Research Journal of Chemical Sciences _____ ISSN 2231-606X
Vol. **3(7),** 90-103, July **(2013)** *Res. J. Chem. Sci.*

Review Paper

1, 5 Benzodiazepines: Overview of Properties and Synthetic Aspects

Pareek Aastha[2]*, Kumar Navneet[1], Agarwal Anshu[2], Sharma Pratima[2] and Kishore Dharma[2]
[1]Raj Kumar Goel institute of Technology, Ghaziabad, UP, INDIA
[2]Banasthali University, Department of Chemistry, Banasthali, Rajasthan, INDIA

Available online at: www.isca.in
Received 20th April 2013, revised 10th May 2013, accepted 9th June 2013

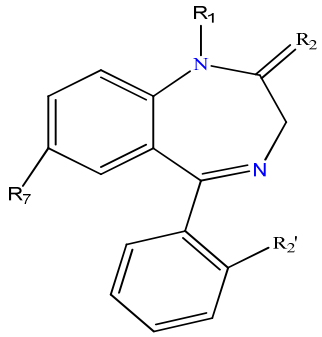
Abstract

Heterocyclic compounds occur widely in nature and quite a few of these are essential to life processes. The literature on heterocyclic compounds is replete with examples of a large number of synthetic methods of naturally occurring systems which are pharmacologically active. Their practical applications range from clinical use to field as diverse as agriculture, photography, biocide formulations and polymer science. The range of known compounds is virtually limitless, encompassing an impressive spectrum of physical, chemical and biological properties. Extensive applications of these compounds in medicine has led to the chemistry of these materials to expand exponentially in the past few decades, so much so that virtually a limitless series of structurally novel compounds with a broad spectrum of reactivity and stability has been developed . The heterocyclic compounds containing nitrogen has expanded exponentially in the past decades due to their uniquephysical properties , specific chemical reactivity and their remarkable potential biological activities 1,2 .A survey of literature on the nitrogen heterocycles reveal that pyrazole, isoxazole, carbazol, pyrimidine , diazepines and oxazepines tc., are important constituents of a wide variety of natural products with pharmacodynamic application.

Keywords: Heterocyclic compounds, uniquphysical properties, pharmacodynamic application.

Introduction

The core structure of benzodiazepines. "R" labels denote common locations of side chains, which give different benzodiazepines their unique properties[1,2]. A benzodiazepine (sometimes colloquially "benzo"; often abbreviated "BZD") is a psychoactive drug whose core chemical structure is the fusion of a benzene ring and a diazepine ring. The first benzodiazepine, chlordiazepoxide (Librium), was discovered accidentally by Leo Sternbach in 1955, and made available in 1960 by Hoffmann–La Roche, which has also marketed diazepam (Valium) since 1963[3]. Benzodiazepines enhance the effect of the neurotransmitter gamma-amino butyric acid (GABA-A), resulting in sedative, hypnotic (sleep-inducing), anxiolytic (anti-anxiety), anticonvulsant, and muscle relaxant properties; also seen in the applied pharmacology of high doses of many shorter-acting benzodiazepines are amnesic-dissociative actions. These properties make benzodiazepines useful in treating anxiety, insomnia, agitation, seizures, muscle spasms, alcohol withdrawal and as a premedication for medical or dental procedures. Benzodiazepines are categorized as either short-, intermediate- or long-acting. Short- and intermediate-acting benzodiazepines are preferred for the treatment of insomnia; longer-acting benzodiazepines are recommended for the treatment of anxiety[4]. In general, benzodiazepines are safe and effective in the short term, although cognitive impairments and paradoxical effects such as aggression or behavioral disinhibition occasionally occur[5]. Long-term use is controversial due to concerns about adverse psychological and physical effects, increased questioning of effectiveness and because benzodiazepines are prone to cause tolerance, physical dependence, and, upon cessation of use after long term use, a withdrawal syndrome. Due to adverse effects associated with the long-term use of benzodiazepines, withdrawal from benzodiazepines, in general, leads to improved physical and mental health. The elderly are at an increased risk of suffering from both short- and long-term adverse effects. Withdrawal from a long term benzodiazepine addiction may cause tinnitus as a side effect[6].



There is controversy concerning the safety of benzodiazepines in pregnancy. While they are not major teratogens, uncertainty remains as to whether they cause cleft palate in a small number of babies and whether neurobehavioural effects occur as a result of prenatal exposure, they are known to cause withdrawal symptoms in the newborn. Benzodiazepines can be taken in overdoses and can cause dangerous deep unconsciousness. However, they are much less toxic than their predecessors, the barbiturates, and death rarely results when a benzodiazepine is

the only drug taken; however, when combined with other central nervous system depressants such as alcohol and opiates, the potential for toxicity and fatal overdose increases[7]. Benzodiazepines are bicyclic heterocyclic compounds in which benzene nucleus is fused to a seven membered ring containing two nitrogen atoms. The term benzodiazepine implies a maximum degree of unsaturation due to the presence of three double bond in the seven membered ring. Considering the relative position of nitrogen atom in the heterocyclic ring, benzodiazepines are classified as 1, 2; 1, 3; 1, 4; 1, 5 and 2, 4 benzodiazepines[8,9]. (figure 1)

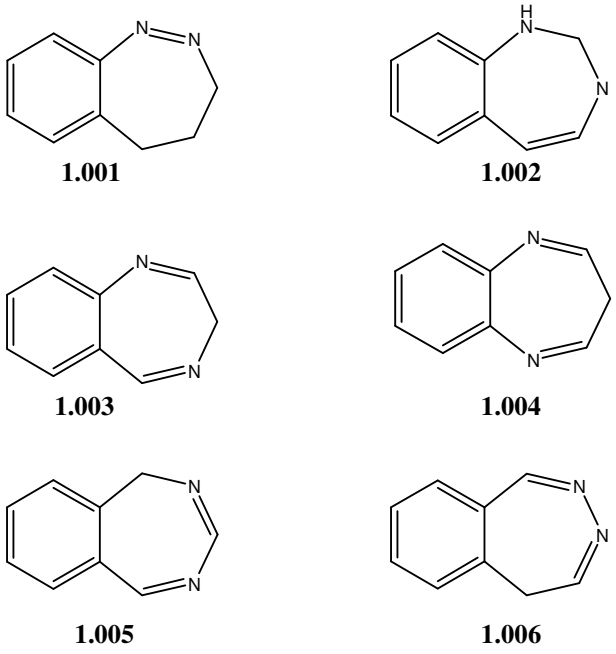


Figure-1

History: The first benzodiazepine, Chlordiazepoxide (Librium) (1.007), was discovered accidentally by Leo Sternbach in 1955, and made available in 1960 by Hoffmann-La Roche, which also marketed diazepam (Valium) (1.008) since 1963. Oxazepam (1.009) was synthesized in 1961, nitrazepam (1.010) in 1962, and temazepam (1.011) and nimetazepam (1.012) in 1964. In 1965 came flurazepam and nordazepam. Benzodiazepines are categorized as either short-, intermediate- or long-acting drugs. Short- and intermediate-acting benzodiazepines are preferred for the treatment of insomnia; longer-acting benzodiazepines are recommended for the treatment of anxiety.

Nomenclature of Benzodiazepines

Benzodiazepines are numbered as shown in figure 3 the numbering of these benzodiazepines proceeds in the opposite direction to that used for the unsaturated diazepines. The position of the odd hydrogen atom (even if occupied by another mono or divalent substituent) is indicated by the term 1H, 2H, 3H etc., In dihydro and tetrahydro benzodiazepines the odd hydrogen is given the lowest possible number.

This is however, complicated by the fact that, first consideration is given to the position of a functional group which is expressed as a suffix to the name of the compound[10].

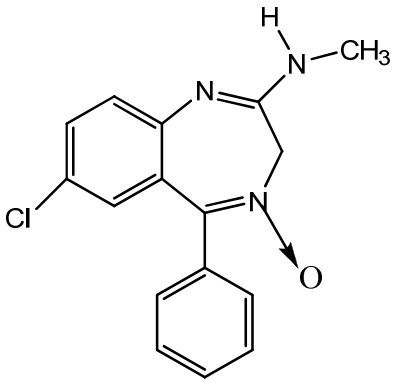
Biological Importance of 1, 5-Benzodiazepines

Benzodiazepines and their polycyclic derivatives are an important class of bioactive compounds. They have attracted attention of chemist in field of drug and pharmaceutical. Their clinical use has been reported by Palfai and Janbiewiz[11]. According to their report, roughly 800 tons of benzodiazepines are consumed every year with 53 million prescriptions for valium only.

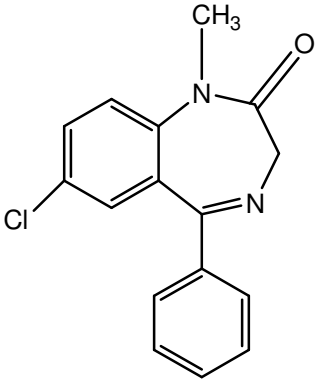
The compounds of this class have been widely used as anticonvulsant, antianxiety, analgesic, sedative, antidepressive, hypnotic and anti-inflammatory agents. They are also used to relieve pain of skeletal muscle joints and the spasticity resulting from cerebral palsy and paraplegia, athetosis and stiff-man syndrome. Recently they have been reported to show antileukamic, antiplatelet, antilucer, endothelia antagonists and vasopressin antagonist activity[12]. Their role in the control and treatment of AIDS has also been recently demonstrated. Benzodiazepines enhance the effect of the neurotransmitter gamma-aminobutyric acid (GABA), which results in sedative, hypnotic (sleep-inducing), anxiolytic[13] (anti-anxiety), anticonvulsant, muscle relaxant and amnesic action. These properties make benzodiazepines useful in treating anxiety, insomnia, agitation, seizures, muscle spasms, alcohol withdrawal and as a premedication for medical or dental procedures. Most are administered orally; however, they can also be given intravenously, intramuscularly or rectally. Benzodiazepines are not FDA (Food and Drug Administration) approved for long term use. They are approved only for the short-term use for several conditions. Benzodiazepine derivatives are also commercially used as dyes for acrylic fibres. Moreover 1, 5-benzodiazepines derivatives are valuable synthons that can be used in preparation of other fused ring compounds such as triazolo-, oxadiazolo-, oxazino-,or furano-benzodiazepines.

Chemistry

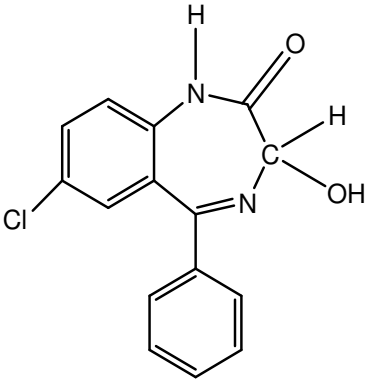
The 1, 4-benzodiazepine ring system. 5-phenyl-1*H*-benzo[*e*][1,4]diazepin-2(3*H*)-one forms the skeleton of many of the most common benzodiazepine pharmaceuticals, such as diazepam (7-chloro-1-methyl substituted) (figure 4).



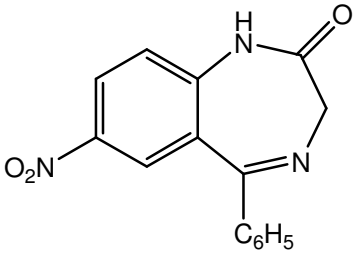
Chlordiazepoxide (Librium)
1.007



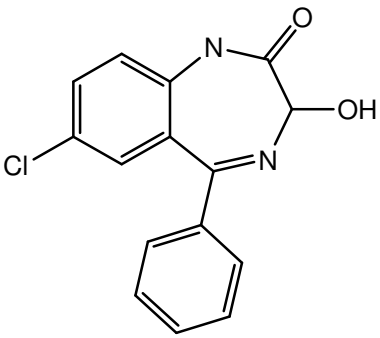
Diazepam (Valium)
1.008



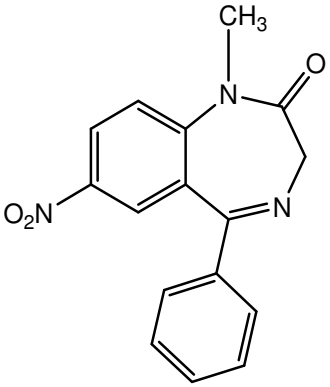
Oxazepam
1.009



Nitrazepam
1.010



Temazepam
1.011



Nimetazepam
1.012

Figure-2

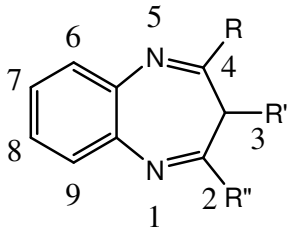


Figure-3

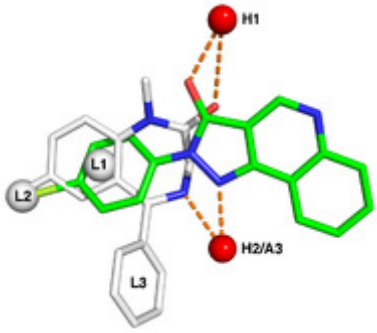
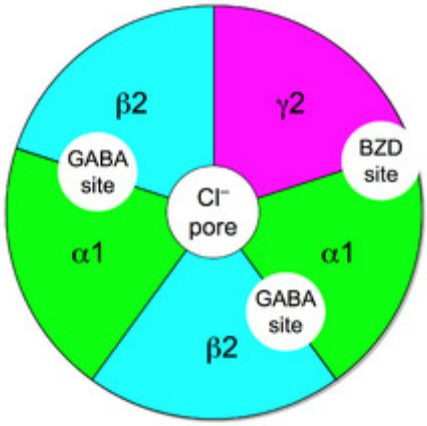


Figure-4

Mechanism of Action: Schematic diagram of the $(\alpha1)_2(\beta2)_2(\gamma2)$ $GABA_A$ receptor complex that depicts the five-protein subunits that form the receptor, the chloride (Cl^-) ion channel pore at the center, the two GABA active binding sites at the α1 and β2 interfaces and the benzodiazepine (BZD) allosteric binding site at the α1 and γ2 interface.Benzodiazepines work by increasing the efficiency of a natural brain chemical, GABA, to decrease the excitability of neurons. This reduces the communication between neurons and, therefore, has a calming effect on many of the functions of the brain.

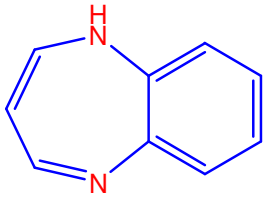


GABA controls the excitability of neurons by binding to the $GABA_A$ receptor[14]. The $GABA_A$ receptor is a protein complex located in the synapses of neurons. All $GABA_A$ receptors contain an ion channel that conducts chloride ions across neuronal cell membranes and two binding sites for the neurotransmitter gamma-aminobutyric acid (GABA), while a subset of $GABA_A$ receptor complexes also contain a single binding site for benzodiazepines. Binding of benzodiazepines to this receptor complex promotes binding of GABA, which in turn increases the conduction of chloride ions across the neuronal cell membrane. This increased chloride ion conductance hyperpolarizes the neuron's membrane potential. As a result, the difference between resting potential and threshold potential is increased and firing is less likely. Different $GABA_A$ receptor[15] subtypes have varying distributions within different regions of the brain and, therefore, control distinct neuronal circuits. Hence, activation of different $GABA_A$ receptor subtypes by benzodiazepines may result in distinct pharmacological actions.In terms of the mechanism of action of benzodiazepines; their similarities are too great to separate them into individual categories such as anxiolytic or hypnotic. For example, a hypnotic administered in low doses will produce anxiety-relieving effects, whereas a benzodiazepine marketed as an anti-anxiety drug will at higher doses induce sleep[16].

The subset of $GABA_A$ receptors that also bind benzodiazepines are referred to as benzodiazepine receptors (BzR). The $GABA_A$ receptor is a heteromer composed of five subunits, the most common ones being two αs, two βs, and one γ ($\alpha_2\beta_2\gamma$). For each subunit, many subtypes exist ($\alpha_{1\text{-}6}$, $\beta_{1\text{-}3}$, and $\gamma_{1\text{-}3}$)[17]. $GABA_A$ receptors that are made up of different combinations of subunit subtypes have different properties, different distributions in the brain and different activities relative to pharmacological and clinical effects[18]. Benzodiazepines bind at the interface of the α and γ subunits on the $GABA_A$ receptor. Binding also requires that alpha subunits contain a histidine amino acid residue, (*i.e.*, α_1, α_2, α_3, and α_5 containing $GABA_A$ receptors). For this reason, benzodiazepines show no affinity for $GABA_A$ receptors containing α_4 and α_6 subunits with an arginine instead of a histidine residue[19]. Once bound to the benzodiazepine receptor, the benzodiazepine ligand locks the benzodiazepine receptor into a conformation in which it has a greater affinity for the GABA neurotransmitter. This increases the frequency of the opening of the associated chloride ion channel and hyperpolarizes the membrane of the associated neuron. The inhibitory effect of the available GABA is potentiated, leading to sedatory and anxiolytic effects. Furthermore, different benzodiazepines can have different affinities for BzRs made up of different collection of subunits. For instance, those with high activity at the α_1 are associated with stronger hypnotic effects, whereas those with higher affinity for $GABA_A$ receptors containing α_2 and/or α_3 subunits have good anti-anxiety activity[20].

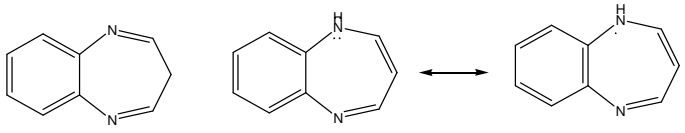
The benzodiazepine class of drugs also interacts with peripheral benzodiazepine receptors. Peripheral benzodiazepine receptors are present in peripheral nervous system tissues, glial cells, and to a lesser extent the central nervous system. These peripheral receptors are not structurally related nor coupled to $GABA_A$ receptors. They modulate the immune system and are involved in the body response to injury. Benzodiazepines also function as weak adenosine reuptake inhibitors. It has been suggested that some of their anticonvulsant, anxiolytic and muscle relaxant effects may be in part mediated by this action.

1, 5-Benzodiazepines: 1, 5-Benzodiazepines are bicyclic compounds with two nitrogen atoms at 1 and 5 positions in a seven membered ring fused to a benzene ring. Basically 1, 5-benzodiazepines are the 2, 3-benzo annelated derivatives of 1, 4-diazepines[21].



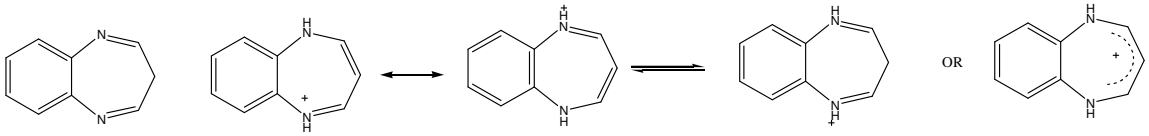
1, 5 benzodiazepine (figure 5)

Benzodiazepines usually occur in the diimine form 1 rather than in the conjugated vinamidine form 2 and 3. In the diimine form 1 some extra stabilization arise due to the conjugation of the imine group with the benzene ring .Cyclic conjugation as in 2 and 3 may indeed lead to destabilization of the molecules because it involves interaction of 12π-electrons around the periphery of the molecules as implied in 2 or of 8π-electrons around the 7-membered ring as in 3 either of these are destabilizing 4n π-electron systems.



1 **2** **3**

Protonation of benzodiazepines lead to the successive formation of monocation **4** and **5**



(5) (4)

The conjugated form, which would have 8π-electrons associated with the 7-membered ring, is electronically an analogue of benzocyclo octatetraene[22]. Annular conjugation around either the diazepines ring or the overall periphery makes no positive

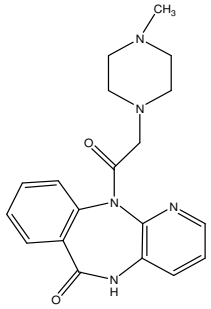
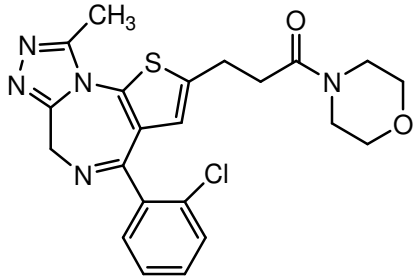
contribution to the stability of the system, whereas electronic interaction between the benzene ring and the two imino groups in the imino form does.

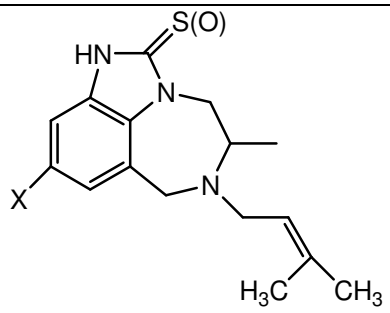
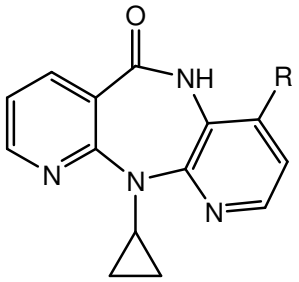
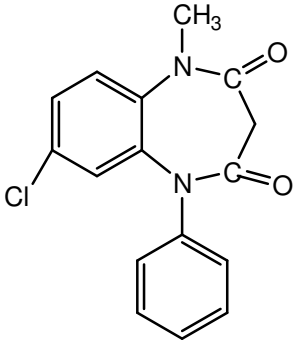
Biological Importance of 1, 5-Benzodiazepines

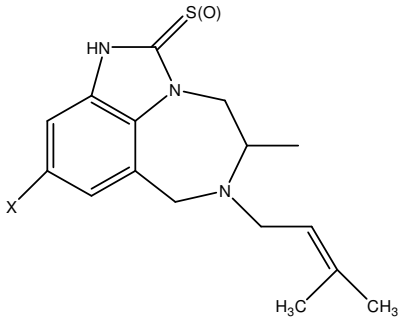
The ascendancy of the 1, 5-benzodiazepines in chemical literature is doubtless a consequence of their easy accessibility and the activity they show against a variety of targets including peptide hormones (such as CCK)· interleukin converting enzymes (ICE)· and potassium blockers (IK)· The enormous amount of research work that has been conducted in the pharmaceutical laboratories on these compounds during last several decades derives its inspiration from the discovery of the remarkable tranquilizing, CNS depressants[23], anti-inflammatory[24], antispasmodic, antidepressive[25], antifungal, antibacterial, antifeedant, analgesic, anticonvulsant, muscle relaxant, hypnotic and sedative activity etc. observed with certain members of this heterocyclic system. Of particular importance are the substituted and tricyclic derivatives which are not only used as anxiolytic or antineoplastic agents but their novel application is continuosly emerging. The recent demonstration that some of their derivatives can serve as potential agents in the control and treatment of AIDS has stimulated further interest in these compounds from yet another perspective. Table- 1 gives the list of substituted and tricyclic 1, 5-benzodiazepines whose antineoplastic and anti-HIV activity has appeared in the literature.

Benzodiazepines and their polycyclic derivatives are known to exhibit a wide spectrum of biological activities and have found applications in the pharmaceutical industry. 1, 5-Benzodiazepines constitute an important class of psychopharmacopea, in particular as tranquilizer and also as potent virucides and non-nucleoside inhibitors of HIV-1 reverse transcriptase. Beside this, 1, 5-benzodiazepines show antifungal, antibacterial, antifeedant, anti-inflammatory, analgesic, antihypnotic, anticonvulsant, antidepressive and sedative activities. Some of their derivatives are used as dyes for acrylic fibers. Some benzodiazepines and allied derivative are known to exhibit muscle relaxant, anticoagulant, antiobesity, antiulcer, calcium channel blockers, cholecystokinin antagonists, thrombopoietin receptor agonist, endothelin antagonist, vasopressin receptor antagonist activity. Some benzodiazepine derivatives shown in figure 6 are highly pharmacologically active molecules. TIBO (1.013), nevirapine (1.014) act as anti-HIV agents, clobazam (1.015) act as anti-epileptic agent and clazapine (1.016) is effective as antipsychotic agent[26].

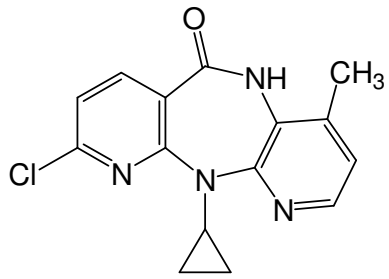
Table-1
Pharmacological Properties of Substituted and Tricyclic Derivatives of 1, 5-Benzodiazepines

S.No	Structure of the Compounds	Name of the Compounds	Pharmacological properties
1.		Pirenzepine	Act selectively as Muscarinic receptor(M1) antagonist
3.		Apofant	Act as the platelet activating factor(PAF) inhibitor

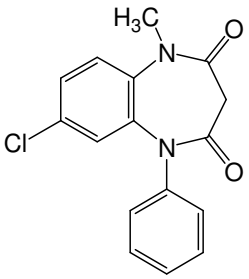
4.		TIBO	Shows Anti-HIV activity
5.		Nivirapine	Act as Anti-HIV agent
6.		Clobazam	Act as Antiepileptic agent



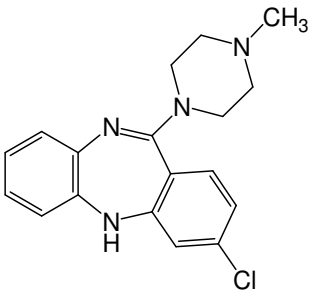
1.013



1.014



1.015

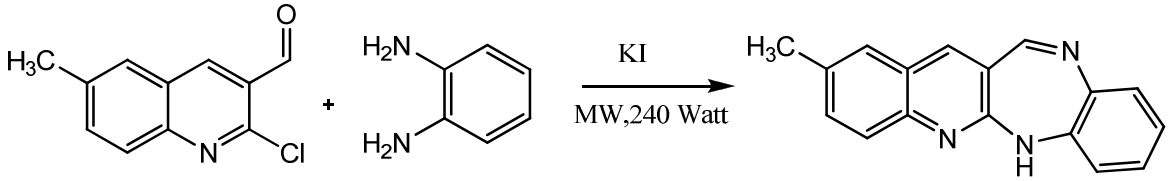


1.016

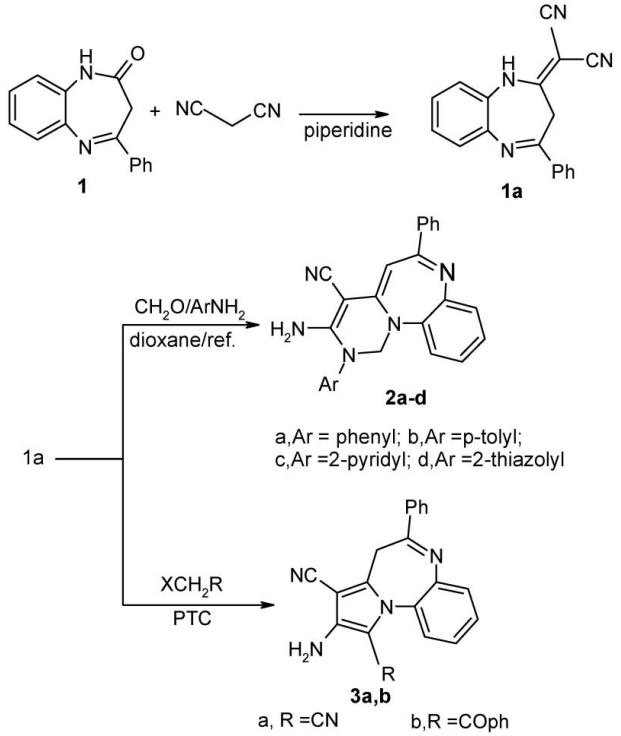
Figure-6

SYNTHETIC ASPECTS OF 1, 5 BENZODIAZEPINES

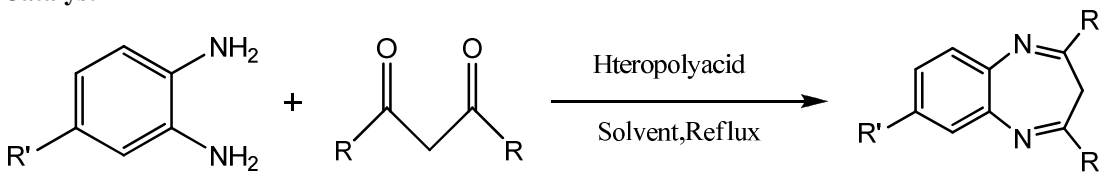
Synthesis of Methylquinolino[3,2-b][1,5]benzodiazepine(MQBD)



Synthesis of New Fused and Spiro 1,5-Benzodiazepines

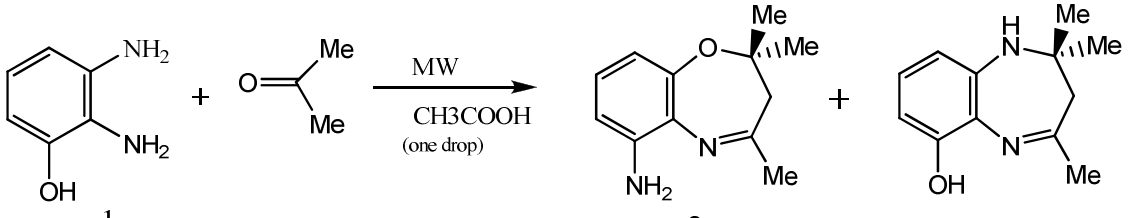


An Efficient Synthesis of 3H-1,5-benzodiazepine Derivatives Catalyzed by Heteropolyacids as a Heterogeneous Recyclable Catalyst

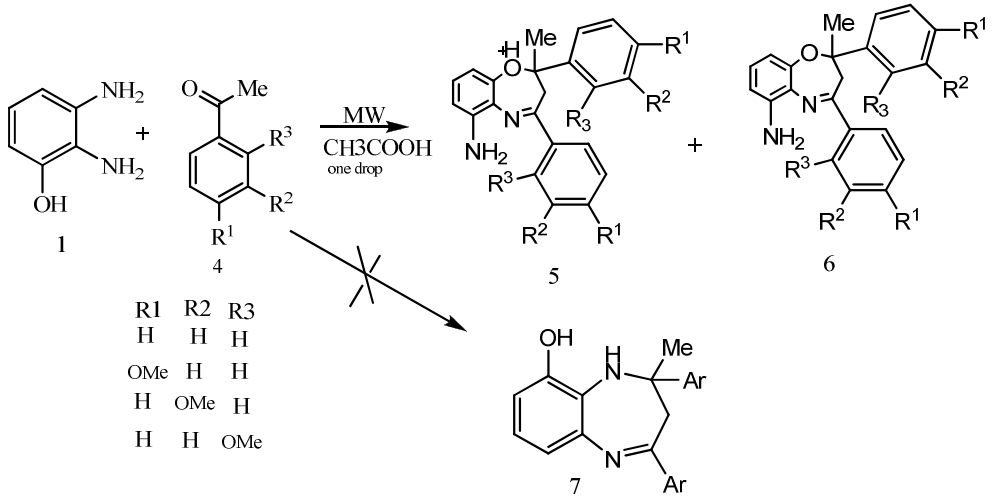


1, 5-Benzoxazepines vs. 1, 5-Benzodiazepines. One-Pot Microwave-Assisted Synthesis and Evaluation for Antioxidant Activity and Lipid Peroxidation Inhibition

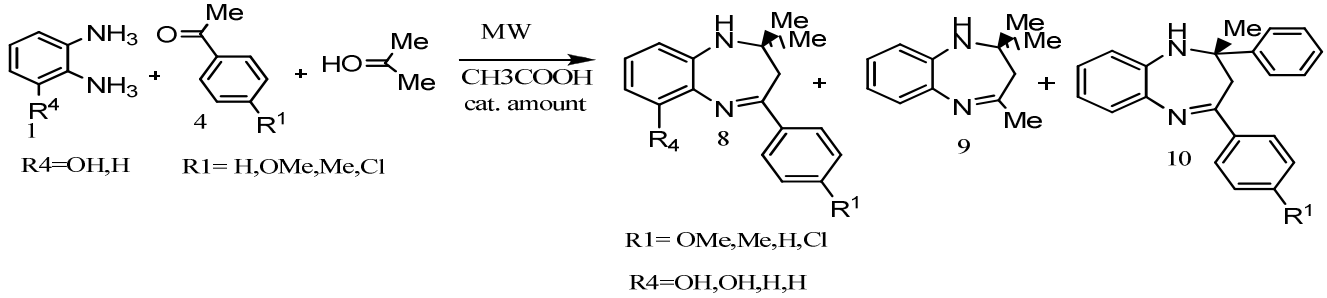
Reaction of 2, 3-Diaminophenol with Acetone



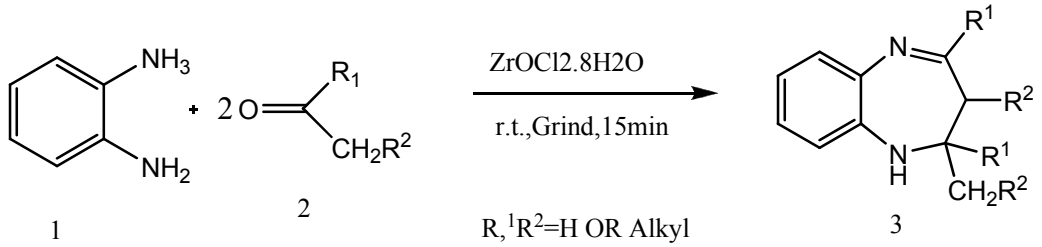
Reaction of 2, 3-Diaminophenol with Substituted Acetophenones



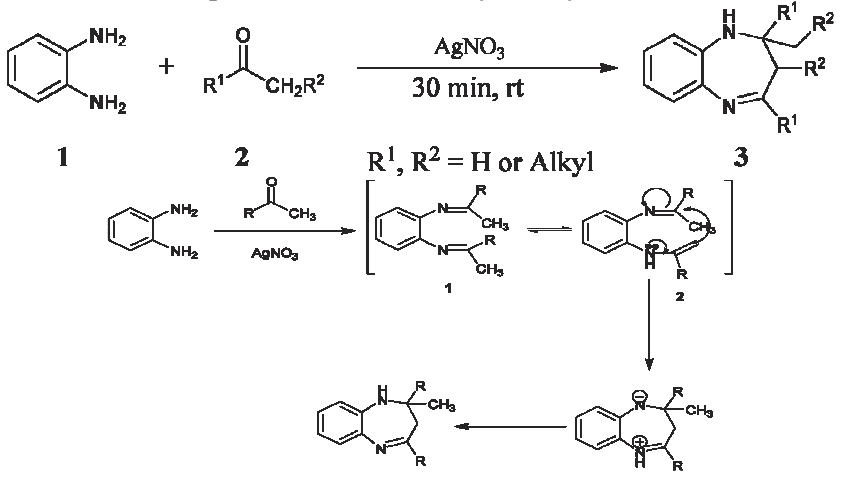
Reaction of Diamines 1 with a Mixture of Acetone and Acetophenone



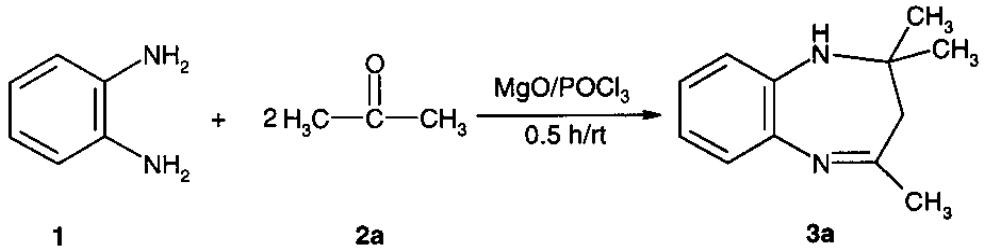
ZOC-Catalyzed an efficient synthesis of 1, 5-Benzodiazepines under mild conditions



An efficient synthesis of 1,5-benzodiazepine derivatives catalyzed by silver nitrate[20]

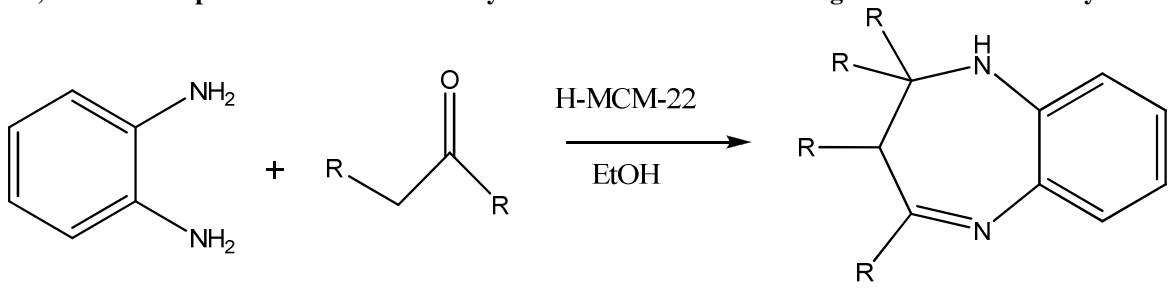


A simple and new method for the synthesis of 1,5-benzodiazepine derivatives on a solid surface

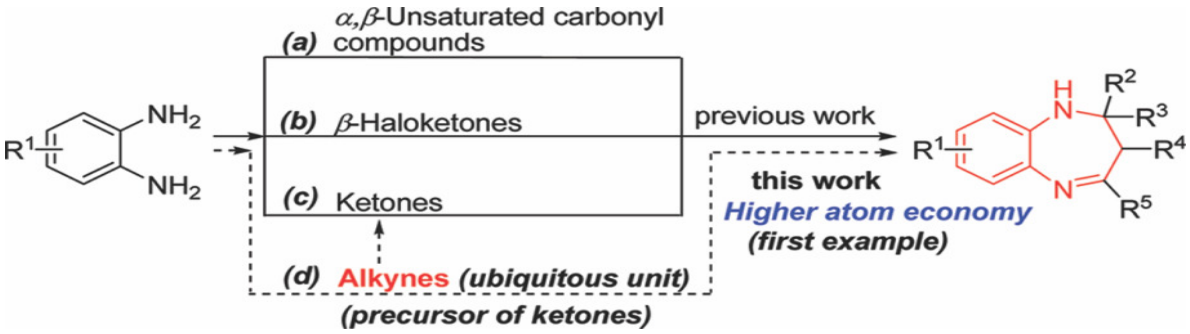


1 **2a** **3a**

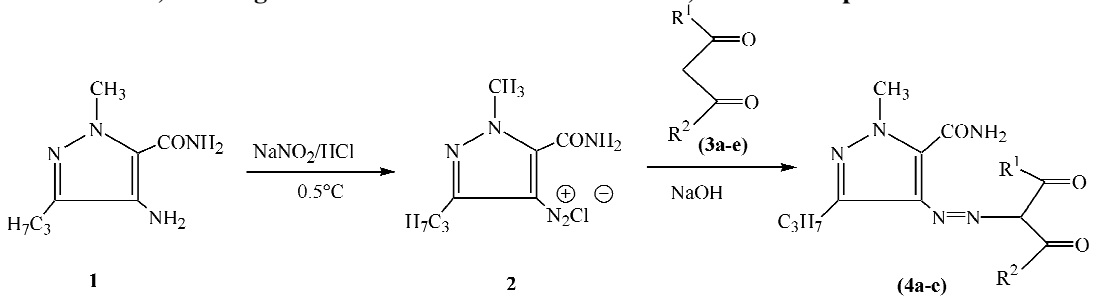
Synthesis of 1,5-Benzodiazepine and Its Derivatives by Condensation Reaction Using H-MCM-22 as Catalyst



Gold(I)-Catalyzed Synthesis of 1,5-Benzodiazepines Directly from O-Phenylenediamines and Alkynes



Synthesis and antimicrobial, antifungal and anthelmintic activities of 3*H*-1,5-benzodiazepine derivatives



1 **2** **(4a-e)**

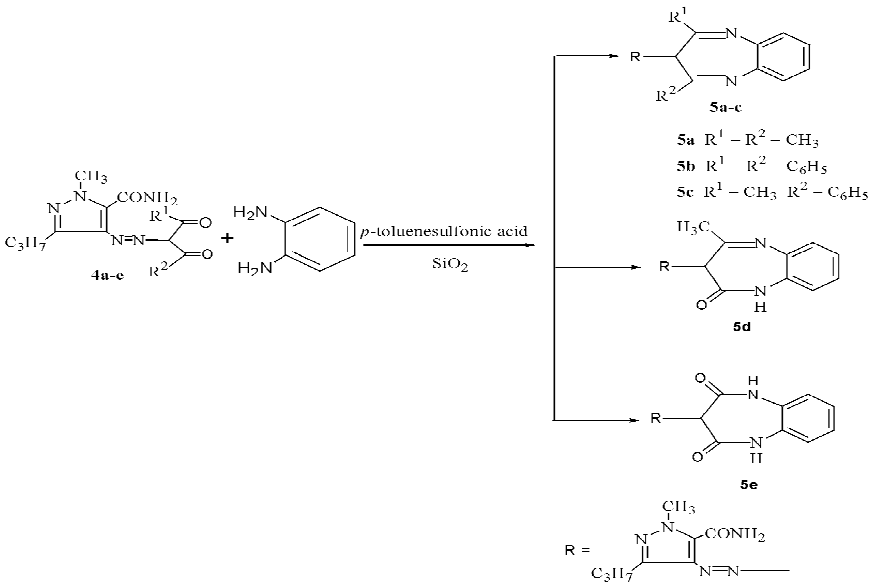
3a/4a $R^1 = R^2 = CH_3$

3b/4b $R^1 = R^2 = C_6H_5$

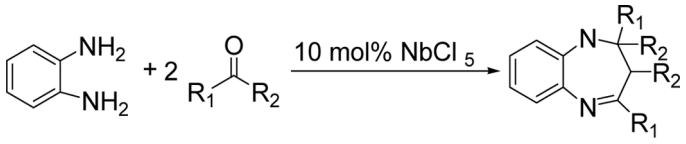
3c/4c $R^1 = CH_3$ $R^2 = C_6H_5$

3d/4d $R^1 = CH_3$, $R^2 = OC_2H_5$

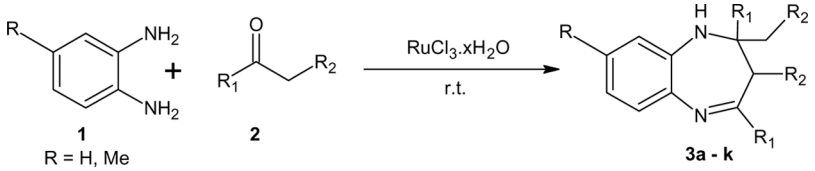
3e/4e $R^1 = R^2 = OC_2H_5$



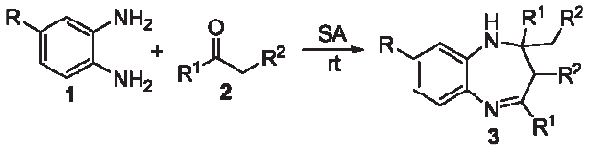
$NbCl_5$ as an Efficient Catalyst for the Synthesis of 1,5-Benzodiazepine Derivatives



$RuCl_3.xH_2O$: A Novel and Efficient Catalyst for the Facile Synthesis of 1,5-Benzodiazepines Under Solvent-Free Conditions

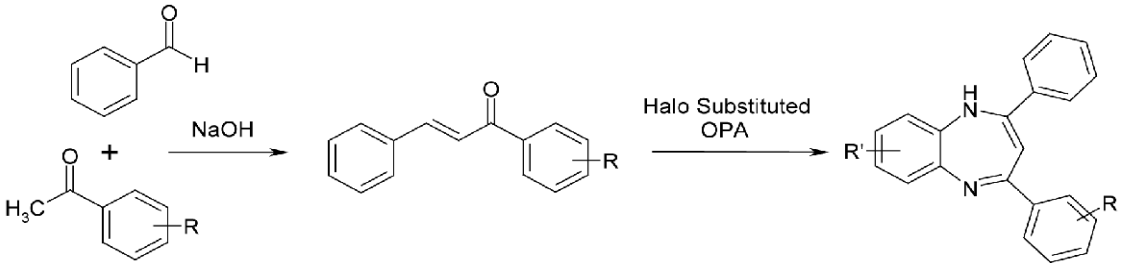


Efficient Synthesis of 1,5-Benzodiazepines Mediated by Sulfamic Acid under Neat Condition or in Solution

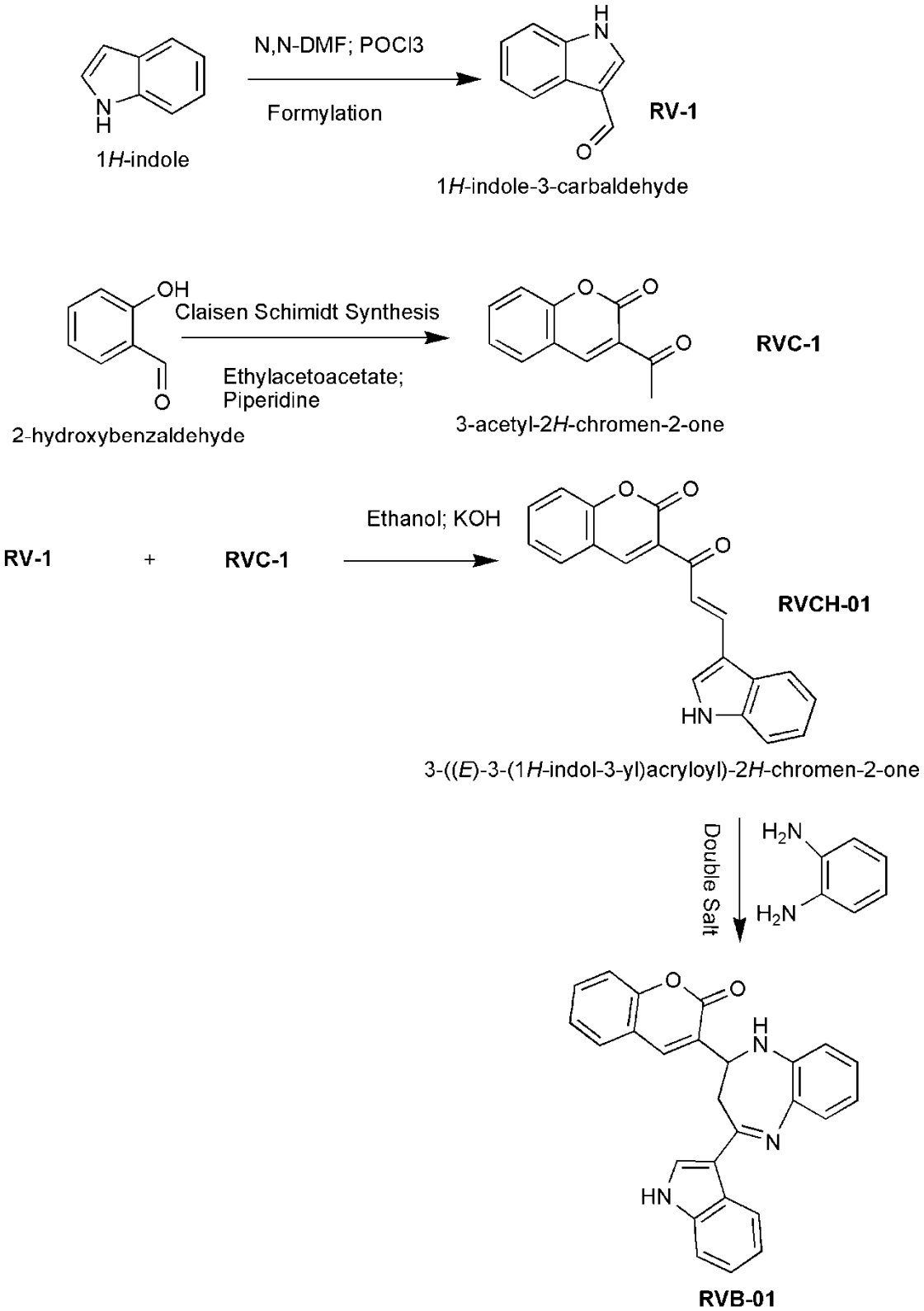


R ¼ H, Me, Cl; R^1 ¼ alkyl, Ph; R^2 ¼ H, alkyl; R^1 2 R^2 ¼ $(CH_2)_n$, n ¼ 3, 4.

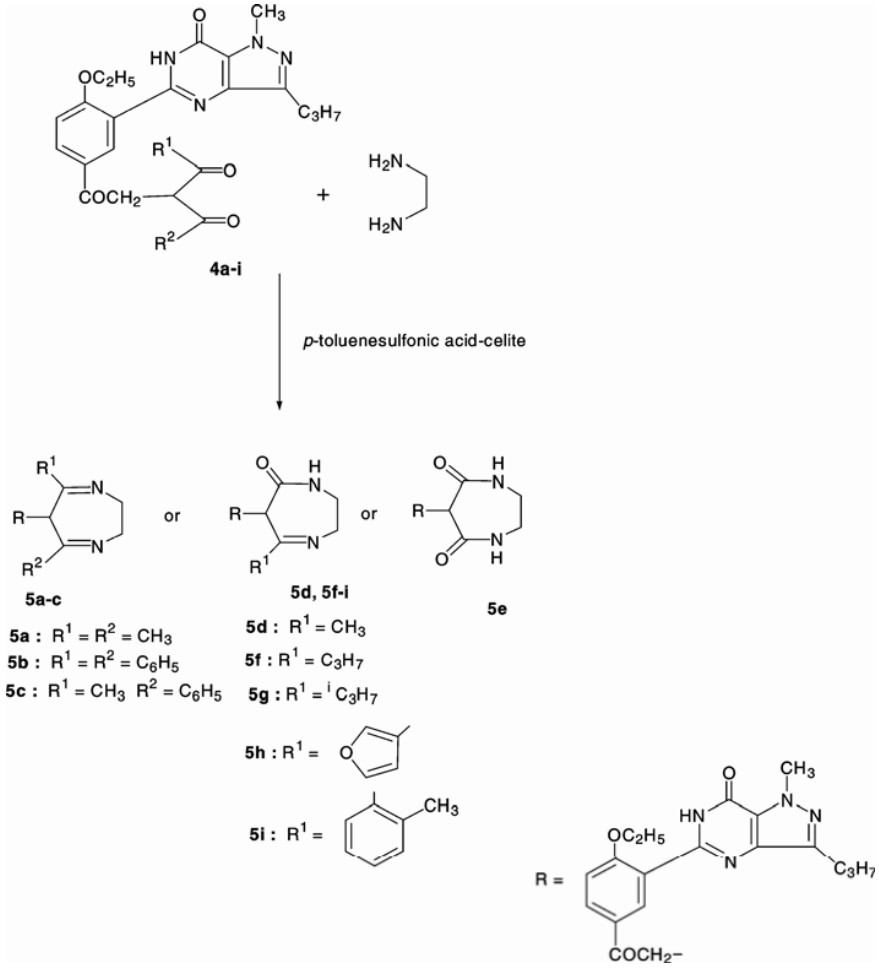
Multiple Linear Regression Study of 2,4-Disubstituted 1,5- Benzodiazepine as Potential Antiinfectives



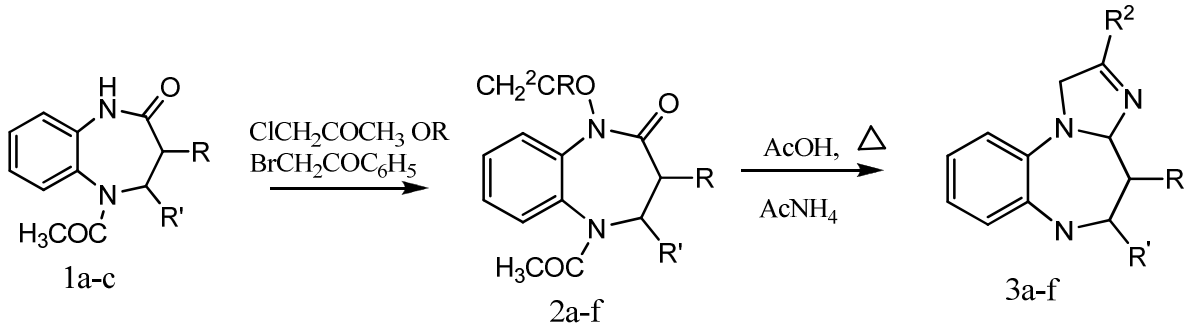
Evaluation of Antimicrobial Activity of 3-(4-1H-Indol-3-yl)-(2,3- dihydro-1H-benzo[b]diazepin-2-yl)- 2H-chromen-2-one



Synthesis, antimicrobial and antifungal activities of novel 1H-1,4-diazepines containing pyrazolopyrimidinone moiety



A convenient synthesis of novel substituted imidazo[1,2-*a*][1,5]benzodiazepine derivatives



	R	R'	R^2
a	H	H	CH_3
b	CH_3	H	CH_3
c	H	CH_3	CH_3
d	H	H	C_6H_5
e	CH_3	H	C_6H_5
f	H	CH_3	C_6H_5

Conclusion

In the last decade, interest on 1, 5 benzodiazepines has expanded exponentially due to their application in several diseases such as cancer, viral infection non-nucleoside inhibitors of HIV-1 reverse transcriptase and cardio vascular disorders. Apart from this 1,5 -benzodiazepine derivatives have received significant attention, and the core is indeed a 'privileged scaffold' found in compounds active against a variety of targets including peptide hormones (such as CCK) interleukin converting enzymes (ICE) and potassium channel blockers (IK)[27]. Moreover, 1, 5-benzodiazepines are valuable synthons for the preparation of other fused compounds such as triazolo, oxadiazolo, oxazino or furobenzodiazepines. Some 1, 5-benzodiazepines such as clobazam[28] have anti-epileptic activiy whereas arfendazam and lofendazam have sedative and anxiolytic effects.

References

1. Olkkola K.T. and Ahonen J., Midazolam and other benzodiazepines, Handbook of Experimental Pharmacology, *Handb Exp Pharmacol,* **182**, 335–60 **(2008)**

2. Dikeos D.G., Theleritis C.G. and Soldatos C.R., Benzodiazepines: effects on sleep, In Pandi-Perumal SR, Verster JC, Monti JM, Lader M, Langer SZ (eds.). *Informa Healthcare Sleep Disorders: Diagnosis and Therapeutics,* **19**, 220–2 **(2008)**

3. Kukla M.J. and Berslin H.J., Synthesis and anti-HIV-1 activity of 4, 5, 6, 7-tetrahydro-5-methylimidazo [4,5,1-jk][1,4] benzodiazepine-2(1H)-one (TIBO) derivatives, *Journal of Medicinal chemistry,* **34**, 746-751 **(1991)**

4. Boyd G.V., Six Membered and Larger Hetero Rings with Maximum Unsaturation, Schauman E. (ed), New York, *In Houben-Weyl,* **26**, 299 **(1998)**

5. Fryer R.I. and Walser A., Chemistry of Hetrocyclic Compounds: Bicyclic Diazepines: Diazepines with an Additional Ring, *Chemistry of Heterocyclic Compounds*, **50**, 20 **(1991)**

6. Llyod D. and Marshall D.R., Resonance energies of heteroaroamtic and other system from pK data: pyrrole, indole, and 2, 3-dihydro-1H-1,4-diazepinium cations, *Chem Ind. (London),* **17**, 335 **(1972)**

7. Shilabin A.G., Seven- Membered Ring Mesomeric Betaines from Anti-Huckel Aromatic to Model Compounds of the pyrrolobenzodiazepines Alkaloids Circumdatin A and B, Dissertation, *Europian journal of chemistry*, **12**, 1-137 **(2005)**

8. Atwal K.S., Bergey J.L. and Hedberg A., Synthesis and biological activity of novel calcium channel blockers: 2, 5-dihydro-4-methyl-2-phenyl-1,5-benzodiazepine-3-carboxylic acid esters, *Journal of Medicinal Chemistry,* **30**, 635 (**1987)**

9. Varala R., Kotra V. and Engulu R., Synthesis of some 1, 5-benzodiazepines derivatives as a new class of antimicrobial agents, *Asian Journal of Chemistry*, **19(7)**, 5435-5442 (**2007)**

10. Pasha M.A. and Jayashankar V.P., An expeditious synthesis of 1,5-benzodiazepines derivatives catalyzed by $CdCl_2$, *Indian Journal of Chemistry*, 45B, 2716-2719 (**2006)**

11. Gatzonis S.D., Angelopoulos E.K., Dakalopoulou E.G. and Chioni A., Convulsive status epilepticus following abrupt high-dose benzodiazepine discontinuation, *Drug and Alcohol Dependence*, **59(1)**, 95-97 **(2000)**

12. Kumar R. and Joshi Y.C., Synthesis, spectral studies and biological activity of 3H-1, 5-Benzodiazepine derivatives, *Arkivoc*, **13**, 142-149 **(2007)**

13. Nawrocka W., Sztuba B. and Wietrzy K., Synthesis and antiproliferative activity in vitro of novel 1,5-benzodiazepines, *J.Arch.Pharm.Pharm.Med.Chem*, **334**, 3-10 (**2001)**

14. Kusanur R.A., Ghate M. and Kulkarni M.V., Synthesis of spiro [indolo-1, 5- benzodiazepines] from 3- acetyl coumarins for use as antianxiety agents, *J. Chem. Sci*, **116**, 265-270 **(2010)**

15. Smith R.H., Jorgen W.L. and Tirado R.J., Prediction of Binding Affinities for TIBO Inhibitors of HIV-1 Reverse Transcriptase Using Monte Carlo Simulations in a Linear Response Method, *Journal of Medicinal Chemistry,* **40**, 823-833 **(1998)**

16. Atwal S.K., Bergey L.J. and Hedberg A., Synthesis and biological activity of novel calcium channel blockers: 2, 5-dihydro-4-methyl-2-phenyl-1, 5-benzothiazepine-3-carboxylic acid esters and 2, 5-dihydro-4-methyl-2-phenyl-1, 5-benzodiazepine-3-carboxylic acid esters, *Journal of Medicinal Chemistry,* **30**, 635 (**1987)**

17. Katritzky A.R., Abonia R. and Yang B., Synthesis of 3,4,7,8-tetrahydro-6H-pyrido1,2,3-ef-1,5-benzodiazepine-2(1H)-ones via benzotriazole methodology, *Synthesis*, 10, 1487 **(1998)**

18. Chimirri A., Gitto R., Grasso S., Manforte A.M., Romeo G. and Zappala M., Annelated 1,5-benzodiazepines, I: Three, four and five membered rings, *Heterocycles,* **36(3)**, 601 **(1993)**

19. Neels H.M., Sierens A.C. and Naelaerts K., Therapeutic drug monitoring of old and newer anti- epileptic drugs, *Clin. Chem. and Lab. Med.*, **42(11)**, 1228 **(2004)**

20. Kumar R., Chaudhary P., Nimesh S., Verma A.K. and Chandra R., An efficient synthesis of 1,5-benzodiazepines derivatives catalysed by silver nitrate, *Green Chem.*, **8**, 519 **(2006)**

21. Yaddanapudi Prabhakar, Kottapalli R.S. Prasad and Jagarlapudi V.S. Kumar, Microwave assisted synthesisof 3-(4-Ethylbenzyl)-1-(4-methoxybenzyl)-6-(methylthio)-1,

3, 5-triazine-2, 4 (1H, 3H)-dione derivatives Under solvent free condition with high yields, *Res. J. Recent Sci.,* **1(ISC-2011),** 105-109 **(2012)**

22. Steffan R.J. and Failli A.A., Preparation of pyrrolobenzodiazepine carboxamide vasopressin agonists, *PCT Int. App*., **228**, 46 **(2000)**

23. Hoekstra W.J. and Dyatkin A.B., Preparation of tricyclic benzodiazepines as vasopressin receptor antagonists, *PCT Int. App.,* **398**, 43 **(2009)**

24. Nawrocka W., Sztuba B. and A., Synthesis and antiproliferative activity in vitro of novel 1, 5-benzodiazepines, *Arch. Phar. Med. Chem*., **334**, 3 **(2001)**

25. Braccio M.D., Grossi G., Roma G., Vargiu L., Mura M.and Marongiu M.E., 1,5-Benzodiazepines. Part: XII: synthesis and biological evalution of tricyclic and tetracyclic 1, 5-benzodiazepine derivatives of niverapine analogues, *Eur. J. Med. Chem.*, **36(11),** 935 **(2001)**

26. Eman A. Alam, Initiation of Pharmaceutical Factories depending on more Application of Biotechnology on some Medicinal Plants Review Article (In Vitro Production of some Antioxidant, Analgesic, Antibacterial, Antidiabetic agent)*, Res.J.Recent Sci.,* **1(ISC-2011),** 398-404 **(2012)**

27. Claremon D.A., Liverton N., Selnick H.G. and Smith G.R., PCT Int. Appl. WO 9640653. *New J Chem,,* **27**, 1644-1648 **(2003)**

28. El-Sayed A.M., Abdel-Ghany H. and El-Saghier A.M.M., A Novel Synthesis of Pyrano (2,3-c)-, 1,3-Oxazino (2,3b)-, 1,2,4-Triazolo(3,4-b)-, Oxazolo(2,3-b)-, Furano(3,2-c)-, and 3-Substituted-(1,5)benzodiazepin-2-ones, *Synth. Commun*., **29**, 3561 **(1999)**