Selective Cu(I) complex with phosphine-peptide (**SarGly**) conjugate contra breast cancer : synthesis, spectroscopic characterization and insight into cytotoxic action.

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Rok wydania

2018

Czasopismo

Journal of Inorganic Biochemistry

Numer woluminu

186

Strony

162-175

DOI

10.1016/j.jinorgbio.2018.06.009

Kolekcja

Naukowa

Język

Angielski

Typ publikacji

Artykuł

Streszczenie

The main disadvantage of conventional anticancer chemotherapy is the inability to deliver the correct amount of drug directly to cancer. Those molecular delivering systems are very important to destroy cancer cells selectively. Herein we report synthesis of phosphine-peptide conjugate (Ph_2PCH_2-Sar-Gly-OH, **PSG**) derived from **SarGly** (sarcosine-glycine), which can be easily exchanged to other peptide carriers, its oxide (OPh_2PCH_2-Sar-Gly-OH, O**PSG**) and the first copper(I) complex ([CuI(dmp)($P(Ph)_2CH_2$-Sar-Gly-OH)], **1-PSG**, where dmp stands for 2,9-dimethyl-1,10-phenanthroline). The compounds were characterized by elemental analysis, NMR (1D, 2D), UV–Vis spectroscopy and DFT (Density Functional Theory) methods. **PSG** and **1-PSG** proved to be stable in biological medium in the presence of atmospheric oxygen for several days. The cytotoxicity of the compounds and cisplatin was tested against cancer cell lines: mouse colon carcinoma (CT26; $^{1\text{-PSG}}IC_{50}$=3.12±0.1), human lung adenocarcinoma (A549; $^{1\text{-PSG}}IC_{50}$=2.01±0.2) and human breast adenocarcinoma (MCF7; $^{1\text{-PSG}}IC_{50}$=0.98±0.2) as well as against primary line of human pulmonary fibroblasts (MRC-5; $^{1\text{-PSG}}IC_{50}$=78.56±1.1). Therapeutic index for **1-PSG** (MCF7) equals 80. Intracellular accumulation of **1-PSG** complex increased with time and was much higher (96%) inside MCF7 cancer cells than in normal MRC5 cells (20%). Attachment of **SarGly** to cytotoxic copper(I) complex *via* phosphine motif improved selectivity of copper(I) complex **1-PSG** into the cancer cells. Precise mechanistic study revealed that the **1-PSG** complex causes apoptotic cells MCF7 death with simultaneous decrease of mitochondrial membrane potential and increase of caspase-9 and -3 activities. Additionally, **1-PSG** generated high level of reactive oxygen species that was the reason for oxidative damages to the sugar–phosphate backbone of plasmid DNA.

Słowa kluczowe

Peptide carriers, Copper(I) complex, Conjugate, DNA, ROS, breast cancer

Adres publiczny

https://doi.org/10.1016/j.jinorgbio.2018.06.009

Strona internetowa wydawcy

http://www.elsevier.com