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Review Article

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

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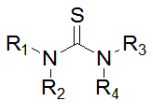
Abstract: Thioureas have great medicinal applications as well as non-medicinal activities in industry, analytical chemistry and metallurgy. This review is a glimpse of methods of synthesis and applications of thioureas in the field of medicine and agriculture. Thioureas have a number of medicinal applications 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

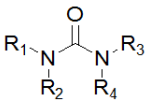
1. Introduction of Thioureas

Thioureas is the class of the organic compounds having sulphur with the general formula $(R_1R_2N)(R_3R_4N)C=S$. 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.



Thioureas

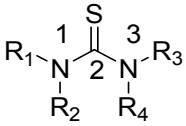
1



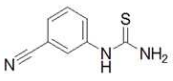
Ureas

2

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]

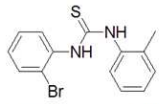


Following are some examples of thioureas with their names.



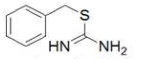
1-(3-cyanophenyl)thiourea

3



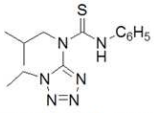
1-(2-bromophenyl)-3-o-tolylthiourea

4



2-benzylisothiourea

5a



1-(1-ethyl-1*H*-tetrazol-5-yl)-1-isobutyl-3-phenylthiourea

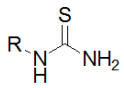
5b

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

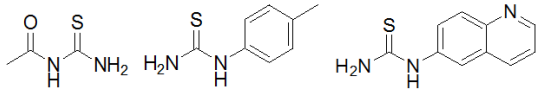
These are obtained if H of NH_2 is replaced by R. General formula of mono N-substituted thiourea is shown below.



6

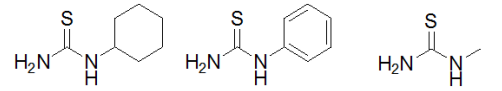
Where R= phenyl, aryl, alkyl, cycloalkyl, hetrocycle, acyl etc.

Following are examples of mono N-substituted thioureas.



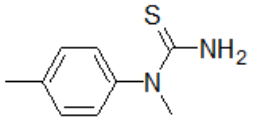
1-acetylthiourea 1-p-toluylthiourea 1-(quinolin-6-yl) thiourea

7 **8** **9**

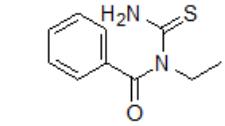


1-cyclohexylthiourea 1-phenylthiourea 1-methylthiourea

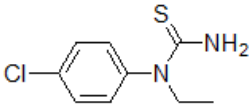
10 **11** **12**



1-methyl-1-p-tolylthiourea

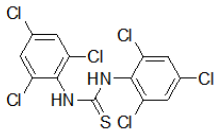


1-benzoyl-1-ethylthiourea

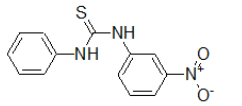


1-(4-chlorophenyl)-1-ethylthiourea

15 **16** **17**

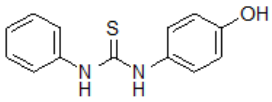


1, 3-bis (2, 4, 6-trichlorophenyl)thiourea



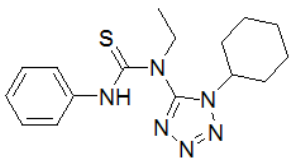
1-(3-nitrophenyl)-3-phenylthiourea

18 **19**

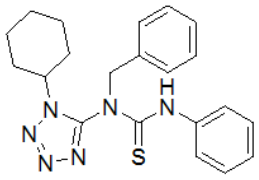


1-(4-hydroxyphenyl)-3-phenylthiourea

20



1-(1-cyclohexyltetrazol-5-yl)-1-ethyl-3-phenylthiourea

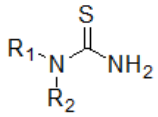


1-(1-cyclohexyltetrazol-5-yl)-1-benzyl-3-phenylthiourea

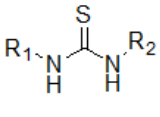
22 **23**

b) Disubstituted thioureas

These are either obtained if two H atoms of same NH_2 group are replaced by R_1 and R_2 or H of one NH_2 group is replaced by $R_1$and H of other 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.



1,1-disubstituted



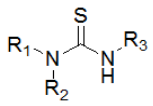
1,2-disubstituted

13 **14**

Where R_1 and R_2= phenyl, aryl, alkyl, cycloalkyl, hetrocycle, acyl or any substituent.

c) 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.



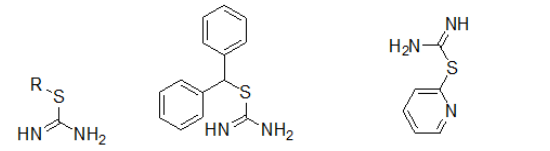
trisustituted thiourea

21

Where R_1, R_2 and R_3= phenyl, aryl, alkyl, cycloalkyl, hetrocycle, acyl

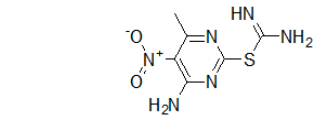
d) Pseudo-thioureas (Mono S-substituted thioureas)

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



psedu thiourea 2-benzhydrylisithiourea 2-(pyridine-2-yl)isothiourea

24 **25** **26**

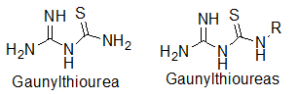


2-(4-amino-6-methyl-5-nitropyrimidin-2-yl)isothiourea

27

e) Guanyl thioureas

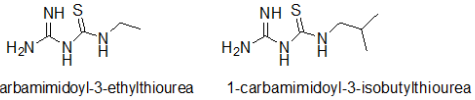
Guanyl thioureas are derivatives of guanidine having a common nitrogen atom between guanidine and thiourea moiety. [2]



Gaunylthiourea Gaunylthioureas

28 **29**

Where R= phenyl, aryl, alkyl, cycloalkyl, hetrocycle, acyl etc.

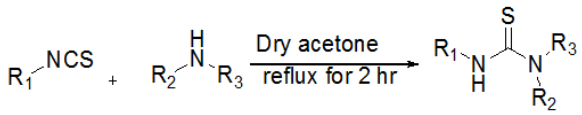


1-carbamimidoyl-3-ethylthiourea 1-carbamimidoyl-3-isobutylthiourea

30 **31**

(a) Thioureas from Isothiocynates

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



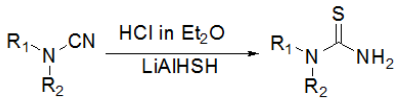
32 **33** **34**

Where R_1 = alkyl, aryl or benzoyl. R_2 = alkyl or phenyl and R_3 = alkyl, phenyl or H.

Scheme 1: General method for synthesis of thioureas from isothiocyanate.

(b) Thioureas from Cyanamid's

Cyanamids 35 and "LiAlHSH" 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]



35 **36**

Where $R_1 = R_2$ = alkyl

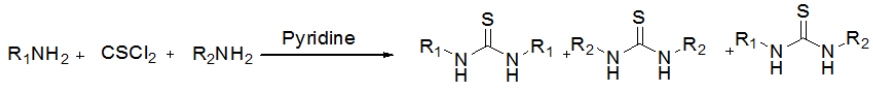
Scheme 2: General method for synthesis of Thiourea derivatives from Cyanamids.

(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 (R_1NH-CS-NHR$_1$). A mixture of thioureas will produce that can be separated by chromatography on using mixture of amines.[5] The composition will be as

3. General Methods for Synthesis

(R_1NH-CS-NHR$_1$), (R_2NH-CS-NHR$_2$), (R_1NH-CS-NHR$_2$).



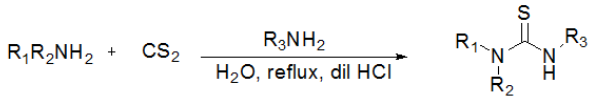
37 **38** **39** **40** **41** **42**

Where R_1=R_2=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]



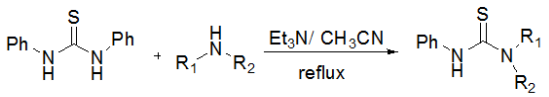
43 **44** **45**

Where R_1=R_2=R_3=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 thioureas) on reaction with 47 (amine) yield 48 (thiourea derivative).



46 **47** **48**

Where R_1=R_2 = alkyl, aryl or R_2 = H

Scheme 5: General method of synthesis of thioureas from thioureas

4. Application of Thiourea Derivatives

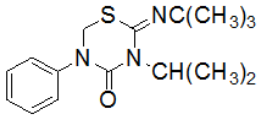
Thioureas have a variety of applications in different fields of life. Some of these are discussed below.

4.1. Application in Agriculture

Thioureas have versatile application in field of agriculture. These are used 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.

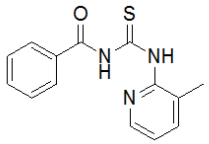


49

49 (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. [8]

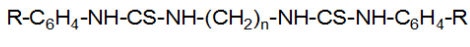
b) Effect on seed germination and plant growth

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]



N-Benzoyl-N'-(3-methylpyrid-2-yl)thiourea

50

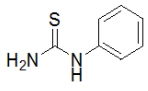


(1,1`-polymethylenebis(3-arylsubstituted)thiourea

51

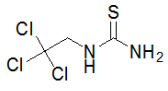
c) Antifungal Activity

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].



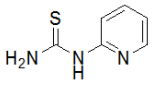
phenyl thiourea

52



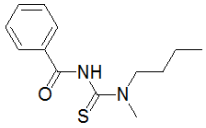
trichloroethyl thiourea

53



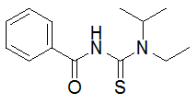
pyridyl thiourea

54



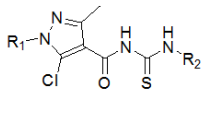
3-benzoyl-1-butyl-1-methylthiourea

55



3-benzoyl-1-ethyl-1-isopropylthiourea

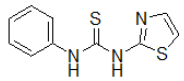
56



pyrazole acyl thiourea

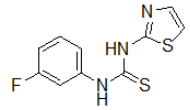
57

d) Herbicidal Activity



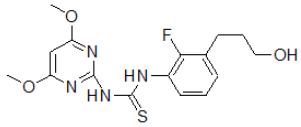
1-phenyl-3-(2-thiazolyl)thiourea

58



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

59



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

60

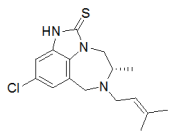
58 and 59 show herbicidal activity against cucumber seedlings and former also showed activity against wheat seedlings. [13] 60 is effective against root and stalk of *Amaranthus retroflexus L.* [14]

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.



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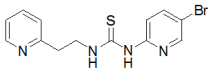

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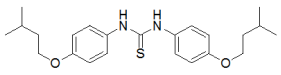

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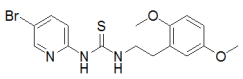

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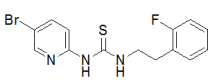

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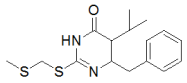
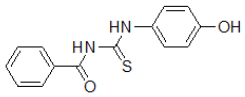


66

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]

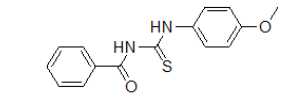
b) Thiourea derivatives as antioxidant

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.



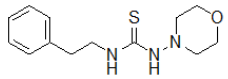
1-benzoyl-3-(p-hydroxyphenyl) thiourea

67



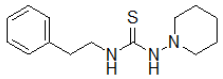
1-benzoyl-3-(p-methoxyphenyl)thiourea

68



1-morpholino-3-phenethylthiourea

69



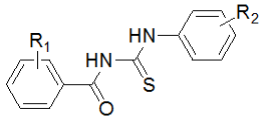
1-phenethyl-3-(piperidine-1-yl)thiourea

70

67 (1-benzoyl-3-(p-hydroxyphenyl) thiourea), 68 (1-benzoyl-3-(p-methoxyphenyl) thiourea), 69 (1-morpholino-3-phenethylthiourea) and 70 (1-phenethyl-3-(piperidine-1-yl) thiourea) are excellent antioxidant. [17]

c) Antibacterial activity of thiourea derivatives

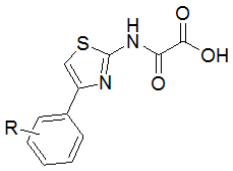
Thiourea derivatives have great potential to act as antibacterial substances. Some 1-aroyl-3-aryl thioureas 71 have activity against *Staphylococcus aureus, Bacillus subtilis* and *E-Coli*. [18]



71

d) Thiourea derivatives as ant allergens

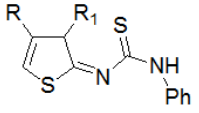
72 (N-(4-substituted-thiazolyl)oxamic acid) derivatives are active anti allergens. Many derivatives showed 50% inhibition at 2mg/k.g. Ethanol amine salt with N-(4-substituted-thiazolyl)oxamic acid showed greater activity against allergy but esters and amide of N-(4-substituted-thiazolyl)oxamic acid are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



72

e) Thiourea derivatives as anti-inflammatory

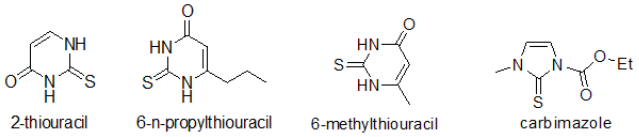
Iminothiazolines on reaction with phenyl isothiocyanate yield thioureas 73 having anti inflammatory activity. [20]



73

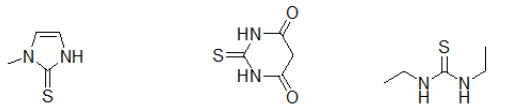
f) Thiourea derivatives as anti-thyroid drugs

Goiter is caused by Hyperthyroidism is cured by anti thyroid drugs. Following thiourea derivatives are used for treatment of hyperthyroidism.



2-thiouracil 6-n-propylthiouracil 6-methylthiouracil carbimazole

74 **75** **76** **77**



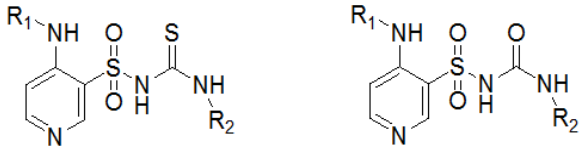
methimazole 2-thiobarbituric acid 1,3-diethyl thiourea

78 **79** **80**

74 (*2*-thiouracil), 75 (6-n-propylthiouracil), 76 (6-methylthiouracil), 77 (carbimazole), 78(methimazole), 79 (1, 3-diethylthiourea), and 80 (*2*-thiobarbituric acid). [21]

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]

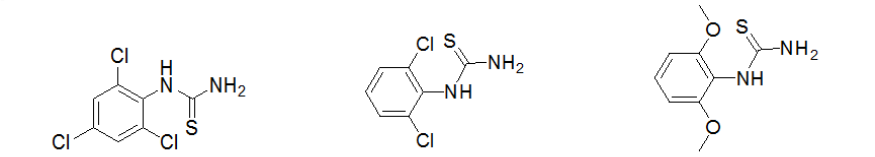


81a **81b**

Where R_1= C_7H_{13}, C_8H_{15} and R_2= C_6H_{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]



1-(2,4,6-trichlorophenyl)thiourea 1-(2,6-dichlorophenyl)thiourea 1-(2,6-dimethoxyphenyl)thiourea

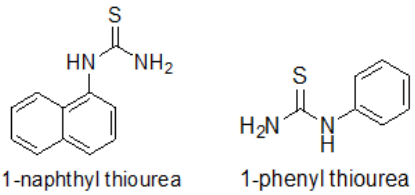
82 **83** **84**

1-(2,6-dimethylphenyl)thiourea 1-(2-methylphenyl)-3,3-dimethylthiourea

85 **86**

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]



1-naphthyl thiourea 1-phenyl thiourea

87 **88**

j) Thiourea derivatives as anti-cancer drug

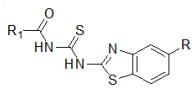
Cancer is an alarming ailment; different types of cancers can be treated effectively, if diagnosed at start. The following are the methods applied for the treatment of cancer; organ transplantation, surgery, palliative care, biotherapy, chemotherapy and radiation therapy.[25] But commonly used are chemotherapy 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
Alkylating agents Interact with DNA to inhibit the cell replication process		
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
Anti-metabolites Induce cell death during the S phase of cell growth, incorporated into RNA, DNA or inhibit enzymes		
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
Topoisomerase inhibitors Makes the enzyme nonfunctional by blocking the ability of the topoisomerase to bind the DNA		
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.
Mitotic inhibitors Arrest the division of cells and cause cell death, By binding to the building blocks of a tubulin protein		
11	Vincristine	Acute leukemia, rhabdomyosarcoma, neuroblastoma, Wilm's tumor, Hodgkin's disease
12	Vindesine	Melanoma, lung cancers, uterine cancers
Kinase Inhibitors Blocks a kinase gene from binding to ATP, preventing the phosphorylation that would benefit the cancerous cell and promote cell division.		

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 tthiourea were efficient in cytotoxicity. [39]



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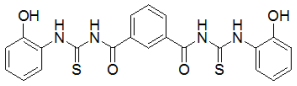

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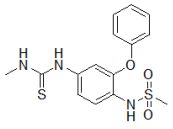
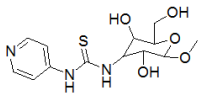


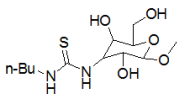
Used for lung cancer

91



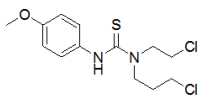
Used for pancreatic and brain tumor cancer cells

92



For treatment of brain tumor cancer cells

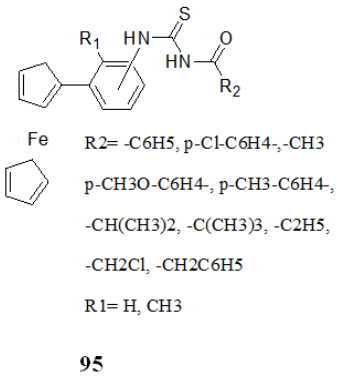
93



active for brain cancer treatment

94

k) Thioureas as DNA binder



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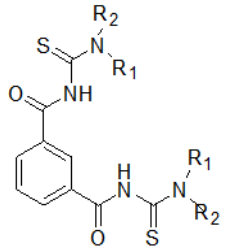
The novel ferrocenyl incorporated thiourea (R1=H, R2=Ph, p-Cl-C6H4-, p-CH3O-C6H4-, p-CH3-C6H4-) of above series showed cytotoxicity against human ovarian tumor models (A2780, A2780cisR, and A2780ZD0473R), cis platin was used as reference standard for the activity. Interaction with pBR322 Plasmid DNA 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 by R= Et with IC50 = 18.22 µg mL−1 [42]

l) Thioureas as Urease Inhibitor



96

R_1 = H (a-d, f, g, i, j), C_6H_5 (e), C_6H_{11} (h) and R_2 = $C_5H_4N_3$(a), 4-C_6H_4COOH(b), 3-$NO_2C_6H_4$(c), 2-$NO_2C_6H_4$(d), C_6H_5(e), 2,4$(CH_3)2C_6H_3$(f), C_6H_{11}(g, h), C_5H_4N(i), 3-$NH_2C_6H_4$(j).

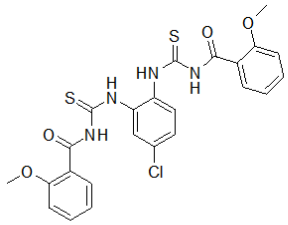
A series of some novel N3, N3'-bis-(disubstituted)isophthalyl-bis-(thioureas), with general formula [C6H4{CONHCSNR1R}2], where R_1 = H (a-d, f, g, i, j), C_6H_5 (e), C_6H_{11} (h) and R_2 = $C_5H_4N_3$(a), 4-C_6H_4COOH(b), 3-$NO_2C_6H_4$(c), 2-$NO_2C_6H_4$(d), C_6H_5(e), 2,4$(CH_3)2C_6H_3$(f), C_6H_{11}(g, h), C_5H_4N(i), 3-$NH_2C_6H_4$(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 compounds were characterized by I. R, ^{1} H-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 compound h also showed great anti bacterial activity. The compounds e, i and j were inactive and showed no inhibition against all bacteria. Ampicillin and ciprofloxacin were used as reference standard and activity was performed by using disc diffusion method. The results of urease inhibition were also appraisable. For Urease Inhibition activity Thiourea itself used as reference standard. Compounds b and c proved to be the most potent urease inhibitor showing an enzyme inhibition activity with an IC_{50} 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 thiourea. The compounds a and d also showed greater activity but compounds i and j showed no activity. [43]

4.3. Applications of Complexes of Thioureas

Thiourea derivatives have a great potential to act as ligand. Especially co-ordination chemistry of benzoyl thioureas 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 ligand. [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 *Staphylococcus aureus.*[45]



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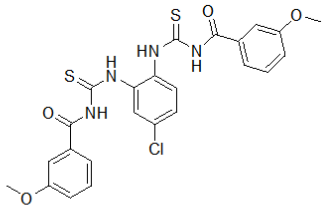

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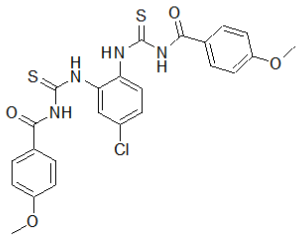
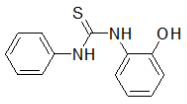


99

Thioureas those are complexed with metal via sulphur antifungal and antibacterial activities. Thioureas can co-ordinate to metals as neutral ligands and anionic ligands. There are multi-bonding possibilities of metals with thioureas due to presence of various donor atoms like N, S and O. Chelating thioureas that have S, N, and O Show a broader range of biological properties.



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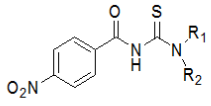
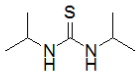


101



102

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 *Escherichia coli, Pseudomonas aeruginoses and Staphylococcusaureus.* [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 *E. coli, P. auruginosa, K. pnemoniae, B. cereus, S. aureus, and B. pumilus.* [48]

Some novel thioureas N3, N3'-bis(disubstituted)isophthalyl-bis(thioureas) and N3, N3, N3', N3'-Tetrakis (disubstituted)isophthalyl-bis(thioureas) compounds with general formula [C6H4{CONHCSNR1R}2], where R1 = H (1-4), C6H11(5), C6H5(6) and R2 = 4-NO2C6H4(1), C6H11(2), 2,4(CH3)2C6H3(3), C5H4N(4), C6H11(5), C6H5(6), and their Cu(II) and Ni(II) complexes

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 depositiontechnique. 103, 104, 105 and 106 are precursor of sulphide nano particles. [50]

$Mn[(CH_3)HNCSNH(CH_3)]_2Cl_2$, **103**

$Cd[(CH_3)HNCSNH(CH_3)]_2Cl_2$, **104**

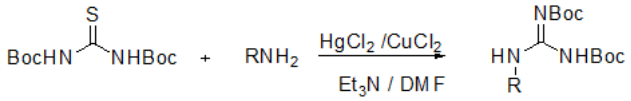
$Cd[(C_6H_5)HNCSNH_2]_2Cl_2$ **105**

$Co[SC(NH_2)NH(C_6H_5)]_4Cl_2$, **106**

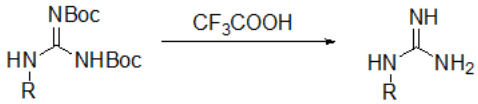
4.4. Thioureas as Precursor

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]

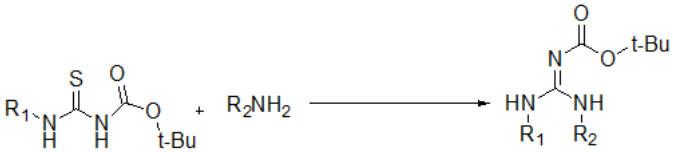


107 **108** **109**



109 **110**

R= alkyl, aryl



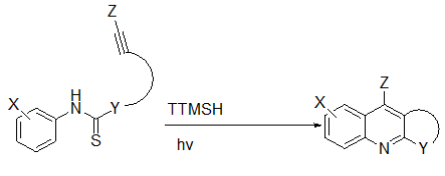
111 **112**

112 **113**

R= alkyl, aryl

ii). Thioureas as precursor of Hetrocycles

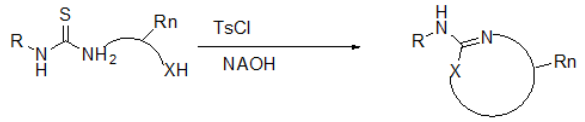
Substituted N-aryl thiocarbamates, thioureas and thioamides on cyclization in presence of tris(trimethylsilyl)silane and U. V light yield indoloquinolines, furoquinolines, cyclopentaquinolines, isofuroquinolines, and related ring systems. [52]



114 **115**

Where Y = O, CH_2, 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-marceptoethyl)-thioureas respectively. [53]



116 **117**

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 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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