Coordination Chemistry Reviews 432 (2021) 213746

Contents lists available at ScienceDirect

Coordination Chemistry Reviews

journal homepage: www.elsevier.com/locate/ccr

Review

Metal complexes of β-carboline: Advances in anticancer therapeutics

Yusuf Oloruntoyin Ayipo [a,b], Wahab Adesina Osunniran [b,*], Mohd Nizam Mordi [a,*]

[a] Centre for Drug Research, Universiti Sains Malaysia, USM 11800, Pulau Pinang, Malaysia
[b] Department of Chemical, Geological and Physical Sciences, Kwara State University, P. M. B. 1530, Malete, Ilorin, Nigeria

ARTICLE INFO

Article history:
Received 12 August 2020
Accepted 10 December 2020
Available online 21 January 2021

Keywords:
β-Carboline
Metal–organic framework
DNA
Autophagy
Photothermal imaging
Anticancer

ABSTRACT

The platinum-based complexes were the first anticancer metallotherapeutics to emerge and since their discovery several other coordination compounds consisting of transition metal ions of variable oxidation states in complex with various ligands have been developed. However, indiscriminative cytotoxicity, unbearable side effects and incessant drug-resistance mainly limit their clinical application, hence, create a strong impetus for alternative chemotherapeutic designs. Consequently, the broad pharmacological spectrum of β-Carboline (βC) ligands against tumour growths prompted the synthesis and probe of their corresponding metal complexes for improved efficacy as multi-mechanistic anticancer agents. However, to our knowledge, the overview of these interesting innovations needed to advance the knowledge-based cancer therapeutic modelling remains sparse. This review is aimed at comprehensive highlights of the scientific up-to-date development towards effective anticancer therapeutic designs through various metal ion complexes of βC derivatives reported in the last decade. The basic synthetic procedures, anticancer activity and systemic toxicity towards healthy cells were focused. This review reveals that the complexes possess interesting efficacy against malignant transformations through various chemotherapeutic, photodynamic therapeutic and combined photothermal-chemotherapeutic mechanisms *in vitro* and *in vivo*. They mostly demonstrate stronger cytotoxicity against several cancer cells including the cisplatin-resistant types than cisplatin and tolerable toxicity to normal cells including the human hepatic cells, breast epithelial cells and lung fibroblasts. Especially, complexes **4**, **9**, **11**–**13**, **15**, **30**, **35**, **36**, **44**, **45**, **48**, **56**–**59** and the nanoparticle composite of **60** deserve further attention. This review presents fundamental updates for further studies on anticancer therapeutic designs through metal complexes of βCs.
© 2020 Elsevier B.V. All rights reserved.

Contents

1. Introduction . . . 2
1.1. Anticancer chemotherapeutics and their mechanisms of action . . . 2
1.1.1. Metal-based anticancer therapeutics . . . 2
1.1.2. Some FDA-approved metallodrugs for cancer treatment . . . 3
2. β-Carboline derivatives as anticancer agents . . . 4
2.1. Metal-β-Carboline complexes as anticancer agents . . . 5
2.1.1. Metal(I) complexes . . . 5
2.1.2. Metal(II) complexes . . . 6
2.1.3. Metal(III) complexes . . . 16
2.2. Other potential medical applications of metal- β-Carboline coordination compounds . . . 19
3. Concluding remarks and future perspectives . . . 20
Authors contribution . . . 20
Declaration of competing interest . . . 20
Acknowledgements . . . 20
Appendix A. Supplementary data . . . 20
References . . . 20

* Corresponding authors.
E-mail addresses: wahab.osunniran@kwasu.edu.ng (W.A. Osunniran), mnizam@usm.my (M.N. Mordi).

https://doi.org/10.1016/j.ccr.2020.213746
0010-8545/© 2020 Elsevier B.V. All rights reserved.

1. Introduction

Cancer is one of the major causes of death globally, especially in high-income countries, second to cardiovascular diseases [1]. Cancer-related global death cases were reported as 9.6 million in 2018 [2]. It is predicted to remain a major cause of morbidity and mortality for the next few decades with a forecasted increase in incidences from 12.7 million to 22.7 million between 2008 and 2030 worldwide [3]. Cancer development varies with some factors including age, gender, genetic and environmental. Some routine dietary and behavioural factors have also been implicated in the initiation of the deadly abnormal cells. These include poor nutrition, consumption of alcohol and tobacco, physical inactivity, high body mass index and exposure to environmental hazards [2,4]. Due to the various implications of these factors, men are more prone to cancer than women. In 2015 for instance, an estimate of 220,800 Americans was diagnosed with prostate cancer while 40% of men were forecasted to experience cancerous infection during their lifetime against 39% women [4,5]. Some infectious agents such as the hepatitis B & C viruses (HBV & HCV), human papillomavirus (HPV) and *Helicobacter pylori* have been reportedly contributing to the on-set cancer development [4]. The deregulation of some critical enzymes and/or proteins in the control of cell division, differentiation and proliferation had been inclusively hypothesized as causes of uninhibited cell growth associated with cancer developments [6,7]. Major types include the carcinoma/adenocarcinoma (e.g. breast, pancreatic, lung, colorectal and prostate cancers), the sarcoma (e.g. cancers of the muscle, bone and blood vessels), the leukaemia (e.g. acute and chronic lymphocytic leukaemia), the lymphoma (Hodgkin and non-Hodgkin lymphoma) and the cancer of the central nervous system (e.g. brain tumour and cancer of the spinal cord) [2]. Oftentimes, they are interrelated. For instance, bone metastases are usually diagnosed in about 70% of patients suffering from breast and prostate cancer, and in around 38% of lung cancer-infected patients [8]. The symptoms include unusual swelling, unbearable pain, haemorrhage, cough, weight loss and neurological diseases. Treatment protocols depend on the type and location. These include surgery, hormonal therapy, genetic modulation, radiotherapy, immunotherapy and chemotherapy (anticancer drugs) [2,7]. Chemotherapy is the most applied treatment option for metastasized tumour, and in combination with others such as the radiological and surgical procedures, thus, remains the predominant therapeutic option [9].

1.1. Anticancer chemotherapeutics and their mechanisms of action

Cancerous cells are characterised by uncontrolled abnormal tissue growth in forms of tumour in some parts of the body and being malignant, easily metastasize across other parts with the aid of blood circulation and/or lymphatic system [2]. The advancement in the identification of drug-target relationships has aided the understanding of mechanisms of actions of the anticancer therapeutics [10]. The chemotherapeutics are usually cytotoxic with various pharmacological pathways including the mitochondrial dysfunction (intrinsic) or cytoplasmic activation (extrinsic) (Fig. 1 (a)) [1,11], inhibition of microtubules and topoisomerases, inhibition of kinases and glutathione-S-transferases, alkylation and intercalation of DNA which lead to DNA damage, disruption of DNA repair and induced cell death [2,12-14]. Some other small drug molecules such as netropsin and distamycin A act by inhibiting the DNA and RNA replication through reversible groove binding and intercalation of planar aromatic systems between two base pairs to cause cell death (Fig. 1(b)) [15-18]. In addition to the tumour cell death mechanisms associated with small molecules, metallodrugs additionally exhibit other multi-target directed actions through interactions with proteins and cell organelles [19] such as the phosphatidylinositol 3-kinase, the mammalian target of rapamycin (mTOR), an important regulator of autophagy [20,21], the kinase spindle protein (KSP) and adenosine triphosphate (ATP) enzymes [22], the cyclin-dependent kinases (CDKs) [23,24], the isocitrate dehydrogenase, histone lysine demethylase, histone deacetylases [25], deoxyhypusine hydroxylase, aminopeptidases, matrix metalloproteinases [26], cytoplasm as well as the autophagosomal-lysosomal fusion, the mechanism through which damaged cells and dysfunctioning proteins are removed otherwise termed lysosomal degradation in cancer therapy [20,27,28]. However, cellular modification through genetic and epigenetic pathways, innate cellular defence mechanisms and complexity of the disease have been reportedly implicated in the incessant drug-resistance and the unpleasant side effects associated with the available small molecule chemotherapeutics [10,29], and this led to the idea of metal complexes.

1.1.1. Metal-based anticancer therapeutics

Metal ions play important roles in the diagnostic and therapeutic aspects of oncology through the applications of their complexes as chemotherapy, bioimaging, biosensing, general photodynamic

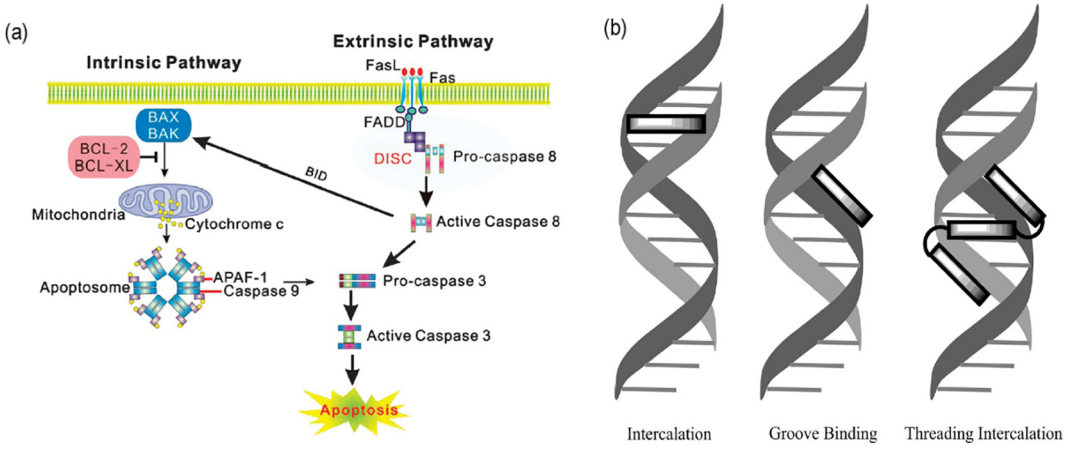


Fig. 1. (a) Intrinsic and extrinsic pathways of apoptosis (Reproduced with permission from [11], Copyright (2014) Royal Society of Chemistry); (b) Classical intercalation, groove binding and threading intercalation of chemical molecules against the DNA (Reproduced with permission from [18], Copyright (2013) Elsevier Masson SAS).

Table 1
Some FDA-approved metallodrugs for cancer treatment.

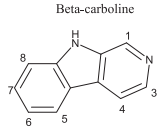
Drug	Class	Target	Cancer	Refs.
Cisplatin	Cytotoxic	DNA synthesis	Bladder, cervical, ovarian, testicular and lymphoma	[33,50]
Oxaliplatin	Cytotoxic	DNA synthesis	Colorectal	[33,50]
Tc-99m Medronate	Target	Bony cortex and hydroxyapatite	Bone metastases	[8,30]
Gallium (Ga-67) citrate	Target	Transferrin, leukocyte lactoferrin and inflammatory proteins	Hodgkin lymphoma and bronchogenic carcinoma	[30,51,52]
Indium-111 capromab pandetide	Target	Prostate-specific membrane antigen	Prostate cancer	[5,30]

therapy (PDT) and combined photothermal-chemotherapy [30,31]. The platinum-based complexes were the first anticancer metallotherapeutics to emerge, with cisplatin discovered around 1969, followed by carboplatin and oxaliplatin, all understood to be mainly DNA-targeted (Table 1), [16,32,33]. The clinical successes recorded for the platinum-based chemotherapy inspired the design of other metal-based agents, some of which act as target drugs. Therefore, most of the FDA-approved metallodrugs are broadly classified as either cytotoxic or target drugs for cancer treatment. Few examples are presented (Table 1).

Despite the exceptional clinical successes, however, the unpleasant side effects associated with platinum-based anticancer drugs including nausea, low blood counts, vomiting, nephrotoxicity, myelosuppression, peripheral neuropathy and ototoxicity, and resistance by tumour cells commonly at effective drug-dose concentration prompted the search for alternative chemotherapeutics with improved pharmacological and less toxicological effects [34–36]. The innovative progression fascinates the coordination of some DNA- and metalloproteinase-inclined metals such as Fe, Ni, Cu and Zn in various ionic states with N, O and S donor, peptides, oxo-groups and other mono-/multi-dentate ligands to produce complexes with strong antitumour potentials [37–39]. Other heavy metals whose ions are reported in organometallic/coordination complexes evaluated as alternatives to the platinum-based anticancer therapeutics include rhenium [10], iridium [20], gold, titanium [34], silver [40], ruthenium, osmium [41–43], vanadium [19,44], palladium, tin, lutetium [45]. These metals are reasonably preferred due to their redox characteristics for broad reactions, strong Stokes shift, long luminescence lifetime and excited-stable state for photo-influenced processes, vacant *d/f* orbitals which dictate their electronic and magnetic properties and also support molecular coordination, electron affinity (as Lewis acids), nuclear permeability and ability to polarize organic ligands to enhance hydrolysis among others [46–49]. These, in turn, enrich the synthetic and biological chemistry of their corresponding complexes such as DNA intercalation to induce damage and disrupt repair processes, lipophilicity and cellular uptake, selective and concentration-dependent toxicity, photophysical and photochemical properties, thermo- and photostability (required for biosensing and bioimaging), induction of apoptosis *via* multifaceted mechanisms which attract their anticancer therapeutic probes [13,21,44,46,48].

1.1.2. Some FDA-approved metallodrugs for cancer treatment

Consequently, some of the transition metal complexes such as Tc-99m medronate, gallium (Ga-67) citrate and indium-111 capromab pandetide in addition to the platinum-based drugs have been approved for cancer treatment (Table 1) while others including NAMI-A, KP1019, KP1339 and TLD1447 have progressed to the clinical trials against various tumour development and metastases [36,43]. Although, despite the interesting efficacy, some of these complexes such as NAMI-A and KP1019 could not be investigated beyond the second stage of the clinical trials due to various limitations including poor solubility in water and stability in other physiological conditions, short half-life within aqueous media and several other side effects in patients [7,43]. Inclusively, other metal-based prodrugs in clinical trials of cancer therapy include the transition metal-complex photosensitizing agents such as the tetrapyrrolic derivatives of Lu(II) (Lutex), Pd(II) (WST11) and Sn (IV) (Purlytin) as well as the polypyridyl complex of Ru(II) (TLD 1433) [45].



1-An important site for antitumour activity, suitable substituent enhances activity.
2-Imino group useful for the formation of quartenary ammonium salt and coordinate bonds. Alkyl/aryl substitution favours activity.
3-Introduction of amino, amide, thiourea groups induces systemic toxicity.
6-Substitution with bromo group enhances cytotoxicity as anticancer agent.
7-Alkoxy substitution induces cytotoxicity, although methoxy substitution may promote neurotoxicity.
9-N-alkylation/arylation enhances DNA intercalation and inhibition of Topoisomerases I & II. Antitumour activities increase both *in vitro* and *in vivo*.A protonation site for pH response.

Fig. 2. SAR of βC as an antitumour agent.

Several other bioactive complexes with different geometries have also been developed in recent years through the coordination of transition metal ions to various organic ligands including the anthracycline, camptothecin [16], porphyrins [53], carbene [54], pyrazole [55], quinolines [56], allyl ligands and other nucleophiles such as the carbon, nitrogen and oxygen nucleophiles [57]. Undoubtedly, the metallodrugs offer enhanced pharmacology and breakthrough against some limitations associated with small organic molecules, however, the resistance of tumour cells, poor physiological stability, non-selective toxicity to cells and several other side effects in patients are major concerns. Therefore, the continuous search for advanced multi-target directed therapeutic alternatives to counter these pathophysiological effects remains important in the field of coordination/medicinal chemistry. In line with this, the complexes consisting of coordinating ligands such as βCs, singly or mixed with other organic moieties such as polypyridyl, phenanthroline etc with heterocyclic/aromatic hydrocarbons show some degrees of rotational freedom useful for groove binding [58]. Their structure–activity relationship (SAR) favour multi-target directed mechanisms of action (Fig. 2). Impressively, they mostly demonstrate competitive and stronger cytotoxic activities against tumour cells, lower systemic toxicity, higher inhibition of metastasis and display an enhanced fluorescence for monitoring intracellular locations in a cell better than cisplatin [59,60]. In PDT for instance, some mechanisms of action of these complexes involve the generation of singlet oxygen ($^1O_2$), a strongly reactive oxidant to destroy the tumour and malignant tissues [47,48,61]. The enhanced anticancer activity of such complexes could be traced to the broad pharmacological spectrum of βCs as anticancer agents.

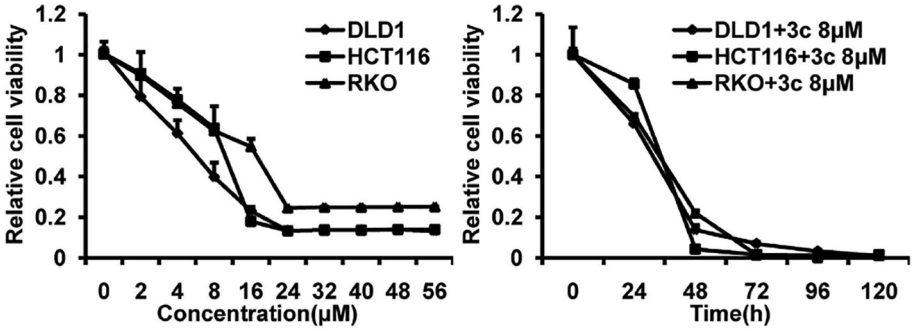


Fig. 3. The relative cell viability of βC, harmine (3c) against colon cancer cells (DLD1, HCT116 and RKO) demonstrated in a concentration- and time-dependent manner. Increase in concentration and time causes more cell death until equilibrium. (Reproduced from [69], Licenced under CC-BY-4.0).

2. β-Carboline derivatives as anticancer agents

β-carbolines are indole heterocyclic alkaloids with a large spectrum of structural and pharmacological diversity including antitumour/anticancer [23,62]. These biologically unique chemicals are vastly present in several ethnomedicinal plants, algae, mammals, invertebrates and can be synthetically derivatised into different structural analogues [6,24,47,63]. They are characterized by multi-dentate aromatic planes, H-bond donor/acceptor groups, the easy formation of the salt bridge through the amine N, photophysical, photochemical and photosensitizing properties, π-π stacking in stability-linked molecular interactions and other bioactive building blocks in SAR (Fig. 2) [1,18,48,64].

They exist in various natural forms as monomers and dimers from which many derivatives have been produced through convenient synthetic routes [29,63]. Natural and synthetic βC derivatives have been documented with interesting anticancer activities, favouring the induction of apoptosis on tumour cells [65,66] through various pathomechanisms such as the inhibition of dual-specificity tyrosine-phosphorylation-regulated kinase 1A (DYRK1A) and kinesin-5 protein (Eg5) [67,68], inhibition of cell proliferation, suppression of phosphatidylinositol-3 kinase-protein kinase B (P13K-AKT/p-AKT) signalling pathway, generation of reactive oxygen species (ROS) [69] and knockdown of the transcriptional co-activator with the postsynaptic density protein-, PDZ-binding motif (TAZ) [70]. The viability of their efficacy against cancer cells is usually shown in a concentration- and time-linearity. For instance, harmine demonstrates strong viability against colon cancer cells as time and concentration increases respectively (Fig. 3).

In combination with other organic molecules, several derivatives of βC have been linked with chalcones, pyrazoles, podophyllotoxins, polypyridyl, acylhydrazone, cinnamide and other chemical fragments to form conjugates and hybrids. In these structural forms, they also express antiproliferative/anticancer effects [58,63,71] through multi-target directed mechanisms commonly implicated in cancer therapy including strong inhibition against topoisomerases I & II through DNA intercalation, cell cycle arrest, inhibition of KSP-ATPase, inhibition of sirtuin 5 (SIRT5), photocleaving effect, blocking of mitotic cell division, modulation of angiogenesis and induce apoptosis on tumour cells [22,25,71–75]. The anticancer activity of ferrocene conjugates and the photo-damaging of DNA by 2′-deoxyadenosine 5′-monophosphate (dAMP) in complex with βC derivatives have also been documented [23,76,77]. Sometimes they exist as counter cations in complex salts also with good biological activities [78]. Subsequently some of these complexes are under cancer-related clinical investigation including (4R)-7-chloro-9-methyl-1-oxo-1,2,4,9-tetrahydrospiro[β-carboline-3,4′-piperidine]-4-carbonitrile, (4R)-7,8-dichloro-1′,9-dimethyl-1-oxo-1,2,4,9-tetrahydrospiro[β-carboline-3,4′-piperidine]-4-carbonitrile and (4R)-N-[4-({[2-(dimethylamino)ethyl]amino}carbonyl)-1,3-thiazol-2-yl]-4-methyl-1-oxo-2,3,4,9-tetrahydro-1H-β-carboline-6-carboxamide with proposed target mechanisms as serine/threonine protein kinase pim-1, death-associated protein kinase and the mitogen-activated protein kinase (MAPK) 2 respectively [52].

Since the molecular structure consideration is an essential factor in the innovative design of any structural-based anticancer drugs especially the organelle-targeting ones including the metallodrugs for biocompatibility [10,42,43], the modification of the building blocks (ligands) significantly affects the bioactivities, systematic bioavailability and inertness for substitution of the corresponding metal complexes [7,34]. Thus, the exceptional ligand pharmacology, bioavailability, planar biocompatibility with metal ions, ability to fill biological spaces, improved selectivity for the acidic environment, cell permeation potentials, enhanced pharmacokinetics and pharmacodynamics etc associated with βC derivatives [9,19], are favourable inspirations for considering their transition metal complexes as anticancer agents. Consequently, series of these agents consisting of βC derivatives in coordination to some transition metal ions such as Ag(I), Re(I), Cu(II), Co(II), Zn(II), Ni(II), Ru(II), Pt(II) and Ir(III) have been reportedly prepared through several synthetic routes and evaluated with interesting therapeutic and pharmacological profiles against various tumour growths. Additionally, Cu(I) and Hg(II) complexes, as well as some (Au/Ag) nanoparticle analogues of βC ligands, were also reported with good antimicrobial potentials. These developments are mostly (≈99%) recorded between 2010 – present, an indication of a new scientific trend which is progressively gaining research interests in form of pharmaceutical designs. However, to the best of our awareness, the overview of these innovations as an advanced knowledge-based revelation of multispecialty interactions useful for modelling and designing of improved anticancer therapeutics remains sparse. Although, some reviews have been documented in respect of few complex analogues of specific metal ions and restricted applications [79–84], however, none has extensively captured the decadal trends to intimate readers with up-to-date scientific progress involving various metal ion complexes of βCs acting through different anticancer therapeutic mechanisms.

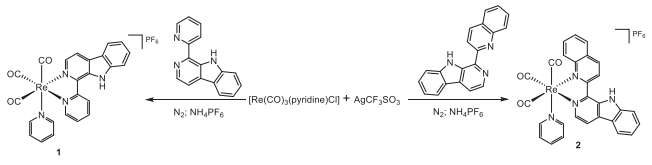
This review aims to comprehensively highlight the significant scientific advances towards effective anticancer therapeutic designs through the synthesis and mechanisms of anticancer actions of some metal complexes of βC derivatives reported in the last decade. The advantages including the convenient synthetic procedures, anticancer efficacy, selective cytotoxicity in favour of healthy cells demonstrated by the complexes will be briefly enumerated according to the oxidation states of the metal ions.

2.1. Metal-β-Carboline complexes as anticancer agents

Transition metal complexes involving βC ligands have been designed with the ligands binding to metal ions mostly through the C-1, C3, 2-N 9-N (Fig. 2) and any available electron-donor atom/group such as O, S, N and OH in their moieties [47]. These complexes have been reported with interesting therapeutic features including antimicrobial, antitumour and anticancer activities [69,75,85]. In a SAR, their anticancer potential is traceable to strong interactions with several biological targets and systems implicated in the pathophysiology and pharmacological mechanisms of cancer therapy. These include the DNA topoisomerases I and II [16,41,44], the mammalian target of rapamycin (mTOR), a major regulator of autophagy [21], the kinases including phosphatidylinositol 3-kinase, cyclin-dependent kinase (CDK) [23], the ubiquitin–proteasome system (UPS) and MAPK [86]. Some cellular events involving the cytoplasm, the autophagosomal-lysosomal fusion, the mechanism through which damaged cells and dysfunctioning proteins are removed otherwise termed lysosomal degradation have also been implicated in the pharmacological mechanisms of metal-βC coordination compounds in cancer therapy [20,27,28]. Most of these complexes also act by modifying the functions and properties of the cell membrane because the electrochemical gradient between the inner and outer membrane of the mitochondria favours a preferential accumulation of their lipophilic cations. Again, the cellular uptake and localisation within eukaryotic cells are enhanced by the indolyl N-methylation of βC ligands in the complexes [74,86]. As strong donor ligands, βCs exhibit additional stability to water and dioxygen [87], an important biomolecule for energy metabolism in living organisms, and the modification of the π-system support the reactivity of their corresponding metal complexes. Nature and oxidation states of the metal ions inclusively dictate the modes of coordination to βC derivatives which subsequently influence their potentials for both cytotoxic and target anticancer mechanisms.

2.1.1. Metal(I) complexes

Two distorted octahedral, phosphorescent Re(I) complexes (**1** and **2**) of CO, pyridine and βC ligands, 1-(pyridin-2-yl)-9H-pyrido[3,4-b]indole and 1-(quinolin-2-yl)-9H-pyrido[3,4-b]indole were synthesized by heating a precursor complex, $[Re(CO)_3(pyridine)Cl]$ under an inert condition with $AgCF_3SO_3$ in pyridine and subsequently introducing a βC ligand in NH_4PF_6 (Scheme 1). The purified crystals were elucidated for structural identification using ^1H NMR, IR, ESI-MS, UV–Visible and elemental analysis. To evaluate their anticancer potentials, photophysical properties, cellular uptake ability and localization were determined, and *in vitro* cytotoxicity was experimented using 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide for MTT assay against A549, A549cisR, MCF-7, HeLa and HLF representing human lung, breast, cervical cancer and human lung fibroblast (non-cancer) cell lines respectively. The IC_{50} values support that the complexes display higher anticancer potentials than cisplatin in multi-folds through the blocking of autophagic flux to induce autophagic-lysosomal imaging, induction of selective apoptosis to cancer cells and pH-dependent phosphorescence [28]. They demonstrate a good tolerability towards the non-cancer (HLF) cells, thus deserve further consideration for therapeutic studies.

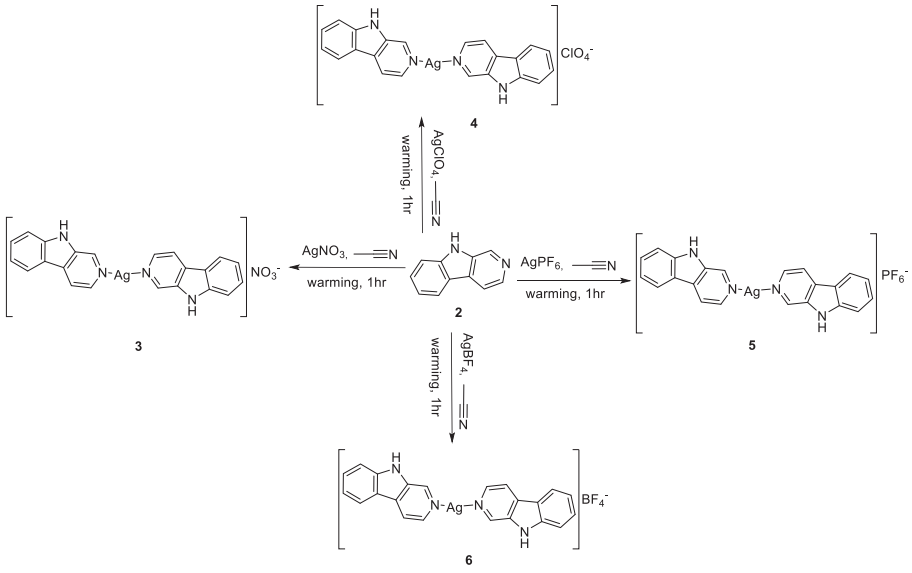


Scheme 1. Synthesis of octahedral Re(I)-βC-pyridine complexes.

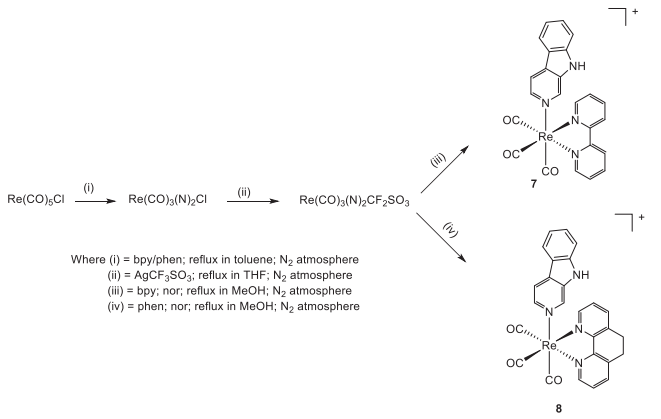
Light-stable linear crystals of Ag(I) complexes (**3, 4, 5** and **6**) with 9H-pyrido[3,4-b]indole (9H-pyrido[3,4-b]indole), a prototype indole heterocycle of βC and other counteranions such as NO_3^-, ClO_4^-, BF_4^- and PF_6^- were prepared by stirring each solution containing $AgNO_3$, $AgClO_4$, $AgPF_6$ and $AgBF_4$ interchangeably with 9H-pyrido[3,4-b]indole in acetonitrile for 1 h under warming (Scheme 2). The resulting crystals were characterized using ^1H NMR, IR, elemental analysis and X-ray diffraction. They were evaluated for antiproliferative effects *in vitro* using the classical MTT assay against A2780 and A549 cell lines for human ovarian and lung cancer cells respectively. The complexes especially **4**, [Ag(9H-pyrido[3,4-b]indole)(ClO_4^-)] demonstrates stronger inhibitory activity than free 9H-pyrido[3,4-b]indole with lower IC_{50} values of 2.38 ± 0.75 and 9.21 ± 2.77 μM against A2780 and A549 cell lines respectively compared to the latter with IC_{50} values > 200 μM in both cases. It also displays a competitive effect to cisplatin, a standard drug, whose IC_{50} values against A2780 and A549 cells are 1.90 ± 0.60 and 8.00 ± 0.50 μM respectively [40]. The improved anticancer potentials of 9H-pyrido[3,4-b]indole upon coordination to Ag(I) ion indicates the importance of coordination chemistry in anticancer drug designs and poses the complex for further therapeutic probes.

In 2015, Maisuls and his co-workers synthesized some Re(I)-βC-polypyridyl complexes (**7** and **8**) using 9H-pyrido[3,4-b]indole, 2′2-bipyridine (bpy) and 1,10-phenanthroline (phen) interchangeably as co-ligands. The novel Re(I)-βC complexes were prepared by refluxing equimolar $[Re(CO)_5Cl]$, a precursor complex and bpy/phen in 25 mL toluene under nitrogen atmosphere for 3 h. The resulting intermediate was treated with $AgCF_3SO_3$ to remove solid AgCl after which the reaction mixture was refluxed with equimolar 9H-pyrido[3,4-b]indole in methanol for 8 h under nitrogen (Scheme 3). The recovered crystals were purified and then characterized using ^1H NMR, ^{13}C NMR, FTIR, elemental analysis, X-ray diffraction, high-resolution electrospray ionization mass spectrometry (HRESI-MS) and ultraviolet matrix-assisted laser desorption/ionization MS (UV-MALDI-MS). The geometry optimization in the ground state by density-functional theory (DFT) calculations showed that the βC ligand, 9H-pyrido[3,4-b]indole coordinated through the pyridine N and generated conformers which differ only in the direction of the pyrrolic NH group. The extensive structural analyses indicate that Re(I) coordinated to the βC and three CO moieties each acting as a monodentate ligand with the octahedral geometry complemented by either bidentate bpy or phen (Scheme 3). The absorption spectrum (200–500 nm wavelength) and Mulliken population analysis were used to observe and estimate the percentage composition respectively of the major molecular orbitals (MOs) responsible for electronic transition in the complexes. Further analysis using DFT and time-dependent DFT shows the spatial plots of selection for the molecular orbitals of the stable facial complex structures (Fig. 4). The complexes were evaluated for anticancer activities through cytotoxicity assay against A549 cell lines for human lung cancer and cellular uptake potentials. They demonstrate strong inhibition and cellular uptake potentials against the cell line through the intercalation of DNA in good comparison with cisplatin [47]. The comprehensive structural elucidation further reveals the chemistry behind the mode of coordination of the βC alkaloids to metal ions and this could partly form the basis for future designs.

Similarly, some crystal Re(I) complexes (**9** and **10**) comprising of βC, 9H-pyrido[3,4-b]indole (nor) and dipyrido[3,2-a:2′,3′-c] phenazine (dpp) were synthesized and characterized through modification of co-ligands in the previously reported protocols (Schemes 3 and 4) [47]. The geometry optimization in the ground state by density-functional theory (DFT) calculations showed that



Scheme 2. Synthesis of Ag(I)- 9H-pyrido[3,4-b]indole complexes.



Scheme 3. Synthesis of Re(I) complex with βC, 2′2-bipyridine and 1,10-phenanthroline.

the βC ligand, 9H-pyrido[3,4-b]indole moves freely in solution. The complexes were evaluated for anticancer activities through cytotoxicity assay against A549 representing the human lung cancer cell and cellular uptake potentials. The complexes display strong inhibition and cellular uptake potentials against the cell line through the intercalation of DNA, especially **9**, $[Re(CO)_3(dpp)(nor)]^+$ whose IC_{50} value (10 μM) was in favourable competition with that of cisplatin (8 μM). The improved efficacy could be traced to the extended π-system enhanced by the βC ligand [48].

In furtherance to their previous works, Maisuls and co-workers in 2018 reported the photosensitizing properties of Re(I)-βC complexes (**9** and **10**) whose synthesis and characterization have been previously reported [48]. The photochemical and photophysical features of the complexes were evaluated through photochemical analysis, pulse radiolysis, interaction study with DNA using Calf thymus (CT-DNA) and Methyl-Viologen (MV) assays and excited state redox behaviour. The complex (**9**) with dipyrido[3,2-a:2′,3′-c] phenazine co-ligand to 9H-pyrido[3,4-b]indole (Scheme 4) demonstrated strong photosensitivity through π-π* excited state accessibility to quenchers when intercalated in DNA. This represents good potential for applicability in PDT aspect of oncology [49]. The photosensitivity of the complex analogues aids their additional pharmacokinetics including reaching the tumour growth targets even in darkness and cell localisation. The summary of the reported metal(I)-βC complexes with multi-mechanistic potentials against various cancer types is presented in Table 2.

2.1.2. Metal(II) complexes

Some ternary Cu(II) and Zn(II) mitochondrial-targeted complexes (**11** and **12**) involving tryptophan, DMSO and βC analogue acting as a monodentate ligand were synthesized by reacting (S)-2-amino-3-(1H-indol-3-yl)propanoic acid (tryptophan) with KOH in methanol at 25 °C for 30 min. The resulting solution was then stirred with $Cu(NO_3)_2{\cdot}6H_2O$ and $Zn(NO_3)_2{\cdot}6H_2O$ each at a time in DMSO/methanol solution for 1 h, then with 9H-pyrido[3,4-b] indole at 70 °C for 4 h (Scheme 5). The final solution was left for 1 week after which the crystals were formed under slow evaporation. The pure crystals were characterized using NMR, UV–Visible, FTIR, ESI-MS, TD-DFT and molar conductivity. Their anticancer potentials were evaluated using *in vitro* MTT assay for cytotoxicity against HepG2, MCF-7 and HEK293, representing the human hepatocellular carcinoma, breast cancer and normal embryonic kidney cells. Other activity-related assessments carried out include 2′,7′-dichlorofluorescein diacetate (H_2DCF-DA) ROS assay, lipid peroxidation (LPO) assay and flow cytometry. The complexes show strong inhibitory mechanisms *in vitro* against the cancer cells especially against MCF-7 with IC_{50} values within 10–24 μM compared to cisplatin with IC_{50} of ≈38 μM. Possibly due to Cu(II) and Zn(II) which are enzyme-friendly, they display more tolerability towards the healthy embryonic kidney cells with lower toxicity values than cisplatin. The suggested mechanisms of action by these compounds include generation of reactive oxygen species (ROS), modulation of glutathione (GSH) and increase in lipid peroxidation (LPO). The complexes could be developed into improved therapeutic and less toxic alternatives to cisplatin [1].

Two stable Cu(II) complexes (**13** and **14**) of βC derivatives were reported with strong anticancer activities. They were prepared by reacting $CuCl_2{\cdot}2H_2O$ in methanol with 9-octyl-1-(pyridin-2-yl)-9H-pyrido[3,4-b]indole and 9-nonyl-1-(pyridin-2-yl)-9H-pyrido[3,4-b]indole interchangeably. Their characterization was achieved using ESI-MS, elemental analysis and X-ray diffraction analysis for single crystals. The characterization results show that all the complexes are mononuclear single crystals consisting

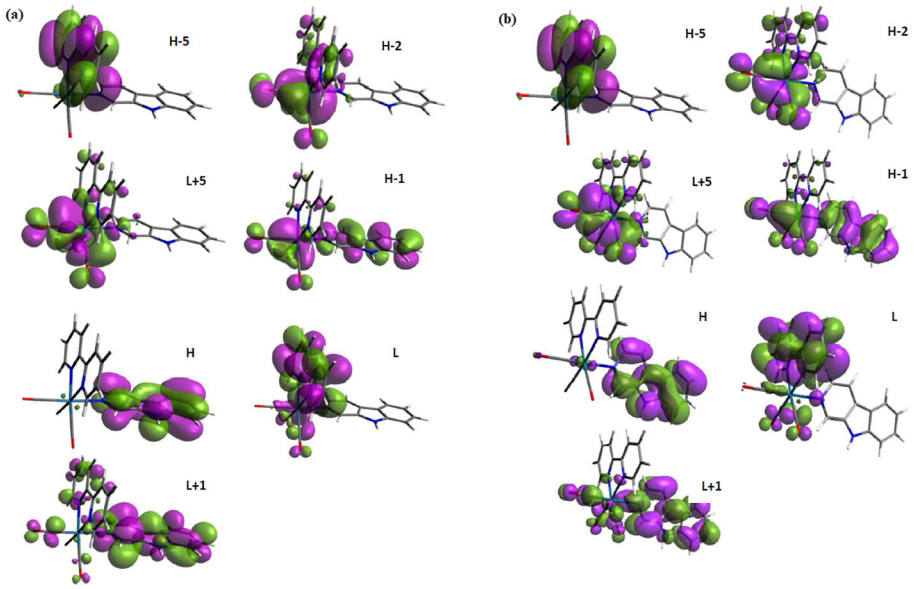
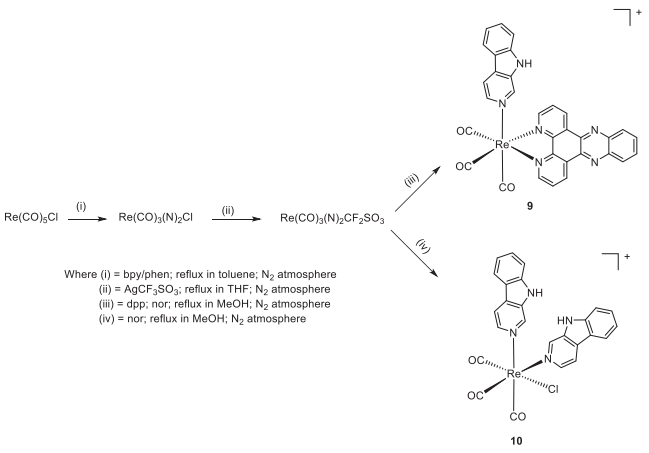


Fig. 4. Spatial plots of most representative molecular orbitals of (a) Complex **7;** (b) Complex **8** (Reproduced with permission from [47], Copyright (2015) Royal Society of Chemistry).

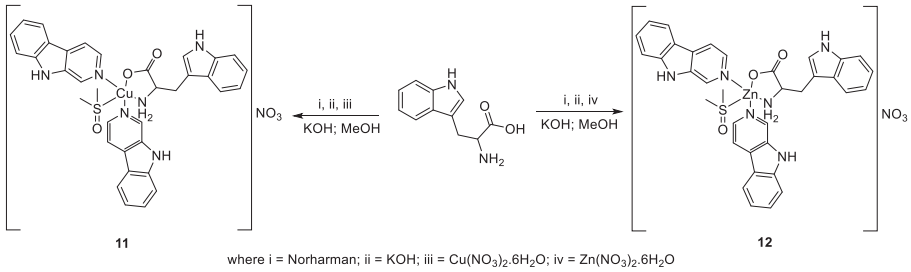


Scheme 4. Synthesis of Re(I) complexes of 9H-pyrido[3,4-b]indole and dipyrido [3,2-a:2′,3′-c] phenazine.

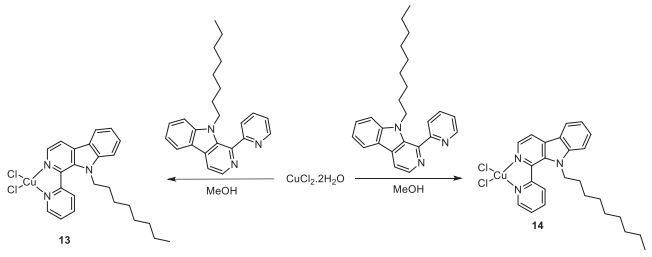
of central Cu(II) ion coordinating to the βC in each case through the indole and pyridine N (as a bidentate ligand) and two chlorine atoms (Scheme 6). The interaction of the complexes with myeloid cell leukaemia 1 (Mcl-1) and B-cell lymphoma (Bcl) homology (BH3) peptides was investigated using fluorescence polarization-based (FP) assay, enzyme-linked immunosorbent assay (Elisa) and Surface Plasmon Resonance-based (SPR) assay. Their inhibitory potentials against Mcl-1 in cell levels were investigated *in vitro* against the Mcl-1-dependent and Mcl-1-independent cells (MM.1S and KMS-12-PE) using the cell counting kit8 (CCK8) assay. The ability of the complex with 9-nonyl-1-(pyridin-2-yl)-9H-pyrido[3,4-b]indole to induce apoptosis was further assessed against Bcl-2-associated X (Bax) and Bcl-antagonist killer (Bak) proteins using Western blotting, Annexin V stain and flow cytometry assay. Their cytotoxicity was evaluated *in vitro* against HepG2, MGC80-3, NCI-H460 and T-24 which represent the human liver, gastric, large lung and urinary bladder cancer cells respectively, and *in vivo* using the mouse model. Its selective cytotoxicity in favour of normal cell was determined using HL-7702 for normal human liver cells. Complex **13** demonstrates a more potent inhibitory activity against Mcl-1 than **14**. It induces the oligomerisation of Bax and Bak, enhances the release of cytochrome *c*, causes the disruption of mitochondrial membrane and overall induces apoptosis (Fig. 1(a)). Further studies also confirm its anticancer properties *via* selective cytotoxicity against the cancer cells and the inactivity display against the normal liver cells in better terms than their parent ligands and cisplatin. The *in vivo* activity study in a mouse model shows a prolonged survival time in tumour-infected mouse, an indication of anticancer effects of the complex [12]. The complex is the first reported metal-based Mcl-1 inhibitor with strong anticancer potentials, thus, worthy of further consideration.

Table 2
Summary of metal(I)-βC complexes and their mechanisms of action against cancer cells.

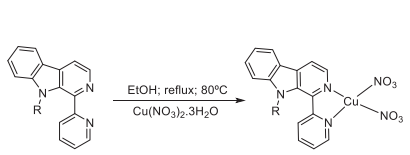
Complex	Mechanism of action	Experimental protocol	Tumour type	Refs.
2	Induction of autophagy through lysosomal imaging, pH-dependent phosphorescence, generation of ROS, apoptosis on cancer cells and inhibition of tumour growth in mouse.	Evaluation of photophysical properties, cellular uptake and localization, lysosome dysfunction and *in vitro* assay against A549 and A549cisR, HeLa, MCF-7 and HLF fibroblast, and *in vivo* mouse model	Lung cancer, cisplatin-resistant lung cancer, cervical cancer and breast cancer	[28]
4	Interaction with DNA and other thiol proteins	*In vitro* MTT assay against A2780 and A549 cell lines	Ovarian and lung cancer	[40]
7, **8**, **9** and **10**	DNA intercalation, mitochondria/lysosomal localisation and cytotoxicity to induce apoptosis.	*In vitro* cellular uptake and cytotoxicity assay against A549 cell lines, and fluorescence microscopy for visualization.	Lung cancer	[47,48]
9 and **10**	Excited-state accessibility to quenchers through DNA intercalation, photodynamic actions.	Photochemical analysis, pulse radiolysis, CT-DNA and MV assay, excited state behaviour evaluation.	Photosensitive tumour cells	[49]



Scheme 5. Synthesis of Cu(II)/Zn(II)-βC complexes.



Scheme 6. Synthesis of Cu(II) complexes of 9-octyl-1-(pyridin-2-yl)-9H-pyrido [3,4-b]indole and 9-nonyl-1-(pyridin-2-yl)-9H-pyrido[3,4-b]indole.



Complex	R
15	-CH_2Ph
16	-CH_2Ph(p-F)
17	-CH_2Ph(p-CH_3)
18	-$(CH_2)_2$Ph
19	-CH_2CH_3
20	-CH_2C3H5
21	-CH_2Naphth
22	-$(CH_2)_2$OPh
23	-$(CH_2)_2OCH_2$Ph
24	-$(CH_2)_2OCH_2CH_3$

Scheme 7. Synthesis of Cu(II) complexes of 9 N-substituted-βC analogues.

In continuation of their investigation on the potency of metal complexes of βC for Mcl-1-dependent and Mcl-1-independent cell inhibition, Lu et al., prepared ten Cu(II) complexes (**15**–**24**) of βC derivatives with modifications at the 9 N-indolyl site by refluxing $Cu(NO_3)_2{\cdot}3H_2O$ with various 9-substituted βC ligands in ethanol at 80 °C (Scheme 7). The complexes were characterized using elemental, ESI-MS and single-crystal X-ray diffraction analyses. They were evaluated for anticancer efficacy *in vitro* and *in vivo* using flow cytometry, binding to Mcl-1 assay, toxicity assay and NCI-H460 xenograft mouse model. Complex **17** (where R = $-CH_2$Ph (p-CH_3) demonstrates the highest potency by selectively inhibiting the growth of Mcl-1-dependent cell lines in 18–49-folds of the effect on Mcl-1-independent cell lines, while cisplatin shows no significant effect on either of them. The complex also induces tumour necrosis, increment in caspase activity and extended survival time in NCI-H460 mouse model all in a concentration- and time-dependent manner (Fig. 5) [88]. Based on the interesting mechnaisms of antitumour activity and the demonstration of safety in mice (Fig. 6), complex **17** could be a good model for further transformational studies to avail a new-dimensional anticancer therapeutic. The 9-substitution-dependent activity supports the importance of site modification as illustrated in SAR (Fig. 2) and the derivatisation of new active analogues can be achieved by targeting the site.

Some series of active Ru(II) complexes (**25–30**) of mixed benzene/*p*-cymene with bidentate βC ligands, 1-(pyridin-2-yl)-9H-pyrido[3,4-b]indole, 1-(quinolin-2-yl)-9H-pyrido[3,4-b]indole and 1-(1H-imidazol-2-yl)-9H-pyrido[3,4-b]indole were prepared by refluxing two equivalent of each βC ligand separately with [Ru (η^6-benzene)Cl] and [Ru(η^6-*p*-cymene)Cl] in absolute methanol for 2½ hours (Schemes 8 and 9). The crystals formed were purified and characterised for structural elucidation using ^{1}H NMR, ESI-MS, elemental analysis and X-ray crystallography. They were evaluated for anticancer activities through various protocols including the *in vitro* cytotoxicity MTT assay on HepG2 (liver cancer), HeLa (cervical cancer), A549 (lung cancer), A559cisR (a cisplatin-resistant form of lung cancer), CNE-2 (nasopharyngeal cancer) and HLF (normal lung fibroblast) cell lines respectively. Cell cycle determination, inhibitory potentials against CDK and apoptosis-inducing activity were also estimated. The complexes demonstrate better cytotoxicity towards the cancer cell lines than cisplatin including the cisplatin-resistant lung adenocarcinoma. Specifically, complex **20** shows in multi-fold higher cytotoxicity against the cancer cells than cisplatin with IC_{50} values in the range 1.5–7.5 μM while the latter has IC_{50} values within 15.5–77.4 μM against the same cells. The complexes increase the ROS level, induce cell arrest in G2M phase and display strong apoptosis-inducing activity selectively on cancer cells [23]. Their safety towards normal cells was displayed with low toxicological effects on the healthy human lung fibroblast cells, and the complexes, therefore, could be transformed into anticancer therapeutics upon further studies

Chen and his co-workers in 2013 reported the synthesis of four Ru(II) complexes (**31**–**34**) incorporating βC, 9H-pyrido[3,4-b]indole as a co-ligand. The 9H-pyrido[3,4-b]indole ligand was dissolved in DMSO and together with each solution of [Ru(L_1)(L_2)Cl]Cl (where L_1 = 2,2′:6′,2″-terpyridine and L_2 = 1,10-phenanthroline; 2,2′-dipyridylamine; 4,7-diphenyl-1,10-phenanthroline or 2-(pyridine-2-yl)pyridine) interchangeably refluxed for 12 h (Scheme 10). The precipitates formed were isolated using column chromatography and characterised using ^{1}H NMR, ESI-MS and elemental analysis. Their apoptosis-inducing potentials as potent anticancer activities were evaluated *via in vitro* cytotoxicity MTT assay, cell cycle arrest, cellular uptake and localisation, and flow cytometry. The complexes demonstrated a comparative antiproliferative potential to cisplatin in terms of IC_{50} values against the selected cell lines, A549/NCI-H460, HepG-2/Bel-7402, HCT-116, MCF-7 and A375 which represent human lung cancer, hepatocellular carcinoma, colorectal cancer, breast cancer and melanoma respectively. They also demonstrated stronger ability for cell accumulation, attributable to the π-systems in the coordinating ligands including the βC 9H-pyrido[3,4-b]indole [32].

Single crystals of Ni(II)-βC complex (**35**) were reportedly prepared *via* the hydrothermal synthetic method and evaluated with strong anticancer properties. The synthesis was achieved by reacting a previously prepared 6-methoxy-1-pyridine-β-carboline with $Ni(NO_3)_3{\cdot}6H_2O$ in 12:1 methanol/DMSO (Scheme 11). The recovered crystals were characterised using UV–Visible, ESI-MS, elemental CHN and X-ray crystallography. Their anticancer activities were assessed through cell cycle assay, Fluo-3/AM flow cytometry assay, caspase activity determination, cell apoptosis assay by Annexin V and *in vitro* MTT cytotoxicity assay against HepG2, MGC-803, T24, NCI-H460, OS-RC-2 and SK-OV3 for human hepato-

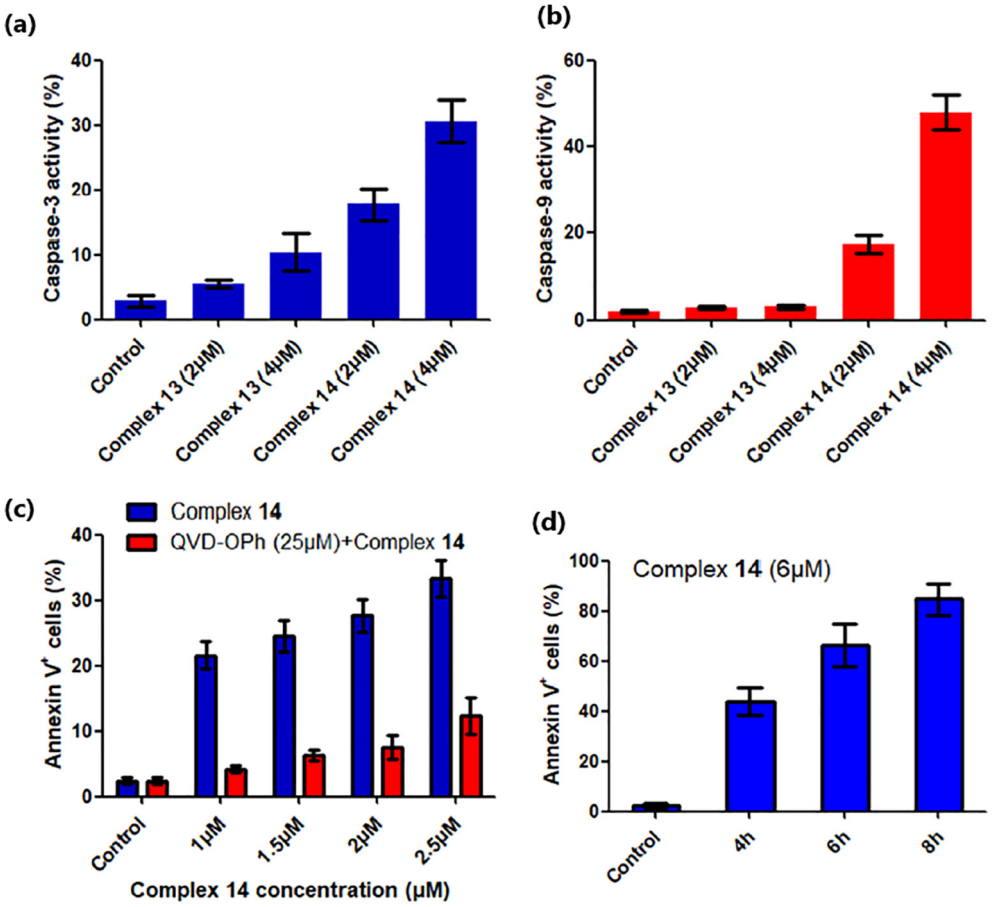


Fig. 5. Caspases-3/9 activity in NCI-H460 cells with complex **16** and **17** (shown as 13 and 14 respectively) for 6 h. (A) Caspase-3 activation assayed by flow cytometry. (B) Caspase-9 activation assayed by flow cytometry. (C) Induction of apoptosis in NCI-H460 cells treated with complex **17** in the presence/absence of the caspase inhibitor QVD-OPh. (D) NCI-H460 cells treated with complex **17** for the periods of 4, 6 or 8 h and analysed by flow cytometry. (Reproduced with permission from [88], Copyright (2020) American Chemical Society).

cellular, gastric, urinary bladder, large cell lung, renal, ovarian cancer cell lines respectively. The selective cytotoxicity of the complex was also tested against the normal human liver cells (HL-7702), all in comparison with the parent βC ligand and cisplatin. The complex demonstrates strong anticancer activities through various mechanisms including the induction of cell cycle arrest at the S phase, the downregulation of phosphor-AKT (p-AKT), cyclin A & E and CDK2. Other anticancer pathomechanisms shown are the generation of ROS, upregulation of a nucleus protein (p27), activation of caspase-3, enhancement of the expression of cytochrome *c* and intracellular $(Ca^{2+})_c$, and the induction of intrinsic apoptosis. The complex shows a concentration-dependent activation of the caspase-3 (Fig. 7a). It also displays stronger selective cytotoxicity against the cancer cell lines especially MGC-803 than the parent βC ligand and cisplatin with IC_{50} values in the range 3.77–15.10 μM against 11 - >20 μM and 10 - >20 μM respectively, and low toxicity to normal cell (HL-7702) (Fig. 7b) [39]. The complex shows strong anticancer properties worthy of development into therapeutic alternative.

Khan and his coworkers reportedly prepared some Cu(II), Zn(II), Co(II) and Ni(II) complexes (**36**–**43**) involving 2,2′-bipyridine (bpy), 1,10-phenanthroline (phen) and 9H-pyrido[3,4-b]indole (nor) as co-ligands. To the methanolic solution of the metal salts, bpy/phen was added under continuous stirring for 30 min after which 9H-pyrido[3,4-b]indole was introduced. The reaction mixture was then stirred for another 12 h and the crystalline complexes were then recovered after slow evaporation (Schemes 12 and 13). The complexes were characterised using 1H NMR, FTIR, UV–Visible, elemental analysis and X-ray crystallography (only on Cu-complex). Their anticancer potentials were evaluated using Annexin V staining, flow-cytometry, *in vitro* cytotoxicity MTT assay against A549 and A2780 representing the human lung and ovarian cancer cell lines respectively. The complexes demonstrate strong cytotoxic potentials against the cancer cells in favourable competition with cisplatin especially the distorted octahedral complex **36** whose potential surpasses that of cisplatin in 7-folds with IC_{50} of 3.57 μM compared to cisplatin with 24.2 μM [42], thus amenable for further studies.

Ruthenium(II)-complexes (**44** & **45**) consisting of mixed ligands, 2-(pyridine-2-yl)pyridine (bpy), 4-methyl-2-(4-methylpyridin-2-yl)pyridine (dmb) and 1-phenyl-9H-pyrido[3,4-b]indole (1-Ph- βC) were synthesized by continuous stirring the solution of $[Ru(dmb/bpy)_2Cl_2]$ with 1-Ph-βC in ethanol for 12 h at room temperature (Scheme 14). The crystals formed were isolated using column chromatography and structurally elucidated by ^{1}H NMR, ESI-MS and elemental analysis. They were experimentally evaluated for *in vitro* cytotoxicity, cell cycle arrest, cellular uptake and localisation and apoptosis-inducing potentials as mechanisms of anticancer using MTT assay, comet assay, flow cytometry, inductively coupled plasma mass spectrometry (ICP-MS), western blotting and inverted fluorescence microscope techniques. The complexes show better antiproliferative potentials with lower IC_{50} values of 1.9–17.2 μM than cisplatin whose IC_{50} values are 13.2–33.2 μM against the selected cell lines, A549, HeLa, NCI-H460, HepG-2 and

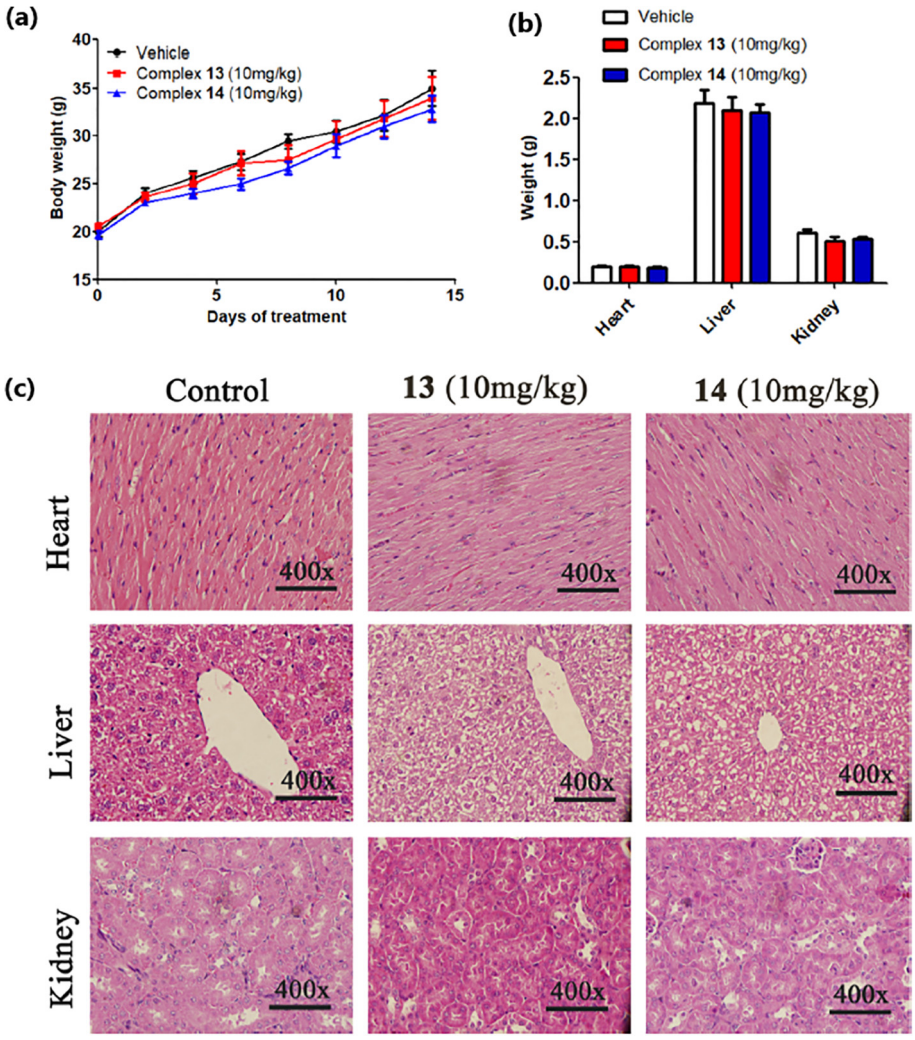
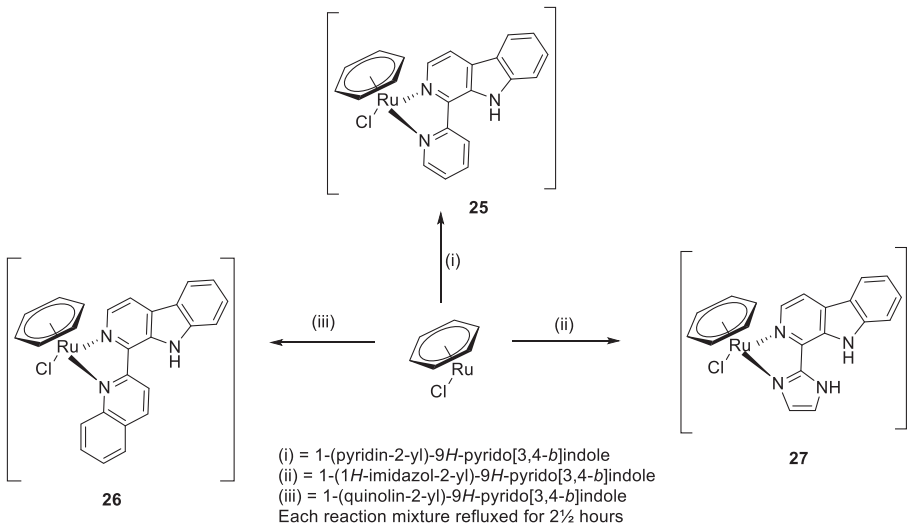
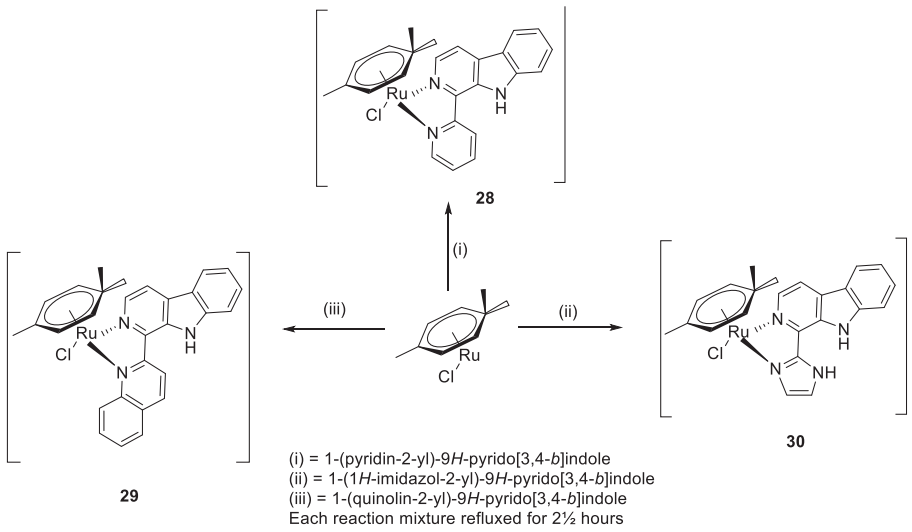


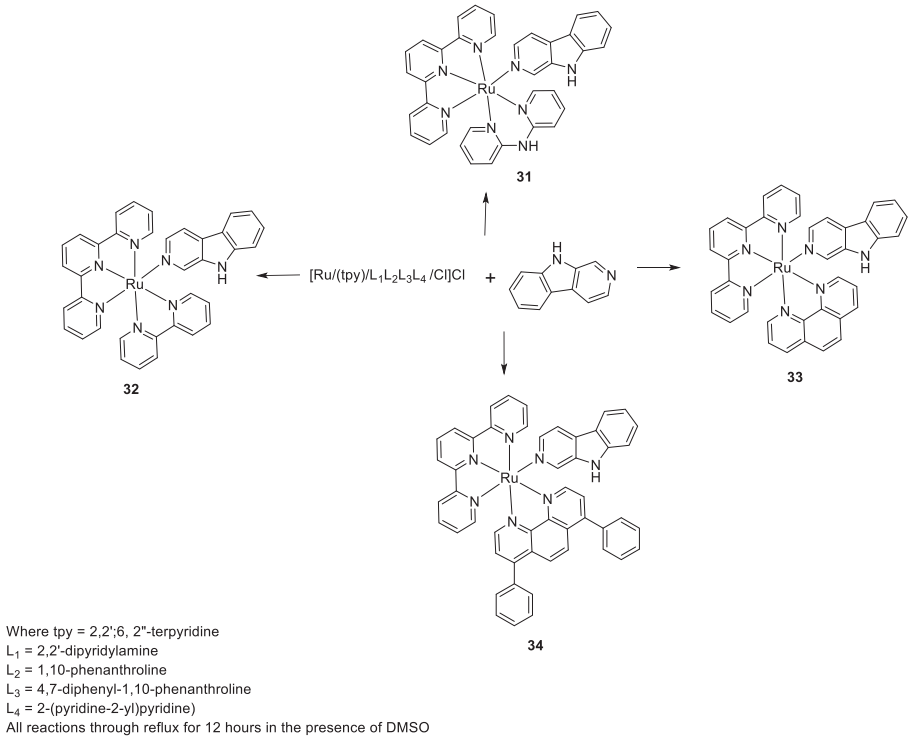
Fig. 6. Safety of complexes **16** and **17** (shown as 13 and 14 respectively) demonstrated in a mouse model. (A0 Bodyweight evaluation of Kunning mice (n = 6, half male and half female) treated by the intraperitoneal administration of vehicle, complexes **16** and **17** (each at 10 mg/kg, once daily). (B) Weights of hearts, livers and kidneys from treated Kunning mice at the endpoint. (C) H & E stained sections (400×, scale bar: 100 μm) of hearts, livers and kidneys from treated Kunning mice. (Reproduced with permission from [88], Copyright (2020) American Chemical Society).



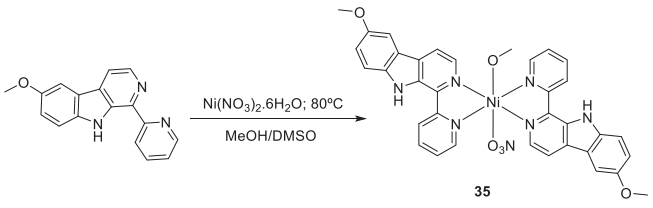
Scheme 8. Synthesis of Ru(II) complexes of mixed η^6-benzene and βC derivatives.



Scheme 9. Synthesis of Ru(II) complexes of mixed η^6-*p*-cymene and βC derivatives.



Scheme 10. Synthesis of four complexes of Ru(II) involving βC 9H-pyrido[3,4-b]indole acting as a monodentate co-ligand.



Scheme 11. Synthesis of deformed octahedral Ni(II)-βC complex.

MCF-7 for human lung adenocarcinoma, cervical, lung, hepatocellular and breast cancer cells respectively. They also demonstrated strong ability for cell accumulation in the G0/G1 phase, induce mitochondrial dysfunction, ROS generation, cell cycle arrest, DNA damage and apoptosis (Fig. 8) [44], therefore, could be further developed into anticancer chemotherapeutic models.

Some nuclear permeable Ru(II) complexes (**46**–**48**) consisting of 2-(pyridin-2-yl)pyridine, 1,10-phenanthroline, 4,7-diphenyl-1,10-phenanthroline and βC, 1-(pyridin-2-yl)-9H-pyrido[3,4-b]indole each as a bidentate ligand were prepared by refluxing a Ru(II) complex precursor, $[Ru(L_1/L_2/L_3)_2Cl_2].2H_2O$ with 1-(pyridin-2-yl)-9H-pyrido[3,4-b]indole in ethanoic solution for 3 h, then ion exchange with NH_4PF_6, where L_1 = 2-(pyridin-2-yl)pyridine, L_2 = 1,10-phenanthroline and L_3 = 4,7-diphenyl-1,10-phenanthroline (Scheme 15). The resulting crystals were characterized using 1H NMR, UV–Visible, ESI-MS and X-ray crystallography. Their anticancer potentials

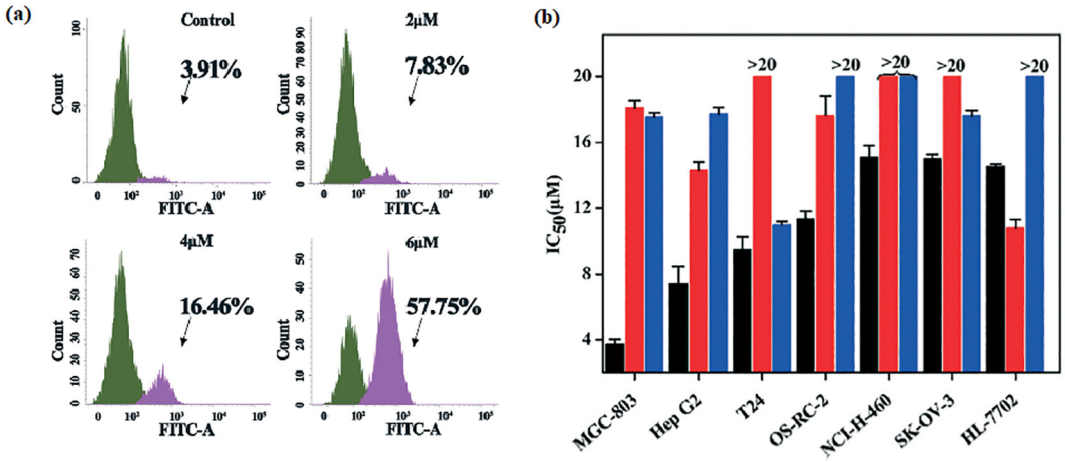
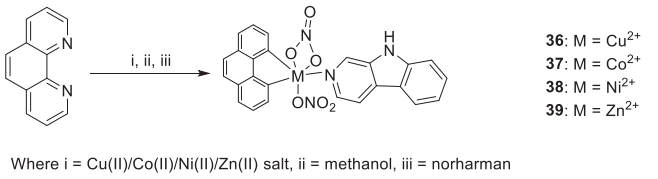
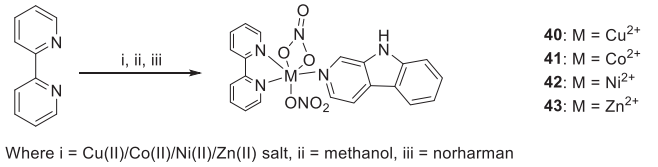


Fig. 7. Sensitivity of the complex **35** against MGC-803 (human gastric cancer) cells. **(a)** Concentration-dependent activation of caspase-3 in MGC-803 cells by the complex after treatment with 2.0, 4.0 and 6.0 μM for 48 h respectively: the percentage of activated caspase (purple) increases with the concentration of the complex. **(b)** IC_{50} values (μM) of the Ni(II)-βC complex (black), parent βC ligand (red) and cisplatin (blue). The complexes display stronger cytotoxicity against the cancer cells especially MGC-803 than the parent ligand and cisplatin, and less toxicity to normal cell (Reproduced with permission from [39], Copyright (2018) Royal Society of Chemistry).



Scheme 12. Synthesis of Cu(II), Co(II), Ni(II) and Zn(II) complexes of mixed 1,10-phenanthroline and 9H-pyrido[3,4-b]indole.



Scheme 13. Synthesis of Cu(II), Co(II), Ni(II) and Zn(II) complexes of mixed 2,2′-bipyridine and 9H-pyrido[3,4-b]indole.

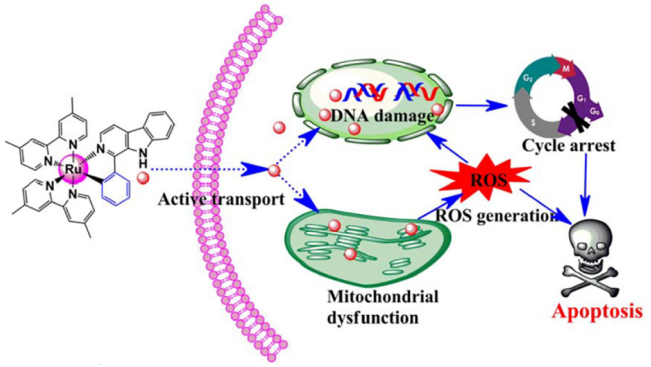
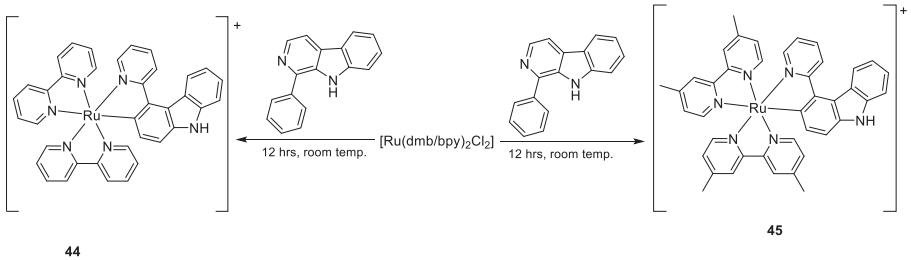


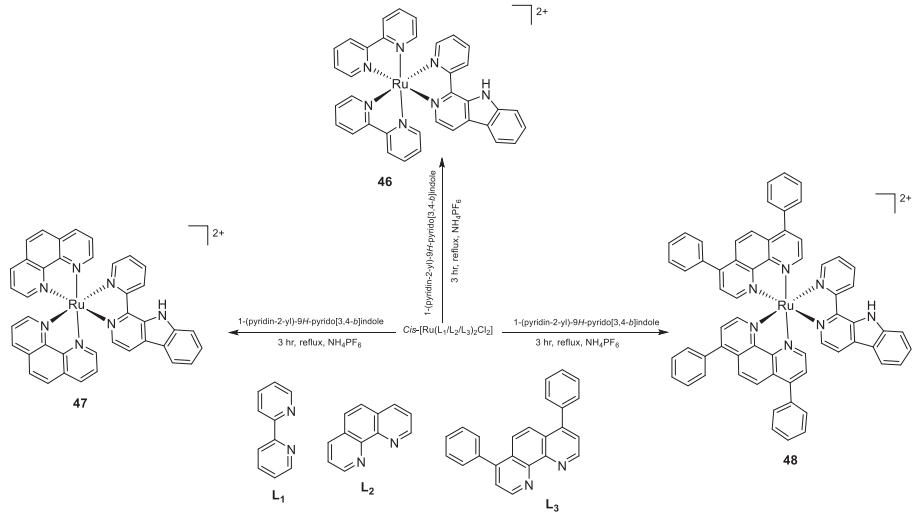
Fig. 8. Mechanisms of anticancer activity of complexes **44** & **45**. Apoptosis is induced *via* multi-mechanistic pathways to enhance efficacy (Reproduced with permission from [44], Copyright (2017) Elsevier Masson SAS).

were investigated through the cellular uptake and localisation assay, lipophilicity determination, fluorescence CLSM visualization, transmission electron microscopy (TEM) measurement, DNA binding assay and *in vitro* cytotoxicity MTT assay against HepG2, HeLa, MCF-7 and MCF-10A representing hepatocellular carcinoma, cervical cancer, breast cancer and normal human breast epithelial cells respectively. The complexes displayed stronger anticancer activity through the induction of ROS-dependent apoptosis in tumour cells, preventive autophagy against mitochondrial-mediated apoptosis and selective cytotoxicity against the cancer cells indicated by lower IC_{50} values than cisplatin especially the complex **48**, whose IC_{50} value against HeLa is 1.9 ± 0.2 μM compared to cisplatin with 16.7 ± 2.5 μM. It shows a very low toxic effect on normal breast epithelial cells compared to cisplatin and thus provides promising therapeutic advantages for further developments [59].

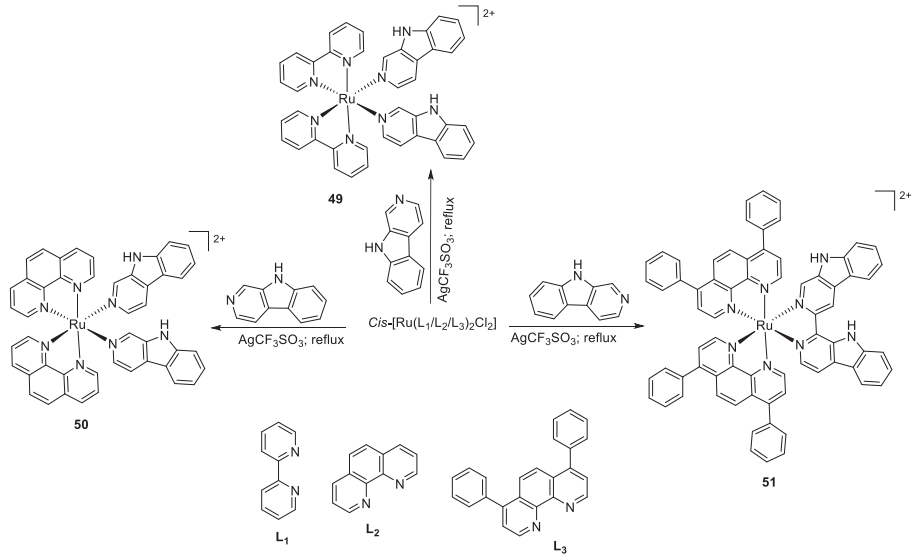
Three Ru(II)-βC complexes (**49**–**51**) were reportedly synthesized and evaluated with strong anticancer potentials. Briefly, the complexes were prepared and characterized according to the protocols [59] with modification in the βC ligand, 9H-pyrido[3,4-b]indole in place of 1-(pyridin-2-yl)-9H-pyrido[3,4-b]indole (Scheme 16). Their anticancer potentials were investigated through cellular



Scheme 14. Synthesis of Ru(II) complexes involving dmb, bpy and 1-Ph-βC as bidentate ligands.



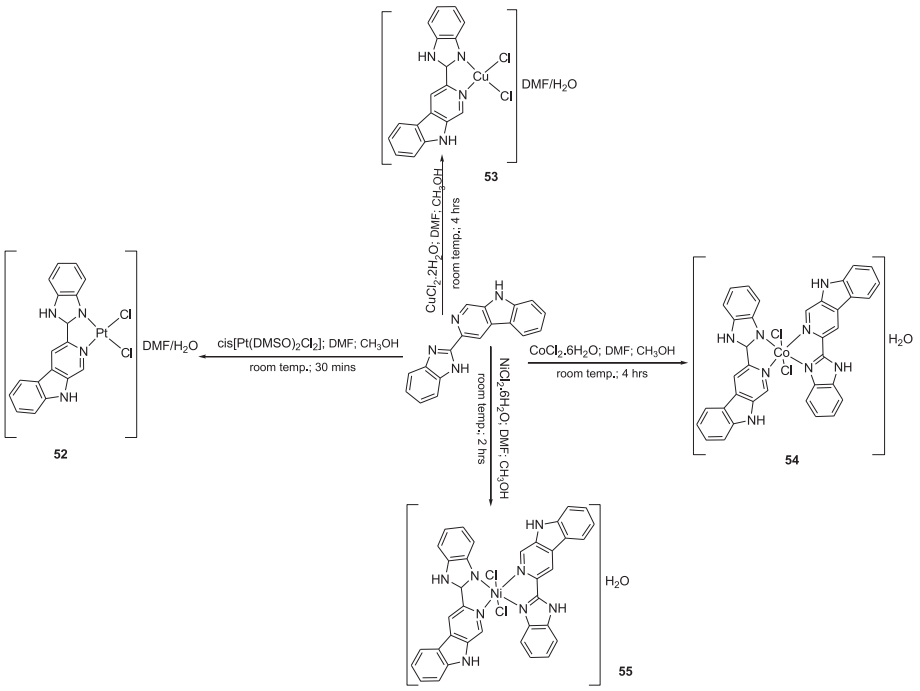
Scheme 15. Synthesis of Ru(II) complexes of mixed 2-(pyridin-2-yl)pyridine, 1,10-phenanthroline, 4,7-diphenyl-1,10-phenanthroline and βC, 1-(pyridin-2-yl)-9H-pyrido [3,4-b]indole.



Scheme 16. Synthesis of Ru(II)-complexes with βC 9H-pyrido[3,4-b]indole, 2-(pyridin-2-yl)pyridine, 1,10-phenanthroline and 4,7-diphenyl-1,10-phenanthroline ligands.

uptake and localisation assay, lipophilicity determination, fluorescence CLSM visualization, transmission electron microscopy (TEM) measurement, DNA binding assay and *in vitro* cytotoxicity MTT assay against HepG2, HeLa, MCF-7 and MCF-10A for hepatocellular carcinoma, cervical cancer, breast cancer and normal human breast epithelial cells respectively. The complexes demonstrate interesting anticancer activities *via* several mechanisms including induction of apoptosis through stressed endoplasmic reticulum, generation of ROS, dysfunctional mitochondria, cell cycle arrest in G0/G1 phase and cytoprotective autophagy. They also display stronger cytotoxicity against the cancer cells especially HeLa than cisplatin and NAMI-A, a Ru(III)-complex under clinical trial with lower average IC_{50} values in the range of 0.74–15.2 μM against the former and the latter with 16.7 μM and 625.8 μM respectively. Their toxicity was considerably low against the normal MCF-10A cells [60], thus offer potentials for further studies.

Jin et al., 2014 reported four complexes (**52**–**55**) of Pt(II), Cu(II), Co(II) and Ni(II) with βC analogue synthesized and complexes **52** and **53** were investigated for anticancer activities. A platinum complex salt, cis[$Pt(DMSO)_2Cl_2$] in dimethylformamide (DMF) solution was reacted at room temperature with 3-(1H-benzo[d]imidazol-2-yl)-9H-pyrido[3,4-b]indole and stirred for 30 min to obtain yellow crystals under slow evaporation. The same procedure was employed for other complexes with modifications in starting materials as $CuCl_2{\cdot}2H_2O$, $CoCl_2{\cdot}.6H_2O$ and $NiCl_2{\cdot}.6H_2O$, and reaction time as 4, 4 and 2 h respectively (Scheme 17). The characterization of the complexes was carried out using ^1H NMR, IR, ESI-MS, thermogravimetric (TG) and CHN elemental analysis. The X-ray crystal structures of the ligand, as well as its Pt(II) complex (52), were given as ORTEB drawings (Fig. 9). The complexes were evaluated for anticancer potentials using absorption spectrophotometry, agarose gel electrophoresis, ethidium bromide (EB) assay and fluorescence spectroscopy to study the complex-DNA interactions. The *in vitro* cytotoxicity was observed against A549, HeLa and HLF representing the lung cancer, cervical cancer and normal lung fibroblast cell line respectively. The complexes display strong DNA



Scheme 17. Synthesis of Pt(II)-, Cu(II)-, Co(II)- and Ni(II)-3-(1H-benzo[d]imidazol-2-yl)-9H-pyrido[3,4-b]indole complexes.

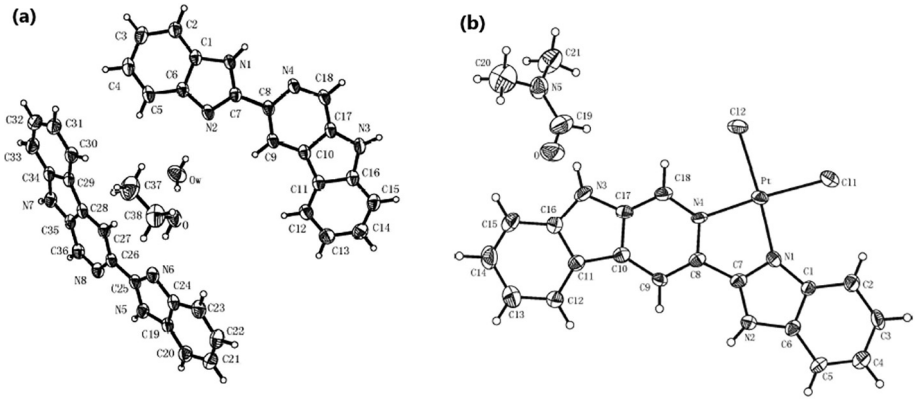
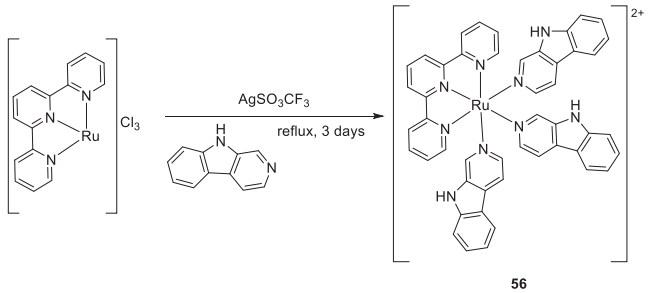


Fig. 9. ORTEP drawing of crystal structures (a) βC ligand, 3-(1H-benzo[d]imidazole-2-yl)-β-Carboline (b) Pt(II)-3-(1H-benzo[d]imidazole-2-yl)-β-Carboline complex **52** (Reproduced with permission from [64], Copyright (2014) Elsevier B. V.)



Scheme 18. Synthesis of Ru(II) complex of mixed βC 9H-pyrido[3,4-b]indole-2,2′:6′,2″-terpyridine.

binding and inhibitory activities against the cancer cell lines competitively with cisplatin and demonstrate selective cytotoxicity against the normal lung cell [64].

An octahedral Ru(II) complex (**56**) was synthesised by reacting $[Ru(L_1)]Cl_3$ with $AgSO_3CF_3$ in ethanol for 12 h after which the AgCl

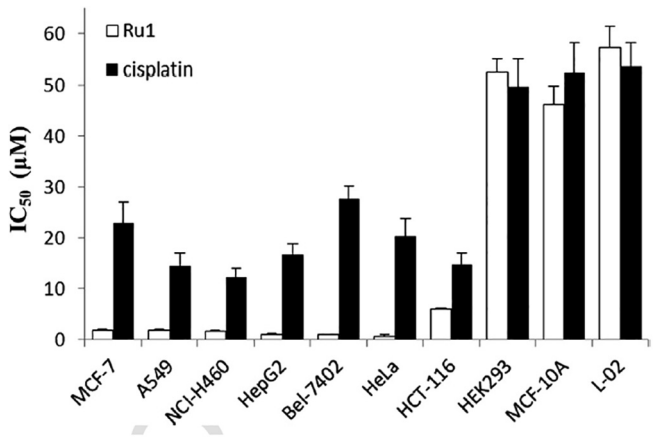


Fig. 10. Complex **56** (Ru1) demonstrates higher cytotoxicity against cancer cells than cisplatin indicated by lower IC_{50} values (Reproduced with permission from [89], Copyright (2017) Elsevier Masson SAS).

Table 3
Summary of metal(II)-βC complexes and their mechanisms of action against cancer cells.

Complex	Mechanism of action	Experimental protocol	Tumour type	Refs
11, 12	Generation of ROS, modulation of glutathione (GSH) and increase in LPO, G2/M phase cell accumulation, arrest and apoptotic inhibition of cell proliferation	*In vitro* MTT assay against HepG2, MCF7 and HEK293 cell lines	Hepatocellular carcinoma, breast cancer and kidney cancer	[1]
13 and **14**	Apoptosis induction *via* inhibition of Mcl-1, induction of oligomerisation of Bax and Bak, enhancement of the cytochrome *c* release, disruption of the mitochondrial membrane, selective cytotoxicity against cancer cells and elongation of survival time of tumour-infected mouse.	FP, SPR, Elisa, Annexin V, Western blotting, flow cytometry assay. *In vitro* cytotoxicity MTT assay using HepG2, MCG80-3, NCI-H460, T-24 and HL-7702. *In vivo* mouse model.	Hepatocellular carcinoma, gastric cancer, large lung cancer and urinary bladder cancer.	[12]
15	Inhibition of Mcl-1-dependent cells, activation of caspases 3 & 9 and induction of concentration-dependent apoptosis	Flow cytometry, binding assay on Mcl-1 and *in vivo* NCI-H460 xenograft mouse model.	Lung cancer	[88]
30	Inhibition of CDK 1/2, induction of mitochondrial dysfunction to trigger apoptosis, generation of ROS, cytotoxic against the cell lines and impact on cell cycle arrest	Mitochondrial membrane analysis, cellular uptake and ROS measurement, Western blotting, Annexin V and cell cycle assay, acute toxicity and MTT assay using HeLa, HepG2, A549 and A549cisR, CNE-2 and HLF cell lines	Cervical cancer, hepatocellular carcinoma, lung cancer and cisplatin-resistant lung cancer and nasopharyngeal carcinoma	[23]
31, 32, 33 and **34**	Cell cycle arrest, cellular uptake and localisation, generation of ROS, mitochondrial dysfunction and apoptosis-induction	*In vitro* MTT assay, comet assay, flow cytometry, ICP-MS), western blotting and IFM techniques using MCF-7, A549/NCI-H460, HepG-2/Bel-7402, HCT-116 and A375 cell lines.	Lung cancer, hepatocellular carcinoma, colorectal cancer, breast cancer and melanoma	[32]
35	Induction of cell cycle arrest at the S phase, downregulation of p-AKT and CDKs. Other is the generation of ROS, upregulation of p27, activation of caspase-3, enhancement of the expression of cytochrome *c* and intracellular $(Ca^{2+})_c$, and the induction of intrinsic apoptosis, stronger selective cytotoxicity against the cancer cell lines especially MGC-803 than the parent βC ligand and cisplatin	Cell cycle assay, Fluo-3/AM flow cytometry assay, caspase activity determination, cell apoptosis assay by Annexin V and MTT *in vitro* cytotoxicity assay against HepG2, MGC-803, T24, NCI-H460, OS-RC-2 and SK-OV3.	Hepatocellular carcinoma, gastric cancer, urinary bladder cancer, large cell lung cancer, renal cancer and ovarian cancer.	[39]
36	Inhibition of tumour cell growth, induction of apoptosis, cytotoxicity against cell lines.	Annexin V Flow-cytometry, *in vitro* cytotoxicity MTT assay against A549 and A2780	Lung cancer and ovarian cancer	[42]
44 and **45**	Generation of ROS, G0/G1 phase cell accumulation, arrest and apoptotic inhibition of cell proliferation	*In vitro* MTT assay, comet assay, flow cytometry, ICP-MS), western blotting and IFM techniques using A549, NCI-H460, HeLa, HepG-2 and MCF-7 cell lines.	Lung cancer, cervical cancer, hepatocellular carcinoma and breast cancer	[44]
46, 47 and **48**	Induction of ROS-dependent apoptosis in tumour cells, preventive autophagy against mitochondrial-mediated apoptosis and selective cytotoxicity against the cancer cells. Lower effects on normal breast epithelial cells (MCF-10A).	Cellular uptake and localisation assay, lipophilicity determination, fluorescence CLSM visualization, transmission electron microscopy (TEM) measurement, DNA binding assay and *in vitro* cytotoxicity MTT assay against HepG2, HeLa and MCF-7	Hepatocellular carcinoma, cervical cancer and breast cancer	[59]
49, 50 and **51**	Induction of apoptosis through stressed endoplasmic reticulum, generation of ROS, dysfunctional mitochondria, cell cycle arrest in G0/G1 phase, cytoprotective autophagy and cytotoxicity against cancer cells.	Cellular uptake and localisation assay, lipophilicity determination, fluorescence CLSM visualization, transmission electron microscopy (TEM) measurement, DNA binding assay and *in vitro* cytotoxicity MTT assay against HepG2, HeLa, MCF-7 and MCF-10A	Hepatocellular carcinoma, cervical cancer and breast cancer.	[60]
52 and **53**	Intercalation and cleavage of DNA to induce apoptosis, caspase activation, interaction with albumin and selective cytotoxicity towards cancer cells	Absorption spectrophotometry, agarose gel electrophoresis, EB assay, *in vitro* cytotoxicity assay against A549, HeLa and HLF	Lung cancer and cervical cancer	[64]
56	Cell cycle arrest, cellular uptake and localisation, generation of ROS, mitochondrial dysfunction, activation of caspase and intrinsic apoptosis-induction	Caspase activity assay, mitochondrial membrane analysis, cellular uptake and ROS measurement, Western blotting, Annexin V and cell cycle assay, acute toxicity and MTT assay using HeLa, HepG2, L-02 and Bel-7402, MCF-7/-10A, A549 and NCI-H460, HEK-293 and HCT-116 cell lines	Cervical cancer, hepatocellular carcinoma, breast cancer, lung cancer, kidney cancer and colorectal cancer	[89]

precipitates formed were removed and the resulting complex solution was refluxed with 9H-pyrido[3,4-b]indole for 3 days, where L_1 = 2,2′:6′,2″-terpyridine (Scheme 18). The crystals formed were isolated using column chromatography and characterised using ^{1}H NMR, ESI-MS and elemental analysis. Anticancer potential of the complex was evaluated in comparison with cisplatin using various *in vitro* experimental protocols including the caspase activity assay, mitochondrial membrane analysis, cellular uptake and ROS measurement, Western blotting, Annexin V and cell cycle assay, acute toxicity and MTT assay using HeLa (cervical), HepG2, L-02 and Bel-7402 (liver), MCF-7/-10A (breast), A549 and NCI-H460 (lung) and HCT-116 (colorectal) cancer cell lines respectively. The complex exhibits stronger inhibitory potentials with lower IC_{50} values in the range 1.0–6.0 μM against the cancer cells compared to cisplatin whose IC_{50} values are in the range of 10.0–38.0 μM (Fig. 10). It was suggested to induce apoptosis *via* the tumour suppressor protein (p53), activation of caspases, mitochondrial pathway as indicated by the loss of mitochondrial membrane and the release of cytochrome *c* with high selectivity towards cancerous cells and tolerable toxicity to normal cells [89]. The complex

possesses a promising therapeutic potential worthy of further exploration. Summary of the metal(II)-βC complexes and their mechanisms of action against tumour cells is presented in Table 3.

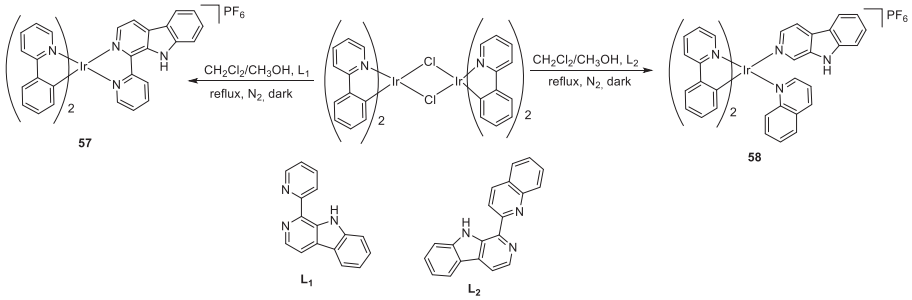
2.1.3. Metal(III) complexes

The potential for another anticancer therapeutic dimension, theranostic diagnosis and treatment was demonstrated by some Ir(III)-βC complexes (**57** and **58**) through a two-photon excited fluorescence (TPEF) for monitoring lysosomal-autophagic system. This technique aids the visualization of biological occurrences within live cells and associated tissues. The complexes were prepared by refluxing [Ir_2(2-phenylpyridine)$_4Cl_2$] separately with 1-(pyridin-2-yl)-9H-pyrido[3,4-b]indole and 1-(quinolin-2-yl)-9H -pyrido[3,4-b]indole in dichloromethane/methanol in darkroom (Scheme 19). Through lysosome-activated phosphorescence, the complexes can be used to specifically tracking lysosome. They induce autophagy, display high photostability in cells and phototoxicity against A549, the human lung adenocarcinoma especially **58**. Additionally, it increases the caspase-3/7 in >2-folds compared to cisplatin, thus, demonstrates good applicability in PDT as potential theranostic agent in cancer treatment [20].

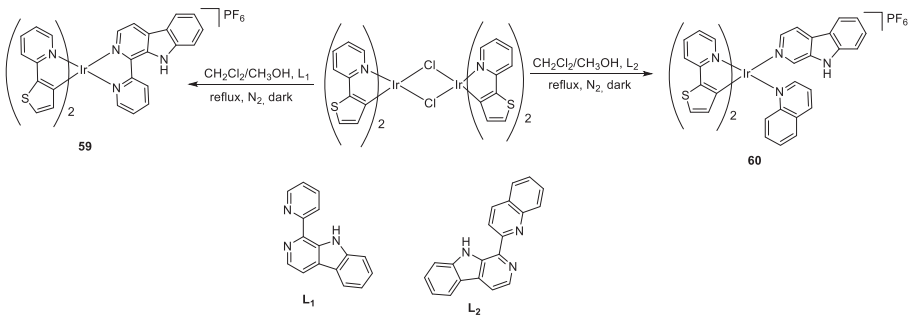
Some stable cyclometalated Ir(III) complexes (**59** and **60**) involving bidentate 2-(thiophen-2-yl)pyridine and βC derivatives, 1-(pyridin-2-yl)-9H-pyrido[3,4-b]indole and 1-(quinolin-2-yl)-9H -pyrido[3,4-b]indole were synthsised and characterized [20] (Scheme 20). The complexes demonstrate strong potentials to induce autophagy, caspase-independent cell death, ROS-mediated apoptosis and *in vitro* strong cytotoxic effects against A549, A549-cisR, HepG2 and HeLa cell lines which represent human lung, cisplatin-resistant lung, liver and cervical cancer cells respectively in stronger terms than cisplatin indicated by IC_{50} values which are lower in multi-folds. Although, they show a little higher toxicity against LO2, the normal hepatic cell than cisplatin. The transmission electron microscopy displayed autophagic morphology caused by the complexes, thus demonstrate autophagy-inducing potentials as anticancer agents [21]. Structural modification through the understanding of SAR as illustrated (Fig. 2) could avail pharmacologically enhanced and less toxic analogues.

He and his co-workers in 2015 also reported the synthesis and lysosome-targeted photodynamic therapeutic potency of some cyclometalated iridium(III) complexes (**61**–**64**). The synthetic protocols of [20] was adopted to prepare the complexes with modified precursor complex and introduction of new βC-ligands, 1-(1H-imidazol-2-yl)-9H-pyrido[3,4-b]indole and 1-(1H-benzo[d]imidazol-2-yl)-9H-pyrido[3,4-b]indole (Schemes 21 and 22). The complexes were characterized and studied for anticancer activities. They demonstrate strong photophysical properties, indicated by the absorptions within 380–450 nm (visible region) in CH_3OH and CH_3CN buffers. They also display good theranostic potentials for real-time tracking and lysosome-specific imaging [27]. The photosensitivity provides additional pharmacological advantages in terms of action and systemic availability at tumour target cells in the presence/absence of light.

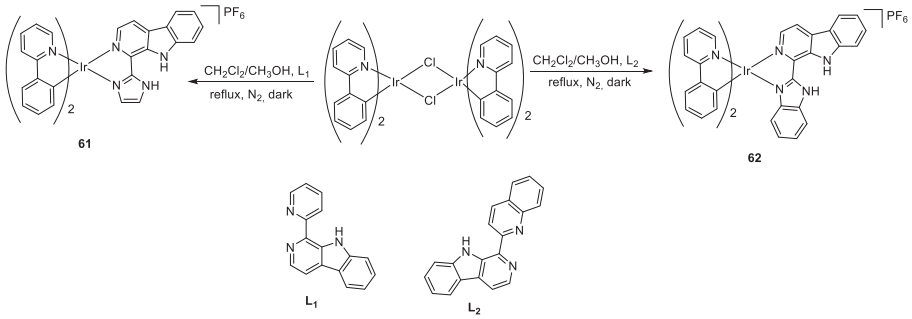
The complex **60**, [Ir(ppy)$_2$(βC)]PF_6 from [20] was incorporated onto polydopamine-β-cyclodextrin-arginine-glycine-aspartic acid (PDA-CD-RGD) complex to produce a phosphorescent nanoparticle composite (Scheme 23) with potent two-photon absorption (TPA) and two-photon phosphorescence characteristics for combined photothermal-chemotherapy and lifetime imaging applications. Anticancer activity of the composite was evaluated *via* cellular uptake and localisation assay using ICP-MS, H2DCF-DA ROS assay, Annexin V assay, Western blotting, *in vitro* MTT cytotoxicity assay against U87, MCF-7, LO2 and MCF-10A which represents the human brain glioma, breast cancer, normal liver and normal breast epithelial cells respectively. The preclinical *in vivo* photothermal activity of the composite was assessed through thermal imaging on tumour growth induced in the mouse by measuring the temperature change after NIR irradiation. Photoacoustic tomography (PAT) was used to image the mouse after intravenous and intratumoral treatment with 2 mg/mL of the nanoparticle. The



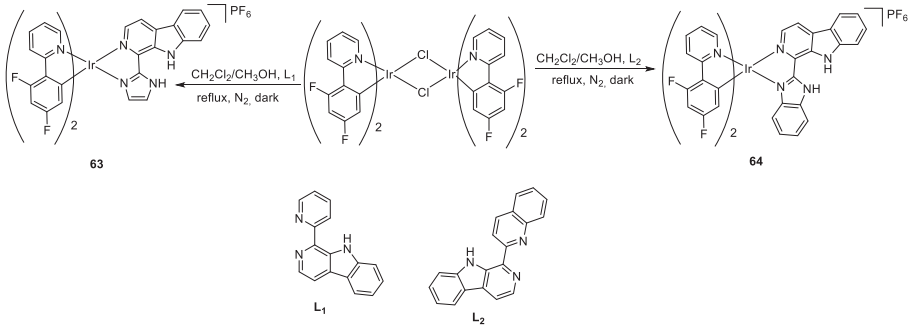
Scheme 19. Synthesis of Ir(III) complexes containing βC derivatives, 1-(pyridin-2-yl)-9H-pyrido[3,4-b]indole and 1-(quinolin-2-yl)-9H-pyrido[3,4-b]indole, and 2-phenylpyridine.



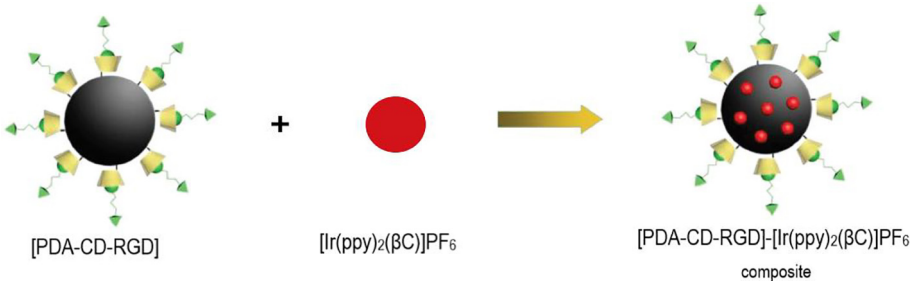
Scheme 20. Synthesis of Ir(III) complexes containing βC derivatives, 1-(pyridin-2-yl)-9H-pyrido[3,4-b]indole and 1-(quinolin-2-yl)-9H-pyrido[3,4-b]indole, and 2-(thiophen-2-yl)pyridine.



Scheme 21. Synthesis of Ir(III)-βC complexes (**61**–**62**) from [Ir_2(2-phenylpyridine)$_4Cl_2$] 1-(1H-imidazol-2-yl)-9H-pyrido[3,4-b]indole and 1-(1H-benzo[d]imidazol-2-yl)-9H-pyrido[3,4-b]indole.



Scheme 22. Synthesis of Ir(III)-βC complexes (**63**–**64**) from [Ir_2(2-(2,4-difluorophenyl)pyridine)$_4Cl_2$] 1-(1H-imidazol-2-yl)-9H-pyrido[3,4-b]indole and 1-(1H-benzo[d] imidazol-2-yl)-9H-pyrido[3,4-b]indole.



Scheme 23. Preparation of nanoparticle composite from [PDA-CD-RGD] and [Ir(ppy)$_2$(βC)]PF_6 (**60**).

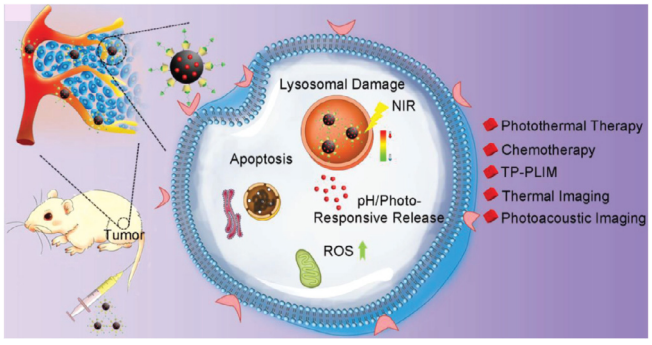
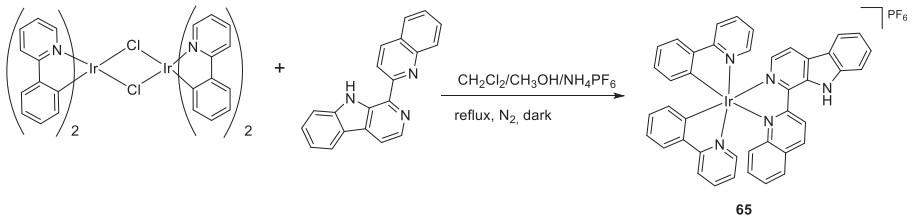


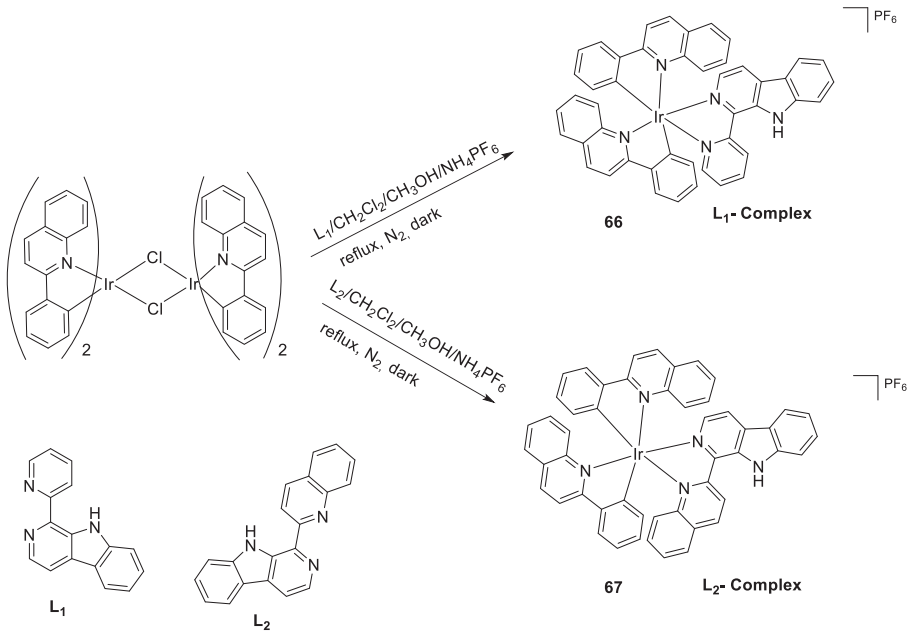
Fig. 11. Photothermal-chemotherapeutic mechanisms of [PDA-CD-RGD]-[Ir(ppy)$_2$(-βC)]PF_6 nanoparticle composite. The composite induces lysosomal damage through NIR and ROS generation and subsequently resulted in the tumour cell apoptosis as experimented *in vivo* mouse model (Reproduced from [31], Licensed under CC-BY-4.0).

nanoparticle displays potential for photothermal-chemotherapeutic applications with high absorption of near-infrared (NIR) lights, resulting in lysosomal damage, photo-mediated generation of ROS and photo-induced apoptosis (Fig. 11). Its strong anticancer activity was also demonstrated through various mechanisms including activation of caspase-3/7, suppression of cellular ATP and induction of cell death. Both the complex **60** and the nanoparticle composite show negligible cytotoxicity in the dark but strong effects against U87 cells in the NIR light, indicated by cell viabilities of 61.2 ± 1.3 and 19 ± 0.86 respectively at 20 μg mL^{-1}. The results support the hypothesis that the combination of chemotherapy with photothermal therapy (PTT) greatly enhances anticancer efficacy [31]. This indicates that formulation of metal-based complexes of βC into nanoparticles could improve their pharmacodynamics and pharmacokinetic profiles which in turn could aid their activities.

Distorted octahedral iridium (III) in a complex (**65**) with βC analogue, 1-(quinolin-2-yl)-9H-pyrido[3,4-b]indole was reportedly synthesized following the previously reported procedure [20] with some modifications. Briefly, a dimeric iridium (III) complex, [Ir_2(2-phenylpyridine)$_4Cl_2$] was refluxed with 1-(quinolin-2-yl)-9H-pyr ido[3,4-b]indole in CH_2Cl_2/CH_3OH, then ion exchange with NH_4PF_6



Scheme 24. Synthesis of a distorted octahedral Iridium(III)-βC complex (**65**).



Scheme 25. Synthesis of photosensitive cyclometalated Ir(III)-βC chelates (**66**–**67**).

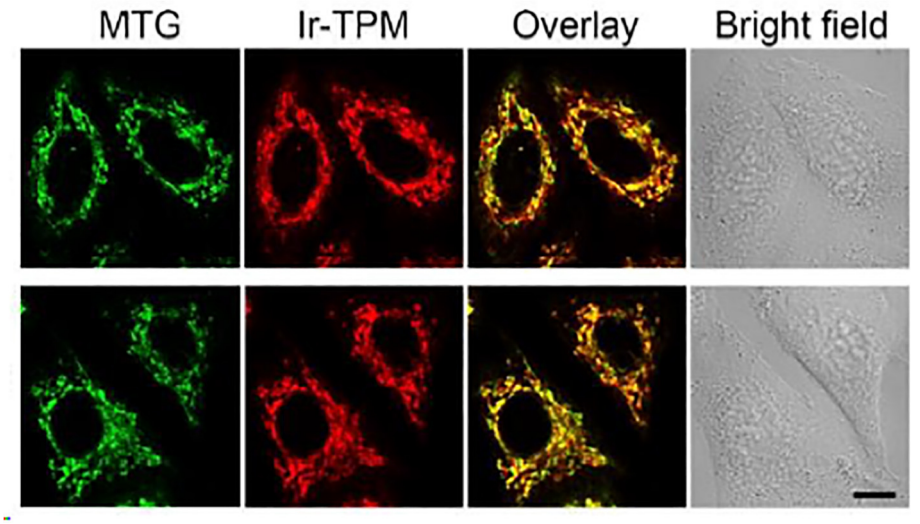


Fig. 12. Two-photon excited confocal laser scanning microscopy (CLSM) images of A549 cells stained with MitoTracker Green (MTG), followed by treatment with L_1/L_2-complex, overlay and the bright field (Reproduced with permission from [90], Copyright (2020) Royal Society of Chemistry).

(Scheme 24). The complex formed was characterized for structural elucidation using ^{1}H NMR, ESI-MS, elemental analysis and X-ray crystallography. The anticancer potentials of the complex were evaluated in terms of photophysical properties, cellular uptake and localization, cell death analysis and *in vitro* MTT cytotoxicity assay against A549 and A549cisR, HeLa and MCF-7 which represent human lung carcinoma, cervical and breast cancer cell line respectively. The complex displayed stronger inhibitory activities

Table 4
Summary of metal(III)-βC complexes and their mechanisms of action against cancer cells.

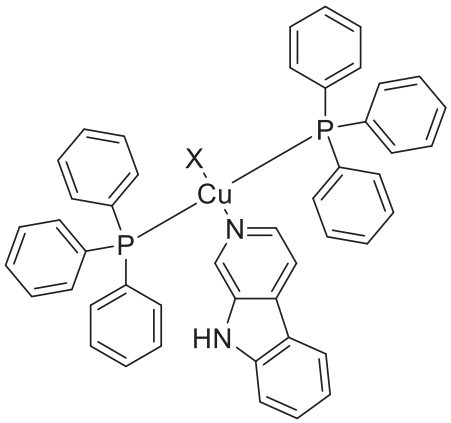
Complex	Mechanism of action	Experimental protocol	Tumour type	Refs
58	Induction of autophagy and apoptosis, lysosomal tracking, activation of caspase, display of strong TPEF and theranostic effects	Caspase-3/7 assay, cell viability and co-localisation assay, eGFP-LC3 analysis, real-time tracking of lysosomes in A549 cell.	Lung cancer	[20]
59 and **60**	Inhibition of CDK, induction of autophagy, ROS-mediated apoptosis, caspase-independent cell death and cell permeation.	*In vitro* anticancer MTT assay against A549, A549cisR, HepG2, HeLa, LO2, TEM, Western blotting.	Lung cancer, hepatocellular carcinoma and cervical cancer.	[21]
64	Induction of autophagy and apoptosis, lysosomal tracking, activation of caspase, display of strong TPEF and theranostic effects	Caspase-3/7 assay, cell viability and co-localisation assay, eGFP-LC3 analysis, real-time tracking of lysosomes in A549 cell.	Lung cancer	[27]
Composite of **60**	High absorption of NIR lights, lysosomal damage, photo-mediated ROS generation, activation of caspase-3/7, suppression of cellular ATP and photo-induced apoptosis	Cellular uptake and localisation assay using ICP-MS, H2DCF-DA ROS assay, Annexin V assay, Western blotting, *in vitro* MTT cytotoxicity assay against U87, MCF-7, LO2 and MCF-10A, and temperature measurement for thermal imaging *in vivo* mouse model.	Brain glioma and breast cancer	[31]
65	Induction of paraptosis, affects the UPS system, signal pathway on MAPK, induces mitochondrial dysfunction through the loss of membrane, ATP depletion and ROS generation. Exhibit antitumour activity *in vivo*.	Photophysical properties, cellular uptake and localization, cell death analysis *in vitro* MTT assay against A549 and A549cisR, HeLa and MCF-7, selective cytotoxicity using LO2 and *in vivo* mouse model.	Lung cancer, cisplatin-resistant lung cancer, cervical cancer and breast cancer	[86]
66 and **67**	Induction of ROS generation, mitochondrial-DNA damage, increased lipid peroxidation, inhibition of proteasomal activities and photodynamic potentials.	Cellular uptake and localisation assay, H_2DCF-DA ROS assay, two-photon fluorescence visualization, proteasomal inhibition assay and *in vitro* MTT cytotoxicity assay against A549, A549cisR, MCF-7 and HeLa cells.	Lung cancer, cisplatin-resistant lung cancer, breast cancer and hepatocellular carcinoma.	[90]

against the cell line compared to cisplatin. The safety of the complex was observed in a normal hepatic cell line (LO2) and no expression on caspase 3/7 compared to cisplatin. It also demonstrates potent anticancer activity *in vivo* mouse model. The mechanisms of action include the induction of paraptosis, signal pathway on the UPS system and MAPK, induction mitochondrial dysfunction through the loss of membrane, ATP depletion and ROS generation. The complex display potential worthy of further study and could proffer a chemotherapeutic alternative to cisplatin [86].

Qin and his co-workers recently reported two photosensitive cyclometalated Ir(III) complexes (**66** and **67**) consisting of 2-phenylquinoline and βC derivatives, 9-methyl-1-(pyridin-2-yl)-9 H-pyrido[3,4-b]indole and 1-(quinolin-2-yl)-9H-pyrido[3,4-b]indo le as chelating agents. The synthesis and characterization protocols [20] was adopted with modification in the ligands and reflux time to prepare the complexes (Scheme 25). The anticancer potentials of the complexes were evaluated using cellular uptake and localisation assay, 2′,7′-dichlorofluorescein diacetate (H_2DCF-DA) ROS assay, two-photon fluorescence visualization, proteasomal inhibition assay and *in vitro* MTT cytotoxicity assay against A549 (lung cancer), A549cisR (cisplatin-resistant form), MCF-7 (breast cancer) and HeLa (cervical cancer) cells. The complexes demonstrated strong anticancer activities especially along a photodynamic pathway, induce ROS generation, decrease in ATP, mitochondrial-DNA damage, increment in lipid peroxidation and inhibition of proteasomal activities. The effects became intensed under the light with cytotoxicity against A549 and general phototoxicity index increase by 2.5 and 93-folds respectively, an indication of PDT potentials (Fig. 12) [90]. The summary of metal(III)-βC complexes and their mechanisms of anticancer activities are briefly presented in Table 4.

2.2. Other potential medical applications of metal- β-Carboline coordination compounds

Coordination compounds involving transition metal in complex with βC analogues have been designed for other biomedical applications in addition to cancer therapy. Silver nanoparticles (NPs) in complex with harmine has been applied in thioguanine detection assay in human plasma through selective turn-on fluorescence [91]. In a similar pattern, the intrinsic fluorescence of βC derivatives, harmine and harman were strongly quenched by their corresponding gold NPs possibly due to energy transfer. This demonstrates the applicability of the NPs as ultra-tracers for silver detection in real water samples [92]. According to Al-Shabib et al., 2018, some biometals could be delivered to the tissues where they are expected to exhibit various biological functions through metal–organic coordination [93]. Coordination compounds involving some biometals with βC derivatives as lone/co-ligands have also shown various pharmacological effects including antimicrobial [93], For instance, copper (I) complexes demonstrated good preventive potentials against foodborne diseases through *in vitro* inhibition of biofilms and quorum sensing of the associated pathogenic bacteria [93]. Alsalme et al. [40], prepared four complexes (**3**–**6**) of Ag(I)-βC using 9H-pyrido[3,4-b] indole (Scheme 2). The complexes were probed for molecular interaction and biochemical behaviour with some protein receptors fundamental to pharmacological phenomena such as the binding to human serum albumin (HSA) using UV–visible spectroscopy, fluorescence spectroscopy, circular dichroism and molecular docking simulation. The binding propensity of the complexes to the protein receptor was reportedly



68

Scheme 26. Luminescent tetrahedral Cu(I) complex of βC.

remarkable, especially for complexes **3** and **4** which demonstrate stronger affinity than the **5** and **6** counterparts. These complexes virtually induce conformational changes to the HSA from its α-helix to a β-sheeted structure. The binding of Ag(I)-βC-NO_3^-/ClO_4^- complexes to HSA in order to induce substantial structural deformation through static quenching mechanism has been earmarked as a model for treating neurological diseases such as Alzheimer's and Parkinson's diseases [62,94]. Due to their extended π-system as carbon-rich compounds, βCs in coordination to metal ions have been designed for some other medical-related applications including measurement of O_2, pH, temperature and as precursors in optical applications. Example of such is the luminescent tetrahedral Cu (I) complex (**68**) consisting of halides, phosphane and βC 9H-pyrido [3,4-b]indole as co-ligands (Scheme 26) [95]. Also, the identification and differentiation of the enantiomeric PDE5 inhibitor, tadalafil, a βC derivative have been reportedly enhanced through its coordination to Ni(II) ion, although, no biological activity was evaluated by the author [96]. Mercury (II) complexes of harmine and harmaline were also reported with good antimicrobial activities, although the structures could not be succinctly validated [85]. The formation of Au(I) complexes usually occur at (non-stable) intermediary stages through carbophilic activation of π-systems in the synthetic routes of βC derivatives [97].

3. Concluding remarks and future perspectives

This review summarizes the pharmacological spectrum of the naturally toxic β-Carboline (βC) derivatives against tumour growths which prompted the synthesis and probe of their corresponding metal complexes for anticancer applicability. Impressively, some limitations associated with free moieties of βC alkaloids including poor water solubility and systemic toxicity have been modulated through coordination to metal ions. The coordination of the transition metal ions to the βC ligands progress through conventional synthetic routes regular to inorganic chemistry. Most of the synthesized complexes demonstrate improved cytotoxicity against various malignant tumour cells than the parent βC ligands and cisplatin, especially **4**, **9**, **11**–**13**, **15, 30**, **35**, **36**, **44**, **45**, **48**, **56**–**59** and the nanoparticle composite of **60**. Interestingly, they also display good tolerability towards healthy human non-cancerous cells, and this could provide a clinical opportunity for discriminative toxicity in their applications as anticancer agents. Their mechanisms of action involve most important pathways implicated in cancer chemotherapy including the DNA intercalation, damaging of lysosome and mitochondrial membrane, activation of caspases, inhibition of kinases, autophagosomal-lysosomal fusion, photo-mediated ROS generation, inhibition of microtubules and topoisomerases I & II, and multi-target apoptotic pathways, an additional opportunity for overcoming drug resistance.

Through the exhibition of the π–π^* exited state for photosensitivity, some complexes such as **9**, **58**, **61**–**67** inclusively display high potentials for theranostic application, photodynamic therapy and combined photodynamic-chemotherapeutic applications. The exceptional characteristics of metal-βC complexes as photosensitizers could provide some extra pharmacological advantages such as the potentials for lifetime imaging, delivery to target tumour cells, control of drug stimulation, action on tumour targets even in darkness and applicability as photoactivatable tracking agents. Furthermore, the contribution of βC ligands to the coordination also enhances the physicochemical and biological profiles of their metal complexes in terms of selectivity towards the acidic environment, stability, pH response, reactivity due to the π-donation, cellular uptake, planar biocompatibility, inertness for substitution and ability to interact with various biological enzyme/organelle targets, a propensity for multi-mechanistic activity and minimal side effects. The abundance of the ligand and its derivatives in vast natural resources, as well as their easy derivatisation, approaches favour global accessibility for future scientific projects. These interesting factors advantageously attract further studies on the trending metal-based bioactive agents as observed in the overview - the rate of research interests has been on the rapid increase since 2010, an indication of preference for metal-βC complexes over other counterparts.

Few of the complexes such as **35**, **59** and **60** display daunting systemic toxicity, although, the understanding of the SAR and easy structural modification could aid their modulation into a more active, less toxic analogues, however, the procedures remain underexplored. Since the nature of the central metal ion and structural modification through substitutions at different sites on their molecules influence both pharmacological and toxicological properties of the corresponding complexes, scientific research can be focused on these to mitigate the deficiencies. Despite their vast presence in natural products, the recovery of pure βCs in good yield has been a major challenge possibly due to their structural complexity. Thus, the most reliable sources of these essential bioactive ligands remain synthetic, as such more innovations are required for their production at cheaper and safer rates.

More so, most of the investigations for quantitative and qualitative assessment of the biological profiles of the reported complexes have been limited to *in vitro* models which cannot show the physiological side effects, an important concern with metal-based prodrugs. Therefore, for future scientists, more robust experimental studies are required for better understanding of the therapeutic and aftereffect activities of the complexes, especially pre-clinical and clinical *in vivo* models for advancing the translation into real-life medicinal uses.

This review reveals that in addition to their interesting pharmacology, the transition metal complexes of βC proffer potentials for overcoming the limitations including incessant resistance, systemic toxicity and unpleasant side effects associated with the platinum-based and other currently available anticancer metallodrugs. It represents a good model for future anticancer drug designs.

Authors contribution

Y. O. Ayipo and W. A. Osunniran designed the study, collated the data and prepared the manuscript while M. N. Mordi supervised the project and revised the manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This work was supported by Tertiary Education Fund, Nigeria, Ministry of Higher Education of Malaysia, HICoE (grant no. 311/CDADAH/4401009) and Universiti Sains Malaysia Graduate Assistant Scheme awarded to Y. O. Ayipo (grant no. 308.AIPS.415401).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ccr.2020.213746.

References

[1] R.A. Khan, M.R. Khan, M. Usman, F. Sayeed, H.A. Alghamdi, S. Alrumman, W. Alharbi, N.N. Farshori, M.M. Al-Oqail, M.R. Siddiqui, M.A. Khanjer, A. Alsalme, β-Carboline copper complex as a potential mitochondrial-targeted anticancer chemotherapeutic agent: Favorable attenuation of human breast cancer MCF7 cells via apoptosis, Saudi J. Biol. Sci. 27 (8) (2020) 2164–2173, https://doi.org/10.1016/j.sjbs.2020.05.001.

[2] B.K. Banika, B.M. Sahoo, Green synthesis and biological evaluation of anticancer drugs, in: Green Approaches Med. Chem. Sustain. Drug Des., 2020, pp. 651–710, https://doi.org/10.1016/B978-0-12-817592-7.00019-8.

[3] F. Bray, A. Jemal, N. Grey, J. Ferlay, D. Forman, Global cancer transitions according to the Human Development Index (2008–2030): a population-based study Freddie, Lancet Oncol. 13 (2012) 790–801, https://doi.org/10.1016/S1470-2045(12)70211-5.

[4] American Cancer Society, Cancer Facts & Figures 2020, CA. Cancer, J. Clin. (2020) 1–76.

[5] J.M. Michalski, T.M. Pisansky, C.A.F. Lawton, L. Potters, in: Prostate CancerClin. Radiat. Oncol., fourth ed., 2016, pp. 1038–1095.

[6] S. Kumar, A. Singh, K. Kumar, V. Kumar, Recent insights into synthetic b - carbolines with anti-cancer activities, Eur. J. Med. Chem. 142 (2017) 48–73, https://doi.org/10.1016/j.ejmech.2017.05.059.

[7] P. Jia, R. Ouyang, P. Cao, X. Tong, X. Zhou, T. Lei, Y. Zhao, N. Guo, H. Chang, Y. Miao, S. Zhou, Review: recent advances and future development of metal complexes as anticancer agents, J. Coord. Chem. 70 (13) (2017) 2175–2201, https://doi.org/10.1080/00958972.2017.1349313.

[8] C.M. Costelloe, N.T. Ueno, P.P. Lin, T.K. Yu, N. Hayashi, J.E. Madewell, Bone metastases, Oncol. Imaging A Multidiscip. Approach (2012) 591–609, https://doi.org/10.1016/B978-1-4377-2232-1.00033-4.

[9] M. Yang, U. Bierbach, Metal-containing pharmacophores in molecularly targeted anticancer therapies and diagnostics, Eur. J. Inorg. Chem. (2016), https://doi.org/10.1002/ejic.201601149.

[10] E.B. Bauer, A.A. Haase, R.M. Reich, D.C. Crans, F.E. Kühn, Organometallic and coordination rhenium compounds and their potential in cancer therapy, Coord. Chem. Rev. J. 393 (2019) 79–117, https://doi.org/10.1016/j.ccr.2019.04.014.

[11] C.-P. Tan, Y.-Y. Lu, L.-N. Ji, Z.-W. Mao, Metallomics insights into the programmed cell death induced by metal-based anticancer compounds, Metallomic. 6 (5) (2014) 978, https://doi.org/10.1039/c3mt00225j.

[12] X. Lu, Y.C. Liu, C. Orvig, H. Liang, Z.F. Chen, Discovery of β-carboline copper(II) complexes as Mcl-1 inhibitor and in vitro and in vivo activity in cancer models, Eur. J. Med. Chem. 181 (2019), https://doi.org/10.1016/j.ejmech.2019.111567.

[13] H.-K. Liu, P.J. Sadler, Metal Complexes as DNA Intercalators, Acc. Chem. Res. 44 (5) (2011) 349–359, https://doi.org/10.1021/ar100140e.

[14] M. Pal, U. Nandi, D. Mukherjee, Detailed account on activation mechanisms of ruthenium coordination complexes and their role as antineoplastic agents, Eur. J. Med. Chem. 150 (2018) 419–445, https://doi.org/10.1016/j.ejmech.2018.03.015.

[15] C. Avendaño, J.C. Menéndez, anticancer drugs that interact with the DNA minor groove, Med. Chem. Anticancer Drugs (2015) 243–271, https://doi.org/10.1016/b978-0-444-62649-3.00006-5.

[16] K. Hevener, T.A. Verstak, K.E. Lutat, D.L. Riggsbee, J.W. Mooney, Recent developments in topoisomerase-targeted cancer chemotherapy, Acta Pharm. Sin. B. 8 (6) (2018) 844–861, https://doi.org/10.1016/j.apsb:2018.07.008.

[17] H. Tanzadehpanah, H. Mahaki, N.H. Moghadam, S. Salehzadeh, O. Rajabi, R. Najafi, R. Amini, M. Saidijam, Binding site identification of anticancer drug Gefitinib to HSA and DNA in the presence of five different probes, J. Biomol. Struct. Dyn. (2018), https://doi.org/10.1080/07391102.2018.1441073.

[18] A. Rescifina, C. Zagni, M.G. Varrica, V. Pistarà, A. Corsaro, Recent advances in small organic molecules as DNA intercalating agents: synthesis, activity, and modeling, Eur. J. Med. Chem. 74 (2014) 95–115, https://doi.org/10.1016/j.ejmech.2013.11.029.

[19] A. Bergamo, P.J. Dyson, G. Sava, The mechanism of tumour cell death by metal-based anticancer drugs is not only a matter of DNA interactions, Coord. Chem. Rev. 360 (2018) 17–33, https://doi.org/10.1016/j.ccr.2018.01.009.

[20] L. He, C.-P. Tan, R.-R. Ye, Y.-Z. Zhao, Y.-H. Liu, Q. Zhao, L.-N. Ji, Z.-W. Mao, Theranostic iridium(III) complexes as one- and two-photon phosphorescent trackers to monitor autophagic lysosomes, Angew. Chemie - Int. Ed. 53 (45) (2014) 12137–12141, https://doi.org/10.1002/anie.201407468.

[21] Z. Mao, L. He, S. Liao, C. Tan, Y. Lu, C. Xu, L. Ji, Cyclometalated iridium(III)-beta-carboline complexes as potent autophagy-inducing agents, ChemComm. 00 (2014) 1–3, https://doi.org/10.1039/C4CC01461H.

[22] M.A. Abdelsalam, O.M. AboulWafa, E.-S. Badawey, M.S. El-Shoukrofy, M.M. El-Miligy, N. Gouda, Design and synthesis of some β-carboline derivatives as multi-target anticancer agents, Future Med. Chem. 10 (24) (2018) 2791–2814.

[23] L. He, S.-Y. Liao, C.-P. Tan, R.-R. Ye, Y.-W. Xu, M. Zhao, L.-N. Ji, Z.-W. Mao, Ruthenium–Arene–b-carboline complexes as potent inhibitors of cyclin-dependent kinase 1: synthesis, characterization and anticancer mechanism studies, Chem. A Eur. J. 19 (2013) 12152–12160, https://doi.org/10.1002/chem.201301389.

[24] S. Li, X. Cheng, C. Wang, A review on traditional uses, phytochemistry, pharmacology, pharmacokinetics and toxicology of the genus Peganum, J. Ethnopharmacol. 203 (2017) 127–162, https://doi.org/10.1016/j.jep.2017.03.049.

[25] C.R. Sahoo, S.K. Paidesetty, R.N. Padhy, Norharmane as a potential chemical entity for development of anticancer drugs, Eur. J. Med. Chem. 162 (2019) 752–764, https://doi.org/10.1016/j.ejmech.2018.11.024.

[26] Z. Jiang, Q. You, X. Zhang, Medicinal chemistry of metal chelating fragments in metalloenzyme active sites: a perspective, Eur. J. Med. Chem. 165 (2019) 172–197, https://doi.org/10.1016/j.ejmech.2019.01.018.

[27] L. He, Y. Li, C.-P. Tan, R.-R. Ye, M.-H. Chen, J.-J. Cao, L.-N. Ji, Z.-W. Mao, Cyclometalated iridium(III) complexes as lysosome- targeted photodynamic anticancer and real-time tracking agents, Chem. Sci. (2015), https://doi.org/10.1039/c5sc01955a.

[28] L. He, Z. Pan, W. Qin, Y. Li, C. Tan, Z. Mao, Impairment of autophagy-related lysosomal degradation pathway by an anticancer rhenium(I) complex, Dalt Trans. (2019) 1–8, https://doi.org/10.1039/C9DT00322C.

[29] J. Kovvuri, B. Nagaraju, V.L. Nayak, R. Akunuri, M.P.N. Rao, A. Ajitha, N. Nagesh, A. Kamal, Design, synthesis and biological evaluation of new β-carboline-bisindole compounds as DNA binding, photocleavage agents and topoisomerase I inhibitors, Eur. J. Med. Chem. 143 (2018) 1563–1577, https://doi.org/10.1016/j.ejmech.2017.10.054.

[30] K.D. Mjos, C. Orvig, Metallodrugs in medicinal inorganic chemistry, Chem. Rev. (2014) A–X, https://doi.org/10.1021/cr400460s.

[31] D.-Y. Zhang, Y. Zheng, H. Zhang, J.-H. Sun, C.-P. Tan, L. He, W. Zhang, L.-N. Ji, Z.-W. Mao, Delivery of phosphorescent anticancer iridium(III) complexes by polydopamine nanoparticles for targeted combined photothermal-chemotherapy and thermal/photoacoustic/lifetime imaging, Adv. Sci. 5 (10) (2018) 1800581, https://doi.org/10.1002/advs.v5.1010.1002/advs.201800581.

[32] Y. Chen, M.Y. Qin, J.H. Wu, L. Wang, H. Chao, L.N. Ji, A.L. Xu, Synthesis, characterization, and anticancer activity of ruthenium(II)-β-carboline complex, Eur. J. Med. Chem. 70 (2013) 120–129, https://doi.org/10.1016/j.ejmech.2013.09.051.

[33] J. Sun, Q. Wei, Y. Zhou, J. Wang, Q. Liu, H. Xu, A systematic analysis of FDA-approved anticancer drugs, BMC Syst. Biol. 11 (S5) (2017), https://doi.org/10.1186/s12918-017-0464-7.

[34] C.C. Konkankit, S.C. Marker, K.M. Knopf, J.J. Wilson, Anticancer activity of complexes of the third row transition metals, rhenium, osmium, and iridium, Dalt. Trans. 47 (30) (2018) 9934–9974, https://doi.org/10.1039/C8DT01858H.

[35] T. Ogihara, T. Nakagawa, M. Hayashi, M. Koyanagi, A. Yonezawa, T. Omura, S. Nakagawa, N. Kitada, S. Imai, K. Matsubara, Improvement of peripheral vascular impairment by a phosphodiesterase type 5 inhibitor tadalafil prevents oxaliplatin-induced peripheral neuropathy in mice, J. Pharmacol. Sci. 141 (4) (2019) 131–138, https://doi.org/10.1016/j.jphs.2019.10.005.

[36] S. Thota, D.A. Rodrigues, D.C. Crans, E.J. Barreiro, Ru(II) compounds: next-generation anticancer metallotherapeutics?, J. Med. Chem. 61 (14) (2018) 5805–5821, https://doi.org/10.1021/acs.jmedchem.7b01689.

[37] C. Santini, M. Pellei, V. Gandin, M. Porchia, F. Tisato, C. Marzano, Advances in copper complexes as anticancer agents, Chem. Rev. 114 (2014) 815–862, https://doi.org/10.1021/cr400135x.

[38] L. Xie, Z. Luo, Z. Zhao, T. Chen, Anticancer and antiangiogenic iron(II) complexes that target thioredoxin reductase to trigger cancer cell apoptosis, J. Med. Chem. 60 (1) (2017) 202–214, https://doi.org/10.1021/acs.jmedchem.6b00917.

[39] J.-M. Yang, Y.-H. Zhu, S. Chen, X. Lu, Y.-M. Wu, F.-E. Ma, L.-P. Li, Y. Yang, Z.-H. Shi, K.-Y. Huang, X. Hong, P. Jiang, Y. Peng, A β-carboline derivative-based nickelIJII) complex as a potential antitumor agent: synthesis, characterization, and cytotoxicity, Medchemcomm 9 (2018) 100, https://doi.org/10.1039/c7md00428a.

[40] R. Ahmad Khan, K. Al-Farhan, A. de Almeida, A. Alsalme, A. Casini, M. Ghazzali, J. Reedijk, Light-stable bis(norharmane)silver(I) compounds: Synthesis, characterization and antiproliferative effects in cancer cells, J. Inorg. Biochem. 140 (2014) 1–5.

[41] M.R. Gill, J.A. Thomas, Ruthenium(II) polypyridyl complexes and DNA—from structural probes to cellular imaging and therapeutics, Chem. Soc. Rev. 41 (2012) 3179–3192, https://doi.org/10.1039/c2cs15299a.

[42] R.A. Khan, A. de Almeida, K. Al-Farhan, A. Alsalme, A. Casini, M. Ghazzali, J. Reedijk, Transition-metal norharmane compounds as possible cytotoxic agents: new insights based on a coordination chemistry perspective, J. Inorg. Biochem. 165 (2016) 128–135, https://doi.org/10.1016/j.jinorgbio.2016.07.001.

[43] K. Lin, Z.Z. Zhao, H. Ben Bo, X.J. Hao, J.Q. Wang, Applications of ruthenium complex in tumor diagnosis and therapy, Front. Pharmacol. 9 (2018), https://doi.org/10.3389/fphar.2018.01323.

[44] J. Chen, F. Peng, Y. Zhang, B. Li, J. She, X. Jie, Z. Zou, M. Chen, L. Chen, Synthesis, characterization, cellular uptake and apoptosis-inducing properties of two highly cytotoxic cyclometalated ruthenium(II) β-carboline complexes, Eur. J. Med. Chem. 140 (2017) 104–117, https://doi.org/10.1016/j.ejmech.2017.09.007.

[45] C. Imberti, P. Zhang, H. Huang, P.J. Sadler, New designs for phototherapeutic transition metal complexes, Angew. Chem. 132 (1) (2020) 61–73, https://doi.org/10.1002/ange.201905171.

[46] R.K. Sodhi, S. Paul, Metal complexes in medicine: an overview and update from drug design perspective, Cancer Ther. Oncol. Int. J. 14 (2019), https://doi.org/10.1016/j.molliq.2020.113695 555883.

[47] I. Maisuls, E. Wolcan, O.E. Piro, G.A. Echeverría, G. Petroselli, R. Erra-Balsells, F. M. Cabrerizo, G.T. Ruiz, Norharmane Rhenium(I) polypyridyl complexes: synthesis, structural and spectroscopic characterization, Dalt. Trans. (2015) 1–27, https://doi.org/10.1039/C5DT02790J.

[48] I. Maisuls, E. Wolcan, O.E. Piro, E.E. Castellano, G. Petroselli, R. Erra-Balsells, F. M. Cabrerizo, G.T. Ruiz, Synthesis, structural characterization and biological evaluation of Rhenium(I) tricarbonyl complexes with β-carboline ligands, ChemistrySelect 2 (27) (2017) 8666–8672, https://doi.org/10.1002/slct.201701961.

[49] I. Maisuls, F.M. Cabrerizo, A.G. Lappin, G.T. Ruiz, G.J. Ferraudi, Photophysical properties of [(norharmane)Re(CO)3 (L)]+ complexes (L = bpy, phen or dppz). Redox behavior of the excited states and their interaction with Calf Thymus DNA, J. Photochem. Photobiol. A Chem. 364 (2018) 169–176, https://doi.org/10.1016/j.jphotochem.2018.05.007.
[50] G. Stelzer, N. Rosen, I. Plaschkes, S. Zimmerman, M. Twik, S. Fishilevich, T.I. Stein, R. Nudel, I. Lieder, Y. Mazor, S. Kaplan, D. Dahary, D. Warshawsky, Y. Guan-Golan, A. Kohn, N. Rappaport, M. Safran, D. Lancet, The GeneCards suite: from gene data mining to disease genome sequence analyses, Curr. Protoc. Bioinform. 54 (1) (2016), https://doi.org/10.1002/cpbi.5.
[51] Lantheus Medical Imaging Inc., Gallium Citrate Ga 67 Injection for Diagnostic Use, (2012) pp. 3–8. <https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/017478s016lbl.pdf>.
[52] D.S. Wishart, Y.D. Feunang, A.C. Guo, E.J. Lo, A. Marcu, J.R. Grant, T. Sajed, D. Johnson, C. Li, Z. Sayeeda, N. Assempour, I. Iynkkaran, Y. Liu, A. Maciejewski, N. Gale, A. Wilson, L. Chin, R. Cummings, D. Le, A. Pon, C. Knox, M. Wilson, DrugBank 5.0: a major update to the DrugBank database for 2018, Nucleic Acids Res. 46 (2018), https://doi.org/10.1093/nar/gkx1037.
[53] J. Tian, B. Huang, M.H. Nawaz, W. Zhang, Recent advances of multi-dimensional porphyrin-based functional materials in photodynamic therapy, Coord. Chem. Rev. 420 (2020) 213410, https://doi.org/10.1016/j.ccr.2020.213410.
[54] S.U. Dighe, S. Khan, I. Soni, P. Jain, S. Shukla, R. Yadav, P. Sen, S.M. Meeran, S. Batra, Synthesis of B-carboline-based N-heterocyclic carbenes and their anti-proliferative and anti-metastatic activities against human breast cancer cells, J. Med. Chem. (2015) 1–47, https://doi.org/10.1021/acs.jmedchem.5b00016.
[55] S. Kuwata, T. Ikariya, Metal–ligand bifunctional reactivity and catalysis of protic N-heterocyclic carbene and pyrazole complexes featuring b-NH units, ChemComm 50 (2014) 14290–14300, https://doi.org/10.1039/c4cc04457f.
[56] Z.-F. Chen, Y.-C. Liu, K.-B. Huang, H. Liang, Alkaloid-metal based anticancer agents, Curr. Top. Med. Chem. 13 (2013) 2104–2115, https://doi.org/10.2174/15680266113139990146.
[57] C.H. Ding, X.L. Hou, Nucleophiles with allyl metal complexes, Compr. Org. Synth. Second Ed. 4 (2014) 648–698, https://doi.org/10.1016/B978-0-08-097742-3.00415-8.
[58] L. Salassa, Polypyridyl metal complexes with biological activity, Eur. J. Inorg. Chem. 2011 (32) (2011) 4931–4947, https://doi.org/10.1002/ejic.201100376.
[59] C. Tan, S. Lai, S. Wu, S. Hu, L. Zhou, Y. Chen, M. Wang, Y. Zhu, W. Lian, W. Peng, L. Ji, A. Xu, Nuclear permeable ruthenium(II) β-carboline complexes induce autophagy to antagonize mitochondrial-mediated apoptosis, J. Med. Chem. 53 (21) (2010) 7613–7624, https://doi.org/10.1021/jm1009296.
[60] C. Tan, S. Wu, S. Lai, M. Wang, Y. Chen, L. Zhou, Y. Zhu, W. Lian, W. Peng, L. Ji, A. Xu, Synthesis, structures, cellular uptake and apoptosis-inducing properties of highly cytotoxic ruthenium-Norharman complexes, Dalt. Trans. 40 (2011) 8611–8621, https://doi.org/10.1039/c1dt10084j.
[61] E. Wolcan, Photosensitized generation of singlet oxygen from rhenium(I) complexes: a review, Inorg. Chim. Acta. 509 (2020) 119650, https://doi.org/10.1016/j.ica.2020.119650.
[62] J. Dai, W. Dan, U. Schneider, J. Wang, European Journal of Medicinal Chemistry b -Carboline alkaloid monomers and dimers: occurrence, structural diversity, and biological activities, Eur. J. Med. Chem. 157 (2018) 622–656, https://doi.org/10.1016/j.ejmech.2018.08.027.
[63] C.E.P. Galvis, V.V. Kouznetsov, Novel approaches in the synthesis of natural and synthetic fused Aza-polycycles toward the development of new bioactive compounds, Stud. Nat. Prod. Chem., Elsevier (2018) 1–51, https://doi.org/10.1016/B978-0-444-64058-1.00001-7.
[64] Q.-M. Jin, Y. Lu, J.-L. Jin, H. Guo, G.-W. Lin, Y. Wang, T. Lu, Synthesis, characterization, DNA binding ability and cytotoxicity of the novel Platinum (II), Copper(II), Cobalt(II) and Nickel(II) complexes with 3-(1H-benzo[d] imidazol-2-yl)-β-carboline, Inorg. Chim. Acta. 421 (2014) 91–99, https://doi.org/10.1016/j.ica.2014.05.036.
[65] J. Yu, Q. Chen, The plant extract of Pao pereira potentiates carboplatin effects against ovarian cancer, Pharm. Biol. 52 (1) (2014) 36–43, https://doi.org/10.3109/13880209.2013.808232.
[66] A. Dey, A. Mukherjee, M. Chaudhury, Alkaloids from apocynaceae: origin, pharmacotherapeutic properties, and structure-activity studies, Stud. Nat. Prod. Chem. 52 (2017) 373–488, https://doi.org/10.1016/B978-0-444-63931-8.00010-2.
[67] A. Carvalhoa, J. Chub, C. Meinguet, R. Kissa, G. Vandenbusscheb, B. Masereelc, J. Woutersc, A. Kornienkoe, J. Pelletier, V. Mathieu, A harmine-derived beta-carboline displays anti-cancer effects in vitro by targeting protein synthesis, Eur. J. Pharmacol. 805 (2017) 25–35, https://doi.org/10.1016/j.ejphar.2017.03.034.
[68] P.A. Barsanti, W. Wang, Z.-J. Ni, D. Duhl, N. Brammeier, E. Martin, D. Bussiere, A.O. Walter, The discovery of tetrahydro-β-carbolines as inhibitors of the kinesin Eg5, Bioorg. Med. Chem. Lett. 20 (1) (2010) 157–160, https://doi.org/10.1016/j.bmcl.2009.11.012.
[69] X.-F. Zhang, R. Sun, Y. Jia, Q. Chen, R. Tu, K. Li, X. Zhang, R. Du, R. Cao, Synthesis and mechanisms of action of novel harmine derivatives as potential antitumor agents, Sci. Rep. 6 (1) (2016), https://doi.org/10.1038/srep33204.
[70] Y. Ding, J. He, J. Huang, T. Yu, X. Shi, T. Zhang, G. Yan, S. Chen, C. Peng, Harmine induces anticancer activity in breast cancer cells via targeting TAZ, Int. J. Oncol. 54 (2019) 1995–2004, https://doi.org/10.3892/ijo.2019.4777.
[71] M. Sathish, S. Chetan Dushantrao, S. Nekkanti, R. Tokala, S. Thatikonda, Y. Tangella, G. Srinivas, S. Cherukommu, N. Hari Krishna, N. Shankaraiah, N. Nagesh, A. Kamal, Synthesis of DNA interactive C3-trans-cinnamide linked β-carboline conjugates as potential cytotoxic and DNA topoisomerase I inhibitors, Bioorg. Med. Chem. 26 (17) (2018) 4916–4929, https://doi.org/10.1016/j.bmc.2018.08.031.
[72] N. Shankaraiah, K.P. Siraj, S. Nekkanti, V. Srinivasulu, P. Sharma, K. Ram, M. Sathish, M.V.P.S. Vishnuvardhan, S. Ramakrishna, C. Jadala, N. Nagesh, A. Kamal, Bioorganic chemistry DNA-binding affinity and anticancer activity of b -carboline – chalcone conjugates as potential DNA intercalators: molecular modelling and synthesis, Bioorg. Chem. 59 (2015) 130–139, https://doi.org/10.1016/j.bioorg.2015.02.007.
[73] A. Kamal, V. Srinivasulu, V.L. Nayak, M. Sathish, N. Shankaraiah, C. Bagul, N.V.S. Reddy, N. Rangaraj, N. Nagesh, Design and synthesis of C3-pyrazole/chalcone-linked beta-carboline hybrids: antitopoisomerase I. DNA-interactive, and apoptosis-inducing anticancer agents, ChemMedChem 9 (9) (2014) 2084–2098, https://doi.org/10.1002/cmdc.201300406.
[74] X. Li, A.K. Gorle, M.K. Sundaraneedi, F.R. Keene, J.G. Collins, Kinetically-inert polypyridylruthenium(II) complexes as therapeutic agents, Coord. Chem. Rev. 375 (2018) 134–147, https://doi.org/10.1016/j.ccr.2017.11.011.
[75] X. Chen, L. Guo, Q. Ma, W. Chen, W. Fan, J. Zhang, Design, synthesis, and biological evaluation of novel N-acylhydrazone bond linked heterobivalent β-carbolines as potential anticancer agents, Molecules 24 (2019) 1–19, https://doi.org/10.3390/molecules24162950.
[76] Z. Kovács, T. Jernei, D. Katona, L. Kocsis, A. Csámpai, Synthesis and structure of novel ferrocene-containing β-carbolines including polycondensed derivatives with the elements of planar-, central- and conformational chirality, J. Organomet. Chem. 794 (2015) 125–135, https://doi.org/10.1016/j.jorganchem.2015.07.004.
[77] M.M. Gonzalez, F.A.O. Rasse-Suriani, C.A. Franca, R.P. Diez, Y. Gholipour, H. Nonami, R. Erra-Balsells, F.M. Cabrerizo, Photosensitized electron transfer within a self-assembled norharmane–2′-deoxyadenosine 5′-monophosphate (dAMP) complex, Org. Biomol. Chem. 10 (2012) 9359–9372, https://doi.org/10.1039/c2ob26462e.
[78] Z.C. Kadirova, S.A. Chepulsky, N.A. Parpiev, S.A. Talipov, K.T. Sharipov, Bis(7-methoxy-1-methyl-4,9-dihydro-3H- b-carbolinium) tetrachloridozincate, Acta Crystallogr. E66 (2010), https://doi.org/10.1107/S1600536810010822 m473.
[79] A. Zamora, G. Vigueras, V. Rodríguez, M.D. Santana, J. Ruiz, Cyclometalated iridium(III) luminescent complexes in therapy and phototherapy, Coord. Chem. Rev. 360 (2018) 34–76, https://doi.org/10.1016/j.ccr.2018.01.010.
[80] P. Štarha, Z. Trávníček, Azaindoles: suitable ligands of cytotoxic transition metal complexes, J. Inorg. Biochem. 197 (2019) 110695, https://doi.org/10.1016/j.jinorgbio.2019.110695.
[81] A. Sharma S, S. P, N. Roy, P. Paira, Advances in Novel Iridium (III) based complexes for anticancer applications. A review, Inorganica Chim. Acta. 513 (2020) 119925, https://doi.org/10.1016/j.ica.2020.119925.
[82] K. Qiu, H. Zhu, T.W. Rees, L. Ji, Q. Zhang, H. Chao, Recent advances in lysosome-targeting luminescent transition metal complexes, Coord. Chem. Rev. 398 (2019) 113010, https://doi.org/10.1016/j.ccr.2019.07.007.
[83] C.N. Ko, G. Li, C.H. Leung, D.L. Ma, Dual function luminescent transition metal complexes for cancer theranostics: the combination of diagnosis and therapy, Coord. Chem. Rev. 381 (2019) 79–103, https://doi.org/10.1016/j.ccr.2018.11.013.
[84] P.-Y. Ho, C.-L. Ho, W.-Y. Wong, Recent advances of iridium(III) metallophosphors for health-related applications, Coord. Chem. Rev. 413 (2020) 213267, https://doi.org/10.1016/j.ccr.2020.213267.
[85] S. Salman, F. Idrees, S. Pervaiz, F.H. Shah, S. Badshah, M. Abdullah, S.M.A. Usman, J.I. Halimi, Evaluation of antimicrobial activities of Harmine, Harmaline, Nicotine and their complexes, Pak. J. Pharm. Sci. 29 (2016) 1317–1320.
[86] L. He, K. Wang, Y. Zheng, J. Cao, M. Zhang, C. Tan, L. Ji, Z. Mao, Cyclometalated iridium(III) complexes induce mitochondria-derived paraptotic cell death and inhibit tumor growth in vivo, Dalt Trans. (2018) 1–12, https://doi.org/10.1039/C8DT00783G.
[87] R.J. Thatcher, D.G. Johnson, J.M. Slattery, R.E. Douthwaite, Charged behaviour from neutral ligands: synthesis and properties of N-heterocyclic pseudo-amides, Chem. - A Eur. J. 18 (14) (2012) 4329–4336, https://doi.org/10.1002/chem.v18.1410.1002/chem.201103319.
[88] X. Lu, Y.-C. Liu, C. Orvig, H. Liang, Z.-F. Chen, Discovery of a Copper-Based Mcl-1 Inhibitor as an Effective Antitumor Agent, J. Med. Chem. 63 (17) (2020) 9154–9167, https://doi.org/10.1021/acs.jmedchem.9b02047.
[89] Y. Chen, M.-Y. Qin, L. Wang, H. Chao, L.-N. Ji, A.-L. Xu, A ruthenium(II) β-carboline complex induced p53-mediated apoptosis in cancer cells, Biochimie 95 (11) (2013) 2050–2059, https://doi.org/10.1016/j.biochi.2013.07.016.
[90] W. Qin, Z. Pan, D. Cai, Y. Li, L. He, Cyclometalated iridium(III) complexes for mitochondria-targeted combined chemo-photodynamic therapy, Dalt. Trans. (2020) 1–9, https://doi.org/10.1039/D0DT00180E.
[91] M. Amjadi, L. Farzampour, Selective turn-on fluorescence assay of 6–thioguanine by using harmine-modified silver nanoparticles, Luminescence 29 (6) (2014) 689–694, https://doi.org/10.1002/bio.2612.
[92] M. Amjadi, L. Farzampour, J.L. Manzoori, Study of the interaction of β-carbolines with gold nanoparticles and its application to turn-on fluorescence detection of silver ion, J. Photochem. Photobiol. A Chem. 286 (2014) 16–21, https://doi.org/10.1016/j.jphotochem.2014.04.011.
[93] N.A. Al-Shabib, F.M. Husain, R.A. Khan, M.S. Khan, M.Z. Alam, F.A. Ansari, S. Laeeq, M. Zubair, S.A. Shahzad, J.M. Khan, A. Alsalme, I. Ahmad, Interference of Phosphane Copper (I) complexes of β-carboline with quorum sensing regulated virulence functions and biofilm in foodborne pathogenic bacteria: a First Report, Saudi J. Biol. Sci. (2018), https://doi.org/10.1016/j.sjbs.2018.04.013.

[94] A. Alsalme, R.A. Khan, A.M. Alkathiri, M.S. Ali, S. Tabassum, M. Jaafar, H.A. Al-Lohedan, β-Carboline silver compound binding studies with human serum albumin: a comprehensive multispectroscopic analysis and molecular modeling study, Bioinorg. Chem. Appl. 2018 (2018) 1–11, https://doi.org/10.1155/2018/9782419.
[95] R.A. Khan, F. Dielmann, X. Liu, F.E. Hahn, K. Al-Farhan, A. Alsalme, J. Reedijk, Tetrahedrally coordinated luminescent copper(I) compounds containing halide, phosphane and norharmane ligands, Polyhedron 111 (2016) 173–178, https://doi.org/10.1016/j.poly.2016.03.046.
[96] L. Wang, Y. Wang, Y. Chai, Y. Kang, C. Sun, S. Zeng, Nickel (II)-assisted enantiomeric differentiation and quantitation of tadalafil by direct electrospray ionization mass spectrometry, J. Mass Spectrom. 52 (7) (2017) 411–416, https://doi.org/10.1002/jms.3939.
[97] C. Praveen, Carbophilic activation of π-systems via gold coordination: Towards regioselective access of intermolecular addition products, Coord. Chem. Rev. 392 (2019) 1–34, https://doi.org/10.1016/j.ccr.2019.04.010.