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CORRELATION BETWEEN THE STRUCTURE AND BIOLOGICAL ACTIVITY OF SOME COORDINATION COMPOUNDS OF ISATIN SCHIFF BASES

The complexes of Co(II), Ni(II), Cu(II) and Zn(II) with isatin Schiff bases were synthesised and their structures established by using elemental analysis, as well as by measuring the molar conductivity, AA, FTIR, UV/VIS and ¹H NMR and applying TG analysis.

Isatin Schiff bases show different antimicrobial activity due to the different nature of the carbonyl and amino components as well as its substituent. The complexes have an enhanced activity compared to the ligands due to the transition metal involved in the coordination. It is also evident that the complexes have different antimicrobial activity, which is related to the nature and type of coordinated metal.

The synthetic versatility of isatin has led to the extensive use of this compound in organic synthesis. This use has originated from interest in the biological and pharmacological properties of its derivatives [1]. The mono- and bishydrazones find wide application in medicine as active physiological preparations, due to their antibacterial, tuberculostatic, fungicidal and activities against certain types of cancers and microorganisms [2]. It has also been found that derivatives of benzilidene have wide application, not only because of their strong activity against some microorganisms, but also because they can act as scavengers of free radicals. Many furan derivatives find wide hemotherapeutic applications in clinical and veterinary medicine. The 5-nitro-furan derivatives generally exhibit considerable antibacterial activity, primarily *in vitro*, against gram-positive and gram-negative organisms [3]. Also, thiosemicarbazone derivatives are of considerable interest because of their chemistry and potentially beneficial biological activities, such as antitumor, antibacterial, antiviral and antimalarial activities [4].

Isatin, due to its *cis*- α -dicarbonyl moiety, is a potentially good substrate for the synthesis of metal complexes, either alone or with other ligands. Their derivatives, mostly those substituted at the C-3, such as isatin-3-hydrazone (the β -hydrazone of isatin) and isatin-3-imines bearing an extra heteroaromatic ring are also generally employed as ligands. In this manner, Schiff bases formed from isatin and amino silica gel are useful sorbents for divalent cations and for Fe(III) [1].

The activity of Schiff bases is derived from the presence of the C=N group and different electron-donor substituents in the *para*-positions [3].

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Rad saopšten na skupu "Savremene tehnologije i privredni razvoj", Oktobar 10-11, 2003, Leskovac, kao sekcijsko predavanje u okviru rada Sekcije za organske hemijske tehnologije i polimerno inženjerstvo.

The presence of the electron pair on the nitrogen atom and the electron-donor characteristic of the double bond enable Schiff bases to behave as bases. Namely, these compounds as Lewis bases give an electron pair to the metal ion and form coordination compounds. As a matter of fact, Schiff bases show their basic characteristics in the best way by forming the complexes with metals. But, the basic character of the C=N group is not sufficient sometimes to coordinate with the metal ion. Sometimes to form stable compounds the presence of a group with a variable hydrogen atom, such as the OH-group is necessary, so that 5- or 6-chelates may be formed.

Coordination compounds with Schiff bases as ligands are easily obtained using reflux in a non-aqueous solvent. This method was used originally by Schiff, who prepared a great number of complexes and determined their structure [5].

Many coordination compounds of transition metals with Schiff bases show greater activity than the ligands themselves.

Considering all of this, it was interesting to synthesize compounds of this nature with potential biological activity. Complexes of Co(II), Ni(II), Cu(II) and Zn(II) with Schiff bases such as N¹-[2-furfurylidene]-N²-[β -isatine]azine (L¹), N¹-[5-nitro-2-furfurylidene]-N²-[β -isatine]azine (L²) and N¹-[salicylidene]-N²-[β -isatine]azine (L³) were prepared. Their structure was established using elemental analysis, as well as molar conductivity, AA, FTIR, UV/VIS and ¹H NMR and applying TGA analysis. The complexes were tested for antibacterial activity against *Staphylococcus aureus* ATTC 6538, *Enterococcus* D, *Proteus mirabilis*, *Escherichia coli* 95, *Bacillus anthracis*, *Pseudomonas aeruginosa* and *Candida albicans* ATTC 10231 in a standard minimum inhibitory concentration (MIC) of serial dilution test.

MATERIALS AND METHODS

Synthesis of compounds

The ligands were obtained from the β -hydrazone of isatin as the amino and 2-furancarboxaldehyde, 5-ni-

tro-2-furancarboxaldehyde and salicylaldehyde as the carbonyl components (1:1 molar ratio) in EtOH solvent as previously reported for other similar compounds [6–9] at pH 4.5.

Since the ligands are partly soluble in 95% ethanol, the coordination compounds were synthesized by the template reaction of the β -hydrazone of isatin and 2-furancarboxaldehyde or 5-nitro-2-furancarboxaldehyde in the presence of metal(II)chloride (1:1 molar ratio for Cu(II) and Zn(II) and 2:1 for Ni(II) Co(II)), and with salicylaldehyde in the presence of metal(II)chloride in 1:1 molar ratio for all the metals [5–8]. The structural formula of the complexes is shown in Fig.1.

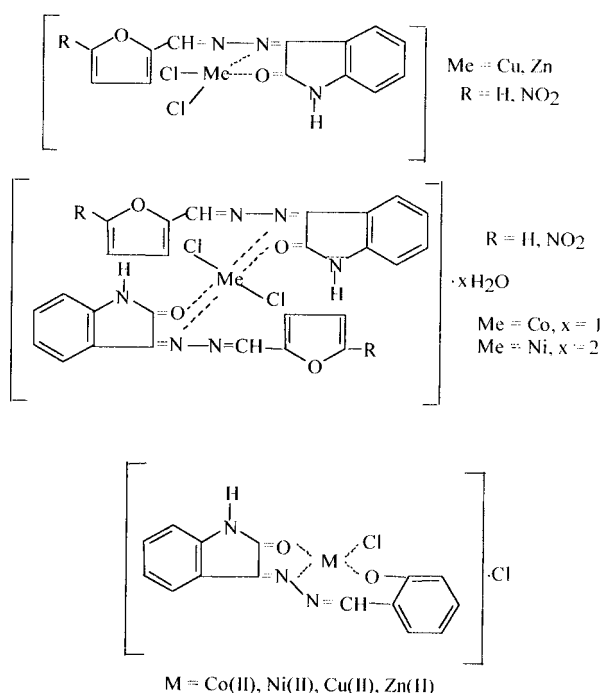


Figure 1. The structure of the coordination compounds

Antimicrobial activity

Bacteria and yeast were inoculated into 5 cm³ of a liquid medium. The antimicrobial activity of the ligands and their metal complexes was determined by following the bacterial growth for 24 h at 35°C and yeast growth for 48 h at 30°C in nutritional medium. The different concentration of the tested compounds in DMF as solvent at which no increase in the optical density was observed after incubation times of 24 h and 48 h, were accepted as the minimal inhibitory concentration (MIC, $\mu\text{g} \cdot \text{cm}^{-3}$) [9]. The results present the average values gained from three measurements.

RESULTS AND DISCUSSION

N¹-[2-furfurylidene]-N²-[β -isatin]azine and N¹-[5-nitro-2-furfurylidene]-N²-[β -isatine]azine as ligands coordinate in the bidentate, while N¹-[salicylidine]-N²-

[β -isatin]azine coordinates in the tridentate manner. The absorption bands of the C=O and C=N stretching vibrations are shifted to lower frequencies in the spectra of the complexes which indicates that the C=O and C=N groups are coordination sites of the ligands. The upward shift is the highest for Ni(II) complexes as the most stable ones (Table 1).

Table 1. FTIR spectral data of the compounds [frequency (cm⁻¹)]

Compound	Assignment of bands ^a			
	$\nu(\text{OH})$	$\nu(\text{C}=\text{O})$	$\nu(\text{C}=\text{N})$ ¹	$\nu(\text{HC}=\text{N})$ ²
β -hidrazone of isatin	-	1685s	1604s	-
L ¹	-	1722 s	1612w	1576w
[CoL ¹ 2Cl ₂] · H ₂ O	3466m	1700m	1600w	1539m
[NiL ¹ 2Cl ₂] · 2H ₂ O	3471m	1700m	1596m	1576w
[CuL ¹ Cl ₂] · H ₂ O	3431m	1720s	1593w	1576w
[ZnL ¹ Cl ₂] · H ₂ O	3425m	1716s	1596m	1576w
L ²	-	1733s	1613w	1576w
[CoL ² 2Cl ₂] · H ₂ O	3496m	1700s	1601w	1541s
[NiL ² 2Cl ₂] · 2H ₂ O	3367m	1694s	1602w	1576w
[CuL ² Cl ₂] · H ₂ O	3444m	1696s	1609w	1578w
[ZnL ² Cl ₂] · H ₂ O	3368m	1697s	1609w	1576w
L ³	3490s	1730s	1615m	1585w
[CoL ³ Cl] · Cl	-	1698m	1616w	1545w
[CuL ³ Cl] · Cl	-	170 m	4618w	1560w
[NiL ³ Cl] · Cl	-	1685s	1615w	1545w
[ZnL ³ Cl] · Cl	-	170 s	4616w	1550w

^aRelative intensity: s-strong, m-medium, w-weak, l-large

¹Vibrations of group from the β -hydrazone of isatin

²Vibrations of the azomethine group

The strong phenolic (OH) bond in the spectra of L³ disappear in the spectra of complexes indicating that the Schiff base was bonded to the metallic ions through the oxygen phenolic atoms [10]. The third coordination site in L³ was confirmed using FTIR and ¹H NMR, where the OH group was located at 3490 cm⁻¹ and 12.56 ppm and the free ligand was absent in the spectrum of the complexes. This indicates the deprotonation of this group during the coordination with metallic ion [11,12].

The presence of lattice water in complexes with L¹ and L² was confirmed by TGA data, where the weight loss in corresponded to two water molecules for Ni(II) and one molecule water for Co(II), Cu(II) and Zn(II) coordination compounds.

The electronic spectra of the complexes, as well as the magnetic moments suggest that the Ni(II) and Co(II) ions are in octahedral, while Cu(II) and Zn(II) are in tetrahedral environment in complexes with L¹ and L². In complexes with L³ the Ni(II) and Cu(II) ions are in a square planar, while the Co(II) and Zn(II) ions are in a tetrahedral environment (Tables 2–4).

Table 2. Electronic spectral data [DMF, frequency(cm^{-1})/ $\epsilon_{\text{max}} \cdot 10^3(\text{mol}^{-1} \cdot \text{dm}^3 \cdot \text{cm}^{-1})$], molar conductance of the complexes with L^1 recorded in DMF and magnetic measurements

Compound	$\nu(10^3\text{cm}^{-1})/\epsilon$	Transitions	Geometry	Mol. con. ($\text{Scm}^2\text{mol}^{-1}$)	μ_{eff}/μ_B
$[\text{CoL}^1_2\text{Cl}_2] \cdot \text{H}_2\text{O}$	21.9/0.69 0.88/0.25	${}^4\text{T}_{1g} \rightarrow {}^4\text{T}_{2g}(\text{F})$ ${}^4\text{T}_{1g} \rightarrow {}^4\text{T}_{1g}(\text{P})$	Octahedral	10	5.1
$[\text{NiL}^1_2\text{Cl}_2] \cdot 2\text{H}_2\text{O}$	25.6/2.100 20.2/0.304 16.4/0.250	${}^3\text{A}_{2g}(\text{F}) \rightarrow {}^1\text{E}_g(\text{z})$ ${}^3\text{A}_{2g} \rightarrow {}^3\text{T}_{1g}(\text{F})$ ${}^3\text{A}_{2g} \rightarrow {}^3\text{T}_{1g}(\text{P})$.	Octahedral	12	3.27
$[\text{CuL}^1\text{Cl}_2] \cdot \text{H}_2\text{O}$	21.4/1.390 15.5/0.320	CT $d \rightarrow \pi^*$ ${}^2\text{E} \rightarrow {}^2\text{T}_2$	Tetrahedral	21	1.88
$[\text{ZnL}^1\text{Cl}_2] \cdot \text{H}_2\text{O}$	26.9/1.393	CT	Tetrahedral	18	–

Table 3. Electronic spectral data [DMF, frequency(cm^{-1})/ $\epsilon_{\text{max}} \cdot 10^3(\text{mol}^{-1} \cdot \text{dm}^3 \cdot \text{cm}^{-1})$], molar conductance of the complexes with L^1 recorded in DMF and magnetic measurements

Compound	$\nu(10^3\text{cm}^{-1})/\epsilon$	Transitions	Geometry	Mol. con. ($\text{Scm}^2\text{mol}^{-1}$)	μ_{eff}/μ_B
$[\text{CoL}^2_2\text{Cl}_2] \cdot \text{H}_2\text{O}$	20.9/0.32 0.87/0.125	${}^4\text{T}_{1g} \rightarrow {}^4\text{T}_{2g}(\text{F})$ ${}^4\text{T}_{1g} \rightarrow {}^4\text{T}_{1g}(\text{P})$	Octahedral	10	5.0
$[\text{NiL}^2_2\text{Cl}_2] \cdot 2\text{H}_2\text{O}$	24.6/2.690 21.4/2.100 15.9/0.250	${}^3\text{A}_{2g}(\text{F}) \rightarrow {}^1\text{E}_g(\text{z})$ ${}^3\text{A}_{2g} \rightarrow {}^3\text{T}_{1g}(\text{F})$ ${}^3\text{A}_{2g} \rightarrow {}^3\text{T}_{1g}(\text{P})$.	Octahedral	10	3.27
$[\text{CuL}^2\text{Cl}_2] \cdot \text{H}_2\text{O}$	25.9/0.400 21.4/0.320 15.7/0.045	CT $d \rightarrow \pi^*$ ${}^2\text{E} \rightarrow {}^2\text{T}_2$	Tetrahedral	28	1.94
$[\text{ZnL}^2\text{Cl}_2] \cdot \text{H}_2\text{O}$	26.9/1.393	$d \rightarrow \pi$ ili CT	Tetrahedral	16	–

Table 4. Electronic spectral data [DMF, frequency(cm^{-1})/ $\epsilon_{\text{max}} \cdot 10^3(\text{mol}^{-1} \cdot \text{dm}^3 \cdot \text{cm}^{-1})$], molar conductance of the complexes with L^1 recorded in DMF and magnetic measurements

Compound	$\nu(10^3\text{cm}^{-1})/\epsilon$	Transitions	Geometry	Mol. con. ($\text{Scm}^2\text{mol}^{-1}$)	μ_{eff}/μ_B
$[\text{CoL}^3\text{Cl}] \cdot \text{Cl}$	16.4/0.391 15.9/0.451 15.5/0.381	${}^4\text{A}_2 \rightarrow {}^4\text{T}_1(\text{P})$	Tetrahedral	89	4.56
$[\text{NiL}^3\text{Cl}] \cdot \text{Cl}$	18.9/0.596 13.5/0.488	${}^1\text{A}_{1g} \rightarrow {}^1\text{A}_{2g}$ ${}^1\text{A}_{1g} \rightarrow {}^1\text{B}_{2g}$	Square-planar	88	diam.
$[\text{CuL}^3\text{Cl}] \cdot \text{Cl}$	21.4/0.412 15.5/0.384	${}^2\text{B}_{1g} \rightarrow {}^2\text{A}_1$ ${}^2\text{B}_{1g} \rightarrow {}^2\text{E}_{1g}$	Square-planar	90	1.88
$[\text{ZnL}^3\text{Cl}] \cdot \text{Cl}$	26.9/0.514	$d \rightarrow \pi^*$ ili CT	Tetrahedral	85	–

The experimental MIC values are shown in Tables 5–8. As may be seen, all the compounds have different antibacterial activity *in vitro* against the tested gram-positive and gram-negative bacteria and yeast.

The mechanism of antimicrobial activity of the metal complexes has not been defined yet. It has been proposed that [13]:

- activity is mostly shown by the ligand, while the metal makes a suitable transport form;

Table 5. MIC values ($\mu\text{g} \cdot \text{cm}^{-3}$) of the metal(II)chloride

Com.	<i>E. coli</i>	<i>P. vulgaris</i>	<i>S. aureus</i>	<i>E. group D</i>	<i>B. anthracis</i>	<i>C. albicans</i>
$\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$	>1000	>1000	>1000	>1000	>1000	500
$\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$	>1000	>1000	>1000	>1000	>1000	500
$\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$	500–1000	>1000	500	>1000	500–1000	250
ZnCl_2	500–1000	>1000	500	500	200–500	200–500

Table 6. MIC values ($\mu\text{g} \cdot \text{cm}^{-3}$) of the complexes with L^1

Com.	<i>E. coli</i>	<i>P. vulgaris</i>	<i>S. aureus</i>	<i>E. group D</i>	<i>B. anthracis</i>	<i>C. albicans</i>
β -hydrazonisation	>1000	>1000	>1000	>1000	>1000	>1000
L^1	>1000	>1000	>1000	>1000	>1000	500–1000
$[\text{CoL}^1_2\text{Cl}_2] \cdot \text{H}_2\text{O}$	200–500	500–1000	<50	200–500	<50	50–200
$[\text{NiL}^1_2\text{Cl}_2] \cdot 2\text{H}_2\text{O}$	500–1000	500–1000	50–200	200–500	200–500	50–200
$[\text{CuL}^1\text{Cl}_2] \cdot \text{H}_2\text{O}$	500–1000	500–1000	50–200	200–500	50–100	50–200
$[\text{ZnL}^1\text{Cl}_2] \cdot \text{H}_2\text{O}$	500–1000	500–1000	200–500	500–1000	<50	<50

Table 7. MIC values ($\mu\text{g} \cdot \text{cm}^{-3}$) of the complexes with L^2

Com.	<i>E. coli</i>	<i>P. vulgaris</i>	<i>S. aureus</i>	<i>E. group D</i>	<i>B. anthracis</i>	<i>C. albicans</i>
L^2	500–1000	500–1000	500–1000	500–1000	500–1000	500–1000
$[\text{CoL}^2_2\text{Cl}_2] \cdot \text{H}_2\text{O}$	50–200	50–200	<50	<50	50–200	200–500
$[\text{NiL}^2_2\text{Cl}_2] \cdot 2\text{H}_2\text{O}$	50–200	200–500	50–200	200–500	50–200	<50
$[\text{CuL}^2\text{Cl}_2] \cdot \text{H}_2\text{O}$	25–50	5–25	5–25	<50	5–25	<50
$[\text{ZnL}^2\text{Cl}_2] \cdot \text{H}_2\text{O}$	25–50	25–50	<5	<50	<5	<25

Table 8. MIC values ($\mu\text{g} \cdot \text{cm}^{-3}$) of the complexes with L^3

Com.	<i>E. coli</i>	<i>P. mirabilis</i>	<i>S. aureus</i>	<i>E. group D</i>	<i>B. anthracis</i>	<i>P. aeruginosa</i>	<i>C. albicans</i>
L^3	500–1000	500–1000	500–1000	500–1000	500–1000	500–1000	500–1000
$[\text{CoL}^3\text{Cl}] \cdot \text{Cl}$	50–200	<50	<50	50–200	50–200	50–200	<50
$[\text{NiL}^3\text{Cl}] \cdot \text{Cl}$	<50	50–200	<50	50–200	<50	50–100	<50
$[\text{CuL}^3\text{Cl}] \cdot \text{Cl}$	<50	<50	<25	<50	<50	<50	<50
$[\text{ZnL}^3\text{Cl}] \cdot \text{Cl}$	<50	<25	<25	<50	<25	<25	<25

• the metal ion shows activity, while the complex is essential for metal transport through the cell membrane;

• the complex ions can react with important centres of the cells.

Compared to the β -hydrazone of isatin (exhibits activity against the tested microorganisms in values > 1000 $\mu\text{g} \cdot \text{cm}^{-3}$) its Schiff bases possess slightly higher activity. Since the activity of the Schiff bases is derived from the presence of the C=N group and different electron-donor substituents in the *para*-positions, this can be explained by the formation of another C=N group in the ligands and by the already antimicrobially active carbonyl components involved in the reaction of condensation.

The Schiff bases as ligands possess different antibacterial activity against selected microorganisms which decreases in the order $L_3 \geq L_2 > L_1$. N^1 -[5-nitro-2-furfurylidene]- N^2 -[β -isatine]azine exhibits better activity than N^1 -[2-furfurylidene]- N^2 -[β -isatine]azine due to the presence of nitro group at position 5 of the furan ring. Its activity is almost equal to the activity of the ligand N^1 -[salicylidine]- N^2 -[β -isatin]azine, which suggests that salicylaldehyde, as the carbonyl component, has a strong influence on ligand activity.

The results show that the coordination compounds have enhanced activity compared to the ligands, which indicates that the coordinated biometals influence the antibacterial effects.

Since all the complexes are soluble in DMF different activity cannot be correlated with different solubility. However, the higher activity of the complexes, as compared to the free ligands, can be understood in terms of the chelation theory. This theory explains that a decrease in the polarizability of the metal could enhance the lipophilicity of the complexes [11].

The metal activity decreases in the order $\text{Zn} \geq \text{Cu} > \text{Co} > \text{Ni}$. This order can be explained by the suggested structure. The complexes of Zn(II) and Cu(II) showed a high activity against most of the tested microorganism cultures. It can be supposed that one of the factors of growth inhibition is also the hydrolysability of the complex. Hence, the more stable complex should be less active [14]. This may also be attributed to the high biological activity of the free Cu(II) and Zn(II) ions. Copper, zinc and cobalt are biometals very important for organism activity, while nickel belonging in this group is debatable. The human body contains ~ 3 g zinc and 0.25 g copper [13]. This is interesting, since the greatest activity was shown by these two metals, so further investigations should be pursued in this direction.

In the series of nickel(II) complexes, the antimicrobial activity against the test microorganisms can be correlated with their ligand abilities, rather than solubility. Compared to the free nickel(II) ion, the complex with L³ exhibits the best activity which can be related not only with the influence of the ligand, but maybe with the 4-coordinated diamagnetic ion [15].

Compared to the similar β -hydrazone of 5-bromisatin, the β -hydrazone of 7-methyl isatin and the β -hydrazone of N-phenyl of isatin derivatives [2], the investigated complexes of β -hydrazone of isatin show better activity against the tested microorganisms. This may suggest that the substituents at the isatin part of the ligand decrease the activity of the whole molecule.

All complexes show the best activity the against the gram-positive bacteria *Staphylococcus aureus* and the yeast *Candida albicans*. This is very important, considering that when it comes to *Staphylococcus aureus*, there are very few medicinal preparations against the disease caused by this microorganism (dermal problems, disease of the respiratory system).

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IZVOD

KORELACIJA IZMEĐU STRUKTURE I BILOŠKE AKTIVNOSTI NEKIH KOORDINACIONIH JEDINJENJA IZATIN SCHIFF-OVIH BAZA

(Naučni rad)

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U ovom radu je dat pregled sintetisanih kompleksa Co(II), Ni(II), Cu(II) and Zn(II) sa izatin Schiff-ovim bazama N¹-[2-furfuriliden]-N²-[β -izatin]azin (L₁), N¹-[5-nitro-2-furfuriliden]-N²-[β -izatin]azin (L₂) i N¹-[saliciliden]-N²-[β -izatin]azin (L₃). Njihova struktura je utvrđena korišćenjem elementarne mikroanalize, molarne provodljivosti, AA, FTIR, UV/VIS, ¹H NMR i termogravimetrijske metode.

Sintetisanim jedinjenjima je ispitivana aktivnost prema gram-pozitivnim i gram-negativnim bakterijama *Staphylococcus aureus*, *Enterococcus D*, *Proteus mirabilis*, *Escherichia coli*, *Bacillus anthracis*, *Pseudomonas aeruginosa* i prema kvascu *Candida albicans*.

Izatin Schiff-ove baze pokazuju različitu antimikrobnu aktivnost, što je u skladu sa prirodom karbonilne i amino komponente iskorišćenih za njihovu sintezu. Uticaj koordiniranog metala na antimikrobnu aktivnost je očigledan, s obzirom da koordinaciona jedinjenja pokazuju bolju aktivnost od samih liganada. Ispitivana jedinjenja su pokazala najbolju aktivnost prema gram-pozitivnoj bakteriji *Staphylococcus aureus* i kvascu *Candida albicans*.

Ključne reči: isatin • Šifove baze • Kobalt (II) • Nikal(II) • Cink(II) • Antimikrobna aktivnost •

Key words: isatin • Schiff base • Co(II) • Ni(II) • Cu(II) • Zn(II) • Antimicrobial activity •