Dedicated to the memory of
acad. Ecaterina Cioranescu-Nenitzescu

New Potential Monoamine Oxidase Inhibitors

MICHAELA DINA STANESCU[1]*, LAURA ALEXANDRESCU[2], OVIDIU OPREA[2], SEMIRAMIDA PERES[2], IOANA JITARU[2]
[1]"Aurel Vlaicu" University, Faculty of Food Engineering, Tourism and Environmental Protection, Chemical and Biological Sciences Department, 2-4 Elena Dragoi, 310330, Arad, Romania
[2] Politehnica University, Faculty of Applied Chemistry and Material Sciences, Inorganic Chemistry Department, 1 Polizu Str., 011061, Bucharest, Romania

The paper reports the synthesis and properties of a number of 3d metal complexes with a ligand having Monoamine Oxidase Inhibitors (MAOI) structure. The compounds have been characterized by spectral methods and their conductivity has been determined. The stability in physiological conditions and their toxicity were also established. The experimental data showed a good anti-bacterial activity for some of the new synthesized compounds.

Keywords: Monoamine Oxidase Inhibitors, 2-[(2'-hydroxyethyl)amino]-1-phenylethanone, complexes of copper, manganese and zinc

Monoamine oxidases (EC 1.4.3.4) are enzymes involved in the transformation of monoamine neurotransmitters, as well as other biogenic amines present in food due to amino acid decarboxylation reaction. They belong to the family of FAD oxido-reductases and are found in the outer membranes of cell mitochondria [1- 3]. The reaction catalyzed by these enzymes is the oxidation of monoamines to aldehydes with concomitant formation of ammonia and hydrogen peroxide:

$$RCH_2NH_2 + H_2O + O_2 \rightarrow RCHO + NH_3 + H_2O_2$$

For a healthy organism, a balance between the amine and aldehyde contents is necessary, the monoamine excess or deficit leading to a variety of central nervous system disorders [4,5]. In the same time the formation of hydrogen peroxide induces a stress in living cells causing injury, the oxidation reaction needing a careful control.

A regulation of the Monoamine oxidase activity is performed by inhibitors (MAOI). MAOIs are a class of powerful antidepressant drugs particularly effective in treating atypical depression [6,7]. The abnormal activity of MAO is implicated in neurological disorders leading to Parkinson's or Alzheimer's diesease [6]. MAOI have also shown efficacy in helping people who want to quit smoking.

The interest for MAOI was expressed since long time by our research group [9-13]. The previously synthesized compounds proved to have also other biological activity, like anti-microbial or, more interesting, anti-carcinogenic, as inhibitors of Matrix Metallo Proteinases (MMP) [14].

By studding the structure of MAOIs, it may be observed that most of the compounds with such biological activity contain a phenyl-ethane moiety in their structure [7,8]. Thus, the synthesis of complexes of a new phenyl-ethane derivative as ligand, with biological active metals, like copper, manganese and zinc, has been performed and the properties of the new prepared compounds presented.

Experimental part

Diffuse reflectance measurements were recorded, at room temperature, with an AbleJasco V550 spectophotometer. IR spectra have been recorded on FTIR Brucker Tensor apparatus.

^{1}H-NMRspectra have been recorded with Varian 60 spectrophotometer in CDCl$_3$ solution at room temperature. Molar electrical conductivity have been measured in 10^{-3} M dimethylformamide solutions, at 25^{0}C, with OK 102/1 Radelkis Conductometer, 0.1 – 0.5 S. All the used reagents are p.a. reagents, supplied by Aldrich.

2-[(2'-hydroxyethyl)amino]-1-phenylethanone (**1**)

The ligand **1** was prepared, as previously described [9], by mixing a solution in ethyl ether of 2-chloro-1-phenylethanone and monoethanolamine, in a molar ratio 1:2.1, for 1 h, at room temperature. The precipitated mono-ethanolamine chlorohydrate was filtered and an oily light yellow product was obtained.

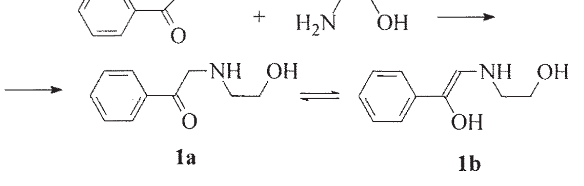
IR spectrum ((CCl$_4$ cm^{-1}) 700m, 770m, 1068m (ν_{C-N}), 1274m, 1383m, 1449m, 1546m, 1600s, 1668m ($\nu_{C=O}$), 2875-2950m, 3200-3600m (ν_{NH}, ν_{OH}); *^{1}H-NMR spectrum* (CDCl$_3$ + CD$_3$COCD$_3$, δ ppm) 2.5-3.0 (m, 2H); 3.2-3.8 (m, 4H); 7.3-7.8 (m, 3H, H$_{arom}$); 7.9-8.2 (m, 2H, H$_{arom}$).

General procedure for preparing the complexes

Solutions in methanol, of ligand **1** and salts of *3d* metals [Mn (II), Cu (II) and Zn (II)], were kept under stirring, for 24 h, at room temperature. After the solvent removal and trituration with solution 1/1 methanol/ethyl ether, the coloured solids have been filtered and dried. The complexes obtained in a 70-80% yield. The prepared compounds general data are presented in table 1.

Results and discussion

The new polydentate ligand **1** (**L**) presents, like similar compounds, a keto-enol tautomery (**1a**, **1b**) [9-14], phenomenon observed also in other systems during metal-complex formation [15]. For steric reasons, the opposite arrangement of the two oxygen atoms seems more plausible, fact that determined compound **1** to be mostly a bi-dentate, and seldom a tri-dentate ligand.



1a **1b**

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* email: stanescu@uav.ro

Table 1
ELEMENTAL ANALYSIS AND MOLECULAR FORMULA FOR COMPLEXES OF LIGAND **L**

Compound	**Colour**	**Formula**	**Elemental analysis**									
			% C		% H		% N		% Cl		% Metal	
			exp.	calc.	exp.	calc.	exp.	calc.	exp.	calc.	exp.	calc.
Comp. **2**	brown	[Mn**L**Cl]Cl	39.38	39.34	4.21	4.26	4.63	4.59	23.32	23.28	18.06	18.03
Comp. **3**	brown	$[Mn\mathbf{L}_2(CH_3COOH)_2]$	54.18	54.23	5.98	6.02	5.31	5.27	-	-	10.36	10.35
Comp. **4**	green	$[Cu\mathbf{L}_2(CH_3COOH)_2]$	53.36	53.33	5.95	5.92	5.21	5.18	-	-	11.84	11.85
Comp. **5**	green	$[Cu\mathbf{L}_2Cl_2]$	48.71	48.68	5.31	5.27	5.72	5.68	14.38	14.40	13.01	12.98
Comp. **6**	white	$[Zn\mathbf{L}_2(CH_3COOH)_2]$	53.28	53.23	5.88	5.91	5.21	5.17	-	-	12.06	12.01

Table 2
COMPOUNDS **2-6** IR SPECTRAL DATA (cm^{-1})

Compound	ν_{NH}, ν_{OH}; δ_{HOH}	$\nu_{C=O}$	$\nu_{C=O\ (acetate)}$	ν_{C-N}	$\nu_{OCO\ (acetate)}$
1 (L)	3200-3600	1670	-	1068	-
2	3200-3600	-	-	1050	-
3	3200-3600	-	1700	1055	1414, 1525
4	3200-3600	1619	1750	1062	1414, 1520
5	3200-3600	1618	-	1063	-
6	3200-3600	1605	1750	1060	1413, 1520

The general data for the newly synthesized compounds **2-6** are presented in table 1. The elemental analysis data for all the compounds are in agreement with the proposed molecular formula.

The structures for compounds **2-6** have been proposed according to the IR and diffuse reflectance spectra, as well as the molecular electrical conductivity measurements (table 2-4).

Based on IR spectral data the following conclusions may be stated:

- in all the compounds the amino group is involved in coordination, the n_{C-N} values being smaller than in the ligand **1**;
- the manganese complexes **2** and **3** have the ligand in the enol tautomeric form, the IR spectra indicating no ketone presence, while the vibration for the corresponding functional group is present in compounds **4-6**;
- the $\nu_{C=O}$ has in the compounds **4-6,** lower values than in compound **1**, indicating the carbonyl group as a coordination centre;
- the vibrations for acetate carbonyl, as well as those for the acetate bending, proved the coordination with the single bond oxygen.

The molecular electrical conductivity gave supplementary information about the compounds **2-6** structures (table 3).

The most probable stereochemistry of the new synthesized compounds was established based on diffuse reflectance measurements presented in table 4.

The electronic spectrum of compound **2** presents a broad band, of low intensity in the 500-1000 domain assigned to the forbidden spin transitions for a *3d*^{5} electron configuration. In the near UV-Vis region a charge transfer band *Ligand → Metal* appears [16]. The compound **3**

Table 3
MOLECULAR CONDUCTIVITY AND TYPE

Compound	Λ_M **(Ω^{-1}cm^{2}mol^{-1})**	**Type**
2	68.1	1:1 electrolyte
3	27.9	nonelectrolyte
4	14.3	nonelectrolyte
5	31.7	nonelectrolyte
6	23.3	nonelectrolyte

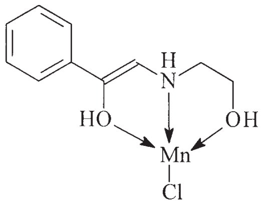
Table 4
ABSORPTION MAXIMA (kK) AND ASSIGNMENTS

Compound	**Colour**	**(kK)**	**Assignment**
2	brown	20.31	TS
		18.18	$^6A_1 \rightarrow {}^4T_2$ (D)
		13.62	$^6A_1 \rightarrow {}^4A_1, {}^4E$ (G)
		11.14	$^6A_1 \rightarrow {}^4T_2$
		9.8	$^6A_1 \rightarrow {}^4T_1$
3	brown	26.11	TS
		19.88	$^6A_{1g} \rightarrow {}^4T_{2g}$ (D)
		12.12	$^6A_{1g} \rightarrow {}^4A_{1g}, {}^4E_g$ (G)
		9.8	$^6A_{1g} \rightarrow {}^4T_{2g}; {}^6A_{1g} \rightarrow {}^4T_{1g}$
4	green	15.15	$z^2 \rightarrow x^2-y^2$ ($a_{1g} \rightarrow b_{1g}$)
		11.41	$xz,yz \rightarrow x^2-y^2$ ($e_g \rightarrow b_{1g}$)
		9.83	$xy \rightarrow x^2-y^2$ ($b_{2g} \rightarrow b_{1g}$)
5	green	15.47	$z^2 \rightarrow x^2-y^2$ ($a_{1g} \rightarrow b_{1g}$)
		10.91	$xz,yz \rightarrow x^2-y^2$ ($e_g \rightarrow b_{1g}$)
		9.09	$xy \rightarrow x^2-y^2$ ($b_{2g} \rightarrow b_{1g}$)

presents all four bands corresponding to the forbidden spin transitions, as well as the charge transfer band *Ligand → Metal.* The compound **3** seems to have an octahedral geometry being hexa-coordinated.

The electronic spectra of copper complexes **4**, **5** may be correlated with a distorted octahedral geometry (650, 900 and 1000-1100 nm) together with a charge transfer band at 380 nm [16].

Based on all this experimental data, the structure established for the compounds **2-6** was the following one:



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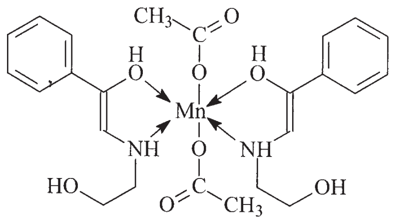

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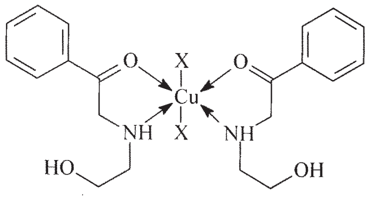
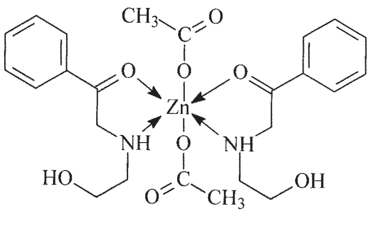
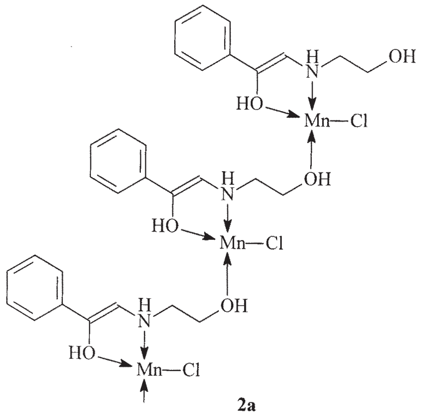


4 (X = Cl)
5 (X = $OCOCH_3$)



6

For the compound **2** a polymer structure **2a** could also be proposed as plausible.



2a

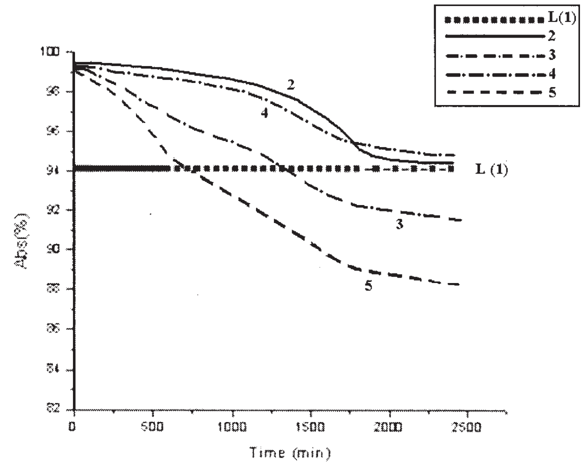
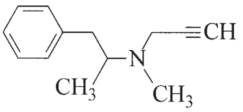


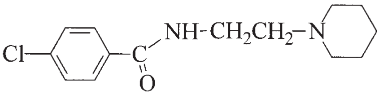
Fig.1. Stability of ligand (**1**) and complex compounds (**2-5**) at physiological pH

The potential drug activity of the complexes was checked, starting with the stability determination, at the physiological *p*H (fig. 1). All the compounds are stable enough. The compounds **3**, **5** and **6**, containing acetate groups seemed less stable because, most probably, the acetate moiety may be easily replaced by water.

An important aspect in connection to the potential MAOI activity is the toxicity. According to the performed experiments, the toxicity of these compounds (LD$_{50}$) is comparable with that of the two well known MAOIs namely, Deprenyl (**7**) and Moclobemide (**8**):



Deprenyl



Moclobemide

Toxicity tests have been performed on white Swiss mice, the compounds being used intra-peritoneal (i.p.) and per os (p.o.). The LD$_{50}$ (mg/kg) values are presented in table 5.

Table 5
EXPERIMENTAL VALUES FOR LD$_{50}$ (mg/kg)

Compound	DL$_{50}$ (i.p.)	DL$_{50}$ (p.o.)
1	2720	1930
2	3550	2540
3	3380	2400
4	3415	2470
5	3125	2120
6	2910	1890
7	3680	2570
8	3350	2810

Table 6

ANTIFUNGAL ACTIVITY (mm)

Compound	pH 6	pH 8
Streptomycin	10	12
1	13	10
2	1	4
4	12	5

Once again the properties of the complexes are superior to those of the ligand **1**, all the coordination compounds proving to be less toxic. It can also be noticed the lower toxicity of complex compounds with chlorine by comparison to complex compounds with acetate, fact that can be correlated to the better stability at physiological pH of the formers. The toxicity of compound **2** is similar to drugs used in clinics Deprenyl and Moclobemide.

The stability in physiological conditions and the toxicity values, recommend these compounds as candidates for new MAOI. Moreover, some of these compounds have also anti-fungal activity. The assertion is based on the results obtained after treatment of *Bacillus cereus* at pH 6 and 8 with compounds **1**, **2** and **4**.

The experimental data, together with values for a well known compound, Streptomycin, are presented in table 6. At *p*H 6 the ligand **1** has a higher activity compared with the classical antibiotic.

Conclusions

A new poly-dentate ligand and its coordination complexes with Mn, Cu and Zn have been prepared. The structure of the newly synthesized compounds have been proposed based on elemental analysis, IR and electronic spectral data. All the compounds are stable in physiological conditions and proved to have antifungal activity.

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