

New Derivatives of Thiazolidine and Their Complexes with Cu²⁺ and Ag⁺: Synthesis, Theoretical Study, and Anti-Breast Cancer Activity

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Abstract: Thiazolidine complexes have attracted interest due to their diverse coordination properties and biological activities. In this study, four new thiazolidine-4-carboxylic acid complexes (L1–L4) were synthesized by reacting L-cysteine with different aromatic and aliphatic aldehydes, followed by reaction with Cu(II) and Ag(I) ions in a 1:2 ratio. These complexes were extensively characterized by elemental analysis, FTIR, UV-vis, NMR, mass spectroscopy, magnetic susceptibility, molar conductivity, thermogravimetric analysis, scanning electron microscopy (SEM), and energy-dispersive X-ray spectroscopy (EDX). From spectroscopic analysis, it was revealed that all the complexes were bidentate NO-donor type, exhibiting square-planar or octahedral geometries around Cu(II) ion and tetrahedral geometries around Ag(I) ion. The cytotoxic activities of some complexes were evaluated against MCF-7 breast cancer cell lines. The results showed that all four ligands exhibited moderate cytotoxicity, whereas the Cu(L3)₂ and Ag(L4)₂ complexes showed greater cytotoxicity than their free ligands. DFT calculations were performed to confirm the study's results, which revealed that thiazolidine derivative complexes have greater potential to be developed into effective metal-based anticancer drugs.

Keywords: thiazolidine; DFT; anti-breast cancer; MTT; metal complexes

■ INTRODUCTION

Thiazolidines are a family of sulfur- and nitrogen-containing heterocyclic compounds, known for their diverse biological activities and applications as drugs [1–3]. Among the members of this family, thiazolidine-4-carboxylic acid is a crucial structural motif, which is responsible for the synthesis of various bioactive compounds due to its anticancer and antibacterial activities [4–6]. Beyond their inherent biological importance, thiazolidines are known for their coordination abilities, which make them suitable for the development of various metal complexes, underscoring their role as ligands in coordination and bioinorganic chemistry [7].

The coordination behavior of thiazolidines as a ligand towards various transition metal ions is based on the principle of Lewis acid-base interactions, where the

metal ions act as electron pair acceptors, and the hetero-atoms present in the thiazolidine ring are the electron pair donors [8–9]. The coordination behavior of thiazolidines has been extensively studied [10], and various complexes have been shown to exhibit promising anti-HIV and anticancer activities, including inhibition of tumor cell proliferation and restoration of contact inhibition [11–13].

In particular, Cu(II) is an essential transition metal ion with biological significance, participating in redox reactions, electron transport, and defense mechanisms [14–15], while Ag(I) complexes have also shown promise as therapeutic agents [16–18]. However, coordination complexes containing thiazolidine-4-carboxylic acid as a ligand have received little attention, underscoring the need to conduct a series of studies on their synthesis, characterization, and biological activities [19]. The

choice of Cu(II) and Ag(I) coordination centers is determined by their specific electronic configurations and coordination abilities, as well as their effects on the biological activity of metal-based bioactive compounds. Cu(II), with its d^9 configuration, forms stable complexes with nitrogen- and oxygen-donor ligands and exhibits redox activity that may significantly affect its interactions with biological targets and anticancer activities. On the other hand, Ag(I), with its d^{10} configuration, forms redox-inactive but structurally stable complexes, enhancing lipophilicity and cellular uptake of ligands. The use of both metals enables comparison of redox-active and redox-inactive systems and their effect on the biological activity of thiazolidine-based complexes.

Recent studies have shown increasing interest in thiazolidine-derived compounds for potential applications in anticancer therapy. Although a large volume of literature is devoted to organic thiazolidine structures and their biological activity, coordination complexes with thiazolidine-derived ligands remain under investigated. For example, thiazolidine-thiourea complexes of silver and gold have been reported, with preliminary results indicating that they exhibit greater cytotoxicity against lung cancer cells than their free forms. These results point to the impact of coordination on thiazolidine-derived structures [20]. In another study, new bis-thiazolidine amide complexes were evaluated for their potential in anticancer therapy using density functional theory (DFT) calculations and cytotoxicity assays. These results point to a growing interest in thiazolidine-derived structures with potential applications in anticancer therapy [21]. Furthermore, although not coordination complexes per se, thiazolidine-derived structures bearing metal phthalocyanines have demonstrated cytotoxic activity against various cancer cell lines [22]. These results indicate growing interest in thiazolidine-derived structures with potential applications in anticancer therapy. Overall, it is apparent that thiazolidine-derived structures are increasingly being evaluated for potential applications in anticancer therapy, whereas studies on metal complexes with thiazolidine-derived ligands, particularly with biologically relevant metals such as Cu(II) and Ag(I), are limited.

In this study, we report on the synthesis and characterization of such complexes and their evaluation with a view to their potential use in anticancer therapy [23]. The general objective of the present study is to synthesize, characterize, and evaluate novel thiazolidine-4-carboxylic acid derivatives and their Cu(II) and Ag(I) complexes as prospective anticancer agents. Specifically, the study aims to: (i) synthesize novel thiazolidine ligands based on L-cysteine and different aldehydes, (ii) synthesize Cu(II) and Ag(I) complexes with the novel ligands, characterize them by different techniques, (iii) determine the coordination geometry of the synthesized complexes, (iv) evaluate the in vitro cancer cell growth inhibition by the ligands or complexes against the MCF-7 breast cancer cell line, and finally, and (v) support the experimental results with theoretical evidence by carrying out DFT calculations on the ligands or complexes, focusing on their electronic properties.

■ EXPERIMENTAL SECTION

Materials

All chemicals used in this study were of analytical grade ($\geq 98\%$ purity) and purchased from Sigma-Aldrich, Scharlau, and BDH, and were used without further purification. L-cysteine (26 mmol, 3.16 g) and various aldehydes, namely 3,5-dimethoxy-4-hydroxybenzaldehyde (26 mmol), 4-(diethylamino)benzaldehyde (26 mmol, 4.60 g), (*E*)-2-methyl-3-phenylacrylaldehyde (26 mmol, 3.65 g), and phenanthrene-9-carbaldehyde (26 mmol, 5.36 g), were employed in the synthesis of the ligands. Metal salts, including $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ (2 mmol, ~ 0.85 g) and AgNO_3 (2 mmol, ~ 0.84 g), were used for the preparation of the metal complexes. Solvents such as ethanol, distilled water (10 mL), methanol, diethyl ether, dimethyl sulfoxide (DMSO), and deuterated dimethyl sulfoxide ($\text{DMSO}-d_6$) were used as received. Tetramethylsilane (TMS) was utilized as an internal standard for NMR measurements, while potassium bromide (KBr) was used for FTIR analysis. For biological assays, RPMI-1640 and DMEM media, supplemented with fetal bovine serum (10%), streptomycin (100 $\mu\text{g/mL}$), and penicillin (100 U/mL), along with trypsin/EDTA and phosphate-

buffered saline (PBS), were obtained from Gibco. Cisplatin was used as a reference drug in cytotoxicity evaluations.

Instrumentation

The melting points of ligands and complexes were ascertained using Thermo Scientific 9100. An FTIR spectrophotometer (Shimadzu model IR Affinity-1) was used to obtain Infrared spectra as KBr discs. UV-vis spectra were acquired using a Shimadzu UV1800 spectrometer, with DMSO as the solvent. The ^1H - and ^{13}C -NMR spectra of the ligands were acquired with a Bruker 400 MHz spectrometer. Mass spectra were obtained by the electron ionization (EI) method with Agilent Technologies spectrometers at an electron energy of 70 eV. Thermogravimetric Analysis of metal complexes was conducted using TGA Q50 V 6.7 at a heating rate of 10 °C/min within a temperature range of 20–750 °C. The Phoenix-986 Spectrometer assessed the proportion of Ag(I) and Cu(II) ions using the flame atomic absorption method. A balance from Sherwood Scientific magnetic was used to assess the magnetic susceptibility of metal complexes at ambient temperature as powdered materials. A conductivity meter (HI 2315) was used to measure the molar electrical conductivity of metal complexes at a concentration of 1×10^{-3} M.

Procedure

Synthesis of ligands

A mixture of L-cysteine (26 mmol, 3.16 g) and 3,5-dimethoxy-4-hydroxy benzaldehyde (26 mmol) in 60 mL ethanol and water (10 mL) was stirred at room temperature for 24 h. After this reaction, TLC is used to monitor the reaction's completion. The precipitate was collected via filtration and rinsed with diethyl ether. The solid obtained from a mixture of water and hot ethanol was recrystallized twice to yield a white powder [24]. The same procedure was used to synthesize the ligands L2, L3, and L4, but employing 4-(diethylamino)benzaldehyde (26 mmol, 4.60 g), (*E*)-2-methyl-3-phenylacrylaldehyde (26 mmol, 3.65 g), phenanthrene-9-carbaldehyde (26 mmol, 5.36 g), and (*E*)-2-methyl-3-phenylacrylaldehyde (26 mmol, 3.65 g), respectively. The structure of the L1–L4 is shown in Fig. 1.

(2*R*,4*R*)-2-(4-hydroxy-3,5-

dimethoxyphenyl)thiazolidine-4-carboxylic acid (L1). UV-vis (DMSO, nm): 275 (π - π^*), 308 (n - π^*). *cis*-isomer (33%): ^1H -NMR (DMSO- d_6 , δ , ppm): 5.53 (*s*, 1H, H2); 4.34 (*m*, 1H, H4 J = 3.92 Hz); 3.75 (*m*, 1H, H5a J = 8 Hz); 3.37 (*m*, 1H, H5b J = 7.6 Hz), 3.80 (*s*, 6H, H_{8,10}), 6.58–6.78 (*m*, 2H, Ar-H). ^{13}C -NMR: 38.28 (CH₂)C5, 64.78 (CH)C4, 38.28 (CH)C2, 128.70–147.80 (C-Ar), 172.19 (C=O), δ 56.03 (–OCH₃). *trans*-isomer (64%): ^1H -NMR (DMSO- d_6 , δ , ppm): 5.54 (*s*, 1H, H2); 4.33 (*m*, 1H, H4 J = 3.6 Hz); 3.76 (*m*, 1H, H5a J = 7.9, 8 Hz); 3.31 (*m*, 1H, H5b J = 7.8 Hz); 3.80 (*s*, 6H, H_{8,10}); 6.58–6.78 (*dd*, 2H, Ar-H); 8.47 (*s*, 1H, OH). ^{13}C -NMR: 37.73 (CH₂)C5, 65.45 (CH)C4, 72.45 (CH)C2, 128.70–147.80 (C-Ar), 173.16 (C=O), 56.07 (–OCH₃). MS (EI, m/z (%): 282.2 [M^+ , 167.1 base peak]).

(2*R*,4*R*)-2-(4-(diethylamino)phenyl)thiazolidine-4-carboxylic acid (L2).

A white-yellowish solid powder. UV-vis (DMSO, nm): 298 (π - π^*). *cis*-isomer (39%): ^1H -NMR (DMSO- d_6 , δ , ppm): 5.33 (*s*, 1H, H2); 3.31 (*s*, 1H, H3); 4.71 (*dd*, 1H, H4 J = 12.1 Hz); 3.51 (*t*, 1H, H5a J = 12 Hz); 3.48 (*t*, 1H, H5b J = 8.22 Hz); 1.37 (*tri*, 6H, H₉); 2.78 (*t*, 4H, H_{8,8'}); 6.58–6.78 (*dd*, 4H, Ar-H J = 12.3 Hz). ^{13}C -NMR: 38.06 (CH₂)C5, 64.76 (CH)C4, 72.13 (CH)C2, 115.23–145.62 (6C) (C-Ar), 172.24 (C=O), δ 14.77 (–CH₃), 112 (–NCH₃). *trans*-isomer (61%): ^1H -NMR (DMSO- d_6 , δ , ppm): 5.27 (*s*, 1H, H2); 3.31 (*s*, 1H, H3); 4.45 (*dd*, 1H, H4 J = 8 Hz); 3.43 (*dd*, 1H, H5a J = 12.2 Hz); 3.31 (*t*, 1H, H5b J = 8 Hz); 1.06 (*tri*, 6H, H_{9,9'}); 2.75 (*t*, 4H, H_{8,8'}); 7.30–7.67 (*dd*, 4H, Ar-H). ^{13}C -NMR: 39.06 (CH₂)C5, 65.39 (CH)C4, 71.52 (CH) C2, 115.23–145.62 (6C) (C-Ar), 172.14 (C=O), 14.77 (–CH₃), 112 (–NCH₃). MS (EI, m/z (%): 280.1 [M^+ , 178.1 base peak].

(2*R*,4*R*)-2-(phenanthren-9-yl)thiazolidine-4-carboxylic acid (L3).

A white solid powder. UV-vis (DMSO, nm): 302.50 (π - π^*). *cis*-isomer (38%): ^1H -NMR (DMSO- d_6 , δ , ppm): 6.47(*s*, 1H, H2); 3.31 (*s*, 1H, H3); 4.34 (*dd*, 1H, H4 J = 4 Hz); 3.43 (*t*, 1H, H5a J = 3.9 Hz); 3.47 (*t*, 1H, H5b J = 4.2 Hz); 7.63–8.90 (*m*, 9H, Ar-H). ^{13}C -NMR: 37.64 (CH₂)C5, 65.05 (CH)C4, 68.27 (CH)C2, 122.69–135.57 (C-Ar), 172.30 (C=O). *trans*-isomer (62%): ^1H -NMR (DMSO- d_6 , δ , ppm): 6.28 (*s*, 1H, H2); 4.14 (*dd*, 1H, H4 J = 4.1 Hz); 3.49 (*t*, 1H, H5a J = 4.4 Hz);

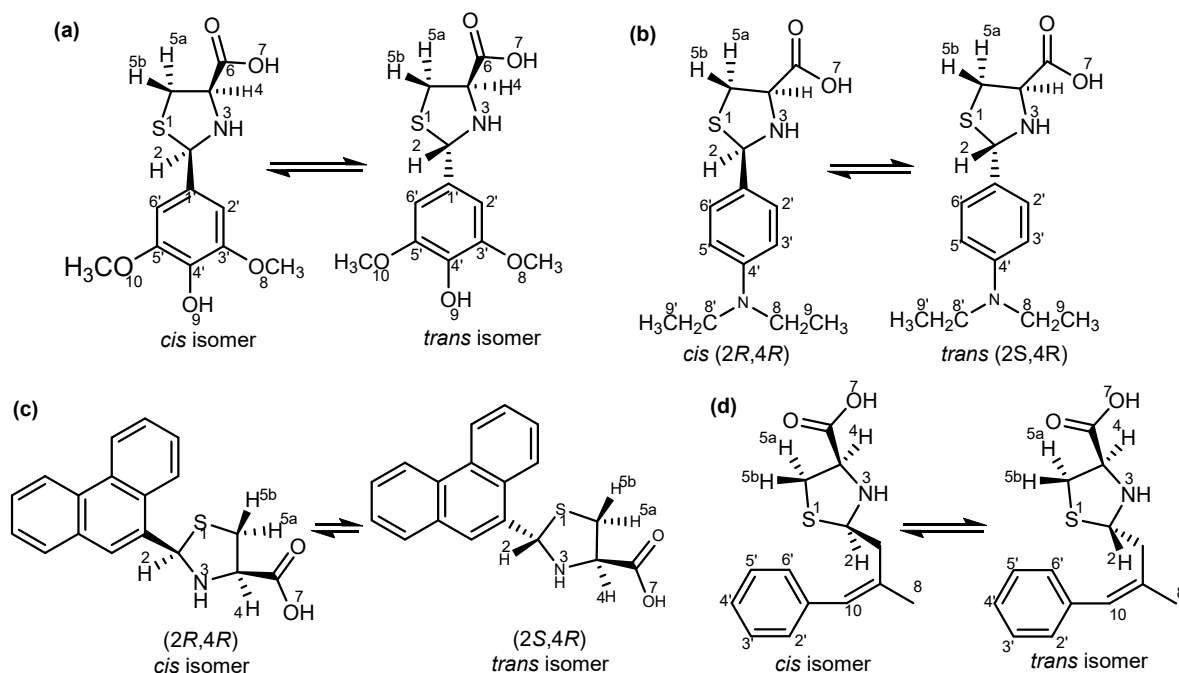


Fig 1. *cis* and *trans* Diastereoisomer of (a) L1, (b) L2, (c) L3, and (d) L4 ligand

3.44 (*d*, 1H, H5b *J* = 4.8 Hz); 7.65–8.89 (*m*, 8H, Ar-H). ¹³C-NMR: 37.77 (CH₂)C5, 65.28 (CH)C4, 68.62 (CH)C2, 122.69–135.57 (C-Ar), 172.24 (C=O). MS (EI, *m/z* (%): 308.2 [M⁺, 218.1 base peak].

(2R,4R)-2-((E)-2-methyl-3-phenylallyl)thiazolidine-4-carboxylic acid (L4). A white solid powder. UV-vis (DMSO, nm): 285.50 (π-π*), 340 (π-π*). *cis*-isomer (39%): ¹³C-NMR: (DMSO-*d*₆, δ, ppm) 39.05 (CH₂)C5, 65.30 (CH)C4, 75.45 (CH)C2, 124.55–137.24 (6C) (C-Ar), 172.45 (C=O), 13.3 (–CH₃). *trans*-isomer (61%). ¹³C-NMR: 37.45 (CH₂)C5, 64.45 (CH)C4, 76.35 (CH)C2, 124.55–137.24 (6C) (C-Ar), 173.05 (C=O), 13.3 (–CH₃). MS (EI, *m/z* (%): 249.1 [M⁺, 146.1 Base peak]. SEM morphology (small, irregular crystals).

Synthesis of metal complexes

Metal complexes (1, 2, 3, 4, 5, 6, and 7) were synthesized by combining hot methanol containing ligands L1, L2, L3, and L4 (2 mmol) with a heated solution of metal salt (2 mmol). The resultant mixture was then refluxed for 2 to 4 h. The isolated complexes were subjected to hot filtration, followed by washing with methanol and subsequently with diethyl ether to eliminate residual water. They were desiccated at 70 °C.

[Cu(L1)₂·2H₂O]·½H₂O (1). (Wt. g): L1 = 1.42, CuCl₂·2H₂O = 0.85. Color: dark grey. UV-vis. (DMSO, nm): 205 (π-π*), 308 (n-π*). μ_{eff} (B.M): 1.34. Molar conductivity: 13 Ω⁻¹ cm² mol⁻¹ in DMSO.

[Ag(L1)₂]·½H₂O (2). (Wt. g): L1 = 1.42, AgNO₃ = 0.84. Color: yellowish white. UV-vis. (DMSO, nm): 295 (π-π*), 368 (C-T). μ_{eff} (B.M): 0.90. Molar conductivity: 16.5 Ω⁻¹ cm² mol⁻¹ in DMSO.

[Cu(L2)₂]Cl₂·½H₂O (3). (Wt. g): L2 = 1.40, CuCl₂·2H₂O = 0.85. Color: dark grey. UV-vis. (DMSO, nm): 291 (π-π*), 340 (C-T). μ_{eff} (B.M): 1.73. Molar conductivity: 111.2 Ω⁻¹ cm² mol⁻¹ DMSO.

[Ag(L2)₂]·½H₂O (4). (Wt. g): L2 = 1.40, L2 = 1.66. AgNO₃ = 0.84. Color: yellowish white. UV-vis. (DMSO, nm): 277 (π-π*), 343 (π-π*), 360 (n-π*), 380 (C-T). μ_{eff} (B.M): 0.9. Molar conductivity: 25.20 Ω⁻¹ cm² mol⁻¹ in DMSO.

[Cu(L3)₂]·½H₂O (5). (Wt. g): L3 = 1.54, CuCl₂·2H₂O = 0.85. Color: Dark grey. μ_{eff} (B.M): 1.78. Molar conductivity: 11.25 Ω⁻¹ cm² mol⁻¹ in DMSO.

[Cu(L4)₂]Cl₂·½H₂O (6). (Wt. g): L4 = 1.54, CuCl₂·2H₂O = 0.85. Color: dark grey. μ_{eff} (B.M): 1.89. Molar conductivity: 50.6 Ω⁻¹ cm² mol⁻¹ in DMSO. SEM morphology (crystalline rod-shaped).

[Ag(L4)₂] $\cdot\frac{1}{2}$ H₂O (7). (Wt. g): L4 = 1.24, AgNO₃ = 0.84. color: yellowish white. μ_{eff} (B.M): 0.91. Molar conductivity: 8.60 $\Omega^{-1} \text{ cm}^2 \text{ mol}^{-1}$ in DMSO. SEM morphology (mushroom crystal type).

Anticancer activity

To evaluate the *in vitro* cytotoxicity of the investigated compounds, an MTT assay [19] was used. Human breast cancer (MCF-7 cell line) was obtained from the National Cell Bank of Iran. Cells were grown in RPMI-1640 and DMEM media, respectively, supplemented with antibiotics (100 $\mu\text{g/mL}$ streptomycin and 100 U/mL penicillin) and 10% FBS. Trypsin/EDTA, as well as PBS solution, were used to pass the cells, which were kept at 37 °C in wet air with 5% CO₂ (PBS). The same cultured media and external factors used for single-layer cell culture were also employed for the 3D cell colonies. Cisplatin was used as a standard drug for comparison. The cytotoxicity test was conducted as a primary test. The reported IC₅₀ values are from a single experiment; therefore, no standard deviation is provided.

Computational study

DFT calculations for ligands L1, L2, L3, and L4 were performed using the BLYP functional and the DNP basis set [25]. The Materials Studio-DMol3 5.5 version of the software was used. The output file provided several quantum-chemical parameters computed using Eqs. (1–6), in addition to the molecular orbital energy values E_{LUMO} and E_{HOMO} [26–27].

$$\text{Electronegativity}(\chi) = -\frac{1}{2}(E_{\text{HOMO}} + E_{\text{LUMO}}) \quad (1)$$

$$\text{Chemical potential}(\mu) = -\chi = \frac{1}{2}(E_{\text{HOMO}} + E_{\text{LUMO}}) \quad (2)$$

$$\text{Chemical hardness}(\eta) = \frac{1}{2}(E_{\text{HOMO}} - E_{\text{LUMO}}) \quad (3)$$

$$\text{Global softness}(S) = \frac{1}{2}\eta \quad (4)$$

$$\text{Global electrophilicity}(\omega) = \frac{\mu^2}{2\eta} \quad (5)$$

$$\text{Absolute softness}(\sigma) = \frac{1}{\eta} \quad (6)$$

RESULTS AND DISCUSSION

Synthesis of the Ligands and Their Metal Complexes

Thiazolidine derivatives L1, L2, L3, and L4, which were produced in a good yield via the reaction of L-

cysteine with 3,5-dimethoxy-4-hydroxy benzaldehyde, 4-(diethylamino)benzaldehyde, phenanthrene-9-carbaldehyde, and (*E*)-2-methyl-3-phenylacrylaldehyde. This condensation yielded a mixture of the diastereomers *cis*-(2*R*,4*R*) and *trans*-(2*S*,2*R*), which were inseparable. The synthesis of metal complexes was accomplished through the reaction of L1, L2, L3, and L4 with Cu(II) and Ag(I) ions in a 1:2 ratio (M:L), as illustrated in Fig. 2.

Characterization

Mass spectrometry, FTIR, ¹H-, and ¹³C-NMR have been used to propose the ligand structure. Mass spectra of the synthesized ligands showed molecular ion peaks at $m/z = 282.2, 280.1, 309.1,$ and 249.1 for L1, L2, L3, and L4, respectively, but with low relative abundance. The appearance of a set of fragments indicated the presence of the proposed compound. The complexes' mass spectra didn't show the peaks expected for their molecular ions, as illustrated in Fig. S1–S4.

Table 1 presents the IR spectral data for the synthetic compounds. L1, L2, L3, and L4 showed broad, strong, or medium bands of ligands and complexes at 3421–3552 cm^{-1} attributed to stretching vibration of O–H, and a band at the range 1635–1610 cm^{-1} attributed to stretching vibration of C=O, while the appearance of the stretching $\nu(\text{C}=\text{C})$ band occurred in the range of 1489–1589 cm^{-1} . The difference in band position between the complexes and ligands causes metal–ligand coordination. Zwitterions in amino acids can be distinguished by their bands at 2846, 2708, and 2636 cm^{-1} in the spectra of L1, L2, L3, and L4 [28], which is a result of the formation related to the internal balance of the amino secondary (NH_2^+) and carboxylate groups (COO^-) [29–30]. The absence of these bands in the spectrum of the metal complexes indicates that the metal ions are coordinated with oxygen and nitrogen atoms.

Ligands' ¹H-NMR spectra show that the thiazolidine was formed as a (2*S*,4*R*) and (2*R*,4*R*)-diastereomer mixture, as the 2-substituted thiazolidine, when there is a chiral carbon atom [31–32]. The ¹H-NMR spectra of ligands L1, L2, and L3, as presented in Fig. S5–S7, show a multiplet signal at 6.74–6.97, 6.85–7.67, and

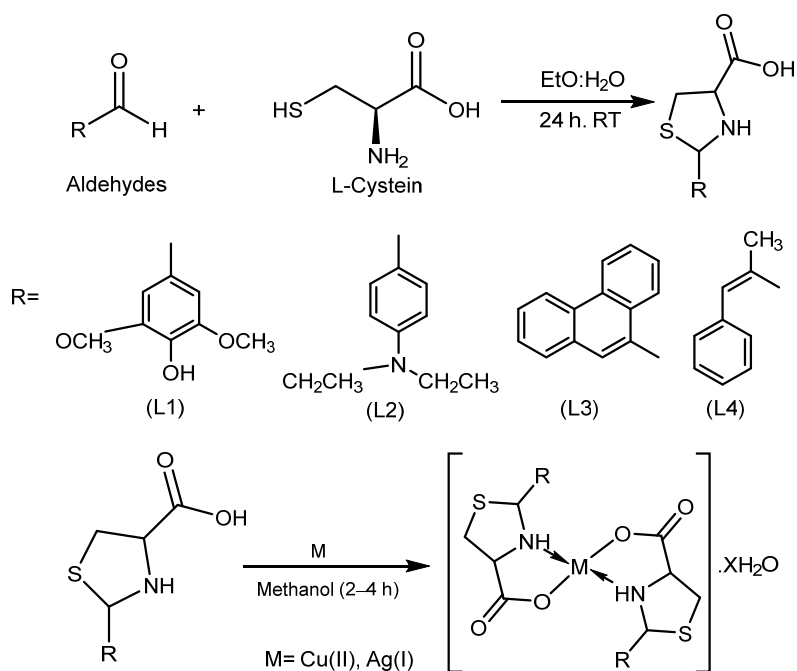


Fig 2. Synthesis route of ligands (L1, L2, L3 and L4) and their complexes

Table 1. FTIR data, melting point, and yield of synthesized compounds

Compound	IR assignment						m.p. (°C)	Yield%
	v(O-H) str.	v(N-H) str.	v(C-H) str. aromatic	v(C-H) str. alpha	v(C=O) str. acid	v(C=C) str. ar		
L1	3552 s (phenol)	3408 br.	3078 w	2966 w 2943	1635 s	1571 s	139–140	93
L2	-	3442 w	3001 w	2972 w sym 2933 w asym	1610 s	1519 w	188–189	81
L3	-	3444 m	3018 w	2972 w	1629 w	1571	169–169.6	77
L4	-	3412 m	3051 w	2970 w 2922 w	1622 s	1585 1492	163–164	78
1	3442 br	3226 w	3020 w	2916 w	1622 s	1489	280	58
2	3545 (carboxylic) 3458	3417	3045	2916 w	1620 s	1587	295	60
3	3469 w	3234 w	3035	2918 w	1620 s	1589 w	>300	52
4	3429 s	3305	3059	2976 2914	1616	1581	>300	55
5	3421 br	3240 m	3126 w	2920 w	1627 vs	1487 m	>300	55
6	3466 br	3232 w	3030 w	2918 w 2588 w	1620 vs	1587 s	290–292 dec	67
7	-	3433	3126 w	2920 w	1639 s	1591	>300 dec	55

7.63–8.90 ppm, respectively, which were attributed to aromatic protons. Because the protons were not equivalent, a multiplet signal was observed compared to the protons on other ring carbon atoms; proton H2 was

considered to be markedly deshielding, which could be attributed to the presence of the phenyl ring on the same carbon atom. Based on the molecule's overall structure, the proton H4 was found to resonate at 4.34, 4.43, and

4.35 ppm, attributed to L1, L2, and L3, respectively. Overlapping doublets of doublets are caused by H4 protons, while the resonance of the proton H2 yielded a singlet at 5.53, 5.27, and 6.47 ppm attributed to L1, L2, and L3, respectively. At 8.47 ppm for L2, the proton appeared to be associated with the hydroxyl group. However, the zwitterion phenomenon led to the disappearance of protons from carboxylic and amine groups [33-34].

All ligands' ^{13}C -NMR spectra (L1, L2, L3, and L4) are characterized by three kinds of signals, as displayed in Fig. S8-S11. Signals appearing in the range of 10–80 ppm refer to the aliphatic carbon (sp^3), signals appearing in the range of 100–160 ppm are attributed to the aromatic signals (sp^2 hybridized carbons), and the signals appearing within the range of 171–173 and 168–171 ppm are attributed to carboxylic acid [35]. An equilibrium is established in C(2) between two isomers. The solvent type significantly influenced the *cis-trans* ratios; in $\text{DMSO-}d_6$, the *trans* diastereoisomer predominated upon complete equilibration [36-37].

Flame-atomic absorption was used to determine the mole ratio of metal-ligand in the complexes, which revealed that metal ions (Cu(II) and Ag(I)) formed 1:2 chelates with L1, L2, L3, and L4 ligands. The molar conductivity values of Cu-complexes (1, 3, 5, and 6) were found to be 24.3, 11.3, 111.2, and $50.6 \Omega^{-1} \text{ cm}^2 \text{ mol}^{-1}$, respectively. Both L5 and L6 possess electrolyte properties that contain a counter-ion, but L1, L3, and L5 possess non-electrolyte properties. At the same time, Ag-complexes 2, 4, and 7 had conductive values of 16.5, 25.2, and $8.6 \Omega^{-1} \text{ cm}^2 \text{ mol}^{-1}$, respectively, indicating that they have non-electrolyte properties, and they did not contain counter ions [38].

Cu-complexes (1, 3, 5, 6) were characterized by the presence of an unpaired electron in the *d*-orbital, which is confirmed by the values of the effective magnetic moment (μ_{eff}) in the range 1.73–1.92 B.M. Hence, square planar (dsp^2) was the suggested geometric shape around the copper ion [27-28]. Except that complex (1) was octahedral. Ag-complexes 2, 4, and 7 were characterized by the presence of unpaired electrons, as indicated by their effective magnetic moment (μ_{eff}) values of 0.90, 0.91, and 0.90 B.M., respectively. Tetrahedral (sp^3) was the expected geometric

shape of these complexes [39].

The results of the decomposition stages and thermograms indicate the presence of lattices and coordinated water in the structures of certain complex molecules. These decompose in the early stages of disintegration at 50–210 °C, while later stages involve the loss of parts of the ligands. The stages of thermal decomposition of metal complexes are shown in Table 2.

Anti-Breast Cancer Study

The cytotoxicity of all ligands (L1–L4) was tested against MCF-7 breast cancer cells using five concentrations of each ligand, ranging from 31.25 to 500 $\mu\text{g/mL}$, while their metal complexes were tested using lower concentrations, ranging from 0.781 to 12.5 $\mu\text{g/mL}$, as detailed in Table S1. The percentage of cell growth inhibition and IC_{50} values were calculated using Eq. (7) [40]:

$$\text{Viability\%} = \frac{\text{mean of OD}_{\text{sample}}}{\text{mean of OD}_{\text{control}}} \times 100\% \quad (7)$$

In this study, the increase in cytotoxicity of metal complexes relative to their free ligands provides clear evidence of metal-mediated effects. Although ligands L1 to L4 have demonstrated weak to moderate activities ($\text{IC}_{50} > 70 \mu\text{g/mL}$, except L2), upon coordination with Cu(II) and Ag(I), there was a significant decrease in the IC_{50} values, especially in complexes 3, 6, and 7. This pattern implies that metal incorporation is a significant factor in biological activity, not just the ligands [6-7].

Among these compounds, complex 6, which contains Cu(II), exhibited superior cytotoxicity compared to its parent ligand L4, with an IC_{50} of 4.63 $\mu\text{g/mL}$. It is therefore implied that the ability of copper, which is capable of performing redox reactions, enhances cytotoxic efficiency. This is consistent with the potential role of Cu(II) complexes in inducing oxidative stress in cancer cell mitochondria. At the same time, complex 7 is seen to depict the highest inhibition (85.29%), also with a very low $\text{IC}_{50} = 3.10 \mu\text{g/mL}$, implying that coordination with silver significantly enhances its ability as a potential anticancer drug, possibly via its ability to form well-coordinated interactions with the

Table 2. Thermogravimetric analysis data of metal complexes

Complexes	Stages	Temp. range (°C)	%Weight loss		Decomposition parts
			Found	Calculated	
[Cu(L1) ₂ ·2H ₂ O]·½H ₂ O (1)	I	50–110	1.21	1.18	½H ₂ O
	II	110–170	11.16	10.31	2H ₂ O
	III	170–190	18.30	19.80	2(OCH ₃)
	IV	190–210	10.03	10.30	2CN
	V	210–270	14.29	15.10	2(OH)
[Ag(L1) ₂]·½H ₂ O (2)	I	50–180	1.70	1.30	½H ₂ O
	II	180–260	30.20	29.47	2(C ₆ H ₆)·CO ₂
	III	260–800	10.01	10.03	-OCH ₃ ·OH
[Cu(L2) ₂]Cl ₂ ·H ₂ O (3)	I	50–130	2.08	2.55	H ₂ O
	II	130–160	4.33	4.17	C ₂ H ₅
	III	160–250	46.85	44.64	3(C ₃ H ₅ SN)·HCl
	IV	250–425	7.14	7.59	CO
[Ag(L2) ₂]·½H ₂ O (4)	I	50–120	1.60	1.32	½H ₂ O
	II	100–210	3.50	4.10	CO
	III	210–280	33.00	33.40	2(C ₆ H ₆ ·C ₂ H ₅)
[Cu(L3) ₂]·½H ₂ O (5)	I	50–150	1.88	1.30	½H ₂ O
	II	150–200	34.86	34.29	3(C ₆ H ₆)
	III	200–260	18.40	17.39	C ₆ H ₆
	IV	260–440	5.89	4.59	OH
[Cu(L4) ₂]Cl ₂ ·½H ₂ O (6)	I	50–130	1.92	1.40	½H ₂ O
	II	130–170	6.82	6.94	CO ₂
	III	170–210	17.65	17.14	2(-CH ₃ Cl)
	IV	210–280	27.30	26.00	2(C ₃ H ₅ N)·OH
[Ag(L4) ₂]·½H ₂ O (7)	I	50–110	1.50	1.46	½H ₂ O
	II	110–180	3.50	4.20	CH=CH
	III	180–260	37.00	37.50	2(C ₃ H ₅ SN)·CO ₂

biological targets, especially given the abundance of sulfur and nitrogen atoms in biomolecules [41–42].

In general, comparing ligands and their metal complexes shows that the metal ion and the coordination environment affect cytotoxicity. The results reinforce the notion that the anticancer properties arise from a combination or synergistic effect of the ligand and the metal, rather than from either in isolation. The MCF-7 cell line was selected as a representative estrogen receptor-positive (ER⁺) human breast cancer cell line and is widely used for the preliminary evaluation of anticancer drugs. MCF-7 cells are extensively studied and exhibit a consistent growth pattern, making them a suitable candidate for investigating the cytotoxicity of metal-based compounds, which is essential for comparing results with previous work. At this stage, the biological evaluation was

conducted to screen compounds for promising anticancer activity. Further studies comparing results across other breast cancer cell lines and normal cells are a significant area for future work.

SEM and EDX Analysis

The SEM is a technique that generates images by scanning the outer surface of a sample coated with gold and directing a concentrated beam of accelerated electrons at it. This interaction with the sample's atoms produces signals that provide valuable information about the overall shape and structure of the sample's outer surface [43]. The chemical L4 and its complexes (6 and 7) were analyzed by EDX to identify surface elements and verify the presence of Ag and Cu atoms in the structures of the synthesized complexes (6 and 7) [44].

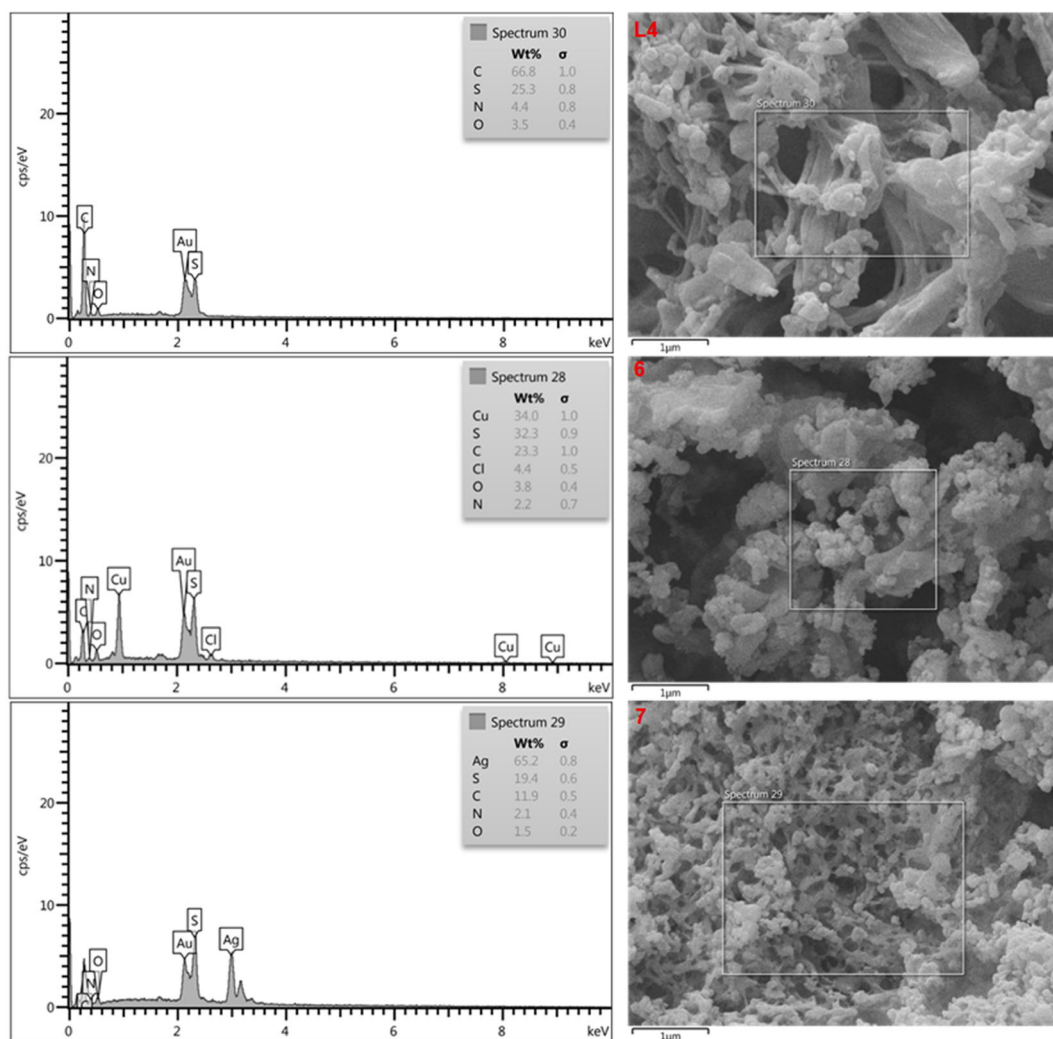


Fig 3. SEM and EDX plot of a thiazolidine ligand (L4) and its metal complexes 6 and 7

The ligand L4 produced irregularly tiny, sheet-like crystals, whereas complex 6 exhibited a crystalline rod-shaped morphology. Conversely, the particles of complex 7 manifested as mushroom-shaped crystals. Fig. 3 depicts the SEM images and EDX analysis of the examined substances.

Computational Study

The geometry of all ligands was optimized with DFT. In quantum chemical calculations, the molecular orbital energies of the lowest unoccupied molecular orbital (LUMO) and highest occupied molecular orbital (HOMO) are critical parameters, as presented in Fig. 4. The LUMO orbital functions as the principal electron acceptor, whereas the HOMO orbital operates as the primary electron donor. The synthesized compounds were stable, as indicated by their negative molecular orbital

energy values. Table 3 demonstrates that the synthesized compounds are stable, as evidenced by negative values for the E_{HOMO} and E_{LUMO} orbitals. The energy gap $E_{\text{LUMO}} - E_{\text{HOMO}}$ (ΔE), chemical softness (S), absolute softness (S_a), and chemical hardness (η), are linked to the chemical characteristics of molecules. Molecules L1, L2, L3, and L4 demonstrate significant hardness; yet, they possess diminished absolute softness and softness values. Consequently, all these compounds are comparatively stable and intricate molecules.

Thus, their use in biological cases is flexible [45]. The average energy of the HOMO and LUMO orbitals is the chemical potential (μ), while the negative of the chemical potential is referred to as electronegativity (χ). These are two contrasting values employed to determine

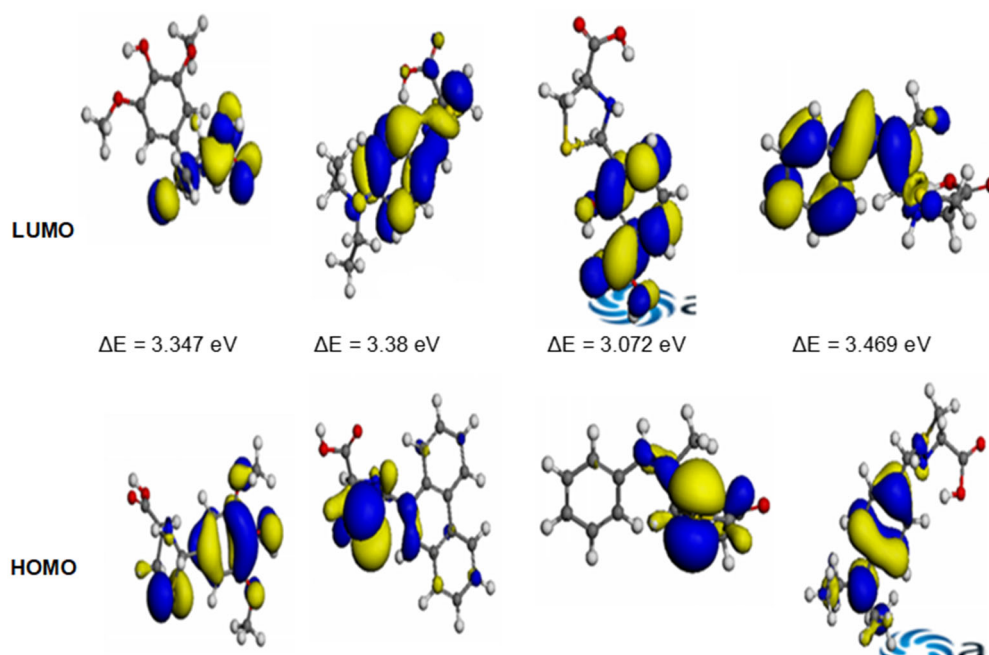


Fig 4. HOMO and LUMO orbital structures of the ligands L1, L2, L3, and L4

Table 3. Conformational parameters (eV) for all optimized structures

Compounds	E_{HOMO}	E_{LUMO}	$\Delta E_{\text{LUMO}-E_{\text{HOMO}}}$	χ	μ	η	S	ω	σ
L1	-4.786	-1.439	3.347	3.1125	-3.112	1.673	-0.836	2.894	0.597
L2	-4.438	-0.958	3.480	2.698	-2.698	1.740	-0.87	2.091	0.574
L3	-4.840	-1.768	3.072	3.304	-3.304	1.536	-0.768	3.567	0.651
L4	-5.235	-1.766	3.469	3.500	-3.500	1.734	-0.867	3.532	0.576

the dipolar degree at the molecular level [46]. Global electrophilicity (ω) is an important indicator of reactivity and can be used to assess the ability of different compounds to donate electrons [47].

The energies of the frontier molecular orbitals of the synthesized ligands are used to quantify their stability and reactivity. In general terms, the higher the ΔE , the more kinetically stable and the less reactive the ligand will be, while the opposite is true of ligands with smaller ΔE . The ΔE values of the ligands L1–L4 are in the range of 3.07–3.48 eV [48–49].

The η , or S , is also relevant to this discussion. The relatively high η of these frameworks suggests a robust structure, whereas their S reflects how these ligands rearrange their electron density upon interaction with metals and biological targets. From a purely biological perspective, higher S tends to correlate with more effective ligand delivery to targets such as proteins and

DNA due to better charge-transfer ability. Thus, a balance between η and S in this ligand set yields effective complexes without compromising biological activity [50]. In addition, it is expected that metal coordination will decrease the ΔE and increase the S of the molecules relative to the free ligands, leading to stronger bonding between the metal and the ligands and between the metal and cancer cell constituents. This electronic modulation may account for the enhanced cytotoxicity of the metal complexes relative to the free ligands, as indicated by the experimental results.

CONCLUSION

The structural information derived from synthesized substances corresponds with the data reported in this paper. The existence of ligand molecules as zwitterions was validated by FTIR, ^1H -, and ^{13}C -NMR spectra, as well as mass spectrometry; this form

disappeared upon coordination to metals. L1, L2, L3, and L4 functioned as bidentate ligands of type NO with Cu^{2+} and Ag^+ . The geometries of the complexes were square planar (dsp^2) and octahedral (sp^3d^2) for Cu^{2+} and tetrahedral (sp^3) for Ag^+ . The results indicate that all chemicals, including thiazolidine and its complexes, have diverse biological actions against cancer cells. Therefore, we advocate synthesizing various thiazolidine derivatives and testing them across multiple cancer cell lines, including alternative breast cancer cell lines, for potential therapeutic applications. The scientific investigation revealed that solely copper complexes with L3 and silver complexes with L4 exhibit efficacy against the MCF-7 breast cancer cell line.

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■ CONFLICT OF INTEREST

The authors have stated that there is no conflict of interest in relation to this study.

■ AUTHOR CONTRIBUTIONS

Rafid Humaidan Al-Asadi: Conceptualization; Methodology; Characterization and Data Analysis; Theoretical Study; Writing – Original Draft Preparation; Writing – Review & Editing; Supervision; Project Administration. Hiba Mohamed Dagher: Synthesis and Experimental Work; Characterization and Data Analysis; Project Administration. Mohammed Khalaf Mohammed: Writing – Original Draft Preparation; Supervision; Project Administration. Khawla Salman Abd-Alrasool: Writing – Review & Editing. All authors read and agreed to the final version of the manuscript.

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