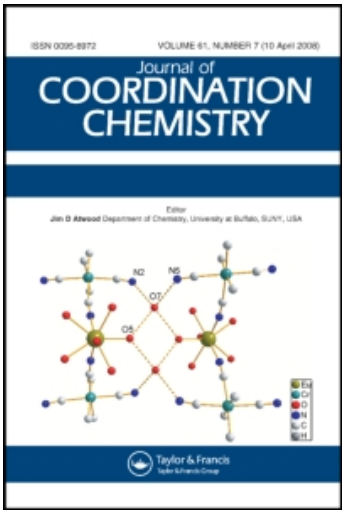

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Synthesis, characterization and bioactivity of Schiff base copper(II) complexes derived from L-glutamine and L-asparagine

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Synthesis, characterization and bioactivity of Schiff base copper(II) complexes derived from L-glutamine and L-asparagine

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To investigate the structure–activity relationship of L-glutamine and L-asparagine Schiff base copper complexes in applications, L-glutamine and L-asparagine Schiff bases (GV and AV) and their copper complexes $[Cu_3(GV)_2(CH_3COO)_2(H_2O)] \cdot 2H_2O$ (GVC) and $[CuAV(H_2O)_3]$ (AVC) have been synthesized and characterized by molar conductance, elemental analysis, UV-Vis, IR, ^{1}H-NMR, and TG-DTG. We examined the geometries of GV, AV, GVC, and AVC through Hartree–Fock method and electronic absorption spectra. We also tested their antibacterial activity against *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Bacillus subtilis* bacteria and antiproliferation activity on human breast cancer MDA-MB-231 cells. The side chain difference between L-glutamine and L-asparagine results in different geometry of GV and AV, which leads to different geometry of GVC and AVC. GVC, a trinuclear Cu(II) complex, shows the highest antibacterial activity and the highest growth inhibition activity on MDA-MB-231 cells. Our results suggest that GVC has potential as an antibacterial and anticancer agent.

Keywords: Glutamine copper complex; Schiff base; Characterization; Antibacterial activity; Anticancer activity

1. Introduction

A large number of amino acid Schiff base complexes have been investigated for their important biological properties. These complexes exhibit antibacterial activity [1], valuable non-enzymatic models of the action of Vitamin B6 enzyme [2, 3], scavenging effect on $O_2^{-\bullet}$ [4, 5], and other activities [6, 7]. Considerable attention has been given to Cu(II) Schiff base complexes due to their anticancer activities [8, 9]. However, most of the complexes are insoluble, severely hampering their clinical application. O-vanillin, a positional isomer of vanillin (the primary chemical component of the vanilla bean extracts), contains a hydroxyl group which could improve solubility of complexes.

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Research has emphasized L-α-amine acids [10], whereas L-glutamine and L-asparagine Schiff base copper complexes are seldom reported [11].

Glutamine, a conditional essential amino acid, has been applied in clinical nutrition support and cancer therapy [12]. Asparagine, a non-essential amino acid, is the first amino acid isolated from asparagus juice. Glutamine and asparagine have a carboxamide group, the side chain's functional group, which was used as an anticonvulsant [13]. The structural difference between glutamine and asparagine is that glutamine has an extra 3-methylene group. But the structure–activity relationship of glutamine and asparagine copper complexes in antibacterial and anticancer fields have not been reported.

Our aim is to investigate the structure–activity relationship of glutamine and asparagine copper complexes in biological applications. In this article, we have synthesized water-soluble glutamine and asparagine Schiff bases and their copper complexes and characterized their structures by molar conductance, elemental analysis, UV-Vis, IR, ^{1}H-NMR, and TG-DTG, examined the geometries of GV, AV, GVC, and AVC by Hartree–Fock method and electronic absorption spectra and investigated their antibacterial and anticancer activities.

2. Experimental

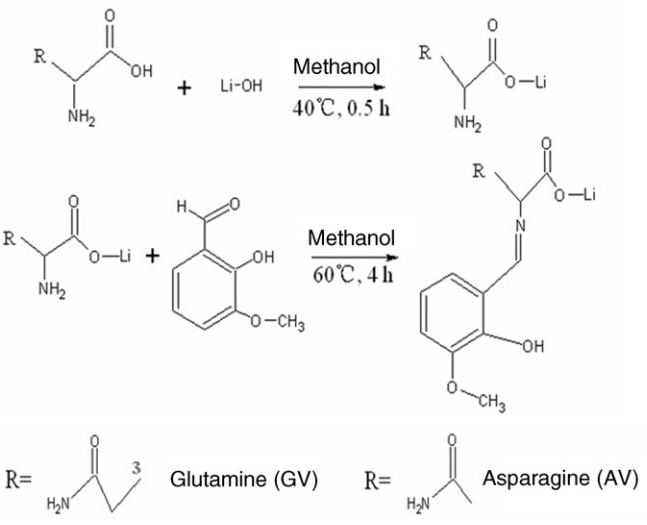
2.1. *Materials and methods*

All chemicals were of analytical reagent grade and used directly without purification. 3-[4,5-Dimethylthiazol-2-yl]-2,5-diphenyl-tetrazolium bromide (MTT) was purchased from Sigma-Aldrich. DMEM/F-12 was purchased from Invitrogen. Elemental analyses were performed on a Perkin–Elmer 2400 elemental analyzer. Electronic spectra were recorded in DMSO solution using a Varian Cary 100 UV-Vis spectrophotometer. The molar conductance was measured with a Shanghai DDS-312 type conductivity meter at room temperature (20°C). Infrared spectra of the ligands and complexes were recorded from 4000 to 400 cm^{-1} using KBr pellets on an AVATAR 360 FT-IR spectrometer. ^{1}H-NMR spectra were recorded in DMSO-d_6 (as a solvent) at 600 MHz with a JNM ECP-600 spectrometer using tetramethylsilane (TMS) as an internal standard. Thermogravimetric (TG) and derivative thermogravimetric (DTG) curves were obtained using a Perkin–Elmer TGA7 thermogravimeter with a protecting N_2 flux of 20 mL min^{-1} at a heating rate of 10°C min^{-1}. The MTT values were recorded in Perkin–Elmer, Victor3 (Wellesley, MA, USA).

2.2. *Synthesis of Schiff bases*

L-Asparagine and L-glutamine are analogs. Literature procedures were used for preparation of L-glutamine-o-vanillin (GV) and L-asparagine-o-vanillin (AV) [14]. The synthetic strategy for Schiff bases is shown in scheme 1.

2.2.1. Preparation of L-glutamine-o-vanillin. L-Glutamine (0.298 g, 2.0 mmol) and lithium hydroxide (0.0835 g, 2.0 mmol) were stirred at 40°C for 0.5 h in anhydrous



Scheme 1. Synthesis of GV and AV.

methanol (30 mL) and filtered to make pellucid solution. Next, the solution was slowly dripped into 5 mL anhydrous methanol solution containing o-vanillin (0.308 g, 2.0 mmol) with stirring at 60°C for 4 h to give a clear golden solution. Then the volume of the solution was reduced to 5 mL and added into 10 mL isopropanol. The golden product was collected by filtration and washed three times with 2 mL isopropanol and dried under vacuum at 50°C. Yield: 53%. Anal. Calcd for (GV containing one molecule of crystal water) $C_{13}H_{17}LiN_2O_6$ (%): C, 51.32; H, 5.63; N, 9.21. Found (%): C, 51.83; H, 5.53; N, 9.34.

2.2.2. Preparation of L-asparagine-o-vanillin. L-Asparagine (0.303 g, 2.0 mmol) and lithium hydroxide (0.0839 g, 2.0 mmol) were stirred at 40°C for 0.5 h in anhydrous methanol (30 mL) and filtered to make pellucid solution. Next, the solution was slowly dripped into 5 mL anhydrous methanol solution containing o-vanillin (0.304 g, 2.0 mmol) with stirring at 60°C for 4 h giving a clear golden solution. Then the solution was distilled till about 5 mL, followed by adding into 10 mL isopropanol. The golden product was collected by filtration and washed three times with 2 mL isopropanol and dried under vacuum at 50°C. Yield: 80%. Anal. Calcd for (AV containing two molecules of crystal water) $C_{12}H_{17}LiN_2O_7$ (%): C, 46.76; H, 5.56; N, 9.09. Found (%): C, 46.28; H, 5.65; N, 9.41.

2.3. *Synthesis of copper complexes*

$Cu(CH_3COOH)_2 \cdot H_2O$ (0.402 g, 2 mmol) in 60 mL anhydrous methanol was slowly dripped into the clear golden solution with constant stirring at 65°C. Eight hours later, the solvent was reduced to 10 mL and then added into 20 mL isopropanol. The dark green product obtained was collected by filtration and washed three times with 2 mL isopropanol and dried under vacuum at 50°C. The obtained complexes are L-glutamine-o-vanillin-copper (GVC) and L-asparagine-o-vanillin-copper (AVC) in

less than 50% yield. GVC and AVC are dark green, insoluble in non-polar organic solvents, but soluble in H_2O and DMSO. Their molar conductivities in DMSO are 20.1 $\Omega^{-1}cm^2 mol^{-1}$ (GVC) and 3.67 $\Omega^{-1}cm^2 mol^{-1}$ (AVC), indicating that they are non-electrolytes [15]. Anal. Calcd for (GVC) $C_{30}H_{40}Cu_3N_4O_{17}$ (%): C, 39.20; H, 4.39; N, 6.09. Found: C, 38.89; H, 4.60; N, 6.34. Anal. Calcd. for (AVC) $C_{12}H_{18}CuN_2O_8$ (%): C, 37.75; H, 4.75; N, 7.34. Found (%): C, 38.33; H, 4.20; N, 7.64.

2.4. *Antibacterial assay*

All antibacterial properties were investigated at the National Institute for the Control of Pharmaceutical and Biological Products.

Escherichia coli (*E. coli*) (Gram-negative), *Pseudomonas aeruginosa* (*P. aeruginosa*) (Gram-negative), *Staphylococcus aureus* (*S. aureus*) and *Bacillus subtilis* (*B. subtilis*) (both Gram-positive) were cultured by inoculating in beef broth (which was sterilized by autoclaving at 121°C for 20 min) and incubated at 37°C for 24 h. Agar culture medium, which was sterilized by autoclaving at 121°C for 20 min, was prepared by dissolving peptone, beef broth, agar and sodium chloride in distilled water and adjusting pH to 7.2–7.4. Cultured *E. coli*, *P. aeruginosa*, *S. aureus*, and *B. subtilis* were added to the warm nutrient agar plates. The agar plates were then incubated at 37°C overnight. Digital calipers were used to measure the diameter of the area of inhibition around the wells [16]. The compound was divided into 10, 10^0, 10^{-1}, 10^{-2}, 10^{-3}, and 10^{-4} mg mL^{-1}, and then used.

2.5. *Cell culture and cell proliferation assay*

MDA-MB-231 human breast cancer cells were obtained from American Type Culture Collection (Manassas, VA) and grown in DMEM/F-12 supplemented with 10% fetal bovine serum and maintained at 37°C and 5% CO_2.

The MTT assay was used to determine the effects of these agents on overall proliferation of cells [17]. The MDA-MB-231 cells were plated in a 96-well plate and grown until 70 to 80% confluence, followed by addition of each compound at an indicated concentration for 24 h. MTT (1 mg mL^{-1}) in PBS was then added to wells and incubated at 37°C for 4 h to allow for complete cleavage of the tetrazolium salt by metabolically active cells. Next, MTT was removed and 100 μL of DMSO was added, followed by colorimetric analysis using a multilabel plate reader at 560 nm. Absorbance values plotted are the mean from triplicate experiments.

3. Results and discussion

The syntheses of GV and AV are shown in scheme 1. The structures of L-glutamine and L-asparagine contain two amino groups. One is α-amino group and the other is a terminal amide. Activation of both amino groups is affected by pH [14]. The activation of α-amino occurs at the physiological pH, but activation of terminal amide group needs a pH of 10. Thus, we used lithium hydroxide to control the reaction to physiological pH, suitable for the activation of α-amino group. The Schiff bases were

synthesized by nucleophilic addition forming a hemiamine, followed by dehydration to generate an imine.

3.1. *Electronic spectra*

Electronic spectra of ligands and complexes (figure 1) in DMSO exhibit intense bands in the range of 200–500 nm. Bands at 258 and 280 nm in spectra of ligands and their copper complexes are assigned to $\pi \rightarrow \pi^*$ transitions of benzene rings [18]. In addition, bands at 422 nm in spectra of ligands are assigned to $n \rightarrow \pi^*$ transition [19, 20]. They shift 40 to 382 nm in spectra of their copper complexes which can be assigned to electronic transition from nitrogen of CH=N to copper [21]. The GVC, trinuclear Cu(II) complex, is generated by 2-fold symmetry with one Cu atom lying on the rotation axis. The central Cu atom is five-coordinate in a distorted square-pyramidal geometry [22]. The terminal Cu is four-coordinate in a distorted tetrahedral geometry [22]. The Cu of AVC is six-coordinate in a distorted octahedral geometry, due to Jahn–Teller effect [23].

3.2. *Infrared spectra*

Assignments in table 1 are based on some general references [24–28]. In spectra of GV and AV, two sharp bands at 3180–3230 and 3360–3400 cm^{-1} are attributed to $\nu(\alpha\text{-}NH_2)$ stretch [24]. In infrared spectra of GV and AV, there are no characteristic absorptions

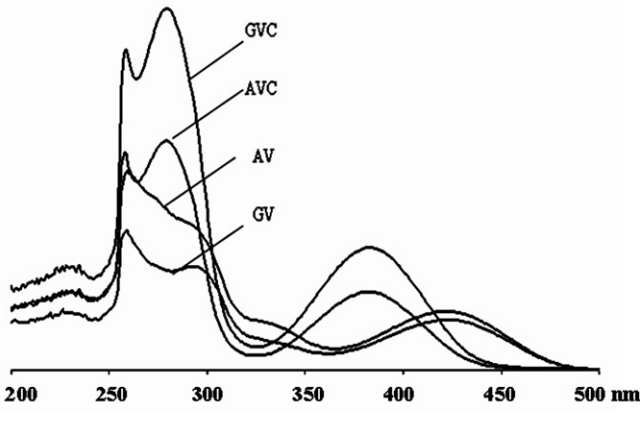


Figure 1. Electronic spectra of GV, AV and their copper complexes GVC and AVC.

Table 1. Main assignments of the IR spectra of ligands and their copper complexes (cm^{-1}).

Compound	ν(C = N)	ν(Ar–O)	5(NH_2)amide	ν(C–O–C)	$\nu_{as}(COO^-)$	$\nu_s(COO^-)$	ν(Cu–O)	ν(Cu–N)
GV	1634 vs	1221 m	1660 vs	1311 m	1522 m	1408 m	–	–
GVC	1631 vs	1245 m	1660 vs	1311 m	1603 m	1443 m	460 w	552 w
AV	1634 vs	1248 m	1656 vs	1337 m	1541 m	1405 m	–	–
AVC	1627 vs	1245 m	1656 vs	1337 m	1644 m	1393 m	456 w	543 w

of aldehyde carbonyl at 1700 cm^{-1} and the C=N stretch occurs at 1634 cm^{-1}, indicating that the Schiff base has formed. The ν(C=N) shifted from 1634 to 1631 cm^{-1} in the spectrum of GVC or to 1627 cm^{-1} in the spectrum of AVC, suggests formation of C=N–Cu. The ν(Ar–O) at 1221 cm^{-1} in the spectrum of GV or 1248 cm^{-1} in the spectrum of AV shifts to 1245 cm^{-1} in the spectra of GVC and AVC confirming phenolic hydroxyl oxygen coordination with copper. In the spectra of GV and AV, the peak at 1660 and 1656 cm^{-1}, respectively, can be assigned to νNH_2 of amide. It is unaltered in spectra of GVC and AVC, indicating NH_2 of amide does not coordinate with copper [25]. The ν(C–O–C) at 1311 cm^{-1} in the spectrum of GV or 1337 cm^{-1} in the spectrum of AV does not move in the spectrum of GVC or AVC, indicating that the oxygen of the methoxy does not coordinate with copper. Vibrations $\nu_{as}(COO^-)$ and $\nu_s(COO^-)$ in the spectrum of GV at 1522 and 1408 cm^{-1} shift to 1603 and 1443 cm^{-1} ($\Delta\nu = 160\,cm^{-1}$) in the spectrum of GVC, suggesting bridging carboxylate [26]. The $\nu_{as}(COO^-)$ and $\nu_s(COO^-)$ in the spectrum of AV at 1541 and 1405 cm^{-1} shift to 1644 and 1393 cm^{-1} ($\Delta\nu = 251\,cm^{-1}$) in the spectrum of AVC, suggesting monodentate carboxylate [27]. Peaks at ~460 and ~550 cm^{-1} are from ν(Cu–O) [28] and ν(Cu–N), respectively.

3.3. *^{1}H-NMR spectra*

The ^{1}H-NMR spectra of the GV and GVC (Supplementary material) were recorded in DMSO-d_6 (as a solvent). The phenolic OH proton at 14.23 ppm in the spectrum of the GV disappears in the spectrum of the GVC, indicating GV is bonded to copper ion through replacement of the phenolic hydrogen [29]. The peak at 8.29 ppm in the spectrum of GV can be assigned to CH=N proton. Due to increased conjugation [30], it shifts to 7.28 ppm in the spectrum of GVC confirming azomethine coordination with copper. In the spectrum of GV, the signals within the range of 6.69–6.87 ppm are assigned to aromatic protons which shift to 6.51 ppm forming a broad singlet [31]. In the spectrum of GV, the $-OCH_3$ proton appears at 3.72 ppm and at 3.77 ppm in GVC indicating the $-OCH_3$ is not bound to copper.

3.4. *Thermal decomposition analysis*

The TG and DTG curves of GVC (Supplementary material) show mass losses in four steps between 33 and 900°C. The first from 33 to 130°C with mass loss of 4.23% (Calcd 3.92%) corresponds to the loss of hydrate water [32]. Subsequent steps (130–900°C) begin with a fast process, followed by a slow process, corresponding to mass loss of 63.04%. CuO is the final residue with mass of 32.73% (Calcd 26.12%), due to carbon deposition from decomposition in N_2 [33]. The TG and DTG curves of AVC also show mass losses in four steps between 40 and 900°C. The first at 40–140°C with mass loss of 7.16% (Calcd 8.10%) corresponds to loss of methoxy. The steps (140–900°C) which begin with a slow process, followed by a fast process, correspond to the total mass loss of 79.79% (Calcd 79.10%). CuO is the final residue with mass of 20.21% (Calcd 20.90%). The last mass loss 813.9°C occurs with mass loss of 18.11%, attributed to pyrolysis of the carbonaceous product.

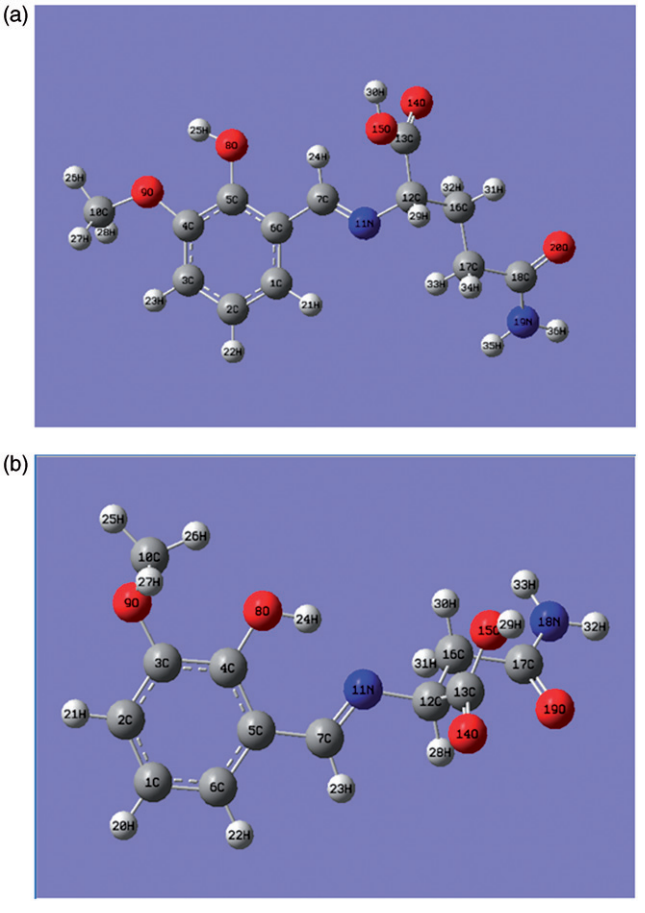


Figure 2. Calculated geometry of GV and AV. (a) The stable geometry of GV. (b) The stable geometry of AV.

3.5. *Calculated geometry of GV and AC*

The L-glutamine and L-asparagine are analogs (scheme 1) with L-glutamine side chain containing one more 3-methylene group (scheme 1). We hypothesized that this methylene affects the geometry of GV and AV and also their copper complexes. In order to investigate our hypothesis we used the Hartree–Fock method [34] with basis sets 6-31G to calculate the stable geometry of GV and AV (figure 2). In the stable geometry of GV (figure 2a), the O(8)–C(5)–C(6)–C(7) torsion angle is fixed at 0° and the C(5)–C(6)–C(7)–N(11) torsion angle is fixed at −178° indicating O(8) and phenyl ring are coplanar, but N(11) is twisted above or below the phenyl ring. In the stable geometry of AV (figure 2b), the torsion angles of O(8)–C(4)–C(5)–C(7) and C(4)–C(5)–C(7)–N(11) both are fixed at 0°, indicating O(8) and N(11) are coplanar with phenyl ring.

The side chain difference between L-glutamine and L-asparagine affects the coordination with o-vanillin to form GV and AV in different geometries and, therefore, affects the coordination of GV and AV with copper to form GVC and AVC. These data are consistent with data discussed earlier.

Table 2. Minimal inhibition concentration of the ligands and their copper complexes ($\mu g\,ml^{-1}$).

Compounds	*E. coli*	*P. aeruginosa*	*S. aureus*	*B. subtilis*
GV	100	1000	1000	100
GVC	10	100	1	10
AV	10,000	1000	10,000	100
AVC	1000	1000	100	100

Using corresponding concentration of minimal antibacterial ring as the minimal inhibition concentration (MIC): *E. coli* and *P. aeruginosa* (Gram-negative); *S. aureus* and *B. subtilis* (Gram-positive).

3.6. *Antibacterial activity*

Minimal inhibition concentration (MIC) to the growth of bacteria has been determined using agar dilution [35]. A lower value of MIC implies higher antibacterial activity. The minimal inhibition concentrations are recorded in table 2. GV, GVC, AV, and AVC have antibacterial activity against the four tested bacteria. GVC has higher potency against the four tested bacteria with MIC values of GVC 10- to 1000-fold lower than that of GV. Noticeably, GVC was much more potent against *S. aureus* ($MIC = 1\,\mu g\,mL^{-1}$) than other tested bacteria. AVC is more potent aganist *E. coli* ($MIC = 1000\,\mu g\,mL^{-1}$) and *S. aureus* ($MIC = 100\,\mu g\,mL^{-1}$) than AV. The MIC values of AVC against *E. coli* and *S. aureus* were 10- to 100-fold lower than that of AV, respectively. AV and AVC have similar effects against *P. aeruginosa* ($MIC = 1000\,\mu g\,mL^{-1}$) and *B. subtilis* ($MIC = 100\,\mu g\,mL^{-1}$). We also observed that the MIC values of GVC and AVC were 1 to $100\,\mu g\,mL^{-1}$ and 100 to $1000\,\mu g\,mL^{-1}$ against the four tested bacteria, respectively.

The copper complexes have higher or similar effects as the ligands. Furthermore, when compared with AVC, GVC has a higher antibacterial activity against the four tested bacteria, especially against *S. aureus*.

3.7. *Antiproliferation activity*

In the current study, we also investigated the antiproliferation potency of GV, GVC, AV, AVC, and $CuCl_2$ alone on human breast cancer MDA-MB-231 cells followed by MTT assay. Cells treated with DMSO were used as solvent control. We found that GV, GVC, AV, AVC, and $CuCl_2$ inhibited proliferation of MDA-MB-231 cells in a concentration-dependent manner (figure 3). GVC and AVC exhibited higher antiproliferation potency on MDA-MB-231 cells. Furthermore, compared with AVC ($\sim$40% inhibition), GVC inhibited $\sim$80% cell growth at 50 μmol. Copper chloride alone had little effect.

4. Conclusion

The results presented here clearly indicate that GV and AV have formed Schiff base ligands, and with the addition of copper ion they have formed Schiff base complexes GVC and AVC, respectively. The composition of the GVC and AVC are

$[Cu_3(GV)_2(CH_3COO)_2(H_2O)] \cdot 2H_2O$ (GV = L-glutamine-o-vanillin) and [CuAV $(H_2O)_3$] (AV = L-asparagine-o-vanillin). These ligands and their corresponding copper complexes were synthesized and characterized by molar conductance, elemental analysis, UV-Vis, IR, ^{1}H-NMR, and TG-DTG thermoanalysis. The composition corresponded to a metal–ligand ratio in GVC and AVC of 2 : 3 and 1 : 1, respectively. Their putative structures are shown in figure 4.

Calculated geometries indicate that N(11) is non-planar with O(8) and the phenyl ring in the stable geometry of GV (figure 2a), but is coplanar with O(8) and the phenyl ring in the stable geometry of AV (figure 2b). The 3-methylene group in the side chain of glutamine makes GV prone to coordinate with Cu to form trinuclear copper complex GVC. Due to O(8) and N(11) being coplanar with the phenyl ring, AV coordinates with Cu to form six-coordinate mononuclear copper complex AVC.

Antibacterial experiments indicated that the GV, GVC, AV, and AVC have certain *in vitro* antibacterial activity against *E. coli* and *P. aeruginosa* (Gram-negative) and *S. aureus* and *B. subtilis* (Gram-positive). The results showed that GV, GVC, AV, and AVC inhibit the growth of bacteria; GVC and AVC exhibit higher activity than GV and AV.

GVC at 50 μmol potently inhibited proliferation of human breast cancer MDA-MB-231 cells by ~80%. In contrast, AVC inhibited only ~40% cell proliferation. GV and AV at 50 μmol had little inhibitory effect (figure 3). It has been reported that some copper complexes inhibit cellular proteasome and cause inhibition of cancer cell growth [36, 37]. We previously reported that GVC has a similar pathway [38]. A possible mechanism of antibacterial and antiproliferation activity is that GVC may penetrate the cell membrane and transport more copper ions into the cells and also bind to cellular targets, and thereby inhibit bacterial growth and proliferation of human breast cancer MDA-MB-231 cells.

Due to the different geometries of GVC and AVC, their antibacterial and antiproliferation activities are completely different to GVC, having higher antibacterial and antiproliferation activities than AVC. Due to the enhanced hydrophilicity of GVC and superior biological activity, GVC acts as a promising bactericidal and

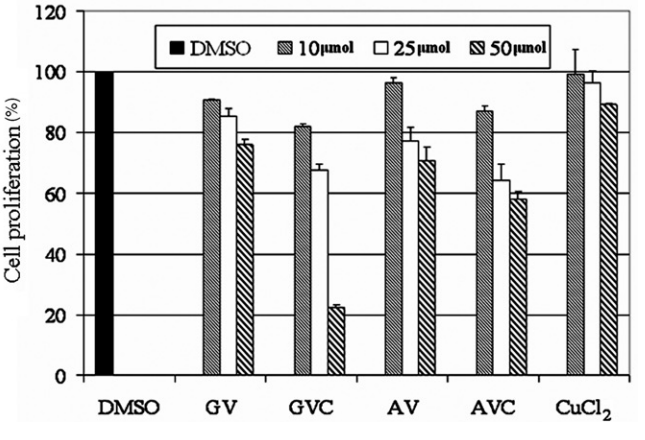


Figure 3. MTT assay in MDA-MB-231 human breast cancer cells.

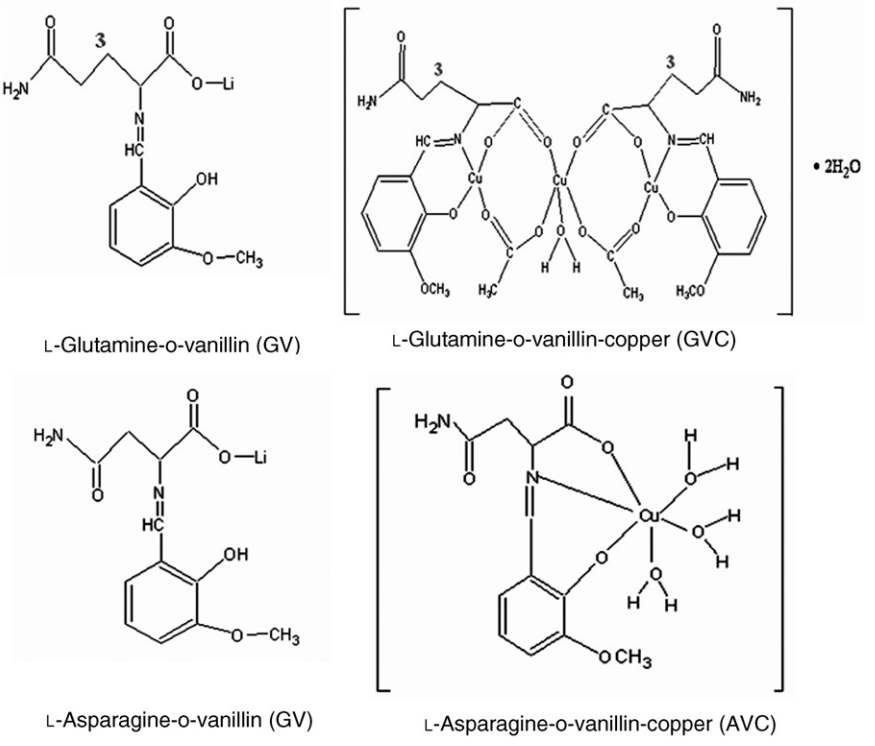


Figure 4. Structures of GV, GVC, AV, and AVC. The structures of GV and AV are without adding crystal water.

anticancer agent. Our study has paid considerable attention to potential clinical applications.

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