Review Article

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Advancement in schiff base complexes for treatment of colon cancer

https://doi.org/10.1515/revic-2024-0068
Received August 9, 2024; accepted September 30, 2024;
published online October 30, 2024

Abstract: Schiff bases have proven to be beneficial in medicine and have interesting complexation capabilities with transition metals. The +4, +5, and +6 oxidation states of schiff base metal complexes have been the subject of recent review, which have highlighted their notable cytotoxic effects against various colon cancer cell lines (HT-29, HCT-116, SW-480, Coco-2, CT-26, LT-174, LoVo). Extensive research has focused on schiff base metal complexes in the +4 and +6 oxidation states, exhibiting distinct geometries and significant thermodynamic stability. These studies provide IC_{50} values for these complexes in colon cancer cell lines along with comprehensive structural representations that shed light on how different substituents affect cytotoxicity. When compared to schiff base ligands alone, metal complexes of schiff bases have been shown to significantly reduce colon cancer cell invasion and proliferation. The studied literature emphasizes schiff base metal complexe's potential in biological applications and suggests that more study may be necessary to fully comprehend their biology. To enable more sophisticated multidisciplinary study in this field, future investigations should focus on synthesizing novel complexes with enhanced bioavailability, solubility, and low toxicity.

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Keywords: schiff base complexes; metal complexes; anticancer activity; colon cancer cells; cytotoxic activity

1 Introduction

Cancer seems to be an enormous issue, with rising incidence and rates of mortality as life expectancy increases.[1–3] As the second greatest cause of mortality worldwide, cancer affects more than one in three people at least once in their lives. The tremendous health impact of cancer is shown by the fact that it is responsible for approximately one in four fatalities in the United States.[4] These rates are still rising in spite of advances in treatment. Notably, Colorectal cancer is common and ranked 4th in the USA and the EU.[5] After the breast cancer, it is also the second most prevalent and major cause of cancer death among females, with the highest incidence occurring in Portugal.[6–8] Malignant adenomatous polyps, which are the result of alterations in the colorectal epithelium, are the initial stage of this disease and can grow out of control, infiltrate nearby tissues, and spread to distant locations, especially in advanced stages.[9] Advanced colorectal cancer is typically treated with chemotherapy, which combines drugs such as oxaliplatin, capecitabine, leucovorin, and 5-fluorouracil (5-FU).[10,11] Despite their effectiveness, platinum-based chemotherapy treatments have a history of systemic toxicity and tumor resistance.[12,13] Using the anticancer impact of metal-based drugs, a lot of research is being done on treating colon cancer.[14] Since the features of metal complexes can be adjusted by changing the central metal ion or its oxidation state, they are attracting more attention globally due to their promise in therapeutics. Basic concepts like thermodynamics and kinetics are impacted by this optimization.[15] They are also adaptable choices for a range of biological applications due to their superior photophysical and photochemical characteristics.[16] Owing to their distinct reactivity and involvement in pathways connected to cancer, metals can be targeted as anticancer drugs and play important roles in biochemical processes.[17,18] Therefore, in order to better control colorectal cancer, research is concentrated to

develop new metal-based anticancer drugs with enhanced safety features and unique modes of action.[19,20]

Schiff bases are developed by the condensation reaction of primary amines alongside aldehydes or ketones and make up one of the most significant groups of biologically active ligands due to their ease of synthesis and superior solubility (Figure 1).[21–24] Schiff bases with aryl substituents are easier to synthesis and more stable than those with alkyl substituents. Aliphatic aldehyde schiff bases are easily polymerized.[25,26] In the synthesis of transition-metal complexes, schiff bases functioned as variety of ligands, including bidentate, tridentate, tetradentate, and polydentate. These complexes were more active because of their coordination. The efficacy of the resultant metal complexes is enhanced by the varied dentate character of schiff bases.[27,28]

Significant biological activities are shown by schiff bases, including anti-inflammatory, anti-bacterial, anti-fungal, anti-cancer, and antidiabetic properties.[29–33] Their biological interactions and activities are influenced by the type of substituent that is attached to the aromatic ring, which plays a major role in the effectiveness of the compounds.[34,35] Numerous studies utilizing transition metal ions alongside with schiff-base ligands showed the anticancer potential of these complexes.[36,37] The biological activity of schiff base ligands is mediated by the azomethine bond, whereas the nitrogen atom's lone pair electrons have chemical and biological functions as well. Studies have shown that complexation to a metal ion enhances the anticancer efficiency and bioactivity of numerous Schiff base ligands.[38–40] Although schiff bases have heteroatoms, they can be structurally modified to affect metal-centered electrical variables, which may provide superior therapeutic effects than cancer treatments based on platinum.[41,42] Schiff base treatments are dependent on a number of factors, including hydrophilicity, coordination sites, ligand structure, metal ion type, and the addition of polar groups such as azomethine or imine.[43,44] This review focuses on studies conducted within the last five years and looks at current research on the use of Schiff base metal complexes in the treatment of colorectal cancer. It emphasizes ligand complexes that exhibit efficient cytotoxicity, including bridging and mixed ligand complexes, as well as complexes with oxidation states of +4, +5, and +6. The review describes how these complexes work better than Schiff base ligands alone to inhibit the proliferation and invasion of cancer cells. To improve safety, solubility, and bioavailability, more study is encouraged.

2 Complexes with coordination number six

The development of different Schiff base ligands and the investigation of their anticancer potential have been the main subjects of the researcher. To increase their deadly effects on cancer cells, these schiff base ligands frequently combined with transition metals and form complexes. Anita et al., synthesized complexes **C1–C3** (Z)-2-(2-methyl-1-phenylpropylidene)hydrazine-1-carbothioamide (**L1**) as a ligand (Figure 2). The synthesized complexes showed octahedral coordination geometries. The complexes **C1–C3** were tested against colon cancer cell line HT-29 using SRB Assay. All the newly synthesized complexes have higher IC_{50} values than the standard Adverse drug reactions (ADR). However, in comparison **C1** complex is the most active than **C2** and **C3** and having an IC_{50} value > 80 μM for resistance to the colon (HT-29) cell line.[45] Using $ZnCl_2$ and macrocyclic ligands (**L2–L4**), novel schiff base macrocyclic Zn(II) complexes (**C4–C6**) were synthesized, resulting in octahedral geometry with two attached chloro groups. The antitumor potential of these complexes against the human colon cancer cell line HCT-116 was assessed by selecting doxorubicin as standard drug. The purpose of the study was to ascertain the cytotoxic effects of these substances while highlighting their intricate structural makeup and possible therapeutic use in the treatment of cancer. Although all the synthesized complexes show great potency against cancer cell line as compared to their respective ligands, however macrocyclic complex **C6** showed notable anticancer activity against HCT-116 cells among the produced schiff base macrocyclic compounds (**L2–L4**) and their corresponding Zn(II) complexes **C4** and **C5**. Its cytotoxicity was superior to that of normal doxorubicin, evidenced by its IC_{50} value of 3.12 ± 0.31 μM as shown in Table 1. Because of its strong ability to block cell proliferation, this study highlights **C6** as a potentially cytotoxic drug and suggests that it may be developed further for use in the treatment of cancer.[46] Melika et al. condensed 3,5-dichloro

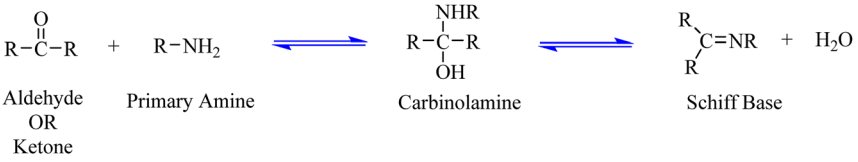

Figure 1: General method for the synthesis of schiff bases.

Table 1: Comparison of IC_{50} values of ligands with their respective hexa coordinated metal complexes (C1–C24) as well as standard drugs '=' sign indicates same as above or value is repeated from previous entry and '-' sign indicates data not available for this particular field.

Complex	Geometry	Cell line	IC_{50} Value
C1	Octahedral	HT-29	>80 μM
L2	-	HCT-116	10.1 ± 0.35 μM
L3	-	=	7.5 ± 0.65 μM
L4	-	=	7.4 ± 0.24 μM
C4	Octahedral	=	6.5 ± 0.31 μM
C5	=	=	3.75 ± 0.37 μM
C6	=	=	3.12 ± 0.31 μM
Doxorubicin	-	=	0.72 ± 0.19 μM
L5	-	SW-480	26.14 μM
C7	Octahedral	=	45.30 μM
C8	=	=	8.33 μM
L6	-	Coco-2	2.17 μM
L7	-	=	2.14 μM
L8	-	=	1.92 μM
L9	-	=	1.55 μM
C9	-	=	0.88 μM
C10	-	=	1.62 μM
C11	-	=	1.60 μM
C12	-	=	1.13 μM
Docetaxel	-	=	0.30 μM
L10	-	HCT-116	10.2 μg
C13	Octahedral	=	36.6 μg
C14	=	=	0.7 μg
C15	=	=	30.5 μg
L11	-	Caco-2/L-929	80,365/96,446 μM
C16	Octahedral	=	6,096/100,878 μM
C17	=	=	51,026/121,383 μM
L12	-	HCT-116	52.87 μM
C18	Octahedral	=	57.1 μM
C19	=	=	48.5 μM
C20	=	=	26.5 μM
C21	=	=	29.5 μM
L13	-	=	22.97 μg/mL
C22	Octahedral	=	3.41 μg/mL
C23	=	=	6.81 μg/mL
Vinblastine	-	=	4.02 μg/mL
L14	-	SW-480	102 μg/mL
C24	-	=	0.973 μg/mL
C24a	-	=	8.35 μg/mL

salicylaldehyde with 1,2-phenylenediamine to produce **L5**, a tetradentate symmetrical ligand. The two novel mononuclear Co(III) Schiff base complexes (**C7**) and (**C8**), were formed by the ligand **L5**, which has donor atoms [N_2O_2]. Initial detection and treatment with compounds based on schiff bases can lower the death rate from colorectal cancer.[47–49] The synthesized compounds (**C7**–**C8**) were evaluated for their *in vitro* antiproliferative activities against SW-480 cancer cells and compared with 5-fluorouracil which is used as a standard, according to previously reported procedure (Figure 2).[48]

The findings of the study showed that the synthesized complexes were more effective than the standard at inhibiting SW-480 cancer cells. At 48 h, complex **C8** demonstrated stronger cytotoxic effects (IC_{50} = 8.33 μg/mL) than complex **C7** (IC_{50} = 45.30 μg/mL) and the ligand (**L5**) (IC_{50} = 26.14 μg/mL). The anticancer activity of the complex **C8** was markedly improved by the presence of morpholine derivatives, indicating the structural influence on Co(III) ion cytotoxicity.[50]

Using the hydrothermal technique (HT), four new sulfa drug derivatives (**L6–L9**) and their associated Zn(II) complexes (**C9–C12**) were synthesized (Figure 3). According to published research, compounds produced from sulfonamides have strong antitumor activity against a range of human cancer cell lines and strong cytotoxic effects that are comparable to those of well-known cancer therapies, even at low concentrations.[51–54] The Caco-2 cell line, a model for human colorectal cancer, was used to test the cytotoxic potential of these substances. They were tested in the trial with the well-known anticancer drug docetaxel. Based on the viability percentage of the investigated drugs and docetaxel on Caco-2 cells, the IC_{50} values showed that all zinc(II) complexes (**C9–C12**) had higher anticancer potency than their corresponding ligands (**L6–L9**). Notably, complex **C9** (IC_{50} = 0.88 μM) outperformed the other synthesized complexes in terms of cytotoxicity, and its IC_{50} value was nearly comparable with the standard drug docetaxel (IC_{50} = 0.30 μM) (Table 1). The complexes' increasing cytotoxicity was ranked **C9** > **C12** > **C11** > **C10** and for ligands **L9** > **L8** > **L7** > **L6**.[55] A Schiff base ligand (**L10**) was developed via condensation reaction between 2-hydroxy naphthaldehyde and (1H-benzimidazole-2-yl) methanamine, as reported in the literature.[56] The metal complexes designated as **C13**, **C14**, and **C15** were formed by complexing this ligand with metal salts such as $CrCl_3{\cdot}6H_2O$, $MnCl_2{\cdot}4H_2O$, and $ZnCl_2$, respectively. The Sulforhodamine B (SRB) assay was used to assess the cytotoxic activity of **C13–C15** complexes against the human colon cancer cell line HCT 116. With an IC_{50} value of 0.7 μg, the manganese complex **C14** stood out as having the most promising results. It showed notable cytotoxic effects. With an IC_{50} value of 10.2 μg, the ligand **L10** itself demonstrated significant cytotoxicity. In contrast, complexes **C13** and **C15** showed less cytotoxic activity when compared to complex **C14** and the ligand, which may indicate that they are less effective at stopping the growth of cancer cells. These results highlight the manganese complex **C14**'s improved cytotoxic activity against HCT 116 cells, which makes it an ideal choice for additional research and development as an anticancer drug.[57] Two metal (II) complexes of a new Schiff base ligand [CoClL11$(H_2O)_2$]·$2H_2O$ (**C16**) and [RuCl(*p*-cymene) L11] (**C17**), were synthesized. The geometry of the **C16** and **C17** complexes was octahedral. The MTT assay was used to

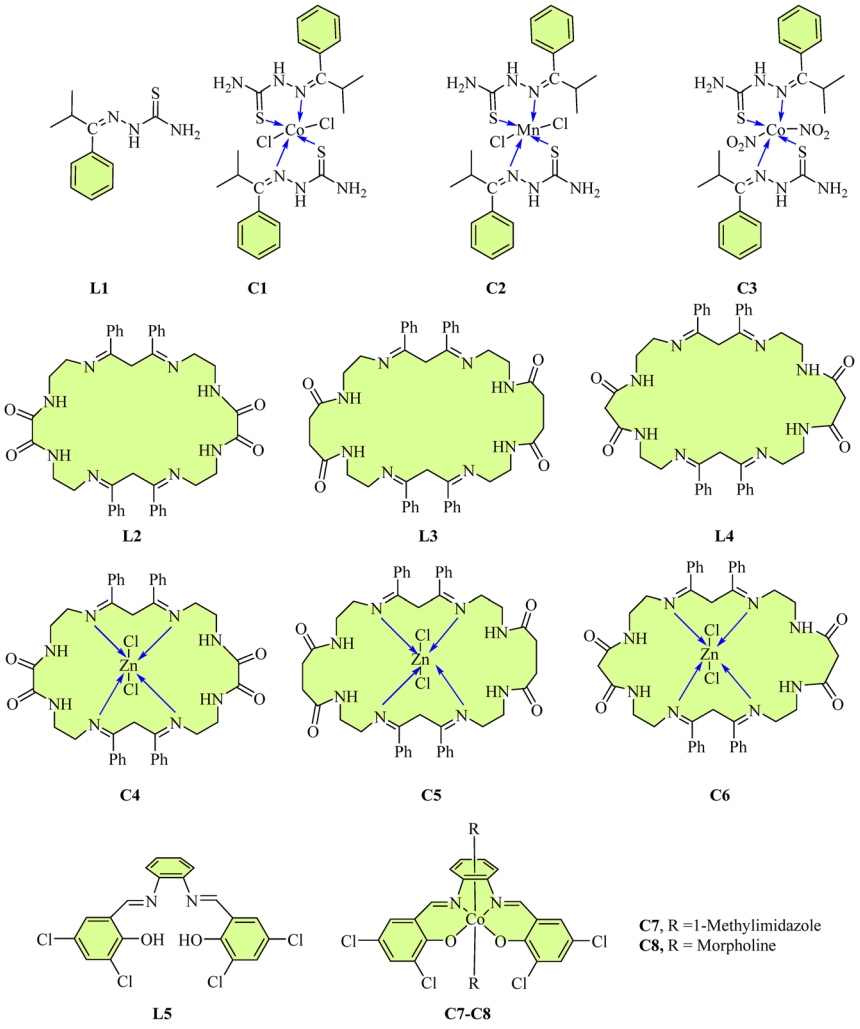

Figure 2: Structural representation of schiff base ligands and their metal complexes (**C1–C8**).

assess the anticancer properties of the Schiff base ligand **L11**, complex C16, and C17 against the human colon cancer cell line (Caco-2) and normal fibroblast cells (L-929). Testing the **C17** complex *in vitro* indicated that it was minimally cytotoxic to L-929 normal cells and that it was most cytotoxic to Caco-2 colon cancer cells, with the lowest IC_{50} values of 6,096 µM. Slightly less effective than the **C17** complex, the **C16** complex similarly showed notable cytotoxic effects (IC_{50} = 51,026 µM). Yet, as shown by the highest IC_{50} values 80,365 µM in the Caco-2 cell line, the Schiff base ligand exhibited the least anticancer action. The study also looked into how these complexes' cytotoxicity was affected by electrochemotherapy (ECT). When compared to the complexes alone, it was discovered that applying electroporation (EP) in conjunction with the complexes greatly increased their cytotoxic activity. Particularly, when combined with EP, the cytotoxicity of the **C16** and **C17** complexes increased by 2.07 and 2.12 times, respectively. This indicates that these **C16–C17** complexes have potential as potent chemotherapeutic agents for the treatment of colon cancer, especially when paired with ECT.[58]

C. Shiju et al. developed the Schiff base ligand 4-nitrobenzaldehyde-glycylglycine (**L12**) and its complexes Co(II), Ni(II), Cu(II), and Zn(II) (**C18–C21**). These complexes were all water soluble. According to spectral study, **L12** coordinates through the nitrogen atoms of the carboxylato, deprotonated peptide, and azomethine. It is a tridentate monobasic ligand.[59] It was found that the complexes have octahedral geometries as shown in Figure 4. Human colon cancer cells (HCT116) were used to test the synthetic complexes **C18–C21's** anticancer activity. Despite being an effective anticancer medicine, cisplatin has serious adverse effects, including neurotoxicity and nephrotoxicity.[60] Using an MTT assay, newly synthesized complexes containing the ligand **L12** were examined for their ability to inhibit the proliferation of HCT-116 cancer cells. The complex **C20** combination exhibited higher cytotoxic activity, with an IC_{50} value of 26.5 µM as compared to ligand (IC_{50} = 52.87 µM) (Table 1). On

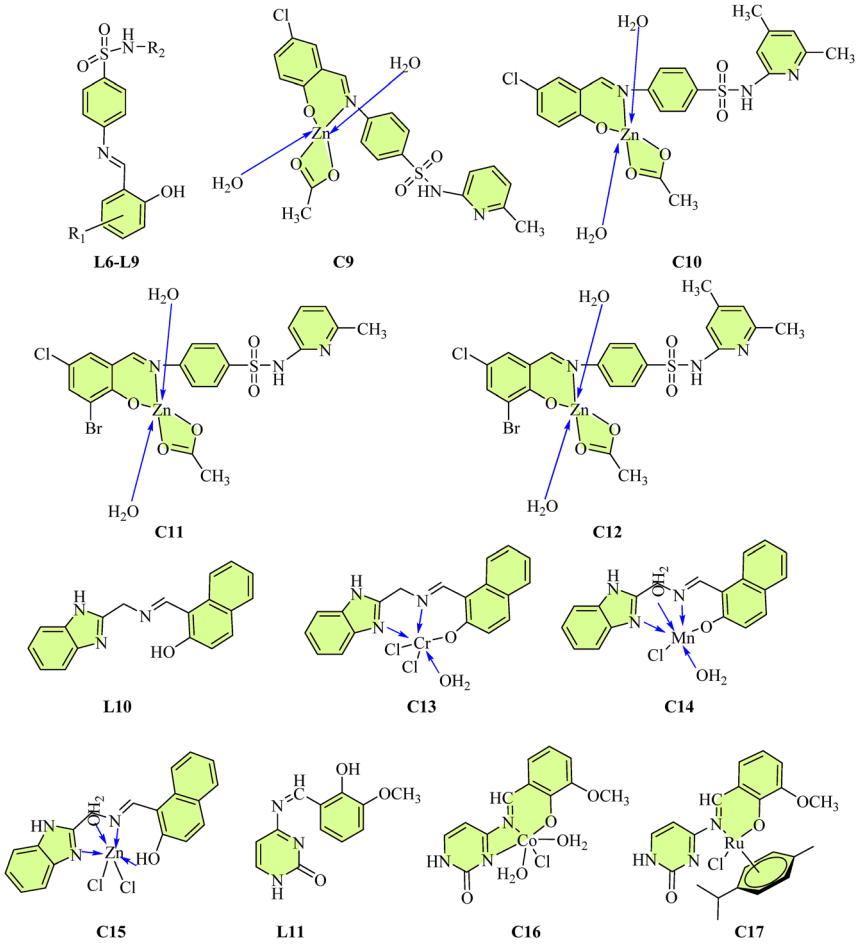

Figure 3: The structural representation of schiff base complexes **C9–C17**.

the other hand, compared to free ligand **L12**, complex **C18** and **C19** showed greater IC_{50} values, indicating decreased activity. The order of the decrease in cytotoxicity were the following, **C20** > **C21** > **C19** > **L12** > **C18**. **C20** complex had reduced activity when compared to therapeutically used pharmaceutical drugs like etoposide and cisplatin, even if their IC_{50} values were better than those of several Ru(II) complexes.[61–63] An innovative Schiff base ligand **L13**, including aminothiohydantoin, was synthesized together with its metal complexes with Mn(II) and Zn(II) to investigate their potential as anticancer agents. The primary objective was to synthesize schiff base complexes of metal (II) thiohydantoin with low toxicity for the treatment of colon cancer. HCT-116 colon carcinoma cells were used to test the *in vitro* anticancer effectiveness of these produced compounds, designated as **C22** (Mn(II) complex) and **C23** (Zn(II) complex). In order to evaluate the efficiency of the new compounds in potentially providing additional therapeutic options for colon cancer treatment, the results were compared with those of a well-known clinical anticancer drug, vinblastine (VBL). Compared to the free ligand **L13**, which showed an IC_{50} of 22.97 ± 1.3 µg/mL, the metal complexes **C22** and **C23** showed greater cytotoxicity against cancer cells. **C22** complex outperformed the reference drug Vinblastine (IC_{50} = 4.02 ± 0.77 µg/mL) with greater activity, measuring 3.41 ± 0.89 µg/mL. As opposed to Vinblastine, **C23** complex demonstrated a lower level of effectiveness, with an IC_{50} of 6.81 ± 0.96 µg/mL. **C22** proved to be the most successful of the chemical compounds examined overall.[64] Talebi *et.al.,* used the ligand allylamine L14 to synthesizing the schiff base complexes Co(L14)3 (**C24**) and Ni(L14)2 (**C25**). Based on structural study, it was shown that **C24** has an octahedral geometry around its center metal ions, whereas **C25** has a square planar geometry. Utilizing the human colorectal cancer cell line SW-480, the anticancer activity of both complexes was assessed.

Researchers were evaluated the potential of these novel allyl-based metal complexes **C24–C24a** in the treatment of cancer by investigating their effectiveness and structural influence on biological activity. According to a study that looked into how different central metal ions affected the cytotoxicity of metal complexes, **C24** complex were more potent than **C24a** complex. With an IC_{50} value of 0.973 µg/mL, **C24** complex also specifically showed a substantially

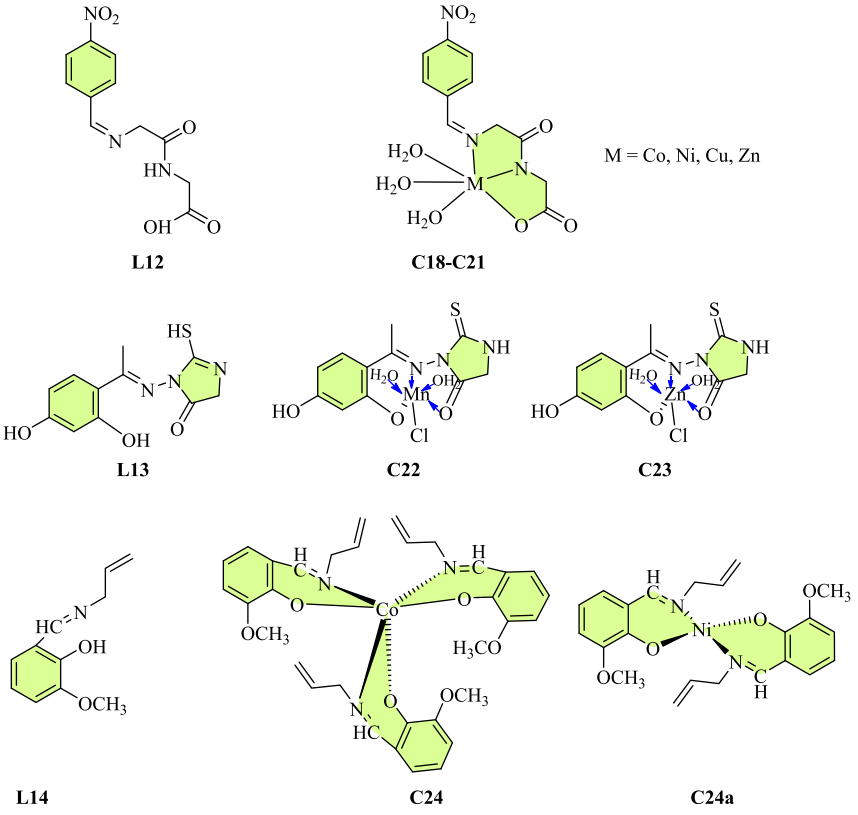

Figure 4: Structural representation of schiff base complexes **C18–C24a**.

stronger anti-cancer activity than the standard drug 5-fluorouracil, which has an IC_{50} of 5 µg/mL. This suggested that the **C24** complex inhibits cancer cell proliferation more effectively. By comparison, the anti-proliferative effects of the ligand **L14** alone and its **C24a** complex were found to be lower, with 48-h IC_{50} values of 102 µg/mL and 8.35 µg/mL, respectively (Table 1). Based on the data, increasing cytotoxic action is dependent on the ligand's structural configuration around the central metal ion. The **L14** ligand exhibited the lowest cytotoxicity of all the drugs tested, indicating a negligible anti-tumor effect. The findings highlighted the importance of ligand coordination and metal ion selection in maximizing the cytotoxic impact of metal-based anticancer drugs.[65]

3 Complexes with coordination number five

The biological significance and economic viability of therapeutic drugs containing 3 d transition metals, such as zinc(II), make them exceptionally valuable.[66,67] The combined medicinal effects of these hydrazone ligands and their zinc(II) complexes, which include antioxidant, anti-inflammatory, antibacterial, analgesic, and anticancer characteristics, make them noteworthy.[68,69] In order to change the steric factors of the 'R' group, Sanchari Dasgupta et al., were synthesized three asymmetric schiff base ligands **L15**, **L16**, and **L17** of tridentate acyl hydrazone by condensation with different aldehydes and ketones. Using conventional physicochemical techniques, the corresponding mononuclear zinc(II) complexes [Zn (L25)Cl_2]·$2H_2O$ (**C25**) [Zn (L26)Cl_2] (**C26**), and [Zn (L27)Cl_2] (**C27**) were synthesized and characterized (Figure 5).[70] Using HCT116, the complexes' anti-cancer efficacy was investigated. It was discovered that the newly synthesized zinc(II) complexes (**C25–C27**) had effective cytotoxic effect. Advantages were offered by zinc(II) including less toxicity, improved metabolic integration, decreased reactivity, and easier removal from body, it is more biocompatible and abundant than platinum.[71] The complexes exhibited superior activity

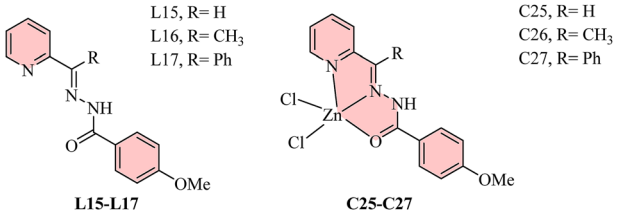

Figure 5: Penta coordinated schiff base metal complexes.

Table 2: Comparison of IC_{50} values of penta coordinated schiff base complexes (C25–C27).

Complex	Geometry	Cell line	IC_{50} Value
C25	-	HCT-116	43.70 ± 0.56 μg/mL
C26	Square pyramidal	=	38.66 ± 0.91 μg/mL
C27	=	=	70.44 ± 1.18 μg/mL

against HCT-116 in comparison to some ruthenium-based complexes.[72] Out of the three complexes, Complex **C26** exhibited the strongest anti-cancer activity, with an IC_{50} value of 38.66 ± 0.91 μg/mL as shown in Table 2. Because of its effectiveness and bio-relevance, it is regarded as a promising and reasonably priced therapeutic treatment.[70]

4 Complexes with coordination number four

As shown in Figure 6, a schiff base ligand, 2-[(5-iodo-2-hydroxybenzilidene)amino)]phenol (**L18**) was used for the synthesis of Co(II), Ni(II), Cu(II), and Zn(II) complexes (**C28–C31**) (Figure 6). The cytotoxicity studies were performed using XTT assay, The **C28–C31** complexes showed significantly enhanced cytotoxicity against HT-29 cells compared to the ligand alone. However, the **C28** complex showed cytotoxic effects similar to standard chemotherapeutic agent carboplatin (IC_{50} = 40.2 μM) with IC_{50} value of 48.9 μM (Table 3). The following was the sequence in which cytotoxicity decreased: **C28** > **C29** > **C31** > **C30**; these results underscore the potential of transition metal complexes **C28–C31** as strong cytotoxic agents in cancer therapy. The **C28** complex was more effective against cancer cells than other complexes, possibly because of its longer stability within cells as indicated by its better cytotoxic activity.[73] The ligand 2-N-(salicylidene) benzothiazole (**L19**) was used for the synthesis of complexes **C32** and **C33**. Using HT-29 cancer cells, the anticancer activity of the **L19** and complexes **C32** and **C33** was evaluated. Complex **C32** demonstrated a strong level of activity, with an IC_{50} of 258.92 μM. The anticancer properties of the **C32** and **C33** complex are probably largely attributed to active functional groups and the ethylenediamine bridge spacer. Crucially, the complexes' promise therapeutic efficacy was highlighted by their increased cytotoxicity as compared to the ligand alone before palladium was added.[74] Machado et al., recently synthesized four Co(III)-cyclopentadienyl complexes (**C34–C37**) containing N,N-heteroaromatic bidentate and phosphane ligands (**L20-L23**) respectively. Cobalt complexes may develop into effective anticancer medicines, according to a number of *in vitro* investigations.[75,76] Human fibroblasts and colorectal cancer cells (HCT-116) were used to test their *in vitro* cytotoxicity. Due to processes like the production of reactive oxygen species (ROS), the triggering of apoptosis and autophagy, and the breakdown of mitochondrial membranes, these complexes demonstrated strong cytotoxic effects against cancer cells.[77] Using the MTS test, complexes **C34–C37** were exposed to doses ranging from 0.1 to 50 μM for 48 h before their cytotoxicity against the HCT-116 colorectal cancer cell line was evaluated. Interestingly, complexes C**35–C37** showed a dose-dependent reduction in cell viability. Complex **C36** had the highest efficacy, followed by complexes **C37, C35,** and **C34** in decreasing order, according to the IC_{50} values, which showed differing degrees of cytotoxicity. The efficacy of complexes **C37** and **C36** in this cell line was correlated with the ligands' cytotoxicity, with NH_2phen (**L23**) exhibiting the highest potency (IC_{50} = 2.3 μM) and Phen (**L22**) (IC_{50} = 4.1 μM). Complex **C35** displayed an IC_{50} (15.3 μM) value that was comparable to complex **C36** (13.4 μM), although having the less cytotoxic Me_2bipy ligand (**L21**) (Table 3). Complexes **C34–C37's** antiproliferative properties were also examined in fibroblasts, which are healthy human cells. In this healthy cell line, none of the complexes (all IC_{50} > 100 μM) are cytotoxic.[78]

A new organometallic compounds **C38** was developed by Adnan et al., with Ru(II) coupled with *p*-cymene, a chlorido ligand, and a bidentate Schiff base made of N,N-dimethylethylenediamine and 4-methoxybenzaldehyde (Figure 7). By utilizing both anticancer and antibacterial activities, this complex seeks to showcase its potential in helping cancer patients with their healthcare needs. The organometallic complex's (**C38**) cytotoxic effects on the human colorectal cancer cell line CaCo-2 were assessed in this investigation. The results showed significant activity, pointing to possible therapeutic advantages in the treatment of cancer. Compound (**C38**) exhibited strong cytotoxicity against CaCo-2 cells with an IC_{50} of 2.48 μM, surpassing the effects of cisplatin, benzotriazole-functionalized N-heterocyclic carbenes, ruthenium (II) complexes (**C39–C40**),[79] and diruthenium (II,III)–ketoprofen complexes having IC_{50} = 84–165 μM.[80] On the other hand, its efficacy against human myelomonocytic tumor cells was rather mild (IC_{50} = 57.97 μM). Relative to (**C38**), thiosemicarbazone derivatives containing thiophene exhibited better cytotoxic effects.[81,82] *Hamid* et al., synthesized a novel Enro-Schiff base, H_2Enro-*o*-phdn (**L24**), and used thermal and spectroscopic tests to assess how well it chelated with lanthanum (III), zirconium (IV), yttrium (III), and iron (III). Evaluations of antibacterial activity of these chelated complexes **C41–C44** against various bacteria and fungi indicated higher effectiveness in comparison to the

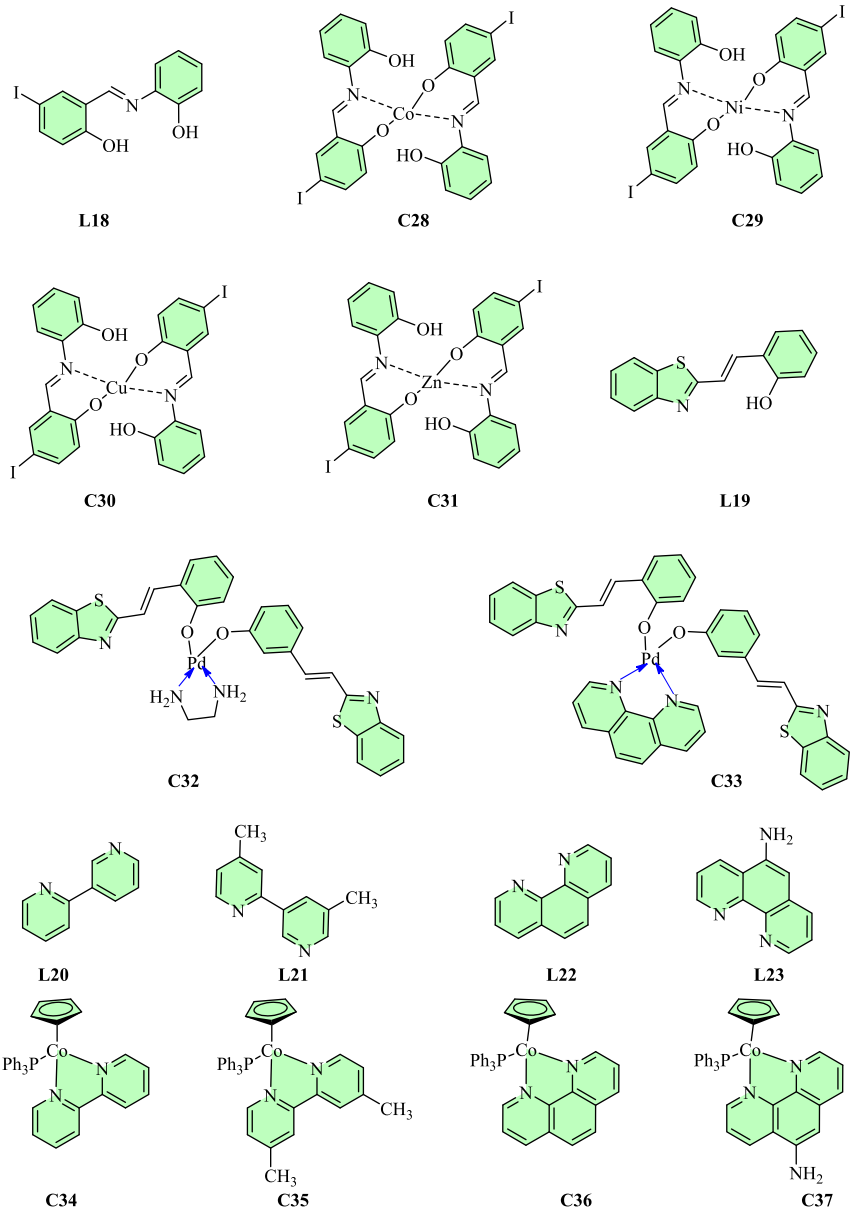

Figure 6: Structural representation of tetra coordinated schiff base complexes (**28–37**).

free ligand **L24**. Moreover, studies on CT-26 colon cancer cells were carried out to explore possible anticancer capabilities. These studies concentrated on the modification of pro-apoptotic P53 protein levels, indicating a potential function in cancer therapy.[83] Beyond conventional antibacterial uses, these results point to the dual therapeutic potential of H_2Enro-*o*-phdn complexes. According to the study, the **C42** complex outperformed cisplatin (IC_{50} = 16.77 ± 0.42 µM) in terms of anti-proliferative activity against CT-26 colon cancer cells, exhibiting the maximum level of activity at 4.03 ± 0.05 µM. Strong anticancer effects were also demonstrated by the **C44** (IC_{50} = 6.38 ± 0.06 µM) and **C41** (IC_{50} = 5.36 ± 0.34 µM) complexes (Table 3). On the other hand, **L24** by itself demonstrated cytotoxicity, with an IC_{50} of 12.06 ± 0.07 µM, which is comparable to cisplatin. The possibility of the metal complexes especially the **C41** and **C42** complexes as therapeutic agents for colon cancer has been suggested by Western blot analysis, which verified that treatment with the complexes increased P53 protein levels in CT-26 cells.[84]

Schiff bases, adaptable ligands in organic synthesis, interact with copper because of their ease of synthesis, solubility, and variety of biological activity.[85] Significant bioactivities are shown by complexes, and the selection of ligands affects bioactive properties; with increased lipophilicity, membrane penetration and effectiveness.[86,87] The MTT assay was utilized to assess the cytotoxicity of [Cu(ethylenediamine-bis-acetylacetonate)] (**C45**) and its derivatives, **C46**, **C47**, and **C48**, against LS-174 colon

Table 3: Comparison of IC_{50} values of ligands with their respective tetra coordinated metal complexes (C28–C61).

Complex	Geometry	Cell line	IC_{50} Value
L18	-	HT-29	>100 μM
C28	Tetrahedral	=	48.9 μM
C29	=	=	70.9 μM
C30	=	=	>100 μM
C31	=	=	85.8 μM
Carboplatin	-	=	40.2 μM
L19	-	=	4,557.31 μM
C32	Square planer	=	258.92 μM
C33	=	=	455.36 μM
L20	-	HCT-116	>50 μM
L21	-	=	12.4 μM
L22	-	=	4.1 μM
L23	-	=	2.3 μM
C34	Piano-stool	=	>50 μM
C35	=	=	15.3 μM
C36	=	=	13.4 μM
C37	=	=	14.1 μM
Fibroblasts	-	=	>100 μM
Cisplatin	-	=	15.6 μM
C38	Piano-stool	Caco-2	2.48 μM
C39	Distorted square planar	=	100 μM
C40	=	=	90 μM
L24	-	CT-26	12.06 μM
C41	Distorted octahedral	=	5.36 μM
C42	=	=	4.03 μM
C43	=	=	8.1 μM
C44	=	=	6.38 μM
Cisplatin	-	=	16.77 μM
C45	Tetrahedral	LS-174	15.35 μM
C46	=	=	18.79 μM
C47	=	=	15.22 μM
C48	=	=	17.47 μM
Cisplatin	-	=	24.68 μM
C49	Square planar	=	251.09 μg/mL
L26	-	Caco-2/ L-929	38.7/302.21 μM
C50	Square planar	=	31.38/285 μM
C51	Octahedral	=	100.4/206.63 μM
C52	Square planar	=	25.35/114.28 μM
5-FU	-	=	60.2/94.35 μM
C53	Square planar	LS-174	51.166/229.2 μg/mL
L28	-	HCT-116	28 μg/mL
C55	Tetrahedral	=	48 μg/mL
C56	=	=	22 μg/mL
C57	Trigonal bipyramidal	=	27 μg/mL
Cisplatin	-	=	6.92 μg/mL
C58	Square pyramidal	LoVo	6.65 μM
Cisplatin	-	=	12.36 μM
L29	-	HCT-116	156 μg/μL
C59	Square planar	=	14 μg/μL
C60	Tetrahedral	=	16.6 μg/μL
C61	Distorted square pyramidal	=	19 0.6 μg/μL

adenocarcinoma cells following a 72-h incubation period. Cisplatin was used in the trial to compare the effectiveness of each drug. Their potential as cancer therapeutic agents was highlighted by the results, which showed that the complexes exhibited various degrees of cytotoxic action. Regardless of the length of treatment, human colon cancer cells (LS-174) showed notable dose-dependent cytotoxicity towards the copper complexes **C45–C48**. Their cytotoxic potential (IC_{50} = 15.22–18.79 μM) was assessed, higher to that of cisplatin. Crucially, as compared to the reference drug, **C45–C48** complexes showed almost two times the higher selectivity towards cancer cell line LS = 174. **C47** and **C45**, with IC_{50} values of 15.22 ± 3.02 and 15.35 ± 2.66 μM, respectively, demonstrated the highest sensitivity among the investigated complexes (Table 3). In contrast, the IC_{50} value of cisplatin was 24.68 ± 3.48 μM. From these results, it can be concluded that **C47** and **C45** have a cytotoxic effect on LS-174 cells that is significantly higher than that of the standard and other manufactured Cu(II) complexes.[88] Researchers should look at molecular insights and pharmacological optimization for clinical trial development in order to fully explore their potential as anticancer drugs. Recently, scientists used the novel schiff base ligand **L25** to synthesize a platinum (II) complex (**C49**) (Figure 8). This ligand has three sites open for binding to a metal ion due to its tridentate structure. In this instance, the ligand and Pt (II) ion combine to produce a square planar **C49** complex. Through nitrogen and oxygen atoms from 6-amino penicillanic acid and a nitrogen atom from 4-amino antipyrine, the ligand coordinates with the platinum. In order to evaluate this **C49** complex's potential as an anticancer treatment, the scientists examined its effects on two different cell types: the normal VERRO cell line and the LS 174T human colon cancer cell line (CRC). The compound's cytotoxicity was measured using an MTT assay, a widely used technique for assessing cell viability. The findings showed that the **C49** complex was superior to the normal cells in preventing the formation of cancerous cells. In particular, the **C49** complex had a reasonably strong inhibitory impact against the LS 174T cancer cells, as evidenced by its IC_{50} value of 251.09 μg/mL. On the other hand, the IC_{50} value of 697.59 μg/mL for the VERRO normal cells indicates that the compound is less harmful to normal cells. This implies that the **C49** complex, with relatively less damage to normal cells, has considerable potential as an anticancer drug, especially for targeting colon cancer cells.[89] The anticancer properties of newly synthesized Cu(II) (**C50**), Ru(II) (**C51**), and Pd(II) (**C52**) complexes containing the schiff base ligand **L26** were assessed. The inhibitory effect of these complexes against

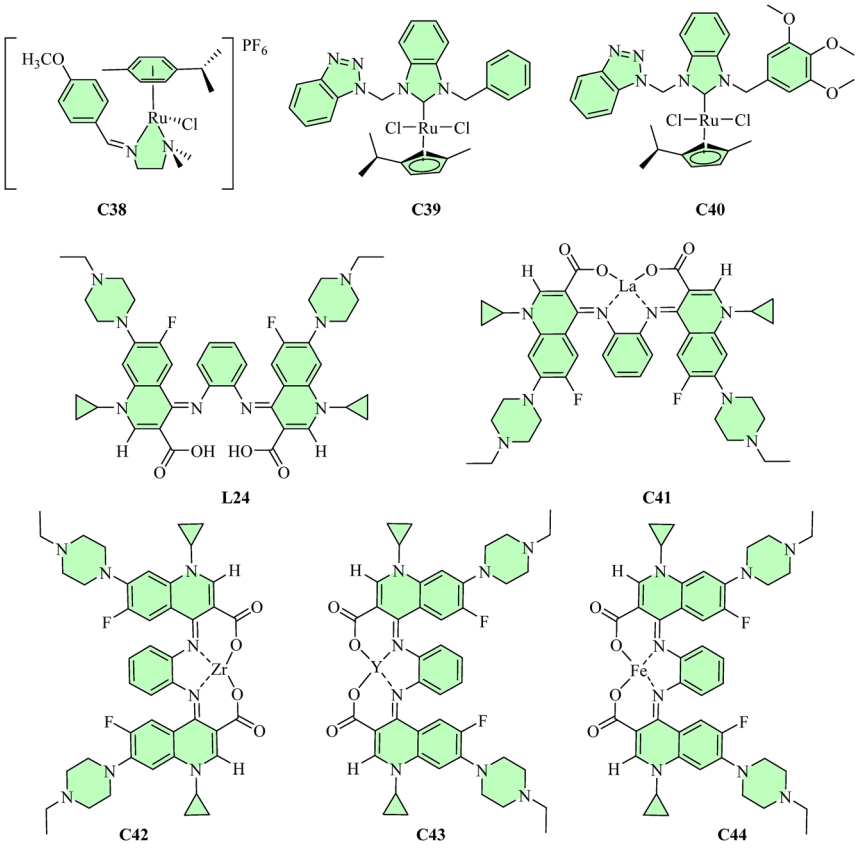

Figure 7: Structural representation of schiff base complexes (**C38–C44**).

human colon cancer cells (Caco-2) and fibroblast cells (L-929) was evaluated using *in vitro* MTT assays, and 5-fluorouracil (5-FU) was used as a reference drugs.[90] The ligand **L26** and its **C50** and **C52** complexes were found to have more potent cytotoxic effects on Caco-2 cells than 5-FU, as evidenced by their respective IC50 values of 38.7 µM, 31.88 µM, and 25.35 µM (Table 3). By comparison, the **C51** complex demonstrated reduced cytotoxicity, with an IC_{50} of 100.4 µM. The IC_{50} values for these compounds were 4–9 times greater for L-929 fibroblast cells than for Caco-2 cells, suggesting that they are selective for cancer cells. Moreover, the **C52** complex exhibited the greatest increase in activity when electroporation (EP) was investigated as a means of enhancing the anticancer effects. This implies that the ligand and its **C50** and **C52** complexes have potential as effective anticancer drugs.[91] Au (III) and Pt (II) metals were coordinated with the produced Schiff base ligand (**L27**). The ligand's azomethine nitrogen was the only way for achieving coordination for these Au (III) (**C53**) and Pt (II) (**C54**) complexes.[92] The square planar shape was adopted by the complexes (**C53–C54**), as indicated by spectral and magnetic data. The main objective of the study was to compare both the biological and toxicological impacts of the gold complex **C53** on human cells, with a particular focus on LS-174 colon cancer cells and healthy chimpanzee cells. As shown in Table 3, with an effective cytotoxicity of 51.166 µg/mL against LS-174 cells, the complex **C53** demonstrated significant selectivity for cancer cells. By comparison, the **C53** complex was substantially less hazardous to normal cells, as evidenced by the IC_{50} for healthy cells, which was 229.2685 µg/mL. This indicates that because of its strong efficiency against cancer cells and minimal effect on normal cells, **C53** complex is a good candidate for selective cancer therapy. Complexes that have basic chemical groups in their structure are much more effective at preventing the spread of disease.[93] The complex's biological efficacy is largely dependent on the β-lactam ring, which improves both its selectivity and inhibitory action.[94] In general, colon cancer can be effectively targeted by **C53** with minimal damage to normal cells.[92]

In coordination chemistry, it is essential to design Schiff base ligands from salicylaldehyde and o-vanillin, which have bidentate or multi-dentate characteristics.[95] There are several uses for these schiff bases and their metal complexes in biosensing, medicine, and catalysis.[96,97] Due to its numerous health advantages, ortho-vanillin is also well-known for its usage as a flavoring ingredient and in biological research.[98,99] With benefits over conventional techniques, microwave-assisted synthesis, a crucial component

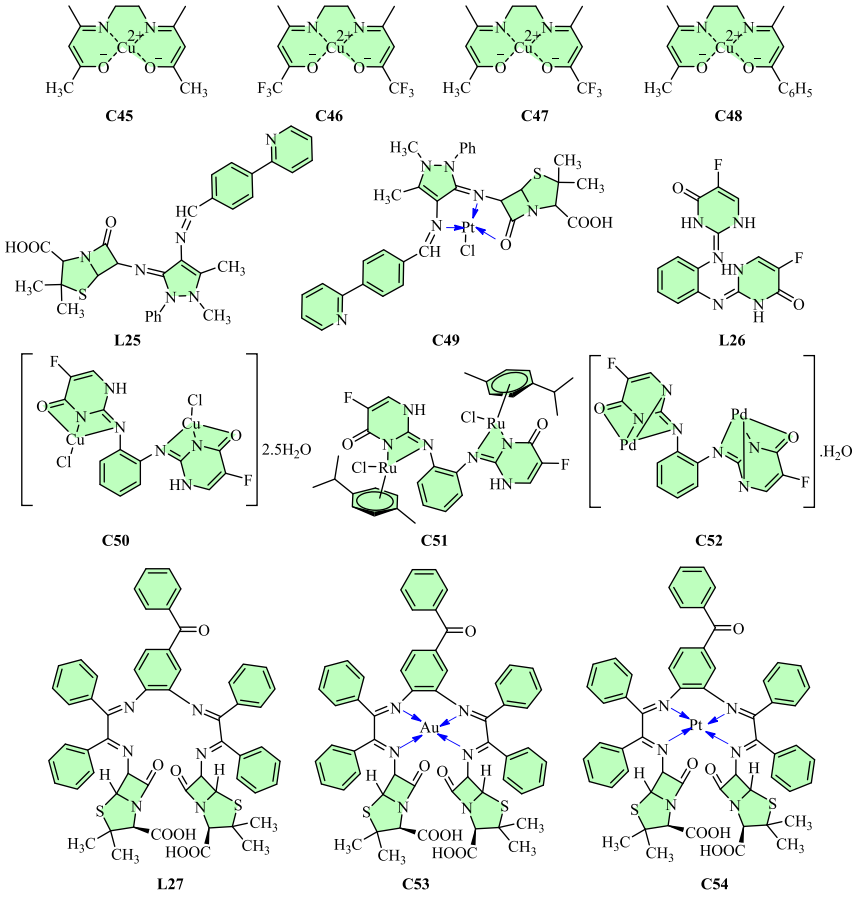

Figure 8: Tetra coordinated schiff base complexes (**C45–C54**).

of green chemistry, was utilized to synthesize a schiff base ligand **L28** from o-vanillin, 4-aminoazobenzene, and its transition metal complexes, Ni(II) (**C55**), Cu(II) (**C56**), and Zr(IV) (**C57**) (Figure 9).[100] This method increases efficiency while lowering pollutants.[101,102] Studies were conducted on HCT-116 cancer cells to examine the anticancer properties of the ligand **L28** and its metal complexes **C55–C57**. Since **C56** complex has less side effects and lower IC_{50} values than ligand **L28** and became attractive options for novel cancer therapies. **C56** complex outperformed the ligand alone in terms of cytotoxicity against HCT cancer cells among the schiff base ligand and its metal complexes **C55** and **C57**, with an IC_{50} value of 22 µg/mL. With an IC_{50} of 27 µg/mL, the **C57** complex exhibited noteworthy activity as well (Table 3). Conversely, the **C55** complex exhibited decreased efficacy and lower cytotoxicity, as evidenced by a larger IC_{50} value compared to the ligand. While **C55** complex was less useful in such circumstances, these results showed the promising potential of **C56** complex in cancer therapy with least IC_{50} value i.e., 22 µg/mL. These metal complexes' remarkable efficacy can be attributed to their capacity to bind with proteins and DNA, resulting in oxidative stress and S-phase cell cycle arrest.[103,104] **C56** complex specifically disrupts the oxidant-antioxidant equilibrium by cleaving DNA via Fenton-type reactions and oxidative stress generation.[105–107] This highlighted the possibility of Cu complexes as potent anticancer medicines by increasing the mortality of cancer cells.[100,108] A novel Schiff base Cu(II) complex, named **C58**, was synthesized by Rui-Dan Bao et al. and referred to as [N,N′-bis(2′-hydroxyphenylacetone) – o-ethanediamine] Cu(II). The cytotoxicity of **C58** was evaluated using the LoVo cancer cell line in addition to normal cell lines LO2 and HUVEC, with cisplatin serving as a reference. The IC_{50} value of **C58** against LoVo cells was determined to be 6.65 µM, which is lower than that of cisplatin (12.36 µM), suggesting that **C58** may be effective in targeting cancer cells. Moreover, **C58** demonstrated less toxic to cells in LO2 and HUVEC cells (6.27 µM and 11.68 µM) compared to cisplatin (2.61 µM and 2.01 µM), suggesting that **C58** may provide reduced systemic toxicity in comparison to cisplatin.[109] The N_3-tridentate imine ligand 2,6-diacetylpyridinediphenylhydrazone (**L29**) was utilized in the synthesis of Pd(II), Ag(I), and Vo(IV) metal complexes. Square planar geometry was displayed by the Pd(II) complex (**C59**), tetrahedral geometry by the Ag(I) complex (**C60**), and a distorted square pyramidal structure by the Vo(IV) complex (**C61**). Cytotoxic potential of these complexes **C59–C34** was

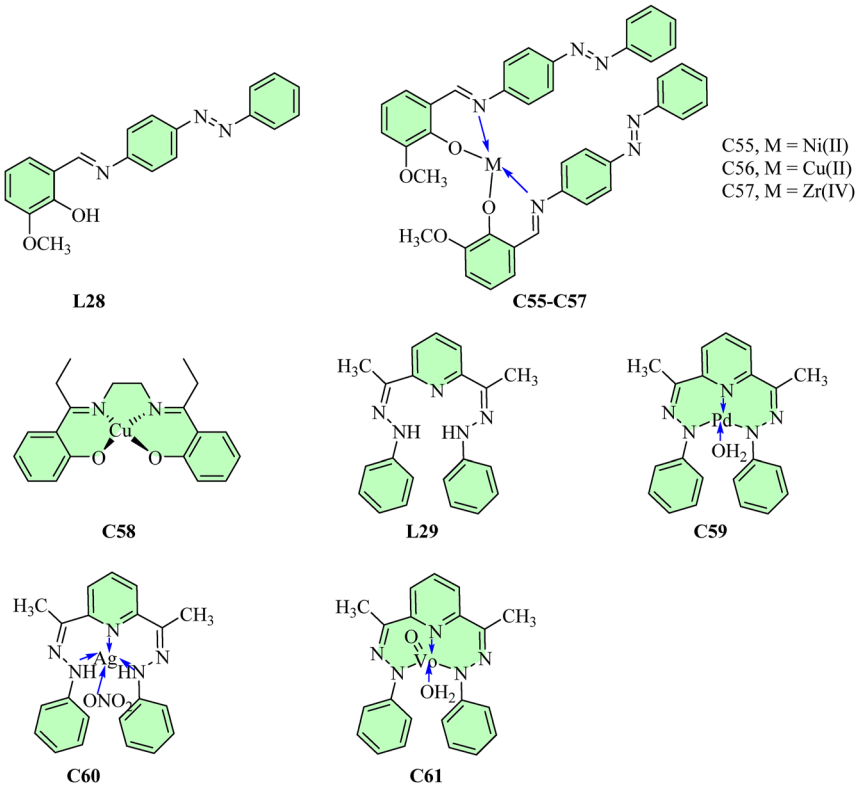

Figure 9: Structural representation of tetra coordinated schiff base complexes (**C55–C61**).

evaluated by sulfo-rhodamine-B (SRB) staining on HCT-116 human colon cancer cells. These metal complexes **C59–C61** show promise for treating cancer, as demonstrated by the activity's comparison to the standard drug vinblastine.[110] According to Tweedy's chelation concept, the central metal atom's identity affects the cytotoxic potential of metal complexes. The interaction of the complex with biological targets can be influenced by the distinctive features of the central metal. For the complex to be successful in cytotoxicity, the metal choice is essential.[111,112] After assessing the cytotoxicity of metal chelates on cancer cells, it was found that the **C59** complex had the highest potency, with an IC_{50} of 14 µg/µL, followed by the **C60** and **C61** complexes, which had IC_{50s} of 16.6 and 19.6 µg/µL, respectively (Table 3). In contrast, the cytotoxicity of the unbound L12 ligand was substantially lower, with an IC_{50} of 156 µg/µL. As a result, **C59** > **C60** > **C61** > **L29** was the sequence in which cytotoxicity increased, suggesting that metal chelates are more potent than free ligand.[113]

5 Schiff base bridging complexes

Cu(II)–terpyridine complexes have garnered attention recently due to their increased stability and capacity to interact with DNA through major groove binding and π-stacking.[114–119] By regulating complex geometry and ROS production, structural changes of 2,2′:6′,2″-terpyridine derivatives affect cytotoxicity rates.[120–123] In contrast to non-cytotoxic [$CuCl_2$(R-terpy)], cytotoxic Cu(4′-(2-quinolinyl)-terpy)Cl promotes apoptosis and has low toxicity *in vivo*.[122] Through structural analysis and biological evaluation, the researcher emphasizes [Cu_2Cl_2(R-terpy)$_2$](PF_6)$_2$ complexes (**C62–C65**) and explored their potential as potent and selective anticancer agents. The R-terpy ligands (**L30-L33**) reliably attaches to the Cu(II) ion through three nitrogen atoms in the terpyridine framework in the Cu(II) complexes that are studied, providing stable coordination (Figure 10). This coordination mechanism influences the complexes' anticancer potential by improving their stability and facilitating interactions with DNA. The MTS test was utilized to examine the cytotoxicity of **C62–C65** complexes. This colorimetric approach evaluates cell viability based on metabolic activity.[124] **C62–C65** complexes exhibit strong cytotoxicity against the colorectal cancer cell lines HCT-116 and HCT116DoxR, with IC_{50} values ranging from 0.1 to 0.3 µM (Table 4). This suggests that the more resistant HCT116DoxR line is more effective. Typically, HCT-116 has larger IC_{50} values than HCT116DoxR, indicating that the latter has more antiproliferative action. Furthermore, the Dox-sensitive line's IC_{50} values are less than those of cisplatin (15.60 µM) and Doxorubicin (Dox) (>0.6 µM), highlighting their potential as potent agents, especially in overcoming Dox resistance in HCT116DoxR cells. Comparing the IC_{50} values in

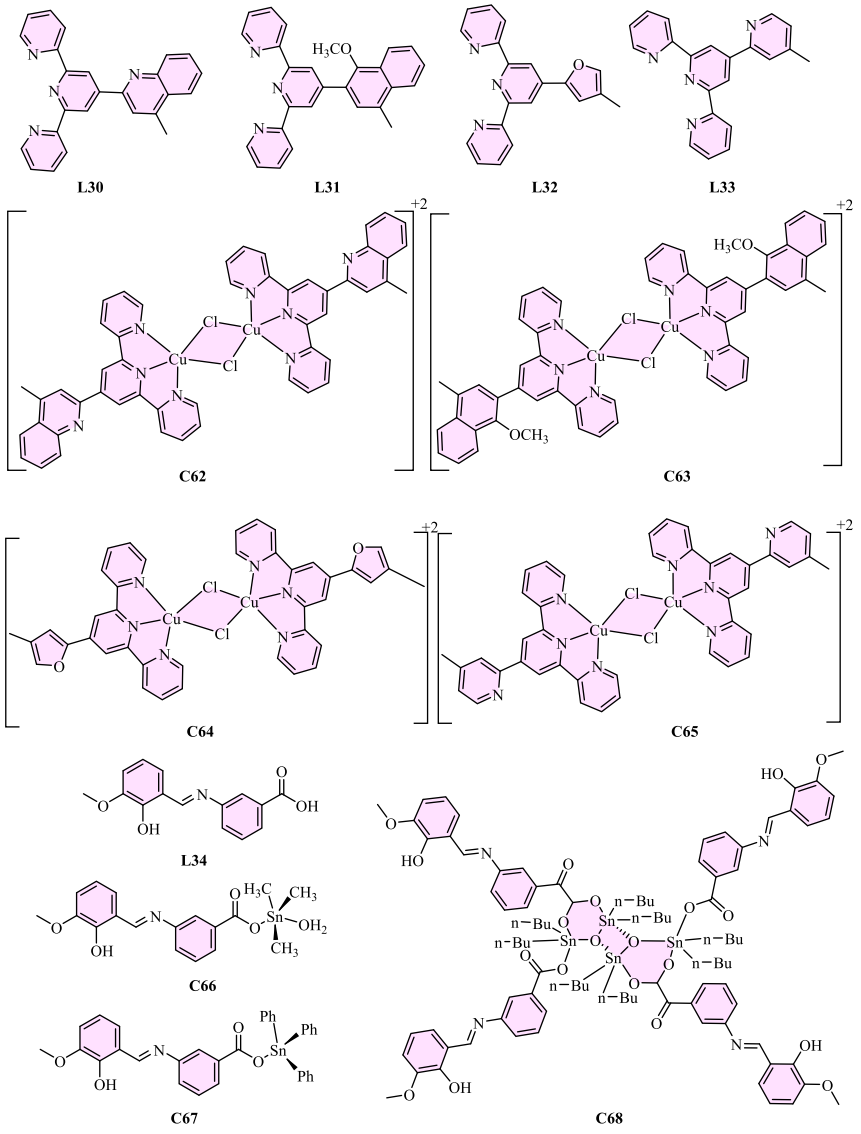

Figure 10: Structural representation of schiff base bridging complexes.

HCT116DoxR, it is evident that complexes **C62**, **C64**, and **C65** reflect the high specificity shown by ligands **L30**, **L32**, and **L33**, suggesting a significant antiproliferative effect. HCT116DoxR selectivity is improved by the coordination of ligands **L30** and **L32** with Cu(II) and chlorine, underscoring their potential for specific cancer treatment.[125] Schiff base carboxylic acid ligand (**L34**) were used for the production of three novel organotin (IV) complexes [$Me_3Sn(L5)$ (H_2O)] (**C66**) [$Ph_3Sn(L5)$] (**C67**), and [({[$(n\text{-}Bu)_2Sn(L5)]_2O$}$_2$] (**C68**). A deformed trigonal bipyramidal geometry with three Me groups in the equatorial plane and two O atoms in axial positions characterizes the five-coordinate tin atom in **C66**.[126] Three phenyl ipso-C atoms and one carboxylate O-atom coordinate tin in **C67**, which has a deformed tetrahedral shape. With a Sn_2O_2 four-membered ring, **C68** is a centrosymmetric dimer consisting of four tin atoms connected by two bridging carboxyl groups and two extra groups functioning as monodentate ligands.[127] Chemotherapy resistance is a significant problem in cancer treatment; although Sn(IV) complexes exhibit potential against cancer cells, their effectiveness against chemotherapy-resistant cells has not received as much attention.[128,129] Thus, the investigator concentrated on assessing the cytotoxicity of these complexes in cancer cells resistant to cisplatin 130. The *in vitro* cytotoxic activity of complexes **C66–C68** was assessed against three colon cancer cell lines (Caco-2, HCT-116, HT-29) resistant to cisplatin. Previous research has shown that the organo-ligand R (Me, Ph, n-Bu) bonded to the tin atom is crucial.[131] The phenyl and butyl derivatives (**C67, C68**) showed considerable activity, whereas the methyl derivative (**C66**) showed weak cytotoxicity among the tested Sn(IV) complexes. When studied

Table 4: Comparison of IC_{50} values of schiff base ligands with their bridging complexes.

Compound	Geometry	IC_{50} (μM)			
		HCT-116	HCT116DoxR	CaCo-2	HT-29
L30	-	-	0.40 ± 0.02	-	-
L31	-	-	0.20 ± 0.02	-	-
L32	-	-	0.60 ± 0.02	-	-
L33	-	-	0.50 ± 0.06	-	-
C62	-	0.31 ± 0.01	0.25 ± 0.02	-	-
C63	-	0.13 ± 0.02	0.15 ± 0.01	-	-
C64	-	0.26 ± 0.03	0.22 ± 0.01	-	-
C65	-	0.23 ± 0.01	0.19 ± 0.01	-	-
Dox	-	0.50 ± 0.10	>6	-	-
Cisplatin	-	15.60 ± 5.30	-	-	-
L34	-	>37	-	>37	>37
C66	Trigonal bipyramidal	18.90 ± 1.23	-	22.10 ± 0.18	29.23 ± 0.38
C67	Deformed tetrahedral	0.11 ± 0.01	-	0.46 ± 0.13	0.22 ± 0.02
C68	-	0.03 ± 0.01	-	0.59 ± 0.19	0.85 ± 0.15
Cisplatin	-	>33	-	>33	>33

against the same tumor cell lines, all complexes showed higher inhibitory effects than cisplatin. The result showed that complex **C67** was most effective against Caco-2 and HT-29 cell lines, the di-n-butyltin (IV) complex **C68** exhibits the best cytotoxic activity against HCT-116 cells (Table 4). Complex **C68**'s steric hindrance restricts the efficacy, while complex **C67**'s increased activity is probably attributed to fewer coordination sites that facilitate the synthesis of the active Ph_3Sn^+(IV) moiety.[132] Complex **C66** lower cytotoxicity attributed to its ability to form a 1D supramolecular chain due to presence of intramolecular H-bonds. Tin atoms play a crucial part in the cytotoxicity of the complexes, as evidenced by the Schiff base ligand's minimal effectiveness when used alone against cancer cells.[133]

6 Schiff base mixed ligand complexes

Symmetrical schiff-base ligands (SBLs) despite their difficult synthesis from aliphatic diamines, provide precise stereo-electronic fine-tuning, making them ideal for modifying the properties of transition-metal complexes. SBLs are advantageous for metallo-medicinal chemistry because of their easy synthesis and variable electro-steric properties with substituents.[134,135] Copper complexes are being investigated extensively as possible anticancer drugs, particularly those with N and O donor ligands such as SBLs. The development of these drugs was inspired by the higher uptake of copper by cancer cells in comparison to normal cells, with the goal of enhancing effectiveness and minimizing side effects in contrast to conventional treatments such as cisplatin.[136,137] Through increasing cellular uptake and triggering apoptosis, mixed-ligand copper complexes that incorporate unsymmetrical SBLs with N-donor co-ligands such as 2,2′-bipyridine (bpy) and 1,10-phenanthroline (phen) have strong anticancer potential.[138] Research conducted by *Zhang* et al., highlights the role that phen plays as a facilitator in these complexes, which helps them to have better biological activities than conventional anticancer drugs like cisplatin.[139,140] As shown in Figure 11, researcher were synthesized novel Cu(II) complexes **C69–C71** with a tridentate NN′O type unsymmetrical Schiff-base primary ligand and a co-ligand py in (**C69**), bpy in (**C70**), and phen in (**C71**) on the basis of previously reported literature.[141,142] The formation of the schiff base comes from the condensation of 1,3-propanediamine with 2-hydroxy-4-methoxybenzaldehyde during the synthesis of complexes. The antitumor activity of the complexes was assessed in Human Colorectal (HCT-116) cells. Complexes **C69–C71** demonstrated dose-dependent cytotoxic effects over 24 and 48 h, with extended incubation times exhibiting increased efficacy. After being incubated for 24 and 48 h, complex C70 showed the highest level of cytotoxicity among complexes **C69, C70,** and **C71**, as evidenced by its lower IC_{50} values in comparison to the other compounds. These IC_{50} values were likewise smaller or on level with those of 5-FU, a popular chemotherapy drug. More specifically, complex **C70** may be a powerful anticancer agent because its IC_{50} value were lower than those of oxaliplatin standard drug at incubation time period of 24 h (Table 5). Its therapeutic potential and mode of action need to be completely explored through more research.[143–145]

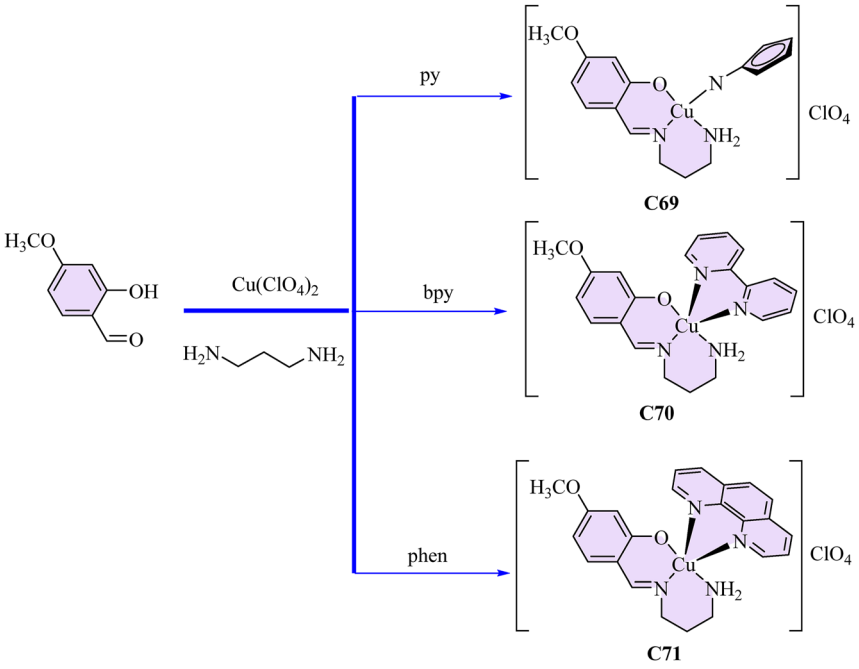

Figure 11: Synthesis of schiff base mixed ligand metal complexes (**C69–C71**).

Table 5: Time dependent comparison of IC_{50} values of mixed ligand metal complexes.

Compound	Geometry	Cell line	IC_{50} (μM)	
			24 h	48 h
C69	-	HCT-116	55.46	37.88
C70	Square-based pyramidal	=	8.98	7.82
C71	-	=	97.95	29.43
5-FU	-	=	84.21	36.9
Oxaliplatin	-	=	17.4	5.56

7 Conclusions

Focusing on studies published in the last five years that emphasize the chemical structures of schiff base metal complexes, this review investigates their potential involvement in the fight against colorectal cancer. In addition to their well-documented therapeutic benefits, schiff bases are well-known for their efficient ability to form complexes with transition metals. Some of the metals that are frequently utilized in these complexes and are of pharmaceutical significance are identified in this review. These metals include zinc, palladium, manganese, copper, vanadium, nickel, platinum, chromium, cobalt, silver, rubidium, and iron. Schiff base metal complexes with oxidation states of +4, +5, +6, alongside the bridging as well as mixed ligand have been primarily highlighted in the review. As a result of their distinct geometries and notable thermodynamic stability, the +4 and +6 states have received the majority of attention in recent time. In addition to providing IC_{50} values and structural representations to clarify the effects of various substituent groups on their efficiency, the review details the cytotoxic activity of these complexes against colon cancer cell lines. The bridging complexes showed the strongest cytotoxic activity among all of them. On the other hand, complexes with coordination number +6 were more active than those with number +4. Less cytotoxic action was seen in complexes with coordination number +5. The IC_{50} values reveal that Sn complexes in bridging mode were more cytotoxic than Cu; period 5 transition metals with oxidation state +4, such as Zr, Y, and Ru, having more potential; Zn and Mn complexes were the most cytotoxic among metals with oxidation state +6. Moreover, it has been observed that metal complexes of Schiff bases, as opposed to Schiff base ligands alone, are more successful in inhibiting colon cancer cell invasion and growth. The review presents an in-depth understanding of the cytotoxic potential of these complexes by incorporating contemporary literature. Future multidisciplinary research in this developing field appears to have a lot of potential, especially when it comes to synthesizing new Schiff base metal complexes that have improved bioavailability, minimum toxicity, and solubility. These developments may have a major impact on the production of more potent colorectal cancer treatments.

Research ethics: Not applicable.
Informed consent: Not applicable.
Author contributions: Afaf Murtadha Kadhum: Writing-original draft, Software. Shaimaa Hassan Mallah: Resources and Validation. Azal Shakir Waheeb: Data curation, Visualization. Abbas Washeel Salman: Review and editing, Software. Ayesha Zafar: Review and formatting. Nafees Sajjad Ahamd: Validation and review. Saira Siraj: Grammatical and formal analysis. Muhammad Adnan Iqbal; Conceptualization, Resources, Supervision, Overall guidance.
Use of Large Language Models, AI and Machine Learning Tools: None declared.
Conflict of interests: The authors declare no conflict of interest.
Research funding: The authors are thankful to the Pakistan Science Foundation (PSF) for awarding the research grant PSF/Cons/676.
Data availability: Data will be provided on demand.

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