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Synthesis, characterization and cytotoxicity of mixed ligand Mn(II), Co(II) and Ni(II) complexes

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Abstract: Complexes of the type [ML′L(OH)(H_2O)], where M = Ni(II), Co(II) or Mn(II), L′ = isatin and HL = 3-(2-phenylhydrazono)acetylacetone, 3-(2-(4--chlorophenyl)hydrazono)acetylacetone or 3-(2-(4-bromophenyl)hydrazono)-acetylacetone, were synthesized by equimolar reaction of a metal(II) chloride with isatin and a 3-(2-arylhydrazono)acetylacetone. The resulting complexes were characterized by elemental analyses, molar conductivity, spectral data (IR and mass spectrometry) and magnetic moments. Furthermore, the ligands and their metal complexes were screened for their cytotoxicity against different human cancer cell lines using the sulforhodamine B (SRB) assay. The results showed that most of the mixed ligand metal complexes have high cytotoxicity in comparison with the reference drugs used.

Keywords: 3-(2-arylhydrazono)acetylacetone; isatin; transition metals; mixed ligands; cytotoxicity.

INTRODUCTION

One of the main goals for research chemists and pharmacologists is the synthesis of novel bioactive compounds for the development of better drugs to fight diseases. Thus, coordination chemistry has developed very rapidly mainly in the last 15 years since many ligands of no or low biological activity become more active when transferred to their metal complexes[1,2] and some drugs show increased activity when administered as metal complexes.[3–5] In addition, complexes containing heterocyclic ligands having nitrogen and/or sulfur have inc-

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reased biological activities compared to the original ligands.[6,7] Recently, there is an increasing interest in the synthesis of mixed ligand metal complexes due to their biological significance. These complexes play important roles in biological processes since enzymes are known to be activated by metal ions.[8,9] Moreover, they have wide antituberculosis, antifungal,[10] antibacterial[11] and antitumor[12,13] pharmacological activities.

A literature survey reveals that isatin (indole-2,3-dione) and its derivatives shows a wide range of antimicrobial,[14] anticonvulsant,[15] anticancer[16,17] and anti-HIV activities.[18] On the other hand, arylhydrazono-1,3-diketone derivatives have been widely used as intermediates in the preparation of a large number of biologically important heterocyclic compounds.[19–21]

In view of these facts and continuing our interest in the synthesis of compounds with promising biological activities,[22,23] Ni(II), Co(II) and Mn(II) complexes of 3-(2-arylhydrazono)acetylacetone with isatin were prepared and characterized by IR and UV–Vis spectroscopy, elemental analyses, molar conductivity and magnetic susceptibility measurements. The study was extended to screen the ligands and their metal complexes against different human cancer cell lines.

EXPERIMENTAL

Chemistry

All melting points were measured on a Gallenkamp melting point apparatus and are uncorrected. The IR spectra were recorded (KBr disk) on a Perkin-Elmer 1650 FT-IR instrument. The ^{1}H-NMR (500 MHz) spectra were recorded on a Varian 500 MHz spectrometer in DMSO-d_6 using TMS as an internal standard. The FAB mass spectra of the complexes were recorded on a JEOL JMS/AX-500 mass spectrometer. Elemental analyses were obtained from the Micro Analytical Data Center at Cairo University, Egypt. The magnetic susceptibilities were measured at 20 °C by the Gouy method at the Faculty of Science, Cairo University. The electronic absorption spectra were recorded on a PG Instruments Ltd., +80+ automatic UV–Vis spectrophotometer in DMSO. The molar conductance values of solutions of the metal complexes in DMF (10^{-3} mol L^{-1}) were measured using Metrohem 660 conductivity meter.

Acetylacetone, *p*-chloroaniline, *p*-bromoaniline, aniline, sodium acetate, methanol and hydrochloric acid were of Merck AR grade, Germany. Isatin was supplied by Riedel de Haën AG, Germany. The employed $NiCl_2{\cdot}6H_2O$, $CoCl_2{\cdot}6H_2O$ and $MnCl_2{\cdot}4H_2O$ salts (Fluka, Germany) were of AR grade.

Preparation of 3-(arylhydrazono)acetylacetones)

The 3-(arylhydrazono)acetylacetone derivatives (HL) were prepared by coupling acetylacetone with different diazonium salts. Thus, a solution of acetylactone (0.01 mol) and sodium acetate (5 g) in ethanol (50 mL) was cooled to 0–5 °C and then the diazonium salt (0.01 mol) was added under stirring. The reaction was allowed to proceed at 0–5 °C for 30 min. The 3-(arylhydrazono)acetylacetone derivatives were precipitated and collected by filtration, washed with cold deionized water and recrystallized from ethanol.[24]

*Preparation of the complexes **1–9***

A solution of the metal chloride (3.4 mmol) in a minimum amount of water was added to a hot solution of the mixed ligand (3.4 mmol) in methanol, whereby a clear solution was obtained. The pH was increased from 6.0 to 8.0 with dilute NaOH solution. The mixture was refluxed under stirring for 6 h. The formed complex was filtered off, washed several times with hot methanol and dried under reduced pressure.

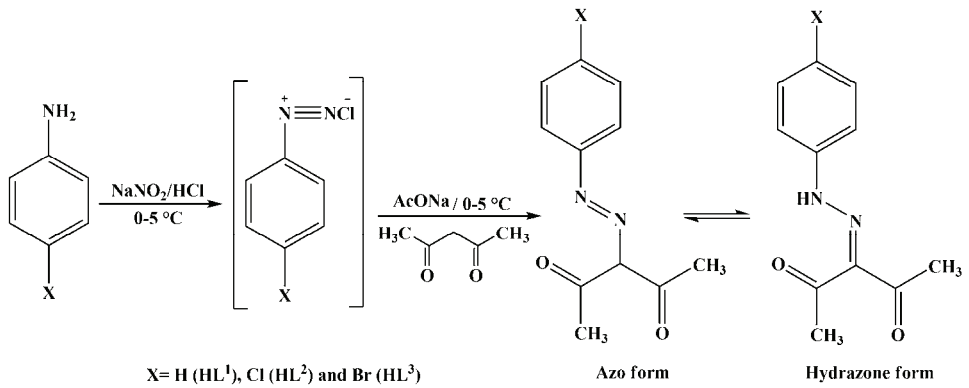
Biological experiments

In vitro *cytotoxicity screening.* The tested compounds were subjected to *in vitro* disease--oriented primary antitumor screening. Different tumor cell lines were utilized. The human tumor cell lines of the cancer screening panel were grown in RPMI 1640 medium containing 5 % fetal bovine serum and 2 mM L-glutamine. In a typical screening experiment, 100 µL of cells were inoculated into 96-well microtiter plates at plating densities ranging from 5000 to 40000 cells well^{-1}, depending on the doubling time of the individual cell lines. After cell inoculation, the microtiter plates were incubated at 37 °C, 5 % CO_2, 95 % air and 100 % relative humidity for 24 h prior to the addition of the experimental drugs. After 24 h, two plates of each cell line were also fixed *in situ* with trichloroacetic acid (TCA) to represent a measurement of the cell population for each cell line at the time of drug addition (T_z). Experimental drugs were solubilized in DMSO at 400-fold of the desired final maximum test concentration and stored frozen prior to use. At the time of drug addition, an aliquot of frozen concentrate was thawed and diluted to 2-times the desired final maximum test concentration with complete medium containing 50 µg ml^{-1} gentamicin. Four additional 10-fold or 0.5log serial dilutions were made to provide a total of five drug concentrations plus a control. Aliquots of 100 µL of these different drug dilutions were added to the appropriate microtiter wells already containing 100 µL of medium, resulting in the required final drug concentrations. Following drug addition, the plates were incubated for an additional 48 h at 37 °C, 5 % CO_2, 95 % air and 100 % relative humidity. For adherent cells, the assay was terminated by the addition of cold TCA. The cells were fixed *in situ* by the gentle addition of 50 µL of cold 50 % (*w*/*V*) TCA (final concentration, 10 % TCA) and incubated for 60 min at 4 °C. The supernatant layer was discarded and the plates were washed five times with tap water and air-dried. Sulforhodamine B (SRB) solution (100 µL) at 0.4 % (*w*/*V*) in 1 % acetic acid was added to each well and the plates were incubated for 10 min at room temperature. After staining, the unbound dye was removed by washing five times with 1 % acetic acid and the plates were air dried. The bound stain was subsequently solubilized with 10 mM Trizma® base and the absorbance was read on an automated plate reader at a wavelength of 515 nm. For suspension cells, the methodology was the same except that the assay was terminated by fixing the settled cells at the bottom of the wells by gently adding 50 µL of 80 % TCA (final concentration, 16 % TCA). The parameter IC_{50} which is the concentration of the drugs inducing a 50% inhibition of cell growth of treated cells when compared to the growth of control cells.[25-27]

RESULTS AND DISCUSSION

Chemistry

The ligands. The 3-(arylhydrazono)acetylacetone derivatives (HL) are prepared *via* coupling between diazotized aromatic amine derivatives and acetylacetone in a 1:1 molar ratio according to Scheme 1.[24] The structures of these ligands were confirmed by elemental analyses and their spectral data (IR and ^{1}H-NMR), which are discussed later with their metal complexes.



Scheme 1. Synthesis of 3-(arylhydrazono)acetylacetone derivatives (HL).

The complexes. Reactions of the hydrated metal(II) chloride with 3-(arylhydrazono)acetylacetone and isatin in equimolar ratios resulted in formation of the complexes **1**–**9**, shown in Scheme 2.

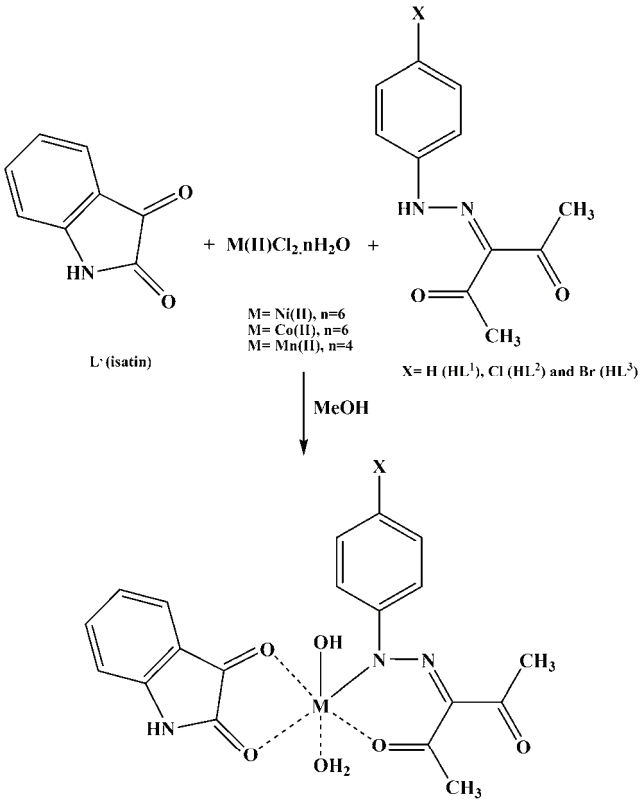
The physical, analytic and spectral data for the ligand and their metal complexes are given in the Supplementary material to this paper.

Infrared spectra of the ligands and their complexes

In the infrared spectra of the ligands (HL^1, HL^2 and HL^3), the broad band in the range 3428–3086 cm^{-1} indicates the existence of strong intramolecular hydrogen bonding.[28] Furthermore, there are two strong bands at 1673 and 1623 cm^{-1} assignable to ν(C=O, free) and ν(C=O, hydrogen bonded), respectively. The ν(C=N) band appears at 1593 cm^{-1}, which remains almost unaffected in the spectra of all the complexes suggesting that the nitrogen atom is not involved in the coordination, while the ν(C=O) band at 1623 cm^{-1} is shifted to lower frequencies in the spectra of the complexes, suggesting that this oxygen atom is involved in the coordination, while the carbonyl group at ≈1673 cm^{-1} remains almost unchanged in the spectra. The prominent band present at ≈1518 cm^{-1} of the ligands is due to δ(N–H) vibrations, which disappears in the spectra of all the complexes because of the replacement of the hydrazone NH proton with a metal ion. The infrared spectrum of isatin (L′) shows a band at 3191 due to ν(N–H) and two ν(C=O) group absorptions at 1745 and 1731 cm^{-1}. The IR spectra of the complexes show that the two carbonyl groups of isatin ligand are shifted to lower frequency, suggesting that both groups are involved in the coordination, while ν(N–H) at 3191 cm^{-1} is not changed, indicating that the (N–H) group is not involved in the coordination.

Conclusive evidence of bonding was also given by the observation that new bands in the spectra of all metal complexes **1**–**9** appear in the low frequency regions at 493–438 and 584–540 cm^{-1} characteristic of ν(M–O) and ν(M–N)

stretching vibrations, respectively.[29] Furthermore, the observed broad band at 3550 cm^{-1} in all complexes were attributed to the OH group and the OH stretching vibrations of lattice water molecules.[10]



Complexes	M(II)	X	Complexes	M(II)	X
1	Ni	H	6	Mn	Cl
2	Co	H	7	Ni	Br
3	Mn	H	8	Co	Br
4	Ni	Cl	9	Mn	Br
5	Co	Cl			

Scheme 2. Synthesis of mixed ligand complexes of the type [ML′L(OH)(H_2O)].

Nuclear magnetic resonance of the ligands

The ^{1}H-NMR spectrum of HL revealed a single proton at $\delta \approx 14.02$ ppm due to the N–H···O=C group.[30,31] The ^{1}H-NMR spectrum of HL^2 is illustrated in Fig. S-1 of the Supplementary material to this paper.

Mass spectra of the complexes

The molecular ion peaks in the mass spectra of some complexes were used to confirm the molecular formula. Thus, the mass spectra of the Ni(II) complexes confirmed the molecular formulas, *e.g.*, [NiL′L^1(OH)(H$_2$O)] and [NiL′L^3(OH)(H$_2$O)] confirmed $C_{19}H_{19}N_3NiO_6$ and $C_{19}H_{18}BrN_3NiO_6$, respectively. Similarly, the mass spectra of the Co(II) complexes confirmed the molecular formulas, *e.g.*, [CoL′L^2(OH)(H$_2$O)] and [CoL′L^3(OH)(H$_2$O)] confirmed the molecular formulas $C_{19}H_{18}ClCoN_3O_6$ and $C_{19}H_{18}BrCoN_3O_6$, respectively. Moreover, the mass spectrum of the Mn(II) complex, *e.g.*, [MnL′L^3(OH)(H$_2$O)] confirmed the molecular formula $C_{19}H_{18}BrMnN_3O_6$.

Electronic spectra and magnetic moments

The UV–visible spectra of the free ligands HL^1, HL^2, HL^3 and L′ showed absorption bands at 292–297 and 418–440 nm due to $\pi\rightarrow\pi^*$ and $n\rightarrow\pi^*$ transitions, respectively. These bands were blue- or red-shifted in the spectra of the complexes due to coordination in the ligands.

The Mn(II) complexes **3**, **6** and **9** exhibited two weak bands at 618–622 and 520–526 nm which were attributed to $^6A_{1g} \rightarrow {}^4T_{1g}(^4G)$ and $^6A_{1g} \rightarrow {}^4T_{2g}(^4G)$ transitions, respectively. These absorptions are consistent with an octahedral geometry around the Mn(II) atom. The magnetic moment values of the Mn(II) complexes were in the range of 5.82–5.90 μ_B, corresponding to five unpaired electrons, which is also indicative of octahedral geometry.[33]

The electronic spectra of the Co(II) complexes **5** and **8** showed two d–d transitions in the ranges 654–661 and 540–548 nm due to the $^4T_{1g}(F) \rightarrow {}^4A_{2g}(F)$ and $^4T_{1g}(F) \rightarrow {}^4A_{2g}(p)$ transitions, respectively, indicating an octahedral configuration around the Co(II) atom. The $^4T_{2g}(F) \rightarrow {}^4T_{1g}(F)$ transition (1237–1242 nm) would be observed in the near IR region. This region was out the range of the employed spectrophotometer.[34] The $\boldsymbol{\mu}_{eff}$ values for the Co(II) complexes were in the range 4.87–4.94 μ_B, which are similar to those reported for octahedral Co(II).[35]

The Ni(II) complexes **1**, **4** and **7** exhibited two absorption bands in the ranges 963–988 and 572–581 nm, which are assigned to $^3A_{2g}(F) \rightarrow {}^3T_{2g}(F)$ and $^3A_{2g}(F) \rightarrow {}^3T_{1g}(F)$ transitions, respectively. However, the absorption bands at 420–422 nm due to $^3A_{2g}(F) \rightarrow {}^3T_{1g}(p)$ was overlapped with the ligand absorption bands. The spectra of these complexes support an octahedral stereochemistry around the Ni(II) atom. The room temperature magnetic moment values of the Ni(II) complexes were 3.17–3.20 μ_B, which are in the normal range observed for octahedral Ni(II) complexes.[36]

Molar conductance measurements

The molar conductivities of 10^{-3} mol L^{-1} solutions of the complexes in DMF were measured at room temperature. The results were in the range 22.1–11.6 Ω^{-1} cm^2 mol^{-1}, indicating that all the metal complexes had molar conductance values in the range characteristic for non-electrolytes.[37]

Biological activity

In vitro *cytotoxicity screening.* The cytotoxicities of the mixed ligand complexes [ML′L(OH)(H_2O)], the ligands HL^1–HL^3 and L′ were determined using the SRB assay on different human cancer cell lines including: cervical carcinoma (KB), ovarial carcinoma (SK OV-3), CNS cancer (SF-268), non-small cell lung cancer (NCl H460), colon adenocarcinoma (RKOP 27) (Table I), anti-leukemia (HL60, U937, K562), melanoma (G361, SK-MEL-28) and neuroblastoma (GOTO, NB-1) (Table II). The cytotoxic effect of the ligands and their metal complexes [ML′L(OH)(H_2O)] on the cell lines HeLa (cervical), MCF-7 (breast), HT1080 (fibrosarcoma) and HepG2 (liver) were also tested (Table III). The results are expressed as the IC_{50}, which is the concentration of a drug that causes a 50 % reduction in the proliferation of cancer cells when compared to the growth of the control cells.

TABLE I. Cytotoxicity (IC_{50} / nM, the concentration required for 50 % inhibition of cell growth) of the ligands and the mixed ligand complexes determined by using SRB assay on different human cancer cell lines; the values for most potent compound are marked by "*"

The ligands and their metal complexes	Cell line				
	KB	SK OV-3	SF-268	NCI H460	RKOP27
L′	4.40	5.40	4.50	0.65	7.50
HL^1	6.70	5.46	0.35*	0.89	2.30*
1	0.32*	3.20	0.55	0.44	4.30
2	4.40	3.40	3.50	0.40*	5.50
3	5.60	6.70	0.43	0.56	7.60
HL^2	9.80	8.80	9.90	0.68	4.50
4	0.55	0.55*	5.60	0.66	7.80
5	0.45	8.80	0.50	0.43	8.80
6	0.45	7.60	0.40	0.67	6.40
HL^3	0.65	0.67	4.50	0.87	4.80
7	8.00	7.70	0.75	0.57	4.30
8	0.67	5.60	0.65	0.43	4.50
9	0.90	0.89	0.85	0.84	2.30*
Fluorouracil	4.46	–	–	–	–
Doxorubicin	–	4.16	–	–	–
Cytarabine	–	–	7.68	–	–
Gemcitabine HCl	–	–	–	2.13	–
Capecitabine	–	–	–	–	4.33

TABLE II. Cytotoxicity (IC_{50} / nM, the concentration required for 50 % inhibition of cell growth) of the ligands and the mixed ligand complexes determined by using SRB assay on different human cancer cell lines; the values for most potent compound are marked by "*"

The ligands and their metal complexes	Cell line						
	Leukemia			Melanoma		Neuroblastoma	
	HL60	U937	K562	G361	SK-MEL-28	GOTO	NB-1
L′	8.00	6.80	3.70	0.43*	5.00	0.65	4.80
HL^1	6.50	7.70	0.87	0.87	4.00	3.00	3.60
1	0.75	9.00	0.60	0.57	4.00	6.80	9.87
2	5.30	5.40	5.40	0.77	5.00	5.87	3.00
3	3.40	7.30	0.60	0.88	1.00*	7.60	4.00
HL^2	6.00	8.70	9.00	0.50	8.00	7.50	2.30
4	0.44	0.65	6.00	8.80	4.00	0.57	0.70
5	0.56	3.50	0.68	0.64	6.00	0.68	0.69
6	0.32*	6.00	0.90	0.59	8.00	0.67	0.56
HL^3	0.67	0.43*	6.40	0.54	7.00	4.70	0.36*
7	8.00	6.30	0.40*	0.70	8.00	0.50	7.60
8	0.33	8.00	0.50	0.70	7.00	0.34*	9.00
9	0.80	0.79	8.00	0.60	8.00	0.56	0.65
Doxorubicin	1.13	4.45	6.66	–	–	4.73	5.15
Aldesleukin	–	–	–	6.66	3.45	–	–

TABLE III. Cytotoxicity (IC_{50} / nM, the concentration required for 50 % inhibition of cell growth) of the ligands and the mixed ligand complexes determined by using SRB assay on different human cancer cell lines; the values for most potent compound are marked by "*"

The ligands and their metal complexes	Cell line			
	HeLa (cervical)	MCF-7 (breast)	HT1080 (fibrosarcoma)	HepG2 (liver)
L′	0.449	3.650	7.86	2.30
HL^1	9.860	0.790	0.45	0.64
1	0.009*	9.600	0.09*	0.80
2	7.680	8.400	8.69	0.79
3	0.897	4.587	0.54	0.47
HL^2	6.600	7.600	5.80	3.64
4	0.780	0.900	3.65	0.77
5	5.640	4.970	0.99	0.91
6	0.600	0.764	0.87	0.89
HL^3	0.960	5.800	2.50	0.54*
7	6.500	9.600	0.86	8.50
8	0.770	4.600	7.00	0.79
9	0.444	0.760*	0.59	6.50
Tamoxifen	0.114	0.155	1.16	1.31

Screening the cytotoxicity of the mixed ligand complexes [ML′L(OH)(H_2O)] and the ligands HL^1, HL^2, HL^3 and L′ on cervical carcinoma (KB), where 5-fluorouracil was used as a standard drug (IC_{50} = 4.46 nM), shows that the complexes **1**, **4**, **5**, **6**, **8**, and **9**, and the ligand HL^3 were more potent than the standard drug.

In the case of the ovarial carcinoma (SK OV-3) cell line, the tested complexes **4** and **9** and the ligand HL^3 (IC_{50} = 0.55, 0.89 and 0.67 nM, respectively) were found to be more potent than the standard drug doxorubicin (IC_{50} = 4.16 nM).

Studying the cytotoxicity of the tested complexes and the ligands on the CNS cancer (SF-268) cell line using cytarabine (IC_{50} = 7.68 nM) as a standard drug, reveals that all the tested complexes and the ligands except HL^2 (IC_{50} = = 9.90 nM) were more potent than the standard drug.

In the case of the non-small cell lung cancer (NCl H460) cell line, all of the tested complexes and the ligands were found to be more potent than the standard drug gencitabine hydrochloride (IC_{50} = 2.13 nM).

In the case of the colon adenocarcinoma (RKOP 27) cell line, the ligand HL^1 and the complex **9** (IC_{50} = 2.30 nM) were found to be more potent than the standard drug capecitabine (IC_{50} = 4.33 nM).

The study of the cytotoxicity on the leukemia (HL60) cell line indicated that the ligands L′, HL^1, HL^2 and the complexes **2**, **3** and **7** were less potent compounds than doxorubicin (IC_{50} = 1.13 nM).

In the case of the leukemia (U937) cell line, the ligand HL^3 (IC_{50} = 0.43 nM) was the most potent, while complex **1** (IC_{50} = 9.00 nM) was the least bioactive.

In the case of the leukemia (K562) cell line, the tested complexes and the ligands, except ligand HL^2 and complex **9,** were more active than the standard drug doxorubicin (IC_{50} = 6.66 nM); the ligand HL^3 and complex **4** had activity comparable to that of doxorubicin.

On estimation of the cytotoxicity on the melanoma (G361) cell line, the tested complexes and the ligands, expect complex **4** (IC_{50} = 8.80 nM) were more active than the standard drug aldesleukin (IC_{50} = 6.66 nM).

In the case of the melanoma (SK-MEL-28) cell line, the tested complexes and the ligands were less active than the standard drug Aldesleukin (IC_{50} = 3.45 nM), expect complex **3** that was more active (IC_{50} = 1.00 nM)

Cytotoxicity of the tested complexes and the ligands on neuroblastoma (GOTO) cell line showed that complex **8** was the most potent (IC_{50} = 0.34 nM) and more active than the standard drug doxorubicin (IC_{50} = 4.73 nM).

In the case of the neuroblastoma (NB-1) cell line, complex **2** was less active than the standard drug doxorubicin (IC_{50} = 5.15 nM), while ligand HL^3 (IC_{50} = = 0.36 nM) was the most active.

The cytotoxicity of the tested complexes and the ligands on the HeLa (cervical) cell line showed that complex **1** (IC_{50} = 0.009 nM) was the most potent and more active than the standard drug tamoxifen (IC_{50} = 0.114 nM).

In the case of the MCF-7 (breast) cell line, the standard drug tamoxifen (IC_{50} = = 0.155 nM) was more active than all the other tested complexes and ligands.

In the case of the HT1080 (fibrosarcoma) cell line, complex **1** (IC_{50} = 0.09 nM) was the most potent and complex **2** (IC_{50} = 8.69 nM) was found to be less potent than tamoxifen (IC_{50} = 1.16 nM).

The cytotoxicity of the tested complexes and the ligands on the HepG2 (liver) cell line shows that the complexes **1**–**6** and **8**, and the ligands HL^3 and HL^1 were more active than the standard drug tamoxifen (IC_{50} = 1.16 nM), whereby complex **3** (IC_{50} = 0.47 nM) was the most promising one.

CONCLUSIONS

Ni(II), Co(II) and Mn(II) complexes of 3-(2-arylhydrazono)acetylacetone (HL) and isatin (L′) were synthesized. The ligands (L′ and HL^1–HL^3) act as bidentate molecules, whereby L′ was coordinated through two oxygen atoms while the 3-(2-arylhydrazono)acetylacetones were coordinated by oxygen and nitrogen atoms. The prepared complexes **1**–**9**, which were non-electrolytes, have octahedral geometry with the general structural formula [ML′L(OH)(H_2O)]. The cytotoxicity results of the ligands and their complexes **1**–**9** against different human cancer cell lines indicated that most of the complexes exhibited high cytotoxicity at very low concentrations in comparison with the reference drugs considered.

SUPPLEMENTARY MATERIAL

Physical, analytic and spectral data of the ligands and complexes are available electronically at http://www.shd.org.rs/JSCS/, or from the corresponding author on request.

ИЗВОД

СИНТЕЗА, КАРАКТЕРИЗАЦИЈА И ЦИТОТОКСИЧНА АКТИВНОСТ КОМПЛЕКСА МАНГАНА(II), КОБАЛТА(II) И НИКЛА(II) СА МЕШОВИТИМ ЛИГАНДИМА

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У реакцијама одговарајућег метал(II)-хлорида са изатином и 3-(2-арилхидразоно)ацетилацетоном синтетизовани су комплекси опште формуле [ML′L(OH)(H_2O)] (где је M = Ni(II), Co(II) или Mn(II), L′ = изатин и HL = 3-(2-фенилхидразоно)ацетилацетон, 3-(2-(4-хлорфенил)хидразоно)ацетилацетон или 3-(2-(4-бромфенил)хидразоно)ацетилацетон). Комплекси су окарактерисани применом елементалне микроанализе, спектроскопских метода (IR спектроскопија и масена спектрометрија) и мерењем моларне проводљивости и магнетног момента. Испитивана је цитотоксична активност лиганда и комплекса на различитим туморским ћелијским линијама применом SRB теста. Добијени резултати су показали да већина комплекса показује већу цитотоксичну активност у поређењу са стандардним лековима.

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