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SYNTHESIS AND BIOLOGICAL EVALUATION OF SOME NEW BENZOTHIAZOLE DERIVATIVES

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ABSTRACT: Some new hydrazino group substituted benzothiazole derivatives have been synthesized and their characterization was done by IR, NMR and MASS spectral data. The antimicrobial activities of these synthesized compounds was done by cup-plate diffusion method in DMSO against some Gram positive and Gram negative bacteria. Some of synthesized derivatives exhibited potent activity when compared with standard drug Streptomycin.

INTRODUCTION: The chemistry and biological study heterocyclic compounds has been an interesting field for a long time in medicinal chemistry. Benzothaizole derivative are an important class of compounds, which is becoming increasingly important due to their broad spectrum of biological activities. Literature survey shows that many Benzothaizole derivatives are known to exhibit pharmacological activities such as antiviral and antitumor, antiproliferative, antimicrobial, antibacterial, anthelmintic as Cholinesterase inhibitor, antidiabetic, anti-inflammatory, antimalarial, antifungal etc. Hence synthesis of such compounds are of considerable interest. It is well known that the introduction of hydrazine into an organic molecule causes dramatic changes in its biological profile, mainly due to high electronegative atoms substituted on hydrazine and acetophenone causes increase lipid solubility.

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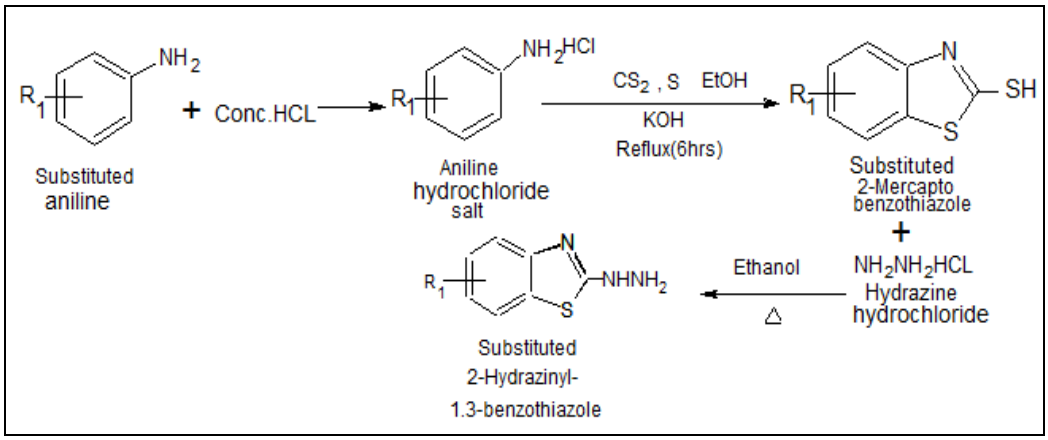
Hence, in the present study, some new derivatives of 2-[6-(phenyl) 2-thio 1, 3-oxazin-3yl] amino benzothiazole have been synthesized. Their characterization was done by spectroscopic methods. Further, antimicrobial activities of these derivatives have been studied in DMSO.

2. Experimental: Reagents grad**e** chemicals were used without further purification. All the melting points were taken in open capillaries and are uncorrected. The purity of the synthesized derivatives was checked by Thin Layer Chromatography.

2.1 Synthesis of substituted 2-hydrazinyl 1, 3-benzothiazole: Take equimolar amount of substituted aniline and conc. hydrochloric acid and triturate it thus solid of salt of Aniline hydrochloride obtained. Mix aniline hydrochloride salt and sulphur into 1:3 proportion respectively stir it continuously by addition of equivalent amount of carbon disulphide in KOH and add 15-20ml of ethanol, reflux it for 5hrs 2-mecaptobenzothiazole obtained, recrystallize with methanol. Take equimolar of 2-mecaptobenzothiazole and hydrazine hydrochloride and add 10-15ml of ethanol stir it and heat mixture at 150-155^{0}C

temperature for 2-3hrs, solid mass was obtained which recrystallize from ethanol, to get substituted 2-hydrazinyl 1,3-benzothiazole derivatives.



2.2 Synthesis of 2-[6-(phenyl) 2-thio 1,3-oxazin-3yl] amino benzothiazole derivatives: Take equimolar amount of substituted 2-hydrazinyl 1,3-benzothiazole derivatives and substituted acetophenone in methanol, add 2-4ml of formaldehyde and add few drops of conc. hydrochloride acid with constant stirring and reflux for 2hrs cooled and recrystallize with methanol to get 3-[substituted benzothiazole] hydrazino-1-substituted phenyl propan-1-one. In this add equal amount of sodium borohydride in methanol and constantly stir for 3hrs, stand for overnight, thus solid of 3-[substituted benzothiazole] hydrazino-1-substituted phenyl propan-1-ol gets separated recrystallize with methanol. Take solution 3-[substituted benzothiazole] hydrazino-1-substituted phenyl propan-1-ol in dry chloroform and 2-3ml of carbon disulphide was added dropwise. The resulting mixture was refluxed for 7hrs and distilled-off the excessive solvent. Recrystallized the residue obtained with methanol to get2-[6-(phenyl) 2-thio 1,3-oxazin-3yl] amino benzothiazole derivatives.

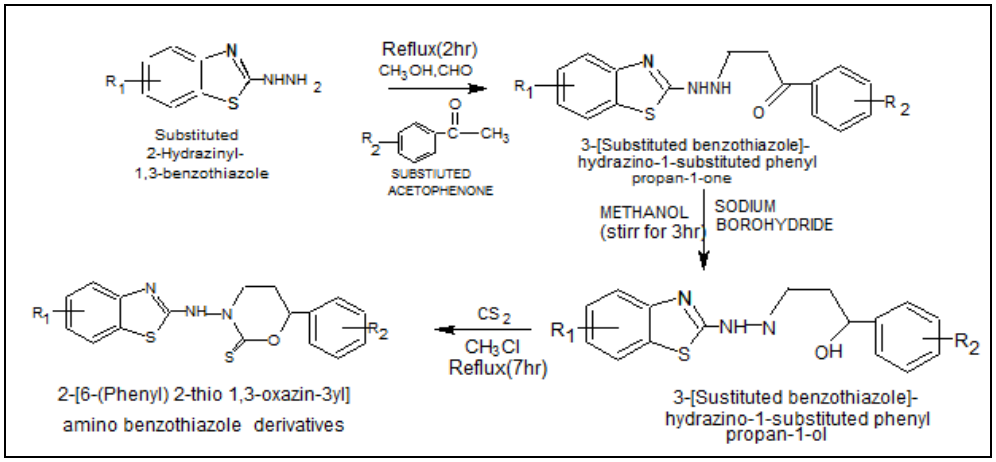


TABLE 1: PHYSICAL DATA OF SYNTHESIZED COMPOUNDS

Compounds Code	R1	R2	Melting Point	Rf Value	% Yield
GS-1	-H	-OH	192-194	0.57	60.4
GS-2	-2Cl	-4NH_2	201-203	0.69	65.5
GS-3	-2Cl	-H	232-234	0.75	58.0
GS-4	-4Br	-4OH	202-204	0.85	40.5
GS-5	-4Br	-H	175-177	0.45	58.5
GS-6	-4NO_2	-4NH_2	166-168	0.35	73.5
GS-7	-4NO_2	-4OH	233-235	0.84	72.5

2.3 Spectroscopic study: The characterization of synthesized compounds was done by IR, NMR and MASS spectral data.IR spectra were scanned on SHIMADZU FTIR-8400 Spectrophotometer in frequency range of 4000-400cm^{-1} by KBr-DRS method. ^{1}H NMR spectral was recorded in DMF with tetramethylsilane(TMS) as the internal standard at 400 MHz on a BRUKER ACF-400 spectrophotometer. The chemical shifts are reported as parts per million (ppm). The mass spectra of synthesized compounds were recorded by GCMS-SHIMADZU-QP2010.

2-[6-(4-Hydroxyphenyl) 2-thio1, 3 – oxazin - 3yl] aminobenzothiazole (GS-1): IR (KBr) (cm^{-1}); 1612.13(ArC=C), 1665.7 & 3402.54 (N-H), 3064.98 & 1456.23(ArCH), 1254.46(C=S), 1779.0(C=O), 3650(CH-OH). ^{1}H NMR (400 MHz) (δppm); 3.69-3.71 (t,4H-CH_2), 2.59-2.61 (t, 4H-CH_2), 3.33 (s, 2H-CH_2), 9.15 (s, 1H-NH), 7.66-7.69 (q, 1H, Ar-H), 7.61-7.64 (dd, 1H, Ar-H), 7.13-7-18 (m, 1H, Ar-H), 1.8 (H-CH_2-OH). Mass, m/z; 295 (M^+).

2-[6-(4-Aminophenyl) 2-thio1, 3 - oxazin - 3yl] amino 4-chloro benzothiazole (GS-2): IR (KBr) (cm^{-1}); 3253.09 &1600.97 (N-H), 3078.97& 1452.48 (Ar-CH), 1256.81 (C-N), 1358.0 (C=S), 1632.38 (C=O), 1535.39 (ArC=C), 668.31 (H-CH_2-Cl). ^{1}H NMR (400 MHz) (δ ppm); 3.68-3.61 (t,4H-CH_2), 3.01-3.05 (t, 4H-CH_2), 3.12 (s, 2H-CH_2), 8.96 (s, 1H-NH), 7.68-7.79 (q, 1H, Ar-H), 6.91-6.94 (dd, 1H, Ar-H), 7.63-7-08 (m, 1H, Ar-H), 2.1 (H-NH), 3.0-3.02 (H-CH_2-Cl). Mass, m/z; 370 (M^+).

2-[6-(Phenyl) 2-thio 1,3-oxazin-3yl] amino 6-bromo benzothiazole (GS-3): IR (KBr) (cm^{-1}); 3321.08 &1613.23 (N-H), 3099.97& 1398.48 (Ar-CH), 1358.81 (C-N), 1396.10 (C=S), 1701.38 (C=O),1536.39 (ArC=C), 779.01 (H-CH_2-Cl). ^{1}H NMR (400 MHz) (δ ppm); 3.73-3.76 (t,4H-CH_2), 2.98-3.01 (t, 4H-CH_2), 2.91 (s, 2H-CH_2), 9.12 (s, 1H-NH), 6.98-7.04 (q, 1H, Ar-H), 6.87-6.92 (dd, 1H, Ar-H), 7.83-7-11 (m, 1H, Ar-H), 3.3-3.51 (H-CH_2-Cl). Mass, m/z; 293 (M^+).

2-[6-(4-Bromophenyl) 2-thio1, 3 - oxazin-3yl] amino 6-bromo benzothiazole (GS-4): IR (KBr) (cm^{-1}); 3252.09 & 1600.87 (N-H), 3068.98& 1454.54 (Ar-CH), 1300.10 (C-N), 1296.10 (C=S), 1631.38 (C=O),1525.38 (ArC=C), 778.01 (H-CH_2-Br), 3401.23(CH-OH). ^{1}H NMR (400 MHz) (δ ppm); 3.34-3.36 (t,4H-CH_2), 2.77-2.83 (t, 4H-CH_2), 3.51 (s, 2H-CH_2), 11.26(s, 1H-NH), 6.98-7.04 (q, 1H, Ar-H), 7.50-7.62 (dd, 1H, Ar-H), 6.83-6-11 (m, 1H, Ar-H), 3.5-3.81 (H-CH_2-Br), 1.8 (H-CH_2-OH). Mass, m/z; 428 (M^+).

2-[6-(Phenyl) 2-thio1,3-oxazin-3yl] amino 6-chloro benzothiazole (GS-5): IR (KBr) (cm^{-1}); 3357.09 & 1608.87 (N-H), 3068.98& 1454.54 (Ar-CH), 1305.85 (C-N), 1319.19 (C=S), 1681.38 (C=O),1562.39 (ArC=C), 698.01 (H-CH_2-Br), 3410.23(CH-OH). ^{1}H NMR (400 MHz) (δ ppm); 3.20-3.36 (t,4H-CH_2), 2.87-2.98 (t, 4H-CH_2), 3.37 (s, 2H-CH_2), 11.56(s, 1H-NH), 7.98-8.04 (q, 1H, Ar-H), 7.60-7.72 (dd, 1H, Ar-H), 7.83-6711 (m, 1H, Ar-H), 3.5-3.71 (H-CH_2-Cl), 2.0 (H-CH_2-OH). Mass, m/z; 298 (M^+).

2-[6-(4-Aminophenyl) 2-thio1, 3 - oxazin-3yl] amino 6-nitro benzothiazole (GS-6): IR (KBr) (cm^{-1}); 3254.19 &1600.87 (N-H), 3108.97& 1452.48 (Ar-CH), 1256.81 (C-N), 1368.0 (C=S), 1632.38 (C=O), 1536.49 (ArC=C). ^{1}H NMR (400 MHz) (δ ppm); 3.01-3.06 (t,4H-CH_2), 4.01-4.05 (t, 4H-CH_2), 3.16 (s, 2H-CH_2), 8.96 (s, 1H-NH), 7.58-7.69 (q, 1H, Ar-H), 7.01-7.04 (dd, 1H, Ar-H), 7.96-7-18 (m, 1H, Ar-H), 2.1 (H-NH), 5.2-5.4 (H-CH_2-NO_2). Mass, m/z; 287 (M^+).

2-[6-(4Hydroxyphenyl) 2-thio1, 3 – oxazin - 3yl] amino 6-nitro benzothiazole (GS-7):
IR (KBr) (cm^{-1}); 1612.13 (ArC=C), 1665.7 & 3368.54 (N-H), 3164.98 & 1456.23 (ArCH), 1301.01 (C-N), 1254.46 (C=S), 1669.0 (C=O), 3450 (CH-OH). ^{1}H NMR (400 MHz) (δ ppm); 3.59-3.68 (t,4H-CH_2), 2.79-2.84 (t, 4H-CH_2), 3.53 (s, 2H-CH_2), 10.15 (s, 1H-NH), 7.76-7.80 (q, 1H, Ar-H), 7.61-7.64 (dd, 1H, Ar-H), 7.13-7-18 (m, 1H, Ar-H), 1.8 (H-CH_2-OH). Mass, m/z; 295 (M^+).

3. Biological activity: All the synthesized compounds have been screened for in-vitro antibacterial activity against two gram positive bacteria *B. Stercothermophilus* and *S. citrus* and two gram negative bacteria *E. coli* and *S. typhi* by using cup-plate dilution method, compared with standard drug streptomycin.

3.1 Preparation of solutions: All the synthesized compounds were recrystallized from methanol prior to use. The DMSO used for antimicrobial study was also purified before use bystandard method. For all compounds and standard, solutions of concentration of 10µg/ml were prepared repectively.

3.2 Cup-plate Dilution Method: The antimicrobial evaluation was done by cup-plate dilution method Nutrient agar (Hi-media) medium. The agar cup-plate dilution method was preferred to be used in this study since it was found to be better than the agar disc diffusion method as suggested Parekh et al. The bacterial strains were activated by inoculating a loop full of strain in 10 ml of N-broth and the same was incubated for 24 hrs in an incubator at 37^0C.

0.1 ml of the activated strain was inoculated in Nutrient agar kept at 45^0C. It was then poured in the petridishes and allowed to solidify. After solidification of the media, 4-5 mm cup was made in the plates using sterile stainless steel borer. Each cup was filled with 0.1 ml of the test solution. Petri dishes were incubated at 37 °C for 24 hrs. The value obtained for each cup was used to calculate zone of growth inhibition of each sample. The controls were maintained for each bacterial strain, where pure solvent (DMSO) was inoculated into the cup. The inhibition zone formed by these compounds against the particular test bacterial strain determined the antimicrobial activities of the synthetic compounds.

4. RESULTS AND DISCUSSION:

The purpose of the present work was to synthesize a series of desired title compounds 2-hydrazinyl 1, 3-benzothiazole (GS1-GS7) by reacting hydrazine hydrochloride and substituted 2-mercaptobenzo thiazole. Furthermore, the procedure used commercially available reagents, giving the desired compounds in moderate yields (45-75%). The versatility of this methodology makes it suitable for library synthesis in drug discovery efforts.

The synthesized compounds exhibit antimicrobial activity. Synthetic compounds GS2, GS3, GS4, GS5 have shown significant antimicrobial activity. Compounds GS2 & GS3was most significant. We were pleased to observe significant activity of compound compounds GS2, GS3, GS4, GS5 activity against *B. stercothermophilus*, *S. citrus*, *E. coli* and *S. typhi* by compared with standard drug streptomycin. While other compounds shown less significant activity. The antimicrobial activity studies have shown in **Table 2**.

TABLE 2: RESULTS OF ANTIMICROBIAL ACTIVITY (ZONE OF INHIBITION* IN MM, MIC# in ug/ml)

Sr. No.	Compound code	*B. stercothermophilus*	*S. citrus*	*E. coli*	*S. typhi*
01	STD	34	35	32	36
02	GS1	16	19	21	20
03	GS2	26	25	22	24
04	GS3	27	28	20	29
05	GS4	25	24	21	25
06	GS5	28	24	26	29
07	GS6	18	20	21	17
08	GS7	18	21	19	24

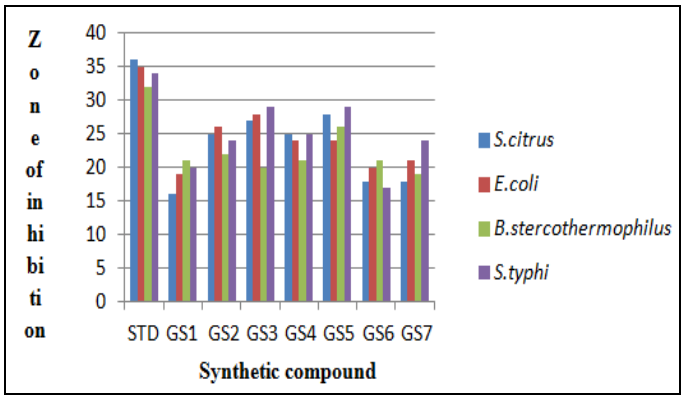


FIG 1: ANTIMICROBIAL ACTIVITY OF SYNTHETIC COMPOUNDS AGAINST GRAM-POSITIVE AND GRAM-NEGATIVE BACTERIA IN DMSO COMPARED WITH STANDARD DRUG STREPTOMYCIN (IN MM)

CONCLUSION: Various benzothiazole derivatives having hydrazinyl substituents and different substituents at position 4 and position 6 of electronegative atoms were synthesized with a view of enhancing the biological activity. The structure of newly synthesized compounds was confirmed by IR, ^{1}NMR, Mass spectra. Further evaluation of antimicrobial activity was carried out. The synthesis of various substituted2-[6-(phenyl) 2-thio 1,3-oxazin-3yl] amino benzothiazole derivatives by the described method resulted in products with good yield. Micro biological evaluation of the synthesized compounds showed good to moderate activity.

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