SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL ACTIVITY OF PHENOL-2,6-PYRIDINEDIAMIDE COMPLEXES WITH Fe(III) AND Mo(VI)

Mihaela ALEXIE[1], Florina DUMITRU[2], Denisa MÂNZU[3], Ticuța NEGREANU-PÂRJOL[4], Cornelia GURAN[5]

*Lucrarea prezintă rezultatele cercetărilor privind sinteza şi caracterizarea prin metode fizico-chimice (analiză chimică elementală, spectroscopie IR si RMN, spectrometrie de masă ESI-MS) a unui ligand, **L**,- bis(p-hidroxifenil)-2,6-piridindiamidă - ce poate constitui un analog biomimetic al sideroforilor pentru Fe(III) si Mo(VI). Pentru acest ligand, au fost obţinuţi complecşi cu Fe(III) sau Mo(VI) cu stoechiometria M:L de 1:1 sau 1:2. Formulele probabile ale complecşilor: $[MoO_2(OH_2)_2(L)]Cl_2 \cdot 2H_2O$, $[Fe(OH_2)_3(L)](ClO_4)_3$, $[MoO_2(L)_2]Cl_2 \cdot 2CH_3CN$, $[Fe(L)_2](ClO_4)_3 \cdot 2H_2O$ au fost atribuite pe baza analizei chimice elementale, spectroscopie IR, UV-Vis şi RMN. Noii compuşi sintetizaţi au activitate antibacteriană şi antifungică asupra Staphylococcus aureus (bacterie gram pozitivă), Pseudomonas aeruginosa ser. VI, Escherichia coli, Proteus mirabilis (bacterie gram negativă) şi Candida albicans (fungi), compusul $[Fe(OH_2)_3(L)](ClO_4)_3$ prezentând efecte comparabile cu ale antibioticelor Kanamicină, Tetraciclină şi Amoxicilină.*

The paper is focused on the synthesis and characterization of a new ligand (amide-phenolate) N2,N6-bis(4-hydroxyphenyl)pyridine–2,6–dicarboxamide, L, that may be used as biomimetic analogue of Fe(III) or Mo(VI)-siderophores. Complex compounds of this ligand with Fe(III) or Mo(VI) have been obtained for a metal-ligand molar ratio of 1:1 and 2:1. The general proposed formulae [MoO2(OH2)2(L)]Cl2·2H2O, [Fe(OH2)3(L)](ClO4)3, [MoO2(L)2]Cl2·2CH3CN, [Fe(L)2](ClO4)3·2H2O were supported by elemental chemical analysis, electronic and vibrational spectra, NMR spectra. The newly synthesised compounds possess antibacterial and antifungal activity against Staphylococcus aureus (as gram positive bacteria), Pseudomonas aeruginosa, Escherichia coli and Proteus mirabilis, (as gram negative bacteria) and Candida albicans as fungi species, [Fe(OH2)3(L)](ClO4)3 complex showing effects comparable to Kanamycin, Tetracycline and Amoxicillin.

[1] PhD student, Department of Inorganic Chemistry, University POLITEHNICA of Bucharest, Romania, mihaela_ciuca2002@yahoo.com

[2] Reader, Department of Inorganic Chemistry, University POLITEHNICA of Bucharest, Romania

[3] Assist., PhD student, Department of Inorganic Chemistry, University POLITEHNICA of Bucharest, Romania

[4] Reader, Faculty of Dentistry and Pharmacy, "OVIDIUS" University, Constanța, Romania

[5] Prof., Department of Inorganic Chemistry, University POLITEHNICA of Bucharest, Romania, cornelia_guran@yahoo.com
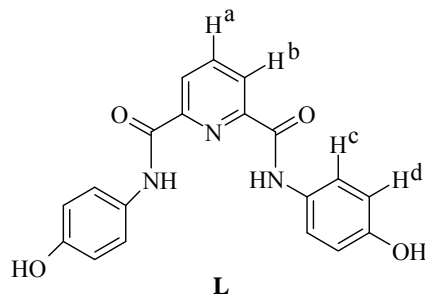
1. Introduction

Iron is an essential element for all forms of life, playing a crucial role in red blood cell (RBC) formation, oxygen transport, energy production, immune function. In general, organisms have large requirements for iron, creating a need for both transport and storage systems. Iron is also involved in major biological processes such as the synthesis of chlorophyll and heme, oxygen and electron transport, nitrogen fixation and DNA synthesis [1]. Iron, as well as molybdenum, is a component of the conventional nitrogenase and both metals are essential for the optimal growth of *Azobacter vinelandii* [2]. Molybdenum is an essential oligoelement for several important enzymes: xanthine oxidase, xanthine dehydrogenase, aldehyde oxydase, sulphite oxydase, nitrate reductase and nitrogenase. Molybdenum acts as an electron carrier in these enzymes, catalysts of the nitrate reduction and nitrogen fixation. Molybdenum competes with iron for siderophore released by the N_2-fixing cells of *A. vinelandii*, but nowadays there is little information regarding molybdenum–siderophore interactions.

Siderophores are bacterial iron chelators mostly containing catecholate or hydroxamate groups as chelating ligands. Most siderophores have three bidentate binding sites and form octahedral complexes with iron and molybdenum. Many efforts have been devoted to the development of synthetic molecules that mimic the properties of the natural siderophores; these siderophore-analogues can serve as probes to establish the essential structural requirements for biological action and compare receptors of different biological origins [3].

Our current interest is focused on the synthesis and characterization of a new ligand, **L**, that may be used as biomimetic analogue of Fe(III) or Mo(VI)-siderophores. New complex compounds of this ligand with Fe(III) or Mo(VI) have been obtained for a metal-ligand molar ratio of 1:1 or 1:2.

L

The general proposed formulae $[MoO_2(OH_2)_2(\mathbf{L})]Cl_2 \cdot 2H_2O$ (**1**), $[Fe(OH_2)_3(\mathbf{L})](ClO_4)_3$ (**2**), $[MoO_2(\mathbf{L})_2]Cl_2 \cdot 2CH_3CN$ (**3**), $[Fe(\mathbf{L})_2](ClO_4)_3 \cdot 2H_2O$ (**4**) were supported by elemental chemical analysis, electronic and vibrational spectra. NMR spectra have been carried out for diamagnetic molybdenum(VI) complexes. The complexes were tested for their ability to inhibit the growth of pathogenic organisms, such as *Staphylococcus aureus* (as gram positive bacteria), *Pseudomonas aeruginosa ser. VI, Escherichia coli* and *Proteus mirabilis* (as gram negative bacteria) and *Candida albicans* as fungi species. Furthermore, some known antibiotics were tested toward these bacteria or fungi as well as the synthesized compounds. The selected antibiotics are Tetracycline, Nitrofurantoin, Ceftazidine, Ofloxacin, Amikacin, Amoxicillin, Cephalothin, Cefuroxime, Metilmicine, Ceftriaxone, Amoxicillin and clavulanic acid, Unasyn, Oxaciline, Imipenem, Penicillin, Gentamicin, Chloramphenicol, Piperacillin, Co-trimoxazole, Kanamycin, Nalidixic acid, Erythromycin, Rifampicin, Vancomycin, Amphotericin B, Itraconazole, Econazole, Ketoconazole, Nystatin, Miconazole.

2. Experimental

All reagents were obtained from commercial suppliers and used without further purification.

Vibrational spectra were recorded with a Bruker Equinox55 spectrophotometer in the wavenumbers range of 400-4000 cm^{-1}.

Molar electrical conductivities were determined in DMF or EtOH solutions at 25°C with OK 102/1 Radelkis Conductometer.

Elemental analyses were carried out on a Heraeus CHNO-Rapid apparatus.

^{1}H‒NMR and ^{13}C-NMR spectra were recorded on a DRX 400 MHz Bruker Avance spectrometer in CDCl$_3$ and DMSO-d$_6$, with the use of the residual proton of the deuterated solvent or tetramethylsilane as reference. Chemical shifts are given in ppm relative to the reference and the following abbreviations are used to express the multiplicities: s-singlet, d-doublet, t-triplet, q-quartet, m-multiplet, br-broad or/and overlapped.

The electronic spectra were recorded at the room temperature on a Jasco V560 spectrophotometer in diffuse reflectance technique.

ESI-mass spectra were carried out on a MSQ+ Thermo Fisher LC-MS spectrometer, in isocratic mobile phase (100% CH$_3$CN).

Synthesis of the ligand (N^2, N^6-bis(4-hydroxyphenyl)pyridine–2,6–dicarboxamide, L) and complexes of L

- The ligand precursor pyridine-2,6-dicarbonyl dichloride was obtained according to [4]. Pyridine-2,6-dicarboxylic acid (5g, 0.03 moles) was

dissolved in thionyl chloride in excess (53 mL) and the mixture heated at reflux for 8 hours using a Liebig condenser fitted with a $CaCl_2$ drying tube, until it becomes a clear solution. After leaving the mixture to stand for 2 nights, the thionyl chloride excess was removed by rotary evaporation for 30 minutes. The residue was recrystallised from n-hexane and pale cream crystals were formed. The mixture was stored at +4°C overnight and then the pyridine-2,6-dicarbonyl dichloride crystals (5.919g, 97%) were filtered by vacuum. $C_7H_3NO_2Cl_2$, m.p. 58-60°C.

^{1}H-NMR (400MHz, $CDCl_3$, ppm): 8.370-8.351 (d, 2H, H^{py}, *J=7.6Hz*), 8.220-8.181 (t, 1H, H^{py}, *J=7.8Hz*).

^{13}C-NMR (400MHz, $CDCl_3$, ppm): 129.04 (C^{py}), 139.49 (C^{py}), 149.08 (C^{py}-N), 169.18 (C=O).

IR (cm^{-1}): $\nu_{c=o}$ 1750, ν_{C-Cl} 870.

- The ligand (N^2, N^6-bis(4-hydroxyphenyl)pyridine–2,6– dicarboxamide, **L**) was synthesized according to the following procedure:

To a solution of *p*-aminophenol in THF (25 mL), was added dropwise a mixture of pyridine-2,6-dicarbonyl dichloride (1g, 0.005 mmol) and Et_3N (1.5 mL) in THF (20 mL). The reaction mixture was stirred at room temperature for 8h until the starting material was completely consumed as indicated by TLC ($CHCl_3$:MeOH 9:1 v/v). Triethylamine hydrochloride was filtered off, the solvent was removed under vacuum and the crude product was redissolved in the minimum volume of CH_3OH. The solution was stored at +4°C overnight and yielded **L** as a yellow, fine powder (0.991g, η=58%).

F.M. $C_{19}H_{15}N_3O_4$, *Calcd*. 65.32%C , 4.29%H, 12.03% N, *Found* 63.41%C , 4.5%H, 11.17%N

^{1}H-NMR (400MHz, DMSO-d_6, ppm): 10.868 (s, 2H, NH), 8.364-8.344 (dd, 2H, H^b, *J= 8 Hz*), 8.281-8242 (t, 1H, H^a, *J=7.8Hz*), 7.653-7.631 (d, 2H, H^c, *J=8.8Hz*), 6.849-6.827 (d, 2H, H^d, *J=8.8 Hz*)

^{13}C-RMN (400MHz, DMSO, ppm): 161.151 (C=O), 154.321 (C-OH), 148.982 (C^{py}-N), 139.690 (C^a), 129.342 (C-NH), 124.769 (C^b), 123.212 (C^c), 115.083 (C^d).

IR (cm^{-1}): ν_{CONH} 1650.70, ν_{O-H} 3233.83, $\nu_{C-Harom}$ 2975.07, ν_{NH} 3333.47, δ_{NH} 1218.23-1247.70.

MS (ESI-): m/z (%): 348.23 (100) [**L**-H]$^-$

- All complexes have been synthesised according to the following general procedure: methanol (for 1:1 M:L) or acetonitrile (for 1:2 M:L) solutions containing the metal salts, $Fe(ClO_4)_3 \cdot xH_2O$, MoO_2Cl_2 and the

ligand L, were mixed with stirring 2-4h at 60°C in M:L =1:1 and 1:2 molar ratios. The yields were around 72-75%.

Main characteristics of the N^2,N^6-bis(4-hydroxyphenyl)pyridine–2,6–dicarboxamide, (**L**) complexes are given below:

1. $[MoO_2(OH_2)_2(L)]Cl_2 \cdot 2H_2O$

Calculated for $C_{19}H_{23}O_{10}N_3MoCl_2$, M=620 g/mol, %C= 36.77, %H= 3.70, %N= 6.77. Found: %C= 34.96, % H= 3.68, %N= 6.28.
Molar electrical conductivity 168 $\mu S \cdot cm^{-1} \cdot mol^{-1}$ *(10^{-3}M DMF solution)*. Electrolyte type = 1:2.
IR (cm^{-1}): $\nu_{C=O}$ 1659.22 si 1625.63, ν_{O-H} 3336.39, $\nu_{C-Harom}$ 2980.51, ν_{NH} 3450, δ_{NH} 1247.79-1296.51, $\nu_{Mo=O}$= 953.61, 911.92.
UV/VIS (nm): ν_1 = 737.35 nm, ν_2 = 318.4 nm, ν_3 = 247.24 nm, ν_4 = 209.47 nm, ν_5 = 382.91 nm, ν_6 = 411 nm, ν_7 = 275 nm.
^{1}H-NMR (400MHz, DMSO-d_6, ppm): 10.852 (s, 2H, NH), 9.395 (s, 2H, OH), 8.352-8.334 (dd, 2H, H^b, *J= 7.2Hz*), 8.277-8.239 (t, 1H, H^a, *J=7.6Hz*), 7.641-7.619 (d, 2H, H^c, *J=8.8Hz*), 6.831-6.809 (d, 2H, H^d, *J = 8.8Hz*).
^{13}C-NMR (400MHz, DMSO-d_6, ppm): 115.052 (C^d), 123.192 (C^c), 139.695 (C^a), 124.767 (C^b), 148.984 (C^{py}-N), 161.161 (C=O), 154.270 (C-OH), 129.352 (C-NH).

2. $[Fe(OH_2)_3(L)](ClO_4)_3$

Calculated for $C_{19}H_{21}O_{19}N_3FeCl_3$, M=757.5g/mol, %C=30.09, %H=2.77, %N=5.54. Found %C=31.07, %H= 2.89, %N=5.74.
Molar electrical conductivity 340 $\mu S \cdot cm^{-1} \cdot mol^{-1}$ *(10^{-3}M DMF solution)*. Electrolyte type = 1:3.
IR (cm^{-1})**:** $\nu_{C=O}$ 1658.45, ν_{O-H} 3320.32, $\nu_{C-Harom}$ 2989.26, ν_{NH} 3456.37, δ_{NH} 1221.09-1269.18, ν_{ClO4}- 617.34, 1048.21.
UV/VIS (nm): ν_1 = 576.52 nm, ν_2 = 437.85 nm, ν_3 = 749.87 nm

3. $[MoO_2(L)_2]Cl_2 \cdot 2CH_3CN$

Calculated for $C_{42}H_{36}O_{10}N_8MoCl_2$, M=979g/mol, %C=51.48, %H=3.67, %N=11.44. Found %C= 52.84, %H= 3.79, %N=12.15.
Molar electrical conductivity 132 $\mu S \cdot cm^{-1} \cdot mol^{-1}$ *(10^{-3}M DMF solution)*. Electrolyte type = 1:2.
IR (cm^{-1})**:** $\nu_{C=O}$ 1652.18, ν_{O-H} 3336.29, $\nu_{C-Harom}$ 2893.69, ν_{NH} 3400, δ_{NH} 1247.44, $\nu_{Mo=O}$ =950.96 si 908.79.

UV/VIS (nm): v_1 = 215.3 nm, v_2 = 717.84 nm, v_3 = 334.9 nm, v_4 = 373.28 nm, v_5 = 263.7 nm, v_6 = 395.1 nm, v_7 = 212.8 nm.

^{1}H-NMR (400MHz, DMSO-d_6, ppm): 10.838 (s, 2H, NH), 9.383 (s, 2H, OH), 8.356-8.336 (dd, 2H, H^b, *J= 8Hz*), 8.278-8.240 (t, 1H, H^a, *J=7.6Hz*), 7.637-7.615 (d, 2H, H^c, *J=8.8Hz*), 6.830-6.808 (d, 2H, H^d, *J = 8.8 Hz*).

^{13}C-NMR (400MHz, DMSO-d_6, ppm): 161.127 (C=O), 154.254 (C-OH), 148.948 (C^{py}-N), 139.703 (C^a), 129.333 (C-NH), 124.756 (C^b), 123.185 (C^c), 115.050 (C^d).

4. [Fe(L)$_2$](ClO$_4$)$_3\cdot$2H$_2$O

Calculated for $C_{40}H_{37}O_{22}N_7FeCl_3$, M=1129.5 g/mol, %C=42.49, %H=3.27, %N=8.67. Found %C= 42.37, % H= 4.03, %N=8.66
Molar electrical conductivity 127 μS·cm^{-1}·mol^{-1} *(10^{-3}M EtOH solution)*. Electrolyte type = 1:3.

IR (cm^{-1}): $v_{C=O}$ 1660.16, v_{O-H} 3300, $v_{C-Harom}$ 3100, v_{NH} 3340.44, δ_{NH} 1225.85, v_{ClO4}^- 620.30, 1107.67

UV/VIS (nm): v_1 = 571 nm, v_2 = 766.28 nm.

3. Results and discussion

A survey of literature up to date revealed that, despite its simple chemical structure, the symmetrical ligand L, obtained from reaction of pyridine-2,6-dicarbonyl dichloride with 4-aminophenol in a 1:2 ratio, was not reported until the submission of this paper. The molecular structure of **L** was assessed by means of mono-and two-dimensional NMR-experiments and IR spectroscopy.

The resonance peaks from ^{1}H-NMR and ^{13}C-NMR spectra were assigned unambiguously with the help of COSY ^{1}H-^{1}H, ^{13}C-DEPT, HMQC, HMBC ^{1}H-^{13}C spectra. The large downfield shift of the N-H protons of **L** (δ=10.868 ppm) suggests, as numerous literature data on 2,6-pyridindicarboxamide derivatives already pointed out [5], that the two amide protons are hydrogen bonded with the nitrogen of the pyridyl ring. The ^{1}H-NMR spectrum of **L** reveals that it exists only in one conformation in DMSO-d_6; for intramolecular hydrogen bonding between the N-H proton and the nitrogen of pyridyl ring, the amide group has to be in the *trans* form (Fig. 1).
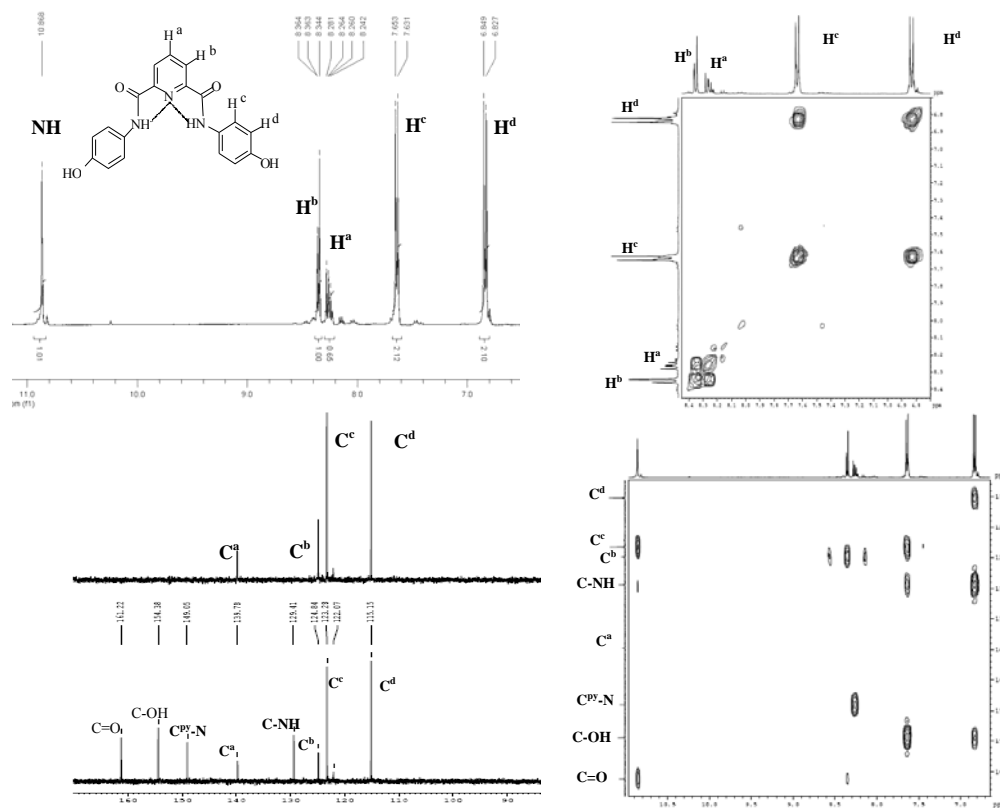
Fig.1. NMR spectra of **L a.** ^{1}H-NMR, **b.** cosy ^{1}H-^{1}H, **c.** ^{13}C-NMR and ^{13}C-DEPT, **d.** HMBC ^{1}H-^{13}C

From the IR spectrum of ligand **L** it was observed that the specific band from the precursor pyridine-2,6-dicarbonyl dichloride ($\nu_{C=O}$ 1750cm^{-1}) [6] dissapears and new absorption bands (ν_{CONH} 1650.70 cm^{-1}), shifted to lower wavenumbers, characteristic to the newly formed amide bonds, - with a greater amount of delocalised, mesomeric forms - are present.

The general formulae of complexes **1-4** have been suported by the elemental analysis, molar conductivity data, IR and UV-VIS spectra, and NMR spectra for Mo(VI)-diamagnetic complexes.

The molar conductances of the complexes **1-3** in DMF were in the ranges 132-340 μS·cm^{-1}·mol^{-1}, while the molar conductance value of complex **4** in EtOH is 127 μS·cm^{-1}·mol^{-1}. The molar conductance data indicate that the complexes **1** and **3** are 1:2 electrolytes while the complexes **2** and **4** are 1:3 electrolytes.

The IR spectra of compounds **[MoO$_2$(OH$_2$)$_2$(L)]Cl$_2$·2H$_2$O, 1** and **[MoO$_2$(L)$_2$]Cl$_2$·2CH$_3$CN, 3** present two distinctive absorption maxima for MoO$_2$$^{2+}$ moiety at about 950 and 910 cm^{-1}. The first peak was attributed to a

symmetric Mo=O stretching vibration and the second peak was assigned to the asymmetric Mo=O stretching vibration. The lowering of the Mo=O stretching vibrations (from 960 cm^{-1} in MoO_2Cl_2 to 908-950 cm^{-1} in complexes) may be ascribed to complexation.

Although in NMR spectra of Mo(VI) complexes (**1** and **3**), the signal due to NHCO group is slightly shifted downfield after complexation and the signals of aromatic and heteroaromatic protons show a minor change, this fact does not rule out the possibility of coordination of the NHCO group.

For the complexes **2** and **4**, the CONH stretching vibrations appear at higher wavenumber values in complexes (1658.45 cm^{-1}, 1660.16 cm^{-1}) than in the free ligand (1650.70 cm^{-1}). This fact is explained by the involving of the nitrogen electrons in the coordination of the metal ions. In the IR spectra of complexes **2** and **4** appear new bands characteristic to ClO_4^- ion (1065-1040 cm^{-1}, respectively 620-625 cm^{-1}).

In order to obtain wavelength specific to the transition energy, the electronic spectra of the complexes have been analysed by deconvolution procedure, using a program (PeakFit v3.15) with Gauss cumulative function.

For diamagnetic complexes **[MoO$_2$(OH$_2$)$_2$(L)]Cl$_2$·2H$_2$O**, **1** and **[MoO$_2$(L)$_2$]Cl$_2$·2CH$_3$CN, 3,** (Mo(VI) d^0 configuration), one may assume that all the electronic spectral bands are due to the charge transfer absorption from the ligand to the metal.

The complexes **[Fe(OH$_2$)$_3$(L)](ClO$_4$)$_3$, 2** and **[Fe(L)$_2$](ClO$_4$)$_3$·2H$_2$O, 4** present, in their electronic spectra, absorption bands in the range 13.05-22.83 kK, which are characteristic for Fe^{3+} ions (d^5) in deformed octahedral geometry. The general aspect of the electronic spectra of the complexes **2** and **4** is in good agreement with literature data [7].

Biological activity assay

The diffusion agar technique was used to evaluate the antibacterial activity of the synthesized complexes. The investigated organisms were: *Staphylococcus aureus* (as gram positive bacteria), *Pseudomonas aeruginosa ser. VI*, *Escherichia coli* and *Proteus mirabilis* (as gram negative bacteria) and *Candida albicans* as fungi species. The complexes **1-4** (0.01 g) were laid on the agar-agar solid medium surface pre-inseminated with the above-mentioned bacteria. When the testing substance has antibacterial action, in the higher concentration area than minimum inhibitory concentration (MIC) the inseminated bacteria are inhibited. Thus, we have determined the width (mm) of inhibition area for the synthesised complexes toward the selected bacteria (Table 1, Fig.1.1-1.9).

The biological assay results are the following:

a) The ligand **L** has no activity toward the organisms used to evaluate the biological activity: *Staphylococcus aureus*, *Pseudomonas aeruginosa ser. VI, Escherichia coli, Proteus mirabilis* and *Candida albicans*.

b) **[MoO$_2$(OH$_2$)$_2$(L)]Cl$_2$2H$_2$O, 1** is resistant against *Escherichia coli* bacterial strain, but it shows a remarkable activity toward *Staphylococcus aureus* and *Proteus mirabilis* (width of inhibition area = 13-14 mm), superior to Oxaciline and Amoxicillin+clavulanic acid antibiotics. This complex has also microbiostatic activity toward *Pseudomonas aeruginosa* and *Candida albicans* (width of inhibition area = 8-10mm).

c) **[Fe(OH$_2$)$_3$(L)](ClO$_4$)$_3$, 2** has a microbiostatic activity toward all the studied organisms: *Staphylococcus aureus*, *Pseudomonas aeruginosa ser. VI* (Fig. 2), *Escherichia coli, Proteus mirabilis* (Fig. 3) and *Candida albicans*, with 7-14 mm width of inhibition area. **[Fe(OH$_2$)$_3$(L)](ClO$_4$)$_3$, 2** is more efficient than Kanamycin, Tetracycline, Amoxicillin, antibiotics that have resistance effect toward *Proteus mirabilis*.

d) **[MoO$_2$(L)$_2$]Cl$_2$ 2CH$_3$CN, 3** has no activity toward any tested bacteria.

e) The data collected in Table 1 show that **[Fe(L)$_2$](ClO$_4$)$_3$·2H$_2$O, 4** has resistance effect toward *Proteus mirabilis* and *Candida albicans*, but microbiostatic activity toward *Escherichia coli* (Fig. 5), *Pseudomonas aeruginosa* (Fig. 6)*, Staphylococcus aureus* with 6-9 mm width of inhibition area.
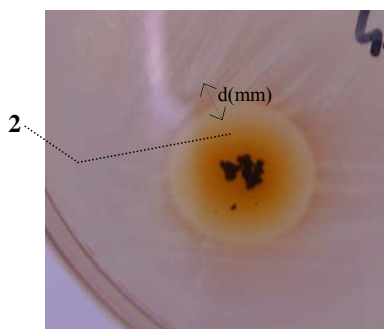

Fig.2. *Pseudomonas aeruginosa* bacterial culture with **[Fe(OH$_2$)$_3$(L)](ClO$_4$)$_3$, 2**

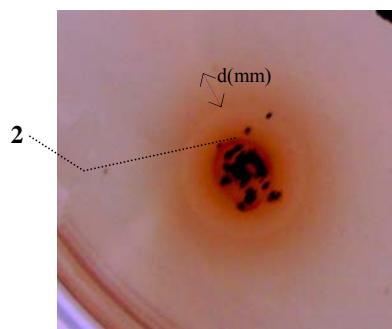Fig.3. *Proteus mirabilis* bacterial culture with **[Fe(OH$_2$)$_3$(L)](ClO$_4$)$_3$, 2**

Table 1

Results of antibacterial activity assay

Compound	Gram pozitive		Gram negative		Fungi
	Staphylococcu s aureus	*Proteus mirabilis*	*Pseudomona s aeruginosa VI*	*Escheric hia coli*	*Candida albicans*
L	R	R	R	R	R
[MoO$_2$(OH$_2$)$_2$(L)]Cl$_2$·2H$_2$O	13	14	8	R	10
[Fe(OH$_2$)$_3$(L)](ClO$_4$)$_3$	12	9	14	7	10
[MoO$_2$(L)$_2$]Cl$_2$·2CH$_3$CN	R	R	R	R	R
[Fe(L)$_2$](ClO$_4$)$_3$·2H$_2$O	9	R	9	6	R
Tetracycline	R	R	Nd	R	Nd
Nitrofurantoin	Nd	R	Nd	21	Nd
Ceftazidine	Nd	24	Nd	21	Nd
Ofloxacin	Nd	Nd	Nd	22	Nd
Amikacin	17	17	21	15	Nd
Metilmicine	Nd	14	14	16	Nd
Amoxicillin	Nd	Nd	Nd	R	Nd
Cephalothin	Nd	20	Nd	17	Nd
Ciprofloxacine	Nd	35	25	21	Nd
Cefuroxime	Nd	Nd	R	Nd	Nd
Ceftriaxone	25	Nd	Nd	Nd	Nd
Amoxicillin+clavulanic acid	18	R	R	17	Nd
Unasyn	R	Nd	R	Nd	Nd
Oxaciline	R	Nd	Nd	Nd	Nd
Imipenem	Nd	26	28	Nd	Nd
Penicillin	R	Nd	Nd	Nd	Nd
Chloramphenicol (standard)	Nd	Nd	R	Nd	Nd
Gentamicine	17	Nd	14	Nd	Nd
Piperacillin	Nd	Nd	20	Nd	Nd
Co-trimoxazole	20	Nd	R	Nd	Nd
Kanamycin	Nd	R	Nd	Nd	Nd
Nalidixic acid	Nd	15	Nd	Nd	Nd
Erythromycin	22	Nd	Nd	Nd	Nd
Rifampicin	23	Nd	Nd	Nd	Nd
Vancomycin	18	Nd	Nd	Nd	Nd
Amphotericin B	Nd	Nd	Nd	Nd	15
Itraconazole	Nd	Nd	Nd	Nd	R
Econazole	Nd	Nd	Nd	Nd	18
Ketoconazole	Nd	Nd	Nd	Nd	25
Nystatin	Nd	Nd	Nd	Nd	20
Miconazole	Nd	Nd	Nd	Nd	24

Nd = non detected, R = resistance. Inhibition values = 1-5 mm = (less active); inhibition values = 6-10 mm = (moderate active); inhibition values = 11 -15 mm = (highly active);
The values represent the width (mm) of inhibition area identified on different samples containing 0.01g of **1-4** complexes.

4. Conclusions

A new amide-phenolate siderophore ligand, N^2,N^6-*bis(4-hydroxyphenyl)pyridine – 2,6 – dicarboxamide* has been prepared and characterized by elemental chemical analysis, IR and NMR spectra, and ESI-MS spectrum.

Complex compounds of this ligand with Fe(III) or Mo(VI) have been obtained for a metal-ligand molar ratio of 1:1 or 1:2. The proposed formulae of the complexes: **$[MoO_2(OH_2)_2(L)]Cl_2 \cdot 2H_2O$, $[Fe(OH_2)_3(L)](ClO_4)_3$, $[MoO_2(L)_2]Cl_2 \cdot 2CH_3CN$, $[Fe(L)_2](ClO_4)_3 \cdot 2H_2O$** were supported by elemental chemical analysis, electronic and vibrational spectra, or NMR spectra for diamagnetic Mo(VI) complexes.

The synthesised complexes show remarkable biological activity toward *Staphylococcus aureus* (as gram positive bacteria), *Pseudomonas aeruginosa ser. VI, Escherichia coli* and *Proteus mirabilis* (as gram negative bacteria) and *Candida albicans* as fungi species. The results indicated that **$[Fe(OH_2)_3(L)](ClO_4)_3$** is more efficient than Kanamycin, Tetracycline, Amoxicillin, antibiotics that have resistance effect toward *Proteus mirabilis*.

Acknowledgements

R E F E R E N C E S

[1] *J.B.Neilands*, J. Biol. Chem., **270(45)**, 1995, 26723-26726
[2] a) *A.-K.Duhme*, J. Chem. Soc., Dalton Trans., 1997, 773–778; b) *S.L. Jain, P.Bhattacharyya, H.L.Milton, A.M.Z.Slawin, J.A.Crayston, J.D.Woollins*, Dalton Trans, 2004, 862–871
[3] *a) G.Bernier, V.Girijavallabhan, A.Murray, N.Niyaz, P.Ding, M.J.Miller, F.Malouin*, Antimicrobial Agents and Chemotherapy, **49(1),** 2005, 241–248; *b) K.N. Raymond*, Pure & Appl. Chem., **66(4)**, 1994, 773-781; *c) S.L.Jain, P.Bhattacharyya, H.L.Milton, A.M.Z.Slawin, J.A.Crayston, J. D.Woollins*, Dalton Trans., **2004**, 862–871; *d) S.Wittmann, M.Schnabelrauch, I.S.Hofmann, U.M.llmann, D.A.Fuchs, L.Heinisch*, Bioorganic&Medicinal Chemistry, **10**, 2002, 1659–1670
[4] *M.D.K.N.Towers, P.D.Woodgate, M.A.Brimble*, ARKIVOC, Part (i), 2003, 43-55
[5] *a) C.A. Hunter, D. H. Purvis*, Angew. Chem. **104**, 1992, 779–782; *Angew. Chem. Int. Ed. Engl*., **31**, 1992, 792–795; *b) J. F. Malone, C. M. Murray, G. M. Dolan, R. Docherty, A. J. Lavery*, Chem. Mater. **9**, 1997, 2983 –2989; *c) K. Kavallieratos, S. R. de Gala, D. J. Austin, R.*

H. Crabtree, J. Am. Chem. Soc. **119**, 1997, 2325 –2326; *d) K. Kavallieratos, C. M. Bertao, R. H. Crabtree*, J. Org. Chem. **64**, 1999, 1675 –1683; *e) N.C. Singha, D. N. Sathyanarayana*, J. Mol. Str., **403**, 1997, 123-135

[6] *M.Alexie*, *F.Dumitru*, *D.Manzu*, *A.Razvan*, *C.Guran*, 2007 CEEX Conference, Ed.Tehnică, ISSN 1843-5904, 2007**, 245-1/245-6

[7] *A.B.P. Lever*, Inorganic electronic spectroscopy, 2 ed., Elsevier, Amsterdam 1984**.