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Thiosemicarbazone Ligands and TheirTransition Metal Complexes as Antioxidants: A Review

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ABSTRACT

Antioxidant molecules prevent the harmful reaction of oxidants inside the body by providing a single electron or a hydrogen atom, based on their mechanism. Different forms of oxidants, such as reactive oxygen species (ROS) or reactive nitrogen species (RNS), could harm the proteins, lipids, and DNA. Due to the chain reactions of oxidants in the medium that exist, unwanted consequences could happen inside the body. The antioxidants, by reacting with oxidants, prevent the damage caused by the chain reaction of oxidants. Synthetic antioxidants such as thiosemicarbazones, either in the form of ligand or their metal complexes, could exhibit potent antioxidant capacity/activity comparable to or sometimes more potent than the natural antioxidant. This study fills the gap of evaluating the relationship between the structure of thiosemicarbazones and their transition metal complexes with their corresponding antioxidant capacity/activity by CUPRAC (CUPric Reducing Antioxidant Capacity), DPPH (2,2-di(4-tert-octyl phenyl) 1-picrylhydrazyl and ABTS (2,2′-azino-bis (3-ethylbenzthiazoline-6-acid) assays. The comprehensive study of the relevant research papers in the field, and by using the narrative method, the results of the study have been reflected in the anatomy of this review paper. The findings of the study have clearly stated that in most cases, the introduction of transition metal complexes in the structure of thiosemicarbazone ligands enhances the antioxidant capacity/activity of such compounds. The potent antioxidant capacity/activity of thiosemicarbazones has led to them being considered a promising chemical drug and emphasizes further research in elucidating their antioxidant capacity/activity.

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INTRODUCTION

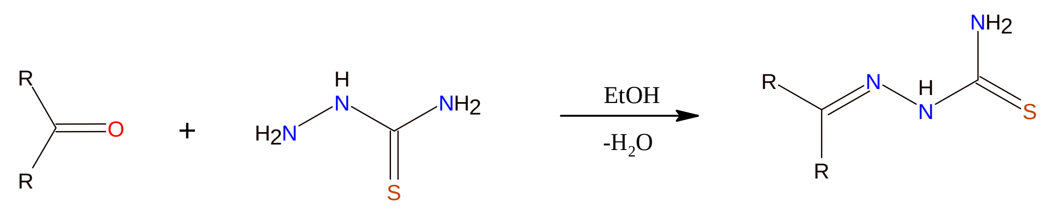
Antioxidants are an important group of com pound owing to their protective behavior in food because of their role against oxidative deterioration and their role against oxidative stress in the body (Gulcin, 2020). Reactive oxygen species (ROS) and Reactive nitrogen species (RNS) are common examples that cause oxidative damage to proteins, lipids, and DNA (Sharma et al., 2012). ROS and RNS are an important class of oxidants that are formed inside the body. The free radicals that belong to ROS are such as superoxide radicals ($O_2^{-\cdot}$), hydroxyl radicals ($^{\cdot}OH$), and non-radical oxidants such as hydrogen peroxide (H_2O_2) and hypochlorous acid

(HOCl) (Ali et al., 2020). Variouse types of antioxidant such as natural antioxidants and synthetic antioxidants, play an important role in reducing the damage caused by oxidants.

Thiosemicarbazones are an important class of compounds that are obtained by the condensation of thiosemicarbazide with an aldehyde or ketone group Figure 1, Pitucha et al., 2023). Thiosemicarbazones and their metal complexes exhibit antioxidant activity; often, their antioxidant activity exceeds the activity of natural antioxidants and some medicines used as antioxidants (Graur et al., 2023). Thiosemicarbazones exhibit various biological activities apart from antioxidant activity, such as antitubercular (Ain et al., 2023), antibacterial (Khalaji et al., 2016), antiviral (Basyouni et al., 2021), antimalarial (Savir et al., 2021), antiproliferative (Findik et al., 2023), and antitumor (Fuior et al., 2022) activities, and hence they are comprehensively studied because of their potential biological activities (Ortaboy et al., 2024).

To determine the antioxidant capacity/activity of thiosemicarbazones, different methods that are based on single electron transfer (SET), such as the CUPRAC method (Cárdenas et al., 2014) and hydrogen atom transfer (HAT), such as DPPH (Ghafoor et al., 2024) and ABTS methods, are considered (Pohanka, 2023). The latter two methods (DPPH and ABTS) are considered to be at the center of the SET and HAT methods.

As it is known from literature, the synthesis and antioxidant capacity/activity of thiosemicarbazones have been reported in the form of research papers, but a comprehensive study of the antioxidant capacity/activity of thiosemicarbazones and their transition metal complexes based on the relationship between the structure and their antioxidant capacity/activity is rarely reported. This study aims to find the role of transition metal complexes in the enhancement of antioxidant capacity/activity of such compounds and to evaluate the relationship between the structure of thiosemicarbazones and their antioxidant capacity/activity. On the other hand, in this study, the clear and simple answers are in the focus for research questions such as relationship between the structure and antioxidant capacity/activity of thiosemicarbazones, the role of enhancement of antioxidant capacity/activity of such compounds by introducing the transition metals in the structure of compounds and evaluation of antioxidant capacity/activity of thiosemicarbazones by CUPRAC (CUPric Reducing Antioxidant Capacity), DPPH (2,2-di(4-tert-octyl phenyl) 1-picrylhydrazyl and ABTS (2,2′-azino-bis (3-ethylbenzthiazoline-6-acid) assays.



(Aldehyde or Ketone group) (Thiosemicarbazide) (Thiosemicarbazone)

Figure 1. *Synthetic route of thiosemicarbazones*

In this review, among the various methods of determining the antioxidant capacity/activity of thiosemicarbazones, the CUPRAC, DPPH, and ABTS methods are selected due to their vast usage in determining the antioxidant capacity/activity of thiosemicarbazones in the literature. In this study, the antioxidant capacity/activity of thiosemicarbazones is well-analyzed, and the reported data are plotted as graphs.

METHODS AND MATERIALS

A comprehensive literature search has been conducted through well-known scientific papers databases such as Science Direct, Google Scholar, Web of Science, and Scopus to find the most relevant peer-reviewed papers as per the demands of the study. This study has been designed as a narrative review, and in some parts, the results of the study have been critically considered. In this review, no time limit has been applied to find the related research papers in the area of determining the antioxidant activity/capacity of thiosemicarbazones and their corresponding transition metal complexes via CUPRAC, DPPH, and ABTS assays. In this review, more than a hundred research and review papers have been collected and comprehensively studied, and among them, fifty research papers have been cited. The selected research papers have been studied based on the scope of antioxidant capacity/activity determination through the aforementioned assays, and those research papers that include other assays for the determination of antioxidant capacity/activity have been excluded from the research threshold. The outcomes of this study have resulted from qualitative and quantitative analyses of the studied research papers. The qualitative analysis has been concluded as a narrative part, and the quantitative analysis has been depicted as graphs. At the threshold of searching research papers for this study, the keywords such as thiosemicarbazone ligands, metal complexes, antioxidant capacity/activity, CUPRAC assay, DPPH assay, and ABTS assay have been deeply explored.

RESULTS AND DİSCUSSİON

CUPRAC Method

The CUPRAC method is based on the reduction of cupric neocuproine complex (Cu(II)-Nc) by antioxidants to the yellow-orange colored cuprous chelate (Cu(I)-Nc) as described by Apak et al (Apak et al., 2004). To determine the antioxidant capacity of thiosemicarbazones, the reaction mixture of CUPRAC antioxidant capacity consists of $CuCl_2.2H_2O$, neocuproine (Nc), NH_4Ac buffer solution (at pH 7), x mL of the synthesized compound and H_2O, respectively (Özyürek et al., 2011). The prepared mixture is incubated at room temperature for 30 min, and after that, the absorbance is recorded at 450 nm against the reagent blank. The calibration curves (absorbance vs. concentration graphs) of assayed compounds are plotted, and their Trolox equivalent antioxidant capacities (TEAC coefficients) are calculated.

DPPH Method

The DPPH free radical scavenging activity of thiosemicarbazones are studied based on Brand-Williams et al methods (Brand-Williams et al., 1995). The assayed solutions are prepared in the order of 2 mL of DPPH, x mL of sample at different concentrations, and x mL of methanol in the test tube (Milardović et al., 2005). The mixture with a total volume of 4 mL is stirred vigorously and incubated in the dark for about 30 min. The decrease in the absorbance of the assayed solutions is measured spectrophotometrically at 515 nm against methanol (Martysiak-Żurowska & Wenta., 2012). The equation FRS (%) = $[(A_0 – A_s)/A_0] \times 100$, where A_0 is the absorbance of control DPPH and as is the absorbance of the assayed thiosemicarbazones, is used to calculate the percentage of the free radical scavenging activity of thiosemicarbazones (Mareček et al., 2016).

ABTS Method

This ABTS method is based mostly on the single-electron transfer (SET) mechanism. The stock solution of ABTS is prepared by dissolving ABTS in sodium persulphate solution based on the working conditions (Erel, 2004). After preparing the stock solution, it is stored in the dark for a few hours. The working solution is obtained by diluting the stock solution with methanol, and the absorbance is taken at 734 nm spectrophotometrically. The assayed samples are mixed with ABTS, and the absorbance is measured at 734 nm against the reference (methanol). The antioxidant capacity of samples is expressed as Trolox Equivalent based on the calibration curve (Floch et al., 2007).

Eğlence-Bakır et al. have reported the synthesis of eight new dioxomolybdenum(VI) complexes from 4-benzyloxysalicylidene N- or S-alkyl substituted thiosemicarbazones, in which the alkyl group is methyl, ethyl, propyl, or butyl (Figure 2). The synthesized compounds have been fully characterized by using analytical and spectroscopic techniques. The synthesized ligands (L^1-L^8) and metal complexes (1-8) were assayed for their total antioxidant capacities using the cupric reducing antioxidant capacity (CUPRAC) method. The thiosemicarbazone ligands (L^5-L^8) with the ONN donor sets have been shown to have higher Trolox equivalent antioxidant capacity (TEAC) compared to the ONN donor sets thiosemicarbazone Ligands (L^1-L^4). Among the complexes, complex 3 has shown higher antioxidant capacity ($TEAC_{CUPRAC}$=1.51) compared to others. Additionally, it has been found that the TEAC values for complexes 2, 3, and 8 are higher than those of ascorbic acid. Overall, the antioxidant activities of ligands and complexes are in the order: $L^4 = L^1 > L^2 > 1 > L^3 > 4 > 2 > 3$ for the ONS donor sets and $L^5 > L^6 = L^8 > L^7 > 5 > 6 = 7 > 8$ for the ONN donor sets (Figure 3). As mentioned by the author, the increased S/N-alkyl chain affected the given higher TEAC values of compounds (Eğlence-Bakır et al., 2021).

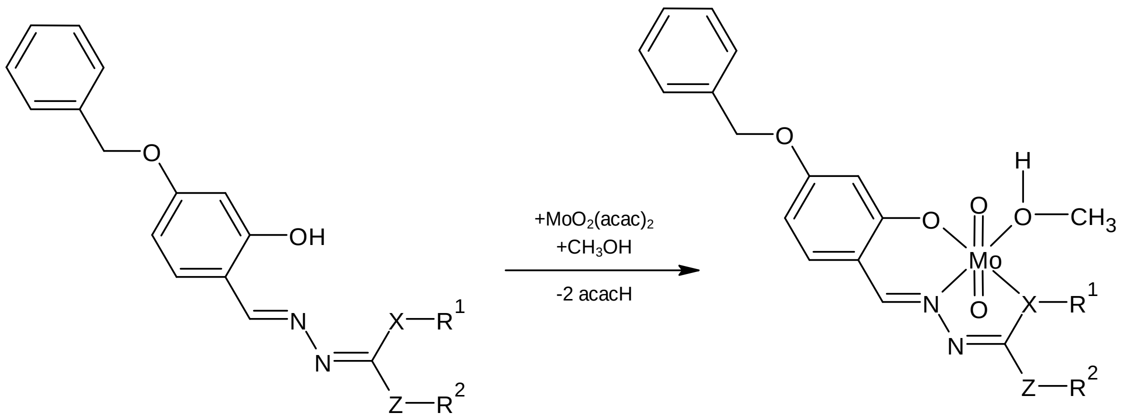


Figure 2. *The chemical synthesis of the complex*

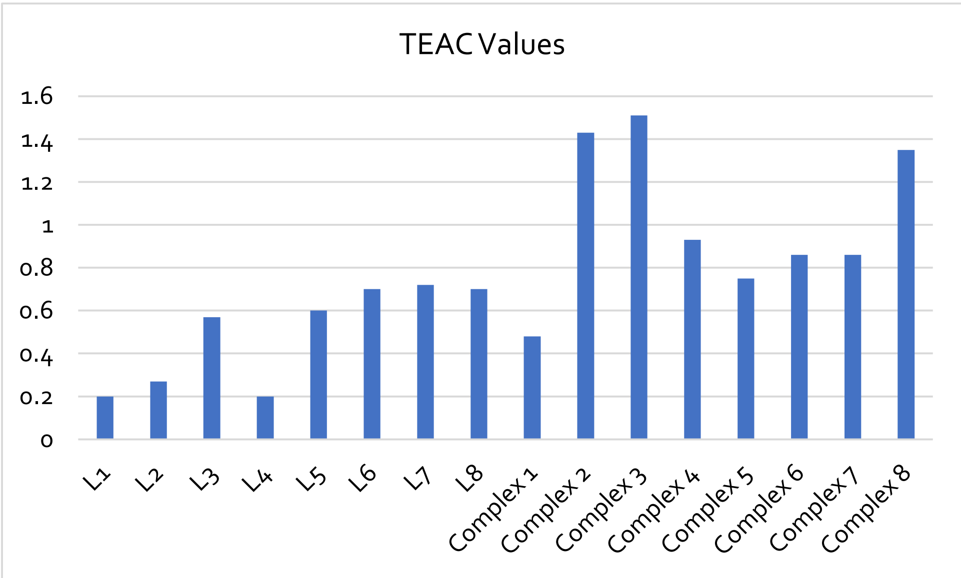


Figure 3. *The obtained TEAC values of assayed compounds*

Some copper(II) and nickel(II) mixed ligand complexes have been synthesized from 4-methoxysalicylaldehyde-*N*-phenyl-thiosemicarbazone and 3,5-lutidine by Avcu Altiparmak et al (Figure 4). The synthesized compounds have been characterized by elemental analysis, IR, UV, ^{1}H NMR, and ESI-MS spectra. The antioxidant capacity and the free radical scavenging activities of ligands and their corresponding metal complexes have been investigated by CUPRAC and DPPH assays, respectively. Based on the obtained results from the TEAC values of compounds, the metal complexes have shown higher antioxidant capacity compared to the ligand (Figure 5). Moreover, the FRS% of compounds has been assayed in different concentration rates from 5 µM to 25 µM. In these concentration rates, all the assayed compounds have exhibited scavenging activity, in which the ligand has shown higher FRS% at 25 µM compared to the complexes (Figure 6). This reduction in RFS% of complexes over the ligand could be interpreted as a complexation process of metal complexes (Altiparmak et al., 2021).

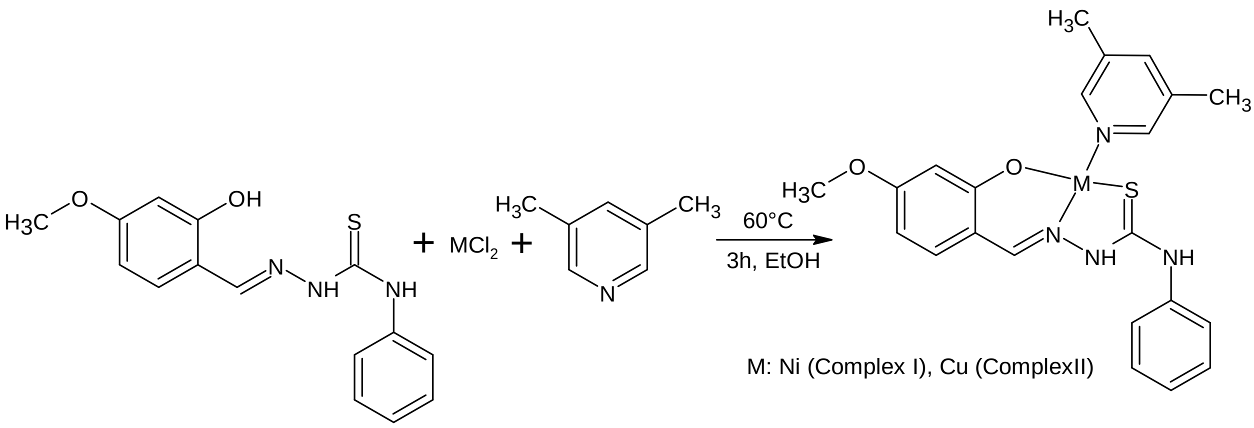


Figure 4. The chemical formation of complexes.

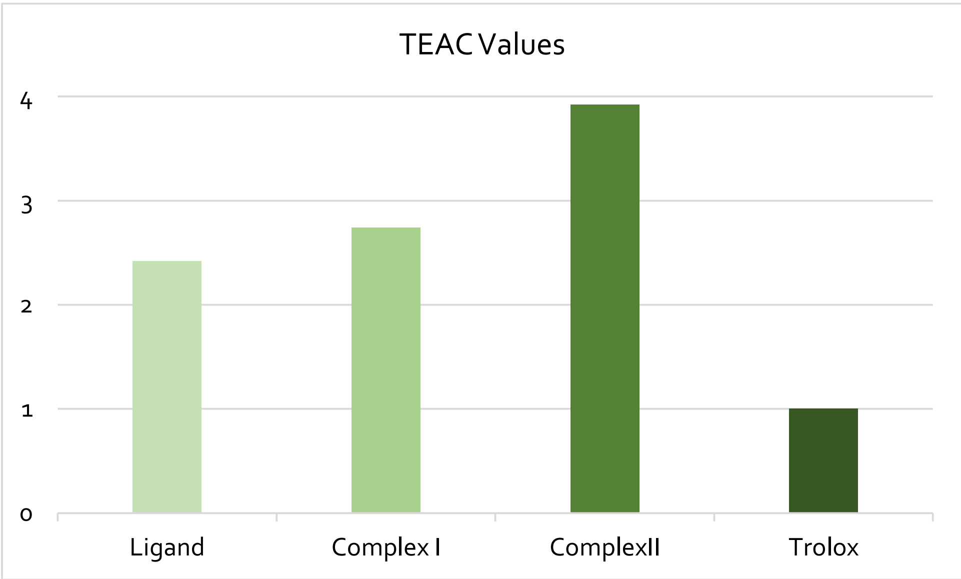


Figure 5. *The obtained TEAC values of assayed compounds*

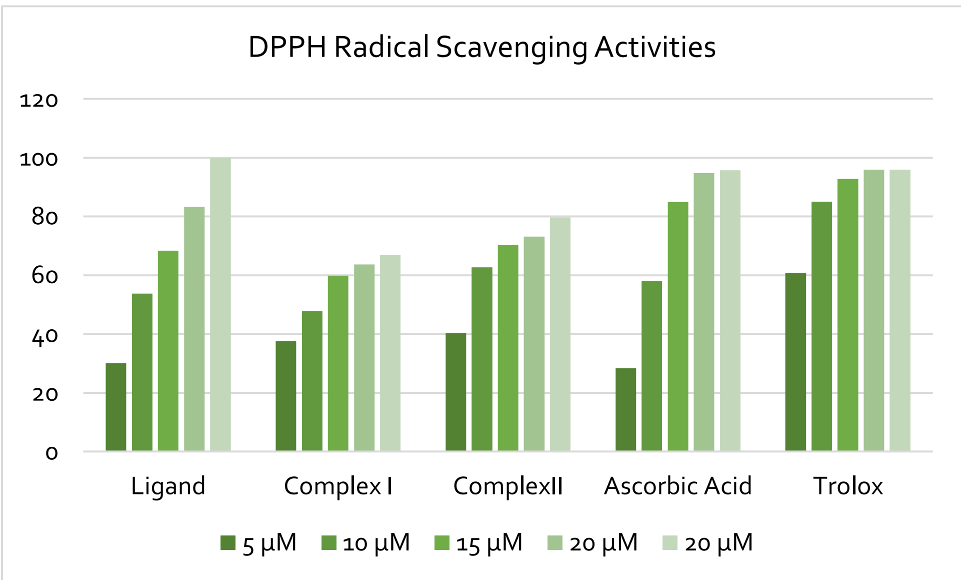


Figure 6. *The FRS% activities of assayed compounds*

In a study by Berat Ilhan-Ceylan, the synthesis of N_2O_2-type chelate complexes of oxovanadium(IV) (2) and nickel(II) from 2,2′ -Dihydroxybenzophenone-S-methyl-thiosemicarbazone ligand (1) has been reported (Figure 7). The obtained compounds have been characterized by using various analytical and spectroscopic techniques. The antioxidant capacity of compounds 1-3 has been investigated by using the CUPRAC method, in which the oxovanadium(IV) complex (2) has shown higher antioxidant capacity compared to others. As a result of the antioxidant capacity, the TEAC values of compounds 1-3 are 1.5, 2.0, and 0.6, respectively (Figure 8) (İlhan-Ceylan, 2020).

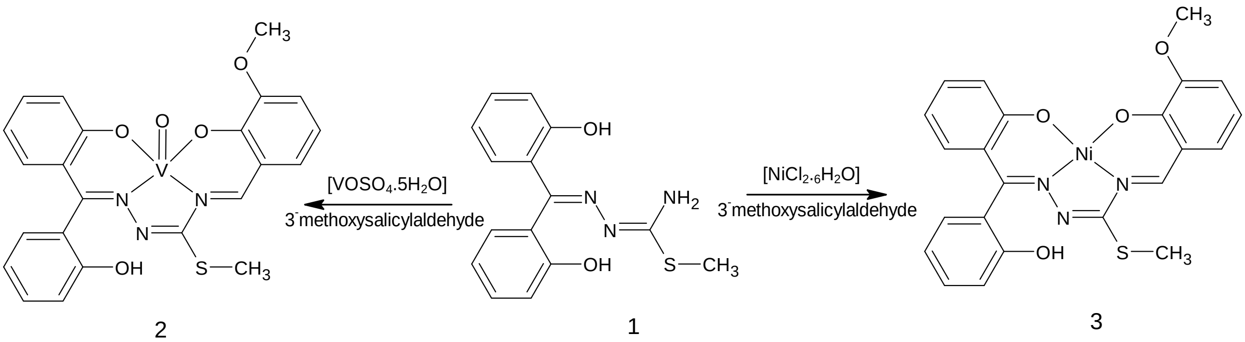


Figure 7. *The chemical synthesis of complexes*

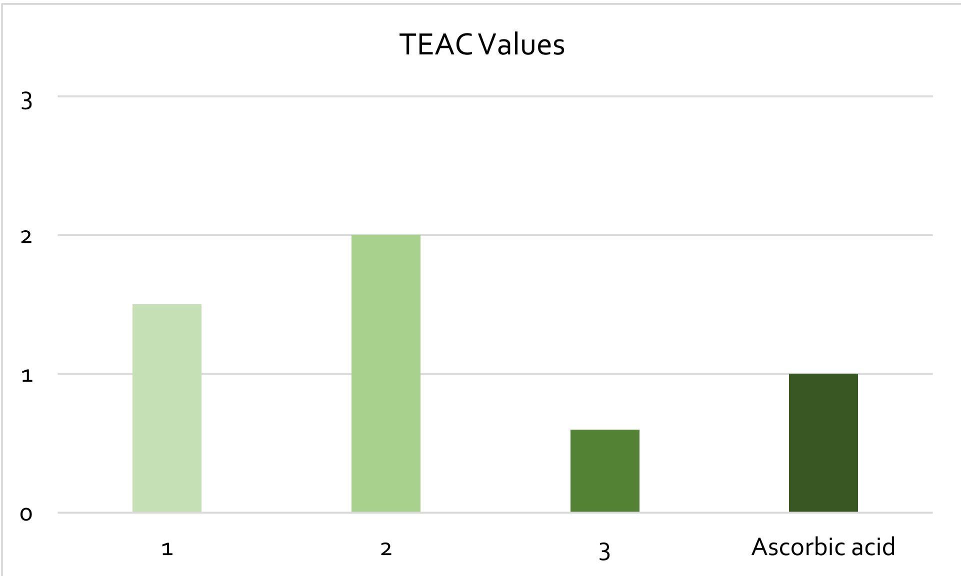


Figure 8. *The obtained TEAC values of assayed compounds*

In another study, the synthesis of Co(II), Ni(II), and Cu(II) complexes from 2,4-dihydroxy benzaldehyde n(4)-methyl(phenyl)thiosemicarbazone (L) has been reported by Nibila et al (Figure 9). The corresponding structures of the complexes (CoL, NiL, and CuL) have been elucidated by FT-IR, ^{1}H NMR, UV-Vis, EPR spectral analyses, and magnetic moment measurements. All the synthesized compounds have been tested for their free radical scavenging activity by using the DPPH assay. The results of the test by DPPH assay have shown the higher antioxidant activity of the CoL complex compared to the ascorbic acid, and the order of the activities of complexes was found to be CoL>NiL>CuL (Figure 10) (Nibila et al., 2021).

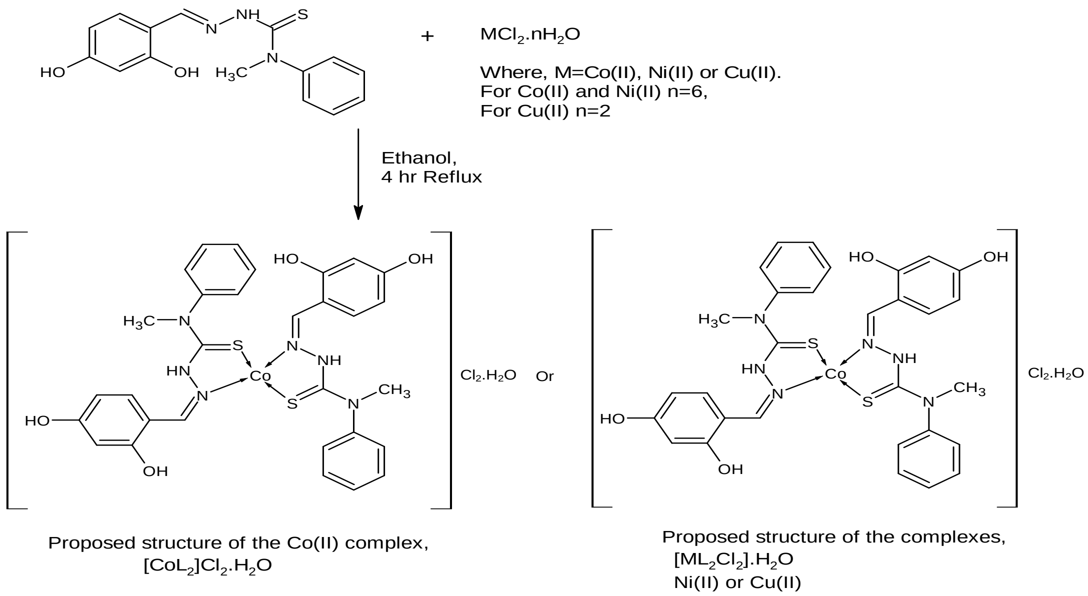


Figure 9. *The synthetic route of the metal complexes*

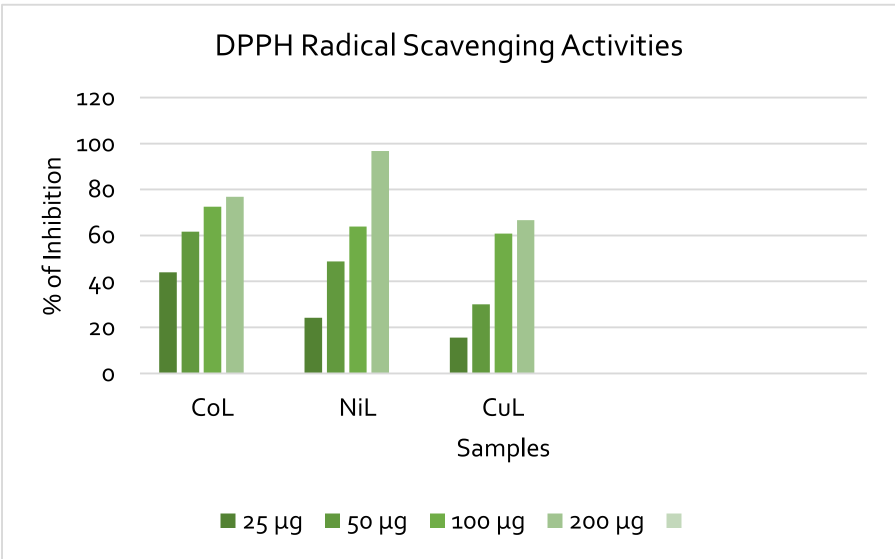


Figure 10. *The radical scavenging activities of complexes*

In a study by our group, an N_2O_2-type zinc(II) complex has been synthesized by the template reaction of Pyridoxal-S-methylthiosemicarbazone and 2-hydroxy-4-methoxy-benzaldehyde (Figure 11). The structures of ligand (1) and complex (2) have been elucidated by various analytical and spectroscopic techniques. In this study, the antioxidant capacity and free radical scavenging activity of the compounds have been determined by CUPRAC and DPPH methods, respectively. The obtained results from both methods have confirmed the relatively higher antioxidant capacity (Figure 12) and free radical scavenging activity (Figure 13) of ligand (1) compared to the zinc(II) complex (2) (Poladian et al., 2021).

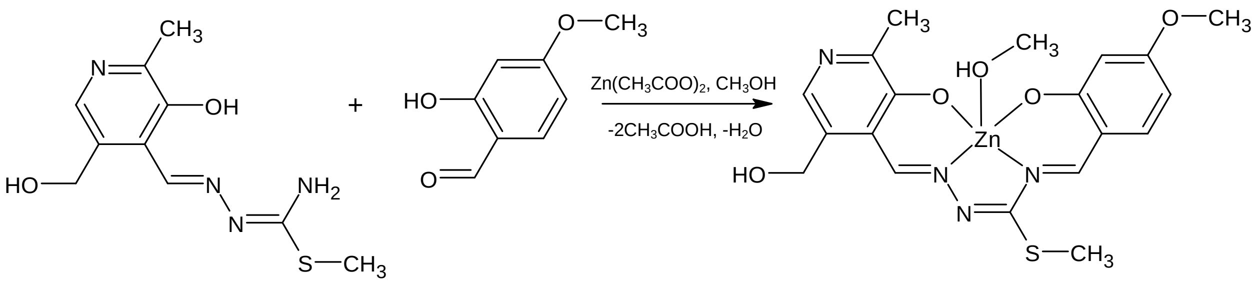


Figure 11. Synthesis of Zn(II) complex.

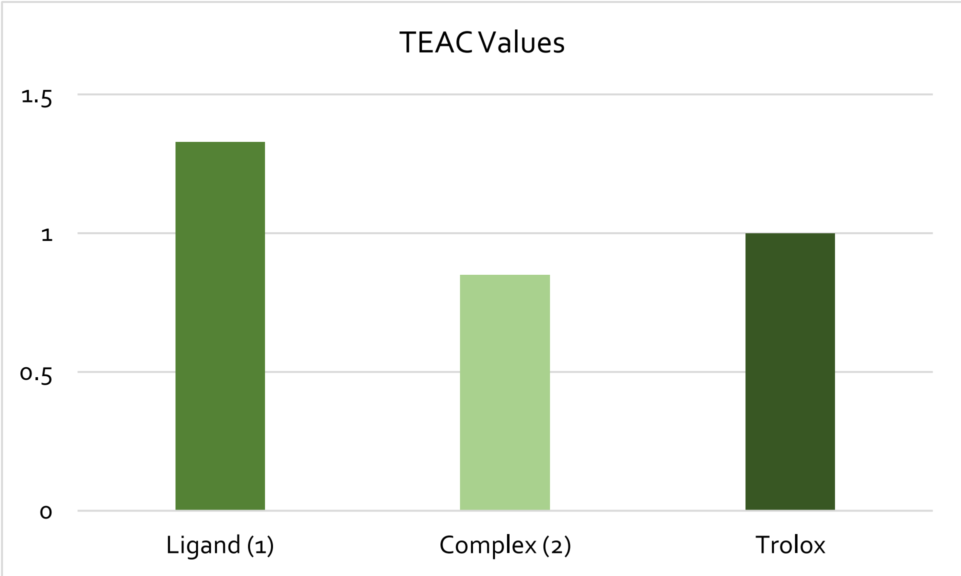


Figure 12. The obtained TEAC values of assayed compounds.

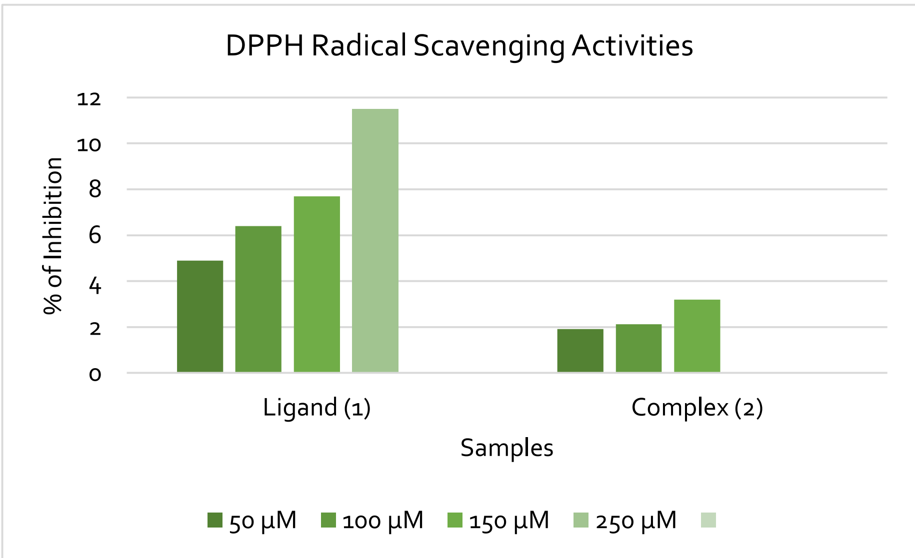


Figure 13. *The radical scavenging activities of compounds*

The synthesis of nickel(II) and ruthenium(II) complexes from Pyridoxal-N-allyl-thiosemicarbazone and triphenylphosphine have been performed by Demirici et al. The chemical composition of compounds has been characterized by analytical and spectroscopic methods. The synthesized compounds have been tested for their antioxidant capacity and free radical scavenging activities by CUPRAC and DPPH assays, respectively. The obtained results from the CUPRAC assay have shown the potent antioxidant capacity of both ligand and metal complexes compared to the Trolox (Figure 14). Moreover, the free radical scavenging activities of compounds have resulted in the following order: Trolox>Ligand>Ru-Complex(II)>Ni-Complex(I) (Figure 15) (Bal-Demirci et al., 2019).

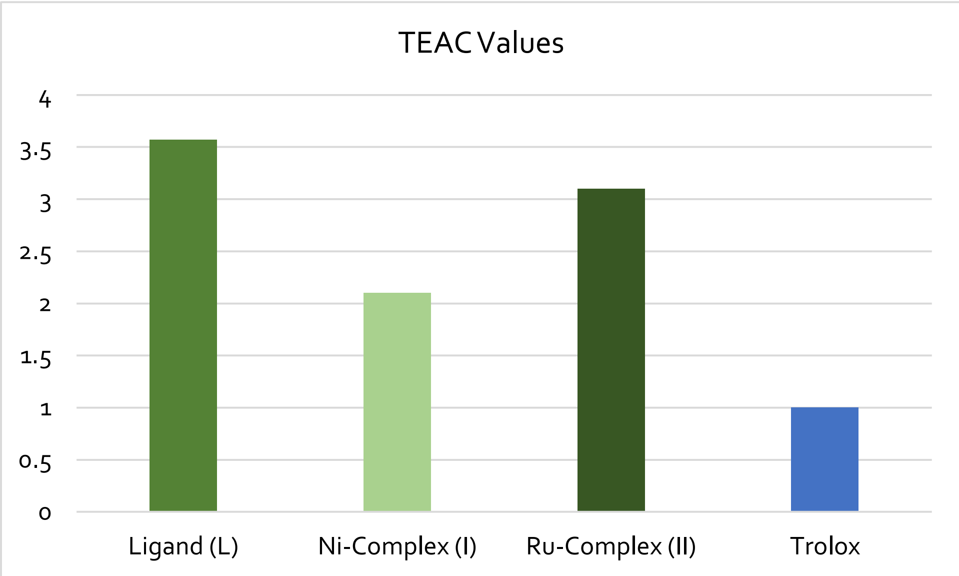


Figure 14. *The obtained TEAC values of assayed compounds*

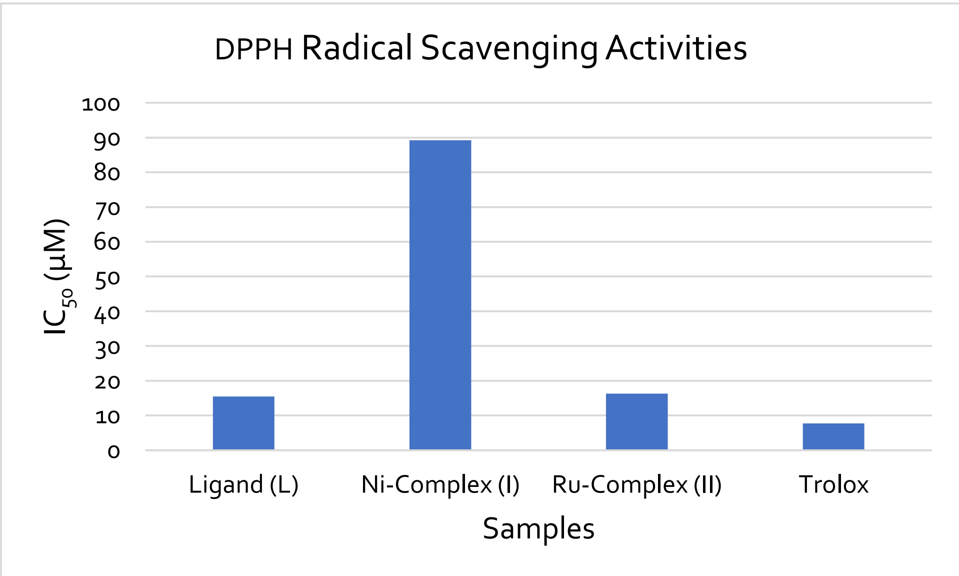


Figure 15. *The radical scavenging activities of compounds*

Zhang et al. have synthesized a series of novel thiosemicarbazone derivatives (1, 2, and 3) and characterized their structures by using FT-IR, NMR spectroscopy, and elemental analysis (Figure 16). The free radical scavenging ability of compounds analyzed by DPPH assay. Based on the results, it was found that the scavenging abilities of compounds increased with the enhancement of concentrations. In the concentration of 300 μg/mL, all the assayed compounds showed no significant scavenging ability. While the concentration reached 500 μg/mL, all the synthesized thiosemicarbazone compounds showed the highest scavenging abilities. Overall, the antioxidant ability of compounds resulted in the order of 3>2>1, which clearly shows the highest antioxidant potential of compound 3 (Zhang et al., 2019).

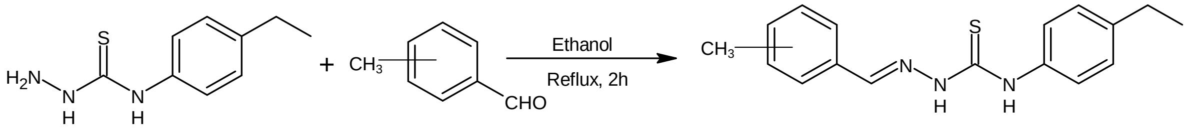


Figure 16. The chemical synthesis of novel thiosemicarbazone derivatives

Some dioxomolybdenum(VI) complexes of 3-methoxysalicylidene N-alkyl-thiosemicarbazones (L) (where alkyl is propyl, butyl, pentyl, or hexyl) have been synthesized and characterized using analytical and spectroscopic methods by Songül Eğlence-Bakır et. al (Figure 17). The antioxidant activities of compounds have been evaluated by using the DPPH assay, and the obtained results have shown the highest radical scavenging activity of ligand L^4 with the IC_{50} value of 0.13 μM. The antioxidant activities of ligands with standard compounds are in the order of rutin>L^4>L^3>L^2>L^1. Moreover, the DPPH radical scavenging activity of complexes has shown no significant results due to the lack of hydroxyl groups in the structures of complexes. The overall DPPH radical scavenging activities of compounds are shown in Figure 18 (Eğlence-Bakır et al., 2019).

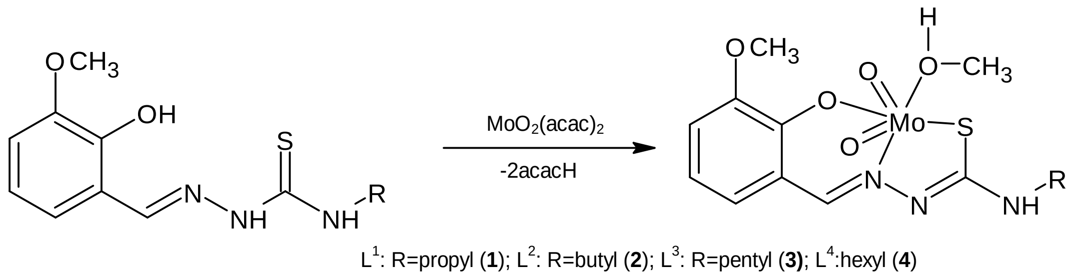


Figure 17. *The chemical structures of compounds*

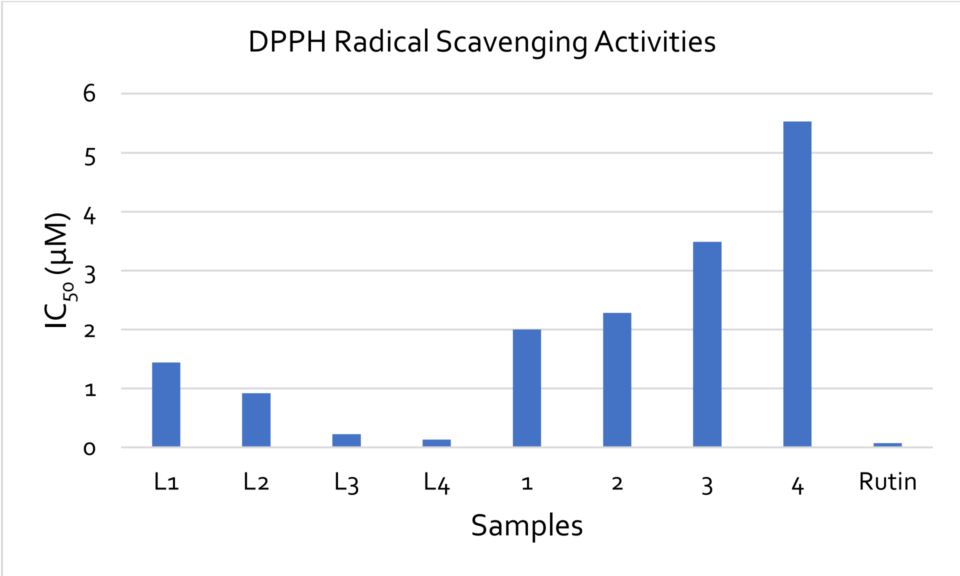


Figure 18*. The radical scavenging activities of assayed compounds*

In a study by T.A. Yousef and G.M. Abu El-Reash, the synthesis of a new ligand, 3-(4-hydroxyphenyl)-1-phenyl-1h-pyrazole-4-carbaldehyde 4n-(2-pyridyl)thiosemicarbazone (H_2L) and its complexes $[CdHL(CH_3COO)(H_2O)_2]H_2O$, $[ZnHL(CH_3COO)(H_2O)_2]H_2O$, $[CuH_2LCl_2]$, $[NiHLCl(H_2O)_2]H_2O$, $[CoH_2LCl_2(H_2O)_2]H_2O$ and $[Mn_2HLCl_3(H_2O)_5]H_2O$ have been realized. The obtained compounds have been characterized using various spectroscopic, electronic absorption, and magnetic techniques. The antioxidant activity of compounds has been elucidated by ABTS and DPPH radical scavenging activity assays. Based on the obtained results from DPPH radical scavenging activity, the ligand showed more potent free radical-eliminating activity compared to the metal complexes. Among the metal complexes, the Co(II) complex has shown the least radical scavenging activity, while the Cu(II) complex has shown moderate activity with IC_{50} 0.714 mg/mL (Figure 19). The ABTS assay has shown powerful antioxidant activity of ligand (H_2L), followed by Mn(II), Cd(II), Zn(II), and Ni(II) complexes. Moreover, the Cu(II) complex has shown moderate activity, while the Co(II) complex has shown very weak or totally no antioxidant activity by ABTS assay Figure 20, Yousef & El-Reash, 2019).

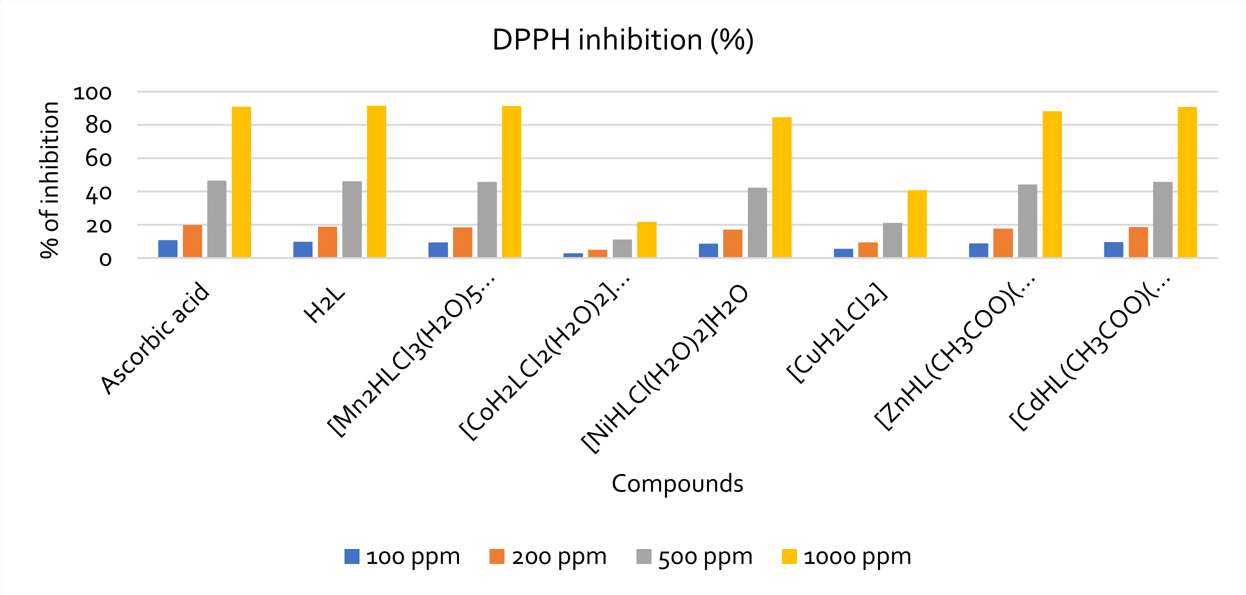


Figure 19. *The DPPH free radical scavenging activity of compounds*

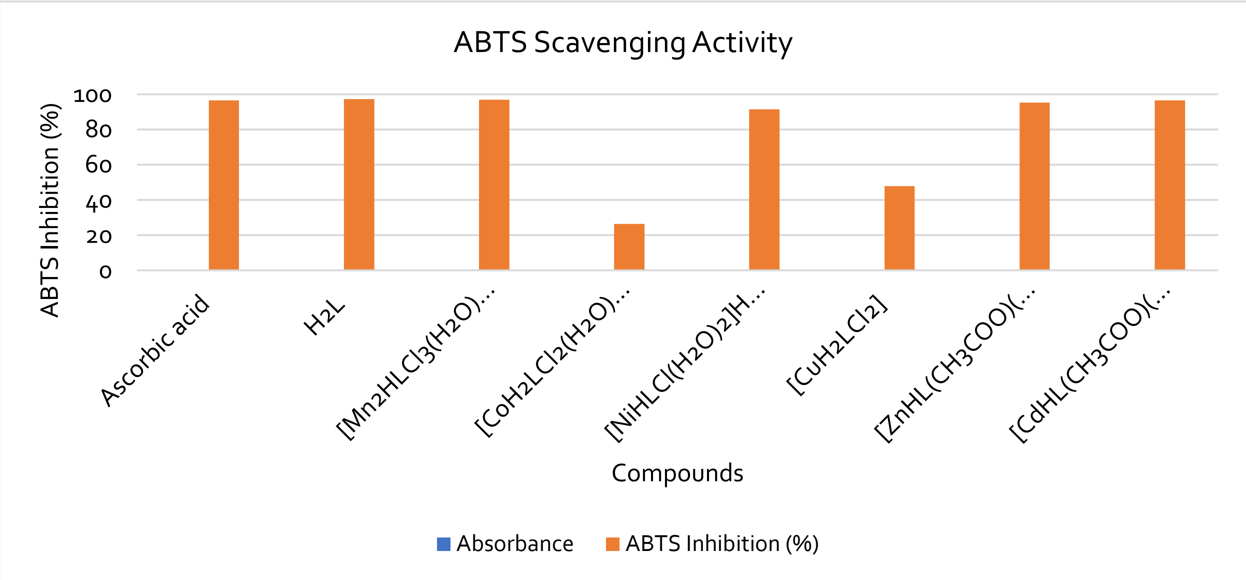


Figure 20. *The ABTS Scavenging activity of compounds*

Sivaraj Saranya and co-workers have synthesized the isatin thiosemicarbazone compounds (1-10) and characterized the composition of compounds by elemental analysis, UV-visible, FT-IR, and NMR spectroscopic methods (Figure 21). The compounds have been evaluated for their in vitro antioxidant activity using the DPPH assay. Based on the obtained results by DPPH assay, the compounds have shown dose-dependent antioxidant activity in which compounds 1, 5-8, and 10 have shown good radical scavenging activity with IC_{50} of 25, 10,10,25, and 50 µg/mL, respectively. On the other hand, compounds 2,3,4, and 9 have shown the least radical scavenging property. Overall, one can conclude that compounds 5,6 and 7 have shown higher antioxidant activity at the concentration of 10 µg/mL (Saranya et al., 2019).

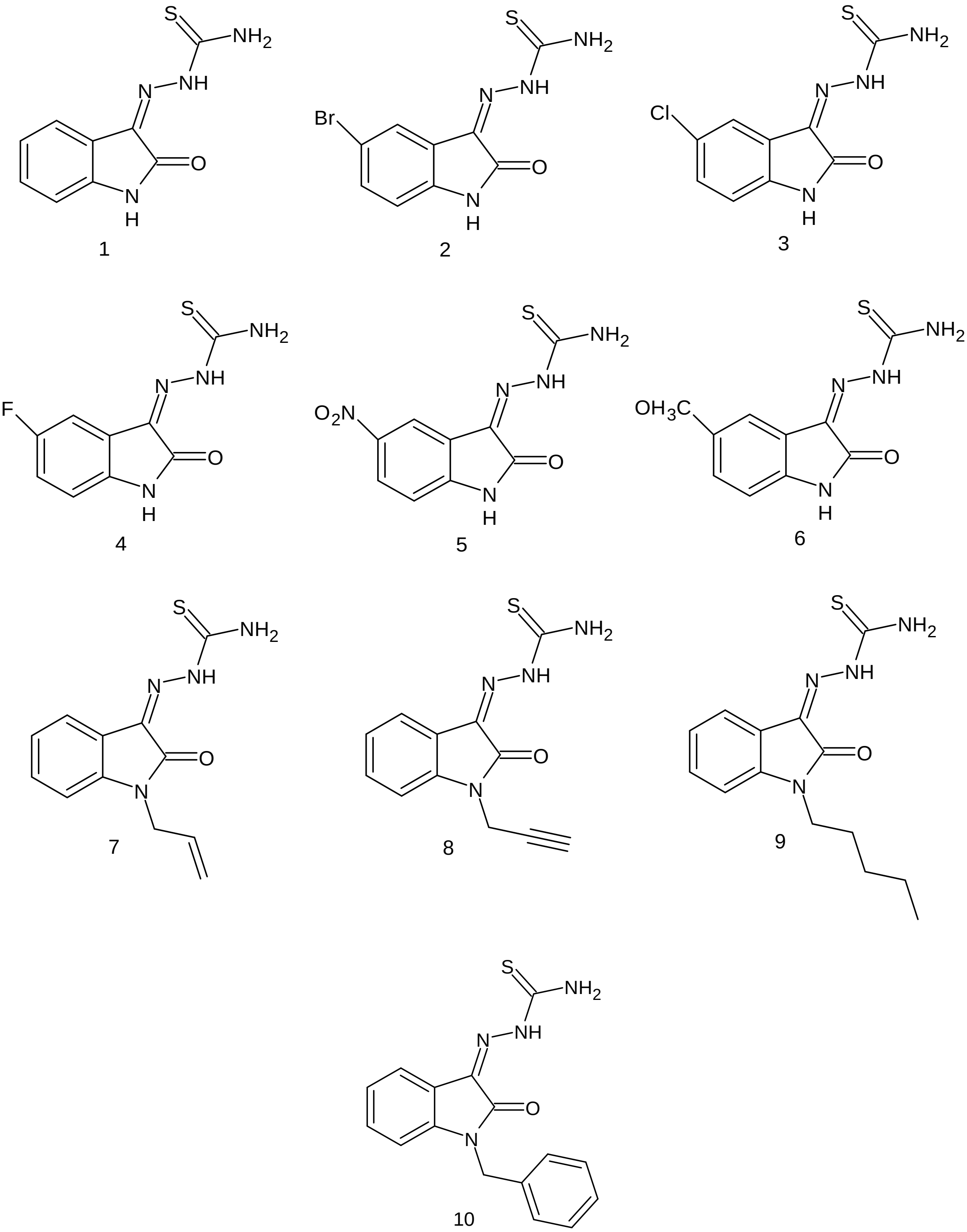


Figure 21. *Synthesized isatin-based thiosemicarbazone compounds*

Some substituted heterocyclic isatin thiosemicarbazone ligands (L1-L3) have been synthesized by Munikumari et al (Figure 22). The corresponding palladium(II) complexes have been synthesized from these ligands and $PdCl_2$ accordingly (Figure 23). For the analysis and characterization of synthesized compounds both analytical and spectroscopic methods have been used. To determine the antioxidant activity of compounds, the DPPH assay has been tested. The results have shown the potent free radical scavenging activity of complex 3 among the ligands and palladium complexes. Complex 1 has shown moderate activity with an IC_{50} value of 17.29, while the order of activity is obtained to be 3>1>2>L2>L1>L3 Figure 24 (Munikumari et al., 2019).

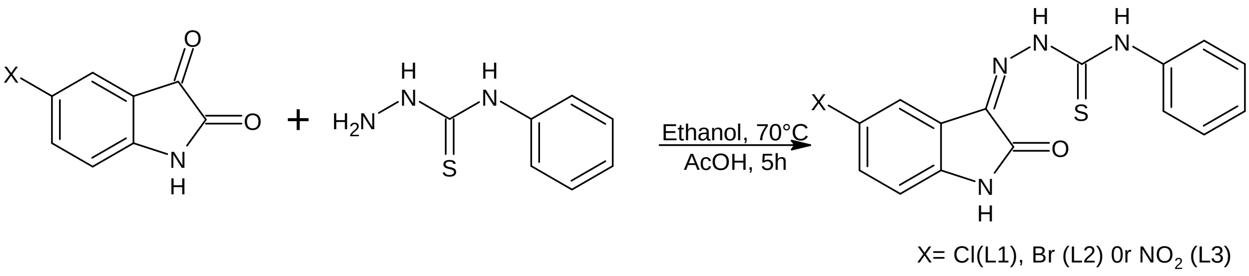


Figure 22. *Synthesis of isatin-based thiosemicarbazone ligands*

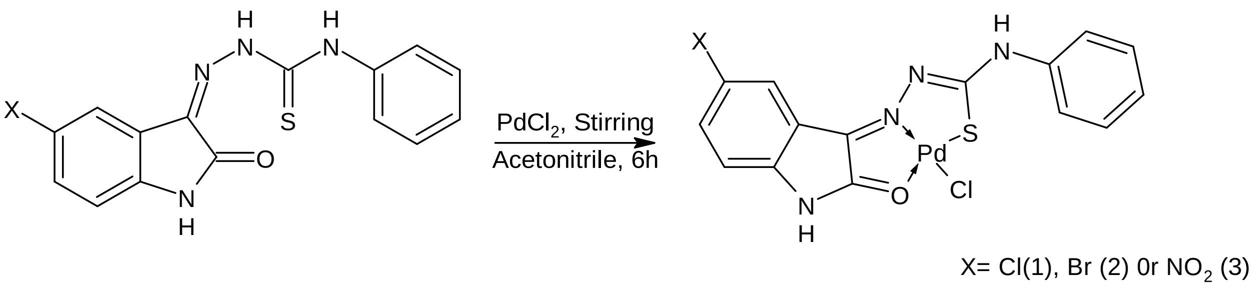


Figure 23. *Synthesis of Palladium complexes*

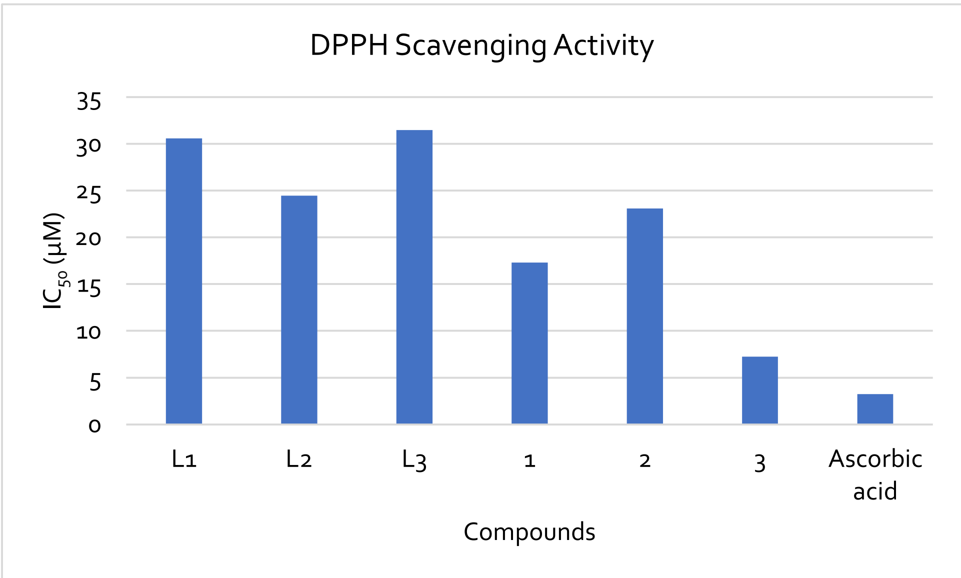


Figure 24. *DPPH scavenging activity of ligands and palladium complexes*

Aneesrahman et al. has reported the synthesis of copper(II) complexes (1-3) from 5-methoxyisatin thiosemicarbazone ligands with different N-terminal substituents (Figure 25). The structure of complexes has been characterized using different spectral techniques. The radical scavenging activity of complexes (1-3) has been determined using the DPPH method. Based on the obtained results, complex 1 has shown good scavenging activity (IC_{50}: 19.23±1.05 µM) compared to the ascorbic acid as a reference drug. On the other hand, complex 2 has shown moderate activity and complex 3 has shown the least activity among the synthesized complexes (Figure 26). Based on the above results, the order of the activity could be 1>2>3 (Aneesrahman et al., 2019).

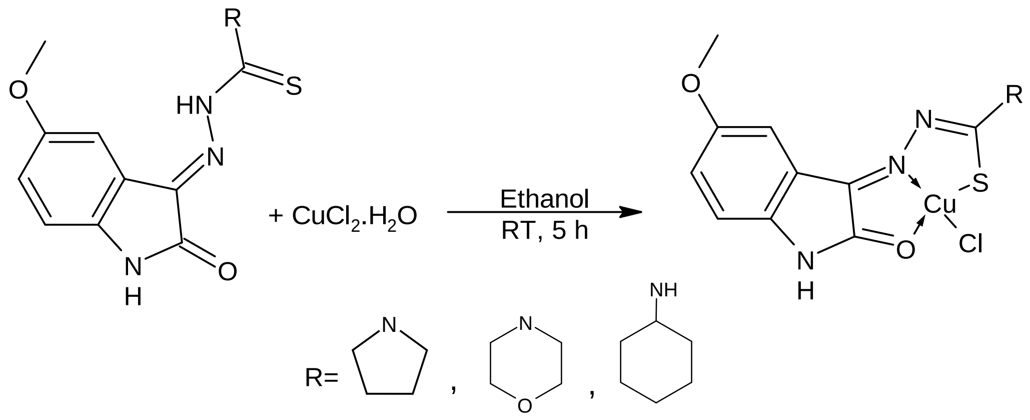


Figure 25. *Synthesis route of copper(II) complexes*

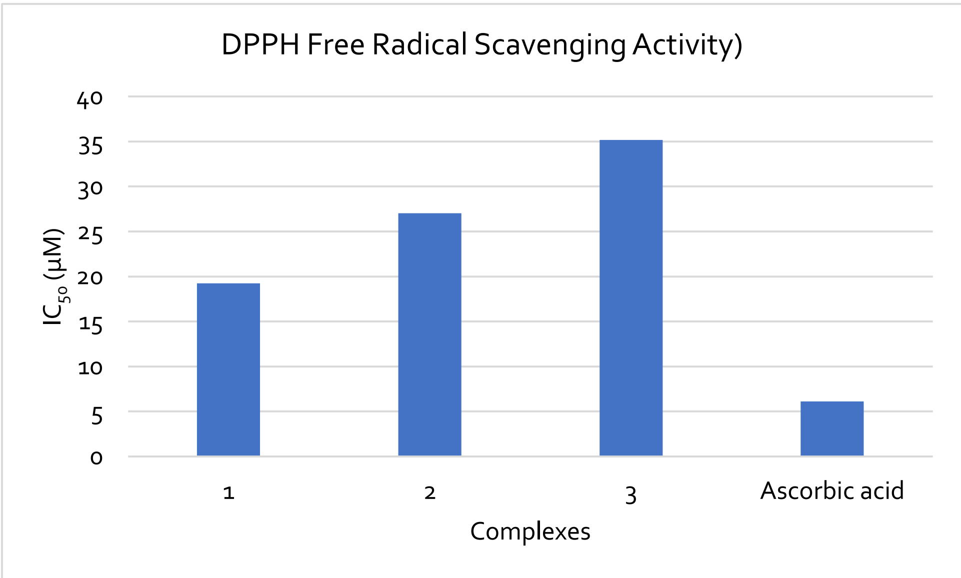


Figure 26. *DPPH free radical scavenging of complexes (1-3)*

New iron(III) and manganese(III) complexes have been synthesized from 1-phenyl-1,3-butanedione-S-propyl-thiosemicarbazone (1) with salicylaldehyde as an auxiliary ligand by Kaya et al (Figure 27). The complexes have been characterized by various analytical and spectroscopic methods such elemental analysis, FTIR, ^{1}H NMR and Ms. The total antioxidant capacity (TEAC) and free radical scavenging activities (%FRS) of compounds have been evaluated. The results from TEAC methods have shown the higher TEAC value for compound 1 compared to the metal complexes (1a and 1b). However, the metal complexes (1a and 1b) have shown higher TEAC values than ascorbic acid (Figure 28). Based on the results, compound 1 has shown moderate radical scavenging activity, while the complexes (1a and 1b) have shown lower activities compared to ascorbic acid Figure 29 (Kaya et al., 2019).

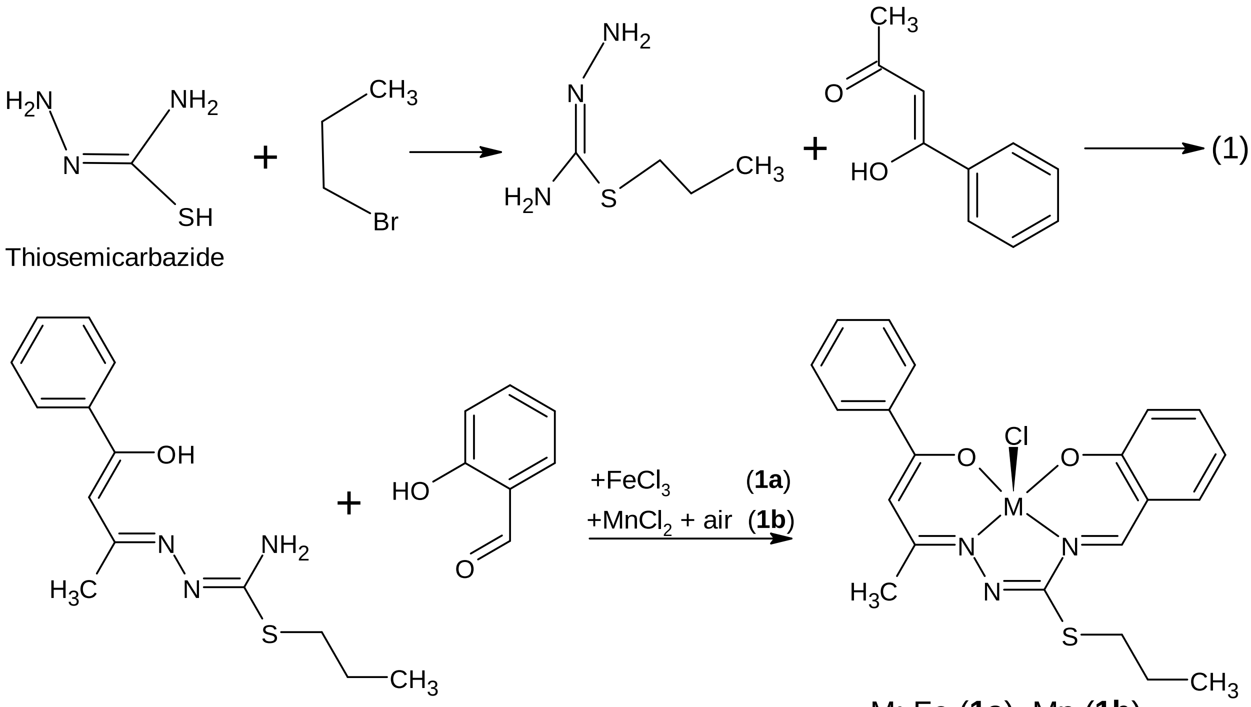


Figure 27. *Synthesis route of iron(III) (1a) and manganese(III) (1b) complexes*

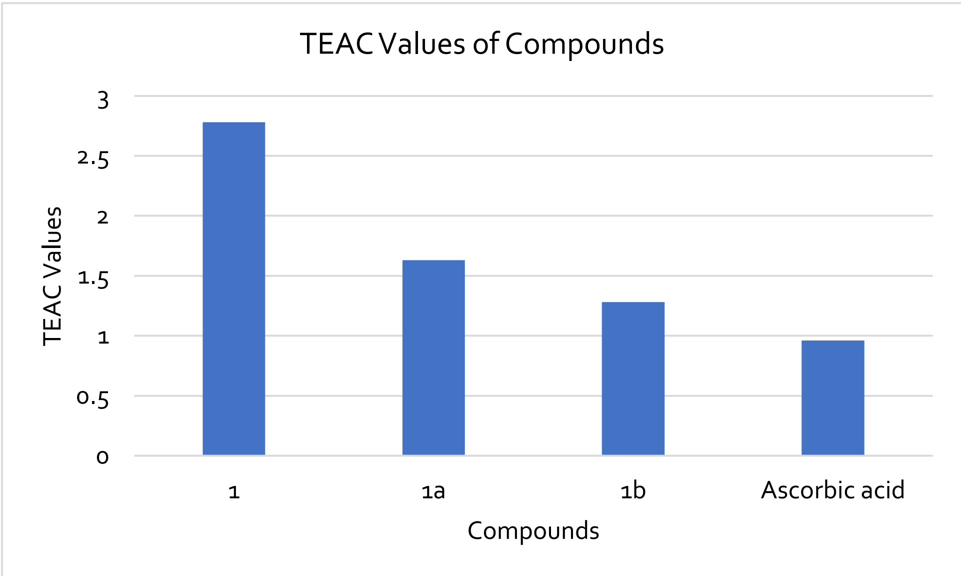


Figure 28. *The TEAC Values of compounds*

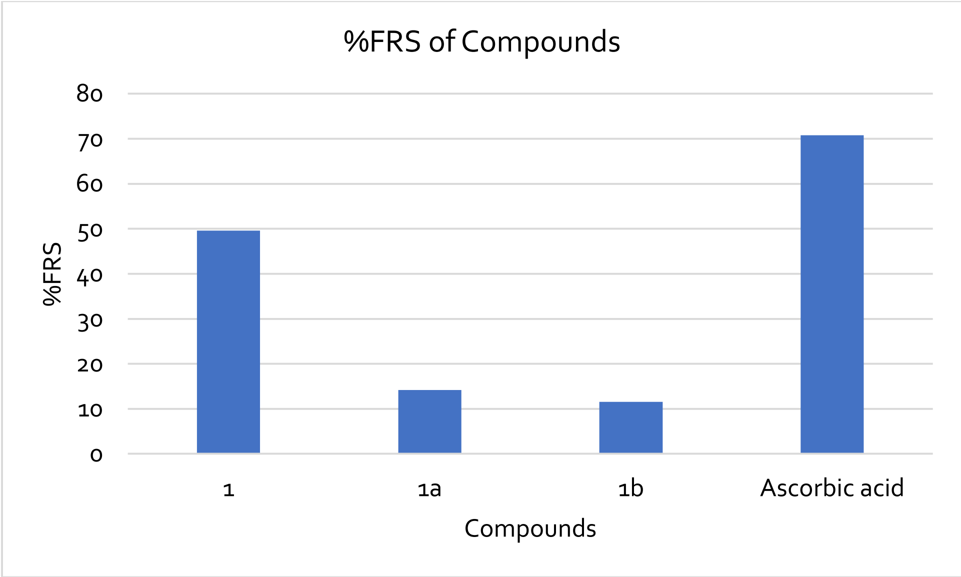
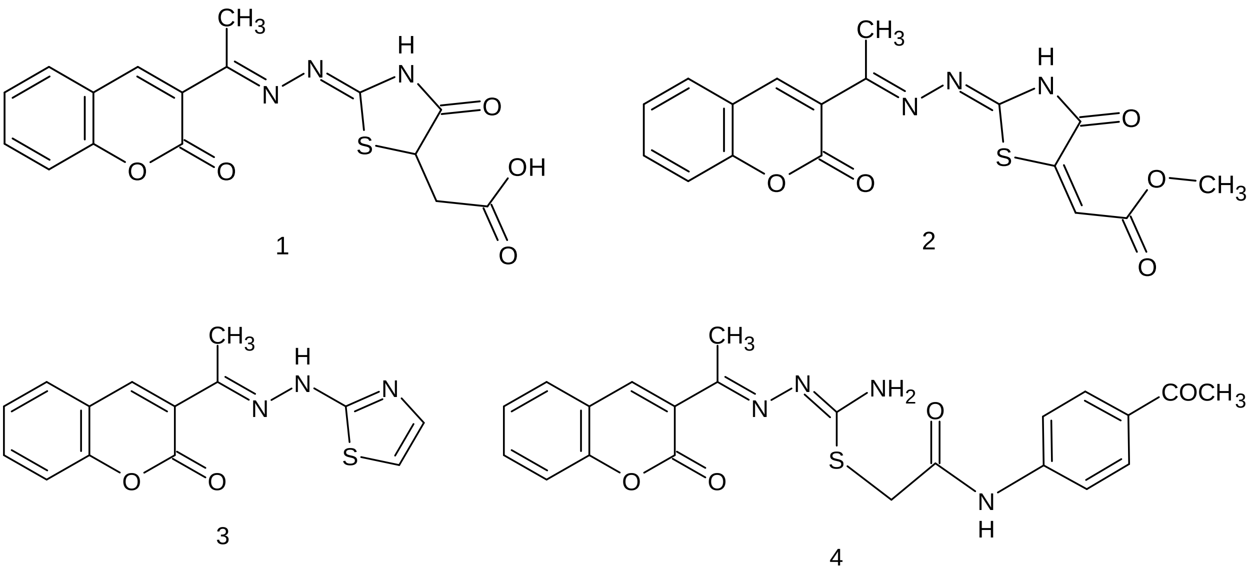


Figure 29. *The free radical scavenging activity of compounds*

El-Helw et al. have reported the synthesis of some coumarin derivatives from 2-(1-(2-oxo-2H-chromen-3-yl)ethylidene)hydrazine carbothioamide with some carbon electrophiles (Figure 30). The structure of compounds has been characterized using analytical and spectral methods. The antioxidant activity of compounds has been elucidated using the ABTS assay. The obtained results confirm the higher antioxidant activity of compound 6 compared to other compounds. The compound 4 has shown moderate antioxidant activity by the ABTS assay. All the synthesized compounds have shown less antioxidant activity based on the ABTS assay compared to the ascorbic acid Figure 31, El-Helw et al., 2019).



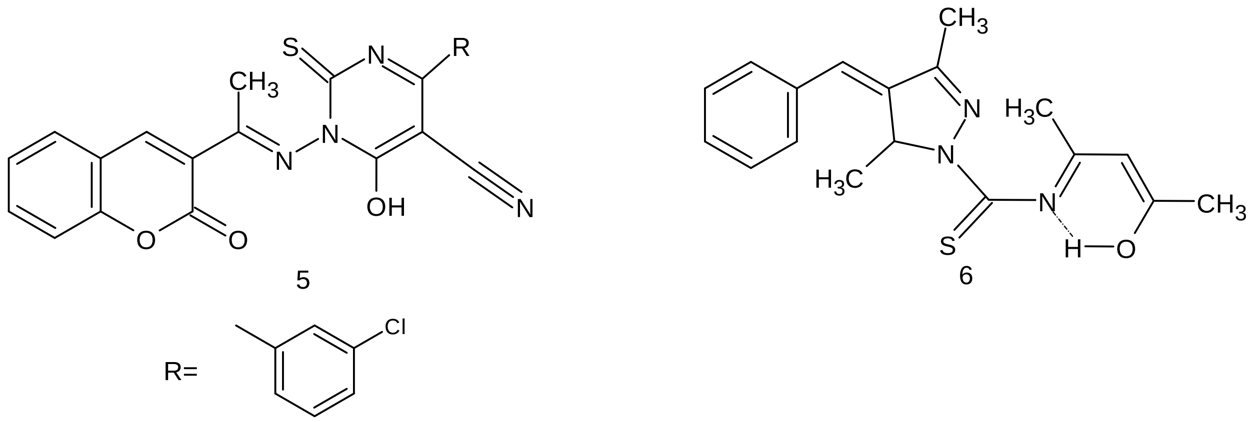


Figure 30. *The structure of antioxidant active compounds*

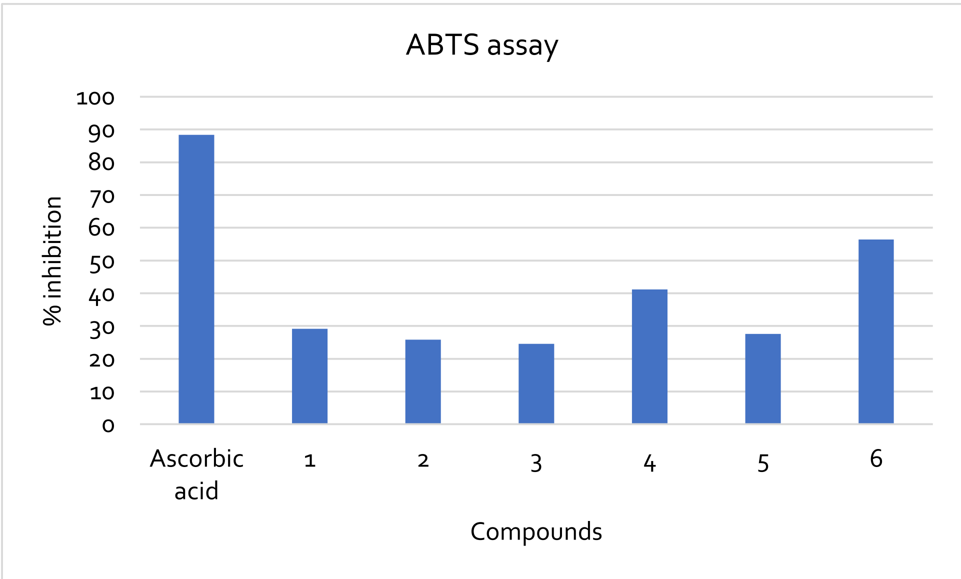


Figure 31. *Antioxidant activity of compounds based on the ABTS assay*

In a study, the synthesis of a thiosemicarbazone ligand as starting material (Figure 32) and its six metal complexes [Cu(L)X] (X=Cl^- (1), NO_3^- (2)), [Cu(A)(L)NO_3](A=1,10-phen (3), 2,2'-Bpy(4)), [Ni(HL)$_2$](NO_3)$_2$ (5), and [Fe(L)$_2$]Cl (6) have been performed by Graur et al. The structures of newly synthesized compounds have been characterized using various analytical and spectroscopic techniques. The antioxidant activities of the thiosemicarbazone ligand (HL) and its six metal complexes have been determined by applying ABTS assay (Figure 33). Based on the obtained results of the ABTS assay, the thiosemicarbazone ligand has exhibited higher antioxidant activity with IC_{50} values of 56.4 µM compared to the complexes (1, 2, 3, 4, and 6), but relatively less antioxidant activity compared to the Trolox as reference. Among the synthesized metal complexes, complex 5 has shown potent antioxidant activity compared to other metal complexes and thiosemicarbazone ligands, which may be described as the positive effect of nickel(II) ions in the structure of the complex (Graur et al., 2023).

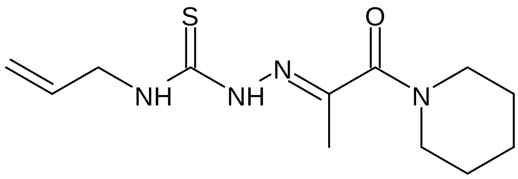


Figure 32. The structure of the thiosemicarbazone ligand as a starting material.

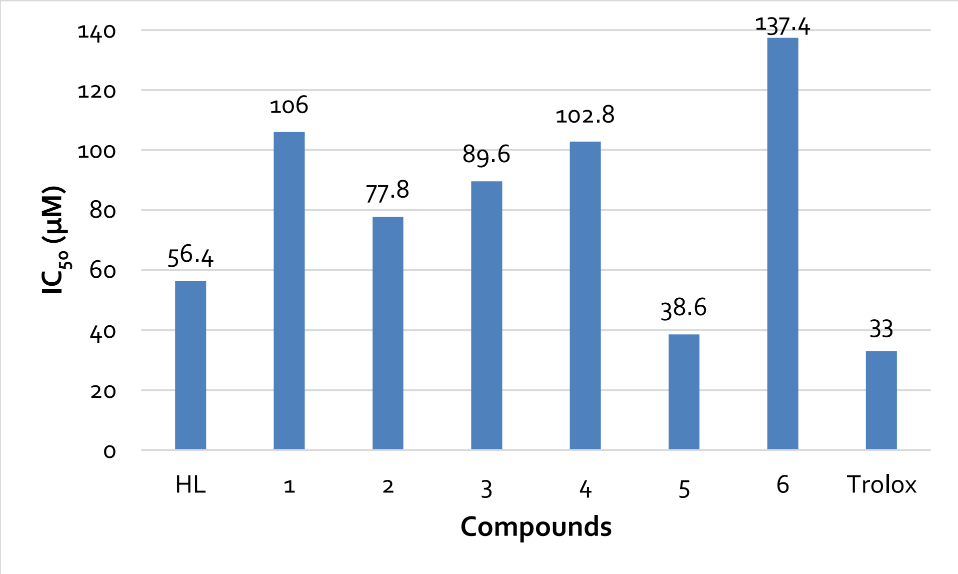


Figure 33. *The antioxidant activities of compounds based on the ABTS assay*

Masuri et al. have reported the synthesis of hydroxylated coumarin-based thiosemicarbazone ligands (T1-T6) and their characterization using various analytical and spectroscopic techniques (Figure 34). The synthesized compounds have been tested for their radical scavenging activities using 1,1-diphenyl-2-picrylhydrazyl (DPPH) and 2,2′-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid (ABTS) assays. Based on the obtained results from the DPPH assay (Figure 35). The compounds (T1-3) have shown no radical scavenging activities at all. The compound (T4) has shown modest antioxidant activity, while the compounds (T5-T6) have exhibited the most potent antioxidant activities because of their dehydroxylated structures. Moreover, the obtained results from the ABTS assay (Figure 36) have confirmed the potent antioxidant activities of compounds (T5-T6) that are compatible with those of the DPPH assay. The difference in the antioxidant activities of assayed compounds may be described by the presence and positions of hydroxyl groups in the compounds (Masuri et al., 2023).

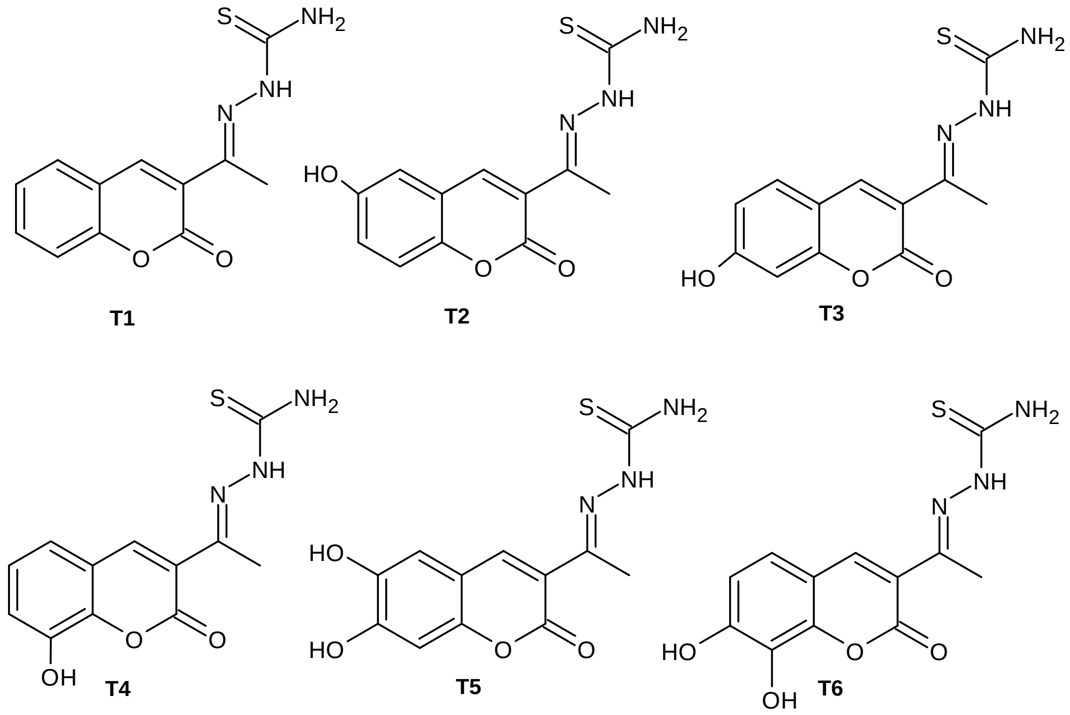


Figure 34. *The chemical structures of Coumarin-based thiosemicarbazones*

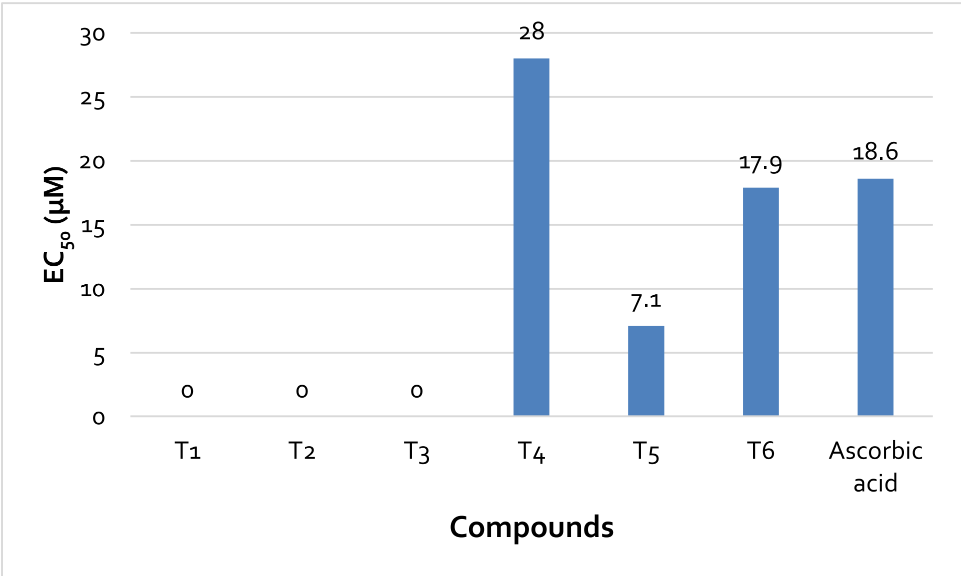


Figure 35. *The radical scavenging activities of compounds based on the DPPH assay*

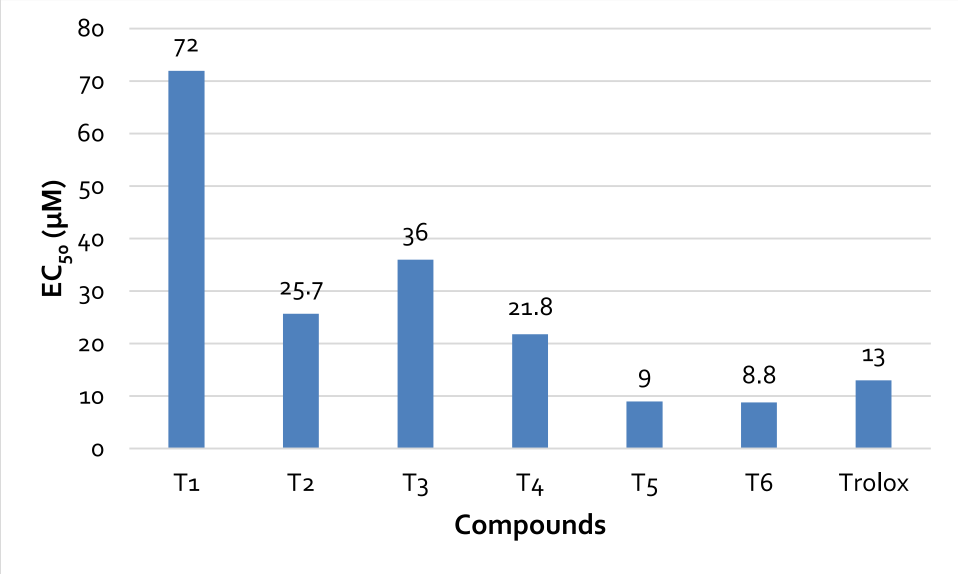
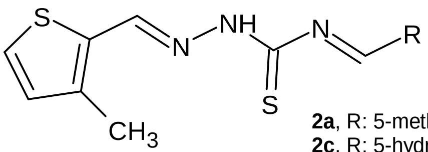


Figure 36. *The radical scavenging activities of compounds based on the ABTS assay*

In a study, the synthesis and evaluation of novel thiosemicarbazones have been performed by Kaya et al (Figure 37). The structures of newly synthesized compounds have been characterized by using ^{1}H NMR, ^{13}C NMR, and MS analysis. The DPPH assay has been used for the determination of radical scavenging activities of compounds. According to the results (Figure 38), compound 2b has manifested the most potent antioxidant activity among the other. As shown from the obtained results, the compounds 2c and 2f have shown moderate antioxidant activities. One can conclude that the presence of 5-nitrofuran (2b), 5-hydroxymethylfuran (2c), and 5-nitrothiophene (2f) groups has caused a positive contribution to the antioxidant activities of the compound (Kaya et al., 2024).



2a-2f

2a, R: 5-methylfuran-2-yl; **2b**, R:5-nitrofuran-2-yl
2c, R: 5-hydroxymethylfuran-2-yl; **2d**, R:thiophen-2-yl
2e, R:5-methylthiophen-2-yl; **2f**, R: 5-nitrothiophen-2-yl

Figure 37. *The structures of novel thiosemicarbazones*

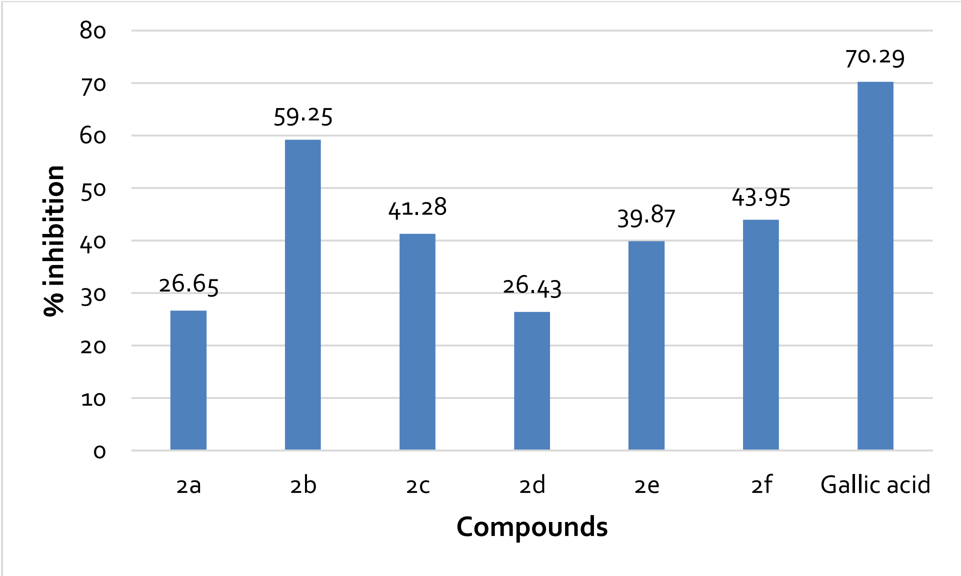


Figure 38. *The DPPH radical scavenging activities of compounds*

In another study, 3-benzylidene-2,4-pentanedione-S-methyl-thiosemicarbazone hydrogen iodide (TSC), and from this, by using template condensation reaction, the nickel(II) complexes (Ni1-4) have been synthesized and fully characterized using elemental analysis, IR, ^{1}H NMR, and single crystal X-ray diffraction by Karakurt et al (Figure 39). The antioxidant capacity and radical scavenging activities of compounds have been evaluated by using the CUPRAC and DPPH methods, respectively. In this study, ascorbic acid has been used as a reference for the determination of antioxidant capacity and radical scavenging activities of compounds. The obtained TEAC values by the CUPRAC method have confirmed the antioxidant capacity of compounds in the order of TSC>Ni3>Ni4>Ni2>Ni1 (Figure 40). As it is obvious from TEAC values, the TSC has shown comparable antioxidant capacity with that of ascorbic acid as a reference, but the corresponding nickel(II) complexes have shown lower antioxidant capacities as compared to ascorbic acid. On the other hand, the TSC has shown lower radical scavenging activity against DPPH radical, whereas the nickel(II) complexes have shown no radical scavenging activity in the assayed range. This may be due to the nature of the metal ions and the steric hindrance of big molecules such as DPPH with the metal complexes (Karakurt et al., 2022).

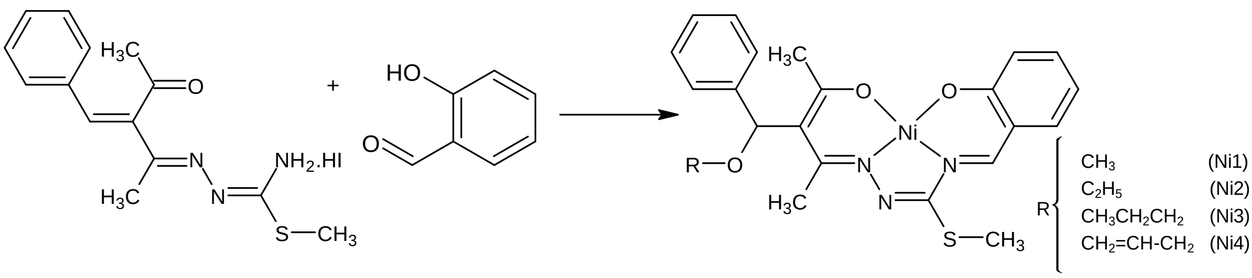


Figure 39. *The structures of thiosemicarbazone ligand and its nickel(II) complexes*

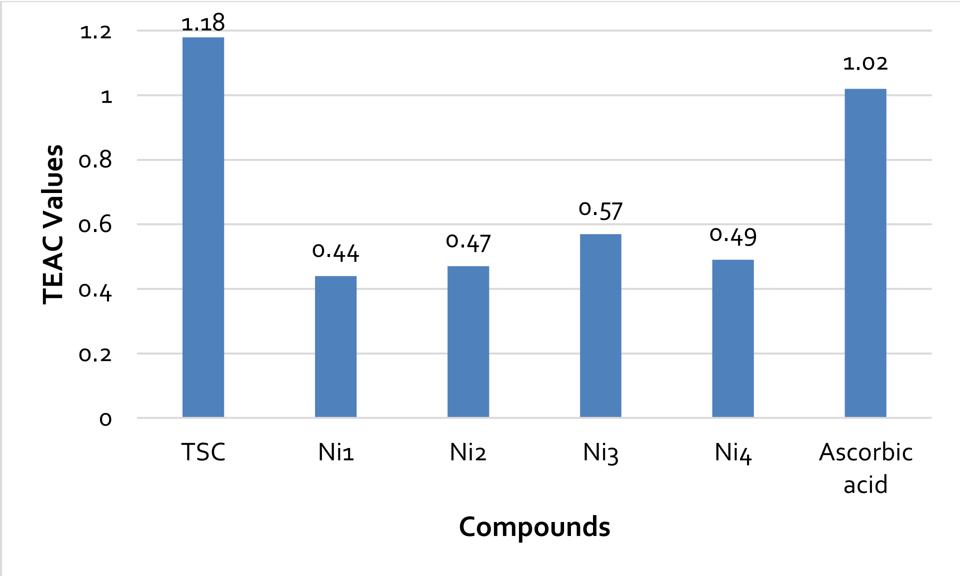


Figure 40. *The antioxidant capacity of compounds is based on the CUPRAC method*

Ortaboy et al. have reported the synthesis of two manganese(III) complexes (Mn1 and Mn2) from the thiosemicarbazone ligand, and the characterization of the compounds has been accomplished using experimental and theoretical methods (Figure 41). The antioxidant capacity and radical scavenging activity of complexes have been determined using CUPRAC and DPPH assays, respectively. In the antioxidant determination assays, ascorbic acid has been used as a reference. Based on the obtained results from the CUPRAC assay (Figure 42), the antioxidant capacity of compounds is in the order of Mn2>Mn1>ascorbic acid, respectively. The complex (Mn2) has shown almost three times more antioxidant capacity than ascorbic acid. Moreover, the radical scavenging activity of compounds has been determined using the DPPH assay, which shows a compatible order with the CUPRAC assay (Figure 43). According to the results of both assays, the complex (Mn2) has shown higher antioxidant capacity/activity compared to complex (Mn1), which may be due to the presence of an azide group in the structure of the complex (Mn2) (Ortaboy et al., 2024).

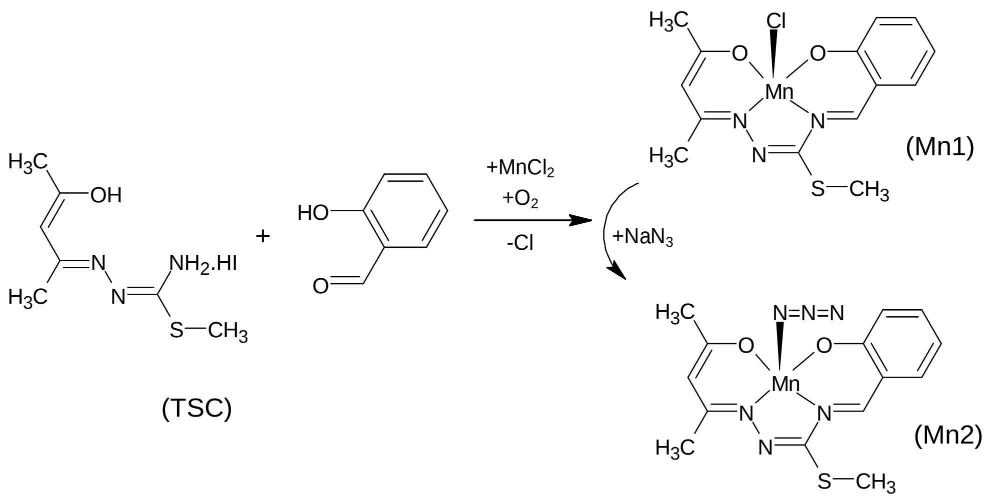


Figure 41. *The synthesis route of compounds*

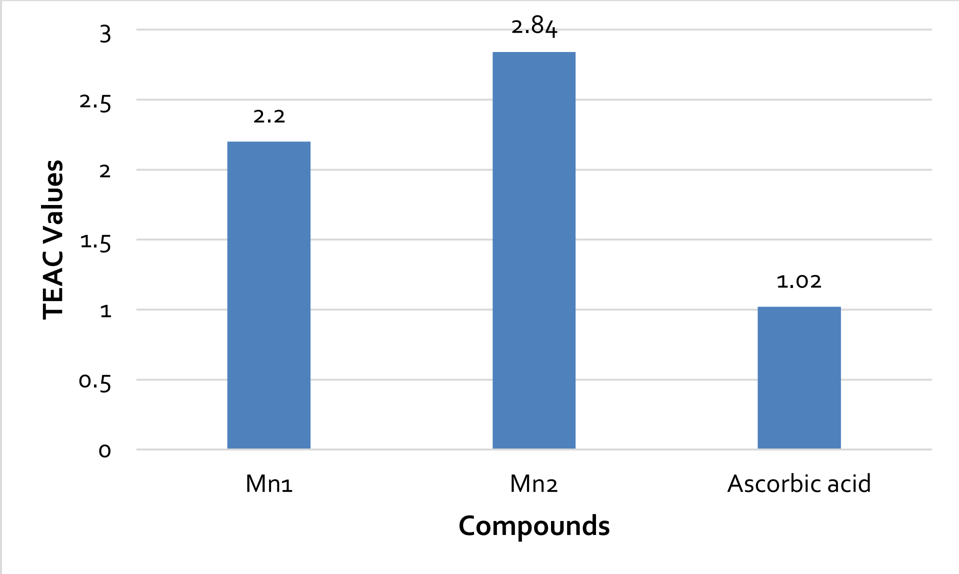


Figure 42. *The antioxidant capacity of compounds*

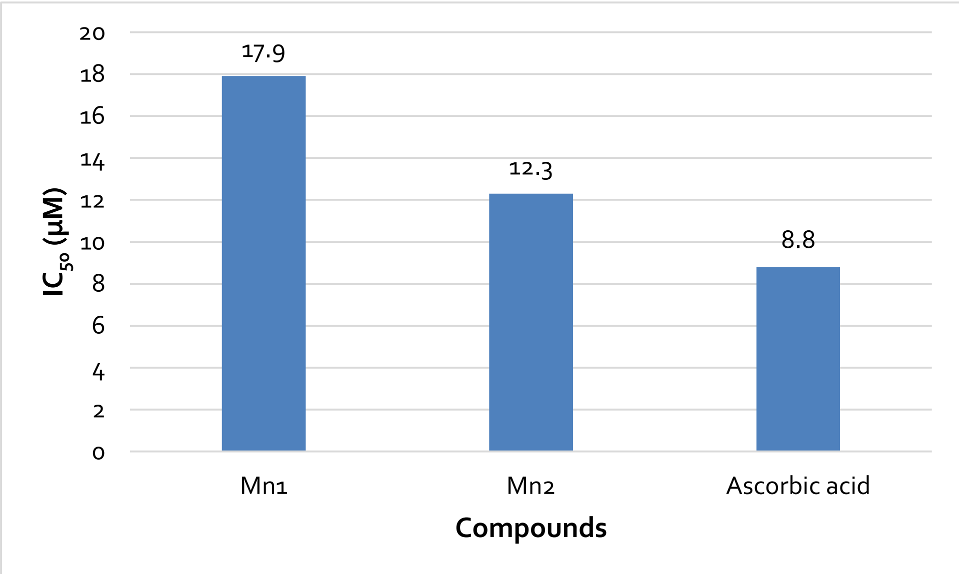


Figure 43. *The radical scavenging activity of compounds*

Some metal complexes of Co(II), Ni(II), Cu(II), and Zn(II) have been synthesized from thiosemicarbazone ligands via condensation reaction by Rani et al (Figure 44). The chemical structures of the compounds have been elucidated by using FT-IR, ^{1}H NMR, ^{13}C NMR, mass spectrometry, UV-Vis, SEM, ESR, and powder XRD techniques. The radical scavenging activities of thiosemicarbazone ligands and metal complexes have been determined using DPPH assay. According to the results, the radical scavenging activities of thiosemicarbazone ligands lie in the order of $HL^3>HL^4>HL^2>HL^1$, respectively. The higher radical scavenging activity of thiosemicarbazone ligand HL^3 can be explained based on the presence of moiety in the structure of the ligand for the prevention of radical production. On the other hand, the obtained antioxidant data has shown the order of activities as: ascorbic acid>Ni(II)>Co(II)>Zn(II)>Cu(II), respectively. The antioxidant results show the potent radical scavenging activities of Ni(II) complexes and the lower radical scavenging activities of Cu(II) complexes, accordingly (Rani et al., 2023).

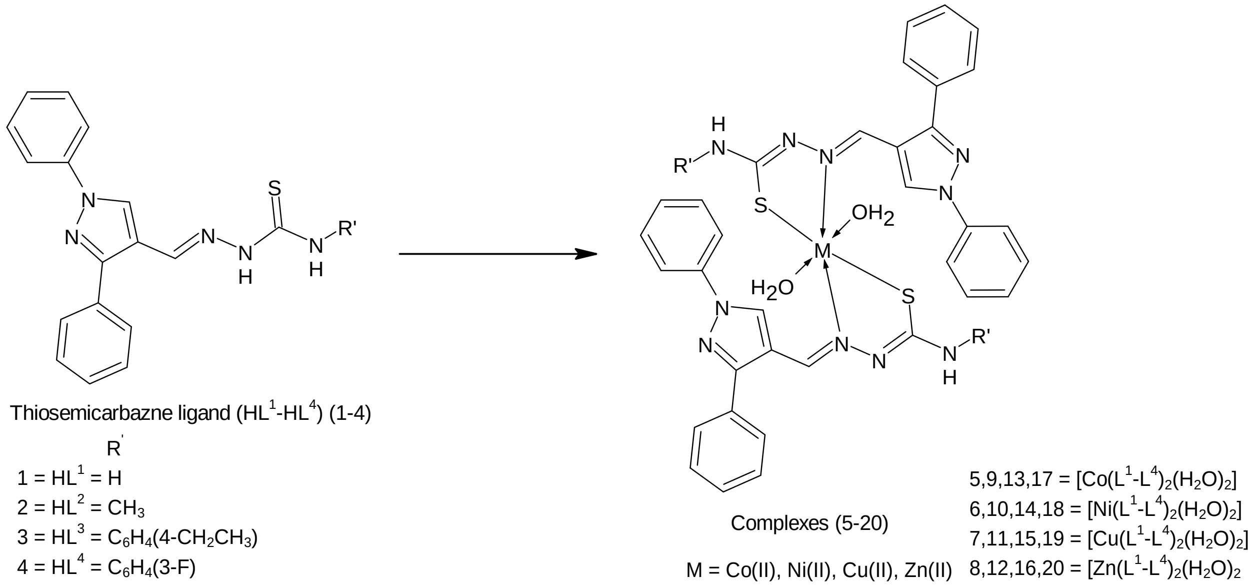
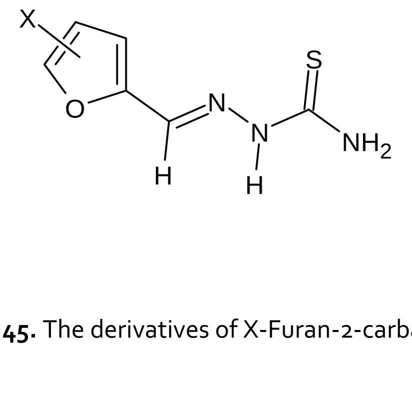


Figure 44. *The chemical structures of the synthesized compounds*

Ten new derivatives of thiosemicarbazone, furan-2-carbaldehyde thiosemicarbazone (1), 3-methyl- furan-2-carbaldehyde thiosemicarbazone (2), 5-hydroxymethyl- furan-2-carbaldehyde thiosemicarbazone (3), 5-trifluoromethyl- furan-2-carbaldehyde thiosemicarbazone (4), 5-nitro- furan-2-carbaldehyde thiosemicarbazone (5), 5-phenyl-furan-2-carbaldehyde thiosemicarbazone (6), 5-(2-fluorophenyl)- furan-2-carbaldehyde thiosemicarbazone (7), 5-(4-methoxyphenyl)- furan-2-carbaldehyde thiosemicarbazone (8), 5-(1-naphthyl)- furan-2-carbaldehyde thiosemicarbazone (9), and 5-(1H-Pyrazol-5-yl)- furan-2-carbaldehyde thiosemicarbazone (10) have been synthesized and characterized using various spectroscopic and analytical techniques Hernandez et al (Figure 45). The synthesized compounds have been tested for their antioxidant activity using the DPPH assay (Figure 46). According to the results, compounds (1 and 4) have shown a relatively higher antioxidant activity compared to other compounds. Moreover, compound (1) has shown higher antioxidant activity among the synthesized compounds, but lower antioxidant activity compared to ascorbic acid as a reference (Hernández et al., 2023).



1 (X=H)
2 (X=3-CH_3)
3 (X=5-CH_2OH)
4 (X=5-CF_3)
5 (X=5-NO_2)
6 (X=5-Ph)
7 (X=5-(2'-FPh))
8 (X=5-(4'-OCH_3Ph)
9 (X=5-Naphthoyl))
10 (X=5-(1H-Pyrazoyl))

Figure 45. The derivatives of X-Furan-2-carbaldehyde thiosemicarbazone.

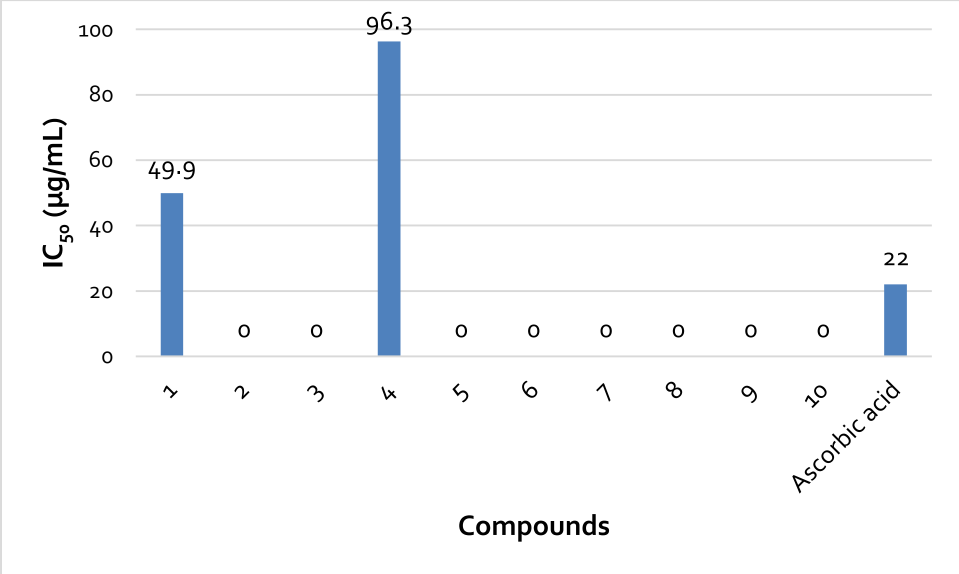


Figure 46. The antioxidant activity of compounds based on the DPPH assay.

An iron(III) complex with the general formula of $[Fe(L^1)Cl] \cdot H_2O$ has been synthesized via template condensation of 1,1,1-trifluoroacetylacetone-S-methylthiosemicarbazone hydrogen iodide (L) and 2,3-dihydroxybenzaldehyde by Büşra Kaya (Figure 47). The structure of the complex has been characterized by using IR, ESI MS, and X-ray diffraction techniques. The free radical scavenging (FRS) activity and antioxidant capacity of compounds have been determined via DPPH and CUPRAC assays, respectively. Based on the obtained results by DPPH assay (Figure 48), the free radical scavenging activity of compounds is in the order of ascorbic acid>$[Fe(L^1)Cl] \cdot H_2O$>L, respectively. The results of the CUPRAC assay have confirmed the potent antioxidant capacity of iron(III) complex three times more than that of ascorbic acid as a reference (Figure 49). In conclusion, the iron(III) complex has shown potent antioxidant activity and capacity by both assays, which may originate from the phenolic hydroxyl group in the structure of the complex (Kaya, 2022).

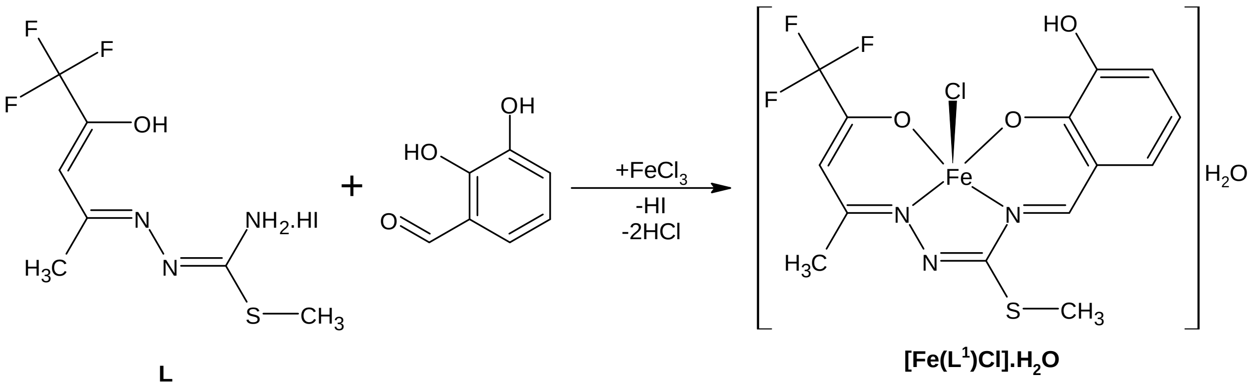


Figure 47. *The synthetic route of compounds*

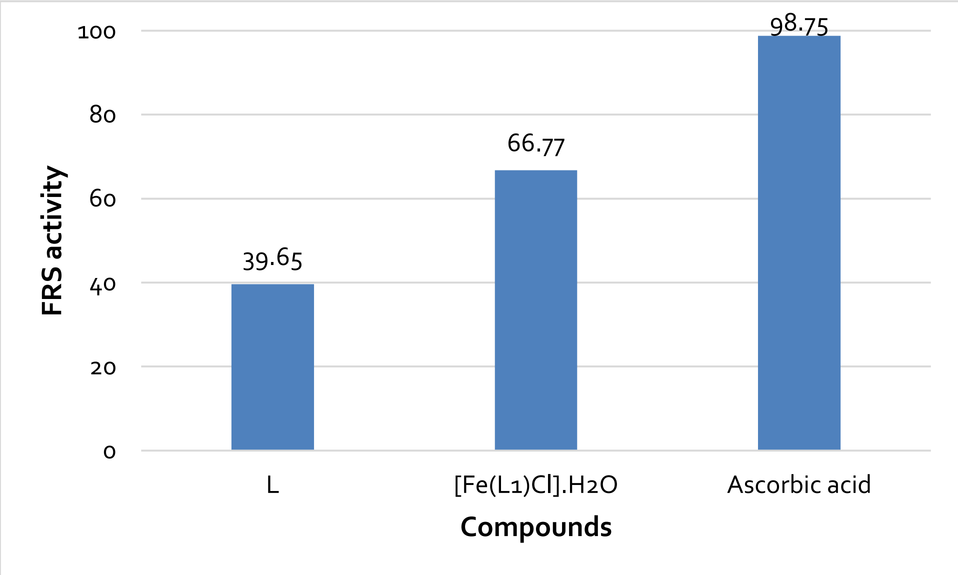


Figure 48. *The free radical scavenging (FRS) activity of compounds*

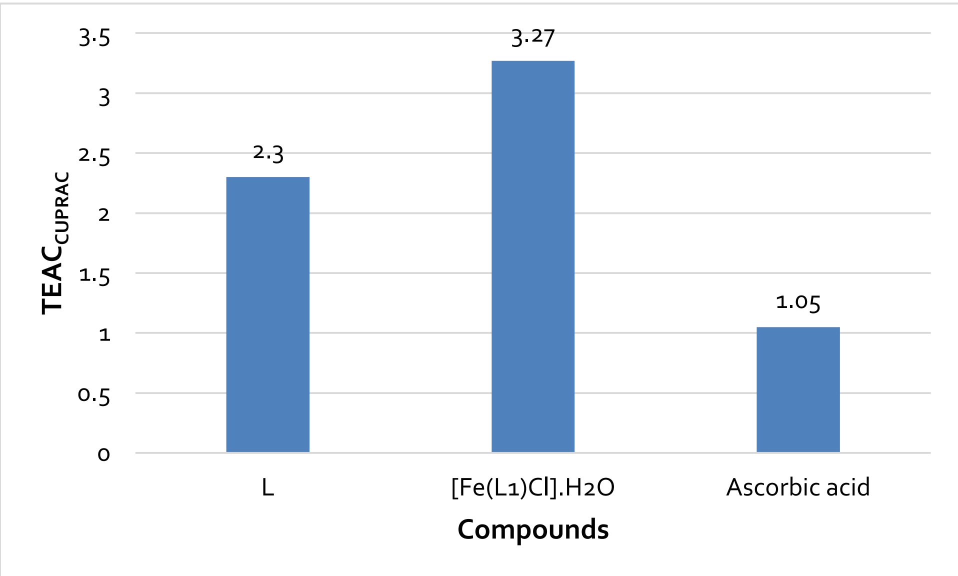


Figure 49. *The antioxidant capacity of compounds based on the CUPRAC assay*

In another study by Kathiresan et al. the synthesis and characterization of a novel thiosemicarbazone ligand (L) based on imidazole and its metal complexes Cu(II), Co(II), Ni(II) and Zn(II) (1-4) have been accomplished (Figure 50). The antioxidant activity of newly synthesized compounds has been evaluated using DPPH method. The obtained results have depicted the higher antioxidant activity of metal complexes (1, 2, and 3) as compared to the thiosemicarbazone ligand (Figure 51). Among the complexes, complex 1 has shown more potent antioxidant activity compared to standard vitamin C, while complex 4 has shown no significant antioxidant activity in the range of performed assay (Kathiresan et al., 2023).

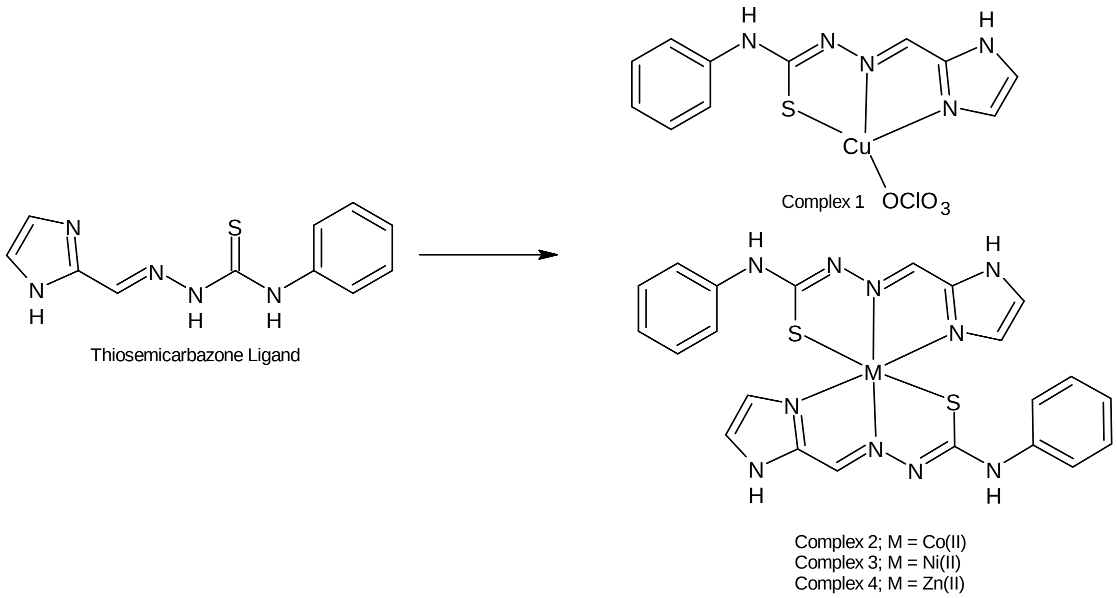


Figure 50. The synthesis of thiosemicarbazone ligand and its metal complexes.

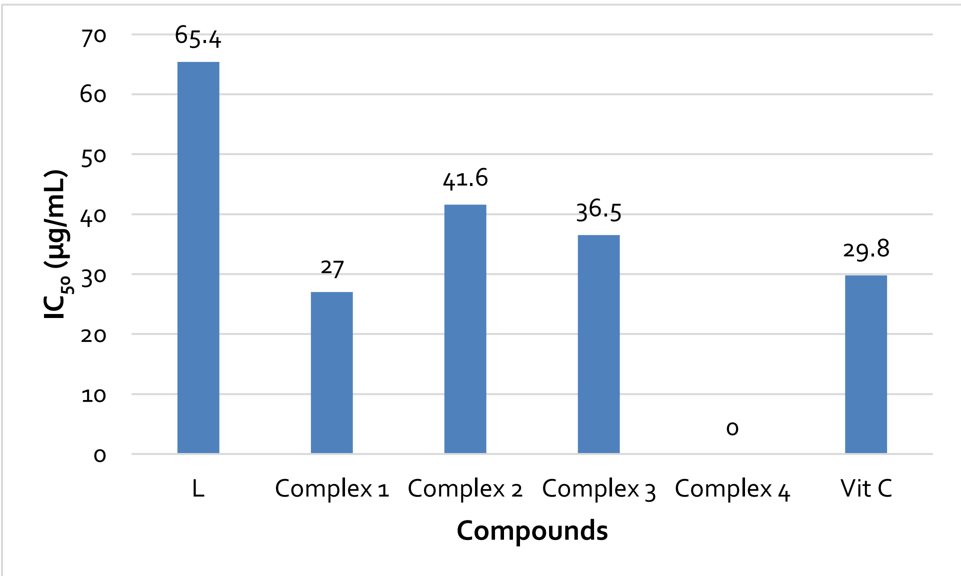


Figure 51. *The antioxidant activity of compounds is based on the DPPH assay*

Some eleven new complexes of copper(II) and nickel(II) $[Cu(L)Br]_2$ (1), [Cu(L)Cl] (2), $[Cu(L)NO_3]$ (3), [Ni(L)Cl] (4), $[Ni(HL)_2](NO_3)_2$ (5), and $[Cu(A)(L)]NO_3$, where A is 1,10-phenanthroline (6), 2,2′-bipyridine (7), 3,4-dimethylpyridine (8), 3-methylpyridine (9), pyridine (10) and imidazole (11) have been synthesized from 3-(morpholin-4-yl)propane-2,3-dione 4-allylthiosemicarbazone (HL) as starting materiel by Graur et al (Figure 52). The structures of synthesized compounds have been fully characterized by using various analytical and spectroscopic techniques. The thiosemicarbazone ligand (HL) and its metal complexes have been tested for their antiradical activity via the ABTS method. According to the obtained results (Figure 53), the introduction of nickel(II) with thiosemicarbazone ligand has resulted in the elevation of antiradical activity of compounds compared to the introduction of copper(II) ion with thiosemicarbazone ligand. Overall, the complexes (1, 2, and 3) have shown no significant antiradical activities among the other complexes, while the complexes (4 – 11) have shown even higher antiradical activities compared to the ligand and Trolox as a reference. On the other hand, complexes (8 and 9) have shown the most potent antiradical activities as compared to all tested compounds which may be due to the presence of heterocyclic groups in the structures of complexes (Graur et al., 2024).

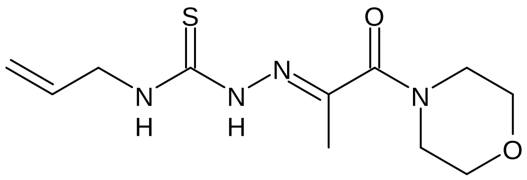


Figure 52. *The structure of the thiosemicarbazone ligand as a starting material*

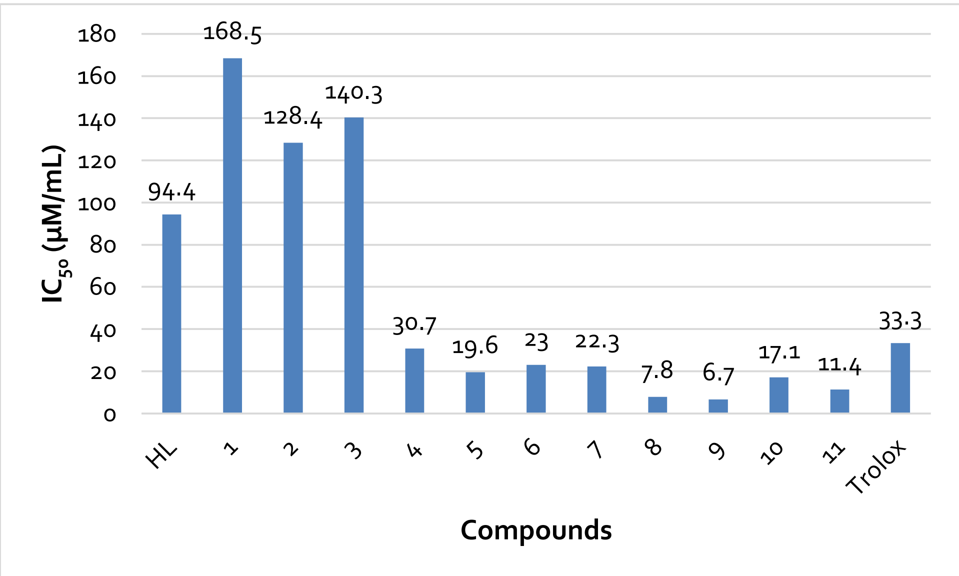


Figure 53. *The antiradical activity of compounds based on the ABTS assay*

In a study by Graur et al. the synthesis of 2-hydroxybenzaldehyde 4, S-diallylisothiosemicarbazone (HL), and its metal complexes (copper(II), nickel(II), cobalt(III), and iron(III) with the following formulas of [Cu(L)Cl] (1), [Cu(L)NO_3] (2), [Cu(3,4-Lut)(L)NO_3] (3), [Ni(L)OAc] (4), [Co$(L)_2$]Cl (5) and [Fe$(L)_2$]NO_3 (6) have been accomplished and their corresponding structures have been elucidated using elemental analysis, FTIR, molar electrical conductivity and single X-ray diffraction techniques (Figure 54). The synthesized compounds have been tested for their antioxidant activity using the ABTS assay, and based on the obtained result (Figure 55), the thiosemicarbazone ligand (HL) and metal complexes have manifested higher antioxidant activity compared to Trolox, which is used as medicine to reduce oxidative damage. Moreover, among the synthesized complexes, complex 4 has shown the most potent antioxidant activity compared to other complexes, and the order of the antioxidant activity resulted in Ni≈Fe>Co>Cu, respectively (Graur et al., 2023).

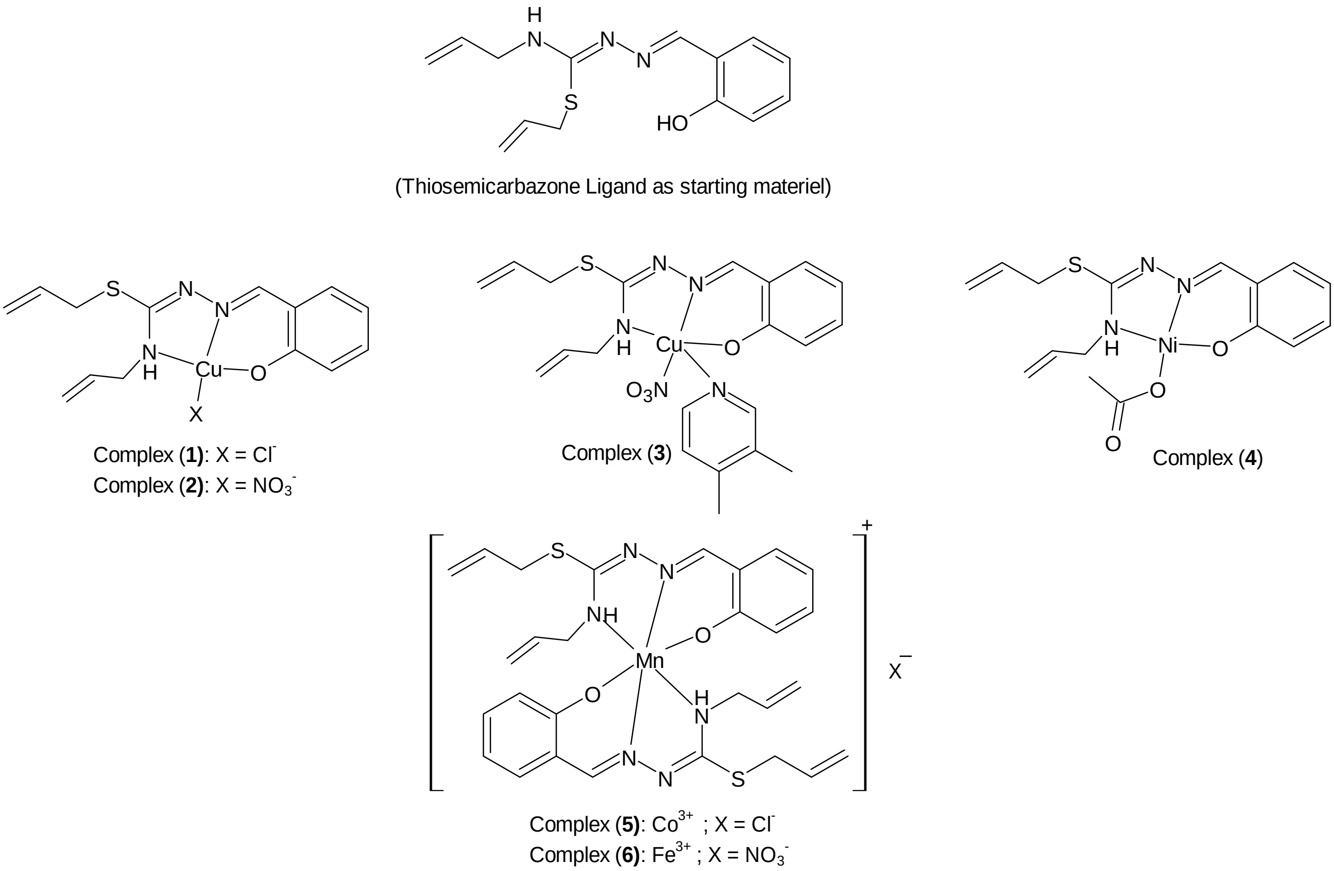


Figure 54. *The structures of thiosemicarbazone ligand and its metal complexes*

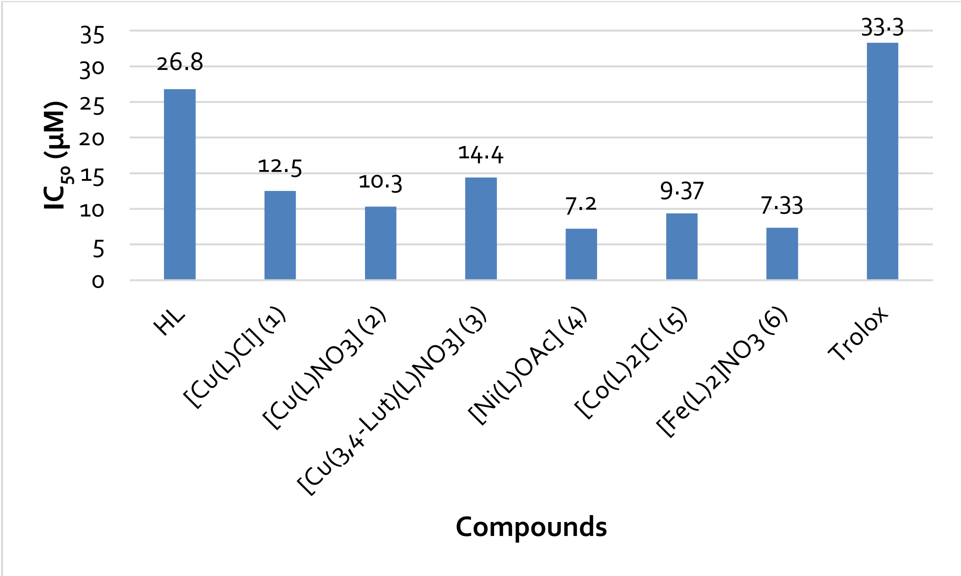


Figure 55. The antioxidant activity of compounds based on the ABTS assay.

In another study by our group, the N_2O_2-type tetradentate thiosemicarbazone ligand (5-ethoxy-2-hydroxy-acetophenone-S-methylthiosemicarbazone) has been synthesized, and from this via template reaction by addition of 2-hydroxy-benzaldehyde (1)/2-hydroxy-4-methoxy-benzaldehyde (2) as auxiliary ligands, the zinc(II) metal complexes (1 and 2) have been created (Figure 56). The antioxidant capacity and activity have been determined using CUPRAC and DPPH assays. According to the results from the CUPRAC assay (Figure 57), all the synthesized compounds have shown lower antioxidant capacity compared to Trolox as a reference. Among the compounds, complex 2 has shown a relatively higher antioxidant capacity as compared to the thiosemicarbazone ligand and complex 1. Moreover, based on the obtained results by DPPH assay (Figure 58), the thiosemicarbazone ligand (H_2L) and complex 1 have manifested some free radical scavenging activities lower than that of ascorbic acid as a reference, while in the same condition and concentration, complex 2 has shown no antioxidant activity. These fluctuations in the antioxidant capacity and activity could be described as the results of template condensation, lack of free hydroxyl group, and steric hindrance of big molecules (Poladian et al., 2023).

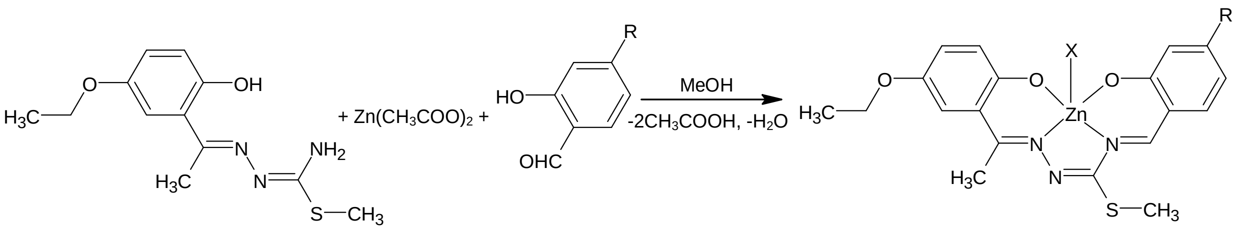


Figure 56. *The synthetic route of compounds*

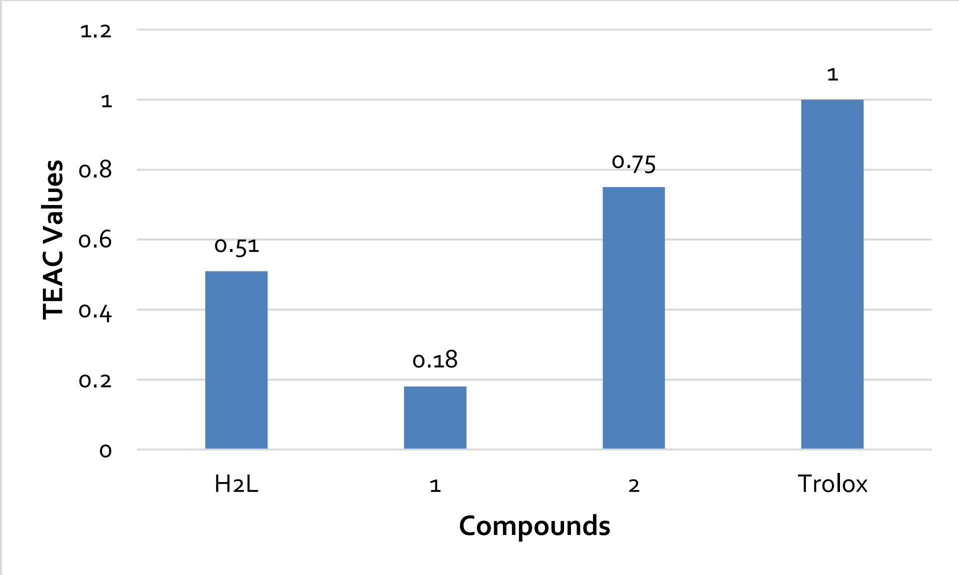


Figure 57. *The antioxidant capacity of compounds based on the CUPRAC assay*

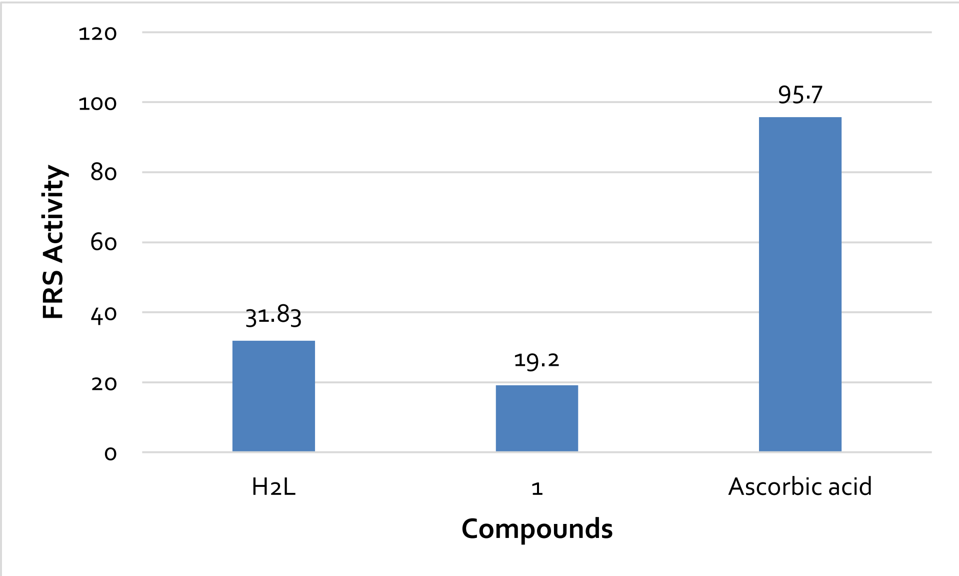


Figure 58. *The free radical scavenging (FRS) activity of compounds*

Parallel Studies

To investigate the antioxidant capacity and activity of thiosemicarbazone ligands and their corresponding transition metal complexes, three methods, such as CUPRAC, DPPH, and ABTS, have been comparatively studied. Based on the methods, to find the antioxidant capacity of thiosemicarbazone ligands and metal complexes, the CUPRAC method has been used for evaluation. The two other methods, DPPH and ABTS, have been used to determine the antioxidant activity of assayed compounds. As a sample for comparative study, Table 1 illustrates the antioxidant capacity/activity of some potent thiosemicarbazones that have been shown to have comparable antioxidant capacity/activity based on the standard antioxidants.

Table 1 *Comparative antioxidant activity/capacity of studied compounds based on the CUPRAC, DPPH, and ABTS assays as potent antioxidants*

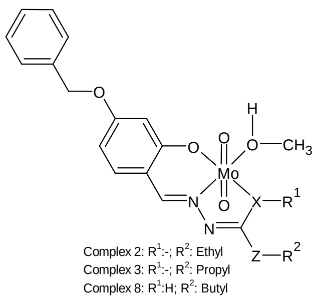
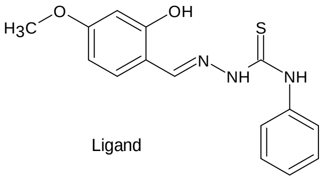
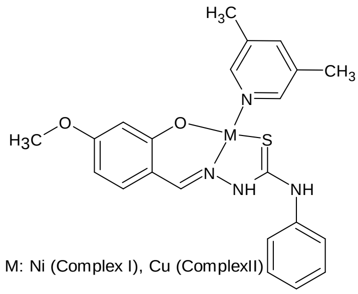
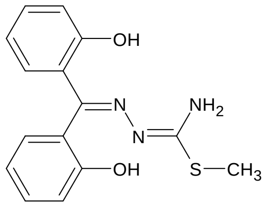
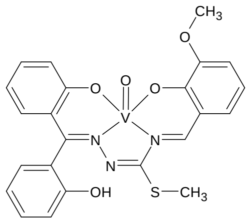
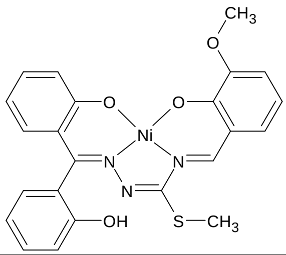
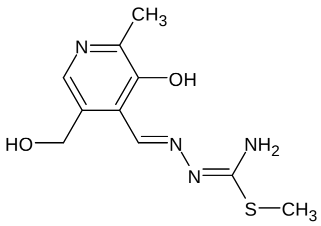
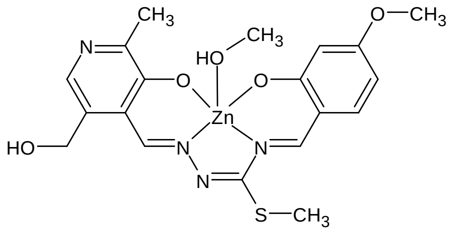
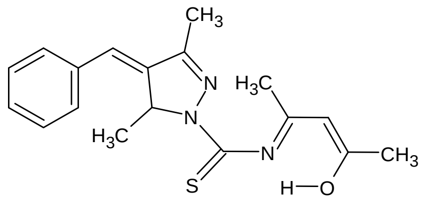
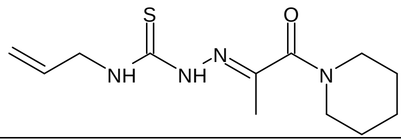
Chemical structure	Assayed samples	CUPRAC assay	DPPH assay	ABTS assay	Ref
	Complex 2	Higher than standard antioxidant	-	-	(Eğlence-Bakır et al., 2021)
	Complex 3	Higher than standard antioxidant	-	-	
	Complex 8	Higher than standard antioxidant	-	-	
	Ligand	Higher than standard antioxidant	Higher than standard antioxidant	-	(Altiparmak et al., 2021)
	Complex I	Higher than standard antioxidant	Less than standard antioxidant	-	
	Complex II	Higher than standard antioxidant	Less than standard antioxidant	-	
	1	Higher than standard antioxidant	-	-	(İlhan-Ceylan., 2020)
	2	Higher than standard antioxidant	-	-	
	3	Less than standard antioxidant	-	-	

Table 1 continued

Chemical structure	Assayed samples	CUPRAC assay	DPPH assay	ABTS assay	Ref
	Ligand (1)	Higher than standard antioxidant	Less than standard antioxidant	-	(Poladian et al., 2021)
	Complex (2)	Less than standard antioxidant	Less than standard antioxidant	-	
	Compound 6	-	-	Less than standard antioxidant	(El-Helw et al., 2019)
	Ligand (HL)	-	-	Less than standard antioxidant	(Graur et al., 2023)

Note: - standard antioxidant (Trolox and ascorbic acid), CUPric Reducing Antioxidant Capacity (CUPRAC), 2,2-di(4-tert-octyl phenyl) 1-picrylhydrazyl (DPPH), 2,2′-azino-bis (3-ethylbenzthiazoline-6-acid (ABTS), "- " not assayed

Suggestions for Future Research

Thiosemicarbazones in the form of free ligands with different chemical structures, such as chain, aromatic, and heterocyclic, and their metal complexes have various applications in chemistry, catalytic processes, enzymes, medicine, pharmacy, polymer industry, agriculture, cosmetics, dyes, and the petrochemical industry. The vast area of usage has made this group of compounds one of the most attractive research aims for researchers. As the scope of this study, the antioxidant activity/capacity of thiosemicarbazones has been explored, and the findings are highlighted in the manuscript. Through the study of antioxidant activity/capacity of thiosemicarbazones, some findings may lead to further investigation and research, which are highlighted as follows:

I. The large amount of synthesis of thiosemicarbazones as free ligands and metal complexes that are reported in research papers requires further investigation of their antioxidant activity/capacity to find the most proper compounds as antioxidant drugs.

II. Thiosemicarbazones with proper antioxidant activity/capacity, determined as an in vitro process, could be potential candidates for clinical trials and end up as usable drugs.

III. The various applications of thiosemicarbazones in other interdisciplinary areas have made them a focus point to explore their applications as further research opportunities.

IV. As it's obvious from the reported research papers, some thiosemicarbazones have shown totally no antioxidant activity/capacity or very less antioxidant activity/capacity compared to the references they have used in their research by determining via CUPRAC, DPPH, and ABTS assays, and in some other reports, these group of compounds have shown potent antioxidant activity/capacity as compared to the standard antioxidant drugs that may lead them as toxic drugs. Hence, to find the proper thiosemicarbazones as an antioxidant drug that should be comparable with standard antioxidants, further investigation and deep research are needed.

V. To find the exact application of thiosemicarbazones in various areas of interest, long-term research may help to explore the vast properties of thiosemicarbazones and their applications in the related area that are connected with this group of compounds.

Thiosemicarbazones exhibit a wide range of applications and can be synthesized through multiple routes. To identify the most effective derivatives as valuable intermediates in their respective fields, further systematic investigations are required to elucidate their physicochemical and biological properties. In particular, evaluation of their antioxidant activity and capacity by established assays such as CUPRAC, DPPH, and ABTS remains a significant area of research. Furthermore, the application of additional analytical methodologies is encouraged to provide a more comprehensive understanding of these properties.

CONCLUSION

Synthetic thiosemicarbazones as ligands and metal complexes have the ability to be good, compatible, and in some cases better antioxidant agents as compared to natural antioxidants. The antioxidant activity/capacity of thiosemicarbazone ligands and their transition metal complexes varies based on the chemical structure of ligands, the effect of different substituents, and the introduction of various transition metal ions to the chemical structure of complexes. In some thiosemicarbazones, based on the chemical structure and the existence of different groups in the structure of ligands, the ligands have shown a relatively higher antioxidant activity/capacity compared to their corresponding transition metal complexes, as stated in the manuscript. Moreover, in some other thiosemicarbazones, the introduction of transition metal ions in the chemical structure of complexes has resulted in the enhancement of the antioxidant activity/capacity of compounds. As well as the CUPRAC, DPPH, and ABTS methods that are used to determine the antioxidant activity/capacity of thiosemicarbazones, based on their working mechanisms, have shown compatible and different results for the same compounds. The synthetic antioxidants that the thiosemicarbazones exert antioxidant property, in most cases, exhibit more potent antioxidant capacity/activity as compared to natural antioxidants, which may lead to toxicity. Hence, it is the limitations of thiosemicarbazones as antioxidant drugs that need further research to find the most convenient thiosemicarbazones to act as usable antioxidants. Overall, based on the obtained results from the antioxidant activity/capacity of synthetic thiosemicarbazones, one can conclude that synthetic thiosemicarbazones have the ability to be promising antioxidant drugs for treatment purposes and have the capacity for further research.

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CONFLICT OF INTEREST STATEMENT

The author declared no conflict of interest.

DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this publication. Additional data are available from the corresponding author upon reasonable request.

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