Exploring ternary copper coordination compounds interacting with DNA as a promising anticancer and antibacterial drug

I. Kekez[1], K. Mišković Špoljarić[2], D. Vušak[1], M. Belas[1], D. Kučera-Čavara[1], B. Prugovečki[1]

[1]University of Zagreb, Faculty of Science, Department of Chemistry, Horvatovac 102a, 10000 Zagreb, Croatia, [2]University Josip Juraj Strossmayer Osijek, Faculty of Medicine, Josipa Huttlera 4, 31000 Osijek, Croatia

ikekez@chem.pmf.hr

Ternary metal complexes are gaining increasing attention in drug discovery due to their unique structural and biological properties [1-2]. These complexes feature a central metal ion coordinated by two distinct ligands, often resulting in enhanced stability, selectivity, and therapeutic potential. Among them, copper(II) coordination compounds with amino acidates and heterocyclic bases form a well-studied subclass known as Cassiopeia, recognized for their anticancer activity [3]. We have recently been involved in synthesizing novel copper ternary coordination compounds with different amino acids and heterocyclic bases, including 2,2'-bipyridine and 1,10-phenanthroline, as potential DNA binders with antiproliferative activity towards various cancer cells [4-5]. In this work, we have investigated anticancer activity of three different copper(II) ternary coordination compounds with glycine and 1,10-phenanthroline (**1** - {[Cu(Gly)(H_2O)(phen)][Cu(μ-Gly)(phen)]$SO_4 \cdot 2H_2O$}*n*, **2** - [Cu(Gly)(H_2O)(phen)][Cu(Gly)(SO_4)(phen)]$\cdot 5H_2O$ and **3** - [Cu(Gly)(phen)(H_2O)]$_2SO_4 \cdot 6H_2O$). All three compounds (**1–3**) exhibited potent antiproliferative activity against five human cancer cell lines MDA-MB 231 (breast), Hep-G2 (liver), KATO III (gastric), PANC-1 (pancreatic duct) and Caco-2 (intestinal) with IC_{50} values ranging from 0.6 to 2.8 μmol dm^{-3}. The most potent and selective activity was observed against KATO III gastric cancer cells (IC_{50} = 0.6 μmol dm^{-3}), with lower cytotoxicity against MRC-5 healthy fibroblast control cells (IC_{50} = 4 μmol dm^{-3}). The antibacterial activity of compound **2** was also assessed against two Gram-positive (*S. aureus* ATCC 29213, *E. faecalis* ATCC 29212) and two Gram-negative strains (*E. coli* ToIC-Tn10, *M. catarrhalis* ATCC 23246). It displayed moderate activity against Gram-positive bacteria and pronounced activity against Gram-negative strains, with the lowest minimal inhibitory concentration (MIC) observed for *M. catarrhalis* (*MIC* = 4 μg/mL). The binding affinity of compound **2** toward the double-stranded oligonucleotide **DNA** (ds(CGCGAATTCGCG)) was explored by spectroscopic and crystallographic methods. Absorption and fluorescence spectra suggested a moderate binding affinity of **2** to the double-stranded DNA dodecamer. Co-crystallization experiments were carried out using the Oryx8 crystallization robot, and obtained crystals were further analysed using the X-ray diffraction method on XRD2 Elettra synchrotron beamline (Trieste, Italy). A new crystal form of double-stranded DNA dodecamer ds(CGCGAATTCGCG) was obtained, crystallizing in trigonal space group – *H*3 with unit cell parameters $a = b$ = 38.520 Å, c = 99.200 Å, $\alpha = \beta = 90°$, $\gamma = 120°$. These findings highlight the potential of copper-based ternary complexes as dual-function anticancer and antibacterial agents. Their capacity to engage with DNA and exhibit selective biological activity positions them as promising candidates in the development of next-generation metallodrugs.

[1] Zhang, Z., Wang, H., Wang Q., Yan, M., Wang, H., Bi, C., Sun, S. & Fan, Y. (2016). *Int. J. Oncol.* **49(2)**, 691–699.

[2] Rajeshwari, K., Vasantha, P., Sathish Kumar, B. & Anantha Lakshmi, P. V. (2022). *Biol. Trace Elem. Res.* **200**, 5351-5364.

[3] Bravo-Gómez, M. E., García-Ramos, J.C., Gracia-Mora, I. & Ruiz-Azuara L. (2009). *J. Inorg. Biochem.* **103(2)**, 299-309.

[4] Vušak, D., Ležaić, K., Jurec, J., Žilić, D. & Prugovečki, B. (2022). *Heliyon* **8(6)**, e09556.

[5] Vušak, D., Šimunović Letić, M., Tašner, M., Matković-Čalogović, D., Jurec, J., Žilić, D. & Prugovečki, B. (2024). *Molecules 29***(23)**, 5621.