**Article**

**Synthesis, X-ray Structure, Antimicrobial and Anticancer Activity of a Novel [Ag(ethyl-3-quinolate)\(_2\)\(\text{citrate}\)] Complex**

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1. **Introduction**

Silver(I) complexes have garnered a lot of attention because of their pharmacological and biological characteristics, which make them promising antibacterial and antifungal agents [1–4]. Cisplatin, as well as its derivatives, has been the most widely applied metal-based drug in cancer treatment. Their mechanisms of action are recognized by their interactions with DNA. However, their use is restricted due to potential side effects, toxicity, and acquired drug resistance [5,6]. To avoid the drawbacks of cisplatin, researchers have looked into a new class of metal-based drugs that are less poisonous and more efficient in chemotherapy for inhibiting the growth of human tumor cell lines, as well as harmful microbes. In recent decades, Ag(I) has also gained popularity as an anticancer therapeutic. A set of literature reviews discussed silver(I) complexes with various types of ligands,
including amino acids, nitrogen, carboxylic acids, sulfur or phosphorus donor ligands, that have specific effects against a range of various tumor cells [7–9].

Numerous silver(I) complexes, especially those containing N-heterocyclic ligands, have demonstrated great cytotoxicity against a variety of mammalian cancer cells [10]. The development of new, simple, inexpensive and safe silver complexes containing bioactive ligands is a needed target from researchers. In order to improve and gain better biological drugs, mixed ligands have been applied in the coordination process with Ag(I) ions. In general, mixed-ligand complexes have demonstrated greater biological properties than the corresponding mono-ligand complexes. Since these complexes have so many functional groups and binding sites, they can be used in a variety of ways in drugs and the pharmaceutical industry. In addition, mixed-ligand complexes provide a better understanding of biological systems in which mixed chelation is the most common type of bonding. Furthermore, different ligand combinations will produce a wide range of physical and chemical features [11,12]. The study of silver(I) carboxylates is yet another important contributor to the development of new medications [13–15]. Silver citrate in combination with N-heterocycles is thought to be very appealing for future therapeutic, biomedical or pharmaceutical applications. According to a review of the literature, these complexes are likely to act synergistically as enhancers of antimicrobial activity, antioxidants and anticancer agents [16–19]. As a result, we are interested in synthesizing a new Ag(I) complex with mixed bioactive ligands, ethyl-3-quinolate and citric acid (Figure 1), in search of a more effective multipurpose compound that can be used as both an anticancer and antimicrobial agent. This study presents the synthesis and X-ray crystal structure of a novel Ag(I) citrate complex. Additionally, the antimicrobial and anticancer activities of the Ag(I) complex were investigated.

![Figure 1. Structures of the studied ligands.](image)

2. Materials and Methods
2.1. Physicochemical Characterizations

Chemicals used were purchased from Sigma-Aldrich. The FTIR analysis was performed at 4000–400 cm$^{-1}$ in KBr pellets by Bruker Tensor 37 FTIR equipment, Waltham, MA, USA. A Perkin Elmer 2400 Elemental Analyzer was utilized to perform the CHN analysis (PerkinElmer, Inc., 940 Winter Street, Waltham, MA, USA). A Shimadzu atomic absorption spectrophotometer (AA-7000 series, Shimadzu, Ltd., Kyoto, Japan) was used to measure the Ag content.

2.2. Synthesis of [Ag(Et3qu)$_2$(citrate)]

Silver citrate can be properly synthesized by the method mentioned in the literature [16]. Since it has a limited solubility in water [16], silver citrate (299 mg, 1 mmol) was dissolved in a 5-mL aqueous solution of citric acid (20 mg, 0.1 mmol), then mixed with two equivalents of ethyl quinoline-3-carboxylate (402 mg, 2 mmol) in 10 mL of ethanol. The mixture was stirred for few minutes while it warmed. The solution was filtered, and the clear filtrate was kept at room temperature. After one week, colorless crystals suitable for X-ray diffraction were isolated and air dried.

[Ag(Et3qu)$_2$(citrate)]: Yield: 86%; Anal. Calc. C$_{30}$H$_{29}$AgN$_2$O$_{11}$: C, 51.37; H, 4.17; N, 3.99; Ag, 15.38%. Found: C, 51.22; H, 4.21; N, 3.25; Ag, 15.41%. FTIR cm$^{-1}$: 3429, 3059, 2990,
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1718, 1617, 1597, 1577, 1528, 1503, 1373, 1338, 1290, 1243, 1199, 1020, 790, 585, 524, 492, 442
(Figure S1, Supplementary Data). Ligand (Et3qu): 3046, 2978, 1711, 1617, 1569, 1423, 1373,
1294, 1245, 1197, 1097, 1018, 973, 477 (Figure S2, Supplementary Data).

2.3. Biological Studies

The antimicrobial [20] and anticancer [21] activities of Et3qu and its Ag(I) complex
were determined as described in Methods S1 and S2 (Supplementary Data).

2.4. Crystal Structure Determination

The crystal structure measurements and solution details of [Ag(Et3qu)2(citrate)] are
depicted in the Supplementary Data [22–25]. The crystallographic details are summarized
in Table 1. The topology analyses were performed using the Crystal Explorer 17.5 pro-
gram [26].

Table 1. Crystal data of [Ag(Et3qu)2(citrate)].

| CCDC      | 2151811 |
|-----------|---------|
| empirical formula | C30H29AgN2O11 |
| fw        | 701.42 |
| temp (K)  | 120(2) K |
| λ (Å)     | 1.54184 Å |
| crystal system | Triclinic |
| space group | P-1 |
| a (Å)     | 8.6475(2) Å |
| b (Å)     | 11.4426(3) Å |
| c (Å)     | 15.2256(3) Å |
| α (deg)   | 73.636(2)° |
| β (deg)   | 79.692(2)° |
| γ (deg)   | 86.832(2)° |
| V (Å³)    | 1422.19(6) Å³ |
| Z         | 2 |
| ρ calc (Mg/m³) | 1.638 Mg/m³ |
| μ (Mo Kα) (mm⁻¹) | 6.273 mm⁻¹ |
| No. refns | 39671 |
| Unique refns | 5968 |
| Completeness to θ = 67.684° | 99.9% |
| GOOF (F²) | 1.068 |
| R int     | 0.0295 |
| R1 a (I ≥ 2σ) | 0.0236 |
| wR2 b (I ≥ 2σ) | 0.0597 |

a R1 = Σ||Fo|| - |Fc||/Σ||Fo||. b wR2 = [Σ[w(Fo² - Fc²)²]/Σ[w(Fo²)²]]¹/².

3. Results and Discussion

3.1. Crystal Structure Description

The structure of the [Ag(Et3qu)2(citrate)] complex was unambiguously determined
using an X-ray single crystal structure. The structure of the asymmetric unit is presented in
Figure 2. This silver(I) complex crystallized in the Triclinic crystal system and P-1 space
group. The unit cell parameters are a = 8.6475(2) Å, b = 11.4426(3) Å, c = 15.2256(3) Å,
α = 73.636(2)°, β = 79.692(2)° and γ = 86.832(2)°. The unit cell volume is 1422.19(6) Å³,
and the number of molecules per unit cell is two. The structure comprised disorder at the
ethyl groups of the ester group in both Et3qu ligand units. Such a situation led to some
different orientations for the conformation of the ethyl groups in the coordinated Et3qu, as
shown in the lower part of Figure 2. Furthermore, the Ag(I) is coordinated with two Et3qu
molecules as monodentate ligands, where both Et3qu units are located syn to one another.
The two Ag-N bond distances differ marginally from each other, where the Ag1-N1 and
Ag1-N2 distances are 2.1818(14) and 2.1848(14) Å, respectively. In addition, the Ag(I) is
coordinated with one oxygen atom from the central carboxylate group of the citrate anion.
with a Ag1-O6 bond distance of 2.540(14) Å. The Ag-N distances are comparable with those found in the structurally related Ag(I) complexes with quinoline-type ligands [27]. For example, the Ag-N distances in [Ag(6-quinolinecarboxylic acid)$_2$]NO$_3$ are found to be 2.1597(15) and 2.1680(15) Å, respectively. The Ag-O distances showed wide variations depending on the structure of the organic ligand [27]. The N1-Ag1-N2 angle is found bent (169.29(5)$^\circ$), possibly due to the presence of some steric hindering between the bulky Et$_3$qu ligand units and the coordinated citrate anion. The Ag1⋯O5 distance is significantly long (2.907(1) Å). Hence, the citrate anion is acting as a monodentate ligand via O6 as a donor atom. On the other hand, the N2-Ag1-O6 and N1-Ag1-O6 angles are 90.53(5) and 99.90(5)$^\circ$, respectively (Table 2). As a result, the coordination environment could be described as a slightly distorted T-shape where the torsion angles C9N1Ag1O6 and C21N1Ag1O6 are 2.81 and 2.85$^\circ$, respectively. Additionally, the distances between the mean planes of the two quinoline rings and the central Ag atom are only 0.806 and 0.403 Å for the quinoline rings of lower and higher atom numbering, respectively. These results indicate an almost planar AgN2O coordination sphere. In literature, the T-shaped coinage metal complexes are well-known, but such an arrangement of donor atoms around the metal ion is still uncommon [28–31]. For example, the di-nuclear [Ag(methylnicotinate)$_2$(ClO$_4$)$_2$] comprised a tri-coordinated Ag(I) with a T-shaped coordination environment [31]. In this complex, the Ag–N and Ag–O distances are 2.158(2) and 2.752 (3) Å, respectively, while the N–Ag–N and N–Ag–O angles are 171.26(9) and 92.76(9)–89.70(9)$^\circ$, respectively.

Figure 2. Crystal structure of the [Ag(Et$_3$qu)$_2$(citrate)] complex. The structure showed some disorder at the ethyl groups of the ester moieties in the coordinated Et$_3$qu ligand units.
Table 2. Bond lengths (Å) and angles (°) for the [Ag(Et3qu)2(citrate)] complex.

| Bond            | Distance | Bonds         | Angle  |
|-----------------|----------|---------------|--------|
| Ag(1)-N(2)      | 2.1818(14) | N(2)-Ag(1)-N(1) | 169.29(5) |
| Ag(1)-N(1)      | 2.1848(14) | N(2)-Ag(1)-O(6)  | 90.53(5)  |
| Ag(1)-O(6)      | 2.5401(14) | N(1)-Ag(1)-O(6)  | 99.90(5)  |

The structure of the [Ag(Et3qu)2(citrate)] complex was found to be stabilized by three intramolecular H···O contacts, where the two C21-H21···O6 and O7-H7···O5 interactions are common in the two disordered parts shown in Figure 2. The donor–acceptor distances of these interactions are 3.151(2) and 2.593(2) Å, respectively. Additionally, part B comprised another intramolecular interaction (C24B-H24E···O10), with a donor–acceptor distance of 3.352(6) Å. The different intramolecular and intermolecular H···O interactions present in the structure of the [Ag(Et3qu)2(citrate)] complex are depicted in the left part of Figure 3, while the right part of the same figure presents the packing view of the complex unit via O10-H10···O8 and O10-H10···O8B intermolecular interactions found in parts A and B, respectively. The donor–acceptor distances of these hydrogen-bonding interactions are 2.798(18) and 2.569(7) Å, respectively (Table 3).

![Figure 3. Hydrogen bond contacts (left), and view of the hydrogen bond packing scheme (right) of part A (upper).](image)

Table 3. Hydrogen bond parameters (Å, °) in the [Ag(Et3qu)2(citrate)] complex.

| D-H···A     | d(D-H) | d(H···A) | d(D···A) | <(D-H···A) |
|------------|--------|----------|----------|-----------|
| C(21)-H(21)···O(6) | 0.95   | 2.39     | 3.151(2) | 137       |
| O(10)-H(10)···O(8B) #1 | 0.75(3) | 2.10(4)  | 2.798(18) | 155(3)    |
| O(10)-H(10)···O(8) #1 | 0.75(3) | 1.83(4)  | 2.569(7)  | 170(4)    |
| C(24B)-H(24E)···O(10) | 0.98   | 2.44     | 3.352(6) | 155.3     |
| O(7)-H(7)···O(5)      | 0.77(3) | 2.05(3)  | 2.593(2)  | 127(3)    |
| O(9)-H(9)-O(6)         | 0.78(4) | 1.72(4)  | 2.499(2)  | 176(4)    |

#1 x + 1, y, z.
In addition, there are two significant π–π stacking interactions between the two quinoline rings (Figure 4). The shortest C14···C18 contact distance is 3.384 Å, and the centroid C18C19C20C21N2C13-to-centroid C13C14C15C16C17C18 distance is 3.659 Å.

![Figure 4. The π–π stacking interactions in the [Ag(Et3qu)2(citrate)] complex.](image)

3.2. Analysis of Molecular Packing

The Hirshfeld analysis of the two complex parts A and B was used to calculate the percentages of all intermolecular interactions in the crystal structure of the [Ag(Et3qu)2(citrate)] complex. The results are depicted in Table 4 and presented in Figure 5. The results indicated that the intermolecular interactions in parts A and B are almost the same. The most dominant contacts are the H···H (39.3–40.1%) and O···H (33.2–34.0%) interactions. Additionally, the C···C and C···H contacts shared significantly in the packing of the studied Ag(I) complex. Their percentages are 9.1–9.5% and 7.2–7.4%, respectively.

Additionally, the analysis of shape index revealed the presence of red/blue triangles, and the curvedness map showed the flat green area corresponding to the regions included in the π–π stacking interactions (Figure 6). Additionally, the decomposed fingerprint plot with a characteristic peak for short-distance contacts is considered as evidence of the presence of π–π stacking interactions.

| Contact | A      | B      |
|---------|--------|--------|
| Ag···Ag | 0.2    | 0.2    |
| Ag···N  | 0.4    | 0.3    |
| Ag···C  | 0.3    | 0.4    |
| Ag···H  | 2.0    | 2.0    |
| O···O   | 0.5    | 0.5    |
| C···O   | 2.9    | 3.5    |
| O···H   | 33.2   | 34.0   |
| N···N   | 0.4    | 0.4    |
| C···N   | 1.9    | 1.9    |
| N···H   | 1.2    | 1.2    |
| C···C   | 9.5    | 9.1    |
| C···H   | 7.4    | 7.2    |
| H···H   | 40.1   | 39.3   |
Figure 5. Distribution of the intermolecular interactions in the [Ag(Et3qu)2(citrate)] complex. A and B refer to the disordered parts of the [Ag(Et3qu)2(citrate)] complex.

Figure 6. Evidence from the Hirshfeld surfaces on the π–π stacking interactions in the [Ag(Et3qu)2(citrate)] complex.

3.3. FTIR Spectra

The free ligand, Et3qu, exhibits three major absorption bands in its IR spectrum (Figure S2, Supplementary Data). The band at 1710 cm\(^{-1}\) is attributed to the stretching vibration of the C=O of the ester group, while the bands at 1617 and 1568 cm\(^{-1}\) correspond to the ν(C=C) and ν(C=N) stretching modes of the quinoline ring, respectively. In the Ag(I) complex, the corresponding values for ν(C=O), ν(C=C) and ν(C=N) are 1718, 1617 and 1577 cm\(^{-1}\), respectively (Figure S1, Supplementary Data). The observable shift in the position and shape of the ν(C=N) band in [Ag(Et3qu)2(citrate)] indicates its direct coordination to the silver center. The noticeable change in the intensity of ν(C=O) of the mixed-ligand complex compared to the free ligand is attributed to the carbonyl group of the coordinated ethyl-3-quinolate and that of citric acid. In addition, the appearance of two new bands in the range 1335–1375 and 1597 cm\(^{-1}\) in the spectrum of the complex can be assigned to the symmetric and asymmetric stretching vibrations of the COO\(^-\) group, respectively, indicating a monodentate mode of the citrate group around the Ag(I) ion [32,33]. Finally, some new moderate-intensity IR bands are observed in the complex spectrum in the regions 480–570 and 400–460 cm\(^{-1}\). These bands can be assigned to the vibrational modes of Ag–O and Ag–N bonds, respectively [34].

3.4. Antimicrobial Studies

The antimicrobial activity of Et3qu and its [Ag(Et3qu)2(citrate)] complex were determined. The sizes of the inhibition zones for the two compounds at 10 mg/mL against different microbes are listed in Table 5. The free ligand showed good antifungal activity against A. fumigatus and C. albicans. The inhibition zone diameters were determined to be
30 and 19 mm, respectively. Additionally, the Et3qu ligand and the [Ag(Et3qu)2(citrate)] complex have similar results against A. fumigatus (30 mm), but the Ag(I) complex is less active against the fungus C. albicans (15 mm). On the other hand, the [Ag(Et3qu)2(citrate)] complex has good activity against the Gram-positive bacteria S. aureus (13 mm) and B. subtilis (12 mm), while the free Et3qu showed no activity at the applied concentration against these microbes. On the other hand, Et3qu and its [Ag(Et3qu)2(citrate)] showed good activity against E. coli and P. vulgaris as Gram-negative bacteria. Both compounds have the same size of inhibition zones for E. coli (12 mm) while the Ag(I) complex has a larger-size inhibition zone (18 mm) against P. vulgaris than the free Et3qu (12 mm). In comparison with Ketoconazole as a standard antifungal agent, Et3qu and [Ag(Et3qu)2(citrate)] have better activity against A. fumigatus. Regarding the antibacterial activity, the Ag(I) complex has lower sizes of inhibition zones than the standard Gentamycin. The lower antibacterial activity of the [Ag(Et3qu)2(citrate)] complex compared to Gentamycin indicated that the Ag(I) complex has broad-spectrum action against both bacteria and fungi, and the MICs results revealed these observations very well. The best MIC results were for both compounds against A. fumigatus, where the Ag(I) complex had lower MIC value and better activity than the free Et3qu and the standard Ketoconazole as well. It was believed that the biological action of Ag(I) complexes depends on the ease of Ag(I) release to biological fluids. In this regard, silver complexes comprising the relatively weak Ag-N and Ag-O bonds [35] are desirable as antimicrobial agents [36–38].

Table 5. Inhibition zone diameters (mm) and MIC (µg/mL) values for Et3qu and its [Ag(Et3qu)2(citrate)] complex a.

| Microbe   | Et3qu | [Ag(Et3qu)2(citrate)] | Control |
|-----------|-------|----------------------|---------|
| A. fumigatus | 30 (9.7) | 30 (4.8) | 17 (156.25) b |
| C. albicans | 19 (312.5) | 15 (312.5) | 20 (312.5) b |
| S. aureus  | NA (NA) d | 13 (1250) | 24 (9.7) c |
| B. subtilis | NA(NA) d | 12 (625) | 26 (4.8) c |
| E. coli    | 12 (2500) | 12 (1250) | 30 (4.8) c |
| P. vulgaris | 12 (2500) | 18 (1250) | 25 (4.8) c |

a MIC values are in parentheses. b Ketoconazole. c Gentamycin. d NA: not active.

3.5. MTT Assay

The inhibitory activity against lung (A-549) and breast (MCF-7) carcinoma cells for Et3qu and its [Ag(Et3qu)2(citrate)] complex was determined using the MTT assay (Figure 7). The detailed MTT assay results are given in Tables S1–S4 (Supplementary Data). The results indicated that both compounds showed inhibitory activity against both cell lines, where the Ag(I) complex has promising anticancer activity. The IC_{50} values were generally lower for the Ag(I) complex than the free Et3qu. The [Ag(Et3qu)2(citrate)] had IC_{50} values of 1.87 ± 0.09 µg/mL and 0.95 ± 0.06 µg/mL against the MCF-7 and A-549 cell lines, respectively. The corresponding values for the free Et3qu were 30.64 ± 1.98 and 22.89 ± 1.48 µg/mL, respectively. These results indicated the higher anticancer activity of [Ag(Et3qu)2(citrate)] compared to the free Et3qu. Additionally, the studied complex exhibited significantly higher cytotoxicity against both cancerous cell lines compared to the reference anticancer drugs doxorubicin and cis-platin (Table 6). It was believed that the interaction between the target compound and DNA via noncovalent interactions could damage the cancer cell, leading to the death of these malignant cells [9]. Recently, the anticancer activity of Ag(I) complexes was linked to both the metal and coordinating ligand rather than just the metal ions [39,40]. Many factors such as the complex stability and its hydrophilic–lipophilic characters are crucial factors for the anticancer activity of Ag(I) complexes [7,40–44].
Figure 7. MTT assay of Et3qu and its [Ag(Et3qu)₂(citrate)] complex.

Table 6. Anticancer screening (expressed as IC₅₀ (µg/mL)) of the newly synthesized complex, its corresponding free ligands and the reference drugs against the tested human cancer cell lines.

| Cell Line                  | Cisplatin [45] | Doxorubicin [46] | Et3qu          | [Ag(Et3qu)₂(citrate)] |
|----------------------------|----------------|------------------|----------------|-----------------------|
| Lung carcinoma (A-549)     | 2.46           | 1.91             | 22.89 ± 1.48   | 0.95 ± 0.06           |
| Breast carcinoma (MCF-7)   | 3.23           | 1.51             | 30.64 ± 1.98   | 1.87 ± 0.09           |

4. Conclusions

The structure of the novel [Ag(Et3qu)₂(citrate)] was elucidated based on the results of X-ray single crystal diffraction. It comprised a tri-coordinated Ag(I) with two Et3qu and one citrate as monodentate ligands. The supramolecular structure aspects were analyzed quantitatively using a Hirshfeld analysis. The percentages of the H···H, O···H, C···C and C···H contacts were 39.3–40.1%, 33.2–34.0%, 9.1–9.5% and 7.2–7.4%, respectively. Biological experiments indicated promising antimicrobial and anticancer activities of the [Ag(Et3qu)₂(citrate)] complex. The results indicated higher anticancer activity of the Ag(I) complex against the MCF-7 and A-549 cell lines than the free ligand. Additionally, the [Ag(Et3qu)₂(citrate)] complex has good activity against both Gram-negative and Gram-positive bacteria and the fungi as well, while the free Et3qu ligand showed no activity against the Gram-positive bacteria.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/cryst12030356/s1, Crystal structure determination details. Method S1: Antimicrobial activity assay. Method S2: Evaluation of the cytotoxic effects against the A-549 cell line. Figure S1: The FTIR spectrum of the complex [Ag(Et3qu)₂(citrate)]. Figure S2: The FTIR spectrum of the free ligand Et3qu. Table S1: MTT assay for the Ag(I) complex against the MCF-7 cell line. Table S2: MTT assay for Et3qu against the MCF-7 cell line. Table S3: MTT assay for the Ag(I) complex against the A-549 cell line. Table S4: MTT assay for Et3qu against the A-549 cell line.

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