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Recent Developments in N,S,O Donor Schiff Base Molecules as Anti-Cancer Therapeutics

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Abstract: Biological importance in many fields, including anti-cancer activity, and advances in inorganic chemistry with biological applications have heightened the scope of interest in Schiff bases and their complexes due to the combination of an aldehyde with an amine are useful chelate to produce coordination spheres with mixed N/O donors. The discovery of Schiff base and its complexes' antitumor activity against various tumor cell lines captures the interest of researchers seeking to develop new anti-cancer drugs with no side effects. O-vanillin is a very useful aldehyde for preparing Schiff base ligands. It is found in the extract of vanilla. It is readily soluble in water. This aldehyde can combine with several different types of amine to form Schiff base which can form complexes with high stability with the majority of metals, which is caused by the azomethine group's nitrogen (N) in addition to two oxygen (O) atoms from the hydroxyl and methoxy groups. Apoptosis is a natural death process of damaged, senescent, or abnormal cells that stops cancer development. It is reduced or blocked in cancer cells and can be triggered again by anti-cancer drugs. Therefore, in anti-cancer research, inducing cancer cell apoptosis is a favourable goal to be achieved by a new molecule blocked in cancer cells and can be triggered again by anti-cancer drugs. This review focuses on recent advances in N,S,O donor Schiff base molecules for Anti-cancer applications.

Keywords: Apoptosis, Inhibition, Malignant, Therapeutic.

I. Introduction

Schiff bases can form the most stable complexes with transition, actinides, and main group elements [1-2]. However, transition metal complexes with suitable ligands are versatile as they can have different oxidation states, coordination geometry, and coordination numbers [3]. Schiff base are mostly either bi- or tri-dentate and can form complexes with metal ions. Nowadays, much work is done on Schiff base, and is studied for its remarkable and important properties like catalytic activity, photochromic properties, industrial and biological properties, and complexing ability towards toxic metals [4]. Schiff bases with transition metal complexes played a vital role in the inhibition of cancer [5]. Although organic compounds are most commonly used as drugs for such activity, their use is limited because not much modification in their structure can be done which has given rise to bacteria/fungi resistant drugs [6]. Different types of aldehyde can combine with different types of amine to form a Schiff base. The -COOH and -NH_2 coordinating sites are present in amino acids. These sites can readily coordinate with metal ions by condensing with aldehydes or ketones to generate Schiff bases. Different types of amino acids are functionally engaged in a variety of biological activities. The majority of Schiff bases are generated from amino acids and their metal complexes have varying pharmacological effects [7]. Since the azomethine group's nitrogen (N) is next to two oxygen (O) atoms from the hydroxyl and methoxy groups, they can form complexes with most metals that are highly stable. Thus, transition metal complexes with suitable ligands are versatile as they can have different oxidation state, coordination geometry and coordination number. Moreover, it has been observed that often, a change in metal ion give rise to significant change in its properties and hence applications. In addition, to those metal complexes can undergo ligand exchange or release reaction, can generate reactive oxygen species and have unique redox, spectroscopic and catalytic activity. Such mechanisms are difficult if not impossible to replicate with purely organic compounds [8]. Thus, if transition metal ion nucleus is available at the core of the structure of drug, the fine tuning of the structural aspect of the drug becomes easier. As a result, it will help the medicinal chemist to formulate new approaches leading to the discovery of new drugs. For a long time, cancer has been the leading cause of death worldwide. There are more than 270 types of cancer that are highly resistant to chemotherapy drugs and will cause recurrence after the initial cure. Hence, discovery of new molecules having potential drug like activity is need of the hour. An effective chemotherapy method is to use drugs with metals as active ingredients, which can more effectively treat multi-drug resistant infections. Finally, in 1978, the metal complex-based drugs reached their pinnacle with the approval of Platinum-based chemotherapeutic agent Cisplatin. Many other variations of cisplatin are also available now such as cis-diamine (1,1-cyclobutane dicarboxylate) platinum (II) (carboplatin) which was approved in 1993 or trans-R,R-cyclohexane- (1,2-diamine) oxalatoplatinum(II) (oxaliplatin) which was approved in the year 2002 [9]. Although these drugs are very effective they have

severe side effects like nausea, kidney failure, and hair loss and have dosage limits. In the last two decades, several Platinum, Ruthenium, Copper, and Iron-based complexes have reached up to human trial stage for treatment for treatment of cancer, malaria, and other neurodegenerative diseases. Apoptosis is a process by which damaged, senescent, or aberrant cells naturally die; it halts the growth of cancer. Anti-cancer medications can reactivate it, as it is either decreased or stopped in cancer cells. This review mainly focuses on applications of naturally derived amino acid Schiff base as a potential anti-cancer drug [9].

II. Global Status of Cancer

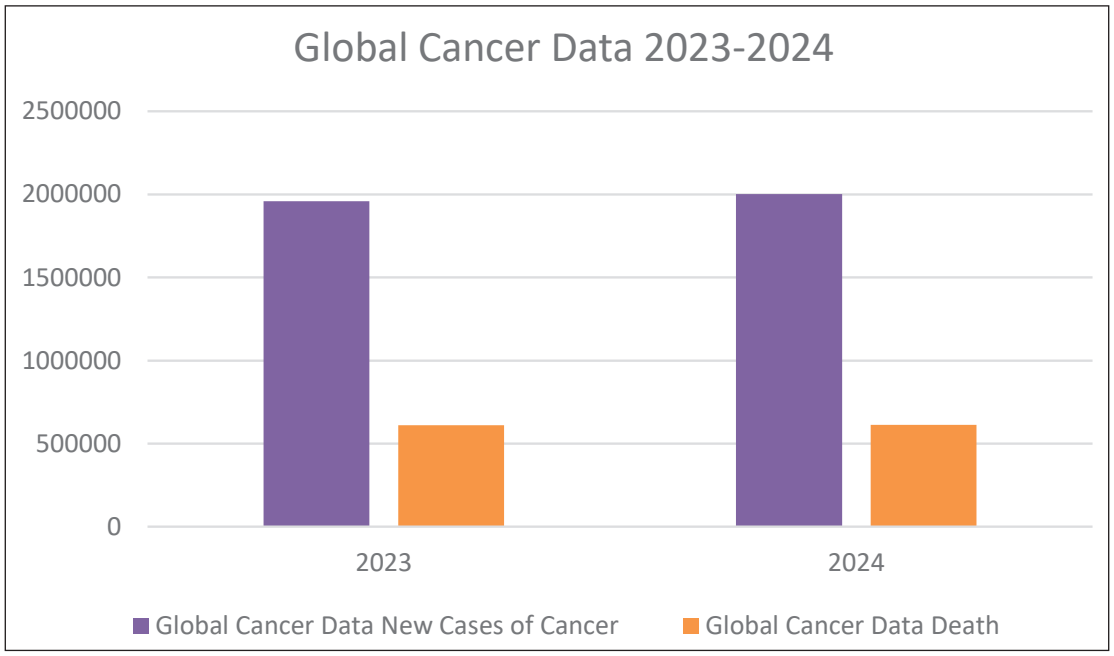


Fig. 1: Recent Global Cancer Data of New Cases and Death Statistics

After heart disease, Cancer is the world's largest second disease in the world, leading to the death of humans. This particular type of disease is characterized by aberrant cell proliferation, metastasis, and invasion [10]. Cancer cells are formed when normal cells in the body grow out of control. Most of the cancer cells travel the body through blood, where they start to grow and get spread to most of the body parts (e.g. breast cancer cells spread to the liver through blood vessels) [11]. For the treatment of cancer, anti-cancer agents are made to stop the multiplication of abnormal cells, which may lead to death. The world's first anti-cancer drug was the alkylating agent mechlorethamine, nitrogen mustard used for the lungs and spleen.

According to the National Center for Health Statistics, it is anticipated that there will be 611,720 cancer deaths and 2,001,140 new cancer cases in 2024. Cancer death rates decreased until 2021 [12]. World Health Organization (WHO) Lung cancer accounted for 2.5 million new cases globally, or 12.4% of all new cases, making it the most frequent cancer. After the deaths from stomach cancer (970000 cases, 4.9%), colorectal cancer (1.9 million cases, 9.6%), prostate cancer (1.5 million cases, 7.3%), and female breast cancer (2.3 million cases, 11.6%). In 2050, there will likely be more than 35 million new cases of cancer, a 77% increase from the projected 20 million cases in 2022. The world's cancer burden is rising at an accelerating rate due to changes in risk factor exposure, some of which are associated with socioeconomic development, as well as population aging and expansion. The three primary causes of the rising cancer incidence are obesity, alcohol use, and tobacco use, and air pollution continues to be a major contributor to environmental risk factors [13].

The biological and chemical fields depend heavily on amino acids. Transition metals can form compounds with amino acids. Knowing these complexes is crucial for creating novel applications and comprehending biological processes. Usually, amino acids bind as N, and O bidentate ligands to metal ions. They make use of the carboxylate and amino groups. Amino acids can function as chelating agents due to their heteroatoms in the ring structure and the amine ($-NH_2$) and carboxylate (COO^-) groups inside their chains. These residues have a variety of biological activities. For a metal center to coordinate and have a catalytic effect on proteins, side-chain groups are essential. They play a role in the creation of the molecular environment, weak contact molecular recognition, metal binding, and enzyme catalysis [7].

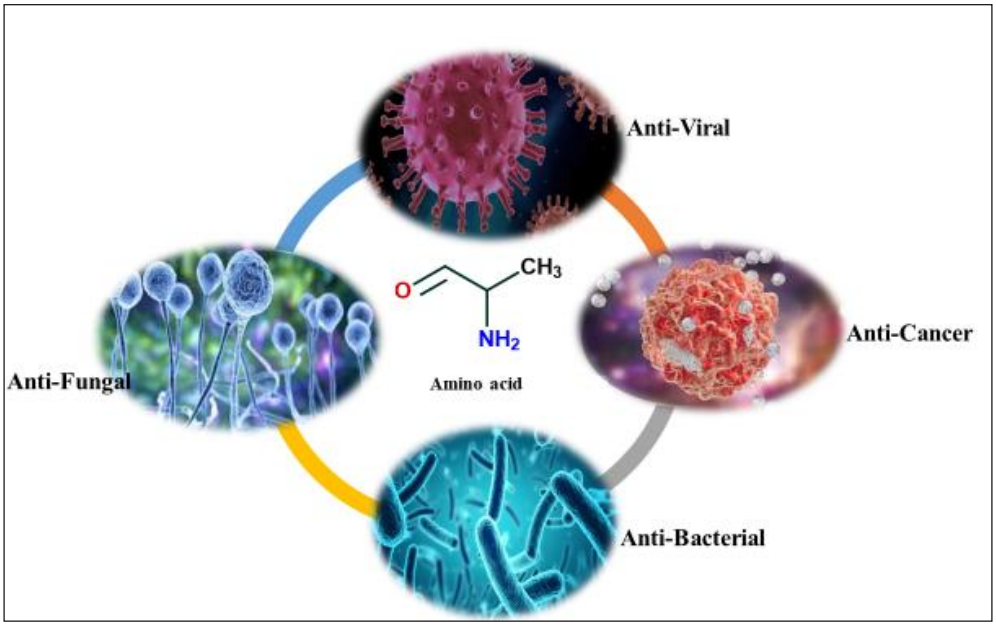


Fig. 2: Use of Amino Acid Moieties for Synthesizing Bioactive Molecules for Application in Biomedical Field

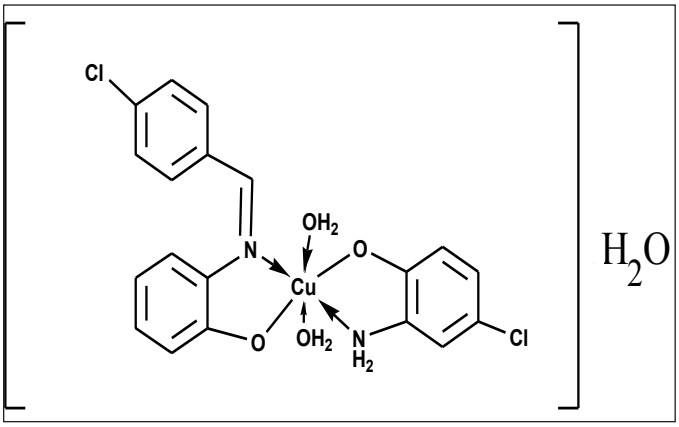
III. Biological Applications

A. Anti-Cancer Activity

The world's first anti-cancer drug was the alkylating agent mechlorethamine, nitrogen mustard used for lungs and spleen. Cancer is mainly caused by sudden changes (mutation) in DNA. In DNA there are single genes, that contain information telling each gene, how to perform in the body. If there is any fault, it will form cancer cells. Most common cancers occur because of excessive smoking, drinking, exposure to sunlight, working in chemical industries, etc and lead to lung cancer, liver cancer, abdominal cancer, and skin cancer. Cancer cells are almost similar to normal cells, they lead to the development of numerous cancers and show various side effects, such as hair loss, mouth sores, etc. The environment is also the main cause for the growth of the number of cancerous cells. To stop the growth of abnormal cells and further multiplication of these cancerous cells, there is an urgent need to make effective anti-cancer agents.

Schiff base of 2-chlorobenzaldehyde and 2-aminophenol, by condensation method, Ag(I), Pd(II), and Cu(II), complexes were prepared [14].

The anti-cancer activity of Compounds was tested for the Hep-G2 cell line (hepatocellular carcinoma), MCF-7 cell line (breast carcinoma), and HCT-116 cell line (colon carcinoma). Cytotoxicity was shown by AgL CuL2, and PdL complexes. The complexes showed great effect in comparison to the ligand and the reference drug vinblastine. Molecular docking experiments were performed to ascertain the binding energy and mechanism of the drug's interaction with DNA molecules. The findings show that the majority of the docked complexes fit in the DNA's minor groove and involve hydrogen bonding and hydrophobic interactions with DNA bases. Much of the GC area findings were found. Prepared complexes binding interactions showed that CuL2 shows good binding results.

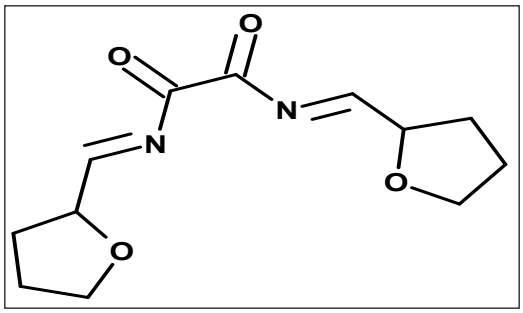


Scheme 1: Structure of Metal Complexes [Abdel-Rehman *et al.,* 2018]

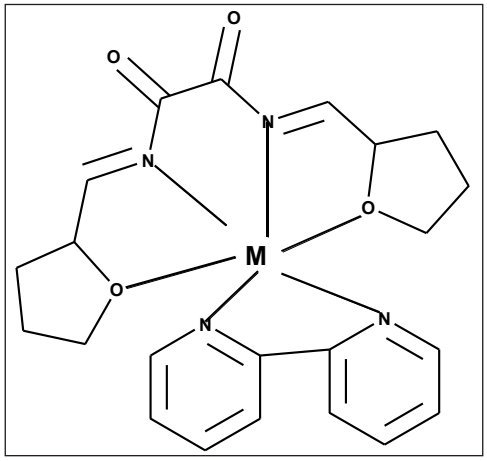
Similarly, aryl imidazole's are important heterocycles and have played an important role in medicinal chemistry. The novel coordination compounds Cu(II), Cr(III), and Fe(III) were produced with a new ligand that is based on thearyl imidazole moiety [15]. The synthesized coordination compounds were checked for their ability to inhibit the growth of colon cancer, Breast cancer cell line, and human hepatic cell carcinoma (HCT-116), (MCF-7), (Hep-G2) using vinblastine as reference. With IC_{50} values ranging from 20.24 to 40.47 mg/ml for hepatocellular carcinoma (Hep-G2 cell line), the investigated

drugs demonstrated strong anti-cancer activity. According to published data, the IC_{50} values for colon cancer (HCT-116 cell line), which has been demonstrated to have less activity, varied from 28.1 to 65.47 mg/mm. Aryl imidazole ligand and other compounds tested have cytotoxicity against "colon carcinoma (HCT-116 cell line), breast cancer (MCF-7 cell line) and hepatocellular carcinoma (Hep-G2 cell line)". All over, the effect was greater than that of the already existing aryl imidazole ligand. The result revealed that aryl chelation of imidazole ligand with metal ions was essential for the action. The reason may be that Copper possesses large coordination geometries, producing different species from the same starting reagent, intercalation for both minor and major grooves.

Condensation of oxamide and 2-furan carboxaldehyde was reported to create a Schiff base ligand as shown in schemes 2&3. The ligand was employed as a secondary ligand in the production of the complexes of Cu(II), Co(II), Ni(II), Zn(II), Cr(III), Mn(II), Fe(III) along with the bidentate ligand 2,2' bipyridine [16].



Scheme 2: Structure of Ligand (L)



Scheme 3: Structure of Mixed Ligand (M) [Omar *et al.,* 2017]

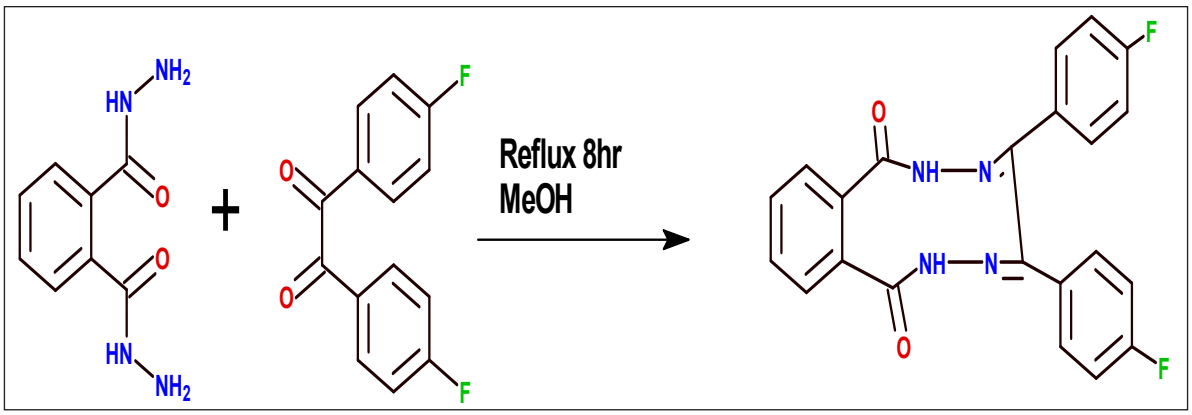
The cytotoxic effect of the newly synthesized ligand and the mixed ligand complexes were investigated against tumor cell lines HCT-116, colon cancer, tumor cell lines, breast cancer lines. A concentration-dependent investigation was conducted in addition to determining the effective dose. In contrast to breast cancer cell lines, it was discovered that Co(II) complexes were highly efficient against colon cancer cell lines (HCT-116). Except for the Cu(II) complex, other complexes are particularly effective against breast cancer cell lines. Additionally, according to the authors, neither the free ligand nor the Cd(II) complex exhibit any anti-cancer activity. Breast cancer lines 3.99 to 41.4 g ml1 and colon cancer lines 5.81 to 35.80 µg/ml are the respective IC_{50} values.

A similar Strategy of using mixed ligand to study anti-cancer activity was also adopted by El-Halim *et al.* [17]. Schiff base from quinoline-2-carboxaldhyde with 2-aminophenol was prepared by condensation method. Co(II), Cu(II), Mn(II), Fe(III), Zn(II), and Cr(III). Several methods were also employed to create transition metal mixed ligand complexes with 1,10 phenanthroline functioning as a co-ligand.

The anti-cancer activities of the ligand, co-ligand and the synthesized complexes were studied against HCT-116 and MCF-7 cells in terms of $IC_{50.}$ The outcome showed that IC_{50} values of metals complexes were higher than HL, when it was investigated for breast cancer cell line. The results indicated that the anti-cancer activity is enhanced once phenanthroline ligand compared to the case where only phenanthroline is present as ligand. The increased cytotoxic activity can be ascribed to increased actidity of the coordinated ligand that bears proton and hence can form strong hydrogen bond which enhance biological activity.

Different complexes can be used for future work, in order to improve anti-cancer activity of the drugs. Mixed ligands have shown good results than free ligands, Different mixed ligands can be used for further scope. Coordination complexes are playing great role due to its variable geometries and intercalation with DNA. Complexes with fewer side effects and a broad spectrum of diseases are still desirable [18].

By condensation of 1,3-dicarbonyl-phenyl-dihydrazide with 4,4'-difluoro benzil, Schiff base ligand, and its different metal complexes were created. Metal complexes were tested for their anti-cancer efficacy using Squamous Cell Carcinoma (SCC4). Additionally, it was tried at different periods and dosages. Molecular docking studies were used to further examine the mechanism of macrocyclic Schiff base ligand-induced suppression of the epidermal growth factor receptor (EGFR) (PDB ID: 1M17) kinase [19].



Scheme 4: Schiff Base Ligand 1,3-dicarbonyl-phenyl-dihydrazide and 44-diflurobenzil

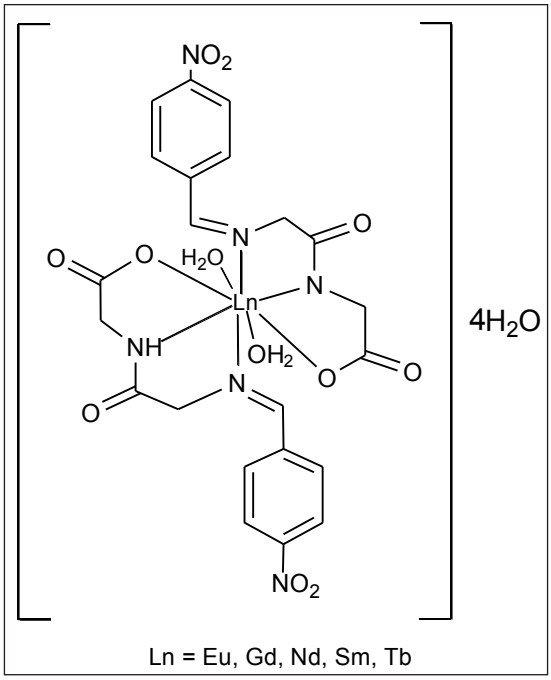
To comprehend the lethal activity of complexes, the IC_{50} values of the ligand and compared with the well-known anti-cancer drug, Cisplatin. IC_{50} values were calculated using the MTT assay at 24, 48, and 72 hours after the start of the drug treatment. Against the SCC4 cancer cell line, some of the investigated complexes have shown moderate to considerable cytotoxicity using the common MTT bioassay at different time scales. Higher concentrations of the compounds were found to reduce the average cell viability ratio, demonstrating that the activity of the complexes was concentration-dependent. Complexes consistently exerted more cytotoxicity than the ligand, in a dose-dependent manner [20].

The antitumor activity of the complexes using Schiff base ligands and the molecular docking of the complexes against the SCC4 cancer cell was tested using similar protocols. In this work, Jain *et al.* synthesized the Schiff base ligands 2-methoxy-6-[(E)-(1,3-thiazol-2-ylimino) methyl] phenol and N-[(E)-pyridin-2-ylmethylidene]. thiazol-2,3-amine. Basic media were used to produce Cu(II) complexes [21].

With concentration, the activity of the complexes increased while as overall average cell survival rate decreased. 6-Methoxy-2-[(E)-Aryliminomethyl] paladium complexes-phenol (Aryl = Phenyl; 2,6-dimethyl; 2,6-diisopropylphenyl; 2,6-dichlorophenyl) showed remarkable antiproliferative activity and has effectively caused apoptosis by DNA damage in malignant cell lines, including MCF-7 (breast carcinoma), SKOV3 (ovarian carcinoma) and A549 (lung carcinoma). Further Schiff base ligands derived from 3,4,5-trimethoxybenzamide moieties have demonstrated antiproliferative activity against MCF-7 cells by blocking the cellular cycle at the G2/M stage phase and is a strong apoptotic substance [22].

B. N,S,O Donor Schiff Base Ligands and Complexes and Their Anti-Cancer Activity

Multidonor Schiff base ligands with N/S/O donor atoms have been proven versatile molecules in biomedical applications over the last few decades. Synthesis of the 4-nitrobenzaldehyde-glycylglycine (4-NBA-GG) and its Ni(II), Cu(II), Zn(II), and Co(II) complexes, have shown significant results in anti-cancer investigations of complexes employed on HeLa and HCT-116 human colon cancer cell lines. The results showed that the Eu(III) and Nd(III) complexes were more effective against both cancer cells than the Gd(III), Sm(III), Tb(III), and free ligand complexes [23].

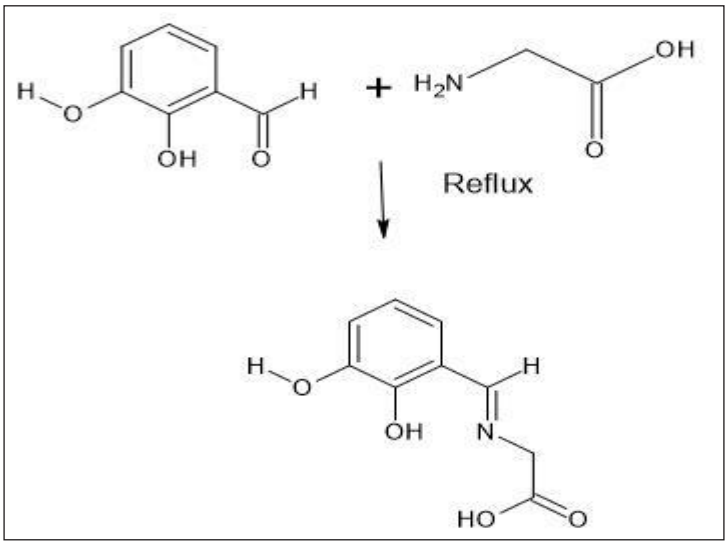


Scheme 5: Synthesized Structure of Ln(III)-4-NBA-GG Complex

To ascertain whether the complexes might inhibit the growth of human liver cancer (Hep-G2), human cervical cancer (HeLa) cell lines, and human prostate cancer (PC3), Chang *et al.* prepared tris-(2-aminoethyl) amine as the coligand and used L-alanine and L-Valine as Schiff bases. In vitro studies using the MTT (Microculture Tetrazolium) assay were conducted in this work. The outcomes demonstrate that a significant part

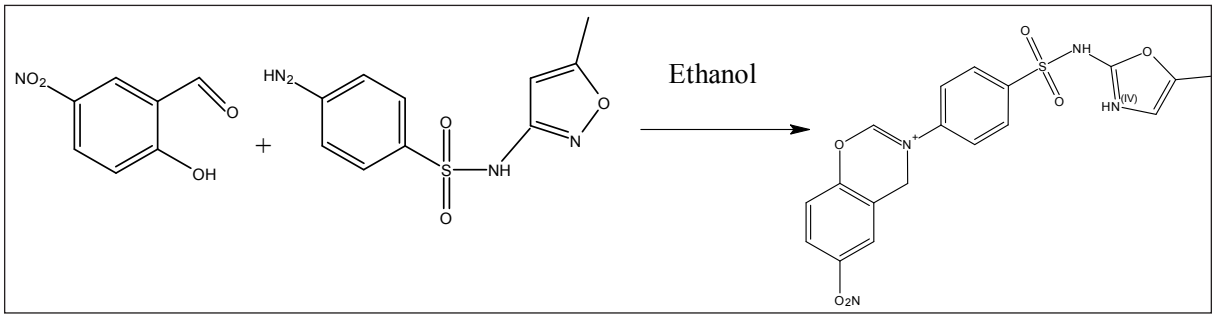
of mediating the cytotoxicity of the three metal complexes is carried out by the coordinated Ni (II), which was produced and has shown less than the free ligands' IC_{50} values in all of the cell lines [24].

(E)-2-(2-hydroxy-3-methoxybenzylideneamino) acetic acid and its complexes with Cu(II), Mn(II), Co(III), Ni(II), Zn(II) and Fe(II) were synthesized by De *et al.* using molecular docking studies, the interactions between produced metal complexes and ligands with the relevant Tyrosine Kinase (1T46) and EGFR Kinase (1M17) were investigated. The copper(II) complex exhibited the highest binding affinity with this receptor molecule [25].



Scheme 6: Formation of Multifunctional Ligand from Glycine and *o*-Vanillin

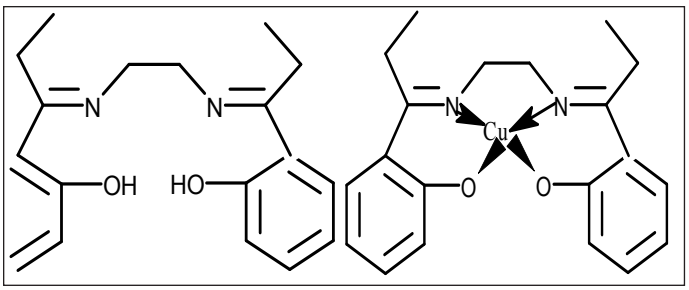
An O, N donor-containing bidentate Schiff base ligand (HL1) was generated by reacting sulfamethoxazole with 5-nitrosalicylaldehyde (Scheme 7). By treating the DMF-ethanolic mixture solution of the ligand of two equivalents with one equivalent of copper acetate, the copper complex was synthesized. The ligand and its copper complex were tested for in vitro cytotoxicity using two different human tumor cell lines, HCT-116 and MDA-MB-231. Following the cytotoxicity tests, the compound was more active against MDA-MB-231 than both carboplatin and cisplatin [26].



Scheme 7: Synthesis of N,S,O Donor Ligand using Sulfamethoxazole with 5-Nitro Salicylaldehyde

Following the metalation of tetradentate macrocyclic nitrogen ligands, a novel series of mononuclear Fe(II), Co(II), Ni(II), Cu(II) and Pd(II) metal complexes were tested in vitro against two distinct types of cancer cells: human hepatocarcinoma cells (Hep-G2) and human breast cancer cells (MCF-7). Remarkably, it was discovered that the metal complexes had a greater ability to kill the harmful cells. The Ni (II) complex's IC_{50} values for MCF-7 and Hep-G2 were found to be 1.6 µg/mL and 1.7 µg/mL, respectively [27].

A novel Schiff base was developed by Bao *et al.* (2020) using ethylenediamine, 2-hydroxyphenyl acetone, and its Cu(II) complex. testing for their cytotoxicity against various cell lines to investigate their potential as growth inhibitors of cancer cells. It was discovered that the complex inhibited the proliferation of eight distinct kinds of malignant cells. In LO2 and HUVEC cells, the chemical was shown to have an IC_{50} value between 5.13 and 11.68 µM and to be less hazardous than cis-platin [28].



Scheme 8: Synthesized Ligand and Metal Complexes using Ethylenediamine, 2-Hydroxyphenyl Acetone, and its Cu(II) Complex

IV. Conclusion

In view of the demand for non-toxic biocompatible and naturally derived anti-cancer therapeutics, many researchers have utilized the potential of multifunctional moieties with N,S,O atoms to derive Schiff-based molecules. These molecules are proven wonderful anti-cancer scaffolds owing to their versatility, solubility, and biocompatibility. Most of the ligands and complexes are showing less toxicity which could further be improved using coligands to improve their drug ability and ADME characteristics. This review provides insight and information about recent advancements in the designing and preparation of N/S/O based Schiff base molecules in the mixed ligand frameworks. It would help the researchers or students to further modify the process of synthesis of these molecules to get the ideal therapeutics.

References

[1] E. Raczuk, B. Dmochowska, J. Samaszko-Fiertek, and J. Madaj, "Different Schiff bases - Structure, importance and classification," *Molecules*, vol. 27, no. 3, p. 787, 2022.

[2] W. Al Zoubi, and Y. Gun Ko, "Organometallic complexes of Schiff bases: Recent progress in oxidation catalysis," *Journal of Organometallic Chemistry*, vol. 822, pp. 173-188, 2016.

[3] S. K. Nandanwar, and H. J. Kim, "Anti-cancer and antibacterial activity of transition metal complexes," *Chemistry Select*, vol. 4, no. 5, pp. 1706-1721, 2019.

[4] S. Jain, M. Rana, R. Sultana, R. Mehandi, and Rahisuddin, "Schiff base metal complexes as antimicrobial and anticancer agents," *Polycyclic Aromatic Compounds*, vol. 43, no. 7, pp. 6351-6406, 2023.

[5] I. P. Ejidike, and P. A. Ajibade, "Transition metal complexes of symmetrical and asymmetrical Schiff bases as antibacterial, antifungal, antioxidant, and anticancer agents: Progress and prospects," *Reviews in Inorganic Chemistry*, vol. 35, no. 4, pp. 191-224, 2015.

[6] N. Vaou, E. Stavropoulou, C. Voidarou, C. Tsigalou, and E. Bezirtzoglou. "Towards advances in medicinal plant antimicrobial activity: A review study on challenges and future perspectives," *Microorganisms*, vol. 9, no. 10, p. 2041, 2021.

[7] A. Arunadevi, and N. Raman. "Biological response of Schiff base metal complexes incorporating amino acids – A short review," *Journal of Coordination Chemistry*, vol. 73, no. 15, pp. 2095-2116, 2020.

[8] A. Biswas, L. K. Das, M. G. B. Drew, G. Aromí, P. Gamez, and A. Ghosh, "Synthesis, crystal structures, magnetic properties and catecholase activity of double phenoxido-bridged penta-coordinated dinuclear nickel (II) complexes derived from reduced Schiff-base ligands: Mechanistic inference of catecholase activity," *Inorganic Chemistry,* vol. 51, no. 15, pp. 7993-8001, 2012.

[9] S. J. Harland, D. R. Newell, Z. H. Siddik, R. Chadwick, A. H. Calvert, and K. R. Harrap, "Pharmacokinetics of cis-diammine-1, 1-cyclobutane dicarboxylate platinum (II) in patients with normal and impaired renal function," *Cancer Research*, vol. 44, no. 4, pp. 1693-1697, 1984.

[10] P. Anand, A. B. Kunnumakara, C. Sundaram, K. B. Harikumar, S. T. Tharakan, O. S. Lai, B. Sung, and B. B. Aggarwal, "Cancer is a preventable disease that requires major lifestyle changes," *Pharmaceutical Research*, vol. 25, no. 9, pp. 2097-2116, 2008.

[11] S. C. Rastogi, *Cell and Molecular Biology*. New Age International, 2006.

[12] R. L. Siegel, A. N. Giaquinto, and A. Jemal, "Cancer statistics, 2024," *CA Cancer J Clin*, vol. 74, no. 1, pp. 12-49, 2024.

[13] D. Singh, J. Vignat, V. Lorenzoni, M. Eslahi, O. Ginsburg, B. Lauby-Secretan, M. Arbyn, P. Basu, F. Bray, and S. Vaccarella. "Global estimates of incidence and mortality of cervical cancer in 2020: A baseline analysis of the WHO Global Cervical Cancer elimination initiative," *The Lancet Global Health*, vol. 11, no. 2, pp. e197-e206, 2023.

[14] L. H. Abdel-Rahman, Mohd. S. S. Adam, A. M. Abu-Dief, H. Moustafa, M. T. Basha, A. S. Aboraia, B. S. Al-Farhan, and H. El-Sayed Ahmed, "Synthesis, theoretical investigations, biocidal screening, DNA binding, in vitro cytotoxicity and molecular docking of novel Cu (II), Pd (II) and Ag (I) complexes of chlorobenzylidene Schiff base: Promising antibiotic and anti-cancer agents," *Applied Organometallic Chemistry*, vol. 32, no. 12, p. e4527, 2018.

[15] L. H. Abdel-Rahman, A. A. Abdelhamid, A. M. Abu-Dief, Mohd. R. Shehata, and Mohd. A. Bakheet, "Facile synthesis, X-Ray structure of new multi-substituted aryl imidazole ligand, biological screening and DNA binding of its Cr (III), Fe (III) and Cu (II) coordination compounds as potential antibiotic and anti-cancer drugs," *Journal of Molecular Structure*, vol. 1200, p. 127034, 2020.

[16] M. M. Omar, H. F. Abd El-Halim, and E. A. M. Khalil, "Synthesis, characterization, and biological and anti-cancer studies of mixed ligand complexes with Schiff base and 2, 2′-bipyridine," *Applied Organometallic Chemistry*, vol. 31, no. 10, p. e3724, 2017.

[17] H. F. Abd El-Halim, G. G. Mohamed, and M. N. Anwar, "Antimicrobial and anti-cancer activities of Schiff base ligand and its transition metal mixed ligand complexes with heterocyclic base," *Applied Organometallic Chemistry*, vol. 32, no. 1, p. e3899, 2018.

[18] L. H. Abdel-Rahman, A. A. Abdelhamid, A. M. Abu-Dief, Mohd. R. Shehata, and Mohd. A. Bakheet, "Facile synthesis, X-Ray structure of new multi-substituted aryl imidazole ligand, biological screening and DNA binding of its Cr (III), Fe (III) and Cu (II) coordination compounds as potential antibiotic and anti-cancer drugs," *Journal of Molecular Structure*, vol. 1200, p. 127034, 2020.

[19] P. Jain, V. Singh, S. Ali, V. Tripathi, and U. Saraswat, "Synthesis, characterization, molecular docking and biological activity of 5, 6-bis-(4-fluoro-phenyl)-3, 4, 7, 8-tetraaza-bicyclo [8.3.1] tetradeca-1 (13), 4, 6, 10 (14), 11-pentaene-2, 9-dione and its transition metal complexes," *Journal of Saudi Chemical Society*, vol. 22, no. 5, pp. 546-557, 2018.

[20] G. Coffetti, M. Moraschi, G. Facchetti, and I. Rimoldi, "The challenging treatment of cisplatin-resistant tumors: State of the art and future perspectives," *Molecules*, vol. 28, no. 8, p. 3407, 2023.

[21] P. Jain, M. Guin, A. De, and M. Singh, "Molecular docking, synthesis, anti-cancer activity, and computational investigations of thiazole-based ligands and their Cu (II) complexes," *Journal of Physical Organic Chemistry*, vol. 36, no. 12, p. e4384, 2023.

[22] H. Li, C. Dang, X. Tai, L. Xue, Y. Meng, S. Ma, and J. Zhang, "VALD-3, a Schiff base ligand synthesized from o-vanillin derivatives, induces cell cycle arrest and apoptosis in breast cancer cells by inhibiting the Wnt/β-catenin pathway," *Scientific Reports*, vol. 11, no. 1, p. 14985, 2021.

[23] C. Shiju, D. Arish, and S. Kumaresan, "Synthesis, characterization, cytotoxicity, DNA cleavage, and antimicrobial activity of lanthanide (III) complexes of a Schiff base ligand derived from glycylglycine and 4-nitrobenzaldehyde," *Arabian Journal of Chemistry*, vol. 10, pp. S2584-S2591, 2017.

[24] H.-Q. Chang, L. Jia, J. Xu, T.-F. Zhu, Z.-Q. Xu, R.-H. Chen, T.-L. Ma, Y. Wang, and W.-N. Wu, "Syntheses, crystal structures, anti-cancer activities of three reduce Schiff base ligand based transition metal complexes," *Journal of Molecular Structure*, vol. 1106, pp. 366-372, 2016.

[25] A. De, H. P. Ray, P. Jain, H. Kaur, and N. Singh, "Synthesis, characterization, molecular docking and DNA cleavage study of transition metal complexes of o-vanillin and glycine derived Schiff base ligand," *Journal of Molecular Structure*, vol. 1199, p. 126901, 2020.

[26] I. Rama, and R. Selvameena, "Synthesis, structure analysis, anti-bacterial and in vitro anti-cancer activity of new Schiff base and its copper complex derived from sulfamethoxazole," *Journal of Chemical Sciences*, vol. 127, pp. 671-678, 2015.

[27] H. A. El-Boraey, and O. A. EL-Gammal, "Novel (N4) macrocyclic metal complexes: Synthesis, characterization, spectral studies and anti-cancer activity," *Open Chemistry Journal*, vol. 5, no. 1, 2018.

[28] R.-D. Bao, X.-Q. Song, Y.-J. Kong, F.-F. Li, W.-H. Liao, J. Zhou, J.-H. Zhang et al., "A new Schiff base copper (II) complex induces cancer cell growth inhibition and apoptosis by multiple mechanisms," *Journal of Inorganic Biochemistry*, vol. 208, p. 111103, 2020.