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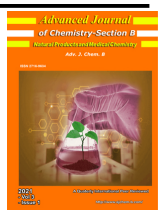

Review Article

Chemical and Biological potentials of semicarbazide and thiosemicarbazide derivatives and their metals complexes

Mohammad Asif[a]* Saad Alghamdi[b],

[a]*Glocal School of Pharmacy, Glocal University, Mirzapur Pole, Saharanpur, Uttar Pradesh, India.*
[b]*Laboratory Medicine Department, Faculty of Applied Medical Sciences, Umm Al-Qura University, Makkah, 21955, Saudi Arabia.*

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transition metal complexes.

ABSTRACT

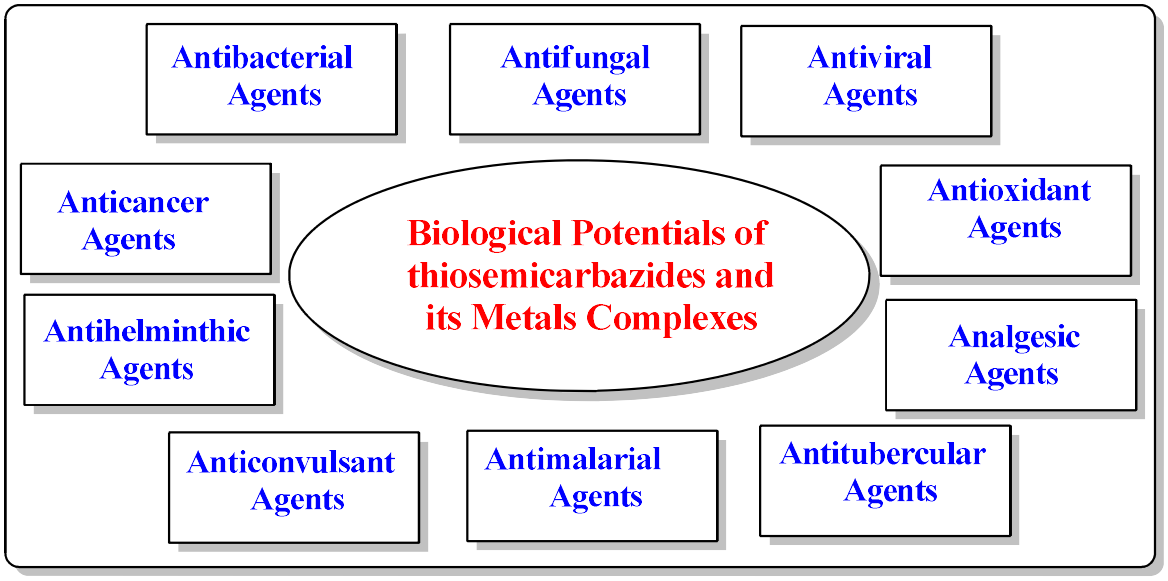
Organic compounds have plays vital role in biological chemical activities and also use for increase people's quality of life. Semicarbazide and thiosemicarbazide are sulfur and nitrogen-containing organic compounds with diverse biological activities. They are Schiff's bases formed by the condensation product of aldehydes or ketones with different amines. These derivatives are urea and thiourea derivatives depend on the attached aldehydes or ketones moiety. Antibacterial, antifungal, anticonvulsant, antitubercular, antimalarial, anticancer, analgesic, antipyretic, anti-inflammatory, antioxidant, antiviral, and other biological activities are all possible with semicarbazide and thiosemicarbazide derivatives. The addition of hydrazides to various isocyanates and isothiocyanates is one of the most convenient methods for the synthesis of semicarbazide and thiosemicarbazide derivatives, but they also used as a starting material for the synthesis of various Schiff's bases, metal chelating complexes, and anticorrosion agents. Various biological activities of semicarbazide and thiosemicarbazide derivatives, and their uses in the drug development phases, are the subject of this study.

HIGHLIGHTS

- Semicarbazides and thiosemicarbazides are sulfur and nitrogen-containing organic compounds with diverse biological activities.
- Semicarbazides and thiosemicarbazides and its metal complexes possess antimicrobial, anticancer, anticonvulsant, antitubercular, antimalarial, analgesic, antipyretic, anti-inflammatory, antioxidant, antiviral, and other biological activities.
- Various metal complexes containing different transition metals such as Ni(II), Cu(II), and Pd (II) of semicarbazide, thiosemicarbazide derivatives are used as bioactive compounds and chemical applications.

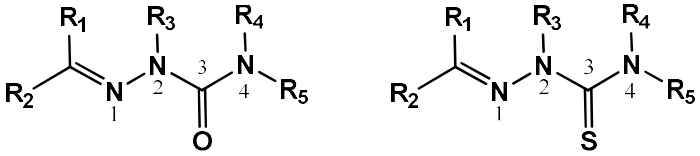
* Corresponding author: Mohammad Asif
✉ E-mail: aasif321@gmail.com
☏ Tel number: +91-9897088910

GRAPHICAL ABSTRACT



1. Introduction

Small molecules have traditionally been a credible tool for finding new biologically active compounds. In synthetic and medicinal chemistry, organo-nitrogen and sulfur compounds have dominated. Biological activities of small molecules dependent on triazole, oxadiazole, and thiadiazole, heterocycles have been recorded [1-4]. Several studies on the synthesis and biological testing of bioactive heterocyclic compounds in the aryl-containing semicarbazide and thiosemicarbazide derivatives have been published [5]. Semicarbazones are imine derivatives generated by the condensation of different aldehydes or ketones with semicarbazide. Semicarbazone counterpart thiosemicarbazone has a sulfur atom in place of the oxygen atom. **Figure 1** depicts the general form and IUPAC counting of thiosemicarbazones.



R_1, R_2, R_3, R_4 = H, alkyl or aryl group

Figure 1. The basic structure of thiosemicarbazone and thiosemicarbazone.

An appropriate substitution on thiamide nitrogen, a sulfur atom, or a hydrazine nitrogen atom will yield a variety of thiosemicarbazone derivatives. These are flexible intermediates that can be easily synthesized with good yields using simple methods. Semicarbazide and thiosemicarbazide have long held a prominent position in the pharmaceutical industry. The use of these compounds in organic synthesis has become a standard method for producing a variety of heterocycles. Their reactions with compounds with C=O and C=N groups are a

common way to make biologically active compounds like triazoles and thiazoles.

Their oxidation pathways may provide a greater understanding of their biological activities. S-oxygenation is commonly accepted as the requirement for thio compounds to convey their physiological activities [6]. Many cellular functions, including reductive degradation of polypeptide hormones and proteins, protein synthesis control, intracellular redox potential maintenance, cell defense from oxidative damage, and so on, tend to be influenced by oxidation of organo-sulfur compounds [7]. Because of their wide chemical applications and biological activities, the chemistry of hydrazine derivatives such as semicarbazides, thiosemicarbazides, and their hydrazones is of great concern [8]. Semicarbazides and thiosemicarbazides, as well as their derivatives, have been shown to have a variety of biological functions, including anticancer [9], anti-HIV [10], antibacterial [11], antiviral [12], and antifungal [5]. They play an important role in plant growth control and their capacity to diffuse across the semi-permeable membrane of cell lines [13-17]. These compounds have sparked a lot of curiosity for potential medicinal applications due to their abundance in plants and ease of synthesis. Because of their action against protozoa, measles, smallpox virus, fungi, and cancer, these sulfur and nitrogen donor ligands and their coordination complexes have gotten a lot of recognition. Anticorrosion and antifouling effects are two industrially significant practices [18].

Their ability to form chelates with metals is based on their biological activities. These compounds are known to have a variety of biological activities as a group [19]. Researchers have begun to regard semicarbazide and thiosemicarbazones as interesting ligands for synthesizing metal complexes because of their ability to undergo tautomerism and form planar, rigid Schiff bases capable of interacting with metal cations [20]. The preparation of transition metal complexes, in which the Lewis acid is coordinated by hetero atoms possessing free lone pairs of electrons, has greatly enriched chelating chemistry. Potential pharmacological operations are metal complexes with Lewis bases containing nitrogen, sulfur, and phosphorous donors [21]. Semicarbazones and thiosemicarbazones are chelating ligands that contain donor imine groups that react with vacant d-orbitals in transition metals to form complexes. There are neutral and anionic versions of these multifunction ligands [22].

The complexes may have bioactivities that the free ligands don't have. The preparation and elucidation of the composition of these ligands' transition metal complexes are primarily motivated by their biological activities. Chemical sensors [23], antiviral [23], and catalyst [24-28] are only a few of the applications for transition metal complexes. Antifungal, anticancer, antibacterial, antimalarial, anticonvulsant, antitubercular, and anti-proliferative agents are also included. Chemotherapy employs transition metal complexes based on titanium, gold, cobalt, and platinum [29]. Any nickel (II) complexes containing octadiene-semicarbazones inhibited Staphylococcus aureus and Escherichia coli effectively. On MCF-7 human breast cancer cells, in vitro anticancer tests of multiple nickel (II) complexes with naphthoquinone semicarbazone and thiosemicarbazone.

The addition of aromatic substituents that can associate with biomolecules to their composition improves their biological activity. As a result, libraries of thiosemicarbazones with structural differences have been synthesized to see whether the changes have had a positive impact on the biological function of the compounds. Semicarbazide and thiosemicarbazide are structural moieties with the ability to show chemical versatility in biologically active molecules, and optimizing this configuration may lead to the development of a new class of therapeutic agents.

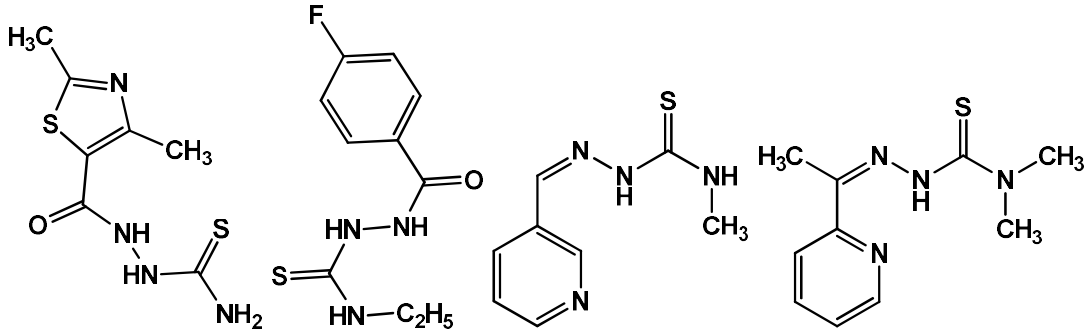
2. Biological activities of thiosemicarbazone derivatives

The shortest hydrazine derivative of thiocarbamide acid is thiosemicarbazide (NH_2-NH-$CSNH_2$). The molecular thiosemicarbazide is similar to its semicarbazide analogs, but the thione group has greater chemical versatility than the keto group, resulting in more complex actions of thiosemicarbazide derivatives. Thiosemicarbazide derivatives are one of the more promising candidates for drug design and production among the growing number of heterocyclic sulfur and nitrogen-containing compounds being sought in both industry and academia.

At the moment, there is a lot of curiosity in learning about chemical properties and observable biological processes [30-32]. The following are previously recorded thiosemicarbazones with potent biological activity.

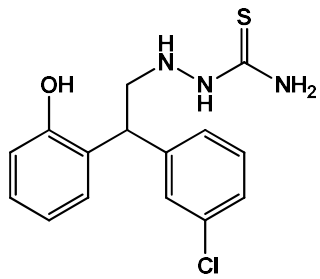
2.1. Antibacterial Activity

Thiosemicarbazide derivatives have shown to be effective antibacterial agents. Thiosemicarbazide derivatives have been possessing excellent antibacterial activities. Compounds 1-(2,4-dimethyl thiazole-5-carboxyl)-N-4-ethyl-thiosemicarbazide (**1**), 1-(4-fluoro benzoyl)-N-4-ethyl thiosemicarbazide (**2**), 2-pyridine-aldehyde-4-N-methyl thiosemicarbazone (**3**) and 2-acetyl pyridine-4-N, N'-dimethylthio-semicarbazone (**4**) were tested for their *in vitro* antibacterial activities against *E. coli* at 0.4-0.5μM concentration. Compound **2** has the greatest lipophilic capacity to affect the penetration of Gram-negative species such as E. coli. Compounds **3** and **4** have specific antibacterial effects on both *E. coli* and *S. aureus* at 0.1 mg/ml. Compounds **1** and **2** have specific antibacterial effects on *E. coli* at a concentration of 0.1 mg/ml [33].



1 **2** **3** **4**

Compounds 2-(4-chlorophenyl)(2-hydroxyphenyl)methyl-thiosemicarbazide (**5**) and 2-(2-hydroxyphenyl)(4-hydroxyphenyl)methyl-thiosemicarbazide (**6**) showed antibacterial activity against Gram-positive B. subtilis and S. aureus, as well as Gram-negative S. Typhi and S. dysentery [34].



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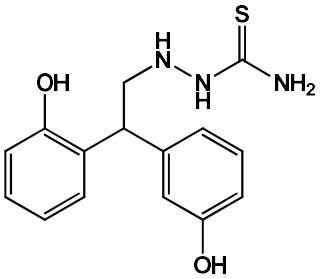

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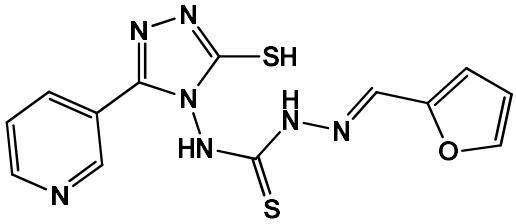

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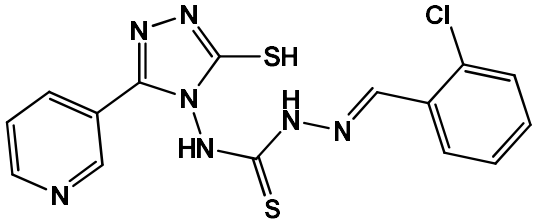

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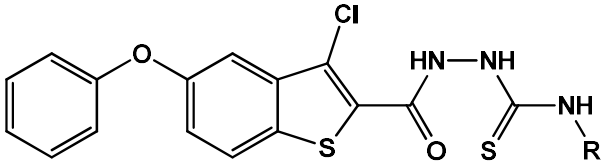
Antibacterial activity of substituted N-(5-mercapto-3-pyridyl-3-yl-4H-1,2,4-triazol-4-yl)-thiosemicarbazone against *S. aureus* and *E. coli* was investigated. At a concentration of 100µg/ml, the 2-furyl derivative (**7**) and 2-chlorophenyl derivative (**8**) showed strong antibacterial activity, with inhibitory zones of 12 mm and 11 mm, respectively [35].

The N-substituted arylthiosemicarbazide derivatives were synthesized by the reaction of 2-hydrazinocarbonyl-3-chloro-5-phenoxy-benzo[b]thiophene with substituted phenylisothio-cyanates. Compounds N1-(3'-chloro-5'-phenoxybenzo[b]thiophen-2'-yl)-N4-(3-chlorophenyl)thiosemicarbazide (**9**), N1-(3'-chloro-5'-phenoxybenzo[b]thiophen-2'-yl)-N4-(2-methylphenyl)thiosemicarbazide (**10**) and N1-(3'-chloro-5'-phenoxybenzo [b] thiophen-2'-yl)-N4-(4-methoxyphenyl) thiosemi-carbazide (**11**) were exhibited good antimicrobial activity against *E. coli*, while compounds **9**, **10**, **11**, N1-(3'-chloro-5'- phenoxybenzo [b] thiophen-2'-yl)-N4-(4-methylphenyl) thiosemicarbazide (**12**) and N1-(3'-chloro-5'-phenoxybenzo[b]thiophen-2'-yl)-N4-(2-methoxyphenyl)thiosemicarbazide (**13I**) were also effective against *Bacillus megaterium* [36,37].



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9: R = 3-Cl,C_6H_4

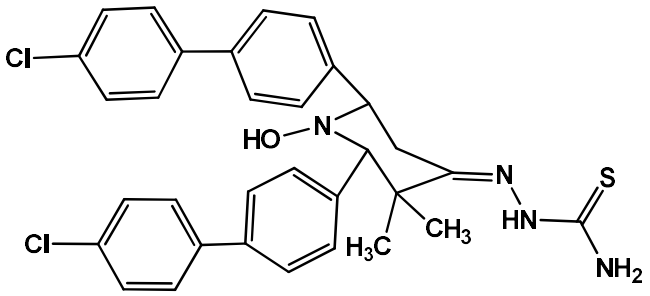
10: R=2-CH_3,C_6H_4

11: R = 4-OCH_3,C_6H_4

12:R=4-CH_3,C_6H_4

13: R=2-OCH_3,C_6H_4

A series of N-hydroxy-3,3-dimethyl-2,6-diarylpiperidin-4-one thiosemicarbazones were exhibited *in vitro* antibacterial and antifungal activities. Compound N-hydroxy-3,3-dimethyl-2,6-bis(p-chlorophenyl)piperidin-4-one thiosemicarbazone (**14**) was exhibited a wide spectrum of antibacterial activities against Gram +ve and Gram -ve bacteria viz. *S. aureus*, β-*haemolytic streptococcus*, *Vibreo cholerae*, *Salmonella typhii*, *E. coli*, *Klebsiella pneumonia,* and *Pseudomonas* [38].



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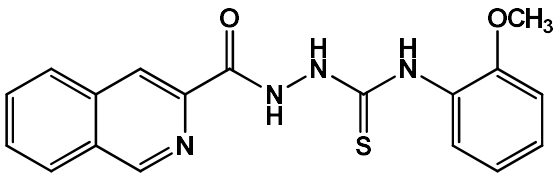
2.2. Antifungal activity

The antifungal activity of isoquinoline derivatives of 4-aryl thiosemicarbazides was investigated in vitro. *Candida albicans* was tested on some of the derivatives. The most active antifungal agents were found to be two isoquinoline derivatives with an o-methoxy and o-methyl group at the phenyl ring (**15** and **16**) [5].



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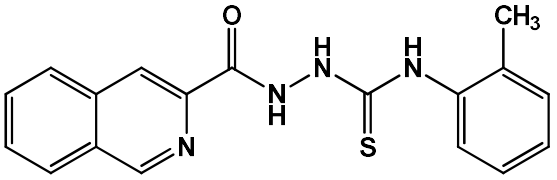

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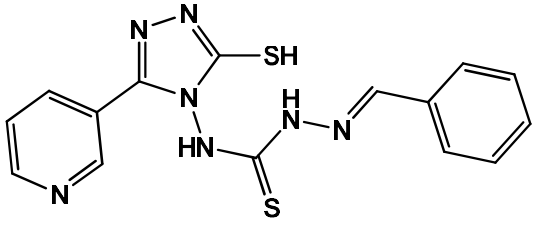
The role of these derivatives in ligand identification and antifungal activities was revealed by molecular docking of these derivatives into active sites of sterol 14-demethylase (CYP51), topoisomerase II (topo II), L-glutamine: D-fructose-6-phosphate amidotransferase (GlcN-6-P), secreted aspartic proteinase (SAP), N-myristoyltransfer NMT was identified as a potential antifungal target, and isoquinoline thios-emicarbazides were found to have higher affinity than the native ligand. The 4-benzylamido-thiosemicarbazide and its 2-furyl & 2-thinyl derivatives are selective against *Alternaria solani, Cunninghmella blakesleema,* and *Sclerotium rolfsii* [39], with toxicity comparable to 8-hydroxyquinoline sulphate. The effect of benzene ring substituents was studied, and the phenolic group was found to be the most powerful, in the following order: dimethyl aminophenyl ~ amino < methyl ~ chloro < nitro < phenolic. The 2-chlorophenyl (**8**), phenyl (**17**), and 4-methoxyphenyl derivatives (**18**) of N-(5-mercapto-3-pyridyl-3-yl-4H-1,2,4-triazol-4-yl)-thiosemicarbazone had antifungal action against *C. albicans* [35].

Compounds **10-13** were found to be active against *S. aureus* in addition to their excellent antibacterial activity, while compounds **9-11** and N1-(3'-chloro-5'-phenoxybenzo[b]thiophen-2'-yl)-N4-(2-nitrophenyl)thiosemicarbazide (**19**) were found to be active against *A. niger* [36].



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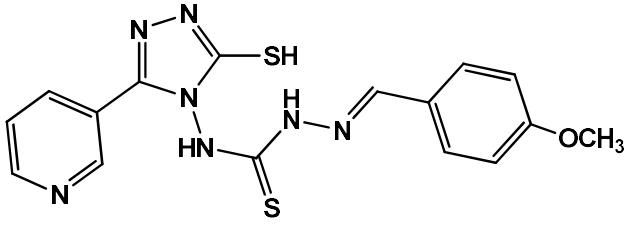

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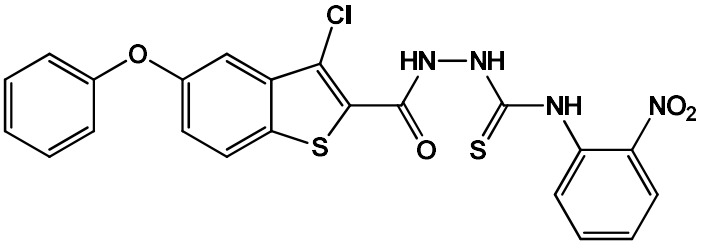

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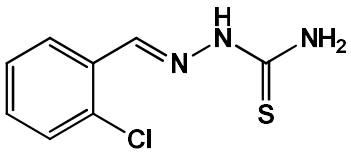

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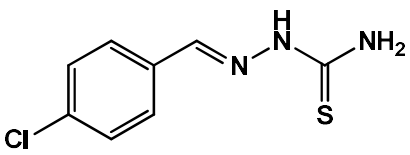

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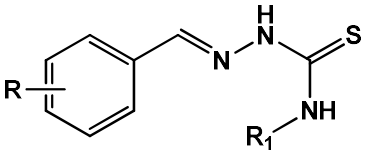

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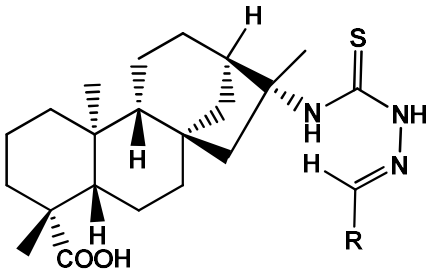
The inhibitory kinetics of the 2-chlorobenzaldehyde thiosemicarbazone (2-Cl-BT) (**20**) and 4-chlorobenzaldehyde thiosemicarbazone (4-Cl-BT) (**21**) on mushroom tyrosinase activity were investigated. The results showed that these compounds had a strong inhibitory effect on tyrosinase monophenolase and diphenolase function. Inhibition of tyrosinase has a wide range of uses in medicine, cosmetics, food preservation, and pest control. Compound 16 was also shown to be effective against *A. flavus, Mucor,* and *Microsporum gypseum* [40]. Thiosemicarbazones with benzylidene substitutions (**22**) were exhibited anti-microbial activities against certain bacteria and fungi [41].

2.3. Antihelminthic activity

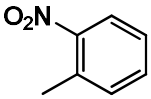
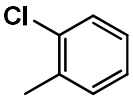
The antitrypanosomal ability of a sequence of thiosemicarbazones obtained from the natural diterpene kaurenoic acid was tested against epimastigote variants of Trypanosoma cruzi. With IC_{50} values ranging from 2-24.0 μM, five thiosemicarbazones were found to be more potent than kaurenoic acid. The most effective compounds were found to be o-nitro (**23**), o-chloro (**24**), p-methyl (**25**), p-methoxyl (**26**), and m-nitrobenzaldehyde-thiosemicarbazone (**27**) with selectivity index values of 9.0, 8.4, 7.3, 5.7, and 5.6, respectively. Furthermore, with an IC_{50} of 2.0 μM, o-nitrobenzaldehyde-thiosemicarbazone (**28**) was the most active compound [42].

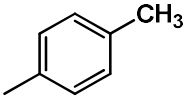
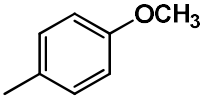
Antitrypanosomal activity of thiosemicarbazides and thiosemicarbazones against *T. cruzi* was investigated. Compounds (**29** and **30**) showed significant anti- *T. cruzi* activity at concentrations that was non-cytotoxic to mammalian cells [43].

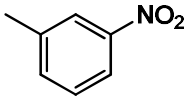
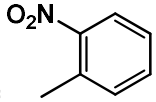
Docking experiments were conducted on the compounds to determine their binding patterns for the *T. cruzi* cysteine protease cruzain (TCC) enzyme (1U9Q). The binding characteristics of these ligands in the *T. cruzi* cysteine protease cruzain revealed vital and basic associations that can be used to describe the affinity of these molecules to the cruzain. The trypanocidal activity of many aromatic thiosemicarbazones was tested in vitro on *T. brucei brucei* [44-46]. All of these compounds were found to be active against T. brucei brucei, but 4'-chloroacetophenone thiosemicarbazone (**31**), 4'-bromo-acetophenone thiosemicarbazone (**32**), and acetonaphtone thiosemicarbazone (**33**) were found to be particularly effective, with IC_{50} values of 11.07, 17.02, and 9.62 μM, respectively [47].

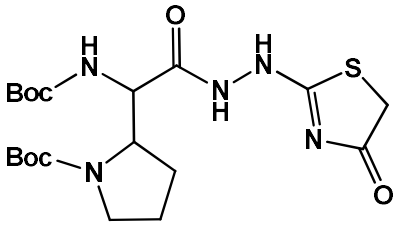


23-28

23 R=  , **24** R= 

25 R=  ,**26** R = 

27 R =  **28** R= 



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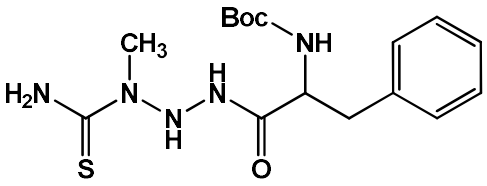

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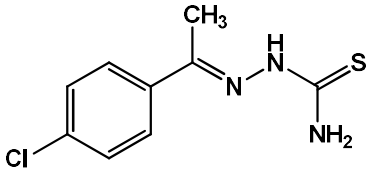

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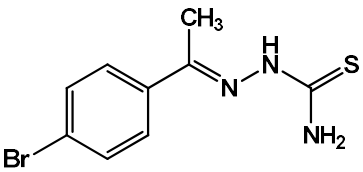

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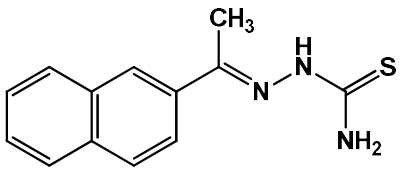


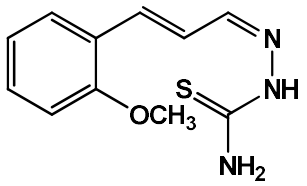
33

The effects of different substituents on trypanocidal behavior is discussed. Compounds with no substituent on the nucleus have the maximum IC_{50} value (212.50 μM), according to research. Substitutions of chlorine (IC_{50} =199.97 μM) and bromine (IC_{50} =70.44 μM) at positions 2 and 3 is less exciting than substitutions of chlorine (IC_{50}=11.07 μM) or bromine (IC_{50}=17.02M) at position 4. The trypanocidal effect of thiosemicarbazone (IC_{50} =9.62 μM) was increased when phenyl was replaced with naphthyl. Anti-trypanosomal behavior of styryl thiosemicarbazones was investigated. Styryl thiosemicarbazones were tested for their anti-trypanosomal activity. The most effective compound was found to be 4-N-(2'-methoxystyryl)-thiosemicarbazone (**34**) [48].

2.4. Antimalarial Activity

Substituted 1-[l-(2-pyridyl)ethyl]-3-thiosemicarbazides were tested as potential antimalarial agents. These compounds were a bit more active as antimalarial agents in *Plasmodium berghei* infected mice than the thiosemicarbazones. The progress of activity was attended by enhancing in toxicity.

3-azabicyclo[3.2.2]nonane-3-carbothioic acid 2-[1-(2-pyridyl)ethyl] hydrazide (**34**) was exhibited most potent antimalarial agent which could cure two test animals at a dose of 10mg/kg [49].



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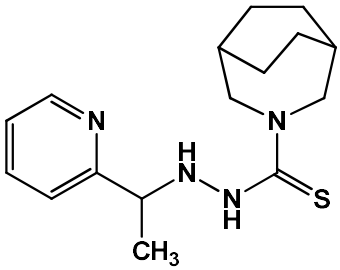

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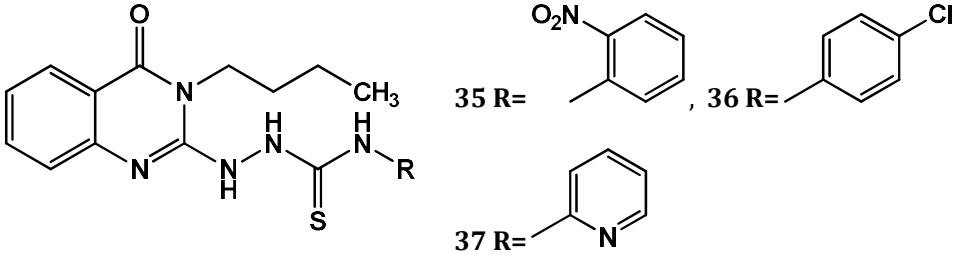
2.5. Antitubercular activity

The antitubercular activity of a sequence of thiosemicarbazide derivatives was measured, and the MIC value for *Mycobacterium tuberculosis* H37RV was 6.25g/ml [36]. Compound 1-(4-oxo-3-butyl-3,4- dihydro-quinazolin-2-yl)-4-(2-nitrophenyl)thiosemicarbazide (**35**) showed strong activity, with a MIC of 6.25µg/ml and a 21% inhibition. The reaction of 3-butyl-2-hydrazino quinazolin-4(3H)-one with various methyl esters of dithiocarbamic acid yielded a sequence of 1-(4-oxo-3-butyl-3,4-dihydroquinazolin-2-yl)-4-(substituted) thiosemicarbazides. *In vitro* anti-TB activity of these compounds were inhibited the growth of *M. tuberculosis*. Among these compounds (**35**), 1-(4-oxo-3-butyl-3,4-dihydro-quinazolin-2-yl)-4-(4-chloro phenyl) thiosemicarbazide (**36**) and 1-(4-oxo-3-butyl-3,4-dihydro-quinazolin-2-yl)-4-(2-pyridyl) thiosemicarbazide (**37**) were exhibited activity against *M. tuberculosis* with MIC of 6 µg/ml [50].



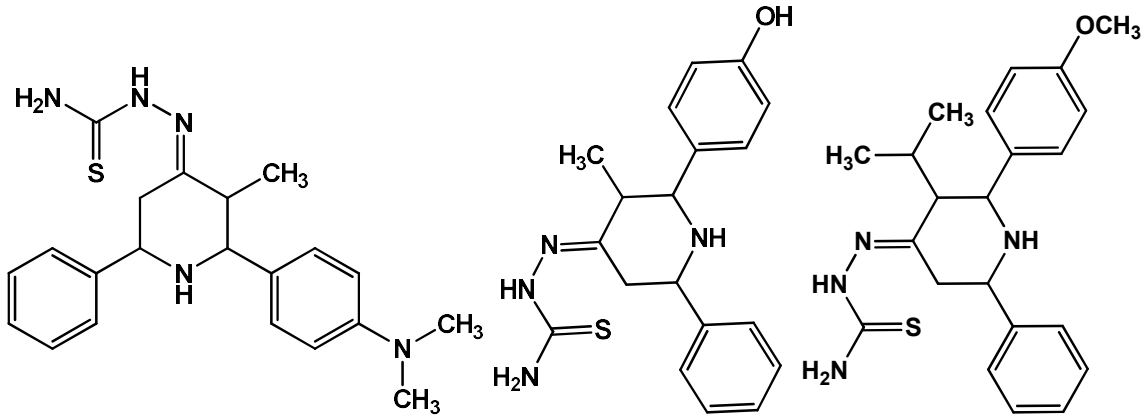
35 R= , **36 R=**

37 R=

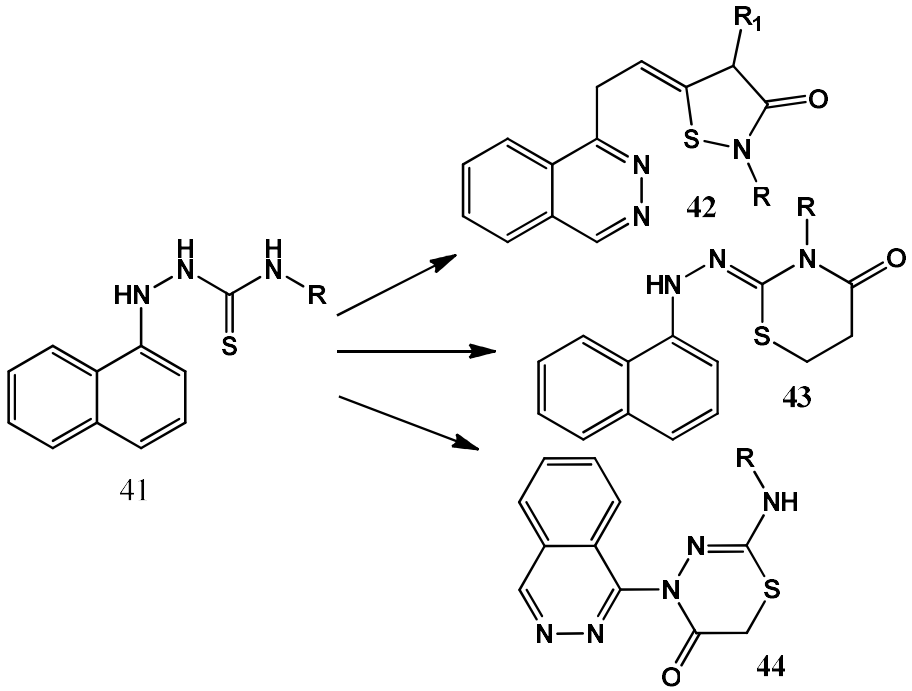
35-37

2.6. Anticonvulsant Activity

Thiosemicarbazone derivatives of 2,6-diaryl-3-methyl-4-piperidones were tested for their *in-vivo* anticonvulsant activity by maximal electroshock (MES) method in rats. Some compounds 2-[4-(dimethylamino)phenyl]-3-methyl-6-phenyl-piperidin-4-thiosemicarbazone (**38**), 2-(4-hydroxyphenyl)-3-methyl-6-phenylpiperidin-4-thiosemicarbazone (**39**) and 3-isopropyl-2-(4-methoxyphenyl)-6-phenylpiperidin-4-thiosemicarbazone (**40**) showed maximum anticonvulsant activity [51].



38 **39 s** **40**



41 **42** **43** **44**

Derivatives of 1-phthalazine thiosemicarbazide were exhibited potential anticonvulsant activity. Converted 1-phthalazine thiosemicarbazide to 3-substituted-4-oxothiazolin-2-yl-(1-phthalazinyl) hydrazones (**41, 42**), 3-substituted-4-oxo-5,6-dihydro-1,3-thiazin-2-yl-(1-phthalazinyl) hydrazones (**43**) and 2-substituted-amino 5-oxo-4-(1-phthalazinyl)-6-hydro-1,3,4-thiadiazines (**44**) were exhibited anticonvulsant activities on mice (**Table 1**) [52].

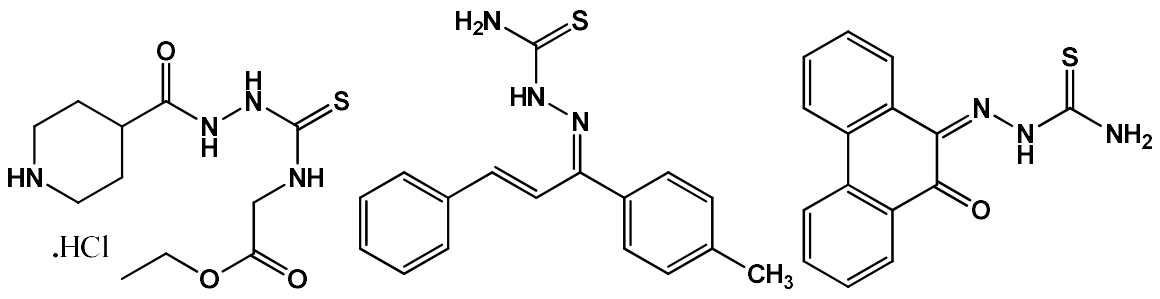
N-phenyl-N-phenyl-N-phenyl-N-phen (5-mercapto-3-pyridyl-3-yl-4H-1,2,4-triazol-4-yl) -thiosemicarbazone (7) has demonstrated possible anticonvulsant efficacy, with a faster recovery period for hind limb extension than phenytoin, which was used as a guide drug at a dosage of 30 mg/kg (and was found to protect 100 percent against triggered convulsions) [35].

Table-1. Anticonvulsant activity of thiosemicarbazone compounds (**41-44**).

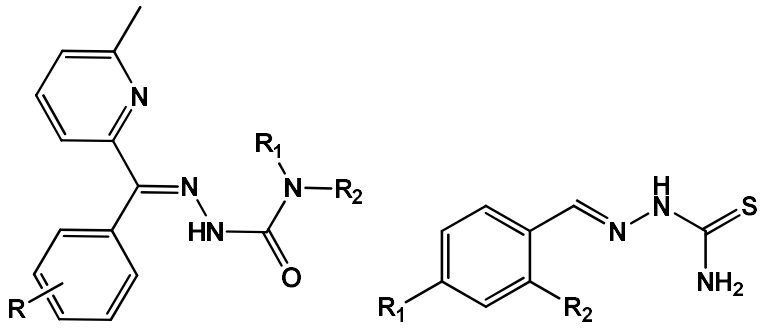
Compound	**R_1**	**R_2**	(% Protection)
3-Substituted-4-oxothiazolin-2-yl-(1-phthalazinyl)hydrazones			
41a	C_6H_{11}	H	70
41b	$C_6H_5CH_2$	H	20
42a	C_2H_5	CH_3	10
42b	$C_6H_5CH_2$	CH_3	40
3-Substituted-4-oxo-5,6-dihydro-1,3-thiazin-2-yl-(1-phthalazinyl)hydrazones			
43a	C_2H_5	-	30
43b	CH_2=$CHCH_2$	-	00
43c	C_6H_{11}	-	20
43d	C_6H_5	-	30
43e	$C_6H_5CH_2$	-	10
2-Substituted-amino-5-oxo-4-(1-phthalazinyl)-6-hydro-1,3,4-thiadiazines			
44	C_2H_5	-	50

2.7. Antitumor activity

Using an MTT assay [53], the cytotoxic activity of 4-ethoxy-carbonyl methyl-1-(piperidine-4-ylcarbonyl)-thiosemicarbazide hydrochloride (**45**) was determined, and the compound reduced the number of viable cells in both estrogen receptor-positive MCF-7 and estrogen receptor-negative MDA-MB-23 breast cancer cells, with IC_{50} values of 146±2 and 132±2 μM, respectively [54]. The biological activities of a series of chalcone thiosemicarbazide derivatives as possible EGFR kinase inhibitors are investigated. Compound **46** had the most potent biological activity of the compounds (IC_{50} =0.78-0.05 mM for HepG2 and IC50=0.35 mM for EGFR), which was equal to the positive controls. To assess the likely binding model, docking simulations were used to place compound 46 into the EGFR active site. Any of these compounds had strong antiproliferative action against human hepatocellular liver carcinoma cells (HepG2), according to the findings [55]. The antitumor activity of the palladium complex of phenanthrenequinone thiosemicarbazone (**47**), a possible antitumor metal compound, chloro, mono(phenanthrenequinone thiosemi-carbazonato) palladium(II) dimethylformamide solvate, has been recorded. The compound showed strong efficacy against drug-resistant and drug-sensitive breast cancer cell lines while being comparatively nontoxic to normal mammary epithelial cells. Apoptosis, a physiologic mechanism of cell death, was primarily responsible for the drug's killing effect on breast cancer cell lines [56].



45 **46** **47**

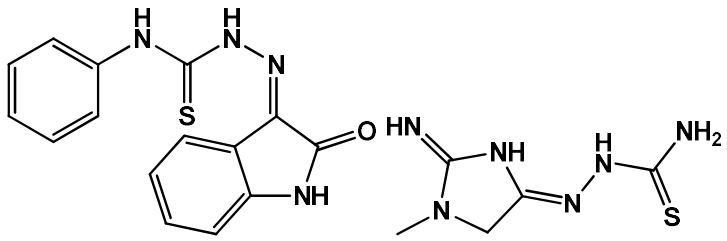


48 **49**

A series of thiosemicarbazone derivatives (**48**) with substitutions at thiamide nitrogen that showed significant anti-cancer activity against human neuroblastoma and human foetal lung fibroblast cell lines have been reported [57]. Anti-neoplastic activity against L1210 leukemia and CDP reductase activity of 3- and 5-amino derivatives of pyridine-2-carboxaldehyde thiosemicarbazones (**49**) has been reported [58].

2.8. Antioxidant Activity

They assessed the conjugated diene production in serum and LDL, as well as the depletion of tryptophan fluorescence in LDL, caused by two oxidants, 2,2-azobis(2-amidinopropane dihydrochloride) (AAPH) and Cu^{2+}, which are responsible for the increase in the formation of oxidized low-density lipoprotein (LDL). LDL plays a critical role in the onset and progression of atherosclerosis. The findings showed that the AAPH and Cu^{2+}-induced formation of conjugated dienes was decreased, the lag step and $t_{1/2}$ of tryptophan fluorescence were increased in a dose-dependent manner, and the TBARS formation was reduced in LDL, plasma, and rat tissues, with no toxicity to aortic slices. These findings suggested that IBTC's antioxidant properties made it a promising antiatherogenic agent [59]. The imidazole substituted thiosemicarbazone Schiff-base 2-(2-imino-1-methylimidazolidin-4-ylidene)hydrazine carbothioamide (**51**) showed anti-oxidant and anti-microbial behaviors using various methods [60].



50 **51**

2.9. Other applications

To evaluate the presence of platinum (IV) in a sample, a clear, highly sensitive, and selective spectrophotometric method was developed [61]. It is dependent on the reaction of 1-phenyl-4-ethyl thiosemicarbazide (HPETS) with Pt(IV) at pH=3, which produces a green complex, Pt(IV): PETS (1:2), which floats quantitatively with oleic acid surfactant. In aqueous and surfactant media, the molar absorptivities were 0.14x105 and 0.5x105mol/l, respectively. The effects of various analytical considerations on the floatation and decision routes were investigated. The suggested protocol was used to analyze Pt(IV) in natural waters, prepared solid complexes, and simulated samples with great results. Furthermore, several physical and chemical experiments on solid complexes isolated from aqueous and surfactant layers indicate a floatation process.

3. Computational studies

The inhibitory action of thiosemicarbazone derivatives against tyrosinase as a receptor was studied using three-dimensional quantitative structure-activity relationships (3D-QSARs) with thiosemicarbazone derivatives as a substrate molecule [62]. For the quantitative discussion, they used comparative molecular field analysis (CoMFA) [63] and comparative molecular similarity indices analysis (CoMSIA) [64].

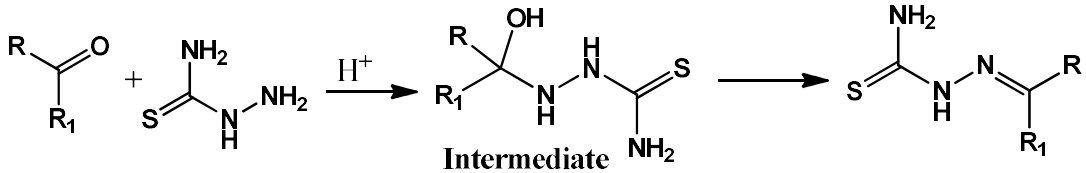
Molecular docking revealed that the substrate molecules' inhibitory action against tyrosinase (1WX2) was due to competitive inhibition rather than uncompetitive inhibition based on the formation of a chelate between copper atoms in the active site of tyrosinase and thiosemicarbazone moieties of the substrate compounds. Antimicrobial and docking trials were used to compare the behaviors of 4-benzoyl-1-(4-methyl-imidazole-5-yl)-carbonylthio-semicarbazide and 4-benzoyl-1-(indol-2-yl)-carbonyl-thiosemicarbazide against type II topoisomerase, where it was discovered that the inhibitory action against topoisomerase is due to indole derivative preferential binding in the ATP binding pocket [65]. Using the flex software [66], docking simulations with the ATP binding domain of hTopoII (1ZXM) and the DNA binding site of hTopoII (3QX3) were used to investigate the mode of inhibitory action of compound **45**. Compound **45**'s inhibitory effect is linked to the ATP binding pocket. Incorporating bulky aromatic substituents into the composition of these thiosemicarbazones raises their pharmacological efficiencies, according to the literature. Encouraged by the findings, it was proposed that the thiosemicarbazone moiety be introduced into biologically active 2-chloroquinoline-3-formaldehydes and new quinoline derivatives are synthesized and tested for their different in vitro and in-silico biological properties [67].

4. Synthesis of thiosemicarbazone derivatives

For the synthesis of thiosemicarbazone derivatives, several methods have been established. The following are few examples of methods:

4.1. The general synthesis process

The condensation reaction between thiosemicarbazide and carbonyl compounds (aldehydes or ketones) produces thiosemicarbazone derivatives (**52**) in general, as seen in **Scheme 1**. They are imine derivatives since they are formed when an aldehyde or ketone reacts with the semicarbazide's terminal $-NH_2$ group.



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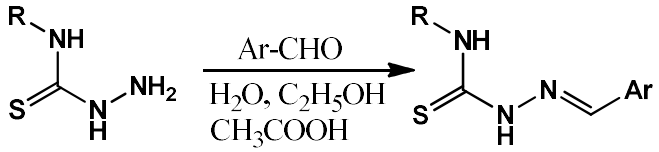
Scheme 1. Synthesis of general thiosemicarbazone derivatives

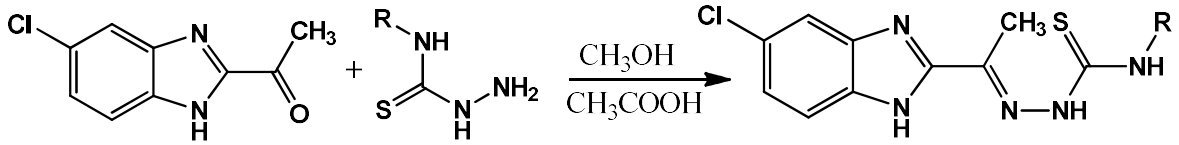
The following are some previously mentioned examples of thiosemicarbazone derivative synthesis. In the presence of H_2O/ethanolic media containing a few drops of acetic acid as catalyst (**Scheme 2**), a simple synthesis of benzaldehyde thiosemicarbazone derivatives (**53**) with satisfactory yields from the corresponding substituted thiosemicarbazides and benzaldehyde has been published [68].



53

Scheme 2. Synthesis of benzaldehyde thiosemicarbazone derivatives.

Thiosemicarbazones with benzimidazole moiety (**53**) derived from 1-(5-chloro-1H-benzimidazol-2-yl)ethanone, as well as related thiosemicarbazides with alkyl, aromatic substitutions on the terminal $-NH_2$ group (**Scheme 3**), have anti-cancer, anti-HIV, and anti-bacterial activity [69].



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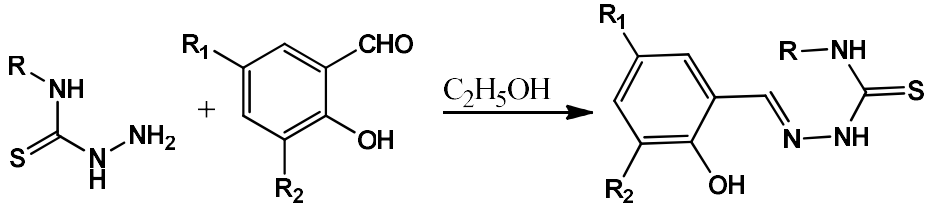
Scheme 3. Synthesis of thiosemicarbazones containing benzimidazole moiety.

By refluxing ethanolic solutions of hydroxyl aldehydes with the thiosemicarbazides for 2 hours (**Scheme 4**) [70], thiosemicarbazones bearing hydroxybenzaldehydes (**55**) with different substituents at terminal nitrogen were synthesized.



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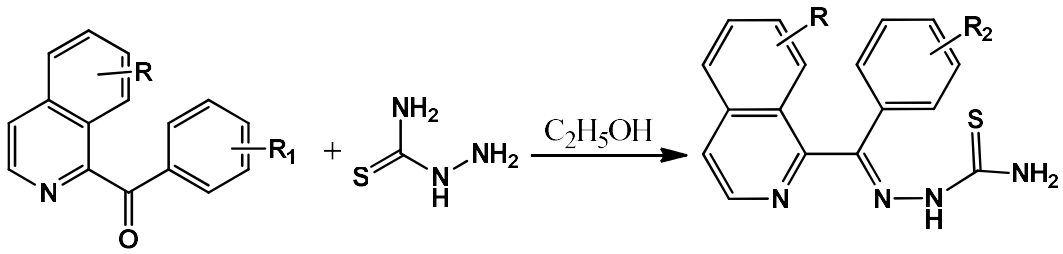
Scheme 4. Synthesis of thiosemicarbazones bearing hydroxybenzaldehydes.

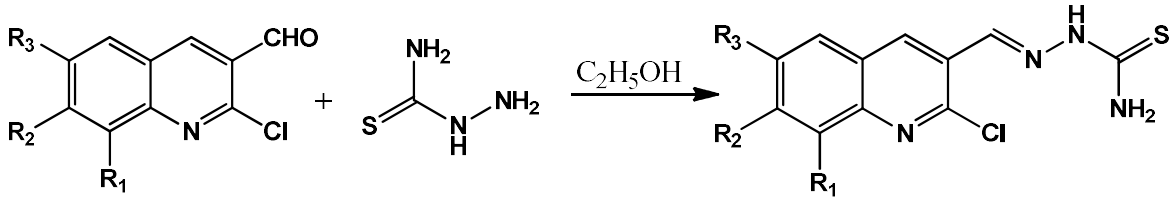
Carbonyl compounds with thiosemicarbazide in refluxing ethanol in the presence of glacial acetic acid or concentrated HCl is used to make analogs of isoquinoline thiosemicarbazones (**56**) (**Scheme 5**). These compounds were shown to have antimalarial and cytotoxic properties [71].



56

Scheme 5. Synthesis of isoquinoline thiosemicarbazone derivatives.

Quinoline thiosemicarbazones were synthesized, as well as their cyclization of thiadiazole derivatives. The quinoline thiosemicarbazones (**57**) (**Scheme 6**) were obtained by reacting 2-chloroquinoline-3-formaldehyde with thiosemicarbazide in refluxing ethanol for 2 hours.



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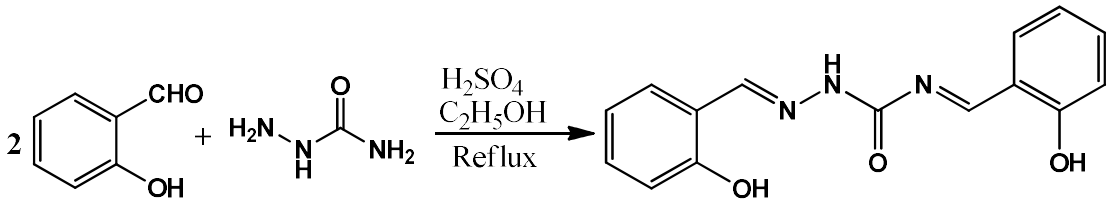
Scheme 6. Synthesis of quinoline thiosemicarbazone derivatives

5. Biological Activities of semicarbazide and thiosemicarbazides and their metal complexes

Cu(II) complexes with two Schiff base ligands were synthesized from salicylaldehyde and semicarbazide (HL1, **57**) (**Scheme 7**) and thiosemicarbazide (HL2, **58**) (**Scheme 8**) reactions, respectively. The Cu-HL2 (**60**) (**Scheme 10**) complex had more antibacterial activity than the Cu-HL1 complex (**59**), according to the biological activity of synthesized complexes (**Scheme 9**). Antibacterial activity was higher in the metal complexes than in the free Schiff base ligand [73].



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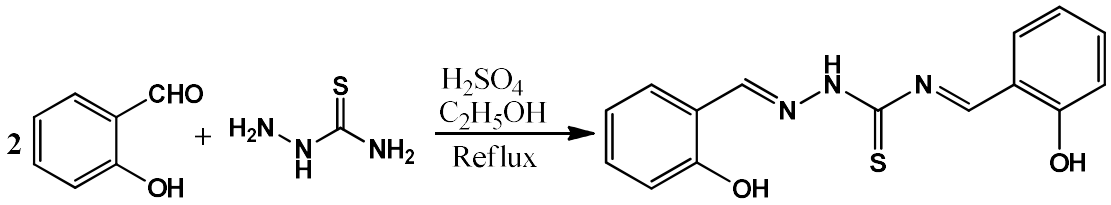
Scheme7. Synthetic pathway of semicarbazide Schiff's base (HL1).



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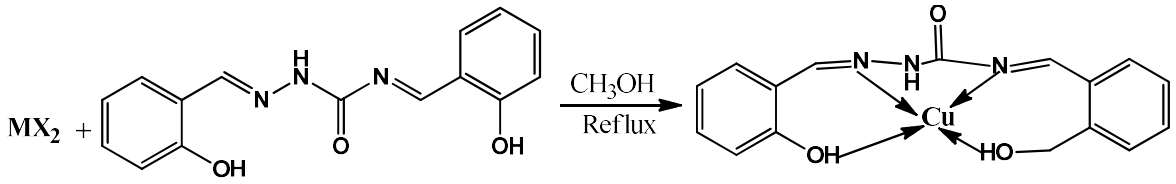
Scheme 8. Synthetic pathway of thiosemicarbazide Schiff's base (HL2).



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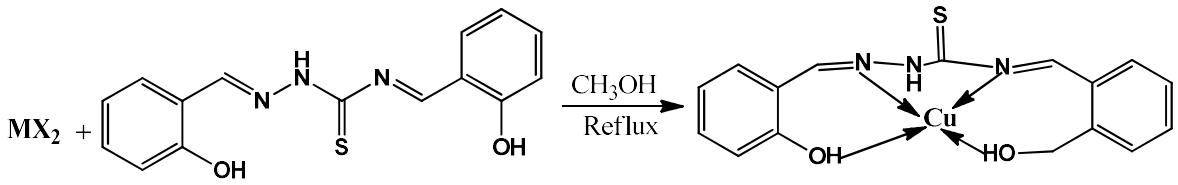
Scheme 9. Synthetic route of $[C_{15}H_{11}CuN_3O_3]$ Complex.



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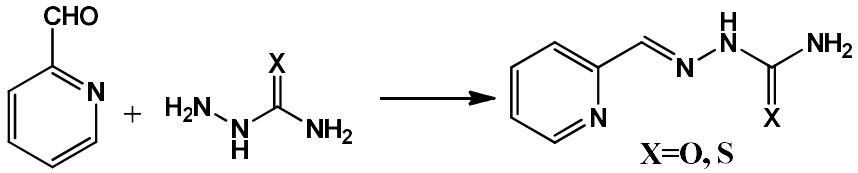
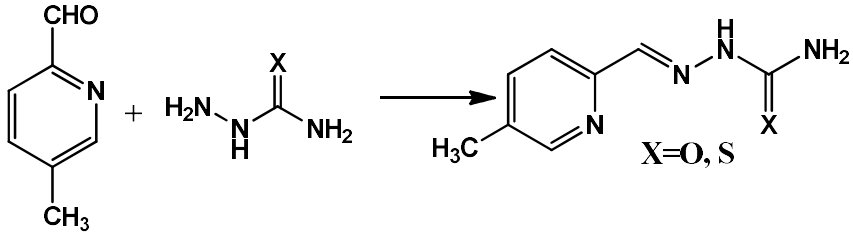
Scheme 10. Synthetic route of $[C_{15}H_{11}CuN_3O_2S]$ Complex.

Synthesized Cu(II) complexes containing 2-formyl pyridine semicarbazone (L1, **61**), 2-formyl pyridine thiosemicarbazone (L2, **62**) (**Scheme 11**), 5-methyl-2-formyl pyridine semicarbazone (L3, **63**), and 5-methyl 2-formyl pyridine thiosemicarbazone (L4, **59**) (**Scheme 12**). The complexes were found to have general composition $[Cu(L)_2X_2]$ (where L=L1, L2, L3, and L4, X =Cl–]½SO_4^{2-}, NO_3- (**65-68**). The anions occupy an axial position in these complexes, which have tetragonal twisted octahedral geometries and planar coordination of the ligand around the Cu^{2+} ion [74].



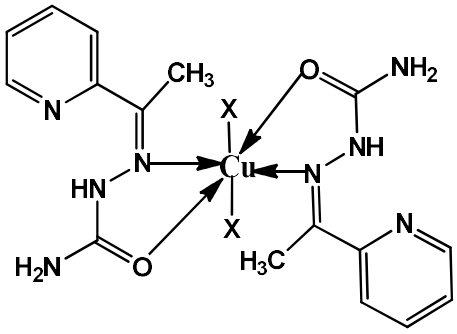
61 and **62**

Scheme 11. Synthesis of 2-formyl pyridine semicarbazone (L1), 2-formyl pyridine thiosemicarbazone (L2)



63 and **64**

Scheme 12. Synthesis of 5-methyl-2-formyl pyridine semicarbazone (L3) and 5-methyl 2-formyl pyridine thiosemicarbazone (L4).



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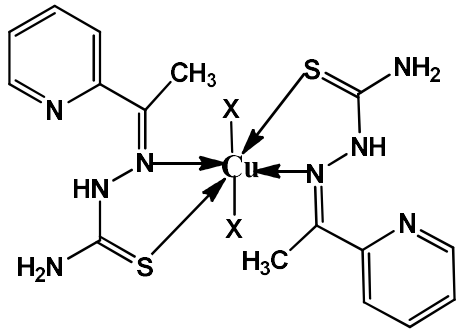

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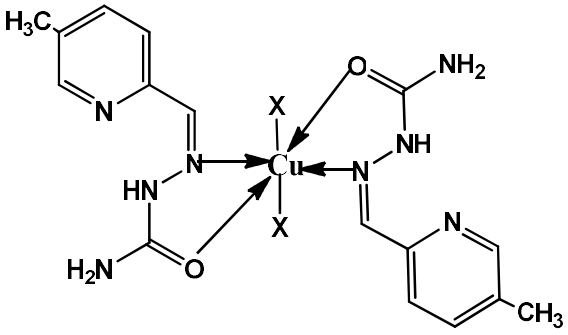

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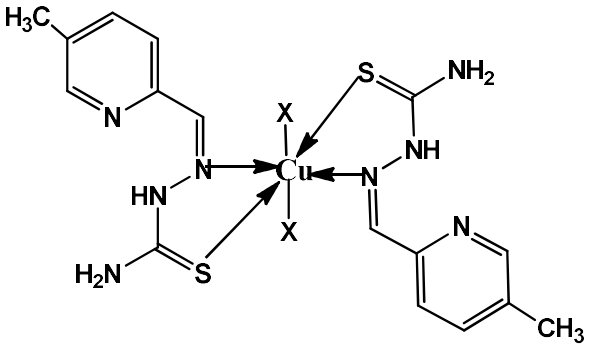

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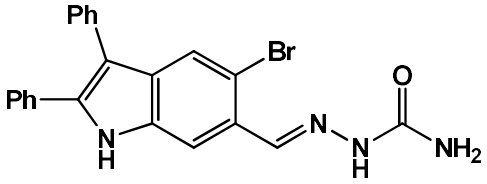
Vilsmier-Haack formylation of 5-bromo-2,3-diphenyl indole yielded a 6-formyl derivative, which was then condensed to yield heterocyclic rings bound to the starting compound at position 6 (**69-72**). These compounds' biological activities included antibacterial activity against *B. subtilis* and *E. coli* [75].



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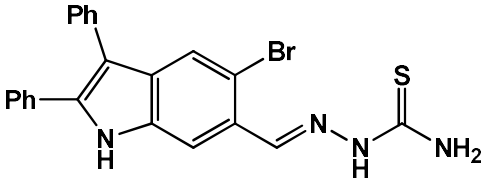

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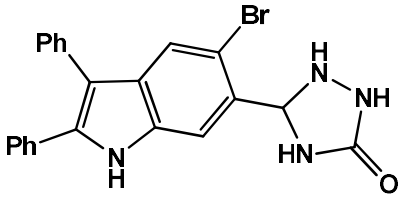

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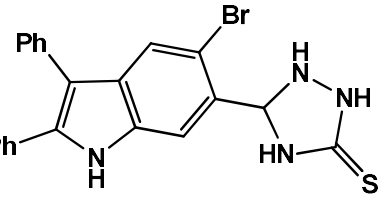
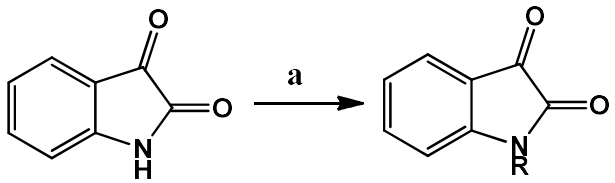


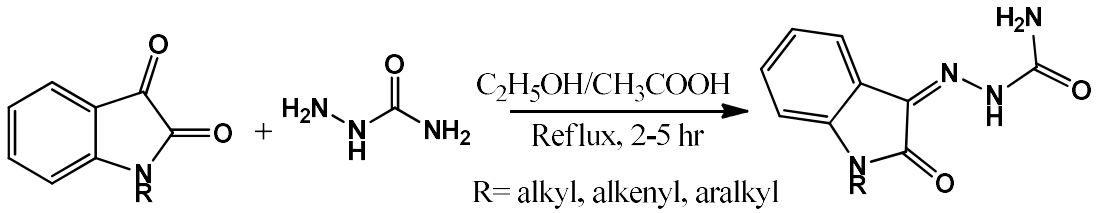
72

Semicarbazone (**74a-i**) and thiosemicarbazone (**75a-c, 75f-h**) isatins (**73a-i**) with various biological activities were studied (**Scheme 13a-13c**). The cytotoxic and antimicrobial activities of isatin semicarbazones (**74a-i**) and thiosemicarbazones (**75a-c, 75f-h**) were determined in vitro in this study [76]. They discovered that isatin thiocarbazone complexes with metals like Pd(II), Zn(II), and Hg(II) had higher antimicrobial activity than their respective ligands [77].



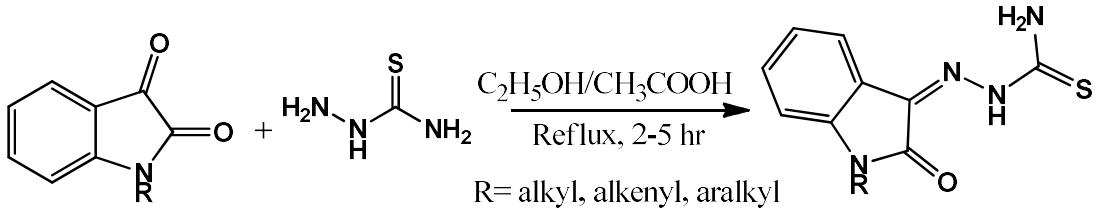
73a-i

Scheme 13a. Synthesis of isatin derivatives.



74a-i

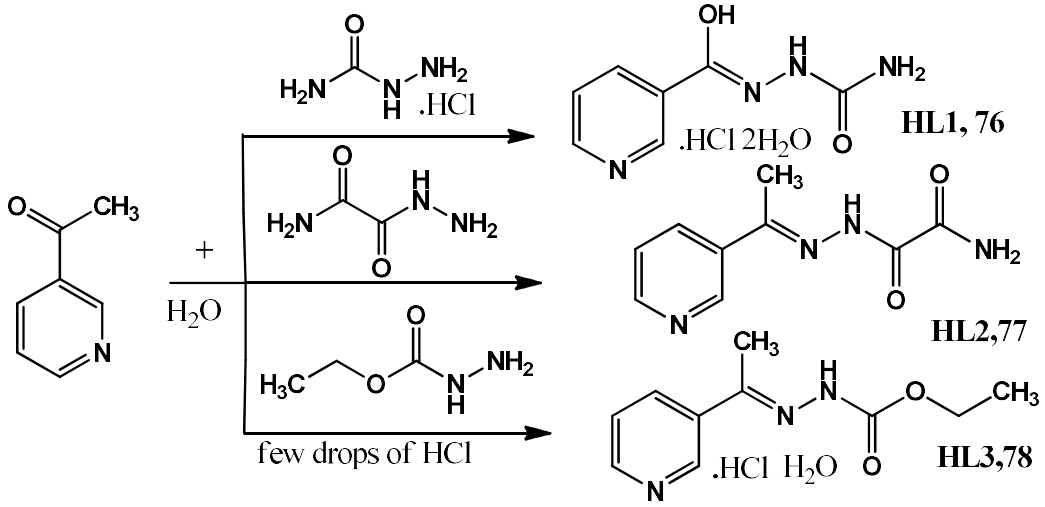
Scheme 13b. Synthesis of isatin containing semicarbazone derivatives.



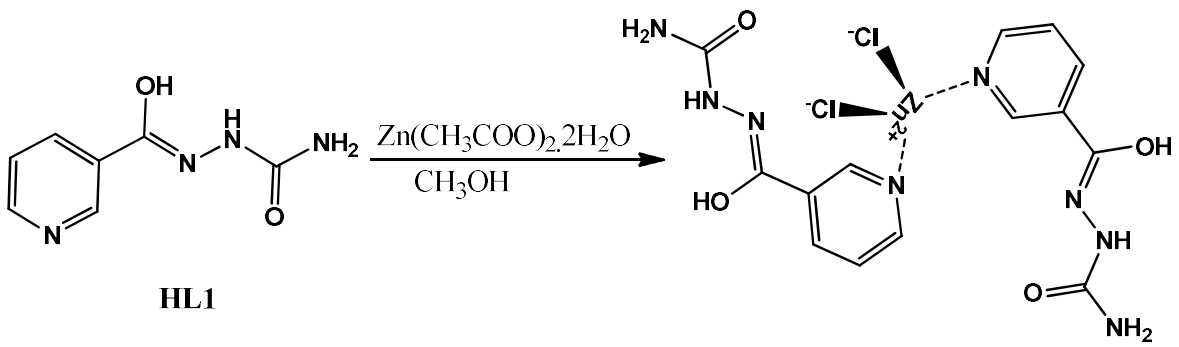
75a-c, 75f-h

Scheme 13c. Synthesis of isatin containing thiosemicarbazone derivatives.

Schiff base complexes (**Scheme 14**) were synthesized from 3-acetylpyridine and semicarbazide, as well as the tetrahedral Zn(II) (**Scheme 15**). Despite the presence of many donor atoms, statistical studies revealed that the ligand coordinated as monodentate. Although the ligand was largely inert, the complex had mild antibacterial, antifungal, and cytotoxic activity. In tumor cell lines, the complex strongly induced the development of reactive oxygen species, influenced cell cycle progression, and induced autophagy [78].



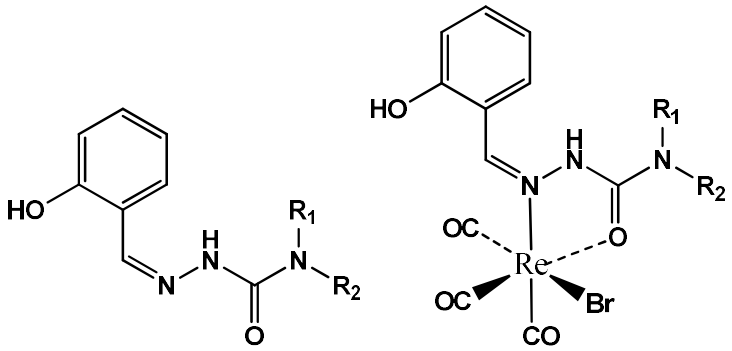
Scheme 14. Synthesis of the semicarbazide ligands (**76-78**).



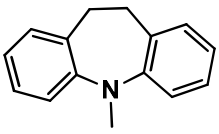
HL1 **79**

Scheme 15. Synthesis of complexes $[ZnCl_2/(HL1)_2$.

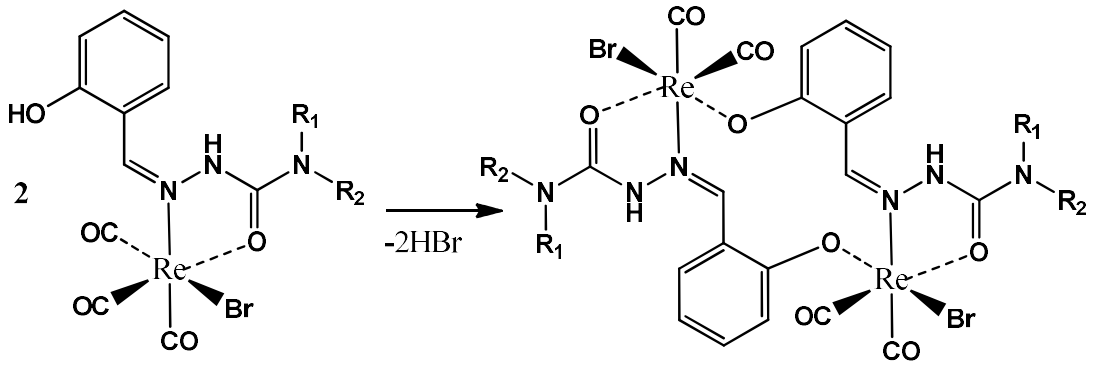
A sequence of N, N-disubstituted salicylaldehyde semicarbazones (SSCs) (80) and rhenium (I) tricarbonyl complexes (**81**) were synthesized (**Scheme 16**). The imino nitrogen and carbonyl oxygen atoms in ligands serve as bidentate, according to crystallographic studies. MOLT-4 cells are cytotoxic to the [ReBr $(CO)_3$(SSC)] complexes in a low to a high level [79].



80 **81**

Ligand	**R_1**	**R_2**	**Ligand**	**R_1**	**R_2**
H2Bu2	Butyl	Butyl	H2MePh	Methyl	Phenyl
H2Hex2	Hexyl	Hexyl	$H2Ph_2$	Phenyl	Phenyl
H2Ben2	Benzyl	Benzyl	H2BF	$-NR_1R_2$= 	

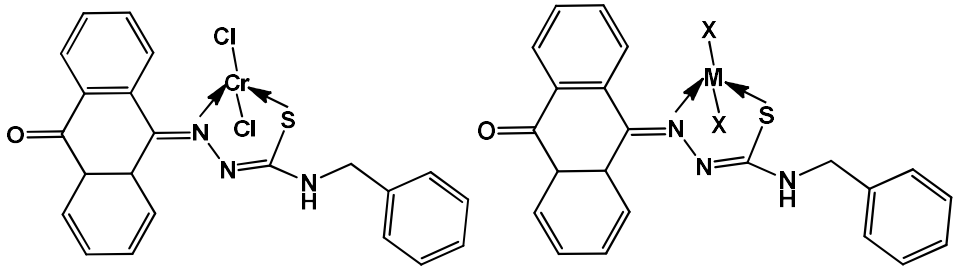
The salicylaldehyde semicarbazide and rhenium (I) carbonyl complexes synthesized



82

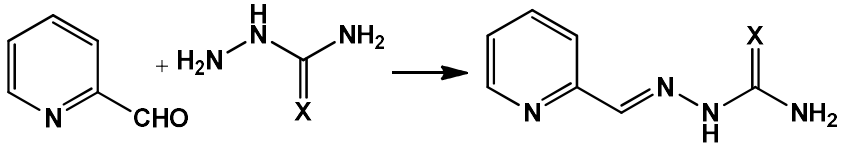
Scheme **16**. Synthesized ligands and their corresponding complexes.

The effect of N4-substitution, additional donor sites, and complexation on the biological activity of anthraquinone N4 benzyl-thiosemicarbazone Cr (III) complex (**83**) and metal complex (**84**) with the potential to function as an anti-cancer drug has been studied. The complexes formed a family of antibacterial compounds capable of inhibiting the growth of at least one to ten different bacterial species. The impact of extra binding sites, N4 substitution, and metal ion complexation on biological behavior has been studied [80].

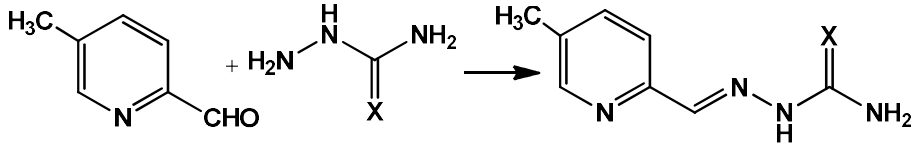


83 **84**

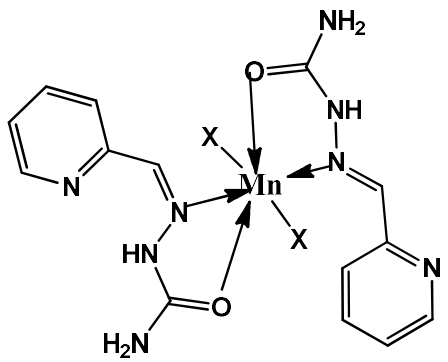
The Mn(II) complexes (**85-88**) with four semicarbazide and thiosemicarbazide-based ligands such as 2-formyl pyridine semicarbazone (L1), 2-formyl pyridine thiosemicarbazone (L2), 5-methyl 2-formyl pyridine semicarbazone (L3), and 5-methyl 2-formyl pyridine thiosemicarbazone (L4). The twisted octahedral geometry of complexes has been proposed based on IR electronic and EPR spectral data [81].



(X=O or S in L1 and L2 respectively)



(X=O or S in L3 and L4 respectively)



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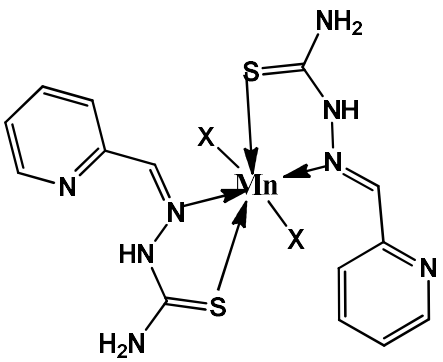

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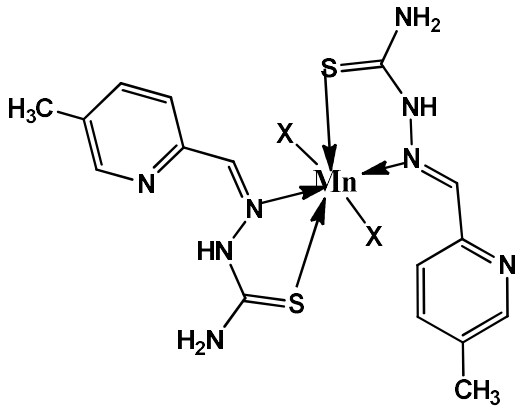
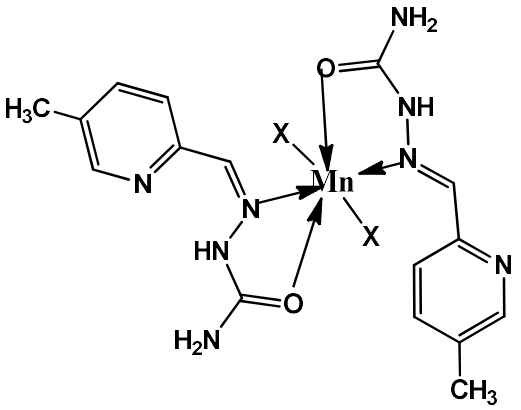
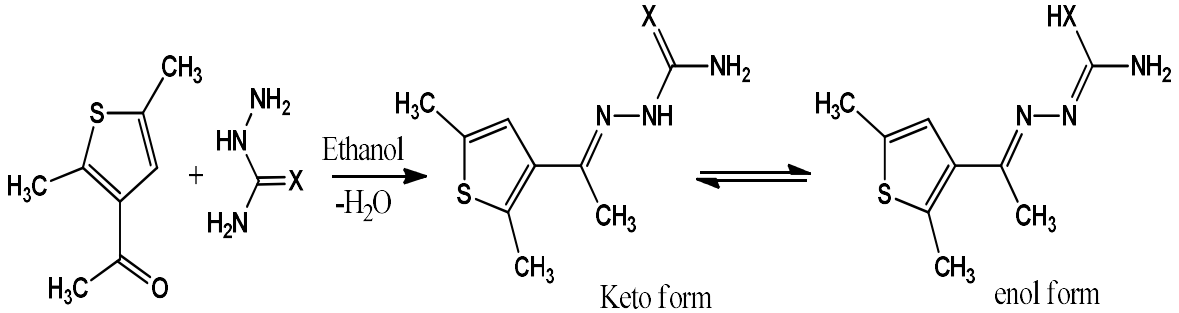


(where X=Cl, NO_2) **87**



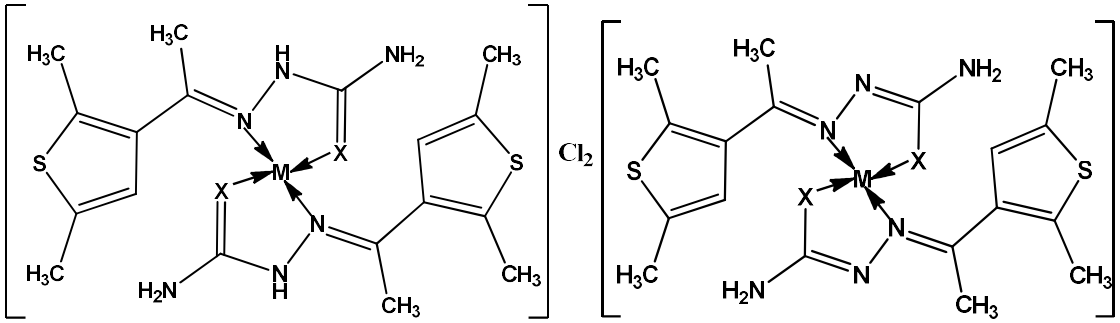
88

3-acetyl-2,5-dimethylthiophene thiosemicarbazone (L1H) and 3-acetyl-2,5-dimethylthiophene semicarbazone (L2H) are heterocyclic ketimines formed by reacting 3-acetyl-2,5-dimethylthiophene with thiosemicarbazide and semicarbazide hydrochloride (**Scheme 16**). Metal salts were mixed in 1:2 molar ratios with these ligands to make the Pd(II) and Pt(II) complexes. These ligands coordinate to the metal atom in a monobasic bidentate way, and the complexes have been suggested to have a square planar environment around the metal atoms. Both the ligands and their palladium derivatives have been shown to have anti-amoebic action against the protozoan parasite *Entamoeba histolytica* [82].



89 90

Scheme 16. Synthesis of 3-acetyl-2,5-dimethylthiophene thiosemicarbazone and 3-acetyl-2,5-dimethylthiophene semicarbazone ligands



91 $[M(LH)_2]Cl_2$ **92 $[M(L)_2]$**

6. Conclusion

Antibacterial, antitubercular, antifungal, anthelmintic, anticancer, antimalarial, and other valuable chemical and biological processes are found in semicarbazide and thiosemicarbazide derivatives [83-90]. They are physiologically and pharmacologically active compounds that have also been effective in the CNS and cardiovascular disorders. The existence of multiple aryl substituents has increased the moiety's efficacy. The challenge of treating microbial diseases prompted researchers to investigate the biological activities of metal complexes containing different transition metals such as Ni(II), Cu(II), and Pd (II). In pharmacological science, this method may lead to compounds with higher biological activity. Semicarbazide, thiosemicarbazide derivatives, and their metal complexes will be used in various bioactive compounds as well as chemical applications in the future.

Acknowledgment

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Conflict of interest

The authors declare that they have no conflicts of interest.

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