Review

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From Chemistry to Biology: Furanic Complexes as Samples

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Abstract: In order to demonstrate the links between chemistry and biology, some biological properties of a few furanic compounds have been described, starting from the synthesis and the structural characteristics. Also some features of the furan compounds with oximes; semicarbazones and thiosemicarbazones have been pointed out.

Keywords: furanic campounds, structure, biological properties.

Introduction

Chemistry is a very general word covering many very large areas, organic chemistry, inorganic chemistry, biochemistry and also several scales from micrograms to many thousand tons.

Many chemistry laboratories try to connect chemistry and biology, mainly in pharmaceutical plants and laboratories. The purpose of this review is to describe some links between chemistry and biology. Starting from the synthesis and the structural characterisation of some furanic compounds, we describe some biological properties. There is an evidence for any chemist working in Pharmacy faculty to test new synthesised compounds for their biological properties.

Chemistry. Among furan compounds, derivatives of aldehydes or ketones were widely described. In this review, we point out some features with oximes, semicarbazones and thiosemicarbazones obtained with simple furan aldehydes: 2-furfural, 3-furfural, (furyl-2)-3 prop 2-enal (or furylacrolein). The synthesis of these compounds is very easy.

Only one molecule has been studied as a ligand: 2-furfuraldoxime (Bouet, 1986; Gupta and Bhat, 1979a & b, 1978, 1977; Sen and Pickerell, 1973). So, it was possible to prepare new oximes as well as semicarbazones and thiosemicarbazones. If we look at the furan cycle (Fig. 1), we note the presence of four hydrogen atoms, which could be readily substituted by various groups. It is well known that only the 2 and 5 positions are sufficiently reactive to accept substitution and attach alkyl or nitro groups for instance. Some derivatives with substituents in position 3 are known.

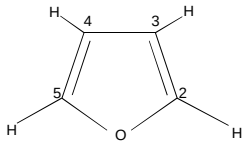
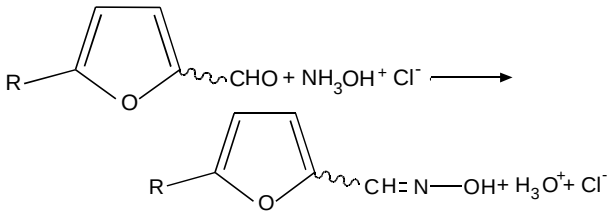


Fig. 1. Furan ring.

Synthesis and characterisation of the ligands. All compounds were characterised using usual structural techniques: infrared and UV-visible spectroscopies, NMR, X-ray diffractions.

Oximes. In the case of oximes the preparation was first described by Brady and Goldstein(1927): the aldehyde is allowed to stand with hydroxylammonium chloride (stoichiometric amounts) and sodium acetate in a mixture of ethanol and methanol (Scheme 1, Table 1).



Scheme 1

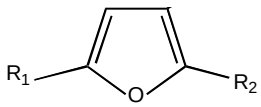


Table 1. Furanic oximes as ligands (Khan *et al*.,1991; Bouet *et al*., 1990; Bouet and Dugue, 1989; Bouet, 1986; Bouet and Jolivet, 1981)

R_1	R_2	Abbreviation
H	CH=N-OH	2-FDH
CH_3	CH=N-OH	M5FDH
C_2H_5	CH=N-OH	E5FDH
NO_2	CH=N-OH	5-NO_2FDH
H	CH=CH=N-OH	FAOH
CH_3	CH=CH=N-OH	M5FAOH

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2-furfuraldoxime mainly presents *E* form because of the presence of hydrogen bonding (Khan, *et al.*, 1991; Bouet and Dugué, 1990). The coordination of metal cations involves the break of this bond.

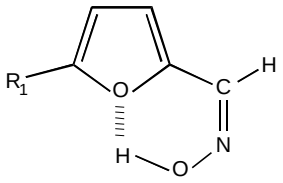
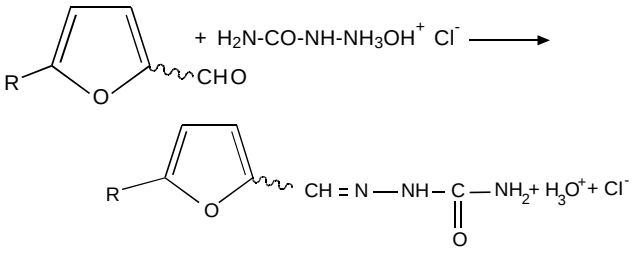


Fig. 2. Hydrogen bonding in furanic oximes.

Semicarbazones. The semicarbazones were prepared in a similar way with semicarbazidium chloride and aldehydes (Ibrahim *et al.*, 1999, 1997) (Scheme 2, Table 2).



Scheme 2

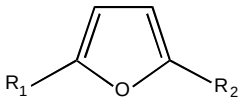
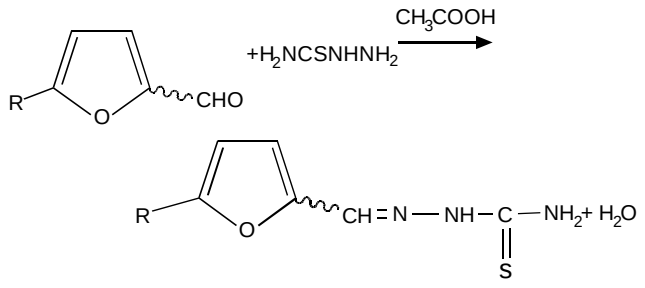


Table 2. Furanic semicarbazones as ligands

R_1	R_2	Abbreviation
H	CH=N-NH-CO-NH_2	FSC
CH_3	CH=N-NH-CO-NH_2	M5FSC
H	CH=N-NH-CO-NH-C_6H_5	FPSC
H	CH=CH-CH=N-NH-CO-NH_2	FASC

Thiosemicarbazones. In the case of thiosemicarbazones, the reaction was made with aldehydes and thiosemicarbazide in the presence of pure acetic acid (Jouad *et al.*, 2001) (Scheme 3).



Scheme 3

The ligands are summarised in Table 3.

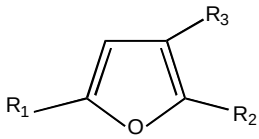


Table 3. Furanic thiosemicarbazones as ligands

R_1	R_2	R_3	Abbreviation
H	CH=N-NH-CS-NH_2	H	FTSC
CH_3	CH=N-NH-CS-NH_2	H	MFTCS
H	H	CH=N-NH-CS-NH_2	3FTSC
H	CH=CH-CH= N-NH-CS-NH_2	H	FATSC

All the structures of these ligands present some identical properties and the crystallographic data allow us to note some important points about their structures:

- All the ligands are quite planar as shown in Fig. 3, except FATSC.
- The configuration around C_1-N_2 bond is an *E*-configuration.
- Consequently a hydrogen bond occurs between N_3 and terminal NH_2, stabilising the structure.

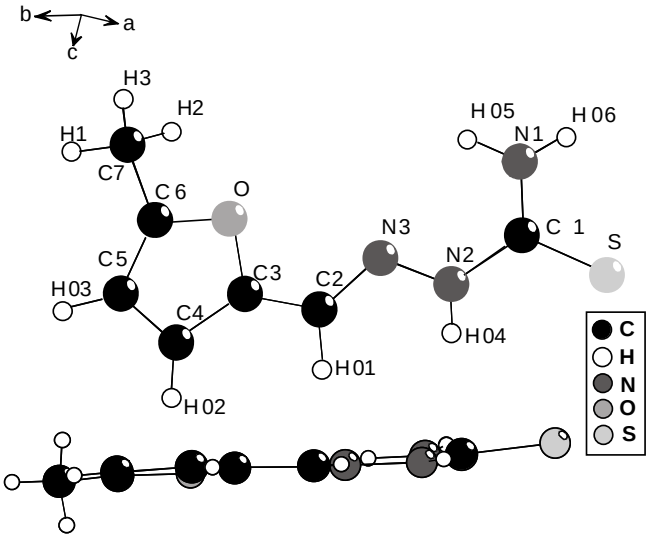
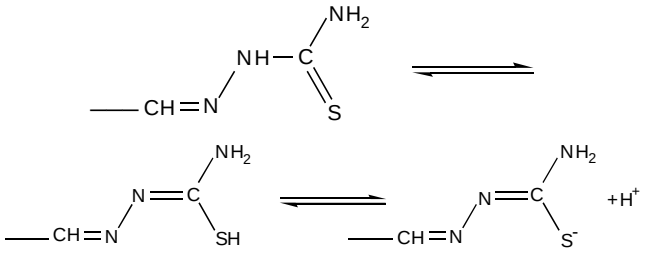


Fig. 3. Structure of 5-methylfurfural thiosemicarbazone (MFTSC).

- In the thiosemicarbazone moiety, the bond distances are typical of single bonds with partial double bond characters, showing π electrons delocalisation along this system. This is typical of a thione-thiol equilibrium (Tian *et al.*, 1997). We note that a deprotonation may occur leading to thiolate anion (Scheme 4).



Scheme 4

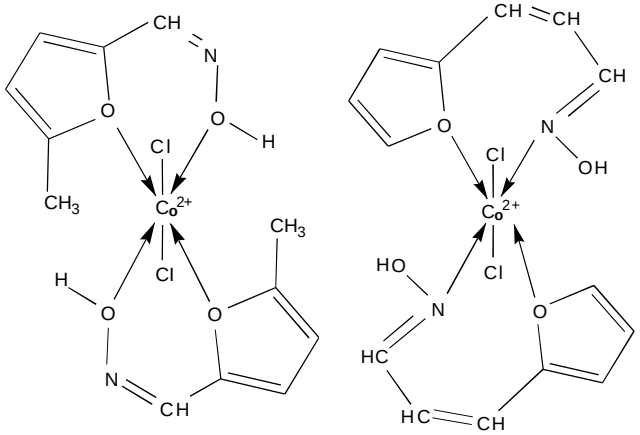
Synthesis and characterisation of complexes. The general synthetic pathway to obtain the metal complexes consists in reacting stoichiometric amounts mainly in ethanol. They were characterised using elemental analysis, conductivity, magnetic moments and infrared spectroscopy, UV-visible spectroscopy, NMR (diamagnetic species) and X-rays diffraction.

Oximes complexes. In the case of oximes ligands, it is possible to obtain two series of complex compounds according to the temperature. When reacting in refluxing ethanol, the complexes $[ML_2X_2]$ are obtained; when the reaction took place at 4 °C, $[ML_4X_2]$ compounds are formed. The structures are the followings:

- $[ML_2X_2]$ complexes coordinate through O-ring and O-oxime atoms when the side chain is short;
- $[ML_2X_2]$ species with 3 C atoms are bounded using O-ring atom and N-oxime atoms;
- finally, all the complexes with 4 organic ligands $[ML_4X_2]$ coordinate through N-oxime atom.

To illustrate these coordination modes, two structures of cobalt(II) complexes are given in Fig. 4.

The structures of two $[ML_4X_2]$ cobalt complexes have been determined using X-ray diffraction (Bouet and Dugué ,1990).



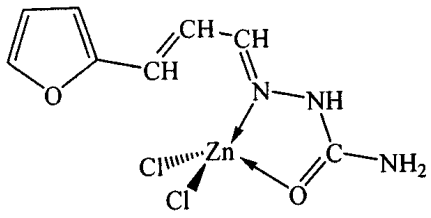
$[Co(M5FDH)_2Cl_2]$

Fig. 4. Cobalt (II) complexes with oximes.

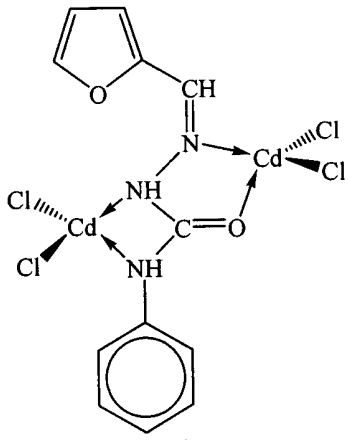
The molecules are quite identical. The cobalt ion, in an octahedral geometry, is located at the symmetry centre of the P1 group and there are only two independent ligands.

We have synthesised and characterised a complete series (Bouet,1986) of cadmium (II) species using NMR spectroscopy as they are diamagnetic compounds.

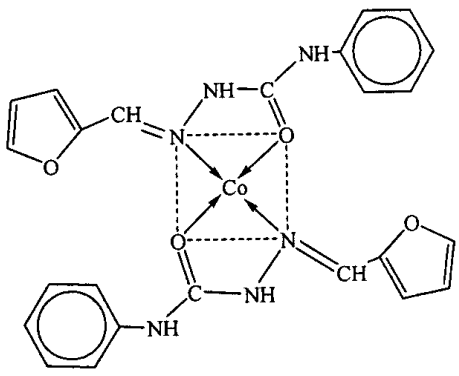
Semicarbazones complexes. For semicarbazones, there are five atoms bearing electronic pairs, owing to give coordination bonds: 3 N from semicarbazone moiety, one oxygen atom belonging to keto group and finally the O in the ring (Fig. 5). The terminal NH_2 may be one of the coordination sites. If a phenyl



$[ZnCl_2(FASC)]$



$[CdCl_2(FASC)]$



$[CoCl_2(FASC)_2]$

Fig. 5. Semicarbazones complexes structures.

ring substitutes this functional group, steric hindrance may eventually prevent from coordination bonding. That is why we have prepared the ligand FPSC, with a phenyl ring. We have prepared three series of complexes according to the coordinating atoms.

In all compounds we remark an octahedral arrangement around the central ion. But Zn(II) and Cd(II) complexes (d^{10}) exhibit a typical tetrahedral geometry. As you can see, there are many coordination modes according to the length of the side chain. We note that the substituting group in 5 does not modify the coordinating atoms.

Some cell parameters were calculated from powder diffraction patterns in the case of complexes deriving from furylacrolein semicarbazone (Table 4). All determinations show a triclinic unit cell.

Table 4. Cell parameters: furylacrolein semicarbazone complexes

Compound	a (Å)	b (Å)	c (Å)	α (°)	β(°)	γ(°)	V (Å^3)
$[CoCl_2(FASC)_2]$	16.23	13.56	11.96	125	130	82	1514
$[CoBr_2(FASC)_2]$	11.36	8.48	9.33	84	93	113	821
$[NiCl_2(FASC)_2]$	12.31	7.67	8.47	69	120	110	632
$[NiBr_2(FASC)_2]$	11.99	8.22	6.32	105	95	116	523
$[CuCl_2(FASC)_2]$	13.05	11.98	6.78	83	92	111	982
$[CuBr_2(FASC)_2]$	12.38	12.58	7.22	107	87	113	987
$[CdCl_2(FASC)]$	13.02	12.38	8.03	75	101	117	1111

Thiosemicarbazones complexes. We have obtained a large variety of complexes with thiosemicarbazones and some structures are given.

This complex (Fig. 6), with a square planar geometry, shows that the thiolate form is involved in this case. You can also see that the configuration around C_1-N_2 bond is now a *Z*-configuration.

This second one (Fig. 7), with copper in a tetrahedral geometry, is obtained through thiol and not thiolate.

- This neutral species show a square-planar geometry around copper (II) ion.
- In this last example (Fig. 8), 2 DMF molecules (because DMF was the recrystallization solvent) are inserted in the structure in which the four coordinating atoms are in a square planar arrangement and the molecule is neutral (Fig. 8)

Besides these various behaviours, some common features should be pointed out:

- In all the complexes the ligand are bidentate.
- In every case, the coordinating atoms are S (protonated or not) and N (imine).
- A 180° rotation around C_1-N_2 bond occurs and consequently the initial E-configuration around C_1-N_2 becomes a *Z*-configuration.

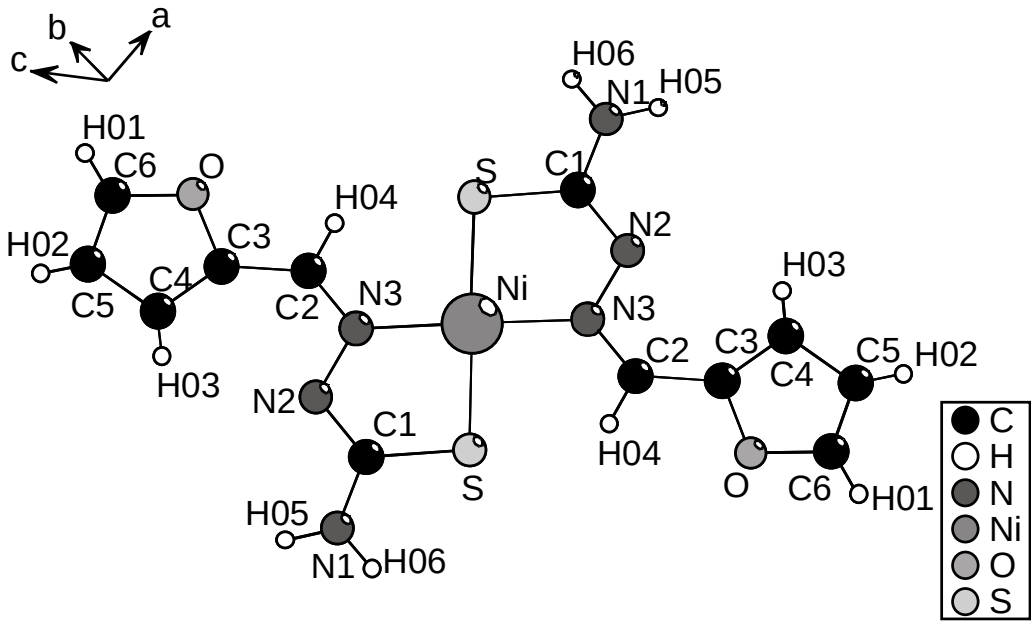
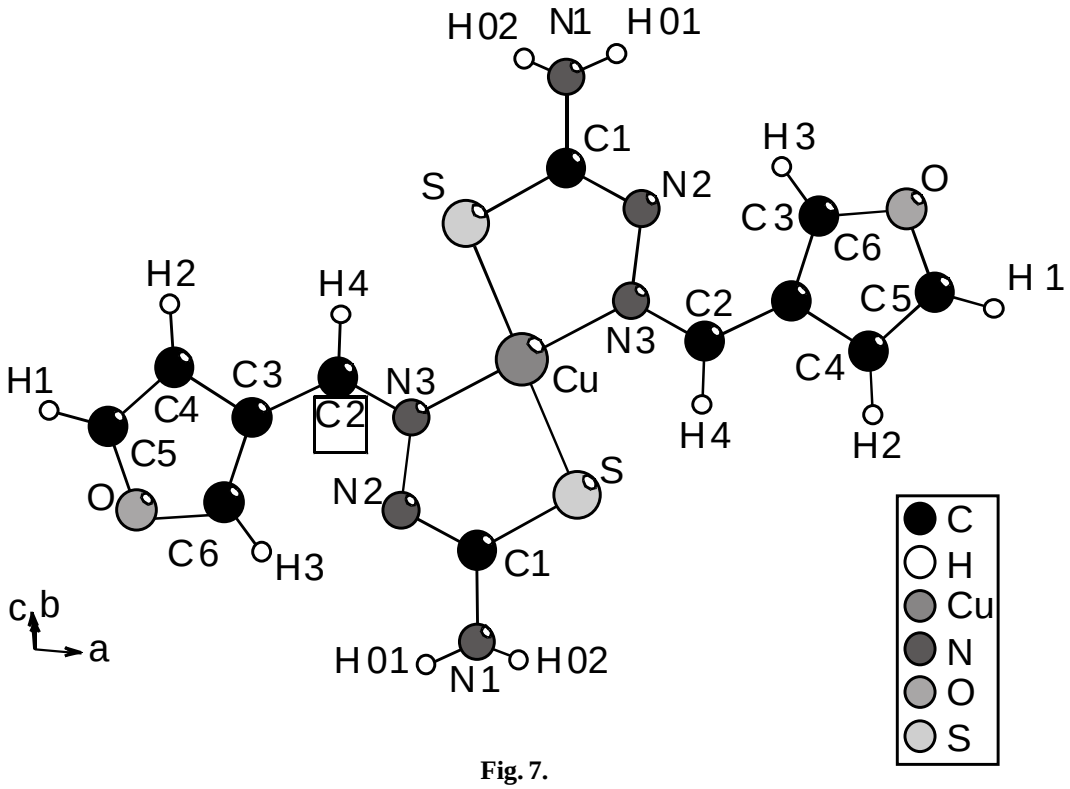


Fig. 6.


H02
N1
H01
C1
H3
S
N2
O
C3
C6
H2
H4
C2
C5
H1
N3
C4
H1
C3
N3
Cu
C4
C2
H4
H2
C5
S
O
N2
C6
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c
b
a
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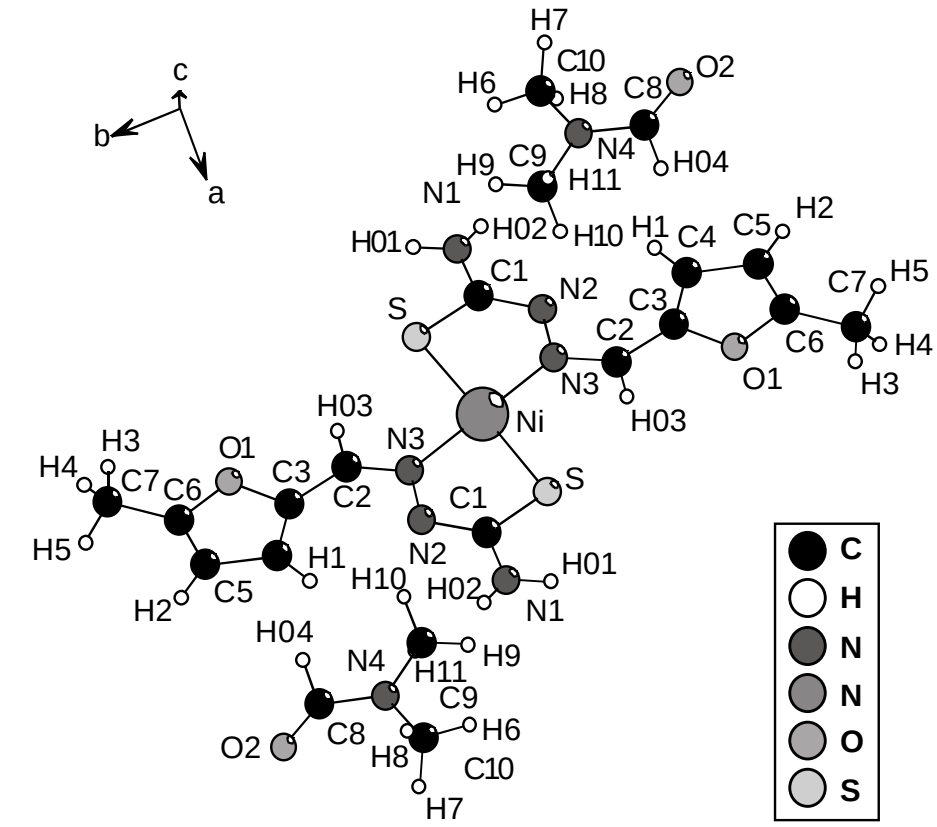
N1
H02
C
H
Cu
N
O
S

Fig. 7.


H7
C10
H6
H8
C8
O2
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N4
H9
C9
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H10
H1
C4
C5
H2
C1
N2
C7
H5
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H04
N4
H9
H11
C9
C8
H6
O2
H8
C10
H7
C
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N
N
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Fig. 8.

Complexes stability. The stability constants of some complexes (Table 5) have been determined in ethanolic solution at 25 °C, using microcalorimetry (Bouet *et al.,* 1989) or spectrophotometric determination (Jouad *et al.,* 2007). These compounds are relatively stable in these experimental conditions. It was not possible to point out a direct relation between the nature of the ligand and the complex structure, but in any case, we have noted that the stability (Khan, *et al.,* 1997, 1996) followed the well-known Irving - Williams series.

Table 5. Stability constants in ethanol at 25 °C

Complex	Method	M/L	Constant(s)
$[CoCl_2(FAOH)_2]$	Microcalorimetry	1 :2	$K_1 = 15$
			$K_2 = 125$
$[CoCl_2(2\text{-FDH})]$	UV-vis	1 :1	$K_1 = 12$
$[CoCl_2(3\text{-FDH})]$	UV-vis	1 :1	$K_1 = 125$
$[CuCl_2(FASC)]$	UV-vis	1 :1	$K_1 = 38200$
$[CuCl_2(FPSC)]$	UV-vis	1 :1	$K_1 = 33100$
$[CuCl_2(FTSC)_2]$	UV-vis	1 :2	$\beta_2 = 89$
$[CuCl_2(3FTSC)_2]$	UV-vis	1 :2	$\beta_2 = 32360$
$[CuCl_2(FATSC)]$	UV-vis	1 :1	$K_1 = 44$

Biological studies. Many simple biological tests could be performed with: antifungal, antibacterial, cytotoxicity.... and, in the mean time, it is possible to explore the chronobiology, i.e. the modifications of the observed effects along time e.g. (one day, one week, one month, one year) Bjarnason (1995), Reinberg (1976), Reinberg and Halberg (1971). In this review, we describe some biological properties without taking into account the chronobiology. We have studied fungicidal properties, cytotoxic or antitumor effects on cultured cells and toxicity in mice.

Fungicidal tests. The fungicidal tests were performed with thiosemicarbazones complexes. The spectrophotometric MIC (minimum inhibitory concentration) endpoint was calculated from the turbidimetric data as the lowest drug concentration giving rise to an inhibition of growth equal to or greater than 80% of that of the drug-free control. In this study, the fungitoxicity of $[NiCl_2(M5HFTSC)_2]$ and $[CuCl_2(M5HFTSC)]$ complexes has been evaluated against two important human pathogen fungi: the filamentous *Aspergillus fumigatus* and the yeast *Candida albicans* (Table 6). In contrast to a previous study with furfuraldehyde thiosemicarbazone, no antifungal activity for the ligand was found. However, it was observed that after complex formation with nickel and copper, the combined activities were not modified in comparison to the activities of free metals.

Table 6. Antifungal activity of some furanic complexes

Compounds	Antifungal activity MIC_{80} values (µg/ml)	
	A. fumigatus	*C. albicans*
Amphotericin B	8	1
M5FTSC	125	>250
$CuCl_2.2\,H_2O$	8	250
$[CuCl_2(M5FTSC)]$	13	32
$NiCl_2, 6\,H_2O$	125	16
$[NiCl_2(M5FTSC)]$	>250	16

Toxicity tests. We have also performed some *in-vivo* assays. These experiments are useful in determining the toxicity of the complex molecules. As indicated above, the toxicity depends upon the time: e.g. some compounds could be less toxic in autumn than in spring and this change occurs for some of our biologic studies about some semicarbazones for instance (Jamali *et al.,* 1998).

The toxicity of the complex $[NiCl_2(M5FTSC)_2]$ was tested in male Swiss mice (Jouad *et al.,* 2002). The effect of this compound was compared to the effects of the vehicle (aqueous NaCl, 9 g/l), of the metal salt $NiCl_2$ and of the ligand alone. The main results in autumn are given in Table 7. Male rodents are chosen because of their weight gain and the absence in oestral cycle with changes in hormonal status which could lead to errors in *in-vivo* experiments (Laroche and Rousselet, 1990). The animals received one dose by intraperitoneal injection and the number of living mice was determined 7 days after the

Table 7. Toxicity of $[NiCl_2(M5FTSC)_2]$ in male Swiss mice

Doses (mmol/kg)[a]	Living animals	
Control	10	
2.75	10	
5.45	10	LD_0
6.80	7	LD_{30}
8.15	5	LD_{50}
10.90	2	LD_{80}
12.50	0	LD_{100}
16.00	0	

[a] = kg body weight

injection (Table 7). These experiments allow to determine lethal doses (e.g.: LD_{50} is the dose killing 50% of the animals after 7 days).

Conclusion

In this short review, we have described synthesis of some metallic complexes together with a few biologic results obtained from some metallic complexes. Many other experiments could be performed but in many cases the choice is linked to opportunities. Among several assays, it is a great challenge to test new molecules for cancer or AIDS treatment.

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