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International Journal of Current Research
Vol. 9, Issue, 09, pp.58043-58068, September, 2017

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

ISSN: 0975-833X

RESEARCH ARTICLE

REVIEW ON RECENT PREPARATION METHODS OF BENZODIAZEPINES (BZD's)

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ARTICLE INFO

Article History:
Received 19th June, 2017
Received in revised form
27th July, 2017
Accepted 15th August, 2017
Published online 30th September, 2017

Key words:

Benzodiazepines (BZD's), Oxadiazole, Triazole, Tetrazole, Imidazole.

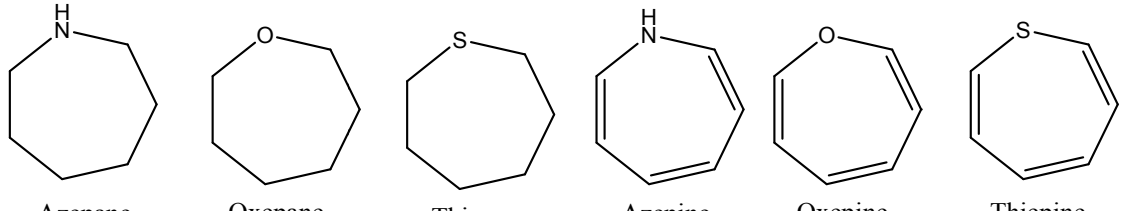
ABSTRACT

Benzodiazepines are well known class of antianxiety and hypnotic agents. They have replaced the traditional barbiturates and dicarbamates which were used for such treatments in 1990's. Benzodiazepines are more effective in alleviating anxiety and stress as they have fewer and less severe side effects. BZD's are also frequently prescribed as drugs for heart and circulatory problems. Objective of this review is to present a literature survey of preparation methods of [1,4] and [1,5]-benzodiazepines and their uses in synthetic organic chemistry. Few of these methods involve minor structural modifications so as to increase polarity, water solubility, metabolic degradation or better metabolic pathway. Some synthetic methods involve combination of pharmacologically active heterocyclic rings such as pyrole, oxadiazole, triazole, tetrazole or imidazole along with diazepine ring which is a promosing drug design strategy for site specificity.

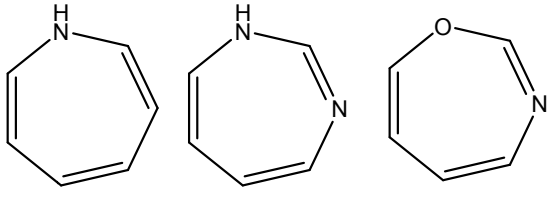
Citation: Suryawanshi, M. B. and Bobade, V. D., 2017. "Review on recent preparation methods of benzodiazepines (BZD's)", *International Journal of Current Research*, 9, (09), 58043-58068.

INTRODUCTION

With seven membered rings, the heteroatom must be able to provide an empty pi-orbital for normal aromatic stabilization to be available otherwise homoaromaticity may be possible. The unsaturated seven membered heterocycles with one N, O or S atom are named systematically as azepines,oxepines and thiepines respectively. Thiepins are known only with bulky substituents but oxepine and 1H-azepine have both been synthesized.



Azepane Oxepane Thiepane Azepine Oxepine Thiepine



Azepine Diazepine Oxazepine

Unsaturated monocyclic 1,4-Diazepines are all very unstable. In the dihydro-1,4-diazepines, the 2, 3-dihydro-1H-compounds have been studied most.

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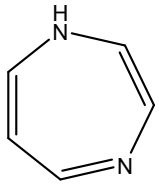
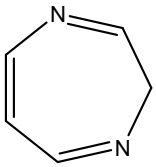
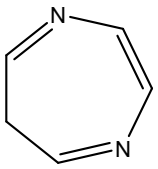
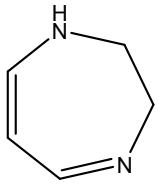

1H-1,4-Diazepine

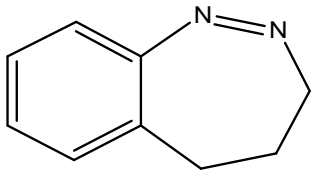
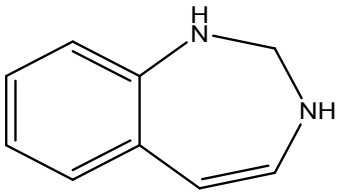
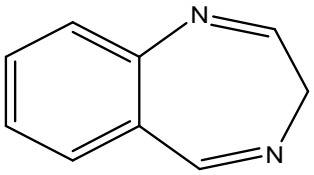
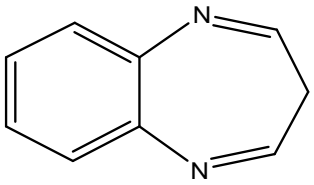
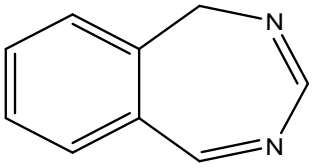
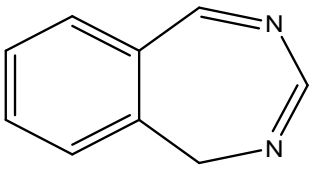

2H-1,4-Diazepine


6H-1,4-Diazepine

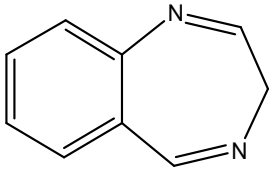

2,3-Dihydro-1H-1,4-Diazepine

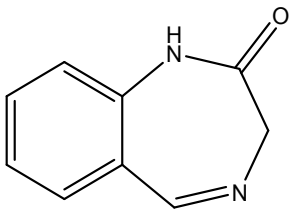
Benzodiazepines (BZD,s)

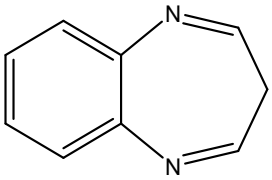
Benzodiazepines are bicyclic heterocyclic compounds in which benzene nucleus is fused to seven membered ring containing two nitrogen atoms. The term benzodiazepine implies a maximum degree of unsaturation due to the presence of three double bond in the seven membered ring. Considering the relative position of nitrogen atom in the heterocyclic ring benzodiazepines are classified as 1,2 /1,3/1,4/1,5 and 2,4-benzodiazepines (Atwal *et al.,* 1987 and Varala *et al.,* 2007).

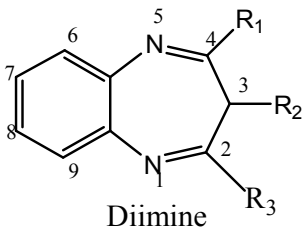
For benzo-analogues the 3H-series are usually more stable than 1H and although the parent compounds of both the series are unknown,there is an extensive chemistry on substitutd analogues especially in 3H-series. The benzodiazepine-2-ones have been widely studied as benefits of their commercial importance (Pasha *et al.,* 2006).

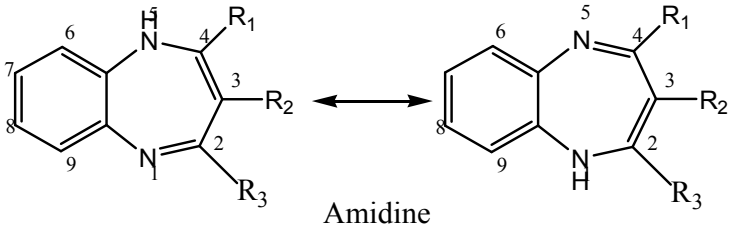

3H-1,4-Benzodiazepine


1H-1,4-Benzodiazepin-2 (3H)-one


3H-1,5-Benzodiazepine

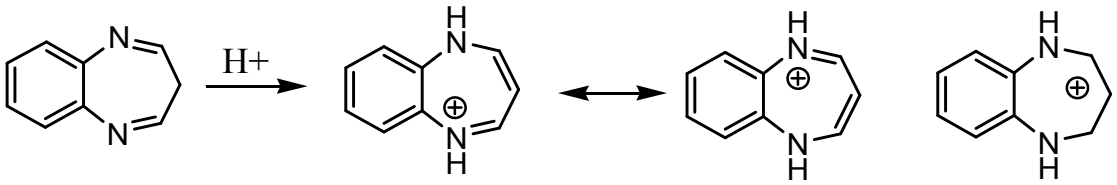
Nomenclature of benzodiazepines


Diimine


Amidine

1,5-Benzodiazepines are bicyclic compounds with two nitrogen atoms at 1and 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-diazepine. Benzodiazepines are numbered as shown in the figure. 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. Benzodiazepines usually occur in the diimine form rather than in the conjugated amidine form. In the diimine form some extra stabilization arise due to the conjugation of the imine group with the benzene ring. Cyclic conjugation in amidine may

indeed lead to destabilization of the molecules because it involves interaction of 12-pi-electrons around the periphery of the molecules as implied in one structure or 8-pi-electrons around seven membered ring in the other resonating structure, either of these are destabilizing 4n-pi-electron system. Protonation of benzodiazepines lead to the successive formation of monocations. The conjugated form which would have 8-pi-electrons associated with 7-membered ring is electronically an analogue of benzocyclo-octatetraene. Annular conjugation around either the diazepine ring or the overall periphery makes no positive contribution to the stability of the system, whereas electronic interaction between the benzene ring and two imino groups in the imino form does (Yaddarpudi *et al.,* 2012 and Steffan *et al.,* 2000).

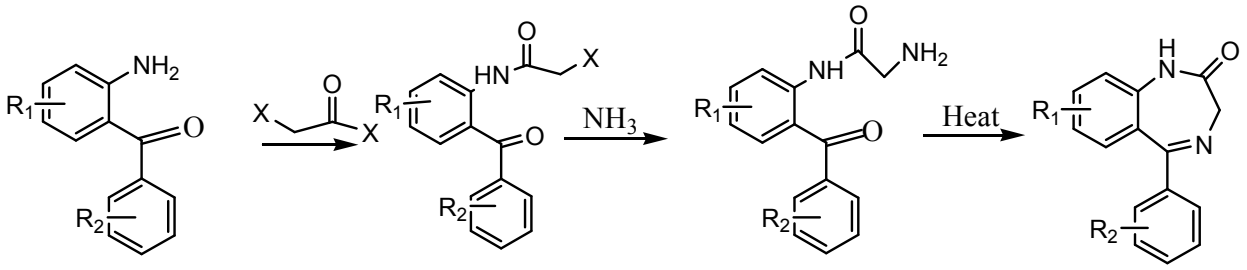


Biological importance of benzodiazepines

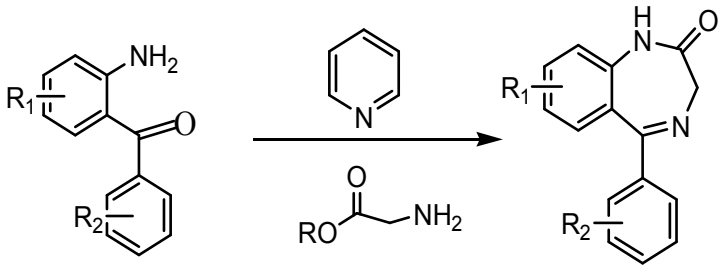
- Benzodiazepines (BZD,s) as a class of antianxiety, hypnotic and muscle relaxing agents have replaced traditional barbiturates.
- Benzodiazepines are more effective in alleviating anxiety and stress and they have fewer and less severe side effects (Venter *et al.,* 1986 and Rudolph, 1999).
- Consequently, BZD,s continue to be used to treat such conditions as phobic and panic disorders as well as depression and migrains (Covelli *et al.,* 1998).
- In addition to treating anxiety, BZD,s are often prescribed for treating insomnia, alcohol withdrawal and more recently epilepsy (Tecott, 2000 and Costa *et al.,* 1996).
- Due to the possible adverse effects such as sedation and amnesia however research in this area continues.
- Superior drugs with increased potency or more specific properties will hopefully be discovered.
- General practitioners prescribe about 80% of benzodiazepines which are the most frequently prescribed drugs for heart and circulatory problems.
- Pyrrole[2,1-c][1,4] benzodiazepines (PBD,s) are a family of naturally occurring compounds isolated from various streptomyces species exhibiting potent antitumour activity which includes anthramycin, DC-81,tomaymycine and sibiromycin.
- In the last decade the area of biological interest of 1,5-benzodiazepines has been extended to several diseases such as cancer,viral infection and cardiovascular disorders (Melukzi *et al.,* 1990 and Sayed *et al.,* 2007).
- In addition 1,5-benzodiazepines are key intermediates for the synthesis of various fused ring systems such as triazolo, oxadiazolo, oxazino or furanobenzodiazepines (Nagaraja *et al.,* 2006, Nabih *et al.,* 2004, Reddy *et al.,* 2000, Haris *et al.,* 1968).
- Besides benzodiazepine derivatives are also of commercial importance as dyes for acrylic fibers in photography (Clarmant 2006).
- Recently they have been reported to show antileukemic, antiplatelate, antiulcer, endothelia antagonists and vasopressin antagonist activity.
- Their role in the control and treatment of AIDS has also been recently demonstrated.
- Five atom heterocyclic fused 1,4-benzodiazepine ring system occupy prominent place among drugs for CNS disorder.
- The introduction of alprazolam, triazolam, brotizolam and etizolam in chemotherapy has enhanced the interestin the preparation of five atom heterocyclic fused 1,4 BZD's system.

Synthetic methods for the preparation of 1,4- benzodiazepines

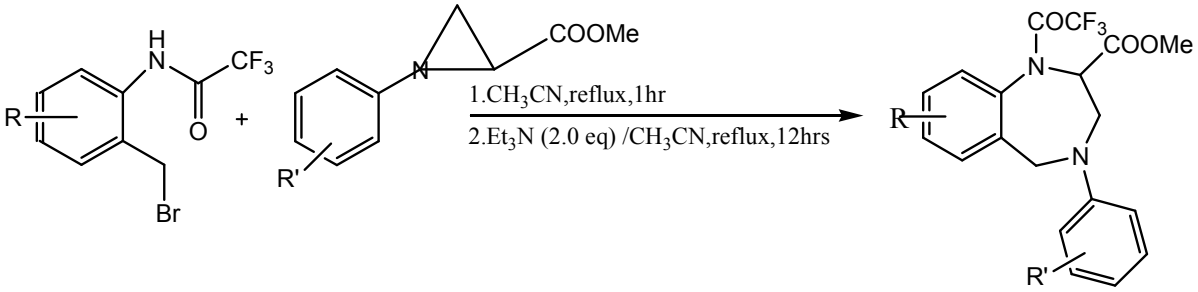
1. The most extensively used method for preparing 1,4-Benzodiazepines begins with ortho-amino benzophenone. The first step involve treatment of the appropriate aminobenzophenone with haloacetyl halide to afford amide followed by addition of ammonia to first displace the chlorine giving the glycinamide. Then cyclisation by imine formation will give benzodiazepine (Sternbach *et al.,* 1962, Lednicer 1998, Lednicer *et al.,* 1977).



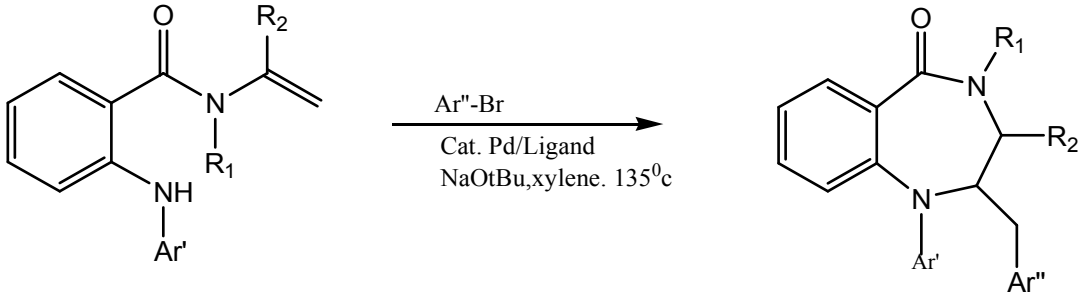
2. The other method involves treating orthoamino ketone with an amino acid ester hydrochloride in pyridine.



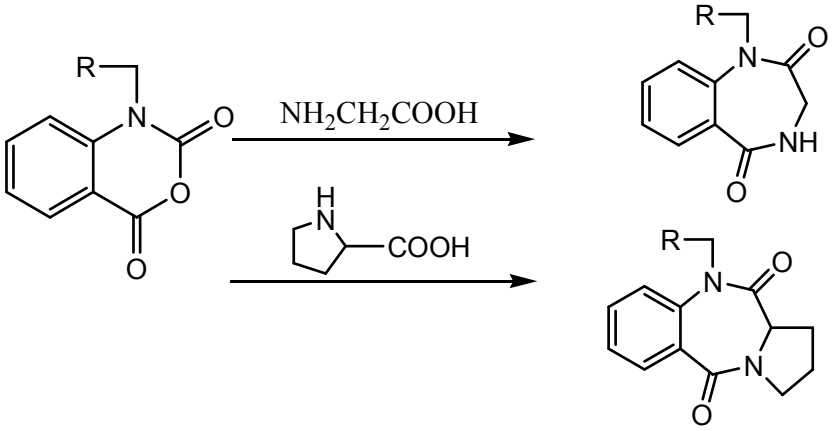
3. Wang *et al.,* 2008 have developed a new strategy for the synthesis of 1,4-benzodiazepine from methyl 1-aryl-aziridine-2-carboxylates with N-[2-bromo methyl (phenyl) trifluoroacetamides. The reaction proceeds through the N-benzylation and highly regioselective ring opening reaction of aziridine by bromide anion followed by triethyl amine mediated intramolecular nucleophilic displacement of the bromide by the amide nitrogen.



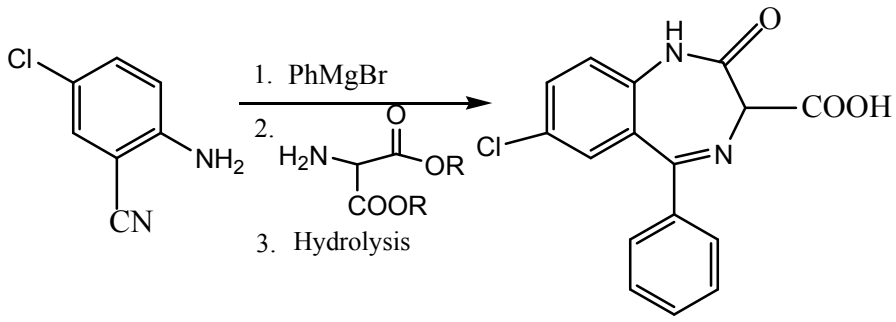
4. Recently, Joshua *et al.,* 2011 has reported the synthesis of saturated 1,4-benzodiazepines and 1,4-benzodiazepin-5-one via Pd-catalysed carboamination reactions using sodium tert-butoxide base and xylene as a solvent at refluxing condition.



5. Yadav *et al.,* 2011 has developed an efficient microwave assisted protocol for the exclusive one pot synthesis of N-aminomethyl substituted 1,4-benzodiazepine derivatives by the reaction of N-aminomethyl substituted isatoic anhydride with glycine and L-Proline respectively has been described.

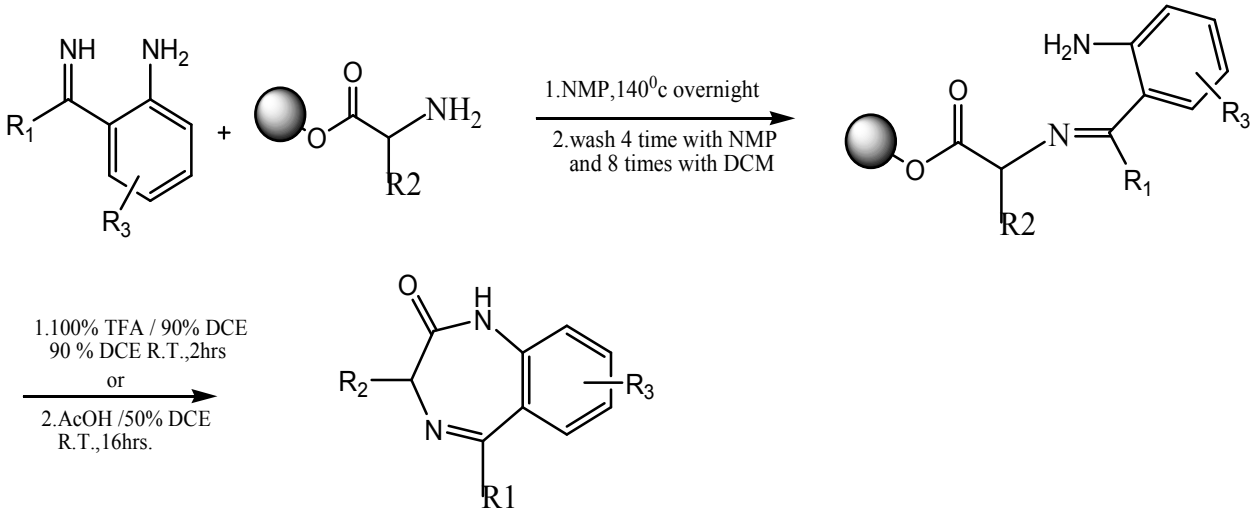


6. Schmidt in 1970 develop a method which includes Grignard addition to benzonitriles to afford benzophenone imine intermediate before condensation with the corresponding 2-aminomalonic ester derivative. This involve a straightforward and efficient access to clorazepate.

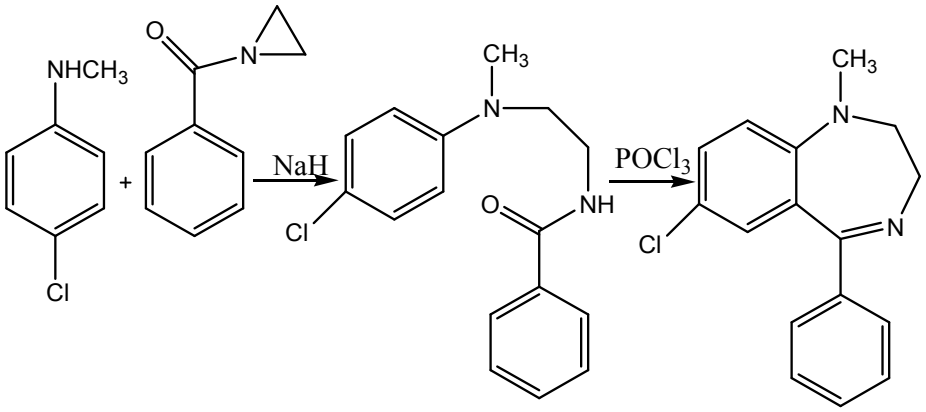


Chlorazepate

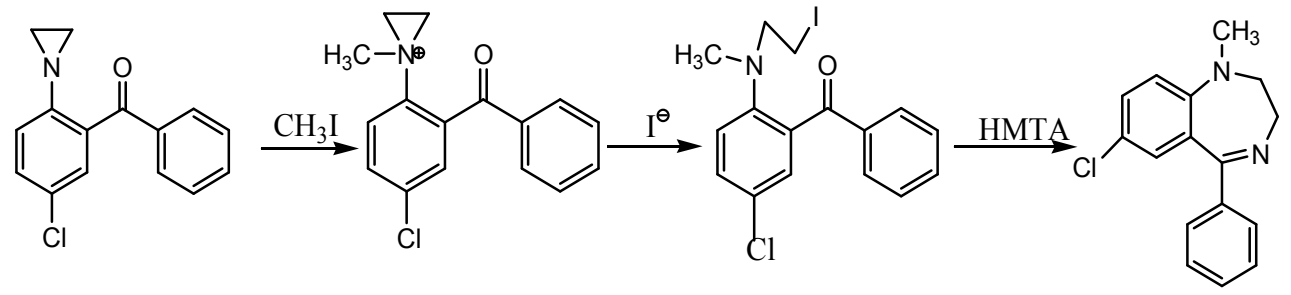
7. Lausten *et al.,* 2007 has developed an efficient solid phase method for the parallel synthesis of 1,3-dihydro-1,4-benzodiazepin-2-one derivatives. A key step in this procedure involves catching crude 2-aminobenzoimine products on an amino acid Wang resin. Mild acidic conditions then promote a ring closure and in the same step cleavage from the resin to give pure benzodiazepine products.



8. Structure activity relations in the benzodiazepine series are sufficiently flexible to tolerate a simple tertiary amine rather than amide carbonyl at the 1-position. An interesting scheme for preparing such compounds relies on an aziridine for supplying the required two carbon fragment and subsequent cyclodehydration reaction to form the diazepine ring. The concise sequence starts with the reaction of the anion from para –chloro-N-methylaniline with the benzoic acid amide of aziridine. Opening of the reactive three membered ring leads the amide that now contains the requisite atoms for forming the seven membered ring. Treatment of that amide with phosphorous oxychloride leads to cyclodehydration and formation of the diazepine, medazepam an antianxiety agent.

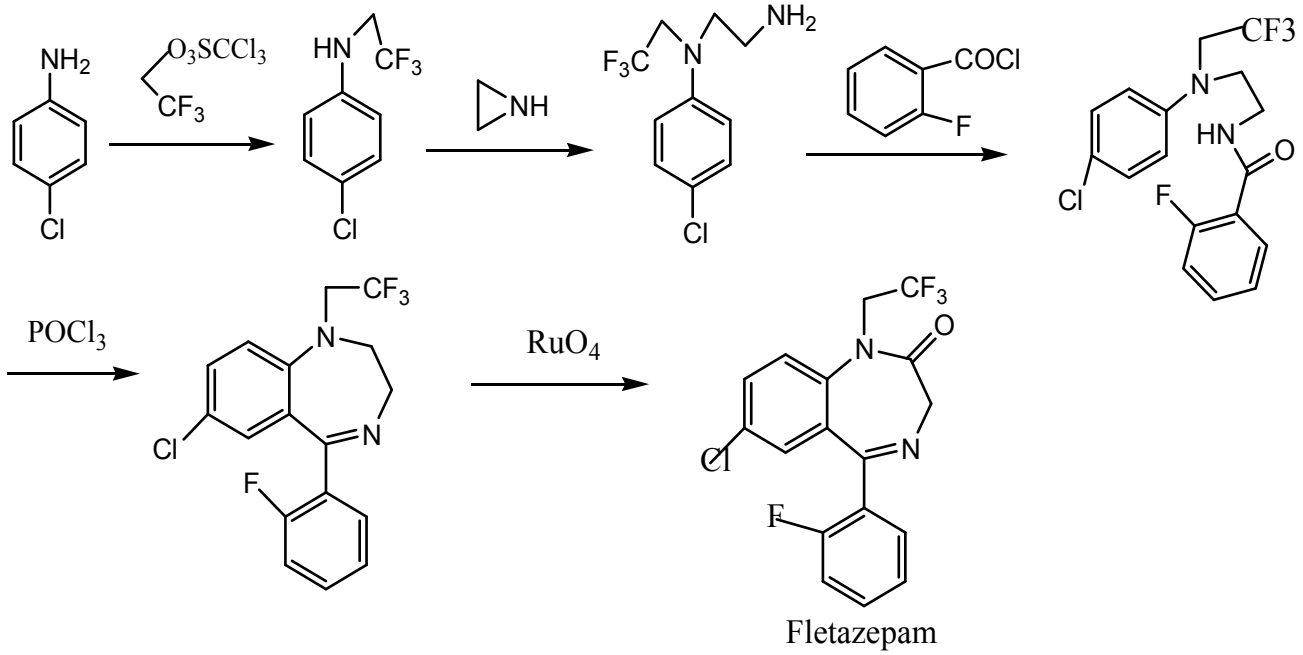


9. An alternate and equally concise approach to same compound starts with the reaction of aziridino benzophenone with methyl iodide. The outcome of this reaction can be rationalised by assuming the initial formation of quaternary salt. An attack on the strained ring by the iodide counterion will open the ring to afford the N-iodoethyl derivative, which also affords melazepam on reaction with HMTA.



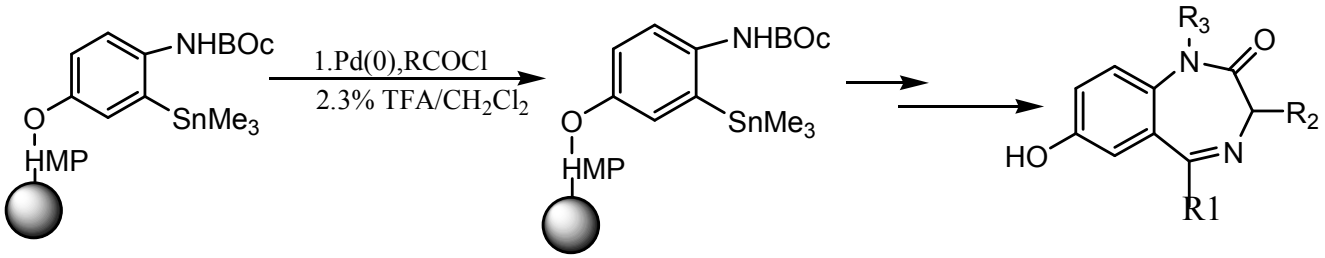
melazepam

10. Alkylation of para-chloroaniline with 2,2,2-trifluoroethyl trichloromethyl sulfonate affords the corresponding trifluoroethylated derivative. Reaction of the anion from that with aziridine leads to the formation of diamine. Acylation of that compound with orthofluorobenzoyl chloride proceeds to give the amide. Cyclodehydration of that amide with phosphorous oxycloride gives benzodiazepine. Ruthenium tetroxide preferentially oxidises the 2-position rather than 3-position adjacent to the imine function. This results in the formation of fletazepam.

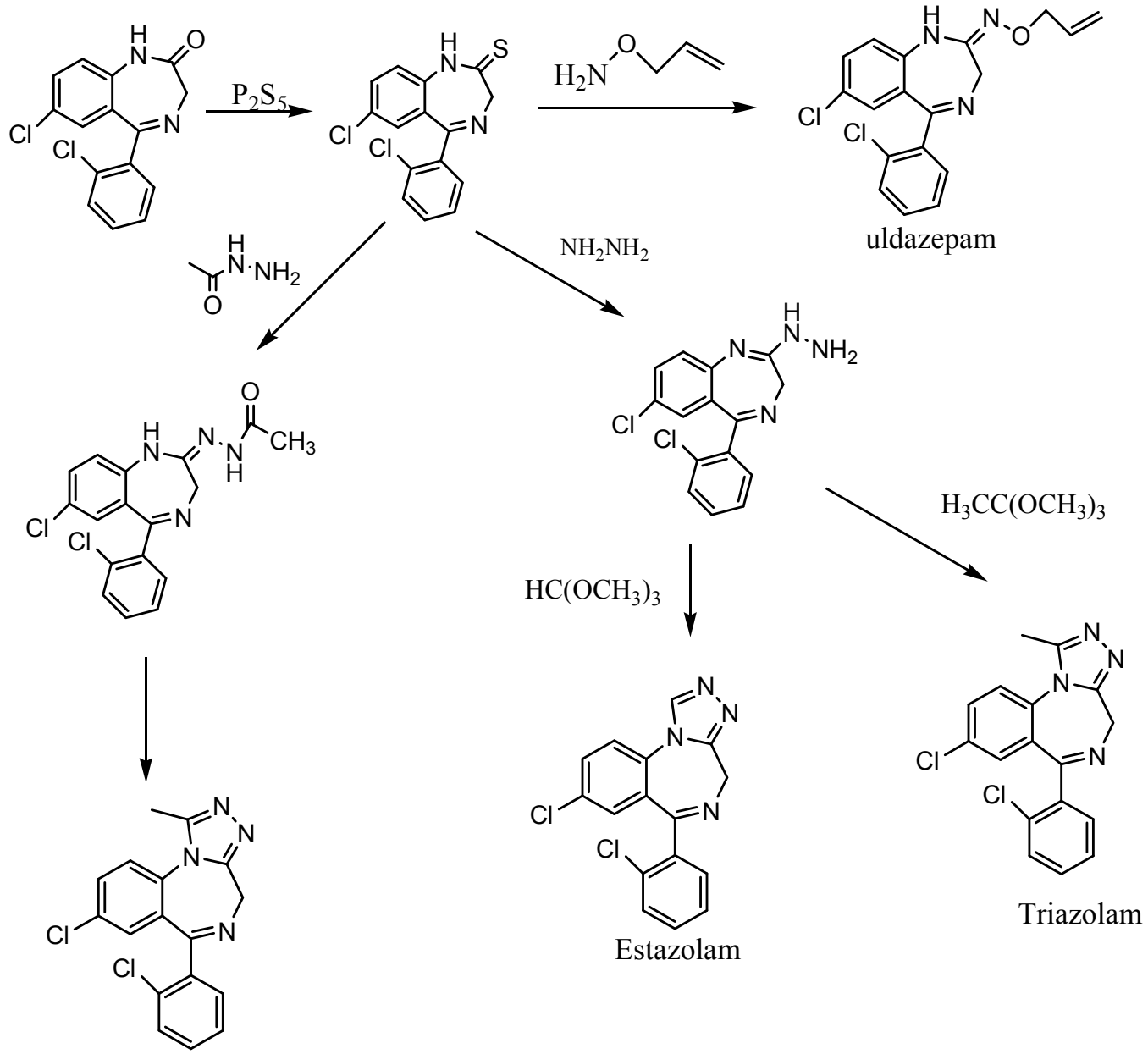


Fletazepam

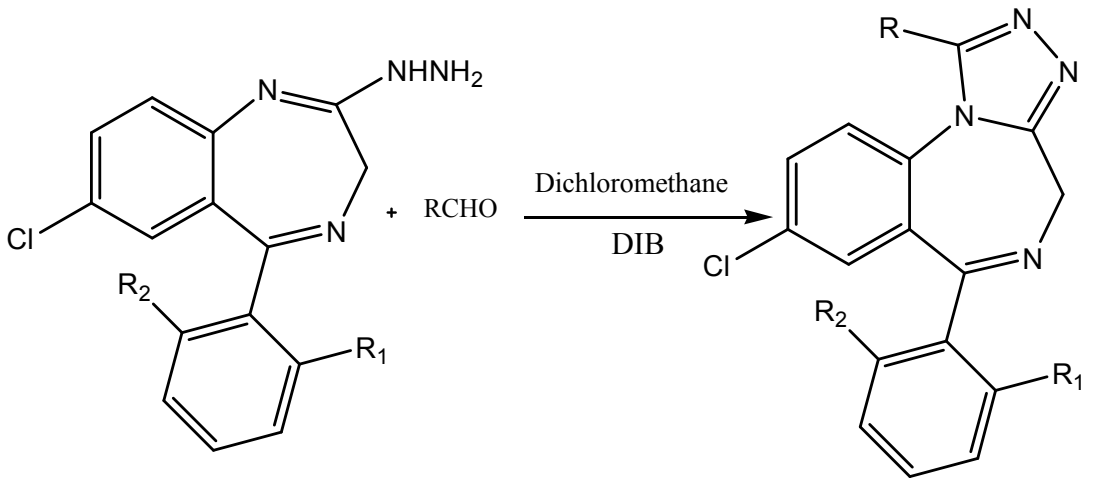
11. Stille coupling was used to synthesize a library of 2-aminoaryl ketones on solid support (Ellman 1996). The 2-(4-biphenyl) is opropyloxycarbonyl (Bpoc) protected aminoaryl stannane is prepared from commercially available starting material and is coupled to the support using the HMP linker. Stille coupling is employed with avariety of acid chlorides in the presence of catalyst $Pd_2(dba)_3$. $CHCl_3$. The Bpoc group is removed with treatment of 3% TFA/CH_2Cl_2 solution affording the support bound aminoaryl ketones.

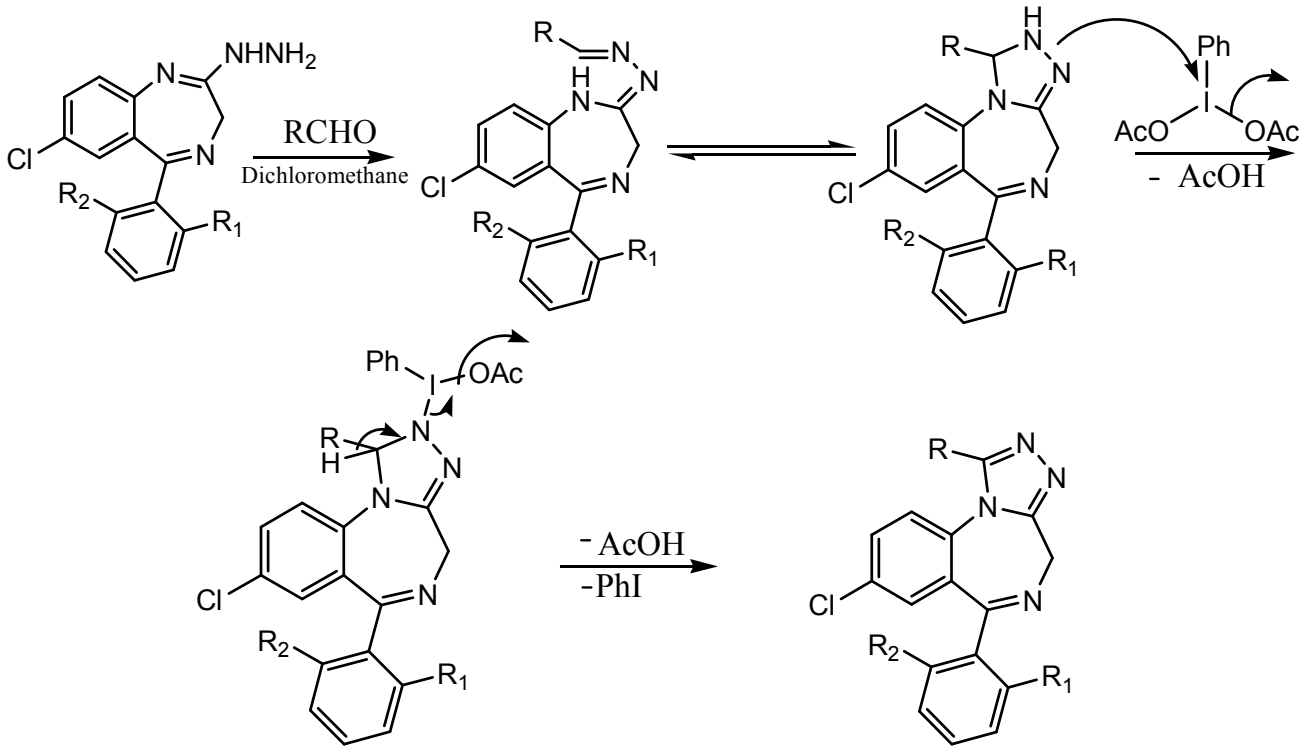


12. Conversion of an amide to thioamide enhances the reactivity of that function since it favors the enol form and provides a better leaving group for addition elimination reactions. The thioamide function provides a means for building additional heterocyclic rings onto the basic benzodiazepine nucleus.



13. An efficient one pot synthesis of [1,2,4]triazolo[4,3-α][1,4] benzodiazepine derivatives were synthesized by oxidative cyclization reaction of 2-hydrazino-1,4-benzodiazepines with various aldehydes in presence of diacetoxy iodobenzene by Bobade *et. al.* (Review author) (Bobade *et al.,* 2010)

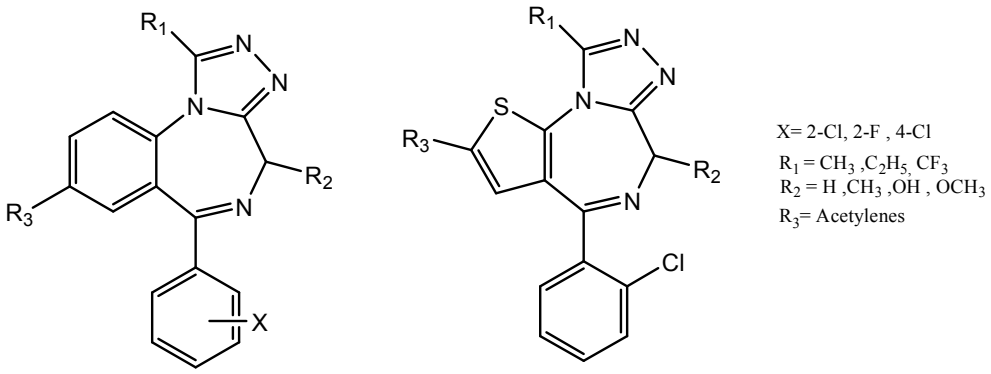




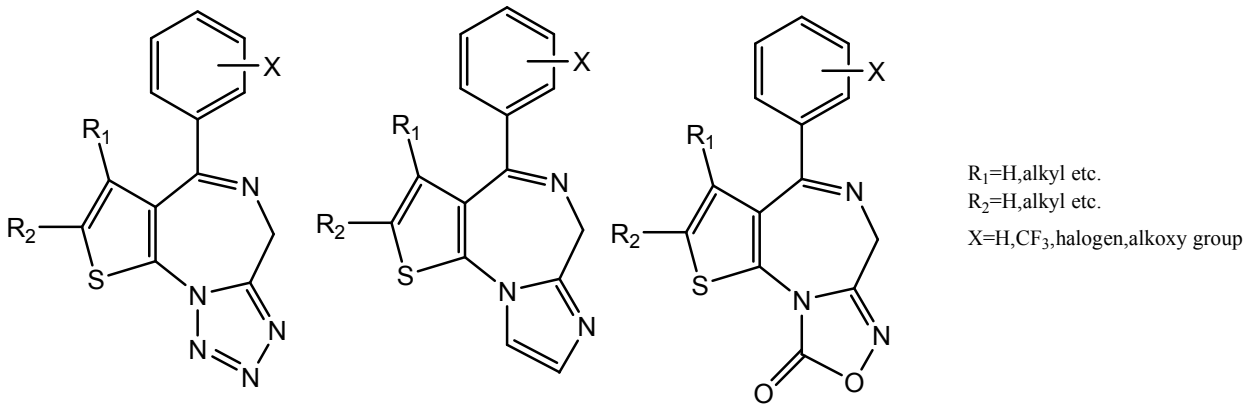
Possible mechanism using DIB

First step is reaction of 2-hydrazino-1,4-benzodiazepine with aldehyde to give an intermediate. Ligand-exchange reaction between electrophile DIB and first intermediate will generate second intermediate. The overwhelming tendency of iodobenzene for reductive elimination from this intermediate will give the triazolo 1,4-benzodiazepine derivative.

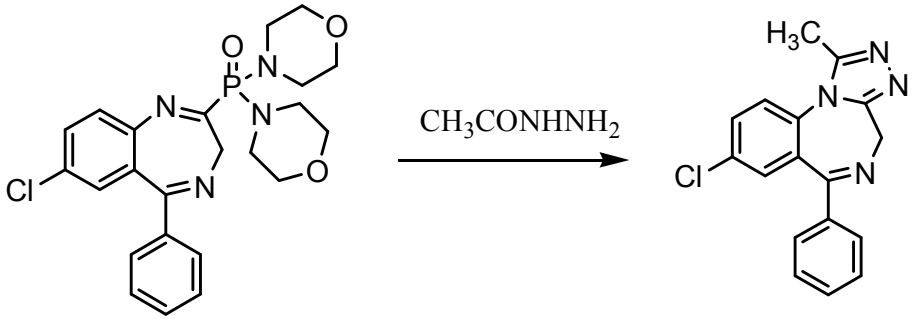
14. Walser *et al.,* 1991 have reported [1,2,4] triazolo [4,3-a][1,4]benzodiazepines bearing an ethynyl functionality at the 8-position and the isosteric thieno [3,2-f][1,2,4]triazolo [4,3-a][1,4] diazepines and evaluated as antagonists of platelet activating factor.



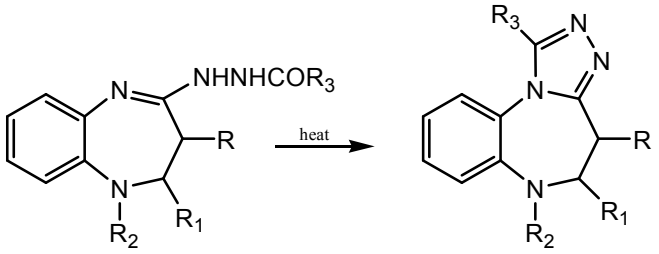
15. Nakanishi *et al.,* 1975 have reported the synthesis and pharmacological activity of tetrazolo, oxadiazolo and imidazothienodiazepine derivatives. Some of them were found as minor tranquillizers.



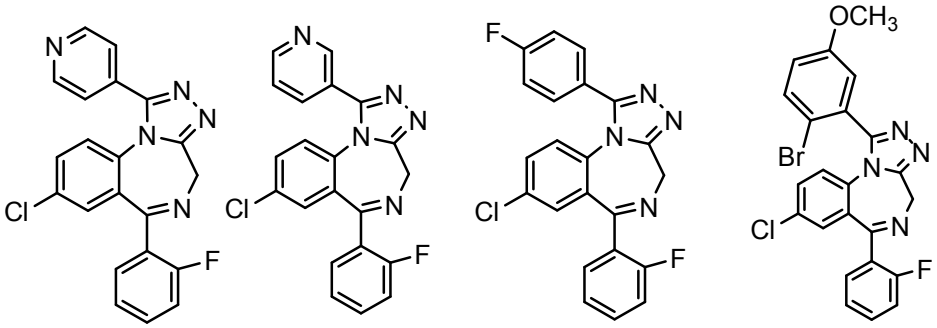
16. Robert *et al.,* 1976 have reported the reaction of 1,4-benzodiazepines with a variety of nucleophiles to give various 2-substituted benzodiazepines. The variety of 7-chloro-2-(di-4-morpholinylphosphinyloxy)-5-phenyl-3H-1,4-benzodiazepines as an intermediate has been further demonstrated by its facile conversion to 1-methyl-6-phenyl-4H-triazolo[4,3-a] [1,4] benzodiazepine, which is of clinical interest.



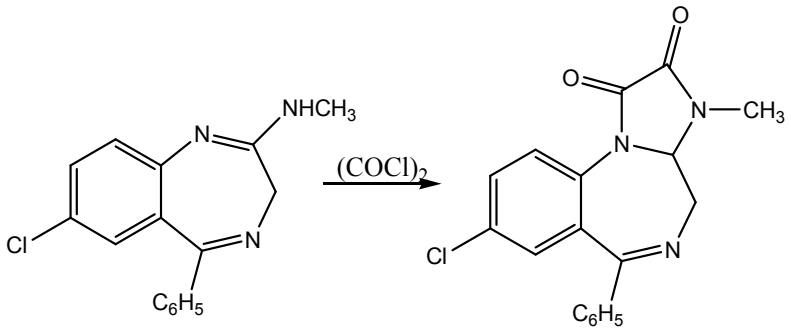
17. Kosychova *et al.,* 2004 have reported the synthesis of a series of substituted 5,6-dihydro-4H-[1,2,4] triazolo-[4,3-a][1,5]benzodiazepines by thermal cyclization of acylhydrazino-2,3-dihydro-1H-[1,5]-benzodiazepines.



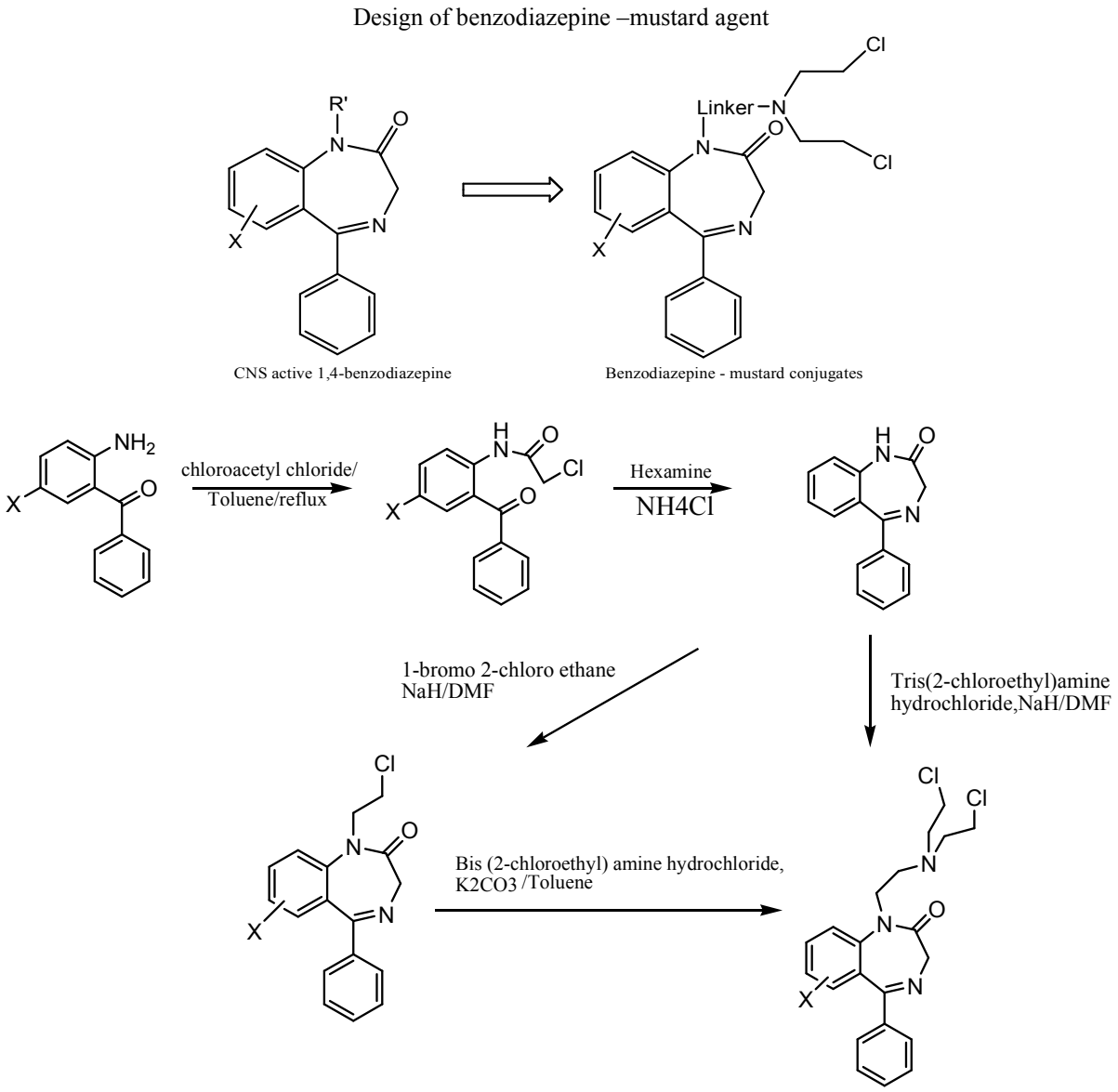
18. Narayana *et al.,* 2006 have synthesized some new substituted triazolo [4,3-a][1,4]-benzodiazepine derivatives. The compounds were tested for anticonvulsant activity. The tested compounds exhibited excellent anticonvulsant activity in comparison with the standard drug diazepam.



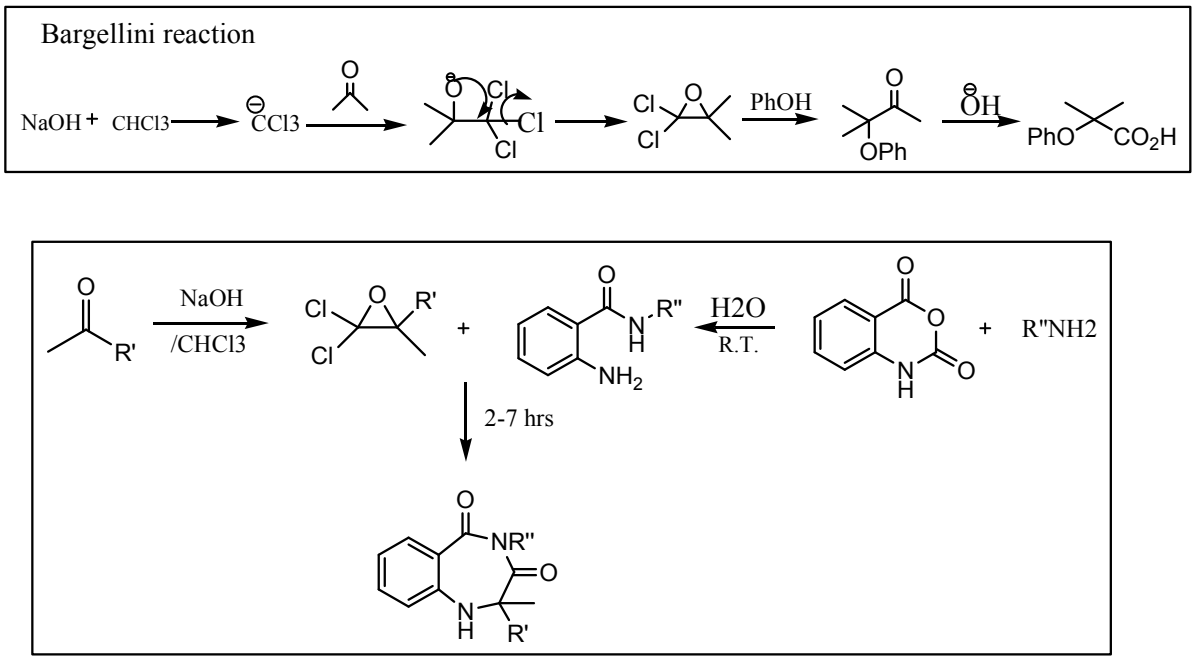
19. Treatment of 1,4-BZD with oxalyl chloride gave the expected imidazolinedione.



20. Singh *et al.,* 2013 has designed, synthesised and has done in vitro cytotoxicity study of benzodiazepine-mustard conjugates as potential brain anticancer agents. The combination of two pharmacological entities in a single compound has been utilized as a promising drug design strategy for site specificity. So two nitrogen mustard agents were synthesized by conjugating mustard with the benzodiazepine nucleus in the hope to obtain CNS antitumour agents. The benzodiazepine part is aimed to serve as a CNS actve carrier enabling the alkylating moiety to cross BBB by altering its physicochemical properties.



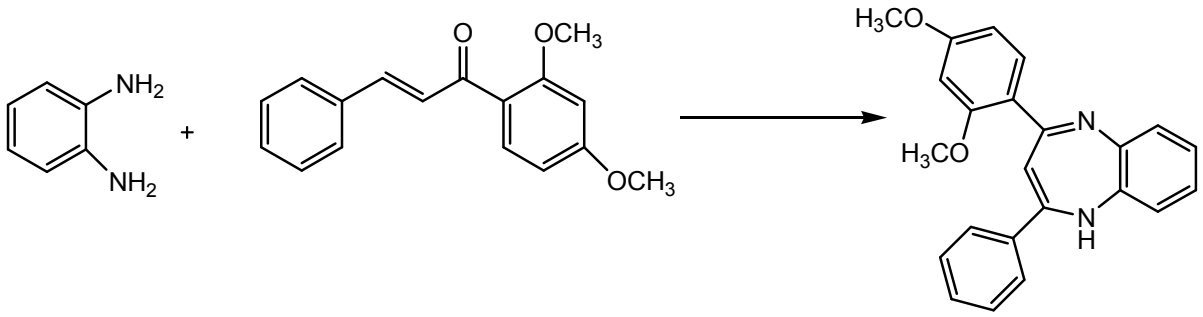
21. Mahadevi *et al.,* 2012 reported a user friendly synthesis of 1,4-benzodiazepine 3,5-dione derivatives via Bargellini type reaction. The corresponding products were obtained using various 2-amino benzamide under Bargellini reaction condition in good yield without unfavourable side reaction.



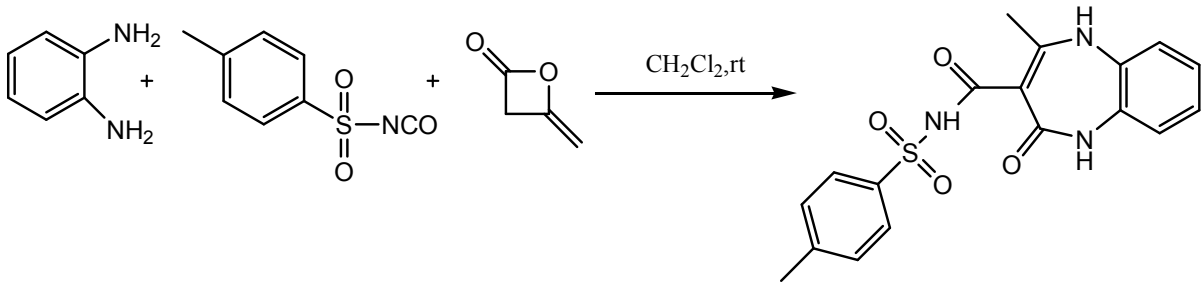
Synthetic methods for the preparation of 1,5- benzodiazepines

Various methods for the synthesis include condensation reactions of orthophenylene diamine with α,β-unsaturated carbonyl compounds with ketones in the presence of BF_3. Et_2O,$NaBH_4$, polyphosphoric acid or SiO_2, $MgO/POCl_3$, $Yb(OTf)_3$, Al_2O_3/P_2O_5 or AcOH under microwave conditions, Amberlyst-15 in the ionic liquid,1-t-butyl-3-methylimidazolium bromide ([bmim]Br),$CeCl_3$. $7H_2O$/NaI supported on silica gel, $InCl_3$,CAN, $ZnCl_2$, $AgNO_3$ etc. (Balakrishna *et al.,* 2001, Curini *et al.,* 2001, Kaboudin *et al.,* 2001, Pozarentzi *et al.,* 2002, Yadav *et al.,* 2002, Yadav *et al.,* 2005, De *et al.,* 2005).

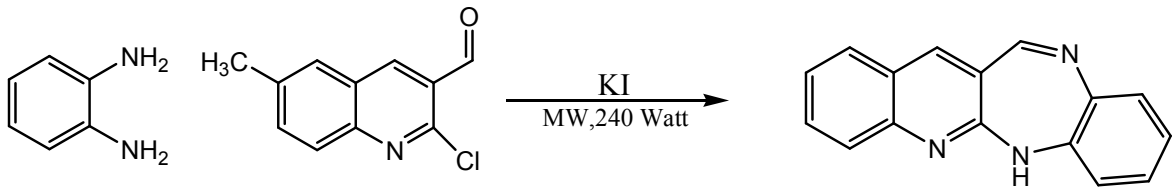
2,4-disubstituted 1,5-Benzodiazepine derivatives containing different functional groups have been synthesised and screemed for their antibacterial activity. The 2,4-disubstituted 1,5-benzodiazepine were synthesised by reacting substituted chalcones synthesized using Aldol condensation with ortho-phenylene diamine(Bhatia *et al.,* 2008).



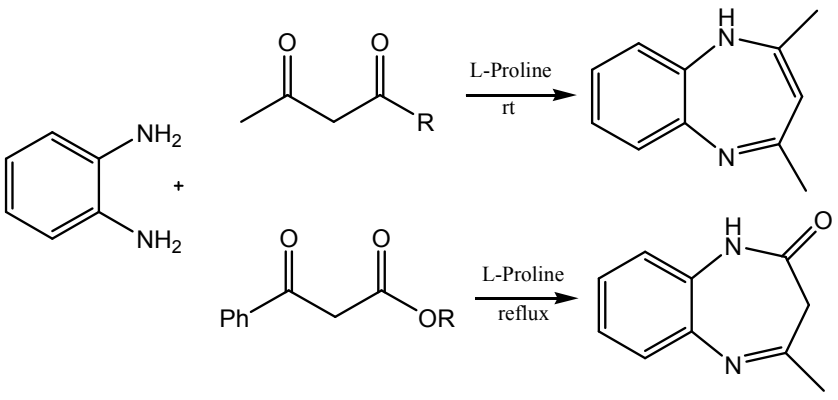
A facile and efficient synthesis of 1,5-Benzodiazepine with an aryl sulfanamido substituent at C(3) is described. 1,5-Benzodiazepine derived from the condensation of benzene 1,2-diamine and diketene,reacts with an arylsulphonylisocyanate via an enamine intermediate to produce 1,5-benzodiazepines in good yield(Alizadeh *et al.,* 2010).



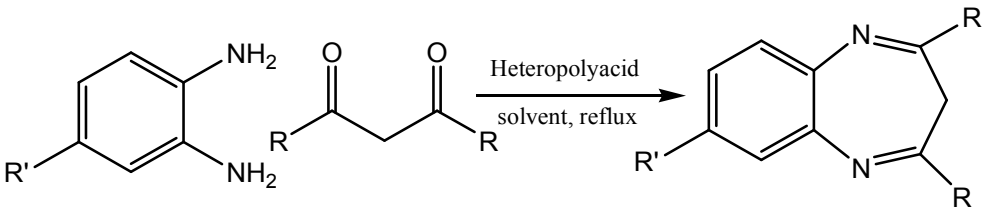
Synthesis of methylquino[3,2-b][1,5] benzodiazepine. (MQBD]



Goswami and Das reports the organo catalysed one pot synthesis of substituted 1,5-Benzodiazepines by condensation of o-phenylenediamine and 1,3-dicarbonyl compounds at room temperature or under reflux in the presence of catalytic amount of L-proline. (Goswami *et al.,* 2010)

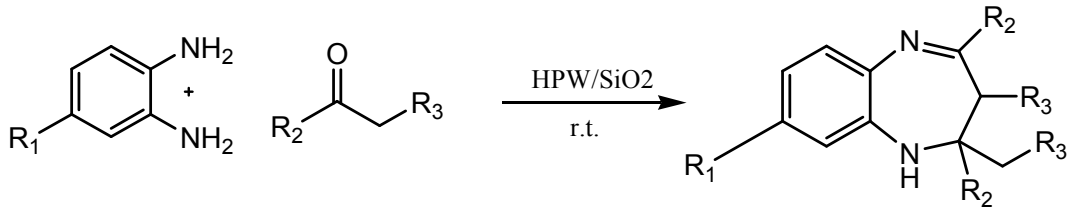


An efficient synthesis of 3H-1,5-Benzodiazepine derivatives catalysed by heteropolyacids as a heterogeneous recyclable.

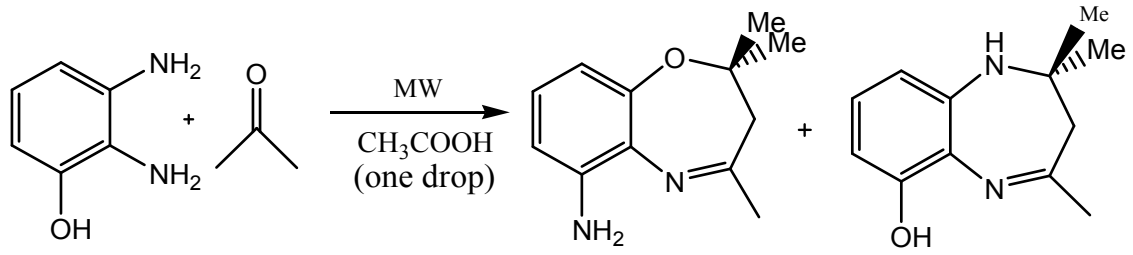


Abdollahi-Alibeik *et al.,* reported a novel synthesis of 1,5-benzodiazepines catalysed by silica silica supported dodecatungstophosphoric acid in 10th international conference on synthetic organic chemistry. Silica supported 12-tungstophosphoric acid catalyses efficiently the reaction of o-phenylene diamines with ketones under solvent free condition to afford the corresponding 1,5-benzodiazepine in good yields. The catalyst can be recovered by simple filtration and reused.

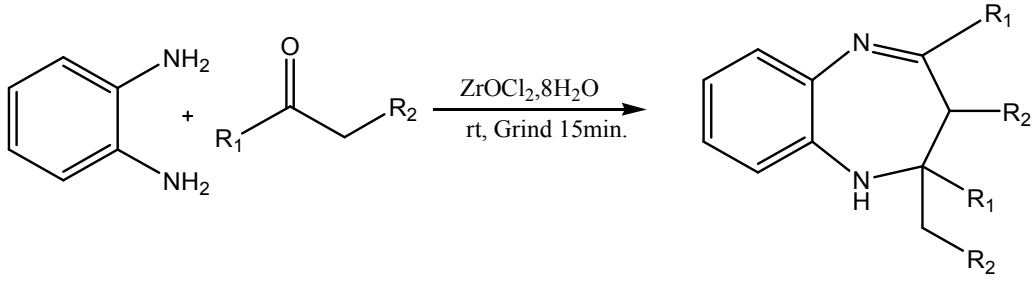
12-tungstophosphoric acid : $PW_{12}O_{40}/SiO_2$



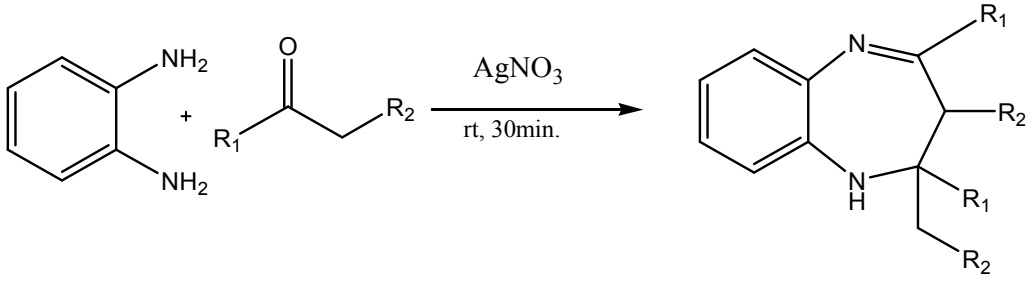
1,5-Benzooxazepines vs. 1,5-Benzodiazepines : One pot microwave assisted synthesis and evaluation for antioxidant activity using 2,3-diaminophenol and ketones.



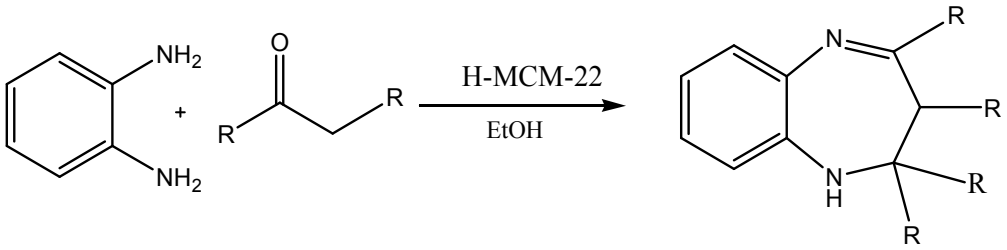
ZOC-Catalysed an efficient synthesis of 1,5-Benzodiazepine under mild conditions.



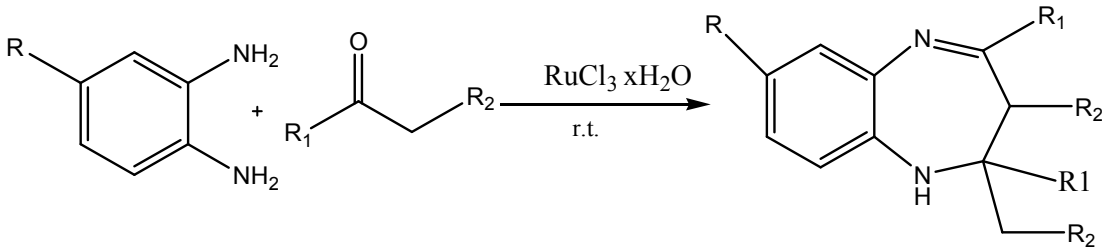
An efficient synthesis of 1,5-benzodiazepine derivatives catalysed by silver nitrate.



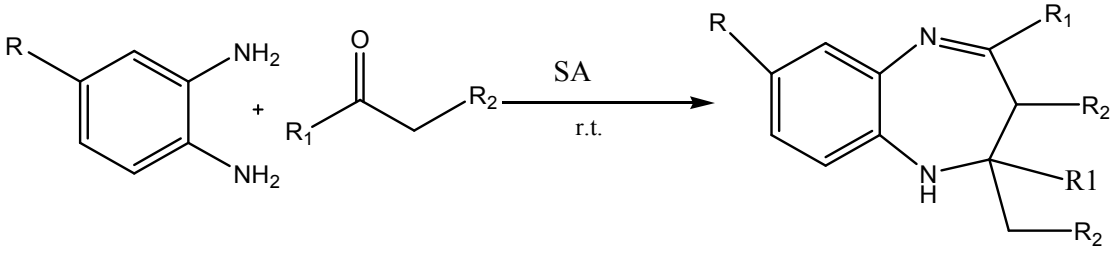
Synthesis of 1,5-Benzodiazepine and its derivatives by condensation reaction using H-MCM-22 as catalyst.



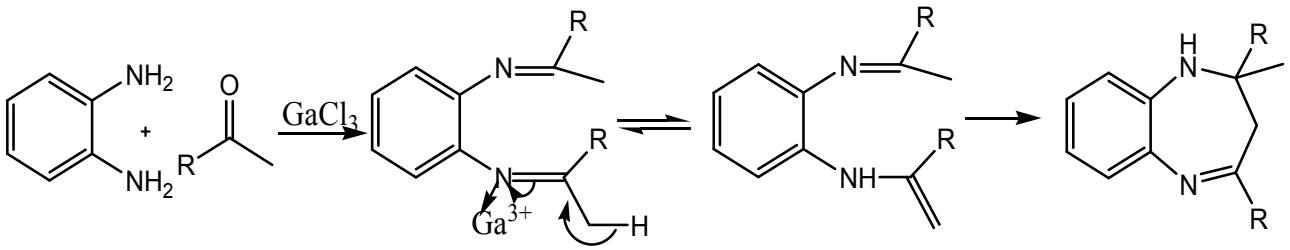
$RuCl_3$. xH_2O : A novel and efficient catalyst for the facile synthesis of 1,5-BZD's under solvent free conditions.



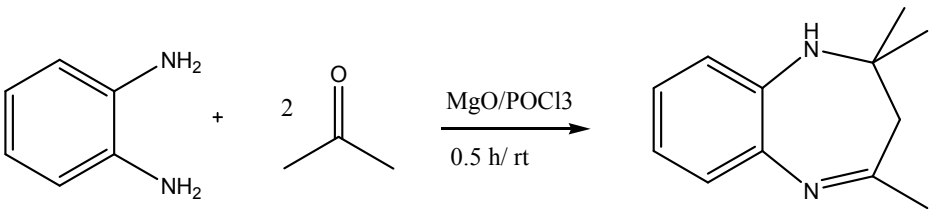
Efficient synthesis of 1,5-Benzodiazepine mediated by sulphamic acid under neat condition or in solution.



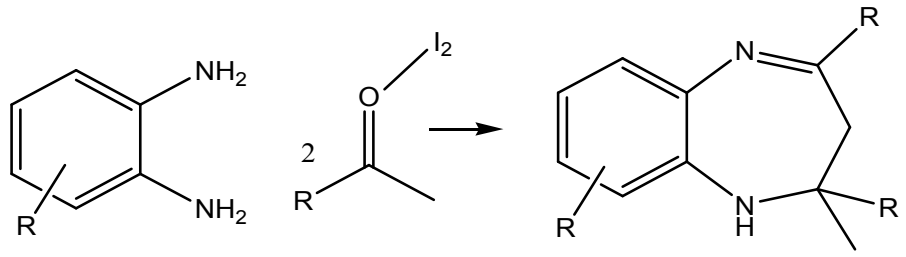
Various 1,5-benzodiazepine derivatives have been synthesized from OPDA and ketones using catalytic amount of $GaCl_3$ (5mol%) under solvent free conditions. This method is facile, efficient,environmentally benign and affords 1,5-Benzodiazepines in excellent yield.



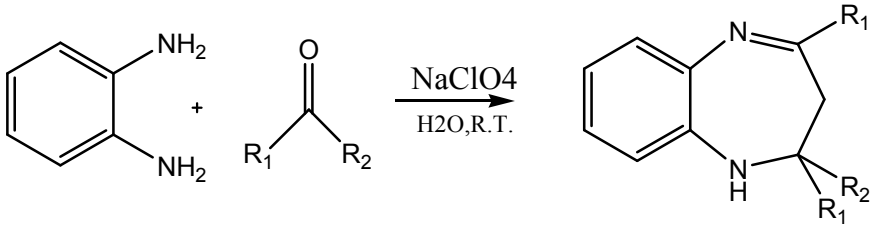
Balakrishna (IIT) Pawai, India and B. Kaboudin (IASAS) Zanjan, Iran : reported a simple and new method for the synthesis of 1,5-benzodiazepine derivatives on a solid surface. Magnesium oxide/phosphorus oxychloride (MOPO) was found to be an efficient reagent for the preparation of 1,5-benzodiazepine derivatives of o-phenylene diamine and ketones. This method is an easy, rapid, solvent free and high yielding reaction for the synthesis of 1,5-benzodiazepine derivatives.



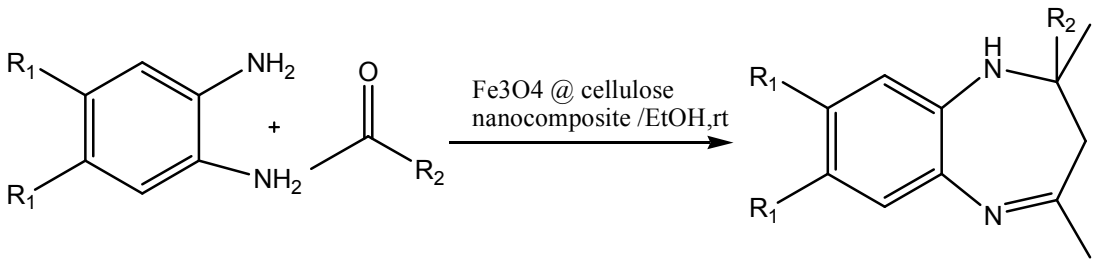
Parveen *et al.,* 2011 reported mechanistic synthesis of 1,5-benzodiazepine using molecular iodine. Molecular iodine catalyst improved procedure of the synthesis of various 1,5-benzodiazepines from o-phenylene diamine and acetone at room temperature and excellent isolated yield has been reported. This is a simple, straight forward ,high yielding, non hazardous and inexpensive catalyst. The synthesis is purely solvent free.



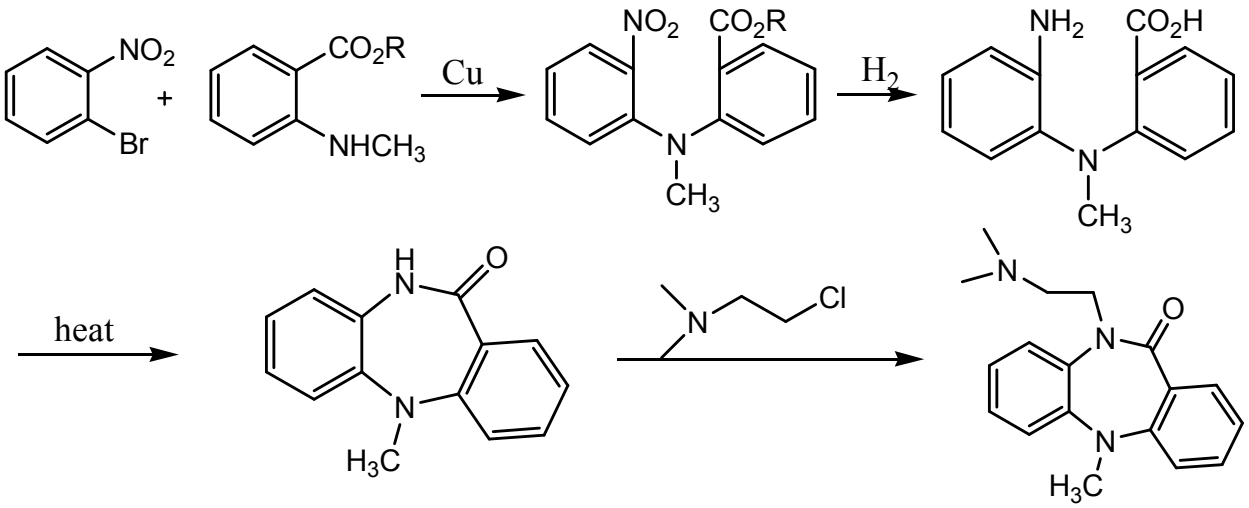
Makone *et al.,* 2012 and Dattatraya B. Vyawahare reported sodium perchlorate catalysed synthesis of 1,5-benzodiazepine in an aqueous media. Sodium perchlorate was found to be an efficient agent for the preparation of 2,3-dihydro-1H-1,5-benzodiazepine derivatives by the condensation of OPDA and various ketones in the presence of stoichiometric amount of $NaClO_4$ in aqueous media.



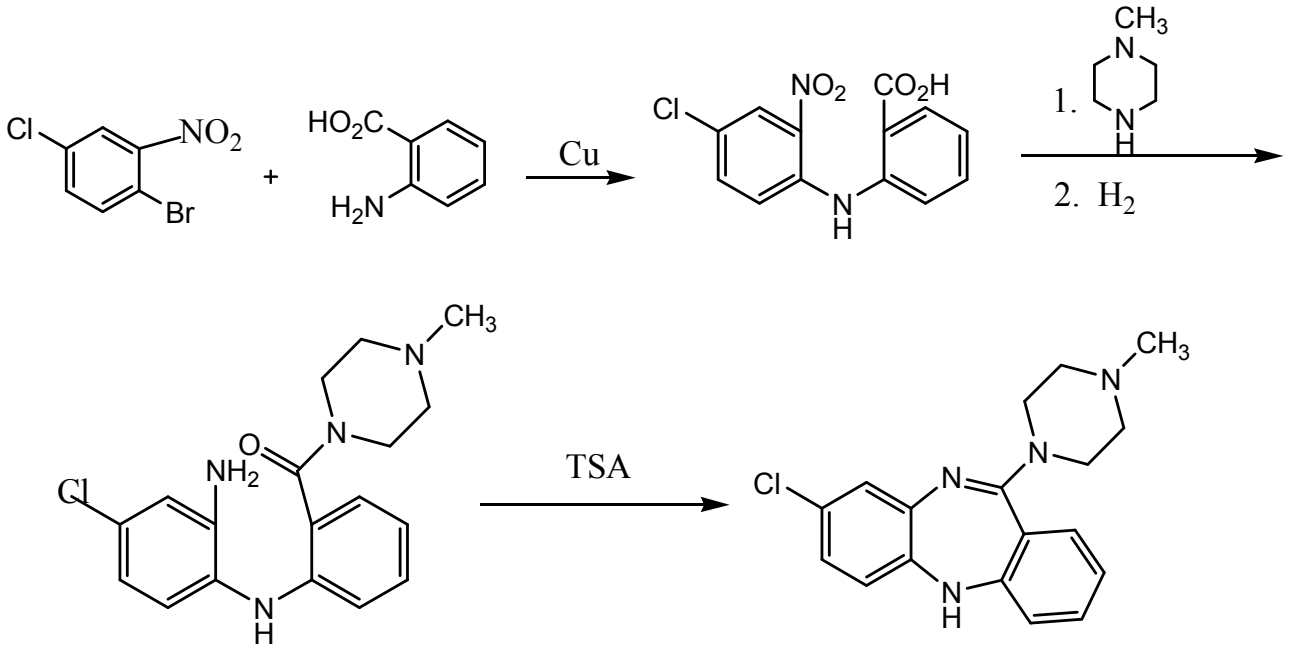
Maleki *et al.,* 2012, 2013 reported biopolymer supported iron oxide nanocomposite: preparation and catalytic application in the synthesis of benzodiazepine derivatives. Cellulose based nanocomposite containing high contents of Fe_3O_4 nanoparticles used as a catalyst in the condensation reaction between o-phenylene diamine and ketones for the synthesis of benzodiazepines in good to excellent yields under mild conditions.



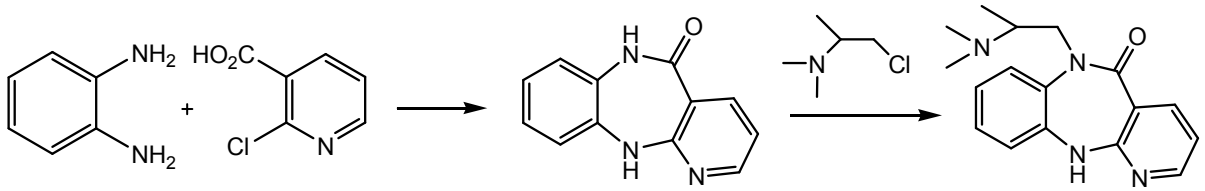
The Ullman reaction provides the key for preparing the diaryl amines. Copper catalysed coupling of methyl N-methylanthranilate with nitrobromobenzene leads to the aryl aniline. The ester is then saponified and nitro group is reduced to the corresponding amine. That product cyclises to the lactam nitrogen to form an anion. Alkylation with 2-chloroethyl dimethyl amine then affords dibenzepin, a compound that shows antidepressant activity (Hunziker *et al.,* 1963).



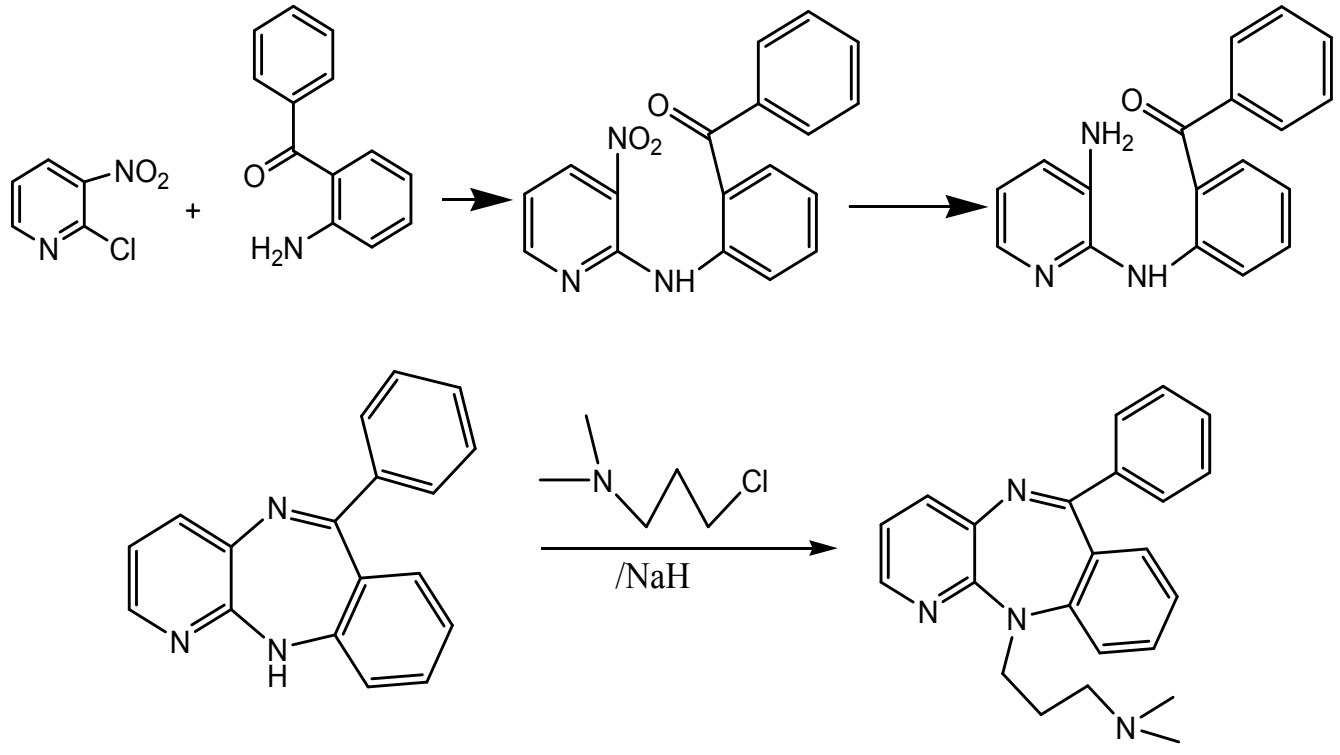
Synthesis of antipsychotic drug Clozapine involve Ullman coupling of anthranilic acid with 2,4-dichloronitrobenzene to give the substituted anthranilate. The carboxyl group is then converted to N-methylpiperazinamide via a suitably activated intermediate. The nitro group is then reduced to amine by means of catalytic hydrogenation. Intramolecular Schiff base formation catalysed by toluene sulphonic acid then completes the synthesis of clozapine (Hunziker *et al.,* 1967)



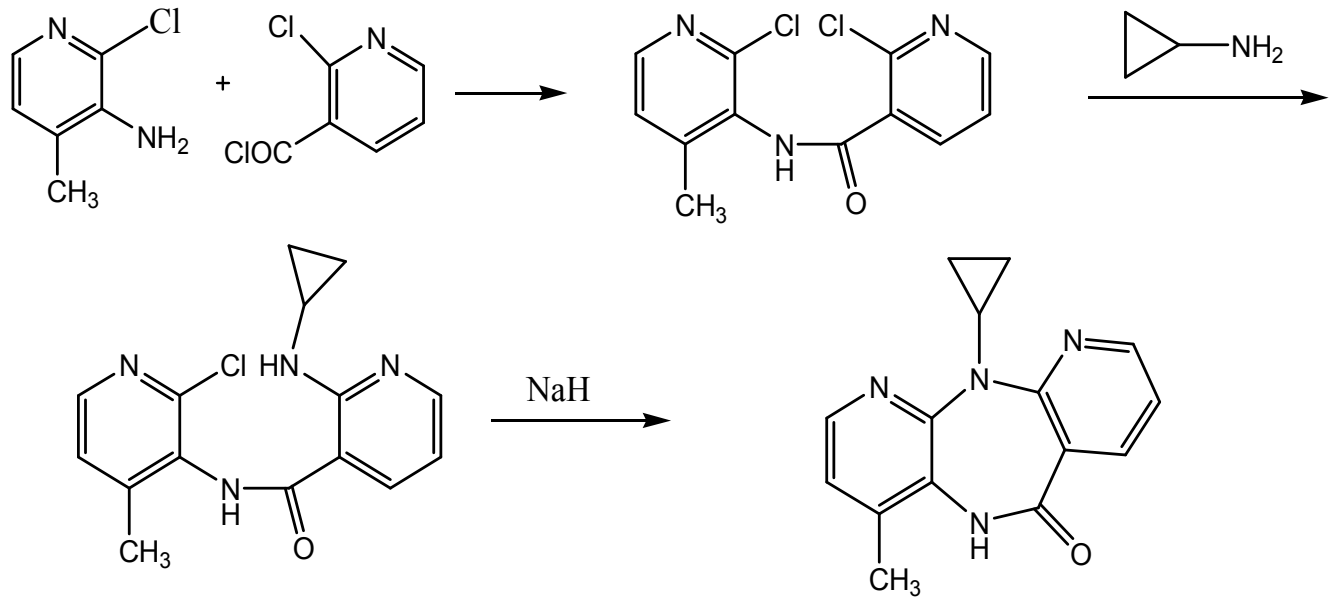
Pyridine based fused tricyclic compounds : In a one pot reaction,condensation of the 2-chloro nicotinic acid with ortho phenylene diamine leads to the lactum. The order in which two steps, aromatic displacement and amide formation take place has not been elucidated. Simple alkylation of the anion from the product with 3-chloro-2-(N,N-dimethylamino) propane affords the antidepressant agent propizepine. (Hoffmann *et al.,* 1966)



The antidepressant agent tampramine can be viewed as distant analogue of imipramine that contains an extra benzene ring and two additional nitrogen atoms. The preparation of this compound starts by Ullman coupling of chloropyridine with the aminobenzophenone more frequently used for benzodiazepine synthesis,reduction of the nitro group in the product leads to a diamine that readily cyclises to form pyridodiazepine. Alkylation of the anion from the treatment of this with sodium hydride with 3-chloro-1-dimethylamino-propane affords tampramine. (Lo *et al.,* 1984).



The bis-pyridodiazepinone nevirapine was the first NNRTI (nonnucleoside reverse transcriptase inhibitor)approved for treating HIV and still finds extensive use. The first step in the synthesis comprises the acylation of the amino pyridine with the chlorinate nicotyl chloride to afford amide. Treatment of the product with cyclopropylamine leads to the selective displacement of the halogen adjacent to the activating carbonyl. The anion from the reaction of that intermediate then displaces the corresponding halogen on the adjacent pyridyl function to form the diazepinone ring. This then affords the NNRTI nevirapines (Hargrave *et al.,* 1991).



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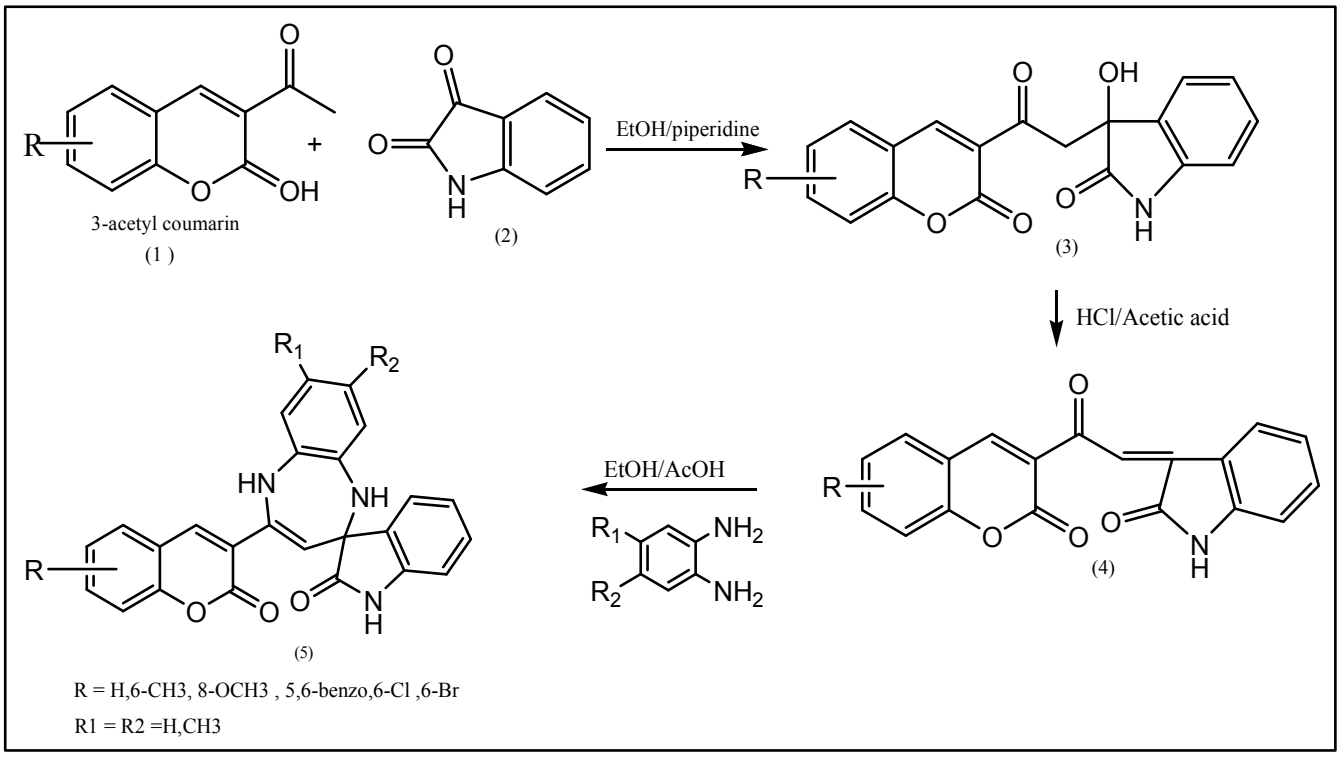
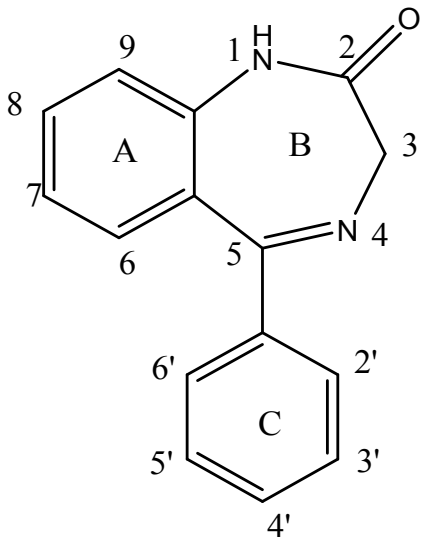
Kasanur *et al.,* 2004 reported the synthesis of spiro [indolo-1,5-benzodiazepines] from 3-acetyl coumarins for use as possible antianxiety agent. The fusion of a heterocyclic system to the benzodiazepine ring appears quite promising for the synthesis of derivatives with greater activity and specificity. Coumarins containing nitrogen heterocycles at C-3 position are used as dyes.

They are also used in manufacturing of printed circuits. 3-acetyl coumarin (1) when allowed to react with isatin (2) gave corresponding 3-(3'-hydroxy,2'-oxoindolo) acetyl coumarins (3) which on dehydration afforded the corresponding α,β-unsaturated ketones (4). Cyclocondensation of (4) with substituted o-phenylene diamines resulted in novel 3-coumarinyl spiro [indolo-1,5-benzodiazepines] (5).



Structure-activity relationship

A) Benzodiazepines



Classical 1,4-benzodiazepine

In the basic structure of 1,4-BZ,early SAR studies indicated that the seven membered imino ring B was essential for its affinity towards the BZ-binding site (Fryer *et al.,* 1982). Further QSAR and SAR (Borea *et al.,* 1984, Ghose *et al.,* 1990, Greco *et al.,* 1992, Gupta *et al.,* 1992, Maddalena *et al.,* 1995) studies found that the molecular lipophilicity properties of numerous BZs played a significant role in their corresponding receptor affinity. Additionally the carbonyl group at position 2 and the 4,5 double bond within the ligand have also been shown to substantially contribute to the binding affinity of the compound. The removal of carbonyl group results in a decrease in the binding affinity of the BZ by two orders of magnitude, while saturation of the 4,5-double bond results in a complete loss of in vitro affinity. Recently, the QSAR analysis of 1,4-BZ's with different substituents at positions 1,3,7,8,2' and 6' were performed by three research groups (Karplus 1996, Hasegawa *et al.,* 1998, Doble *et al.,* 1982), which reported very similar structure-affinity relationships among the various ligands.

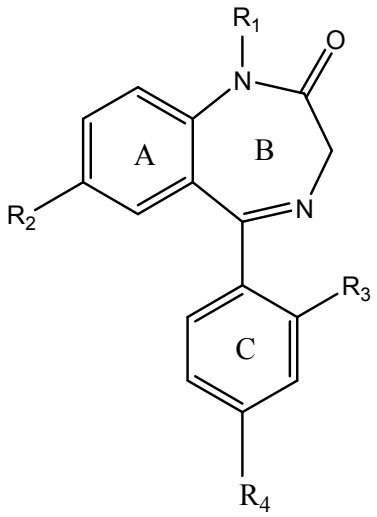
The primary chemical moieties of the compounds, which contribute to high receptor binding affinity are restricted to positions 7,2' and 1. Position 7 is the most effective location in these molecules for enhancing the affinity of the compound for the BZ-binding site. Increases in the lipophilicity and electronic charge of substitutions at position 7 are directly related to an increased affinity of the ligand for the binding site, while substitutions at position 2' represent the second most important functional group location associated with receptor affinity. The presence of an electrophilic and bulky substituent at position 2' results in a strong increase in receptor binding affinity of the corresponding compounds. On the other hand, molar refractivity is the most important parameter at position 1, suggesting that the molecular size of the substituent needs to be restricted at position 1 for effective ligand binding. The effects of substitutions at positions 6',3 and 8 on the affinity of the ligand for the BZ-binding site are less pronounced than those at positions 7,2' and 1. However, these studies documented that the molecular size of the substituent has to be restricted at position 6',whereas electrostatic influences are important at positions 3 and 8 in order to maintain ligand binding.
According to the above QSAR analysis the optimal functional groups at positions 7,2' and 1 are as follows : position 7 : C > CH_2CF_3 > I > Br > CF_3 > Cl > $C(CH_3)_3$ > NO_2 > F > N_3 >CH=CH_2

Position 2': NO_2 > F > CN > Cl > CF_3
Position 1 : OH > F > NH_2 > H > NHOH > Me > Cl > CF_3 > Br > Et

Recently, structural modification has been done in diazepine ring system to enhance biological activity. Diazepine ring system modified at N and 3-position has been studied exclusively. They have been tested clinically as an antitrypanasomal activity (Spencer *et al.,* 2011), antiplasmodial falcipain-inhibitors (Bova *et al.,* 2010), antileukemic agents (Gaundalini *et al.,* 2008) and endothelin receptor antagonists (Bolli *et al.,* 2004). V. I. Pavlovsky *et al.,* (Pavlovski *et al.,* 2007) has reported that 3-arylidine and 3-heterylidine 1,4-diazepinederivatives afford good affinity toward CNS benzodiazepine receptors.

Effect of substituents on the biological activity of BZD's

With such a large library of benzodiazepines available, structure activity relationships have been studied thoroughly. The set of rules that were established by Sternbach proved to be very valuable in the synthesis of more potent and selective benzodiazepines. Substitution on the rings had a pronounced effect on biological activity. Substitution at the R_2 position of ring A with electron withdrawing groups (halogen and nitro groups) imparted high activity, while having electron donating groups (methyl and methoxy) at this position causes a significant activity decrease.



R_1 positive effect : H,CH_3,Et,i-Bu

negative effect : tBu

R_2 positive effect :Cl,F,NO_2,CF_3

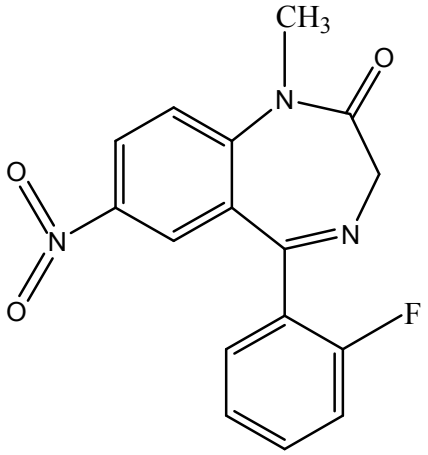
negative effect : Me, OMe

R_3 positive effect :H,F,Cl

R_4 positive effect : H

negative effect :anything else

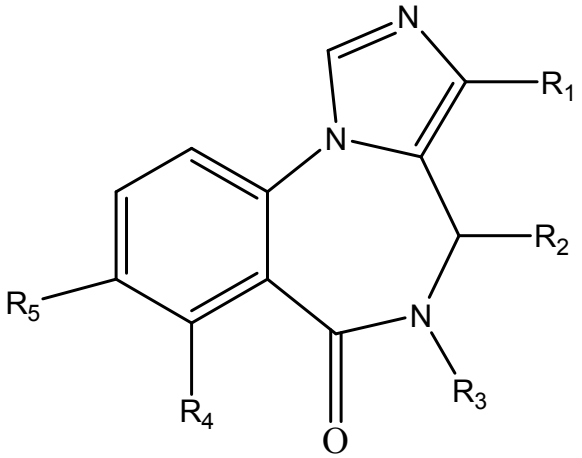
The nitrogen atom at the R_1 position in ring B tolerates substitution by a methyl group, whereas larger groups in this position such as tertiary butyl led to significantly decreased activity. Substitution of the R_3 position on ring C with halogens leads to increased activity, but any substitution at the R_4 position strongly decreases anxiolytic activity. Based on these findings a library was prepared, consisting of over 80 benzodiazepines with varying substitution at the R_1 and R_2 positions. Eventually one of the most potent benzodiazepines to date was synthesized combining all the moieties that induce high activity. The compound, Flunitrazepam has a methyl group at R_1,a nitro group at R_2 and a fluorine at the R_3 position. It is prescribed in Switzerland as a potent hypnotic.



Flunitrazepam

B) Imidazobenzodiazepines

Substitutions at positions 1 and 2 of 1,4-BZ with either an imidazo or triazolo ring lead to a significant increase in receptor affinity for only the classic 1,4-BZ which initially possessed a relatively low affinity. This was not true for the high affinity class of 1,4-BZ compounds. The following figure represents the core structure of the various imidazobenzodiazepines.

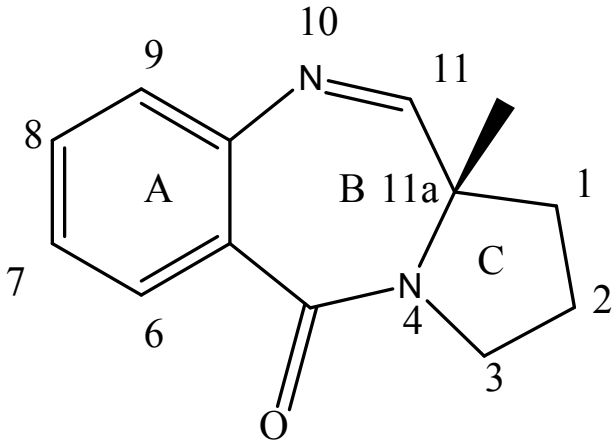


Imidazobenzodiazepine

Imidazobenzodiazepines were identified as one of several chemical families, including imidazobenzodiazepine, pyrazoloquinolinones and β-carbolines that exhibit high to moderate potency for diazepam-insensitive (DI) $GABA_A$ subtypes. The DI receptor subtype is characterised by low affinity for the prototypical 1,4-BZ's such as diazepam or flunitrazepam which exhibit a high affinity for the diazepam –sensitive (DS) subtype.

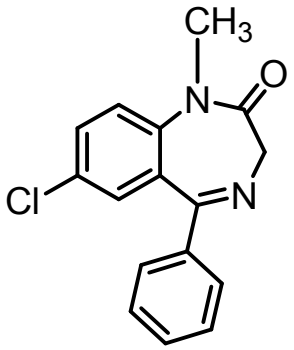
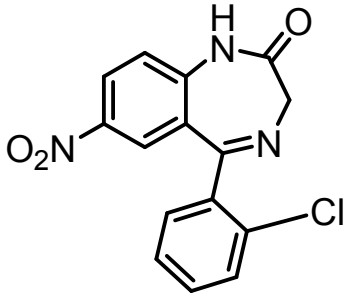
C) Pyrrolo-benzodiazepines (PBD's)

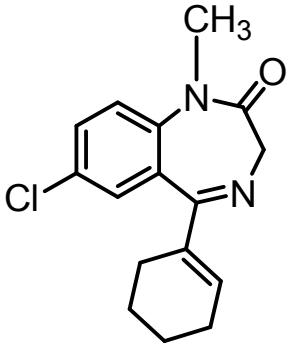
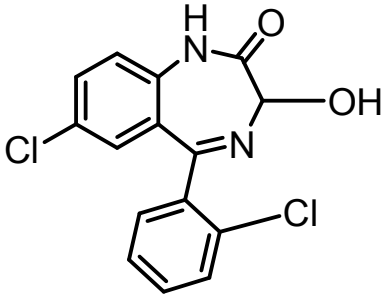
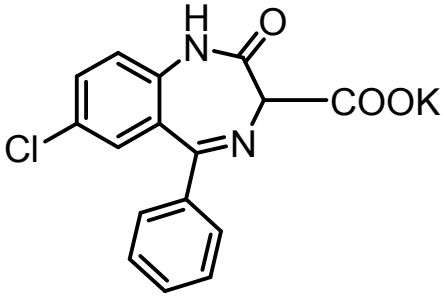
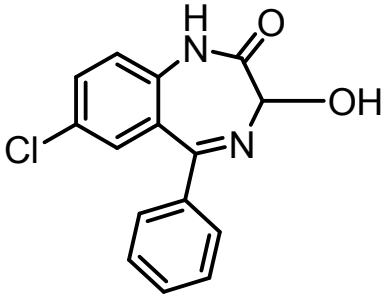
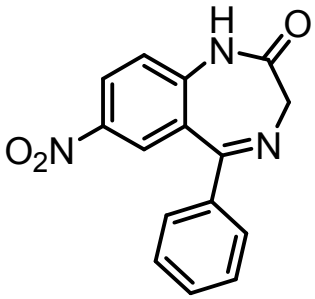
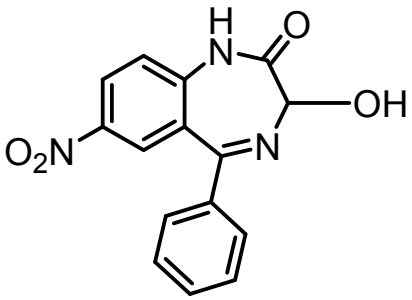
These compounds based on the common skeleton as shown in the fig. These are tricyclic compounds consisting of an aromatic A ring, a pyrrolidine C-ring either fully saturated or unsaturated at either C_2-C_3 (endocyclic) or at C_2 (exocyclic) and a 1,4-diazepin-5-one presenting a N_{10}-C_{11} imine- carbinolamine moiety.

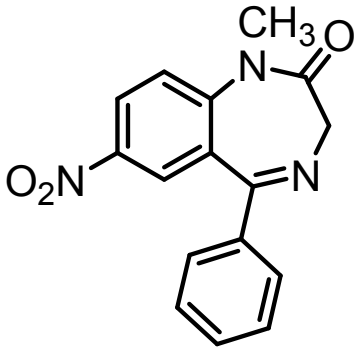
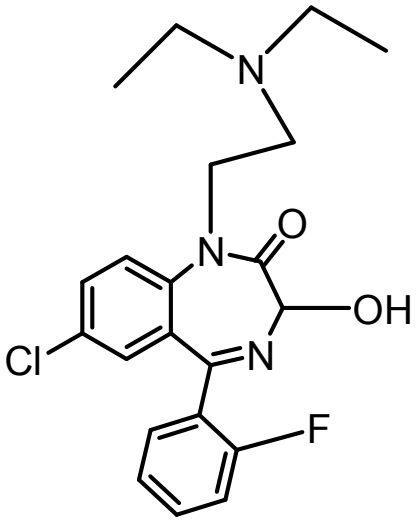
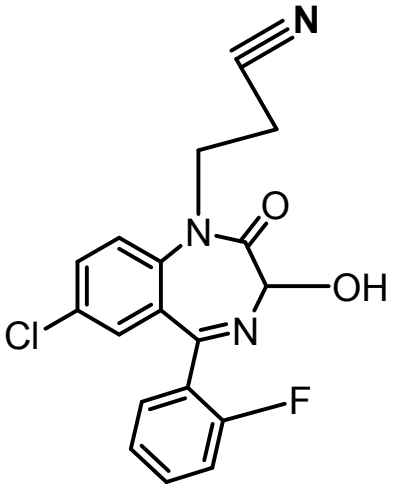
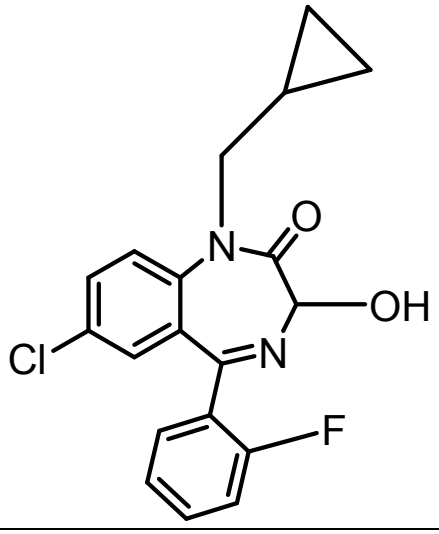


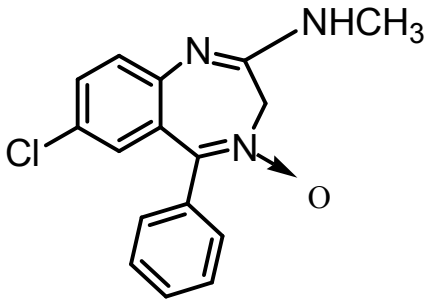
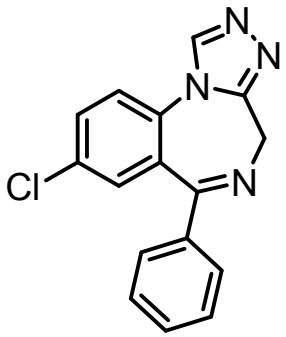
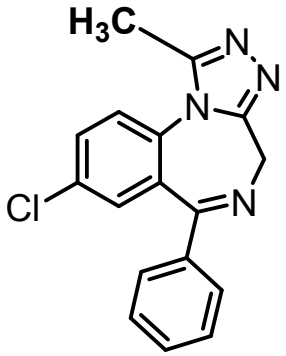
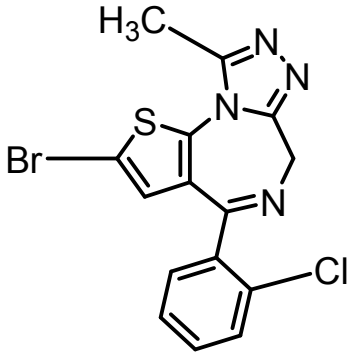
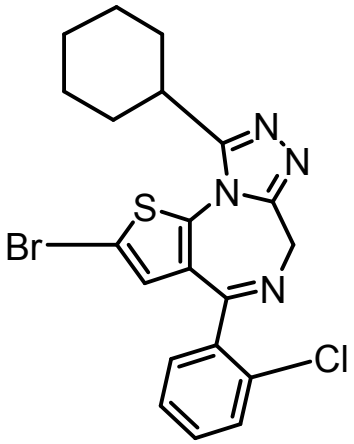
The naturally occurring PBD's differ in the number,type and position of substitution in the aromatic A-ring, the pyrrole C –ring, which can be both saturated or unsaturated at C_2-C_3 (endocyclic) or at C_2 (exocyclic). All naturally occurring compounds possess the (S) configuration at C-11a, which convey a right handed helical conformation to the polycyclic system. Hence the PBD rings can be considered by medicinal chemists as ideal scaffold for the development of new, selective and highly cytotoxic antitumour drugs.

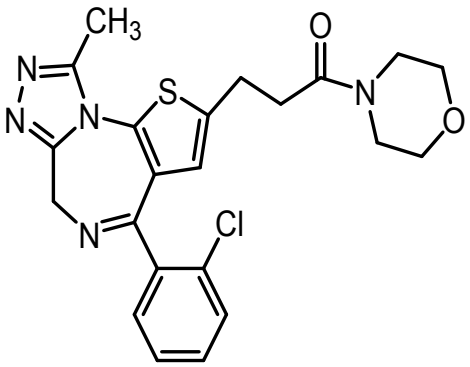
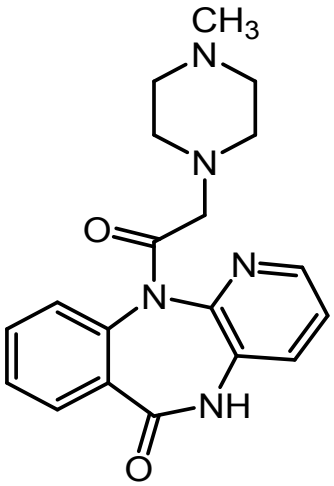
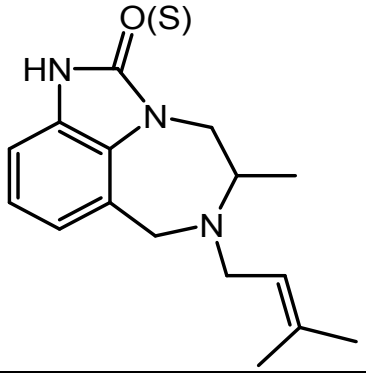
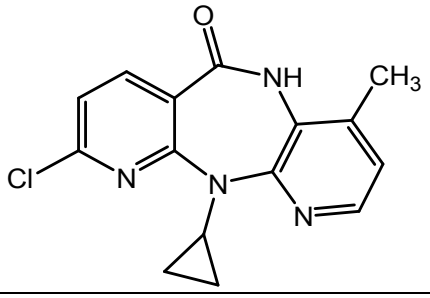
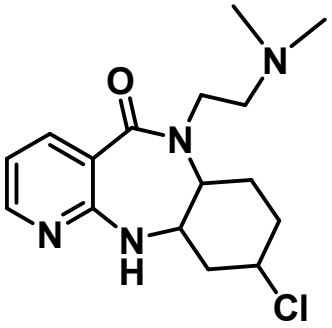
Some benzodiazepine based drugs available in clinical uses

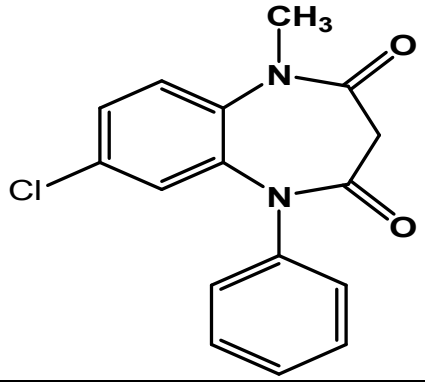
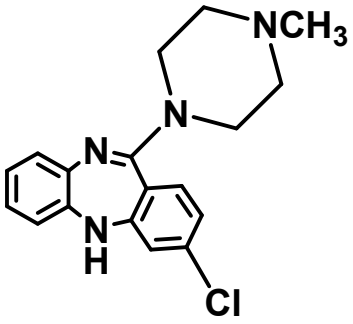
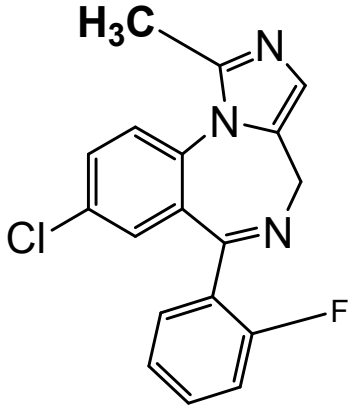
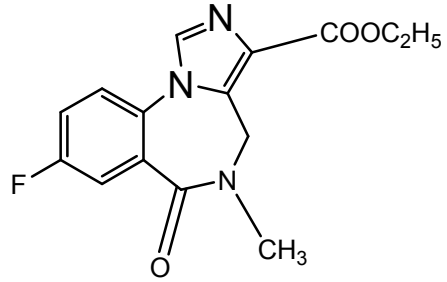
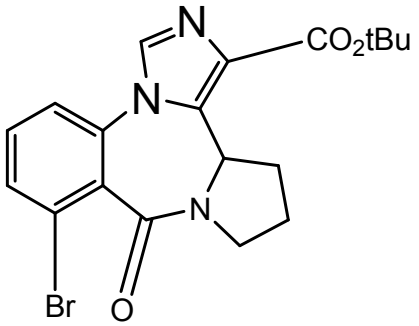
Drug	Brand name	Structure	Therapeutic uses
Diazepam	Valium (1963)		Anticonvulsant, muscle relaxant
Clonazepam	Klonopin (1975)		Hypnotic

Tetrazepam			Skeletal muscle relaxant
Iorazepam	Ativan (1977)		Treatment of anxiety,seizure,insomnia ,panic disorder and alcohol withdrawal. Use as an adjunctive antiemetic.
Clorazepate			
Oxazepam	Serax		anxiety,insomnia, alcohol withdrawal. Common metabolite of many 2-ketobenzos following their oxidation to desmethyldiazepam.
Nitrazepam			
Temazepam			

Nematazepam			
Flurazepam	Dalmane		Hypnotic
Cinnolazeapm			Hypnotic
Flutoprazepam			Anxiolytic

chlordiazepoxide	librium		
Triazolo [1,4]benzodiazepine			
Estazolam	Prosom		Short term treatment of Insomnia
Alprazolam	Xanax		Tranquillizer
Brotizolam			Sedative,Hypnotic
Ciclotizolam			GABA-A receptor agonist

Apofant			Act as platelet activating factor (PAF)inhibitor
Pirenzipine			Act selectively as muscarinic receptor antagonist
TIBO			anti HIV agent
Nivirapine			
Clobenzapam			Prophylactic agent,Chronic treatment of mild atopic asthama in children

Clobazam			Antiepileptic agent
Clozapine			Antipsychotic agent
Imidazo [1,4] benzodiazepine			
Midazolam			
Flumazenil			Antagonist
Bretazenil			

REFERENCES

Ali maleki, Maryam Kamalzare ECSOC-17, 2013 / Maleki A. Tetrahedron 2012, 68, 7827 /Maleki A. Tetrahedron let 2013, 54, 5055.

Alizadeh A., Zohreh N., Helv. *Chim Acta* 2010, 93, 1221.

Arshia parveen, Vishal A. Patil, Mohammad A. Baseer, S. K. Ahmad. *International journal of industrial chemistry*, Vol 2, No. 3, 2011, pp 144-153

Atwal K. S., Bergy 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 Med. Chem.* 30, 635 (1987)

Balakrishna M. S., Kaboudin B., Tetrahedron lett, 2001, 42, 1127.

Bhatia M. S., Choudhari P. B., Ingale K. B., *Oriental J. Chem.* 2008, 24, 147.

Bolli M. H., Marfurt J., Grisostomi C., Boss C., Binkert C., Hess P., Trieber A., Thorin E., *Morrison J. Med Chem,* 2004, 47, 2776.

Borea PA, Bonora A. Brain receptor binding and lipophilic character of benzodiazepine analogues, requirement for receptor affinity and activity. *Mol. Pharmacol.,* 1984 : 26 : 19-34.

Bova F., Ettari R., Micale N., Carnovale C., Leippe M., Grasso S. *Bioorganic and medicinal chemistry,* 2010, 18, 4928.

Claramunt R. M., Sanz D. J. Arkivoc 2006, 35.

Costa E, Guidotti A, Benzodiazepines on trial, a research strategy for their rehabilitation. Trends Pharm. Sci. 1996, 17, 192.

Covelli V., Maffione A. B., Nacci C., Tato E. Immunopharmacol. And Immunotoxicol. 1998, 20, 199.

Curini M, Epifano F., Marcotulio M. C., Rosati O., Tetrahedron let 2001, 42, 3193.

De S. K., Gibbs R. A. Tetrahedron letter 2005, 46, 1811.

Doble A, Martin II Richards DA. GABA modulation predicts biological activity of ligands for the benzodiazepine receptor. Br J. Pharmacol 1982 : 76 : 238-244.

E. L. Sayed, A. M. Khodairy, Abdel-Ghang H, Phosphorus, sulphur, silicon related elements. 2007, 182, 711.

Ellman J. A., Design, synthesis and evaluation of small molecule libraries. Acc. Chem. Res. 1996, 29, 132.

Fryer RI, Leimgruber W, Trybulski K, Quinazolines and 1, 4-benzodiazepines 90. Structure activity relationship between substituted 2-amino-N-(2-benzoyl-4-chlorophenyl) acetamides and 1, 4-benzodiazepinones. J Med. Chem 1982 : 25 : 1050-1055.

Gaundalini, L ; Cellai C ;Laurenzana A ;Scappecchi S ;Paoletti F ;Romanelli M. N. ;Bioorganic and medicinal chemistry letters, 2008, 18, 5071.

Ghose A. K., Crippen GM. Modeling the benzodiazepine receptor binding site by the general three dimensional structure directed quantitative structure activity relationship method. Mol Pharmacol 1990 : 37 : 725-734.

Goswami P., Das B., Synthetic communication 2010, 40, 1685.

Greco G, Novellino E, Silipo C, Vittoria A. Study of benzodiazepine receptor sites using a combined QSAR-CoMFA approach. Quant Struct – Act Relat 1992, 11 :461-477.

Gupta S. P., Saha RN, Mulchandani V. Quantitative structure activity relationship studies on benzodiazepine receptor binding : Recognition of active sites in receptor and modelling of interaction. J Mol Recognition 1992 ; 5 : 75-80.

Hargrave K. D., Grozinger K. G., Cullen E., Kapadia S. R., Patel J. R., Behnke M. L., et. al. J. Med. Chem. 1991, 34, 2231.

Haris R. C., Straley J. M. U. S. Patent 1, 537, 757., 1968 [Chem. Abst. 1970, 73, 100054w]

Hasegawa K, Funatsu K, GA strategy for variable selection in QSAR Studies. GAPLS and D-optimal designs for predictive QSAR model. J Mol Struct (Theochem) 1998 :425:225-262.

Hoffmann C., Faure A., Bull Soc. Chim Fr. 1966, 2316.

Hunziker F., Fischer E., Schmutz J., Helv Chim Acta. 1967, 50, 1588.

Hunziker F., Launer H., Schmutz J., Arzneim., Forsch., 1963, 13, 324.

Joshua D., Neukom A. S., Aquino J. P., Wolfe., Org. Let. 2011, 13, 9.

Kaboudin B., Navaee K., Heterocycles 2001, 55, 1443.

Kosychova L., Stumbreviciute Z., Jancienne R., Puodziunaite B. D., "Synthesis of substituted 5, 6-dihydro-4H-[1, 2, 4]triazolo-[4, 3-a][1, 5]benzodiazepines. " Chemistry of heterocyclic compounds 40(6), pp 811-815, 2004.

Lausten L. S., Sams C. K. J. Comb. Chem. 2007, 9, 1094.

Lednicer D., The organic chemistry of drug synthesis. Wiley Interscience. New York, 1998.

Lednicer D., Mitschew L. A., The organic chemistry of drug synthesis. Wiley Interscience. New York. 1977.

Lo Y. S., Taylor C. R., 1984, U. S. Patent 4, 480, 100.

Maddalena DJ, Johnston GAR. Prediction of receptor properties and binding affinity of ligands to benzodiazepine/$GABA_A$ receptors using artificial neutral networks. J Med Chem 1995 : 38 :715-724.

Melukzi V., Hargrave K. D., Labadia M. C., Grozinger K., Skoog M., Shin C. K., Eckner R. J., J. L. Science 1990, 250, 1441.

Mohammad Mahadevi, Mehdi Asdi, Mina Saeedi Synthetic letter 2012, 23, 2521-2525.

Nabih K, Hasnaoui A, Synthetic communication 2004, 34, 3565.

Nagaraja G. K., Vaidya V. P. Phosphorus, sulphur, silicon related elements. 2006, 181, 2797.

Nakanishi M., Tahara T., Araki K., Shiroki M., US patent 3920679, 1975.

Narayana B., Vijayraj K. K., Ashalata B. V. and Kumari N. S. "Synthesis of some new substituted triazolo[4, 3-a][1, 4] benzodiazepinederivatives as potent anticonvulsants" European Journal of Medicinal Chemistry 41, pp 417-422, 2006.

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

Pavlovsky V. I. ; Bachinskii S. Yu. ;Tkachuk N. A., Makan S Yu ; Andronati S. A ;Simonov Yu A ; Filipova I. G;. Gdaniec M; Chemistry of heterocyclic compounds, 2007, 8, 43.

Pozarentzi M, Stephnatou J. S., Tsolerides C. A., Tetrahedron let 2002, 43, 1755.
R. K. Singh Journal of soudi chemical society jscs, 2013, 10, 004.
Raviraj A. Kasanur, Manjunath Ghate and manohar V. Kulkarni J chem. Sci vol 116 No. 5 Sept. 2004, pp. 265-270
Reddy K. V., Rao P. S., Synthetic communication 2000, 30, 1825.
Robert Y. N., Fryer R. I., Pradeep M., Sluboski B., Reactions of some Di-4-morpholinylphosphinyloxy imines ; J. Org. Chem. 41, 16(1976).
Rudolph U. Benzodiazepine actions mediated by specific gamma aminobutyric acid (A) receptor subtypes. Nature 1999, 401, 796.
S. S., Karplus M. Genetic neutral networks for quantitative structure activityrelationship : Improvements and application of benzodiazepine affinity for benzodiazepine/ $GABA_A$ receptors. J med Chem 1996 :39 : 5246-5256.
Sachin S. Patil, Rahul P Jadhav, Sachin V. Patil and Vivek D. Bobade ; Journal of Chemical and Pharmaceutical Research, 2010, 2(4) : 52-59.
Sangita S. Makone *et al.,* Pelagia Research library Der Chemica sinica 2012, 3(6), 1369-1373)
Spencer J, Ratnam RP, Harvey, A. L., Clements C. J., Clark R. L., Barrett M. P., Wong P. E., Coles S. J., Mackay S. P. ;Bioorganic and medicinal chemistry., 2011, 19, 1802.
Steffan R. J. and Failli A. A. Preparation of pyrrole benzodiazepinecarboxamide vasopressin agonists. PCT Int. App. 228, 46 (2000).
Stern bach L. H., Fryer R. I., Meilescics W., Reeder E., Sach G, Stemple A. J. Org. Chem. 1962, 27, 3788.
Tecott L. H., Designer genes and antianxiety drugs. Nature Neurosci. 2000, 3, 529.
Varala R., KotraV. And Engula R. Synthesis of some 1, 5-benzodiazepine derivatives as a new class of antimicrobial agents. Asian Journal of chemistry 19 (7), 5435-5442 (2007).
Venter J. C. Harrison L. C., Benzodiazepines /GABA receptors and chloride channels, Alan R. Liss INC. 1986, vol. 5
Walser A., Flynn T., Mason C., Crowley H., Maresca C., Yaremko B., O'Donnell M., J. Med. Chem, 1991, 34, 1209.
Wang J. Y., Feiguo X., Wang D. X., Haung Z. T., Wang M. X., J. Org. Chem. 2008, 73, 1979.
Yadav J. S., Reddy B. V. S., Kumar S. P., Synthesis 2005, 480.
Yadav J. S., Reddy B. V. S., Eshwariah B., Anuradha K., Green chem., 2002, 4, 592.
Yadav V., Yadav N., Arch. Appl. Scie. Res. 2011, 3(1), 139.
Yaddarapudi Prabhakar, Kottapalli R. S., Jagalapudi V. S. Kumar : Microwave assisted synthesis of 3-(4-ethyl benzyl) 1-(4-methoxybenzyl)-6-(methylthio)-1, 3, 5 triazine-2, 4 (1H, 3H)-dione derivatives under solvent free condition with high yield. Res. J. Recet Sci. 1(ISC-2011) 105-109(2012).

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