Novel Complexes of La(III), Pr(III), Nd(III) with Piroxicam
Synthesis, characterization and antimicrobial studies

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This article reports the synthesis of novel rare-earth coordination complexes with piroxicam. Microanalytical data, magnetic susceptibility, conductivity data, IR, UV-Vis spectroscopy and termogravimetric analysis were used to confirm their compositions and structure. The molecular formula proposed for these complexes is the following $Ln_2(HPir)_2(CH_3COO)_4 \cdot 2H_2O$ (Ln = La(III), Pr(III), Nd(III)). All complexes and piroxicam were screened for their antimicrobial activity against 7 microbial strains: Enterococcus faecium E5, Escherichia coli ATCC 25922, Candida albicans 1760, Pseudomonas aeruginosa ATCC 27857, Bacillus subtillis ATCC 6683, Staphylococcus aureus ATCC 6538, Klebsiella pneumoniae IC 13420. The ability of the compounds to inhibit the microbial adherence to the inert substrata was also evaluated. The results demonstrated that the tested compounds exhibit moderate antimicrobial and antibiofim activity.

Keywords: piroxicam, lanthanides, coordination compounds, antimicrobial activity.

Metal complexes containing active therapeutic compounds as ligands have found an increasing interest in the last years, the main goal being to develop new drugs, more efficient and with less side effects.

Piroxicam and meloxicam are currently the most widely used non-steroidal anti-inflammatory drugs (NSAIDs) for the treatment of inflammatory conditions in patients suffering from rheumatism. They are also used to reduce pain in different arthritis and other post-operative conditions. Several studies have shown chemopreventive and chemosuppressive effects of these drugs in different cancer cell lines[1-6].

Piroxicam [4-hydroxy-2-methyl-N-(2-pyridyl)-1,2-benzothiazine-3-carboxamide 1,1-dioxide] is the most famous member of the oxicam class belonging to the benzothiazinone dioxide series of heterocyclic molecules. Many studies demonstrated the ability of these molecules to form metal complexes with many transition metals in which mostly they act as monodentate through the pyridyl nitrogen towards Pt(II) [7], as singly deprotonated bidentate chelate through the pyridyl nitrogen and the amide oxygen towards Cu(II), Cd(II) [8], Ru(II) [9] and as a singly deprotonated tridentate ligand through the enolic oxygen, the pyridyl and the amide nitrogen atoms in the Sn(IV) complex [10]. A number of transition metal complexes of piroxicam and meloxicam have been reported earlier [11-19].

It is well known that lanthanide ions are subject of increasing interest in bioinorganic and coordination chemistry [20]. In the last years a sustained research activity has been devoted to lanthanide complexes, because of their successful application as diagnostic tools in biomedical analysis as MRI contrast agents [21]. Lanthanide complexes have been found to exhibit antitumor [22-24], antimicrobial [25] and fungicidal properties [26]. Due to their special electronic configuration, lanthanide complexes have inspired many efforts on the design and synthesis as potential anticancer and antibacterial agents [27]. A survey of the literature revealed only very few studies concerning the interaction of lanthanide ions with ligands belonging to oxicam family [28,29]. Based on the importance of lanthanide ions, we considered that a study concerning the interaction between piroxicam and lanthanide ions would be very useful.

In the present study we report on the piroxicam lanthanide (La(III), Pr(III), Nd(III)) interaction in an attempt to examine the mode of binding and possible synergetic effects. The coordination manner of the ligand to the metal centers was investigated by means of FTIR and UV–Vis spectroscopy, magnetic and conductance measurements, elemental chemical and thermal analysis. The biological activity of the piroxicam complexes has been investigated by examining the in vitro antimicrobial and antibiofilm activity against seven pathogenic bacteria (*Enterococcus faecium* E5, *Escherichia coli* ATCC 25922, *Candida albicans* 1760, *Pseudomonas aeruginosa* ATCC 27857, *Bacillus subtillis* ATCC 6683, *Staphylococcus aureus* ATCC 6538, *Klebsiella pneumoniae* IC 13420).

Experimental part

Materials, methods and equipment

$La(CH_3COO)_2 \cdot xH_2O$, $Pr(CH_3COO)_2 \cdot xH_2O$, $Nd(CH_3COO)_2 \cdot xH_2O$ (Strem Chemicals, France), piroxicam (Boehringer-Ingelheim, Germany), triethylamine (Sigma, Germany), absolute ethanol (Chimreactiv, Romania) were used without further purification.

Elemental analyses were performed on a Perkin Elmer CHNS/O Analyzer 2400 Series II. Molar conductance of 10^{-3} M solutions in DMF was measured at room temperature on a Mettler Toledo SevenGo Duo SG23 conductivity meter. Infrared spectra were recorded on a Jasco FTIR 4100 spectrophotometer in wavenumber region 4000–400 cm^{-1} using KBr disks. Absorption spectra were recorded at room temperature with a JASCO V-670 spectrophotometer. The molar magnetic susceptibilities were measured on solid

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Compound	Elemental chemical analysis % Found (Calculated)				$\chi_M T$	Molar conductance (Ω^{-1} mol^{-1} cm^2)
	C	H	N	S		
$La_2(HPir)_2(CH_3COO)_4 \cdot 2H_2O$	37.75 (37.65)	3.20 (3.30)	6.92 (6.93)	5.05 (5.28)	diamagnetic	29.8
$Pr_2(HPir)_2(CH_3COO)_4 \cdot 2H_2O$	37.35 (37.53)	3.65 (3.29)	6.87 (6.91)	5.39 (5.26)	2.87	22.3
$Nd_2(HPir)_2(CH_3COO)_4 \cdot 2H_2O$	37.97 (37.34)	3.59 (3.27)	6.98 (6.88)	5.30 (5.24)	2.60	23.2

Table 1
ELEMENTAL ANALYSES AND PHYSICAL PROPERTIES OF THE COMPOUNDS

samples using the Faraday method. The thermal decomposition of the compounds was followed with a Netzsch TG 449C STA Jupiter thermal analyzer. Samples were placed in alumina crucible and heated with 10°C min^{-1} from room temperature to 900°C, in air.

Synthesis of the complexes

The complexes were prepared according to the following procedure: a hot ethanolic solution of lanthanide acetate (La(III), Pr(III), Nd(III)) (5 mL, 1 mmol) was added to a hot ethanolic solution of deprotonated piroxicam (20 mL, 3 mmol). The resulting clear yellow solution was refluxed under stirring for approximately 3 h. After ~10-15 minutes of mixing a microcrystalline powder started to precipitate. It became increasingly abundant during the refluxing time. The solid compound was filtered, washed with hot ethanol and dried in dessicator under P_4O_{10} at room temperature.

The deprotonation of piroxicam (H_2Pir) was realized by the addition of equimolar quantities of warm ethanol solution of H_2Pir and triethylamine. The resulting anion $HPir^{-1}$ was not isolated and used as solution.

The prepared complexes are stable at ambient temperature, insoluble in water and soluble to a limited extent in methanol and ethanol while freely soluble in DMF and DMSO. The complex compounds were dissolved in DMF and the molar conductivities of 10^{-3} M of their solutions at 18 °C were measured.

Antimicrobial activity

The antimicrobial activity was studied against the following reference and clinical microbial strains: *Pseudomonas aeruginosa* ATCC 27857, *Escherichia coli* ATCC 25922, *Klebsiella pneumoniae* IC 13420, *Enterococcus faecium E5, Staphylococcus aureus* ATCC 6538, *Bacillus subtillis* ATCC 6683, *Candida albicans* 1760.

Microbial cultures of 16-18 h obtained on solid media at 37°C, were used for preparing suspensions of 1.5 x 10^8 CFU/mL density in sterile saline. The antimicrobial assays were performed using Mueller-Hinton Agar (MHA) medium. The compounds were solubilized in DMSO and the starting stock solution was of 1 mg/mL concentration. The qualitative assay of the antimicrobial activity was performed by an adapted disc diffusion method as previously reported [30].

The quantitative assay of the antimicrobial activity was performed by the liquid medium microdilution method, in 96 multi-well plates, in order to establish the minimal inhibitory concentration (MIC). Serial two-fold dilutions of the compounds ranging between 1000μg/ml and 1.95 μg/mL were performed in a 200 μL volume of broth and each well was seeded with 50 μL of microbial inoculum. Sterility control (wells containing only culture medium) and culture controls (wells containing culture medium seeded with the microbial inoculum) were used. The influence of the DMSO solvent was also quantified in a series of wells containing DMSO, diluted accordingly with the dilution scheme used for the complexes. The plates were incubated for 24 h at 37°C, and MIC values were considered as the lowest concentration of the tested compound that inhibited the visible growth of the microbial cultures incubated overnight.

The assessment of the complexes influence on the microbial ability to colonize the plastic inert substratum and the establishment of minimum biofilm eradicating concentration (MBIC) was performed by the micro-titration method, following previously described protocols [31]. The absorbance at 490 nm was measured with an ELISA reader Apollo LB 911. All biological experiments were performed in triplicates.

Results and discussions

Microanalytical data, molar conductance data and magnetic moments of the complexes are given in table 1. The analytical data agree well with the general formula $Ln_2(HPir)_2(CH_3COO)_4 \cdot 2H_2O$. The small conductance values of the metal complexes support their non-electrolytic nature [32].

IR assessments

The IR spectra of the compounds were recorded in the region from 4000 to 400 cm^{-1} on KBr pellets. They were compared with ligand spectrum. The strong and sharp band at 3340 cm^{-1} attributed to the stretching vibrations of O-H bond could not be detected in the IR spectra of the complexes. After complexation, this region is dominated by two strongly broadened bands related to the stretching modes of the water molecules. This is consistent with the deprotonation of the enolate group in the coordinated piroxicam. The characteristic amide vibrations of free piroxicam (1629, 1529, 1300 cm^{-1}) are shifted to 1634, 1517 and 1306 cm^{-1} respectively in the corresponding coordination compounds. The band located at 1300 cm^{-1} in piroxicam, usually known as amide III, is very sensitive to geometrical changes in the O=C-N(H)-C moiety [33]. Since after complexation the carbonyl group is involved in coordination, such changes are obviously important in this part of the molecule. The bands located at 1352 and 1182 cm^{-1} assigned to the antisymmetric and symmetric stretching vibrations of the SO_2 group are slightly shifted to lower frequency in all three complexes. As the SO_2 group is not involved in coordination, this shift must be related to hydrogen bonding effects.

It is known that in the simple metallic complexes of pyridine the vibrations in the high frequency region are not appreciably shifted comparing with free pyridine whereas the ring deformations found at 604 and 405 cm^{-1} in free pyridine are shifted to higher frequencies in these type of

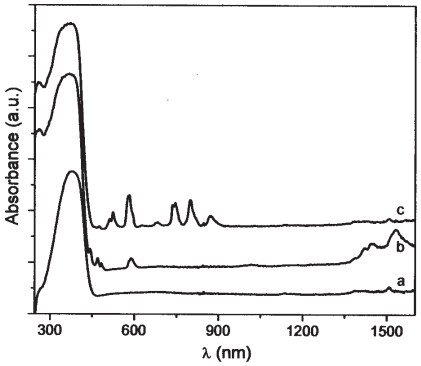

Fig. 1 UV-Vis-NIR spectra of: a) $La_2(HPir)_2(CH_3COO)_4 \cdot 2H_2O$; b) $Pr_2(HPir)_2(CH_3COO)_4 \cdot 2H_2O$; c) $Nd_2(HPir)_2(CH_3COO)_4 \cdot 2H_2O$.

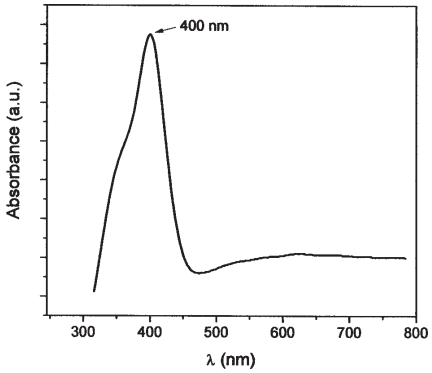

Fig. 2 UV-Vis spectrum of piroxicam

complexes [34]. Therefore these two shifts are very useful in establishing the involvement of pyridine in complex formation. In the uncoordinated piroxicam the first band at 604 cm^{-1} corresponding to in plane ring deformation (in free pyridine) is probably overlapped by the 626/619 cm^{-1} doublet. In lanthanide complexes this dublet disappears and a new band appears at 633 cm^{-1}. The second band appears at 430 cm^{-1}. These shifts are consistent with the participation of pyridine in complex formation. Based on these data we can assume that the $HPir^-$ anion acts as chelator through the nitrogen atom of the pyridil moieties and amidic oxygen atom.

The presence of acetate anions in the spectra of the complexes is confirmed by the appearance of two new bands at 1570 and 1440 cm^{-1}, respectively, which can be assigned to antisymmetric and symmetric stretching vibrations of acetate ligand. The difference in frequency ($\nu_{as}(COO^-) - \nu_s(COO^-)$) is 130 cm^{-1} (164 cm^{-1} for free acetate ion), indicating the bridging coordination mode of acetate group to metal centres [33].

Electronic spectra

The electronic spectra of the complexes and piroxicam (free ligand) are presented in figures 1, 2. The electronic spectrum of the piroxicam exhibits one absorption band at 400 nm due to $\pi \rightarrow \pi^*$ transitions (fig. 2).

This band is present in the spectra of all the complexes with a slight blue shift and overlaps the less intense and sharp bands characteristic to the transitions within the $4f^n$ configuration of the Ln^{3+} ions. The absorption bands of Pr(III) and Nd(III) complexes in the near infrared and visible region appear due to transitions from the ground levels $^3H_4$ and $^4I_{9/2}$ respectively to the excited levels of 4f configuration.

The absorption spectrum of $Pr_2(HPir)_2(CH_3COO)_4 \cdot 2H_2O$ complex shows four bands centered at 440, 467, 484 and 590 nm characteristic to the following transitions $^3H_4 \rightarrow {}^3P_2$, $^3H_4 \rightarrow {}^3P_1(+{}^1I_6)$, $^3H_4 \rightarrow {}^3P_o$, and $^3H_4 \rightarrow {}^1D_2$, respectively. In the near infrared region the absorption spectrum shows two bands at ~1448 and 1531 nm assigned to $^3H_4 \rightarrow {}^3F_4$ and $^3H_4 \rightarrow {}^3F_3$ transitions of Pr^{3+} ion. In the electronic spectra of $Nd_2(HPir)_2(CH_3COO)_4 \cdot 2H_2O$ complex, the sharp bands located at 508 (525), 579, 682, 742, 799 and 870 nm correspond to $^4I_{9/2} \rightarrow {}^4G_{9/2}$, $^4G_{7/2}$,, $^4I_{9/2} \rightarrow {}^4G_{5/2}$, $^4I_{9/2} \rightarrow {}^4F_{9/2}$, $^4I_{9/2} \rightarrow {}^4F_{7/2}$, $^4I_{9/2} \rightarrow {}^4F_{5/2}$, $^2H_{9/2}$ and $^4I_{9/2} \rightarrow {}^4F_{3/2}$, $^3H_{9/2}$ transitions, respectively [35].

Thermal analysis

The thermo-gravimetric analysis for the metal complexes was carried out from ambient temperature up to 900°C in air. Thermal analysis curves (TG/DSC) for all the studied compounds are given in figure 3. The correlations between the decomposition steps of the complexes and the corresponding mass losses are summarized in table 2. The decomposition profiles are similar and occurs in four well-defined steps.

The first step of decomposition corresponds to the loss of two water molecules with a mass loss of 3.91% for $La_2(HPir)_2(CH_3COO)_4 \cdot 2H_2O$, 3.91% for $Nd_2(HPir)_2(CH_3COO)_4 \cdot 2H_2O$ and 3.46% for $Pr_2(HPir)_2(CH_3COO)_4 \cdot 2H_2O$. The DSC curves show that this step is an endothermic process for all three compounds. After dehydration, the decomposition of the complexes associated with the complete pyrolysis of the organic parts and the oxidation of metal into its stable oxide occurs progressively in three steps in the temperature range 180–900 °C. According to the DSC curves (fig. 3 and table 2), these decomposition steps give exothermic peaks.

Table 2
THERMOANALYTICAL DATA OF PIROXICAM COMPLEXES

Complex	Temperature range (°C)	Peak temperature in DSC (°C)	Mass loss (Δm) %
$La_2(HPir)_2(CH_3COO)_4 \cdot 2H_2O$	25-180	178(-)	3.91
	180-285	285(+)	21.69
	285-500	460(+)	20.89
	500-900	593(+)	21.69
$Pr_2(HPir)_2(CH_3COO)_4 \cdot 2H_2O$	25-170	169(-)	3.46
	170-289	289(+)	22.60
	289-500	467(+)	21.91
	500-900	546(+)	18.22
$Nd_2(HPir)_2(CH_3COO)_4 \cdot 2H_2O$	25-163	160(-)	3.91
	163-292	292(+)	24.43
	292-500	465(+)	20.09
	500-900	557(+)	19.64

(-) = Endothermic, (+) = Exothermic

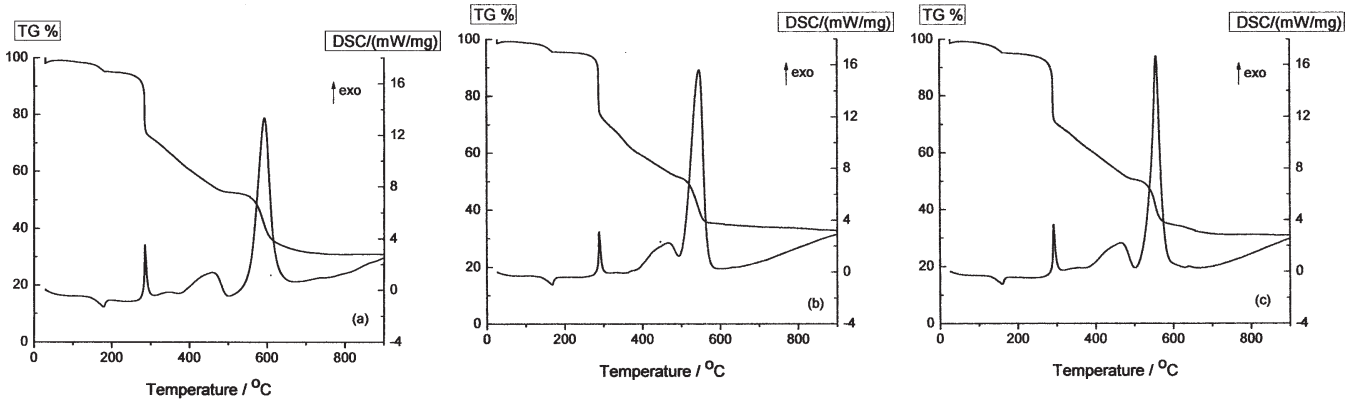

Fig. 3 TG/DSC curves of the piroxicam complexes: (a) $La_2(HPir)_2(CH_3COO)_4 \cdot 2H_2O$; (b) $Pr_2(HPir)_2(CH_3COO)_4 \cdot 2H_2O$; (c) $Nd_2(HPir)_2(CH_3COO)_4 \cdot 2H_2O$

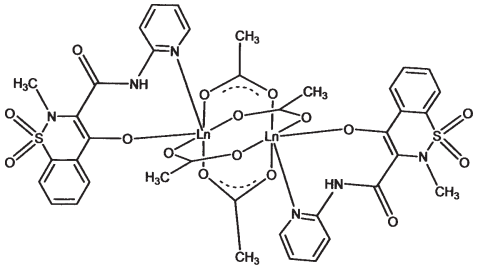

Fig. 4 The proposed structure of the complexes

Based on the above studies, the proposed structure of the metal complexes is shown in figure 4.

Antimicrobial activity assays

The antimicrobial activity of the complexes and free ligand was performed using reference and clinical microbial strains belonging to *Escherichia coli*, *Klebsiella pneumoniae, Pseudomonas aeruginosa, Staphylococcus aureus*, *Enterococcus faecium Bacillus subtilis* and *Candida albicans*. The results of the qualitative and quantitative assays of the antimicrobial activity of the tested compounds are listed in table 3 and 4. Qualitative screening tests indicated that all tested compounds show a broad spectrum of antimicrobial activity being active against all Gram positive and Gram negative bacteria and fungi strains tested, excepting *S. aureus ATCC 6538*. A comparative study of the ligand and their complexes indicates that complexes exhibit higher antimicrobial activity than the free ligand excepting the case of *C. albicans* 1760.

Quantitative assay of antimicrobial activity were performed only for the compounds that produced inhibitory growth zones. High MIC values (mostly >1000 - 500 μg/mL) indicating a low antimicrobial activity were registered for the all tested compounds against the microbial strains. Among the tested compounds the piroxicam exhibited a good antimicrobial activity with a MIC value of 125 μg/mL against *B. subtilis* ATCC 6683 strain, while for the other compounds MIC values were higher (indicating a weak antimicrobial activity) ranging from 1000 to 500 μg/mL (table 4).

The analysis of antibiofilm properties revealed that the effect on biofilm development on inert substrata was lower than the microbicidal activity in case of the majority of the tested compounds. The tested compounds inhibited the ability of different microbial strains to colonize the inert substratum, the inhibitory effect being observed at concentrations ranging between >1000 μg/mL and 250 μg/mL. It is to be noticed the good antibiofilm activity exhibited by the tested compounds against *B. subtilis* ATCC 6683 strain demonstrated by their minimum biofilm inhibitory concentration values, 250 μg/mL (table 5).

Compound	*E. faecium* E5	*E. coli* ATCC 25922	*C. albicans* 1760	*P.aeruginosa* ATCC 27857	*B. subtilis* ATCC 6683	*S. aureus* ATCC 6538	*K. pneumoniae* IC 13420
H_2Pir	5	6	7	4	7	0	5
$La_2(HPir)_2(CH_3COO)_4 \cdot 2H_2O$	8	6	5	4	6	0	9
$Nd_2(HPir)_2(CH_3COO)_4 \cdot 2H_2O$	6	6	4	5	7	0	7
$Pr_2(HPir)_2(CH_3COO)_4 \cdot 2H_2O$	8	6	4	6	7	0	10
DMSO	0	4	6	4	4	0	0

Table 3
THE INHIBITORY EFFECT OF THE TESTED COMPOUNDS ON PATHOGENIC BACTERIA (DIAMETERS OF INHIBITORY ZONES IN mm)

Compound	*E. faecium* E5	*E. coli* ATCC 25922	*C. albicans* 1760	*P.aeruginosa* ATCC 27857	*B. subtilis* ATCC 6683	*K. pneumoniae* IC 13420
H_2Pir	1000	500	1000	1000	125	500
$La_2(HPir)_2(CH_3COO)_4 \cdot 2H_2O$	1000	1000	1000	1000	500	>1000
$Nd_2(HPir)_2(CH_3COO)_4 \cdot 2H_2O$	1000	1000	1000	1000	500	1000
$Pr_2(HPir)_2(CH_3COO)_4 \cdot 2H_2O$	1000	1000	1000	1000	1000	>1000
DMSO	>1000	>1000	1000	1000	1000	1000

Table 4
MINIMUM INHIBITORY CONCENTRATION OF THE COMPOUNDS AGAINST TESTED MICROORGANISMS (μg/mL)

Compound	*E. faecium* E5	*E. coli* ATCC 25922	*C. albicans* 1760	*P.aeruginosa* ATCC 27857	*B. subtillis* ATCC 6683	*K. pneumoniae* IC 13420
H_2Pir	>1000	>1000	>1000	>1000	250	>1000
$La_2(HPir)_2(CH_3COO)_4 \cdot 2H_2O$	>1000	>1000	>1000	500	250	>1000
$Nd_2(HPir)_2(CH_3COO)_4 \cdot 2H_2O$	>1000	>1000	>1000	>1000	250	>1000
$Pr_2(HPir)_2(CH_3COO)_4 \cdot 2H_2O$	>1000	>1000	>1000	>1000	250	>1000
DMSO	>1000	>1000	1000	500	>1000	>1000

Table 5
MBIC VALUES (μg/mL)

Conclusions

In summary, a series of novel lanthanide (III) complexes with piroxicam were synthesized and characterized by elemental, spectral, magnetic and thermal analysis. Based on the above data, the proposed general formula of the complexes were $Ln_2(HPir)_2(CH_3COO)_4 \cdot 2H_2O$ for Ln = La(III), Pr(III), Nd(III). IR data indicated that piroxicam acts as a monoanionic bidentate ligand, coordinating through the nitrogen atom of the pyridyl ring and amidic oxygen atom to the metal ions. A four-stage decomposition process is shown in the thermogravimetric analyses of all the complexes. The antimicrobial studies revealed that all the compounds and the free ligand show a moderate antimicrobial against bacteria and fungi strains tested. Good antibiofilm activity against *B. subtillis* ATCC 6683 were observed for all the compounds.

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