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Desulfurization of thiosemicarbazones: the role of metal ions and biological implications

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Abstract

Thiosemicarbazones are biologically active substances whose structural formula is formed by an azomethine, an hydrazine and a thioamide fragments, to generate a $R_2C{=}N{-}NR{-}C(=S){-}NR_2$ backbone. These compounds often act as ligands to generate highly stable metal-organic complexes. In certain experimental conditions, however, thiosemicarbazones undergo reactions leading to the cleavage of the chain. Sometimes, the breakage involves desulfurization processes. The present work summarizes the different chemical factors that influence the desulfurization reactions of thiosemicarbazones, as pH, the presence of oxidant reactants or the establishment of redox processes as those electrochemically induced, the effects of the solvent, the temperature and the electromagnetic radiation. Many of these reactions require coordination of thiosemicarbazones to metal ions, even those present in the intracellular environment. The nature of the products generated in these reactions, their detection *in vivo* and *in vitro*, together with the relevance for the biological activity of these compounds, mainly as antineoplastic agents, is discussed.

Keywords

Antitumor · Biological activity · Cyclization · Desulfurization · Metal complexes · Thiosemicarbazone

1. Introduction

Thiosemicarbazones (TSCs) constitute a broad family of compounds that have been under consideration since middle of last century because of their rich coordination chemistry with a wide range of transition and non-transition metal ions and their wide biological and pharmacologic activities, as exemplified by pioneering Bayley work in the 60s, who reported different copper complexes derived from thiosemicarbazone that showed antifungal activities [1,2].

Thiosemicarbazone ligands can be obtained under mild conditions by reaction between a suitable carbonyl compound (aldehyde or ketone) and a thiosemicarbazide [3]. In this process an imine bond is formed as part of the thiosemicarbazone $R^1R^2C{=}N{-}NR^3{-}C(=S){-}NR^4R^5$ skeleton, with the release of a water molecule. The structure of a basic thiosemicarbazone skeleton is depicted in Fig. 1, where R^1 and R^2 may be nucleophilic groups and atoms, while R^4 and R^5 are the terminal $N_{thioamide}$ substituents. The wide structural diversity found in thiosemicarbazone chemistry is the result of modifying the type of carbonyl compound (aldehydes or ketones), substituents attached to the carbonyl moiety, the metal ion and its oxidation state, geometries, counterion, presence of solvent, added molecules, substituents on the S or $N_{thioamide}$-atoms, or synthetic methodology [4,5,6]. They are highly delocalized systems, particularly when attached to the azomethine carbon.

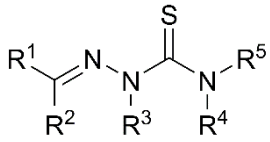


Fig. 1 A general thiosemicarbazone skeleton

In solution, TSCs where $R^3 = H$ may exist as an equilibrium mixture of thione and thiol tautomeric forms [7] depending on the pH of the medium, with the thione form being the most stable in the solid state [8,9,10]. Upon coordination, the thione tautomer ligand usually acts in a neutral and bidentate mode [11], whereas the removal of the hydrazide NH proton gives rise to monoanionic thiolate ligands. These two coordination modes (Fig. 2) are strongly dependant on the reaction conditions, specifically the pH, or on the experimental methodology employed (chemical or electrochemical). Conformational and configurational changes occur, as those related with the $N_{hydrazine}–C_{thioamide}$ bond being the *cis* configuration/*syn* conformation the usually formed after metal ion coordination [12]. In the presence of an additional coordinating group introduced *via* carbonyl compound, the TSC ligand increases its denticity. The alkylation of the thiocarbonyl sulfur in the derivatives causes complexation from the terminal amino group also leading to acidic character [13]. The properties of the thiosemicarbazones can be altered with the modifications in their chelating power and the binding patterns to the metal atom [14]. Under certain experimental conditions, carbonyl thiosemicarbazones also undergo cyclization. In these cases, the ligands can coordinate through the sulfur, the azomethine nitrogen and other heteroatoms present in the structure [15].

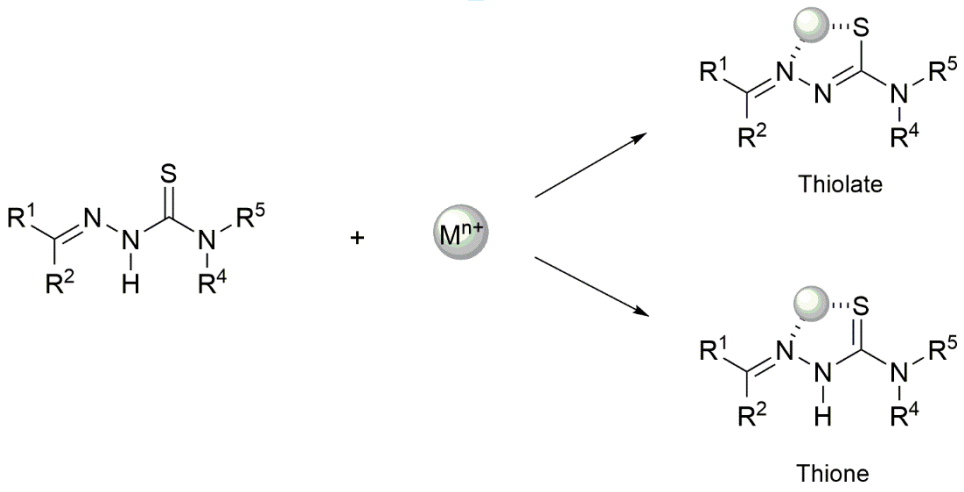


Fig. 2 Usual bidentate coordination modes of a thiosemicarbazone ligand

The versatility exhibited by TSC ligands is illustrated by the introduction of small modifications in the TSCs skeleton that can improve their therapeutic properties [16-18], highlighting that these properties can also be enhanced by the formation of complexes with different metal ions [18-20]. It seems that the coordination of metal ions modifies the lipophilicity that regulates the cell entry. It has been also found that some of the thiosemicarbazone complexes are more active than the uncoordinated precursor ligands. The biological activity of thiosemicarbazone complexes can be modulated by tuning the aromatic moiety as exemplified by the α(N)-heterocyclic tridentate thiosemicarbazone series. In the case of these ligands the hydrophobic moiety is more exposed to the solvent making it feasible to cross the cell membrane and to interact with essential enzymes in cells [21].

Taking into account all the features mentioned above, the coordination chemistry of thiosemicarbazone compounds and its biological applications have been of great interest and for that reason both aspects have been deeply explored in parallel during the last decades, giving rise to a long list of reviews on TSCs derived metal complexes and their biological properties. These reviews emphasised the relation between structural features in TSCs and the biological activities of their complexes. Some of the most relevant are commented below. Regarding to this, it is important to mention that in the present review, the abbreviations of the most biologically relevant TSCs are maintained as they appear in the literature.

The first review based on the coordination chemistry of thiosemicarbazones was published in 1975 by Campbell [22], with the focus on the study of the structure and bonding in different TSC transition metal complexes. In this report, the author highlights the influence of the sulfur atom nature on the behaviour of TSCs, which in all cases is coordinated to the metal ion. Since then, excellent reviews on TSCs have been published, completing Campbell's thiosemicarbazone study [23] or focusing on copper compounds [11], metal ions of groups 12, 13, 14 and 15 [24], palladium and platinum complexes [25], organotin(IV) [26] compounds. These reviews explore the potential as antitumour compounds [27] and, in particular, the ability of some thiosemicarbazone iron complexes to mediate in the generation of damaging reactive oxygen species (ROS) [28], deeping into their application as medicinal radiopharmaceuticals [19,29] and theranostic agents [30], or expanding the insight into antiviral, antimalarial and antifungal activities [31,32], highlighting those related to medicinal applications [33-42].

The first study on possible applications of TSCs in therapy is attributed to Domagk et al. [43]. In 1946, they suggested that these substances could be useful against tubercle bacilli given their chemical analogies with the antitubercular sulfamide and sulfone drugs. Since that, it has been explored their use against neurological pathologies [44,45], microbial diseases like small-pox [46], influenza, malaria, leishmaniosis, Chagas, leprosy and tuberculosis diseases [47-51], as antifungal compounds [31,52] and as potential theranostic agents [19,30,29,53,54]. The leap into the field of antitumour substances was made by Brockman et al. [55], who found antileukemic activity in pyridine-2-carbaldehyde thiosemicarbazone (HPTSC) and the corresponding thiocarbohydrazone. Many other studies have been performed in the field of cancer [20,31,26,56-80]. The seminal work performed during the 1960s established the basis for the TSCs with proved carcinostatic activity [81-83]. As a summary, TSCs have to be α-(N)-heterocyclic substituted, mainly with pyridine moieties, to give NNS tridentate ligand systems, which excludes semicarbazones that usually show a lower activity. In fact, these characteristics are present in all the TSCs screened in Phase I-III clinical trials until now (Fig. 3) [84-94]. Note that the common fragment to all of them is the structure of the pyridine-2-carbaldehyde thiosemicarbazone. Catalytic applications of transition thiosemicarbazone metal complexes have also been reviewed [95].

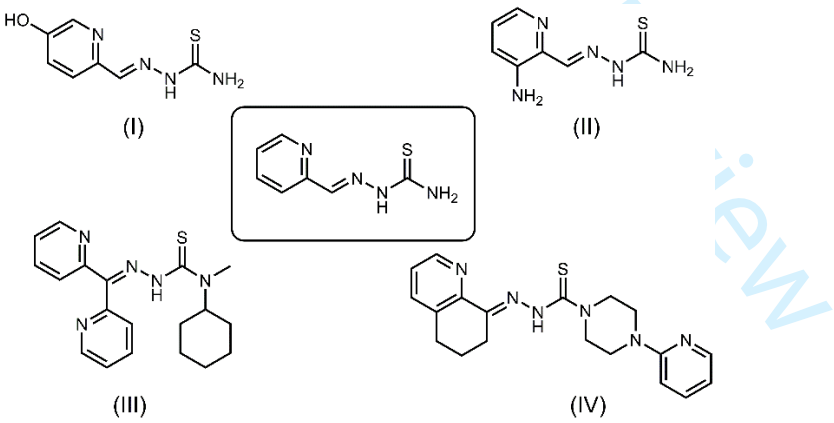


Fig. 3 TSCs tested in clinical trials: 5-hydroxypyridine-2-carbaldehyde thiosemicarbazone (5-HP, I), 3-aminopyridine-2-carbaldehyde thiosemicarbazone (3-AP or Triapine®, II), di-2-pyridylketone 4-cyclohexyl-4-methyl-3-thiosemicarbazone (DpC, III), and (E)-N'-(6,7-dihydroquinolin)-8(5H)-ylidene 4-(pyridin-2-yl)piperazine-1-carbothiohydrazide (COTI-2, IV). In the middle of the scheme, the pyridine-2-carbaldehyde thiosemicarbazone (HPTSC), as a common fragment to all of them

Different biological targets have been identified, like RNA [96], DNA [97-99], and several enzymes as thioredoxin reductase [100,101], xanthine oxidoreductase [102], RNA-dependent DNA polymerases [103], topoisomerase IIa [104,106] or succinate and NADH dehydrogenases [107]. Perhaps one of the most relevant findings about targets for the biological activity of TSCs was carried out by Sartorelli and Moore, who discovered that TSCs were able to inhibit the activity of the ribonucleotide reductases (RDRs), enzymes that catalyse the reduction of ribonucleoside diphosphates to deoxyribonucleoside diphosphates [108,109,110]. It is demonstrated that TSC-Fe complexes [111,112] generate ROS in the presence of O_2 that destroy the tyrosyl radical present in the M2 subunit of the enzyme, but binding to the protein surface and further chelation of Fe(III) ions from the active site has also been proposed [113]. The metal complexes,

or the presence of redox-active metal ions in the physiological medium, triggers the interaction with cell thiols and further reoxidation processes leading to the formation of ROS that destroy different cell structures [114-116].

The coordination to essential metal ions existing inside the cell seems to be necessary for TSCs to develop biological activity, to the point that the actual active forms are the TSC-Fe [117], and TSC-Cu complexes [118-122]. The inductive effects of the substituents in the TSC chain also have a notable influence on the redox properties and the biological activity of the TSC-metal complexes [123]. On the other hand, an increment of the lipophilicity of the metal complexes by modulating the substituents in the TSC backbone have been proved to increase the intracellular redox activity and to improve the antiproliferative efficacy [124-126], if the value of the Partition coefficient (P_{calcd}) is kept inside an optimal range log P_{calcd} 3.1–4.5 [127].

It is well established that transition metals induce activation and transformations in the carbon-sulfur bonds [128-133]. In the case of TSCs, the confluence of metal ions coordination and different physicochemical factors can lead to changes in the ligand skeleton involving the loss of the sulfur atom. Generally, a desulfurization process can be described as an oxidation reaction in which the sulfur is lost from the thioamide group. Nowadays, the literature shows a variety of examples of desulfurization reactions in thiosemicarbazone ligands but, as far as we are aware, there are still no reviews available. In this review we will give an insight of different desulfurization processes in thiosemicarbazone complexes that have been reported to date. It also explores the conditions that make possible desulfurization processes in TSC-metal complexes, the products arisen from those and the biological relevance of these reactions. We have performed a tentative classification of desulfurization process in TSCs depending on the factors involved: pH induced desulfurizations, desulfurization in electrochemical processes and desulfurization by oxidant reactants and others (radiation-, thermal-, solvent- and coordination-induced desulfurizations). Also, a section of biological implications of these processes is reported.

2. A survey for desulfurization reactions in thiosemicarbazone metal complexes

2.1. pH induced desulfurizations

Extreme pH values have been proved to provoke ruptures in the thiosemicarbazone chain of metal complexes, leading to different products coming from the ligand desulfurization. Notwithstanding, some effects of the medium are detected even at neutral pH values. The present section summarizes some key reactions dealing with desulfurization induced by acid or basic media.

a) Conversion of thiosemicarbazones into carbonitriles in basic medium

Aqueous solutions of the $CuL(NO_3)$ compound (HL = pyridine-2-carbaldehyde thiosemicarbazone, HPTSC) basified by NaOH addition to pH = 9–11 undergo partial desulfurization to yield brown precipitates containing, as a major component of the mixture of phases, the $[CuL(L^{CN})]$ compound [134], where HL^{CN} = (pyridine-2-ylmethylene)hydrazinecarbonitrile, following the general reaction depicted in Fig. 4. The crystal structure of $[CuL(L^{CN})]$ reveals its square pyramidal geometry. The carbonitrile ligand acts as bidentate and the bond distances in the NCN terminal moiety fall in intermediate values between cyanamide (N–C≡N) and carbodiimide (N=C=N) character. The presence of the carbonitrile can be easily checked by a characteristic infrared band at 2108 cm^{-1} corresponding to ν(CN).

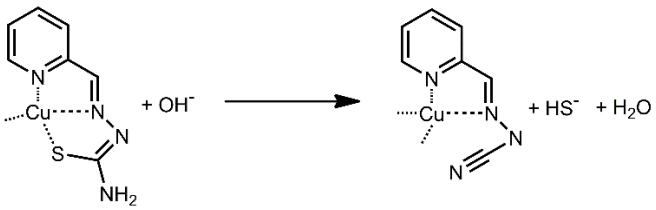


Fig. 4 Transformation of pyridine–2–carbaldehyde thiosemicarbazonatocopper(II) (PTSC-Cu) into the (pyridine-2-ylmethylene)hydrazinecarbonitrilecopper(II) complex

An extensive study has been carried out to elucidate the conditions and mechanism of this reaction, whose transcendence will be discussed in other sections. The main results are given below.

1. Trials at different pH values (7.4, 9.0, 11.0 and 13.0), temperatures (40, 50 and 80 °C) and times (1 and 5 h) allowed to establish the best conditions to achieve mixtures with the highest [CuL(L^{CN})] content at pH 9.0, 80 °C and 1 h. Excess of base (pH 11−13), heating and time led to mixtures rich in inorganic matrix where sulfide and sulfate anions were qualitatively detected.

2. No desulfurization reactions are observed for the free HPTSC ligand in the same experimental conditions.

3. The reaction is not sensible to the co-ligand, and suspensions of the CuLCl compound, less soluble than $CuL(NO_3)$, behave in a similar way. CuLCl and $CuL(NO_3)$ are, actually, the dinuclear $[\{CuLCl\}_2]$ and the 2D $[CuL(NO_3)]_n$ compounds, respectively [135,136].

4. The same results are obtained with different bases, as KOH, triethylamine (NEt_3) and a 0.5 M $Na_2CO_3/NaHCO_3$ buffer.

5. The process strongly depends on the addition order, because only affects to preformed $[CuL]^+$ entities. Note that the addition of Cu(II) solution to an aqueous HL solution at pH 13.0 affords the attainment of the $[CuL_2]$ complex, retaining the TSC integrity.

6. No evidences of TSC breakage have been observed for Pb(II), Fe(II,III), Co(III), Ni(II) and Zn(II) ions in experiments carried out at pH 11.0 for 1 h (Fig. 5) [137]. Attempts of desulfurization of the HPTSC ligand using $HgCl_2$ and $Pb(AcO)_2$ were also unsuccessful [138].

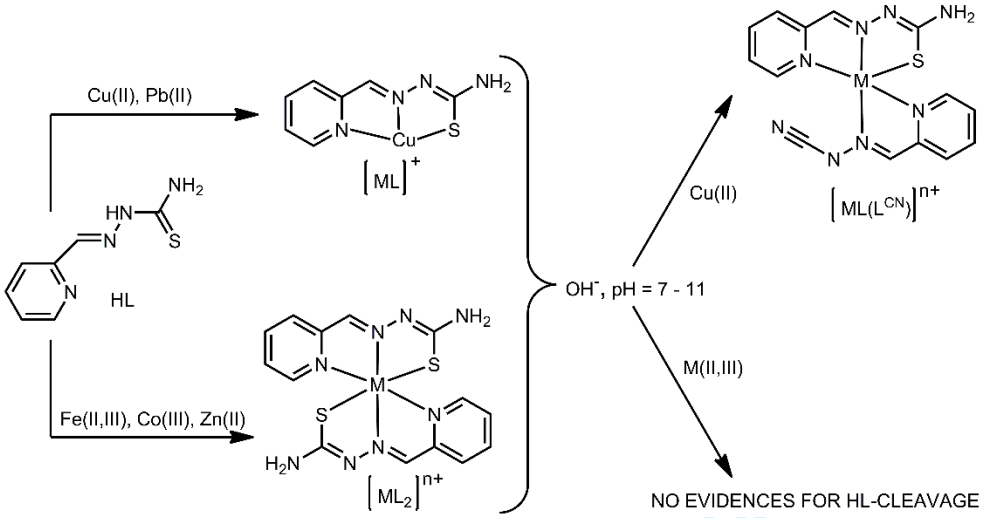


Fig. 5 Summary of the behavior of different metal ions coordinated to PTSC at basic pH values

In order to unveil the features of the reaction, solids precipitated from reactions between equimolar amounts of HL and $Cu(NO_3)_2$ at pH values of 2.0 (no addition of base), 4.0, 7.4 and 9.0 were analysed [139]. IR spectra recorded on the dark brown solids revealed the presence of medium to intense bands in the 2116–2106 cm^{-1} region in the samples obtained at pH 7.4 and 9.0, which suggests ruptures in the TSC chain. In the mass spectra of these compounds were also detected peaks at m/z 628.99 and 630.99 attributed to $[Cu_2L_2(L^{CN})]^+$ and $[Cu_2(HL)_2(L^{CN})]^+$ ions, whose intensity increased in those experiments performed at 80 °C. These species could be related to the partial desulfurization of dinuclear $[Cu_2L_3]^+$ cations. These dinuclear entities have been isolated and crystallized, from the reaction of $Cu(ClO_4)_2$ with thio- and selenocarbazones in soft basic media by addition of NaOH (pH = 7.6, HL = HPTSC [139]) NaAcO (HL = 2-acetylpyridine 4-N-phenylthiosemicarbazone [140]) and NEt_3 (HL = 2-acetylpyridine 4,4-dimethyl-3-selenosemicarbazone) [141]. Their stabilization as solids containing $[Cu_2L_3]^+$ cations seems to require the presence of low coordinating co-ligands, as perchlorate or nitrate [139].

Mass spectrometry studies carried out on aqueous solutions at pH 4.0, 7.4, 9.0, 11.0 and 13.0 showed the presence of peaks attributed to $[Cu_2L_3]^+$ and $[Cu_2(HL)_2L]^+$ species only at pH 7.4. The detection of peaks attributed to $[Cu_2L_3]^+$ species at physiological pH values have been reported for the Cu(II) derivative of the antitumour drug Triapine®, the 3-aminopyridine-2-carbaldehyde thiosemicarbazonecopper(II) complex [142,143].

Taking these results into account, it can be proposed that the desulfurization may proceed even at physiological pH values, at least in a certain extent. Considering the key role that $[Cu_2L_3]^+$ entities could play, a mechanism has been proposed and its validity checked by quantum mechanical calculations (see Fig. 6) [139]. The theoretical study identifies a highly exergonic ($\Delta G = -146.1$ kcal·mol^{-1}) nucleophilic attack of a hydroxide anion to one of the thioamide carbon in these $[Cu_2L_3]^+$ species, which could trigger the process. It must be emphasized that all the stages of the mechanistic sequence proposed are built with monomer or dinuclear metal complexes whose crystal structures have been previously reported as $[CuL(OH_2)]^+$ entities in $[\{CuL(OH_2)\}_2](SiF_6)\cdot 4H_2O$ [144], $[CuL_2]$ [134], $[CuL(L^{CN})]$ [134], and $[\{CuL(SH)\}_2]$ [137]. The latter could arise from dehydration of the $[\{CuL(OH_2)(SH)\}_2]$ (VIII) dimers acting the crystal packing as driving force through the strong non-covalent interactions (hydrogen bonding and π-π stacking) present in the lattice.

The complexity of this reaction could hide other important influences, as the concentration of $[CuL]^+$ cations, which could be dramatic for the formation of $[Cu_2L_3]^+$ species, or the coexistence of simultaneous redox processes involving the Cu(II) ions. The latter could involve the participation of the TSC ligands, in the same way that the self-reduction processes described for the $[FeL_2]^+$ complexes at pH > 6 to give $[FeL_2]$ [145-147].

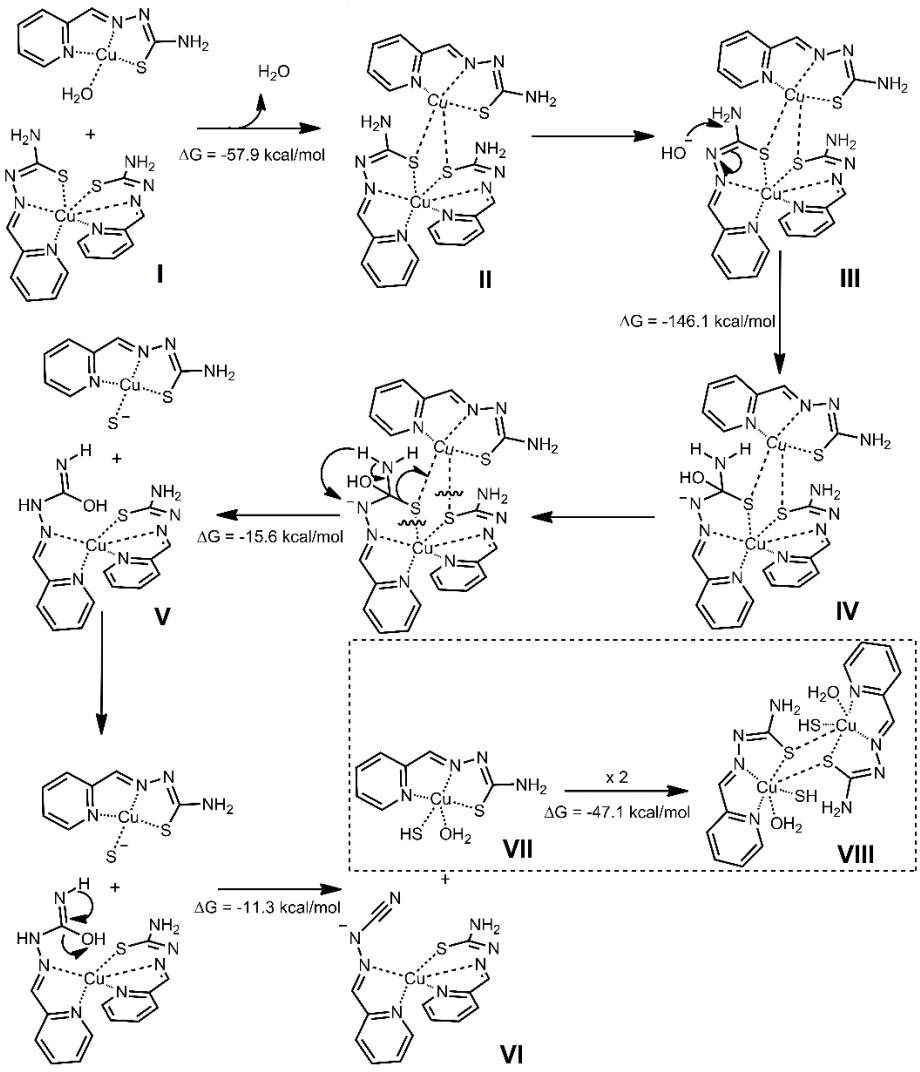


Fig. 6 Proposal for a mechanism of the desulfurization of HPTSC to carbonitriles in basic media. Values of the Gibbs free energy arisen from DFT calculations are indicated for each step. The dynamic of transformations is represented by arrows

Apart from mechanistic proposals, the possibility of visualizing the terminal NCN fragment as cyanamide (N–C≡N) or carbodiimide (N=C=N) connects this process with broader desulfurization reactions dealing with thioamide groups, as the reduction of thioamide to imine by triethylsilane at 80 °C with Fe catalyst [148], the conversion of thioamide into nitrile in the presence of a Rh catalyst in benzene basified by NEt_3 [149], or even the use of base to synthesize 1*H*-1,2,4-triazol-3-amines from condensation of amidines, isothiocyanates and hydrazines [150].

b) Appearance of sulfate from thiosemicarbazone breakage in acid and basic media

In other processes, often less understood, sulfate ions were identified, the origin of which only can be the release of the thioamide sulfur atom.

Due to the strong similarities with the system shown in Section 2.1.a), we start describing the behaviour of the $[\{Cu(L')(NO_3)\}_2]$ compound when is exposed to basic media (HL' = pyridine-2-carbaldehyde 4-N-methylthiosemicarbazone, HPTSC4m) [137,151]. Experiments performed on this compound at pH 9.0 and 80 °C for 1 h yielded a dark brown compound with no evidence of TSC breakage. However, an increase in pH to 11.0, even at lower temperatures (50 °C) provoked the release of irritant gases, whose analysis by gas chromatography-mass spectrometry revealed the presence of methylisothiocyanate ($S=C=N-CH_3$), pyridine 2-carbaldehyde and N-methylthiosemicarbazide ($H_2N-NH-C(=S)-NH-CH_3$). It must be pointed out that these chemicals are starting materials for the synthesis of HPTSC4m. Once filtered the suspension, slow evaporation of the mother liquors resulted in the attainment of single crystals of the $[\{Cu(L')(OH_2)\}\{Cu(L')(OSO_3)\}]\cdot 5H_2O$ derivative, where sulfate anions arise from the loss and oxidation of the sulfur atom of the thiosemicarbazone ligand. Notwithstanding, when the addition of base to pH 11.0 was carried out in a cold water bath (T < 15 °C) and the solution was kept at 5 °C inside a freezer for 2 months, crystals of $[\{Cu(L')\}_2(O_2NO)](OH)\cdot 5H_2O$ were obtained, which contain unmodified HPTSC4m ligand. No desulfurization process is observed for the free HL' ligand in the experimental conditions reported above.

The heterogeneous content of the identified products suggests that a very complex set of processes take place simultaneously in this reaction, which precludes a clear and univocal mechanistic proposal. These facts, put all together, demonstrate that coordination to Cu(II) ions is required for the transformation of TSCs into carbonitrile triggered by basic medium.

c) Other desulfurization processes of thiosemicarbazone metal complexes in basic medium

A very interesting combination of desulfurization and cyclization processes in TSCs was reported by Castiñeiras and García-Santos in reactions of pyridine-2-formamide thiosemicarbazone (HFTSC) with $Mn(ClO_4)_2\cdot 6H_2O$ [152]. They attained the $[Mn(HFTSC)_2](ClO_4)_2$ compound, which contained the unaltered HFTSC ligand, when the reaction proceeded in ethanol under reflux for 2 h. However, if drops of NEt_3 were added in the presence of 2,2'-bipyridine (bpy), a yellowish-brown precipitate was obtained. After removing it, crystals of $[Mn(bpy)_2(NCS)_2]$ could be isolated from the mother liquors by slow evaporation, where thiocyanato ligands came from the breakage of HFTSC.

In addition, when aqueous solutions of $Mn(ClO_4)_2\cdot 6H_2O$-bpy-HFTSC (in a 1:2:1 molar ratio) were basified with NaOH and refluxing for 2 h, a brown precipitate identified as $[Mn(bpy)(pdo)_{0.5}(pta)](SO_4)$ was recovered, where pta = 3-(pyridine-2-yl)1H-1,2,4-triazol-5-amine, and pdo = 2,4-pentanediol. Further recrystallization of this solid in pyridine (py) yielded crystals of $[Mn(py)_4Mn(py)_2(OH_2)_2(\mu\text{-}SO_4)_2]\cdot 4H_2O$, whereas the recrystallization from DMSO/$CHCl_3$ or DMF/diethyl ether mixtures afforded yellow crystals of $[Mn(pdo)(pta)_2]_4(SO_4)_2\cdot 4H_2O\cdot S_8$. Note that pta, pdo, S_8, and sulfate anions only could arise from desulfurization and decomposition of the TSC ligand, that authors attributed, at least in part, to the role of the Mn(II) ion as redox catalyst. The formation of pta is depicted in Fig. 7.

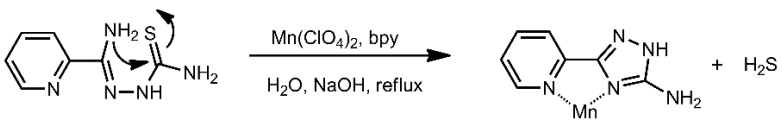


Fig. 7 Transformation of HFTSC into pta induced by coordination to Mn(II) in aqueous basic medium

d) Conversion of thiosemicarbazones into thiocyanate in acid medium

Slow addition of 1-8 drops of $HClO_4$(c) over mixtures of HPTSC and $Cu(ClO_4)_2$ in ethanol yielded, at a first stage, a brown compound identified as the 1D complex $\{[Cu(PTSC)(OH_2)][Cu(PTSC)(OClO_3)]\}_n \cdot nClO_4 \cdot 2nH_2O$. Once filtered off and days after, bright green prismatic crystals of $[Cu(HPTSC)(NCS)](ClO_4)$ could be gathered from the mother liquors, whose crystal building exhibited an incommensurate modulated structure [139]. Analogous results were serendipitously obtained by reaction of $Cu(NO_3)_2$ and HPTSC in a water:methanol mixture (1:1) in the presence of Na_2ATP (adenosine-5'-triphosphate disodium salt), which spontaneously evolved to pH 0.6 by slow evaporation for two months, to yield the $[Cu(HPTSC)(NCS)][Cu(HPTSC)(NCS)_{0.72}(NO_3)_{0.28}](NO_3)_2$ compound [137]. The stabilization of the complex in so extremely acid medium ratifies the high affinity between Cu(II) ions and HPTSC. The bands at 2136 cm^{-1} and 2097 cm^{-1} in the infrared spectra of the perchlorate and nitrate derivatives, respectively, allowed to easily identify the presence of the pseudohalide. No traces of thiocyanate were detected in solids arisen from acid treatments of the free HPTSC ligand.

A proposal for the desulfurization process is provided in Fig. 8. Coordination of Cu(II) ions to the thioamide group in the neutral TSC would trigger a nucleophilic attack by a water molecule. The formation of intermediates as 2-(hydrazinomethyl)pyridine (RNH_2) and carbamothioic O-acid, together with further dehydration and deprotonation of the latter, would generate the thiocyanate groups.

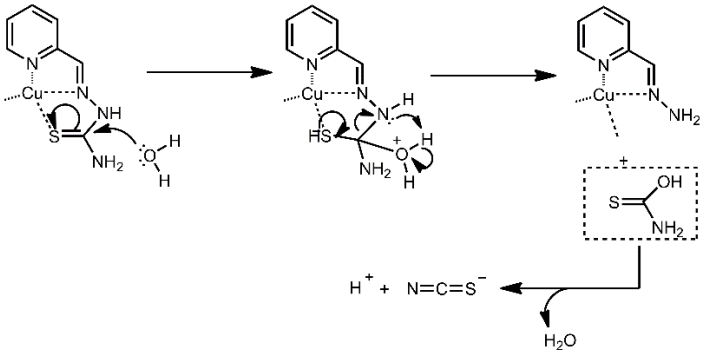


Fig. 8 Proposal for a mechanism of the desulfurization of HPTSC to thiocyanate in acid media

Formation of thiocyanate in chemical systems similar to TSCs, however, has been also described in basic media, as that reported for bis(N-alkyldithiocarbamato)cadmium(II) complexes in the presence of Et_3N to give alkyl isothiocyanate Fig. 9 [153].

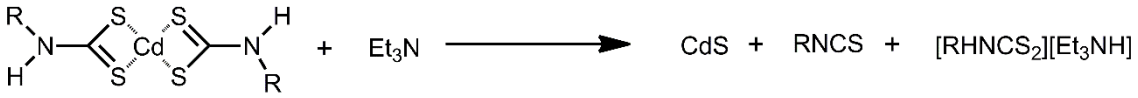


Fig. 9 Formation of alkyl isothiocyanate from dithiocarbamatocadmium(II) complexes in basic medium

Desulfurization reactions in other sulfur-containing ligands have been reported, as the conversion from thiourea to urea-derivatives induced by basic-neutral media of NaAcO in ethanol [154].

e) Influence of pH in other reactions: from TSC to picolinate and formation of disulfide

Single crystals of the $[Cu(PTSC)Cl]_2[Cu(pic)_2]\cdot 2H_2O$ compound were serendipitously obtained after slow evaporation of aqueous suspensions of $CuCl_2$, HPTSC and guanine at pH 5.6. The bis(picolinato)copper(II) species arose from the breakage of the TSC ligand [137], as will be discussed later for other reactions.

Chalcogenide elements, sulfur in particular, are of substantial relevance considering potential biomimetic applications. In biological environments, thione/thiol - disulfide exchange reactions have an important role on enzymatic processes involved in cellular functions, including redox activity, protein folding, DNA expression/repair or apoptosis. Disulfide formation induced by a redox process implies a weakening of the C=S thioamide bond in TSCs and this process could underlie desulfurization reactions as an intermediate

step. For that reason, a better compression of the factors involved in the S-S bond cleavage and formation is required. In this sense Hong and co-authors studied factors affecting to the interconversion between Cu(II) and Zn(II) thione-disulfide dinuclear thiosemicarbazone complexes, thus demonstrating feasible interconversion with acid-base or solvent changes (Fig. 10), whereas interconversion did not take place in the absence of metal ions [155].

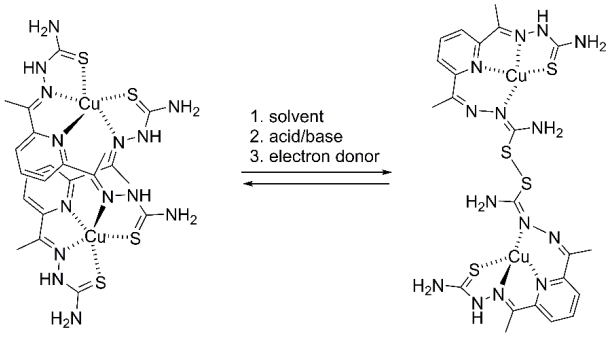


Fig. 10 Disulfide formation in TSC-Cu(II) complexes

2.2. Desulfurization in electrochemical processes

Electrochemical synthesis has emerged as an interesting synthetic methodology leading to compounds usually different from those obtained from starting metal salts. Despite of the electrochemical conditions has not been identified as crucial for desulfurization reactions to occur, the great number of examples obtained from electrochemical mother liquors justified a section an in this review.

During electrochemical reactions of the thiosemicarbazone *N*-{2-([4-*N*-ethylthiosemicarbazone]methyl)phenyl}-*p*-toluenesulfonamide, H_2L^1, with manganese and copper metals, interesting catalysed processes were found to occur, with remarkable consequences regarding the ligand skeleton structure. In synthesising the manganese complex, it was obtained an unexpected dithiolate thiosemicarbazone tosyl ligand, H_2L^2, as a side-product. The disulfide ligand H_2L^2 presented here was formed by an oxidation process of the initial thiosemicarbazone ligand H_2L^1 during experiments on the electrochemical synthesis of the manganese complex. The proposed mechanism could start with a thione–thiol equilibrium in solution, followed by coordination of manganese atoms to two different doubly-deprotonated ligand units and coordination of the thiolate sulfur atom as a μ_2-bridge between the two Mn(II) ions. This step was followed by a reductive elimination process resulting in the coupling of two thiolate units, thereby creating the disulfide bond (Fig. 11). The oxidation of the thiosemicarbazone to disulfide under physiological conditions could lead to a reinterpretation of the biological properties of some thiosemicarbazone systems, primarily those aspects related to their possible therapeutic uses [156].

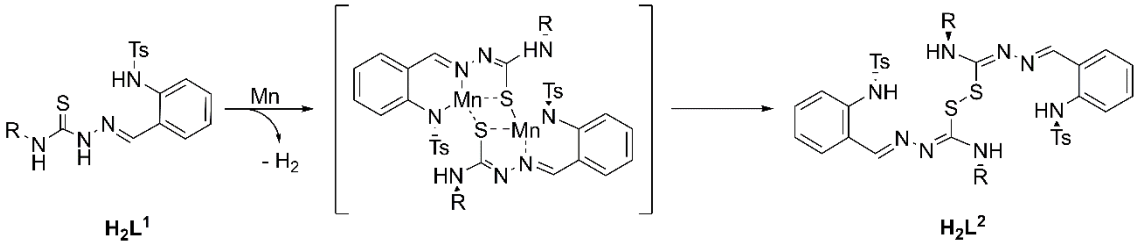


Fig. 11 Mechanism proposed for the formation of the disulfide ligand H_2L^2

In the case of copper, the solid complex was $[CuL^1]_2$, but the crystallized product showed the copper atoms bound to a new cyclized thiosemicarbazone ligand, H_2L^3, as was shown in the structures of the complexes $[Cu(L^3)]_2{\cdot}CH_3CN$ and $[Cu(L^3)(H_2O)]_2{\cdot}CH_3CN{\cdot}H_2O$. Oxidative cyclization of the original ligand H_2L^1 by Cu(II) ions followed by the addition of an acetamide fragment, accompanied by a reductive elimination process led to the formation of the new tetradentate ligand H_2L^3. The new ligand features a five-membered 1,2,4-triazole ring, formed by nucleophilic attack of the thioamide nitrogen on the imine carbon (Fig. 12), followed by the addition of an acetamide fragment to a Cu(II) ion and the sulfur atom. The presence of an

acetamide residue in the reaction medium may possibly be explained in terms of copper-catalysed hydrolysis of acetonitrile whereas the attachment of an acetamide fragment to the formed 1,2,4-triazole-3-thione ring could take place by coordination of the metal followed by a reductive elimination process.

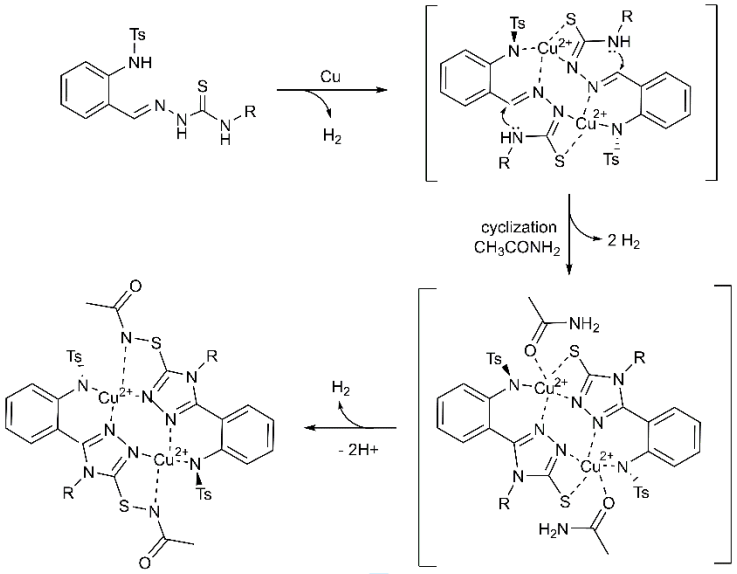
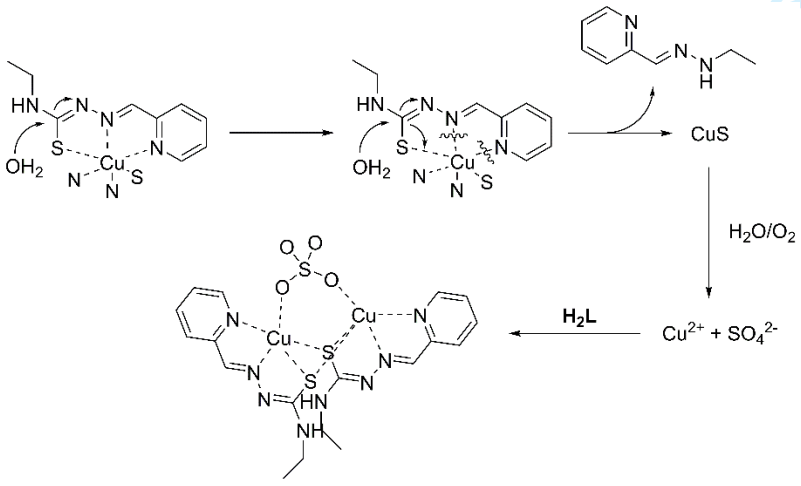


Fig. 12 Proposed mechanism for the formation of the complexes $[Cu(L^3)]_2 \cdot CH_3CN$ and $[Cu(L^3)(H_2O)]_2 \cdot CH_3CN \cdot H_2O$ by copper-catalysed oxidative cyclization of the ligand H_2L^1 followed by addition of an acetamide group

Another case of sulfate generated by thiosemicarbazone desulfurization was found in the complex $[Cu_2(LEt)_2(SO_4)]$, isolated by slow recrystallization of the mother liquors obtained after separation from the expected solid complex $Cu(L^{Et})_2$ (HL^{Et}= pyridine-2-carbaldehyde-4-*N*-ethyl-thiosemicarbazone). The complex consists of a neutral dinuclear Cu(II) entity, acting the sulfate group as bidentate ligand to achieve electroneutrality [157]. Some other Cu(II) dimer complexes derived from 2-pyridincarbaldehyde thiosemicarbazones and incorporating sulfate groups arising from desulfurization processes have been published before but, in these cases, the sulfate group acted as monodentate ligand. The mechanism explaining this desulfurization process starts with a nucleophilic attack, probably of a water molecule to the thioamide carbon atom (Fig. 13) and the subsequent release of copper sulfide to the media during the electrochemical synthesis. Slow oxidation of copper sulfide by oxygen from the water or the air could convert the copper(II) sulfide into copper(II) sulfate. Finally, the assembly of complex $[Cu_2(LEt)_2(SO_4)]$ would take place by coordination of the ligands H_2L^{Et} and sulfate to the Cu(II) metal ions.



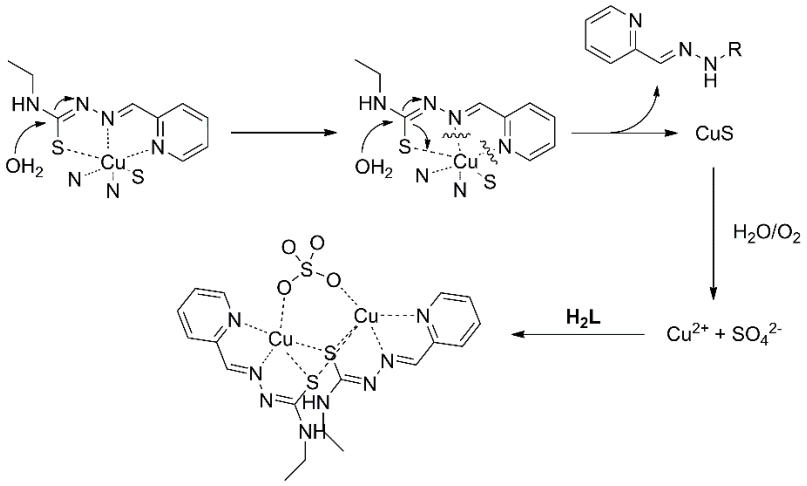


Fig. 13 Proposed mechanism for the desulfurization of pyridine-2-carboxaldehyde-4-*N*-ethyl-thiosemicarbazonecopper(II) complexes to form sulfate ions

Metal-free thiosemicarbazones have also been electrochemically studied, in particular isatin derivatives. Thus, upon oxidation, it was proposed the breakage the of the C=N bond, generating isatin and thiourea fragments for all evaluated molecules (Fig. 14). Regarding the reduction, the cleavage of the N-N bond as well as the generation of 3-aminoindolin-2-one and thiourea moieties was proposed [158].

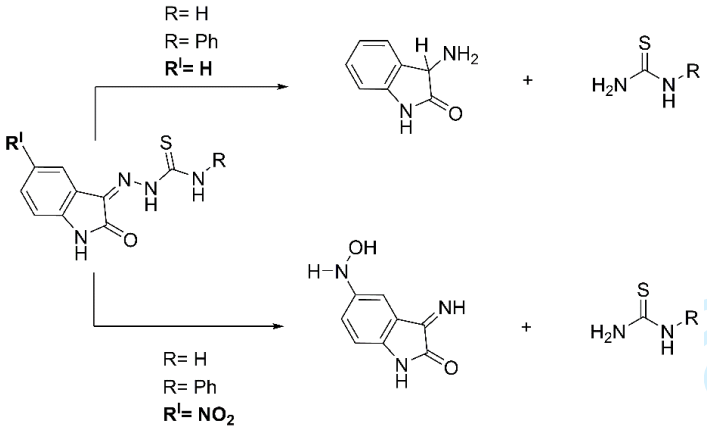


Fig. 14 Electrochemically induced cleavage of isatin thiosemicarbazone

Electrochemistry, coupled to high resolution mass spectrometry (HRMS), was also employed to investigate the possible relationship between the structure of α-N-heterocyclic thiosemicarbazones and their metabolic behaviour. To this end, the metabolites of ten different Triapine® derivatives with a wide range of antitumour activities were analysed. In general, for all the investigated thiosemicarbazones, the identified processes of the metabolic reactions were hydroxylation, oxidative desulfurization (formation of the amidrazone and, for some derivatives, also the semicarbazone) and disulfide dimer formation and dehydrogenation in some cases (Fig. 15). In general, desulfurization was detected for all the investigated compounds, thus confirming that the study of desulfurization process is crucial for a better understanding of the thiosemicarbazones biological activity [159].

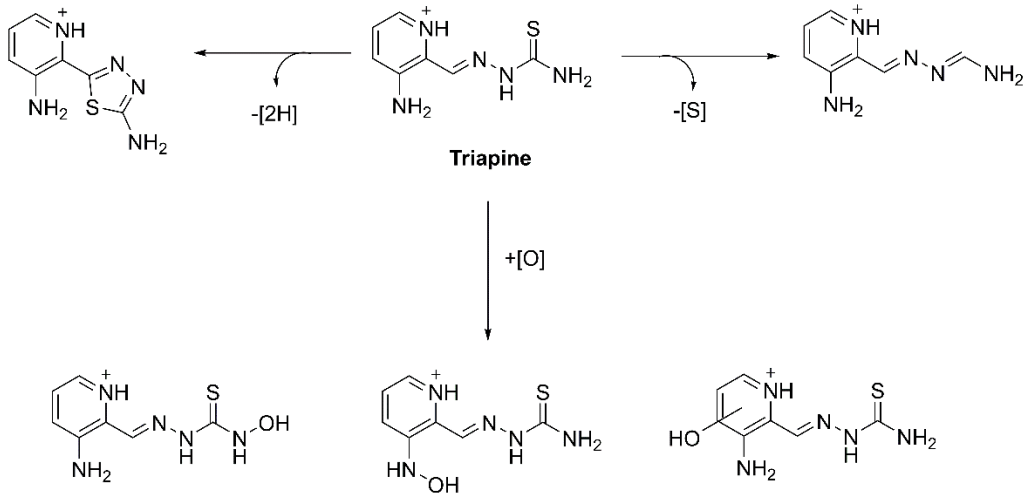


Fig. 15 Key metabolites of Triapine®: the dehydrogenated ring-closed thiadiazole and hydroxylated species

2.3. Desulfurizations by oxidant reactants

The interaction between thiosemicarbazone complexes and oxidants can give rise to desulfurization by reactions often involving oxidative cyclization processes. Some of them are described in the present section.

a) Conversion of thiosemicarbazones into 1,3,4-oxadiazoles by halate ions

The addition of bromate to aqueous solutions of HL (where HL = HPTSC and HPTSC4m) triggered a complex process whose main reaction led to 1,3,4-oxadiazole derivatives [160,161], that could be regarded as is shown in Fig. 16.

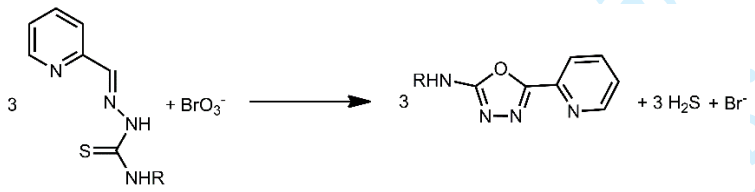


Fig. 16 Transformation of thiosemicarbazones into 1,3,4-oxadiazoles. Thiosemicarbazones: pyridine–2–carbaldehyde thiosemicarbazone (R = H, HL = HPTSC) and pyridine-2-carbaldehyde 4-N-methylthiosemicarbazone (R = CH_3, HL = HPTSC4m). Oxadiazoles: 2-amino-5-pyridin-2-yl-1,3,4-oxadiazole (R = H, L_{oxad} = 134OXAD) and 2-methylamino-5-pyridin-2-yl-1,3,4-oxadiazole (R = CH_3, L_{oxad} = 134OXADm)

The study of different well-characterized solids isolated from this process allowed to distinguish several steps, which are drawn in Fig. 17, despite some stages in the mechanism remain unclear. The reaction proceeded smoothly with the addition of bromate to aqueous solutions of preformed $CuL(NO_3)$ complexes at pH ~ 6 (Step 3). An olive-green precipitate corresponding to the centrosymmetric S-bridged $[\{CuLBr\}_2]$ dimer appeared (Step 3) and, after filtering it, the initial dark green colour of the solution gradually became lighter. Simultaneously, the pH decreased to 3–4 and an irritant gas was released. Two days later, single crystals of $[\{Cu(L_{oxad})(OH_2)_2(OSO_3)\}_2]$ were obtained (Step 4). The addition of $K_4[Fe(CN)_6]\cdot 3H_2O$ led to the coprecipitation of purple $K_2Cu[Fe(CN)_6]\cdot H_2O$ and L_{oxad}, whose particle sizes were different enough to eliminate the complex in the filtrate while the white organic compound was retained in the filter and, afterwards, recrystallized in ethanol (5). The use of $NaHCO_3$ instead of $K_4[Fe(CN)_6]\cdot 3H_2O$ also allowed to isolate the oxadiazole ligand. The rate of the reaction was increased with heating and addition of small

amounts of acid. However, brown suspensions were attained in the excess of acid or strong heating, whose filtration allowed to isolate crystals of bis(pyridine-2-carboxylate)copper(II) (6).

The reaction also took place without Cu(II) ions, but strong acid media was required (pH = 0−1) and, after filtration of a dark red unidentified solid, further treatment with NaOH to pH = 3–4. In the presence of acid media, mixtures of compounds were invariably obtained and purification was needed. The use of KIO_3 in acid media yielded the same results than $KBrO_3$, but the formation of iodine, probably due to comproportation between I^- and IO_3^-, made more difficult the purification of the product. Furthermore, the addition of KIO_3 to the $CuL(NO_3)$ complexes at pH ~ 6 led, firstly, to the attainment of a green compound identified as $CuL(IO_3)$, which evolved when the suspension was kept with stirring to yield $[\{CuLI\}_2]$ dinuclear compounds in a final step, but oxadiazole derivatives were not attained. The analogous $CuL(BrO_3)$ compound could not be isolated in these experiments. On the contrary, none of the attempts carried out by using chlorate as oxidant gave any evidence for oxidative cyclization, which could be due to kinetic factors. Finally, no oxidation compounds were attained by using pyridine–2–carbaldehyde 4,4'-N-dimethylthiosemicarbazone (HPTSC44m) neither free nor coordinated to Cu(II) ions, which suggests steric influences in the process.

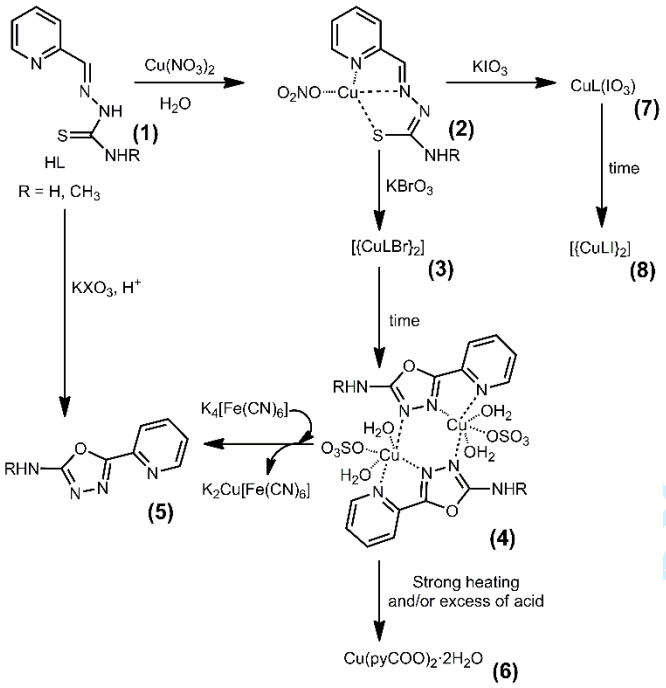


Fig. 17 Reaction pathways identified for the different reactants and conditions

A plausible mechanism can be proposed taking into account the experimental evidences, which is depicted in Fig. 18 for the free ligand, but it could be extrapolate, at least in part, for the Cu(II) complexes.

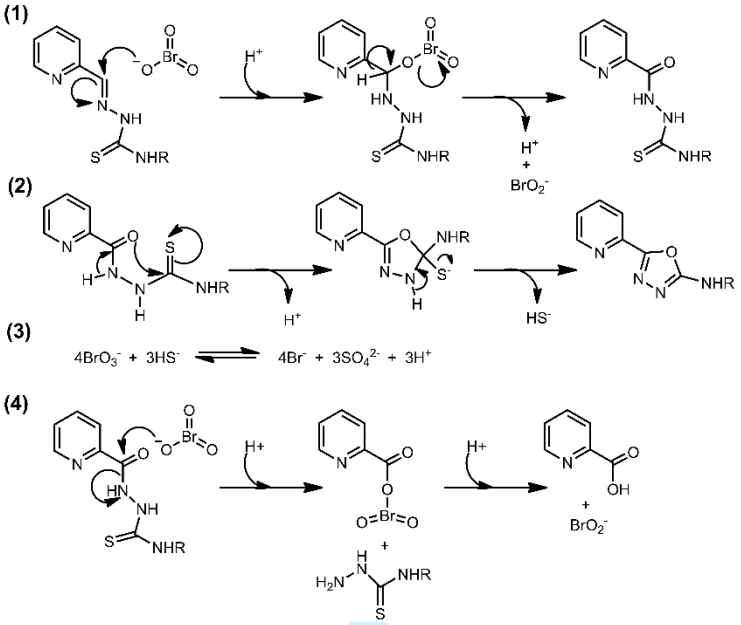


Fig. 18 Mechanism suggested for the halate-induced oxidative cyclization of TSCs to 1,3,4-oxadiazoles

These processes allow to prepare 2-amino-1,3,4-oxadiazoles as the only product through easy and unexpensive reactions, sometimes in less than an hour.

Oxidations of acyl thiosemicarbazides, acyl carbodithioates and acyl thioureas to oxadiazoles, often promoted by metal ions, have been frecuently described in the literature [162-183].

b) Other desulfurization of thiosemicarbazones by oxidant reactants

The use of other oxidants to desulfurize and cyclize TSCs has been described for a long time, as it was reported by Landquist in the attainment of triazolinones by reaction with MnO_2 [184].

From a broader point of view apart from TSCs, the use of oxidants as H_2O_2, $^1O_2$ and I_2 has been described for the desulfurization of other sulfur-containing molecules, as 8-thioguanosine to guanosine [185] or dithiocarbamato-Ru(II) complexes [186,187], among others.

Desulfurization of TSCs through processes involving redox-active metal ions is discussed in Section 2.4.d.

2.4. Others (radiation-, thermal-, solvent- and coordination-induced desulfurizations)

a) Solvent-induced desulfurizations

Another factors like light, pressure or solvent must be considered to have a relevant role in thiosemicarbazone desulfurization reactions. In this sense, recently it was presented the dinuclear helicate $[Ag_2(H_2L)_2]SO_4$ obtained by crystallization of the bisthiosemicarbazone cluster helicate $[Ag_4L_2]_2$ in the absence of any sulfate source, after a rare desulfurization process that takes place only in chloroform (Fig. 19). Three factors were investigated in this conversion: solvent, light and time. Only those recrystallizations performed in chloroform in the presence of light led to the formation of the sulfate helicate crystals. Regarding to time, the appearance of the sulfate crystals took place after a long crystallization period of 3-4 weeks. Some ^{1}H NMR studies mimicking the recrystalization conditions demonstrated that the acid pH resulting from chloroform degradation triggers the desulfurization process by protonation of the hydrazine NH groups, thus resulting on the dihelicate unit $[Ag_2(H_2L)_2]^{2+}$. It is relevant to mention that two side-products were identified along the desulfurization: silver hydrogen sulfide/sulfide, that easily evolved to the sulfate counterion by oxidation by moisture oxygen, and the organic fragment semicarbazone released

from the oxidative desulfurization. Finally, the remaining dinuclear complex combined with the sulfate thus generating the final crystallized sulfate dihelicate $[Ag_2(H_2L)_2]SO_4$ [188].

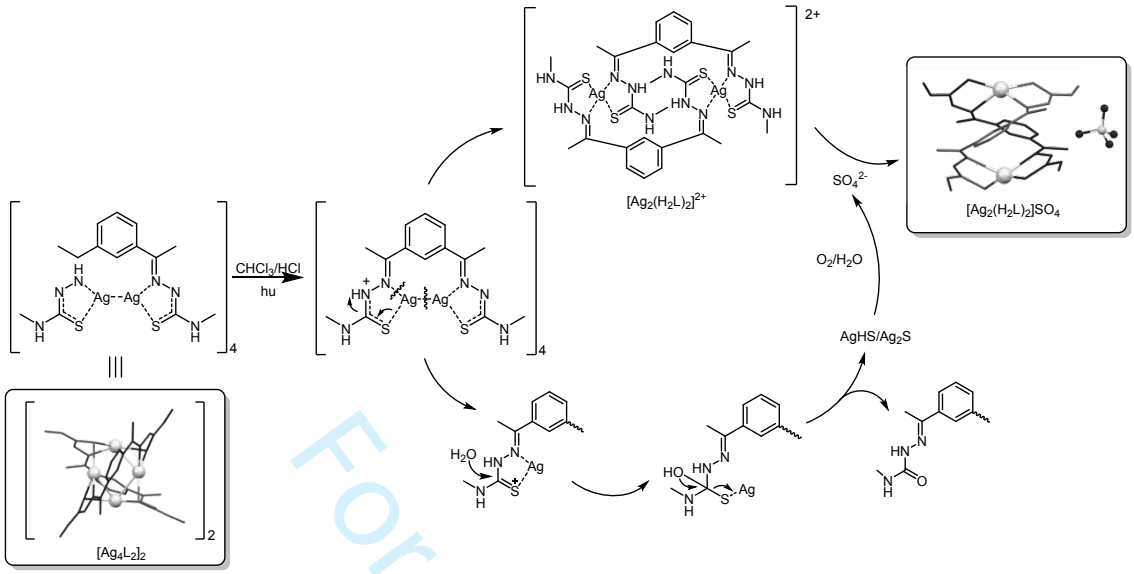


Fig. 19 Formation of the dinuclear helicate $[Ag_2(H_2L)_2](SO_4)$ by desulfurization of the double-tetranuclear cluster helicate $[Ag_4L_2]_2$

Notwithstanding, it must be admitted that not always coordination to metal ions is required to provoke solvent-induced desulfurization in TSCs. For instance, Peach and Dilworth et al. [189] described intramolecular cyclization reactions in recrystallization experiments of bisthiosemicarbazones that involved the loss of one of the thioamide sulfur atoms. The isolated product depended on the kind of solvent used, as is shown in Fig. 20.

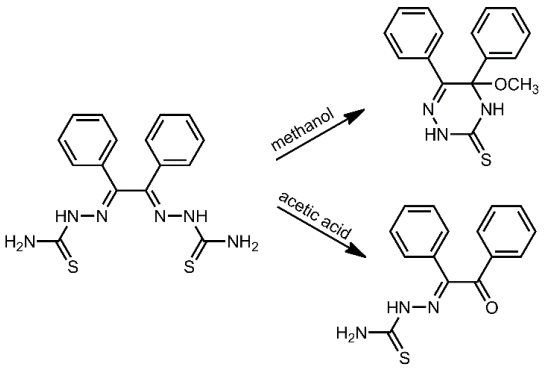


Fig. 20 Benzil bis(4-phenyl-3-thiosemicarbazone) and related cyclized products of solvent-induced desulfurization processes

b) The influence of the electromagnetic radiation

Microwave radiation is known to promote desulfurization in organo-sulfur compounds being this process of great importance for reducing harmful emissions during the combustion process [190]. Microwave irradiation of thiosemicarbazones gave the corresponding isothiocyanates, which on addition of either activated nitriles or aldehydes furnished various types of azines (Fig. 21) [191]. This process was also reported for thiosemicarbazone analogues, as thiocarbohydrazones [192].

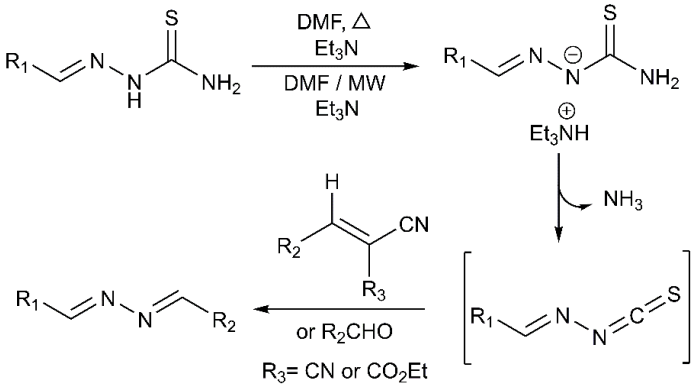


Fig. 21 Azine fragments formed after microwave irradiation of thiosemicarbazones

Visible light has been used as an agent for desulfurization of thiols and disulfides [193]. However, as far as we are aware, none of these processes has been reported for TSCs.

c) Thermal induced desulfurizations

Heating is another point to be considered in desulfurization processes experienced by TSC complexes. Thus, prolonged treatment in refluxing aqueous solutions of the complex $CuL(NO_3)$, being HL= pyridine-2-carbaldehyde thiosemicarbazone, induced breakage of a portion of the thiosemicarbazone molecules to give HS^- ligands that were identified in the structure of $[\{CuL(SH)\}_2]$, whose crystals were collected from the mother liquors (Fig. 22). In contrast, the free ligands remain unaltered under the same experimental conditions. Extending the studies to other metal ions, as Fe(III), Co(III), Zn(II) and Pb(II), it was found that only bis(thiosemicarbazonato)iron(III) species underwent breakage whereas there was no evidence for desulfurization processes in the Co(III), Zn(II) and Pb(II) derivatives. The IR data suggested that breakage of HL ligands gave rise to thiocyanato ligands in the above mentioned Cu(II) derivatives, while a non-coordinated thiocyanate anion was present in the Fe(III) decomposition product [137].

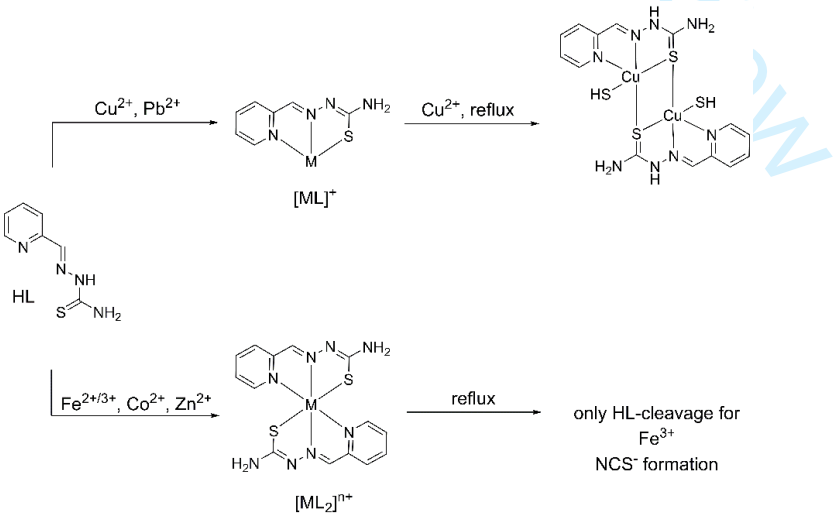


Fig. 22 Summary of desulfurization processes by refluxing on $[ML]^+$ and $[ML_2]_{n+}$ entities, HL = pyridine-2-carbaldehyde thiosemicarbazone

Ghosh et al. [194] reported the conversion of methyl 2-pyridyl ketone 4-(4-tolyl)thiosemicarbazone (HL) into methyl(2-pyridyl)methyleneimine (L') by refluxing in ethanol for 24 h a mixture of the preformed $[RuCl(L)(PPh_3)_2]$ compound and a six-fold excess of the HL ligand (Fig. 23).

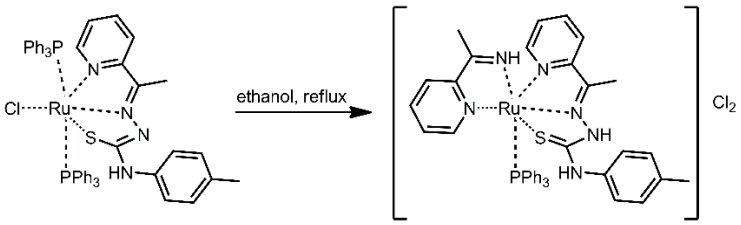


Fig. 23 Attainment of methyl(2-pyridyl)methyleneimine (L') by transformation of $[RuCl(L)(PPh_3)_2]$ into $[Ru(HL)(L')(PPh_3)]Cl_2$

Thermally activated desulfurizations, for instance by refluxing solvents with high boiling temperature, have been applied for synthetic methods using sulfur derivatives analogous to TSCs, as bisthioureas [195].

d) Oxidative desulfurization of thiosemicarbazones induced by metal ions

The mere coordination of TSC to metal ions can promote desulfurization. Sometimes, this kind of breakage reveals the existence of redox processes. For instance, the reaction of $Na[AuCl_4]$ with the disulfured TSC derived from N-[N′,N′- dialkylamino(thiocarbonyl)]benzimidoyl chloride gives rise to a partial reduction of Au(III) to Au(I), as Abram et al. have reported [196]. As a result, apart from the major product I, a certain amount of the ligands undergo oxidative cyclization, through an intermediate thiatriazine-Au(III), leading to the loss of one of their sulfur atoms to yield N-(hexamethylene)-N′-1-(5-diethylamino-3-phenyl-1,2,4-triazolyl)thiourea, that acts as monodentate ligand linking through the remaining sulfur atom to Au(I) ions in the minor product II (Fig. 24).

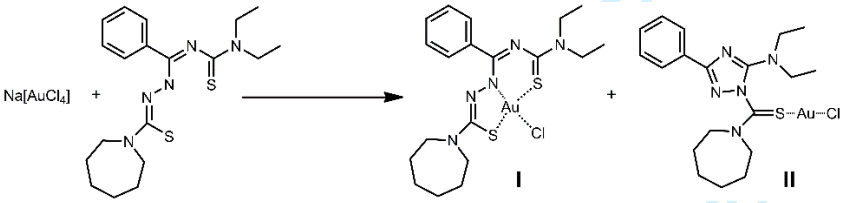


Fig. 24 Reduction of Au(III) to Au(I) by partial desulfurization of a TSC to give a triazole derivative

In the same way, the reaction of an aqueous solution of $[Cu(HPTSC)(ox)(OH_2)]$, acidified with HNO_3 to pH 0.8 in the presence of an excess of $VOSO_4$ (molar ratio 1:10), and further addition of base while vigorous stirring to pH 3.7 yielded, after filtration and slow evaporation of the mother liquors, crystals of the $\{[Cu(HPTSC)(OH_2)]_2[Cu(PTSC)S]_2(H_4V_{10}O_{28})\}_n$ compound [197]. The sulfido ligands, arisen from partial desulfurization of the TSC and probably caused by oxidation of V(IV) to V(V), play the role of μ_2-S^{2-} bridges between $[Cu(PTSC)]^+$ entities to build $[\{Cu(PTSC)S\}_2]^{2-}$ dimers that connect the decavanadate clusters.

Other complex redox process was reported by Dilworth et al. in the reaction of pyridine-2-carbaldehyde thiosemicarbazone (HL) and analogues with the Re(V)-containing $[ReOCl_3(PPh_3)_2]$ compound [198]. Surprisingly, the reaction usually gave rise to $[ReL_2]Cl$ products, where Re(V) had been reduced to Re(III) probably by the released PPh_3 ligands. However, one of the resulting complexes, derived from 2-acetylpyridine thiosemicarbazone, contained a methyl(2-pyridyl)-methyleneimine ligand (L') as a result of a reductive cleavage of the hydrazinic N–N bond in the TSC (Fig. 25). The product, of formula $[ReCl_2L(PPh_3)_2][ReO_4]$ excluding the solvent molecules, contained both Re(III) and Re(VII) ions, the later formed through the redox processes that provoke the breakage of the ligand. In fact, the product in this reaction had a precedent in that reported by Ghosh et al [194] discussed in a previous section.

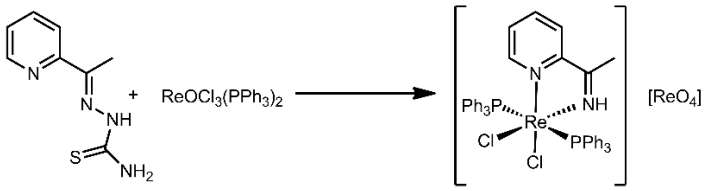


Fig. 25 The breakage of 2-acetylpyridine thiosemicarbazone to methyl(2-pyridyl)-methyleneimine by redox reaction and further coordination to Re(III) ions

Regarding to the influence of the metal ion coordination in these processes, Souza et al. [199] described that reaction of 3,5-diacetyl-1,2,4-triazole bis(4-ethylthiosemicarbazone) (H_5L) with $PdCl_2$ and LiCl in methanol led to the tetranuclear $[Pd_4(\mu_2\text{-}\eta^2\text{-}S_2)(H_2L)_2]$ compound, which exhibits a disulfide bridge between the four metal ions whose origin is the partial breakage of some of the TSCs.

Due to the strong analogies with TSCs, we include in this review the paper reported by Duan, He et al. about the fluorescent sensor tetra-2-pyridylthiocarbazone (H_2L), which desulfurized and cyclized to HL' in the presence of $Hg(NO_3)_2{\cdot}0.5H_2O$ or $HgCl_2$ [200], and a new pyridazine ring arose upon desulfurization (Fig. 26). The reaction was performed in H_2O/CH_3OH (90:10, v/v) mixtures and led to the attainment of crystals of the $[\{Hg(L')(SH)\}_2]$ and $[Hg(HL')Cl_2]$ compounds, whose structures were solved. Note that, in the first case, SH^- ligands coming from thioamide were coordinated to Hg(II) ions. An increase in the fluorescence intensity at 530 nm accompanied the reaction. No significant changes were observed for other metal ions, as Mg(II), Ca(II), Ba(II), Cr(III), Mn(II), Fe(II), Co(II), Ni(II), Cu(II), Ag(I) and Pb(II). However, the addition Zn(II) and Cd(II) also provoked an increase in the luminescence.

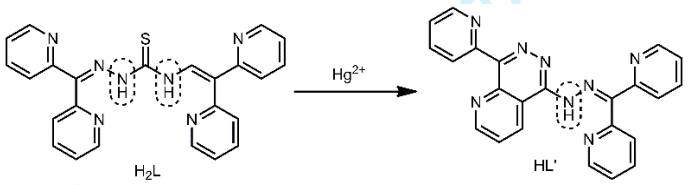


Fig. 26 Tetra-2-pyridylthiocarbazone (H_2L) and corresponding cyclization product (HL'), where the nitrogen positions able to deprotonate are marked with dotted boxes

Another Hg(II)-based chemodosimetric system based on thiosemicarbazone was investigated (Fig. 27). In this work, the conversion of the thiocarbonyl into a carbonyl group selectively exerted by Hg(II) ions and the dimerization of semicarbazone resulted in a pronounced OFF/ON-type fluorescent signalling behaviour [201].

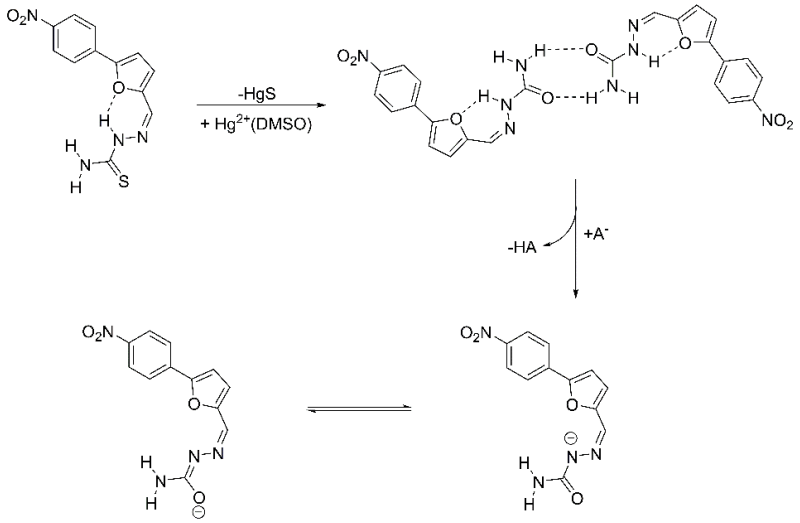


Fig. 27 Desulfurization of 5-(4-nitro)phenyl-2-furaldehyde thiosemicarbazone in the presence of Hg(II) ions and further dimerization of the resulting semicarbazone

Coordination-induced desulfurizations have been reported for acetylthioureas by coordination to Ag^+ ions [202], for 1,3-bis(3-methylpyridin-2-yl)thiourea after reaction with $[PtCl_2(dmso)_2]$ in methanol [203] or, in the same solvent, thiocarboxylates linked to Cu(II) ions to give carboxylates [204], for nickel dithiolenes to give 5,5'-bis(1,3-dialkyl-4-imidazolidine-2-thione-4-thiolate) [205], and thiosemicarbazide coordinated to Cu(II) to provide thiocyanate [206]. It has also been described the Cu(II) assisted desulfurization of 1-R-tetrazole-5-thiols to tetrazoles in ethanol or acetonitrile [207].

Finally, it is noteworthy that different chemical treatments sometimes give rise to the same product. As an example, Marchio et al. reported how a thioxo-1,2,4-triazolecopper(II) compound underwent desulfurization towards the 1,2,4-triazole derivative through different chemical pathways [208], as represented in Fig. 28.

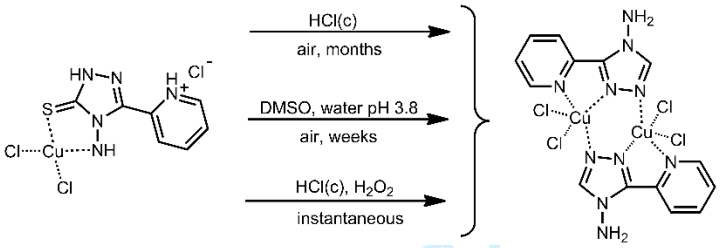


Fig. 28 Chemical versatility of the desulfurization of a thioxo-1,2,4-triazolecopper(II) complex

3. Biological implications

3.1. The physiological relevance of the triggering factors

As mentioned before, several factors have been probed to trigger desulfurization in thiosemicarbazones like pH, oxidants, temperature, radiation or solvents. In this context, it is important to mention that some of these factors intrinsically are crucial in cells, especially the pH and oxidation environments caused by ROS.

Physiologically normal intracellular fluid pH is commonly between 7.0 and 7.4, although there is variability between tissues [209]. However, the pH within organelles is tailored for its specific function. For instance, lysosomes are degradative organelles that need high internal acidity (4.5−5.0 range) to successfully perform their intended function [210]. In contrast, mitochondria have an internal pH of around 8.0, specifically pH 7.6−8.3, which is approximately 0.9 pH units higher than that of intermembrane space to generate large quantities of ATP [211,212]. Regarding the extreme pH values found in the diverse organs of mammals, they range from the gastric pH 1.5−3.5 to the pH 7.35−7.45 in blood [213,214].

Malignant tumour cells have acid pH values, in the 5.6-6.8 range. Thus, every tumour needs to change its metabolism to obtain the energy levels required for its high proliferative rates, and these adaptations lead to alterations in the extra- and intracellular pH. The changes in pH are common to all solid tumours, and can be used either as therapeutic targets, blocking the cell proton transporters and reversing the pH changes, or as means to specifically deliver anticancer drugs [215]. In short, taking all this into account, it can be deduced that the experimental conditions at which TSC-metal complexes show pH-induced desulfurization processes in the laboratory can be easily reached *in vivo*.

The presence of different oxidants in the biological media, mainly in aerobic organisms, is ubiquitous [216,217]. Therein, the attack of these species to the TSC backbone provoking alterations as those described in the previous section is feasible. Oxidant reactants are more likely produced in the chloroplasts, mitochondria, and peroxisomes surroundings [218,219]. The fighting against these entities to maintain the redox balance inside the cell requires the presence of reductant counterparts [220,221]. One of them is glutathione, the most abundant thiol in mammalian cells. The reduced/oxidized glutathione (GSH/GSSG)

couple is the main intracellular regulator of redox homeostasis in animals and plants. GSH controls the thiol oxidation state of proteins and acts as defence against oxidative stress, by directly scavenging ROS and by repairing their damage via enzymatic processes. Thus, GSH is a crucial compound for living cells, and targeting GSH metabolism is of wide interest for therapeutic purposes, in particular for fighting against cancer [222]. The activity of GSH strongly depends on different factors, as the presence of metal ions [223,224] or the pH [225]. In particular, the reactivity against reduced glutathione and, therefore, the production of ROS, seems to be notably enhanced with acidity in thiosemicarbazonecopper(II) complexes [226]. So, the interplay between the TSCs breakage and the increase in acidity of the medium could drastically modify the biological activity of these compounds.

The normal body temperature value about 36−37 ºC could be non-innocent in several processes when it combines with other factors, as neutral-basic media, in the way we have shown in Section 2.1.

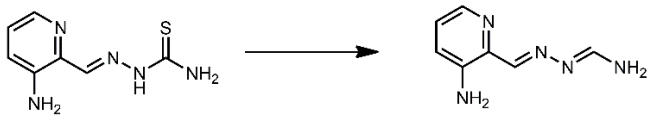
3.2. Detection of TSC desulfurization in *in vitro*, *in vivo* and clinical assays

The actual way of assessing the extent of the desulfurization of TSCs during their biological activity is the detection of these processes *in vivo*. One of the first works in this field suggested the transformation of 1-methylisatin 3-thiosemicarbazone into *syn* and *anti* isomers of 1-methylisatin 3-semicarbazone in incubation medium of the fungus Cladosporium resinae [227].

Few years after, it was published the fundamental paper by Sartorelli et al. dealing with the antineoplastic activity of 5-hydroxypyridine-2-carbaldehyde thiosemicarbazone (5-HP, Fig. 3) and isoquinoline-1-carbaldehyde thiosemicarbazone (IQ-1) on mice and dogs [228]. They used ^{14}C and ^{35}S isotopically labelled thiosemicarbazones to verify both the tissue distribution and the nature of the metabolites excreted in urine. The results showed that metabolic pathways for IQ-1 led to extensive desulfurization with liberation of sulfate as the major contribution, 59.6 % of the excreted derivatives. A second contribution was the side-chain cleavage with release of CO_2 (up to 20 % in mice), urea and thiourea (6.4 %) and the hydrolysis to semicarbazide and thiosemicarbazide (6.0 %). In fact, the breakage of the TSC chain actually seemed to obey to two types of cleavage. An attack on the hydrazine =N−NH− moiety, to yield thiourea and urea, was tentatively attributed to the action of azoreductase enzymes. In this case, the amount of urea was found to be about 4 % of urinary radioactivity, suggesting that desulfurization does not need to precede the TSC chain cleavage. In addition, there was hydrolysis of the azomethine –CH=N− fragment yielding thiosemicarbazide and semicarbazide fragments. Finally, a 13.3 % was apparently in form of glucuronides formed by ring hydroxylation and further reaction of the hydroxylated IQ-1 derivatives with glucuronic acid.

Analogous studies were performed by the same research team with 5-HP during the first Phase I clinical trials on TSCs reported in the literature [229]. They showed that glucuronide of 5-HP was the major component of the urinary label (41−62 %) because of the reaction of the hydroxyl substituent. No measurable amounts of urea, thiourea or semicarbazide could be found, indicating that the integrity of the TSC chain in 5-HP was unaffected by the metabolism in humans.

Precisely the discouraging results obtained in those first clinical trials caused, at least in part, a thirty-year hiatus until a new member of the family of TSCs was tested in humans. It was the 3-aminopyridine-2-carbaldehyde thiosemicarbazone (3-AP, Fig. 29). Kowol et al. carried out an extensive study on the metabolism of 3-AP by electrochemical techniques that simulated oxidative liver reactions, together with analysis of human liver microsomes and *in vivo* distribution experiments in mice [230]. As a result, several metabolites were identified, among them small amounts of the desulfurated formamidine derivative, depicted as (II) in Fig. 29. This oxidative desulfurization would proceed through the oxidation of the thioamide to give −NH−C(=SO_2)−NH_2, and further release of SO_2 and attainment of the formamidine –N=CH–NH_2.



(I) (II)

Fig. 29 Chemical structures of 3-AP (I) and the related formamidine (II)

The above-mentioned investigation was extended to 10 derivatives of 3-AP [159]. The panoplia of metabolic pathways involving oxidative desulfurization processes are represented in Fig. 30, and includes semicarbazone (II), amidrazone (IV) and the formation of ring-closed 1,3,4-oxadiazole (III) and triazole (V). The presence of semicarbazone (II) and amidrazone (IV) was detected for all the studied TSCs, however in some cases the amount of them was low. Dehydrogenation after the oxidative desulfurization led to the oxadiazole and triazole rings, which were not always observed. It is worth mentioning that the value of the m/z peak attributed to (V), about 190.11, entirely coincides with the possible nitrile-derivative of (IV) analogous to that described in Section 2.1.

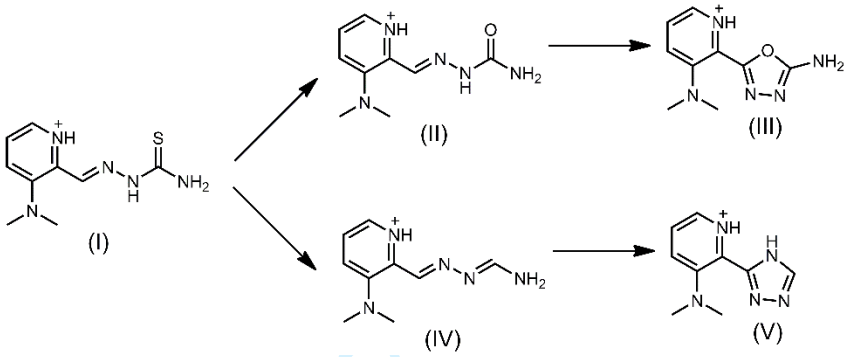


Fig. 30 Metabolites of 3-AP derivatives

Kovarikova et al. [231] performed an *in vivo* and *in vitro* liquid chromatography tandem mass spectrometry analysis (LC-MS/MS) to characterize the metabolites of 2-benzoylpyridine 4-ethyl-3-thiosemicarbazone (Bp4eT, Fig. 31). The studies *in vitro* were carried out using subcellular fractions of rat microsomes and cytosol, and male human liver samples. Male rats were used for the experiments *in vivo*. They found two metabolites of Bp4eT *in vitro* arisen from desulfurization: benzoylpyridine 4-ethylsemicarbazone (II) and N3-ethyl-N1-[phenyl(pyridine-2yl)methylene] formamidrazone (III). Both metabolites were also discovered *in vivo*, being present in plasma, urine, and feces, together with a new metabolite tentatively identified as a hydroxylated form of the amidrazone (III). More recent studies performed by Richardson and Kovarikova on DpC (di(2-pyridyl)ketone 4-cyclohexyl-4-methyl-3-thiosemicarbazone) and Dp44mT (di(2-pyridyl)ketone 4,4-dimethyl-3-thiosemicarbazone) found negligible oxidation of the thioamide to give formamidrazone metabolites, discarding a relevant role in the toxicity or efficacy of the products arisen from slow hydrolytic processes [232].

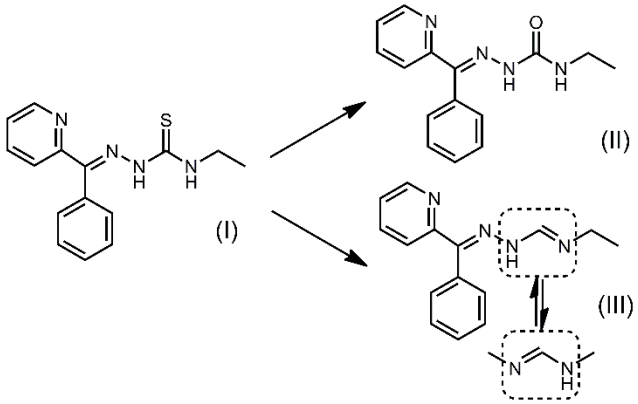


Fig. 31 Metabolites of 2-benzoylpyridine 4-ethyl-3-thiosemicarbazone (Bp4eT, I): 2-benzoylpyridine 4-ethylsemicarbazone (II) and N3-ethyl-N1-[phenyl(pyridine-2yl)methylene] formamidrazone (III)

3.3. The biological activity of the products arisen from the desulfurization reactions

It is well known since the early studies in the 60s of the last century that semicarbazones, which sometimes derived from desulfurization processes of TSCs *in vivo*, use to exhibit a lesser biological activity than the analogous TSCs [81, 233]. Forty years after, Richardson et al. compared the anti-proliferative activity of

different iron chelators derived from di-2-pyridylketone isonicotinoyl hydrazone [234]. They found that NNS thiohydrazones were 103-134-fold more active than their corresponding NNO carbonyl ligands. Surprisingly, the antiproliferative effects of the NNO ligands were 2-8-fold greater than the parent SNS compounds. Their work suggested that the antiproliferative activity of the NNS thiohydrazones were related to the low redox potentials of the NNS-Fe complexes, facilitating the generation of ROS. In fact, thioamide group was found to facilitate reversible Fe(III/II) reactions, in contrast to the amide moiety [235].

In the same way, Simunek et al. [236] described that the amidrazone and the semicarbazone metabolites arisen from desulfurization reactions of 2-benzoylpyridine 4-ethyl-3-thiosemicarbazone (Bp4eT, Fig. 31) showed more than 300-fold less cytotoxic activity than Bp4eT towards both cancer and normal cell lines.

The triazole-Au(I) (II) derivative described by Abram et al. [196] (Fig. 24), arisen from cyclization and desulfurization of TSC after reduction of Au(III), showed a much less activity against human MCF-7 breast cancer cells than its TSC-Au(III) counterpart (I).

It is, however, well established that 1,3,4-oxadiazoles show interesting biological properties [237]. Notwithstanding, as far as we are aware, no comparison has been carried out among them and their parent TSCs, in spite of the synthetic relationships due to the use of acetylthiosemicarbazides to prepare oxadiazole derivatives [176,182].

Finally, the inorganic sulfur species generated in these processes, as elemental sulfur, hydrogen sulfide and sulfate, play different biological roles in living beings. Sulfur is an essential element for life, being present in peptides, as amino acids and proteins, vitamins (thiamin, biotin, and coenzyme A) and several biomolecules as glycosaminoglycans, chondroitin sulfate, dermatan sulfate, and hyaluronic acid, among others [238]. However, elemental S_8 sulfur is toxic, and it is oxidized during the metabolic pathways to generate sulfite and sulfate [239]. Sulfate homeostasis in human body is maintained, at least in part, through renal clearance mechanisms. This oxoanion acts as detoxification agent and is necessary for the biosynthesis of numerous biomolecules [240]. On the other hand, despite its toxicity, hydrogen sulfide is involved in many physiological processes, including relaxation of vascular smooth muscles, mediation of neurotransmission, inhibition of insulin signalling and regulation of inflammation [241]. It is known long time ago that methemoglobine interacts with H_2S in the presence of oxygen to give a green compound, which has been modelled through the preparation and structural resolution of an analogous complex [242]. Notwithstanding the variety of biological processes and metabolic pathways involving sulfur species, the amounts of these arisen from TSCs desulfurization and the influence in the therapeutic activity of TSCs is far to be understood.

4. Conclusions

In summary, different chemical factors can trigger desulfurization reactions in TSCs. Among them, the most thoroughly studied are (not always) extreme pH values, the presence of oxidizing agents or the establishment of redox processes as those electrochemically induced, the influence of the solvent, the temperature and the electromagnetic radiation. Many of these reactions only occur when TSCs are bound to metal ions. Taking into account that coordination to intracellular essential metal elements, in particular Cu and Fe, seems to be pivotal for the biological activity of TSCs, the possibility for the desulfurization of the ligand *in vivo* becomes relevant. In fact, some physiological conditions reproduce the environments that make possible the desulfurization process (pH, temperature, chemicals…) and, actually, desulfurizations of TSCs have been detected in experiments performed *in vitro* and *in vivo*. These desulfurization processes lead to different products, as semicarbazone and semicarbazide, amidrazone, urea, sulfate, sufide and elemental sulfur, among others. The products often exhibit less activity than intact TSCs. In any case, despite the early detection of some of the species generated from such processes *in vivo*, further studies should be performed to identify new products and to elucidate the actual transcendence of these reactions at a cellular level. These results could shed light into pharmacokinetics leading to improvements in the use of TSCs as drugs.

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Financial interests

The authors declare they have no financial interests.

Author contributions

RP and JGT contributed to the idea, conception, and design of the present work. All the authors performed the literature search and analysis, and equally contributed to the writing of this manuscript. All the authors read and approved the final manuscript.

Declarations

Competing interests: The authors have no competing interests to declare that are relevant to the content of this article.

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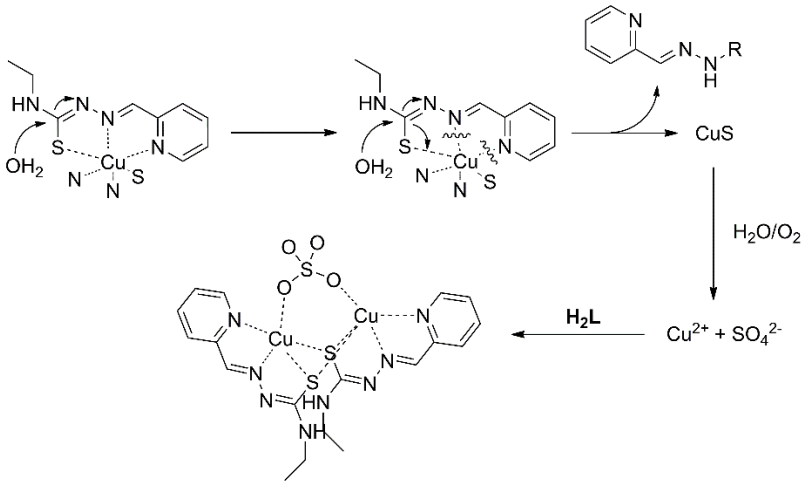

Fig. 13 Proposed mechanism for the desulfurization of pyridine-2-carboxaldehyde-4-*N*-ethyl-thiosemicarbazonecopper(II) complexes to form sulfate ions

Metal-free thiosemicarbazones have also been electrochemically studied, in particular isatin derivatives. Thus, upon oxidation, it was proposed the breakage the of the C=N bond, generating isatin and thiourea fragments for all evaluated molecules (Fig. 14). Regarding the reduction, the cleavage of the N-N bond as well as the generation of 3-aminoindolin-2-one and thiourea moieties was proposed [158].

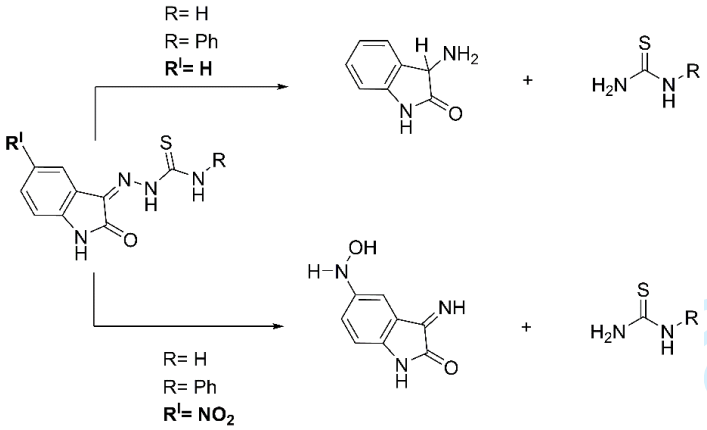

Fig. 14 Electrochemically induced cleavage of isatin thiosemicarbazone

Electrochemistry, coupled to high resolution mass spectrometry (HRMS), was also employed to investigate the possible relationship between the structure of α-N-heterocyclic thiosemicarbazones and their metabolic behaviour. To this end, the metabolites of ten different Triapine® derivatives with a wide range of antitumour activities were analysed. In general, for all the investigated thiosemicarbazones, the identified processes of the metabolic reactions were hydroxylation, oxidative desulfurization (formation of the amidrazone and, for some derivatives, also the semicarbazone) and disulfide dimer formation and dehydrogenation in some cases (Fig. 15). In general, desulfurization was detected for all the investigated compounds, thus confirming that the study of desulfurization process is crucial for a better understanding of the thiosemicarbazones biological activity [159].

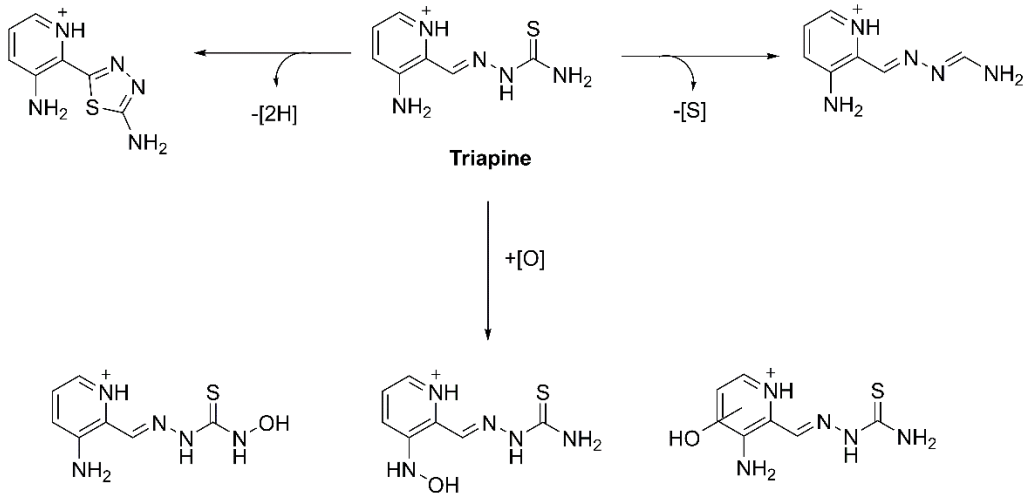

Fig. 15 Key metabolites of Triapine®: the dehydrogenated ring-closed thiadiazole and hydroxylated species

2.3. Desulfurizations by oxidant reactants

The interaction between thiosemicarbazone complexes and oxidants can give rise to desulfurization by reactions often involving oxidative cyclization processes. Some of them are described in the present section.

a) Conversion of thiosemicarbazones into 1,3,4-oxadiazoles by halate ions

The addition of bromate to aqueous solutions of HL (where HL = HPTSC and HPTSC4m) triggered a complex process whose main reaction led to 1,3,4-oxadiazole derivatives [160,161], that could be regarded as is shown in Fig. 16.

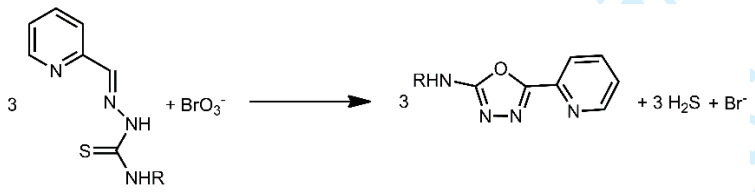

Fig. 16 Transformation of thiosemicarbazones into 1,3,4-oxadiazoles. Thiosemicarbazones: pyridine–2–carbaldehyde thiosemicarbazone (R = H, HL = HPTSC) and pyridine-2-carbaldehyde 4-N-methylthiosemicarbazone (R = CH_3, HL = HPTSC4m). Oxadiazoles: 2-amino-5-pyridin-2-yl-1,3,4-oxadiazole (R = H, L_{oxad} = 134OXAD) and 2-methylamino-5-pyridin-2-yl-1,3,4-oxadiazole (R = CH_3, L_{oxad} = 134OXADm)

The study of different well-characterized solids isolated from this process allowed to distinguish several steps, which are drawn in Fig. 17, despite some stages in the mechanism remain unclear. The reaction proceeded smoothly with the addition of bromate to aqueous solutions of preformed $CuL(NO_3)$ complexes at pH ~ 6 (Step 3). An olive-green precipitate corresponding to the centrosymmetric S-bridged $[\{CuLBr\}_2]$ dimer appeared (Step 3) and, after filtering it, the initial dark green colour of the solution gradually became lighter. Simultaneously, the pH decreased to 3–4 and an irritant gas was released. Two days later, single crystals of $[\{Cu(L_{oxad})(OH_2)_2(OSO_3)\}_2]$ were obtained (Step 4). The addition of $K_4[Fe(CN)_6]\cdot 3H_2O$ led to the coprecipitation of purple $K_2Cu[Fe(CN)_6]\cdot H_2O$ and L_{oxad}, whose particle sizes were different enough to eliminate the complex in the filtrate while the white organic compound was retained in the filter and, afterwards, recrystallized in ethanol (5). The use of $NaHCO_3$ instead of $K_4[Fe(CN)_6]\cdot 3H_2O$ also allowed to isolate the oxadiazole ligand. The rate of the reaction was increased with heating and addition of small

amounts of acid. However, brown suspensions were attained in the excess of acid or strong heating, whose filtration allowed to isolate crystals of bis(pyridine-2-carboxylate)copper(II) (6).

The reaction also took place without Cu(II) ions, but strong acid media was required (pH = 0−1) and, after filtration of a dark red unidentified solid, further treatment with NaOH to pH = 3–4. In the presence of acid media, mixtures of compounds were invariably obtained and purification was needed. The use of KIO_3 in acid media yielded the same results than $KBrO_3$, but the formation of iodine, probably due to comproportation between I^- and IO_3^-, made more difficult the purification of the product. Furthermore, the addition of KIO_3 to the $CuL(NO_3)$ complexes at pH ~ 6 led, firstly, to the attainment of a green compound identified as $CuL(IO_3)$, which evolved when the suspension was kept with stirring to yield $[\{CuLI\}_2]$ dinuclear compounds in a final step, but oxadiazole derivatives were not attained. The analogous $CuL(BrO_3)$ compound could not be isolated in these experiments. On the contrary, none of the attempts carried out by using chlorate as oxidant gave any evidence for oxidative cyclization, which could be due to kinetic factors. Finally, no oxidation compounds were attained by using pyridine–2–carbaldehyde 4,4'-N-dimethylthiosemicarbazone (HPTSC44m) neither free nor coordinated to Cu(II) ions, which suggests steric influences in the process.

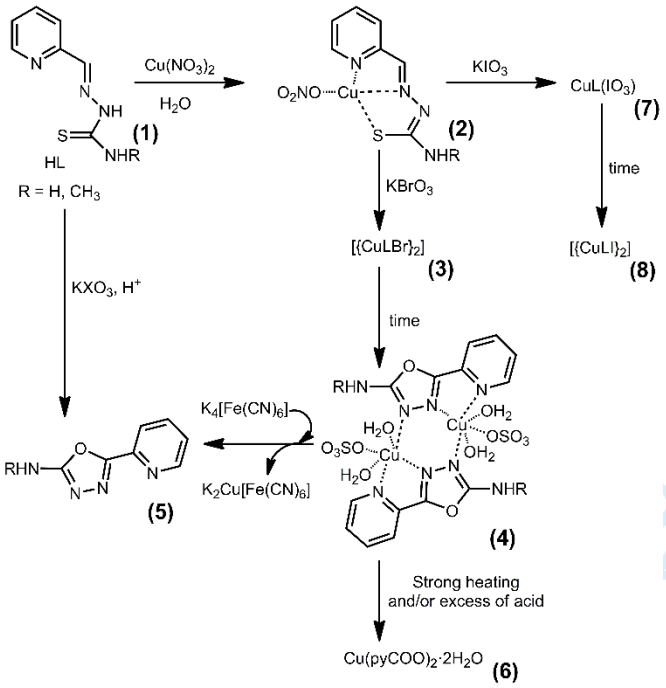

Fig. 17 Reaction pathways identified for the different reactants and conditions

A plausible mechanism can be proposed taking into account the experimental evidences, which is depicted in Fig. 18 for the free ligand, but it could be extrapolate, at least in part, for the Cu(II) complexes.

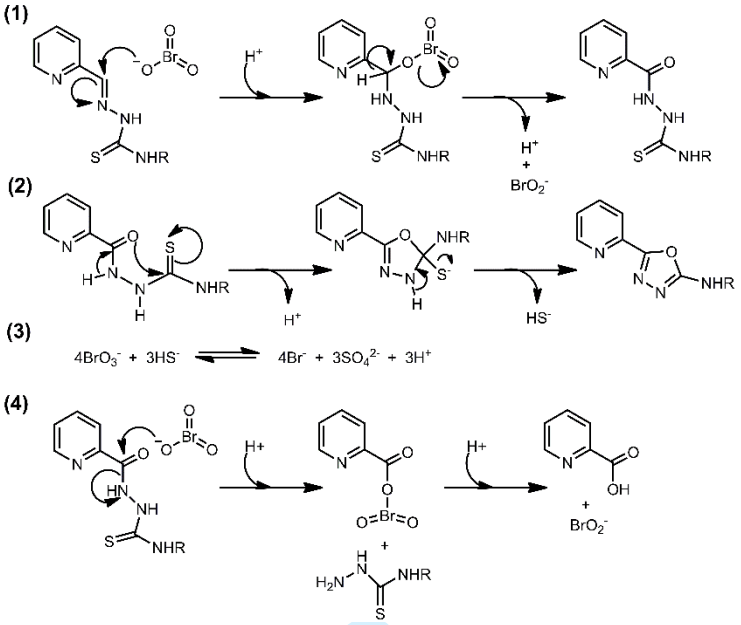

Fig. 18 Mechanism suggested for the halate-induced oxidative cyclization of TSCs to 1,3,4-oxadiazoles

These processes allow to prepare 2-amino-1,3,4-oxadiazoles as the only product through easy and unexpensive reactions, sometimes in less than an hour.

Oxidations of acyl thiosemicarbazides, acyl carbodithioates and acyl thioureas to oxadiazoles, often promoted by metal ions, have been frecuently described in the literature [162-183].

b) Other desulfurization of thiosemicarbazones by oxidant reactants

The use of other oxidants to desulfurize and cyclize TSCs has been described for a long time, as it was reported by Landquist in the attainment of triazolinones by reaction with MnO_2 [184].

From a broader point of view apart from TSCs, the use of oxidants as H_2O_2, $^1O_2$ and I_2 has been described for the desulfurization of other sulfur-containing molecules, as 8-thioguanosine to guanosine [185] or dithiocarbamato-Ru(II) complexes [186,187], among others.

Desulfurization of TSCs through processes involving redox-active metal ions is discussed in Section 2.4.d.

2.4. Others (radiation-, thermal-, solvent- and coordination-induced desulfurizations)

a) Solvent-induced desulfurizations

Another factors like light, pressure or solvent must be considered to have a relevant role in thiosemicarbazone desulfurization reactions. In this sense, recently it was presented the dinuclear helicate $[Ag_2(H_2L)_2]SO_4$ obtained by crystallization of the bisthiosemicarbazone cluster helicate $[Ag_4L_2]_2$ in the absence of any sulfate source, after a rare desulfurization process that takes place only in chloroform (Fig. 19). Three factors were investigated in this conversion: solvent, light and time. Only those recrystallizations performed in chloroform in the presence of light led to the formation of the sulfate helicate crystals. Regarding to time, the appearance of the sulfate crystals took place after a long crystallization period of 3-4 weeks. Some ^{1}H NMR studies mimicking the recrystalization conditions demonstrated that the acid pH resulting from chloroform degradation triggers the desulfurization process by protonation of the hydrazine NH groups, thus resulting on the dihelicate unit $[Ag_2(H_2L)_2]^{2+}$. It is relevant to mention that two side-products were identified along the desulfurization: silver hydrogen sulfide/sulfide, that easily evolved to the sulfate counterion by oxidation by moisture oxygen, and the organic fragment semicarbazone released

from the oxidative desulfurization. Finally, the remaining dinuclear complex combined with the sulfate thus generating the final crystallized sulfate dihelicate $[Ag_2(H_2L)_2]SO_4$ [188].

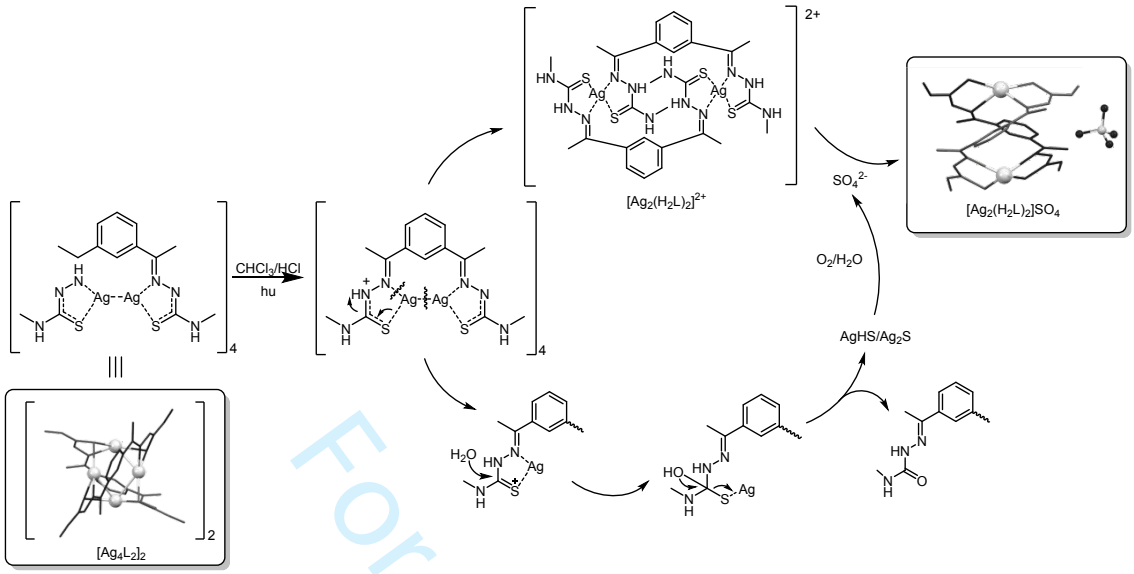

Fig. 19 Formation of the dinuclear helicate $[Ag_2(H_2L)_2](SO_4)$ by desulfurization of the double-tetranuclear cluster helicate $[Ag_4L_2]_2$

Notwithstanding, it must be admitted that not always coordination to metal ions is required to provoke solvent-induced desulfurization in TSCs. For instance, Peach and Dilworth et al. [189] described intramolecular cyclization reactions in recrystallization experiments of bisthiosemicarbazones that involved the loss of one of the thioamide sulfur atoms. The isolated product depended on the kind of solvent used, as is shown in Fig. 20.

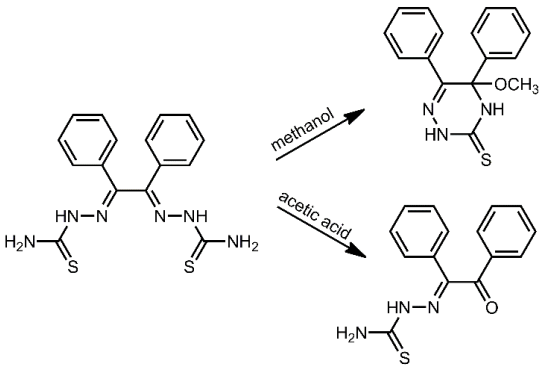

Fig. 20 Benzil bis(4-phenyl-3-thiosemicarbazone) and related cyclized products of solvent-induced desulfurization processes

b) The influence of the electromagnetic radiation

Microwave radiation is known to promote desulfurization in organo-sulfur compounds being this process of great importance for reducing harmful emissions during the combustion process [190]. Microwave irradiation of thiosemicarbazones gave the corresponding isothiocyanates, which on addition of either activated nitriles or aldehydes furnished various types of azines (Fig. 21) [191]. This process was also reported for thiosemicarbazone analogues, as thiocarbohydrazones [192].

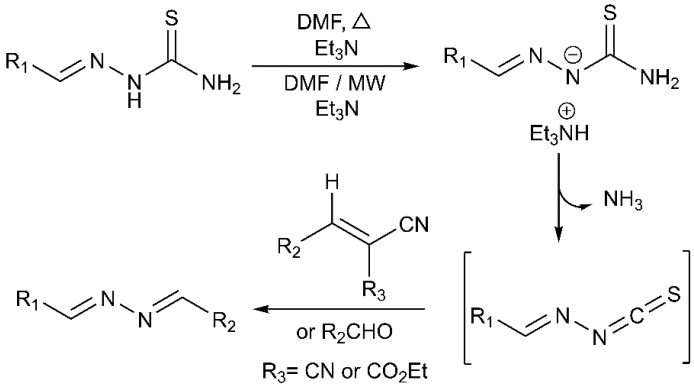

Fig. 21 Azine fragments formed after microwave irradiation of thiosemicarbazones

Visible light has been used as an agent for desulfurization of thiols and disulfides [193]. However, as far as we are aware, none of these processes has been reported for TSCs.

c) Thermal induced desulfurizations

Heating is another point to be considered in desulfurization processes experienced by TSC complexes. Thus, prolonged treatment in refluxing aqueous solutions of the complex $CuL(NO_3)$, being HL= pyridine-2-carbaldehyde thiosemicarbazone, induced breakage of a portion of the thiosemicarbazone molecules to give HS^- ligands that were identified in the structure of $[\{CuL(SH)\}_2]$, whose crystals were collected from the mother liquors (Fig. 22). In contrast, the free ligands remain unaltered under the same experimental conditions. Extending the studies to other metal ions, as Fe(III), Co(III), Zn(II) and Pb(II), it was found that only bis(thiosemicarbazonato)iron(III) species underwent breakage whereas there was no evidence for desulfurization processes in the Co(III), Zn(II) and Pb(II) derivatives. The IR data suggested that breakage of HL ligands gave rise to thiocyanato ligands in the above mentioned Cu(II) derivatives, while a non-coordinated thiocyanate anion was present in the Fe(III) decomposition product [137].

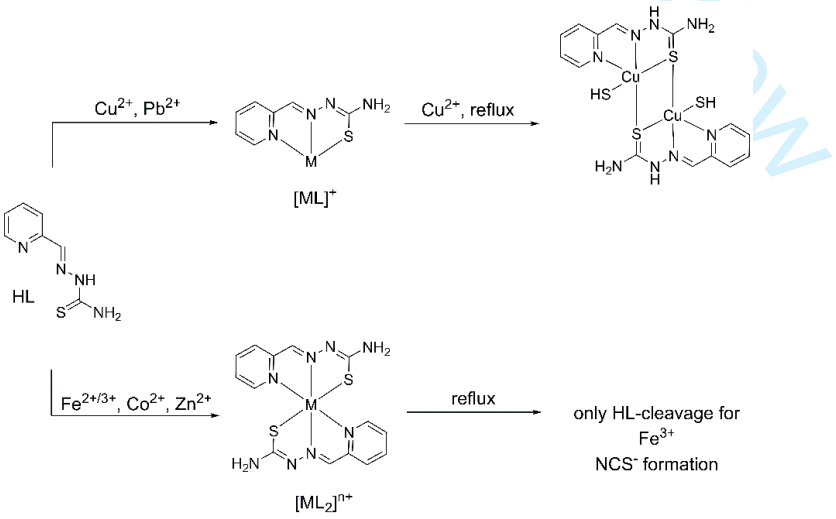

Fig. 22 Summary of desulfurization processes by refluxing on $[ML]^+$ and $[ML_2]_{n+}$ entities, HL = pyridine-2-carbaldehyde thiosemicarbazone

Ghosh et al. [194] reported the conversion of methyl 2-pyridyl ketone 4-(4-tolyl)thiosemicarbazone (HL) into methyl(2-pyridyl)methyleneimine (L') by refluxing in ethanol for 24 h a mixture of the preformed $[RuCl(L)(PPh_3)_2]$ compound and a six-fold excess of the HL ligand (Fig. 23).

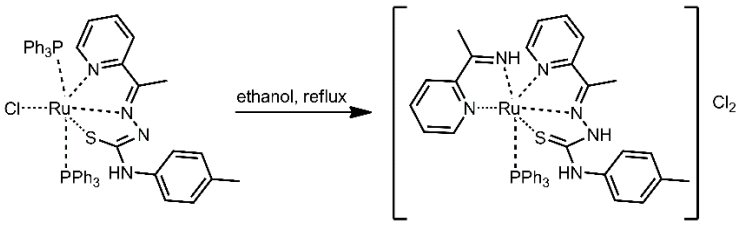

Fig. 23 Attainment of methyl(2-pyridyl)methyleneimine (L') by transformation of $[RuCl(L)(PPh_3)_2]$ into $[Ru(HL)(L')(PPh_3)]Cl_2$

Thermally activated desulfurizations, for instance by refluxing solvents with high boiling temperature, have been applied for synthetic methods using sulfur derivatives analogous to TSCs, as bisthioureas [195].

d) Oxidative desulfurization of thiosemicarbazones induced by metal ions

The mere coordination of TSC to metal ions can promote desulfurization. Sometimes, this kind of breakage reveals the existence of redox processes. For instance, the reaction of $Na[AuCl_4]$ with the disulfured TSC derived from N-[N′,N′- dialkylamino(thiocarbonyl)]benzimidoyl chloride gives rise to a partial reduction of Au(III) to Au(I), as Abram et al. have reported [196]. As a result, apart from the major product I, a certain amount of the ligands undergo oxidative cyclization, through an intermediate thiatriazine-Au(III), leading to the loss of one of their sulfur atoms to yield N-(hexamethylene)-N′-1-(5-diethylamino-3-phenyl-1,2,4-triazolyl)thiourea, that acts as monodentate ligand linking through the remaining sulfur atom to Au(I) ions in the minor product II (Fig. 24).

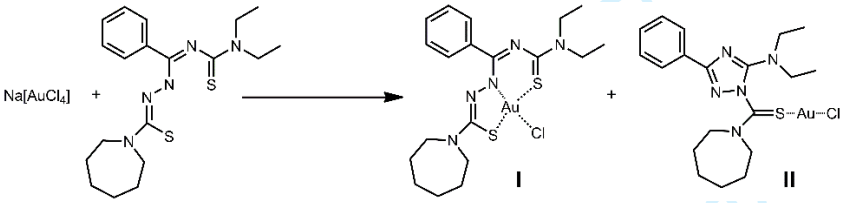

Fig. 24 Reduction of Au(III) to Au(I) by partial desulfurization of a TSC to give a triazole derivative

In the same way, the reaction of an aqueous solution of $[Cu(HPTSC)(ox)(OH_2)]$, acidified with HNO_3 to pH 0.8 in the presence of an excess of $VOSO_4$ (molar ratio 1:10), and further addition of base while vigorous stirring to pH 3.7 yielded, after filtration and slow evaporation of the mother liquors, crystals of the $\{[Cu(HPTSC)(OH_2)]_2[Cu(PTSC)S]_2(H_4V_{10}O_{28})\}_n$ compound [197]. The sulfido ligands, arisen from partial desulfurization of the TSC and probably caused by oxidation of V(IV) to V(V), play the role of μ_2-S^{2-} bridges between $[Cu(PTSC)]^+$ entities to build $[\{Cu(PTSC)S\}_2]^{2-}$ dimers that connect the decavanadate clusters.

Other complex redox process was reported by Dilworth et al. in the reaction of pyridine-2-carbaldehyde thiosemicarbazone (HL) and analogues with the Re(V)-containing $[ReOCl_3(PPh_3)_2]$ compound [198]. Surprisingly, the reaction usually gave rise to $[ReL_2]Cl$ products, where Re(V) had been reduced to Re(III) probably by the released PPh_3 ligands. However, one of the resulting complexes, derived from 2-acetylpyridine thiosemicarbazone, contained a methyl(2-pyridyl)-methyleneimine ligand (L') as a result of a reductive cleavage of the hydrazinic N–N bond in the TSC (Fig. 25). The product, of formula $[ReCl_2L(PPh_3)_2][ReO_4]$ excluding the solvent molecules, contained both Re(III) and Re(VII) ions, the later formed through the redox processes that provoke the breakage of the ligand. In fact, the product in this reaction had a precedent in that reported by Ghosh et al [194] discussed in a previous section.

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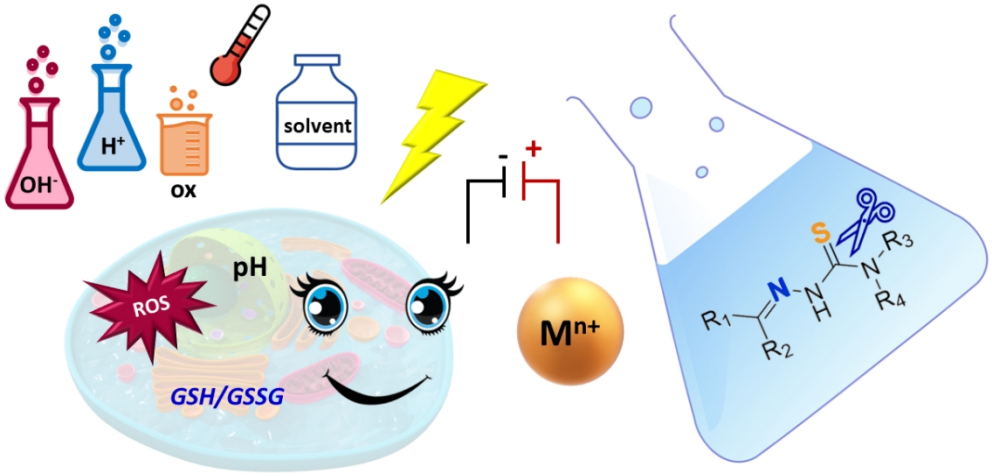

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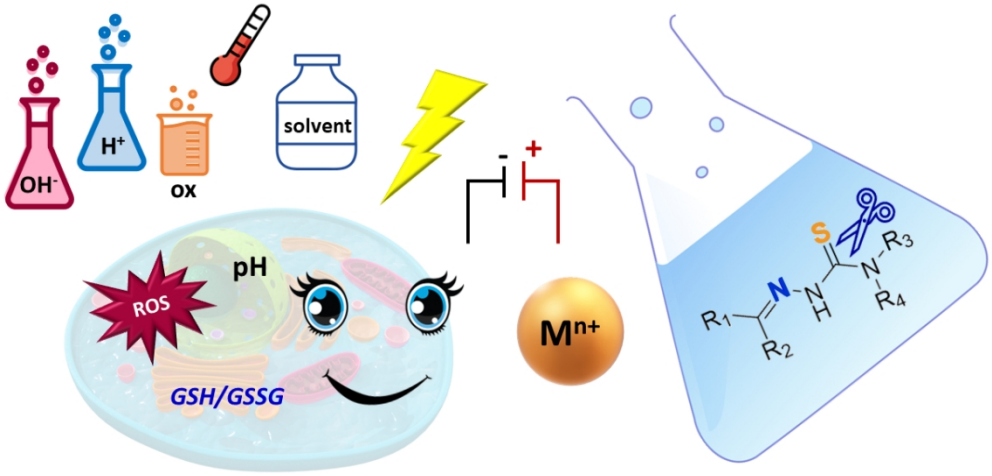

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