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Synthesis, Spectral Characterization and Biological Evaluation of Novel Substituted 2, 4-Dithiobiuretes with Benzothiazole Backbone

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Abstract

Drugs containing heterocyclic compounds showed remarkable and noticeable drug effect: hence they create their own importance in medicinal, agricultural and drug sciences. A simple and efficient method has been developed for the synthesis of a series of novel 2,4-dithiobiuret derivatives. In this work, a new series of 2-(5-subtituted-2,4-dithiobiurete) benzothiazole derivatives have been prepared by the interaction 1:1 molar proportion of 1-(benzo[d]thiazol-2-yl)thiourea (I a) with substituted isothiocyanates (II a-g) in 60% acetone-ethanol medium and the reaction mixture refluxed on water bath, recrystallized the product by using ethanol. This method provides the rapid and easy access of the product in very good yield. The recrystallized products were characterized on the basis of elemental analysis, chemical characteristics and spectral data. Screening of antimicrobial and antioxidant activities of novel synthesized compounds.

***Keywords*:** 1-(benzo[d]thiazol-2-yl) thiourea, substituted isothiocyanates, 60% acetone-ethanol medium, Biological evaluation.

Introduction

Heterocyclic compounds exhibits number of application in numerous fields like pharmaceutical, medicinal, therapeutic, drug and agricultural. 2, 4- Dithiobiuretes it is a significant biological moiety[1-3] and also a good intermediate in the synthesis of different type of vital active heterocycles. Synthesis and biological valuation of novel 2,4-dithiobiurets is thrilling field in the organic chemistry. 2,4- dithiobiuretes have many application in biological[4], medicinal[5], pharmaceutical[6.] Further specifically, nitrogen and sulphur containing heterocycles and derived compounds from the benzothiazole moiety possess a variety of antimicrobial activity[7-10] and antioxidant activities[11-12]. 2,4-Dithiobiurates are used as drug and also showed biological applications and significances, hence many analogs of them are used in various medicinal, industrial, agricultural, biochemical sciences[13-14]. 1,2,4-Dithiazoles were obtained by an oxidative cyclisation of 2,4-dithiobiuret making use of bromine in chloroform[15], 1,3,5-dithiazines were synthesized from 2,4-dithiobiurets and isocyanodichlorides[16]and these 1,3,5-dithiazines gave directly 1,3,5-triazines by simple isomerization[17].

Considering all these facts, it was planned to design, synthesize and to explore reactions of 1-(benzo[d]thiazol-2-yl) thiourea (Ia) with different alkyl/arylisothiocynates (IIa-f) in 60% acetone-ethanol medium were investigated.

Materials and Method

All the chemical used in the present research were MERCKS (India Made). Starting compounds (I) were synthesized by literature method[18]. Method employed in the present experiments for the synthesis of various substituted 2,4-dithiobiuertes based benzothiazole is conventional refluxing under electronic water bath for different hours for different experiments. Melting points of all the synthesized compounds estimated using

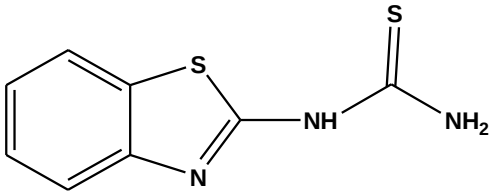
paraffin oil and uncorrected. The purity of the compounds was check by TLC on silica gel in petroleum ether and ethyl acetate [80:20]. The carbon, hydrogen, sulphur and nitrogen analysis was carried out on Carlo-Ebra-1106 analyzer and Colman-N-analyzer-29. IR spectra were recorded on SCIMADZU FTIR spectrometer in the range 4000-400 cm-1:1 in KBr pellets. PMR spectra were recorded on BRUKER AVANCE II 400 NMR spectrometer with TMS as an internal standard using CDCl3 and DMSO-d6 as a solvent. Mass spectra were recorded on WATERS,Q-TOF micromass(ESI-MS).

Experimental

General Procedure

2-(5-substituted-2,4-dithibiurete) benzothiazole (III a-f) was synthesized by the interaction of 1-(benzo[d]thiazol-2-yl) thiourea (I) with different isothiocyanates(II a-f) in 60% ethanol - acetone medium reflux for four hours. During heating reactant dissolved into the solvent. After distillation of excess solvent crystals were obtained, which recrystallized from ethanol to obtain 2-(5-substituted-2,4-dithibiurete) benzothiazole (IIIa-f).

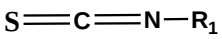
General reaction scheme for synthesis of various 2,4-dithiobiuret



1-(benzo[*d*]thiazol-2-yl)thiourea

(I)

\+

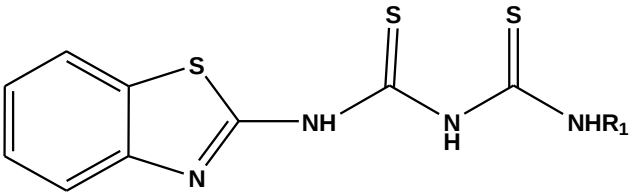


Substituted Isothiocyanates

(II a-f)

R1 = -Ph, -Allyl, -Et, -Benzyl, -4-flurophenyl, -4-Nitrophenyl

60% Ethanol-acetone



2(5-substituted-2,4-dithiobiureto) Benzothiazole

(III a-f)

Synthesis of 2-(5-Phenyl-2,4-dithibiurete) benzothiazole (III a)

In 100 ml round bottom flask a reaction mixture of 1-(benzo[d]thiazol-2-yl) thiourea (I) and Phenylisothiocyanate (IIa) in 1:1 molar proportions was refluxed in 60% acetone-ethanol medium for 4 hours on water bath, brownish crystals were separated out, filtered and dried at room conditions. Recrystallized from ethanol, Completion of reaction was monitoring by TLC. Yield 80%, melting point-199^{o}C.

Similarly, 1-(benzo[d]thiazol-2-yl) thiourea (I) interacted with methylisothiocyanate (IIb), Ethlylisothiocyanate (IIc), Benzylisothiocyanate (IId), 4-flurophenylisothiocyanates (IIe), 4-Nitrophenylisothiocyanate (IIf) to isolate 2-(5-allyl-2,4-dithibiurete) benzothiazole (IIIb), 2-(5-Ethyl-2,4-dithibiurete) benzothiazole (IIIc), 2-(5-Benzyl-

2,4-dithibiurete) benzothiazole (IIId), 2-[5-(4-flurophenyl)-2,4-dithibiurete]benzothiazole (IIIe), 2-[5-(4-Nitrophenyl)-2,4-dithibiurete]benzothiazole (IIIf), by above mentioned method and enlisted in **Table No.1**.

Table No. 1

Sr.No.	2-(5-substituted-2,4-dithibiurete) benzothiazole (III a-f)	Yield %	M.P. ºC
1	2-(5-methyl-2,4-dithibiurete) benzothiazole (IIIb)	81	198
2	2-(5-Ethyl-2,4-dithibiurete) benzothiazole (IIIc)	83	201
3	2-(5-Benzyl-2,4-dithibiurete) benzothiazole (IIId)	79	200
4	2-[5-(4-flurophenyl)-2,4-dithibiurete]benzothiazole (IIIe)	89	223
5	2-[5-(4-Nitrophenyl)-2,4-dithibiurete]benzothiazole (IIIf)	91	241

Result And Discussion

Spectral characterization results for all the synthesized compounds are given below.

SPECTRAL CHARACTERIZATION

Synthesis of 2-(5-Phenyl-2,4-dithibiurete) benzothiazole (III a)

Colour-Brownish, **Molecular formula**- $C_{15}H_{12}N_4S_3$, **Yield** 81%, **M.P**. 198^{0}C, **% Composition found (calculated)** C-52.30 , H-3.83 , N-26.20, S-26.21 , **FTIR (Kbr) vcm**- 3323.22 N-H stretching, 3001.47 (C-H Ar Stretching), 3136.38 (N-H Amido), 1946.37 (C-H Ar Bending,), 1184.99 (C=S Stretching), 680.04(=C-H bending); **1H NMR (400MHz $CDCL_3$ δ ppm)**, δ 2.02 ppm (1H, Singlet, -NH), Singlet of 2H of –NH at δ 3.8 ppm, doublet of 2CH aromatic benzothiazole at δ 8.20ppm and δ 8.10 ppm, multiplate 5H of Ph at δ 6.46 ppm - δ 7.04 ppm. **Mass** m/z 344.12.

Synthesis of 2-(5-Methyl-2,4-dithibiurete) benzothiazole (III b)

Colour-Green Solid, **Molecular formula**- $C_{10}H_{10}N_4S_3$, **Yield** 80%, **M.P**. 199^{0}C, **% Composition found (calculated)** C-40.30 , H-2.90 , N-18.10, S-33.12 , **FTIR (Kbr) vcm**-1 3414 N-H stretching., 2972 C-H stretching.,1734 N=C-N stretching., 1616 C=C stretching., 1541 N-C=S stretching., 1149 C-N stretching **1H NMR (400MHz $CDCL_3$ δ ppm)**, doublet of 3H of –CH3 at δ 2.38 ppm, singlet of 1H of aromatic –NH at δ 3.80 ppm, singlet of 1H at δ 1.90 ppm, doublet of 2CH of aromatic benzothiazole at 8.20ppm and 8.10 ppm. **Mass** m/z 280.12.

Synthesis of 2-(5-ethyl-2,4-dithibiurete) benzothiazole (III c)

Colour-Brownish Solid, **Molecular formula**- $C_{11}H_{12}N_4S_3$, **Yield** 83%, **M.P**. 201^{0}C, **% Composition found (calculated)** C-42.57 , H-3.08 , N-17.20, S-33.12 , **FTIR (Kbr) vcm**-1 3004.80 Ar-H streching, 3380.98, 3371.34 N-H stretching, 1589.23 N-H Bending, 1145.64, 1089.71 C=S Streching, 1149 C-N stretching. **1H NMR (400MHz $CDCL_3$ δ ppm)**, Ar-H proton at δ 7.55 ppm – δ 8.23 ppm, , -NH protons at δ 3.90 ppm, CH2 protons at δ 3.30 ppm,CH3 protons at δ1.16 ppm. **Mass** m/z 295.43.

2-(5-Benzyl-2,4-dithibiurete) benzothiazole (IIId)

Colour-Brownish Solid, **Molecular formula**- $C_{16}H_{14}N_4S_3$, **Yield** 79%, **M.P**. 200^{0}C, **% Composition found (calculated)** C-52.60 , H-2.94 , N-15.20, S-26.24 , **FTIR (Kbr) vcm**-1 3295.87 N-H stretching, 3098.44 C-H Ar Stretching, 650.8, 752.25 C=C bending, 1168.73 C=S Stretching, 1370, 1554 C-H bending. **1H NMR (400MHz $CDCL_3$ δ ppm)**, Multiplate of 5H of Ph at δ 7.06 ppm – δ 7.14 ppm, singlet of 2H of –CH3 at δ 4.70 ppm, Singlet of 2H of –NH at δ 2.20 ppm, singlet of Ar-NH protons at δ 3.90 ppm, doublet of 2CH aromatic benzothiazole at δ 8.20ppm and δ 8.10 ppm . **Mass** m/z 357.50.

2-[5-(4-flurophenyl)-2,4-dithibiurete]benzothiazole (IIIe)

Colour- Greenish Solid, **Molecular formula**- $C_{15}H_{11}FN_4S_3$, **Yield** 89%, **M.P**. 223^{0}C, **% Composition found (calculated)** C-48.70 , H-3.06 , F-5.10, N-14.52, S-26.24 , **FTIR (Kbr) vcm**-1 3295.87 N-H stretching, 3098.44 C-H Ar Stretching, 752.25 C=C bending, 1168.73 C=S Stretching, 1370, 1554 C-H bending. **1H NMR (400MHz $CDCL_3$ δ ppm)**, Singlet of 2H of –NH at δ 3.20 ppm, singlet of -NH protons at δ 2.30 ppm, doublet of 2CH aromatic benzothiazole at δ 8.20ppm and δ 8.10 ppm . **Mass** m/z 361.00.

2-[5-(4-Nitrophenyl)-2,4-dithibiurete]benzothiazole (IIIf)s

Colour- Yellow Solid, **Molecular formula**- $C_{15}H_{11}N_5O_2S_3$, **Yield** 91%, **M.P**. 241^{0}C, **% Composition found (calculated)** C-46.70 , H-2.60, N-17.52, O-8.22, S-24.26 , **FTIR (Kbr) vcm**-1 1523 N-O stretching, 3295.87 N-H stretching, 3098.44 C-H Ar Stretching, 752.25 C=C bending, 1168.73 C=S Stretching, 1370, 1554 C-H bending. **1H NMR (400MHz $CDCL_3$ δ ppm)**, doublet of 2H of Ph –CH at δ 7.60 ppm and δ 6.50 ppm Singlet of 2H of –NH at δ 3.20 ppm, singlet of -NH protons at δ 2.30 ppm, doublet of 2CH aromatic benzothiazole at δ 8.20ppm and δ 8.10 ppm . **Mass** m/z 390.16.

PHARMACOLOGICAL STUDIES

Antimicrobial Activity

All the synthesized compounds (IIIa) to (IIIf) were screened for their in Vitro antibacterial activity against IIIarious microorganisms such as gram positive Staphylococcus aureus, gram negative Escherichia coli by Disc diffusion method was performed using Nutrient agar medium. Each compound was tested at concentration 50 µg/mL in DMSO. The zone of inhibition of tall the synthesized compounds were measured after 24 h incubation at 37ºC. Standard drug used to compare the activity was Ciprofloxacin (25 µg/mL).

	Dimeter of zone of inhibition (mm)			
	Escherichia coli		***Staphylococcus aureus***	
Compound	**25mg/ml**	**50mg/ml**	**25mg/ml**	**50mg/ml**
IIIa	7±0.1	9 ±1	10 ±0.6	11 ±1.0
IIIb	5 ±2.0	5 ±1.0	---	----
IIIc	9 ±1	5 ±1.0	11 ±1.5	8 ±1.0
IIId	7 ±2.0	13 ±2.0	11±1	16±1
IIIe	11 ±1.0	11 ±1.0	8 ±1.0	13 ±1.0
IIIf	14 ±11	15 ±2.0	9±2.0	11 ±1.5
Ciprofloxacin	17 ±08	26 ±	19 ±11	28 ±13

Conclusion

In the present research of synthesis of compounds (IIIa-IIIf), percentage of yield of compound (IIIf) is highest i.e. 91%. Variation in the yield of each compound is due to substitution at Nitrogen in the alky/aryl isothiocynate (IIa-f). It is also Observed that, change in the substituent at nitrogen leads not only the yield of product but also it affects the melting point and antibacterial activities against the gram positive and gram negative bacteria more specially, *Escherichia coli* and *Staphylococcus aureus* respectively. Among synthesized series of compounds of 2,4-dithiobiurets i.e. (IIIa-IIIf), it can conclude that compound (IIIe) and (IIIf) displayed the excellent anti-microbial results in compare with the ciprofloxacin as a standard drug. After studying the toxicities of the (IIIe) and (IIIf), these compounds may be act as good drugs for the living beings.

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