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ORIGINAL PAPER

Development of oxopyrrolidine-based anti-cancer compounds: DNA binding, in silico, cell line studies, drug-likeness and mechanism at supra-molecular level

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Due to an increasing demand for effective anti-cancer drugs, an oxopyrrolidine-based ligand, sodium 1-(3-(2-aminoethylamino)propyl)-5-oxopyrrolidine-2-carboxylate, was synthesised by the sodium hydride-assisted coupling of pyroglutamic acid with 1,3-diiodopropane under a nitrogen atmosphere. The intermediate thus formed was allowed to react with ethylenediamine in acetonitrile. The ligand formed individual complexes with Cu(II) and Ni(II) metal ions, respectively. The complexes were relatively resistant to degradation in PBS at physiological pH. The DNA-binding constants (K_b) for the ligand, copper and nickel complexes were 2.09×10^4 M^{-1}, 2.37×10^4 M^{-1} and 2.11×10^4 M^{-1}, respectively, revealing the strong binding of these complexes with DNA. Haemolysis assays indicated that the ligand and its complexes were less toxic to rabbit RBCs than doxorubicin. Lipinski's parameters calculated for the reported compounds indicated their good oral bioavailability. All the compounds exhibited good activities towards MCF-7 (wild type) cancer cell lines. The results of in silico studies, DNA-binding and anti-cancer activities indicated that the reported compounds might be interacting with DNA as one of their possible mechanisms of action.

Keywords: oxopyrrolidine-based ligand, DNA-binding, in silico studies, haemolysis assays, anti-cancer profiles, supra-molecular mechanism of action

Introduction

Cancer is a devastating disease due to the lack of a safe and effective treatment. It is the second most common disease after cardiovascular diseases, responsible for maximum numbers of deaths all over the world. The modernisation of our society is a major factor contributing to the increasing incidence of cancer (Ali et al., 2011a, 2011b; Siegel et al., 2013). Despite the advent of chemotherapeutic agents for cancer treatment, millions of people die from cancer every year (Ali et al., 2011c). The discovery of cisplatin and the development of its second and third generation analogues have led to a significant advancement in cancer chemotherapy. A few platinum-based drugs are in use for the treatment of different types of cancer but there are serious side-effects associated with these drugs. Moreover, after prolonged use of these drugs, cancerous cells often become resistant. It was these issues that prompted the investigation of novel non-platinum metal complexes as anti-cancer agents (Ott & Gust, 2007; Tan et al., 2010a; Ali et al., 2013a).

Pyrrolidine-based heterocyclic compounds are of special interest due to their unique chemical and biological properties. The anti-tumour properties exhibited by several compounds embedded with pyrrolidine and oxopyrrolidine nuclei have been reported (Fiaux et al., 2008; Bello et al., 2010; Guo et al., 2012; Zhang et al., 2011). Selection of the appropriate ligands fine-tunes the various structural and chemical features of

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