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MONOMETALNI I HETEROBIMETALNI KOMPLEKSI *N*-HETEROCIKLA – SINTEZA, STRUKTURNA KARAKTERIZACIJA I BIOLOŠKA AKTIVNOST

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U okviru disertacije proučavani su *N*-heterociklički ligandi i njihovi metalni kompleksi. Provedena je sinteza heterocikličkih spojeva, poput derivata piridina, 2,2'-dipiridilamina, benzimidazola i benzotiazola, koji sadrže monodentatne, bidentatne i tridentatne koordinirajuće skupine, te njihovih koordinacijskih kompleksa s prijelaznim metalima. Pripravljeni derivati podijeljeni su u šest klasa. Bidentatni i tridentatni heterociklički ligandi sintetizirani su višestupnjevitom sintezom primjenom konvencionalnih sintetskih metoda i reakcijama „zelene“ kemije potpomognutih mikrovalovima. Strukture ligadana i metalnih kompleksa potvrđene su spetroskopskopijom NMR, IR i UV i difrakcijom rendgenskog zračenja u jediničnom kristalu, a heterobimetalni kompleksi karakterizirani su voltametrijski te računalnom analizom.

Pripravljenim ligandima i metalnim kompleksima ispitano je antiproliferativno djelovanje na niz tumorskih staničnih linija *in vitro*, kao i na zdrave stanice uz referentne kliničke lijekove. Koordinacija metalom poboljšala je antitumorsku aktivnost i selektivnost u većini slučajeva. Heterobimetalni kompleks konjugata ferocena i 2,2'-dipiridilamina s bakrom(II) [Cu(**A8c**)$_2$](CF$_3$SO$_3$)$_2$ pokazao je selektivno inhibitorno djelovanje na stanice HeLa, MES-OV, A549 i MDA-MB-231 uz povećanje stanične populacije u fazama staničnog ciklusa S i G2/M. Aktivnost 2,2'-dipiridilaminskih kompleksa poboljšana je koordinacijom s Re(I), pri čemu je najizraženiju aktivnost, bolju u odnosu na cisplatinu, pokazao kompleks [Re(**B4a**)CO$_3$]Cl. Kompleks strukturno fleksibilnijeg bis(2,2'-pikolil)aminskog liganda i Ni(II), [Ni(**C1**)$_2$](NO$_3$)$_2$, pokazao je istaknuto antiproliferativno djelovanje ometajući proces replikacije DNK i smanjujući ekspresiju antiapoptotskog markera Bcl-2. Rutenijevi(II) polusendvič kompleksi 2-arilbenzotiazola i 2-pikolila povezani 1,2,3-triazolnom premosnicom imali su antiproliferativno djelovanje u submikromolarnom području, pokazujući selektivnost prema PANC1 stanicama. Konjugati acil-tiourea i benzotiazola te njihovi Ru(II) kompleksi imali su inhibitorno djelovanje u niskom mikromolarnom i nanomolarnom području na stanice H460, MCF-7, SW 620 i HepG2, s izraženim djelovanjem na staničnoj liniji raka dojke (MCF-7). Spojevi su, osim toga, pokazali

slabo do umjereno antibakterijsko djelovanje prema *E. faecalis*. Ligand **E5c** i kompleksi **D4a$_{Ru}$**, **E4c$_{Ru}$** i **E5c$_{Ru}$** odabrani su za daljnja testiranja mehanizma biološkog djelovanja.

Ključne riječi: *N*-heterocikli, metalni kompleksi, organometalni kompleksi, antiproliferativno djelovanje, antibakterijsko djelovanje

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MONOMETALLIC AND HETEROBIMETALLIC COMPLEXES OF *N*-HETEROCYCLES – SYNTHESIS, STRUCTURAL CHARACTERIZATION AND BIOLOGICAL EVALUATION

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In this dissertation, selected *N*-heterocyclic ligands and their metal complexes were studied. The synthesis of heterocyclic compounds, such as derivatives of pyridine, 2,2'-dipyridylamine, benzimidazole and benzothiazole, containing monodentate, bidentate and tridentate coordinating groups, and their coordination complexes with transition metals was carried out. The prepared derivatives are divided into corresponding six classes~~groups~~. The bidentate and tridentate heterocyclic ligands were synthesized by multi-step synthesis using conventional synthetic methods and „green“ microwave-assisted synthesis. The structures of the ligands and metal complexes were confirmed by NMR, UV and IR-spectroscopy and single-crystal X-ray diffraction. Heterobimetallic complexes were additionally characterized by voltammetry and computational analysis.

The prepared ligands and metal complexes were evaluated for their antiproliferative activity *in vitro* against several tumor cell lines, as well as on normal cells with clinical drugs as references. Generally, metal coordination improved activity and selectivity in most cases. The heterobimetallic complex of ferrocene and 2,2'-dipyridylamine conjugate with copper(II) $[Cu(\mathbf{A8c})_2](CF_3SO_3)_2$ showed a selective inhibitory effect on HeLa, MES-OV, A549 and MDA-MB-231 cells with an increase in cell population in the S and G2/M phase of the cell cycle. The activity of 2,2'-dipyridylamine complexes was improved by coordination with Re(I), where [Re(**B4a**)CO_3]Cl showed the most pronounced activity, better than cisplatin. The Ni(II) complex of the more structurally flexible bis(2,2'-picolyl)amine ligand, $[Ni(\mathbf{C1})_2](NO_3)_2$, showed prominent antiproliferative activity by interfering with the DNA replication process and reducing the expression of the antiapoptotic marker Bcl-2. Ruthenium(II) half-sandwich complexes of 2-arylbenzothiazole and 2-picolyl linked by a 1,2,3-triazole bridge showed antiproliferative activity in the submicromolar range, showing selectivity towards PANC1 cells. Acyl thiourea and benzothiazole conjugates and their Ru(II) complexes showed cytostatic activity in the low micromolar and nanomolar range against H460, MCF-7, SW 620 and HepG2 cells, with

prominent activity against the MCF-7 breast cancer cell line. Besides, compounds showed weak to moderate antibacterial activity against *E. faecalis*. Ligand **E5c** and complexes **D4a$_{Ru}$**, **E4c$_{Ru}$** and **E5c$_{Ru}$** were selected for further evaluation of their mechanism of biological action.

Keywords: *N*-heterocycles, metal complexes, organometallic complexes, antiproliferative activity, antibacterial activity