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Spectral Studies, Synthesis and Antibacterial Evaluation of 8-Substituted-2,3-Dihydro -4-(2,4-Dihydroxyphenyl) -2-(4- Methoxyphenyl)-1,5-Benzothiazepines

KEYWORDS: Substituted 2-Aminobenzenethiols, 2,4-dihydroxyacetophenone, Dry HCl gas, Dry ethanol .

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ABSTRACT *1,5-benzothizepine moiety shows various biological activities, play a major role in the field of pharmaceutical chemistry, motivate to synthesize new series of 1,5-benzothizepine derivatives. For the synthesis of 8-substituted-2,3-dihydro-4-(2,4-dihydroxyphenyl)-2-(4-methoxyphenyl)-1,5-benzothiazepines,equimolar proportion of 1-(2,4-dihydroxyphenyl)-3-(4-methoxyphenyl)-2-propenone were reacted with 5-substituted-2-amino benzenethiols, the substituent's being fluoro,Chloro, bromo, methyl, methoxy, and ethoxy in dry ethanol saturated with dry HCl gas, refluxing for 6 hours obtained in good yield. The structural investigations are based on the result of micro analytical data of elements and spectroscopic studies based on IR, H1 NMR, and mass spectra.*

INTRODUCTION

Human beings suffer from different type of diseases and scientists are fighting to find the solution in the form of various medications. The literature survey seems that 1,5-benzothiazepine moiety were possess different biological activities such as anti HIV[1], HIV-1 reverse transcriptase inhibitor[2], antibacterial[3,4], antifungal[5], anticonvulsant[6], anti-breast cancer[7], anti-lung cancer[8], CNS activity[9] etc. Incorporation of substituents in fused benzene ring and in heterocyclic ring enhances biological activities[3,510,11] . Due to various biological activities of 1,5-benzothiazepine moiety motivate to synthesize present work. The synthesis and spectral studies of a series of 8-substituted-2,3-dihydro-4-(2,4-dihydroxyphenyl)-2-(4- methoxyphenyl)-1,5-benzothiazepines have been undertaken and reported in the present communication.

MATERIALS AND METHODS

All the melting points were determined in open capillary tubes and were uncorrected .The purity of the compounds was checked by TLC on silica gel G coated glass plates using benzene-ethanol-ammonia (7:2:1) as solvent system .Equimolar quantities of 1-(2,4-dihydroxyphenyl)-3-(4-methoxyphenyl)-2-propenone and5-substituted-2-aminobenzenethiols were refluxed in dry ethanol saturated with dry HCl gas for 6-7 hrs to obtain the title products, 8-substituted-2,3-dihydro-4-(2,4-dihydroxyphenyl)-2-(4-methoxyphenyl)-1,5-benzothiazepines in one step in 50-70% yields. The purity of the final product was checked by TLC. The structural assignments are based on the results of elemental analysis for C, H, and N (Table-1) and spectroscopic studies based on IR, H^1 NMR, and mass spectra.

EXPERIMENTAL SECTION

The IR spectra were recorded on potassium bromide pellets using Perkin-Elmer RX1 FT IR spectrometer (range:4000-450cm^{-1}). The H^1 –NMR spectra were recorded on Bruker avance 400 (FT NMR) using $CDCl_3$ as solvent. The mass spectra were recorded on JMS-T100LC, Accu TOF (DARTMS) mass spectrometer. The spectral and elemental analysis were carried out at the Sophisticated Analytical Instrumentation Facility, Central Drug Research Institute, Lucknow.

Synthesis of 5-substituted-2-aminobenzenethiols 4a-f.

Six 5-substituted-2-aminobenzenethiols **4a-f**, were prepared by literature[12] reported methods

Synthesis of 1- (2, 4 - dihydroxyphenyl) -3 - (4- methoxyphenyl) - 2 - propenone.

Equimolar quantities of 2,4-dihydroxyacetophenone 1.52 ml (0.01) and 4-methoxybenzaldehyde 1.36 ml(0.01) were dissolved in ice-cold ethanol (40ml) in a round bottom flask place in ice bath to this NAOH solution (10 ml, 60%) were added drop wise with continues stirring for 30 min. The mixing was continued for another 2.30 hrs at room temp. Turbidity appeared in the mixture which was then diluted with cold water (40ml) and neutralized to litmus paper with 2N HCl. The product (ppt) was filtered, washed well with cold water and dried in air to afford the chalcone, 1-(2-hydroxyphenyl)-3-(4-methoxyphenyl)-2-propenone (**3**, yellow crystals, m.p. 176^{0}C, (reported-177.58)[14] yield 63%).

Procedure for the preparation of 8-floro-2,3-dihydro-4-(2,4-dihydroxyphenyl)-2-(4-methoxyphenyl)-1,5-benzothiazepines .(5a)

5-floro-2-aminobenzenthiols (0.001 mole, 0.14g)**4a** and 1-(2,4-dihydroxyphenyl)-3-(4-methoxyphenyl)-2-propenone (0.001 mole, 0.27g) **3a** were dissolved in dry ethanol separately and mixed saturated with dry HCl gas . Reaction mixture was refluxed for 6 hrs when colour changed from pale yellow to deep red. The reaction mixture was cooled and removed under reduced pressure. The residue obtained after concentration was crystallized from ethanol to give crystals of 8-floro-1-(2,4-dihydroxyphenyl)-3-(4-methoxyphenyl)-1,5- benzothiazepines.5a. m.p. 175-177^{0}C, yield 67%, R_f –0. 64.

On the similar pattern b-f were prepared. The analytical and spectral data of **5a-f** are given in the **Table I** and **II** respectively.

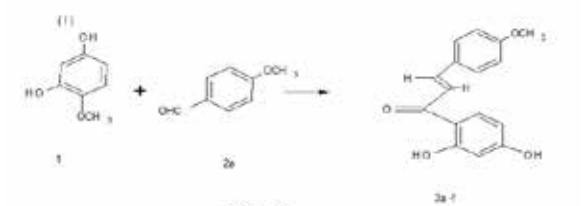
RESULT AND DISCUSSION

Acid catalyzed stirring of 2,4-dihydroxyacetophenone **1** with 4-methoxybenzeldehyde **2a,** afforded 1-(2,4-dihydroxyphenyl)-3-(4-methoxyphenyl)-2-propenone **3a-f** which was reacted with six 5-substituted-2-aminobenzenethiols **4a-f** the substituents being fluoro,Chloro, bromo, methyl, methoxy, and ethoxy to give the title compounds On refluxing the precursors 1 and 2 for 3 hr, the products were obtained in yield of 60-70% in acidic me-

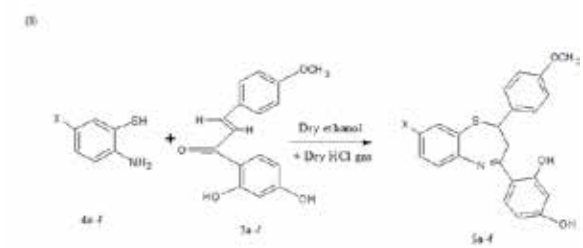
Volume : 5 | Issue : 9 | September 2015 | ISSN - 2249-555X

dium .

For the synthesis of target benzothiazepine, the reaction sequences were followed as outlined in the **Scheme II**. Thus the equimolar quantities of 1-(2,4-dihydroxyphenyl)-3-(4-methoxyphenyl)-2-propenone **3** prepared as per **Scheme-I**, was condensed with 5-substituted-2-aminobenzenethiols in the presence of dry ethanol saturated by dry HCl gas.



Scheme I



Scheme II

compd.	5a	5b	5c	5d	5e	5f
	F	Cl	Br	CH_3	OCH_3	OC_2H_5

SPECTRAL ANALYSIS

The IR spectra of final product **(5a-f)** showed strong absorption in the region 1615-1596 cm^{-1}which indicates the presence of C=N. Absence of absorption peak around 1700-1640 cm^{-1} was indicated the absence of carbonyl group. That show both precursors have reacted to give the target compound. The peak at 3400-3300 cm^{-1} confirms the presence the OH group. The peak at 669 cm-1 which indicated the presence of C-Cl in the compound of **5b**.

In ^{1}H-NMR spectra of all final product **(5a-f)** showed a triplet at δ 4.52-4.60 (t,1H,J=12.6) integrating for one proton, which may be assigned to C_2H. A doublet at δ 3.26-3.42 (d,2H,J=7.5) may be assigned to C_3H proton. Multiplets at around δ 6.64-8.02 (m,10H) may be assigned to aromatic protons. The absorption at δ 12.85-12.98 as a singlet may be assigned two proton of OH group. In the spectra of **5d** , the absorption at δ 3.82 as a singlet may be assigned to 3 protons of OCH_3 group and the absorption at δ 2.35 as a singlet integrated for three protons indicated the presence of methyl group in **5d**. Two singlet equivalent to 3H each at δ 3.82 and δ 3.86 indicated the presence of two methoxyl groups in the product **5e**. In ^{1}H-NMR spectra of **5f** , the absorption at δ 3.78 as a quartet equivalent to 3H and a triplet at δ 1.96 with the same value of J= 6 Hz may be assigned to protons of OC_2H_5 group.

The mass spectra of compounds **5c,** The presence of molecular ion peaks, m/z showed $[M]^+$ and $[M+2]^+$ peak at 439.9 and 441.9 correspond to the molecular mass of the product. The intensity of $[M+2]^+$ peak was found to be nearly equal to the M+ peak which confirmed the presence of bromine in compound **5c**.

ANTIBACTERIAL ACTIVITY

All the reported compounds were evaluated for their relative antibacterial activity against the gram-nagative bacteria E- coil and Pseudomonas aeruginosa by using reference compound Ampicillin . The paper disc method[13] was used and zone of inhibition of the test and reference compound were measured in millimetres at the concentration of 100ug/disc in 24 hr incubation period. The result was show in table 3. All the synthesized compounds of the series showed significant antibacterial activity .

Table-I Characterisation data of Compounds 5a-f

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Compound NO.	R	M.P. °C	Rf	Yield %	Molecular Formula (Mol. Wt.)	Elemental Analysis % Found (Calcd)		
						C	H	O
5a	F	175-177	0.64	67	$C_{22}H_{18}O_2SNF$ (379)	69.69 (69.65)	4.68 (4.75)	8.50 (8.44)
5b	Cl	178-182	0.62	62	$C_{22}H_{18}O_2SNCl$ (395.5)	67.69 (66.75)	4.48 (4.55)	8.29 (8.09)
5e	Br	164-170	0.68	65	$C_{22}H_{18}O_2SNBr$ (440)	61.38 (60.00)	4.10 (4.09)	7.98 (7.27)
5d	CH_3	150-152	0.76	52	$C_{23}H_{21}O_2SN$ (375)	73.57 (73.60)	5.95 (5.60)	8.58 (8.53)
5e	OCH_3	158-162	0.83	64	$C_{23}H_{21}O_3SN$ (391)	70.87 (70.58)	5.91 (5.37)	12.48 (12.27)
5f	OC_2H_5	154-156	0.78	58	$C_{24}H_{23}O_3SN$ (405)	71.90 (71.11)	5.54 (5.67)	11.48 (11.85)

Table-II – Characteristic Data of Compounds **5a-f**

Table-II – Characteristic Data of Compounds **5a-f**

Compd.	^{1}HNMR (δ, ppm)				
	C_2-XH	C_2-H (1H,t,J=12.6)	C_3-H (1H,d,J=7.5)	Aromatic Protons	OCH_3(s-3H)
5a	-	4.54	3.30	6.80 - 7.92	3.78
5b	-	4.60	3.36	6.86 - 7.94	3.80
5c	-	4.56	3.32	6.76 - 7.90	3.84
5d	2.40(s,3H)	4.52	3.42	6.78 - 8.16	3.82
5e	3.82(s,3H)	4.54	3.38	6.90 - 8.04	3.86
5f	3.78(q,2H,J=12.6Hz) 1.96(t,3H,J=12.6Hz)	4.58	3.26	6.96 - 8.09	3.88

Table .III Antimicrobial activity of 5 a-f

Comp. No.	Bacteria	
	E-coli	Pseudomonas aeruginosa

Volume : 5 | Issue : 9 | September 2015 | ISSN - 2249-555X

5a	14	15
5b	13	14
5c	10	-
5d	-	12
5e	15	16
5f	17	18
Ampicillin	24	22

Zone of inhibition are given in mm

Concentration of test and reference compounds were 100ug/disc

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