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Evaluation of Anticancer Activity of Schiff bases Derived from Pyridine and their Metal Complexes (A Review)

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ABSTRACT

Cancer is a deadly disease; many treatment strategies are available to cure/treat cancer. After the metal-based anticancer drug (Cisplatin), metal complexes play a vital role in pharmaceutical science. We aimed to analyze the anticancer activity of pyridine Schiff base complexes. This review article searched the anticancer studies of pyridine Schiff base metal complexes from 2015 to 2021. Information was gathered from the selected studies to analyze and highlight the importance of anticancer agents. A total of sixty six full-length articles were collected and evaluated. On the critical assessment, we found that compared to Schiff base ligand, the metal complexes exhibited excellent activity towards various cancer cell lines (including MCF-7, HeLa, HCT-116, Hepa-2).We identified more complexes that exhibited promising activity against various cell lines and revealed IC_{50} values equal to or even lower than the reference drug used.

Keywords: Pyridine, Metal complexes, Anti cancer activity, Cell viability, IC_{50}.

INTRODUCTION

Cancer is a fatal disease characterized by abnormal cell development in a specific section of the body and can destroy normal body tissues. The formed mass of tissues is called a tumor. These tumors can be malignant or benign. This benign tumor is not life threatening, while a malignant tumor is cancerous[1]. According to the Indian Council of Medical Research (ICMR) data from 2018, 2.25 million Indians are affected by cancer. Every year, there are 11, 57, 294 new cases and 7, 84, 821 deaths. In India, 9.81% of males and 9.42% of females are at the risk of developing cancer before 75 years.

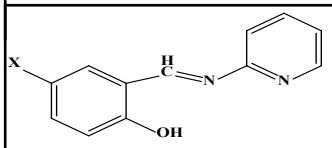
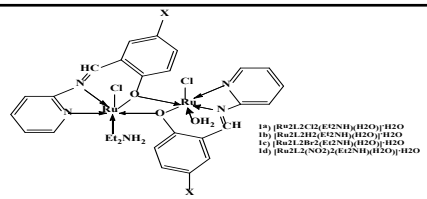
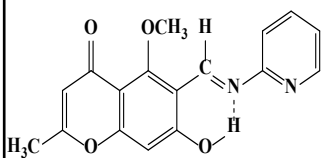
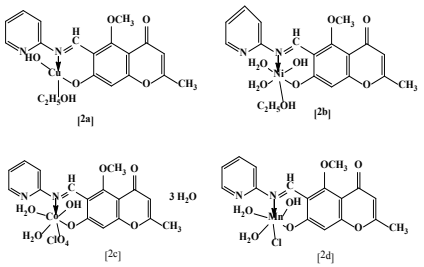
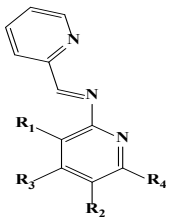
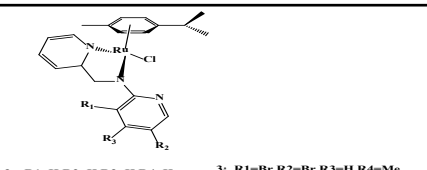
According to the National center for health statistics (2021), 18, 98, 160 new cancer cases and 6, 08, 570 cancer deaths occur in the united states[2]. Early diagnosis and immediate medical treatment are of utmost essential in cancer. The existing treatments such as radiotherapy, surgery, endocrine therapy has serious obstacles, with multidrug resistance (MDR) being the major challenge[3,4]. Scientists are curious to develop new effective anticancer

drugs to treat life-threatening cancer without acute side effects. Schiff base metal complexes are active in the medicinal and pharmaceutical fields because of their anticancer, antibacterial, anti-malarial, antifungal, antiviral, anti-inflammatory, anti-tuberculosis, insecticidal, anti-HIV activities. Schiff bases (R1R2C=NR3) (R-represent alkyl or aryl substituent) are an organic compound that contains the imine group (-C=N-) or azomethine (-CH=N-) [5]. Schiff base ligands are defined as "Privileged ligands" due to their affordability, easiness to synthesis, exhibiting various biological activities, and ability to form complexes with almost all metals such as transition metals, lanthanides, actinides, and more[1]. In this review, we mainly focused on Schiff base metal complexes containing pyridine moiety in their structure. Pyridine is a heterocyclic moiety containing a six-membered ring with one nitrogen atom. The presence of pyridine ring in Schiff base metal complex had a considerable interest in the medicinal field due to their structural modification property to target a particular disease by achieving the desired molecular structure. Although numerous reviews on Schiff bases and their metal complexes have been published, there is no systematic assessment of the anticancer activity of pyridine-based Schiff bases and their metal complexes in the literature[1,5-8]. The excellent therapeutic capabilities of Schiff base and pyridine drew the attention of scientists. In the coming years, we anticipate that this review paper will serve as a valuable resource for designing and synthesizing benign anticancer medicines based on pyridine-based Schiff bases and their metal complexes.

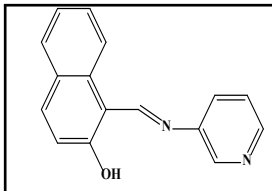
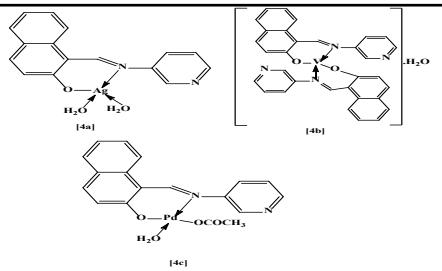
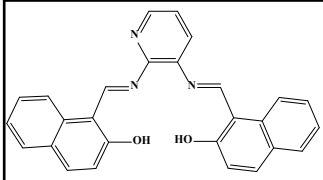
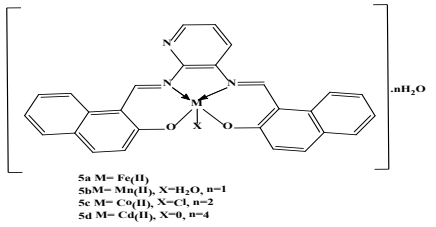
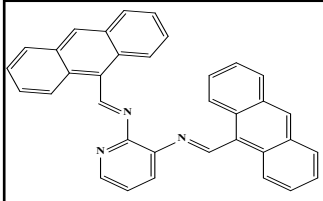
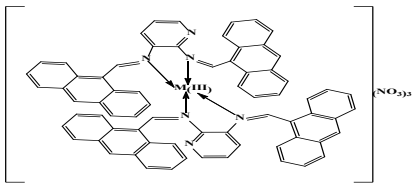
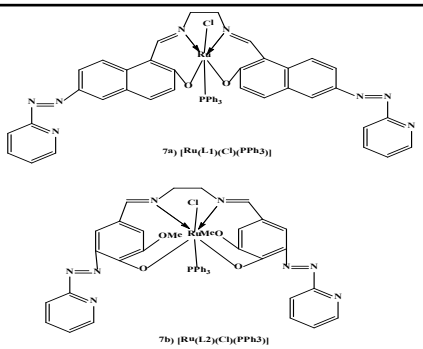
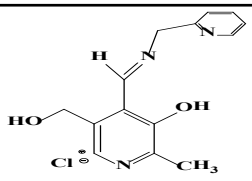
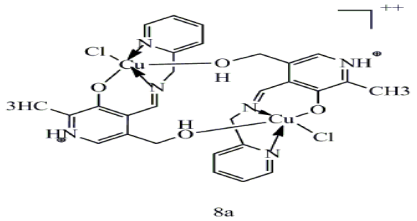
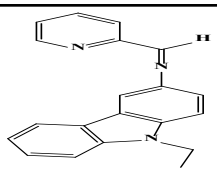
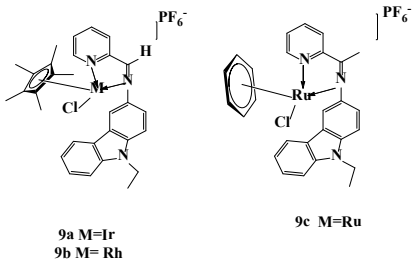
A systematic review of databases related to the anticancer activity of pyridine Schiff base metal complexes was conducted, with additional searches on Google scholar and Sci-Finder using a combination of subject headings and keywords: Schiff bases, pyridine, Schiff base metal complexes, Anticancer activity.

A total of sixty six full-length articles on the subject were examined, the results were summarized, and the activity against different cell types was given as IC_{50} values or inhibition percentages shown in Table 1.

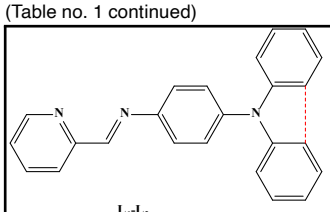
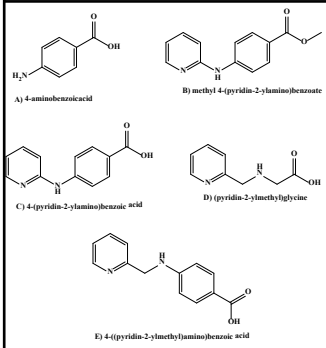
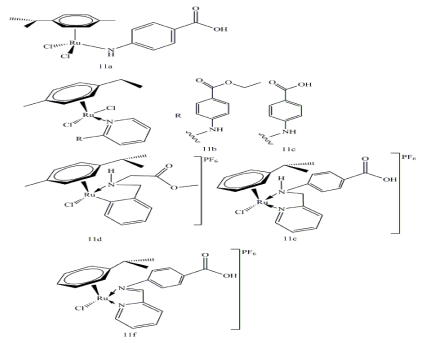
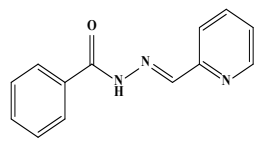
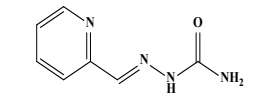
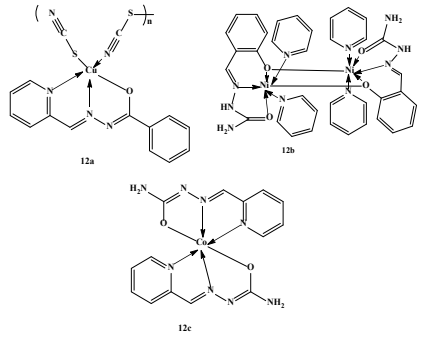
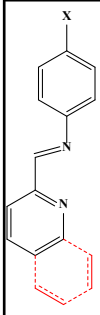
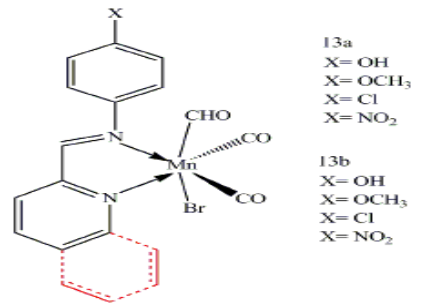
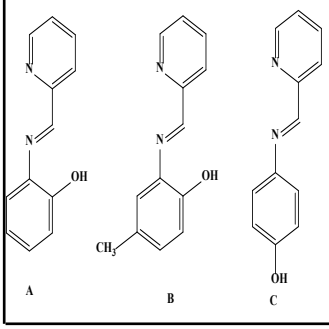
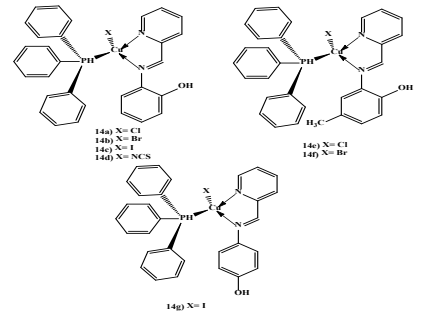
Table 1: Cytotoxic activity of metal complexes

Ligand	Metal Atom	Metal complex	Cytotoxic activity[IC_{50} (μM)]
 N-(2-Pyridyl)-5-X-salicylideneimine X= H, Cl, Br, NO2	Ru(II)	 1a) [Ru2L2Cl2(Et2NH)(H2O)]·H2O 1b) [Ru2L2H2(Et2NH)(H2O)]·H2O 1c) [Ru2L2Br2(Et2NH)(H2O)]·H2O 1d) [Ru2L2(NO2)2(Et2NH)(H2O)]·H2O	HeLa :1b (1.16±0.48μM) SW620 : 1b(1.99±0.56μM) A549: 1b(0.68±0.88μM) MCF-7: 1b(4.09±0.78μM) WI-38: 1b(2.51±98.88μM)
	Cu(II) Co(II) Mn(II) Ni(II)	 [2a] [2b] [2c] [2d]	Inhibition %: Mn-L: HeLa-FAS(80%) HeLa(53%) Huh-7(43%) HepG2(20%)
	Ru(II)	 3a. R1=H,R2=H,R3=H,R4=H 3b. R1=Br,R2=Me,R3=H,R4=H 3c. R1=Br,R2=Br,R3=H,R4=H 3d. R1=H,R2=Br,R3=H,R4=H 3e. R1=Me,R2=H,R3=H,R4=H 3f. R1=H,R2=H,R3=,MeR4=H 3g. R1=OH,R2=H,R3=H,R4=H 3h. R1=H,R2=Me,R3=H,R4=H 3i. R1=H,R2=Cl,R3=H,R4=H 3j. R1=Br,R2=Br,R3=H,R4=Me 3k. R1=Cl,R2=Cl,R3=H,R4=H 3l. R1=H,R2=I,R3=H,R4=H 3m. R1=NO2,R2=Br,R3=Me,R4=H 3n. R1=H,R2=Br,R3=Me,R4=H 3o. R1=NO2,R2=NO2,R3=H,R4=H 3p. R1=H,R2=NO2,R3=H,R4=H 3q. R1=NO2,R2=Br,R3=H,R4=H 3r. R1=H,R2=h,R3=H,R4=Me	MCF-7:3o(07.76±0.88(μM)[2]) HeLa:3o(07.10±1.28(μM)[2])

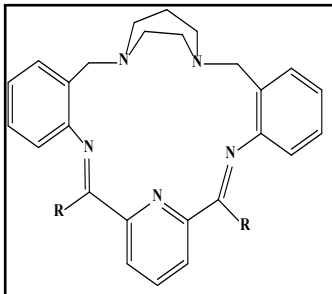
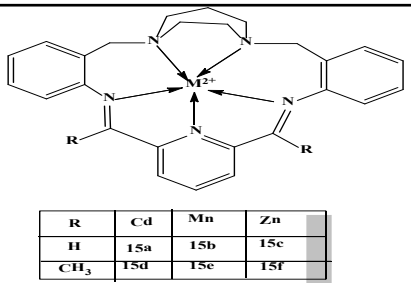
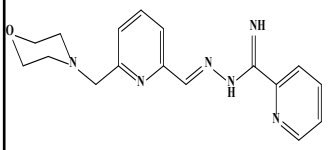
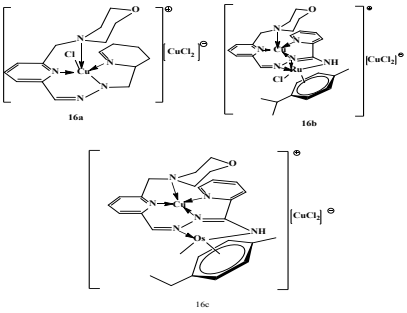
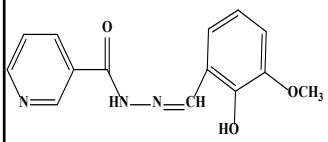
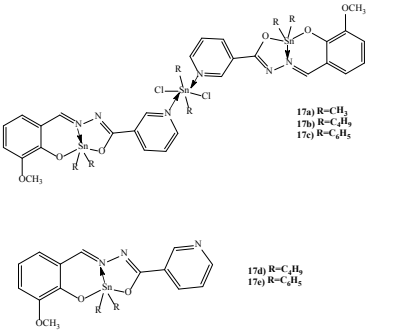
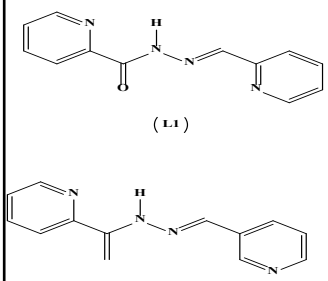
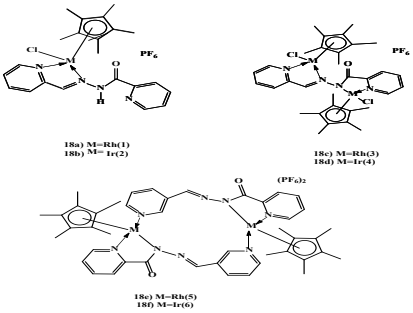
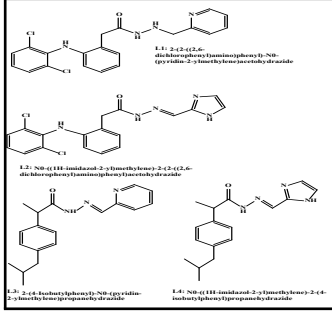
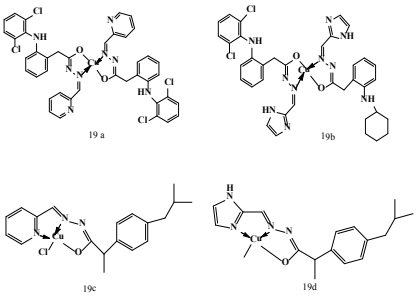
(Table no. 1 continued)

 [1(pyridine-3-yl-iminomethyl) naphthalene-2-ol] (HNAP)	Ag(I) Pd(II) VO(II)	 [4a] [4b] [4c]	HepG-2: 4c (7.90µg/µL) MCF-7 4c (10.60µg/µL)
 1,1'-(pyridine-2,3-dimethyliminomethyl)naphalene-2,2'-diol (HNDAP)	Mn(II) Fe(II) Co(II) Cd(II)	 5a M= Fe(II) 5bM= Mn(II), X=H_2O, n=1 5c M= Co(II), X=Cl, n=2 5d M= Cd(II), X=0, n=4	HepG-2: 5c (~11-18µg/mL) HCT-116: 5b (~10-18µg/mL)
 N,N bis (anthracen-9-ylmethylene) pyridine-2, 3-diamine	Er Pr Yb	 6a M= Er, 6b M=Pr 6c M= Yb	At 25µg/mL: In MCF-7, Vero, HeLa cell lines: 6b(~49-50%)
2-aminopyridine, 2-hydroxy napthaldehye/ vanillin and ethylene diamine	Ru(III)	 7a) $[Ru(L1)(Cl)(PPh3)]$ 7b) $[Ru(L2)(Cl)(PPh3)]$	MCF-7 7a : 25.85µg/mL NH3T3 7a:102.2µg/mL
	Cu(II)	 8a	HeLa HCT
	Ir(III) Rh(III) Ru(II)	 9a M=Ir 9b M= Rh 9c M=Ru	MCF-7 9a (5 µM)

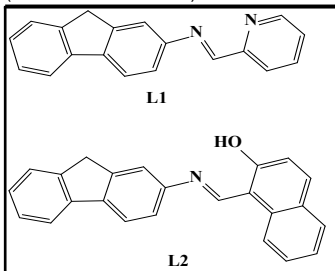
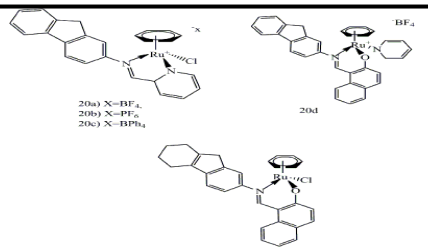
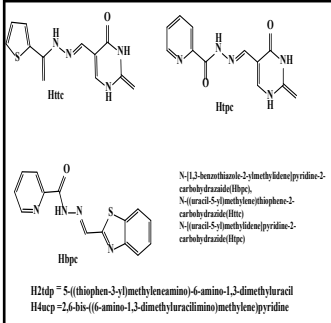
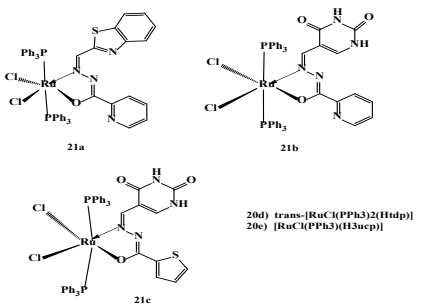
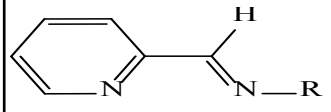
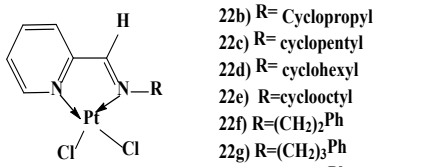
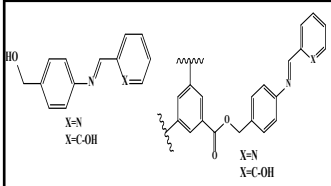
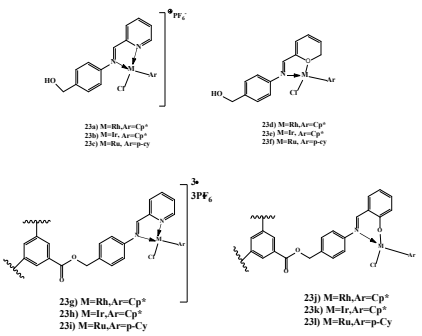
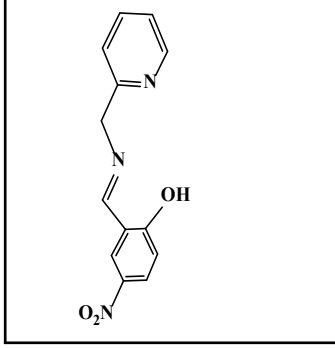
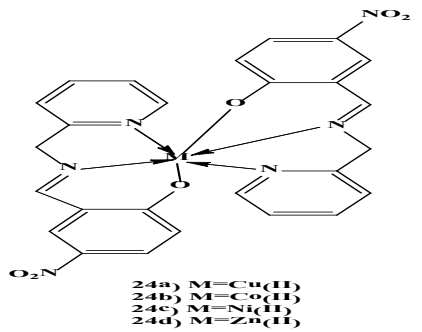
(Table no. 1 continued)

 L_1-L_2 2-formylpyridine and amino substituted triphenylamine	Ir(III)	10a)$[(\eta^5\text{-}C_5Me_5)Ir(L_1)Cl]PF^6$ 10b)$[(\eta^5\text{-}C_5Me_4C_6H_5)Ir(L_1)Cl]PF^6$ 10c) $[(\eta^5\text{-}C_5Me_5)Ir(L_2)Cl]PF^6$ 10d)$[(\eta^5\text{-}C_5Me_4C_6H_5)Ir(L_2)Cl]PF_6$	A549: 10d (2.9±0.2μM) HeLa: 8505C:
 A) 4-aminobenzoicacid B) methyl 4-(pyridin-2-ylamino)benzoate C) 4-(pyridin-2-ylamino)benzoic acid D) (pyridin-2-ylmethyl)glycine E) 4-((pyridin-2-ylmethyl)amino)benzoic acid (A, B, C, D, E = Ligands)	Ru(II)	 11a 11b 11c 11d 11e 11f	D(58.2±11.6μM), 11a(69.1±2.5μM) MCF-7: A(20.2±3.5μM), 11a(36.3±2.6μM) SW-480: D(44.1±5.1μM),
 A) (E)-N'-(pyridine-2-ylmethylene)benzohydrazide  B) (E)-2-(pyridine-2-ylmethylene)hydrazine-1-carboxamide	Cu(II) Ni(II) Co(II)	 12a 12b 12c	AGS &SW742: (12a-12c) > A&B
 pyridine-2-carboxaldehyde or quinoline-2-carboxaldehyde and para substituted aniline derivatives	Mn(I)	 13a X= OH X= OCH_3 X= Cl X= NO_2 13b X= OH X= OCH_3 X= Cl X= NO_2	HepG-2: 13b>13a
 A B C	Cu(I)	 14a) X= Cl 14b) X= Br 14c) X= I 14d) X= NCS 14e) X= Cl 14f) X= Br 14g) X= I	U87: 14c (20 ± 1.5μM)

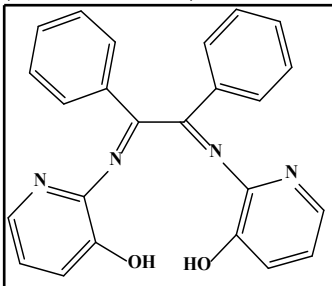
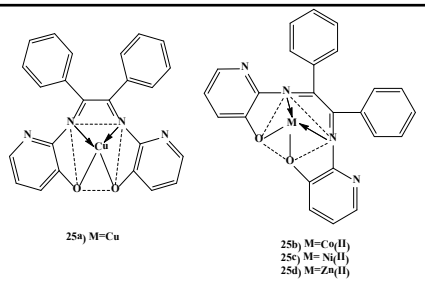
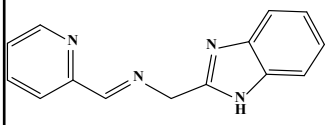
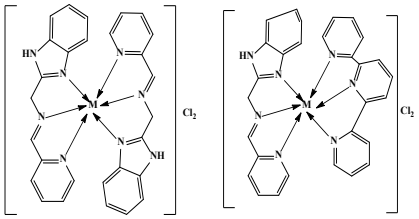
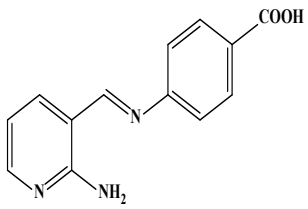
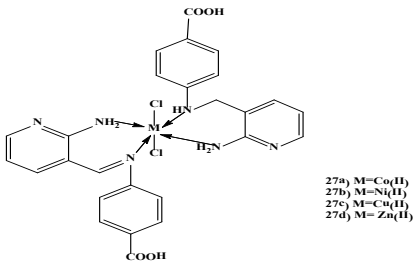
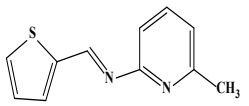
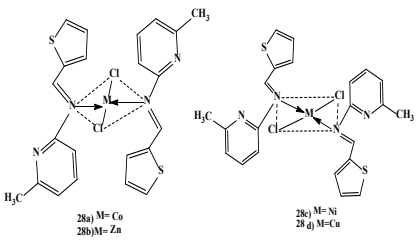
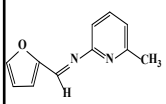
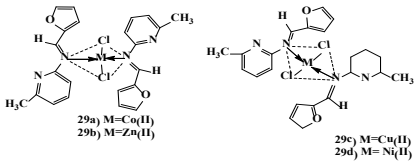
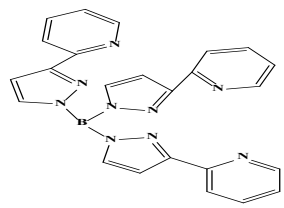
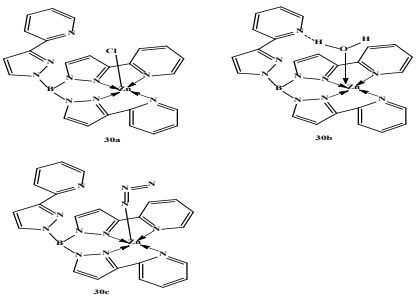
(Table no. 1 continued)

	Cd(II) Mn(II) Zn(II)	 **R** / **Cd** / **Mn** / **Zn** H / 15a / 15b / 15c CH_3 / 15d / 15e / 15f	A2780:15b(25.41±1.3μM) H1299:15b(25.41±1.3μM) U37 MG:15b(20.73±1.5μM)
	Cu(II) Ru(II) Os(II)	 16a 16b 16c	A2780: 16a(15±3μM) A2780cisR:16a(23±5μM) HeLa:16a(32±7μM) HEK293:16c(70±15μM)
	Sn	 17a) R=CH_3 17b) R=C_4H_9 17c) R=C_6H_5 17d) R=C_4H_9 17e) R=C_6H_5	A549: 17b (0.583 ± 0.245μg/mL) MCF-7: 17b (0.459 ± 0.185μg/mL) HeLa: 17b (0.399 ± 0.142μg/mL)
 (L1) (L2)	Rh Ir	 18a) M=Rh(1) 18b) M=Ir(2) 18c) M=Rh(3) 18d) M=Ir(4) 18e) M=Rh(5) 18f) M=Ir(6)	DL tumor cells
 L1: 2-(2-((2,6-dichlorophenyl)amino)phenyl)-N0-(pyridin-2-ylmethylene)acetohydrazide L2: N0-((1H-imidazol-2-yl)methylene)-2-(2-((2,6-dichlorophenyl)amino)phenyl)acetohydrazide L3: 2-(4-Isobutylphenyl)-N0-(pyridin-2-ylmethylene)propanehydrazide L4: N0-((1H-imidazol-2-yl)methylene)-2-(4-Isobutylphenyl)propanehydrazide	Cu(II)	 19 a 19b 19c 19d	A549: 19a (18.36 ± 1.26μM) HCT116: 19d (45.10 ± 3.24μM) MDA MB-231: L4 (2.26 ± 0.35μM)

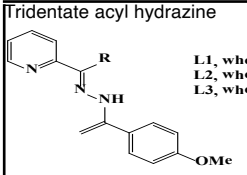
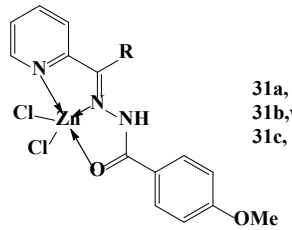
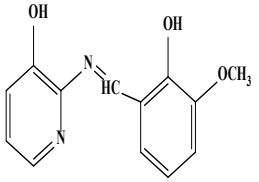
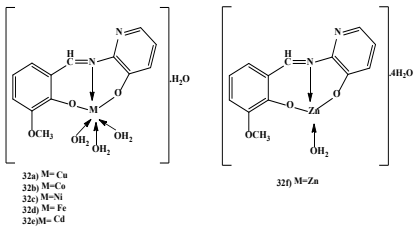
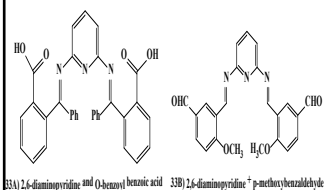
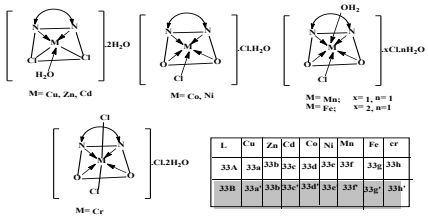
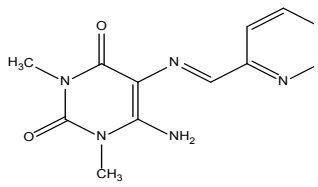
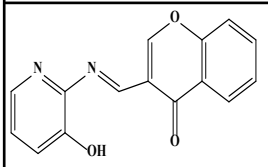
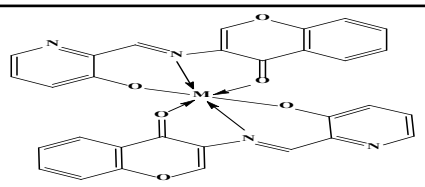
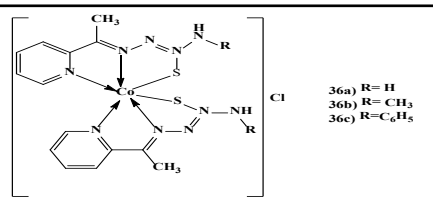
(Table no. 1 continued)

	Ru		MCF-7: 20e (14.7 (±1.4)μM) T47D: 20e (6.2 (±0.6)μM)
	Rh(II)		HCC-70: 21d (3.4 ± 0.010μM)
Pyridin-2-ylcarboxaldimine 	Pt(II)		LN405: 22i(3±4μM) LN18: 22e(11±1μM)
	Rh(II) Ir(II) Ru(II)		A2780: 23h (11.58±4.35μM) A2780cisR: 23g (10.61±0.40μM) KMST-6: 23g (43.39±3.72μM)
	Cu(II) Co(II) Ni(II) Zn(II)		HeLa: 24a(44.02±2μM) HepG-2: 24d (42.09 ±2μM) MCF-7: 24c(49.75±2μM) NHDF: 24a(88.76±2μM)

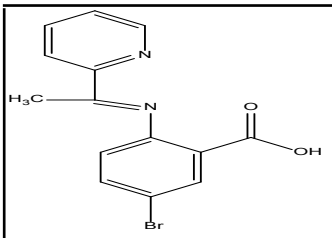
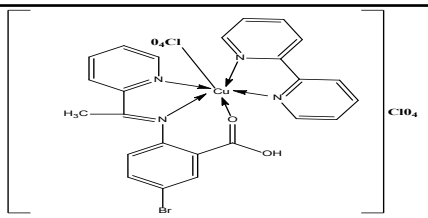
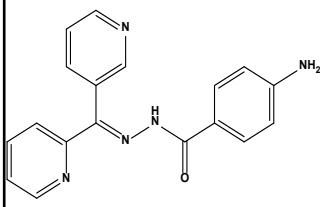
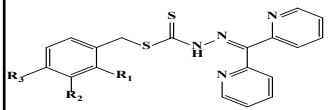
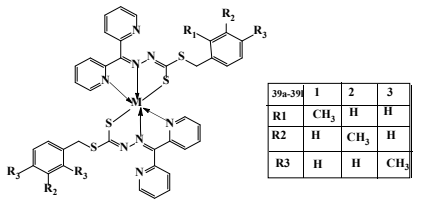
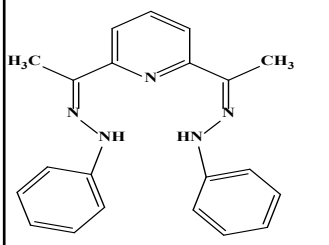
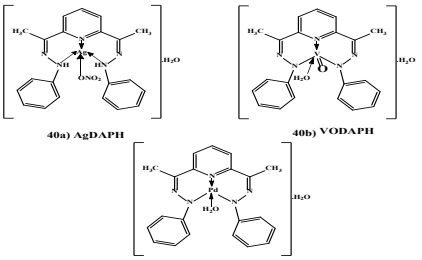
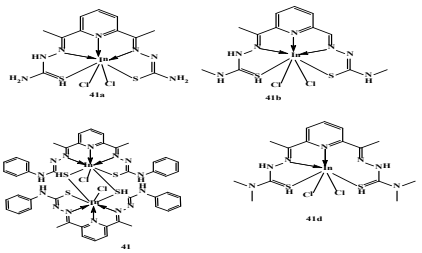
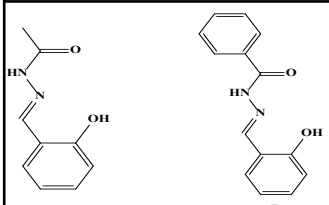
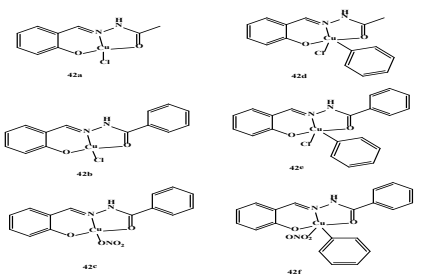
(Table no. 1 continued)

	Co(II) Ni(II) Zn(II)	 25a) M=Cu 25b) M=Co(II) 25c) M= Ni(II) 25d) M=Zn(II)	MCF-7: 25a (20±0.8μM) HepG-2: 25a (18±0.8μM) HBL100: 25a (78±0.8μM)
	Cu(II) Ni(II) Zn(II)	 26a) M=Cu(II) 26b) M=Co(II) 26c) M=Ni(II) 26d) M=Zn(II) 26e) M=Cu(II) 26f) M=Co(II) 26g) M=Ni(II) 26h) M=Zn(II)	HeLa: 26a (~53 mg/mL) MCF-7: 26e (~34 mg/mL) HepG-2:26h (~49 mg/mL)
4-aminobenzoic acid with 2-aminoicotinaldehye 	Co(II) Ni(II) Cu(II) Zn(II)	 27a) M=Co(II) 27b) M=Ni(II) 27c) M=Cu(II) 27d) M= Zn(II)	IMR-32: 27d (7.81±0.52μM) HeLa: 27a (5.94±1.13μM) MCF-7: 27d (7.41±0.32μM) HepG-2:27d(15.28±1.26μM) A549: 27d (6.18±1.15μM)
 (*E*)-*N*-(6-methylpyridin-2-yl)-1-(thiophen-2-yl)methanimine	Co(II)	 28a) M= Co 28b)M= Zn 28c) M= Ni 28 d) M=Cu	L929 28d (LC_{50}=30μg/mL)
Furfural–MAP 	Co(II) Zn(II) Cu(II) Ni(II)	 29a) M=Co(II) 29b) M=Zn(II) 29c) M=Cu(II) 29d) M= Ni(II)	PA1 L929: 29c(> 51% viable)
 tris(3-(pyridin-2-yl)-1*H*-pyrazol-1-yl)borane	Zn(II)	 30a 30b 30c	MDA-MB-231: 30a(6.81 ± 0.98μM) MDA-MB-468: 30b(10.85 ± 1.72μM) HCC1937: 30b(10.60 ± 1.04μM) HS578T: 30b(6.68 ± 1.16μM)

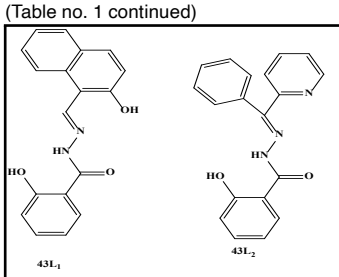
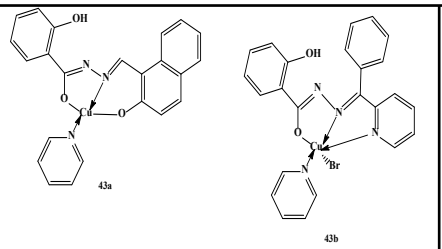
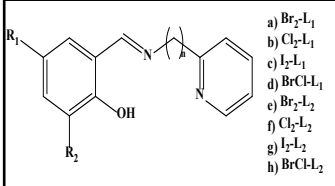
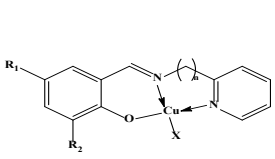
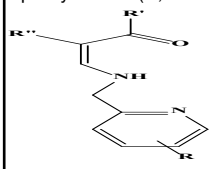
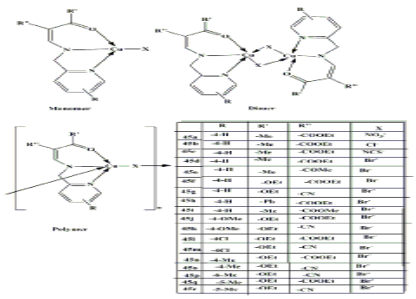
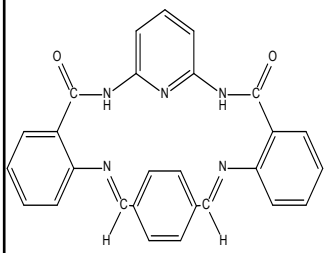
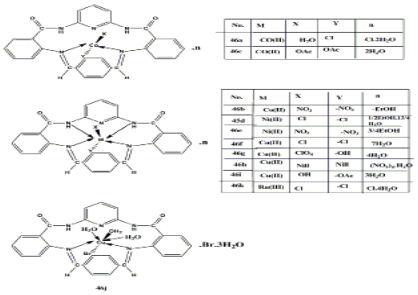
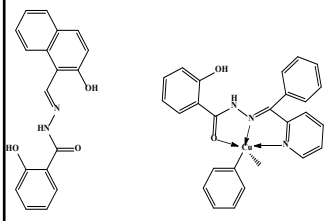
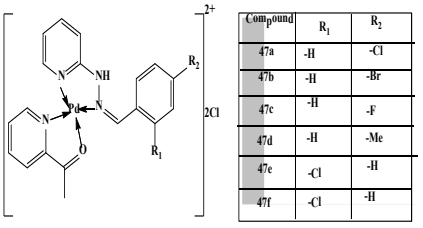
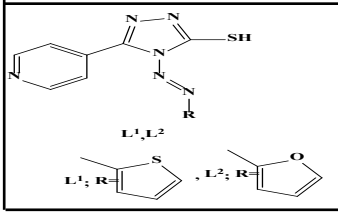
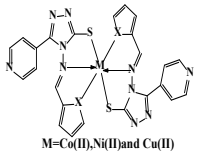
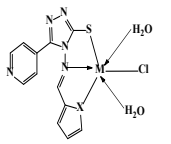
(Table no. 1 continued)

Tridentate acyl hydrazine 	Zn(II)		HCT116:31b(38.66±0.91µM) HepG2:31b(19.83±1.6µM) A549: 31b(41.85±0.57µM)
 2-[(2-hydroxy-3-methoxy-benzylidinr)-amino]-pyridin-3-ol	Cu(II) Co(II) Ni(II) Fe(II) Zn(II) Cd(II)	 32a) M= Cu 32b) M=Co 32c) M=Ni 32d) M= Fe 32e)M= Cd 32f) M=Zn	HCT-116: 32b (3.30µg/µL) MCF-7: 32a (3.26 µg/µL) HepG-2: 32e (3.26 µg/µL)
 33A) 2,6-diaminopyridine and O-benzoyl benzoic acid 33B) 2,6-diaminopyridine + p-methoxybenzaldehyde	Cr(III) Mn(II) Fe(III) Co(II) Ni(II) Cu(II) Zn(II) Cd(II)	 M= Cu, Zn, Cd M= Co, Ni M= Mn; M= Fe; x= 1, n= 1 x= 2, n=1 M= Cr	MCF-7: 33a (19.7µg/µL) 33d' (3.50µg/mL)
 (E)-6-amino-1,3-dimethyl-5-((pyridin-2-ylmethylene)amino)pyrimidine-2,4(1H,3H)-dic	Ni(II) Zn(II) Cd(II) Cu(II)	34a)[Cu(DAAUPicH−$_1$)(phen)]ClO_4 34b)[Cu(DAAUPicH−$_1$)(phen)]Br 34c){[Cu(DAAUPicH−$_1$)(H_2O)]ClO_4}n 34d)[Cu(NO_3)(DAAUPicH−$_1$)(H_2O)]·H_2O 34e) [CuBr(DAAUPicH−$_1$)]$_2$ 34f) [CuBr(DAAUPicH−$_1$)] 34g) [CuI(DAAUPicH−$_1$)]$_2$ 34h) [CuI(DAAUPicH−$_1$)] 34i) [Ni(DAAUPic)$_2$](NO_3)2·H_2O 34j)[Ni(SCN)$_2$(DAAUPic)(H_2O)]·1.5H_2O 34k) Ni(AcO)(DAAUPicH-$_1$) 34l) [Ni(DAAUPicH-$_1$)$_2$]·H_2O 34m) [Zn(AcO)(DAAUPicH-$_1$)]$_2$ 34n)[Zn(DAAUPic)$_2$](ClO_4)$_2$·½H_2O 34o)[Zn(DAAUPicH-$_1$)$_2$]·H_2O·CH_3OH 34p)[Cd(NO_3)(DAAUPicH$_1$)(H_2O)]$_2$·2H_2O 34q)[Cd(NO_3)(DAAUPicH$_1$)(H_2O)]$_2$·2H_2O 34r) [CdI_2(DAAUPic)]	C6 glioma cell line 34a-34h: 330-400nM MCF-7: 34i-34r (5µM) MDA-MB-231: 34i-34r (4µM)
 3-(3-hydroxypyridin-2-yl)imino)methyl)-4H-chromen-4-one	Cu(II) Zn(II)	 35a) M= Cu(II) 35b) M=Zn(II)	PA-1 Cell Viability: 35a= 30.12%
2-acetylpyridine- N-substituted thiosemicarbozone	Cu(II)	 36a) R= H 36b) R= CH_3 36c) R=C_6H_5	A431:36c(9.3±0.03µM) MCF-7: 36c(1.99±0.13µM)

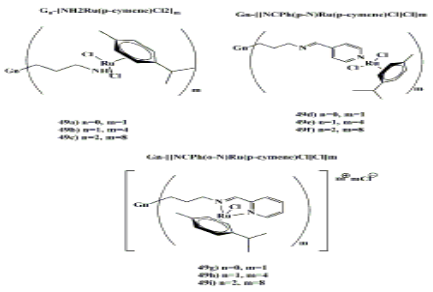
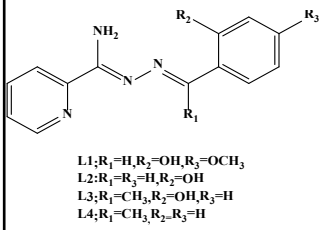
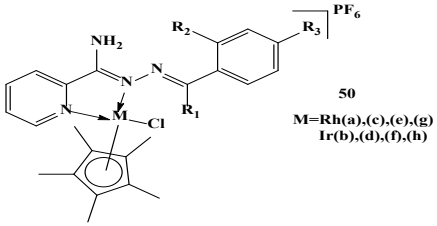
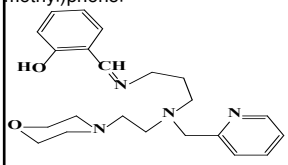
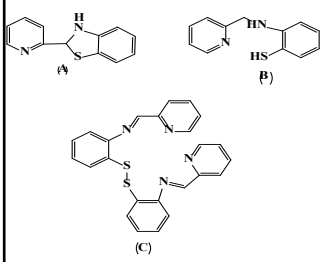
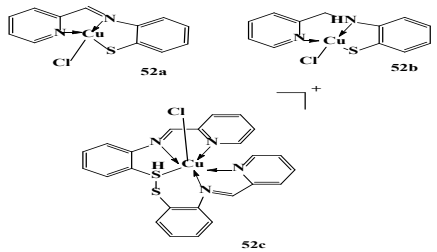
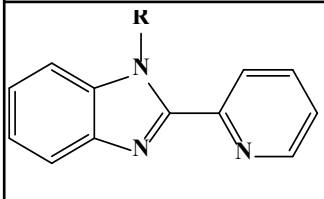
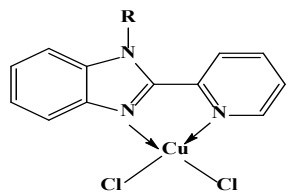
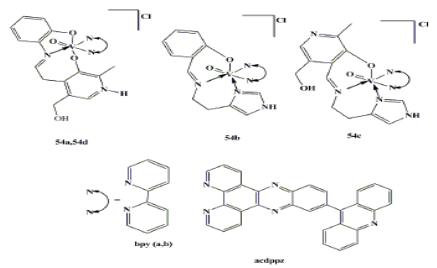
(Table no. 1 continued)

	Cu(II)	 37	MCF-7: (5.95μM)
 di-2-pyridylketone with isonicotinicacid hydrazide	Cu(II)	{[Cu(L)(H_2O)]·H_2O·NO_3}n	Bel-7402:38(4.12 ± 0.36μM) HeLa:38(2.37± 0.21μM) MCF-7: 38(1.47 ± 0.09μM) MCF-7/ADR:38(1.52±0.12μM) WI – 38: 38(6.28 ± 0.58μM)
S-n-β-N–(di-2-pyridine) methylene dithiocarbazate  Where n= 2methyl/3-meth -yl/4-methyl benzyl	Cu(II) Ni(II) Cd(II)	 M=Cu(II),Ni(II),Cd(II)and Zn(II)	MCF-7: 39f(0.4 μg/mL) MDA-MB-231: Zn(II) 39g(0.4μg/mL)
 Diacetyl Pyridine phenylhydrazone (DAP	Pd(II) V(IV) Ag(I)	 40a) AgDAPH 40b) VODAPH 40c) PdDAPH	HepG-2 40c(6.50±0.09 μM) HCT-116 40c(14.00±0.05 μM) MCF-7 40c(9.50±0.09 μM)
2,6-diacetylpyridinebis (thiosemicarbozide)	In(II)	 41a 41b 41c 41d	H460:41d(20.25 ± 1.33μM) SKOV-3:41d(19.11±1.07μM) MGC-803: 41d(11.77±0.88 μM) HeLa: 41d(15.22 ± 1.02 μM) t24: 41d (8.65 ± 0.68μM) HL-7702: 41d(21.09±1.01μM)
 A B	Cu(II)	 42a 42b 42c 42d 42e 42f	Bel-7402: 42f (2.27±0.21μM) MCF-7: 42f (1.12±0.23μM) A549: 42f (3.65±0.47μM) A549cisR: 42f (3.77±0.34μM) WI-38: 42f

(Table no. 1 continued)

	Cu(II)		(5.59±0.53μM) HepG2:43b(1.57±0.08 μM) Bel-7402:43b(1.86±0.09μM) MCF-7:43b(1.69±0.18 μM) A549: 43b (2.86±0.21 μM) A549cisR:42b(2.91±0.17μM) WI–38: 42b (4.19±0.32 μM)
 a) Br_2-L_1 b) Cl_2-L_1 c) I_2-L_1 d) BrCl-L_1 e) Br_2-L_2 f) Cl_2-L_2 g) I_2-L_2 h) BrCl-L_2 2-hydroxy-3,5 halogen-substituted salicylaldehyde + 2-(2-pyridyl)ethylamine and 2-picolylamine	Cu(II)	 44a) Cu(Cl_2-L_1)Cl 44b) Cu(Br_2-L_1)Cl 44c) Cu(BrCl-L_1)Cl 44d) Cu(Cl_2-L_1)NO_3 44e) Cu(Br_2-L_1)NO_3 44f) Cu(I_2-L_1)Cl 44g) Cu(I_2-L_1)NO_3 44h) Cu(BrCl-L_1)NO_3 44i) Cu(Br2-L2)Cl 44j) Cu(Cl2-L2)Cl 44k) Cu(I2-L2)Cl 44l) Cu(BrCl-L2)Cl 44m) Cu(Br2-L2)NO3 44n) Cu(Cl2-L2)NO3 44o) Cu(I2-L2)NO3 44p) Cu(BrCl-L2)NO3	HCT-116: 44d (18.1±1.78μM) A2780: 44d (4.2±2.2μM) MCF-7:44d (29.9±6.86μM)
NNO β-acylenamine ligand from 2-picolyl-amine (R,R′ and R″) 	Cu(II)		HCT-116wt: 45j (4.7 ± 0.1μM) 518A2: 45j (5.9 ± 0.4μM) HT-29: 45j (2.2 ± 0.3μM) HCT-116p53-/-: 45j (2.2 ± 0.3μM) HeLa: 45n(9.0 ± 0.8μM)
	Co(II) Ni(II) Cu(II) Ru(III)		MCF-7: 46a(1.33μg/mL) HepG-2: 46a(1.5μg/mL)
	Pd(II)		HCT-116: 47d (51 μg/mL)
	Co(II) Cu(II) Ni(II)	 M=Co(II),Ni(II)and Cu(II) 48a-48f  M=Co(II),Ni(II) and Cu(II) 48g-48l	Inhibition(%) at 10 μM HepG-2: 48i (49%) MCF-7: 48j (38%)

(Table no. 1 continued)

Carbosilane metallo dentrimers with three different aldehydes (4-pyridinecarboxal -dehyde, 2-pyridine -carboxaldehyde and salicylaldehyde)	Ru(II)		HeLa: 49e (4.4±0.1μM) MCF-7: 49e (2.5±0.1μM) HT-29: 49e (3.3±0.2μM) MDA-MB-231: 49b (4.5±0.4 μM)
 L1:R_1=H,R_2=OH,R_3=OCH_3 L2:R_1=R_3=H,R_2=OH L3:R_1=CH_3,R_2=OH,R_3=H L4:R_1=CH_3,R_2=R_3=H	Rh(II) Ir(II)	 50 M=Rh(a),(c),(e),(g) Ir(b),(d),(f),(h)	HT-29: 50e(46.17 ± 12.78μM) ARPE-19: 50e(97.39 ± 4.53 μM)
Synthesis of 2-({3-[2-morpholinoe -thylamino] -N3-([pyridine-2-yl] methyl)phenol 	Cu(II) Co(II) Zn(II) Ni(II) Cd(II) Mn(II) Ag(I) Fe(III)	51a) $[ZnL](ClO_4)$ 51b) $[CdL](ClO_4)$ 51c) $[MnL](ClO_4)$ 51d) $[NiL](ClO_4)$ 51e) $[CuL](ClO_4)$ 51f) $[AgHL(NO_3)]$ 51g) $[FeLCl_2]$ 51h) $[CoL](ClO_4)$	MCF-7: 51f (10.9 ± 0.03μM) MDA-MB-231: 51f (10.2 ± 0.06μM) PC-3: 51f (28.5 ± 0.30μM) WI-38: 51e (15.45 ± 0.03μM)
	Cu(II)		Cellviability(%) at 5μM: HeLa: 51c(34.5%) HEK293: 51c(84%)
 pbzX	Cu(II)	 53a)pbzH 53b) pbzMe 53c) pbzBz 53d) pbzF 53e) $pbzF_2$ 53f) $pbzF_5$ 53	A549: 53b (5.5 ± 0.4 μM)
Vitamin-B6 Schiff base	V(IV)		In visible light: HeLa: 54d (0.24 ± 0.02μM) MCF-7: 54d (0.53 ± 0.03 μM) MCF-10A: 54a (85± 2μM)

DISCUSSION

Anti-proliferative activity of pyridine Schiff base complexes

A series of transition metal complexes of Schiff bases, derived from the condensation reaction of 2-amino pyridine with different aldehydes (5-substituted salicylaldehyde.[8] 6-formyl-7-hydroxy-hyphen-5methoxy benzo *puran*-4-one[9] and pyridine-2-carboxaldehyde[10]) were prepared.

The anticancer activity of complexes (1a-1d) was investigated against HeLa, SW620, A549, MCF-7, and WI-38 cell lines. All tested complexes showed a strong anti-proliferative effect even in the meager μM range (IC_{50}=half maximal inhibitory concentration). Complex 1b had the highest proliferative activity against the A-549 cell line. The synthesized complexes (1a-1d) had high cytotoxicity against control cell lines, which was the major drawback[8].

Complexes (2a-2d) were tested against normal 3T3 cells with different concentrations (10-70μML-1). Mn(II) complex was less toxic than Schiff base up to 30μML^{-1}. The cytotoxicity was screened against cancerous cell lines at this concentration, and the result indicated promising activity. The Mn(II) complex inhibited HeLa-Fas cells (80%), HeLa cells (53%), Huh-7 cells (43%), and HepG-2 cells (20%)[9]. The cytotoxic effect of 3a-3r was screened against MCF-7 and HeLa cell lines and compared to standard drugs (Cisplatin and doxorubicin). The IC_{50} values for these complexes ranged from 7-25μM (MCF-7) and 7-29 μM (HeLa). The complexes 3o, 3c, 3j, and 3b were remarkably active against both the cell lines than Cisplatin[10].

A novel azomethine ligand [1(pyridine-3-yl-imino methyl) naphthalene-2-ol] and its Ag(I), Pd(II), and VO(II) complexes (4a-4c) have been prepared and investigated against various carcinoma cell lines, including HCT-116, MCF-7, and HepG-2. The calculated IC_{50} values showed that complex (4b) has the highest ability to inhibit the growth of both MCF-7 (IC_{50}=10.60μM) and HepG-2 (IC50=10.60μM) cells when compared to vinblastine. It may be considered a promising pharmaceutical drug for liver tumors[11].

The Schiff base synthesized from 2, 3-diamino pyridine and 2-hydroxy-1-naphthaldehyde and its metal complexes (5a-5d) were prepared with Mn(II), Fe(II), Co(II), and Cd(II) metals. Schiff base and its metal complexes were tested against two cancer cell lines, namely (HCT-116) and (HepG-2) cell lines. Complexes 5c and 5a were more potent against HepG-2 and HCT-116 cell lines[12].

A series of lanthanide complexes (6a-6c) was obtained from Schiff base ligand named N,N-bis (anthracen-9-yl methylene)pyridine-2, 3-diamine. The synthesized metal complexes were elaborately tested for cytotoxic activity against various cancer cell lines such as Vero, MCF-7, and HeLa. The synthesized complexes efficiently induced apoptosis in a dosage-dependent manner among these three cell lines. The test results on Vero cells depicted that the biocompatibility of Pr complex was more effective than the Er complex. The cytotoxic behavior of Pr and Er complexes against MCF-7 and HeLa cell lines exhibited cell death up to ~49% and ~42-51%, respectively[13].

Azo Schiff base ligands obtained from 2-aminopyridine and 2-hydroxy naphthaldehyde(L1) vanillin and ethylenediamine(L2) are converted into Ru(III) complexes (7a-7b). These complexes were screened for anticancer activity against MCF-7 and normal NH3T3 cell lines. The obtained results confirmed that Ru complexes were much less toxic towards NH3T3 (IC_{50}=102.2 μg/mL). The number of cells decreased with an increase in the concentration of complexes[14].

The cytotoxic activity of binuclear Cu(II) complex (8a) with tridentate ligand, prepared by the condensation reaction of 2-aminomethyl pyridine and pyridoxal, was evaluated against HeLa and HCT cells through MTT assay. The results showed that the complex would be mildly cytotoxic towards HCT and HeLa cell lines, and it could be used for biological imaging in very low dose[15].

The anti-proliferative activity of a series of transition metal complexes with Schiff base (derived from pyridine carboxaldehyde and 9-ethyl-9H-carbazole-3-amine) were tested against various cancer cell lines and reported. The anticancer study demonstrated that the new half-sandwich Ir(III), Rh(III), and Ru(II) complexes (9a-9c) potent against MCF-7 at low concentrations. The complexes 9a and 9b were found to be more potent than 9c[16].

Antitumor of half-sandwiched Ir(III) complexes (10a-10d) was tested against A549 and HepG-2. The results revealed that all these compounds exhibited IC_{50} value in the range of 1.4±0.1μM to 11.5±0.5μM which confirms that the synthesized complexes were effective antitumor agents[17].

Antitumor studies were done on several human cell lines (8505C, MCF-7, SW-480, and 518A2) with a series of Ru(II) arene complexes (11a-11f) of mono and bidentate N-donor ligands (A-D). The result revealed that the MCF-7 cell line was the most sensitive cancer cell, while others were almost resistant to the synthesized complexes. 11a and 11b show the highest cytotoxic activity against MCF-7 cells among all tested complexes[18].

The Schiff bases (E)-N′-(pyridine-2-yl-methylene)benzo hydrazide and (E)-2-(pyridine-2-yl-methylene)hydrazine-1-carboxamide were complexed with Cu and then the complexes (12a-12c) were screened for cytotoxic activity against AGS and SW742. It is interesting to note that all the complexes have higher activity than the free ligand. This might be due to the presence of the chelation in the complexes[19].

Synthesized photo-induced tricarbonyl manganese(I) compounds (13a-13b) were prepared and evaluated against HepG-2 with and without illumination. In comparison, complex 13b with methoxy supplements revealed higher cytotoxicity among the investigated compounds in a dose-dependent manner with an IC_{50} value of 7.1 μM[20].

A Series of complexes (14a-14g) were synthesized by interacting Cu(I) metal cation with imine ligand, and the potential anticancer effect was assessed for U87. All complexes exhibited dose-dependent cytotoxicity towards U87 cells. The 14c complex had the intensified anticancer activity[21].

Schiff base complexes (15a-15f) were synthesized by the condensation between 2,6-diacetyl pyridine and 2-((4-(2-amino benzyl)-1,4-diazepan-1-yl)methyl)benzenamine in the presence of Cd(II), Mn(II) and Zn(II) ions. The potency of complexes was evaluated on A2780, U-37MG, and H1299 cell lines using the MTT method. The investigated compounds 15b showed an excellent inhibitory effect on U37MG cells. The inhibitory effect of complex 15a showed a potent effect in U37MG cells and moderate potency against H1299 and A2780 cell lines[22].

Cu(II)-Ru(II) and Cu(II)-Os(II) complexes (16a-16c) have been synthesized by using Schiff base derived from 2-pyridin amidraone and 6-(morpholino ethyl)-pyridine-2-carboxaldehyde. The anti-proliferative activity of synthesized complexes and ligands was evaluated against A2780 and A2780cisR, HeLa, and human embryonic kidney cell line HEK293. All the tested complexes displayed more significant cytotoxicity than the ligand, and complexes 16a and 16b had the high selectivity to cancer cell lines over non-cancerous HEK293 cells, which might be helpful in their further clinical development[23].

A series of organotin(IV) hydrazine compounds (17a-17e) synthesized by using the ligand N′-[(1E)-(2-hyroxyl-3-methoxyphenyl) methylidene]pyridine-3-carbohydrazone. The cytotoxicity of the 17a-17e was assessed on A549, HeLa, and MCF-7 cell lines. All the compounds showed prominent antitumor activity towards cancer cell lines. Among all, Compound 17b and 17c were more suitable anticancer drugs[24].

The half sandwiched organometallic Rh and Ir complexes (18a-18f) with ligands (pyridine-2-yl-methylene picolinic hydrazine(L1) and pyridine-3-yl-methylene picolinic hydrazine (L2)) were synthesized. The in vitro antitumor activity of the complexes 18a and 18b by fluorescence-based apoptosis was evaluated against DL cells at different concentrations. In higher doses (60-100μg/mL), 18a and 18b exhibited moderate apoptotic effect with ~22% and~30% apoptotic cell death. The cytotoxicity of 18a and 18b on normal cells has been noticed as half of their activity on the DL tumor cells[25].

In vitro anti proliferative activity of Cu(II) complexes (19a-19d) of hydrazones with ligands (2-(2-((2,6-dichloro phenyl)amino)phenyl)-N0-(pyridin-2-yl-methylene)aceto hydrazide (L1), N0-((1H-imidazol-2-yl)methylene)-2-(2-((2,6-dichloro phenyl)amino) phenyl) aceto hydrazide(L2), 2-(4-Isobutylphenyl)-N0-(pyridin-2-yl methylene)propane hydrazide (L3), and N0-((1H-imidazol-2-yl)methylene)-2-(4-isobutyl phenyl)propane hydrazide) (L4) were tested against A549, HCT-116 and MDA MB-23 cell lines by MTT

assay. L1-L4 are active against these cell lines, and they exhibited better activity against MDA MB-231 cell lines. As compared to Cisplatin 19a-19d possess excellent potency as an anticancer drug with lower IC_{50} values (3.38-6.62 μM)[26].

Ruthenium arene complexes (20a-20e) with fluorene bearing Schiff base ligand prepared. Furthermore, the ligand is obtained by the condensation reaction of 2-amino fluorene with an aldehyde (2-formyl pyridine or 2-hydroxy naphaldehyde). The complexes 20a-20e were tested on MCF-7 and T47D cell lines. 20a and 20b did not influence the viability of MCF-7 and T47D cells. The activity of 20c was found to be slightly lower than Cisplatin against MCF-7 but more active against T47D, and complexes 20d and 20e were found to be more active than Cisplatin[27].

The metal complexes (21a-21e) were synthesized by the reactions of trans-[$RuCl_2(PPh3)_2$] with N-[1,3-benzothiozole-2-ylmethylidene]pyridine-2-carbohydrazide, N-[(uracil-5-yl)methylene] thiophene-2-carbohydrazide, N-[(uracil-5-yl) methylene]pyridine-2-carbohydrazide, 5-((thiophen-3-yl)methylene amino)-6-amino-1,3-dimethyluracil and 2,6-bis-((6-amino-1,3-dimethyl uracil imino) methylene)pyridine. These compounds were screened against HCC-70 cell line and the result showed that 21a and 21b were not toxic below 100μM. Among the 20a-20e complexes 20d showed more cytotoxicity with IC_{50} value of 3.4μM[28].

Eleven pyridine carbo aldimines were prepared from the condensation reaction of 2-pyridine carboxaldehyde and the corresponding lipophilic primary amines and its Pt(II) complexes (22a-22k). The cytotoxicity of seven novel Pt complexes was tested against LN18 and LN405 using Cisplatin as a control. Complex 22i displayed the lowest IC_{50} value against LN405, and 22e displayed the lowest IC_{50} value against LN18[29].

The Schiff base ligand was prepared from the condensation reaction of 4-amino phenyl methanol/2-pyridine carboxaldehyde of salicylaldehyde. These ligands were used to synthesize a series of trinuclear half-sandwich Ru(II), Rh(III), and Ir(II) polyester organometallic complexes (23a-23l). The anti-proliferative activity of 23a-23l was evaluated against A2780, A2780cisR, and non-tumorous cells KMST-6. The result showed that trimeric complexes 23g-23l had higher activity towards A2780 and A2780cisR than the free ligand and monomeric complexes. In the A2780 cell line, complex 23 h showed the highest activity with the IC_{50} of 11.58μM, while in the A2780cisR cell line, complex 23 g showed the highest activity with 10.61μM[30].

The cytotoxic nature of non platinated transition metal (II) complexes (Cu(II), Co(II), Zn(II) & Ni(II)) were evaluated against different cancer cell lines. The different Schiff bases were prepared as follows: the condensation reaction of 2-hydroxy-4-nitrobenzaldehyde with pyridine-2-yl-methamine,[31] benzyl with 2-amino-3-hydroxy pyridine,[32] 2-(aminomethyl)benz imidazol dihydrochloride with pyridine 2-carboxaldehyde,[33] 2-aminobenzoic acids with 2-amino nicotinaldehyde,[34] thiophene-2-carboxaldehyde with 2-amino-6-picoline[35], and furfural with 6-methyl-2-aminopyridine[36]. The prepared complexes with these Schiff bases are (24a-24d), (26a-26h), (27a-27d), (28a-28d) and (29a-29d) respectively. The complexes (24a-24d) showed cytotoxic behavior against human cancer cell lines (HeLa, MCF-7, and HepG-2). The toxicity of these compounds was less on the normal cell line (NHDF). The 24a complex showed slightly higher activity than the rest of the complexes[31]. The In vitro cytotoxic activity of synthesized complexes (25a-25d) was evaluated against MCF-7, HepG-2, and non-cancer cell line from human breast milk HBL100 by MTT assay, and Cisplatin acts as a standard drug. The IC_{50} values reduce with rising the concentration of metal complexes, and all the metal complexes showed good anticancer activity. Among all the tested complexes, 25a showed greater anticancer activity[32]. The antitumor activity of 26a-26d complexes evaluated against a selected human cancer cell line HeLa, MCF-7, and HepG-2 along with NHDF by colorimetric (MTT) assay. It was shown that the complexes with terpyridine (26e-26h) as co-ligand exhibited a better cytotoxic effect than the other complexes 26a-26d[33]. The anti-proliferative activity of complexes 27a-27d assessed against different human cancer cell lines IMR-32, MCF-7, COLO-205, A549, HeLa, and HEK293 which revealed that complex 27d showed excellent anti-proliferative activity against IMR-32, A549, and HepG-2 with an IC_{50} value 7.81±0.52 μM, 6.18±1.15μM and 15.28±1.26μM respectively. Similarly, complex 27a showed potent

activity against HeLa, HepG-2, A549, and MCF-7. The potent compounds 27a & 27d were tested against normal cancer cell line HEK293. The results indicated that none of the complexes interrupted the viability of the cell line[34]. Synthesized complexes (28a-28d) were tested against L929 fibroblast. The cytotoxicity of [CoL2Cl2] (28a) and [CuL2Cl2] (28d) showed the LC_{50} values 40μg/mL and 30μg/mL respectively in lethal concentration[35].

In anticancer activity evaluation, the Cu(II) complex showed better activity than other synthesized complexes (29a-29d) when investigated against PA1 and L929 cell lines at different concentrations. The cell viability of L929 cells was greater than 51%, indicating that 29c can be used as a safe compound for therapeutic biomedical application[36].

Three differently coordinated Tris-(2-pyridine)-pyrazolyl borate zinc(II) complexes (30a-30c) were synthesized and tested for in vitro cytotoxic ability on four triple-negative breast cancer cells lines (MDA-MB-231, MDA-MB-468, HCC1937 & HS578T). The results conclude that all the complexes were potent anticancer agents exhibiting excellent activity on all the four cancer cell lines with IC_{50} values ranging from 6.72 to 16.87μM owing to the presence of the pyrazole and pyridine units in the synthesized complexes. In comparison with the clinical drug Cisplatin (IC_{50}=32.38μM), the synthesized complexes exhibited better activity[37].

Zinc(II) complexes of a tridentate Schiff base ligand N,N′-bis(1-(2-pyridine)ethylidene)-2,2-dimethylpropane-1,3-diamine) were screened for their cytotoxic activity against MCF-7 cell line. The cell inhibition of Zinc complex was recorded as 8%, 39% and 62% at 5,10 and 20μg/mL concentrations respectively[38].

The Schiff base ligands were synthesized via condensation of 4-methoxy benzo hydrazide with picolinaldehyde, 1-(pyridine-2-yl)ethanone, and phenyl(pyridine-2-yl)methanone. The Zinc(II) complexes (31a-31c) were prepared by treatment of zinc(II) chloride with corresponding ligands, and the complexes were investigated against HCT-116, HepG-2, and A529 cells. All the complexes showed IC_{50} values greater than Cisplatin. Among all the complexes, complex 32b exhibited better activity[39].

The new nano-sized complexes of Cu(II), Co(II), Ni(II), Fe(II), Cd(II), and Zn(II) (32a-32f) with Schiff base derived from the condensation of 2-amino-3-hydroxy pyridine and 3-methoxy salicylaldehyde and these complexes were screened against various cancer cell lines. Complexes 32a-32d were investigated against HCT-116, and MCF-7, and complexes 32d-32f were screened against HCT-116 and HepG-2. Cytotoxic conclusions indicated that all the tested complexes (32a-32f) were demonstrated potent activity against HCT-116 cell lines. In HCT-116, the cobalt complex (32b) showed the highest cytotoxic effect (IC_{50}=3.30μg/μL) and in MCF-7, copper complex (32a) showed highest cytotoxic effect (IC_{50}=3.26 μg/μL). In HepG-2, the Cd complex (32e) had the highest cytotoxicity (IC_{50}=1.45μg/μL)[40,41].

Two different Schiff bases (33A, 33B) were prepared by the condensation reaction of 2,6-diamino pyridine with o-benzoyl benzoic acid[42] and 2,6-diamino pyridine with p-methoxy benzaldehyde, respectively.[43] The transition metals [Cr(III), Mn(II), Fe(III), Co(II), Ni(II), Cu(II), Zn(II) and Cd(II)] complexed with 33A and 33B to form 33a-33h and 33a′-33h′ complexes respectively. The IC_{50} value of complexes 33a-33h was found to be 19.7- 45.2 μM, and 33a exhibited the higher anti-cancer activity among all. The IC_{50} value of complexes 33a′-33h′ showed in the range of 3.5 to 41.9μg/mL, which are lower than lomefloxacin drug (11.2 to 43.1μg/mL), which indicates the effective anticancer activity of the prepared complexes[42,43].

The Schiff base (E)6-amino-1,3-dimethyl-5-((pyridine-2-yl-methylene)amino)pyrimidine-2,4(1H,3H)-dione prepared and its metal complexes (34a-34r) prepared with Cu(II), Ni(II), Zn(II), and Cd(II) metal ions. The Cytotoxic assay was performed for Copper complexes (34a-34h) to assess the anti-proliferative potential complexes using the C6 glioma cell line. The tested complexes showed a similar cytotoxic effect on C6 cell growth in higher doses (330-400nM). The percentage of apoptotic cells increased steadily in a dose-dependent manner, in which 34a, 34c, 34e and 34h had the highest cell death percentage[44]. The anticancer activity of Ni(II), Zn(II), and Cd(II) complexes (34i-34r) were explored and their effects on renin-angiotensin system (RAS) regulating amino-peptidases on estrogen dependent and MCF-7, MDA-MB-231breast cancer cell line reported effective anticancer activity[45].

A Copper and Zinc chelates with Schiff base 3-(3-hydroxy pyridin-2-yl)imino)methyl)-4H-chromen-4-one were tested against the cytotoxicity on human ovarian teratocarcinoma cell line (PA-1) evaluated by the MTT assay. It is interesting to note that 35a exhibits a higher cytotoxic effect than 35b[46]. Two different Schiff bases derived from condensation reaction of 2-acetyl pyridine with N-substituted thiosemicarbozone(L1)[47] and 2-acetyl pyridine with 2-amino-5-bromobenzoic acid(L2)[48]. The Co(III) complexes (36a-36c) from L1 were tested against A431 and MCF-7 cell lines which completely removed the cancer cells even at low concentrations. The complexes 36a-36c showed higher activity than that of Cisplatin[47]. The Cu(II) complex (37) from L2 showed promising anti breast cancer activity with the IC_{50} value of 5.95μM against MCF-7 cell line[48].

The Cu complex containing Schiff base was prepared by the condensation reaction of di-2-pyridine ketone with iso nicotinic acid hydrazide and evaluated against various cancer cell lines Bel-7402, HeLa, MCF-7 and MCF-7/ADR. The MTT assay revealed that the free ligand and Cu(II) salt had low activity against the cancer cells, while complex 38 exhibited better inhibition on cancer cells with lower IC_{50} values (1.47-4.12μM) than Cisplatin. And complex 38 has less toxicity towards the normal WI-38 cell line with an IC_{50} value of 6.28μM[49].

The complexes 39a-39l were synthesized with the ligand S-n-β-N–(di-2-pyridine)methylene dithiocarbazate (n=2-methyl benzyl/3-methyl benzyl/4-methyl benzyl) and these complexes were examined against two breast cancer cell lines MCF-7 and MDA-MB-231. Among all the complexes, 39f active against MCF-7 and 39g, 39j were active against MDA-MB-231 cell line[50].

The N3 tridentate imine ligand 2, 6-diacetyl pyridine diphenyl hydrazone and its Pd(II), V(IV) and Ag(I) complexes (40a-40c) were prepared and cytotoxic activity estimated via three human cancer cell lines HepG-2, MCF-7 and HCT-116. Among all the tested complexes Pd (40a) complex had the highest cytotoxicity on HepG-2 cancer cells with IC_{50} value of 6.50 μM[51].

Four different novel In(III) 2,6-diacetylpyridine bis(thiosemicarbazide) complexes (41a-41d) synthesized and the cytotoxicity were calculated at five tumor cell lines H460, SKOV-3, MGC-803, HeLa, t24 and non-tumor cell HL-7702. The complexes 41a-41c showed no cytotoxicity against these cell lines. 41d showed good cytotoxicity on cancer cell lines but lower activity in normal cells. Therefore 41d could be promising multi-target anticancer metal lead drug[52].

A new Schiff base synthesized from 3-pyridine carboxaldehyde with benzene sulfono hydrazide and in silico anticancer studies done which showed that the compound is similar to drug and it made favorable binding interaction with selected anticancer drug target[53].

A series of 1:1 Cu(II) complexes (42a-42c) and 1:1:1 Cu(II) complexes (42d-42f) were prepared and tested for anticancer activity against Bel-7402, MEF-7, A549, and A549cisR cancer cell lines. As a result, the 1:1:1 mixed ligand Cu(II) complexes exhibited two to eightfold better activity than the 1:1 Cu(II) complexes. The introduction of the co-ligand pyridine moiety increases the anticancer activity of compounds[54].

Two mixed ligands, which contained different aryl hydrazone as ligands and pyridine as a co-ligand, were prepared. Its Cu(II) complexes (43a-43b) anticancer activity was evaluated against humans cancer cells using MTT assay. The result displayed that the ligands and Cu^{2+} had low activity against cancer cells, but 43a & 43b exhibited high cytotoxicity. Both synthesized Cu(II) complexes showed a broad spectrum of inhibition with IC_{50} values ranging from 1.57 to 5.23μM, which were lower than those of Cisplatin (A549cisR). The 43b complex displayed higher cytotoxicity than the 43a complex. Both the complexes were less potent towards WI-38 and had great potential to display anti-metastatic activity via the inhibition of cancer cell migration[55].

A series of sixteen Cu(II) complexes (44a-44p) using eight ligands (a-h) were prepared by the condensation of 2-amino methyl pyridine and 2-hydroxy-3,5-halogen-substituted salicylaldehyde. The anti-proliferative effect of synthesized Cu(II) complexes was evaluated in three human cancer cell lines, A2780, HCT-116, and MCF-7. The 44a-44d complexes {Cu(Cl2-L1)Cl, Cu(Br2-L1)Cl, Cu(BrCl-L1)Cl and Cu(Cl2-L1)NO3}demonstrated the greatest antiproliferative activity in A2780 cell compared to HCT-116 cells. In vitro selectivity of

complexes in A2780 tumor cells compared to normal cells 44d was the most promising with a higher therapeutic window[56].

A series of eighteen Cu(II) complexes (45a-45r) with tridentate NNO β-acyl enamine ligand is prepared, which is derived from 2-picolin amine and bearing different substituents (R, R′, and R″) on the pyridine ring and the chelate cycle. All compounds cytotoxic activity was evaluated against human cell line 518A2, HT-29, HCT-116wt, HCT-116p53 and HeLa using the standard MTT assay. Complex 45j and 45n showed the highest activity among all the investigated compounds, including the clinical standard drug Cisplatin against all cancer cell lines. Complexes with a cyanide side chain (45k & 45º) were inactive (IC_{50}>50μM)[57].

A novel series of transition metal complexes (46a-46k) with a 19 membered pyridine base macrocyclic ligand (1, 5, 12, 16-tetraaza-3, 4:7, 10:13, 14-tribenzol 1,16 (2, 6-pyrido) cyclonadecan-5, 11diene 2, 15diene) has been prepared and investigated against the cancer cell lines MCF-7 and HepG-2. Except for Ru(III) complex, the ligand and all complexes showed great activity towards MCF-7 and HepG-2 cells. These complexes are considered as a promising anticancer agent[58].

A series of substituted hydrazilyl pyridine-based Schiff base ligand and corresponding palladium(II) complexes (47a-47f) were synthesized. The synthesized complexes were tested for In vitro anticancer activity against the HCT-116 cancer cell line with Cisplatin as the positive control. The IC_{50} values of the mixed ligand palladium(II) complex 47d are lower than carboplatin(64.97μM). The anticancer activity of palladium complexes found in decreasing order of 47d(51μM)>47e(132μM)>47b(138μM)> 47a(165μM)>47f(272μM)>47c(238μM)[59].

Two biologically active Schiff base ligands were prepared from the condensation reaction of 2-amino-5-(pyridine-4-yl)-4H-1,2,4-triazole-3-thiol with thiophene-2-carbaldehyde and furan-2-carbaldehyde. The prepared Schiff base was used for complexation with different metal ions [Co(II), Ni(II), and Cu(II)], and the cytotoxic effect of these complexes on cancer cell line MCF-7 and HepG-2 were investigated. All the complexes (48a-48l) showed moderate to significant %inhibition on HepG-2 and MCF-7 cells. The cell proliferation of the complexes 48f & 48i showed 38% and 49% inhibition on HepG-2, respectively. 48i, 48j and 48k showed 34%, 38% and 33% inhibition on MCF-7 cell line respectively[60].

The Schiff base ligands were synthesized using three different aldehydes (4-pyridine carboxaldehyde, 2-pyridine carboxaldehyde, and salicylaldehyde) and coordinated with ruthenium metal ion. These organo ruthenium complexes (49a-49i) were evaluated against HeLa, MCF-7, Ht-29, and MDA-MB-231 cell lines and non-cancerous HEK-293T cells. Complex 49a and 49f were selective towards HeLa, MCF-7, Ht-29 cell lines but less active on MDA-MB-231 cells[61].

Schiff base ligands, namely (2-hydroxy-4-methoxy benzylidene)2-pyridine amidrazone (L1), (2-hydroxy benzylidene)2-pyridine amidrazone (L2), (1-(2-hydroxy phenyl)ethylidene)2-pyridine amidrazone (L3), (1-phenyl ethylidene), 2-pyridine amidrazone (L4), and its corresponding rhodium and iridium half sandwiched metal complexes (50a-50h) were synthesized. The complexes (50a-50h) were evaluated against HT-29 and non-cancer cell line ARPE-19. All the complexes were found to be active against the HT-29 cell line, and 50e showed more activity[62].

A new Schiff base ligand was prepared from N1-(2-morpholino ethyl)-N1-([pyridine-2-yl]methyl)propane-1,3diamine and hydroxyl benzaldehyde, then its metal complexes (51a-51h) were synthesized. The cytotoxic effect of each compound against MCF-7, MDA-MB-231, PC-3, and WI-38 was examined using an MTT assay. All the complexes except 51h had higher potency towards MCF-7 and MDA-MB-231, and complex 51f had higher potency towards PC-3 (IC_{50}=28.5±0.30) compared to Cisplatin[63].

The three Cu(II) chloro complexes (52a-52c) containing N-(2-pyridine methyl)-2-mercapto aniline and (2,2′-di(pyridine-2-ethyleneimine)diphenyl disulfide) were prepared, and their biological activity was evaluated. The MTT assay showed that all complexes exhibited appreciable toxicity at 5μM dose on HeLa cell line with IC_{50} values of 1.27, 4.13, and 3.92 μM, respectively. The anti-proliferative activity of these complexes tested against normal HEK293 cells and 52c showed the minor activity in 5μM and

10μM concentrations. But the complex 51c at five μM concentration exhibited significant toxicity of 34.5% at HeLa and 84% in normal HEK293 cell lines[64].

The anticancer activity of Cu(II) complexes (53a-53f) developed by $CuCl_2$ and 2-(2-pyridinyl) benzimidazole were evaluated against A549 cells. The IC_{50} values of these complexes ranged from 5.5-12μM and showed promising cytotoxic activity. As compared to all the synthesized Cu(II) complexes, 53b showed the most potent activity[65].

Oxovanadium(IV) complexes of the new Schiff base ligands ((acridinyl)dipyrido-phenazine (acdppz) and vitamin B6) were synthesized, and the cytotoxicity of the complexes (54a-54d) were evaluated in the dark and visible light against HeLa, MCF-7, and normal MCF-10A cell lines. The MTT assay showed complexes 54c and 54d were photo-cytotoxic to the cancerous cells and non-toxic to MCF-10A cells. In visible light irradiation, the IC_{50} values of the complexes 54c and 54d in HeLa cells were 0.36±0.04μM and 0.24±0.02μM and in MCF-7 cells were 0.91±0.05μM and 0.53±0.03μM. In the dark, these complexes were non-toxic against the tested cell lines[66].

CONCLUSION

Cancer is a complex disease; there are numerous therapeutic options available. The success of platinum-based anticancer medications has paved the way for developing new metal-based cancer treatments that are free of side effects. Schiff bases are a well-known ligand that has gained much interest in several fields because of their biological actions. This review gathered all contemporary research findings on pyridine Schiff base complexes and their anticancer potential against various cancer cell lines. The majority of the complexes showed good activity against various cell lines, with IC_{50} values equal to or even lower than the reference drug. This review discovered that the metal complexes were more potent than the Schiff base ligands. We conclude that this review article will aid researchers in developing new Schiff base complexes with pyridine moiety as anticancer agents.

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Conflict of Interest

There is no conflict of interest among the authors.

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