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RESEARCH ARTICLE

SYNTHESES OF 1,5-BENZOTHIAZEPINES: PART 43: SYNTHESES AND ANTIMICROBIAL EVALUATION OF 8-SUBSTIUTUTED-2,5-DIHYDRO- 2- (3-CHLOROPHENYL / 4-CHLOROPHENYL) -4- (4-METHYLPHENYL)-1,5-BENZOTHIAZEPINES

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Abstract

Two enolisable ketones, 3-(3-chlorophenyl)-1-(4-methylphenyl)-2-propenone and 3-(4-chlorophenyl)-1-(4-methylphenyl)-2-propenone, were reacted with 5-substituted-2-aminobenzenethiols in dry ethanol containing dry hydrogen chloride, to obtain 8-substituted-2,5-dihydro-2-(3-chlorophenyl/4-chlorophenyl)-4-(4-methylphenyl)-1,5-benzothiazepines in satisfactory yields ranging from 51.9-67%. The structure of the final products has been elucidated by micro estimation for C, H, N and S; and IR, ^{1}H NMR, and mass spectroscopies. The synthesized compounds were studied for their relative antimicrobial activity by selecting gram-positive bacteria *Staphylococcus aureus* and gram-negative bacteria *Pseudomonas aeruginosa* against the reference compound Vancomycin and Amikacin respectively. The activity of these compounds against the fungi, *Candida albicans* and *Aspergillus niger* was also studied. The compounds having two chloro substitutents, **3b** and **3h** showed one and a half times higher antifungal activity with respect to the reference standards, against *Candida albicans* and *Aspergillus niger*, respectively.

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Keywords: Unsaturated carbonyl compounds; 1,5-benzothiazepines; *Staphylococcus aureus; Pseudomonas aeruginosa; Candida albicans; Aspergillus niger*

Introduction

Diltiazem, the cardiovascular drug belonging to the 1,5-benzothiazepine series of compounds, is useful in the treatment of angina pectoris and is useful in coronary vasodilation (Buckley *et al*, 1990), hypertension (Chiesi et al, 1987), regulation of Ca^{+2} concentration (Kuzelova and Svec, 1993), migraine therapy, cancer therapy (Zenke et al, 1996) etc. The second generation drug, clentiazem, has a chloro substituent at position-8 in the fused benzene ring of diltiazem. Our study revealed that the introduction of chlorine as a chlorophenyl substituent, at various positions in 1,5-benzothiazepine nucleus, has fruitfully resulted in obtaining compounds having pharmacological activity (Barot et al, 2001), such as cardiovascular activity, anti-depressive, tranquilizing, anti-ulcerous (Weiss et al, 1989), anti-cancerous, anti-cholinergic etc. besides anti-bacterial and antifungal activity.

The utilization of the analogous 1,4-benzodiazepine compounds as central nervous system drugs, namely Chlordiazepoxide (L.H. Sternbach et al,1964), clobazam (F.Barzaghi et al,1973), flurazepam (Chem.Abstr,1987), and the finding of cardiovascular drug clentiazem (K. Kinoshita et al,1995) showing better activity than diltiazem, suggest that the halogen present may have acted as a pharmacophore. These observations have encouraged us to focus on the syntheses, characterization and the antimicrobial studies of such 1,5-benzothiazepines (Pant et al, 2005; 1992; 2008; Jadhav, 2011).

Thus, the syntheses of 1,5-benzothiazepines having 3-chlorophenyl or 4-chlorophenyl group, in addition to a 4-methylphenyl, were chosen to study the effect of increased chlorine towards antibacterial and antifungal activity.

Material and Methods

The required α, β-unsaturated carbonyl compounds (Rasschart et al, 1966), 3-(3-chlorophenyl)-1-(4-methylphenyl)-2-propenone **(1a)**, or 3-(4-chlorophenyl)-1-(4-methylphenyl)-2-propenone **(1b)** was reacted with 5-substituted-2-aminobenzethiols **(2a-f)**, prepared from p-substituted anilines (Pant et al, 2013), the substituents being halogens as fluoro, chloro, bromo, methyl, methoxyl and ethoxyl, in dry ethanol, saturated with hydrogen chloride gas to give the target compounds, 8-substituted-2,5-dihydro-2-(3-chlorophenyl/4-chlorophenyl)- 4- (4-methylphenyl)-1,5- benzothiazepines (**3a-l**, **Scheme I**).

Experimental

General procedure for the syntheses of 8-substituted-2,5-dihydro-2-(3-chlorophenyl/4-chlorophenyl)-4-(4-methylphenyl)-1,5-benzothiazepines (3a-l)

To the ethanolic solution of 3-(3-chlorophenyl/4-chlorophenyl)-1-(4-methylphenyl)-2-propenone (**1**, 0.001 mol), the alcoholic solution of 5-substituted-2-amino benzenethiol (**2,** 0.001 mol) was added drop wise with stirring on magnetic stirrer. The reaction mixture was saturated with dry hydrogen chloride and was refluxed for 10-12 hrs, till the color change became constant. Concentration and cooling of the resulting mixture afforded the crude solid; which was crystallized from ethanol to obtain the title compounds, 8-substituted-2,5-dihydro-2-(3-chlorophenyl/4-chlorophenyl)-4-(4-methylphenyl)-1,5-benzothiazepines in 51.9-67% yields **(Table 1)**.

All the melting points are uncorrected. Purity of the compounds was checked by tlc on silica gel 'G' coated glass plates, 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 spectrum RX1 FT IR spectrophotometer. ^{1}H NMR spectra was recorded on a Bruker DRX-300 (300 MH_2 FT NMR) instrument using $CDCl_3$ as solvent and TMS as internal standard **(Table 2).**

The DART-MS was recorded on a JEOL-AccuTOF JMS-T100LC Mass spectrometer. Dry Helium was used with 4 LPM flow rate for ionization at 350°C. Microestimations for carbon, hydrogen, nitrogen and sulphur were carried out on Elemental Analyzer, Carlo Erba 1108. The spectral and elemental analyses were carried out at the Sophisticated Analytical Instrumentation facility, Central Drug Research Institute, Lucknow.

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 antifungal *Pseudomonas aeruginosa* with Vancomycin, Amikacin as reference drugs; and activity against the fungi, *Candida albicans* and *Aspergillus niger* using Itriconazole as the reference drug. The Paper Disc Method (Pant et al, 2013) was used to evaluate activity in the form of activity index, i.e. as the ratio of zone of inhibition exhibited by the test compounds to that of the reference compounds.

Result and Discussion

The reactions are initiated by nucleophilic attack of the sulphhydryl electrons of 5-substituted-2-aminobenzenethiols at the activated β-carbon atom of the α,β-unsaturated carbonyl compounds, to give Michael adduct type intermediates, which simultaneously undergo dehydrative cyclisation to give seven membered heterocyclic products.

Such types of reactions have been reported to be carried out under different reaction conditions, as in methanol containing Piperidine (Stephens and Field, 1959), in anhydrous toluene (Levai and Bognar, 1979), methanol containing glacial acetic acid, methanol saturated with hydrochloric acid (Reid and Marx, 1957) etc. It has also been found that cyclized products were obtained in a single step in maximum yield in the acidic medium. Hence, the reaction of 3-(3-chlorophenyl)-1-(4-methylphenyl)-2-propenone **(1a)** or 3-(4-chlorophenyl)-1-(4-methylphenyl)-2-propenone **(1b)**, with 5-substituted-2-aminobenzenethiols **(2a-f)** were carried out in dry ethanol saturated with dry hydrogen chloride to obtain twelve new title compounds, the 8-susbtituted-2,5-dihydro-2-(3-chlorophenyl / 4-chlorophenyl) - 4-(4-methylphenyl) - 1,5-benzothiazepines (**3a-l, Scheme-I**).

IR Spectral Analyses

The IR spectra of the final products **(3a-l)** did not show characteristic absorptions for υ C=O and υ NH_2 in the region 1685-1650 cm^{-1} and 3500-3400 cm^{-1} respectively. However, a broad absorption in

Scheme 1. Syntheses of Substituted 1,5- Benzothiazepines, 3a-l

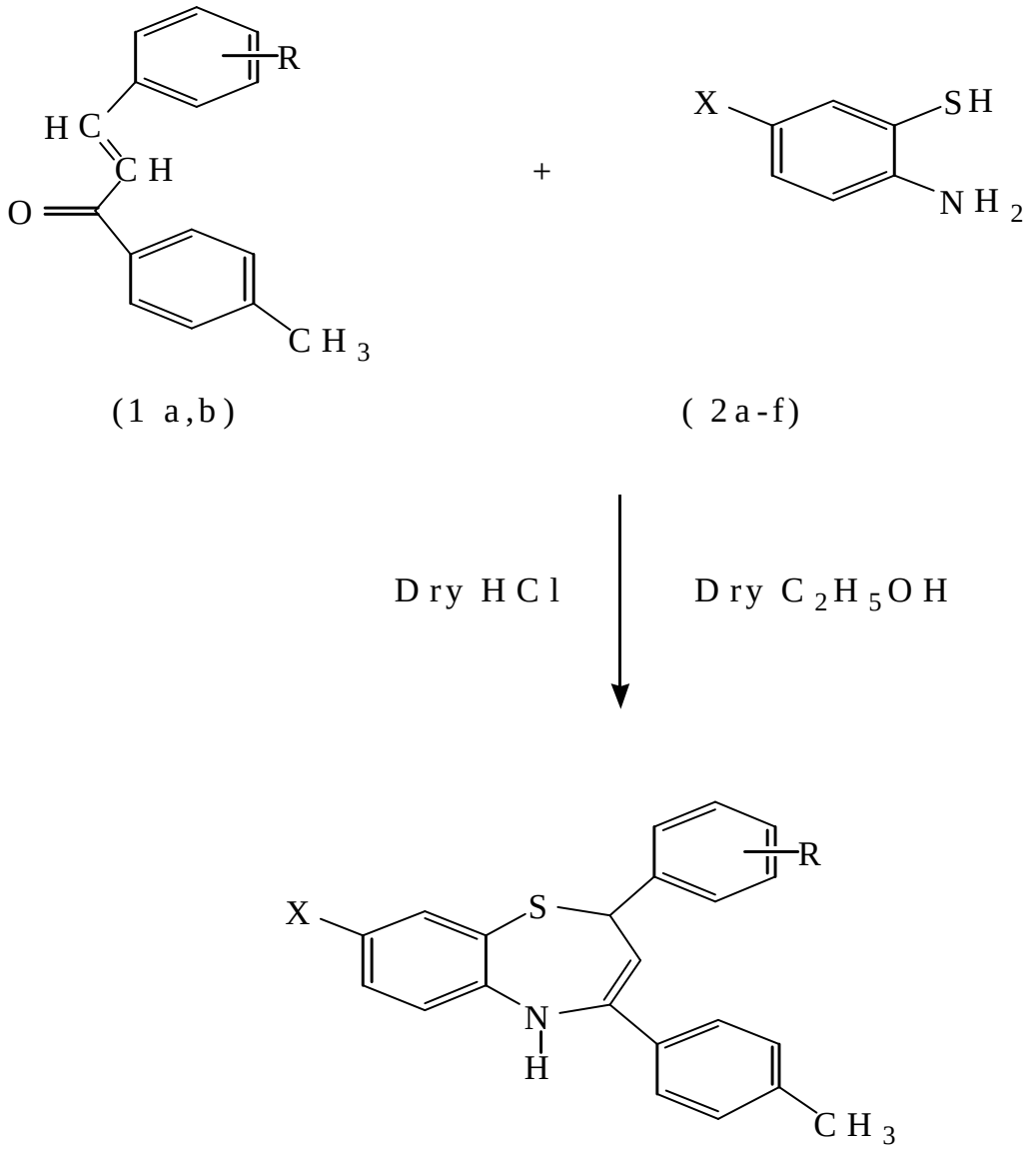

Table. 1 Physical constants and analytical data of 3a-l

Compound No.	X	R	Compound No	X	R
3a	F	3-Cl	3g	F	4-Cl
3b	Cl	3-Cl	3h	Cl	4-Cl
3c	Br	3-Cl	3i	Br	4-Cl
3d	CH_3	3-Cl	3j	CH_3	4-Cl
3e	OCH_3	3-Cl	3k	OCH_3	4-Cl
3f	OC_2H_5	3-Cl	3l	OC_2H_5	4-Cl

Table. 1 Physical constants and analytical data of 3a-l

Comp. No.	M.P. (°C)	R_f	Yield (%)	Mol. Formula (Mol. Wt.)	Elemental analyses (Calcd) (%)Found			
					C	H	N	S
3a	100	0.68	53.47	$C_{22}H_{17}ClFNS$ (381.5)	-	-	3.50 (3.66)	7.86 (8.38)
3b	152-124	0.71	56.78	$C_{22}H_{17}Cl_2NS$ (398)	66.30 (66.33)	4.25 (4.27)	-	-
3c	100-102	0.80	58.75	$C_{22}H_{17}BrClNS$ (442.5)	-	-	3.32 (3.16)	6.18 (7.23)
3d	98	0.71	61.19	$C_{23}H_{20}ClNS$ (377.5)	-	-	3.60 (3.70)	7.82 (8.47)
3e	88-90	0.78	53.62	$C_{23}H_{20}ClNOS$ (393.5)	69.89 (70.13)	4.99 (5.08)	3.58 (3.55)	8.18 (8.13)
3f	122-124	0.86	64.29	$C_{24}H_{22}ClNOS$ (407.5)	70.61 (70.67	5.60 (5.39)	-	-
3g	108	0.78	51.90	$C_{22}H_{17}ClFNS$ (381.5)	69.02 (69.20)	4.38 (4.45)	-	-
3h	116	0.83	52.76	$C_{22}H_{17}Cl_2NS$ (398)	66.56 (66.33)	4.32 (4.27)	-	-
3i	200	0.86	54.23	$C_{22}H_{17}BrClNS$ (442.5)	-	-	3.41 (3.16)	7.12 (7.23)
3j	130-132	0.76	64.37	$C_{23}H_{20}ClNS$ (377.5)	-	-	3.62 (3.70)	7.04 (8.47)
3k	120-122	0.86	67.09	$C_{23}H_{20}ClNOS$ (393.5)	-	-	3.52 (3.55)	8.26 (8.13)
3l	118	0.80	60.85	$C_{24}H_{22}ClNOS$ (407.5)	70.52 (70.67)	5.23 (5.39)	3.47 (3.43)	8.16 (7.85)

Table. 2 Characteristic IR absorptions bands (λ in cm^{-1}) and ^1H NMR data of 3a-l

Comp. No.	IR	^1H NMR					
	N-H	N-H (br,1H)	CH_3 (s,3H)	C_2-H (d,1H,J8)	C_3-H (d,1H,J8)	C_8-XH	Ar Protons (m,11H)
3a	3144	4.10	2.42	6.88	7.10	-	6.93-7.99
3b	3148	4.14	2.38	7.04	7.99	-	7.18-7.92
3c	3150	4.08	2.41	7.08	8.00	-	7.11-7.92
3d	3142	4.12	2.44	7.30	7.95	2.39(s,3H)	7.37-7.75
3e	3140	4.10	2.44	6.97	7.92	3.90(s,3H)	7.24-7.81
3f	3146	4.10	2.44	7.05	7.93	1.46(t,3H,J7) 4.09(q,2H,J7)	7.26-7.75
3g	3142	4.09	2.44	6.99	7.95	-	7.04-7.88
3h	3145	4.10	2.42	7.11	7.99	-	6.83-7.85
3i	3150	4.12	2.39	7.06	7.90	-	6.89-7.87
3j	3135	4.12	2.42	7.03	8.02	2.39(s,3H)	7.22-7.94
3k	3140	4.11	2.41	7.08	7.96	3.90(s,3H)	7.19-7.92
3l	3146	4.15	2.44	7.08	7.94	1.47(t,3H,J7) 4.10(q,2H,J7)	7.26-7.78

Table. 3 Antimicrobial activity of 3a-l

Comp. No.	Bacteria		Fungi	
	Staphylococcus aureus	***Pseudomonas aeruginosa***	***Candida albicans***	***Aspergillus niger***
3a	17(1.30)	6(0.37)	17(1.21)	19(1.35)
3b	12(0.92)	10(0.62)	18(1.28)	21(1.50)
3c	--	6(0.37)	11(0.78)	--
3d	11(0.84)	8(0.50)	18(1.28)	18(1.28)
3e	11(0.84)	14(0.87)	20(1.42)	--
3f	8(0.61)	--	-	13(0.92)
3g	11(0.84)	10(0.62)	15(1.07)	18(1.20)
3h	16(23)	15(0.93)	21(1.50)	15(1.00)
3i	--	7(0.43)	--	--
3j	12(0.92)	15(0.93)	17(1.21)	21(1.40)
3k	13(1.00)	7(0.43)	15(1.07)	11(0.73)
3l	--	11(0.68)	14(1.00)	--

Zones of inhibition are given in mm; Values in parentheses represent activity index; Zone of inhibition of Vancomycin for *Staphylococcus aureus* is 13 mm; of Amikacin for *Pseudomonas aeruginosa* is 16 mm; of Itriconazole for *Candida albicans* is 14 mm; of Itriconazole for *Aspergillus niger* for compounds **3a-f** is 14 mm and for **3g-l** is 15 mm; Concentration of test and reference compounds were 100µg/disc.

the region 3150-3130 cm^{-1} was obtained which may be assigned to the secondary amino group **(Table 2)**. The final product **3a-l** showed strong absorption band in the region, 1096-1089 cm^{-1} due to C-Cl stretching**.**

^{1}H NMR Spectral Analyses

The ^{1}H NMR spectra of all the final products **(3a-l)**, showed one proton doublet at 6.88-7.30 (d, 1H, J= 7Hz) which may be assigned to C_2-H, and another doublet of 7.10-8.02 (d, 1H, J= 7Hz) integrating for one proton, may be assigned to the proton present at C_3-H; the downfield absorptions may be due to the protons lying in the deshielding zone of aryl rings. A broad absorption signal shown in the region, δ 4.08-4.15 (br, 1H) may be assigned to N-H. Multiplets at around δ 6.83-7.99 may be assigned to the 11 aromatic protons. The singlet of three protons in the region 2.38-2.44 may be assigned to methyl protons in all the synthesized products. The singlet at δ 3.90 (s, 3H) of three protons each may be assigned to methoxyl group protons in compounds **3e** and **3k** at position-8. Compound **3f**, showed a triplet at 1.46 (t, 3H, J=7Hz) and quartet at of 4.09 (q, 2H, J = 7Hz), due to methyl and methylene protons of the ethoxyl group**.** Absorption as a triplet at δ 1.47 (t, 3H, J= 7Hz) and a quartet at δ 4.10 (q, 2H, J = 7Hz) with the same coupling constant may be assigned to methyl and methylene protons of ethoxyl group in the spectrum of **3l (Table 2).**

Mass Spectral Analyses

The mass spectra of **3b** and **3h** showed cluster of the molecular ion peak, m/z, $[M]^+$, $[M+2]^+$ and $[M+4]^+$ at 398, 400 and 402 respectively, corresponding to the molecular mass of the product. The intensity of the $[M+2]^+$ peak was found nearly one third of the M^+ peak, which ascertained the presence of chlorine in the compounds. The mass spectra of **3c** and **3i** showed molecular ion peaks, m/z, $[M]^+$ and $[M+2]^+$ at 442 and 444; the intensity of $[M+2]^+$ peak was found to be nearly equal to the M^+ peak which confirmed the presence of bromine. The results of elemental analyses were found to be satisfactory being within the permissible limits of error.

Antibacterial Activity

Most of the compounds, **3b, 3d, 3e, 3g, 3j** and **3k** showed antibacterial activity against *Staphylococcus aureus* almost equal to the reference standard Vancomycin.

Relatively less antibacterial activity was shown against the gram-negative bacteria, *Pseudomonas aeruginosa* with respect to the reference compound Amikacin.

Antifungal Activity

Good antifungal activity was shown by all the compounds against *Candida albicans* and *Aspergillus niger,* using Itriconazole as the reference standard. Against the fungus *Candida albicans,* maximum relative activity was shown by compound **3h** (activity index = 1.50). Against *Aspergillus niger*, compound **3b** was found to show maximum relative activity (activity index = 1.50).

Conclusion

Most of the compounds were found to show good to moderate activity against the bacteria, *Staphylococcus aureus.* The newly synthesized compounds having greater percentage of chlorine, **3b** and **3h,** exhibited one and a half time greater antifungal activity against *Aspergillus niger* and *Candida albicans*, besides showing good antimicrobial activity against all the microbes studied.

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