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SYNTHESIS AND ANTIMICROBIAL ACTIVITIES OF SOME NEW 2, 3-DIHYDRO-1, 5-BENZODIAZEPINE DERIVATIVES

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ABSTRACT: A series of some New 2, 3-dihydro-1, 5-benzodiazepines has been synthesized using condensation reaction of *o*-phenylenediamine and various substituted chalcones in presence of DMF as solvent and screening of antibacterial and antifungal activities of synthesized compounds.

INTRODUCTION: Chalcones either natural or synthetic are well known to exhibit promising biological activities such as antibacterial, antitumor, anti-inflammatory analgesic antipyretic [1], antimalarial [2], and antituberculosis [3].

Chalcones are important starting materials for the synthesis of various classes of heterocyclic compounds such as thiazines, pyrazolines isoxazolines [4] and benzodiazepines [5] etc. Most of these compounds are highly bioactive and are widely used in pharmaceutics.

Benzodiazepines scaffold have recently received considerable attention because of their promising biological activities [6]. They also show anticancer [7], anticonvulsant [8] antimicrobial, antioxidant, anthelmintic and antibacterial activities [9].

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Due their wide range of pharmacological, industrial and synthetic applications, the synthesis of 1, 5-benzodiazepines are the have received considerable attention.

Generally, the method for the synthesis of 1, 5-benzodiazepines involves acid catalyzed cyclocondensation *o*-phenelenediamine with α, β-unsaturated carbonyl compounds [10], ketones [11], using piperidine-AcOH [12], $Ga(OTf)_3$ [13], HPW/SiO_2 [14], MoO_3SiO_2 [15], sulfated zirconia [16] and use of microwave irradiation technique [17] have well estabilished. However, most of these methods suffer from several disadvantages such as long reaction time, expensive reagent, harsh reaction conditions and high reflux temperature. Herein, we wish to report our results on the synthesis and antimicrobial activities of some novel 1, 5-benzodiazepine derivatives.

MATERIAL AND METHODS: 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, ^1H NMR was determined on a Bruker Avance II 400 Spectrometer against TMS as

internal standard. Mass spectra were recorded on waters Micromass Q-Tof Micro spectrometry. The purity of the compounds was checked by thin layer chromatography (TLC).

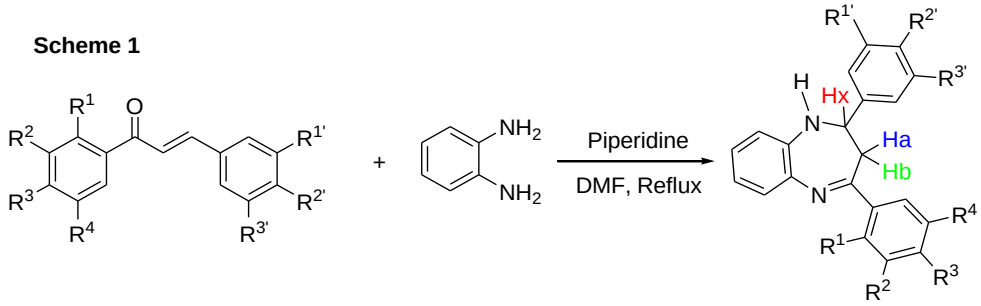
General procedure for the preparation of 1, 5-benzodiazepines (3a-j): A reaction mixture of α,β-unsaturated carbonyl compound **1c** (1mmol) and *o*-phenylenediamine **2** (1.5mmol) in DMF (15 ml) with few drops of piperidine was refluxed for 4-6 hrs. The progress of the reaction was monitored by using TLC.After completion of reaction, the reaction mixture was distilled to remove the excess solvent and poured into crushed ice. The crude solid product obtained was filtered, washed with water and recrystalized from ethanol to get product **(3c)** in good yields with high purity. Similarly other derivatives were also synthesized.

2,3-dihydro-2-(3,4,5-trimethoxyphenyl)-1*H*-1,5-benzodiazepine-4-yl)-4,6-diiodo-phenol (3c): ^{1}HNMR ($CDCl_3$, δ ppm): 2.9 (d, 1H, Ha); 3.1 (d, 1H, Hb); 3.7 (s, 9H, OMe); 5.1 (d, 1H, Hx); 6.10 (s, 1H, OH); 6.3 (d, 2H, Ar-H); 6.5 (m, 1H, Ar-H) 6.7 (d, 1H, Ar-H); 7.8 (m, 2H, Ar-H) 8.0 (s, 1H, NH). IR (KBr, cm^{-1}): 3334 (NH), 2916 (CH_3), 2850 (CH), 1589 (C=N), 1450 (Ar-H). Mass: m/z 657 (M+).

2,3-dihydro-2-(3,4,-dimethoxyphenyl)-1*H*-1,5-benzodiazepine-4-yl)-2,3-diiodobenzene-1,4-diol (3f): ^{1}HNMR ($CDCl_3$, δ ppm): 2.8 (d, 1H, Ha); 3.3 (d, 1H, Hb); 3.9 (s, 6H, OMe); 5.2 (d, 1H, Hx); 6.5-6.9 (m, 4H, Ar-H); 7.2 (m, 2H, Ar-H); 8.1 (m, 1H, Ar-H); 9.4 (s, 1H, NH). IR (KBr, cm^{-1}): 3429 (NH); 1647 (C=N); 1550, 1492 (ArH**).** Mass: m/z 642 (M+)

RESULT AND DISCUSSION: In the present work, involves the synthesis of 1, 5-benzodiazepines from the *o*-phenylenediamine and chalcones respectively **Scheme 1.** A condensation reaction of chalcones **1c** (1 mmol) and *o*-phenylenediamine **2** (1.5 mmol), was dissolved in DMF with few drops of piperidine was reflux for an appropriate time of 4-6 h. After completion of reaction, reaction mixture was worked-up to give the corresponding compound **3c** in 4 h with good yield **80%.**

Scheme 1



1 **2** **3a-i**

The products of reaction were purified by recrystallization process in ethanol solvent. With these optimized reaction conditions in hand, several substituted α, β-unsaturated carbonyl compound were treated with *o*-phenylenediamine and results are summarized in **Table 1.** Substituted α,β-unsaturated carbonyl compound carrying either electron releasing or electron withdrawing substituents in the *ortho*, *meta* and *para*–positions of the phenyl ring afforded good yields of benzodiazepines. The structures of some the compounds were established from IR, ^{1}HNMR and mass analysis.

TABLE 1: SYNTHESIS OF 2, 3-DIHYDRO-1,5-BENZODIAZEPINES USING PIPERIDINE IN DMF SOLVENT

Product	R_1	R_2	R_3	R_4	R_1'	R_2'	R_3'	Yield (%)	M.P. (°C)
3a	OH	Br	CH_3	Cl	OCH_3	OCH_3	H	74	133-134
3b	OH	Br	H	CH_3	OCH_3	OCH_3	H	78	120-122
3c	OH	I	H	I	OCH_3	OCH_3	OCH_3	80	162-163
3d	H	I	OH	I	OCH_3	OCH_3	OCH_3	76	130-131
3e	H	Br	OH	Br	OCH_3	OCH_3	OCH_3	77	170-171
3f	OH	I	OH	I	OCH_3	OCH_3	H	69	180-181
3g	OH	I	H	Cl	OCH_3	OCH_3	H	70	131-132
3h	OH	I	H	I	OCH_3	OCH_3	H	71	111-112
3i	OH	Br	H	Cl	OCH_3	OCH_3	H	68	126-127
3j	OH	Br	H	Cl	OCH_3	OCH_3	OCH_3	78	105-106

[a]Isolated yield

Antibacterial activity: The cup plate agar diffusion method [16-17] was employed for determining the antibacterial activity of the newly synthesized compounds **(3a-i)** against two gram positive bacteria viz., *Bacillus subtilis*, S*taphylococci aureus* and two gram negative bacteria viz., *Escherichia coli*, *Salmonella typhi*. The solutions of different compounds under test at a concentration of 200 ppm in 5% DMSO were poured in the cup/well of bacteria seeded agar plates. These plates were incubated at 37^{o}C for 24 hours for *E. coli*, whereas plates of other three bacteria were incubated at 27^{o}C for 24 hr. The standard antibiotics used were ampicillin (all at 200 ppm). The solution without compound i.e. only 5% DMSO was used as control which did not reveals any inhibition. The zone of inhibition produced by each compound was measured in mm. The results of antibacterial studies are given in **Table 2**.

TABLE 2: ANTIBACTERIAL ACTIVITY OF 2, 3-DIHYDRO-1, 5-BENZODIAZEPINE DERIVATIVES

Compound	Zone of inhibition in mm			
	B. subtilis	***S. aureus***	***E. coil***	***S. typhi***
3a	10	14	16	12
3b	12	16	19	14
3c	10	17	22	19
3d	14	12	16	16
3e	16	--	18	15
3f	11	12	16	12
3g	12	14	12	--
3h	22	--	19	10
3i	--	16	18	12
3j	--	15	22	19
Ampicillin	**27**	**28**	**26**	**25**

(--) indicates no zone of inhibition.

Antifungal activity: All those compounds screened for antibacterial activity were also tested for their antifungal activity using the same cup plate methode against *Aspergillus niger*, *Aspergillus oryzae*, *Aspergillus fumigatus and Candida parapsilosis.* The standard antibiotics used were ampicillin (all at 200 ppm). The solution without compound i.e. only 5% DMSO was used as control which did not reveals any inhibition. The zone of inhibition produced by each compound was measured in mm. The result of antibacterial studies is given in **table 3**.

TABLE 3: ANTIFUNGAL ACTIVITY OF 2, 3-DIHYDRO-1, 5-BENZODIAZEPINE DERIVATIVES

Compound	Zone of inhibition in mm			
	A. niger	***A. oryzae***	***A. fumi***	***C. para***
3a	15	14	20	12
3b	10	20	19	13
3c	19	19	--	23
3d	14	22	12	19
3e	--	15	16	10
3f	10	12	14	16
3g	13	10	12	17
3h	19	20	18	20
3i	15	14	15	10
3j	18	16	--	17
Ampicillin	**25**	**25**	**25**	**25**

(--) indicates no zone of inhibition.

CONCLUSION: The screening results revealed that the compounds 3a-j showed significant antimicrobial activity. In particular compounds 3a, 3b, 3c, 3d and 3f showed good to moderate antibacterial activity against the entire organism employed. Compounds 3b, 3h and 3j have showed high potency especially against *E. coli*, *B. subtilis and S. typhi*. Similarly compounds 3a, 3b, 3d, 3f, 3g, 3h and 3i showed good to moderate antifungal activity against the entire organism employed. Compound 3b, 3d, and 3h showed high inhibitory action on *Aspergillus oryzae.*

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