Cancer-cell-selective cytotoxicity of a dicopper complex having 1,8-naphthalimide as a targeting unit

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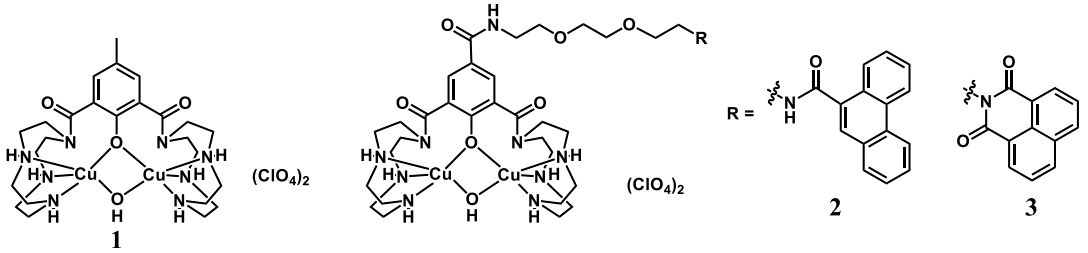
Bleomycin is an antibiotic anticancer agent that shows high catalytic activity in cleavage of double-strand DNA. However, it exerts heavy side effects to lungs in the long-term use.[1] The reason is that it acts on both cancer and normal cells non-selectively. So, metal complexes exerting cancer-cell-selective cytotoxicity may be useful to develop a new type of anticancer agent that suppresses the side effects. So, we focus on specific environments of cancer cells. The mitochondrial dysfunction in cancer cells increases H_2O_2 concentration. Metal complexes capable of targeting mitochondrial DNA (mtDNA) and activating H_2O_2 may induce mitochondrial apoptosis by cutting mtDNA. This may lead to the development of new anticancer agents that enable the cancer-cell-selective cytotoxicity.

Recently, we reported that a dicopper(II) complex with a *p*-cresol-derived ligand having two amide-tether connected 1,4,7,10-tetraazacyclododecane groups at 2,6-positions (Hbcamide), $[Cu_2(\mu\text{-OH})(\text{bcamide})](ClO_4)_2$ (**1**). This complex shows oxidative DNA cleavage activity in the presence of H_2O_2, but **1** showed relatively low cytotoxicity.[2] In this study, to enhance the DNA cleavage activity and cytotoxicity by mimicking role of a DNA-targeting site of bleomycin, we synthesized new dicopper complexes having a phenanthrene and 1,8-naphthalimide conjugates as a DNA-targeting, $[Cu_2(\mu\text{-OH})(\text{bcamide-P3-phen})](ClO_4)_2$ (**2**) and $[Cu_2(\mu\text{-OH})(\text{bcamide-P3-naph})](ClO_4)_2$ (**3**). The DNA targeting effects of **2** and **3** were 9-fold higher in DNA cleavage activity, and about 20-fold higher in cytotoxicity than **1**, and **1**–**3** show cancer-cell-selective cytotoxicity. The intracellular visualization and caspase activity assays revealed that **2** and **3** exerts cytotoxicity via mitochondrial apoptosis. Therefore, the mitochondrial apoptosis may explain the relatively high cancer-cell-selective toxicity of **1**–**3**. These results may shed light on the development of new anticancer drugs to reduce the heavy side-effects.



1 **2** **3**

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