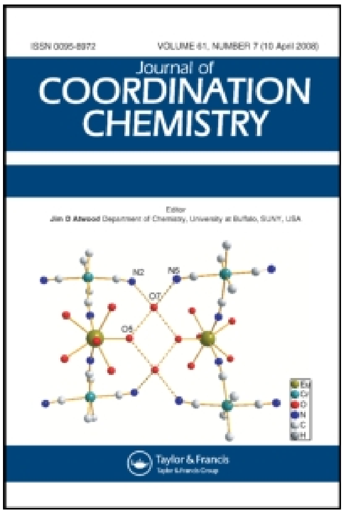

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Iron(III) and nickel(II) template complexes derived from benzophenone thiosemicarbazones

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New iron(III) and nickel(II) chelates were synthesized by template reaction of 2,4-dihydroxy- and 2-hydroxy-4-methoxy-benzophenone *S*-methylthiosemicarbazones with 2-hydroxy- and 5-bromo-2-hydroxy-benzaldehydes. The template complexes were isolated as stable solids and characterized by elemental analysis, conductivity and magnetic measurements, IR, ^{1}H NMR, UV–Visible, and mass spectra. The crystal structure of N^1-(2-hydroxy-4-methoxyphenyl)(phenyl)methylene-N^4-(2-hydroxy-phenyl)methylene-*S*-methyl-thiosemicarbazidato-Fe(III) was determined by X-ray diffraction. A five-coordinate, distorted square-pyramidal geometry was established crystallographically for the iron(III) complex. Cytotoxicity and proliferation properties were determined using human erythromyeloblastoid leukemia and HL-60 mouse promyelocytic leukemia cell lines. For K 562 and HL-60 cells, compounds **1a** and **2b** were found to be cytotoxic at concentrations of 10 and $20\,\mu g\,mL^{-1}$.

Keywords: Thiosemicarbazone; 2-hydroxybenzophenone; Iron(III) and nickel(II); Crystal structure; Cytotoxicity properties

1. Introduction

Thiosemicarbazones and their metal chelates have a wide range of biological activities depending on the parent carbonyl compounds and metal ion [1]. After chemotherapeutic effective platinum complexes of thiosemicarbazide derivatives were isolated [2], a large number of thiosemicarbazone complexes have been synthesized and their biological acitivities have been investigated. In addition to antitumor effects of transition metal complexes of thiosemicarbazones [3–5], they also show antimicrobial [6–8], antiviral [9–11], antioxidant [12], and cytotoxic [13, 14] effects.

Numerous template complexes based on 2-hydroxy-benzaldehyde or acetylacetone thiosemicarbazones, especially their Fe(III) and Ni(II) compounds, have been synthesized [15–20]. Also, limited template complexes with cobalt(II) [21, 22], zinc(II) [23, 24], uranyl(II) [25–27], vanadyl(II) [28, 29], and palladium(II) [30] were reported.

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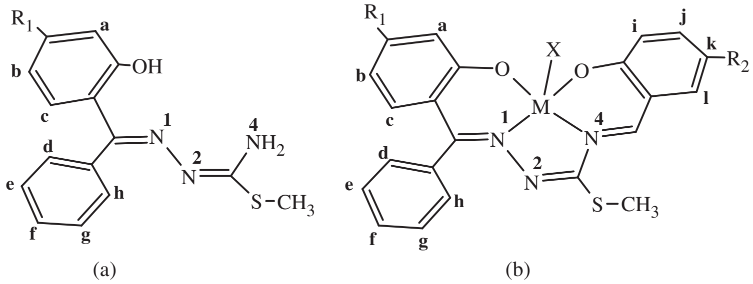

Figure 1. (a) The benzophenone thiosemicarbazones R: OH (**1**), CH_3O (**2**). (b) The templates. Metal/R_1/R_2/X: Fe/OH/H/Cl (**1a**), Ni/OH/H/– (**1b**), Fe/CH_3O/H/Cl (**2a**), Ni/CH_3O/H/– (**2b**), Fe/CH_3O/Br/Cl (**2c**), Ni/CH_3O/Br/– (**2d**).

In this work, we present the synthesis and characterization of new iron(III) and nickel(II) template complexes derived from benzophenone *S*-methylthiosemicarbazones, **1** and **2** (figure 1a). In the course of our investigation on structural and cytotoxic properties of thiosemicarbazone derivatives [14], the template compounds N^1-(2-hydroxy-4-R_1-phenyl)(phenyl)methylene-N^4-(2-hydroxy-5-R_2-phenyl)methylene-*S*-methyl-thiosemicarbazidato-Fe(III)/Ni(II) (**1a–b, 2a–d**) (figure 1b) were characterized by elemental analysis, conductivity and magnetic measurements, IR, ^1H NMR, UV–Visible (UV–Vis), and mass spectroscopies. The structure of iron template (**2a**) was determined by single crystal X-ray diffraction. Cytotoxicity and proliferation properties of the compounds were investigated by using K562 chronic myeloid leukemia and HL-60 mouse promyelocytic leukemia cell lines.

2. Experimental

2.1. *Chemicals and apparatus*

All chemicals were of reagent grade and used as commercially purchased. Analytical data were obtained with a Thermo Finnigan Flash EA 1112 analyser and Unicam Solar 929 atomic absorption spectrometer. IR spectra were recorded as KBr disks with a Mattson 1000 FT-IR spectrometer. UV–Vis spectra were obtained on a ATI-Unicam UV–Vis spectrometer UV2 Series. The ^1H NMR spectra were recorded on a Varian UNITY INOVA 500 MHz spectrometer. The ESI-MS analyses were carried out in positive and negative ion modes using a Thermo Finnigan LCQ Advantage MAX LC/MS/MS. Molar conductivities were measured using a digital CMD 750 conductivity meter. Magnetic measurements were carried out at room temperature by the Gouy technique with an MK I model device obtained from Sherwood Scientific.

2.2. *X-ray structure solution and refinement*

The crystals of the templates were grown from saturated CH_2Cl_2 solutions at different temperatures, and a single crystal of **2a** suitable for X-ray diffraction studies was obtained at 15°C.

A black crystal prism of $C_{23}H_{19}ClFeN_3O_3S$ having dimensions 0.50 × 0.30 × 0.20 mm was mounted on a glass fiber. All measurements were made on a Rigaku RAXIS RAPID imaging plate area detector with graphite monochromated Mo-Kα radiation. The data were corrected for Lorentz and polarization effects. An empirical absorption correction was applied, which resulted in transmission factors ranging from 0.79 to 1.00. Unique F^2 data (4930) were used in the final cycle of the full-matrix least-squares refinement of 308 variables. The structure was solved by direct methods using the program SIR92 [31]. Hydrogen atoms were refined using the riding model and non-hydrogen atoms were refined anisotropically. All calculations were performed using the Crystal Structure crystallographic software package [32, 33].

2.3. *Synthesis of the benzophenone S-methylthiosemicarbazones*

The *S*-methylthiosemicarbazones, **1** and **2**, were prepared with small modifications of general methods [34, 35]. About 3 mmol of 2,4-dihydroxybenzophenone (or 2-hydroxy-4-methoxy) thiosemicarbazone was dissolved in 8 mL THF at 60°C on a water bath. To this solution, 3.6 mmol of methyl iodide was added and the mixture was allowed to stand at room temperature for 24 h. The precipitated hydroiodide salt was filtered and washed with 5 mL of cold diethyl ether. The colorless product was dissolved in 5 mL alcohol by heating and neutralized with a sufficient amount of aqueous $NaHCO_3$ solution (%10, w/w). The precipitate was collected by filtration and washed with 5 mL portions of water and diethylether, respectively. Recrystallization of the crude product from ethanol gave pure compound.

1: White, m.p. 184.8–186.0°C, yield 61%, Anal. Calcd for $C_{15}H_{15}N_3O_2S$ (301.36 g mol^{-1}): C, 59.78; H, 5.02; N, 13.94; S, 10.64. Found: C, 59.81; H, 4.98; N, 13.88; S, 10.59%. UV–Vis (in DMF): λ_{max}, nm(log ε): 233 (4.64), 266 (4.19), 302 (4.23), 334 (4.26). FT-IR (KBr, cm^{-1}): ν(2-OH) 3453, ν_a(NH) 3345, ν(4-OH) 3172, ν_s(NH) 3141, ν(C=N^1) 1628, ν(N^2=C) 1597, ν(C–O) 1120, ν(C–S) 746. ^{1}H NMR (DMSO-d$_6$, 500 MHz, 25°C, δ ppm): 11.03, 10.46 (*cis*/*trans* ratio: 2/1, s, 1H, 2-OH), 9.59 (s, 1H, 4-OH), 6.64 (s, 2H, NH_2), 7.60 (d, 1H, *f*), 7.45–7.43 (m, 2H, *d*, *h*), 7.35–7.33 (m, 2H, *e*, *g*), 6.68 (d, 1H, *c*), 6.31 (d, 1H, *a*), 6.24 (d, 1H, *b*), 2.41, 2.36 (*cis*/*trans* ratio: 3/2, s, 3H, S–CH_3).

2: White, m.p. 122.8–124.2°C, yield 94%, Anal. Calcd for $C_{16}H_{17}N_3O_2S$ (315.39 g mol^{-1}): C, 60.93; H, 5.43; N, 13.32; S, 10.17. Found: C, 60.85; H, 5.39; N, 13.30; S, 10.11%. UV–Vis (in DMF): λ_{max}, nm(log ε): 237 (4.61), 260 (4.34), 320 (4.47). FT-IR (KBr, cm^{-1}): ν(2-OH) 3437, ν_a(NH) 3410, ν_s(NH) 3330, ν(C=N^1) 1612, ν(N^2=C) 1585, ν(C–O) 1112, ν(C–S) 742. ^{1}H NMR (DMSO-d$_6$, 500 MHz, 25°C, δ ppm): 10.19 (s, 1H, 2-OH), 8.40, 8.24 (*cis*/*trans* ratio : 1/1, s, 2H, NH_2), 7.67 (d, 1H, *d*, *h*), 7.37–7.33 (m, 3H, *e*, *f*, *g*), 6.97 (d, 2H, *a*), 6.62 (d, 1H, *c*), 6.60 (d, 1H, *b*), 3.80 (s, 3H, 4-OCH_3), 2.42 (s, 3H, S–CH_3).

2.4. *Synthesis of the iron(III) template (2a)*

One millimole of $FeCl_3\,6H_2O$ was dissolved in 10 mL absolute ethanol and then *ortho*-formic ester (1.5 mL) was added to the solution. After standing for 24 h at room temperature, a solution of **2** (1 mmol) and 2-hydroxy-benzaldehyde (1 mmol) in 10 mL absolute ethanol was added dropwise to the metal salt solution. After a few days, the resulting bright black precipitates were filtered off, washed with a mixture of ethanol/ether (1 : 1, 10 mL), and dried *in vacuo* over P_2O_5.

The iron(III) and nickel(II) templates (**1a–b** and **2c–d**) were prepared by a similar procedure. The analytical, physical and spectral data of the template complexes, **1a–b** and **2a–d**, were given as follows:

1a: m.p. > 350°C, yield 69%, μ_{eff}: 5.88 BM, Λ: 5.5 $\Omega^{-1}\,\mathrm{cm}^2\,\mathrm{mol}^{-1}$ (10^{-3} M DMF). Anal. Calcd for $C_{22}H_{17}N_3O_3SClFe$ (494.75 $\mathrm{g\,mol^{-1}}$): C, 53.41; H, 3.46; N, 8.49; S, 6.48, Fe, 11.29. Found: C, 53.39; H, 3.41; N, 8.42; S, 6.35, Fe, 11.22%. UV–Vis (in DMF): $\lambda_{\max}$, nm(log ε): 230 (4.61), 265 (4.50), 295 (4.52), 402 (4.29), 482 (4.70). FT-IR (KBr, cm^{-1}): $\nu(C{=}N^1)$ 1626, $\nu(N^4{=}C)$ 1605, $\nu(N^2{=}C)$ 1578, $\nu(C\text{–}O)_{\mathrm{arom}}$ 1156, 1123. *m*/*z* (+*c* ESI): 494.71 (M^+, 1.83%), 459.21 ($M^+ - Cl$, 100%).

1b: Bright black, m.p. > 350°C, yield 28%, μ_{eff}: 0.28 BM, Λ: 3.2 $\Omega^{-1}\,\mathrm{cm}^2\,\mathrm{mol}^{-1}$ (10^{-3} M DMF). Anal. Calcd for $C_{22}H_{17}N_3O_3SNi$ (462.15 $\mathrm{g\,mol^{-1}}$): C, 57.18; H, 3.71; N, 9.09; S, 6.94; Ni, 12.70. Found: C, 57.11; H, 3.67; N, 9.02; S, 7.05; Ni, 12.55%. UV–Vis (in DMF): $\lambda_{\max}$, nm(log ε): 232 (4.60), 267 (4.53), 300 (4.32), 336 (4.27), 418 (4.29), 485 (4.11), 560 (3.66). FT-IR (KBr, cm^{-1}): $\nu(C{=}N^1)$ 1624, $\nu(N^4{=}C)$ 1608, $\nu(N^2{=}C)$ 1582, $\nu(C\text{–}O)_{\mathrm{arom}}$ 1157, 1127. ^{1}H NMR (500 MHz, 25°C, δ ppm): 10.15 (s, 1H, 4-OH), 8.21 (s, 1H, $N^4{=}CH$), 7.74 (d, 1H, *f*), 7.51−7.44 (m, 4H, *d*, *e*, *g*, *h*), 7.26 (d, 1H, *k*), 7.24 (d, 1H, *j*), 7.01 (d, 1H, *n*), 6.72 (d, 1H, *i*), 6.64 (d, 1H, *c*), 6.31 (d, 1H, *a*), 6.10 (d, 1H, *b*), 2.21 (s, 3H, $S\text{–}CH_3$). *m*/*z* (+*c* ESI): 462.25 (M^+, 100%).

2a: Bright black, m.p. 290.8°C, yield 40%, μ_{eff}: 5.8 BM, Λ: 9 $\Omega^{-1}\,\mathrm{cm}^2\,\mathrm{mol}^{-1}$ (10^{-3} M DMF). Anal. Calcd for $C_{23}H_{19}N_3O_3SClFe$ (508.79 $\mathrm{g\,mol^{-1}}$): C, 54.30; H, 3.76; N, 8.26; S, 6.30; Fe, 10.98. Found: C, 54.32; H, 3.78; N, 8.24; S, 6.40; Fe, 10.94%. UV–Vis (in DMF): $\lambda_{\max}$, nm(log ε): 237 (4.60), 266 (4.36), 290 (4.49), 403 (4.18), 473 (4.04). FT-IR (KBr, cm^{-1}): $\nu(C{=}N^1)$ 1610, $\nu(N^4{=}C)$ 1601, $\nu(N^2{=}C)$ 1582, $\nu(C\text{–}O)_{\mathrm{arom}}$ 1152, 1123. *m*/*z* (+*c* ESI-MS): 508.65 (M^+, 1.93%), 473.05 ($M^+ - Cl$, 100%).

2b: Bright black, m.p. 288.7°C, yield 35%, μ_{eff}: 0.35 BM, Λ: 1.9 $\Omega^{-1}\,\mathrm{cm}^2\,\mathrm{mol}^{-1}$ (10^{-3} M DMF). Anal. Calcd for $C_{23}H_{19}N_3O_3SNi$ (476.17 $\mathrm{g\,mol^{-1}}$): C, 58.01; H, 4.02; N, 8.82; S, 6.73; Ni, 12.33. Found: C, 57.88; H, 4.10; N, 8.63; S, 6.61; Ni, 12.14%. UV–Vis (in DMF): $\lambda_{\max}$, nm(log ε): 235 (4.61), 267 (4.46), 301 (4.26), 333 (4.26), 414 (4.23), 485 (4.01), 560 (3.57). FT-IR (KBr, cm^{-1}): $\nu(C{=}N^1)$ 1610, $\nu(N^4{=}C)$ 1607, $\nu(N^2{=}C)$ 1580, $\nu(C\text{–}O)_{\mathrm{arom}}$ 1150, 1123. ^{1}H NMR (500 MHz, 25°C, ppm): 8.22 (s, 1H, $N^4{=}CH$), 7.76 (d, 1H, *j*), 7.52−7.43 (m, 3H, *e*, *f*, *g*), 7.39 (d, 1H, *l*), 7.27 (d, 1H, *d*), 7.18 (d, 1H, *h*), 6.99 (d, 1H, *b*), 6.73 (d, 1H, *k*), 6.69 (d, 1H, *c*), 6.50 (d, 1H, *i*), 6.20 (d, 1H, *a*), 3.77 (s, 3H, OCH_3), 2.19 (s, 3H, $S\text{–}CH_3$). *m*/*z* (+*c* ESI): 476.3 (M^+, 100%).

2c: Bright black, m.p. > 350°C, yield 45%, μ_{eff}: 5.86 BM, Λ: 9.9 $\Omega^{-1}\,\mathrm{cm}^2\,\mathrm{mol}^{-1}$ (10^{-3} M DMF). Anal. Calcd for $C_{23}H_{18}N_3O_3SBrClFe$ (587.67 $\mathrm{g\,mol^{-1}}$): C, 47.01; H, 3.09; N, 7.15; S, 5.46; Fe, 9.50. Found: C, 47.04; H, 3.11; N, 7.19; S, 5.53; Fe, 9.42%. UV–Vis (in DMF): $\lambda_{\max}$, nm(log ε): 233 (4.61), 263 (4.36), 289 (4.47), 408 (4.16), 461 (4.07). FT-IR (KBr, cm^{-1}): $\nu(C{=}N^1)$ 1605, $\nu(N^4{=}C)$ 1601, $\nu(N^2{=}C)$ 1578, $\nu(C\text{–}O)_{\mathrm{arom}}$ 1151, 1131, *m*/*z* (+*c* ESI): 587.51 (M^+, 1.03%), 552.01 ($M^+ - Cl$, 100%).

2d: Bright black, m.p. 322.3°C, yield 30%, μ_{eff}: 0.52 BM, Λ: 2.5 $\Omega^{-1}\,\mathrm{cm}^2\,\mathrm{mol}^{-1}$ (10^{-3} M DMF). Anal. Calcd for $C_{23}H_{18}N_3O_3SBrNi$ (555.07 $\mathrm{g\,mol^{-1}}$): C, 49.77; H, 3.27; N, 7.57; S, 5.78; Ni, 10.57. Found: C, 49.84; H, 3.35; N, 7.63; S, 5.64; Ni, 10.34%. UV–Vis (in DMF): λ_{max}, nm(log ε): 238 (4.67), 268 (4.53), 297 (4.20), 334 (4.17), 412 (4.15), 491 (3.97), 572 (3.50). FT-IR (KBr, cm^{-1}): $\nu(C{=}N^1)$ 1609, $\nu(N^4{=}C)$ 1605, $\nu(N^2{=}C)$ 1582, $\nu(C{-}O)_{arom}$ 1149, 1123. ^1H NMR (500 MHz, 25°C, δ ppm): 8.35 (s, 1H, $N^4{=}CH$), 8.12 (d, 1H, *l*), 7.60−7.55 (m, 4H, *e*, *f*, *g*, *j*), 7.34 7.33 (d, 2H, *d*, *h*), 7.02 (d, 1H, *b*), 6.76 (d, 1H, *c*), 6.55 (d, 1H, *i*), 6.27 (d, 1H, *a*), 3.83 (s, 3H, OCH_3), 2.24 (s, 3H, S–CH_3). *m*/*z* (+*c* ESI): 556.0 (M^+, 100%).

2.5. *Cell cultures and cytotoxicity assay*

Cytotoxic effects of the compounds were evaluated for K562 and HL-60 cell lines. For cells grown in culture, humidified CO_2 incubator at 37°C (Heraeus), DMEM/F-12 (1 : 1) medium (Biological Industries 11-170-1M) supplemented with 10% fetal calf serum (FCS, Sigma F-7524) for K562 human erythromyeloblastoid leukemia and HL-60 mouse promyelocytic leukemia cell lines, 10%, 24-well plates, polystyrene cell culture flasks (Greiner Inc.) were used.

Stock solutions of the chelates were prepared in DMSO (Sigma D-5879). Then aqueous concentrations in DMEM/F-12 medium were prepared from each solution. Compounds were added with final concentrations of 20, 10, 5, 1, 0.1 $\mu g\,mL^{-1}$ into 24-well microplates containing cell suspension (10^6 cells mL^{-1}). Total cell counts and non-viable cell counts based on dye uptake method were performed with C-Reader-CRP-300 automated cell counter (InCyto, Bio Technologies Co. Ltd.) at 24 and 72 h [36]. Cytotoxicity assay was repeated three times for each concentration of all compounds.

Cytotoxicity index was calculated with the formula:

$$\text{Cytotoxicity} = [1 - \text{viability in experiment}/\text{viability in control}] \times 100.$$

3. Results and discussion

3.1. *Some physical properties*

The crystalline powders of ligand samples were soluble in methanol, ethanol, and chlorinated hydrocarbons. The template condensation of **1** and **2** with the 2-hydroxy-aldehydes in the presence of iron(III)/nickel(II) ions give the chelates in the compositions, Fe(**L**)Cl and Ni(**L**). These black bright colored template products form a very fine crystalline material. All of the *N*^{1},*N*^{4}-diarylidene-*S*-methylthiosemicarbazone templates are soluble in chlorinated hydrocarbons such as dichloromethane, and more soluble in donor solvents such as dimethylformamide and dimethyl sulphoxide.

The μ_{eff} values of iron(III) complexes (**1a**, **2a**, and **2c** are 5.88, 5.80, and 5.86, respectively), indicate five unpaired electrons and high-spin iron(III) [15, 37]. Reactions of the iron(III) chelates **1a**, **2a**, and **2c** with $AgNO_3$ in ethanol–water mixture yielded a white precipitate of silver chloride in the course of time, and the chloride fragment was also recorded in mass spectra. The magnetic measurement results of nickel(II) templates (0.28–052 BM) show a square-planar structure.

Molar conductivity values (1.9–9.9 $\Omega^{-1}\,cm^2\,mol^{-1}$) indicate non-ionic character of the templates and it can be said that the relatively high molar conductances of the iron templates are due to the weakly coordinated chloride atom.

3.2. *Spectral data*

UV–Visible spectra of **1**, **2**, **1a**–**b**, and **2a**–**d** were obtained in 3×10^{-5} M DMF between 200 and 800 nm. The spectra showed the $\pi \rightarrow \pi^*$ bands at 232–237 and 260–267 nm. Broad bands at 289–302 and 320–336 can be assigned to a combination of bands due to $n \rightarrow \pi^*$ transitions of the azomethine and thioamide of thiosemicarbazone moiety [38, 39].

The electronic spectra of the nickel(II) complexes (**1b**, **2b**, and **2d**) display three bands at 412–418, 485–491, and 560–572 nm attributed to $^1A_{1g} \rightarrow {}^1B_{2g}$; $^1A_{1g} \rightarrow {}^1A_{2g}$, and $^1A_{1g} \rightarrow {}^1E_g$ transitions, respectively [38, 40]. The appearances of these bands and the diamagnetic nature of **1b**, **2b**, and **2d** are consistent with square-planar geometry around nickel(II). The absorptions of the iron(III) complexes, **1a**, **2a**, and **2c**, are two main bands in the 402–405 and 461–482 cm^{-1} regions assigned to LMCT transitions. Electronic spectra of the iron(III) templates did not give information about the square-pyramidal structure of the five-coordinate iron(III) due to low band intensities in the 500–700 nm region.

The template reactions of the *S*-methylthiosemicarbazones and aldehydes can be easily monitored by IR and ^{1}H NMR spectra. In the IR spectra of the template compounds, the NH_2 and 2-OH bands of the thiosemicarbazones disappear due to condensation. The ν(OH) band of the 4-substituted hydroxyl groups is at 3172 cm^{-1} in the spectra of **1a** and **1b**. By the template reaction, the $\nu(C{=}N^1)$ and $\nu(N^2{=}C)$ bands of the *S*-methylthiosemicarbazones shift to lower energies *ca* 2–20 cm^{-1} and a new azomethine band, $(N^4{=}C)$, appeared at 1608–1601 cm^{-1} due to condensation of the thioamide nitrogen and aldehyde.

In ^{1}H NMR spectra of **1**, **2**, **1b**, **2b**, and **2d** the expected chemical shift values were monitored for the aromatic, azomethine, and *S*-methyl protons [41]. The $N^4{=}CH$ signal, which is a singlet and equivalent to one proton, indicates the template formation. The recorded peak patterns between 8.05 and 6.20 ppm and also the integral values of the ring protons clearly indicate the presence of three aromatic rings in the structure. The ^{1}H NMR data of the template compounds do not show any isomer peaks, whereas the amide and *S*-methyl protons of the *S*-methylthiosemicarbazones have *cis-trans* isomers [28, 29, 34].

As a supplementary spectral data, it can be mentioned that the M^+ and $M^+ - Cl$ peaks in the mass spectra justify the compositions of the iron(III) and nickel(II) chelates.

3.3. *Crystal structure of (2a)*

The basic crystal data and structure refinement parameters for **2a** are shown in table 1 and selected bond distances and angles are presented in table 2.

The condensation of an aldehyde occurs by *syn*-conformation of the *S*-methylthiosemicarbazone backbone, and the obtained ONNO-ligand coordinates to the metal ion (figure 2). The iron template shown in figure 3 has a square-pyramidal geometry with O2, N1, N3, and O3 atoms of the tetradentate thiosemicarbazone chelate forming a square plane, and chloride in the apical position (figure 3).

In coordination of ligand with iron, three metallo-rings are formed: one five-membered FeN_2C_2 and two six-membered $FeNC_3O$. The Fe–O2 and Fe–O3 bonds are relatively short in comparison with the Fe–N1 and Fe–N3, therefore the

Table 1. Crystal data and structure refinement parameters of **2a**.

Empirical formula	$C_{23}H_{19}N_3O_3ClFeS$
Formula weight	508.78
Crystal color, habit	Black, prism
Crystal system	Triclinic
Space group	P-1(#2)
Lattice type	Primitive
Unit cell dimensions (Å, °)	
a	10.17730(10)
b	11.0486(3)
c	12.7262(3)
α	65.885(6)
β	71308(7)
Z/V (Å^3)	2/1150.64(4)
D_{Calcd} (g cm^{-3})	1.468
F_{000}	522.00
μ(Mo-Kα, cm^{-1})	8.91
Radiation (Å)	0.71070
Pixel size/$2\theta_{\max}$	0.100 mm/60.3°
Reflection collected/unique reflection	90,796/6757
R_{int}	0.072
R [$I > 3.00\sigma(I)$]	0.086
Rw [$I > 3.00\sigma(I)$]	0.064
Max/min peak in final different map (e Å^{-3})	1.80/−0.72
Goodness-of-fit indicator	1.081

Table 2. Selected bond lengths and angles of **2a**.

Bond distances (Å)		Angles (°)			
Fe1–Cl1	2.221(2)	Cl1–Fe1–O2	110.5(1)	O2–Fe1–O3	94.25(9)
Fe1–O2	1.868(2)	Cl1–Fe1–N1	99.48(9)	O2–Fe1–N3	144.8(1)
Fe1–O3	1.892(2)	Cl1–Fe1–O3	109.5(1)	N1–Fe1–O3	148.7(1)
Fe1–N1	2.069(2)	Cl1–Fe1–N3	102.1(1)	N1–Fe1–N3	75.26(9)
Fe1–N3	2.076(3)	O2–Fe1–N1	86.27(8)	O3–Fe1–N3	87.1(1)

five- and six-membered chelate rings are not regular. Also, the angles of the coordination bonds indicate that the O2N1N3O3 donor are at the edges of a deformed square planar and iron is over this square base. Chloride is weakly coordinated to the iron atom, as evidenced by the 2.221 Å bond length. The chloride atom is closer to N1 compared to other edges of pyramid base, and the square-pyramid is distorted in three axes.

The crystal structure of **2a** showed intermolecular hydrogen bonds between O2 and H19 with the following parameters, C23–H19 0.949°, H19$\cdots$O2$^{\mathrm{i}}$ 2.482°, C23$\cdots$O2 3.338°, $\langle$O2–H19–C23 158.28°, (i) $-x$, $1-y$, $1-z$ (figure 3). Pairs of these hydrogen bonds connect two molecules into a dimer and Cl1 lies to opposite directions outside the dimer. The dimer structure repeats itself through short contact between Cl1 and H16 and the equivalent chelate ring planes of two molecules become parallel. These short interaction parameters in crystal are Fe1–Cl1 2.221, H16$\cdots$Cl1$^{\mathrm{ii}}$ 2.924, Fe1$\cdots$H16 5.084°, $\langle$Fe1–Cl1–H16 162.27°, (ii) $-x$, $1-y$, $-z$.

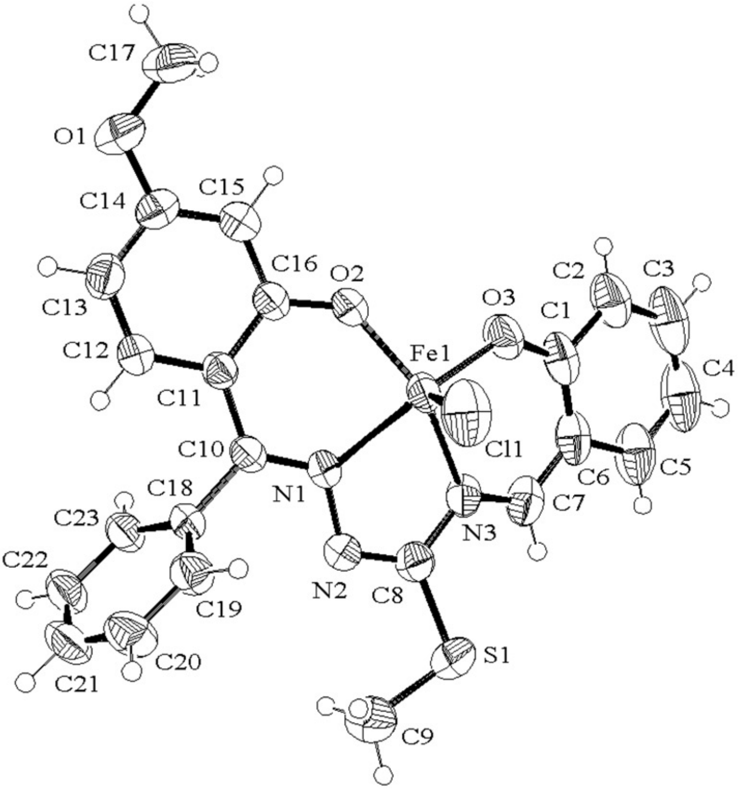

Figure 2. ORTEP diagram and atom numbering scheme for **2a**.

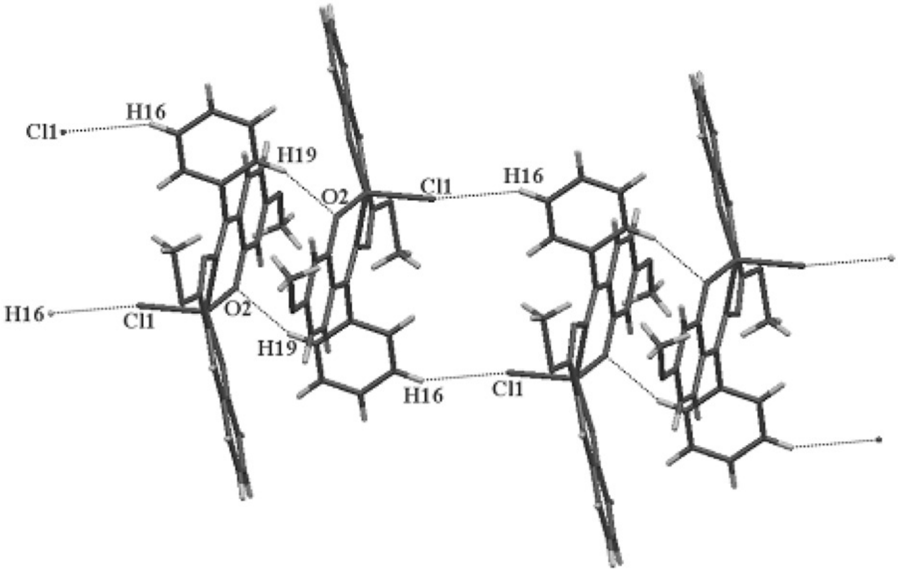

Figure 3. Short interactions of **2a** molecules.

3.4. *Cytotoxicity results*

The template compounds did not show any cytotoxic or cytostatic effect on both tumor cell lines in concentrations between 5 and 0.1 $\mu g\,mL^{-1}$. However, significant results were obtained with higher concentrations of **1a** and **2b** ($p < 0.001$ in 20 $\mu g\,mL^{-1}$ and $p < 0.01$ in 10 $\mu g\,mL^{-1}$, respectively). Cytotoxicity indices of the compounds are given as supplementary material (Supplementary Material).

4. Conclusion

Template condensation of some aldehyde-thiosemicarbazones in the presence of various metal ions are reported in many papers [15–30]. In our study, we achieved the first template condensation of benzophenone thiosemicarbazones, **I** and **II**, showing that N^1-nitrogen has coordination ability in spite of the steric bulk of the phenyl ring in these ONNO chelates. The Fe(III) and Ni(II) templates of benzophenone thiosemicarbazones are promising for cytotoxic potential.

Supplementary materials

Crystallographic data (excluding structure factors) for the structure reported in this article have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 637663 for N^1-(2-hydroxy-4-methoxy-phenyl)(phenyl)methylene-N^4-(2-hydroxy-phenyl)methylene-*S*-methyl-thiosemicarbazidato-Fe(III). These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: (+44) 1223-336-033; or Email: deposit@ccdc.cam.ac.uk

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