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Synthesis and Antifungal Activity of Some Bis-1,4-(3-Mercapto-5-Oxymethyl-1,2,4-Triazole-5-yl) Benzene & Bis-1,4-(5-Amino-2-Oxymethyl-1,3,4-Thiadiazole-2-yl) Benzene

Rashmi Rautela[1], Sapna Bora[2,*]

Abstract

Heterocyclic compounds are well known for their pharmacological application. Among all N-containing heterocyclic compounds, triazole emerges superior application. Triazole have two core structures 1,2,4-triazole and 1,2,3-triazoles. They both can give a broad range of substitutions with their structures, due to these characteristics, they have significant biological applications. They are also important in organocatalysis, agrochemicals, and material science. We aim to explore suitable molecular modifications in thiadiazole and triazole derivatives to enhance their pharmacological profiles. This paper outlines the methodology used to investigate the structure and antifungal properties of heterocyclic compounds derived from hydroquinone. The synthesis included compounds, such as Bis-1,4-(3-mercapto-5-oxymethyl-1,2,4-triazole-5-yl) benzene and Bis-1,4-(5-amino-2-oxymethyl-1,3,4-thiadiazole-2-yl) benzene. To confirm the structures of these newly synthesized compounds, gravimetric analysis, melting point determination, elemental analyses, and infrared (IR) spectra (recorded using KBr) were conducted using a Perkin–Elmer spectrometer. Additionally, NMR spectra were obtained in DMSO-d6 on an EM-360 spectrometer (60 MHz), using TMS as the internal standard. The antifungal efficacy of these compounds was evaluated against Aspergillus flavus, Helminthosporium tetramera, and Penicillium decumbens by the paper disc plate method at concentration levels of 2.0 and 0.2% (w/v) in dimethyl sulfoxide standard PDA medium.

Keywords: 1,3,4-Thiadiazole, heterocyclic compounds, thiosemicarbazide Bis-heterocydes, triazoles, Aspergillus flavus, Helminthosporium tetramera, Penicillium decumbens

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INTRODUCTION

Heterocyclic compounds are crucial in the pharmaceutical industry. This research focused on designing and synthesizing a new series of derivatives from triazole and thiadiazole. Regarding the important role of heterocyclic compounds in the drug industry [1], a new series of triazole and thiadiazole derivatives was designed and synthesized. They have diverse biological application in agrochemistry, pharmaceutical and material science. Thiadiazoles are known for their wide range of biological activities, which include antibacterial [2], anti-inflammatory [3], anti-parasitic [4], antiviral [5], and anticancer [6], antifungal [7, 8], anti-tumoral and diuretic action

effects. Additionally, they are used as oxidation inhibitors, cyanine dyes, and anti-corrosion agents [9], they have been shown to alleviate conditions like diabetes, inflammation, and Alzheimer's [10]. The main structural constitution of thiadiazole is a linear arrangement of two N-atoms and one S-atom and two neighbouring carbon atoms [11]. Among the different isomers, 1,2,4-thiadiazole has been the focus of significant research, leading to discoveries regarding its structural characteristics and reactivity. Thiadiazole derivatives play an essential role in the pharmaceutical industry, serving as a basis for numerous drugs and biological substances. Given their various applications and the continuous research efforts, they are important targets for organic and medicinal chemists aiming to create innovative compounds with improved effectiveness and safety [9]. Thiadiazole derivatives possess interesting biological activity, probably conferred to them by the strong aromaticity of this ring system, which leads to great in vivo stability and generally, a lack of toxicity [12]. The sulphur atom of thiadiazole imparts improved liposolubility and mesoionic nature to it, which makes these compounds better able to cross the cellular membrane. Heterocyclic compounds are well known for their pharmacological application.

Among all N-containing heterocyclic compounds. Triazoles emerge with superior pharmacological applications. Structurally, there are two types of five-membered triazoles 1,2,3-triazole and 1,2,4-triazole. Due to the structural characteristics, both 1,2,3- and 1,2,4-triazoles can accommodate a broad range of substituents (electrophiles and nucleophiles) around the core structures, i.e., they show diverse novel bioactive molecular properties. Triazoles are a significant platform in medicinal chemistry and chemical biology, which play key roles in various biological mechanisms related to infections, cancer, convulsions, inflammation, neurodegeneration, and oxidative stress [13, 14].

Triazole compounds containing three nitrogen atoms in the five-membered ring are readily able to bind with a variety of enzymes and receptors in biological systems via diverse non-covalent interactions are display various biological activities. They have a broad range of therapeutic applications. Hence, this review focuses on the structural features, synthesis, and biological properties of triazoles and thiadiazole compounds. With the above studies, triazole and thiadiazole have tremendous antimicrobial [15], anticancer [16], antimicrobial, antibacterial [17], and antifungal [18] activity. Hence, we have selected this drug for the suitable molecular modifications of the reported scheme and compound we have attempted to design the synthesis of thiadiazole, triazole derivatives for versatile pharmacological profiles.

EXPERIMENTAL

All reagents, starting materials, and solvents utilized were of analytical grade and acquired commercially. The melting points of the compounds synthesized were determined using open capillaries in a sulfuric acid bath. Infrared spectra (KBr) were obtained with a Perkin–Elmer spectrometer, covering the range of 4000-400 cm^{-1} and 400-100 cm^{-1}. Additionally, the H^1NMR spectra (DMSO-d6) were recorded on an EM-360 spectrometer (60 MHz), using TMS as an internal reference.

- *Hydroquinone diethyl acetate:* A mixture of hydroquinone (0.5 mole), chloroethyl acetate (1 mole), and anhydrous potassium carbonate (0.5 mole) was heated. The reaction mixture was shaken occasionally. It was then refluxed for 24 hours, cooled, and poured into ice-cold water. The residue thus obtained was filtered, washed with water, and crystallized from ethanol. M.P. 72°C, yield 92%.
- *Hydroquinone diacetic acid hydrazide:* Hydroquinone diacetic acid hydrazide was prepared by refluxing a mixture of hydroquinone diethyl acetate (0.01) in absolute alcohol until a clear solution was obtained. To this mixture, hydrazine hydrate, 98% (0.02 mole) was added dropwise and refluxed for about 8 hrs. The excess solvent was removed by distillation under reduced pressure. The solid product was filtered and crystallized from ethanol, M.P. 225°C, yield 85%.
- *Hydroquinone diacetyl bis-(3-thiosemicarbazide):* A mixture of hydroquinone diacetic acid hydrazide (1mole), KCN (2 mole), conc. HCl (11.6 ml) and water (20 ml) were refluxed for about 4 hours. The reaction mixture was poured into ice-cold water. The resulting precipitate was filtered, washed with water, dried, and crystallized from glacial acetic acid. Molecular formula

$C_{12}H_{16}N_6O_4S_2$, M.P. > 250, yield 64.42% (found S 17.12, N, 22.47%, calculated S, 17.20, N, 22.58%); max(cm^{-1}): 3210 (N–H), 1680 (–CO–NH–),1190 (C=S), 820 (1,4-disubstituted benzene); δ6.75 (S, 4H, ArH), 4.5 (S, 4H, $2OCH_2$).

- *Bis-1,4-(3-mercapto-5-oxymethyl-1,2,4-triazole-5-yl) benzene:* Hydroquinone diacetyl bis(3-thiosemicarbazide) (0.005 mole) was refluxed in a solution of sodium hydroxide solution (8%) (50 ml) for about 4–6 hrs. The reaction mixture was cooled and diluted with water and filtered. The filtered solution was then acidified with HCl. The precipitate thus obtained was filtered, washed with water, dried and crystallized from ethanol, molecular formula $C_{12}H_{12}N_6O_2S_2$, M.P. > 250, yield 62.50% (found: N, 24.88, S, 19.13% calculated N, 25, S,19.04%); IR: 3170(N–H), 1630 (C=N aromatic), 1570 (C=C aromatic), 810 (1,4-disubstituted benzene); δ 6.75 (S, 4H, Ar H), 4.5 (S,4H, 2X OCH_2) (Figure 1).

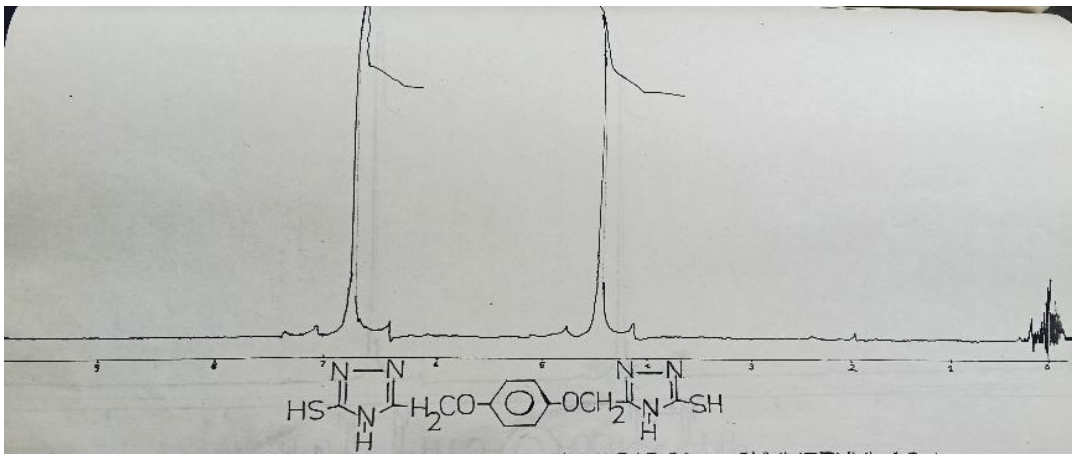

Figure 1. NMR spectrum of Bis-1,4-(3-mercapto-5-oxymethyl-1,2,4-triazole-5-yl) benzene.

- *Bis-1,4-(5-amino-2-oxymethyl-1,3,4-thiadiazole-2-yl) benzene:* Hydroquinone diacetyl bis-(3-thiaosemicarbazide) (0.01 mole) was added with steering to anhydrous phosphoric acid (20 ml) during 20 min. The flask was heated on an oil bath at 120°C for 30 min, and the slurry was poured over ice-cold water. The solid thus separated was filtered and crystallized from ethanol, molecular formula $C_{12}H_{12}N_6O_2S_2$, M.P. > 250, yield 77.38% (found: N 28.86, S 19.13%, calculated: N 29, S 28.86%); max(cm^{-10}): 3200 (N–H), 1630 (C=N aromatic), 1580 (C=C aromatic), 805 (1,4-disubstituted benzene);δ 6.75 (S, 4H, ArH), 4.45 (S, 4H, $2XOCH_2$) (Figure 2).

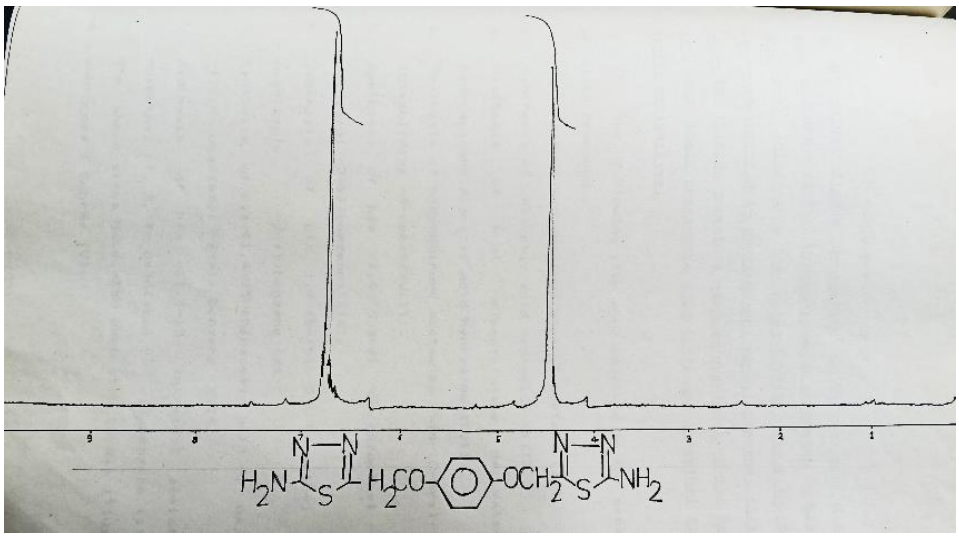

Figure 2. NMR spectrum of Bis-1,4-(5-amino-2-oxymethyl-1,3,4-thiadiazole-2-yl) benzene.

- *Bis-1,4-(2-oxymethyl-6-phynlimidazol [2,1-b]-1,3,4-thiadiazole-2-yl) benzene:* A mixture of bis-1,4-(5-amino-2-oxymethyl-1,3,4-thiadiazole) (0.005 mole) phenacyl bromide (0.01mole) was refluxed in absolute alcohol +DMF (1:1) for 6 hrs on a steam bath. The solvent is removed under reduced pressure, and the residue was washed with either and treated with sodium bicarbonate solution. After keeping over night the free base obtained was filtered, washed with water, dried and crystallized from ethanol, molecular formula $C_{28}H_{20}N_6O_2S_2$, M.P. 200°C, yield 46.76% (found: N 15.38, S 11.72% calculated: N 15.45, S 11.77%); max(cm^{-1}): 1650(C=C, aromatic), 1580 (C=N), 810 (1,4-disubstituted benzene).
- *Screening for antifungal activity:* These compounds were screened for their antifungal activity against *Aspergillus flavus*, *Helminthosporium tetramera* & *Penicillium decumbens* as the test fungi by the paper disc plate method at the concentration level of 2.0 and 0.2% (w/v) in dimethyl sulfoxide. Standard PDA medium was used.

RESULTS AND DISCUSSION

Thiadiazole and triazole have exhibited a wide range of biological activities, making them interesting candidates for drug discovery and development, this paper reported different overview to synthesis of Bis-1,4-(3-mercapto-5-oxymethyl-1,2,4-triazole-5-yl) benzene and Bis-1,4-(5-amino-2-oxymethyl-1,3,4-thiadiazole-2-yl) benzene (Figures 3 and 4).

These newly synthesized compounds were examined for their antifungal potential against *Aspergillus flavus, Helminthosporium tetramera, & Penicillium decumbens.* Antifungal activity of Bis-heterocyclic compounds recorded in Tables 1 & 2 indicates that bis-1-4-(3-mercapto-5oxymethyl-1,2,4-triazole-5-yl) benzene was effective against all the test fungi. These compounds were active against *Aspergillus flavus* and *Helminthosporium Teramera*, but against *Aspergillus flavus* and *Penicillium decumbens* they showed weak antifungal activity (Tables 3 & 4).

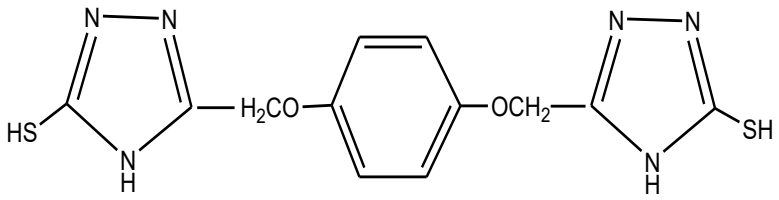

Figure 3. Synthesised bis-1,4-(3-mercapto-5-oxymethyl-1,2,4-triazol-5-yl) benzene.

Table 1. Bis-1,4-(3-mercapto-5-oxymethyl-1,2,4-triazol-5-yl) benzene.

	M.P. (^{O}C)	Yield %	Molecular Formula	Analysis %	
R				**Calculated / Found**	
				N	**S**
C_6H_5	>250	59.05	$C_{24}H_{20}N_6O_2S_2$	16.27	12.4
				16.35	12.35
p-$CH_3C_6H_4$	250	85.27	$C_{26}H_{24}N_6O_2S_2$	15.44	11.76
				15.37	11.71
p-ClC_6H_4	245	51.3	$C_{24}H_{15}N_6O_2S_2Cl_2$	14.35	10.94
				14.28	10.89
p-BrC_6H_4	>250	48.07	$C_{24}H_{15}N_6O_2S_2Br_2$	12.46	9.49
				12.52	9.96
p-$OCH_3C_6H_4$	> 250	62.73	$C_{26}H_{24}N_6O_4S_2$	14.58	11.11
				14.51	11.06

Table 2. Antifungal activity of bis-1,4-(3-mercapto-5-oxymethyl-1,2,4-triazol-5-yl) benzene.

	Diameter of Zones of Inhibition in Mm for Pathogenic Fungi Ar Concentrations					
	(%W/V)					
	Aspergillus flavus		***Pennicilliun decomben***		***Helminthosporium tetramera***	
	2	0.2	2	0.2	2	0.2
	22	16	22	16	16	14
Dithane -78	23	20	25	21	25	22
Thiran 75-W	30	26	27	22	28	24

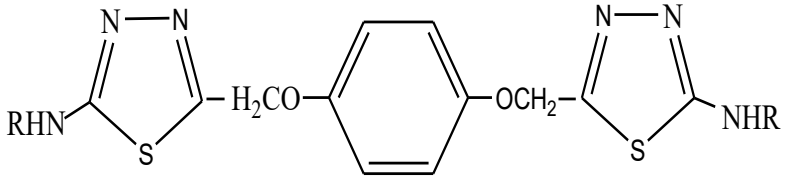

Figure 4. Synthesized Bis-1,4-(5-amino-2-oxymethyl-1,3,4-thiadiazole-2-yl) benzene.

Table 3. Bis-1,4-(5-amino-2-oxymethyl-1,3,4-thiadiazol-2-yl) benzene.

R	**M.P.°C**	**Yield %**	**Molecular Formula**	**Analysis %**	
				Calculated / Found	
				N	**S**
C_6H_5	140	79.05	$C_{24}H_{20}N_6O_2S_2$	16.6	12.64
				16.68	12.7
$CH_3C_6H_4$	220	74.07	$C_{26}H_{24}N_6O_2S_2$	15.44	11.76
				15.37	11.71
ClC_6H_4	160	78.76	$C_{24}H_{15}N_6O_2S_2Cl_2$	14.35	10.94
				14.38	10.89
BrC_6H_4	195	78.91	$C_{24}H_{15}N_6O_2S_2Br_2$	12.65	9.63
				12.66	9.68
$OCH_3C_6H_4$	240	68.44	$C_{26}H_{24}N_6O_4S_2$	14.58	11.11
				14.51	11.16

Table 4. Antifungal activity of bis-1,4-(5-amino-2-oxymethyl-1,3,4-thiadiazol-2-yl) benzene.

	Diameter of Zones of Inhibition in Mm for Pathogenic Fungi Ar Concentrations					
	(%W/V)					
	Aspergillus flavus		***Pennicilliun decombens***		***Helminthosporium tetramera***	
	2	0.2	2	0.2	2	0.2
	22	18	18	16	–	–
Dithane-78	23	20	25	21	25	22
Thiran 75-W	30	26	27	22	28	24

Elemental analysis, I.R spectra (KBr) were recorded on a Perkin–Elmer spectrometer, and H^1NMR spectra (DMSO-d_6) on an EM-360 spectrometer (60 MHz) using TMS as an internal standard, confirmed the structures of the newly synthesised compounds.

CONCLUSIONS

In summary, the present study highlights the successful synthesis of two novel bis-heterocyclic compounds: Bis-1,4-(3-mercapto-5-oxymethyl-1,2,4-triazole-5-yl) benzene and Bis-1,4-(5-amino-2-oxymethyl-1,3,4-thiadiazole-2-yl) benzene. These molecules, derived from triazole and thiadiazole scaffolds, were explored for their antifungal efficacy, leveraging the known biological versatility of these heterocycles.

The antifungal screening revealed that Bis-1,4-(3-mercapto-5-oxymethyl-1,2,4-triazole-5-yl) benzene exhibited significant activity against *Aspergillus flavus*, *Helminthosporium tetramera*, and *Penicillium decumbens*, suggesting its broad-spectrum potential. Meanwhile, both compounds demonstrate varying degrees of activity, with comparatively weaker effects against *Aspergillus flavus* and *Penicillium decumbens* in specific cases.

These findings support the potential of bis-heterocyclic compounds as promising antifungal agents and warrant further investigation, including structural optimization and in vivo evaluations, to fully realize their therapeutic utility in fungal disease management.

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