Journal of Inorganic Biochemistry 240 (2023) 112100

Contents lists available at ScienceDirect

Journal of Inorganic Biochemistry

journal homepage: www.elsevier.com/locate/jinorgbio

Exploring heterometallic bridged Pt(II)-Zn(II) complexes as potential antitumor agents

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ARTICLE INFO

Keywords:
Heterometallic complexes
Structure-reactivity correlation
Antitumor agents

ABSTRACT

The four novel complexes [{*cis*-PtCl(NH_3)$_2$(μ-4,4′-bipyridyl)ZnCl(terpy)}](ClO_4)$_2$ (**C1**), [{*trans*-PtCl(NH_3)$_2$(μ-4,4′-bipyridyl)ZnCl(terpy)}](ClO_4)$_2$ (**C2**), [{*cis*-PtCl(NH_3)$_2$(μ-pyrazine)ZnCl(terpy)}](ClO_4)$_2$ (**C3**) and [{*trans*-PtCl(NH_3)$_2$(μ-pyrazine)ZnCl(terpy)}](ClO_4)$_2$ (**C4**) (where terpy = 2,2′:6′,2″-terpyridine) were synthesized and characterized. Acid–base titrations and concentration dependent kinetic measurements for the reactions with biologically relevant ligands such as guanosine-5′-monophosphate (5′-GMP), inosine-5′-monophosphate (5′-IMP) and glutathione (GSH), were studied at pH 7.4 and 37 °C. The binding of the heterometallic bridged *cis*- or *trans*-Pt(II)-Zn(II) complexes to calf thymus DNA (CT-DNA) was studied by UV absorption and fluorescence emission spectroscopy and molecular docking. The results indicated that the complexes bind strongly to DNA, through groove binding, hydrogen bonds, and hydrophobic or electrostatic interaction. The possible *in vitro* DNA protective effect of *cis*- and *trans*-Pt-L-Zn complexes has shown that **C3** had significant dose-dependent DNA-protective effect and the same ability to inhibit peroxyl as well as hydroxyl radicals. Antiproliferative effect of the complexes, mRNA expression of apoptosis and repair-related genes after treatment in cancer cells indicated that newly synthesized **C2** exhibited highly selective cytotoxicity toward colon carcinoma HCT116 cells. Only treatment with *trans* analog **C2** induced effect similar to the typical DNA damaging agent such as cisplatin, characterized by p53 mediated cell response, cell cycle arrest and certain induction of apoptotic related genes. Both *cis*- and *trans*-isomers **C1** and **C2** showed potency to elicit expression of PARP1 mRNA and *in vitro* DNA binding.

Abbreviations: terpy, 2,2′:6′,2″-terpyridine; CDDP, *cis*-diamminedichloridoplatinum(II), *cis*-[$PtCl_2(NH_3)_2$]; 5′-GMP, guanosine-5′-monophosphate; 5′-IMP, inosine-5′-monophosphate; GSH, glutathione; DMF, dimethylformamide; ESI, electrospray ionization; CT-DNA, calf thymus deoxyribonucleic acid; B-DNA, right-handed double helix; cDNA, complementary DNA; EB, ethidium bromide; MTT, 3-(4,5-dymethylthiazol-yl)-2,5-diphenyltetrazolium bromide; A549, human lung adenocarcinoma cells; HCT116, human adenocarcinoma colon cells; LS-174, human caucasian colon adenocarcinoma; MDA-MB-231, human breast carcinoma cell; MRC-5, non-tumor fibroblast cell line; IC_{50}, inhibitor concentration; DDR, DNA damage response; DMSO, dimethyl sulfoxide; RNaseA, Ribonuclease A from bovine pancreas; AZD2461, 4-[[4-Fluoro-3-[(4-methoxy-1-piperidinyl)carbonyl]phenyl]methyl]-1(2H) - phthalazinone; SDS, sodium dodecyl sulfate; PI, propidium iodide; HEPES, 4-(2-hydroxyethyl)piperazine-1- ethanesulfonic acid; PBS, phosphate-buffered saline; D_2O, deuterium oxide; TSP, trimethylsilylpropionic acid; DFT, density functional theory; AAPH, 2-methylpropionamidine dihydrochloride; qRT-PCR, quantitative real-time polymerase chain reaction; Bax, bcl-2-like protein 4; Bcl2, B-cell lymphoma 2; XRCC2, X-ray repair cross complementing 2; ERCC1, endonuclease non-catalytic subunit; TP53, *homo sapiens* tumor protein p53; PARP1, poly(ADP-ribose) polymerase; H2AX, H2A histone family member X; GAPDH, glyceraldehyde-3-phosphate dehydrogenase.

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https://doi.org/10.1016/j.jinorgbio.2022.112100
Received 19 October 2022; Received in revised form 3 December 2022; Accepted 10 December 2022
Available online 14 December 2022