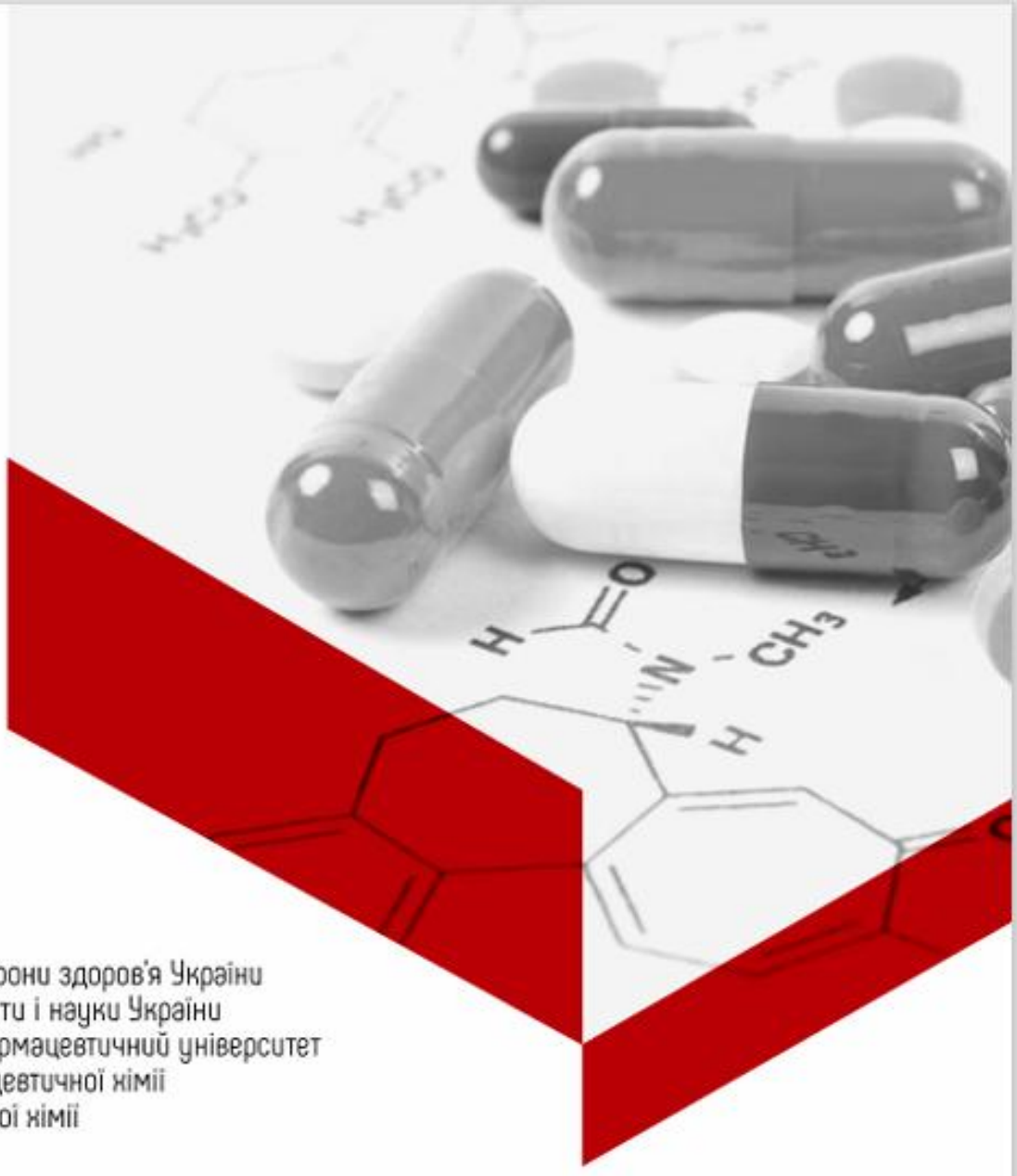

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Synthesis and Analysis of Copper(II) Complexes for G-Quadruplex Targeting

Lidiia Petrushova[1]*, Riccardo Bonsignore, Giampaolo Barone[2]

[1]*National University of Pharmacy, Department of Pharmaceutical Chemistry, Valentynivska st., 4, 61168 Kharkiv, Ukraine*
[2]*University of Palermo, Department of Biological, Chemical and Pharmaceutical Sciences and Technologies (STEBICEF), Viale delle Scienze, Edificio 17 90128 Palermo, Italy*
*lidiia.petrushova@unipa.it

Introduction. Guanine quadruplexes (G4s) are non-canonical four-stranded DNA structures that are predominantly found in oncogenes such as c-MYC, VEGF and BCL-2. These structures play a key role in gene regulation and are a promising therapeutic target for cancer treatment. Selective stabilisation of G4s can inhibit the transcription of oncogenes, offering a unique mechanism for cancer treatment. Metal-based G4-binding compounds, especially those containing copper(II) ions, are of interest due to their redox activity and ability to induce reactive oxygen species (ROS), which may enhance their cytotoxicity towards cancer cells.

Materials and methods. The present study concerns the synthesis of copper(II) Schiff base complexes, using ethanol and water as solvents, with the use of copper(II) perchlorate and copper(II) acetate as the metal source. The products were purified and characterised using mass spectrometry, elemental analysis, whilst FRET (Fluorescence Resonance Energy Transfer) DNA melting assay was used to assess their G4-binding capabilities. Double-helical DNA, as well as hTelo, c-MYC, VEGF, cKIT1, cKIT2 and BCL-2 G-quadruplexes, were tested. The influence of substance concentration on the melting point of G4-DNA solutions was also studied.

Results and discussion. The synthesised copper(II) complexes exhibited interesting binding affinity for G4 structures, although their capacity to stabilise these complexes exhibited variability. The FRET analysis indicated that RB303 demonstrated the most promising stabilizing effect of genes as cKIT1 and BCL-2 with ΔT values 9.0±0.62°C and 4.71±0.20°C respectively. It is noteworthy that no substantial stabilization was observed for the VEGF and c-MYC quadruplexes. This implies that the introduction of specific ligand modifications may potentially enhance the selective G4-binding properties and cytotoxicity in cancer cells.

Conclusions. This study underscores the potential of copper(II)-based complexes as selective G4 stabilisers in oncogenes, with encouraging outcomes observed for RB303. Further optimisation of the ligand structures and biological testing are required to enhance the specificity and cytotoxicity of these compounds towards cancer cells. The findings lend support to the proposition that G4-targeting compounds represent a promising avenue for the development of novel cancer therapies.

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