Bulgarian Chemical Communications, Volume 49, Special Edition B (pp. 83 – 88) 2017

Synthesis, characterization and *in vitro* cytotoxic activity of zinc(II), cobalt(II) and nickel(II) complexes with tridentate ONO Schiff base 3-methoxysalicylaldehyde benzoylhydrazone

B. I. Nikolova-Mladenova[1]*, G. Ts. Momekov[2]

[1] *Department of Chemistry, Faculty of Pharmacy, Medical University of Sofia, 2 Dunav, Street, 1000 Sofia, Bulgaria*
[2] *Department of Pharmacology, Pharmacotherapy and Toxicology, Faculty of Pharmacy, Medical University of Sofia, 2 Dunav, Street, 1000 Sofia, Bulgaria*

Received February 20, 2017; Revised March 15, 2017

Dedicated to Acad. Bogdan Kurtev on the occasion of his 100th birth anniversary

New Zn(II), Co(II) and Ni(II) complexes were synthesized with a cytotoxic ligand 3-methoxysalicylaldehyde benzoylhydrazone. IR, UV-Vis spectroscopy and elemental analysis techniques were applied for characterization. The spectral data of the complexes were interpreted on the basis of comparison with the spectrum of the free ligand. The complexes are mononuclear with 1:2 metal-to-ligand molar ratios. The analysis revealed coordination through phenolic-oxygen, azomethine-nitrogen and amide-oxygen atoms. The new complexes were tested for *in vitro* cytotoxicity against a panel of human leukemic and tumor cell lines by MTT-dye reduction assay. The pharmacological screening showed that the Zn(II) complex causes 50% inhibition of the cellular viability in low micromolar concentrations. The Ni(II) complex is less active, whereas the Co(II) complex is practically devoid of cytotoxic effects.

Key words: 3-methoxysalicylaldehyde; aroylhydrazones; metal complexes; cytotoxic activity

INTRODUCTION

Hydrazones are widely studied biologically active compounds which exhibit an extensive spectrum of activities, such as anti-inflammatory [1, 2], analgesic [2], antituberculosis [3, 4], antibacterial [5], antimicrobial [6], anti-HIV [6, 7] and anticancer [6, 8, 9] activity. The wide variety of the observed pharmacological properties in combination with their relatively easy synthesis has made them attractive ligands. Aroylhydrazones of the type R-CO-NH-N=CH-R′, derived by condensation of aromatic aldehydes and acid hydrazides form a series of biologically active ligands used in medicinal chemistry as iron chelators effective in chemotherapy of Fe overload diseases [10–13]. Besides the ability to chelate iron, hydrazones synthesized from salicylaldehyde and its derivatives additionally display an expressed antiproliferative activity [14–19]. Hydrazones obtained from 3-methoxysalicylaldehyde exerted potent antiproliferative effect on a wide spectrum of human tumor cell lines [16, 17]. This activity may be due to the high ability of the hydrazones to chelate Fe(III) from cells, and thereby, to inhibit the proliferation of the neoplastic cells [20]. Salicylaldehyde derived hydrazones are polydentate ligands that contain many coordination centers and may chelate other metal ions which organisms use in their metabolism. Zinc is one of the most abundant transition metals in the human body that is essential for the structure and function of a large number of macromolecules and for a variety of enzymatic reactions, which mediate a wide range of biochemical and nutritional processes [21, 22]. It interacts with a wide range of organic ligands [23] and participates in the metabolism of RNA and DNA, signal transduction and gene expression. In blood plasma, zinc is bound to and transported by albumin (60%) and transferrin (10%) [24]. Cobalt is valuable for humans because it is a constituent of Vitamin B_{12} which has a key role in the normal functioning of the brain and nervous system, and for blood formation (hemopoiesis). It is normally involved in the metabolism of all human cells, especially affecting DNA synthesis and regulation, but also fatty and amino acid metabolism [25, 26].

In view of the significant role played by transition metal ions and their complexes in biological systems, here we report the synthesis and characterization of zinc(II), cobalt(II) and nickel(II) complexes with a cytotoxic hydrazine, 3-methoxysalicylaldehyde benzoylhydrazone. The cytotoxic properties of the new complexes were tested by MTT-dye reduction assay on a panel of four different human leukemic cell lines.

* To whom all correspondence should be sent:
E-mail: *borianank@abv.bg*

EXPERIMENTAL

Materials and measurements

All chemicals used for the synthesis of the compounds: 3-methoxysalicylaldehyde, benzhydrazide, $Zn(CH_3COO)_2.2H_2O$, $Co(CH_3COO)_2.4H_2O$, $Ni(CH_3COO)_2.4H_2O$, and 96% ethanol were purchased from commercial sources and used without any further purification. All of the other chemicals were of analytical grade. The carbon, nitrogen and hydrogen contents of the compounds were determined by elemental analyses on a "Euro Vector SpA" apparatus. The melting point of the ligand was determined in open capillary tube using a Büchi B-535 apparatus. The thermogravimetric analyses were performed on a Setaram Setsys TG-DSC 15 in air atmosphere with a heating rate of 10 °C/min. The IR spectra were recorded in solid state (in KBr pellets) on a Bruker Tensor 27 spectrophotometer in the range of 4000–400 cm^{-1}. The UV-Vis spectra were recorded on a Hewlett Packard 8452 spectrophotometer in DMSO. The ^1H NMR and ^{13}C NMR spectra of the ligand were recorded on a Bruker Avance DRX 250 in DMSO-d_6 solvent. Chemical shifts (δ) were reported in parts per million (ppm), J values were given in Hz.

The synthesis of the ligand was published in our previous work [16].

3-methoxysalicylaldehyde benzoylhydrazone: Yield 90%; m.p. 126–127 °C; Color: Pale yellow; Anal. Calcd for $C_{15}H_{14}O_3N_2.H_2O$: C 62.49, H 5.59, N 9.72. Found: C 62.59, H 5.63, N 9.68; IR (KBr) *ν* (cm^{-1}): 3366 (Ar-OH), 3207 (N-H), 1652 (C=O), 1607 (C=N), 1576 (C-NH), 1247 (C-O); ^1H NMR (250 MHz, DMSO-d_6) δ ppm: 3.81 (s, 3H, -OCH_3), 6.85 (t, 1H, *J* = 7.88 Hz, $ArH_{aldehyde}$), 7.02 (d, 1H, *J* = 8 Hz, $ArH_{aldehyde}$), 7.15 (d, 1H, *J* = 7.75 Hz, $ArH_{aldehyde}$), 7.56 (m, 3H, $ArH_{hydrazide}$), 7.96 (d, 2H, *J* = 8 Hz, $ArH_{hydrazide}$), 8.69 (s, 1H, CH=N), 11.08 (s, 1H, NH), 12.15 (s, 1H, OH). ^{13}C NMR (250 MHz, DMSO-d_6) δ ppm: 55.85 (OCH_3), 148.02 (CH=N), 162.98 (C=O).

Synthesis of the complexes

The metal complexes were obtained using the following general procedure: The corresponding metal acetates (1 mmol) were dissolved in 50% ethanol (10 mL) at constant stirring and heating at 30 °C. To avoid the hydrolysis of the metal salt some drops of concentrated CH_3COOH were added. The received solutions were slowly mixed drop-wise with the solution of 3-methoxysalicylaldehyde benzoylhydrazone (2 mmol) in boiling 96% ethanol (15 mL) and immediately precipitates were formed. The mixtures were stirred for 60 min to complete the reaction and then were allowed to stand undisturbed overnight at room temperature. Fine crystals were collected by filtration, washed with ethanol and dried over P_2O_5 in a vacuum desiccator.

Bis-(3-methoxysalicylaldehyde benzoylhydrazone) zinc (II) [$Zn(C_{15}H_{13}O_3N_2)_2$]: Yield 95%; Color: Yellow; Anal. Calcd for [$Zn(C_{15}H_{13}O_3N_2)_2$]: C 59.66, H 4.34, N 9.28. Found: C 59.55, H 4.51, N 9.17; IR (KBr) *ν* (cm^{-1}): 3197 (N-H), 1607 (C=O), 1542 (C=N), 518 (Zn-O), 433 (Zn-N).

Bis-(3-methoxysalicylaldehyde benzoylhydrazone) cobalt (II) [$Co(C_{15}H_{13}O_3N_2)_2$]: Yield 97%; Color: Bright brown; Anal. Calcd for [$Co(C_{15}H_{13}O_3N_2)_2$]: C 60.31, H 4.39, N 9.38. Found: C 59.86, H 4.64, N 9.15; IR (KBr) *ν* (cm^{-1}): 3194 (N-H), 1601 (C=O), 1541 (C=N), 525 (Co-O), 435 (Co-N).

Bis-(3-methoxysalicylaldehyde benzoylhydrazone) nickel (II) [$Ni(C_{15}H_{13}O_3N_2)_2$]: Yield 94%; Color: Dark yellow-greenish; Anal. Calcd for [$Ni(C_{15}H_{13}O_3N_2)_2$]: C 60.33, H 4.39, N 9.38. Found: C 60.22, H 4.63, N 9.24; IR (KBr) *ν* (cm^{-1}): 3196 (N-H), 1602 (C=O), 1540 (C=N), 525 (Ni-O), 438 (Ni-N).

Cell lines and culture conditions

The study was carried out with the following cell lines: HL-60 – human acute myeloid leukemia, established from the peripheral blood of a 35-year-old woman with acute myeloid leukemia; SKW-3 – T-cell leukemia, established from the peripheral blood of a 61-year-old man with T cell chronic lymphocytic leukemia; BV-173 – human B cell precursor leukemia, established from the peripheral blood of a 45-year-old man with chronic myeloid leukemia in blast crisis; K-562 – human chronic myeloid leukemia, established from the pleural effusion of a 53-year-old woman with chronic myeloid leukemia in terminal blast crisis, were purchased from the German Collection of Microorganisms and Cell Cultures (DSMZ, Braunschweig, Germany). The cell lines were cultured under standard conditions – RPMI-1640 liquid medium supplemented with 10% fetal bovine serum (FBS) and 2 mM L-glutamine, in cell culture flasks, housed at 37 °C in an incubator "BB 16-Function Line" Heraeus (Kendro, Hanau, Germany) with humidified atmosphere and 5% CO_2. Cells were kept in log phase by supplementation with

fresh medium after removal of cell suspension aliquots, two or three times weekly.

Cytotoxicity assessment (MTT-dye reduction assay)

The cell viability after exposure to the tested compounds was assessed using the MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] dye reduction assay as described by Mossman [27]. The method is based on the reduction of the yellow tetrazolium salt MTT to a violet formazan product via the mitochondrial succinate dehydrogenase in viable cells. Exponentially growing cells were seeded in 96-well flat-bottomed microplates (100 μL/well) at a density of $1x10^5$ cells per ml and after 24 h incubation at 37 °C they were treated to various concentrations of the tested compounds for 72 h. For each concentration a set of 8 wells were used. After the exposure period with the test compounds 10 μL MTT solution (10 mg/mL in PBS) aliquots were added to each well. The microplates were further incubated for 4 h at 37 °C and the MTT-formazan crystals formed were dissolved through addition of 100 μL/well 5% HCOOH in 2-propanol. The MTT-formazan absorption was determined using a microprocessor controlled microplate reader (Labexim LMR-1) at 580 nm.

Bioassay data processing and statistics

The cell survival data were normalized as percentage of the untreated control (set as 100% viability), were fitted to sigmoidal dose response curves and the corresponding IC_{50} values (concentrations causing 50% suppression of cellular viability) were calculated using non-linear regression analysis (GraphPad Prizm Software for PC). The statistical processing of biological data included the Student's t-test whereby values of $p \leq 0.05$ were considered as statistically significant.

DNA fragmentation assay

The characteristic for apoptosis mono- and oligonucleosomal fragmentation of genomic DNA was detected using 'Cell Death Detection' ELISA (enzyme-linked immunosorbent assay) kit following a 24 h exposure to either ligand or Zn(II) and Ni(II) metal complexes. Cytosolic fractions of 1×10^4 HL-60 cells per group (treated or untreated controls) served as an antigen source in a sandwich ELISA, utilizing a primary anti-histone antibody-coated microplate and a secondary peroxidase-conjugated anti DNA-antibody. The photometric immunoassay for histone-associated DNA-fragments was executed according to the manufacturer's instructions at 405 nm, using a microprocessor-controlled microplate reader (Labexim LMR-1). The results were expressed as a oligonucleosome enrichment factor (representing a ratio between the absorption in the treated versus the untreated control samples). Each test was run in triplicate.

RESULTS AND DISCUSSION

Chemistry

The ligand 3-methoxysalicylaldehyde benzoyl-hydrazone, shown on Fig. 1, was synthesized as previously described [16] by the condensation of 3-methoxysalicylaldehyde and benzhydrazide in ethanol. The complexes were prepared by a direct reaction of the hydrazone and the respective metal acetates in good yields.

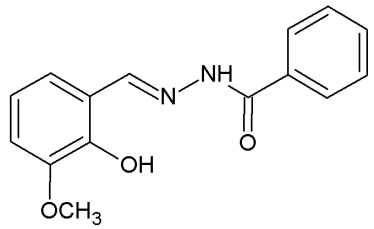

Fig. 1. Structure of the ligand.

The ligand and its Zn(II), Co(II) and Ni(II) complexes were characterized by elemental analysis as a basis for the determination of their empirical formulae. Experimental and calculated C, H, N values reveal molar ratio metal:ligand = 1:2 in the complexes and suggest molecular formula $[M(L^-)_2]$ for all complexes.. The data from the elemental analysis are summarized in the Experimental section.

The composition derived from the elemental analyses was proved by thermal analysis of the obtained compounds. The TGA and DTA data were used to determine the content of H_2O in the compounds. The thermal decomposition of the hydrazone starts with the stage of dehydration and it comes between 70-115 °C. The experimental mass loss of 6.10% (calc. 6.25%) is due to the loss of one H_2O molecule and it is accompanied by the DTG endo peak at 100 °C. The thermal investigations of the complexes show absence of weight loss up to 190 °C which indicates that the complexes do not contain crystallization water molecules. Above this temperature the complexes began to decompose and at 570–600 °C the decomposition process stopped and stable metal oxides were formed.

The structures of the complexes in the solid state were determined using their IR spectra. The comparative IR spectral study of the ligand and its complexes revealed the coordination mode of the hydrazone during the complex formation. The medium intensity band at 3366 cm^{-1} in the IR spectrum of the ligand due to phenolic OH group had disappeared in the spectra of the complexes. This supports the suggestion for deprotonation of the ligand during the coordination and the displacement of a proton by the metal ion. The band observed at 1607 cm^{-1} in the spectrum of the ligand which is attributed to azomethine C=N group was shifted to lower wave numbers in spectra of the complexes indicating the involvement of N-atom of the azomethine group in the complex formation. An intense band which appears at 1652 cm^{-1} in the spectrum of the ligand is assigned to the stretching vibration of the carbonyl group C=O. In the spectra of the complexes a considerable negative shift is observed showing coordination through the carbonyl–oxygen atom of the free ligands. The NH stretching vibration in the free ligand occurs at 3207 cm^{-1} and remains unaffected after complexation. This precludes the possibility of coordination through imine nitrogen atom. In addition, the appearance of medium bands at 518–525 cm^{-1} and 433–438 cm^{-1} in the spectra of the complexes can be assigned to *ν*(M–O) and *ν*(M–N), respectively.

The characterization of the complexes in solution was performed by UV–Vis spectroscopy. The moderate solubility of the complexes in DMSO was enough for the detection of electronic spectra as the solutions used were much diluted (10^{-5}–10^{-6} mol/L in DMSO). However, it was difficult to prepared suitable solutions to register NMR-spectra of the complexes. The UV–Vis spectral data for the free ligand and complexes are summarized in Table 1.

Table 1. UV–Vis spectral data for the free ligand and complexes.

Compound	λ_{max}(nm)		
Ligand	280	304	-
Zn(II)-complex	260	316	400
Co(II)-complex	262	312	403
Ni(II)-complex	262	306	416

UV–Vis spectrum of the ligand has two intensive bands at 280 nm and 304 nm indicating n→π* and π→π* transitions in phenolic OH- and azomethine C=N- groups, respectively. Upon complexation these bands are slightly shifted relative to the ligand with maxima at 260–262 nm and 306–316 nm which can be considered as an evidence for the complex formation. The spectra of the complexes additionally exhibited broad band in the visible part of the spectrum at 400–416 nm as a result of d-d transitions responsible for the characteristic colors of the complexes.

The comparison of the IR and UV–Vis spectroscopy data of the Zn(II), Co(II) and Ni(II) complexes with those of the free ligand suggests that 3-methoxysalicylaldehyde benzoylhydrazone act as monoanionic tridentate ligand and coordinate through a deprotonated phenolic-oxygen, azomethine-nitrogen and amide-oxygen atoms forming two chelate rings. The complexes are neutral and mononuclear. Based on the above results, the structure for the transition metal complexes was suggested (Fig. 2).

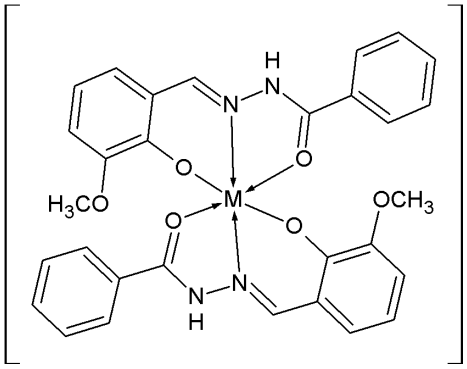

Fig. 2. The suggested structure of the complexes (M= Zn^{2+}, Co^{2+} or Ni^{2+}).

Pharmacology

The new complexes were further tested for *in vitro* cytotoxicity. The cytotoxic activity was assessed by the MTT-dye reduction assay after 72 h incubation against a panel of human leukemic cell lines. The results were fitted to sigmoid dose-response curves and the corresponding IC_{50} values were calculated using non-linear regression (GraphPad Prizm software for PC). Throughout the screening investigation the data about the new compounds were compared with the clinically used antineoplastic drugs Cisplatin. The IC_{50} values obtained are summarized in Table 2. Each data point represents the arithmetic mean ± standard deviation (sd) of at least eight experiments. IC_{50} values were calculated as concentrations of the tested compounds causing 50% decrease of cell survival.

The tested compounds inhibited the growth of tumor cells in a concentration-dependent manner.

Table 2. Cytotoxic activity of 3-methoxysalicylaldehyde benzoylhydrazone and its Zn(II), Ni(II) and Co(II) complexes against a panel of human tumor cell lines after 72 h continuous exposure (MTT-assay).

Compound	IC_{50} (μmol/L)			
	HL-60	SKW-3	K-562	BV-173
Ligand	11.3 ± 2.6	9.8 ± 3.1	27.0 ± 2.7	20.8 ± 4.2
Zn(II)-complex	10.4 ± 2.6	9.2 ± 3.3	28.2 ± 2.4	39.5 ± 2.1
Co(II)-complex	> 200.0	> 200.0	> 200.0	> 200.0
Ni(II)-complex	32.9 ± 1.9	11.8 ± 2.2	50.1 ± 3.6	19.4 ± 6.2
Cisplatin	4.7 ± 3.4	5.2 ± 3.5	12.5 ± 4.2	4.2 ± 2.1

Acute myeloid leukemia HL-60 cell line and T-cell leukemia cell line SKW-3 exhibit the highest sensitivity to the Zn(II) complexes with IC_{50} values slightly lower than these of the ligand. The results showed that the Zn(II)-complex demonstrated superior activity as compared to Ni(II) complex, although its potency was generally inferior to that of the reference agent Cisplatin. The Co(II) complex is devoid of cytotoxic activity against all leukemic cell lines within the tested concentration range (6.25–200 μmol/L).

In order to elucidate the mechanistic aspects of the observed effects we evaluated the propensity of ligand 3-methoxysalicylaldehyde benzoyl-hydrazone and its Ni(II) and Zn(II) complexes to trigger oligonucleosomal DNA-fragmentation, key hallmark of apoptosis. As evident from the data presented in Fig. 3, the 24 h exposure of HL-60 to equieffective concentration of the tested compounds led to statistically a significant increase of the cellular content of histone-associated DNA-fragments. These findings indicate that the cell growth inhibitory effects of metal complexes are at least partly mediated by induction of programmed cell death through apoptosis.

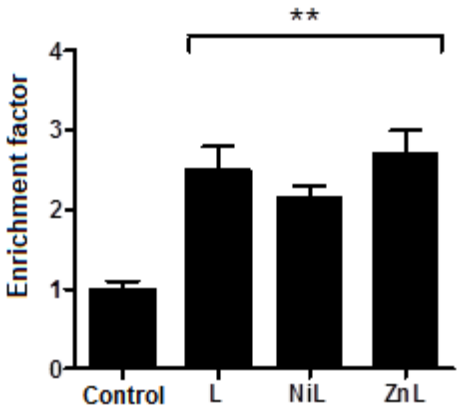

Fig. 3. Apoptotic DNA-fragmentation in HL-60 cells after 24 h exposure to ligand and metal complexes. The cytosolic nucleosomal enrichment was determined using a commercially available ELISA kit. Each bar is representative for three experiments.

CONCLUSION

New Zn(II), Co(II) and Ni(II) complexes were synthesized and characterized with elemental analyses, thermal and spectral investigations. The analytical data suggest molecular formula $[M(L^-)_2]$ and absence of coordinated water in compounds, which was further supported by the thermal analysis. The ligand 3-methoxysalicylaldehyde benzoylhydrazone acted as monoanionic tridentate ligand coordinating to the metal ions through ONO donor sites and thus forming stable six-membered chelates. The preliminary cytotoxicity screening revealed that Zn(II) and Ni(II) complexes induced 50% inhibition of the cell viability at micromolar concentrations. Taking into consideration the superior relative potency of Zn(II) complex, however, as well as its capability to induce programmed cell death we could conclude that Zn(II) complexes with hydrazones deserve further attention in search of anticancer compounds.

REFERENCES

1. Z. A. Kaplancikli, M. D. Altintop, A. Ozdemir, G. Turan-Zitouni, S. I. Khan, N. Tabanca, *Lett. Drug Des. Discovery*, **9**, 310 (2012).
2. W. B. Júnior, M. S. Alexandre-Moreira, M. A. Alves, A. Perez-Rebolledo, G. L. Parrilha, E. E. Castellano, O. E. Piro, E. J. Barreiro, L. M. Lima, H. Beraldo, *Molecules*, **16**, 6902 (2011).
3. A. Ozdemir, G. Turan-Zitouni, Z. A. Kaplancikli, G. Revial, *Marm. Pharm. J.*, **14**, 79 (2010).
4. B. Koçyiğit-Kaymakçıoğlu, E. E. Oruç-Emre, S. Unsalan, S. Rollas, *Med. Chem. Res.*, **18**, 277 (2009).
5. T. Govindasami, A. Pandey, N. Palanivelu, A. Pandey, *Int. J. Org. Chem.*, **1**, 71 (2011).
6. L. Savini, P. Massarelli, V. Travagli, C. Pellerano, E. Novellino, S. Cosentino, M. B. Pisano, *Eur. J. Med. Chem*., **39**, 113 (2004).
7. P. Vicini, M. Incerti, P. L. Colla, R. E. Loddo, *Eur. J. Med. Chem.*, **44**, 1801 (2009).
8. T. B. Chaston, R. N. Watts, J. Yuan, D. R. Richardson, *Clin. Cancer Res.*, **10**, 7365 (2004).

9. D. K. Johnson, T. B. Murphy, N. J. Rose, W. H. Goodwin, L. Pickart, *Inorg. Chim. Acta*, **67**, 159 (1982).
10. P. Ponka, D. Richardson, E. Baker, H. M. Schulman, J. T. Edward, *Biochim. Biophys. Acta*, **967**, 122 (1988).
11. E. Baker, D. R. Richardson, S. Gross, P. Ponka, *Hepatology*, **15**, 492 (1992).
12. D. R. Richardson, P. Ponka, *J. Lab. Clin. Med.*, **131**, 306 (1998).
13. J. L. Buss, E. Arduini, P.Ponka, *Biochem. Pharmacol.*, **64**, 1689 (2002).
14. D. B. Lovejoy, D. R. Richardson, *Blood*, **100**, 666 (2002).
15. D. R. Richardson, K. Milnes, *Blood*, **89**, 3025 (1997).
16. B. Nikolova-Mladenova N. Halachev, R. Iankova, G. Momekov, D. Ivanov, *J. Arzneim.-Forsch.*, **61**, 714 (2011).
17. B. Nikolova-Mladenova, G. Momekov, D. Ivanov, *Pharmacia*, **LVIII (1-4)**, 41 (2011).
18. B. Nikolova-Mladenova, G. Momekov, Ts. Gerasimova, M. Topashka-Ancheva, *J. Med. & Biol. Sci.*, **1**, 44 (2014).
19. B. Nikolova-Mladenova, A. Bakalova, G. Momekov, D. Ivanov, *J. Med. & Biol. Sci.*, 1, 16 (2015).
20. D. R. Richardson, *Antimicrob. Agents Chemother.*, **41**, 2061 (1997).
21. H. Tapiero, K.D. Tew, *Biomed. Pharmacother.*, **57**, 399 (2003).
22. B. Szewczyk, M. Kubera, G. Nowak, *Prog. Neuropsychopharmacol. Biol. Psychiatry*, **35**, 693 (2011).
23. K. M. Hambidge, N. F. Krebs, *J. Nutr*,. **137**, 1101 (2007).
24. L. Rink, P. Gabriel, *Proc. Nutr. Soc.*, **59**, 541 (2000).
25. K. Yamada, in: Interrelations between Essential Metal Ions and Human Diseases. Metal Ions in Life Sciences 13, A. Sigel, H. Sigel; R.K.O. Sigel. Springer, 2013, p. 295.
26. V. Cracan, R. Banerjee, L. Banci In: Metallomics and the Cell. Metal Ions in Life Sciences 12, Springer, 2013.
27. T. Mosmann, *J. Immunol. Methods*, **65**, 55 (1983).

СИНТЕЗ, ОХАРАКТЕРИЗИРАНЕ И *IN VITRO* ЦИТОТОКСИЧНА АКТИВНОСТ НА Zn(II), Co(II) И Ni(II) КОМПЛЕКСИ С ТРИДЕНТАТНИЯ ONO-ЛИГАНД 3-МЕТОКСИСАЛИЦИЛАЛДЕХИД БЕНЗОИЛХИДРАЗОН

Б. И. Николова-Младенова[1]*, Г. Цв. Момеков[2]

[1] *Катедра Химия, Фармацевтичен Факултет, Медицински Университет – София, ул. Дунав 2, София 1000, България*

[2] *Катедра по Фармакология, Фармакотерапия и Токсикология, Фармацевтичен Факултет, Медицински Университет – София, ул. Дунав 2, София 1000, България*

Постъпила на 20 февруари 2017 г.; Коригирана на 15 март 2017 г.

(Резюме)

Синтезирани са нови Zn(II), Co(II) и Ni(II) комплекси с активния цитотоксичен лиганд 3-метоксисалицилалдехид бензоилхидразон. Съединенията са охарактеризирани чрез елементен и термогравиметричен анализ и спектрални методи. Спектралните данни на комплексите са интерпретирани чрез сравнение със спектрите на свободния лиганд. Комплексите са моноядрени с молно съотношение на метала към лиганда 1:2. Анализите доказват, че лигандът е тридентатен и координира металните йони чрез депротонирания фенолен кислороден атом, азотния атом от азометиновата група и кислородния атом от амидната група. Новите комплекси са тествани за *in vitro* цитотоксичност върху спектър от 4 човешки левкемични клетъчни линии чрез MTT-тест. Фармакологичните изследвания показват, че Zn(II) комплекс води до инхибиране на 50% от клетъчната жизнеспособност в ниски микромоларни концентрации. Ni(II) комплекс е по-слабо активен, докато Co(II) комплекс практически не проявява цитотоксични ефекти в проучения диапазон от концентрации (6.25–200 μmol/L).