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Synthesis of Symmetrical and Unsymmetrical Thiourea Derivatives and their Biological Activities

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ABSTRACT

In this study different derivatives of thiourea have been prepared; both symmetrical and unsymmetrical. For the synthesis of symmetrical thiourea derivatives, substituted anilines were combined with carbon disulphide (CS2) in water, whereas for the synthesis of unsymmetrical thiourea derivatives, potassium thiocyanate (KSCN) was first combined with acid chlorides derivatives in dry acetone before primary amines were gradually added to this solution. Thin layer chromatography (TLC) was used to check each response. The reaction mixtures were filtered and rinsed with ethanol after the completion of the reaction.

The synthesized products were characterized by different spectroscopic techniques. For their ability to fight germs and leishmania, all of these substances were examined. These substances demonstrated excellent activity while some of them showed only moderate activity.

Keywords : Synthesis, Thiourea Ligands, Complexes, Antibacterial And Antileishmanial Activity

I. INTRODUCTION

Thiourea is an organic compound having (>N-C(S)-N<) functional group while their derivatives can be obtained by replacing hydrogen by other elements. These compounds have S and N atoms and therefore are biologically important [1]. Thiourea and their derivatives have N, O and S atoms which donates electron when react with various d-block metals and form biologically important complexes [2].

Cyclohexyl thiourea and phenyl thiourea are important thiourea derivatives that are used in pharmaceuticals as effective treatment agents against HCV and HIV [3].

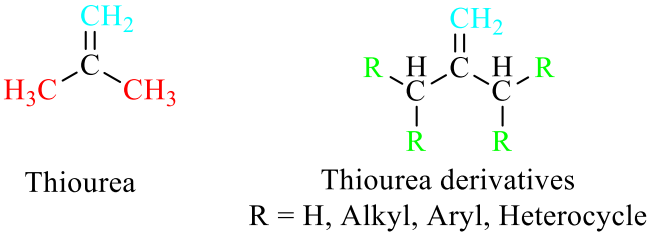


Figure 1: Thiourea and derivatives

Neuki originally produced thiourea in 1873 [4]. When compared to those made from sources like urea and poisonous dicyanamide, the polymeric g-C3N4 made from readily accessible and affordable thiourea has a higher level of photoactivity. Ag, Cu, and Au(I) complexes have effective anticancer properties [5, 6].

By reacting CS_2 with amine or aniline in an ethanol solvent in the presence of sunshine, symmetrical

thiourea can be prepared however, when phenyl isothiocyanate and N, N-dimethylaniline react under the influence of visible light, asymmetrical thiourea is produced [7]. Due to the presence of S, O, and N, thiourea acts as monoanions, dianions, and neutral ligands and has the capacity to coordinate in a variety of ways that have drawn significant interest in different fields [8]. Heck cross coupling process has employed picoline thiourea ligands as a homogeneous catalyst. By reacting with Pd (II), pyridine containing thiourea forms square planar complexes [9]. Pt-acylthiourea has antiviral and antifungal inhibitory effects on viruses. The aroyl/acyl derivatives of thiourea react with platinum (II), ruthenium (II), palladium (II), copper (I), gold (III), and silver (I) as neutral monodentate ligands. Numerous complexes of copper with thiourea derivatives are often found in the I, II, and III oxidation states [10]. Because thiourea complexes with Ag(I) are more volatile than ionic compounds, they are utilized to create silver nanofilms, nanoparticles, and their chalcogenides [11]. Complexes of chiral thiourea derivatives have been employed as metal corrosion inhibitors and as organo-catalysts. Phenylthiocyanate and Amines together produce Thiourea used as a catalyst for pharmaceutical drugs [12]. The interaction between centrosymmetric thiourea and transition metal salts has produced non-centrosymmetric compounds, which are very significant in the nonlinear optical area [13, 14]. Due to their capacity for forming both even and odd configurations and their sensitivity to molecular environments, Schiff base ligands, in particular those with O and N donor elements, and their complexes, are very important [15]. The biological activity of thiourea derivatives is enhanced by the chelation with transition metals. The N-benzoyl-N-substituted thiourea's ability to coordinate the S atom is enhanced by the intermolecular and intramolecular H-bonding [16]. Nickle (II) and cobalt (III) complexed acylthiourea derivatives exhibit in vitro biological characteristics. Metals are advantageous semiconductors, and thiourea derivatives can be used to produce bismuth sulphide. Al-Obeidi has created complexes made from mixed ligands and the metals Cu (II) and Zn (II) that are utilised as corrosion inhibitors [17]. Because they are utilised in medications, mixed metal complexes are pharmacologically active compound [18]. N, N' Diphenyl is employed in the treatment of leprosy to distinguish ferric sulphides from other metal sulphides and to create metal complexes with the metals Os, Ru, and Ir [19]. Comparing the Pd(II) complex to the non-electrolytic platinum(II) complex, the Pd(II) complex demonstrated better breast cancer suppression characteristics with lower IC_{50} values [20]. Iron, nickel, and cobalt complexes exhibit high axial zero-field splitting (ZFS) and low coordination numbers [21]. Thiourea and its derivatives are utilised as nonionic surfactants, anions acceptors, intermediates in heterocyclic synthesis, and coordination agents for metals, among other things [22]. The thiourea-containing chemicals and their derivatives have potent antimicrobial properties, anticancer and antiangiogenic, anti-urease, antioxidant activities anti-tobacco mosaic viral inhibitors, antibacterial, anti-tuberculosis, anti-viral properties, anti-diabetic activity, anti-leishmanial properties, anti-convulsant activity, anti-inflammatory properties, corrosion inhibitors, as sensor agent to fluoride ion [16, 23-32].

II. METHODS AND MATERIAL

1 Chemicals used

Different reagents were used such as,

a. For symmetrical thiourea

Amines, Anilines **and** CS_2

b. For unsymmetrical thiourea

Phenylacetyl chloride, KSCN and amines

c. For cyclization

Oxalic acid, Tartaric acid, Acetyl chloride, Acetic acid and Thiourea

d. For complex

$Ni(II)Cl_2$, Cu(II)Cl, Cu(I)Cl, $Hg(II)I_2$ and Thiourea ligands

e. Solvents

Water, Ethanol, Methanol, Acetone, n-hexane, ethyl acetate

2 Instruments and glassware used

During experiments various instruments and glassware were used,

- **RB:** For holding the reaction mixture RB were used with condenser for preparation of thiourea derivatives.
- **TLC:** was used for monitoring of the reactions.
- **Hot plate:** were used for heating and stirring.
- **Stands:** different stands were used for holding all the reactions system.
- **Condensers:** were used in reflux condition.
- **Solid filter paper and funnel:** were used for separation of precipitate.
- **Electro thermal apparatus:** was used for melting point determination
- **Beakers:** for holding, mixing, heating and stirring liquid or solid samples
- **Magnetic stirrer:** for stirring the reaction mixture
- **Petri dishes:** used to culture cells /to culture microorganism

3 Synthesis of symmetrical thiourea derivatives

The interaction of carbon disulfide with various amines in water led to the synthesis of symmetrical thioureas; it is a green technique for the synthesis of thioureas, requiring no catalyst and producing high yields. Each of the reactions were monitored using TLC, took between 4 and 12 hours to complete, and the solid precipitate was separated using filter paper before being purified by washing with hot water and recrystallizing from ethanol. The melting point was determined in the end. The preparation of chemicals Aa, Ab, Ac, and Ad followed the same process.

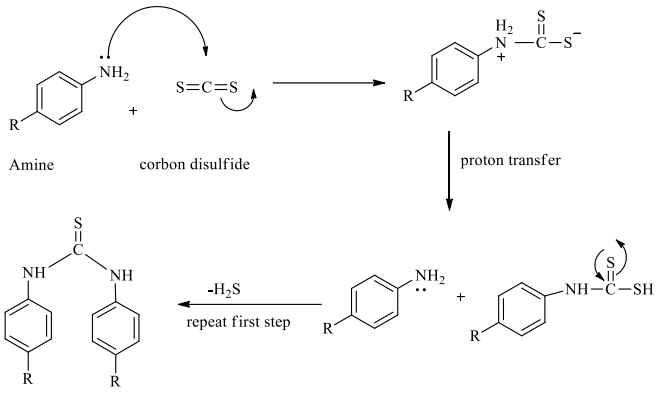
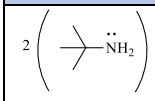
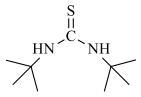
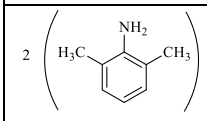
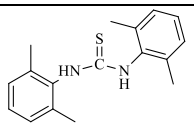
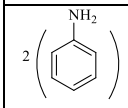
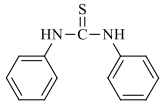
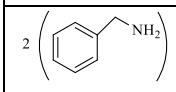
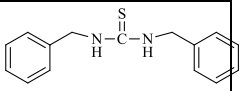


Figure-2: Symmetrical thiourea Synthesis

Table-1 : Symmetrical Thioureas synthesized

Symmetrical thiourea	
Starting Material	**Products**
	**Aa** 
	**Ab** 
	**Ac** 
	**Ad** 

4 Synthesis of Unsymmetrical thiourea derivatives

We obtained acid isothiocyanate derivative and KCL by adding a solution of acid chloride derivative in acetone (25 ml) to a solution of potassium thiocyanate in acetone (25), in accordance with published procedure. Following the addition of primary amine in drops, the mixture was stirred for an hour, precipitate of asymmetric thioureas developed. The mixture was then filtered, and ethanol and dichloromethane solution were employed in a 1:2 ratio for recrystallization. The preparation of chemicals Ba, Bb, Bc and Bd followed the same process.

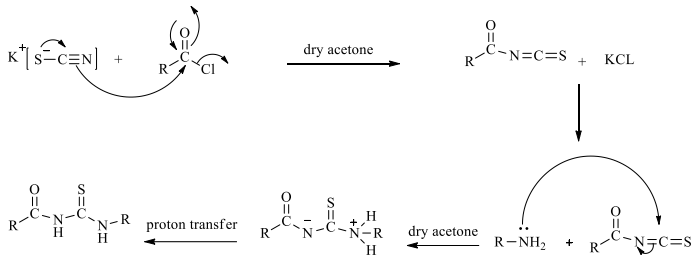
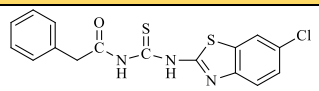
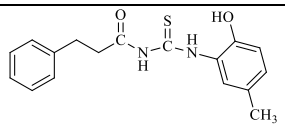
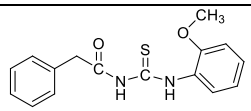
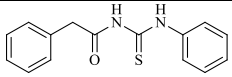


Figure-3: Unsymmetrical thiourea synthesis

Table-2 : Unsymmetrical Thioureas synthesized

Unsymmetrical thiourea obtained	
Ba	
Bb	
Bc	
Bd	

III.RESULTS AND DISCUSSION

Biological activity

antileishmanial assays

Activities that target axenic amastigotes and promastigotes

On promastigote and amastigote (axenic) cultures of Leishmania tropica (L. tropica), test compounds' antileishmanial activity was assessed. Using the 2-(4, 5-dimethyl-2-thiazolyl)-3, 5-diphenyl-bromide (MTT; Sigma, St. Louis, MO, US) viability colorimetric test, the experiment was carried out in vitro in line with an advanced technique with minor modifications. In the beginning the medium RPMI-1640 was created by mixing it with 10% FBS, 100 U/ml of penicillin, and 100 mg/ml of streptomycin in Pen/strep mixture. The medium was incubated for 24 hours at 37 °C to check for bacterial contamination. Then a culture of L. tropica was introduced into this medium to confirm the decision of infertility. The temperature and PH of the medium were adjusted for axenic amastigote and promastigote in accordance with the culture environment.

The experiment used Leishmania culture at a cell density of 1106 cells/ml. Compound dilutions were carried out in accordance with different concentrations (1-200 g/ml).

1% DMSO and amphotericin B (Fungizone) were employed as positive and negative controls, respectively. In a 96-well microtiter plate, different concentrations of formulations containing the target compounds and controls were added in separate wells. In every well of the 96-well microtiter plate, there were drooping parasites (1106/ml). Sample dilutions. The parasites were cultured for 72 hours at 24°C/33°C. After that, all of the assay's wells were filled with incubation stock MTT solution (20 l), and microtiter plates were once more incubated at 24/33°C for 4 hours. Separated supernatant was used to create formazan crystals. Crystals were afterwards dissolved using 100 l of DMSO. Preparations were absorbed at 540 nm with the aid of a microplate reader (Biotech/USA, microplate reader Elx/800).

Statistical investigation

Experiments were run in triplicate. The data analysis was carried out with SPSS 22 and verified with GraphPad Prism version 5. The mean and standard deviation of the data were displayed.

Table-3 : IC50 Values of in g/ml against two distinct morphological types of Tropical leishmaniasis

Compound	Values of the IC50 for a number of substances (g/ml) against two distinct morphological types Tropical leishmaniasis	
	Promastigotes	**Amastigotes**
Aa	0	0
Ab	0	0
Ac	0	0
Ad	0	0
Ba	200 µg/ml	210 µg/ml

Bb	325 µg/ml	330 µg/ml
Bc	150 µg/ml	µg/ml
Bd	220µg/ml	235µg/ml

Bioassay for anti-bacteria

The antibacterial activity of the tested thiourea compounds was evaluated using the agar wall diffusion assay. Escherichia coli and staphylococcus aureus, two types of bacteria (one gramme positive and two gramme negative) were utilised in the experiment. First, 50 mL of distilled water was used to prepare the nutritional broth solution. At 7.0 pH, 0.4 g of nutritional broth was dissolved, then autoclaved. Then, to prepare the nutrient agar medium, 2.3 g of nutritional agar medium was dissolved in 100 mL of distilled water, autoclaved at 121 °C and 7.0 pH. This medium was then drained into petri-dishes. A 0.5 McFarland standard was created by mixing 0.05 mL of 1.175 % barium chloride dihydrate ($BaCl_2.2H_2O$) with 9.95 mL of 1% sulfuric acid (H_2SO_4). 1.5 × 108 cells per mL are equivalent to a 0.5 McFarland standard. The bacteria were grown in nutrient broth medium suspension a day before to the experiment. In order to meet the 0.5 McFarland criterion, the bacterial inoculum was modified and placed in nutrients agar plates. After that, 4 mm-deep wells were constructed in perti-plates. Thiourea compounds were applied to the wells of the petri plates at three different doses (dissolved in DMSO) and then incubated for 24 hours at 37 °C. After 24 hours, the test drugs' inhibition zone was estimated. Results were documented and presented appropriately.

Table-4 : Anti-bacterial activities at 3 different doses against 2 different strains of bacteria (Inhibition zone is shown in mm)

	Escherichia coli			*Staphylococcus aureus*		
	µg / ml					
	2000	1000	500	2000	1000	500
Aa	0	0	0	11	0	0
Ab	0	0	0	11	0	0
Ac	0	0	0	10	0	0
Ad	0	0	0	10	0	0
Ba	0	0	0	0	0	0
Bb	0	0	0	0	0	0
Bc	0	0	0	16	14	12
Bd	0	0	0	0	0	0

Zone of inhibition length in millimetres.

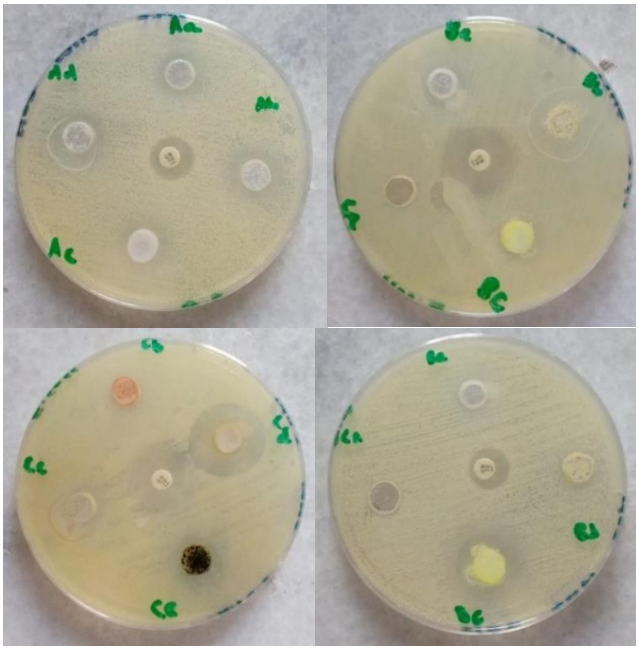


Figure-4.2.1: Antibacterial activity shown by thiourea compounds.

IV.CONCLUSION

Different thiourea derivatives were produced as part of this study. For the preparation of thiourea derivatives, both aliphatic and aromatic amines were used. Best yields were achieved for all thiourea derivatives. Compounds were characterized using different spectroscopic techniques. Further, antibacterial properties were assessed; some showed

poor activities, while others shown the excellent activities.

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