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N_2O_2 Schiff Base and Their Metal Complexes as Anticancer Agents: A Review of Their Synthesis, Characterization and Anticancer Activity

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Abstract: *This review provides a thorough analysis of the potential use of N_2O_2 Schiff bases and metal complexes as anticancer agents, focusing on their promising anticancer activities. N_2O_2 Schiff bases are mainly recognized by their ability to coordinate with metal ions. Here an attempt was made to elaborate the synthesis and characterization of these N_2O_2 Schiff base metal complexes and how the structural features of these complex influence the biological activity. Few mechanisms of action include the induction of apoptosis via the generation of ROS and DNA binding. The structure-activity relationship was explained with respect to substitution and the size of the ring and coordination geometry, which directly influence the modulating anticancer effects of these compounds. In addition, the potential applications of N_2O_2 Schiff base metal complex in combination therapies connection with conventional treatments of cancer, were probed. Last but not least, toxicity, stability, delivery system optimization and present challenges were addressed with future directions in research that may bring their full realization of therapeutic potential of this class of N_2O_2 Schiff base metal complexes*

Keywords: ROS, DNA, Anti- Cancer, Anti-Tumour, N_2O_2 Schiff Bases, combination therapies, conventional treatments

I. INTRODUCTION

1.1 Overview of Cancer and the Need for Novel Therapies

Cancer is one among the biggest global health problems. The World Health Organization says that this disease causes nearly 10 million deaths in a year. Though early detection and treatment mechanisms have improved, cancer endures one of the leading causes of morbidity and mortality globally. Apart from having its own limitation, existing traditional therapies like surgery, chemotherapy, and radiotherapy are beneficial up to a certain level only. These include severe side effects, such as invasion of carcinoma cells into healthy tissue, and resistance where the carcinoma cells grow to become less responsive to treatments over time (Ferlay et al., 2021).

The nature of cancer is broad; various types of cancer require distinct approaches when treating them. Even with cancer of the same type, a body respond differently due to differences in the varied nature of bodies. For example, chemotherapy is focussed on the nontargeted and nonspecific rapidly dividing cells, which triggers the common side effects of hair loss, fatigue, and immune suppression. Additionally, many tumours acquire mechanisms that help in evading or resisting the treatments as cancer evolves. Thus, the treatments become much less effective. This calls for a new, targeted therapies which do not only increase efficacy but also show less harm to the healthy cells. The objective is to produce agents that target unusual molecular pathways within the cancerous cells and even reduce the mechanism of drug resistance, thus making the treatment outcome far more successful.

1.2 Introduction to Schiff bases and their Biological Importance

Schiff bases are an important class of organic compounds that are synthesized by the condensation of a primary amine to an aldehyde or ketone presented in figure 1. Schiff bases include an imine (-C=N-) functional entity that plays a vital

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role in their chemical reactivity and coordination with metal ions (Meena et al., 2023). Schiff bases have also found great application in medicinal chemistry owing to their enormous and wide spectra of biological activities, such as antifunfal, anti-inflamatoty, anti-microbial, and anti-cancer activity (Cao et al., 2019).

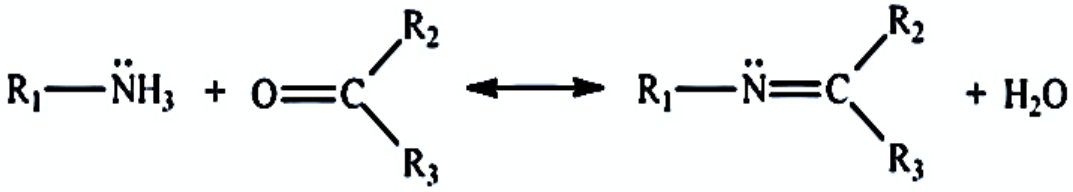

Figure 1: General layout of the Schiff base construction

The biological importance of Schiff bases primarily stems from their ability to act as ligands in coordination chemistry, where they coordinate with metal ions-copper, nickel, zinc, and iron, among others. These metal-schiff base complexes often possess biological activity than the free Schiff base. This is because the metal centre allows for interactions with biological molecules that increase their therapeutical potential. For instance, coordination of metals to Schiff bases often increases their capabilities toward binding to DNA, inhibition of enzymes, or generation of ROS, all very important in anticancer mechanisms (Arun et al., 2024). Schiff bases are of high interest today as a potentially effective drug design system, particularly in anti-tumor drugs (Tehrani et al., 2015)

1.3 N_2O_2 Schiff Bases and their Potential in anti- cancer Therapies

Among Schiff base derivatives, N_2O_2 Schiff bases have drawn much attention nowadays due to its prospect in anti-tumor therapy. These Schiff bases contain two nitrogen (N) and two oxygen (O) donor atoms, and because the ligands contain both types of donor atoms, they are classified as tetradentate ligands. This therefore enables them to form stable complexes with transition metals. Incorporation of the both nitrogen and oxygen donor groups makes N_2O_2 type Schiff bases better chelating agents for such metal species as copper, nickel, or zinc, engaged in basic biological processes such as DNA replication` and repair (Singh et al., 2016).

While the anticancer potential of N_2O_2 Schiff bases are emphasized in the fact that they form metal complexes, which interact with the critical cellular components, including DNA and proteins, thereby disrupting critical processes in the cancer cells, a number of copper-Schiff base complexes were reported to induce oxidative stress by the production of ROS, which usually damages cancer cells, contributing to their apoptosis or programmed cell death. (Ramaswami et al., 2013).

In addition, these metal complexes could also inhibit cancer cell proliferation through coordination to and structural modification of DNA, leading to inhibition of replication and transcription. The N_2O_2 Schiff bases were found to exhibit selective toxicity against the cancer cells without harming normal healthy cells to a greater extent than that of the conventional chemotherapeutic drugs.

Such selectivity is believed to be due to the properties of cancer cells, which frequently show increased rates of oxidative metabolism and higher concentrations of metal ions, making them more sensitive to oxidative stress and DNA damage caused by the interaction of metal-Schiff base complexes (Mushtaq et al., 2024).

Further optimization of anticancer activity of N_2O_2 Schiff bases is being explored by studying the structure-activity relationships, and promising prospects for additional structural modifications of the Schiff base or choice of the metal ion Favour potency and reduce toxicity. The N_2O_2 Schiff bases have emerging promise as new anticancer agents since they could provide selective action, reduced side effects, and a good prospect in overcoming drug resistance. Many ongoing studies on their mechanisms of action, structural optimization, and formulation improvement promise great prospects in future clinical application.

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II. SYNTHESIS AND CHARACTERISATION OF N_2O_2 SCHIFF BASES

2.1 Overview of Synthesis Methods

Comparing organic chemistry to conventional synthetic techniques, including heating reactants in metal, oil, or sand baths, reveals advantages for the environment and the wallet. This method demands different reaction conditions, avoiding the use of ecologically hazardous organic solvents or toxic compounds. Green techniques aim to reduce reaction times, increase selectivity, and make product isolation easier. Without the need for a solvent or low solvent conditions, Schiff bases synthesized with microwave assistance reduce reaction durations, improve conversion, and occasionally increase selectivity. This method has several applications and is now the most popular and simple way for these reactions.

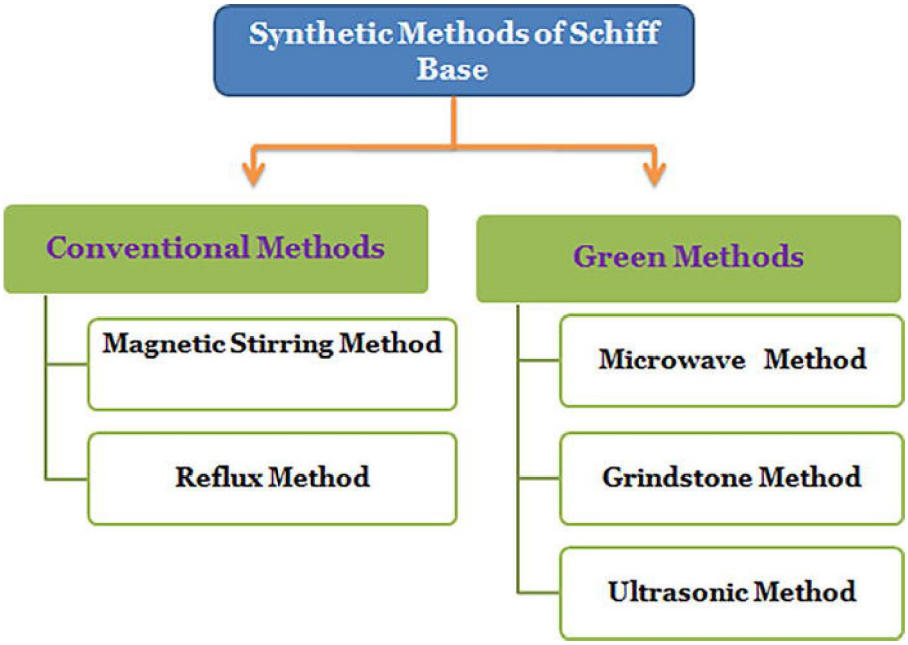

Figure 2: Synthetic Method of Schiff Base (Meena et al., 2023)

Schiff bases are used to create stable complexes due to their affinity for chelation towards transition metal ions. Better than symmetrical ligands, unsymmetrical ligands attach to metal ions containing two groups and lack a rotation or mirror axis. They are more effective in biological systems because they mix natural and artificial structural components more readily and anticipate metal ion binding sites with greater accuracy. Figure 2 displays the homoleptic complexes are distinguished from heteroleptic complexes primarily by having identical ligands attached to a metal center.

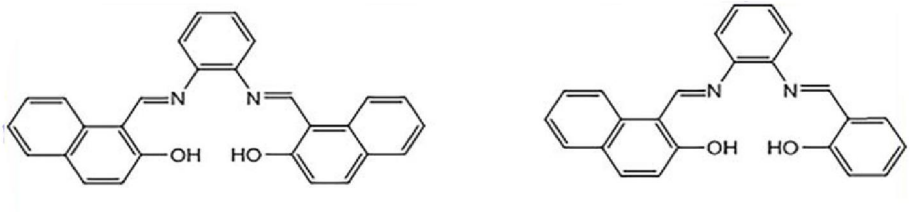

Figure 3: Homoleptic and Heteroleptic Schiff Base (Meena et al., 2023)

Synthesis usually involves the condensation reaction of a diamine, a compound containing two amine groups, with a carbonyl compound.

Synthesis methods that optimize N_2O_2 Schiff bases have included traditional reflux methods and, more recently, microwave-assisted synthesis.

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Microwave-assisted synthesis has gained popularity due to its ability to reduce reaction times while maximizing yields. Microwave-assisted synthesis increases the rate of heating of the reaction mixture through microwave radiation, thereby enhancing molecular interaction, thus making the formation of the Schiff base complex faster (Raju et al., 2022). Common reflux techniques often make use of heating the reaction mixture under controlled conditions for long time periods, during which the Schiff bases form slowly. However, this approach still requires longer times in comparison to the cutting-edge techniques like microwave-assisted synthesis. In template synthesis, a metal ion acts as a scaffold around which the Schiff base grows.

The method enables the preparation of a stable ligand-metal complex in a one-pot process, thus avoiding post-synthesis coordination of the metal ion Figure 4. The metal catalyses not only the formation of the imine bond, but also influences the overall geometry and stability of the complex (Ahmed et al., 2009). The other modifications, such as the introduction of aromatic aldehydes, are found to increase the stability of Schiff bases and thus enhance their pharmacological application efficiency.

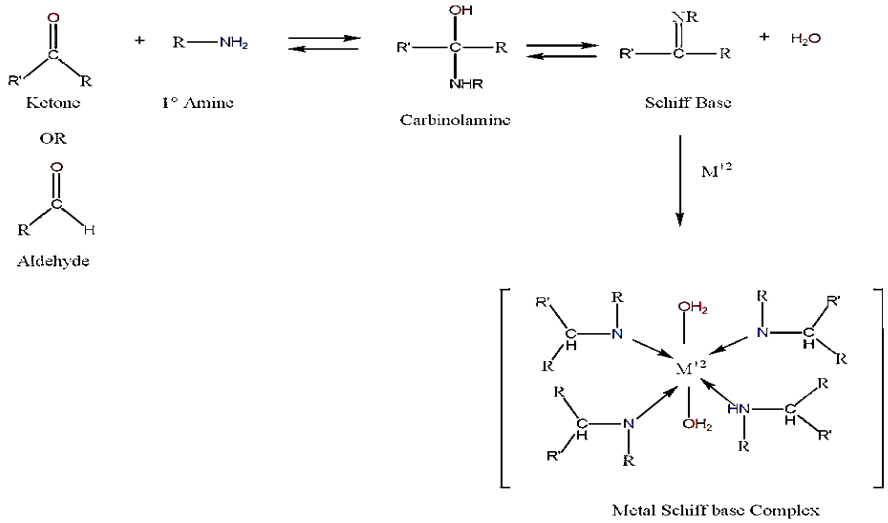

Figure 4: Interaction of metal ions with Schiff bases with N_2O_2 donor sites

2.2 Discussion of Characterization Techniques

Once N_2O_2 Schiff bases and their metal complexes are synthesized, the structure and chemical nature must be properly characterized. This is possible with a group of spectroscopic and analytical techniques.

2.2.1 NMR Spectroscopy

NMR spectroscopy is a good tool for the investigation of Schiff bases at the atomic level of their structural features. N_2O_2 Schiff bases NMR provides information much more precise than ever about the electronic environment around the nitrogen and oxygen donor atoms, the carbon-nitrogen imine bond. From the evaluation of spin states of protons or carbon nuclei in a magnetic field, NMR obtain exact chemical shifts that divulge the chemical structure of the ligand (Mermer et al., 2023). In an NMR spectrum, peaks equate to specific hydrogen or carbon environments in a Schiff base.

2.2.2 Infrared (IR) Spectroscopy

IR spectroscopy was frequently used as an indicator to identify the functional groups found in Schiff base compounds, mainly at the imine (-C=N-) bond. The typical stretching frequency of the imine bond usually falls in the 1,600 to 1,640 cm $^{-1}$ range; whenever such a frequency is available it indicates the proper formation of Schiff base in addition, IR identify other crucial functional groups such as hydroxyl or carboxyl and look into the coordination sphere of the metal.

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It provides a lead for the vibrational modes of the Schiff base framework, reflecting the ligand-metal interactions of the complex.

2.2.3 Mass Spectrometry (MS)

Mass spectroscopy is carried out to find the molecular weight and establishes the composition of the N_2O_2 Schiff base complexes. MS allows researchers to identify the structure and confirm the presence of specific atoms or groups by ionizing the compound and measuring the mass-to-charge (m/z) ratio of fragments. The utility of this technique lies more in the confirmation of the molecular integrity of the Schiff base complex and in the identification of fragmentation patterns that occur on ionization. The MS is generally used in combination with NMR and IR for obtaining an all-round view of the synthesized Schiff base structure. These all play a pivotal role in verifying the fact that the synthetic methodology was indeed successful and that the N_2O_2 Schiff bases, in respect of their chemical and biological properties, have the correct structure. By evaluating these methods together, this becomes vital for testing the purity, geometry, and bonding patterns of the Schiff bases and their metal complexes. These are substantial for understanding the potential biological activity, especially in anti-tumor therapy.

2.3 Various structural frame work of N_2O_2 Schiff Bases.

There are several structural variations in of N_2O_2 Schiff bases and those were synthesized in terms of coordination behaviour and biological activity.

The diversity of metals and geometries now possible with N_2O_2 Schiff bases highlight their flexibility, which will be even more adaptable to modifications in the Schiff base structure or choice of metal ion. Thus, one can control the properties of such complexes for targeting specific cancer types or biological pathways, offering the great promise of a new generation of therapeutic agents. (Ramos et al., 2015).

1. Salicylaldehyde and diamine Derived Complexes

The most common structural frame work of N2O2 schiff base ligands are those derived from the condensation of Salicylaldehyde and diamine derivatives with ethylenediamine derivatives are most common among all N2O2 Schiff-base ligands. These complexes are the product of salicylaldehyde donating oxygen donor sites via the phenolic oxygen as well as nitrogen donor by the imine formed with ethylenediamine. Such a Schiff base produces stable complexes with transition metals, copper, nickel, and zinc. The stable complex is either square planar or octahedral in nature, depending on the character of the metal center. A strong anticancer activity was reported by metal complexes, mainly through apoptosis induction on cancer cells by enhancement of ROS generation.

2. Morpholine- and Piperidine-Derived Schiff Bases

Three new Schiff bases N-O-S were synthesized from 2-carbaldehyde-8-hydroxyquinoline with amines, transporting in the composition piperidine or morpholine fragments. Combining the later Schiff bases with the Cu (II) and Zn (II) ions in the composition of ML_2 has led to the creation of the latter coordination complex. Schifff base ligands L1–L3 coupled through the nitrogen and oxygen donor atoms to form stable dinuclear complexes both displayed intense cytotoxic action against A375 melanoma cancer cells. Importantly, it was confirmed that the copper complexes were nearly twice as cytotoxic as the popular anticancer chemotherapeutic drug cisplatin. This means they could potentially be used as drugs in oncology.

3. Schiff bases, synthesised from benzyldehydes and diamines such as 1,2-phenylenediamine

Another category of examples are the Schiff bases, which are synthesized through reactions between benzaldehydes and diamines, such as 1,2-phenylenediamine. These ligands adopt a square planar geometry about the metal center, forming N2O2 type chelate complexes when coordinated to metal ions such as Cu (II) or Ni (II). Such chelates were cytotoxic against cancer cell lines that corresponded to lung and breast cancers and proven to possess excellent anticancer activity through DNA strand cleavage and interference with cell replication of the cancerous cells. The findings were expanded upon in other places (El-ajaily et al., 2013). The plane R1-4 is the one that he determined best represents the molecular shape of compounds 1-3 as seen in Figure 5

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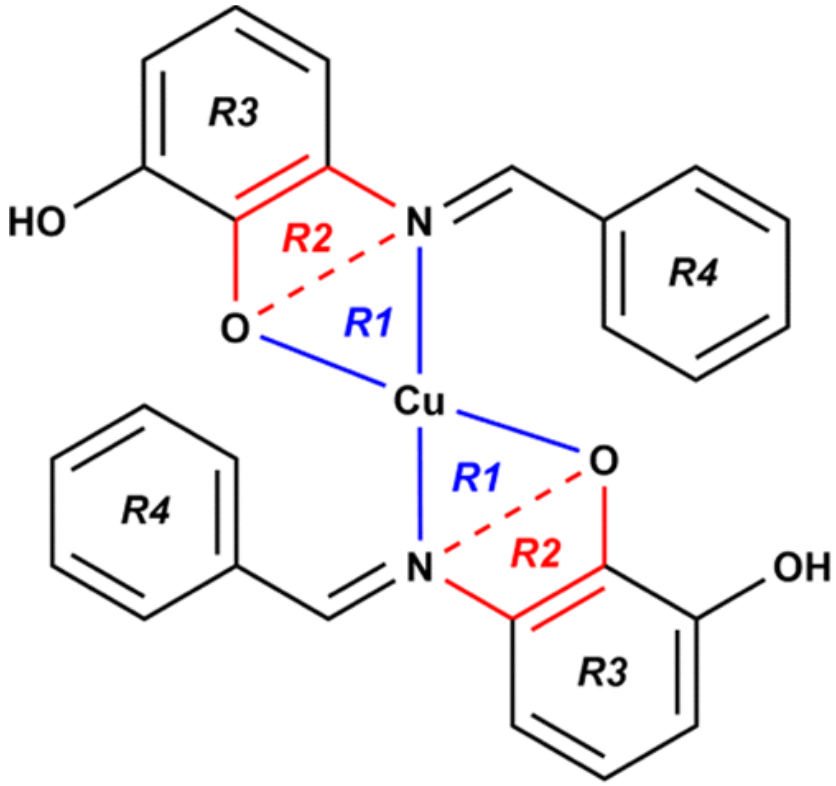

Figure 5: The Cu(II) complexes 1-3 contain planes identified as R1, R2, R3, and R4.

4. Copper (II) and Nickel (II) Complexes of Substituted Salicylaldehyde Schiff Bases

Copper (II) and nickel (II) complexes of substituted salicylaldehyde Schiff bases have different properties due to the substituents attached at the aromatic ring such as nitro and methoxy groups. A great influence on electrical characteristics of the ligand itself was shown by these substituents, and, at the same time, they determined the influence of biological activity of metal complexes, regarding their potential interaction with biomolecules and enhancing therapeutic efficacy. For example, the DNA is found to be highly sensitive to intercalation with electron-donating Schiff bases such as the following compounds. The increased activities on these compounds result in effective differentiation and effectiveness of these compounds against a number of cancer cell lines in relation to ovarian and colon cancers by inhibiting DNA functions and proliferation of the cancer cells (Vernekar et al., 2023).

5. Schiff Base Complexes with Macrocyclic Ligands

Moreover, the inclusion of macrocyclic structures with Schiff bases reported to increase their biological activities. Thus, cyclohexane diamine - salicylaldehyde-based macrocyclic Schiff bases form stable metal complexes like copper (II) and cobalt (II), which display antimicrobial and anticancer activity, showing specific effectiveness against leukaemia and pancreatic cancer due to the generation of ROS and interaction with DNA (Vernekar & Sawant, 2023). This N_2O_2 Schiff base compound synthesis is illustrated below in Figure 6. It involves refluxing a chloro-substituted aromatic aldehyde with a cyclic diamine in methanol to produce imine bonds (C=N).

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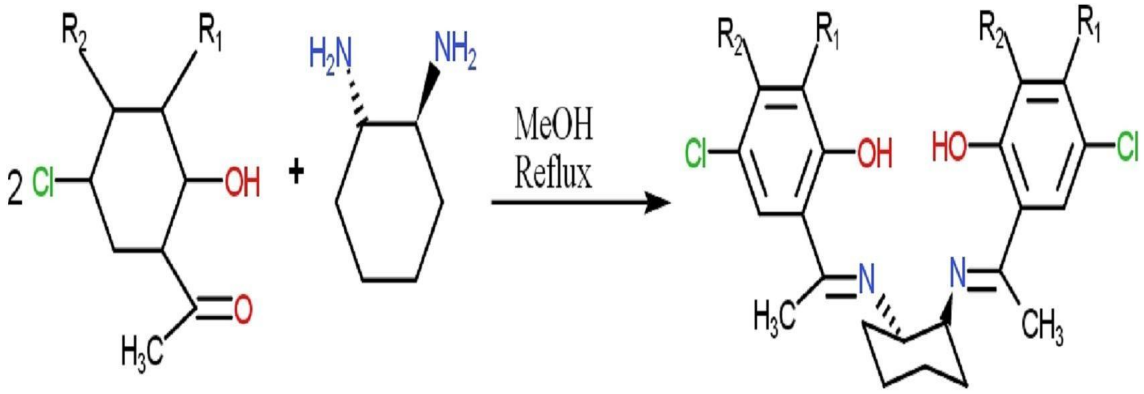

Figure 6: Structures of Schiff base ligand (Vernekar & Sawant, 2023)

The N_2O_2 Schiff bases exhibited good potentiality in metal complex the synthesis, primarily transition metal like copper, nickel or zinc due to their ability as potential chelates possessing versatile coordination properties. The examples above demonstrate the structural diversity of N_2O_2 Schiff bases as well as their potential therapeutic applications in anticancer treatments. Such Schiff bases affect some crucial cellular functions like DNA replication, apoptosis, and ROS generation that lead them to be of great importance in the search for drug leads (Ibrahim, 2015).

III. BIOLOGICAL EVALUATION OF N_2O_2 SCHIFF BASES

Biological evaluation of N_2O_2 Schiff bases was done in good detail with regard to targeting anticancer activity with their *in-vitro* and *in-vivo* testing. Transition metal-coordinated Schiff base complexes exhibit notable cytotoxic activity against various cell lines of cancerous tissues. The high specificity of these compounds toward cancer cells while causing apoptosis and interference with the normal cellular process makes them a considerable agent toward the development of new cancer drugs.

3.1 Discussion of *in-vitro* and *in-vivo* Studies

In-vitro and *in-vivo* studies are incomplete without the exploration of therapeutic potential in anticancer agents such as N_2O_2 Schiff bases. Out of the two, *in-vitro* studies provide insight into the nature of their interaction with the cell, cytotoxic effects, and mechanisms of action, such as DNA binding and induction of apoptosis, in controlled environments. In contrast, *in-vivo* studies evaluate the efficacy, bioavailability, and toxicity of such molecules within living organisms, thus giving an all-encompassing understanding of their pharmacokinetic and pharmacodynamic properties. Altogether, these studies pave the way forward for advancing Schiff bases towards their clinical utilization in cancer therapy.

3.1.1 *In-vitro* Studies

In-vitro studies have revealed that N_2O_2 Schiff base complexes were cytotoxic to an array of cell lines of various cancers, such as liver and breast cancer, among others, for example, HepG2 and MCF-7. Compounds were reported to possess selectivity toward cancerous cells, which would not affect normal cells, making it to have a greater likelihood for therapy, as reported by (Tadele and Tsega, 2019). One mechanism of action is through the generation of ROS. N_2O_2 Schiff bases catalytically introduce ROS inside the cancer cell after the chelation of transition metals such as copper, nickel, or vanadium. These ROS cause oxidative stress. The latter increase in ROS upsets the mitochondrial membrane potential, which leads to apoptosis-also termed programmed cell death. According to Wang et al. 2020. In addition to that, ROS further damage cellular constituents like proteins, lipids, and DNA, which are other mechanisms contributing to the cytotoxic effects of these complexes.

Apart from the generation of ROS, N_2O_2 Schiff bases were shown to have anticancer activity through interference with the cell cycle of cancerous cells. For example, experiments using derivatives of Schiff bases of pyrazole-naphthalene and 2-thiouracil sulfonamides showed that these compounds cause arrest of certain phases of cell cycle in cancer cells

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so interfere with their proliferation. Schiff bases based on quinazoline displayed strong activities against HepG2 and MCF-7 cell lines and hence proved efficacy for different types of cancers (Tadele & Tsega, 2019).

Another significant mechanism by which N_2O_2 Schiff bases exhibit anticancer activity is through their ability to directly chelate to DNA. The interaction of these compounds with the DNA of cancerous cells inhibits the crucial processes of DNA replication and transcription, ultimately leading to cell death. Research has pointed out that Schiff base complexes, especially copper (II) and nickel (II), intercalate between DNA, which in turn inhibits the sequence of base pairing, disrupting all important cellular functions. Direct DNA-binding capability makes N_2O_2 Schiff bases more potent in terms of their antitumor activity as they are highly effective against rapidly dividing tumor cells-a key characteristic of aggressive tumors.

3.1.2 *In-vivo* Studies

In addition, more *in-vivo* studies offer more evidence of the anticancer properties of N_2O_2 Schiff bases, especially in various models of animals. These compounds substantially inhibit the growth of tumors. In fact, considerable reduction in the size and progression of tumors is shown by the mice and rat models. An interesting characteristic of these compounds is that they would induce apoptosis in cancer cells while causing minimal damage to normal tissues, which is a very good character to apply in less toxic therapies in anticancer conditions (Ahmed et al., 2009).

The *in-vitro* and *in-vivo* efficacy of Pd (II) and Pt (II) Schiff base complexes were evaluated that significantly inhibit breast cancer xenografts. Coordination metal complexes enhance the cytotoxic effects on interruptions with mitochondria and the generation of ROS if coordinated with N_2O_2 Schiff bases (Wang et al., 2020). Such metal-Schiff base complexes are not only pro-apoptotic but also anti-angiogenetic. Angiogenesis is a process wherein new blood vessels form in a tumor to distribute nutrients to such growing conditions.

In-vivo studies were also carried out for the pharmacokinetics of N_2O_2 Schiff bases. The findings are that these compounds are relatively stable in biological systems and accumulate favourably in tumour tissues. They are delivered effectively at the site of action, and hence, they qualify as leads for further drug development. There are also some studies about delivery systems from drugs in the form of nanoparticles that could ensure better bioavailability and targeting of N_2O_2 Schiff bases *in-vivo*.

3.2 Examination of Anti-Cancer Activity Against Various Cancer Cells

The acyclic Schiff base is another member of Schiff bases that coordinate to the transition metals and play an important role in biological processes. Many biological activities were shown to be exhibited by these ligands, including antibacterial, anti-covid, anticancer, and antiproliferative properties. Schiff bases are well known for coordination capability with numerous metal ions in view of the lone pair of the imine nitrogen atom, which encompasses a extensive range of biological activities. The thermodynamic stability of the chelating nature of polydentate ligands of the Schiff base type is greater.

The widely recognized acyclic Schiff base salen is prepared by the condensation of salicylaldehyde and ethylenediamine. Theoretical analysis of the keto-enol equilibrium, made possible by discovery of the crystalline form of the drug in 1978, disclosed a two-step equilibrium: the most stable isomer of salen has two enol groups and C2 symmetry. Figure 5 illustrates how biological effects of Schiff base compounds and their metal complexes, for example, anticonvulsant, antioxidant, and anticancer properties are making them important therapeutic agents.

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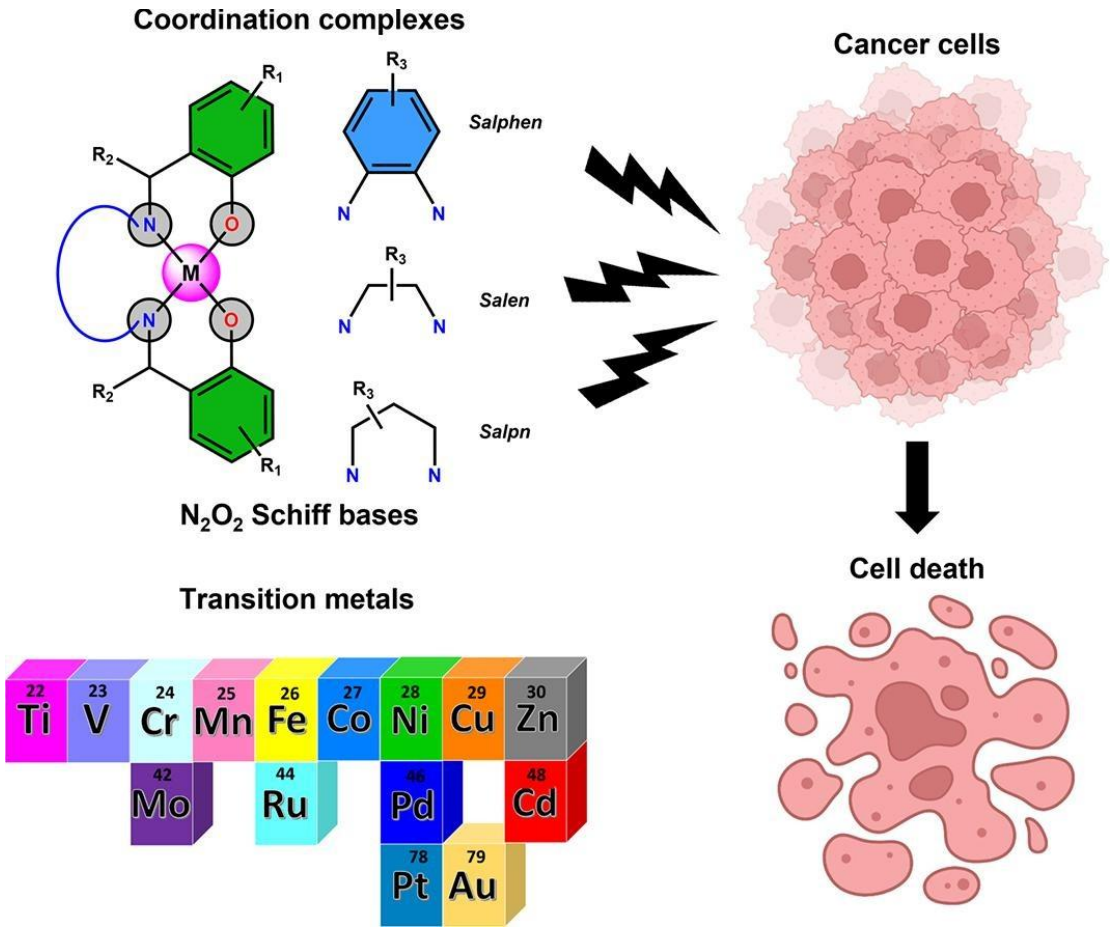

Figure 5: Transition Metal complexes with N_2O_2 Schiff Bases Possess Anti-Cancer Activity (Alfonso-Herrera et al., 2024)

N_2O_2 Schiff bases are anticancer drugs mainly through mechanisms like the induction of apoptosis, cell cycle arrest, and DNA interaction. In the study made by (Uddin et al. 2019), it was observed that Schiff bases develop ROS and oxidative stress which was an influential reason for causing apoptosis in the cancerous cells. The compounds selectively target the cancerous cells without affecting the normal cells; that makes them perfect for being introduced as a medicinal agent. A number of research articles reported the Schiff bases of N_2O_2 and their metal complexes for *in-vitro* anticancer activity against various cancer cells that possesses tremendous therapeutic potential: Table 1 illustrates the documented Schiff based anti-cancer properties against various cell lines in a particular duration of time.

Table 1: Anticancer properties of Schiff's base against various cell lines (Majeed et al., 2022)

Cell lines	Schiff Base type	IC_{50}	Duration Time (h)
MCF-7	Benzothiazole-containing schiff bases	200 µg/mL	72 h
HepG2, MCF-7, RPE-1	Bis-Schif bases of pyrazoles 9–24	84.2 µM 99.4 µM 127.7 µM	48 h
HepG2, MCF-7	Schiff-bases derived from tetrahydrobenzo[d]thiazoles (4,5,6,7).	1.29 µM 34.52 µM	48 h
MCF-7	bisphenol bis (azaneylylidene) bis	250 µg/mL	72 h

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	(methaneylylidene)		
A549 cell line	Tetronic Schiff bases	39.63 µM	72 h
HepG2, MCF-7, A549, and HCT116	Salicyaldehyde with 2-amino-4-phenyl-5-methyl thiazole serves as the schiff base.	6.20 to 9.22 and 6 to 10 μgmL^{-1} respectively	48 h
HepG2, Caco-2, MCF-7 and PC-3	Schiff base ligands	>100	24 h
MCF7	Morpholine schiff base ligand	100 µM	48 h
A549 cells	Water-soluble Schiff Bases	L-Cu - 12 µM, L-Zn - 80 µM	24 h
MCF-7	4-chloro-o-phenylenediamine and 3,5-dichloro-2-hydroxyacetophenone based Schiff base ligand.	2.5 to 100 μgmL^{-1}	36 h
MCF-7	4-(((10- chloroanthracene-9 -yl) methylene) amino)-1,5- dimethyl l-2- phenyl-1,2-dihydro-3H- pyrazole -3-one	< 0.1 mM	72 h
MCF-7	4-(((8-hydroquinoline-2 yl) methylene) amino)-1,5-dimethyl2-phenyl-1,2-dihydro-3H-pyrazole-3-one	0.14 mM	72 h
MCF-7	Schiff bases made on salicylaldehyde or bromosalicylaldehyde produced from aminobenzothiazole derivatives	44.12 µM	72 h
HeLa, PC-3, and SKOV3	Schiff base ligand, 2-((E)-((4-(((E)-benzylidene) amino) phenyl) imino) methyl)–naphthalene-1-ol-Cu (II) complex	0.161, 0.063, and 0.087 µg/mL	72 h
Colon cancer in humans (HCT116)	Schiff base 2,2'-((1E,1'E) -((2,2-dimethylpropane 1,3 diyl) bis(azanylylidene)) bis(methanylylidene)) bis(4-fluorophenol) (L2F) and Pd (II) complex (PdL2F)	90.00 and 4.10 µg/mL	
A549, BT549, PC3, and 3T3-L1 cells	Schiff Bases: Generated from 2, 4-triazole, phenathroline, 4-amino-3,5-dimethyl-1, and bipyridine dicarboxaldehydes	50, 1/4200, and 70 µM	
HepG-2, HCT-116, and MCF-7	3-amino[3,2-c] 4-hydroxy-2H-pyranoquinoline based Schiff's base	8.06, 1.82, and 6.49 µg/mL	

Mechanisms of Action (apoptosis, DNA binding, etc.).

In general, as mentioned above, the anticancer activities of N_2O_2 Schiff bases mainly depend on their ability to induce apoptosis and interfere in DNA processing. As mentioned before, the production of ROS serves as the starting point of apoptosis. Metal ions catalyse the formation of ROS within N_2O_2 Schiff base complexes, affect the mitochondria, and generate dysfunction, hence evoking the pathway of apoptosis. This subsequently results in the activation of caspases, a family of proteases that are involved in apoptosis, and fragmentation of DNA within cancer cells.

Apart from that, its anticancer activities are improved by the binding property of N_2O_2 Schiff bases to DNA. When the DNA double helix intercalates or binds Schiff base complexes to the grooves with metals, copper, nickel, and platinum interrupt the process of DNA replication and transcription, leading to cell death of cancerous cells. Such an interaction with DNA is typically accompanied by oxidative DNA damage, which will further damage the survival of the cancer cell. That is to say, the biological activity of Schiff bases N_2O_2 highlights their potential for functioning as anticancer agents, the activity proceeding by a mechanism of ROS generation, induction of apoptosis, cell cycle arrest, and DNA

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binding. The *in-vitro* and *in-vivo* studies doubly emphasize the effectiveness in many cell lines and in tumours against cancer (Yin et al., 2022).

IV. STRUCTURE-ACTIVITY RELATIONSHIPS OF N_2O_2 SCHIFF BASES

The anticancer activity of Schiff bases N_2O_2 was highly dependent on their structural characteristics. To explain their anticancer activity, it depends upon suitable substituents on the aromatic rings, which affect the ring size and the coordination geometry of the metal complex; the latter determines the extent of binding to DNA, ROS generation, and apoptosis in cancer cells. Any further optimization of Schiff bases for therapeutic applications needs to be facilitated by understanding the relationship between these structural features and biological activities (Figure 6).

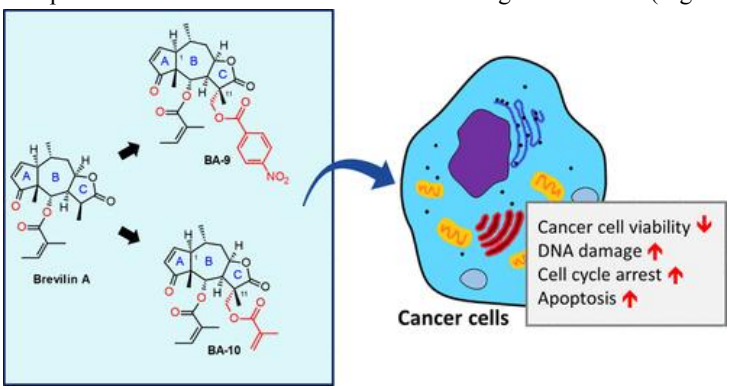

Figure 6: Structure- Activity Relationship of Cancer Cells (Lee et al., 2020)

Correlation of structural features with biological activity.

The square planar structure of those complexes is most frequently met with copper (II) and nickel (II) complexes of Schiff base, allowing the intercalating process between DNA base pairs. Due to the fact that such complex approaches DNA much closer in the planar form, it becomes quite difficult for the DNA system to copy structural changes. Intercalation, and thus disruption of DNA structure, appears to mediate the anti-proliferative properties of these chemicals. Because these have anti-proliferative action that would make them apparent candidates for cancer therapy, this DNA-binding feature is pertinent (Ciaramella et al.,2024).

For example, Schiff bases bearing hydroxyl or methoxy groups as electron donors, are more nucleophilic. This property improves their chelating ability toward the metal ion and improves their ability to interact with biological targets like DNA; this of course, further increases their lethality to the malignant cells. On the other hand, nitro groups typically reduce the ligand's activity; in such cases, this leads to the general loss of biological activity in the entire pharmacological process. Apart from being anticancer compounds, several copper and nickel Schiff base complexes also induce oxidative stress and act on cancer cells by inducing apoptosis through the formation of ROS (Anand et al., 2021).

In relation to this, the cooperation of these Schiff bases with metal ions heightens the thermodynamic stability and cytotoxic properties. Studies show that Schiff bases having the donor tetradentate ON-NO ligand produce metal complexes with copper, nickel, and vanadium, which display remarkable biological activity. Apart from the generation of ROS, these complexes, because of their tight interaction with DNA, perform another step of cancer cell replication disruption.

4.2 DISCUSSION OF SUBSTITUENTS, RING SIZE, COORDINATION GEOMETRY EFFECT

4.2.1 Substituents Effect

The choice and substitution at the aromatic ring of Schiff bases were largely developed to predict their biological activity. The presence of substituents dramatically impacts the electronic properties of ligands, affecting the complexing ability toward the metal ions and biological target interactions in return. Electron-donating groups like hydroxyl and

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methoxy increase the nucleophilicity of the ligand, which improve coordination with metal and consequently favour better binding capacity towards DNA and the production of ROS. This increases the cytotoxicity potential of the compound towards the cancerous cell.

Schiff base complexes containing electron-withdrawing groups, like nitro groups, have lower reactivity that decrease the biological activity. However, the impact of the substituent is not only on electronic levels as they also impact lipophilicity of the complex and this aspect is critical because it determines the extent to which it penetrate cancer cell membrane or not, thus affecting the anticancer activity. In this context, Schiff bases containing lipophilic substituents showed superior ability to transverse the membranes of cancerous cells and therefore improve their therapeutic effectiveness (Malik et al., 2017).

4.2.2 Ring Size Effects

The aromatic ring size of Schiff base ligands is a factor of significant importance in determining the planarity of such systems, and consequently, in their tendency toward DNA intercalation: Schiff bases with larger aromatic systems, such as naphthyl groups, enhance the planarity of the complex, thereby enhancing the stacking interaction toward DNA. The more for the planarity of this improved increased enhances it, enabling ease in simply placing the Schiff base in between the base pairs of DNA and therefore blocking the replication and transcription mechanisms that are of key importance to anticancer activity

Often, smaller aromatic rings, although effective, do not interact at the same level with DNA as larger, more planar systems. Larger aromatic systems in Schiff bases are reported to be more active when the DNA-binding ability is enhanced in anticancer agents.

4.2.3 Coordination Geometry Effect

Another key aspect determining the anticancer potential of the N_2O_2 Schiff base complex is the coordination geometry. Square planar and octahedral are the most common coordination geometries of Schiff base metal complexes. These geometries further influence how the resultant complex interacts with biological targets like DNA and proteins. Those which possess square planar complexes, as quite widely found in Schiff base complexes of copper (II) and nickel (II), have a structure that allows the intercalating process between the DNA base pairs. (Abdolmaleki et al.,2024) The complex, because of its planar structure, gets much closer to DNA, that makes structural changes hard for DNA to replicate. The intercalation which disrupts the DNA structure is what helps these compounds to function as anti-proliferative agents. Thus, this DNA-binding property seems relevant with regard to their anti-proliferative effect that makes them potential candidates for cancer therapy (Raczuk et al., 2022).

Octahedral complexes: In these compounds, Schiff base complexes having an octahedral geometry interact by different modes. Though they are not intercalated into the DNA as readily as with square planar complexes, they might still interact hydrogen-bonded and electrostatically with the DNA backbone whose charges are negative. This mode of binding might even inhibit the replication of DNA, although it would do so by yet another mechanism than intercalation.

Coordination geometry of the Schiff base complexes plays a significant role in catalysing ROS formation since it is the first critical event that would lead to cancer cell apoptosis. Among these, there are specially catalytically active copper (II) complexes of square planar geometry. This increased ROS production results in oxidative stress inside the cancer cells, which causes damage to proteins, lipids, and DNA and eventually leads to the death of the cells. Not only does it affect the efficacy of generation of ROS but also improves the overall antitumor efficacy of Schiff base complexes making it a viable candidate for cancer cure. (Sadia et al., 2020).

Structure-activity relationships that control the structure of N_2O_2 Schiff base complexes determine, to a large extent, their anticancer efficacy. The substituents, the size of aromatic ring, and the coordination geometry are all pivotal factors in the biological activity of these complexes. Fine-tuning these structural features would help enhance DNA binding affinity, improve ROS generation, and add overall cytotoxicity toward cancer cells by Schiff base complexes. The further exploration of such relationships holds a lot of promise for developing more effective anticancer agents based on the chemistry of Schiff bases (Yin et al.,2022)

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Volume 5, Issue 11, April 2025
Impact Factor: 7.67

V. POTENTIAL THERAPEUTIC APPLICATIONS

The N_2O_2 Schiff bases are the most interesting type of anticancer agents since they induce selective apoptosis in cancer cells. Overcoming drug resistance is one major aspect of this area, which has brought them into the mainstream of the field, along with their versatility in combination therapy strategy. Optimizing their pharmacokinetics and pharmacodynamics is a challenge to bring them into clinical development. Further research is needed so that these Schiff base complexes will be effective and safe for application in the field of cancer treatment.

5.1 N_2O_2 Schiff Bases as Potential Therapeutic Agents

N_2O_2 Schiff bases are now promising candidates in the treatment of cancer mainly because of their multifaceted actions on different pathways involved in cancer. They exhibit a high anticancer activity against various tumour types, thus revealing their versatility both in single-therapy and combination therapy modalities. Their structure increasingly allows for selective binding to cancerous cells, thereby increasing their therapeutic efficacy. Besides, beneficial pharmacokinetic properties, such as bioavailability and metabolic stability, pose higher future potential as some feasible anticancer agents. Versatility in endogenous biology now calls for further research and development into the full exploitation of oncology.

5.1.1 Potential Types of Cancers Targeted by N_2O_2 Schiff Bases

N_2O_2 Schiff bases were found to possess a high anti-tumour activity against various cancers such as those identified in the breast, lung, colon, and liver. Their capacity to induce selective apoptosis while leaving the normal tissues in its normal state is the reason behind this selectivity that is important in handling aggressive types of cancers, as other forms of treatment usually react with both the cancerous and healthy cells, where the side effects arise as a major concern.

N_2O_3 Schiff base complexes, for instance, have considerable anticancer activity against MCF-seven cell lines for breast cancer through cell cycle disruption and induced apoptosis. Schiff base complexes interact with the DNA in lung and colon cases through disruption of their ability to proliferate and repair themselves. The N-O-Schiff bases generated reactive oxygen species and produced malfunction of mitochondria, thus proving to be a strong tumour-targeting agent in the cancer models through the inhibition of further growth of the tumour.

Cancerous breast cells: *In-vitro* anticancer activity of Schiff base complexes on MCF-seven cancerous breast cells. The result of the findings showed that the Schiff base complexes offered remarkable activity and thus induced apoptosis along with DNA fragmentation. These caused an inhibition of cell proliferation.

Liver Cancer: Schiff bases N_2O_2 are highly potent against HepG2 cells in liver cancer. There was highly significant decrease in cell viability and dose-dependent cytotoxicity induced through generation of ROS and mitochondrial dysfunction.

Melanoma: In addition, Schiff base complexes were evaluated for their antiproliferative activities against A375 malignant melanoma cells. In the latest study on Cu (II) complexes, it was indicated that they were very cytotoxic against the cell lines, with an IC50 value < 10 µM by being amazingly higher than the free ligands and even that of cisplatin (Alfonso-Herrera et al., 2024).

Colon Cancer: Schiff bases, which were prepared from various aldehydes, exhibited the ability to affect Caco-2 human colon cancer cells. The scientific research found that such compounds disrupt cellular activities, thus decreasing cell survival while increasing apoptosis in cancerous cells of the colon.

The above broad-spectrum activity against several different cancers makes N_2O_2 Schiff bases an attractive therapeutic option, especially for challenging-to-treat or drug-resistant malignancies.

5.2 Discussion of Combination Therapy Strategies

Schiff bases of N_2O_2 combined with the established chemotherapeutic agents is one promising approach to bettering therapeutic outcomes. From preclinical data, it is revealed that Schiff bases combined with drugs such as doxorubicin and cisplatin have improved the therapeutic index by functioning on various pathways in cancer development.

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Volume 5, Issue 11, April 2025
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Therefore, for instance, the use of an N_2O_2 Schiff base in combination with cisplatin has proven the increased damage to DNA and higher death of cancerous cells (Durgun et al., 2020).

Combination therapies with N_2O_2 Schiff bases could benefit from several factors, including Figure ting resistance and reducing the consumption of conventional drugs or dose, thereby reducing side effects. Acting at various mechanisms, such as intercalation within the DNA molecule, generation of ROS, and induction of apoptosis, Schiff bases can synergize with other treatments for offering an intensive attack on cancer cells. The combination therapies that have shown synergistic effects are promising in the treatment of drug-resistant cancers, which fail conventional chemotherapy. There is a report that N_2O_2 Schiff bases sensitize cancer cells to known drugs, so there might be an opportunity for drug therapy to be effective. Characterization of pharmacokinetic and pharmacodynamic properties will be crucial for the validation and validation efforts during clinical trials in patients as the research goes forward.

5.3 Considering Pharmacokinetic and Pharmacodynamic Properties

Reports on potent anticancer activity of N_2O_2 Schiff bases exist, but the pharmacokinetic and pharmacodynamic properties must be optimized for clinical utility. Among those factors decisive for therapeutic success, besides bioavailability, tissue distribution, metabolic stability, and drug clearance rates, careful examination and optimization should be performed.

Pharmacokinetic studies revealed that appropriately formulated N_2O_2 Schiff bases achieve a very good bioavailability with proper distribution in tumour tissues. The challenge lies in the delivery system to maximize the accumulation of these species at the tumour site while minimizing the contribution of systemic toxicity. (Fulton & Najahi-Missaoui, 2023) Researchers are now studying nanoparticle-based delivery systems as well as liposomal formulations to more effectively target N_2O_2 Schiff bases to the cancer cells, thus reducing off-target effects and ensuring better therapeutical outcomes.

An important factor that must be evaluated is the metabolic pathway of N_2O_2 Schiff bases, which predict the potential stability in the body. Therapeutic window is directly affected by rates of metabolism and excretion, so maximizing the rates improve effectiveness and safety both.

In addition, their pharmacodynamics research will show the therapeutic index wherein efficacy versus toxicity will be more pronounced. Given these Schiff bases, they must selectively kill cancerous cells without affecting normal tissue; hence, there is a need for refinement of dosing regimens and delivery strategies in order to strike such a delicate balance. Further pharmacokinetic and pharmacodynamic studies are needed for further research into these compounds to push them closer to clinical applications.

Schiff bases as N_2O_2 are one of the interesting classes of anticancer agents known to be applied in various types of cancers. These candidates are good as they induce selective apoptosis among cancer cells and versatility in strategies of combination therapy. An important developmental challenge still exists in optimizing pharmacokinetic and pharmacodynamic properties, but such ongoing research is necessary to ensure that such Schiff base complexes are both effective and safe for use in clinical settings.

VI. CHALLENGES AND FUTURE DIRECTIONS

N-O-Schiff base complexes, particularly their metal complexes, have exhibited high cytotoxicity against different lines of cancer cells, putting them at the forefront of candidate anticancer therapy agents. However, there are many barriers and restrictions in this regard for their formulation and application in therapeutic practices. The main issues regarding the matter of N_2O_2 Schiff bases come before this review, along with potential directions for further study to reach maximum therapeutic efficiency.

6.1 Discussion of Limitations and Challenges

Regarding Schiff bases containing N2O2 as anticancer agents, their primary setbacks in the treatment process are drug resistance, toxicity, stability, and bioavailability. Cancer cells respond by changing the cell's sensitivity to avoid cytotoxic impacts of chemotherapeutic agents. Good Schiff base complexes are normally stable; however, hydrolysis

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Volume 5, Issue 11, April 2025
Impact Factor: 7.67

degrades bioactivity as well as bioavailability in aqueous solutions; thus, proper solubility and stability improve the formulation of anticancer drugs.

6.1.1 Drug Resistance

The creation of cancer cell lines resistant to drugs was one of the significant challenges in the application of N_2O_2 Schiff bases in chemotherapy. This is because the cancer cells would most probably adapt with mechanisms that help it counter the cytotoxic effects of the drugs, generally reducing the overall therapeutic response. Resistance occurs by mechanisms such as increased drug efflux, mutation of target proteins or an intensified DNA repair mechanism which enables cancer cells to survive. Such findings indicate that multiple pathways that contribute to the resistance process prevail. While Schiff bases are extensively used in clinical activities, these resistance pathways must be studied and novel combination therapies or alterations must be designed to make them more efficient.

6.1.2 Toxicity

The major drawbacks for potential *in-vivo* applications of N_2O_2 Schiff bases and their metal complexes are their toxicity potential. Despite the hundreds of examples having potent anticancer activities, the therapeutic window-between the appropriate and toxic doses-were not studied adequately. For instance, although the Cu (II) complexes seemed to be more toxic than their Zn (II) counterparts, at high concentration, they also have demonstrated a greater ability to cause cytotoxic effects on normal cells and to produce side effects (Alfonso-Herrera et al., 2024; Ahmed et al., 2009).

6.1.3 Stability

Stability is another critical factor in designing Schiff base complexes for medical use. Hydrolysis or decomposition of most complexes before administration deteriorate their *in-vivo* bioactivity and bioavailability. In addition, stability under physiological conditions becomes essential in having effective Schiff base complexes *in-vivo*. Some Schiff base complexes decompose in biological fluids resulting in reduced therapeutic activity and untimely pharmacokinetics.

6.2 Future Directions for Research

Further research is needed to optimize the structure of N_2O_2 Schiff bases for enhanced anticancer activity. Advanced drug delivery systems, such as nanoparticles and polymeric carriers, improve solubility and stability. Future research should explore N_2O_2 Schiff bases in combination therapies, focusing on synergistic interactions to minimize drug resistance. *In-vivo* efficacy studies and mechanistic studies are also needed to advance these compounds into clinical use.

6.2.1 Structure Activity Optimization

Further research is required to design an optimal structure of N_2O_2 Schiff bases, having enhanced anticancer activity. Such includes the effect of variable substituents on the aromatic rings, different coordination geometries, and suitable choice of metal ions on bioactivity. The SAR will provide a basis for designing more powerful and selective anticancer agents.

6.2.2 Development of delivery systems

Advanced drug delivery systems, such as a nanoparticle delivery system and polymeric carriers are considered to solve the drawbacks of bioavailability and target delivery. The solubility and stability of N_2O_2 Schiff bases which result in the effective targeted deposit of the compound within the tumour tissue are improved. This should minimize systemic toxicity by decreasing the exposure to healthy tissues.

6.2.3 Combination Therapies

It is an exciting prospect for future research to explore N_2O_2 Schiff bases in combination therapies with known chemotherapeutic agents. Preliminary investigations point towards synergistic interactions with drugs like doxorubicin

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ISSN: 2581-9429
Volume 5, Issue 11, April 2025
Impact Factor: 7.67

or cisplatin; thus, the development of drug resistance would be minimized and the outcomes of therapy would be improved. Future research would concentrate on explaining the mechanisms through which these synergistic interactions occur and strive to optimize dosing regimens for combination therapies.

6.2.4 *In-vivo* Efficacy Studies

Comprehensive *in-vivo* efficacy studies on the N_2O_2 Schiff base derivatives are in urgent need to establish their anticancer properties. Firstly, pharmacokinetic, pharmacodynamics, and long-term safety and efficacy information from preclinical models in animals should be gathered for these compounds to advance to human clinical research.

6.2.5 Mechanistic Studies

A better understanding of the mechanisms by which N_2O_2 Schiff bases act would explain how these compounds are interfering with cancer cells to induce cytotoxic death. Potential areas for exploration in future include ROS generation, DNA-binding affinity, and other potential molecular targets. Results of such studies provide insights that help in the design of more efficacious therapeutic strategies and prediction of resistance mechanisms that appear within cancer treatments. The N_2O_2 Schiff bases hold exciting opportunities in the chemotherapy of cancer with high cytotoxicity against many lines of cancer cells. However, challenges to be addressed include issues of toxicity, stability, bioavailability, and drug resistance as a means for further improvement of therapeutic capabilities. Future study should be focused on optimisation structures, state-of-the-art delivery systems, combination therapies, *in-vivo* efficacy, and mechanistic studies to translate the compounds from the laboratory into the clinical area.

VII. CONCLUSION

Schiff bases of N_2O_2 were one of the most promising classes of compounds, with great and favourable applications within anti-tumor therapy. These Schiff bases were very active in different types of cancer cell lines, like breast, lung, colon, and liver cancers, especially at metal complexes levels, which caused their therapeutic action towards the induction of apoptosis via generations of ROS and interference in DNA replication. What makes these compounds interesting is that they selectively target cancer cells but spare the normal tissues, thus mitigating many side effects. The anticancer value of such complexes is very sensitive to structural changes that might alter their biological activities. Such sensitivity requires fine-tuning of their structure to ensure attainment of maximum therapeutic efficacy. Overall, N_2O_2 Schiff bases, particularly as metal complexes, hold tremendous promise for the development of targeted cancer therapies.

7.1 Summary of Key Findings

Key factors such as an activity-position-dependent nature of the substituents in aromatic rings, size of the ligating shell, and coordination geometry with metal ions influence their effectiveness to a significant. These structural parameters must be optimized to increase their anticancer activities and develop potent therapeutic agents.

Potential for Combination Therapy: Preliminary studies regarding the application of Schiff bases N_2O_2 with a known chemotherapeutic agent indicated that these compounds could ultimately enhance the course of therapy through synergistic effects. Such combinations might eliminate the problems of drug resistance and enhance treatment efficacy in the general treatment process.

Despite its promise, there are still a lot of issues to be overcome: above all, toxicity, stability, and low bioavailability. N_2O_2 Schiff bases will thus require innovative drug delivery systems, structural optimization, and proper *in-vivo* studies, translating these compounds from the lab bench to patients.

7.2 Emphasis on the Potential of N_2O_2 Schiff Bases in Anti-Tumour Therapy

The potential of therapeutic application attributed N_2O_2 Schiff bases is high due to the multifaceted anticancer mechanisms, diversity in structure, and effectiveness for combination therapies. Further therapy of cancer increasingly promises much better potential nowadays now that the complexities in their interactions with biological systems are

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Volume 5, Issue 11, April 2025
Impact Factor: 7.67

unravelled. Continued research into their pharmacokinetic and pharmacodynamic profiles in conjunction with new methods of drug delivery will be important to fully realize the therapeutic potential of N_2O_2 Schiff bases. Overcoming the present challenges and exploiting their unique properties, N_2O_2 Schiff bases become essential parts of effective anti-tumor regimens, thereby contributing towards better patient outcomes in cancer therapy.

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