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SYNTHESIS CHARACTERIZATION AND BIOLOGICAL EVALUATION OF 1, 5-BENZODIAZEPINES

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ABSTRACT

Benzodiazepines are interesting compounds due to their therapeutic properties. Microbial chemotherapy is highly regulated, and Its research is often considered non-remunerative. Hence, there remains a pressing requisite to discover novel, potent, and safe anti-microbial agents. In the present work, a series of four derivatives of 1, 5-Benzodiazepines were synthesized by condensation of o-phenylenediamines with various substituted chalcone. Further these synthesized derivatives were analyzed by IR, NMR and MASS spectral studies and are screened for antimicrobial activity. Among these, potent activity were observed for compounds 4c (MIC 6.25 µg/mL) shows good antibacterial activity where as compound 4a in same MIC shows good antifungal activity. In conclusion, we synthesized four 1, 5-Benzodiazepines derivatives with selective anti-microbial activity.

Keywords: Benzodiazepines, *Antibacterial activity, Antifungal activity,* Ciprofloxacin, Fluconazole.

I. INTRODUCTION

1,5-Benzodiazepines is a class of outstanding organic molecules with a wide array of biological activities and therapeutic functions. They are commonly used as anxiolytic and anticonvulsive drugs.[1] The use of 1,5-benzodiazepines for therapeutic purposes is not confined to the treatment of anxiety and stress conditions because minor changes in their structures can produce various biological activities, and novel applications of these compounds are continuously emerging.[2] Recently, 1,5-benzodiazepines and their derivatives have been also reported to exhibit excellent antibacterial and antifungal properties.[3,4] In addition, previous studies on 1,5-benzodiazepines have indicated that the free ester group present at different positions in the nuclei of the molecules can enhance the pharmacological properties of the compounds, and this effect is attributed to their high hydrophobicity.[5] Moreover five-membered heterocycle compounds, such as thiophene or thiazole were reported to be significant structural units of potent antimicrobial agents, and they were also vital pharmacodynamic heterocyclic nuclei.[6,7] 1,5-Benzodiazepines composed of five-membered heterocycle compounds show superior biological activity.[8]

In view of the above-mentioned findings, and as a continuation of our effort to identify new candidates that may be valuable in designing new, potent, selective, and less toxic antimicrobial agents, we have reported herein the synthesis of 4 novel 1,5-benzodiazepine derivatives by reaction of substituted hydroxyl chalcone with *o*phenylenediamine in presence of piperidine as catalyst. All the synthesized compounds were screened for their in vitro antimicrobial activities against fungi (*Aspergillus niger*, *Aspergillus flavus*, *Penicillium chrysogenum* and *Fusarium moniliforme*) and a representative Gram-negative bacterium (*Escherichia coli, Pseudomonas aeruginosa* and *Salmonella typhi*) and Gram-positive bacteria (*Bacillus licheniformis, Bacillus species, Staphylococcus aureus, Streptococcus pyogenes, Bacillus subtilis*). This combination was suggested to investigate the influence of such hybridization and structure variation on the anticipated biological activities, hoping to add some synergistic biological significance to target compounds.

II. MATERIALS

All the chemicals were purchased from Aldrich Chemical Company (USA) and were used without further purification. The reactions were monitored by pre-coated aluminum silica gel TLC plates. Iodine vapors are used as visualizing agents. Melting points (m.p) were determined using an SRS-EZ Melt automated melting

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point instrument, without correction. The IR spectra were recorded on BRUKER FT-IR (software - OPUS 6.4) spectrometer using KBr disc method and the values were expressed in cm-1. The 1 H-NMR spectra of the compounds were recorded in DMSO-d6 or CDCl3 with BRUKER AVANCE 400 MHz NMR spectrometer (software – Topspin 3.2) and chemical shifts were expressed in δ (ppm). Shifts reported are relative to the signal of the solvent used in each case and coupling constants are reported in Hz (s: singlet, bs: broad singlet, d: doublet, t: triplet, dd: double doublet, dt: double triplet, m: multiplet). The mass spectra were recorded on AGILENT QQQ LC-MS (ESI-MS) spectrometer (software - Mass Hunter B.03.01).

III. METHODS

General Method for the Synthesis of Hydroxy Chalcones

A mixture of 1-acetyl-2-naphthol (1mmol) with different substituted aromatic aldehyde (1mmol) were dissolved in minimum quantity 90% ethyl alcohol in warm condition to this solution 40% of aq.KOH were added drop wise with constant shaking at room temperature. The reaction mixture was freely corked and kept in bulb oven at about 55-60℃ for about 12-13 hrs. The resulting reaction mixture were poured into cold water and neutralized by dilute HCl. The separated solid was filtered (with suction pump), washed with ice cold water, dried and recrystalized from ethanol to get corresponding hydroxy chalcones. (Schem -1)

Synthesis of 3-(2, 4-dihydroxyphenyl)-1-(2-hydroxynaphthalene-1-yl)prop-2-en-1-one (3a)

1-(2-hydroxynaphthalen-1-yl)ethanone (0.01 mol) and 2,4-dihydroxybenzaldehyde (0.01 mol) were dissolved in minimum quantity of 90% ethyl alcohol in warm condition to this solution 40% of aq.KOH were added drop wise with constant shaking at room temperature. The flask of reaction mixture was freely corked & kept in bulb oven at about 55-60°C for about 12 hrs. The resulting reaction mixture were neutralized by dilute HCl & poured into cold water. The obtained solid was filtered (with suction pump), washed with ice cold water, dried & recrystalized from ethanol to get 3-(2, 4-dihydroxyphenyl)-1-(2-hydroxynaphthalene-1-yl)prop-2-en-1-one.

Synthesis of 3-(3-bromo-4-hydroxy-5-methoxyphenyl)-1-(2-hydroxynaphthalene-1-yl)prop-2-en-1-one (3b)

1-(2-hydroxynaphthalen-1-yl)ethanone (0.01 mol) and 3-bromo-4-hydroxy-5-methoxybenzaldehyde (0.01 mol) were dissolved in minimum quantity of 90% ethyl alcohol in warm condition to this solution 40% of aq.KOH were added drop wise with constant shaking at room temperature. The flask of reaction mixture was freely corked & kept in bulb oven at about 55-60°C for about 12 hrs. The resulting reaction mixture were neutralized by dilute HCl & poured into cold water. The obtained solid was filtered (with suction pump), washed with ice cold water, dried & recrystalized from ethanol to get 3-(3-bromo-4-hydroxy-5-methoxyphenyl)-1-(2-hydroxynaphthalene-1-yl)prop-2-en-1-one.

Synthesis of 3-(4-chlorophenyl)-1-(2-hydroxynaphthalene-1-yl)prop-2-en-1-one (3c)

1-(2-hydroxynaphthalen-1-yl) ethanone (0.01 mol) and 4-chlorobenzaldehyde (0.01 mol) were dissolved in minimum quantity of 90% ethyl alcohol in warm condition to this solution 40% of aq.KOH were added drop wise with constant shaking at room temperature. The flask of reaction mixture was freely corked & kept in bulb oven at about 55-60°C for about 12 hrs. The resulting reaction mixture were neutralized by dilute HCl & poured into cold water. The obtained solid was filtered (with suction pump), washed with ice cold water, dried & recrystalized from ethanol to get 3-(4-chlorophenyl)-1-(2-hydroxynaphthalene-1-yl)prop-2-en-1-one.

Synthesis of 3-(4-benzyloxy)-3-methoxyphenyl)-1-(2-hydroxynaphthalene-1-yl) prop-2-en-1-one (3d)

1-(2-hydroxynaphthalen-1-yl) ethanone (0.01 mol) and 4-(benzyloxy)-3-methoxybenzaldehyde (0.01 mol) were dissolved in minimum quantity of 90% ethyl alcohol in warm condition to this solution 40% of aq.KOH were added drop wise with constant shaking at room temperature. The flask of reaction mixture was freely corked & kept in bulb oven at about 55-60°C for about 12 hrs. The resulting reaction mixture were neutralized by dilute HCl & poured into cold water. The obtained solid was filtered (with suction pump), washed with ice cold water, dried & recrystalized from ethanol to get 3-(4-benzyloxy)-3-methoxyphenyl)-1-(2-hydroxynaphthalene-1-yl)prop-2-en-1-one.

General Method for the Synthesis of 1,5-Benzodiazepines

In 50 ml round bottom flask a mixture of substituted chalcone (1 mmol) and *o*phenylenediamine (2 mmol) were dissolve in pure 2-ethoxy ethanol (8ml) and then catalytic amount of piperidine was added and refluxed

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for 3-4 hrs. The completion of the reaction was followed by TLC using petroleum ether/ethyl acetate (7:3) as the mobile phase on precoated sheets of silica gel-G using iodine vapour/UV lamp. After completion, reaction mixture was kept overnight at room temperature. Solid separated out, and then filtered by suction pump, washed with cold aqueous ethanol and recrystallized from ethanol. The structures of the synthesized compounds were characterized by their melting points, Elemental analysis, IR, ^{1}H NMR and ^{13}CNMR and Mass spectra.

Synthesis of 4-(4-(2-hydroxynaphthalen-1-yl)-2,3-dihydro-1*H*benzo[b] [1,4] diazepin-2-yl)benzene-1,3-diol (4a).

In 50 ml round bottom flask a mixture of 3-(2,4-dihydroxyphenyl)-1-(2-hydroxynaphthalene-1-yl)prop-2-en-1-one (1mmol) and *o*-phenylenediamine (2 mmol) were dissolve in pure 2-ethoxy ethanol (8ml) and then 2-3 drops of piperidine was added and refluxed for 3 hrs. The completion of the reaction was followed by TLC using petroleum ether/ethyl acetate (7:3) as the mobile phase on precoated sheets of silica gel-G using iodine vapour/UV lamp. After completion, reaction mixture was kept overnight at room temperature. Solid separated out and then filtered by suction pump, washed with cold aqueous ethanol and recrystallized from ethanol to get 4-(4- (2-hydroxynaphthalen-1-yl)-2,3-dihydro-1*H*-benzo[b][1,4]diazepin-2-yl)benzene-1,3-diol (**Scheme 2**).

4.4.2 Synthesis of 1-(2-(3-bromo-4-hydroxy-5-methoxyphenyl)-2,3-dihydro-1*H* benzo [b] [1,4] diazepin-4-yl)naphthalen-2-ol. (4b)

In 50 ml round bottom flask a mixture of 3-(3-bromo-4-hydroxy-5-methoxyphenyl)-1-(2-hydroxynaphthalene-1-yl)prop-2-en-1-one (1mmol) and *o*-phenylenediamine (2 mmol) were dissolve in pure 2-ethoxy ethanol (8ml) and then 2-3 drops of piperidine was added and refluxed for 3 hrs. The completion of the reaction was followed by TLC using petroleum ether/ethyl acetate (7:3) as the mobile phase on precoated sheets of silica gel-G using iodine vapour/UV lamp. After completion, reaction mixture was kept overnight at room temperature. Solid separated out and then filtered by suction pump, washed with cold aqueous ethanol and recrystallized from ethanol to get 1-(2-(3-bromo-4-hydroxy-5-methoxyphenyl)-2,3-dihydro-1*H* benzo [b] [1,4] diazepin- 4-yl)naphthalen-2-ol.

Synthesis of 1-(2-(4-chlorophenyl) 2, 3-dihydro-1*H*-benzo[b][1,4]diazepin-4-yl) naphthalen-2-ol. (4c)

In 50 ml round bottom flask a mixture of 3-(4-chlorophenyl)-1-(2-hydroxynaphthalene-1-yl)prop-2-en-1-one (1mmol) and *o*-phenylenediamine (2 mmol) were dissolve in pure 2-ethoxy ethanol (8ml) and then 2-3 drops of piperidine was added and refluxed for 3 hrs. The completion of the reaction was followed by TLC using petroleum ether/ethyl acetate (7:3) as the mobile phase on precoated sheets of silica gel-G using iodine vapour/UV lamp. After completion, reaction mixture was kept overnight at room temperature. Solid separated out and then filtered by suction pump, washed with cold aqueous ethanol and recrystallized from ethanol to get 1-(2-(4-chlorophenyl) 2,3-dihydro-1*H*-benzo[b][1,4]diazepin-4-yl)naphthalen-2-ol.

Synthesis of 1-(2-(4-benzyloxy)-3-methoxyphenyl)-2,3-dihydro-1*H*-benzo [b] [1,4]diazepin-4- yl) naphthalen-2-ol. (4d)

In 50 ml round bottom flask a mixture of 3-**(**4-benzyloxy)-3-methoxyphenyl)-1-(2-hydroxynaphthalene-1-yl)prop-2-en-1-one (1mmol) and *o*-phenylenediamine (2 mmol) were dissolve in pure 2-ethoxy ethanol (8ml) and then 2-3 drops of piperidine was added and refluxed for 3 hrs. The completion of the reaction was followed by TLC using petroleum ether/ethyl acetate (7:3) as the mobile phase on precoated sheets of silica gel-G using iodine vapour/UV lamp. After completion, reaction mixture was kept overnight at room temperature. Solid separated out and then filtered by suction pump, washed with cold aqueous ethanol and recrystallized from ethanol to get 1-(2-(4-benzyloxy)-3-methoxyphenyl)-2,3-dihydro-1*H*-benzo[b][1,4]diazepin-4-yl) naphthalen-2-ol.

The melting point, yield and elemental analysis of newly synthesized compounds are shown in **Table-1**.

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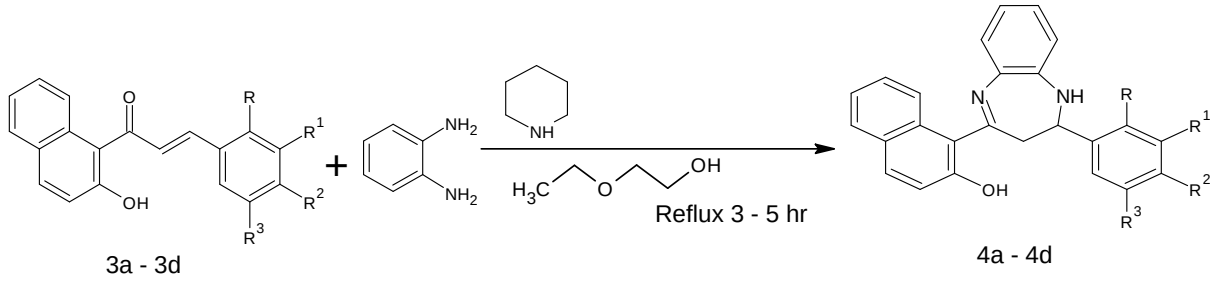
3a. R= OH, R1= H, R2 = OH, R3 = H; **3b.** R= H, R1= OCH3, R2 = OH, R3 = Br; **3c.** R= H, R1= H, R2 = Cl, R3 = H; **3d.** R= H, R1= OCH3, R2 = OCH2C6H5, R3 = H

SCHEME 1



4a. R= OH, R1= H, R2 = OH, R3 = H; **4b.** R= H, R1= OCH3, R2 = OH, R3 = Br; **4c.** R= H, R1= H, R2 = Cl, R3 = H; **4d.** R= H, R1= OCH3, R2 = OCH2C6H5, R3 = H

SCHEME 2

IV. RESULTS

Characterization of synthesized compounds

4-(4-(2-hydroxynaphthalen-1-yl)-2,3-dihydro-1H-benzo[b][1,4]diazepin-2-yl)benzene-1,3 diol.

IR: ν max cm^{-1}: *3450 (OH), 3371 (OH), 3220 (NH), 1653 (C=N), 1636, 1558, 1541 (Ar).*

^{1}H NMR (CDCl3): *δ 3.15 (dd, 1H, HA), δ 3.80 (dd, 1H, HB), δ 4.60 (dd, 1H, HX), δ 5.95 (s, 1H, NH), δ 6.80-8.45 (m, 13H, Ar-H), δ 12.25 (s, 2H, OH), δ 13.00 (s, 1H, OH).*

MS m/z: *396 (M$^+$).*

1-(2-(3-bromo-4-hydroxy-5-methoxyphenyl)-2,3-dihydro-1H-benzo[b][1,4]diazepin-4-yl) naphthalen-2-ol.

IR: ν max cm$^{-1:}$ *3372(OH), 3190 (NH), 1635 (C=N), 1591, 1541, 1456 (Ar), 723 (Ar-Br).*

^{1}H NMR (CDCl3) : *δ 3.10 (dd, 1H, HA), δ 3.45 (s, 3H, OCH3), δ 3.90 (dd, 1H, HB), δ 4.50 (dd, 1H, HX), δ 5.90 (s, 1H, NH), δ 6.80-8.20 (m, 12H, Ar-H), δ 11.70 (s, 1H, OH), δ 12.90 (s, 1H, OH).*

MS m/z: *489 (M$^+$).*

1-(2-(4-chlorophenyl) 2,3-dihydro-1H-benzo[b][1,4]diazepin-4-yl) naphthalen-2-ol.

IR: ν max cm^{-1}: *3344 (OH), 3214 (NH), 1636(C=N), 1576, 1540, 1456 (Ar), 862 (Ar-Cl).*

^{1}H NMR (CDCl$_3$): *δ 3.20 (dd, 1H, HA), δ 3.65 (dd, 1H, HB), δ 4.80 (dd, 1H, HX), δ 6.25 (s, 1H, NH), δ 7.25-8.60 (m, 14H, Ar-H), δ 12.80 (s, 1H, OH).*

MS m/z: *398 (M$^+$).*

1-(2-(4-benzyloxy)-3-methoxyphenyl)-2,3-dihydro-1H benzo [b] [1,4] diazepin-4- yl)naphthalen-2-ol.

IR: ν max cm^{-1}: *3380 (OH), 3240 (NH), 1647 (C=N), 1635, 1576, 1456 (Ar).*

^{1}H NMR (CDCl$_3$) : *δ 3.25 (dd, 1H, HA), δ 3.50 (s, 3H, OCH3), δ 3.80 (dd, 1H, HB), δ 4.50 (dd, 1H, HX), δ 5.10 (s, 2H, OCH2), δ 5.90 (s,1H, NH), δ 6.74-8.25 (m,18H, Ar-H), δ 12.70 (s, 1H, OH).*

MS m/z: *500 (M$^+$).*

Table 1: Physical and Analytical Data of 1,5-Benzodiazepines (4a-d)

Compound	Colour	Mol. Formulae	M.P. (0C)	% Yield	Elemental Analysis Found (in %)		
					C	H	X
4a	Yellow	$C_{25}H_{20}O_3N_2$	160	74	75.75	5.06	---
4b	Yellow	$C_{26}H_{21}O_3N_2Br$	164	68	63.80	4.30	16.32
4c	Brown	$C_{25}H_{19}ON_2Cl$	158	78	75.26	4.82	8.87
4d	Yellow	$C_{33}H_{28}O_3N_2$	164	81	79.14	5.61	---

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BIOLOGICAL ACTIVITY

In vitro antimicrobial screening The antimicrobial susceptibility testing was performed in vitro by Agar well diffusion method.[9] The test organisms used were: fungi (*Aspergillus niger*, *Aspergillus flavus*, *Penicillium chrysogenum* and *Fusarium moniliforme*) and a representative Gram-negative bacterium (*Escherichia coli, Pseudomonas aeruginosa* and *Salmonella typhi*) and Gram-positive bacteria (*Bacillus licheniformis, Bacillus species, Staphylococcus aureus, Streptococcus pyogenes, Bacillus subtilis*). All the compounds were tested at a dose level of 100µg (0.1mL) and DMSO was used as a control whereas **Ciprofloxacin** and **Fluconazole** were taken as standard drugs. None of the compounds had shown antibacterial and antifungal activity.

Table 2: Antibacterial Activity of 1,5-Benzodiazepines

Sl. No.	Compounds	zone of inhibition in mm (MIC values µg mL-1)			
		Gram +ve bacteria		Gram –ve bacteria	
		S.aureus	*B.subtilis*	*E.coli*	*S.typhi*
1	4a	10 ± 0.9(6.25)	12 ± 1.0(6.25)	<11 (50)	<9 (50)
2	4b	15 ± 1.2(6.25)	13 ± 1.1(6.25)	12 ± 1.0(12.5)	14 ± 0.8(12.5)
3	4c	23 ± 0.9(6.25)	18 ± 1.0(6.25)	19 ±1.0(6.25)	16 ± 0.8(6.25)
4	4d	21 ± 0.9(6.25)	16 ± 1.0(6.25)	19 ±0.9(12.5)	16 ± 1.0(6.25)
5	Ciprofloxacin	28 (6.25)	23 (6.25)	29 (6.25)	22 (6.25)

Results were expressed Mean±SD, n=3

Table 3: Antifungal Activity of 1, 5-Benzodiazepines

Sl. No.	Compounds	zone of inhibition in mm (MIC values µg mL-1)			
		A. niger	*A. flavus*	*P.chrysogenum*	*F.moniliforme*
1	4a	21 ± 1.1(6.25)	16 ± 1.0(6.25)	18 ±0.9(6.25)	15 ± 1.0(12.5)
2	4b	17 ± 0.9(6.25)	15 ± 1.1(6.25)	14 ± 1.2(12.5)	15 ± 0.8(12.5)
3	4c	11 ± 1.0(6.25)	12 ± 1.0(12.5)	12 ±1.0(12.5)	----
4	4d	14 ± 0.9(25)	<11 (50)	----	----
5	Fluconazole	23 (6.25)	24 (6.25)	25 (6.25)	24 (6.25)

Results were expressed Mean±SD, n=3

A total of four 1, 5-Benzodiazepines derivatives were synthesized by using established protocols. The compounds were obtained in good yield and were characterized by using spectral analysis including NMR, IR and Mass. The synthesized 1,5-benzodiazepines were screened for their antibacterial activity and we observed that the compounds 4c having electron withdrawing group at para position exhibit excellent antibacterial activity against all bacterial strain. Whereas the compounds 4a having electron releasing group at para position displayed better antifungal activity. Hence, it is found that the electron withdrawing and electron releasing group at para position on phenyl ring play important role for increase in antibacterial and antifungal activity respectively. It can be further modified to reveal better potency than the standard drug. Finally, we conclude, this type of compounds certainly holds great assurance towards discovery of new class of antimicrobial potential.

V. CONCLUSION

Finally conclude that we have synthesized and characterized new nitrogen, oxygen and sulfur containing heterocycles by using 2-ethoxy ethanol as a reaction medium which increases the yield of product. The present study provides good starting point for the further development of optimization of solvents, also the synthesized compounds on further pharmacophoric modification can be act as good therapeutic drug particularly 2-pyrazolines synthesized from isoniazid which shows higher antimicrobial activity on comparing with standard

drug used. This research work finds meaning to provide alternative drugs for the treatment of disease caused due to multi drug resistant microorganisms.

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