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# Review on Preparation Methods and Different Biological Activity of 1, 5-Benzodiazepines

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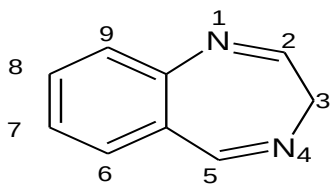
**ABSTRACT:**
Benzodiazepine are well known class of antidepressant agent. Benzodiazepine as more effective in alleviating anxiety and stress as they have fewer or less severe side effect. 1,5-BZD is used as adjuvant therapy in resistant cases of epilepsies. BZDs exhibit potent anticonvulsant actions in a wide variety of animal seizures models. Extensive applications of these compounds in medicine have anti-bacterial, anti-inflammatory,anti-oxidant, muscle relaxant, anti-anxiety, antipsychotic, anti-depressant and anti-tubercular. Objective of this review is to present a literature survey of preparation methods of [1,5]-benzodiazepine and their different pharmacological uses in synthetic organic chemistry. Some of these methods involve minor modifications so as to increase polarity, metabolic degradation, water solubility and gives better activity as compare to standard drug. Some synthetic method involves combination of pharmacologically active aromatic or heterocyclic ring such as pyrazole, oxadiazole, imidazole, tetrazole, etc. at 2 &4 position of 1,5 benzodiazepine ring which is a promising drug design strategy for site specification.Subsequently 1,5-benzodiazepines were highlighted as important biologically active scaffolds. The current review article focuses on pharmacological profile, various routes of synthesis utilized, the numerous solvents employed and catalyst used associated with 1,5-benzodiazepines.This review encompasses the research work that has been accomplished since the past decade.

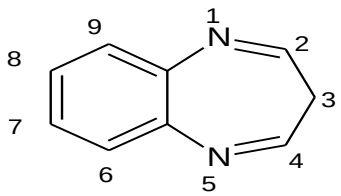
**KEYWORDS:**1,5-benzodiazepine, Anti-depressant, Anti-inflammatory, Anti-microbial.

## I. INTRODUCTION:

Benzodiazepine are an important class of organic molecules with a wide array of biological activities and therapeutic functions. Benzodiazepines are bicyclic heterocyclic compounds in which benzene nucleus is fused to seven membered rings 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 rings. Considering the relative position of nitrogen atom in the heterocyclic ring benzodiazepines are classified as 1,4 and 1,5[1,2].




1,4-benzodiazepine




1,5-benzodiazepine

**Figure 1 Chemical structure of 1,4 and 1,5-benzodiazepine**

They are generally use as anticonvulsive and anxiolytic drug[3,4,5,6]. They are wide application in the field of drug and pharmaceuticals such as sedative[7], muscle relaxant[8], anti-inflammatory[9,10], antimicrobial[11,12,13,14,15,16,17,18]as well asantioxidant[19]. Moreover, benzodiazepine derivatives are commercially used as dyes for acrylic fibers. 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[16].

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**Nomenclature of 1,5-benzodiazepine-**

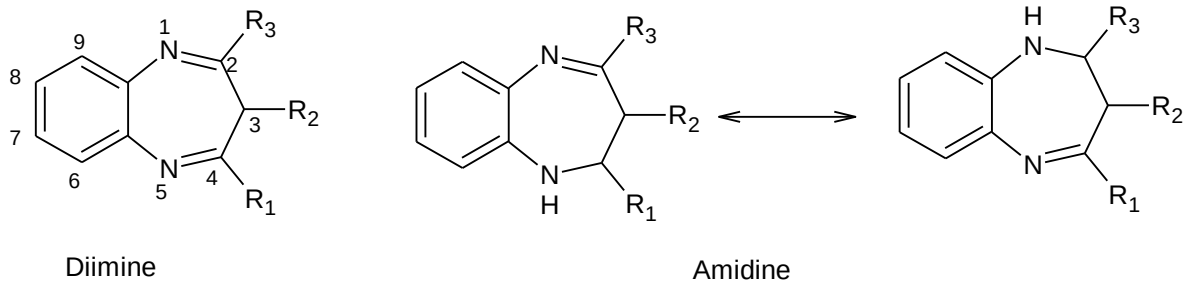


**Figure 2 Chemical structure of Diimine and Amidine**

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-diazepine. Benzodiazepines are number shown in fig. The numbering of these benzodiazepine revenue 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 arise in the diimine form rather than in the conjugated amidine form. In the diimine form some extra stabilization occur due to the conjugation of the imine group with the benzene ring. Protonation of benzodiazepines lead to the successive formation of monocations. The conjugated form which would have 8-pi-electrons correlate 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[20,21].

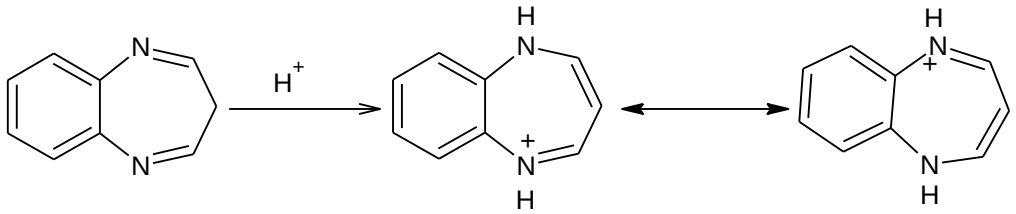

**Figure 3Annular conjugation of 1,5-benzodiazepine**

**A. ANTIDEPRESSANT ACTIVITY OF 1,5-BENZODIAZEPINE**

1.Ghogareetal. reported a series of 1,5-benzodiazepine derivative that demonstrate anticonvulsant activity. In this study combination of thiazolidine nucleus and benzodiazepine was carried out using hybrid approach. The benzoylation of 2-amino-3-carboethoxy-4-methylthiophene yielded some intermediate then hybridization of this intermediate gave other compound which on formation of Schiff base with a cinnamaldehyde yielded derivative then further it cyclized with mercaptoacetic acid in presence of anhydrous $ZnCl_2$ to afford thiazolidinone derivative further treatment with different aromatic aldehydes gives some compound which on further treatment with o-phenylenediamineand xylene as solvent yielded 1,5-benzodiazepine derivatives.

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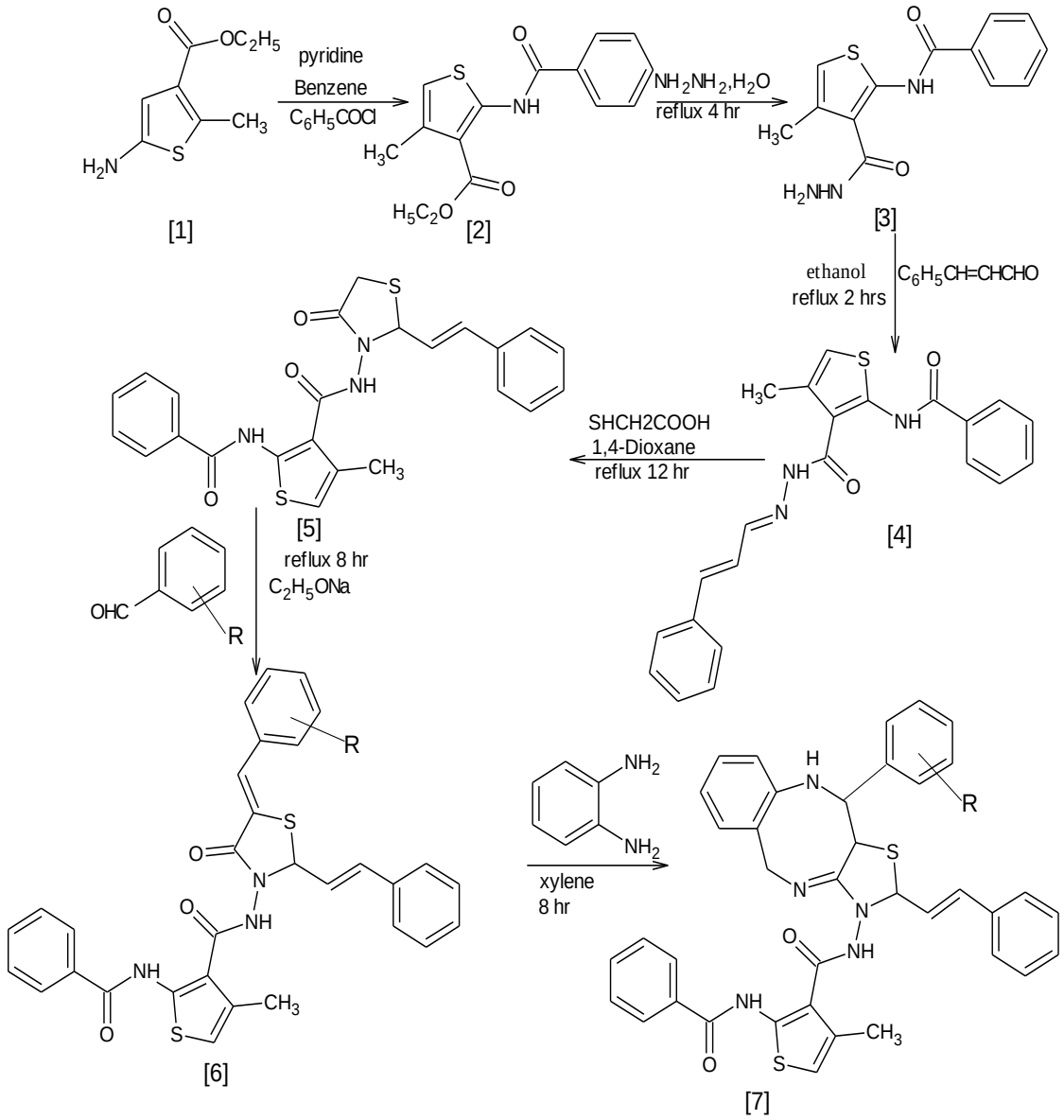


**Figure 4 synthesis of 1,5-benzodiazepine derivatives**

**Table 1: Derivatives of 1,5-benzodiazepine as anticonvulsant agent.**

| Sr. No. | Compound | R |
|---|---|---|
| 1 | 7a | -2-OH |
| 2 | 7b | -3-$NO_2$ |
| 3 | 7c | -2-Cl |
| 4 | 7d | -4-N, $N(CH_3)_2$ |
| 5 | 7e | -4-($OCH_3$) |
| 6 | 7f | -4-F |

The anticonvulsant activity of the synthesized compounds was determined by evaluation of the ability of the compounds to protect mice against convulsion induced by a lethal dose of isoniazidhydrazone (INH) and electroshock models. Diazepam was considered as a reference

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standard for anticonvulsant effect in all the models. The pharmacological result of all the newly synthesized compound was obtained with the benzodiazepine containing 4-methoxy group at aromatic ring had shown good anticonvulsant activity as compared with other. The compound was found to be less potent anticonvulsant as compared to diazepam.

2. Verma et al. reported the present work three different series of 1,5-benzodiazepine bearing various substitutions at 2 and 4 position of the benzodiazepine core were synthesized by condensing different substituted chalcones with o-phenylenediamine in the presence of piperidine as a base catalyst. All the synthesized compounds were subjected to in vivo neuropharmacological studies to screen their CNS depressant and anticonvulsant activity.

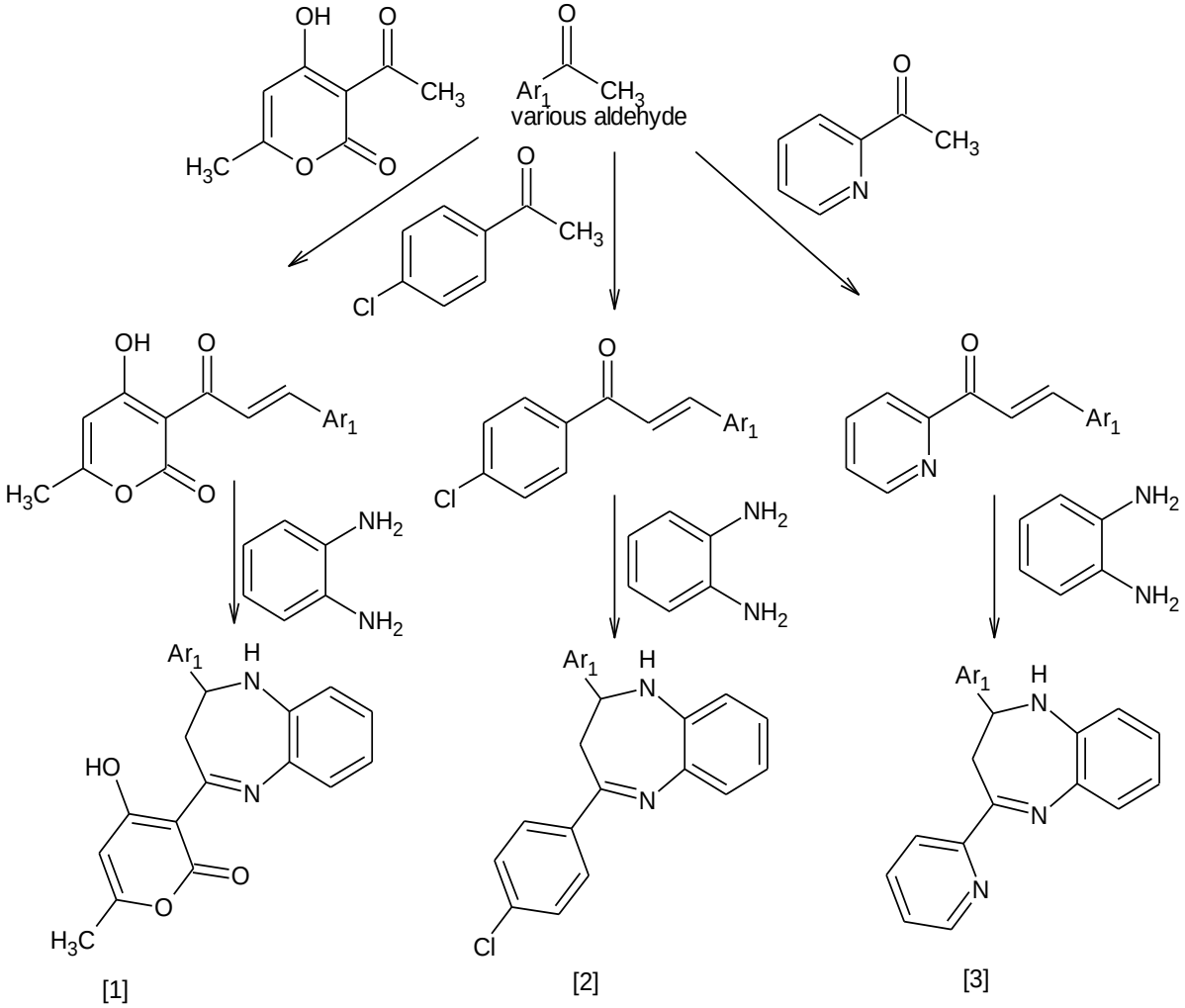


**Figure 5 synthesis of 1,5-benzodiazepine derivatives**

**Table 2: Derivatives of 1,5-benzodiazepine as CNS depressant and anticonvulsant agent.**
Incorporation of various substitution on aromatic ring i.e., $Ar_1$.

| **Compound no.** | **1** | **2** | **3** |
|---|---|---|---|
| **Ketone** | pyrano | p-chlorophenyl | pyridyl |
| **$Ar_1$** | $C_6H_5$ | $C_6H_5$ | $C_6H_5$ |
| **a** | 4-$OCH_3C_6H_5$ | 4-$OCH_3C_6H_5$ | 4-$OCH_3C_6H_5$ |
| | | 4-$NO_2C_6H_5$ | |
| **b** | 4-$NO_2C_6H_5$ | 4-Pyridyl$C_6H_5$ | 4-$NO_2C_6H_5$ |
| | 4-Pyridyl$C_6H_5$ | 2-Theinyl$C_6H_5$ | |

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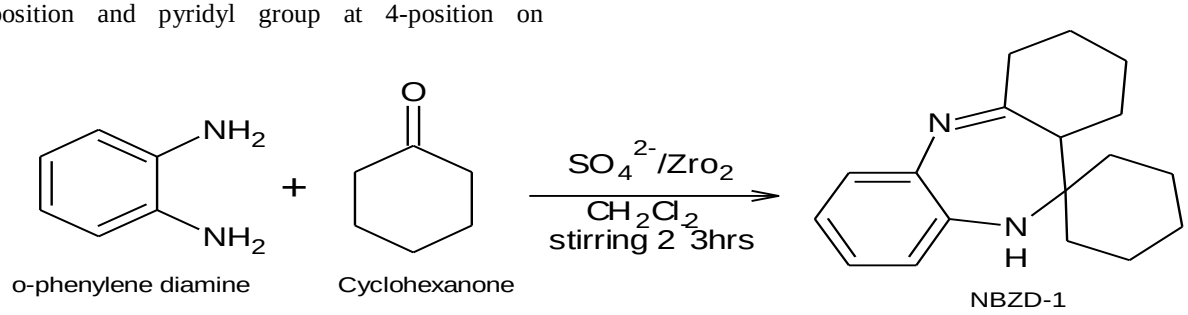
| | | | |
|---|---|---|---|
| **c**<br><br>**d**<br><br>**e** | - | | -<br>- |

All studies were carried out by using male rats the required number of groups of animals for both CNS depressant and anticonvulsant activity. The result of biological evaluation revealed that most of the tested compounds exhibited a decrease in the locomotor activity when compared with diazepam. Compound 3b containing 2- pyridyl and incorporation of acetoxy group on aromatic ring at 4-position it displayed a maximum decrease in locomotor activity which was close to the reference drug diazepam. After observing biological data, it was evident that compound possessing pyridine moiety attached to the position 2 of the benzodiazepine which display maximum inhibition of locomotor activity whereas, compound having pyrano or phenyl substitution revealed comparatively less potency. The anticonvulsant activity was monitored by employing the MES method. Compound containing p-chlorophenyl at 2 position and pyridyl group at 4-position on aromatic ring it displayed good anticonvulsant activity as compared to another synthesized derivative.

3.Pandeya et al. reported a synthesis of various Mannich and Schiff bases of 1,5-benzodiazepine as anticonvulsant agent. Synthesis of fused ring benzodiazepine nucleus in presence of zirconia involves 2 steps: first, preparation of catalyst and second, synthesis of benzodiazepine.

Preparation of catalyst by adding zirconium oxychloride was dissolved in doubly distilled water (pH-2). Dilute aq. ammonia was then added dropwise from a burette with vigorous (pH = 8). Precipitate was washed with distilled water several times and dried for 24 h. Sample was ground to fine powder and immersed in an 0.5 M H2SO4 solution (30 mL) for 30 min. Excess water was evaporated on water bath, and the resulting sample was oven dried.




o-phenylene diamine Cyclohexanone NBZD-1

Scheme 1: Synthesis of fused ring benzodiazepine.

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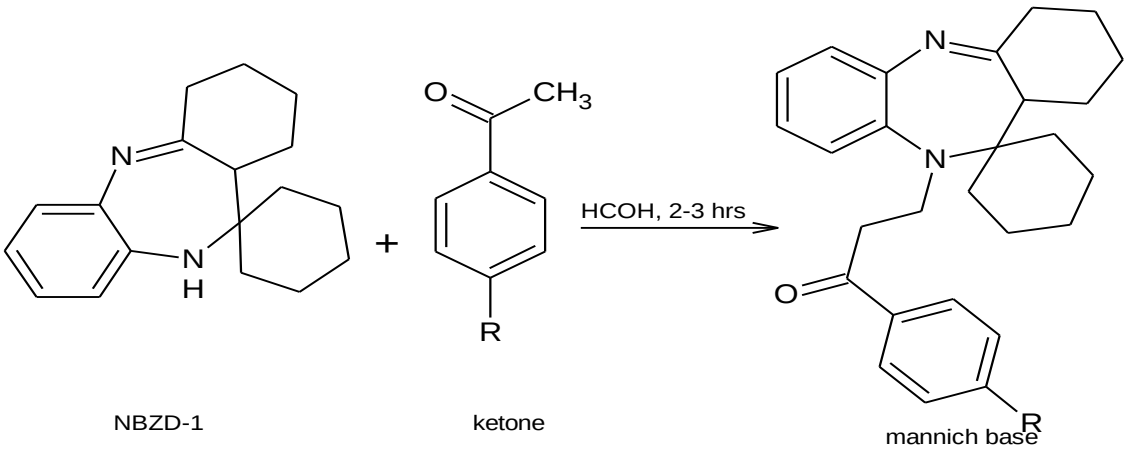
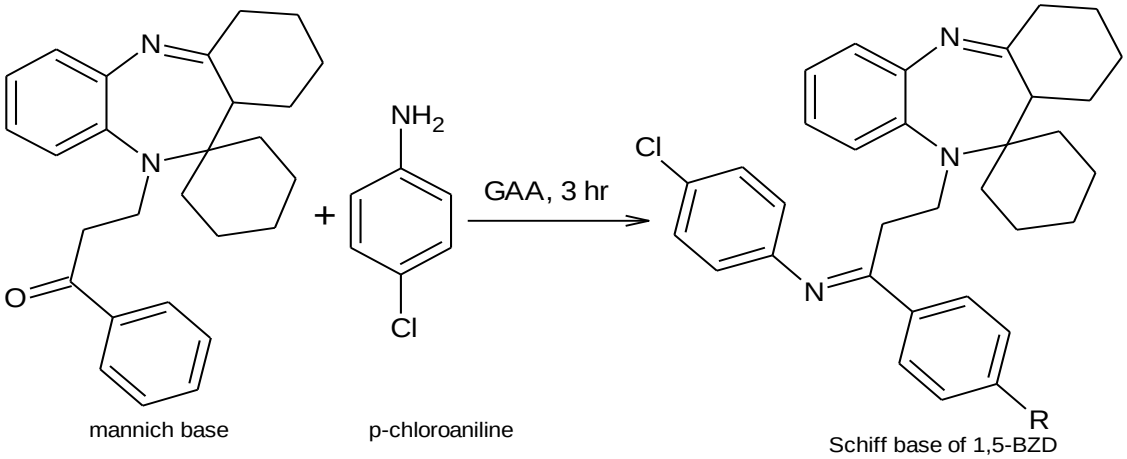



NBZD-1 ketone mannich base

R = H (NBZD-3),
R = Cl (NBZD-5)
R = NO2 (NBZD-4),

Scheme 2: Synthesis of various Mannich base derivatives of fused ring benzodiazepines.




mannich base p-chloroaniline Schiff base of 1,5-BZD

R = H (NBZD-6),
R = Cl (NBZD-8)
R = NO2 (NBZD-7),

Scheme 3: Synthesis of Schiff base derivative of fused ring benzodiazepine from p-chloroaniline

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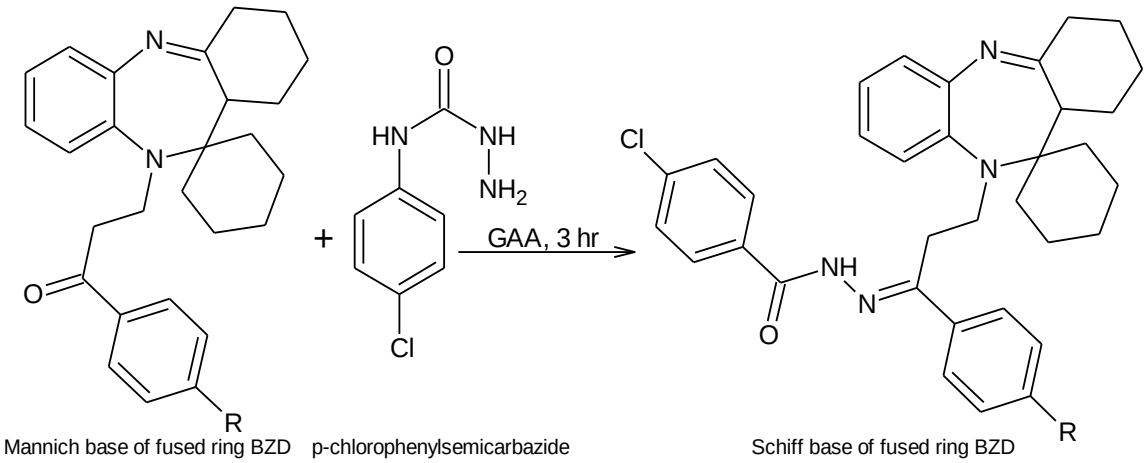
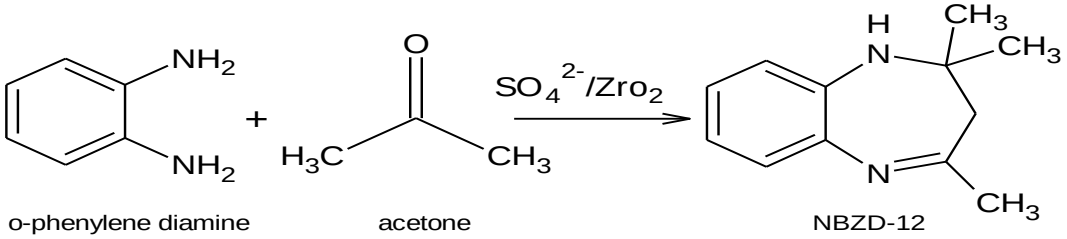
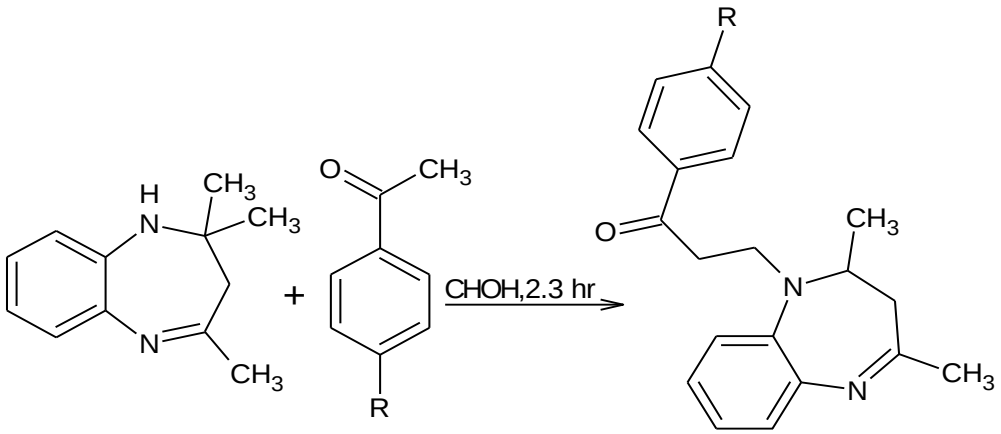



Scheme 4: Synthesis of Schiff base derivative of fused ring benzodiazepine from p-chlorophenylsemicarbazide.




Scheme 5: synthesis of 1,5-benzodiazepine




Scheme 6: Synthesis of various Mannich base derivatives of 1,5-benzodiazepines.

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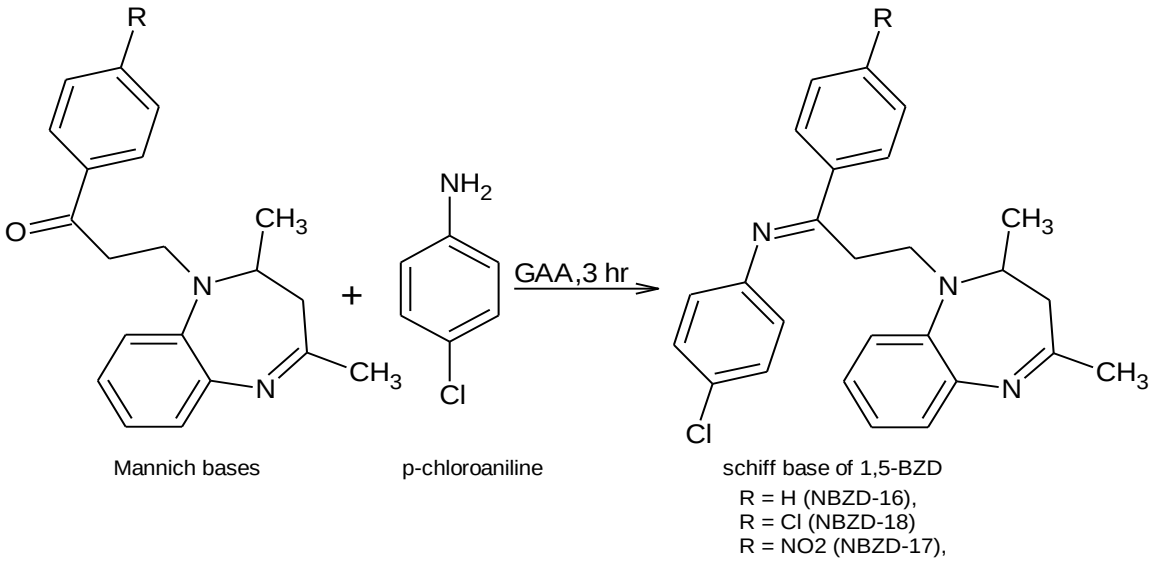
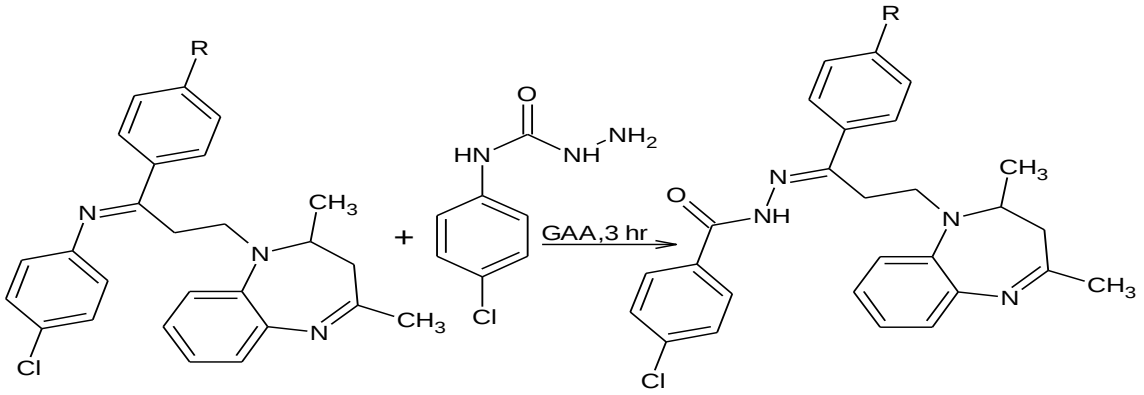



Mannich bases p-chloroaniline schiff base of 1,5-BZD

R = H (NBZD-16),
R = Cl (NBZD-18)
R = NO2 (NBZD-17),

Scheme 7: Synthesis of Schiff base derivative of 1,5-benzodiazepine from p-chloroaniline.




Mannich base of 1,5-BZD p-chlorophenylsemicarbazide Schiff base of 1,5-BZD

R = H (NBZD-19),
R = Cl (NBZD-21)
R = NO2 (NBZD-20)

Scheme 8: Synthesis of Schiff base derivative of 1,5-benzodiazepine from p-chlorophenylsemicarbazide.

**Figure 6 synthesis of 1,5-benzodiazepine derivatives**

All studies were carried out by using mice of about weight 22-25g the required number of groups of animals for anticonvulsant activity. All the synthesized 1,5-benzodiazepine derivatives were evaluated at the dose of 30 mg/kg b.w for anticonvulsant activity by isoniazid induced convulsion model and the compounds NBZD-3 and NBZD-8 were found to be most active among all compounds. Among all the synthesized 1,5-benzodiazepine derivatives, compounds NBZD-13 and NBZD-17 were found to be most active among all compounds using thiosemicarbazide induced model. Activity of the drugs interfering with motor coordination was moniter by the rotarod test. Among all the tested compounds none of the synthesized compounds were found to be neurotoxic at a dose of 30 mg/kg b.w. The compounds NBZD-1, NBZD-3, NBZD-4, NBZD-7, NBZD-11, NBZD-12, NBZD-14, NBZD-15, NBZD-17, NBZD-20, NBZD-21 were found to cause sedation. Although NBZD-8, NBZD-10, and NBZD-18 are the compounds which had shown good anticonvulsant activity and have an advantage over that, they were not sedative.

4.Nanchiket SD. et al. reported a solvent free synthesis and biological evaluation of 1,5-benzodiazepin as sedative activity.

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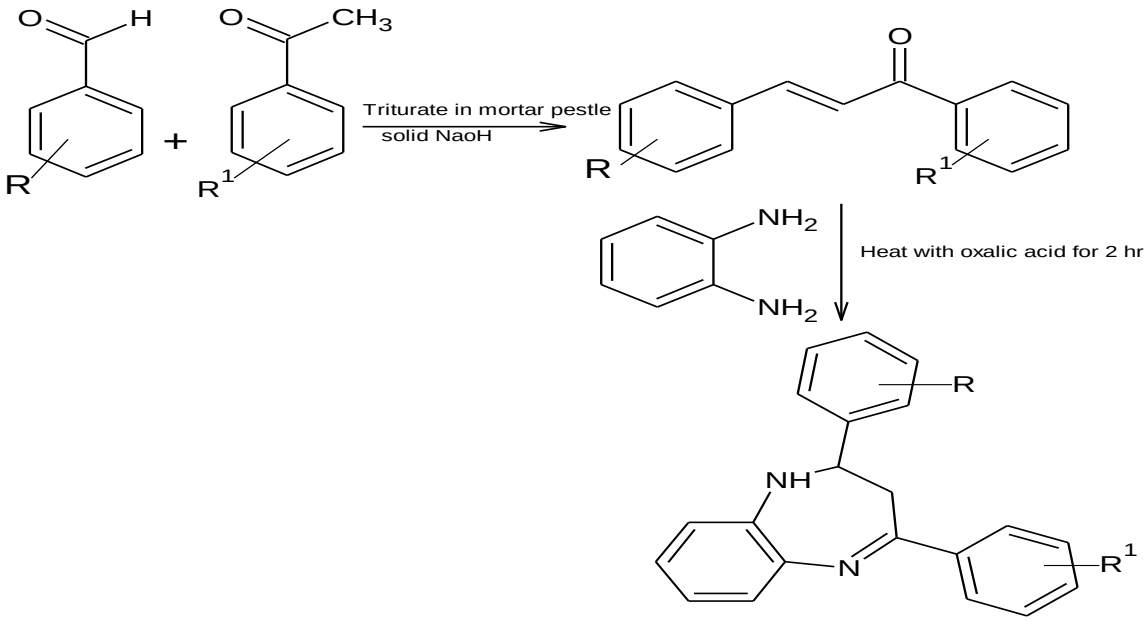


**Figure 7 synthesis of 1,5-benzodiazepine derivatives**

**Table 3: Derivatives of 1,5-benzodiazepine as sedative agent.**

| **Compound Code** | **-R** | **-R$^1$** |
|---|---|---|
| $A_1$ | o-OH | p-$OCH_3$ |
| $A_2$ | p-OH | p-$OCH_3$ |
| $A_3$ | H | p-$OCH_3$ |
| $A_4$ | o-OH | H |
| $A_5$ | p-OH | H |
| $A_6$ | H | H |

All the synthesized compounds were evaluated to sedative activity using spontaneous locomotor activity measurement by using actophotometer model. The number of locomotions counted and compared with Diazepam. Compounds A2, A4 and A5 shows significant sedative activity.

5.Kusanur et al. reported a Synthesis of spiro[indolo-1,5-benzodiazepines] from 3-acetyl coumarins for use as possible antianxiety agents. 3-Acetyl coumarins when allowed react with isatin gave corresponding 3-(3'-hydroxy-2'-oxo indolo) acetyl coumarins, which on dehydration afforded the corresponding α, β-unsaturated ketones. Cyclocondensation of unsaturated ketone with substituted o-phenylenediamines resulted in novel 3-coumarinyl spiro [indolo-1,5-benzodiazepine].

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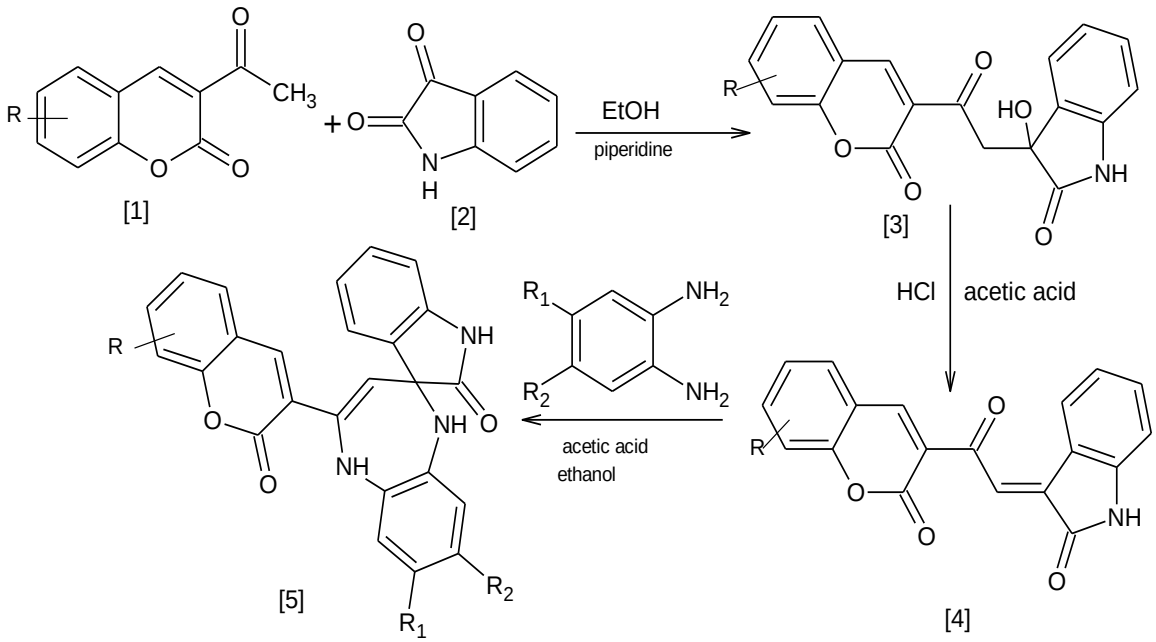


**Figure 8 synthesis of 1,5-benzodiazepine derivatives**

**Table 4: Derivatives of 1,5-benzodiazepine for antianxiety activity.**

| Sr.no. | Compound | R | $R_1$ | $R_2$ |
|---|---|---|---|---|
| 1 | 5a | H | H | H |
| 2 | 5b | H | $CH_3$ | $CH_3$ |
| 3 | 5c | 6-$CH_3$ | H | H |
| 4 | 5d | 6-$CH_3$ | $CH_3$ | $CH_3$ |
| 5 | 5e | 8-$OCH_3$ | H | H |
| 6 | 5f | 8-$OCH_3$ | $CH_3$ | $CH_3$ |
| 7 | 5g | 5,6-Benzo | H | H |
| 8 | 5h | 5,6-Benzo | $CH_3$ | $CH_3$ |
| 9 | 5i | 6-Cl | H | H |
| 10 | 5j | 6-Cl | $CH_3$ | $CH_3$ |
| 11 | 5k | 6-Br | H | H |
| 12 | 5l | 6-Br | $CH_3$ | $CH_3$ |

All the newly synthesized benzodiazepines were screened for their antianxiety activity on mice weighing 25 g were chosen and were sorted into five animals in a group using sodium pentobarbitone as the standard. They were allowed free access to food, water and libitum. Drugs or test samples in DMF were given at the dose of 20 mg/kg body weight.

Compound 5a with R = H, R1 = R2 = H have shown comparable activity with the standard and the other compounds are moderately active.

6.Subramanian et al. reported synthesis of 1, 5-benzodiazepines using the catalysts like Formic Acid and Glacial Acetic Acid and pharmacological activity are screened using animal models for muscle relaxant property and catatonic activity and are showing significant effect when compared with the standard drug diazepam.

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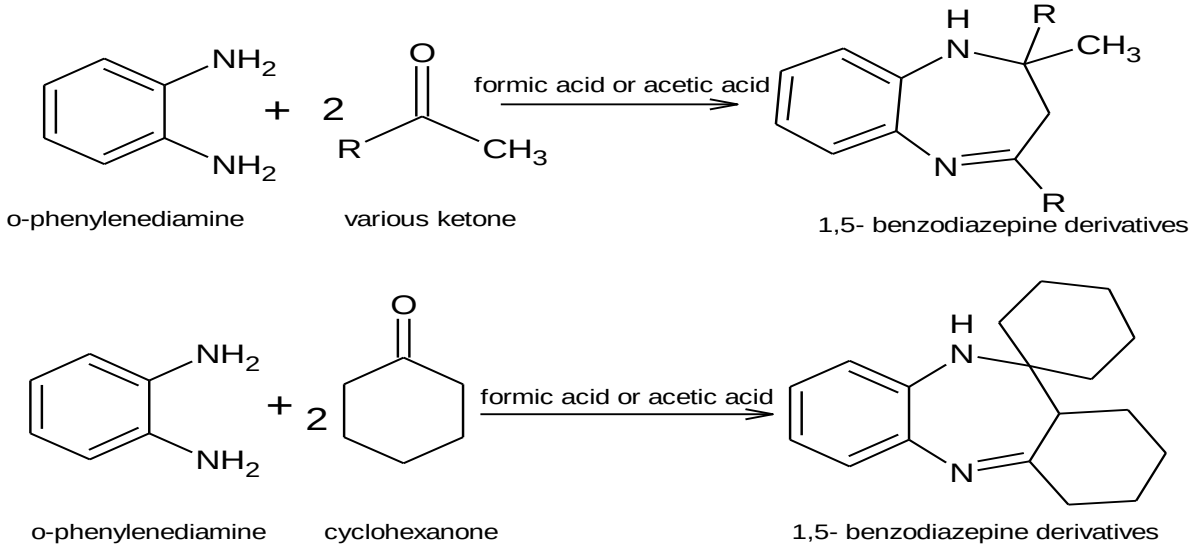


**Figure 10 synthesis of 1,5-benzodiazepine derivatives**

**Table 5: Derivatives of 1,5-benzodiazepine for muscle relaxant property.**

| Compound no. | Catalyst | R |
|---|---|---|
| $A_1$ | HCHO | $-CH_3$ |
| $A_2$ | $CH_3CHO$ | |
| $B_1$ | HCHO | $-C_6H_5$ |
| $B_2$ | $CH_3CHO$ | |
| $C_1$ | HCHO | Cyclohexanone |
| $C_2$ | $CH_3CHO$ | |

Synthesized compounds when evaluated for acute toxicity are found to be safe for animal studies at concentrations less than 5mg/kg. Further they were evaluated for Muscle relaxant property by using Rotarod Apparatus and catatonic activity. All three compounds are found to be producing moderately significant activity when compared to the standard drug diazepam. The compound A was found to be more active among all three synthesized compounds.

**1.ANTI-INFLAMMATORY ACTIVITY OF 1,5-BENZODIAZEPINE**

1. BhatIshwar et al. reported the synthesis of novel derivatives of 1,5-benzodiazepine derived from various substituted chalcones to improve the biological spectrum of benzodiazepine. The substituted compound was prepared by condensing cinnamaldehyde with various aromatic ketone in the presence of 20% NaOH as base. The formation of intermediate compound was treated with o-phenylenediamine in presence of NaOH as base resulted in various diazepine derivatives.

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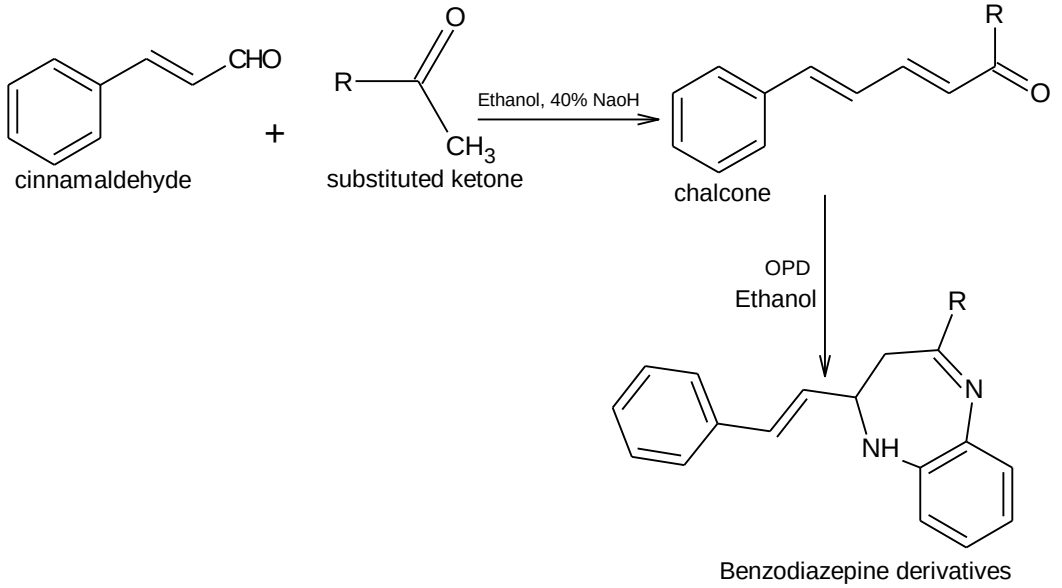


**Figure 11 synthesis of 1,5-benzodiazepine derivatives**

**Table 6: Derivatives of 1,5-benzodiazepine for anti-inflammatory activity.**
Where R is substituted as different substitution on aromatic ring at different position

| **Compound No.** | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **R ($C_6H_5$)** | H | 4-$OCH_3$ | 4-$CH_3$ | 4-$NO_2$ | 4-Cl | 4-$NH_2$ | 3-$NO_2$ | 3-$NH_3$ | 4-F | 2-Br | 2,4-Cl | 3,4-Cl |

The compounds 4, 5, 7, 9, 10, 11, and 12 containing 4-nitrophenyl, 4-chlorophenyl, 3-nitrophenyl, 4-fluorophenyl, 4-bromophenyl and 3-chlorophenyl benzodiazepine derivatives exhibited significant anti-inflammatory activity compared with the standard diclofenac sodium. The presence of electron withdrawing groups such aschloro,fluoro,nitro and bromo resulted in increased anti-inflammatory activity. After synthesized some novel 1,5 benzodiazepine derivatives from chalcone only this compound showed significant anti-inflammatory activity whereas remaining compound showed poor anti-inflammatory activity.

2. Sang Keun et al. reported a new series of 1,5-benzodiazepines that demonstrate anti-neuroinflammatory activity. In this study they designed benzodiazepine derivatives to identify novel neuroprotective agent. 2,3-dihydro-1,5-benzodiazepine synthesized by treating o-phenylenediamine with various ketone in presence of silica gel-supported sulfuric acid as a catalyst in methanol.

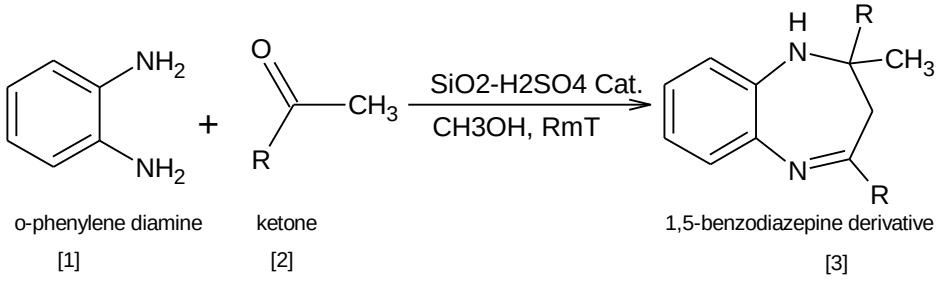


**Figure 12 synthesis of 1,5-benzodiazepine derivatives**

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**Table 7: Derivatives of 1,5-benzodiazepine for anti-neuroinflammatory activity.**

| Sr. no. | Compound | R |
|---|---|---|
| 1 | 3a | Methyl |
| 2 | 3b | Ethyl |
| 3 | 3c | Phenyl |
| 4 | 3d | Isopropyl |
| 5 | 3e | 2-thiophenyl |
| 6 | 3f | 3-thiophenyl |
| 7 | 3g | 4-chlorophenyl |
| 8 | 3h | 3-chlorophenyl |
| 9 | 3i | 4-methylphenyl |
| 10 | 3j | 2-nitrophenyl |

The inhibitory activity of 1,5-benzodiazepine varied according to the structure of R. The highest inhibitory effect among the compound tested in this study was obtained with the benzodiazepine containing 2-thiophenyl ring whereas 3-thiophenyl gives poor inhibitory activity it might be due to electronic effects.The benzodiazepine containing a phenyl ring at the R position showed better effect as anti-neuroinflammatory as compared with alkyl groups.

**C.ANTIMICROBIAL ACTIVITY OF 1,5 BENZODIAZEPINE**

1. Konda et al. reported a new series of imidazolecontaining 1,5- benzodiazepine have been synthesized by the condensation of chalcones with o-phenylenediamine using piperidine in polyethylene glycol (PEG400) as an efficient and green reaction solvent. A new class of 1,5-benzodiaepine derivative that demonstrate antimicrobial activity.

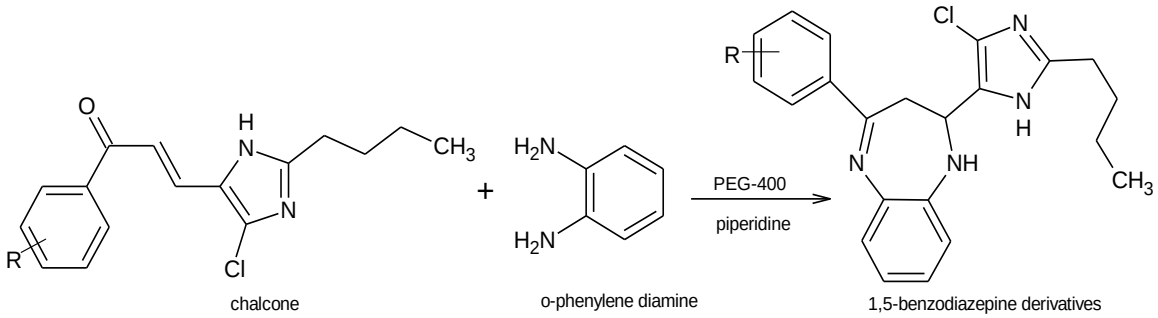


**Figure 13 synthesis of 1,5-benzodiazepine derivatives**

**Table 8: Derivatives of 1,5-benzodiazepine for antimicrobial activity.**

Where, 2,3,4 and 5 is the incorporation of various substitution on aromatic ring,

| Compound no. | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Position 2** | OH | - | OH | OH | OH | OH | OH | OH | OH | OH | OH | OH |
| **Position 3** | - | - | I | Br | - | I | Br | I | Br | I | Br | Cl |
| **Position 4** | - | Cl | - | - | $CH_3$ | $CH_3$ | - | - | - | - | - | - |
| **Position 5** | Cl | - | Cl | Cl | Cl | Cl | Cl | $CH_3$ | $CH_3$ | I | Br | Cl |

The compound 3, 4, 10, 11, 12 containing 2-hydroxy-3-iodo-5-chlorophenyl, 2-hydroxy-3-bromo-5-chlorophenyl, 2-hydroxy-3,5-diiodophenyl, 2-hydroxy-3,5-dibromophenyl, 2-hydroxy-3,5-dichlorophenyl benzodiazepine derivatives exhibited good antifungal and antibacterial activity.

2. Lan-Zhi Wang et al. reported a synthesis of 1,5-Benzodiazepine derivatives as potential antimicrobial agents.

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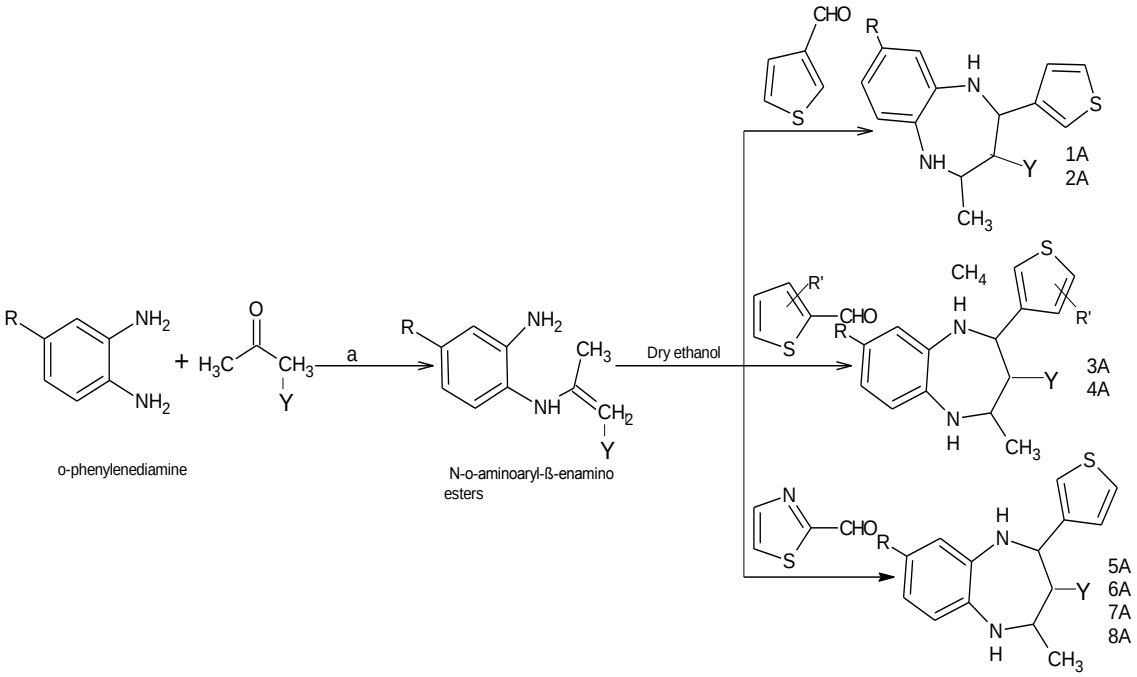
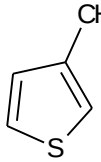
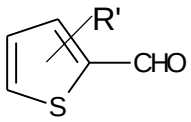
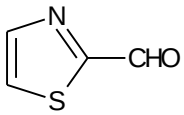



**Figure 14 synthesis of 1,5-benzodiazepine derivatives**

**Table 9: Derivatives of 1,5-benzodiazepine for anti-microbial activity.**

| Compound | Derivatives | R | R' | Y | Aldehyde ring |
|---|---|---|---|---|---|
| 1A | 1Aa | H | | $COOC_2H_5$ |  |
| | 1Ab | $CH_3$ | | | |
| | 1Ac | Br | | | |
| 2A | 2Aa | H | | $COOCH_3$ | |
| | 2Ab | $CH_3$ | | | |
| 3A | 3Aa | H | H | $COOC_2H_5$ |  |
| | 3Ab | $CH_3$ | 3-$CH_3$ | | |
| | 3Ac | Br | 5-$CH_3$ | | |
| 4A | 4Aa | H | H | $COOCH_3$ | |
| | 4Ab | $CH_3$ | H | | |
| 5A | 5Aa | H | | $COOC_2H_5$ |  |
| | 5Ab | $CH_3$ | | | |
| | 5Ac | Br | | | |
| | 5Ad | F | | | |
| 6A | 6Aa | H | | $COOCH_3$ | |
| | 6Ab | $CH_3$ | | | |
| | 6Ac | Br | | | |
| 7A | 7Aa | H | | $COOCH_2CH_2CH_3$ | |
| | 7Ab | $CH_3$ | | | |
| 8A | 8Aa | H | | $COOCH(CH_3)_2$ | |
| | 8Ab | $CH_3$ | | | |

The target compounds 1A-8A were evaluated for their in vitro antibacterial activities using the disk-diffusion method at a concentration of 200µg per disc. Among compounds 1Aa-1Ac with 3-thienyl group at the $C_2$-position, compounds 1Aa and 1Ab showed moderate to high activity

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against all tested fungi and slight broad-spectrum activity against all tested bacteria, whereas compound 1Ac was found inactive against the tested microorganisms. In general, 1Aa and 1Ab exhibited better antimicrobial activity against fungi than against bacteria. Compounds 3Ab–3Ac presented a methyl substituent at positions 3 or 5 on the thiophene ring. These compounds showed obvious inhibition potency and specificity to C. albicans alone except 3Ac. Compounds 5Aa–5Ad, which were composed of 2-thiazolyl at the $C_2$-position, showed good to excellent antimicrobial activity against all of the tested microorganisms.

Among the all synthesize compounds screened, compounds 5Aa, 5Ab, 6Aa, 7Aa, 7Ab and 8Aa exhibit remarkable antimicrobial activities at different concentrations.

3.Ying-shuang An et al. reported a series of novel 1,5-benzodiazepine derivatives as potential antimicrobial agent. 1,5-benzodiazepine have been synthesized by stirring mixture of ethyl acetoacetate with various o-phenylenediamine then addition of a pyridine aldehyde and PMA in dry ethanol it's form different novel derivatives.

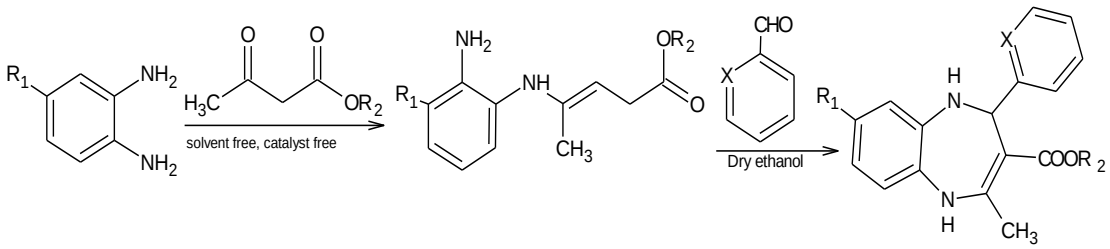


**Figure 15 synthesis of 1,5-benzodiazepine derivatives**

**Table 10: Derivatives of 1,5-benzodiazepine for anti-microbial activity.**

| Compound | $R_1$ | X | $R_2$ |
|---|---|---|---|
| 2a | H | N | $-CH_2CH_3$ |
| 2b | $CH_3$ | N | $-CH_2CH_3$ |
| 2c | F | N | $-CH_2CH_3$ |
| 2d | Br | N | $-CH_2CH_3$ |
| 2e | H | C | $-CH_2CH_3$ |
| 2f | $CH_3$ | C | $-CH_2CH_3$ |
| 2g | Br | C | $-CH_2CH_3$ |
| 3a | H | N | $-CH_3$ |
| .3b | $CH_3$ | N | $-CH_3$ |
| 3c | F | N | $-CH_3$ |
| 3d | Br | N | $-CH_3$ |
| 4a | H | N | $-CH_2CH_2CH_3$ |
| 4b | $CH_3$ | N | $-CH_2CH_2CH_3$ |
| 4c | F | N | $-CH_2CH_2CH_3$ |
| 4d | Br | N | $-CH_2CH_2CH_3$ |
| 5a | H | N | $-CH\ (CH_3)_2$ |
| 5b | $CH_3$ | N | $-CH\ (CH_3)_2$ |
| 5c | F | N | $-CH\ (CH_3)_2$ |
| 5d | Br | N | $-CH\ (CH_3)_2$ |

The pharmacological effect of novel 1,5 -benzodiazepine derivatives was synthesized compound obtained with the among all the synthesized compound 2b showed the highest antimicrobial activity and compound 2a, 2c, 2d, 3a, 3b and 4b show excellent antimicrobial activity. It revealed that the 1,5-benzodiazepine derivatives containing pyridine ring had good antimicrobial activity.

4.Shaikh et al. reported a new class of 1,5-benzodiazepine demonstrate the antibacterial and antifungal activities of synthesized compound. A new class of some new 2,3-dihydro-1,5-benzodiazepine has been synthesized using condensation reaction of o-phenylenediamine and

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various substituted chalcones in presence of DMF as solvent.

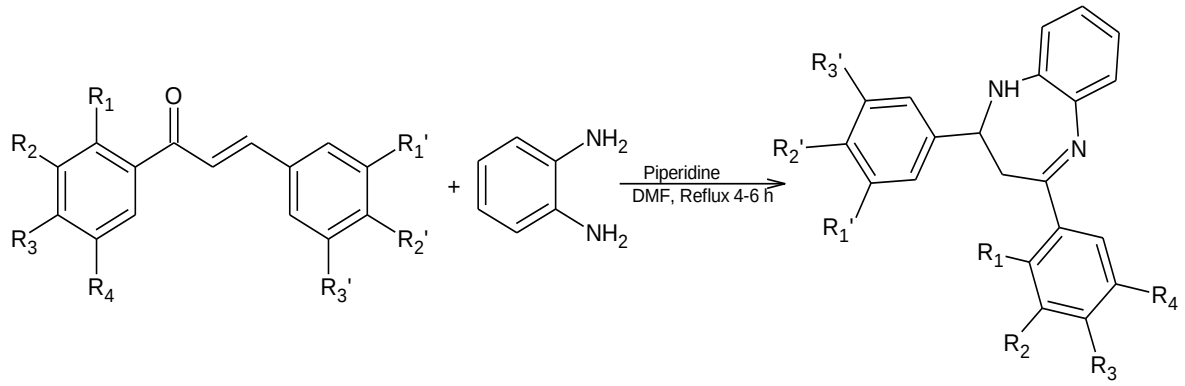


**Figure 16 synthesis of 1, 5-benzodiazepine derivatives**

**Table 11: Derivatives of 1,5-benzodiazepine for anti-microbial activity.**

| **Compound no.** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** |
|---|---|---|---|---|---|---|---|---|---|---|
| **$R_1$** | OH | OH | OH | H | H | OH | OH | OH | OH | OH |
| **$R_2$** | Br | Br | I | I | Br | I | I | I | Br | Br |
| **$R_3$** | $CH_3$ | H | H | OH | OH | OH | H | H | H | H |
| **$R_4$** | Cl | $CH_3$ | I | I | Br | I | Cl | I | Cl | Cl |
| **$R'_1$** | $OCH_3$ | $OCH_3$ | $OCH_3$ | $OCH_3$ | $OCH_3$ | $OCH_3$ | $OCH_3$ | $OCH_3$ | $OCH_3$ | $OCH_3$ |
| **$R'_2$** | $OCH_3$ | $OCH_3$ | $OCH_3$ | $OCH_3$ | $OCH_3$ | $OCH_3$ | $OCH_3$ | $OCH_3$ | $OCH_3$ | $OCH_3$ |
| **$R'_3$** | H | H | $OCH_3$ | $OCH_3$ | $OCH_3$ | H | H | H | H | $OCH_3$ |

The result of biological evaluation revealed that the compound showed significant antimicrobial activity. In particular compound 1, 2, 3, 4, and 5 showed good to moderate antimicrobial activity against the entire organism employed. The compound 1, 2, 3, 4, 6, 7, 8, and 9 containing 2,3-dihydroxy-1,5-benzodiazepine derivative exhibited good to moderate antibacterial activity against the entire organism employed.

5.Thakrar et al. reported a new series of highly functionalized 1,5-benzodiazepine derivatives have been synthesized from 3-acetyl-4-hydroxy coumarin which is reacted with o-phenylenediamine in ethanol then formation of some intermediate it further reacted with substituted pyrazole aldehyde in methanol. They report the synthesis of pyrazole containing 1,5-benzodiazepine by screening for their antimicrobial and antifungal activity.

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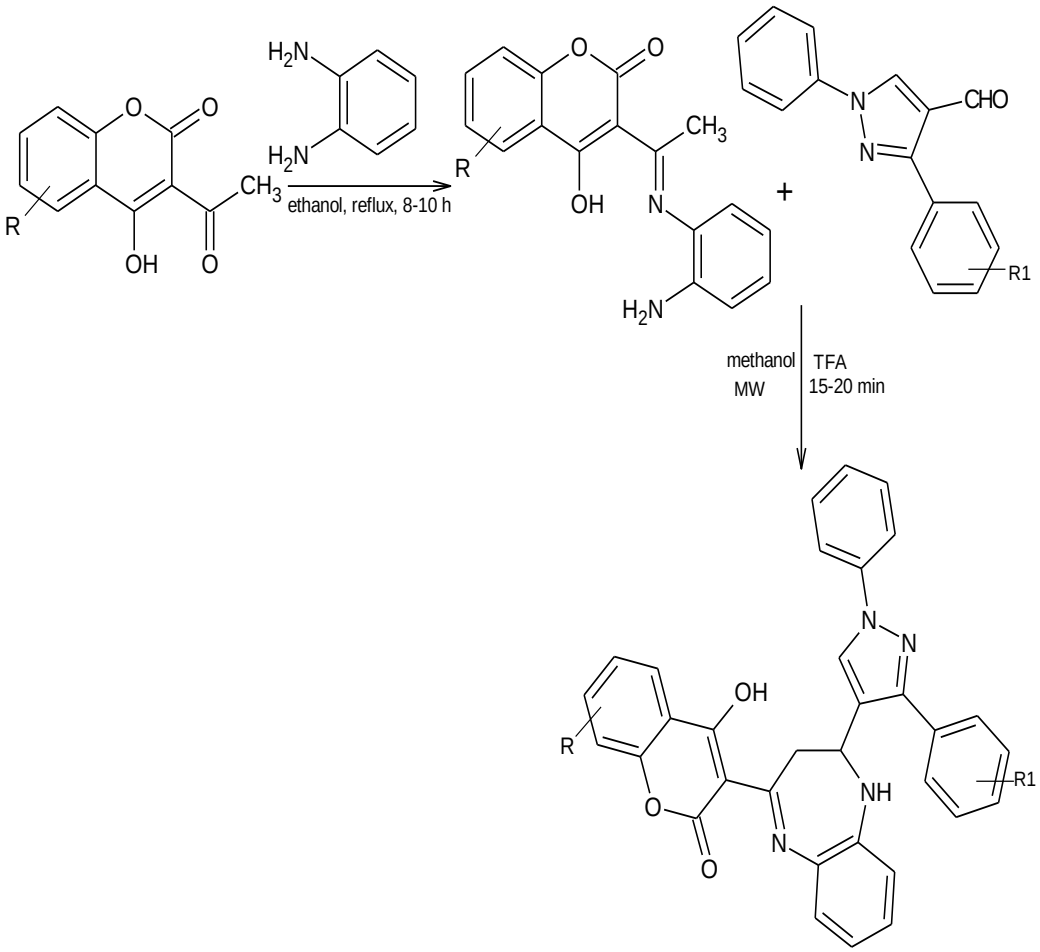


**Figure 17 synthesis of 1,5-benzodiazepine derivatives**

**Table 12: Derivatives of 1,5-benzodiazepine for anti-microbial activity.**

| **Compound no.** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** |
|---|---|---|---|---|---|---|---|---|---|---|
| **$R_1$** | H | 4-F | H | 4-$NO_2$ | 3-$NO_2$ | 4-F | 4-Cl | 3-$NO_2$ | 4-F | 3-$NO_2$ |
| **R** | H | H | 8-$CH_3$ | 8-$CH_3$ | 8-$CH_3$ | 8-$CH_3$ | 5,8-di$CH_3$ | 5,8-di$CH_3$ | 5,8-di$CH_3$ | H |

The antimicrobial activity of novel 1,5-benzodiazepine derivative was evaluated against various bacteria and fungi. Compound 10 seems to be most active among the whole data series because it has shown potency to all four strains, whereas compound 2, 3, 4, 5, 6, and 9 are moderately active molecules. Compound 10 can be optimized for the broad spectrum of activity. Herein -$NO_2$ strong electron donating group at 3 position shown more potency.

6.Palonisamy et al. reported a series of novel 1,5-benzodiazepine derivatives containing thiochromenoand benzothiepino moieties. They demonstrate antimicrobial activity of synthesized compounds.

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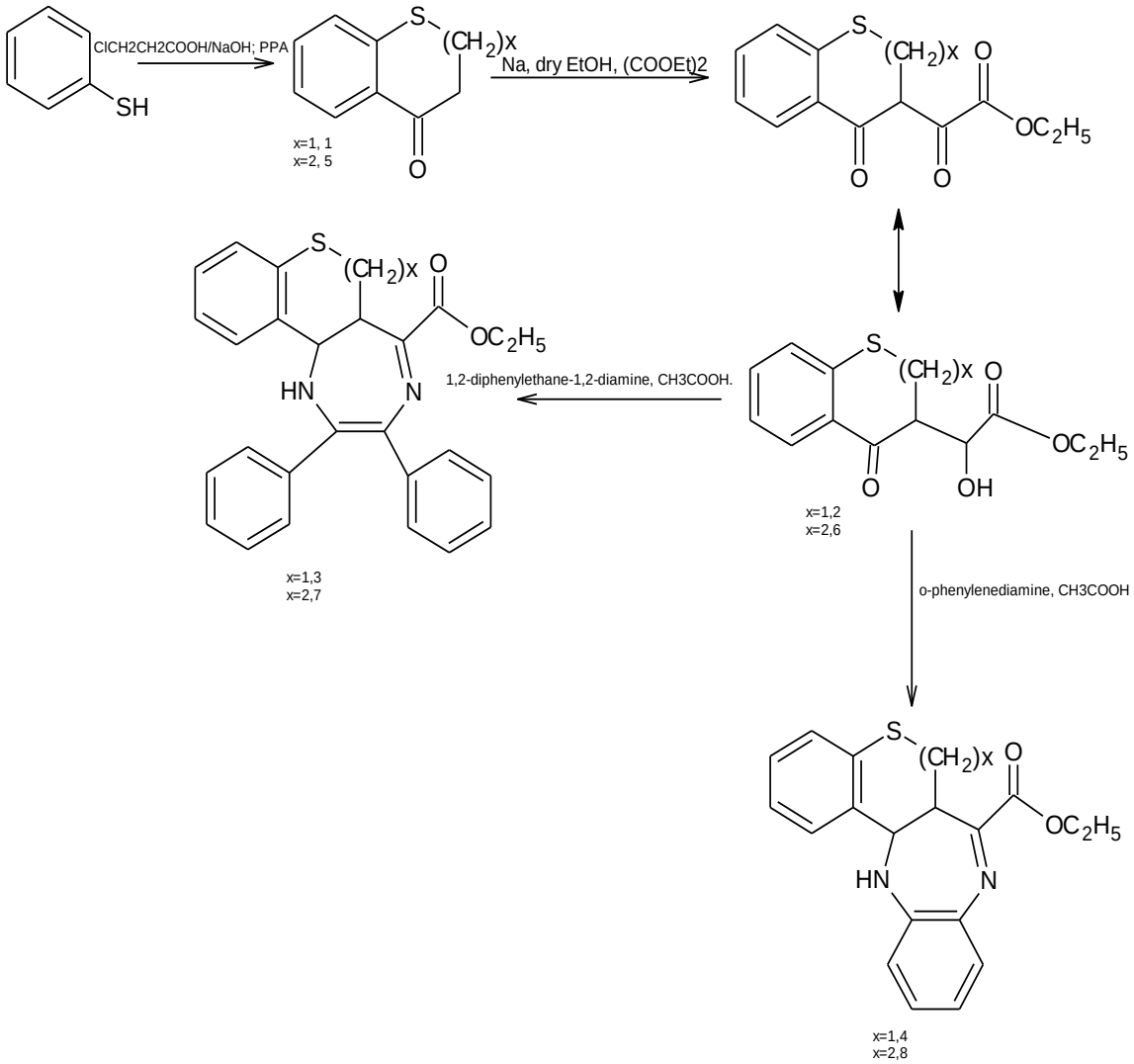


**Figure 18 Synthesis of 1,5-benzodiazepine derivatives**

An agar-diffusion method was used for the determination of the preliminary antibacterial and antifungal activity. Amikacin, chloramphenicol, and clotrimazole were used as reference drugs. The results were recorded for each tested compound as the average diameter of inhibition zones (IZ) of bacterial or fungal growth around the discs in mm. The minimum inhibitory concentration (MIC) measurement for these compounds showed significant growth inhibition zones (>20 mm) by a two-fold serial dilution method. The result of synthesized novel benzodiazepine compound produces more inhibitory activity then pyrazole, isoxazole and pyrimidine derivatives.

8.Varala et al. reported synthesis of some 1,5-benzodiazepine derivatives as a new Class of Antimicrobial Agents. It is synthesized by treating substituted o-phenylenediamine with substituted acetophenone in presence of ceric ammoniumnitrate as a catalyst.

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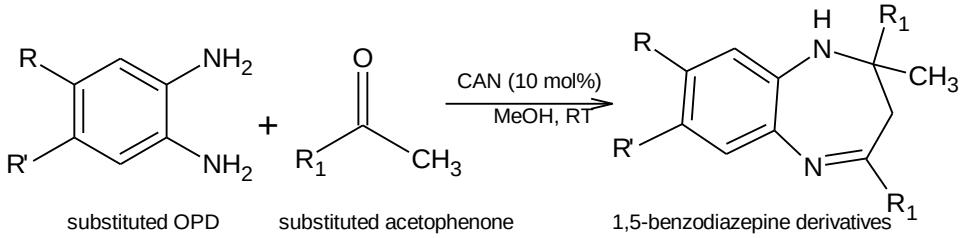


**Figure 19 synthesis of 1,5-benzodiazepine derivatives**

**Table 13: Derivatives of 1,5-benzodiazepine for anti-microbial activity.**

| Compound | R | R' | $R_1$ |
|---|---|---|---|
| A | H | H | p-$OHC_6H_5$ |
| B | Cl | Cl | p-$CH_3C_6H_5$ |
| C | H | H | p-$BrC_6H_5$ |
| D | H | H | p-$FC_6H_5$ |
| E | H | H | p-$IC_6H_5$ |
| F | Cl | Cl | $CH_3$ |
| G | H | H | $C_6H_5$ |
| H | $CH_3$ | $CH_3$ | p-$CH_3C_6H_5$ |
| I | H | H | p-$ClC_6H_5$ |
| J | H | H | p-$CH_3C_6H_5$ |
| K | H | H | p-$NO_2C_6H_5$ |

The compounds were active against all the tested microorganisms when compared with ciprofloxacin drug as standard. The in vitro antifungal and antibacterial activities of the compounds were tested by paper disc diffusion method. The minimum inhibitory concentration (MIC) of all the synthesized compounds was also determined by agar streak dilution method. Compound E (p-I $C_6H_5$) was found to exhibit the most potent in vitro antimicrobial activity. All the compounds exhibited potent antibacterial activity but less antifungal property.

9. Sharma et al. reported synthesis of 1,5-benzodiazepine derivatives from chalcone and o-phenylenediamine and evaluated their pharmacological activity as antibacterial activity.

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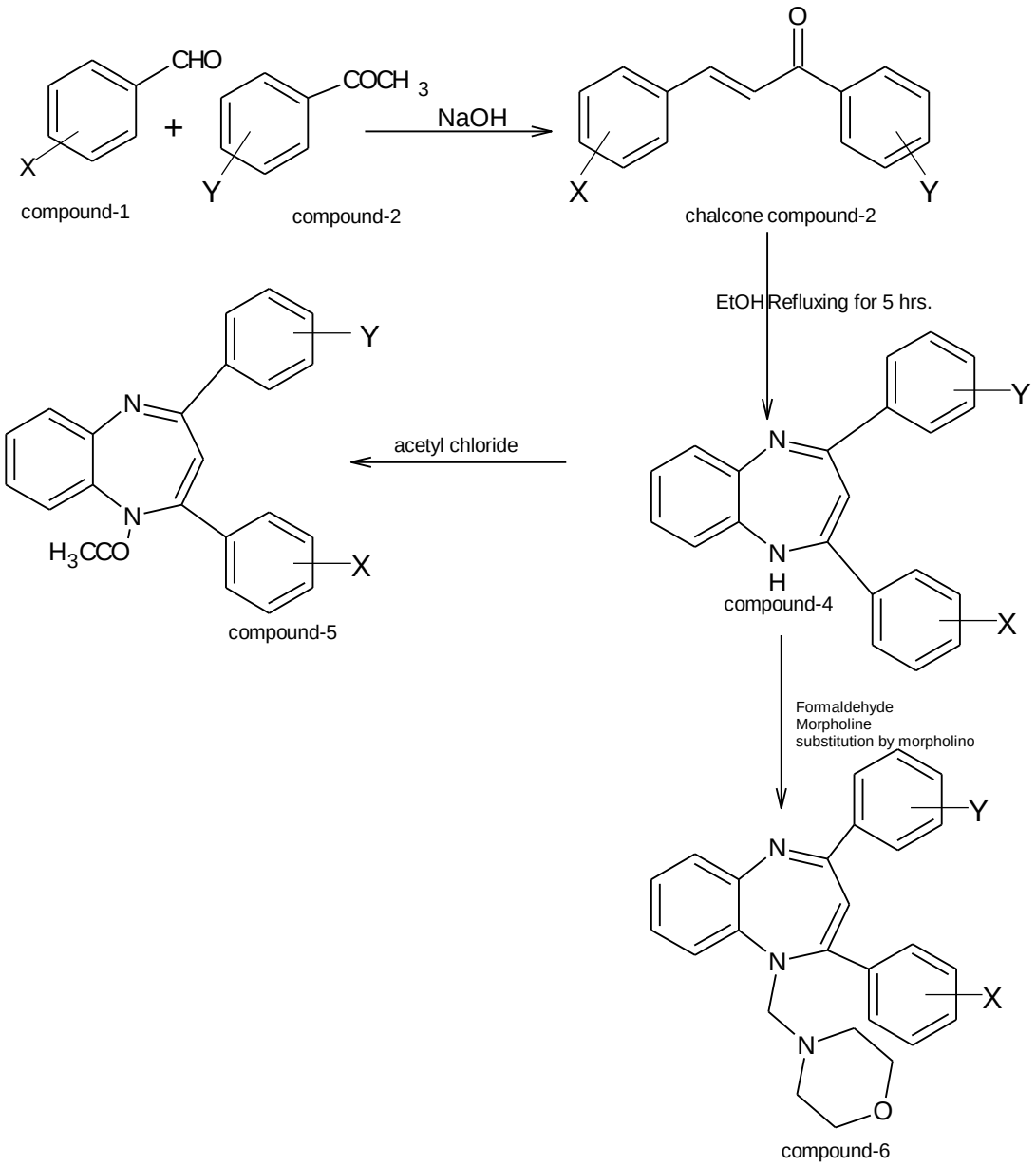


**Figure 20 synthesis of 1,5-benzodiazepine derivatives**

**Table 14: Derivatives of 1,5-benzodiazepine for anti-microbial activity.**

| Sr. No. | Compound | | X | Y |
|---|---|---|---|---|
| 1 | 5a | 6a | 4-$OCH_3$ | 4-F |
| 2 | 5b | 6b | 4-$OCH_3$ | 4-H |
| 3 | 5c | 6c | 4-F | 4-H |
| 4 | 5d | 6d | 4-$OCH_3$ | 4-Br |
| 5 | 5e | 6e | 4-$OCH_3$ | 4-Cl |
| 6 | 5f | 6f | 4-F | 4-H |
| 7 | 5g | 6g | 4-Cl | 4-h |
| 8 | 5h | 6h | Furyl | 4-Br |
| 9 | 5i | 6i | Furyl | 4-F |

| | | | | |
|---|---|---|---|---|
| 10 | 5j | 6j | Furyl | 4-Cl |

The result of biological evaluation revealed that the compound showed significant antimicrobial activity. All the synthesized compounds were evaluated in vitro for antibacterial activity by using filter paper disc method against different strains of bacteria. All the compounds test along with standard antibacterial ampicillin were used at 100, 200,300,400 concentrations. Compounds with electron releasing groups such as methoxy, hydroxyl showed better antibacterial activity than the others not having such groups. Compounds having pharmacophores such as cholro, dichloro and fluoro groups have exhibited more activity on all the three bacteria than the others.

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## REFERENCES:

[1]. AtwalKS.,Bergy JL. andHedberg 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. 1987; 30, 635.

[2]. Varala R., KotraV. And Engula R. Synthesis of some 1, 5-benzodiazepine derivatives as a new class of antimicrobial agents. Asian Journal of chemistry. 2007; 19 (7): 5435-5442.

[3]. Ghogare JG., Bhandari SV., et al. Design, synthesis and pharmacological screening of potential anticonvulsant agents using hybrid approach, European Journal of Medicinal Chemistry. 2010; 45: 857–863.

[4]. Verma R., Bhatia R., et al. Design, Synthesis and Neuropharmacological Evaluation of New 2,4-Disbsituted-1,5-Benzodiazepines as CNS Active Agents. Bioorganic Chemistry. 2020.

[5]. Pandeya SN. and Rajput N. Synthesis and Anticonvulsant Activity of Various Mannich and Schiff Bases of 1,5-Benzodiazepines. Hindawi Publishing Corporation, International Journal of Medicinal Chemistry. 2012; 1-10.

[6]. Kusanur RA., Ghate M. and Kulkarni MV. Synthesis of spiro[indolo-1,5-benzodiazepines] from 3-acetyl coumarins for use as possible antianxiety agents. Journal of Chemical Sciences. 2004; 116(5): 265–270.

[7]. Nachiket SD., AtulKW., and Deepak SM. Solvent Free Synthesis and Biological Evaluation Of 1, 5-Benzodiazepine. Nano Sci Nano Technol. 2017; 11(1): 112.

[8]. Subramanian SN.,Suvarna MC.,et al. Effectof Catalyston Synthesis of 1, 5-Benzodiazepine Derivatives and Evaluation of their Pharmacological Activity. Indo American Journal of Pharmaceutical Research. 2017

[9]. Bhat IK., Kumar A. Synthesis and Anti-inflammatory Activity of Some Novel 1,5 Benzodiazepine Derivatives. Asian J Pharm Clin Res. 2016; 9(4): 63-66.

[10]. Sang KH.,Donthabhaktuni S., et al. Anti-neuroinflammatory activity of 1,5-benzodiazepine derivatives. Bioorganic & Medicinal Chemistry Letters.2010; 20: 3969–3971.

[11]. Steffan RJ. andFailli AA. Preparation of pyrrolebenzodiazepinecarboxamide vasopressin agonists. PCT Int. App.2000; 228, 46.

[12]. Wang LZ., Xiao-Qing L. and Ying SA. 1,5-Benzodiazepine derivatives as potential antimicrobial agents: design, synthesis, biological evaluation, and structure–activity relationships. Organic &Biomolecular Chemistry. 2015.

[13]. Konda SG., Shaikh BM. et al. Polyethylene glycol (PEG-400): An efficient and recyclable reaction medium for the synthesis of novel 1; 5-benzodiazepines and their antimicrobial activity. Chinese Chemical Letters.2011; 22: 65–68.

[14]. Ying-shuang A., Zhen-fang H., et al. Efficient Synthesis and Biological Evaluation of a Novel Series of 1,5-Benzodiazepine Derivatives as Potential Antimicrobial Agents. ChemBiol Drug Des. 2016; 88: 110–121

[15]. Shaikh S. and Baseer MA. Synthesis and Antimicrobial Activity of Some New 2, 3-Dihydro-1, 5- Benzodiazepine Derivatives. IJPSR. 2013; 4(7): 2717-2720.

[16]. Thakrar S., Bavishi A., et al. Microwave-Assisted Rapid Synthesis of Novel 1,5-Benzodiazepine Derivatives as Potent Antimicrobial Agent. J. Heterocyclic Chem.2013; 50: E73.
[17]. Pandaram P., Samson J. et al. Synthesis, characterization, antimicrobial, anticancer, and antituberculosis activity of some new pyrazole, isoxazole, pyrimidine and benzodiazepine derivatives containing thiochromeno and benzothiepino moieties. The Royal Society of Chemistry. 2013.
[18]. Sharma S., Jain R., and Chawla C. Synthesis and Biological Activities of Some Benzodiazepine Derivatives. Journal of Chemical and Pharmaceutical Research. 2013; 5(7): 46-55.
[19]. SinglaRK.,Bhat V., et al. An Efficient Synthesis of 1,5-Benzodiazepine Derivatives Catalyzed by Potassium Aluminium SulfateDodecahydrate& Evaluation of Their Antioxidant Activity. Indo Global Journal of Pharmaceutical Sciences. 2012; 2(3): 279-285.
[20]. Yaddarapudi P., KottapalliRS.,Jagalapudi VS. 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. 2012; 105-109.
[21]. Steffan RJ. andFailli AA. Preparation of pyrrolebenzodiazepinecarboxamide vasopressin agonists. PCT Int. App.2000; 228, 46.