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SYNTHESIS AND BIOLOGICAL STUDY OF SOME NEW 2,4-SUBSTITUTED-1,5-SUBSTITUTED-BENZOTHIAZEPINE

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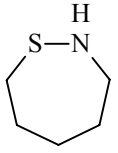
ABSTRACT

Synthesis of 2,4-substituted-1,5-substituted-benzothiazepine was carried out. First step was synthesis 1-(4-bromo-1-hydroxynaphthalen-2-yl)ethanone by the acetylation of 4-bromo-alphanapthol in presence of glacial acetic acid and zinc chloride. In the second step 1-(4-bromo-1-hydroxynaphthalen-2-yl)-3-aryl-prop-2-en-1-one obtained by treating 1-(4-bromo-1-hydroxynaphthalen-2-yl) ethanone with aromatic aldehydes using ethanol as a solvent and 40% KOH. The synthesized compound on microwave irradiation in presence of substituted aminobenzenethiol and zinc acetate gave titled benzothiazepine derivatives. The synthesized compounds are characterized by elemental analysis, ^{1}H NMR, IR Spectroscopy. Newly synthesized compound were also studied for their biological activities.

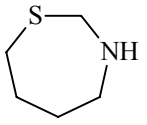
Key words: Synthesis, Benzothiazepine, Antimicrobial, Antifungal, Biological studies.

INTRODUCTION

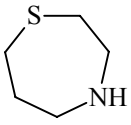
Benzothiazepines are the benzocondensed derivatives of three structural isomers of thiazepines.



1,2-thiazepane



1,3-thiazepane



1,4-thiazepane

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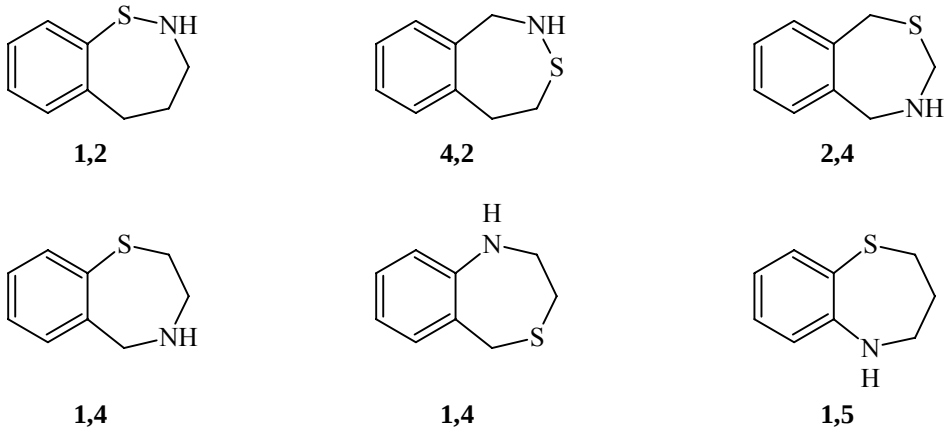
1,3-Thiazepine may be the parent compound of four benzothiazepines (1, 2-, 2, 3-, 3, 2-, and 2, 1-benzothiazepines). Of these several 1,2-benzothiazepine derivatives have been described (I), whereas of the number of benzologs of 1,3-thiazepine (1,3-,2,4-, and 3,1-benzothiazepine), only 2,4-benzothiazepine derivatives are known to us.

Derivatives of all the benzologs of 1,4-thiazepine (1,4-,4,1-, and 1,5-benzothiazepine) are known in the literature[1]. The structures of currently known benzothiazepines and their numbering in agreement with IUPAC rules are given in the scheme below:



1,2 **4,2** **2,4**

1,4 **1,4** **1,5**

Benzothiazepines

Benzothiazepines are seven membered heterocyclic compounds. Benzothiazepines have received a considerable attention nowadays because of its versatile biological activities like anticonvulsant[2], CNS depressant[3-5], anticancer[6], antifungal[7] and antimicrobial activities[8,9]. As disease poses a major threat to human beings and scientists are fighting to find solutions in the form of various medications, benzothiazepine finds its importance in bioinorganic and medicinal chemistry in designing new therapeutic agents with improved pharmacological properties[10,11]. Present work deals with the synthesis of 2,4-substituted-1,5-substituted-benzothiazepine, their characterization by spectral analysis (IR, ^{1}H NMR) and biological studies.

EXPERIMENTAL

All the melting points were taken in silicon oil bath with open capillary tubes and are uncorrected. IR spectra were recorded on a Nicolet-Impact 400 FT-IR spectrometer ^{1}H NMR spectra were recorded on a Brucker AC 300 FNMR spectrometer (300 MHz), using TMS as

an internal standard. Microanalysis of nitrogen was obtained by Kjeldahal's method. Thin layer chromatography on silica gel-G, was used to check the purity of the compounds.

Procedure for the synthesis of 1-(4-bromo-1-hydroxynaphthalen-2-yl)ethanone (2a)

In hot glacial acetic acid, fused $ZnCl_2$ was added and refluxed till dissolved, then powdered substituted 4-bromo-alphanapthol was added and the mixture was refluxed for about 8 hrs then cooled & poured in acidulated water. The solid obtained was filtered, washed, dried and recrystallized from rectified spirit to obtain compound **(2a)**.

Synthesis of 1-(4-bromo-1-hydroxynaphthalen-2-yl)-3-aryl-prop-2-en-1-one (3a-3c)

1-(4-bromo-1-hydroxy-naphthalene-2-yl)ethanone and aromatic aldehydes were added in ethanol solvent. To this mixture KOH (10%) solution was added drop wise with constant stirring. The reaction mixture was kept overnight. Then the mixture was poured over crushed ice & little HCl. The product was filtered and recrystallized from ethanol to obtain the compounds **(3a-3c)**.

Synthesis of 4-bromo-2-(7-substituted-2-aryl-2,3,4,5-tetrahydro-1,5-benzothiazepin-4-yl)naphthalen-1-ol (4a-4f)

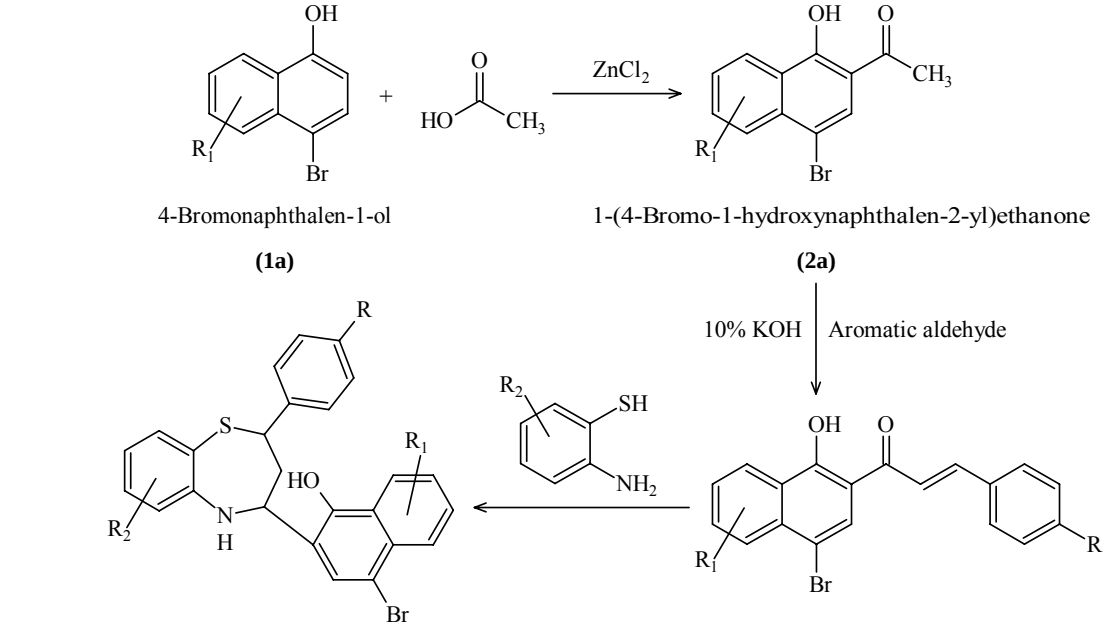
1-(4-bromo-1-hydroxynaphthalen-2-yl)-3-aryl-prop-2-en-1-one and substituted 2-aminobenzenethiol was heated in presence of catalyst zinc acetate to obtain a compound 4-bromo-2-(7-substituted-2-aryl-2,3,4,5-tetrahydro-1,5-benzothiazepin-4-yl)naphthalen-1-ol. The physical data of newly synthesized compounds is given in Table 1.

Table 1: Physical and analytical characterization data of newly synthesized compounds

Compd.	R_1	R	R_2	Melting point (^oC)	Yield (%)	% Nitrogen		R. F. Value
						Found	Calculated	
2a	H	-	-	205	72	--	--	--
3a	H	OCH_3	-	197	62	--	--	--
3b	H	Cl	-	178	66	--	--	--
3c	H	Br	-	172	58	--	--	--
4a	H	OCH_3	H	202	38	2.83	2.85	0.56
4b	H	Cl	H	262	41	2.79	2.82	0.59

Cont…

Compd.	R_1	R	R_2	Melting point (^oC)	Yield (%)	% Nitrogen		R. F. Value
						Found	Calculated	
4c	H	Br	H	233	37	2.59	2.59	0.48
4d	H	OCH_3	OCH_3	225	42	2.66	2.68	0.51
4e	H	Cl	OCH_3	250	39	2.65	2.66	0.55
4f	H	Br	OCH_3	243	41	2.43	2.45	0.62



R_1 = H

R = OCH_3, Cl, Br

R_2 = H, OCH_3

Scheme

Spectral interpretation

Compound **4b**: IR (KBr) cm^{-1}: 3318 (-OH), 3123 (-NH), 680 (C-Br), NMR ($CDCl_3$ + DMSO-d6) δ: 3.83 (s, 3H, OCH_3), 7.120-7.530 (m, 13 H, Ar – H), 11.69 (s, 1H, OH).

Biological studies

All above benzothiazepine derivatives have been studied for their antimicrobial activity against *Escherichia coli*, *Proteus mirabilis*, *Staphylococcus aureas*, *Pseudomonas aeruginosa* and antifungal activities against *Candida albicans* and *Aspergillus niger.* The culture of each species was incubated at 37^{o}C and the zone of inhibition was measured after 24 hr. Most of these compounds were found active.

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