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Recent Advances in Iron Complexes as Potential Anticancer Agents

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Abstract

The revelation of the anticancer properties of cisplatin inspired research in metal complexes for the treatment of cancer. Several second and third generations of cisplatin analogues were developed with the claim of good anticancer properties and reduced side effects. However, persistence of some side effects and the resistance by cancer cells tempted scientists to explore new metal complexes as anticancer drugs. Therefore, the approach of rational drug design was extended to the development of non-platinum anticancer drugs, and since then a large number of such complexes have been developed. Iron complexes have been of interest to inorganic medicinal chemists for development of anticancer agents. Anticancer potency of iron complexes was first reported in ferrocenium picrate and ferrocenium trichloroacetate salts, which was attributed to their ability to form reactive oxygen species leading to an oxidative DNA damage. This review discusses the advances in iron complexes as anticancer agents. The aspects of photocytotoxicity, redox-activity and multinuclearity in anticancer iron complexes have been discussed in addition to a discussion of ferrocenyl derivatives and salen complexes. The legacy of nanotechnology and synergism in harnessing the potential of iron complexes has been highlighted. Finally, current challenges and future perspectives of iron complexes as anticancer agents have been outlined.

Keywords: Recent advances, Photocytotoxic iron complexes, Redox-active iron complexes, Multinuclear iron complexes, Ferrocenyl derivatives, Nano-formulations, Synergism, Current challenges and future perspectives.

1. Introduction

Cancer stands as the second most common disease after cardiovascular diseases responsible for human deaths all over the world [1]. Cancer has turned into a major public health problem in the United States with one death out of every four deaths. It is estimated that 1,658,370 new cancer cases will be diagnosed in the United States in 2015 with deaths of about 589,430 patients [2]. Cancer has also been recognized as the most common cause of death in Europe after cardiovascular diseases. Cancer is the second most common disease in India in terms of human mortality [1]. Overall, cancer is a serious concern the world over. The prevalence of this disease is increasing alarmingly. Cancers of lungs, breasts, colorectum, prostate, stomach, liver, cervix and esophagus are the most prevalent ones, globally [3].

Metal complexes have enough potential to offer multipurpose platforms for rational drug design strategies. Therefore, they have occupied a pioneer niche in inorganic medicinal chemistry [4]. Cisplatin is the most famous metal complex used in the chemotherapy of various cancers [5]. The accidental discovery of the anticancer properties of cisplatin [6] brought about a significant improvement in cancer chemotherapy. Several other cisplatin analogues including carboplatin oxaliplatin, nedaplatin, heptaplatin and lobaplatin; were developed as a result of further experimentation. All these cisplatin analogues are being used for current cancer chemotherapy. Irrespective of these developments, only a limited number of cancers have been treated and the patients suffer from some deleterious side effects. Additionally, the drug-resistance further lowers the essentiality of these metallodrugs [7-9]. These drawbacks of platinum based anticancer therapy tempted scientists towards the design of safe and effective non-platinum metal complexes as anticancer agents. The interesting preclinical and clinical results of the non-platinum metal complexes created a hope for future anticancer medications [7].

In animals, iron is generally assimilated into the heme complex. Heme is an essential component of cytochrome proteins that mediates redox reactions of oxygen carrying proteins including hemoglobin, myoglobin and leghemoglobin. Iron also serves as an important nutrient in the proliferation of cancer cells [10-13]. Bleomycin, an iron chelating glycopeptide antitumor antibiotic is being used in the current anticancer chemotherapy [14,15]. Bleomycin in presence of O_2 and H_2O_2 causes oxidative DNA damage and consequent death of cancer cells [16-21]. Besides, iron(II) chelators also displayed potent anticancer activities and glimpses of the potential to overcome resistance to conventional chemotherapy [20-28]. Therefore, it was thought that iron complexes with wide ligand diversity may also act as anticancer agents *via* a similar or a different mechanism. In the present scenario, iron complexes in different oxidation states, with different ligand systems are being developed all over the world in a quest to fight with cancer cells effectively without any adverse effects to the normal cells and tissues of the body.

2. Review Background

A thorough literature survey was carried out through SciFinder. It was observed that about more than 214 research papers have appeared on iron complexes as anticancer agents. A statistical analysis of the number of publications on "iron complexes as anticancer agents" from 2000-15 indicated a steadily growing interest in the research in this field. The time period from 2000-15 was divided into three intervals *viz.* 2001-04, 2005-09 and 2010-15, and a graph was plotted as shown in **Fig. 1**. It is clear from this figure that the number of research reports has increased remarkably from 14 during 2000-04 through 42 during 2005-09 to 104 during 2010-15. A keen look into literature updates indicated that only five reviews have been published wherein a very little discussion of the anticancer properties of iron complexes has been made [5, 29-33]. These reviews are quite old and do not discuss the recent advances, future perspectives and mechanistic

insights of anticancer iron complexes. Therefore, it was considered worthwhile to review the advances in iron complexes as anticancer agents with emphasis on photocytotoxicity, redox-activity and multinuclearity. In addition, the efficacy of nano-formulations of iron complexes has been discussed. Finally, mechanistic insights, and current challenges and future perspectives of iron complexes as anticancer drugs have been discussed.

We hope this article will become a useful reference material for the researchers actively involved in the design and development of iron complexes as anticancer drugs.

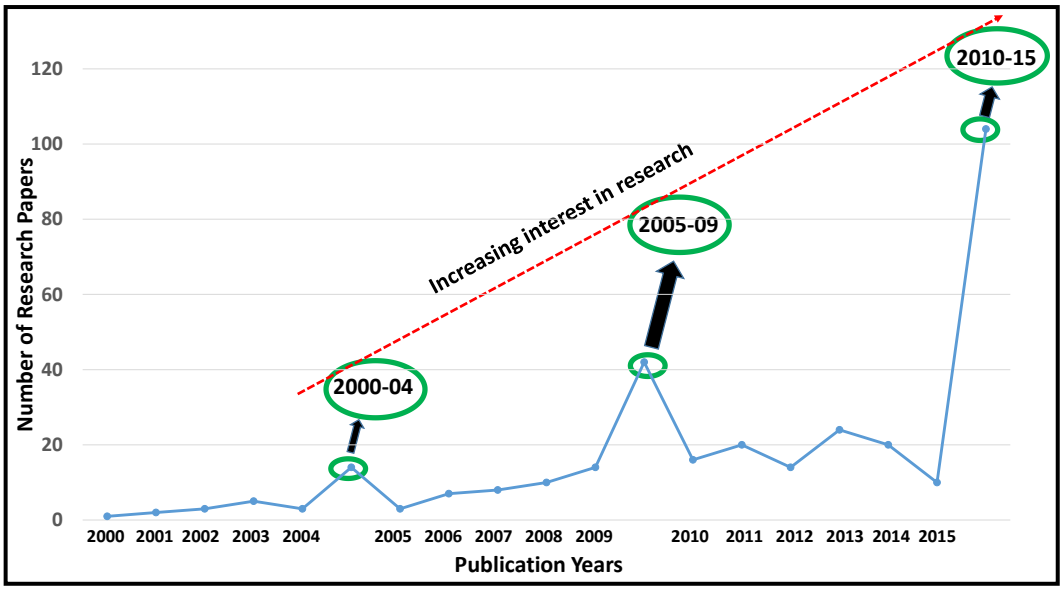
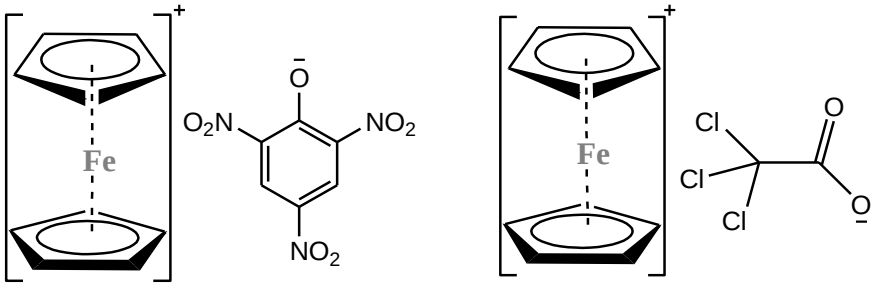


Fig. 1: A pictorial depiction of the steadily growing interest in the research on iron complexes as anticancer agents from 2000-04 through 2005-09 to 2010-15.

3. Iron Complexes as Anticancer Agents

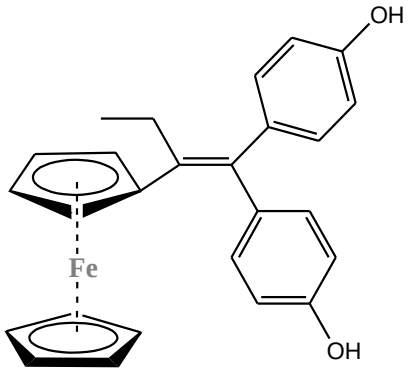
Iron is an essential element for the proper and healthy sustenance of human health because of its involvement in several important biological processes [34]. Upon incorporation into target proteins, it participates in a variety of cellular biochemical processes [35], such as electron transport, DNA synthesis, erythropoiesis, etc. Generally, iron exists in two common oxidation states *viz.* the ferrous form [Fe(II)] and the ferric form [Fe(III)]. This ability of iron to undergo transformation from one form to the other *via* the donation or acceptance of an electron enables it

to carry out a wide range of biological functions [36]. The association of this metal with several important cellular biochemical pathways makes its coordination complexes useful for anticancer drug development. Anticancer properties of iron complexes were first reported in ferrocenium picrate and ferrocenium trichloroacetate salts (**Fig. 2**) [37]. The activities of these salts were attributed to the formation of ROS leading to oxidative DNA damage. Ferrocene derivative of the anti-estrogen tamoxifen (**Fig. 3**) has also displayed interesting antiproliferative properties, which have been attributed to its redox behavior [38-40]. Some iron complexes, e.g., iron(II) complexes containing pentadentate pyridyl ligands (**Fig. 4**; **1-3**) were found to display apoptotic effects with high cytotoxic activities. These complexes were stable at physiological conditions and cleaved supercoiled plasmid DNA *in vitro.* [41].



Ferrocenium picrate Ferrocenium trichloroacetate

Fig. 2: Chemical structures of ferrocenium picrate and ferrocenium trichloroacetate; the first reported iron containing salts with anticancer activities [37].



Ferrocene derivative of tamoxifen

Fig. 3: Chemical structure of ferrocene derivative of the anti-estrogen tamoxifen [38].

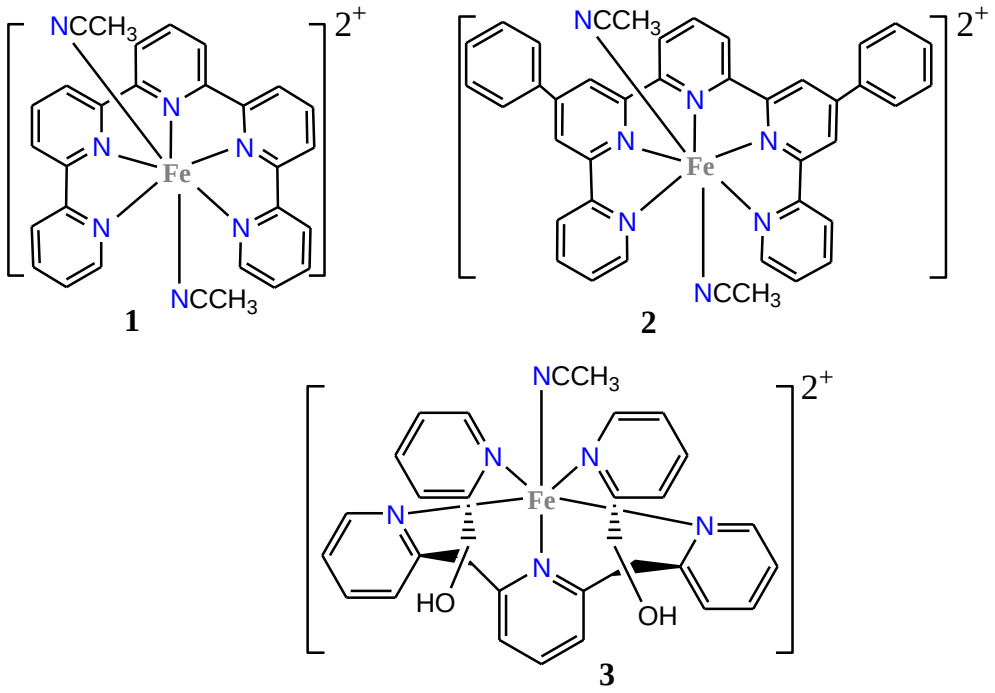


Fig. 4: Iron(II) complexes (**1-3**) with pentadentate pyridyl ligands [41].

Heterocyclic thiosemicarbazones and their metal complexes with different transition metals have received considerable attention in inorganic medicinal chemistry due to their enormous potential as anticancer drugs [42]. Thiosemicarbazone-based iron(III) complexes have displayed stronger anticancer effects and inhibition of DNA synthesis in comparison to free thiosemicarbazones [43,44]. These interesting facts have stimulated research on the development of metal complexes of pyrazolyl thiosemicarbazones as possible anticancer agents. Ghosh et al. [45] reported the cytotoxicities of two iron(III) complexes (**Fig. 5**; **4** and **5**) of 5-methyl-3-formylpyrazole-N(4)-dimethylthiosemicarbazone and 5-methyl-3-formylpyrazole-N(4)-diethylthiosemicarbazone, respectively. Both the complexes were active against HeLa cells in a dose-dependent manner and were more active than their corresponding ligands.

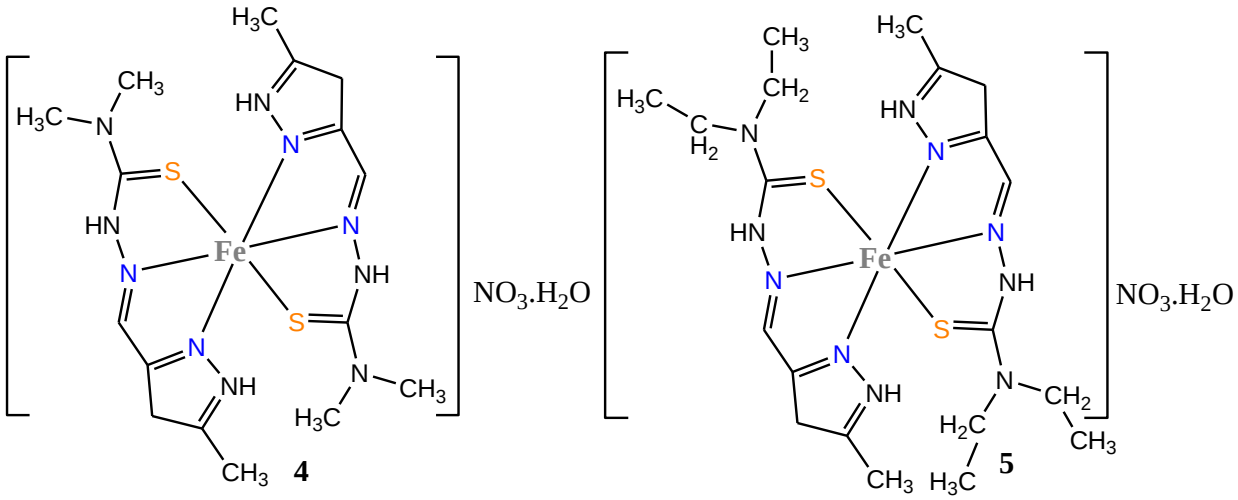
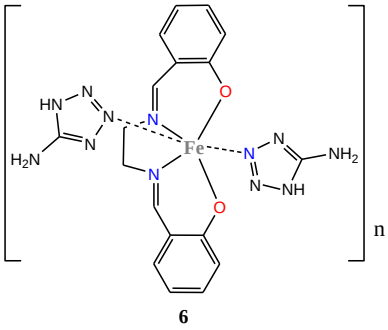
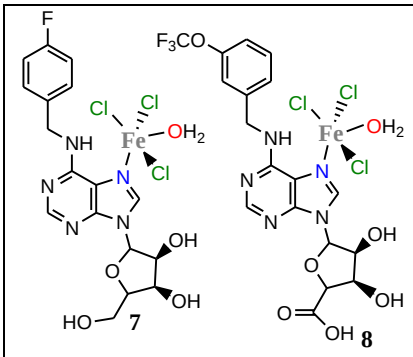
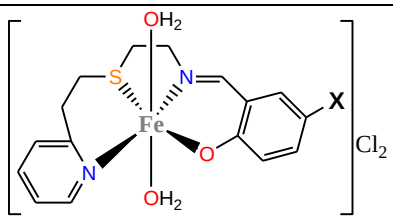
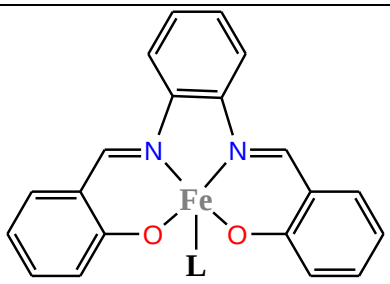
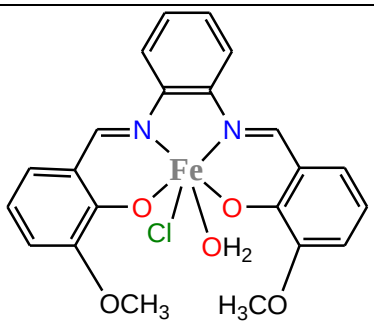


Fig. 5: Chemical structures of the iron complexes (**4** and **5**) of 5-methyl-3-formylpyrazole-N(4)-dimethylthiosemicarbazone and 5-methyl-3-formylpyrazole-N(4)-diethylthiosemicarbazone [45].

An overview of some other iron complexes reported with anticancer properties is given in **Table 1**.

Table 1: Chemical structures, anticancer activities and mechanisms of action of some iron complexes.

Chemical Structures of Active Complexes	Anticancer Activity	No. of Cells Tested (Experimental Time)	Mechanism of Action	Reference
 **6**	**6** was the most active complex against K562 and MCF-7 cells with IC_{50} values of 6.4±1.2 and 13.1±2.1 μM, respectively. It was more active than oxaliplatin (IC_{50} values of 9.0 and 18.0 μM). However, its activity was comparable to cisplatin (IC_{50} values of 5.0 and 11.0 μM) against K562 and MCF-7 cells, respectively.	5×10^4 cells/mL (72 h)	ROS generation	46

	**7** and **8** were the most active complexes against HOS, K-562 and MCF-7 cell lines, with IC_{50} values in the range of 8-16 and 4->50 µM, respectively.	1.25×10^5 cells/mL (72 h)	Not available	47
 For **9,** X = I For **10,** X =Br	**9** and **10** were active against K562 and Jurkat (human T lymphocyte carcinoma). However, both complexes had lower activities than cisplatin.	5×10^4 cells/mL (72 h)	Apoptosis	48
 For **11**, L = None For **12,** L = Cl	**11** and **12** displayed strong inhibitory effects on human lymphoma and leukemia cells.	1×10^6 cells/mL (36 h)	Apoptosis *via* a strong release of Cu/Zn SOD	49
 **Fe-SP (13)**	**Fe-SP** (Iron-salophene complex; **13**) showed selective activity against SKOV-3 and OVCAR-3 cell lines at concentrations between 100 nM and 1 µM. Besides, intra-peritoneal administration of Fe-SP to rats showed no systemic toxicity.	5×10^3 cells/well (24 h)	Apoptosis *via* the activation of the extrinsic (Caspase-8), intrinsic (Caspase-9) pathway and executioner Caspase-3 markers along with the deactivation of PARP-1	50

It is clear from the discussion in this section and the data in **Table 1** that iron complexes containing different types of ligand systems have displayed exciting anticancer properties against different human cancer cell lines. The more important aspect of iron complexes is that their anticancer action mechanisms are different from the platinum drugs. The dependence of the anticancer properties of some iron complexes on their redox behavior is an added asset. Besides, the potential of some iron complexes in overcoming the resistance by cancer cells is an aspect of immense consideration. Hopefully, some of the complexes may be expected to emerge as future anticancer candidates.

4. Recent Advances

Development of anticancer metallodrugs is a hot field of research. Iron complexes are being extensively investigated as anticancer agents owing to their biological essentiality and involvement in several important biological processes. Presently, researchers are in a constant hunt to develop iron complexes with unique features. The recent advances in the development of iron complexes as anticancer agents have been discussed in the following sub-sections.

4.1 Photocytotoxic and Redox-active Iron Complexes

Selectivity towards molecular targets is very crucial in chemotherapy [51]. Increased selectivity of drugs might improve their success rates in chemotherapy. Developing prodrugs is an attractive strategy to reduce the side effects of systemic chemotherapy. Such drugs are designed in such a way that they selectively activate to cytotoxic species in and in the vicinity of a tumor. Some of the clinically useful anticancer agents are produgs, whose success is dependent on this fact.

Photodynamic therapy is an emerging treatment strategy for tumors [52-58], which involves the cumulative presence of light, oxygen and photosensitizing drugs to get the required

photocytotoxic effect. On irradiation within the range of the PDT spectral window, the photosensitizer undergoes various reactions with electron and energy transfer being the most prevalent. Generally, radicals and singlet oxygen species formed during these processes damage cancer cells. The basic requirements for the design of metal complexes in PDT are the metal ion bio-compatibility, redox-activity and reversibility, photoactivity within range of the PDT spectral window, and DNA binding ability. The development of photo-activatable non-platinum metal complexes as anticancer agents is focused at increasing the selectivity and lowering toxicity [59].

Metal complexes are known to intervene in cellular redox processes either directly or indirectly. The direct interference occurs through ligand or metal redox centers whereas the indirect intereference involves binding to biomolecules participating in cellular redox pathways. Therefore, the targeting of the redox balance in cancer cells may serve as an effective strategy. Basically, a number of active metallodrugs involve redox processes in their mechanism of action. As a result, combination therapy together with redox modulators can be exploited to increase the anticancer potency of such complexes. This may lower the doses of metal complexes to be administered. Ruthenium(II) and osmium(II) arene complexes and iridium(III) cyclopentadienyl complexes have shown potency in the nanomolar range towards cancer cells in combination with L-buthionine sulfoximine as a redox modulator [4]. Some metal complexes are “prodrugs” which get transformed to active state by ligand substitution and redox processes before they reach the target site [60].

Recently, Basu et al. [61] demonstrated the potential of iron(III) catecholates (**Fig. 6**; **14-18**) for cellular imaging and photocytotoxicity in red light. The complexes showed FeIII/FeII redox couple near -0.4 V versus an SCE in DMF/0.1M TBAP. The complexes (**15-18**) showed exceptional photocytotoxicity in red light (600-720 nm) against HeLa, HaCaT, MCF-7 and A549

cells, with IC_{50} values in the range of 2.2-14.1 μM. It was further observed that the photocytotoxic death of the cancer cells was due to ROS generated by the complexes. The high anticancer activity and ROS generation indicated a strong candidature of these photocytotoxic complexes for further development as anticancer agents.

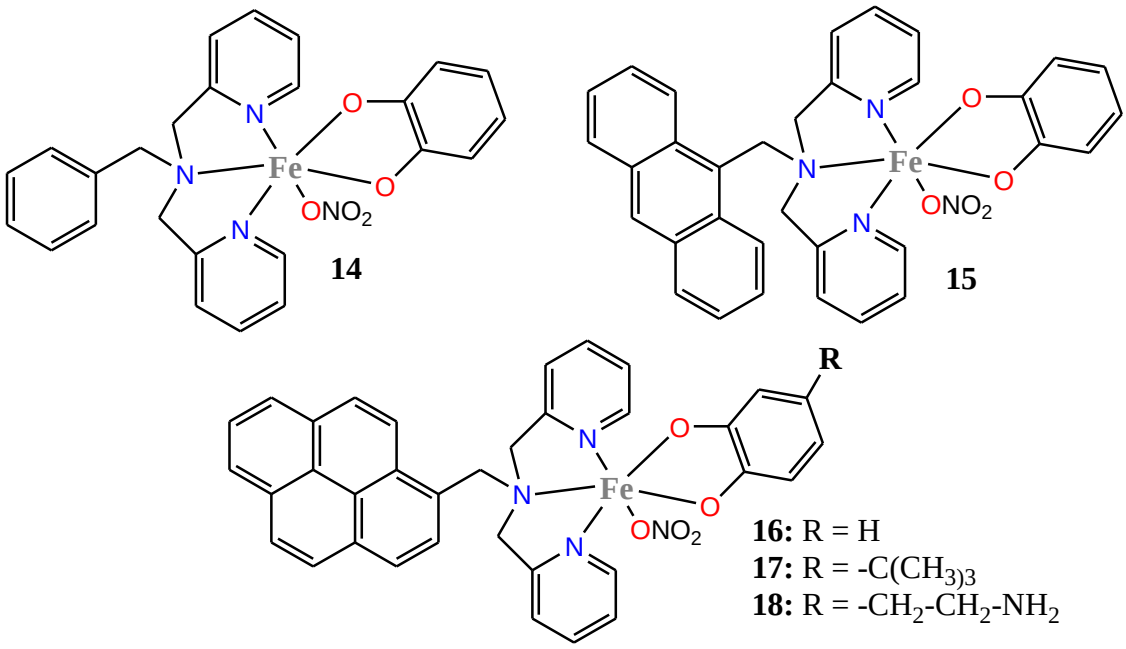
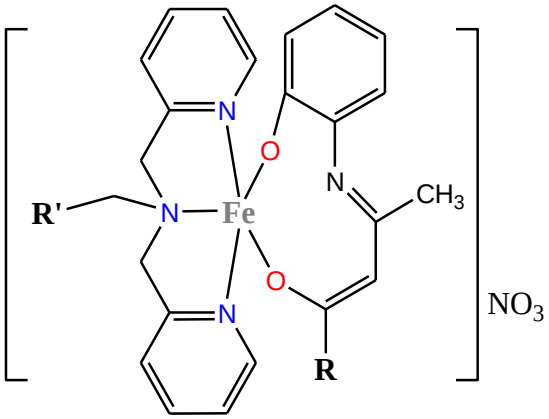


Fig. 6: Photocytotoxic iron(III) catecholates (**14-18**) reported by Basu et al [61].

For the successful design and working of PDT agents, selective accumulation of the photosensitizer into cancer cells without affecting the normal cells is required. Therefore, the targeting of a PDT agent can be enhanced by increasing its selective accumulation inside tumor cells. This can be achieved by developing complexes with ligands entangled with sugars, peptides, aptamers, etc. These moieties help in specific binding of complexes with specific receptors overexpressed on cancer cells [62,63]. Glyco-conjugation is an operative approach for the enhancement of the interactions of conjugates with lectin type receptors overexpressed in certain malignant cells [64-68]. Basu et al. [69] reported photocytotoxic properties of three glucose-appended photocytotoxic iron(III) complexes (**Fig. 7**; **19-21**) of a tridentate Schiff base

phenolate ligand. The high-spin iron(III) complexes exhibited an irreversible Fe(III)-Fe(II) redox couple near -0.6 V versus saturated calomel electrode. The complexes strongly bound to Ct-DNA, and in addition, caused photocleavage of supercoiled pUC19 DNA in red (647 nm) and green (532 nm) lights. Complexes **20** and **21** were significantly photocytotoxic with an IC_{50} value of ~20 μM against HeLa and HaCaT cells in red light, and significantly non-toxic in dark. These complexes showed their cytotoxic effects *via* the generation of ROS. Additionally, preferential internalization of **20** and **21** was reported in HeLa cells. This report indicated the enhancement of cytotoxic, redox-active and internalization/uptake properties of iron complexes on account of glyco-conjugation. Really, conjugation of iron complexes with biologically active scafolds can improve their pharmacological properties. Therefore, further research in this direction is highly encouraged. Saha et al. [70] documented the tumour-targeting and photocytotoxic properties of iron(III) complexes (**Fig. 8**; **22-25**) conjugated with biotin against HepG2, HeLa and HEK293 cancer cell lines. The high-spin iron(III) complexes demonstrated Fe(III)/Fe(II) redox couple near -0.7 V versus the saturated calomel electrode in dimethyl sulfoxide-0.1 M tetrabutylammonium perchlorate. Interestingly, **23** displayed higher photocytotoxicity in HepG2 cells as compared to HeLa or HEK293. Besides, the internalization of the biotin complexes **23** and **25** into HepG2 cells was observed, which might have occurred possibly by receptor-mediated endocytosis.



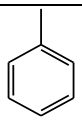
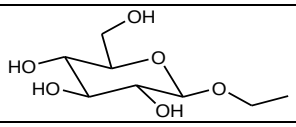
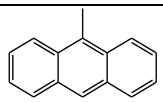
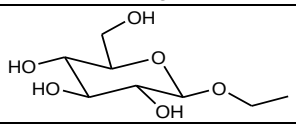
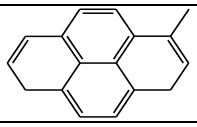
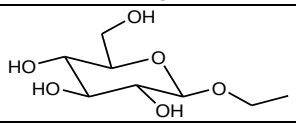
Complexes	R	R´
19		
20		
21		

Fig. 7: The glucose-appended photocytotoxic iron(III) complexes (**19-21**) of a tridentate Schiff base phenolate ligand [69].

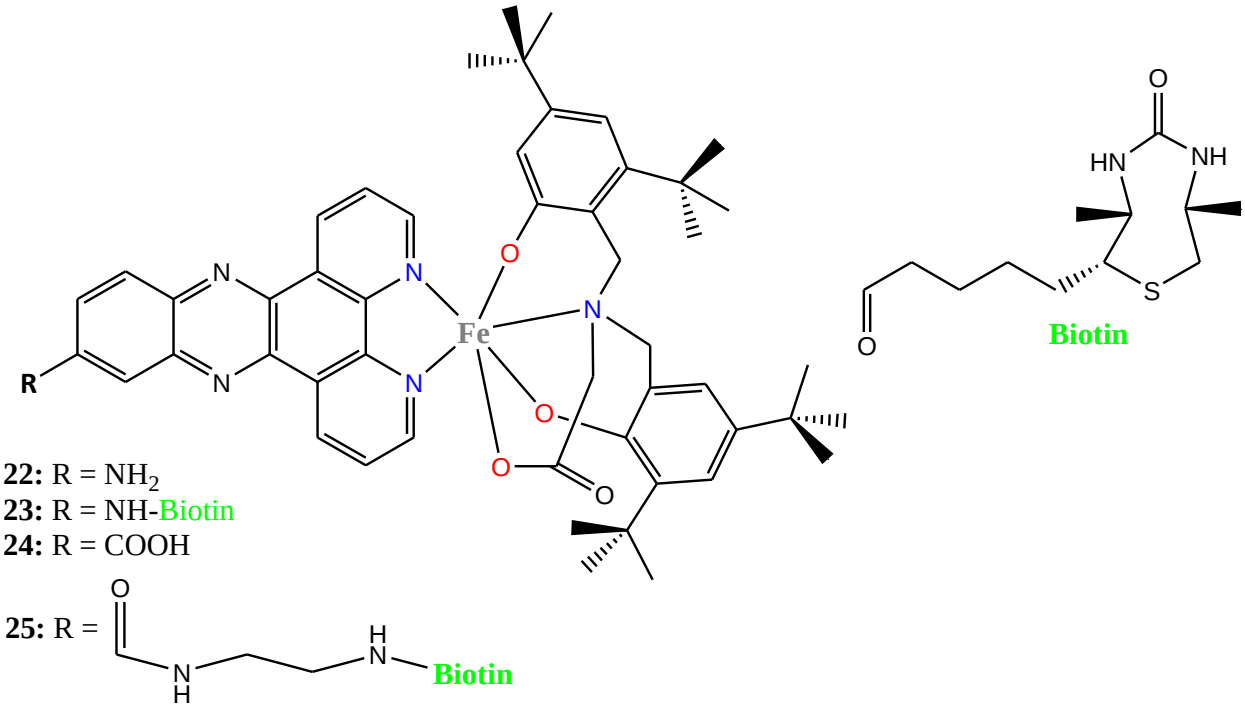
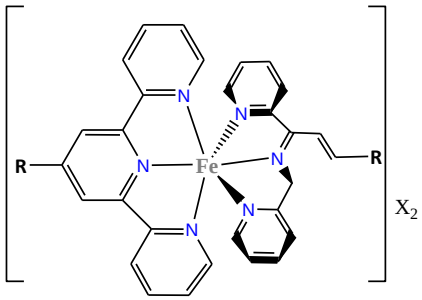
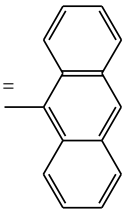
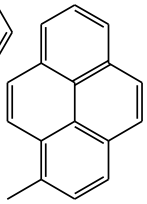
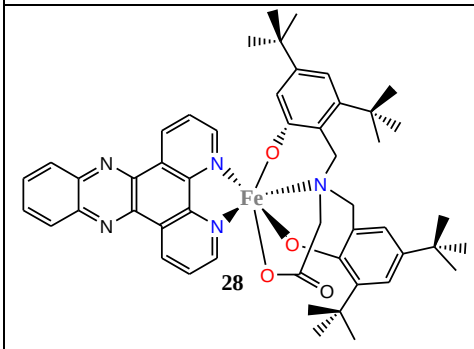
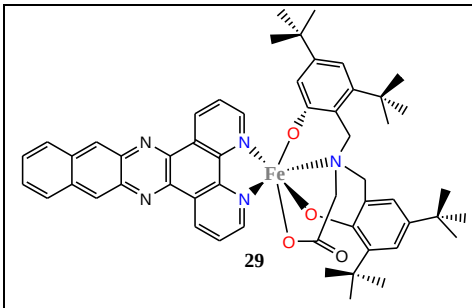
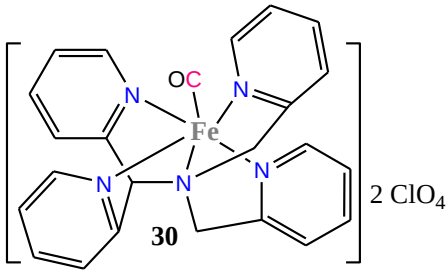
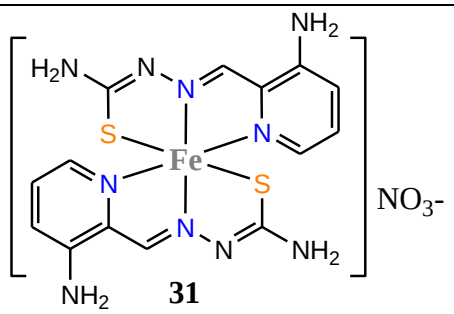


Fig. 8: Photocytotoxic iron(III) complexes (**22-25**) conjugated with biotin [70].

An account of the some other photocytotoxic and redox-active complexes is given in **Table 2**.

Table 2: Chemical structures, anticancer activities and mechanisms of action of some photocytotoxic and redox-active iron complexes.

Chemical Structures of Active Complexes	Anticancer Activity	Redox-couple Voltage	No. of Cells Tested (Experimental Time)	Mechanism of Action	Reference
 For **26** X= ClO_4^- and R =  For **27**: X= ClO_4^- and R = 	**26** and **27** exhibited a remarkable photocytotoxic effect in HeLa cancer cells (IC_{50} = 9 μM) in visible light (400-700nm), while remaining non-toxic in dark (IC_{50} = 90 μM). However, the activities of these complexes were lower than photofrin (IC_{50} = 4.28±0.20 μM).	0.0	8×10^3 cells in 96-well culture plate (19 h)	ROS generation	71
 **28**	**28** displayed photocytotoxicity in HeLa and HaCaT cell lines with IC_{50} values of 3.59 and 6.07 μM in visible light and 251 nM and 751 nM in UV-A light of 365 nm wavelength, respectively. No cytotoxicity was observed in dark. This complex was more active than photofrin against both HeLa and HaCaT cell lines.	-0.6	8×10^3 cells in 96-well culture plate (19 h)	Apoptosis *via* Caspase 3/7 dependent pathway	59

 **29**	**29** was highly active against HeLa cells in visible light with IC_{50} value of 0.77 µM. It was more active than both photofrin (4.28±0.2 µM) and cisplatin (68.7±3.4 µM).	-0.69	8×10^3 cells in 96-well culture plate (19 h)	Apoptosis after photoactiva-tion	72
 **30**	**30** showed potent photo-initiated activity in PC-3 cells with IC_{50} value in the range of 1-10 µM.	NA	Cells seeded in triplicate in 2 96-well plates (10 h)	NA	73
 **31**	**31** was active against 41M cells with an IC_{50} value of 1.50 µM.	+0.01	4×10^3 cells/well (96 h)	ROS generation	74

It can be concluded from the discussion in this section and the data in **Table 2** that iron complexes containing different ligand architectures have displayed selective and exciting anticancer properties against different human cancer cell lines. The absence of activity in dark and the achievement of controlled activity in the presence of specific wavelengths of light looks like a controlled 'activity switch'. Besides, some iron complexes have shown activities several folds higher than cisplatin. The more important facet of these iron complexes seems that their anticancer effects are well governed by their redox behavior and the nature of the light used for activation. Besides, some iron complexes have potential to overcome the resistance by cancer cells. Therefore,

it may be safely said that the future of redox- and photo-active iron complexes is bright, and some of the complexes may be expected to lead to the development of possible anticancer candidates.

4.2 Multinuclear Iron Complexes

Multinuclear complexes usually contain more than one linked metal centers; each capable of covalently binding with DNA. Such types of complexes form completely different DNA adducts as compared to the classical metallodrugs [75]. Multinuclear complexes promise to show enormous potential as anticancer agents, which may in part be due to the additive effect of the individual metal centers. Multinuclear complexes usually exhibit novel DNA binding leading to long range DNA cross links, phosphate clamps, bis-intercalation, interduplex cross links and DNA-protein cross-links [76]. The improved anticancer activity of multinuclear metal complexes due to enhanced DNA binding may be true when the compounds reach DNA, which usually happens with platinum complexes. Recently, iron complexes with high nuclease activity showed low cytotoxicity to cancer cells [77]. Hence, efficient *in vitro* DNA binding may not be an enough factor for multinuclear complexes to exhibit enhanced anticancer activity. Dvorak et al. [78] documented the *in vitro* anticancer activities of some polymeric one-dimensional chain iron complexes containing N-donor heterocyclic ligands like imidazole, 1,2,4-triazole, benztriazole, 5-methyltetrazole, 5-aminotetrazole and 5-phenyltetrazole (**Fig. 9**; **33-37**); against human cancer cell lines *viz.* A549, HeLa, HOS, G361, MCF-7, A2780 and A2780cis. The complexes showed promising anticancer activities against A2780 cells with IC_{50} values in the range of 0.39-0.48 µM. Their activities were quite higher than cisplatin (IC_{50} = 11.5 µM against A2780 cells). Besides, the complexes **36** and **37** also displayed high toxicities against all the tested cells (IC_{50} = 2.5-37.7 µM). Sanina and co-workers [79] reported the anticancer properties of a tetranitrosyl binuclear iron complex (**Fig. 10**; **38**) against SCOV3, LS174T, MCF-7 and A549 cell lines. The complex was

active against all the tested cell lines with IC_{50} values in the range of 27-74 µM. The sulfur-containing ligand with the ortho-substituted amino group in the phenyl ring enabled the nitrosyl iron complex to generate NO in aqueous solutions for longer periods and exhibit a wider range of cytotoxic activities compared to the nitrosyl iron complex with thiophenol.

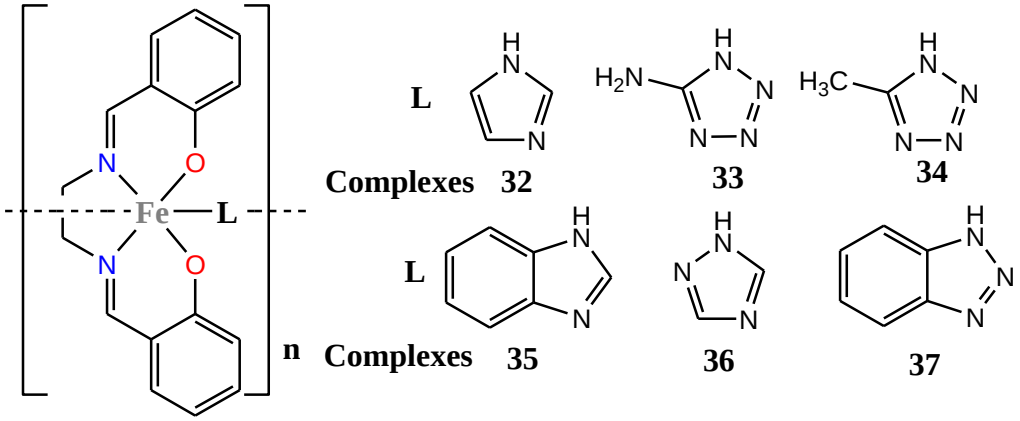
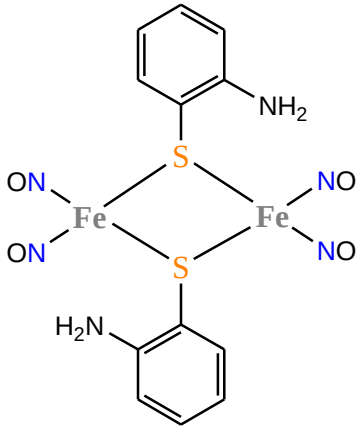


Fig. 9: One-dimensional chain iron complexes (**32-37**) reported by Dvorak et al [78].



38

Fig. 10: Chemical structure of the tetranitrosyl binuclear iron complex (**38**) reported by Sanina and co-workers [79].

Literature witnesses a huge interest in the development of heterometallic complexes as possible anticancer agents. It is believed that having two different active metals within the same molecule may increase the activity of the overall molecule. The activity enhancement may be due to additive effects of the two different metal centers and the interaction of the different metals with

multiple biological targets. Besides, the improved chemico-physical features of the resulting heterometallic complex cannot be ruled out. The anticancer efficacies of several complexes increase by the incorporation of the organometallic ferrocene moiety in their framework. This may be due to the low toxicity, high lipophilicity, and distinctive electrochemical behavior of ferrocene moiety [23-25,80]. There are several examples of heterometallic complexes containing a ferrocene motif and a second cytotoxic metal, e.g., Au(I) Pt(II), Pd(II), Ru(II), Rh(I), Ir(I) and Cu(I) [81-86]. Interestingly, most of the complexes had improved anticancer activities in comparison to the corresponding ferrocenyl motifs. Lease et al. [87] reported the anticancer activities of a series of gold(III) and palladium(II) heterometallic complexes (**Fig. 11**; **39-42**) with iminophosphorane ligands against A2780S/R and MCF-7 cancer cells, and HEK-293T normal cell line. The trimetallic complexes (**39** and **41**) were more cytotoxic than their corresponding monometallic fragments and cisplatin against the resistant A2780R and the MCF-7 cell lines. Interaction studies of the trimetallic complexes with DNA and the zinc-finger protein PARP-1 revealed that their *in vitro* anticancer effects were due to different mechanisms with respect to cisplatin. Tauchman and co-workers [88] documented the anticancer activities of a series of heterodinuclear p-cymene ruthenium ferrocene complexes (**Fig. 12**; **43-57**). All the complexes were active against both cisplatin sensitive as well as resistant A2780 cells with IC_{50} values in the range of 7.8-50.3 μM. Thus, these complexes seemed to be effective candidates for further examination on some other cell lines. Sathyadevi et al. [89] documented the anticancer activities of copper(I) hydrazone Schiff base complexes (**Fig. 13**; **58** and **59**) bearing ferrocenyl motifs against HeLa and A431, and non-tumour NIH 3T3 cell lines. Complexes **58** and **59** were moderately active against HeLa and A431 tumour cells, and were very less damaging towards NIH 3T3 non-tumorous cells. Furthermore, it was encouraging to see that the presence of less electronegative sulphur atom in the thiophene

moiety of the hydrazone in complex **65** favoured strong interactions with biomolecules than complex **64** containing the more electronegative oxygen atom in the furan moiety of the respective hydrazone. This study concludes that the type of hetero atom present in the molecular skeleton of the hydrazone complexes affects their activities in addition to affecting their affinities towards bimolecular interactions.

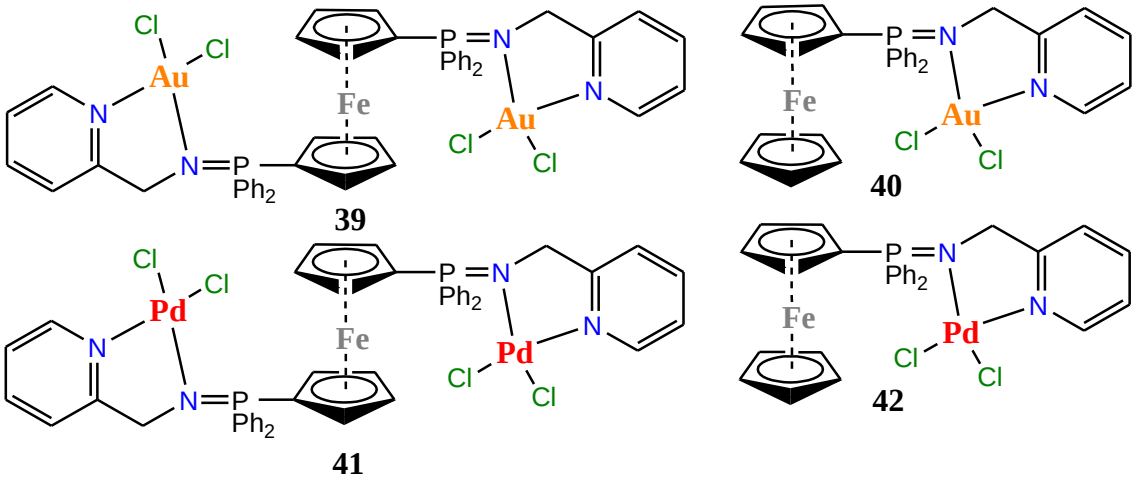
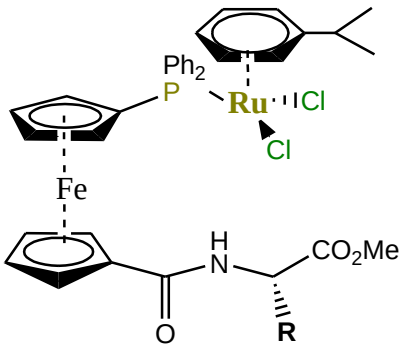
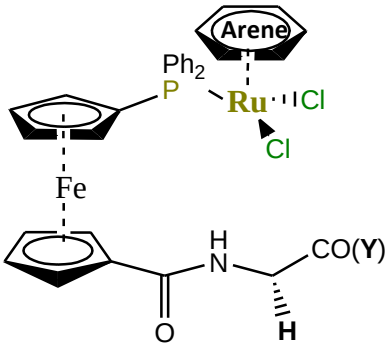


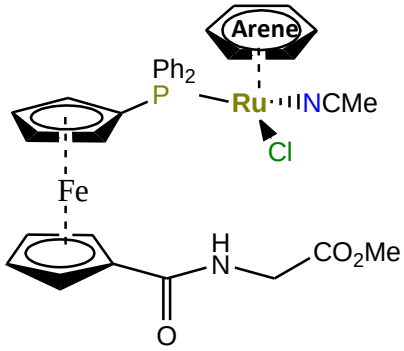
Fig. 11: Trimetallic (**39** and **41**) and bimetallic (**40** and **42**); gold(III) (**39** and **40**), and palladium(II) (**41** and **42**) heterometallic complexes containing iminophosphorane ligands [87].



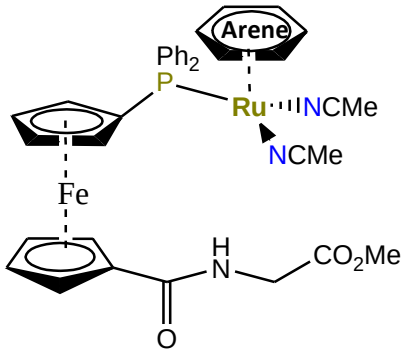
43: R = (S)-Me
44: R = (S)-$CHMe_2$
45: R = (S)-CH_2OMe
46: R = (S)-CH_2SMe
47: R = (S)-$CH_2CH_2CO_2Me$



48: Arene = C_6H_6 and Y = OMe
49: Arene = p-$MeC_6H_4Pr^i$ and Y = OMe
50: Arene = C_6Me_6 and Y = OMe
51: Arene = p-$MeC_6H_4Pr^i$ and Y = NH_2



52: Arene = C_6H_6
53: Arene = p-$MeC_6H_4Pr^i$
54: Arene = C_6Me_6



55: Arene = C_6H_6
56: Arene = p-$MeC_6H_4Pr^i$
57: Arene = C_6Me_6

Fig. 12: Heterodinuclear p-cymene ruthenium ferrocene complexes (**43-57**) reported by Tauchman and co-workers [88].

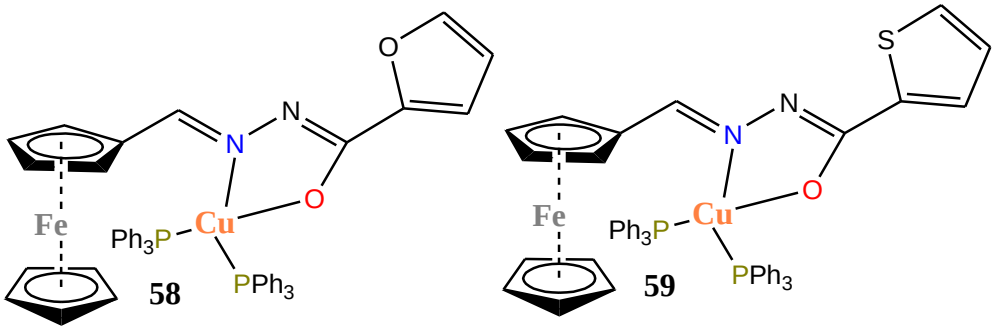
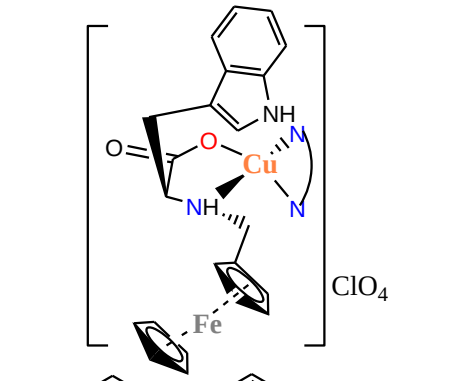
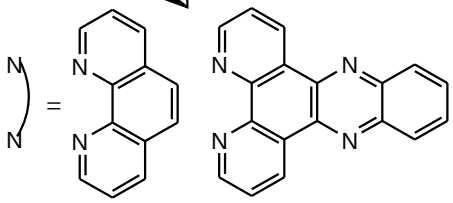
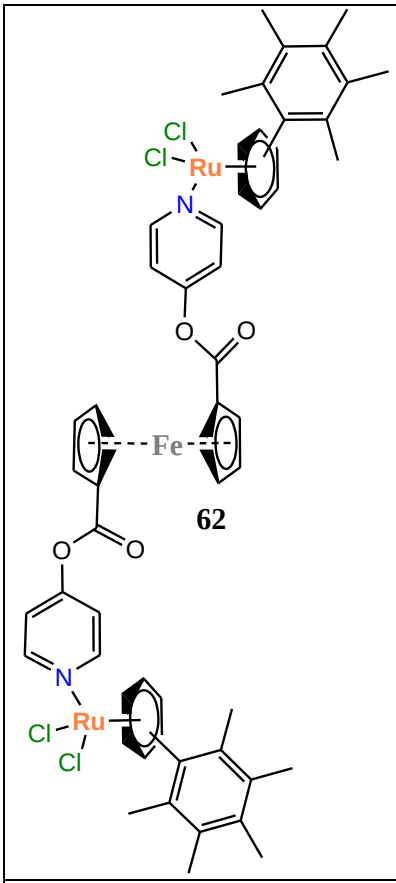
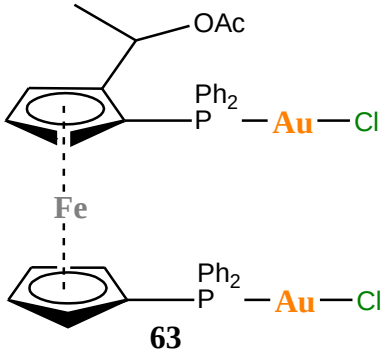
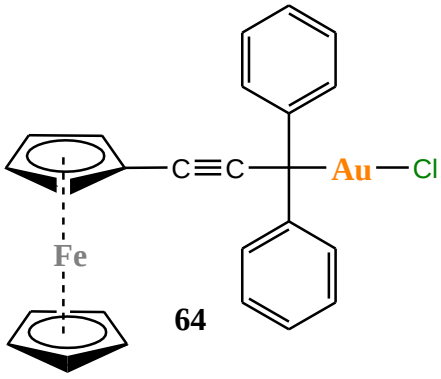


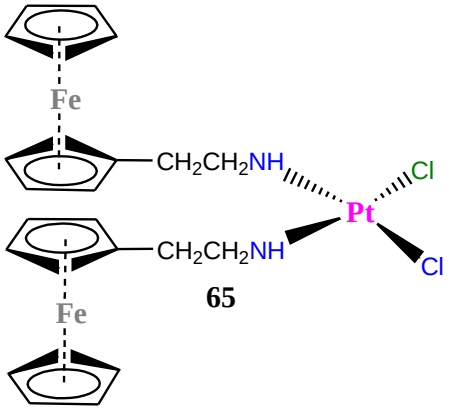
Fig. 13: Copper(I) hydrazone Schiff base complexes (**58** and **59**) bearing ferrocenyl motifs reported by Sathyadevi et al [89].

An overview of some other multinuclear iron complexes along with their anticancer profiles is given in **Table 3**.

Table 3: Chemical structures, anticancer activities and mechanisms of action of some multinuclear iron complexes.

Chemical Structures of Active Complexes	Anticancer Activity	No. of Cells Tested (Experimental Time)	Mechanism of Action	Reference
  **60** **61**	**60** and **61** were the most active complexes against HeLa and MCF-7 cells with IC_{50} values of 4.74 & 1.29, and 2.02 & 0.65 µM, respectively. **67** was more active than photofrin (IC_{50} = 4.3±02 µM) against HeLa cells.	1.5×10^4 HeLa cells and 2×10^4 MCF-7 cells in 96-well culture plate (27 h)	Caspase-independent apoptosis.	90

 **62**	**62** was the most active complex with IC_{50} values of 14.8 and 17.7 µM, respectively against A2780 and A2780cisR cells. However, it was less active than cisplatin (IC_{50} values of 1.6 and 8.6 µM for A2780 and A2780cisR, respectively).	Cells seeded in 96-well plates (72 h)	NA	91
 **63**	Complex **63** was active against HeLa cells with an IC_{50} value of 9.0±0.5 µM. However, it was less active in comparison to cisplatin (IC_{50} = 1.4±0.1 µM).	5×10^2 cells/well (84 h)	NA	92
 **64**	**64** was the most active complex against HeLa cells with an IC_{50} value of 4.6 µM. However, it was less active than cisplatin (IC_{50} = 0.19±0.01 µM).	5×10^2 cells/well (84 h)	NA	93

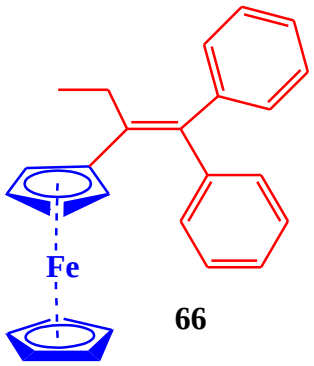
 **65**	**65** was the most active complex against HBL-100, HeLa, SW1573 and WiDr cell lines with GI_{50} values in the range 1.7-2.3 µM. The complex was also active against the cisplatin resistant cells. Interestingly, **71** was more active than cisplatin (IC_{50} range ~ 2.0-26 µM) against HeLa, SW1573 and WiDr cell lines.	1.0×10^4 cells/well for HBL-100, HeLa and SW1573 cells, and 2×10^4 cells/well for WiDr cells (48 h)	NA	94

It can be concluded from the discussion in this section and the data in **Table 3** that multinuclear iron complexes containing different ligands have displayed promising anticancer properties against several human cancer cell lines. Besides, some multinuclear iron complexes have showed potential to overcome the resistance by cancer cells as they interact differently with the biological targets within cancer cells. Hence, it can be said that multinuclear complexes offer certain advantages that are not possible with monometallic complexes. However, the choice of the metal ion has great effects on the specificity and activity of the complexes. The differently incorporated metal ions into a molecular structure alter geometries and the consequent interactions with biological targets. Therefore, further studies are required to develop some rationales into the selection of metal ions so that more active and selective complexes may be obtained.

4.3 Ferrocenyl Derivatives

The popularity of ferrocene and its derivatives for biological investigations may be attributed to their stability in aqueous and aerobic media, suitability of derivatization and suitable electrochemical properties [95-102]. The exploration of the anticancer efficacies of ferrocene derivatives can be traced back to the early studies of Fiorina et al., who reported anticancer activity of ferrocenyl complexes with amine or amide groups against lymphocytic leukemia P-388 [103].

This was an enough stimulus to the development of several classes of ferrocenyl complexes with interesting anticancer activities [104-113]. de Oliveira et al. [114] reported the anticancer activities of 2-ferrocenyl-1,1-diphenylbut-1-ene (**Fig. 14**; **66**) against HL-60, HCT-8, SF-295, MDA-MB-435, OVCAR-8 and GBM non-cancerous cells. The complex displayed a selective concentration-dependent decrease in tumor cells mainly *via* apoptosis. Besides, it affected the cell cycle, leading to accumulation of cells in the G1/G0 phase. It was quite interesting to note that both 1,1,2-triphenylbut-1-ene and ferrocene (**Fig. 14**) did not show any activity against HL-60 cells, non-cancer cell lines and were non-reactive with DNA. This report strongly favours the fact that the approach of conjugating ferrocene to tamoxifen derivatives may help in the search of new agents with anticancer activities. Tan and co-workers [115] reported a series of complexes (**Fig. 15; 67-70**) with a ferrocenyl group tethered to catechol *via* a conjugated system. The complexes were tested for their cytotoxic effects towards MDA-MB-231 cancer cell lines. The catechol complexes had good anticancer activities (IC_{50} = 0.48-1.21 μM) in comparison to their corresponding phenolic analogues (0.57-12.7 μM). Owing to the results shown by these complexes, further investigations on some other cell lines are encouraged.



66

Fig. 14: Chemical structure of 2-ferrocenyl-1,1-diphenylbut-1-ene (**66**). Blue and red portions indicate the ferrocene and 1,1,2-triphenylbut-1-ene residues, respectively [114].

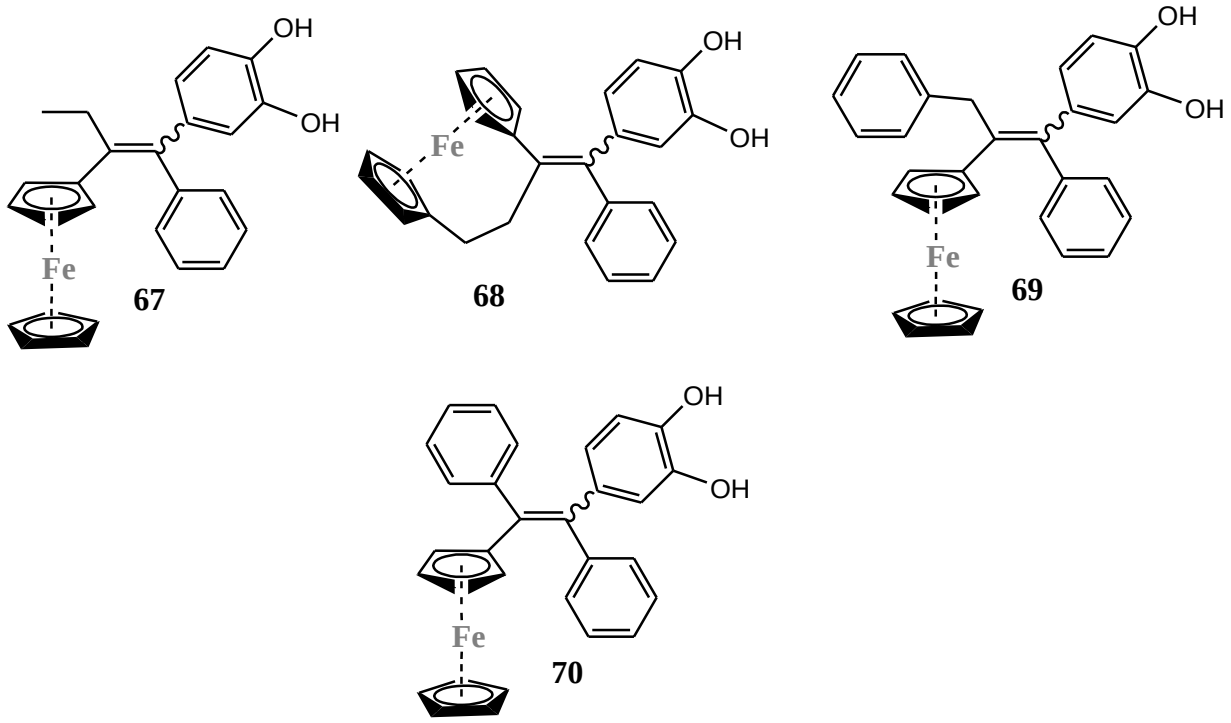


Fig. 15: Chemical structures of the complexes (**67**-**70**) containing a ferrocenyl group tethered to catechol *via* a conjugated system [115].

Nucleosides are building blocks of nucleotides and in turn DNA. Nucleoside templates have always been interesting for the design of new drugs. Changing the carbohydrate and nucleobase moieties has led to the development of some of the important anticancer agents [116-119]. James et al. [120] reported some ferrocenyl nucleoside analogues displaying anticancer activities *via* induction of apoptosis in BJAB cells and primary lymphoblasts from children with ALL both *in vitro* and *ex vivo*. Complexes **71** and **72** (**Fig. 16**) exhibited considerable apoptosis in the lower micromolar range (LD_{50} = 10-20 μM). Moreover, complex **71** overcame resistance in an *ex vivo* experiment with primary lymphoblasts isolated from children with a relapse of ALL. This report clearly describes ferrocenyl nucleosides with marked apoptosis-inducing activity dependent on their structures, and opens a new window for the development of ferrocene-based nucleosides as promising organometallic anticancer agents.

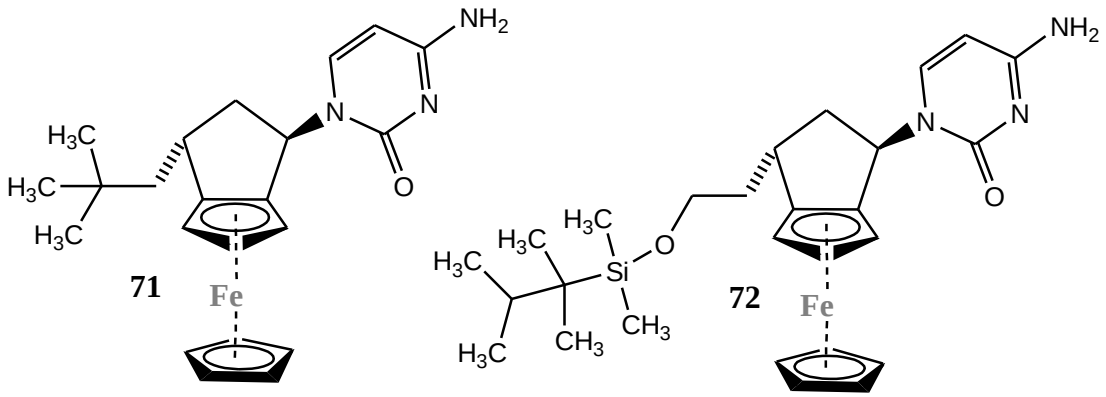
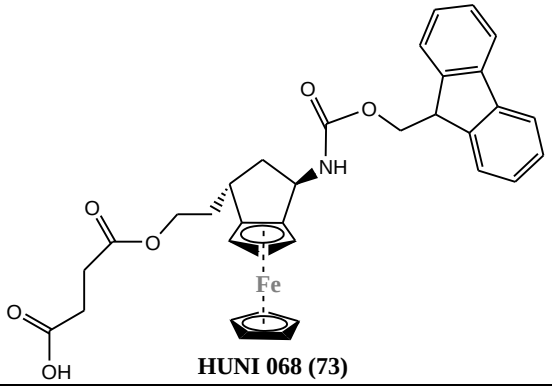
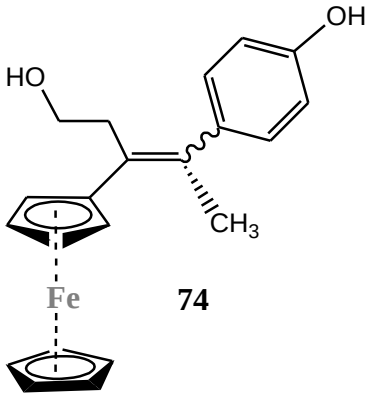
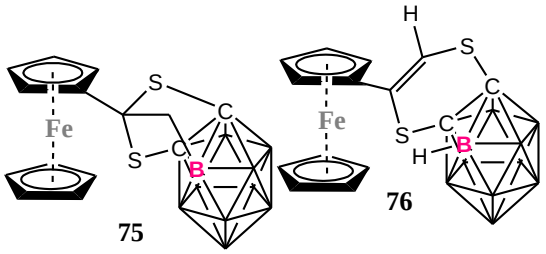
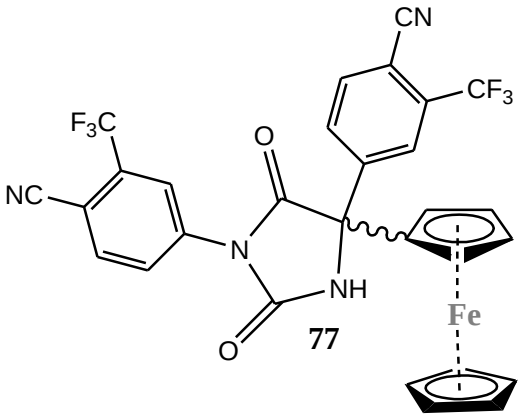
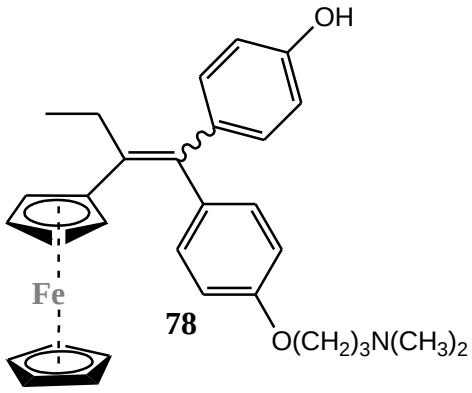


Fig. 16: Ferrocenyl nucleoside analogues (**71** and **72**) reported by James et al. [120].

An account of some ferrocenyl derivatives along with their anticancer profiles is given in **Table 4**.

Table 4: Chemical structures, anticancer activities and mechanisms of action of some ferrocenyl derivatives.

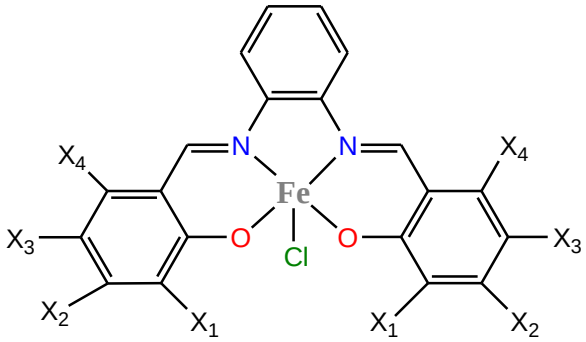
Chemical Structures of Active Complexes	Anticancer Activity	No. of Cells Tested (Experimental Time)	Mechanism of Action	Reference
 **HUNI 068 (73)**	**HUNI 068 (73)** was active against BJAB and Nalm-6 cells with IC_{50} values in the range of 30-40 µM.	1.0×10^5 cells/ml (24 h)	Apoptosis *via* intrinsic mitochondrial pathway	121
 **74**	**74** was the most active complex against MDA-MB-231 cells with an IC_{50} value of 0.14 µM.	2×10^4-3×10^4 cells/ml (48 h)	NA	122

	**75** and **76** were potent against SMMC-7721 and HepG2, cells, but were inactive towards the HELF cells. Both the complexes were more active than cisplatin.	7×10^3 in 96-well plate (24 and 48 h for 81 and 82, respectively)	G0/G1 phase arrest of cell cycle	123
	**77** was the most effective complex against PC3 cells with an IC_{50} value of 5.4 µM.	1.5×10^4-2.5×10^4 cells/ml (24 h)	Interaction with cannabinoid receptors	124
	**78** was highly toxic to primary malignant cells including WM9, WM35 and WM793 and significantly non-toxic to normal cells.	1.0×10^4 cells in 24-well plates (96 h)	NA	104

It can be concluded from the discussion in this section and the data in **Table 4** that several ferrocenyl derivatives have displayed exciting anticancer properties against different human cancer cell lines. In addition, several classes of ferrocenyl derivatives have displayed selectivity towards cancer cells without harming non-cancerous ones with distinct mechanisms of action. Therefore, further research is encouraged so that some ferrocene-derived molecules with improved therapeutic profiles may be obtained as more specific and safe anticancer agents.

4.4 Salen Complexes

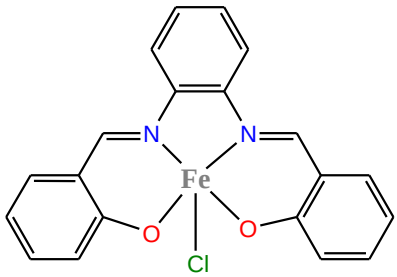
Iron complexes with salen ligands or their derivatives such as alkoxy-, hydroxy-, alkyl-, or trihalomethyl, etc. have shown potential as anticancer agents [125-129]. Some of these complexes exhibited ten folds higher activities than cisplatin. Besides, some complexes based on ortho-vanillin and 1,2-phenylenediamine Schiff bases overcame the resistance of specific human cancer cell lines [130, 131-135]. Hilee and Gust [136] reported the anticancer activities of a series of methoxy-substituted iron(III)-salophene complexes (**Fig. 17**; **79**-**83**) against MCF-7, MDA-MB-231 and HT-29 cancer cell lines. A time-dependent chemosensitivity assay revealed the dependence of activities of the complexes on the position of methoxy substituents in the salicylidene moieties. The order of activities of the complexes was 3-OCH_3 (**80**) < 5-OCH_3 (**82**) < H (**79**) < 4-OCH_3 (**81**) = 6-OCH_3 (**83**). The complexes **81** and **83** displayed cytocidal effects at 0.5 μM concentration. Interestingly, both **80** and **82** exhibited similar time response curves, but 5-folds lower than that of **81** and **83**. The biological activities of these complexes were thought to be governed by the influence of the electron-donating methoxy groups on the redox behaviour of the complexes. The methoxy groups were assumed to increase the electron density at the Fe-O bond differentially that caused the differences in activities.



Complexes	Substituents
79	X1 = H, X2 = H, X3 = H and X4 = H
80	X1 = OMe, X2 = H , X3 = H and X4 = H
81	X1 = H, X2 = OMe , X3 = H and X4 = H
82	X1 = H, X2 = H, X3 = OMe and X4 = H
83	X1 = H, X2 = H, X3 = H and X4 = OMe

Fig. 17: Chemical structures of the methoxy-substituted iron(III)-salophene complexes (**79-83**), which were active against MCF-7, MDA-MB-231 and HT-29 cancer cell lines [136].

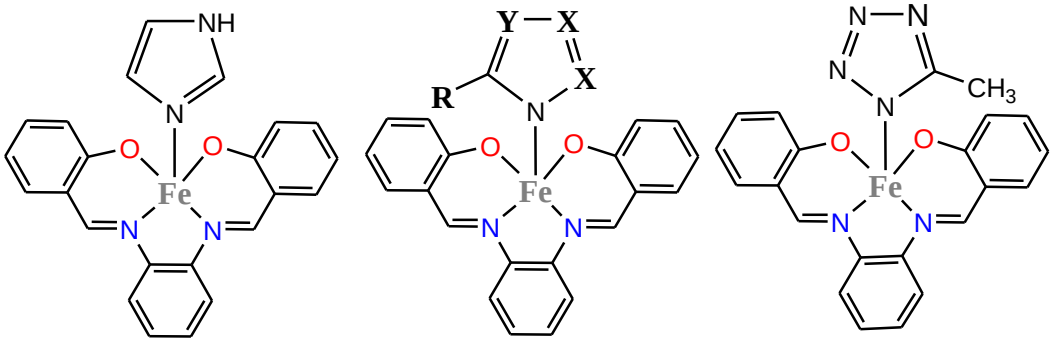
Lee et al. [130] demonstrated the *in vitro* and *ex vivo* cytotoxic potential of the Schiff base salen iron complex (**Fig. 18**; **84**) and its ability to overcome MDR in vincristine and daunorubicine resistant Nalm-6 cells. Treatment of BJAB cells with **84** led to the exclusion of unspecific necrosis, a concentration-dependent inhibition of proliferation and a specific apoptotic cell death. The authors further detected a significant loss of the mitochondrial membrane potential in lymphoma cells. Besides, an up and down regulation of various apoptosis relevant genes was observed, which indicated the involvement of the intrinsic mitochondrial pathway. The results encouraged *in vivo* studies; as this complex seems to be a promising agent for antitumor therapy.



84

Fig. 18: Chemical structure of the Schiff base iron complex (**84**) reported by Lee et al. [130].

Recently, Vanco et al. [134] documented high level and broad-spectrum anticancer activities of a series of iron(II/III) salophen complexes (**Fig. 19; 85-90**) containing monodentate azole-derived ligands against six human cancer cell lines *viz.* HOS, MCF-7, A549, HeLa, A2780 and G-361. All the complexes were highly cytotoxic and several folds more active than cisplatin. Interestingly, the complex **90** showed a very high activity against A2780 cell line with an IC_{50} value of 58 nM (200 times more effective than cisplatin). A critical analysis of this report indicates a bright scope of these complexes for their further studies as anticancer agents.

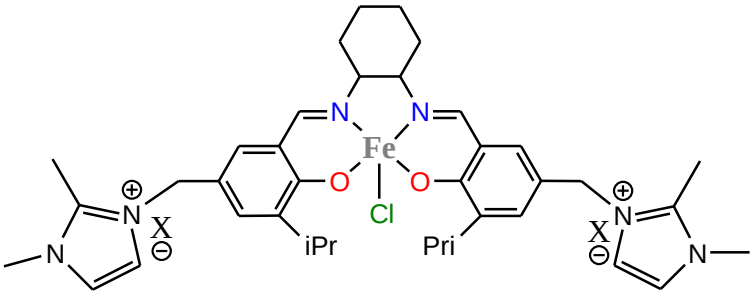


85 **90**

86: X = CH, Y = Nand R = H
87: X = N, Y = C and R = annealated benzene
88: X = N, Y = N and R = NH
89: X = N, Y = N and R = phenyl

Fig. 19: Iron(II/III) salophen complexes (**85-90**) containing monodentate azole-derived ligands were reported by Vanco et al. [134].

Water solubility has been a serious concern for medicinal inorganic chemists, since it is one of the basic requirements of a bioavailable and therapeutically active drug [137]. Elshaarawy and co-workers [138] documented the anticancer activities of some water soluble bis-imidazolium complexes (**Fig. 20**; **91-93**) with a saldach scaffold. The complexes **91-93** displayed anticancer activities against HepG-2 and MCF-7 cell lines with IC_{50} values in the range of 45.86->50 µM. On account of the water solubility of these complexes, we suppose these complexes be further investigated on some other cell lines, and even NCI-60 screening is fully encouraged.

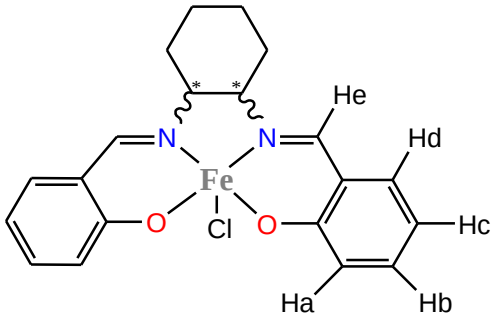


91: X = Cl
92: X = PF_6
93: X = BF_4

Fig. 20: Water soluble iron complexes (**91-93**) reported by Elshaarawy co-workers [138].

Interaction of enantiomerically pure metal complexes with the chiral DNA double helix might lead to diastereomeric adducts. In addition to the different stereochemical features of the DNA cross-links of metal complexes bearing enantiomerically pure ligands, such complexes work differently within the cellular machinery [139]. The ongoing research in this direction has revealed the effects of different stereochemical features of complex-DNA adducts on cell response and, therefore, are highly contributing to the understanding of the processes crucial for antitumor activity. Hilee et al. [140] documented the relationship between the anticancer activity and stereochemistry of saldach ligands and their iron(III) complexes (**Fig. 21**; **94-97**). Different ligand stereoisomers including (R,R)-, (S,S)- and (R,S)-N,N'-bis(salicylidene)-1,2-diaminocyclohexane and their iron(III) complexes were tested for anticancer activity against MCF-7, MDA-MB 231 and HT-29 cell lines. The complexes **94-97** were active within a concentration range of 1-5 µM, and were more active than cisplatin at 5 µM.

The development of chiral iron complexes is yet an immature field of research and further efforts are needed to get good insights into the factual basis of the effects of chirality of iron complexes on their molecular targets and the resulting anticancer properties. Therefore, it is urgent to look for their real molecular targets and optimize the cytotoxic effects.



94: rac-trans
95: (R,R)-trans
96: (S,S)-trans
97: (R,S)-cis

Fig. 21: Several stereo-isomeric iron complexes of saldach (**94-97**) reported by Hilee and co-workers [140].

Overall, the discussion in this section indicates that several complexes containing salen ligands and their derivatives are bestowed with potential anticancer properties. Development of water soluble complexes is an area of achievement for inorganic medicinal chemists. Besides, the dependence of anticancer activity on chirality and stereochemistry of complexes is a fine observation. Therefore, further research is needed for developing new iron complexes with diverse ligand systems based on core salen moieties for the development of effective anticancer agents.

4.5 Miscellaneous Iron Complexes

In addition to photocytotoxic and redox-active iron complexes, multinuclear iron complexes, ferrocenyl derivatives and salen complexes; several other iron complexes have been reported with promising anticancer properties. Concalves et al. [141] demonstrated the anticancer activities of four iron(II) cyclopentadienyl complexes (**Fig. 22**; **98-101**) with imidazoles. The IC_{50} values for the complexes **98-101** ranged from 0.22-3.0, 0.81-3.1 and 1.4-6.3 μM, respectively against A2780, MCF-7 and HeLa cells, respectively. The most interesting observation was that the activities of the complexes were higher than cisplatin, especially for the MCF-7 cells. Apparently, these compounds are expected to be promising as anticancer drugs, and therefore, should be further investigated in *in vivo* experiments.

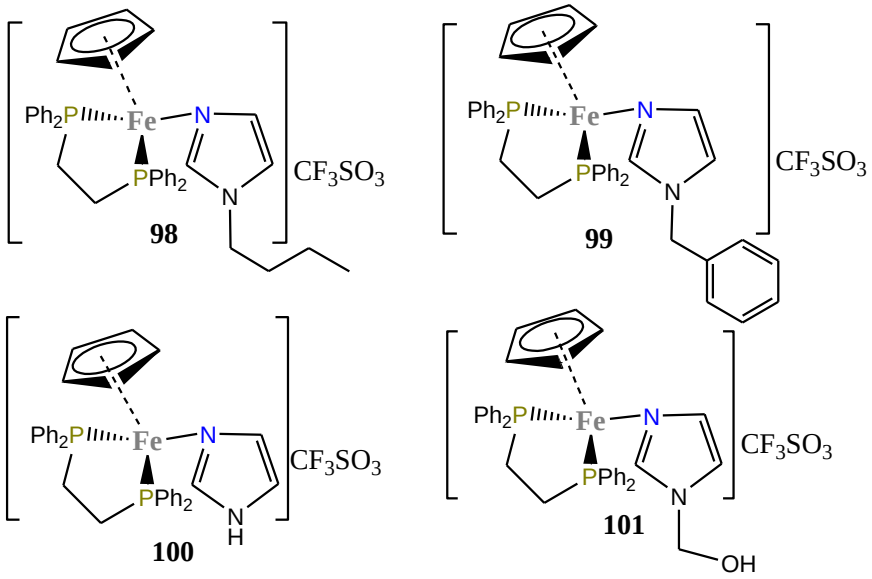


Fig. 22: Iron(II) cyclopentadienyl complexes (**98-101**) with imidazoles displayed higher anticancer activities than cisplatin [141].

Pyrazolines are an important class of nitrogen-containing five-membered ring heterocyclic compounds. Pyrazoline derivatives are pharmacologically important. They have been found to possess diverse biological properties including anticancer [135, 142-144]. Saleem et al. [145] reported the anticancer activities, DNA binding, solution stability and hemolysis assays of an iron complex (**Fig. 23**; **102**) of a pyrazoline-based ligand. The iron complex demonstrated appreciable binding with DNA, robust nature in PBS at pH 7.4 and good anticancer activity against MCF-7 cells. Besides, the complex was less hemolytic towards rabbit red blood corpuscles as compared to the standard drug, doxorubicin.

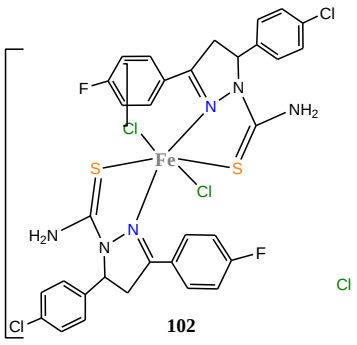


Fig. 23: Pyrazoline-based iron complex (**102**) reported by Saleem et al. [145].

It can be concluded from the discussion in this section that iron complexes with organic ligands with diverse chemical architectures have displayed promising anticancer properties. Therefore, further research is needed for exploring new ligand systems whose iron coordination can bring out molecular systems with improved therapeutic profiles.

5. Nano-formulations of Iron Complexes

Nano-sized drug delivery systems are being increasingly demanded in pharmaceutical industry. Nano-formulations remarkably improve the pharmacokinetics and biodistribution of drugs leading to reduction of side effects and improvement of patient compliance. Since the approval of liposome containing doxorubicin in 1995, large numbers of nano-formulations, such as polymer-drug conjugates, dendrimers and inorganic nanoparticles have entered clinical trials [146]. Pharmaceutical formulations including nanosized drugs generally, referred to as nanopharmaceuticals are quite significantly beneficent to the patient in comparison to the conventional drugs. Nano-formulations have several advantages such as enhanced solubility, oral bioavailability, dose proportionality, reduced side effects and suitability for administration *via* all routes [147]. Several studies have demonstrated increase in the therapeutic index of iron complexes in terms of increased activity, lower toxicity, improved solubility and stability; after conjugation or functionalization into nanostructures [148-153]. Tao et al. [154] optimized the delivery and imaging of cancer cell targeting using antiproliferative nanoparticle complexes. Rhodamine B isothiocyanate doped silica-coated (RBITC-SiO_2) (**Fig. 24**) were prepared by microemulsion method. Fe(III) complex of di(picolyl)amine was conjugated onto the surface RBITC-SiO_2 to produce final nanosphere (RBITC-SiO_2@dpa-Fe) with a mean hydrodynamic diameter of 74 nm. The Fe(III)-di(picolyl)amine complex modified nanospheres displayed enhanced *in vitro* uptake by HeLa cells; indicative of selective cancer cell payload delivery. The

conjugate of dpa-Fe(III) complex and fluorescence core-shell nanoparticles RBITC-SiO_2 represents a novel class of multi-functional nanoparticles. These nanoparticles display the features of active cancer-targeting through Fe(III) complex mediated intracellular drug delivery and compatibility with fluorescence imaging. Xu and co-workers [155] described a synthetic approach to generate metallosalphen prodrugs as coordination polymer nanoparticles (coordination polymer particles). The coordination polymer nanoparticles were structurally constituted of a magnetite nanocrystal colloidal cluster as core and salphen-In(III) coordination polymer as shell. In addition to the intense photoluminescence, sensitive magnetic responsiveness and pH-responsive degradability, these nanoparticulates served as prodrugs to facilitate intercellular conversion from non-toxic nanoparticles [Fe_3O_4@Salphen-In(III)] to pharmacologically active complexes (Fe-salphen) (**Fig. 25**). This conversion and the intercellular generation of Fe-salphen complexes selectively inhibited the proliferation of A549 cancer cells over normal non-malignant 16HBE cells *via* caspase activation. This report encourages the investigation of other pH-dependent intercellular nanoparticulate-based conversions (involving other iron complexes) for the development of effective and safe chemotherapeutic systems.

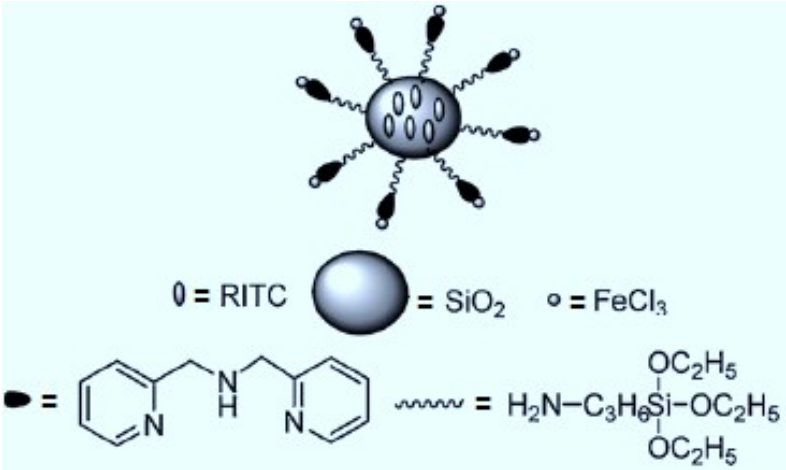
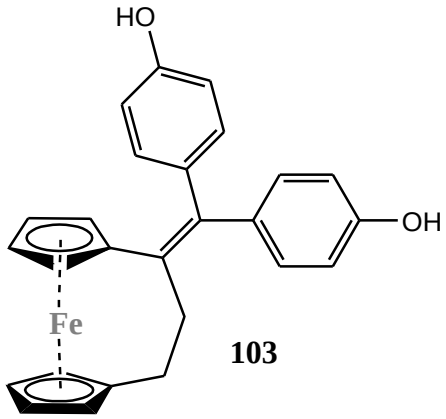


Fig. 24: Synthesis of RBITC-SiO2@dpa-Fe nanoparticulate systems. (Reproduced with permission from Elsevier, copyright 2015).

Fig. 25: Synthesis of Fe_3O_4@Salphen-In(III) CPPs and progressive degradation of salphen-In(III) CPP shell and Fe_3O_4 nanocluster core at 5.0 pH. (Reproduced with permission from Elsevier, copyright 2015).

One of the major medical challenges for scientists in the current scenario is the treatment of malignant brain tumor. There is an urgent need to develop strategies for the safe and effective treatment of brain cancers. Laine et al. [156] reported the inhibition of ectopic glioma tumor cells by a ferrocenyl complex (**Fig. 26**; **103**) encased in stealth LNCs. The complex was appropriately encased into 40 nm measuring LNCs, which had a high loading capacity of 6.4%. The complex **103** displayed a potent effect on 9L cells (IC_{50} = 0.1μM). Besides, the anticancer effect was associated with oxidative stress and dose-dependent alteration of cell cycle. A remarkable tumor growth inhibition was observed in rats bearing ectopic glioma on repeated intravenous administrations of stealth **103** LNCs. More importantly, there was no liver damage in the treated rats. These results were indicative of the fact that stealth **103** LNCs be considered as an effective and safe modality for cancer chemotherapy.



103

Fig. 26: Ferrocenyl complex (**103**), which was encased in stealth LNCs by Laine et al. [156].

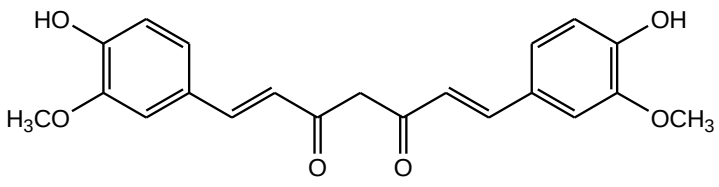
It is clear from the discussion in this section that nano-formulations of iron complexes have displayed several exciting properties not possible with conventional iron complexes. Fluorescence imaging, selectivity and enhanced and prolonged therapeutic effects are the requirements which may qualify any therapeutic entity as a treatment modality. Therefore, we strongly hope that the research in this direction will expand further and some exciting results will be made available to the world soon enough.

6. Synergism of Iron Complexes with Other Agents

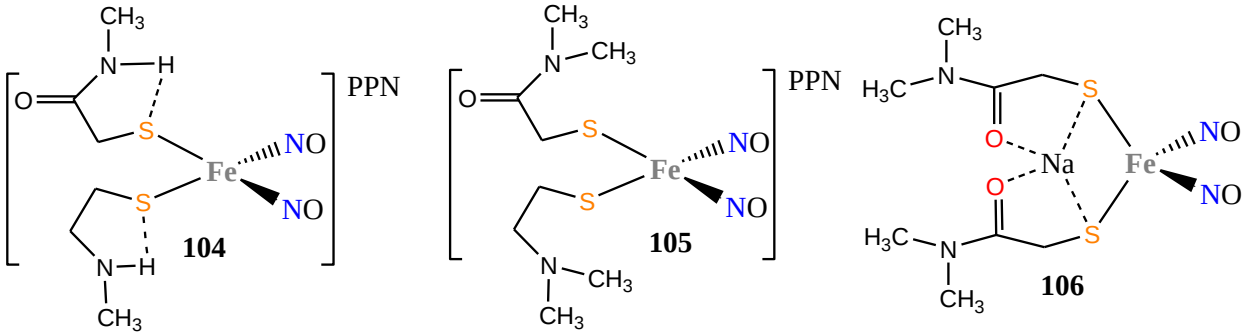
In Greek terminology, s*ynergy* simply refers to working together. Generally, synergy generates effects more than the individual sum of the combined effects of the synergized substrates. Synergy finds several applications in medicine, pharmacology, physiology, biochemistry, etc. The synergism of drugs is visible when their interaction in some way boosts or amplifies one or several therapeutic aspects of the synergized drugs [157]. The main goals of synergistic combination therapies for disease treatment are the achievement of synergized effects, toxicity reduction, and reduction or delay of drug resistance [158].

Wen et al. [159] demonstrated the *in vitro* synergism of the cytotoxic effects of curcumin and DNICs (**Fig. 27**; **104-106**) on mouse melanoma B16-F10 cells. The complexes **104-106** damaged plasmid DNA *via* the release of NO under UV irradiation. Besides, the complexes

displayed *in vitro* cytotoxicity towards B16-F10 cells. Surprisingly, no evidences of synergism were reported for the combination treatments of these three complexes with curcumin. However, synergism was observed when the cells were pretreated with curcumin for 4 h and then allowed to the treatment by **106**. Worthwhile, **106** pretreatment followed by curcumin treatment displayed no synergism. Despite the fact that no exciting results were reported in this research article, this study still opened window for further examination of curcumin combination with other NO donors. Shiau and co-workers [160] demonstrated the inhibition and enhancement of DNA cleavage, and the synergism in cytotoxicity of a synthetic nitrosyl-iron complex (**Fig. 28**; **107**) in combination therapy with curcumin. In the absence of UV radiation, higher and lower concentrations of curcumin inhibited and enhanced the DNA cleavage activity of **107**, respectively. It was interesting to note that the co-treatment of **107** and curcumin complemented each other against the inhibition of mouse melanoma B16-F10 cells. This report serves as a necessary stimulus for the evaluation of the synergistic effects of other agents with iron complexes as potential treatment approaches to cancer.



Curcumin



PPN = Bis(triphenylphosphine)iminium

Fig. 27: Chemical structure of curcumin and DNICs (**104-106**) reported by Wen et al. [159].

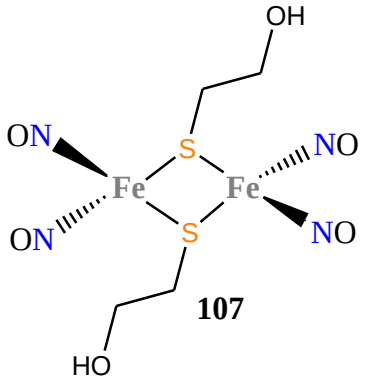


Fig. 28: Chemical structure of nitrosyl-iron complex (**107**) reported by Shiau et al. [160].

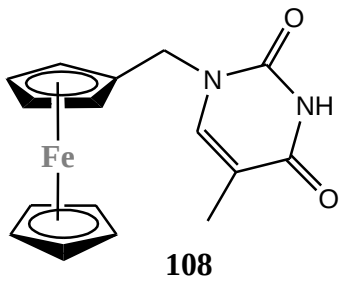
A critical observation of this section clearly indicates that iron complexes synergized with curcumin and the properties of the former were affected. Therefore, it is worthwhile to envisage that synergistic studies of iron complexes with other naturally occurring molecules as well as the synthetic drugs may be a boon to anticancer chemotherapy.

7. *In Vivo* Status of Iron Complexes

Anticancer activity assessments of drugs in animal tumor models are the most common steps that usually follow the *in vitro* assays. There are several advantages of using animal models

over *in vitro* cell cultures. Tumors are known to develop vasculature and interact with stroma; therefore, *in vivo* activity investigations allow evaluation of actual toxicity and also give details about the pharmacokinetic data of the drugs. The development strategy for an anticancer agent requires studies on preclinical models wherein important parameters of effectiveness such as increase in lifetime and tumor growth delay in tumor bearing mice; are monitored according to standard protocols. Even though iron complexes are being heavily investigated as anticancer agents, the *in vivo* studies of iron complexes have not been carried out with much enthusiasm. However, literature indicates that some ferrocenyl alky nucleobases and DNICs have been investigated in some *in vivo* experimental models [161].

Simenel et al. [162] demonstrated the *in vivo* antitumor activity of ferrocenylmethyl thymine **(Fig. 29**; **108)** against solid tumor models, carcinoma 755 and LLC. **108** showed a strong antitumor effect against carcinoma 755 with 70% coefficient of tumor growth inhibition with respect to control. Besides, the complex also demonstrated therapeutic synergism of antitumor activity with cyclophosphamide against carcinoma 755.

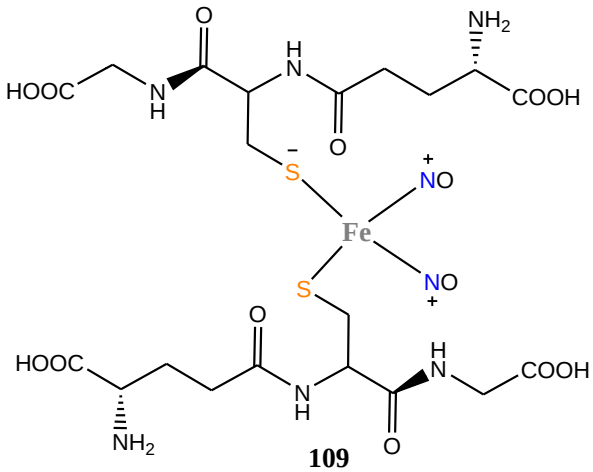


108

Fig. 29: Chemical structure of ferrocenylmethyl thymine complex **(108)** [162].

Recently, Burgova and co-workers [163] reported the experimental suppression of endometriosis in rats on treatment with DNICs (**Fig. 30**; **109**). Intraperitoneal treatment of Group 1 rats with DNICs (12.5 μmoles/kg, per day, for 12 days), was begun on day 4 after surgery (grafting of two 2 mm-thick uterine fragments onto the abdominal wall). This was succeeded by a

14-day schedule on a standard feeding plan (without medication). The treatment procedure resulted in whole inhibition of the growth of EMIs in the majority of tumour-grafted rats. It was interesting to note that the ratio of mean EMI volumes in Group 1 control and experimental rats was 14:1. However, the ratio after a similar treatment in Group 2 rats for 4 weeks after surgery was 1.4:1. Besides, a complete disappearance of endometrial cysts in the EMI samples from experimental rats of Group 2 suggested a cytotoxic effect of DNICs on the tumours. In another experimental setup, Vanin and co-workers [164] studied the *in vivo* antitumor activity of DNICs along with glutathione against solid tumour in mouse LLC. DNICs in combination with glutathione inhibited the progression and development of LLC at dosages of 21, 42 and 105 mg/kg daily for 10 days. The antitumor effect of DNIC-glutathione was ascribed to the degradation of DNICs in the vicinity of tumors due to the release of iron chelating compounds from the tumors. This led to a high concentration of nitric oxide molecules and nitrosonium ions, which affected the tumors by way of the cytotoxic effect. These reports indicated that the administration of DNICs with glutathione and also other thiol-containing ligands holds promise for the design and development of drugs for the treatment of cancers.



109

Fig. 30: Chemical structure of dinitrosyl iron complex with glutathione (**109**) [163].

Overall, the few reports discussed above indicate the promising anticancer activities demonstrated by iron complexes in *in vivo* experiments. Therefore, more research is needed to focus on the *in vivo* studies of iron complexes in future.

8. Mechanistic Insights

Mechanistic studies of drugs have always been fascinating to medicinal chemists. The information obtained from mechanistic studies may be properly used for the design and development of safe and effective drugs. Iron complexes have shown a broad spectrum of anticancer activities. Indeed some complexes show selectivity and lower toxicity, and are suggested to be able to overcome inherited or acquired resistance by cancer cells. These characteristics are quite indicative of the fact that some iron complexes exhibit mechanisms of action different from platinum metallodrugs.

DNA is one of the most important molecular targets for anticancer drugs. Cisplatin, its analogues, and several other metallodrugs exert their anticancer effects by binding to DNA forming monofunctional, bifunctional or some other types of adducts and intercalates. Therefore, DNA binding is one of the most essential steps for the action of a large number of metal complexes as anticancer drugs [165]. DNA binding is less known as the mechanism of action in anticancer iron complexes. However, some iron complexes have been reported as efficient DNA binders and cleavers [145]. Hydroxy-salicylidene-ethylenediamine iron complexes have been reported to act as efficient DNA cleavers. The hydroxyl groups on the two salicylidene moieties form a hydroquinone system that cooperates with the iron redox system and in turn facilitates the spontaneous formation of free radicals [166]. Selvaraj et al. [167] reported the DNA binding properties of a rutin iron complex (**Fig. 31**) and predicted the anticancer nature of the complex on account of its DNA binding efficiency. The rutin-iron complex was proposed to bind to DNA *via*

an intercalative mode of interaction. Ramakrishnan [168] et al. documented DNA cleavage and promising anticancer activities of tris(diimine)iron(II) complexes (**Fig. 32**; **110-113**). The complexes were active against MCF-7 cells and the order of activity was **112** (IC_{50} = 0.8) > **113** (IC_{50} = 20.0) > **111** (IC_{50} = 28.0) > **110** (IC_{50} = 32.0 μM). It was interesting to note that complex **112** was more potent than **110**, **111**, **113** and cisplatin. The complexes interacted with Ct-DNA in the order, **113** > **111** > **112** > **110**. Besides, the DNA cleavage abilities of the complexes at 10 μM concentration in presence of 100 μM H_2O_2 followed the order as, **112** > **110** > **111** > **113**. The complexes after severe investigations were proposed to cause the death of cancer cells *via* oxidative DNA binding and cleavage.

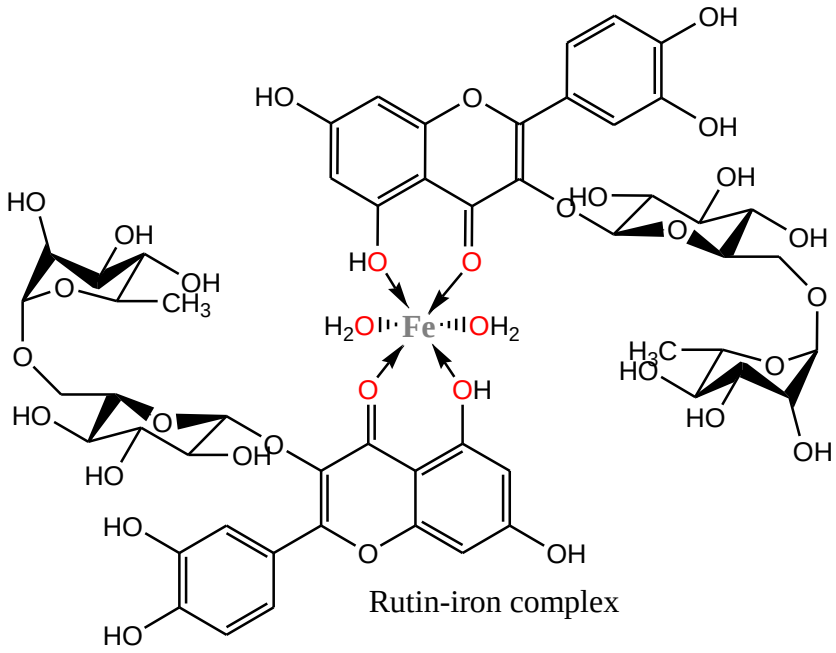


Fig. 31: Chemical structure of rutin-iron complex [167].

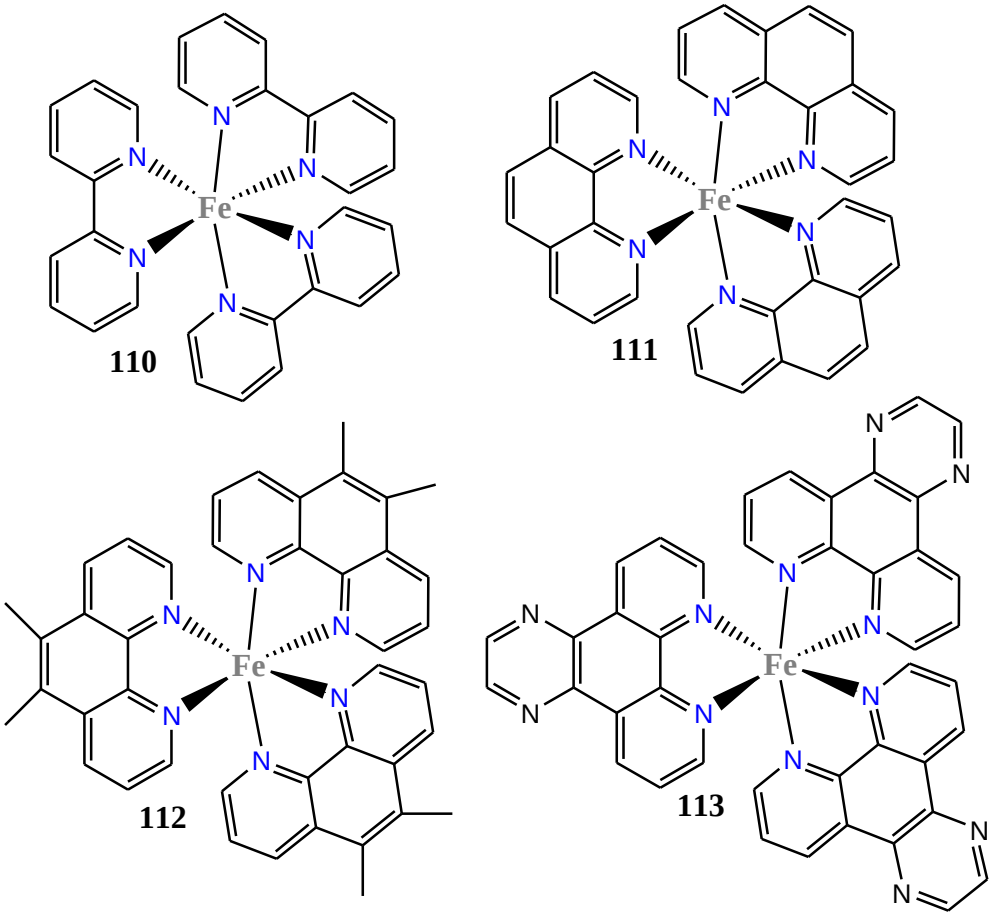
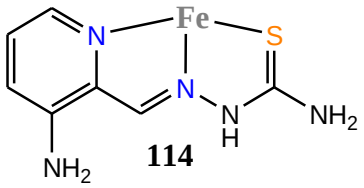


Fig. 32: Chemical structures of tris(diimine)iron(II) complexes (**110-113**) [168].

ROS represent a class of exceptionally reactive molecules or groups with unpaired electrons, e.g., hydrogen peroxide, hydroxyl radicals and superoxide anion. ROS are continually produced and destroyed in biological. They are required to drive regulatory pathways [169]. Generally, cancer cells have more ROS stress than normal cells due to several factors such as oncogenic stimulation, increased metabolic activity and mitochondrial malfunction. It is very important to note that at low concentrations, ROS eases cancer cell survival because of the fact that cell-cycle progression which is driven by growth factors and RTKs requires ROS for activation [170]. Additionally, chronic inflammation (a major mediator of cancer) is controlled by ROS levels. Interestingly, a high ROS level can suppress tumor cell growth by driving the sustained activation of cell-cycle inhibition [171,172]. In addition, induction of cell death and

senescence by damaging macromolecules may also happen due to higher ROS levels. As a matter of fact, it is well known that most of the chemotherapeutic-agents destroy cancer cells by increasing ROS stress [173,174]. Indeed, the dosage, duration, type, and site of production of ROS fully controls the power of cancer cells to distinguish between ROS level as a subsistence or apoptotic signal.

A number of iron complexes are reported to exhibit their mechanisms of anticancer action *via* the production of ROS [46, 71, 76, 175, 176]. Shao et al. [177] reported the formation of ROS by a ferrous-triapine complex (**Fig. 33**; **114**). This complex inactivated the human ribonucleotide reductase, which plays a crucial role in the proliferation of cells by providing deoxyribonucleotide precursors for DNA synthesis and repair. It was confirmed from the spin-trapping experiments with 5,5-dimethyl-1-pyrroline-N-oxide that **114** reduced O_2 to give ROS. Besides, *in vitro* activity screening proved **114** as a more potent inhibitor of hRRM2/hRRM1 and p53R2/hRRM1 than triapine.



114

Fig. 33: Chemical structure of ferrous-triapine complex (**114**) [177].

Apoptosis is actually a process involving programmed cell death with a series of characteristic cellular changes in living organisms [178]. Blebbing of cells, cell shrinkage, nuclear fragmentation, chromatin condensation and chromosomal DNA fragmentation are some of the cell changes that generally occur during apoptosis. There are several apoptotic pathways, and all of them lead to the death of cells. Apoptosis has been the mechanism of action of most of the iron complexes with anticancer properties [48-50, 59, 72, 90, 179-181]. Ansari and co-workers [133] reported the ability of Fe(III)-salen and salphen complexes (**Fig. 34**; **115-128**) in causing the

apoptosis of MCF-7 cells *via* caspase activation. The complexes selectively affected cancer cell viability, and induced nuclear fragmentation and apoptosis. The complexes induced caspase-3/7 activation and ensured the release of cytochrome c from the mitochondria to cytosol, which suggested the mitochondrial pathway of apoptosis as the main mechanism of action of these complexes.

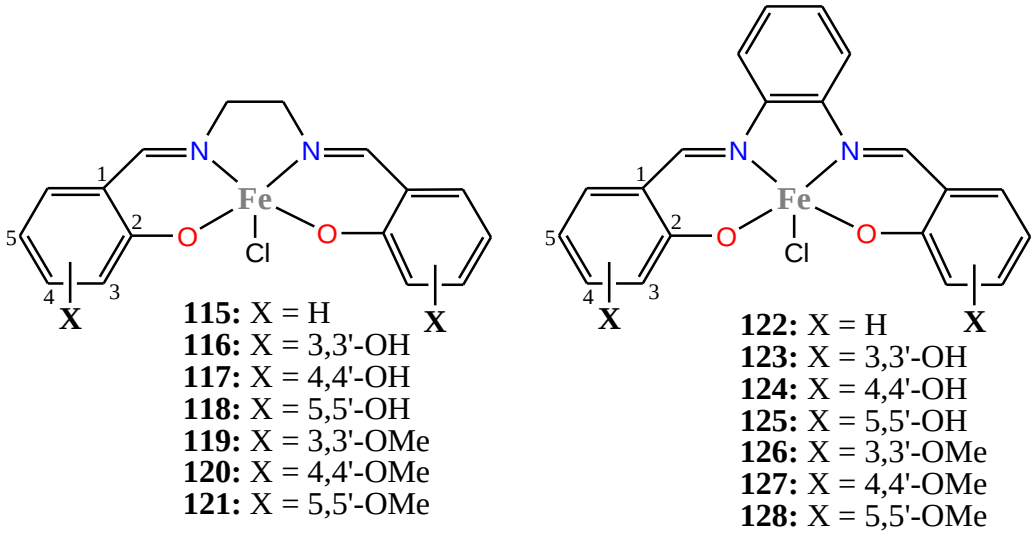
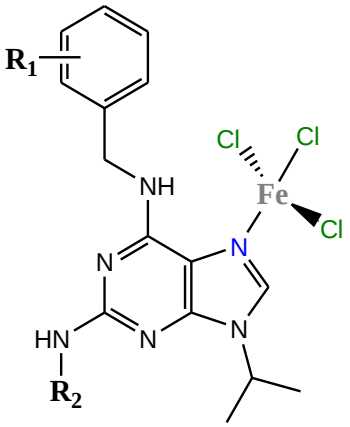
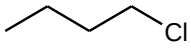


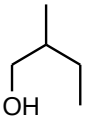
Fig. 34: Fe(III)-salen and salphen complexes (**115-128**) induced caspase activation and apoptosis in MCF-7 cells [133].

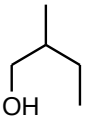
Protein kinases are known to catalyze phosphorylation of suitable proteins in addition to changing their conformation and activity. Thus, protein kinases, which are temporally and spatially controlled participate almost in all phases of cell biology [182]. CDKs are a subgroup of serine/threonine protein kinases that control several cellular events, including cell division. CDKs are often deregulated in cancer cells. Hence, they act as rational drug targets for anticancer drugs [183]. Thus, metal complexes may be expected to inhibit the proliferation of cancer cells by the inhibition of protein kinases deregulated on cancer cells. Iron-adriamycin complex has been reported to cause a strong inhibition of protein kinase C whereas the uncomplexed adriamycin was a poor inhibitor [184]. Iron(III) and copper(II) bio-active complexes with N^6-benzylaminopurine

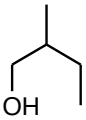
ligands have demonstrated anticancer activities and potent inhibition of $p34^{cdc2}$ kinase [185]. In this direction, Travnicek et al. [186] reported the anticancer activities and CDK2/cyclinE kinase inhibition of some Fe(III) complexes (**Fig. 35**; **129-134**) with CDK inhibitors. The complexes were active against G-361, HOS, K-562 and MCF-7 cell lines and displayed a remarkable inhibition of CDK2/cyclinE kinase. The complexes **131** and **134** were the most potent inhibitors and even reached a low sub-micro molar range of inhibition. The authors suggested that the complexes inhibit the growth of cancer cells by means of kinase inhibitory mechanism.

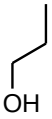


129: R1 = H and R2 = 

130: R1 = 2-OH-5Me and R2 = 

131: R1 = OH and R2 = 

132: R1 = H and R2 = 

133: R1 = H and R2 = 

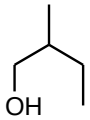
134: R1 = 3-OH-5-OH and R2 = 

Fig. 35: Fe(III) complexes (**129-134**) with CDK inhibitors reported by Travnicek et al. [186].

TRs (or TrxRs) are enzymes that reduce Trx [187]. Trx is known to play essential roles in several physiological processes such as the reduction of nucleotides to deoxyriboucleotides, detoxification of xenobiotics, oxidants and radicals, etc. [188]. Viability and normal functioning of cells is dependent on redox homeostasis. Cellular redox homeostasis is regulated by glutathione and thioredoxin systems. Thioredoxin system, which includes Trx, TrxR and NADPH regulates the cellular redox state and cell apoptosis. Basically, Trx works as a protein disulfide reductase; vital for the function of Trx system. The biological activity of Trx is dependent on its reducing form and TrxR is the only cellular enzyme which catalyzes the reduction of Trx in presence of

NADPH. It is the reduction of Trx or its own direct effects towards various substrates that qualifies TrxR for several cellular functions. Recently, TrxR has been reported to be upregulated in some malignant tumors. It has been established that inhibiting TrxR could prevent the initiation and progression of tumors. These findings clearly suggested TrxR as a target of promise for the development of new anticancer agents. Besides, the highly nucleophilic and accessible selenocysteine active site was suggested as the prime target for drug design. Different types of TrxR inhibitors have been developed as anticancer agents [189]. Recently, TrxR has been supposed as a molecular target for several classes of metallodrugs [190]. As a matter of fact, Citta et al. [191] reported the TrxRs targeting of two hydroxyferrocifens (**Fig. 36**; **135** and **136**) and their corresponding quinone methides (**Fig. 36**; **137** and **138**). It was observed that the quinone methides, **137** and **138** ($IC_{50} \approx 2.5$ μM) were more potent than the hydroxyferrocifens, **135** and **136** ($IC_{50} \approx 15$ μM) as TrxR inhibitors *in vitro*. Both the complexes **137** and **138** caused the inhibition of TrxRs to the same extent along with accumulation of oxidized forms of thioredoxin in Jurkat cells. However, **135** and **136** were hardly effective in Jurkat cancer cells. This differential behaviour of ferrocenyl derivatives was attributed to competitive transformation of **136** into an inactive indene in protic medium.

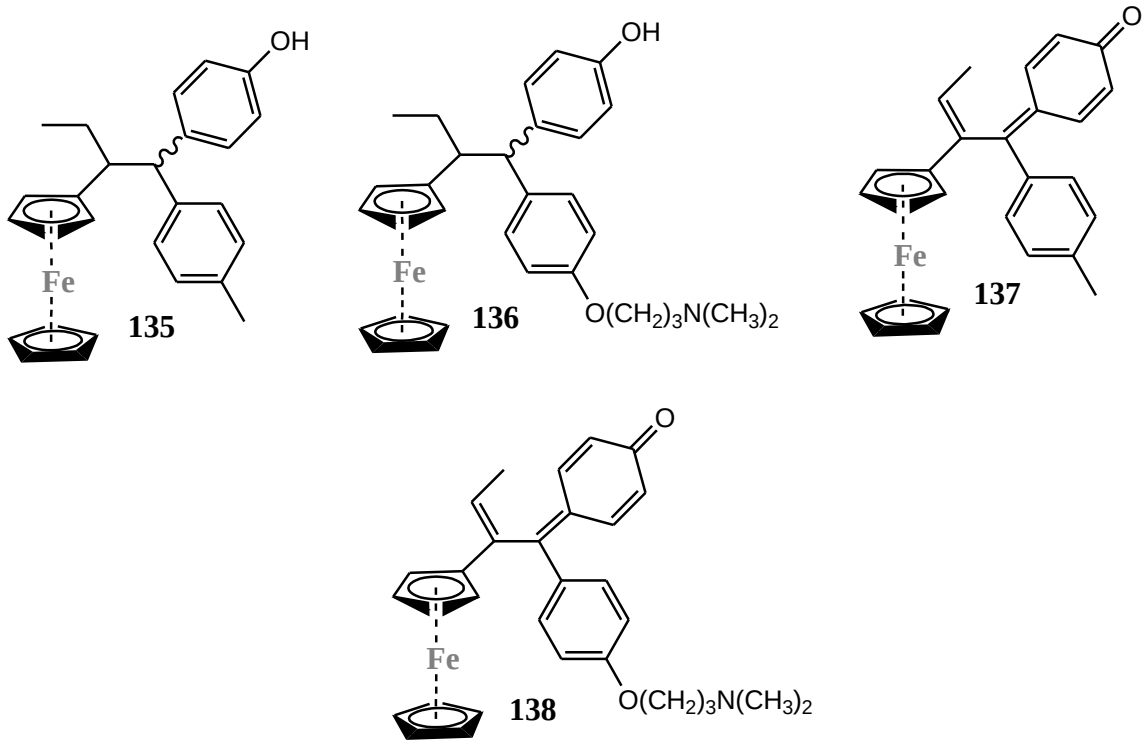


Fig. 36: Chemical structures of hydroxyferrocifens (**135** and **136**) and their corresponding quinone methides (**137** and **138**) [191].

Conclusively, the mechanistic considerations involving iron complexes as anticancer agents are still in the early developmental stages. However, enormous work is being carried out in this direction, and we hope some new molecular targets and processes are explored soon enough.

9. Pharmacologically Important Systems

The idea behind every drug design strategy is to obtain new drugs with better activity, fewer toxic effects and other advantages in comparison to the established drugs [192]. In this review, the discussion on the anticancer properties of iron complexes with diverse ligand frameworks revealed several classes of iron complexes with promising anticancer properties against different human cancer cell lines. Some of the complexes have displayed anticancer activities higher than cisplatin and thus, hold promise for further investigations. In addition to displaying better activities than cisplatin, several examples herein have demonstrated better selectivities and the potential to overcome drug resistance in human cancer cell lines.

Schiff base ligand systems have been reported to form metal complexes with iron that display exciting anticancer properties. Schiff base iron complex (**84**) overcame MDR in vincristine and daunorubicine resistant Nalm-6 cells. Several glucose-appended photocytotoxic iron(III) schiff base complexes (**19-21**) strongly bound to Ct-DNA, and caused photocleavage of supercoiled pUC19 DNA in red and green lights. The complexes **20** and **21** were significantly photocytotoxic against HeLa and HaCaT cells in red light, and were significantly non-toxic in dark. Additionally, preferential internalization of **20** and **21** was reported in HeLa cells.

Salophene complexes (**6** and **13**) demonstrated exciting anticancer properties against K562 and MCF-7 cells. Complex **6** was more active than oxaliplatin against K562 and MCF-7 cells. On the other hand, complex **13** exhibited selective activity against SKOV-3 and OVCAR-3 cell lines at concentrations between 100 nM and 1 μM. In addition, there was no systemic toxicity in rats on intra-peritoneal administration of **13**. The iron(II/III) salophen complexes (**85-90**) containing monodentate azole-derived ligands displayed several folds higher anticancer activity than cisplatin against HOS, MCF-7, A549, HeLa, A2780 and G-361 cell lines. The eye-catching complex in this series was **90**. This complex contains monodentate methyl tetrazole as the second ligand, and is 200 times more active than cisplatin against A2780 cells.

Polymeric one-dimensional chain iron complexes containing N-donor heterocyclic ligands (**32-37**) showed quite higher activities than cisplatin against A2780 cells. Development of complexes with the ability to overcome resistance in the otherwise cisplatin resistant cancer cells is a challenge in medicinal inorganic chemistry. It can be seen from the discussion in this review that the hetero-trimetallic complexes (**39** and **41**) were more active than cisplatin against the resistant A2780R and MCF-7 cell lines. Besides, these two complexes displayed anticancer effects due to different mechanisms of action with respect to cisplatin. The heterometallic platinum(II)

compound with β-aminoethylferrocenes (**65)** showed activity against several cisplatin resistant cells. Besides, this complex was more active than cisplatin against HeLa, SW1573 and WiDr cell lines. The iron(II) cyclopentadienyl complexes with imidazoles (**98-101**) displayed high anticancer activities against A2780, MCF-7 and HeLa cells. The interesting observation was that the activities of the complexes were higher than cisplatin for the MCF-7 cells. Iron(III) catecholates (**15-18**) showed exceptional photocytotoxicity in red light against HeLa, HaCaT, MCF-7 and A549 cells. It was further observed that the photocytotoxic death of the cancer cells was due to ROS generated by the complexes. The high anticancer activity and ROS generation indicated a strong candidature of these photocytotoxic complexes for their further development. Iron(III) complexes of saldach ligands including (R,R)-, (S,S)- and (R,S)-N,N'-bis(salicylidene)-1,2-diaminocyclohexane (**94-97**) demonstrated anticancer activity within a concentration range of 1-5 μM (more active than cisplatin at 5 μM) against MCF-7, MDA-MB 231 and HT-29 cell lines.

The dipyridophenazine-based iron complex **28** displayed better photocytotoxicity than the standard drug photofrin in HeLa and HaCaT cells under visible and UV-A light irradiation; with no cytotoxicity in dark. It's another structural relative (**29**) exhibited better photocytotoxicity than both photofrin and cisplatin against HeLa cells in visible light. Ferrocene-conjugated L-tryptophan copper(II) complexes of phenanthroline bases; **60** and **61** showed pronounced activity against HeLa and MCF-7 cells. Interestingly, the complex **61** was more active than photofrin against HeLa cells. The ferrocenyl-dithio-o-carborane conjugates (**75** and **76**) displayed pronounced and selective activities against SMMC-7721 and HepG2 cells. Both the complexes were more active than cisplatin. One more exciting observation was that DNIC (**109**) caused the experimental suppression of endometriosis in Group 1 rats on intraperitoneal treatment. DNICs

along with glutathione against solid tumour in mouse LLC inhibited the progression and development of LLC.

The discussion of the nanoparticulate iron complexes in this review highlights some unique systems with exciting properties. The ferrocenyl complex (**103**) encased in stealth LNCs caused strong inhibition of ectopic glioma tumor cells. The nanoparticulate complex showed a remarkable tumor growth inhibition in rats bearing ectopic glioma on repeated intravenous administrations of stealth **103** LNCs with no liver damage in the treated rats. Some other nano-formulations of iron complexes also ensured active cancer-targeting *via* intracellular drug delivery and compatibility with fluorescence imaging. Besides, some prodrug systems have also been successfully achieved by nanotechnological applications.

Overall, the ligand systems including schiff bases, polymeric one-dimensional chains, salophenes, N-donor heterocycles, heterometallics, cyclopentadienyls, catecholates, dipyridophenazine, DNICs, and saldachs including (R,R)-, (S,S)- and (R,S)-N,N'-bis(salicylidene)-1,2-diaminocyclohexane formed stable complexes with iron with very good anticancer properties. Thus, the ligand systems and the influence of the coordination sphere in these complexes may be regarded as important factors governing the anticancer effects of their iron complexes.

Developing new metal complexes on the idea that "the iron complexes of the above mentioned ligand systems have displayed promising anticancer properties" may be a good approach. Therefore, the future development of the complexes discussed in this section seems bright on account of their high anticancer properties, lower toxic effects towards normal cells and different mechanisms of action. It is also encouraging that these systems be investigated on other

cancer cell lines as well. Besides, the evaluation of the most potent complexes in *in vivo* models will be a major achievement in the development of iron complexes as anticancer drugs.

10. Conclusions and Perspectives

Despite of the exciting advancements in science and technology, the treatment of cancer is still a major challenge [193]. The market available anticancer drugs lack the ability of complete cancer treatment, and hence, higher death cases in comparison to survival cases are reported. Besides, cancer cells and tissues develop resistance to the long term uses of the available anticancer drugs, which greatly limits their applications. In addition, the market selling anticancer drugs have high costs and are thus unaffordable by the common people.

Development of safe and effective metallo anticancer drugs has many impediments. The main hindrance is that no general guideline towards the synthesis of new active metal complexes has been established till now. Few structure-activity relationships were established in some studies, however, there are no established general rules. To decide which complex is expected to be active and should be investigated in near future still remains a mystery. Although, significant progress has been made in understanding the molecular etiology of cancer, ideal therapeutic strategies are still largely missing. As a consequence of these facts, it is very important to expedite the development of new therapeutic agents against cancer [194]. Design and development of new and efficient drugs for the treatment of cancer have been the top priority goals for different areas of research including natural products chemistry, biochemistry, molecular biology, pharmacology and medicinal chemistry [195].

A keen look into the literature fully supports the idea that the therapeutic potential of metal complexes can be harnessed for the design of novel and efficient anticancer agents. Cisplatin, its analogues, some ruthenium complexes among others have proved that metal complexes play

important roles in modern anticancer chemotherapy. Therefore, it is quite worthy to progress the exploration of other transition metal complexes as anticancer drugs. Targeting and activation strategies should be encouraged for the development of new generations of drugs which can overcome some of the disadvantages associated with cisplatin therapy. The drugs obtained should display no or the least side-effects with broad activity range, and capable to avoid the occurrence of drug resistance [196]. It is very important to understand the parameters by which ligands control the reactivity of transition metal ions, and the reciprocal effects which metal ions have on the properties of ligands since both play important roles in the recognition of target sites and the resulting biological activity. Modern theoretical methods such as DFT and techniques like high resolution electrospray mass spectrometry, multinuclear polarization transfer NMR spectroscopy can improve our understanding of the chemical and biochemical reactivity of metal complexes and the construction of meaningful structure-activity relationships. Besides, the studies of the chemical biology of metal complexes under physiologically-relevant conditions (*e.g.* biological screening conditions) become very important.

A pictorial representation of the current challenges and future perspectives of iron complexes as anticancer agents is given in **Fig. 37**. Several drug features such as physio-chemical properties, insufficient solubility and hydrolytic instability challenge the design and development of metal complexes as anticancer agents. Metal complexes with targeted action and lower side effects can be obtained by synthesizing their nano counterparts. Encasing or functionalizing iron complexes into nano cages may help in avoiding their poor bioavailability, and ensure their selective, specific and fast action; increasing the longevity of patients [197]. Nano identities of iron complexes may be expected to cure a number of cancers with fewer side effects; the need of future [198]. Drug combination strategies have led to synergistic effects in several cancer cases.

Therefore, drug combination therapies of iron complexes with other agents may be tried to get novel drug combinations. In the present scenario, software and simulation programmes, and theoretical analysis (such as AutoDock, Percepta Platform, Lipinski's rule) allow us to estimate the therapeutic efficiency of drugs even before their actual synthesis. Therefore, the molecularly screened iron complexes having good bioavailability, maximum solubility, remarkably less side effects and higher efficiency need to be designed and developed. Besides, several software simulation programmes, which can help in identifying the biological targets of interest should be used for the proper design and optimization of structural diversity of new iron complexes in future. Drug delivery systems work as innovative vehicles for the transport and targeting of anticancer drugs. It would be great to look into the effect of the delivery of newly synthesized iron complexes to their target sites *via* nanodrug delivery systems decorated with cell specific antibodies. Besides, mechanisms should be developed so that the complexes get delivered only at their sites of action (such as pH triggering mechanism). Generally, multiple complex biochemical pathways are implicated in diseases like cancer whose successful treatment usually depends on pharmaceutical intervention at multiple pathways, and, often with a combination of different drugs. DMLs that act at multiple biological targets may be quite helpful in the eradication of the deadly disease cancer [199]. Therefore, it might be suggested that the development of iron complex-based DMLs might be effective. Keeping these points in view, there is an urgent need to understand the molecular mechanism of apoptosis induced by new iron complexes and work on the parameters that need to be optimized.

Although a large number of iron complexes with different ligand systems have displayed exciting therapeutic benefits in comparison to the market selling anticancer metallodrugs like cisplatin, oxaliplatin and photofrin; many issues are yet to be resolved. Several examples of iron

complexes highlighted in this paper overcome cancer cell resistance, display high cytotoxicities with selectivity, pose lower toxic effects and act *via* different mechanisms of action (e.g., ROS generation, mitochondrial involvement and thioredoxin reductase reduction among others). Besides, a few reports demonstrate the potential of iron complexes (DNICs) in *in vivo* tumor models. However, there are very limited studies available on the *in vivo* investigations of iron complexes as anticancer agents. Therefore, it is encouraged to explore the potential of the potent iron complexes highlighted above in *in vivo* antitumor models. Moreover, it would be very much exciting to explore these novel iron complexes on other cancer cell lines. Besides, it is important to evaluate the potential side effects that iron complexes can cause in human beings so that the possibility of their applications in human beings may be estimated. Researchers the entire world over need to work collaboratively in order to develop safe iron complexes (either in nano regime or the molecular size range) for the treatment of all cancer types. Overall, cancer is a deadly fatal disease affecting the social and economic status of patients drastically and thus, needs to be eradicated as soon as possible. Definitely, the future of iron-based metallo-anticancer drugs is bright. Their development is certainly a step in the right direction towards the eradication of cancer.

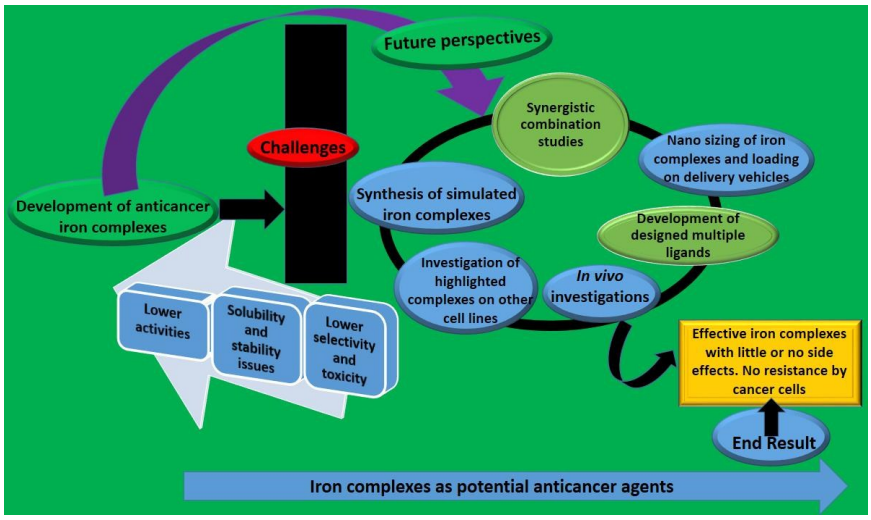


Fig. 37: A pictorial depiction of the current challenges and future perpectives of the development of iron-based anticancer drugs.

Abbreviations

µM: Micromolar concentration.
16-HBE: Human bronchial epithelial cells.
41M: Ovarian carcinoma.
9L cells: Gliosarcoma cells.
A2780: Human ovarian carcinoma.
A2780cis: Cisplatin sensitive human ovarian carcinoma.
A2780S/R: Cisplatin resistant human ovarian carcinoma.
A431: Human epidermoid carcinoma.
A549: Human non-small cell lung carcinoma.
AIDS: Acquired immuno deficiency syndrome.
ALL: Acute lymphoblastic leukemia.
B16-F10: Mouse melanoma cells.
BBR3464: Triplatin tetranitrate.
BJAB: Burkitt-like lymphoma cells.
CDK2: Cyclin dependent kinase 2.
CDKs: Cyclin-dependent kinases.
CPPs: Coordination polymer particles.
Ct-DNA: Calf thymus deoxyribonucleic acid.
DFT: Density Functional Theory.
DMF: Dimethylformamide.
DMLs: Designed multiple ligands.
DNA: Deoxyribonucleic acid.
DNICs: Dinitrosyl iron complexes.
EMI: Endometrioid implants.
G361: Human Caucasian malignant melanoma.
GBM: Glomerular basement membrane non-cancerous cell line
HaCaT: Human keratinocytes.
HCT-8: Human ileocecal colorectal adenocarcinoma cell line.
HEK293: Human embryonic kidney cells.
HEK-293T: Non-tumorigenic human embryonic kidney cells.
HeLa: Human cervical carcinoma.
HELF: Normal human embryonic lung fibroblast cells.
HepG2: Human hepatocellular carcinoma.
HL-60: Human promyelocytic leukemia cells) cell line.
HOS: Human osteosarcoma.
HT-29: Human colorectal adenocarcinoma.
IC_{50}: Half maximum inhibitory concentration.
K-562: human immortalised myelogenous leukemia.
LD_{50}: Lethal concentration 50%
LLC: Lewis lung carcinoma
LNCs: Stealth lipid nanocapsules.
LS174T: Human epithelial colon cell line.
M: Molar concentration.
MCF-7: Human breast carcinoma.
MDA-MB-231: Human breast carcinoma.

MDA-MB-435: Metastatic human breast cancer cell line.
MDR: Multidrug resistance
NADPH: Nicotine adenine dinucleotide phosphate hydrogen.
Nalm-6: Human pre-B cell leukemia.
NCI-60: National Cancer Institute (NCI) 60 human tumour cell line anticancer drug screen.
NIH 3T3: Mouse embryonic fibroblasts
nM: Nanomolar concentration.
NMR spectroscopy: Nuclear magnetic resonance spectroscopy.
NO: Nitric oxide
OVCAR-8: Human ovarian cancer cell line.
PARP-1: Poly [ADP-ribose] polymerase 1.
PBS: Phosphate buffered saline.
PC3: human prostate cancer cell lines.
PDT: Photodynamic therapy
pUC19 DNA: Plasmid DNA
R: Rectus (right).
RBITC-SiO_2: Rhodamine B isothiocyanate doped silica-coated.
ROS: Reactive oxygen species.
RTK: Receptor tyrosine kinase.
S: Sinister (left).
SCE: Saturated calomel electrode.
SCOV3: Human ovarian cancer cell line.
SF-295: Human glioblastoma cancer cell line.
SMMC-7721: Human hepatocarcinoma cell line.
TBAP: Tetrabutylammonium perchlorate.
Trx: Thioredoxin.
TrxRs and TRs: Thioredoxin reductases.
UV: Ultraviolet visible.
WM35: interleukin-6 sensitive human melanoma cell line.
WM793: Metastatic human melanoma cell line.
WM9: interleukin-6 unresponsive cell line human melanoma cell line.

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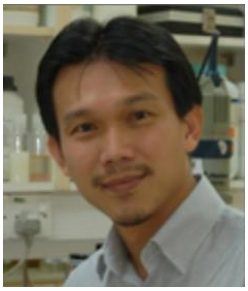
Conflicts of Interest

There are no conflicts of interest to declare.

Author Biographies

Dr. Waseem A. Wani received his M.Sc. degree in Chemistry from Jamia Millia Islamia, New Delhi in 2008. For his Ph.D., he worked with Prof. Kishwar Saleem and Prof. Imran Ali at the same university with focus on anticancer metallodrug development. From 2014 to 2015, he worked as a postdoctoral research fellow at Universiti Teknologi Malaysia (UTM). His interests are in anticancer metallodrugs, nanofunctionalization of anticancer metallodrugs and natural product chemistry.

Dr. Lee Ting Hun earned his doctorate degree in Bioprocess Engineering from Universiti Teknologi Malaysia (UTM). Dr. Lee has set up and currently heads the Edible bird's nest unit in UTM. He is a pioneer in bird's nest and swiftlet ranching research in Malaysia. He has made several contributions to industry winning him the Malaysian Scientist Award. His interests are in bioprocessing and bioproduct development, and natural product chemistry.



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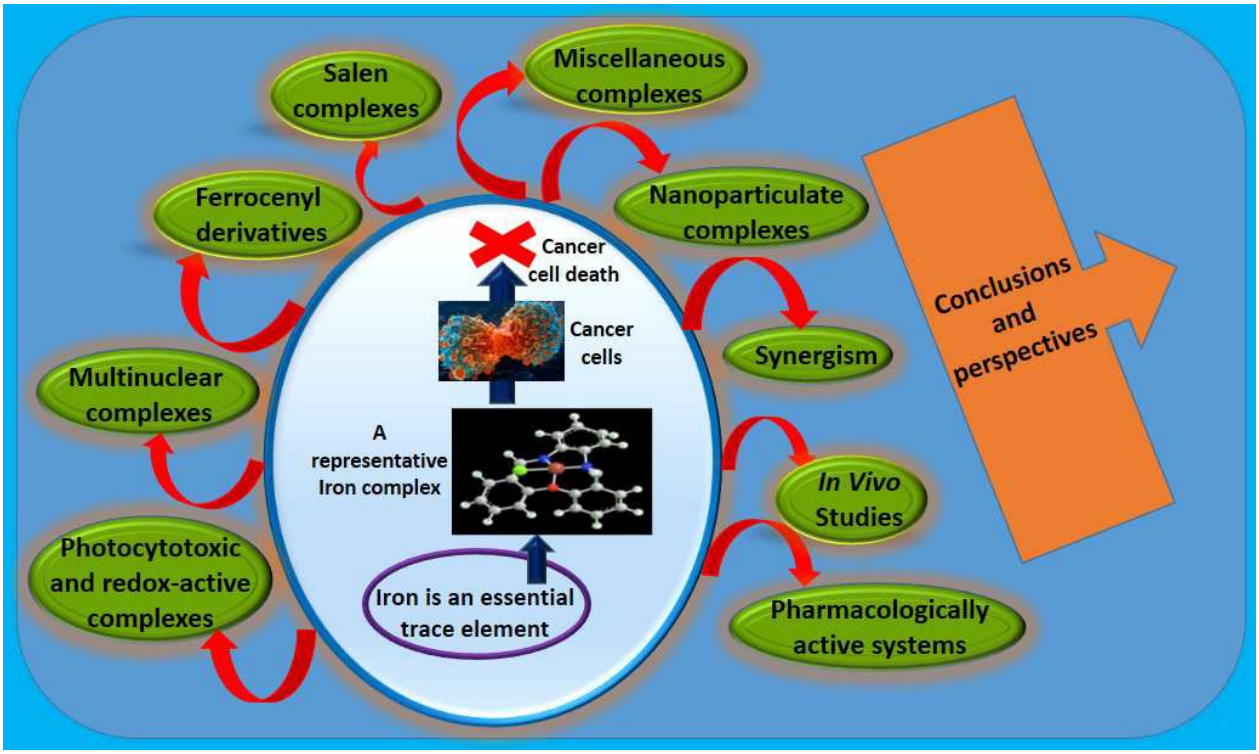
Graphical Abstract



Iron complexes discussed in this review seriously highlight their promising future as anticancer agents.