-1} 1688, 1638 and 1599; ^1H NMR ($CDCl_3$, 400 MHz) δ ppm 2.30 (s, 3H), 2.52 (s, 3H), 2.97 (t, 2H, *J* = *12.1* Hz), 4.21 (t, 2H, *J* = *12.1* Hz), 7.73 (d, 2H, *J* = *9.0* Hz), 7.86 (d, 2H, *J* = *9.0* Hz), 8.01 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 13.7, 14.6, 18.02, 51.6, 108.6, 118.8, 126.8, 128.5, 130.7, 132.4, 134.3, 135.7, 151.7, 154.9, 163.9, 196.9. MS (CI) *m/z* = 416.02 (M+1). Anal. Calcd for $C_{18}H_{15}BrN_4OS$: C, 52.06; H, 3.64; N, 13.49%. Found: C, 52.12; H, 3.69; N, 13.55%.

118i: m.p. 225-227 °C; IR (KBr) ν cm^{-1} 1692, 1629 and 1592; ^1H NMR ($CDCl_3$, 400 MHz) δ ppm 2.37 (s, 3H), 2.59 (s, 3H), 4.96 (s, 2H), 7.33 (d, 2H, *J* = *8.7* Hz), 7.64 (d, 2H, *J* = *7.9* Hz), 7.76 (d, 2H, *J* = *7.9* Hz), 7.97 (s, 1H), 8.22 (d, 2H, *J* = *8.7* Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) 14.4, 18.7, 62.2, 106.7, 124.75, 127.4, 128.9, 130.6, 131.8, 134.8, 135.8, 145.7, 150.1, 151.7, 155.8, 165.5, 195.9. MS (CI) *m/z* = 454.02 (M+1). Anal. Calcd for $C_{21}H_{17}BrN_4OS$: C, 55.64; H, 3.78; N, 12.36%. Found: C, 55.60; H, 3.85; N, 12.41%.

118j: m.p. 204-206 °C; IR (KBr) ν cm^{-1} 1683, 1635 and 1583; ^1H NMR ($CDCl_3$, 400 MHz) δ ppm 1.53 (t, 2H, *J* = *14.2* Hz), 2.32 (s, 3H), 2.59 (s, 3H), 3.81 (d, 2H, *J* = *14.1* Hz), 7.57~7.81 (m, 5H, aromatic), 7.99 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 12.7, 14.1, 18.3, 53.7, 107.6, 127.5, 128.1, 129.3, 132.9, 134.2, 135.5, 151.8, 154.9, 163.9, 195.0. MS (CI) *m/z* = 312.13 (M+1). Anal. Calcd for $C_{17}H_{17}N_3OS$: C, 65.57; H, 5.50; N, 13.49%. Found: C, 65.52; H, 5.42; N, 13.54%.

Synthesis of 1,5-dimethyl-4-(methylthio)-6-phenyl-1*H*-pyrazolo[*3,4-b*]pyridine:

A dry 100 mL flask was charged with 2-methyl-3,3-bis(methylthio)-1-phenylprop-2-en-1-one **122** (11.2 mmol), acetamide (11.2 mmol), 1-methyl-1*H*-pyrazol-5(4*H*)-one **119** (10.2

mmol), KF-alumina (1 g), and CH_3Cl (10 mL). The mixture was refluxed for 12–24 h. The reaction after completion (monitored by TLC), was cooled to room temperature, the solvent was evaporated in vacuum, and the crude product was purified by silica gel column chromatography using methanol-DCM (2:20) as eluent to obtain **123a**.

123a: m.p. 167-168 °C; IR (KBr) ν cm^{-1} 1691, 1621 and 1556; ^1H NMR ($CDCl_3$, 400 MHz) δ ppm 2.31 (s, 3H), 2.45 (s, 3H), 3.69 (s, 3H), 7.34~7.76 (m, 5H, aromatic), 7.94 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 10.8, 14.6, 45.7, 104.7, 126.4, 127.4, 128.7, 129.6, 134.2, 137.3, 150.9, 153.6, 157.9.MS (CI) *m/z* = 270.13 (M+1). Anal Calcd for $C_{15}H_{15}N_3S$ C, 66.88; H, 5.61; N, 15.60%. Found C, 66.80; H, 5.56; N, 15.66.

123b: m.p. 170-172 °C; IR (KBr) ν cm^{-1} 1684, 1627 and 1559; ^1H NMR ($CDCl_3$, 400 MHz) δ ppm 1.56 (d, 3H, J = *6.7* Hz), 2.37 (s, 3H), 2.43 (s, 3H), 3.71 (t, 2H, J = *14.2* Hz), 7.56~7.87 (m, 5H, aromatic), 8.01 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 10.1, 13.8, 15.4, 53.9, 106.1, 126.9, 127.9, 128.7, 130.7, 134.9, 137.3, 151.2, 153.9, 158.4. MS (CI) *m/z* = 284.11 (M+1). Anal. Calcd for $C_{16}H_{17}N_3S$ C, 67.81; H, 6.05; N, 14.83%. Found C, 67.72; H, 6.01; N, 14.89%.

123c: m.p. 174-175 °C; IR (KBr) ν cm^{-1} 1685, 1630 and 1592; ^1H NMR ($CDCl_3$, 400 MHz) δ ppm 0.99 (d, 6H, J = *6.5* Hz), 1.65~1.68 (m, 1H), 2.21 (s, 3H), 2.36 (s, 3H), 3.42 (d, 2H, J = *8.1* Hz), 7.41~7.85 (m, 5H, aromatic), 8.01 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 10.6, 13.7, 21.2, 25.9, 59.7, 103.7, 126.1, 126.7, 127.1, 128.7, 132.8, 134.9, 150.6, 153.9, 157.7.MS (CI) *m/z* = 312.16 (M+1). Anal. Calcd for $C_{18}H_{21}N_3S$: C, 69.43; H, 6.80; N, 13.49%. Found C, 69.39; H, 6.80; N, 13.47%.

123d: m.p. 179-180 °C; IR (KBr) ν cm^{-1} 1692, 1637 and 1598; ^1H NMR ($CDCl_3$, 400 MHz) δ ppm 2.27 (s, 3H), 2.54 (s, 3H), 2.92 (d, 2H, J = *8.2* Hz), 4.03 (d, 2H, J = *8.2* Hz), 7.44~7.82 (m, 5H, aromatic), 8.03 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 10.9, 14.8, 15.7, 54.9, 105.9, 118.6, 126.8, 127.7, 128.5, 129.8, 133.9, 136.9, 151.8, 154.5, 158.9. MS (CI) *m/z* = 309.12 (M+1). Anal. Calcd for $C_{17}H_{16}N_4S$: C, 66.21; H, 5.23; N, 18.17%. Found C, 66.28; H, 5.29; N, 18.23%.

123e: m.p. 187-189 °C; IR (KBr) ν cm^{-1} 1690, 1638 and 1590; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 2.41 (s, 3H), 2.58 (s, 3H), 5.12 (s, 3H), 7.12 (d, 2H, *J* = *7.7* Hz), , 7.35~7.83 (m, 5H, aromatic), 7.97 (s, 1H), 8.06 (d, 2H, *J* = *7.7* Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) 11.6, 15.9, 60.7, 106.5, 123.8, 126.9, 127.5, 128.2, 129.5, 133.0, 135.7, 143.7, 147.9, 151.2, 154.9, 158.1. MS (CI) *m/z* = 347.10 (M+1). Anal. Calcd for $C_{20}H_{18}N_4S$: C, 69.34; H, 5.24; N, 16.17%. Found C, 69.26; H, 5.18; N, 16.10%.

123f: m.p. 175-177°C; IR (KBr) ν cm^{-1} 1683, 1627 and 1572; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 2.26 (s, 3H), 2.52 (s, 3H), 3.74 (s, 3H), 7.38 (d, 2H, *J* = *7.9* Hz), 7.61 (d, 2H, *J* = *7.9* Hz), 7.96 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 11.3, 15.3, 44.9, 105.4, 120.7, 128.3, 129.9, 131.8, 134.9, 135.9, 150.4, 152.8, 156.3. MS (CI) *m/z* = 349.04 (M+1). Anal. Calcd for $C_{15}H_{14}BrN_3S$ C, 51.73; H, 4.05; N, 12.07%. Found C, 51.79; H, 4.12; N, 12.18%.

123g: m.p. 178-180 °C; IR (KBr) ν cm^{-1} 1677, 1620 and 1550; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 1.51 (t, 3H, *J* = *6.4* Hz), 2.30 (s, 3H), 3.51 (s, 3H), 2.69 (q, 2H, *J* = *1.4* Hz), 7.58 (d, 2H, *J* = *8.0* Hz), 7.79 (d, 2H, *J* = *8.0* Hz), 7.94 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 14.2, 15.6, 19.4, 45.3, 106.9, 120.9, 129.3, 132.2, 133.2, 134.2, 135.7, 150.3, 154.7, 157.4. MS (CI) *m/z* = 284.11 (M+1). Anal. Calcd for $C_{16}H_{16}BrN_3S$ C, 53.04; H, 4.45; N, 11.60%. Found C, 53.01; H, 4.54; N, 11.52%.

123h: m.p. 178-179 °C; IR (KBr) ν cm^{-1} 1676, 1638 and 1583; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 0.96 (d, 6H, *J* = *6.9* Hz), 1.50 (t, 3H, *J* = *6.9* Hz), 1.69~1.72 (m, 1H), 2.5 4 (s, 3H), 2.69 (q, 2H, *J* = *1.9* Hz), 3.42 (d, 2H, *J* = *8.1* Hz), 7.54 (d, 2H, *J* = *8.2* Hz), 7.79 (d, 2H, *J* = *8.2* Hz), 7.96 (s, 1H); ^{13}C NMR (CDCl$_3$, 100 MHz) 14.5, 15.7, 19.6, 20.7, 26.6, 59.9, 104.9, 120.7, 129.5, 132.2, 134.5, 136.4, 150.9, 153.5, 156.4. MS (CI) *m/z* = 405.06 (M+1). Anal. Calcd for $C_{19}H_{22}BrN_3S$: C, 56.43; H, 5.48; N, 10.39%. Found C, 56.48; H, 5.56; N, 10.45%.

123i: m.p. 184-186 °C; IR (KBr) ν cm^{-1} 1689, 1630 and 1593; ^{1}H NMR (CDCl$_3$, 400 MHz) δ ppm 1.28 (t, 3H, *J* = *12.6* Hz), 2.56 (s, 3H), 2.75 (q, 2H, *J* = *8.9* Hz), 2.90 (d, 2H, *J* = *8.3* Hz), 4.12 (d, 2H, *J* = *8.3* Hz), 7.47 (d, 2H, *J* = *7.7* Hz), 7.83 (d, 2H, *J* = *7.7* Hz), 8.07 (s, 1H); ^{13}C NMR (CDCl$_3$, 100 MHz) 14.5, 15.0, 15.7, 19.6, 54.7, 106.5, 116.9, 120.9, 129.3, 132.9, 133.6, 134.6, 136.2, 151.8, 154.5, 158.9. MS (CI) *m/z* = 402.04 (M+1). Anal. Calcd for $C_{18}H_{17}BrN_4S$: C, 53.87; H, 4.27; N, 13.96%. Found C, 53.80; H, 4.22; N, 13.90%.

123j: m.p. 198-200 °C; IR (KBr) ν cm^{-1} 1685, 1630 and 1592; ^{1}H NMR (CDCl$_3$, 400 MHz) δ ppm 1.26 (t, 3H, *J* = *12.1 Hz*), 2.32 (s, 3H), 2.72 (q, 2H, *J* = *8.3* Hz), 5.16 (s, 3H), 7.31 (d, 2H, *J* = *8.0* Hz), 7.54 (d, 2H, *J* = *7.3* Hz), 7.93 (d, 2H, *J* = *7.3* Hz), 8.01 (s, 1H), 8.57 (d, 2H, *J* = *8.0* Hz); ^{13}C NMR (CDCl$_3$, 100 MHz) 13.1, 14.1, 17.9, 62.3, 104.1, 120.1, 123.9, 129.1, 131.6, 133.6, 134.1, 134.7, 145.9, 148.7, 150.3, 153.6, 156.7. MS (CI) *m/z* = 438.13 (M-1). Anal. Calcd for $C_{21}H_{19}BrN_4S$: C, 57.41; H, 4.36; N, 12.75%. Found C, 57.38; H, 4.38; N, 12.72%.

Synthesis of pyrazolo[*1,5-a*]pyrimidines

A dry 100 mL flask was charged with 1*H*-pyrazol-5(4*H*)-one **124** (11.9 mmol), and aryl oxoketene dithioacetals (13.1 mmol) **120**; the reaction mixture was refluxed in toluene (15 mL). The reaction after completion (monitored by TLC), was cooled to room temperature, the solvent was evaporated in vacuum, and the crude product was purified by silica gel column chromatography using methanol-DCM (2:20) as an eluent to obtain **125**. **125** (3.8

mmol) was refluxed with substituted amides (4.2 mmol) in presence of KF-Alumina (1 gm) in CCl_4. The reaction upon completion was cooled, the solvent evaporated in vacuum, and the crude product was purified by silica gel column chromatography using ethyl acetate-hexane (10:10) as an eluent to obtain the final product **126a-h**.

126a: m.p. 245-246 °C; IR (KBr) ν cm^{-1} 1675, 1623 and 1587; ^1H NMR ($CDCl_3$, 400 MHz) δ ppm 2.24 (s, 3H), 2.41 (s, 3H), 6.74 (d, 1H, J = *9.1* Hz), 7.42~7.71 (m, 5H, aromatic), 8.12 (d, 1H, J = *9.1* Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) 13.1, 19.2, 98.3, 126.3, 127.3, 129.9, 130.9, 134.6, 135.9, 147.3, 159.8, 166.7, 195.9. MS (CI) *m/z* = 284.41 (M+1). Anal. Calcd for $C_{15}H_{13}N_3OS$: C, 63.58; H, 4.62; N, 14.83%. Found C, 63.56; H, 4.60; N, 14.80%.

126b: m.p. 180-182 °C; IR (KBr) ν cm^{-1} 1691, 1629 and 1595; ^1H NMR ($CDCl_3$, 400 MHz) δ ppm 2.24 (s, 3H), 2.42 (s, 3H), 6.75 (d, 1H, J = *8.5* Hz), 7.51 (d, 2H, J = *7.0* Hz), 7.69 (d, 2H, J = *7.0* Hz), 8.01 (d, 1H, J = *8.5* Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) 14.9, 18.5, 96.0, 127.5, 129.5, 131.9, 133.2, 135.7, 138.5, 147.6, 160.6, 166.9, 194.6. MS (CI) *m/z* = 319.02 (M+1). Anal. Calcd for $C_{15}H_{12}ClN_3OS$: C, 56.69; H, 3.81; N, 13.22%. Found C, 56.75; H, 3.88; N, 13.29%.

126c: m.p. 187-189 °C; IR (KBr) ν cm^{-1} 1695, 1634 and 1599; ^1H NMR ($CDCl_3$, 400 MHz) δ ppm 2.28 (s, 3H), 2.40 (s, 3H), 6.72 (d, 1H, J = *8.0* Hz), 8.01 (d, 2H, J = *7.2* Hz), 8.19 (d, 2H, J = *7.2* Hz), 8.05 (d, 1H, J = *8.0* Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) 14.2, 18.0, 97.8, 120.5, 127.7, 130.6, 133.8, 140.9, 148.3, 160.5, 166.5, 196.2. MS (CI) *m/z* = 329.09 (M+1). Anal. Calcd for $C_{15}H_{12}N_4O_3S$: C, 54.87; H, 3.68; N, 17.06%. Found C, 54.81; H, 3.73; N, 17.01%.

126d: m.p. 174-175 °C; IR (KBr) ν cm^{-1} 1689, 1638 and 1590; H^1 NMR ($CDCl_3$, 400 MHz) δ ppm 2.29 (s, 3H), 2.49 (s, 3H), 6.71 (d, 1H, J = *9.0* Hz), 7.58 (d, 2H, J = *7.2* Hz), 7.76 (d, 2H, *J* = *7.2* Hz), 8.06 (d, 1H, *J* = *9.0* Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) 13.5, 18.6, 96.6, 126.5, 127.6, 129.9, 130.8, 133.6, 135.1, 146.8, 159.6, 167.2, 195.9. MS (CI) m/z = 361.21 (M-1). Anal. Calcd for $C_{15}H_{12}BrN_3OS$: C, 49.73; H, 3.34; N, 11.60%. Found C, 49.70; H, 3.31; N, 11.63%.

126e: m.p. 170-172 °C; IR (KBr) ν cm^{-1} 1680, 1628 and 1579; H^1 NMR ($CDCl_3$, 400 MHz) δ ppm 1.19 (t, 3H, *J* = *12.1* Hz), 2.40 (s, 3H), 2.51 (q, 2H, *J* = *5.7* Hz), 6.78 (d, 1H, *J* = *8.5* Hz), 7.48~7.76 (m, 5H, ArH), 7.96 (d, 1H, *J* = *8.5* Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) 13.2, 14.7, 21.6, 98.1, 126.2, 128.1, 129.6, 131.5, 133.9, 135.0, 147.5, 167.8, 170.6, 196.6. MS (CI) m/z = 298.11 (M-1). Anal. Calcd for $C_{16}H_{15}N_3OS$: C, 64.62; H, 5.08; N, 14.13%. Found C, 64.69; H, 5.12; N, 14.21%.

126f: m.p. 177-178 °C; IR (KBr) ν cm^{-1} 1688, 1621 and 1579; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 1.15 (t, 3H, *J* = *14.0* Hz), 2.37 (s, 3H), 2.57 (q, 2H, *J* = *5.9* Hz), 6.73 (d, 1H, *J* = *8.1* Hz), 7.52 (d, 2H, *J* = *7.1* Hz), 7.79 (d, 2H, *J* = *7.1* Hz), 7.99 (d, 1H, *J* = *8.1* Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) 13.8, 14.9, 24.3, 97.7, 126.8, 130.1, 132.7, 133.2, 135.3, 139.6, 147.1, 168.1, 170.9, 196.2. MS (CI) *m/z* = 333.23 (M+1). Anal. Calcd for $C_{16}H_{14}ClN_3OS$: C, 57.91; H, 4.25; N, 12.66%. Found C, 57.83; H, 4.20; N, 12.72%.

126g: m.p. 177-179 °C; IR (KBr) ν cm^{-1} 1688, 1633 and 1579; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 1.21 (t, 3H, *J* = *14.1* Hz), 2.41 (s, 3H), 2.41 (s, 3H), 2.75 (q, 2H, J = 8.7 Hz), 6.71 (d, 1H, *J* = *9.1* Hz), 8.01 (d, 1H, *J* = *9.1* Hz), 8.12 (d, 2H, *J* = *7.1* Hz), 8.41 (d, *J* = *7.1* Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) 13.1, 14.2, 25.6, 97.6, 120.1, 125.6, 129.5, 134.9, 140.1, 146.5, 150.6, 165.9, 170.6, 196.1 MS (CI) *m/z* = 343.05 (M+1). Anal. Calcd for $C_{16}H_{14}N_4O_3S$: C, 56.13; H, 4.12; N, 16.36%. Found C, 56.11; H, 4.15; N, 16.39%.

126h: m.p. 186-187 °C; IR (KBr) ν cm^{-1} 1676, 1618 and 1565; ^{1}H NMR (CDCl$_3$, 400 MHz) δ ppm 1.12 (t, 3H, *J* = *14.3* Hz), 2.39 (s, 3H), 2.52 (q, 2H, *J* = *5.5* Hz), 6.75 (d, 1H, *J* = *8.0* Hz), 7.63 (d, 2H, *J* = *7.0* Hz), 7.83 (d, 2H, *J* = *7.0* Hz), 8.02 (d, 1H, *J* = *8.0* Hz); ^{13}C NMR (CDCl$_3$, 100 MHz) 13.9, 14.4, 24.9, 97., 126.8, 130.1, 132.7, 133.2, 135.3, 139.6, 147.1, 168.1, 170.9, 196.2. MS (CI) *m/z* = 331.02 (M+1). Anal. Calcd for $C_{15}H_{12}BrN_3O$: C, 54.56; H, 3.66; N, 12.73%. Found C, 54.63; H, 3.74; N, 12.79%.

REFERENCES:

1. (a) Straub, A. Stasch, Alonso-Alija, J.P. C. Bioorg. *Med. Chem. Lett.* **2001**, *11*, 781. (b) Elnagdi, M.N. Elmoghayar, M.R.H. Elgemeie, G.E.H., *Adv. Heterocyclic. Chem.* **1987**, *41*, 320-329.
2. Tomcufcik, A. S.; Albright, J. D.; Dusza, J. P. U.S. Patent 4654347, 1987; *Chem. Abstr.* **1985**, *25*, 220889m.
3. (a) Chen, Y. L. JP Patent 2000502723; *Chem. Abstr.* **1998**, *17*, 20490s. (b) Dusza, J. P.; Albright, J. D.; Tomcufcik, A. S. U.S. Patent 5538977, 1996; *Chem. Abstr.* **1996**, *13*, 168011c.
4. Boes, M.; Stadler, H.; Riemer, C. U.S. Patent 6194410, 2001; *Chem. Abstr.* **1999**, *16*, 214304z.
5. O'Donnell, P. B.; Thiele, W. J. U.S. Patent 6384221, 2002; *Chem. Abstr.* **2001**, *15*, 212744f.
6. (a) Kendall, R. L.; Rubino, R.; Rutledge, R.; Bilodeau, M. T.; Fraley, M. E.; Thomas, K. A., Jr.; Hungate, R. W. U.S.Patent 6235741, 2001; *Chem. Abstr.* **1999**, *4*, 033028w. (b) Fraley, M. E.; Hoffman, W. F.; Rubino, R. S.; Hungate, R.W.; Tebben, A. J.; Rutledge, R. Z.; McFall, R. C.; Huckle, W. R.; Kendall, R. L.; Coll, K. E.; Thomas, K. A. *Bioorg.Med. Chem. Lett.* **2002**, *12*, 2767-2770
7. (a) Emelina, E. E.; Petrov, A. A.; Firsov, A. V. *Russ. J. Org.Chem.* **2001**, *37*, 852-858. (b) Chern, J.-W.; Lee, C.-C.; Liaw, Y.-C. W.; Andrew H.-J. *Heterocycles* **1992**, *34*, 1133-1145. (c) Balicki, R. *Pol. J. Chem.* **1983**, *57*, 1251-1261. (e) Auzzi, G.; Costanzo, A.; Bruni, F.; Clauser, M.; Guerrini, G.; Selleri, S.; Pecori Vettori, L. *Farmaco* **1990**, *45*, 1193-1205. (f) Bruni, F.; Chimichi, S.; Cosimelli, B.; Costanzo,

A.; Guerrini, G.; Selleri, S. *Heterocycles* **1990**, *31*, 1141-1149. (g) Elnagdi, M. H.; Erian, A. W. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1854-1856. (h) Abdelrazek, F. M. *J. Prakt. Chem.* **1989**, *331*, 475-478. (i) Hussain, S. M.; El-Reedy, A. M.; El-Sharabasy, S. A. *Tetrahedron* **1988**, *44*, 241-246. (j) Ried, W.; Aboul-Fetouh, S. *Tetrahedron* **1988**, *44*, 7155-7162. (k) Ho, Y.-W. *J. Chin. Chem. Soc.* (*Taipei*) **1999**, *46*, 955-962.

8. (a) Elnagdi, M. H. Negm, A. M. Sadek, K. U. Synlett **1995**, 27. (b) Quiroga, J. Insuasty, B. Hormaza, A. *J. Heterocyclic Chem.* **1999**, *36*, 1311. (c) Quiroga, J. Hormaza, Insuasty, A. Marquez, B. M. *J. Heterocycl. Chem.* **1998**, *35*, 409.
9. (a) Emelina, E. E.; Petrov, A. A.; Firsov, A. V. *Russ. J. Org.Chem.* **2001**, *37*, 852. (b) Chern, J.-W.; Lee, C.-C.;Liaw, Y.-C. W.; Andrew H.-J. *Heterocycles* **1992**, *34*, 1133. (c) Balicki, R. *Pol. J. Chem.* **1983**, *57*, 1251.(e) Auzzi, G.; Costanzo, A.; Bruni, F.; Clauser, M.; Guerrini,G.; Selleri, S.; Pecori Vettori, L. *Farmaco* **1990**, *45*, 1193. (f) Bruni, F.; Chimichi, S.; Cosimelli, B.; Costanzo,A.; Guerrini, G.; Selleri, S. *Heterocycles* **1990**, *31*, 1141. (g) Elnagdi, M. H.; Erian, A. W. *Bull. Chem. Soc.Jpn.* **1990**, *63*, 1854. (h) Abdelrazek, F. M. *J. Prakt.Chem.* **1989**, *331*, 475. (i) Hussain, S. M.; El-Reedy,A. M.; El-Sharabasy, S. A. *Tetrahedron* **1988**, *44*, 241 (j) Ried, W.; Aboul-Fetouh, S. *Tetrahedron* **1988**, *44*, 7155. (k) Ho, Y.-W. *J. Chin. Chem. Soc.* (*Taipei*) **1999**, *46*,955.
10. (a) R.V.A. Orru, M. Greef, *Synthesis*, **2003**, 1471; (b) A. Domling, I. Ugi, *Angew. Chem. Int. Ed. 39*, **2000**, 3168; (c) L. Weber, K. Illegen, M. Almstetter, *Synlett,* **1999**, 366.

LIST OF PUBLICATIONS

1. Synthesis of substituted 4-(3-alkyl-1,2,4-oxadiazol-5-ylmethyl)-3,4-dihydro-2*H*-1,4-benzoxazines and 4-(*1H*-benzimidazol-2-ylmethyl)-3,4-dihydro-2*H*-1,4-benzoxazines.**Pushpak Mizar** and Bekington Myrboh ***Tetrahedron Letters*** 47 **2006**, 7823–7826.

2. Three-component synthesis of 5:6 and 6:6 fused pyrimidines using KF-alumina as a catalyst. **Pushpak Mizar** and Bekington Myrboh. ***Tetrahedron Letters*** 49, **2008,** 5283-5285.

3. Synthetic studies on KF-Alumina catalysed reaction of substituted and unsubstituted aryl-oxoketene dithioacetals and 1*H*-pyrazone-5(4*H*)-one: a convenient synthesis of pyrazolo[*3,4-b*]pyridine and pyrazolo[*1,5-a*]pyrimidine. **Pushpak Mizar** and Bekington Myrboh ***Tetrahedron Letters*****,** 50, **2009,** 3088-3091

4. Synthesis of Substituted 4-(5-alkyl-thiazol-2-ylmethyl)-3,4-dihydro-2*H*-1,4-benzoxazines and 5-(2,3-dihydro-1,4-benzoxazin-4-ylmethyl)-4-methyl-1-phenyl-1*H*-pyrazol-3-ylamine **Pushpak Mizar** and Bekington Myrboh ***J. Het. Chem***. 46, **2009**, 39-43.

5. Synthesis of 2,3-dihydro-6*H*-1-oxa-3a-aza-phenalene and there benzo/hetero fused analogue. **Pushpak Mizar** and Bekington Myrboh (In Press)

6. A facile, three-component method for the synthesis of substituted fused pyrimidines, pyridines and quinolines; catalysed by KF-Alumina. **Pushpak Mizar** and Bekington Myrboh (In Press).

7. A facile method for the synthesis of Pyridazines using Ruthenium trichloride as a catalyst. **Pushpak Mizar** and Bekington Myrboh (In Press)

8. A novel method for the synthesis of indole alkaloids (communicated)

9. KF-alumina as a facile catalysed for the synthesis pyridazines and releated heterocylic molecules. **Pushpak Mizar**, Badaker M. Laloo, and Bekington Myrboh (under preparation)