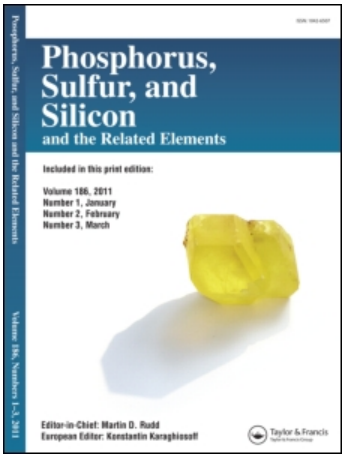

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Syntheses of 1,5-Benzothiazepines: Part XXXVI—Syntheses and Antimicrobial Evaluation of 2-(2-Chlorophenyl)-4-(4-chlorophenyl/2-thienyl)-2,5-dihydro-8-substituted-1,5-benzothiazepines

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Six 5-substituted-2-aminobenzenethiols have been reacted with 3-(2-chlorophenyl)-1-(4-chlorophenyl)-2-propenone and 3-(2-chlorophenyl)-1-(2-thienyl)-2-propenone in dry ethanol saturated with dry HCl gas, to obtain twelve new compounds, 8-substituted-2-(2-chlorophenyl)-4-(4-chlorophenyl/2-thienyl)-2,5-dihydro-1,5-benzothiazepines in satisfactory yields. The structures of the final products have been assigned by elemental microanalyses data for elements, C, H, and N and by IR, ^1H NMR, and mass spectroscopies. The synthesized compounds have been evaluated for their relative antimicrobial activity against the gram-positive bacteria, Staphylococcus aureus, gram-negative bacteria, Pseudomonas aeruginosa and the fungus, Candida albicans. The compounds have been found to show little antibacterial activity, but interestingly, showed significant antifungal activity.

Keywords Antifungal; chlorophenyl; clentiazem; diltiazem

INTRODUCTION

Drug designing attempts to obtain improved versions of diltiazem have resulted into the discovery of clentiazem,[1] which has a chlorine atom as a substituent in the fused benzene ring of 1,5-benzothiazepine nucleus. Introduction of chlorine as a chlorophenyl substituent at

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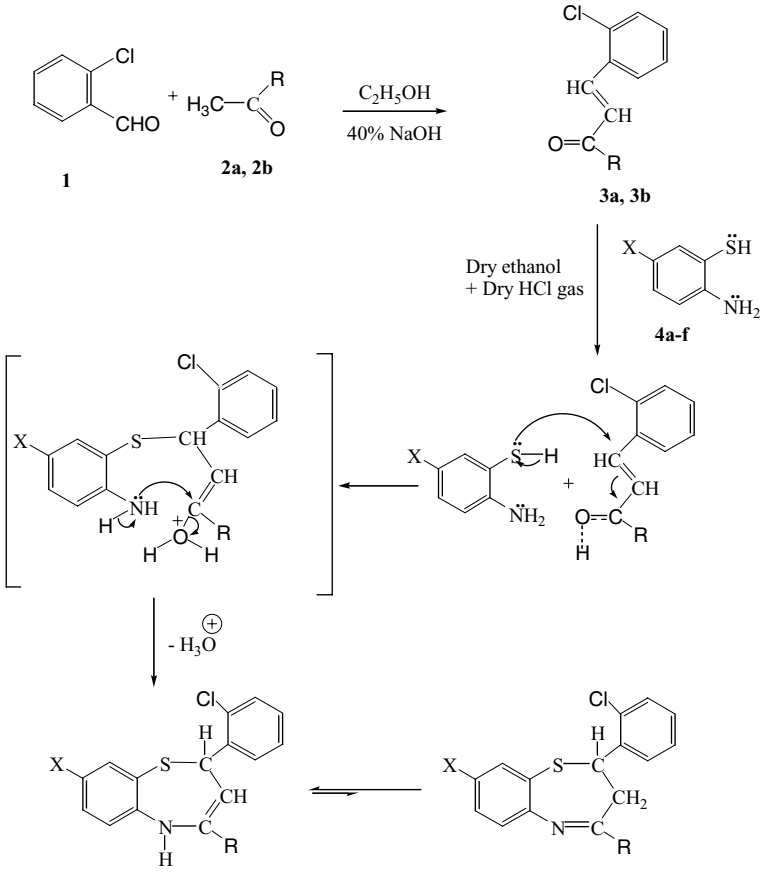
various positions of 1,5-benzothiazepine nucleus has been found fruitful to yield compounds possessing[2–5] antiulcerous, antidepressive, antihypertensive, anticancerous, and Ca^{2+} antagonist activity. These have also been reported to possess antibacterial[6] and antifungal[6] activity. Antiulcerous,[7] analgesic,[8] vasodepressant,[9] antibacterial,[10] antifungal,[11] etc., activity have been reported in 1,5-benzothiazepines having chlorophenyl group along with different heterocyclic groups at positions 2, 3, and 4. We have synthesized and reported[12–17] different series of 1,5-benzothiazepines, having chlorophenyl group at various positions. A series of benzopyranobenzothiazepines having a chlorophenyl group[18] and monochlorophenyl and dichlorophenyl substituents were studied to find out the effects of increased proportion of chlorine on antimicrobial activity.[19] Antimicrobial studies of 1,5-benzothiazepines having heterocyclic substituents such as thienyl and pyridyl have been reported recently.[20] Synthesis and antimicrobial activities of two series of 1,5-benzothiazepines are reported here to evaluate the effect of chlorine as chlorophenyl vis-à-vis thienyl by studying 2-chlorophenyl with 4-chlorophenyl substituent and 2-chlorophenyl along with thienyl.

RESULTS AND DISCUSSION

In order to have a substituent in the fused benzene ring and having a chlorophenyl group as 2-chlorophenyl and 4-chlorophenyl and heterocyclic group as thienyl in the thiazepine ring of 1,5-benzothiazepine nucleus, the starting materials, 5-substituted-2-aminobenzenethiols[12–20] (**4a–f**), and other precursors, a ketone, 3-(2-chlorophenyl)-1-(4-chlorophenyl)-2-propenone[21] (**3a**), and an α,β-unsaturated heterocyclic carbonyl compound, 3-(2-chlorophenyl)-1-(2-thienyl)-2-propenone[22] (**3b**) were prepared. Equimolar quantities of these reactants **4a–f** and **3a** or **3b** were reacted to obtain the title compounds, 2-(2-chlorophenyl)-4-(4-chlorophenyl/2-thienyl)-2,5-dihydro-8-substituted-1,5-benzothiazepines (**5a–l**, Scheme 1).

It has been well established that such reactions[12–18] take place in two steps. In the first step, nucleophilic attack by the sulfhydryl electrons of 5-substituted-2-aminobenzenethiols takes place on the activated β-carbon atom of the α,β-unsaturated carbonyl compounds to give Michael-adduct type intermediates, which simultaneously undergo dehydrative cyclization to give final products in the second step. The formation of the intermediate and/or cyclized product has been found to depend significantly on the reaction conditions.[23–25] We have found[12–17] that the cyclized products were obtained in a single step in maximum



5a-l (i) **5a-l (ii)**

5	X	R	5	X	R
a	F	4-ClC_6H_4	**g**	F	2-C_4H_3S
b	Cl	4-ClC_6H_4	**h**	Cl	2-C_4H_3S
c	Br	4-ClC_6H_4	**i**	Br	2-C_4H_3S
d	CH_3	4-ClC_6H_4	**j**	CH_3	2-C_4H_3S
e	OCH_3	4-ClC_6H_4	**k**	OCH_3	2-C_4H_3S
f	OC_2H_5	4-ClC_6H_4	**l**	OC_2H_5	2-C_4H_3S

SCHEME 1

yields in an acidic medium i.e. in methanol/ethanol saturated with dry hydrogen chloride gas. Hence, the reactions of 5-substituted-2-aminobenzenethiols (**4a–f**) with 3-(2-chlorophenyl)-1-(4-chlorophenyl)-2-propenone (**3a**) and 3-(2-chlorophenyl)-1-(2-thienyl)-2-propenone (**3b**) have been carried out in dry ethanol saturated with hydrogen chloride to obtain 12 new compounds,

2-(2-chlorophenyl)-4-(4-chlorophenyl/2-thienyl)-2,5-dihydro-8-substituted-1,5-benzothiazepines (**5a–l**, Scheme 1) in a single step in 58−68% yields. The structures of the final products were ascertained by microanalysis data of C, H, N (Table I) and spectral analysis comprising IR, ^{1}H NMR (Table II) and mass spectra.

SPECTROSCOPIC STUDIES

The IR spectra of the final products did not show characteristic absorptions for C = O and NH_2 in the region 1690−1650 cm^{-1} and 3445−3200 cm^{-1}, respectively. However, they showed an absorption band in the region 3150−3140 cm^{-1}, which is due to secondary amino group. These observations indicate that the reactions between, 3-(2-chlorophenyl)-1-(4-chlorophenyl/2-thienyl)-2-propenone (**3a, 3b**) and 5-substituted-2-aminobenzene-thiols (**4a–f**) had taken place negating the formation of the intermediates.

The ^{1}H NMR spectra showed[12−17,20] two doublets at δ 6.70−6.95 (d, 1H, J = 7Hz) and δ 7.94−8.20 (d, 1H, J = 7Hz), integrating for one proton each, which may be assigned to C-2-H and C-3-H absorption peaks, respectively. The downfield absorption of C-2-H may be accounted for its attachment with an electronegative sulfur atom and electronegative phenyl group. A broad singlet of one proton absorption at δ 4.07−4.13 (1H) may be assigned to NH. The formation of 2,5-dihydro structure (an enamino form (**5a–l**, **i**), a more stable form rather than 2,3-dihydro form (an imino structure (**5a–l**,**ii**), may be understood to take place due to extended conjugation through p electrons of nitrogen with π electrons (**5a–l**, **i**). The ^{1}H NMR spectra of **5d** and **5j** showed a singlet of three protons at δ 2.34 and 2.36 (s, 3H) assigned to methyl protons and also a singlet of three protons at δ 3.82 and 3.94 (s, 3H) in compounds **5e** and **5k** respectively, assigned to methoxyl group protons. Compound **5f** and **5l**, showed a triplet at δ 1.34−1.44 (t, 3H, J = 7Hz) and quartet at δ 4.03−4.10 (q, 2H, J = 7Hz), due to methyl and methylene protons of ethoxyl group. Absorption peaks as multiplets of aromatic protons were found at δ 6.90−8.15 (m, 11H) in compounds **5a—f** and at around δ 6.85−8.02 (m, 10H) in compounds **5g–l** (Table II).

TABLE I Physical Constants and Microanalytical Data of 2-(2-Chlorophenyl)-4-(4-chlorophenyl/2-thienyl)-2,5-dihydro-8-substituted-1,5-benzothiazepines (5a–l)

					Elemental analysis Found (calcd.) (%)		
Compd. no.	M.P. (°C)	R_f	Yield (%)	Mol. Formula (Mol. Wt.)	C	H	N
5a	86–88	0.60	62	$C_{21}H_{14}SNCl_2F$ (402)	62.52 (62.68)	3.52 (3.48)	3.38 (3.48)
5b	80–82	0.68	60	$C_{21}H_{14}SNCl_3$ (418.5)	60.38 (60.21)	3.26 (3.34)	3.42 (3.34)
5c	104–105	0.58	60	$C_{21}H_{14}SNCl_2Br$ (463)	54.29 (54.42)	3.11 (3.02)	2.98 (3.02)
5d	65–67	0.62	67	$C_{22}H_{17}SNCl_2$ (398)	66.26 (66.33)	4.19 (4.27)	3.47 (3.51)
5e	88–90	0.56	62	$C_{22}H_{17}OSNCl_2$ (414)	63.67 (63.76)	4.14 (4.10)	3.32 (3.38)
5f	89–90	0.60	68	$C_{23}H_{19}OSNCl_2$ (428)	64.56 (64.48)	4.32 (4.43)	3.16 (3.27)
5g	98–99	0.61	60	$C_{19}H_{13}S_2NClF$ (373.5)	61.15 (61.04)	3.54 (3.48)	3.68 (3.74)
5h	120–121	0.56	59	$C_{19}H_{13}S_2NCl_2$ (390)	58.39 (58.46)	3.26 (3.33)	3.66 (3.58)
5i	113–114	0.52	58	$C_{19}H_{13}S_2NClBr$ (434.5)	52.41 (52.47)	3.08 (2.99)	3.09 (3.22)
5j	130–132	0.54	61	$C_{20}H_{16}S_2NCl$ (369.5)	65.07 (64.95)	4.26 (4.33)	3.91 (3.78)
5k	88–90	0.58	58	$C_{20}H_{16}OS_2NCl$ (385.5)	62.32 (62.25)	4.02 (4.15)	3.72 (3.63)
5l	110–112	0.58	63	$C_{21}H_{18}OS_2NCl$ (399.5)	62.94 (63.07)	4.61 (4.50)	3.41 (3.50)

TABLE II Characteristic IR Absorptions (ν in cm^{-1}), ^1H NMR ($CDCl_3$, δ Values in ppm, J in Hz) Signals of 2-(2-Chlorophenyl)-4-(4-chlorophenyl/2-thienyl)-2,5-dihydro-8-substituted-1,5-benzothiazepines (5a–l)

Compd. no.	νNH	NH (br, 1H)	C-2-H (d, 1H, J = 7)	C-3-H (d, 1H, J = 7)	C-8-XH	Aromatic protons (m)
5a	3140	4.12	6.85	8.15	—	6.90–8.09
5b	3150	4.11	6.90	8.12	—	7.00–8.00
5c	3142	4.12	6.80	8.02	—	6.95–8.00
5d	3145	4.10	6.70	7.95	2.34 (s, 3H)	6.95–7.80
5e	3142	4.09	6.95	8.20	3.82 (s, 3H)	7.02–8.15
5f	3140	4.13	6.72	8.15	1.37 (3H, t, J = 7) 4.03 (2H, q, J = 7)	6.95–8.02
5g	3140	4.11	6.83	7.99	—	6.85–8.00
5h	3145	4.09	6.82	8.00	—	6.94–7.95
5i	3142	4.07	6.90	8.05	—	6.94–8.00
5j	3150	4.07	6.84	7.94	2.36 (s, 3H)	6.98–7.92
5k	3141	4.12	6.82	8.00	3.94 (s, 3H)	6.94–8.02
5l	3146	4.13	6.92	8.02	1.44 (3H, t, J = 7) 4.10 (2H, q, J = 7)	7.00–7.99

The mass spectrum of **5b** showed cluster of isotopic molecular ion peaks, m/z, 417, 419, 421, and 423 which corresponded to $[M]^+$, $[M+2]^+$, $[M+4]^+$, and $[M+6]^+$, respectively, while compound **5h** showed molecular ion peaks, m/z, $[M]^+$ at 389, $[M+2]^+$ at 391 and $[M+4]^+$ at 393. The pattern of molecular ion peaks confirmed the presence of three chlorine atoms in the **5b** and two chlorine atoms in **5h**. The elemental analyses of the final products were found to be satisfactory within the permissible limits of error (Table I).

ANTIMICROBIAL ACTIVITY

All the synthesized compounds, **5a–l** were screened for their relative antibacterial activity against the gram-positive bacteria, *Staphylococcus aureus* and the gram-negative bacteria, *Pseudomonas aeruginosa* and antifungal activity against the fungus, *Candida albicans* by using Plate Disc Method[26–28] at the concentration of 100 μg/disc. Gatifloxin, natilmicin, and fluconazole were used as reference compounds for*S. aureus*, *P. aeruginosa* and *C. albicans* respectively. The zone of inhibition exhibited by test and reference compounds were measured in 40 h incubation period and relative activity was calculated as activity index

(Table III).

$$\text{Activity Index} = \frac{\text{Zone of inhibition exhibited by test compound}}{\text{Zone of inhibition exhibited by the reference compound}} \quad (1)$$

EXPERIMENTAL

All the melting points are uncorrected. The purity of compounds was checked by TLC on glass plates coated with silica gel 'G' using Solvent system, benzene: ethanol: aq. ammonia (50%) (7:3:1). The IR spectra were taken in KBr pellets on Shimadzu 8201 PC spectrophotometer. NMR spectra were recorded on a Bruker DRX-300 (300 MHz FT NMR) instrument using $CDCl_3$ as solvent and TMS as internal standard. The FAB mass spectra were recorded on JEOL-SX 102/DA-6000 Mass spectrometer/Data system using Argon/Xenon (6kV, 10 mA) as the FAB gas. The accelerating voltage was 10 kV and spectra were recorded at room temperature. *m*-Nitrobenzyl alcohol (NBA) was used as the matrix. Microestimations for carbon, hydrogen, and nitrogen were carried out in Elemental Analyzer, Carlo Erba 1108. The spectral analysis and

TABLE III Zone of Inhibition[a] and Activity Index[b] of 5a—l[f] Against the Bacteria, *Staphylococcus Aureus*[c] and *Pseudomonas Aeruginosa*[d] and the Fungus, *Candida Albicans*[e]

Compd. no.	*S. aureus*	*P. aeruginosa*	*C. albicans*
5a	13 (0.52)	8 (0.33)	—
5b	15 (0.68)	10 (0.42)	22 (1.57)
5c	—	24 (1.00)	10 (0.71)
5d	14 (0.56)	—	10 (0.71)
5e	14 (0.56)	18 (0.75)	18 (1.29)
5f	14 (0.56)	10 (0.42)	18 (1.29)
5g	8 (0.36)	16 (0.67)	—
5h	15 (0.68)	17 (0.71)	22 (1.57)
5i	20 (0.91)	17 (0.71)	—
5j	8 (0.36)	18 (0.75)	20 (1.43)
5k	18 (0.81)	—	18 (1.29)
5l	8 (0.36)	12 (0.50)	24 (1.71)

[a]Zone of Inhibitions is in mm.[b]Values in parentheses represent activity index.[c]Zone of Inhibition of Gatifloxin for *S. aureus* is 25 mm for **5a–f** and 22mm for **5g–l**.[d]Zone of Inhibition of Natilmicin for *P. aeruginosa* is 24 mm.[e]Zone of Inhibition of Fluconazole for *C. albicans* is 14 mm.[f] Concentration used for the test and reference compounds were 100 μg/disc.

elemental analysis were carried out at the Sophisticated Analytical Instrumentation Facility, Central Drug Research Institute, Lucknow.

α, β - Unsaturated carbonyl compound, 3-(2-chlorophenyl)-1-(4-chlorophenyl)-2-propenone[21] (**3a**), α,β-unsaturated heterocyclic ketone, 3-(2-chlorophenyl)-1-(2-thienyl)-2-propenone[22] (**3b**) and 5-substituted-2-aminobenzenethiols[12–20](**4a–f**) were prepared by literature reported methods**.**

General Procedure for the Preparation of 2-(2-chlorophenyl)-4-(4-chlorophenyl/2-thienyl)-2,5-dihydro-8-substituted-1,5-benzothiazepines (5a-l)

Equimolar quantities of 5-substituted-2-aminobenzenethiols (**4**, 0.001 mol) and 3-(2-chlorophenyl)-1-(4-chlorophenyl/2-thienyl)-2-propenone (**3a/3b**, 0.001 mol) were taken in dry ethanol (15 mL) saturated with dry HCl gas. The reaction mixtures were refluxed till the color changed from light brown to deep red and concentrated under reduced pressure to obtain crude solid. The crude solid thus obtained was crystallized from methanol to obtain title compounds (**5a–l**).

The microanalytical and spectral data of **5a–l** are given successively in the Tables I–II.

ANTIMICROBIAL ACTIVITY

The Plate Disc Method was used for determining the antibacterial and antifungal activity given as follows:

The nutrient agar culture media needed for testing antibacterial activity was prepared by mixing a mixture of agar-agar (15 g), NaCl (5 g), beef extract (1.5 g), yeast extract (1.5 g) and peptic digest of animal tissues (5 g) in one litre of distilled water. The pH of the culture media was maintained at 7.4 ± 0.2. For testing antifungal activity, the sabouraud dextrose agar culture media was prepared by mixing mycological peptone (10 g), dextrose (40 g), and agar-agar (15 g) in 1 L of distilled water. The pH of the culture media was maintained at 5.6 ± 0.2. The Petri plates containing the culture were inoculated with the required bacterial suspension or by even streaking of fungal suspension. The density of bacterial or fungal suspension (approximately 10^8 bacteria or fungi/ml) was standardized by dilution with sterile saline or broth to a density visually equivalent to McFarland standard or barium sulfate standard. Filter paper discs of test and reference compounds of dose 100 μg/disc were placed onto these plates and incubated for 40 h at 37°C. The zone of inhibition was measured and compared with

standard reference drugs. The results have been reported as activity index (Table III).

CONCLUSION

All the synthesized compounds showed only mild antibacterial activity. Compound **5i** showed the highest relative activity against the gram-positive bacteria *Staphylococcus aureus*; whereas, compound **5c** showed meaningful activity index, equal to that of the reference compound against the gram-negative bacteria, *Pseudomonas aeruginosa.*

Compounds **5b**,**5h**, and **5j** showed high activity against the fungus, *Candida albicans* whereas; compound **5l** showed significant and most profitable activity (Table III).These observations lead us to state that the 4-(2-thienyl)-substituted 2-(2-chlorophenyl)-1,5-benzothiazepines were found to be more active than the compounds 4-(4-chlorophenyl)-substituted 2-(2-chlorophenyl)-1,5-benzothiazepines, i.e., 2-thienyl substituent at position 4 vis-à-vis 4-chlorophenyl substituent rendered more activity to the compounds.

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