Story of Young Innovators in Health Sciences

Design, synthesis, characterization and remarkable anticancer activity of rhenium tricarbonyl complexes containing biphenyl appended NNN donor sulfonamide ligands towards lung cancer

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Overview: According to the statistics reported by World Health Organization, lung cancer is the 6th leading cause of the death globally, and the 4th leading cause of death in middle, upper and high income countries in the year 2019. Lung cancer is also reported to be the deadliest and has received the least attention according to the data reported by the American Cancer Society. Conventional cancer therapies for lung cancer include surgery, radiotherapy, and chemotherapy. Cisplatin [*cis*-$PtCl_2(NH_3)_2$] is an extensively used the heavy metal chemotherapy drug to treat lung cancer. However, limitations of Cisplatin such as toxic side effects and drug resistance towards lung cancer has been reported in literature. Hence, it is important to investigate new drug leads to replace the platinum-based drugs in the treatment of lung cancers. This has stimulated our interest in investigating new drug candidates containing metal centers to replace Cisplatin, specifically to treat lung cancer. Among the potential alternative transition metals, complexes of gold, titanium, ruthenium and rhenium have demonstrated anticancer activity via novel mechanisms of action. In our effort to synthesize novel compounds to treat lung cancer, our research efforts have been channeled towards rhenium tricarbonyl complexes bearing suitable ligand systems.

Our attention was caught by biphenyl $(C_6H_5)_2$ which has displayed remarkable anti-cancer properties in early studies. Similarly, sulphonamides with S-N bond are a group of molecules that has been utilized in range of biological applications including cancer treatment. The ligand design was further motivated by the previous studies which revealed the anticancer activities related to dipicolylamine (dpa). Thus, in designing suitable ligands for our study, we paid attention on above mentioning functional groups while expecting a better cellular uptake.

Objectives: The main objective of this study was to synthesize new biphenyl derivatives and integrate such with the rhenium tricarbonyl core as a potential bio tool to recognize and treat lung cancerous cells in the human body.

Method: Two novel ligands; L1: N(SO_2bip)dpa and L2: N(SO_2bip)dienH were designed to incorporate the biphenyl group via a sulfonamide linkage to the dipicolylamine and diethylenetriamine moieties. Thereby, the new ligands were utilized in the reaction with the *fac*-[$Re(CO)_3(H_2O)_3$]OTf precursor to form new Re-N bonded complexes (C1: [$Re(CO)_3$(N(SO_2bip)dpa)]PF_6 and C2: [$Re(CO)_3$(N(SO_2bip)dien)]) which were both assessed for the potential applicability as anti-cancer agents. All four compounds were characterized by ^{1}H NMR, UV-Vis, FTIR spectroscopies and L1, also by single crystal X-ray diffraction. The cytotoxic activity of compounds towards the NCI-H292 cell line was analyzed for all four new compounds where they were exposed to the compounds in a concentration gradient. Half maximal inhibitory concentration (IC_{50}) was determined for each compound at 24 h, 48 h and 72 h.

Findings: Both the ligands and complexes display significant cytotoxicity towards NCI-H292 cells at low concentrations. The lower concentration of the drugs is desirable for cancer treatment to prevent the occurrence of side effects. Moreover, these values are comparatively better than IC_{50} of cisplatin used in chemotherapy against lung cancer. IC_{50} value of N(SO_2bip)dpa (L1) has reduced 3.7 folds after 48 h compared to the value obtained at 24 h whereas [$Re(CO)_3$(N(SO_2bip)dpa)]PF_6 (C1) treatment resulted in a reduction of only 2.7 folds. Interestingly, the cells treated with C1 demonstrate recovery over time where the values have increased beyond the value obtained at 24 h. (IC_{50} values reported for ligands and the complexes at 24, 48, and 72 h incubation period: for *N*(SO_2bip)dpa (L1): 52.85 µM (24h), 13.91 µM (48h) and 18.25 µM (72 h), for [$Re(CO)_3$(*N*(SO_2bip)dpa]PF_6 (C1): 97.72 µM (24h), 35.84 µM (48h), 110.93 µM (72 h), for *N*(SO_2bip)dienH (L2): 16.65 µM (24h), 10.05 µM (48h), 2.37 µM (72 h), for [$Re(CO)_3$(*N*(SO_2bip)dien)] (C2): 39.91 µM (24h), 10.25 µM (48h), 15.47 µM (72 h))

Conclusion: Two novel ligands and their corresponding rhenium complexes were synthesized in good yield in high purity. L1: N(SO_2bip)dpa, C1: [$Re(CO)_3$(N(SO_2bip)dpa)]PF_6, L2: N(SO_2bip)dienH and C2: [$Re(CO)_3$(N(SO_2bip)dien)] were characterized using ^{1}H NMR, UV-visible, FTIR and fluorescence spectroscopies. L1 was further characterized by single crystal X-ray diffraction. The two ligands are in compliance with calculated drug likeness scores that indicate their potential applicability as drug leads. A preliminary study was carried out to assess the *in vitro* cytotoxicity of these compounds on lung cancer cell line NCI-H292 using SRB assay. All the compounds displayed a significant cytotoxic activity. IC_{50} values, obtained for L2 was the lowest out of all four compounds which was decreased with increasing incubation time which lead to exhibit promising characteristic for an anticancer drug lead.

Practical implications: The sustained cytotoxicity is a sign of potency for L1 to be considered as a lead compound in anti-cancer drug development. All four compounds (L1, L2, C1 and C2) have shown cytocidal and cytostatic effect and can be further tested to develop them as anticancer drug leads. Furthermore, in vivo trials are required to support therapeutic use and design a suitable dosage form to produce a new drug to treat cancer.

Novelty: Four novel compounds were synthesized and introduced which have immense potential to be used as therapeutic agents against cancer. The cytotoxicity of the novel compounds bearing biphenyl group have been found to be at least 4 folds higher than that of the renowned and widely used anticancer drug, cisplatin towards lung cancer. Overall, L2: $N(SO_2bip)dienH$ is a promising compound with specific cytotoxicity against NCI-H292 lung cancer cells and can be further studied as a promising anticancer drug lead.

Benefits to the society: Lung cancer remains one of the leading causes of death globally. The currently used drugs are reported to have side effects and resistance to lung cancer. The drug leads that has been successfully synthesized in our study can be utilized to manufacture drugs to treat the deadliest lung cancer.

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