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Synthesis and In vitro Antioxidant Activity of Novel 1,2,4-Dithiazole Scaffold Bearing Benzothiazole

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KEYWORDS
oxidative cyclization, dithiazoles, oxidizing agent, Antioxidant activity.

ABSTRACT:

A single step synthesis of N-(5-(substitutedimino)-5H-1,2,4-dithiazol-3-yl)benzo[d]thiazol-2-amine (II a-f) was carried out by oxidative cyclisation of 2-(5-substituted-2,4-dithiobiurete) benzothiazole (I a-f) using liquid bromine in chloroform medium as an oxidizing agent. The products were isolated, characterized and justified on the basis of conventional chemical characteristics and spectral studies. Screening in vitro antioxidant activities of some synthesized compounds.

Introduction

Dithiazole is a five-membered heterocyclic compound containing nitrogen and sulfur in its structure, exhibits significant biological potential. Its presence enhances various biological activities, pharmaceutical applications, and industrial uses[1]. Reactive intermediates containing thiocarbonyl functionalities conjugated with a nitrogen moiety have been extensively investigated as versatile building blocks for the synthesis of valuable heterocyclic compounds[2]. Recently reported some newer thiadiazole along with pyridine for the anti-bacterial activities[3-4] and effect of germination pattern of jowar, Bhagwatkar[5] synthesized and reported the thiadiazole based triazine for the antibacterial activities and some different substituent's attached thiadiazole directly or indirectly shows effect directly in their biological, pharmaceutical and agricultural applications[6-7]. The benzothiazole based heterocycles are five membered heterocycles containing sulphur and nitrogen as a heteroatom were created its own background in the synthetic organic chemistry[8-12]. The biological as well as industrial applications of benzothiazole get enhanced, due the presence of the thiadiazole nucleus in their structure. Trusting the literature ideas in mind it is decided to design such organic moiety should contain thiadiazole along with the benzothiazole; to synthesize such series of benzothiazole based five member heterocycle containing sulphur and nitrogen as a heteroatom[13-19].

In order to synthesize novel dithiazoles, it has been planned to design and synthesize novel series of N-(5-(substitutedimino)-5H-1,2,4-dithiazol-3-yl)benzo[d]thiazol-2-amine (II a-f) in this laboratory with the easiest and cheaper method by oxidative cyclisation of 2-(5-substituted-2,4-dithiobiureto) benzothiazole (I a-f) with liquid bromine in chloroform medium. The present method utilized somewhat suitable, convenient, cheaper, more practical utility and only a single step direct method for the synthesis of (IIa-f). Screening in vitro antioxidant activities of some synthesized compounds.

Experimental section

Materials:

All chemicals used were of Mercks Millipore (Indian made). 2-(5-substituted-2,4-dithiobiureto) benzothiazole (I a-f) were prepared by known literature method.

Method:

Method employed in the present experiments for the synthesis of series 1,2,4-dithiazole based benzothiazole is conventional refluxing under water bath for different hours for different experiments. The melting points of synthesized compounds were recorded using hot paraffin

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bath and uncorrected. IR spectra were recorded on Perkin Elmer spectrometer in the range 4000-400 cm-1 in KBr pellets. PMR spectra were recorded on BRUKER AIIIANCE II 400 NMR spectrometer with TMS as an internal standard using $CDCl_3$ and DMSO-d_6 as a solvent. The purity of the compounds was checked on silica gel – G plates by TLC with layer thickness of 3mm.

General procedure:

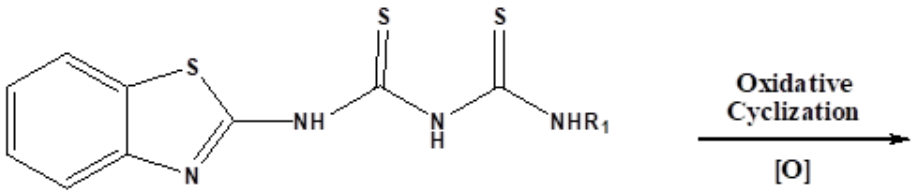
Experiment no. 1

Synthesis of N-(12Z)-(5-(Methylimino)-5H-1,2,4-dithiazol-3-yl)benzo[d]thiazol-2-amine (IIa):

The pest of 2-(5-methyl-2,4-dithiobiureto) benzothiazole (Ia) was prepared in chloroform in a clean china dish and liquid bromine in chloroform was added with constant stirring at room temperature. During the addition of bromine in chloroform solution to the pest of (Ia), firstly the colour of bromine disappear, further addition of bromine in chloroform colour of bromine appears and persists. Such solution of bromine in chloroform and (Ia) kept for 4 hours at room temperature. Basification of the reaction mixture with dilute ammonium hydroxide solution gives the formation bright cream yellow coloured product (IIa). Recrystallization of the product was done using ethanol. Yield 89%, M. P. 172^{0}C.

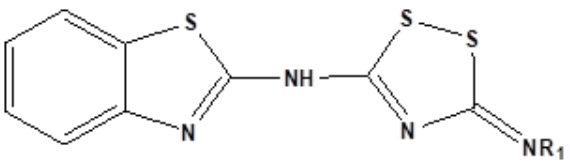
Similarly, N-(12Z)-(5-(ethylimino)-5H-1,2,4-dithiazol-3-yl)benzo[d]thiazol-2-amine (IIb), N-(12Z)-(5-(phenylimino)-5H-1,2,4-dithiazol-3-yl)benzo[d]thiazol-2-amine(IIc), N-(12Z)-5-(4-nitrophenylimino)-5H-1,2,4-dithiazol-3-yl)benzo[d]thiazol-2-amine (IId), N-(12Z)-5-(4-flurophenylimino)-5H-1,2,4-dithiazol-3-yl)benzo[d]thiazol-2-amine(IIe), N-(12Z)-5-(4-methoxphenylyimino)-5H-1,2,4-dithiazol-3yl)benzo[d]thiazol-2-amine (IIf) were synthesized from the oxidative cyclisation of 2-(5-ethyl-2,4-dithiobiureto) benzothiazole (Ib), 2-(5-phenyl-2,4-dithiobiureto) benzothiazole (Ic), 2-(5-(4-Nitropenyl)-2,4-dithiobiureto) benzothiazole (Id), 2-(5-(4-flurophenyl)-2,4-dithiobiureto) benzothiazole (Ie), 2-(5-(4-Methoxyphenyl)-2,4-dithiobiureto) benzothiazole (If), with liquid bromine in chloroform medium respectively by the above mentioned method in Experiment No. 1 to 6 and the data obtained by the characterization of synthesized compound in a series (IIa-f) is given result section.

Reaction scheme:



(Ia-f)

R1 = -Me -Et, -Ph,-4-Nitrophenyl,-4-flurophenyl,-4-Methoxy



N-(5-(substitutedimino)-5*H*-1,2,4-dithiazol-3-yl)benzo[*d*]thiazol-2-amine

(III a-f)

R1 = -Me -Et, -Ph,-4-Nitrophenyl,-4-flurophenyl,-4-Methoxy

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Results and discussion:

Spectral data obtained from the present research support the formation of designed or target products. Spectral characterizations of all the synthesized compounds are also given below:

Data analysis:

N-(12Z)-(5-(Methylimino)-5H-1,2,4-dithiazol-3-yl)benzo[d]thiazol-2-amine (IIa):

Cream Yellow solid, $C_{10}H_8N_4S_3$, Yield-89 %, M.P. 172, **FTIR (KBr) ν cm**-3085.89-3004.89 (Ar C-H stretching), 574.75(S-S stretching), 1587.31 (S-C=N stretching), 794.62-761.83 (C-S stretching); **^{1}H NMR (400 MHz CDCl3 δ ppm)**, singlet of 3H of –CH3 at δ 1.10 ppm, singlet of 1H of NH at δ 3.50ppm, quartrate of 2H at δ 7.20 ppm of benzothiazole. **Mole. mass** 280.12.

N-(12Z)-(5-(ethylimino)-5H-1,2,4-dithiazol-3-yl)benzo[d]thiazol-2-amine (IIb):

Dark Yellow solid, $C_{11}H_{10}N_4S_3$, Yield-92%, M.P. 168^{0}C, **FTIR (KBr) ν cm**-3085.89-3004.89 (Ar-H Stretching), 574.75(S-S stretching), 1587.31(-C=N stretching), 794.62-761.83(C-S stretching),; **1H NMR (400 MHz CDCl3 δ ppm)**, triplet of 3H of CH3 at δ 1.10 ppm, quartrate of 2H of CH2 at δ 1.30 ppm, m. 1 proton of NH- attach between benzothiazole ring and thionyl group dishielded due to thioamide position and give siglet at δ 3.4 ppm, quartrate of 2H at δ 7.20 ppm of benzothiazole. **Molecular Mass** 293.42.

N-(12Z)-(5-(phenylimino)-5H-1,2,4-dithiazol-3-yl)benzo[d]thiazol-2-amine(IIc):

Yellow, $C_{15}H_{10}N_4S_3$, Yield-88%, M.P. 174ºC, **FTIR (KBr) ν cm**- 3056.96-3004.89 (Ar-H Stretching), 592.11 (S-S stretching), 1587.31 (-C=N stretching), 794.62-761.83 (C-S stretching),; **1H NMR (400 MHz CDCl3 δ ppm)**, multiplate of 5H of Ph at δ 7.40 ppm, 1 proton of NH- attach between benzothiazole ring and thionyl group dishielded due to thioamide position and give siglet at δ 3.4 ppm, quartrate of 2H at δ 7.20 ppm of benzothiazole. **Molecular Mass** 343.42.

N-(12Z)-5-(4-nitrophenylimino)-5H-1,2,4-dithiazol-3-yl)benzo[d]thiazol-2-amine (IId):

Colour- Brown Solid, **Molecular formula**- $C_{15}H_9N_5O_2S_3$, **Yield** 78%, **M.P**. 208^{0}C, , **FTIR (Kbr) vcm**-1 1550 N-O stretching, 3295.87 N-H stretching, 3098.44 C-H Ar Stretching, 752.25 C=C bending, 1168.73 C-S Stretching, 1340, 1554 C-H bending. **1H NMR (400MHz CDCL$_3$ δ ppm)**, multiplate of 4H δ 8.10 – 8.20 ppm, singlet of 1H of –NH at δ 3.80 ppm. **Molecular Mass** 388.46.

N-(12Z)-5-(4-flurophenylimino)-5H-1,2,4-dithiazol-3-yl)benzo[d]thiazol-2-amine(IIe):

Colour- white Solid, **Molecular formula**- $C_{15}H_9FN_4S_3$, **Yield** 79%, **M.P**. 202^{0}C, **FTIR (Kbr) vcm**-1 1370 C-F stretching, 3414 N-H stretching., 2972 C-H stretching.,2080 N=C-S stretching., 1616 C=C stretching., 1149 C-N stretching. 1650 C=N stretching. **1H NMR (400MHz CDCL$_3$ δ ppm)** Ar-H protons at δ7.00-8.23ppm, singlet -NH protons at δ 3.53 ppm, **Molecular Mass:** 361.26

Antioxidant Activity

DPPH Radical scavenging activity

The DPPH (1,1-diphenyl-2-picryl hydrazine) radical scavenging action of various chemical compounds was calculated according to the method explained by Kato et al 1998 with some adaptations. Reaction mixture contains freshly prepared 1 mL DPPH (0.1 mM) solution in absolute ethanol with dissimilar concentrations. The blank sample consisted of 2 mL of absolute ethanol while the control contained 2 mL DPPH ethanolic solution only. Reaction mixture was prepared by mixing independent chemical compounds with equal amount 1mL of DPPH radical in absolute ethanol solution. Absorbance of sample, blank and control was measured at 517 nm, after 30 min incubation of reaction in the dark at room temperature, using UV-Visible spectrophotometer (Blois M.S. et al 1958, Roberta R et al 2006). Obtained results were compared with ascorbic acid (Vitamin C) which acts as a reference.

Sr. No	Compound	DPPH radical scavenging activity (%)
1	III a	18.25 + 0.22
2	III b	20.64 + 0.12
3	III c	17.08 + 0.38
4	III d	04.15 + 0.22
5	III e	07.56 + 0.72

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6	**III f**	**30.04 + 0.18**
7	**Ascorbic Acid**	**90.15 + 0.53**

Conclusion

In summary, this study reports that the successful synthesis of the 1,2,4- Dithiazole compounds in good yield and characterized by IR, 1H-NMR and mass spectral analysis. The antioxidant activity of the synthesized compounds was determined by DPPH free radical scavenging activity. All tested compounds were compatible with DPPH radical scavenging activity, the compounds III f and III b shows higher antioxidant activity.

Authors Contributions

All the author have contributed equally

Conflict Of Interests

Declared none

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