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Synthesis, Characterization and Microbial Activity of 5-[1-(1,3-Benzothiazol-2-Ylsulfanyl)Alkyl]-1,3,4-Thiadiazole-2-(3h)-Thione

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***Abstract*-** A number of benzothiazole-2-ylsulfanyl derivatives 2-(1,3-Benzothiazol-2-ylsulfanyl)alkanoylhydrazide (IA – IG) and 5-[1-(1,3-Benzothiazol-2-ylsulfanyl)alkyl]-1,3,4-thiadiazole-2-(3H) thione (IIA-IIG) have been synthesised from (1,3-Benzothiazol-2-ylsulfanyl)acetic acid. These compounds were synthesied and characterized from their F.T.I.R, and H-NMR spectral studies. The compound (IIA to IIG) were screened for antibacterial activity and antifungal properties. The compound 2A-2G showed appreciable antifungal and antibacterial activity.

***Index Terms*-** Benzothiazole derivatives, synthesis, Microbial activity.

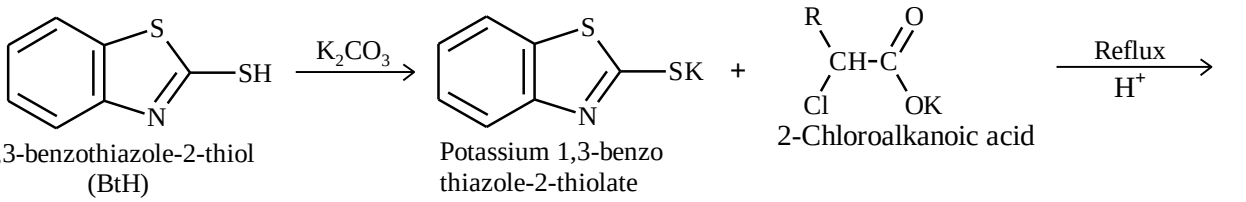
I. Introduction

The benzimidazole and benzothaizole derivatives are most promising molecules for pharmacological point of view[1,2]. A large number of benzothiazole and benzimidazole derivatives are used as potential drugs in treatment of various diseases[3-5]. A considerable number of benzothiazole and benzimidazole derivatives are used as antidiabatic[6], antihistaminic[7], analgesic[8], antiviral[9], Chemotherapeutic[10], antifungal[11], antiparasitic[12], antiulcer[13], antiHIV[14], anticancer[15] and antibiotic[16] substances.

II. Result and Discussion

2-Mercaptobenzothiazole(BtH) reacts with potassium salt of 2-Chloroacetic acid or related α-chloroalkanoic acid in presence of K_2CO_3 to yield 2-(1,3-benzithiozol-2-ylsulfanyl)alkanoic acid (as shown in Scheme-I). The alkanoic acid derivatives are converted to its ethyl ester with dry ethanol in presence of catalytic amount of conc. H_2SO_4. The ester on refluxing with 98% hydrazine gave 2-(1,3-benzothiazol-2-ylsulfanyl)alkanoylhydrazide(IA to IG).

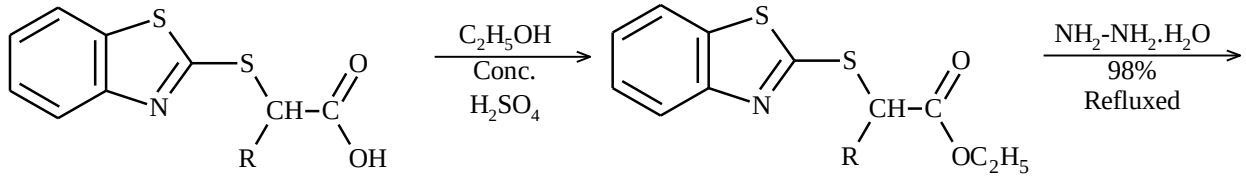
Scheme-I



1,3-benzothiazole-2-thiol (BtH)

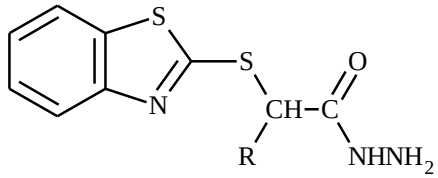
Potassium 1,3-benzo thiazole-2-thiolate

2-Chloroalkanoic acid



2-(1,3-benzothiazol-2-ylsulfanyl)alkanoic acid

ethyl 2-(1,3-benzothiazol-2-ylsulfanyl) alkanoate

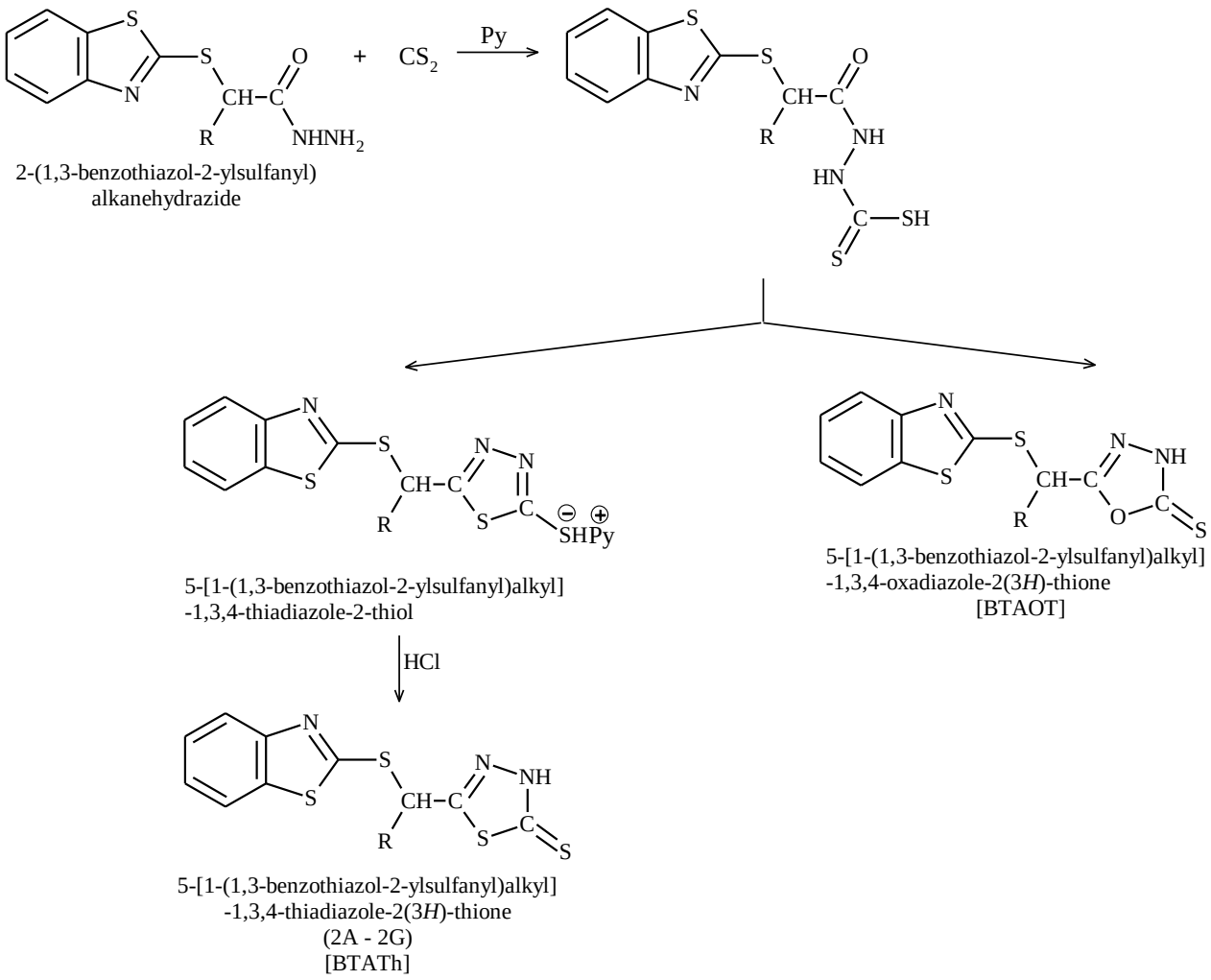


2-(1,3-benzothiazol-2-ylsulfanyl)alkanehydrazide (1A to 1G)

The group R taken for IA to IG are

IA = H, IB = $-CH_3$, IC = $-CH_2-CH_3$, ID = $-CH_2-CH_2-CH_3$, IE = $-CH_2-CH(CH_3)_2$, IF = $-CH_2(CH_2)_2-CH_3$ and IG = $-CH_2-C_6H_5$

The alkanoylhydrazide (IA to IG) were prepared crystallised, analysed and these were used to synthesised the thiadiazole derivative (2A to 2G). The interaction of alkanoyl hydrazide (IA to IG) with CS_2 in pyridine on refluxing gave thiadiazole derivatives 2A-2G (BTATDT) according to **Scheme-2**



2-(1,3-benzothiazol-2-ylsulfanyl) alkanehydrazide

5-[1-(1,3-benzothiazol-2-ylsulfanyl)alkyl] -1,3,4-thiadiazole-2-thiol

5-[1-(1,3-benzothiazol-2-ylsulfanyl)alkyl] -1,3,4-oxadiazole-2(3*H*)-thione [BTAOT]

5-[1-(1,3-benzothiazol-2-ylsulfanyl)alkyl] -1,3,4-thiadiazole-2(3*H*)-thione (2A - 2G) [BTATh]

The products BTATh are major product while oxadiazole (BTAOT) were obtained in small fraction in impure form are not being reported.

EXPERIMENTAL

The organic chemical used were obtained from BDH, E Merck, Fluka (Germany), Sigma Aldrich, Loba chem. And Sd fine chemicals. The solvents used were extrapure chemical. The meeting points of compounds were determined by open capillary tube and are uncorrected. The ^{1}HNMR and ^{13}CNMR spectral of compounds were recorded at C.D.R.I Lucknow and FTIR spectra spectra at IIT Patna. The microbial tests were performed at Biotechnology, Department of Science College, Patna.

Elemental analysis of compounds were obtained from BIT Mesra, Ranchi (Vario EL CHNS analyser) Mass and Electronic absorption spectra were recorded at IIT Patna.

Preparation of compounds:

The compound 5-[1-(1,3-benzothiazol-2-ylsulfanyl)alkyl]-1,3,4-thiadiazole-2-(3H)-thione (2A-2G) were prepared from 2-mercaptobenzothiazole, α-Chloroalkanoic acid, hydrazine and carbon disulphide in three steps as out lined in **Scheme-I**.

Step I, II

Preparation of 2-[1,3-benzothiazol-2-ylsulfanyl]alkanoylhydrazide (IA-IG) from 2-Mercapto1,3-benzothiazole.

Step III

Preparation of 5-[1-(1,3-Benzothiazol-2-ylsulfanyl)alkyl]-1,3,4-thiadiazol-2-(3H)-thione from IA to IG.

Procedure of preparation of IA to IG.

These compounds were synthesised by common procedure from 1,3-Benzothiazol-2-ylthiol.

Step-I

About 0.1 mole 2-mercaptobenzothiazol was taken in 50 ml aqueous ethanol and treated with 6 gram K_2CO_3 (0.05 moles). The resulting solution was heated on a steam bath with 0.1 mole of potassium salt of chloroacetic acid dissolved in 20 ml aqueous ethanol for two to three hours and left over night. The cold solution was neutralised with dilute hydrochloric acid and free 2-(1,3-benzothiazol-2-ylsulfanyl)acetic acid separated was filtered and dried in desiccator. (Yeild 96-97%).

Step-II

The prepared acid (0.05 mol) was dissolved in 30 ml dry ethanol and treated with 0.5-1 ml conc H_2SO_4 and refluxed on water bath for 3 to 4 hours and excess of ethanol was removed by distillation. The ester formed was treated with 20 ml hydrazine hydrate (98%) heated on steam bath at 60- 70^0C for 4-5 hours and left overnight. The resulting product was suspended in 30-40 ml water to remove soluble hydrazine sulphate. The water insoluble 2-(1,3-benzothiazol-2-ylsulfanyl)alkanoylhydrazide was filtered and recrystallised with hot ethanol. The M.P and analytical results of compound IA to IG are given in **Table-I**

Synthesis of 5-[1-(1,3-benzothiazol-2-ylsulfanyl)alkyl]-1,3,4-thiadiazole (2A to 2B)

These compounds were prepared by same common procedure.

Procedure:

About 0.02 mole of 2-(1,3-benzothiazol-2-ylsulfanyl)alkanoylhydrazide was taken in 20 ml distilled pyridine and treated with 2.5 ml carbon disulphide and resulting mixture was refluxed on steam bath for 3-4 hours till evolution of H2S ceased. The excess of pyridine was distilled at reduced pressure when yellow viscus mass was left. The product was dissolved in hot ethanol and insoluble portion probably impure oxadiazole derivative was rejected. The solution on cooling gave crystalline precipitate of pyridinium salt of 5-[1-(1,3-benzothaizol-2-ylsulfanyl)alkyl]-1,3,4-Thiadiazole were obtained. The product was suspended in hot water and neutralised with dilute HCl to liberate free 1,3,4-Thiadiazole derivatives 2A -2G. The yield was 70-75%. The product was recrystallised with hot ethanol tetrahydrofuran mixture.

The products were analysed and results of C,H,N,S analysis reported in **Table-I**

Table-1
Elemental analysis of compound 1A-1G and 2A – 2G

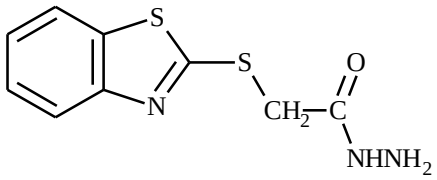
	% Elemental analysis- Found (Calculated)			
Comps-M.P^{0}C (Formula)	C	H	N	S
1A- 269 ($C_9H_9N_3S_2O$)	45.36 (45.18)	3.61 (3.76)	17.36 (17.57)	26.41 (26.77)
1B- 262 ($C_{10}H_{11}N_3S_2O$)	47.31 (47.43)	4.31 (4.35)	16.40 (16.60)	25.11 (25.29)
1C-259 ($C_{11}H_{11}N_3S_2O$)	49.13 (49.43)	4.53 (4.86)	15.61 (15.73)	23.61 (23.97)
1D- 263 ($C_{12}H_{15}N_3S_2O$)	51.10 (51.24)	5.11 (5.33)	14.71 (14.94)	22.11 (22.27)
1E-267 ($C_{12}H_{15}N_3S_2O$)	51.34 (51.24)	5.31 (5.33)	14.78 (14.94)	22.41(22.27)
1F-269 ($C_{13}H_{17}N_3S_2O$)	52.28(52.88)	5.61(5.76)	14.10(14.23)	21.41(21.69)
1G-284 ($C_{16}H_{15}N_3S_2O$)	58.11 (58.36)	4.41(4.55)	12.71(12.76)	19.16(19.45)
2A-281 ($C_{10}H_7N_3S_4$)	40.61 (40.40)	2.46 (2.35)	14.36(14.4)	43.01(43.09)
2B-278 ($C_{11}H_9N_3S_4$)	42.32 (42.44)	2.96(2.89)	13.69 (13.50)	41.23 (41.15)
2C-273 ($C_{12}H_{11}N_3S_4$)	44.16 (44.30)	3.28 (3.38)	12.93 (12.92)	39.18 (39.38)
2D-275 ($C_{13}H_{13}N_3S_4$)?	45.84 (46.01)	3.93 (3.83)	12.56 (12.38)	37.69(37.75)
2E-269 ($C_{13}H_{13}N_3S_4$)?	45.78 (46.01)	4.01(3.83)	12.41(12.38)	37.57 (37.75)
2F-280 ($C_{14}H_{15}N_3S_4$)	47.41(47.59)	4.12(4.24)	11.73(11.89)	36.01(36.26)
2G-294 ($C_{17}H_{13}N_3S_4$)	52.41(52.71)	3.51(3.36)	10.78(10.85)	32.90(33.07)

Table-4

^{1}HNMR results of IA – IG and 2A -2G

^{1}HNMR Spectra for some hydrazide A-G and finally isolated mixed benzothiazole-2-ylsulfanylmethyl substituted 1,3,4-thiadizole-2-(3H)-thiones were recorded in DMSO or $CDCl_3$. The ^{1}HNMR signals of compounds recorded are tabulated in **Table-4**. ^{13}CNMR spectra of few samples were recorded at CDRI Lucknow to support the structure of thiadiazole derivatives.

The ^{1}HNMR spectrum of 2-(1,3-benzothiazol-2-ylsulfanyl)ethanoic acid hydrazide (I-A).
shows (-S-CH_2-CO) proton signal as singlet at δ = 4.215 ppm and phenyl ring



2-(1,3-benzothiazol-2-ylsulfanyl)acetohydrazide
(IA)

proton signals between δ = 7.346-7.874 ppm as multiplet. The NH and NH_2 proton signals were observed at δ = 8.001 and 8.027 ppm. The ^{1}HNMR proton signal are consistent with structure of hydrazide I-A. The ^{1}HNMR spectrum of sulfanylpropanoylhydrazide (I-B) shows –CH_3 proton signals as double at 2.165 and 2.195 ppm and (S-CH-CO) proton signals as quarterate at 4.125-4.179 ppm with J value 18 Hz. The phenyl ring (CH) signals were obtained as multiplete δ = 7.384-7.804 ppm and NH as well as NH_2 proton band at 8.121-8.189 ppm. ^{1}HNMR signal of phenylethanoic acid derivative hydrazide I-G shows (S-CH-CO) proton signal at 4.282 ppm as singlet and phenyl as well as benzothiazole phenyl ring (CH) proton band as multiplete between δ = 7.046 and 7.874 ppm.

I-A, 2-(1,3-Benzothiazol-2-ylsulfanyl)ethanolylhydrazide ($C_9H_9N_3S_2O$) (S-CH_2-CO) proton signal, singlet δ = 4.215 ppm, phenyl ring (C—H) proton band multiplet δ = 7.346 -7.874 ppm. NH_2 and NH proton bands δ = 8.001 and 8.027 ppm.

IB, 2-(1,3-benzothiazol-2-ylsulfanyl)propanoylhydrazide ($C_{10}H_{11}N_3S_2O$), (S-CH(CH_3)-CO) group CH_3 proton signals as double δ = 1.795 & 1.803. J value 8 Hz and (S-CH-CO) proton signals as quartrate δ = 4.173 – 7.195 ppm. The phenyl ring proton signals as multiplet δ = 7.287-7.875 ppm. The –NH_2 and NH proton signals at δ = 8.125 and δ = 8.186 ppm.

1C, 2-(1,3-benzothaizol-2-ylsulfanyl)butanoylhydrazide ($C_{11}H_{13}N_3S_2O$), (S-CH(Et)-CO) group –CH_2-CH_3 proton signals as multiplet δ = 1.735-1.815 ppm, and (S-CH-CO) proton as triplet δ = 4.215-4.224 ppm. The phenyl ring (CH) band δ = 7.268-7.728 ppm as multiplet for 4 proton. The –NH_2 and NH proton band at δ = 8.176 and 8.248 ppm as broad band.

IR Spectra

The spectrum of IA shows NH_2 and NH streches at 3310, 3245 and 3175 cm^{-1}. The υCO band of IA was observed as strong band at 1672 cm^{-1}. A medium band at 1625 cm^{-1} is attributed to -NH_2 deformation vibration and strong band at 1595 cm^{-1} as ring (C=N) stretch. The δNH of hydrazide was assigned to a IR band at 1508 cm^{-1}. The prominent i.r bands of 2-(1,3-benzothiazol-2-ylsulfanyl)alkanoyl hydrazide are given in **Table C**. The occurrence of υ(CO) band between 1670-1685 and NH_2 and NH stretches between 3342-3140 cm–1 as well as benzothiazole ring υ(C=N) stretch between 1590-1602 cm^{-1} are consistent with assigned structure of 1-A to 1G. The i.r spectra of 5-[1-(1,3-benzothiazol-2-ylsulfanyl)methyl]-1,3,4-thiadiazole-2-(3H)-thione in KBr disc show the absence of υ(CO) stretche near 1670-1685 cm^{-1} supporting the cyclization of alkanoyl hydrazide (-CO-) group. The ring (N-H) stretch was observed as medium band at 3310-3240 cm^{-1} and alkyl CH stretching frequency was observed medium band at 2860-2960 cm^{-1}. The ring υ(C=N) was observed at 1605-1593 cm^{-1} and thione υ(C=S) vibration between 1306-1330 cm^{-1}. The ring (C-S-C) stretch was assigned to a medium band at 698-712 cm^{-1}. The promiment i.r bands of compound 2A to 2G are recorded in **Table-D**. The i.r spectral bands of υ(C=N), υ(C=S), υ(C—S—C) and ring (N-H) vibration are consistent with thione structure of compound 2A-2G.

Table-2
Diagnostic IR bands of compoud 1A to 1G in cm^{-1}

Compound	NH_2 & NH stretches	CH_2, CH- stretch	υ(CO)	δ(NH_2)	υ(CN)	δ(NH)	υ(CSC)
1A	3310, 3245, 3145	3045, 2940	1672	1625	1595	1508	726
1B	3315, 3240	3052, 2945, 2840	1670	1622	1596	1512	715
1C	3318, 3215, 3142	3096, 2942, 2865	1678	1626	1590	1501	721
1D	3341, 3248, 3147	3055, 2945, 2862	1676	1620	1592	1506	728
1E	3301, 3218, 3116	3042, 2940, 2861	1682	1626	1594	1512	725
1F	3342, 3218, 3140	3060, 2928, 2865	1674	1623	1597	1501	706
1G	3301, 3205, 3162	3045, 2922, 2842	1685	1618	1602	1506	723

Table-3
Prominent IR bands of compound 2A – 2G

Compound	υ(NH) + υ(C-H)	υ(CH_2)	υ(C=N)	υ(C=S)	υ(NH)	υ(C-S-C)
2A	3284, 2928	2840	1604	1322	1482	705
2B	3302, 2920	2862	1601	1318	1484	712

2C	3240, 2942	2862	1595	1312	1495	707
2D	3215, 2941	2855	1593	1321	1491	698
2E	3302, 2925	2861	1601	1328	1501	710
2F	3295, 2960	2847	1596	1306	1505	705
2G	2309, 3010	2910	1604	1330	1501	707

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