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# A review of recent research on the antimicrobial activities of thiosemicarbazone-based compounds

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**Keywords:**
*Thiosemicarbazone, Antimicrobial, Antibacterial, Antifungal, Biological activity*

**Abstract** — Thiosemicarbazones can be synthesized by condensation of thiosemicarbazides with ketones or aldehydes and play a role as precursors in the synthesis of many compounds such as thiazoles. They can exhibit many biological activities such as anti-inflammatory, antitumor, and antimicrobial properties. The discovery of antibiotics was an important milestone in the treatment of bacterial infections. However, antimicrobial resistance developed by microorganisms has created the need to discover new antimicrobial agents. Thiosemicarbazones and thiosemicarbazone-based compounds show significant antimicrobial potential. This review investigates the antimicrobial activity results of 244 Thiosemicarbazones and Thiosemicarbazone-based compounds over the last five years. We summarized some articles on thiosemicarbazones and their hybrids showing only antibacterial and antifungal activity in Web of Science (WOS) between 2019 and 2024.

**Subject Classification (2020):**

## 1. Introduction

Thiosemicarbazones (TSC) are a class of compounds containing nitrogen and sulfur and allow the synthesis of different molecules [1]. These compounds are generally obtained by the condensation of thiosemicarbazide and ketone or aldehyde [2] (Figure 1). Moreover, they play an important role among the styrene base ligands through the association of the hydrazine group with the aldehyde or ketone [3]. They are also known as thiourea derivatives that contain sulfur instead of the oxygen found in semicarbazones [1]. Thiosemicarbazones have an extended conformation caused by electron delocalization across the moiety [3]. They coordinate metal ions with one of the sulfur or hydrazine nitrogen atoms, and with this behavior, they are among good chelating ligands [4]. In addition, thiosemicarbazones have structural flexibility and many biological activities [1].

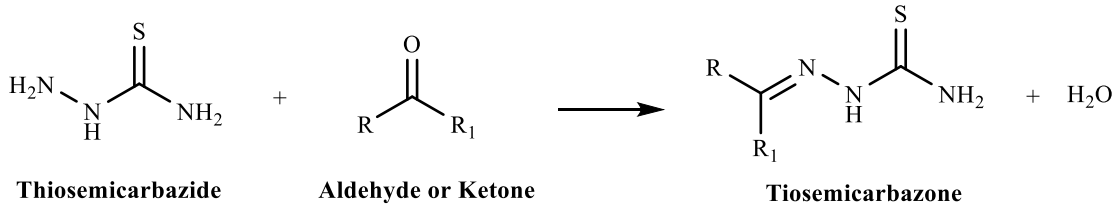


**Figure 1.** General structure of thiosemicarbazones [5]

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Thiosemicarbazone derivatives exhibit many biological activities: antiviral [6], antioxidant [7], antitumor [8], anti-inflammatory [9], antifungal [10], and antibacterial [11]. These compounds have a high affinity for sulfur- and nitrogen-containing molecules such as some amino acids, peptides, and proteins [11]. The biological activities of metal complexes of thiosemicarbazones may be higher or weaker than the original ligands [4,12]. For this reason, many studies are comparing the biological activities of thiosemicarbazones with their metal complexes. Khan and Yusuf synthesized thiosemicarbazone derivatives and their palladium II metal complexes in their study in 2009. Antibacterial analyses show that the activities of metal complexes are stronger [4].

In addition, the literature also shows the antimicrobial activities of thiosemicarbazone derivatives, including natural polymers such as chitosan. In a study in 2014, three new thiosemicarbazones were synthesized by the condensation reaction of a chitosan derivative and some benzaldehyde derivatives. The results show that the antibacterial and antifungal activities of thiosemicarbazone derivatives are higher than O-carboxymethyl chitosan [13]. In another study, a thiosemicarbazone compound and its six coordination compounds were synthesized. Antioxidant analysis shows that the thiosemicarbazone compound shows stronger activity than almost all other complexes [14]. In addition, thiosemicarbazones have the ability to form colored complexes with metal ions. With this ability, they serve as sensors in the detection of metal ions [15]. They exhibit different sensor properties such as colorimetric [15], fluorimetric, and electrochemical [1].

There are also many studies on the structure-activity relationship of thiosemicarbazones. It has been reported that changes in the amino substituents or N-heterocyclic ring of the compounds affect the biological activity [3]. In addition, changes in the structure of the aldehyde or ketone also affect the antibacterial and anticancer activity. In 2023, Masuri et al. investigated the role of the presence, number, and position of -OH groups in the biological activities of thiosemicarbazones. In this study, they synthesized six coumarin-based thiosemicarbazone compounds with different -OH variants. The results show that -OH variations in the structure are effective on activity [16].

We compiled studies that received 10 or more citations in articles published between 2019 and 2022. Since the studies in 2023 and 2024 were published recently, we did not take the citation criteria into account in these studies. In this study, we will share the antimicrobial activity results of a total of 244 TSCs and their complexes.

## 2. Antimicrobial Activities of Thiosemicarbazones

Çakmakçı et al. synthesized a thiosemicarbazone derivative **(T1)** and its cobalt, palladium, nickel, and zinc **(T2-T5)** metal complexes (Figure 2). Compounds were evaluated against some bacteria and one fungal strain by disc diffusion and microdilution methods. While TSC ligand **(T1)** was inactive against *Serretia marcescens* and *Candida. albicans,* it gave a MIC value against other bacterial strains at a concentration of 312-2500 μg/mL. Metal complexes showed activity in the range of 39-2500 μg/mL, except for the Ni(II) complex, which did not show activity against *S. marcescens* and *C. albicans.* In disk diffusion analysis, it is seen that the TSC ligand creates 1.2, 7.1, and 1.1 mm zones against *S. aureus, E. feacalis,* and *C. albicans,* respectively. Metal complexes have created zones between 0.8-12.1 mm against the microorganisms in which they are active. Positive controls appear to form a zone between 18-26 mm: Amphicillin: 26-28 mm for gram-positives; Genthamycin 18-24 mm for gram-negatives; Flucanazole: 26 mm for fungus). The results show that, among the complexes whose activities were detected, there is no finding that reduces the activity of the **T1** ligand, while some complexes increase the activity. The same situation is observed in disk diffusion analysis, except for the activity of the Ni(II) complex **(T4)** against *C. albicans* [17].

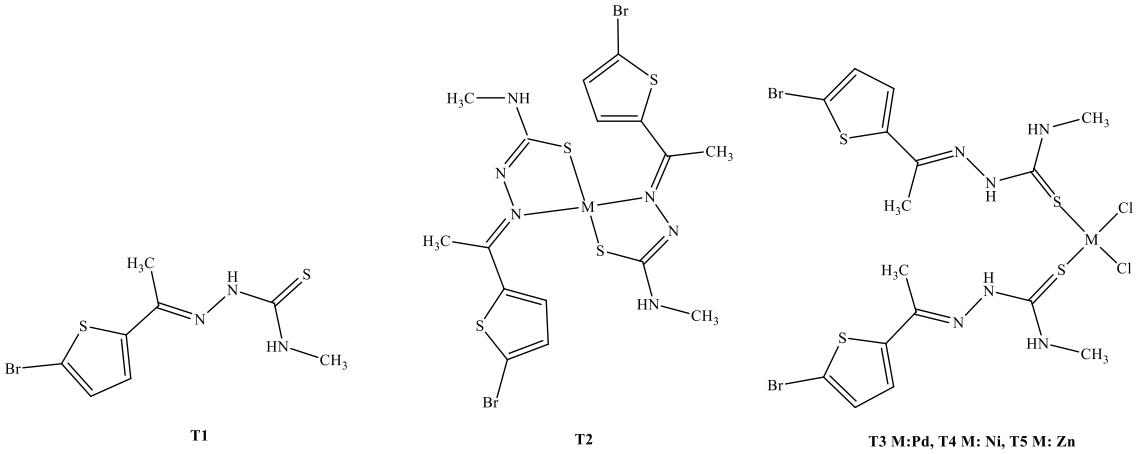



**Figure 2.** Compounds synthesized by Çakmakçı et al. [17]

In another study, Sharma et al. synthesized semicarbazone and thiosemicarbazone Schiff bases from symmetrical chalcones (Figure 3). They investigated the antimicrobial activities of the compounds against one gram-negative *Escherichia coli* MTCC42 and one gram-positive bacteria *Bacillus subtilis* MTCC736 using the agar well diffusion method. The compounds formed an inhibition zone of 18.5-27.8 (Standard Streptomycin: 22 mm) and 13.6-18.5 mm (Streptomycin: 26 mm) against *B. subtilis* and *E. coli*, respectively. While some of the synthesized compounds showed activity close to the standard drug, the compound numbered **T11**, which has a substituent of -4$CH_3$Ph, showed a higher effect than the standard against gram-positive bacteria. Within the synthesized group, thiosemicarbazones exhibit stronger activity than semicarbazones [18].

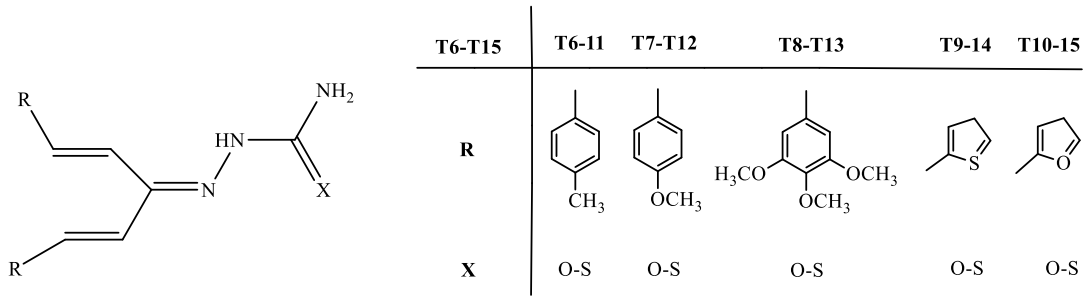



**Figure 3**. Compounds synthesized by Sharma et al. [18]

The antimicrobial activities of three thiosemicarbazones and their fac-Re(I) tricarbonyl organometallic complexes were investigated by Diksha et al (Figure 4). The compounds were analyzed by microdilution technique against three gram-negative and one gram-positive bacterial strains. All compounds were ineffective against gram-negative bacteria up to 64 μg/mL. Antibacterial activities were detected against the gram-positive *Staphylococcus aureus* ATCC 29213 bacterial strain (MIC values: 0.5-64 μg/mL). The results show that the metal complexes increased the antimicrobial activities of **T16, T17**, and **T19** thiosemicarbazone ligands against the *S. aureus* bacterial strain by 32, >128, and >2-fold, respectively. It has been reported that the metal complex of phenyl-substituted thiosemibarcazone **(T20)** has a strong antibacterial effect with a MIC value of 0.5 μg/mL (Standard Levofloxacin: 0.125 μg/mL) [19].

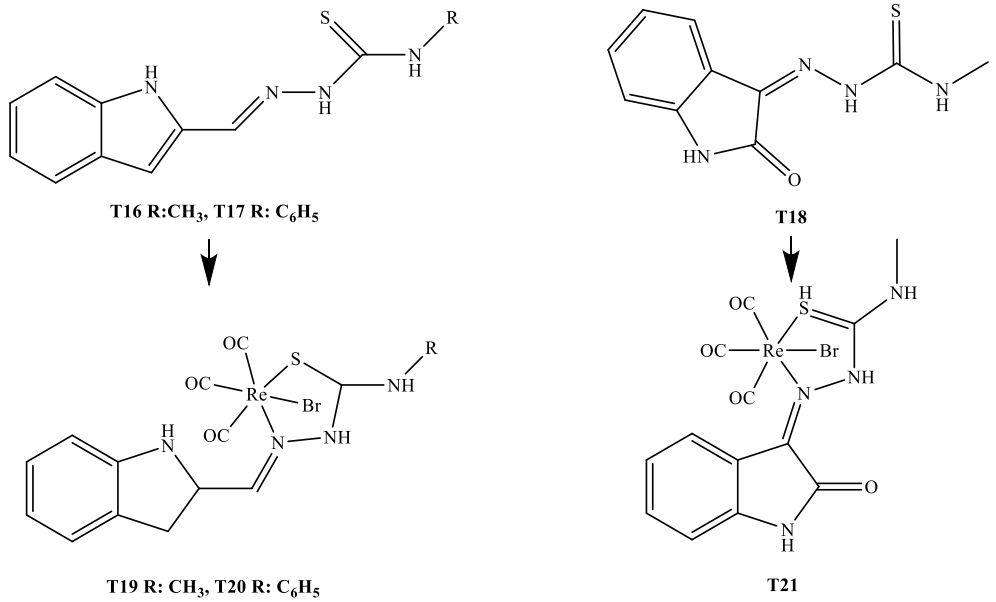



**Figure 4.** Compounds synthesized by Diksha et al. [19]

Aly and colleagues synthesized a series of thiosemicarbazones **(T22-27)** and their Pd and Ag complexes **(T28-T39)** (Figure 5). They investigated the antimicrobial activity of thiosemicarbazone complexes against one fungus, two gram-positive, and two gram-negative bacteria by microdilution method. The complex compounds exhibited very potent antimicrobial (MIC: 0.018-1.135 μg/mL). Ag-thiosemicarbazone complex **(T39)** with 3-$CH_3O$-Ph substituent gave the same MIC value (0.018 μg/mL) as Ciprofloxacin, the standard drug against *E. coli* and *S. aureus* bacterial strains [20].

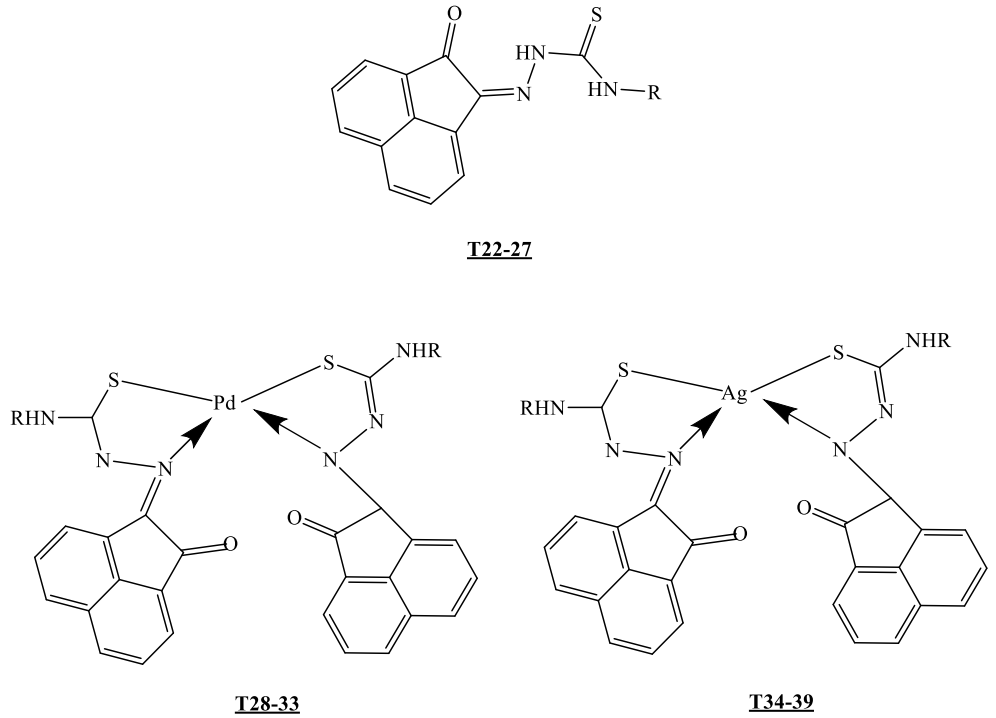
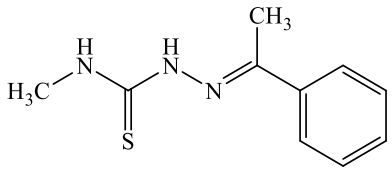


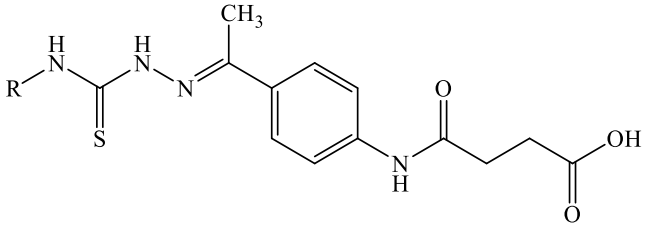

**Figure 5.** Thiosemicarbazone derivatives synthesized by Aly et al.[20]

In a recent study in 2024, Beltr´an-Torres and his colleagues synthesized five thiosemicarbazone derivatives **(T40-44)** with over 78% yield and formed their bismuth(III) complexes with microwave irradiation (Figure

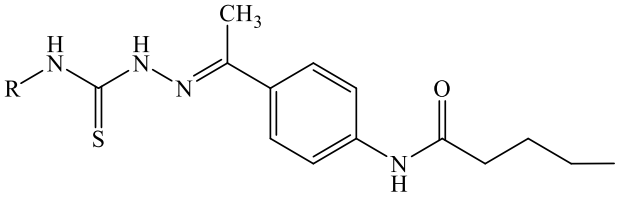
6). They investigated the antibacterial potential of the compounds against *Salmonella spp*. and *S. aureus* bacterial strains using agar well diffusion, microdilution, and viable count cell methods. While thiosemicarbazones and bismuth(III) complexes had no antimicrobial activity on *S. aureus*, they showed antibacterial activity against *Salmonella spp.* % bacterial growth inhibition rates reported that the complexes (72-85%) were more effective than the corresponding thiosemicarbazone derivatives (32-63%) [21].



**T40**



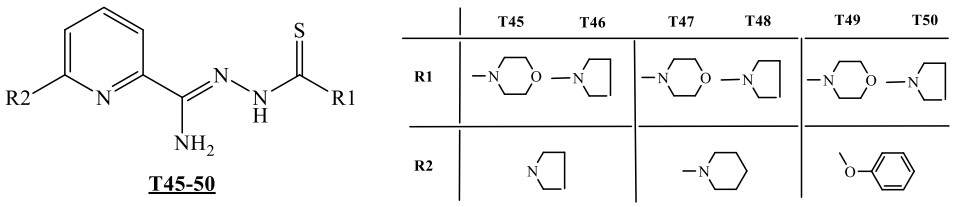
**T41** R:H, **T42** R: $CH_3$



**T43** R:H, **T44** R:$CH_3$

**Figure 6.** Thiosemicarbazone ligands synthesized by Beltr´an-Torres [21]

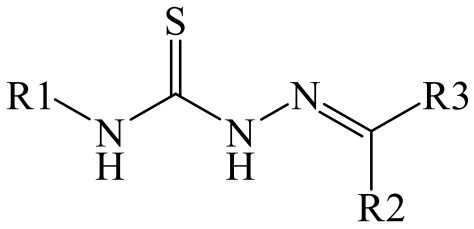
Since Ziembicka et al. knew the antimicrobial activities of thiosemicarbazones and pyridine rings, they combined these two structures and synthesized six thiosemicarbazone derivatives **(T45-50)** to examine their antimicrobial activities (Figure 7). They evaluated the antimicrobial activities of the compounds against a total of fifteen strains of microorganisms: two *M. tuberculosis* strains that cause tuberculosis (H37Rv and Spec. 210); four gram-negative bacteria (*E. coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Proteus mirabilis*)five gram-positive bacteria (*B. subtilis, Bacillus cereus, S. aureus, Staphylococcus epidermidis, Micrococcus luteus*,); and fungi (*C. albicans, Candida parapsilosis*). MIC values of the compounds were reported as follows: 0.5-16 μg/mL against *Mycobacterium tuberculosis* bacterial strains; no activity against gram-negative bacterial strains was detected (>1000 μg/mL); 0.49-7.8 μg/mL (except **T49**) against gram-positive bacterial strains; 7.8-1000 and >1000 μg/mL against fungal strains. It was reported that compounds numbered **T46** and **T48** showed antimicrobial activity equal to or higher than standard drugs [22].




**T45-50**

**Figure 7.** Thiosemicarbazone derivatives synthesized by Ziembicka [22]

Thiosemicarbazones **(T51-69)** seen in Figure 8 were synthesized by Pitucha and colleagues. The compounds were investigated against *S aureus, S. epidermidis, Enterococcus hirae,* and *M. tuberculosis* strains. The compound with the strongest antituberculosis activity, T69, showed 4 μ/cm$^3$ activity against *M. tuberculosis* H37Rv (Standard Isonicotinic acid hydrazide: 0.125 μ/cm$^3$). Against other bacterial strains, **T57** and **T58** exhibited moderate activity with a MIC of 64-128 μg/mL [23].

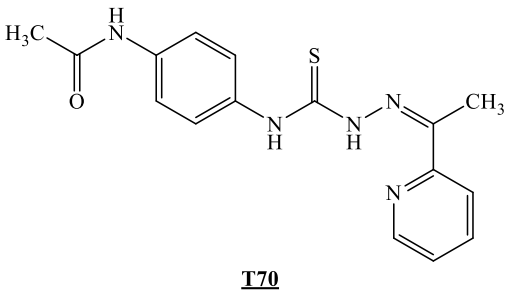


**T51-69**

| | R1 | R2 | R3 | | R1 | R2 | R3 |
|---|---|---|---|---|---|---|---|
| **T51** | $C_6H_5$ | H | 3,4-di$CH_3OC_6H_3$ | **T61** | 2-$ClC_6H_4$ | $CH_3$ | H |
| **T52** | $CH_3$ | H | 4-$BrC_6H_4$ | **T62** | 2-$ClC_6H_4$ | H | 3,4-di$ClC_6H_3$ |
| **T53** | $CH_3$ | H | 3,4-di$CH_3OC_6H_3$ | **T63** | 3-$ClC_6H_4$ | H | 4-Br |
| **T54** | $CH_3$ | $CH_3$ | 4-$NH_2C_6H_4$ | **T64** | 3-$ClC_6H_4$ | H | 3,4-di$CH_3OC_6H_3$ |
| **T55** | $CH_3$ | H | 3,4-di$ClC_6H_3$ | **T65** | 3-$ClC_6H_4$ | H | 3,4-di$ClC_6H_3$ |
| **T56** | 2-$CH_3C_6H_4$ | H | 4-$BrC_6H_4$ | **T66** | 4-$ClC_6H_4$ | H | 3,4-di$CH_3OC_6H_3$ |
| **T57** | 2-$CH_3C_6H_4$ | H | 3,4-di$CH_3OC_6H_3$ | **T67** | 4-$ClC_6H_4$ | H | 3,4-di$ClC_6H_3$ |
| **T58** | 2-$CH_3C_6H_4$ | H | 3,4-$Cl_2C_6H_3$ | **T68** | 4-$ClC_6H_4$ | H | 4-$BrC_6H_4$ |
| **T59** | 2-$ClC_6H_4$ | H | 4-$BrC_6H_4$ | **T69** | 3-$ClC_6H_4$ | $CH_3$ | H |
| **T60** | 2-$ClC_6H_4$ | H | 3,4-di$CH_3OC_6H_3$ | | | | |

**Figure 8.** General structure of thiosemicarbazones synthesized by Pitucha et al. [23]

Rusnac and co-workers synthesized a paracetamol-containing thiosemicarbazone **(T70)** and its five Cu(II) complexes **(T71-75)** (Figure 9). MIC results show that **T70** exhibit no antibacterial activity up to 500 μg/mL. MIC values of 62.5 **(T72)** and 250 μg/mL **(T74)** of the two complexes against *E. coli* were detected. Moreover, the same complexes (15.6 and 31.3 μg/mL, respectively) showed antifungal activity close to the standard drug Miconazole (16 μg/mL) on the *C. albicans* fungal strain. **T70** also exhibited strong antifungal activity against *C. albicans* with 31.3 μg/mL. While **T71** gives 15.6 μg/mL MIC against *S. aureus*, the other four complexes show stronger activity than the standard drug Nitrofurazone (4.7 μg/mL) with a concentration of 3.9 μg/mL. Minimum bacteriocidal concentration evaluation shows that all complexes whose activity was detected have bacteriocidal activity. The results show that metal complexes can significantly increase the antibacterial activity of the thiosemicarbazone compound, while the same is not observed for antifungal activity. [24].



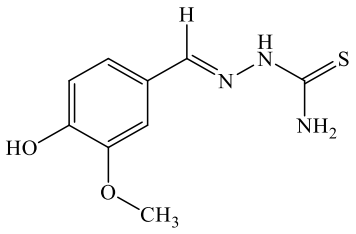
**T70**

**T71:** Cu(T70)$CH_3COO$
**T72:** [{Cu(T70)Cl}2] $H_2O$
**T73:** [Cu(T70)$H_2O$ DMF]$NO_3$
**T74:** [Cu(T70)Br]
**T75:** [Cu(T70) $H_2O$]$ClO_4$

**Figure 9.** Thiosemicarbazone and its complexes synthesized by Rusnac et al. [24]

Swaminathan et al. synthesized the **T76** thiosemicarbazone compound by the reaction of 4-hydroxy-3-methoxybenzaldeide and thiosemicarbazide (Figure 10). The antibacterial activity of thiosemicarbazone derivative and its precursor compound, 4-hydroxy-3-methoxybenzaldeid, was investigated against the *E. coli*

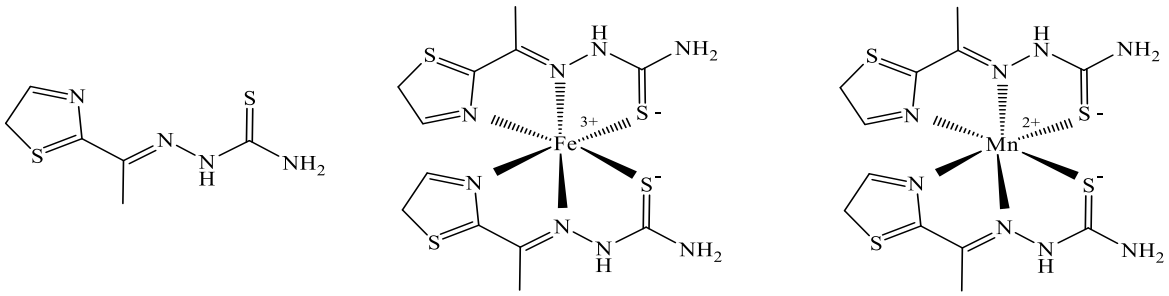
JM101 bacterial strain by disk diffusion method. The authors measured the inhibition zone of the benzaldehyde derivative precursor compound as 12 mm, while the inhibition zone of the thiosemicarbazone compound was measured as 30 mm, an increase of more than 2.5 times [25].



**T76**

**Figure 10.** Thiosemicarbazone derivative synthesized by Swaminathan [25]

Another study from 2023 gives the synthesis and antimicrobial properties of a thiosemicarbazone compound **(T77)** and its Fe(III) **(T78)** and Mn(II) **(T79)** metal complexes (Figure 11). The antimicrobial potential of the compounds **T77-79** was evaluated against many bacteria, yeasts, and fungi. MIC values of the compounds indicate that they have antibacterial activity: Free TSC **(T77)** 0.42-0.84 mM; Fe(III) complex 0.28-0.56 mM; Mn(II) complex 0.17-0.34 mM; standard (Chloramphenicol) 0.05-0.77. While **T77** (0.84 mM) showed very close activity to the standard drug (0.77 mM) against *P. aeruginosa* and *Clostridium sporogenes* bacterial strains, the Fe(III) metal complex exhibited stronger activity against the same microorganisms (0.56 mM, 0.28 mM, respectively). Mn(II) complex **T79** became the most potent antibacterial compound in the study, exhibiting stronger activity than the standard drug against *Proteus hauseri, E. coli, K. pneumoniae, and C. sporogenes*. The results show that the antifungal potent of the compounds are similar to their antibacterial activities, in order from lowest to highest, TSC (0.84-168 mM), Fe(III) complex (0.56-1.12 mM), Mn(II) complex (0.34-1.37 mM). The authors explain the relatively lower activity of the Fe(III) complex as possibly resulting from the covalence of the Fe-S bonds and the high bond order. [26].



**T77** **T78** **T79**

**Figure 11**. The compounds synthesized by Stojickov et al. [26]

Ezzat et al. synthesized a thiosemicarbazone derivative **(T80)** and its copper and zinc complexes via the reaction of 5-(morpholinisulfonyl)isatin and thiosemicarbazide (Figure 12). The compounds **T80-82** were analyzed by measuring MIC and inhibition zones. Two gram-positive, two gram-negative, and one fungal strain were used in the study. Inhibition zone measurements show that TSC ligand **T80** gives the same inhibition zone as the Zn metal complex **T82** against *E. coli* and creates a higher zone than both metal complexes in all other microorganism strains. In addition, **T80** showed stronger activity against other bacterial and fungal strains (*B. subtilis, S. aureus, P. aureginosa*, and *C. albicans*) than the standard drugs Tetracycline and Amphotericin B. **T81** Cu(II) complex, which showed low activity in zone measurement, was not tested by microdilution. MIC results show that the **T80** TSC ligand (8.2-32.84 μM) has stronger activity against all bacterial strains than the Zn(II) metal complex (24.59-98.42 μM). Both compounds exhibited stronger activity against the standard drug tetracycline (35.14-140.62 μM). **T80** (22.24 μM) had stronger antifungal activity than the Zn(II) complex (24.59 μM), while the positive control showed similar but weaker activity to Amphotericin B (16.90 μM) [27].

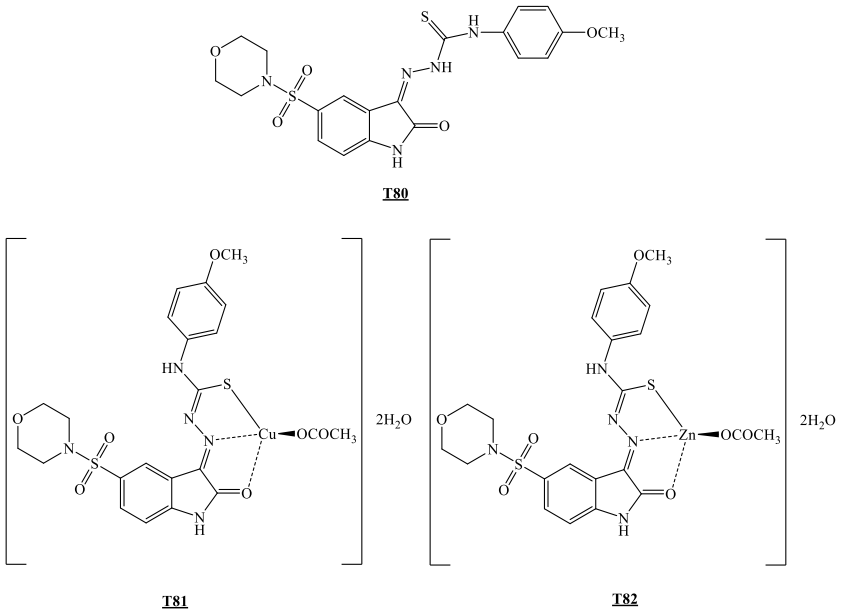


**Figure 12.** The compounds synthesized by Ezzet et al. [27]

In another study, a similar team synthesized the methyl-substituted derivative of T80 **(T83)** and its Cu **(T84)** and Zn **(T85)** complexes with a different two-step method (Figure 13). They investigated the antimicrobial activities of the compounds against the same group of microorganisms using microdilution and agar well diffusion methods. Inhibition zones for bacteria are 22-24 mm, 11-14 (inactive for some bacteria), 22-27 mm, and 20-25 mm for TSC, Cu, Zn complex and standard Tetracycline, respectively. They created 21 mm, 12 mm, and 25 mm inhibition zones in the same order against the *C. albicans* fungus strain (Standard Amphotericin B: 22 mm). TSC ligand **T83** and Zn complex gave MICs of 7.81-31.25 μg/mL and 3.9-27.77 μg/mL against all microorganisms, respectively. Zn complex showed stronger activity than standard drugs against all microorganisms. While TSC is less effective than the Tetracycline drug against *E. coli* and *C. albicans*, it is less effective against *S. aureus*. It exhibited more potent activity than the Tetracycline against *B. subtilis* and *P. aeruginosa*. The antimicrobial potential of the compounds is listed in the following order from highest to lowest: Zn-complex **(T85)**, TSC **(T83)**, and Cu-complex **(T84)**. The antimicrobial potential order is parallel to the -$OCH_3$ substituent TSC **T80** and metal complexes **(T81, T82)** in the previous study. [28]

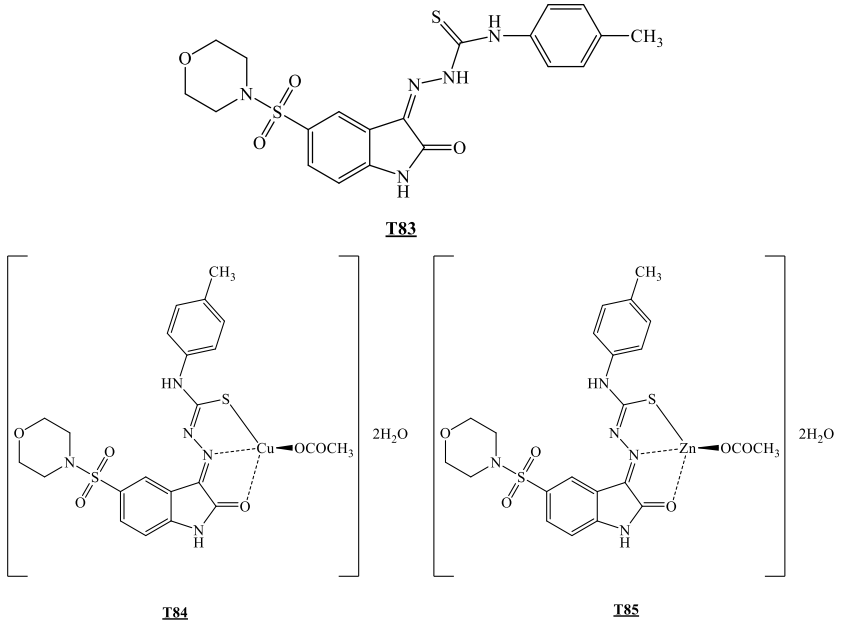


**Figure 13**. The compounds synthesized by Ragap et al. [28]

Jevtovic and colleagues synthesized Pyridoxal-S-methyl-isothiosemicarbazone **(T86)** and its Co(III) **(T87)** complex (Figure 14). They evaluated the antibacterial activities of the Co(III) complex and the Zn(II) complex **(T88)**, which they synthesized in previous studies, by microdilution and agar well diffusion methods. They prepared two dilutions from 0.25 to 2 mg/mL for the agar well diffusion method. The results show that the inhibition zone increases as the concentration increases. The results obtained at the highest concentration are as follows for **T87** and **T88** complexes, respectively: 17 mm, 4.8 mm for S. aureus; 14 mm, 3.4 mm for *E. coli*. Microdilution test was performed in the range of 1000-20 μg/mL. The Zn complex did not show activity in this range against either bacterial strain. The Co complex **T87** exhibited antibacterial activity against *E. coli*, *P. aeruginosa*, and *S. aureus* bacterial strains at concentrations 30 μg/mL, 30 μg/mL, and <20 μg/mL, respectively (Standard Chloram fenicol in the same order 50 μg/mL, 5 μg/mL, 5 μg/mL) [29].

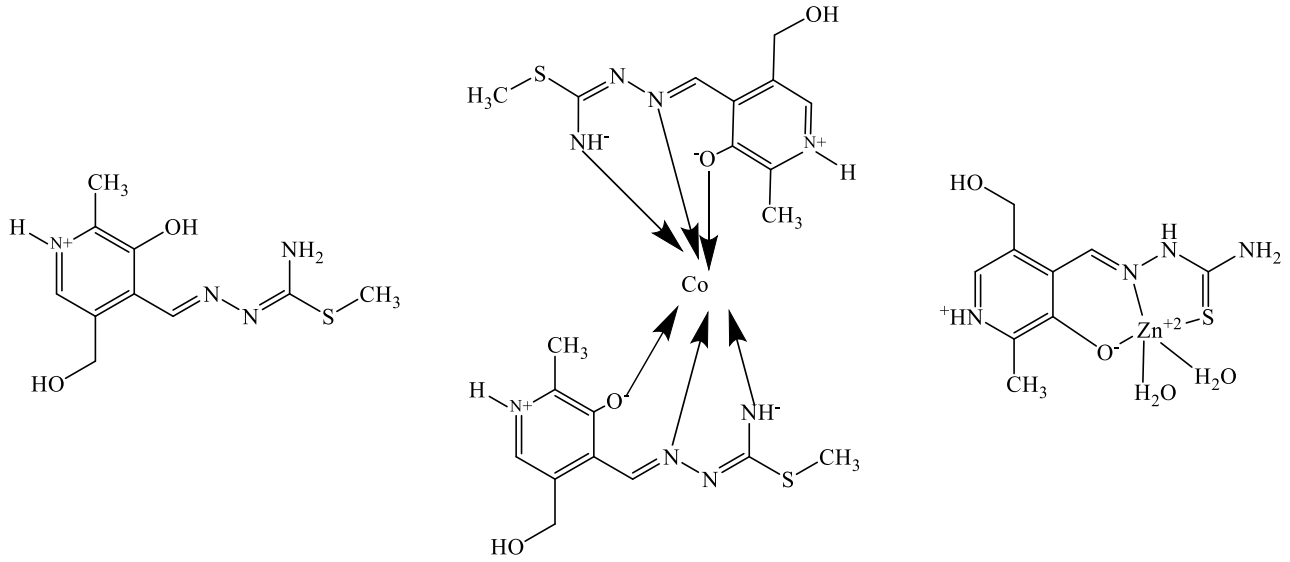



**Figure 14.** Compounds that Jevtovic et al. investigated for their antimicrobial activities [29]

Alzahrani and colleagues synthesized a number of compounds from an Indolin-2,3-dione derivative: 3-(thiosemicarbazone)indolin-2 -one, indolin-2-one Schiff's base, thiazolo-indolin-2-one, 5-(2-oxoindolin-3-ylidene)thiazol-4-one. In this section, we will only share the antimicrobial results of the thiosemicarbazone-indoline derivative **(T89)** shown in Figure 15 and the thiazole compounds **(T90-92)** synthesized from this compound. The compounds were evaluated by microdilution method against four gram-positive, four gram-negative bacteria, and one fungal strain (They worked with two different strains of *S. aureus* and *P. aeruginosa*). While TSC derivative **T89** exhibited no activity against *B. subtilis, S. aureus*, *Salmonella typhimurium,* and *C. albicans*, it exhibited activity against five other bacteria in the MIC range of 125-1000 μg/mL. Thiazole derivatives **(T90-92)** exhibited activity in the range of 1.9-500 μg/mL. In particular, **T91** exhibited higher activity than the standard drug Levofloxacin (8.1-130 μg/mL) against all bacterial strains except *B. subtilis*, with MIC values 1.9-31.2 μg/mL [30].

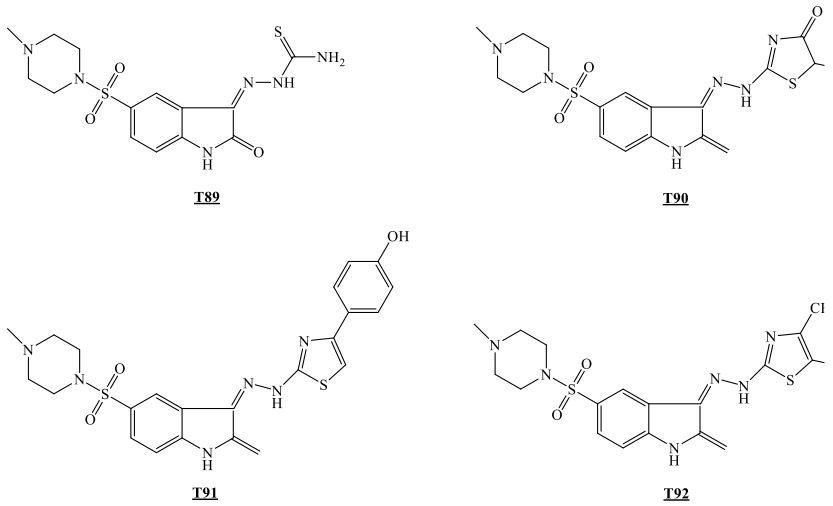
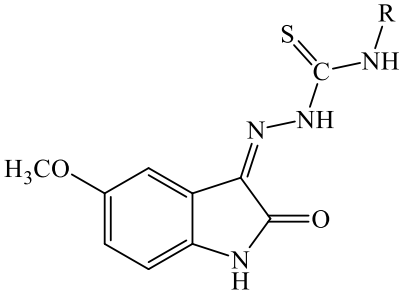



**Figure 15.** The compounds synthesized by Alzahrani et al. [30]

In a study in 2022, Koçyiğit et al synthesized fifteen isatin-thiosemicarbazone derivatives (Figure 16). They analyzed antibacterial and antifungal activities using the microdilution method. *B. cereus, S. aureus, E. coli, P. aeruginosa* bacterial strains and, *C. albicans*, *Candida tropicalis* fungal strains were used in the analysis. While the compounds did not show activity against microorganism strains other than *S. aureus* up to a concentration of 5000 μg/mL, they exhibited antibacterial effect against *S. aureus* with a concentration of 39-625 μg/mL. The compounds showing the strongest activity were reported as follows: compounds **T103** and **T104** were 39 μg/mL, and compounds **T94, T105, and T106** were 78 μg g/mL. [31].



**T93-T107**

**T93** R: 4-F-$C_6H_5$
**T94** R: 3-Cl-$C_6H_5$
**T95** R: 2-$OCH_3$-$C_6H_5$
**T96** R: 2-F-$C_6H_5$
**T97** R: 4-$OCH_3$-$C_6H_5$
**T98** R: 3-F-$C_6H_5$
**T99** R: 4-$NO_2$-$C_6H_5$
**T100** R: 2,4diCl-$C_6H_5$
**T101** R: $CH_2CH_2C_6H_5$
**T102** R: 2-$CH_3$-$C_6H_5$
**T103** R: 4-Cl-$C_6H_5$
**T104** R: $C_6H_5$
**T105** R: $CH_2C_6H_5$
**T106** R: 4-$CH_3$-$C_6H_5$
**T107** R: 2-Cl-$C_6H_5$

**Figure 16.** The compounds synthesized by Koçyiğit et al.[31]

Gaber and colleagues synthesized the methoxy thiosemicarbazone derivative **(T108)** and its mononuclear and binuclear $Co^{2+}$, $Ni^{2+}$, $Cu^{2+}$, and $Zn^{2+}$ metal complexes **(T109-T116)** (Figure 17). Antibacterial and antifungal activities of **T108-T116** were tested against some microorganisms by the agar well diffusion method: *B. subtilis, S. aureus, E. coli, Proteus vulgaris* bacterial strains, and *Aspergillus flavus, C. albicans* fungal strains. The results show that all metal complexes exhibit higher antibacterial activity than the TSC ligand **T108**. In addition, **T113** and **T114** exhibited at least as much activity against *B. subtilis* and *P. vulgaris* as the standard drug gentamicin (26 mm, 25 mm in the same order) with an inhibition zone of 33 mm and 25-26 mm, respectively. While no metal complex exhibited activity against the *A. flavus* fungal strain, **T108** created a 10 mm inhibition zone and the standard drug ketoconazole created a 16 mm inhibition zone. Against another fungal strain, *C. albicans*, all complexes **(T109-T116)** created an 8-12 mm inhibition zone, while TSC ligand **T108** created an 11 mm inhibition zone and ketoconazole created a 20 mm inhibition zone. Only the metal complex numbered **T113** showed stronger antifungal activity than **T108** by creating a 12 mm zone. The results show that metal complexes increased the antibacterial activity of **T108** while decreasing the antifungal activity of all except compound **T113** [32].

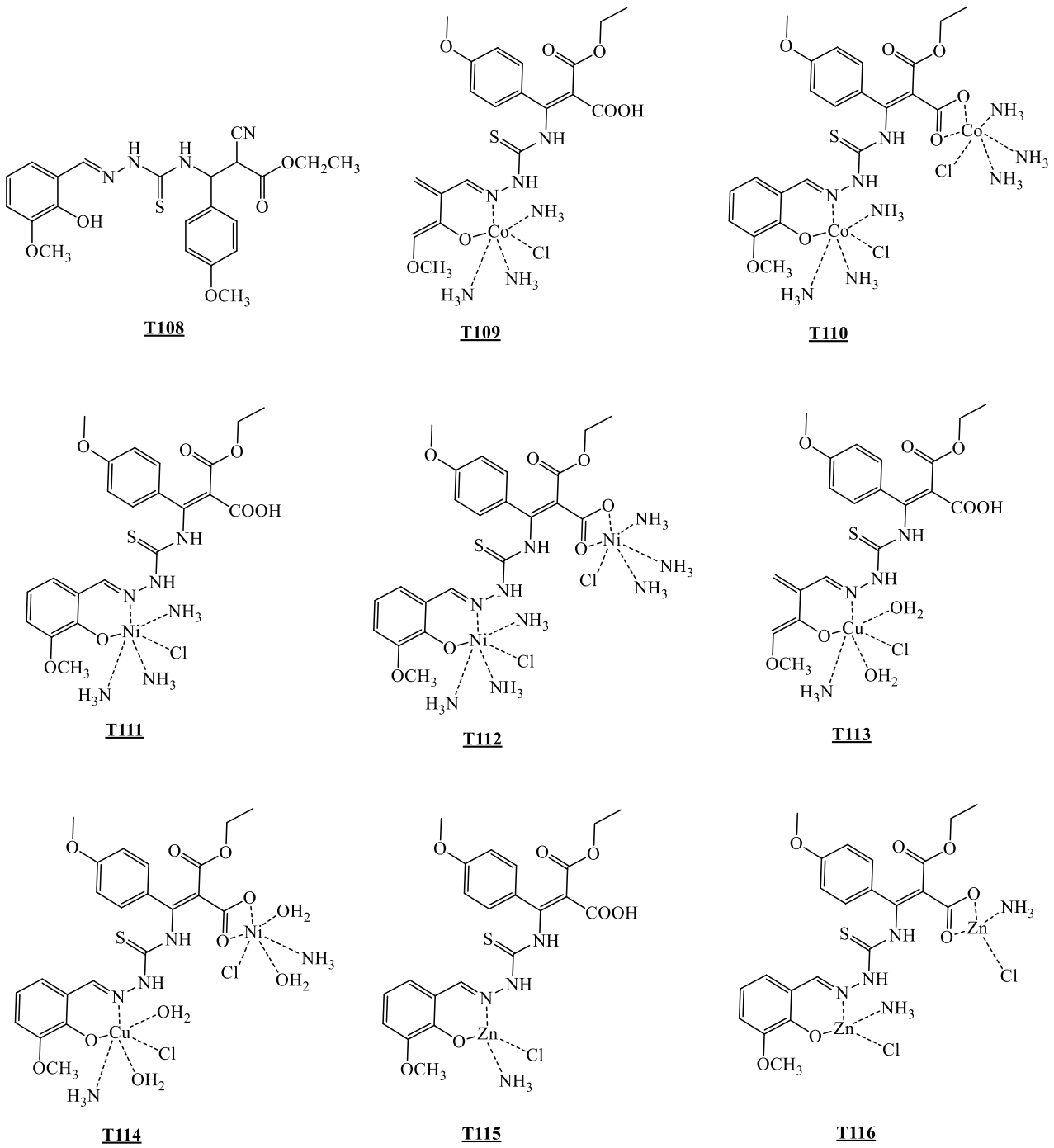
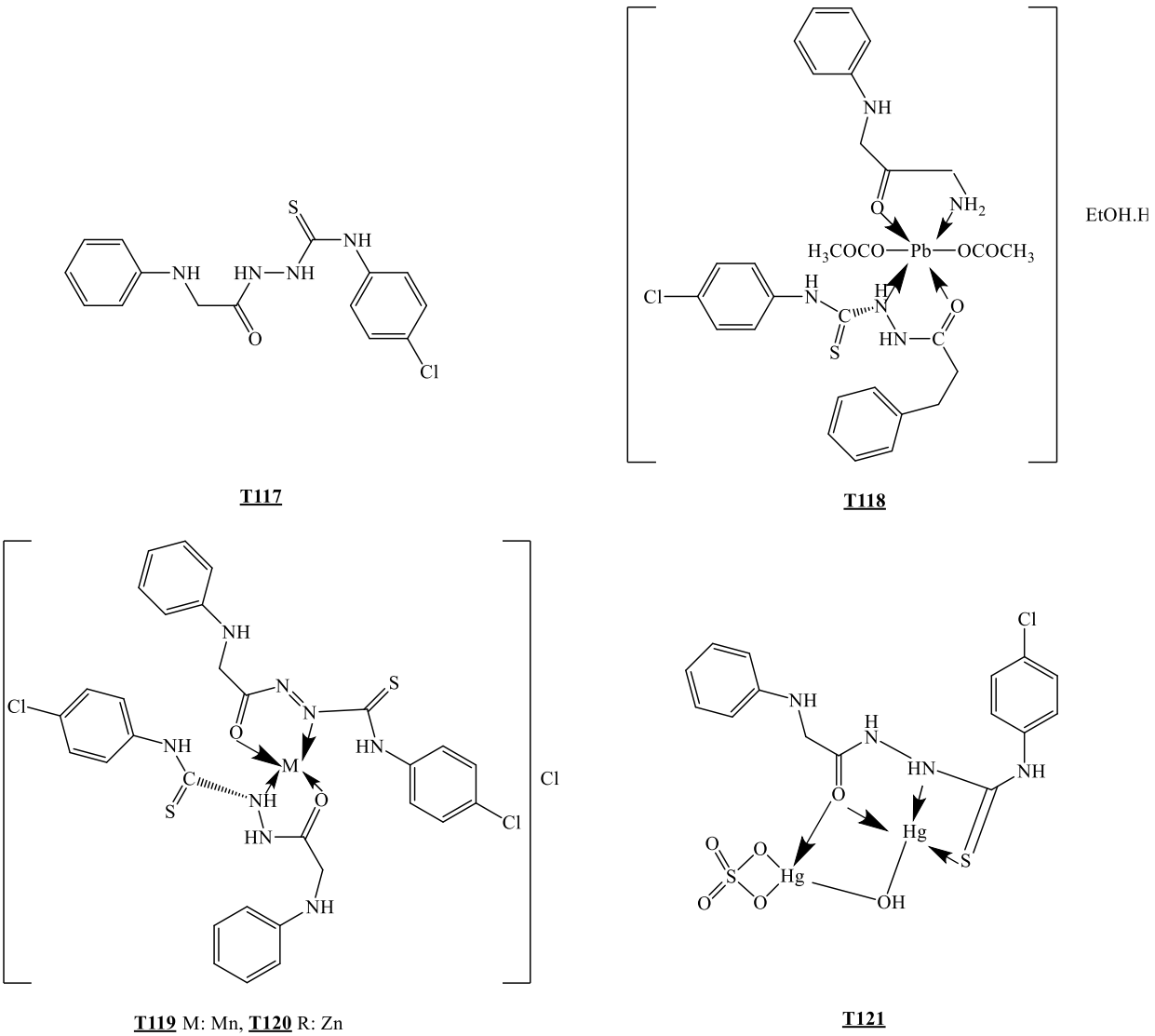



**Figure 17.** The compounds synthesized by Gaber et al. [32]

Another study investigating the antimicrobial activities of thiosemicarbazones shares a thiosemicarbazone derivative **(T117)** and some of its Pb, Mn, Hg, and Zn complexes **(T118-121)** (Figure 18). The antibacterial and antifungal activities of the compounds were compared with disk diffusion results before and after exposure to irradiation. While **T117** showed no activity against *Streptococcus mutants* and *C. albicans*, it created a 13.6-15.3 mm inhibition zone against *S. aureus, E. coli,* and *K. pneumoniae*. Among the metal complexes, only **T121** exhibited antimicrobial activity: 21.3-36.6 mm for bacteria, 23.6 mm, and 29.6 mm for fungi. The results show that metal complexes generally reduce the antibacterial activity of thiosemicarbazone, while only the **T121** complex appears to increase antibacterial and antifungal activity. In addition, it was observed that irradiation increased the activities of the compounds in some cases and decreased them in some cases [33].

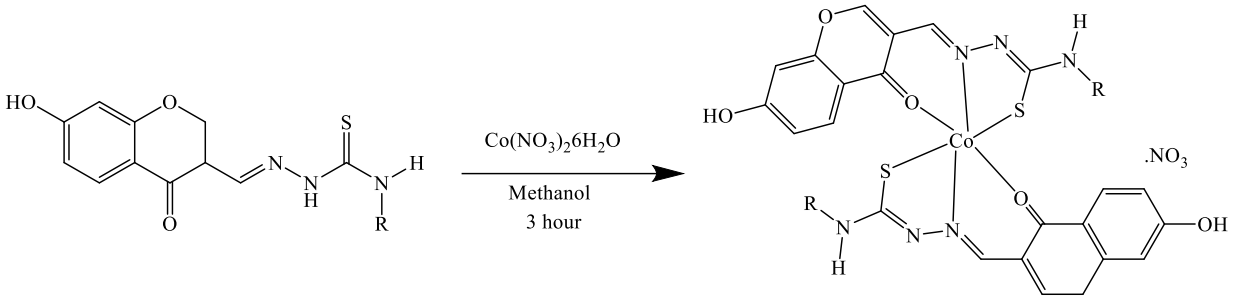


**T117** **T118**

**T119** M: Mn, **T120** R: Zn **T121**

**Figure 18.** The thiosemicarbazones and their complexes synthesized by Alzahrani et al. [33]

Kalaiarasi and co-workers synthesized three thiosemicarbazone derivatives **(T122-125)** and their Co(III) complexes **(T126-129)** (Figure 19). They examined the antimicrobial activities of metal complexes in the concentration range of 25, 50, and 100 μg/mL by microdilution method and agar well diffusion. It was determined that some complexes did not create an inhibition zone against some microorganisms at a concentration of 25 μg/mL and the activity increased with increasing concentration. At the highest concentration of 100 μg/mL, inhibition zones of **T126-129** were 17.46-17.82 mm, 18.19-18.98 mm, 19.12-19.39 mm, and 16.61-18.41 mm, respectively. **T128** exhibited the strongest antibacterial activity, close to the standard drug Gentamicin (20.32-20.39 mm). In the antifungal evaluation against four fungal strains, the complexes created a zone of inhibition of 16.17-19.43 mm against all strains at a concentration of 100 μg/mL (Standard Ketoconazole: 19.48-24.12 mm). Additionally, the MIC values of the complexes were measured as 22.73-40.89 μM against bacteria (Standard Gentamicin: 6.27-10.00 μM) and 20.97-40.05 μM against fungi (Standard Ketoconazole: 7.30-10.03 μM). Similar to the agar well diffusion results, **T128** exhibited the strongest activity [34].

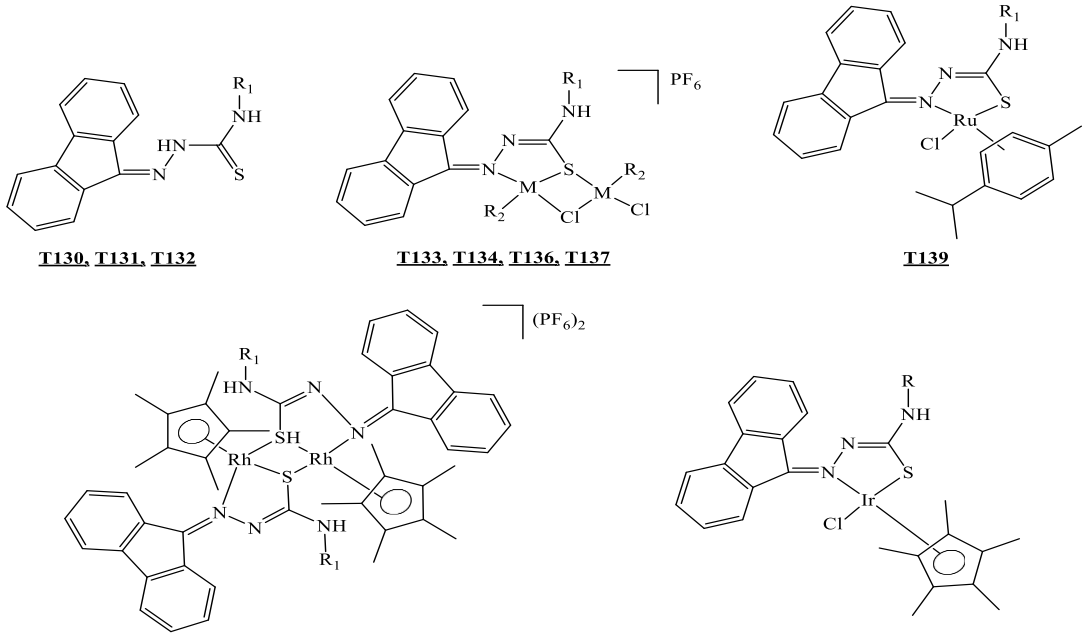



**T122** R: H
**T123** R: $CH_3$
**T124** R: $C_2H_5$
**T125** R: $C_6H_5$

**T126** R: H
**T127** R: $CH_3$
**T128** R: $C_2H_5$
**T129** R: $C_6H_5$

**Figure 19.** The compounds synthesized by Kalaiarasi et al. [34]

Another study reported the synthesis of a series of Rh, Ru, and Ir complexes by reacting halide-bridged metal precursors with three thiosemicarbazone ligands **(T130-132)** (Figure 20). All compounds were examined by the agar well diffusion method against two gram-negative (*E. coli*, *P. aeruginosa*) and two gram-positive (*S. aureus, Bacillus thuringiensis*) bacterial strains at a concentration of 5 mg/mL. The results show that all TSC ligands **(T130-132)** and metal complexes **(T133-141)** are inactive against gram-negative bacterial strains. While the standard drug Gentamicin against *B. thuringiensis* and *S. aureus* bacterial strains creates a zone of 22 and 23 mm, respectively, the zone measurements of active compounds are as follows in the same order: **T130-132**: 0 mm; **T134**: 19 and 17mm; **T135**: 22 and 21mm; **T137**: 21 and 20mm; **T138**: 22 and 21mm; **T139**: 23 and 21mm. Most of the compounds appear to exhibit activity close to that of the standard drug [35].



**T130, T131, T132** | **T133, T134, T136, T137** | **T139**

**T140** | **T135, T138, T141**

| | T130 | T131 | T132 | T133 | T134 | T135 | T136 | T137 | T138 | T139 | T140 | T141 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| R1 | H | $CH_3$ | Ph | H | H | H | $CH_3$ | $CH_3$ | $CH_3$ | Ph | Ph | Ph |
| M | - | - | - | Ru | Rh | Ir | Ru | Rh | Ir | * | * | Ir |
| R2 | - | - | - | | | - | | | - | - | - | - |

* M was given in the figure

**Figure 20.** The compounds synthesized by Nongpiur et al. [35].

Nibila et al derived a TSC ligand **(T142)** and its cobalt **(T143)**, nickel **(T144),** and copper **(T145)** complexes (Figure 21). The antibacterial and antifungal activities of the compounds were measured against the microorganism strains *S. aureus, B. subtilis, P. aeruginosa, E. coli,* and *C. albicans*, *A. niger* at 400 and 800 μg/mL concentrations by the agar diffusion method. According to the results (800 μg/mL), metal complexes showed no activity against *P. aeruginosa*, while the **T142** ligand created a 16 mm zone. Against *E. coli* only the **T144** complex formed 12 mm; against *S. aureus* the **T144** and **T145** complexes formed 12 and 11 mm, respectively; **T142-145** compounds against *B. subtilis* created 20, 11, 20, and 25 mm zones, respectively [36].

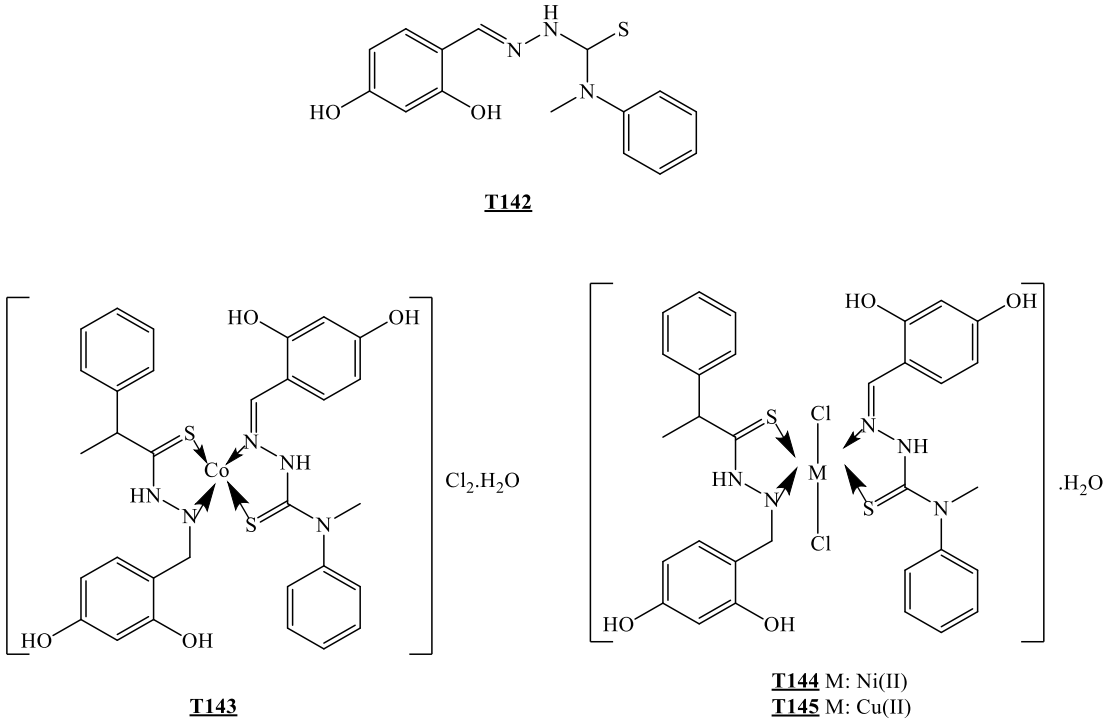
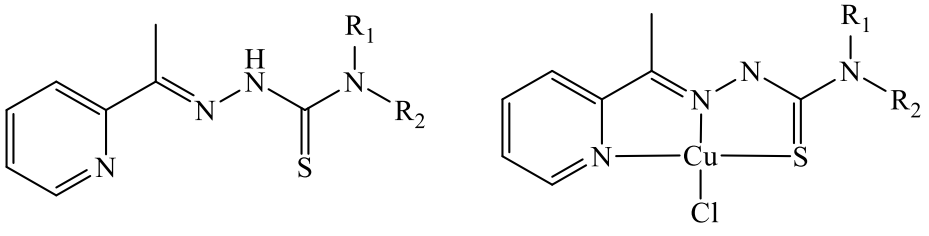



**Figure 21**. The compounds synthesized by Nibila et al. [36]

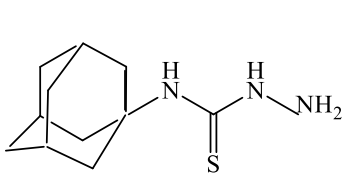
In a study in 2020, Qi and colleagues synthesized a series of thiosemicarbazone derivatives and their copper complexes (Fig 22). The compounds were evaluated against some bacterial strains: *S. aureus, S. epidermidis, E. coli,* and *P. aeruginosa*. While all ligands were inactive against *S. aureus*, **T147** and **T148** created an inhibition zone of 12.22, and 13.74 mm against *E. coli*, respectively. The complexes exhibited activity against both bacterial strains (14-25.78 mm). The MIC values of the compounds were supported by the zone measurements: 128, 256, and >256 μM for **T146-148** ligands; 16-128 μM for complexes. The strongest active ligand was determined as **T148** and the strongest complex was determined as T148-Cu(II) complex **T151** [37].



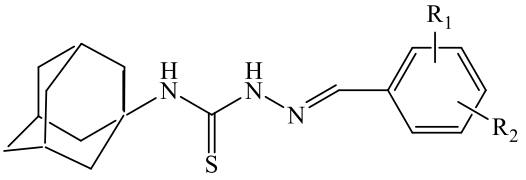

| | $R_1$ | $R_2$ |
|---|---|---|
| T146, T149 | H | H |
| T147, T150 | H | Me |
| T148, T151 | Me | Me |

**Figure 22.** Thiosemicarbazone derivative and its copper complexes synthesized by Qi et al. [37]

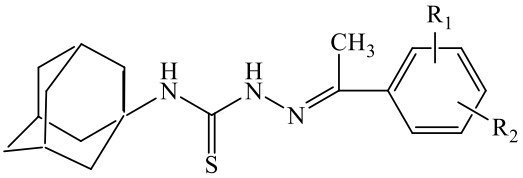
Pham et al. synthesized thiosemicarbazone derivatives containing adamantane skeletons as a result of the reaction of 4-(1-adamantyl)-3-thiosemicarbazide with acetophenone or benzaldehyde (Figure 23) and examined the antimicrobial activities of the compounds by the microdilution method. All compounds showed no antibacterial activity against *E. coli* and *Salmonella enterica*. Among gram-negative bacteria, only **T156** and **T160** gave a MIC value of 100 μM against *P. aeruginosa*. In gram-positives (*E. feacalis, S. aureus, B. subtilis*), all compounds except **T156** exhibited stronger activity than the standard Streptomycin (175-350 μM), with MIC values of 25-100 μM. All of the compounds exhibited highly potent activity against the fungal strain *C. albicans* at 6.25-25 μM compared to Standard Cycloheximide (114 μM) [38].



**T152**



**T153-T163**



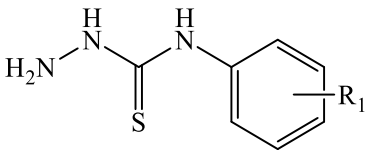
**T164-T173**

| | T153 | T154 | T155 | T156 | T157 | T158 | T159 | T160 | T161 | T162 | T163 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **R1** | H | H | H | H | H | H | H | 2-OH | 3- $NO_2$ | 3-$NO_2$ | 2-$CH_3$ |
| **R2** | H | 3-$NO_2$ | 4-$OCH_3$ | 2-OH | 4-$NO_2$ | 4-$OC_2H_5$ | 4-Cl | 5-$CH_3$ | 4-$OC_2H_5$ | 4-Cl | 5-$CH_3$ |

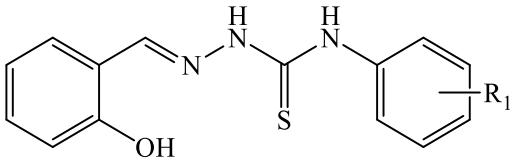
| | T164 | T165 | T166 | T167 | T168 | T169 | T170 | T171 | T172 | T173 |
|---|---|---|---|---|---|---|---|---|---|---|
| **R1** | H | H | H | H | H | 3- $NO_2$ | H | H | 3-$NO_2$ | 3-$NO_2$ |
| **R2** | H | 3-$NO_2$ | 4-Br | 4-OH | 4-$NO_2$ | 4-Br | 4-Cl | 4-$CH_3$ | 4-$OCH_3$ | 4-Cl |

**Figure 23**. The compounds synthesized by Pham et al. [38]

Ameryckx et al. synthesized many compounds that are thought to exhibit antimicrobial activity by inhibiting the D-Alanyl-D-alanine ligase (Ddl) enzyme involved in peptidoglycan biosynthesis (Figure 24): phenylthiosemicarbazones, 1,2,4-thiotriazole-3-thions, diacylthiosemicarbazides, 1,3,4-thiadiazoles, and thiourea derivatives. Among all compounds whose antibacterial activities were examined against *Enterococcus faecalis* and *S. aureus* by microdilution, the 3.4-diCl substituted thiosemicarbazone compound **(T77)** exhibited the strongest activity against both bacterial strains with a MIC value of 4.20 μg/mL (Standard D-cycloserine: 32, 128 μg/mL). Ten compounds showing activity were reevaluated against three different *E. feacalis* bacterial strains, including vancomycin-resistant enterococcus (VRE), and five different *S. aureus* bacterial strains, including vancomycin-resistant (VRSA) strains and methicillin-resistant (MRSA). **T177** thiosemicarbazone compound attracted attention as the most potent compound with MIC values of 1.06-2.10 μg/mL against VRE strains and 4.25-8.50 μg/mL against MRSA and VRSA strains [39].



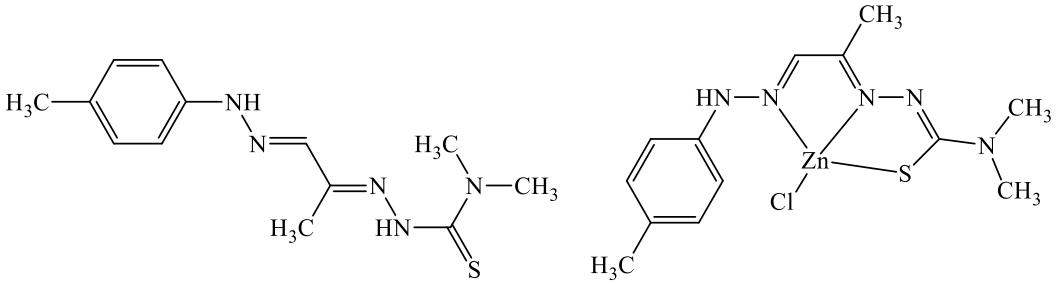
**T174** R: H, **T175** R: 3,4-diCl



**T176** R: H, **T177** R: 3,4-diCl

**Figure 24.** The phenylthiosemicarbazones synthesized by Ameryckx et al. [39]

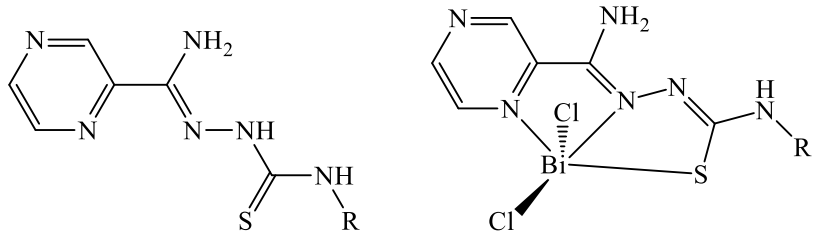
**T178** thiosemicarbazone ligand and its zinc **(T179)** and cadmium **(T180)** complexes were synthesized by Aljahdali et al. (Figure 25). They evaluated antimicrobial activity by disk diffusion method against two gram-positive bacteria (*S. aureus* and *B. subtilis*), two gram-negative bacteria (*E. coli* and *Neisseria gonorrhoeae*), and two fungal strains (*A. flavus* and *C. albicans*). While the compounds form no zones against the *A. flavus* fungal strain, **T178-180** against *C. albicans* formed zones of 15, 18, 22 mm, respectively (Standard Amphotericin B: 21 mm); 16, 18, 20 mm against *S. aureus*; 10, 14, 18 mm against *B. subtilis*; against *N. gonorrhoeae* 9, 13, 17, mm; against *E. coli* 13, 15, 19 mm (Standard Amphicillin: 21-28 mm against all bacteria). The results show that both complex compounds show stronger activity than the TSC ligand, however, the strongest activity is exhibited by the Cd(II) **T180** complex against all microorganisms. [40].




**T178** **T179**

**Figure 25.** The compounds synthesized by Aljahdali et al. [40]

Almeida et al synthesized five thiosemicarbazones **(T180-184)** and their Bi(III) complexes **(T185-189)** (Figure 26). The antituberculosis activity of the obtained compounds was examined against *M. tuberculosis* H37Rv ATCC 27294 strains. Microdilution results showed that free **T180-184** TSC ligands did not have antituberculosis activity. Moreover, it is seen that only **T188** and **T189** of the complexes exhibit weak activity with MIC values of 181.4 μmol/L and 438.4 μmol/L, respectively (Standart Isoniazid: 2.27 μmol/L) [41].

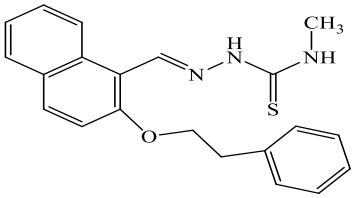



**T180-T184** **T185-189**

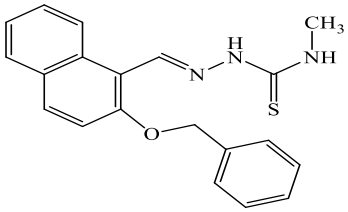
| | T180 | T181 | T182 | T183 | T184 |
|---|---|---|---|---|---|
| | **T185** | **T186** | **T187** | **T188** | **T189** |
| **R** | H | $CH_3$ | $CH_2CH_3$ | $C_6H_{11}$ | $C_6H_5$ |

**Figure 26.** The compounds synthesized by Almeida et al. [41]

In 2019, Devi et al. They synthesized a total of twenty compounds with **T190-193** TSC ligands and their cobalt, nickel, copper, and zinc complexes **(T194-209)** via thiosemicarbazide derivative and salicylaldehyde condensation (Figure 27). The compounds were tested as antifungal and antibacterial with many bacterial and fungal strains: Gram-positives *S. aureus, Streptococcus gordonii*; Gram-negatives *E. coli, P. aeruginosa*; two fungus strains *C. albicans* and *A. niger* TSC ligands gave MIC values of 0.0170-0.0506 μM/mL against gram-positive bacteria, 0.0340-0.0506 μM/mL against gram-negative bacteria, and 0.0170-0.0506 μM/mL against fungi (Standard Ciprofloxacin: 0.0047 μM/mL for bacteria; Standard Flucanazole: 0.0051-0.0102 μM/mL for fungus). **T207-209** complexes showed activity close to the standard drug against *A. niger* with MIC values of 0.0134, 0.107, and 0.0107 μM/mL, respectively. Except for **T209** against *C. albicans*, all metal complexes exhibited more potent activity than TSC ligands. The authors gave the antifungal powers of the complexes in the following order from lowest to highest: nickel, cobalt, copper, and zinc [42].



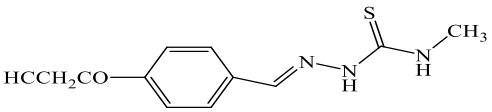
**T190**



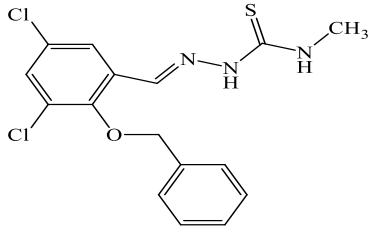
**T191**

**T194:** Co(T189).$(CH_3COO)_2 2H_2O$
**T195:** Ni(T189).$(CH_3COO)_2 2H_2O$
**T196:** Cu(T189).$(CH_3COO)_2 2H_2O$
**T197:** Zn(T189).$(CH_3COO)_2 2H_2O$

**T198:** Co(T190).$(CH_3COO)_2 2H_2O$
**T199:** Ni(T190).$(CH_3COO)_2 2H_2O$
**T200:** Cu(T190).$(CH_3COO)_2 2H_2O$
**T201:** Zn(T190).$(CH_3COO)_2 2H_2O$



**T192**



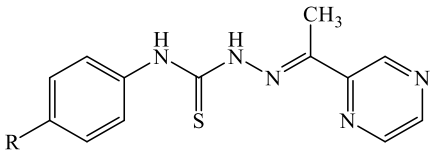
**T193**

**T202:** Co(T191).$(CH_3COO)_2 2H_2O$
**T203:** Ni(T191).$(CH_3COO)_2 2H_2O$
**T204:** Cu(T191).$(CH_3COO)_2 2H_2O$
**T205:** Zn(T191).$(CH_3COO)_2 2H_2O$

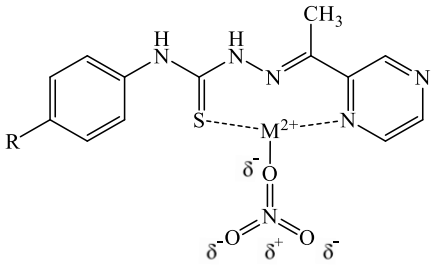
**T206:** Co(T192).$(CH_3COO)_2 2H_2O$
**T207:** Ni(T192).$(CH_3COO)_2 2H_2O$
**T208:** Cu(T192).$(CH_3COO)_2 2H_2O$
**T209:** Zn(T192).$(CH_3COO)_2 2H_2O$

**Figure 27.** The compounds synthesized by Devi et al. [42]

Pole-Ceron synthesized tridentate thiosemicarbazone derivatives **(T210-211)** and its copper **(T212-213)** and nickel **(T214-215)** complexes (Figure 28). The compounds were evaluated against gram-positive (*S. aureus, Listeria monocytogenes*, and *B. cereus*) and gram-negative (*E. coli*, *S. typhimurium*, and *K. pneumoniae*) bacterial strains. The activities of **T210-211** ligands against gram-positive bacterial strains were measured in the range of 500-2000 μg/mL, while their Cu(II) and Ni(II) complexes gave MIC values of 3.9-31.3 μg/mL and 63-125 μg/mL, respectively. It was observed that the **T211** ligand was inactive against *E. coli* and *K. pneumoniae*. Apart from this, the ligands showed very low activity with MIC values of 500-2000 μg/mL. Zn (II) metal complex affects the antibacterial potential against gram-negative bacteria by 0.5 - 2 times. In addition, the **T213** complex appears to increase activity against gram-negative bacteria by at least 4-fold [43].



**T210** R: H, **T211** R: Cl



**T212** R: H M: $Cu^{2+}$, **T213** R: Cl M: $Cu^{2+}$
**T214** R: H M: $Ni^{2+}$, **T215** R: Cl M: $Ni^{2+}$

**Figure 28.** Thiosemicarbazone complexes synthesized by Pole-Ceron [43]

In another study, three 5-methoxyisatin thiosemicarbazones and their copper complexes were synthesized (Figure 29). These compounds were measured as antibacterial and antifungal against many microorganisms by microdilution method. Metal complexes showed higher activity than ligands in all *S. epidermis, E. coli, and P. vulgaris* bacterial strains. While it was measured that the **T219** and **T221** complexes increased the activity against *B. subtilis*, the enhancing or decreasing effect of the **T220** complex could not be determined within the

tested range. While no change in activity could be detected in *P. aeruginosa* at **T219**, it was found to decrease the activity at **T220** compared to its ligand. On the other hand, it was determined that while **T219** and **T220** complexes decreased the activity against *S. aureus*, **T221** significantly increased the activity with a MIC value of 8.56 μg/mL (Standard Ciprofloxacin: 6.25 μg/mL). Antifungal evaluation shows that metal complexes generally increase activity in the remaining fungal strains (*A. flavus, A. niger, Fusarium solani*), while **T220** and **T219** complexes reduce activity in *C. albicans* and *Cochliobolus lunata*, respectively. While the highest antifungal activity was exhibited by the **T221** complex against *A. flavus* with a MIC value of 8.14 μg/mL (Standard Nystatin: 2.81 μg/mL), the strongest antibacterial activity was exhibited by the same compound against *S. epidermis* with a MIC of 6.50 μg/mL (Standard Ciprofloxacin: 3.12 μg/mL) [44].

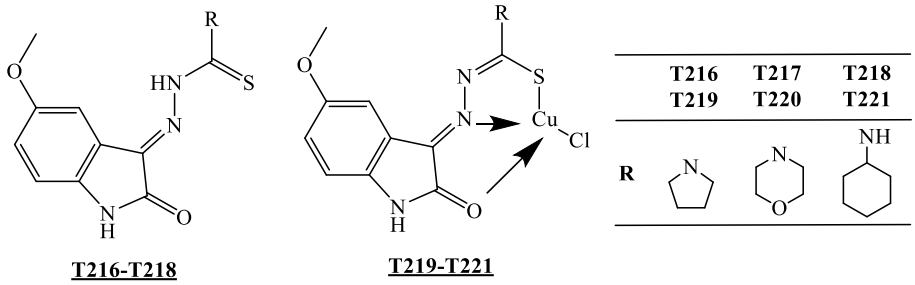



**Figure 29.** The compounds synthesized by Aneesrahman et al. [44]

Figure 30 shows the **T222** thiosemicarbazone derivative and the thiazole derivatives **(T223-238)** synthesized from T222. Antimicrobial activities of **T222, T224-227 T228, T230,** and **T235-237** were determined by agar well diffusion method against gram-positive (*S. aureus* and *B. subtilis*), gram-negative bacteria (*S. typhimurium* and *E. coli)* and two fungi (*A. flavus* and *C. albicans*). While all compounds were ineffective against the *A. flavus*, only **T225, T227** and **T230** created an inhibition zone of 9, 14, and 14 mm, respectively, against the *C. albicans* (Standard Ketoconazole: 20 mm). Against *S. aureus*, only **T222, T225, T227, T228, and T230** created zones of 5, 9, 14, 14, and 14 mm, respectively (Standard Gentamycin: 24 mm). While **T226 T236-237** compounds were ineffective against *B. subtilis*, other compounds created a 10-16 mm zone (Standard Gentamycin: 26 mm). For *S. typhimurium*, compounds **T222, T224,** and **T227-229** created a zone of 13, 12, 13, 16, and 15 mm, respectively (Standard Gentamycin: 17 mm). It was observed that only **T226** was inactive against *E. coli* and other compounds formed a zone between 10-15 mm (Standard Gentamycin: 30 mm). The highest antimicrobial activities are seen as follows: compounds **T227** and **T230** for *A. flavus*; **T227, T228, T230** for *S. aureus*; **T222** and **T230** for *B. subtilis*; **T230** for *S. typhimurium* and *E. coli* [45].

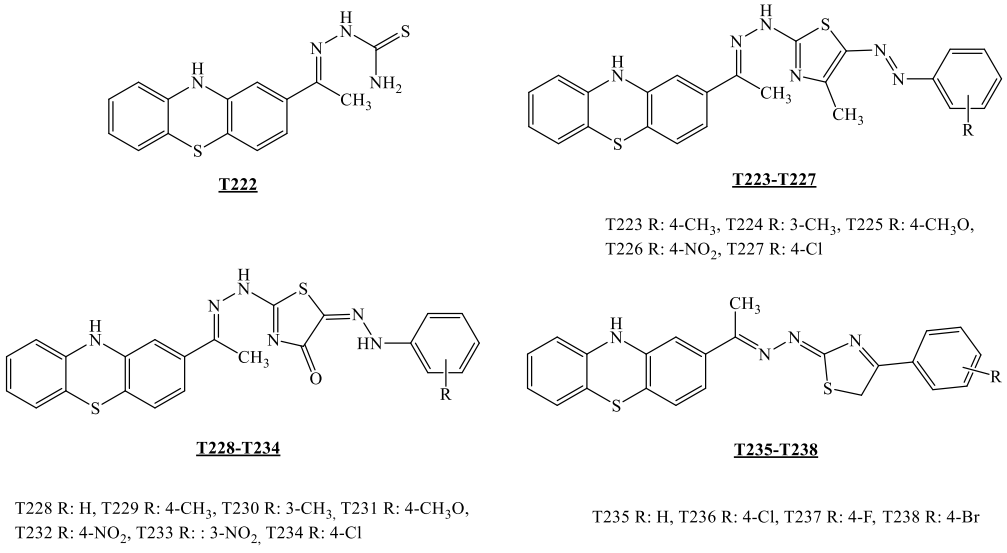



**Figure 30.** The compounds synthesized by Alsharekh et al. [45]

In the last article we researched in this review, we will share the antimicrobial activities of thiosemicarbazone derivatives **(T239-241)** and their palladium(II) complexes synthesized by Munikumari et al in 2019 (Figure 31). Microdilution results against *B. subtilis, S. aureus, E. coli*, and *K. pneumoniae* bacterial strains show that only the **T241** TSC ligand gives a MIC value of 50 μg/mL against *B. subtilis*, and **T239** gives a MIC value of 25 μg/mL against *K. pneumoniae*. While the **T242** complex was ineffective against other microorganisms, it increased the antibacterial activity against *K. pneumoniae* (6.17 μg/mL) approximately fourfold compared to its TSC ligand. Complex **T243** significantly increased the activity of the **T240** ligand, exhibiting 5.67-50 μg/mL activity against all bacteria. While **T244** created a MIC value of 25 μg/mL for *S. aureus* and *K. penumonaie*, it did not show activity against other bacteria. The results show that Palladium(II) complexes are not showing a reducing effect of antibacterial activity, moreover significantly increase the activity against some bacteria: **T243** was found to be 17 times more active than the **T240** ligand against *B. subtilis* [46]

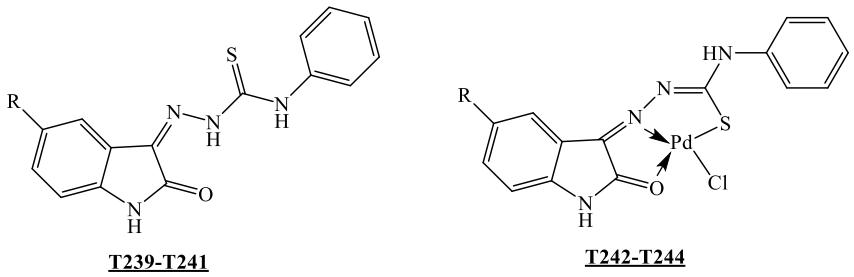



**Figure 31.** The compounds synthesized by Munikumari et al.

## 3. Conclusion

In the review of 244 compounds included in the articles scanned in WOS from 2019 to the present, it is seen that TSC ligands, TSC-based compounds, and TSC-metal complexes exhibit antibacterial and antifungal activity. In particular, both TSC-metal complexes, such as **T39**, and free TSC ligands, such as **T77**, exhibited stronger antimicrobial activity than the positive control groups. As included in this review, there are many studies investigating the effect of metal complexes of TSCs on the activity. In some articles, we see that metal complexes increase the activity of TSC ligands, while in others they decrease the activity. Additionally, some results show that a TSC-metal complex increases activity against some microorganisms, while the same complex reduces antimicrobial activity against another microorganism. We believe that thiosemicarbazones will make exciting contributions to the discovery of new antimicrobial agents with their flexible and easy synthesis opportunities.

## Author Contributions

All the authors equally contributed to this work. This paper is derived from the first author's doctoral dissertation supervised by the second and third author. They all read and approved the final version of the paper.

## Conflict of Interest

All the authors declare no conflict of interest.

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