Thiourea Derivatives in Drug Design and Medicinal Chemistry: A Short Review

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Abstract: Thioureas have great medicinal applications as well as non-medicinal activities in industry, analytical chemistry and metallurgy. This review is a glimpse 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, thioureas are used as insect growth regulator, anti-fungal agents and herbicides.

Keywords: Thioureas, Synthesis, Molecule Design, Biological Activities, Cancer Studies

1. Introduction of Thioureas
Thioureas is the class of the organic compounds having sulphur with the general formula (R1R2N)(R3R4N)C=S. 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.

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 named as isothioureas. Thiourea system is numbered as below. [1]

Following are some examples of thioureas with their names.

2. Types of Thioureas
Thioureas are classified into following categories on the basis of no. of substituent attached to thiourea moiety.

a) Mono N-Substituted thioureas
These are obtained if H of NH2 is replaced by R. General formula of mono N-substituted thiourea is shown below.
Where $R=\text{phenyl, aryl, alkyl, cycloalkyl, hetrocycle, acyl}$ etc.

Following are examples of mono N-substituted thioureas.

$b) \text{Disubstituted thioureas}$

These are either obtained if two $H$ atoms of same $\text{NH}_2$ group are replaced by $R_1$ and $R_2$ or $H$ of one $\text{NH}_2$ group is replaced by $R_1$ and $H$ of other $\text{NH}_2$ group is replaced by $R_2$.

Disubstituted thiourea are either $1,1$-disubstituted or $1,3$-disubstituted. There are some examples of these along with their general formula.

Where $R_1$ and $R_2=\text{phenyl, aryl, alkyl, cycloalkyl, hetrocycle, acyl or any substituent}$.

c) $\text{Trisubstituted thioureas}$

Trisubstituted thioureas are obtained by replacing two $H$ atoms of one amino group by $R_1$, $R_2$ and one $H$ atom of other amino group by $R_3$. Trisubstituted thioureas are $1,1,3$-trisubstituted. Their general formula is given below.

Where $R_1$, $R_2$ and $R_3=\text{phenyl, aryl, alkyl, cycloalkyl, hetrocycle, acyl}$.
**d) Pseudo-thioureas (Mono S-substituted thioureas)**

S-substituted thioureas are called pseudo-thioureas or isothiourea.

![Diagram of pseudo-thioureas](image)

**e) Guanyl thioureas**

Guanyl thioureas are derivatives of guanidine having a common nitrogen atom between guanidine and thiourea moiety. [2]

![Diagram of guanyl thioureas](image)

**3. General Methods for Synthesis**

**(a) Thioureas from Isothiocyanates**

Alkyl Isothiocyanates 32 on reaction with primary and secondary amines 33 yield thiourea derivatives 34. [3]

![Scheme 1: General method for synthesis of thioureas from isothiocyanates](image)

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

**Scheme 1:** General method for synthesis of thioureas from isothiocyanates.

**(b) Thioureas from Cyanamid’s**

Cyanamids 35 and "LiAIHSH" in the presence of HCl solution having conc. 1N in Dry diethyl ether to produce N, N-disubstituted thioureas 36. (Scheme 2) This method can also yields monosubstituted thioureas. Lithium aluminium hydride on reaction with sulphur yields LiAlHSH. [4]

![Scheme 2: General method for synthesis of Thiourea derivatives from Cyanamids.](image)

Where R₁ = R₂ = alkyl

**Scheme 2:** General method for synthesis of Thiourea derivatives from Cyanamids.

**(c) Thioureas from Thiophosgene**

In the presence of Pyridine, thioureas can be produced by condensing 37 and 39 with 38. (Scheme 3) If a single amine is used symmetrical thioureas will obtain (R₁NH-CS-NHR₁). A mixture of thioureas will produce that can be separated by chromatography on using mixture of amines.[5] The composition will be as

![Scheme 3: General method of synthesis of thioureas from thiophosgene.](image)

Where R₁=R₂=alkyl or aryl.

**Scheme 3:** General method of synthesis of thioureas from thiophosgene.

**(d) Thioureas from Carbon disulphide**

Symmetrical and Unsymmetrical thioureas can be prepared by reaction of 43 and 44. Reaction intermediate in this case is amino dithiol derivative instead of isothiocyanate. [6]

![Scheme 4: General method of synthesis of thioureas from Carbon disulphide.](image)

Where R₁=R₂=R₃=alkyl or aryl.

**Scheme 4:** General method of synthesis of thioureas from Carbon disulphide.
(e) From Thioureas

Symmetrical thioureas are precursor of unsymmetrical thioureas. This method is used to prepare disubstituted and trisubstituted thiourea derivatives. [7] 46 (Symmetrical thiourea) on reaction with 47 (amine) yield 48 (thiourea derivative).

\[ \text{R}_1 = \text{R}_2 = \text{alkyl, aryl or R}_2 = \text{H} \]

Scheme 5: General method of synthesis of thioureas from thioureas

4. Application of Thiourea Derivatives

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

4.1. Application in Agriculture

Thioureas have versatile application in field of agriculture. These are used 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 planthopper Nilaparvata lugens is an insect of rice crop. This insect destroys the crop by sucking cell sap and transmitting viral diseases.

49 (thiourea 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. [8]

b) Effect on seed germination and plant growth

Many organic compounds effect the germination and growth of seed. 50 effects elongation of roots of linseed. Elongation of root is decreased up to 50% at conc. 0.18 µ. At higher concentrations, on mustard tomatoes, ryegrass, lettuce and cress similar effects were observed. This compound has same effect as that of trifluralin. A study of analogues proved that this structural requirement is extremely specific for this activity. [9] Most of the compounds belonging to series of 51 showed plant growth regulating properties. [10]

c) 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 52, 53 and 54 are active fungicides. 52 and its p-chloro and p-nitro derivatives are most active ones. 55, 56 and their complexes show antifungal activity against the fungus yeast Saccharomyces cerevisiae and Penicillium digitatum. [11] Derivatives of 57 show significant antifungal and anti-viral activity of curative rates. [12]

d) Herbicidal Activity
58 and 59 show herbicidal activity against cucumber seedlings and former also showed activity against wheat seedlings. [13] 60 is effective against root and stalk of *Amaranthus retroflexus* L. [14]

### 4.2. 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) 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.

  Tetrahydroimidazobenzodiazepinthiones (TIBO) derivative 61 (9-chloro TIBO), 62 (Trovirdine) and are used for H. I. V treatment. 63 (ISOXYL) is used for treatment of T. B. [15] 64 (D-PTB), 65 (F-PTB) and 66 (S-BABO) are active against H. I. V. virus as well as these have spermicidal effect. But spermicidal activity of Novel derivatives is a function of time and concentration. [16]

- **b) Thiourea derivatives as antioxidant**
  
  The compounds that prevent the oxidation of other substances are referred as antioxidant. In these reactions electrons and hydrogen is transferred to oxidizing agent.

  These can result in free radicals that can destroy cell.

- **c) Antibacterial activity of thiourea derivatives**
  
  Thiourea derivatives have great potential to act as antibacterial substances. Some 1-aryloxy-3-aryl thioureas 71 have activity against *Staphylococcus aureus*, *Bacillus subtilis* and *E-Coli*. [18]

- **d) Thiourea derivatives as ant allergens**
  
  72 (N-(4-substituted-thiazolyl)oxamic acid) derivatives are active anti allergens. Many derivatives showed 50% inhibition at 2mg/kg. Ethanol amine salt with N-(4-substituted-thiazolyl)oxamic acid showed greater activity against allergy but esters and amide of N-(4-substituted-thiazolyl)oxamic acid are less active than N-(4-substituted-thiazolyl)oxamic acid. [19]

- **e) Thiourea derivatives as anti-inflammatory**
  
  Iminothiazolines on reaction with phenyl isothiocyanate yield thioureas 73 having anti inflammatory activity. [20]
**f) 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.

\[ \text{74 (2-thiouracil), 75 (6-n-propylthiouracil), 76 (6-methylthiouracil), 77 (carbimazole), 78(methimazole), 79 (1, 3-diethylthiourea), and 80 (2-thiobarbituric acid).} \]  

**g) Thiourea derivatives as anti-epileptic drugs**

Derivatives of 81a and 81b are active anti-convulsant with 50% effect dose of 1.72 and 1.19 mg/k.g respectively. [22]

\[ \text{Where R}_1 = \text{C}_7\text{H}_{13}, \text{C}_8\text{H}_{15} \text{ and } \text{R}_2 = \text{C}_6\text{H}_{11} \]

**h) Thiourea derivatives as anti-hypertensive**

Mono and Disubstituted phenylthiourea act as anti-hypertensive compound. 82, 83, 84, 85 and 86 show anti-hypertensive activity but greatest activity was observed for 85. [23]

**i) Thioureas as rodenticide**

Thioureas are best rodenticides. 87 (Alphanaphthyl thiourea) and 88 (phenyl thiourea) are most commonly used rodenticide. Alphanaphthyl thiourea is especially active in brown rats. [24]

**j) 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.[25] 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.[26] Chemotherapy is used for various types of cancers. Chemotherapy use medicines to kill the origin of cancer or kill cancer. Radiotherapy can easily be applied to cure tumors restricted to a small area. Radiotherapy can be applied internally and externally. The rate of Cure is diminished by metastasis in internal radiotherapy. In case of small tumors surgery and radiotherapy are approximately forty percent efficient. Due to metastasis of cancer cells sixty percent is still on its last legs. [27] Chemotherapy is less expensive than surgery and radiotherapy. Metastasized tumors can easily be treated by chemotherapy.[28] The anti-cancer drug eliminates cancerous cells without affecting the normal cells can be regarded as best one. In actual all anti cancer drugs destroy normal cells and have vomiting like side effects. In chemotherapy different drugs are used to slow down the cell
cycle. Drug should slow down at least one stage of cell division to check cell division. Anti cancer drugs are classified into following categories i.e. alkylating agents, Anti-metabolites, Topoisomerase inhibitors, Mitotic inhibitors and Mitotic inhibitors.

Table 1. A brief listing of representative commercial chemotherapeutic agents [29-38].

| Sr. No. | Chemotherapeutics          | Cancer against which practiced                                                                 |
|---------|----------------------------|-------------------------------------------------------------------------------------------------|
| 1       | Nitrogen Mustards (Mechlorethamine) | Hodgkin’s disease, non-Hodgkin’s lymphoma breast and lung                                     |
| 2       | Nitrosoureas (Carmustine)      | Brain tumors, Hodgkin’s disease, non-Hodgkin’s lymphoma, melanoma, lung cancer, colon cancer  |
| 3       | Alkyl Sulfonates (Busulfan)    | Chronic myelogenous leukemia                                                                  |
| 4       | Ethylenimines (Thiotepa)       | Breast cancer, ovarian cancer, Hodgkin’s disease, and non-Hodgkin’s lymphoma                  |
| 5       | Pyrimidines (Flurouracil)      | Breast, head, neck, adrenal, pancreatic, gastric, colon, rectal, esophageal, liver             |
| 6       | Purines (6-Mercaptopurine )    | Acute lymphocytic leukemia                                                                    |
| 7       | Folate antagonists (Pemetrexed)| Mesothelioma, non-small cell lung cancer                                                       |
| 8       | Hydroxyurea                   | Melanoma, chronic myelogenous leukemia, squamous cell carcinomas                               |
| 9       | Doxorubicin                   | Hodgkin’s lymphoma, bladder, breast, stomach, lung, ovaries, thyroid, soft tissue sarcoma, multiple myeloma |
| 10      | Mitoxantrone                  | Breast cancer, acute myeloid leukemia, non-Hodgkin’s lymphoma.                                 |
| 11      | Vincristine                   | Acute leukemia, rhabdomyosarcoma, neuroblastoma, Wilm’s tumor, Hodgkin’s disease               |
| 12      | Vinodesine                    | Melanoma, lung cancers, uterine cancers                                                       |

One of the most important applications of Thiourea derivatives is their anti-cancer activity. 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. Novel thioureas having general formula 89 were prepared and screened for their anti-cancer activity using Hela cells and MCF-7. Most of thiourea were efficient in cytotoxicity. [39]

The novel ferrocenyl incorporated thiourea (R1=H, R2=Ph, p-Cl-C6H4, -CH3O-C6H4, -CH3-C6H4) of above series showed cytotoxicity against human ovarian tumor models (A2780, A2780cisR, and A2780/ZD0743R), cis platin was used as reference standard for the activity. Interaction with pBR322 Plasmid DNA proved that the compounds don’t cause change in DNA conformation. Compounds don’t bind covalently with DNA. The electrostatic interactions between compound and anionic phosphate DNA backbone are strong enough to cause DNA cleavage or cell kill. [40] Some of these compounds have low oxidation potential than ferrocene reflects that ferrocene moiety can easily be oxidized. Phenyl derivative (R1=H, R2=Ph) of the series shows intercalation but methyl derivative shows electrostatic interaction.[41] Six novel ferrocenyl thioureas (R1=CH3, R2=CH3, -CH(CH3)2, -CH2C6H5, -CH2Cl, -C2H5, -C(CH3)3) were prepared, their DNA binding abilities and anti-oxidant properties were investigated. It was found that some compounds showed strong electrostatic interaction with DNA in its oxidized form rather than in reduced form. Fe$^{3+}$ in ferrocenyl moiety interact
with negatively charged phosphate group of nucleotides. Anti-oxidant assay was performed by DDPH showed that maximum activity for R= Me with IC50 = 15.66 µg mL−1 followed by R= Et with IC50 = 18.22 µg mL−1 [42]

l) Thioureas as Urease Inhibitor

\[
\begin{align*}
R_1 &= H \text{ (a-d, f, g, i, j), C}_6\text{H}_5 \text{ (e), C}_6\text{H}_11 \text{ (h) and R}_2 = \text{ C}_6\text{H}_11\text{N}_2(a), 4\text{-C}_6\text{H}_4\text{COOH}(b), 3\text{-NO}_2\text{C}_6\text{H}_4(c), 2\text{-NO}_2\text{C}_6\text{H}_4(d),} \\
&\quad \text{ C}_6\text{H}_11(e), 2,4(\text{CH}_3)2\text{C}_6\text{H}_7(f), \text{ C}_6\text{H}_11(g, h), \text{ C}_6\text{H}_2\text{N}(i), 3\text{-NH}_2\text{C}_6\text{H}_4(j).} \\
\end{align*}
\]

A series of some novel N3, N3'-bis-(disubstituted)isophthalyl-bis-(thioureas), with general formula \([\text{C}_6\text{H}_4\{\text{CONHCSNR}_1\text{R}\}_2]\), where \(R_1 = \text{H} \) (a-d, f, g, i, j), \( \text{C}_6\text{H}_5 \) (e), \( \text{C}_6\text{H}_11 \) (h) and \( R_2 = \text{C}_6\text{H}_11\text{N}_2(a), 4\text{-C}_6\text{H}_4\text{COOH}(b), 3\text{-NO}_2\text{C}_6\text{H}_4(c), 2\text{-NO}_2\text{C}_6\text{H}_4(d), \) \( \text{C}_6\text{H}_11(e), 2,4(\text{CH}_3)2\text{C}_6\text{H}_7(f), \text{C}_6\text{H}_11(g, h), \text{C}_6\text{H}_2\text{N}(i), 3\text{-NH}_2\text{C}_6\text{H}_4(j) \) have been prepared in good to excellent yields by reaction of isophthaloyl isothiocyanate with primary and secondary amines using dry acetone as solvent. These compound s were characterized by I. R, and \( \text{NMR spectroscopy and elemental analysis.} \) These novel compounds tested for Urease inhibition activity and anti-bacterial activity of six different stains. The compounds a, c and f exhibited potent activity against all tested bacteria with highest inhibition zones. The compounds b and c proved to be the most potent urease inhibitor showing an enzyme inhibition activity with an IC50 value of 26.3 ± 0.5 µM and 26.7 ± 0.5 µM respectively. These values are comparable to 21.0 ± 0.1 µM of the standard. Compounds b and c proved to be the most potent urease inhibitor showing an enzyme inhibition activity with an IC50 value of 26.3 ± 0.5 µM and 26.7 ± 0.5 µM respectively. These values are comparable to 21.0 ± 0.1 µM of the standard. These compounds don’t show conductivity indicate that there is no free ion in complexes. These complexes show considerable anti-bacterial activity against \( \text{E. coli, P. auruginosa, K. pneumoniae, B. cereus, S. aureus, and B. pumilus.} \) [48]

98 when complexed with Pt(II), Pd(II), Hg(II), Ni(II), Co(II), Zn(II), Mn(II) and Cd(II) showed significant anti-bacterial activity against \( \text{Escherichia coli, Pseudomonas aeruginoses and Staphylococcus aureuses.} \) [46] 101 form stable complex with Ni (II), and Cu(II) that show antibacterial activity higher than corresponding ligands. [47] 102 ligand acts as monodentate ligand through the sulfur atom forming stable complexes with Co(II), Zn(II), Cu(II) and Fe(III). These compounds don’t show conductivity indicate that there is no free ion in complexes. These complexes show considerable anti-bacterial activity against \( \text{E. coli, P. auruginosa, K. pneumoniae, B. cereus, S. aureus, and B. pumilus.} \) [48]

Some novel thioureas \( \text{N3, N3'-bis(disubstituted)isophthalyl-bis(thioureas) and N3, N3', N3'-Tetrakis (disubstituted)isophthalyl-bis(thioureas) compounds with general formula \([\text{C}_6\text{H}_4\{\text{CONHCSNR}_1\text{R}\}_2] \), where \( R_1 = \text{H} \) (1-4), \( \text{C}_6\text{H}_11(5), \text{C}_6\text{H}_5(6) \) and \( R_2 = 4\text{-NO}_2\text{C}_6\text{H}_4(1), \text{C}_6\text{H}_11(2), 2,4(\text{CH}_3)2\text{C}_6\text{H}_3(3), \text{C}_5\text{H}_4\text{N}(4), \text{C}_6\text{H}_11(5), \text{C}_6\text{H}_5(6) \), and their Cu(II) and Ni(II) complexes

4.3. Applications of Complexes of Thioureas

Thiourea derivatives have a great potential to act as ligand. Especially co-ordination chemistry of benzoil thiouyles satisfactorily explained. These form more stable complexes having six membered rings. These thioureas have capability to act as chelating agents because of the presence of C=S and C=O functional groups. That’s why novel thioureas have attention researchers due to their property to act as ligan. [44]

i). Biological properties

Thioureas itself and their metal complexes show a number of biological properties such as anti-cancer, anti-microbial, anti-fungal etc. The compounds 97, 98 and 99 after complexation with Cu(II) show enhanced antibacterial activity against \( \text{Staphylococcus aureus} \) [45]
have been synthesized. All the synthesized compounds were characterized by I. R, $^1$H-NMR spectroscopy and elemental analysis. These six ligands and their metal complexes were then tested for anti-bacterial activity. Ampicillin and ciprofloxacin were used as reference standard and activity was performed by using disc diffusion method. The antibacterial activity of ligands enhanced after complexation. The compounds 5 and 6 showed no activity against any stain except S. typhi. The compound 1 and their Ni and Cu complexes showed highest activity. [49]

**ii). As precursor of Metal Sulphides Nano Particle**

Metal complexes of thioureas as precursor of metal sulphide nano particles. Studies revealed that thiourea and its derivative that co-ordinate to M (II) cations via sulphur are good precursor of Metal sulphide nano particles. Stability of complexes was checked by thermogravimetric analysis and potential as precursor of metal sulphide thin film was estimated by chemical vapour deposition technique. 103, 104, 105 and 106 are precursor of sulphide nano particles. [50]

**4.4. Thioureas as Precursor**

**i). Thioureas as precursor of Guanidines**

107 reacts with 108 in the presence of mercuric chloride to produce 109 (bis-Boc protected guanidine) that on deprotection yield 110 (mono alkylated guanidines). Acylated thioureas react with amines to give guanidines via acylated guanidines as intermediate. [51]

**ii). Thioureas as precursor of Heterocycles**

Substituted N-aryl thiocarbamates, thioureas and thioamides on cyclization in presence of tris(trimethylsilyl)silane and U. V light yield indoloquinolines, furoquinolines, cyclopentaquinolines, isofuroquinolines, and related ring systems. [52]
Where Y = O, CH₂, NH
A variety of 2-amino-substituted 1-aza 3-(oxo, aza or thio) heterocycles of different ring size and substitution can be prepared by using TsCl / NaOH as reagent starting from N-(2-hydroxyethyl)-thioureas, N-(2-aminoethyl)-thioureas and N-(2-marcetoethyl)-thioureas respectively. [53]

Where X=C, O, NH

5. 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 are for treatment of co-infection, as antioxidant, as ant allergens, as anti-inflamatory, 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 guaainides and heterocyclic ring systems.

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