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FUSED TRIAZOLE DERIVATIVES AND TRIAZOLE: PREPARATION, CHARACTERIZATION, AND ANTIOXIDANT EVALUATION

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1.1 ABSTRACT

Fused heterocyclic triazole derivatives and triazoles such as thiadiazoles, Schiff bases, thiadiazine, thiadiazepine, and among others, were prepared and characterized using MS (mass), IR (infrared), and 1H NMR (proton NMR). Using DMSO as a solvent, the triazole derivatives were tested for antioxidant activity using DPPH scavenging activity.

1.2 INTRODUCTION

Heterocycles' wide range of applications has put them at the forefront of research1. Because of the triazole ring system's diverse biological activity and practical uses, it is particularly interesting in the field of medicinal chemistry.2, 3. Many triazole compounds have been linked to positive pharmacological and biological effects, including antitumor, anticancer, anti-inflammatory, antibacterial, antihypertensive, and antifungal properties. Moreover, fused heterocyclic triazoles have significant therapeutic uses10. Apart from their significant biological uses, 1,2,4-triazoles were very helpful in synthetic organic chemistry and have practical uses in the polymer12 and agriculture11 industries. Due to bacterial resistance to older medications and other side effects, the primary goal of pharmaceutical research is the creation of new, improved pharmaceuticals and their successful introduction into clinical practice. Because triazole compounds have these qualities, we can synthesize novel derivatives and assess their antioxidant capabilities.

Oxygen species that react known as ROS and additional different oxidizing agents were connected into numerous illnesses and conditions, as per an expanding collection of studies. The study has made scientists aware of the importance of antioxidants in the prevention of illness, treatment, and human health maintenance [13]. Numerous biological processes, including anti-aging, anti-carcinogenic and anti-mutagenic reactions, are derived out of the body's innate antioxidative mechanism [14, 15]. Free radicals are stabilized or neutralized by antioxidants, frequently prior to their assault on biological cell targets [16]. Due to the fact that naturally occurring antioxidants are complex within their multiplicity and quantity of action

and provide vast potential for rectifying imbalances, interest in their usage in food, cosmetic, and pharmaceutical products has surged recently [17, 18].

1.3 RESOURCES AND TECHNIQUES

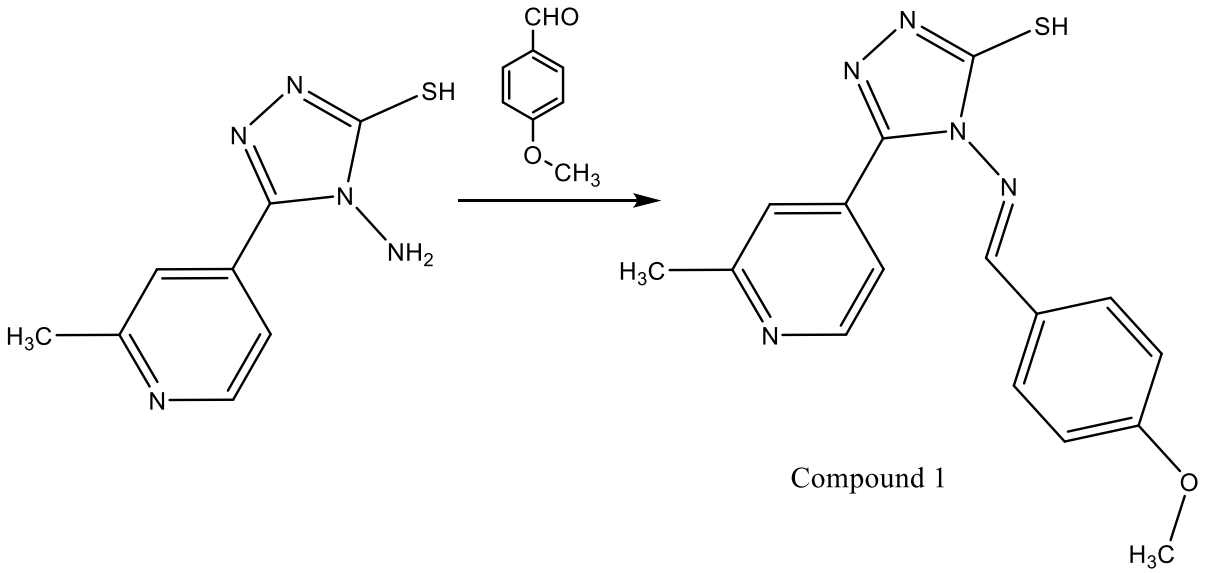
Each Melting point measurements were made using the Veergo melting point instrument and open capillaries. While recording 1H NMR, Tetramethylsilane (TMS) was used as an internal standard at 300 MHz on a Bruker 300 MHz spectrometer. A Perkin Elmer Spectrum 100 FTIR spectrometer was used to record the IR spectra, and a Waters Micromass Q-ft device was used to record the mass spectra. The chemicals utilized were purchased at the neighborhood store and are of LR grade.

1.4 Findings and Discussion

1.4.1 PREPARATION

The process for preparation of compound (1-7)

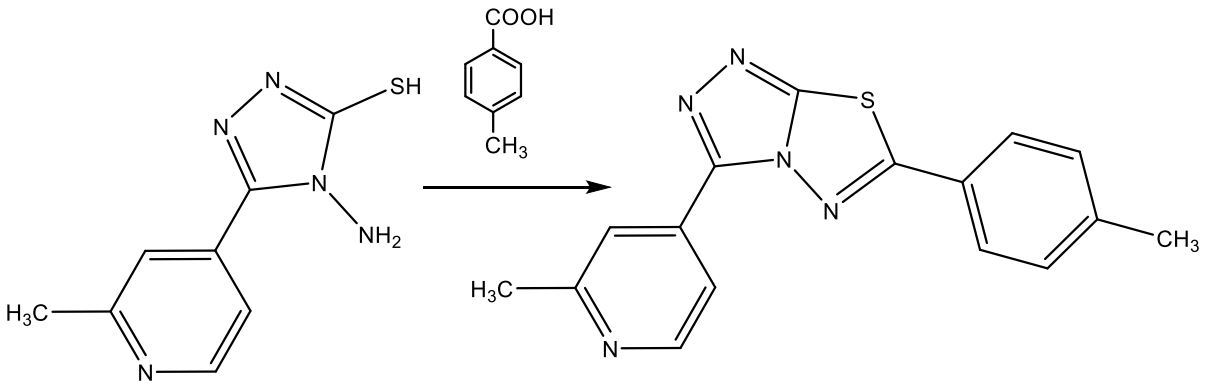
Compound 1: (E)-4-((4-methoxybenzylidene)amino)-5-(2-methylpyridin-4-yl)-4H-1,2,4-triazole-3-thiol: The Compound 1, 4-amino-5-(6-methylpyridin-3-yl) combination after adding two to three drops of acetic acid to a 25 ml solution containing p-methoxy benzaldehyde (0.01M) and 4H-1,2,4-triazole-3-thiol having a concentration of 0.01M, For about 10 hours, the reaction mixture was refluxed. Absolute alcohol have been used to separate and crystallize the product (1). The finished item was weighed and dried.



Compound 1

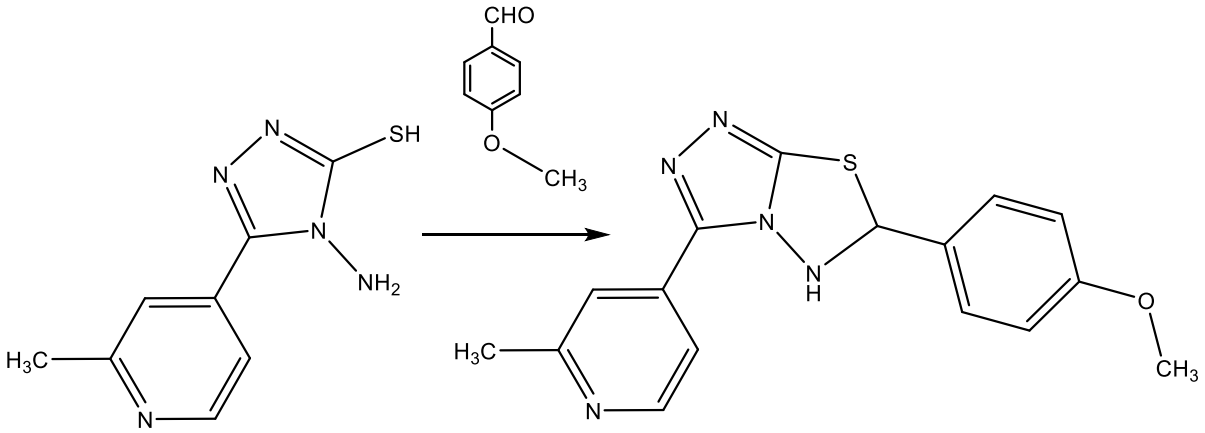
Compound 2: 3-(2-methylpyridin-4-yl)-6-(p-tolyl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole: 0.01M concentration of reactant and 0.01M of $CH_3C_6H_4CO_2H$ were combined together with 25 (ml) milliliters of POCl3. After 10 hours of reflux, After obtaining the reaction mixture, crushed ice was added. Water (H_2O) was used to filter as well as to clean the resulting solid. Following

its crystallization from ethanol, the end product (2) underwent drying and weighing.



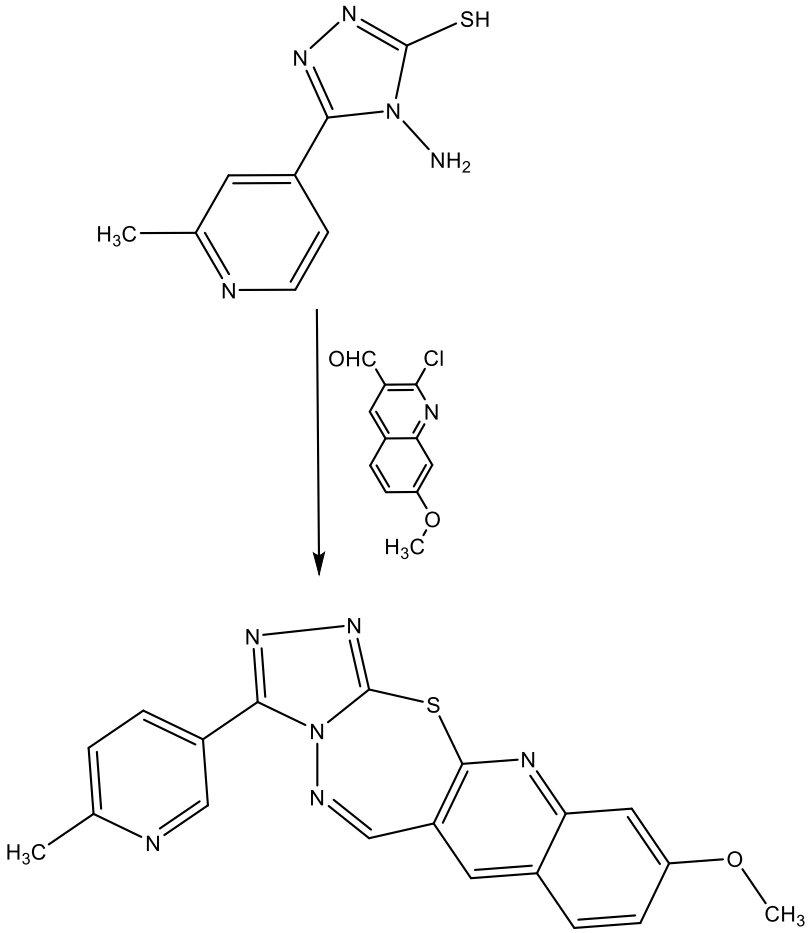
Compound 2

Compound 3: 10-methoxy-3-(6-methylpyridin-3-yl)-[1,2,4]triazolo[3',4':2,3][1,3,4]thiadiazepino[7,6-b]quinoline: A mixture of (0.01M) reactant and P-anisaldehyde (0.01M) was added to 50 milliliters of dimethylformamide. and was mixed with 50 mg of (p-TsOH) p-toluene sulphonic acid. Following the addition of the reaction mixture to crushed ice, refluxing it for ten hours, after then, the solid was filtered out. and further used water to wash. Following its crystallization using ethanol, the end compound(3) underwent drying and weighting.



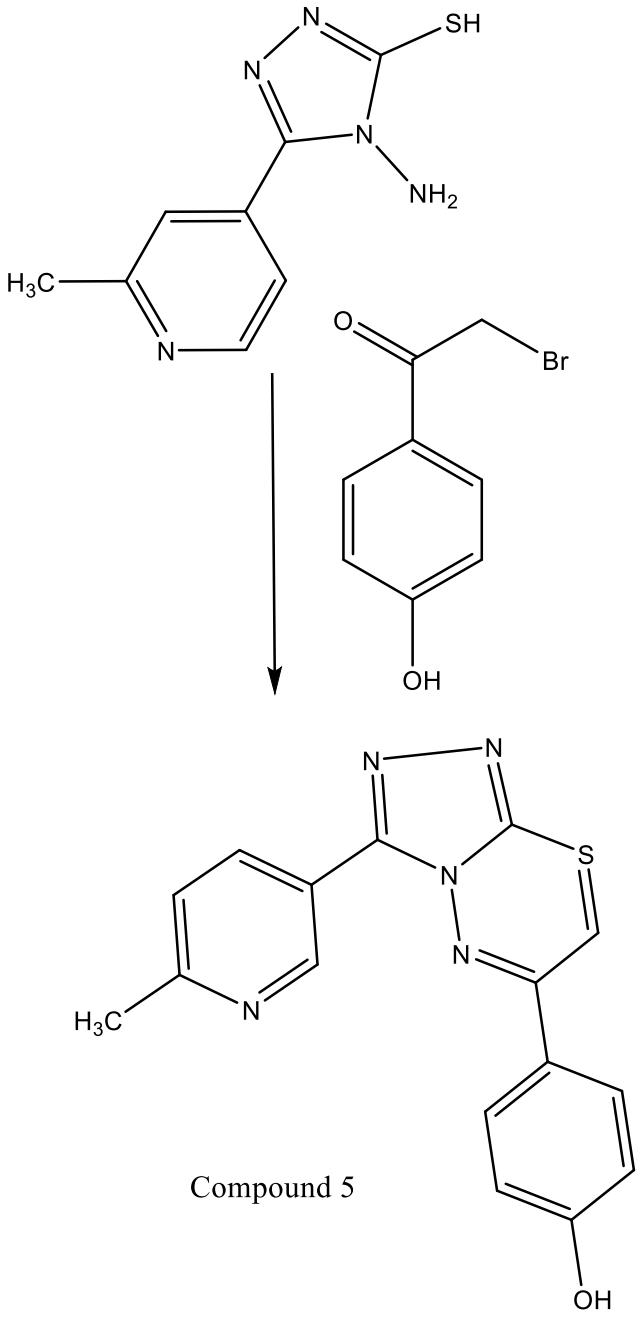
Compound 3

Compound 4: 4-(3-(6-methylpyridin-3-yl)-8l3-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-6-yl)phenol: The mixture of 0.01M of reactant, and 20ml of dry DMF containing 0.01M of 2-chloro-3-formyl-7-methoxy quinoline were refluxed at 80°C for four hours after the addition of 2.4% anhydrous K2CO3 (2.09 g). the sample was cool down and then pour over shattered ice. The obtained compound (4) from the ethanol was separated, allowed to crystallize, air-dried, and also weighed.



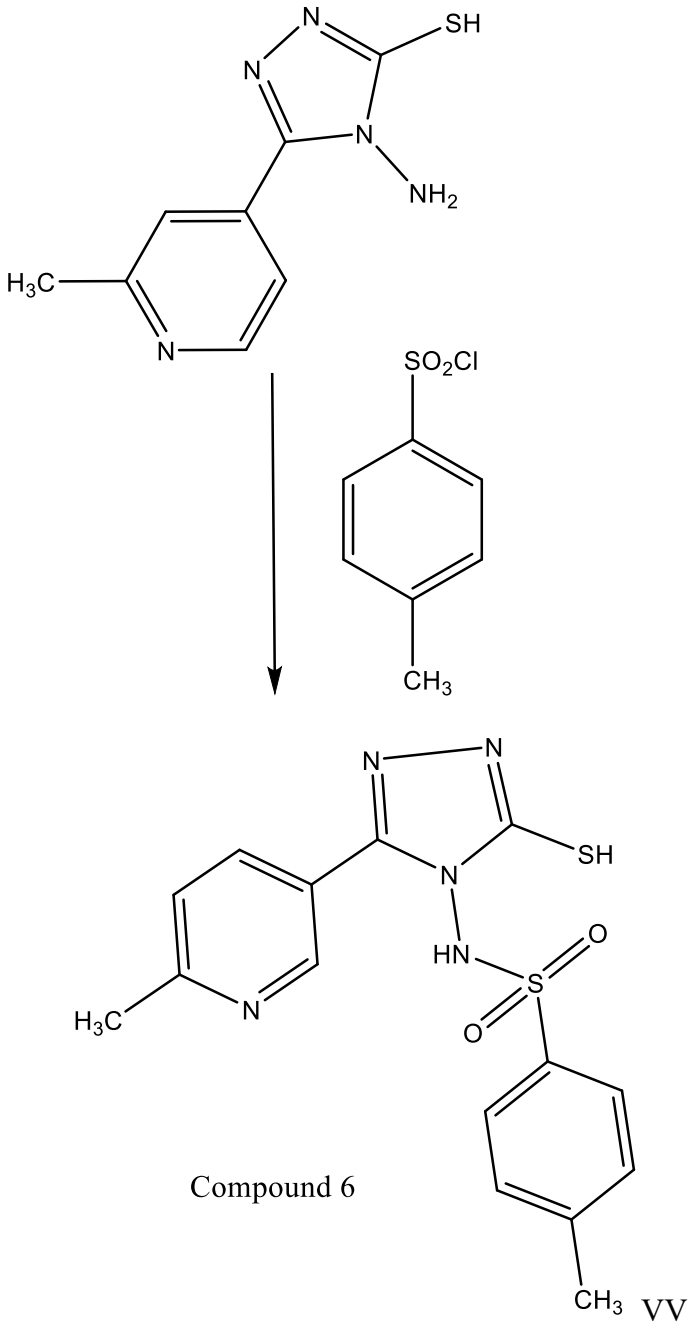
Compound 4

Compound 5: 4-(3-(6-methylpyridin-3-yl)-8l3-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-6-yl)phenol: A mixture of 0.01M of reactant and 0.01M of p-hydroxy-phenacyl bromide was taken 50ml dry methanol and was further heated under reflux conditions about five hours before being cool down and neutralized using a aqueous solution of potassium carbonate. The resultant (5), which had been extracted, and crystallized in ethanol, was then dried properly and further weighed.



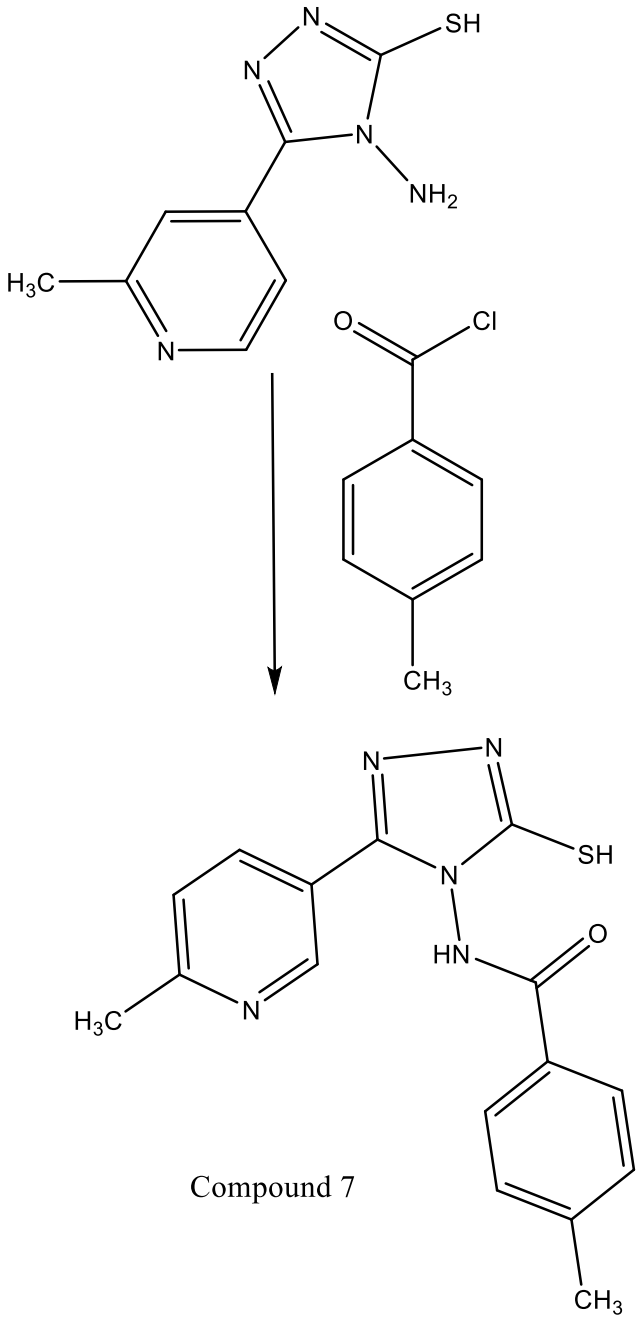
Compound 5

Compound 6: N-(3-mercapto-5-(6-methylpyridin-3-yl)-4H-1,2,4-triazol-4-yl)-4-methylbenzenesulfonamide. Two solutions were refluxed in dry pyridine for four to five hours: p-toluene sulfonyl chloride (0.01M) and 0.01M of reactant. Product (6) was removed from the ethanol and allowed to crystallize. It was then dried and weighed.



Compound 6 VV

Compound 7: N-(3-mercapto-5-(6-methylpyridin-3-yl)-4H-1,2,4-triazol-4-yl)-4-methylbenzamide: Dry pyridine was refluxed for eight hours with the combination of 0.01 molar reactant and 0.01 molar p-methylbenzoyl chloride. Product (7) was removed from the ethanol and allowed to crystallize. It was then dried and weighed.



Compound 7

1.4.2 ANTIOXIDANT ACTIVITY

I mg/ml concentration of the sample was dissolved using 95% methanol, each sample was diluted in order to form a series of concentrations for antioxidant testing. As a point of comparison, all experiments used reference compounds.

1.4.3 Assay for DPPH antioxidant activity (11, 12)

The DPPH activity was utilized to quantify the fractions capacity to scavenge free radicals in vitro using the previously discussed technique in working Chapter 1 [11, 12]. To make the stock

solution, 24 milligrams of DPPH were dissolved in 100 milliliters of methanol solution and it is preserved- at 20°C. The operating sample was prepared by the dilution of DPPH in CH3OH and further, at 517 nm, the absorbance was determined with a spectrophotometer. The different concentration of (10-500mg/ml) sample was mixed with 3 milliliter aliquot of compound. The reaction mixture was mixed, further, it was kept at room temperature for about 15 minutes under dark conditions. At 517 nm, the value of absorbance was then measured. The control was carried out without the use of a sample, just as previously mentioned. The following formula was used to determine the scavenging activity of the sample.

Scavenging Activity= [Absorbance of control - Absorbance of sample]/ Absorbance of control X 100

1.4.4 Characterization of prepared compounds

The molecular formula of the samples, the molecular weight of obtained compounds, its melting point, and the percentage yield of all produced substances. The mass spectrum, infrared, NMR, and elemental analytical data are shown below.

Compound I, the molecular formula for the prepared compound was found to be $C_{16}H_{15}N_5OS$ and its molecular weight of 325.38 melting point of was 215 percentage yield of 67.8%. 1H NMR (400 MHz, DMSO) SH-13.51, Aromatic Proton CH (8.88, 7.05, 8.24, 7.83, 7.83, 7.05, 7.83, 9.97), CH3-3.81, CH3-2.69, 13C NMR, 159.0, 151.1, 162.9, 158.5, 138.1, 145.1, 124.6, 114.4, 112.6, 109.5, 130.3, 114.4, 112.6, 109.5, 130.2, 114.4, 130.2, 55.8, 154.3, 24.2, m/z: 325.10, Elemental Analysis: C, 59.06; H, 4.65; N, 21.52; O, 4.92; S, 9.85

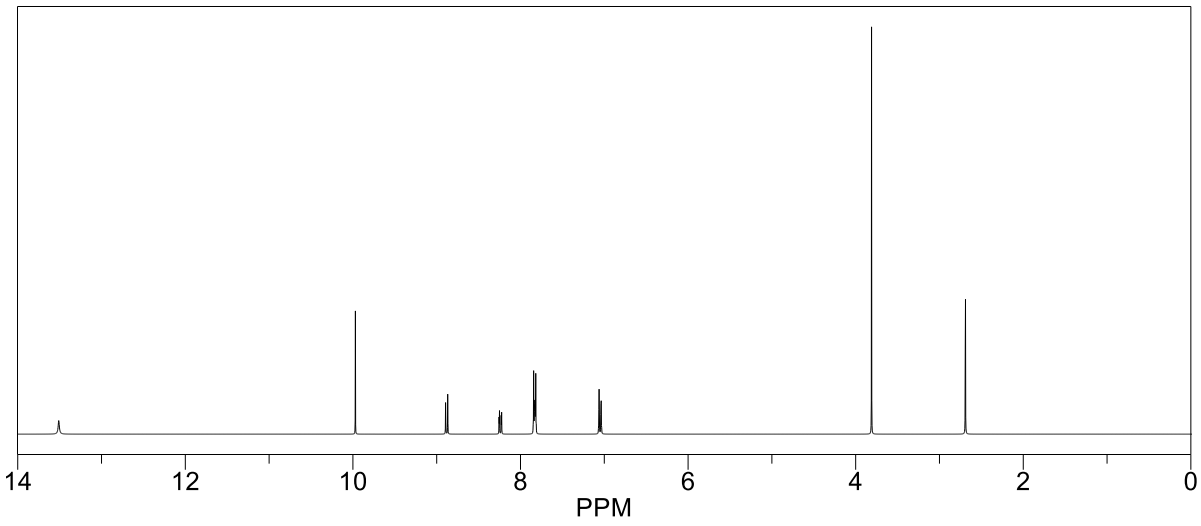


Figure 1: 1H NMR of Compound 1.

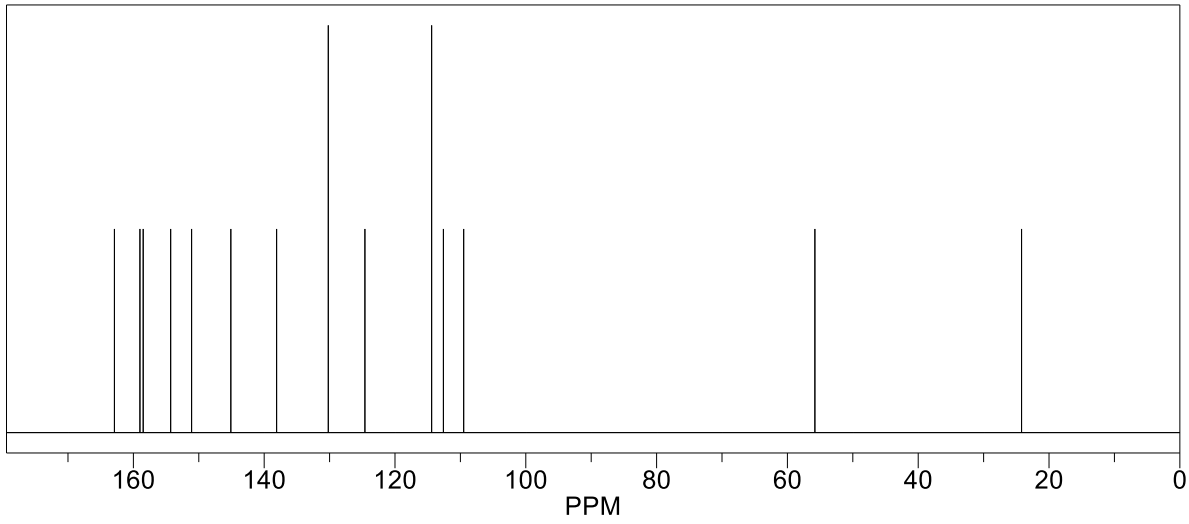


Figure 2: 13C NMR of Compound 1.

Compound II was discovered to have a molecular weight of 307.37 and a melting point of 214 percentage yield of 78%. Its chemical formula was determined to be C16H13N5S. 1H NMR (400 MHz, DMSO) Aromatic Proton CH (8.88, 8.24, 7.83, 7.72, 7.26), CH3-2.69, CH3-2.34, 13C NMR: 167.6, 43.3, 151.1, 158.5, 138.1, 130.5, 145.1,131.7, 112.6, 109.5, 127.4, 129.5, 127.4, 129.5, 24.2, 21.3, m/z: 307.09, Elemental Analysis: C, 62.52; H, 4.26; N, 22.78; S, 10.43

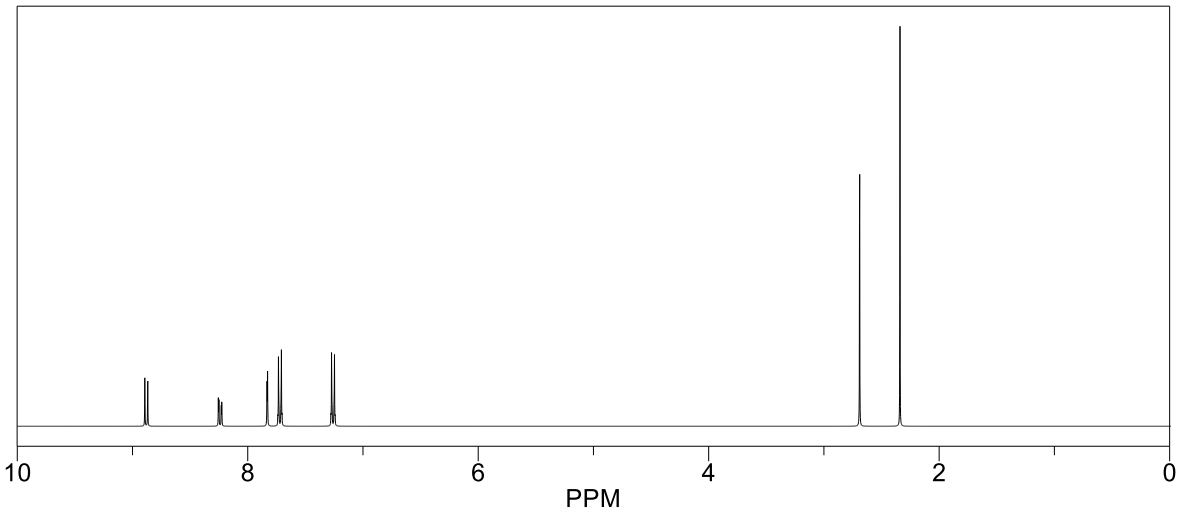


Figure 3: 1H NMR of Compound 2.

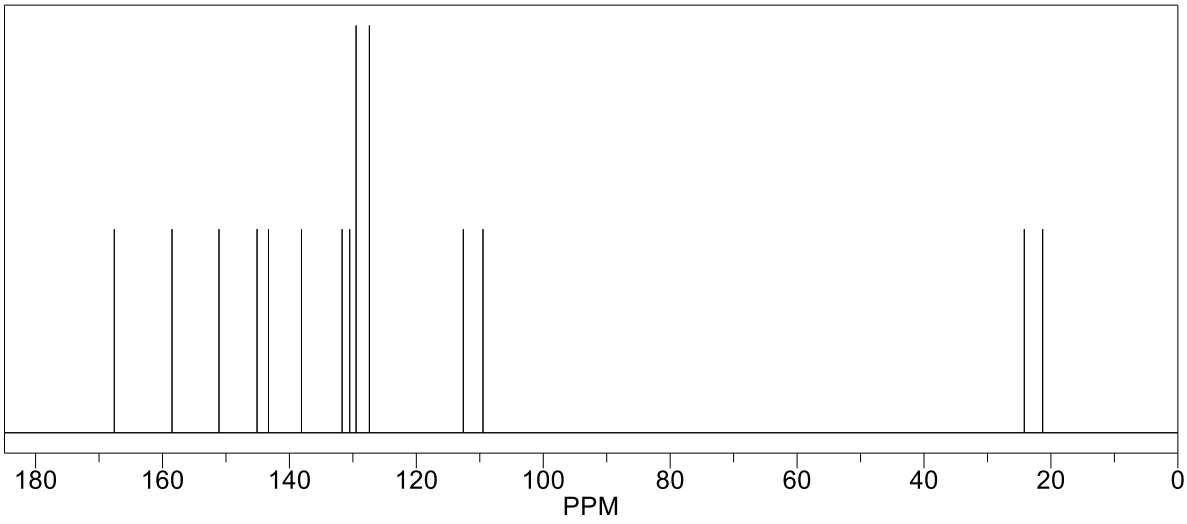


Figure 4: 13C NMR Compound 2.

Compound III's molecular formula, which was determined to be C16H15N5OS, had a melting point of 215 percent and a molecular weight of 325.38. Its yield was 66.8%. 1H NMR (400 MHz, DMSO) Aromatic Proton CH (9.01, 7.34, 7.34, 8.08, 8.70, 7.11, 7.64, 7.5), CH3-3.87, CH3-2.54, 13C NMR 159.0,151.1,181.0, 147.4, 150.0, 142.8, 156.3, 130.4, 122.4, 116.3, 107.2, 122.1, 132.7, 137.0, 117.6, 129.8, 55.8, 23.9, m/z: 374.09, Elemental Analysis: Carbon, 60.95; Hydrogen, 3.77; Nitrogen, 22.45; Oxygen, 4.27; Sulphur, 8.56

It was found that Compound IV had a melting point of 149 percent yielding a molecular weight of 374.41. It was found to have the chemical formula C19H14N6OS. 1H NMR (400 MHz, DMSO) OH-9.68, Aromatic Proton CH (9.01, 6.82, 7.34, 8.08, 7.64, 6.82, 7.64), CH3-2.54, 13C NMR: 148, 151.1, 232, 160.8, 155.4, 142.8, 156.3, 130.4, 125.7, 116.0, 122.1, 132.7, 130.6, 116.0, 130.6, 23.9 m/z: 322.08, Elemental Analysis: C, 59.61; H, 3.75; N, 21.73; O, 4.96; S, 9.95

It was found that Compound V had a melting point of 276 percent yield and a molecular weight of 323.37. It was found to have the chemical formula C16H13N5OS. 1H NMR (400 MHz, DMSO) OH-9.68, Aromatic Proton CH (9.01, 6.82, 7.34, 8.08, 7.64, 6.82, 7.64), CH3-2.54, 13C NMR: 148, 151.1, 232, 160.8, 155.4, 142.8, 156.3, 130.4, 125.7, 116.0, 122.1, 132.7, 130.6, 116.0,130.6, 23.9, m/z: 322.08, Elemental Analysis: C, 59.61; H, 3.75; N, 21.73; O, 4.96; S, 9.95

It was found that Compound VI had a melting point of 182 percent yield and a molecular weight of 361.44. The formula for it was found to be C15H15N5O2S2. 1H NMR (400 MHz, DMSO) SH 13.79, NH 7.2, Aromatic Proton CH (9.01, 7.68, 7.34, 8.08, 7.38, 7.68, 7.38), CH3 2.54, CH3 2.43, 13C NMR: 167.1, 151.1, 136.7, 142.8, 156.3, 130.4, 137.6, 128.3, 122.1, 132.7, 129.3, 128.3, 129.3, 23.9, 21.3, m/z: 361.07, Elemental Analysis: Carbon, 49.85; Hydrogen, 4.18; Nitrogen, 19.38; O, 8.85; S, 17.74.

It was found that Compound VII had a melting point of 189 percent yield and a molecular weight of 325.38. It was found that its chemical formula was C16H15N5OS. 1H NMR (400 MHz, DMSO), 13C NMR: SH1-3.79, NH-7.7, Aromatic Proton CH (9.01, 7.34, 8.08, 7.84, 7.32, 7.84, 7.32), CH3-2.54, CH3-2.41m/z: 325.10, Elemental Analysis: C, 59.06; H, 4.65; N, 21.52; O, 4.92; S, 9.85

1.4.5 Assessment of antioxidant activity *in-vivo*

After 30 minutes of spinning at 12,000 g and 4°C, 10% homogenate liver tissue was produced in a pH 7.4 (100 mM KH2PO4 buffer solution) carrying 1 milimolar EDTA (Ethylenediaminetetraacetic acid). Supernatant was gathered and used in the studies that followed, as indicated below.

Compound	**A_s , Absorbance of sample**	% **Inhibition**
Control	0.857±0.025	–
1	0.659±0.025	23.1
2	0.746±0.020	12.95
3	0.809±0.020	5.60
4	0.748±0.020	12.71
5	0.832±0.025	2.91
6	0.754±0.025	12.02
7	0.659±0.025	23.1
Ascorbic acid	0.642±0.015	25.09

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