Chemotherapeutic Interest: Green Approach towards Synthesis of fused 1,5 -Benzothiazepine and their *invitro* antimicrobial Screening

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ABSTRACT:

A simple and convenient route is described the reaction of o-aminothiophenol and its derivative as precursor for synthesis of polyfunctionalised 1,5-benzothiazepine derivatives as pharmacological and medicinal interest. 1,5-benzothiazepine and its derivative prepare cyclocondensation reaction with carbonyl functionalities, takes place by nucleophilic addition followed by cyclisation using recyclable poly (ethylene glycol-400) as an alternative reaction solvent. The reaction is clean with excellent yield, shorter reaction time and reduces the use of volatile organic compounds (VOCs).The chemical structure of the newly synthesized compounds was confirmed by IR, ^{1}HNMR and Mass spectral data. Furthermore, all the synthesized compounds were evaluated for their antimicrobial screening against several pathogenic representatives. Synthesis of such 1,5-benzothiazepine derivatives and their potential to develop better chemotherapeutic agents.

KEYWORDS:

Cyclocondensation, *O*-aminothiophenol, Chalcone, Polyethylene glycol (PEG-400), Green Reaction.

INTRODUCTION

Chemical properties of 1,5-benzothiazepine derivatives have been reviewed in the last few years. However, the usefulness of 1,5-benzothiazepine as a privileged system in medicinal chemistry has prompted the advances on the chemotherapeutic potential of this system. The preparative methods include ring closure reaction, aromatization and ring transformation[1,2], Biological properties[3,4], medicinal chemistry[5], 1,5-benzothiazepine derivatives have been privileged scaffolds in drug discovery. The 1, 5-benzothiazepine class of compounds are important as calcium channel blockers with proven utility such as diltiazem and those in which the fused benzene ring is substituted at various positions have been found to have enhanced pharmacological properties[6]. The presence of benzothiazepine scaffolds in natural product and pharmaceutical determines their potential use as antipsychotic agents[7]. The 1, 5-benzothiazepine derivatives has been reported as hypertensive agent's cletiazem[8]. 1, 5-benzothiazepine derivatives and evaluated for their antibacterial activities.[9] various substitution on phenyl ring were also tried to give potent antibacterial compounds[10]. Several 4, 6-Bis (2'-substituted-2, 3-dihydro-1, 5-benzothiazepin-4-yl) resorcinol have been found to be potential antifeedants[7], benzothiazepine as prospective cardiovascular agents [11] anticonvulsant and CNS depressant activity[12] Recently, liquid

polymers or low melting polymers have emerged as alternative green reaction media with unique properties, such as thermal stability, commercial availability, non-volatility, immiscibility with a number of organic solvents, and recyclability. Polyethylene glycol (PEG) solvent is preferred over other polymers because they are inexpensive, completely non- halogenated, easily degradable, and of low toxicity. To avoid the use of volatile organic solvents can minimize the generation of waste, which is a requirement of one of the principles of green chemistry.[13-14]

MATERIAL AND METHODS

Melting points were uncorrected and determined in open capillary tubes. The purity of the products was checked by thin layer chromatography (TLC) on precoated sheets of silica gel-G of 0.25 mm thickness. IR spectra were recorded (in KBr palates) on FTIR Schimadzu spectrometer. 1H NMR spectra were recorded in DMSO-d6 in Avance 300 MHz spectrometer using TMS as an internal standard. The mass spectra were recorded on Ei-Shimadju-GC-MS mass spectrometer. Elemental analyses were performed on a Carlo Erba 106 Perkin-Elmer model 240 analyzer.

General method for the Synthesis of 2,4-(substituted-aryl)-2, 3-dihydro-1, 5-benzo thiazepines

An equimolar mixture of 2-aminothiophenol (0.001 mol) and substituted 2'-hydroxy chalcone (0.001mol) in 10 ml Polyethylene Glycol-400 in presence of NaOH (10 mol %) was refluxed for 40 min. The corresponding 1, 5-benzothiazepines were obtained in 85-95 % yield, completion of the reaction was monitored by TLC [eluent; ethyl acetate; pet ether (3:7)]. The reaction mixture was poured on crushed ice. The solid crude product was washed with cold water and purified by recrystallization using suitable solvent. Which were further purified by column chromatography [ethyl acetate: pet ether (3:7)].

Scheme: Synthesis of 1, 5-benzothiazepines derivatives

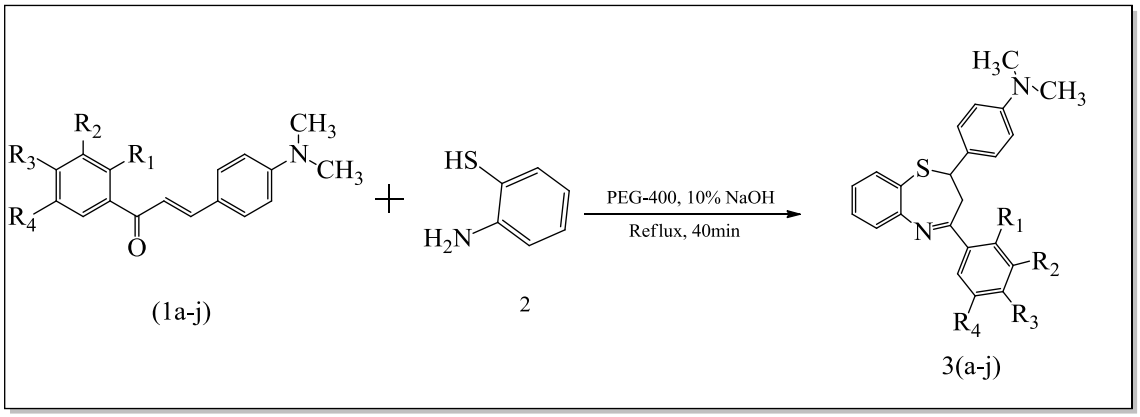

Table-1: **Substituted data of synthesized 1, 5-benzothiazepine derivatives** 1(**a-j**)

Sr. No	Entry	R_1	R_2	R_3	R_4
1	**a**	OH	I	H	I
2	**b**	OH	I	H	CH_3

3	**c**	OH	Cl	H	Cl
4	**d**	OH	I	H	Cl
5	**e**	OH	Br	H	CH_3
6	**f**	OH	Br	H	Cl
7	**g**	OH	Br	H	Br
8	**h**	OH	I	H	Br
9	**i**	OH	H	CH_3	Cl
10	**j**	OH	H	H	Br

EXPERIMENTAL

Synthesis of 2-(4'-Dimethylamino-phenyl)-4-(3-bromo-5-methyl-2-hydroxy-phenyl)-2,3-dihydro-1, 5-benzothiazepine 3(e):

An equimolar mixture of 2-aminothiophenol (0.125 gm, 0.001 mol) and 1-(3-bromo-5-methyl-2-hydroxy-phenyl)-3-(4'-dimethylamino-phenyl)prop-2-en-1-one (0.36 gm, 0.001mol) in 10 ml PEG-400 was refluxed for 40 min, in presence of NaOH (10mol %). The corresponding 2-(4'-dimethylamino-phenyl)-4-(3-Bromo-5-methyl-2-hydroxy-phenyl)-2,3-dihydro-1,5-benzothiazepine is obtained in 85-95 % yield; completion of the reaction was monitored by TLC [eluent; ethyl acetate; pet ether (3:7)]. The reaction mixture was poured on crushed ice. The solid crude product was washed with water and purified by recrystallization using suitable solvent, which was further purified by column chromatography [ethyl acetate: pet ether (3:7)].

Similarly all the other compounds of the series were also prepared by the same procedure. The physical data of synthesized compounds listed in **Table-2.**

Table 2: Physico-analytical data of synthesized 1, 5-benzothiazepine derivatives 3(a-j)

Sr. No.	Entry	Molecular formula	Yield in (%)	Melting Point (^{0}C)	Time in (min)
1	**3a**	$C_{23}H_{20}N_2I_2OS$	85	108	40
2	**3b**	$C_{24}H_{23}N_2IOS$	82	158	38
3	**3c**	$C_{23}H_{20}N_2Cl_2OS$	86	139	45
4	**3d**	$C_{23}H_{20}N_2IClOS$	86	123	36
5	**3e**	$C_{24}H_{23}N_2BrOS$	79	128	38

6	**3f**	$C_{23}H_{20}N_2BrClOS$	88	139	35
7	**3g**	$C_{23}H_{20}N_2Br_2OS$	92	155	42
8	**3h**	$C_{23}H_{20}N_2IBrOS$	86	140	40
9	**3i**	$C_{24}H_{23}N_2ClOS$	90	178	45
10	**3j**	$C_{23}H_{20}N_2BrOS$	84	162	45

Spectroscopic data of selected compounds:

2-(4'-Dimethylamino-phenyl)-4-(3-iodo-5-methyl-2-hydroxy-phenyl)-2,3-dihydro-1, 5-benzothiazepine : 3(b)

IR (KBr): 3176, 3030, 2982, 2888, 2800, 1589, 1522, 1380, 1345, 1340, 1265,1128, 947, 816, 630 cm^{-1}; 1H NMR (DMSO-d6, 300 MHz δ 2.1 (s, 3H, CH_3), δ 2.72 (s, 6H, $(CH_3)_2$), δ 3.02 (dd, 1H, H_A), δ 3.54 (dd, 1H, H_B), δ 5.52 (t, 1H, H_X), δ 6.80-7.90 (m, 10H, Ar-H), δ 10.48 (s, 1H, OH) δ ppm; EIMS (m/z): 514 (M+1), 499, 482, 323, 207, 190, 147, 121, 78, 43.

2-(4'-Dimethylamino-phenyl)-4-(3-bromo-5-methyl-2-hydroxy-phenyl)-2,3-dihydro-1, 5-benzothiazepine : 3(e)

IR (KBr): 3169, 3038, 2985, 2886, 2800, 1589, 1519, 1381, 1342, 1342, 1265,1126, 941, 817, 632, 547cm^{-1}; 1H NMR (DMSO-*d6*, 300 MHz δ 2.2 (s, 3H, CH3), δ 2.70 (s, 6H, $(CH_3)_2$), δ 3.01 (dd, 1H, H_A), δ 3.51 (dd, 1H, H_B), δ 5.50 (t, 1H, H_X), δ 6.80-7.90 (m, 10H, Ar-H), δ 10.45 (s, 1H, OH) δ ppm; EIMS (*m/z*): 467 (M+1), 423, 207, 190, 147, 121, 77, 42.

2,4-dibromo(4'-Dimethylamino-phenyl)-4-(2-hydroxy-phenyl)-2,3-dihydro-1,5-benzothiaze- pine : 3(g)

IR (KBr): 3178, 2924, 2800, 1612, 1519, 1450, 1404, 1350, 1165, 1057, 871, 817, 648, 540 cm^{-1} 1H NMR (DMSO-*d6*, 300 MHz) δ 2.8 (s, 6H, $(CH_3)_2$), δ 2.95 (dd, 1H, H_A),δ 3.42 (dd, 1H, H_B), δ 5.61 (t, 1H, H_X),δ 6.8-7.8 (m, 10H, Ar-H), δ 10.50 (s, 1H, OH) δ ppm; EIMS (*m/z*): 534 (M+1), 294, 280, 235, 172, 158, 147.

4-bromo(4'-Dimethylamino-phenyl)-4-(3-iodo-5-methyl-2-hydroxy-phenyl)-2,3-dihydro-1,5-benzothiazepine : 3(h)

IR (KBr): 3182, 2920, 2878, 1618, 1456, 1406, 1358, 1156, 1058, 870, 822, 649, cm^{-1}; 1H NMR (DMSO-*d6*, 300 MHz) δ 2.9 (s, 6H, $(CH_3)_2$), δ 2.92 (dd, 1H, H_A),δ 3.40 (dd, 1H, H_B), δ 5.61 (t, 1H, H_X),δ 6.8-7.98 (m, 10H, Ar-H), δ 10.52 (s, 1H, OH) δ ppm; EIMS (*m/z*): 579 (M+1), 528,446, 394, 348, 280, 235, 170, 148.

Antimicrobial Screening:

The antimicrobial activities of the synthesized compounds **3(a-j)** were determined by agar well diffusion method[15].The compounds were evaluated for antibacterial activity against *Escherichia coli*, *Bacillus subtilis*, *Staphylococcus aureus* and *Salmonella typhi.* The antifungal activity was evaluated against

Aspergillus niger, Aspergillus flavus, Candida albicans and *Penicillium chrysogenum* were procured from Institute of Microbial technology (IMTech), Chandigarh, India. The antibiotic penicillin (25µg/mL) was used as reference drug for antibacterial and *Nystatin* (25µg/mL) used as antifungal activities. Dimethyl sulphoxide (1%, DMSO) was used a control without compound.

The culture strains of bacteria were maintained on nutrient agar slant at 37±0.5 °C for 24hrs. The antibacterial activity was evaluated using nutrient agar plate seeded with 0.1 mL of respective bacterial culture strain suspension prepared in sterile saline (0.85%) of 105 CFU/mL dilutions. The wells of 6 mm diameter were filled with 0.1 mL of compound solution of concentration 25 to 150µg/mL separately for each bacterial strain. All the plates were incubated at 37±0.5 °C for 24 hrs. Zone of inhibition of compounds in mm were noted and minimum inhibitory concentrations (MICs) were noted. The results of antibacterial studies are given in Table 3. For antifungal activity, all the culture strains of fungi maintained on potato dextrose agar (PDA) slant at 27±0.2 °C for 24-48 hrs, till sporulation. Spore of strains were transferred in to 5 mL of sterile distilled water containing 1% Tween-80 (to suspend the spore properly). The spores were counted by haemocytometer (106 CFU/mL). Sterile PDA plate was prepared containing 2% agar; 0.1 mL of each fungal spore suspension was spread on each plate and incubated at 27±0.2 °C for 12 hrs. After incubation well prepared using sterile cork borer and each agar well was filled with 0.1 mL of compound solution at concentration 25 -150 µg/mL. The plates were kept in refrigerator for 20 minutes for diffusion and then incubated at 27±0.2 °C for 24-28 hrs. After incubation, zone of inhibition of compounds were measured in mm along with standard and minimum inhibitory concentrations (MICs) were noted. The results of antifungal studies are given in Table 4.

Table-3: Antibacterial activity of synthesized compounds 3(a-j)

Product	*Escherichia coli*	*Bacillus subtilis*	*Staphylococcus aureus*	*Salmonella typhi*
3a	16(25)	18(25)	13(25)	15(25)
3b	20(25)	16(25)	20(25)	14(25)
3c	14(25)	15(25)	28(50)	29(50)
3d	18(50)	17(25)	----	22(50)
3e	22(50)	11(50)	25(50)	30(50)
3f	20(50)	15(50)	10(50)	30(50)
3g	20(25)	17(50)	25(50)	18(50)
3h	16(50)	18(50)	14(50)	----
3i	18(50)	18(50)	12(50)	30(50)
3j	26(50)	12(50)	-----	18(50)
Reference-1	20(25)	18(25)	24(25)	18(25)

Table-4: Antifungal activity of synthesized compounds 3(a-j)

Product	*Aspergillus niger*	*Aspergillus flavus*	*Candida albicans*	*Penicillium chrysogenum*
3a	19(25)	13(25)	18(25)	16(25)

3b	18(25)	20(25)	17(25)	14(25)
3c	20(25)	22(25)	14(25)	14(25)
3d	18(25)	17(25)	16(25)	14(25)
3e	16(50)	10(50)	20(50)	19(50)
3f	18(25)	17(25)	15(50)	18(25)
3g	18(25)	16(25)	18(25)	15(25)
3h	16(50)	14(50)	12(50)	16(50)
3i	14(50)	15(50)	------	15(50)
3j	15(50)	16(50)	18(50)	15(50)
Reference-2	20(25)	18(25)	22(25)	18(25)

Zone of inhibitions are expressed in mm, MIC values (mg/mL) are given in brackets. Reference-1=Penicilllin, Reference-2=Nystatin, -- MIC > 50 mg L –1, and Solvents: DMSO, water

The examination of the data Table (3) and Table (4) reveals that majority of the compounds showed antibacterial and antifungal activity when compared with standard drug. The results of in vitro antibacterial activities of compounds 3(a-j) against various bacterial strains are summarized in Table 3. It has been observed that some of compounds exhibited interesting antibacterial activity. In comparison with reference antibacterial, compounds 3a and 3g shows good zone of inhibition against *Escherichia coli* as well as compounds 3b and 3g were showed maximum zone of inhibition against *Escherichia coli.* Compounds 3a, 3b and 3d were also displayed comparative activity against *Bacillus subtilis*. Compounds 3b display moderate to good activity against *Staphylococcus aureus*. 3a and 3b shows promising activity against *Salmonella typhi.* 3a, 3b and 3g display reduced activity against all tested bacteria.

Antifungal data in Table (4) revealed that compounds 3b, 3c, 3d and 3g showed good to moderate activity against *Aspergillus niger*. Compounds 3b, 3c, 3d and 3g were also showed most promising activity compared to standard antifungal against *Aspergillus flavus*. Compounds 3a and 3g were showed good activity against *Candida albicans*. Only the compound 3a and 3f was showed stronger activity compared with standard drug against Penicillium chrysogenum. Only the compounds 3b, 3c and 3g shows reduced activity against all tested fungi. When structure activity relationships are concerned, the antimicrobial activity might be increased by the presence of halo (I, Br and Cl) groups as substituents at R_2 $R_3$and R_4-position on the benzene ring.

Considering the results obtained from antibacterial and antifungal activities, it is possible to say that most of the tested compounds showed good zone of inhibition against bacteria and fungi also the minimum inhibitory concentrations (MICs). Therefore, the present study is useful drugs in medicinal investigation against bacterial and fungal diseases.

RESULTS AND DISCUSSION:

As part of our research programme and in continuation of our work on the development of environmentally friendly methodologies using Polyethylene glycol (PEG-400) as a reaction solvent for the preparation of biologically active compounds[16], herein we report an efficient synthesis of substituted1,5-Bezothiazepine derivatives an equimolar mixture were taken in PEG-400 with NaOH (10% mol) and reaction mixture was reflux 40min. shows in **(Scheme-1)** in good yield. The newly synthesized

compounds were evaluated for their antibacterial and antifungal activity. The substitution of benzothiazepine scaffold emerged as active in both antibacterial and antifungal evaluation and found to be excellent yield and shorter reaction time. The newly synthesized compounds confirmed by the spectral analysis. The absorption band at 3150-3350 cm^{-1} is due to –OH stretching. And 1610-1590 cm^{-1} (>C=N stretching). Beside this band at 680-800cm^{-1} is due to >C-Cl stretching and 600-700cm^{1} due to >C-Br appear whenever present in the respective compound. The ^{1}HNMR spectra revealed that H_A, H_B, H_X, pattern of 1, 5-benzothiazepine ring were seen as doublet of doublets at δ3.1-3.25, δ3.43-3.61, δ5.15-5.3 ppm respectively, due to the two magnetically non-equivalent protons of the methylene group at position 3 of the 1, 5-benzothiazepine ring. The mass spectra of synthesized 1, 5-benzothiazepines are also in agreement with their molecular formula weights.

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