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Drug Design and Medicinal Chemistry of Thiourea Derivatives : A Review

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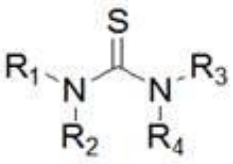
ABSTRACT

The literature concerning thiourea and its derivatives is voluminous. These compounds have found their way into almost every branch of chemistry. In the academic field thioureas are of great value in the characterization of organic compounds and great medicinal applications as well as non-medicinal activities in industry, analytical chemistry and metallurgy. This review is a sight of methods of synthesis and applications of thioureas in the field of medicine and agriculture. thioureas have a number of medicinal applications and a number of thioureas are in clinical use. Medicinal applications of thioureas are increasing with the passage of time. In the field of agriculture, Thiourea has been investigated for its multiple desirable properties as a fertilizer especially under the condition of environmental stress and are used as insect growth regulator, anti-fungal agents and herbicides.

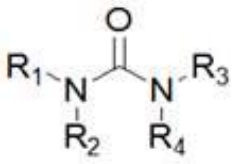
I. INTRODUCTION

Thiourea, also called thiocarbamide, an organic compound that resembles urea (*q.v.*) but contains sulfur instead of oxygen; *i.e.,* the molecular formula is CS(NH2)2, while that of urea is CO(NH2)2. It plays an important role in the construction of heterocycles.These have structural resemblance to ureas, except that the oxygen atom of ureas is replaced by a sulfur atom; the chemical properties of urea and thiourea are quite different from each other.



Thioureas

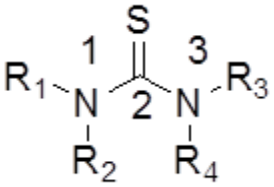
1



Ureas

2

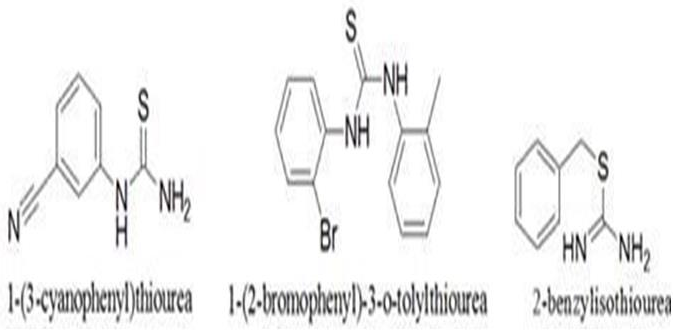
The Thiourea system is numbered as shown below:



Compounds produced from urea, isourea, or their derivatives by substituting sulfur by oxygen are named by adding a prefix thio before urea. S-Substituted thioureas are referred to as pseudothioureas rather than isothioureas.

Thiourea subsidiaries have different natural properties, for example, antibacterial, anticancer, antimicrobial, antifungal, antimalarial and antituberculosis that make them broadly utilized in many field particularly pharmaceutical enterprises. This is on the grounds that oxygen, nitrogen and sulfur contributor iotas in thiourea subordinates give

different restricting conceivable outcomes. Other than that, the protonation of sulfur particle that can happen in acidic arrangement causes thiourea subsidiaries to be known as fascinating natural inhibitors with regards to consumption action. Some of the thioures are,

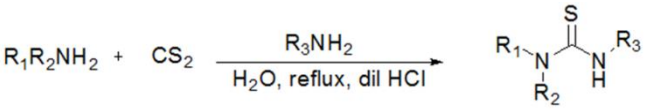


3 4 5

II. GENERAL METHODS OF SYNTHESIS

There are several common synthesis for derivatives of thiourea. Many variations have been applied to each of these when circumstances demanded it. As might be expected, certain advantages and disadvantages arise from the use of any one of these methods of Synthesis.

a) Thioureas from Carbon disulphide



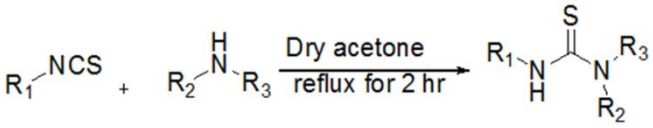
6 **7** **8**

Where R1=R2= H, alkyl or aryl.

The reaction shown in the above equation is the common way of describing the overall reaction of primary amines **6** ($R_1 = R_2 = H$) with carbon disulfide **7** to give 1,3-disubstituted thioureas **8**. It does not, however, tell the whole story. Many theories concerning the mechanism of this reaction have been published and the conclusions are somewhat conflicting. Reaction intermediate in this case is amino dithiol derivative instead of isothiocyanate.

b) Thioureas from Isothiocynates

Alkyl Isothiocynates**9** on reaction with primary and secondary amines**10** yield thiourea derivatives**11**.



9 **10** **11**

Where R1 = alkyl, aryl or benzoyl. R2 = alkyl or phenyl and R3 = alkyl, phenyl or H.

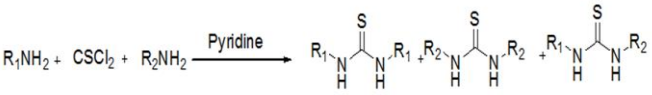
This is the most common method of preparing unsymmetrical thioureas. The addition of the amine to the isothiocyanate is usually carried out in the presence of a solvent such as alcohol. Frequently the reaction is exothermic, and cooling may be necessary to keep it from getting out of hand. In some cases it is necessary to heat, the mixture, and then a higher alcoholor preferably an inert solvent such as benzene or toluene may be used. Since similarly substituted thioureas melt at nearly the same temperature and isomorphism may make mixed melting points unreliable, elemental analysis or an infrared spectrum is often essential in the identification of the reaction product.

c) Thioureas from Thiophosgene

Primary amines react with thiophosgene to give either an isothiocyanate **12** or a 1,3-disubstituted thiourea depending upon the ratio of the reactants. Secondary amines give only symmetrical thioureas

$CSCl_2 + RNH_2 \longrightarrow RNCS + 2HCl$

12

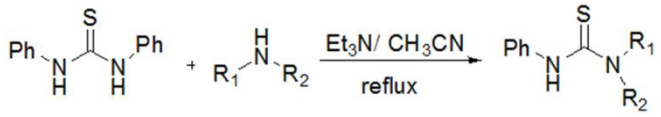


Preparation of thioureas by this method is best carried out by refluxing one mole of thiophosgene with two moles of the amine in an aqueous, chloroform-aqueous or acetone-aqueous medium. When thiophosgene no longer appears in the reflux condenser, a mole of potassium carbonate is added and the heating continued for several hours. The product

is then isolated and purified in a manner appropriate to the particular compound.

d) From Thioureas

Symmetrical thioureas are precursor of unsymmetrical thioureas. This method is used to prepare disubstituted and trisubstituted thiourea derivatives. **13** (Symmetrical thioureas) on reaction with **14**(amine) yield **15**(Thiourea derivative).



13 **14** **15**

Where R1=R2 = alkyl, aryl or R2 = H

III. APPLICATION OF THIOUREA DERIVATIVES

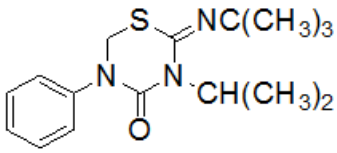
Thioureas have a variety of applications in different fields of life. Some of these are discussed below.

3.1 Application in Agriculture

Thioureas have versatile application in field of agriculture. These are used as to control the growth of insects, effect plant growth and seed germination, as fungicide and herbicide.

a) Insect Growth Regulator

IGRs are chemicals that are used to control the population of insects by inhibiting their life cycle. Hormonal IGRs and chitin synthesis inhibitors are types of IGRs. The brown planthooper Nilaparvata lugens stal is an insect of rice crop. This insect destroys the crop by sucking cell sap and transmitting viral diseases.



16

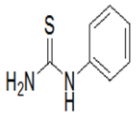
16 (thiourera derivative) control the growth of insects by destroying nymph at a conc. less than 1 ppm. This is environment friendly because don't destroy beneficial insects.

Thiocarbamido- DDT is more effective than DDT against bed bugs, although its action is of shorter duration

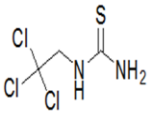
Simple compounds such as phenyl-, allyl-, and tolyl-thiourea are useful in destroying larvae and adults of various strains of Drosophila melanogaster. 1-Allyl-3-(4-chloro-2-methylphenyl) thiourea has been claimed to be effective in controlling the Japanese beetle or the mexican jumping bean beetle.

b) Antifungal Activity

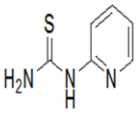
The chemicals or biological organisms that are used to kill fungus and fungal spores are called fungicide. Fungicides are very important in agriculture because fungus cause serious damage to crop. Thiourea derivatives **17, 18** and **19** are active fungicides. **17** and its p-chloro and p- nitro derivatives are most active ones.



phenyl thiourea



trichloroethyl thiourea

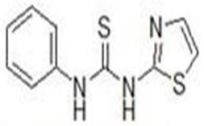


pyridyl thiourea

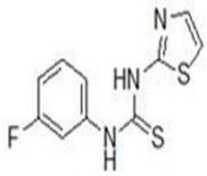
17 **18** **19**

c) Herbicidal Activity

20 and **21** show herbicidal activity against cucumber seedlings and former also showed activity against wheat seedlings. **22** is effective against root and stalk of Amaranthus retroflexus L.

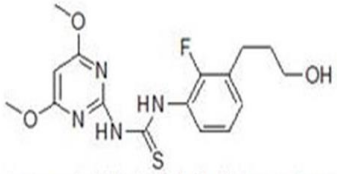


1-phenyl-3-(2-thiazolyl)thiourea



1-(3-fluorophenyl)-3-(2-thiazolyl)thiourea

20 **21**



1-(4, 6-dimethoxypyrimidin-2-yl)-3-(3-(2-flourophenyl)propanol) thiourea

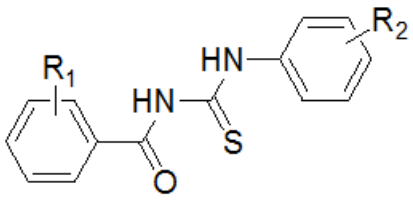
22

3.2 Medicinal Applications of Thiourea Derivatives

Applications of thiourea derivatives in field of medicine can't be neglected. These are being used in all aspects of medicine.

a) Antibacterial activity of thiourea derivatives

Various types of thioureas have been reported to have antibacterial activity. An aromatic or heterocyclic amine with an alkyl side chain when incorporated into a thiourea shows specific action for the bacteria which cause abortion in cattle. Some 1-aroyl-3-aryl thioureas **23** have activity against Staphylococcus aureus, Bacillus subtilis and E-Coli.



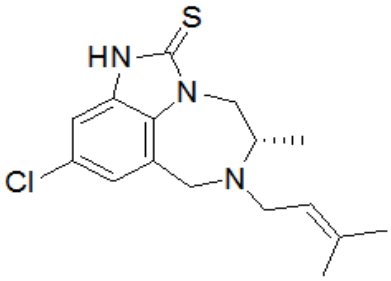
23

Thiocarbamido derivatives of diary1 sulfones and sulfides, both mono and bis, have shown marked antibacterial properties.

b) For treatment of co-infections

Patients that are carrier of H. I. V have greater risk of T. B and other infections. So there was a need to develop a single class of drug that can be used for the treatment of both diseases simultaneously. In this regard thiourea derivatives act as a promising class. Due this development patient avoid from

pill burden as well overlapping toxicity developed by treatment of H. I. V and T. B.



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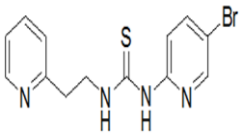

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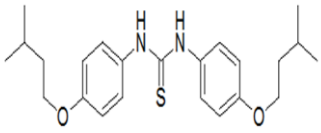
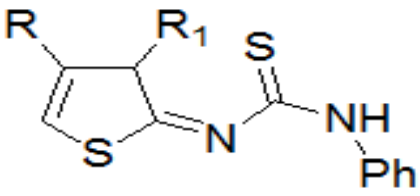


26

Tetrahydroimidazobenzodiazepinthiones (TIBO) derivative **24** (9-chloro TIBO), **25** (Trovirdine) and are used for H. I. V treatment. **26** (ISOXYL) is used for treatment of T. B.

c) Thiourea derivatives as anti-inflammatory

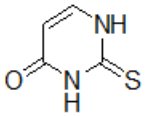
Iminothiazolines on reaction with phenyl isothiocyanate yield thioureas 73 having anti-inflammatory activity.



27

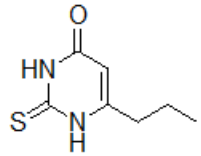
d) Thiourea derivatives as anti-thyroid drugs

Goiter is caused by Hyperthyroidism is cured by anti-thyroid drugs. Following thiourea derivatives are used for treatment of hyperthyroidism. Thiourea has approximately one-tenth the activity of thiouracil. Replacement of one, two, or three of its hydrogen atoms by methyl groups has no appreciable effect on the activity.**28**,**29** and **30** are shows anti-thyroid activity.



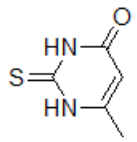
2-thiouracil

28



6-n-propylthiouracil

29



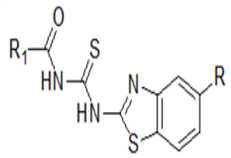
6-methylthiouracil

30

e) Thiourea derivatives as anti-cancer drug

Cancer is an alarming ailment; different types of cancers can be treated effectively, if diagnosed at start. The following are the methods applied for the treatment of cancer; organ transplantation, surgery, palliative care, biotherapy, chemotherapy and

radiation therapy. But commonly used are chemotherapy and radiation therapy. Mostly these are used in combination. Nature of disease decides the type of treatment. Every treatment has its own risks and benefits. Generally, chemotherapy is the most common method. Many thioureas are being used as anti-cancer therapeutics and a lot of are in clinical trial. Because of genotoxicity and cytotoxicity to normal cells caused by anti-cancer drugs medical science is in search of novel and safer anti- cancer agents. These side effects limit both their use and efficiency. Thioureas, ureas and benzothiazoles are the most active anti-cancer drugs. Ureas and thioureas in combination with benzothiazoles produce DNA topoisomerase or HIV reverse transcriptase inhibitors.



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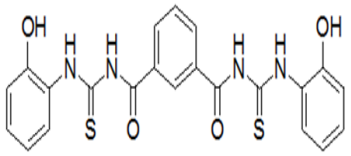

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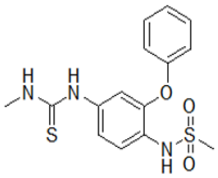
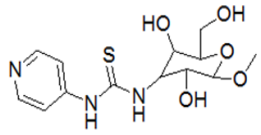


used for lung Cancer



used for pancreatic and Brain tumor Cancer cells

IV. CONCLUSION

Thioureas are versatile chemicals with outstanding biological applications. These are used in agriculture, analytical industry, metallurgy, industry and in the field of medicine. Most prominent biological applications of Thioureas is for treatment of co-infection, as antioxidant, as ant allergens, as anti bacterial agents, as anti-inflammatory, as anti-thyroid drugs, as anti-epileptic drugs, as anti-hypertensive, as rodenticide, as anti-cancer drug, as DNA binder and as Urease Inhibitors. Complexes of thioureas are used as precursors and antibacterial agents. Thioureas act as precursor of gaunidines and hetrocyclic ring systems.

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