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REVIEW

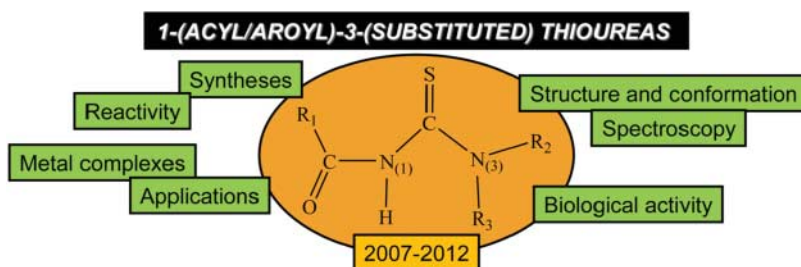
A review on the chemistry, coordination, structure and biological properties of 1-(acyl/aroyle)-3-(substituted) thioureas

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This review provides an overview of the chemistry, structure and potential applications of 1-(acyl/aroyle)-3-(mono-substituted) and 1-(acyl/aroyle)-3,3-(di-substituted) thioureas, with general formula $R^1C(O)N_{(1)}HC(S)N_{(3)}R^2R^3$. In recent years, the title compounds have found extensive applications as ligands in coordination chemistry. The effect that nitrogen substituents exert on the intra- and intermolecular hydrogen-bonding interactions is discussed, including their role on the coordination properties displayed by these ligands. Novel applications of transition metal complexes bearing 1-(acyl/aroyle)-3-(mono- and di-substituted) thioureas are introduced. Biological aspects are also highlighted. As recently demonstrated, high-throughput screening assay and structure–activity analyses are feasible for this class of compounds. The chemical versatility of 1-(acyl)-3-(substituted) thiourea molecules and the derived metal complexes, together with the possibility of determining detailed structural properties, join biological applications in a promising interdisciplinary approach. The bibliography includes 382 references with emphasis on the literature appearing after 2007.



Keywords: biological activity; metal complexation; molecular structure; sulfur chemistry; thiourea; vibrational properties

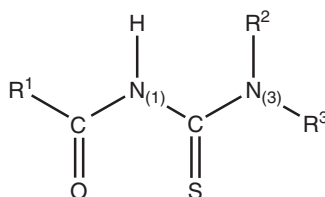
1. Introduction

It is well known that compounds containing the ($>N-C(S)-N<$) functionality are identified as thioureas.[1,2] These may be mono-, di-, tri- or tetra-substituted thiourea derivatives depending

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upon the extent of substitution on the nitrogen atoms. The 1-(acyl/aroyle)-substitution implies the presence of a carbonyl group bonded to the thiourea core. The first example of this class of molecule, the $\text{CH}_3\text{C}(\text{O})\text{NHC}(\text{S})\text{NH}_2$ species, has been known for more than a century.[3] Substitution can occur also on the second nitrogen atom, giving 1-(acyl/aroyle)-3-(mono-substituted) and 1-(acyl/aroyle)-3,3-(di-substituted) thioureas, with general formula $\text{R}^1\text{C}(\text{O})\text{N}_{(1)}\text{HC}(\text{S})\text{N}_{(3)}\text{R}^2\text{R}^3$ (Scheme 1), where R may be an alkyl, aryl, aralkyl or heterocyclic substituent.



Scheme 1. General chemical structure of 1-(acyl/aroyle)-3-substituted thioureas.

The last decade has witnessed an unprecedented upsurge in the synthesis and applications of a wide range of 1,3-di-substituted thioureas. 1-(acyl/aroyle)-3-substituted thioureas are extremely versatile starting materials for the synthesis of a wide variety of heterocyclic compounds due to the presence of two free hydrogen atoms, one at each nitrogen atom.[4] In 2007, Aly et al. [5] updated the available information on the chemistry of aroyle substituted thioureas and their potential applications. Moreover, it has been recognized that the presence of hard and soft donor sites in these compounds offers a huge bonding potential since both carbonyl and thiocarbonyl groups can coordinate metallic ions in different manners. The coordination chemistry of 1-(acyl/aroyle)-3-(alkyl)- and 1-(acyl/aroyle)-3,3-(di-alkyl)-thioureas, especially in relation to platinum group metals, was reviewed by Koch [6] more than 10 years ago. Acylthiourea compounds are versatile “collectors” for the selective complexation of soft metal cations used in mineral extraction by froth flotation processes.[7,8] In recent years, a variety of metal complexes having thiourea ligands have been prepared and probed as useful intermediates used in environmental control and as ionophores in ion-selective electrodes (ISEs).[9,10] New properties and applications for these metal complexes involve interesting luminescent properties [11] and their ability to function as precursor for metal sulfide nanoparticles, among others.[12,13]

The biological importance of this kind of compounds has been highlighted recently.[14] Also, the availability of X-ray crystal structures on the title compounds has grown impressively in the past few years. Thus, interesting structure–activity analyses are feasible for this class of compounds, including high-throughput screening on libraries and structure–activity relationship analysis to optimize drug-like properties.[15]

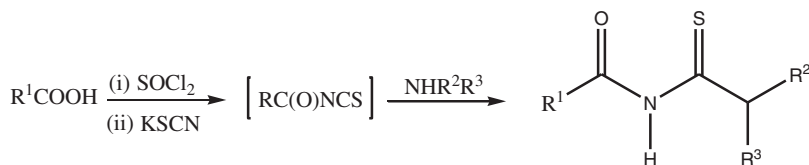
In this review, special attention is devoted to the synthesis and chemistry, and structural, spectroscopic and biological aspects of 1-(acyl/aroyle)-3-substituted and 3,3-di-substituted thioureas. We focus our attention on the literature appearing after 2007, although some earlier works will be mentioned in order to give proper perspective on new developments.

2. Synthesis

2.1. Preparation of acylthioureas

The most important synthetic access to thioureas is still the method reported by Douglas-Dains,[16] involving the reaction of acyl isothiocyanates produced in situ by the reaction of the

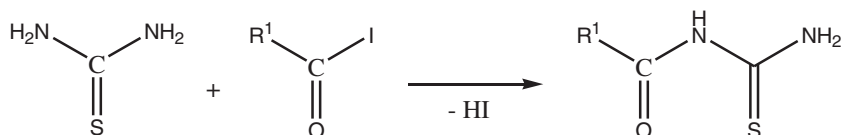
corresponding acid chloride with potassium or ammonium thiocyanate,[17] followed by treatment with a suitably substituted aliphatic or aromatic amino-compound (Scheme 2). This reaction is usually carried out in dry acetone or acetonitrile; however, other conditions have also been used including ionic liquids like 1-butyl-3-methylimidazolium tetrafluoroborate-, [18] PEG-400 [19] or solvent-free conditions.[20]



Scheme 2. Isothiocyanate-mediated synthesis of 1-(acyl/aryl)-3-substituted thioureas.

As reported earlier, acylthioureas can also be prepared by treatment of aminothiocabonylimidoyl chlorides with potassium thiocyanate followed by hydrolysis,[21] or reacting *N*-acyl aminoimidoyl chlorides with hydrogen sulfide.[22–24]

As shown in Scheme 3, acyl iodides react with thiourea at room temperature to give the corresponding *N*-acetyl derivative, as recently showed by Voronkov and coworkers.[23]



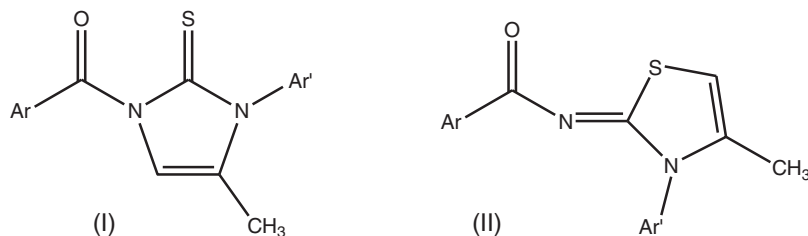
Scheme 3. Synthesis of 1-acyl thioureas from thiourea and acyl iodides.

Other available methods for the synthesis of 1-acyl-thioureas [25] includes the treatment of methyl-*N*-arylcarbomodihiates [26] and acyl isothiocyanates [27] with amines and the reaction of iminophosphoranyl thioureas with carboxylic acids.[28] The hydrolysis of *N*-aminothiocarbonylcarbodiimides with mineral acids also affords the corresponding 1-acyl-substituted thiourea product.[29] More recently, Maddani and Prabhu [30] showed that the condensation of amines and carbon disulfide in aqueous basic medium followed by reaction with amines is an efficient method for the synthesis of symmetrical and unsymmetrical substituted thioureas.

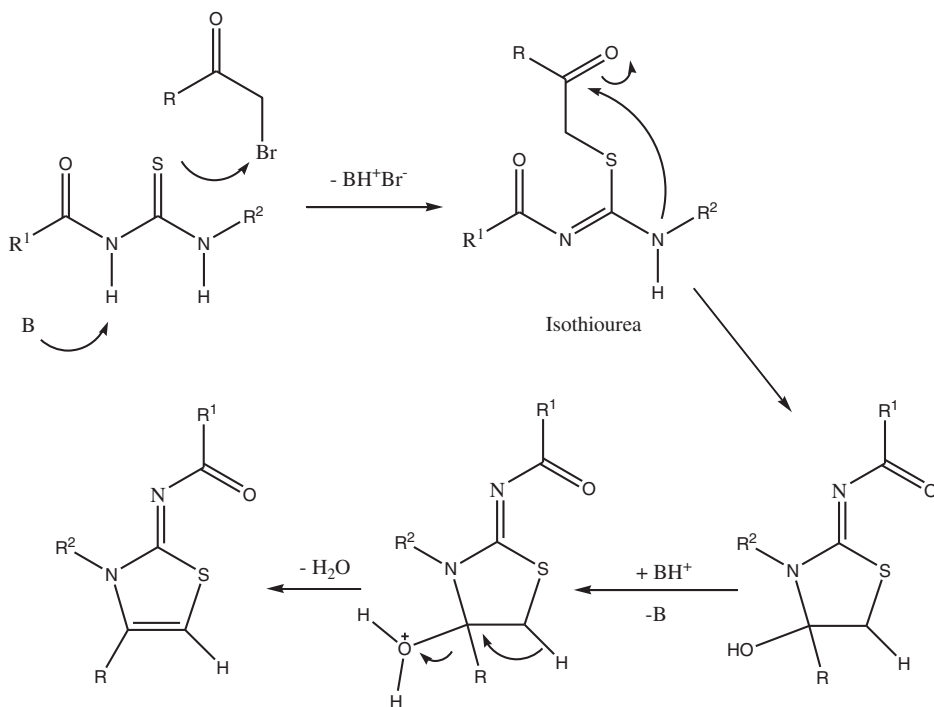
2.2. Heterocyclization reactions

Among the most important heterocyclization reactions of thioureas are the condensations with α -halocarbonyl compounds yielding 2-amino-1,3-thiazoles.[31] Zou and coworkers reported the formation of imidazole-2-thiones by cyclization of 1-aryl-3-aryl thioureas with enolizable α -halocarbonyl compounds.[32] Soon after, Wang et al. [33] independently published similar results when the reaction was performed in aqueous medium. However, Saeed et al. reported that under these conditions the thermodynamically more stable isomeric thiazol-2-imines (see structure II in Scheme 4) are the authentic products instead of the imidazole-2-thiones (structure I in Scheme 4), as unequivocally established by X-ray crystallography. Indeed, these isomeric compounds are hard to differentiate on the basis of spectroscopic, mass and elemental analyses data.[34–36]

Subsequently, Patel and coworkers [37] using 1-benzoyl-3-phenyl thioureas with bromine and enolizable ketones reached the same conclusion, that is, thiazolidene-2-imine derivatives are



Scheme 4. Chemical structure of isomeric imidazole-2-thione (I) and thiazol-2-imine (II) compounds.



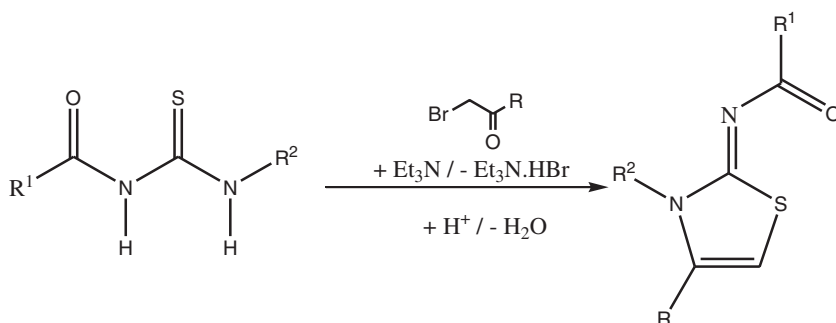
Scheme 5. Proposed mechanism [adapted from 34,37] for the heterocyclization reactions of 1-(acyl/aryl)-thioureas with α -halocarbonyl compounds.

the reaction products, as supported by X-ray structure determination of 1-benzoyl-3-phenyl-4-methylthiazolidene-2-imine. The proposed mechanism [34,37] involves the formation of an isothiurea intermediate, as shown in Scheme 5.

In an eco-friendly variation of the same method, the synthesis of fluorinated imino-3-aryl-4-methyl-1,3-thiazoline derivatives was performed by the cyclization of corresponding 1-(fluorobenzoyl)-3-(fluorophenyl)thioureas with α -bromoacetone in basic aqueous media.[38] Using the same approach, some 3,5-dichloro-*N*-(3-(4-substitutedphenyl)-4-phenylthiazole-2(3*H*)-ylidene)benzamides were prepared by base-catalyzed cyclization of the corresponding 2,4-dichloro-*N*-benzamides with acetophenone.[39] Similarly, *N*-(4-methyl-3-tolylthiazol-2(3*H*)-ylidene) substituted benzamides were synthesized in good to excellent yields by a microwave-irradiation-assisted base-catalyzed direct cyclization of the corresponding 1-tolyl-3-aryl thioureas

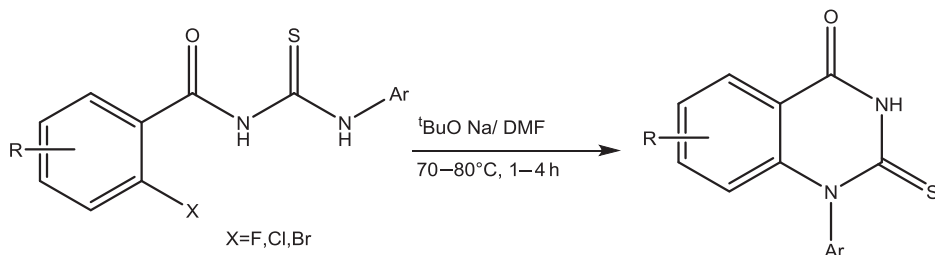
with 2-bromoacetone in a solvent-free medium.[40,41] Regioselective syntheses of 2-arylimino-3-aryl-thiazolidin-4-ones were carried out by cyclization of 1-aryl-3-aryl thioureas with chloroacetyl chloride in the presence of pyridine in dioxane.[42] By using microwave irradiation and solvent-free conditions, a variety of *N*-(5-acetyl-4-methyl-3-(substituted phenyl)-thiazol-2-ylidene)-4-methyl (substituted) benzamides were obtained by heterocyclization of the corresponding 1-substituted benzoyl-3-arylthioureas with 3-chloropentane-2,4-dione.[43] Moreover, 4-amino-2-iminothiazole derivatives were recently prepared by the cyclization of unsymmetrical 1-aryl-3-arylthioureas with a variety of 2-bromo-2-arylacetonitriles in the presence of triethylamine.[36,44]

Patel and coworkers [4] prepared substituted thiazol-2-imines related to pifithrin- α by the condensation of carbonyl compounds and 1,3-di-substituted thioureas (Scheme 6) using 1,10-(ethane-1,2-diyl)dipyridinium dibromide as a brominating agent. It is worth mentioning that unsymmetrical 3,3-di-substituted thioureas gave regioselective products with symmetrical ketones, whereas symmetrical thioureas gave regioselective products with symmetrical carbonyl compounds as a result of the regioselective bromination of ketones.[37]



Scheme 6. General strategy for condensation of carbonyl compounds and 1,3-di-substituted thioureas.

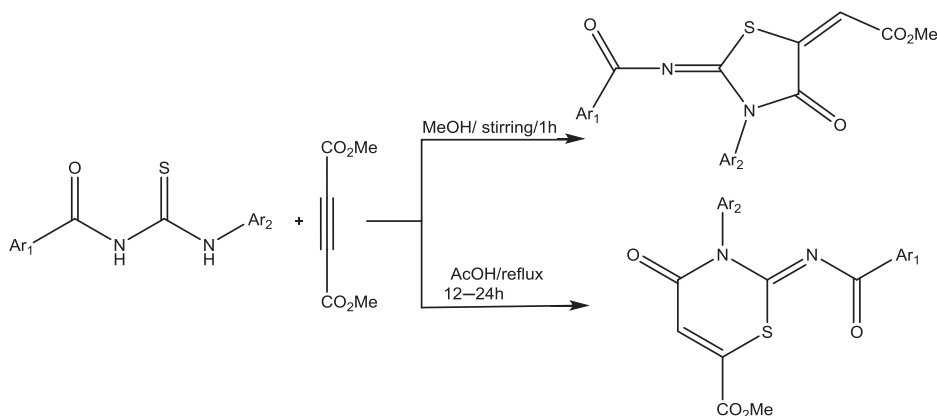
The base-catalyzed intramolecular nucleophilic cyclization of 1-(2-haloaryl)-3-aryl thioureas resulted in the formation of the corresponding 1-aryl-2-thioxo-2,3-dihydro-1*H*-quinazolin-4-ones (Scheme 7). Mechanistic studies support an intramolecular nucleophilic substitution ($S_{\text{N}}\text{Ar}$ mechanism) rather than an intramolecular aromatic substitution ($S_{\text{RN}}1$ mechanism).[45]



Scheme 7. Base-catalyzed intramolecular nucleophilic cyclization of 1-(2-haloaryl)-3-aryl thioureas.

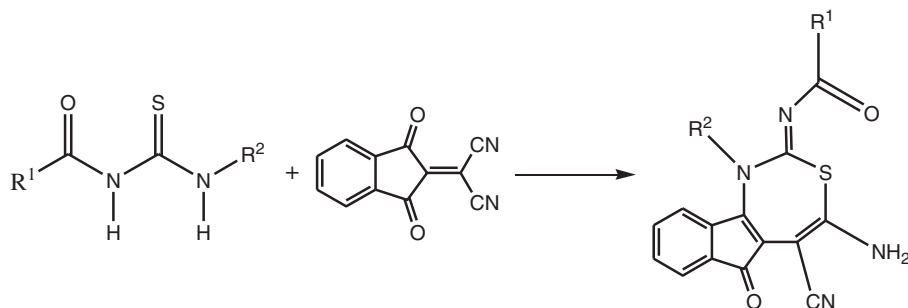
The second important heterocyclization of acyl thioureas includes the reaction with dimethyl acetylenedicarboxylate (DMAD), a highly electrophilic reagent, a potent Michael acceptor and a

widely employed dienophile in cycloaddition reactions, such as the Diels–Alder reaction. Thus, as shown in Scheme 8 (top), methyl [4-oxo-2-(substituted benzoylimino)-3-(substituted phenyl)thiazolidin-5-ylidene]acetates were obtained by cyclocondensation of 1-acyl-3-arylthioureas with DMAD in methanol at room temperature in excellent yields, whereas methyl 2-benzamido-4-oxo-3-aryl-3,4-dihydro-2*H*-1,3-thiazine-6-carboxylates were obtained when reaction was carried out in refluxing acetic acid (Scheme 8).[46] In a similar approach, reaction of 1-aryl-3-arylthioureas with DMAD in dichloromethane catalyzed by triphenylphosphine at -5°C led to (*Z*)-methyl 2-[(*Z*)-2-(4-arylthio)-4-oxo-3-aryl-1,3-thiazolidin-5-ylidene]acetates.[47] Also, 2-benzamido-4-oxo-3-aryl-3,4-dihydro-2*H*-1,3-thiazine-6-carboxylates are accessible by this method.[48]



Scheme 8. Different routes for cyclocondensation of 1-(acyl)-3-(aryl)thioureas with dimethyl acetylenedicarboxylate (DMAD) in methanol at room temperature (top) and in refluxing acetic acid (bottom).

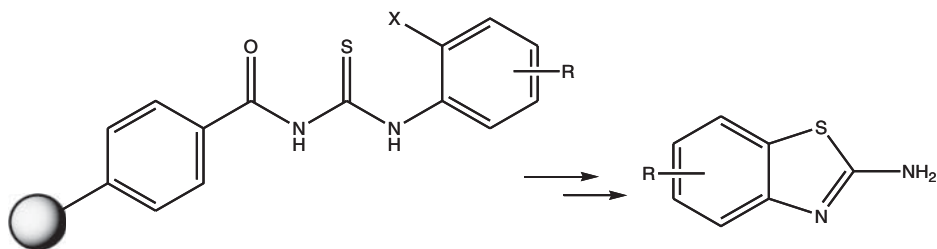
The reaction between 1-aryl-3-arylthioureas with 2-(1,3-dioxindan-2-ylidene)malononitrile furnished indeno[1,2-*d*][1,3]thiazepines (Scheme 9) in 70–85% yields.[49]



Scheme 9. Reaction between 1-(aryl)-3-(aryl)thioureas with 2-(1,3-dioxindan-2-ylidene)malononitrile.

A small, focused library of substituted 2-aminobenzothiazoles (Scheme 10) was prepared by solid-phase synthesis, involving the cyclization of 1-acyl-3-phenyl thioureas. Hydrazine monohydrate was used as a useful deprotecting agent. The cyclization conditions used were a function

of the identity of the ortho substituent on the phenyl ring. Thus, for X = H, F, and Br, bromine and acetic acid, NaH at 25°C, and NaH at 100°C in dimethylformamide were used, respectively.[50]



Scheme 10. Solid-phase synthesis of substituted 2-aminobenzothiazoles by cyclization of 1-(acyl)-3-(phenyl)thioureas.

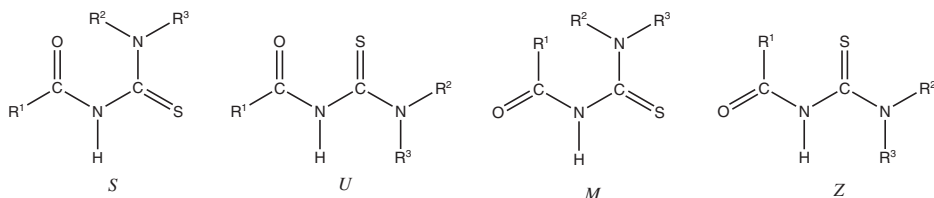
Finally, 1-acyl thioureas are versatile reagents for the regioselective synthesis of 3-aryl/alkylamino 5-aryl/alkyl 1,2,4-oxadiazoles.[51]

3. Molecular and crystal structure

Several crystal structures of 1-acyl-thiourea compounds have been reported, establishing that the molecular structure depends on the degree of substitution at the N₍₃₎ atom. A summary of recently published X-ray crystal structures of 3-mono- [52–190] and 3,3-di-substituted thioureas [191–216] are given in Tables S1 and S2, respectively. Although not exhaustive, the list of molecules showed in these tables serves as an updated review on the available molecular and crystal structures and provides a guide for further analysis of structural aspects. The most relevant structural aspects are summarized below.

3.1. Conformational and structural properties

In principle, several conformations are feasible for this kind of compound, depending on the dihedral values around the acyl-N₍₁₎ bond and the adjacent C–N₍₃₎–C bonds.[151,178,217] Following Woldu and Dillen,[218] the four main forms can be denoted as *S*, *U*, *M* and *Z*, where the letter reflects the position of the C=O and C=S double bonds relative to the vertically drawn N–H bond (Scheme 11).



Scheme 11. Plausible conformations of 1-(acyl)-3-substituted thioureas around the central –C(O)NHC(S)N< moiety. Each conformation is represented by capital letters according to [218].

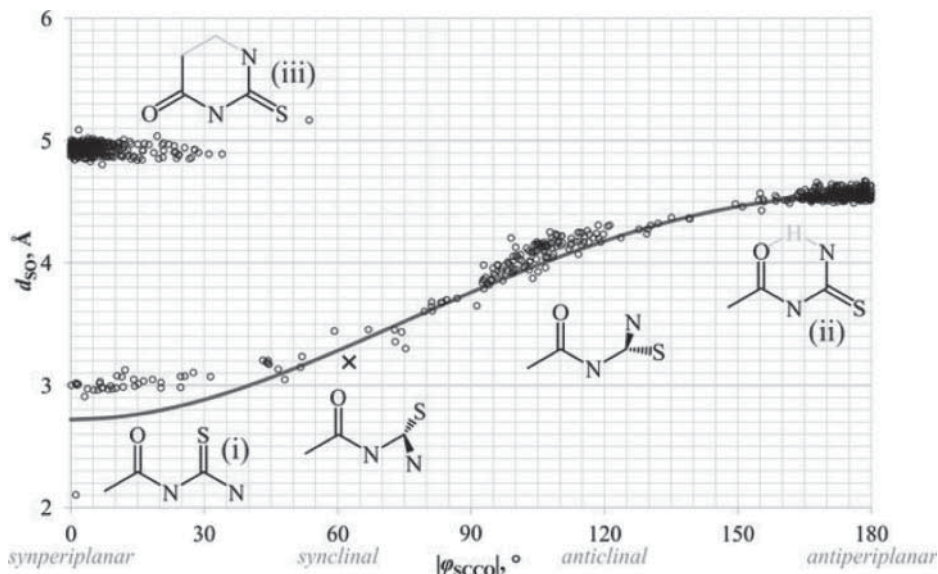
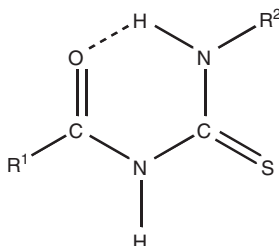


Figure 1. Plot of S–O distance (d_{SO}) against absolute value of S=C–C=O torsion angle ($|\varphi_{SCCO}|$) for 739 structures containing CC(=O)NC(=S)N fragment (taken from [216] and reproduced by permission of the International Union of Crystallography).

In a recent article, Becker and coworkers [216] analyzed 739 structures containing the $-\text{C}(\text{C}=\text{O})\text{N}(\text{C}=\text{S})\text{N}-$ moiety found in the Cambridge Crystallographic Database. From this set, a correlation between the S...O distance (d_{SO}) and C=S...O=C improper torsion angle (φ_{SCCO}) in terms of 980 numerical values of bond lengths and bond angles was determined. The graphical representation of these data is shown in Figure 1 (reproduced with permission of the International Union of Crystallography). From this study, the prevalence of the *S* and *U* forms are clearly established. In particular, for 1-(acyl/aryl)-3-(mono-substituted) thiourea derivatives, with $\text{R}^2 = \text{H}$, a local planar structure of the central $-\text{C}(\text{O})-\text{NH}-\text{C}(\text{S})-\text{NH}-$ moiety is preferred, with opposite orientation between the C=O and C=S double bonds (“S-shape”). As shown in Scheme 12, in this conformation the C=O and H–N groups form a pseudo-six-membered ring, favoring an intramolecular interaction through a hydrogen bond.[116,158,183] On the other hand, when the formation of a suitable hydrogen bond is prevented, as in 1-(acyl/aryl)-3,3-(di-substituted) thiourea derivatives ($\text{R}^2, \text{R}^3 \neq \text{H}$), the *anticlinal* geometry (*U* form) is preferred.[219]



Scheme 12. *S*-shape conformation for 1-(acyl/aryl)-3-(mono-substituted) thioureas stabilized by a C=O...H–N intramolecular hydrogen bond.

The conformation around the amidic group has been also studied. A search in the Cambridge Crystallographic Database for the fragment $\text{Ph}-\text{C}(\text{O})-\text{N}-\text{C}(\text{S})-\text{N}-\text{Ph}$ yielded 116 hits.[164]

In all of them, the torsion angle $\text{O}=\text{C}-\text{N}-\text{C}$ adopts values from -13° to 24° representing near-*cis* conformations.

From the analysis of the available crystal data, it is worth noting that a definite trend in the C–N bond distances is recognized,[6,177,220] with the lengths increasing in the order $\text{C}(\text{S})-\text{N}_{(3)} < \text{C}(\text{O})-\text{N}_{(1)} < \text{C}(\text{S})-\text{N}_{(1)}$. Thus, it is likely that resonance interactions between the nitrogen lone pairs and the $\text{C}=\text{O}$ and $\text{C}=\text{S}$ double bonds are extended over the whole planar $-\text{C}(\text{O})\text{NHC}(\text{S})\text{NH}-$ moiety, similar to that reported for the related thiocarbamate species.[148,218,221–223]

3.2. X-ray crystal packing

The crystal packing of 1-(acyl)-3-(alkyl)thiourea compounds is usually dominated by hydrogen-bonding interactions, subtle differences in the substituents attached to the thiourea group seem to determine the preference of the $\text{N}-\text{H}\cdots\text{X}=\text{C}$ ($\text{X}=\text{O}$ or S) network. The most typical arrangement consists of centrosymmetric dimers connected by intermolecular $\text{N}-\text{H}\cdots\text{S}$ hydrogen bonds [148, 224] where the donor is an amide-like $\text{N}-\text{H}$ group. Very recently, Pérez et al. [210] reported that a search of the Cambridge Structural Database for acyl thiourea substructures revealed 440 such crystal structures. From this analysis, the majority (236 structures) of the reported compounds display a characteristic intermolecular pattern, forming dimers *via* $\text{N}-\text{H}\cdots\text{S}$ hydrogen bonding. This interaction can be better described as an $\text{R}_2^2(8)$ hydrogen-bonding motif,[200] which is stabilized by an eight-membered ring.

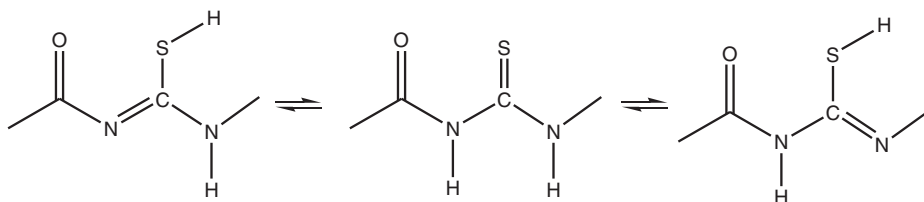
Other $\text{D}-\text{H}\cdots\text{A}$ patterns are also known, with $\text{N}-\text{H}\cdots\text{O}$, $\text{N}-\text{H}\cdots\text{S}$ and/or $\text{C}-\text{H}\cdots\text{O}$ forming infinite chains,[145] two-dimensional sheets [124] or three-dimensional networks with a combination of dimers and chains.[135] Bifurcated $\text{N}-\text{H}$ hydrogen bonds are also usually observed,[65,216,225] the $\text{N}-\text{H}$ group forming both an intramolecular and intermolecular $\text{N}-\text{H}\cdots\text{O}$ hydrogen bond.[205] The analysis of selected isomeric species reveals that intra- and intermolecular hydrogen bonds played an essential role in determining the specific conformation around the planar thiourea moiety.[116,117,149]

In the case of 1-acyl-3,3-disubstitued thioureas, the lack of a second $\text{N}_{(3)}-\text{H}$ donor contributes to major differences in the crystal structure, when compared with the mono-substituted analogues. In general, bifurcated $\text{C}-\text{H}\cdots\text{O}$ hydrogen-bond interactions are mainly found, giving rise to chains whose links are composed of alternating centrosymmetrical dimers ($\text{R}_2^2(10)$ and even $\text{R}_2^2(20)$ motifs). These results confirm the important role of $\text{C}-\text{H}\cdots\text{O}$ hydrogen bonds in the molecular conformation and in the crystal structure.[200,210] In substituted aromatic species, $\pi-\pi$ stacking interactions between R_1 and R_2 are also observed.[134,176,191]

3.3. Thione–thiol tautomerism

Similar to thiosemicarbazones,[226] thione–thiol tautomerism is plausible for acylthioureas since a thioamide $-\text{NH}-\text{C}=\text{S}-$ functional group is present, as well as a carbonyl group, which can accept hydrogen-bonding donor groups.[227] In Scheme 13, the thione (middle structure) and thiols tautomers are shown.

The thione form is strongly preferred, and to the best of our knowledge, there are no reports on compounds showing the thiol form as the most stable tautomer. Zhou and coworkers [147] reported the infrared spectrum of solid 1-(2-fluorobenzoyl)-3-(4-methoxyphenyl) thiourea, where a weak band appearing at 2438 cm^{-1} could be assigned to the $\nu(\text{S}-\text{H})$ stretching mode. Aydin et al. [143] suggested that tautomeric equilibrium exists in 4-(3-benzoylthioureido)benzoic acid, promoted by an intramolecular proton shifts between the thioketo-sulfur and the amine-nitrogen, via intramolecular hydrogen bonding $\text{N}-\text{H}\cdots\text{S}$ or $\text{S}-\text{H}\cdots\text{N}$.



Scheme 13. Thione–thiol tautomerism plausible for acylthioureas.

4. Spectroscopic properties

The vibrational properties of the title compounds have been investigated mainly by using Fourier transform infrared (FTIR) and Raman spectroscopies. In recent years, these analyses have been complemented with quantum chemical calculations, which allowed for a better description of the fundamental modes.[199] For instance, for $R^1C(O)NHC(S)NHR^2$ compounds, quantum chemical calculations predict that the two $\nu(N-H)$ stretching modes are very different in frequencies and intensities. In fact, the $\nu(N-H)$ fundamental of the $N-H$ group involved in the intramolecular hydrogen bond appears as a strong absorption at lower wavenumbers (typically observed at around 3150 cm^{-1}) when compared with the amide-like $N-H$ group expected as a broadband at ca. 3350 cm^{-1} . [116,117,183]

The detailed analysis of the region between 1700 and 1800 cm^{-1} is very instructive, since the $\nu(C=O)$ carbonyl stretching mode is sensitive to the local environment. In general, relative low values are observed for the $\nu(C=O)$ fundamental of mono-substituted acyl-thioureas, which is in accordance with the presence of a intramolecular $C=O\cdots H-N$ interaction in the $-C(O)NHC(S)NH-$ moiety.[219] Alternatively, resonance interactions between the carbonyl and the phenyl ring have been invoked for explaining the red-shift observed in 1-(benzoyl)-3-substituted thiourea.[151] It is worthy to mention that the $C=O$ stretching mode is appreciably coupled with the $C-N$ stretching and the $N-H$ bending modes, as observed for related compounds.[228–230]

Infrared spectroscopy has been also applied for the characterization of metal complexes with thioureato ligands (see below). In many cases, the absence of a broadband above 3200 cm^{-1} is a direct indication that deprotonation of the thiourea group occurs upon complexation. Moreover, deprotonation induce electronic delocalization and the $\nu(C=O)$ stretching vibration frequency decreases up to 180 cm^{-1} , indicating that coordination through the oxygen atom may also occur.[204]

In (thio)amide compounds several infrared absorption bands which are called “(thio)amide bands” are important for studying structural and electronic properties because they are sensitive to intermolecular hydrogen bonding and conformational changes.[231] This approach has also recently been applied in the analysis of urethane [231] and thiourea derivatives.[219] Four characteristic vibrational bands can be defined in compounds containing the thioamide group, called thioamide bands I, II, III and IV, with large contributions from $\delta(N-H)$ (I), $\nu(C-N)$ (II and III) and $\nu(C=S)$ (IV) motions which are usually reported around 1500 , 1300 , 1100 and 750 cm^{-1} , respectively.[147,232] However, the region for the $\nu(C=S)$ (thioamide band IV) is tentative and controversies are found in the literature. It should be noted that in the thiourea molecule, the $\nu(C=S)$ is assigned to the absorption appeared at 1094 cm^{-1} in the infrared spectrum (1105 cm^{-1} Raman).[233] For more complex molecules, the formation of $C=S\cdots H-X$ intermolecular hydrogen bonds seems to influence the frequency of the $\nu(C=S)$ mode.[197,199,234] Similar disagreement are also found for other vibrational modes: as recognized by Athiş et al. [118] the

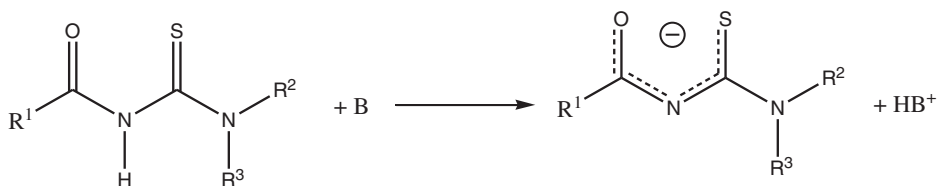
identification of C–N vibrations usually is a difficult task, since the presence of other modes from the R¹ and R² groups are possible in this region.

Electronic properties of 1-(acyl/aryl)-3-(alkyl)-substituted thioureas have been also studied. 1-Benzoyl thiourea derivatives usually show interesting luminescent properties that strongly depend on the molecular structure features, especially the tilt angle of the central –C(O)NHC(S)N– group. Dual fluorescence has been observed in polar solvent, consistent with locally excited and excited state intramolecular proton transfer or twisted intramolecular charge transfer emission.[147] 1-(2-Fluorobenzoyl)-3-(4-tolyl) thiourea displays double fluorescence bands in both non-polar and polar solvents. The fluorescence emission at 350–360 nm originates from the transitions of $\pi^* \rightarrow \pi$ state and is assigned to S₂ fluorescence, supported by MP2 and CASSCF calculations.[148] Fluorescent and luminescent chemosensors base on 1-(aryl)-3,3-(dialkyl) thioureas for the detection of anions have been successfully developed.[235]

5. Metal complexes

An early review of the coordination chemistry of 1-(acyl)-3-substituted thioureas, particularly their coordination with some first- and second-row transition metals was published by Beyer et al. [236] and updated in 2001 in Koch's [6] review. 1-(Aroyl/acyl)-3-(alkyl/aryl)-thioureas containing both carbonyl (C=O) and thiocarbonyl (C=S) groups can coordinate to metals using both oxygen and sulfur atoms. It was recognized that the presence of these hard and soft donor sites offers a huge array of bonding possibilities, since these thioureas can be considered as substituted analogues of β -diketones acting as potential S,O-donor ligands.[237–239] Three different coordination modes have been found so far for 1-(benzoyl)-3,3-(di-alkyl/aryl) thiourea ligands in their mononuclear transition metal complexes. They are a monobasic bidentate or chelating mode (O,S),[240] and neutral monodentate (S),[241] and neutral bidentate (O,N) [242] modes. An update of newly reported X-ray structures of metal complexes bearing 1-(acyl)-substituted thioureas is presented in Table S3 in the Supporting Information.[53,201,204,208,243–269]

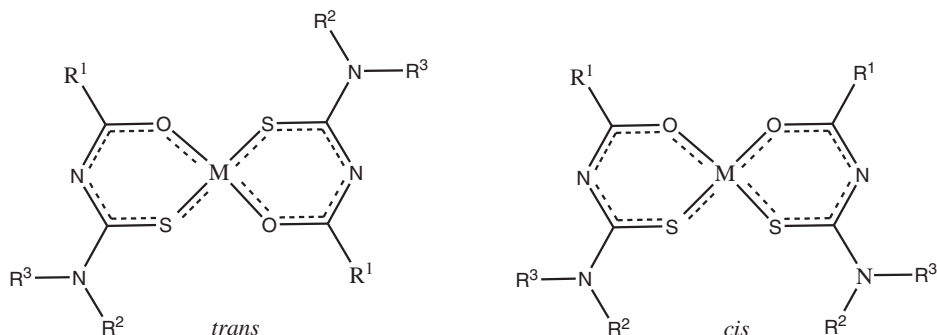
The ionization constants of benzoyl thiourea derivatives have been reported recently.[270] The negative charge is delocalized on the central thioureato group, as shown in Scheme 14.



Scheme 14. Deprotonation of the N₍₁₎–H group in 1-(acyl/aryl)thioureas to form the corresponding thioureato anion.

The chelating coordination mode, involving formation of square planar bis(chelate) metal complexes of the type *cis*-[M{ κ^2 S,O-R¹C(O)NC(S)NR²R³}₂] is of common occurrence, especially when 3,3-di-substituted thioureas are considered. This coordination mode is shown in Scheme 15. In the past few years, Arslan's group has prepared a series of metal complexes bearing 1-acyl thiourea as ligands.[243,249,252,253,255,259,271] For instance, 2,2-diphenyl-*N*-(diethylcarbamothioyl)acetamide, HL¹, and bis(2,2-diphenyl-*N*-(diethylcarbamothioyl)acetamido) nickel(II), Ni(L¹)₂, were both characterized by a single-crystal X-ray diffraction study. The ligands coordinate bidentate (O, S chelated) to the metal yielding neutral complexes of the type *cis*-[ML₂].[208] *N*-(*R*-carbamothioyl)cyclohexanecarboxamides (*R*: diethyl, di-*n*-propyl, di-*n*-butyl,

diphenyl and morpholine-4) and their Ni(II) and Cu(II) complexes have also been synthesized and characterized, and shown to be *cis*-complexes with slightly distorted square planar coordination of the central nickel by two oxygen and two sulfur atoms.[201]



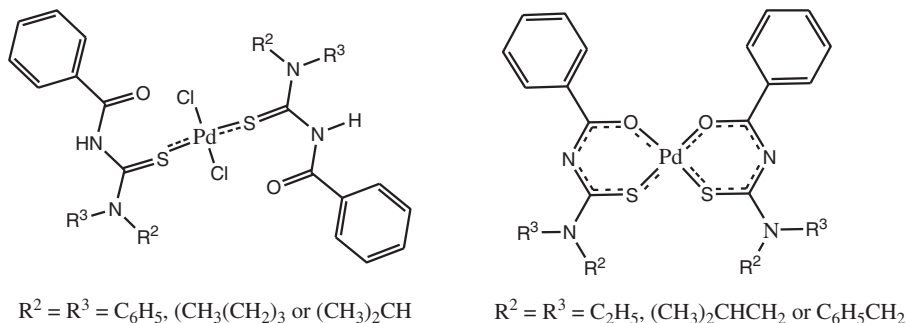
Scheme 15. Formation of square planar bis(chelate) metal complexes of the type *cis*-(right)/*trans*-(left) $[M\{\kappa^2S, O-R^1C(O)NC(S)NR^2R^3\}_2]$.

Several Ni(II) complexes were also synthesized by the group of Pérez, Duque and coworkers using 1-(benzoyl)-3,3-(di-substituted) thioureas. The Ni(II) ion is coordinated by the S and O atoms of two ligands in a slightly distorted square planar coordination geometry, the two O and two S atoms are mutually *cis* to each other.[256,257,261,272] Using similar procedures, a series of Ni(II), Pd(II) and Cu(II) metal complexes with closely related aroylamino-carbo-*N*-thiopyrrolidine ligands were prepared. The X-ray structures were determined for a couple of cases, showing that the usual chelating coordination around the Ni(II) metal prevails.[267,273]

The preference for the square planar coordination is also observed for Pd(II) and Pt(II) d^8 metals, as expected. Cîrcu et al. [247] reported the use of simple 1-(benzoyl)-substituted thiourea derivatives as ancillary ligands in luminescent platinum(II) 2-phenylpyridine complexes. Mohr and coworkers utilized 2,6-F₂C₆H₃C(O)NHC(S)N(C₂H₅)₂ as a ligand in the preparation of monocationic Pd(II) and Pt(II) complexes with O,S bidentate coordination, together with ^tBu₂bpy as a co-ligand.[254] Very recently, two glucose-derived thioureas containing the 4-nitrobenzoyl group were prepared along with their Pd(II) complexes. In these compounds, the thiourea coordinates to the metal as monoanionic O,S chelate ligands.[274]

Also Pd(II) complexes of 1-(benzoyl)-3,3-(di-alkyl) thiourea have been synthesized.[250] Unexpectedly, these ligands exhibited two different coordination modes with Pd(II) in complexes obtained under similar reaction conditions. As shown in Scheme 16 (adapted from [250]) the 1-(benzoyl)-3,3-(di-alkyl) thiourea ligands are able to exhibit neutral monodentate coordination through the S atom as well as the normal monobasic O,S bidentate coordination.[250]

New complexes of Co(II) and Cu(II) with 1-(acyl)-3,3-(di-substituted) thioureas have been prepared and characterized by elemental analysis and spectroscopic techniques.[275] The Co(II) complexes with 1-furoyl-3,3-diethyl- and 1-benzoyl-3,3-diethyl-thioureas are isostructural with the analogous Ni(II) complex previously reported: the furoyl [272] and benzoyl [276] thiourea molecules adopt a *cis* conformation, bounded to the central ion by two S and two O atoms. Moreover, the structure of 1-(furoyl and benzoyl)-3,3-(diethyl) thiourea and its Co(III) complexes were determined by X-ray crystallography.[265] The structural data are consistent with a slightly distorted square planar coordination around the Co(III) with the C9O and C9S groups adopting a mutual *cis* conformation. Cobalt complexes with fluorobenzamide-substituted thioureas have been prepared by Weiqun's [277] group and their crystal structure showed that the Co(III) center is chelated by three ligand anions, each of which coordinates in the bidentate (O,S) anion mode.

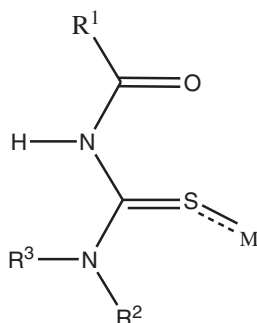


Scheme 16. Neutral monodentate through the S atom (left) and monobasic O,S bidentate (right) coordination modes found in Pd(II) complexes of 1-(benzoyl)-3,3-(di-alkyl) thioureas. Adapted from reference [250].

Within the octahedral geometry defined by the O_3S_3 donor set, the three S and O atoms occupy one face of the octahedron surrounding the metal atom (*fac* isomer). Bond angles deviate from the ideal octahedral geometry, with the *cis* angles ranging from 84.0° to 94.9° . [248] Similar structural properties have been determined for cobalt(III) complexes of the type $[Co(L)_3]$ containing the *N*-[di(alkyl/aryl)carbamothioyl]benzamide ligand. [260,268]

Nguyen and Abram [278] reported the feasibility of 1-(benzoyl)-3,3-(dialkyl) thioureas to form air-stable chelate complexes of rhenium and technetium. Irrespective of the oxidation states of the metals, the thiourea ligands act as monoanionic chelates. [279] The coordination sites of the metal ions can be controlled by the reaction conditions applied and by co-ligands such as phosphines or alcoholates. [278] The same group reported that $(NBu_4)[ReOCl_4]$ reacts with 1-benzoyl-3-picolythiourea (Hpicbtu) in acetone to form the deep-green oxorhenium(V) complex $(NBu_4)_2[Re_2O_2Cl_5(Hpicbtu)_2O]$ with the acylthiourea molecule showing an atypical bridging coordination geometry. [280]

Monodentate neutral coordination (Scheme 17) solely through sulfur is less common, and a few examples were early reported with soft d^{10} metal, such as Cu(I), [281,282] Ag(I), [283] Au(I), [241] and Hg(II) [284] complexes. This behavior resemble that encountered for the analogues 1-acyl-3-substituted selenoureas recently reviewed by Molter et al. [285] and Molter and Mohr. [286] Similarly, for the related *N*-phosphorylated thioureas $RNHC(S)NHP(O)(OR)_2$, the first example of coordination through the sulfur atom was the only found for Pd(II) complexes, as reported by Safin et al. [287]



Scheme 17. Neutral monodentate mode (through the S atom) favored for 1-(acyl/aryl)-3-(mono-substituted) thioureas.

A series of 1-furoyl 3-mono- and 3,3-di-substituted thioureas were used as ligands with Cd(II) and Hg(II) d^{10} metal ions.[288] Coordination through the sulfur atom of the thiocarbonyl group was observed in both series of thioureas studied, characterized by an intense low-frequency Raman signal located between 230 and 300 cm^{-1} , which was assigned to the metal–sulfur stretching mode in the complex.

Recent examples of monodentate coordination include the ligand *N*-[(dibenzyl/methyl)pentyl] carbamothioyl] benzamide, which exhibit exclusively neutral monodentate coordination through the sulfur atom to copper forming a distorted tetrahedral, CIP_2S around the Cu(I) center.[264] An X-ray diffraction study of the Ag(I) complex of the 1-(benzoyl)-3,3-(dibutyl) thiourea provided evidence that both chelate and monodentate coordination modes of complexation to silver(I) are present. Hence, each silver atom is coordinated to sulfur and oxygen atoms from one ligand in the (O,S) anionic mode and to bridging sulfur from another thiourea ligand.[269]

Other interesting examples where related 1-acyl thioureas display dual mono- and bi-dentate coordination can be found in the recent work by Gerber and coworkers as products of the reactions of 1-(benzoyl)-3,3-(dialkyl)-(HL₁) and 3,3-(diphenyl) thiourea (HL₂) with $[\text{Re}(\text{CO})_5\text{Br}]$. With HL₁, the complex *fac*- $[\text{Re}(\text{CO})_3(\text{HL}_1)_2\text{Br}]$ was isolated, in which HL₁ is coordinated as a neutral monodentate ligand *via* the thiocarbonyl sulfur atom. The reaction with HL₂ led to the dimeric complex $[\text{Re}_2(\text{CO})_6(\text{L}_2)_2]$, in which L₂ acts as a monoanionic bidentate with coordination via the C=O oxygen and the C=S sulfur atoms, as a bridge between the two rhenium(I) centers.[289]

Neutral monodentate coordination is found preferably in 1-acyl-3-mono-substituted thioureas (H₂L), since the C=O...N–H intramolecular hydrogen bond favors the coordination through the S donor atom to the metal ions. This coordination mode was already discussed in the review article by Koch [6] for 1-benzoyl-3-propyl thiourea, which readily forms *cis/trans*- $[\text{M}(\text{H}_2\text{L}-\text{S})_2\text{X}_2]$ complexes with M = Pt(II) and Pd(II) and their isomerization equilibrium was established by using an NMR technique.[290] *cis*- $[\text{M}(\text{L}-\text{S},\text{O})_2]$ Pt(II) and Pd(II) complexes of 1-(3,4,5-trimethoxybenzoyl)-3,3-diethyl thiourea undergo reversible photo-induced isomerization to the corresponding *trans* isomer upon irradiation with visible light in the 320–570 nm range.[291] Similarly, the simple compound 1-benzoyl-3-phenyl-thiourea ($\text{R}^1 = \text{R}^2 = \text{C}_6\text{H}_5$, $\text{R}^3 = \text{H}$) also acts as a monodentately neutral ligand through sulfur in $[\text{RhCl}(\text{C}_8\text{H}_{12})(\text{C}_{14}\text{H}_{12}\text{N}_2\text{OS})]$.[245] The geometry of the coordination sphere is approximately square planar about the Rh(I) atom, with two bonds to the π -electrons of the 1,5-cyclooctadiene ligand, one bond to the Cl^- ligand and one bond to the S atom of the thiourea ligand. Thus, the preferred coordination of the metal center toward soft donor ligands is clearly established.

The self-association of $[\text{Pt}^{II}(1,10\text{-phenanthroline})(\text{N-pyrrolidyl-}N\text{-}(2,2\text{-dimethylpropanoyl})\text{thiourea})]^+\text{Cl}^-$ (M) has been investigated by means of NMR spectroscopy. The formation of a “dimer” M–M aggregate is proposed and in the presence of the fluoranthene, interactions between the complex and the aromatic molecule occur in acetonitrile.[292] The dimerization of mixed ligand $[\text{Pt}^{II}(1,10\text{-phenanthroline})(1\text{-}2,2\text{-dimethylpropanoyl-}3\text{-pyrrolidyl thiourea})\text{Cl}][\text{Pt}^{II}(\text{phen})(\text{L}^1\text{-S},\text{O})\text{Cl}]$ was very recently established by Kotze et al.[293] The complex cation ($\text{M}^+ = [\text{Pt}^{II}(\text{phen})(\text{L}^1\text{-S},\text{O})]^+$) aggregates to form dimers, $2\text{M}^+ \rightleftharpoons \{\text{M}^+\}_2$, presumably via non-covalent face-to-face cation– π interactions. The association constants range from $K_D(\text{CD}_3\text{CN}) = 17 \pm 2\text{M}^{-1}$ to $K_D(30\% \text{ (v/v) D}_2\text{O}-\text{CD}_3\text{CN}) = 71 \pm 8\text{M}^{-1}$ at 299.3 K. Interestingly, in water-rich solvent mixtures from >30% (v/v) $\text{D}_2\text{O}-\text{CD}_3\text{CN}$ to pure D_2O , the extent of aggregation significantly increases until a critical aggregation concentration is reached, estimated to be 9.6 and 10.3 mM. Above this concentration, the formation of well-defined nano-structures (“metallogels”) formulated as $\{[\text{Pt}^{II}(\text{phen})(\text{L}^1\text{-S},\text{O})]^+\}_n\text{Cl}_y^-$ ($n, y > 2$) was indicated.

The structure of the complex formed between 1-(ethoxycarbonyl)-3-(*n*-butyl) thiourea and Cu(I) was reported by Boyd et al.,[53] resulting in discrete hexameric clusters displaying a Cu_6S_6 core consisting of two Cu_3S_3 chair-shaped rings linked by coordination of the deprotonated amide nitrogen atom to a copper atom in the adjacent ring, forming a paddlewheel structure.[53,294] Each

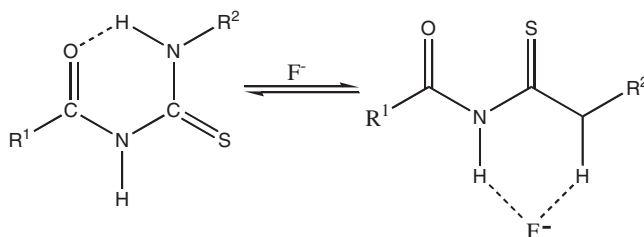
ligand acts as a $\mu^3(\text{N,S})$ donor to three copper atoms which define one face of the central copper octahedron. As pointed out by the authors, the orthogonal orientation of the ligands with respect to the copper octahedral face is such that the ligands are able to contribute, with significant electron density, to the Cu–S bonds, and to the overall stability of the cluster, from the delocalized $p\pi$ orbitals in the thioureido group. According to previous reports based on surface-enhanced Raman spectroscopy,[7] the formation of this complex is the key factor that determines the effectiveness of this ligand in the selective extraction of copper by froth flotation processes from copper sulfide ores.[53]

From the previous examples, it is clear that the peripheral substitution pattern significantly influences the coordination behavior of 1-(acyl/aroyle)-3-(substituted) thioureas, in close relation to the geometrical properties already discussed. Thus, when a tri-substituted thiourea ligand [1-(acyl/aroyle)-3,3-(di-substituted)thiourea] is employed, the thiourea coordinates principally as a monoanionic bidentate ligand, whereas a di-substituted thiourea [1-(acyl/aroyle)-3-(mono-substituted)thiourea] coordinates only through its sulfur atom as a neutral monodentate ligand which is stabilized through intramolecular hydrogen bonding.[245] One of these hydrogen bonds ensures that the sulfur and oxygen atoms are in a mutual *trans* position, which stabilizes the molecule in such a way that bidentate coordination is prevented. In the tri-substituted variation, this intramolecular interaction is not possible, which enables the ligand to coordinate through its sulfur and oxygen atoms simultaneously.[251]

6. Applications

6.1. Anion receptors and ionophores

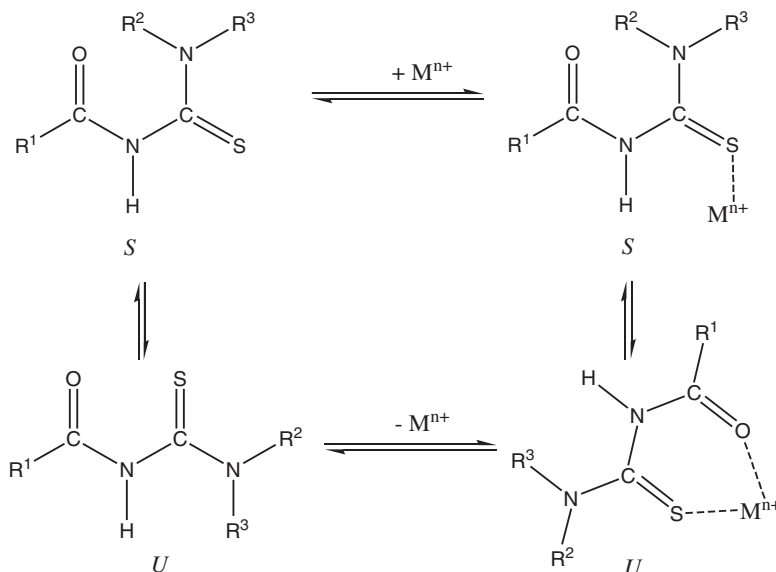
The hydrogen-bonding ability of the thiourea moiety has been used extensively in the construction of anion receptors.[295–297] Following the creative works by Fabbrizzi and coworkers,[298,299] a variety of receptors containing the urea and the thiourea groups have been designed for anion recognition.[235,300,301] The capabilities of 1-(acyl)-3-(mono)-substituted thioureas as anion receptors were first demonstrated by Zhang et al.[302,303] As shown in Scheme 18 for the case of fluoride anion, the thiourea group offers the central binding site for hydrogen bond interactions, whereas the R^1 and R^2 groups can act as chromophore units as well as interact with the guest anion.



Scheme 18. 1-(acyl)-3-(mono-substituted) thioureas as anion receptors.

The colorimetric recognition properties of a series of novel salicylic acid-oriented thiourea receptors have been described as promising compounds for developing novel selective and sensitive naked-eye recognition chemosensors for biologically important anions such as the fluoride ion.[304] The incorporation of an isatin group in acyl thiourea derivatives promotes a high binding affinity toward acetate anion, due to the cooperative multiple hydrogen bond interactions with both the acyl-thiourea moiety and N–H group in the indole unit of the receptor.[305]

1-(Aroyl)-3,3-(di-substituted) thioureas have been successfully used in environmental control, as ionophores in ISEs.[9,10,306] In earlier work, Otazo-Sanchez et al. [9] prepared 46 thiourea derivatives and demonstrated their potential use as ionophores for ISEs. Some of these were used as potentiometric sensors for heavy metals Pb (II), Cd(II) [263,307] and Hg(II).[308] A new approach reported recently involves the generation of new organic-inorganic hybrid materials prepared by covalently anchoring 1-furoyl thiourea on mesoporous silica, which exhibited good ability to remove Hg(II) from aqueous solutions.[309] When 1-(2-furoyl)-3-(1-naphthyl)thiourea was introduced into a sonogel-carbon matrix, it exhibited improved detection limits and good reproducibility toward Cd(II) ions ($0.8 \mu\text{g l}^{-1}$).[310] The structural and conformational properties of *N*-(diethylcarbamothioyl)benzamide both free and in complexes with heavy metal ions were studied and the behavior of the molecule as an ionophore and as a typical model for an ISE membrane has been simulated.[311] Based on spectroscopic data, the coordination to the metal by both the carbonyl and thiocarbonyl groups has been suggested. As already discussed, opposite orientation of the C=O and C=S groups (form *S*) is preferred in 1-(aroyl)-3,3-(di-substituted) thioureas, and thus an interconversion to the *U* form is assumed to take place upon metal coordination. In Scheme 19, the proposed mechanism is shown (adapted from [311]), from which it can be deduced that conformationally more flexible molecules are better than rigid ones as candidates for ISE ionophores.



Scheme 19. Proposed mechanism for the conformational interconversion between the *S* and *U* forms of 1-(aroyl)-3,3-(di-substituted) thioureas upon metal coordination. Adapted from reference [311].

Organic sulfur compounds are used in mineral extraction by froth flotation processes. Not surprisingly, 1-(acyl)-3-(substituted) thioureas have been found to be an important ligand for the selective complexation of soft metal cations. 1-(Ethoxycarbonyl)-3-(*n*-butyl) thiourea is a commercially available compound (Aero 5500,TM from Cytec Industries) for the recovery of copper from copper sulfide minerals.[7] The closely related species 1-(ethoxycarbonyl)-3-(*n*-propyl) thiourea showed a high efficiency toward copper sulfide minerals and good selectivity against other metal sulfides also present in the porphyry ore, especially iron sulfide.[8]

Recently, Koch and coworkers [312,313] reported the extraction and transport of Au(III) involving six acyl(aryl)thiourea ligands, as well as a crystal structure of Au(I) with the ligand 1-(camphanyl)-3,3-(diethyl)thiourea. 1-Acyl thiourea ligands have been used as active ligands for ion transport experiments from chloroform solutions containing mixed metal ions through a membrane into an aqueous receiving phase and showed high transport selectivity for Ag(I).[269] Experiments using analogue *N*-(thio)phosphorylated (thio)amide and thiourea ligands also showed similar selectivity toward Ag(I).[314]

6.2. New materials

Another important area in which understanding of the metal complexation of thioureas is of immediate practical benefit is that of material chemistry. Transition metal complexes are increasingly finding applications in this field. The thermal behavior of 1-(2-chlorobenzoyl)-3-(pyrrolidine)thiourea, and their Ni(II), Cu(II) and Co(II) metal complexes were studied by thermal analysis in the temperature range of 298–1450 K. The final products were identified as Ni₃S₂, Cu_{1.96}S and Co₄S₃ by X-ray diffraction analysis.[315] Thermal decomposition of bis[1-(benzoyl)-3,3-(diethyl thioureato)]cadmium(II) under mild conditions may be used as a single-source precursor for the synthesis of hexadecylamine stabilized, spherical CdS nanoparticles, which show quantum confinement.[13] Very recently, lead complexes bearing the analogous selenoureato ligand have been recognized as single-source precursors in the synthesis of PbSe nanowires.[316]

Further developments include the preparation of new epoxy polymers containing Cu(II) and Ni(II) ions by the addition of thiourea metal complexes into the polymer matrix, resulting in a material with good tensile strength and high thermal stability.[162] On the basis of the analysis of the vibrational spectra, it has been predicted that increasing conjugation and dissymmetry of the thiourea results in high nonlinear hyperpolarizabilities,[150,151] with promising applications of these compounds as nonlinear optical materials. 1-(Benzoyl)-3,3-dialkyl thioureas have been used in the design of liquid crystalline materials. A systematic study of the influence of the alkyl chain length, number and position of the alkoxy groups, as well as branching of alkyl chain on the mesomorphic behavior of a series of 1-(benzoyl)-3-(aryl) thiourea derivatives have recently been reported.[317] Several monomesogens of ferrocene derivatives bearing these bidentate ligands have been synthesized by Seshadri et al.[318] A non-symmetric dimesogen compound has also been synthesized, in which two structurally different mesogenic groups, the thiourea and cholesteryl moieties, are inter-linked by a changeable spacer group. The achiral monomesogens exhibit enantiotropic smectic C and nematic phases, while the chiral monomesogens show exclusively a cholesteric phase with selective reflection in the infrared region. The dimesogen, on the other hand, exhibits an enantiotropic cholesteric phase with selective reflection in the visible region with iridescent colors.[318]

6.3. Use in catalysis

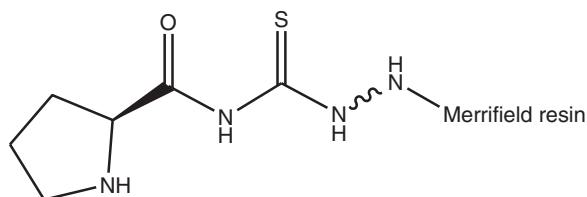
Karvembu et al. have scrutinized the potential application of 1-(acyl) thiourea metal complexes as catalyst components for oxidation reactions. The Ru(III) and Ru(II) complexes have been prepared incorporating *N*-[di(alkyl/aryl)carbamothioyl]benzamide ligands together with the PPh₃/AsPh₃ donors. These complexes display catalytic activity for the oxidation of primary, secondary, cyclic, allylic, aliphatic and benzylic alcohols to the corresponding carbonyl compounds (aldehydes and ketones) with *N*-methylmorpholine-*N*-oxide as oxidant at room temperature.[319,320] Cobalt(III) complexes containing *N*-[di(alkyl/aryl)carbamothioyl]benzamide complexes were

used as effective catalysts in combination with *tert*-butyl hydroperoxide for the oxidation of various alcohols at 80°C.[260]

Tetrahedral copper(I) complexes have been synthesized from the reactions between $[\text{CuCl}_2(\text{PPh}_3)_2]$ and 1-benzyl-3,3-(diphenyl/diethyl) thioureas (HL) in benzene. The combination of $[\text{CuCl}(\text{HL})(\text{PPh}_3)_2]_2$ with hydrogen peroxide in acetonitrile at room temperature is found to be an active catalyst for the oxidation of primary and secondary alcohols.[262]

6.4. Use in asymmetric catalysis

A series of thioureas have been designed, synthesized, and utilized as efficient catalysts for a variety of asymmetric reactions. These are among the most popular and versatile class of organocatalysts, due to being environmentally friendly and cost-effective, their ease of recovery and reuse, and efficacy under mild and neutral conditions to accommodate acid-sensitive substrates. Furthermore, thiourea catalysts can be bound to polymer resins and are effective in very small amounts and are water compatible. A number of review articles are available on application of thioureas as organocatalysts.[321–324] Recent advances on the use of 1-acyl-3-substituted thioureas are presented below.

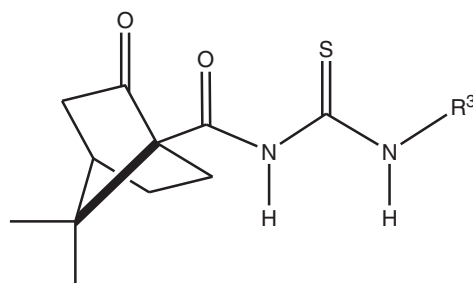


Scheme 20. General chemical structure of recyclable resin-supported thiourea organocatalysts.

Chiral acyl-substituted thioureas have been used as catalysts in Strecker reactions, in hydrophosphonylation of imines, in Mannich reactions, in cyanosilylation of ketones and in Pictet–Spengler reactions.[325] Chiral bifunctional organic catalysts containing a thiourea group and a tertiary amino group connected through a chiral backbone were developed to promote the addition of acetylacetone to β -nitrostyrene in high yields and enantioselectivities of up to 85% *ee*.[326]

Recyclable Merrifield resin-supported thiourea organocatalysts containing L-proline (Scheme 20) were employed for asymmetric aldol reactions of ketones and aromatic aldehydes.[327] The compounds have excellent enantioselectivities with high yields and moderate diastereoselectivities. Merrifield resin-supported catalysts can be recovered and reused for at least four cycles, with high enantioselectivities and with only slightly decreasing yields.

Bifunctional thiourea-amine organocatalysts based on the camphor structural units (Scheme 21, $\text{R}^3 = 4$ -hydroxyproline-2-carboxylic acid-phenyl-amide) were synthesized in good yields



Scheme 21. General chemical structure of bifunctional thiourea-amine organocatalysts.

from inexpensive starting materials and were proven to directly catalyze the aldol reaction. The anti-aldol products were obtained in excellent yield and high diastereo- and enantioselectivity in water.[328] A plausible mechanism involves a transition state conformation organized by hydrogen bond formation involving the organocatalyst and the substrate. The hydrophobic nature of the substituents, together with electrostatic as well as steric interactions, may account for the stereochemical bias of the reaction.

7. Biological aspects

Thiourea derivatives exhibit a broad spectrum of bioactivities, as inferred from valuable studies that explored different potential biological applications. Most of these efforts are non-systematic and the mechanism of action remains unclear. For instance, 1-acyl-3-(2'-aminophenyl)thioureas are anti-intestinal nematode pro-drugs [329] and 1-aryl-3-(substituted-2-benzothiazolyl)thioureas [330] exhibit potent antibacterial activity. 1-(Benzoyl)-3-(substituted) thioureas are antimicrobial agents [331] and the fluorinated analogues exhibit, in general, better antifungal than antibacterial activity.[118]

Limban and Missir prepared a series of thioureides of 2-(4-methyl/methoxy-phenoxy)methyl-benzoic acid with antimicrobial activity.[332–335] Similar antimicrobial activity against pathogenic bacteria and fungi were reported for chlorinated derivatives.[118] In similar fashion, thiourea derivatives bearing benzothiazole moiety possessed a broad spectrum of activity against microorganisms showing higher activity against fungi than bacteria.[88,330] A series of 1-(benzoyl)-3-(4-methyl-phenoxy)methyl thioureas were tested against anti-parasitic activity.[336] Thiophene-substituted thiourea species also showed significant antifungal activities against microbial species.[337] 6-Thioureido-4-anilinoquinazolines are antimalarial agents [338] and poly-substituted 1-(acyl) thioureas are a novel class of potent influenza virus inhibitors,[339] while 1-acetyl-3-(o-fluorophenoxy)thioureas possess herbicidal properties.[340]

Fluorinated 1-(aryl) thioureas represent a new class of potent anti-trypanosomal agents [341] and also a novel class of potent influenza virus neuraminidase inhibitors.[339] 1,3-Dialkyl/diaryl thioureas exhibit significant antifungal activity against plant pathogens *Pyricularia oryzae* and *Drechslera oryzae*. [342] Very recently, anthranilic diamides containing the 1-(acyl)thiourea and 1-(acyl)urea linkers were designed and synthesized, with changing length and flexibility of the linkers to compare to known anthranilic diamide insecticides.[343] Their insecticidal activities against oriental armyworm (*Mythimna separata*), mosquito larvae (*Culex pipiens pallens*) and diamondback moth (*Plutella xylostella*) were evaluated and indicated that the introduction of the 1-(acyl) thiourea group into some structures is important for retention of insecticidal activity.[343] *N*-[3-(2,4-dichlorophenyl)-5-methylisoxazol-4-ylcarbonyl]-*N'*-(4,6-di-substituted pyrimidin-2-yl)thioureas [344] exhibit good phytotoxic activity against *Echinochloa crusgalli* L., *Digitaria ciliaris* L., *Brassica napus* L. and *Chenopodium serotinum* L.

A series of 1-(acetoxyl-benzoyl) thiourea derivatives with aryl and amino acid ester side chains were prepared by reaction of acetoxylbenzoyl isothiocyanate, an acyloxy benzyl ester-based derivative of aspirin, with aryl amines or amino-functionalized amino acids. The products that display a thiourea segment as a linker showed improved antibacterial properties in comparison with aspirin.[345]

Thiourea derivatives as well as metal complexes have been proven to be effective against fungi.[277] The *in vitro* anti-yeast activity of thiourea derivatives and their metal Ni(II) and Cu(II) complexes has been demonstrated.[271] Zhou and coworkers [248] reported four new thiocarbonyl fluorobenzamides and their complexes with cobalt, including structural studies. The antibacterial properties of these compounds against different bacteria were investigated. The experiments

showed that both the ligands and their complexes have antibacterial activities against all of the studied bacteria. The thioylbenzamides had stronger affinity for the bacteria of *Escherichia coli*, *Staphylococcus aureus*, *Bacillus subtilis* and *Pseudomonas aeruginosa* than their corresponding cobalt complexes. Structure–relationship analysis showed that para-substitution of a fluorine atom increased antibacterial activities against *Shewanella* sp., while fluorine atom substitution on ortho-benzoyl diminished antibacterial activity. The polarity of the carbonyl group also correlates with a higher antibacterial activity. Structure–activity analysis also demonstrated that thioylbenzamides linked to piperidine instead of a morpholine group may increase the antibacterial activities [248] of thiourea compounds.

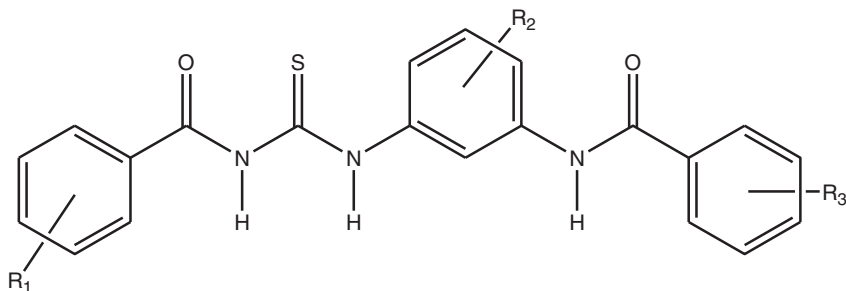
A series of new 1-(acyl)-substituted thiourea derivatives of the physiologically active alkaloid anabasine were synthesized and their antibacterial and antifungal activities were demonstrated.[346] The preparation of *N*-(β -D-glucopyranosyl)-*N'*-substituted thioureas were accomplished by reaction of β -D-glucopyranosylammonium carbamate with an isothiocyanate in dry pyridine at room temperature.[347] The biological activity of macromolecules containing the 1-(acyl)thiourea group has also been evaluated. Thus, derivatives of chitosan were synthesized and their structures were characterized by FTIR spectroscopy.[348,349] The antimicrobial behaviors against four species of bacteria and four crop-threatening pathogenic fungi were investigated. The results indicated that the antimicrobial activities of the acyl thiourea derivatives are much better than that of the parent chitosan.[348] Acetyl, chloroacetyl and benzoyl thiourea derivatives of carboxymethylchitosan are more potent in case of Gram-positive bacteria than Gram-negative bacteria. Analogous derivatives containing the chloroacetyl thiourea group showed that the antifungal activity is higher than with acetyl or benzoyl groups which may be due to the presence of the chlorine atom.[349] Moreover, the introduction of thiourea groups into the chitosan skeleton results in the formation of species that display in situ gelling properties due to the pH-dependent formation of inter-molecular disulfide bonds. This property provides a control mechanism for the release of the embedded therapeutic ingredients with potential application on intestinal mucosa.[350]

The group of Khan and coworkers [351] has extensively reported the use of urea and thiourea compounds as agents for treatment of cancer cells because of the ability of these compounds to interfere with microtubule assembly causing mitotic arrest and eventually cell death. A novel series of substituted 1-benzoyl-3-phenyl urea/thiourea analogues were synthesized and evaluated for antitumor activity. In particular, the sulfur analogues were shown to possess increased potency against cancer cell lines when compared with new agents such as NSC-639829 (in Phase I clinical trials).[352] A series of unsymmetrical 1-acyl-3,3-(di-substituted) thioureas containing the hydrophenanthrene group were synthesized and their antitumor activities against SMMC7721 and A549 tumor cells were evaluated.[353]

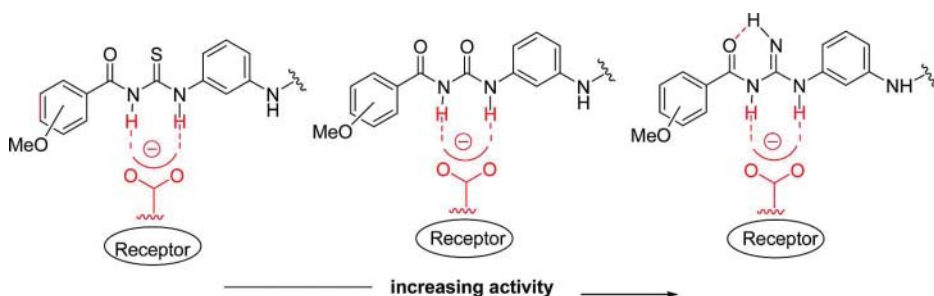
Very recently, on the basis of the structure of the acylthiourea smoothed (Smo) antagonist,[354] Solinas et al. prepared a number of different series of analogous compounds by ligand-based structural optimization.[14,355] *N*-(3-benzamidophenylcarbamothioyl)-3,4,5-trimethoxybenzamide was identified as a “top-scoring ligand” by using virtual screening methodology (Scheme 22: $R_1 = 3, 4, 5\text{-OCH}_3$; $R_2 = 4\text{-CH}_3$, $R_3 = 4\text{-C}_6\text{H}_5$).

Taking advantage of the chemical versatility discussed in the previous section, the 1-(acyl)-3-(mono- and di-substituted) thiourea compounds originally identified (Scheme 22) as active were also converted into the corresponding acylureas or acylguanidines. The authors have argued that the similarity of their biological activities, in spite of discrete structural differences, may reveal the existence of hydrogen-bonding interactions between the ligands and the receptor pocket.[14] The proposed H-bonding network for the three bio-isosteric structures (acylthiourea, acylureas and acylguanidines) toward a putative carboxylate anion located on Smo is shown in Scheme 23.

Using high-throughput screening on a library of 206,000 small molecules, Dai and coworkers [15] identified two acylthiourea derivatives active against viruses. To further improve antiviral potency and to optimize drug-like properties, an exhaustive structure–activity relationship analysis



Scheme 22. General chemical structure for 1-(aryl)-3-(benzamide)substituted thioureas showing promising biological activities.

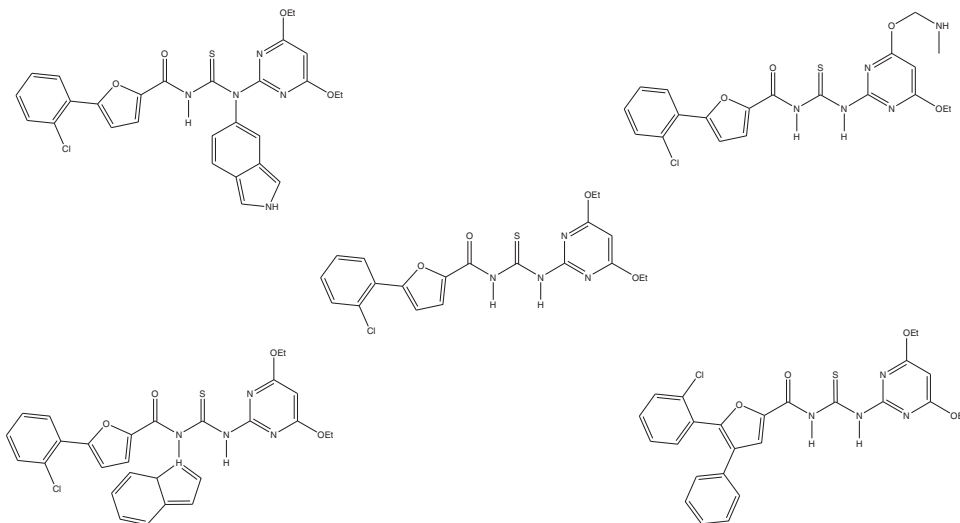


Scheme 23. Proposed H-bonding network for acylthiourea, acylureas and acylguanidines toward a putative carboxylate anion. Reprinted with permission from Solinas et al. [14] Copyright (2012) American Chemical Society.

was accomplished. From this study, two substituted-benzoyl thioureas were selected as compounds with potential broad-spectrum antiviral properties. [15] One of these compounds with $R_1 = 4$ -*tert*-butyl, $R_2 = 4$ -CH₃O, $R_3 = 2$ -Cl-C₆H₄ in Scheme 22 displayed submicromolar antiviral activity in cytopathic effect assays against both *vaccinia* ($EC_{50} = 0.25 \mu\text{M}$) and *La Crosse* ($EC_{50} = 0.27 \mu\text{M}$) viruses. The similarity with the previous series of compounds is apparent. These studies reveal that a bulky, lipophilic group (*i.e.* *tert*-butyl or trimethoxy groups) and the central 1-(acyl)thiourea moiety are required for broad-spectrum antiviral activity.

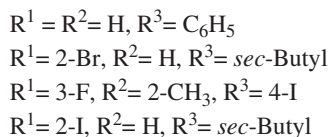
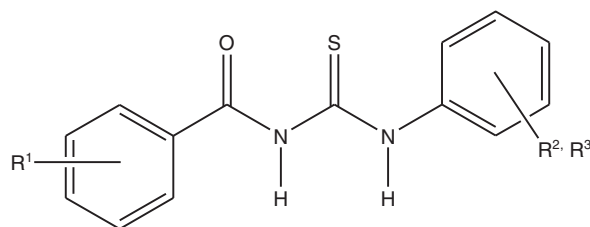
Docking and quantitative structure–activity relationship (QSAR) models [356] methods were applied to study interactions between poly-substituted pyrimidinyl and *tert*-butylaminocarbonyl acylthiourea analogs and neuraminidase. Two factors have been recognized as important for characterizing the neuraminidase inhibition activity: hydrogen-bonding and electrostatic interactions highly correlate with the activities, followed by hydrophobic and steric factors. [357,358] The most active sample is shown in the center of Scheme 24. It was suggested that this molecule interacts with up to nine hydrogen bonds with key amino acid residues in the active site of the glycoprotein. By using this molecule as a “template,” four new compounds were selected by QSAR model and docking studies for which improved binding energy and enhanced inhibitory activity is predicted. In all these compounds, the central acyl thiourea group is maintained, as shown in Scheme 24.

Using a high-throughput screening assay, Severson et al. [359] evaluated a 100,000 compound library against *influenza A* virus. Only 26 compounds met the criteria of activity after dose response at 14 and 114 μM concentration in the cell toxicity assay. After a structure–activity relationship analysis, 21 compounds were evaluated for their antiviral activity, cell toxicity and selectivity in dose–response experiments. The authors have identified six compounds



Scheme 24. General chemical structure for 1-(acyl)-3-(pyrimidinyl substituted) analogs with neuraminidase inhibition activity.

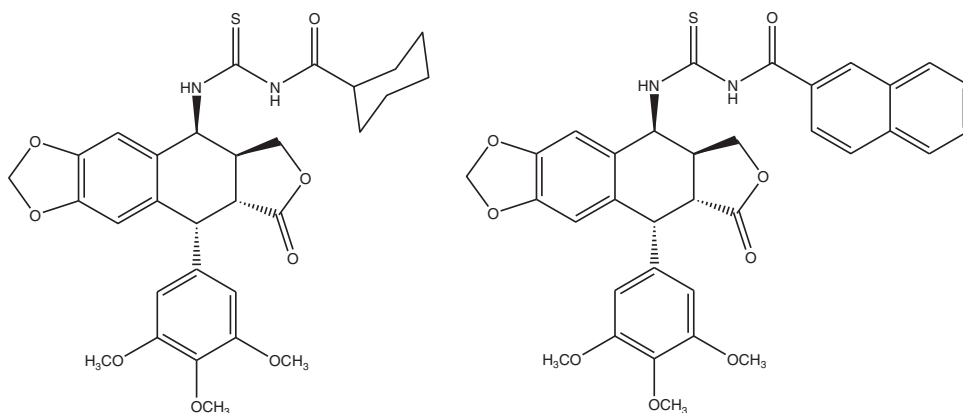
that exhibited a 2-log reduction or >100-fold difference from the control. Among them, four compounds are 1-benzoyl-3-arylthiourea derivatives as shown in Scheme 25 ($R^1 = R^2 = H$, $R^3 = C_6H_5$; $R^1 = 2-Br$, $R^2 = H$, $R^3 = sec\text{-Butyl}$; $R^1 = 3-F$, $R^2 = 2-CH_3$, $R^3 = 4-I$, $R^1 = 2-I$, $R^2 = H$, $R^3 = sec\text{-Butyl}$). According to the authors' recommendations, the design, synthesis and evaluation of targeted analogs *should lead toward the identification of compounds possessing greatly improved potency and selectivity that can be developed into clinically useful therapeutic agents.*[359]



Scheme 25. General chemical structure for 1-(benzoyl)-3-(aryl)thiourea derivatives with promising activities against *influenza A* virus.

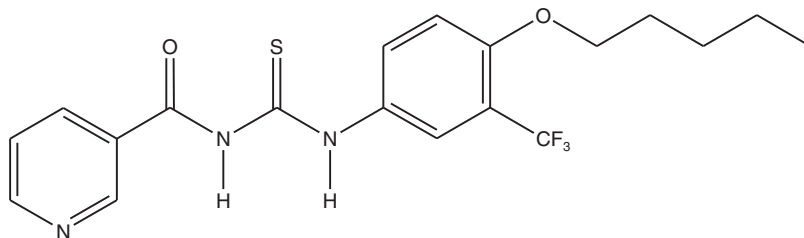
Very recently, new acyl thiourea derivatives of epipodophyllotoxin were designed, synthesized (Scheme 26) and their cytotoxic activity were evaluated against four human tumor cell lines, exhibiting better cytotoxicity than that of the control etoposide.[360] The Structure–activity relationship (SAR) study found that the 1-acyl thiourea group substituted with a bulky group as well as the electron density and configuration of the epipodophyllotoxin group in these molecules are

critical factors for the derivatives' activity. These compounds are promising new candidates for further development as anticancer agents.



Scheme 26. General chemical structure for 1-acyl thiourea derivatives of epipodophyllotoxin evaluated as anticancer agents.

The compound showed in Scheme 27, 1-(4-pentyloxy-3-trifluoromethylphenyl)-3-(pyridine-3-carbonyl)thiourea (ACH-806), is an inhibitor of *hepatitis C virus* (HCV), with a novel mechanism of action and resistance pathway.[361] A phase 1b proof-of-concept study showed significant antiviral activity at the lowest dose tested and demonstrated synergy effects when combined with other small-molecule inhibitors.[362]



Scheme 27. Chemical structure of 1-(4-pentyloxy-3-trifluoromethylphenyl)-3-(pyridine-3-carbonyl)thiourea, an effective inhibitor of *hepatitis C virus*.

The previously discussed results suggest that the title compounds may have broad pharmaceutical and biological applications. However, very little is known about their molecular mechanism and physiological role. The elucidation of these aspects is perhaps one of the most promising areas of future development 1-(acyl/aryl)-3-(substituted) thioureas.

8. Bis-di-thiourea

Bis-di-acyl thiourea compounds can be classified as belonging to the same class of molecules covered in this review, since they are characterized by the presence of two $-C(O)NHC(S)N<$ groups. In general, the physicochemical properties are similar to those already described for the

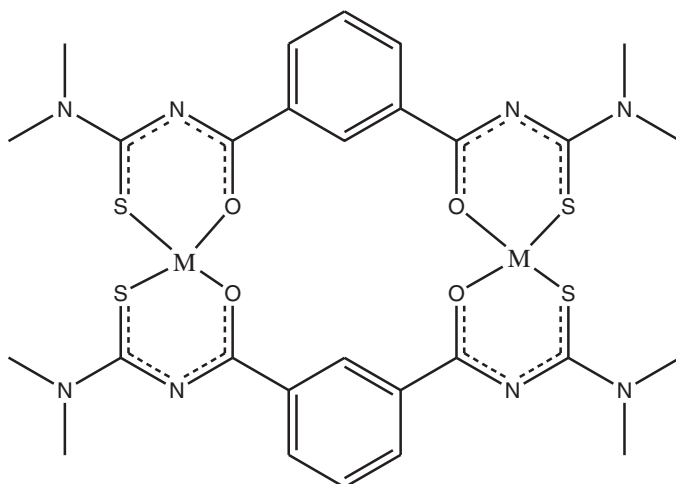
acyl thiourea analogues. For the sake of completeness, the most recent advances in the chemistry, structure and potential applications of these species are given in this section.

The first bis-di-thiourea derivatives were obtained from aliphatic diamines, including *o*-cyclohexanediamine,[363,364] having a bis[1-(benzoyl)thiourea] group.[216,365–368] The same procedure can be applied for aromatic diamines.[224,369–372] In general, these molecules belong to the $C_i = S_2$ point-group symmetry, with a crystallographic center of inversion located in the middle of the (alkyl) bridge. Similar to the thiourea analogues, bifurcated hydrogen bonds (N–H...O and N–H...S) are observed in the crystals.[216,373] The crystal structures of 3,3,3',3'-tetra(2-hydroxyethyl)-1,1'-isophthaloylbis(thiourea) and its nickel complex are reported in the context of their supramolecular behavior dictated by the use of hydrogen-bonding end-groups on the ligand.[374]

1,1'-(Naphthalene-1,8-diyl)-3,3'-dibenzoyl-bisthiourea, based on a 1,8-naphthalene skeleton bearing bis-thiourea groups proved to be an efficient and selective naked-eye detector for the fluoride, cyanide and hydroxide ions.[375] The synthesis and biological activity of 1,3-benzenedicarbonyldithioureas were described recently.[376] Bioassay results indicated that these compounds exhibit cytotoxicity against various cancer cells. Di-fatty acyl thiourea, which has antibiotics and antifungal biological activities has been synthesized from palm oil and thiourea using sodium ethoxide as catalyst.[377] 1,3-Bis(*N'*-benzoyl/furoyl-thioureido)benzene derivatives showed high selectivity toward Pb(II) ion when incorporated as ionophores in membrane ISEs.[10]

It is well known that bis-di-thiourea can be also prepared by condensation of di-thiocyanates with two equivalent of the corresponding amines.[378] Recently, Koch and coworkers [379] prepared a series of *N,N*-dialkyl-*N'*-(acyl)thioureas with “flexible” alkyl-type (C_3 , C_4 and C_6) spacers. The donor O and S atoms in each acylthiourea unit assume opposing orientations, as usual. Interestingly, in the crystal structure of 3,3,3',3'-tetraethyl-1,1'-(propane-1,3-diyl)dicarbonylbis(thiourea), $C_{15}H_{28}N_4O_2S_2$, molecules are linked by two intermolecular hydrogen bonds between the S atom of one molecule and the thioamide H atom of a neighboring molecule *via* a peculiar cooperative or resonance-assisted hydrogen bond.[379]

“Bipodal” derivatives of 1-aryl 3,3-dialkyl thioureas can be obtained.[380] These molecules are interesting ligands in view of the fact that two potentially S,O-chelating groups are linked



Scheme 28. Square planar 2:2 complexes of first-row transition metals with bipodal 1,3-aryl linked bis-acylthioureas.

through a “spacer.” Bipodal 1,3-aryl linked bis-acylthioureas such as 3,3,3',3'-tetraethyl-1,1'-isophthaloylbis(thiourea) result in the facile formation of 2:2 square planar complexes of first-row transition metals,[381,382] as shown in Scheme 28. Nguyen et al. [266] showed that the coordination chemistry of oxorhenium(V) compounds with 3,3,3',3'-tetraalkyl-1,10-isophthaloylbis(thiourea) ligands gives access to binuclear compounds, in which the metal ions are each coordinated by two bidentate O,S moieties of the organic ligands.

9. Conclusions

The main purpose of this review has been to summarize the chemistry and reactivity of 1-(acyl/aryl)-3-(mono-substituted) and 1-(acyl/aryl)-3,3-(di-substituted) thioureas and the possible applications as precursors in different heterocyclization reactions. This review also shows how the title compounds, easily prepared from commercially available starting compounds, can be used as ligands in coordination chemistry. Recently reported structural aspects and promising applications for these metal complexes have been discussed. Finally, the biological activity of 1-(acyl/aryl)-3-(substituted) thioureas has been highlighted, including new methodologies designed to select and optimize drug-like properties.

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Supplemental data

Summary of X-ray data available for 1-(acyl/aryl)-3-(mono-) and thioureas 3,3-(di-substituted) thioureas are given in Tables S1 and S2, respectively. Table S3 contains relevant X-ray data available for metal complexes bearing 1-(acyl/aryl)-3-(mono/di-substituted) thiourea ligands. Supplemental data for this article can be accessed <http://dx.doi.org/10.1080/17415993.2013.834904>.

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