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An Iron(III)-S-methylthiosemicarbazone Complex: Synthesis, Spectral Characterization, and Antioxidant Potency Measured by CUPRAC and DPPH Methods

Büşra Kaya*

Istanbul University-Cerrahpasa, Faculty of Engineering, Department of Chemistry, 34320, Istanbul, Turkey.

Abstract: An iron(III) complex, $[Fe(L^1)Cl].H_2O$, was synthesized by template condensation reaction of 1,1,1-Trifluoroacetylacetone-S-methylthiosemicarbazone hydrogen iodide (L) and 2,3-dihydroxybenzaldehyde in the presence of iron(III) ions. The complex was characterized by IR, ESI MS and X-ray diffraction techniques. Free radical scavenging (FRS) ability and antioxidant capacity of the S-methylthiosemicarbazone and the iron(III) complex were evaluated through DPPH and CUPRAC methods, respectively. The complex exerted better than the S-methylthiosemicarbazone in both TEAC and FRS% values. In addition, iron(III) complex was found to be 3.1 times more antioxidant than the reference ascorbic acid according to the CUPRAC method.

Keywords: Thiosemicarbazone; iron complex; X-ray analysis; antioxidant activity.

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***Corresponding author. E-mail:** busra.kaya@istanbul.edu.tr.

INTRODUCTION

Iron plays a vital role in adjusting many redox processes essential for cell homeostasis and is also substantial for cellular respiration, oxygen carry, ATP production, heme and DNA synthesis (1,2). Research on iron-based complexes to discover chemotherapeutic ingredients is often preferred in medical chemistry (3). On the other side; thiosemicarbazones are a rising class of compounds that display marked and selective antitumor activity and can overcome resistance to standard chemotherapy (4–6). The metal complexes of thiosemicarbazones show variable binding properties and structural diversity, as well as promising anticancer activities (7–10). Especially, metal complexes of S-alkylthiosemicarbazones exert significant cytotoxic activity against various cancer cells (11–13). For instance, an iron(III) complex with an N_2O_2 donor S-methylthiosemicarbazone showed a significant cytotoxicity on HeLa and HT-29 cells (14). Another iron(III)-S-metylthiosemicarbazone complex with the same donor atom set was cytotoxic in K562 cells at very low concentrations (15).

Free radicals are forms of atoms or molecules with unpaired electrons, which are unsteady and very reactive against chemical reactions (16). Under physiological conditions, specific organelles of the cell produce reactive oxygen species (ROS) as by-products of metabolism, normal respiration, and autoxidation of xenobiotics or as an outcome of stress associated with certain diseases (17,18). Therefore, it is necessary to investigate new antioxidants that can be effective in protecting organisms. Metal complexes are an alternative to the use of well-known antioxidants as they offer benefits such as variation in coordination geometry and number, and oxidation states that facilitate and support the redox processes involved in antioxidant effect (19).

Thiosemicarbazones and their metal complexes often exhibit useful antioxidant activity *in vitro* (20). In recent years, antioxidant properties of some nickel(II), manganese(III) oxovanadium(IV),

iron(III) and zinc(II) complexes with S-alkylthiosemicarbazones have been reported (21–25). In a study; oxovanadium(IV), nickel(II) and iron(III) complexes of 3-hyroxysalicylaldehyde-S-methylthiosemicarbazone have been tested according to the CUPRAC method and observed that the iron(III) complex displayed a higher TEAC value than the other complexes (26). Another study showed that iron(III) complexes of S-alkylthiosemicarbazones have usable levels of inhibition against reactive oxygen species, H_2O_2, $O_2^{\bullet-}$ and •OH (27).

To discover new iron(III) derivatives of S-alkylthiosemicarbazones with potent antioxidant activity, S-methylthiosemicarbazone (L) and its iron(III) complex $[Fe(L^1)Cl].H_2O$ were synthesized. Since it is generally assumed that the antioxidant activity is related to the number of hydroxyl groups in the phenyl ring (16), it was aimed to increase the antioxidant activity by adding a hydroxyl group to the complex structure. The structural characterization of the complex was performed using elemental analysis, IR, ESI MS and X-ray diffraction techniques. The antioxidant potential of the S-methylthiosemicarbazone and iron(III) complex was screened in the scavenging activity of DPPH• and cupric ions (Cu^{2+}) reducing power (CUPRAC) *in vitro*.

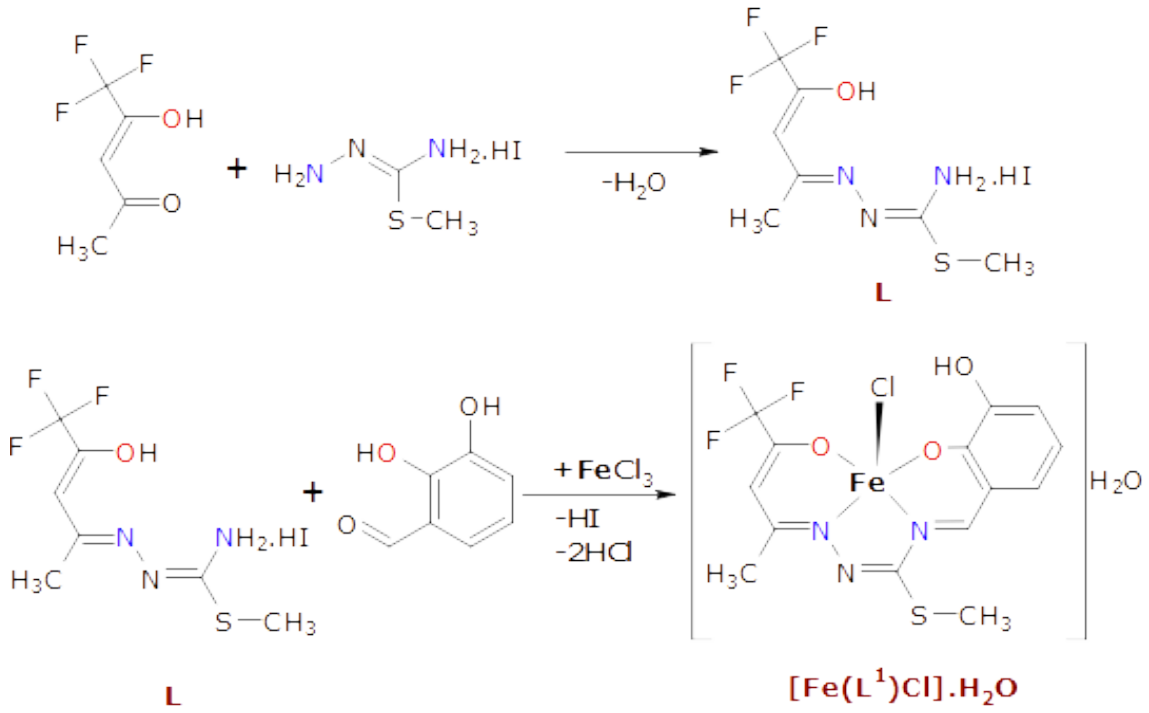

Figure 1: The synthesis of the iron(III) complex.

EXPERIMENTAL SECTION

Physical Measurements

Thermo Finnigan Flash EA 1112, Agilent Carry 630 FTIR, Varian UNITY INOVA 500 MHz NMR and Thermo Finnigan LCQ Advantage Max LC/MS were used for elemental, IR, NMR and ESI MS analysis, respectively. Magnetic moment measurement was performed using the Gouy technique with Sherwood Scientific's MK I model device at room temperature.

The crystallographic data for the suitable crystal of $[Fe(L^1)Cl].H_2O$ was collected at room temperature with a D8-QUEST diffractometer equipped with graphite-monochromatic Mo-Kα radiation. Following procedures was used for analysis: solved by direct methods; SHELXS-2013 (28); refined by full-matrix least-squares methods; SHELXL-2013 (29); data collection: Bruker APEX2 (30); molecular graphics: MERCURY (31); solution: WinGX (32). The crystallographic data of the complex are listed in Table 1 and selected bond distances and angles, in Table 2.

Synthesis

Starting material, 1,1,1-Trifluoro-acetylacetone-S-methylthiosemicarbazone hydrogen iodide (L), was prepared in accordance with a standard procedure reported earlier (33,34). Briefly, 1,1,1-Trifluoroacetylacetone and S-methylthiosemicarbazide hydrogen iodide were reacted in ethanol. The resulting cream colored compound was filtered and dried *in vacuo*. Elemental analysis and spectroscopic data for the thiosemicarbazone was confirmed its preparation.

Yield: 2.42 g, 65.0%; m.p. (°C): 149; Calc. for $C_7H_{11}N_3OSF_3I$ (M_r=369.14), %: C, 22.78; H, 3.00; N,

11.38; S, 13.04. Found, %: C, 22.51; H, 2.75; N, 11.43; S, 12.75. IR (cm^{-1}): $\nu_{as}(NH_2)$ 3352, $\nu_s(NH_2)$ 3250, ν(OH) 3040, $\delta(NH_2)$ 1641, ν(C=N) 1624, 1547. ^{1}H NMR (ppm): 9.84 (s, 2H, N*H*$_2$), 9.46 (s, 1H, O*H*), 3.70 (s, 2H, -C*H*$_2$-), 2.63 (s, 3H, S-C*H*$_3$), 2.12 (s, 3H, C-C*H*$_3$). m/z ESI MS (relative abundance%): [M-I] 242.0 (100%).

The iron(III) complex was synthesized using the literature methods (14,33). 1,1,1-Trifluoroacetylacetone-S-methylthiosemicarbazone hydrogen iodide (0.37 g, 1 mmol) and 2,3-dihydroxybenzaldehyde (0.14 g, 1 mmol) were dissolved in ethanol (10 mL) and the solution was added to a solution of $FeCl_3.6H_2O$ (0.27 g, 1 mmol) in ethanol (5 mL). Et_3N (0.1 mL) was added and the mixture was left to stand at room temperature for 6-8 hours. The solid was filtered off and recrystallized from a mixture of ethanol-dichloromethane (1:3).

Yield: 0.16 g, 35%. M.p. 275 °C. μ_{eff} (μ_B): 5.89. Anal. Calc. for $C_{14}H_{14}ClF_3FeN_3O_4S$ (468.64 g.mol^{-1}): C, 35.88; H, 3.01; N, 8.97; S, 6.84. Found: C, 35.53; H, 2.79; N, 8.71; S, 6.48%. IR: ν(OH) 3477-3442; ν(C=N^1) 1602; ν(N^2=C) 1578; ν(N^4=C) 1530. m/z ESI MS (relative abundance%): [M-H_2O-Cl] 415.1 (30.58%), 416.1 (6.51%), 417.2 (2.43%), [(M-H_2O-Cl)+CH_3OH] 446.5 (100%), 447.6 (16.30%), 448.5 (5.99%), [(M-H_2O-Cl) +CH_3OH+SCH_3] 492.9 (46.85%), 493.9 (9.76%), 494.8 (5.93%), [(M-H_2O)+Na+CH_3] 487.9 (27.52%), 488.9 (5.56%), 490.9 (2.71%).

Antioxidant Tests

1 mL of 1.10^{-4} M each compound was added to 2 mL of the DPPH (2,2-diphenyl-1-picrylhydrazyl) solution (4 mg/100 mL) and the final volume was completed to 4 mL using methanol. Reference solution was obtained by adding 2 mL of methanol to 2 mL of DPPH. The mixture was shaken and incubated. After 30 min absorbances were measured at 515 nm (35). The percentage of scavenging activity was calculated from the following equation: Radical scavenging activity(%) = [($A_{control}$ – A_{sample})/$A_{control}$] × 100.

CUPRAC (Cupric ion reducing antioxidant capacity) method was applied for determining cupric ions reducing potentials of the compounds (36). Briefly, 1 mL of each $CuCl_2$ (10 mM), neocuproine (Nc, 7.5 mM) and NH_4CH_3COO (1 M) solutions were added to the samples at 4.88-24.4 µM concentrations. Each of the volumes was adjusted to 4.1 mL with distilled water and incubated for 30 min. The increasing absorbance at 450 nm indicates the cupric reducing potential of the compounds. Trolox equivalent antioxidant capacities as TEAC values were calculated as the ratio of the molar absorption of each compound to that of trolox (ε_{trolox}: $1.58x10^4$ L mol^{-1} cm^{-1}).

RESULTS AND DISCUSSION

Synthesis and Structural Description

The thiosemicarbazone (L) was prepared by reacting 1,1,1-Trifluoroacetylacetone with S-methylthiosemicarbazide hydrogen iodide. The iron(III) complex, [Fe(L^1)Cl].H_2O, was synthesized by the reaction of equimolar ratio of 1,1,1-Trifluoroacetylacetone-S-methylthiosemicarbazone hydrogen iodide, the iron(III) salt ($FeCl_3.6H_2O$) and 2,3-dihydroxybenzaldehyde (Figure 1). The complex was obtained as black-looking crystals and it was soluble in solvents, such as $CHCl_3$, CH_2Cl_2, DMF, DMSO, and MeOH. The elemental analysis value and spectroscopic data were consistent with the proposed formulation of the iron(III) complex. The effective magnetic moment value of the complex was μ_{eff} = 5.89 μ_B, which corresponds to a high-spin state of iron(III) (37,38).

In the infrared spectra of the thiosemicarbazone, the $\nu_{as}(NH_2)$, $\nu_{as}(NH_2)$ and $\delta(NH_2)$ bands were observed at 3352, 3250 and 1641 cm^{-1}, respectively (Figure S3), were not present in the spectrum of the complex due to chelation. The band associated with the -OH bending mode at 3040 cm^{-1} was not seen in the spectrum of the complex because thiosemicarbazone is involved in complex formation with the deprotonated form. The ν(OH) bands of the 3-substituted hydroxyl group on the aromatic ring and one H_2O molecule in the complex structure were recorded around 3460 cm^{-1} (Figure S4). The C=N stretching bands of the thiosemicarbazone were observed at 1623 and 1541 cm^{-1}. After the formation of the complex, the ν(N^4=C) band of a new imine group formed by condensation of the thioamide nitrogen (N^4) and aldehyde was recorded at 1530 cm^{-1}.

The ESI MS data of the compounds were collected in positive ion mode using methanol (Figures. S1 and S2). For the thiosemicarbazone, the base peak (100% relative abundance) was registered at m/z 242 assigned to [M-I] structure. The monoisotopic mass of iron(III) complex, with the formula $C_{14}H_{14}ClF_3FeN_3O_4S$, is 467.97 Da and it was not seen prominently in the spectrum. The main peak of the complex was recorded at m/z 446.5 (100% relative abundance), along with a cluster of isotopes at m/z 447.6 and 448.5, which is related to [(M-H_2O-Cl) +CH_3OH]. The secondary noticeable peak was observed at m/z 492.9 (46.85%), attributed to [(M-H_2O-Cl)+CH_3OH+SCH_3], and it also showed isotope peaks at m/z 493.9 and 494.8. The cation adduct formation, [(M-H_2O)+Na+CH_3], was recorded in the range of m/z 487.9-490.9. The peak belonged to [M-H_2O-Cl] structure was recorded at m/z 415.1 (30.58% relative abundance) and it showed isotope peaks at m/z 416.1 and 417.2.

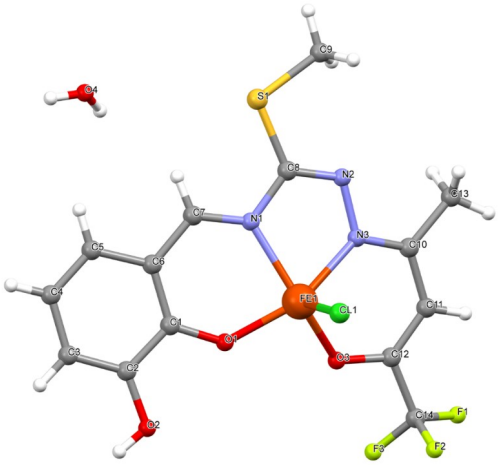

Figure 2: The molecular structure of $[Fe(L^1)Cl].H_2O$, showing the atom numbering scheme.

X-ray Analysis

The molecular structure of $[Fe(L^1)Cl].H_2O$ is shown in Figure 2 with an atom numbering scheme. The asymmetric unit of complex $[Fe(L^1)Cl].H_2O$ contains one Fe(III) ion, one L^1 ligand, one coordinated chlorine atom and one non-coordinated water molecule. The Fe(III) ion is coordinated by two oxygen [Fe1-O1= 1.893(2) Å and Fe1-O3= 1.935(3) Å] and two nitrogen atoms [Fe1-N1= 2.083(3) Å and Fe1-N3= 2.075(3) Å] from the thiosemicarbazidato structure and chlorine atom [Fe1-Cl1= 2.2114(13) Å]. The tau value, [τ =(β-α)/60, α and β being the two largest angles around the central atom], can be usefully used to estimate the degree of distortion from a square pyramidal to trigonal bipyramid structures. For an ideal square pyramidal geometry, the τ value is equal to zero, while it becomes one for a perfect trigonal bipyramidal geometry (39). The value of τ for the iron(III) ion is 0.09, indicating a distorted square pyramid. The molecules of $[Fe(L^1)Cl].H_2O$ are connected by O-H···O and O-H···F hydrogen bonds (Table 3). The O4 atom of water molecule at (x, y, z) acts as a hydrogen-bond donor, via H4A atom, to $O3^{ii}$ and $F3^{ii}$ atoms, forming a $R_1^2(5)$ ring. Similarly, the O4 atom at (x, y, z) acts as a hydrogen-bond donor, via H4B atom, to $O1^{ii}$ and $O2^{ii}$ atoms, forming a $R_1^2(5)$ ring. The combination of hydrogen bonds produces edge-fused $R_1^2(5)$, $R_2^2(6)$ and $R_4^4(8)$ rings (Figure 3).

Table 1: Crystal data and structure refinement parameters for $[Fe(L^1)Cl].H_2O$.

CCDC	2132527
Empirical formula	$C_{14}H_{14}ClF_3FeN_3O_4S$
Formula weight	468.64
Space group	P-1
Crystal system	Triclinic
a (Å)	7.928 (3)
b (Å)	8.744 (3)
c (Å)	14.269 (5)
α (º)	97.039 (11)
β (º)	94.454 (11)
γ (º)	109.047 (9)
D_c (g cm^{-3})	1.691
V (Å^3)	920.6 (6)
μ (mm^{-1})	1.13
Z	2
Independent refls.	4578
Measured refls.	35138
S	1.12
R_{int}	0.047
R1/wR2	0.055/0.143
T_{max}/T_{min}	1.03/-0.43

Table 2: Selected bond distances (Å) and angles (º) for [Fe(L^1)Cl].H_2O.

Fe1-O1	1.893(2)	Fe1-O3	1.935(3)
Fe1-N3	2.075(3)	Fe1-N1	2.083(3)
Fe1-Cl1	2.2114(13)		
O1-Fe1-O3	92.96(11)	O1-Fe1-N3	149.45(12)
O3-Fe1-N3	87.52(12)	O1-Fe1-N1	86.99(11)
O3-Fe1-N1	143.46(12)	N3-Fe1-N1	75.02(11)
O1-Fe1-Cl1	106.66(9)	O3-Fe1-Cl1	107.63(10)
N3-Fe1-Cl1	102.24(9)	N1-Fe1-Cl1	107.33(9)

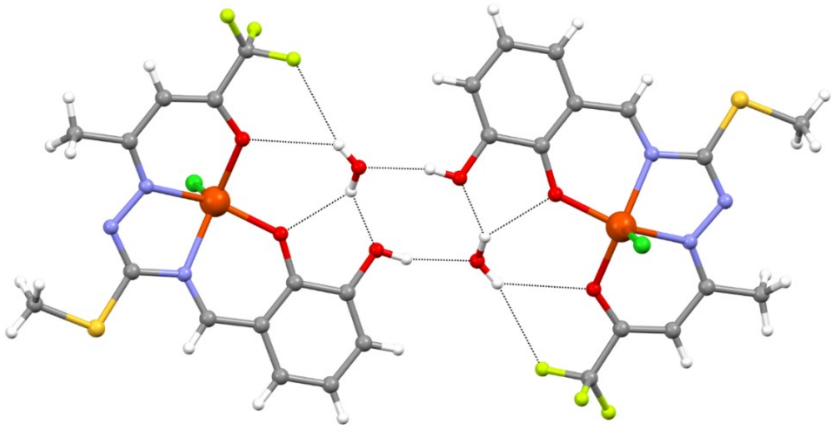

Figure 3: Crystal structure of [Fe(L^1)Cl].H_2O, showing the formation of $R_1^2(5)$, $R_2^2(6)$ and $R_4^4(8)$ rings.

Table 3: Hydrogen-bond parameters for [Fe(L^1)Cl].H_2O (Å, º).

D-H· · ·A	D-H	H···A	D···A	D-H···A
O2—H2···O4^{i}	0.82	1.94	2.740 (4)	164
O4—H4A···F3^{ii}	0.79 (7)	2.52 (7)	3.292 (6)	166
O4—H4A···O3^{ii}	0.79 (7)	2.57 (7)	3.136 (4)	130
O4—H4B···O1^{ii}	0.85 (7)	2.28 (7)	2.978 (4)	140
O4—H4B···O2^{ii}	0.85 (7)	2.25 (7)	3.009 (5)	149

Symmetry codes: (i) x−1, y−1, z; (ii) −x+1, −y+1, −z+1.

Antioxidant Properties

The DPPH radical is stable and commonly used for specifying the capability of an antioxidant agent (40). The result reveals that free radical (DPPH) scavenging activity follows the order: ascorbic acid > [Fe(L^1)Cl].H_2O > L (Table 4). According to this order, the iron complex is a more active radical scavenger than the free thiosemicarbazone (L). This might be due to the phenolic hydroxyl group in the complex structure. Based on the literature data, it was confirmed that the radical scavenging activities of the compounds were quite controlled by the number of phenolic hydroxyl groups (41,42). Among synthetic antioxidants, TBHQ with two hydroxyl groups has been shown to be a more potent antioxidant than BHA and BHT with one hydroxyl group (16). In a study, the DPPH assay showed that the ruthenium thiosemicarbazone complex is a more potent scavenger than the nickel thiosemicarbazone complex because it has two free hydroxyl groups (43). It was also reported that zinc(II) complexes containing four free hydroxyl groups showed remarkable scavenging activity (44).

Table 4: The free radical scavenging (FRS) activity as inhibition ratio %.

Compounds	FRS activity
L	39.65±2.43
[Fe(L^1)Cl].H_2O	66.77±1.44
Ascorbic acid	98.75±1.45

The CUPRAC method is based on the ability of a compound to reduce a [Cu(II)-Nc] complex to a [Cu(I)-Nc] complex. (19). The TEAC coefficients are given in Table 5. According to the results, the antioxidant capacity of both iron(III) complex and free thiosemicarbazone was superior to standard ascorbic acid. Especially, the TEAC value of the iron(III) complex was found to be 3.1 times higher than the value of ascorbic acid. Similar to the antiradical activity, the antioxidant capacity obtained for the iron(III) complex was also higher than for the free thiosemicarbazone.

In the literature, the antioxidant activity of the metal complexes was found to be higher (45,46) or lower (47,48) than the corresponding free ligands. The CUPRAC assay demonstrated that Zn(II), Co(II), Cu(II) and Ni(II) complexes of a chicoric acid ligand increased antioxidant properties compared to their free ligands (49). In another study, the antioxidant activity of the Zn(II) complex of chlorogenic acid ligand was tested and it was found that coordination with the metal nucleus increases the ability to reduce the ligand by about 1.5 times (50).

Table 5: The TEAC coefficients with regard to the CUPRAC assay.

Compounds	Molar absorptivity (L mol^{-1} cm^{-1})	$TEAC_{CUPRAC}$	Correlation coefficient (r)
L	3.6361 x 10^4	2.30 ± 0.15	0.9993
[Fe(L^1)Cl].H_2O	5.1590 x 10^4	3.27 ± 0.41	0.9977
Ascorbic acid	1.6590 x 10^4	1.05 ± 0.22	0.9989

CONCLUSION

The new iron(III) complex with S-methylthiosemicarbazone was synthesized and structurally confirmed. The crystal analysis showed that the complex had 6,5,6-membered chelate rings formed by coordination of the two oxygen and nitrogen atoms on the thiosemicarbazidato structure to the iron(III). The fifth coordination was completed with a chlorine atom, and coordination geometry around iron(III) could be defined as a distorted square pyramid.

The cupric ions (Cu^{2+}) reducing power (CUPRAC) and DPPH• scavenging activity of the synthesized S-methylthiosemicarbazone and iron(III) complex were studied. TEAC values showed that the iron(III) complex had a higher antioxidant capacity than the free thiosemicarbazone and ascorbic acid, and its DPPH radical scavenging ability was higher than that of the free thiosemicarbazone. The superior antioxidant properties of the iron(III) complex might be due to the presence of the hydroxyl group in the phenyl ring. Consequently, the complex with potent antioxidant activity is a promising component for research related to oxidative stress-induced diseases and likely cancers.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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An Iron(III)-S-methylthiosemicarbazone Complex: Synthesis, Spectral Characterization, and Antioxidant Potency Measured by CUPRAC and DPPH Methods

SUPPLEMENTARY INFORMATION

Büşra Kaya*

Istanbul University-Cerrahpasa, Faculty of Engineering, Department of Chemistry, 34320, Istanbul, Turkey.

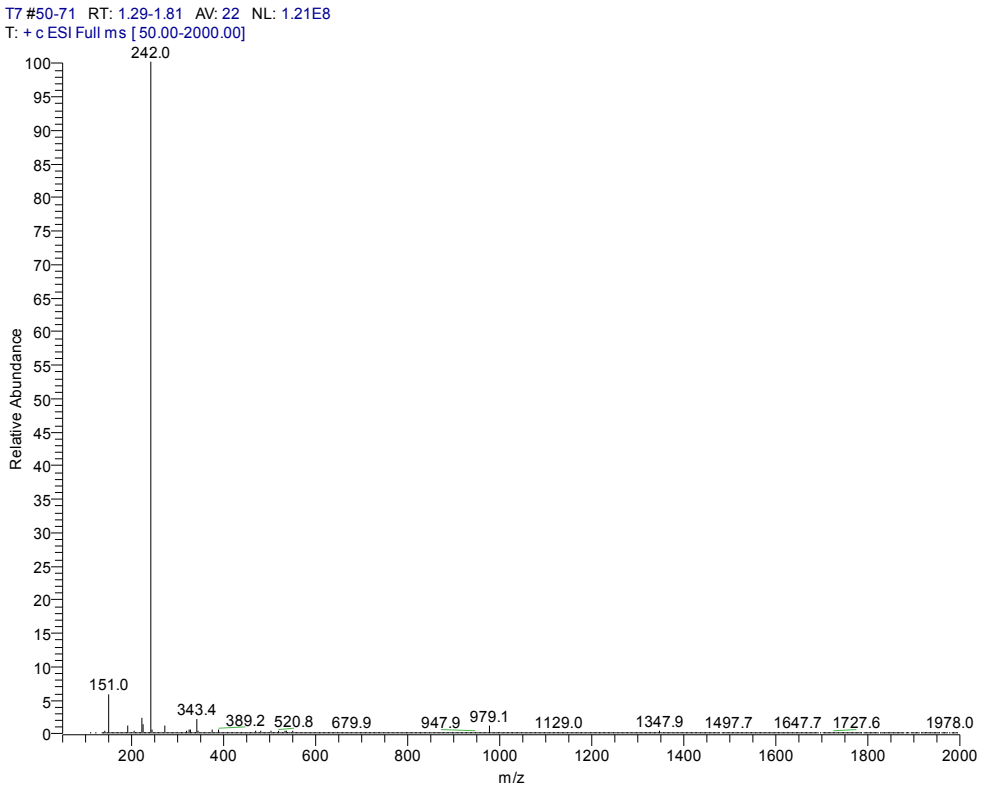

Figure S1: ESI MS of L in MeOH.

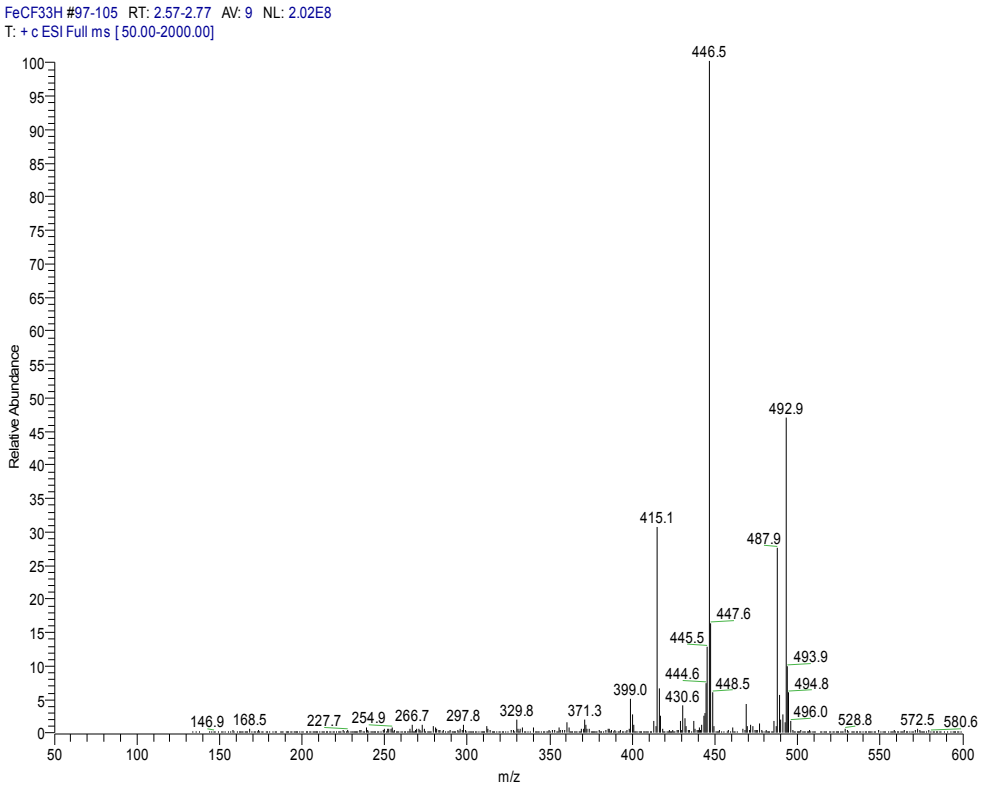

Figure S2: ESI MS of $[Fe(L^1)Cl].H_2O$ in MeOH.

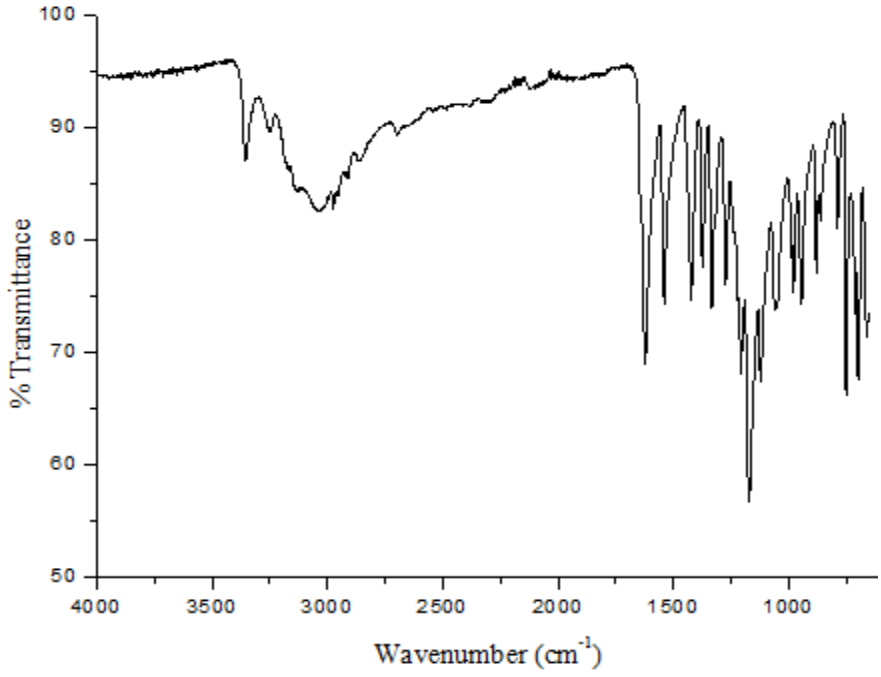

Figure S3: IR spectrum of L.

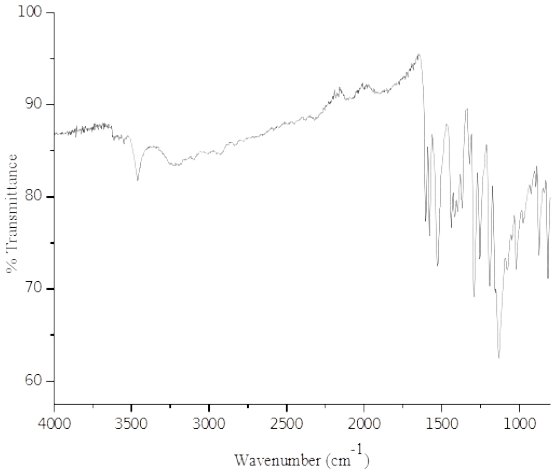

Figure S4: IR spectrum of $[Fe(L^1)Cl].H_2O$.

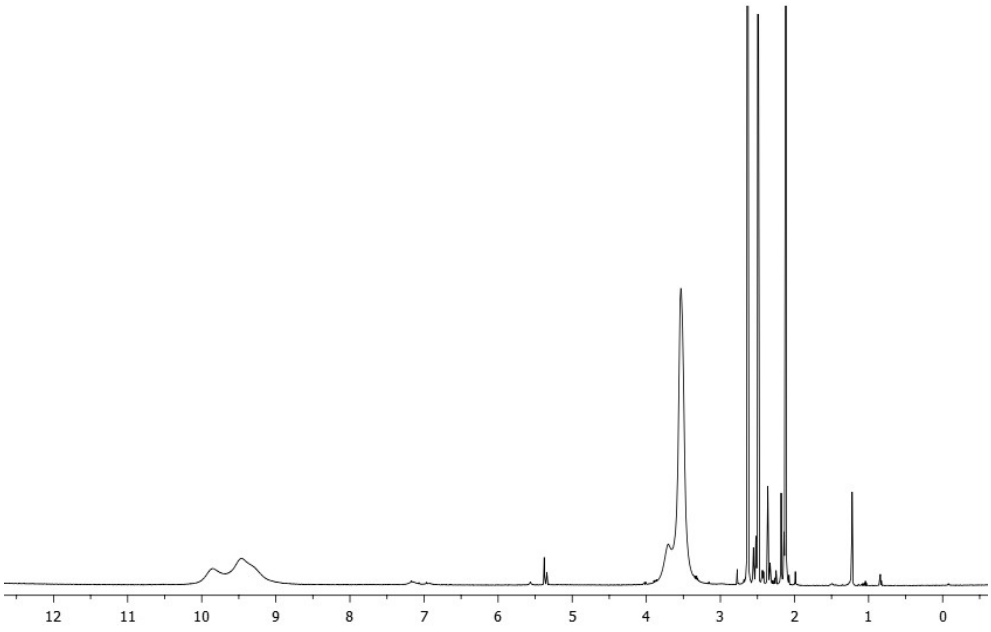

Figure S5: ^1H NMR spectrum of **L** in DMSO-d_6.