

## Complex compounds with thioxanthene drugs

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### Abstract

*The present paper deals with the synthesis and characterization of some new metallic complexes with thioxanthene drugs as ligands, having the general formula:  $[CuLX_2]_2$  ( $L = 10$ - $(3$ -dimethylaminopropyl) thioxanthene, noted in this paper, **cptx**;  $X = Cl, CH_3COO^-$ ),  $[ML_2X_2]$  ( $M(II) = Co, Ni, Cu$ ;  $L = \text{cptx}$  or  $10/2$  -  $(1'$ -methyl- $2'$ -piperazyl) propylidene -  $2'$ -dimethylaminosulphuryl-thioxanthene, noted in this paper **ttx**;  $X = Cl, CH_3COO^-$ ) and  $[ML^+Cl_3]$  ( $M(II) = Ni, Cu$   $L^+ = \text{cptxH}, \text{ttxH}$ ). The complexes were characterised by elemental chemical analysis, molecular electrical conductivity, electronic, epr and FT-IR spectra. The estimation of the electronic densities in MO diagram calculations confirms the experimental data and suppositions about the structural formulas of the isolated complexes. The formation of such complexes may be the support of a possible action mechanism of the thioxanthene drugs in Wilson's disease.*

### Introduction

The use of D-penicillamine in the treatment of Wilson's disease that is caused by an inability of the body to metabolise copper in the normal way is well known. In many cases, D-penicillamine is associated with neuroleptic drugs of thioxanthene or phenothiazine type.

The large spectrum of action of the thioxanthene derivatives (antihistaminic, antiemetic, anti-inflammatory, antimicrobial, antitumoral, antibacterial, as well as neuroleptic and antipsychotic) is very probable, like in the case of phenothiazine derivatives, the result of various molecular mechanisms and of many interaction possibilities between these drugs and different biomolecules (for example, the formation of Cu(II) - from enzymes - charge transfer complexes with phenothiazine derivatives) [1-19].

The study “in vitro” and than “in vivo” of metallic complexes with these drugs could bring important data about their possible action mechanism at the molecular level.

This paper deals with the synthesis and characterization of some new complexes with:

- two aliphatic thioxanthenes: inactive–chlorprothixene (**cptx**) and active-chlorprothixene hydrochloride (**cptxH-Cl**) pharmacological form and
- two piperazinic thioxanthenes: inactive - thiothixene (**ttx**) and active-thiothixene hydrochloride (**ttxH-Cl**) pharmacological form, respectively.

In well established conditions, the following complex compounds have been obtained:  $[\text{CuLX}_2]_2$  (L = 10-(3-dimethylaminopropylidene) thioxanthene, **cptx**; X = Cl<sup>-</sup>, CH<sub>3</sub>COO<sup>-</sup>),  $[\text{ML}_2\text{X}_2]$  (M(II) = Co, Ni, Cu; L = **cptx** or 10/2-(1'-methyl-2'-piperazyl)propylidene-2'-dimethylaminosulphuryl-thioxanthene, **ttx**; X=Cl<sup>-</sup>, CH<sub>3</sub>COO<sup>-</sup>) and  $[\text{ML}^+\text{Cl}_3]$  (M(II) = Ni, Cu; L<sup>+</sup> = **cptxH**, **ttxH**).

The structural formulae of the complexes have been established by means of elemental chemical analysis, electrical conductivity measurements, electronic, epr and FT-IR spectra. The estimation of the electronic densities in MO diagram calculations confirms the coordination manner of the thioxanthene derivatives in good agreement with the experimental data.

## Materials and Methods

### *Syntheses of complexes:*

$[\text{CuLX}_2]_2$  (L = 10-(3-dimethylaminopropylidene) thioxanthene, **cptx**; X= Cl<sup>-</sup>, CH<sub>3</sub>COO<sup>-</sup>) complexes have been prepared at reflux, during five hours, in ethanol of L and CuX<sub>2</sub> (X=Cl<sup>-</sup>, CH<sub>3</sub>COO<sup>-</sup>) in a molar ratio 1:1, when a pale green solution was obtained. After solvent evaporation by heating in a water bath, the obtained solids (dark green for X=Cl<sup>-</sup> and brown for X=CH<sub>3</sub>COO<sup>-</sup>) were filtered, washed with ethanol-water (1:1 mixture) and dried in air. Yield 60-65%.

$[\text{ML}_2\text{X}_2]$  (M(II) = Co, Ni, Cu; L = **cptx** or 10/2-(1'-methyl -2'-piperazyl) propyliden-2'-dimethylaminosulphuryl-thioxanthene, **ttx**; X=Cl<sup>-</sup>, CH<sub>3</sub>COO<sup>-</sup>) complexes have been prepared at reflux (during two hours) in ethanol of L and MX<sub>2</sub> using a molar ratio MX<sub>2</sub> : L = 1:2. Solid compounds – green-brown for M=Co, green for M=Ni and dark brown for M=Cu - are obtained. Yield 75-80%.

$[\text{ML}^+\text{Cl}_3]$  (M = Ni, Cu; L<sup>+</sup> = **cptxH**, **ttx** with HCl) have been isolated by boiling in reflux, during ten hours, of an aqueous slightly acidulated (pH = 3.5-4) solution of MX<sub>2</sub> and an ethanolic solution of L<sup>+</sup>Cl (L<sup>+</sup> = **cpzH**, **tdzH**) in 1:1 molar ratio. After the solvent evaporation in air, the obtained solids were triturated with cold ethanol-diethylether 1:1 mixture and dried in a dessicator on P<sub>4</sub>O<sub>10</sub>. Yield 65-70%.

***Analysis (mass percentages):***

Found for: **(1)** [Cu(cptx)Cl<sub>2</sub>]<sub>2</sub> (Cu<sub>2</sub>C<sub>36</sub>H<sub>46</sub>N<sub>2</sub>S<sub>2</sub>Cl<sub>6</sub>)

Cu 14.53; N 3.85; S 7.45; Cl 24.10

Calcd.

Cu 13.96; N 3.07; S 7.03; Cl 23.07

Found for: **(2)** [Cu(cptx)(CH<sub>3</sub>COO)<sub>3</sub>]<sub>2</sub> (Cu<sub>2</sub>C<sub>40</sub>H<sub>52</sub>N<sub>2</sub>S<sub>2</sub>Cl<sub>2</sub>O<sub>4</sub>)

Cu 15.35; N 3.40; S 7.50; Cl 9.10

Calcd.

Cu 14.33; N 3.16; S 7.22; Cl 8.01

Found for **(3)** [Ni(cptxH)Cl<sub>3</sub>] (NiC<sub>18</sub>H<sub>24</sub>NSCl<sub>4</sub>)

Ni 11.70; N 3.70; S 7.70; Cl 29.90

Calcd.

Ni 11.93; N 2.88; S 6.58; Cl 29.22

Found for : **(4)** [Ni(ttxH)Cl<sub>3</sub>] (NiC<sub>23</sub>H<sub>35</sub>N<sub>3</sub>S<sub>2</sub>Cl<sub>3</sub>O<sub>2</sub>)

Ni 10.10; N 7.95; S 10.80; Cl 18.11

Calcd.

Ni 9.45; N 6.84; S 10.43; Cl 17.28

Found for : **(5)** [Cu(cptxH)Cl<sub>3</sub>] (CuC<sub>18</sub>H<sub>24</sub>NSCl<sub>4</sub>)

Cu 11.10; N 3.95; S 7.20; Cl 30.10

Calcd.

Cu 11.85; N 2.80; S 6.45; Cl 29.15

Found for : **(6)** [Cu(ttxH)Cl<sub>3</sub>] (CuC<sub>23</sub>H<sub>35</sub>N<sub>3</sub>S<sub>2</sub>Cl<sub>3</sub>O<sub>2</sub>)

Cu 11.90; N 7.85; S 11.70; Cl 18.90

Calcd.

Cu 10.25; N 6.78; S 10.34; Cl 17.20

Found for: **(7)** [Co(cptx)<sub>2</sub>Cl<sub>2</sub>] (CoC<sub>36</sub>H<sub>46</sub>N<sub>2</sub>S<sub>2</sub>Cl<sub>4</sub>)

Co 7.84; N 3.89; S 8.72; Cl 19.01

Calcd.

Co 7.53; N 3.64; S 8.31; Cl 18.44

Found for: **(8)** [Ni(cptx)<sub>2</sub>Cl<sub>2</sub>] (NiC<sub>36</sub>H<sub>46</sub>N<sub>2</sub>S<sub>2</sub>Cl<sub>4</sub>)

Ni 7.40; N 3.90; S 8.75; Cl 19.50

Calcd.

Ni 7.55; N 3.65; S 8.32; Cl 18.45

Found for : **(9)** [Cu(cptx)<sub>2</sub>Cl<sub>2</sub>] (CuC<sub>36</sub>H<sub>46</sub>N<sub>2</sub>S<sub>2</sub>Cl<sub>4</sub>)

Cu 6.50; N 3.70; S 9.35; Cl 18.90

Calcd.

Cu 7.45; N 3.50; S 8.25; Cl 18.30

Found for: **(10)** [Co(ttx)<sub>2</sub>Cl<sub>2</sub>] (CoC<sub>46</sub>H<sub>48</sub>N<sub>6</sub>S<sub>4</sub>Cl<sub>2</sub>O<sub>4</sub>)

Co 5.91; N 8.75; S 13.09; Cl 6.84

Calcd.

Co 5.65; N 8.19; S 12.49; Cl 6.53

Found for: **(11)** [Ni(ttx)<sub>2</sub>Cl<sub>2</sub>] (NiC<sub>46</sub>H<sub>68</sub>N<sub>6</sub>S<sub>4</sub>Cl<sub>2</sub>O<sub>4</sub>)

Ni 5.90; N 8.90; S 12.75; Cl 7.16

Calcd.

Ni 5.66; N 8.20; S 12.50; Cl 6.95

Found for : **(12)** [Cu(ttx)<sub>2</sub>Cl<sub>2</sub>] (CoC<sub>46</sub>H<sub>48</sub>N<sub>6</sub>S<sub>4</sub>Cl<sub>2</sub>O<sub>4</sub>)

Cu 5.81; N 8.56; S 12.89; Cl 7.09

Calcd.

Cu 5.60; N 8.15; S 12.45; Cl 6.85

Found for: **(13)** [Co(cptx)<sub>2</sub>(CH<sub>3</sub>COO)<sub>2</sub>] (CoC<sub>40</sub>H<sub>52</sub>N<sub>2</sub>S<sub>2</sub>O<sub>4</sub>)

Co 6.30; N 3.90; S 9.60

Calcd.

Co 7.75; N 3.75; S 8.58

Found for : **(14)** [Ni(cptx)<sub>2</sub>(CH<sub>3</sub>COO)<sub>2</sub>] (NiC<sub>40</sub>H<sub>52</sub>N<sub>2</sub>S<sub>2</sub>O<sub>4</sub>)

Ni 7.70; N 4.10; S 9.05

Calcd.

Ni 7.74; N 3.74; S 8.57

Found for: **(15)** [Cu(cptx)<sub>2</sub>(CH<sub>3</sub>COO)<sub>2</sub>] (CuC<sub>40</sub>H<sub>52</sub>N<sub>2</sub>S<sub>2</sub>O<sub>4</sub>)

Cu 8.35; N 4.90; S 9.50

Calcd.

Cu 7.70; N 3.71; S 8.52

Found for **(16)** [Co(ttx)<sub>2</sub>(CH<sub>3</sub>COO)<sub>2</sub>] (CoC<sub>50</sub>H<sub>74</sub>N<sub>6</sub>S<sub>4</sub>O<sub>8</sub>)

Co 6.10; N 7.80; S 11.55

Calcd.

Co 5.41; N 7.83; S 11.94

Found for **(17)** [Ni(ttx)<sub>2</sub>(CH<sub>3</sub>COO)<sub>2</sub>] (NiC<sub>50</sub>H<sub>74</sub>N<sub>6</sub>S<sub>4</sub>O<sub>8</sub>)

Ni 6.10; N 8.10; S 12.90

Calcd.

Ni 5.40; N 7.82; S 11.93

Found for (18)  $[\text{Cu}(\text{ttx})_2(\text{CH}_3\text{COO})_2]$  ( $\text{CuC}_{50}\text{H}_{74}\text{N}_6\text{S}_4\text{O}_8$ )

Cu 6.40; N 7.95; S 11.90

Calcd.

Cu 5.35; N 7.77; S 11.85

*Electronic spectra* have been recorded at room temperature on a VSU-2G spectrophotometer using MgO as standard sample.

*EPR spectra* were registered on polycrystalline powders by using a spectrophotometer of the type ART-IFIN Bucharest in the 9000 MHz frequency ranges with a magnetic field modulation of 100 kHz.

*Molar electrical conductivities* were recorded in DMF solutions at 25<sup>0</sup>C, with an OK 102/1 Radelkis Conductometer with a 0.1 S – 0.5 S measuring range.

*FT-IR spectra* have been recorded with a Perkin-Elmer spectrophotometer using KBr pellets as reference.

## Results and Discussion

Three general types of M(II) complexes with studied thioxanthene derivatives (L and L<sup>+</sup>) have been isolated: two types corresponding to the M:L molar ratio of 1:1 and one type corresponding to the M:L molar ratio of 1:2.

The proposed formulae are supported by elemental chemical data and molar conductivity measurements, all complex compounds being of nonelectrolyte type (**Table 1**).

The electronic spectra of all Cu(II) – thioxanthene derivatives (L and L<sup>+</sup>) present a large, asymmetric band in visible range (600-780 nm) that suggest a strong distorted tetrahedral up to square planar geometry of the complexes (Jahn-Teller effect and nonequivalency of the ligands). In all synthesized complexes the maximum coordination number is four, very probable due to the bulk ligands used [20].

The electronic spectra of Ni(II) complexes show two bands (one in near UV at 410 nm and another in Vis at 610 nm) characteristic to square planar geometry.

The aspect of electronic spectra of Co(II) complex compounds is also characteristic to a strongly distorted tetrahedral configuration.

Supplementary informations about the stereochemistry of the complexes have been obtained from epr spectra of Cu(II) complexes.  $[\text{CuLX}_2]_2$  complexes are slightly

paramagnetic due to of a partial compensation of Cu(II) ( $d^9$ ) electronic spins (the compensation of Cu(II) electronic spins in the dinuclear complexes is not total, due to the large distance between Cu(II) ions).

The  $[\text{CuL}^+\text{X}_3]$  complexes present an epr signal with different values of  $g$  parameters, characteristic to the strongly distorted configurations.

In order to obtain more information about the complexes, the FT-IR spectra has been recorded particularly, to confirm our suppositions regarding the coordination manner of the thioxanthene derivatives and of the anions  $\text{Cl}^-$  and  $\text{CH}_3\text{COO}^-$ . For comparison, the IR spectra of the free ligands (chlorprothixene and thiothixene) have also been registered; characteristic frequencies of the C-heterocyclic S (at  $670\text{ cm}^{-1}$  and  $750\text{ cm}^{-1}$ ) and N- $\text{CH}_3$  (at  $2810\text{ cm}^{-1}$ ) were observed (**Table 2**).

The most important conclusions [21] from the IR spectra of the isolated complexes were:

- in the spectra of  $[\text{CuLX}_2]_2$  ( $\text{L} = \text{cptx}; \text{X} = \text{Cl}^-, \text{CH}_3\text{COO}^-$ ) complexes, the shifting of the C-heterocyclic S and of the N- $\text{CH}_3$  frequencies to lower values ( $640\text{ cm}^{-1}$ ,  $705\text{ cm}^{-1}$  and  $2790\text{ cm}^{-1}$ , respectively) is a consequence of L coordination as a bidentate ligand, through endocyclic sulphur and amine nitrogen from the side chain;
- the frequency of the carboxyl group ( $\nu_{\text{as}(\text{OCO})}$ ) from the spectrum of  $[\text{Cu}(\text{cptx})(\text{CH}_3\text{COO})_2]_2$  complex is obscured by some specific bands of the thioxanthene derivatives, but  $\nu_{\text{s}(\text{OCO})}$  occurs at  $1610\text{ cm}^{-1}$  as a well defined, sharp and intense band indicating the coordination of  $\text{CH}_3\text{COO}^-$  ion;
- in the spectra of  $[\text{ML}_2\text{X}_2]$  ( $\text{L} = \text{cptx}, \text{ttx}; \text{X} = \text{Cl}^-, \text{CH}_3\text{COO}^-$ ) complexes, the N- $\text{CH}_3$  group frequency occurs at the same value as in the spectrum of free ligands indicating a monodentate coordination of the ligand through endocyclic sulphur;
- in the spectra of  $[\text{ML}^+\text{X}_3]$  ( $\text{L}^+ = \text{cptxH}, \text{ttzH}; \text{X} = \text{Cl}^-$ ) complexes, the C-cyclicS frequency is shifted to lower value as a consequence of monodentate coordination of the ligands, through endocyclic sulphur;
- specific frequencies of the Cu-N, Cu-S and respectively Cu-Cl occur in the far IR range [21].

The estimation of the electronic densities in MO diagram calculations confirm our experimental data and supposition referring at the structural formulae of the studied complexes. In **Figure 1** are presented the proposed structural formulas for complexes of inactive and active pharmacological forms of the studied thioxanthene derivatives.

In the  $[\text{ML}^+\text{X}_3]$  complexes, intramolecular hydrogen bonding between the negative center,  $\text{MX}_3^-$  and the positive part of quaternary ammonium of the ligands is possible to form.

## Conclusions

Three general types of M(II) complexes with thioxanthene derivatives in their inactive (L) and active (L+Cl<sup>-</sup>) pharmaceutical forms have been obtained:

- [CuLX<sub>2</sub>]<sub>2</sub> (L = cplx; X=Cl<sup>-</sup>, CH<sub>3</sub>COO<sup>-</sup>)
- [ML<sub>2</sub>X<sub>2</sub>] (M(II) = Co, Ni, Cu; L = cplx, ttx; X=Cl<sup>-</sup>, CH<sub>3</sub>COO<sup>-</sup>) and
- [ML+X<sub>3</sub>] (M(II) = Ni, Cu; L+ = cplxH, ttxH; X=Cl<sup>-</sup>).

The ligands in inactive pharmaceutical form act as bidentate (through endocyclic sulphur and amine nitrogen from the side chain of thioxanthene derivatives) forming bridges in dimeric complexes or as monodentate (through endocyclic sulphur of thioxanthene) in monomeric complexes. The active pharmaceutical forms coordinate as positively, monodentate (through endocyclic sulphur) ligands. The estimation of the electronic densities in MO calculations supports the suppositions about the structure of complexes.

The formation of such complexes may be the support of a possible action mechanism of the thioxanthene drugs in Wilson's disease.

At the substantia nigra level, Cu (II) in excess probably blocks the D<sub>2</sub>-dopaminergic receptors (D<sub>2</sub>R) obstructing dopamine's action and causing extrapyramidal parkinson-like symptoms.

The unattached to the D<sub>2</sub>R dopamine reaches in excess at the mesolimbic and mesocortical nuclei (uninvolved in Wilson's disease) causing schizophrenia-like symptoms:

D<sub>2</sub>R-Dopamine + Cu(II) ® D<sub>2</sub>R-Cu + Dopamine  
The administrated neuroleptics (for example, cplxH, in this paper) have the ability to bind copper, liberating the D<sub>2</sub>R:

D<sub>2</sub>R-Cu + (neuroleptic cplxH) ® D<sub>2</sub>R + Cu-cplxH

Also, at the mesolimbic and mesocortical level, the Cu (II)-cplxH complex, due to its geometry (the unsaturated coordination of Cu(II)) binds to the D<sub>2</sub>R, thus blocking the action of dopamine in excess.

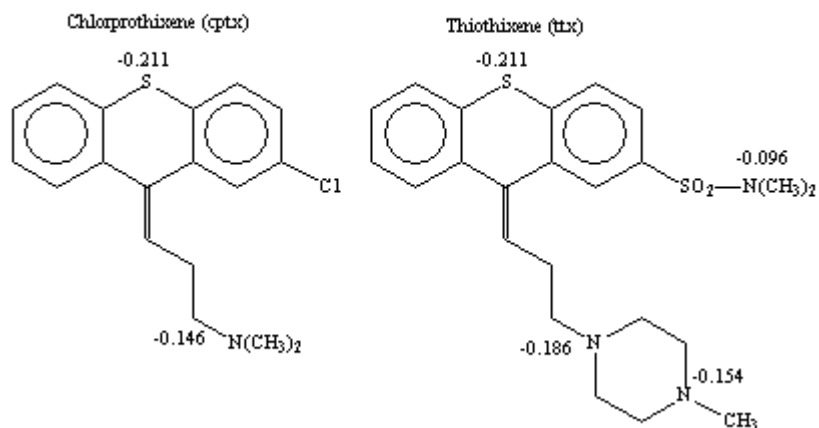
The binding of the Cu(II)-thioxanthene complex to the D<sub>2</sub>R can be explained by the affinity of thioxanthene derivatives to this type of receptors and by the Cu(II) unsaturated coordination in complexes formed by this cation with this type of drug.



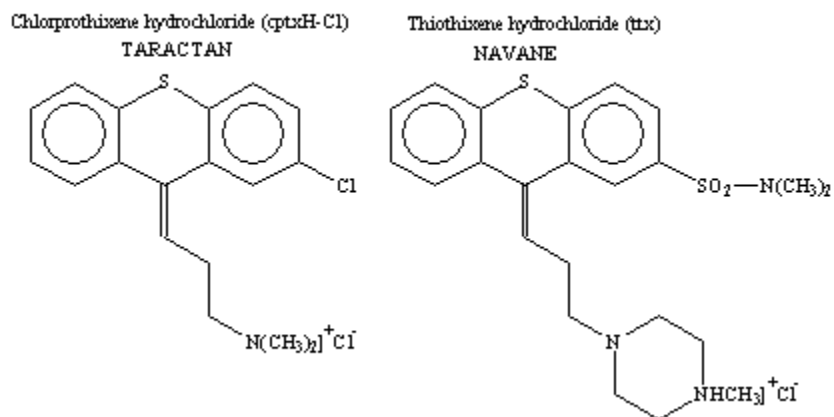
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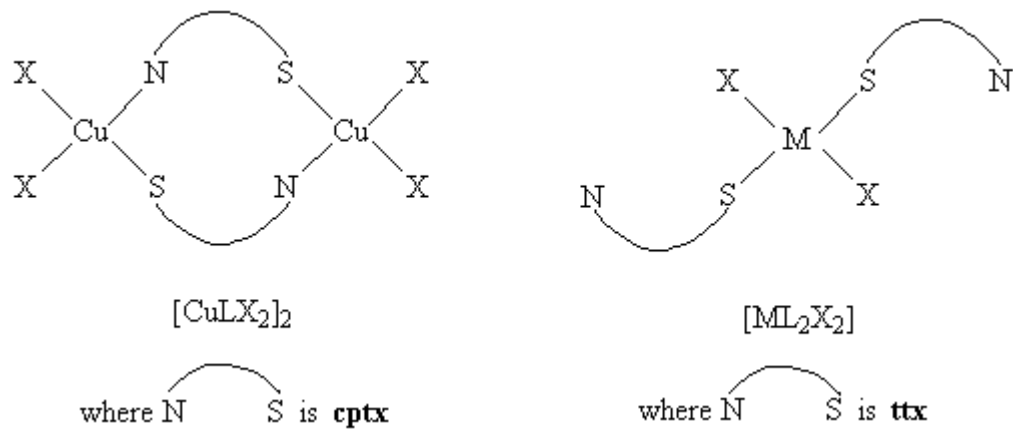
### Inactive pharmacological forms



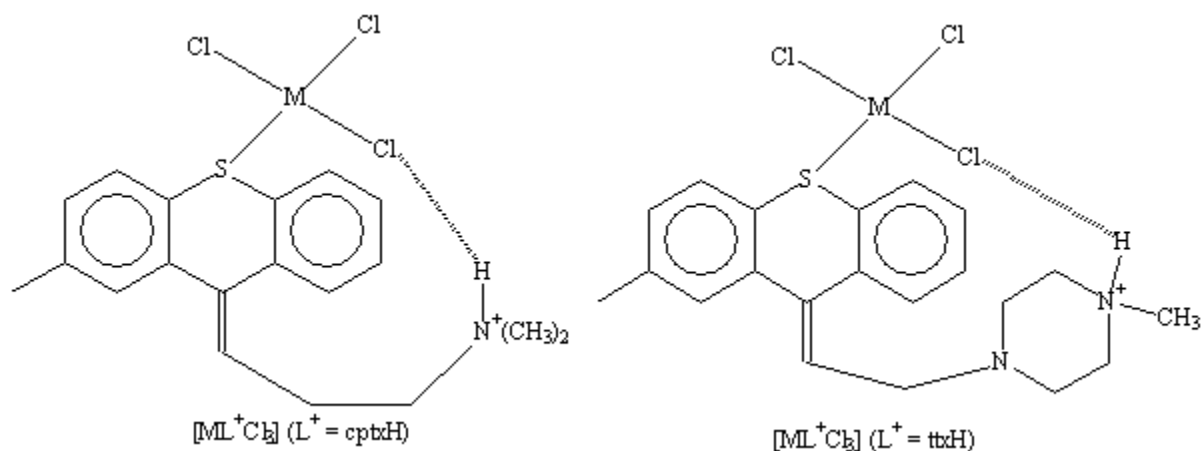
### Active pharmacological forms



### Coordination of inactive forms



## Coordination of active forms



**Figure 1.** Structural proposed formulae of the isolated complexes.

**Table 1.** Molar conductivity and data of electronic and epr spectra.

Complex compound	Conductivity ( $\square S cm^2 mol^{-1}$ )	Electronic spectra $\square$ (nm)	Epr spectra
(1)	29.30	700-760	
(2)	30.10	680-730	
(3)	25.15	410 (a1g $\square$ b1g) 610 (b2g $\square$ b1g)	-
(5)	28.30	700-750	gII = 2.040 g $\square$ = 2.190
(6)	25.70	690-740	gII = 2.050 g $\square$ = 2.195
(8)	30.10	380 620	-
(10)	30.20	480 720	-
(11)	29.50	700-760	gII = 2.060 g $\square$ = 2.210

**Table 2.** IR characteristic frequencies of the studied complexes.

Compound	$\square$ C-Scyclic	$\square$ CN (NCH <sub>3</sub> )	$\square$ as.s (OCO)	$\square$ Cu-N	$\square$ Cu-S	$\square$ N-CH <sub>3</sub>
<b>L=cptx</b>	670	1080	-	-	-	2810
	750	1210				
<b>(1)</b>	640	1020	-	385	350	2790
	705	1170				
<b>(2)</b>	640	1030	1600	390	320	2750
	700	1185	1380			
<b>(7)</b>	635	1080	-	-	330	2810
	705	1205				
<b>L<sup>+</sup>=cptxH</b>	870	1060	-	-	-	2810
	750	1200				
<b>(5)</b>	640	1060	-	-	325	2810
	700	1200			330	
<b>L=ttx</b>	680	1020	-	-	-	2800
	740	1170				
<b>(9)</b>	620	1020	-	-	330	2800
	690	1170			345	
<b>(16)</b>	630	1020	1595	-	325	2810
	700	1180	1380		333	
<b>L<sup>+</sup>=ttxH</b>	680	1020	-	-	-	2810
	750	1170				
<b>(6)</b>	620	1020	-	380	320	2810
	700	1170			335	