Review Paper:

Schiff Bases and their Metal Complexes as Potential Anticancer Agents: A Critical Review

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Abstract

Schiff bases are celebrated ligands in coordination chemistry due to their strong chelating behavior which enables them to form stable complexes with transition metal ions of various oxidation states. This versatility makes them valuable in diverse fields ranging from catalysis to materials science and medicinal chemistry with low toxicity concerns. Platinum-based drugs like cisplatin have been instrumental in cancer treatment but they come with significant side effects and limitations such as resistance development. Non-platinum metal-based anticancer agents offer a promising alternative due to their potentially different mechanisms of action and ability to overcome resistance.

Some of the metal complexes can indeed interact with cells and trigger various responses including the activation of transcription factors and signaling pathways. These interactions can lead to several downstream effects within cancer cells such as cellular signal transduction pathways leading to apoptosis and the activation of tumor suppressor genes, cell-cycle arrest, cytotoxic effects and modulation of cellular adhesive molecules. For anticancer drugs, the focus might be on inhibiting enzymes involved in cancer cell proliferation or interfering with cellular processes specific to cancer cells. By modifying the structure of Schiff bases, medicinal chemists can fine-tune their interactions with these specific targets, optimizing efficacy against the cancer while minimizing side effects on healthy cells. This flexibility makes Schiff bases promising candidates for drug development and cancer treatment. This review highlights anticancer activities of some selected Schiff base ligands and their metal complexes.

Keywords: Schiff Base, Metal complexes, Biological applications, Anti-cancer activity.

Introduction

Tremendous interest is growing among researcher's worldwide to do further research in synthesis of Schiff base and their metal complexes and in addition, its diverse biological activities glorify it as a privileged ligand in co-ordination chemistry. Various research groups are exploring their potential applications in the field of pharmaceutical and medicinal chemistry[6,11,39,49,59,71,73]. Schiff base and their metal complexes are flexible compounds synthesized from the condensation of an amino compound with carbonyl compounds followed by treatment with metal halides/nitrates/acetates etc. The general method used for the synthesis of Schiff base is treatment of ketone or aldehyde with primary amine. First step is condensation of carbonyl compounds and primary amine resulting in formation of unstable carbinolamine intermediate and second step is formation of immine with expulsion of water from the intermediate.

Furthermore, transition metal ions can easily form bonds with nitrogen atom of imine producing stable complexes having geometries such as tetrahedral, square planar, octahedral geometry where central metal ions are embedded by the ligands. In fact, hydrazone acts as ligands depending on number donor groups attached to it, when unidentate ligand means single donor N-atom but subgroups attached either with C or with N of the azomethine group facilitate them to act as bidentate (N, O), tridentate (N, O, C=O/C=S, N, S) or tetradentate (O/S, N, N, O/S) ligands as can be depicted in scheme 1 with various kinds of metal ions[21,53,57,65,66]. The presence of –N=C– moiety is mainly responsible for the biological activity of hydrazone.

The compounds having this moiety represent a versatile class of compounds as pharmaceutical and medicinal agents with a wide range of pharmacological activity including anti-inflammatory[67], antitumor[70], anticancer[27,46,78], antimalarial[22,75], antimicrobial and antiprotozoal agent[10,14,56], antiviral[12,35] and anthelmintic[34] properties. However, the biological activity and the applications of Schiff bases and their metal complexes mainly depend upon a large extent to their molecular structure and the kinds of central metal ions. Various groups have been also working on designing flexible polydentate Schiff base compounds for material science, organic synthesis, catalytic and biological applications[33,43,52].

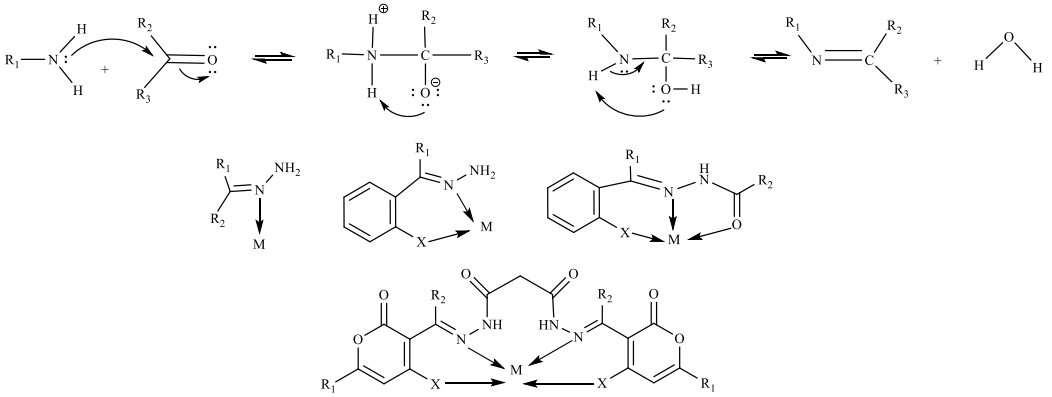
The Schiff base ligands were also used in analytical chemistry due to their strong complexation ability with various metal ions. Schiff bases were also used as a stereo-dynamic chemo-sensor[15,19] in food and beverage industries[32] as dye and pigments[7,42] etc. It was observed that few biologically active drugs are used for treatment of cancer. Furthermore, the majority of metals are toxic to the human body since they can also cause adverse effects when present in excessive levels and its excretion is not easier from the biological system. Metal ions bind to proteins and enzymes,

altering their activity and causing damage and carcinogenesis. It also causes neurotoxicity, generates free radical which facilitates oxidative stress thereby damaging lipids, proteins and DNA molecules. Elevated level of Reactive oxygen species (ROS) induces apoptosis in various cancer cells due to interfering into mitochondrial metabolism.

Increase in intracellular ROS can lead to mitochondrial dysfunction, causes DNA damage and eventually induce apoptosis. Overall, the ease of synthesis, metal complexation potential and vast application range make Schiff bases a promising area of research with the potential to significantly impact our lives. This review provides current information about the biological applications of Schiff bases and their transition metal complexes. It provides information regarding the potent anticancer activities of Schiff base metal complexes of Cr(III), Mn(II), Fe(II), Fe(III), Ru(II), Co(II), Ni(II), Cu(II), Zn(II), Zn(III), Cd(II), Zr=O(IV), V=O(V), Pt(II), La(III), Er(III), Yb(III), Gd(III), Sm(III), Nd(III) and UO_2(IV) and can also be beneficial for researchers in designing and synthesizing pharmaceutically active compounds.

Anticancer activity of some of the selected Schiff base transition metal complexes: Correia et al[13] synthesized a series of five copper(II) complexes, [Cu(sal-Gly)(bipy)](1), [Cu(sal-Gly)(phen)] (2), [Cu(sal-L-Ala)(phen)] (3), [Cu(sal-D-Ala)(phen)] (4), [Cu(sal-L-Phe)(phen)] (5) and five oxidovanadium(IV) complexes, [VO(sal-Gly)(bipy)] (6), [VO(sal-Gly)(phen)] (7), [VO(sal-L-Phe)(H_2O)] (8), [VO(sal-L-Phe)(bipy)] (9), [VO(sal-L-Phe)(phen)] (10) (sal = salicylaldehyde, bipy = 2,2′-bipyridine, phen = 1,10-phenanthroline).

The cytotoxicity of these complexes against distinct human cancer cell types (human MCF7 breast and A2780 ovarian cancer cells) over varying incubation times was carried out with reference to Cisplatin. More attention was paid for complexes (1), (2), (5) on HL60 (human promyelocytic leukemia cells) and HeLa (human cervical cancer cells). It is clear from the table 1 that all the complexes show cytotoxicity against different human tumor cell lines but compound (5) demonstrated superior inhibitory activities against MCF7 breast, A2780 ovarian, HL60 and HeLa, even outperforming cisplatin.



Scheme 1: General schemes for formation of Schiff bases and Hydrazone having mono-(N), bi-(N, S/N/O) or tri-(N/S/O, N, O) and tetra-(O/S,N,N,O/S) dentate ligands with metal ion

Table 1
Cytotoxic activity (IC_{50} values) of the (1-10) and reference drug Cisplatin for 24 h and 72 h against different cancer cell lines.

Compound No.	A2780	MCF7	HL-60		HeLa	
	72 h	72h	24h	72h	24h	72h
(1)	5.5 ± 1.9	52 ± 16	12.3 ± 7.6	12.6 ± 9.5	6.4 ± 24.4	14.4 ± 8.9
(2)	3.2 ± 0.7	1.6 ± 0.3	6.3 ± 1.9	4.39 ± 1.43	7.1 ± 1.43	6.3 ± 2.0
(3)	0.75 ± 0.2	2.5 ± 0.6				
(4)	0.54 ± 0.2	2.7± 0.8				
(5)	0.29 ± 0.01	3.5± 1.2	4.0 ± 1.3	1.51 ± 0.37	5.1 ± 1.4	4.2 ± 0.6
(6)	20.8 ± 0.5	53 ± 20				
(7)	4.9 ± 1.3	77 ± 13				
(8)	14.1 ± 3.9	57 ± 16				
(9)	17.1 ± 3.9	95 ± 37				
(10)	4.7 ± 1.8	68 ± 14				
Cisplatin	2.5 ± 0.1	28 ± 6.0	15.6 ± 1.2	2.2 + 0.1	20	4

Furthermore, Cu(II) complexes ligated with 1,10-phenanthroline exhibited lower IC_{50} values than the corresponding vanadium analogues and the reference drug cisplatin. Phenanthroline based complexes are better DNA intercalator, bring Cu nearer to sugar molecules, which facilitate ROS attack than the bipy containing complexes. DNA photo-clevage activity studies showed that complexes (2) and (5) are the most efficient DNA cleavage agent, they can cleave DNA even in the absence of activating agents. Most of the complexes show cytotoxicity against different human tumor cell lines. The measured cytotoxicity and DNA cleavage ability showed that [Cu(sal-L-Phe)(phen)] (5) is the most active against all the cancer lines that is 10-times more cytotoxic than reference drug cisplatin. Amongst vanadium complexes, (7) and (10) are more potent against A2780 ovarian cancer cells. In general, the Cu(II) complexes showed much lower IC_{50} values (higher cytotoxic activity) than the corresponding vanadium complexes and even lower than the reference drug cisplatin. In this series, Saeed et al[64] synthesized five Schiff base compounds, derived from 3-amino-4-hydroxy-2H-pyrano[3,2-c]quinoline-2,5(6H)-dion e (11-15) and their anticancer activities were investigated against HepG2 liver cancer, HCT-116 colon carcinoma and MCF-7 breast cancer lines where 5-fluorouracil was used as a reference drug. All the cancer cell lines like HepG2, HCT-116 and MCF-7 were incubated with tested compound for 24 h.

The results revealed that most of the compounds inhibited cell proliferation, some of them were even showing comparable activity with respect to reference drug as depicted in table 2. The order of anticancer activity exhibited by compounds **(**11-15) are as: (15) > (12) > (13) > (14) > (11); (15) > (12) > (13) > (11) > (14) and (15) > (12) > (13) > (11) > (14) against HePG-2, HCT-116 and MCF-7, respectively. The compound (15) demonstrated highest anti-proliferative activity with IC_{50} values (µg/mL) 1.82, 6.49 and 8.06 against HepG2, HCT-116 and MCF-7 respectively that is three times more than the reference drug 5-fluorouracil under the same cancer lines (IC_{50} value 6.44, 21.5 and 28).

The order of lipophilicity is denoted as: F < CF_3 < OCF_3 < SCF_3. The main factor responsible for increase in lipophilicity may be due to the presence of the O–CF_3 substituent which lies orthogonally to the aromatic plane in para position of Schiff base (15) as well as the azo group attached to aryl system facilitates to bind the active site of the target protein causing the inhibition of DNA, RNA and protein synthesis[41,54,60].

A series of Cu(II) complexes (16-19) was reported with the Schiff bases which were derived from the Chiral (D/L) N-(2-hydroxy-1-naphthylidene)valine and (D/L) N-(2-hydroxy-1-naphthylidene)phenylalanine by Zehra et al[81]. These complexes were screened against MCF-7, HeLa and MIA-Pa-Ca-2 cell lines by the SRB assay. Results showed that metal complexes exhibited good anticancer activity with the lethal concentration LC_{50} (in µM) values of > 8, > 8 >, 8 and < 1; > 8, > 8 >, 8 and < 1; 2.44, 3.81, 5.05 and < 1; < 1, 1.66, 5.66 and < 1 against MCF-7, HeLa and MIA-Pa-Ca-2 cell lines for (16-19) and adriamycin as standard drug respectively.

The L-enantiomeric Cu(II) complex (19) displayed highest cytotoxicity with a significantly lowest GI_{50} value less than 1 µM against MCF-7 as compared to its D-enantiomer which showed GI_{50} value 2.44 µM against identical cell line. The higher cytotoxicity activity was attributed to the increased lipophilicity of chelated L-enantiomeric Cu(II) (19) having planar phenylalanine moiety for their easy passage in the bio membrane as well as it binds with the tRNA molecule, followed by D-enantiomeric Cu(II) (18). The cytotoxicity of (19) supported by DNA photocleavage studies showed efficient cleavage at low micromolar concentration (40 µM). The reduction in activity for the enantiomeric complexes (16) and (17) may be attributed due to their polymeric nature.

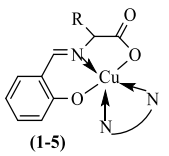
The compound (19) may warrant further biological investigation for the future designing of new chiral copper-based antitumor drug. Moghadam et al[47] prepared Schiff base ligand by condensation reaction of 4-acyl-3-methyl-1-phenyl-2-pyrazolin-5-one (acylpyrazolone) with phenylene diamine derivative to produce HL^1 (20), HL^2 (21), HL^3 (22), which on subsequent treatment with [K_2PtCl_4] form [PtL^1Cl] (23), [PtL^2Cl] (24) and [PtL^3Cl] (25). The anticancer activity was studied by the MTT method towards human breast cancer cell lines SKBR3 and MDA-MB-231. Results showed that metal complexes revealed good anticancer activity with the IC_{50} (in µM) values of (35±2 and 24±2); (43±1 and 34±2); (65±3 and 59±4) against SKBR3 and MDA-MB-231 cell lines for (23-25) respectively.

Table 2
Cytotoxicity (IC_{50}) of compounds (11-15) against HePG-2 (human liver cancer) HCT-116 (human colon cancer), MCF-7 (breast cancer)

Complexes	IC_{50} (µg/mL)			Complexes	IC_{50} (µg/mL)		
	HePG-2	HCT-116	MCF-7		HePG-2	HCT-116	MCF-7
	24 h	24 h	24 h		24 h	24 h	24 h
(11)	11.6	28.6	15.2	(14)	7.74	60.9	24.2
(12)	3.07	7.25	11.26	(15)	**1.82**	**6.49**	**8.06**
(13)	5.29	9.92	13.76	5-fluoro uracil	6.44	21.5	28

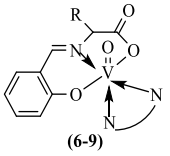
The complexes (23) and (24) demonstrated highest anticancer activity against SKBR3 and MDA-MB-231 cell lines respectively more effective than the reference drug carboplatin under the same cancer lines (IC_{50} value 45±4 and 38±3) but less effective than cisplatin (IC_{50} value 26±1 and 17±2). It means IC_{50} values of complex (23) and (24) found were higher than cisplatin against cancer cells MDA-MB-231 and SKBR3 and lower than carboplatin, whereas the IC_{50} value of (25) was highest of all, even higher than both the platinum drugs. The order of increasing hydrocarbon chains in (23) < (24) < (25) should facilitate increasing both lipophilicity and cytotoxicity.

But it displayed inverse cytotoxic effect where the order of cytotoxicity of the complex is (23) > (24) > (25) in suppressing SKBR3 and MDA-MB-231 cell growth, followed by lowering the cytotoxicity of the complexes and increasing the IC_{50} value. All the three metal complexes (23-25) comprised of N, N, O-donor ligand and one terminal Chloride whereas, Pt(II) of cisplatin was having two terminal donor N of NH_3 and two Cl group. It displayed that chelated metal complexes (23-25) boosted stability and lipophilicity in comparison to cisplatin, thereby, metal complexes easily penetrate into the cell membrane leading to death of cancer cells. They may act as suitable candidate in advanced anticancer research.

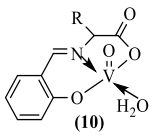


(1-5)

[Cu(sal-Gly)(bipy)] R = H, N-N = bipy **(1)**,
[Cu(sal-Gly)(phen)] R = H, N-N = phen **(2)**,
[Cu(sal-L-Ala)(phen)] R = CH_3, N-N = phen **(3)**,
[Cu(sal-D-Ala)(phen)] R = CH_3, N-N = phen **(4)**,
[Cu(sal-L-Phe)(phen)] R = CH_2-C_6H_5, N-N = phen **(5)**

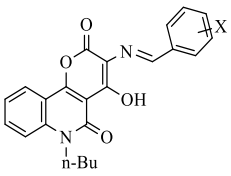


(6-9)

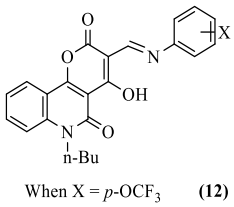


(10)

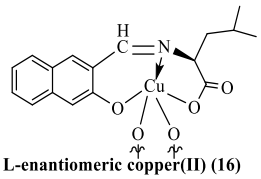
[VO(sal-Gly)(bipy)] R = H, N-N = bipy **(6)**,
[VO(sal-Gly)(phen)] R = H, N-N = phen **(7)**,
[VO(sal-L-Phe)(bipy)] R = CH_2-C_6H_5,, N-N = bipy **(8)**,
[VO(sal-L-Phe)(phen)] R = CH_2-C_6H_5, N-N = phen **(9)**,
[VO(sal-L-Phe)(H_2O)] R = CH_2-C_6H_5, **(10)**



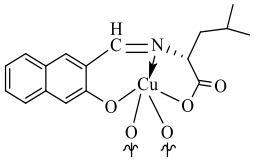
When X = *m*-F **(11)**



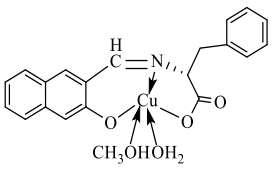
When X = *p*-OCF_3 **(12)**
When X = *m*-CF_3 **(13)**



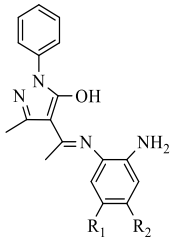
L-enantiomeric copper(II) (16)



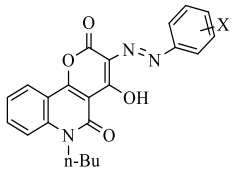
D-enantiomeric copper(II) (17)



D-enantiomeric copper(II) (18)

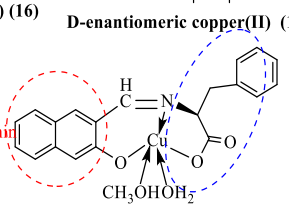


HL^1 (R_1= R_2 = H) **(20)**
HL^2(R_1= H, R_2 = CH_3) **(21)**
HL^3 (R_1= R_2 = CH_3) **(22)**



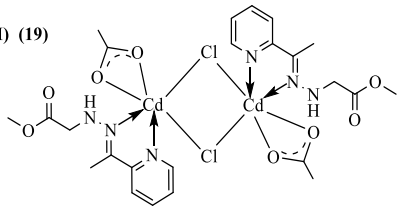
When X = *m*-F **(14)**
When X = *p*-OCF_3 **(15)**

Presence of aromatic group facilitates intercalation within the nucleobases

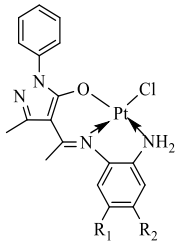


L-enantiomeric copper(II) (19)

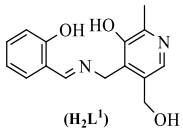
Presence of aromatic amino acid group mainly targets tRNA and increases lipophilicity



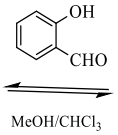
$[Cd_2Cl_2(AcO)_2(aphaOMe)_2]$ **(26)**



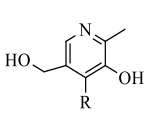
$[PtL^1Cl]$ (R_1= R_2 = H) **(23)**
$[PtL^2Cl]$ (R_1= H, R_2 = CH_3) **(24)**
$[PtL^3Cl]$ (R_1= R_2 = CH_3) **(25)**

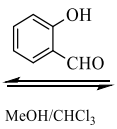


(H_2L^1)
(27)

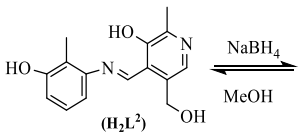


MeOH/$CHCl_3$
KOH, D
R = -CH_2-NH_2



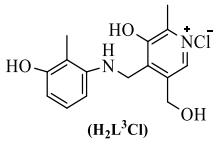


MeOH/$CHCl_3$
KOH, D
R = -CHO

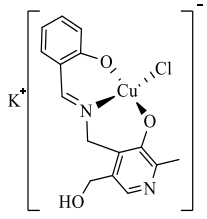


(H_2L^2)
(28)

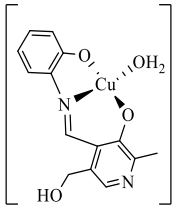
NaBH$_4$
MeOH



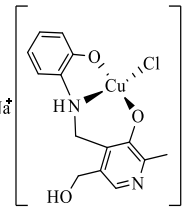
(H_2L^3Cl)
(29)



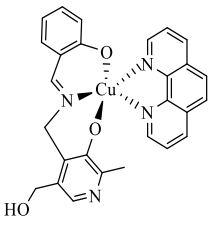
K[Cu(L^1)Cl] (30)



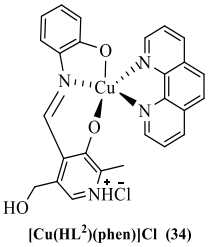
[Cu(L^2)H_2O] (31)



Na^+[Cu(L^3)Cl] (32)



Cu(L^1)(phen) (33)



[Cu(HL^2)(phen)]Cl (34)

Bjelogrlića et al[8] reported hydrazone-based Cd(II) dimeric complex formulated as $[Cd_2Cl_2(OAc)_2(aphaOMe)_2]$ (26), by the reaction of methanolic solution of methylhydrazinoacetate hydrochloride and acetylpyridine followed by addition of $Cd(AcO)_2.2H_2O$. *In vitro* cytotoxicity of complex was carried out after 24 h incubation by an Annexin V/PI dual staining method against human mammary adenocarcinoma cells (MCF-7) and human pancreatic AsPC-1 cancer stem cells. Values of anticancer activity in LC_{50} value (mM) for complex (26) (0.316 ± 0.007 mM) were significantly higher than for cisplatin (0.006 ± 0.004 mM), which suggests that cis-platin induced higher incidence of lethality in comparison to (26). Complex is susceptible to human serum albumin (HSA) and HSA can easily transport and store complex.

Fluorescence spectroscopy and molecular docking studies revealed that complex attached firmly with minor groove of DNA. The screening results revealed that complex interfered with DNA replication process or it may be due to ability of complex to induce apoptosis through the generation of reactive oxygen species (ROS)[72,76,82] and an increase in mitochondrial ROS production results into mitochondrial permeability transition pore (mPTP) opening followed by disappearance of mitochondrial transmembrane potential (MTP) and causing cell death[85]. Complex exhibited a potent anticancer activity against human mammary adenocarcinoma cells (MCF-7) and human pancreatic AsPC-1 cancer stem cells. The complex may act as a strong candidate for the treatment of highly resistant pancreatic cancer in further *in vivo* trial.

Nunes et al[51] synthesized H_2L type Schiff base (H_2L^1(27), H_2L^2 (28) and H_3L^3Cl (29)) derived from pyridoxal and three novel Cu(II) complexes [Cu(L)(X)] (30-32) where X = H_2O or Cl followed by two [Cu(L)(phen)] containing 1,10-phenanthroline (33-34).

The *in vitro* cytotoxicity of these synthesized metal complexes displays promising activity against ovarian A2780 and breast MCF7 cell lines. It was found that the complexes (33) and (34) being most potent kill ~50% of the cancer cell population even at a concentration as low as in the range between 0.6 to 12.5 µM against A2780 and MCF7 and surpassing the standard drugs cisplatin (IC_{50} value = 36 ± 8.0 and 59 ± 12). Complex (31) showed IC_{50} value 6.8 ± 3.5 against MCF7. Results of the IC_{50} value of the ligands showed its inertness against A2780 and MCF7 whereas most of the complexes showed moderate to excellent activity as depicted in table 3.

The highest cytotoxicity of phen containing complex $[Cu(HL^2)(phen)]Cl$ (34), may be due to its capability to bind ctDNA thereby, lowering IC_{50} value 0.7 ± 0.1 µM, contributing significant increase in cytotoxicity against both the cancer cells. Most of the complexes can be studied in future as potential anticancer drugs. Noser et al[50] reported novel amino acid Schiff base ligands 2-(1-(4-(4-oxo-2-Phenylquinazolin-3(4H)-yl) phenyl) ethylideneamino)-2-phenyl acetic acid (35) and 2-((1H-indol-3-yl) methyleneamino)-2-phenylacetic acid (36). Compound (35) demonstrated the highest anticancer activity on MCF-7 with IC_{50} = 64.05 ± 0.14 µg/mL whereas, compound (36) exhibited the best cytotoxic effect on MDA-231 with IC_{50} = 46.29 ± 0.09 µg/mL.

Compounds also showed significant activation of AMPK protein and oxidative stress, which led to elevated expression of p53 and Bax, reduced Bcl-2 expression and caused cell cycle arrest at the sub-G_0/G_1 phase. They also showed remarkable inhibition of the mTOR protein and hexokinase enzyme resulting in cancer cell death due to poor quantity of ATP. These observations demonstrated that both the compounds follow Lipinski's rule of five and could be used as candidate for cancer therapy. Alorini et al[2] reported a new Schiff base ligand, 2-((E)-((4-(((E)-benzylidene)amino)phenyl)imino)methyl)-naphthalene-1-ol (HL) (37) by condensation of p-phenylenediamine with 2-hydroxy-1- naphthaldehyde and benzaldehyde, followed by their metal complexes $[(HL)Mn(Cl)_2(H_2O)_2]$, Mn(II) (38); $[(HL)Cu(Cl)_2(H_2O)_2]$, Cu(II) (39); $[(HL)(L)V(Cl)_2]$, V(III) (40); $[(HL)(L)Cr(Cl)_2]$, Cr(III) (41), $[(L)_2Fe(Cl)(H_2O)]$, Fe(III) (42); $[(L)_2Co(Cl)(H_2O)]$, Co(III) (43); $[(HL)(L)Ni(Cl)(H_2O)]$, Ni(II) (44) and $[(HL)_2Zn(Cl)_2$, Zn(II) (45).

The anticancer activity of these complexes was evaluated against different human tumor cell lines. PC-3, SKOV3 and HeLa tumor cell lines were determined using SBR assays with six different concentrations of each compound. Schiff base and all the complexes showed anticancer activity against PC-3, SKOV3 and HeLa tumor cell lines. The $[(HL)Cu(Cl)_2(H_2O)_2]$, Cu(II) (39) complex demonstrated remarkable anticancer activity with IC_{50} value 0.1612 ± 0.005, 0.0630 ± 0.003 and 0.0872 ± 0.01 and $[(HL)(L)Ni(Cl)(H_2O)]$, Ni(II) (44) with IC_{50} value 1.8287 ± 0.10, 1.2502 ± 0.20 and 3.8453 ± 0.32 against PC-3, SKOV3 and HeLa tumor cell lines. This revealed that the prepared compounds (37-45) as listed in table 4 displayed much better activities than the reference drug such as cisplatin[62] with IC_{50} = 2.4 mg/mL and etoposide with IC_{50} = 17.4 mg/mL[5].

Metal complexes of $[Ph_2Sn(HL)]$ **(**46) and $[Ru(\eta^6$-p-cymene) (HL)Cl] (47) of Schiff bases (HL) (48), derived from the condensation reaction of 2-amino-2-methyl-1,3-propanediol with salicylaldehyde, were reported by Khan et al[38]. The anticancer activity of (46) and (47) was screened against human liver carcinoma (Huh7), prostate cancer (Du145) and the normal prostate cell line (PNT 2) and its effect on the cell viability was assessed using 3-[4,5-dimethylthiazol-2-yl]-2,5- diphenyl tetrazoliumbromide (MTT) assay.

Results showed that metal complexes exhibited good anticancer activity with the lethal concentration LC_{50} (in µM) values of 8.0, 12.6 and 14.9; 12.5, 11 and 80.5; NA, NA

and 16 against Huh7, Du145 and PNT 2 for (46), (47) and standard drug cisplatin respectively. Amongst them, compound (46) exhibited highest cytotoxicity against the liver cancer cell line (Huh7), leading to cell death with the treatment of exceptionally low μM concentration of (46).

Table 3
IC_{50} values of ligands and metal complexes (27-29) and (30-34) on two human cancer cells (A2780 and MCF7) after 24 h of incubation.

Complexes	A2780	MCF7	Complexes	A2780	MCF7
Ligand phen, H_2L^1**(27),** H_2L^1**(28)** and H_3L^3Cl **(29)**	> 100	> 100	**(33)**	1.8 ± 0.6	9.3 ± 3.0
(30)	86 ± 38	34 ± 11	**(34)**	0.7 ± 0.1	2.6 ± 1.0
(31)	23 ±8.5	6.8 ± 3.5	**Cisplatin**	36±8.0	59 ± 12
(32)	49 ± 18	19 ± 5.			

The presence of hydrophobic groups in the form of diphenyl in (46) and alkyl groups of p-cymene in (47) interacts with RNA surfaces as well as hydrogen bonding interactions between oxygen atoms of free −OH in (46) and (47) with RNA bases responsible for inhibiting the growth of drug-resistant cells but it is worth noting that no remarkable cell death was observed when tested against the normal PNT2 cell line. Both the complexes may act as promising antitumor agents in future research.

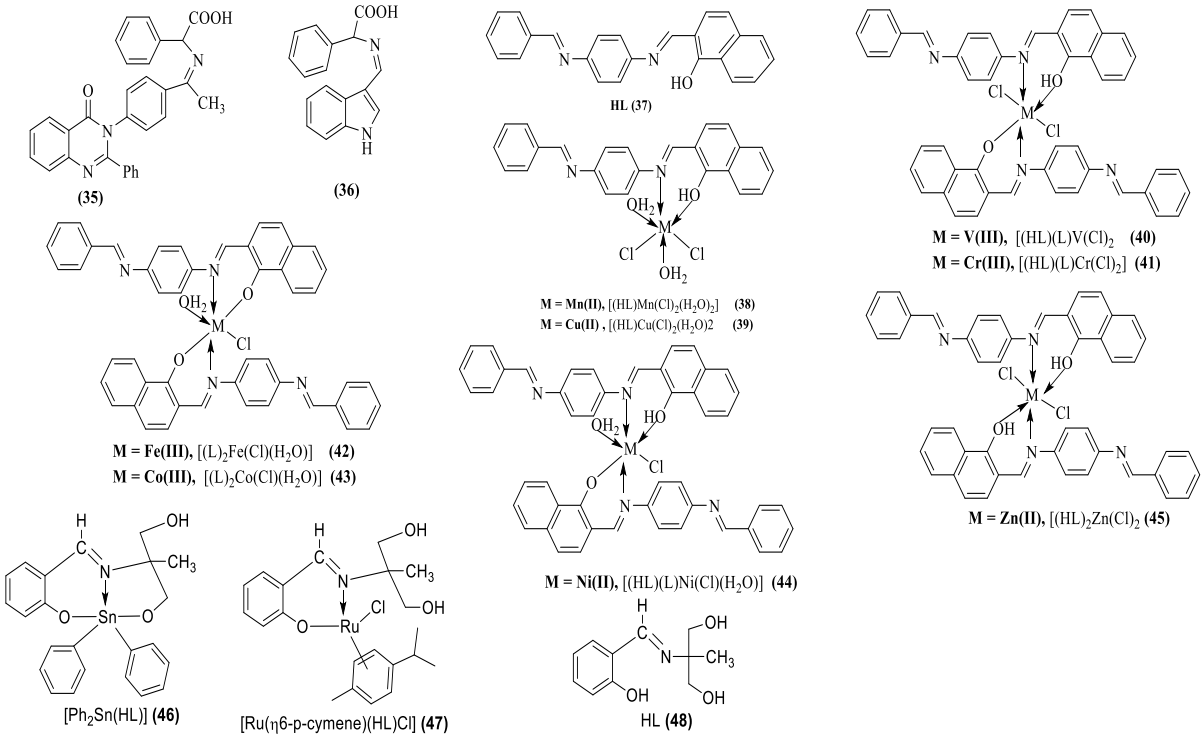


Table 4
IC_{50} values of ligand (37) and metal complexes (38–45) for PC-3, SKOV3 and HeLa tumor cell lines.

Complexes	PC-3	SKOV3	HeLa
37	1.0123 ± 0.05	0.2163 ± 0.005	0.5877 ± 0.14
38	0.1786 ± 0.02	0.2189 ± 0.05	0.9254 ± 0.05
39	**0.1612 ± 0.005**	**0.0630 ± 0.003**	**0.0872 ± 0.01**
40	0.7262 ± 0.14	0.1997 ± 0.03	0.0719 ± 0.02
41	0.7027 ± 0.25	0.0678 ± 0.03	0.7606 ± 0.05
42	0.3188 ± 0.02	0.8128 ± 0.20	1.5340 ± 0.30
43	1.0607 ± 0.16	0.0615 ± 0.02	0.3921 ± 0.03
44	1.8287 ± 0.10	1.2502 ± 0.20	3.8453 ± 0.32
45	0.4436 ± 0.07	0.1646 ± 0.04	1.3064 ± 0.46

Table 5
The IC_{50} and CC_{50} Values (µg/mL) of the ligand (49) and its metal complexes (50-54) against different human cell lines.

Complexes	IC_{50} (µg/mL)			CC_{50} (µg/mL)
	HePG-2	**A-549**	**PC-3**	**WI-38**
49	163.05±6.29	187.83± 6.35	181.12±5.35	168.93±5.82
50	123.61±3.95	176.73±5.79	167.29±6.75	143.41±6.34
51	29.14±0.74	23.04±0.82	34.25±2.84	111.08±5.12
52	**8.24±0.32**	**7.55±0.29**	**13.81±1.08**	**82±3.82**
53	14.23±0.39	12.41±0.35	15.32±1.96	96.13±4.27
54	58.42±2.76	61.5±3.17	93.02±3.96	123.15±4.93

The study reported by Alorini et al[3] focused on the synthesis of new Schiff base ligand, 2-((E)-((4-(((E)-4-methoxybenzylidene)amino)phenyl)imino)methyl)naphthalen-1-ol, HL (49) and their respective metal complexes formulated as $[Fe(HL)(L)(Cl)_2]$, Fe(III) (50); $[Co(HL)(L)(Cl)_2]$, Co(III) (51); $[Ni(HL)(Cl)_2(H_2O)_2].2H_2O$, Ni(II) (52); $[Cu(HL)_2(Cl)_2]$ $.2H_2O$, Cu(II) (53); $[Zn(L)(Cl)(H_2O)_3]$, Zn(II) (54). The table revealed that the Ni(II) complex (52) displayed the highest cytotoxicity with IC_{50} values (in mm) 8.24±0.32, 7.55±0.29 and 13.81±1.08, followed by Cu(II) complex (53) with IC_{50} values 14.23±0.39, 12.41±0.35 and 15.32±1.96 against A549 (human lung cancer), HepG-2 (human hepatocellular cancer) and PC-3 (human prostate cancer) cancer cell lines, respectively.

The cytotoxicity of the compounds was found to be in order of (52) > (53) > (51) > (54) > (50) > (49), according to table 5. Results showed the selectivity index values for (49): (1.04, 0.90, 0.93); (50): (1.16, 0.81, 0.86); (51): (3.81, 4.82, 3.24); (52): (9.95, 10.86, 5.93); (53): (6.76, 7.75, 6.27); (54): (2.11, 2.00, 1.32) against A549, HepG-2 and PC-3 cancer cell lines respectively. The compound (51) and (53) revealed the maximum anticancer activity toward selected cancer cell lines, with an SI value > 3, which is the prerequisite for a compound to display anticancer activity[31]. The cytotoxicity may be due to capability of above compounds to bind with DNA and to aggressively destroy its structure and functions, as well as to interfere with transcription and replication processes leading to cell death. In addition, lipophilicity of the complexes increases due to the presence of methoxy group in Schiff base ligand (49)[18].

Saswati et al[68] reported three Schiff base ligand H_2L^1 = 4–(p–methoxyphenyl) thiosemicarbazone of o–hydro xynapthaldehyde (55), HL^2 = 4–(p–methoxyphenyl) thiosemicarbazone of benzoyl pyridine (56) and H_2L^3 = 4–(p–chlorophenyl)thiosemicarbazone of o–vanillin (57) and their three novel dimeric Zn(II) ($[\{ZnL^1(DMSO)\}_2]\cdot DMSO$ (58), $[\{ZnL^2\ Cl\}_2]$ (59) and a novel tetrameric Zn(II) complex ($[(Zn_2L^3)_2(\mu\text{–}OAc)_2(\mu_3\text{–}O)_2]$ (60). The *in vitro* cytotoxicity of metal complexes (58-60) was determined using the MTT assay with HeLa and HT–29 cells in the concentration range of 12.5–100 µM. Results of anticancer activity demonstrated the inhibition rates and IC_{50} values (in µM) of two cell lines *viz.* for compound (58): 16.26 ± 2.63 and 18.32 ± 0.97; (59): 53.8 ± 2.49 and 19.2 ± 1.17; (60): 30.87 ± 2.62 and 33.14 ± 2.07; for cisplatin 12.2 µM and 70 µM against HeLa[63] and HT–29 cell lines[74] respectively.

The IC_{50} values are comparable to that of reference drug cisplatin against both HeLa and surpassing against HT–29 cell lines. Results clearly showed that complex (58) seems to be more effective amongst metal complexes even at such a low concentration 12.5 µM against both HeLa and HT–29 cell lines whereas complex (59) showed significant cytotoxicity only against HT–29 cell line. The ligands exhibiting high IC_{50} values of > 100 µM indicated that the coordination of ligand with metal ions of zinc is responsible for increase in the cytotoxicity of the metal complexes due to a reduction in polarity of the ligand and the central metal ion causing easier permeation of the complexes through the lipid layer of the cell membrane.

Yin et al[79] synthesized a set of nine transition metal complexes, namely, $[Ni(HL^I)_2]\cdot 0.5(H_2O)$ (61), $[Zn(HL^I)_2]\cdot 0.5(H_2O)$ (62), $[Ni(HL^{II})_2]\cdot 0.5(H_2O)$ (63), $[Zn(HL^{II})_2]\cdot 0.25(H_2O)$ (64) $[Zn(HL^{III})_2]\cdot DMF\cdot H_2O$ (65), $[Ni(HL^{IV})_2]\cdot 0.5(C_2H_5OH)$ (66), $[Zn(HL^{IV})_2]\cdot 0.5(H_2O)$ (67), $[Ni(HL^{V})_2]\cdot 0.25(H_2O)$ (68), $Zn(HL^V)_2$ (69) starting from H_2L^I = (E)-4–chloro-2-((2-(6-chloropyridin-2-yl) hydrazineylidene)methyl)phenol; H_2L^{II} = (E)-4–bromo-2-((2-(6-chloropyridin-2-yl)hydrazineylidene)methyl)phenol; H_2L^{III} = (E)-2,4-dibromo-6-((2-(6-chloropyridin-2-yl)hydrazineylidene)methyl)phenol; H_2L^{IV} = (E)-2-((2-(6-bromopyridin-2-yl)hydrazineylidene)methyl)-4-chlorophenol; H_2L^V = (E)-4–bromo-2-((2-(6-bromopyridin-2-yl) hydrazineylidene)methyl)phenol; DMF = N,N-dimethyl formamide.

An excellent cytotoxic effect was exhibited by the tested compounds (61–69) at 20 µM concentration for 48 h using the MTT method against HepG2, NCI-H460, MGC80–3, BEL-7404 and HL-7702 normal liver cell line. Results of anticancer activity demonstrated the inhibition rates and IC_{50} values (in µM) of six cell lines *viz.* for complex (61): (58.18±0.63% and 10.11±0.68) and (55.54±1.49 % and 12.13±1.52) against NCI-H460 and BEL-7404 cancer cell lines; (62): (60.13±1.42 % and 9.52±1.39) and (57.14±0.55 and 10.75±0.59) against HepG2 and MGC80–3 cancer cell lines; (63): (56.11±0.71% and 10.89±0.83) against NCI-H460 cancer cell line; (64): (57.02±0.77 % and 10.58±0.79)

and (54.03±1.69% and 15.64±1.72) against HepG2 and MGC80–3 cancer cell lines; (66): (54.02±1.25 and 11.42±1.22) against NCI-H460 cancer cell line, which are either comparable and are surpassing the reference drug cisplatin.

Higher is the inhibition rate, the lower is the IC_{50} value, suggesting that the effect of the treatment on tumor cells was most effective[29]. Table 6 and table 7 show that some selected compounds can be used as potential anti-tumor drugs for future research. Savcı et al[69] synthesized Schiff base ligand (70) from the condensation reaction of benzene-1,2-diamine and 5-fuoropyrimidine-2,4(1H,3H)-dione (5-FU) and their Fe(II) (71), Co(II) (72) and Ni(II) (73) complexes. The anticancer studies of the synthesized compounds were carried out on MCF-7 (human breast cancer) and L-929 (fibroblast) cell lines using the MTT assay. Results of anticancer activity demonstrated IC_{50} values (in μM) of two cell lines *viz.* for compound (70): 83.77 and 204.43; (71): 102.47 and 169.78; (72): 46.43 and 85.16; (73): 9.43 and 231.44; against cancer (MCF-7) and healthy (L-929) cell lines, the Ni(II) (73) surpassing the reference drug 5-FU (IC_5 value 45.52 and 62.89 μM).

Results suggests novel Co(II) and Ni(II) complexes as an effective anticancer agent against MCF-7 breast cancer cells and less susceptible to healthy cells (L-929), hence making an excellent candidate for future research on ECT based studies. Patra et al[58] synthesized three tetradentate N, N′ -dimethyl-N, N′-bis-(5-chloro-2-hydroxy-3-methyl-benzyl)-1,2-diaminoethane (H_2L^1) (74), N,N′-dimethyl-N,N′-bis-(5-chloro-2-hydroxy-3-isopropyl6- methyl-benzyl)-1,2-diamino-ethane (H_2L^2) **(**75) and N, N′-bis-(5-chloro-2-hydroxy-3-isopropyl-6-methyl-benzyl)- 1,2-diaminocyclo hexane (H_2L^3) (76) and their metal complexes [V^VOL^1 (OCH_3)] (77); [$V^VOL^{2–3}$]$_2$(μ-O) (78) and [V^VOL^3]$_2$(μ-O) (79).

The *in vitro* cytotoxicity of these synthesized metal complexes displays promising activity against cancerous (MCF-7 and HT-29) and noncancerous cell lines that is normal mouse embryonic fibroblast (NIH-3T3). It was found that the complexes (77) and (79) being most potent, kill ~50% of the cancer cell population even at a concentration as low as 12.5 μM as their inhibitory order is shown as: (79) > (77) > (78) against MCF-7 and HT-29 as compared to the standard drugs 5-Fluorouracil (13.65 ± 0.05 and 12.2 ± 2.3) and cisplatin (21.78 ± 0.09 and 8.7 ± 4.0)[40]. Results of the IC_{50} value of complexes (77) 15.53 ± 2.64 and 9.96 ± 0.83) and (79) (8.17 ± 0.36 and 5.07 ± 0.47 μM) surpassed both the standard drugs whereas complex (78) displayed lower toxicity that is 49.16 ± 2.56 and 48.27 ± 5.58 for both cell lines even at high concentrations.

Above results were also supported by oxaliplatin comprising of cyclohexane-diamine backbone[23,24]. The higher cytotoxicity of (79) may be due to the presence of electron donating cyclohexane diamine moiety in the ligand skeleton which increases the polarity around the Trp moiety in the protein, helping their cell penetration. Results of the IC_{50} value of complexes (77) 52.08 ± 2.5 and (78) 79.68 ± 2.55 showed lower toxicity towards NIH-3T3 cell line whereas (79) showed 9.13 ± 0.47 higher toxicity on same line.

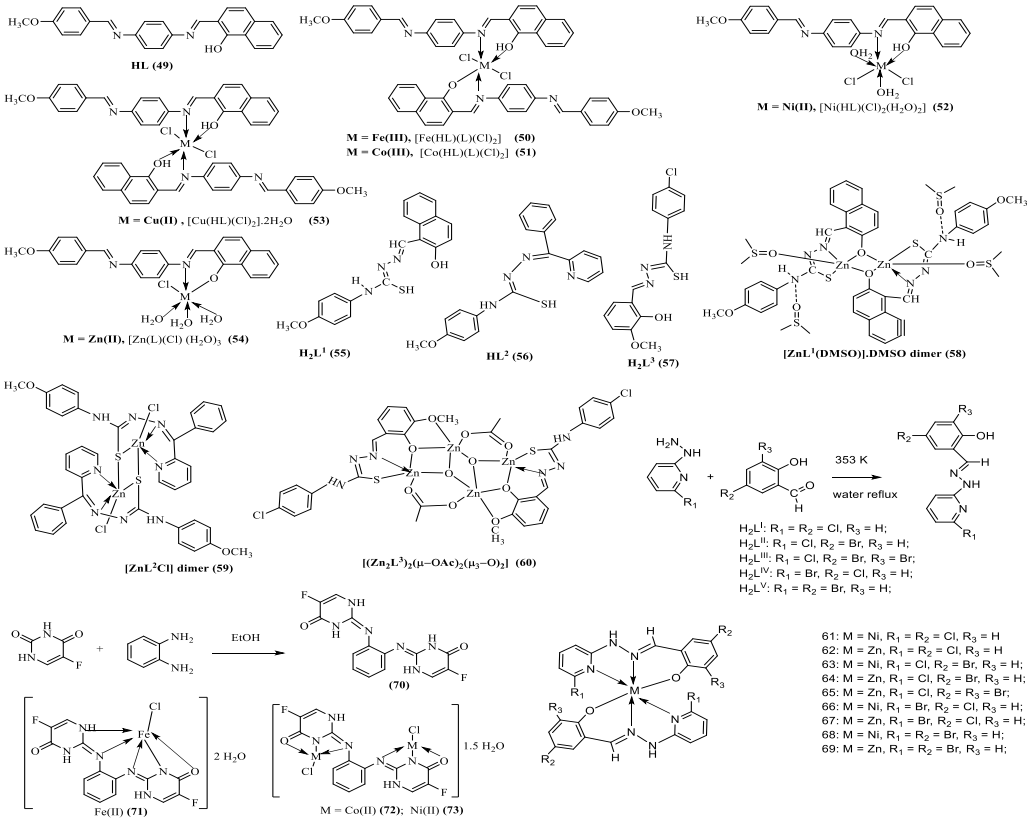


Table 6
The Inhibition rate on different cells of of complexes 1–9 and H_2L^I-H_2L^V (%).

Complexes	HepG2	NCI-H460	MGC80–3	BEL-7404	HL-7702
H_2L^I	38.06±1.06	25.03±0.43	32.12±1.14	37.14±1.74	28.06±1.26
61	40.22±0.33	58.18±0.63	40.99±1.32	55.54±1.49	31.02±0.51
62	60.13±1.42	42.13±1.76	57.14±0.55	40.21±1.02	30.99±1.77
H_2L^{II}	32.85±0.75	20.16±0.67	30.24±1.23	36.09±0.65	25.09±1.65
63	38.55±1.12	56.11±0.71	35.06±1.42	50.13±0.67	34.06±1.03
64	57.02±0.77	40.16±1.17	54.03±1.69	38.25±0.41	29.01±1.85
H_2L^{III}	32.12±1.01	30.11±0.43	28.36±1.25	28.79±1.47	26.36±1.17
65	38.96±1.17	40.12±0.91	39.36±0.31	41.26±1.45	33.02±0.46
H_2L^{IV}	30.18±1.54	18.64±1.09	27.09±0.78	34.84±1.16	24.88±0.95
66	37.56±1.07	54.02±1.25	32.42±1.76	41.02±1.06	37.88±0.54
67	55.02±0.75	35.02±1.94	50.99±0.56	35.09±0.49	30.12±0.46
H_2L^V	29.04±1.65	15.36±0.69	25.36±1.24	30.15±0.39	24.56±2.05
68	32.91±1.47	50.14±1.09	29.14±1.78	40.32±2.02	33.06±2.06
69	48.02±1.04	30.12±0.79	50.34±1.11	32.53±1.88	25.03±0.46
Cisplatin	55.15±1.18	60.63±0.99	50.88±3.69	47.58±2.65	60.63±0.99

Table 7
The IC_{50} on different cells of complexes 61–69 and H_2L^I-H_2L^V(μM).

Complexes	HepG2	NCI-H460	MGC80–3	BEL-7404	HL-7702
H_2L^I	86.09±1.08	115.06±0.65	91.04±1.11	70.33±1.66	116.06±1.33
61	43.09±0.49	**10.11±0.68**	39.66±1.40	**12.13±1.52**	87.25±0.57
62	**9.52±1.39**	29.63±1.81	**10.75±0.59**	42.06±1.06	87.99±1.79
H_2L^{II}	94.18±0.69	153.84±0.78	104.32±1.26	75.06±0.61	130.26±1.78
63	57.86±1.15	**10.89±0.83**	54.12±1.47	20.14±0.62	81.09±1.09
64	**10.58±0.79**	36.09±1.21	**15.64±1.72**	62.03±0.39	99.56±1.93
H_2L^{III}	120.12±1.06	>150	>150	>150	>150
65	60.12±1.19	35.03±0.94	50.21±0.35	29.56±1.33	83.29±0.58
H_2L^{IV}	105.48±1.51	186.03±1.13	112.06±0.95	83.06±1.20	140.16±1.04
66	53.06±1.10	**11.42±1.22**	89.03±1.79	39.69±1.11	72.03±0.61
67	15.06±0.76	57.14±1.91	19.86±0.63	86.06±0.54	89.03±0.57
H_2L^V	108.25±1.72	195.06±0.77	135.64±1.31	92.32±0.44	141.09±2.01
68	88.45±1.24	20.15±1.16	104.12±1.89	44.03±2.05	82.06±2.01
69	25.18±1.06	73.13±0.82	20.12±1.04	23.06±1.47	131.02±0.51
Cisplatin	14.06±0.33	15.03±0.73	15.59±1.09	17.02±0.46	16.01±1.2

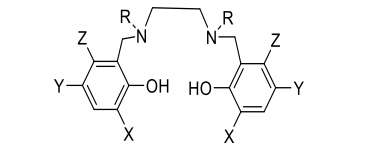
Break et al[9] investigated novel macroacyclic Schiff base ligands (80-89) and their respective Cu (II) complexes (90-99) by condensation reaction of dicarbonyls of varying chain lengths with S-methyl dithiocarbazate (SMDTC) and S-benzyl dithiocarbazate (SBDTC). The anticancer activities of ligand as well as their Cu(II) complexes against MCF-7 and MDA-MB-231 cell line were summarized in the table 8. Complexes (90-99) demonstrated cytotoxic activity either comparable to cisplatin or surpassing against MCF-7 and MDA-MB-231 cancer cell lines, displaying IC_{50} values (in μM) of 1.7± 0.1 and 1.4± 0.1; >50 and >50; 46 ± 1.0 and 19 ± 4.1; 11 ± 1.9 and 38 ± 7.5; 14 ± 2.1 and 16 ± 4.6; >50 and 9 ± 1.2; 45 ± 2.3 and >50; 7.3 ± 2.8 and 12 ± 0.5; 20 ± 1.5 and >50; >50 and >50; Cisplatin: 25 ± 0.3 and 16 ± 4.6 respectively.

Results showed that Cu(II) complex (90) showed highest cytotoxic activity against MCF-7 and MDA-MB-231 with IC_{50} values of 1.7 μM and 1.4 μM respectively. From the table 8, it was also found that SMDTC-derived analogues were more active than SBDTC-derived analogues against MDA-MB-231 cells. Most of the compounds either ligands or copper complexes seem to be highly promising cytotoxic agents and may act as potent anticancer drugs in future.

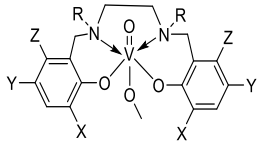
Yousef et al[80] have reported the synthesis of Mn(II) and Co(II) complexes of hydrazones, derived from 2-hydrazino-2-oxo-N-phenylacetamide and P-vanillin (H_2L_1) (100) and O-vanillin (H_2L_2) (103).The compounds (100), (101), (102), (103), (104) and (105) exhibited notable cytotoxicity against hepatocellular carcinoma (liver) HePG-2 and mammary gland (breast) MCF-7, demonstrating IC_{50} values (in μmol/L) of 2.61 and 6.62; 2.81 and 6.98; 3.56 and 7.63; 2.73 and 6.78; 4.09 and 8.35; 4.93 and 9.16 respectively. It is noted that both ligands (100) and (103) show excellent activity (2.61 and 2.73 μmol/L) against HePG2 and (6.62 and 6.78 μmol/L) for MCF-7 comparable to that of

fluorouracil reference where it has IC_{50} value 2.48 and 6.35 on the same cancer line. The activity of the compounds is in following order: $H_2L_1 > H_2L_2 > [Mn(H_2L_1)2Cl_2](0.5H_2O) > [Co(H_1L_1)_2(H_2O)_2](H_2O) > [Mn(HL_2)Cl(H_2O)_2](H_2O) > [Co(HL_2)Cl(H_2O)_2](H_2O)$.

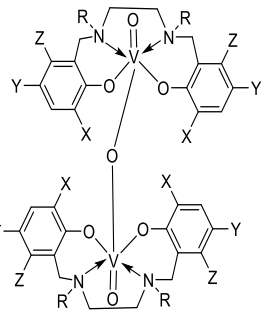
Zhao et al[83,84] synthesized Schiff base derived from salicylaldehyde and L-phenylalanine (106) from 2-hydroxy-1-naphthaldehyde and L-phenylalanine (107); from o-vanillin and L-phenylalanine (108) and their corresponding Ni(II) hexadentate complexes (109), (110) and (111), respectively and were evaluated for antiproliferative action against CAL-27 cells using MTT test assay and cis-platin as reference drug. Comparison of the antiproliferative activity of these metal complexes indicated that complex (111) displayed highest activity than the other complexes. Complex (111) inhibited CAL-27 cells with lowest IC_{50} values of 15.90 mM much closer to IC_{50} of cisplatin, followed by (110) and then (109), whereas, (106), (107) and (108) displayed no cytotoxicity on same cancer line. Complex (111) binds DNA strongly as compared to complexes (109) and (110).



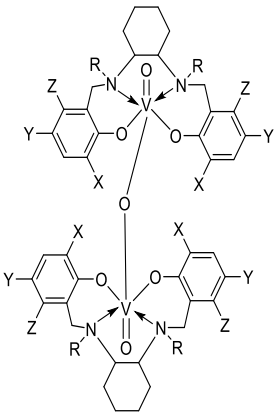
(R = Me, X = CH_3, Y = Cl and Z = CH_3 H_2L^1 **(74)**
(R = Me, X = ^{i}Pr, Y = Cl and Z = CH_3 H_2L^2 **(75)**
(R = H, X = ^{i}Pr, Y = Cl and Z = CH_3 H_2L^3 **(76)**



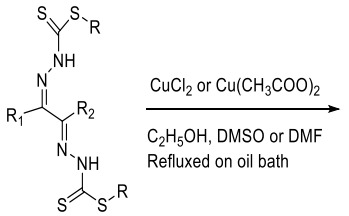
$[V^VOL^1(OCH_3)]$ **(77)**

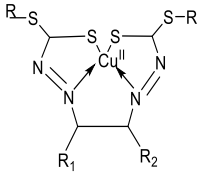


$[V^VOL^2]_2(\mu\text{-}O)$ **(78)**

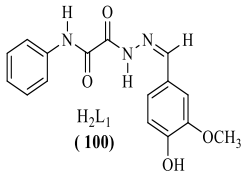


$[V^VOL^3]_2(\mu\text{-}O)$ **(79)**

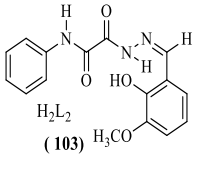




corresponding Cu(II) complexes **(90-99)**



H_2L_1 **(100)**



H_2L_2 **(103)**

$[Co(HL_1)_2(H_2O)_2](H_2O)$ **(101)**; $[Mn(H_2L_1)_2Cl_2](0.5H_2O)$ **(102)**

$[Mn(HL_2)Cl(H_2O)_2](H_2O)$ **(104)**; $[Co(HL_2)Cl(H_2O)_2](H_2O)$ **(105)**

R = CH_3, R_1 = H, R_2 = H **(80)**
R = $C_6H_5CH_2$, R_1 = H, R_2 = H **(81)**
R = CH_3, R_1 = CH_3, R_2 = CH_3 **(82)**
R = $C_6H_5CH_2$, R_1 = CH_3, R_2 = CH_3 **(83)**
R = CH_3, R_1 = CH_3CH_2, R_2 = CH_3 **(84)**
R = $C_6H_5CH_2$, R_1 = CH_3CH_2, R_2 = CH_3 **(85)**
R = CH_3, R_1 = $CH_3CH_2CH_2$, R_2 = CH_3 **(86)**
R = CH_3CH_2, R_1 = $CH_3CH_2CH_2$, R_2 = CH_3 **(87)**
R = CH_3, R_1 = $CH_3CH_2CH_2CH_2$, R_2 = CH_3 **(88)**
R = $C_6H_5CH_2$, R_1 = $CH_3CH_2CH_2CH_2$, R_2 = CH_3 **(89)**

Table 8
Cytotoxic activity, median inhibitory concentration (IC_{50}) in µg/mL of the (80-99) schiff base and their metal complexes against MCF-7 and MDA-MB-231cancer cell lines.

Cancer Cell lines	**(80)**	**(90)**	**(81)**	**(91)**	**(82)**	**(92)**
MCF-7	6.9± 0.3	1.7± 0.1	2.6± 0.8	>50	20 ± 0.3	46 ± 1.0
MDA-MB-231	>50	1.4± 0.1	4.5± 0.7	>50	4.2± 0.7	19 ± 4.1

(83)	**(93)**	**(84)**	**(94)**	**(85)**	**(95)**	**(86)**	**(96)**
49 ± 5.4	11 ± 1.9	11.5	14 ± 2.1	22 ± 1.2	>50	12 ± 0.4	45 ± 2.3
>50	38 ± 7.5	22 ± 2.0	16 ± 4.6	>50	9 ± 1.2	4 ± 0.2	>50

(87)	**(97)**	**(88)**	**(98)**	**(89)**	**(99)**	**Cisplatin**
7.3 ± 0.8	7.3 ± 2.8	9.8 ± 0.1	20 ± 1.5	5.7 ± 0.1	>50	25 ± 0.3
12 ± 1.1	12 ± 0.5	6 ± 0.2	>50	22 ± 0.8	>50	48 ± 3.5

The electron-donating group o-vanillin coordinated with Ni as well as planar 1, 10-phenanthroline, an electron acceptor group facilitating Ni(II) complex to get attached into double-stranded DNA which further results in strong π–π stacking interaction between adjacent metal complexes as supported by UV-visible studies, since π∗ orbital of the planar 1,10-phenanthroline couple with π orbital of DNA base results in red shift of π→π∗ transition having lower ε value suggesting metal complexes bind with DNA by intercalation. Results for the superoxide scavenging activity using nitrotetrazolium blue chloride (NBT) light reduction method showed IC_{50} values 4.4×10^{-5} M, 5.6×10^{-5} M and 3.1×10^{-5} M for complexes (109), (110), (111) respectively.

The complex (111) showed greater superoxide anion radical scavenging effect in comparison to complex (109) and complex (110). The intrinsic binding constant K_b values 1.82×10^4, 1.96×10^4, 2.02×10^4 and 3.3×10^5 M^{-1} for complexes (109), (110), (111) and ethidium bromide (EB) to DNA respectively attributed that these complexes have a weaker binding power to DNA due to their distorted geometry. Khalil and Mohamed[37] have synthesized new Schiff base ligand (N1-(diphenylmethylene)naphthalene-1,8-diamine) (112), derived from condensation of benzophenone and 1,8-naphthylenediamine and their mixed ligand metal complexes of (114), (115), (116), (117), (118), and (119) where (113) acts as a secondary ligand known as 1,10-phenanthroline.

The anticancer activity revealed that amongst all these complexes, the most effective and promising one is the La(III) complex (117) with lowest IC_{50} value = 4.48 µg/mL against human breast cancer cell line MCF-7, surpassing the ligand (112) which has IC_{50} value = 29 µg/mL followed by Ni(II) (116) with IC_{50} value = 44 µg/mL. Results demonstrated that the inhibition ratio for Schiff base ligand was about 65%, whereas metal complexes inhibition ratio values were found to range from 55-86%. Hajari et al[25] investigated the anticancer activities of M(II) (where M = Zn, Cd, Mn) complexes with Schiff base ligand synthesized from 2,2-(piperazine1,4-diyl)dianiline and 2,6-diacetylpyridine.

Synthesized complexes were screened for their *in vitro* anticancer activity using MTT assay, amongst them Zn(II) (120) demonstrated higher cytotoxic effect with an IC_{50} value of 6.43±0.21 µM and 7.21±0.33 µM surpassing the other two complexes (8.96±0.81 µM and 9.24±0.82 µM for Cd(II) (121) and 10.41±0.92 µM and 10.85±0.93 µM for Mn(II) (122) against MCF-7 (breast) and A549 (lung) adenocarcinoma cells respectively. Al-Shboul et al[4] reported novel Schiff base ligands Z1H1 (123), Z1H1 (124), Z1H1 (125), Z1H1 (126), synthesized by the condensation reaction of 2,2'-diamino-6,6'-dibromo-4,4'-dimethyl-1,1'-biphenyl or 2,2'-diamino-4,4'-dimethyl-1,1'-biphenyl and 3,5-dichloro- or 5-nitro-salicylaldehyde and their metal complexes with Cu(II) (127-130), Fe(II) (131-134) and Zn(II) (135-138).

From the table 9, *in vitro* cytotoxicity studies against A549, MCF-7 and HDF cells revealed that complex (128) exhibited highest cytotoxicity with IC_{50} values of 4, 1.9 and 1.5 µg/mL respectively. Amongst the ligand, (123) is more effective against all the cancer lines. It can also be visualized that complexes (127), (130), (135), (136) and (137) exhibited higher toxicity towards MCF-7 cell lines whereas (127), (129), (130), (134), (137) and (138) exhibited toxicity towards HDF cell lines as depicted in table 9.

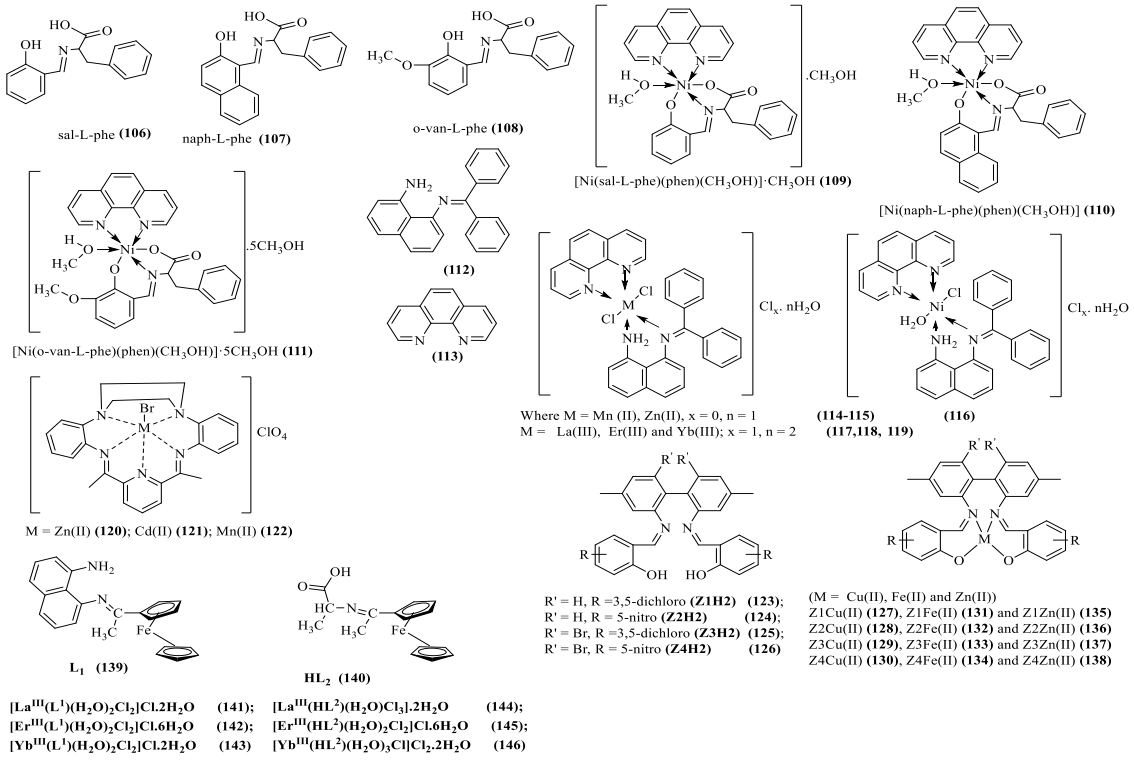


Table 9
Cytotoxic activity (IC_{50} values in (µg/mL)) of the (123-138) and reference drug Doxorubicin for 24 h and 72 h against different cancer cell lines. (note NA for No Activity)

Complexes	A549	MCF7	HDF	Complexes	A549	MCF7	HDF
	24 h	24 h	24 h		24 h	24 h	24 h
(123)	25.2	20.5	46.8	**(132)**	118.1	41.4	134.1
(124)	320.3	231.7	291.8	**(133)**	NA	NA	NA
(125)	41.0	77.5	71.1	**(134)**	68.6	36.5	16.7
(126)	62.17	NA	69.2	**(135)**	224.9	17.3	68.2
(127)	43.7	10.4	8.5	**(136)**	81.2	25.2	68.7
(128)	4	1.9	1.5	**(137)**	119.4	17.7	27.6
(129)	130.0	172.0	29.2	**(138)**	25.2	14.1	28.3
(130)	34.7	19.2	10.4	Doxorubicin	0.15	0.03	0.37
(131)	NA	NA	NA				

Deghadi et al[17] investigated novel La (III), Er (III) and Yb (III) complex with Schiff bases ligand synthesized from condensation between 1,8-naphthalenediamine/ alanine and 2-acetylferrocene. Results of *in vitro* cytotoxicity studies for ligand and their metal complexes showed IC_{50} values (in µM) 20.2, 50.2, 21.5, 34, 12, 22, 16, 9 and 4.13 µM against breast cancer (MCF-7) for ligand (139), (140) and metal complexes (141-146) and standard drug Doxorubicin respectively. The complex (146) exhibited higher cytotoxicity with IC_{50} values of 9.0 µM followed by 12.0 µM for (143). The increased cytotoxicity of complex (146) shows that the lipophilicity develops due to presence of ferrocenyl group in the ligand structure, which anchors the cell membrane and the peptide chain blocks the openings of the channels in the cell membrane simultaneously, leading to apoptosis.

Hassan et al[26] explored (OV-Azo) Schiff base ligand (147), derived by a condensation o-vanillin and 4-aminoazobenzene and green synthesis of its metal complexes- based on Mn(II) (148), Co(II) (149), Ni(II) (150), Cu(II) (151), Zn(II) (152) and O=Zr(IV) (153) under microwave condition. The synthesized compounds were also screened for anticancer activity against HepG-2 and HCT as compared to cisplatin as a reference drug. Results of anticancer activity demonstrated IC_{50} values (in µg/mL) of 24 and 28; 20 and 24; 42 and 50; 35 and 48; 18 and 22; 39 and 45; 20 and 27; against HepG-2 and HCT-116 cell lines with reference to cisplatin as standard drug for (147-153) respectively. Results showed that Cu(II) complex (151) exhibited highest cytotoxicity, followed by Mn(II) complex (148) and then by O=Zr(IV) (153) against HepG-2 and HCT-116 respectively.

Furthermore, the complex displayed inhibitory effects on human hepatocellular and human colon cancer cell migration, induced the activation of apoptosis and ROS levels. The Cu(II) complex displayed that largest cytotoxic activity may be governed by a well-known mechanism of action via DNA interaction followed by cleavage, where DNA is degraded by a Fenton-type reaction[30,77]. El-Gammal et al[20] reported a new hydrazone Schiff base (H_2L) (154) by condensation reaction between salicylaldehyde and 4-(3-cyano-4,6-dimethylpyridin-2-ylamino)benzohydrazide and their Co(II) (155), Ni(II) (156) and Cu(II) (157) complexes.

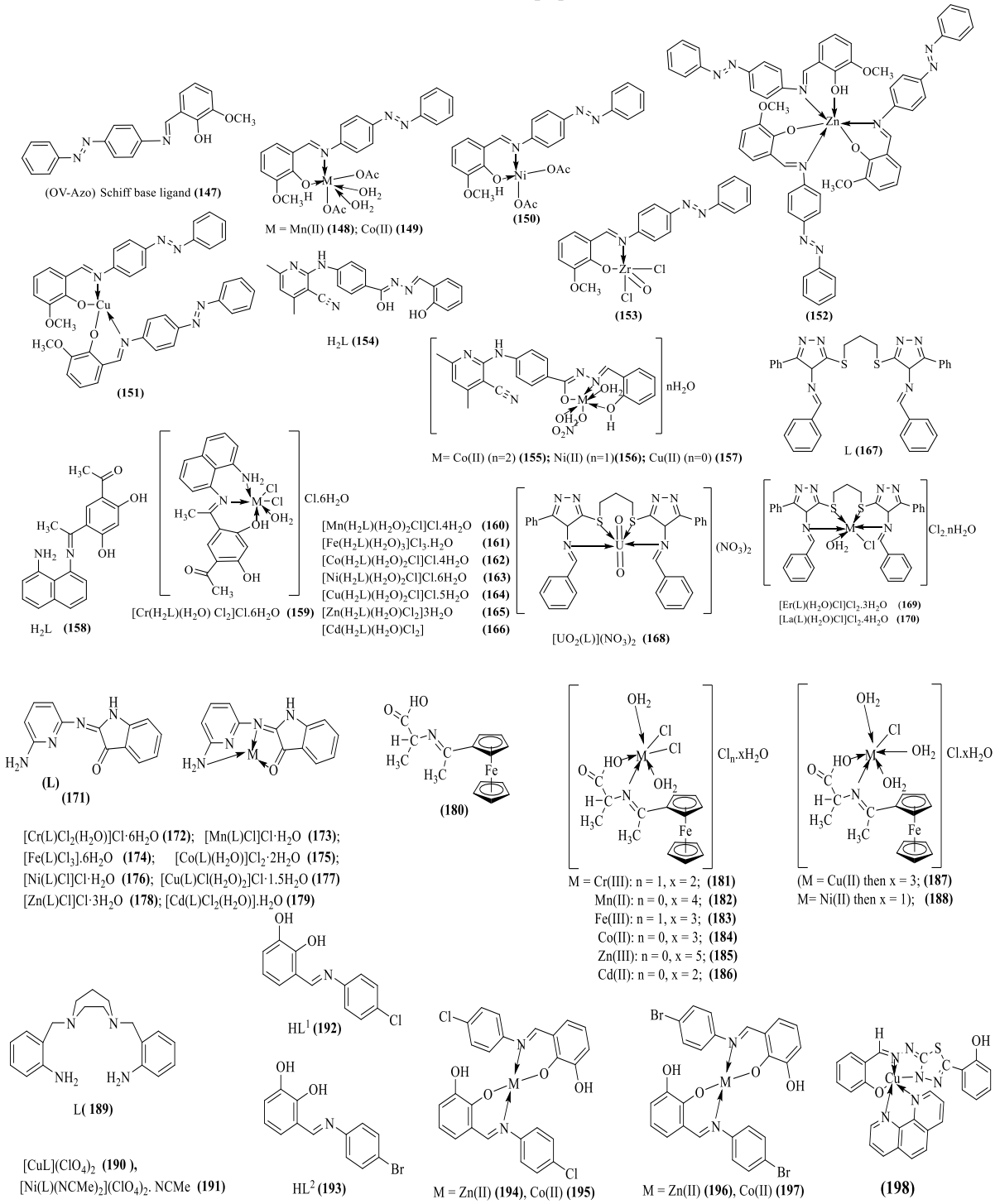
The synthesized compounds were screened for anticancer activity against MCF-7 and HepG2 cell lines and were compared with the uncoordinated ligand. Results of anticancer activity demonstrated IC_{50} values (in µM) of 20.7 ± 1.6 and 12.3 ± 1.8; 101 ± 4.8 and 76.8 ± 4.9; 14.9 ± 0.7 and 9.15 ± 0.9; 3.35 ± 0.3 and 2.14 ± 0.2 against MCF-7 and HepG2 cell lines with reference to vinblastine as standard drug for (154), (155), (156) and 157) respectively. The complex (157) is more effective anticancer drug comparable to vinblastine which has IC_{50} 6.2 ± 0.02 and 4.4 ± 0.02 µM against MCF-7 and HepG2 cell lines.The significant activity may be attributed due to the ability of these metal complexes to induce S-phase arrest in cancer cells associated with increased expression of tumor suppressors genes[28].

Ahmed et al[1] have reported Schiff base ligand (158) obtained by reaction of 2-aminophenol/o-phenylenediamine and terepthaldehyde and their new series of Cr(III) (159), Mn(II) (160), Fe(III) (161), Co(II) (162), Ni(II) (163), Cu(II) (164), Zn(II) (165) and Cd(II) (166) complexes. The *in vitro* anticancer activities of the synthesized Schiff base ligand and its complexes against breast cancer (MCF-7) cell line. IC_{50} values of (158), (160), (163), (164) and (166) were found to be 24.5, >50, 50, >50 and 46 µg/ml respectively. It is a fact that the lower IC_{50} value of 24.5 µg/ml for (158), make it an excellent candidate for future research. The chelated metal complexes (160), (163) and (165) and (166), act as potential antitumor agents due to attachment of hydrophobic group in rigid ligand, which facilitates the permeation of the complex through the lipid layer of the cell membrane leading to a reduction in polarity of the ligand and the central metal ion[45].

Deghadi et al[16] have reported the synthesis of UO_2(IV), Er (III) and La (III) complexes of hydrazones derived from condensation of 1,3-bis(4-amino-5-phenyl-1,2,4-triazol-3-ylsulfanyl)propane with benzaldehyde. The synthesized compounds **(**167), (168), (169) and (170) were screened for anticancer activity against MCF-7 and HepG2 cell lines. They exhibited notable cytotoxicity, demonstrating IC_{50}

values (in μM) of 23 and ~50; ~50 and 17.6; 35 and 18; 36 and 33 against MCF-7 and HepG2 cell lines respectively. The lowest IC_{50} values were 17.6 μM for (168) against MCF-7 and 23 μM for ligand (167) against HepG2 cell lines, which make them important candidates of effective anticancer drugs in the future *in vivo* research.

Mohamed et al[48] reported the anticancer activities of metal complexes (172), (173), (174), (175), (176), (177), (178) and (179) comprising of tridentate (2-(1-((8-aminonaphthalen-1-yl)imino)ethyl)cyclopenta-2,4-dien-1-yl) (L) (171), from condensation reaction between isatin drug and 2,6-diaminopyridine. To assess potential as an anticancer agent, cytotoxicity tests were performed on (MCF-7) breast cancer cell line. Results for ligand and metal complexes exhibited promising anticancer activity with IC_{50} (μg/mL) values: 15.5, 21.7, 12.4, 18.1, 22, 16.5, 18.6, 20.2, 18.5 for (171 - 179) respectively. Inhibition of growth of malignant cells has been found to be between 74 to 86 % and their IC_{50} values in the rane between 12.4 to 22 for the ligand and complexes. It is worth noting that the Mn(II) complex (173) which has the lowest IC_{50} value with a particle size of 29.71 nm can be used as a powerful drug in cancer treatment because of its easy penetration into tissues leading to apoptosis.



Mahmoud et al[44] studied ferrocenyl based heterocyclic Schiff base ligand, (2-(1-((1-carboxyethyl)imino) ethyl)cyclopenta-2,4-dien-1-yl)(cyclopenta-2,4-dien-1-yl) iron (180) and its mononuclear (181), (182), (183), (184), (185), (186), (187) and (188) complexes by treating $CrCl_3.6H_2O$, $MnCl_2.2H_2O$, $FeCl_3.6\ H_2O$, $CoCl_2.6H_2O$, $ZnCl_2$, $CdCl_2$, $CuCl_2.2H_2O$ and $NiCl_2.6H_2O$ with (180) respectively and investigated *in vitro* cytotoxicity studies against breast cancer cell line (MCF-7 at concentration 100 µg/ml). Complex (184) acts as the most active and effective complex that could be used as anticancer drug against breast cancer in future. It exhibited higher cytotoxicity with IC_{50} values of 10.2 µg/mL, surpassing the ligand and other four complexes. Ligand HL (180) showed, 50.2 µg/ml; complex (181), 30.8 µg/ml; (186), 24.8 µg/ml; (187), 42.2 µg/ml.

The increased cytotoxicity of complex (184) may be attributed to the increase in π-electron delocalization in the (ferrocenyl) ligand moiety on complexation, as a result, reduces the polarity of the metal complexes, facilitating their efficient cell penetration via lipid layer of cell membranes. Keypour et al[36] investigated 1,4-bis(o-aminobenzyl)-1,4-diazacycloheptane (L) (189) and their complexes, $[CuL](ClO_4)_2$ (190) and $[Ni(L)(NCMe)_2](ClO_4)_2.NCMe$ (191). Results for anticancer activity for the ligand and their metal complexes demonstrated high cytotoxicity against MCF-7 cancer cells, where complex **(**190) showed IC_{50} value of 1.44 µM, followed by (191) with IC_{50} value 1.67 µM and then the ligand with IC_{50} value 3.39 µM.

It was also observed that all complexes are more active than the free ligand, although their anticancer activity is still less than cisplatin as the positive control. The increase in cytotoxic activity can be attributed to the presence of positive charge of the metal, which increases the acidity of the proton-holding coordinated ligand, leading to the formation of stronger hydrogen bonds that enhance anticancer activity. Rauf et al[61] synthesized four transition metal complexes ZnL^1_2 (194), CoL^1_2 (195), ZnL^2_2 (196) and CoL^2_2 (197) with novel Schiff base, 3-(((4-chlorophenyl) imino)methyl)benzene-1,2-diol (HL^1) (192) and 3-(((4-bromophenyl)imino)methyl)benzene-1,2-diol (HL^2) (193) derived from condensation reaction of 2,3-dihydroxybenzaldehyde and respective 4-haloaniline. They also investigated anticancer activity of two ligands and four metal complexes and their impact on the viability and apoptosis of human hepatocellular carcinoma HepG2 cell line.

Cell cultures exposed to the compounds at concentration of 200 mg/mL for 24 h were followed by SRB assay analysis. Results showed that ZnL^2_2 (196) with relative viability = 26.67 ± 3.97 and CoL^2_2 (197) with 32.53 ± 2.54 were biologically active against HepG2 cells whereas HL^2 exhibited slight toxicity against the cultures. Furthermore, HL^1 (192) showed relative viability, 36.78 ± 2.85 was more toxic when compared to ZnL^1_2 (194) and CoL^1_2 (195). The complex ZnL^2_2 (196) and CoL^2_2 (197) displayed inhibitory effects on human hepatocellular carcinoma HepG2 cell migration and also induced morphological changes in the cells by cellular clumping and blebbing thus, leading to activation of programmed cell death. The ligand HL^1 induced a significantly higher level of apoptosis in the HepG2 cell line compared to other five compounds.

Parsekar et al[55] reported mononuclear Cu(II) complex $[Cu(HL)(phen)]\cdot H_2O$ (198). Synthesized complexes were found to bind to HSA in subdomain IIA by molecular docking studies and its IC_{50} values 0.8047 ± 0.1378 µM and 0.4390 ± 0.1139 µM were obtained from the MTT assay with HeLa and MCF7 cells respectively, indicating significant *in vitro* anticancer activity as compared to cisplatin in both the tested cell lines, which has IC_{50} values 31.24 ± 1.38 µM and 99.6481 ± 0.051 µM. Electronic spectroscopic studies in presence of calf thymus DNA (CT-DNA) showed strong binding affinity and displayed intercalative binding of DNA, causing significant oxidative cleavage of pUC19 DNA.

Conclusion

Schiff base metal complexes displayed different structural, chemical, biological and medicinal properties than its corresponding free ligands. They act as potential scaffold for the development and discovery of novel drugs. The incorporation of central metal ion into Schiff base ligands increases various biological and medicinal properties. The metal complexation provides novel chemical properties and reactivities such as targeted drug delivery vehicle for controlled release of anticancer drugs, redox processes, catalysis, protein binding.

References

1. Ahmed Y.M., Mahmoud W.H., Omar M.M. and Mohamed G.G., Synthesis, Characterization and Biological Activity of Transition Metals Schif Base Complexes Derived from 4,6-Diacetylresorcinol and 1,8-Naphthalenediamine, *Journal of Inorganic and Organometallic Polymers and Materials*, **31**, 2339–2359 **(2021)**

2. Alorini T.A., Al-Hakimi A.N., Saeed S.E, Alhamzi E.H.L. and Albadri A.E.A.E., Synthesis, characterization, and anticancer activity of some metal complexes with a new Schiff base ligand, *Arabian Journal of Chemistry*, **15(2)**, 103559 **(2021)**

3. Alorini T., Daoud I., Al-Hakimi A.N. and Alminderej F., Synthesis, characterization, anticancer activity and molecular docking study of some metal complexes with a new Schiff base ligand, *Journal of Molecular Structure*, **1276**, 1-16 **(2023)**

4. Al-Shboul T.M.A., El-khateeb M., Obeidat Z.H., Ababneh T.S., Al-Tarawneh S.S., Al-Zoubi M.S., Alshaer W., Seni A.A., Qasem T., Moriyama H., Yoshida Y., Kitagawa H. and Jazzazi T.M.A., Synthesis, Characterization, Computational and Biological Activity of Some Schiff Bases and Their Fe, Cu and Zn Complexes, *Inorganics*, **10**, 1-15 **(2022)**

5. Aras B. and Yerlikaya A., Bortezomib and etoposide combinations exert synergistic effects on the human prostate cancer cell line PC-3, *Oncology Letters*, **11(5)**, 3179-3184 **(2016)**

6. Azam M., Warad I., Al-Resayes S., Shakir M., Ullah M.F., Ahmad A. and Sarkar F.H., A novel Ru(II) complex derived from hydroxydiamine as a potential antitumor agent: Synthesis and Structural Characterization, *Inorganic Chemistry Communications*, **20**, 252-258 **(2012)**

7. Bar N., Chowdhury P., Roy D., Adhikari S., Mondal S., Das G.K. and Chandra S.K., Photochromism of dye containing Schiff base-metal complex: A revisit through spectro-kinetic, thermodynamic and theoretical analyses for the design of a molecular logic gate, *J Photochemistry Photobiology A: Chemistry*, **420**, 1-13 **(2021)**

8. Bjelogrlić S., Todorović T.R., Cvijetić I., Rodić M.V., Vujčić M., Marković S., Araškov J., Janović B., Emhemmed F., Muller C.D. and Filipović N.R., A novel binuclear hydrazone-based Cd(II) complex is a strong pro-apoptotic inducer with significant activity against 2D and 3D pancreatic cancer stem cells, *Journal of Inorganic Biochemistry*, **190**, 45-66 **(2019)**

9. Break M.K.B., Fung T.Y., Koh M.Z., Ho W.Y., Tahir M.I.M., Elfar O.A., Syed R.U., Khojali W.M.A., Alluhaibi T.M., Huwaimel B., Wiart C. and Khoo T.J., Synthesis, Crystal Structure, Antibacterial and *In Vitro* Anticancer Activity of Novel Macroacyclic Schiff Bases and Their Cu (II) Complexes Derived from S-Methyl and S-Benzyl Dithiocarbazate, *Molecules*, **28**, 1-19 **(2023)**

10. Ceramella J., Iacopetta D., Catalano A., Cirillo F., Lappano R. and Sinicropi M.S., A Review on the Antimicrobial Activity of Schiff Bases: Data Collection and Recent Studies, *Antibiotics*, **11**, 1-23 **(2022)**

11. Cerella C., Sobolewski C., Dicato M. and Diederich M., Targeting COX-2 expression by natural compounds: A promising alternative strategy to synthetic COX-2 inhibitors for cancer chemoprevention and therapy, *Biochemical Pharmacology*, **80(12)**, 1801-1815 **(2010)**

12. Clercq E.D., Strategies in the design of antiviral drugs, *Nature Reviews Drug Discovery*, **1**, 13-25 **(2002)**

13. Correia I., Roy S., Matos C.P., Borovic S., Butenko N., Cavaco I., Marques F., Lorenzo J., Rodríguez A., Moreno V. and Pessoa J.C., Vanadium(IV) and copper(II) complexes of salicylaldimines and aromatic heterocycles: Cytotoxicity, DNA binding and DNA cleavage properties, *Journal of Inorganic Biochemistry*, **147**, 134-146 **(2015)**

14. Da Silva C.M., Da Silva D.L., Modolo L.V., Alves R.B., De Resende M.A., Martins C.V.B. and De Fatima A., Schiff bases: A short review of their antimicrobial activities, *Journal of Advanced Research*, **2(1)**, 1-8 **(2011)**

15. De los S.Z.A., Ding R. and Wolf C., Quantitative chirality sensing of amines and amino alcohols via Schiff base formation with a stereodynamic UV/CD probe, *Organic and Biomolecular Chemistry*, **14**, 1934-1939 **(2016)**

16. Deghadi R.G., Abbas, A.A. and Mohamed G.G., Theoretical and experimental investigations of new bis (amino triazole) schiff base ligand: Preparation of its UO2(II), Er (III) and La (III) complexes, studying of their antibacterial, anticancer and molecular docking, *Applied Organometallic Chemistry*, **35(8)**, 1-17 **(2021)**

17. Deghadi R.G., Elsharkawy A.E., Ashmawy A.M. and Mohamed G.G., Can One Novel Series of Transition Metal Complexes of Oxy-dianiline Schiff Base Afford Advances in Both Biological Inorganic Chemistry and Materials Science?, *Comments on Inorganic Chemistry***, 42(1)**, 1-46 **(2022)**

18. Devi J., Yadav M., Jindal D.K., Kumar D. and Poornachandra Y., Synthesis, spectroscopic characterization, biological screening and *in vitro* cytotoxic studies of 4-methyl-3-thiosemicarbazone derived Schiff bases and their Co (II), Ni (II), Cu (II) and Zn (II) complexes, *Applied Organometallic Chemistry*, **33(10)**, 1-23 **(2019)**

19. Ejiah F.N., Rofiu M.O., Oloba-Whenu O.A. and Fasina T.M., Schiff bases as analytical tools: synthesis, chemo-sensor and computational studies of 2-aminophenol Schiff bases, *Materials Advances*, **4**, 2308-2321 **(2023)**

20. El-Gammal O.A., Mohamed F.S., Rezk G.N. and El-Bindary A.A., Structural characterization and biological activity of a new metal complexes based of Schiff base, *Journal of Molecular Liquids*, **330**, 1-16 **(2021)**

21. Fabbrizzi L., Beauty in Chemistry: Making Artistic Molecules with Schiff Bases, *Journal of Organic Chemistry*, **85**, 12212-12226 **(2020)**

22. Feng L.S., Xu Z., Chang L., Li C., Yan X.F., Gao C., Ding C., Zhao F., Shi F. and Wu X., Hybrid molecules with potential in vitro antiplasmodial and in vivo antimalarial activity against drug-resistant Plasmodium falciparum, *Medicinal Research Reviews*, **40(3)**, 931-971 **(2019)**

23. Galanski M., Slaby S., Jakupec M.A. and Keppler B.K., Synthesis and *in vitro* Antitumor Potency of (Cyclohexane-1,2-Diamine)Platinum(II) Complexes with Aminotris (Methylenephosphonic Acid) as Bone-Seeking Ligand, *Bioinorganic Chemistry and Applications*, **3(3-4)**, 179-190 **(2005)**

24. Galanski M., Yasemi A., Slaby S., Jakupec M.A., Arion V.B., Rausch M., Nazarov A.A. and Keppler B.K., Synthesis, crystal structure and cytotoxicity of new oxaliplatin analogues indicating that improvement of anticancer activity is still possible, *European Journal of Medicinal Chemistry*, **39(8)**, 707-714 **(2004)**

25. Hajari S., Keypour H., Rezaei M.T., Farida S.H.M. and Gable R.W., New 15-membered macrocyclic Schiff base ligand; synthesis some Cd(II), Mn(II) and Zn(II) complexes, crystal structure, cytotoxicity, antibacterial and antioxidant activity, *Journal of Molecular Structure*, **1251**, 1-8 **(2022)**

26. Hassan A.M., Said A.O., Heakal B.H., Younis A., Aboulthana W.M. and Mady M.F., Green Synthesis, Characterization, Antimicrobial and Anticancer Screening of New Metal Complexes Incorporating Schiff Base, *ACS Omega*, **7**, 32418-32431 **(2022)**

27. Hreusova M., Novohradsky V., Markova L., Kostrhunova H., Potocnak I., Brabec V. and Kasparkova J., Gallium (III) Complex with Cloxyquin Ligands Induces Ferroptosis in Cancer Cells and Is a Potent Agent against Both Differentiated and Tumorigenic Cancer Stem Rhabdomyosarcoma Cells, *Bioinorganic Chemistry and Applications*, **2022(1)**, 3095749 **(2022)**

28. Hsu J.D., Kao S.H., Ou, T.T., Chen Y.J., Li Y.J. and Wang C.J., Gallic acid induces G2/M phase arrest of breast cancer cell MCF-

7 through stabilization of $p27^{Kip1}$ attributed to disruption of $p27^{Kip1}$/Skp2 complex, *Journal of Agricultural and Food Chemistry*, **59(5)**, 1996-2003 **(2011)**

29. Hussain I., Ullah A., Khan A.U., Khan W.U., Ullah R., Naser A.A.S.A.A. and Mahmood H.M., Synthesis, Characterization and Biological Activities of Hydrazone Schiff Base and its Novel Metals Complexes, *Sains Malaysiana*, **48(7)**, 1439-1446 **(2019)**

30. Iakovidis I., Delimaris I. and Piperakis S.M., Copper and Its Complexes in Medicine: A Biochemical Approach, *Molecular Biology International*, **2011**, 1-14 **(2011)**

31. Indrayanto G., Putra G.S. and Suhud F., Validation of in-vitro bioassay methods: Application in herbal drug research, *Profiles of Drug Substances, Excipients and Related Methodology*, **46**, 273-307 **(2021)**

32. Jiawei L., Hecheng M., Xiaobing G., Zhongsheng T. and Shujuan Y., Natural Aldehyde-Chitosan Schiff Base: Fabrication, pH-Responsive Properties and Vegetable Preservation, *Foods*, **12**, 2921-2932 **(2023)**

33. Juyal V.K., Pathak A., Panwar M., Thakuri S.C., Prakash O., Agrwal A. and Nand V., Schiff base metal complexes as a versatile catalyst: A review, *Journal of Organometallic Chemistry*, **999**, 1-37 **(2023)**

34. Kareem A., Laxmi, Arshad M., Nami S.A.A. and Nishat N., Herbo-mineral based Schiff base ligand and its metal complexes: Synthesis, characterization, catalytic potential and biological applications, *Journal of Photochemistry and Photobiology B: Biology*, **160**, 163-171 **(2016)**

35. Kaushik S., Paliwal S.K., Iyer M.R and Patil V.M., Promising Schiff bases in antiviral drug design and discovery, *Medicinal Chemistry Research*, **32**, 1063-1076 **(2023)**

36. Keypour H., Fatemikia H., Zeynali H., Karamian R., Sorboni S.G. and Gable R.W., Molecular docking and biological studies of the Cu(II) and Ni(II) macroacyclic complexes with 1,4-bis(o-aminobenzyl)-1,4-diazacycloheptane, a ligand containing the homopiperazine moiety, *Inorganic Chemistry Communications*, **149**, 1-13 **(2023)**

37. Khalil E.A.M. and Mohamed G.G., Preparation, spectroscopic characterization and antitumor-antimicrobial studies of some Schiff base transition and inner transition mixed ligand complexes, *Journal of Molecular Structure*, **1249**, 1-15 **(2022)**

38. Khan H.Y., Maurya S.K., Siddique H.R., Yousuf S. and Arjmand F., New Tailored RNA-Targeted Organometallic Drug Candidates against Huh7 (Liver) and Du145 (Prostate) Cancer Cell Lines, *ACS Omega*, **5**, 15218-15228 **(2020)**

39. Kumbar M., Patil S.A., Toragalmath S.S., Jawoor S.S. and Shettar A., Synthesis of novel metal (II) complexes tailored from 9-oxo-9H-fluorene-1-carboxylic acid via green protocol: DNA cleavage and anticancer studies, *Inorganica Chimica Acta*, **500,** 1-10 **(2020)**

40. Kundu B.K., Mobin S.M. and Mukhopadhyay S., Studies on the influence of the nuclearity of zinc (II) hemi-salen complexes on some pivotal biological applications, Dalton Transactions, **49(43)**, 15481-15503 **(2020)**

41. Leroux F.R., Manteau B., Vors J.P. and Pazenok S., Trifluoromethyl ethers – synthesis and properties of an unusual substituent, *Beilstein Journal of Organic Chemistry*, **4(13)**, 1-15 **(2008)**

42. Leonard E., Takeda C. and Akitsu T., Azobenzene-Containing Schiff-Bases—Syntheses and Dyes Applications, *Colorants*, **3**, 53–72 **(2024)**

43. Liu X. and Hamon J.R., Recent developments in penta-, hexa- and heptadentate Schiff base ligands and their metal complexes, *Coordination Chemistry Reviews*, **389**, 94-118 **(2019)**

44. Mahmoud W.H., Deghadi R.G., Desssouky M.M.I.E. and Mohamed G.G., Transition metal complexes of nano bidentate organometallic Schiff base : Preparation, structure characterization, biological activity, DFT and molecular docking studies, *Applied Organometallic Chemistry*, **33(7)**, 1-21 **(2019)**

45. Mahmoud W.H., Deghadi R.G. and Mohamed G.G., Metal complexes of novel Schiff base derived from iron sandwiched organometallic and 4-nitro-1,2-phenylenediamine: Synthesis, characterization, DFT studies, antimicrobial activities and molecular docking, *Applied Organometallic Chemistry*, **32(4)**, 1-22 **(2018)**

46. Matela G., Schiff Bases and Complexes: A Review on Anti-Cancer Activity, *Anticancer Agents in Medicinal Chemistry*, **20**, 1908-1917 **(2020)**

47. Moghadam M.E., Esfahani M.H., Behzad M., Zolghadri S., Ramezani N. and Azadi Y., New platinum (II) complexes based on schiff bases: synthesis, specifcation, X-ray structure, ADMET, DFT, molecular docking and anticancer activity against breast cancer, *JBIC Journal of Biological Inorganic Chemistry*, **28**, 519–529 **(2023)**

48. Mohamed G.G., Omar M.M.A., Moustafa B.S., Abdel-halim H.F. and Farag N.A., Spectroscopic investigation, thermal, molecular structure, antimicrobial and anticancer activity with modelling studies of some metal complexes derived from isatin Schiff base ligand, *Inorganic Chemistry Communications*, **141**, 1-13 **(2022)**

49. Nguyen Q.T., Thi P.N.P. and Nguyen V.T., Synthesis, Characterization and *In Vitro* Cytotoxicity of Unsymmetrical Tetradentate Schiff Base Cu(II) and Fe(III) Complexes, *Bioinorganic Chemistry and Applications*, **2021(1)**, 1-10 **(2021)**

50. Noser A.A., Abdelmonsef A.H., El-Naggar M. and Salem M.M., New Amino Acid Schiff Bases as Anticancer Agents via Potential Mitochondrial Complex I-Associated Hexokinase Inhibition and Targeting AMP-Protein Kinases/mTOR Signaling Pathway, *Molecules*, **26**, 1-27 **(2021)**

51. Nunes P., Marques F., Cavacoa I., Pessoa J.C. and Correia I., Exploring the therapeutic potential of Cu(II)-complexes with ligands derived from pyridoxal, *Inorganica Chimica Acta*, **507**, 1-13 **(2020)**

52. Ou H.W., Lo K.H., Du W.T., Lu W.Y., Chuang W.J., Huang B.H., Chen H.Y. and Lin C.C., Synthesis of Sodium Complexes Supported with NNO-Tridentate Schiff Base Ligands and Their

Applications in the Ring-Opening Polymerization of l-Lactide, *Inorganic Chemistry*, **55**, 1423-1432 **(2016)**

53. Pal R., Kumar V., Gupta A.K. and Beniwal V., Synthesis, characterization and DNA photo cleavage study of dehydroacetic acid based tridentate Schiff base and its metal complexes of first transition series, *Medicinal Chemistry Research*, **23(9)**, 4060-4069 **(2014)**

54. Park C., Lim J.S., Lee Y., Lee B., Kim S.W. and Lee J., Optimization and morphology for decolorization of reactive black 5 by *Funalia trogii*, *Enzyme and Microbial Technology*, **40(7)**, 1758-1764 **(2007)**

55. Parsekar S.U., Paliwal K., Haldar P., Antharjanam P.K.S. and Kumar M., Synthesis, Characterization, Crystal Structure, DNA and HAS Interactions and Anticancer Activity of a Mononuclear Cu(II) Complex with a Schiff Base Ligand Containing a Thiadiazoline Moiety, *ACS Omega*, **7(3)**, 2881-2896 **(2022)**

56. Patel N.B., Patel J.N., Purohit A.C., Patel V.M., Rajani D.P., Moo-Puc R., Lopez-Cedillo J.C., Nogueda-Torres B. and Rivera G., In vitro and in vivo assessment of newer quinoxaline–oxadiazole hybrids as antimicrobial and antiprotozoal agents, *International Journal of Antimicrobial Agents*, **50**, 413-418 **(2017)**

57. Pathan I.R. and Patel M.K., A comprehensive review on the synthesis and applications of Schiff base ligand and metal complexes: A comparative study of conventional heating, microwave heating and sonochemical methods, *Inorganic Chemistry Communications*, **158**, 1-25 **(2023)**

58. Patra S.A., Mohanty M., Banerjee A., Kesarwani S., Henkel F., Reuter H. and Dinda R., Protein binding and cytotoxic activities of monomeric and dimeric oxido-vanadium(V) salan complexes: Exploring the solution behavior of monoalkoxido-bound oxido-vanadium(V) complex, *Journal of Inorganic Biochemistry*, **224**, 1-19 **(2021)**

59. Przybylski P., Huczynski A., Pyta K., Brzezinski B. and Bartl F., Biological Properties of Schiff Bases and Azo Derivatives of Phenols, *Current Organic Chemistry*, **13(2)**, 124-148 **(2009)**

60. Raman N., Mitu L., Sakthivel A. and Pandi M.S., Studies on DNA Cleavage and Antimicrobial Screening of Transition Metal Complexes of 4-Aminoantipyrine Derivatives of N_2O_2 Type, *Journal of the Iranian Chemical Society*, **6(4)**, 738-748 **(2009)**

61. Rauf A., Shah A., Munawar K.S., Khan A.A., Abbasi R., Yameen M.A., Khan A.M., Abdur R.K., Qureshi I.Z., Kraatz H.B. and Zia-ur-Rehman, Synthesis, spectroscopic characterization, DFT optimization and biological activities of Schiff bases and their metal (II) complexes, *Journal of Molecular Structure*, **1145**, 132-140 **(2017)**

62. Ray S., Mohan R., Singh J.K., Samantaray M.K., Shaikh M.M., Panda D. and Ghosh P., Anticancer and Antimicrobial Metallopharmaceutical Agents Based on Palladium, Gold and Silver N-Heterocyclic Carbene Complexes, *Journal of American Chemical Society*, **129(48)**, 15042-15053 **(2007)**

63. Reytman L., Braitbard O. and Tshuva E.Y., Highly cytotoxic vanadium(V) complexes of salan ligands; insights on the role of hydrolysis, *Dalton Transactions*, **41(17)**, 5241-5247 **(2012)**

64. Saeed A.M., Al Neyadi S.S. and Abdou I.M., Anticancer activity of novel Schiff bases and azo dyes derived from 3-amino-4-hydroxy-2H-pyrano[3,2-c]quinoline-2,5(6H)-dione, *Heterocyclic Communications*, **26**, 192-205 **(2020)**

65. Saini R.P., Kumar V., Gupta A.K. and Gupta G.K., Synthesis, characterization and antibacterial activity of a novel heterocyclic Schiff's base and its metal complexes of first transition series, *Medicinal Chemistry Research*, **23(2)**, 690-698 **(2014)**

66. Saini R.P., Kumar V., Gupta A.K. and Beniwal V., Synthesis, characterization and DNA photocleavage study of a novel dehydroacetic acid based hydrazone Schiff base and its metal complexes, *Medicinal Chemistry Research*, **23(7)**, 3327-3335 **(2014)**

67. Sakkaravarthy Shanmugapriya, Sukumaran Latha, Chinnasamy Kanagaraj and Murugan Rashika, Recent advances in chemopreventive effect of geraniol against endometrial cancer cell lines: A review of key trials based on signalling pathways, *Res. J. Biotech.*, **18(12)**, 142-146 **(2023)**

68. Saswati, Mohanty M., Banerjee A., Biswal S., Horn Jr. A., Schenk G., Brzezinski K., Sinn E., Reuter H. and Dinda R., Polynuclear Zinc(II) complexes of thiosemicarbazone: Synthesis, X-ray structure and biological evaluation, *Journal of Inorganic Biochemistry*, **203**, 1-13 **(2020)**

69. Savcı A., Buldurun K., Alkis M.E., Alan Y. and Turan N., Synthesis, characterization, antioxidant and anticancer activities of a new Schif base and its M(II) complexes derived from 5-fuorouracil, *Medical Oncology*, **39**, 1-11 **(2022)**

70. Shi S., Yu S., Quan L., Mansoor M., Chen Z., Hu H., Liu D., Liang Y. and Liang F., Synthesis and antitumor activities of transition metal complexes of a bis-Schiff base of 2-hydroxy-1-naphthalenecarboxaldehyde, *Journal of Inorganic Biochemistry*, **210**, 1-10 **(2020)**

71. Sinha D., Tiwari A.K., Singh S., Shukla G., Mishra P., Chandra H. and Mishra A.K., Synthesis, characterization and biological activity of Schiff base analogues of indole-3-carboxaldehyde, *European Journal of Medicinal Chemistry*, **43**, 160-165 **(2008)**

72. Sinha K., Pal P.B. and Sil P.C., Cadmium (Cd2+) exposure differentially elicits both cell proliferation and cell death related responses in SK-RC-45, *Toxicology in Vitro*, **28**, 307-318 **(2014)**

73. Soroceanu A. and Bargan A., Advanced and Biomedical Applications of Schiff-Base Ligands and Their Metal Complexes: A Review, *Crystals*, **12**, 1-15 **(2022)**

74. Stockert A., Kinder D., Christ M., Amend K. and Aulthouse A., Improving the Efficacy of Cisplatin in Colon Cancer HT-29 Cells via Combination Therapy with Selenium, *Austin Journal of Pharmacology and Therapeutics*, **2(2)**, 1-6 **(2014)**

75. Thuy L.T. et al, Design, synthesis and in vitro antimalarial evaluation of new quinolinylhydrazone derivatives, *Letters in Drug Design and Discovery*, **9(2)**,163–168 **(2012)**

76. Wang J., Zhu H., Liu X. and Liu Z., N-acetylcysteine protects against cadmium-induced oxidative stress in rat hepatocytes, *Journal of Veterinary Science*, **15(4)**, 485-493 **(2014)**

77. Wang Y., Zhang, X., Zhang Q. and Yang Z., Oxidative damage to DNA by 1,10-phenanthroline/ L-threonine copper (II) complexes with chlorogenic acid, *BioMetals*, **23**, 265-273 **(2010)**

78. Wilke N.L., Abodo L.O., Frias C., Frias J., Baas J., Jakupec M.A., Keppler B.K. and Prokop A., The gallium complex KP46 sensitizes resistant leukemia cells and overcomes Bcl-2-induced multidrug resistance in lymphoma cells via upregulation of Harakiri and downregulation of XIAP *in vitro*, *Biomedicine and Pharmacotherapy*, **156**, 1-11 **(2022)**

79. Yin L., Zhang S., Zhou T., Zhen'guang H. and Zhang S., Synthesis, characterization and anticancer activity of mononuclear Schiff-base metal complexes, *Journal of Molecular Structure*, **1275**, 1-8 **(2023)**

80. Yousef T.A., Abu El-Reash G.M. and El-Tabai M.N., Comparative studies on P-vanillin and O-vanillin of 2-hydrazinyl-2-oxo-N-phenylacetamide and their Mn(II) and Co(II) complexes, *Journal of Molecular Structure*, **1159**, 246-258 **(2018)**

81. Zehra S., Roisnel T. and Arjmand F., Enantiomeric Amino Acid Schiff Base Copper(II) Complexes as a New Class of RNA-Targeted Metallo-Intercalators: Single X-ray Crystal Structural Details, Comparative in Vitro DNA/RNA Binding Profile, Cleavage and Cytotoxicity, *ACS Omega*, **4**, 7691-7705 **(2019)**

82. Zhao J., Zhang L., Li J., Wu T., Wang M., Xu G., Zhang F., Liu L., Yang J. and Sun S., A novel pyrazolone-based derivative induces apoptosis in human esophageal cells via reactive oxygen species (ROS) generation and caspase-dependent mitochondria-mediated pathway, *Chemico-Biological Interactions*, **231**, 1-9 **(2015)**

83. Zhao P., Qiu H., Wei Q., Li Y., Gao L. and Zhao P., Anti-tumor efect of novel amino acid Schif base nickel (II) complexes on oral squamous cell carcinoma cells (CAL-27) *in vitro*, *Molecular & Cellular Toxicology*, **19**, 265-275 **(2023)**

84. Zhao P., Zhai S., Dong J., Gao L., Liu X., Wang L., Kong J. and Li L., Synthesis, Structure, DNA Interaction and SOD Activity of Three Nickel(II) Complexes Containing L-Phenylalanine Schiff Base and 1,10-Phenanthroline, *Hindawi Bioinorganic Chemistry and Applications*, **2018**, 1-16 **(2018)**

85. Zorov D.B., Juhaszova M. and Sollott S.J., Mitochondrial reactive oxygen species (ROS) and ROS-induced ROS release, *Physiological Reviews*, **94(3)**, 909-950 **(2014)**.

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