German J Pharm Biomaterials 2022; 1(1): 6-28
https://doi.org/10.5530/gjpb.2022.1.3

GJPB

Review Article

Silver Complexes as Anticancer Agents: A Perspective Review

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Received: 16 March 2022; Revised: 7 April 2022; Accepted: 10 April 2022

Abstract

Metal complexes gained more attention in the medical field, particularly cancer treatment, due to their enhanced potential and redox ability. These complexes exhibited more significant anti-proliferation potential by triggering the generation of reactive oxygen species (ROS), altering cell membrane, changing cell redox potential and by DNA replication inhibition. Platinum-based metal complex Cisplatin was prepared. It was widely used in treating lung, breast, ovarian and testicular cancers; however, these complexes showed many adverse effects such as renal insufficiency and electrolyte abnormalities, neurotoxicity, ototoxicity, nausea, vomiting and drug resistance. To overcome these side effects and drug resistance mechanisms, silver metal is highly employed as a cytotoxic agent by DNA binding through the formation of disulphide bonds. Moreover, silver complexes exhibited more significant cytotoxicity with the lowest toxicity. This review highlighted silver complexes' anticancer and cytotoxic potential with various bioactive ligands.

Keywords: silver complex; anticancer; chemotherapy; cytotoxicity; ligands

Introduction

Cancer is one of the most hazardous, highly complex diseases that results in abnormal proliferation, invasion and metastasis activation and uncontrollable replication. Hence it is essential to design a powerful agent targeting the tumour cells [1]. Some critical techniques were employed for treating cancer, including biological immunisation, chemical medication, chemotherapy, radiotherapy and surgery. Metal and its compounds were employed in medicine in ancient times. It emerges greater attention from the scientists with its more comprehensive model of action after isolating the first metal complexes containing metal ions and organic ligands. Among various metal ions, a large group of metals and their complexes were used as a diagnostic aid in treating different diseases. Previously copper, arsenic trioxide, gold and mercury sulphide were employed for treating leukaemia, psoriasis, rheumatoid diseases and syphilis. In organometallics, it is well known that the ligands can have significant effects on the complexes. Metal complexes with unique characteristics, including reactivity, different coordination routes and redox ability, showed tremendous potential in cancer therapy. These complexes showed a better cytotoxic action than the ligands through reactive oxygen species (ROS) production, cell membrane alteration, inhibiting DNA replication, affecting electron transport and perturbation of enzyme action and altering redox potential of the cell [2-6].

Cisplatin and its derivatives, such as carboplatin and oxaliplatin, are utilised in clinical trials worldwide, and numerous other platinum analogues, such as lobaplatin, nedaplatin, and heptaplatin, have been approved in several countries. The structures of the platinum-based complexes are given in Figure 1. However, major adverse effects such as kidney, heart, ear and liver toxicity and a reduction in

immunity, bleeding, and gastrointestinal issues limit the usage of platinum compounds. The emergence of drug resistance has also restricted platinum-based medicines in clinical environments. Platinum-based treatment competence is challenged by cross-resistance and multiple changes, including a decreased accumulation of the drug, a reduction in DNA-drug adducts, a modification in cell survival gene expression, and alteration of DNA damage repair mechanisms, modifications of transporters, protein trafficking and altered cell metabolism [7]. Scientists have made some efforts to design metal-based drugs which exhibit lower toxicity with a broader spectrum of activity and overcome the resistance mechanism. Based on the previous studies, the resistance mechanism can be prevented by heterometallic complexes, which exhibit a synergistic effect because of the presence of two metal centres that produce cytotoxic effects with varying mechanisms. The adverse effects and drug resistance for platinum complexes, particularly cisplatin, emerged the researchers to design new metal complexes for the anticancer activity with the lower toxic effects [8-11].

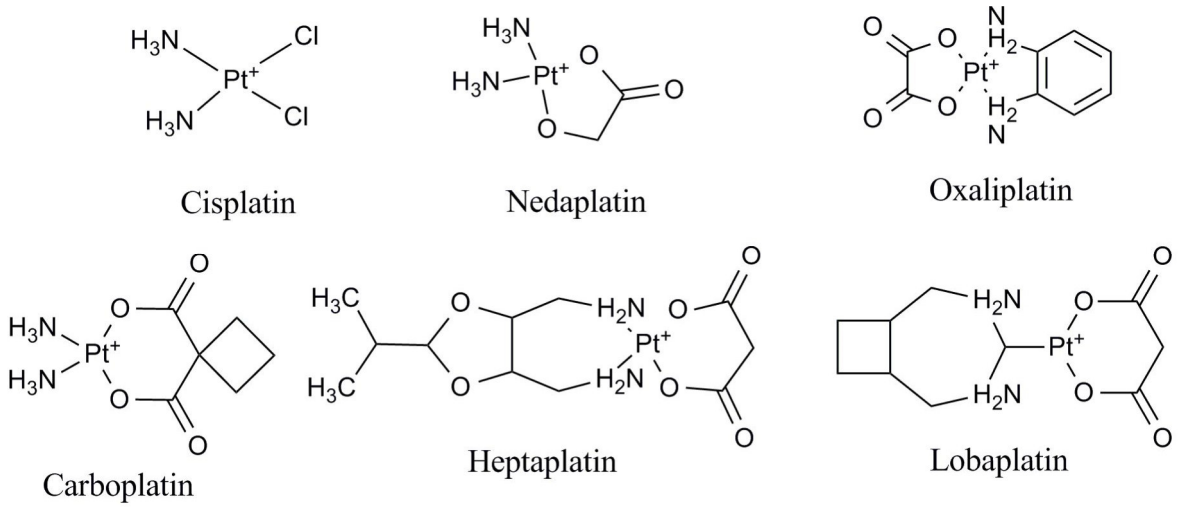


Figure 1. Structures of Platinum based Complexes.

Silver is one of the biological metals found in our body in trace amounts. Silver was previously used as a water cleanser and antibacterial agent and used to prevent eye infections in newborns. The extensive use of silver sulphadiazine as a topical agent in treating burns ensured a safety measure of silver [2,4]. The antibacterial mechanisms of silver were found to be mitochondrial dysfunction, DNA interaction, inducing reactive oxygen species (ROS) formation and cell wall disruption. Because of its various mechanisms, silver ions can interfere with the redox reactions of the thiol group, which may lead to blockage of electron transfer, cellular respiration, inactivating the essential enzymes and binding to DNA by means of formation of disulphide bond and fundamentally play an essential role in damaging the tumor cells [12-16]. In the silver complexes, the existence of ligands and a greater number of silver centre ions results in their improved biological function. Notably, the binuclear silver (I) complexes exhibited a more significant antiproliferation activity in cancer cells than the normal cells and exhibited low toxicity. Based on the reports of recent studies, among various metal complexes, silver metal complexes are more efficient as an anticancer agent in treating various types of cancer, including breast, colorectal, ovarian and lung cancer, compared with cisplatin [17,18]. In this review, only those literature indexed in ScienceDirect, PubMed, Springer, Karger, Molecules, Cross mark and Royal Society of Chemistry databases between 2011 and 2021 were surveyed. The keywords for this survey include metal complexes, silver, cytotoxicity, N-heterocyclic carbenes, and chemotherapy, both individually and in combination, which were applied and shortlisted according to the purpose of this study. This review focuses on the anticancer activity of the silver metal complexes with N-heterocyclic carbenes (NHCs), 5-fluorouracil, NSAIDS, phosphines, carboxylates, Schiff bases, dehydronorcantharidin and some other bioactive complexes.

Anticancer potential of various silver complexes

Cisplatin, carboplatin and oxaliplatin are platinum-based metal complexes that have been widely utilised in cancer treatment. Because of the resistance mechanism of platinum complexes, various reports were focused on developing the other organometallic complexes that show better cytotoxic activity than cisplatin. Among various metals, including ruthenium, iridium, rhodium, vanadium, gold, arsenic, antimony, bismuth, iron and platinum, silver ions have better cytotoxic activity with the lowest toxicity. Donor atoms like phosphorus, nitrogen, oxygen and sulphur of silver complexes exhibit more excellent activity against the cancer cell lines [2,19,20]. Most silver complexes were synthesised with N-heterocyclic carbenes (NHCs), 5-fluorouracil, NSAIDs, phosphines, carboxylates, Schiff bases, dehydronorcantharidin and other bioactive complexes are discussed as follows.

Silver-NHC Complexes

Because of the neutral nature of electron donors, NHCs can bind with metal ions through the σ-donation. It also plays a significant role in the research field, particularly in catalysis, because of its better stability and easy derivability. Most studies have displayed the imidazole-based nucleus, but some benzimidazole derivatives were rarely studied. Ag-NHC complexes exhibit a slow-release rate of silver. Arduengo and coworkers have designed the first Ag-NHC complex with the usage of free carbenes, but its synthesis was limited due to some complications in getting free carbenes. It has been reported that the capability of the Ag-NHCs in the transmetallation reaction as a carbene transfer agent facilitates the synthesis of various metal-NHC complexes [5,21,22]. All the structures of Ag-NHC complexes are given in Figure 2-4.

Benzimidazolium salt-based NHC-Ag (I) complexes **1 a-c** were synthesised, and its cytotoxicity was evaluated against MCF-7, MDA-MB-231 cancer cell lines and MCF 10A cell line using MTT assay in which **1a** showed better cytotoxicity in MCF-7 cell line due to the presence of 3-propyl substituent as compared to MCF 10A non-cancer cell line, whereas **1b** resulted in better cytotoxicity in MDA-MB-231 cell line due to the presence of 3-isopropyl substituent as compared to MCF-7 and MCF 10A cell lines. The cytotoxicity of **1c** was found to be less active than cisplatin, **1a** and **1b,** whereas after 72h of incubation, **1c** produced better anticancer activity towards MCF-7 cells than MCF 10A cells [1]. The in vitro anticancer efficiency of the designed 1,2,3-benzotriazole mediated NHC-Ag complexes **2-4** against MCF-7, Caco-2 cancer cell lines and L-929 non-cancer cell lines were performed using MTT assay. All these complexes exhibited better anticancer activity as compared to cisplatin. Mainly, the complex **2** showed potent cytotoxicity towards the Caco-2 cell line. Against the non-cancer cell line, benzimidazole based complex **3** showed better anti-proliferative activities than cisplatin [5].

A series of Ag-NHC complexes were designed and evaluated their cytotoxicity against various cell lines. The better activity was achieved by inducing the apoptosis-inducing factor (AIF) and caspase-12 translocation from mitochondria into the cell's nucleus, which may cause DNA fragmentation and finally lead to apoptosis. Among 14 complexes, only 3 complexes **5, 6 & 7** displayed the high efficiency towards the KB cells for the initial screening. Anti-proliferative activity was screened against HTC 116, HCT 15, MCF-7, MCF7R, HL60, HL60R cancer cell lines and MRC5, EPC (non-cancer cell lines). The IC_{50} measurements of the complex **5** and complex **6** exhibited more significant inhibition on HCT 116, MCF-7 and HL60 cell lines, whereas the IC_{50} measurements of the complex 6 exhibited significantly lesser inhibition on HCT 116 and MCF-7 cell lines [8].

N-isopropyl substituted ortho/meta/para xylyl linked bis-benzimidazolium salts with hexafluorophosphate or bromide were synthesized, and their cytotoxic potential was evaluated. The morphological characters confirmed the cytotoxic activity of the complexes **8-10**, including apoptotic bodies formation, nuclear condensation, and membrane bleeding [12]. Benzimidazole-based NHC-Ag (I) complexes **11 a-b**, and **12** were designed and evaluated for the in vitro cytotoxic potential against HCT 116 and HT29 cancer cell lines using MTT assay. Complexes **11 a-b** and **12** showed a better effect on cell viability and morphology of the cancer cell lines compared with the standard 5-fluorouracil (5-FU). Complexes **11 a-b** showed more vigorous activity toward the HCT 116 cell line, whereas the binuclear complex 12 showed more cytotoxicity towards the HCT 116 cell line than **11a** and **11b**. While

compared with nitrile mediated benzimidazole based NHC-Ag (I) complex, it showed greater in vitro and in vivo cytotoxic effect on cancer cells. Because of complexes' symmetrical and unsymmetrical substitution, **11a** and **11b** exhibited more activity, while **12** showed decreased activity against the HT29 cell line [16]. The Ag-NHC complex **13** was synthesized using xanthine derivatives like caffeine, theobromine and theophylline (xanthine based imidazolium salts), and it is in vitro anticancer activity was evaluated against A375, HCT 116, HT-29, LN 229, U-87 MG, U-251, panc-1 and Sitta cell lines using MTT assay. It showed significant anti-proliferation activity against the respective cell lines, and the better activity was due to the presence of the phenyl group, which lowered the release rate of silver [22]. The anticancer activity of the amino linked NHC against three human cancer cell lines including MCF-7, MDA-MB-231 and U-87 MG using palladium, gold and silver metal complexes by p53 bak pathway triggering apoptosis was determined. The IC_{50} value of the Ag+ complex **14** indicated the better anticancer activity against the MCF-7 and MDA-MB-231, which are closer to the IC_{50} value of cisplatin, whereas, in the U-87 MG cell line, the Ag+ complex showed a lesser activity in comparing with Pd and Au complexes [23].

Ag(I)-NHC complexes containing imidazolium linked cyclophanes based ligand exhibited significant stability and better fluorescence properties due to the presence of the anthracene group. The in vitro cytotoxic effect of the Ag-NHC complexes **15 & 16** was evaluated using MTT assay against the cancer cell lines HeLa, A549, cisplatin-resistant A549, MDA-MB-231 cancer cell lines and LO_2 cell line. These Complexes exhibited maximum cytotoxicity towards cancer cell lines, but against the normal human liver LO_2 cells, they showed lesser cytotoxicity on comparing with cisplatin and also, and these complexes could overcome the resistance of cisplatin. Complexes **15 & 16** showed anti-proliferation activity by inducing reactive oxygen species (ROS) and caspase, which resulted in early apoptosis [24].

Using SRB assay, the coumarin substituted benzimidazole-2-ylidenes derived Ag-NHC complex 17 against H1975, and A549 cell lines showed strong cytotoxic efficiency [25]. The Ag(I)-allyl substituted NHC complexes **18 a-d** were synthesized and evaluated their cytotoxicity against DU-145, MCF-7, MDA-MB-231 cancer cell lines and L-929 cell line using MTT assay. All these complexes exhibited significant activity; specifically, **18d** exhibited better efficiency than other complexes. The overall order of efficiency was determined as **18d>18c>18a>18b** [26]. Fluorescent compound functionalized complex like fluorescent 1-(9-anthracenyl methyl)-3-(1-trimethyl silyl-3-propynil)-benzimidazole-2-ylidene functionalized NHC-Ag (I) complex **19** was synthesized and demonstrated that the complex was active against A549, SW480 and HepG2 cancer cells with the most robust activity as that of cisplatin. The stronger reactivity of this complex was proportional to the faster inactivation of the cell [27].

Benzimidazolium based complexes **20 a-c** were synthesized, and their anti-proliferation activity was evaluated against MCF-7, MDA-MB-231, DU-145 cancer cell lines and L-929 regular cell line using MTT assay. The complex **20c** showed more significant activity because of an increased number of rings, and the order of activity of the complexes was expressed as **20c>20b>20a. 20a** and **20b** complexes showed potent anticancer activity towards MCF-7 and MDA-MB-231 breast cancer cell lines [28]. The anticancer efficiency of the non-symmetrically and symmetrically substituted Ag(I)-NHC complexes **21 a-c** concerning the benzimidazolium salts against MCF-7, HCT 116 and K-562 cancer cell lines was determined using MTT assay. The anticancer evaluation of the Ag-NHC complex showed the capability of Ag (I) ions to inhibit uncontrollable cell proliferation through the inhibition of cellular transcription and its specific ability based on its compatibility and bioavailability. Among the complexes, **21b** and **21c** showed extreme cytotoxicity towards HCT 116 and MCF-7 cancer cell lines [29].

On the other hand, Ag (I)-benzimidazolium acridine based NHC complex **22** was also synthesised to determine its *in vitro* anticancer activity against MCF-7 and MCF 10A cell lines using the standards tamoxifen and paclitaxel. The IC_{50} value of the acridine complex was closer to the standards and showed more significant anticancer activity, which has not affected the non-cancer cell line [30]. Benzimidazole-2-ylidene based complexes **23 a-d** were also employed to determine anti-proliferation activity against MCF-7, MDA-MB-231, DU-145 cancer cell lines and L-929 using MTT assay. The complexes showed greater anticancer activity toward the MDA-MB-231 cancer cell line, complex **23c** and **23d** expressed

more excellent activity in all cell lines, whereas **23a** and **23b** showed greater activity towards the DU-145 cancer cell line [31].

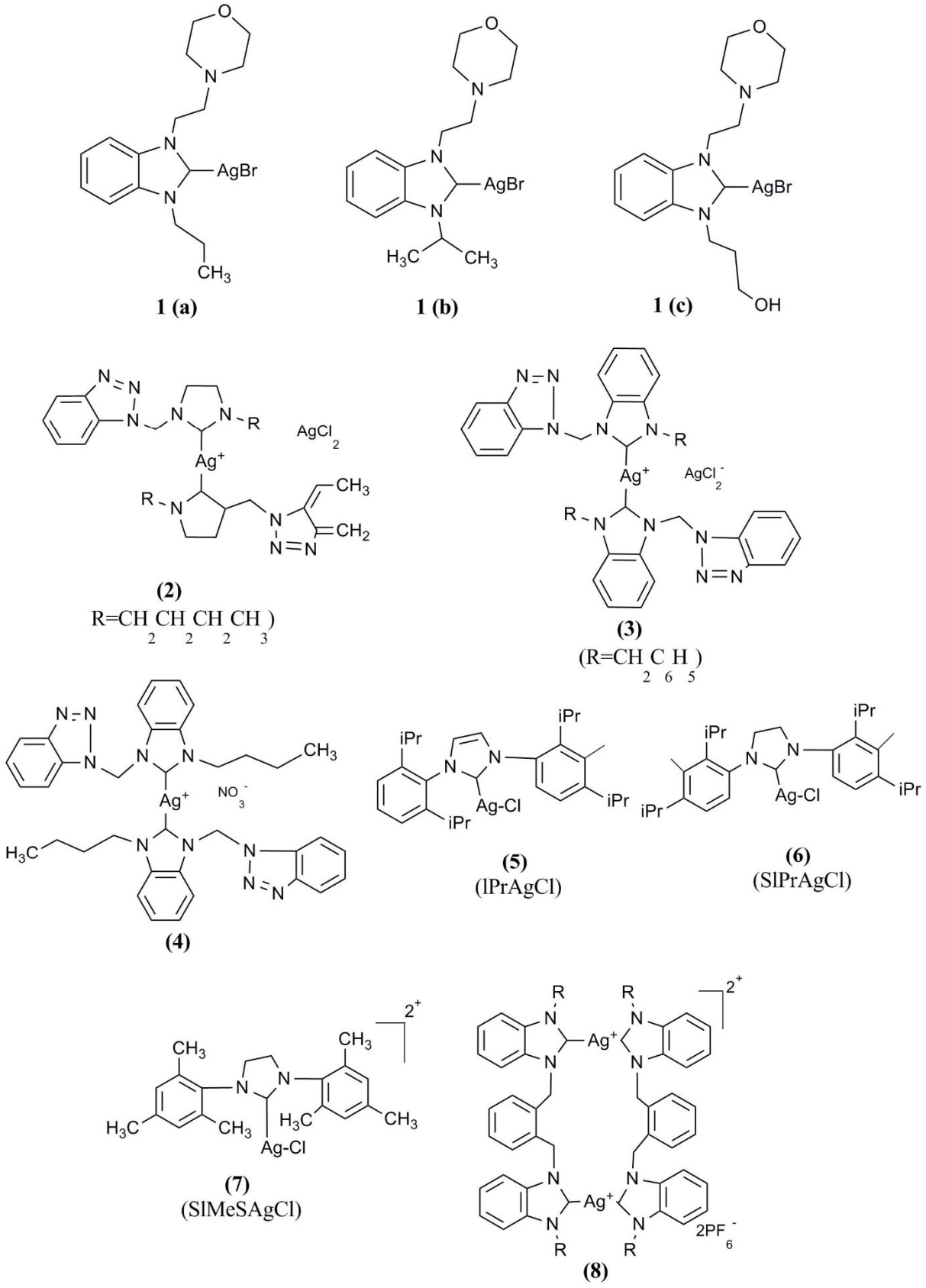


Figure 2. Structures of Silver-NHC Complexes (1-8).

The anticancer activity of propylene linked bis-benzimidazolium based NHC-Ag (I) complexes **24 a-d** against MCF-7 cell line was demonstrated using MTT assay. These complexes showed dose-dependent cytotoxic potential against the MCF-7 cell line, and the mechanism of the complex was binding of Ag+ on the proteins of the cell wall, which may damage the cell wall and its functions. Complex stability can be increased by enhancing lipophilicity by either substituting alkyl chain length or propylene linkage. Thus, the Ag+ complex may also be worked by interacting with the metabolism and cellular respiration of the biological molecules [32].

Silver-5-Fluorouracil Complexes

5-fluorouracil is an anticancer agent of fluoropyrimidine analogue of uracil and an important ligand that express synergistic activities when coupled with the metal ions. It is commonly used to treat digestive tract and breast and colorectal cancers. It prevents the nucleotide synthetic enzyme thymidylate synthase and is incorporated into deoxyribonucleic acid (DNA) and ribonucleic acid (RNA), which may destroy DNA. Against the ovarian multidrug-resistant cancer cell line (NCI/ADR-RES), cytotoxicity was evaluated using the Rh123 assay, which promoted the mitochondrial membrane depolarization, resulting in cell death [14]. [Ag3(fu)(fu-H)] complex **25** was synthesized and evaluated for its anticancer activity in comparison with the standard cisplatin. Cisplatin destroys DNA through the coordination of nitrogen bases and Pt(II) ions, whereas 5-fluorouracil acts by disturbing DNA replication through thymidylate synthase enzyme inhibition. Thus, complex **25** possessed more significant activity against (NCI/ADR-RES) ovarian multidrug-resistant cancer cells. Combining 5-fluorouracil with silver metal ions resulted in overcoming the tumour resistance [19]. The structure of this complex is given in Figure 5.

Silver-NSAIDs Complexes

Non-steroidal anti-inflammatory drugs (NSAIDs) are used as analgesic, antipyretic and anti-inflammatory agents. They are widely used as an anti-tumour agent by inhibiting prostaglandin production using cyclooxygenase (COX) mediated pathways either dependently or independently. The Ag (I) complexes with mefenamic acid (NSAIDs) and 2-pyridine ethanol/2-pyridine methanol was synthesized and evaluated its anti-proliferation activity against HT-29 (colon), MCF-7 (breast), and HepG2 (hepatocarcinoma) cancer cell lines and 3T3L1 (mouse fibroblast) non-tumour cell line using lactate dehydrogenase (LDH) and 2,3-Bis-(2-Methoxy-4-Nitro-5-Sulfophenyl)-2H-Tetrazolium-5-Carboxanilide (XTT) assays. The complex [Ag_2(μ-mef)$_2$(2-pymet)$_2$] exhibited dose-dependent cytotoxicity against the MCF-7 cell line, whereas the [Ag_2(μ-mef)$_2$(2-pyet)$_2$] complex showed greater activity against HepG2 cell line. The anticancer mechanism of these two complexes was found to be modulation of the activity of caspase-3 and p53 activated-Bax/Bcl-2 ratio and by inhibiting aldo-keto reductase 1C activity [4,18].

Tofenamic acid is commonly used to treat migraine, an N-phenylanthranilic acid derivative used in the veterinary field. The cytotoxicity of the synthesised tolfenamic acid and Ag (I) complexes using 2-picoline and 4-picoline as ligands were evaluated against MCF-7, MDA-MB-453 (breast) cancer cell lines and 3T3L1 (healthy) cell line using XTT assay. The complex [Ag_2(μ-tolf)$_2$(4-pic)$_2$] showed greater cytotoxic potential against MCF-7 and MDA-MB-453 (breast) cancer cell lines than the complex [Ag_2(μ-tolf)$_2$(2-pic)$_2$] as compared to cisplatin and 5-fluorouracil. The cytotoxic mechanism of these complexes includes mitochondrial membrane depolarisation, inducing nitric oxide (NO) and ROS generation, activating various caspase, p13k/Akt phosphorylation prevention and S-phase cell cycle arrest [18]. The heteroleptic Ag (I) complex **(26)** with 4′-(4-substituted)-2,2′:6′2″-terpyridine and naproxen was designed and evaluated in vitro anticancer activity against MCF-7, HeLa, Hep-2, HepG2 cancer cell lines and NHDF (human dermal fibroblasts) regular cell line using MTT reduction assay. Complex **26** showed increased DNA synthesis at S-phase through Go-G1 and G2/M phase reduction and exhibited more excellent activity towards HepG2 cells by arresting the cells at S-phase through DNA damage [33]. The structure of this complex is given in Figure 5.

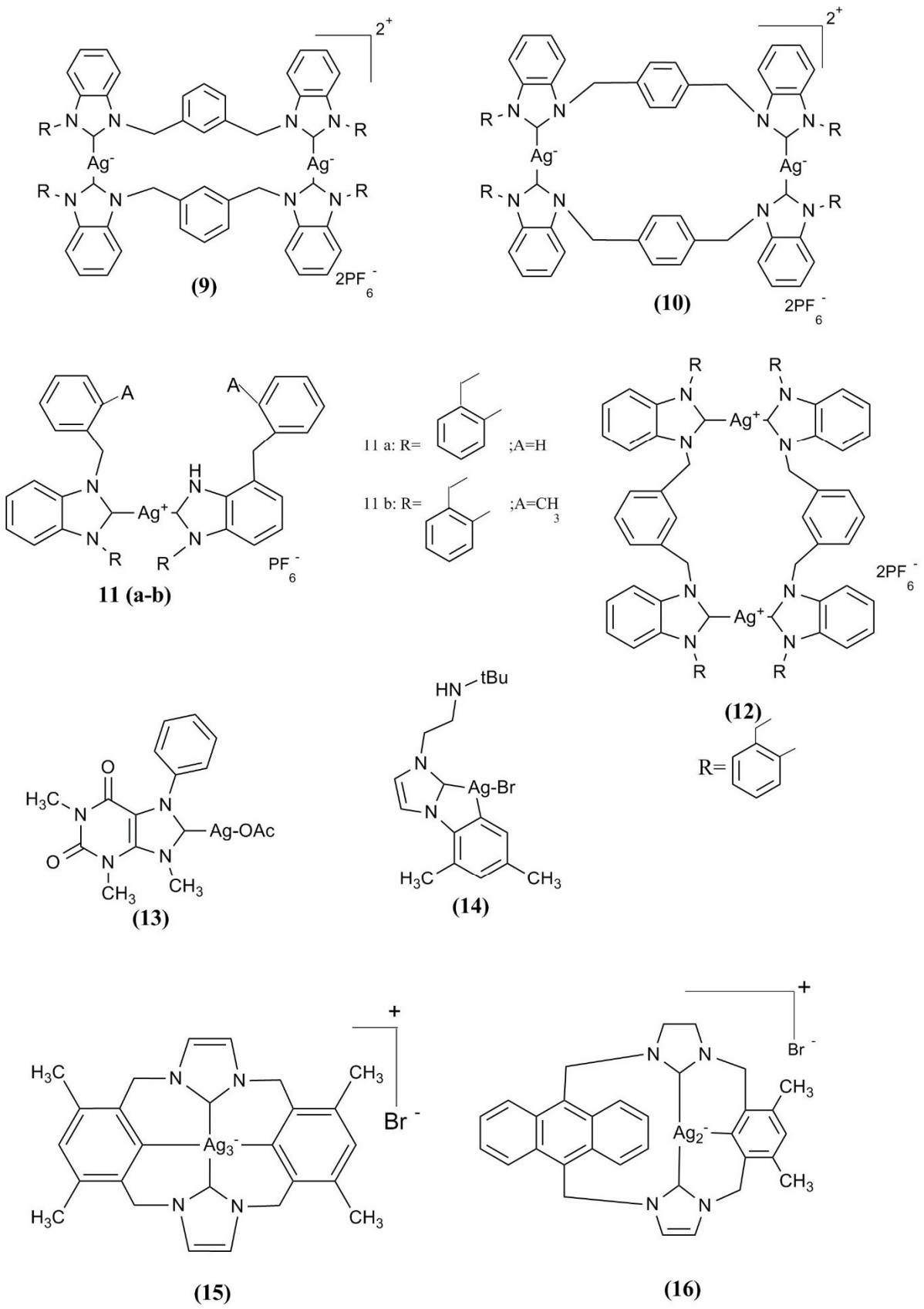


Figure 3. Structures of Silver-NHC Complexes (9-16).

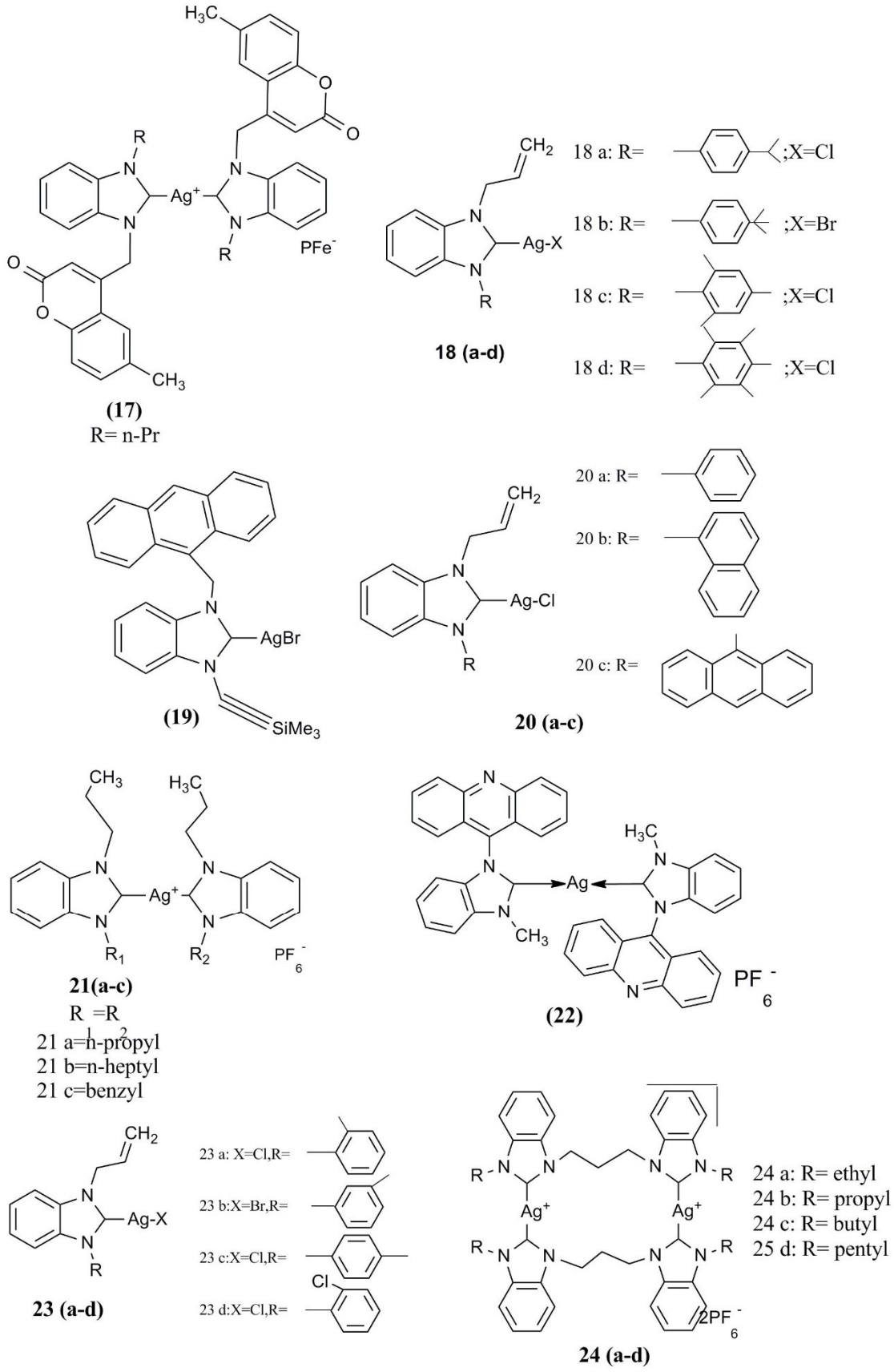
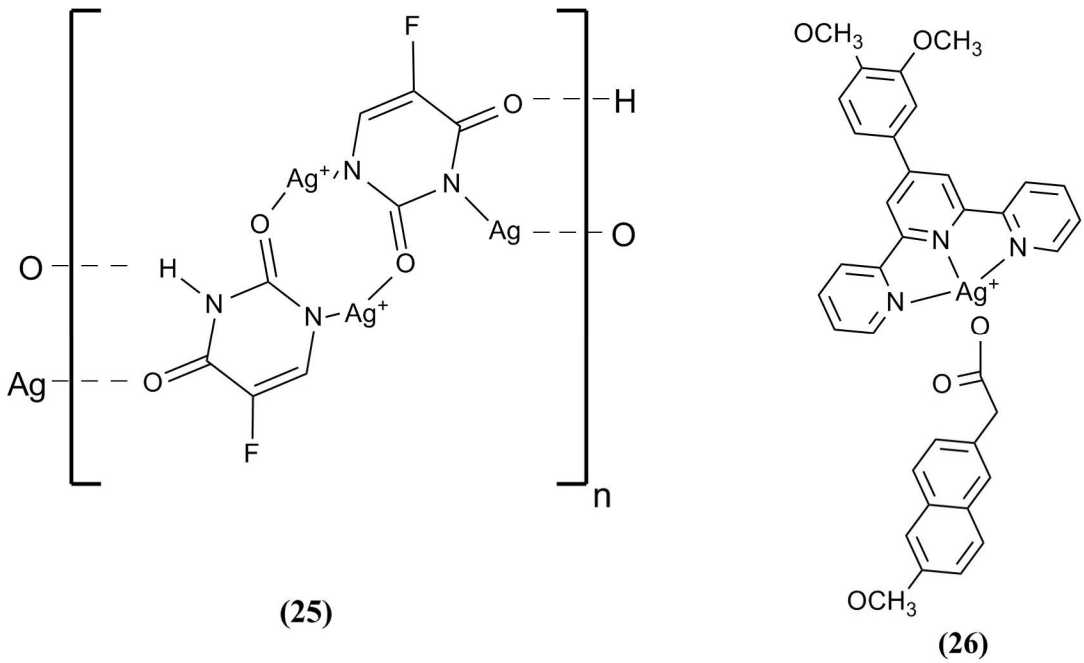


Figure 4. Structures of Silver-NHC Complexes (17-24)



(25) **(26)**

Figure 5. Structure of Silver-5-Fluorouracil Complex (25) and Silver-Naproxen Complex (26).

Silver-Phosphine Complexes

Phosphines or phosphanes are σ-donors and π-acceptors, which are highly employed in the catalytic process. Because of its lipophilic nature, phosphine can easily aim the mitochondria of cancer cells [2]. The anticancer activity of binuclear Ag (I)-triphenylphosphine complex [$(pph3)_3Ag(L1)$] and [$(pph3)_3Ag(L1)](A_3$) against HCT116 and MDA-MB-231 cell lines were demonstrated using cell counting kit-8 (CCK-8) assay. This A3 complex expressed more significant anti-proliferation activity against all cancer cell lines [6]. The cytotoxicity of Ag (I)-5,5-diethyl barbiturate-bis(diphenyl phospino) alkane complexes **27-30** against MCF-7, A549, PC-3, HT29 cancer cell lines and MCF 10A (non-cancer) cell lines were determined using SRB assay. Complex **28** and **30** showed greater cytotoxicity against the HT-29 cell line. Complex **28** and **29** showed higher activity against the MCF-7 cell line compared with carboplatin. All complexes displayed lesser toxicity against the standard cell line MCF 10A. The anti-proliferation mechanism of these complexes **27-30** includes damaging plasma membrane integrity of cells, arresting A-549 and MCF-7 cell lines in S and G_2/M phases, inducing apoptosis and ROS production, mitochondrial membrane depolarisation and triggering DNA oxidative damage [34]. Ag (I) thiocyanate 4-methoxyphenyl phosphine [Ag $SCN\{p(4\text{-}MeOC_6H_4)_3\}_2]_2$ was synthesized, and the anti-proliferation activity against SNO (esophageal squamous cancer cell line) was determined. Complex **31** showed cytotoxicity, and the anti-proliferative mechanism includes plasma membrane destruction, inducing caspases 3-9 cleavage activity, nuclear fragmentation and chromatin condensation, which results in cell apoptosis [35]. The silver complexes of triphenylphosphine and heterocyclic thiones, which are mixed ligands, produce more excellent anti-microbial activity but do not possess any significant activity towards the cancer cells [36]. The silver complexes that contain mixed ligands such as phosphine and thiazolidine were found to possess greater *in vitro* cytotoxicity towards MDA-MB-231 and MCF-7 (breast cancer) and HT-29 (colon cancer) cell lines [37]. The structures of the Ag-Phosphine complex are given in Figure 6.

Silver-Carboxylate Complexes

The silver carboxylates ($AgO_2CCH_2OCH_3$) **32**, ($AgO_2CCH_2OCH_2CH_2OCH_3$) **33** and ($AgO_2CCH_2OCH_2CH_2OCH_2CH_2OCH_3$) **34** were designed, and their cytotoxic potential was investigated on HeLa cell line by MTT assay. Among these three complexes, complex **32** was found to be more active due to a shorter chain of carboxylates and complex **34** exhibits lesser activity due to the presence of a longer chain of carboxylates [38].

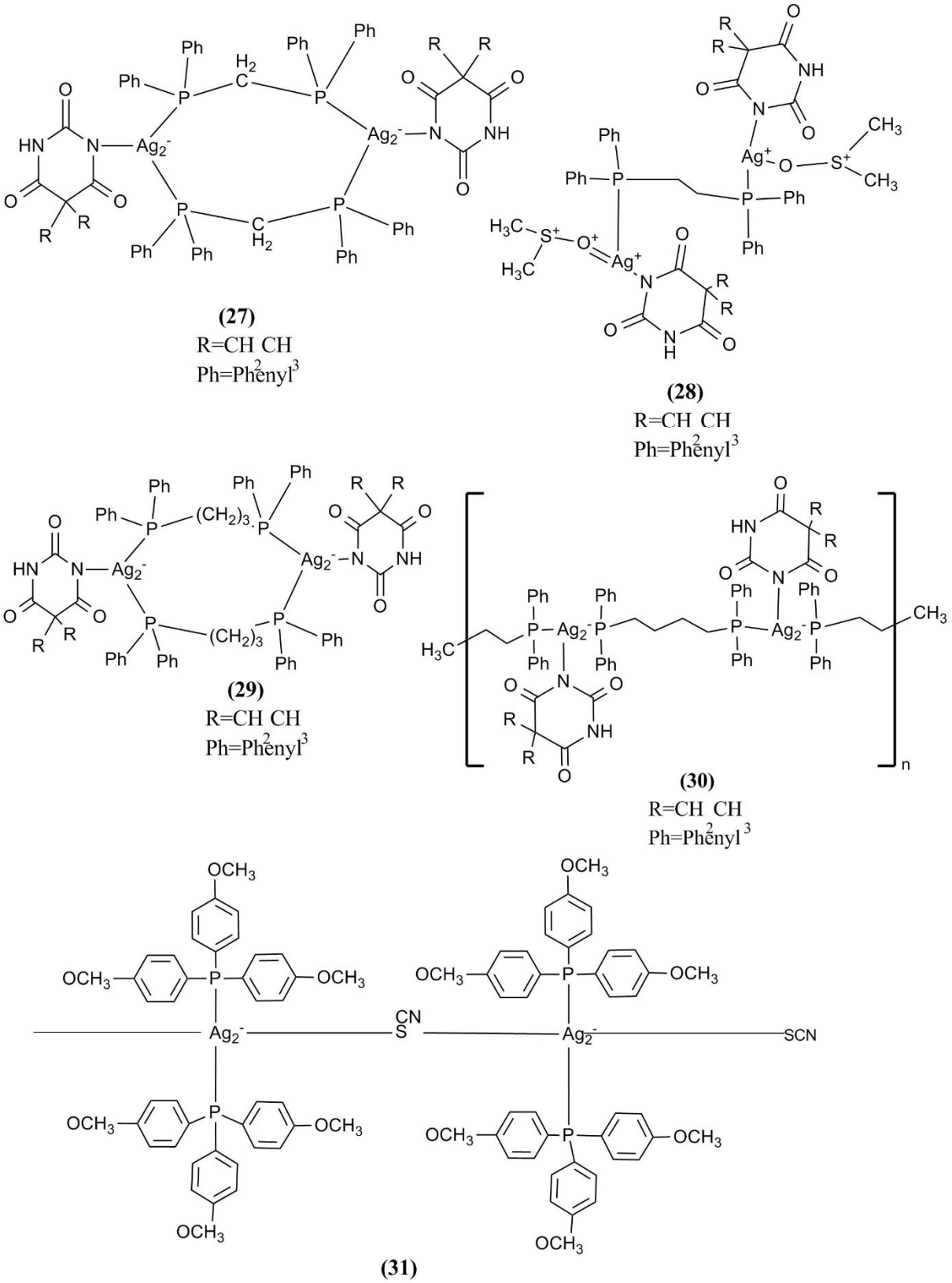


Figure 6. Structures of Silver-Phosphine Complexes.

Ag-camphor complex **35**, including camphor carboxylate and camphor carboxamides, was determined against the A2780 cancer cell line and A2780 cisplatin-resistant cell line MTT assay and showed greater cytotoxic activity against the tested cell line as compared with the non-cancer cell line [39]. The structures of the Ag-Carboxylate complex are given in Figure 7.

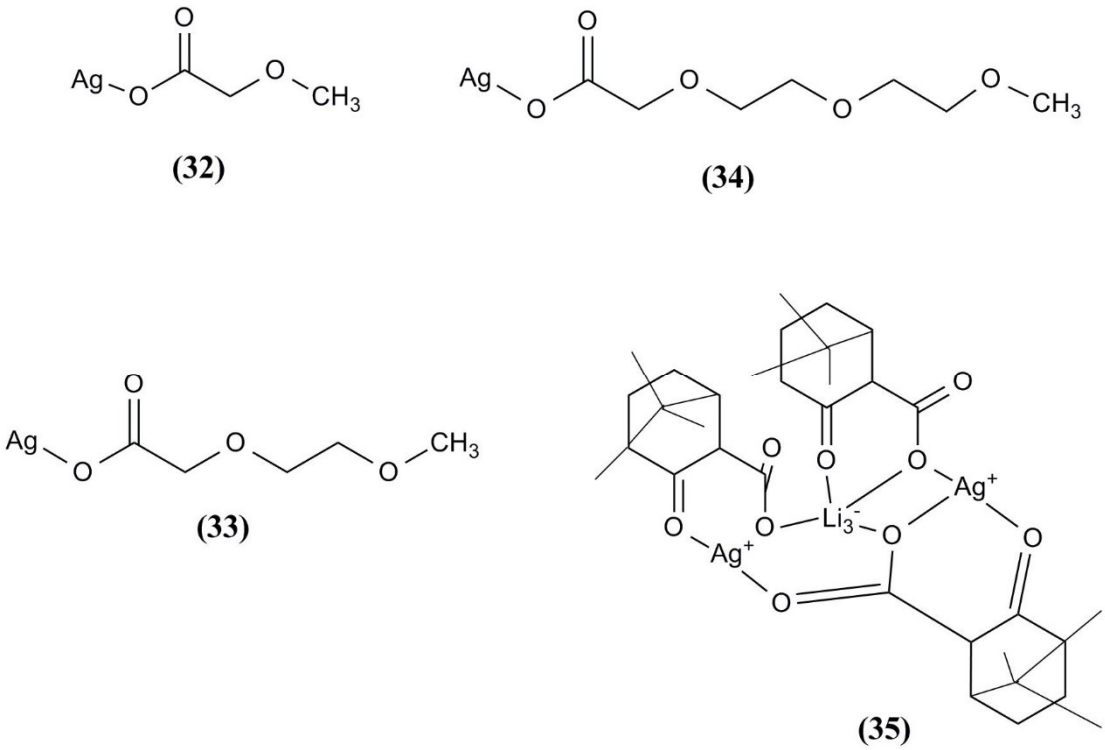


Figure 7. Structures of Silver-Carboxylate Complexes.

Silver-Schiff base Complexes

Cytotoxic potential of Ag (I)-Schiff base complexes **(36)** $[Ag(Th\text{-}Th)]_2.2(NO_3)$ and **(37)** $[Ag(Py\text{-}Py)]_2.2(NO_3)$ were prepared using 2-acetylthiazole (Th-Th), and 2-acetylpyrazine (Py-Py) were tested against A549 cell line using MTT assay. Both complexes **(36)** and **(37)** exhibited enhanced inhibition towards A549 cells as that of cisplatin and silver nitrate [40]. The cytotoxicity, Schiff bases methoxycarbonyl-hydrazono acetic acid, and ethoxy carbonyl-hydrazono acetic acid in Ag (I) complexes against MCF-7, HeLa cancer cell lines and HBL100 non-cancerous cell lines were determined using MTT assay. $[Ag(HL1)(L1)].H_2O$ showed greater activity due to the substitution of methyl group results in enhancing cell inhibition, whereas $[Ag(HL2)_2][Ag(L2)_2]$ showed lesser activity due to the substitution of a higher alkyl group. The morphological changes evaluated the cell apoptosis through Ao/EtBr and DAPI staining method, which may lead to chromatin condensation and nuclear fragmentation [41].

The potency of Schiff base and bimetallic Ag (I) complex as DNA and BSA binders for the anticancer therapy was investigated. The Ag (I) complex $[Ag_2l_2](PF_6)_2$ partially pushed out Hoechst-33258 and EB from its luminescent DNA complexes due to the external electrostatic binding, leading to significant structural perturbations of the helix, which may result in cell apoptosis [42]. Adeleke et al. evaluated the cytotoxic potential of quinoline mediated Schiff base-Ag (I) complexes **(38-40)** against HeLa, MDA-MB-231 and SHSY5Y cells lines. Because the presence of methyl and benzothiazole substitution on the phenyl ring in the complexes **(39)** and **(40)** exhibited greater cytotoxic potential towards HeLa cells and exhibited moderate cytotoxic potential towards MDA-MB-231 and SHSY5Y cells, whereas complex **(38)** showed lesser toxicity through the unusual mode of coordination [43]. The structures of Ag-Schiff base complexes are given in Figure 8.

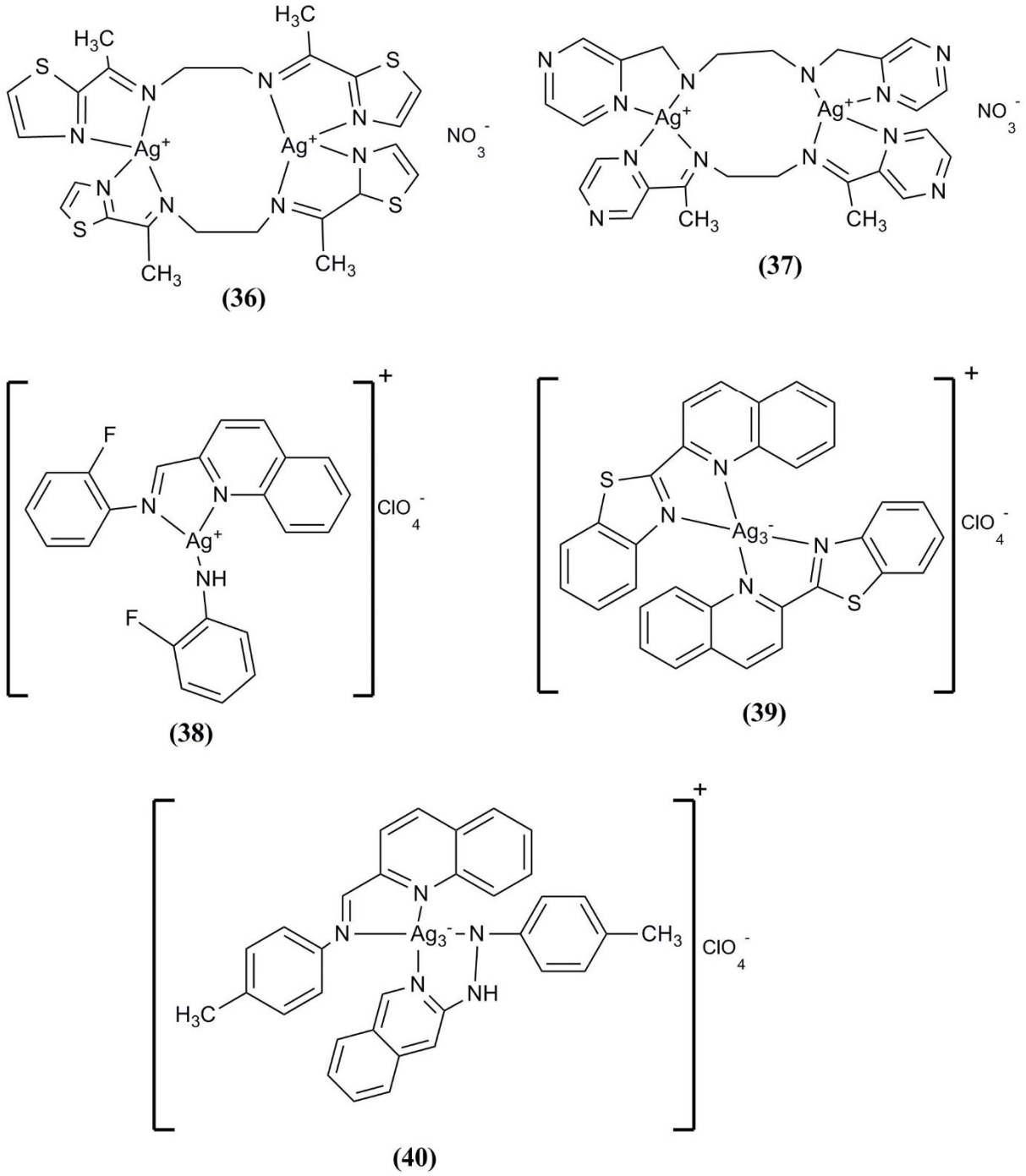


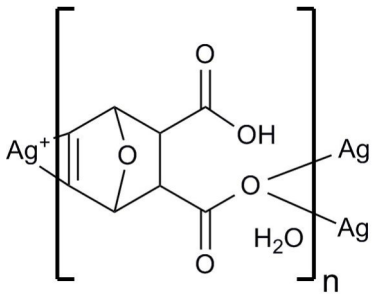
Figure 8. Structures of Silver-Schiff base Complexes.

Silver-Dehydronorcantharidin Complexes

The anti-proliferative activity of the silver-singly protonated dehydronorcantharidin complex against the A549 (lung) cancer cell line was determined, and the complex **41** showed a cytotoxic effect on the lung cancer cell line as that of cisplatin. Treating the complex **41** with GSH (glutathione) will prevent cells from Ag+ complex induced cell death by increasing GSH level intracellularly. The anticancer mechanism of the complex includes inducing ROS production, decreasing Bcl-2 and increasing p53 expression in A549 cells, mitochondrial membrane destruction and inducing caspase apoptosis either independently or dependently [44].

The *in vivo* and *in vitro* cytotoxicity of the singly protonated complex was evaluated using CT-26 cell line and revealed that the Ag complex showed apoptosis towards the colon cancer cell line. The

mechanism of this complex involves inducing ROS generation, overload of calcium, activating caspase-3 and mitochondrial damage, which results in cell apoptosis [45]. The structure of the Ag-Dehydronorcantharidin complex is given in Figure 9.



(41)

Figure 9. Structure of Silver-Dehydronorcantharidin Complex.

Silver-Bioactive Compound Complexes

Ubiquitin-Proteasome System (UPS) is the degradation pathway of eukaryotes by maintaining the homeostasis of proteins. It plays a significant role in cell differentiation, proliferation, DNA damage, and cell apoptosis. Cancer cells depend on the enhanced activity of proteasomes for proliferating the cells. Delanzomib, bortezomib and ixazomib like proteasome inhibitors were used widely to target multiple myeloma. In investigating the synergistic effect against the cancer cells, metal-based proteasome inhibitors were synthesized using Disulfiram (DSH) which showed greater in vivo and in vitro cytotoxic potential [45-48].

The Ag-6-mercaptopurine complex **42**, in which 6-mercaptopurine is an approved anticancer agent, and its cytotoxic ability of the complex **42** toward HeLa cancer cell line was evaluated using MTT assay. The results indicated that complex **42** showed more potent cytotoxicity than cisplatin [3]. Ag/DSF in combination with disulfiram (DSF) resulted in proteasomal deubiquitinases (DUBs) inhibition through protein accumulation. The antiproliferative potential was evaluated against the A549 cancer cell line using the MTS assay, which lowers the proteasomal activity without inhibiting the activity of the 20S proteasome. Thus, (Ag/DSF) complex induced cell apoptosis without inducing the proteasome inhibition in the A549 cancer cell line [10]. Silver thiosulfate based silver complex (STS), $[Ag(S_2O_3)_2]^{3-}$ was synthesized and investigated for the anticancer activity against MCF-7 and K562 cell lines using MTS assay. The complex showed concentration-dependent activity in the MCF-7 cell line through elevated ROS accumulation, resulting in G1-phase cell cycle arrest by decreasing the level of GSH [13]. Because of the presence of amino and carboxylic groups, 4-amino benzoic acid (PABA) is considered a vital ligand that plays a vital role in the biosynthetic pathway of folic acid. Thus, Aquaroni et al. evaluated in vitro anti-proliferation activity of Ag-PABA complex against MCF-7, 786-O, PC-3, HT-29, K562, U 251, NCI-ADR/RES cancer cell lines and NCI-H460 non-cancer cell line. Ag-PABA complex can be used to treat skin cancer caused by bacteria [15]. The Ag-thiourea complexes **43** and **44** containing phosphine groups were developed and demonstrated their in vitro cytotoxic potential against A549, HeLa and Jurkat cell lines using MTT assay. Complex **43** showed more significant cytotoxicity in HeLa cells, whereas complex **44** showed greater activity against the Jurkat cell line through coordination with phosphorus atom [17].

The anthraldehyde thiosemicarbazone based Ag-complex **45** showed more significant cytotoxicity against DU-145, HeLa and HCT-15 cancer cell lines compared to the standard drug 5-FU by MTT assay [49].

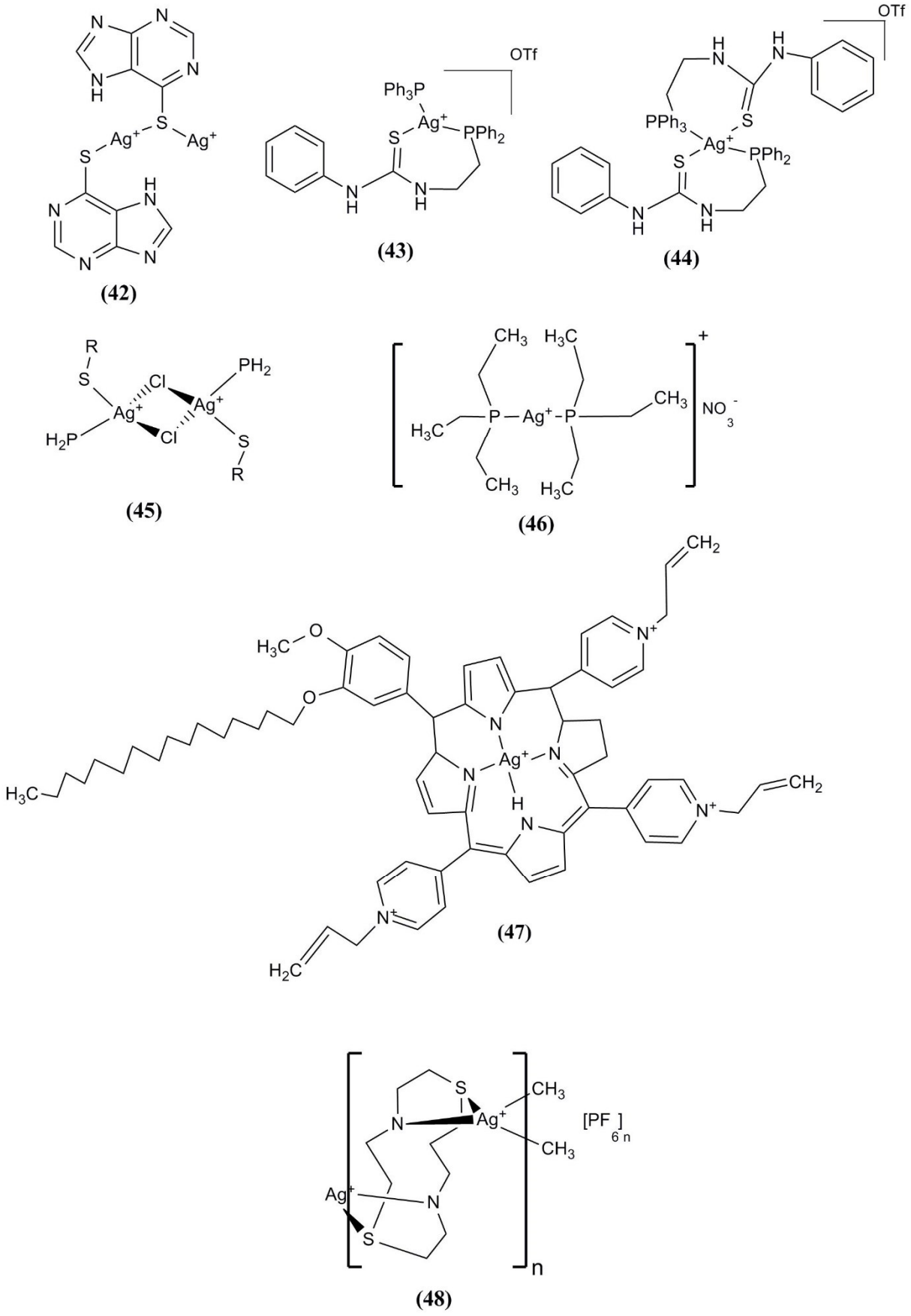


Figure 10. Structure of Silver-Bioactive Compound Complexes.

Auranofin based silver complex **46** was synthesized and exhibited the growth inhibition of leukaemia cells by inhibiting proteasomes against CCRF-CEM, and CEM/ADR5000 resulted in trypsin-like (T-L) inhibition [50]. Ag-glycine and nicotinamide based complexes $[Ag(HGly)_2]_2(NO_3)_{2n}$ and $[Ag(Nam)_2]NO_3.H_2O$ were designed and evaluated the anticancer activity in the L1210 cancer cell line, which resulted in cell death through the plasma membrane blebbing, nuclear condensation and shrinking of cells. The silver-glycine and nicotinamide complexes showed topoisomerase I and II inhibition [51,52]. The amphiphilic cation porphyrin-Ag (II) complex **47** was prepared as an anti-proliferative agent. Porphyrins are the photosensitizers used to target tumours because of their enhanced phototoxic ability. To induce cell apoptosis, porphyrin enhances the superoxide anion level intracellularly. Cytotoxicity of the complex **47** was estimated against HeLa, HEP-3B, MCF-7 and LN-308 cell lines. It showed dose-dependent activity because of long lipophilic substituents than cisplatin. Mainly, complex **47** was more active toward the KCL-22 cell line-the mechanism involved in damaging heritable chromosomes and arresting cells in S-phases [53].

The dithiacylam-Ag (I) complex **48** reacted with the GSH redox buffering system of the cell lines HMLER or HMLER-shEcad, thereby inducing ROS intracellularly elevation caspase-dependent cell apoptosis [54]. The cytotoxic activity of Ag (I)-dipeptide complex against MCF-7, MDA-MB-231, HCT 116, BLM and Jurkat cancer cells and BJ-5ta (non-cancer) cells were evaluated using an MTS assay. Ag (I)-dipeptide complex showed more robust activity towards MCF-7 and MDA-MB-231 cell lines. The Ag (I)-dipeptide complex mechanism includes inhibition of Topoisomerase I, arresting cell cycle in G_2/M phase resulting in cell apoptosis [55]. Korkmaz and co-workers evaluated the *in vitro* anti- proliferation potential of the Ag (I)-bimetallic dicyanido argenate complexes $[Ni(edbea)Ag_3(CN)_5]$ **49**, $[Cu(edbea)Ag_2(CN)_4].H_2O$ **50**, $[Cd(edbea)Ag_3(CN)_5].H_2O$ **51** and $[Cd(edbea)2][Ag(CN)_2]_2.H_2O$ **52** against HeLa, HT29 and C6 cancer cells. Complexes **50** and **51** showed greater anticancer activity towards all the cell lines through the mechanism of topoisomerase-I inhibition [56].

Ag(I)-aminoacidate complexes with the aromatic amino acids, namely alanine and phenylalanine, were evaluated for their anticancer activity using the colourimetric MTS assay against HeLa, HCT 116 and Jurkat cancer cell lines. Ag (I)-alanine complex exhibited more significant cytotoxic potential towards all the cancer cell lines than Ag (I)-phenylalanine complex effectively. Ag (I)-aminoacidate complexes had the ability in PUC19 DNA cleavage [57]. $[Ag(ka)(PPh_3)].H_2O$ complex was prepared, whose greater lipophilicity and hydrolytic stability played an essential role in its biological activity. As an anticancer agent, $[Ag(ka)(PPh_3)].H_2O$ complex exhibited dose-dependent activity towards the B16F10 (skin) cancer cell line and induced carcinogenesis of thyroid follicular cells [58]. Silver pyridine-2-sulfonate complex synthesized, which showed enhanced anti-proliferation potential towards L1210 cancer cell line through topoisomerase-I inhibition by cleaving the DNA pBR322, resulting in cell death [59]. All the structures of these complexes are given in Figure 10.

The bis(1,10-phenanthroline)-Ag (I) acetate monohydrate complex [Ag-Phen] complex was synthesized and evaluated its cytotoxic potential towards the A549 cancer cell line using MTT assay. [Ag-Phen] complex showed dose-dependent anti-proliferation activity towards A549 cells. The capability of the [Ag-Phen] complex in depolarising the mitochondrial membrane inhibited the production of ROS, resulting in cell apoptosis by changing the oxidative phosphorylation pathway of mitochondria [60]. The IC50 values of various Ag-complexes with respective cell lines are given in Table 1.

Table 1. Anticancer activity of silver complexes along with its respective cell lines, IC_{50} values and mechanisms of action are reported. IC_{50}: Half minimal inhibition concentration.

S.No	Ag complex	Cell line	IC50 value (μm)	Mechanism	Reference
1.	Complex 1 a	MCF-7	18±2.12	Arresting cell cycle in G1 phase and inhibiting caspase-3 activity	[1]
		MDA-MB-231	8		
		MCF 10A	18±2.82		
2.	Complex 1 b	MCF-7	17±1.41	Arresting cell cycle in G1 phase and inhibiting caspase-3 activity	[1]
		MDA-MB-231	7.5±0.77		
		MCF 10A	14±2.72		
3.	Complex 1 c	MCF-7	23±7.63	Arresting cell cycle in G1 phase and inhibiting caspase-3 activity	[1]
		MDA-MB-231	12±1.69		
		MCF 10A	25±1.14		
4.	Complex 2	MCF-7	34.43±0.61	DNA interaction	[5]
		Caco-2	11.65±0.21		
		L-929	109.82±9.51		
5.	Complex 3	MCF-7	32.17±0.25	DNA interaction	[5]
		Caco-2	13.82±0.63		
		L-929	38.08±2.33		
6.	Complex 4	MCF-7	46.01±0.17	DNA interaction	[5]
		Caco-2	14.93±0.33		
		L-929	-		
7.	Complex 5	MCF-7	55±5	Translocation of apoptosis-inducing factor (AIF) and caspase-12 (from mitochondria and endoplasmic reticulum)	[8]
		MCF-7R	120±2		
		HCT116	30±10		
		HCT15	95±15		
		HL60	35±5		
		HL60R	120±20		
8.	Complex 6	MCF-7	75±15	Translocation of apoptosis-inducing factor (AIF) and caspase-12 (from mitochondria and endoplasmic reticulum)	[8]
		MCF-7R	125±5		
		HCT116	28±1		
		HCT15	85±5		
		HL60	58±1		
		HL60R	125±5		
9.	Complex 7	MCF-7	375±75	Translocation of apoptosis-inducing factor (AIF) and caspase-12 (from mitochondria and endoplasmic reticulum)	[8]
		MCF-7R	2480±20		
		HCT116	200±20		
		HCT15	860±260		
		HL60	90±40		
		HL60R	2990±210		
10.	Complex 8	HCT116	43	Apoptotic bodies formation, nuclear condensation, memdrane bleeding	[12]
11.	Complex 9	HCT116	44.5	Apoptotic bodies formation, nuclear condensation, memdrane bleeding	[12]
12.	Complex 10	HCT116	9.7	Apoptotic bodies formation, nuclear condensation, memdrane bleeding	[12]
13.	Complex 11 a	HCT116	10.5±1.0	Producing changes in the morphology of the cell	[16]
		HT29	7.6±0.7		
14.	Complex 11 b	HCT116	18.7±1.6	Producing changes in the morphology of the cell	[16]
		HT29	5.5±0.8		
15.	Complex 12	HCT116	1.20±0.3	Producing changes in the morphology of the cell	[16]
		HT29	103.0±2.3		
16.	Complex 13	A375	11.5±5.3	Increased penetration to the cell membrane by the hydrophilic complexes	[22]
		HCT116	19.5±2.3		
		HT29	21.4±6.4		
		Panc-1	7.6±3.2		
		LN229	11.2±1.5		
		U-251	14.2±2.5		
		U-87 MG	17.6±4.5		
		SiHa	13.1±3.7		
17.	Complex 14	MCF-7	26.68	Inhibition of cell proliferation, molecular hydrophobicity	[23]
		MDA-MB-231	46.58±2.13		
		U87 MG	25.24±0.21		

18.	Complex 15	A549	19.2±4.0	Inducing the generation of ROS and caspase	[24]
		Cispltin resistant A549	20.1±1.2		
		HeLa	19.1v1.0		
		MDA-MB-231	22.0±0.5		
		LO2	91.3±4.2		
19.	Complex 16	A549	16.5±0.6	Inducing the generation of ROS and caspase	[24]
		Cispltin resistant A549	16.7±0.8		
		HeLa	12.4±1.9		
		MDA-MB-231	14.3±0.2		
		LO2	64.6±3.3		
20.	Complex 17	A549	8.3±0.40	Inducing larger empty spaces of the cells	[25]
		H1975	9.8±1.0		
21.	Complex 18 a	DU-145	1.69±0.21	Mitochondrial membrane depolarisation	[26]
		MCF-7	2.14±0.13		
		MDA-MB-231	1.10±0.19		
		L-929	14.2±0.22		
22.	Complex 18 b	DU-145	2.09±0.43	Mitochondrial membrane depolarisation	[26]
		MCF-7	2.19±0.22		
		MDA-MB-231	1.57±0.19		
		L-929	8.93±0.12		
23.	Complex 18 c	DU-145	1.41±0.55	Mitochondrial membrane depolarisation	[26]
		MCF-7	<1		
		MDA-MB-231	<1		
		L-929	4.67±0.11		
24.	Complex 18 d	DU-145	1.21±0.23	Mitochondrial membrane depolarisation	[26]
		MCF-7	<1		
		MDA-MB-231	<1		
		L-929	3.56±0.20		
25.	Complex 19	A549	10±1	Faster inactivation of the cell by TrxR inhibition	[27]
		HepG2	8±1		
		SW480	7±2		
26.	Complex 20 a	MCF-7	5.82±0.5	Mitochondrial membrane depolarisation	[28]
		MDA-MB-231	<1		
		DU-145	16.3±0.23		
		L-929	13.0±0.41		
27.	Complex 20 b	MCF-7	<1	Mitochondrial membrane depolarisation	[28]
		MDA-MB-231	2.19±0.5		
		DU-145	6.94±0.15		
		L-929	6.87±0.03		
28.	Complex 20 c	MCF-7	2.05±0.72	Mitochondrial membrane depolarisation	[28]
		MDA-MB-231	1.83±0.03		
		DU-145	3.90±0.09		
		L-929	2.89±0.04		
29.	Complex 21 a	MCF-7	15.1	Inhibiting the uncontrollable cell proliferation fastly through the inhibition of cellular transcription	[29]
		HCT116	0.31		
		K-562	7.0		
30.	Complex 21 b	MCF-7	16.1	Inhibiting the uncontrollable cell proliferation fastly through the inhibition of cellular transcription	[29]
		HCT116	15.1		
		K-562	17.9		
31.	Complex 21 c	MCF-7	35.2	Inhibiting the uncontrollable cell proliferation fastly through the inhibition of cellular transcription	[29]
		HCT116	1.99		
		K-562	10.7		
32.	Complex 22	MCF-7	20±3	DNA cleaving ability	[30]
		MCF 10A	69±3		
33.	Complex 23 a	MCF-7	<1	Inducing toxicity by interfering celluler respiration and metabolism of the cells	[31]
		MDA-MB-231	<1		
		DU-145	6.02±0.30		
		L-929	5.08±0.20		
34.	Complex 23 b	MCF-7	<1	Inducing toxicity by interfering celluler respiration and metabolism of the cells	[31]
		MDA-MB-231	<1		
		DU-145	5.16±0.33		
		L-929	4.68±0.15		

35.	Complex 23 c	MCF-7 MDA-MB-231 DU-145 L-929	3.64±0.16 <1 4.97±0.25 12.61±0.21	Inducing toxicity by interfering celluler respiration and metabolism of the cells	[31]
36.	Complex 23 d	MCF-7 MDA-MB-231 DU-145 L-929	1.60±0.17 <1 6.5±0.18 11.97±0.24	Inducing toxicity by interfering celluler respiration and metabolism of the cells	[31]
37.	Complex 24 a	MCF-7	9	Damaging cell wall and its function, and by increasing lipophilicity	[32]
38.	Complex 24 b	MCF-7	7	Damaging cell wall and its function, and by increasing lipophilicity	[32]
39.	Complex 24 c	MCF-7	18	Damaging cell wall and its function, and by increasing lipophilicity	[32]
40.	Complex 24 d	MCF-7	11	Damaging cell wall and its function, and by increasing lipophilicity	[32]
41.	Complex 25	NCI/ADR-RES	0.36	Disturbing DNA replication through tymidilate synthase enzyme inhibition	[19]
42.	Complex 26	MCF-7 HeLa Hep-2 HepG2 NHDF	8.21 8.89 8.42 5.61 >100	Cell cycle arrest at S-phase by damaging DNA	[33]
43.	Complex 27	A549 MCF-7 MCF 10A HT-29 Pc-3	>100 >100 41.6±5.3 >100 >100	Damaging plasma membrane integrity of the cell, S and G2/M phase cell arrest, DNA oxidative damage, mitochondrial membrane depolarisation	[34]
44.	Complex 28	A549 MCF-7 MCF 10A HT-29 Pc-3	15±1.9 37.0±0.8 8.5±1.1 7.4±0.7 >100	Damaging plasma membrane integrity of the cell, S and G2/M phase cell arrest, DNA oxidative damage, mitochondrial membrane depolarisation	[34]
45.	Complex 29	A549 MCF-7 MCF 10A HT-29 Pc-3	56.1±2.4 55.6±3.5 26.1±0.3 7.5±0.5 >100	Damaging plasma membrane integrity of the cell, S and G2/M phase cell arrest, DNA oxidative damage, mitochondrial membrane depolarisation	[34]
46.	Complex 30	A549 MCF-7 MCF 10A HT-29 Pc-3	>100 >100 >100 >100 >100	Damaging plasma membrane integrity of the cell, S and G2/M phase cell arrest, DNA oxidative damage, mitochondrial membrane depolarisation	[34]
47.	Complex 31	SNO	3.5±0.91	Caspase 3-9 cleavage activity, nuclear fragmentation, chromatin condensation	[35]
48.	Complex 32	HeLa	2.60±0.5	Nuclear condensation, S-phase cell cycle arrest	[38]
49.	Complex 33	HeLa	4.96±1.4	Nuclear condensation, S-phase cell cycle arrest	[38]
50.	Complex 34	HeLa	6.10±1.2	Nuclear condensation, S-phase cell cycle arrest	[38]
51.	Complex 35	A2780	7.3±3.1	Topoisomerase I and II inhibition	[39]
52.	Complex 36	A549	3.15±0.5	DNA synthesis inhibition	[40]
53.	Complex 37	A549	9.73±1.1	DNA synthesis inhibition	[40]
54.	Complex 38	HeLa MDA-MB-231 SHSY5Y	≥100 ≥100 ≥100	Cell apoptosis	[43]
55.	Complex 39	HeLa MDA-MB-231 SHSY5Y	≥100 22.80±3.11 41.62±4.25	Cell apoptosis	[43]
56.	Complex 40	HeLa MDA-MB-231 SHSY5Y	≥100 22.34±4.86 38.84±4.33	Cell apoptosis	[43]

57.	Complex 41	A549	7.41±0.78	Increasing intracellular GSH level , increasing p53 expression, mitochondrial membrane destruction, caspase apoptosis	[44]
58.	Complex 42	HeLa	30.0	DNA cleavage	[3]
59.	Complex 43	A549	7.06±1.95	Elevating ROS accumulation, G1 phase cell cycle arrest, decreasing GSH level	[17]
		HeLa	10.17±1.74		
		Jurkat	3.89±0.19		
60.	Complex 44	A549	0.79±0.04	Elevating ROS accumulation, G1 phase cell cycle arrest, decreasing GSH level	[17]
		HeLa	0.87±0.06		
		Jurkat	0.64±0.04		
61.	Complex 45	HCT-15	6.831±0,791	Mitochondrial damage	[49]
		HeLa	7.144±0.829		
		DU-145	6.329±0.458		
62.	Complex 46	CCRF-CEM	1.39±0.04	Inhibiting leukemia cells growth by inhibiting proteasomes results in trypsin-like (T-L) inhibition	[50]
		CEM/ADR 5000	4.24±0.05		
63.	Complex 47	MCF-7	6.0±1.4	Damaging heritable chromosomes, arresting cells in S-phase	[53]
		HeLa	9.0±0.5		
		HEP-3B	5.6±1.3		
		LN-308	6.3±0.8		
64.	Complex 48	HMLER HMLER-shEcad	15.70±0.03	Elevating intracellular ROS, caspase dependent cell apoptosis	[54]
			15.67±0.12		
65.	Complex 50	HeLa	1.68	Topoisomerase I inhibition	[56]
		HT29	1.38		
		C6	1.80		
66.	Complex 51	HeLa	3.57	Topoisomerase I inhibition	[56]
		HT29	1.86		
		C6	3.42		

Conclusion

Silver metal complexes have gained more attention because of their wide variety of biological actions. We make a summary on the silver metal complexes with various ligands with special emphasis on cancer because of the complex pathways in cancer progression. Silver metal complexes play an important role in destructing the tumour cells with various mechanisms including DNA binding and cleavage, topoisomerase enzyme inhibition, generation of ROS and induction of apoptosis. Silver complexes have shown an ability to exhibit greater activity with lower toxicity. Various silver-bioactive ligand complexes discussed in this review are more promising and hopeful which needs further more research and can be used for future research works.

Acknowledgement

We thank the Management and Dr. G. Murugananthan, Principal of our college for giving constant support and encouragement for writing this review.

Authors Contribution

All the authors have contributed equally.

Declaration of interest

The authors declare no conflict of interest.

Financial Support

This work has not received any funds from national and international agencies.

Abbreviations

ROS-Reactive oxygen species; DNA-Doexy ribonucleic acid; RNA-Ribonucleic acid; NHCs-N-Heterocyclic carbenes; 5-FU-5-Fluorouracil; AIF-Apoptosis inducing factor; SRB-Sulforhodamine B colorimetric assay; COX-Cyclooxygenase; DSF-Disulfiram; DUBs-Proteasomal deubiquitinases; MTT-

3-(4, 5-dimethyl thiazol-2-yl)-2, 5-diphenyl tetrazolium; XTT- (2, 3-Bis-(2-Methoxy-4-Nitro-5-Sulfophenyl)-2*H*-Tetrazolium-5-Carboxanilide); LDH-Lactate dehydrogenase.

Tumour cell lines

MCF-7, MCF7R, MCF10A, MDA-MB-231, MDA-MB-453-Breast cancer; HCT 116, HCT 15, SW480-Colon cancer HT29, Caco2-Colorectal cancer; HL60, HL60R-Promyelocytic cancer; A549, H1955-Lung cancer; Panc-1, pc-3-Pancreatic cancer; HeLa-Cervical cancer; A375-Malignant melanoma; Sitta-Squamous cell carcinoma cervix (grade II); DU145-Prostate cancer; CT-26-Murine carcinoma cells; HepG2-Liver cancer; Hep-2-Epitheiloma; SHSY5Y-neuronal cancer; 786-O-Kidney cancer; Jurkat-Human T lymphocyte cells; K-562-Erythromyeloblastoid leukemia; CCRF-CEM-Leukemia; NCI/ADR-RES-Ovarian multidrug resistant cells.

Non-Tumour cell lines

LO2-Human normal liver cells; L-929, 3T3L1-Mouse fibroblast cells; NHDF-Human dermal fibroblasts HBL 100-Normal breast epithelial cells.

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How to cite this article:
Raju SK, Karunakaran A, Kumar S, Sekar P, Murugesan M, Karthikeyan M. Silver Complexes as Anticancer Agents: A Perspective Review. German J Pharm Biomaterials. 2022;1(1):6-28.