



Evaluation of Antioxidant and Anticancer Activity of Amino Acid Derived Schiff Bases and their Metal Complexes – A Review

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Simple condensation of an aldehyde or ketone with a primary amine, also known as an azomethine or an imine (-HC=N-) bond, forms Schiff bases. Amino acids are organic compounds comprising a single carbon atom, known as α -a carbon atom, along with an amino group (-NH_2) and a carboxylic acid group (-COOH). Cancer leads to millions of deaths worldwide and is expected to increase by 12.8 percent in 2025 compared to 2020. Additionally, our body needs antioxidants to reduce harmful diseases, eliminate free radicals, and prevent oxidation. Schiff bases derived complexes tried to improve biological activity. A novel class of Schiff bases generated from amino acids and their metal complexes exhibits an enhanced broad spectrum of pharmacological actions. Their most significant medical applications include antibacterial, antifungal (including anti-yeast), antiviral, antitumor, anti-inflammatory, antipyretic, antimalarial, anticancer, antioxidant, and anesthetic properties. The finds of Schiff bases derived amino acids, and their complexes provide a range of activity rate that depends on their orientation and metal atom. They need to be exposed further to other biological studies. The review includes synthesizing, characterizing, and analyzing anticancer and antioxidant activity compounds. On critical evaluation, we established that these studies show some effect on therapy and lower the risk of diseases.

Keywords: Antioxidant activity, Anticancer activity, Cisplatin/Carboplatin

Schiff bases are a diverse class of chemical ligands that are important pharmacophores. Due to the conjugation effect, aromatic amines and aldehydes/ketones produce more stable Schiff bases. The coordination of transition metal atoms with Schiff bases results in a broad range of complexes. The application of these Schiff base complexes in analytical, clinical, industrial, biological, and pharmacological studies is extensive. The field of metal-based pharmaceuticals is driven by Schiff base compounds and their metal complexes. Schiff base metal complexes show a broad spectrum of biological activity. Amino acids are ingenious bio-ligand that forms complexes as they combine amines and carboxylic acid groups¹. This led to the finding that amino acid Schiff base complexes are excellent chelating agents for transition metal atoms². Due to the carbonyl and amine moiety, amino acids serve as outstanding bidders for the condensation of Schiff bases. Schiff base amino acid complexes of metal atoms have received much attention due to their high

biological activity. Schiff bases have many uses, including dyes, pigments, catalysts, intermediates in chemical synthesis, and stabilizers for polymers³. The presence of side chain groups in the amino acid is significant for coordinating the metal centre⁴.

Amino acid-based drugs possess excellent permeability, bio-availability, low toxicity, and metabolic and pharmacokinetic properties. The synthesis of several transition metal complexes has been attempted in this biological sector since Schiff base ligands can significantly influence the bioactive character of the organic ligands⁵. Amino acid-derived Schiff base complexes have numerous biological effects in pharmacological research and pay attention due to broad properties such as antibacterial, antifungal (including anti-yeast), antiviral, antitumor, anti-inflammatory, antipyretic, anti-malarial, anticancer, antioxidant, and anesthetic activities. Oxidative stress happens when the body's antioxidant defense mechanism fails to work out, leading to lipid peroxidation, cell membrane deterioration, nucleic acid oxidation, and cell damage⁶. Oxidative stress increases due to an imbalance between the production and elimination of free radical species and causes diseases like acute pancreatitis, diabetes mellitus, and

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inflammation processes, and thereby further. It is essential to develop substances with more significant antioxidant activity to treat diseases and injuries carried about by free radicals. According to WHO, in 2040, the worldwide risk of cancer is expected to quadruple to between 29 and 37 million new cases, with LMICs expected to have the most significant increases. Recently, some chemotherapy drugs still use cisplatin and its analogs as a medication. These medications, however, have even fewer therapeutic benefits and substantial side effects. In order to treat cancer cells and oxidative stress, amino acid-derived Schiff bases and complexes have been analyzed to develop new drugs. This paper summarizes the recent literature reports of amino acid-derived Schiff bases and their complexes with their anticancer and antioxidant activity of the previous seven years.

Antioxidant Activity

Lekha Logu *et al.*⁷ have synthesized $[\text{Ln}(\text{L})(\text{NO}_3)_2(\text{H}_2\text{O})]\cdot\text{NO}_3$ (L = Schiff base ligand) six novel Ln(III) Schiff base complexes using rare earth metals with threonine and 5-bromo salicylaldehyde, namely Pr(III), Sm(III), Gd(III), Tb(III), Er(III) and Yb(III) Schiff bases (Fig. 1). These complexes were characterized by elemental analysis, FTIR, UV spectra, molar conductivity, and thermogravimetry–differential thermal analysis. A fluorescent study indicates that the Schiff base ligand is an excellent chelating organic chromophore that can absorb and transfer energy to the Ln(III) ions. The synthesized compounds show enhanced antimicrobial activity and antifungal activity. The ligand and its complexes have been evaluated for Antioxidant activity using the DPPH radical scavenging method, and they have shown only moderate Antioxidant activity.

The monosodium salts of amino acid Schiff bases and iron(III) complexes of the N-(5-nitro

salicylidene)-amino acids, where the amino acid is D-alanine, D-valine, and D-phenylalanine. $[\text{NaL}]\cdot n\text{H}_2\text{O}$ (L= N-(2-hydroxy-5-nitro benzylidene)alaninate (L1Na), N-(2- hydroxy-5-nitro benzylidene)valinate (L2Na), and N-(2-hydroxy-5-nitro benzylidene) phenyl alaninate, (L3Na) were synthesized by Ozlem Oedzmiret *et al.*⁸ These monosodium salts compounds were characterized by elemental analysis, UV-vis spectra, FTIR, conductivity measurements and 2D NMR techniques. Monosodium salts have moderate antioxidant activity as this order $\text{L2Na} > \text{L1Na} > \text{L3Na}$. The compounds' excellent activity may be related to the strong electron-withdrawing group (NO_2) and the phenyl group for L3Na.

Yorur-Goreci, C. *et al.*⁹ have synthesized new Schiff bases by condensation reactions of benzaldehyde, salicylaldehyde, pyrrole-2-carbaldehyde, pyridine-2-carbaldehyde, fluorene-2-carbaldehyde, and terephthalaldehyde with 2-phenyl glycine methyl ester hydrochloride by both conventional method and microwave irradiation. The synthesized compounds were characterized by UV, FTIR, ^1H NMR, and LC-MS spectral data. By using microwave irradiation, the product yield was increased from 37% up to 96% and obtained with reduced time, waste, and formation of a by-product than the conventional method. The most significant advantage of this method is that reactions were completed within 5.5-8.5 minutes. The synthesized compounds (1a-f) showed good free radical scavenging activity by inhibiting DPPH radical in a concentration-dependent manner. Compound 1c, with a pyrrole ring, exhibited the best antioxidant activity of 78.27%, which is similar to that of reference antioxidants, butylated hydroxyl toluene (BHT), and α -tocopherol.

A new Schiff base transition metal complexes derived from o-hydroxy acetophenone and L-tryptophan

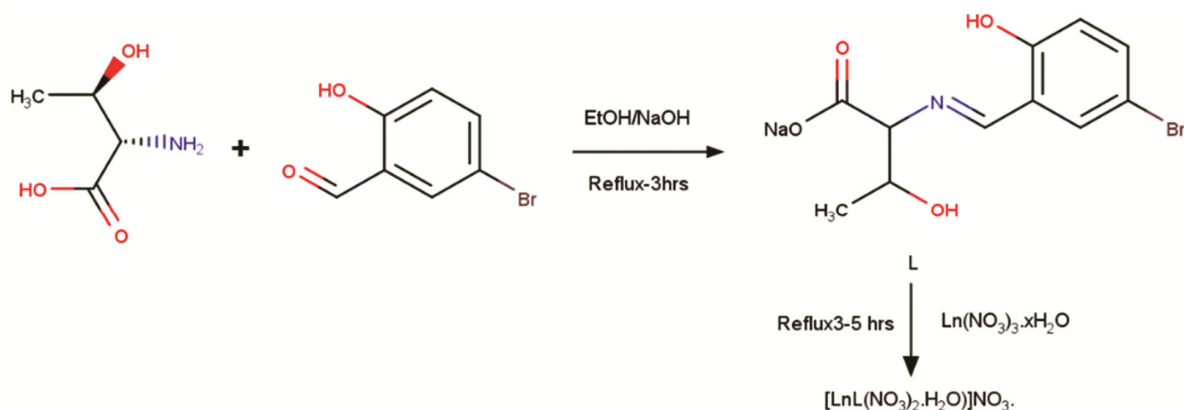


Fig. 1 — Synthesis of Schiff base Ligand(L) and Ln(III) Schiff base Complexes

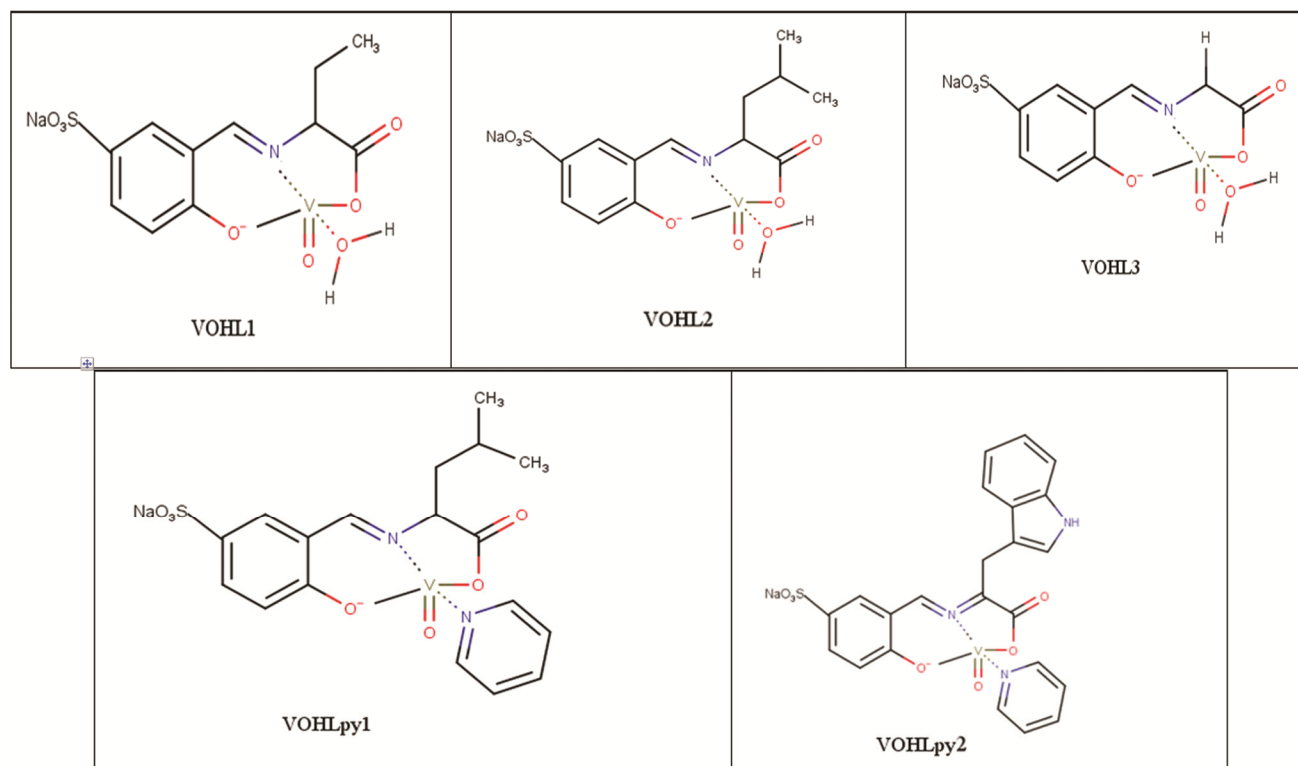


Fig. 2 — The synthetic pathway and the molecular structure of the VO-Salicyldiene amino acid Complexes

characterized by molar conductance, elemental analysis, and spectral studies such as UV-Vis., and FTIR, which was reported by Lakshmi, S. S., & Geetha¹⁰. Among the synthesized metal complexes, Cu(II) and Zn(II) complexes exhibited higher zone of inhibition against *E. coli* and *Mucor*. All the metal complexes showed moderate Antioxidant activity and antibacterial activity.

Mohamed Shaker S. Adam *et al.*¹¹ have synthesized new oxo-vanadium N-Salicyl diene amino acid Schiff base complexes with some amino acids, alanine (VOHL1), leucine (VOHL2) or glycine (VOHL3) in an aqueous media, and leucine (VOHLpy1) or tryptophan (VOHLpy2) in pyridine with vanadyl acetyl acetonate (Fig. 2). These synthesized complexes were characterized by IR, UV-Visible, mass spectra, elemental analysis, TGA, conductivity, and magnetic measurements. The VO complexes were analyzed for all biological activities. All VO complexes show highly toxic effects, but VOHL2 is less than can be applied to humans. The antioxidant activity is exhibited for all VO complexes, but more than 50% is recorded by the VOHL3 complex. In VO complexes, VOHL2 shows antibacterial, antifungal, and anti-proliferative activity.

One-pot synthesis of a new anhydrous Copper(II) complex derived from N-(2'-hydroxy acetophenone)

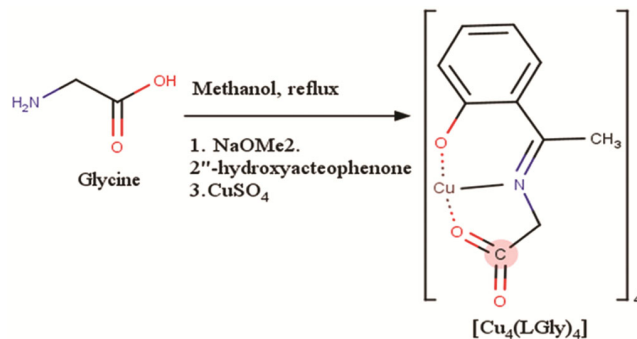


Fig. 3 — Synthesis of $[Cu_4(LGly)_4]$

glycinate ligand (LGly) results in $[Cu_4(LGly)_4]$ (Fig. 3) and characterized by UV-Vis, IR spectra, and single crystal X-ray diffraction and catalytic activity. $[Cu_4(LGly)_4]$ effectively deactivates the ABTS radical and shows higher antioxidant activity, were explained by Soberanes, Y. *et al.*¹²

A new Schiff base, 6-amino-2-[(4-(dimethylamino)benzylidene)amino]hexanoic acid was investigated by Mehwish Aftab *et al.*,¹³ and to form $Ce(NO_3)_3 \cdot 6H_2O$ and $La(NO_3)_3 \cdot 6H_2O$ complexes (Fig. 4). The complexes were characterized by ¹H NMR, UV-Vis, FTIR, and ICP techniques. Schiff base metal complexes showed good Antioxidant activity, which is compared with standard Trolox, and it also inhibits

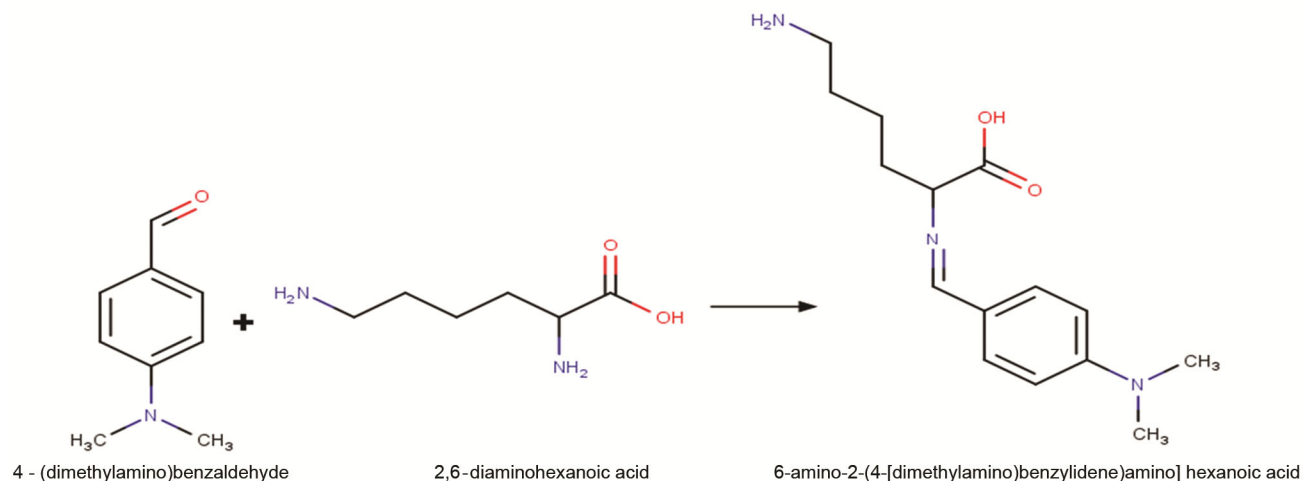


Fig. 4 — Synthesis of ligand, 6-amino-2-[(4-(dimethylamino)benzylidene)amino]hexanoic acid

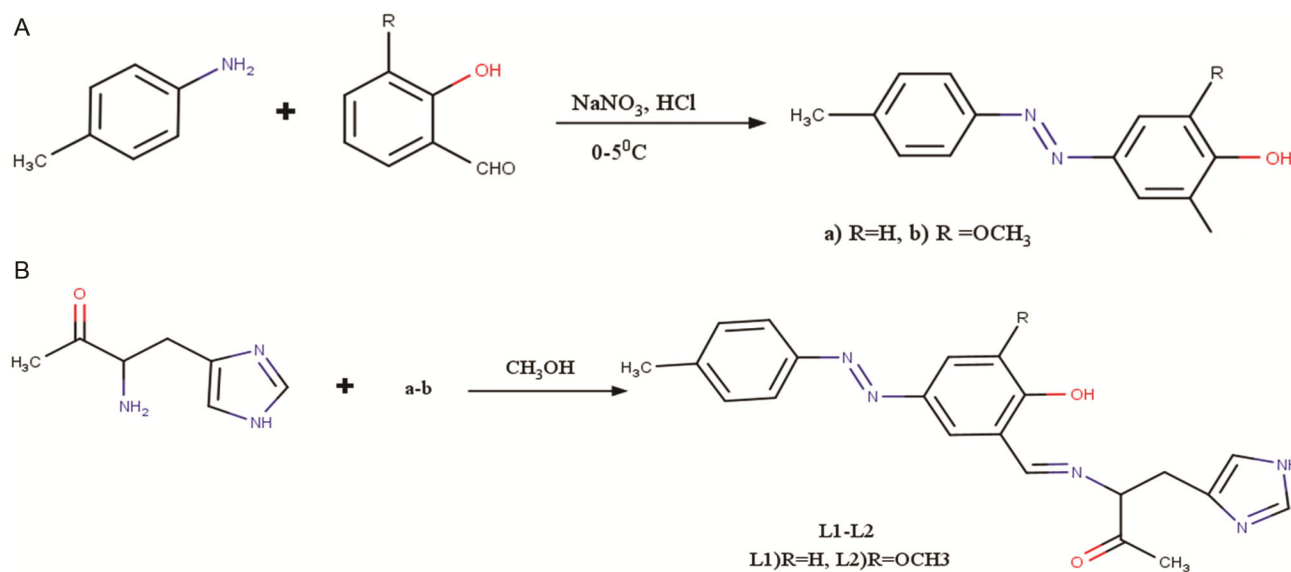


Fig. 5 — (A) Synthesis of Schiff base ligands L¹; and (B) Synthesis of Schiff base ligands L2

diphenyl picryl hydrazine (DPPH). These metal complexes also specifically exhibit antimicrobial activity.

Slassi S., *et al.*¹⁴ have synthesized bidentate Schiff base ligands (L1, L2) derived from histidine methyl ester (Fig. 5A & B) and their Cu(II) and Zn(II) complexes (Fig. 6) and they are characterized by the UV-vis, ¹H and ¹³C NMR and molar conductivity spectral data. From the data results, the metal Cu(II) and Zn(II) ions coordinated with the imine linkage of nitrogen and phenolic oxygen atoms. *In vitro*, antibacterial activity showed that Cu(II) complexes increase inhibition activity more than Schiff base ligands and Zn(II) complexes. Additionally, the

scavenging effect on DPPH radicals is carried out by the antioxidant activity. Typically, the ligands show more active results than the Copper and Zinc complexes.

Anticancer Activity

Schiff bases derived amino acid of alanine and glycine Copper complexes of [Cu(II) (SalCl-Gly)(H₂O)₂] (1) SalCl-Gly = 5-chloro-2-hydroxy benzylidene-glycine, [Cu(II)(SalCl-Ala)(H₂O)] (2) SalCl-Ala = 5-chloro-2-hydroxy benzylidene-alanine [Cu(II)(SalCl-Gly)(bipy)]0.5H₂O (3) 5-chloro salicylaldehyde-glycine bipy = 2,2'-bipyridine. Li, A., Liu, Y.H., *et al.*¹⁵ fabricated an experimental setup to characterize compounds by elemental

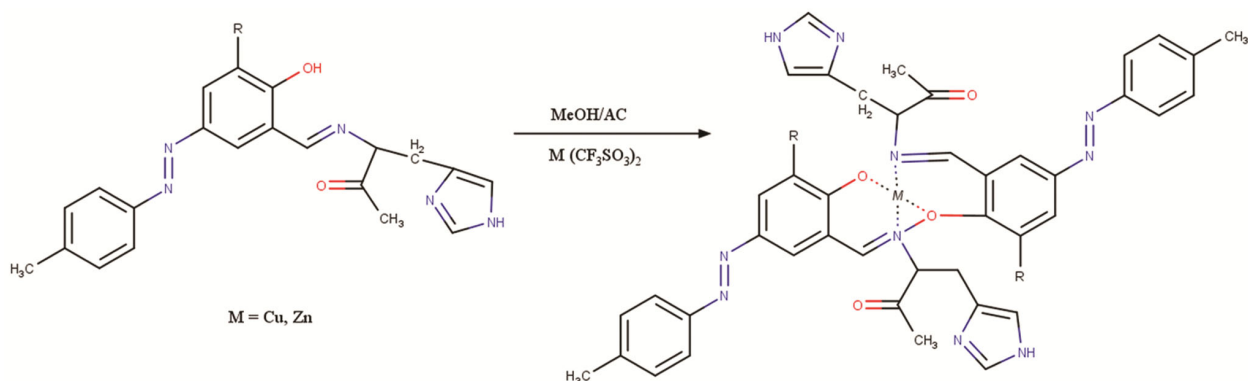


Fig. 6 — Synthesis and proposed structures of Cu(II) and Zn(II) Complexes

analysis, X-ray crystallography, FTIR, and fluorescence spectroscopy. These complexes' DNA (CT-DNA) binding sites are studied by viscosity measurement and fluorescence spectroscopy. Among these complexes 2, 2'-bipyridine group to (1), the resulting complex (3) shows enhanced intercalation to DNA. MTT assay was carried out to antiproliferative activity of complexes against (HepG-2 and NCI-H460) tumor cells.

Yaping Cao *et al.*¹⁶ aimed to develop a novel series of four new amino acid Schiff base oxovanadium(V) complexes. [VO(desa-met)(phen)].MeOH.2H₂O (**1**) (desa-met = Schiff base derived from 4-(diethylamino)salicylaldehyde and DL-methionine, phen = 1,10-phenanthroline), [VO(o-van-met)(phen)].MeOH.CH₂Cl₂.3H₂O (**2**) (o-van-met = Schiff base derived from o-vanillin and DL-methionine), [VO(dtbs-napa)(phen)].2H₂O (**3**) (dtbs-napa = Schiff base derived from 3,5-di-tert-butyl salicylaldehyde and 3-(1-naphthyl)-L-alanine) and [VO(hyna-napa)(phen)].1.5H₂O (**4**) (hyna-napa = Schiff base derived from 2-hydroxy-1-naphthaldehyde and 3-(1-naphthyl)-L-alanine) and these synthesized complexes (Fig. 7) were characterized by single crystal X-ray diffraction, UV-Vis spectra, IR, HRMS, and molar conductance.

All four complexes (**1-4**) show six-coordinated in a distorted octahedral environment. Descriptive crystal structures were studied for these complexes. In this, there are CH- π stacking interactions between the phen and Schiff base ligands in complexes 1 and 4's supra molecular structures, and the interactions between the aromatic rings in complexes 2 and 3 can be seen as π - π stacking. *In vitro* Anticancer activities were studied for complexes 1-4 against A-549 and HeGp2 cell lines tested by MTT assay. Complexes 2-4 show moderate Anticancer activity against human lung carcinoma and hepatoma cell lines.

Series of two new complexes, namely Platinum (PtL2) and Ruthenium (2) with α -amino acid, L-alanine, and 2, 3-dihydroxy benzaldehyde derived Schiff base (L) (Fig. 8). The synthesized complexes were characterized by elemental analysis, IR, Proton & ¹³C NMR, ESR, and ESI-MS techniques. Ali Alsalmeh, *et al.*¹⁷ have investigated the protein binding site interactions of synthesized complexes studied by UV-Visible, fluorescence, and circular dichroism techniques with a model protein, human serum albumin (HSA), *In vitro* cytotoxicity activity analyzed towards human hepatocellular carcinoma cancer (HepG2) cell line. Furthermore, the evaluation of reactive oxygen species revealed a significant significance for cytotoxicity.

Complexes based on platinum and ruthenium are now being studied for their potential to bind proteins and fight cancer. When tested against the human HepG2 cell line, platinum-based complexes exhibit moderate protein binding interactions and minimal Anticancer efficacy. The (HepG2) human hepatocellular carcinoma cancer cell line is more sensitive to ruthenium-based complexes, producing more Reactive Oxygen Species (ROS) and having a higher binding affinity for protein interactions.

Camacho-Camacho, C. *et al.*¹⁸ made a one-pot synthesis of six new tri-n-butyl Tin(IV) and amino acid derivatives from L-alanine, L-valine, L-isoleucine, L-methionine, L-phenylalanine and L-tryptophan of Schiff bases. The structural characterization of synthesized compounds was studied by solid-state, one- and two-dimensional solution NMR (¹H, ¹³C, and ¹¹⁹Sn), one- and two-dimensional solution NMR (¹H, ¹³C), and elemental analysis. Moreover, single-crystal X-ray diffraction was performed to validate their crystal structures. The compounds of tin are monomeric and four-

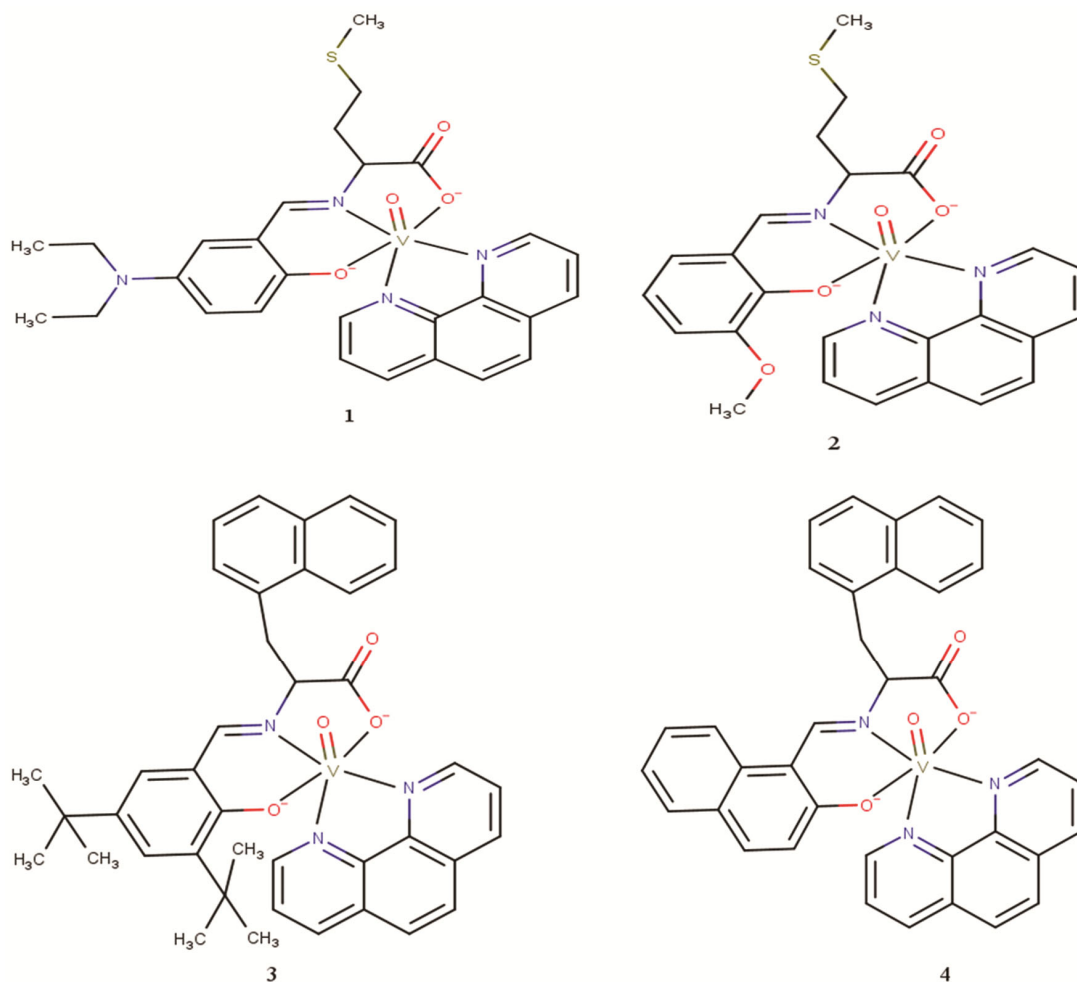


Fig. 7 — The Molecular Structure of oxo-Vanadium (IV) Complexes 1, 2, 3 and 4

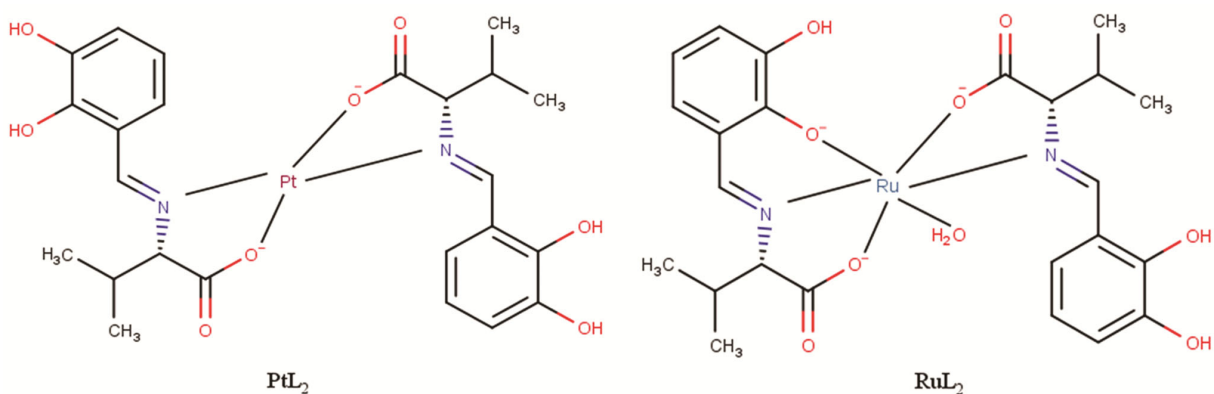


Fig. 8 — Structures of (PtL₂) and (RuL₂) Complexes

coordinated in solution, despite being five-coordinated and polymeric in the solid form. Tin(IV) carboxylates derived from organic amino acids have more excellent activity and selectivity. *In vitro*, antiproliferative screening activity was studied for compounds 1-6 against the tumor (HeLa, CaSki, and ViBo) cell line. The compounds

derived from L-alanine and L-isoleucine show a higher cytotoxicity effect, which is crucial for this activity. Compounds 2, 4, 5, and 6 exhibit antiproliferative activity without showing cytotoxic activity which makes them, strong candidates to be studied as potential therapeutic agents against cancer.

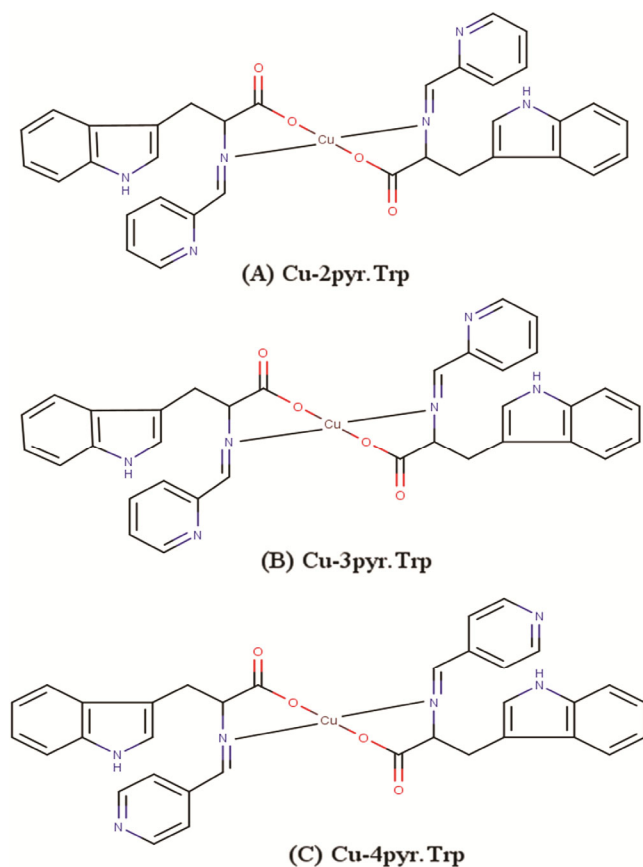


Fig. 9 — Structures of Schiff bases and their Copper Complexes (A), (B), (C)

New series Schiff base Copper(II) complex (Fig. 9) derived from L-tryptophan (Trp) and isomeric 2-, 3- and 4-pyridine carboxaldehyde, namely (Cu-2pyr.Trp(A), Cu-3pyr.Trp(B), and Cu-4pyr.Trp(C)). Malakyan, M. *et al.*¹⁹ reported the L-tryptophan Schiff bases 2pyr.Trp, 3pyr.Trp and 4pyr.Trp compounds. The yield of target products was obtained as 75-85%. The synthesized Schiff bases and complexes were structurally characterized by elemental analysis and FTIR techniques. The position of carboxaldehyde at 2, 3, and 4 concerning nitrogen of the pyridine ring in the aldehyde component of the L-tryptophan derivative Schiff bases and their complexes play an essential role in the variation of the biological activity. Schiff bases and their copper complexes are tested *In vitro* on the Hela and KCL22 cell lines to determine their cytotoxicity. According to cytotoxicity experiments, the compounds 2pyr.Trp, Cu-2pyr.Trp, and Cu-4pyr.Trp has residual toxicity to humans, whereas 3pyr.Trp, 4pyr.Trp, and Cu3pyr.Trp is non-toxic. According to studies, Carboxaldehyde group positions 2 and 4 exhibits

higher cytotoxicity activity than complexes in position 3. The copper content causes higher cytotoxicity.

Sifteen Zehra *et al.*²⁰ synthesized chiral enantiomeric amino acid (valine and L/D-phenyl alanine) Schiff base Copper(II) complexes 1 and 2 (a and b), i.e., [C₁₆H₁₅CuNO₃] **1a**, [C₁₆H₁₅CuNO₃] **1b**, [C₂₁H₂₁CuNO₅], **2a**, [C₂₁H₂₁CuNO₅] **2b** (Fig. 10). The complexes were characterized by UV-Vis, EPR, FTIR, electrospray ionization-mass spectrometry, circular dichroism, and single X-ray crystal diffraction analyses. These studies have established the binding interaction of ct-DNA and t-RNA (2a > 2b > 1a > 1b), the enantiomeric behavior of complexes, and cleavage studies. The most cytotoxicity activity shows that L- enantiomeric complexes 2a holds good Anticancer activity against the human cancer cell lines MCF-7 breast cancer cell line with a GI50 value of <1 μM.

New series of hexa-coordinated octahedral Nickel(II) complexes, Schiff base derived from tryptophan and salicylaldehyde, o-vanillin, 2-hydroxy-1-naphthaldehyde and phen = 1, 10-phenanthroline have been investigated by Li, Y., Dong, *et al.*²¹ The prepared complexes are [Ni(Trp-sal)(phen)(CH₃OH)] (**1**), [Ni(Trp-o-van)(phen)(CH₃OH)]•2CH₃OH (**2**) and [Ni(Trp-naph)(phen)(CH₃OH)] (**3**). The structure of the complexes was studied in detail by single crystal X-ray crystallography, which possesses a distorted octahedral environment around nickel(II) ions. The synthesized complexes show moderate Anticancer activity against oesophageal cancer cell line Eca-109. These complexes show and inhibit cancer cell growth through mitochondrial dysfunction, intracellular ROS accumulation, and ROS-mediated DNA damage.

Synthesized a novel series of L-histidine amino acid-derived Schiff base ligands and their metal-complexes [Mn(II), Co(II), Cu(II), Ni(II), and Zn(II) (**1-5**)] were reported by Sridevi, N., & Maheshwari, D²². These complexes (Fig. 11) were characterized by FTIR, UV-vis, and ESI-MS spectral techniques. All (1-5) complexes exhibit Antioxidant activity, with significant free radical scavenging activity against the free radical DPPH. Complex 3, shows higher cytotoxicity against breast cancer cell lines (MCF-7), thereby possessing Anticancer activity. They show anti-microbial activity towards Gram-positive and Gram-negative bacteria as well as Fungi.

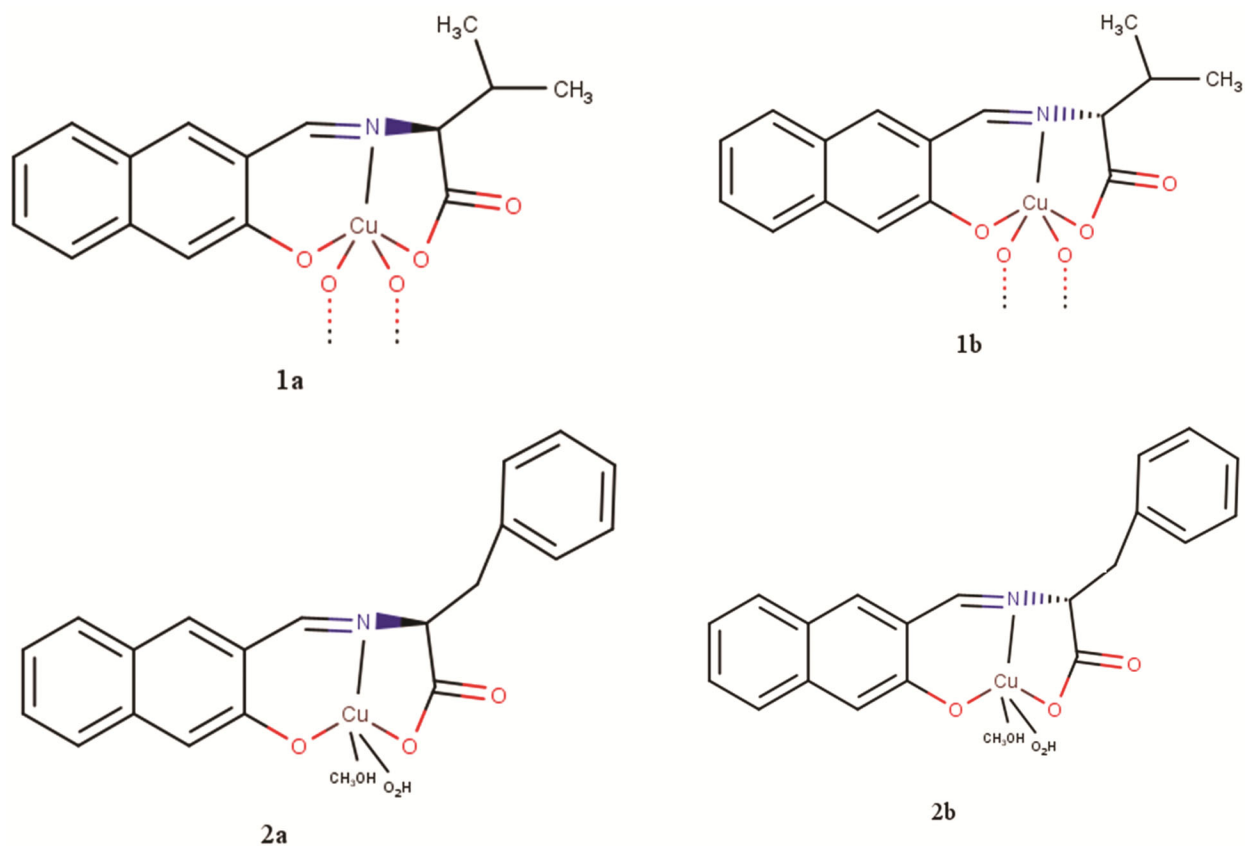


Fig. 10 — Structure of the Complexes 1 and 2 (A and B)

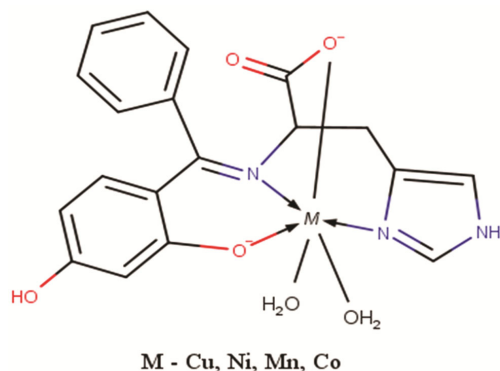


Fig. 11 — Structure of L-histidine derived Schiff base Complexes (1-5)

Mohamad, A. D., *et al.*²³ have synthesized new water-soluble Cu(II) complexes (Cu-PSA and Cu-PSL) which are obtained from Schiff bases of amino acids (D, L-phenylalanine and D, L-leucine) ligands as sodium salts (Fig. 12). These two novel complexes were chemically characterized by IR, UV-vis, mass spectra, NMR, molar conductivities, TGA, magnetism, and CHN micro-analyses. The synthesized Cu complexes were tested for Anticancer, anti-microbial, and anti-fungal activity. The results

show that complexes inhibit more significantly than the free ligands due to the central metal ion (Cu²⁺). The Cu-PSA and Cu-PSL complexes have high catalytic activity due to the salt Na⁺, SO₃ groups presence.

Dinev, D. *et al.*²⁴ have synthesized two Cu(II) and Co(II) mononuclear complexes with mixed ligands, which results in the condensation of o-vanillin with D, L-tryptophan, L-serine, L-tyrosine, and L-threonine. These complexes were characterized by elemental analysis, FTIR, UV-vis and magnetic measurements. The Anticancer activity is exhibited by CuVanSer [Cu(Van)(bipy)].H₂O and CoVanSer [Co(Van)(bipy)].3H₂O against HeLa and LSR-SF-SR cells. The cytotoxicity effect is more pronounced in LSR-SF-SR cells than HeLa cells.

Novel series Schiff base ligands derived from glycine, asparagine, and alanine (L1, L2, L3) shown in (Fig. 13A, B & C) to form silver complexes (Fig. 14). These complexes are characterized by FTIR, ¹H NMR, UV-vis, and molar conductance techniques. Anti-bacterial activity shows that the L¹ and L² complexes are active and L³ is inactive. Antioxidant activity of all synthesized compounds has

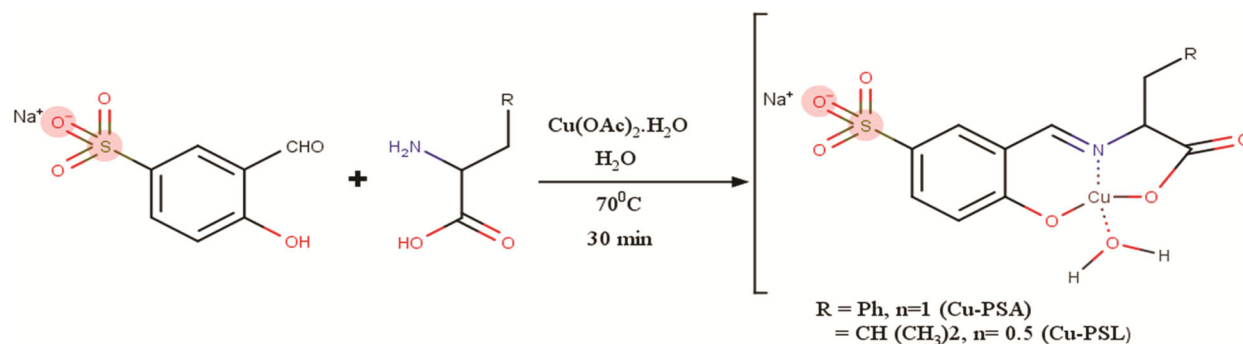


Fig. 12 — The synthetic route of Cu-PSA and Cu-PSL in an aqueous media.

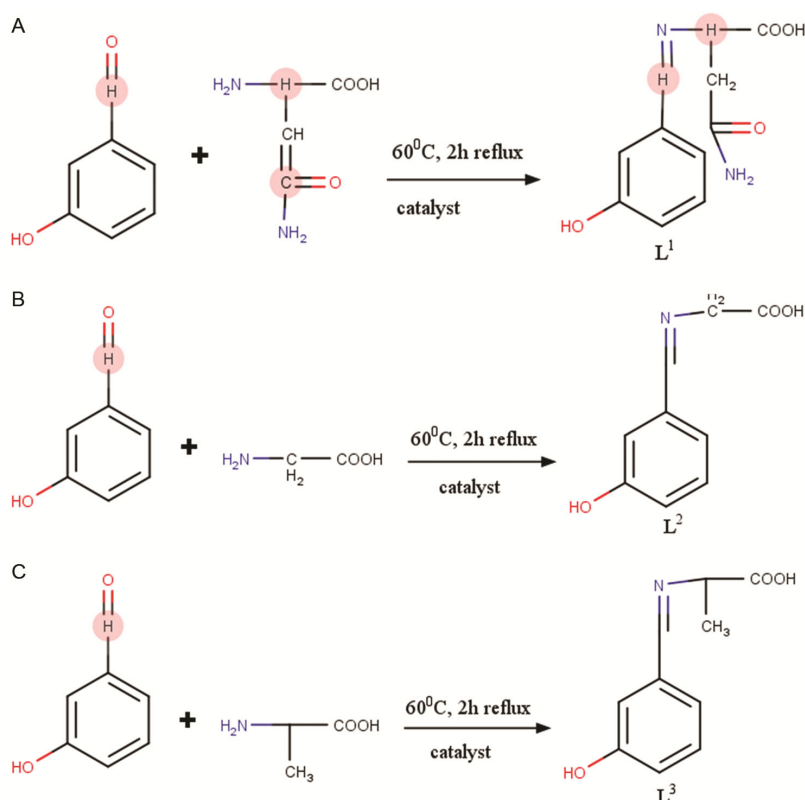


Fig. 13 — (A) Synthesis and the chemical structures of L^1 ; (B) Synthesis and the chemical structures of L^2 ; and (C) Synthesis and the chemical structures of L^3

lower concentrations and showed more significant results. MTT assay was carried out to screen the cytotoxicity activity. The results show that all synthesized compounds have sound cytotoxicity effects have been investigated by Aftab, M. *et al.*²⁵.

Zhao, P. *et al.*²⁶ reported three hexa-coordinated octahedral Nickel(II) complexes with phenyl alanine, namely $[\text{Ni}(\text{sal-L-phe})(\text{phen})(\text{CH}_3\text{OH})] \cdot \text{CH}_3\text{OH}$ (1), $[\text{Ni}(\text{naph-L-phe})(\text{phen})(\text{CH}_3\text{OH})]$ (2), $[\text{Ni}(\text{o-van-L-phe})(\text{phen})(\text{CH}_3\text{OH})] \cdot 5\text{CH}_3\text{OH}$ (3). *In vitro* cytotoxicity assay was carried out. The results show that complex 3 has significant activity against CAL-

27 cells, which occurs through intracellular ROS accumulation and ROS-mediated DNA damage mitochondrial dysfunction.

Results and Discussion

A total of 45 articles were included from searching databases. The searched article was studied for titles and abstracts, and 23 articles included in the full-text review were identified as relevant studies. The findings reveal that all synthesized compounds were characterized by UV-vis, FTIR, LC-MS, ¹H, and ¹³C NMR, molar conductance, and magnetic

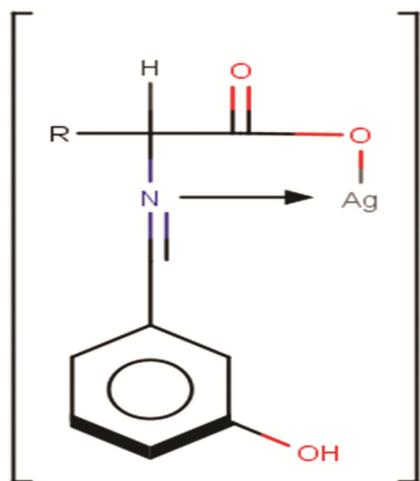


Fig. 14 — Proposed Structure of Metal Complexes (where R = R', R'', R'''; R' = CH₃- (alanine), R'' = NH₂CO-CH₂- (asparagine), R''' = H- (glycine))

measurements. Some reported compounds have undergone toxicological studies during the development of new drugs.

Oxidative stress plays a crucial role in severe diseases like Alzheimer's disease, Parkinson's disease, diabetes, cardiovascular diseases, and eye diseases. The literature review reveals that Schiff bases derived amino acid compounds are efficient for oxidative and cancer diseases. Mehwish Aftab *et al.*¹³ reported that new Schiff bases hexanoic acid are compared with standard Trolox drugs, which neutralize free radicals and can be used to treat pathological diseases. This activity arises due to the electron-donating group of metal complexes than the ligand atom. In contrast, the presence of the (-OCH₃) donor group of ligands has high potent Antioxidant activity than the complexes developed by Slassi, S. *et al.*¹⁴

Cisplatin is a more potent drug first discovered as a metal-based chemotherapeutic drug to cure cancer. It is a platinum-based Anticancer drug that is sold worldwide, but it is resistant owing to nephrotoxicity, ototoxicity, hepatotoxicity, gastrointestinal toxicity side effects, relapsing, and drug resistance. Carboplatin and oxaliplatin are some of the derivatives of cisplatin drugs. The binding of pharmaceuticals to proteins is crucial to represent the pharmacokinetics of medications. Ali Alsalmeh, *et al.*¹⁷ have stated that Ruthenium-based complex drugs are more potent against HepG2 cells with IC₅₀=32.9, which is compared with cisplatin (IC₅₀=26.8) drugs. So, much research has led to the development of less toxic, more potent metal-based

drugs for various types of cancer cells. Further investigations on specific proteins whose complexes target cancer cells demand the design of chemotherapeutic drugs.

Conclusion

Schiff bases derived amino acids, and their metal complexes are essential in pharmacodynamics and pharmacokinetics. Since it is frequently simple to produce, modern research has evolved the extent of synthesis of novel compounds that are likely Schiff bases of amino acid complexes. Schiff base ligands and metal complexes of new compounds provide a very moderate to higher Antioxidant activity owing to an aromatic moiety and electron-attracting group of some amino acids. The application of in-vitro cytotoxicity activity against well-known HeGP2, HeLa, MCF, and many other cancer line cells was studied, which shows the good Anticancer activity as a consequence of Schiff base ligands and complexes, including the existence of position as well as enantiomer of peculiar amino acids. Furthermore, utilizing Schiff bases derived amino acids, their metal complexes possess various applications. This paper explicitly exposes the importance of amino acids, an excellent ligand to coordinate with central metals to form complexes that have a tremendous biological approach. Based on the present review, the future development of new amino acid-derived Schiff bases and their complexes may focus on the following view; Anticancer activity can be correlated to the Antioxidant activity (scavenging activity), and the development of effective, low toxicity, fewer side-effects' drugs for the treatment of cancer can be evolved from this type of metal-based drugs.

Conflicts of Interest

All authors declare no conflict of interest.

References

- 1 Waheed EJ, ObaidS MH & Al-Hamdani AAS, Biological activities of amino acid derivatives and their complexes a review. *Res J Pharm Biol Chem Sci*, 2 (2019) 1624.
- 2 Rahman LHA, Abu-Dief AM, Hashem NA & Seleem AA, Recent advances in synthesis, characterization and biological activity of nano-sized Schiff base amino acid M (II) complexes. *Int J Nano Chem*, 2 (2015) 79.
- 3 Singh S, Synthesis, spectroscopic studies and pesticidal activity of transition metal complexes with unsymmetrical Schiff base. *Indian J Biochem Biophys*, 58 (2021) 565.
- 4 Rajee AO, Babamale HF, Lawal A, Aliyu AA, Osunniran WA, Sheriff AO, Lawal M & Obaleye JA, Mn(II), Co (II), Ni (II), and Cu (II) complexes of amino acid derived Schiff

- base ligand: Synthesis, characterization and *in vitro* antibacterial investigations. *Bull Chem Soc Ethiop*, 1 (2021) 97.
- 5 Kothari R, Agrawal A & Rai S, Molecular docking and Antibacterial activities of Cobalt (II) complexes derived from precursors of Hydrazones. *Indian J Biochem Biophys*, 59 (2022) 640.
 - 6 Nithiyandam S, Jaisankar V, Parthasarathy M, Katturajan R & Prince SE, Antioxidant mediated defensive potency of *Caesalpinia bonducella* nut on Acetaminophen-inebriated spleen and cardiotoxicity: Implications on oxidative stress and tissue morphology in an *In vivo* model. *Indian J Biochem Biophys*, 60 (2023) 297.
 - 7 Logu L, Raja Kamatchi K, Rajmohan H, Manohar S, Gurusamy R & Deivanayagam E, Invitro antimicrobial and antioxidant evaluation of rare earth metal Schiff base complexes derived from threonine. *Appl Organomet Chem*, 2 (2015) 90.
 - 8 Özdemir Ö, Gürkan P, Sarı M & Tunç T, Synthesis of monosodium salts of N-(5-nitro-salicylidene)-D-amino acid Schiff bases and their iron (III) complexes: spectral and physical characterizations, antioxidant activities. *J Coord Chem*, 14 (2015) 2565.
 - 9 Yorur-Goreci C, Demir Z & Altaş N, Green Synthesis of New Amino Acid Schiff Bases and their Biological Activities. *J Turkish Chem Soc*, 3 (2016) 15.
 - 10 Lakshmi SS & Geetha K, Synthesis, characterization and biological studies of tridentate amino acid (L-tryptophan) Schiff base transition metal complexes. *J Chem Pharm Res*, 8 (2016) 668.
 - 11 Adam MS & Elsayy H, Biological potential of oxovanadium salicylidene amino-acid complexes as cytotoxic, antimicrobial, antioxidant and DNA interaction. *J Photochem Photobiol B Biol*, 184 (2018) 34.
 - 12 Soberanes Y, López-Gastélum KA, Moreno-Urbalejo J, Salazar-Medina AJ, del Carmen Estrada-Montoya M, Sugich-Miranda R, Hernandez-Paredes J, Gonzalez-Córdova AF, Vallejo-Cordoba B, Sotelo-Mundo RR & Velázquez-Contreras EF, Tetrameric copper (II) metallocyclic complex bearing an amino acid derived Schiff base ligand: Structure, catalytic and antioxidant activities. *Inorg Chem Commun*, 94 (2018) 1394.
 - 13 Aftab M, Mahmud T, Basra MA, Gulzar A, Basharat S & Junaid HM, Schiff Base 6 Amino 2 4 (Dimethylamino) Benzylidene) Amino] Hexanoic Acid and its Lanthanide(III) Complexes have Antioxidant and Antimicrobial Activities. *Pak J Zool*, 1 (2019) 167.
 - 14 Slassi S, Aarjane M & Amine A, New bidentate Schiff base ligands derived from histidine and their metal complexes: synthesis, structural analysis, antibacterial and antioxidant evaluation. *J Iran Chem Soc*, 7 (2022) 3117.
 - 15 Li A, Liu YH, Yuan LZ, Ma ZY, Zhao CL, Xie CZ, Bao WG & Xu JY, Association of structural modifications with bioactivity in three new copper (II) complexes of Schiff base ligands derived from 5-chlorosalicylaldehyde and amino acids. *J Inorg Biochem*, 146 (2015) 52.
 - 16 Cao Y, Yi C, Liu H, Li H, Li Q, Yuan Z & Wei G, Syntheses, crystal structures and invitro anticancer activities of oxovanadium (IV) complexes of amino acid Schiff base and 1, 10-phenanthroline ligands. *Transit Met Chem*, 41 (2016) 531.
 - 17 Alsalmeh A, Laeeq S, Dwivedi S, Khan MS, Al Farhan K, Musarrat J & Khan RA, Synthesis, characterization of α -amino acid Schiff base derived Ru/Pt complexes: Induces cytotoxicity in HepG2 cell via protein binding and ROS generation. *Spectrochim Acta A Mol Biomol Spectrosc*, 163 (2016) 1.
 - 18 Camacho-Camacho C, Rojas-Oviedo I, Garza-Ortiz A, Toscano RA, Sánchez-Sánchez L, Cardenas J & López-Muñoz H, Schiff base complexes with amino acid derivatives: synthesis, characterization and biological activity. *Appl Organomet Chem*, 4 (2016) 199.
 - 19 Malakyan M, Babayan N, Grigoryan R, Sarkisyan N, Tonoyan V, Tadevosyan D, Matosyan V, Aroutiounian R & Aakelyan A, Synthesis, characterization and toxicity studies of pyridine carboxaldehydes and L-tryptophan derived Schiff bases and corresponding copper (II) complexes. *F 1000 Research*, 5 (2016) 1921.
 - 20 Zehra S, Roisnel T & Arjmand F, Enantiomeric amino acid Schiff base copper (II) complexes as a new class of RNA-targeted metallo-intercalators: Single X-ray crystal structural details, comparative *In vitro* DNA/RNA binding profile, cleavage, and cytotoxicity, *ACS Omega*, 26 (2019) 7691.
 - 21 Li Y, Dong J, Zhao P, Hu P, Yang D, Gao L & Li L, Synthesis of amino acid Schiff base nickel (II) complexes as potential anticancer drugs *In vitro*. *Bio Inorg Chem Appl*, (2020).
 - 22 Sridevi N & Madheswari D, Theoretical and experimental studies of novel histidine derived Schiff base metal complexes, active towards biomedical and MCF 7 cell lines. *Indian J Chem*, 59A (2020) 1768.
 - 23 Mohamad AD, El-Shrkawy ER, Al-Hussein MF & Adam MS, Water-soluble Cu (II)-complexes of Schiff base amino acid derivatives as biological reagents and sufficient catalysts for oxidation reactions. *J Taiwan Inst Chem Eng*, 113 (2020) 27.
 - 24 Dinev D, Popova KB, Zhivkova T, Dyakova L, Abudalleh A, Alexandrova R, Culita DC, Mocanu T, Maxim C & Marinescu G, Synthesis, structural characterization, and cytotoxic activity in tumor cells of Cu (II) and Co (II) complexes with o-Vanillin amino acids Schiff bases. *Appl Organomet Chem*, 10 (2022) e6862.
 - 25 Aftab M, Mazhar N, Shah MT, Batool MA, Mahmud T, Basra MAR, Bratu G & Mitu, L, Synthesis, characterization and biological evaluation of three new Schiff bases derived from amino acids and their Ag (I) complexes. *Bull Chem Soc Ethiop*, 1 (2022) 45.
 - 26 Zhao P, Qiu H, Wei Q, Li Y, Gao L & Zhao P, Anti-tumor effect of novel amino acid Schiff base nickel (II) complexes on oral squamous cell carcinoma cells (CAL-27) invitro. *Mol Cell Toxicol*, 13 (2022) 1.