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Comparative, synthesis and characterization studies of some metal complexes derived from *L*-lysine.HCl and *L*-lysine.2HCl by tribochemical reactions (part 2)

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ABSTRACT

Tribochemical reaction of *L*-lysine.HCl with MX_2 affords four new complexes with the general formula, $R_2[MCl_4]$ (R=*L*-lysine.HCl). The complexes were synthesized by grinding the reactants in the solid state in a mortar. The isolated solid complexes derived fromCu^{2+},Ba^{2+}, Cd^{2+} and Pd^{2+}chloridesare characterized by elemental analyses, conductivities, spectral (IR, UV-Vis, Far-IR) and magnetic measurements. Molar conductance values of the isolated solid complexes suggest their electrolytic nature in DMSO butthe complexes are easily decomposed in H_2O. Spectral and magnetic measurements suggest that the metal ions form tetrahedral geometry around the metal ion. The $[MCl_4]^{2-}$ anion and its counter ions are connected through a hydrogen bonds between Cl of the anion and OH (carboxylate)forming O-H···Cl interaction. The results of Far-IR spectra suggest the stretching and bendingvibrations of M-Cl. Also, a comparative study between the complexes isolated from *L*-lysine.HClandour previous studies derived from*L*-lysine.2HCl has been illustrated. Finally, the complexes were tested against different types of cancer and some of the complexes give promising results.

KEYWORDS

Tetrahalometallate complexes;
L-lysine.HCl and *L*-lysine.2HCl;
Biological activity;
Tribochemical reactions;
Far-IR spectra.

INTRODUCTION

In continuation of our earlier workof the synthesis and characterization of some metal complexes derived from *L*-lysine.2HCl[1] as well as the complexes derived from various ligands by tribochemical reactions[2-6],we extend this work to include *L-lysine.HCl*with MX_2 (Cu^{2+}, Ba^{2+}, Cd^{2+} and Pd^{2+}). Adams et al[7] reported the reactions of Pd^{2+} and Pd^{2+} chloride complexes with imidazole and pyrazole or their hydrochloride in the solid state which produce novel metal complexes andthe crystal structure of the $Cu^{2+}$was determined by single crystal X-ray crystallography[8]. The copper complex has a distorted-tetrahedral geometry and the $[CuCl_4]^{2-}$ anion and its counter ions is connected through a hydrogen bonds between Cl of the dianion and hetero aromatic rings by Cl-π, π-π and O-H ··· π, interactions. The main goal of thiswork is to compare the results under investigation with our earlier work[1] and to study the

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biological activity of the isolated complexes against different types of cancer.

EXPERIMENTAL

Materials and methods

Metalcontents were determined at the Microanalytical Unit, Cairo University, Egypt. Pd and Cd were determined by complexometric titration using Xylenol orange as indicator[9]. Cu and Ba contents were performed byatomic absorption spectrometermodel Perkin-Elmer in the Micro Analytical Center, Faculty of Science at Cairo University. The conductance measurements in DMSO were carried out using a conductivity bridge TDS model 72 at Domiat University, Egypt. IR spectra were recorded on an 800-PC FTIR Schimadzu spectrophotometer using KBr pellets (4000-400 cm^{-1}) at Cairo University. Far-IRspectra were recorded using spectrophotometer model 6300 FTIR in the Egyptian Petroleum Research Institute. Magnetic moments were determined using a Sherwood balance at room temperature (25 ^{o}C) with $Hg[Co(NSC)_4]$ as a celebrant at Mansoura University. Diamagnetic corrections for *L-lysine.HCl* and the metal atoms were computed using Pascal's constants[10]. Electronic spectra of the complexes in Nujol mulls were recorded on a Unicam UV2 spectrophotometer at Mansoura University.

Synthesis of ligand and metal complexes

The synthesis of new metal complexes with the general formula,$R_2[MCl_4]$,were obtained by grinding 2 moles of*L-lysine.HCl* with MX_2 (1 mole; M = Cu^{2+}, Ba^{2+}, Cd^{2+} and Pd^{2+}) in agate mortar at room temperature till the reactants become in fine powder. The isolated solid complexes were dried in an oven at 60 ^{o}C and kept in desiccators over anhydrous $CaCl_2$.

Biological activity

Cytotoxicity Assay

Evaluation of the cytotoxicity of the synthesized complexes against HCT-116 (colon) and MCF-7 (breast) cell lines was carried out in the Regional Center for Mycology and Biotechnology (Al-Azhar University) as reported earlier[1]. The relationship between the surviving fraction and drug concentration was plotted to get the survival curve of each tumor cell line after specific compound was added. Inhibition of cell proliferation (IC_{50}) for test compounds (A, B and D) (µg sample/L) were recorded. The IC_{50} is the concentration of treatment required to induce 50% inhibition of cell growth[1].

RESULTS AND DISCUSSION

Comparison of elemental analyses for the calculated and found percentages indicates that the compositions of the complexes coincide with the proposed formulae as shown in TABLE 1. All the complexes are freely soluble in DMF and DMSO. The decomposition of complexes in H_2O, derived from *L-lysine.HCl*islower than the complexes isolated

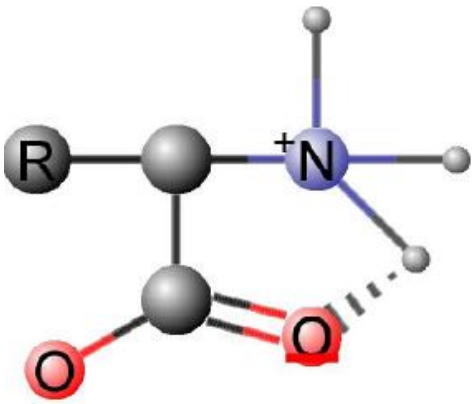
TABLE 1 : Elemental analyses and some physical data of the isolated metal complexes

Complex; chemical formula	M.p., ^{o}C	$\lambda_{max.}$	Λ_m (DMSO;ohm^{-1}cm^2 mol^{-1})	$U_{eff..}$ (B.M)	C% F(Calc.)	H% F(Calc.)	N% F(Calc.)	M% F(Calc.)
$[NH_2\text{-}HC\text{-}COOH\text{-}(CH_2)_4\text{-}NH_3]_2\ [CuCl_4]$; $C_{12}H_{30}N_4O_4CuCl_4$(M.Wt =499.756) (1)	155	314 336 384 440	47	2.19	28.4 (28.8)	5.6 (6.1)	10.7 (11.2)	11.9 (12.7)
$[NH_2\text{-}HC\text{-}COOH\text{-}(CH_2)_4\text{-}NH_3]_2[BaCl_4]$; $C_{12}H_{30}N_4O_4BaCl_4$(M. Wt = 573.543) (2)	215	234 272 380	----	Diamag.	24.9 (25.1)	4.4 (5.2)	10.2 (9.8)	23.9 (24.4)
$[NH_2\text{-}HC\text{-}COOH\text{-}(CH_2)_4\text{-}NH_3]_2$ $[CdCl_4].2H_2O$; $C_{12}H_{34}N_4O_6CdCl_4$(M. Wt = 584.658) (3)	196	310 358 414	81	Diamag.	24.4 (24.7)	4.9 (5.9)	10.5 (9.6)	18.8 (19.2)
$[NH_3\text{-}HC\text{-}COOH\text{-}(CH_2)_4\text{-}NH_3][PdCl_4]$; $C_{12}H_{30}N_4O_4PdCl_4$(M. Wt = 542.636) (4)	194	310 418 516	47	Diamag.	26.2 (26.6)	5.3 (5.6)	9.7 (10.3)	20.0 (20.7)

from *L*-lysine.2HCl. This is mainly due to the strong hydrogen bond formed within the former complexes than the latter complexes derived from *L*-lysine.2HCl. The values of molar conductance in DMSO (TABLE 1)suggest that all the complexes are electrolytic in nature[11], exceptthe Ba complex which insoluble in DMSO. The values of molar conductance for the complexes isolated from *L-lysine.HCl* are lower than the values of the complexes separated from *L*-lysine.2HCl. The low values are explained on the strength of hydrogen bonding in the complexes derived from *L-lysine.HCl*as well as the low speed of the large ions in the solvent. The melting points of the solid complexes (TABLE 1)lie in the 155-215°Crange. These valuessuggest that the strength of the bond between *L-lysine.HCl* and the metal ions on heating areless stable in comparison to the complexes isolated from *L*-lysine.2HCl[1].

IR spectra of the complexes derived from L-lysine.HCl

The IR spectrum of the free ligand (*L*-lysine.HCl) shows the presence of new bands in the 3400-3100 cm^{-1} region. This suggests that one of the two NH_2 groups of *L*-lysine.HClis changed to NH_3^+ and the other remains as NH_2. Also, the results suggestthe absence of H_2O molecules within the compound as shown in Figure 1. Several bands are observed at 3024, 2814, 1725, 1620 and 1571 cm^{-1}. The first two strong bands are mainly due to the strong hydrogen bond between the OH andNH_3 (N….H—O) vibration. The latter two bands at 1725, and 1620 cm^{-1} are attributed to the ν_{as}(COO) and ν_s(COO) vibrations[12-17]. The last band at 1571 $cm^{-1}$is assigned to the NH_3^+ group.



$R = -(CH_2)_2-NH_2$

Figure 1 : Hydrogen bond in lysine.HCl

Also, the most important assignments of the metal complexes, $[NH_3\text{-}CH(COOH)\text{-}(CH_2)_4\text{-}NH_3]_2[CuCl_4]$ (1), $[NH_3\text{-}CH(COOH)\text{-}(CH_2)_4\text{-}NH_3]_2[BaCl_4]$ (2), $[NH_3\text{-}CH(COOH)\text{-}(CH_2)_4\text{-}NH_3]_2[CdCl_4].2H_2O$ (3) and $[NH_3\text{-}CH(COOH)\text{-}(CH_2)_4\text{-}NH_3]_2[PdCl_4]$ (4), are observed in the regions 3402-3461, 3286-3167, 2978-2929, 1600-1631 and 1505-1525 cm^{-1} assigned to $\nu_{as}(NH_2)$ attached to the CH group, $\nu_s(NH_2)$ attached to $(CH_2)_4$, ν(OH) hydrogen-bonded, ν_{as}(COO) and ν_s(COO) vibrations[14-17], respectively. Also, the band observed at ≈ 1585 cm^{-1} is assigned to NH_3^+ group suggesting that the ligand (lysine.HCl) is mainly existed in the form of Zwitterion. Also, the data suggest that the ligand is bonded to the metal ions forming ionic bond in the complexes of the type $[L]^{2+}[MX_4]^{2-}$. The bond in these complexes is a type of ionic interaction. Doubtless this type of interaction causes the shifts of both the carboxylate and the NH_2 groups to lower wavenumbers. The IR spectrum of the *L-l*ysinetetrachloropalladate (II),$R_2[PdCl_4]$,in KBr complex is recorded in Figure 2.

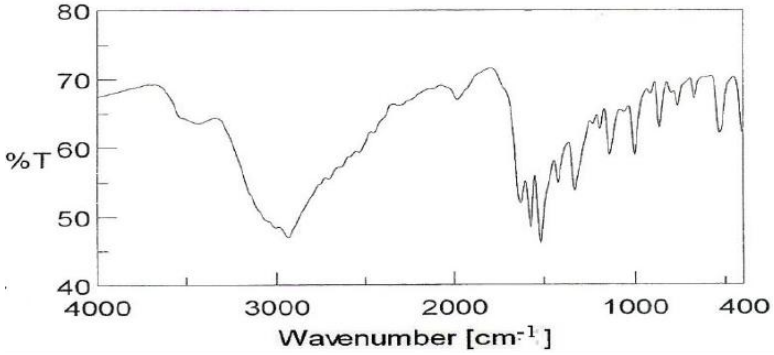


Figure 2 : IR spectrum of $R_2[PdCl_4]$in KBr

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The most important bands in the metal complexes, $[NH_3\text{-}CH(COOH)\text{-}(CH_2)_4\text{-}NH_2]_2[CuCl_4]$ (1), $[NH_3\text{-}CH(COOH)\text{-}(CH_2)_4\text{-}NH_2]_2[BaCl_4]$ (2), $[NH_3\text{-}CH(COOH)\text{-}(CH_2)_4\text{-}NH_2]_2[CdCl_4]$ (3), $[NH_3\text{-}CH(COOH)\text{-}(CH_2)_4\text{-}NH_2]_2[PdCl_4]$ (4), are observed in the regions 3493-3409, 3234-3002, 2927-2900, 1735-1681 and 1680-1587 cm^{-1}. The observation of the bands in the 3493-3409 and3234-3002 regions assigned to NH_2 vibration indicating that one of the NH_3^+ group in the free ligand is changed to NH_2 on complex formation. These bands are assigned to $\nu_{as}(NH_2)$ and $\nu_s(NH_2)$ vibrations, respectively. The band observed in the 2927-2900 regions isν(CH) vibration. The last two bands are assigned toν_{as}(COO) and ν_s(COO) vibrations[18-22], respectively. Also, the band observed at 1585 cm^{-1} is assigned to NH_3^+ group suggests that the ligand is mainly existed in the form of Zwitterion. Also, the data obtainedsuggest that the ligand is bonded to the metal ions forming a complex of the type $[L]_2^{2+}[MX_4]^{2-}$. Finally, the bands observed in all complexes in the 1900-2000 and 2600-2500 cm^{-1} region suggests the presence of O—H….Clhydrogenbond[23] and represented by the Pd^{2+} complex as shown in Figure 3.

In contrary to our previous work[1] the IR spectra of lysine.2HCl and its complexes showed the absence of the NH_2 bands due to the formation of two $(NH_3)^+$ groups as shown in Figure 4. Also, the results suggest that the bands at 1735-1681and 1680-1587 $cm^{-1}$are assigned toν_{as}(COO) and ν_s(COO) vibrations, respectively.

Electronic spectraand magnetic measurements

The electronic spectrum of the Cu^{2+}complex is shown in Figure 5. All the complexes show two main bands in the 272-418 and 374-516 nm regions which are mainly assigned to $\pi \rightarrow \pi^*$ (COOH) and $n \rightarrow \pi^*$ (COOH) transitions[24], respectively. The Cu^{2+} complex exhibits three bands at 315, 390 and 735 nm. The first two bands are due to charge-transfer while the third band is attributed to d-d transition. The observation of these bands suggests that the Cu^{2+}complex has a distorted-tetrahedral geometry around the Cu^{2+}ion[25]. The value of magnetic moment for the Cu^{2+}complex (2.19BM)suggests the absence of Cu-Cu interactions[26,27].

Far-IR spectra of the metal complexes

The Far-IR spectrum (600-50 cm^{-1}) of the tetrahalopalladate(II) complex of the general formula, $R_2[PdCl_4]$, is recorded in Figure 6. The spectra in the complexesshow two bands in the 265-295 and 54-84 cm^{-1}regions assigned to ν(M-Cl) stretching[28] and ν(Cl-M-Cl) bending, respectively.

Evaluation of cytotoxic activity on human tumor cell lines

Activity against breast cancer cell lines (MCF-7)

The data illustrate that the order of theactivity of the complexes against breast cancer is in the order: 3 >1 >4 > 2 with IC_{50} values of (0.47, 6, 34.3 and 37

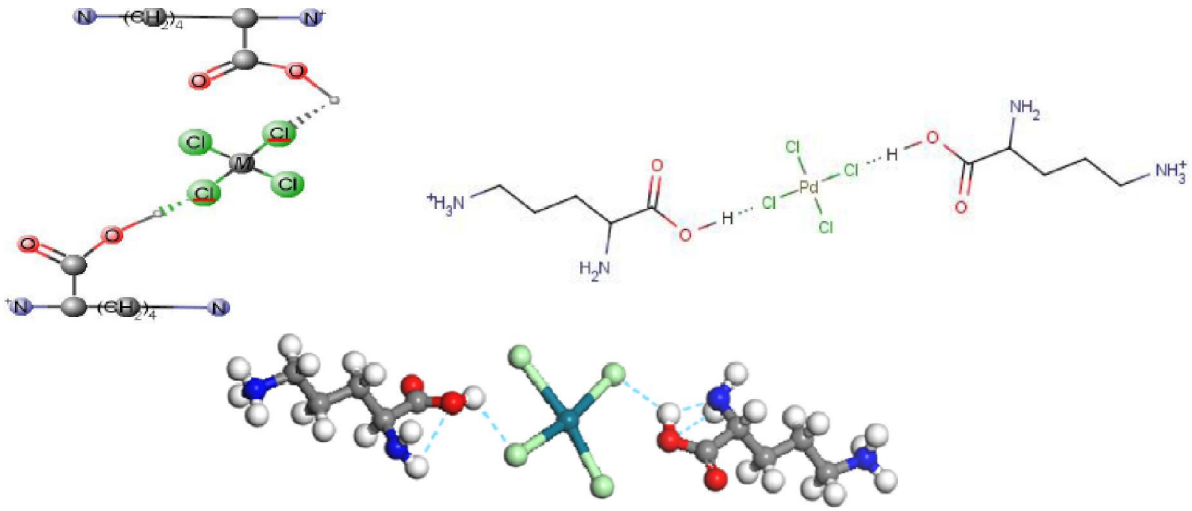

Figure 3 : The structure of the complexes with the general formula $R_2[PdCl_4]$

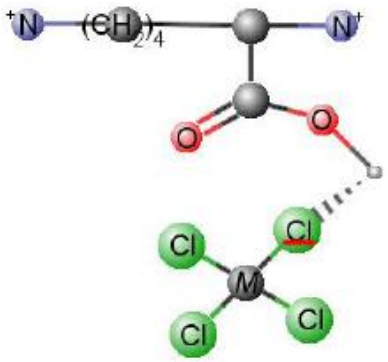

Figure 4 : Complexstructurewith the formula $R[MCl_4]$

µg/m). Doxorubicin (DOX) a drug with antineoplastic activity was used in this study as standard drug, since it is widely used in the treatment of tumor cells. *L*-lysinetetrachlorocadmate (3) is promising to inhibit the growth of breast cancer lines while*L*-lysinetetrachloropalladate complex(4) shows the least antitumor activity due toits low solubility.

Activity against cervical cancer

All tested compounds are effective against HELA (Cervical cancer) illustrate that the order of their activities is 3> 1 > 4 > 2.*L*-lysine tetrachloocadmate (3) and*L*-lysinechlorocuprate (1) are very successful to inhibit the growth of the cervical cancer. The results show that *L*-lysinetetrachlorobarimate (2) hasthe worst effect.

Activity against .colon cancer

The activity of tested compounds against HCT (colon cancer) illustrates that the order of their activities is in the order: 3 > 1 > 2 > 4. *L*-lysinetetrachlorocadmate (1) is very potential agent to inhibit the growth of the colon cancer followed by*L*-lysinediiododichlorocadmate (I_e) and *L*-lysinetetrachloropalladate (4) has the lowest potent activity. Cytotoxic activities of these complexesare mainlydue their differential solubility.

Activity against larynx cancer

The activity of compounds under investigation against HEP2 (Larynx cancer) shows that the order of their activities is as follow: 3 > 1> 2 ≈ 4. Both of *L*-lysinetetrachlorocadmate(3) and*L*-lysinetetrachloropalladate (1) are the most potent while *L*-lysinetetrachlorobarimate (2) and*L*-lysinetetrachloro palladate (4) are the least effective *3. 4. 5. Activity against Heptacellular cancer.* The activities of compound against HEPG2 (Heptacellular cancer) illustrate that the order of their activities is as follow: 3 > 1 > 4 > 2. *L*-lysinetetrachlorocadmate (3), and *L*-lysinetetrachlorocuprate (1) are very successful to inhibit the growth of the heptacellular cancer. Both the *L*- lysinetetrachloropalladate (4) and*L*-lysinetetrachlorobarimate (2) show less activity. All the data are recorded in TABLE 2. in activity against

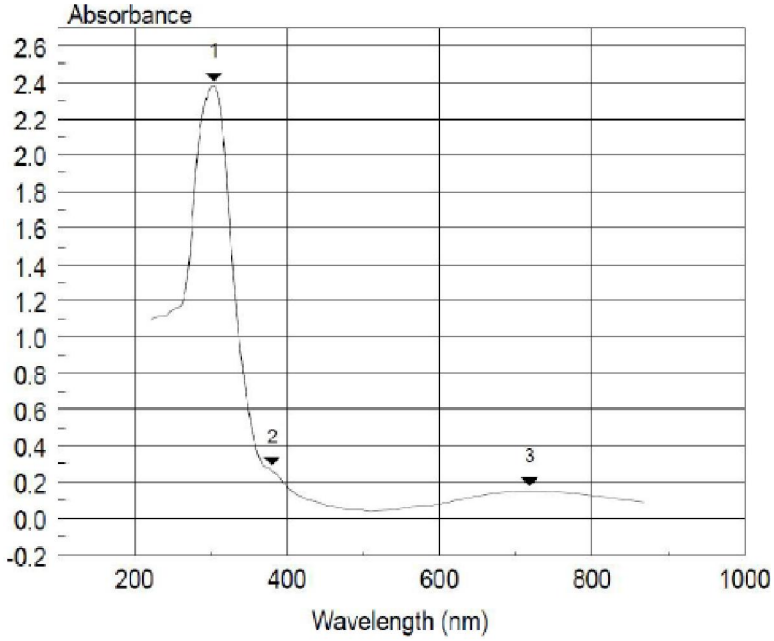

Figure 5 : The electronic spectrum of the Cu^{2+} complex, $R_2[CuCl_4]$

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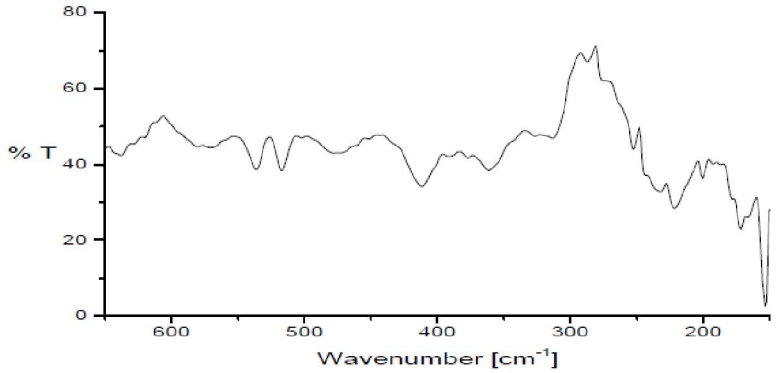

Figure 6 : Far-IR spectrum of$L_2[PdCl_4]$

TABLE 2 : Inhibition of cell proliferation (IC_{50} µg sample/L) for complexes

Complex	Breast cancer	Cervical cancer	Colon cancer	Larynx cancer	Hepatocellular cancer
L-lysinetetrachlorocuprate(II) (1)	6.0	9.3	6.9	9.7	10.9
L-lysinetetrachlorobarimate(II)(2)	37.0	37.6	36.6	40.0	32.1
L-lysinetetrachlorocadmate(II) dihydrate(3)	0.47	0.47	0.73	0.51	0.69
L-lysinetetrachloropalladate(II)(4)	34.3	16.5	47.8	40.0	21.8

HEP2 (Larynx carcinoma).

Activity against Heptacellular cancer

The activities of compound against HEPG2 (Heptacellular cancer) illustrate that the order of their activities is as follow:3 > 1 > 4 > 2. *L*-lysinetetrachlorocadmate (3), and *L*-lysinetetrachlorocuprate (1) are very successful to inhibit the growth of the heptacellular cancer. Both the *L*-lysinetetrachloropalladate (4) and*L*-lysinetetrachlorobarimate (2) show less activity.

All the data are recorded in TABLE 2.

Cadmium and copper complexes(3 and 1) are the most active compounds against all tumor cell lines. Theresults suggest that the positively charged polar head of the complexes provides the basis for its anticancer specificity, whereas the amino acid tail may aid in its insertion into the plasma membrane altering its mosaic structure in response to the negative trans-membrane potential. It should be also noted that effects of these complexes are found to be dependent on the typeof the tested tumor cell line. Results illustrated that cadmium complex shows excellent cytotoxic activity, which can be attributed to the abilityof cadmium complex to produce non-covalently interact with DNA double helix rather than forming coordinated covalent adducts with DNA. The non-covalent DNA interactions included intercalative, electrostatic and groove binding of metal complexes along the major or minor DNA groove. In most cases, the metal acted as an inorganic modifier of the organic backbone of the bioactive molecule and ligands granted DNA affinity and specificity[29].

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