ANTI-INFECTIVE AND ANTI-TUMOR ACTIVITY OF SOME METAL COMPLEXES (M^{II}-M^{IV}) WITH SCHIFF BASES

PROFESSIONAL PAPER

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ABSTRACT

Research and application of metal complexes of ruthenium, platinum, palladium and other d-block elements has been popular in recent time because the complexes of said metals with a wide range of organic ligands shown to be extremely efficient in the treatment of infectious and malignant diseases. In addition to platinum used long time as Cisplatin, Carboplatin and oxaplatin, new generation of anticancer complexes in their structure containe mainly Ru(II) and Ru(III). In the synthesis of anti-infective and anti-tumor drugs, emphasis is indicated on their cytotoxicity. Specifically, the aim is that the new anti-infective and anti-tumor agent does not damage healthy cells and affects only malignant cells or infectious agents.
In this paper we make reference on some recent and significant researches in the field of inorganic synthesis of metal complexes with strong anti-tumor and anti-infective properties. Special emphasis is placed on the Schiff bases as organic ligands which are specially used in the synthesis of such agents.

Keywords: metal complex, antimicrobial activity, organic ligands, in vitro

INTRODUCTION

Schiff bases are formed when any primary amine reacts with an aldehyde or a ketone under specific conditions[1].The general reaction of forming Schiff base is shown in Figure 1.The stability of Schiff base varies depending on the substituents on the amine or carbonyl group. Some Schiff bases undergo to hydrolyse, so it is necessary to continuously remove water that is formed during the reaction[2]. It is observed that Schiff bases from the aldehydes are formed much easier than Schiff bases from the corresponding ketones, which is to be expected due to the higher reactivity of aldehydes compared to ketones, and due to their lower steric hindrance. It is also known that Schiff bases with an aromatic substituents, as in the carbonyl and in the amine, are much stable[2].
One of the interesting ability of Schiff bases is their ability to act as ligands of coordination compounds (mono-, di-, tri-, and tetradentate), followed by deprotonation
of the Schiff base. These compounds are usually prepared by coordination with a metal acetates which easily deprotonate imines forming acetic acid[2,3].Biological activities of Schiff bases is reflected in the antibacterial, antifungal and antitumor activity. Some transition metal complexes of Schiff's bases,whichare biologically active and have antibacterial activity, are used as radiopharmaceutical agent, system models of biological macromolecules and as transporters of molecular oxygen[4].

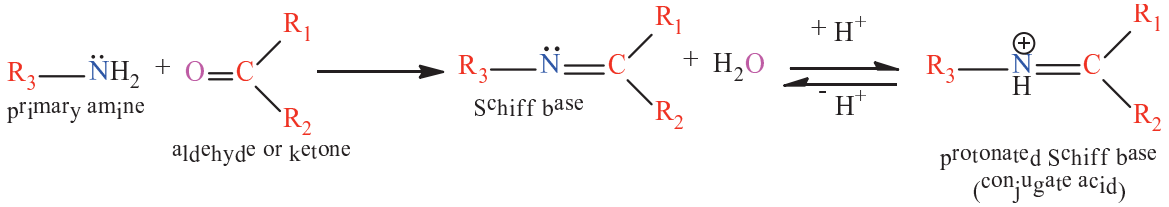

Figure 1. The general reaction of forming Schiff base

Complex with anti-infective properties

Metal complexes of Schiff base derived from 2-thiophene carboxaldehyde and 2-aminobenzoic acid (HL) and Fe(III) or Co(II) or Ni(II) or UO_2(II) showed good antibacterial activity against *Escherichia coli*, *Pseudomonas aeruginosa* and *Staphylococcus pyogenes*. Fe(III), Cu(II), Zn(II) and UO_2(II) complexes caused inhibition for E. coli. The importance of this lies in the fact that these complexes could be applied fairly in the treatment of some common diseases caused by *E. coli*. However, Fe(III), Co(II), Cu(II), Zn(II) and UO_2(II) complexes were specialized in inhibiting Gram-positive bacterial strains (*Staphylococcus pyogenes* and *P. aeruginosa*)[1].Four Platinum(II) Schiff bases complexes containing of salicylaldehyde and 2-furaldehyde with o- and p-phenylenediamine were reported as antibacterial against *E. coli*, *Bacillus subtilis*, *P. aeruginosa*, *Staphylococcus aureus*. The activity data show that the platinum(II) complexes are more potent antimicrobials than the parent Schiff base ligands against one or more microorganisms[1,5].

Antimicrobial properties exhibit complexes M(II) with Schiff bases derived from cefotaxime with 1H-indole-2,3-dione (isatin) and 4-N, N-dimethyl amino-benzaldehyde. Synthetic scheme of two Schiff bases derived cefotaxime is shown in Figure 2.[6].

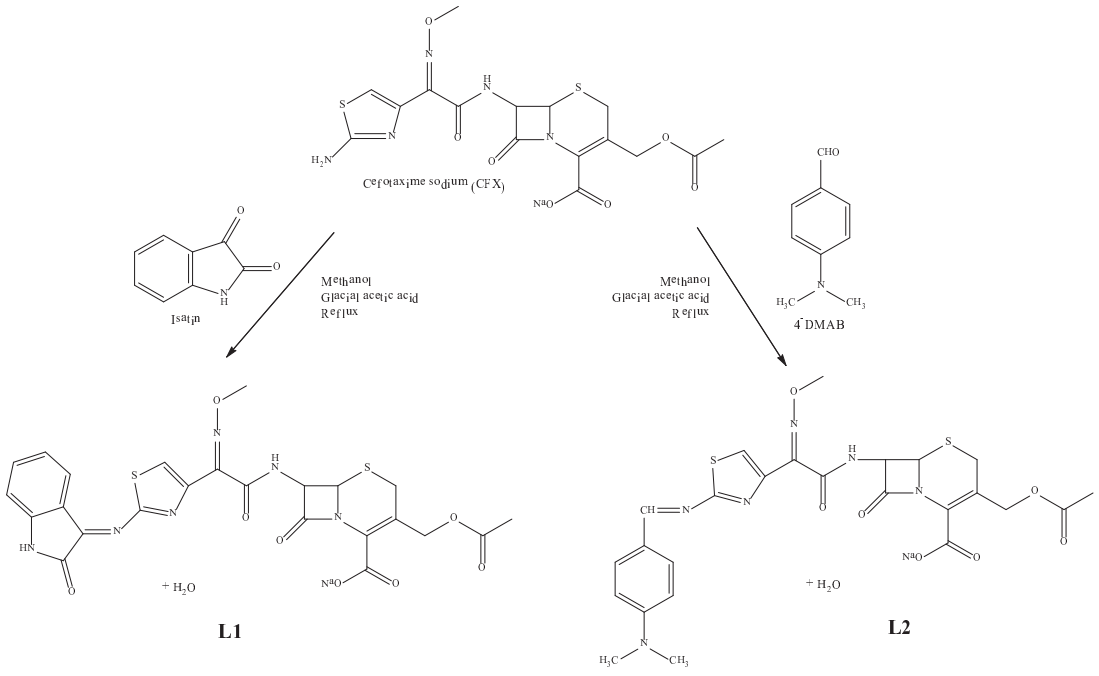

Figure 2. Synthetic route of the two Schiff base derivatives of cefotaxim

As a part of this study, synthesis of complexes Co(II), Ni(II), Cu(II), Cd(II), $PdCl_2(PhCN)_2$] and K_2PtCl_6 with the obtained ligands were performed. By subjecting the resulting products of thermal elemental analysis, NMR and FT-IR spectroscopy was found to be a tridentate ligand and that all the complexes have an octahedral geometry, except square planar structureof Pd(II) complex. Investigation of antimicrobial activity of complex prepared in DMSO (1 mg/ml) is performed in vitro on *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Streptococcus pneumoniae*, using the agar diffusion technique.Main ligands have proved to be completely inactive in all research culture at the selected concentration, indicating that the original amino group of antibiotic has an important role in inhibiting the growth of bacterial cultures. All metal complexes showed selective activity against one or two bacterial species, other than the complex [Pt(LII)Cl_3] H_2O · 0.5 EtOH which acted against all culture and showed greater activity against *Streptococcus pneumoniae* and *Pseudomonas aeruginosa*, compared to free antibiotics (Cefotaxime). Other complexes have proven to be moderately active against *Staphylococcus aureus*[6].

Complexes of some transition metals with certain Schiff bases derived from o-phenylenediamine and 5-nitrosalicyl-aldehyde were subjected to standard antimicrobial assay against *Staphylococcus aureus*, *E. coli*, *Pseudomonas aeruginosa* and *Salmonella typhi*[7]. Synthesis of Schiff base used in the following study is shown in Figure 3.

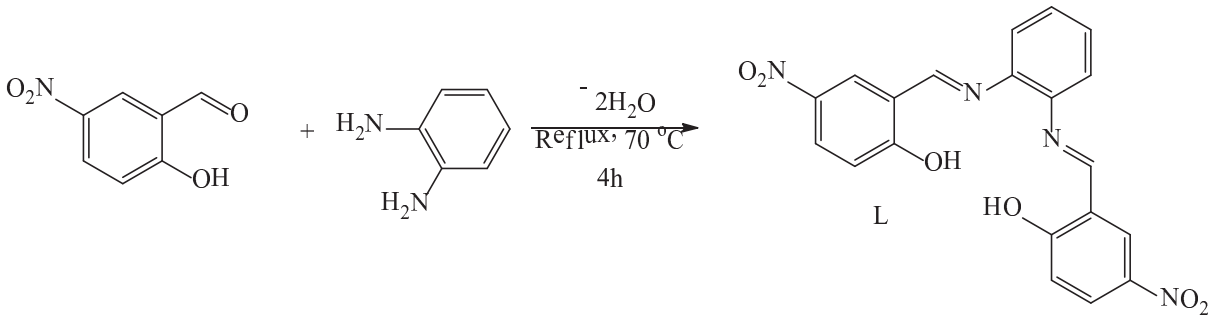

Figure 3. Synthesis of Schiff base from o-phenylenediamine and 5-nitrosalicylaldehyde

For synthesis of complexes were used Cu(II), Ni(II), Co(II) and Fe(III). Complex concentrations for investigations of antimicrobial properties against *E. coli*, *S. typhi*, *S. aureus* and *P. aeruginosa* were 5 mg/mL. Table 1 presents the obtained results[7].

Table 1. Antimicrobial activity of Schiff base as ligand and synthesized complexes

Diameter of inhibition zone of bacteria (mm)				
Compound	*S.typhi*	**S.aureus**	*P. aeruginosa*	*E.coli*
L	12	12	-	16
Fe-L	5	-	-	10
Co-L	12	16	-	8
Ni-L	8	10	-	8
Cu-L	10	10	-	11

From the table it can be clearly concluded that a Schiff base ligand having pronounced antimicrobial properties in comparison to the synthesized complex M-L. The researchers found that thegeometry of formed complexes is important for their antimicrobial activity. Namely, a square planar geometry of complex (in the case of Ni(II) and Cu(II)) showing lower activity against all strains of the bacteria compared to the parent ligand. Octahedral cobalt complex shows high activity against Gram-positive *S. typhi* and *S. aureus*[7].

Antimicrobial and antifungal study of complexes of Zn(II) with Schiff bases was made by scientists in India. After synthesis of two Schiff base, IR spectroscopic characterization is carried of the same and their proposed structure is shown at Figure 4.[8] After synthesis of ligand, complexes ZnL and ZnL_2 has been synthesized, and their proposed structures are shown in Figure 5.

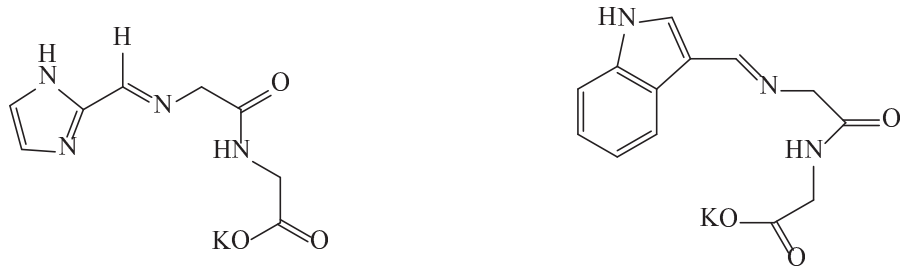

Figure 4. Proposed structure of two Schiff bases

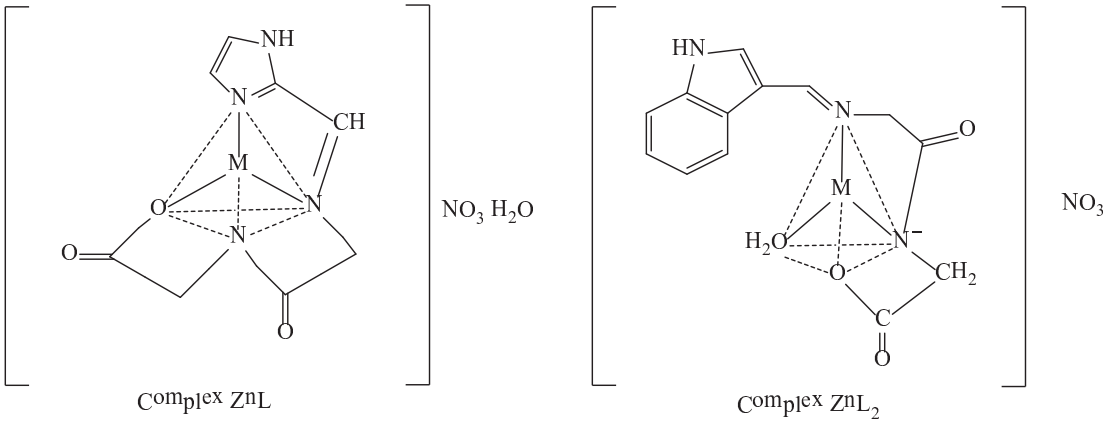

Figure 5. Proposed structure of complexes ZnL and ZnL_2

Antimicrobial activity *in vitro* of ligand and synthesized complexes were tested on *Staphylococcusaureus, Escherichia coli, Klebsiella pneumaniae, Proteus vulgaris* and *Pseudomonas aeruginosa*, whereas the antifungal activity was tested on *Aspergillus niger, Rhizopus stolonifer, Aspergillus flavus*, *Rhizoctonia bataicola* and *Candida albicans*. The study showed that both compounds showed a high activity in bacterial strains of *S. aureus, E. coli* and *P. aeruginosa*. In case of *Klebsiella pneumaniae*, ZnL complex indicates moderate activity, while the other complex (ZnL_2) is significantly more active. As for the antifungal activity of both complexes, for ZnL was found to have a higher activity of *A. niger*, *R. stolonifera* and *A. flavus*. ZnL_2 complex shows a higher activity of *A. niger, A. flavus and C. albicans* in comparison to *R. Stolonifer* and *R. bataicola*[8].

Complex with anti-tumor properties

Due to the increase of malignant diseases in the world, a great emphasis is placed on the synthesis of new inorganic, antitumorcomplexes. In the following it will be described some interesting papers in this area.

Anti-tumor activity of complexes Pt(IV), Au(III) and Pd(II) with Schiff base derived from 2-furaldehyde and 4-aminoantipyrine were performed by the scientists from University Princess Nora Bint Abdul Rahman. The structure of Schiff base (4 -[(furan-2-ylmethylene) -amino] -1,5-dimethyl-2-phenyl-1,2-dihydro-pyrazol-3-one, short 4APF) and the proposed structure of formed complexes are shown at Figure 6.[9].

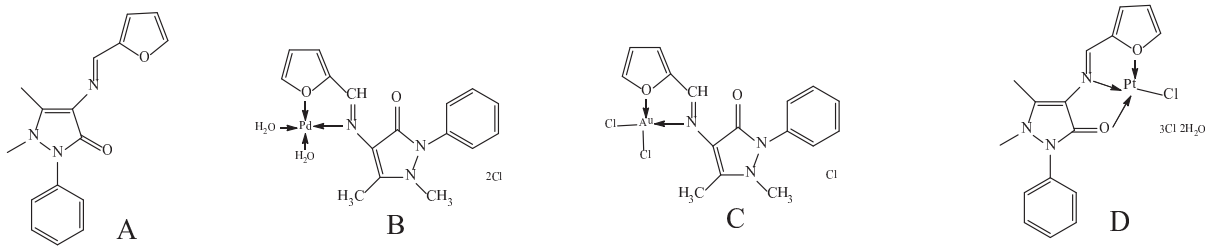

Figure 6. Structure of Schiff base derived from 2-furaldehyde and 4-aminoantipyrine and the proposed structure of synthesized complexes: A) 4 - [(furan-2-ylmethylene) -amino]-1,5-dimethyl-2-phenyl-1,2 dihydro-pyrazol-3-one (4APF); B) $[Pd(4APF)]Cl_2$; C) $[Au(4APF)(Cl)_2]Cl$; D) $[Pt(4APF)Cl]Cl_3$

Antitumor activity was tested on breast cancer cells (MCF-7 cell line). The results showed significant anti-tumor activity of the complex synthesized in said cell lines. Different concentrations of complexes (50; 25; 12,5; 6,25; 3,125 and 1,56 mg) were used and the cell viability (%) was determined by colorimetric method. The inhibitory concentration for parent ligand was 3,2 mg, 4,7 mg of Pt(IV) complex, 3,82 mg of Au(III) and 18,6 mg of the Pd(II). This paper suggests clinically achievable concentrations of 4-APF Schiff bases which may be useful in the destruction of the MCF-7 breast cancer cell lines[9]. Since platinum is one of the main metal used for the synthesis of anticancer complexes, considerable research is based precisely on the application of this metal. A group of scientists investigated antitumor activity of Pt-complex and have published their work in the Canadian Journal of Chemistry. Scheme of the synthesis of seven new (salicilaldiminato) platinum (II) complexes is shown in Figure 7, and their antitumor activities were examined.[10].

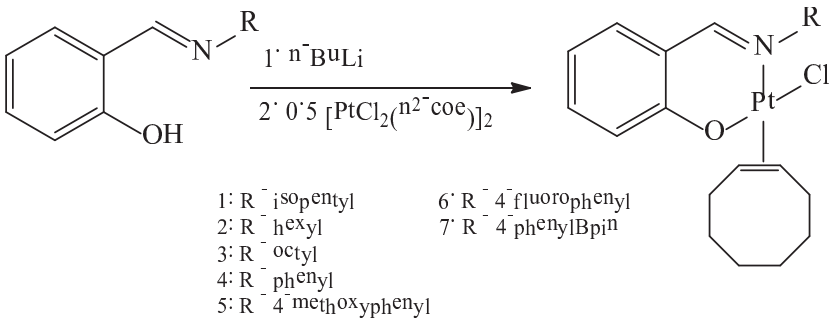

Figure 7. The synthesis of seven new (salicilaldiminato) platinum(II) complexes

Antitumor activity of synthesized complexes were subjected i*n vitro* to aggressive breast cancer (cell line MB231) and RCC cell lines. Complex indicated as 7 proved to be unstable, so antitumor activity was examined for the remaining complexes. Complex 3, which includes the longest aliphatic chain (R-octyl group) proved to be promising in inducing apoptosis of MB231 cell lines. On the other hand, complexes 4-6 (R-aromatic group) showed significant cytotoxicity in RCC cell lines. However, a disadvantage of these complexes is to cause damage to healthy cells which is not desired in the treatment of oncological diseases[10].

Complexes of ruthenium have great potential for use in cancer therapy and is the only non-platinum complexes which have entered the phase of clinical testing as chemotherapeutics. Rutheniumcomplexes have at least three significant characteristics, which is considered that could be successfully applied in therapy: kinetics of ligand exchange, a wide range of oxidation states and rutheniumproperty to imitate iron in biochemical processes[11].

Today, a large number of Ru(II) and Ru(III) complexeswith a wide spectrum of organic ligands are investigated. One of interesting research is performed by scientists at the Faculty of Natural Sciences and Agriculture, University of Fort Hare in South Africa. Specifically, they examined antitumor activity of Ru(III) complexes with tridentate Schiff bases. They examined anti-tumor potential of complex in MCF-7 breast cancer cell lines, renal TK-10 cell lines, and UACC-62 melanoma cell lines[12]. Synthesis of Ru(III) complex is shown in Figure 8.Results i*n vitro* studies of anticancer properties of complex which structure is shown in Figure 8, are presented in Table 2.[12]

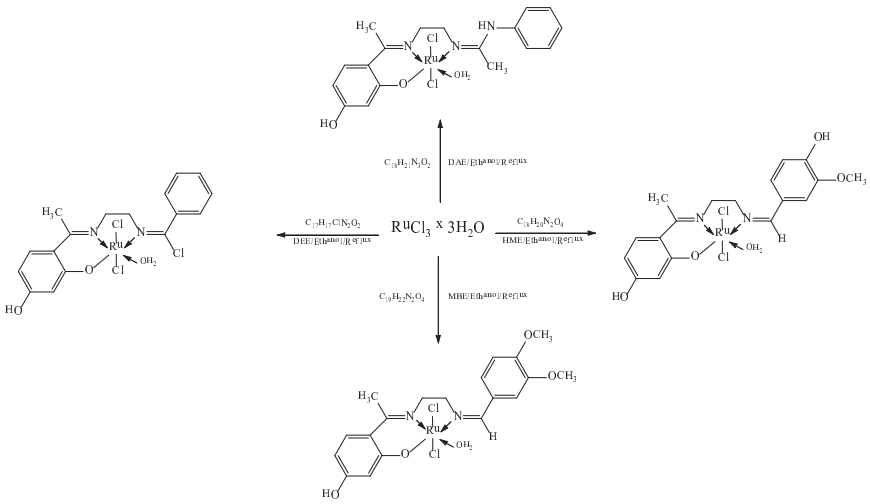

Figure 8. Synthesis of Ru(III) complexes with tridentate Schiff bases

Table 2. *In vitro* antitumor activity of Ru(III)-Schiff base complex against TK-10, UACC-62 and MCF-7 cell lines

Compounds	Molecular formula	Anticancer activity IC_{50} (μM) 48 h		
		TK-10	UACC-62	MCF-7
$[Ru(DAE)Cl_2(H_2O)$	$C_{18}H_{24}N_3O_4RuCl_2$	9,06 ± 1,18	6,44 ± 0,38	3,57 ± 1,09
$Ru(HME)Cl_2(H_2O)$	$C_{18}H_{23}N_2O_6RuCl_2$	41,09 ± 4,44	6,31 ± 1,47	4,88 ± 1,28
$Ru(DEE)Cl_2(H_2O)$	$C_{17}H_{20}N_2O_4RuCl_3$	13,10 ± 2,81	5,14 ± 1,09	3,43 ± 1,48
Parthenolide*	$C_{15}H_{20}O_3$	0,50 ± 1,43	0,89 ± 2,18	0,44 ± 2,02

* Standard cytotoxic drug

The cell lines were treated with various concentrations of complex in order to achieve 50% inhibition during 48 hours. The order of complexactivity against UACC-62 is: [Ru(DEE) $Cl_2(H_2O)$] > [Ru (HME)$Cl_2(H_2O)$] > [Ru(DAE) $Cl_2(H_2O)$]. In the case of activity of anti-TK-10 cell lines, based on the table data, it is clearly contemplated that the maximum activity shows [Ru(DAE)$Cl_2(H_2O)$ and the lowest Ru(HME) $Cl_2(H_2O)$. Based on previous reports, compounds which have an IC_{50} in the range of 10 to 25 μM have been characterized as a drug with poor antitumor activity, and those compounds whose IC_{50} in the range 5-10 μM are agents with a moderate antitumor activity. Compounds having an IC_{50} less than 5 μM are classified in strong anti-tumor agents[13]. In comparison to the research Ru(III) complexes of other scientists, these complexes have proved to be antitumor agents of high activity[12].

CONCLUSION

Based on some results presented in the field of chemistry of complex compounds, compounds with anti-tumor and anti-infective properties are today topics in interest of many scientists. The results show that there is a wide range of organic ligands in the form of complexes with a specified metal ions (such as Ru(III), Pt(IV), etc.) show the excellent efficacy in the treatment of malignant and infectious diseases. However, it still has not found an adequate way that will reduce the negative impact of these compounds on healthy cells, which certainly should be subject of additional interest and interpretation in the next period.

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