We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,300

Open access books available

172,000

International authors and editors

190M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

The Anticancer Profile of Benzimidazolium Salts and Their Metal Complexes

*Imran Ahmad Khan, Noor ul Amin Mohsin,
Sana Aslam and Matloob Ahmad*

Abstract

Cancer is the most lethal ailment throughout the world in the present era. The development of new anticancer remedies with minor unhealthful effects and an alternate mechanism is crucial. Benzimidazole is a distinguished heterocyclic compound and is now recognized as the privileged scaffold for new drug discovery. This chapter deals with the anticancer capability of benzimidazolium salts and their metal complexes. The benzimidazolium derivatives have been prepared by the introduction of aliphatic and aromatic groups at two nitrogen atoms of the benzimidazole ring. Other modifications include hybridization with other pharmacophores and the preparation of metal complexes. The potent derivatives presented in this review can serve as novel drug candidates against cancer.

Keywords: benzimidazolium salts, Benzimidazole, metal complexes, salts, hybrid, silver, breast cancer (MCF-7) cell line, colon cancer (HCT-116) cell line

1. Introduction

Cancer is among the most dreadful diseases and a significant cause of assassinations all over the globe. In 2018, 9.6 million expirations were because of this malady [1]. Breast cancer is the paramount form of cancer in women all over the world. In 2018, 2.3 million victims and 627,000 fatalities were reported due to breast cancer. Prostate cancer is the second most common cancer in males and 1.3 million patients were reported in 2018 [1]. It has been deduced that more than 13 million people will die due to cancer in 2030 [2]. The major risk factors associated with cancer are chronic infections, inherited mutations in genes, overweight, no physical activity, exposure to ionizing radiation, and carcinogens such as polychlorinated biphenyls, chloroform, Dichlorodiphenyltrichloroethane (DDT), and formaldehyde [3]. Treatment patterns for cancer involve radiotherapy, surgery, and drug therapy. Drug therapy includes inorganic, organic, organometallic monomers, and polymers as well as nanoparticles [4]. Drug therapy is associated with severe adverse properties such as alopecia, anemia, and infertility. There is also the development of resistance against currently

Figure 1.
Anticancer drugs based on benzimidazole scaffold.

available drugs [5]. Consequently, the development of new anticancer drugs affiliated with low toxicities is very significant.

Nitrogen-containing heterocycles are abundantly present in natural and synthetic drug molecules [6]. Benzimidazole is one of the most significant members of nitrogen-containing heterocycles. This heterocycle is a constituent of the structures of some natural compounds such as vitamin B12 [7]. Benzimidazole derivatives have antihypertensive [8], anti-inflammatory [9], antimicrobial [10], antiulcer [11], antiviral [12], antioxidant [13], antitumor [14], lipid modulator, and anticoagulant properties [15]. Benzimidazole derivatives have also the major therapeutic activities against cancer [16–18]. Benzimidazole is also the main pharmacophore of anticancer drugs (**Figure 1**) such as bendamustine (1), selumetinib (2), and galeterone (3) out of which bendamustine is approved for clinical use, while the other two are in clinical trial stages [19, 20]. The structural resemblance of benzimidazole with nucleotides makes them very vital from the biological point of view [21]. Benzimidazolium salts are 1,3-disubstituted benzimidazole derivatives and possess acidic hydrogen at position 2. Benzimidazole salts find application as a carbene precursor for the preparation of n-heterocyclic carbenes (NHC) with different metals [22]. These benzimidazolium salts and their complexes have displayed significant antimicrobial and anticancer properties [23]. This review deals with the anticancer activities of benzimidazolium salts and their metal complexes.

2. Anticancer properties of benzimidazolium salts

Benzimidazolium salts and their anticancer capabilities have been reviewed in the following sections.

2.1 Hybrid molecules containing benzimidazolium salts

Molecular hybridization has become an effective approach for new drug discovery. In molecular hybridization, two or more pharmacophores are linked to each other to produce the new molecules [24, 25]. Yang et al. synthesized hybrid molecules in which benzimidazolium salts were linked to trimethoxy phenyl chalcones. Compound 4 (**Figure 2**) demonstrated excellent anticancer potential against leukemia (HL-60), breast carcinoma (MCF-7), and colon carcinoma (SW480) cell lines presenting IC_{50} values of 0.83, 1.57, and 2.92 μ M, respectively, which is 5–11-folds higher than the standard drug cisplatin. In compound 4, 2-naphthylmethyl substituent is attached

Figure 2.
 Hybrid molecules comprising benzimidazole salts and natural compounds.

to benzimidazole nitrogen. The superior activity of these salts was related to the high solubility of benzimidazolium salts. Benzimidazole derivatives with substituents at positions 5, 6 showed greater activity as compared to unsubstituted benzimidazoles [26]. Karatas et al. reported a series of hybrid molecules in which coumarin was attached to the substituted benzimidazolium chlorides. Anticancer screening by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) assay showed that these compounds have the potential to discontinue the cell cycle for human prostate (PC-3) and ovarian (A2780) cancer cells. Specifically, compound 5 ($IC_{50} = 44.5 \mu M$) showed some inhibitory potential against PC-3 at the dose of $1 \mu M$ [27]. Next year, Wang et al. produced the 3-benzyl coumarin imidazolium salts using the hybrid molecular strategy. The anticancer activity evaluation showed that compound 6 is one of the most active derivatives having IC_{50} values ranging from 2.04 to $4.51 \mu M$. The best activity was displayed *versus* the MCF-7 cell line having an IC_{50} value of $2.04 \mu M$. The 5, 6-dimethyl-substituted benzimidazole hybrids exhibited prominent activity as compared to unsubstituted benzimidazoles or imidazoles. These molecules showed selectivity for MCF-7 and SW-480 cancer cell lines. Compound 6 also showed the apoptosis in liver carcinoma (SMMC-7721) cell line [28]. Deng et al. linked benzimidazolium salts with steroidal molecules such as cholesterol, dehydroepiandrosterone, and diosgenin. Anticancer activities were carried out against HL-60, A-549, SMMC-7721, SW480, and MCF-7 cancer cell lines. Diosgenin-imidazolium salts displayed higher activity, and compound 7 was the most effective having IC_{50} values from 0.44 to $0.79 \mu M$ against different cell lines.

Compound **7** disrupted the cell cycle in G1/G0 stage and showed apoptosis in the SMMC-7721 cell line. Structure-activity relationship (SAR) studies showed that 5,6-dimethyl-substituted benzimidazolium salts showed excellent anticancer activity. Attachment of 2-bromobenzyl with 2-naphthyl methyl at position 3 of benzimidazole also amplified the activity [29]. Brazilin is a natural compound and possesses extensive bioactivities such as anti-inflammatory, anticancer, and antioxidant [30]. Huang et al. connected aza-brazilin with imidazolium salts to produce hybrid molecules. Anticancer activity was evaluated against A549, SMMC-7721, MCF-7, and SW480 cell lines. Derivative **8** appeared as the most active ($IC_{50} = 0.35 \mu M$) against the MCF-7 cell line and displayed more potency as compared to cisplatin. Derivatives having a 5,6-dimethylbenzimidazole ring displayed prominent activity. The introduction of electron-withdrawing groups on the aza-brazilin nucleus produced more active derivatives. Derivatives having an alkyl chain as linker groups produce higher potency as compared to acyl chains [31]. Zhou et al. also used a hybrid molecular strategy to conjugate *N*-substituted tetrahydro- β -carboline with imidazolium salts. Compound **9** exhibited prominent activity with IC_{50} values ranging from 2.61 to 17.13 μM against five different cancer cell lines. Most prominent activity was achieved against MCF-7 ($IC_{50} = 2.79 \mu M$) and SW-480 ($IC_{50} = 9.46 \mu M$) cancer cell lines. Compound **9** carries a naphthyl methyl scaffold at position 3 of benzimidazole. Compound **9** also showed the phenomenon of apoptosis in the MCF-7 cell line as well as inhibited the cell cycle in the G1 phase [32].

Xu et al. coupled a three-substituted indole ring with imidazolium salts to produce new hybrid molecules. Upon evaluation of anticancer activity, compound **10** (**Figure 3**) showed prominent performance against MCF-7 ($IC_{50} = 3.19 \mu M$), A549 ($IC_{50} = 3.51 \mu M$), SW480 ($IC_{50} = 11.57 \mu M$), and SMMC-7721 ($IC_{50} = 3.60 \mu M$) cancer cell lines. SAR studies showed that 5,6-dimethyl-substituted benzimidazole derivatives showed prominent activity as compared to unsubstituted benzimidazoles. Compound **10** carries a naphthyl acyl ring at position 3 of the benzimidazole nucleus. Further studies showed that compound **10** is capable of inducing apoptosis and caused cell cycle blockage in the S phase [33]. Li et al. synthesized carbazole and imidazolium salts using the molecular hybridization technique. Replacement of the imidazole ring by the benzimidazole increased the anticancer selectivity against a particular cell line. Among the benzimidazolium salts, derivative **11** showed excellent activity against the HeLa cell line ($IC_{50} = 0.02 \mu M$) as compared to standard drug cisplatin ($IC_{50} = 13.61 \mu M$) [34]. Wang et al. synthesized imidazolium salts and dibenzofuran comprising hybrid molecules. The estimation of anticancer activity against five cancer cell lines showed that 2-methylbenzimidazolium and dibenzofuran hybrid molecular salts are more active as compared to individual molecules. 2-Methyl-substituted benzimidazolium salts showed higher activity as compared to unsubstituted and 5,6-dimethylbenzimidazolium salts. Compound **12** expressed prominent activity ($IC_{50} = 0.64\text{--}1.47 \mu M$) against MCF-7, A549, SW480, HL-60, and SMMC-7721 cancer cell lines. Most prominent activity was observed against MCF-7 ($IC_{50} = 0.64 \mu M$) and SW-480 ($IC_{50} = 0.88 \mu M$) cell lines. Compound **12** carries a 4-methoxy phenacyl substituent at position 3 of the benzimidazole nucleus. Replacement of 4-methoxy phenacyl substituent by 2-naphthylacyl also produced potent derivatives [35]. Zhang and co-workers synthesized hybrid molecules comprising 2,3,6,7-tetrahydrobenzodifuran and imidazolium salts. Compound **13** appeared as the most active derivative against five cancer cell lines having an IC_{50} value less than 4.34 μM . Compound **13** showed selectivity for A549, SMMC-7721, and SW-480 cancer cell lines. Some derivatives of this series also exhibited the phenomenon of apoptosis and seized

Figure 3.
Hybrid molecules of benzimidazole salts with synthetic molecules.

cell cycle in the G1 stage [36]. Zhou et al. manufactured hexahydropyrrolo[2,3b]indole-1*H*-imidazolium salts as anticancer agents. The nitrogen at position 3 of the benzimidazole ring was linked to 2-bromobenzyl and 2-naphthyl methyl scaffolds. Compound **14** emerged as the most active derivative against HL-60, MCF-7, SMMC-7721, A549, and SW-480 cell lines having an IC_{50} value less than 2.68 μ M. The introduction of the *N*-benzyl group at the indole nitrogen also increased the activity [37].

2.2 Benzimidazolium salts having aromatic and aliphatic substituents

Akkoc et al. reported benzimidazolium salts screened for anticancer potential against human embryonic kidney (HEK-293 T), human colon epithelial colorectal adenocarcinoma (DLD-1), and human breast epithelial adenocarcinoma (MDA-MB-231) cancer cell lines by using MTT assay. Palladium (Pd) metal complexes were also prepared and found inactive against these cells lines having IC_{50} values over 100 μ M. The naphthalen-1-yl-methyl incorporated benzimidazolium chloride **15** (Figure 4) (IC_{50} = 26.09 μ M) showed most cytotoxicity against DLD-1 cell line [38]. In an additional study, Akkoc and his coworkers reported a

Figure 4.
Benzimidazole salts having aromatic substituents.

novel series of benzimidazolium salts containing cyanobenzyl, nitrophenyl, and *N*-methylphthalimide substitutions. All salts were tested for their cytotoxicity against DLD-1 and human breast cancer (MDA-MB-231) cell lines. Compounds **16** and **17** demonstrated exceptional activity against MDA-MB-231 cell lines with IC_{50} values of 1.26 and 2.01 μM and were considerably better than cisplatin ($IC_{50} = 5.77 \mu M$). Derivatives **16** and **17** contain anthracene and naphthalene rings, respectively, attached with the nitrogen of benzimidazole. The N^1 and N^3 substituents produced a prominent effect on anticancer activity [39]. In 2019, Akkoc extended his previous finding of cytotoxicity of benzimidazolium salts. In this regard, 2-hydroxyethyl-containing benzimidazolium salts along with respective Pd-complexes were prepared and their anticancer capacity was noted against human cancer cell lines. Surprisingly, compound **18** exhibited notable activity against MDA-MB-231 ($IC_{50} = 7.59 \mu M$) and DLD-1 ($IC_{50} = 39.51 \mu M$) cell lines in comparison with their Pd-complexes [40].

Lin et al. synthesized 1,3-bis-naphthyl-substituted benzimidazolium bromides and estimated for activity against MDA-MB-468 as well as PC-3 cell lines. As compared to the standard drug tamoxifen ($IC_{50} = 22.5 \mu M$), compound **19** (Figure 5) was found as an active agent ($IC_{50} = 9.7 \mu M$) against MDA-MB-468. The presence of the naphthyl group was vital for the activity of these derivatives [41]. Wright et al. synthesized naphthalene-substituted imidazolium salts and evaluated the anticancer performance against non-small-cell lung cancer (NSCLC) cell lines. The anticancer activity was evaluated by the MTT assay. Compound **20**, the benzimidazolium salt, displayed IC_{50} values of 3, 4, and 5 μM against NCI-H460, NCI-H1975, and HCC-827, respectively. Compound **20** carries naphthyl rings at both nitrogens of benzimidazole [42]. Stromyer et al. synthesized benzimidazole

Figure 5.
Benzimidazole salts having naphthalene and quinoline rings.

salts having triphenylphosphonium group. The nitrogen atoms of benzimidazole were linked with naphthyl methyl groups. Compound **21** revealed marvelous activity against bladder cancer cell lines RT4, RT112, UMUC3, and SW780. This compound also showed apoptosis by causing mitochondrial damage. The drug causes a rapid and irreversible effect against bladder cancer [43]. Shelton et al. synthesized *N,N*-bis-arylmethyl-substituted benzimidazolium salts *via* cyclization of *o*-phenylenediamine or 2-(2-(2-methoxy ethoxy)ethoxy)acetic acid with 2-(chloromethyl) quinolone or 2-(bromomethyl)-naphthalene followed by alkylation and quaternization. Various hydrophilic and hydrophobic groups were added at both nitrogen atoms of benzimidazole. Insight into *in vitro* cytotoxicity of synthesized salts, compound **22** showed adequate activity against NSCLC cancer cells having IC_{50} values ranging between 1 and 7 μM comparable to the standard drug, cisplatin. This compound bears quinoline and naphthalene rings to both nitrogen atoms of benzimidazole. The presence of ether linkage at position two increased the hydrophilicity of this compound [44].

Bansode et al. carried out the synthesis of ferrocene-linked ionic liquids by incorporating long alkyl chains. Anticancer activity was evaluated against MCF-7 by using sulforhodamine B assay. These ferrocene-quaternized azolium salts showed significant cytotoxic potential against MCF-7 and 1-(ferrocenylmethyl)-3-tetradecylbenzimidazolium bromide **23** (Figure 6) was found to be most potent ($GI_{50} = 0.016 \mu M$) as compared to standard drug doxorubicin ($GI_{50} = 0.018 \mu M$). Derivatives in this followed the Lipinski rule of five and showed excellent pharmacokinetic properties [45]. Kucukbay et al. synthesized *N,N*-disubstituted benzimidazolium bromides and evaluated anticancer activity against PC-3 and ovarian (A2780) cancer cell lines. Derivatives **24-26** presented prominent activity against PC-3 and A2780 cancer cell lines having IC_{50} values in micromolar concentration. These compounds bear a 4-methoxyphenyl ethyl group at the benzimidazole nitrogen [46]. Haque et al. prepared a collection of bis-benzimidazolium salts and evaluated against human colon cancer (HCT-116). All compounds showed superior activity than the reference

Figure 6.
Bis-benzimidazolium and ferrocene-linked benzimidazolium salts.

drug, fluorouracil. Derivatives having *N*-methylene phenyl substituents presented prominent activities. The highest anticancer potential was observed in the case of derivative **27** ($IC_{50} = 0.2 \mu M$) remarkably better than reference drug, 5-fluorouracil ($IC_{50} = 19.2 \mu M$) [47]. Noor ul Huda et al. synthesized bis-NHC benzimidazolium salts and evaluated them as antimicrobial and anticancer agents. Compound **28** exhibited prominent activity against HCT-116 cancer cell lines showing 75% inhibition at 1 mg/ml as determined by using sulforhodamine B assay. Compound **28** contains a lipophilic alkyl chain and the lipophilicity of the alkyl chain was linked to the increased activity of this derivative [48].

2.3 Benzimidazolium silver metal complexes

Cisplatin is the first metal-based drug used for the cure of cancer [49]. The serendipitous discovery of cisplatin stimulated the search for new metal-based anticancer agents. Silver (Ag) salts have been used as antimicrobial agents for purification of drinking water and wound healing [50, 51]. Based on its antimicrobial property, silver has also been explored as an anticancer agent. *N*-Heterocyclic carbenes (NHC) are a prominent family of organometallic ligands.

2.3.1 Bis-benzimidazolium silver metal complexes

Iqbal and his coworkers performed a detailed study to reduce the risk of malignant neoplasm and reported novel binuclear benzimidazolium salt and corresponding Ag (I) NHC complex. Compound **29** (Figure 7) presented prominent activity ($IC_{50} = 1.7 \mu M$) against HCT-116 cell line. This compound also showed significant inhibition of inflammatory cytokines such as tumor necrosis factor- α and interleukin in human macrophages. Compound **29** showed apoptotic activity *via* inhibition of the caspase pathway. Photomicrographs of the cell treated with compound **29** showed deposition of silver in cells [52]. Gadhayeb et al. carried out the synthesis of mono- and bis-NHC complexes having palladium (Pd) and silver metals. The anticancer activity was evaluated out against HCT-116 cell line. Compounds

Figure 7.
Mono and binuclear bis-benzimidazolium silver metal complexes.

30 and **31** exhibited prominent activities having IC₅₀ values of 12.3 ± 1.2 μM and 10.6 ± 1.8 μM, respectively. The mono-NHC showed more activity as compared to bis-NHC. The increased activity of compound **31** could be due to the increased release of silver from the mono-NHC complex. These compounds contain a butyl chain at the benzimidazole nitrogen [53]. Following this principle, Sarhan et al. reported benzimidazolium-acridine-based salts and metal complexes with pronounced biological potential. Specifically, compound **32** can be considered an excellent *in vitro* anticancer agent against MCF-7 (IC₅₀ = 21 μM) and selectivity index of 3.6. Therefore, Ag-NHC complexes demonstrated prominent activity [54]. A series of 5-methyl benzimidazole-based *n*-heterocyclic carbene (NHC) salts and their silver (I)-complexes were prepared by Habib et al. The Ag (I)-benzimidazolium complexes showed dominant activity against human breast cancer (MDA-MB-231) and colon cancer (HCT-116) as compared to NHC salts. Compound **33** showed promising activity against MDA-MB-231 (IC₅₀ = 4.2 ± 0.24 μM, SI = 7.63) and HCT-116 (IC₅₀ = 7.43 ± 0.23 μM SI = 4.33) as compared to reference drug (IC₅₀ = 8.20 ± 0.14 μM and 5.5 ± 0.34 μM) against these cell lines respectively. Compound **33** carries pentyl chains at both nitrogen atoms of the benzimidazole core. Derivatives having a longer alkyl chain were found more active. These molecules showed dose-dependent cytotoxicities and apoptosis by mitochondrial pathways [55]. A range of substituted Ag(I)-benzimidazolium carbene complexes were reported by Atif et al. and *in vitro* anticancer studies were carried out against MCF-7, HCT 116, and erythromyeloblastoid leukemia (K-562)

cell lines. Promising anticancer activity was shown by **34** ($IC_{50} = 0.31 \mu M$) against the K-562 cell line. Compound **34** is a bis-benzimidazole silver complex and carries propyl groups at both nitrogen atoms of benzimidazole rings [56].

Achar et al. reported a novel series based on benzimidazolium salts linked with coumarin heterocycle, and their silver cationic bis-NHC and Ag neutral mono-NHC were synthesized. The anticancer activity was evaluated by sulforhodamine assay. Complex **35** (**Figure 8**) exhibited moderate activity against the A549 cell line having an IC_{50} value of $8.3 \pm 0.40 \mu M$. Compound **35** is the bis-NHC-coordinated Ag hexafluorophosphate (PF₆) salt. The mono-NHC coordinates Ag acetate complexes showed inferior activity with IC_{50} values greater than $10 \mu M$. Bis-NHC complexes also showed prominent antibacterial activity [57]. Yasar et al. also worked out to yield novel zwitterionic-sulfonated benzimidazolium salts and their Ag-(I) complexes by following a reported synthetic approach. Anticancer activity was assessed against human cervix carcinoma (HeLa), human adenocarcinoma (HT29), and mouse fibroblast (L929) cancer cell lines. Silver complexes were found most active as compared to their salts. Compound **36** ($IC_{50} = 11 \pm 1 \mu M$) showed higher potency against HT29 cancer cell line as compared to cisplatin ($IC_{50} = 42 \pm 6 \mu M$). Compound **36** was found to be the least toxic ($IC_{50} = 126 \pm 3 \mu M$) against non-cancer L929 cell lines [58]. Karlık et al. prepared a series of aqua-bis-benzimidazole Ag (I) *p*-toluene sulfonate complexes *via* a multistep approach and investigated their anticancer properties against human colorectal (Caco-2) and MCF-7 cancer cell lines. Salts were found to be ineffective against these cell lines. Benzimidazolium Ag complex **37** (IC_{50} value of $9 \pm 3 \mu M$) showed excellent activity against the Caco-2 cell line but was inactive against the MCF-7 cell line. Derivatives **37** carries an *o*-chloro-substituted benzyl group attached with the nitrogen of benzimidazole and this substituent was found more effective at

Figure 8.
Bis-benzimidazolium silver metal complexes having alkyl chain, heterocyclic and aromatic scaffold.

this position as compared to *o*-methyl and *p*-methyl analogues [59]. Fatima et al. successfully explored the cytotoxic effect of different alkyl chains on benzimidazolium-based Ag complexes. It was observed that compound **38** containing longer n-alkyl chains showed the best cytotoxic potential against HCT-116 ($IC_{50} = 0.02 \mu M$) as compared to 5-fluorouracil ($IC_{50} = 10.2 \mu M$) as a standard drug. The incorporation of silver ions and elongation of the alkyl chain amplified the anticancer activity [60].

Similarly, Haque et al. prepared Ag(I) complexes containing nitrile-functionalized benzimidazolium salt as an active agent against HCT-116. Among all synthesized complexes, compound **39** ($IC_{50} = 14.9 \pm 0.8 \mu M$) showed the highest cytotoxicity as compared to fluorouracil ($IC_{50} = 5.2 \pm 0.3 \mu M$). The activity was linked to the nitrile group (**Figure 9**) at the meta position of the benzyl group causing the weak electron-withdrawing effect [61]. Early on, Haque et al. also synthesized silver metal complexes containing benzimidazolium ligand. These silver-based benzimidazolium complexes are capable of slow release of the silver ion at the cancerous cell, affecting cell morphology. Complex **40** ($IC_{50} = 1.20 \pm 0.3 \mu M$), a binuclear silver entity, expressed superior activity as compared to fluorouracil ($IC_{50} = 5.2 \pm 0.3 \mu M$) against HCT-116. Complex **40** was found to be the least active ($IC_{50} = 103 \pm 2.3 \mu M$) against the HT29 cell line. Therefore, the HT-29 cell line was found to be resistant to this complex [62]. Hussaini et al. successfully formulated silver (I)-benzimidazolium carbenes. A series of propylene-linked bis-benzimidazolium salts having different alkyl chains and respective binuclear silver complexes were prepared. Complexes showed dose-dependent cytotoxicities. Their cytotoxic studies against the MCF-7 cell line revealed compound **41** as the most active ($IC_{50} = 7 \pm 1 \mu M$) complex as compared to tamoxifen ($IC_{50} = 11 \pm 2 \mu M$). The presence of the propyl chain at the benzimidazole nucleus was found to be optimum for anticancer activity [63]. Later on, in 2018,

Figure 9.
Bis-benzimidazolium silver metal complexes containing aliphatic nitriles, aromatic nitriles, benzyl and alkyl chains.

Hussaini and his coworkers reported benzimidazolium salts having aliphatic nitrile group and their Ag (I)-benzimidazolium carbenes complexes. All of these NHC complexes showed good cytotoxicities with IC_{50} values in the range of 7.0–12.9 μM against the MCF-7 cell line. Compound **42** ($IC_{50} = 7 \pm 1.06 \mu M$) was found to be the most potent and it carries a pentyl chain attached to the benzimidazole nitrogen. Cytotoxicities of these compounds increase as the alkyl chain length expands [64].

2.3.2 Benzimidazolium silver and gold metal complexes

Akkoc et al. reported a series of silver- and palladium-based metal complexes with benzimidazolium ligand. This attempt was made in search of the non-platinum anti-tumor drugs due to the observed side effects of cisplatin and nedaplatin. However, silver complex **43** (**Figure 10**) showed promising *in vitro* cytotoxic potential against DLD-1 ($IC_{50} = 12.41 \mu M$), MDA-MB-231 ($IC_{50} = 11.98 \mu M$) cancer cell lines, and HEK-239 ($IC_{50} = 4.2 \mu M$) non-cancer cell lines. Therefore, the silver complex was found more potent than the palladium complex [65]. Sahin et al. employed the conventional technique to synthesize *n*-allyl-substituted benzimidazolium-based carbene and corresponding Ag-(I) complexes. The first step was to obtain *n*-alkylated benzimidazole and later followed by salt formation. Silver dioxide was used to obtain the allyl-linked benzimidazolium Ag-(I) complex. Among all synthesized compounds, derivatives **44** ($IC_{50} = 1.41 \mu M$) and **45** ($IC_{50} = 1.21 \mu M$) showed the best *in vitro* anticancer potential against DU-145 and MCF-7, and MDA-MB-231 ($IC_{50} < 1 \mu M$) cancer cell lines. Derivatives **44** and **45** also exhibited some degree of selectivity [66]. Ozdemir et al. carried out the synthesis of silver and gold (Au) NHC-propyl sulfonate complexes. Silver complexes presented dominant activity as compared to gold salts. Compounds **46** ($IC_{50} = 2.32 \pm 0.089 \mu M$) and **47** ($IC_{50} = 9.31 \pm 0.95 \mu M$) presented prominent *in vitro* activities against adenocarcinoma (HEP3B) cancer cell lines. Complexes **46** and **47** are silver and gold complexes, respectively. These complexes

Figure 10.
Benzimidazolium silver and gold metal complexes.

possess a dimethoxyethyl group at the benzimidazole nitrogen. Replacement of dimethoxyethyl group by diethoxyethyl group produced less active derivatives [67].

Similarly, the synthetic work of Cevik Yildiz and his coworkers resulted in the formation of novel benzimidazolium salt. These benzimidazolium salts were used as a ligand to obtain corresponding novel Ag (I)- benzimidazolium complexes. Cytotoxic studies of salts and complexes were carried out against MCF-7, MDA-MB-23, DU-145 by MTT assay. Compound **48** (Figure 11) displayed prominent activity ($IC_{50} < 1 \mu M$) against breast cancer MCF-7 and MDA-MB-23 cell lines. Compound **49** also showed prominent activity ($IC_{50} < 1 \mu M$) against the MCF-7 cell line than standard drug. These compounds showed concentration-dependent killing and also showed selectivity for cancer cell lines [68]. Aktas et al. carried out the synthesis of 2-morpholine ethyl-substituted benzimidazolium salts and their Ag-NHC complexes. Compounds **50** ($IC_{50} = 6.59 \mu M$) and **51** ($IC_{50} = 6.56 \mu M$) exhibited prominent activity against MCF-7 cell line. Ag-NHC complexes presented prominent activity as compared to benzimidazolium salts. Compounds **50** and **51** carry methyl and tetra-methyl benzyl groups at the benzimidazole nitrogen [69]. A series of di-isopropylamine ethyl benzimidazolium salts have been reported by Kızrak et al. These salts were further used as a precursor for the syntheses of corresponding silver and gold benzimidazolium carbene complexes. Resultant derivatives displayed prominent activity against the human brain (SHSY5Y) cell line and compounds **52**, **53** were most prominent presenting IC_{50} values of 5.23 and 4.74 μM , respectively. Compounds **52** and **53** are

Figure 11.
Benzimidazolium silver metal complexes.

silver and gold complexes, respectively. Therefore, the gold complex was found more potent than silver complexes. Compound **52** was also found significant against HEP3B ($IC_{50} = 6.19 \pm 1.09 \mu M$) and HTC-116 ($IC_{50} = 8.44 \pm 1.07 \mu M$) cancer cell line [70]. Sahin-Bolukbasi and Sahin synthesized two new benzimidazolium salts and reacted with silver dioxide (Ag_2O) to obtain Ag-(I) benzimidazolium complexes. Evaluation of the anticancer potential of all these compounds reflected the higher cytotoxicity ($IC_{50} < 1 \mu M$) of **54** against DU-145, MCF-7, and MDA-MB-231. This compound carries 2-methyl propenyl and *p*-isopropyl benzyl substituents at the N¹ and N³ positions of benzimidazole ring [71]. Early on, Sahin-Bolukbasi et al. synthesized unsymmetrical benzimidazolium salt and respective Ag-(I) complexes. All of the synthesized compounds were subjected to cytotoxic evaluation. Higher cytotoxicity was noted for benzimidazolium-based Ag complexes as compared to benzimidazolium salts, and particularly **55** and **56** were most active ($IC_{50} < 1 \mu M$) against MCF-7, MDA-MB-231 cancer cell lines. These compounds also demonstrated activity against DU-145 cell line having IC_{50} values of $6.02 \pm 0.30 \mu M$ and $5.16 \pm 0.33 \mu M$, respectively. The *ortho*-substituted benzyl group proved more active as compared to *meta*- and *para*-substituted benzyl groups. And in *ortho*-substituted derivatives methyl group was found more potent as compared to the chlorine atom [72].

2.4 Selenium-based benzimidazolium salts and complexes

Selenium (Se) is very important for the human body and its deficiency can lead to cancer, diabetes, and cardiovascular diseases [73]. Selenium is present in some food and drinks in traces [74]. Recently, selenium has been incorporated in new anticancer agents due to its low toxicity. Kamal et al. applied a green synthetic approach to obtain novel benzimidazolium salts and Se-based benzimidazolium-heterocyclic carbenes. The *in vitro* anticancer potential was evaluated against RGC-5, Hela, MCF-7, and mouse melanoma (B16F10) cancer cell lines using fluorouracil as a standard drug. Prominent anticancer activity was observed against Hela and RCG cell lines. Among benzimidazolium salts (**Figure 12**), compounds **57** ($IC_{50} = 0.04 \pm 0.31 \mu M$) and **58** ($IC_{50} = 0.24 \pm 0.22 \mu M$) displayed prominent activity against Hela cell line.

Figure 12.
Benzimidazolium salts and selenium metal complexes.

The corresponding Se-NHC-adducts compounds **59** ($IC_{50} = 0.11 \pm 0.20 \mu M$) and **60** ($IC_{50} = 4.3 \pm 0.11 \mu M$) were found most active against Hela cell line. Compound **59** was also effective against RCG cell line ($IC_{50} = 9.16 \pm 0.27 \mu M$). Molecular docking investigation of compounds **59** and **60** with epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), and cyclooxygenase (COX-1) displayed strong interactions [75]. Similarly, green synthesis of benzimidazolium salts and di-Se-N-heterocyclic carbene complexes was carried out by Iqbal et al. The benzimidazolium salts **61** ($IC_{50} = 3.94 \mu M$) and respective Se-NHC **62** ($IC_{50} = 3.49 \mu M$) displayed prominent activity against HCT-116 cell line as compared to fluorouracil ($IC_{50} = 4.9 \mu M$). Both compounds possess benzyl groups at positions 1 and 3 of the benzimidazole nucleus. Compounds **61** and **62** also showed some degree of apoptosis by the mitochondrial pathway. Further pro-apoptotic evaluation for HCT-116 even at low concentration due to a strong release of selenium metal for DNA interaction was successfully reported [76].

2.5 Ruthenium complexes based on benzimidazolium salts

Organic compounds having ruthenium (Ru) metal are also being used as anti-cancer agents. Akkoc et al. synthesized methylpyridine-linked benzimidazolium salt and corresponding Ru (II) complexes containing benzimidazolium ligand. The antiproliferative assay revealed that **63** (**Figure 13**) showed DNA binding as well as the best cytotoxic potential against MCF-7 ($IC_{50} = 23.8 \mu M$), Caco-2 ($IC_{50} = 18.0 \mu M$) cell lines, respectively. Compound **63** carries a hexamethyl phenyl ring at position 2 of the benzimidazole ring. Compound **63** showed electrostatic and hydrophobic interaction with DNA and presented a binding affinity of -13.779 kcal/mol [77]. Omar et al. synthesized benzotriazole-functionalized palladium and ruthenium complexes. Comparison of cytotoxic studies revealed that ruthenium complexes are better than palladium complexes against MCF-7 and Caco-2 cancer cell lines. Although the activity displayed by these compounds

Figure 13.
Ruthenium complexes.

was not prominent, these compounds were found inert for normal cell line L-929. Compound **64** ($IC_{50} = 90 \mu M$) is one member of this series [78]. Lam and his coworkers aimed for the novel benzimidazolium-based Ru complexes with halogen ligands for exploration of cytotoxic potential against HCT-116, SiHa, and NCI-H460 cell lines. Promising cytotoxic potential was observed in case of **65** against HCT-116 ($IC_{50} = 6.2 \pm 0.4 \mu M$), SiHa ($IC_{50} = 8.4 \pm 0.2 \mu M$), and NCI-H460 ($IC_{50} = 7.8 \pm 1.0 \mu M$) cancer cell lines. Replacement of ruthenium by osmium (Os) also presented equal cytotoxicity against HCT-116 cell line [79].

2.6 Miscellaneous metal complexes

As mentioned earlier, NHC-carbenes are highly reactive species depending upon the nature of the ligand and transition metal used; consequently, different transition metals have been coordinated with benzimidazolium ligand for a better cytotoxic effect. Troung et al. studied the cytotoxicity of rhodium (Rh)- and iridium (Ir)-based benzimidazolium complexes. A series of rhodium and iridium complexes were prepared and evaluated for anticancer potential against HCT-116, NCI-H460, SiHa, SW480 human cancer cell lines. Compounds **66** and **67** (**Figure 14**)

Figure 14.
Benzimidazole metal complexes with gold, rhodium, iridium, and palladium.

advertised notable activity against HCT-116 ($IC_{50} = 7.4 \pm 0.5 \mu M$, $11 \pm 0.1 \mu M$), NCI-H460 ($IC_{50} = 11 \pm 1 \mu M$, $23 \pm 3 \mu M$), SiHa ($IC_{50} = 10 \pm 1 \mu M$, $19 \pm 1 \mu M$), SW ($IC_{50} = 5.8 \pm 1 \mu M$, $19 \pm 1 \mu M$) cancer cell lines. Compounds **66** and **67** are Ir and Rh metal complexes, respectively. These compounds contain benzyl groups at both nitrogen atoms of benzimidazole. Studies of the mode of action of rhodium complexes are based on the fact that instead of interaction with DNA, it accumulates in the cytoplasm [80]. Zhao et al. synthesized naphthyl NHC-Rh complexes by incorporating a hydroxy alkyl chain at benzimidazole nitrogen. Upon evaluation against MCF-7 cell line, compounds **68** ($IC_{50} = 0.38 \mu M$), **69** ($IC_{50} = 0.45 \mu M$), and **70** ($IC_{50} = 0.72 \mu M$) showed excellent activity as compared to standard drug paclitaxel ($IC_{50} = 1.38 \mu M$). Therefore, the introduction of the hydroxyl group and alkyl group at the benzimidazole nitrogen is beneficial for the activity [81]. Sanchez-Mora et al. reported the formation of two benzimidazolium-based Ir(I) complexes as new cytotoxic agents. The benzimidazole ring was substituted by benzyl and pentafluorobenzyl groups. The benzyl-substituted derivative presented prominent activity and compound **71** was found to be the strongest agent against PC-3 ($IC_{50} = 10.6 \pm 0.9 \mu M$) and SKLU-7 ($IC_{50} = 10.4 \pm 1.5 \mu M$) cell lines. This compound showed less toxicity for normal cell line COS-7 [82]. Choo et al. synthesized pyridine-functionalized Pd-based imidazolium and benzimidazolium carbenes. Imidazolium Pd complex showed prominent activity against cancer cell lines. Benzimidazolium Pd complex **72** is also an excellent candidate for anticancer studies. Generally, NHC-Pd complexes create covalent bonding with DNA resulting in cross-linking of guanine base [83]. Early on in 2012, Sivaram and his coworker were able to synthesize new gold (I) and gold (III) complexes bearing benzimidazolium ligand. These complexes were mono-, homo-bis-, and hetero-bis-benzimidazole NHC. The hetero-bis-benzimidazole complexes are nonclassical pyrazole-derived NHC. Complexes **73** ($IC_{50} = 0.284 \pm 0.11 \mu M$) and **74** ($IC_{50} = 0.24 \pm 0.01 \mu M$) exhibited prominent inhibitory action against NSCLC (NCI-H1666) cell line. These complexes are isopropyl-substituted homo-bis and hetero-bis NHC complexes, respectively [84]. Rehm et al. synthesized benzimidazole platinum complexes having different alkyl chains such as methyl, ethyl, butyl, and octyl chains. The bis-phosphane complexes showed the excellent anticancer activity against seven cancer cell lines. Compound **75** appeared as the most effective against different cancer cell lines having IC_{50} values placing from 0.10 to 0.30 μM . Complex **75** displayed prominent activity ($IC_{50} = 0.10 \pm 0.01 \mu M$) against multidrug-resistant strains of MCF-7. Cell cycle analysis of some complexes indicated that they produced cell blockage in the G1 stage [85].

3. Conclusion

The pharmacological properties of benzimidazolium salts have attracted the attention of medicinal chemists. The resemblance of benzimidazole scaffold with purine bases establishes it biologically significant. Benzimidazolium salts have demonstrated promising activities against various cancer cell lines. Benzimidazolium salts derivatives have been prepared by the functionalization of two nitrogen atoms in the imidazole ring along with the preparation of hybrid molecules, and metal complexes. The hybridization of benzimidazole salts with natural compounds such as chalcones and steroids exhibited prominent activities ($IC_{50} < 1 \mu M$) against various cancer cell lines. Some hybrids compounds also showed the phenomenon of apoptosis. Compounds

carrying alkyl chains and aromatic rings at benzimidazole nitrogen showed pronounced activity. The introduction of phenyl, naphthalene, anthracene, and quino-line rings at the benzimidazole nitrogens through methylene groups intensified the anticancer activity. The 5,6-dimethyl-substituted benzimidazole derivatives were also found more active as compared to unsubstituted benzimidazole rings. In the case of silver metal complexes, bis-benzimidazolium complexes exhibited exceptional activity against colon cancer ($IC_{50} < 1 \mu M$) cell line. But silver metal complexes presented less selectivity indices. Mono-benzimidazolium metal complexes proved more active against breast cancer ($IC_{50} < 1 \mu M$) cell lines. In some derivatives, the introduction of a long alkyl chain at the benzimidazole nitrogen is beneficial for the augmentation of anticancer activity. The activity of selenium metal complexes was almost equivalent to their respective salts. While the halogen-substituted ruthenium benzimidazole metal complexes showed moderate activity. Rhodium, platinum, and gold complexes have also shown encouraging anticancer activities and are excellent candidates for future investigations. The *in vivo* investigations of potent compounds mentioned in this chapter could lead to further developments in the field.

Author details

Imran Ahmad Khan¹, Noor ul Amin Mohsin², Sana Aslam³ and Matloob Ahmad^{1*}

¹ Department of Chemistry, Government College University, Faisalabad, Pakistan

² Department of Pharmaceutical Chemistry, Faculty of Pharmaceutical Sciences, Government College University, Faisalabad, Pakistan

³ Department of Chemistry, Government College Women University Faisalabad, Pakistan

*Address all correspondence to: matloob.ahmad@gcuf.edu.pk

IntechOpen

© 2022 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

References

- [1] Bray F, Ferlay J, Soerjomataram I. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians*. 2018;**68**(6):394-424. DOI: 10.3322/caac.21492
- [2] Bray F, Jemal A, Grey N. Global cancer transitions according to the Human Development Index (2008-2030): A population-based study. *The Lancet Oncology*. 2012;**13**(8):790-801. DOI: 10.1016/S1470-2045(12)70211-5
- [3] Danaei G, Vander Hoorn S, Lopez AD, Comparative Risk Assessment collaborating group (Cancers). Causes of cancer in the world: Comparative risk assessment of nine behavioural and environmental risk factors. *The Lancet*. 2005;**366**(9499):1784-1793. DOI: 10.1016/S0140-6736(05)67725-2
- [4] Pucci C, Martinelli C, Ciofani G. Innovative approaches for cancer treatment: Current perspectives and new challenges. *Ecancermedicallscience*. 2019;**13**:961. DOI: 10.3332/ecancer.2019.961
- [5] Masoud V, Pages G. Targeted therapies in breast cancer: New challenges to fight against resistance. *World Journal of Clinical Oncology*. 2017;**8**(2):120-134. DOI: 10.5306%2Fwjco.v8.i2.120
- [6] Vitaku E, Smith DT, Njardarson JT. Analysis of the structural diversity, substitution patterns, and frequency of nitrogen heterocycles among us FDA approved pharmaceuticals. *Journal of Medicinal Chemistry*. 2014;**57**(24):10257-10274. DOI: 10.1021/jm501100b
- [7] Barker HA, Smyth RD, Weissbach H. Isolation and properties of crystalline cobamide coenzymes containing benzimidazole or 5, 6-dimethylbenzimidazole. *Journal of Biological Chemistry*. 1960;**235**(2):480-488. DOI: 10.1016/s0021-9258(18)69550-x
- [8] Khan MT, Razi MT, Jan SU. Synthesis, characterization, and antihypertensive activity of 2-phenyl substituted benzimidazoles. *Pakistan Journal of Pharmaceutical Sciences*. 2018;**31**(3):1067-1074. DOI: 10.36721/pjps.2019.32.6.reg.2585-2597.1
- [9] Kaur G, Silakari O. Benzimidazole scaffold-based hybrid molecules for various inflammatory targets: Synthesis and evaluation. *Bioorganic Chemistry*. 2018;**80**:24-35. DOI: 10.1016/j.bioorg.2018.05.014
- [10] Al-Blewi FF, Al-mehmadi MA, Aouad MR. Design, synthesis, ADME prediction, and pharmacological evaluation of novel benzimidazole-1, 2, 3-triazole-sulfonamide hybrids as antimicrobial and antiproliferative agents. *Chemistry Central Journal*. 2018;**12**(1):1-14. DOI: 10.1186/s13065-018-0479-1
- [11] Scheinfeld N. Cimetidine: A review of the recent developments and reports in cutaneous medicine. *Dermatology Online Journal*. 2003;**9**(2):4. DOI: 10.5070/D33s15q645
- [12] Vausselin T, Seron K, Lavie M. Identification of a new benzimidazole derivative as an antiviral against hepatitis C virus. *Journal of Virology*. 2016;**90**(19):8422-8434. DOI: 10.1128/JVI.00404-16
- [13] Ozil M, Parlak C, Baltas N. A simple and efficient synthesis of benzimidazoles containing piperazine or morpholine skeleton at C-6 position as glucosidase

inhibitors with antioxidant activity. *Bioorganic Chemistry*. 2018;**76**:468-477. DOI: 10.1016/j.bioorg.2017.12.019

[14] Hussain A, Alajmi MF, Rehman M. Evaluation of transition metal complexes of the benzimidazole-derived scaffold as promising anticancer chemotherapeutics. *Molecules*. 2018;**23**(5):1232-1250. DOI: 10.3390/molecules23051232

[15] Bharadwaj SS, Poojary B, Nandish SKM. Efficient synthesis and in silico studies of the benzimidazole hybrid scaffold with the quinolinylloxadiazole skeleton with potential α -glucosidase inhibitory, anticoagulant, and antiplatelet activities for type-II diabetes mellitus management and treating thrombotic disorders. *ACS Omega*. 2018;**3**(10):12562-12574. DOI: 10.1021/acsomega.8b01476

[16] Wang YT, Shi TQ, Zhu HL. Synthesis, biological evaluation, and molecular docking of benzimidazole grafted benz sulfamide-containing pyrazole ring derivatives as novel tubulin polymerization inhibitors. *Bioorganic & Medicinal Chemistry*. 2019;**27**(3):502-515. DOI: 10.1016/j.bmc.2018.12.031

[17] Ibrahim HS, Albakri ME, Mahmoud WR. Synthesis and biological evaluation of some novel thiobenzimidazole derivatives as anti-renal cancer agents through inhibition of c-MET kinase. *Bioorganic Chemistry*. 2019;**85**:337-348. DOI: 10.1016/j.bioorg.2019.01.006

[18] Min R, Wu W, Wang M. Discovery of 2-(1-(3-(4-Chloroxyphenyl)-3-oxo-propyl) pyrrolidine-3-yl)-1*H*-benzo [d] imidazole-4-carboxamide: A potent poly (ADP-ribose) polymerase (PARP) inhibitor for treatment of cancer. *Molecules*. 2019;**24**(10):1901. DOI: 10.3390/molecules24101901

[19] Gaba M, Mohan C. Development of drugs based on imidazole and

benzimidazole bioactive heterocycles: Recent advances and future directions. *Medicinal Chemistry Research*. 2016;**25**(2):173-210. DOI: 10.1007/s00044-015-1495-5

[20] Purushottamachar P, Ramalingam S, Najar VC. Development of benzimidazole compounds for cancer therapy. In: *Chemistry and Applications of Benzimidazole and its Derivatives*. 2019. pp. 1-15. DOI: 10.5772/intechopen.86691

[21] Narasimhan B, Sharma D, Kumar P. Benzimidazole: A medicinally important heterocyclic moiety. *Medicinal Chemistry Research*. 2012;**21**(3):269-283. DOI: 10.1007/s00044-010-9533-9

[22] Gupta S, Basu B, Das S. Benzimidazole-based palladium-*N*-heterocyclic carbene: A useful catalyst for C-C cross-coupling reaction at ambient condition. *Tetrahedron*. 2013;**69**(1):122-128. DOI: 10.1016/j.tet.2012.10.055

[23] Medici S, Peana M, Crisponi G. Silver coordination compounds: A new horizon in medicine. *Coordination Chemistry Reviews*. 2016;**327**:349-359. DOI: 10.1016/j.ccr.2016.05.015

[24] Viegas-Junior C, Danuello A, da Silva Bolzani VDS. Molecular hybridization: A useful tool in the design of new drug prototypes. *Current Medicinal Chemistry*. 2007;**14**(17):1829-1852. DOI: 10.2174/092986707781058805

[25] Singh A, Singh JV, Rana A. Monocarbonyl curcumin-based molecular hybrids as potent antibacterial agents. *ACS Omega*. 2019;**4**(7):11673-11684. DOI: 10.1021/acsomega.9b01109

[26] Yang JL, Ma YH, Li YH. Design, synthesis, and anticancer activity of novel trimethoxyphenyl-derived chalcone-benzimidazolium salts. *ACS*

Omega. 2019;**4**(23):20381-20393.
DOI: 10.1021/acsomega.9b03077

[27] Karatas MO, Tekin S, Alici B. Cytotoxic effects of coumarin substituted benzimidazolium salts against human prostate and ovarian cancer cells. Journal of Chemical Sciences. 2019;**69**:131. DOI: 10.1007/s12039-019-1647-0

[28] Wang XQ, Chen XB, Ye PT. Synthesis and biological evaluation of novel 3-benzylcoumarin-imidazolium salts. Bioorganic & Medicinal Chemistry Letters. 2020;**30**(4):126896. DOI: 10.1016/j.bmcl.2019.126896

[29] Deng G, Zhou B, Wang J. Synthesis and antitumor activity of novel steroidal imidazolium salt derivatives. European Journal of Medicinal Chemistry. 2019; **168**:232-252. DOI: 10.1016/j.ejmech.2019.02.025

[30] Nirmal NP, Rajput MS, Prasad RGSV. Brazilin from *Caesalpinia sappan* heartwood and its pharmacological activities: A review. Asian Pacific Journal of Tropical Medicine. 2015;**8**(6):421-430. DOI: 10.1016/j.apjtm.2015.05.014

[31] Huang M, Duan S, Ma X. Synthesis and antitumor activity of aza-brazilan derivatives containing imidazolium salt pharmacophores. MedChemComm. 2019;**10**(6):1027-1036. DOI: 10.1039/C9MD00112C

[32] Zhou B, Liu ZF, Deng GG. Synthesis and antitumor activity of novel N-substituted tetrahydro-beta-carboline-imidazolium salt derivatives. Organic & Biomolecular Chemistry. 2016;**14**(39):9423-9430. DOI: 10.1039/C6OB01495J

[33] Xu XL, Wang J, Yu CL. Synthesis and cytotoxic activity of novel 1-((indol-3-yl)methyl)-1H-imidazolium salts. Bioorganic & Medicinal Chemistry

Letters. 2014;**24**(21):4926-4930. DOI: 10.1016/j.bmcl.2014.09.045

[34] Li YH, Zhou B, Shi YM. Novel 3-substituted N-methylcarbazole-imidazolium salt derivatives: Synthesis and cytotoxic activity. Chemical Biology & Drug Design. 2018;**92**(1):1206-1213. DOI: 10.1111/cbdd.13178

[35] Wang XQ, Ye PT, Bai MJ. Synthesis and biological activity of new bisbenzofuran-imidazolium salts. Bioorganic & Medicinal Chemistry Letters. 2020;**30**(13):127210. DOI: 10.1016/j.bmcl.2020.127210

[36] Zhang CB, Liu Y, Liu ZF. Synthesis and cytotoxic activity of novel tetrahydrobenzodifuran-imidazolium salt derivatives. Bioorganic & Medicinal Chemistry Letters. 2017;**27**(8):1808-1814. DOI: 10.1016/j.bmcl.2017.02.053

[37] Zhou Y, Duan K, Zhu L. Synthesis and cytotoxic activity of novel hexahydropyrrolo[2,3-b]indole imidazolium salts. Bioorganic & Medicinal Chemistry Letters. 2016; **26**(2):460-465. DOI: 10.1016/j.bmcl.2015.11.092

[38] Akkoc S, Kayser V, Ilhan IO. New compounds based on a benzimidazole nucleus: Synthesis, characterization and cytotoxic activity against breast and colon cancer cell lines. Journal of Organometallic Chemistry. 2017;**839**: 98-107. DOI: 10.1016/j.jorgchem.2017.03.037

[39] Akkoc S, Kayser V, Ilhan IO. Synthesis and *in vitro* anticancer evaluation of some benzimidazolium salts. Journal of Heterocyclic Chemistry. 2019;**56**(10):2934-2944. DOI: 10.1002/jhet.3687.svg

[40] Akkoc S. Antiproliferative activities of 2-hydroxyethyl substituted

benzimidazolium salts and their palladium complexes against human cancerous cell lines. *Synthetic Communications*. 2019;**49**(21):1-12. DOI: 10.1080/00397911.2019.1650187

[41] Lin ZJ, Bies J, Johnson SS. Synthesis and anti-proliferative activity of *N*, *N'*-bis-substituted 1,2,4-triazolium salts against breast cancer and prostate cancer cell Lines. *Journal of Heterocyclic Chemistry*. 2018;**56**(2):533-538. DOI: 10.1002/jhet.3428

[42] Wright BD, Deblock MC, Wagers PO. Anti-tumor activity of lipophilic imidazolium salts on select NSCLC cell lines. *Medicinal Chemistry Research*. 2015;**24**:2838-2861. DOI: 10.1007/s00044-015-1330-z

[43] Stromyer ML, Southerland MR, Satyal U. Synthesis, characterization, and biological activity of a triphenylphosphonium-containing imidazolium salt against select bladder cancer cell lines. *European Journal of Medicinal Chemistry*. 2020;**185**:111832. DOI: 10.1016/j.ejmech.2019.111832

[44] Shelton KL, Debord MA, Wagers PO. Synthesis, anti-proliferative activity, SAR study, and preliminary in vivo toxicity study of substituted *N*,*N'*-bis(arylmethyl) benzimidazolium salts against a panel of non-small cell lung cancer cell lines. *Bioorganic & Medicinal Chemistry*. 2017;**25**(1):421-439. DOI: 10.1016/j.bmc.2016.11.009

[45] Bansode P, Patil P, Choudhari P. Anticancer activity and molecular docking studies of ferrocene tethered ionic liquids. *Journal of Molecular Liquids*. 2019;**290**:111182. DOI: 10.1016/j.molliq.2019.111182

[46] KucuKbay H, Mumcu A, Tekin S. Synthesis and evaluation of novel *N*, *N'*-disubstituted benzimidazolium

bromides salts as antitumor agents. *Turkish Journal of Chemistry*. 2016;**40**(3):393-401. DOI: 10.3906/kim-1510-15

[47] Haque RA, Iqbal MA, Ahamed MBK. Design, synthesis and structural studies of meta-xylyl linked bis-benzimidazolium salts: Potential anticancer agents against human colon cancer. *Chemistry Central Journal*. 2012;**6**(1):68. DOI: 10.1186/1752-153x-6-68

[48] Huda NU, Islam S, Zia M. Anticancer, antimicrobial and antioxidant potential of sterically tuned bis-*N*-heterocyclic salts. *Zeitschrift für Naturforschung - Section C Journal of Biosciences*. 2018;**74**(1):17-23. DOI: 10.1515/znc-2018-0095

[49] Rosenberg B, Van Camp L, Krigas T. Inhibition of cell division in *Escherichia coli* by electrolysis products from a platinum electrode. *Nature*. 1965;**205**:698-699. DOI: 10.1038/205698a0

[50] Da Silva B, Habibi M, Ognier S. Silver nanocluster catalytic microreactors for water purification. *The European Physical Journal Special Topics*. 2016;**225**:707-714. DOI: 10.1140/epjst/e2015-50262-6

[51] Varaprasad K, Mohan YM, Vimala K. Synthesis and characterization of hydrogel-silver nanoparticle-curcumin composites for wound dressing and antibacterial application. *Journal of Applied Polymer Science*. 2011;**121**(2):784-796. DOI: 10.1002/app.33508

[52] Iqbal MA, Umar MI, Haque RA. Macrophage and colon tumor cells as targets for a binuclear silver(I) *N*-heterocyclic carbene complex, an anti-inflammatory and apoptosis mediator. *Journal of Inorganic*

- Biochemistry. 2015;**146**:1-13.
DOI: 10.1016/j.jinorgbio.2015.02.001
- [53] Ghadhayeb MZ, Haque RA, Budagumpi S. Mono- and bis-*N*-heterocyclic carbene silver(I) and palladium(II) complexes: Synthesis, characterization, crystal structure and *in vitro* anticancer studies. Polyhedron. 2017;**121**:222-230. DOI: 10.1016/j.poly.2016.09.065
- [54] Sharhan O, Heidelberg T, Hashim NM. Benzimidazolium-acridine-based silver *N*-heterocyclic carbene complexes as potential anti-bacterial and anti-cancer drug. Inorganica Chimica Acta. 2020;**504**: 119462. DOI: 10.1016/j.ica.2020.119462
- [55] Habib A, Nazari VM, Iqbal MA. Unsymmetrically substituted benzimidazolium based Silver(I)-*N*-heterocyclic carbene complexes: Synthesis, characterization and in vitro anticancer study against human breast cancer and colon cancer. Journal of Saudi Chemical Society. 2019;**23**(7):795-808. DOI: 10.1016/j.jscs.2019.03.002
- [56] Atif M, Bhatti HN, Haque RA. Synthesis, structure and anticancer activity of symmetrical and non-symmetrical silver(I)-*N*-heterocyclic carbene complexes. Applied Biochemistry and Biotechnology. 2020;**191**:1171-1189. DOI: 10.1007/s12010-019-03186-9
- [57] Achar G, Shahini CR, Patil SA. Sterically modulated silver(I) complexes of coumarin substituted benzimidazol-2-ylidenes: Synthesis, crystal structures and evaluation of their antimicrobial and antitumor cancer potentials. Journal of Inorganic Biochemistry. 2018;**183**:43-57. DOI: 10.1016/j.jinorgbio.2018.02.012
- [58] Yasar S, Koprulu TK, Tekin S. Synthesis, characterisation and cytotoxic properties of *N*-heterocyclic carbene silver(I) complexes. Inorganica Chimica Acta. 2018;**479**:17-23. DOI: 10.1016/j.ica.2018.04.035
- [59] Karlik O, Balcioglu S, Karatas MO. Synthesis, structural characterization and cytotoxicity studies of T-shaped silver(I) complexes derived from 1-benzyl-3*H*-benzimidazolium *p*-toluenesulfonates. Polyhedron. 2018;**142**:63-70. DOI: 10.1016/j.poly.2017.12.033
- [60] Fatima T, Haque RA, Razali MR. Effect of lipophilicity of wingtip groups on the anticancer potential of mono *N*-heterocyclic carbene silver(I) complexes: Synthesis, crystal structures and *in vitro* anticancer study. Applied Organometallic Chemistry. 2017;**31**(10): e3735. DOI: 10.1002/aoc.3735
- [61] Haque RA, Choo SY, Budagumpi S. Synthesis, crystal structures, characterization and biological studies of nitrile-functionalized silver(I) *N*-heterocyclic carbene complexes. Inorganica Chimica Acta. 2015;**433**: 35-44. DOI: 10.1016/j.ica.2015.04.023
- [62] Haque RA, Choo SY, Budagumpi S. Silver(I) complexes of mono- and bidentate *N*-heterocyclic carbene ligands: synthesis, crystal structures, and *in vitro* antibacterial and anticancer studies. European Journal of Medicinal Chemistry. 2015;**90**:82-92. DOI: 10.1016/j.ejmech.2014.11.005
- [63] Hussaini SY, Haque RA, Asekunowo PO. Synthesis, characterization and anti-proliferative activity of propylene linked bis-benzimidazolium salts and their respective dinuclear Silver(I)-*N*-heterocyclic carbene complexes. Journal of Organometallic Chemistry. 2017;**840**:56-62. DOI: 10.1016/j.jorgchem.2017.04.011

- [64] Hussaini SY, Haque RA, Fatima T. Nitrile functionalized silver(I) *N*-heterocyclic carbene complexes: DFT calculations and antitumor studies. *Transition Metal Chemistry*. 2018;**43**: 301-312. DOI: 10.1007/s11243-018-0216-6
- [65] Akkoc S, Ozer Ilhan I, Gok Y. *In vitro* cytotoxic activities of new silver and PEPPSI palladium *N*-heterocyclic carbene complexes derived from benzimidazolium salts. *Inorganica Chimica Acta*. 2016;**449**:75-81. DOI: 10.1016/j.ica.2016.05.001
- [66] Sahin N, Sahin-Bolukbasi S, Tahir MN. Synthesis, characterization and anticancer activity of allyl substituted *N*-Heterocyclic carbene silver (I) complexes. *Journal of Molecular Structure*. 2019;**1179**:92-99. DOI: 10.1016/j.molstruc.2018.10.094
- [67] Ozdemir I, Ciftci O, Evren E. Synthesis, characterization and antitumor properties of novel silver(I) and gold(I) *N*-heterocyclic carbene complexes. *Inorganica Chimica Acta*. 2020;**506**:119530. DOI: 10.1016/j.ica.2020.119530
- [68] Cevik-Yildiz E, Sahin N, Sahin-Bolukbasi S. Synthesis, characterization, and investigation of antiproliferative activity of novel Ag (I)-*N*-heterocyclic Carbene (NHC) compounds. *Journal of Molecular Structure*. 2020;**1199**:126987. DOI: 10.1016/j.molstruc.2019.126987
- [69] Aktas A, Kelestemur U, Gok Y. 2-Morpholinoethyl-substituted *N*-heterocyclic carbene (NHC) precursors and their silver (I) NHC complexes: Synthesis, crystal structure and *in vitro* anticancer properties. *Journal of the Iranian Chemical Society*. 2018;**15**:131-139. DOI: 10.1007/s13738-017-1216-8
- [70] Kızrak U, Ciftci O, Ozdemir I. Amine-fnctionalized silver and gold *N*-heterocyclic carbene complexes: Synthesis, characterization and antitumor properties. *Journal of Organometallic Chemistry*. 2019;**882**: 26-32. DOI: 10.1016/j.jorganchem.2018.12.018
- [71] Sahin-Bolukbasi S, Sahin N. Novel Silver-NHC complexes: Synthesis and anticancer properties. *Journal of Organometallic Chemistry*. 2019;**891**: 78-84. DOI: 10.1016/j.jorganchem.2019.04.018
- [72] Sahin-Bolukbasi S, Sahin N, Tahir MN. Novel *N*-heterocyclic carbene silver(I) complexes: Synthesis, structural characterization, and anticancer activity. *Inorganica Chimica Acta*. 2019;**486**:711-718. DOI: 10.1016/j.ica.2018.11.044
- [73] Roman M, Jitaru P, Barbante C. Selenium biochemistry and its role for human health. *Metallomics*. 2014;**6**(1): 25-54. DOI: 10.1039/c3mt00185g
- [74] Eiche E, Nothstein AK, Gottlicher J. The behaviour of irrigation induced Se in the groundwater-soil-plant system in Punjab, India. *Environmental Science. Processes & Impacts*. 2019;**21**(6):957-969. DOI: 10.1039/C9EM00009G
- [75] Kamal A, Nazari M, Yaseen M. Green synthesis of Selenium-*N*-heterocyclic carbene compounds: Evaluation of antimicrobial and anticancer potential. *Bioorganic Chemistry*. 2019;**90**:103042. DOI: 103042, 10.1016/j.bioorg.2019.103042
- [76] Iqbal MA, Haque RA, Ng WC. Green synthesis of mono- and di-Selenium-*N*-heterocyclic carbene adducts: Characterizations, crystal structures and pro-apoptotic activities against human colorectal cancer. *Journal of*

Organometallic Chemistry. 2016;**801**: 130-138. DOI: 10.1016/j.jorganchem.2015.10.023

[77] Akkoc M, Balciolu S, Gurses C. Protonated water-soluble *N*-heterocyclic carbene ruthenium(II) complexes: Synthesis, cytotoxic and DNA binding properties and molecular docking study. *Journal of Organometallic Chemistry*. 2018;**869**:67-74. DOI: 10.1016/j.jorganchem.2018.06.003

[78] Onar G, Gurses C, Karatas MO. Palladium (II) and ruthenium (II) complexes of benzotriazole functionalized *N*-heterocyclic carbenes: Cytotoxicity, antimicrobial, and DNA interaction studies. *Journal of Organometallic Chemistry*. 2019;**886**: 48-56. DOI: 10.1016/j.jorganchem.2019.02.013

[79] Lam NYS, Truong D, Burmeister H. From catalysis to cancer: Toward structure-activity relationships for benzimidazol-2-ylidene-derived *N*-heterocyclic-carbene complexes as anticancer Agents. *Inorganic Chemistry*. 2018;**57**(22):14427-14434. DOI: 10.1021/acs.inorgchem.8b02634

[80] Truong D, Sullivan MP, Tong KKH. Potent inhibition of thioredoxin reductase by the Rh derivatives of anticancer M(arene/Cp*) (NHC)Cl₂ complexes. *Inorganic Chemistry*. 2020;**59**(3):3281-3289. DOI: 10.1021/acs.inorgchem.9b03640

[81] Zhao X, Shi L, He W. Synthesis of novel NHC–Rh complexes with anti-tumor activity against MCF-7 human breast cancer cells. *ARKIVOC*. 2020;**vi**:94-104. DOI: 10.24820/ark.5550190.p011.129

[82] Sanchez-Mora A, Valdes H, Ramirez-Apan MT. NHC-Ir (I)

complexes derived from 5, 6-dinitrobenzimidazole. Synthesis, characterization and preliminary evaluation of their *in vitro* anticancer activity. *Inorganica Chimica Acta*. 2019;**496**:119061. DOI: 10.1016/j.ica.2019.119061

[83] Choo KB, Mah WL, Lee SM. Palladium complexes of bidentate pyridine *N*-heterocyclic carbenes: Optical resolution, antimicrobial and cytotoxicity studies. *Applied Organometallic Chemistry*. 2018;**32**: e4377. DOI: 10.1002/aoc.4377

[84] Sivaram H, Tan J, Huynh HV. Syntheses, characterizations, and a preliminary comparative cytotoxicity study of gold(I) and gold(III) complexes bearing benzimidazole- and pyrazole-derived *N*-heterocyclic carbenes. *Organometallics*. 2012;**31**(16):5875-5883. DOI: 10.1021/om300444c

[85] Rehm T, Rothmund M, Bar A. *N*, *N*-dialkylbenzimidazol-2-ylidene platinum complexes - effects of alkyl residues and ancillary cis-ligands on anticancer activity. *Dalton Transactions*. 2018;**47**(48):17367-17381. DOI: 10.1039/C8DT03360A