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SYNTHESIS AND ANTIMICROBIAL EVALUATION OF SOME NOVEL 2, 3-DIHYDRO-1, 5-BENZOTHIAZEPINE DERIVATIVES

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ABSTRACT: In the present investigation, a series of some novel 4-[substituted-2-hydroxy-phenyl]-2-(4′-dimethylamino-phenyl)-2, 3-dihydro-1, 5-benzothizepines (2a-l) have been synthesized by the treatment of 1-(substituted-2-hydroxy-phenyl)-3-(4′-dimethylamino-phenyl)-prop-2-en-1-ones (chalcones) (1a-l) with 2-aminothiophenol using ethanol as a solvent in the presence of catalytic amount of Lanthanum Nitrate in short reaction time with excellent yield (70-80%) by a conventional method. The products were tested for purity by TLC, and structures of newly synthesized compounds were confirmed by IR, ^{1}H NMR, and Mass spectral analysis. All these newly synthesized compounds were evaluated for their antibacterial activity against *Escherichia coli*, *Salmonella typhi*, *Staphylococcus aureus*, and *Bacillus subtilis* and antifungal activity against *Aspergillus niger*, *Penicillium chrysogenum*, *Fusarium moneliforme*, and *Aspergillus flavus*, using Penicillin and Greseofulvin as standard drugs. Most of the compounds showed significant activity.

INTRODUCTION: Heterocyclic chemistry is the branch of science that involves synthesis, properties, and applications of heterocycles. Hetero-cyclic system containing sulphur, nitrogen, and oxygen atoms. 1,4-benzothiazepines and 1,5-benzothiazepines are seven member heterocyclic compound containing sulphur and nitrogen atoms. 1, 5-benzothiazepines retained the interest of researchers due to the unique structural properties and broad spectrum of biological activities [1-2]. Benzothiazepines are well-known CNS depressant compounds and have emerged important area of research of treatment for traumatic conditions [3].

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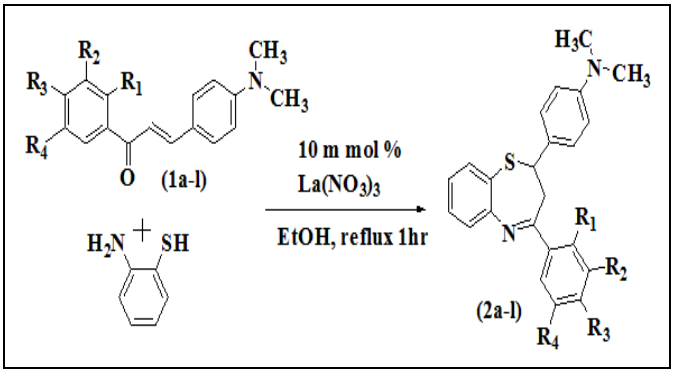
1, 5-benzothizepine showed a large number of pharmacological properties such as anti-inflammatory, [4] antiviral activities, [5] antiangiogenic and antioxidant agents [6] anticancer, [7-8] anti-bacterial, [9-10] cytotoxic agents, [11-12] antifungal, [13-14] anticonvulsant Agent [15] *etc*. It is well known that halogen substituted 1,5-benzothizepine compounds are also strongly biologically active [16-17]. On the other hand, halogens, methyl and hydroxy group substitution on benzene ring of 1,5-benzothiazepine molecules also exhibit good biological activities [18-19].

The 1, 5 benzothiazepine derivatives show locomotor inhibitory activity was explored in Swiss albino rat which may be translated with antianxiety or hypnotic effects by the fabricated molecules [20]. Therefore there has been a particular interest in the synthesis of halogen, methyl, and hydroxyl groups substituted 1, 5- benzothiazepines. In view of these observations, in the present investigation, we report

here the synthesis of a number of novel 1, 5-benzothiazepine derivatives (2a-l), having chloro, bromo, iodo, hydroxy, and methyl groups with an aim to find new most active antibacterial and antifungal agents. We have synthesized a novel series of 2- (4′- (dimethylamino-phenyl)- 4- (substituted-2-hydroxy-phenyl)-2, 3-dihydro-1, 5-benzothizepines as an antimicrobial agents by refluxing the substituted 2′-hydroxychalcones with 2-aminothiophenol in the presence of catalytic amount Lanthanum nitrate. The structures of the newly synthesized compounds (2a-l) were established on the basis of IR, ^{1}H NMR and Mass spectral data. All the newly synthesized compounds were tested for their *in-vitro* antibacterial activity against *Escherichia coli, Salmonella typhi, Staphylococcus aureus* and *Bacillus subtilis* and antifungal activity against *Aspergillus niger, Penicillium chrysogenum, Fusarium moneliforme* and *Aspergillus flavus,* using Penicillin and Greseofulvin as standard drugs.

MATERIALS AND METHODS: All the solvents and reagents were obtained from commercial sources and were used without further purification. The melting points were determined by the Open Capillary method and are uncorrected. The mass spectra were obtained with a Shimadzu GC-MS spectrophotometer. The IR spectra in KBr were recorded on Shimadzu Spectrophotometer, and ^{1}HNMR spectra were recorded in DMSO on Avance 300 MHz Spectrometer using TMS as internal standard. The chemical shift values are expressed in part per million (ppm) downfield from the internal standard, and signals are quoted as s (singlet), d (doublet), t (triplet), and m (multiplet). TLC was used to monitor the progress of all reactions and to check the purity of compounds by using ethyl acetate and petroleum ether as an eluent in the ratio of (3:7), which were further purified by column chromatography [ethyl acetate: pet ether (7:3)]. All the compounds were tested for their antibacterial and antifungal activities by the agar diffusion method.

General Method for the Synthesis of 2, 4-(substituted-phenyl)- 2, 3- dihydro- 1, 5-benzothiazepines: An equimolar reaction mixture of 2-aminothiophenol (0.001mol) and substituted 2′-hydroxy chalcone (0.001mol) in ethanol (10 ml) was refluxed for 1 h, in the presence of Lanthanum Nitrate (10 m mol %). The progress of the reaction was monitored by using TLC [eluent: ethyl acetate; pet ether (3:7)]. After completion of the reaction, the reaction mixture was distilled to remove the excess solvent, and the reaction mixture was poured on crushed ice. The solid crude product obtained was filtered off, washed with cold water, dried, and recrystallized by using ethanol to get corresponding 2,4-(substituted-aryl)-2,3-dihydro-1,5-benzothiaze-pine, which were further purified by column chromatography [ethyl acetate: pet ether (3:7)] in 70-80 % yield.



SCHEME 1: SYNTHESIS OF 2, 4-(SUBSTITUTED-PHENYL)-2, 3-DIHYDRO-1, 5-BENZOTHIAZEPINES

TABLE 1: PHYSICAL DATA OF NEWLY SYNTHESIZED 1, 5-BENZOTHIAZEPINE DERIVATIVES (2a-l)

S. no.	Entry	R_1	R_2	R_3	R_4	Molecular Formula	Yield in %	M. P. In °C
1	2a	OH	I	H	I	$C_{23}H_{20}N_2I_2OS$	75	105
2	2b	OH	I	H	CH_3	$C_{24}H_{23}N_2IOS$	72	157
3	2c	OH	Cl	H	Cl	$C_{23}H_{20}N_2Cl_2OS$	70	138
4	2d	OH	I	H	Cl	$C_{23}H_{20}N_2IClOS$	76	117
5	2e	OH	Br	H	CH_3	$C_{24}H_{23}N_2BrOS$	75	122
6	2f	OH	Br	H	Cl	$C_{23}H_{20}N_2BrClOS$	75	137
7	2g	OH	Br	H	Br	$C_{23}H_{20}N_2Br_2OS$	70	155
8	2h	OH	I	H	Br	$C_{23}H_{20}N_2IBrOS$	76	142
9	2i	OH	H	CH_3	Cl	$C_{24}H_{23}N_2ClOS$	77	172
10	2j	OH	H	H	Br	$C_{23}H_{20}N_2BrOS$	78	160
11	2k	H	Br	OH	Br	$C_{23}H_{20}N_2Br_2OS$	74	158
12	2l	H	I	OH	I	$C_{23}H_{20}N_2I_2OS$	75	105

RESULTS AND DISCUSSION: In recent years, one of the most important conventional methods used for the syntheses of 2, 4-substituted-phenyl-2, 3-dihydro-1, 5-benzothiazepine has been the reaction of α, β-unsaturated carbonyl compound, such as substituted 2′-hydroxy chalcone with 2-aminothiophenol [21]. 2-aminothiophenol and α, β-unsaturated carbonyl compounds or chalcones (1a-l) in ethanol was refluxed for 1 h, in the presence of Lanthanum nitrate. The reaction mixture was distilled to remove the excess of solvent, and the reaction mixture was poured on crushed ice and recrystallized by using ethanol to get 2,4-(substituted-phenyl)-2,3-dihydro-1,5-benzothiaze-pines (2a-l) in 70-80% yield. In the literature, 2-aminothiophenol has been reported to react with α, β-unsaturated carbonyl compounds or chalcones to give a Michael addition type adduct formed by the nucleophilic attack of the electron-rich thio group of the thiol on the β carbon atom of the chalcone, rendered electrophilic attack by a carbonyl group when the reaction is carried out under mild reaction conditions by using a basic medium [22]. It has also been reported that final products were obtained under basic reaction conditions. In this type of Michael addition reaction, the cyclized product obtained was isolated in one step as a final product. We identified the synthesized product exclusively, based on spectral observations.

In the present work, a series of novel 1, 5-benzothiazepines (2a-l) were synthesized by cyclization of corresponding o-hydroxychalcones (1a-l). All the synthesized 1, 5-benzothizepines didn't give positive Wilson test and red coloration with concentration H_2SO_4, which confirmed the formation of 1,5-benzohiazepines. The newly synthesized compounds have been confirmed first by TLC, and the Melting Points of the product were different from that of corresponding reactants. The structures of newly synthesized 2, 4-substituted phenyl-2,3-dihydro-1,5-benzothizepine derivatives were confirmed by IR, ^{1}H NMR and Mass spectral data. The IR spectrum of compound 2c exhibited peaks due to group C=N at 1589 cm^{-1} and C-S at 632 cm$^{-1,}$ respectively. The ^{1}H NMR spectrum shows characteristic peaks of a double doublet at δ 3.0 and δ 3.45 respectively due to proton of methylene group of seven member thiazepine rings, due to germinal and vicinal coupling of -CH_2 protons of the thiazepine ring.

Further, the -CH proton of the ring resonated as a triplet at δ 5.6 due to two vicinal couplings with the two non-equivalent protons of the methylene group at position three of the thiazepine ring. These observations are in agreement with the spectral data [23-24] as reported. All the newly synthesized 1, 5-benzothiazepines were evaluated for their antibacterial activity against the selected four different pathogens, such as *E. coli*, *S. typhi*, *S. aureus*, and *B. subtilis*. All the 1, 5-benzothizepine compounds does not show activity against *E. coli*. The compounds 2a, 2d, 2g, 2h, and 2j showed weak activity against *S. typhi*, while 2b, 2c, 2f, 2k and 2l showed stronger activity in comparison with standard (Penicilin) drugs. All the synthesized compounds of benzothiazepine except 2b, 2e showed moderate activity against *S. aureus*. The bromine substituted compounds 2j and 2k showed significant activity against *B. subtilis* as compared with standard drugs. All the newly synthesized compounds were evaluated for their antifungal activity against the four different pathogens *Aspergillus niger, Penicillium chrysogenum, Fusarium moneliforme and Aspergillus flavus*. The antifungal activity of some 1, 5-benzothiazepine compounds showed good activity against four pathogens. The presence of more electronegative substituted halogen atoms was found responsible for increasing antimicrobial activity.

Spectroscopic Data of Synthesized Compounds:

2- (4′- Dimethylamino-phenyl)- 4- (3-bromo-5-methyl- 2- hydroxy-phenyl)- 2, 3-dihydro- 1, 5-benzothiazepine (2e); Yield 75 % melting point 122 °C**,** IR (KBr): 3171 (-OH), 1589 (C=N) 1519 (C=C), 817 (C-Br), 632 (C-S) cm^{-1}; ^{1}H NMR (DMSO): δ 2.1 (s, 3H, CH_3), δ 2.80 (s, 6H, N-$(CH_3)_2$), δ 3.0 (dd, 1H, H_A), δ 3.45 (dd, 1H, H_B), δ 5.6 (t, 1H, H_X), δ 6.8-7.9 (m, 10H, Ar-H), δ 10.45 (s, 1H, OH, D_2O exchangeable); MS (m/z): 467 (M+1).

2- (4′- Dimethylmino-phenyl)- 4- (3- Bromo- 5-Chloro- 2- hydroxy-phenyl)- 2, 3- dihydro-1, 5-benzothizepine (2f); Yield 75 % melting point 137 °C**,** IR (KBr): 3194 (Ar-OH), 1610 (C=N), 1517 (C=C), 812 (C-Cl), 627 (C-S) cm^{-1}; ^{1}H NMR (DMSO): δ 2.80 (s, 6H, -N-$(CH_3)_2$), δ 3.0 (dd, 1H, H_A), δ 3.5 (dd, 1H, H_B), δ 5.50 (t, 1H, H_X), δ 6.7-7.9 (m, 10H, Ar-H), δ 10.50 (s, 1H, OH, D_2O exchangeable); MS (m/z):488 (M+1).

2-(4′-Dimethylamino-phenyl)-4-(3, 5-dibromo-2-hydroxy-phenyl)- 2, 3-dihydro- 1, 5-benzothizepine (2g): Yield 70% melting point 155 °C, IR (KBr): 3178 (Ar-OH), 1612 (C=N), 1519 (C=C),8 17 (C-Br), 648 (C-S) cm^{-1}; ^1H NMR (DMSO): δ 2.8 (s, 6H, N-$(CH_3)_2$), δ 3.0 (dd, 1H, H_A), δ 3.5 (dd, 1H, H_B), δ 5.55 (t, 1H, H_X), δ 6.8-7.8 (m, 10H, Ar-H), δ 10.50 (s, 1H, OH, D_2O exchangeable); MS (m/z); 532 (M+1).

2-(4′-Dimethylmino-phenyl)-4-(4-methyl-5-Choro-2-hydroxy-phenyl)-2,3-dihydro-1,5-benzo-thizepine (2i): Yield 77% melting point 172 °C, IR (KBr): 3172 (Ar-OH), 1588 (C=N), 1519 (C=C), 815 (C-Cl), 622 (C-S) cm^{-1}; ^1H NMR (DMSO): δ 2.2 (s, 3H, CH_3), δ 2.85 (s, 6H, -N-$(CH_3)_2$), δ 3.05 (dd, 1H, H_A), δ 3.45 (dd, 1H, H_B), δ 5.50 (t, 1H, H_X), δ 6.7-7.7 (m, 10H, Ar-H), δ 10.55 (s, 1H, OH, D_2O exchangeable); MS (m/z); 423 (M+1).

TABLE 2: ANTIMICROBIAL ACTIVITY OF SYNTHESIZED 1, 5-BENZOTHIAZEPINE DERIVATIVES (2a-l)

		Bacteria (Zone of Inhibition in mm)				Fungi (Zone of Inhibition in mm)			
S. no.	**Entry**	**A**	**B**	**C**	**D**	**E**	**F**	**G**	**H**
1	2a	--	15	22	11	RG	-ve	-ve	-ve
2	2b	--	18	--	23	-ve	-ve	-ve	-ve
3	2c	--	18	22	--	RG	-ve	-ve	-ve
4	2d	--	14	21	14	-ve	-ve	-ve	-ve
5	2e	--	16	--	--	-ve	-ve	-ve	-ve
6	2f	--	18	14	15	-ve	-ve	-ve	-ve
7	2g	--	16	18	--	-ve	-ve	-ve	-ve
8	2h	--	15	18	18	RG	-ve	-ve	-ve
9	2i	--	17	21	14	-ve	-vr	-ve	_ve
10	2j	--	13	21	28	RG	RG	-ve	-ve
11	2k	--	18	18	28	-ve	-ve	-ve	-ve
12	2l	--	18	16	18	-ve	RG	-ve	-ve
+ve Control DMSO		-ve	-ve	-ve	-ve	+ve	+ve	+ve	+ve
Penicillin		12	20	34	22	X	X	X	X
-ve Control (Griseofulvin)		X	X	X	X	-ve	-ve	-ve	-ve

(Zone of Inhibition in mm), *A = Escherichia coli, B = Salmonella typhi, C = Staphylococcus aureus, D =Bacillus subtilis E = Aspergillus niger, F = Penicillium chrysogenum, G = Fusarium moneliforme, H = Aspergillus flavus*, - = No Antibacterial activity, RG = Reduced Growth (Moderate Activity), -ve = Growth (Antifungal Activity Observed), X= Not Applicable

Antimicrobial Activity: All the newly synthesized 1, 5-benzothiazepine compounds (2a-l) were assessed for their antibacterial and antifungal activities against four different strains of bacteria such as *E. coli*, *S. typhi*, *S. aureus*, and *B. subtilis* and four fungi like *Aspergillus niger, Penicillium chrysogenum, Fusarium moneliforme* and *Aspergillus flavus*. The test for antibacterial activity was carried by agar cup method [25-26] (cup size 8mm) with nutrient agar as a medium, whereas antifungal activity was carried out by using potato-dextrose agar (PDA) medium by the same agar cup plate method. All newly synthesized compounds were dissolved in DMSO and used as control; the concentration of each test compound was 25µg/ml. The experiments were performed in triplicate in order to minimize the errors. The zone of inhibition was recorded after incubation at 37 °C for 24 h; the zone of inhibition produced by each compound was measured in mm. By using Standard drugs like Penicillin and Greseofulvin were used for comparison purposes. All the 1, 5-benzothizepine compounds does not show activity against *E. coli*. The compounds 2a, 2d, 2g, 2h and 2j showed lower activity against *S. typhi*, while 2b, 2c, 2f, 2k and 2l showed maximum activity in comparison with standard (Penicillin) drug. All the synthesized compounds of benzothiazepine except 2b, 2e showed moderate activity against *S. aureus*. The bromine substituted compounds 2j and 2k showed significant activity against *B. subtilis* in comparison with standard drugs. All the newly synthesized compounds were evaluated for their antifungal activity against the four different pathogens *Aspergillus niger, Penicillium chrysogenum, Fusarium moneliforme* and *Aspergillus flavus*. The antifungal activity of some benzothiazepine compounds showed good activity against four pathogens. The electronegative substituted halogen atoms were responsible to increase antimicrobial activity.

CONCLUSION: In conclusion, it can be summarized that, we have successfully synthesized

2, 4-(substituted-hydroxy-phenyl)-2, 3 dihydro-1, 5-benzothiazepine derivatives. The reaction described is a simple and highly efficient condensation reaction between substituted 2′-hydroxychalcones with *o*-aminothiophenol using Lanthanum Nitrate in ethanol. The advantages of the present protocol are simplicity of operation, time-saving, and high yield of the product. All the 1, 5-benzothizepine compounds do not show activity against *E. coli*. All the synthesized compounds of benzothiazepine except 2b, 2e showed moderate activity against *S. aureus*. The bromine substituted compounds 2j and 2k showed significant activity against *B. subtilis* as compared with the standard drug. The antifungal activity of some benzothiazepine compounds showed good activity against four pathogens selected. The presences of electronegative halogen atom were responsible for increasing antimicrobial activity.

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CONFLICTS OF INTEREST: The authors declare that there is no conflict of interest.

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