Abstract

Cancer is one of the deadliest diseases and leading reasons of mortality in human beings. The worldwide efforts to mitigate cancer include new approaches for a better understanding of the disease, early diagnosis, effective treatment and advanced post-treatment monitoring facilities. Chemotherapy is considered central to several cancer treatments developed over time including surgery, radiotherapy, immunotherapy and hormonal therapy. Medicinal inorganic chemistry has played a significant role in developing mainstream chemotherapeutic drugs and it continues to supply a vast library of potential anti-cancer metal complexes in pursuit of an ideal chemotherapy drug that qualifies merit of effectiveness, selectivity and safety.

In contribution to global cancer research, we designed and prepared several series of gold(I) and gold(III) complexes bearing biologically active carbon (C), sulfur (S), phosphorus (P) and nitrogen (N) donor ligands. Briefly, series A and B represent nine gold(I) N-heterocyclic carbene (NHC) thione complexes (SG-A1 *to* SG-A5, SG-B1 *to* SG-B4) with a general formula of [(IPr)Au(Thione)]PF_6 where IPr refers to 1,3-bis(2,6-diisopropylphenyl)-1,3-dihydro-2H-imidazol-2-ylidene and thiones include 1,3-imidazolidine-2-thione, 1,3-diazinane-2-thione and 1,3-diazipane-2-thione ligands with mono/di-alkyl and isopropyl substitutions. Series C comprises three phosphanegold(I) dithiocarbamate (DTC) complexes (SG-C1, SG-C2 and SG-C3) with the general formula [(PR_3)Au(DTC)] where DavePhos-AuCl was employed as phosphanegold(I) precursor and DTCs include sodium salts of dialkyl and diaryl DTCs. The mentioned DTCs were also chelated with gold(III) alongside tetrabromo-1,10-phenanthroline (Phen$(Br)_4$), 1,10-phenanthroline-5,6-dione (Phen$(CO)_2$) and 2,6-bis(2-benimidazolyl)pyridine (BZIMPY) to give three series of gold(III) complexes represented as [(Phen$(Br)_4$)Au(DTC)], [(Phen$(CO)_2$)Au(DTC)] and [(BZIMPY)Au(DTC)], respectively. Each of the three series constitutes four complexes labelled as SG-D1–SG-D4, SG-E1–SG-E4 and SG-F1–SG-F4.

All complexes were structurally confirmed by CHNS analysis, FTIR, ^{1}H and ^{13}C NMR spectroscopy. Of these, six complexes namely SG-A1, SG-A3, SG-A4, B1, B4 and SG-C1 were also characterized by X-ray diffraction (XRD) analysis. The spectroscopic analyses confirmed the formation of complexes and agreed with literature reports. The

XRD analysis of complexes SG-A1, SG-A3 and SG-A4 showed the existence of $[(IPr)Au(Thione)]^+$ and PF_6^- as counter ions with a nearly linear coordination geometry of gold(I) ion and C—Au—S bond angles of 177.13 (11), 172.86 (9) and 176.56 (12) for SG-A1, SG-A3 and SG-A4 respectively. Likewise, SG-B1 and SG-B4 were shown to consist $[(IPr)Au(Thione)]^+$ and PF_6^- as counter ions with the C—Au—S bond angles of 177.27 (10) and 177.94 (12)° for SG-B1 and SG-B4, respectively. X-ray crystal structure of SG-C1 revealed that attachment of gold(I) with P and S atoms of DavePhos and dimethyl-DTC, respectively, with an almost linear P1—Au1—S1 angle of 179.54 (5)°.
The *in vitro* anti-tumor tests of all the synthesized complexes were performed against numerous human tumors, including colon cancer (HCT-15 and HCT-116), breast cancer (MCF-7 and MDA-MB-231), lung cancer (A549), melanoma cancer (CHL-1), and pancreatic cancer (MIA PaCa-2) cell lines. The first two series showed mild to no cytotoxic activities. The electrochemical studies, including cyclic and square wave voltammetry, were performed to elucidate the interactions of these gold complexes with tryptophan and lysozyme. The cytotoxic activities of many complexes from the subsequent series either matched or extraordinarily surpassed the commercial drug cisplatin. In particular, complexes SG-C1 and SG-C2 showed much more advanced cancer inhibition than cisplatin against MCF-7 and MDA-MB-231, CHL-1 and comparable or better activity against HCT-116 and A549 tumor cells. Complex SG-D3 also exhibited far higher anti-cancer potential against HCT-116 compared with cisplatin. SG-E1, SG-E2, SG-E3 and SG-E4 proved most potent of all the synthesized complexes with higher cytotoxicity than cisplatin by multiple folds against HCT-116 and MIA PaCa-2 tumor cells. Finally, cytotoxic activity of SG-F2 and SG-F3 also exceeded cisplatin in treating HCT-116 and MIA PaCa-2 tumor cells. *In vivo* cytotoxic studies of this series are underway.
Overall, the study produced several new gold(I) and gold(III) complexes showing great potential as future anti-cancer medicine. The results inferred from the study will contribute to the progress of new anti-cancer therapeutic drugs and the repurposing of the existing ones for higher efficiency and improved safety.