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Syntheses of 1,5-Benzothiazepines: Part-50: 8-Substituted 2,3/2,5-dihydro-2,4-diaryl-1,5-benzothiazepines as Potential Antimicrobial Agents

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The syntheses of two novel series of 8-substituted 2,5-dihydro-2,4-*bis*(2,4-dichlorophenyl)-1,5-benzothiazepines and 8-substituted 2,3-dihydro-2-(2,4-dichlorophenyl)-4-(2-hydroxyphenyl)-1,5-benzothiazepines being reported herein were achieved by the reactions of 5-substituted 2-aminobenzenethiols, the substituents being fluoro, chloro, bromo, methyl, methoxy, ethoxy, with α,β-unsaturated carbonyl compounds. The enolizable ketone, 1,3-*bis*(2,4-dichlorophenyl)-2-propenone, or 3-(2,4-dichlorophenyl)-1-(2-hydroxyphenyl)-2-propenone, was reacted with the 5-substituted 2-aminobenzenethiols in dry ethanol containing trifluoroacetic acid, to obtain 12 new compounds, 8-substituted 2,3/2,5-dihydro-2,4-diaryl-1,5-benzothiazepines by Michael type condensation reaction. The products were characterized on the basis of micro analytical data and spectral analysis comprising IR, ^{1}H NMR and mass spectral studies. All the compounds were screened for antimicrobial activity, against the Gram-positive *Staphylococcus aureus* and Gram-negative bacteria, *Enterobacter cloacae* and *Klebsiella aerogenes* with various reference drugs, Vancomycin for *Staphylococcus aureus* and *Enterobacter cloacae*, polymyxin B for *Klebsiella aerogenes* and against the fungus *Candida albicans* with reference drug fluconazole.

Keywords: 1,5-Benzothiazepines, 2-Aminobenzenethiols, Michael condensation, Antimicrobial activity.

INTRODUCTION

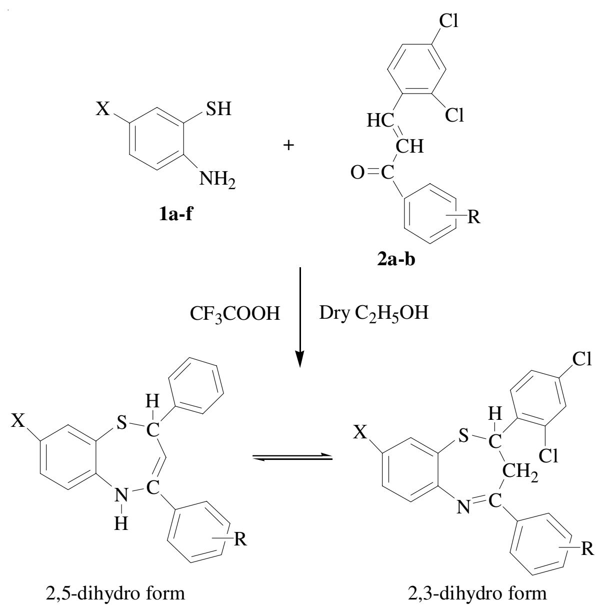
The chemotherapeutic utilization of halogenated 1,4- and 1,5-benzodiazepines, *e.g.* chlordiazepoxide [1], clobazam [2], triflubazam [3] as CNS drugs prompted the study of analogous benzothiazepine compounds. Interestingly, these compounds have been found to show pronounced cardiovascular activities, the most prominent emergent drug being diltiazem [4], which has been found to be useful in the treatment of angina pectoris and is useful in coronary vasodilation and regulation of Ca^{2+} concentration. The possession of better therapeutic properties by clentiazem [5], having an 8-chloro substituent in the 1,5-benzothiazepine nucleus has lead to greater studies in the field of 1,5-benzothiazepine compounds. Besides cardiovascular activity, other pharmacological activities, namely, antidepressive, tranquilizing, antiulcer [6], anticancer [7,8], anticholinergic [9], antibacterial [10-12] and antifungal activities [13-15] have also been reported. These studies suggest that the halogen present may have acted as a pharmacophore and may have imparted bioactivity to these compounds. Some hydroxy substituted 1,5-benzothiazepines have been reported [16,17] as potent inhibitors of butyl cholinesterase. Thus, the syntheses of 8-substituted 2,3/2,5-dihydro-2,4-diaryl-1,5-benzothiazepines were undertaken and are being reported in the present communication.

EXPERIMENTAL

All the recorded melting points are uncorrected. Homogeneity of the compounds was checked by TLC on glass plates coated with silica gel G using solvent system, benzene:ethanol: aq. ammonia (50 %) (7:2:1, upper layer). The IR spectra were taken in KBr pellets on a Perkin Elmer Spectrum Version 10.03.06. NMR spectra were recorded on Agilent 700vnmrs700 instrument using DMSO/Bruker DRX-300 using $CDCl_3$ as solvent. The FAB mass spectra were recorded on a JEOL-SX 102/DA-6000 Mass spectrometer using Argon/Xenon (6kV, 10 mA) as the FAB gas. The accelerating voltage was 10kV and spectra were recorded at room temperature. *m*-Nitrobenzyl alcohol was used as the matrix. Micro estimations for carbon, hydrogen and nitrogen were carried out in elemental analyzer, Carlo Erba 1108. The spectral and elemental analyses of some of the compounds were carried out at the Sophisticated Analytical Instrumentation Facility, Central Drug Research Institute, Lucknow, India.

5-Substituted 2-aminobenzenethiol (**1a-f**) was required to be reacted with α,β-unsaturated carbonyl compound, 1,3-*bis*(2,4-dichlorophenyl)-2-propenone (**2a**) or 3-(2,4-dichlorophenyl)-1-(2-hydroxyphenyl)-2-propenone (**2b**), to obtain two novel series of bicyclic 8-substituted 2,5-dihydro-2,4-*bis*(2,4-

dichlorophenyl)-1,5-benzothiazepines (**3a-f**) and 8-substituted 2,3-dihydro-4-(2-hydroxyphenyl)-2-(2,4-dichlorophenyl)-1,5-benzothiazepines (**3g-l**). The precursors, 5-substituted 2-aminobenzenethiols (**1a-f**) [15] and chalcone [18,19], compound **2** were prepared in the laboratory using literature reported methods. Equimolar quantity of the propenone was then reacted with 5-substituted 2-aminobenzenethiols, in acidic medium to obtain the title products **3a-l** (**Scheme-I**). Using paper disc method [20], all the compounds were evaluated for antimicrobial activity, comprising antibacterial and antifungal, by comparing their zones of inhibition with respect to their respective reference standards.



3a-l

Compound	X	R	Compound	X	R
3a	F	2,4-$(Cl)_2$	**3g**	F	2-OH
3b	Cl	2,4-$(Cl)_2$	**3h**	Cl	2-OH
3c	Br	2,4-$(Cl)_2$	**3i**	Br	2-OH
3d	CH_3	2,4-$(Cl)_2$	**3j**	CH_3	2-OH
3e	OCH_3	2,4-$(Cl)_2$	**3k**	OCH_3	2-OH
3f	OC_2H_5	2,4-$(Cl)_2$	**3l**	OC_2H_5	2-OH

Scheme-I

Preparation of 8-substituted 2,3/2,5-dihydro-2,4-diaryl-1, 5-benzothiazepines (3a-l): Equimolar quantities of 5-substituted 2-aminobenzenethiol (**1a-f**, 0.001 mol) and 1,3-diaryl-2-propenone (**2a-b**, 0.001 mol) were dissolved in dry ethanol (15 mL) containing TFA and mixed together with stirring; and then refluxed for 3-7 h. Excess of the solvent was removed under reduced pressure and the resultant reaction mixture was kept in refrigerator for 24 h to obtain crude solid, which on crystallization from ethanol gave crystals of the targeted bicyclic-1,5-benzothiazepines (**3a-l**). The physico-chemical data of the synthesized compounds is given in Table-1.

RESULTS AND DISCUSSION

The reactions are known to be initiated by nucleophilic attack of sulfhydryl electrons on β-carbon atom of α,β-unsaturated carbonyl system [21], which is made more electrophilic in acidic medium. The protonation of the carbonyl group makes the β-carbon atom susceptible to nucleophilic attack by the thiol, leading to the formation of Michael type adduct, which under the strongly acidic reaction conditions, undergoes dehydrative cyclization, to give the final products in a single concerted step. The structures of the final products were ascertained on the basis of elemental and spectral analysis comprising IR, ^{1}H NMR (Tables 2 and 3) and mass spectra.

The IR spectra of **3a-f** showed a broad absorption corresponding to ν(N-H) around 3175-3165 cm^{-1}. However, the spectra of compounds **3g-l** showed strong characteristic ν(C=N) absorption bands in the range 1609-1593 cm^{-1}, in place of the N-H absorptions. None of the products showed any absorption band in the range of 1650-1700 cm^{-1} and 3450-3350 cm^{-1}, characteristic of carbonyl group of α,β-unsaturated ketone and primary amino group ($-NH_2$), respectively and an absorption band at around 2600-2500 cm^{-1} due to ν(S-H) group was also found to be absent. The absence of these absorptions bands indicated that the respective thiols had reacted with chalcones to give the final products without the isolation of the intermediate, in a single step. Other absorptions observed at about 800 cm^{-1} may be assigned to C-Cl stretching absorptions; broad

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

Compd. No.	m.p. (°C)	R_f	Yield (%)	m.f.	m.w.	Antimicrobial Activity			
						S. aureus	*E. coli*	*K. aerogenes*	*C. albicans*
3a	66	0.81	53.19	$C_{21}H_{12}NSCl_4F$	470.00	–	6 (0.33)	8 (0.72)	11 (0.44)
3b	180	0.73	70.84	$C_{21}H_{12}NSCl_5$	487.50	13 (0.76)	–	9 (0.81)	10 (0.40)
3c	200	0.67	62.03	$C_{21}H_{12}NSBrCl_4$	532.00	14 (0.82)	8 (0.44)	–	8 (0.32)
3d	220	0.85	74.94	$C_{22}H_{15}NSCl_4$	467.00	–	10 (0.55)	7 (0.63)	–
3e	186	0.78	89.09	$C_{22}H_{15}NOSCl_4$	483.00	15 (0.88)	–	–	13 (0.52)
3f	210	0.88	58.98	$C_{23}H_{17}NOSCl_4$	497.00	–	12 (0.66)	6 (0.54)	14 (0.56)
3g	80-84	0.61	82.00	$C_{21}H_{14}NOSCl_2F$	418.31	–	–	13 (1.18)	4 (0.16)
3h	90-92	0.63	86.17	$C_{21}H_{14}NOSCl_3$	434.76	15 (0.88)	15 (0.88)	10 (0.90)	14 (0.56)
3i	105-107	0.67	88.70	$C_{21}H_{14}NOSBrCl_2$	479.21	–	–	–	6 (0.24)
3j	110-112	0.61	83.00	$C_{22}H_{17}NOSCl_2$	414.34	16 (0.94)	–	–	10 (0.40)
3k	120-122	0.64	86.00	$C_{22}H_{17}NO_2SCl_2$	430.34	–	–	13 (1.18)	4 (0.16)
3l	80-82	0.67	80.00	$C_{23}H_{19}NO_2SCl_2$	444.37	15 (0.88)	2 (0.11)	–	5 (0.20)

Zone of inhibition are given in mm, values in parentheses represent activity index.
Zone of Inhibition of vancomycin for *Staphylococcus aureus*, *Enterobacter cloacae* is 15-21 mm.
Zone of Inhibition of polymyxin-B for *Klebsiella aerogenes* is > 12 mm.
Zone of Inhibition of fluconazole for *Candida albicans* is 25 mm.
Concentration of test and reference compounds was 200 µg/disc.

TABLE-2
IR (cm^{-1}) AND ^{1}H NMR (DMSO, δ VALUES IN ppm, *J* IN Hz) SPECTRAL DATA OF COMPOUNDS **3a-f**

Comp. No.	IR		^{1}H NMR			
	ν(C-Cl)	ν(N-H)	NH (br, 1H)	C_2-H (1H, d, *J* 7 Hz)	C_3-H (1H, d, *J* 7 Hz)	Aromatic protons (9H, m)
3a	810	3165	4.10	7.41	8.04	7.51-7.85
3b	798	3170	4.14	7.35	8.15	7.49-8.00
3c	805	3175	4.08	7.25	8.29	7.12-8.13
3d	811	3171	4.12	7.21	8.10	7.32-8.00
3e	800	3166	4.10	7.28	8.26	7.32-8.12
3f	789	3370	4.10	7.22	8.15	7.28-7.97

TABLE-3
IR (cm^{-1}) AND ^{1}H NMR ($CDCl_3$, δ VALUES IN ppm, *J* IN Hz) SPECTRAL DATA OF COMPOUNDS **3g-l**

Comp. No.	IR			^{1}H NMR			
	ν(O-H)	ν(C=N)	ν(C-Cl)	H_A (dd; J_{AB} 16, J_{AX} 8)	H_B (dd; J_{AB} 16, J_{BX} 7)	H_X (dd; J_{AX} 8, J_{BX} 7)	Aromatic protons (10H, m)
3g	3435	1600	1010	2.82	3.05	5.78	6.88-8.34
3h	3400	1605	998	2.80	3.04	5.70	6.78-7.99
3i	3420	1593	805	2.79	2.99	5.80	6.93-8.29
3j	3410	1609	1011	2.83	3.80	5.78	6.92-8.24
3k	3400	1600	870	2.75	3.84	5.68	6.37-7.48
3l	3440	1605	889	2.80	3.01	5.81	7.05-8.87

signals around 3400 cm^{-1} to O-H stretching and the signals for phenolic C-O stretch and O-H stretching vibrations were observed at 1215.7-1201.5 and 1405.87-1403.92 cm^{-1}.

The ^{1}H NMR spectra of the bicyclic benzothiazepines, 8-substituted 2,5-dihydro-2,4-*bis*(2,4-dichlorophenyl)-1,5-benzothiazepines (**3a-f**) showed two doublets, each integrating for one proton, in the region δ 7.21-7.41 (d, *J* = 7 Hz, 1H), assigned to C_2-H and in the region δ 8.04-8.29 (d, *J* = 7 Hz, 1H), assigned to C_3-H; the downfield absorptions may be due to their presence in the deshielding zone of aryl ring and proximity to electronegative sulfur atom. A broad absorption due to one proton at δ 4.08-4.14 may be assigned to secondary amino proton in all the compounds. The presence of one hydrogen at C_3 and –NH indicated the preferential formation of 2,5-dihydro enamino form (**Scheme-I**). The continuation of p-π conjugation makes 2,5-dihydro form more stable than the tautomeric 2,3-dihydro form. While the spectrum of compound **3d** showed a three proton singlet at δ 2.35 corresponding to 8-methyl group, a singlet of three protons at δ 3.73 was observed corresponding to the methoxy protons in the spectrum of compound **3e**. Aromatic protons were observed in the range δ 7.12-8.13. In the mass spectra of all the compounds, the clusterous pattern of the molecular ion peaks affirmed the presence of chlorine.

The ^{1}H NMR spectra of compounds **3g-l** showed double doublets signals corresponding to the methylene and methine protons at C-3 and C-2, in the ABX pattern in the range, δ 2.75-2.99 (dd; J_{AB} 16, J_{AX} 8; 1H), δ 2.99-3.85 (dd; J_{AB} 16, J_{BX} 7; 1H) and δ 5.52-5.85 (dd; J_{AX} 8, J_{BX} 7; 1H). The appearance of these signals may be assigned to the presence of hydrogen bond between the protons at C-3 and *o*-hydroxy group of aryl ring present at C_2 and/or C_4 position. These observations indicated the preferential formation of 2,3-dihydro over 2,5-dihydro form (**Scheme-I**).

8-Methyl and 8-methoxy groups absorbed as singlets of three protons at 2.81 and 3.62 in the spectra of **3j** and **3k**; while the spectrum of **3l** showed the three proton triplet at 1.45 and the two proton quartet at 3.94, which corresponded to 8-ethoxy group.

Antimicrobial activity: Against the Gram-positive bacteria, *Staphylococcus aureus*, compound **3j** showed maximum activity (activity index = 0.94) and compounds **3h, 3l** showed good activity (activity index = 0.88). In case of Gram-negative bacteria *Klebsiella aerogenes*, compounds **3h** and **3k** showed higher activity (activity index = 1.18) than reference compound and **3i** showed good activity (activity index = 0.90) (Table-1).

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