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# NOVEL ANALOGUES OF 1,5-BENZODIAZEPINE: SYNTHESIS, CHARACTERIZATION, AND ANTIMICROBIAL EVALUATION

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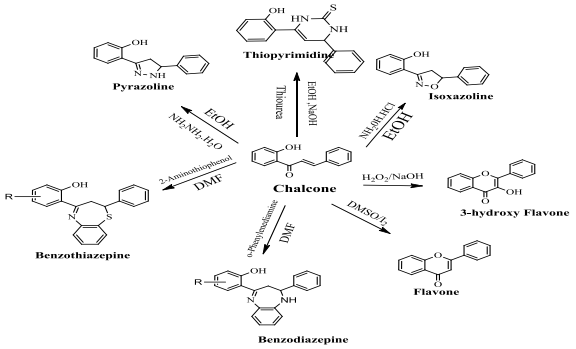
## ABSTRACT

By the condensation of o-phenylendiamine and various chalcone, a new series of 1,5-benzodiazepine derivatives were synthesized. The synthesized compounds were characterized by Physical and spectral methods IR, $^1$H-NMR and Mass analysis. All the synthesized compounds have been screened and evaluated for antibacterial activity against *Staphylococcus aureus* gr +ve, *Escherichia coli* gr –ve *Bacillus subtilis* gr +ve, *Salmonella typhi* gr –ve and antifungal activity against *Aspergillus oryzoe*, *Aspergillus niger*, using disc diffusion method. Most of the compounds were showed significant antibacterial and antifungal activities.

**KEYWORDS:** Chalcones, 1, 5-benzodiazepine, Antimicrobial activities.

## INTRODUCTION

Benzodiazepines have recently attracted attention as important class of heterocyclic compounds in the field of drugs and pharmaceuticals. These compounds are widely used as anticonvulsant, antianxiety, analgesic, sedative, antidepressive hypnotic agents.[1] as well as anti-inflammator agents.[2] Other than their biological importance, benzodiazepines derivatives are also commercially used as dyes for a crylic fibers.[3] Morever, 1,5-benzodiazepines derevatives are valuable synthon that can be used in the preparation of other fused ring compounds such as triazolo, oxazino or furano benzodiazepines.[4] As a result, research in this area is still very active and is directed towards the synthesis of compounds with enhanced pharmacological activity. Generally, benzodiazepines were synthesized by the condensation of o-phenylene diamines with α,β-unsaturated carbonyl compounds.[5], βhaloketones, or ketones.[6] A variety of reagents, such as $BF_3$-etherate.[7], $NaBH_4$.[8], polyphosporic acid.[9], $SiO_2$, $MgO/POCl_3$.[10], $Yb(OTf)_3$.[11], $Sc(OTf)_3$, $Al_2O_3/P_2O_5$, or AcOH under mic rowave irradiation.[12] and even in the of ionic liquids.[13-14] Different heterocyclic ring systems are synthesized from chalcones like pyrazolines, cyanopyridines, isoxazoles, pyrimidines, benzodiazepines and benzthiazeoines, chalcones serve as fundamental building blocks for their synthesis.



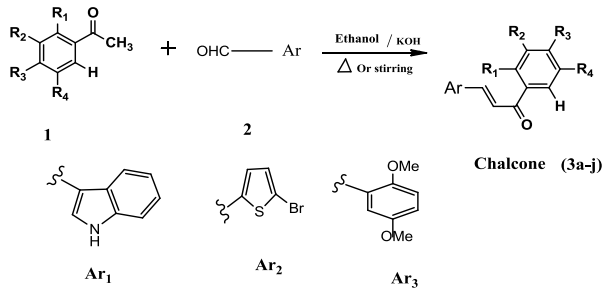

## MATERIALS AND METHODS EXPERIMENTAL

Melting points of the compounds were determined in open capillary tubes and are uncorrected, IR Spectra were recorded on Shimadzu FT-IR Spectrometer using potassium bromide pellets,[1] H NMR was determined on a Bruker Avance II 400 Spectrometer against TMS as internal standard. Mass spectra were recorded on waters Micromass Q-T of Micro spectrometry.

### *General method for the synthesis of Chalcones*

A mixture of substituted acetophenone (1 mmol), substituted aldehyde (1 mmol) and KOH (2 mmol, in minium $H_2O$) were taken in ethanol and stirred at 50-60°C temperature for one hour. The completion of reaction was monitored by TLC. The products were isolated by acidification of the cool diluted acid solution and obtained solid product was filtered and washed with water and recrystallize by ethanol to get pure product.

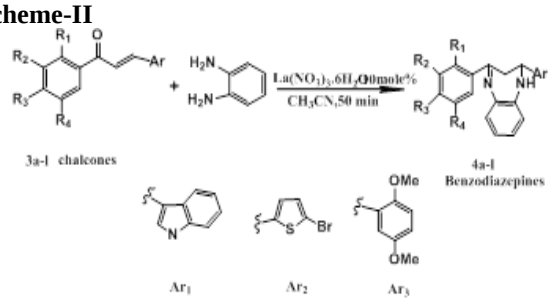
**Scheme-I**




***General Procedure for the Synthesis of 1, 5-benzodiazepine(4a-g).***

A mixture of Chalcones (1 mmol), o-Phenylenediamine(1 mmol) and $La(NO_3)_3$ (10 mol %) in 10 ml of MeCN was stirred at 50 $^0$C for 50 min. After completion of the reaction as monitored by TLC [eluent: ethyl acetate: pet. ether (3:7)], the crude product washed with water and extracted into ethyl acetate and purified by column chromatography to afford pure 2, 4-disubstituted-1, 5-benzodiazepines (4a-g) in 80-92% yield [Scheme-II].

**Scheme-II**




**RESULT AND DISCUSSION**

A novel chalcones were synthesized via Claisen-Schmidt condensation of substituted acetophenones and aromatic benzaldehyde. The reaction proceeded at room temperature. Work up procedure is simple and yield of the product is excellent. And a new series of benzodiazepines were synthesized by reaction of o-Phenylenediamine and Chalcones in the presence of Lanthanum Nitrate as a catalyst. Work up procedure is simple and yield of the product is excellent. All the newly (3a-l),(4a-l) synthesized compounds were characterized by their chemical, physical and spectral analysis data (Table-2), and are further subjected to antimicrobial studies(Table-4) which exhibit moderate to good activity.

**Table-1. Substituted data of Synthesized Chalcones (3a-l).**

| Comp.no | Product | $R_1$ | $R_2$ | $R_3$ | $R_4$ | Ar |
|---|---|---|---|---|---|---|
| **1** | 3a | H | I | OH | I | $Ar_1$ |
| **2** | 3b | OH | I | H | I | $Ar_1$ |
| **3** | 3c | OH | I | H | Cl | $Ar_1$ |
| **4** | 3d | OH | I | H | $CH_3$ | $Ar_1$ |
| **5** | 3e | H | I | OH | I | $Ar_2$ |
| **6** | 3f | OH | I | H | I | $Ar_2$ |
| **7** | 3g | OH | I | H | Cl | $Ar_2$ |
| **8** | 3h | OH | I | H | $CH_3$ | $Ar_2$ |
| **9** | 3i | H | I | OH | I | $Ar_3$ |
| **10** | 3j | OH | I | H | I | $Ar_3$ |
| **11** | 3K | OH | I | H | Cl | $Ar_3$ |
| **12** | 3l | OH | I | H | $CH_3$ | $Ar_3$ |

**Table-2. Physical data of synthesized Chalcones**

| Comp.no | Product | Mol. Formula | Yield % | M.P.(°C | Solubility |
|---|---|---|---|---|---|
| **1** | 3a | $C_{17}H_{11}NI_2O_2$ | 88 | 150 | DMF |
| **2** | 3b | $C_{17}H_{11}NO_2I_2$ | 92 | 130 | DMF |
| **3** | 3c | $C_{17}H_{11}NIClO_2$ | 80 | 120 | DMF |
| **4** | 3d | $C_{18}H_{14}NIO_2$ | 92 | 142 | DMF |
| **5** | 3e | $C_{13}H_7O_2I_2BrS$ | 90 | 178 | DMF |
| **6** | 3f | $C_{13}H_7O_2I_2BrS$ | 92 | 162 | DMF |
| **7** | 3g | $C_{13}H_7O_2ClIBrS$ | 80 | 178 | DMF |
| **8** | 3h | $C_{14}H_{10}O_2IBrS$ | 92 | 142 | DMF |
| **9** | 3i | $C_{17}H_{14}O_4I_2$ | 86 | 164 | DMF |
| **10** | 3j | $C_{17}H_{14}O_4I_2$ | 88 | 176 | DMF |
| **11** | 3k | $C_{17}H_{14}O_4ClI$ | 80 | 178 | DMF |
| **12** | 3l | $C_{18}H_{17}O_4I$ | 90 | 159 | DMF |

**Table-3 Substituted data of synthesized benzodiazepine (4a-l)**

| Entry | $R_1$ | $R_2$ | $R_3$ | $R_4$ | Ar |
|---|---|---|---|---|---|
| **4a** | H | I | OH | I | $Ar_1$ |
| **4b** | OH | I | H | I | $Ar_1$ |
| **4c** | OH | I | H | Cl | $Ar_1$ |
| **4d** | OH | I | H | $CH_3$ | $Ar_1$ |
| **4e** | H | I | OH | I | $Ar_2$ |
| **4f** | OH | I | H | I | $Ar_2$ |
| **4g** | OH | I | H | Cl | $Ar_2$ |
| **4h** | OH | I | H | $CH_3$ | $Ar_2$ |
| **4i** | H | I | OH | I | $Ar_3$ |
| **4j** | OH | I | H | I | $Ar_3$ |
| **4k** | OH | I | H | Cl | $Ar_3$ |
| **4l** | OH | I | H | $CH_3$ | $Ar_3$ |

**Table-4 Physical data of synthesized compounds(4a-l)**

| Comp.no | Product | Mol. Formula | Yield % | M.P.(°C) |
|---|---|---|---|---|
| **1** | 4a | $C_{23}H_{17}ON_3I_2$ | 90 | 164 |
| **2** | 4b | $C_{23}H_{17}ON_3I_2$ | 85 | 102 |
| **3** | 4c | $C_{23}H_{17}ON_3ICl$ | 90 | 112 |
| **4** | 4d | $C_{24}H_{20}ON_3I$ | 80 | 142 |
| **5** | 4e | $C_{19}H_{13}ON_2I_2BrS$ | 75 | 150 |
| **6** | 4f | $C_{19}H_{13}ON_2I_2BrS$ | 80 | 152 |
| **7** | 4g | $C_{19}H_{13}ON_2IClBrS$ | 85 | 166 |
| **8** | 4h | $C_{20}H_{16}ON_2IBrS$ | 75 | 174 |
| **9** | 4i | $C_{23}H_{20}O_3N_2I_2$ | 90 | 100 |
| **10** | 4j | $C_{23}H_{20}O_3N_2I_2$ | 90 | 186 |
| **11** | 4k | $C_{23}H_{20}O_3N_2ICl$ | 85 | 182 |
| **12** | 4l | $C_{24}H_{23}O_3N_2I$ | 75 | 174 |

(*E*)-3-(5-bromothiophen-2-yl)-1-(5-chloro-2-hydroxy-3-iodophenyl)prop-2-en-1-one

**$^1$HNMR (DMSO-$d_6$) (□ ppm):** 7.12(d, 1H,$H_3$),7.21(d,1H,$H_4$),7.27(d, 1H, Hα,J=15Hz), 7.97(d, 1H, H β,J=15Hz),8.23(s, 1H,$H_5$), 8.47(s,1H ,$H_6$), 13.46(s, 1H,OH). **IR (KBr, cm$^{-1}$):** 3436(OH), 1635(C=O), 1526(C=C), 1419(C-C Aromatic str), 621(C-Br).802(C-Cl). **M.S. (m/z):** 468(M-1).

(*E*)-3-(2,5-dimethoxyphenyl)-1-(2-hydroxy-3-iodo-5-methylphenyl)prop-2-en-1-one

**$^1$HNMR (DMSO-$d_6$) (□ ppm):** 3.80(s,3H,OMe),3.85(s,3H,OMe),7.03(S,1$H_5$)7.22(d,1$H_3$)7.50(d,1$H_4$),8.04(d, 1H, Hα,J=15Hz), 8.12(d, 1H, H β,J=15Hz), 8.16(s,1H,$H_6$),8.26(s,1$H_7$), 13.51(s,1H, OH).

**IR (KBr, cm$^{-1}$):** 3440(OH),1631(C=O),1562(C=C), 1430(C-C Aromatic str). **M.S. (m/z):** 423 (M-1).

**(R)-2-(2-(5-bromothiophen-2-yl)-2,3-dihydro-1H-benzo[b][1,4]diazepin-4-yl)-4-chloro-6-iodophenol.**
M.P = 166$^0$C, Yield = 75%**$^1$HNMR(DMSO-$d_6$) (□ ppm):-** 2.79(dd, 1H,$H_1$, J=12),3.78(dd,1H ,$H_2$, J=12),5.36(s, 1H, NH), 5.64(t, 1H, $H_3$), 6.40(t, 1H,$H_8$), 6.72(d,1H ,$H_6$), 6.92(d, 1H, $H_4$), 7.09(d, 1H, $H_5$), 7.31(t, 1H, $H_7$), 7.41(d, 1H, $H_9$), 7.95(s1H, $H_{11}$), 8.03(s, 1H, $H_{10}$), 15(s, 1H, OH)**. FTIR (KBr, cm$^{-1}$)**: 3374(NH), 3062(C-H), 1582(C=N), 1469(C-C Aromatic str). **M.S. (m/z): (M)**= 559(M+).

**(R)-2-(2-(2,5-dimethoxyphenyl)-2,3-dihydro-1H-benzo[b][1,4]diazepin-4-yl)-6-iodo-4-methylphenol.**
M.P = 1740C, Yield = 80%.

**$^1$HNMR(DMSO-$d_6$) (□ ppm):**-- 2.29(s, 3H, $CH_3$) ,2.88(dd,1H ,$H_1$, J=13) ,3.09(dd, 1H, $H_2$, J=13), 3.76(s, 3H, $OCH_3$) , 3.79(s, 3H, $OCH_3$), 5.79(t,1H ,$H_3$, J=13), 6.92(d, 1H, $H_4$), 7.08(s, 1H, $H_6$), 7.19(d, 1H, $H_5$), 6.96-7.59(m.4H,Ar-H), 7.22(s,1H, $H_8$), 7.57(s, 1H, $H_7$), 7.89(s, 1H, NH),16.57(s, 1H, OH). **FTIR (KBr, cm$^{-1}$):** 3390(NH),2922(C-H),1602(C=N), 1458(C-C Aromatic str). **M.S. (m/z): (M)=** 514(M+).

**Antimicrobial activity**

Antimicrobial screening was done using disc diffusion method[15] at a concentration of 100µg/ml. The test was performed according to the disk diffusion method[15] adopted with some modification for the prepared compound using Penciline and streptomycin as references. The prepared compounds were tested against one strain of Gram +ve bacteria, Gram –ve bactria, fungi. The compounds were evaluated for antibacterial activity against *Staphylococcus aureus* gr +ve, *Escherichia coli* gr –ve *Bacillus subtilis* gr +ve, *Salmonela typhi* gr –ve, and antifungal activity against *Aspergillus oryzoe*, *Aspergillus niger*,. DMSO was used as solvent control. The results of antimicrobial data are summarized in tables 5 and 6. The compounds show the moderate to good activity against bacteria and fungui.

**Table-5 Antimicrobial activity of Chalcones (3a-l).**

| compounds | Gram positive bacterias | | Gram negative bacterias | | Fungus | |
|---|---|---|---|---|---|---|
| | Staph aureus | Bacillus subtilis | Escherichia coli | Pseudomonas aeruginosa | Aspergillus oryzoe | Aspergillus niger, |
| 3a | ++ | ++ | - | ++ | ++ | + |
| 3b | + | + | - | + | - | + |
| 3c | + | + | - | - | + | + |
| 3d | + | + | + | + | + | + |
| 3e | ++ | ++ | - | ++ | ++ | + |
| 3f | - | - | - | - | - | - |
| 3g | - | - | - | - | - | - |
| 3h | - | - | - | - | - | - |
| 3i | ++ | ++ | - | ++ | - | - |
| 3j | - | - | - | - | - | - |
| 3k | - | - | - | - | - | - |
| 3l | - | - | - | - | - | - |
| Penciline 1 | + | + | + | + | x | x |
| Streptomycin 2 | ++ | ++ | ++ | ++ | x | x |
| Greseofulvin | x | x | x | x | - | - |

++ = Clear Zone of Inhibition , + = Minimum Zone of Inhibition, - = No Effect, X = Not plicable Standerd.[1] Penciline + Standerd.[2] Streptomycin ++.

**Table-6 Antimicrobial activity of Benzodiazepines (4a-l).**

| compounds | Gram positive bacterias | | Gram negative bacterias | | Fungus | |
|---|---|---|---|---|---|---|
| | Staph aureus | Bacillus subtilis | Escherichia coli | S. typhi | Aspergillus oryzoe | Aspergillus niger, |
| 4a | + | ++ | ++ | - | + | + |
| 4b | - | - | - | - | - | - |
| 4c | - | - | - | - | - | - |
| 4d | + | - | - | - | - | - |
| 4e | + | ++ | + | - | - | - |
| 4f | - | - | - | - | - | - |
| 4g | ++ | + | + | - | + | + |
| 4h | - | - | - | - | - | - |
| 4i | ++ | ++ | ++ | - | - | - |
| 4j | - | - | - | - | - | - |
| 4k | - | - | - | - | - | - |
| 4l | - | - | - | - | - | - |
| DMSO | - | - | - | - | + | - |
| Penciline 1 | + | + | + | + | x | x |
| Streptomycin 2 | ++ | ++ | ++ | ++ | x | x |
| Greseofulvin | x | x | x | x | - | - |

++ = Clear Zone of Inhibition, + = Minimum Zone of Inhibition, - = No Effect, X = Not applicable, Standerd.[1] Penciline +, Standerd.[2] Streptomycin ++.

## CONCLUSION

By using neat and simple procedures we have synthesized chalcones via Claisen-Schmidt condensation of substituted acetophenones and aromatic benzaldehyde. The reaction proceeded at room temperature. And a new series of benzodiazepines were synthesized by reaction of o-phenylenediamine and Chalcones in the presence of Lanthanum Nitrate as a catalyst. Work up procedure is simple and yield of the product is excellent. The newly synthesized chalcones were confirmed by spectral analysis and further evaluated for their antimicrobial activity. The compounds show the moderate to good activity against bacteria and fungui.

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