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Syntheses of 1,5-Benzothiazepines: Part 52: Syntheses of 8-Substituted 2,5-Dihydro-4-(4-bromophenyl)-2-(2-furyl/2,4-dichlorophenyl)-1,5-benzothiazepines

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ABSTRACT

Two enolizable ketones, 1-(4-bromophenyl)-3-(2,4-dichlorophenyl)-2-propenone and 1-(4-bromophenyl)-3-(2-furyl)-2-propenone were reacted with six 5- substituted-2-amino benzenethiols, in dry ethanol containing trifluoroacetic acid to obtain 12 new compounds, 8-substituted-2,5-dihydro-4-(4-bromophenyl)-2-(2,4-dichlorophenyl/2-furyl)-1,5-benzothiazepines in 59-73 % yields. The products were characterized on the basis of microanalytical data and spectral analysis comprising IR, ^{1}H NMR, and mass studies. All the synthesized compounds have been screened for their antimicrobial activity against the Gram-positive bacteria, *Staphylococcus aureus* and Gram-negative bacteria, *Escherichia coli*, *Enterobacter cloacae* and the fungus, *Candida albicans* with respective reference compounds. 8-Ethoxy-4-(4-bromophenyl)-2-(2,4-dichlorophenyl)-2,5-dihydro-1,5-benzothiazepine and 8-bromo-4-(4-bromophenyl)-2-(2-furyl)-2,5-dihydro-1,5-benzothiazepine compounds displayed notable antibacterial activity against *Staphylococcus aureus*, which was higher than that of the reference standard vancomycin at the concentration of 200 µg/disc. Six of the newly synthesized compounds were found to show significant antifungal activity against *Candida albicans*.

KEYWORDS

Enolisable ketones, Trifluoroacetic acid, Antibacterial, Antifungal activity

INTRODUCTION

Benzothiazepines are seven membered heterocyclic compounds that are bioisosters of benzodiazepines [1]. Studies on the bioavailability of heterocyclic chalcones from natural sources are limited, but synthetic heterocyclic chalcones have been reported to have a wide range of biological properties, especially antibacterial [2] and antifungal activities [3]. Out of the analogous 1,5-benzodiazepines, 5-furoyl-2,2,4-trimethyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine has been found to act as inflammatory agent [4]. On survey of literature, 1,5-benzothiazepines having different heterocyclyl groups at positions 2, 3 and 4 have been found to function as Ca^{2+} antagonist [5], antiulcer [6], analgesic [7], vasodepressant [8,9], antihypertensive [10], antiamnesia and antidementia [11] agents, besides acting as antibacterial [12] and antifungal [13] agents.

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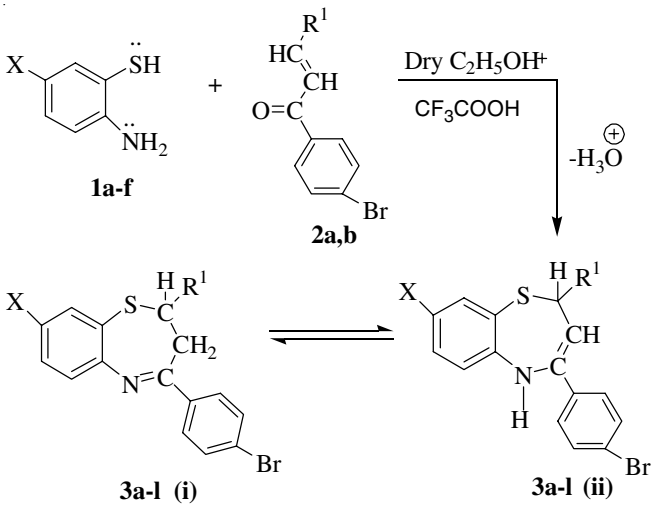
In an effort to develop potent antimicrobial agents by comparing the effect of presence of heterocyclyl furyl and chlorophenyl moiety, we herein report our studies on 12 novel compounds, 8-substituted-2,5-dihydro-4-(4-bromophenyl)-2-(2,4-dichlorophenyl/2-furyl)-1,5-benzothiazepines (**3a-l**), the substituents being fluoro, chloro, bromo, methyl, methoxy and ethoxy. All the synthesized compounds have been screened for their antibacterial and antifungal activity using paper disc method [14] against Gram-positive bacteria, *Staphylococcus aureus*, Gram-negative bacteria, *Escherichia coli* and *Enterobacter cloacae* and fungus, *Candida albicans* with reference compounds vancomycin, gatifloxacin and fluconazole, respectively.

EXPERIMENTAL

For the syntheses of target compounds, precursors 5-substituted 2-aminobenzenethiols (**1a-f**), were reacted with enolizable ketones, 1-(4-bromophenyl)-3-(2,4-dichlorophenyl/2-furyl)-2-propenone (**2a,b**) in order to obtain twelve new products, 8-substituted 2,5-dihydro-2-(2,4-dichlorophenyl/2-furyl)-4-phenyl-1,5-benzothiazepines (**3a-l**).The reactants were refluxed for 4-7 h in dry ethanol saturated with trifluoroacetic acid to obtain the targeted products in 54-93 % yields in a single step (**Scheme-I**).



Compd. No.	X	R^1	Compd. No.	X	R^1
3a	F	2,4-$C_6H_3Cl_2$	**3g**	F	2-C_4H_3O
3b	Cl	2,4-$C_6H_3Cl_2$	**3h**	Cl	2-C_4H_3O
3c	Br	2,4-$C_6H_3Cl_2$	**3i**	Br	2-C_4H_3O
3d	CH_3	2,4-$C_6H_3Cl_2$	**3j**	CH_3	2-C_4H_3O
3e	OCH_3	2,4-$C_6H_3Cl_2$	**3k**	OCH_3	2-C_4H_3O
3f	OC_2H_5	2,4-$C_6H_3Cl_2$	**3l**	OC_2H_5	2-C_4H_3O

Scheme-I: 8-Substituted 2,5-dihydro-4-(4-bromophenyl)-2-(2,4-dichlorophenyl/2-furyl)-1,5-benzothiazepines

The progress of reactions was monitored by TLC, on silica gel 'G' coated glass plates, using the solvent system benzene: ethanol:aq. NH_3 (upper layer, 50 %) in the ratio 7:2:1. The structures of final products were ascertained by microanalyses for C, H and N (Table-1) and spectral analyses comprising IR, ^{1}H NMR, and mass studies. All the compounds were evaluated for antibacterial and antifungal activities by measuring the activity index.

General method for synthesis of 8-substituted-4-(4-bromophenyl)-2-(substituted aryl/furyl)-2,5-dihydro-1,5-benzothiazepines (3a-l): To an ethanolic solution of propenone (2, 0.001 mol) was added the solution of 5-substituted 2-amino benzenethiol (**1**, 0.001 mol) in dry ethanol (5 mL) with continuous stirring. Trifluoroacetic acid (1 mL) was added into this mixture and the resultant refluxed for 4-7 h, when its colour change became constant. The reaction mixture was cooled and excess of the solvent was removed under reduced pressure to obtain the crude solid. The solid thus obtained was crystallized from ethanol to afford the desired compounds (**3a-l**).

Melting points of all newly synthesized compounds are uncorrected. The IR spectra were taken in KBr pellets on a Perkin Elmer Spectrum RX1 FT IR spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker DRX-300. TMS was used as internal standard.

The mass spectra were recorded on JEOL-SX-102 (FAB)/ Da-600 mass spectrometer/data system using Argon/Xenon (6 kV, 10 mA) as FAB gas. The accelerating voltage was 10 kV and spectra were recorded at room temperature. *m*-Nitrobenzyl alcohol (NBA) was used as matrix. Microestimations for carbon, hydrogen and nitrogen were carried out in elemental analyzer, Carlo Erba 1108. The spectral analyses and elemental analyses of some compounds were carried out at Sophisticated Analytical Instrumentation Facility (SAIF), Central Drug Research Institute, Lucknow, India.

RESULTS AND DISCUSSION

The IR spectra of final products (**3a-l**), showed a single absorption band in the region 3270-3100 cm^{-1}, which may be due to the presence of secondary amino group and absorptions at around 2950-2920 cm^{-1} may be assigned to stretching vibrations of aliphatic C-H; an absorption band in the region of 680-580 cm^{-1}, which may be assigned to νC-Br, was also exhibited by all the compounds. The final products **3a-f** showed absorption bands in the region 805-735 cm^{-1} due to C-Cl. It has been established [11,15] that acid catalyzed reactions of 5-substituted 2-aminobenzenethiols with α,β-unsaturated ketones occur in a single step to give the heterocyclic 1,5-benzothiazepines.The first formed Michael type adduct, undergoes simultaneous dehydrative cyclization to give the target compounds. The absence of absorptions corresponding to carbonyl, thiol and primary amino groups in their respective regions indicated the single step formation of final compounds **3a-l**. Besides, the signal absorption in the region of 3270-3140 cm^{-1} indicated the presence of a secondary amino group. The ^{1}H NMR spectra of all the compounds exhibited a distinct set of two doublets in the downfield region 6.15-6.99 and 6.91-7.01, which may be assigned to C_2-H and C_3-H, respectively. The downfield absorption of C-2 proton may be accounted to its orientation in the deshielding zone of aryl ring and its attachment to electronegative sulphur atom whereas downfield absorption of C_3-H may be due to it being a vinylic proton. The appearance of ^{1}H NMR spectra indicates the preferential formation of 2,5-dihydro tautomer.

The ^{1}H NMR spectra (Table-2) of all the final products **3a-l** showed a doublet at δ 6.15-6.99 integrating for one proton, assigned to C_2-H, as it is split into a doublet by C-3 proton and

TABLE-1
PHYSICO-CHEMICAL AND ANTIMICROBIAL DATA OF COMPOUNDS **3a-l**

Compd. No.	m.p. (°C)	R_f	Yield (%)	m.f.	Elemental analysis (%): Found (calcd.)				Bacteria			Fungus
									Gram-positive	Gram-negative		
					C	H	N	S	*S. aureus*	*E. coli*	*E. cloacae*	*C. albicans*
3a	82-84	0.81	68.39	$C_{21}H_{13}NSBrCl_2F$	–	–	2.78 (2.93)	6.59 (6.71)	15 (1.00)	11 (0.36)	–	–
3b	92-94	0.68	88.31	$C_{21}H_{13}NSBrCl_3$	51.98 (52.15)	3.97 (4.00)	2.67 (2.64)	–	14 (0.93)	–	–	–
3c	86-88	0.69	88.19	$C_{21}H_{13}NSBr_2Cl_2$	–	–	2.45 (2.44)	–	–	–	–	9 (0.36)
3d	84-86	0.73	89.77	$C_{22}H_{16}NSBrCl_2$	56.45 (56.60)	4.53 (4.75)	2.67 (2.75)	–	16 (1.06)	–	–	12 (0.48)
3e	92-94	0.67	90.76	$C_{22}H_{16}NOSBrCl_2$	–	–	–	6.08 (6.10)	–	–	–	–
3f	108-110	0.63	92.57	$C_{23}H_{18}NOSBrCl_2$	–	4.82 (4.86)	2.59 (2.60)	–	16 (1.06)	12 (0.40)	–	–
3g	57-59	0.57	78.12	$C_{19}H_{13}NOSBrF$	58.10 (58.07)	4.67 (4.87)	–	–	14 (0.93)	14 (0.46)	–	–
3h	58-60	0.62	87.55	$C_{19}H_{13}NOSBrCl$	–	–	–	7.09 (7.11)	–	–	–	11 (0.44)
3i	80-82	0.64	81.23	$C_{19}H_{13}NOS\ Br_2$	50.89 (50.93)	4.28 (4.27)	2.34 (2.83)	6.43 (6.47)	15 (1.00)	–	–	15 (0.60)
3j	56-58	0.61	78.32	$C_{20}H_{16}NOSBr$	–	5.61 (5.62)	3.20 (3.25)	–	13 (0.86)	–	–	–
3k	57-59	0.66	69.11	$C_{20}H_{16}NO_2SBr$	58.90 (59.19)	5.39 (5.42)	–	–	–	–	–	8 (0.32)
3l	60-62	0.62	59.34	$C_{21}H_{18}NO_2SBr$	–	–	3.12 (3.04)	6.93 (6.96)	16 (1.06)	14 (0.46)	–	–

Zone of inhibition are given in mm; Values in parentheses represent activity index; Zone of inhibition of vancomycin for *Staphylococcus aureus* is 15 mm; Zone of inhibition of polymixin B for *Enterobacter cloacae* is 11 mm; Zone of inhibition of fluconazole for *Candida albicans* is 25 mm; Concentration of test and reference compounds were 200 µg/disc.

TABLE-2
CHARACTERISTIC ^{1}H NMR SIGNALS OF **3a-l** ($CDCl_3$, δ VALUES IN ppm, *J* IN Hz)

Compound No.	NH (br, 1H)	C_2-H (1H, d, *J* = 7 Hz)	C_3-H (1H, d, *J* = 7 Hz)	C_8-XH	Aromatic protons (10H, m)
3a	3.76	6.15	6.99	–	6.20-7.30
3b	3.78	6.17	6.96	–	6.00-7.70
3c	3.76	6.95	6.93	–	6.07-7.20
3d	3.78	6.99	6.01	2.49 (s, 3H)	6.10-7.00
3e	3.76	6.93	6.89	3.85 (s, 3H)	6.00-7.30
3f	3.78	6.99	7.01	1.46 (t, 3H, *J* = 7); 4.09 (q, 2H, *J* = 7)	6.60-7.20
3g	3.76	6.44	6.89	–	6.58-7.96
3h	3.85	6.47	7.01	–	6.54-7.92
3i	3.82	6.45	6.95	–	6.57-7.95
3j	3.85	6.43	7.00	2.42 (s, 3H)	6.56-7.93
3k	3.78	6.44	6.91	3.93 (s, 3H)	6.57-7.96
3l	3.80	6.47	6.91	1.46 (t, 3H, *J* = 7); 4.11 (q, 2H, *J* = 7)	6.54-7.97

another doublet at δ 6.91-7.01 (d, 1H, *J* = 7 Hz) assigned to C-3 proton. Broad one-proton absorption was shown in the region, δ 3.76-3.85 that may be assigned to the proton of secondary amino group. Multiplets at around δ 6.00-7.97 may be assigned to the aromatic protons. The presence of methyl group in **3d** and **3j**, methoxy in **3e** and **3k** and ethoxy groups in **3f** and **3l** were indicated by their characteristic pattern in their respective regions (Table-2). The pattern of spectra indicated the formation of 2,5-dihydro form **3a-l (ii)** instead of 2,3-dihydro form **3a-l (i)**.

In mass spectra of all the compounds, clusters of peaks comprising the molecular ion peaks and isotopic peaks, indicating the presence of halogens were obtained.

Antimicrobial activity: All the synthesized compounds, **3a-l** were screened for antibacterial activity against the Gram-positive bacteria *Staphylococcus aureus* and the Gram-negative bacteria *Escherichia coli* and *Enterobacter cloacae*, and antifungal activity against the fungus, *Candida albicans* at the concentration of 200 µg/disc, with vancomycin, imipenem, polymixin B and fluconazole as the reference drugs, respectively. Most of the synthesized compounds were found to show moderate activity against the bacteria, *Staphylococcus aureus* (activity index = 0.46-1.13) and fungus *Candida albicans* (activity index = 0.32-0.92) but none of the compounds exhibited any activity against the bacteria *Escherichia coli*. Against the Gram-positive

bacteria, *Staphylococcus aureus*, compounds **3e**, **3f**, **3g**, **3h**, **3i** and **3k** showed moderate relative activity (activity index = 0.46-0.66). Compounds **3c** and **3l** showed maximum activity (activity index = 1.06-1.13) in comparison with reference compounds while **3d** also showed highest antifungal activity against *Candida albicans* (Table-1).

In the studies on antimicrobial activities of substituted 1,5-benzothiazepines, some compounds have been reported to exhibit good antibacterial activity against *Staphylococcus aureus* with gentamycin as the reference drug [13] . In present studies, most of the newly synthesized compounds were found to show good activity with respect to the reference drug vancomycin. Good antibacterial activity against *Staphylococcus aureus* has also been reported by Wang *et al*. [16]. The presence of heterocyclyl or aromatic moiety does not seem to affect the antimicrobial properties of compounds against the bacteria and fungus studied.

Conclusion

Presence of heterocyclic ring as substituent at C-4 in the final compounds may have led to lower percentage yields of **3g-l** in comparison to **3a-f** which did not have the heterocyclic moiety. Most of the compounds showed good antibacterial activity for Gram-positive bacteria *Staphylococcus aureus* and antifungal activity for *Candida albicans* irrespective of type of substituents present. None of the compounds showed any antibacterial activity for Gram negative *Escherichia coli* whereas only one compound showed some antibacterial activity against *Enterobacter cloacae*.

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