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Synthesis and Antibacterial Activity of 1,5-Benzothiazepine Derivatives

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Several new 2-substituted aryl-4-[2′-hydroxy-4′-(*p*-trifluoromethyl/nitro-phenoxy) - phen-1′-yl) - dihydro-1,5-benzothiazepines (II) have been prepared by reaction of 1-[2′-hydroxy-4′-(*p*-trifluoromethyl/nitro-phenoxy)-phen-1′-yl)-3-substituted aryl-2-propen-1-ones (I) with 2-amino-thiophenol in ethanol. Few of these compounds are characterised by IR and NMR spectra. All these synthesized 1,5-benzothiazepines have been screened against a few microorganisms for antibacterial activity.

Key Words: Synthesis, Antibacterial, Activity, 1,5-Benzothiazepine derivatives.

INTRODUCTION

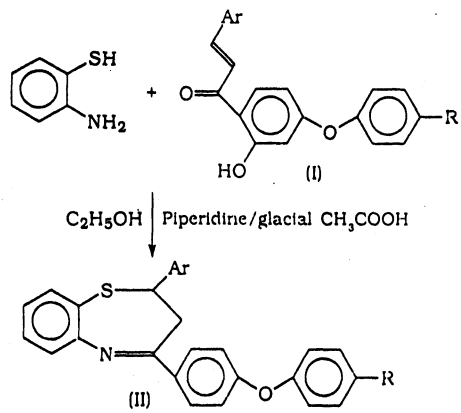
Benzothiazepine is a benzo-annelated example of thiazepine. Thiazepine is a seven-membered ring containing N and S as heteroatoms. There are three forms of thiazepines, *viz.*, 1,2-thiazepine, 1,3-thiazepine and 1,4-thiazepine. There has been more interest in 1,4-thiazepine because of the pharmacological value of benzo and di-benzothiazepines as antidepressants and coronary vasodilators[1].

2-Amino ethanethiol reacts with α, β unsaturated ketones to give 1,4-thiazepine derivatives. In a similar fashion 2-amino thiophenol can react with α,β-unsaturated ketones to yield 1,5-benzothiazepines[2]. Several workers synthesised 1,5-benzothiazepines from chalcones and 2-amino thiophenol in alcohol and checked their anitmicrobial activity[3–7]. Further an introduction of fluorine atom or —CF_3 group into an organic molecule may alter the biological activities as reported[8]. Moreover 2-hydroxy-chalcones with nitro group as additional substituent are reported to exhibit very good antibacterial activity[9]. Therefore it was thought interesting to synthesize 1,5-benzothiazepines from 2-amino thiophenol and chalcones containing —CF_3 and —NO_2 substituents in *p*-position of phenoxy substituent and to screen them as anitbacterial agents.

EXPERIMENTAL

Preparation of 1,5-benzothiazepine derivatives: To a mixture of 1-[2′-hydroxy-4′-(*p*-trifluoromethyl/nitro-phenoxy)-phen-1′-yl]-3-substituted aryl-2-propen-1-one (I) (0.01 mol) and 2-amino-thiophenol (0.01 mol) in ethanol (50 mL), a few drops of piperidine were added and reaction mixture was refluxed on

water bath at 70–80°C for 2 h. It was acidified with glacial acetic acid (10 mL) and further refluxed for 2 h. Then the reaction mixture was kept overnight. Solid thus separated was then filtered, dried and crystallised from ethanol.



Infrared spectra of the compounds were recorded in solid state using KBr pellet method. The spectra were recorded on Perkin-Elmer FT-IR Spectrophotometer (Model-Rx-1). The PMR spectra of compounds were recorded in DMSO-d_6 solvent at room temperature using TMS as a reference compound. The spectra were recorded on Perkin-Elmer Model-32 NMR spectrometer at 300 MHz. The facilities at CDRI Lucknow were used for this purpose.

The antibacterial activity of synthesized compounds and standard drugs were checked against gram positive bacteria *B. Subtilis.* and *S. aureus* and gram negative bacteria *E. coli* and *S. typhi* using Agar cup method.

RESULTS AND DISCUSSION

Characteristics of compounds **(II)** and result of antibacterial activity are given in Table-1.

The main absorption bands observed in IR spectra are as follows: 1623–1612 ν(C=N), 3295–3221 ν(O—H), 1228–1200 ν(C—O—C), 1139–1118 ν(C—F), 1530–1520 and 1380–1370 cm^{-1} due to ν(N=O).

The position of signals in NMR spectra can be assigned to different types of protons as follows: δ = 2.788 : 2 protons of —CH_2— of benzothiazepine), δ = 4.818–proton of CH of benzothiazepine), δ = 6.788 to 8.028 (aromatic protons) δ = 9.917 (proton of —OH group).

Diameter of zone of inhibition (in mm) of standard drug ampicillin against *B. subtilis* and *S. aureus* (gram positive) and *E. coli* and S. typhi (gram negative) were found to be 24, 22, 17 and 16 respectively, while tetracycline gave 18, 17, 21 and 22 respectively under identical conditions.

As compared to standards ampicillin and tetracycline 1,5-benzothiazepines have been found to possess moderate to good activity. Among trifluoromethyl substituted 1,5 benzothiazepines, compound **IIf** and **IIh** containing 4-methoxy-

TABLE-1
PHYSICAL CHARACTERISTICS AND ANTIBACTERIAL ACTIVITY OF 1,5-BENZOTHIAZEPINE DERIVATIVES

Comp. No.	Ar	R	m.w.	Yield (%)	m.p. (°C)	Elemental analysis (%) Found (Calcd.)		Antibacterial activity diameter of zone of inhibition (in mm)			
						N	S	Gram positive		Gram negative	
								B. subtilis	*S. aureus*	*E. coli*	*S. typhi*
IIa	$-C_6H_5$	$-CF_3$	491	66	159	2.74 (2.85)	6.43 (6.51)	8	7	8	9
IIb	$-4-Cl-C_6H_4$	$-CF_3$	525.5	68	168	2.59 (2.66)	5.99 (6.08)	8	10	7	10
IIc	$-2-Cl-C_6H_4$	$-CF_3$	525.5	65	151	2.58 (2.66)	6.01 (6.08)	9	7	6	8
IId	$-2,4-Cl_2-C_6H_3$	$-CF_3$	560	76	157	2.40 (2.50)	5.68 (5.71)	14	14	15	13
IIe	$-4-F-C_6H_4$	$-CF_3$	509	70	171	2.68 (2.75)	6.18 (6.28)	15	13	14	15
IIf	$-4-(OCH_3)-C_6H_4$	$-CF_3$	521	67	159	2.59 (2.68)	6.18 (6.14)	18	18	19	20
IIg	$-2-(OCH_3)-C_6H_4$	$-CF_3$	521	65	173	2.52 (2.68)	6.19 (6.14)	10	7	9	7
IIh	$-3,4-(OCH_3)_2-C_6H_3$	$-CF_3$	551	72	182	2.48 (2.54)	5.79 (5.80)	19	18	20	17
IIi	$-3,4,5-(OCH_3)_3-C_6H_2$	$-CF_3$	581	74	179	2.31 (2.40)	5.48 (5.50)	6	8	10	7
IIj	$-4-\{N(CH_3)_2\}Cl-C_6H_4$	$-CF_3$	534	69	174	5.19 (5.24)	6.02 (5.99)	10	6	8	9

Comp. No.	Ar	R	m.w.	Yield (%)	m.p. (°C)	Elemental analysis (%) Found (Calcd.)		Antibacterial activity diameter of zone of inhibition (in mm)			
								Gram positive		Gram negative	
						N	S	*B. subtilis*	*S. aureus*	*E. coli*	*S. typhi*
IIk	—C_4H_3O-(2-furyl)	-CF_3	481	68	174	2.83 (2.91)	6.71 (6.65)	14	18	13	19
III	—C_6H_5	—NO_2	478.5	56	161	5.70 (5.98)	6.72 (6.83)	8	5	6	7
IIm	4-Cl—C_6H_4	—NO_2	502.5	60	196	5.41 (5.57)	6.28 (6.36)	5	7	6	8
IIn	2-Cl—C_6H_4	—NO_2	502.5	57	158	5.48 (5.57)	6.25 (6.36)	6	6	5	—
IIo	-2,4$(Cl)_2$—C_6H_3	—NO_2	537	65	166	5.11 (5.21)	5.96 (5.95)	7	7	8	5
IIp	-4-F—C_6H_4	—NO_2	486	66	187	5.42 (5.76)	6.59 (6.58)	12	13	11	12
IIq	-4-(OCH_3)—C_6H_4	—NO_2	498	60	174	5.50 (5.62)	6.39 (6.42)	5	6	8	7
IIr	-2-(OCH_3)—C_6H_4	—NO_2	498	58	159	5.48 (5.62)	6.28 (6.42)	7	8	6	7
IIs	-3,4-$(OCH_3)_2$—C_6H_3	—NO_2	528	65	187	5.24 (5.30)	5.94 (5.06)	17	18	16	15
IIt	-3,4,5-$(OCH_3)_3$—C_6H_2	—NO_2	558	64	170	5.48 (5.01)	5.61 (5.73)	15	16	16	17
IIu	-4-[$N(CH_3)_2$]—C_6H_4	—NO_2	511	64	174	8.18 (8.21)	6.17 (6.26)	6	5	—	7
IIv	—C_4H_3O (2-furyl)	—NO_2	458	62	191	6.02 (6.11)	7.00 (6.98)	7	6	5	8

phenyl and 3,4-dimethoxy-phenyl substituent respectively showed very good activity against all four micro-organisms. Compounds **IId** and **IIe** containing 2,4-dichloro-phenyl and 4-fluoro- phenyl substituent respectively exhibited moderate activity. Compound **IIk** containing 2-furyl substituent showed moderate activity against *B. subtilis* and *E. coli* while good activity against *S. aureus* and *S. typhi*. All other compounds had poor activity.

In the case of nitro substituted 1,5-benzothiazepines, compounds **IIs** and **IIt** containing 3,4-dimethoxy-phenyl and 3,4,5-trimethoxy-phenyl substituent respectively showed good activity aginst all four micro-organisms. Compound **IIp** containing 4-fluoro-phenyl substituent exhibited moderate activity. Compound **IIn** containing 2-chloro-phenyl substituent was found inactive only against *S. typhi*, while compound **IIu** containing 4-N,N-dimethyl amino phenyl substituent found inactive only against *E. coli*. Activity of all other compounds was not satisfactory.

It can be concluded that benzothiazepine derivatives prepared from trifluoromethyl phenoxy-chalcones showed better activity than corresponding derivatives prepared from nitro substituted phenoxy chalcones.

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