NEW METHODS FOR THE SYNTHESIS OF SUBSTITUTED DIAZEPINES AND OTHER *N*-HETEROCYCLES

(ABSTRACT)

Submitted by

RUDOLF MANTON MANIH

DEPARTMENT OF CHEMISTRY
SCHOOL OF PHYSICAL SCIENCES

DOCTOR OF PHILOSOPHY

IN

CHEMISTRY

To

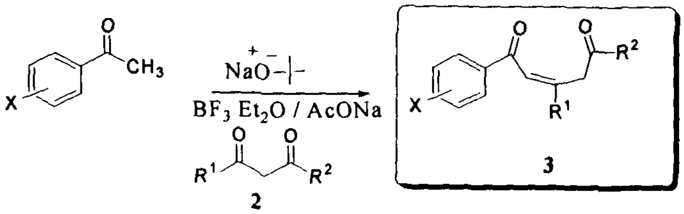
THE NORTH-EASTERN HILL UNIVERSITY
SHILLONG-793022
MEGHALAYA, INDIA

May, 2009

The thesis consists of six chapters.

CHAPTER I:

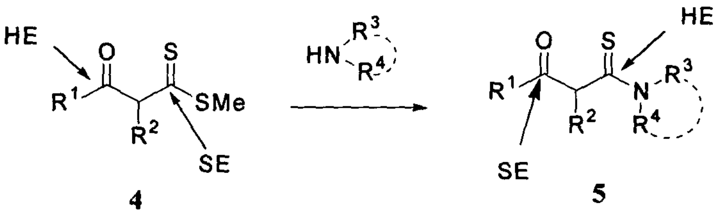
Chapter I deals with general introductions of the chemistry of heterocyclic compounds which constitutes one of the broadest and the most complex branches of Chemistry. The importance of nitrogen heterocycles in natural product chemistry and *pharmacology is the main reason for the continuing interest in the search for new* methods for their synthesis. The main thrust of our investigation was the preparation of versatile intermediates such as 1,5-dicarbonyl compounds, *β*-oxodithioesters and *β*-oxothioamides. Firstly, the 1,5-dicarbonyl compound obtained by treating 1,3-diketone with acetophenone in presence of sodium tertiary butoxide and boron trifluoroetherate to get the 1,5-dicarbonyl intermediate. For example 3,5-dimethyl-7-Aryl-4*H*-1,2-diazepines may be synthesized by reacting substituted acetophenone **1** with sodium tertiary butoxide and 2,4-pentanedione or acetyl acetone **2** to give the intermediate product **3** (Scheme 1). In a similar fashion, treatment of 1,3-diketones **2** such as phenyl acetyl acetone or benzoylphenone[1] with acetophenone give the 1,5-dicarbonyl intermediate **3a** and **3b** which on subsequent treatment with hydrazine yields the substituted-4*H*-1,2-diazepines derivatives.



X= Cl, Br, NO_2, MeO,
R^1= CH_3, Ph **3a**
R^2= Ph, Ph **3b**

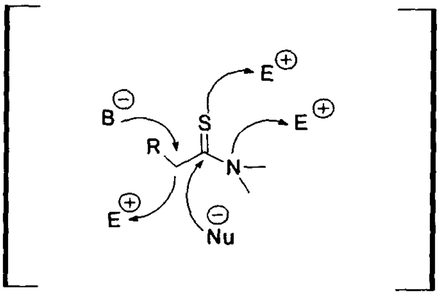
Scheme 1

Secondly, the β-oxodithiocarboxylates[2,3] **4** are versatile three carbon synthons generally employed for the synthesis of a variety of heterocyclic compounds. They are easily prepared[4,5] by reacting the corresponding active methylene compounds with dimethyltrithiocarbonate[6] in presence of suitable base. The β-bisthioalkyl group in these intermediates are activated by the presence of polar substituents at the α-position and can therefore be displaced sequentially, either one or both by various carbon, nitrogen and oxygen nucleophiles, creating further scope for introducing new functionalities at the β-position which find application in many synthetic transformations. The β-oxodithioesters owe their potential synthetic applications to their varied intrinsic chemical properties. The presence of carbonyl functionality and its position at the β-carbon to the bisthioalkyl group places them among the versatile 1,3-electrophilic 3-carbon equivalents making them highly functionalised master key intermediates, which could encompass the wide range of 1,3-electrophilic three-carbon fragments that are of great synthetic importance. The carbonyl and the β-carbon atoms in these systems can also be regarded as hard and soft electrophilic centres, since the carbonyl is adjacent to the hard-base oxygen, while the β-carbon is flanked by the soft-base thiomethyl groups (Scheme 2).



Scheme 2. Hard-soft affinity inversion in beta-oxodithioester **4** and beta-oxothioamide **5**, HE = hard electrophile, SE = soft electrophile.

Thirdly, the chemical and physical properties of thioamides **5** are determined by the two active centres. One of them is associated with the nitrogen atom with the unshared pair of electrons, and the other one is localized on the thiocarbonyl group. Two nucleophilic centers in thioamides are localized on the heteroatoms (sulfur and nitrogen). A potential third centre appears in the thioamides having a hydrogen atom on the α–carbon. An electrophilic centre is associated with the thiocarbonyl carbon atom (Scheme 3). These versatile intermediates are used to synthesize various *N*-heterocycles.

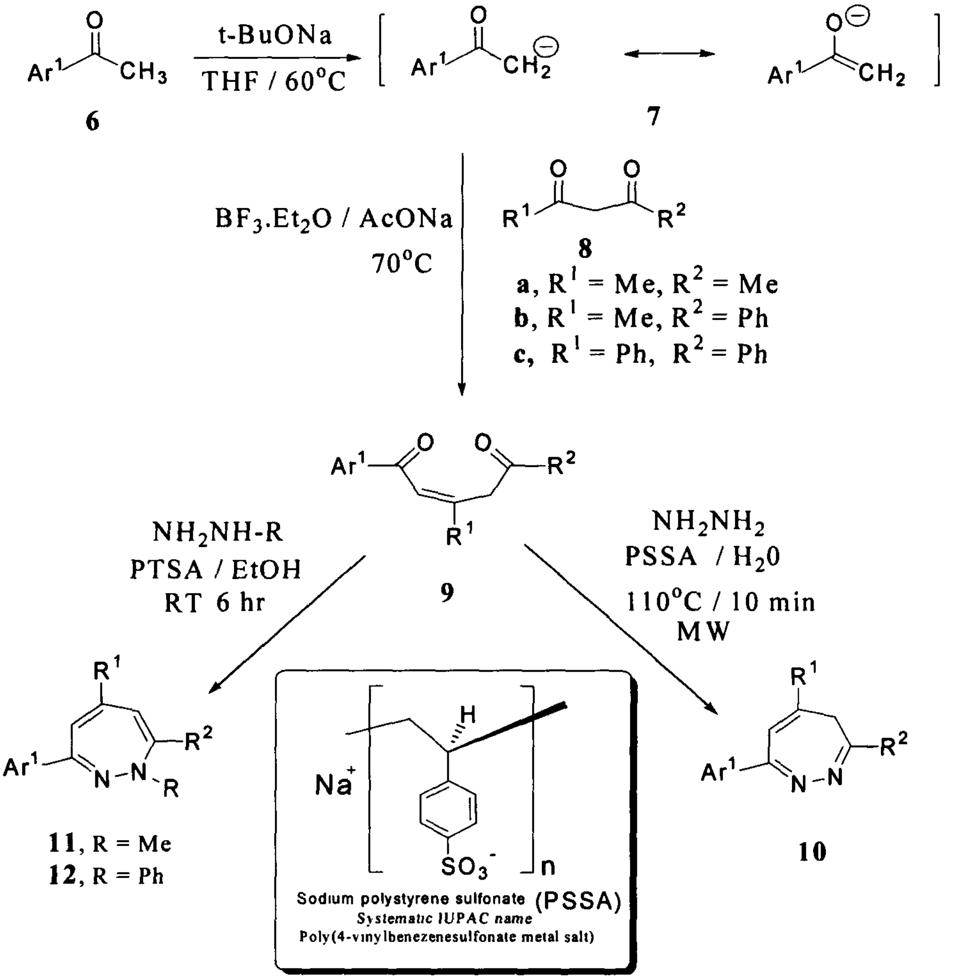


Scheme 3

CHAPTER II:

As part of our quest for greener synthetic pathways which have environmental and economic advantages,[7,8] we reported (chapter II) an expeditious synthesis of 1,2-diazepines by the reaction of *α,β*-unsaturated 1,5-diketones **9** with hydrazines using catalyzed reactions of polystyrene sulfonic acid[9] (PSSA) which proceeds efficiently in water in absence of any organic solvent forming 3,5,7-trisubstituted-4*H*-1,2-diazepine **10** (Scheme 4).

The *α,β*-unsaturated 1,5-dicarbonyl compound **9** is the versatile intermediate for the synthesis of *N*-heterocycles. The treatment of 1,5-dicarbonyl intermediate with hydrazine and PSSA as acid catalyst in water medium proceeds cleanly and efficiently under the condition of microwave assisted reaction to give the 3,5,7-trisubstituted-4*H*-1,2-diazepine **10** in good yields. However, for the sake of comparison, conventional reactions are also performed, using *p*-toluene sulfonic acid (PTSA) to study the condensation of intermediate **9** with hydrazine, by stirring at room temperature for 6-8 hours. The product 2-(*N*-alkyl/aryl)-3,5,7-trisubstituted-4*H*-1,2-diazepine **11, 12** was isolated, resulted in low yield and rate of the reaction is far inferior than in the case of PSSA.

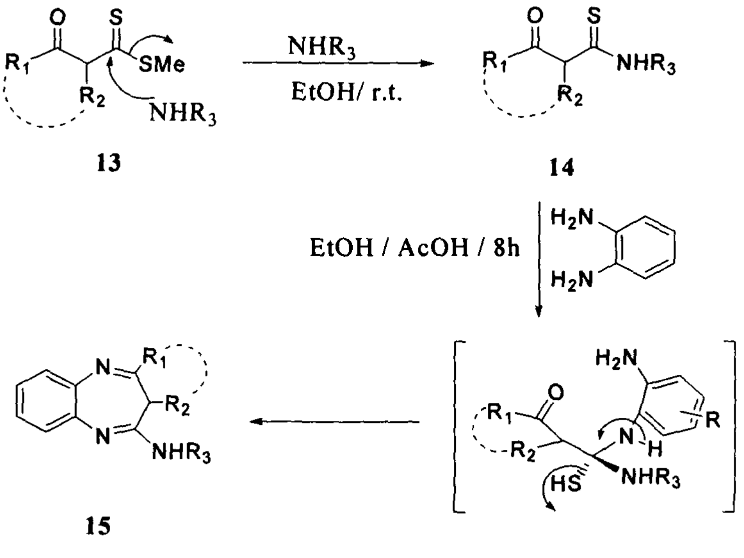


Ar^1 = $-C_6H_5$, p-Cl-C_6H_4, p-Br-C_6H_4, p-NO_2-C_6H_4 , p-MeO-C_6H_4, 3,5-dimethoxy-C_6H_3, 3,5-dihydroxy-C_6H_3, 3,5-dimethyl-C_6H_3.

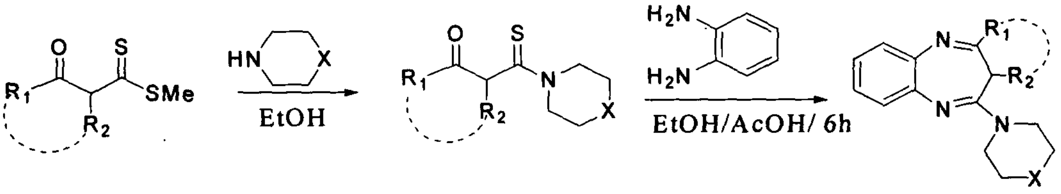
Scheme 4

CHAPTER III:

In Chapter III we described two general methods for the synthesis of 2-substituted amino-4-aryl-3*H*-dihydro-benzo-[*b*][1,4]-diazepines **15** and 2-(*N*- cycloamino)-4-Aryl-3*H*-dihydro-benzo-[*b*][1,4]-diazepines **17** using *β*-oxodithioesters. One involving the general dethiomethylation of *β*-oxodithioesters **13** with primary amines, the other with secondary cyclic amines, forming two different *β*-oxothioamides **14** and **16** followed by subsequent reaction and cyclisation with *o*-phenylenediamine yielding 2-substituted amino-4-aryl-3*H*-dihydro-benzo-[*b*][1,4]-diazepines **15** and 2-(*N*-cycloamino)-4-Aryl-3*H*-dihydro-benzo-[*b*][1,4]-diazepines **17** (Scheme 5 and 6).



Scheme 5

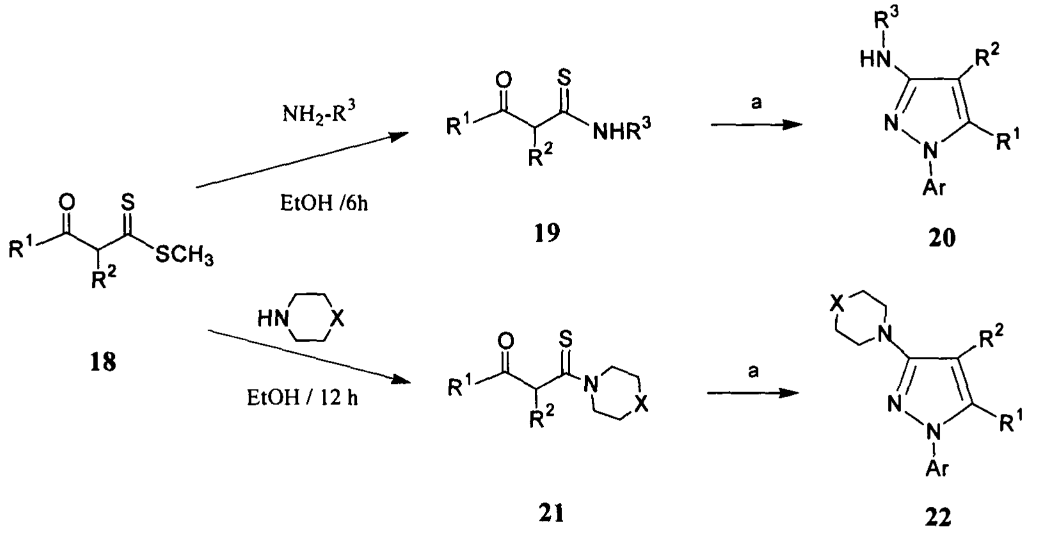


13 16 17

Scheme 6

CHAPTER IV:

In Chapter IV we described the development of efficient and general synthetic routes for five-membered heterocycles utilizing *β*-oxothioamides[10] obtained from *β*-oxodithioester as versatile three-carbon building blocks by tuning the reactivity of these ambident electrophiles toward unsymmetrical heterobinucleophiles. Herein, we describe the general method for the synthesis of 3-(*N*-substituted amino/cycloamino 5-aryl/alkyl) pyrazoles using *β*-oxothioamides **19, 21** which to our knowledge, has not been reported in the literature. During the course of these studies, we wanted to replace the thiomethyl group in *β*-oxodithioester with an amino/cycloamino group, which on further treatment with unsymmetrical binucleophiles such as phenylhydrazine in ethanol and acetic acid would yield 1-Aryl-3-*N*-substituted amino/cycloamino-5-aryl/alkyl pyrazoles **20, 22** (Scheme 7).



a; $ArNHNH_2$ / EtOH/AcOH / 12-16h /Δ

Scheme 7

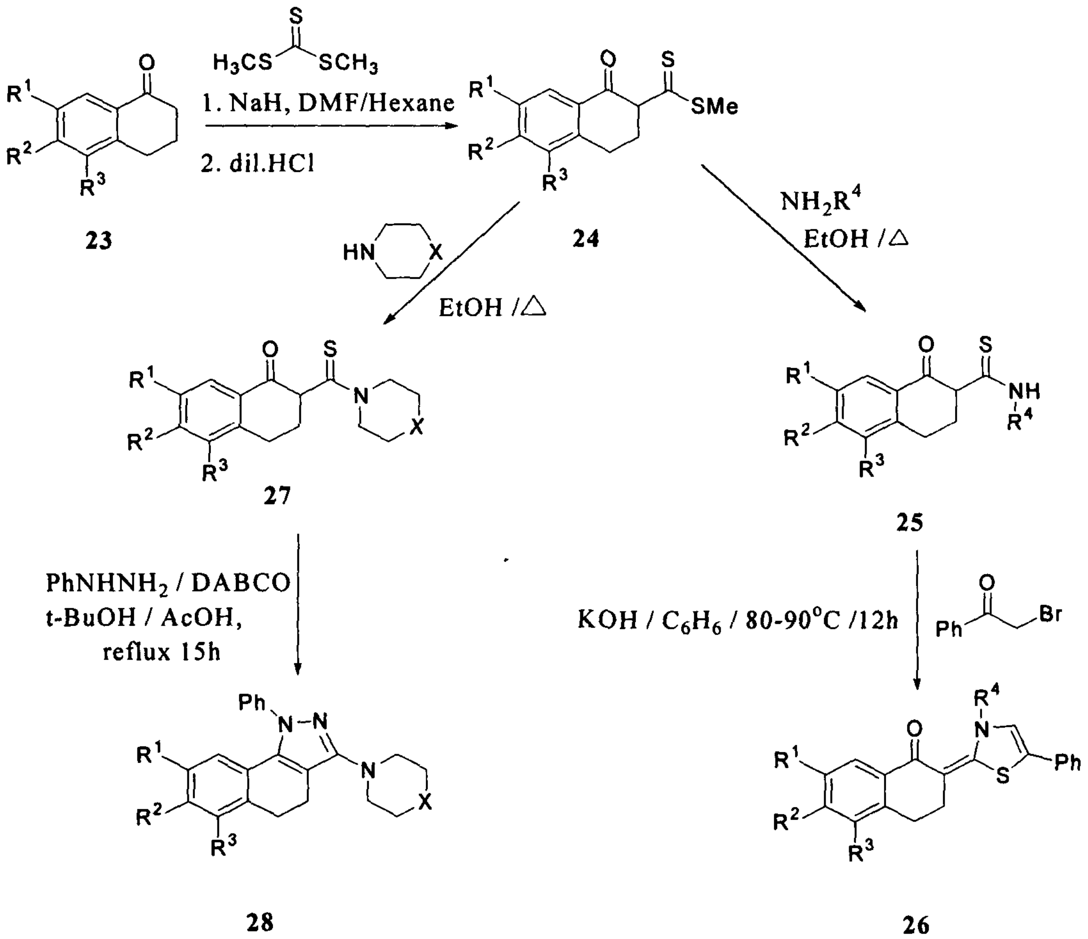
CHAPTER V:

In chapter V, we reported a facile synthetic route for the synthesis of substituted-(3-Methyl-4-phenyl-3*H*-thiazol-2-ylidene)-3,4-dihydro-2*H*-naphthalen-1-one and 1-aryl-3-(*N*-cycloamino)-4,5-dihydro-1*H*-benzo[*g*]indazole derivatives using *β*-oxodithioesters. In the course of our studies on the *β*-ketodithioesters and *β*-ketothioamides chemistry, we became interested in the corresponding thiazole and indazole chemistry which, to our knowledge has not been reported using *β*-ketodithioesters **23** as starting materials (Scheme 8). Herein, we reported the synthesis

of thiazoles **26** and indazoles **28** using the *β*-ketodithioesters **24** starting from simple 3,4-dihydro-2*H*-naphthalen-1-one (or *α*-tetralone) and other substituted *α*-tetralones **23**.

The presence of phenacyl bromide as a dielectrophilic reagent promotes condensation and cyclization affording a five membered ring. It is observed that the process tolerates both electron-donating and electron-withdrawing substituents in α-tetralones **23**. Thus the reaction of *β*-ketothioamides **25** with dielectrophilic reagents such as phenacyl bromide, proceeded efficiently at ambient temperature which on dehydration gave a series *N*-substituted(3,4-dihydro-2*H*-naphthalen-1-one)-3*H*-thiazol-2-ylidene compounds, **26**.

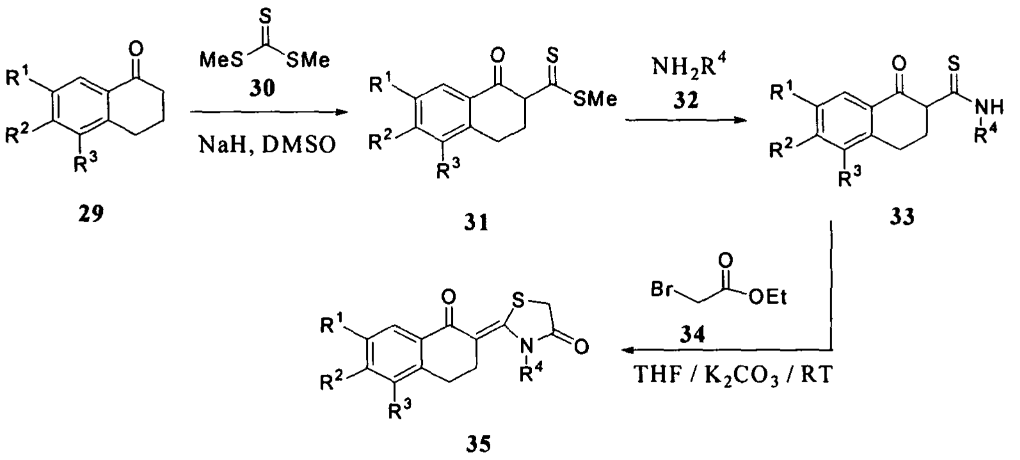
To further extend the scope of the reaction using *β*-ketothioamide derived from *β*-ketodithioesters **24** of α-tetralone, the *β*-ketothioamides **27** were reacted with phenyl hydrazine with a view to synthesize 1-aryl-3-(*N*-cycloamino)-4,5-annulated indazoles under DABCO-catalyzed conditions. The reaction proceeded as expected to afford **28** in good yields (Scheme 8).


H3CS SCH3 S
1. NaH, DMF/Hexane
2. dil.HCl
23
24
SMe
HN X
EtOH /△
NH2R4
EtOH /△
27
25
PhNHNH2 / DABCO
t-BuOH / AcOH,
reflux 15h
KOH / C6H6 / 80-90°C /12h
Ph Br
28
26
Ph
R1
R2
R3
R4
X

Scheme 8

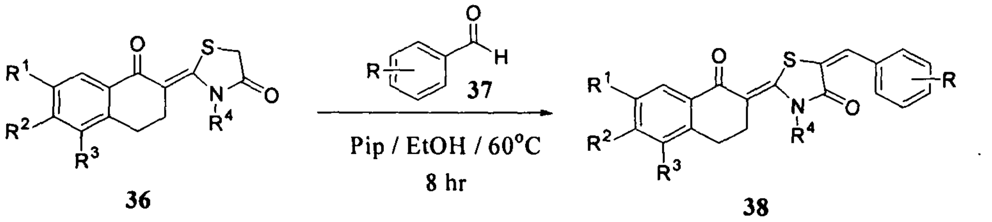
CHAPTER VI:

Chapter VI describes the synthesis of substituted-(3,4-dihydro-1*H*-naphthalen-2-ylidene)-thiazolidin-4-one derivatives **35** and 5-substituted arylidene-3-alkyl/aryl-2-substituted-(1-oxo-3,4-dihydro-1*H*-naphthalen-2-ylidene)-thiazolidin-4-ones **37** using the *β*-oxothioamide **33** derived from *β*-oxodithioester **31**.



Scheme- 9

The investigation was further extended to the synthesis of substituted 5-arylidene-2-(1-oxo-3,4-dihydro-1*H*-naphthalen-2-ylidene)-thiazolidin-4-one **38** derived from substituted-(3,4-dihydro-1*H*-naphthalen-2-ylidene)-thiazolidin-4-one derivatives **36.** Interestingly the acidic hydrogen at the thiazolidin-4-one moiety on treatment with piperidine base, undergo condensation with various aromatic benzaldehydes **37** in ethanol solution under refluxing condition for about 8 hours, to afford a series of 5-arylidene-2-(1-oxo-3,4-dihydro-1H-naphthalen-2-ylidene)-thiazolidin-4-one **38** (Scheme 10).



Scheme- 10

REFERENCES

1. Furniss, A. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. *Vogel's Textbook of Practical Organic Chemistry Fifth New Edition Pearson education.*
2. (a) Dalgard, L.; Jensen, L.; Lawesson, S. O. *Tetrahedron* **1974**, *39*, 93.
   (b) Ramdas, S, R.; Srinivasan, P. S.; Ramachandran, J.; Sastry, V. V. S. K. *Synthesis* **1983**, 605.
3. (a) Voss, J. Synthesis of Thioesters and Thiolactones, In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1990; Vol. 6, pp 435-460.
   (b) Nair, S. K.; Samuel, R.; Asokan, C. V. *Synthesis* **2001**, 573.
4. (a) Nair, S. K.; Asokan, C. V. *Synth. Commun.* **2001**, 22, 1453.
   (b) Nair, S. K.; Asokan, C. V. *Synth. Commun.* **1999**, 29, 791.
5. Singh, G.; Bhattacharjee, S. S.; Ila, H.; Junjappa, H. *Synthesis* **1982**, 693-694.
6. Haugwitz, R. D. *U.S. Patent* 3, 660, 412, May **1972**.
7. (a) Kidwai, M.; Mothsra, P. *Synthetic Communications*, **2006**, 36, 817-824.
   (b) Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford University Press: Oxford, NY, 1998.
8. (a) Holbrey, J. D.; Turner, M. B.; Rogers, R. D. *Ionic Liquids as Green Solvents*; ACS Symposium Series 856; American Chemical Society: Washington, DC, 2003; pp 2-12. (b) Varma, R. S. *Advances in Green Chemistry: Chemical Syntheses Using Microwave Irradiation*; AstraZeneca Research Foundation India: Bangalore, India, 2002. (c) Varma, R. S. Organic Synthesis using Microwaves and Supported Reagents. In *Microwaves in Organic Synthesis*; Loupy, A., Ed.; Wiley-VCH: Weinheim, Germany, 2002; pp 181-218. (d) Kappe, C. O.; Stadler, A. In

Microwaves in Organic and Medicinal Chemistry; Mannhold, R., Kubinyi, H., Folkers, G., Eds.; Wiley-VCH: Werlag GmbH & Co. KGaA, Weinheim, Germany, 2005.

9. (a) Ju, Y.; Varma, R. S. *Org. Lett.* **2005**, *7*, 2409-2411; (b) Ju, Y.; Kumar, D.; Varma, R. S. *J. Org. Chem.* **2006**, *71*, 6697-6700; (c) Ju, Y.; Kumar, D.; Varma, R. S. *J. Org. Chem.* **2006**, *71*, 135-141; (d) Polshettiwar, V.; Varma, R.S. *J. Org. Chem.* **2007**, 72, 7420-7422; (e) Polshettiwar, V.; Varma, R.S. *Tetrahedron Lett.* **2007**, 48, 7343-7346.
10. Jagodzinski, Tadeusz S. *Chem. Rev.*, **2003**, *103*, 197-227.

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A THESIS
SUBMITTED
IN
FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

To

THE NORTH-EASTERN HILL UNIVERSITY
SHILLONG-793022
MEGHALAYA (INDIA)

May, 2009

DEDICATED TO MY PARENTS

NORTH EASTERN HILL UNIVERSITY
NEHU Campus, Shillong – 793022, Meghalaya, INDIA

Prof B. Myrboh
Supervisor and Head
Department of Chemistry
North Eastern Hill University, Shillong
Meghalaya, Shillong 793022, India

Tel:0364-2722601(O)
-2722602(O)
Fax: +913642228213
E-mail: bmyrboh@nehu.ac.in

CERTIFICATE

This is to certify that the thesis entitled "*New methods for the synthesis of substituted diazepines and other N-heterocycles*" is based on the original work done by Rudolf M. Manih, under my supervision in the Department of Chemistry, School of Physical sciences, North Eastern Hill University, Shillong, Meghalaya. This work has not previously formed the basis for the award of any degree, diploma, associateship, fellowship or any other similar title, and that it represents entirely and independent work on the part of the Candidate.

Prof. B. Myrboh
Supervisor

Professor
Department of Chemistry
North-Eastern Hill University
Shillong [illegible]

NORTH-EASTERN HILL UNIVERSITY
NEHU Campus, Shillong – 793022, Meghalaya, INDIA

Dated 14th May, 2009

DECLARATION

I, **Rudolf M. Manih** hereby declare that the subject matter of this thesis is the record of the work done by me, that the contents of this thesis did not form the basis of the award of any previous degree to me or to anybody else to the best of my knowledge. I have not submitted the thesis for any degree in any other University or Institution. This is being submitted to the North-Eastern Hill University, Shillong for the degree of Doctor of Philosophy in Chemistry.

R. M. Manih
Candidate

Prof. B. Myrboh
Supervisor

Professor
Department of [illegible]istry
North-Eas[illegible] H[illegible] [illegible]versity
Shil[illegible] [illegible]022

Head
Department of Chemistry
North-Eastern Hill University

Head
Department of Chemistry
North-Eastern Hill University
Shillong- 793022

Acknowledgements

I would like to express my deepest sense of gratitude to my supervisor Prof. B. Myrboh Supervisor and Head Department of Chemistry NEHU, for his inspiring, untiring guidance and constant encouragement throughout the course of my research work.

I wish to extend my gratitude to Prof. K. Ismail, Dean of Physical sciences NEHU, Prof. R. K. Poddar, Prof. R. H. D Lyngdoh, Dr R. L. Nongkhlaw, Dr E. Rymmai, Prof. (Ms) P. Nongkynrih (Head Department of Physics, NEHU), and all the teaching and non-teaching staffs of the Department of Chemistry NEHU, for their valuable service and co-operation they rendered to me.

I am grateful to Prof. H. Ila (IIT Kanpur) for valuable suggestions and discussion. My sincere thanks goes to the Directors and technicians especially Mr P.S. Dkhar, Dr W Rynjah, Mrs D. Myrboh of RSIC-SAIF Shillong and IISc Bangalore for providing spectroscopic analysis.

To the UGC-NERO Guwahati for the award of FDP Fellowship (Teacher fellowship in the form of study leave) and Minor Research Project. The Government of Meghalaya is gratefully acknowledged.

I am thankful to Dr S. R. Lyndem, Principal Union Christian College for the invaluable service and encouragement rendered towards my research work. To all my colleagues of the Union Christian College, Umiam and especially to Dr A. Malhotra, Mrs H. Shangpliang, Dr C. Lyngdoh and Mr P. Lynser, Department of Chemistry, Union Christian College for their co-operation and support.

I express my gratefulness to Mrs Darry E. Manih, Siam Neihsal, Gunajyoti Das and my fellow Research Scholars in the Department of Chemistry for their generosity and service rendered to me. Thanks goes to Bremil, Bennette and to my Labmates Pushpak, Hormi, Mantu, Geromy, Icydora, Badaker and Iadei who always stand with me through thick and thin during my stay and work in the Lab.

I am gratefully indebted to my Parents, brother, sister and all my family members for their continuous love, inspiration and support throughout the course of my study.

Above all, to my Lord and saviour Jesus Christ for His blessings showered upon me.

Rudolf M Manih

CONTENTS

Preface

The aim of this thesis is to collect the works done and which deals with the chemistry of seven-membered heterocyclic compounds containing two nitrogen atoms and for compounds containing N-heterocycles. The field of diazepines, although emphasizing the more recent work, the present review also includes older background material. To a large extent the recent interest in this field is due to the discovery of newer methodology and medicinal activity of these compound derivatives.

In this thesis, the literature through early 1960's has been covered as Introduction in Chapter I. Synthetic methods leading to the various diazepine ring systems are summarized and the reactions and properties that have been studied for these ring systems are discussed. For convenience the chapters are divided into Chapter II for a monocyclic ring diazepines with nitrogen atoms in the 1,2-positions formed from *α,β*-unsaturated 1,5-dicarbonyl compound as a viable intermediate for formation of a N-heterocyclic seven membered ring. This section are then further extended to Chapter III by taking into account rings fused to the diazepine using a *β*-ketodithioesters as a new and versatile intermediate for seven membered ring i.e., the benzodiazepine with nitrogen atoms at 1,4-positions. Chapter IV is for the synthesis of substituted pyrazoles. All substituent's containing heterocyclic compounds with two nitrogen atoms on monocyclic ring and fused ring are considered under the outline of the first four chapters. The preceding chapters are then aim to collect the synthesis using the *β*-ketodithioester and *β*-ketothioamide as highly efficient synthons for compounds containing other N-heterocycles. Chapter V describes the synthesis of thiazoles and indazoles derivatives derived from *β*-oxodithioester and Chapter VI for derivatives of substituted thiazolidin-4-ones derived from β-oxothioamide which are of biological importance.

Each Chapter is divided into Introduction, results and discussion and experimental section. The entire documentation in this thesis is supported by appropriate references at the end of each Chapter.

CHAPTER I

INTRODUCTION

(INTRODUCTION AND REVIEW OF LITERATURE)

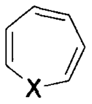
CHAPTER I

INTRODUCTION

INTRODUCTION AND REVIEW ON THE SYNTHESIS OF SUBSTITUTED DIAZEPINES AND N-HETEROCYCLES

The Chemistry of heterocyclic compounds constitutes one of the broadest and the most complex branches of Chemistry. It is of immense interest because of its theoretical implications, the diversities of its synthetic procedures and the physiological and industrial significance of the heterocyclic compounds. The importance of nitrogen heterocycles in natural product chemistry and pharmacology is the main reason for the continuing interest in the search for new methods for their synthesis. An important approach for the synthesis of these types of compounds involves the application of the annelation method, i.e. construction of cyclic compounds from open chain precursors. Heterocyclic units of diazepines and benzodiazepines and their analogues are of special interest in pharmacology because of their biological activities.[1,2,3] An enormous amount of research has been conducted in pharmaceutical laboratories on tranquilizers, sedatives, antidepressants, anti inflammatory and hypnotic agents,[4] all of which are derivatives benzodiazepines. Members of this class of compounds have also been identified as platelet aggregation inhibiting mimics of the arginine-glycine-aspartic acid (RGD) peptide sequence, as anticonvulsant agents,[5] and as antitumor compounds.[6-8]

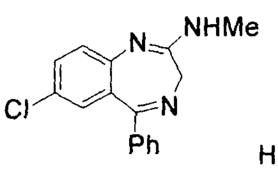
Of late the synthesis of diazepines and 1,2-diazepines in particular has been attracting a lot of attention. These highly unsaturated seven-membered ring heterocycles are of recent synthetic origin and their evolution is linked to advances in theoretical and medicinal chemistry. Starting from the 1960's there is an intense inquiry with regard to the antiaromaticity character of the 8π-electron systems in 1*H*-azepine (**1a**), oxepin (**1b**), and thiepin (**1c**) and the potent aromatic character of the seven membered ring systems in 1,2-diazepines[9] which prompted serious efforts to synthesize these molecules.[10-12]



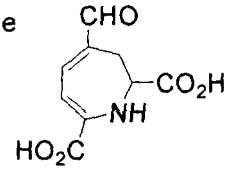
1

a, X = NH
b, X = O
c, X = S

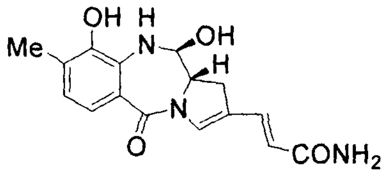
These findings resulted in a dominant market position of several therapeutic agents such as Librium **2** and the increase in synthetic activity toward other benzo- and dibenzo-annelated seven-membered-ring heterocycles.[13] Additional stimulus was injected by the discovery of natural products exhibiting the azepine [muscaflavin **3**[14]], benzazepine [rhoeadine,[13c] cephalotaxine[15]], and 1,4-benzodiazepine [anthramycin **4**[16]] moiety. Not surprisingly, these findings also encouraged advances in the methodology of heterocyclic ring construction. The first 1,3-diazepine, has only recently been synthesized.[17a] Interestingly some of the unique examples of 1,3-diazepines biosynthesized in nature are the metabolite conformycin **5**, the anticonvulsant agents such as 1,4-Benzodiazepine-2,5-diones (BZDs) **6** and Imidazo [4,5-d][1,2]diazepine 7 whose structural elucidation has prompted the search for synthetic analogues.[17b,c] The current literature offers ample evidence for an accelerating growth in our knowledge of seven-membered-ring heterocyclic compounds.[18]



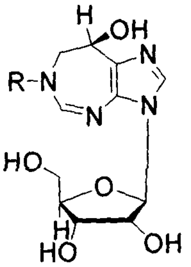
Librium
2



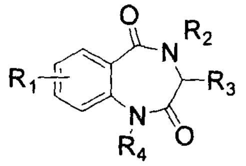
Muscaflavine
3



Anthramycin
4

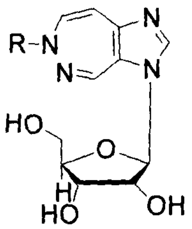


Conformycin
5

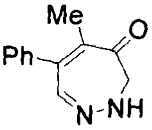


1,4-Benzodiazepine-2,5-dione (BZDs)

6



Imidazo [4,5-d][1,2] diazepine
7

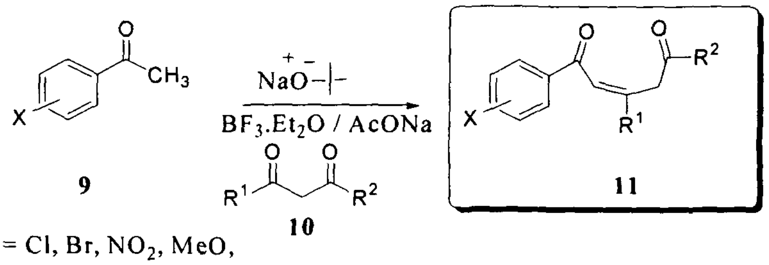


8

Various substituted 1,3-diaroylpropanes were previously condensed with hydrazine to give diazepines in varying yields.[19] Other reports of the synthesis of diazepines involve the use of thiapyrilium salts[20] by the photochemical reaction of pyridinium ylide.[21,22] Klingsberg's original finding[23] that thiapyrilium salt intermediates undergo smooth reaction with hydrazine to yield a broad range of (4*H*)-1,2-diazepines[24] including some condensed trialkyl systems assures ready access to many (1*H*)-1,2-diazepine derivatives.[25] Similarly the synthesis of unsaturated 1,2-diazepines of the type shown (**8**) were for a long time limited to the work done by Moore and his collaborators.[26,27]

I.1: 1,5-dicarbonyl compound as a versatile intermediate for the synthesis of 1,2-*diazepine*:

The main thrust of our investigation was the synthesis of trisubstituted 1,2-diazepines obtained by treating 1,3-diketone with acetophenone in presence of sodium tertiary butoxide to get the 1,5-dicarbonyl intermediate. For example 3,5-dimethyl-7-aryl-4*H*-1,2-diazepines may be synthesized by reacting substituted acetophenone **9** with sodium tertiary butoxide and 2,4-pentanedione or acetyl acetone ($R^1 = CH_3$, $R^2 = CH_3$) **10a** to give the intermediate product **11a** (Scheme 1). In a similar fashion treatment of 1,3-diketones such as phenyl acetyl acetone ($R^1 = CH_3$, $R^2 = Ph$) **10b** with acetophenone give the 1,5-dicarbonyl intermediate **11b**. Similarly condensation of 1,3-Diphenyl-propane-1,3-dione ($R^1 = Ph$, $R^2 = Ph$) **10c** with substituted acetophenone in presence of sodium tertiary butoxide gives the 1,5-dicarbonyl intermediate **11c** which on subsequently treatment with hydrazine yields the substituted-4*H*-1,2-diazepines derivatives.



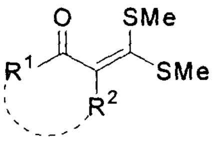
X= Cl, Br, NO_2, MeO,

10a, $R^1 = CH_3$, $R^2 = CH_3$	**11a**
10b, $R^2 = CH_3$, $R_2 = Ph$	**11b**
10c, $R^2 = Ph$, $R_2 = Ph$	**11c**

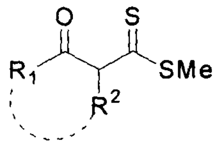
Scheme 1

I.2: Introduction to polarised *β*-oxodithioesters:

The polarised ketene dithioacetals[28] of the general formula **12**, which may carry either one or two electron withdrawing groups at the *α*-carbon atom belong to a class of intermediates, known as either polarised,[29] push-pull[29a,b] or donor-acceptor[29b] ethylenes. Similarly, the β-oxodithiocarboxylates[30,31] **13** are versatile three carbon synthons generally employed for the synthesis of a variety of heterocyclic compounds.



12



13

They are easily prepared by reacting the corresponding active methylene compounds with dimethyltrithiocarbonate[30,31] in presence of suitable base or with 10 equivalent carbon disulphide in the presence of a suitable base followed by alkylation with 1 equivalent of alkyl halide,[28a] often in a one-pot reaction[28-31] or by demethylation[31b] or sulfhydrolysis[31c-d] of α-oxoketene dithioacetals. Many experimental variations have been developed within this broad procedural framework to suit the substrate characteristics, such as the acidities of active methylene hydrogens, specific base-sensitive functional groups and the optimum yields of the corresponding dithioacetals. A large number of active methylene compounds could therefore be converted into the polarised β-oxodithiocarboxylates (Chart 1) with many permutations and combinations of substituents.

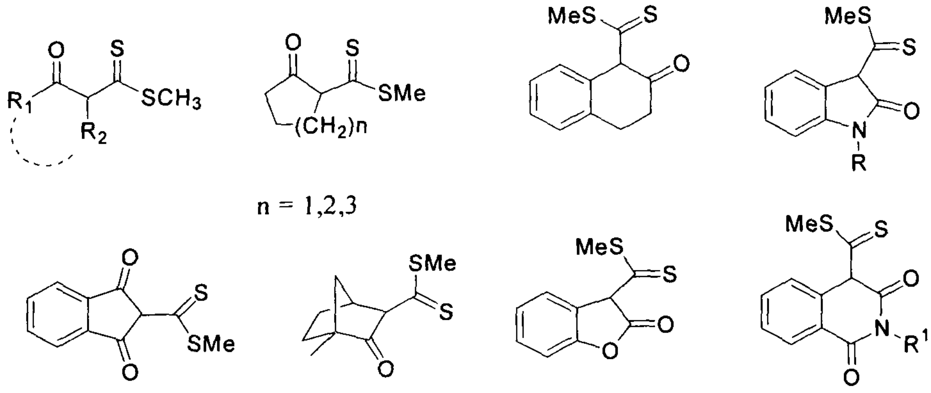
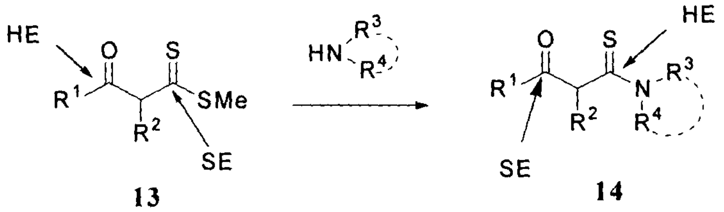


Chart 1. Cyclic and heterocyclic beta-oxodithioesters.

The β-bisthioalkyl group in these intermediates are activated by the presence of polar substituents at the α-position and can therefore be displaced sequentially, either one or both, by various carbon, nitrogen and oxygen nucleophiles, creating further scope for introducing new functionalities at the β-position which find application in many synthetic transformations. The β-oxodithioesters owe their potential synthetic applications to their varied intrinsic chemical properties. The presence of carbonyl functionality and its position at the β-carbon to the bisthioalkyl group places them among the versatile 1,3-electrophilic 3-carbon equivalents. The β-ketodithiocarboxylates[31] can be considered as masked β-ketodithioesters that can be distinguished by having ambident electrophilicity at 1,3 carbon centres, due to the presence of bisthioalkyl groups, which can be converted into α-oxoketenedithioacetals functionality when desired.[32,33] Similarly, their immediate derivatives **12** and **13** can be considered as equivalents of β-diketones and β-ketoaldehydes respectively, making them highly functionalised master key intermediates, which could encompass the wide range of 1,3-electrophilic three-carbon fragments that are of great synthetic importance.

The carbonyl and the β-carbon atoms in these systems can also be regarded as hard and soft electrophilic centres, since the carbonyl is adjacent to the hard-base oxygen, while the β-carbon is flanked by the soft-base thiomethyl groups (Scheme 2). Thus many regioselective reagents can be selected either from hard nucleophiles that can undergo 1,2-addition or from soft nucleophiles that can add preferentially in 1,4-fashion depending on the regiodemands in the product.



Scheme 2. Hard-soft affinity inversion in beta-oxodithioester **13** and beta-oxothioamide **14**, HE = hard electrophile, SE = soft electrophile.

Interestingly, this hard-soft dissymmetry can be inverted[34] either under suitable reaction conditions or by structural modifications, by replacing a thiomethyl group with an amino group so that the same group of nucleophiles can be made to react with either of the carbon atoms to yield the respective regioisomers. Our literature survey reveals only a limited number of examples based on this concept can be recognized, while the future possibilities remain largely unexplored. The flexible functional group manipulation, coupled with hard-soft dissymmetry and its possible inversion, make these intermediates **13** and **14** attractive for many synthetic schemes used to construct a variety of acyclic, cyclic and heterocyclic systems.

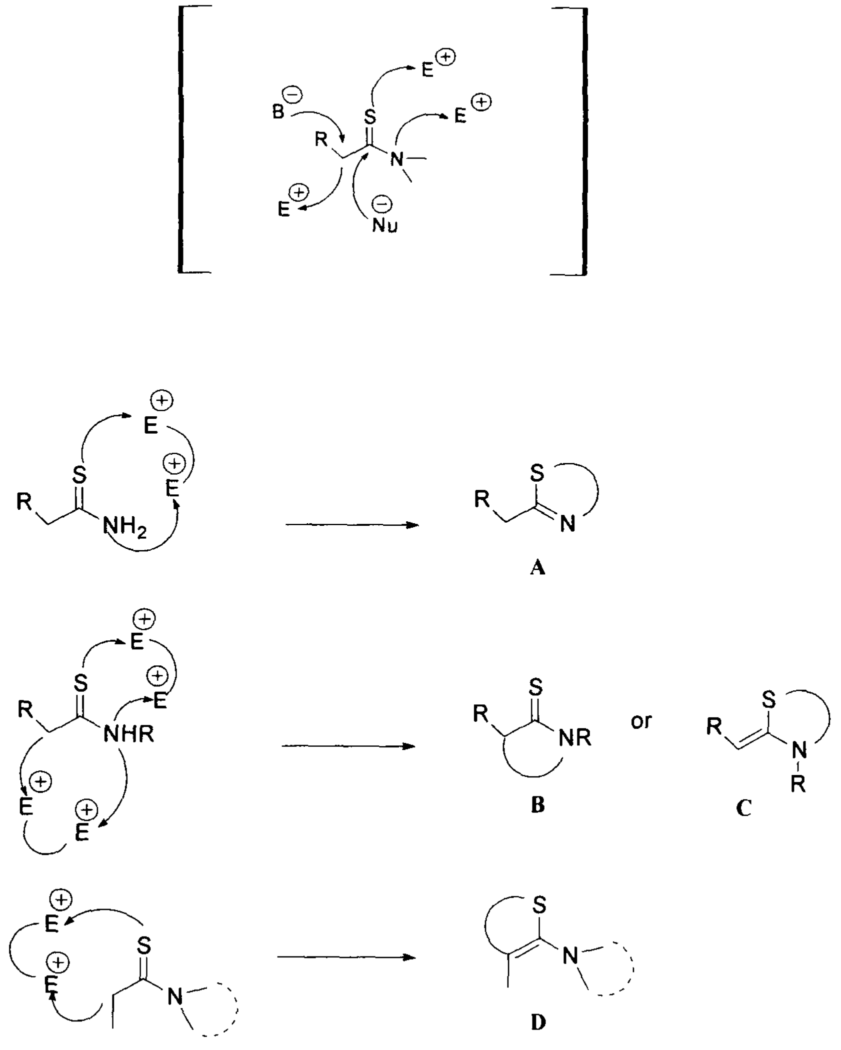
While working on these synthons, much of the chemistry of these compounds was confined to their preparation and properties, while their synthetic potential remained scantly explored. Over the years, many groups have made significant contributions to the chemistry of these compounds and a recent review by Dieter[28a] and Jagodzinski[35] highlights the chronology of the development of their chemistry, structure and synthetic applications. The review is based on their chemical reactivity rather than product novelty, which may be appreciated by those who are interested in further exploration of the hidden synthetic potential of these intermediates.

1.3: Synthesis of *N*-heterocyclic compounds using the thioamide group as a single building Unit:

Many interesting papers which have appeared lately report on functionalization of thioamides and their use in organic synthesis, including regio- and stereoselective heterocyclization reactions. In particular, this concerns the thioamides which have another reactive center in the molecule and therefore may serve as convenient building blocks. Thioamides are most often prepared by simple thionation of the corresponding amides with the aid of phosphorus pentasulfide or the Lawesson reagent.[36,37] The practical use of this method is limited by the availability of the starting amide. Other methods for thioamide synthesis have been reviewed previously.[36,38,39]

Reactions with dielectrophiles

The chemical and physical properties of thioamides are determined by the two active centres. One of them is associated with the nitrogen atom with the unshared pair of electrons, and the other one is localized on the thiocarbonyl group. The inductive and conjugation effects of the introduced substituents face in thioamides the mesomeric effect due to delocalization of π electrons and lability of the unshared electron pairs on the nitrogen and sulphur atoms. Two nucleophilic centers in thioamides are localized on the heteroatoms (sulfur and nitrogen). A potential third centre appears in the thioamides having a hydrogen atom on the α-carbon. An electrophilic centre is associated with the thiocarbonyl carbon atom (Scheme 3). Due to the presence of those active centers, the reactions of thioamides with dielectrophilic reagents may lead, depending on the structure of the starting thioamide, the nature of the dielectrophile, and the reaction conditions, to the formation of different heterocyclic compounds (structures **A-D**, Scheme 3).



Scheme 3

1.4: REACTIONS WITH BIFUNCTIONAL HETERONUCLEOPHILES:
A Review on the Synthesis of *N*-Heterocycles using α-oxoketene dithioacetals

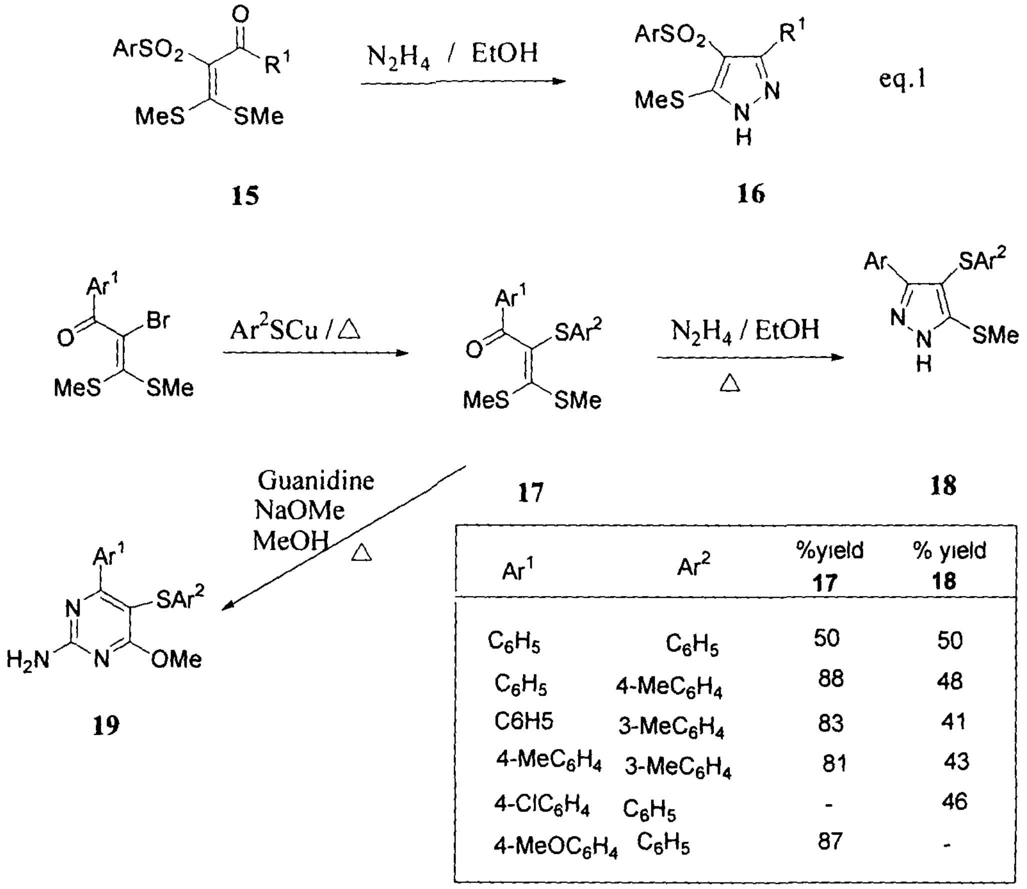
The α-oxoketene dithioacetals have been recognized as useful 3-carbon 1,3-electrophilic fragments which have been exploited extensively for the construction of five- and six-membered heterocycles. Some of their reactions with hydrazine,[40] hydroxylamine,[40a] guanidine, amidines, [40c,41] enamine, cyanoacetamide anions,[42,43] 1,2-diamine, 1,2-aminoalcohol and 1,2-aminothiols[44,45a] have been discussed before.

Myrboh *et al*[46] explain that the oxoketene dithioacetals possessing ambident electrophilic centres in an α,β-enone moiety with either one or two β-alkylthio groups follow different pathways of reduction, depending on the nature of the reducing agents. Myrboh and co-workers discovered that the carbinolacetals[47] could be efficiently converted into the α,β-unsaturated thiolesters or to the corresponding *o*-methyl esters in the presence of $BF_3.Et_2O$/methanol. The overall transformation can be viewed as the homologation of active methylene ketones at the α-position, involving 1,3-carbonyl transposition.

Furthermore, they reported the selective dethiomethylation of α-oxoketene dithioacetals employing the $NaBH_4/NiCl_2$ (nickel boride) combination to yield vinylogous thiolesters in moderate to good yields.[48] They further extended the 1,2-reduction and methanolysis methodology to polyene ester synthesis. Thus cinnamolylketene dithioacetals underwent 1,2-reduction with sodium borohydride and subsequent methanolysis to give 5-aryl-pentadienoates afforded the 7-aryl-2,4,6-heptatrienoates.[49]

Subsequent developments involving their structural flexibility and reactivity with a variety of heteronucleophiles to afford a novel class of heterocycles have been covered in their review.[50] Example, the new development in the pyrazole synthesis includes additional functionalisation and some interesting rearrangements. Thus 4-

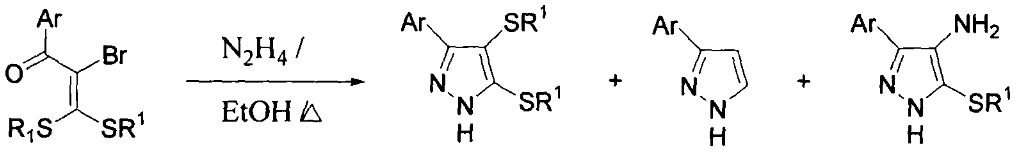
arylsulphonyl[51] **15** and 4-arylthiopyrazoles[52] **16** have been obtained by reacting hydrazine hydrate with the appropriate arylsulphonyl and arylthioketene dithioacetals (eq. 1, Scheme 4).



Ar^1	Ar^2	%yield **17**	% yield **18**
C_6H_5	C_6H_5	50	50
C_6H_5	4-MeC_6H_4	88	48
C6H5	3-MeC_6H_4	83	41
4-MeC_6H_4	3-MeC_6H_4	81	43
4-ClC_6H_4	C_6H_5	-	46
4-MeOC_6H_4	C_6H_5	87	-

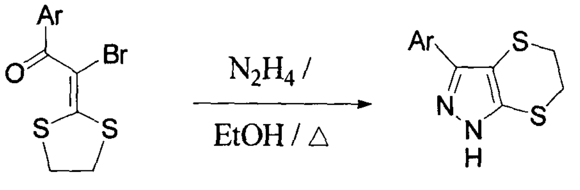
Scheme 4

Junjappa and Ila have observed an interesting 1,2-alkylthio shift during the reaction of α-bromo-α-oxoketene dithioacetals[53] with hydrazine hydrate to afford a mixture of pyrazoles **18-22** in varying yields (Scheme 4 and 5).[54] Subsequent events involve either reductive elimination of the methylthio group and molecular nitrogen to give **21** or elimination of ammonia and methylthio group to afford the imine intermediate, which on further reduction with hydrazine hydrate and subsequent cyclisation yields the pyrazole **22**. The cyclic bromoketene dithioacetals **23** on the other hand react with hydrazine hydrate to yield only 1,4-dithiinopyrazoles **24** exclusively in good yields (Scheme 6).[54] The absence of any other rearranged pyrazoles in this reaction suggests that the formation of **24** does not involve the strained bicyclic episulphonium ion intermediate and instead, appears to proceed by concerted 1,2-alkylthio migration followed by elimination of bromine.



20 **21** **22**

Scheme 5



23 **24**

Ar = C_6H_5,	76%
Ar = 4-ClC_6H_4	80%
Ar = 4-$MeOC_6H_4$,	62%

Scheme 6

1.5: CONCLUSION

The *α,β*-unsaturated 1,5-dicarbonyl compounds and the *β*-oxodithioesters have been shown to be a class of versatile intermediates in synthetic transformations. They further serve as parent precursors for synthesis of *N*-heterocycles such as 1,2-diazepines, benzodiazepine, pyrazoles, pyrimidines, quinazolines etc.

The *β*-oxothioamide has also emerged as another important class of highly functionalized 1,3-electrophilic synthons. The two electrophilic centres in *β*-oxodithioesters differ in their electrophilicity and thus display hard-soft dissymmetry. The presence of bis(methylthio) groups renders the *β*-carbon atom into a soft electrophilic centre, while the oxo carbon remains as a hard electrophile thereby permitting a better regioselectivity depending on the hard-soft profiles of nucleophiles. This hard-soft dissymmetry can be reversed under suitable reaction conditions or by replacing the alkylthio group by amino group and the resulting *β*-oxothioamide undergo exclusive 1,4-addition with a variety of nucleophiles. This aspect of hard-soft affinity inversion remains to be explored and holds considerable synthetic importance in future. The success of aromatic annelation through *β*-oxodithioesters has been well established as a new general method. Further exploration of this methodology depends on the generation of suitably functionalized aliphatic, aromatic and alicyclic compounds. Its extension to heteroaromatic annelation requires further investigation for the formation of five-, six- and seven-membered *N*-heterocycles with various substituted functional groups. The potential application of these intermediates has been emphasized for the construction of a variety of heterocycles in the proceeding chapters. Many transformations described, amply demonstrate that *β*-oxodithioesters promise further synthetic potential with the many new reagents appearing in the literature at an increasing rate.

1.6: REFERENCES

1. (a) South, M. S. and Jakuboski, T. L. *Tetrahedron Lett.*, **1995**, *36*, 5703.

   (b) South, M. S.; Jakuboski, T. L.; Westmeyer, M. and Dukesherer, D. R. *Tetrahedron Lett.*, **1996**, *37*, 1351.

2. Popp, F.D. and Noble A.C. *Advance Heterocycl. Chem.* **1967**, *8*, 21.

3. (a) Carboni, R. and Lindsay, R.V. *J. Am. Chem. Soc.*, **1959**, *81*, 4342.

   (b) Rahman, R. M. A. and Chareib, M. *Ind. J. Chem.*, **1987**, *26(B)*, 496.

   (c) Mansour, A.K.; Eid, M.M. and Hassan, R. A. *J. Heterocycl. Chem.*, **1988**, *25*, 279.

   (d) Rahman, R. M. A. *Ind. J. Chem.*, **1988**, *27(B)*, 548.

4. (a) Schultz, H. Benzodiazepines: Springer Heidelberg **1982**.

   (b) Landquist, J.K. "In Comprehensive Heterocyclic Chemistry" Katritzky A.R. and Rees, C.W. Eds. Pergamon: Oxford **1984**, *1*, 166.

5. (a) Cho, N. S.; Song, K.Y. and Parkanyi C. *J. Heterocycl. Chem.* **1989**, *26*, 1807-1810.

   (b) Bauer, A.; Weber, K.; Danneberg, P. and Kuhn, F. *U. S. Patent.* **1975**, *216*, 3914.

6. Jones, G. B.; Davey, C. L.; Jenkins, T. C.; Kamal, A.; Kneale, G.; Neidle, S.; Webster G. D. and Thurston, D. E. *Anti-Cancer Drug Des.* **1990**, *5*, 249

7. Ananthan, S.; Clayton, S. D.; Ealick, S. E.; Wong, G.; Evoniuk, G. E. and Skolnick. P. *J.Med. Chem.* **1993**, *36*, 479-490.

8. Wong, G.; Koehler, K. F.; Skolnick, P.; Ananthan, S.; Schonholzer, P.; Zhang, W. and Cook, J. M. *J. Med. Chem.* **1993**, *36*, 1820-1830.

9. Katritzky, A. R. and Boulton, A. J. *Advances in Heterocyclic Chemistry* **1967**, *8.*

10. Vogel, E.; Gunther, H. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 385.

11. Paquette, L. A. "Nonbenzenoid Aromatics"; Snyder, J. P., Ed.; Academic Press: New York, **1969**; *Vol. 1*, p 24.

12. Similar incentive catalyzed synthetic work on more unusual 7-membered unsaturated heterocycles of (a) phosphorus [Markl, G.; Schubert, H. *Tetrahedron Lett.* **1970**, 1273], (b) Silicon [Barton, T. J.; Kippenban, B.C.; Nelson, A. J. *J. Am. Chem. Soc.* **1974**, *96*, 2272] and (c) boron [Eisch, J. J.; Galle, J. E. *Ibid.* **1975**, *97*, 4436].

13. (a) Kasparek, S. *Adv. Heterocycl.Chem.* **1974**, *17*, 45. (b) Kricka, L. J.; Ledwith, A Chem. *Rev.* **1974**, *74*,101. (c) Kametani, T.; Fukumoto, K. *Heterocycles* **1975**, *3*, 931.

14. Barth. H.; Kobayashi, M.; Musso, H. *Helv. Chim. Acta* **1979**, *62*, 1231.

15. Finlay, J. A. *Int. Rev. Sci. Org. Chem. Ser. 2* **1976**, *9*, 23

16. Hurley, L. H. *Acc. Chem. Res.* **1980**, *13*, 263.

17. (a) Moore, J. A.; Jokelson, H. B.; Freeman, W. J. and Blout, J. F. *J.Org. Chem.* **1979**, 44, 2683. (b) Nakamura, H.; Koyama, G.; Iitaka, Y.; Ohno, M.; Yagisawa, N.; Kondo, S.; Maeda, K. and Umezawa H. *J. Am. Chem. Soc.* **1974**, *96*, 4327. (c) Thiellier, H. M. P.; Koomen, G. J. and Pandit, U. K. *Tetrahedron* **1977**, *33*, 2609 and references therein.

18. See, inter alia: 1,4-Diazepines: Ohtsuka, Y. *J. Org. Chem.* **1976**, *41*, 829. 1,3-Oxazepines: Schmidt, R. R.; Berger, G. *Synthesis* **1974**, 187. 1,3-Dithiepin: Semmelback, C. L.; Chiu, L-C.; Grobmann, K. G. *J. Am. Chem. Soc.* **1976**, *98*, 2005. 1,2-Azaphosphepine: Eberhard, L.; Lampin, J.-P.; Mathey, F.; Badellon, *C. Tetrahedron* **1973**, *20*, 2000. 1,2,4-Triazepine: Hasnaoui, A.; Lavergne, J.-P.;

Viallefont, P. *J. Heterocycl. Chem.* **1978**, *15*, 71. 1,2,7-Azadiphosphepine: Zeiss, W.; Henjes, H. *Chem. Ber.* **1978**, *111*, 1655.

19. Ried W. and Kocher E. U. *Angew. Chem.* **1958**, *70*, 164.
20. Harris, D. J.; Gordon, Y.; Snieckus V. and Klingsberg E. *Can. J. Chem.* **1974**, *Vol. 52*, 2798.
21. Klingsberg E. *Abstr. Am. Chem. Soc. Meeting, Sept.*, 66S, **1965.**
22. Streith, J.; Luttringer J.P. and Nastar, M. *J.Org. Chem.* **1971**, *36*, No.20.
23. Klingsberg's, E. "Abstracts of Papers", 150th National Meeting of American Chemical Society Sept 1967; American Chemical Society: Washington, D.C., **1967**; p66S.
24. (a) Reissenweber G. and Sauer J. *Tetrahedron Lett.* **1977**, 4393.

    (b) Harris, D.J.; Kan, G.Y.P.; Tschamber T. and Sniekus V. *Can. J. Chem.* **1980**, *58*, 494.
25. Bemi, L.; Thomas M. T. and Snieckus V. *Synthesis* **1979**, 130.
26. (a) Moore, J. A.; Mitchell, E. *Heterocycl. Compd.* **1967**, *9*, 224. Moore, J. A.; Binkert, J. *J. Am. Chem. Soc.* **1959**, *81*, 6029.

    (b) Nabeya, A.; Culp, F. B.; Moore A. *J. Org.Chem.* **1976**, *35*, 2015.
27. For extensive reviews, see (a) Nastasi, M. *Heterocycles* **1976**, *4*, 1509.
28. For review see: (a) Dieter, R. K. *Tetrahedron* **1986**, *42*, 3029-3096;

    (b) Borrman, D. Houben-Weyl, *Methoden der Organischen Chemie*, Band VII/4, **1968**, pp. 404-441, Thieme: Stuttgart (c) Yokoyama M. and Imamoto, T. *Synthesis* **1984**, 797-824; (d) Tominaga Y. and Matsuda, Y. J. *Heterocycl. Chem.* **1985**, *22*, 937-949; (e) Tominaga, Y. and Matsuda, Y. *J. Synth. Org. Chem.* (Japan) **1985**, *7*, 669-679.

29. (a) Ericsson, E.; Marnung, T.; Sandstrom J. and Wennerbeck, I. *J. Mol. Struc.* **1975**, *24*, 373-387; (b) Isaksson G. and Sandstrom, J. *Acta Chem. Scand.* **1973**, *27,* 1183-1191 and references therein.

30. (a) Dalgard, L.; Jensen L. and Lawesson, S. O. *Tetrahedron* **1974**, *39*, 93.
(b) Rumbas, S, R.; Srinivasan, P. S.; Ramachandran J. and Sastry, V. V. S. K. *Synthesis* **1983**, 605 (c) Voss, J. Synthesis of Thyestes and Thiolactones, In *Comprehensive Organic* Synthesis; Trost, B. M., Ed.; Pergamon Press: Oxford, **1990**, Vol. *6*, pp 435- 460.

31. (a) Peruncheralathan, S.; Khan, T. A.; Ila H. and Junjappa, H, *J. Org. Chem.* **2005**, *70*, 10030-10035.
(b) Nair, S. K.; Samuel R. and Asokan, C. V. *Synthesis* **2001**, 573.
(c) Nair S. K. and Asokan, C. V. *Synth. Commun.* **2001**, *22*, 1453.
(d) Nair S. K. and Asokan, C. V. *Synth. Commun.* **1999**, *29*, 791.

32. Shahak I. and Sasson, Y. Tetrahedron *Lett.* **1973**, 4207-4210.

33. (a) Junjappa, H.; Ila H. and Asokan C.V. *Tetrahedron* **1990**, 5423
(b) Chauhan, S. M. S. and Junjappa, H. *Tetrahedron* **1976**, *32*, 1779-1787 ibid., **1976**, *32,* 1911-1916.

34. Fuji, K. in Nucleophilicity *Advances in Chemistry Series 21,* Harris J. M. and McManus, S. P. Eds.; Washington: American Chemical Society; Ch. *15*, p. 215.

35. Jagodzinski, Tadeusz S. *Chem. Rev.*, **2003**, *103*, 197-227.

36. Bauer, W.; Kühlein K. *Houben-Weyl's Methoden der Organischen Chemie*; Georg Thieme Verlag: Stuttgart, New York, **1985**, Vol. E5, pp 1218-1279.

37. Cava, M. P.; Levinson, M. I. *Tetrahedron* **1985**, *41*, 5061.

38. Hurd, R. N.; Delamater, G. *Chem. Rev.* **1961**, *61*, 45.

39. Schaumann, E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, **1991**; Vol. *6*, pp 419-434.

40. (a) Gompper, R. and Topfi, W. *Chem. Ber.* **1962**, *95*, 2881-2884; (b) Chauhan, S. M. S. and Junjappa, H. *Synthesis* **1975**, 798-801; (c) Apparao, S.; Rahman, A. Ila, H. and Junjappa, H. *Synthesis* **1982**, 792-795; (d) Rudorf, W. D. and Augustin, M. *J. Prakt. Chem.* **1978**, *320*, 585-599, (e) *ibid* **1978**, *320*, 576-584; (f) Rudorf, W.-D. *Tetrahedron* **1978**, *34*, 725-730; (g) Stachel, H. D. *Arch. Pharm.* **1962**, *295*, 224-33; Chem. *Abstr.* **1963**, *58*, 4540b; (h) Saquet, M. and Thuillier, A. C. *R. Acad. Sci. Paris, Ser. C.* **1968**, 266; *Chem. Abstr.* **1968**, *69*, 36019.

41. (a) Gompper, R. and Topfl, W. Chem. *Ber.* **1962**, *95*, 2871-2880; (b) Singh, L. W.; Gupta, A. K.; Ila, H. and Junjappa, H. *Synthesis* **1984**, 516-518.

42. Kumar, A. Ila, H. and Junjappa, H. *J. Chem. Res.* **1979**, (S) 268; *J. Chem. Res.* **1979**, (*M*) 3001.

43. (a) Rastogi, R. R.; Ila H. and Junjappa, H. *J. Chem. Soc. Chem. Commun.* **1975**, *645*. (b) Rastogi, R. R.; Kumar, A.; Ila, H.; Junjappa, H. *J. Chem. Soc. Perkin Trans. I* **1978**, 549-553. (c) Rastogi, R. R.; Kumar, A.; Ila H. and Junjappa, H. *J. Chem. Soc. Perkin Trans. I* **1978**, 554-558. (d) Kumar, A.; Ila H. and Junjappa, H. *J. Chem. Soc. Perkin Trans. I* **1978**, 857-862. (e) Rudorf, W. D. and Augustin, M. *Synthesis* **1980**, 1022-1023. (f) Augustin, M.; Bielka, S. *Z. Chem.* **1980**, *20*, 96-97.

44. Augustin, M.; Groth, Ch. *J. prakt. Chem.* **1979**, *321*, 215-225.

45. (a) Rudorf, W. D. and Augustin, M. *J. Prakt. Chem* **19**, *319*, 545-560; (b) Augustin, M.; Jahreis, G. *J. Prakt. Chem.* **1979**, *321*, 699-703.

46. Myrboh, B.; Ila, H.; Junjappa, H. *J. Org. Chem.* **1983**, *48*, 5327-5332.

47. (a) Dieter, R. K.; Jenkitkasemwong, Y. *Tetrahedron Lett.* **1982**, *23*, 3747-3750.
    (b) Dieter, R. K.; Lin Jenkitkasemwong, Y.; Dieter, J.W. *J. Org. Chem.* **1984**, *49*, 3183-3195.
48. Myrboh, B.; Ila, H.; Junjappa, H. *Synthesis* **1982**, 307-309.
49. Myrboh, B.; Asokan, C.V.; Ila, H.; Junjappa, H. *Synthesis* **1984**, 50-51.
50. Junjappa H. *et al. Tetrahedron* Report Number **1990**, *278*, 5423-5506.
51. Kashima, K.; Hidaki, S.; Tominaga, Y.; Matsuda, Y.; Kobayashi G. and Sakemi, K. *Yakugaku Zasshi* **1979**,99, 38-44; *Chem. Abstr.* **1979**, *90*, 186863v.
52. Singh, G.; Deb, B.; Ila H. and Junjappa, H. *Synthesis* **1987**, 286-287.
53. Singh, G.; Ila H. and Junjappa, H. *Synthesis* **1985**, 165-169.
54. Singh, G.; Ila H. and Junjappa, H. *J. Chem. Soc. Perkin Trans. I* **1987**, 1945-1949.

CHAPTER II

A GREENER AND FACILE SYNTHESIS OF 3,5,7-TRISUBSTITUTED-4*H*-[1,2]DIAZEPINES

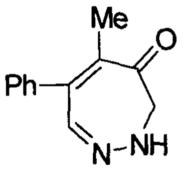
CHAPTER II

A greener and facile synthesis of 3,5,7-trisubstituted-4*H*–[1,2]diazepines

II.1 **INTRODUCTION**

Heterocyclic units of diazepines and benzodiazepines and their analogues are of special interest in pharmacology, due to their important biological activities.[1,2,3] These compounds have been widely studied regarding their activities as tranquilizers, sedatives, antidepressants, anti inflammatory and hypnotic agents.[4] Members of this class have been identified as platelet aggregation inhibiting mimics of the arginine-glycine-aspartic acid (RGD) peptide sequence, as anticonvulsant agents,[5] antitumor compounds[6] and as precursors of benzodiazepines[7-8]. They all constitute an important class of bioactive compounds. The synthesis of diazepines and 1,2-diazepines in particular has been attracting much attention due to their wide range of applications.

These highly unsaturated seven-membered ring heterocycles are of recent synthetic origin and their evolution is linked to advances in theoretical and medicinal chemistry. For a long time the synthesis of highly unsaturated 1,2-diazepines was limited to the thorough investigations of compound **25** by Moore and his collaborators.[19,20] The parent hexahydro-1,2-diazepine **26**, (R = H) has been prepared[21] by condensation of 1,2-dicarbethoxyhydrazine and 1,5-dibromopentane in dimethylformamide.[22] Overberger and co-workers reported[23] that heptane-2,6-dione, hydrazine sulfate, and sodium cyanide gave the diazepine **27**, however, it was later shown that on preparation[24] and oxidation[25] of this compound, the product was the aminopiperidine **28**.



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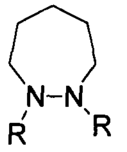

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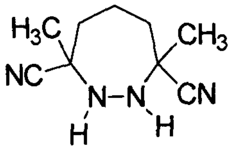

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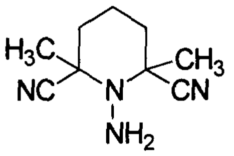

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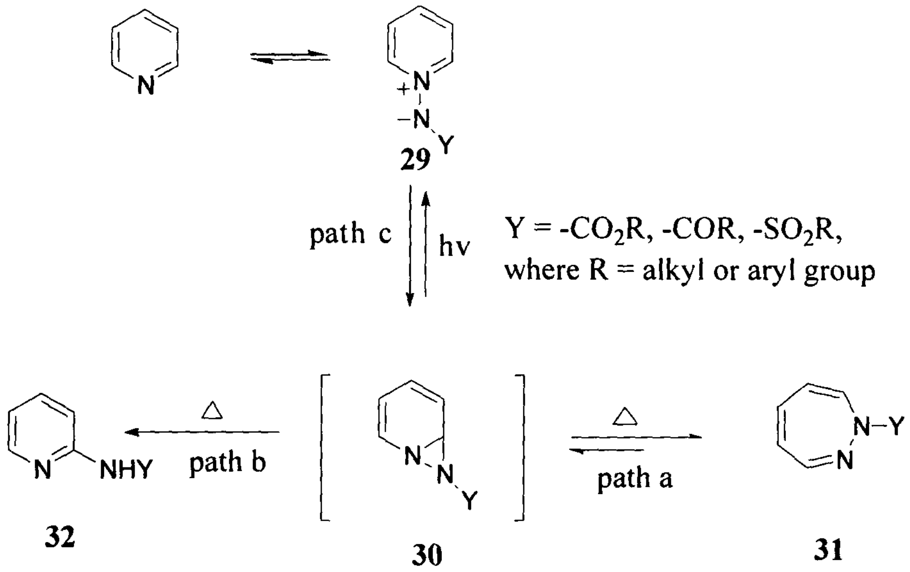
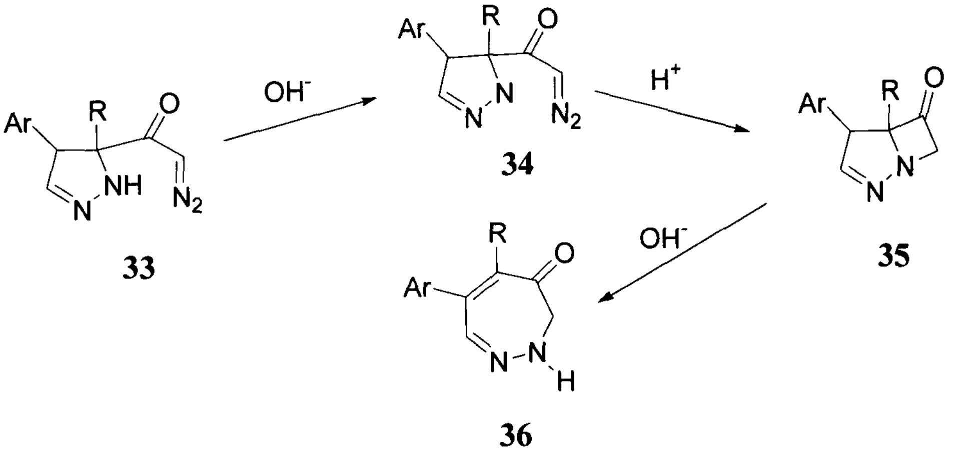
Andrzej Frankowski[26a] described the synthesis of 1,2-diazepines **31** which was achieved by photoinduced rearrangements of *N*-iminopyridinium ylide **29** (Scheme 7). The diaziridine **30** has been postulated as an intermediate **31**,[8] which could result from a photo-induced concerted electrocyclic ring closure of the *N*-iminopyridinium ylide **29** as the aromatic 1,3-dipolar species. The intermediate **30** may undergo either ring expansion (valence tautomerisation) to give the 1,2-diazepines **31** [4-9] or N-N bond fission to give the 2-aminopyridine derivatives **32**.[9,10] Jacques Streith[26b] described similar results wherein 1,2-diazepines could be obtained by the photochemical reaction of 1-iminopyridinium ylide.[26c]



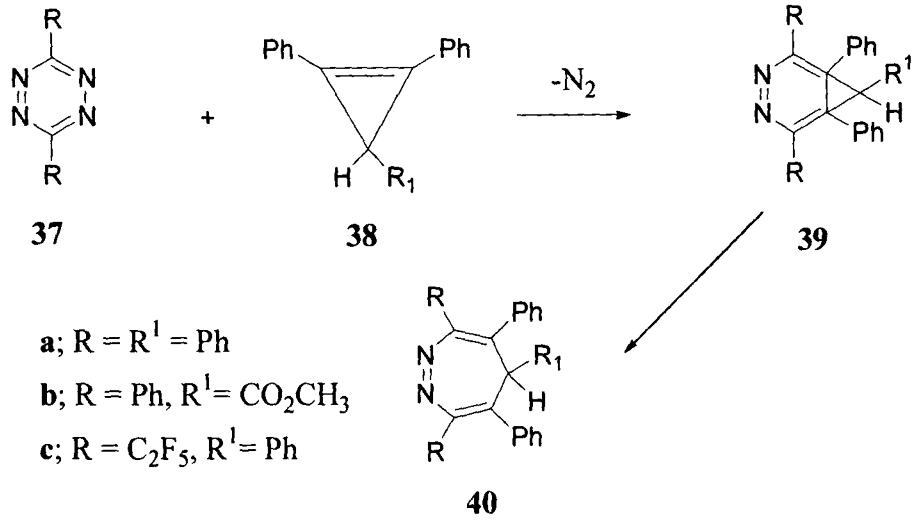
Scheme 7

James A. Moore showed another effective approach[27] for the formation of seven membered ring compound by conversion of the intermediate diazopropionyl pyrazoline **33** to the dihydrodiazepinone **36** which involves three steps: isomerization to the 5-pyrazoline **34**, acid-catalyzed cyclisation[28] to a [3.2.0] bicyclic ketone **35**, and ring opening[29] to **36** (Scheme 8).



Scheme 8

Thomas J. Barton reported[30] the reaction of several cyclopropenes **38** with heterocylic dienes **37** which afforded a convenient synthetic route to unsaturated seven-membered heterocyclic ring systems. This simple and convenient diene synthesis of substituted 5*H*-1,2-diazepines (3,4-diazacyclohepta-1,3,5-trienes) **40** describe a novel valence tautomeric structure **39** (Scheme 9) which formed as an intermediate in the isomerisation and thermal fragmentation process, which shows similar results of which were reported by Sauer and Heinrichs.[31]



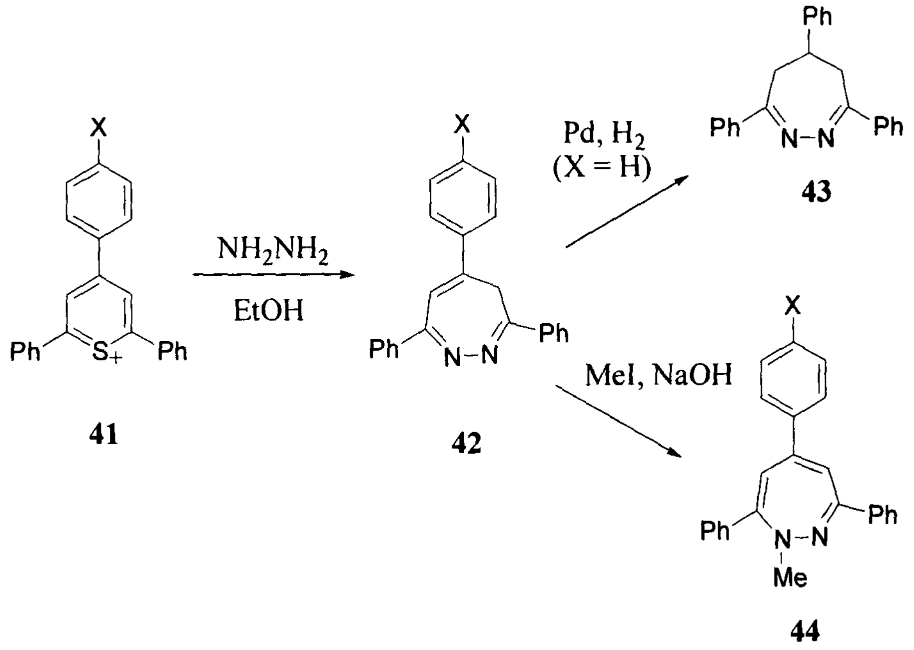
a; R = R^1 = Ph

b; R = Ph, R^1= CO_2CH_3

c; R = C_2F_5, R^1= Ph

Scheme 9

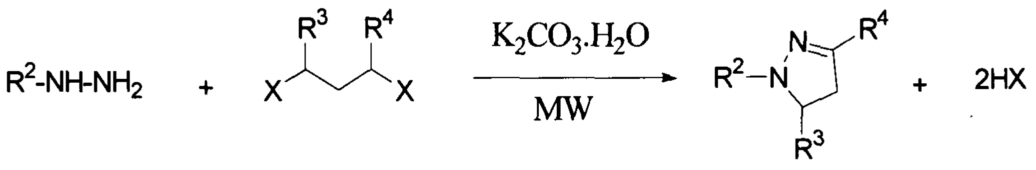
While contemplating ways by which *N*-alkyl and *N*-aryl-1,2(1*H*)-diazepines could be prepared, our attention was drawn to a report[32,33] by Klingsberg on the reaction of thiapyrylium salts with hydrazines. Harris *et al.* reported[33] that thiapyrylium salts[34] intermediates **41** undergo smooth reaction with hydrazine to yield a broad range of substituted-(4*H*)-1,2-diazepines including some condensed trialkyl systems that assure ready access to substituted-(1*H*)-1,2-diazepines **42** (X=H) derivatives[35] in good to excellent yields. Under catalytic hydrogenation using Pd as catalyst and on methylation and under slight variation of work up conditions product **43** and **44** are obtained[33] (Scheme 10).



Scheme 10

The use of solid support reagents has received considerable importance in organic synthesis because of their ease in handling, enhanced reaction rates, greater selectivity, simple workup, and recoverability of the catalyst. Recently, a convenient, solvent-free, green approach is described for the synthesis of 1,5-benzodiazepine using ethylacetoacetate, aromatic aldehydes and *o*-phenylenediamine without using any catalytic reagent at pH 7.[36a] The concept of "green chemistry" is now widely adopted to meet the fundamental scientific challenges of protecting the human health and environment while simultaneously achieving commercial viability.[36b,37] The emerging area of green chemistry envisages minimum hazard as the performance criteria while designing new chemical processes. The target is to explore alternative reaction conditions[38,39] and reaction media to accomplish the desired chemical transformations with minimum by-products or waste generation, as well as to eliminate the use of conventional organic solvents.

Varma and co-worker described the synthesis of nitrogen-containing heterocycles **47** from alkyl dihalides **46** (ditosylates) and hydrazines **45** (Scheme 11) via a simple and efficient cyclocondensation in an alkaline aqueous medium that occurs under microwave irradiation.[40]

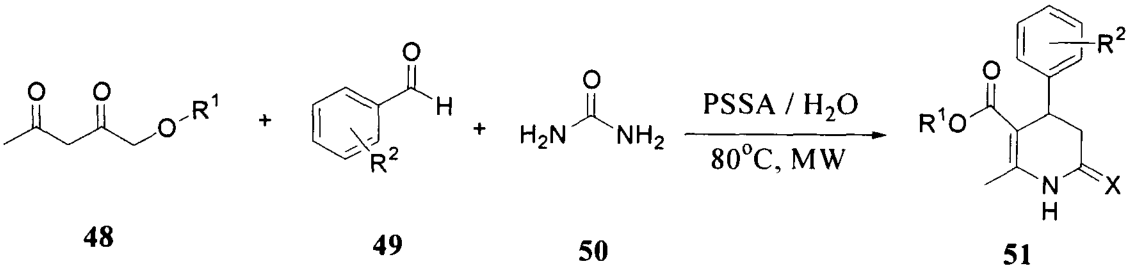


45 **46** **47**

$R, R^1, R^2 = H$, alkyl, aryl
$R^3, R^4 = H$, alkyl
$X = Cl, Br, I, TsO$

Scheme 11

In continuation of the green chemistry programme, R. S. Varma *et al*[39] employed PSSA which efficiently catalysed the reaction in water.[41] They explored the use of this polymer supported polystyrenesulfonic acid as a catalyst, using Biginelli protocol for the synthesis of various substituted 3,4-dihydropyrimidin-2(1*H*)-ones **51** (Scheme 12) by the condensation of ethyl acetoacetate **48**, 4-chloro benzaldehyde **49** and urea **50** in water under MW irradiation.[42]



Scheme 12

This improved greener synthetic methodology establishes a convenient and flexible method for further synthetic design of various *N*-heterocyclic compounds such as substituted diazepines, pyrazoles, pyrrolidines, pyrazolidines, piperidines, azetidines, azepanes etc., and that these reactions are working well in an aqueous medium without using any phase-transfer catalyst. This may be due to selective absorption of microwaves by reactants, intermediates, and polar aqueous medium.[43] Utilization of water as reaction media[44] in conjunction with microwave irradiation[45] is one of the emerging nonconventional methods being recognized as viable environmentally benign alternatives.[46]

II.2 RESULTS AND DISCUSSIONS

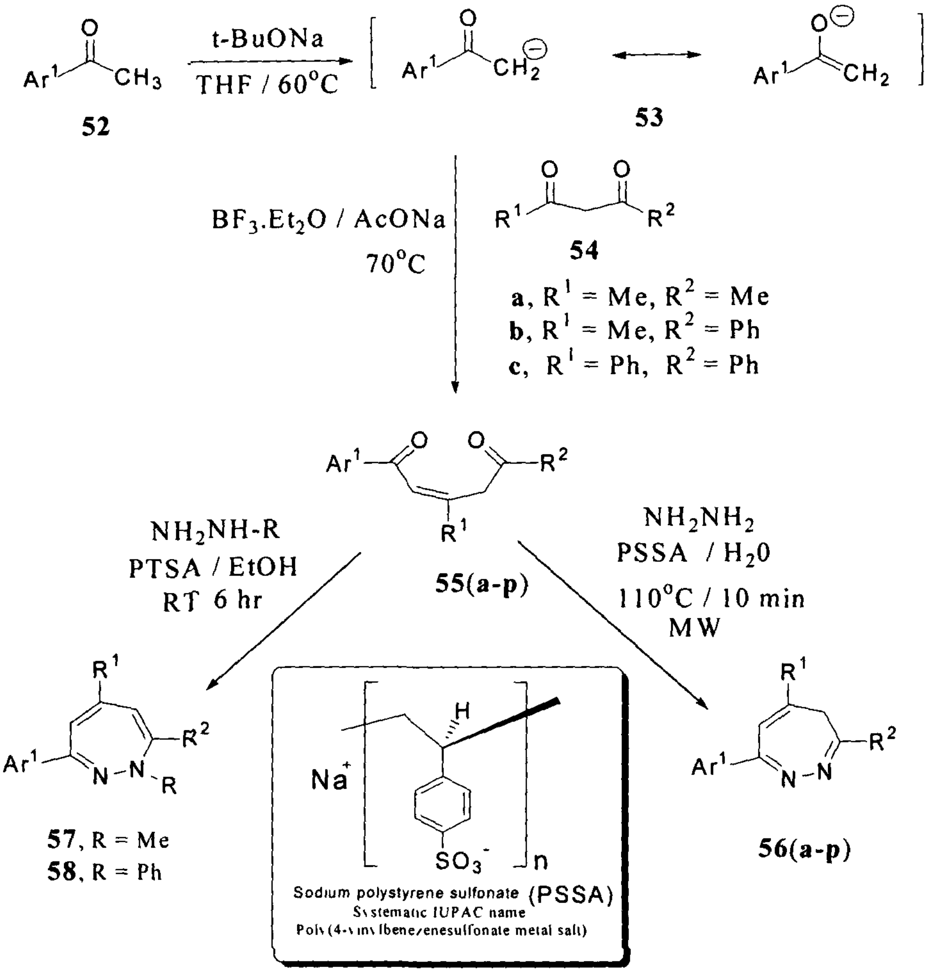
As part of our quest for greener synthetic pathways which have environmental and economic advantages,[36,37] we wish to report an expeditious synthesis of 1,2-diazepines **56, 57** by the reaction of *α,β*-unsaturated 1,5-diketones **55** with hydrazines catalyzed by polystyrene sulfonic acid[39] (PSSA). The reaction proceeded efficiently in water[44] in absence of any organic solvent forming 3,5,7-trisubstituted-4*H*-1,2-diazepine **56** (Scheme 13).

Acetophenone **52** was first treated with a sodium *tert*-butoxide to provide the anion **53** which when treated with 1,3-diketone **54**, such as 2,4-pentanedione **54a** ($R^1 = CH_3$, $R^2 = CH_3$) or phenyl acetylacetone **54b** ($R^1 = CH_3$, R^2 = Ph) or benzoyl phenone **54c** (R^1 = Ph, R^2 = Ph) in presence of boron trifluoride etherate solution under refluxing condition underwent an aldol-type condensation. Careful workup[49] of the reaction mixture yielded an *α,β*-unsaturated 1,5-dicarbonyl intermediate **55** (Scheme 13). The *α,β*-unsaturated 1,5-dicarbonyl compound is a versatile intermediate for the synthesis of *N*-heterocycles. The treatment of 1,5-dicarbonyl intermediate **55(a-p)** with hydrazine and PSSA as acid catalyst in water medium proceeded cleanly and efficiently under microwave irradiation to give the 3,5,7-trisubstituted-4*H*-1,2-diazepine **56(a-p)** in good yields (**Table I**).

However, for the sake of comparison, the reaction was also performed using *p*-toluene sulfonic acid (PTSA) to study the condensation of intermediate **55** with hydrazine by stirring at room temperature for 6-8 hours. The product 2-*N*-alkyl/aryl-3,5,7-trisubstituted-4*H*-1,2-diazepine **57, 58** was also obtained but the yield was inferior to the PSSA catalysed reaction.

The formation of intermediate **55(a-p)** was determined by IR spectrum (KBr) which exhibited stretching frequencies at 1712 cm^{-1}, 1646 cm^{-1} corresponding to C=O and acyclic CH=CH; 2968 cm^{-1} for methylene sp^3 CH_2 stretching; 3025 cm^{-1} and 1570 cm^{-1} for aromatic ring stretching respectively. The ^1H NMR spectrum ($CDCl_3$) showed singlets at δ 2.02 ppm (3H) and δ 4.56 ppm (2H) assigned to methyl and methylene protons and at δ 6.82 ppm (1H) assigned to sp^2 CH. For example, the compound **55a** mass spectrum showed molecular ion peak at *m/z* 202. Similarly the diazepine ring **56a** showed stretching frequencies at 2925 cm^{-1} corresponding to the sp^3 CH_2 and 1653 cm^{-1} for HC=N. ^1H NMR analysis showed resonances at δ 1.78 ppm (s, 3H, CH_3) for methyl group, at δ 3.48 ppm (s, 2H) for the methylene group and at δ 5.02 ppm (s, 1H) for a proton at the diazepine moiety. Aromatic proton pattern occurs at δ 7.2-7.6 ppm (m, ArH) and the ^{13}C NMR showed signals at δ ppm 18.20, 23.42 for methyl carbons, 35.72 for methylene carbon, 108.04 for olefinic sp^2 carbon, 164.15 for sp^2 carbon (>C=N). Moreover, compound **56a** was analyzed for $C_{13}H_{14}N_2$ (Expected C, 78.78; H, 7.07; N, 14.14. Found: C, 78.72; H, 7.10; N, 14.12%) and its mass spectrum showed molecular ion peak at *m/z* 198, which was expected for all the corresponding 3,5,7-trisubstituted-4*H*-1,2-diazepine compounds **56(b-p)** respectively and are described in the experimental section.

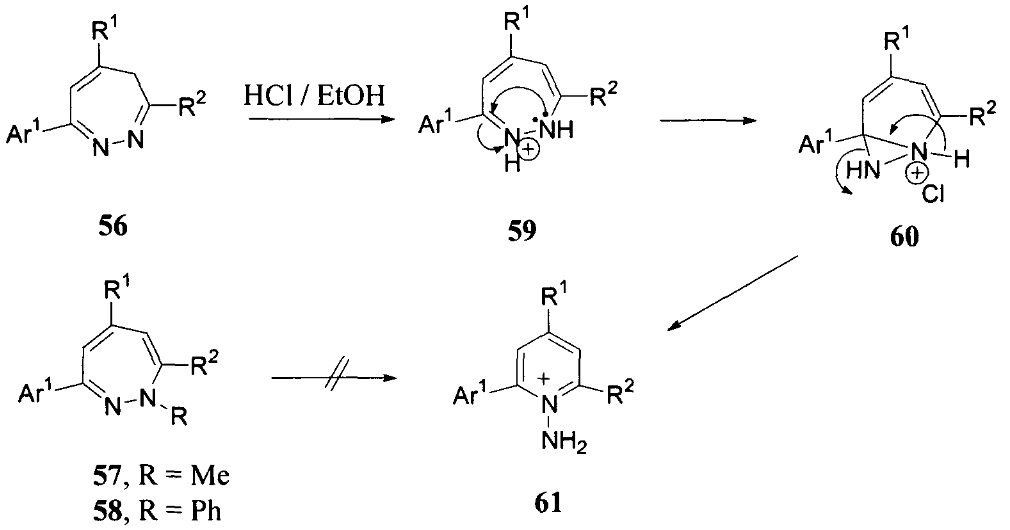
Thus our approach establishes a convenient and flexible method for the green synthesis of various *N*-heterocyclic compounds in an aqueous medium without the use of any phase-transfer catalyst.



Ar^1 = $-C_6H_5$, p-Cl-C_6H_4, p-Br-C_6H_4, p-NO_2-C_6H_4, p-MeO-C_6H_4, 3,5-dimethoxy-C_6H_3, 3,5-dihydroxy-C_6H_3, 3,5-dimethyl-C_6H_3.

Scheme 13

Interestingly the product **56a** when treated with an acid at room temperature (15 hr) ring contraction took place, which led to the formation of *N*-aminopyridinium compound **61**. Evidently, protonation takes place at the nitrogen atom **59** which enhances the formation of an unstable bicyclic intermediate[47] **60** resulting in the formation of the ring contracted product. However, 1,2-diazepines **57** and **58** obtained from the intermediate **55** by reaction with methyl hydrazine and phenyl hydrazine failed to yield the compound **61** under similar condition. This shows that blocking of the hydrogen N-2 by the methyl or phenyl group in compound **57** and **58** precludes this ring contraction[48] (Scheme 14).



Scheme 14

The formation of 1-Amino-2,4-dimethyl-6-phenyl-pyridinium **61a** from **56a** was confirmed on the basis of analytical and spectral data: thus the **61a** was analyzed for $C_{13}H_{15}N_2$ (Expected C, 78.36; H, 7.61; N, 14.08. Found: C, 78.32; H, 7.58; N, 14.02%) and its mass spectrum showed molecular ion peak at *m/z* 199. Its IR spectrum (KBr) showed absorption at 3290 cm^{-1} and 1622 cm^{-1} for NH amino group and C=N. ^1H NMR ($CDCl_3$) showed singlets at δ 2.47 and 2.87 (3H) for methyl protons, broad singlet at δ 5.73 (2H) for protons NH_2, δ 6.76 (1H) for the methine proton CH of the pyridinium ring and a multiplet at 7.26-7.94 (7H) due to aromatic protons of phenyl group. The spectral data of **61b** and **61c** are included in the experimental section.

Table I —PSSA catalysed synthesis of 3,5,7-trisubstituted-4*H*-1,2-diazepine **56(a-p)**

Entry	Intermediate	R^1	R^2	Ar^1	Time/min	Product	Yield (%)[a]
1	**55a**	CH_3	CH_3	Ph	10	**56a**	92
2	**55b**	CH_3	Ph	Ph	10	**56b**	90
3	**55c**	Ph	Ph	Ph	12	**56c**	87
4	**55d**	CH_3	CH_3	*p*-Cl- C_6H_4	10	**56d**	86
5	**55e**	CH_3	Ph	*p*-Cl- C_6H_4	10	**56e**	88
6	**55f**	CH_3,	CH_3	*p*-Br- C_6H_4	10	**56f**	85
7	**55g**	Ph	Ph	*p*-Br- C_6H_4	12	**56g**	83
8	**55h**	CH_3	CH_3	*p*-NO_2-C_6H_4	15	**56h**	91
9	**55i**	CH_3	Ph	*p*-NO_2-C_6H_4	15	**56i**	87
10	**55j**	CH_3	CH_3	*p*-MeO-C_6H_4	10	**56j**	82
11	**55k**	CH_3	Ph	*p*-MeO-C_6H_4	12	**56k**	86
12	**55l**	CH_3	CH_3	3,5-dimethoxy-C_6H_3	10	**56l**	91
13	**55m**	Ph	Ph	3,5-dimethoxy-C_6H_3	10	**56m**	89
14	**55n**	CH_3	CH_3	3,5-dihydroxy-C_6H_3	12	**56n**	74
15	**55o**	CH_3	CH_3	3,5-dimethyl-C_6H_3	10	**56o**	84
16	**55p**	CH_3	Ph	3,5-dimethyl-C_6H_3	10	**56p**	81

[a] Isolated yields obtained under Microwave-Assisted reaction. All the compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR and MS.

The reaction tube was placed inside the cavity of a CEM Discover focused microwave synthesis system, operated at 110°C (temperature monitored by a built-in infrared sensor), power of 70-100 W, and a pressure of 60-100 psi for 20 min. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AMX 400 instrument using $CDCl_3$ as the solvent. Chemical shifts are reported in ppm using tetramethylsilane as internal standard. *J* values are given in Hz. The following abbreviations are used to describe peak patterns when appropriate: br = broad, s = singlet, d = doublet, dd = double doublet, dt = double triplet, t = triplet, q = quartet, m = multiplet. IR spectra were recorded on a Perkin-Elmer BX spectrophotometer. Electrospray Ionisation (ESI) mass spectra were measured on an ion trap analyzer Esquire 3000 (Bruker Daltonics). Masses (MS) are reported in unit of mass over charge (*m/z*), the molecular or base peaks and relative intensities are indicated by (M^+) and (%) respectively. CHN analyses were recorded on a Vario EL analyser. Column chromatography was performed using silica gel (60-120 mesh, Merck).

All reactions were performed in oven dried (120°C) glassware under a positive dry argon/nitrogen atmosphere. Analytical thin layer chromatography (TLC) were performed on glass plates coated with ACME's silica gel containing 13% calcium sulphate as binder and various combination of visualization of spots was accomplished by exposure iodine vapour or by spraying potassium permanganate (acidic) solution. Eluents for column chromatography were used after simple distillation of commercial solvents. All solvent evaporations were done using a rotaevaporator and a steam bath.

Chemical Reagents and Solvents:

Para-toluene sulphonic acid (PTSA) and polystyrene sulphonic acid (PSSA), were purchased (Sigma-Aldrich) as bottle grade. Pure (THF) was obtained by keeping the deperoxidised THF over sodium-benzophenone. Anhydrous ether and dichloromethane (DCM) was obtained by keeping the bottle grade over calcium chloride over night and finally stored over sodium wire or Type 3A molecular sieve. Dry benzene was obtained by washing with concentrated sulphuric acid followed by azeotropic distillation and stored over sodium wire. Sodium tertiary butoxide was freshly prepared for each reaction.

Starting Materials:

Acetophenone and substituted acetophenones (Sigma-Aldrich) were used for the preparations of 1,5-dicarbonyl compound. Hydrazine hydrate used was the analytical reagent bottle grade (Merck). Commercially available, ethanol were used which were purified by simple distillation and kept in Type 3A molecular sieve.

General procedure for the preparation of α,β-unsaturated-1,5-dicarbonyl compound 55. In a typical experiment[49], to a stirring solution of Sodium t-butoxide (3 g, 0.031 mole) in THF (20 mL), substituted acetophenone **52** (5 mL, 0.025 mole) was added with constant stirring for 2 hr at room temperature, followed by the dropwise addition of 1,3-diketone[49] **54** (0.01 mole) and boron trifluoride-etherate (6 mL, 0.035 mole) at 0°C with constant stirring for 2 hr. The reaction mixture becomes coloured, a solution of sodium acetate (4.5 g, 0.054 mole) in water (15 mL) was added, and stirring was continued for another 4 hr at 70°C. Under work up, the reaction mixture was poured into ice-cold saturated solution of $NaHCO_3$ (2 x 25 mL), extracted with DCM (2 x 50 mL), washed with H_2O (2 x 50 mL), brine (1 x 50 mL), and dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum and the resulting yellow semi-solid is recrystallised from EtOH-H_2O affording the product **55**.

3-Methyl-1-phenyl-hex-2-ene-1,5-dione 55a: Yield 88%, m.p. 156-157°C; IR: 1710, 1665 (C=O), 1646 (CH=CH), 2964 (CH_2), 3025, 1570 cm^{-1} (aromatic ring); ^1H NMR (400 MHz, $CDCl_3$): δ 7.34-7.87 (m, 5H), 6.82 (s, 1H), 3.56 (brs, 2H, CH_2), 2.02 (s, 3H, CH_3), 1.70 (s, 3H, CH_3); EIMS: *m/z* (%) 202 (M^+, 100).

3-Methyl-1,5-diphenyl-pent-2-ene-1,5-dione 55b: Yield 90%, m.p. 142-143°C; IR: 1712, 1664 (C=O), 1644 (CH=CH), 2965 (CH_2), 3024, 1568 cm^{-1} (aromatic ring); ^1H NMR (400 MHz, $CDCl_3$): δ 7.14-7.76 (m, 10H, ArH), 6.80 (s, 1H), 3.53 (brs, 2H, CH_2), 1.70 (s, 3H, CH_3); EIMS: *m/z* (%) 264 (M^+, 100).

1,3,5-Triphenyl-pent-2-ene-1,5-dione 55c: Yield 92%, m.p. 12-163°C; IR: 1669, 1662 (C=O), 1648 (CH=CH), 2968 (CH_2), 3023, 1586, 731 cm^{-1} (aromatic ring); ^1H NMR (400

MHz, $CDCl_3$): δ 7.14-7.76 (m, 16H), 6.65 (s, 1H), 3.20 (brs, 2H, CH_2); EIMS: *m/z* (%) 326 (M^+, 100).

Synthesis of 3,5,7-trisubstituted-4*H*-1,2-diazepine 56(a-p) using Microwave-Assisted reaction. The reaction tube containing the intermediate compound **55** (0.01 mole), hydrazine hydrate (2 mL, 0.1 mole) and 5 mL of 25% PSSA solution in water was placed inside the cavity of a CEM Discover focused microwave synthesis system, operated at 110°C (temperature monitored by a built-in infrared sensor), powered to between 70-100 W, pressure of 60-100 psi and a ramp time of 10 minutes. After completion of the reaction (monitored by TLC), the crude product was isolated by simple filtration (few mL of water was added to facilitate easy filtration) and further purified by column chromatography over silica gel using hexane-EtOAC (10:1) as eluent.

3,5-Dimethyl-7-phenyl-4*H*-[1,2]diazepine 56a: Yield 92%, pale yellow solid, m.p. 192-193°C; IR (KBr): 2944, 2925, 1654, 1612, 1483 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.78 (brs, 3H, CH_3), 3.48 (s, 2H, CH_2), 5.02 (s, 1H, CH), 7.25-7.66 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.08, 23.76, 35.8, 108.09, 128.02, 128.42, 129.02, 129.36, 130.22, 131.14, 142.3, 164.18, 164.37; EIMS: *m/z* (%) 198 (M^+, 100); Anal. Calcd for $C_{13}H_{14}N_2$: C, 78.78; H, 7.07; N, 14.14. Found: C, 78.72; H, 7.10; N, 14.12%.

5-Methyl-3,7-diphenyl-4*H*-[1,2]diazepine 56b: Yield 90%, pale yellow solid, m.p. 173-174°C; IR (KBr): 2948, 2922, 1652, 1618, 1486 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.72 (s, 3H), 3.42 (s, 2H, CH_2), 4.82 (brs, 1H, CH), 7.32-7.67 (m, 10H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.76, 35.7, 108.05, 128.01, 128.02, 128.14, 128.18, 129.02, 129.06, 129.13, 129.17, 130.22, 130.28, 131.14, 131.22, 142.3, 164.18, 164.37; EIMS: *m/z* (%) 260

(M$^+$, 100); Anal. Calcd for $C_{18}H_{16}N_2$: C, 83.04; H, 6.17; N, 10.74. Found: C, 83.02; H, 6.10; N, 10.52%.

3,5,7-Triphenyl-4*H*-[1,2]diazepine 56c: Yield 87%, pale yellow solid, m.p. 137-138°C; IR (KBr): 2946, 2923, 1658, 1619, 1484 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.46 (brs, 2H), 5.42 (s, 1H, CH), 7.22-7.87 (m, 15H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 35.7, 105.05, 126.20 (2), 127.11, 128.2 (2), 128.42 (2), 128.60 (2), 129.02 (2), 129.21 (2), 130.22, 130.35, 131.18 (2), 134.90, 145.2, 164.18, 164.37; EIMS: *m/z* (%) 322 (M$^+$, 100); Anal. Calcd for $C_{23}H_{18}N_2$: C, 85.68; H, 5.63; N, 8.64. Found: C, 85.60; H, 5.60; N, 8.58%.

7-(4-Chloro-phenyl)-3,5-dimethyl-4*H*-[1,2]diazepine 56d: Yield 86%, light brown solid, m.p.182-183°C; IR (KBr): 2940, 2922, 1653, 1616, 1487 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.72 (s, 3H), 2.64 (s, 3H, CH_3), 3.46 (s, 2H, CH_2), 4.87 (s, 1H, CH), 7.32 (d, J = 8.4 Hz, 2H, ArH); 7.67 (d, J = 8.0 Hz, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.28, 23.3, 35.74, 108.24, 128.41, 129.30, 129.87, 130.21, 130.54, 136.12, 142.43, 164.86, 164.88. 198; EIMS: *m/z* (%) 232 (M$^+$, 100); Anal. Calcd for $C_{13}H_{13}ClN_2$: C, 67.10; H, 5.65; N, 12.02. Found: C, 67.12; H, 5.52; N, 12.12%.

7-(4-Chloro-phenyl)-5-methyl-3-phenyl-4*H*-[1,2]diazepine 56e: Yield 88%, yellow solid, m.p.148-149°C; IR (KBr): 2945, 2923, 1654, 1618, 1484 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.56 (s, 3H, CH_3), 3.44 (s, 2H, CH_2), 5.74 (s, 1H, CH), 7.02-7.34 (dd, J = 8.4, 2.8 Hz, 4H, ArH), 7.67-7.82 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.28, 35.74, 105.24, 126.27 (2), 128.03 (2), 129.30, 129.87, 130.21, 130.54, 136.12, 145.43, 164.86; EIMS: *m/z* (%) 294 (M$^+$, 100); Anal. Calcd for $C_{18}H_{15}ClN_2$: C, 73.07; H, 5.15; N, 9.28. Found: C, 73.32; H, 5.21; N, 9.12%.

7-(4-Bromo-phenyl)-3,5-dimethyl-4*H*-[1,2]diazepine 56f: Yield 85%, brown solid, m.p.138-139°C; IR (KBr): 2942, 2925, 1656, 1617, 1485 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.72 (s, 3H), 2.64 (brs, 3H, CH_3), 3.46 (s, 2H, CH_2), 4.87 (s, 1H, CH), 7.32 (d, *J* = 8.4 Hz, 2H, ArH), 7.67 (d, *J* = 8.0 Hz, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.25, 23.30, 35.57, 108.32, 128.43, 129.32, 129.87, 130.21 (2), 136.12, 142.42, 164.83, 164.82; EIMS: *m/z* (%) 276 (M^+, 100); Anal. Calcd for $C_{13}H_{13}BrN_2$: C, 56.34; H, 4.73; N, 10.11. Found: C, 56.12; H, 4.65; N, 10.02%.

7-(4-Bromo-phenyl)-3,5-diphenyl-4*H*-[1,2]diazepine 56g: Yield 83%, yellow solid, m.p. 137-138°C; IR (KBr): 2946, 2922, 1656, 1619, 1484 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.47 (s, 2H, CH_2), 5.42 (s, 1H, CH), 7.22-7.87 (m, 14H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 35.7, 105.05, 125.4, 126.2 (2), 127.11, 127.14, 128.01 (2), 128.42 (2), 129.02 (2), 129.32 (2), 130.2 (2), 131.14 (2), 134.12, 145.2, 164.18, 164.37; EIMS: *m/z* (%) 400 (M^+, 100); Anal. Calcd for $C_{23}H_{17}BrN_2$: C, 68.84; H, 4.27; N, 6.98. Found: C, 68.60; H, 4.20; N, 6.82%.

3,5-Dimethyl-7-(4-nitro-phenyl)-4*H*-[1,2]diazepine 56h: Yield 91%, yellow solid, m.p.198-199°C; IR (KBr) : 2948, 2926, 1658, 1614, 1482 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.78 (s, 3H), 3.46 (s, 2H, CH_2), 2.67 (s, 3H, CH_3), 4.86 (s, 1H, CH), 7.87-8.20 (m, 4H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.52, 23.43, 35.87, 108.24, 123.27 (2), 129.30 (2), 137.21, 142.43, 150.54, 164.26, 164.67; EIMS: *m/z* (%) 243 (M^+, 100); Anal. Calcd for $C_{13}H_{13}N_3O_2$: C, 64.81; H, 5.59; N, 7.52. Found: C, 64.19; H, 5.39; N, 7.22%.

5-Methyl-7-(4-nitro-phenyl)-3-phenyl-4*H*-[1,2]diazepine 56i: Yield 87%, light brown solid, m.p.134-135°C; IR (KBr): 2946, 2924, 1656, 1618, 1482 cm^{-1}; ^{1}H NMR (400 MHz,

$CDCl_3$): δ 1.72 (s, 3H), 3.49 (s, 2H, CH_2), 4.82 (s, 1H, CH), 7.02-7.67 (m, 5H, ArH), 7.94 (d, *J* = 8.2, Hz, 2H, ArH) 8.26 (d, *J* = 8.0 Hz, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.30, 35.57, 108.32, 123.7 (2), 128.63 (2), 129.32 (2), 129.87 (2), 130.21, 131.54, 137.12, 142.42, 150.78, 164.83 (2); EIMS: *m/z* (%) 305 (M^+, 100); Anal. Calcd for $C_{18}H_{15}N_3O_2$: C, 70.81; H, 4.93; N, 13.76. Found: C, 70.79; H, 4.68; N, 13.72%.

7-(4-Methoxy-phenyl)-3,5-dimethyl-4*H*-[1,2]diazepine 56j: Yield 82%, light brown solid, m.p.152-153°C; IR (KBr): 2946, 2923, 1653, 1612, 1484 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ), 2.26 (s, 3H), 3.40 (s, 2H, CH_2), 3.74 (s, 3H, OMe), 4.85 (s, 1H, CH), 6.82 (d, *J* = 8.2 Hz, 2H, ArH), 7.57 (d, *J* = 7.4 Hz, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.5, 23.31, 35.74, 56.04, 108.24, 114.2 (2), 123.52, 130.31(2), 142.43, 164.22, 164.66 (2); EIMS: *m/z* (%) 228 (M^+, 100); Anal. Calcd for $C_{14}H_{16}N_2O$: C, 73.66; H, 7.02; N, 12.28. Found: C, 73.12; H, 6.98; N, 12.22%.

7-(4-Methoxy-phenyl)-5-methyl-3-phenyl-4*H*-[1,2]diazepine 56k: Yield 86%, light brown solid, m.p.182-186°C; IR (KBr): 2942, 2926, 1655, 1617, 1483 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.35 (s, 3H), 3.42 (brs, 2H, CH_2), 3.76 (s, 3H, OMe), 4.87 (s, 1H, CH), 6.82 (d, *J* = 8.4 Hz, 2H, ArH), 7.57 (d, *J* = 7.4 Hz, 2H, ArH), 7.37-7.82 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.31, 35.74, 56.04, 108.24, 114.2 (2), 123.52, 128.67 (2), 129.30 (2), 130.03 (2), 130.68, 131.35, 142.43, 164.32, 164.68 (2); EIMS: *m/z* (%) 290 (M^+, 100); Anal. Calcd for $C_{19}H_{18}N_2O$: C, 78.07; H, 6.25; N, 9.68. Found: C, 78.12; H, 6.29; N, 9.62%.

7-(3,5-Dimethoxy-phenyl)-3,5-dimethyl-4*H*-[1,2]diazepine 56l: Yield 91%, light brown solid, m.p.145-146°C; IR (KBr): 2944, 2925, 1656, 1614, 1485 cm^{-1}; ^{1}H NMR (400 MHz,

$CDCl_3$): δ 1.72 (s, 3H, CH_3), 3.45 (s, 2H, CH_2), 3.87 (s, 3H, OMe), 4.8 (s, 1H, CH), 6.23 (s, 1H, ArH), 6.7 (brs, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.23, 23.36, 35.87, 56.21 (2), 102.4, 106.92 (2), 108.24, 133.4, 142.43, 163.12 (2), 164.06, 164.17; EIMS: *m/z* (%) 258 (M^+, 100); Anal. Calcd for $C_{15}H_{18}N_2O_2$: C, 69.87; H, 7.05; N, 10.87. Found: C, 69.82; H, 7.02; N, 10.81%.

7-(3,5-Dimethoxy-phenyl)-3,5-diphenyl-4*H*-[1,2]diazepine 56m: Yield 89%, pale yellow solid, m.p. 138-139°C; IR (KBr): 3342, 2946, 2924, 1658, 1619, 1484 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.12 (s, 2H, CH_2), 3.87 (s, 3H, OMe), 5.2 (s, 1H, CH), 6.3 (s, 1H, ArH), 6.7 (brs, 2H, ArH), 7.02-7.65 (m, 10H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 35.7, 56.04 (2), 102.4, 105.05, 107.15 (2), 126.2 (2), 127.71, 128.42 (2), 128.76 (2), 129.02 (2), 130.42 (2), 130.86, 131.14, 133.5, 134.12, 145.2, 164.61 (2); EIMS: *m/z* (%) 338 (M^+, 100); Anal. Calcd for $C_{25}H_{22}N_2O_2$: C, 78.64; H, 5.87; N, 7.38. Found: C, 78.60; H, 5.80; N, 7.32%.

3,5-Dimethyl-7-(3,5-dihydroxy-phenyl)-4*H*-[1,2]diazepine 56n: Yield 74%, light brown solid, m.p.165-166°C; IR (KBr): 3340, 2943, 2927, 1654, 1612, 1482 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.82 (s, 3H), 2.52 (brs, 3H, CH_3), 3.47 (s, 2H, CH_2), 4.68 (s, 1H, CH), 5.12 (brs, 2H, OH), 6.2 (s, 1H, ArH), 6.87 (brs, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.23, 23.36, 35.87, 105.04, 108.24, 108.32, 108.87, 134.22, 142.43, 158.22, 158.34, 164.06, 164.17; EIMS: *m/z* (%) 230 (M^+, 100); Anal. Calcd for $C_{19}H_{18}N_2O$: C, 67.87; H, 6.15; N, 12.18. Found: C, 67.72; H, 6.12; N, 12.11%.

7-(3,5-Dimethyl-phenyl)-3,5-dimethyl-4*H*-[1,2]diazepine 56o: Yield 84%, light brown solid, m.p.140-141°C; IR (KBr): 2940, 2922, 1655, 1616, 1484 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.72 (s, 3H), 2.63 (brs, 3H, CH_3), 3.38 (s, 2H, CH_2), 2.87 (s, 3H), 4.8 (s, 1H, CH), 6.2-7.4 (m, 3H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.23, 21.12, 21.22, 23.36, 35.87, 108.24, 126.23, 126.42, 131.12, 134.22, 137.21, 137.27, 142.43, 164.06, 164.17; EIMS: *m/z* (%) 226 (M^+, 100); Anal. Calcd for $C_{15}H_{18}N_2$: C, 79.61; H, 8.15; N, 12.18. Found: C, 79.52; H, 8.12; N, 12.11%.

7-(3,5-Dimethyl-phenyl)-5-methyl-3-phenyl-4*H*-[1,2]diazepine 56p: Yield 81%, light brown solid, m.p.124-125°C; IR (KBr): 2944, 2926, 1652, 1614, 1483 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.72 (s, 3H), 2.38 (s, 3H, CH_3), 2.87 (brs, 3H, CH_3), 3.43 (s, 2H, CH_2), 4.8 (brs, 1H, CH), 6.4-7.8 (m, 8H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.23, 21.12, 21.22, 23.36, 35.87, 108.24, 126.23, 126.42, 128.2, 128.14, 129.22, 129.24, 131.12, 134.22, 137.21, 137.27, 142.43, 164.06, 164.17; EIMS: *m/z* (%) 288 (M^+, 100); Anal. Calcd for $C_{20}H_{20}N_2$: C, 83.31; H, 6.45; N, 9.71. Found: C, 83.28; H, 6.42; N, 9.62%.

Preparation of 1,5,7-Trimethyl-3-phenyl-1*H*-[1,2]diazepine 57a. To a solution of 1,5-diketone **55a** (0.51 g, 0.05 mole) in ethanol (10 mL), methylhydrazine sulphate (0.72 g, 0.005 mole) and catalytic amount of PTSA (0.85 g, 0.005 mole) were added and vigorously stirred for 6 hr at room temperature. The reaction mixture was then concentrated under reduced pressure and washed with 10% $NaHCO_3$ solution (2 x 50 mL), extracted with $CHCl_3$ (3 x 20 mL), brine (50 mL), and dried over Na_2SO_4. The solvent was evaporated under vacuum to afford the crude product which was purified by column chromatography over silica gel using hexane/EtOAc (10:1) as eluent to give **57a** as yellow crystals, m.p. 202-203°C in 60% overall yield; IR (KBr): 2942, 2925, 1654 (HC = CH), 1612 (C=N), 1564 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.78 (brs, 3H, CH_3), 2.48 (s, 3H, CH_3), 4.87 (s, 1H, CH), 5.08 (s, 1H, CH), 7.25-7.66 (m, 5H, ArH); ^{13}C NMR (100 MHz,

$CDCl_3$): δ 20.60, 23.26, 35.9, 101.12, 115.11, 128.02 (2), 129.36 (2), 130.26, 131.34, 146.3, 147.22, 155.41; EIMS: *m/z* (%) 212 (M^+, 100); Anal. Calcd for $C_{14}H_{16}N_2$: C, 79.21; H, 7.60; N, 13.20. Found: C, 79.18; H, 7.62; N, 13.15%.

Preparation of 5,7-Dimethyl-1,3-diphenyl-1*H*-[1,2]diazepine 58a. To a solution of 1,5-diketone **55a** (0.510 g, 0.05 mole) in ethanol (10 mL), phenyl hydrazine (0.82 g, 0.0075 mole) and catalytic amount of PTSA (0.85 g, 0.005 mole) was added with constant stirring for about 5 hr at room temperature, the reaction being monitored by TLC. The reaction mixture was concentrated under reduced pressure and extracted with DCM (3 x 20 mL), brine (50 mL), and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product which was purified by column chromatography over silica gel using hexane/EtOAc (10:1) as eluent to give **58a** as yellow crystals, m.p. 187-188°C in 58% overall yield. IR (KBr): 2947, 2924, 1656 (HC = CH), 1614 (C=N), 1567 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.76 (brs, 3H, CH_3), 5.02 (s, 1H, CH), 5.78 (s, 1H, CH), 6.85-7.46 (m, 8H, ArH), 8.02 (d, *J* = 8.6, Hz, 2H, ArH) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.56, 23.24, 35.9, 99.54, 115.43, 115.06 (2), 118.54, 128.12 (2), 129.10 (2), 129.61 (2), 130.22, 131.37, 146.7, 147.12, 155.61; EIMS: *m/z* (%) 274 (M^+, 100); Anal. Calcd for $C_{19}H_{18}N_2$: C, 83.18; H, 6.60; N, 10.23. Found: C, 83.12; H, 6.58; N, 10.25%.

Procedure for the preparation of 1-Amino-2,4-dimethyl-6-phenyl-pyridinium 61a from 56a. To a two-necked flask equipped with a drying guard tube of anhydrous calcium chloride, the compound **56a** (0.91 g, 0.005 mole) and hydrazine hydrate (10 mL) in ethanol (25 mL) were added sequentially with constant stirring at 0°C for about 1 hr. 6N HCl (5 mL) was added drop wise with continuous stirring under nitrogen atmosphere for 1 hr at -30°C (liquid N_2-acetone). The reaction mixture was brought to room temperature and further stirred for 2 hr and refluxed for 10-12 hr to complete the reaction (monitored by TLC). It was then cooled, poured into ice cold saturated solution of $NaHCO_3$ (100 mL), and extracted with DCM (2 x 50 mL). The combined organic extract was washed with water (3 x 50 mL), brine (2 x 25 mL) and dried over anhydrous Na_2SO_4. The solvent was distilled under reduced pressure and the crude solid thus obtained was purified by column chromatography over silica gel using hexane-EtOAC (10:1) as eluent and recrystallised from ethanol to give light brown crystals of **61a**. Yield: 77%, m.p.127-128°C; IR (KBr): 3290, 2948, 1622, 1440 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.47 (s, 3H, CH_3), 2.87 (s, 3H, CH_3), 5.73 (brs, 2H, NH_2), 6.76 (brs, 1H, CH), 7.26-7.94 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.40, 21.6, 120.12, 120.78, 127.02, 127.41(2) 129.02 (2), 139.12, 147.92, 157.58, 159.37; EIMS: *m/z* (%) 199 (M$^+$, 100); Anal. Calcd for $C_{13}H_{15}N_2$: C, 78.36; H, 7.61; N, 14.08. Found: C, 78.32; H, 7.58; N, 14.02%. For pyridinium **61b** and **61c** were prepared following a similar procedure using compound **56b** and **56c**.

1-Amino-4-methyl-2,6-diphenyl-pyridinium 61b: Yield: 68%, Brown solid, m.p.163-164°C; IR (KBr): 3294, 2944, 1628, 1448 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.37 (s, 3H), 5.68 (brs, 2H, NH_2), 6.76 (s, 2H, CH), 7.23-7.49 (m, 6H), 8.02-8.12 (dd, J = 8.6, 4.2

Hz, 4H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.6, 127.02, 127.08 (2), 127.24, 128.57, 128.64, 129.02 (2), 129.08, 129.12, 129.36 (2), 136.12, 136.45, 142.52, 142.58, 148.48; EIMS: *m/z* (%) 261 (M^+, 100); Anal. Calcd for $C_{18}H_{17}N_2^+$: C, 82.76; H, 6.81; N, 10.72. Found: C, 82.72; H, 6.78; N, 10.67%.

1-Amino-2,4,6-triphenyl-pyridinium 61c: Yield 72%, Light brown solid, m.p.114-115°C; IR (KBr): 3292, 2946, 1626, 1446 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.74 (brs, 2H, NH_2), 7.26 (brs, 2H, CH), 7.49-7.68 (m, 15H), 8.02-8.12 (dd, *J* = 8.6, 4.2 Hz, 4H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 127.02, 127.08, 127.12 (2), 127.35 (2), 128.57, 128.64, 128.74, 129.02 (2), 129.08, 129.12 (2), 129.44, 129.52 (2), 136.42 (2), 136.57, 142.52, 142.58, 148.48; EIMS: *m/z* (%) 323 (M^+, 100); Anal. Calcd for $C_{23}H_{19}N_2^+$: C, 85.42; H, 5.91; N, 8.67. Found: C, 85.38; H, 5.88; N, 8.61%.

II.4. REFERENCES

1. (a) South, M.S.; Jakuboski T.L. *Tetrahedron Lett.*, **1995**, *36*, 5703.

   (b) South, M.S.; Jakuboski T.L.; Westmeyer M.; Dukesherer D.R., *Tetrahedron Lett.*, **1996**, *37*, 1351.

2. Popp F.D.; Noble A.C. *Advance Heterocycl. Chem.* **1967**, *8*, 21,

3. (a) Carboni R.; Lindsay R.V. *J. Am. Chem. Soc.*, **1959**, *81*, 4342.

   (b) Rahman, R. M. A.; Chareib, M. *Ind. J. Chem.*, **1987**, *26*(B), 496.

   (c) Mansour, A.K.; Eid, M.M.; Hassan, R. A. *J. Heterocycl. Chem.*, **1988**, 25, 279.

   (d) Rahman, R. M. A. *Ind. J. Chem.*, **1988**, *27*(B), 548.

4. (a) Schultz, H.; Benzodiazepines: Springer Heidelberg 1982.

   (b) Landquist, J.K. "In Comprehensive Heterocyclic Chemistry" Katritzky, A. R.; Rees, C.W. Eds. Pergamon: Oxford 1984, 1, 166.

5. (a) Cho, N . S.; Song, K.Y.; Parkanyi, C. *J. Heterocycl. Chem.* **1989**, 26, 1807-1810.

   (b) Bauer, A.; Weber, K.; Danneberg, P.; Kuhn, F. *U. S. Patent.* **1975**, 3914, 216,

6. Jones, G.B.; Davey, C. L.; Jenkins, T. C.; Kamal, A.; Kneale, G.; Neidle, S.; Webster, G D.; Thurston, D. E. *Anti-Cancer Drug Des.* **1990**. 5, 249.

7. Ananthan, S.; Clayton, S. D.; Ealick, S. E.; Wong, G.; Evoniuk, G.E.; Skolnick. P. *J.Med. Chem.* **1993**, *36*, 479-490.

8. Wong, G.; Koehler, K.F.; Skolnick, P.; Ananthan, S.; Schonholzer, P.; Zhang, W.; Cook J. M. *J. Med. Chem.* **1993**, 36, 1820-1830.

9. Katritzky, A.R.; Boulton, A. J. Advances in Heterocyclic Chemistry 8, **1967**.

10. Vogel, E.; Gunther, H. *Angew. Chem., Int. Ed. Engl.* **1967**, 6, 385.

11. Paquette, L. A. "Nonbenzenoid Aromatics"; Snyder, J. P., Ed.; Academic Press: New York, **1969**; Vol. 1, p 249.
12. Similar incentive catalyzed synthetic work on more unusual 7-membered unsaturated heterocycles of (a) phosphorus [Markl, G.; Schubert, H. *Tetrahedron Lett.* **1970**, 1273], (b) Silicon [Barton, T.J.; Kippenban, B.C.; Nelson, A.J.*J. Am. Chem. Soc.* **1974**, 96, 2272] and (c) boron [Eisch, J. J.; Galle, J. E. *Ibid.* **1975**, *97*, 4436.
13. (a) Kasparek, S. *Adv. Heterocycl. Chem.* **1974**, *17,* 45. (b) Kricka, L. J.; Ledwith, A *Chem. Rev.* **1974**, *74,*101. (c) Kametani, T.; Fukumoto, K. *Heterocycles* **1975**, *3,* 931.
14. Barth. H.; Kobayashi, M.; Musso, H. *Helv. Chim. Acta* **1979**, *62,* 1231.
15. Finlay, J. A. *Int. Rev. Sci. Org. Chem. Ser. 2,* **1976**, *9*, 23
16. Hurley, L. H. *Acc. Chem. Res.* **1980**, *13,* 263.
17. (a) Stoodley, R. J. *Tetrahedron* **1975**, *31*, 2321.
    (b) Lloyd, D.; Cleghorn, H. P.; Marshall, D. R. *Adv. Heterocyl. Chem.* **1974**, 17, 1.
    (c) Moore, J. A.; Jokelson, H. B.; Freeman, W. J.; Blout, J. F. *J.Org. Chem.* **1979**, 44, 2683 (d) Nakamura, H.; Koyama, G.; Iitaka, Y.; Ohno, M.; Yagisawa, N.; Kondo, S.; Maeda, K.; Umezawa, H. *J. Am. Chem. Soc.* **1974**, 96, 4327 (e) Thiellier, H. M. P.; Koomen, G. J.; Pandit, U. K. *Tetrahedron* **1977**, 33, 2609 and references therein.
18. See, inter alia: 1,4-Diazepines: Ohtsuka, Y. *J. Org. Chem.* **1976**, *41*, 829. 1,3-Oxazepines: Schmidt, R. R.; Berger, G. *Synthesis* **1974**, 187. 1,3-Dithiepin: Semmelback, C. L.; Chiu, L-C.; Grobmann, K. G. *J. Am. Chem. Soc.* **1976**, *98,*

2005. 1,2-Azaphosphepine: Eberhard, L.; Lampin, J.-P.; Mathey, F.; Badellon, C. *Tetrahedron* **1973**, *20,* 2000; 1,2,4-Triazepine: Hasnaoui, A.; Lavergne, J.-P.; Viallefont, P. *J. Heterocycl. Chem.* **1978**, *15,* 71; 1,2,7-Azadiphosphepine: Zeiss, W.; Henjes, H. *Chem. Ber.* **1978**, *111,* 1655.

19. (a) Moore, J. A.; Mitchell, E. *Heterocycl. Compd.* **1967**, *9,* 224; (b) Moore, J. A.; Binkert, J. *J. Am. Chem. Soc.* **1959**, *81*, 6029; (c) Nabeya, A.; Culp, F. B.; Moore, J. A. *J. Org.Chem.* **1976**, *35,* 2015.

20. For extensive reviews, see (a) Nastasi, M. *Heterocycles* **1976**, *4,* 1509; (b) Moore, J. A. *J. Am. Chem. Soc.* **1955**, *77*, 3417; (c) Moore, J. A. and Medeiros, R. W. *J. Am. Chem. Soc.* **1959**, *81*, 6026; (d) Moore, J. A.; Holton, W. F. and Wittle, E. L. *J. Am. Chem. Soc.* **1962**, *84*, 390; (e) Moore, J. A. and Pandya, L. J. *J. Org. Chem.* **1964**, 29, 336; (f) Moore, J. A., and Zoll, E.C. *J. Org. Chem.* **1964,** *29*, 2124; (g) Shriner, R. L. and Boermans, P. G. *J. Amer. Chem. Soc.* **1944**, *66,* 1810; (h) Pleiss, M. G. and Moore, J. A. *J. Amer. Chem. Soc.* **1968**, *90,* 4738.

23. Overberger, C. G.; Gibb, T. B., Chibnik, Jr., Huang, S. P. T. and Monagle, J. J. *J. Am. Chem. Soc.* **1952**, *74*, 3290.

24. Overberger C. G. and Marks, B. S., *J. Am. Chem. Soc.* **1955**, *77*, 4097.

25. Overberger, C. G.; Huang, P. T. and Gibb, T. B. Jr., *J. Am. Chem. Soc.* **1953**, *75,* 2082.

26. (a) Frankowski, A. *Tetrahedron* **1986**, *42*, No. 5, 1511-1528.
(b) Bemi, L.; Thomas, M. T.; Snieckus, V. *Synthesis* **1979**, 130.
(c) Streith, J.; Luttringer, J. P.; Nastasi, M. *J. Org. Chem.* **1971**, Vol 36, No.20.

27. Veale, A. C.; Rheingold, A. L. and Moore, J. A., *J. Org. Chem.* **1985**, *50*, 2141-

2145.

28. Moore, J. A.; Marascia, F. J.; Medeiros, R. W.; Wineholt, R. L. *J. Org. Chem.* **1966**, *31*, 34.

29. McClure, D. E.; Lumma, P. K.; Arison, B. H.; Jones, J. H.; Baldwin, J. J. *J.Org. Chem.* **1983**, *48*, 2675.

30. (a) Battiste, M. A. and Barton, J. B. *Tetrahedron Letters*, **1967**, *13*, 1227-1231. (b) Battiste, M. A. *J. Am. Chem. Soc.*, **1963**, *85*, 2175.

31. Sauer, J. and Heinrichs, G. *Tetrahedron Letters*, **1964**, 4979.

32. (a) Klingsberg. E. "Abstracts of Papers". 150th National Meeting of the American Chemical Society: Washington, D.C., Sept 1967; p 668. (b) Ried, W.; Kocher, E. U. *Angew. Chem.* **1958,** *70*, 164.

33. (a) Harris, D. J.; Gordon Y.; Snieckus V.; Klingsberg, E. *Can. J. Chem.* **1974**. 52, 2798-2804. (b) Harris, D. J.; Kan, Gordon. Y. P.; Tschamber, T.; Snieckus, V. *Can. J. Chem.* **1980**, *58*, 494.

34. Klingsberg, E. *Abstr. Am. Chem. Soc. Meeting, Sept.,* **1965**, 66S.

35. Reissenweber, G.; Sauer, J. *Tetrahedron Lett.* **1977**, 4393.

36. (a) Kidwai, M.; Mothsra, P. *Synthetic Communications*, **2006,** 36, 817-824. (b) Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford University Press: Oxford, NY, 1998.

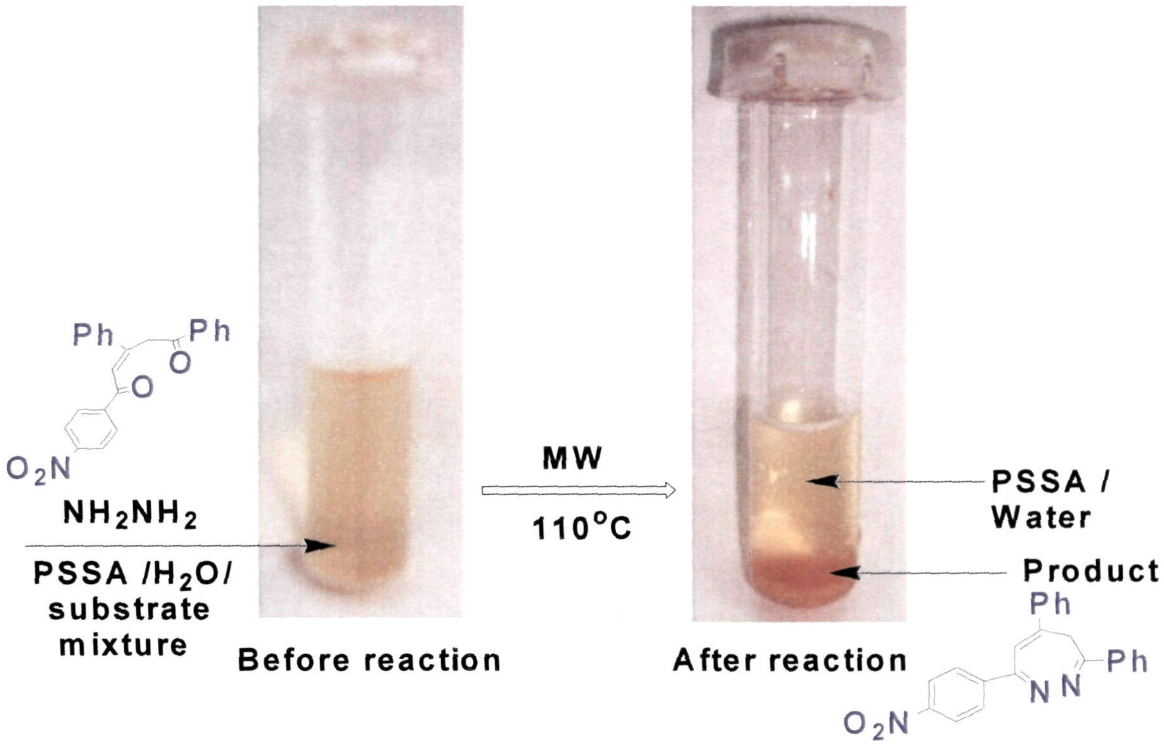
37. (a) Holbrey, J. D.; Turner, M. B.; Rogers, R. D. *Ionic Liquids as Green Solvents*; ACS Symposium Series 856; American Chemical Society: Washington, DC, 2003; pp 2-12. (b) Varma, R. S. *Advances in Green Chemistry: Chemical Syntheses Using Microwave Irradiation*; AstraZeneca Research Foundation India:

Bangalore, India, 2002. (c) Varma, R. S. Organic Synthesis using Microwaves and Supported Reagents. In *Microwaves in Organic Synthesis*; Loupy, A., Ed.; Wiley-VCH: Weinheim, Germany, 2002; pp 181-218. (d) Kappe, C. O.; Stadler, A. In *Microwaves in Organic and Medicinal Chemistry*; Mannhold, R., Kubinyi, H., Folkers, G., Eds.; Wiley-VCH: Werlag GmbH & Co. KGaA, Weinheim, Germany, 2005.

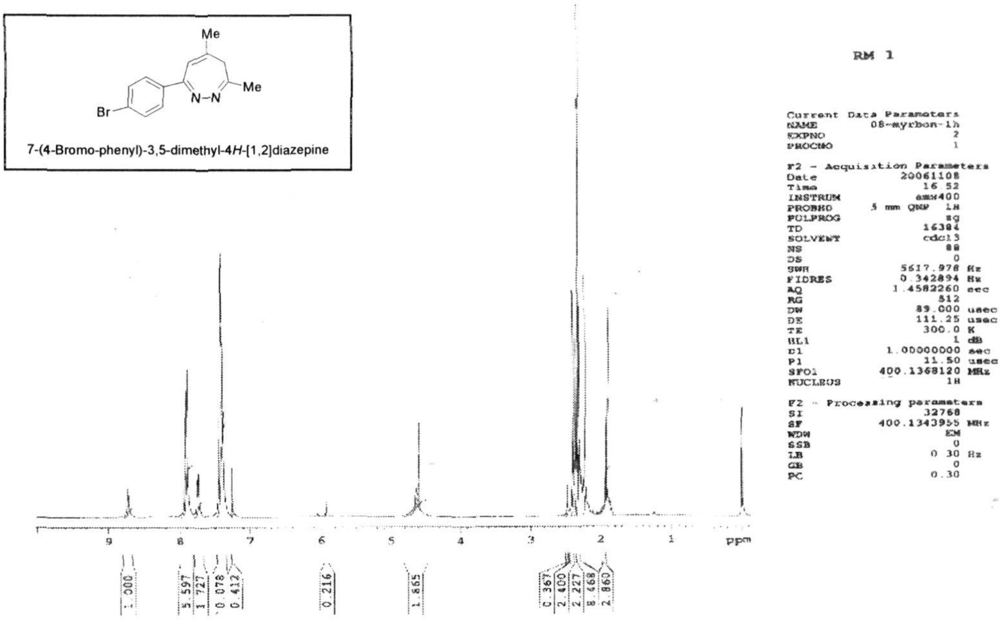
38. (a) Heller, S.T.; Natarajan, S. R. *Org. Lett.* **2006**, *8*, 2675-2678; (b) Deng, X.,; Mani, N.S. *Org. Lett.* **2006**, *8*, 3505-3508; (c) Armstrong, A.; Jones, L. H.; Knight, J.D.; Kelsey, R. D. *Org. Lett.* **2005**, *7*, 713-716.
39. (a) Polshettiwar, V.; Varma, R.S. *Tetrahedron Lett.* **2008**, 49, 397-400; (b) Polshettiwar, V.; Varma, R.S. *J. Org. Chem.* **2007**, 72, 7420-7422.(c) Polshettiwar, V.; Varma, R.S. *Tetrahedron Lett.* **2007**, 48, 7343-7346; (d) Ju, Y.; Kumar, D.; Varma, R. S. *J. Org. Chem.* **2006**, *71*, 6697-6700.(e) Ju, Y.; Kumar, D.; Varma, R. S. *J. Org. Chem.* **2006**, *71*, 135-141; (f) Ju, Y.; Varma, R. S. *Org. Lett.* **2005**, *7*, 2409-2411.
40. Yuhong Ju and Rajender S. Varma *J. Org. Chem.* **2006**, *71*, 135-141.
41. Polshettiwar, V.; Varma, R. S. *Tetrahedron Lett.* **2007**, *48*, 5649.
42. Polshettiwar, V.; Varma, R. S. *Tetrahedron Lett.* **2007**, *48*,7343–7346
43. (a) Dallinger, D.; Kappe, C. O. *Chem. Rev.* **2007**, *107*, 2563-2591. (b) Iimura, S.; Manabe, K.; Kobayashi, S. *Org. Biomol. Chem.* **2003**, *1*, 2416-2418.
44. (a) Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250. (b) Jachuck, R. J. J.; Selvaraj, D. K.; Varma, R. S. *Green Chem.* **2006**, *8*, 29. (c) Bose, A. K.; Manhas, M. S.; Ganguly, S. N.; Sharma, A. H.; Banik, B. K. *Synthesis* **2002**, 1578. (d)

Baghurst, D. R.; Mingos, D. M. P. *Chem. Soc. Rev.* **1991**, *20*, 1. (e) Leadbeater, N. E. *Chem. Commun.* **2005**, 2881. (f) An, J.; Bagnell, L.; Cablewski, T.; Strauss, C. R.; Trainor, R. W. *J. Org. Chem.* **1997**, 62, 2505.

45. (a) Ju, Y.; Varma, R. S. *Org. Lett.* **2005**, *7*, 2409. (b) Ju, Y.; Varma, R. S. *J. Org. Chem.* **2006**, *71*, 135. (c) Ju, Y.; Varma, R. S. *Green Chem.* **2004**, *6*, 219.
46. (a) Varma, R. S.; Naicker, K. P. *Tetrahedron Lett.* **1998**, *39*, 2915. (b) Varma, R. S.; Naicker, K. P.; Kannan, P.; Aschberger, J. *Synth. Commun.* **1999**, *29*, 2823. (c) Varma, R. S.; Naicker, K. P.; Kumar, D. *J. Mol. Catal. A: Chem.* **1999**, *149*, 153.
47. H. C. Van Der Plas., "Ring Transformation of Heterocycles" Volume 2, **1973**, Academic press.
48. (a) Moore J A & Binkert J, *J Amer Chem Soc* 81, **1959**, 6029;
    (b) Moore J A, *J Amer Chem Soc,* 77, **1955**, 3418.
49. Furniss, A. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. *Vogel's Textbook of Practical Organic Chemistry Fifth New Edition Pearson education.*



PSSA catalyzed synthesis of 3,5,7-trisubstituted-4*H*-1,2-diazepine using a Microwave -Assisted reaction



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PROCNO                   1

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PULPROG                 zg
TD                   16384
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DS                       0
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FIDRES            0.342894 Hz
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RG                     512
DW                  89.000 usec
DE                  111.25 usec
TE                   300.0 K
PL1                      1 dB
D1              1.00000000 sec
P1                   11.50 usec
SFO1           400.1368120 MHz
NUCLEUS                 1H

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Figure 1. ^{1}H NMR spectra of compound **56f**

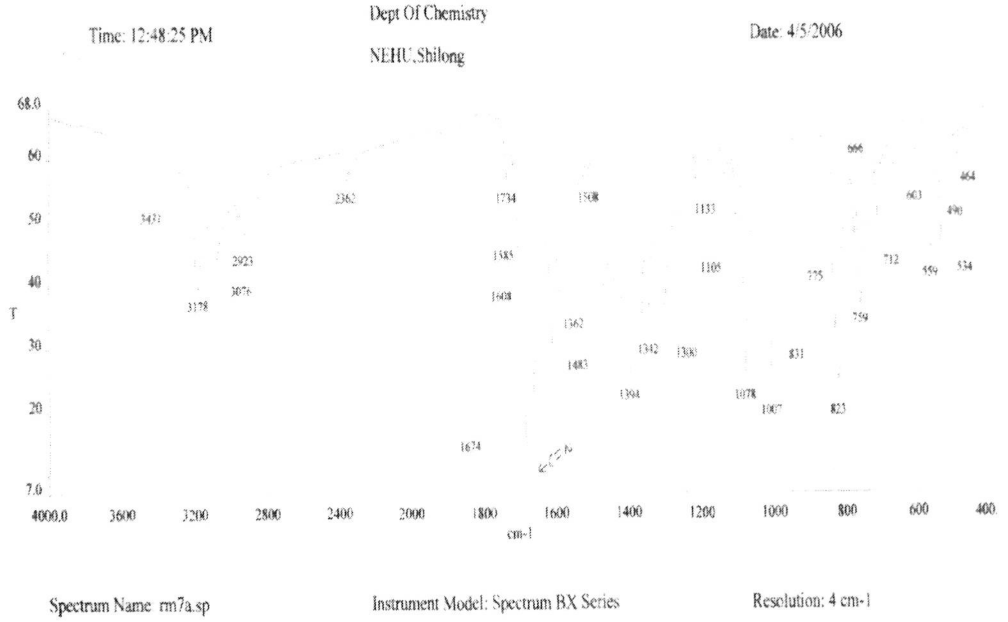
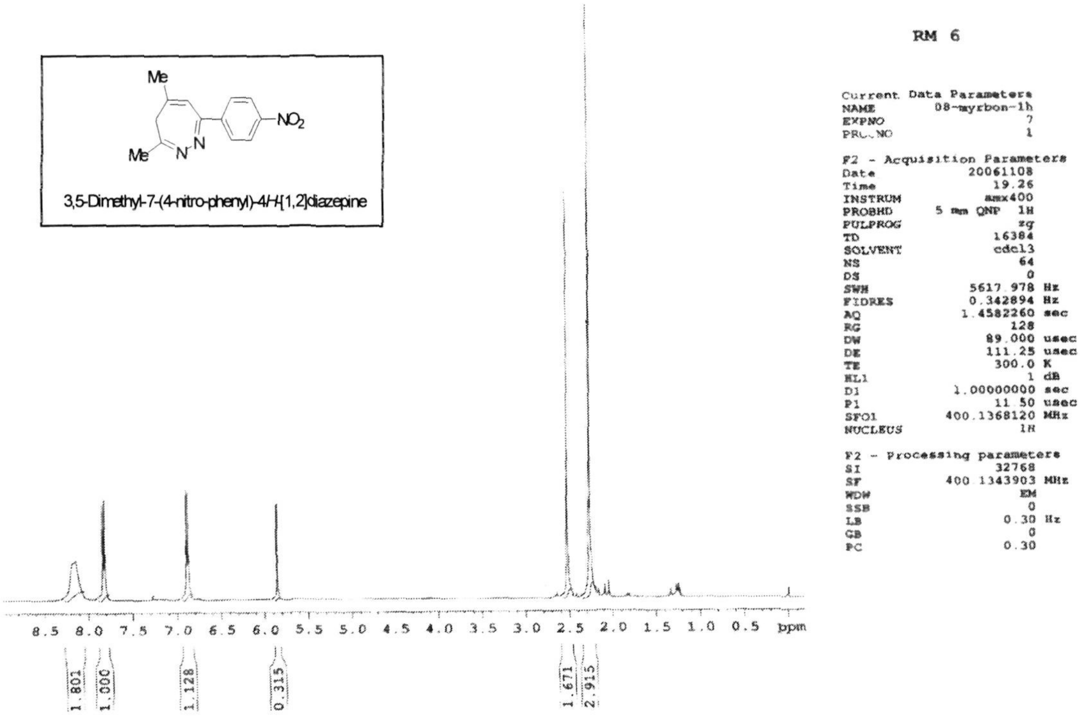


Figure 2. IR spectra of compound **56f**.



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RM 6

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PRC.NO                   1

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TD                   16384
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DE                  111.25 usec
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P1                   11.50 usec
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NUCLEUS                 1H

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Figure 3. ^{1}H NMR spectra of compound **56h**.

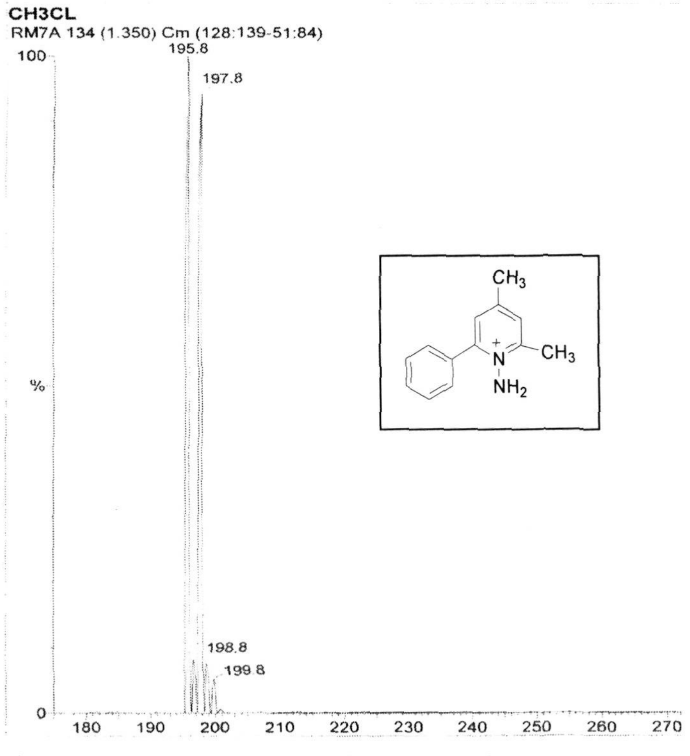


Figure 4. Mass spectrum of compound **61a**

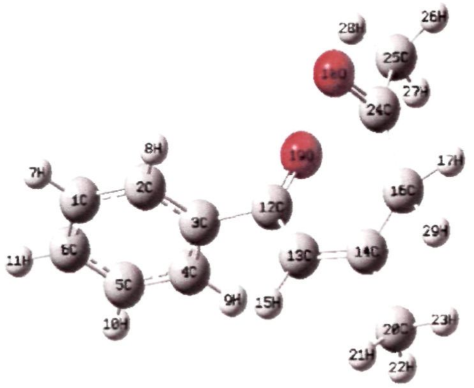


Figure 5: Compound Intermediate **55a**.

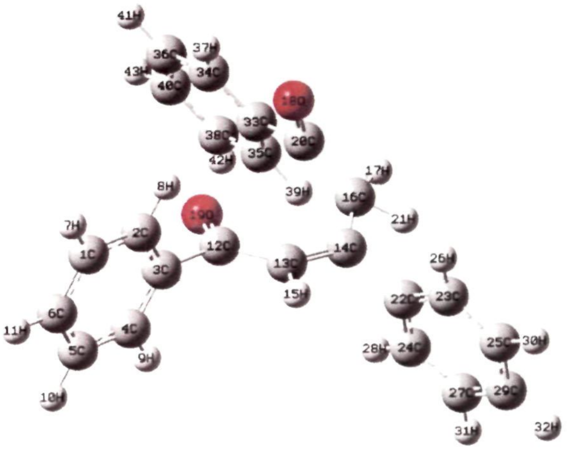


Figure 6: Compound Intermediate **55c**.

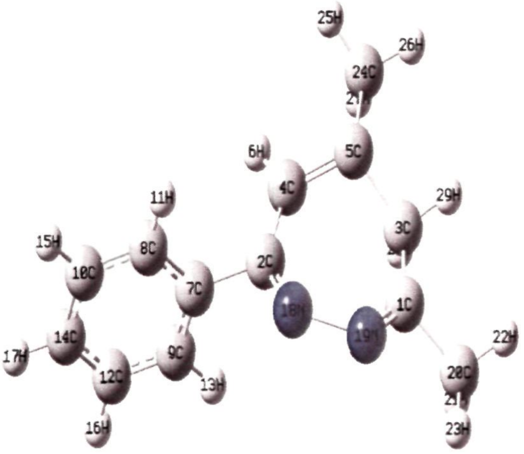
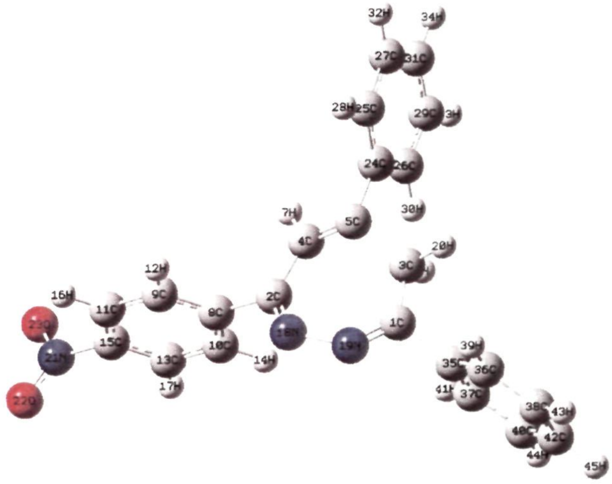


Figure 7: Compound **56a.**



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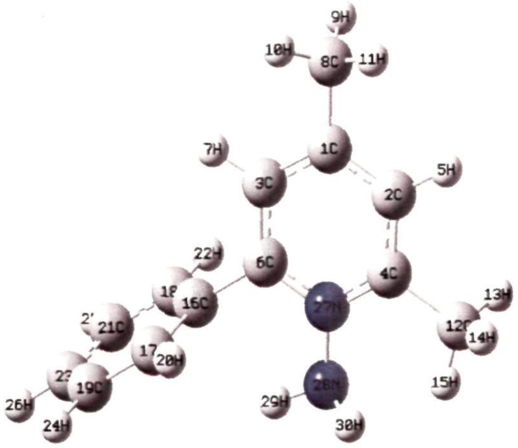


Figure 9: Compound **61a**.

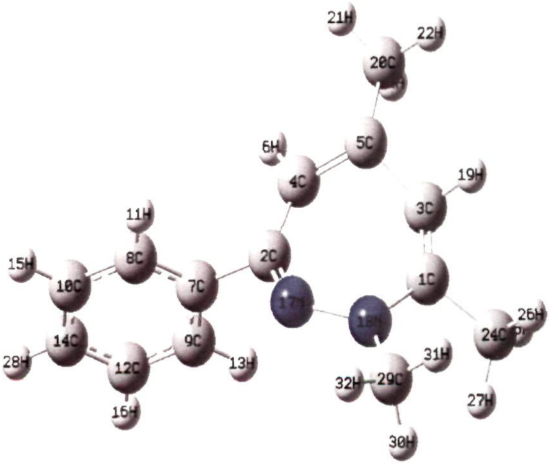


Figure 10: Compound **57a**.

Computer 3D models in Gaussview

CHAPTER III

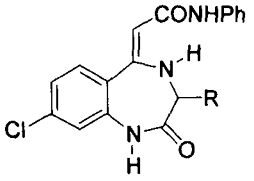
A *β*-OXODITHIOESTERS MEDIATED SYNTHESIS OF 2-SUBSTITUTED AMINO-4-ARYL-3*H*-DIHYDRO-BENZO-[*b*][1,4]-DIAZEPINES AND 2-(CYCLOAMINO)-4-ARYL-3*H*-DIHYDRO-BENZO-[*b*][1,4]-DIAZEPINES

CHAPTER III

A *β*-oxodithioesters mediated synthesis of 2-substituted amino-4- aryl-3*H*-dihydro-benzo-[*b*][1,4]-diazepines and 2-(*N*-cycloamino)-4-Aryl-3*H*-dihydro-benzo-[*b*][1,4]-diazepines

III.1 INTRODUCTION

The earliest known benzodiazepines are the minor tranquilizers chlordiazepoxide and diazepam which are of pharmacological importance.[1] They constitute an important family of compounds exhibiting diverse biological activities[2,3] and has undergone extensive chemical investigation. Benzodiazepine compounds have been considered as the most extensively consumed psychoactive drugs worldwide due to their anxiolytic and anticonvulsant activity, and are commercially available as drugs, which are widely used as anticonvulsant, antianxiety, anti-inflammatory,[4] antibiotics,[5] sedative, hypnotic agents,[6] and anti-HIV agents.[7] For example, Clozapine, Olanzapine and Quetiapine are used to treat schizophrenia; Clonazepam, Diazepam, Lorazepam, Nitrazepam, and Oxazepam are used as antianxiety drugs. In addition, they are the basis of cholecystokinin receptor (CCK) A and B antagonists,[8] oxytocin antagonists,[9] inhibitors of protein-DNA interactions[10] and farnesyltransferase inhibitors[11] found in therapeutics.[12] Novel benzodiazepine derivatives of general structure **62**, were designed by receptor mapping techniques to identify new glycine antagonists, based on the known pharmacophore model of the glycine binding site.[13]



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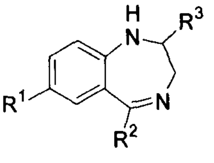
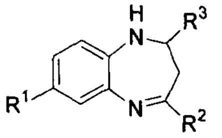


63

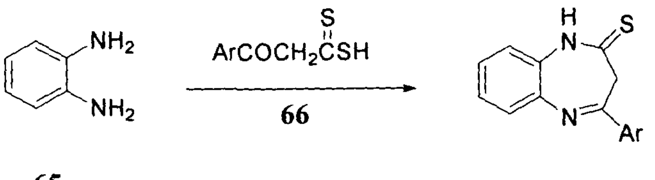


64

Similarly, the dihydro benzodiazepines derivatives[14] **63** and **64** have generated considerable interest as CNS active anticonvulsant drugs, also as *in vitro* non-nucleoside inhibitors of HIV-1 reverse transcriptase.[15,16]

In recent years, Savelli *et al.*[17] described pyrido[2,3-b]-[1,4]diazepinone structures, which revealed interesting neuroleptic properties. However, because of the failure of the reactions of simple *β*-diketones, that is, pentan-2,3-dione or benzoylacetone with 2,3-diaminopyridine to yield 3*H*-pyrido[2,3-b][1,4]diazepine structures[18a,] acyclic and cyclic *β*-ketoesters have only been used as precursor since 1974 for a series of pyrido[2,3-b][1,4]diazepin-2-ones[19] and their respective isomers.[20]

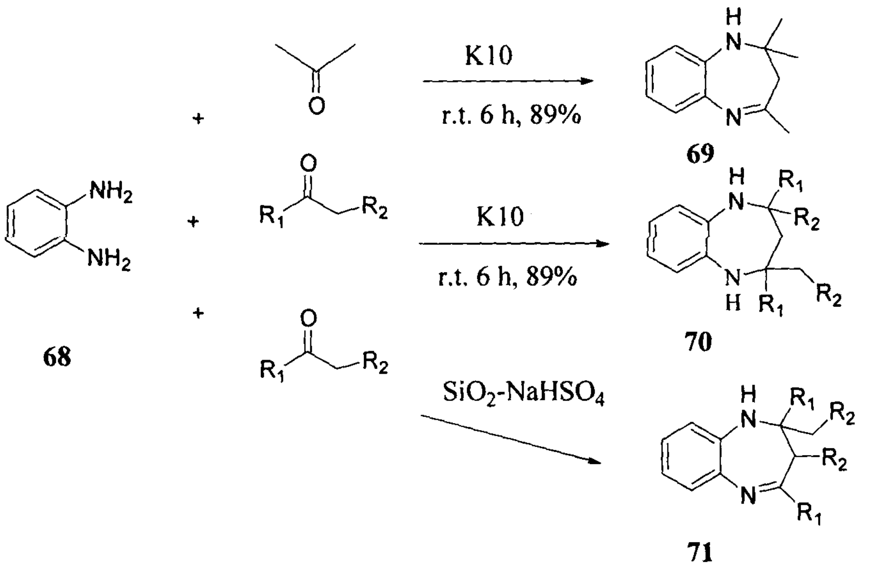
The most commonly employed methods involve the cyclocondensation of 1,2-diamines with ketones,[21] enones,[22] or *β* –haloketones[23] in the presence of acid catalysts such as BF_3-etherate[24] and $NaBH_4$.[25] In 1978, Nardi *et al.*[26] reported the synthesis of 4-aryl-1,3-dihydro-2*H*-[1,5]-benzodiazepine-2-thiones **67** by condensation of 1-aryl-3,3-dimercaptoprop-2-en-1-ones **65** with *o*-phenylenediamine **66** (Scheme 15).



65 **67**

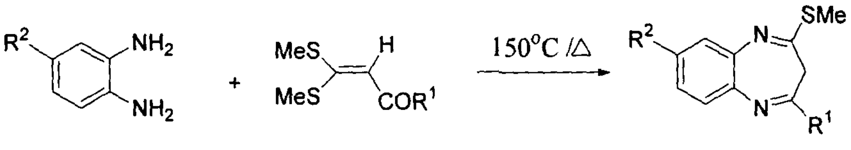
Scheme 15

In general, the condensation of *o*-phenylenediamine with ethyl acetoacetate or ethyl benzoylacetate has been shown to yield 4-methyl or 4-phenyl-1,3-dihydro-2*H*-[1,5]-benzodiazepin-2-ones as the major products.[27] Li-Tao An *et al.*[28] reported a solvent-free method for the synthesis of 1,5-benzodiazepines **69,70** using *o*-phenylenediamine **68** with different ketones in the presence of montmorillonite K10 at room temperature and under heterogeneous reaction conditions.[29] Montmorillonite K10 is one of the most important inorganic solid acids, which has been extensively reported to promote acid-dependent reactions[30] and as carrier of catalyst.[31] Among the various heterogeneous catalyst, silica gel impregnated with sodium bisulfate (SiO_2-$NaHSO_4$) has the advantage, because of low cost, ease of preparation and as eco-friendly catalyst affording **71**[32] (Scheme 16).



Scheme 16

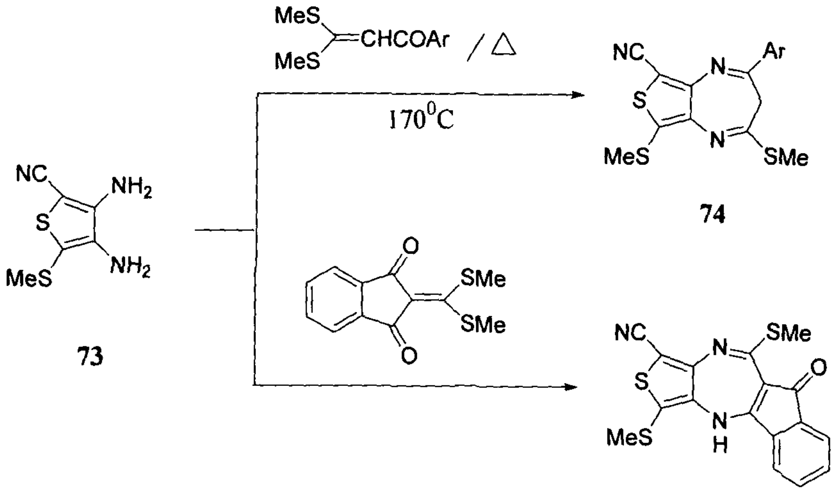
Kobayashi and co-workers[33] have reacted *o*-phenylenediamine with α-oxoketenedithioacetals to afford 8-substituted 4-aryl-2-methylthio-1,5-benzodiazepine **72** regioselectively in moderate to good yields (Scheme 17). Similarly the corresponding thienodiazepine derivatives **74** and **75** were obtained by condensation of 5-substituted-3,4-diaminothiophenes **73** with oxoketene dithioacetals[34] (Scheme 18).



R¹	R²	% yield
C_6H_5	NO_2	55
4-ClC_6H_4	NO_2	73

72

Scheme 17



73

74

75

Scheme 18

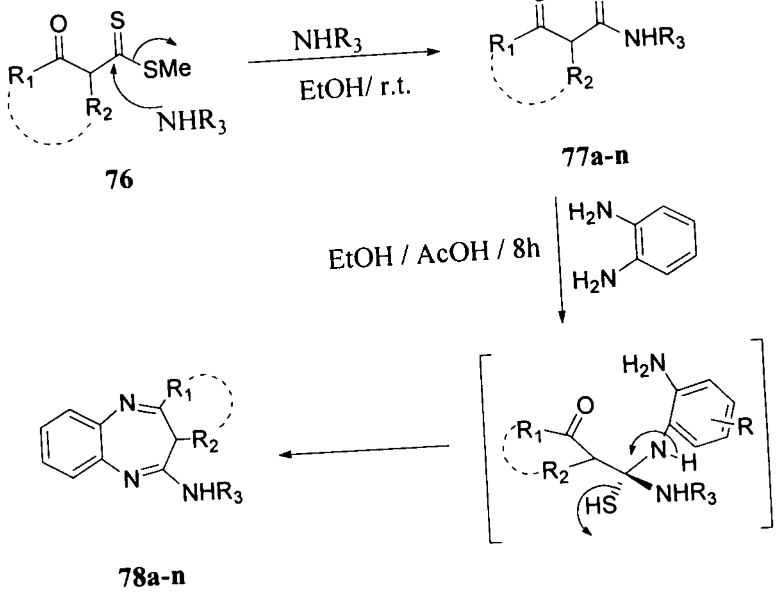
M. Kidwai and P. Mothsra reported the synthesis of [1,4]-benzodiazepine and [1,5]-benzodiazepine using ethylacetoacetate, aromatic aldehydes and o-phenylenediamine without using any catalytic reagent at pH 7.[35] However, many of the reported methods use drastic reaction conditions, high temperature and involved relatively expensive reagents thus leaving enough scope for the development of newer, milder and more efficient procedure for the synthesis of 1,4-benzodiazepines.

The present work describes two general methods for the synthesis of 2-substituted amino-4-aryl-3*H*-dihydro-benzo-[*b*][1,4]-diazepines and 2-(*N*-cycloamino)-4-Aryl-3*H*-dihydro-benzo-[*b*][1,4]-diazepines. The first method involved the dethiomethylation of *β*-oxodithioesters with primary amines while the second method involved reaction with secondary cyclic amines to give the two different *β*-oxothioamides respectively which were then subsequently subjected to cyclisation reaction with *o*-phenylenediamine.

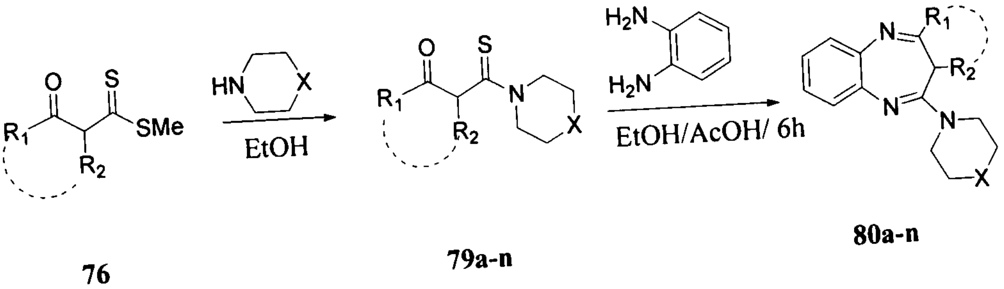
III.2 RESULTS AND DISCUSSION

During our literature survey we found that none of the reported methods for the synthesis of benzodiazepines involved the use of β-oxodithioesters or β-oxothioamide as precursors[36]. We therefore deemed it interesting to attempt the construction of substituted [1,4]-benzodiazepines using *o*-phenylenediamine and β-oxothioamide obtained from β-oxodithioesters. Our attempt to displace the methylthio group from β-*oxodithioesters* **76** *was achieved by using equimolar amount of aliphatic, alicyclic or* aromatic primary and secondary amines in ethanol to give β-oxothioamide 77. The thioamide then undergo cyclocondensation with *o*-phenylenediamine, to give the corresponding 2-substituted amino-4-aryl-3*H*-dihydro-benzo-[*b*][1,4]-diazepines **78(a-n)** (Scheme 19) and 2-(*N*-cycloamino)-4-aryl-3*H*-dihydro-benzo-[*b*][1,4]-diazepines derivatives **80(a-n)** (Scheme 20).

The β-oxodithiocarboxylates[37,38] **76** were prepared according to the reported procedures[39,40] with minor modifications. In a typical reaction, a solution of respective β-oxodithioesters **76** (5 mmol) obtained, is treated with 1 eqv. of primary or secondary amines (aliphatic, aromatic, alicyclic or cyclic) and ethanol with constant stirring for about 6 h at room temperature when β-ketothioamide 77 and **79** is formed (monitored by TLC). To the β-ketothioamide 77 and **79** generated *in situ*, *o*-phenylenediamine (0.01 mole) and catalytic amount of acetic acid (3 mL) was added in presence of dry ethanol (15 mL) and refluxed for 12-16 h with constant stirring. The completion of the reaction was monitored by TLC.



Scheme 19



Scheme 20

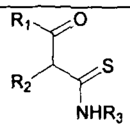
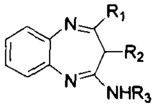
The reaction mixture was concentrated under reduced pressure and poured into ice-cold saturated solution of $NaHCO_3$ (100 mL), extracted with DCM (3 x 50 mL), washed with H_2O (2 x 50 mL) and brine (1 x 50 mL), and dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum to give crude products **78, 80** which were purified by column chromatography over silica gel using hexane/EtOAc (10:1) as eluent. All compounds **78(a-n)** showed characteristic spectral properties for 2-substituted amino-4-aryl-3*H*-dihydro-benzo-[*b*][1,4]-diazepines and **80(a-n)** for 2-(*N*-cycloamino)-4-aryl-3*H*-dihydro-benzo-[*b*][1,4]-diazepines derivatives as showned (**Table II** and **Table III**).

All the products were characterized by ^1H and ^{13}C NMR spectroscopy, IR, melting points and elemental analyses. The formation of Methyl-(4-phenyl-3*H*-benzo[b][1,4]diazepin-2-yl)amine **78a** was confirmed on the basis of analytical data and spectral evidences. Thus, it was analyzed for $C_{16}H_{15}N_3$ (Expected C, 77.08; H, 6.06; N, 16.85. Found: C, 77.01; H, 6.03; N, 16.22%) and its mass spectrum showed the molecular ion peak at *m/z* 249. Its IR spectrum (KBr) exhibited a sharp absorption band at 1620 cm^{-1} which is characteristic for C=N stretching frequency and one at 3374 cm^{-1} for the N-H stretch. The final structural proof was obtained from its ^1H NMR ($CDCl_3$), which showed one singlet at δ 3.42 ppm (2H), a doublet at δ 2.48 ppm (3H) and a distorted quartet at 4.89 ppm (1H) NH proton. The aromatic protons were observed as multiplets at δ 7.25–7.44 ppm (7H) and doublets at 7.67 ppm (2H). ^{13}C NMR ($CDCl_3$) showed resonances at δ ppm 27.10, 30.23, 164.2 and 164.7 for methyl carbon sp^3, methylene carbon, C-2 and C-4 of the diazepine ring which are in accordance with the proposed structure. The analytical and spectral data for other 2-substituted amino-4-aryl-3*H*-dihydro-benzo-[*b*][1,4]-diazepines **78(b-n)** and for 2-(*N*-cycloamino)-4-aryl-

3*H*-dihydro-benzo-[*b*][1,4]-diazepines **80(a-n)** derivatives are in conformity with the assigned structure, and are described in the experimental section.

In summary, we have developed a highly efficient protocol for the synthesis of 2-substituted amino-4-aryl-3*H*-dihydro-benzo-[*b*][1,4]-diazepines **78(a-n)** and for 2-(*N*-cycloamino)-4-aryl-3*H*-dihydro-benzo-[*b*][1,4]-diazepines **80(a-n)** from *β*-oxodithioester as common synthons for the synthesis. Our efforts to extend this protocol to a wide range of *β*-oxodithioesters or *β*-oxothioamide derived from various cyclic/heterocyclic ketones with primary and secondary amines is currently under progress.

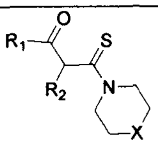
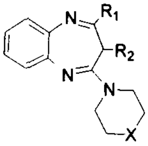
Table II. Synthesis of 2-substituted amino-4-aryl-3*H*-dihydro-benzo-[*b*][1,4]-diazepines **78**.

Entry	77	R_1	R_2	R_3	78	yield%
						
1	**77a**	Ph	H	CH_3	**78a**	87
2	**77b**	Ph	H	Et	**78b**	82
3	**77c**	Ph	H	$CH(CH_2CH_3)_2$	**78c**	58
4	**77d**	Ph	H	Ph	**78d**	84
5	**77e**	Ph	CH_3	CH_3	**78e**	63
6	**77f**	Ph	CH_3	Et	**78f**	77
7	**77g**	4-MeO-C_6H_4	H	Et	**78g**	87
8	**77h**	4-MeO-C_6H_4	H	Ph	**78h**	78
9	**77i**	4-Br-C_6H_4	H	Et	**78i**	85
10	**77j**	4-Br-C_6H_4	H	Ph	**78j**	76
11	**77k**	4-NO_2-C_6H_4	H	Et	**78k**	75
12	**77l**	4-NO_2-C_6H_4	H	Ph	**78l**	82
13	**77m**	4-MeO-C_6H_4	CH_3	Et	**78m**	68
14	**77n**	4-MeO-C_6H_4	CH_3	Ph	**78n**	76
15	**77o**	*i*-Pr	H	Et	**78o**[b]	
16	**77p**	*i*-Pr	H	Ph	**78p**[b]	

[a] Yields obtained are determined after work-up and Chromatographic purification.

[b] Not isolated

Table III. Synthesis of 2-(*N*-cycloamino)-4-aryl-3*H*-dihydro-benzo-[*b*][1,4]-diazepines **80**.

Entry	**79**	R_1	R_2	**80**	(yield%)[a]
					
1	**79a**, X=H	Ph	H	**80a**	87
2	**79b**, X=O	Ph	H	**80b**	74
3	**79c**, X=NBn	Ph	H	**80c**	62
4	**79d**, X=N-(2-Pyridyl)	Ph	H	**80d**	58
5	**79e**, X=H	Ph	CH_3	**80e**	63
6	**79f**, X=O	Ph	CH_3	**80f**	77
7	**79g**, X=H	4-MeO-C_6H_4	H	**80g**	87
8	**79h**, X=O	4-MeO-C_6H_4	H	**80h**	78
9	**79i**, X=NBn	4-Br-C_6H_4	H	**80i**	65
10	**79j**, X=N-(2-pyridyl)	4-Br-C_6H_4	H	**80j**	76
11	**79k**, X=H	4-NO_2-C_6H_4	H	**80k**	85
12	**79l**, X=O	4-NO_2-C_6H_4	H	**80l**	82
13	**79m**, X=H	4-MeO-C_6H_4	CH_3	**80m**	68
14	**79n**, X=O	4-MeO-C_6H_4	CH_3	**80n**	71
15	**79o**, X=H	*i*-Pr	Et	**80o**[b]	
16	**79p, X=O**	*i*-Pr	Ph	**80p**[b]	

[a] Yields obtained are determined after work-up and Chromatographic purification.
[b] Not isolated

III.3 EXPERIMENTAL

Melting points were determined on a "Thomas Hoover" capillary melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker AMX 400 instrument using $CDCl_3$ as the solvent. Chemical shifts are reported in ppm using tetramethylsilane as internal standard. J values are given in Hz. The following abbreviations are used to describe peak patterns when appropriate: br = broad, s = singlet, d = doublet, dd = double doublet, dt = double triplet, t = triplet, q = quartet, sept = septuplet, m = multiplet. IR spectra were recorded on a Perkin-Elmer BX spectrophotometer. ESI mass spectra were measured on an ion trap analyzer Esquire 3000 (Bruker Daltonics). Masses (MS) are reported in unit of mass over charge (*m/z*), the molecular or base peaks and relative intensities are indicated by (M^+) and (%) respectively. CHN analyses were recorded on a Vario EL analyser. Column chromatography was performed using silica gel (60-120 mesh, Merck).

All reactions were performed in oven dried (120°C) glasswares under a positive dry nitrogen atmosphere. Analytical thin layer chromatography (TLC) were performed on glass plates coated with ACME's silica gel containing 13% calcium sulphate as binder, and various combination of visualization of spots was accomplished by exposure to UV lamp or iodine vapour or by spraying potassium permanganate (acidic) solution. Eluents for column chromatography were used after simple distillation of commercial solvents. All solvent evaporations were done using a rotary evaporator and a steam bath.

Chemical Reagents and Solvents:

Commercially available NaH, 50% suspension (SISCO, SPECTROCHEM) was used, *N,N*-dimethyl formamide (Aldrich) was purchased bottle grade and dried over CaH, distilled and store over molecular sieves (4A). Pure (THF) was obtained by keeping the deperoxidised THF over sodium-benzophenone. Anhydrous ether, chloroform and dichloromethane (DCM) was obtained by keeping the bottle grade over calcium chloride over night and finally stored over sodium wire or Type 3A molecular sieve. Dry benzene was obtained by washing with concentrated sulphuric acid followed by azeotropic distillation and stored over sodium wire. Sodium tertiary butoxide was freshly prepared for each reaction.

Starting Materials:

Acetophenone, substituted acetophenones, dimethyl trithiocarbonate (Sigma-Aldrich) were used for the preparations of β-oxodithiocarboxylate ester. Carbon disulfide (CS_2), dimethyl sulfoxide (DMSO), and *o*-phenylenediamine used were analytical reagent bottle grade. Commercially available, methylamine, ethylamine, aniline, piperidine, morpholine, *N*-benzylpiperazine, *N*-pyridinylpiperazine (E-Merck India Ltd.) were used directly without further purification. Dimethyl trithiocarbonate bp 225°C (760 mm) was also prepared in the laboratory according to the reported procedure[41] with some modification. The β-oxodithioester required for the present investigation was prepared (preferably using protective gloves and mask under fume cupboard) according to the earlier reported general procedures[38-40] with minor modification.

General procedure for the preparation of dimethyl trithiocarbonate:

A mixture of 30 mL of DMSO, (17 g, 0.3 mole) KOH and 40 mL (50 g, 0.66 mole) of CS_2 was stirred in a stoppered vessel at room-temperature overnight. The excess CS_2 was decanted and the volume was brought to 90 mL by adding more DMSO. A mixture of 10 mL of the DMSO solution and bromomethane (3.3 g, 0.013 mole methyl bromide) was heated on the steam bath for 10 minutes after which the original red brown colour had turned lighter. About 20 mL of water was added and the product was extracted with ether. On evaporation, of methyl trithiocarbonate (2.7 g, bp 225°C, 760 mm) was obtained which is a yield of 91 percent based on methyl bromide.

General procedure for the Synthesis of β-oxodithioesters 76:

To a well stirred suspension of NaH (2.5 g, 0.05 mole; 50% suspension in mineral oil) in dry DMF/Benzene solvent mixture (50 mL, 1:10; Benzene bp 80°C), dimethyl trithiocarbonate (3.80 g, 0.027 mole) was added to the solution and the mixture is refluxed with stirring for 1 hr. A solution of the acetophenone (0.025 mole) in dry benzene (50 mL) is slowly added dropwise over a period of 3-4 hr, the reaction mixture is further refluxed for 1 hr. The reaction formed an interface between the two layers present in the reaction mixture. The reaction is exothermic, and the reaction mixture was cooled in a water bath at room temperature, and poured into ice-cold water (250 mL). The aqueous layer is separated, washed with benzene (1 x 100 mL), acidified with 3N HCl or 20% acetic acid (20 mL) and extracted with chloroform (2 x 50 mL). The extract is dried with anhydrous sodium sulfate and the solvent was evaporated to give the corresponding β-oxodithiocarboxylates **76** in good yields (single spot on TLC), which is pure enough (>95% purity according to NMR analysis). Purification may be achieved by column chromatography on silica gel using hexane as eluent.

Synthesis of Methyl-(4-phenyl-3*H*-benzo[b][1,4]diazepin-2-yl)amine 78a.

To a solution of respective β-oxodithiopropionic ester **76a** (1.7 g, 0.008 mole) in ethanol (15 mL), methylamine (1.55 g, 0.05 mole) is added and the mixture was stirred for about 6 hr at room temperature. The β-ketothiopropionamide **77a** formed in situ, *o*-phenylenediamine (1.64 g, 0.0152 mole) and catalytic amount of acetic acid (5 mL) was added in presence of dry ethanol (15 mL) and was refluxed for 6-8 hr with constant stirring, the reaction being monitored by TLC. Under work up, the reaction mixture was concentrated under reduced pressure and poured into ice-cold water (50 mL), extracted with diethyl ether (2 x 50 mL), washed with H_2O (2 x 50 mL) and brine (1 x 50 mL), and dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum to give 1,4-benzodiazepines **78a** which were purified by column chromatography over silica gel using hexane/EtOAc (10:1) as eluent. Yield 87% (1.06 g); Yellow solid; mp 126-127°C; R_f 0.74 (9.5:0.5 hexanes-EtOAc); IR (KBr): 3374, 3040, 2210, 1620, 1322, 1175, 1074 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.48 (d, J = 7.2 Hz, 3H, CH_3), 3.42 (s, 2H, CH_2), 4.89 (q, J = 7.2 Hz, 1H, NH), 7.25-7.44 (m, 7H, ArH), 7.67 (dd, J = 8.4, 2.1 Hz, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.10, 30.23, 123.12, 123.24, 128.05, 128.32, 128.46, 128.50, 129.07, 129.32, 130.4, 131.65, 142.54, 146.22, 164.04, 164.68; EIMS (*m/z*, %): 249 (M + 1, 100); 248 (M^+, 90); Anal. Calcd for $C_{16}H_{15}N_3$ (249): C, 77.08; H, 6.06; N, 16.85. Found: C, 77.01; H, 6.03; N, 16.22%. Compounds **78b-n** was synthesized similarly using appropriate amines.

Ethyl-(4-phenyl-3*H*-benzo[b][1,4]diazepin-2-yl)-amine 78b: Yield 82% (1.12 g); Pale yellow solid; mp 122-123°C; R_f 0.71 (9.5:0.5 hexanes-EtOAc); IR (KBr): 3370, 3040, 2210, 1620, 1322, 1175, 1074 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.08 (t, J = 7.6 Hz, 3H), 2.85 (q, J = 7.6 Hz, 2H), 3.48 (brs, 2H, CH_2), 4.37 (t, J = 7.6 Hz, 1H, NH), 7.20-7.64 (m, 7H, ArH), 7.88 (dd, J = 8.4, 2.1 Hz, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.18, 30.38, 36.29, 123.14, 123.26, 128.14, 128.30, 128.54, 128.58, 129.11, 129.13, 130.21, 131.24, 142.44, 146.23, 164.24, 164.78; EIMS (*m/z*, %): 263 (M + 1, 100); 262 (M^+, 90); Anal. Calcd for $C_{17}H_{17}N_3$ (263): C, 77.58; H, 6.56; N, 15.85. Found: C, 77.41; H, 6.43; N, 15.22%.

(1-Ethyl-propyl)-(4-phenyl-3*H*-benzo[b][1,4]diazepin-2-yl)-amine 78c: Yield 58% (0.87g); Pale yellow solid; mp 173-174°C; R_f 0.71 (9.5:0.5 hexanes-EtOAc). IR (KBr): 2944, 2457, 2212, 1624, 1326, 1172, 1072 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.98 (dt, J = 7.7, 2.2 Hz, 3H, CH_3), 1.58 (dq, J = 6.4, 1.2 Hz, 2H, CH_2), 2.65 (sept, J = 6.2 Hz, 1H), 3.40 (s, 2H, CH_2), 4.47 (d, J = 6.8 Hz, 1H, NH), 7.30-7.68 (m, 9H), 7.86 (dd, J = 8.4, 2.1 Hz, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 8.91, 8.96, 29.02, 29.06, 30.38, 53.02, 123.14, 123.26, 128.14, 128.30, 128.54, 128.58, 129.11, 129.13, 130.21, 131.24, 142.44, 146.23, 164.20, 164.72; EIMS (*m/z*, %): 305 (M + 1, 100); 304 (M^+, 90); Anal. Calcd for $C_{20}H_{23}N_3$ (305): C, 78.65; H, 6.56; N, 7.59. Found: C, 78.42; H, 7.44; N, 7.52%.

Phenyl-(4-phenyl-3*H*-benzo[b][1,4]diazepin-2-yl)-amine 78d: Yield 84% (1.22 g); Yellow solid; mp 134-135°C; R_f 0.76 (9.5:0.5 hexanes-EtOAc). IR (KBr): 3440, 3040, 2210, 1620, 1322, 1175, 1074 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.48 (s, 2H), 4.88 (brs, 1H, NH), 6.17-7.76 (m, 7H, ArH), 6.54 (dd, J = 8.2, 2.2 Hz, 2H, ArH), 6.62 (d, J = 7.2 Hz, 1H, ArH), 7.86 (dd, J = 8.4, 2.1 Hz, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.10, 30.23, 123.12, 123.24, 128.05, 128.32, 128.46, 128.50, 129.07, 129.32, 130.4, 131.65, 142.54, 146.22, 164.04, 164.68; EIMS (*m/z*, %): 311 (M + 1, 100); 310 (M^+, 90); Anal. Calcd for $C_{21}H_{17}N_3$ (311): C, 79.65; H, 5.54; N, 13.48. Found: C, 79.04; H, 5.43; N, 13.42%.

Methyl-(3-methyl-4-phenyl-3H-benzo[b][1,4]diazepin-2-yl)-amine 78e: Yield 63% (1.02 g); White solid; mp 107-108°C; R*f* 0.74 (9.5:0.5 hexanes-EtOAc). IR (KBr): 3440, 3044, 2218, 1624, 1324, 1172, 1076 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.48 (d, J = 7.2 Hz, 3H, CH_3), 1.77 (q, J = 7.2 Hz, 1H, CH), 2.68 (d, J = 7.2 Hz, 3H, CH_3), 3.42 (s, 1H, CH), 5.88 (distorted q, J = 7.2 Hz, 1H, NH), 7.05-7.44 (m, 9H, ArH), 7.87 (dd, J = 8.2, 2.1 Hz, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 6.4, 27.16, 27.46, 123.14, 123.26, 128.14, 128.30, 128.54 (2), 129.11 (2), 130.11, 131.24, 142.44, 146.23, 164.26, 164.57; EIMS (*m/z*, %): 263 (M + 1, 100); 262 (M^+, 90). Anal. Calcd for $C_{17}H_{17}N_3$ (263): C, 77.65; H, 6.55; N, 15.98. Found: C, 77.57; H, 6.34; N, 15.82%.

Ethyl-(3-methyl-4-phenyl-3*H*-benzo[b][1,4]diazepin-2-yl)-amine 78f: Yield 77% (1.17 g); White solid; mp 128-129°C; R*f* 0.72 (9.5:0.5 hexanes-EtOAc). IR (KBr): 3442, 3041, 2212, 1623, 1325, 1177, 1072 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.10 (t, J = 7.6 Hz, 3H), 2.42 (q, J = 7.6 Hz, 2H), 2.76 (d, J = 7.2 Hz, 3H, CH_3), 1.87 (q, J = 7.2 Hz, 1H, CH), 3.57 (distorted t, J = 6.2, 1.5 Hz, 1H, NH), 7.06-7.66 (m, 9H, ArH), 7.84 (dd, J = 8.2, 2.1 Hz, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.15, 27.46, 36.38, 52.02, 123.14, 123.26, 128.14 (2), 128.54, 128.58, 129.11 (2), 130.11, 131.24, 142.44, 146.23, 164.26, 164.57; EIMS (*m/z*, %): 277 (M + 1, 100); 276 (M^+, 90); Anal. Calcd for $C_{18}H_{19}N_3$ (277): C, 77.95; H, 6.85; N, 15.18. Found: C, 77.54; H, 6.64; N, 15.12%.

Ethyl-[4-(4-methoxy-phenyl)-3*H*-benzo[b][1,4]diazepin-2-yl]-amine 78g: Yield 87% (1.27 g); White solid; mp 128-129°C; R_f 0.75 (9.5:0.5 hexanes-EtOAc). IR(KBr): 3424, 3044, 2218, 1620, 1326, 1171, 1078 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.06 (t, J = 7.6 Hz, 3H), 2.48 (q, J = 7.4 Hz, 2H), 3.24 (s, 3H, OCH_3), 4.06 (t, J = 7.4 Hz, 1H, NH), 6.80 (dd, J= 8.4, 2.6 Hz, 4H, ArH), 7.06-7.86 (m, 4H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.12, 30.36, 36.43, 56.02, 114.03, 114.62, 123.14, 123.26 (2), 128.14 (2), 129.11 (2), 130.11, 142.44, 146.23, 164.26, 164.57 (2); EIMS (*m/z*, %): 293 (M + 1, 100); 292 (M^+, 90); Anal. Calcd for $C_{18}H_{19}N_30$ (293): C, 73.69; H, 6.58; N, 14.31. Found: C, 73.54; H, 6.54; N, 14.12%.

[4-(4-Methoxy-phenyl)-3*H*-benzo[b][1,4]diazepin-2-yl]-phenyl-amine 78h: Yield 78% (1.17 g); Brown crystals; mp 96-97°C; R_f 0.75 (9.5:0.5 hexanes-EtOAc); IR (KBr): 3440, 3043, 2214, 1626, 1322, 1178, 1078m^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.52 (s, 3H, OCH_3), 3.40 (s, 2H, CH_2), 4.43(s, 1H, NH), 6.75-7.76 (m, 9H, Ar-H), 7.87 (dd, J = 8.4, 2.1 Hz, 4H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.6, 56.0, 114.2, 114.12, 115.09, 115.1, 118.3, 123.5, 123.12, 128.3 (2), 129.32 (2), 130.02, 130.04, 142.4, 146.72, 146.87, 164.6, 164.02, 164.30; EIMS (*m/z*, %): 341 (M + 1, 100); 340 (M^+, 90); Anal. Calcd for $C_{22}H_{19}N_3O$ (341): C, 77.48; H, 5.61; N, 12.45. Found: C, 77.42; H, 5.57; N, 12.42%.

[4-(4-Bromo-phenyl)-3*H*-benzo[b][1,4]diazepin-2-yl]-ethyl-amine 78i: Yield 85% (1.34 g); Yellow crystals; mp 120-121°C; R_f 0.76 (9.5:0.5 hexanes-EtOAc). IR (KBr): 3440, 3044, 2212, 1626, 1328, 1175, 1072 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.06 (t, J = 7 Hz, 3H), 2.74 (q, J = 7 Hz, 2H), 3.46 (s, 2H, CH_2), 4.18 (t, J = 7.4 Hz, 1H, NH), 7.22-7.46 (m, 6H, ArH), 8.22 (dd, J = 7.4, 2.2 Hz, 2H, ArH); ^{13}C NMR (100 MHz,

$CDCl_3$): δ 16.23, 30.27, 36.56, 123.15, 123.14, 128.23 (2), 129.30 (2), 130.12, 130.02, 137.8, 142.4, 146.72, 146.87, 150.04; EIMS (*m/z*, %): 341 (M + 1, 100); 340 (M^+, 90); Anal. Calcd for $C_{17}H_{16}BrN_3$ (341): C, 59.68; H, 4.73 N, 12.27. Found: C, 59.53; H, 4.67; N, 12.14%.

[4-(4-Bromo-phenyl)-3*H*-benzo[b][1,4]diazepin-2-yl]-phenyl-amine 78j: Yield 76% (1.25 g); Yellow crystals; mp 152-153°C; R_f 0.76 (9.5:0.5 hexanes-EtOAc). IR (KBr): 3440, 3044, 2218, 1624, 1326, 1175, 1074 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.46 (s, 2H), 4.14 (s, 1H, NH), 6.42 (dd, J = 7.4, 2.2 Hz, 2H, ArH), 7.12-7.46 (m, 7H, ArH), 7.76 (dd, J = 7.4, 2.2 Hz, 4H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.20, 36.56, 115.03, 115.23, 118.07, 123.15, 123.14, 125.12, 128.23, 128.22, 129.30, 129.32, 130.12, 142.4, 146.72, 146.87, 164.7; EIMS (*m/z*, %): 389 (M + 1, 100); 388 (M^+, 90). Anal. Calcd for $C_{21}H_{16}BrN_3$ (389): C, 69.63; H, 4.73 N, 10.24. Found: C, 69.52; H, 4.65; N, 10.18%.

Ethyl-[4-(4-nitro-phenyl)-3*H*-benzo[b][1,4]diazepin-2-yl]-amine 78k:

Yield 75% (1.20 g); Pale Yellow crystals; mp 91-92°C; R_f 0.73 (9.5:0.5 hexanes-EtOAc). IR (KBr): 3443, 3046, 2217, 1629, 1324, 1177, 1073 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.04 (t, J = 7.6 Hz, 3H), 2.12 (t, 1H, NH), 2.74 (q, J = 7.6 Hz, 2H), 3.48 (s, 2H, CH_2), 7.88-7.27 (m, 4H, ArH), 7.72 (dd, J = 7.4, 2.2 Hz, 2H, ArH), 8.24 (dd, J = 7.4, 2.2 Hz, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.5, 30.23, 36.6, 123.5, 123.12, 128.3, 128.12, 129.32, 129.34, 130.02, 130.04, 137.8, 142.4, 146.72, 146.87, 150.04; EIMS (*m/z*, %): 308 (M + 1, 100); 307 (M^+, 90); Anal. Calcd for $C_{17}H_{16}N_4O_2$ (308): C, 66.28; H, 5.23 N, 18.17. Found: C, 66.23; H, 5.27; N, 18.12%.

[4-(4-Nitro-phenyl)-3*H*-benzo[b][1,4]diazepin-2-yl]-phenyl-amine 78l: Yield 82% (1.52 g); Pale Yellow crystals; mp 124-125°C; R_f 0.74 (9.5:0.5 hexanes-EtOAc); IR (KBr): 3440, 3042, 2213, 16249, 1328, 1176, 1072 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.14 (s, 2H), 5.42 (brs, 1H, NH), 7.08-7.27 (m, 9H, ArH), 7.72-8.76 (dd, J = 7.4 Hz, 4H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.20, 115.03, 115.23, 118.07, 123.15 (2), 123.24 (2), 125.12, 128.23, 128.22, 129.30 (2), 129.32 (2), 130.12, 142.4, 142.7, 146.87, 150.7, 164.7; EIMS (*m/z*, %): 356 (M + 1, 100); 355 (M^+, 90); Anal. Calcd for $C_{21}H_{16}N_4O_2$ (356): C, 70.78; H, 4.53 N, 15.72. Found: C, 70.63; H, 4.52; N, 15.52%.

Ethyl-[4-(4-methoxy-phenyl)-3-methyl-3H-benzo[b][1,4]diazepin-2-yl]-amine 78m: Yield 68% (1.04 g); White solid; mp 112-113°C; R_f 0.72 (9.5:0.5 hexanes-EtOAc). IR (KBr): 3446, 3042, 2214, 1622, 1327, 1174, 1078 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.48 (d, J = 7.2 Hz, 3H, CH_3), 1.77 (q, J = 7.2 Hz, 1H, CH), 2.68 (d, J = 7.2 Hz, 3H, CH_3), 1.06 (t, , J = 7.2 Hz, 3H), 3.73 (s, CH_3, OMe), 5.89 (distorted t, 1H, NH), 6.80 (d, J = 7.4 Hz, 2H, ArH), 7.02-7.36 (m, 4H, ArH), 7.58 (d, J = 7.4, Hz, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 5.7, 16.15, 27.46, 36.38, 56.02, 114.1, 114.4, 123.14 (2), 128.14 (2), 128.54, 128.58, 130.11, 130.24, 142.44, 146.23, 164.26, 164.57; EIMS (*m/z*, %): 307 (M + 1, 100); 306 (M^+, 90); Anal. Calcd for $C_{19}H_{21}N_3O$ (307): C, 74.25; H, 6.85; N, 6.89. Found: C, 74.14; H, 6.68; N, 6.12%.

[4-(4-Methoxy-phenyl)-3-methyl-3*H*-benzo[b][1,4]diazepin-2-yl]-phenyl-amine 78n: Yield 76% (1.17 g); Yellow crystals; mp 118-119°C; R_f 0.75 (9.5:0.5 hexanes-EtOAc); IR (KBr): 3440, 3043, 2214, 1626, 1322, 1178, 1078m^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.98 (d, 3H, CH_3), 3.23 (s, 3H, OMe), 4.07 (q, J = 7.2 Hz, 1H, CH), 4.41 (brs, 1H, NH), 6.80 (d, J = 7.4 Hz, 2H, ArH), 7.02-7.36 (m, 8H, ArH), 7.58 (d, J = 7.4, Hz, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 5.7, 16.15, 27.46, 36.38, 56.02, 114.1 (2), 115.12 (2), 118.02, 123.14 (2), 128.14 (2), 128.54, 128.58, 130.11, 130.24, 142.44, 146.23, 146.33, 164.26, 164.57; EIMS (*m/z*, %): 341 (M + 1, 100); 340 (M^+, 90); Anal. Calcd for $C_{23}H_{21}N_3O$ (355): C, 77.48; H, 5.96; N, 11.82. Found: C, 77.42; H, 5.57; N, 11.64%.

General procedure for Preparation of 2-Aryl/alkyl-4-(*N*-cycloamino)-3*H*-benzo[b][1,4]diazepine 80:

A solution of the respective β-oxodithioesters **76** (0.05 mole) was added to a stirring suspension of secondary cycloamine (0.01 mole) in ethanol (10 mL) at room temperature for a period of 5-6 hr. To the reaction mixture of β-oxothioamide **79** formed (monitor by TLC), *o*-phenylenediamine (0.05 mole) is added with catalytic amount of acetic acid (3-5 mL) in presence of dry ethanol (15 mL) and was refluxed to about 90°C for 6-8 hr with constant stirring (monitor by TLC). The reaction mixture is poured after cooling into saturated NH_4Cl solution (50 mL), and extracted with benzene (2x 25 mL). The combined benzene layer was washed with H_2O (3 x 50 mL) and brine (1 x 50 mL), dried over Na_2SO_4 and distilled under reduced pressure to give benzodiazepines **80** which were purified by column chromatography over silica gel using hexane/EtOAc (10:1) as eluent.

Synthesis of 2-Phenyl-4-piperidin-1-yl-3*H*-benzo[b][1,4]diazepine 80a:

To a suspension of respective 3-oxo-3-phenyl-dithiopropionic acid **76**, (2.25 g, 0.025 mole), with piperidine (2.12 g, 0.025 mole) is stirred with 10 mL of ethanol for about 6 hr at room temperature, where 3-Piperidin-4-yl-1-phenyl-3-thioxo-propan-1-one **79a** formed in situ (monitor by TLC). To the reaction mixture, *o*-phenylenediamine (1.64 g, 0.0152 mole) is added with catalytic amount of acetic acid (3-4 mL) in presence of dry ethanol (15 mL) and was refluxed for 6-8 hr with constant stirring (monitor by TLC). The solvent was evaporated under vacuum to afford product **80a** which were purified by column chromatography over silica gel using hexane/EtOAc (10:1) as eluent. Yield 73% (1.12 g); light brown solid; mp 80-81°C; R*f* 0.67 (9.5:0.5 hexanes-EtOAc); IR (KBr): 3319, 3027, 1617, 1602, 1326, 1216, 1129, 1072 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.56 (q, $J = 7.2$ Hz, 2H), 2.75 (t, $J = 7.6$ Hz, 2H), 4.42 (s, 2H), 7.28-7.36 (m, 7H), 7.68 (d, $J = 7.2$ Hz, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.12, 25.14, 25.23, 28.22, 46.50, 46.52, 123.22, 123.32, 128.30, 128.32, 128.6, 129.12, 129.14, 131.2, 142.7, 146.11, 164.61, 164.62; EIMS (*m/z*, %): 303 (M + 1, 100); 302 (M^+, 90); Anal. Calcd for $C_{20}H_{21}N_3$ (303): C, 79.17; H, 6.68; N, 13.86. Found: C, 79.13; H, 6.57; N, 13.79%. Compounds **80b-n** were synthesized similarly.

2-Morpholin-4-yl-4-phenyl-3*H*-benzo[b][1,4]diazepine 80b: Yield 74% (1.06 g); pale yellow crystals; mp 94-95°C; R*f* 0.72 (9.5:0.5 hexanes-EtOAc). IR(KBr): 3315, 3024, 1616, 1605, 1328, 1214, 1125, 1077 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.40 (s, 2H), 2.86 (t, $J = 7.6$ Hz, 2H), 3.75 (t, $J = 7.6$ Hz, 2H), 7.28-7.36 (m, 7H, ArH), 7.68 (d, $J = 7.2$ Hz, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.71, 28.12, 50.71, 50.72, 71.62, 79.92, 123.22 (2), 128.30 (2), 128.6, 129.12 (2), 131.2, 142.7, 146.11, 164.61, 164.62. 164.67. EIMS (*m/z*, %): 305 (M + 1, 100); 304 (M^+, 90). Anal. Calcd for $C_{19}H_{19}N_3O$ (305): C, 74.77; H, 6.28; N, 13.76. Found: C, 74.73; H, 6.24; N, 13.72%.

2-Phenyl-4-(4-phenyl-piperazin-1-yl)-3*H*-benzo[b][1,4]diazepine 80c:

Yield 62% (0.86 g); pale yellow crystals; mp 114-115°C; R*f* 0.74 (9.5:0.5 hexanes-EtOAc). IR(KBr): 3314, 3028, 1612, 1605, 1324, 1218, 1124, 1074 cm^{-1}. ^1H NMR

(400 MHz, $CDCl_3$): δ 2.42 (s, 2H), 2.86 (t, J = 7.6 Hz, 2H), 3.75 (t, J = 7.6 Hz, 2H), 6.60 (q, J = 7.2 Hz, 1H), 6.56 (d, J = 7.2 Hz, 2H, ArH), 6.88-7.62 (m, 7H, ArH), 7.96 (d, J = 7.2 Hz, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.12, 49.30, 49.32, 58.61, 58.62, 113.11 (2), 118.21, 123.10, 123.12, 128.30 (2), 128.6, 129.12 (2), 130.23, 131.2, 142.7, 144.50, 146.11, 164.61, 164.62; EIMS (*m/z*, %): 380 (M + 1, 100); 379 (M^+, 90). Anal. Calcd for $C_{25}H_{24}N_4$ (380): C, 78.87; H, 6.38; N, 14.76. Found: C, 78.73; H, 6.24; N, 14.72%.

2-Phenyl-4-(4-pyridin-2-yl-piperazin-1-yl)-3*H*-benzo[b][1,4]diazepine 80d: Yield 58% (0.78 g); colourless crystals; mp 127-128°C; R*f* 0.74 (9.5:0.5 hexanes-EtOAc). IR (KBr): 3322, 3022, 1614, 1602, 1326, 1224, 1124, 1076 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.41 (s, 2H), 2.78 (t, J = 7.2 Hz, 2H), 3.18 (t, J = 7 Hz, 2H), 6.62 (d, J = 7.2 Hz, 2H), 7.12 (m, 10H, ArH), 8.14 (d, J = 7.2 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.12, 49.22, 49.25, 58.61 (2), 108.90, 113.11, 118.21, 123.10, 123.12, 128.30 (2), 128.42 (2), 129.02, 130.23, 131.02, 138.4, 142.17, 146.15, 148.91, 161.20, 164.21, 164.62. EIMS (*m/z*, %): 381 (M + 1, 100); 380 (M^+, 90). Anal. Calcd for $C_{24}H_{23}N_5$ (381): C, 75.57; H, 6.25; N, 18.36. Found: C, 75.37; H, 6.14; N, 18.12%.

3-Methyl-2-phenyl-4-piperidin-1-yl-3*H*-benzo[b][1,4]diazepine 80e: Yield 63% (1.02 g); pale yellow solid; mp 121-122°C; R*f* 0.74 (9.5:0.5 hexanes-EtOAc). IR (KBr): 3041, 2294, 2212, 1623, 1325, 1214, 1128, 1072 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.09 (d, J = 5.2 Hz, 3H), 1.50 (t, J = 7.2 Hz, 2H), 2.75 (t, J = 7.6 Hz, 2H), 3.52 (q, J = 7.2 Hz, 1H, CH), 7.06-7.36 (m, 7H, ArH), 7.87 (d, J = 7.2 Hz, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 5.8, 25.20, 25.73 (2), 25.96, 46.78, 46.82, 123.14, 123.26, 128.14 (2), 128.54, 128.58, 129.11 (2), 130.11, 131.24, 142.44, 146.23, 164.26, 164.57; EIMS (*m/z*, %): 317 (M + 1, 100); 316 (M^+, 90); Anal. Calcd for $C_{21}H_{23}N_3$ (317): C, 79.45; H, 7.30; N, 13.28. Found: C, 79.34; H, 7.14; N, 13.12%.

3-Methyl-2-morpholin-4-yl-4-phenyl-3*H*-benzo[b][1,4]diazepine 80f: Yield 77% (1.22 g); pale yellow solid; mp 101-102°C; R_f 0.74 (9.5:0.5 hexanes-EtOAc). IR (KBr): 3042, 2290, 2214, 1626, 1324, 1212, 1126, 1074 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.09 (d, J = 5.4 Hz, 3H), 1.53 (t, J = 7.2 Hz, 2H), 2.77 (t, J = 7.6 Hz, 2H), 3.53 (q, J = 7.2 Hz, 1H, CH), 7.04-7.38 (m, 7H, ArH), 7.78 (d, J = 7.2 Hz, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 5.5, 25.20, 51.23 (2), 71.04, 71.06, 123.14 (2), 128.14 (2), 128.54, 128.58, 129.11, 129.13, 130.11, 131.24, 142.44, 146.23, 164.26, 164.57. EIMS (*m/z*, %): 319 (M + 1, 100); 318 (M^+, 90). Anal. Calcd for $C_{20}H_{21}N_3O$ (319): C, 75.21; H, 6.63; N, 13.18. Found: C, 75.14; H, 6.57; N, 13.12%.

2-(4-Methoxy-phenyl)-4-piperidin-1-yl-3*H*-benzo[b][1,4]diazepine 80g:
Yield 87% (1.42 g); yellow solid; mp 126-127°C; R_f 0.72 (9.5:0.5 hexanes-EtOAc); IR (KBr): 3042, 2290, 2214, 1626, 1324, 1212, 1127, 1070 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.53 (t, J = 7.2 Hz, 2H), 2.77 (t, J = 7.6 Hz, 2H), 3.72 (s, 3H, OMe), 4.22 (s, 2H, CH_2), 6.60 (d, J = 7.2 Hz, 2H), 7.04-7.38 (m, 4H, ArH), 7.78 (d, J = 7.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.20, 25.73, 25.74, 28.94, 46.78, 46.82, 56.04, 114.12 (2), 123.14, 123.26, 128.14 (2), 128.54, 128.58, 129.11 (2), 130.11, 131.24, 142.44, 146.23, 164.26, 164.57; EIMS (*m/z*, %): 333 (M + 1, 100); 332 (M^+, 90); Anal. Calcd for $C_{21}H_{23}N_3O$ (333): C, 75.65; H, 6.95; N, 12.60. Found: C, 75.44; H, 6.74; N, 12.42%.

2-(4-Methoxy-phenyl)-4-morpholin-4-yl-3*H*-benzo[b][1,4]diazepine 80h: Yield 88% (1.52 g); light brown crystals; mp 91-92°C; R*f* 0.67 (9.5:0.5 hexanes-EtOAc); IR(KBr): 3317, 3022, 1617, 1602, 1322, 1217, 1127, 1074 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 2.73 (t, *J* = 7.2 Hz, 2H), 3.67 (t, *J* = 7.6 Hz, 2H), 3.82 (brs, 3H, OMe), 4.21 (s, 2H, CH_2), 6.60 (d, *J* = 7.2 Hz, 2H), 7.04-7.38 (m, 4H, ArH), 7.78 (d, *J* = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 28.12, 50.71, 50.72, 71.62, 79.92, 123.22, 123.32, 128.30, 128.32, 128.6, 129.12, 129.14, 131.2, 142.7, 146.11, 164.61, 164.62. 164.67; EIMS (*m/z*, %): 335 (M + 1, 100); 334 (M^+, 90). Anal. Calcd for $C_{20}H_{21}N_3O_2$ (335): C, 71.67; H, 6.21; N, 12.53. Found: C, 71.51; H, 6.20; N, 12.47%.

2-(4-Bromo-phenyl)-4-(4-phenyl-piperazin-1-yl)-3*H*-benzo[b][1,4]diazepine 80i: Yield 65% (0.97 g); brown crystals; mp 132-133°C; R*f* 0.76 (9.5:0.5 hexanes-EtOAc); IR(KBr): 3318, 3028, 1614, 1605, 1324, 1216, 1128, 1078 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 2.86 (t, *J* = 7.4 Hz, 2H), 3.75 (t, *J* = 7.4 Hz, 2H), 4.12 (s, 2H), 6.60 (d, *J* = 7.2 Hz, 3H, ArH), 7.15-7.82 (m, 11H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 28.12, 49.25, 49.32, 58.61, 58.62, 113.11, 113.14, 118.21, 123.10, 123.12, 125.4, 128.30, 128.32, 128.6, 129.12, 129.14, 130.23, 131.02, 142.17, 144.50, 146.15, 164.60, 164.64; EIMS (*m/z*, %): 458 (M + 1, 100); 457 (M^+, 90); Anal. Calcd for $C_{25}H_{23}BrN_4$ (458): C, 65.37; H, 5.25; N, 12.26. Found: C, 65.17; H, 5.14; N, 12.12%.

2-(4-Bromo-phenyl)-4-(4-pyridin-2-yl-piperazin-1-yl)-3*H*-benzo[b][1,4] diazepine 80j: Yield 76% (1.77 g); Light brown solid; mp 97-98°C; R*f* 0.76 (9.5:0.5 hexanes-EtOAc). IR (KBr): 3320, 3022, 1612, 1602, 1328, 1220, 1124, 1074 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 2.75 (t, *J* = 7.4 Hz, 2H), 3.72 (t, *J* = 7.4 Hz, 2H), 4.32 (s, 2H), 6.60 (d, *J* = 7.2 Hz, 3H, ArH), 7.12 (m, 9H, ArH), 8.12 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR

(100 MHz, $CDCl_3$): δ 28.12, 49.25 (2), 58.61 (2), 108.90, 113.11, 118.21, 123.10 (2), 125.4, 128.30 (2), 130.23, 131.02 (2), 131.89, 131.91, 138.4, 142.17, 146.15, 148.21, 161.20, 164.01, 164.64; EIMS (*m/z*, %): 458 (M + 1, 100); 457 (M^+, 90). Anal. Calcd for $C_{25}H_{23}BrN_4$ (460): C, 65.37; H, 5.25; N, 12.26. Found: C, 65.17; H, 5.14; N, 12.12%.

2-(4-Nitro-phenyl)-4-piperidin-1-yl-3*H*-benzo[b][1,4]diazepine 80k:

Yield 85% (1.42 g); brown crystals; mp 102-103°C; R_f 0.69 (9.5:0.5 hexanes-EtOAc). IR(KBr): 3319, 3028, 1613, 1608, 1329, 1214, 1129, 1077 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.58 (t, J = 7.2 Hz, 2H), 2.77 (t, J = 7Hz, 2H), 4.14 (s, 2H), 7.22 (m, 4H), 7.72 (d, J = 8.4 Hz, 2H), 8.32 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.12, 25.14, 25.23, 28.22, 46.50, 46.52, 123.22, 123.32, 128.30, 128.32, 128.6, 129.12, 129.14, 131.2, 142.7, 146.11, 150.2, 164.61, 164.62; EIMS (*m/z*, %): 348 (M + 1, 100); 347 (M^+, 90); Anal. Calcd for $C_{20}H_{20}N_4O_2$ (348): C, 68.95; H, 5.79; N, 16.05. Found: C, 68.75; H, 5.72; N, 16.02%.

2-Morpholin-4-yl-4-(4-nitro-phenyl)-3*H*-benzo[b][1,4]diazepine 80l:

Yield 82% (1.31 g); brown crystals; mp 152-153°C; R_f 0.72 (9.5:0.5 hexanes-EtOAc); IR(KBr): 3314, 3020, 1616, 1606, 1323, 1212, 1123, 1074 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.58 (t, J = 7.2 Hz, 2H), 2.77 (t, J = 7Hz, 2H), 4.14 (s, 2H), 7.22 (m, 4H, ArH), 7.72 (d, J = 8.4 Hz, 2H, ArH), 8.22 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.22, 50.71, 50.72, 71.12, 71.18, 123.22, 123.32, 128.30, 128.32, 128.6, 129.12, 129.14, 131.2, 137.02, 142.7, 146.11, 150.2, 164.61, 164.62. EIMS (*m/z*, %): 350 (M + 1, 100); 349 (M^+, 90); Anal. Calcd for $C_{19}H_{18}N_4O_3$ (350): C, 65.15; H, 5.19; N, 15.95. Found: C, 65.11; H, 5.12; N, 15.82%.

2-(4-Methoxy-phenyl)-3-methyl-4-piperidin-1-yl-3*H*-benzo[b][1,4]diazepine 80m: Yield 68% (1.01 g); pale yellow crystals; mp 142-143°C; R*f* 0.68 (9.5:0.5 hexanes-EtOAc); IR(KBr): 3310, 3021, 1611, 1604, 1327, 1218, 1127, 1076 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 1.12 (d, *J* = 5.4 Hz, 3H), 1.53 (t, *J* = 7.2 Hz, 2H), 2.62 (t, *J* = 7.6 Hz, 2H), 3.56 (q, *J* = 7.2 Hz, 1H, CH), 3.87 (brs, 3H, OMe), 6.43 (d, *J* = 7.2 Hz, 2H, ArH), 7.04-7.38 (m, 7H, ArH), 7.78 (d, *J* = 7.2 Hz, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 5.84, 25.20 (2), 25.74, 25.92, 56.22, 71.62 (2), 114.22 (2), 123.22, 123.32, 123.26, 128.30 (2), 130.03 (2), 131.2, 142.7, 146.11, 164.56, 164.61 EIMS (*m/z*, %): 347 (M + 1, 100); 346 (M$^+$, 90). Anal. Calcd for $C_{22}H_{25}N_3O$ (347): C, 76.06; H, 7.23; N, 12.12. Found: C, 76.01; H, 7.17; N, 12.01%.

2-(4-Methoxy-phenyl)-3-methyl-4-morpholin-4-yl-3*H*-benzo[b][1,4]diazepine 80n: Yield 71% (1.14 g); pale yellow crystals; mp 97-98°C; R*f* 0.64 (9.5:0.5 hexanes-EtOAc). IR(KBr): 3318, 3024, 1617, 1606, 1323, 1216, 1129, 1078 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 1.10 (d, *J* = 5.4 Hz, 3H), 2.56 (q, *J* = 7.2 Hz, 1H, CH), 2.94 (t, *J* = 7.2 Hz, 2H), 3.62 (t, *J* = 7.6 Hz, 2H), 3.87 (s, 3H, OMe), 6.43 (d, *J* = 8.2 Hz, 2H, ArH), 7.04-7.38 (m, 4H, ArH), 7.78 (d, *J* = 8.2 Hz, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 5.84, 25.20, 51.22, 51.24, 56.78, 71.62, 71.92, 114.22, 114.24, 123.22, 123.32, 123.26, 128.30, 128.32, 130.03, 130.05, 142.7, 146.11, 164.56, 164.61, 164.62; EIMS (*m/z*, %): 349 (M + 1, 100); 348 (M$^+$, 90). Anal. Calcd for $C_{21}H_{23}N_3O_2$ (349): C, 72.18; H, 6.63; N, 12.23. Found: C, 72.15; H, 6.57; N, 12.21%.

III.4. REFERENCES

1. Watthey, Stanton, Peet *Heterocyclic Compounds, Azepines Volume 43 Part 2 Interscience.*
2. (a) *The Benzodiazepines. From Molecular Biology to Clinical Practice*; Costa, E., Ed.; Raven Press: New York, 1983.

   (b) Bradwejn, J. Benzodiazepines for the treatment of panic disorder and generalized anxiety disorder: Clinical issues and future directions. *Can. J. Psychiatry* **1993**, *38*, 109-113.
3. (a) Schutz, H. *Benzodiazepines*; Springer: Heidelberg, 1982; Vol. 2. 240;

   (b) Smalley, R. K. Comprehensive Organic Chemistry; Barton, D., Ollis, W. E., Eds.; Pergamon: Oxford, 1979; Vol.4.p. 600;
4. (a) Landquist, J.K. In Comprehensive Heterocyclic Chemistry: Katritzky, A. R., Russ, C. N., Eds: Pergamon: Oxford, 1984; Vol. 1, p.166; (b) Randall, L.O.; Kamel, B. *Benzodiazepines*; Gorattini, S., Mussini, E., Randall, L. O., Eds.; Raven Press; New York. 1973; p.27 and references cited therein.
5. (a) Leimgruber, W.; Stefanovic, V.; Schenker, F.; Harr, A.; Berger, J. *J. Am. Chem. Soc.***1965**, *87*, 5791;(b) Leimgruber, W.; Batcho, A. D.; Schenker, F. *J. Am. Chem. Soc.***1965**, *87*, 5793.
6. DeBaun, J. R.; Pallos, F. M., Baker. D. R. 5-Furoyl02,24-trimethyl-2,5-dihydro-1H-1,5-benzodiazepine as an anti-inflammatory agent. U.S. Patent 3,978, 227, 1976 Chem.Abstr.1977, *86*, 5498d.
7. (a) Kukla, M. J.; Breslin, H. J.; Diamond, C. J.; Grous, P. P.; Ho, C. Y.; et. al. *J. Med. Chem.* **1991**, *34*, 3187; (b) Parker, K. A.; Coburn, C. A. *J. Org. Chem.* **1992**, *57*, 97.

8. Evans, B. E.; Rittle, K. E.; Bock, M. G.; DiPardo, R. M.; Freidinger R. M.; Whitter, W. L.; Lundell, G. F.; Veber, D. F.; Anderson, P. S.; Chang, R. S. L.; Lotti, V. J.; Cerino, D. J.; Chen, T. B.; Kling, P. J.; Kunkel, K. A.; Springer, J. P.; Hirshfield, J. *J. Med. Chem.* **1988**, *31*, 2235.
9. (a) Evans, B.; Pipe, A.; Clark, L.; Banks, M. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1297;(b) Wyatt, P. G.; Allen, M. J.; Chilcott, J.; Hickin, G.; Miller, N. D.; Woollard, P. M. *Bioorg. Med. Chem. Lett.* **2001**, *11* 1301.
10. Stevens, S. Y.; Bunin, B. A.; Plunkett, M. J.; Swanson, P. C.; Ellman, J. A.; Glick, G. D. *J. Am. Chem. Soc.* **1996**, *118*, 10650.
11. Ding, C. Z.; Batorsky, R.; Bhide. R.; Chao, H. J.; Cho, Y.; Chong, S.; et.al. *J. Med.Chem.* **1999**, *42*, 5241.
12. Strenbach, L. H. *J. Med. Chem.* **1979**, *22*, 1.
13. Di Fabio, R.; Capelli, A. M.; Conti, N.; Cugola, A.; Feriani, A.; Gastaldi, P.; Gaviraghi, G.; Hewkin, C. T.; Micheli, F.; Missio, A.; Mugnaini, M.; Pecunioso, A.; Quaglia, A. M.; Ratite, E.; Rossi, L.; Tedesco, G.; Trist, D. G.; Reggiani, A. *J. Med. Chem.***1997**, *40*, 841.
14. For reviews, see e.g., (a) Archer, G. A.; Sternbach, L. H. *Chem.Rev.* **1968**, *68*, 747–784. (b) Popp, F. D.; Noble, A. C. *Adv.Heterocycl. Chem.* **1967**, *8*, 21–82. (c) Sternbach, L. H. *Angew.Chem.* Int. Ed. Engl. **1971**, *10,* 34–43. (b) Bremner, J. B. *In Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, **1996**; Vol. 9, pp 183–189.
15. For synthetic and pharmacological studies, see e.g., (a) Parker, K. A.; Dermatakis, A. *J. Org. Chem.* **1997**, *62*, 4164–4167. (b) Hargrave, K. D.; Schmidt, G.; Engel, W.; Austel, V. Patent Application: US 91-650141 19910204. Patent Priority: US 89-340937 19890420; US 89-372728 19890628; US 89-438922 19891117; US

90-600554 19901019.

16. (a) Mane, R. A.; Ingle, D. B. *Indian J. Chem., Sect. B* **1982**, *21B*, 973–974. (b) Jadhav, K. P.; Ingle, D. B. *Indian J. Chem., Sect. B* **1983**, *22B*, 180–182.
17. (a) Savelli, F.; Boido, A.; Vazzana, I.; Sparatore, F. *J Heterocycl. Chem.* **1987**, *24*, 1709; (b) Savelli, F.; Boido, A.; Satta, M.; Peana, A.; Marzano, C. *Il Farmaco* **1994**, *49*, 259; (c) Savelli, F.; Boido, A.; Damonte, G. *J. Heterocycl. Chem.* **1996**, *33*, 1737.
18. (a) Barchet, von R.; Merz, K. W. *Tetrahedron Lett.* **1964**, *33*, 2239; (b) Israel, M.; Jones, L. C.; Modest, E. J. *J. Heterocycl. Chem.* **1967**, *4*, 659; (c) Israel, M.; Jones, L. C.; Modest, E. J. *Tetrahedron Lett.* **1968**, *46*, 4811;
19. (a) Israel, M.; Jones, L. C. *J. Heterocycl. Chem.* **1973**, *10*, 201; (b) Savelli, F.; Boido, A.; Piacente, S. *J. Heterocycl. Chem.* **2001**, *38*, 659.
20. Israel, M.; Jones, L. C. *J. Heterocycl. Chem.* **1969**, *6*, 735.
21. Balakrishan, M. S.; Kaboudin, B. *Tetrahedron Lett.* **2001**, 42, 1127.
22. Stahlofen, P.; Ried, W. *Chem. Ber.* **1957**, 90, 815-824.
23. Ried, W.; Torinus, E. *Chem. Ber.* **1959**, 92, 2902-2916.
24. Herbert, J. A. L.; Suschitzky, H. J. *J. Chem. Soc., Perkin Trans.* 1. **1974**, 2657-2661.
25. Morals, H. R.; Bulbarela, A.; Contreras, R. *Heterocycles* **1986**, 24, 135-139.
26. D. Nardi, A. Tajana, and S. Rossi, *J. Heterocyl.Chem.*, **1973**,10, 815.
27. (a) Sexton, W. A. *J. Chem. Soc.*, **1942**, 303; 43,1298; (b) Rossi, A.; Hunger, A.; Kebrle, J. and Hoffmann, K. *Helv.Chim.Acta*, **1960**, 43, 1298; (c) Israel M. and Jones, L.C. *J. Heterocycl.Chem.*, **1969**,6, 735.
28. An, L-T.; Ding, F-Q.; Zou, J-P. and Lu, X-H. *Synthetic Communications*, **2008,** 38, 1259-1267.

29. (a) Balogh, M.; Laszlo, P. Organic Chemistry using Clays; Springer: Berliln, 1993;(b) Varma, R. S. Clay and clay-supported reagents in organic synthesis. *Tetrahedron* **2002**, *58*, 1235–1255.

30. (a) Chauhan, S.; Kumar, A.; Srinivas, K. A. *Synth. Commun.* **2004**, *34*, 2673–2680; (b) Azizian, J.; Karimi, A. R.; Kazemizadeh, Z.; Mohammadi, A. A.; Mohammadizadeh, M. R. *Tetrahedron Lett.* **2005**, *46*, 6155–6157; (c) Shaabani, A.; Teimouri, M.B.; Samadi, S.; Soleimani, K. *Synth. Commun.* **2005**, *35*, 535–541;(d) Crisostomo, F. R. P.; Carrillo, R.; Martin, T.; Martin, V. S. *Tetrahedron Lett.* **2005**, *46*, 2829–2832.

31. (a) Shinde, A. B.; Shrigadi, N. B.; Samant, S. D. *Appl. Catal. A—Gen.* **2004**, *276*, 5–8; (b) Kameyama, H.; Narumi, F.; Hattori, T.; Kameyama, H. *J. Mol. Catal. A—Chem.* **2006**, *258* (1–2), 172–177.

32. Chari, M.A.; Shobha, D. and Syamasundar, K. *J. Heterocyclic Chem.*, **2007,** 44, 929.

33. Ushirogochi, A.; Tominaga, Y.; Matsuda Y. and Kobayashi, G. *Heterocycles* **1980,** *14*, 7-10

34. Tominaga, Y.; Fujito, H.; Norisue, N.; Ushirogochi, A.; Matsuda Y. and Kobayashi, G. *Yakugaku Zasshi* **1980,** *100,* 699-705; *Chem. Abstr.* **1982,** *94,* 47285c.

35. Mazaahir Kidwai and Poonam Mothsra, *Synthetic Communications*, **2006,** 36, 817-824.

36. (a) Chimirri, A.; Grasso, S.; Ortana, R.; Romeo, G.; Zappala, M. *J. Heterocycl. Chem.* **1990**. 27 (1), 371-374. (b) Aversa, M. C.; Ferlazzo, A.; Giannetto, P.; Kohnke, F. I. *Synthesis* **1986** (3), 230-231; (c) Reddy, K. V. V.; Rao, P. S.; Ashok, D. *Synth. Commun.* **2000,** *30* (10), 1825-1836.

37. (a) Dalgard, L.; Jensen, L.; Lawesson, S. O. *Tetrahedron* **1974**, *39*, 93.

(b) Ramdas, S, R.; Srinivasan, P. S.; Ramachandran, J.; Sastry, V. V. S. K. *Synthesis* **1983**, 605.

38. (a) Voss, J. Synthesis of Thioesters and Thiolactones, In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1990; Vol. 6, pp 435-460.

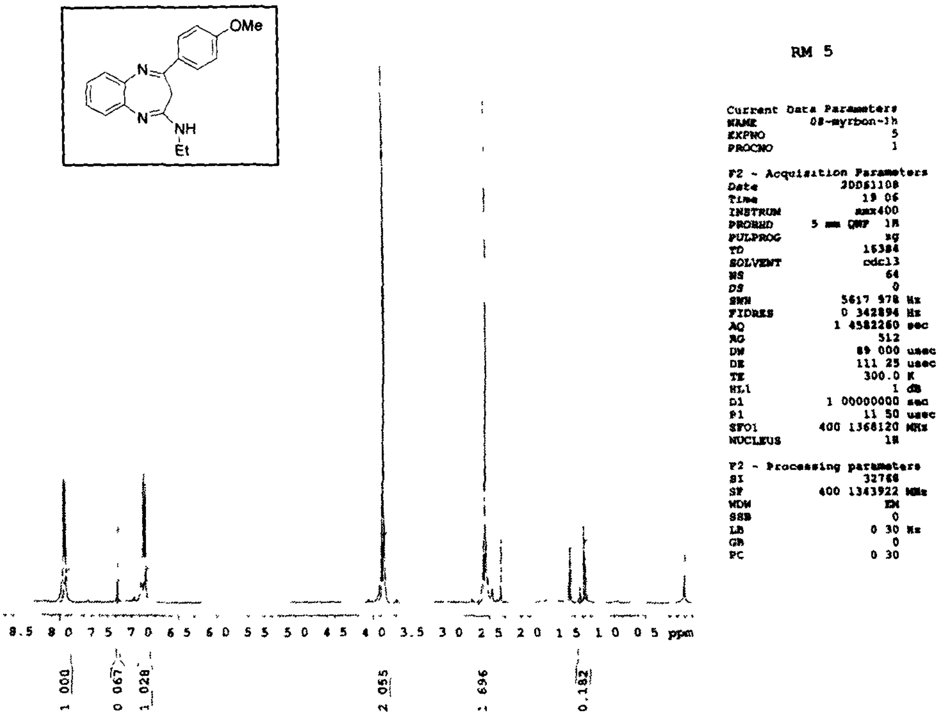
(b)Nair, S. K.; Samuel, R.; Asokan, C. V. *Synthesis* **2001**, 573.

39. (a) Nair, S. K.; Asokan, C. V. *Synth. Commun.* **2001**, 22, 1453.

(b) Nair, S. K.; Asokan, C. V. *Synth. Commun.* **1999**, 29, 791.

40. Singh, G.; Bhattacharjee, S. S.; Ila, H.; Junjappa, H. *Synthesis* **1982**, 693-694.

41. Haugwitz, R. D. *U.S. Patent* 3, 660, 412, May **1972**.



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RM 5

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EXPNO                    5
PROCNO                   1

F2 - Acquisition Parameters
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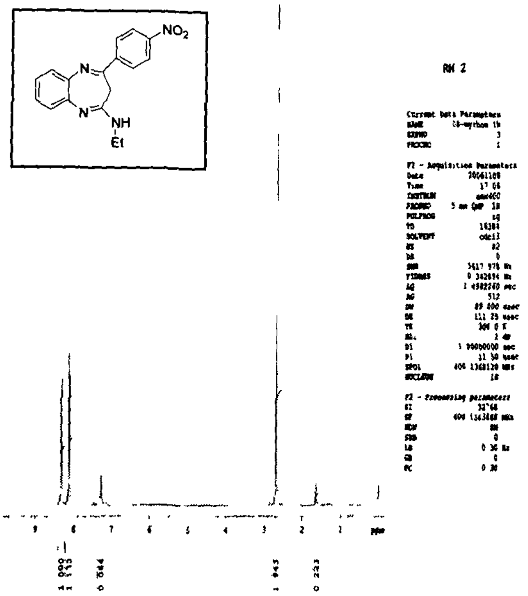
Time                 19 06
INSTRUM             amx400
PROBHD       5 mm QNP  1H
PULPROG                 zg
TD                   16384
SOLVENT              cdcl3
NS                      64
DS                       0
SWH             5617 978 Hz
FIDRES          0 342894 Hz
AQ             1 4582260 sec
RG                     512
DW                  89 000 usec
DE                  111 25 usec
TE                   300.0 K
HL1                      1 dB
D1            1 00000000 sec
P1                   11 50 usec
SFO1         400 1368120 MHz
NUCLEUS                 1H

F2 - Processing parameters
SI                   32768
SF           400 1343922 MHz
WDW                     EM
SSB                      0
LB                    0 30 Hz
GB                       0
PC                    0 30
```

Figure 11. ^{1}H NMR spectra of compound **78g**.



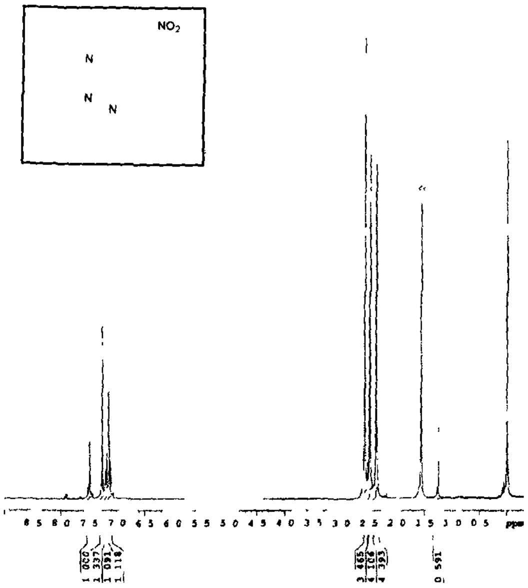


Figure 12. ^{1}H NMR spectra of compound **78k**. Figure 13. ^{1}H NMR spectra of compound **80k**.

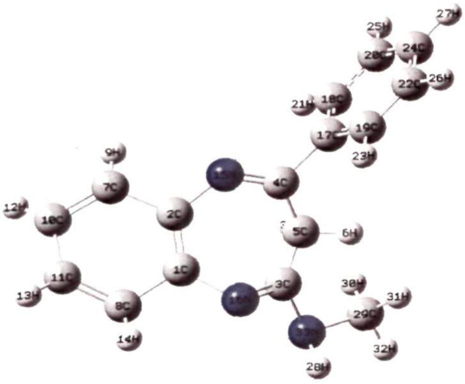


Figure 14: Compound **78a**.

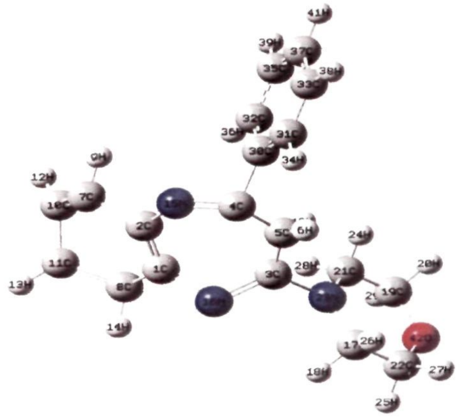


Figure 15: Compound **80b**.

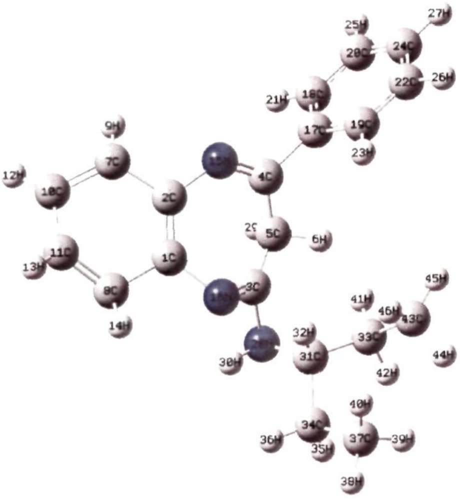


Figure 16: Compound **78c**.

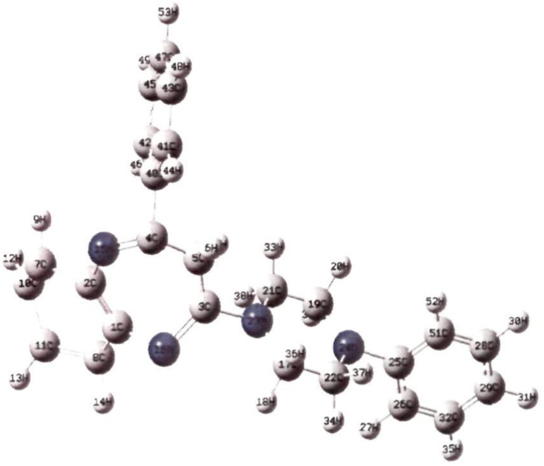


Figure 17: Compound **80c**.

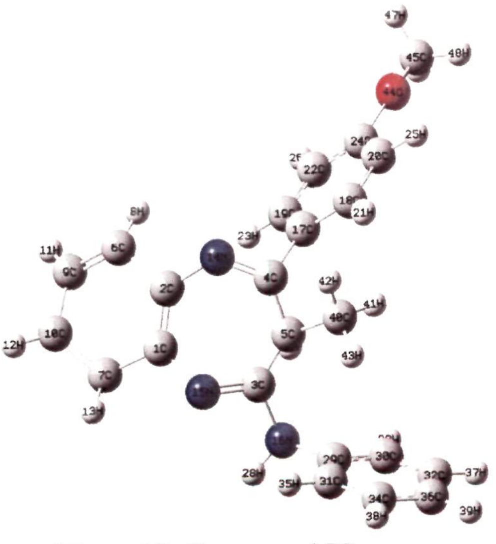


Figure 18: Compound **78n**.

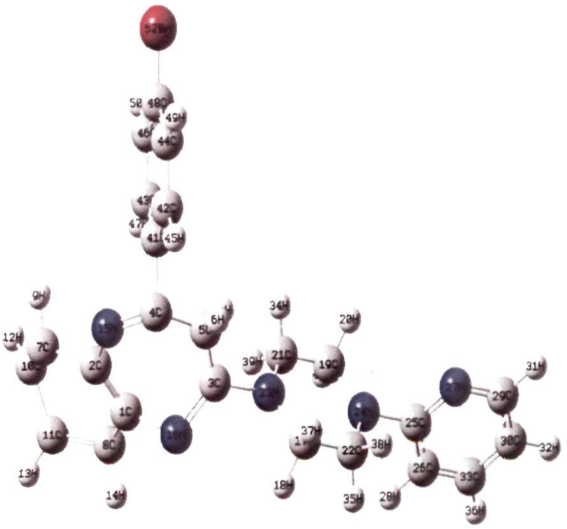


Figure 19: Compound **80j**.

Gaussview 3D models

CHAPTER IV

A FACILE SYNTHESIS OF 1-ARYL-3-(*N*-ALKYL/ARYL/CYCLOAMINO)-5-SUBSTITUTED PYRAZOLES USING *β*-OXOTHIOAMIDE GENERATED FROM *β*-OXODITHIOESTERS

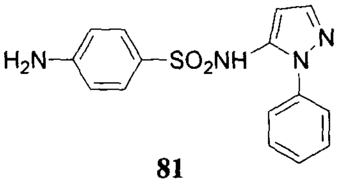
CHAPTER IV

A facile synthesis of 1-Aryl-3-(*N*-alkyl/aryl/cycloamino)-5-arylsubstituted pyrazoles using the *β*-oxothioamide generated from *β*-oxodithioester

IV. 1 INTRODUCTION

Pyrazoles and its derivatives which formed a large class of the *N*-heterocycles have attracted considerable attention in the last two decades since they have become fairly accessible. This class of compounds, like many *N*-heterocycles possess important biological and pharmaceutical activities and exhibit diverse properties.[1] The synthesis of 1-*N*-arylpyrazole ring system continues to attract considerable interest because of its importance in pharmaceutical and agrochemical industry.[2] Drugs such as Celebrex[3] and Viagra[4] contain the 1-*N*-arylpyrazole moiety. Sulfonamides based on pyrazole are of particular interest e.g. Orisul **81** which has a prolonged bacteriostatic action. Compounds such as Isolan **82**, Pyrolan **83** and Pyrazoxon **84** which are too toxic for pharmacology are used as systematic insecticides.[5] Other compounds containing 1-*N*-

arylpyrazole moiety have been shown to exhibit antihyperglycemic, analgesic, anti-inflammatory, sedative, hypnotic activities[2-6] and some of these compounds have emerged as potent ligands for estrogen receptors.[6]



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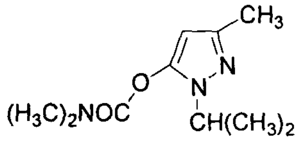

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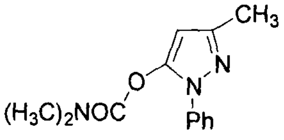

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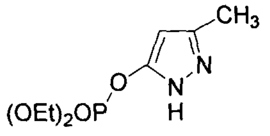
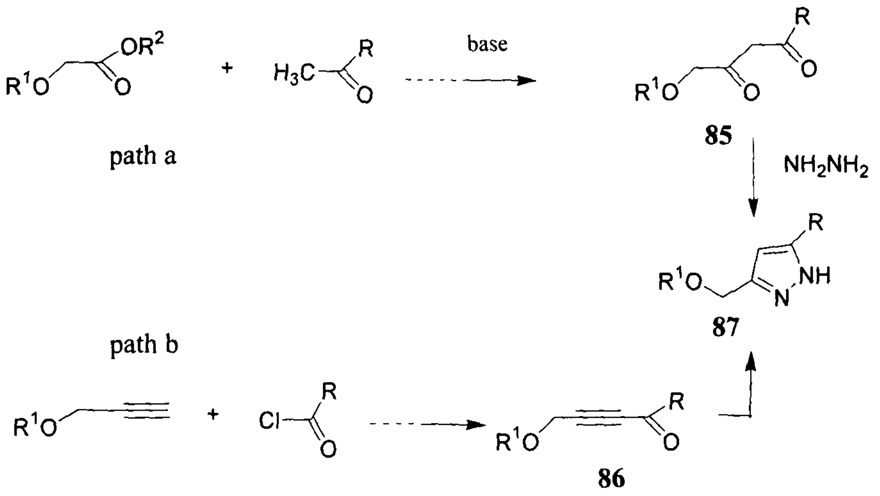


84

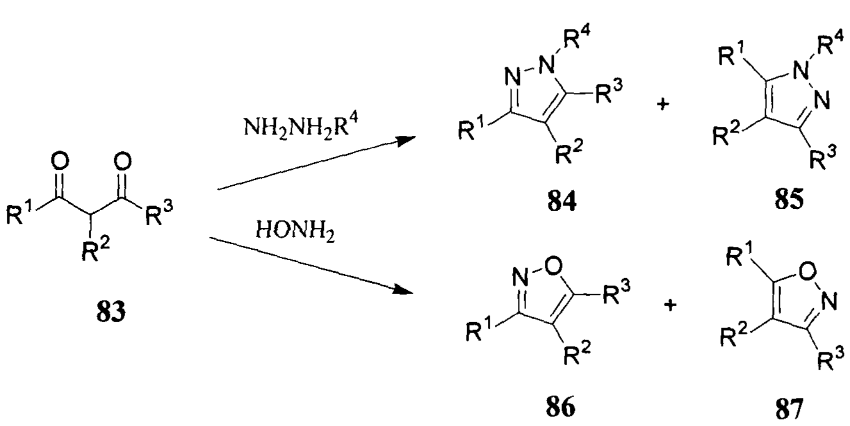
Our literature survey revealed that a number of synthetic methods have been developed for the construction of this important scaffold. An important method for the synthesis of substituted 1-*N*-arylpyrazoles involves cyclocondensation of 1,3-dicarbonyl compounds and their equivalent 1,3-dienophilic synthons such as propargylic ketone, β-dialkylamino/alkoxy/chloroketones with arylhydrazines[5,6,7] 1,3-dipolar cycloaddition of diazoalkanes with alkynes,[8] the reaction of hydrazines with α,β-unsaturated ketones and others assisted by Microwave induced techniques[9a] and several other methods.[9]

The most common route for the synthesis of pyrazoles with different substituents at C3 and C5 is by the condensation of hydrazine with an unsymmetrical 1,3-diketone **85** *path a* (Scheme 21).[13,14-16] Formation of the requisite 1,3-diketone would require selective, directed Claisen condensation between compounds such as those shown in *path a*. However, it was discovered[14,15] that acetylenic ketones **86** can react with hydrazine derivatives in *path b* to give pyrazoles **87**.[16-18]



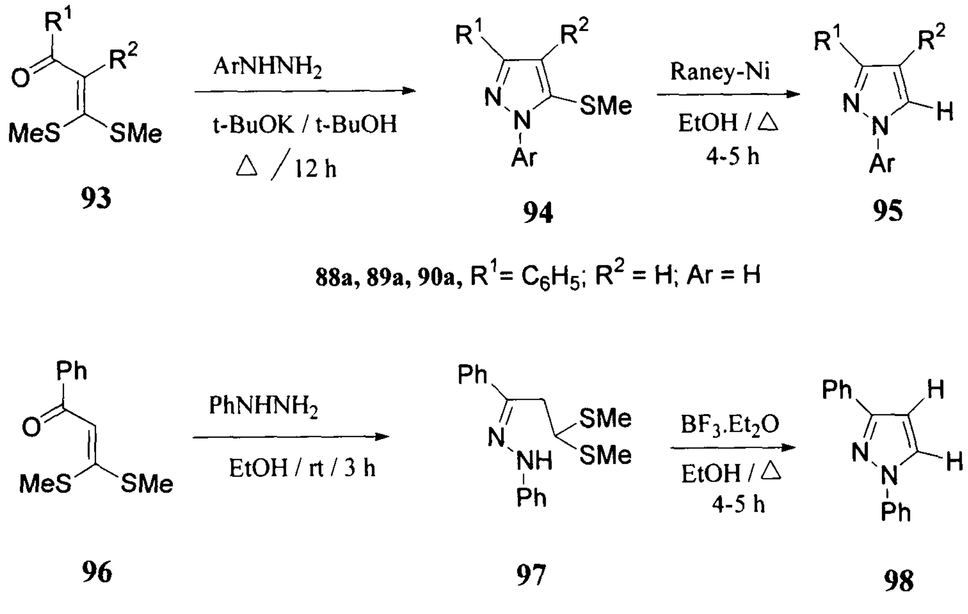
Scheme 21

Alan R. Katritzky *et al*[19] described that condensations of hydrazines'[20] or hydroxylamine[21] with *β*-diketone **88** as equivalent three carbon 1,3-difunctionalized units, bearing sp or sp^2 carbons, such as propargylic ketones giving mixtures of **89-92** regioisomers (Scheme 22).

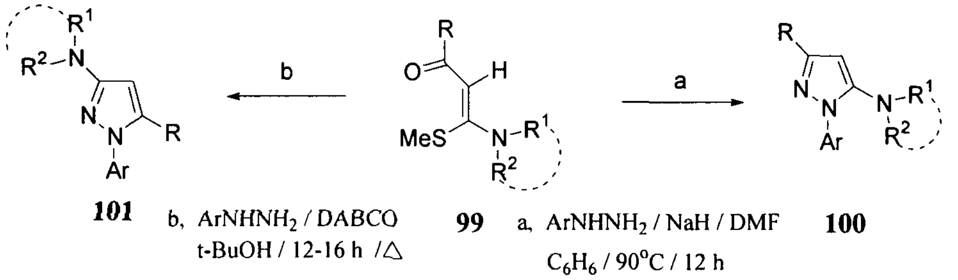


Scheme 22

Earlier work done by Junjappa and Ila has demonstrated the synthetic application of α-oxoketene dithioacetals[22] as useful three-carbon 1,3-electrophiles in their reactions with symmetrical and unsymmetrical binucleophiles. They investigated the reaction of α-benzoyl ketene dithioacetal[24a] **93a** with phenylhydrazine under a variety of reaction conditions (neutral, acidic, basic). They established the structure of **94a** on the basis of its reported[23a] physical and spectral data, and also by its Raney-Ni dethiomethylation to the known 1,3-diphenylpyrazole **95a**.[23b] Also the pyrazole **98** could be synthesized by an alternate route through $BF_3.Et_2O$ induced cyclization of the phenylhydrazone **97** from *β*-oxodithioacetal **96** which unequivocally confirmed the regiochemical assignment of the pyrazole **94a** (Scheme 23). They further reported[24b] the cyclocondensation of common α-oxoketene *N,S*-acetal **99** precursors with aryl hydrazines by variation of reaction conditions to obtained isomeric pyrazoles **100** and **101** (Scheme 24).



Scheme 23



Scheme 24

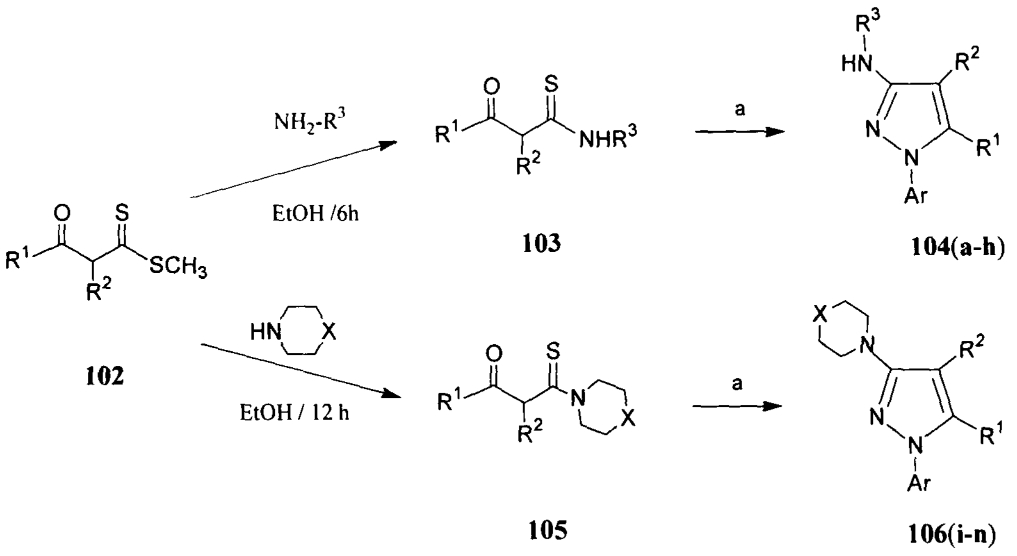
Recently, a greener and rapid access to the synthesis of substituted pyrazoles in aqueous medium has been developed.[25] Although several 5-alkyl/arylamino-1-arylpyrazoles have found applications as pharmaceuticals and agrochemical agents exhibiting a range of biological activities,[26,27] only a few scattered reports are available on the synthesis of 1-aryl-3-(or 5)-*N*,*N*-disubstituted aminopyrazoles which are not well represented in the literature.[27]

IV.2 RESULTS AND DISCUSSION

During the course of our work in the development of efficient general synthetic routes for five- and six-membered heterocycles utilizing *β*-oxothioamides obtained from *β*-oxodithioester as versatile three-carbon building blocks, we learned that it is possible to tune the reactivity of these ambident electrophiles toward unsymmetrical heterobinucleophiles.

Herein, we describe the extension of this protocol to the synthesis of 3-(*N*-substituted amino/cycloamino 5-aryl/alkyl) pyrazoles using *β*-oxothioamides **103, 105** which to our knowledge, has not been reported in the literature. During the course of these studies, we wanted to replace the thiomethyl group in *β*-oxodithioester with an amino/cycloamino group, which on further treatment with unsymmetrical binucleophiles such as phenylhydrazine in ethanol and acetic acid would yield 1-Aryl-3-*N*-substituted amino/cycloamino-5-aryl/alkyl pyrazoles **104, 106** by variation of reaction conditions (Scheme 25, **Table IV**). The formation of the pyrazoles **104(a-h)** and **106(i-n)** was achieved in one pot by refluxing *β*-oxodithioesters **102** in ethanol with equimolar quantities of the amines to generate the *N*-substituted *β*-oxothioamides **103** and **105** (monitored by TLC). On further addition of phenyl hydrazine, ethanol with catalytic amount of acetic acid to **103** in refluxing condition, yielded the cyclocondensed product 3-(*N*-alkyl/aryl-5-substituted)pyrazoles **104(a-h)**.

The *β*-oxodithiocarboxylates[28] **102** have been prepared following the reported procedures[29,30] with minor modifications.



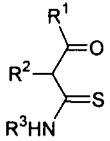
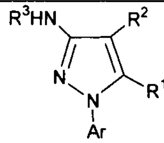
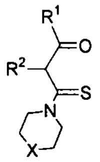
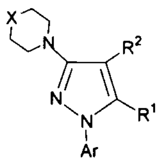
a; $ArNHNH_2$ / EtOH/AcOH / 12-16h /Δ

Scheme 25

All compounds showed characteristic spectral properties for 1-Aryl-3-(*N*-alkyl/aryl)-5-arylsubstituted pyrazoles **104(a-h)** and for 1-Aryl-3-(*N*-cycloamino)-5-arylsubstituted pyrazoles **106(i-n)** derivatives as showed (**Table IV**). All the products were characterized by ^1H and ^{13}C NMR spectroscopy, IR, melting point and elemental analyses. The formation of (1,5-Diphenyl-1H-pyrazol-3-yl)-methyl-amine **104a** was confirmed on the basis of analytical data and spectral evidences. Thus, it was analyzed for $C_{16}H_{15}N_3$ (Expected C, 77.08; H, 6.06; N, 16.84. Found: C, 77.04; H, 6.10; N, 16.81) and mass spectrum of it showed the molecular ion peak at *m/z* 249. Its IR spectrum (KBr) exhibited a sharp absorption band at 1648 cm^{-1} for C=N, 1621 cm^{-1} for the C=C stretching in the pyrazole ring and the band at 2944 cm^{-1} confirm the presence of an aromatic C-H stretching frequency. The final structural proof was obtained from its ^1H NMR spectrum ($CDCl_3$), which showed a singlet at δ 6.70 (1H, CH) for proton at the pyrazole ring moiety, a doublet at δ 2.37 (d, J = 7.6 Hz, 3H) strongly indicates the methyl protons attached to –NH. The aromatic protons were observed as multiplets at δ 7.02–7.84 ppm (10H). The ^{13}C NMR spectrum ($CDCl_3$) showed resonances at δ ppm 162.5, 93.12 and 142.14 for C-3, C-4 and C-5 of the pyrazole moiety. The above spectral information clearly confirmed the product **104a**. The spectroscopic analysis was extended to various substituents of 1-Aryl-3-(*N*-alkyl/aryl/cycloamino)-5-arylsubstituted pyrazoles **104(b-h)** and **106(i-n)** and are described in the experimental section.

In conclusion, we have demonstrated here a new and an efficient procedure for the synthesis of substituted 1-aryl-3-(*N*-alkyl/aryl)-5-arylsubstituted pyrazoles **104** and 1-aryl-3-(*N*-cycloamino)-5-arylsubstituted pyrazoles **106** using β-oxodithioester **102** and β-oxothioamides **103**, **105** as common precursors. Our efforts to extend this protocol to a wide range of β-oxodithioesters or β-oxothioamide derived from various cyclic/heterocyclic ketones with primary and secondary amines, is under progress.

Table IV. Synthesis of 1-Aryl- 3-(*N*-alkyl/aryl/cycloamino)-5-arylsubstituted pyrazoles

Entry	Substrate 103, 105				Product 104, 106	Yield[a] (%)
						
1	**103a**	R^1=Ph	R^2=H	R^3= CH_3	Ar=Ph, **104a**	92
2	**103b**	R^1=Ph	R^2=H	R^3=CH_2CH_3	Ar=Ph, **104b**	90
3	**103c**	R^1=Ph	R^2=H	R^3=*i*-Pr	Ar=Ph, **104c**	77
4	**103d**	R^1=4-$MeOC_6H_4$	R^2=H	R^3= CH_2CH_3	Ar=Ph, **104d**	89
5	**103e**	R^1=4-BrC_6H_4	R^2=H	R^3= CH_3	Ar=Ph, **104e**	76
6	**103f**	R^1=4-ClC_6H_4	R^2=H	R^3= CH_2CH_3	Ar=Ph, **104f**	78
7	**103g**	R^1=4-$NO_2C_6H_4$	R^2=H	R^3= CH_3	Ar=Ph, **104g**	87
8	**103h**	R^1=4-$NO_2C_6H_4$	R^2=H	R^3= Ph	Ar=Ph, **104h**	85
						
8	**105i**	R^1=Me	R^2=H	X=H	Ar=Ph, **106i**	86
9	**105j**	R^1=Ph	R^2=H	X=O	Ar=Ph, **106j**	85
10	**105k**	R^1=4-$MeOC_6H_4$	R^2=H	X=NBn	Ar=Ph, **106k**	64
11	**105l**	R^1=4-$MeOC_6H_4$	R^2=H	X=O	Ar=Ph, **106l**	71
12	**105m**	R^1=4-BrC_6H_4	R^2=H	X=H	Ar=Ph, **106m**	78
13	**105n**	R^1=4-ClC_6H_4	R^2=H	X=N-(2-pyridyl)	Ar=Ph, **106n**	73
14	**105o**	R^1=*i*-Pr	R^2=H	X=O	Ar=Ph, **106o**[b]	

[a] Yields obtained are determined after work-up and Chromatographic purification.
[b] Not isolated.

IV.3 EXPERIMENTAL

Melting points was determined on a "Thomas Hoover" capillary melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AMX 400 instrument using $CDCl_3$ as the solvent. Chemical shifts are reported in ppm using tetramethylsilane as internal standard. *J* values are given in Hz. The following abbreviations are used to describe peak patterns when appropriate: br = broad, s = singlet, d = doublet, dd = double doublet, dt = double triplet, t = triplet, q = quartet, m = multiplet. IR spectra were recorded on a Perkin-Elmer BX spectrophotometer. ESI mass spectra were measured on an ion trap analyzer Esquire 3000 (Bruker Daltonics). Masses (MS) are reported in unit of mass over charge (*m/z*), the molecular or base peaks and relative intensities are indicated by (M^+) and (%) respectively. CHN analyses were recorded on a Vario EL analyser. Column chromatography was performed using silica gel (60-120 mesh, Merck).

All reactions were performed in oven dried (120°C) glasswares under a positive dry argon/nitrogen atmosphere. Analytical thin layer chromatography (TLC) were performed on glass plates coated with ACME's silica gel containing 13% calcium sulphate as binder and various combination of visualization of spots was accomplished by exposure to UV lamp or iodine vapour or by spraying potassium permanganate (acidic) solution. Eluents for column chromatography were used after simple distillation of commercial solvents. All solvent evaporations were done using a rotaevaporator (BUCHI Rotavapor R II, vacuum pump V-700) and a steam bath.

Chemical Reagents and Solvents:

Commercially available NaH, 50% suspension (Sisco, Spectrochem) was used, *N,N*-dimethylformamide (Aldrich) was purchased bottle grade and dried over CaH, distilled and store over molecular sieves (4A). 'Super-dry' ethanol prepared[31] is hygroscopic, it is stored over a Type 4A molecular sieve. Anhydrous ether and dichloromethane (DCM) was obtained by keeping the bottle grade over calcium chloride over night and finally stored over sodium wire or Type 3A molecular sieve. Dry benzene was obtained by washing with concentrated sulphuric acid followed by azeotropic distillation and stored over sodium wire. Sodium tertiary butoxide was freshly prepared for each reaction.

Starting Materials:

Acetophenone and substituted acetophenones, dimethyl trithiocarbonate (Sigma-Aldrich) was used for the preparations of β-oxodithioester. Carbon disulfide (CS_2), dimethyl sulfoxide (DMSO), and phenylhydrazine used were analytical reagent bottle grade. Commercially available bottle grade, methylamine, ethylamine, pyrolidine, piperidine, morpholine, 1-Phenyl-piperazine, 1-Pyridin-2-yl-piperazine (secondary cyclic amines) were used directly without further purification. Dimethyl trithiocarbonate bp 225°C (760 mm) was also prepared according to the reported procedure.[32] β-oxodithioester required for the present investigation were prepared (using protective gloves and mask under fume cupboard) according to the earlier reported general procedures which are given below.

General procedure for the preparation of dimethyl trithiocarbonate:

A mixture of dimethyl sulfoxide (DMSO, 25 mL), KOH (15 g, 0.3 mole) and 30 mL of CS_2 (45 g, 0.60 mole) was stirred in a stoppered vessel at room-temperature overnight. The excess CS_2 was decanted and the volume was brought to 90 mL by adding more DMSO. A mixture of 10 mL of the DMSO solution and bromo methane (methyl bromide 3.3 g, 0.013 mole) was heated on the steam bath for 10 minutes after which the original red brown colour had turned lighter. About 20 mL of water was added and the product was extracted with ether. On evaporation, 2.7 g of methyl trithiocarbonate bp 225°C (760 mm) was obtained which is a yield of 91 percent based on methyl bromide.

General procedure for the synthesis of *β*-oxodithioesters 102.

To a well stirred suspension of NaH (2.5 g, 50 mmol; 50% suspension) in dry DMF/Benzene solvent mixture (50 mL, 1:10; Benzene bp 80°C), dimethyltrithiocarbonate (3.80 g, 27 mmol) is added and the mixture is refluxed with stirring for 1 h. A solution of the acetophenone (25 mmol in 50 mL dry benzene) is slowly added dropwise over a period of 3-4 h. The reaction formed an interface between the two layers present in the reaction mixture. The reaction is exothermic, then allowed to cool, and poured into ice-cold water (250 mL). It was acidified with 3N HCl or 20% acetic acid (20 mL) and extracted with diethyl ether (2 x 50 mL).The extract is dried with anhydrous Na_2SO_4 and the solvent was evaporated to give the corresponding *β*-oxodithiocarboxylates **102** in good yields (single spot on TLC). Purification may be achieved by column chromatography on silica gel (50 g) using hexane as eluent.

General procedure for the preparation of 1-Aryl- 3-(*N*-alkyl/aryl)-5-aryl substituted pyrazoles 104(a-h).

In a typical reaction, a solution of respective *β*-oxodithioesters **102** (5.0 mmol) obtained, is treated with one equivalent of primary amine (5 mmol, either methylamine, ethylamine or phenyl amine) in dry ethanol (25 mL), with constant stirring for about 6 h at room temperature where a *β*-ketothioamide **103** is formed (monitor by TLC). To the *β*-ketothioamide **103** formed *in situ*, phenylhydrazine (0.65 g, 6.018 mmol) and catalytic amount of acetic acid (3 mL) was added in presence of dry ethanol (15 mL) and was refluxed for 12-16 h with constant stirring, the reaction being monitored by TLC. The reaction mixture was concentrated under reduced pressure and poured into ice-cold water, extracted with DCM (3 x 50 mL), washed with H_2O (2 x 50 mL), brine (1 x 50 mL), and dried over Na_2SO_4. The solvent was evaporated under vacuum to give pyrazoles **104** which were purified by column chromatography over silica gel using hexane/EtOAc (10:1) as eluent.

Compounds **104(b-h)** were also synthesized similarly using appropriate amines.

Spectral Data of the selected Products:

(1,5-Diphenyl-1H-pyrazol-3-yl)-methyl-amine 104a: Yield 92% (1.47 g); pale yellow solid; mp 90-91°C; R_f 0.80 (9.5:0.5 hexanes-EtOAc); IR (KBr): 3429, 3025, 2944, 2402, 1626, 1560, 1500, 1498, 1256, 1222 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ ppm 2.37 (d, *J* = 7.6 Hz, 3H), 4.16 (q, 1H, NH), 6.49 (s, 1H), 7.02-7.84 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 35.03, 94.73, 118.2 (x 2C), 127.12, 127.35, 128.5, 129.02, 129.07, 129.12 (x 2C), 135.11, 136.3, 139.12, 142.3, 162.8; MS (*m/z*, %): 249 (M +1, 100); Anal. Calcd for $C_{16}H_{15}N_3$ (249.31): C, 77.08; H, 6.06; N, 16.84. Found: C, 77.04; H, 6.10; N, 16.81.

(1,5-Diphenyl-1H-pyrazol-3-yl)-ethyl-amine 104b: Yield 90% (1.24 g); pale yellow solid; mp 90-91°C; R*f* 0.78 (9.5:0.5 hexanes-EtOAc); IR (KBr): 3424, 3024, 2943, 2404, 1627, 1562, 1504, 1496, 1257, 1225 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ ppm 1.86 (t, *J* = 5.4 Hz, 3H), 3.67 (q, *J* = 7.6 Hz, 2H), 4.15 (q, 1H, NH), 6.32(s, 1H), 7.22-7.56 (m, 10H); ^{13}C NMR (100 MHz, CDCl$_3$): δ ppm 15.03, 44.24, 93.17, 118.08 (x 2C), 126.05, 127.02, 127.06, 128.52, 129.04, 129.07, 129.10, 129.12, 136.1, 139.07, 142.01, 162.4; MS (*m/z*, %): 263 (M + 1, 100). Anal. Calcd for $C_{17}H_{17}N_3$ (263.14): C, 77.56; H, 6.51; N, 15.94. Found: C, 77.53; H, 6.57; N, 15.90.

(1,5-Diphenyl-1*H*-pyrazol-3-yl)-isopropyl-amine 104c: Yield 77% (1.16 g); yellow solid; mp 106-107°C; R*f* 0.71 (9.5:0.5 hexanes-EtOAc); IR (KBr): 3427, 3062, 2942, 2406, 1620, 1516, 1503, 1445, 1378, 1258 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ ppm 1.77 (dd, *J* = 8.2, 2.4 Hz, 3H), 2.87 (sept, *J* = 6.8 Hz, 1H), 4.07 (d, 1H, NH), 6.78 (s, 1H), 7.22-7.54 (m, 10H), 7.84 (d, *J*= 7.6 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ ppm 23.74, 23.83, 50.2, 93.5, 118.40 (2), 126.3, 127.02, 127.18, 127.24, 128.14, 129.2, 129.4, 136.12, 136.40, 139.82, 142.3, 162.5; MS (*m/z*, %): 277 (M + 1, 100); Anal. Calcd for $C_{18}H_{19}N_3$ (277.36): C, 77.95; H, 6.90; N, 5.15. Found: C, 77.31; H, 6.87; N, 15.22.

Ethyl-[5-(4-methoxy-phenyl)-1-phenyl-1*H*-pyrazol-3-yl]-amine 104d: Yield 89% (1.37 g); pale yellow crystals; mp 122-123°C; R*f* 0.76 (9.5:0.5 hexanes-EtOAc); IR (KBr): 3429, 3025, 2944, 2402, 1626, 1560, 1500, 1498, 1256, 1222 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ ppm 1.87 (t, *J* = 5.4 Hz, 3H), 3.12 (q, *J* = 7.2 Hz, 2H), 3.87 (s, 3H, OCH$_3$), 4.42 (t, 1H, NH), 6.14 (s, 1H), 6.87 (d, *J* = 8.4 Hz, 2H), 7.10-7.56 (m, 7H, ArH), 7.86 (d, *J*= 7.6 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ ppm 15.03, 44.17, 56.12, 94.17, 114.05, 118.08, 118.11, 126.05, 128.18, 128.21, 128.24, 129.10, 129.12, 136.1, 139.07, 142.08, 162.40, 162.46; MS (*m/z*, %): 293 (M + 1, 100); Anal. Calcd for $C_{18}H_{19}N_3O$ (293.12): C, 73.69; H, 6.51; N, 14.34. Found: C, 71.31; H, 6.32; N, 14.45.

[5-(4-Bromo-phenyl)-1-phenyl-1*H*-pyrazol-3-yl]-methyl-amine 104e: Yield 82% (1.27 g); Brown solid; mp 141-145°C; R_f 0.84 (9.5:0.5 hexanes-EtOAc); IR (KBr): 3433, 3044, 2960, 2406, 1618, 1527, 1518, 1440, 1334, 1225 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ ppm 2.45 (d, *J* = 7.6 Hz, 3H), 4.02 (q, 1H, NH), 6.72 (s, 1H), 7.04-7.34 (m, 5H, ArH), 7.48 (d, *J* = 8.2 Hz, 2H), 7.64 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 35.20, 93.14, 114.15, 118.16 (2), 124.02 (2), 126.05, 129.10 (2), 136.1, 139.07, 142.02, 142.08, 148.22, 162.12; MS (*m/z*, %): 327 (M + 1, 100); Anal. Calcd for $C_{16}H_{14}BrN_3$ (327.04): C, 58.55; H, 4.36; N, 12.85. Found: C, 58.52; H, 4.23; N, 12.62.

[5-(4-Chloro-phenyl)-1-phenyl-1*H*-pyrazol-3-yl]-ethyl-amine 104f: Yield 78% (1.02 g); Yellow solid; mp 96-97°C; R_f 0.76 (9.5:0.5 hexanes-EtOAc); IR (KBr): 3436, 3048, 2968, 2404, 1614, 1524, 1516, 1442, 1336, 1228 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ ppm 1.87 (t, *J* = 5.4 Hz, 3H), 3.12 (q, *J* = 7.2 Hz, 2H), 4.04 (t, 1H, NH), 6.70 (s, 1H), 7.02-7.24 (m, 9H, ArH), 7.46 (d, *J* = 8.2 Hz, 2H), 7.68 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 35.20, 93.14, 114.15, 118.16 (2), 124.02, 124.07, 126.05, 128.04, 129.10 (2), 136.1, 139.07, 142.02, 142.08, 148.22, 162.12 ; MS (*m/z*, %): 297 (M + 1, 100); Anal. Calcd for $C_{17}H_{16}ClN_3$ (297.10): C, 68.57; H, 5.46; N, 14.15. Found: C, 68.52; H, 5.23; N, 14.42.

Methyl-[5-(4-nitro-phenyl)-1-phenyl-1*H*-pyrazol-3-yl]-amine 104g: Yield 87% (1.22 g); pale yellow solid; mp 114-115°C; R_f 0.87 (9.5:0.5 hexanes-EtOAc); IR (KBr): 3432, 3042, 2962, 2408, 1619, 1523, 1510, 1441, 1338, 1245 cm^{-1}; ^1H NMR (400 MHz,

$CDCl_3$): δ ppm 2.55 (s, 3H, CH_3), 5.54 (q, 1H, NH), 6.68 (s, 1H), 7.04-7.54 (m, 5H), 7.78 (d, $J = 8.4$ Hz, 2H), 8.26 (d, $J = 8.2$ Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 35.06, 93.17, 114.05, 118.08 (2), 124.02, 124.07, 126.05, 129.10 (2), 136.1, 139.07, 142.02, 142.08, 148.02, 162.4; MS (*m/z*, %): 294 (M + 1, 100). Anal. Calcd for $C_{16}H_{14}N_4O_2$ (294.35): C, 65.35; H, 4.76; N, 19.05. Found: C, 65.27; H, 4.53; N, 19.02.

[5-(4-Nitro-phenyl)-1-phenyl-1*H*-pyrazol-3-yl]-phenyl-amine 104h: Yield 85% (1.20 g); pale yellow solid; mp 140-141°C; R_f 0.86 (9.5:0.5 hexanes-EtOAc); IR (KBr): 3430, 3047, 2964, 2406, 1615, 1528, 1518, 1446, 1334, 1242 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ ppm 5.58 (brs, 1H, NH), 6.34 (s, 1H), 6.87 (d, $J = 7.6$ Hz, 2H), 7.04-7.58 (m, 8H, ArH), 7.70 (d, $J = 8.4$ Hz, 2H), 8.26 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 35.06, 93.17, 115.07, 115.12, 118.02 (2), 118.11, 124.02, 124.07, 126.05, 127.22, 128.12, 128.22, 129.10, 129.12, 136.1, 139.07, 142.02, 142.08, 148.02, 162.4; MS (*m/z*, %): 356 (M + 1, 100); Anal. Calcd for $C_{21}H_{16}N_4O_2$ (356.15): C, 70.75; H, 4.54; N, 15.72. Found: C, 70.72 H, 4.51; N, 15.52.

Procedure for preparation of 1-Aryl- 3-(*N*-cycloamino)-4,5-substituted pyrazoles 106(i-n).

A solution of respective *β*-oxodithioesters **102** (5 mmol) is treated with one equivalent of secondary cyclic amine (5 mmol) [either piperidine, morpholine, 1-Phenyl-piperazine or 1-Pyridin-2-yl-piperazine] in 50 mL dry ethanol. The reaction mixture was refluxed with constant stirring for about 6-7 h, where *β*-ketothioamide **105** is formed (monitor by TLC). To the *β*-ketothioamide **105** obtained *in situ*, phenylhydrazine (0.65 g, 6.0 mmol) and catalytic amount of acetic acid is added in presence of dry ethanol (15 mL) and was refluxed for 12-16 h with constant stirring, the reaction being monitored by TLC. The reaction mixture was concentrated under reduced pressure and poured into ice-cold water, extracted with CH_2Cl_2 (3 x 50 mL), washed with H_2O (2 x 50 mL) and brine (1 x 50 mL), and dried over Na_2SO_4. The solvent was evaporated under vacuum to give pyrazoles **106(i-n)** which was purified by column chromatography over silica gel using hexane/EtOAc (10:1) as eluent.

Compounds **106(j-n)** were also synthesized similarly using appropriate cyclic amines.

1-(5-Methyl-1-phenyl-1*H*-pyrazol-3-yl)-piperidine 106i: Yield 86% (1.65 g); yellow crystals; mp 98-99°C; R_f 0.69 (9.5:0.5 hexanes-EtOAc); IR (KBr): 3066, 2942, 2417, 1545, 1528, 1453, 1424, 1304, 1252, 1206 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.45-1.48 (m, 2H), 1.50-1.56 (m, 4H), 2.54 (s, 3H, CH_3), 2.80 (t, J = 7.4 Hz, 2H), 2.82 (t, J = 7.4 Hz, 2H), 6.25 (s, 1H), 7.02-7.74 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 7.22, 25.08, 25.14, 26.20, 54.04, 54.3, 94.6, 118.07, 118.12, 126.2, 126.6, 129.05, 129.16, 136.3, 163.31; MS (*m/z*, %): 241 (M + 1, 100); Anal. Calcd for $C_{15}H_{19}N_3O$ (241.37): C, 74.95; H, 7.96; N, 17.41. Found: C, 74.77; H, 7.75; N, 17.52.

4-(1,5-Diphenyl-1*H*-pyrazol-3-yl)-morpholine 106j: Yield 85% (1.45 g); pale yellow solid; mp 80-81°C; R_f 0.67 (9.5:0.5 hexanes-EtOAc); IR (KBr): 3060, 2946, 2410, 1549, 1527, 1450, 1421, 1308, 1256, 1201 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 2.32 (t, J = 6.4 Hz, 4H), 3.62 (t, J = 6.4 Hz, 4H), 6.05 (s, 1H), 6.87 (d, J = 8.4 Hz, 2H), 7.02-7.74 (m, 8H), 8.22 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 58.23, 58.38, 71.23, 71.42, 93.6, 118.2 (2), 123.4, 126.2, 127.14, 127.15, 128.2, 128.5, 129.12, 129.4, 136.12, 139.6, 142.22, 162.31; MS (*m/z*, %): 305 (M + 1, 100). Anal. Calcd for $C_{19}H_{19}N_3O$ (305.37): C, 74.95; H, 6.61; N, 13.76. Found: C, 74.77; H, 6.53; N, 13.72.

1-[5-(4-Methoxy-phenyl)-1-phenyl-1*H*-pyrazol-3-yl]-4-phenyl-piperazine 106k: Yield 64% (0.76 g); Brown crystals; mp 162-163°C; R_f 0.76 (9.5:0.5 hexanes-EtOAc). IR (KBr): 3084, 2940, 2418, 1550, 1522, 1416, 1418, 1372, 1340, 1297, 1233 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 2.86 (t, *J* = 5.4 Hz, 4H), 3.31 (s, 3H, OMe), 3.26 (t, *J* = 5.4 Hz, 2H), 3.86 (t, *J* = 5.4 Hz, 2H), 6.47 (s, 1H), 6.77 (d, *J* = 8.4 Hz, 2H), 7.12 - 7.27 (m, 10H), 7.67 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 56.11, 57.12, 57.23, 57.18 (2), 93.6, 113.11, 113.14, 114.12, 114.08, 118.0 (2), 126.2, 127.15 (2), 128.2 (2), 129.4, 129.12, 129.18, 129.20, 136.12, 139.6, 142.22, 144.5, 162.31; MS (*m/z*, %): 410 (M + 1, 100); Anal. Calcd for $C_{26}H_{26}N_4O$ (410.21): C, 76.06; H, 6.38; N, 13.65. Found: C, 76.02; H, 6.27; N, 13.62.

4-[5-(4-Methoxy-phenyl)-1-phenyl-1*H*-pyrazol-3-yl]-morpholine 106l: Yield 71% (0.96 g); light brown crystals; mp 121-122°C; R_f 0.88 (9.5:0.5 hexanes-EtOAc); IR (KBr): 3086, 2948, 2416, 1553, 1520, 1415, 1410, 1378, 1348, 1293, 1236 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 2.86 (t, *J* = 5.4 Hz, 4H), 3.31 (s, 3H, OMe), 3.67 (t, *J* = 5.4 Hz, 2H), 6.68 (s, 1H), 6.87 (d, *J* = 8.4 Hz, 2H), 7.12 -7.27 (m, 7H, ArH), 7.47 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 56.11, 58.38, 58.40, 71.22, 93.6, 114.08 (2), 118.12 (2), 126.2, 127.15, 127.17, 128.5, 128.7, 129.4, 129.12, 136.12, 139.6, 142.22, 162.31; MS (*m/z*, %): 335 (M + 1, 100); Anal. Calcd for $C_{20}H_{21}N_3O_2$ (335.40): C, 71.62; H, 6.31; N, 12.53. Found: C, 71.72; H, 6.33; N, 12.62.

1-[5-(4-Bromo-phenyl)-1-phenyl-1*H*-pyrazol-3-yl]-piperidine 106m: Yield 78% (1.14 g); pale yellow solid; mp 137-138°C; R_f 0.82 (9.5:0.5 hexanes-EtOAc); IR (KBr): 3059, 2951, 2414, 1558, 1529, 1417, 1416, 1381, 1353, 1296, 1233 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.41-1.46 (m, 2H), 1.52-1.58 (m, 4H), 2.78 (t, *J* = 7.4 Hz, 2H), 2.82 (t, *J* = 7.4 Hz, 2H), 6.87 (s, 1H), 7.36-7.42 (m, 9H), 7.47 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 25.04, 25.18, 26.20, 54.3, 54.04, 94.6, 118.12 (2), 123.12, 126.2, 129.01, 129.06, 129.15, 132.05 (2), 135.23, 139.04, 142.12, 163.31; MS (*m/z*, %): 382 (M + 1, 100); Anal. Calcd for $C_{20}H_{20}BrN_3$ (382.30): C, 62.46; H, 5.27; N, 10.93. Found: C, 68.72; H, 5.34; N, 10.62.

1-[5-(4-Chloro-phenyl)-1-phenyl-1*H*-pyrazol-3-yl]-4-pyridin-2-yl-piperazine 106n: Yield 73% (0.76 g); Yellow crystals; mp 156-157°C; R$_f$ 0.72 (9.5:0.5 hexanes-EtOAc); IR (KBr): 3082, 2944, 2416, 1552, 1526, 1414, 1417, 1370, 1342, 1292, 1238 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 3.76 (t, *J* = 5.4 Hz, 2H), 3.86 (t, *J* = 5.4 Hz, 2H), 6.60 (d, *J* = 8.2 Hz, 1H), 6.62 (sept, *J* = 7.2, Hz, 2H), 6.76 (s, 1H), 7.38-7.87 (m, 9H, ArH), 7.44 (d, *J* = 7.2 Hz, 1H), 8.12 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 56.11, 57.12, 57.16, 57.32, 57.37, 93.6, 113.11, 114.06, 114.08, 162.31, 118.0, 126.2, 127.14 (2), 128.5 (2), 129.12, 129.20 (2), 129.4, 136.12, 139.6, 142.22, 144.5; MS (*m/z*, %): 415 (M + 1, 100); Anal. Calcd for $C_{24}H_{22}ClN_5$ (415.16): C, 69.36; H, 5.38; N, 16.85. Found: C, 69.28; H, 5.27; N, 16.72.

IV. 4 REFERENCES

1. (a) Doe, I. S.; Smith, J.; Roe, P. *J. Am. Chem. Soc.* **1968**, *90*, 8234; (b) Ache, H. J. *Angew. Chem.*, Int. Ed. Engl. **1989**, 28, 1;(c) Qiao, J. X.; Cheng, X.; Smallheer, J. M.; Galemmo, R. A.; Drummond, S.; Pinto, D. J. P.; Cheney, D. L.; He, K.; Wong, P. C.; Luettgen, J. M.; Knabb, R. M.; Wexler, R. R.; Lam, P. Y. S. *Bioorg. Med. Chem. Lett.* **2007**, 17, 1432;(d) Singh, P.; Paul, K.; Holzer, W. *Bioorg. Med. Chem.* **2006**, 14, 5061 ; (e) Lamberth, C. *Heterocycles,* **2007**, 71, 1467.
2. Reviews: (a) Elguero, J. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R. Rees, C. W.; Potts, K. T., Eds.; Pergamon: Oxford, 1984; Vol. 5, p 167; (b) Elguero, J. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R.; Rees, C.W.; Scriven, E. F. V., Eds.; Pergamon Press: Oxford, 1996; Vol.3, p1. (c) Kost, A. N.; Grandberg, I. I. *Advances in Heterocyclic Chemistry*; Katritzky, A. R.; Boulton, A. J. Eds.; Academic Press: New York, 1966; Vol. 6, p 347. (d) Lee, K.Y.; Kim, J. M.; Kim, J. N. *Tetrahedron Lett.* **2003**, 44, 6737.
3. Penning, T. D.; Talley, J. J.; Bertenshaw, S. R.; Carter, J.S.; Collins, P. W.; Docter, S.; Graneto, M. J.; Lee, L. F.; Malecha, J. W.; Miyashiro, J. M.; Rogers, R. S.; Rogier, D. J.; Yu, S. S.; Anderson, G. D.; Burton, E. G.; Cogburn, J. N.; Gregory, S. A.; Koboldt, C. M.; Perkins, W. E.; Seibert, K.; Veenhuizen, A. W.; Zhang, Y. Y.; Isakson, P. C. *J. Med. Chem.* **1997**, *40*, 1347–1365.
4. Terrett, N. K.; Bell, A. S.; Brown, D.; Ellis, P. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1819–1824.
5. (a) Raizass, G.W.; Clemence, L.W. and Freifelder, M.; *J. Am. Chem. Soc.* **1941**, *63*, 2739. (b) Chang, K. T.; Choi, Y. H.; Kim, S. H.; Yoon, Y. J.: Lee, W. S. *J. Chem. Soc., Perkin Trans. 1* **2002**, 207. (c) Grotjahn, D.B.; Van, S.; Combs, D.; Lev, D. S.; Schneider, C.; Rideout, M.; Meyer, C.; Hernandez, G.; Mejorado, L.

J. Org. Chem. **2002**, *67*, 9200. (d) Sakya, S. M.; Rast, B. *Tetrahedron Lett.* **2003**, *44*, 7629 and references therein.

6. Huang, Y. R.; Katzenellenbogen, J. A. *Org. Lett.* **2000**, *2*, 2833.
7. (a) Heller, S. T.; Natarajan, S. R. *Org. Lett.* **2006**, *8*, 2675; (b) Kost, A. N.; Grandberg, I. I. *Adv. Heterocycl. Chem.* **1966**, *6*, 347; (c) Wang, Z.-X.; Qin, H.-L. *Green Chem.* **2004**, *6*, 90; (d) Xie, F.; Cheng, G.; Hu, Y. *J. Comb. Chem.* **2006**, *8*, 286; (e) Armstrong, A.; Jones, L. H.; Knight, J. D.; Kelsey, R. D. *Org. Lett.* **2005**, *7*, 713.
8. Aggarwal, V. K.; de Vicente, J.; Bonnert, R. V. *J. Org. Chem.* **2003**, *68*, 5381.
9. (a) Grotjahn, D. B.; Van, S.; Combs, D.; Lev, D. A.; Schneider, C.; Rideout, M.; Meyer, C.; Hernandez, G.; Mejorado, L. *J. Org. Chem.* **2002**, *67*, 9200; (b) Bishop, B. C.; Brands, K. M. J.; Gibb, A. D.; Kennedy, D. J. *Synthesis* **2004**, 43; (c) Bhat, B. A.; Puri, S. C. *Synth. Commun.* **2005**, 1135.
10. Elguero, J. Pyrazoles. In *Comprehensive Heterocyclic Chemistry*; Shinkai, I., Ed.; Pergamon: Oxford, 1996; Vol. 3, pp 1-75.
11. Kost, A. N.; Grandberg, I. I. *Adv. Heterocycl. Chem.* **1966**, *6*, 347-429, especially pp 366-368.
12. Wiley, R. H. *Pyrazoles, Pyrazolines, Pyrazolidines, Indazoles, and Condensed Rings*; Interscience Publishers: New York, 1967.
13. Elguero, J. Pyrazoles and Derivatives. In *Comprehensive Heterocyclic Chemistry*; Potts, K. T., Ed.; Pergamon: Oxford, 1984; Vol.5, pp 167-303.
14. Moureu, C.; Delange, R. *Bull. Soc. Chim. Fr.* **1901**, *25*, 302-313.
15. (a) Grotjahn *et al.,* Douglas B. *J. Org. Chem.* **2002**, *67*, 9200-920 (b) Bowden, K.; Jones, E. R. H. *J. Chem. Soc.* **1946**, 953-954. (c) Baddar, F. G.; Al-Hajjar, F. H.; El-Rayyes, N. R. *J. Heterocycl. Chem.* **1976**, *13*, 257-268.

16. (a) Giacomelli, G.; Rosini, C.; Caporusso, A. M.; Palla, F. *J. Org.Chem.* **1983**, *48*, 4887-4891 (b) Rycroft, A. D.; Singh, G.; Wightman, R. H. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2667-2668 and references to previous work.
17. (a) Falorni, M.; Giacomelli, G.; Spanedda, A. M. *Tetrahedron: Asymmetry* **1998**, *9*, 3039-3046.(b) Wang, X.-j.; Tan, J.; Zhang, L. *Org. Lett.* **2000**, *2*, 3107-3109. (c) Cabarrocas, G.; Ventura, M.; Maestro, M.; Mahıa, J.; Villalgordo, J. M. *Tetrahedron: Asymmetry* **2000**, *11*, 2483-2493.
18. (a) Adlington, R. M.; Baldwin, J. E.; Catterick, D.; J., P. G.; Tang, L. T. *J. Chem. Soc., Perkin Trans. 1* **2000**, 303-305.(b) Adlington, R. M.; Baldwin, J. E.; Catterick, D.; Pritchard, G. J.; Tang, L. T. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2311-2316.
19. Katritzky, Alan R. *et al. J. Org. Chem.* **2001,** *66,* 6787-6791.
20. Garcia, H.; Iborra, S.; Miranda, M. A.; Morera, I. M.; Primo, J. *Heterocycles* **1991**, *32*, 1746
21. Barber, G. N.; Olofson, R. A. *J. Org. Chem.* **1978**, *43*, 3015.
22. (a) Chauhan, S. M. S.; Junjappa, H. *Synthesis* **1975**, 798.(b) Rahman, A.; Vishwakarma, J. N.; Yadav, R. D.; Ila, H.; Junjappa, H. *Synthesis* **1984**, 247. (c) Kumar, A.; Aggarwal,V.; Ila, H.; Junjappa, H. *Synthesis* **1980**, 748. (d) Aggarwal, V.; Singh, G.; Ila, H.; Junjappa, H. *Synthesis* **1982**, 214. (e) Satyanarayana, J.; Ila, H.; Junjappa, H. *Synthesis* **1991**, 889.
23. (a) Maquestiau, A.; Van Haverbeke, Y.; Vanovervelt, J. C. *Bull.Soc. Chim. Belg.* **1977**, *86*, 961. (b) Gotthardt, H.; Reiter, F. *Chem. Ber.* **1979**, *112*, 1206.
24. (a) Peruncheralathan, S.; Khan, T. A.; Ila, H.; Junjappa, H.; *J. Org. Chem.* **2005**, *70*, 10030-10035. (b) Peruncheralathan, S.; Yadav, A. K.; Ila, H.; Junjappa, H.; *J. Org. Chem.* **2005**, *70*, 9644-9647.

25. Polshettiwar, V.; Varma, R.S. *Tetrahedron Lett.* **2008**, *49*, 397-400.

26. (a) Tang, J.; Shewchuk, L. M.; Sato, H.; Hasegawa, M.; Washio, Y.; Nishigaki, N. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2985. (b) Braibante, M. E. F.; Braibante, H.T. S.; da Roza, J. K.; Henriques, D. M. *Synthesis* **2003**, 1160.

27. Dodd, D.S.; Martinez, R. L. *Tetrahedron Lett.* **2004**, *45*, 4265.

28. Singh, G.; Bhattacharjee, S. S.; Ila, H.; Junjappa, H. *Synthesis* **1982**, 693-694.

29. (b) Dalgard, L.; Jensen, L.; Lawesson, S. O. *Tetrahedron* **1974**, *39*, 93. (c) Ramdas, S, R.; Srinivasan, P. S.; Ramachandran, J.; Sastry, V. V. S. K. *Synthesis* **1983**, 605. (d) Voss, J. Synthesis of Thioesters and Thiolactones, In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1990; Vol. 6, pp 435- 460.

30. (a) Nair, S. K.; Samuel, R.; Asokan, C. V. *Synthesis* **2001**, 573. (b) Nair, S. K.; Asokan, C. V. *Synth. Commun.* **2001**, *22*, 1453.

31. Furniss, A. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. *Vogel's Textbook of Practical Organic Chemistry Fifth New Edition Pearson education.*

32. Haugwitz, R. D. *U.S. Patent* 3, **1972**, 660, 412.

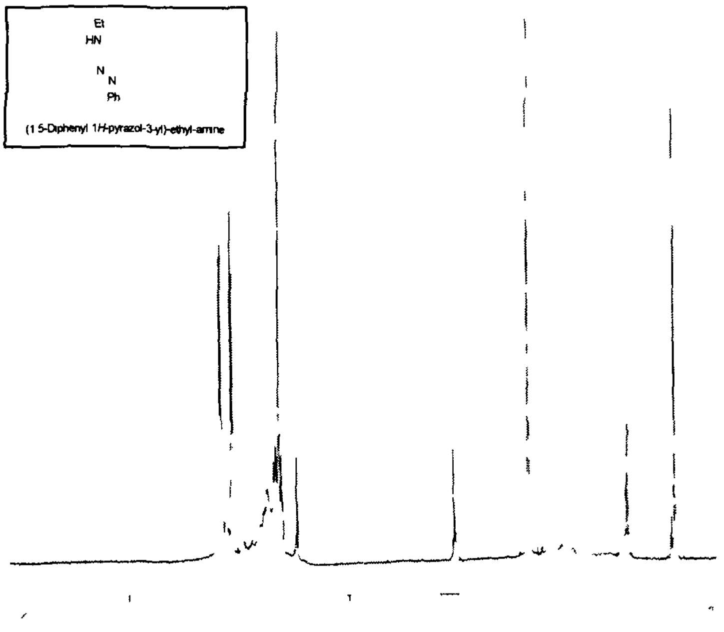


Figure 1. ^{1}H NMR spectra of compound (1,5-Diphenyl-1*H*-pyrazol-3-yl)-methyl-amine.

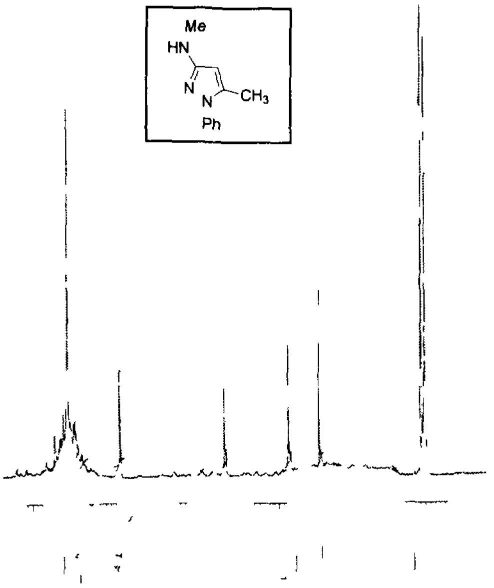


Figure 21. ^{1}H NMR spectra of compound Methyl-(5-methyl-1-phenyl-1*H*-pyrazol-3-yl)-amine.

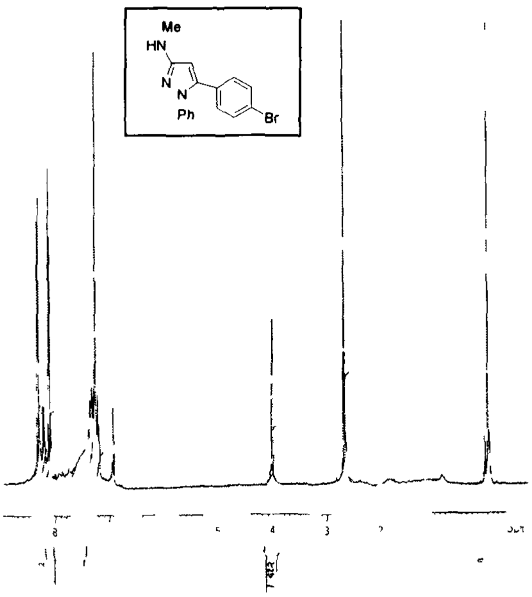


Figure 22. ^{1}H NMR spectra of [5-(4-Bromo-phenyl)-1-phenyl-1*H*-pyrazol-3-yl]-methyl-amine

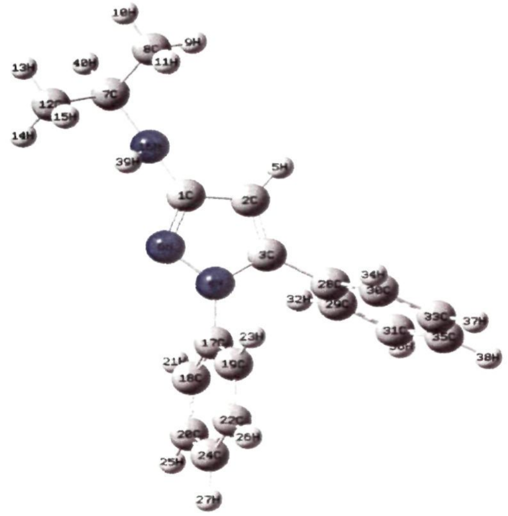


Figure 23: Compound **104c**.

Figure 24: Compound **106j**.

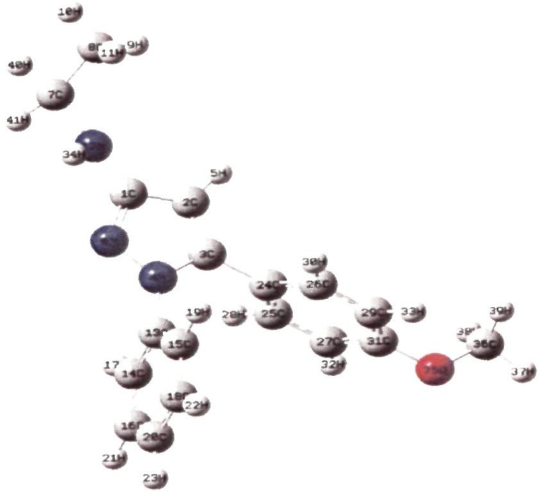


Figure 25: Compound **104d.**

Figure26: Compound **106k**.

Figure27: Compound **104h**.

Figure 28: Compound **106n.**

Gaussview 3D models

CHAPTER V

β-OXODITHIOESTERS AS HIGHLY EFFICIENT SYNTHONS FOR THE SYNTHESIS OF SUBSTITUTED-(3-METHYL-4-PHENYL-3*H*-THIAZOL-2-YLIDENE)-3,4-DIHYDRO-2*H*-NAPHTHALEN-1-ONE AND 1-ARYL-3-(*N*-CYCLOAMINO)4,5-DIHYDRO-3a*H*-BENZO[*g*]INDAZOLE DERIVATIVES USING SUBSTITUTED *α*-TERALONES

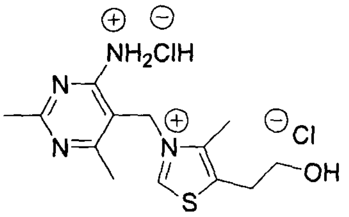
CHAPTER -V

β-oxodithioesters as highly efficient synthons for the synthesis of substituted-(3-Methyl-4-phenyl-3*H*-thiazol-2-ylidene)-3,4-dihydro-2*H*-naphthalen-1-one and 1-aryl-3-(*N*-cycloamino)-4,5-dihydro-1*H*-benzo[*g*]indazole derivatives using substituted α-tetralones

V 1. INTRODUCTION AND REVIEW

β-oxodithioester, generally known as polarised β-oxodithioesters have been used as versatile three carbon synthons for the synthesis of different variants of heterocyclic structures of biological importance. The thiazole and indazole ring systems are common structural motifs in a number of biologically active molecules. In light of this broad array of biological activity, the development of new efficient and more viable routes for thiazole and indazole class of compounds would be of great relevance to both synthetic and medicinal chemists. The syntheses of thiazole and indazole derivatives are well documented and their methods of preparation are manifold and varied. A survey of the literature revealed that the synthesis of thiazole and indazole derivatives using *β*-oxodithioester are not reported yet. In this chapter we report a facile synthetic entry to substituted-(3-Methyl-4-phenyl-3*H*-thiazol-2-ylidene)-3,4-dihydro-2*H*-naphthalen-1-one and 1-aryl-3-(*N*-cycloamino)-4,5-dihydro-1*H*-benzo[*g*]indazole derivatives using *β*-oxodithioesters.

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. Thiazole and its derivatives are very useful compounds in various fields of chemistry[1], numerous natural aromas contain thiazole derivatives like tomato, roasted coffee and roasted peanuts.[2] Several antibiotics, such as althiomycine and micrococcin contain a thiazole ring. An example is the thiazole moiety which is present not only in the skeleton of vitamin B_1 **107** and Penicillin **108** and also in the structures of various drugs. [3] The use of combinatorial chemistry has recently been at the forefront of chemical science due to its impact on the drug discovery process[4] in which thiazoles derived via traceless cleavage of modified Rink resin bound substrates has been reported.[5]



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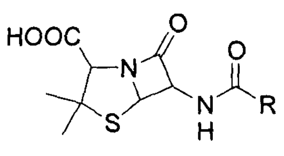
Vitamine B_1



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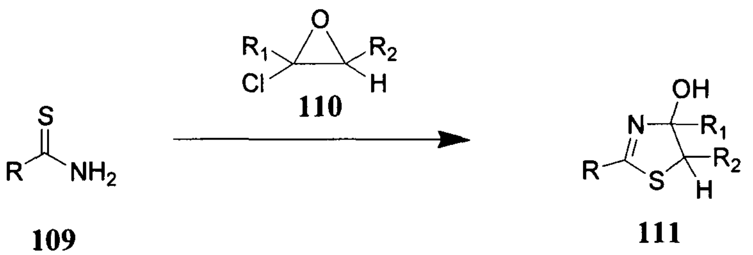
R = $C_6H_4CH_2$-(penicillin G), $C_6H_5CH(NH_2)$-(ampicillin), $C_6H_5OCH_2$-(penicillin V)

These thiazole bearing substrates are particularly desirable structures which has found broad application in drug development[6] for the treatment of inflammation,[7] hypertension,[8] bacterial[9] and HIV infections.[10] Since the thiazole ring is present in the structures of many biologically active compounds, methods for its synthesis still hold the interest of chemists. A wide range of variously substituted thiazoles, such as those bearing ester,[11-19] carboxy,[20] aminoalkyl,[21] and methyl-triphenylphosphonium[22] functions and aryl,[23,24] aryl-alkylamino,[25] and aryl-heterocyclic[26,27] substituents, can be obtained in the reactions of thioamides derived from aliphatic, aromatic, and heterocyclic acids with appropriately functionalized carbonyl compounds.

Hantzsch and Traumann[28] described a general method of synthesis for 2-aminothiazoles by condensation of thiourea with α-halocarbonyl derivatives. However, Liebscher in a comprehensive monograph[10] described the most important methods for the synthesis of 1,3-thiazoles **111**, including those starting with thioamides. Thiazole derivatives[29] were synthesized in the reactions of thioamides **109** with 2-chlorooxiranes **110,** which are isomeric with *α*-chlorocarbonyl compounds (Scheme 26).

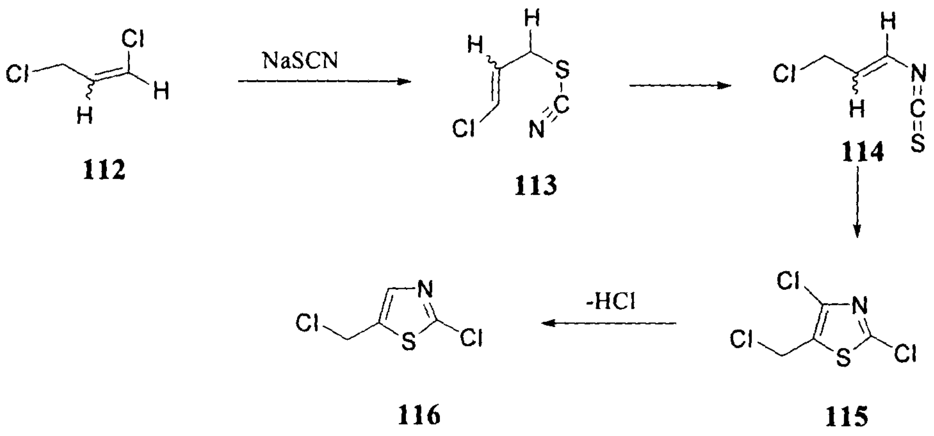


R = Me, R_1 = *i*-Pr, R_2 = H (77%)
R = Me, R_1 = H, R_2 = t-Bu (67%)

Scheme 26

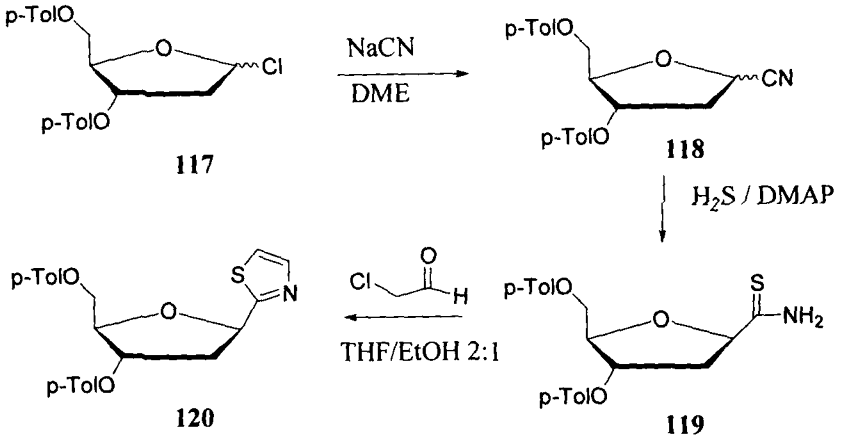
Murugan and co-worker employed the reaction of 1,3-dichloropropene **112** (mixture of cis and trans isomers) with sodium thiocyanate which initially gave the 3-chloro-2-propenylthiocyanate **113** and underwent a [3.3]-sigmatropic rearrangement to give the

1-chloro-2-propenylisothiocyanate intermediate which readily rearranged (1,3-halogen shift) to give 3-chloro-1-propenylisothiocyanate **114**. On chlorination of this mixture gave 2,4-dichloro-5-chloromethylthiazole **115** and 2-chloro-5-chloromethylthiazole **116**[30,31] (Scheme 27).



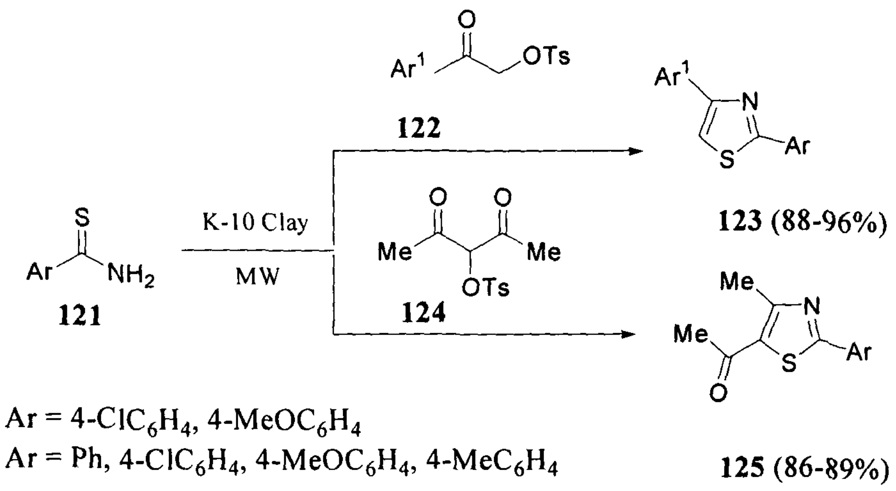
Scheme 27

Robert P. Hammer *et al* reported[32] the successful method of incorporating the thiazole and thiazole *N*-oxide phosphoramidites into DNA, though significant deoxygenation of the *N*-oxide occurred during DNA assembly. The thiazole C-nucleoside analogue **120** was synthesized by the Hantzsch cyclization method from chlorosugar **117** via the substituent nitrile **118** which provided the thioamide **119** to form the thiazole ring (Scheme 28).



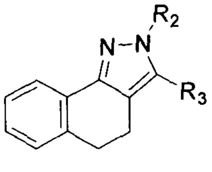
Scheme 28

Varma and co-workers[33] describe an expeditious syntheses of 1,3-thiazoles **123** which are readily obtained from thioamides **121** and α-tosyloxyketones **122** in the presence of montmorillonite K-10 clay in processes that are accelerated by exposure to microwaves. Similarly, in the case of diketone, as exemplified by the reaction of 3-tosyloxypentane-*2,4-dione* ***124*** *with thioamides* ***121****, the formation of 5-acetyl-4-methyl-2-aryl-1,3-*thiazole derivatives **125** are obtained in excellent yields (Scheme 29).

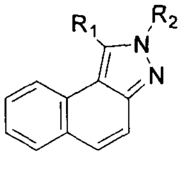


Scheme 29

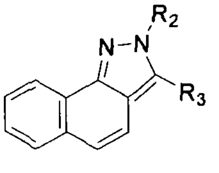
Considerably less has been reported for the preparation and utilization of related benzoannulated indazoles, like 4,5-dihydro-2*H*-benz[*g*]indazoles **126**,[34] 4,5-dihydro-2*H*-benz[*e*]indazoles **127**,[35,36] 2*H*-benz[*g*]indazoles **128**,[37] and *NH*-, *2H*-, or 3*H*-benz[*e*]indazoles **129**,[38,39] the *N*-substituted 2*H*-benz[*e*]indazoles **129** have not been reported.



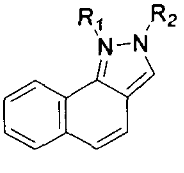
126



127

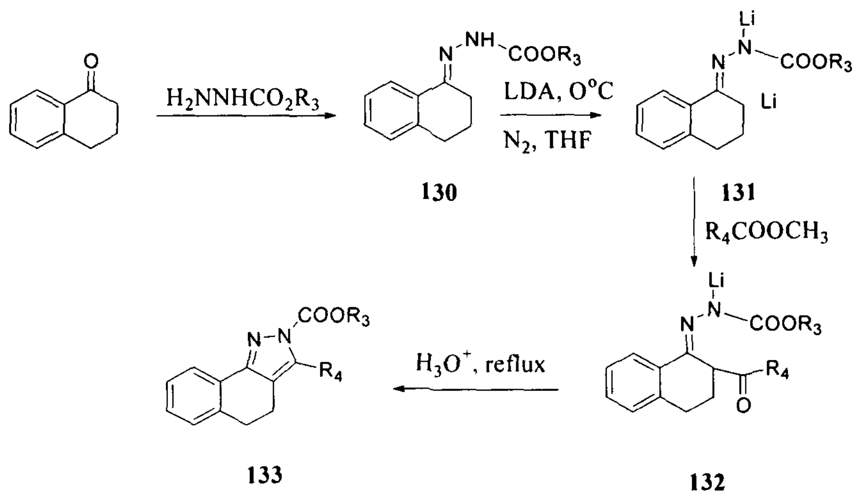


128



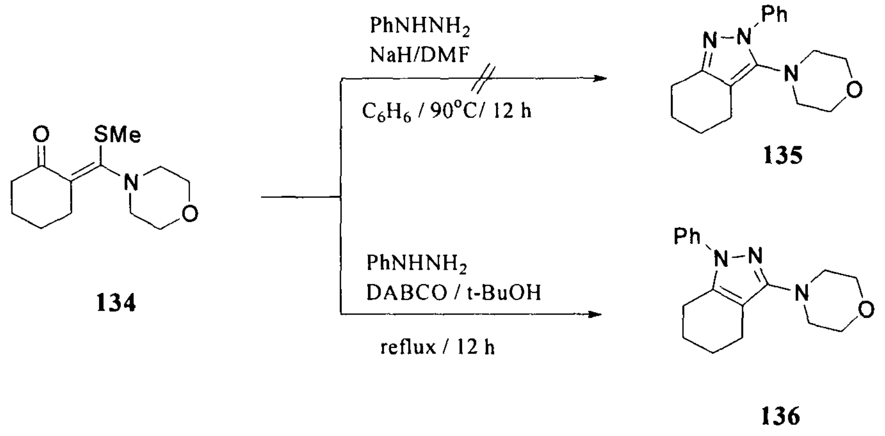
129

Beam *et al* reported[39] the dilithiated 1-tetralone carboalkoxyhydrazones **131** derived from a hydrazone **130** was prepared in excess of lithium diisopropylamide and condensed with a variety of aromatic ester followed by acid cyclisation of C-acylated intermediate **132** to give alkyl 4,5-dihydro-2*H*-benz[*g*]indazole-2-carboxylate **133** (Scheme 30).



Scheme 30

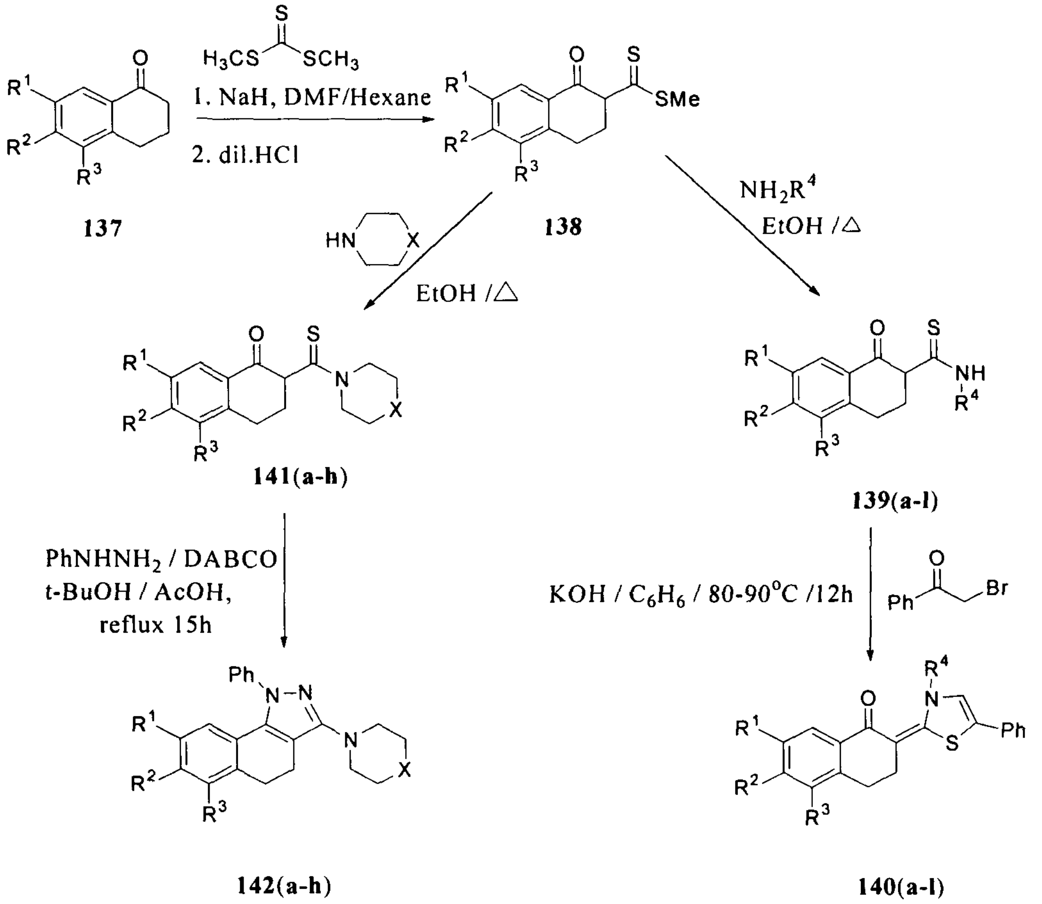
Junjappa and Ila reported[40] the synthesis of annulated 3-(or 5) amino pyrazoles compounds **135** and **136** using the α-oxoketene *N,S*-acetals **134** derived from cyclic ketones when reacted with phenylhydrazine in presence of different bases as shown (Scheme 31).



Scheme 31

Although numerous methods for the synthesis of substituted thiazoles and indazoles and their corresponding derivatives have been developed, the search for new and efficient synthetic routes for these classes of compounds continues to attract a lot of attention.

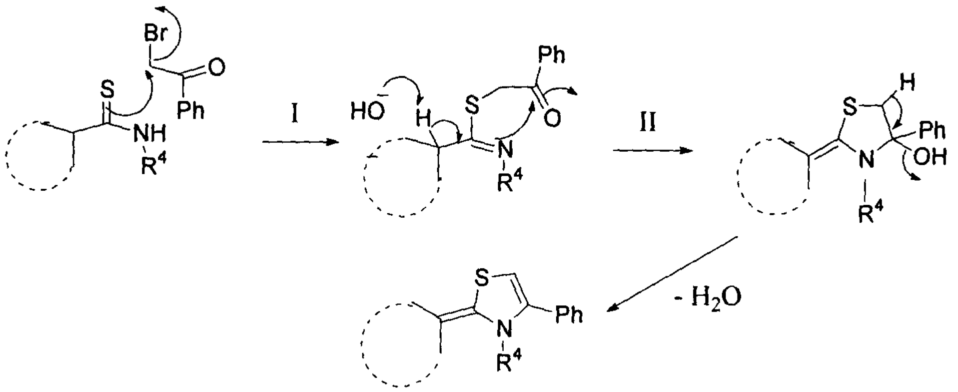
During our literature survey we found that the synthesis of thiazole and indazole starting from *β*-ketodithioesters and *β*-ketothioamides have not been reported. We thus became interested in exploring the possibility employing these easily available starting materials for the synthesis of substituted thiazole and indazole (Scheme 32). Herein, we reported the synthesis of thiazole compounds **140(a-l)** and indazole compounds **142(a-h)** using the *β*-ketodithioesters **138** starting from 3,4-dihydro-2*H*-naphthalen-1-one (or *α*-tetralone) to diverse substituted *α*-tetralones **137**.



Scheme 32

The *β*-oxodithioester are potential C3 fragments which are employed as versatile master key intermediate in a one-pot sequential reaction strategy for the synthesis. It is generally prepared by the reaction of *α*-tetralone **137** with carbon disulfide in basic media (NaH) using DMSO as solvent at 80°C for 2 h. The reaction mixture was then cooled to 0°C and dimethyl sulfate was added simultaneously followed by careful workup of the reaction mixture which affords only 30% yield of methyl-1-tetralone-2-dithiocarboxylate **138**. However, we prepared them using a modified procedure, and in this method *α*-tetralones **137** was treated with dimethyl trithiocarbonate by carrying out the reaction in benzene/dimethylformamide (10:1) at room temperature in the presence of sodium hydride. The reaction was completed within an hour, showing a single spot on TLC to give the corresponding *β*-oxodithiocarboxylates **138** in excellent yields. The enhancement in the reaction rate in DMF can be explained by the stabilizing effect of the polar solvent on the intermediate thiolate ion. The *β*-oxodithiocarboxylate or *β*-oxodithioester **138** is an interesting 1,3-dielectrophilic synthon for the synthesis of a variety of heterocyclic compounds.[41] This reactivity is due to leaving group ability of SMe when reacting with nucleophiles such as primary amine or secondary amine. Thus, when equimolar amount of primary amine or secondary amine in ethyl alcohol is added to the reaction mixture, it generated *in situ* *N*-substituted *β*-ketothioamide **139** and **141** (monitored by TLC). The primary amines used in this synthesis are methyl amine, ethyl amine and phenyl amine while the secondary cyclic amines used are piperidine, morpholine, 1-Phenyl-piperazine, 1-Pyridin-2-yl-piperazine respectively.

The probable mechanism for the formation of thiazole **140** from *β*-ketothioamide **139** in the presence of phenacyl bromide is shown in Scheme 33. The two nucleophilic centres in thioamides are localized on the heteroatoms (sulfur and nitrogen) and due to the presence of those active centres[42] the *β*-ketothioamide have the operational simplicity for reaction with 1,2-dielectrophilic reagent. The presence of phenacyl bromide as a dielectrophilic reagent, promotes condensation in step I and cyclization in step II, affording a five membered ring. It is observed that the process tolerates both electron-donating and electron-withdrawing substituents in α-tetralones **137**. Thus the reaction of *β*-ketothioamides **139(a-l)** with dielectrophilic reagents such as phenacyl bromide, proceeded efficiently at ambient temperature, which on dehydration giving a series *N*-substituted (3,4-dihydro-2*H*-naphthalen-1-one)-3*H*-thiazol-2-ylidene **140(a-l)** compounds (**Table** V, Scheme 33).

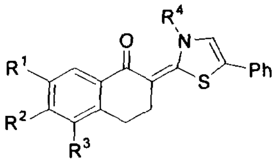


Scheme 33

All the products were characterized by ^{1}H and ^{13}C NMR spectroscopy, IR, melting points and elemental analyses. The formation of 2-(3-Methyl-4-phenyl-3*H*-thiazol-2-ylidene)-3,4-dihydro-2*H*-naphthalen-1-one **140a** was confirmed on the basis of analytical data and spectral evidences. Thus, it was analyzed for $C_{20}H_{17}NOS$ (Expected C, 75.20; H, 5.36; N, 4.39; Found: C, 75.24 H, 5.34; N, 4.36) and its mass spectrum showed the molecular ion peak at *m/z* 319. Its IR spectrum (KBr) exhibited a sharp absorption band at 1690 cm^{-1} which is characteristic for carbonyl stretching frequency and one at 1660 cm^{-1} for the C=N group. The final structural proof was obtained from its ^1H NMR ($CDCl_3$), which showed two singlets at δ 2.46 ppm (3H) and δ 6.62 ppm (1H) and were assigned to $-CH_3$ and C-5 of thiazole moiety. The two triplets was observed at δ 2.24 ppm ($J = 5.8$ Hz) and δ 2.58 ppm ($J = 5.8$ Hz) assignable to 2H, CH_2 of the 3,4-Dihydro-2*H*-naphthalen-1-one protons. The aromatic protons were observed as multiplets at δ 7.12–7.36 ppm (8H) and 7.62-7.76 ppm (1H). ^{13}C NMR ($CDCl_3$) showed resonances at δ ppm 146, 117 and 114 for C-1, C-3 and C-4 of the thiazole ring which are in accordance with the proposed structure. The analytical and spectral data for other thiazole derivatives **140(b-l)** are in conformity with the assigned structure, and are described in the experimental section.

Table V

Preparation of diverse *N*-substituted(3,4-dihydro-2*H*-naphthalen-1-one)-3*H*-thiazol-2-ylidene **140(a-l)**



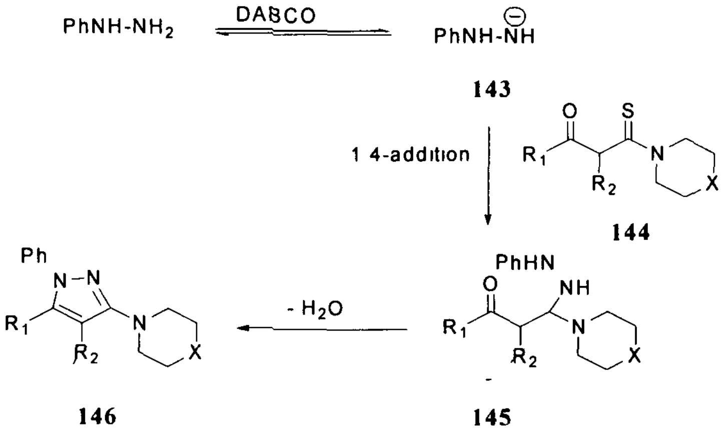
140(a-l)

Entry	Substrate **139(a-l)**	R^1	R^2	R^3	R^4	Product **140(a-l)**	Yield[a] %
1	**139a**	H	H	H	Me	**140a**	77
2	**139b**	H	H	H	Et	**140b**	78
3	**139c**	H	H	H	Ph	**140c**	84
4	**139d**	Me	H	Me	Me	**140d**	82
5	**139e**	Me	H	Me	Et	**140e**	74
6	**139f**	Me	H	Me	Ph	**140f**	82
7	**139g**	H	H	OH	Me	**140g**	85
8	**139h**	H	H	OH	Et	**140h**	86
9	**139i**	H	H	OH	Ph	**140i**	87
10	**139j**	OMe	OMe	H	Me	**140j**	73
11	**139k**	OMe	OMe	H	Et	**140k**	78
12	**139l**	OMe	OMe	H	Ph	**140l**	82

[a] Yields obtained are determined after work-up and Chromatographic purification. All the compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR and MS.

To further extend the scope of the reaction using *β*-ketothioamide derived from *β*-ketodithioester **138** of α-tetralone, the *β*-ketothioamide **141** were reacted with phenyl hydrazine with a view to synthesized 1-aryl-3-(*N*-cycloamino)-4,5-annulated indazoles **142** (Scheme 32) under DABCO-catalyzed conditions which were obtained in good yields.

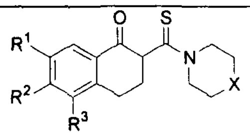
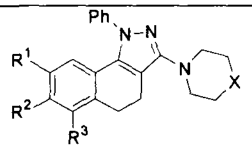
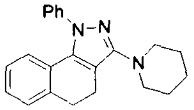
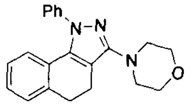
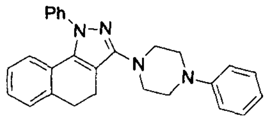
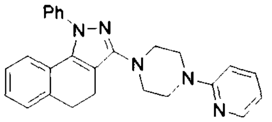
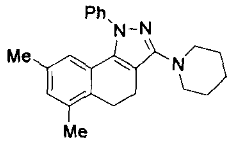
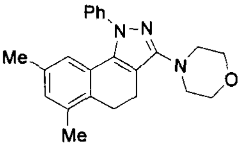
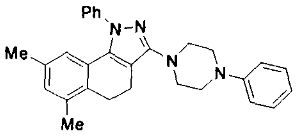
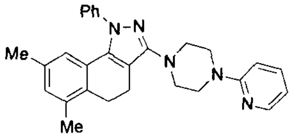
The probable mechanism for the formation of indazoles **142** from *β*-ketothioamide **141** is shown in Scheme 34. In the presence of a weaker and sterically crowded base such as DABCO, phenylhydrazine undergoes abstraction of the less hindered NH_2 proton, resulting in the formation of the anion **143**, which undergoes 1,4-addition elimination with *β*-ketothioamide **141** to give the intermediate adduct **145**.[43] Subsequent intramolecular cyclization of adduct **144** affords the 3-(cycloamino)indazole **146**. The *β*-ketothioamide **144** carrying a cycloamino group was next subjected to cyclization with phenylhydrazine under varying conditions. Best results were obtained when the reaction of **141** with phenylhydrazine was effected in the presence of a catalytic amount of acetic acid, yielding the corresponding 1-aryl-3-(*N*-cycloamino)-4,5-dihydro-1*H*-benzo[*g*]indazoles **142(a-h)** (**Table VI**).



Scheme 34

The formation of 1-aryl-3-(*N*-cycloamino)-4,5-dihydro-1*H*-benzo[*g*]indazoles **142(a-h)** was confirmed on the basis of analytical data and spectral evidences. Thus, it was analyzed for **142a** ($C_{22}H_{23}N_3$) (Expected C, 80.21; H, 7.04; N, 12.76; Found: C, 80.17, H, 7.06; N, 12.72) and the mass spectrum of it showed the molecular ion peak at *m/z* 329. Its IR spectrum (KBr) exhibited a sharp absorption band at 1665 cm^{-1} which is characteristic for C=N stretching frequency and one at 1570 cm^{-1} for a C=C bond in the indazole moiety. The final structural proof was obtained from its ^1H NMR spectrum ($CDCl_3$), which exhibited two triplets at δ 2.79 ppm (2H) and δ 2.88 ppm (J = 5.8 Hz, 2H) assignable to CH_2 protons, a multiplet at 1.50-1.56 (m, 6H) for CH_2 protons on a pyridinyl system. The aromatic protons were observed as multiplets at δ 7.12–7.34 ppm (8H) and one doublet at 7.76 ppm (J = 8.4 Hz, 1H). The ^{13}C NMR spectrum ($CDCl_3$) showed resonances at δ ppm 162.1, 104.02, 141.6 for C-3, C-4 and C-5 of the indazole ring respectively. The analytical and spectral data for other indazole derivatives **142(b-h)** are described in the experimental section.

Table VI. Preparation of 1-aryl-3-(*N*-cycloamino)-4,5-dihydro-1*H*-benzo[*g*] indazoles **142(a-h)**

Entry	Intermediate **141(a-h)**	Product **142(a-h)**		Yield %
				
1	**a,** $R^1, R^2, R^3 = H, X = H$		**142a**	64
2	**b,** $R^1, R^2, R^3 = H, X = O$		**142b**	68
3	**c,** $R^1, R^2, R^3 = H$, X = N-Bn		**142c**	72
4	**d,** $R^1, R^2, R^3 = H$, X = N-2-(pyridyl)		**142d**	76
5	**e,** $R^1 = Me, R^2 = H, R^3 = Me$, $X = H$		**142e**	80
6	**f,** $R^1 = Me, R^2 = H, R^3 = Me$, $X = O$		**142f**	64
7	**g,** $R^1 = Me, R^2 = H, R^3 = Me$, X = N-Bn		**142g**	72
8	**h,** $R^1 = Me, R^2 = H, R^3 = Me$, X = N-2-(pyridyl)		**142h**	78

[a] Yields obtained are determined after work-up and Chromatographic purification. All the compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR and MS.

V. 3. EXPERIMENTAL

Melting points was determined on a "Thomas Hoover" capillary melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AMX 400 instrument using $CDCl_3$ as the solvent. Chemical shifts are reported in ppm using tetramethylsilane as internal standard. *J* values are given in Hz. The following abbreviations are used to describe peak patterns when appropriate: br = broad, s = singlet, d = doublet, dd = double doublet, dt = double triplet, t = triplet, q = quartet, m = multiplet. IR spectra were recorded on a Perkin-Elmer BX spectrophotometer. ESI mass spectra were measured on an ion trap analyzer Esquire 3000 (Bruker Daltonics). Masses (MS) are reported in unit of mass over charge (*m/z*), the molecular or base peaks and relative intensities are indicated by (M^+) and (%) respectively. CHN analyses were recorded on a Vario EL analyser. Column chromatography was performed using silica gel (60-120 mesh, Merck).

All reactions were performed in oven dried (120°C) glasswares under a positive dry argon/nitrogen atmosphere. Analytical thin layer chromatography (TLC) were performed on glass plates coated with ACME's silica gel containing 13% calcium sulphate as binder and various combination of visualization of spots was accomplished by exposure to UV lamp or iodine vapour or by spraying potassium permanganate (acidic) solution or 2% ninhydrin solution. Eluents for column chromatography were used after simple distillation of commercial solvents. All solvent evaporations were done using a rotaevaporator (BUCHI Rotavapor R II, vacuum pump V-700) and a steam bath.

Chemical Reagents and Solvents:

Commercially available NaH, 50% suspension, *t*-BuOH (Sisco Spectrochem) was used, *N,N*-dimethylformamide (Aldrich) was purchased bottle grade and dried over CaH, distilled and store over molecular sieves (4A). 'Super-dry' ethanol prepared is hygroscopic; it is stored over a Type 4A molecular sieve. Commercially available solvents such as benzene, dichloromethane (DCM), etc., were purified either by simple distillation / distillation under reduced pressure before use. Anhydrous ether and dichloromethane (DCM) was obtained by keeping the bottle grade over calcium chloride over night and finally stored over sodium wire or Type 3A molecular sieve. Dry benzene was obtained by washing with concentrated sulphuric acid followed by azeotropic distillation and stored over sodium wire. Sodium tertiary butoxide was freshly prepared for each reaction.

Starting Materials:

Substituted α-tetralones, dimethyl trithiocarbonate was purchased from Sigma-Aldrich and was used for the preparations of *β*-oxodithioester. Carbon disulfide (CS_2), dimethyl sulfoxide (DMSO), phenacyl bromide, DABCO (Aldrich) used were analytical reagent bottle grade. Commercially available, methylamine, ethylamine, aniline, piperidine, morpholine, *N*-benzylpiperazine, *N*-pyridinylpiperazine were used directly without further purification. Trithiocarbonate esters (dimethyl trithiocarbonate bp 225°C, 760 mm) was also prepared according to the reported procedure.[44] *β*-ketothioester required for the present investigation were prepared (using protective gloves and mask under fume cupboard) according to the earlier reported literature procedures[45,46,47] with some minor modifications as shown below.

General procedure for the synthesis of *β*-Oxodithioester 138:

α-tetralone **137** (6.0 mmol) was added to a suspension of NaH (50% suspension in mineral oil, 1.94 g, 40 mmol) in DMF/benzene solvent mixture (50 mL, 1:10; benzene bp 76-80 °C). Dimethyl trithiocarbonate (20 mmol) was added to the solution and stirred well for about 1 hour. The reaction formed at the interface between the two layers present in the reaction mixture. The reaction was exothermic and the reaction was cooled in a water bath at room temperature. After 1 hr, the reaction mixture was acidified with 3N HCl (20 mL), the precipitated dithiocarboxylates were extracted with chloroform (2 x 150 mL).The extract is dried with sodium sulfate and evaporated to give the product **138**.

General procedure for the synthesis of *β*-Oxothioamide 139:

The *β*-oxodithiocarboxylates **138** was treated with equimolar amount of primary amine (methyl amine / ethyl amine / phenyl amine, 10 mmol) in ethanol (15 mL) and the reaction mixture was refluxed with stirring for 2 hr. It was cooled to room temperature, poured over water (2 x 50 mL), quenched with saturated solution of $NaHCO_3$ (1 x 25 mL), extracted with DCM (2 x 50 mL). The extract is dried with anhydrous Na_2SO_4 and the solvent was evaporated to give the corresponding *β*-oxothioamide **139** in good yields (single spot on TLC). Purification may be achieved by column chromatography on silica gel (50 g) using hexane as eluent.

General procedure for the synthesis of 2-(cycloamino-1-carbothioyl)-3,4-dihydro-2*H*-naphthalen-1-one or *β*-Oxothioamide 141:

The *β*-oxodithiocarboxylates **138** was treated with equimolar amount of secondary amines (piperidine, morpholine, N-benzylpiperazine, N-pyridinylpiperazine, 10 mmol) in ethanol (15 mL) and the reaction mixture was refluxed with stirring for 2 hr. It was cooled to room temperature, poured over water (2 x 50 mL), quenched with saturated solution of $NaHCO_3$ (1 x 25 mL), extracted with DCM (2 x 50 mL). The extract is dried with anhydrous Na_2SO_4 and the solvent was evaporated to give the corresponding *β*-oxothioamide **141** in good yields (single spot on TLC). Purification may be achieved by column chromatography on silica gel (50 g) using hexane as eluent.

General procedure for the synthesis of 2-(3-Methyl-4-phenyl-3*H*-thiazol-2-ylidene)-3,4-dihydro-2*H*-naphthalen-1-one 140a:

To a magnetically stirred mixture of *β*-Oxothioamide **139a** (5.0 mmol) in benzene (10 mL) and KOH (0.62 g, 10 mmol), phenacyl bromide (1.10 g, 5.0 mmol) was added in drop wise. The reaction mixture was reflux to 80-90°C for 4-5 hours and left at room temperature over night (monitored by TLC). It was poured over water (2 x 50 mL) and extracted with DCM (3 x 50 mL), brine (1 x 50 mL) and dried over Na_2SO_4. The solvent was evaporated under vacuum to give crude products which were purified by column chromatography over silica gel using hexane/EtOAc (10:1) as eluent affording **140a**: Yield 77 % (1.05 g); colourless crystals, mp 202-203°C; IR (KBr): 3350, 2944, 1710, 1660, 1498, 1286, 1178; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 2.24 (t, $J = 5.8$ Hz, 2H, CH_2), 2.46 (s, 3H, CH_3), 2.58 (t, $J = 5.8$ Hz, 2H, CH_2), 6.62 (s, 1H, C-5 of thiazole), 7.21–7.66 (m, 9H, ArH), 7.78 (d, $J = 8.4$ Hz, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 22.5, 28.4, 35.7, 100, 114.11, 117.33, 126, 127, 128, 129, 134, 136.12, 141.40, 146.5, 187.21; MS (CI) $m/z = 319$; Anal. Calcd for $C_{20}H_{17}NOS$ (319): C, 75.20;

H, 5.36; N, 4.39; Found: C, 75.24 H, 5.34; N, 4.36. Other compounds **135(b-l)** were also prepared using similar procedure.

2-(3-Ethyl-5-phenyl-3*H*-thiazol-2-ylidene)-3,4-dihydro-2*H*-naphthalen-1-one (140b): Yield 78 % (1.12 g); white crystals, mp 127-128°C; IR (KBr): 3354, 2947, 1708, 1664, 1495, 1288, 1174; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.04 (t, 3H, CH_3), 2.28 (t, J = 5.8 Hz, 2H, CH_2), 2.58 (t, J = 5.8 Hz, 2H, CH_2), 2.68 (q, 2H, CH_2), 6.65 (s, 1H, CH of thiazole), 7.12–7.34 (m, 8H, ArH), 7.76 (d, J = 8.4 Hz, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 13.5, 22.5, 22.56, 28.41, 43.7, 100.12, 114.11, 117.33, 126.03, 126.21, 126.47, 127.23, 127.73, 128.43 (x 2C), 129.22, 134.14, 136.12, 141.34, 146.23, 187.27; MS (CI) *m/z* = 333; Anal. Calcd for $C_{21}H_{19}NOS$ (333): C, 75.67; H, 5.73; N, 4.23; Found: C, 75.64 H, 5.64; N, 4.16.

2-(3,5-Diphenyl-3*H*-thiazol-2-ylidene)-3,4-dihydro-2*H*-naphthalen-1-one (140c): Yield 84% (1.36 g); light brown crystals, mp 167-168°C; IR (KBr): 3357, 2947, 1712, 1664, 1490, 1288, 1172; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 2.26 (t, J = 5.8 Hz, 2H, CH_2), 2.57 (t, J = 5.8 Hz, 2H, CH_2), 6.62 (s, 1H, CH of thiazole), 6.46 (d, J = 8.4 Hz, 2H), 7.12–7.34 (m, 10H, ArH), 7.49 (t, J = 7.4 Hz, 1H, ArH), 7.76 (d, J = 8.4 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 22.5, 28.4, 43.7, 100.05, 115.21, 115.28, 117.33, 118.5, 120.2, 126.03, 126.18, 126.24, 127.23, 128.13(x 2C), 128.54, 129.21, 129.32, 129.42, 134.14, 136.12, 141.34, 146.23, 152.5 187.27; MS (CI) *m/z* = 381; Anal. Calcd for $C_{25}H_{19}NOS$ (381): C, 78.69; H, 5.03; N, 4.63; Found: C, 78.64 H, 5.04; N, 4.61.

5,7-Dimethyl-2-(3-methyl-5-phenyl-3*H*-thiazol-2-ylidene)-3,4-dihydro-2*H*-naphthalen-1-one (140d). Yield 82 % (1.13 g); brown crystals, mp 120-121°C; IR (KBr): 3354, 2948, 1707, 1657, 1494, 1280, 1175; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm

2.26 (t, $J = 5.8$ Hz, 2H, CH_2), 2.32 (s, 3H, CH_3), 2.57 (t, $J = 5.8$ Hz, 2H, CH_2), 6.62 (s, 1H, CH of thiazole), 6.46 (d, $J = 8.4$ Hz, 2H, ArH), 7.09 (s, 1H, ArH), 7.12–7.34 (m, 6H, ArH), 7.37 (s, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 15.23, 21.2, 21.6, 22.8, 28.4, 35.7, 100.12, 114.21, 117.24, 126.04, 126.24, 127, 128.21(x 2C), 129.52, 129.58, 135.03, 135.62, 137.52, 139.25, 146.5, 187.01; MS (CI) *m/z* = 347; Anal. Calcd for $C_{22}H_{21}NOS$ (347): C, 76.04; H, 6.09; N, 4.03; Found: C, 76.10 H, 6.03; N, 4.06.

2-(3-Ethyl-5-phenyl-3*H*-thiazol-2-ylidene)-5,7-dimethyl-3,4-dihydro-2*H*-naphthalen-1-one (140e): Yield 74 % (1.02 g); brown crystals, mp 134-135°C; IR (KBr): 3350, 2942, 1710, 1652, 1492, 1284, 1176; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.04 (t, 3H, CH_3), 2.26 (t, $J = 5.8$ Hz, 2H, CH_2), 2.32 (s, 3H, CH_3), 2.57 (t, $J = 5.8$ Hz, 2H, CH_2), 2.68 (q, 2H, CH_2), 6.62 (s, 1H, CH of thiazole), 6.46 (d, $J = 8.4$ Hz, 2H), 7.09 (s, 1H, ArH), 6.68–7.30 (m, 8H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 13.15, 15.14, 21.2, 22.8, 28.4, 35.7, 43.4, 100.27, 114.21, 117, 126.04, 126.17, 127.04, 128.21(x 2C), 129.62, 129.8, 135.03, 135.25, 135.36, 137.52, 146.5, 187.14; MS (CI) *m/z* = 361; Anal. Calcd for $C_{23}H_{23}NOS$ (361): C, 76.43; H, 6.40; N, 4.04; Found: C, 76.30 H, 6.40; N, 4.06.

2-(3,5-Diphenyl-3*H*-thiazol-2-ylidene)-5,7-dimethyl-3,4-dihydro-2*H*-naphthalen-1-one (140f): Yield 82% (1.28 g); pale yellow crystals, mp 148-149°C; IR (KBr): 3356, 2948, 1712, 1655, 1490, 1282, 1172; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 2.26 (t, $J =$ 5.8 Hz, 2H, CH_2), 2.32 (s, 3H, CH_3), 2.58 (t, $J = 5.8$ Hz, 2H, CH_2), 2.64 (q, 2H, CH_2), 6.68 (s, 1H, CH of thiazole), 7.10 (s, 1H, ArH), 7.12–7.34 (m, 6H, ArH), 7.38 (s, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 15.14, 21.2, 21.9, 22.8, 28.4, 35.7, 43.4, 114.21, 115.12, 117.03, 118.07, 120.21, 126.34, 126.36, 127.2, 128.21, 128.34, 129.02, 129.22, 134.11, 135.26, 135.43, 137.52, 139.21, 146.15, 152.09, 187.64; MS (CI) *m/z* =

409. Anal. Calcd for $C_{27}H_{23}NOS$ (409): C, 79.14; H, 5.64; N, 3.48; Found: C, 79.10 H, 5.50; N, 3.36.

5-Hydroxy-2-(3-methyl-5-phenyl-3*H*-thiazol-2-ylidene)-3,4-dihydro-2*H*-naphthalen-1-one (140g): Yield 85% (1.20g); yellow crystals, mp 131-132°C; IR (KBr): 3350, 3342, 1708, 1656, 1492, 1285, 1176; ^1H NMR (400 MHz, $CDCl_3$): δ ppm 2.26 (t, J = 5.8 Hz, 2H, CH_2), 2.42 (s, 3H, CH_3), 2.62 (t, J = 5.8 Hz, 2H, CH_2), 4.97(s, 1H, OH), 6.68 (s, 1H, CH of thiazole), 7.02 (d, J = 7.6 Hz, 2H, ArH), 7.12–7.34 (m, 7H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 18.6, 22.2, 35.06, 100.6, 114.22, 117.12, 121.11, 122.02, 126.21, 126.24, 127.72, 127.81, 128.2, 128.10, 128.12, 128.42, 137.32, 146.52, 157.12, 187.04; MS (CI) m/z = 335: Anal. Calcd for $C_{20}H_{17}NO_2S$ (335): C, 71.62; H, 5.11; N, 4.18; Found: C, 71.44 H, 5.12; N, 4.14.

2-(3-Ethyl-5-phenyl-3*H*-thiazol-2-ylidene)-5-hydroxy-3,4-dihydro-2*H*-naphthalen-1-one (140h). Yield 86% (1.27 g); light brown crystals, mp 128-129°C; IR (KBr): 3354, 3340, 1690, 1651, 1494, 1282, 1172; ^1H NMR (400 MHz, $CDCl_3$): δ ppm 1.12 (t, 3H, CH_3), 2.27 (t, J = 5.8 Hz, 2H, CH_2), 2.42 (s, 3H, CH_3), 2.57 (t, J = 5.8 Hz, 2H, CH_2), 2.69 (q, 2H, CH_2), 5.06(s, 1H, OH), 6.68 (s, 1H, CH of thiazole), 7.02 (d, J = 7.6 Hz, 2H, ArH), 7.12–7.34 (m, 7H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 13.17, 18.2, 22.2, 43.5, 100.43, 114.25, 117.12, 121.40, 122.12, 126.21, 126.36, 127.72, 127.81, 128.12(x 2C), 128.42, 134.91, 137.83, 146.52, 157.24, 187.04; MS (CI) m/z = 349: Anal. Calcd for $C_{21}H_{19}NO_2S$ (349): C, 72.18; H, 5.49; N, 4.01; Found: C, 72.14 H, 5.45; N, 4.04.

2-(3,5-Diphenyl-3*H*-thiazol-2-ylidene)-5-hydroxy-3,4-dihydro-2*H*-naphthalen-1-one (140i): Yield 87% (1.28 g); pale yellow crystals, mp 105-106°C; IR (KBr): 3352, 3344, 1695, 1657, 1495, 1287, 1174; ^1H NMR (400 MHz, $CDCl_3$): δ ppm 2.27 (t, J =

5.8 Hz, 2H, CH_2), 2.42 (s, 3H, CH_3), 2.57 (t, J = 5.8 Hz, 2H, CH_2), 4.89 (s, 1H, OH), 6.62 (t, J = 7.6 Hz, 1H, ArH), 6.48 (d, J = 7.6 Hz, 2H, ArH), 6.68 (s, 1H, CH of thiazole), 7.12–7.34 (m, 10H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 18.6, 22.2, 35.06, 100.6, 114.22, 115.08, 115.12, 118.10, 120.09, 122.02, 126.21, 126.52, 127.76, 127.81, 128.02 (x 2C), 128.12, 128.42, 129.03, 129.24, 134.4, 137.32, 146.32, 157.42, 187.20; MS (CI) m/z = 397: Anal. Calcd for $C_{25}H_{19}NO_2S$ (397): C, 75.54; H, 4.81; N, 3.68; Found: C, 75.44 H, 4.72; N, 3.61.

6,7-Dimethoxy-2-(3-methyl-4-phenyl-3*H*-thiazol-2-ylidene)-3,4-dihydro-2*H*-naphthalen-1-one (140j). Yield 73% (0.98 g); pale yellow crystals, mp 220-221°C; IR (KBr): 3352, 2941, 1687, 1660, 1492, 1288, 1171; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 2.27 (t, J = 5.8 Hz, 2H, CH_2), 2.47 (s, 3H, CH_3), 2.57 (t, J = 5.8 Hz, 2H, CH_2), 3.87 (s, 3H, OMe), 5.72 (s, 1H, CH of thiazole), 6.72 (s, 1H, ArH), 7.11–7.32 (m, 6H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 22.5, 28.7, 32.02, 35.7, 56.12, 56.38, 100.21, 115.12, 116.24, 117.33, 126.21, 126.42, 127, 128.02(x 2C), 129.42, 134.22, 136.12, 145.41, 146.15, 153.14, 187.21; MS (CI) m/z = 379: Anal. Calcd for $C_{22}H_{21}NO_3S$ (379): C, 69.63; H, 5.58; N, 3.69; Found: C, 69.24 H, 5.44; N, 3.56.

6,7-Dimethoxy-2-(3-ethyl-4-phenyl-3*H*-thiazol-2-ylidene)-3,4-dihydro-2*H*-naphthalen-1-one (140k): Yield 78% (1.22 g); yellow crystals, mp 182-183°C; IR (KBr): 3350, 2944, 1682, 1664, 1490, 1282, 1174; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.12 (t, 3H, CH_3), 2.27 (t, J = 5.8 Hz, 2H, CH_2), 2.57 (t, J = 5.8 Hz, 2H, CH_2), 2.69 (q, 2H, CH_2), 3.82 (s, 3H, CH_3), 5.72 (s, 1H, CH of thiazole), 6.71 (s, 1H, ArH), 7.12–7.36 (m, 6H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 13.6, 22.5, 28.7, 35.7, 43.5, 56.12, 56.38, 100.21, 114.11, 115, 116.24, 117.33, 126.03, 126.06, 127.05, 128.04, 128.32, 129.42, 134.22, 136.12, 145.41, 146.15, 187.21; MS (CI) *m/z* = 393: Anal. Calcd for $C_{23}H_{23}NO_3S$ (393): C, 70.23; H, 5.87; N, 3.56; Found: C, 70.14 H, 5.54; N, 3.50.

2-(3,4-Diphenyl-3*H*-thiazol-2-ylidene)-6,7-dimethoxy-3,4-dihydro-2*H*-naphthalen-1-one (140l). Yield 82 % (1.18 g); yellow crystals, mp 124-125°C; IR (KBr): 3354, 2945, 1687, 1667, 1482, 1283, 1177; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 2.28 (t, J = 5.8 Hz, 2H, CH_2), 2.59 (t, J = 5.8 Hz, 2H, CH_2), 3.87 (s, 3H, OMe), 5.72 (s, 1H, CH of thiazole), 6.42 (d, J = 7.6 Hz, 2H, ArH), 6.70 (s, 1H, ArH), 7.11–7.32 (m, 9H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 22.5, 28.7, 56.12, 56.38, 94.3, 109.72, 115.12, 115.21, 115.46, 116.12, 118.2, 126.22 (x 2C), 127.71, 127.14, 128.04 (x 2C), 129.42, 134.22, 136.12, 143.2, 145.41, 146.15, 150.2, 152.22, 153.30, 187.21; MS (CI) *m/z* = 441: Anal. Calcd for $C_{27}H_{23}NO_3S$ (441): C, 73.44; H, 5.25; N, 3.19; Found: C, 73.41; H, 5.14; N, 3.16.

General procedure for preparation of 1-aryl-3-(*N*-cycloamino) annulated indazoles 142a-h. A solution of respective β-ketothioamide **141** (5 mmol), arylhydrazine (6 mmol), and DABCO (0.67 g, 6 mmol) in 50 mL of *t*-BuOH with a catalytic amount of acetic acid (3 mL) was refluxed for 12-16 h with constant stirring, the reaction being monitored by TLC. The reaction mixture was concentrated under reduced pressure and poured into ice-cold water, extracted with DCM (3 x 50 mL), washed with H_2O (2 x 50 mL) and brine (1 x 50 mL), and dried over Na_2SO_4. The solvent was evaporated under vacuum to give indazole **142**, which were purified by column chromatography over silica gel using hexane/EtOAc (10:1) as eluent.

1-Phenyl-3-piperidin-1-yl-4,5-dihydro-1*H*-benzo[*g*]indazole 142a: Yield 64 % (1.02 g); white crystals, mp 98-99°C; IR (KBr): 3354, 2940, 1665, 1570, 1174; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.50-1.56 (m, 6H), 2.79 (t, J = 5.8 Hz, 2H, CH_2), 2.88

(t, $J = 5.8$ Hz, 2H, CH$_2$), 7.12–7.34 (m, 8H, ArH), 7.76 (d, $J = 8.4$ Hz, 1H, ArH); ^{13}C NMR (100 MHz, CDCl$_3$): δ ppm 18.31, 25.5(2), 26.36, 33.6, 54.17, 54.36, 104.24, 118.87, 118.9, 126.07, 126.11, 126.9, 128.41, 128.43, 129.10, 129.27, 135.14, 138.12, 139.7, 141.62, 162.16; MS (CI) *m/z* = 329; Anal. Calcd for $C_{22}H_{23}N_3$ (329.41): C, 80.21; H, 7.04; N, 12.76; Found: C, 80.17, H, 7.06; N, 12.72.

3-Morpholin-4-yl-1-phenyl-4,5-dihydro-1*H*-benzo[*g*]indazole 142b: Yield 68 % (1.14 g); pale yellow crystals, mp 131-132°C; IR (KBr): 3352, 2942, 1664, 1572, 1170; ^{1}H NMR (400 MHz, CDCl$_3$): δ ppm 2.58 (t, $J = 5.8$ Hz, 2H, CH$_2$), 2.86 (t, $J = 5.8$ Hz, 2H, CH$_2$), 2.98 (t, $J = 6.2$, Hz, 4H, CH$_2$), 3.67 (t, $J = 6.2$, Hz, 4H, CH$_2$), 7.12–7.34 (m, 8H, ArH), 7.76 (d, $J = 8.4$ Hz, 1H, ArH); ^{13}C NMR (100 MHz, CDCl$_3$): δ ppm 18.31, 33.6, 58.91, 58.97, 71.46, 71.62, 104.24, 118.87, 118.97, 126.07, 126.11, 126.9, 128.41, 128.43, 129.10, 129.41, 135.14, 138.12, 139.7, 141.62, 162.16; MS (CI) *m/z* = 331; Anal. Calcd for $C_{21}H_{21}N_3O$ (331.17): C, 76.11; H, 6.37; N, 12.68; Found: C, 76.14, H, 6.32; N, 12.63.

1-Phenyl-3-(4-phenyl-piperazin-1-yl)-4,5-dihydro-1*H*-benzo[*g*]indazole 142c: Yield 72 % (1.20 g); white crystals, mp 162-163°C; IR (KBr): 3354, 2944, 1667, 1573, 1172; ^{1}H NMR (400 MHz, CDCl$_3$): δ ppm 2.67 (t, $J = 5.8$ Hz, 2H, CH$_2$), 2.78 (t, $J = 5.8$, Hz, 4H, CH$_2$), 3.25 (t, $J = 6.2$, Hz, 4H, CH$_2$), 3.57 (t, $J = 6.2$, Hz, 4H, CH$_2$), 6.59 (d, $J = 8.4$ Hz, 1H, ArH), 7.01–7.34 (m, 11H, ArH), 7.76 (d, $J = 8.4$ Hz, 1H, ArH); ^{13}C NMR (100 MHz, CDCl$_3$): δ ppm 18.31, 33.6, 57.51, 57.58, 57.72, 57.78, 104.24, 113.16, 113.18, 118.02, 118.07, 118.23, 126.07, 126.11, 126.9, 128.41, 128.43, 129.12, 129.17, 129.40, 129.56, 135.14, 138.12, 139.7, 141.62, 144.5, 162.16; MS (CI) *m/z* = 406; Anal. Calcd for $C_{27}H_{26}N_4$ (406.22): C, 79.78; H, 6.46; N, 13.78; Found: C, 79.75, H, 6.50; N, 13.75.

1-Phenyl-3-(4-pyridin-2-yl-piperazin-1-yl)-4,5-dihydro-1*H*-benzo[*g*]indazole 142d: Yield 76 % (1.22 g); white crystals, mp 140-141°C; IR (KBr): 3356, 2943, 1665, 1572, 1173; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 2.68 (t, J = 5.8 Hz, 2H, CH_2), 2.87 (t, J = 5.8, Hz, 4H, CH_2), 3.26 (t, J = 6.2, Hz, 4H, CH_2), 3.29 (t, J = 6.2, Hz, 4H, CH_2), 6.59 (d, J = 8.4 Hz, 1H, ArH), 7.01–7.34 (m, 10H, ArH), 7.76 (d, J = 8.4 Hz, 1H, ArH), 8.12 (d, J = 8.4 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 18.32, 33.26, 57.55(2), 57.78 (2), 104.26, 108.12, 113.18, 118.19, 118.32, 126.07, 126.14, 126.17, 128.41, 128.43, 129.40, 129.67, 135.14, 138.12, 138.28, 139.7, 141.62, 148.91, 161.14, 162.16; MS (CI) *m/z* = 407; Anal. Calcd for $C_{26}H_{25}N_5$ (407.22): C, 76.64; H, 6.18; N, 17.19; Found: C, 76.58, H, 6.23; N, 17.14.

6,8-Dimethyl-1-phenyl-3-piperidin-1-yl-4,5-dihydro-1*H*-benzo[*g*]indazole 142e: Yield 80 % (1.31 g); yellow crystals, mp 144-145°C; IR (KBr): 3357, 2940, 1662, 1570, 1175; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.50-1.55 (m, 6H), 2.35 (brs, 3H, CH_3), 2.58 (t, J = 5.8, Hz, 2H, CH_2), 2.68 (t, J = 5.8 Hz, 2H, CH_2), 2.88 (t, J = 5.8 Hz, 2H, CH_2), 6.78 (t, J = 2.5 Hz, 1H, ArH), 7.21–7.36 (m, 6H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 15.31, 18.6, 21.50, 25.71, 25.98, 26.24, 27.21, 54.71, 54.97, 104.03, 118.05, 118.84, 124.10, 126.8, 129.50, 129.67, 129.81, 135.02, 135.7, 136.02, 137.7, 139.71, 141.6, 162.14; MS (CI) *m/z* = 357; Anal. Calcd for $C_{24}H_{27}N_3$ (357.20): C, 80.63; H, 7.60; N, 11.75; Found: C, 80.67, H, 7.64; N, 11.70.

6,8-Dimethyl-3-morpholin-4-yl-1-phenyl-4,5-dihydro-3a*H*-benzo[*g*]indazole 142f: Yield 64 % (1.02 g); yellow crystals, mp 176-177°C; IR (KBr): 3348, 2944, 1664, 1573, 1172; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 2.35 (brs, 3H, CH_3), 2.57 (t, J = 5.8, Hz, 2H, CH_2), 2.94 (t, J = 6.2, Hz, 4H, CH_2), 3.67 (t, J = 6.2 Hz, 4H, CH_2), 6.82 (t, J = 2.5 Hz, 1H, ArH), 7.21–7.36 (m, 6H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 15.01, 18.20, 21.7, 27.4, 37.6, 58.7, 58.81, 71.29, 71.87, 118.05, 118.84, 124.10, 126.8, 129.70, 129.92, 129.81, 135.02, 135.7, 136.02, 137.7, 139.71, 141.6, 162.14; MS (CI) *m/z* = 359; Anal. Calcd for $C_{23}H_{25}N_3O$ (359.20): C, 76.86; H, 7.01; N, 11.69; Found: C, 76.82, H, 7.05; N, 11.63.

6,8-Dimethyl-3-morpholin-4-yl-1-phenyl-4,5-dihydro-1*H*-benzo[*g*]indazole 142g: Yield 72 % (1.07 g); yellow crystals, mp 157-158°C; IR (KBr): 3349, 2942, 1666, 1572, 1174; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 2.32 (brs, 3H, CH_3), 2.65 (t, *J* = 5.8, Hz, 2H, CH_2), 2.88 (t, *J* = 5.8, Hz, 2H, CH_2), 3.29 (t, *J* = 6.2, Hz, 4H, CH_2), 3.57 (t, *J* = 6.2 Hz, 4H, CH_2), 6.59 (d, *J* = 8 Hz, 2H, ArH), 6.78 (t, *J* = 2.5 Hz, 1H, ArH), 7.01–7.36 (m, 9H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 15.01, 18.04, 21.20, 27.7, 57.3, 57.64, 58.15, 58.72, 104.22, 113.02, 113.52, 118.0, 118.12, 118.52, 125.10, 126.8, 127.02, 129.4(x 2C), 129.29, 129.57, 135.02, 135.7, 136.02, 137.7, 139.71, 141.6, 144.57, 162.14; MS (CI) *m/z* = 434; Anal. Calcd for $C_{29}H_{30}N_4$ (434.25): C, 80.16; H, 6.96; N, 12.89; Found: C, 80.18, H, 6.91; N, 12.83.

6,8-Dimethyl-1-phenyl-3-(4-pyridin-2-yl-piperazin-1-yl)-4,5-dihydro-1*H*-benzo[*g*]indazole 142h: Yield 78 % (1.17 g); yellow crystals, mp 150-151°C; IR (KBr): 3348, 2946, 1660, 1577, 1170; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 2.38 (brs, 3H, CH_3), 2.68 (t, *J* = 5.8 Hz, 2H, CH_2), 2.87 (t, *J* = 5.8, Hz, 4H, CH_2), 3.29 (t, *J* = 6.2, Hz, 4H, CH_2), 3.58 (t, *J* = 6.2 Hz, 4H, CH_2), 6.78 (t, *J* = 2.5 Hz, 1H, ArH), 6.60–7.46 (m, 9H, ArH), 8.12 (d, *J* = 8 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 15.01, 18.04, 21.20, 27.7, 57.13, 57.38, 58.17, 58.41, 104.12, 108.2, 113, 118.0, 118.12, 125.10, 126.8, 129.4(x 2C), 129.29, 129.63, 135.02, 135.7, 136.21, 137.7, 138.31, 139.71, 141.6, 161.04, 162.57; MS (CI) *m/z* = 435; Anal. Calcd for $C_{28}H_{29}N_5$ (435.57): C, 77.26; H, 6.73; N, 16.08; Found: C, 77.23, H, 6.76; N, 16.02.

V. 4. REFERENCES

1. Hantzsch, A. and Weber, H. J. *Berichte*, **1887,** *20,* 3118.
2. Metzger, V. Jacques *Heterocyclic compounds, Thiazole and its derivatives,* **1979,** 34, I, Interscience Publication.
3. Breslow, R. *J. Am. Chem. Soc.* **1958,** *80,* 3719.
4. (a) Terrett, N. K.; Gardener, M.; Gordon, D. W.; Kobylecki, R. J.; Steele, J. *Tetrahedron* **1995**, *30,* 8135. (b) Balkenhohl, F.; Bussche-Hunnefeld, C.; Lansky, A.; Zechel, C. *Angew. Chem., Int. Ed.Engl.* **1996,** *35,* 2288. (c) Nefzi, A.; Ostresh, J. M.; Houghten, R. A. *Chem. Rev.* **1997**, 449.
5. Pons, J. F.; Mishir, Q.; Nouvet, A.; Brookfield, F. *Tetrahedron Lett.* **2000**, *41,* 4965-4968.
6. (a) Baxter, A. D. *Curr. Opin. Chem. Biol.* **1997**, *1,* 79;(b) Rich, D. H.; Wiley, R. A. *Med. Res. Rev.* **1993**, *13,* 327;(c) Kearney, P. C.; Fernandez, M.; Flygare, J. A. *J. Org. Chem.* **1998**, *62,* 196; (d) Goff, D.; Fernandez, J. *Tetrahedron Lett.* **1999**, *40,* 423.
7. Haviv, F.; Ratajczyk, J. D.; DeNet, R. W.; Kerdesky, F. A.; Walters, R. L.; Schmidt, S. P.; Holms, J. H.; Young, P. R.; Carter, G. W. *J. Med. Chem.* **1988**, *31,* 1719.
8. Patt, W. C.; Hamilton, H. W.; Taylor, M. D.; Ryan, M. J.; Taylor, D. G., Jr.; Connolly, C. J. C.; Doherty, A. M.; Klutchko, S. R.; Sircar, I.; Steinbaugh, B. A.; Batley, B. L.; Painchaud, C. A.; Rapundalo, S. T.; Michniewicz, B. M.; Olson, S. C. J. *J. Med. Chem.* **1992,** *35,* 2562.
9. Tsuji, K.; Ishikawa, H. *Bioorg. Med. Chem. Lett.* **1994,** *4,* 1601.
10. (a) Bell, F. W.; Cantrell, A. S.; Hoegberg, M.; Jaskunas, S. R.; Johansson, N. G.;

Jordon, C. L.; Kinnick, M. D.; Lind, P.; Morin, J. M., Jr.; Noreen, R.; O berg, B.; Palkowitz, J. A.; Parrish, C. A.; Pranc, P.; Sahlberg, C.; Ternansky, R. J.; Vasileff, R. T.; Vrang, L.; West, S. J.; Zhang, H.; Zhou, X. X. *J. Med. Chem.* **1995**, *38*, 4929. (b) Bauer, W.; Kuhlein K. *Houben-Weyl's Methoden der Organischen Chemie*; Georg Thieme Verlag: Stuttgart, New York, 1985; Vol.E5, pp 1218-1279. (c) Liebscher, J. *Houben-Weyl's Methoden der Organischen Chemie*; Georg Thieme Verlag: Stuttgart, 1994; Vol. E8b, Teil 2, pp 1-399.

11. Holzapfel, C. W.; Pettit, G. R. *J. Org. Chem.* **1985**, *50*, 2323.
12. Schmidt, U.; Gleich, P.; Grieser, H.; Utz, R. *Synthesis* **1986**, 993.
13. Schmidt, U.; Utz, R.; Lieberknecht, A.; Grieser, A.; Potzolli, B.;Bahr, J.; Wagner, K.; Fischer, P. *Synthesis* **1987**, 233.
14. North, M.; Pattersen, G. *Tetrahedron* **1990**, *46*, 8267.
15. Bredenkamp, W. P.; Holzapfel, C. W.; Snyman, R. M.; Zyl, W. J. *Synth. Commun.* **1992**, *22*, 3029.
16. Agullar, E.; Meyers, A. I. *Tetrahedron Lett.* **1994**, *35*, 2473.
17. Ohkuro, M.; Kuno, A.; Sakai, H.; Takasugi, H. *Chem. Pharm. Bull.* **1995**, *43*, 947.
18. Du, J.; Qu, F.; Lee, D.; Newton, M. G.; Chu, Ch. K. *Tetrahedron Lett.* **1995**, *36*, 8167.
19. Umemura, K.; Tate, T.; Yamamura, M.; Yoshimura, J.; Yonezawa, Y.; Shin, Ch. *Synthesis* **1995**, 1423.
20. Kelly, C. R.; Gebhard, I.; Wicnienski, N. *J. Org. Chem.* **1986**, *51*, 4590.
21. Uchikawa, O.; Aono, T. *J. Heterocycl. Chem.* **1994**, *31*, 1545.
22. Williams, D. R.; Brooks, D. A. *Tetrahedron Lett.* **1996**, *37*, 983.
23. Carter, J. S.; Rogier, D. J.; Graneto, M. J.; Seibert, K.; Koboldt, C. M.; Zhang, Y.; Talley, J. J. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1167.

24. Sakai, T. T.; Krishna, N. R. *Bioorg. Med. Chem.* **1999**, *7*, 1559.

25. Walczyn′ ski, K.; Timmerman, H.; Zuiderveld, O. P.; Zhanq, M. Q.; Glinka, R. *Farmaco* **1999**, *54*, 533.

26. Belokon, Ya.; Kovalenko, S. N., Silin, A. V.; Nikitchenko, V. M. *Khim. Geterotsikl. Soedin.* **1997**, 1345; *Chem. Heterocycl. Compd.(Engl. Transl.)* **1997**, 1167.

27. Mathvink, R. J.; Tolman, J. S.; Chitty, D.; Candelore, M. R.; Cascieri, M. A.; Colwell, L. F.; Deng, L.; Feeney, W. P.; Forrest, M. J.; Hom, G. J.; MacIntyre, D. E.; Tota, L.; Wyvratt, M. J.; Fisher, M. H.; Weber, A. E. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1971.

28. Hantzsch, A. and Traumann, V *Berichte*, **1888,** *20*, 938.

29. Gasteiger, J.; Herzig, J. *Tetrahedron* **1981**, *37*, 2607.

30. Murugan, R.; Scriven, E. F. V. PCT Int. Appl. WO 98 45,279 (Oct 15, 1998); Reilly Industries Inc., *Chem. Abstr.* **1998**, *129*, 302633v.

31. Jackson, A.; Heyes, G.; Grayson, J. I.; Clarke, R. U.S. Patent 5,705,652 (Jan 6, 1998); Fine Organics Ltd., and Agro-Kanesho Company.

32. Tod J. Miller, Hannah D. Farquar, Arsham Sheybani, Camille E. Tallini, Andrea S. Saurage, Frank R. Fronczek, and Robert P. Hammer *Org. Lett.*, Vol. 4, No. 6, **2002.**

33. Varma, R. S.; Kumar, D.; Liesen, P. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 4093.

34. (a) Chisholm, M. H.; Iyer, S. S.; Streib, W. E. *New J. Chem.***2000**, *24*, 393. (b) Collins, I.; Rowley, M.; Davey, W. B.; Emms, F.; Marwood, R.; Patel, S.; Patel, S.; Fletcher, A.; Ragan, I. C.; Leeson, P. D.; Scott, A. L.; Broten, T. *Bioorg.Med.Chem.* **1998**, *6*, 743 (c) Church, A. C.; Koller, M. U.; Hines, M. A.; Beam, C. F. *Synth. Commun.* **1996**, *26,* 3659. (d) Dandia, A.; Joshi, R.; Sehgal, V.; Sharma, C. S.; Saha, M. *Heterocycl. Commun.* **1996**, *2*, 281.

35. (a) Edwards, M. L. *et al.* WO 0335065 A1 20030501, 2003; *Chem. Abstr.* **2003,**

138, 353988. (b) May, J. A.; Zinke, P. W. U.S. 2003083346 A1 20030501, 2003; *Chem. Abstr.* **2003**, *138*, 353974. (c) Angel, A. J.; Finefrock, A. E.; Williams, A. R.; Townsend, J. D.; Nguyen, T. H. V.; Hurst, D. R.; Heldrich, F. J.; Beam, C. F.; Badejo, I.T. *J. Heterocycl. Chem.* **1999**, *36*, 1231.

36. (a) Beam, C. F.; Bissell, R. L.; Hauser, C. R. *J. Org. Chem.* **1970**, *35*, 2083.
    (b) Bailey, R. J.; Card, P.; Shechter, H. *J. Am. Chem. Soc.* **1983**, *105*, 6096.
    (c) Wiedhaup, K.; Nollet, A. J. H.; Korsloot, J. G.; Huisman, H. *Tetrahedron Lett.* **1965**, 1599.
37. (a) Lopez, C.; Claramunt, R. M.; Trofimenko, S.; Elguero J. *Can. J. Chem.* **1993**, *71*, 678. (b) Nasipuri, D.; Biswas, K. K. *J. Indian Chem. Soc.* **1968**, *45*, 146. (c) Hojo, M.; Masuda, R.; Okada, E. *Synthesis* **1990**, 481. (d) El-Rayyes, N. R.; Al-Jawhary, A. *J. Heterocycl. Chem.* **1986**, *23*, 135.
38. (a) Bailey, R. J.; Shechter, H. *J. Am. Chem. Soc.* **1974**, *96*, 8116.
    (b) Duewell, H.; Haig, T. J. *J. Chem. Soc. C* **1968**,169.
39. Charles F. Beam *et al. Ind. Eng. Chem. Res.* **2007**, *46,* 8959-8967
40. Peruncheralathan, S.; Yadav, A. K.; Ila, H.; Junjappa, H.; *J. Org. Chem.* **2005**, *70*, 9644-9647.
41. (a) Singh G.; Junjappa, H.; *Synthesis*, **1982**, 693. (b) Samuel, R.; Asokan, S. S.; Chandran, P.; Retnamma, S.; Anabha, E. R. *Tetrahedron Letters* **2007**, 48, 8376-8378.
42. Jagodzinski, Tadeusz S. *Chem. Rev.*, **2003**, *103*, 197-227.
43. Robinson, M. J. T.; Kenny, P. W. *Tetrahedron* **1987**, *43*, 4043.
44. Haugwitz, R. D. *U.S. Patent* 3, **1972**, 660, 412.
45. Singh, G.; Bhattacharjee, S. S.; Ila, H.; Junjappa, H. *Synthesis* **1982**, 693-694.
46. (a) Peruncheralathan, S.; Khan, T. A.; Ila, H.; Junjappa, H,; *J. Org. Chem.* **2005**,

70, 10030-10035. (b) Dalgard, L.; Jensen, L.; Lawesson, S. O. *Tetrahedron* **1974**, *39*, 93. (c) Ramdas, S, R.; Srinivasan, P. S.; Ramachandran, J.; Sastry, V. V. S. K. *Synthesis* **1983**, 605. (d) Voss, J. Synthesis of Thioesters and Thiolactones, In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1990; Vol. 6, pp 435-460.

47. (a) Nair, S. K.; Samuel, R.; Asokan, C. V. *Synthesis* **2001**, 573.
(b) Nair, S. K.; Asokan, C. V. *Synth. Commun.* **2001**, *22*, 1453.

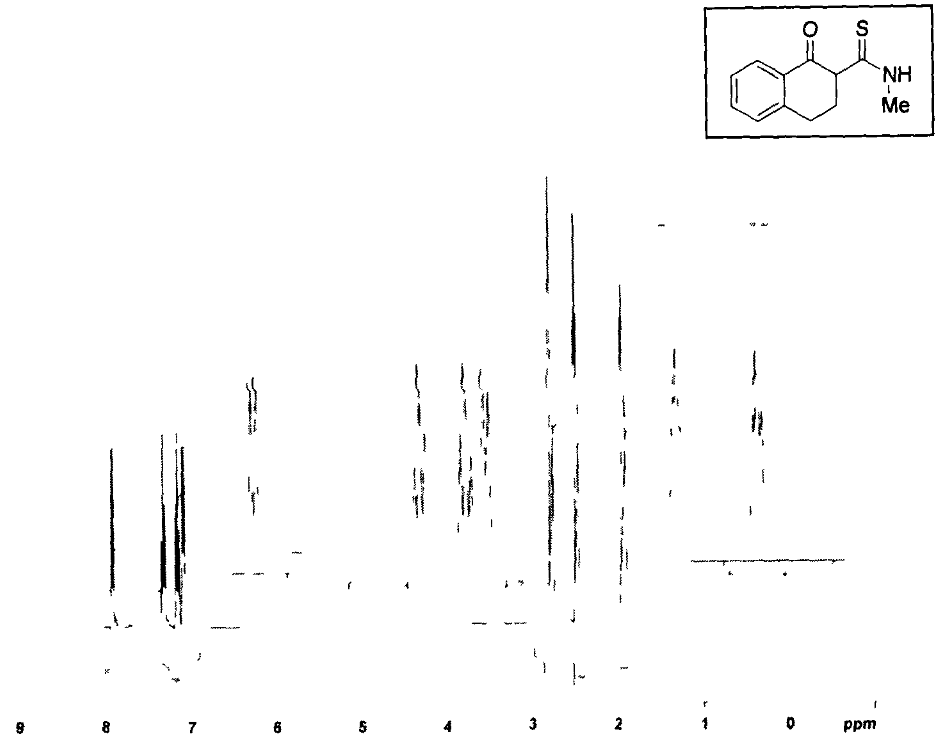


Figure 29. ^{1}H NMR spectra of 1-Oxo-1,2,3,4-tetrahydro-naphthalene-2-carbothioic acid amide.

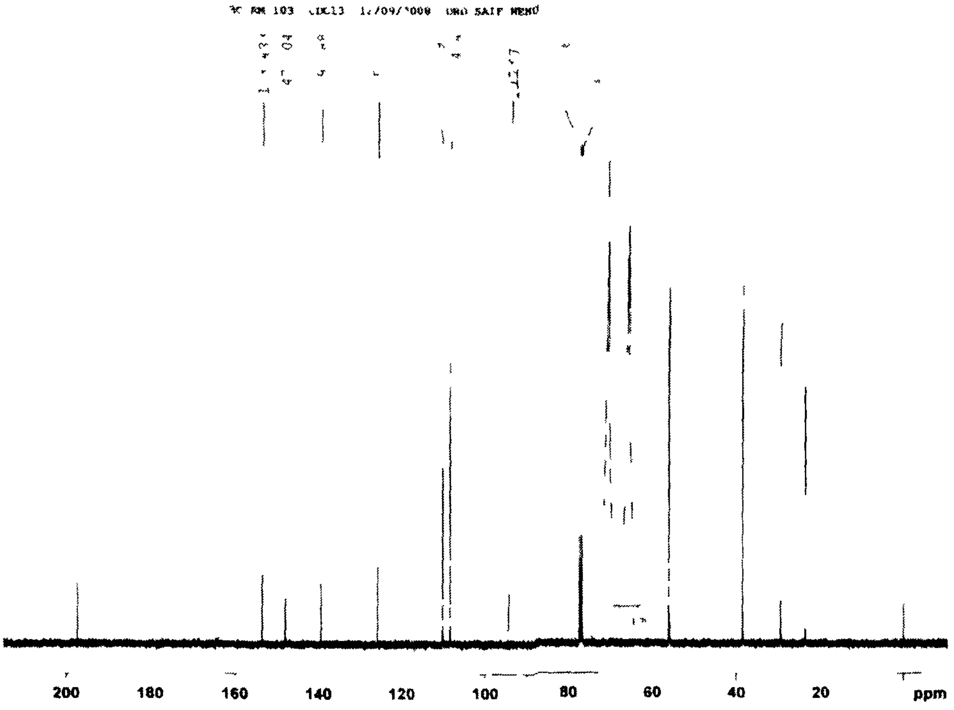


Figure 30. ^{13}C NMR Spectra of 3-Morpholin-4-yl-1-phenyl-4,5-dihydro-1*H*-benzo[*g*]indazole.

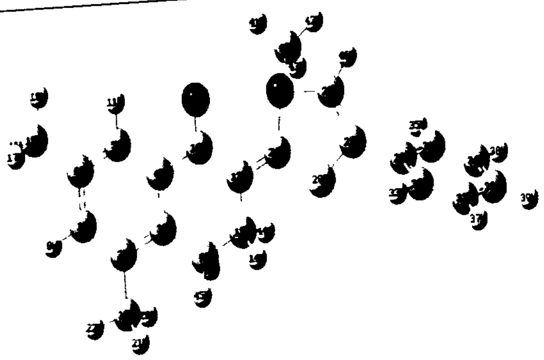


Figure 31: Compound **140d**.

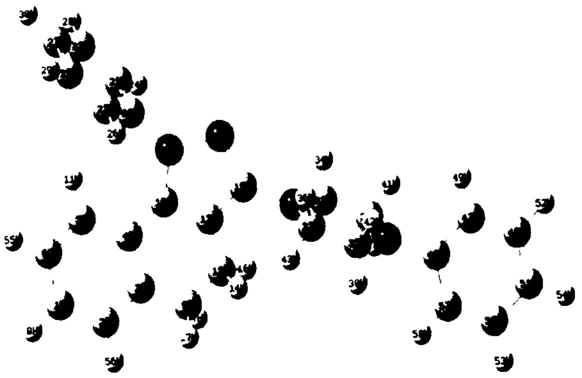


Figure 32: Compound **142d**.

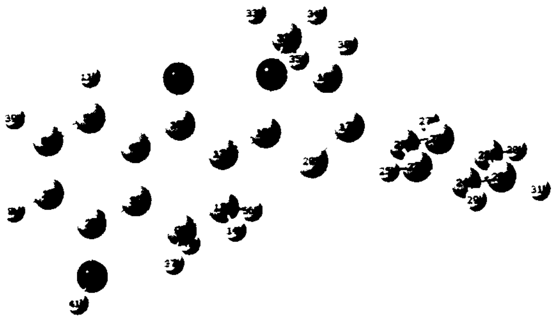


Figure 33: Compound **140g**.

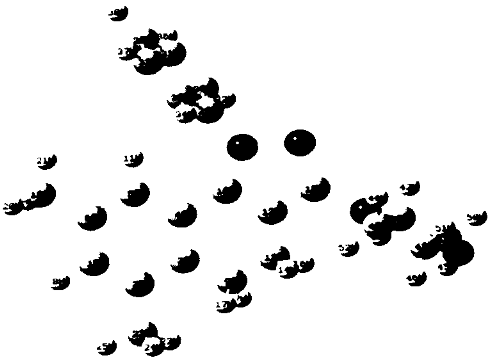


Figure 34: Compound **142f**.

Figure 35: Compound **140j**.

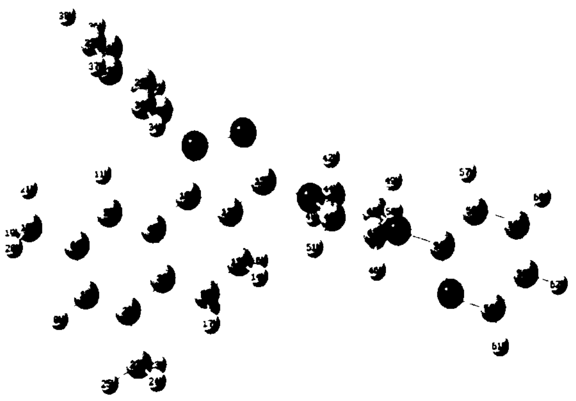


Figure 36: Compound **142h**.

Computer 3D models in Gaussview

CHAPTER VI

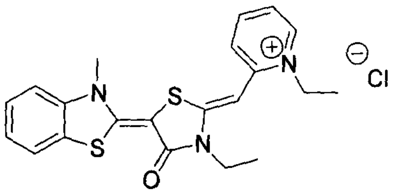
SYNTHESIS OF SUBSTITUTED-(3,4-DIHYDRO-1*H*-NAPHTHALEN-2-YLIDENE)-THIAZOLIDIN-4-ONE DERIVATIVES AND 5-SUBSTITUTED ARYLIDENE-3-ALKYL/ARYL-2-SUBSTITUTED-(1-OXO-3,4-DIHYDRO-1*H*-NAPHTHALEN-2-YLIDENE)-THIAZOLIDIN-4-ONES

CHAPTER VI

Synthesis of substituted-(3,4-dihydro-1*H*-naphthalen-2-ylidene)-thiazolidin-4-one derivatives and 5-substituted arylidene-3-alkyl/aryl-2-substituted-(1-oxo-3,4-dihydro-1*H*-naphthalen-2-ylidene)-thiazolidin-4-ones

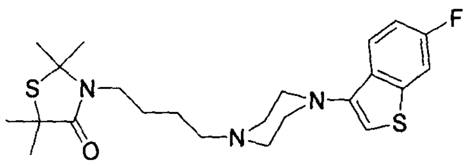
VI. 1. INTRODUCTION AND REVIEW

Heterocycles bearing nitrogen, sulphur and thiazole moieties constitute the core structure of a number of biologically interesting compounds. The chemistry of thiazolidin-4-one ring systems is of considerable interest as it is a core structure in various synthetic pharmaceuticals displaying a broad spectrum of biological activities.[1] Thiazolidin-4-one derivatives are known to exhibit diverse bioactivities such as antidiarrheal,[2] anticonvulsant,[3] antimicrobial,[4] antidiabetic,[5] antihistaminic,[6] anticancer,[7] antiHIV,[8] Ca^{2+} channel blocker,[9] PAF antagonist,[10] cardioprotective,[11] anti-ischemic,[12] cycloxygenase inhibitory,[13] anti-platelet activating factor,[14] non-peptide thrombin receptor antagonist[15] and tumor necrosis factor α-antagonist activities.[16] Also 2-imino-thiazolidin-4-ones have been found to have antifungal activity.[17-19] In a random screening of commercial compounds, a compound with a 4-thiazolidinone core structure for example compounds MKT 077 **143** and HP-236 **144** have been registered as antitumor and antipsyshotic agents while compound **145** and **146** have antimycobacterial activity. Another compound containing thiazolidin-4-one moiety known as CP-060 **147,** is a novel type of Ca^{2+} antagonist[20] possessing both Ca^{2+} overload inhibition and antioxidant activity.[21] Thiazolidinones derivatives like CP-060 and its analogues being antidiabetic drugs are used for the treatment of diabetes.[22] Recently the glycoprotein-independent apoptosis induction by a novel synthetic compound **148** used as cancer resistant drug which selectively kills cancer cell was reported by Fang and co-workers.[23]



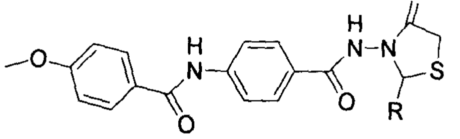
143

[MKT 077]



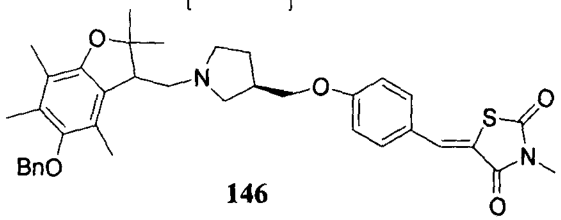
144

[HP-236]



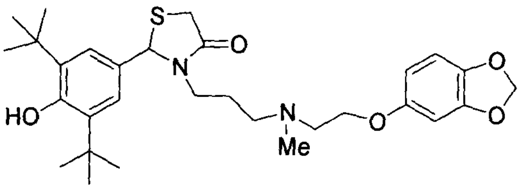
145

[R = CH_3, -$CH_2CH{=}CH_2$, -C_6H_5]



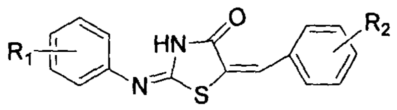
146

[CP-060]



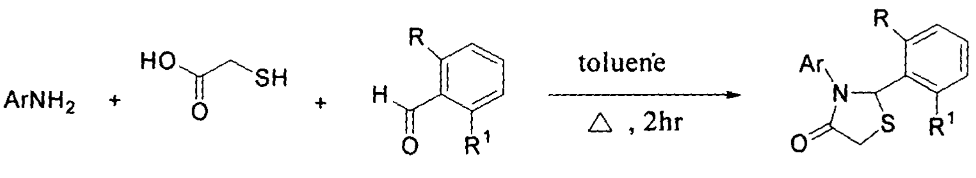
147

[CP-060]



148

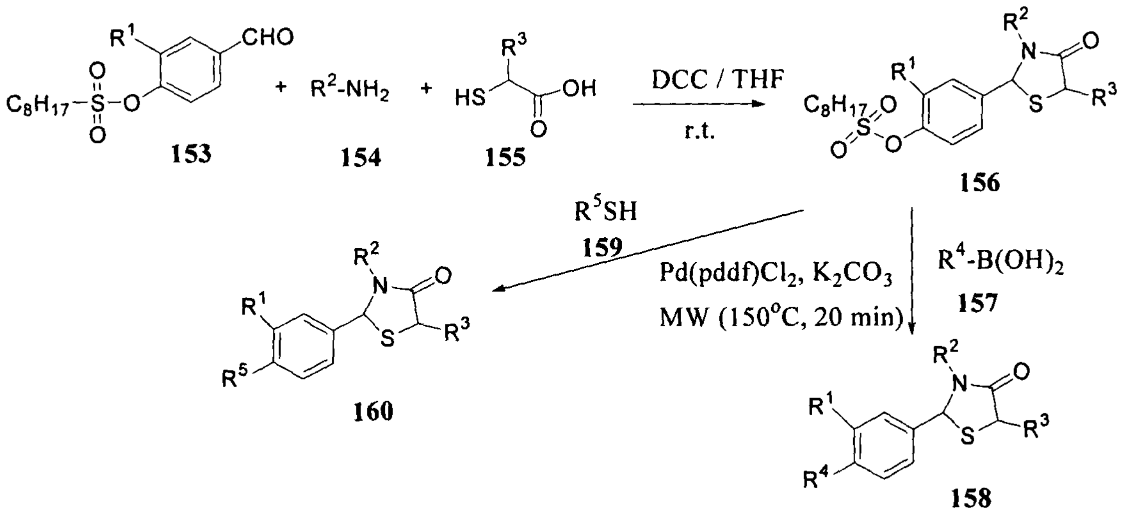
Monforte and co-workers designed and synthesised the new 2,3-diaryl-1,3-thiazolidin-4-ones **152**,[24] which has led to the development of highly potent anti-HIV-1 agents by reacting a suitable 2,6-dihalo-substituted benzaldehyde **151** with an equimolar amount of a (hetero)aromatic amine **149** in the presence of an excess of mercaptoacetic acid **150**in refluxing toluene (Scheme 35).[25]



149 **150** **151** **152**

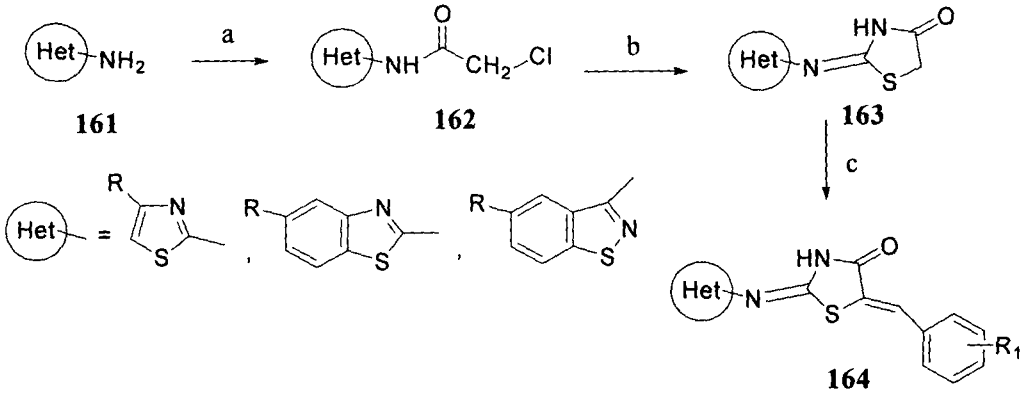
Scheme 35

Bing Yan and co-workers demonstrated[26] a new application of fluorous benzaldehydes **153** in a two-step reaction sequence for the preparation of 4-thiazolidinone **156** by a three component reaction of benzaldehyde **153**, amine **154**, and mercaptoacetic acid **155** under mild room-temperature conditions.[26] They employed boronic acid **157** and thiol **159** for the palladium-catalyzed coupling reactions to introduce new functional group to the heterocyclic systems. The microwave-assisted reactions were carried out using Pd(dppf)Cl_2 as a catalyst, K_2CO_3 as a base and 4:4:1 acetone /toluene /water as a cosolvent giving biaryl-substituted-4-thiazolidinones **158** and thioaryl-substituted-4-thiazolidinones **160** (Scheme 36).



Scheme 36

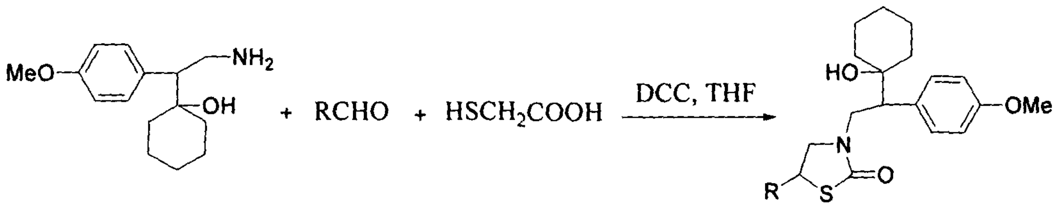
Recently, a three-step reaction protocol reported by Geronikaki *et al.*[27] showed that the first step of the synthetic procedure was carried out by reaction of appropriate amines **161** with chloroacetyl chloride **162** in DMF at room temperature for 2 hr or by heating in dry benzene for 3 hr.[28,29] 2-Chloro-*N*-(thiazole substituted) acetamides efficiently reacted with ammonium thiocyanate in refluxing ethanol to produce 2-(thiazol-2-ylimino)thiazolidin-4-ones or 2-(heteroarylimino)thiazolidin-4-ones **163**.[27] The final compounds **164** were obtained by refluxing products **163** with commercially available aromatic aldehydes and anhydrous sodium acetate in glacial acetic acid[28,29] (Scheme 37).



Reagents and conditions: (a) $ClCOCH_2Cl$, *N,N*-DMF, room temp, 2 hr;
(b) NH_4SCN, EtOH, reflux, 1-3 hr; (c) RC_6H_4CHO, MeCOOH, MeCOONa, reflux 2-4 hr.

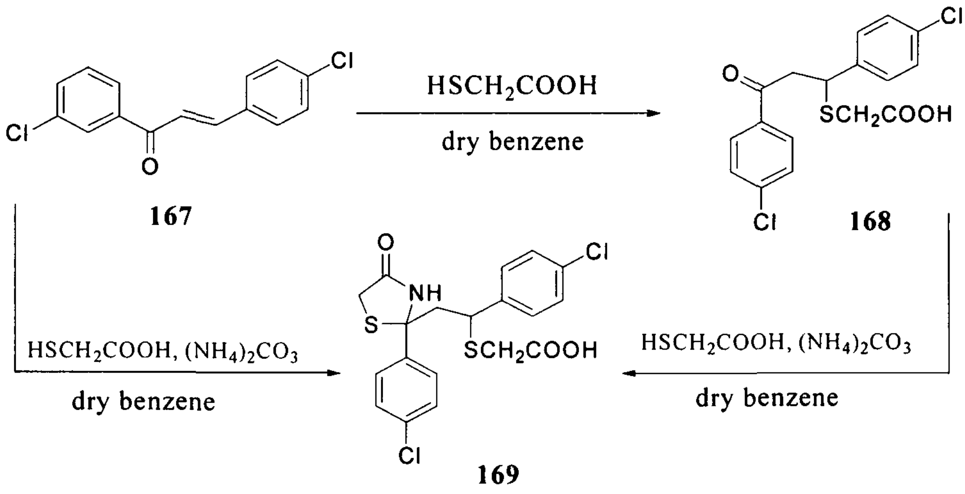
Scheme 37

Rangappa *et al.* reported the condensation of the synthon 1-[2-amino-1-(4-methoxyphenyl)-ethyl]-cyclohexanol **165** with aromatic and heterocyclic aldehydes and thioglycolic acid using DCC which gave compound **166** and it was used as antimicrobials[30] (Scheme 38).



Scheme 38

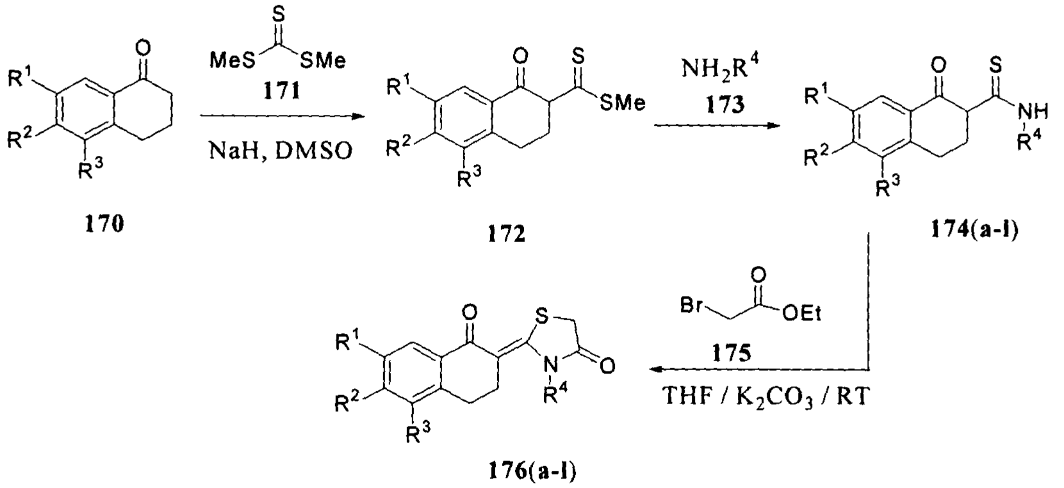
Dommisse and co-workers[31] demonstrated the synthesis of 2-[2-carboxymethylthio-2-(4-chloro-phenyl) ethyl]-2-(4-chlorophenyl)-4-thiazolidinone **169** in a two way process by (a) refluxing a mixture of chalcone **167**, thioglycolic acid and ammonium carbonate in dry benzene or (b) by formation of the thioether **168** *via* refluxing the chalcone **167** and thioglycolic acid in dry benzene and they showed that condensation of thioether **168** with thioglycolic acid and ammonium carbonate furnished **169** (Scheme 39).



Scheme 39

Although considerable amount of work has been done for the synthesis of 4-thiazolidinones derivatives. However, there seems to be enough scope for further work, hence it seems of interest to synthesize thiazolidin-4-one bearing aryl residue by application of the same protocol using the *β*-ketodithioesters and *β*-ketothioamides chemistry (Scheme 40).

Thiazolidin-4-ones **176(a-l)** were easily prepared using α-tetralone **170** on reaction with dimethyl trithiocarbonate **171** forming β-ketodithioester **172** as a key intermediate in *one-pot* sequential reaction strategy. The reactivity is due to the displacement of SMe group when reacting with nucleophiles and subsequent formation of *N*-substituted β-ketothioamides **174** on treatment with primary amines **173** (Scheme 40).

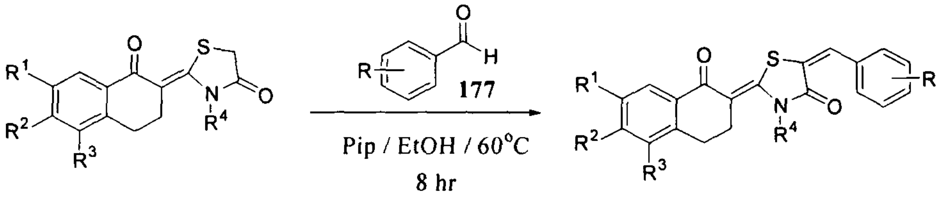


Scheme- 40

In the first step of the reaction, the α-tetralone **170** reacts with equimolar amount of dimethyl trithiocarbonate **171** in basic media (NaH) using DMF/benzene (1:10) as solvent at 80°C for 2 hr. The reaction mixture was then cooled to 0°C and acidified simultaneously affording compound **172**. The β-ketodithioester **172** is an interesting reactive intermediate for the synthesis of a variety of heterocyclic compounds.[12] The easy displacement of the thiomethyl group render the thiocarbonyl carbon as soft electrophilic centre for nucleophilic attack. Thus when equimolar amount of primary amine in ethyl alcohol is added to the reaction mixture *in situ* generated *N*-substituted *β*-ketothioamide **174**. Interestingly, the two nucleophilic centres in thioamides are localized on the heteroatoms (sulfur and nitrogen). The presence of those active centres,[35] allowed the *β*-ketothioamide to undergo a facile cyclisation reaction with 1,2-dielectrophilic reagent. Thus the presence of α-bromoester **175** as a dielectrophilic reagent promotes condensation and cyclization to gave a five membered ring, which on dehydration, a thiazolidin-4-one derivative **176** was afforded (Scheme 40). It was observed that the process tolerates both electron-donating and electron-withdrawing substituents in the *α*-tetralones. The treatment of 1-Oxo-1,2,3,4-tetrahydro-naphthalene-2-carbothioic acid amide **174a** with α-bromoester leads to the formation of 3-Methyl-2-(1-oxo-3,4-dihydro-1*H*-naphthalen-2-ylidene)-thiazolidin-5-one **176a** In all cases, the reactions of *β*-ketothioamides **174(a-l)** with α-bromoester proceeded efficiently in dry THF using K_2CO_3 as a required base under mild conditions of room temperature to afford the corresponding substituted-(3,4-dihydro-1*H*-naphthalen-2-ylidene)-thiazolidin-4-ones **176(a-l)** compounds in good yields (**Table VII**).

All the products were characterized by ^1H and ^{13}C NMR spectroscopy, IR, melting point and elemental analyses. The spectral analysis for 3-Methyl-2-(1-oxo-3,4-dihydro-1*H*-naphthalen-2-ylidene)-thiazolidin-5-one **176a**, for example was analysed for $C_{14}H_{13}NO_2S$ (Expected: C, 64.82; H, 5.06; N, 5.40; Found: C, 64.62 H, 5.14; N, 5.38) and its mass spectrum showed the molecular ion peak at *m/z* 259. Its IR spectrum (KBr) exhibited a strong absorption peak at 1690 cm^{-1} and 1680 cm^{-1} assignable to carbonyl group at the α-tetralone ring system and the C-5 of the thiazolidinone ring. The ^1H NMR spectrum ($CDCl_3$) of it, displayed two singlets at δ 2.48 (3H) and δ 3.86 (2H) ppm for proton $-CH_3$ of methyl group and $-CH_2-$ on the thiazolidin-4-one ring. In all cases, the two triplets was observed at δ 2.24 ppm (J = 5.8 Hz) and δ 2.58 ppm (J = 5.8 Hz) assignable to 2H, CH_2 of the 3,4-Dihydro-2*H*-naphthalen-1-one protons. The aromatic proton appeared as multiplet at δ 7.12–7.78 (3H), and a doublet appeared for one aromatic proton at δ 7.78 ppm which is deshielded by the carbonyl group. ^{13}C NMR showed expected resonances at δ 165, 149 and 38 ppm for C-1, C-3 and C-4 of the thiazolidin-4-one moiety. Some common features obtained are ^{13}C peaks at 22.5 and 28.4 ppm corresponding to 3,4-dihydro methylene carbons of the naphthalene moiety, and 126, 127, 128, 129, 134 ppm for phenyl carbons. The analytical and spectral data analysis for other substituted-(3,4-dihydro-1*H*-naphthalen-2-ylidene)-thiazolidin-4-one derivatives **176(b-l)** are in conformity with the assigned structure, and are described in the experimental section.

The investigation was further extended to the synthesis of substituted 5-arylidene-3-alkyl/aryl-2-(1-oxo-3,4-dihydro-1H-naphthalen-2-ylidene)-thiazolidin-4-one **178(a-l)** derived from substituted-(3,4-dihydro-1*H*-naphthalen-2-ylidene)-thiazolidin-4-one derivatives **176(a-l)**. Interestingly, the acidic hydrogen at the thiazolidin-4-one moiety on treatment with piperidine base undergo condensation with various aromatic benzaldehydes **177(a-l)** in ethanol solution under refluxing condition for about 8 hours, to afford a series of 5-arylidene-3-alkyl/aryl-2-(1-oxo-3,4-dihydro-1H-naphthalen-2-ylidene)-thiazolidin-4-one **178(a-l)** (**Table VIII**, Scheme 41). The purity of the compounds is monitored by TLC technique. The structures of the compounds are confirmed on the basis of their elemental analysis and spectral data. Spectral analysis of 5-Benzylidene-3-methyl-2-(1-oxo-3,4-dihydro-1H-naphthalen-2-ylidene)-thiazolidin-4-one **178a** showed IR stretching frequencies at 1710 and 1689 cm^{-1} assignable to carbonyl group, 1647 cm^{-1} characteristic of olefin (C=C) and 1482 cm^{-1} for ring (C=C) stretching. ^{1}H NMR showed resonances for a proton singlet at δ 6.82 ppm (1H), the two triplets was observed at δ 2.24 ppm (J = 5.8 Hz) and δ 2.58 ppm (J = 5.8 Hz) and the broad multiplet for aryl substitutions at δ 7.04-7.34 ppm. ^{13}C NMR signals are observed at 131.5 and 161.4 ppm for a carbon sp^2 at C-4 and for the carbonyl carbon at C-5 of the thiazolidinone moiety. The other peaks obtained at 22.5 and 28.4 ppm corresponding to 3,4-dihydro methylene carbons of naphthalene ring and 126, 127, 128, 129, 134 ppm for phenyl carbons. Thus, 5-Benzylidene-3-methyl-2-(1-oxo-3,4-dihydro-1H-naphthalen-2-ylidene)-thiazolidin-4-one **178a** was analyzed for $C_{21}H_{17}NO_2S$ (Expected: C, 72.60; H, 4.96; N, 4.03; Found: C, 72.62 H, 4.94; N, 4.05) and its mass spectrum showed the molecular ion peak at *m/z* 347. The analytical and spectral data analysis for other diverse substituted 5-arylidene-3-alkyl/aryl-2-substituted-(1-oxo-3,4-dihydro-1*H*-naphthalen-2-ylidene)-thiazolidin-4-one compounds **178(b-l)** are in conformity with the assigned structure **(Table VIII)**, and are described in the experimental section.



176(a-l) **178(a-l)**

Scheme- 41

In summary, we have developed a simple and efficient method utilising *β*-ketodithioester **172** and *β*-ketothioamide **174** as versatile intermediates for the synthesis of substituted-(3,4-dihydro-1*H*-naphthalen-2-ylidene)-thiazolidin-4-one derivatives **176(a-l)** and substituted 5-arylidene-3-alkyl/aryl-2-(1-oxo-3,4-dihydro-1H-naphthalen-2-ylidene)-thiazolidin-4-ones **178(a-l)**.

TABLE VII

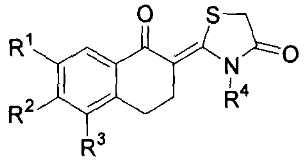


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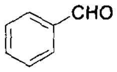
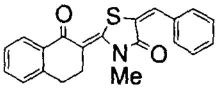
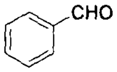
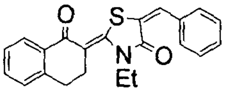
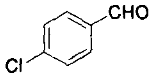
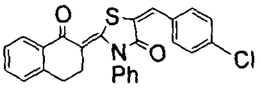
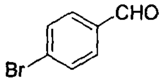
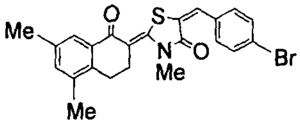
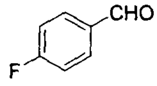
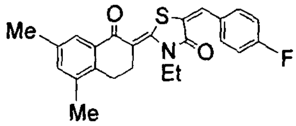
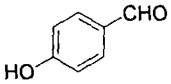
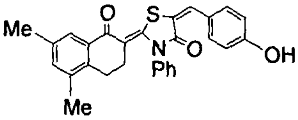
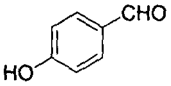
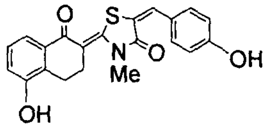
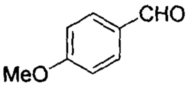
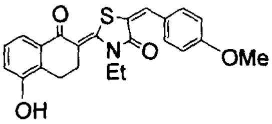
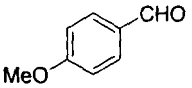
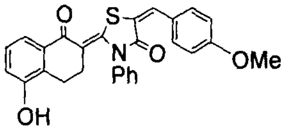
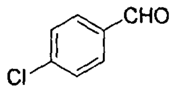
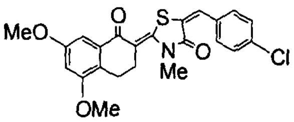
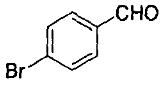
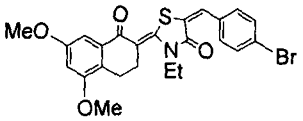
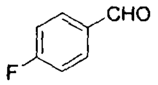
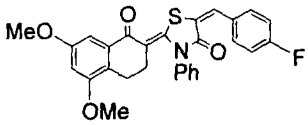
Table VII. Preparation of diverse substituted-(3,4-dihydro-1*H*-naphthalen-2-ylidene)-thiazolidin-4-one (**176**).

Entry	Substrate **170(a-l)**	R^1	R^2	R^3	R^4	Product **176(a-l)**	Yield[a] %
1	**170a**	H	H	H	Me	**176a**	82
2	**170b**	H	H	H	Et	**176b**	67
3	**170c**	H	H	H	Ph	**176c**	68
4	**170d**	Me	H	Me	Me	**176d**	81
5	**170e**	Me	H	Me	Et	**176e**	65
6	**170f**	Me	H	Me	Ph	**176f**	73
7	**170g**	H	H	OH	Me	**176g**	77
8	**170h**	H	H	OH	Et	**176h**	88
9	**170i**	H	H	OH	Ph	**176i**	84
10	**170j**	OMe	OMe	H	Me	**176j**	63
11	**170k**	OMe	OMe	H	Et	**176k**	80
12	**170l**	OMe	OMe	H	Ph	**176l**	78

[a] Yields obtained are determined after work-up and Chromatographic purification All the compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR and MS.

Table VIII. Preparation of substituted 5-arylidene-3-alkyl/aryl-2-substituted-(1-oxo-3,4-dihydro-1*H*-naphthalen-2-ylidene)-thiazolidin-4-one **178**.

Entry	Substrate **176(a-l)**	Aryldehyde **177(a-l)**	Product **178(a-l)**		Time/hr	Yield[a] %
1	**176a**			**178a**	8	64
2	**176b**			**178b**	10	62
3	**176c**			**178c**	12	56
4	**176d**			**178d**	10	67
5	**176e**			**178e**	12	52
6	**176f**			**178f**	8	58
7	**176g**			**178g**	12	63
8	**176**			**178h**	12	57
9	**176i**			**178i**	11	54
10	**176j**			**178j**	8	65
11	**176k**			**178k**	12	70
12	**176l**			**178l**	10	69

[a] Yields obtained are determined after work-up and Chromatographic purification.

VI. 3. EXPERIMENTAL

Melting points was determined on a "Thomas Hoover" capillary melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker AMX 400 instrument using $CDCl_3$ as the solvent. Chemical shifts are reported in ppm using tetramethylsilane as internal standard. *J* values are given in Hz. The following abbreviations are used to describe peak patterns when appropriate: br = broad, s = singlet, d = doublet, dd = double doublet, dt = double triplet, t = triplet, q = quartet, m = multiplet. IR spectra were recorded on a Perkin-Elmer BX spectrophotometer. ESI mass spectra were measured on an ion trap analyzer Esquire 3000 (Bruker Daltonics). Masses (MS) are reported in unit of mass over charge (m/z), the molecular or base peaks and relative intensities are indicated by (M^+) and (%) respectively. CHN analyses were recorded on a Vario EL analyser. Column chromatography was performed using silica gel (60-120 mesh, Merck).

All reactions were performed in oven dried (120°C) glasswares under a positive dry argon/nitrogen atmosphere. Analytical thin layer chromatography (TLC) were performed on glass plates coated with ACME's silica gel containing 13% calcium sulphate as binder and various combination of visualization of spots was accomplished by exposure to UV lamp or iodine vapour or by spraying potassium permanganate (acidic) solution or 2% ninhydrin solution. Eluents for column chromatography were used after simple distillation of commercial solvents. All solvent evaporations were done using a rotaevaporator (BUCHI Rotavapor R II, vacuum pump V-700) and a steam bath.

Starting Materials:

Commercially available solvents such as THF, diethyl ether, chloroform, DMF, etc., were purified either by simple distillation / distillation under reduced pressure before use. Dimethyltrithiocarbonate, substituted 1-tetralones was purchased from Sigma-Aldrich Chemie and purity as supplied, for α-tetralone bp 127-128°C (13 mm Hg, mp 2°C, d 1.096). *β*-ketodithioester required for the present investigation were prepared according to the earlier reported literature procedures[32,33,34] with some minor modifications as described below.

General procedure for the synthesis of *β*-Oxodithioester 172 and *β*-Oxothioamide 174 compounds:

To a well stirred suspension of NaH (2.5 g, 50 mmol; 50% suspension) in dry DMF/Benzene solvent mixture (50 mL, 1:10; Benzene bp 76°C), dimethyltrithiocarbonate (3.80 g, 27 mmol) is added and the mixture is refluxed with stirring for 30 min. A solution of *α*-tetralone **170** (0.9 g, 6.0 mmol) in dimethyl sulfoxide (10 mL) is then slowly added drop wise over a period of 1 h. and refluxing was continued for another 2-3 h. The reaction mixture was allowed to cool, and poured into ice-cold water (250 mL). It was acidified with 3N HCl or 20% acetic acid (20 mL) and extracted with chloroform (2 x 50 mL). The extract is dried with anhydrous Na_2SO_4 and the solvent was evaporated to give the corresponding *β*-oxodithiocarboxylates **172** (single spot on TLC). The *β*-oxodithioester **172** was dissolved in ethanol 30 mL, and was treated with a primary amine [methyl amine (5.0 mmol) / ethyl amine (0.7 mL, 5.0 mmol) / benzyl amine (0.55 mL, 5.0 mmol)] under refluxing condition and stirring was continued for 3 hr at 70°C. It was cooled to room temperature, poured over water (2 x 50 mL), quenched with saturated solution of $NaHCO_3$ (1 x 25 mL), extracted with diethyl ether (2 x 50 mL). The extract is dried with anhydrous Na_2SO_4 and the solvent was evaporated to give the corresponding β-oxothioamide **174** in good yields (single spot on TLC). Purification may be achieved by column chromatography on silica gel (50 g) using hexane as eluent.

General procedure for the Preparation of 3-Methyl-2-(1-oxo-3,4-dihydro-1*H*-naphthalen-2-ylidene)-thiazolidin-4-one 176a. To a stirred equimolar solution of 1-tetralone-2-carbothioic acid methylamide **174a** (1.14 g, 7 mmol) in dry THF (20 mL), bromo-acetic acid ethyl ester **175a** (0.95 g, 5 mmol) was added drop wise over 30 min, followed by addition of anhydrous K_2CO_3 (0.87 g, 6 mmol) under nitrogen atmosphere. Stirring was continued for a period of 6 hr at room temperature (monitored by TLC). The reaction mixture was concentrated under reduced pressure and poured into ice-cold water (100 mL) and extracted with chloroform (2 x 50 mL). The chloroform layer was washed with water (2 x 25 mL), dried over anhydrous Na_2SO_4 and evaporated to give crude product **176a** which were purified by passing through silica gel column using hexane : ethyl acetate (9:1) as eluent. Similarly other compounds **176b-l** were also prepared following the same procedure.

3-Methyl-2-(1-oxo-3,4-dihydro-1*H*-naphthalen-2-ylidene)-thiazolidin-4-one 176a: Brown crystals (1.21 g, 82 %); mp 167-168°C; IR (KBr): 3352, 2946, 1690, 1685, 1650, 1498, 1230; ^1H NMR (400 MHz, $CDCl_3$): δ ppm 2.24 (t, J = 5.8 Hz, 2H, CH_2), 2.58 (t, J = 5.8 Hz, 2H, CH_2), 2.82 (s, 3H, CH_3), 3.96 (s, 2H, CH_2-thiazolidinone), 7.27–7.48 (m, 3H, ArH), 7.76 (d, J = 7 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 22.2, 28.4, 29.1, 36.74, 105, 126.03, 128.14, 129.13, 134.24, 136.22, 141.40, 149.5, 165.21, 187.04; MS (CI) m/z = 259. Anal.Calcd. for $C_{14}H_{13}NO_2S$ (259.32): C, 64.82; H, 5.06; N, 5.40; Found: C, 64.62 H, 5.14; N, 5.38.

3-Ethyl-2-(1-oxo-3,4-dihydro-1H-naphthalen-2-ylidene)-thiazolidin-4-one 176b: Brown crystals (1.01 g, 67 %); mp 156-156°C; IR (KBr): 3353, 2948, 1694, 1686, 1657, 1496, 1238; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.30 (t, 3H, CH_3), 2.24 (t, J = 5.8 Hz, 2H, CH_2), 2.58 (t, J = 5.8 Hz, 2H, CH_2), 3.24 (q, J = 7 Hz, 2H, CH_2), 3.92 (s, 2H, CH_2-thiazolidinone), 7.27–7.38 (m, 3H, ArH), 7.78 (d, J = 7 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 12.9, 22.2, 28.4, 36.74, 37.12, 105.23, 126.12, 128.14, 129.13, 134.24, 136.22, 141.40, 149.5, 165.21, 187.04; MS (CI) *m/z* = 273. Anal.Calcd. for $C_{15}H_{15}NO_2S$ (273.07): C, 66.16; H, 5.18; N, 5.14; Found: C, 66.62 H, 5.14; N, 5.28.

2-(1-Oxo-3,4-dihydro-1H-naphthalen-2-ylidene)-3-phenyl-thiazolidin-4-one 176c: Colourless crystals (1.01 g, 68 %); mp 163-164°C; IR (KBr): 3358, 2944, 1695, 1686, 1656, 1494, 1235; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 2.24 (t, J = 5.8 Hz, 2H, CH_2), 2.58 (t, J = 5.8 Hz, 2H, CH_2), 3.86 (s, 2H, CH_2-thiazolidinone), 7.07-7.78 (m, 9H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 22.2, 28.4, 36.74, 37.12, 105.23, 120.41, 120.44, 124.42, 126.12, 128.11, 128.14, 129.13, 134.24, 136.22, 140.11, 141.40, 149.5, 165.21, 187.04; MS (CI) *m/z* = 321. Anal.Calcd. for $C_{19}H_{15}NO_2S$ (321.37): C, 71.11; H, 4.78; N, 4.34; Found: C, 71.22 H, 4.64; N, 4.38.

2-(5,7-Dimethyl-1-oxo-3,4-dihydro-1*H*-naphthalen-2-ylidene)-3-methyl-thiazolidin-4-one 176d: Brown crystals (1.01 g, 82 %); mp 137-138°C; IR (KBr): 3354, 2944, 1692, 1684, 1652, 1496, 1233; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 2.24 (t, 2H, J = 5.8 Hz, CH_2), 2.34 (s, 3H, CH_3), 2.59 (t, J = 5.8 Hz, 2H, CH_2), 3.86 (s, 2H, CH_2-thiazolidinone), 7.08 (s, 1H, ArH), 7.32 (s, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 15.12, 21.2, 21.87, 22.46, 29.10, 36.84, 105.13, 127.11, 127.34, 135.12, 135.64, 135.97, 137.52, 149.15, 165.81, 187.08; MS (CI) *m/z* = 287. Anal.Calcd. for $C_{16}H_{17}NO_2S$ (287.32): C, 66.82; H, 5.96; N, 4.87; Found: C, 66.72 H, 5.84; N, 4.38.

2-(5,7-Dimethyl-1-oxo-3,4-dihydro-1H-naphthalen-2-ylidene)-3-ethyl-thiazolidin-4-one 176e: Brown crystals (0.94 g, 65 %); mp 143-144°C; IR (KBr): 3352, 2947, 1690, 1687, 1655, 1498, 1238; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.28 (t, 3H, CH_3), 2.22 (t, J = 5.8 Hz, 2H, CH_2), 2.35 (brs, 3H, CH_3), 2.63 (t, J = 5.8 Hz, 2H, CH_2), 3.24 (q, 2H, CH_2), 3.76 (2H, s, CH_2-thiazolidinone), 7.04 (1H, s, ArH), 7.34 (1H, s, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 12.92, 21.22, 21.83, 22.43, 29.18, 36.7, 36.84, 105.10, 127.12, 135.12, 135.62, 135.95, 137.57, 149.17, 165.84, 187.10; MS (CI) *m/z* = 301. Anal.Calcd. for $C_{17}H_{19}NO_2S$ (301.12): C, 67.74; H, 6.36; N, 4.67; Found: C, 67.72 H, 6.38; N, 4.58.

2-(5,7-Dimethyl-1-oxo-3,4-dihydro-1H-naphthalen-2-ylidene)-3-phenyl-thiazolidin-4-one 176f: Brown crystals (1.31 g, 73 %); mp 124-125°C; IR (KBr): 3352, 2940, 1692, 1682, 1652, 1496, 1236; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 2.21 (t, J = 5.8 Hz, 2H, CH_2), 2.35 (brs, 3H, CH_3), 2.62 (t, J = 5.8 Hz, 2H, CH_2), 3.74 (2H, s, CH_2-thiazolidinone), 7.02-7.38 (m, 7H, ArH), 7.76 (d, J = 8 Hz, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 15.92, 21.22, 21.83, 22.43, 29.18, 36.7, 36.84, 100.08, 120.04, 120.12, 124.24, 128.02, 128.27, 135.12, 135.62, 137.57, 140.02, 149.17, 157.04, 165.84, 187.10; MS (CI) *m/z* = 349. Anal.Calcd. for $C_{21}H_{19}NO_2S$ (349.45): C, 72.18; H, 5.46; N, 4.04; Found: C, 72.22 H, 5.38; N, 4.22.

2-(5-Hydroxy-1-oxo-3,4-dihydro-1H-naphthalen-2-ylidene)-3-methyl-thiazolidin-4-one 176g: White crystals (1.35 g, 77 %); mp 136-137°C; IR (KBr): 3351, 3342, 2944, 1697, 1684, 1658, 1495, 1234; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 2.21 (t, J = 5.8 Hz, 2H, CH_2), 2.56 (t, J = 5.8 Hz, 2H, CH_2), 2.73 (s, 3H, CH_3), 3.46 (s, 2H, CH_2-thiazolidinone), 5.25 (s, 1H, OH), 6.92-7.12 (m, 3H, ArH), 7.32 (d, J = 8 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 12.61, 18.24, 22.88, 29.26, 36.44, 105.14, 121.42, 122.26, 128.11, 137.02, 149.14, 157.02, 165.80, 187.04; MS (CI) m/z = 275. Anal.Calcd. for $C_{14}H_{13}NO_3S$ (275.24): C, 61.22; H, 4.76; N, 5.08; Found: C, 61.24 H, 4.72; N, 5.03.

3-Ethyl-2-(5-hydroxy-1-oxo-3,4-dihydro-1*H*-naphthalen-2-ylidene)-thiazolidin-4-one 176h: Brown crystals (1.25 g, 88 %); mp 132-133°C; IR (KBr): 3354, 3340, 2940, 1691, 1682, 1654, 1497, 1234; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.26 (t, 3H, CH_3), 2.24 (t, J = 5.8 Hz, 2H, CH_2), 2.58 (t, J = 5.8 Hz, 2H, CH_2), 3.24 (q, J = 7 Hz, 2H, CH_2), 3.84 (s, 2H, CH_2-thiazolidinone), 5.24 (s, 1H, OH), 6.92-7.12 (m, 2H, ArH), 7.32 (d, J = 8 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 12.61, 18.2, 22.88, 36.44, 37.21, 105.10, 121.43, 122.21, 127.4, 128.12, 137.02, 149.15, 157.2, 165.80, 187.04; MS (CI) m/z = 289. Anal.Calcd. for $C_{15}H_{15}NO_3S$ (289.36): C, 62.42; H, 5.26; N, 4.84; Found: C, 62.47 H, 5.24; N, 4.32.

2-(5-Hydroxy-1-oxo-3,4-dihydro-1*H*-naphthalen-2-ylidene)-3-phenyl-thiazolidin-4-one 176i: Brown crystals (1.17 g, 84 %); mp 122-123°C; IR (KBr): 3350, 3342, 2944, 1698, 1680, 1656, 1496, 1233; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 2.21 (t, J = 5.8 Hz, 2H, CH_2), 2.56 (t, J = 5.8 Hz, 2H, CH_2), 2.73 (s, 3H, CH_3), 3.78 (s, 2H, CH_2-thiazolidinone), 5.27 (s, 1H, OH), 6.94-7.16 (m, 3H, ArH), 7.30 (d, J = 8 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 12.61, 18.2, 22.88, 36.44, 37.21, 100.10, 120.41, 120.46, 121.43, 122.21, 124.17, 128, 128.22, 137.23, 149.15, 157.2, 165.80, 182, 187.04; MS (CI) *m/z* = 337. Anal.Calcd. for $C_{19}H_{15}NO_3S$ (337.16): C, 67.64; H, 4.48; N, 4.15; Found: C, 67.47 H, 424; N, 4.02.

2-(6,7-Dimethoxy-1-oxo-3,4-dihydro-1H-naphthalen-2-ylidene)-3-methyl-thiazolidin-4-one 176j: Yellow solid (0.87 g, 63 %); mp 157-158°C; IR (KBr): 3357, 2940, 1692, 1686, 1658, 1496, 1232; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 2.28 (t, *J* = 5.8 Hz, 2H, CH_2), 2.59 (t, *J* = 5.8 Hz, 2H, CH_2), 2.72 (s, 3H, CH_3), 3.63 (s, 3H, OMe), 3.76 (s, 2H, CH_2-thiazolidinone), 6.51 (1H, s, ArH), 6.84 (1H, s, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 22.80, 29.08, 36.41, 37.12, 56.02, 56.23, 105.10, 115.10, 116.2, 129.4, 134.7, 145, 149.5, 153.2, 165.5, 187.10; MS (CI) *m/z* = 319. Anal.Calcd. for $C_{16}H_{17}NO_4S$ (319.14): C, 60.14; H, 5.37; N, 4.39; Found: C, 60.12 H, 5.34; N, 4.16.

2-(6,7-Dimethoxy-1-oxo-3,4-dihydro-1*H*-naphthalen-2-ylidene)-3-ethyl-thiazolidin-4-one 176k: Pale yellow solid (1.04 g, 80 %); mp 127-128°C; IR (KBr): 3354, 2948, 1690, 1684, 1657, 1494, 1238; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.20 (t, *J* = 7 Hz, 3H, CH_3), 2.26 (t, *J* = 5.8 Hz, 2H, CH_2), 2.57 (t, *J* = 5.8 Hz, 2H, CH_2), 2.72 (s, 3H, CH_3), 3.64 (s, 3H, OMe), 3.76 (s, 2H, CH_2-thiazolidinone), 6.52 (1H, s, ArH), 6.86 (1H, s, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 12.57, 22.80, 36.41, 37.12, 56.02, 56.23, 105.10, 115.10 (x 2C), 116.2, 129.4, 134.7, 145, 149.5, 153.2, 165.5, 187.10; MS (CI) *m/z* = 333. Anal.Calcd. for $C_{17}H_{19}NO_4S$ (333.40): C, 61.24; H, 5.76; N, 4.20; Found: C, 61.54 H, 5.64; N, 4.16.

2-(6,7-Dimethoxy-1-oxo-3,4-dihydro-1*H*-naphthalen-2-ylidene)-3-phenyl-thiazolidin-4-one 176l: Brown crystalline solid (0.98 g, 78 %); mp 151-152 °C; IR (KBr): 3353, 2946, 1690, 1684, 1656, 1492, 1237; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.20 (t, *J* = 7 Hz, 3H, CH_3), 2.26 (t, *J* = 5.8 Hz, 2H, CH_2), 2.57 (t, *J* = 5.8 Hz, 2H, CH_2), 2.72 (s, 3H, CH_3), 3.64 (s, 3H, OMe), 3.76 (s, 2H, CH_2-thiazolidinone), 6.52 (s, 1H, ArH), 6.86 (s, 1H, ArH), 7.02-7.34 (m, 3H, ArH), 7.65 (d, *J* = 8 Hz, 1H, ArH); ^{13}C NMR (100 MHz, CDCl$_3$): δ ppm 28.17, 36.71, 37.12, 56.32, 56.42, 100.5, 115.12 (x 2C), 116.22, 120.02, 124.2, 128.01 (x 2C), 129.04, 134.3, 140.04, 145.2, 153.2, 157, 162.8, 187.18; MS (CI) *m/z* = 381. Anal.Calcd. for $C_{21}H_{19}NO_4S$ (381.10): C, 66.12; H, 5.02; N, 3.62; Found: C, 66.24 H, 5.04; N, 3.56.

General procedure for the preparation of substituted 5-arylidene-3-alkyl/aryl-2-substituted-(1-oxo-3,4-dihydro-1*H*-naphthalen-2-ylidene)-thiazolidin-4-ones

178a-l: Substituted-2-(1-oxo-3,4-dihydro-1*H*-naphthalen-2-ylidene)-thiazolidin-4-one **176** (0.5 mmol) and benzaldehyde **177** (0.6 mmol) were dissolved in 10 mL of absolute ethanol. About 50 μL of piperidine (0.5 mmol) was added to the reaction mixture, and was, refluxed for 10-12 hr at 70°C with constant stirring, the reaction being monitored by TLC. The reaction mixture was concentrated under reduced pressure and poured into ice-cold water (50 mL), extracted with diethyl ether (2 x 50 mL), washed with H_2O (2 x 50 mL) and brine (1 x 50 mL), and dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum to give product **178** which were purified by column chromatography over silica gel using hexane/EtOAc (10:1) as eluent.

5-Benzylidene-3-methyl-2-(1-oxo-3,4-dihydro-1*H*-naphthalen-2-ylidene)-thiazolidin-4-one 178a: Yield 64 %, yellow crystals, mp 142-143°C; IR (KBr): 2970, 2945, 1710, 1689, 1667, 1482, 1244; ^{1}H NMR (400 MHz, CDCl$_3$): δ 2.28 (t, *J* = 5.8 Hz, 2H, CH$_2$), 2.59 (t, *J* = 5.8 Hz, 2H, CH$_2$), 3.02 (s, 3H, CH$_3$), 6.76 (s, 1H, CH), 7.11–7.32 (m, 8H, ArH), 7.87 (d, *J* = 7.6 Hz, 1H, ArH); ^{13}C NMR (100 MHz, CDCl$_3$): δ ppm 22.5, 28.7, 29.30, 114.02, 114.86, 126.22 (x 2C), 126.41, 127.71, 127.14, 128.04, 128.17, 129.42, 131.10, 133.12, 134.20, 134.92, 136.12, 141.2, 161.41, 187.02; ESI-

MS m/z = 347 (M + 1). Anal.Calcd. for $C_{21}H_{17}NO_2S$ (347.12): C, 72.60; H, 4.96; N, 4.03; Found: C, 72.62 H, 4.94; N, 4.05.

5-Benzylidene-3-ethyl-2-(1-oxo-3,4-dihydro-1*H*-naphthalen-2-ylidene)-thiazolidin-4-one 178b: Yield 62 %, pale yellow crystals, mp 136-137°C; IR (KBr): 2971, 2944, 1710, 1687, 1664, 1484, 1245; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.47 (t, J = 7 Hz, 3H, CH_3), 2.28 (t, J = 5.8 Hz, 2H, CH_2), 2.59 (t, J = 5.8 Hz, 2H, CH_2), 2.74 (q, J = 7.4 Hz, 2H, CH_2), 6.74 (s, 1H, CH), 7.12–7.34 (m, 8H, ArH), 7.87 (d, J = 7.6 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 12.34, 22.5, 28.7, 37.30, 114.02, 114.86, 126.18 (x 2C), 126.41, 127.71, 127.14, 128.04, 128.17, 129.42, 131.10, 133.12, 134.20, 134.92, 136.12, 141.4, 141.7, 161.41, 187.02; ESI-MS m/z = 361 (M + 1). Anal.Calcd. for $C_{22}H_{19}NO_2S$ (361.42): C, 73.10; H, 5.36; N, 3.89; Found: C, 73.12 H, 5.84; N, 3.84.

5-(4-Chloro-benzylidene)-2-(1-oxo-3,4-dihydro-1*H*-naphthalen-2-ylidene)-3-phenyl-thiazolidin-4-one 178c: Yield 56 %, pale yellow crystals, mp 104-105 °C; IR (KBr): 2974, 2944, 1710, 1684, 1662, 1480, 1241; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 2.28 (t, J = 5.8 Hz, 2H, CH_2), 2.59 (t, J = 5.8 Hz, 2H, CH_2), 6.76 (s, 1H, CH), 7.12–7.46 (m, 11H, ArH), 7.64 (dd, J = 8.4, 2.4 Hz, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 109.02, 120.14, 120.24, 124.10, 126.22 (x 2C), 126.41, 127.71, 127.14, 128.04, 128.08, 128.17 (x 2C), 129.42, 131.10, 133.12, 133.47, 134.20, 134.92, 136.12, 141.4, 141.7, 150.7, 158.6, 161.41, 187.02; ESI-MS m/z = 443 (M + 1). Anal.Calcd. for $C_{26}H_{18}ClNO_2S$ (443.92): C, 70.34; H, 4.09; N, 3.18; Found: C, 70.32 H, 4.04; N, 3.12.

5-(4-Bromo-benzylidene)-2-(5,7-dimethyl-1-oxo-3,4-dihydro-1H-naphthalen-2-ylidene)-3-methyl-thiazolidin-4-one 178d: Yield 67 %, white solid, mp 164-165°C; IR (KBr): 2970, 2945, 1710, 1689, 1667, 1482, 1244; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 2.28 (t, J = 5.8 Hz, 2H, CH_2), 2.59 (t, J = 5.8 Hz, 2H, CH_2), 2.87 (s, 3H, CH_3), 6.72 (s, 1H, CH), 7.11–7.32 (m, 6H, ArH), 7.87 (s, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 15.67, 21.3, 22.5, 28.7, 29.30, 114.02, 114.86, 122.02, 126.23 (x 2C), 127.71, 127.14, 128.04, 128.17, 129.42, 131.10, 133.12, 134.20, 134.92, 136.12, 141.2, 161.41, 187.02; ESI-MS *m/z* = 454 (M + 1). Anal.Calcd. for $C_{23}H_{20}BrNO_2S$ (454.38): C, 60.86; H, 4.46; N, 3.13; Found: C, 60.82 H, 4.41; N, 3.15.

2-(5,7-Dimethyl-1-oxo-3,4-dihydro-1*H*-naphthalen-2-ylidene)-3-ethyl-5-(4-fluoro-benzylidene)-thiazolidin-4-one 178e: Yield 52 %, yellow crystals, mp 156-157°C; IR (KBr): 2971, 2944, 1710, 1687, 1664, 1484, 1245; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 2.28 (t, J = 5.8 Hz, 2H, CH_2), 2.37 (s, 3H, CH_3), 2.59 (t, J = 5.8 Hz, 2H, CH_2), 6.76 (s, 1H, CH), 7.12–7.34 (m, 6H, ArH), 6.98 (d, J = 7.6 Hz, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 12.34, 15.20, 21.21, 22.8, 28.7, 37.26, 114.02, 114.86, 127.71, 127.14, 128.04, 129.42, 130.2 (x 2C), 131.10, 133.12, 135.4, 135.6, 135.82, 139.24, 141.4, 141.7, 161.41, 187.02; ESI-MS *m/z* = 407 (M + 1). Anal.Calcd. for $C_{24}H_{22}FNO_2S$ (407.12): C, 70.74; H, 5.44; N, 3.48; Found: C, 70.72 H, 5.404; N, 3.38.

2-(5,7-Dimethyl-1-oxo-3,4-dihydro-1*H*-naphthalen-2-ylidene)-5-(4-hydroxy benzylidene) -3-phenyl-thiazolidin-4-one 178f: Yield 58 %, yellow crystals, mp 96-97°C; IR (KBr): 2974, 2942, 1714, 1684, 1662, 1482, 1244; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 2.28 (t, J = 5.8 Hz, 2H, CH_2), 2.37 (s, 3H, CH_3), 2.59 (t, J = 5.8 Hz, 2H, CH_2), 5.68 (s, 1H, OH), 6.74 (s, 1H, CH), 7.10–7.32 (m, 6H, ArH), 6.98 (d, J = 7.6 Hz, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 15.20, 21.21, 22.8, 28.7, 109.8, 115.02 (x 2C), 120.4, 120.8, 127.81, 127.90, 128.04, 129.42, 130.2 (x 2C), 131.10, 133.12, 135.4, 135.6, 135.82, 137.6, 139.24, 141.4, 141.7, 156.10, 158.4, 161.41, 187.02; ESI-MS *m/z* = 453 (M + 1). Anal.Calcd. for $C_{28}H_{23}NO_3S$ (453.12): C, 74.14; H, 5.12; N, 3.09; Found: C, 74.12 H, 5.08; N, 3.05.

5-(4-Hydroxy-benzylidene)-2-(5-hydroxy-1-oxo-3,4-dihydro-1*H*-naphthalen-2-ylidene)-3-methyl-thiazolidin-4-one 178g: Yield 63 %, yellow crystals, mp 112-113°C; IR (KBr): 2978, 2940, 1710, 1684, 1662, 1482, 1244; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 2.27 (t, *J* = 5.8 Hz, 2H, CH_2), 2.56 (t, *J* = 5.8 Hz, 2H, CH_2), 2.75 (s, 3H, CH_3), 5.67 (s, 1H, OH), 6.62 (d, *J* = 7.4 Hz, 2H, ArH), 6.67 (d, *J* = 7.6 Hz, 1H, ArH), 6.87 (s, 1H, CH), 7.12–7.34 (m, 7H, ArH),; ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 18.4, 22.5, 29.7, 115.02 (x 2C), 121.4, 122.2, 127.71, 128.64, 131.10, 131.24, 133.14, 134.20, 136.12, 141.4, 141.7, 157.2, 161.21, 161.41, 182.02, 187.02; ESI-MS *m/z* = 379 (M + 1). Anal.Calcd. for $C_{21}H_{17}NO_4S$ (379.42): C, 66.49; H, 4.52; N, 3.68; Found: C, 66.43, H, 4.48; N, 3.64.

3-Ethyl-2-(5-hydroxy-1-oxo-3,4-dihydro-1*H*-naphthalen-2-ylidene)-5-(4-methoxy-benzylidene)-thiazoldin-4-one 178h: Yield 57 %, yellow crystals, mp 137-138°C; IR (KBr): 2974, 2940, 1710, 1684, 1662, 1482, 1244; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.27 (t, *J* = 7 Hz, 3H, CH_3), 2.27 (t, *J* = 5.8 Hz, 2H, CH_2), 2.56 (t, *J* = 5.8 Hz, 2H, CH_2), 3.07 (q, *J* = 7.4 Hz, 2H, CH_2), 3.75 (s, 3H, OMe), 5.67 (s, 1H, CH), 6.72 (d, *J* = 7.4 Hz, 2H, ArH), 6.87 (s, 1H, ArH), 7.12–7.34 (m, 7H, ArH), 7.87 (d, *J* = 7.6 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 12.34, 22.5, 28.7, 37.30, 56.0, 114.02 (x 2C), 114.54, 121.4, 122.2, 127.71, 128.64, 131.10, 133.14, 134.20, 136.12, 141.4, 141.7, 157.2, 161.21, 161.41, 182.02, 187.02; ESI-MS *m/z* = 407 (M + 1). Anal.Calcd. for $C_{23}H_{21}NO_4S$ (407.12): C, 67.79; H, 5.46; N, 3.48; Found: C, 67.74 H, 5.41; N, 3.42.

2-(5-Hydroxy-1-oxo-3,4-dihydro-1*H*-naphthalen-2-ylidene)-5-(4-methoxy-benzylidene)-3-phenyl-thiazolidin-4-one 178i: Yield 54 %, brown crystals, mp 172-173°C; IR (KBr): 2980, 2944, 1711, 1686, 1665, 1488, 1248; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 2.27 (t, J = 5.8 Hz, 2H, CH_2), 2.56 (t, J = 5.8 Hz, 2H, CH_2), 3.75 (s, 3H, OMe), 5.12 (s, 1H, OH), 6.72 (d, J = 7.4 Hz, 2H, ArH), 6.80 (s, 1H, CH), 7.10-7.32 (m, 8H, ArH), 7.67 (d, J = 7.6 Hz, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 18.23, 22.84, 56.0, 114.02 (x 2C), 114.54, 120.3, 120.8, 121.4, 122.2, 127.71, 127.82, 127.86, 127.92, 128.64, 131.10, 133.14, 134.20, 136.12, 141.4, 141.7, 157.2, 161.21, 161.41, 182.02, 187.02; ESI-MS *m/z* = 455 (M + 1). Anal.Calcd. for $C_{27}H_{21}NO_4S$ (455.12): C, 71.19; H, 4.65; N, 3.08; Found: C, 71.14 H, 4.61; N, 3.02.

5-(4-Chloro-benzylidene)-2-(5,7-dimethoxy-1-oxo-3,4-dihydro-1*H*-naphthalen-2-ylidene)-3-methyl-thiazolidin-4-one 178j: Yield 65 %, yellow crystals, mp 91-92°C; IR (KBr): 2974, 2940, 1710, 1682, 1660, 1480, 1242; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 2.28 (t, J = 5.8 Hz, 2H, CH_2), 2.57 (t, J = 5.8 Hz, 2H, CH_2), 2.74 (s, 3H, CH_3), 3.74 (s, 3H, OMe), 6.52 (s, 1H, ArH), 6.84 (s, 1H, CH), 6.92 (s, 1H, ArH), 7.21-7.34 (m, 4H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 18.20, 22.82, 29.31, 56.01, 56.07, 105.4, 107.6, 114.02, 119.14, 127.21, 127.47, 128.14 (x 2C), 131.10, 133.14, 133.20, 133.32, 138.14, 141.4, 160.02, 161.21, 162.41, 187.02; ESI-MS *m/z* = 441 (M + 1). Anal.Calcd. for $C_{23}H_{20}ClNO_4S$ (441.4): C, 62.52; H, 4.56; N, 3.18; Found: C, 62.47 H, 4.58; N, 3.22.

5-(4-Bromo-benzylidene)-2-(5,7-dimethoxy-1-oxo-3,4-dihydro-1*H*-naphthalen-2-ylidene) -3-ethyl-thiazolidin-4-one 178k: Yield 70 %, yellow crystals, mp 147-148°C; IR (KBr): 2982, 2949, 1711, 1687, 1662, 1484, 1244; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.27 (t, J = 7 Hz, 3H, CH_3), 2.29 (t, J = 5.8 Hz, 2H, CH_2), 2.58 (t, J =

5.8 Hz, 2H, CH_2), 2.76 (s, 3H, CH_3), 3.04 (q, $J = 7.4$ Hz, 2H, CH_2), 3.76 (s, 3H, OMe), 6.54 (s, 1H, ArH), 6.79 (s, 1H, CH), 6.89 (s, 1H, ArH), 7.19-7.38 (m, 4H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 12.92, 18.20, 22.82, 37.21, 56.01, 56.08, 105.4, 107.6, 114.02, 119.14, 122.14, 128.4 (x 2C), 131.10, 131.46, 133.14, 133.20, 133.32, 138.14, 141.4, 160.02, 161.21, 162.41, 187.02; ESI-MS *m/z* = 441 (M + 1). Anal.Calcd. for $C_{24}H_{22}BrNO_4S$ (499.13): C, 57.62; H, 4.52; N, 2.80; Found: C, 57.59 H, 4.57; N, 2.75.

2-(5,7-Dimethoxy-1-oxo-3,4-dihydro-1H-naphthalen-2-ylidene)-5-(4-fluoro-benzylidene) -3-phenyl-thiazolidin-4-one 178l: Yield 69 %, yellow crystals, mp 124-125°C; IR (KBr): 2976, 2947, 1710, 1685, 1662, 1484, 1244; ^1H NMR (400 MHz, $CDCl_3$): δ ppm 2.29 (t, $J = 5.8$ Hz, 2H, CH_2), 2.58 (t, $J = 5.8$ Hz, 2H, CH_2), 3.74 (s, 3H, OMe), 6.57 (s, 1H, ArH), 6.76 (s, 1H, CH), 6.86 (s, 1H, ArH), 6.94-7.38 (m, 7H, ArH), 7.64 (d, $J = 7.6$ Hz, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 18.20, 22.82, 56.01(x 2C), 105.4, 107.6, 115.02 (x 2C), 119.14, 120.10, 120.25, 127.82, 127.94, 128.4 (x 2C), 131.10, 131.46, 133.14, 133.20, 133.32, 138.14, 141.4, 150.12, 158.10, 160.02, 161.21, 162.41, 187.02; ESI-MS *m/z* = 441 (M + 1). Anal.Calcd. for $C_{28}H_{22}FNO_4S$ (487.11): C, 68.86; H, 4.56; N, 2.87; Found: C, 68.78 H, 4.62; N, 2.92.

VI. 4. **REFERENCES**

1. (a) Vigorita, M. G.; Ottana, R.; Monforte, F.; Macer, R.; Trovato, A.; Monforte, M. T.; Taviano, M. F. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2791.

   (b) Chande, M. S.; Suryanarayan V. *J. Chem. Res.* **2005**, *6*, 345.

   (c) Kavitha, C. V.; Basappa, S.; Swamy, N.; Mantelingu, K.; Doreswamy, S.; Sridhar, M. A.; Prasad, S.; Rangappa, K. S. *Bioorg. Med. Chem.* **2006**, *14*, 2290.

   (d) Shiradkar, M.; Shivaprasad, H. N. *Asian J. Chem.* **2006**, *18*, 331.

2. Diurno, M. V.; Mazzoni, O.; Izzo, A. A.; Bolognese, A. *Il Farmaco* **1997**, *52*, 237.

3. Ergene, N.; Capan, G. *Il Farmaco* **1994**, *49*, 449.

4. (a) Desai, S. B.; Desai, P. B.; Desai, K. R. *Asian J. Chem.* **1999**, *2*, 363;

   (b) Sharma, R. C.; Kumar, D. *J. Indian Chem. Soc.* **2000**, *77*, 492;

   (c) Piscapo, E.; Diurno, M. V.; Gagliardi, R.; Mazzoni, O. *Boll. Soc. Ital. Biol. Sper.* **1989**, *65*, 853.

5. Ueno, H.; Oe, T.; Snehiro, I.; Nakamura, S. *US Patent* 5594116, 1997; *Chem. Abstr.* **1977**, *126*, 157507p.

6. (a) Previtera, T.; Vigorita, M. G.; Bisila, M.; Orsini, F.; Benetolla, F.; Bombieri, G. *Eur. J. Med.Chem.* **1994**, *29*, 317. (b) Diurno, M. V.; Mazzoni, O.; Correale, G.; Monterry, I. G.. *Il Farmaco* **1999**, *54*, 579.

7. Eyelid, M. Y.; Fathallah, O. A.; El-Zaher, M. I.; Kamel, M. M.; Abdon, W. A.; Anwar, M. M. *Bull. Fac. Pharm.* **1996**, *34*, 125.

8. Rawal, R. K.; Prabhakar, Y. S.; Katti, S. B.; De Clercq, E. *Bioorg. Med. Chem.* **2005**, *13*, 6771.

9. (a) Kato, T.; Ozaki, T.; Tamura, K. *J. Med. Chem.* **1999**, *42*, 3134;

   (b) Hara, A.; Suzuki, T.; Hashizume, H.; Shishido, N.; Nakamura, M.; Ushikube, F.; Abiko, Y. *Eur. J. Pharmacol.***1999**, *385*, 81.

10. Tanabe, Y.; Suzukamo, G.; Koura, Y.; Imanishi, N.; Morooka, S.; Enomoto, M.; Kojima, A.; Sanemitsu, Y.; Mizutani, M. *Tetrahedron Lett.* **1991**, *32*, 379.

11. Kato, T.; Ozaki, T.; Ohi, N. *Tetrahedron: Asymmetry* **1999**, *10*, 3963.

12. Adachi, Y.; Suzuki, Y.; Homma, N.; Fukazawa, M.; Tamura, K.; Nishie, I.; Kuromaru, O. *Eur. J. Pharmacol.* **1999**, *367*, 267.

13. Ottana, R.; Mazzon, E.; Dugo, L.; Monforte, F.; Macer, R.; Sautebin, L.; De Luca, G.; Vigorita, M. G.; Alcaro, S.; Ortuso, F. *Eur. J. Pharmacol.* **2002**, *448*, 71.

14. (a) Koike, H.; Imanashi, N.; Natsume, Y.; Morooka, S. *Eur. J. Pharm. Mol. Pharm.* **1994**, 269.

    (b) Tanabe, Y.; Yamamoto, H.; Murakami, M.; Yanagi, K.; Kubota, Y.; Okumura, H.; Sanemitsu, Y.; Suzukamo, G. *J. Chem. Soc. Perkin Trans. I* **1995**, 7, 935.

    (c)Tanabe, Y.; Komuro, Y.; Imanishi, N.; Morooka, S.; Enomoto, M.; Kojima, A.; Sanemitsu, Y.; Mizutani, M. *Tetrahedron. Lett.* **1991**, *32*, 379.

15. Kato, Y.; Kita, Y.; Nishio, M.; Hirasawa, Y.; Ito, K.; Yamanaka, T.; Monogamy, Y.; Seki, J. *Eur. J. Pharmacol.* **1999**, *384*, 197.

16. Voss, M. E.; Carter, P. H.; Tobin, A. J.; Scherle, P. A.; Brown, G. D.; Thompson, L. A.; Xu, M.; Lo, Y. C.; Yang-Liu, R. R. Q. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 533.

17. Lakhan, R.; Singh, O. P. *J. Ind. Chem. Soc.* **1984**, *61*, 784.

18. Bhargava, P. N.; Prakash, S.; Lakhan, R. *Ind. J. Chem.* **1981**, *20B*, 927.

19. Lakhan, R. *Agric. Biol. Chem.* **1982**, *46*, 557.

20. Kato, T.; Ozaki, T.; Tamura, K.; Suzuki, Y.; Akima, M.; Ohi, N. Novel Calcium Antagonists with Both Calcium Overload Inhibition and Antioxidant Activity. 1. 2-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3-(aminopropyl)thiazolidinones. *J. Med. Chem.* **1998**, *41,* 4309-4316.

21. Kato, T.; Ozaki, T.; Tamura, K.; Suzuki, Y.; Akima, M.; Ohi, N. *J. Med. Chem.*

1999, *42,* 3134-3146

22. Reddy, K. A.; Lohray, B. B.; Bhushan, V.; Bajji, A. C.; Reddy, K. V.; Reddy, P. R.; Krishna, T.H.; Rao, I. N.; Jajoo, H. K.; Mamidi-Rao, N. V. S.; Chakrabartir, R.; Dileepkumar, T.; Rajagopalanr, R.; *J. Med. Chem.***1999,** *42*, 1927.

23. Teraishi, F.; Wu, S. H.; Sasaki, J.; Zhang, L. D.; Zhu, H. B.; Davis, J. J.; Fang, B. L. P. Glycoprotein-independent apoptosis induction by a novel synthetic compound, MMPT. *J. Pharmacol. Exp. Three.* **2005**, *314*, 355–362.

24. Barreca, M. L.; Chimirri, A.; De Luca, L.; Monforte, A. M.; Monforte, P.; Rao, A.; Zappala, M.; Balzarini, J.; De Clercq, E.; Pannecouque, C.; Witvrouw, M. Discovery of 2,3-diaryl-1,3-thiazolidin-4-ones as potent anti-HIV-1 agents. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1793-1796.

25. M. L. Barreca, J. Balzarini, A. Chimirri, E. De Clercq, L. De Luca, H. D. Holtje, M. Holtje, A. M. Monforte, P. Monforte, C. Pannecouque, A. Rao, and M. Zappala *J. Med.Chem.* **2002,** *45,* 5410-5413.

26. H. Zhou, A. X. Li, X. Ma, W. Feng, W. Zhang and B. Yan *J. Comb. Chem.* **2008,** *10,*303–312.

27. Vicini, P.; Geronikaki, A.; Kitka, A.; Incerti, M.; Zani, F. Synthesis and antimicrobial activity of novel 2-thiazolylimino-5-arylidene-4-thiazolidinones. *Bioorg. Med. Chem.* **2006,** *14,* 3859–3864.

28. Vicini, P.; Amoretti, L.; Chiavarini, M.; Impicciatore, M. Synthesis and local anesthetic activity of alkylaminoacyl derivatives of 3-amino-1,2-benzisothiazoles. *Farmaco* **1990,** *4,* 933–944.

29. Geronikaki, A.; Theophilidis, G. Synthesis of 2-(aminoacetylamino)thiazole derivatives and comparison of their local anesthetic activity by method of action potential. *Eur. J. Med. Chem.* **1992,** *27* (7), 709–716.

30. Kavitha, C.V.; Basappa, A.; Swamg, S. N.; Mantelingu, K.; Doreswamg, S.; Sridhar, M. A.; Prasad, J. S.; Rangappa, K. S. *Bioorg. Med. Chem.* **2006**, *14*, 2290.

31. Mukhtar, S.; Rahman, V. P. M.; Ansari, W. H.; Lemie, G.; De-Droot, A.; Dommise, R. *Molecules*, **1999**, 4, 232.

32. Singh, G.; Bhattacharjee, S. S.; Ila, H.; Junjappa, H. *Synthesis* **1982**, 693-694.

33. (a) Peruncheralathan, S.; Khan, T. A.; Ila, H.; Junjappa, H,; *J. Org. Chem.* **2005**, 70, 10030-10035.(b) Dalgard, L.; Jensen, L.; Lawesson, S. O. *Tetrahedron* **1974**, *39*, 93. (c) Ramdas, S, R.; Srinivasan, P. S.; Ramachandran, J.; Sastry, V. V. S. K. *Synthesis* **1983**, 605. (d) Voss, J. Synthesis of Thioesters and Thiolactones, In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1990; Vol. 6, pp 435- 460.

34. (a) Nair, S. K.; Samuel, R.; Asokan, C. V. *Synthesis* **2001**, 573.
(b) Nair, S. K.; Asokan, C. V. *Synth. Commun.* **2001**, *22*, 1453.

35. Jagodzinski, Tadeusz S. *Chem. Rev.*, **2003**, *103*, 197-227.

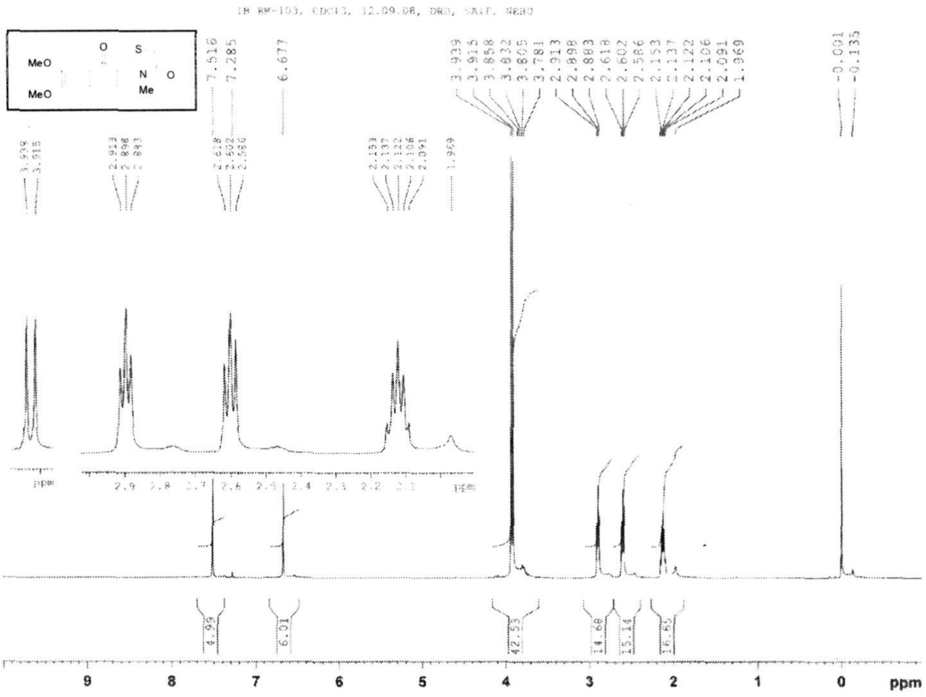


Figure 37. ^{1}H NMR spectra of 2-(6,7-Dimethoxy-1-oxo-3,4-dihydro-1H-naphthalen-2-ylidene)-3-methyl-thiazolidin-4-one **176j**.

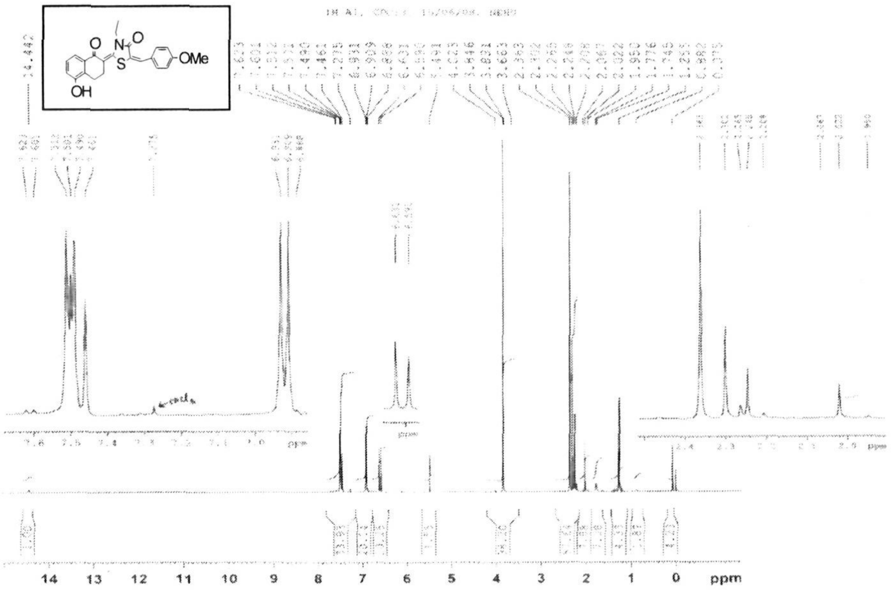


Figure 38. ^{1}H NMR spectra of 3-Ethyl-2-(5-hydroxy-1-oxo-3,4-dihydro-1H-naphthalen-2-ylidene)-5-(4-methoxy-benzylidene)-thiazolidin-4-one **178h**.

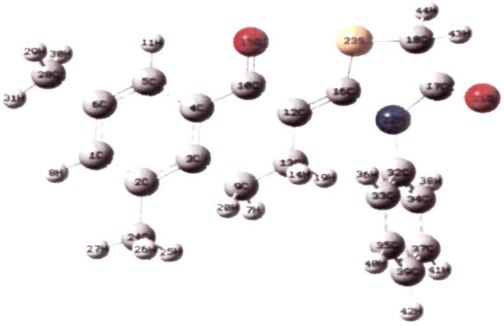


Figure 39: Compound **176f**.

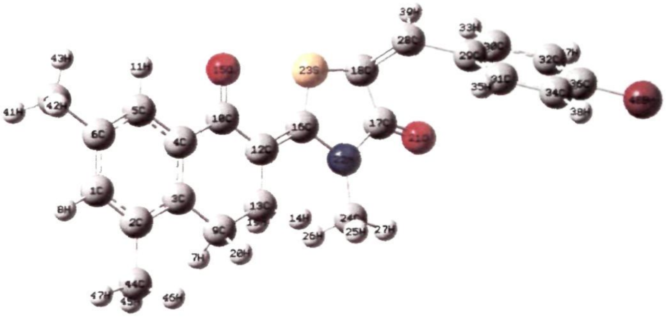


Figure 40: Compound **178d**.

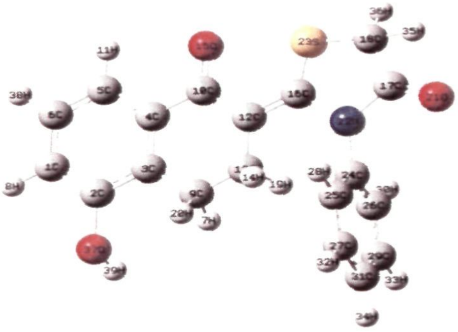


Figure 41: Compound **176i**.

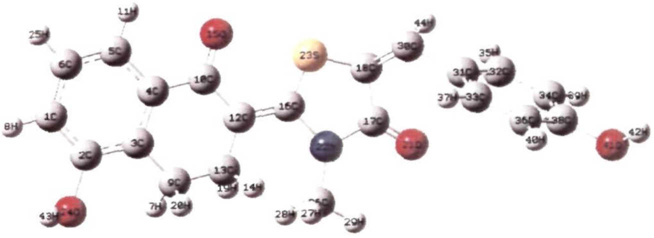


Figure 42: Compound **178g**.

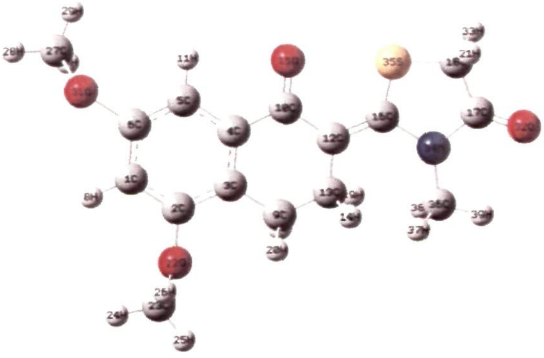


Figure 43: Compound **176j**.

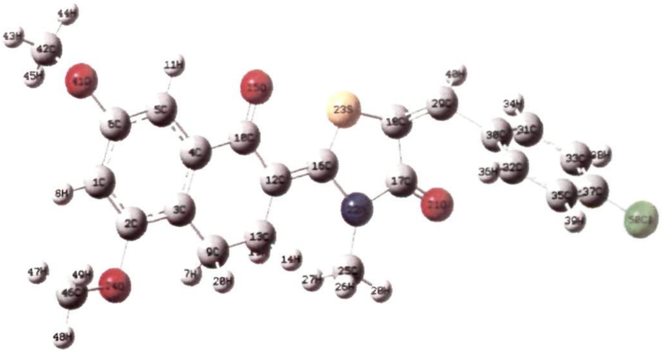


Figure 44: Compound **178j**.

Computer 3D models in Gaussview

APPENDIX

ABBREVIATIONS

Ac	Acetyl
AcOH	Acetic acid
AIBN	2,2′-Azobisisobutyronitrile
Ar	Aryl
Bn	Benzyl
Boc, BOC	tert-Butyloxycarbonyl
brs	broad singlet
s-Bu	*sec*-Butyl
t-Bu	*tert*-Butyl
Bz	Benzoyl
CI	Chemical ionization
$CDCl_3$	Chloroform D
Cp	Cyclopentadienyl
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBE	Double bond equivalent
DBU	1,8-Dizabicyclo[5.4.0]undec-7-ene
DCC	*N,N*-dicyclohexylcarbodiimide
DCM	dichloromethane
DMF	N,N-Dimethylformamide
DMS	Dimethyl sulfide
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
3D	Three dimensional
EtOH	Ethanol
ESR	Electron spin resonance
ESI	Electron spray ionisation
Et	Ethyl
m-CPBA	*meta*-Chloroperoxybenzoic acid
Me	Methyl
NBS	*N*-Bromosuccinimide
N-Bn	*N*-benzyl
N-(2-pyridyl)	Pyridin-2-yl
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser effect
Ph	Phenyl
HPLC	High performance liquid chromatography
HIV	Human immunodeficiency virus
h / hr	hour
IR	Infrared
LDA	Lithium diisopropylamide
PPA	Polyphosphoric acid
ppm	parts per million
Pr	Propyl
i-Pr	*iso*-Propyl
PTC	Phase transfer catalysis
PTSA	*p*-Toluenesulfonic acid
PSSA	Polystyrene sulfonic acid
Pip	piperidine
Py	pyridine
RT/r t	room temperature
Rf	Retention factor or Ratio of front
THF	Tetrahydrofuran
TMS	Trimethylsilyl, tetramethylsilane
TLC	Thin layer chromatography
Ts	p-Toluenesulfonyl. Tosyl
UV	Ultraviolet

LIST OF PUBLICATIONS

1. Synthesis of functionalized diaryl alkanes from azines
   Rudolf M. Manih & Bekington Myrboh
   Indian Journal of Chemistry Vol.48B, January **2009**, pp. 146-151.

2. Synthesis of 2-substituted amino-4-aryl-3*H*-dihydro-benzo-[*b*][1,4]-diazepines and 2-(*N*-cycloamino)-4-Aryl-3*H*-dihydro-benzo-[*b*][1,4]-diazepines using *β*-oxodithioesters
   Rudolf M. Manih and Bekington Myrboh
   Tetrahedron Letters **2009** (Communicated).

3. A facile synthesis of 1-Aryl-3-(*N*-alkyl/aryl/cycloamino)-5-arylsubstituted pyrazoles using the *β*-oxothioamide generated from *β*-oxodithioester
   Rudolf M. Manih and Bekington Myrboh
   Synthetic Communications **2009** (Communicated).

4. A greener and facile synthesis of 3,5,7-trisubstituted-4*H*–[1,2]diazepines
   R. M. Manih and B. Myrboh
   (Communicated).

5. *β*-oxodithioesters as highly efficient synthons for the synthesis of substituted-(3-Methyl-4-phenyl-3*H*-thiazol-2-ylidene)-3,4-dihydro-2*H*-naphthalen-1-one and 1-aryl-3-(*N*-cycloamino)-4,5-dihydro-1*H*-benzo[*g*]indazole derivatives using substituted α-tetralones
   R. M. Manih, D. Myrboh and B. Myrboh
   (Communicated).

6. Synthesis of substituted-(3,4-dihydro-1*H*-naphthalen-2-ylidene)-thiazolidin-4-one derivatives and 5-substituted arylidene-3-alkyl/aryl-2-substituted-(1-oxo-3,4-dihydro-1*H*-naphthalen-2-ylidene)-thiazolidin-4-ones using the *β*-oxothioamide
   R. M. Manih, M. Rajbangshi, H. Mecadon, G. Kharmawphlang and B. Myrboh (Communicated).