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Syntheses and Studies of 8-Substituted-2-(2-Chlorophenyl/3-chlorophenyl)-4-(4-hydroxyphenyl/phenyl)-2,3/2,5-dihydro-1,5-benzothiazepines

SEEMA PANT*, PUSHPA GODWAL and KUMARI SANJU

Department of Chemistry, Lal Bahadur Shastri Government College, Kotputli-303108, India

*Corresponding author: E-mail: drseemapant@yahoo.com

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Syntheses of novel twelve 8-substituted-2-(2-chlorophenyl/3-chlorophenyl)-4-(4-hydroxyphenyl/phenyl)-2,3/2,5-dihydro-1,5-benzothiazepines have been carried out by the reactions of 5-substituted 2-aminobenzenethiols, the substituents being fluoro, chloro, bromo, methyl, methoxy or ethoxy with α,β-unsaturated ketones, 3-(2-chlorophenyl)-1-(4-hydroxyphenyl)-2-propenone or 3-(3-chlorophenyl)-1-phenyl-2-propenone in dry ethanol in acidic medium in quest for the synthesis of 1,5-benzothiazepine compounds, which may have interesting biological activities. The precursors, substituted α,β-unsaturated ketones were obtained by employing the Claisen-Schmidt reaction; and the final products, obtained by Michael condensation, were characterized by analytical and spectral data comprising IR, ^{1}H NMR and mass spectral studies. Two different series, 2,3-dihydro and 2,5-dihydro series of the final compounds were obtained depending on the substituents present, as indicated by the ^{1}H NMR spectra. The newly synthesized compounds were studied for their antimicrobial activities against *Staphylococcus aureus*, *Escherichia coli* and *Candida albicans* taking imipenem, vancomycin and fluconazole as reference standards using Paper Disc method. Five of the compounds tested showed good antifungal activity against *Candida albicans* at the concentration of 200 µg/disc.

Keywords: 1,5-Benzothiazepines, Paper Disc method, α,β-Unsaturated ketones.

INTRODUCTION

1,5-Benzothiazepines possess an important place in the field of drug and pharmaceutical research [1]. Compounds having this structural unit show a broad spectrum of biological activities such as anticonvulsant [2,3], HIV-1 reverse transcriptase inhibitor [4], antifungal [5], antimicrobial [6], anticancer [7], anti-HIV, *etc*. The common strategy for the construction of 1,5-benzothiazepine moiety is the reaction of 1,3-diaryl prop-2-enones with *o*-aminothiophenol [8]. Diltiazem is important cardiovascular drug of 1,5-benzothiazepine class and has been used for the treatment of angina pectoris, coronary vasodilation, hypertension [9], Ca^{2+} concentration [10], migraine therapy, cancer therapy [11,12]. The cardiovascular drug clentiazem [13] shows a better activity than diltiazem, suggests that the chloro substituent at position-8 in the fused benzene ring may have acted as a pharmacophore. Introduction of chlorine as a chlorophenyl substituent at various positions in 1,5-benzothiazepine nucleus has fruitfully resulted in obtaining compounds having pharmacological activity [14], such as cardiovascular, antidepressive, tranquilizing, anti-ulcerous, anticancerous, anticholinergic, besides antibacterial and antifungal activity. In a study on various substituted 1,5-benzothiazepines, *in vitro* cytotoxic activity using Brine shrimp lethality assay has been reported in compounds having a hydroxyphenyl substituent [15]. In another study, using solid-phase synthesis and carrying out biological evaluation of a library of 2,3-dihydro-1,5-benzothiazepine, many compounds showed a significant potential as crown gall tumor inhibitors [16]. The results of the inhibition of cholinesterase revealed that the benzothiazepines have a greater potential as butyryl-cholinesterase inhibitors as compared to acetylcholinesterase. It is also inferred that the substitution of hydroxy group in the thiazepine ring may have led to increased activity. The results reflect a strong exploratory potential in search of new benzothiazepines as source of anticancer agents.

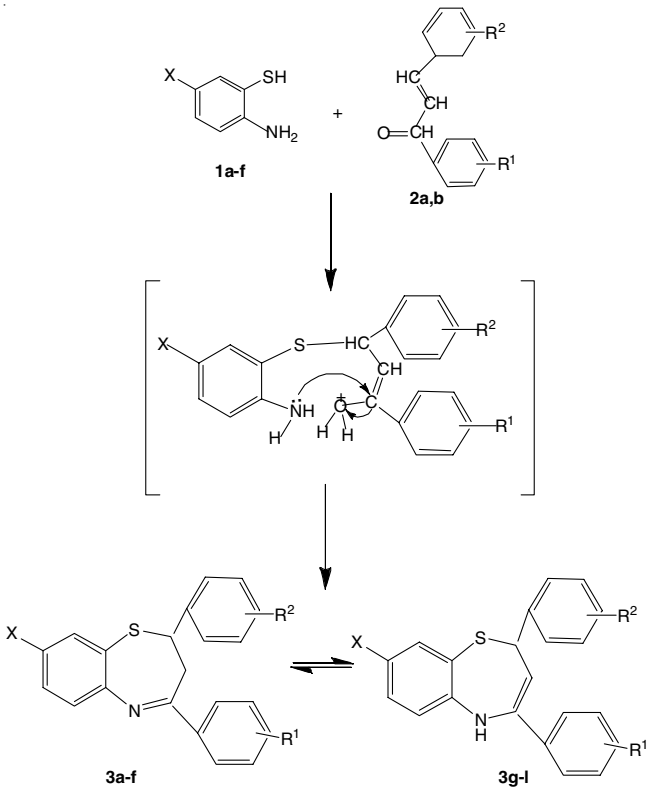
The importance of substituted 1,5-benzothiazepines as potent pharmaceutical compounds as cited above and in continuation

of our ongoing studies on the synthesis of diaryl 1,5-benzothiazepines, the synthesis and antimicrobial activity of new 8-substituted-2-(2-chlorophenyl/3-chlorophenyl)-4-(4-hydroxyphenyl/phenyl)-2,3/2,5-dihydro-1,5-benzothiazepines are being reported here.

EXPERIMENTAL

All the melting points are uncorrected. TLC was used for checking homogeneity of the compounds, using benzene: ethanol: aq. ammonia (50%) in the ratio 7:2:1 as solvent system. The IR spectra were taken in KBr pellets on a Perkin-Elmer RX1 FT IR spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker DRX-300 (300 MHz FT NMR with low and high temperature facility) TMS was used as internal standard and $CDCl_3$ as solvent. The FAB mass spectra were recorded on JEOL-SX 102/DA-600 Mass spectrometer/data system using argon/xenon (6 kV, 10 mA) as the FAB gas. The accelerating voltage was 10 kV and spectra were recorded at room temperature. *m*-Nitrobenzoyl alcohol (NBA) was used as the matrix. Micro estimations for C, H, N and S were carried out in Elemental Analyzer, Carlo Erba 1108. The spectral analyses and elemental analyses of selected compounds were carried out at the Sophisticated Analytical Instrumentation Facility, Central Drug Research Institute, Lucknow, India.

General procedure for the synthesis of 8-substituted 2-(2-chlorophenyl/3-chlorophenyl)-4-(4-hydroxyphenyl/phenyl)-2,3/2,5-dihydro-1,5-benzothiazepines (3a-l): The equimolar quantities of six 5-substitued-2-aminobenzenethiols [17], the substituents being fluoro, chloro, bromo, methyl, methoxy and ethoxy (**1a-f**) and 3-(2-chlorophenyl)-1-(4-hydroxyphenyl)-2-propenone **(2a)** or 3-(3-chlorophenyl)-1-phenyl-2-propen-one (**2b**) [18], in dry ethanol containing catalytic amount of trifluoroacetic acid were refluxed for 3-4 h to obtain twelve new 8-substituted-2-(2-chlorophenyl/3-chlorophenyl)-4-(4-hydroxyphenyl/phenyl)-2,3/2,5-dihydro-1,5-benzothiazepines **(3a-l)** in 62-66% yields (**3a-l**, **Scheme-I**). The physical constants and spectral data (IR and NMR) of the synthesized **3a-l** are given in Tables 1-3.



Scheme-I

Antimicrobial activity: The synthesized compounds have been screened for their antibacterial activity against the Gram-positive bacteria, *Staphylococcus aureus* and Gram-negative bacteria, *Escherichia coli* with reference drugs vancomycin and imipenem and for fungus *Candida albicans* with reference drug fluconazole using paper disc method [19] at the concentration of 200 µg/disc. Zones of inhibition, exhibited by the reference and test compounds were measured and relative activities were calculated as activity index. Zone of inhibition is the diameter of the area in which microorganisms have been destroyed.

TABLE-1
PHYSICAL CONSTANTS AND ANTIMICROBIAL DATA OF COMPOUNDS **3a-l**

Compd. No.	m.p. (°C)	R_f	Yield (%)	m.f.	m.w.	Antimicrobial studies		
						Bacteria		Fungus
						S. aureus	*E. coli*	*C. albicans*
3a	73	0.50	69	$C_{21}H_{15}NOFSCl$	382.5	–	17 (0.56)	20 (0.50)
3b	160	0.60	63	$C_{21}H_{15}NOS\ Cl_2$	399	–	15 (0.50)	–
3c	140	0.66	67	$C_{21}H_{15}NOSClBr$	444.5	13 (0.39)	13 (0.43)	–
3d	150	0.63	65	$C_{22}H_{18}NOSCl$	379.5	25 (0.75)	18 (0.60)	20 (0.50)
3e	110	0.58	63	$C_{22}H_{18}NO_2SCl$	395.5	–	18 (0.60)	–
3f	109	0.70	62	$C_{23}H_{20}NO_2SCl$	409.5	–	–	–
3g	75	0.68	60	$C_{21}H_{15}NFSCl$	367.5	–	13 (0.37)	18 (0.90)
3h	162	0.76	62	$C_{21}H_{15}NSCl_2$	383	13 (0.39)	–	35 (1.75)
3i	70	0.77	61	$C_{21}H_{15}NSClBr$	428.5	–	18 (0.51)	36 (1.80)
3j	185	0.79	64	$C_{22}H_{18}NSCl$	363.5	25 (0.75)	20 (0.57)	40 (2.00)
3k	52	0.78	66	$C_{21}H_{18}NOSCl$	379.5	–	17 (0.48)	25 (1.25)
3l	45	0.82	62	$C_{23}H_{20}NOSCl$	393.5	–	–	30 (1.50)

Zones of inhibition are given in mm. Values in parentheses represent activity index. Zone of inhibition of vancomycin for *Staphylococcus aureus* is 33 mm. Zone of inhibition of imipenem for *Escherichia coli* is 30 (**3a-f**) and 35 (**3g-l**). Zone of inhibition of fluconazole for *Candida albicans* is 40 (**3a-f**) and 20 (**3g-l**).

TABLE-2
IR SPECTRAL DATA (cm^{-1}) OF COMPOUNDS **3a-l**

Compd. No.	ν(O-H)	ν(N-H)	ν(C=N)	ν(C-Cl)
3a	3388	–	1605	999
3b	3386	–	1604	978
3c	3389	–	1605	928
3d	3383	–	1601	1010
3e	3375	–	1603	870
3f	3376	–	1602	889
3g	–	3141	–	989
3h	–	3152	–	970
3i	–	3139	–	929
3j	–	3140	–	1012
3k	–	3143	–	873
3l	–	3135	–	880

RESULTS AND DISCUSSION

Acid catalyzed reaction of 5-substituted 2-aminobenzenethiols (**1a-f**) with the enolizable 3-(2-chlorophenyl/3-chlorophenyl)-1-(4-hydroxyphenyl/phenyl)-2-propenone (**2a-b)** is initiated by the nucleophilic attack of the lone pair of sulphydryl electrons at the activated β-carbon atom of unsaturated ketones [20]. The nucleophilic addition of sulphhydryl electrons to C_2 results in the formation of sulfur-carbon bond, results in sulfur becoming electron deficient and withdrawal of electrons from S-H bond. The carbanionic center at C-3 attracts the hydrogen ion thus resulting in the formation of intermediates, which finally lead to the formation of tautomeric 2,3-dihydro or 2,5-dihydro forms of the final product. The attack by the lone pair of electrons on nitrogen of the amino group on C-3, results in the formation of an N-C bond. This leads to the migration of a proton from nitrogen to electronegative oxygen atom, which thus undergoes dehydrative cyclization to give cyclized seven membered heterocyclic products in the second step. Analytical data of the synthesized compounds are presented in Table-1.

The structures of the final products were ascertained by spectral analyses comprising IR, ^{1}H NMR and mass spectral studies. In the IR spectra of the compounds **3a-f**, a broad absorption was obtained in the region 3389-3375 cm^{-1} which indicated the presence of a hydroxyl group. An absorption band which was obtained in the region 1605-1601 cm^{-1} indicated the presence of a C=N group. These absorptions were conspicuously absent in the IR spectra of compounds **3g-l**. The presence of a secondary amino group was indicated by an absorption band in the range 3152-3135 cm^{-1} in compounds **3g-l** (Table-2).

The ^{1}H NMR spectra of the final compounds **3a-f** showed sharp absorptions in the region δ 2.90-3.93, 3.45-4.00, 5.45-5.80 ppm, occurring as double doublets in ABX pattern, each corresponding to one proton and absorption band at δ 6.55-7.50 ppm, as multiplet corresponding to the aromatic protons. The signals corresponding to the methylene and methine protons at C-3 and C-2, respectively, were found, to occur as double doublets. Due to *vicinal-geminal* coupling of the two protons of C-3 and one proton of C-2, the double doublets occurred in the range, δ 2.90-3.93 (dd; J_{AB} 16, J_{AX} 8; 1H), δ 3.45-4.00 (dd; J_{AB} 16, J_{BX} 7; 1H) and δ 5.45-5.80 (dd; J_{AX} 8, J_{BX} 7; 1H).These observations indicated the formation of 2,3-dihydro form and may occur due to the presence of hydrogen bond between the protons at C-3 and *p*-hydroxy group of aryl ring present at C-2 position (Table-3).

The spectra of compounds **3g-l** compounds showed a broad signal in the range, δ 4.08-4.18 ppm in all the NMR spectra, which may be assigned to N-H absorption. The doublet appearing in the downfield region, at δ 4.40-5.17 ppm (d, 1H, J = 8 Hz), which may be assigned to the proton at C-2; the other doublet at δ 5.67-5.80 ppm (d, 1H, J = 8 Hz), may be assigned to C-3 vinylic proton. The absorptions in the region δ 6.25-7.97 ppm, appearing as multiplet, corresponded to the aromatic protons. The appearance of two doublets, corresponding to one proton each and a broad signal around δ 4 indicates the formation of 2,5-dihydro form of the final products **3g-l**.

Antimicrobial Activity: Reference drugs vancomycin (*Staphylococcus aureus* and *Escherichia coli*), imipenem (*Escherichia coli*) and fluconazole (*Candida albicans*) were used to measure relative antibacterial and antifungal activities in the form of activity index. While moderate antibacterial activity was shown by all the compounds, all the compounds of the second series showed marked antifungal activity, *i.e.*

TABLE-3
^{1}H NMR SPECTRAL DATA OF COMPOUNDS **3a-l** (δ VALUES IN ppm, J IN Hz)

Compd. No.	N-H (br, 1H)	C_2	C_3	C_8	Aromatic protons (12 H, m)
3a	–	5.70 (H_X dd; J_{AX}8, J_{BX}7)	3.00 (H_A dd; J_{AB}16, J_{AX}8); 4.00 (H_B dd; J_{AB}16, J_{BX}7)	–	6.58-7.45
3b	–	5.75 (H_X dd; J_{AX}8, J_{BX}7)	3.01 (H_A dd; J_{AB}16, J_{AX}7); 3.45 (H_B dd; J_{AB}16, J_{BX}7)	–	6.60-7.48
3c	–	5.72 (H_X dd; J_{AX}8, J_{BX}7)	2.96 (H_A dd; J_{AB}16, J_{AX}7); 3.62(H_B dd; J_{AB}16, J_{BX}7)	–	6.58-7.50
3d	–	5.77 (H_X dd; J_{AX}8, J_{BX}7)	3.01 (H_A dd; J_{AB}16, J_{AX}7); 3.65 (H_B dd; J_{AB}16, J_{BX}7)	2.40 (s, 3H)	6.56-7.47
3e	–	5.80 (H_X dd; J_{AX}8, J_{BX}7)	3.93 (H_A dd; J_{AB}16, J_{AX}7); 3.62 (H_B dd; J_{AB}16, J_{BX}7)	3.83 (s, 3H)	6.55-7.45
3f	–	5.45 (H_X dd; J_{AX}8, J_{BX}7)	2.90 (H_A dd; J_{AB}16, J_{AX}7); 3.68 (H_B dd; J_{AB}16, J_{BX}7)	1.40 (3H, t) 4.30 (2H, q)	6.65-7.46
3g	4.10	4.40 (1H, d, *J*8)	5.70 (1H, d, *J*8)	–	6.25-7.40
3h	4.13	5.17 (1H, d, *J*8)	5.67 (1H, d, *J*8)	–	6.45-7.38
3i	4.08	4.55 (1H, d, *J*8)	5.72 (1H, d, *J*8)	–	6.78-7.80
3j	4.12	4.58 (1H, d, *J*8)	5.77 (1H, d, *J*8)	2.37 (3H, s)	6.68-7.85
3k	4.18	4.42 (1H, d, *J*8)	5.80 (1H, d, *J*8)	3.85 (3H, s)	6.70-7.67
3l	4.15	4.47 (1H, d, *J*8)	5.72 (1H, d, *J*8)	1.43 (3H, t) 4.10 (2H, q)	6.99-7.97

greater than the reference used, at the concentration of 200 µg/disc with compound 2-(3-chlorophenyl)-8-methyl-4-phenyl-2,5-dihydro-1,5-benzothiazepine (**3j**) showing double activity shown by the reference standard. This indicates that the presence of *m*-chloro substituted phenyl ring at position-2, along with the phenyl ring at position-4, may have resulted in the enhanced antifungal activity against *Candida albicans* (Table-1).

Conclusion

The formation of 2,3-dihydro of benzothiazepines **(3a-f)** may due to the series of six compounds having a substituent which may stabilize the isomer. Against bacteria, *Escherichia coli,* most of the compounds showed activity higher than the reference standard. The antifungal activity against *Candida albicans* was found to be greater (activity index ≥ 1) than the reference standard in all 2,5-dihydro compounds (**3g-l**).

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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