Research Article

Synthesis, Spectral Characterization, and In Vitro Cytotoxicity of Some Fe(III) Complexes Bearing Unsymmetrical Salen-Type Ligands Derived from 2-Hydroxynaphthaldehyde and Substituted Salicylaldehydes

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Six Fe(III) complexes bearing unsymmetrical salen-type ligands derived from 2-hydroxynaphthaldehyde and substituted salicylaldehydes were synthesized by coordinating the unsymmetrical salen-type ligands with $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$. The synthetic complexes were characterized by electrospray ionization mass spectra (ESI-MS), effective magnetic moments (μ_{eff}), and infrared (IR) and ultraviolet-visible (UV-Vis) spectra. The spectroscopic data are in good agreement with the suggested molecular formulae of the complexes. Their cyclic voltammetric studies in acetonitrile solutions showed that the Fe(III)/Fe(II) reduction processes are electrochemically irreversible. The *in vitro* cytotoxicity of the obtained complexes was screened on human cancer cell lines KB (a subline of HeLa tumor cell line) and HepG2 (a human liver cancer cell line) and a normal human cell line HEK-293 (Human Embryonic Kidney cell line). The results showed that the synthetic Fe(III) complexes are highly cytotoxic and quite selective. The synthetic complexes bearing unsymmetrical salen-type ligands with different substituted groups in the salicyl ring indicate different cytotoxicity.

1. Introduction

The developments in transition metal complexes have gained considerable attention about various structures and potential applications in catalysis, analysis, advanced materials science, and biochemistry especially [1–9]. Besides the meaningful efficiency of platinum complexes as anticancer agents [10–12], recent bioinorganic chemists have focused on the design and preparation of new transition metal complexes with Schiff base ligands [13–15]. Schiff bases with donors (N, O, etc.) have been widely investigated due to their diverse pharmacological applications [16], in which tetradentate Schiff bases are derived from salicylaldehydes and diamines, which form the Schiff bases known as “salen” with an N_2O_2 donor group being able to coordinate with different metal ions [17]. These diamine Schiff bases with OH groups in *ortho* positions are of interest because of the

presence of tautomerism between keto-amine and enol-imine forms [18]. The transition metal complexes of tetradentate Schiff bases have received much attention about their structure, magnetic and electrochemical characterization, and their potential application in biological functions lately. They predominantly show their antiproliferative, antimalarial, antifungal, antipyretic, and antidiabetic activities [19, 20]. Besides, many symmetrical tetradentate Schiff bases and their transition metal complexes have been extensively studied on the preparation, spectral characterization, and biological activity [21–23]; recently, unsymmetrical tetradentate Schiff base ligands and their complexes have been paid attention [24–26]. It should be realized that the coordinated ligands around central metal ions in natural systems are unsymmetrical. Therefore, in this work, we continue with the synthesis, spectral characterization, and *in vitro* anticancer behavior of Fe(III) complexes

bearing unsymmetrical salen-type Schiff bases derived from 2-hydroxynaphthaldehyde and substituted salicylaldehydes.

2. Materials and Methods

Chemical reagents used in the present study, such as *o*-phenylenediamine (98%), 2-hydroxy-1-naphthaldehyde (tech.), and salicylaldehydes, were obtained from Across Organics and used without further purification. All solvents were distilled following the laboratory procedures before use.

Ultrahigh-performance liquid chromatography combined with hydride quadrupole time-of-flight tandem mass spectra (HP-TOF-MS) of the synthetic unsymmetrical tetradentate Schiff base ligands was conducted on an ExionLC AC Series HPLC system coupled with a hybrid quadrupole time-of-flight tandem mass spectrometer (X500R QTOF System) equipped with TurboIonSpray source. Chromatographic separation was performed on a Kinetex C₁₈ column (30 mm × 2.1 mm, 1.7 μm), and the column temperature was maintained at 30°C. The mobile phase consisted of methanol and water containing 0.1% formic acid in a gradient mode of 50% methanol for 0–5 min and 100% methanol at 5 min with a flow rate of 0.3 mL min⁻¹. Electrospray ionization mass spectra (ESI-MS) (*m/z*) were recorded on Agilent 6310 Ion Trap spectrometer. Infrared spectra (IR, 4000–400 cm⁻¹) were carried out on a PerkinElmer Spectrum Two spectrophotometer using a KBr pellet. ¹H-NMR and ¹³C-NMR spectra were determined in DMSO-*d*₆ solution using a Bruker Advance 500 MHz NMR spectrometer with TMS as the internal standard and chemical shifts (δ) recorded in ppm. UV-Visible absorption spectra of the synthetic compounds (200–600 nm) were estimated in methanol solution (3 × 10⁻⁵ M) with PerkinElmer Lambda UV-35 spectrophotometer. Magnetic susceptibility measurements of synthetic Fe(III) complexes were determined at room temperature using a magnetic susceptibility balance (Mark 1, serial No. 25179) of Sherwood Scientific, Ltd.

2.1. Synthesis of Unsymmetrical Salen-Type Schiff Base Ligands. Unsymmetrical salen-type Schiff base ligands were prepared following a two-step procedure similar to the known procedure [27, 28]. In the first step, monocondensed half-units were prepared by the condensation of *o*-phenylenediamine with 2-hydroxy-1-naphthaldehyde. In the second step, the monocondensed half-unit was mixed with an ethanol solution of relative salicylaldehydes. *O*-Phenylenediamine (15.4 mmol) dissolved in ethanol (20 mL) was added in a 100 mL flask containing 2-hydroxy-1-naphthaldehyde (15.5 mmol) in ethanol (15 mL) and was stirred for 3 h. After the monocondensed half-units were obtained completely by TLC checking, relative salicylaldehyde (15.5 mmol) in ethanol (15 mL) was added and the new mixture was put in an ultrasonic case, Hwashin Power Sonic 405, for 1 h. Then, the productive precipitates were collected after being filtered and washed by cold ethanol. The obtained products are soluble in DMSO, methanol, dichloromethane,

and ethyl acetate. The products were recrystallized from ethyl acetate and dried *in vacuo*.

(Z)-1-(((2-((E)-(2-Hydroxybenzylidene) amino) phenyl) amino) methylene) naphthalen-2 (1H)-one (H₂L1): yellow powder, 91%; **HP-TOF-MS** (*m/z*): 367.1430 [*M* + *H*]⁺ (Cal. 367.4199); **IR** (KBr, cm⁻¹): 3060 (ν, C-H), 2678 (ν, O-H), 1611 (ν, C=N), 1571 (ν, C=C), 1483, 1353, 1315 and 1278 (ν, C-N), 1188 and 1153 (ν, C-O); 837, 744 (δ, C-H), 481; **¹H-NMR** (DMSO-*d*₆, 500 MHz, δ (ppm), *J* (Hz)): δ 15.63 (d, *J* = 7.0, 1H, NH), 11.93 (s, 1H, OH), 9.60 (d, *J* = 7.0, 1H, HC-N), 8.99 (s, 1H, HC = N), 8.43 (d, *J* = 8.5, 1H, Naph), 7.99 (d, *J* = 8.5, 1H, Naph), 7.91 (d, *J* = 7.5, 1H, Sal), 7.86 (d, *J* = 9.5, 1H, Naph), 7.73 (d, *J* = 6.5, 1H, Ph), 7.51 (t, *J* = 7.0, 1H, Naph), 7.44 (m, 3H, 1H-Naph, 2H-Sal), 7.36 (t, *J* = 7.5, 1H, Ph), 7.31 (t, *J* = 7.0, 1H, Ph), 7.00 (m, 2H, 1H-Ph, 1H-Sal), 6.90 (d, *J* = 9.5, 1H, Naph); **¹³C-NMR** (DMSO-*d*₆, 125 MHz, δ (ppm)): δ 174.31 (1C, C=O), 162.98 (1C, C=N), 159.70 (1C, C-O), 152.68 (1C, HC-NH), 141.26 (1C, N-C_{Ar}), 137.69 (1C, HN-C_{Ar}), 136.60 (1C, Naph), 133.63 (1C, Naph), 133.47 (1C, Sal), 131.80 (1C, Sal), 128.99 (1C, Naph), 128.14 (1C, Naph), 127.71 (1C, Naph), 126.95 (1C, Naph), 126.31 (1C, Ph), 123.57 (1C, Naph), 123.41 (1C, Ph), 120.21 (1C, Ph), 120.11 (1C, Naph), 119.54 (1C, Naph), 119.32 (1C, Sal), 118.26 (1C, Sal), 116.62 (1C, Sal), 108.51 (1C, Ph); **UV-Vis** (MeOH, 3 × 10⁻⁵ M, λ/nm, ε/cm⁻¹ M⁻¹): 233 (42,000), 266 (22,333), 320 (17,000), 348 (16,333), 450 (12,333), 472 (11,333).

(Z)-1-(((2-((E)-(5-Fluoro-2-hydroxybenzylidene) amino) phenyl) amino) methylene) naphthalen-2 (1H)-one (H₂L2): yellow powder, 93%; **HP-TOF-MS** (*m/z*): 385.1379 [*M* + *H*]⁺ (Cal. 385.4104); **IR** (KBr, cm⁻¹): 2919 (ν, C-H), 2672 (ν, O-H), 1618 (ν, C=N), 1576 (ν, C=C), 1485, 1352, 1313 and 1274 (ν, C-N), 1199 and 1140 (ν, C-O); 824, 745 (δ, C-H), 478; **¹H-NMR** (DMSO-*d*₆, 500 MHz, δ (ppm), *J* (Hz)): δ 15.69 (d, *J* = 8.5, 1H, NH), 11.36 (s, 1H, OH), 9.57 (d, *J* = 8.0, 1H, HC-N), 8.99 (s, 1H, HC = N), 8.42 (d, *J* = 8.5, 1H, Naph), 8.04 (d, *J* = 8.5, 1H, Naph), 7.92 (dd, *J* = 9.0, 3.5, 1H, Sal), 7.85 (d, *J* = 9.0, 1H, Naph), 7.71 (d, *J* = 7.0, 1H, Ph), 7.50 (t, *J* = 7.0, 1H, Naph), 7.44 (m, 2H, 1H-Naph, 1H-Sal), 7.35 (t, *J* = 7.5, 1H, Ph), 7.29 (m, 2H, Ph), 7.00 (q, 1H, Sal), 6.85 (d, *J* = 9.5, 1H, Naph); **¹³C-NMR** (DMSO-*d*₆, 125 MHz, δ (ppm)): δ 175.81 (1C, C=O), 159.79 (1C, C=N), 156.29 and 155.72 (1C, C-O), 154.42 (1C, C-F), 151.44 (1C, HC-NH), 140.79 (1C, N-C_{Ar}), 138.02 (1C, HN-C_{Ar}), 136.30 (1C, Naph), 133.65 (1C, Naph), 129.03 (1C, Naph), 128.19 (1C, Naph), 128.00 (1C, Naph), 126.80 and 126.22 (1C, Sal), 124.20 (1C, Naph), 123.41 (1C, Naph), 121.39 (1C, Naph), 121.33 (1C, Ph), 120.57 and 120.38 (1C, Sal), 120.05 (1C, Ph), 119.05 (1C, Ph), 118.09 and 118.02 (1C, Sal), 117.86 (1C, Naph), 115.56 and 115.37 (1C, Sal), 108.41 (1C, Ph); **UV-Vis** (MeOH, 3 × 10⁻⁵ M, λ/nm, ε/cm⁻¹ M⁻¹): 234 (40,333), 265 (21,667), 320 (15,000), 355 (16,000), 450 (12,000), 472 (11,333).

(Z)-1-(((2-((E)-(5-Chloro-2-hydroxybenzylidene) amino) phenyl) amino) methylene) naphthalen-2 (1H)-one (H₂L3): yellow powder, 93%; **HP-TOF-MS** (*m/z*): 401.1046 [*M* + *H*]⁺ (Cal. 401.8647); **IR** (KBr, cm⁻¹): 3060 (ν, C-H), 2612 (ν, O-H), 1618 (ν, C=N), 1586 (ν, C=C), 1477, 1352, 1314 and 1278 (ν, C-N), 1180 (ν, C-O); 828, 749 (δ, C-H),

488; **¹H-NMR** (DMSO-*d*₆, 500 MHz, δ (ppm), J (Hz)): δ 15.72 (d, J = 8.0, 1H, NH), 11.72 (s, 1H, OH), 9.58 (d, J = 7.0, 1H, HC=N), 8.99 (s, 1H, HC=N), 8.44 (d, J = 8.0, 1H, Naph), 8.15 (d, J = 3.0, 1H, Sal), 8.04 (d, J = 8.0, 1H, Naph), 7.85 (d, J = 9.0, 1H, Naph), 7.72 (d, J = 7.0, 1H, Ph), 7.50 (t, J = 7.0, 1H, Naph), 7.45 (m, 3H, 1H-Naph, 1H-Ph, 1H-Sal), 7.35 (t, J = 7.5, 1H, Ph), 7.31 (t, 1H, Ph), 7.00 (q, 1H, Sal), 6.85 (d, J = 9.5, 1H, Naph); **¹³C-NMR** (DMSO-*d*₆, 125 MHz, δ (ppm)): δ 175.16 (1C, C=O), 160.03 (1C, C=N), 158.12 (1C, C-O), 151.90 (1C, HC-NH), 140.74 (1C, N-C_{Ar}), 137.82 (1C, HN-C_{Ar}), 136.48 (1C, Naph), 133.54 (1C, Naph), 132.94 (1C, C-Cl), 129.80 (1C, Naph), 128.96 (1C, Naph), 128.10 (1C, Naph), 127.97 (1C, Sal), 126.77 (1C, Naph), 126.22 (1C, Naph), 123.94 (1C, Naph), 123.35 (1C, Ph), 123.05 (1C, Sal), 121.98 (1C, Ph), 120.04 (1C, Ph), 119.11 (1C, Sal), 118.54 (1C, Naph), 118.00 (1C, Sal), 108.43 (1C, Ph); **UV-Vis** (MeOH, 3×10^{-5} M, λ /nm, ϵ /cm⁻¹ M⁻¹): 233 (49,333), 264 (23,333), 320 (16,000), 354 (16,667), 450 (12,667), 470 (12,000).

(Z)-1-(((2-((E)-(5-Bromo-2-hydroxybenzylidene) amino) phenyl) amino) methylene) naphthalen-2 (1H)-one (H₂L4): yellow powder, 85%; **HP-TOF-MS** (m/z): 445.0470 [$M+H$]⁺ (Cal. 446.3160); **IR** (KBr, cm⁻¹): 3061 (ν , C-H), 2622 (ν , O-H), 1611 (ν , C=N), 1584 (ν , C=C), 1474, 1351, 1313 and 1276 (ν , C-N), 1179 (ν , C-O); 825, 747 (δ , C-H), 487; **¹H-NMR** (DMSO-*d*₆, 500 MHz, δ (ppm), J (Hz)): δ 15.74 (d, J = 7.5, 1H, NH), 11.78 (s, 1H, OH), 9.58 (d, J = 7.5, 1H, HC=N), 8.98 (s, 1H, HC=N), 8.44 (d, J = 8.5, 1H, Naph), 8.28 (d, J = 2.5, 1H, Sal), 8.03 (d, J = 8.0, 1H, Naph), 7.85 (d, J = 9.0, 1H, Naph), 7.72 (d, J = 7.0, 1H, Ph), 7.56 (dd, J = 8.5, 3.0, 1H, Sal), 7.50 (t, J = 7.0, 1H, Naph), 7.45 (m, 2H, 1H-Ph, 1H-Naph), 7.35 (t, J = 7.0, 1H, Ph), 7.31 (t, 1H, Ph), 6.97 (d, J = 9.0, 1H, Sal), 6.87 (d, J = 9.0, 1H, Naph); **¹³C-NMR** (DMSO-*d*₆, 125 MHz, δ (ppm)): δ 175.10 (1C, C=O), 159.97 (1C, C=N), 158.53 (1C, C-O), 151.95 (1C, HC-NH), 140.72 (1C, N-C_{Ar}), 137.80 (1C, HN-C_{Ar}), 136.51 (1C, Naph), 135.71 (1C, Sal), 133.54 (1C, Naph), 132.83 (1C, Sal), 128.96 (1C, Naph), 128.11 (1C, Naph), 127.98 (1C, Naph), 126.77 (1C, Ph), 126.22 (1C, Naph), 123.92 (1C, Ph), 123.35 (1C, Ph), 122.56 (1C, Naph), 120.05 (1C, Naph), 119.12 (1C, Sal), 118.96 (1C, Naph), 118.01 (1C, Sal), 110.51 (1C, C-Br), 108.43 (1C, Ph); **UV-Vis** (MeOH, 3×10^{-5} M, λ /nm, ϵ /cm⁻¹ M⁻¹): 233 (44,333), 263 (22,000), 320 (14,333), 352 (14,667), 450 (12,000), 472 (11,000).

(Z)-1-(((2-((E)-(5-(Tert-butyl)-2-hydroxybenzylidene) amino) phenyl) amino) methylene) naphthalen-2 (1H)-one (H₂L5): yellow powder, 91%. **HP-TOF-MS** (m/z): 423.2042 [$M+H$]⁺ (Cal. 423.5262). **IR** (KBr, cm⁻¹): 2952 (ν , C-H), 2620 (ν , O-H), 1615 (ν , C=N), 1579 (ν , C=C), 1487, 1351, 1314 and 1288 (ν , C-N), 1177 (ν , C-O); 837, 749 (δ , C-H), 491. **¹H-NMR** (DMSO-*d*₆, 500 MHz, δ (ppm), J (Hz)): δ 15.81 (d, J = 7.5, 1H, NH), 11.46 (s, 1H, OH), 9.58 (d, J = 8.0, 1H, HC=N), 9.01 (s, 1H, HC=N), 8.43 (d, J = 8.5, 1H, Naph), 8.07 (d, J = 2.5, 1H, Sal), 8.02 (d, J = 8.0, 1H, Naph), 7.85 (d, J = 9.0, 1H, Naph), 7.71 (d, J = 7.0, 1H, Ph), 7.51–7.41 (m, 4H, 2H-Naph, 1H-Ph, 1H-Sal), 7.35 (t, J = 7.0, 1H, Ph), 7.30 (t, 1H, Ph), 6.92 (d, J = 9.0, 1H, Sal), 6.84 (d, J = 9.0, 1H, Naph), 1.34 (s, 9H, t-Bu). **¹³C-NMR** (DMSO-*d*₆, 125 MHz, δ (ppm)): δ 175.12 (1C, C=O), 162.22 (1C, C=N), 157.35 (1C, C-O), 151.88 (1C, HC-NH), 141.63 (1C, C-t-Bu), 141.29

(1C, N-C_{Ar}), 137.77 (1C, HN-C_{Ar}), 136.34 (1C, Naph), 133.57 (1C, Naph), 130.75 (1C, Naph), 128.98 (1C, Naph), 128.13 (1C, Sal), 127.83 (1C, Naph), 127.53 (1C, Naph), 126.85 (1C, Naph), 126.22 (1C, Ph), 123.83 (1C, Sal), 123.34 (1C, Ph), 120.02 (1C, Ph), 119.81 (1C, Naph), 119.17 (1C, Naph), 117.95 (1C, Sal), 116.13 (1C, Sal), 108.46 (1C, Ph), 33.91 (1C, C (CH₃)₃), 31.21 (3H, 3CH₃). **UV-Vis** (MeOH, 3×10^{-5} M, λ /nm, ϵ /cm⁻¹ M⁻¹): 234 (38,667), 266 (19,333), 320 (14,667), 353 (14,667), 450 (12,000), 472 (11,333).

(Z)-1-(((2-((E)-(2-Hydroxy-5-methoxybenzylidene) amino) phenyl) amino) methylene) naphthalen-2 (1H)-one (H₂L6): yellow powder, 92%; **HP-TOF-MS** (m/z): 397.1546 [$M+H$]⁺ (Cal. 397.4459); **IR** (KBr, cm⁻¹): 2925 (ν , C-H), 2610 (ν , O-H), 1615 (ν , C=N), 1575 (ν , C=C), 1486, 1316 and 1273 (ν , C-N), 1207, 1156 (ν , C-O); 1040, 834, 748 (δ , C-H), 472; **¹H-NMR** (DMSO-*d*₆, 500 MHz, δ (ppm), J (Hz)): δ 15.81 (d, J = 9.0, 1H, NH), 10.81 (s, 1H, OH), 9.56 (d, J = 9.0, 1H, HC=N), 9.03 (s, 1H, HC=N), 8.43 (d, J = 8.0, 1H, Naph), 8.07 (d, J = 7.5, 1H, Naph), 7.82 (d, J = 9.0, 2H, 1H-Naph, 1H-Sal), 7.70 (d, J = 7.0, 1H, Ph), 7.51–7.41 (m, 3H, 2H-Naph, 1H-Ph), 7.35 (t, J = 7.0, 1H, Ph), 7.29 (t, 1H, Ph), 7.03 (dd, J = 9.0, 3.5, 1H, Sal), 6.92 (d, J = 9.0, 1H, Sal), 6.80 (d, J = 9.0, 1H, Naph), 3.88 (s, 3H, OCH₃); **¹³C-NMR** (DMSO-*d*₆, 125 MHz, δ (ppm)): δ 176.65 (1C, C=O), 159.67 (1C, C=N), 153.51 (1C, C-O), 152.24 (1C, C-OCH₃), 150.57 (1C, HC-NH), 140.81 (1C, N-C_{Ar}), 138.06 (1C, HN-C_{Ar}), 135.91 (1C, Naph), 133.72 (1C, Naph), 128.96 (1C, Naph), 128.11 (1C, Naph), 127.59 (1C, Sal), 126.63 (1C, Naph), 126.06 (1C, Naph), 124.44 (1C, Naph), 123.26 (1C, Ph), 121.48 (1C, Sal), 120.95 (1C, Ph), 119.94 (1C, Ph), 118.65 (1C, Naph), 117.65 (1C, Naph), 117.51 (1C, Sal), 112.34 (1C, Sal), 108.20 (1C, Ph), 55.58 (1C, OCH₃); **UV-Vis** (MeOH, 3×10^{-5} M, λ /nm, ϵ /cm⁻¹ M⁻¹): 234 (44,000), 263 (22,667), 320 (16,667), 350 (16,667), 450 (13,667), 474 (12,667).

2.1.1. Preparation of Unsymmetrical Salen-Type Schiff Base Complexes. Unsymmetrical salen-type Schiff base complexes were prepared from the obtained ligands and FeCl₃·6H₂O in 1:1 molecular ratio following the published procedure similarly [28–30]. 1.0 mmol FeCl₃·6H₂O dissolved in ethanol was added to an ethanol solution of 1.0 mmol ligand. The reaction mixture was refluxed in the presence of 1.0 mmol Na₂CO₃ for 3 hrs; then, the reaction mixture was cooled to room temperature. The productive precipitate was collected after being filtered and washed by cold ethanol and then dried *in vacuo*.

[Fe(III)L1Cl]: brown powder, 89%; **ESI-MS** (m/z): 419.8 [$M-Cl$]⁺ (Cal. 420.2); **IR** (KBr, cm⁻¹): 3054 (ν , C-H), 1597 (ν , C=N), 1532 (ν , C=C), 1437, 1378, 1304 (ν , C-N), 1189 (ν , C-O), 1140, 835, 740 (δ , C-H), 548 (Fe-O), 478, 456 (Fe-N); **UV-Vis** (MeOH, 3×10^{-5} M, λ /nm, ϵ /cm⁻¹ M⁻¹): 227 (44,350), 300 (27,000), 334 (23,350), 372 (20,350), 431 (13,350); μ_{eff} = 5.94 BM.

[Fe(III)L2Cl]: brown powder, 93%; **ESI-MS** (m/z): 437.9 [$M-Cl$]⁺ (Cal. 438.2); **IR** (KBr, cm⁻¹): 3055 (ν , C-H), 1599 (ν , C=N), 1532 (ν , C=C), 1456, 1361, 1303 (ν , C-N), 1185 (ν , C-O), 1142, 826, 741 (δ , C-H), 531 (Fe-O), 497, 455 (Fe-N); **UV-Vis** (MeOH, 3×10^{-5} M, λ /nm, ϵ /cm⁻¹ M⁻¹): 230

(32,670), 295 (18,670), 338 (16,000), 369 (14,350), 437 (9,350); $\mu_{\text{eff}} = 5.78$ BM.

[Fe(III)L3Cl]: brown powder, 92%; ESI-MS (m/z): 453.8 $[M - Cl]^+$ (Cal. 454.6); IR (KBr, cm^{-1}): 3054 (ν , C-H), 1597 (ν , C=N), 1531 (ν , C=C), 1453, 1362, 1307 (ν , C-N), 1188 (ν , C-O), 1166, 828, 742 (δ , C-H), 552 (Fe-O), 498, 456 (Fe-N); UV-Vis (MeOH, 3×10^{-5} M, λ/nm , $\epsilon/\text{cm}^{-1} \text{ M}^{-1}$): 233 (49,000), 300 (24,350), 340 (22,350), 373 (19,350), 440 (13,000); $\mu_{\text{eff}} = 5.86$ BM.

[Fe(III)L4Cl]: brown powder, 94%; ESI-MS (m/z): 497.8 $[M - Cl]^+$ (Cal. 499.1); IR (KBr, cm^{-1}): 3053 (ν , C-H), 1598 (ν , C=N), 1533 (ν , C=C), 1451, 1366, 1308 (ν , C-N), 1187 (ν , C-O), 827, 745 (δ , C-H), 534 (Fe-O), 487, 455 (Fe-N); UV-Vis (MeOH, 3×10^{-5} M, λ/nm , $\epsilon/\text{cm}^{-1} \text{ M}^{-1}$): 234 (48,000), 297 (29,350), 340 (23,000), 374 (20,000), 438 (14,000); $\mu_{\text{eff}} = 6.00$ BM.

[Fe(III)L5Cl]: brown powder, 85%; ESI-MS (m/z): 475.9 $[M - Cl]^+$ (Cal. 476.3); IR (KBr, cm^{-1}): 3061 (ν , C-H), 1600 (ν , C=N), 1532 (ν , C=C), 1456, 1362, 1314 (ν , C-N), 1186 (ν , C-O), 1144, 828, 741 (δ , C-H), 539 (Fe-O), 484, 456 (Fe-N); UV-Vis (MeOH, 3×10^{-5} M, λ/nm , $\epsilon/\text{cm}^{-1} \text{ M}^{-1}$): 230 (45,670), 297 (27,670), 334 (23,350), 378 (17,670), 436 (12,000); $\mu_{\text{eff}} = 5.98$ BM.

[Fe(III)L6Cl]: brown powder, 87%; ESI-MS (m/z): 449.9 $[M - Cl]^+$ (Cal. 450.2); IR (KBr, cm^{-1}): 3056 (ν , C-H), 1596 (ν , C=N), 1530 (ν , C=C), 1454, 1362, 1300 (ν , C-N), 1190 (ν , C-O), 826, 744 (δ , C-H), 545 (Fe-O), 502, 456 (Fe-N); UV-Vis (MeOH, 3×10^{-5} M, λ/nm , $\epsilon/\text{cm}^{-1} \text{ M}^{-1}$): 223 (36,670), 297 (21,350), 342 (17,350), 390 (12,350), 440 (9,000); $\mu_{\text{eff}} = 5.95$ BM.

2.1.2. Electrochemical Studies. The electrochemical studies of all complexes were carried out using the Zahner-elektrik IM6 instrument. The cyclic voltammograms of Fe(III) complexes were recorded using 1.0×10^{-3} M concentration in acetonitrile solution and LiClO_4 0.1 M as supporting electrolyte. The working electrode was a platinum electrode. The reference electrode was Ag/AgCl/KCl and platinum wire was the counterelectrode. All experiments were performed in standard electrochemical cells at room temperature at a scan rate of 100 mV s^{-1} with the potential window -3 V to $+3 \text{ V}$ vs. Ag/AgCl/KCl reference electrode.

2.2. In Vitro Cytotoxicity. *In vitro* cytotoxicity of the synthetic complexes was investigated using the modified MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) assay [31–34]. Briefly, human cancer cells KB (a subline of Hela tumor cell line), HepG2 (a hepatoma cell line), and a normal human cell line HEK-293 (Human Embryonic Kidney cell line) were cultured in DMEM supplemented with 10% fetal bovine serum, $100 \mu\text{g/mL}$ streptomycin, 100 units/mL penicillin, and 2 mM L-glutamine at 37°C in a humidified atmosphere with 5% CO_2 and 95% air. Approximately, 10,000 cells were cultivated in 96 plates for 24 hrs, followed by treatment with different concentrations of synthetic Fe(III) complexes in DMSO and incubated continuously for 48 hrs more. The different concentrations of each tested complexes were 128.0, 32.0,

8.0, 2.0, and $0.5 \mu\text{g/mL}$. Then, tested human cells were exposed to $20 \mu\text{L}$ of freshly prepared MTT (5 mg/mL) solution and incubated for 4 h at 37°C in an atmosphere of 5% CO_2 . The formazan crystals obtained during MTT incubation were dissolved in $100 \mu\text{L}$ of DMSO. The optical density (OD) was determined at 550 nm on Genios TECAN spectrophotometer. The experiments were done in triplicate for every concentration of the tested complexes. The cell viability was calculated with regard to the untreated cell control (positive control), which was set to 100% viability. The dead cell control (negative control) was set to 0% viability.

$$\% \text{ inhibition} = \frac{\text{OD (positive control)} - \text{OD (tested complex)}}{\text{OD (positive control)} - \text{OD (negative control)}} \times 100. \quad (1)$$

The percent cell inhibitions were plotted as a function of concentration to estimate the IC_{50} (the concentration at which a substance exerts half of its maximal inhibitory effect) values presented in Table 1.

3. Results and Discussion

3.1. Synthesis and Characterization. The unsymmetrical tetradentate Schiff base ligands ($\text{H}_2\text{L1}$ – $\text{H}_2\text{L6}$) (Table 2) were synthesized following a two-step procedure in high yields (up to 93%) and excellent purity (>98.7%, Supplementary Materials). The obtained ligands are soluble in organic solvents such as DMSO, methanol, dichloromethane, and ethyl acetate. These synthetic ligands were characterized by HP-TOF-MS, IR, ^1H -NMR, and ^{13}C -NMR spectroscopies. The Fe(III) complexes were prepared following the coordination of $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ with each obtained ligand in good yields (85–94%) in ethanol at pH 9.0 (Scheme 1). The synthetic unsymmetrical tetradentate Schiff base complexes are soluble in DMSO, acetonitrile, methanol, and dichloromethane. These complexes were characterized by ESI-MS, IR, UV-Vis spectroscopies, and magnetic moments (μ_{eff}).

From the high-performance mass spectra, the pseudomolecular ion signals of the obtained ligands are found as $[M + H]^+$, clearly indicating molecular masses suitable for the suggested formulae. On ESI-MS spectra of synthetic unsymmetrical complexes, pseudomolecular ion peaks are assigned to $[M - Cl]^-$ for Fe(III) complexes. They are in excellent agreement with the suggested formulae (Table 2).

On ^1H -NMR spectra, usually, a typical signal at about 15.63 ppm was found for a proton of OH of naphthyl group as a singlet [35], but typical signals at 15.63–15.81 ppm as doublets, so there must be tautomerism between keto-amine and enol-imine forms here (Scheme 1) and protons of NH groups were found. There are typical signals at 10.81–11.93 ppm as singlets were assigned to protons of OH of salicyl groups [36]. The typical signals at 9.56–9.60 ppm as doublets were probably observed for protons of HC–N groups and at 8.98–9.03 ppm as singlets are for protons of HC = N groups. The proton signals of aromatic groups were found at about 6.80–8.44 ppm. When the salicyl group containing fluor ($\text{H}_2\text{L2}$) proton signals were observed as multilets as usual, there are proton signals at 1.34 ppm as

TABLE 1: *In vitro* cytotoxicity of the unsymmetrical salen-type Fe(III) complexes.

Complex	KB	IC ₅₀ (μM)	
		HepG2	HEK-293
H ₂ L1	>100	51.48 ± 2.71	nd
[Fe(III)L1Cl]	0.81 ± 0.08	3.18 ± 0.19	9.33 ± 0.17
[Fe(III)L2Cl]	3.53 ± 0.17	25.45 ± 1.21	nd
[Fe(III)L3Cl]	10.97 ± 0.65	63.31 ± 2.55	nd
[Fe(III)L4Cl]	14.14 ± 0.58	56.53 ± 2.25	nd
[Fe(III)L5Cl]	8.31 ± 0.43	28.31 ± 1.47	nd
[Fe(III)L6Cl]	2.61 ± 0.10	1.87 ± 0.08	6.34 ± 0.10
Ellipticine	1.14 ± 0.08	2.11 ± 0.16	6.69 ± 0.32

nd: not determined.

TABLE 2: Unsymmetrical tetradentate Schiff base ligands and their Fe(III) complexes.

Ligand	R	Fe(III) complex
H ₂ L1	H	[Fe(III)L1Cl]
H ₂ L2	F	[Fe(III)L2Cl]
H ₂ L3	Cl	[Fe(III)L3Cl]
H ₂ L4	Br	[Fe(III)L4Cl]
H ₂ L5	<i>t</i> -Bu	[Fe(III)L5Cl]
H ₂ L6	OCH ₃	[Fe(III)L6Cl]

SCHEME 1: Synthesis of unsymmetrical tetradentate Schiff base ligands and their Fe(III) complexes.

singlet for 9 protons of *t*-butyl and at 3.88 ppm as singlet for 3 protons of methoxy group.

On ¹³C-NMR spectra, there are typical signals at 174.31–176.65 ppm for C¹⁶ of C=O groups (Scheme 1) probably. The typical signals at 159.67–162.98 ppm were found for C⁷ of C=N groups. The typical signals at 153.51–159.70 ppm and 150.57–152.68 ppm are found for the carbons of C-OH and HC-N groups. The typical signals at 140.72–141.29 ppm and 137.69–138.06 ppm were assigned to N-C_{Ar} and HN-C_A carbon groups. The salicyl containing fluoro group (H₂L2) possesses the typical carbon signals in doublets. The carbon signals of *t*-butyl (H₂L4) are found at 33.91 and 31.21 ppm and the carbon signal of methoxy (H₂L5) is observed at 55.58 ppm.

On IR spectra of the obtained ligands, there are typical signals of C=N stretching vibrations for the formation of synthetic unsymmetrical tetradentate ligands at 1611–1618 cm⁻¹ (Table 3). The typical stretching vibrations of C=O bondings are found at 1540–1543 cm⁻¹. The weak broad signals at 2715–2858 cm⁻¹ could belong to O-H and N-H stretching vibrations. There are typical signals at 1273–1288 cm⁻¹ and 1200–1211 cm⁻¹ for C-N and C-O stretching vibrations, respectively. On IR spectra of the complexes, there are no signals for O-H and N-H stretching vibrations. New bands were observed for Fe-N and Fe-O vibrations at 531–552 cm⁻¹ and 455–456 cm⁻¹, respectively. They are obvious evidence for H separation and coordination of N and O with a metal center in the obtained

TABLE 3: Selected typical signals of IR spectra of the obtained ligands and synthetic complexes.

Compound	$\nu(\text{O-H; N-H})$	$\nu(\text{C=N})$	$\nu(\text{C=O})$	$\nu(\text{C-N})$	$\nu(\text{C-O})$	$\nu(\text{M-N})$	$\nu(\text{M-O})$
H ₂ L1	2715	1611	1541	1278	1211	—	—
[Fe(III)L1Cl]	—	1597	1532	1252	1189	548	456
H ₂ L2	2740	1618	1542	1274	1200	—	—
[Fe(III)L2Cl]	—	1599	1532	1246	1185	531	455
H ₂ L3	2780	1618	1543	1278	1211	—	—
[Fe(III)L3Cl]	—	1597	1531	1260	1188	552	456
H ₂ L4	2775	1611	1542	1276	1211	—	—
[Fe(III)L4Cl]	—	1598	1533	1258	1187	534	455
H ₂ L5	2858	1615	1542	1288	1210	—	—
[Fe(III)L5Cl]	—	1600	1532	1256	1186	539	456
H ₂ L6	2836	1615	1540	1273	1207	—	—
[Fe(III)L6Cl]	—	1596	1530	1254	1190	545	456

complexes. The typical bands for stretching vibrations of C=N, C=O, C-N, and C-O of Fe(III) complexes at $1596\text{--}1600\text{ cm}^{-1}$, $1530\text{--}1533\text{ cm}^{-1}$, $1246\text{--}1260\text{ cm}^{-1}$, and $1185\text{--}1190\text{ cm}^{-1}$, respectively. Therefore in the complexes, these bonding vibrations are shifted to a higher field than in the free ligands.

UV-Vis spectra of the synthetic ligands and their metal complexes were measured in methanol solutions of the concentration $3.0 \times 10^{-5}\text{ M}$ at room temperature. UV-Vis spectra of synthetic unsymmetrical salen-type ligands were performed in Figure 1. They showed bands at 233–234 nm and 263–266 nm, which may be assigned to the $\pi \rightarrow \pi^*$ electronic transitions of aromatic rings, at 320 and 348–355 nm assigned to the $n \rightarrow \pi^*$ transitions of free electrons of N and O of C=N and C-O [23], at 450 and 470–474 nm assigned to the electronic transitions of C=O. There are few differences in UV-Vis spectra of the ligands with different substituted groups.

UV-Vis spectra of synthetic unsymmetrical salen-type Fe(III) complexes are obtained in Figure 2. Upon complexation, the maximum absorption bands of obtained ligands were shifted to different wavelengths, indicating the coordination of the ligands to metal [29].

The absorption bands with wavelengths of maximum absorption at 223–234 nm were assigned to $\pi \rightarrow \pi^*$ electronic transition of aromatic rings; 295–300 nm and 334–342 nm could present for $n \rightarrow \pi^*$ electronic transitions of free electrons on N and O of C=N and C-O. A band is observed at 431–440 nm, which can be assigned to the electronic transitions of C=O. A weak band is observed at about 500 nm, which can be assigned to LMCT transitions [24, 37]. The d-d bands were not observed due to the low concentration ($3.0 \times 10^{-5}\text{ M}$) of the solutions. These bands should be of low intensity in the region of 550–650 nm. There are also small differences in UV-Vis spectra of Fe(III) complexes bearing ligands with different substituted groups.

Fe(III) complexes exhibit effective magnetic moment values of 5.78 – 6.00 BM due to the presence of high-spin five unpaired electrons, which indicate an octahedral geometry around Fe(III) ions [38, 39].

3.2. Electrochemical Studies. The electrochemical behaviors of the synthetic unsymmetrical salen-type Fe(III)

FIGURE 1: UV-Vis absorption spectra of unsymmetrical salen-type Schiff base ligands.

FIGURE 2: UV-Vis absorption spectra of unsymmetrical salen-type Fe(III) complexes.

complexes were studied using cyclic voltammetry (CV). Cyclic voltammograms were recorded using a Zahner-elektrik IM6 instrument with a standard three-electrode

FIGURE 3: Cyclic voltammograms of unsymmetrical salen-type Fe(III) complexes.

TABLE 4: Reduction potentials of synthetic Fe(III) complexes.

Complex	E _{pc} (V)
[Fe(III)L1Cl]	-0.693
[Fe(III)L2Cl]	-0.603
[Fe(III)L3Cl]	-0.603
[Fe(III)L4Cl]	-0.648
[Fe(III)L5Cl]	-0.693
[Fe(III)L6Cl]	-0.648

setup, a carbon graphite as the working electrode, a platinum wire as the counterelectrode, and Ag/AgCl as the reference electrode, at room temperature with scan rate = 100 mV s⁻¹. The concentration of complexes in acetonitrile was 1.0 × 10⁻³ M and 0.1 M LiClO₄ was used as supporting electrolyte. The cyclic voltammograms of synthetic Fe(III) complexes are shown in Figure 3. Synthetic Fe(III) complexes possess well-defined cathodic peaks at (-) 0.603–(-) 0.693 V for irreversible reduction of Fe(III) → Fe(II) probably. A similar type of cathodic signal was observed in the reported Fe(III) complexes [40]. Some differences in the reduction potentials of the Fe(III) complexes must be expected from the electronic effects of the electron-withdrawing and electron-donating substituted groups (Table 4).

3.3. In Vitro Cytotoxicity Assay. The cytotoxicity of unsymmetrical salen-type Fe(III) complexes against two human cancer cell lines KB and HepG2 and a normal Human Embryonic Kidney cell line HEK-293 was determined by the MTT dye reduction method using ellipticine as the standard compound and the ligand H₂L1 for comparison purposes. The bioassay results are presented in Table 1.

The results showed that the obtained Fe(III) complexes have very excellent cytotoxicity for KB and HepG2 with IC₅₀ < 15 and 65 μM, respectively. The cytotoxic activity of [Fe(III)L1Cl] is much better than the one of the ligand H₂L1.

The synthetic complexes with different substituted groups possess different anticancer activity. The unsymmetrical salen-type [Fe(III)L1Cl] and [Fe(III)L6Cl] showed the best cytotoxic activity for KB and HepG2, respectively, with IC₅₀ being 0.81 and 1.87 μM, even better than the standard compound, ellipticine, with IC₅₀ = 1.14 and 2.11 μM for KB and HepG2, respectively (Table 1). The cytotoxic activity order of Fe(III) complexes is indicated as [Fe(III)L1Cl] ~ [Fe(III)L6Cl] > [Fe(III)L2Cl] > [Fe(III)L5Cl] > [Fe(III)L3Cl] ~ [Fe(III)L4Cl]. In addition, [Fe(III)L1Cl] and [Fe(III)L6Cl] showed the worse cytotoxic activity in several times for the normal human cell line HEK-293 with IC₅₀ being 9.33 and 6.34 μM, respectively. This selectivity is quite good and similar to the selectivity of ellipticine with IC₅₀ = 6.69 μM for HEK-293.

4. Conclusions

In this study, we have reported the synthesis and characterization of novel Fe(III) complexes bearing various unsymmetrical salen-type ligands. The ligands with electron-donating and electron-withdrawing substituted groups have some effects on their spectral properties. The UV-Vis absorption bands for LMCT of the Fe(III) complexes were observed at 430–440 nm. Interestingly, the cyclic voltammograms of the Fe(III) complexes show cathodic peaks for irreversible reduction of Fe(III) → Fe(II) at (-) 0.603–(-) 0.693 V. The obtained Fe(III) complexes were all estimated on the cytotoxicity *in vitro* for KB and HepG2 human cancer cells. The results showed that the synthetic Fe(III) complexes have excellent cytotoxicity for KB and HepG2 human cancer cells (IC₅₀ < 15 and 65 μM, respectively). Among them, [Fe(III)L1Cl] and [Fe(III)L6Cl] showed the best cytotoxic activity for KB and HepG2 with IC₅₀ = 0.81 and 1.87 μM, respectively, even better than the standard compound, ellipticine, with IC₅₀ = 1.14 and 2.11 μM for KB and HepG2 respectively.

Data Availability

All data used to support this report's findings are included within the article and in supplementary materials.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Supplementary Materials

The spectral data of synthetic unsymmetrical salen-type ligands and their Fe(III) complexes. (*Supplementary Materials*)

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