CHAPTER 1

INTRODUCTION

Thiourea and its derivatives have found their way into every branch of science. They possess a variety of pharmacological, agrochemical and industrial applications. In thiourea, CS(NH$_2$)$_2$, the N-terminals can be substituted either symmetrically or unsymmetrically by aryl, alkyl, aralkyl, acyl, heterocyclic and/or alicyclic groups. S-substituted thioureas are referred to as pseudothioureas. A brief review of the applications of thiourea derivatives and the aim of the present work are given in this chapter.

1.1 APPLICATIONS OF THIOUREAS
1.1.1 Pharmacological applications

In pharmaceuticals, thiourea and its derivatives are used as anti-tubercular, anti-thyroidal, anti-bacterial, anti-viral, anti-depressant and anthelmintic agents.

A series of N-aryl-N'-2(Benzimidazolyl) thiocarbamides and N-aryl-N'-benzene sulphurous thiocarbamides have been tested for antithyroidal activity (Srivastava et al 1981). 1,1',3,3'-tetramethylthiourea is found to be a more potent antithyroid compound (Schroeder 1955). Thiourea derivatives of p-aminosalicylic acid, a number of thiocarbanilides and some of the 1,3-diphenylthioureas have been tested for antitubercular activity (Schroeder 1955 and Shinde et al 1982).

Thiourea derivatives of aromatic heterocyclic compounds with a quaternary nitrogen in the nucleus are said to have anthelmintic activity.
1-Naphthyl thiourea has been found to be efficacious against intestinal parasites in man and dogs (Schroeder 1955). Thiourea derivatives of 6-substituted 2- and 4- amino quinolines are found to possess ovicidal activity and anthelmintic activity against human hookworm (Varajgupta et al 1988).

Piperid-4-yl thiourea and 1-aryl-3-(2-hydroxyethyl) thiourea are used as the antidepressant agents (Archibald et al 1986 and Mc Carthy et al 1976). 1-Tolyl-3-diethylthiourea is known to reduce hypertension in mammals. N-[2-hydroxy-2(chlorophenyl)ethyl]thiourea is used as an anti-ulcer agent (Sato et al 1990).

N-methyl-N’-(o-tolyl)thiourea and N-phenyl-N’-4-hydroxy phenylthiourea were found to possess antiviral activity (Vasilev et al 1976 and Galabov et al 1977). Recently N-[2-(2-pyridyl)ethyl]-N’-(5-bromo-2-pyridyl) thiourea was claimed to inhibit the replication of HIV virus by contact (Lind et al 1993). 1-Aroyl-3-(4-benzosulfonamidopyrimidine) thioureas were found to exhibit antibacterial properties against a number of bacteria (Jia et al 1993). Dimethylphenyl thiourea derivatives were found to have anti-inflammatory activities (Trepanier et al 1976).

Vidaluc et al (1994) synthesised and evaluated the antiacetylcholinesterase activity of a series of aroylthiourea and 2-pyridylthiourea derivatives. Most aroyl thiourea derivatives showed potent inhibitory activity in the sub-micromolar range. They also showed that some of these compounds possess anti-amnestic activity and also act as anti-dementia agents.

1.1.2 Agrochemical applications

Many thiourea derivatives have insecticidal, antiviral, fungicidal and herbicidal properties. Aryl and diaryl thioureas are highly toxic against
insects and these compounds act as contact toxicants (Chatterjee et al 1980; Sengupta et al 1976; Yu et al 1976 and Boeger et al 1989). Vebrugge et al (1990) showed the pesticidal activity of benzoylthioureas on Egyptian cotton leafworm larvae. N-(pyrid-3-yl) thioureas are used as acaricides against some spider mice (Alfons et al 1995). 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. 1-Dodecyl-and 1,3-dodecyl-thiourea are toxic to the flesh fly larva (Schroeder 1955).

Vasilev et al (1987) showed the antiviral activities of 29 thiourea derivatives on potato virus X. Mixtures of N-phenyl-N'-p carboxy phenylthiourea and 2,4-dioxohexahydro-1,3,5-triazine are synergistic plant virucides (Gottfried et al 1992). N,N'- (1,4-phenylene-N3,N3'-diaryl)dithiourea exhibited antiviral activity in silkworm in vivo (Liu et al 1993).

Phosphorous containing thiourea and trichloroethyl thiourea derivatives were found to possess fungicidal properties (Melnikov et al 1988 and Gross Manfred et al 1993). Madan et al (1991) showed the potential fungicidal and nematicidal activities of pyrimidyl and thiazolyl substituted thioureas. Some 1-benzyl-3-aryl-2-thioureas and N-allyl-N'-phenylthiourea possess plant growth regulating activity (Lechkova et al 1991 and Uppal et al 1986).

N-substituted benzoylthioureas and hetero arylthioureas are found to have herbicidal properties (Jirman Josef 1989 and Hans Joachim et al 1986). Vasilev et al (1980) tested the herbicidal activity of certain metal complexes of bis(allyl) thiourea.
1.1.3 Industrial applications

Thiourea and its derivatives are suggested as good corrosion inhibitors (Chandrasekarpillai 1975 and Lawson 1980). Tolyl thiourea is found to inhibit the corrosion of aluminum in hydrochloric acid (Chaudhary et al 1979). Subramanyam et al (1993) studied the corrosion inhibition properties of 1,3-phenylthiourea, diphenylthiourea, allylthiourea, dimethylthiourea and tolylthioureas on aluminum in sodium nitrite environment. Thiourea, 1,3-phenylthiourea and naphthylthiourea are found to have anticorrosion properties for aluminum alloys in nitric acid solution (Singh et al 1981). Agrawal et al (1990) showed the corrosion inhibiting properties of thiourea, allylthiourea and phenylthioureas on 410 stainless steel in sulphuric acid. Some heterocyclic thioureas were also found to possess corrosion inhibiting properties (Ismail et al 1992). Recently, Rajendran et al (1993 and 1995) studied the possibility of using diphenylthiourea to prevent the corrosion of mild steel in a flue gas desulfurization environment.

Thiourea derivatives are used for getting high degree of whiteness in fabrics (Arifoglu et al 1989 and 1990). Some of the thiourea compounds remove protein containing contaminants from contact lenses (Miyajima et al 1986). In photographic film industry, thiourea derivatives are used to manufacture high sensitive silver halide photographic emulsions (Otani Hiroshi et al 1993). A number of hydroxyphenyl thiourea derivatives are used as antioxidants for jet fuels (Shaulov et al 1982).

1.2 AIM OF THE WORK

The biological activities of thiourea derivatives depend on the thiourea structures especially the configuration of the N-terminal substituents and the hydrogen bond formation (Vidaluc 1994). The corrosion rate is influenced by the bulkiness, solubility, and symmetry of the

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substituted thiourea molecules (Lawson 1980). The configuration of the substituted groups, hydrogen bonding formation and closeness of packing may also play a role in the corrosion inhibition behaviour of thiourea derivatives. Although the structure activity relationship has been established earlier (Schroeder 1955), no structural report exclusively concerning substituted thiourea derivatives is available. Only crystal structure analyses of metal complexes of thiourea and a few substituted thioureas have been reported. This may be due to the difficulties encountered in obtaining crystals suitable for X-ray diffraction studies.

Recently, Ramadas et al (1993 and 1995) prepared a number of symmetrical and unsymmetrical thiourea compounds involving a novel cost effective synthetic procedure. These compounds were prepared as a result of their agrochemical importance. Some of these compounds are also reported to have pharmacological and industrial applications. Since the crystal structure analyses of these compounds provide information regarding the configuration of the substituted groups, the hydrogen bond patterns and details of molecular packing, crystallization of these compounds were performed. A total of 7 symmetrical and 9 unsymmetrical thiourea derivatives were successfully crystallized and their crystal structures were determined.

They are

1. 1,3-diethylthiourea (DETU),
2. 1,3-diisopropylthiourea (DIPTU),
3. 1,3-diphenylthiourea (DPTU),
4. 1,3-bis(2-chlorophenyl)thiourea (OCDPTU),
5. 1,3-dibenzylthiourea (DBTU),
6. 1,3-dicyclohexylthiourea (DCHTU),
7. 1,3-di(2,6-diethylphenyl)thiourea (DEPTU),
8. 1-allyl-3-phenylthiourea (ALPTU),
9. 1-cyclohexyl-3-phenylthiourea (CHPTU),
10. 1-cyclohexyl-3-tolylthiourea (CHTTU),
11. 1,1-dimethyl-3-o-tolyliourea (DMTTU),
12. 1,1-diethyl-3-o-tolyliourea (DETTU),
13. 1,1-diethyl-3-cyclohexylthiourea (CHDETU),
14. 1-morpholino-N-phenylcarbothioamide (MPCT),
15. 1-morpholino-N-(2-tolyl)carbothioamide(MTCT) and
16. 1-morpholino-N-(2,6-diethylphenyl)carbothioamide(MDEPCT).

The schematic diagram illustrating various compounds studied are given in Figure 1.1.

The details of X-ray crystal structure determination of these compounds are given in Chapter 3 to Chapter 10. Some of these compounds were tested for their antibacterial and anticorrosion behaviour and the results are given in Chapters 11 and 12. Comparison of the studies and interpretation of the results are summarised in the conclusion Chapter 13.
Symmetrical Thiourea Derivatives

\[
\begin{align*}
&\text{cis-trans} \\
&\text{Compound code} \\
&\text{DETU} \\
&\text{DIPTU} \\
&\text{DPTU} \\
&\text{OCDPTU} \\
&\text{DBTU} \\
&\text{DCHTU} \\
&\text{DEPTU} \\
&\text{R1} \\
&\text{Ethyl} \\
&\text{Isopropyl} \\
&\text{Phenyl} \\
&\text{ortho-Chlorophenyl} \\
&\text{Benzyl} \\
&\text{Cyclohexyl} \\
&\text{(2,6-Diethyl) Phenyl}
\end{align*}
\]

Unsymmetrical Thiourea Derivatives and related Carbothioamide Derivatives

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\begin{align*}
&\text{cis-trans} \\
&\text{Compound code} \\
&\text{CHPTU} \\
&\text{CHTTU} \\
&\text{DMTTU} \\
&\text{DETTU} \\
&\text{ALPTU} \\
&\text{CHDETU} \\
&\text{MPCT} \\
&\text{MTCT} \\
&\text{MDPCT} \\
&\text{R1} \\
&\text{Phenyl} \\
&\text{Tolyl} \\
&\text{Tolyl} \\
&\text{Tolyl} \\
&\text{Phenyl} \\
&\text{Cyclohexyl} \\
&\text{Phenyl} \\
&\text{Tolyl} \\
&\text{(2,6-Diethyl) Phenyl} \\
&\text{R2} \\
&\text{Cyclohexyl} \\
&\text{Tolyl} \\
&\text{Tolyl} \\
&\text{Tolyl} \\
&\text{Cyclohexyl} \\
&\text{Methyl} \\
&\text{Ethyl} \\
&\text{Ethyl} \\
&\text{Methyl} \\
&\text{Ethyl} \\
&\text{R3} \\
&\text{H} \\
&\text{H} \\
&\text{H} \\
&\text{H} \\
&\text{MORPHOLINE} \\
&\text{MORPHOLINE} \\
&\text{MORPHOLINE}
\end{align*}
\]

Figure 1.1 The schematic diagram for substituted thiourea derivatives