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Review

Biomedical applications of selective metal complexes of indole, benzimidazole, benzothiazole and benzoxazole: A review (From 2015 to 2022)

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ABSTRACT

Indole, benzoxazole benzothiazole and benzimidazole are excellent classes of organic heterocyclic compounds. These compounds show significant application in pharmacy, industries, dyes, medicine, polymers and food packages. These compounds also form metal complexes with copper, zinc, cadmium, nickel, cobalt, platinum, gold, palladium chromium, silver, iron, and other metals that have shown to be significant applications. Recently, researchers have attracted enormous attention toward heterocyclic compounds such as indole, benzimidazole, benzothiazole, benzoxazole, and their complexes due to their excellent medicinal applications such as anti-ulcerogenic, anti-cancer, antihypertensive, antifungal, anti-inflammatory, antitubercular, antiparasitic, anti-obesity, antimalarial, antiglycation, antiviral potency, antineuropathic, analgesic antioxidant, antihistaminic, and antibacterial potentials. In this article, we summarize the medicinal applications of these compounds as well as their metal complexes. We hope this article will help researchers in designing and synthesizing novel and potent compounds with significant applications in various fields.

Contents

1. Introduction

Organic heterocyclic compounds containing sulfur, oxygen and nitrogen are very important organic compounds having excellent applications in pharmacy, industries, medicine, sensing, food packages and other fields. (Al-Saidi and Khan, 2022a, 2022b; Aljaar et al., 2019; Alrooqi et al., 2022; Gemili et al., 2019; Gul et al.,

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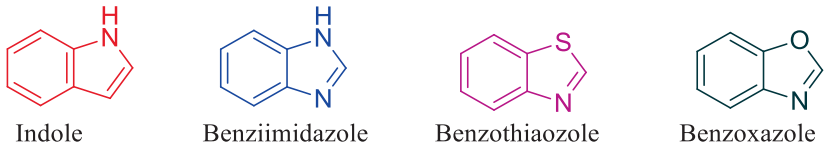


Fig. 1. Chemical structure of Indole, benzoimidazole, benzothiaozole and benzoxazole.

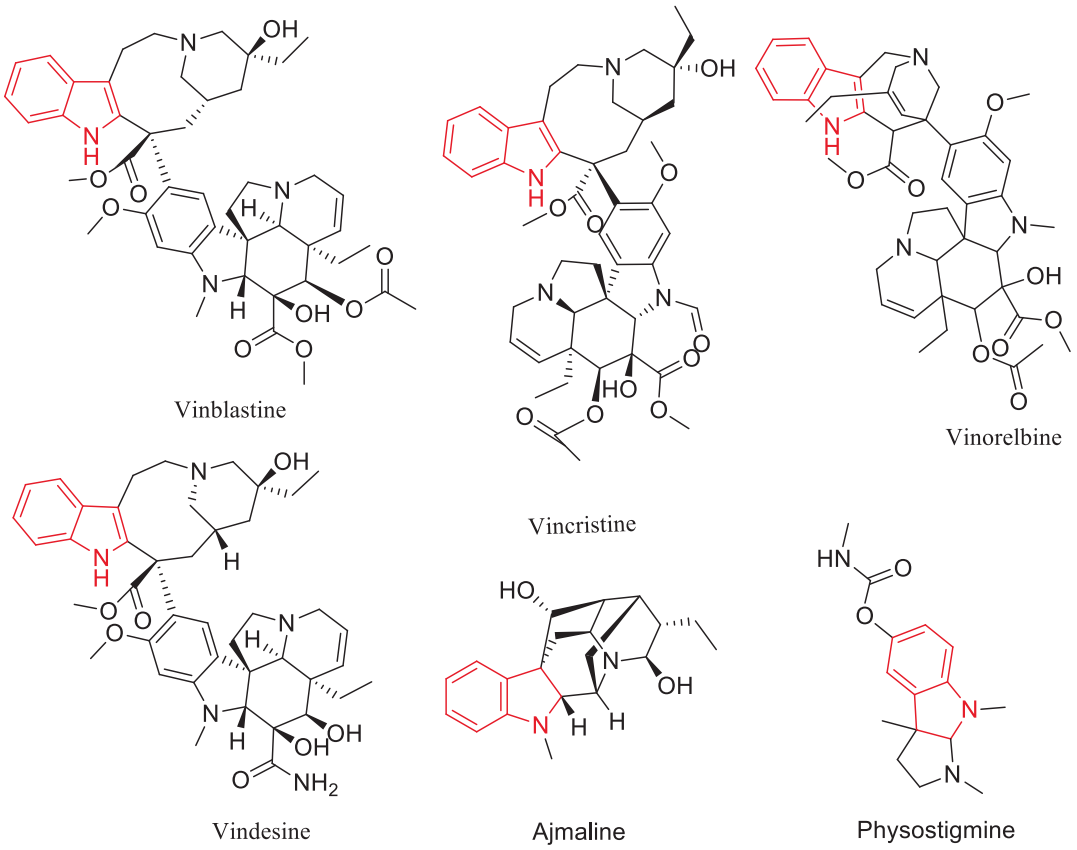


Fig. 2. Indole-based FDA approved drugs for the treatment of Alzheimer's, cancer, glaucoma.

2022; Kabi et al., 2022b; Khan et al., 2020, 2022a, 2022b; Mohammad Abu-Taweel et al., 2022; Muhammad et al., 2022). These compounds have excellent biological applications such as anti-ulcerogenic, anti-cancer, antihypertensive, antifungal, anti-inflammatory, antitubercular, antiparasitic, anti-obesity, antimalarial, antiglycation, antiviral potency, antineuropathic, analgesic antioxidant, antihistaminic, and antibacterial potentials (Aljaar et al., 2023, 2015, 2013; Gujjarappa et al., 2022, 2020; Kabi et al., 2022a; Kaldhi et al., 2019; Shafiei et al., 2020; Vodnala et al., 2018). Indole nucleus (Fig. 1) occupied a unique place in the chemistry of nitrogen-containing organic heterocyclic compounds, due to their diverse biodynamic properties. (Mielczarek et al., 2015; Thanikachalam et al., 2019) This nucleus is present in different physiologically important compounds including reserpine, lysergic acid, indole-3-acetic acid, diethylamide, serotonin, tryptophan, and gramine as well as in important antibiotics like gliotoxin and mitomycin (Rahaman and Mruthyunjayaswamy, 2014). Indole is also very important for the synthesis of highly active pharmaceutical compounds (Norwood and Huigens, 2019). A number of bioactive compounds bearing indole ring have been reported to possess a wide range of biological properties like cardiovascular, antibacterial, anti-inflammatory, anticonvulsant, antiviral, antihistaminic, COX-2 inhibitory and antidepressant activities. Some naturally occurring indole derivatives have gained FDA approval, such as vindesine, vinblastine, vinorelbine and vincristine for the treatment of tumors; physostigmine for Alzheimer's disease and glaucoma and ajmaline(Fig. 2) for anti-arrhythmic activity (Chadha and Silakari, 2017).

Metal complexes of indole have been extensively researched for various therapeutic and biological activities in recent years. These complexes have proven to possess good biological applications like antiviral, anticancer, antimicrobial, anticonvulsant, antihypertensive, antiplatelet aggregation, and other activities (Devi et al., 2020; Haribabu et al., 2016; Varma et al., 2020). In addition, indole-containing compounds are bio-compatible and have excellent sensing applications in aqueous media, which contributed to bio-imaging. (Choe et al., 2021; Li et al., 2010; Rattanopas et al., 2019; Sain et al., 2015; Wang et al., 2022) Similarly, the benzimidazole moiety (Fig. 1) is a heterocyclic system in which the four and five positions of the imidazole ring is fused with a benzene ring (Gaba and Mohan, 2015). There are numerous naturally occurring molecules that include benzimidazole. The pharmaceutical industry has conducted substantial research on benzimidazole and its derivatives for a variety of biological activities that are helpful for drug the designing of novel drugs (Keri et al., 2015a; Wang et al., 2015).

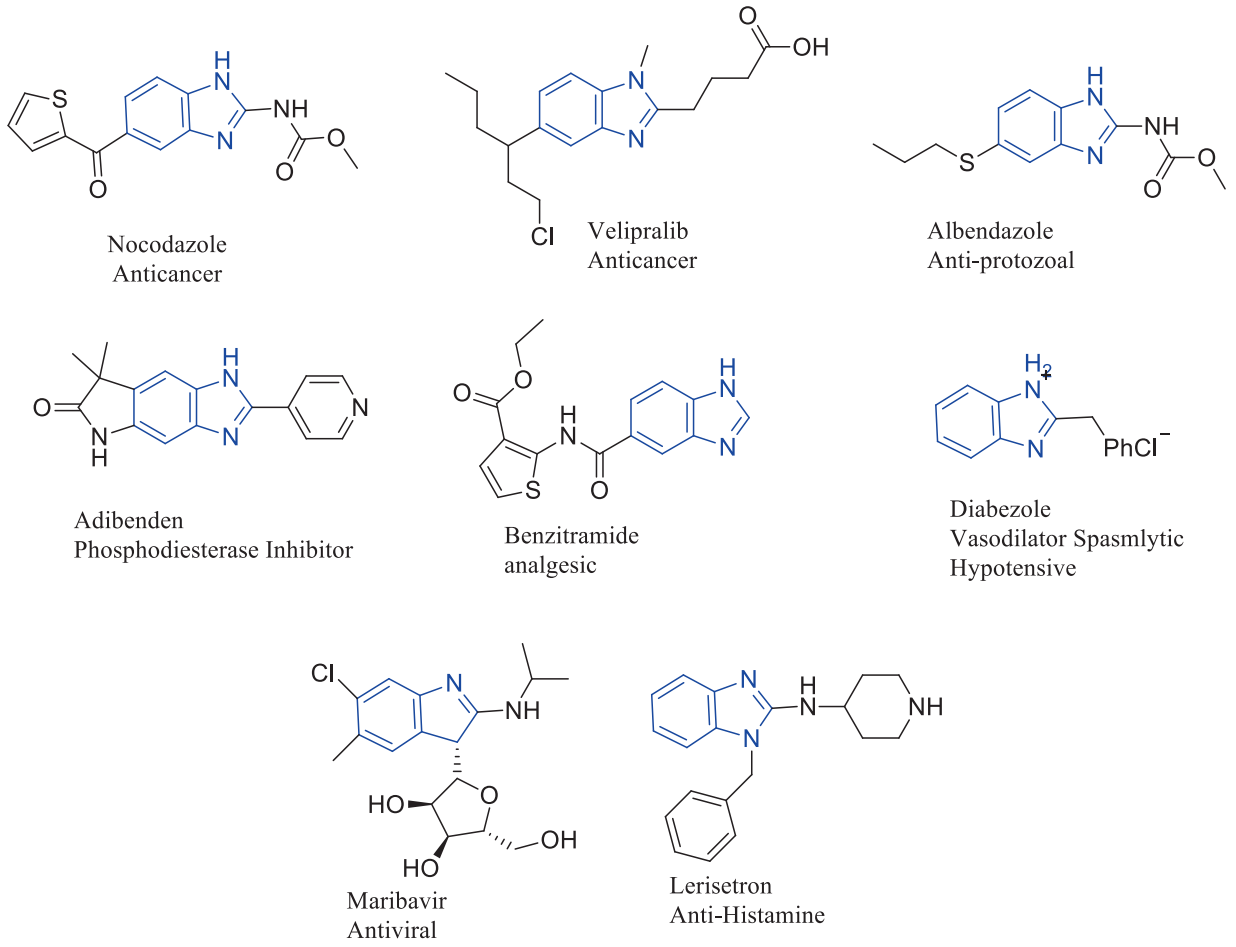


Fig. 3. Some benzimidazole-based drugs different diseases.

Anticoagulants, antiulcer, lipid level modulators, antihypertensives, anti-viral, immunomodulators, anti-tubercular, CNS stimulants & depressants, anti-malarial, anti-protozoal, hormone modulators, anticonvulsant, proton pump inhibitors and antifungal are some of the biological activities that have been reported for these compounds. A few benzimidazole based anticancer, anti-protozoal, anti-histamine, analgesic and antiviral drugs are shown in Fig. 3 which have been marketed. (Bansal and Silakari, 2012; G et al., 2022; Law and Yeong, 2021a; Wu et al., 2022) The various groups that were substituted on the benzimidazole core may have caused different effects. (Aragón-Muriel et al., 2021; Cichero et al., 2021; Law and Yeong, 2021b) As a result, changing the steric and electronic properties of the benzimidazole nucleus will considerably change their capacity to recognize the targeted enzymes and, consequently, their efficacy. The majority of benzimidazole-based medications contain substitutions at positions 1 and 2, which are crucial for biological activity (Keri et al., 2017; Law and Yeong, 2021b; Mavrova et al., 2015; Zhao et al., 2000). These

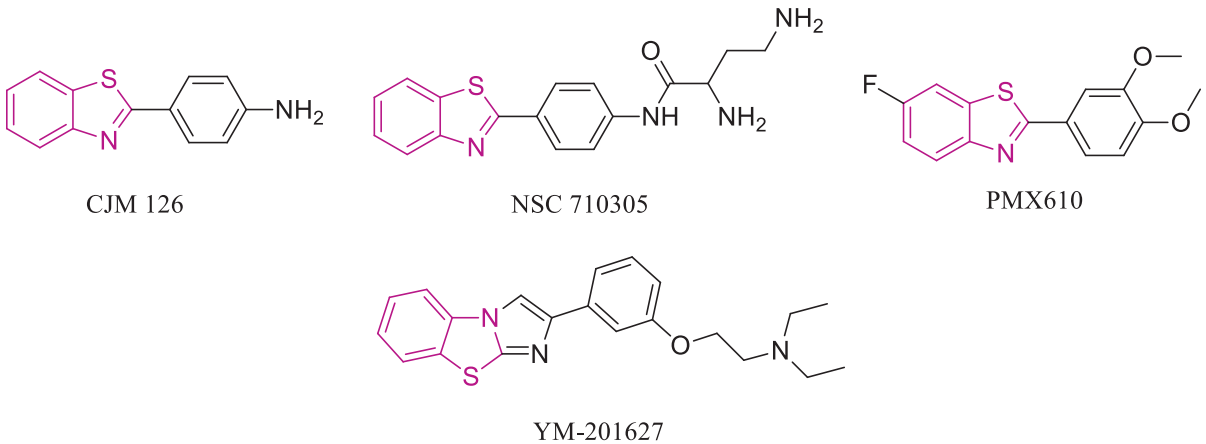


Fig. 4. Some benzothiazole-based anticancer drugs.

compounds can easily coordinate with different metal ions and formed stable metal complexes which play important role in agriculture, industries, and medicine.

Additionally, they are also used in dyes, polymers, dye-sensitized solar cells, (Ashraf et al., 2016; Han et al., 2018; Mahmood et al., 2019; Mohamed et al., 2009; Xiao et al., 2013; Xiu et al., 2011) and catalysts in various reactions, including the hydrogenation of nitroarenes, polymerization of butadiene, Suzuki-Miyaura coupling reactions, epoxidation reactions, and N-alkylation of amines with alcohols, and others reactions (Alexander et al., 2011; Cariou et al., 2010; Demir et al., 2014; Machura et al., 2014; Slimani et al., 2020; Zhang et al., 2011). Another significant organic heterocyclic molecule is benzothiazole, which consists of a benzene ring attached to a thiazole ring. Worldwide, benzothiazole derivatives are employed in a variety of therapeutic applications (Sharma et al., 2013). Numerous benzothiazole-containing analogues have excellent anti-inflammatory, antioxidant, anticonvulsant, antiviral, antimicrobial, anthelmintic, antitubercular, antiasthmatic, antihypertension, antischizophrenia, diuretic, antidiabetic, antimalarial, anticancer, analgesic, anticonvulsant, and antimalarial activities. (Kamal et al., 2015; Keri et al., 2015b; Pathak et al., 2019; Sharma et al., 2013). Some benzothiazole-based anticancer drugs are shown in Fig. 4 (Keri et al., 2015b). Recently, these compounds have been investigated as significant histamine H2 antagonists, LTD4 receptor antagonists, orexin receptor antagonists 2, fatty acid amide hydrolase inhibitors, and amyloid-binding diagnostic agents in neurodegenerative diseases. Additionally, they serve as plant protectors, dye intermediates, photographic sensitizers and imaging agents. These substances also hold a great deal of promise for the detection of several hazardous analytes (Khan et al., 2021; Pothulapadu et al., 2021; Sharma et al., 2013; Zhilitskaya et al., 2021). The complexes of benzothiazole are also used as catalyst for the synthesis of a wide variety of significant synthetic products. It facilitates numerous reactions including the Suzuki-Miyaura cross-coupling reaction, the epoxidation of *cis*-Cyclooctene, transamidation of carboxamide with primary amines, ethylene oligomerization, and intramolecular cyclization. (Gafurov et al., 2021; Vijayapritha and Viswanathamurthi, 2020; Wang et al., 2016, 2018).

Another heterocyclic aromatic system is benzoxazole **(**Fig. 1**)**, in which a benzene ring is fused with four, five-positions of oxazole (Wong and Yeong, 2021). Numerous natural compounds including the benzoxazole moiety, have significant biological applications. Benzoxazole has been used as a key pharmacophore and substructure in numerous pharmaceutical compounds because of its diverse biological characteristics. Many benzoxazole derivatives have been produced and tested for their biological potential, which showed significant antimicrobial, antitumor, anti-inflammatory, anti-histaminic, anti-parasitic, anti-allergic, anthelmintic, antitubercular, anticonvulsant, hypoglycemic, and antiviral potency. (Arulmurugan et al., 2020; Wong and Yeong, 2021) The benzoxazole derivatives have been also reported for the fluorescent and colorimetric sensor for the recognition of different pollutants which is an emerging attractive area of particular interest in chemical biology and analytical chemistry (Xu et al., 2014; Yang et al., 2016). Furthermore, the metal complexes of these compounds also showed excellent biological and catalytic activities (Balaghi et al., 2013; Sun et al., 2022).

2. Biological applications

The metal complexes of indole, benzimidazole, benzothiazole, and benzoxazole possess remarkable antibacterial, antifungal, anticancer and other biological activities. However, most organic compounds have been found to have limited bioavailability due to their rapid metabolism, hydrophobic nature and low intestinal absorption. Hence, to increase the pharmacological effects it is very important to enhance the solubility and bioavailability of these heterocyclic organic compounds. One approach is the formation of coordination compounds with different metals such as Pt, Pd, Au, Mn, Cu, Zn, Fe, Co, Ni, and many other metals to avoid these problems. (Afanas'eva et al., 2001; Ajibade and Ejidike, 2015; Dong et al., 2017).

3. Antimicrobial activities

A novel indole based Copper(II), Cobalt(II), Nickel(II) and Zinc(II) complexes **(MLC1-MLC4) (**Fig. 5**)** were synthesized. Different analytical methods were used to describe the structural characteristics of these compounds. According to the findings, Zn(II) complex **(MLC4)** formed tetrahedral geometry, while Copper(II), Cobalt(II), Nickel(II) **(MLC1-MLC3)** formed octahedral complexes. The antituberculosis, antifungal, antioxidant, and antibacterial activities of these complexes were evaluated. The **MLC1** and **MLC2** showed good antimicrobial potency against *E. coli* and *B. subtilis* with MICs of 12.50 μg/mL. These complexes **(MLC1-MLC3)** were also active against *M. tuberculosis* and showed similar activity in comparison with Ciprofloxacin with a MIC of 3.125 μg/mL. These findings may be beneficial in the designing of novel therapeutic compounds (Yernale et al., 2022). A mononuclear complexes of Sn(IV), Fe(III), Cd(II), and Cu(II) (**MLC5-MLC9**) and binuclear complexes of Hg(II) (**MLC10**) and Ni(II) (**MLC11**) with indole were designed and synthesized. All these compounds (**MLC5-MLC11**) were structurally characterized using thermogravimetry, 3D molecular modelling, elemental analyses, magnetic measurements, IR, ^{1}H NMR, UV–Visible and EPR. The fully characterize complexes were screened against E. coli, A.flavus, S. aureus and C. albicans. The findings showed that every complex exhibited batter antimicrobial activity than its parent ligand. The binuclear complex **(MLC10)** showed excellent antifungal efficacy against A. flavus, even better than Amphotericin B 67, demonstrated considerable antibacterial activity. (Mallikarjuna et al., 2018) Some bioactive metal complexes **(MLC12-MLC16) (**Fig. 6**)** of Fe(III), Ni(II), Cu(II), Co(II) and Zn(II) were prepared. The structure of these compounds were confirmed by NMR, IR, ESR, UV–Visible, elemental analysis, powder XRD, molar conductivity, mass, and magnetic susceptibility tests. Distorted square planar geometry for Ni (II) and Cu (II), tetrahedral geometry for Zn(II), and octahedral geometry for Fe (III) and Co (II) complexes were observed. The antimicrobial activity of the free ligand and their metal complexes was evaluated against *P. aeruginosa, E. coli, S. aureus, C. albicans*. The result showed that these complexes showed increased activities than free ligands. (Mallikarjuna et al., 2018) A novel Zn(II), Co(II), and Cu(II) **(MLC17-MLC19) (**Fig. 6**)** complexes of benzoimidazole with were designed and characterized by molar conductance, magnet measurements, AAS, FT-IR, NMR, and UV–Vis spectroscopy. The antimicrobial activities of the parent ligand and its metal complexes were evaluated. The result showed that the potency of free ligands enhanced upon coordinating with Cu(II), Zn(II), and Co(II). This is because the complex formation decreases the polarity of the metal cation due to the partial sharing of its positive charge with the nitrogen donor atoms of the ligand and the delocalization of π-electrons within the whole chelating ring. This process of complexation enhances the lipophilic nature of Cu^{2+}, Zn^{2+}, and Co^{2+}, which in turn favors its permeation through the lipid layer of the membrane. (Kalarani et al., 2020).

Two benzothiazole-based ligands were synthesized and treated with Co(II), Cd(II), Ni(II), Zn(II), and Cu(II) to synthesize their metal complexes **(MLC20-MLC29)** (Fig. 7). The formation of these compounds were invistigated by UV/vis, FT-IR, mass,elemental and

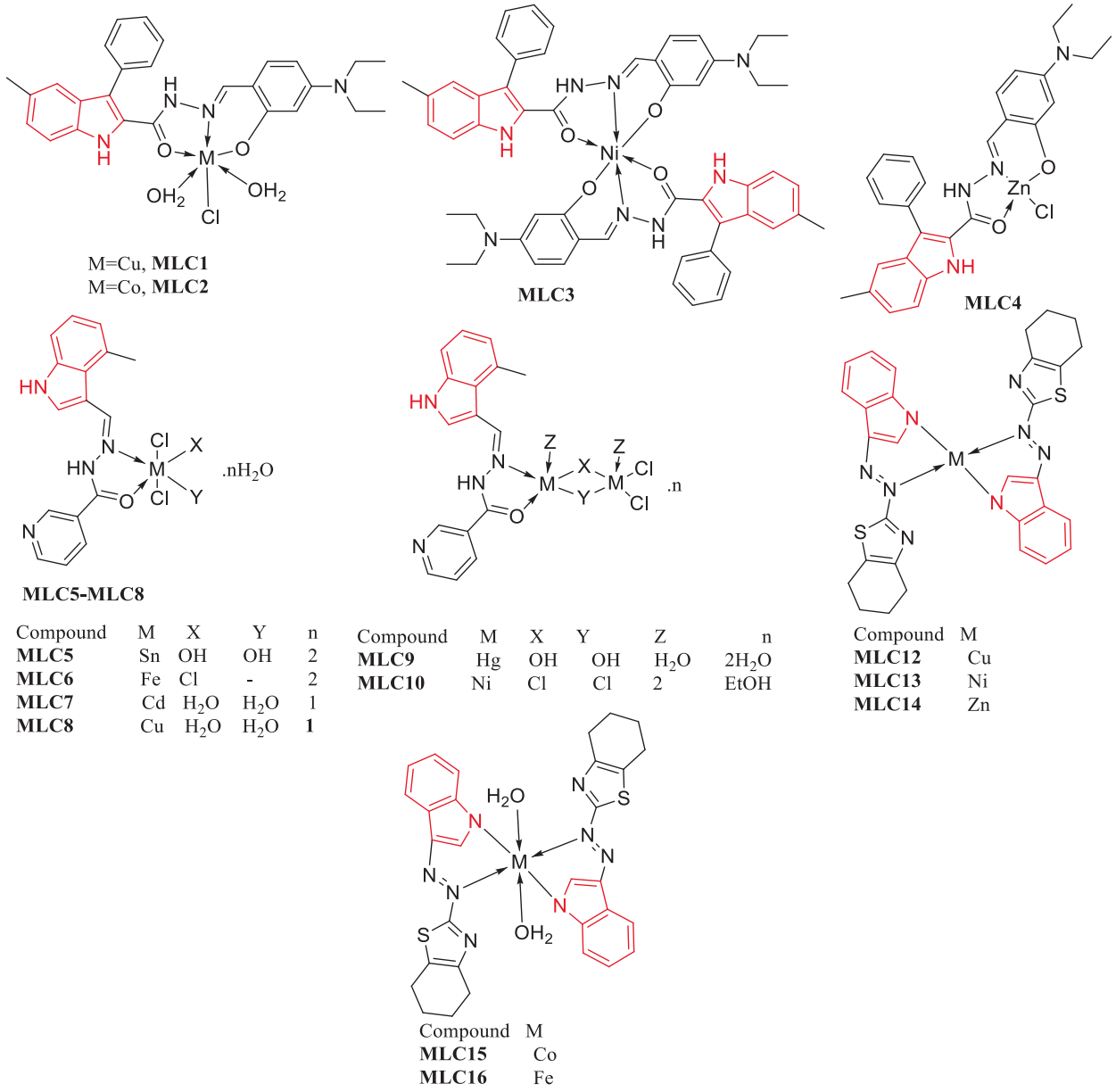


Fig. 5. Some Indole-based metal complexes as antimicrobial agents.

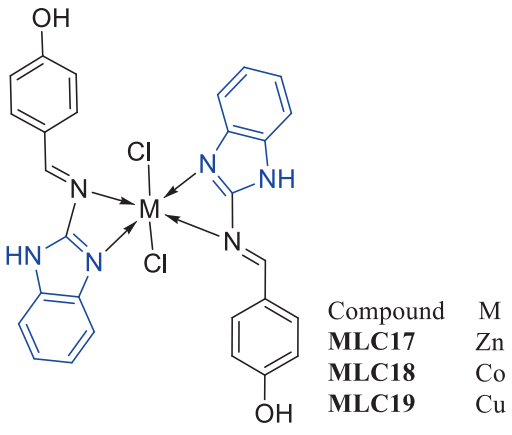


Fig. 6. Some Benzoimidazole-based metal complexes as antimicrobial agents.

NMR analyses. All the compounds were tested for their antimicrobial activities. The results demonstrated that each ligand and their complexes showed sensible activities against tested microbes. In a sharp comparison amongst **MLC20-MLC29**, complexes **MLC20-MLC23** and **MLC25-MLC28** exhibit good activities. The complex **MLC24** and **MLC29** show significant antimicrobial potency which is closer to Streptomycin. Further, the free ligands and their Zn (II) complexes additionally showed higher activities than Ni(II), Co(II) and Cu(II) complexes however less active than Cd(II) complexes. (Mishra et al., 2019) Two novel ligands of benzothiazole, as well as their complexes with Cu(II), Co(II)and Ni(II) **(MLC30-MLC35)** were synthesized and structurally diagnosed with SEM, NMR, EDX, TGA, UV–vis, mass, ESR, IR, powder XRD, magnetic moments, and elemental analysis. The above mentioned techniques support the square planer structures of all the metal complexes **(MLC30-MLC35)**. After structural charectarization the potency of these compounds were investigated toward *M. phaseolina*, *S. rolfsii, E. coli and B. amyloliquefaciens* strain. The results

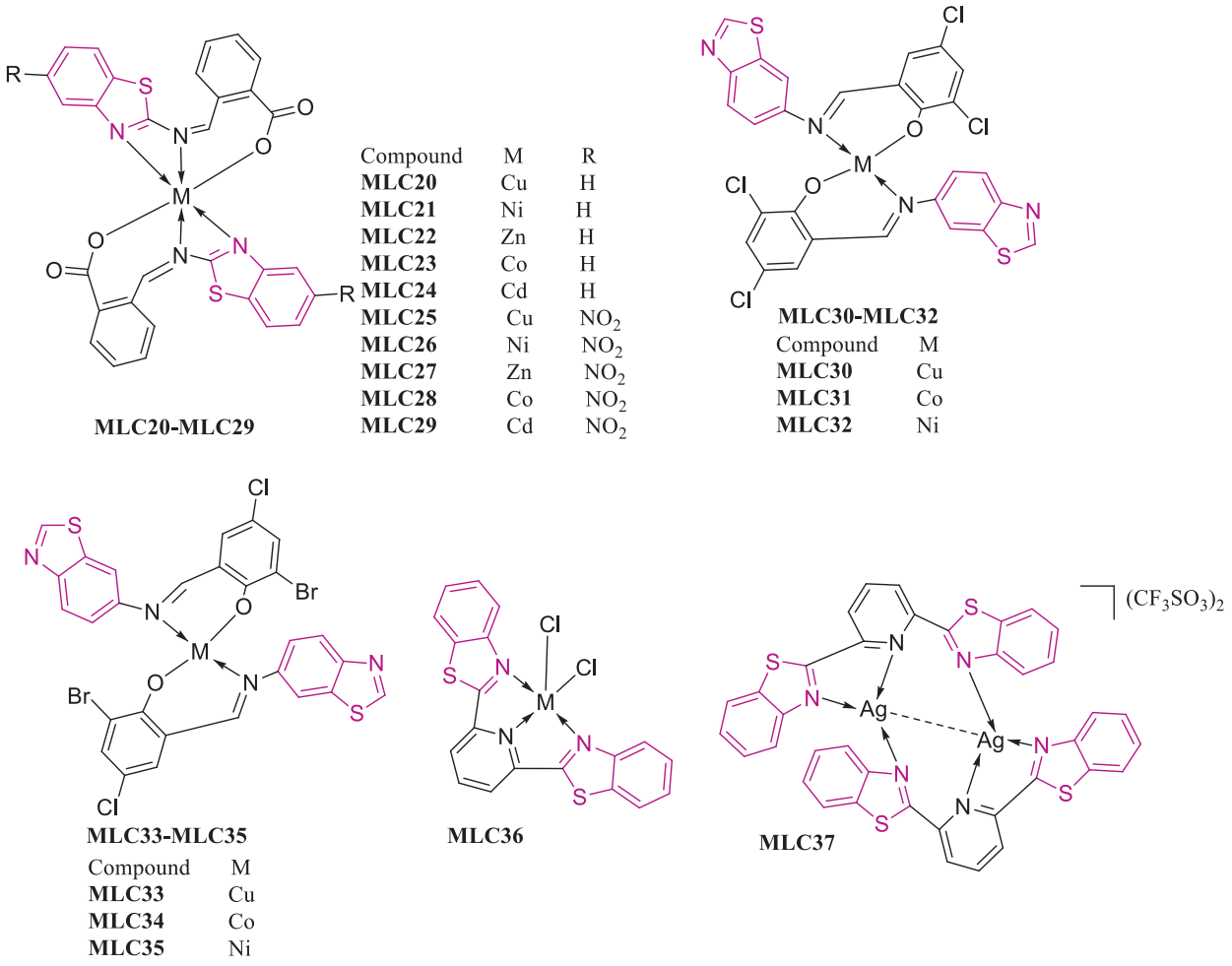


Fig. 7. Benzothiazole-based metal complexes as antimicrobial agents.

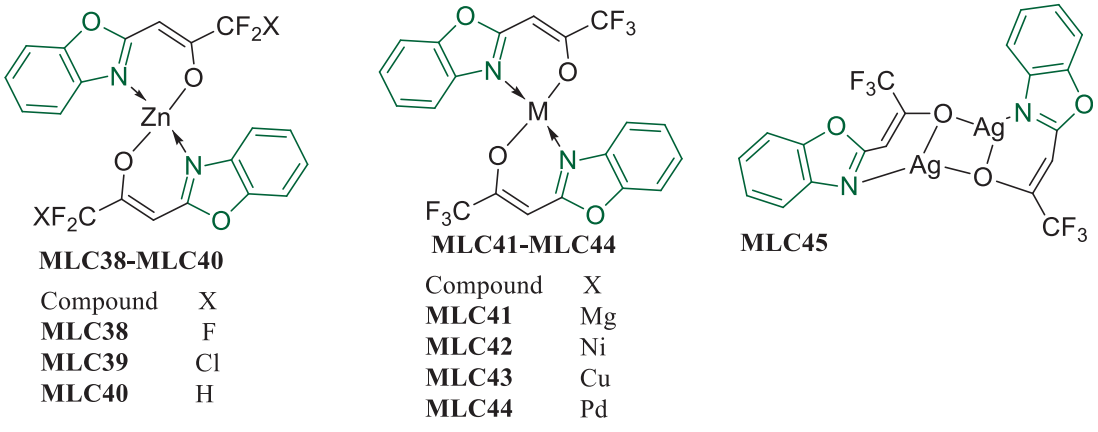


Fig. 8. Benzoxazole-based metal complexes as antimicrobial agents.

indicate larger inhibition space for the complexes than their free ligands, suggesting stronger square measure for metal complexes than free ligands. Among all the tested compounds, the Cu(II) complexes **MLC30** and **MLC33** show excellent activity against the tested micro organisms as compared to other compounds. (Daravath et al., 2017).

Two other novel complexes of Cu(II) and Ag(I) (**MLC36** and **MLC37**) with the ligands 2,6-bis(benzothiazole)-pyridine were designed and synthesized. The structure of both complexes were studied by various techniques, the result showed that **MLC36** was distorted square pyramidal, while the Ag(I) complex **MLC37**, adopt the highly distorted trigonal planar coordination geometry. After structural characterization, the antimicrobial activities of **MLC36** and **MLC37** were investigated against S epidermidis and A.baumannii. These complexes were found to be highly active, and show strong antimicrobial actions against all the tested bacterial strains (Chakraborty et al., 2019). Some Ni(II), Zn(II), Mg(II), Pd (II), Ag(I) and Cu(II) compounds (**MLC38-MLC45**) (Fig. 8) with 2-fluoroacetonylbenzoxazole ligands were prepared and structurally diagnosed with MS, IR, and single XRD analyses and were tested

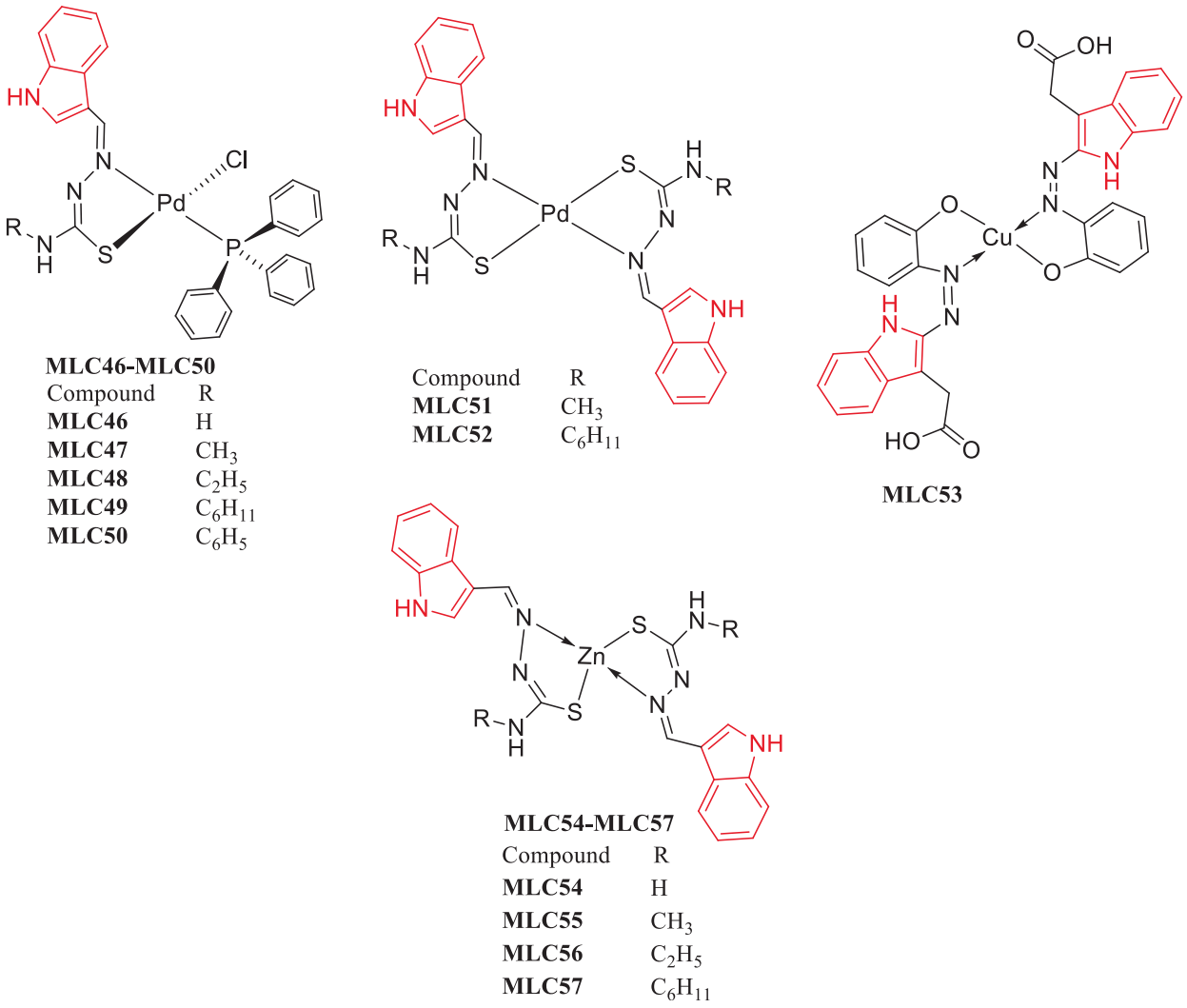
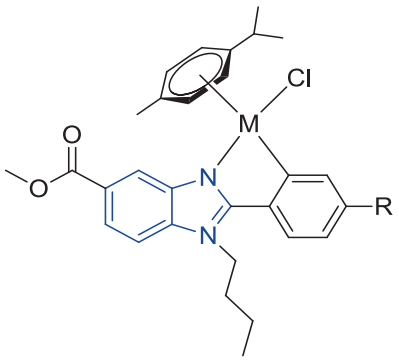


Fig. 9. Indole-based metal complexes as anticancer agents.

against different bacterial strains as antibacterial agent. These compounds were found to be active toward the tested bacterial strains and showed batter activity than free ligands. Among the these complexes, the Ag(I) complex showed batter activity (MIC = 0.7 μM) than Norfloxacin (MIC = 1.5 μM) against *P. aeruginosa*. (Watanabe et al., 2018) It is concluded from the above results that the antibacterial activities of indole, benzimidazole, benzothiazole, and benzoxazole increases upon coordination with metals that can be explained based on the Tweedy chelation theory and Overtone concept. According to the overtone concept of cell permeability, lipophilic compounds can be easily passed through the lipid membrane that surrounds the cell. So, lipophilicity is the main factor that controls the antimicrobial potency. Upon coordinating with ligand the polarity of metal cations is reducing and the delocalization of π-electrons over the chelating ring is enhancing. These phenomenon increased the lipophilic nature and enhancing the penetration of the metal complexes into the lipid membranes. (Watanabe et al., 2018).

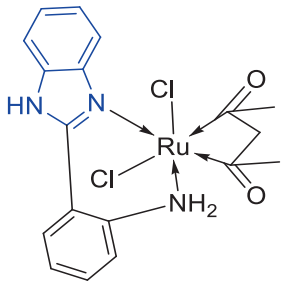
4. Anti-cancer activities

Metal complexes show excellent anticancer potency with certain organic ligands like indole, benzimidazole, benzothiazole and benzoxazole. For example, a novel Pd(II) complexes **(MLC46-MLC52)** (Fig. 9) with indole-3-carbaldehyde thiosemicarbazones were designed and prepared. The compounds were invistigated by ^{31}P NMR, ^{1}H–^{13}C HSQC, ^{1}H NMR, ^{1}H–^{31}P HMBC, ^{13}C NMR, ^{1}H–^{13}C HMBC, DEPT-NMR, ^{1}H–^{1}H COSY, mass FT-IR, UV–visible, and elemental analyses, and single XRD spectroscopic techniques. Crystallographic and spectroscopic studies confirm the coordination of N- and S- atoms of thiosemicarbazone with Pd(II) via the formation of a five-membered ring. The binding activities of all the metal complexes with DNA and bovine serum albumin (BSA) were assessed, which showed that compound **MLC49** and **MLC50** display a higher binding affinity with DNA with respect to other complexes, while the complex **MLC49** showed good binding affinity with BSA. All the complexes were also screened for their cytotoxic activities against three cancer cell lines including MCF7, HepG-2 andA549. These compounds showed moderate activity toward MCF7 and A549 cell lines and outstanding cytotoxic activity against HepG-2 and. The cell death through apoptosis was confirmed from the morphological changes in HepG-2 cancer cells assessed by staining and DNA fragmentation methods. The presence of triphenylphosphine and the bulkiness of the substituent at the terminal N- atom of thiosemicarbazone had a positive effect on the complexes. Therefore, **MLC49** and **MLC50** were the most promising compounds against the tested cancer cell lines. (Haribabu et al., 2018) A novel Cu(II) complex (**MLC53)** of indole based ligand was prepared and characterized by different

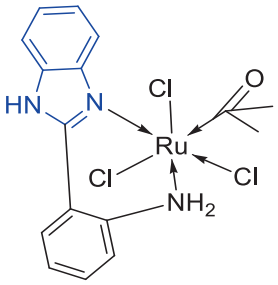


MLC58-MLC71

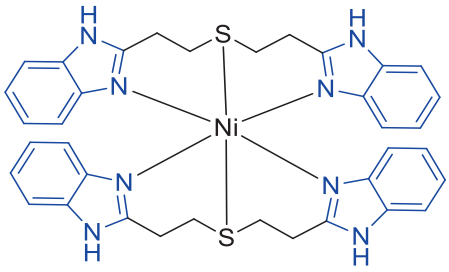
Compound	M	R	Compound	M	R
MLC58	Ru	H	**MLC65**	Ir	H
MLC59	Ru	CH_3	**MLC66**	Ir	CH_3
MLC60	Ru	F	**MLC67**	Ir	F
MLC61	Ru	CF_3	**MLC68**	Ir	CF_3
MLC62	Ru	OMe	**MLC69**	Ir	OMe
MLC63	Ru	NO2	**MLC70**	Ir	NO2
MLC64	Ru	Ph	**MLC71**	Ir	Ph



MLC72



MLC73



MLC74

Fig. 10. Benzimidazole-based metal complexes as anticancer agents.

techniques and their anticancer potency was screened against cancer cell lines (HCT116 and MOLT-4) as well as normal cell line (HEK293T). **MLC53** has lower IC_{50} values against all the tested cancer cell lines, while the complex showed comparable activity to that of ligand against HEK293T. The complex undergoes disturbance in one or more cellular processes like topoisomerase I inhibition etc. The complex shows cell-free topo I inhibition activities against both cancer cell lines. (Ganguly et al., 2017) Four new indole thiosemicarbazone containing Zn(II) complexes **(MLC54-MLC57)** were designed and synthesized and their DNA and BSA binding activities were studied. It was observed that the synthesized compounds interact well with DNA and BSA. Furthermore, the in vitro cytotoxic activities against cancer cell lines (MCF7 and A549) and non-cancerous cell lines (L929, HEK-293 and MCF-10A) were also performed. The data obtained show the best activity of these metal based compounds against MCF7 and A549 cancer cells. The **MLC54-MLC57** complexes IC_{50} values were found to be 91.2, 100.7, 50.2 and 37.9 μM respectively against the A549 and greater than 200 **(MLC54** and **MLC55**), 88.1 and 60.3 μM, respectively against the MCF7. In particular, the **MLC57** complex exhibited good antitumor activity toward A549 cancer cell lines and less toxicity toward non-cancerous cell lines. The fluorescence (Hoechst) staining study also confirmed the apoptosis cell death activity of **MLC57** in both the cancer cell lines (MCF7 and A549) (Balakrishnan et al., 2019).

A novel Ru(II) complexes (**MLC58**-**MLC64**) and Ir(III) complexes (**MLC65**-**MLC71**) **(**Fig. 10**)** of benzimidazole were prepared and screened for their cytotoxic activity toward different cell lines (A427, HT29, SISO, 5637, A2780cisR, LCLC, and A2780). The results demonstrated that the substitution of the phenyl ring at the R position increased the activity of **MLC64** and **MLC71** compared to free ligands in all cancer cell lines. However, the Ru(II) complexes (**MLC58**-**MLC64**) were more effective than the corresponding Ir (III) (**MLC65**-**MLC71** complexes. The Ru(II) and Ir(III complexes increased the caspase-3 activity in A2780 cells, as shown for **MLC58**, **MLC61, MLC65**, and **MLC68** compounds. The **MLC71** Ir (III) complex increases the production of ROS in A2780 cell lines. In addition, all the complexes have the ability to overcome the cisplatin resistance in A2780 cancer cell lines. Some of these complexes were able to inhibit angiogenesis in EA.hy926 at 0.5 μM concentration (Yellol et al., 2015). Another two novel ruthenium (II/III) complexes (**MLC72** and **MLC73)** containing benzimidazole ligand were designed and evaluated for their chemotherapeutic potential. Both the compounds were screened for their cytotoxic activity against two cancer cell lines (MCF7 and Caco2), as well as one normal cell line (THLE-2), in which the complex **MLC73** showed significant anticancer activities against both cell lines. The cytotoxicity of complex **MLC73** is correlated to cause cell apoptosis and cell cycle arrest inG2/M phase. Interestingly, these complexes were found to be inactive against THLE-2. The anticancer activity of **MLC73** were also investigated in an EhrlichAscites Carcinoma (EAC) mouse model. The anticancer potency was more pronounced in vivo, that help in the removal of the cancer burden at such a low dose that resulted in only low levels of nephrotoxicity and hepatotoxicity. Moreover, the **MLC73** reduce oxidative stress as well as increased the levels of antioxidant enzymes, particularly SOD, that reflect the improvement of normal cell repair (Elsayed et al., 2020). A novel Ni(II) complex **MLC74** with ligand 2-[2-[2-(1H-benzimidazol-2-yl)ethylsulfanyl]ethyl]-1H-benzimidazole was synthesized and characterized through XRD. The XRD data confirmed distorted octahedral geometry of the complex. The resulting **MLC73** complex was studied for its anticancer activities against cancer cell lines. That shows excellent anticancer activity. The malignant CACO-2 and MDA-MB-231 readily take the complex while the healthy Hs27 fibroblasts have little affinity for it. (Masaryk et al., 2021).

Two novel mononuclear and binuclear complexes of Pd(II) and Pt(II) (**MLC75** and **MLC76**) **(**Fig. 11**)** with 2,20 -dithiobis (benzothiazole) ligand were prepared and their structure were elucidated through MS spectrometry, ^{1}H NMR, ^{13}C NMR. elemental and FT-IR analysis. The result showed that the complex **MLC75** and **MLC76** display two different coordination modes; in mononuclear complexes of Pd(II) and Pt(II) the ligand are attached through N(3) atoms of the ligand however in binuclear metal complex **MLC75**, the chloride act as a bridging ligand between palladium ions. These complexes were probed and investigated for their anticancer activity against two cancer cell lines (MCF-7 and HepG2). It was observed that only **MLC76** displayed time and dose dependent

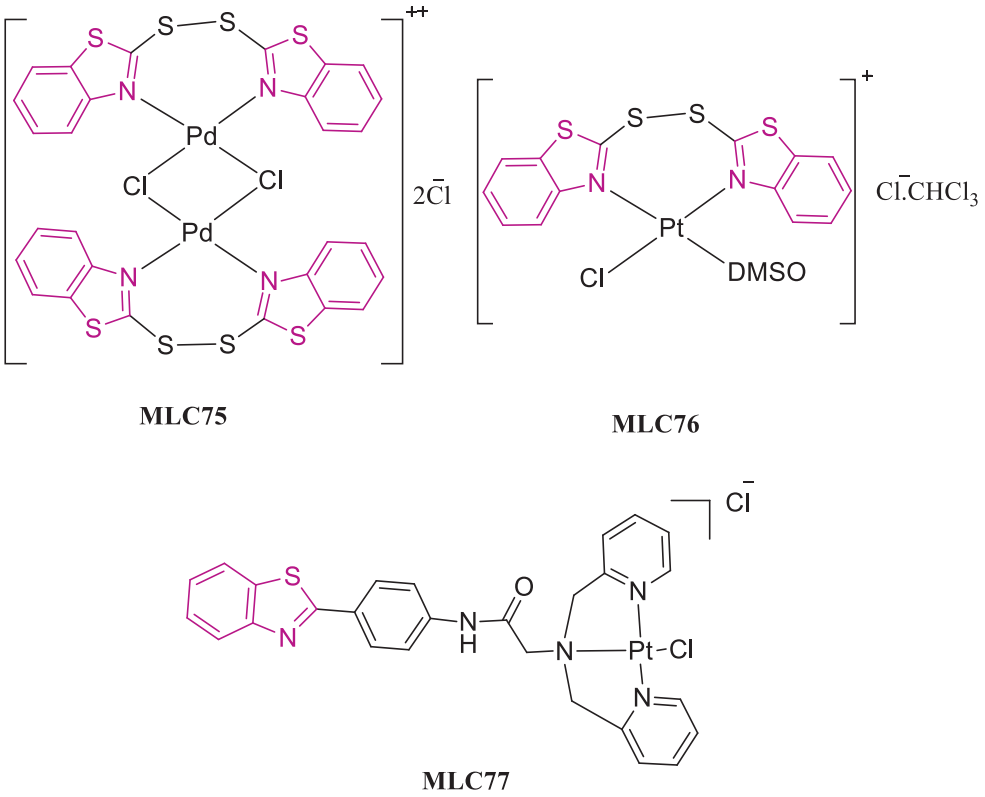


Fig. 11. Benzothiazole-based metal complexes as anticancer agents.

cytotoxicity. The presence of platinum complex **MLC76** inside the cells were confirmed from study on intracellular uptake in both HepG2 and MCF-7 cell lines. (Rubino et al., 2017) Another novel mononuclear anticancer benzothiazole based Pt(II) complex, **MLC77** was synthesized and tested for cytotoxic activity against HeLa, MCF-7 and A-549 cell lines and were compared with free ligands. The result indicates the comparable cytotoxic activity of **MLC77** to that of cisplatin against MCF-7 however, it is more potent against A-549 and HeLa cancer cell lines. While, the free ligand exhibits moderate activity, which shows that the enhancement occur in the cytotoxicity upon coordination of ligand with Pt(II). (Chen et al., 2020) These results clearly show the enhanced cytotoxic activity of the complexes over free ligands with low levels of side effects.

5. Antioxidant activity

Metal complexes derived from organic ligands possess excellent antioxidant activity, for example, **(MLC78) (**Fig. 12**)** containing indole-2-carboxylic acid. The antioxidant activities of the synthesized complex **MLC78** were probed through a DPPH, ABTS and a hydroxyl free radical (OH) scavenging assay. The complex **MLC78** showed excellent inhibitory effects (94% inhibition at 60 μM) on the ABTS radical, followed by DPPH and OH radicals (the degrees of inhibition being56% and 71% respectively) (Wang et al., 2017). Similarly, two other novel copper(II) and zinc(II) complexes (**MLC79** and **MLC80**) with bis(N-ethylbenzimidazol-2-ylmethyl)al lylamine ligand were prepared and characterized through UV–visible, IR, XRD, molar conductivity, and elemental analysis. The spectral analysis of both complexes shows different geometry for **MLC79** and **MLC80** the MLC79 adopts a distorted square pyramidal geometry, while **MLC80** is a distorted tetrahedral complex.

The antioxidant activity of both the complexes were tested. The result indicated that these compounds have significant antioxidant activity of **MLC79** against superoxide and hydroxyl free radicals. The experiments show (3.87 ± 0.02) × 10^{-5} M IC_{50} value for **MLC79** complex, which implies that **MLC79** shows better antioxidant activity than vitamin C and mannitol. The free ligand and **MLC80** do not show any activity (Shen et al., 2018). Another Cu (II) complex **MLC81**, with benzimidazole ligand was designed and synthesized. The structure of the complex and its parent ligand was investigated by UV–Vis, elemental analysis, XRD and FT-IR. The spectral studies indicate a distorted tetrahedral geometry. The in vitro antioxidant study showed the excellent activity of **MLC81** against hydroxyl radicals and superoxide (Tang et al., 2020). A novel metal complexes of Zn(II) and Cu(II) (**MLC82** and **MLC83**) with thiazole ligands were prepared and characterized through different instrumental and spectral techniques like UV–vis, NMR, XRD, IR, molar conductivities, and elemental analyses. The Zn(II) complex adopts a distorted tetrahedral geometry, while the complex **MLC83** rearranged to distorted trigonal bipyramidal. The antioxidant potential of free ligand and their complexes were investigated *in vitro* by the hydroxyl radical and superoxide scavenging methods. The results obtained show even high antioxidant activity than standard antioxidants such as mannitol and vitamin C (Wu et al., 2015).

Another two complexes of Mn(II) and Zn(II) **(MLC84** and **MLC85)** with Bis(N-ethylbenzimidazol-2-ylmethyl)allylamine were prepared. The structure of both complexes were investigated by FT-IR, UV–Vis, XRD, molar conductivities and elemental analyses. The Mn(II) adopts five-coordinated distorted trigonal bipyramidal geometry, while MLC8 is a twisted four-coordinated tetrahedral geometry. The in vitro antioxidant potential was determined through superoxide methods, indicating the high potential antioxidant activities of **MLC84** (Xia et al., 2020). The antioxidant activities of two novel Cu(II) complexes (**MLC86** and **MLC87)** with benzoxazole ligands were determined. Both complexes showed significant activities with IC_{50} values of both complexes were very small (0.112 and 0.191 μM, respectively) indicating their excellent

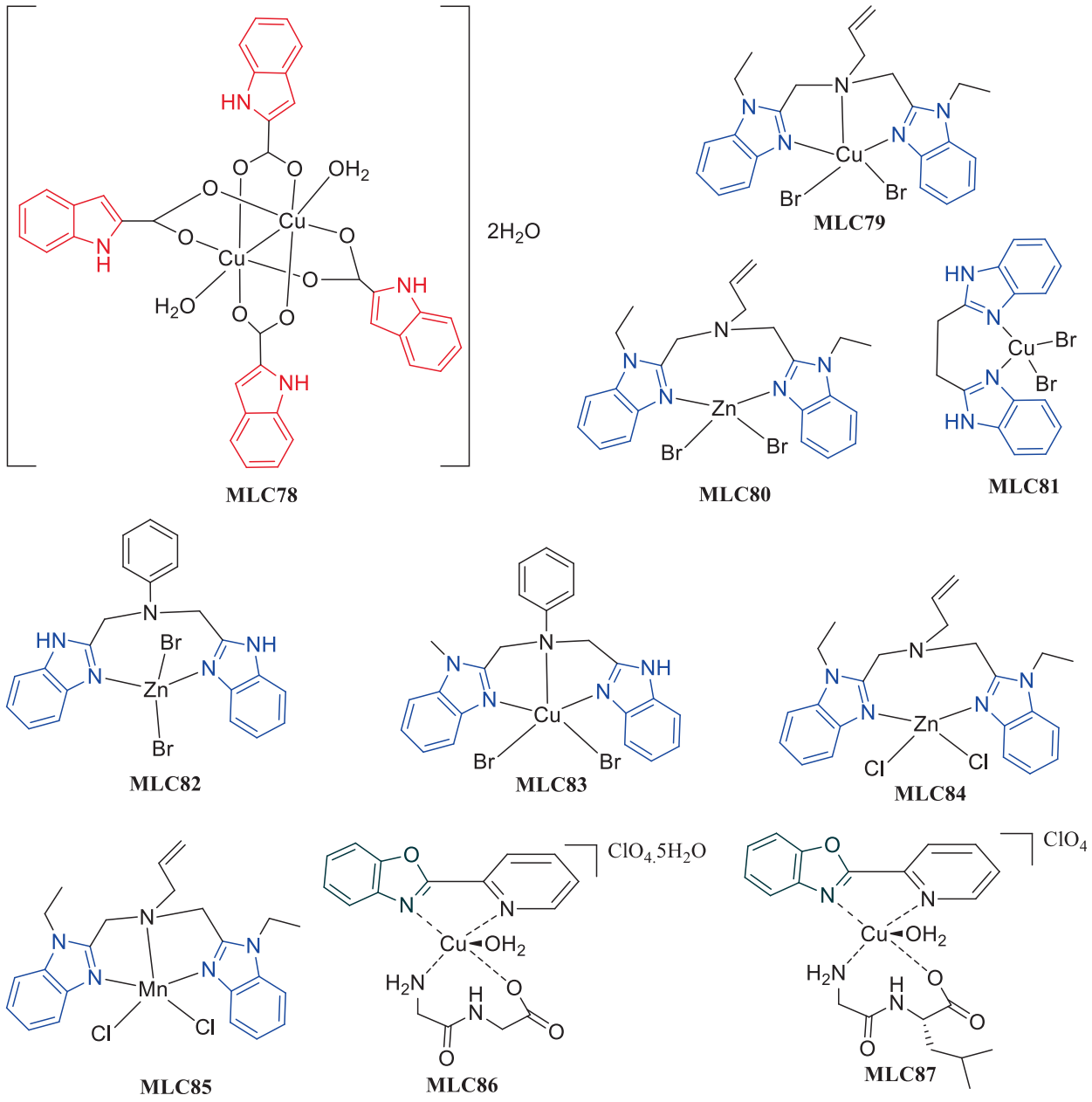


Fig. 12. Metal complexes of Indole **(MLC78)**, benzimidazole **(MLC80-MLC85)** and benzoxazole **(MLC86** and **MLC87)** as antioxidants agents.

antioxidant activities. The high antioxidant activities of these complexes are due to their flexibility in geometry upon the approach of $O_2^{-\bullet}$, which exchange quickly with the weakly bounded water molecule at the axial position [25]. Moreover, the nitrogen electrons, such as oxazole and pyridine can assist in the stability of complex $O_2^{-\bullet}$ interaction in favor of high SOD activity (Gan et al., 2016).

6. Anti-inflammatory, antipyretic and analgesic activities

Two new Cu(II), and Zn(II) complexes (**MLC88** and **MLC89**) **(**Fig. 13**)** with benzimidazole ligand were prepared and characterized by different techniques like elemental analysis EPR, HPLC, NMR, FT-IR, HRMS, and. These compounds were tested for antipyretic activity induced by yeast and acetic acid- analgesic activities produced by acetic acid in mice and carrageenan-inducedpaw edema in rats. The results indicate the high potential for the anti-inflammatory activity of Cu(II) complex at 100 mg/kg b.w, whereas Zn(II) at 50 mg/kg and 100 mg/kg b.w showed excellent activity as compared to standard drugs. These compounds also showed moderate antipyreticactivity (Alajmi et al., 2016). Another two complexes of Cu(II) (**MLC90** and **MLC91**) were synthesized, characterized and screened in vivo on mice and albino rats for anti-inflammatory, analgesic, and antipyretic activities. The results demonstrated that complex **MLC91** showed considerable dose-dependent analgesic and anti-inflammatory activities at a lower concentration. (Hussain et al., 2019).

7. Conclusion and future perspectives

Indole, benzoxazole, benzothiazole and benzimidazole are excellent classes of organic heterocyclic compounds with excellent applications in industries, pharmacy, dyes, medicine, polymers, and food packages. These compounds form metal complexes with

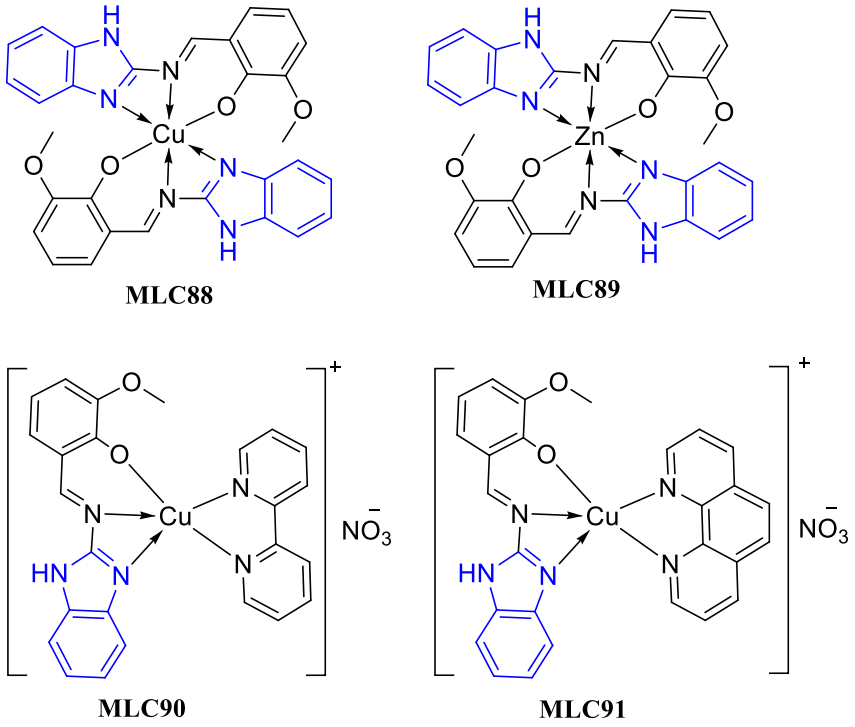


Fig. 13. Metal complexes of benzimidazole as antipyretic, analgesic and anti-inflammatory agents.

copper, zinc, cadmium, nickel, cobalt, platinum, gold, palladium chromium, silver, iron, and other metals that have shown to be significant medicinal applications such as anti-ulcerogenic, anticancer, antihypertensive, antifungal, anti-inflammatory, antitubercular, antiparasitic, anti-obesity, antimalarial, antiglycation, antiviral potency, antineuropathic, analgesic antioxidant, antihistaminic, and antibacterial potentials. Mostly the potency of these compounds enhances upon coordinating with various transition metals. However many of these metal complexes may have side effects like gastrointestinal disturbances, allergic reactions, or organ-specific toxicities. The specific side effects can vary depending on the metal used and the formulation of the complex. The continuous exposure to metal complexes can lead to the development of resistance mechanisms in targeted cells or pathogens. This can reduce the effectiveness of the complexes over time and limit their therapeutic potential. It is important to monitor and study the development of resistance to these complexes to inform future treatment strategies. Therefore, further research is encouraged to improve the potency of these compounds. By dedicating more research efforts to this area, scientists can explore various strategies and approaches to enhance the efficacy and therapeutic potential of metal complexes of indole, benzimidazole, benzothiazole, and benzoxazole.

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.

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