We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900
Open access books available

185,000
International authors and editors

200M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



29

Therapeutic Organometallic Compounds

Beril Anilanmert
Istanbul University, Institute of Forensic Sciences, Turkiye

1. Introduction

Most drugs used today are purely organic compounds. Especially after the enormous success of the cisplatin (Fig 1) in tumor treatment, interest in metal complexes has grown (Allardyce & Dyson, 2006). Synthetic organometallic compounds are generally considered to be toxic or non-compatible with biological systems. Despite this perception, the medicinal properties of organometallic compounds, in particular organo-transition metal compounds, have been probed for a long time and in the last few years the area has grown considerably.

Transition metals have an important place within medicinal biochemistry (Rafique et al, 2010). Transition metals represent the d block element which includes groups 3 - 12 on the periodic table. They have partially filled d-shells in any of their commonly occuring oxidation state. Metal complex or coordination compound is a structure consisting of a central metal atom, bonded to a surrounding array of ligands (molecules or anions), which donate electron pair to the metal. Research has shown significant progress in utilization of transition metal complexes as drugs to treat several human diseases like carcinomas, lymphomas, infection control, anti-inflammatory, diabetes, and neurological disorders. Transition metals exhibit different oxidation states and can interact with a number of negatively charged molecules. This activity of transition metals has started the development of metal-based drugs with promising pharmacological application and may offer unique therapeutic opportunities.

2. Therapeutic applications of some old and new organometallic complexes and discoveries and ongoing studies

Various metal complexes have been tested in anticancer therapy (Meng et al, 2009). The development of metal complexes with platinum central atoms such as cisplatin or carboplatin had an enormous impact on current cancer chemotherapy (Fig 1, 2) (Ott & Gust, 2007). In particular, cisplatin has become one of the most widely used drugs and is highly effective in treating several cancers such as ovarian and testicular cancers (Meng et al, 2009).

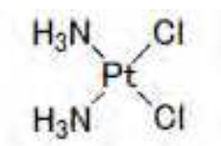


Fig. 1. Molecular structure of cisplatin.

Most of the platinum compounds that entered clinical trials follow the same empirical structure-activity relationships (Abu-Surrah & Kettunen, 2006). A necessary prerequisite for an active Pt-drug seems to be *cis*-coordination by bidentate amine ligands or two amines (at least one -NH group on the amine) and two leaving groups with an intermediate binding strength (e.g. Cl^-, SO_4^{2-}, citrate or oxalate) to platinum. The limitations of cisplatin have stimulated research in the field of platinum antitumor chemistry by giving specific goals. These include reduction in toxicity of cisplatin (nausea, ear damage, vomiting, loss of sensation in hands, and kidney toxicity), acquired drug resistance observed in certain tumors, inefficiency of the drug against some of the commonest tumors (e.g. colon and breast).

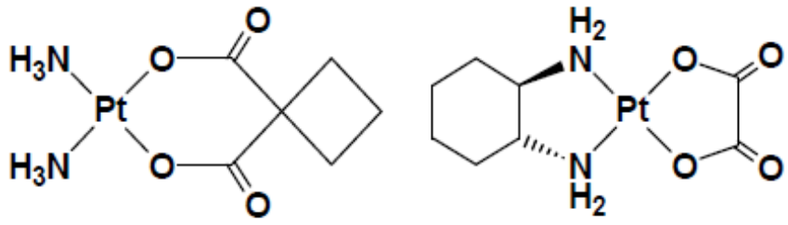
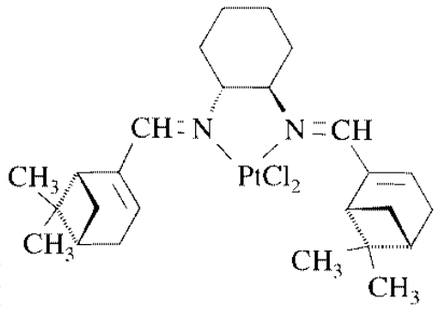


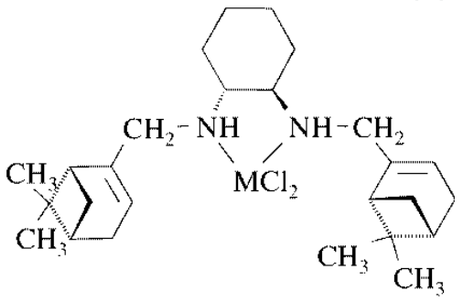
Fig. 2. Structures of carboplatin (left) and oxaliplatin (right) (Hanif, 2010)

Thousands of other platinum complexes have been synthesized and biologically evaluated for their antitumor properties, from which about fourty entered clinical phase I trials but only two carboplatin and oxaliplatin (Fig. 2) have received worldwide approval (Abu-Surrah & Kettunen, 2006). Carboplatin exhibits a tumor inhibiting profile identical to that of cisplatin, however with fewer side effects, whereas oxaliplatin is used in a combination therapy against metastatic colorectal cancer.

Some platinum(II) and palladium(II) complexes with new *trans-l*-dach (1R,2R-cyclohexanediamine) based diamine and diimine donor ligands containing the enantiomerically pure myrtenyl groups as terminal substituents were synthesized in 2008. The anti-proliferative effect of compounds Dichloro[(1R,2R)-(-)-N^1,N^2-bis{(1R)-(-)myrtenyl}-1,2-diamino cyclohexane]-platinum(II).$3H_2O$, Dichloro[1R,2R)-(-)-N^1,N^2-bis{(1R)-(-) myrtenylidene}-1,2-diamino cyclohexane]-platinum(II) and Dichloro [(1R,2R)-(-)-N^1,N^2-bis{(1R)-(-)myrtenyl}-1,2-diaminocyclohexane]-palladium(II).$1.5H_2O$ together with the commercial drugs cisplatin (Cis-Pt) and oxaliplatin (Ox-Pt) were investigated in L1210 Cell line using 3H-thymidine incorporation (Abu-Surrah et. al., 2008). As shown in Figure 3, the platinum compounds Dichloro[(1R,2R)-(-)-N^1,N^2-bis{(1R)-(-)myrtenyl}-1, 2-diaminocyclo hexane]-platinum(II).$3H_2O$ and Dichloro [1R,2R)-(-)-N^1,N^2-bis{(1R)-(-) myrtenylidene}-1,2-diaminocyclohexane]-platinum(II) suppress proliferation more efficiently than the commercial platinum-based drugs with an IC_{50} of 0.6 and 0.7 µL, respectively. Compound Dichloro[(1R,2R)-(-)-N1,N2-bis{(1R)-(-) myrtenyl}-1,2-diaminocyclohexane]- platinum(II).$3H_2O$ is 17-folds more potent than the commercial oxaliplatin and cisplatin. No significant difference could be observed between the complex that contains the diamine nitrogen ligand and the one holding the corresponding diimine ligand. The authors also synthesized the palladium complex; Dichloro[(1R,2R)-(-)-N^1,N^2-bis{(1R)-(-)myrtenyl}-1,2-diaminocyclohexane]-palladium(II).$1.5H_2O$, which also suppresses proliferation efficiently with an IC_{50} of 4.2 µL. This is about 2-folds more potent than the commercial oxaliplatin and cisplatin.



(a) Dichloro[(1R,2R)-(-)-N^1,N^2-bis{(1R)-(-)myrtenyl}-1,2-diamino cyclohexane]-platinum(II).3H_2O



(b) Dichloro[1R,2R)-(-)-N^1,N^2-bis{(1R)-(-) myrtenylidene}-1,2-diamino cyclohexane]-M(II) M=Pt(II), Pl(II)

Fig. 3. The structure of some platinum(II) and palladium(II) complexes with new *trans-l*-dach based diamine and diimine donor ligands containing the enantiomerically pure myrtenyl groups as terminal substituents (Abu-Surrah & Kettunen, 2006).

In a total look, platinum complexes display, along with other kinds of anticancer drugs, two major drawbacks: (a) severe toxicities (neurotoxicity, nephrotoxicity, etc.) and (b) limited applicability to a narrow range of tumors, as several of them exhibit natural or induced resistance. These unresolved problems in platinum-based anticancer therapy have stimulated increased research efforts in the search for novel non platinum-containing metal species as cytostatic agents. Non-platinum metals may have different chemical behavior (oxidation state, redox potential, coordination geometry, additional coordination sites, binding preferences to biomolecules according to the HSAB [hard and soft (Lewis) acids and bases] principle etc.), rate of hydrolysis or kinetics of ligand exchange reactions and the ability to replace essential metals (Abu-Surrah & Kettunen, 2006). Therefore, it is likely that non-platinum metal-based compounds may have different mechanisms of action, biodistribution and biological activity.

The antitumor properties of a number of different metal ions and their complexes have been evaluated, but only a few non-platinum metal-based drugs are currently in clinical studies, the most promising ones contain ruthenium and gallium ions (Abu-Surrah & Kettunen, 2006). Preclinical and clinical investigations confirmed that the development of new metal agents with modes of action different from cisplatin is possible (Ott & Gust, 2007). Thus, complexes with iron, cobalt, or gold central atoms have shown promising results in preclinical studies and compounds with titanium, ruthenium, or gallium central atoms (as in Fig 4) have already been evaluated in phase I and phase II trials. Other metal complexes

that have shown potential anticancer activity are the complexes of Rh(I), Rh(III), Ir(I), Ir(II), Ir(IV), Os(II) and Os(III). Many platinum and non-platinum metal complexes such as palladium, ruthenium, rhodium, copper, and lanthanum, with aromatic N-containing ligands as pyridine, imidazole and 1,10-phenanthroline, and their derivatives (whose donor properties are somewhat similar to the purine and pyrimidine bases), have shown very promising antitumor properties in vitro and in vivo in cisplatin-resistant model systems or against cisplatin-insensitive cell lines (Zhao & Lin, 2005).

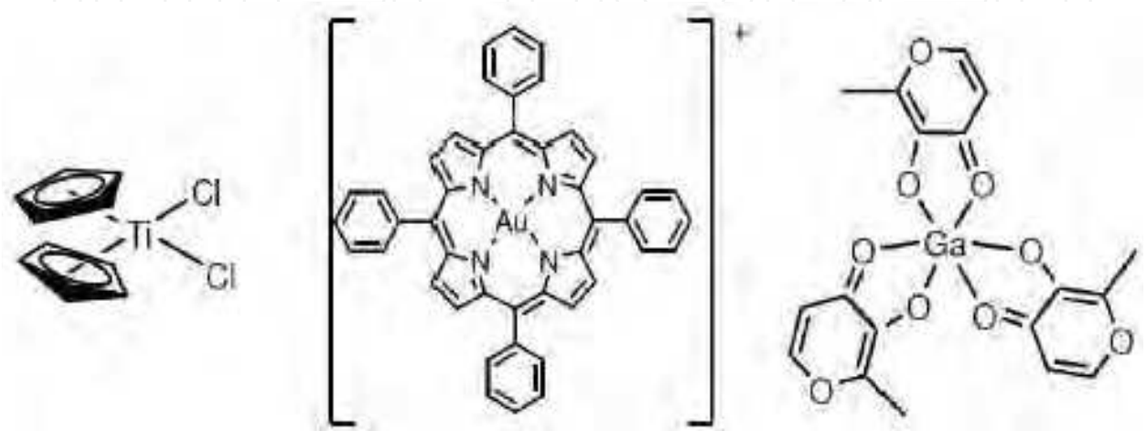


Fig. 4. The chemical structures of titanocene dichloride (a), gold tetraphenylporphyrin (b) and gallium maltolate (c) (Hanif, 2010).

The notable analogy between the coordination chemistry of platinum(II) and palladium(II) compounds has advocated studies of Pd(II) complexes as antitumor drugs (Abu-Surrah & Kettunen, 2006). A key factor that might explain the reason that platinum is most useful, comes from the ligand-exchange kinetics. The hydrolysis of the leaving ligands in palladium complexes is too rapid: 10^5 times faster than their corresponding platinum analogues. They dissociate readily in solution leading to very reactive species that are unable to reach their pharmacological targets. This implies that if an antitumor palladium drug is to be developed, it must somehow be stabilized by a strongly coordinated nitrogen ligand and a suitable leaving group. If this group is reasonably non labile, the drug can maintain its structural integrity *in vivo* long enough. As a way to increase the stability of the palladium(II) complexes, two chelates forming two rings around the central atom were prepared and evaluated. A series of compounds bearing two chelating ligands the N-N and O-O ligand (XO_3: selenite or tellurite) were prepared. The N-N ligand did not influence the activity but the oxygen coordinated leaving group did. Selenite complexes were invariably better cytotoxic agents than tellurite complexes and cisplatin. The complex [bipy)Pd(SeO_3)] (Fig 5) was found to bind to DNA through a coordinate covalent bond. Another study investigated compounds [((1R,2R)-(-)-1,2-diaminocyclohexane)Pd(3-methylorotate)] which gave a high activity for sarcoma 180 but a low one against P388 leukemia and [(1R,2R)-(-)-1,2-diaminocyclohexane)Pd(5-fluroorot)] which also displayed significant antitumor activity. These strong chelating ligands replacing chloro or nitro ligands induce a reduction in the rate of hydrolysis.

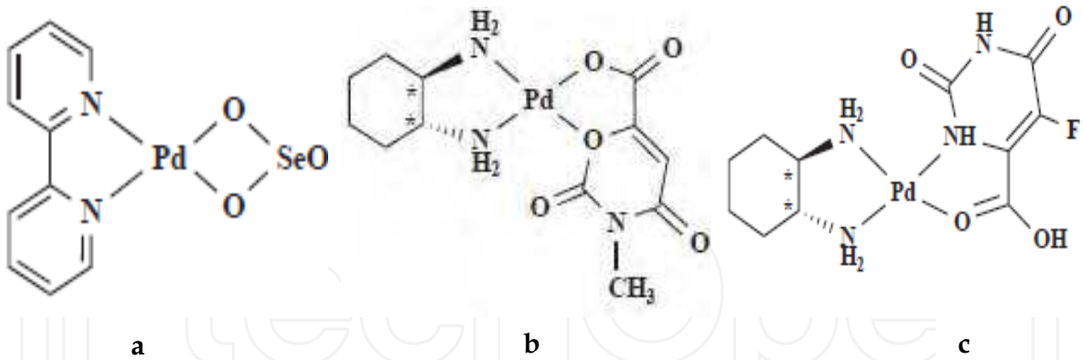


Fig. 5. The geometrical structure of [bipy)Pd(SeO_3)] (a), [((1R,2R)-(-)-1,2-diaminocyclohexane) Pd(3-methylorotate)] (b), [(1R,2R)-(-)-1,2-diaminocyclohexane)Pd(5-fluroorot) (c)] (Abu-Surrah & Kettunen, 2006)

Both ruthenium and osmium, along with iron, are members of group VIIIB and are placed in the fourth, fifth and sixth row of the periodic table, respectively. They are classified as the 'Platinum group' along with rhodium, palladium, iridium and platinum. All these metals often occur together in the same mineral deposits and have closely related physical and chemical properties. The application of iron in group 8 metal complexes in anticancer drug design is the ferrocenyl derivative of tamoxifen (ferrocifen) (Jauen et al, 2006), and two ruthenium containing drug candidates NAMI-A and KP1019 in clinical trials. In trying to find better alternatives to tamoxifen, Jaouen et al. (Top et al, 2001), have investigated tamoxifen analogs that contain an organometallic moiety. The researchers studied the effects of several hydroxy-substituted ferrocifens on the proliferation of two lines of breast cancer cells, one used for tumors mediated by the ERα receptor, and one used for tumors mediated by ERβ. Three of the ferrocifens (Fig 6) exhibited a strong antiproliferative effect in both cell lines while hydroxytamoxifen, as expected, was effective only against the cells having the ERα receptor. Ferrocifenes exhibit anticancer activity against hormone dependent and hormone independent breast cancers (Rafique et al, 2010). The ferrocene derivatives having hydroxyl group in phenyl ring have high affinity for estrogen receptor. Ferrocene by itself had no effect.

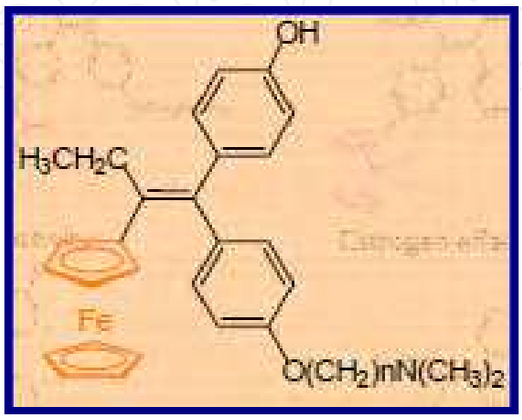


Fig. 6. The main molecular structure of ferrocifenes.

Special attention has been paid to ruthenium compounds because they exhibit cytotoxicity against cancer cells, analogous ligand exchange abilities to platinum complexes, no cross-resistance with cisplatin, and may display reduced toxicity on healthy tissues by using iron transport (Meng et al, 2009). Ruthenium complexes demonstrate similar ligand exchange kinetics to those of platinum(II) antitumor drugs already used in the clinic while displaying only low toxicity (Brabec & Novakova, 2006). This is in part due to the ability of ruthenium complexes to mimic the binding of iron to molecules of biological significance, exploiting the mechanisms that the body has evolved for transport of iron.

Ruthenium complexes tend to accumulate preferentially in neoplastic masses in comparison with normal tissue (Rademaker-Lakhai et al, 2004). They probably use transferrin, for its similarities with iron, to accumulate in the tumor. A transferrin-ruthenium complex can be actively transported into tumor tissues that have high transferrin-receptor densities. Once bound to the transferrin receptor, the complex liberates ruthenium that can be easily internalized in the tumor. Next, ruthenium (III) complexes likely remain in their relatively inactive ruthenium(III) oxidation state until they reach the tumor site. In this environment, with its lower oxygen content and pH than normal tissue, reduction to the more reactive ruthenium(II) oxidation state takes place. This reaction, named "activation by reduction" would provide not only a selective toxicity but also an efficacy toward hypoxic tumors known to be resistant to chemotherapy and/or radiotherapy. Finally, some complexes are more effective against the tumor metastases than against the primary tumor. Due to differing ligand geometry between their complexes, ruthenium compounds bind to DNA affecting its conformation differently than cisplatin and its analogues (Brabec & Novakova, 2006). In addition, non-nuclear targets, such as the mitochondrion and the cell surface, have also been implicated in the antineoplastic activity of some ruthenium complexes. So, ruthenium compounds have a pattern of cytotoxicity and antitumor activity that is different from that of cisplatin tissue (Rademaker-Lakhai et al, 2004). Ruthenium complexes exhibit both nitric oxide release and scavenging functions that can affect vasodilation and synapse firing (Clarke, 2003). Simple ruthenium complexes are unusually effective in suppressing the immune response by inhibiting T cell proliferation. Thus, ruthenium compounds offer the potential over antitumor platinum(II) complexes currently used in the clinic of reduced toxicity, a novel mechanism of action, the prospect of non-cross-resistance and a different spectrum of activity. Although the pharmacological target for antitumor ruthenium compounds has not been completely identified, there is a large body of evidence indicating that the cytotoxicity of many ruthenium complexes correlates with their ability to bind DNA although few exceptions have been reported. One of the first ruthenium compounds described to have anticancer activity was ruthenium red, and further work showed the anticancer potential of ruthenium-containing drugs (Rafique et al, 2010). Since then, several teams have synthesized and characterized new compounds containing ruthenium(II) or ruthenium(III). Ruthenium red and the related Ru360 strongly inhibit calcium ion uptake in the mitochondria (Clarke, 2003).

Ru(II) and Ru(III) complexes have shown very promising properties while the Ru(III) compound NAMI-A (imidazolium *trans*-[tetrachloro(DMSO)(imidazole)ruthenate(III)]) , is the first ruthenium compound that successfully entered phase I clinical trials as an antimetastatic drug candidate (Katsaros & Anagnostopoulou, 2002; Antonarakis & Emadi,

2010). Ruthenium compound KP1019 (indazolium *trans*-[tetrachlorobis(1H-indazole) ruthenate(III)]), as an anticancer drug against colon carcinomas and their metastases has also entered clinical trials so far. It has shown direct antitumor activity against a wide range of primary explants of human tumors by inducing apoptosis (Antonorakis & Emadi, 2010). Both compounds showed relatively little side-effects and better tolerance in clinical phase I trials (Fig. 7). In preclinical studies, NAMI-A has demonstrated inhibitory effects against the formation of cancer metastases in a variety of tumor animal models but appears to lack direct cytotoxic effects (Antonarakis & Emadi, 2010). In case of NAMI-A, DNA is thought to be a less important target, and anti-angiogenic activity based on the NO metabolism has been described (Bharti & Singh, 2009). NAMI-A interaction with the microenvironment involving integrin activation that results in reduced cell invasiveness and migration has been proposed and this may be the reasons for the activity of ruthenium compounds against cisplatin-resistant tumors. Ruthenium compounds ONCO4417 and DW1/2 have been demonstrated to show Pim-1 kinase inhibition in preclinical systems (Sekhon, 2010). A phase I and pharmacokinetic study was also carried out with the new ruthenium complex indazolium trans-[tetrachlorobis(1H-indazole)ruthenate(III)] (KP1019, FFC14A) (Lentz et al, 2009). Seven patients with various types of solid tumours refractory to standard therapy were treated with escalating doses of KP1019 (25-600 mg) twice weekly for 3 weeks. No dose-limiting toxicity occurred. Ruthenium plasma concentration-time profiles after the first dose and under multiple-dose conditions were analysed using a compartmental approach. The pharmacokinetic disposition was characterised by a small volume of distribution, low clearance and long half-life. Only a small fraction of ruthenium was excreted renally.

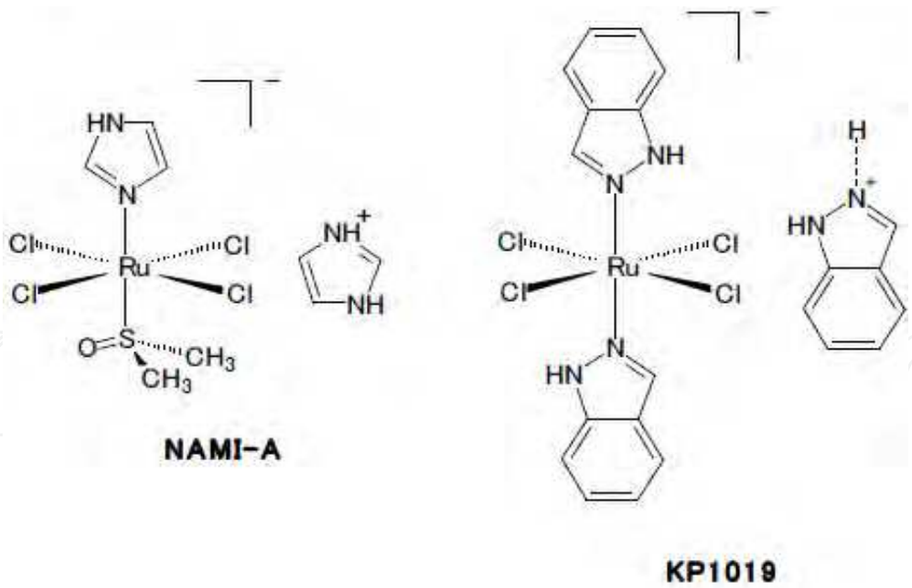


Fig. 7. Structure of ruthenium complexes NAMI-A and KP1019 (Llorca, 2005).

Many biological properties have been attributed to ruthenium complex I (*trans*-$[RuCl_2(nic)_4]$) and ruthenium complex II (*trans*-$[RuCl_2$ (i-nic)$_4]$) including nitric oxide synthase inhibition (Valvassori et al, 2006). However, side effects of the ruthenium compounds should also be evaluated. In the investigation of the pharmacological effects of

these complexes on anxiety and memory formation on adult male Wistar rats, no effects were observed in the anxiety parameters and habituation to an open-field while memory impairment was observed. The ruthenium complexes impaired memory retention compared with vehicle group in the inhibitory avoidance, as when administrated 30 min prior as immediately after training. The memory impairment induced by ruthenium complexes may be due to their nitric oxide synthase inhibition capacity.

Rhodium belongs to the same group as platinum and ruthenium. However, rhodium compounds, analogues to the corresponding platinum and ruthenium compounds that possess significant antitumor properties, were found to be less effective as anticancer agents mainly due to their toxic effects. Dimeric mu-Acetato dimers of Rh(II) as well as monomeric square planar Rh(I) and octahedral Rh(III) complexes have shown interesting antitumor properties.

In 2009, Meng et al. have studied both in vitro and in vivo the biological properties of RDC11 (Fig 8), which contain a covalent bond between the ruthenium atom and a carbon. RDC11 inhibited the growth of various tumors implanted in mice more efficiently than cisplatin. Importantly, in striking contrast with cisplatin, RDC11 did not cause severe side effects on the liver, kidneys, or the neuronal sensory system. It was shown to interact poorly with DNA and induced only limited DNA damages compared with cisplatin, suggesting alternative transduction pathways. The target genes of the endoplasmic reticulum stress pathway, such as Bip, XBP1, PDI, and CHOP, were activated in RDC11-treated cells. Activation of CHOP led to the expression of several of its target genes, including proapoptotic genes. Acting through an atypical pathway involving CHOP and endoplasmic reticulum stress, RDC11 is thought to provide an interesting alternative for anticancer therapy (Meng et al, 2009).

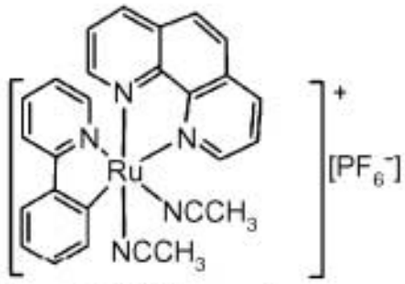


Fig. 8. Molecular structure of RDC11 (Meng et al, 2009).

A class of ruthenium(II)-arene complexes that are weakly cytotoxic in vitro, were also shown to have selective antimetastatic activity in vivo, in the literature (Anga, et. al., 2011). These compounds, [Ru(η6-p-arene)Cl_2(1,3,5-triaza-7-phosphaadamantane)] termed RAPTA, interact strongly with proteins, with the ability to discriminate binding to different proteins, but show a relatively low propensity to bind DNA, which is considered to be the main target of many metal-based drugs. The basic RAPTA structure is quite stable in physiological environments, and studies have shown that aquation of the chloride bonds occurs, it may not be an essential step for anticancer drug activity – direct substitution with biomolecular targets is also possible. Based on the concept of bifunctional radiopharmaceuticals (Ogawa et al, 2007), developed a highly stable ^{186}Re-

mercaptoacetylglycylglycylglycine (MAG3) complex-conjugated bisphosphonate, [[[[(4-hydroxy-4,4-diphosphonobutyl) carbamoylmethyl]carbamoylmethyl]carbamoylmethyl] carbamoylmethane thiolate] oxorhenium (V) (^{186}Re-MAG3-HBP), for the treatment of painful bone metastases. ^{186}Re-MAG3-HBP accumulated at the site where tumor cells were injected in a rat model of bone cancer and significantly inhibited tumor growth and attenuated the allodynia induced by bone cancer without having critical myelosuppressive side effects. The results indicate that ^{186}Re-MAG3-HBP could be useful as a therapeutic agent for the palliation of metastatic bone pain.

Since DNA has often been proposed as the target of these organometallic antineoplastic agents, there is a particular emphasis on those that can interact with nucleic acids (Clarke et al, 1999). Nevertheless, heavy metals are generally toxic by binding to sulfur and nitrogen sites on proteins and, thus, can interfere with a number of modes of metabolism. Several metals also exhibit action through redox activity. Gallium appears to operate through the displacement of metal ions in iron metabolism or bone. In large part, action of gallium complexes seems to be a consequence of the similarity of gallium(III) to iron(III): Gallium interferes with the cellular transport of iron by binding to transferrin, and also interferes with the action of ribonucleotide reductase, which then results in inhibition of DNA synthesis (Hannon, 2007). The key to activity is making gallium(III) bioavailable, and work is focused on ligands which stabilize gallium against hydrolysis and facilitate membrane permeation. Among the developed gallium comounds, tris(8-quinolinolato)gallium(III) (KP46/FFC11) has entered clinical trials (Fig 9).

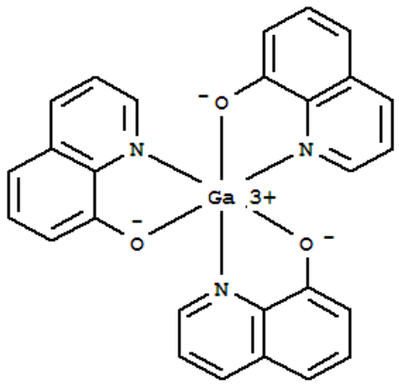


Fig. 9. Molecular structure of Tris(8-quinolinolato)gallium(III)

Gallium-based anticancer chemotherapeutics are appreciably progressing in clinical studies (Timerbaev et al, 2009). The interest of drug developers and clinicians in gallium compounds is due to a proven ability of gallium cations to inhibit tumour growth, and enhanced bioavailability and moderate toxicity provided by the conversion of gallium into chelate complexes. One of the complexes suitable for a more convenient oral administration is tris(8-quinolinolato) gallium(III) (KP46). KP46 is an orally bioavailable gallium complex, which exerts its antitumoral activity via inhibition of ribonucleotide reductase, induction of S phase arrest and apoptosis (Dittrich et al, 2005). In preclinical models KP46 was proved to be a stronger anticancer agent than gallium nitrate and it was effective on a model of tumor-associated hypercalcemia. Nominated from a range of gallium complexes for the clinical stage of development, KP46 has finished phase I trials with the outcome of promising

tolerability and evidence of clinical activity in renal cell carcinoma (Timerbaev et al, 2009). The adverse reactions of the complex, observed in a study, where 7 patients were used were neutropenia and anemia, stomatitis and conjunctivitis, dizziness, headache and acne, fatigue and diarrhaea both (Dittrich et al, 2005). In one out of the 4 patients with renal cell carcinoma an unconfirmed partial response has been observed after 8 weeks and in a second patient with renal cell carcinoma the disease was stabilized for 29 weeks. Peak plasma levels were reached 5-7 h after intake and pharmacokinetic analysis revealed a long terminal half-life (28 h). KP46 has been well tolerated with some preliminary evidence of efficacy in renal cell carcinoma.

The low-spin $5d^6$ Ir^{III} organometallic half-sandwich complexes $[(\eta^5\text{-}Cp^x)Ir(XY)Cl]^{0/+}$, Cp^{xph} : tetramethyl(phenyl)cyclopentadienyl, or Cp^{xbiph}: tetramethyl(biphenyl)cyclopentadienyl, XY = 1,10-phenanthroline, 2,2′-bipyridine, ethylenediamine, or picolinate, were investigated at 2011 (Liu et al, 2011). Complexes with N,N-chelating ligands readily form adducts with 9-ethylguanine but not 9-ethyladenine; picolinate complexes bind to both purines. Cytotoxic potency toward A2780 human ovarian cancer cells increases with phenyl substitution on Cp^x: $Cp^{xbiph} > Cp^{xph}$. The hydrophobicity and intercalative ability of Cp^{xph} and Cp^{xbiph} make a major contribution to the anticancer potency of their Ir^{III} complexes.

Among the metallocene dihalide complexes MX_2Cp_2 (where M=Ti, V, Mo, Nb etc., X= halide and Cp = η5-cyclopentadienide), titanocene (Fig 10), $TiCl_2Cp_2$ or MTK4 is the most successful anticancer agent as shown in phase I/II clinical trials (Bharti & Singh,2009). Titanocene dichloride had been recognized as active anticancer drug against breast and gastrointestinal carcinomas. Previously DNA was supposed to be the target of $[TiCl_2Cp_2]$ in a manner similar to cisplatin due to the similarity in Cl---Cl distances. Later, the aqueous chemistry of $[TiCl_2Cp_2]$ showed that DNA is not the site of action for this drug. The anticancer activity of $TiCl_2Cp_2$ is due to inhibition of collagenase type IV activity, which is involved in regulation of cellular proliferation, protein kinase C and DNA topoisomerase II activities. Titanium may also replace iron in transferrin and facilitate cellular uptake into tumor cells. The titanocene dichloride is believed to be accumulated via the transferrin–dependent pathways. Dose limiting toxicities of titanium compounds include nephrotoxicity and elevation of creatinine and bilirubin levels.

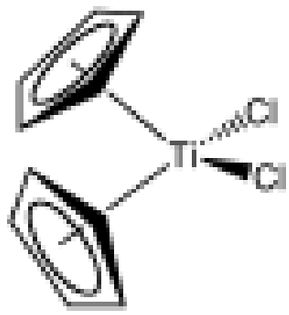
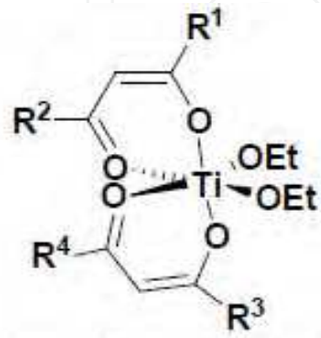


Fig. 10. Molecular structue of titanocene (Hannon, 2007)

Budotitane [cis-diethoxybis(1-phenylbutane-1,3-dionato)titanium (IV)] (Fig 11), was the first non-platinum transition-metal anticancer agent to be tested in clinical trials (Schilling et al, 1995). It is effective against a number of tumors in animals and is well tolerated (Bharti &

Singh, 2009). *In vitro* and *in vivo* experiments with budotitane showed no significant DNA damage. The dose-limiting side effects include cardiac arrhythmia, hepatotoxicity, renal toxicity and a reversible loss of taste (Dabrowiak, 2009; Antonarakis & Emadi, 2010). Ti(IV) compounds are known to inhibit proteases and telomerases. Inhibition of proteases in rapidly growing tumor cells may block the growth of tumor cells. Inhibition of telomerase may control all protein synthesis.



Budotitane (as a mixture of three *cis* isomers)

(i) $R^1 = R^3 = Me$; $R^2 = R^4 = Ph$

(ii) $R^1 = R^3 = Ph$; $R^2 = R^4 = Me$

(iii) $R^1 = R^4 = Me$; $R^2 = R^3 = Ph$

Fig. 11. The molecular structure of budotitane (Bharti & Singh, 2009).

Gold compounds are used for treating arthritis and cancer, they have potential for treating AIDS, malaria and Chagas disease (Dabrowiak, 2009). A property of Au^{+3} that greatly complicates its chemistry is that many of its simple complexes can easily be reduced to Au^{+} by a variety of ligands, including thiols and thioethers found on cysteine and methionine residues of peptides and proteins. Even the disulfide linkage, R-S-S-R', which is generally considered a poorer ligand than a thiol or a thioether, binds to and reduces Au^{+3} to Au^{+}. Since there are agents in the biological system that can oxidize Au^{+} to Au^{+3}, gold compounds can, in principle, exist in a variety of different coordination states in the biological system. These properties, and the fact that the concentrations of gold compounds normally encountered in therapeutic situations are very low, make it difficult to determine the chemistry of gold in the biological environment. Gold thiolate complexes were found especially effective at slowing the progression of rheumatod arthritis. Sodium aurothiomalate (myochrysine), aurothioglucose (solganol) and aurothiosulfate (sanochrysine) are water-soluble polymeric antiarthritic compounds that are administered to the patient by injection, so-called injectable or parenteral drugs, while auranofin, which is only slightly soluble in water, is given to the patient orally in capsule form. The earlywork on auranofin and its analogs revealed that Au^{+} complexes that have phosphine and thioglucose ligands were effective in killing B16 melanoma and P388 leukemia cells in culture. One compound that showed a significantly broader range of activity than auranofin and one of its analogs against a number of different tumor models implanted in mice was the tetrahedral cation $[Au(dppe)_2]^{+}$, bis[1,2-bis(diphenylphosphino) ethane]gold(I).

$[Au(dppe)_2]^+$ is active alone, and in combination with cisplatin, against P388 leukemia in mice, and it is also active against various sarcomas in mice. The compound aurocyanide, $[Au(CN)_2]^-$, which is a biotransformation product in chrysotherapy, has been found to inhibit proliferation of HIV in a strain of CD_4^+. A gold complex with two attached thioglucose ligands has been shown to protect MT-4 cells from the HIV virus by binding to a specific cysteine residue on a 120 kDa protein, gp120, which is part of the outer envelope of the virus. The compound $[bpza][AuCl_4]$, where bpza is the diprotonated-chloride form of a bis-pyrazole ligand, inhibits both reverse transcriptase and HIV-1 protease. Since these enzymes function differently in the life cycle of the HIV virus, inhibiting both with a single compound is unusual. Reverse transcriptase is responsible for converting viral RNA into double-stranded DNA prior to the integration of the latter into genomic DNA of the T cell, and HIV-1 protease controls the maturation and production of infectious virons (virus particles). Since $[bpza][AuCl_4]$ is nontoxic to peripheral blood mononuclear cells in the immune system, the compound is thought to have potential as an anti-HIV agent.

A recent report by Sannella et al. (Sanella et al, 2008) showed that auranofin and other gold compounds inhibit the growth of Plasmodium falciparum, a protozoan parasite carried by Anopheles mosquitoes that causes malaria. The researchers suggested that the mechanism by which the gold compounds inhibit the growth of P. falciparum is related to the ability of the complexes to block the function of the enzyme thioredoxin reductase, TrxR.

Nickel is an essential component in different types of enzymes such as urease, carbon monoxide dehydrogenase, and hydrogenase (Abu-Surrah & Kettunen, 2006). Recently, some results showing also apparent potential of this platinum group element in antitumor studies have been reported. For example the cytotoxicity of the nickel (II) complexes containing 1,2-naphtoquinone-based thiosemicarbazone ligands (NQTS) was tested on MCF7 human breast cancer cell line and compared to free ligand and another naphthoquinone, commercial antitumor drug etoposide. According to the reported data, Ni-NQTS complex has the highest antitumor activity with an IC50 of 2.2 μM. The mechanistic study of action showed inhibition of topoisomerase II. Recent studies showed that the corresponding nickel complexes of semicarbazones (Fig 12) have even greater inhibitory effect on MCF7 cell growth. They display IC50 values in 2-5 μM range and also in general they produce lower side effect than thiosemicarbazones.

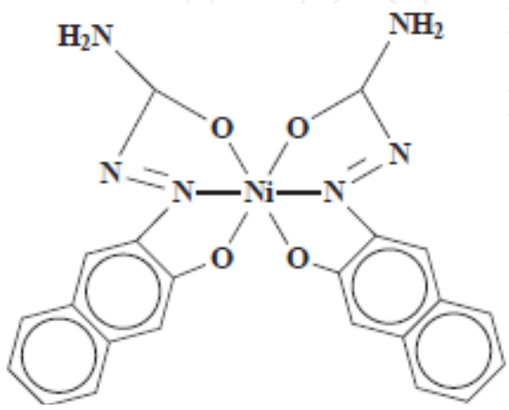


Fig. 12. Structure of a Ni(II)-semicarbazone based antitumor complex (Abu-Surrah & Kettunen, 2006)

In 2010, new methoxy-substituted nickel(II)(salophene) derivatives are synthesized and their anticancer properties were investigated (Lee et al, 2010). It was demonstrated that the most active complex [Ni(II)(3-methoxy-salophene)] (Fig 10) is not necrotic in Burkitt-like lymphoma cells (BJAB) and human B-cell precursor cells (Nalm-6). [Ni(II)(3-methoxy-salophene)] inhibited proliferation and induced apoptosis in a concentration dependent manner, giving evidence for the involvement of CD95 receptor-mediated, extrinsic pathway. Furthermore, [Ni(II)(3-methoxy-salophene)] overcame vincristine drug resistance in BJAB and Nalm-6 cells.

Organometallic compounds like Iron (III)-salophene with selective cytotoxic and antiproliferative properties have also been used in platinum resistant ovarian cancer cells (Rafique et al, 2010).

The low-spin Fe(II) complex sodium nitroprusside (Fig 13) is a clinically used metal-nitrosyl complex (Guo & Sadler, 1999). It is often used to lower blood pressure in humans. Its hypotensive effect is evident within seconds after infusion, and the desired blood pressure is usually obtained within one to two minutes. It is also useful in cases of emergency hypertension, heart attacks, and surgery. Its therapeutic effects depend on release of nitric oxide, which relaxes vascular smooth muscle. Activation in vivo may involve reduction to $[Fe(CN)_5(NO)]^{3-}$, which then releases cyanide to give $[Fe(CN)_4(NO)]^{2-}$ and then nitric oxide.

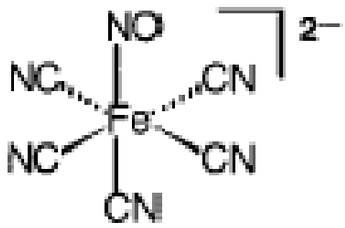


Fig. 13. Fe(II) complex with nitroprusside

The low cytotoxicity of ferrocene, coupled with its lipophilicity ($\log P_{octanol/water}$ = 3.28) and its electrochemical behaviour (redox potential of the ferrocene/ferrocenium couple, E^0 =+0.400 V versus SCE (Saturated Calomel Electrode), suggested that this compound could yield interesting results if incorporated into a known drug (Blackie & Chibale, 2008). The ferrocenyl moiety has several characteristics which make it a good addition to known drug molecules. Its lipophilicity, electron density, relative thermal and chemical stability, and interesting redox behaviour are all favourable in this respect. There are several reported successes of increased efficacy of ferrocenyl analogues of known drugs. Brocard and co-workers, combined Chloroquine and ferrocene in the same molecule by inserting a ferrocenyl group into the side chain of Chloroquine, producing a hybrid compound called Ferroquine (Fig 11), which is more potent than Chloroquine. They have shown that incorporation of a ferrocenyl moiety as an integral part of the side chain of chloroquine between the two nitrogens had superior efficacy to other analogues in which the moiety was terminal on the side chain or bonded to the quinoline nitrogen. Some analogues of the compound were produced bearing different alkyl groups on the terminal tertiary nitrogen. They established that the dimethylamino terminal group was superior in efficacy (Fig 14)

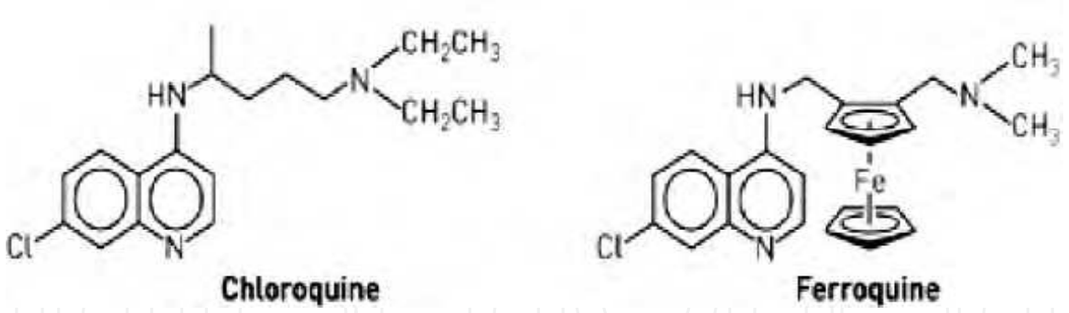


Fig. 14. Molecular structure of Chloroquine and Ferroquine.

The highly established chemistry of ferrocenes that allows an easy and rapid access to a bank of reagents and derivatives has given them a considerable role in the field of analytical chemistry (Rudrangi et al, 2010). Ferrocene-based derivatization of various functional groups and detection techniques is of high interest in particular. The chemistry of ferrocenes is well explored and a wide range of ferrocene derivatives are easily obtained through the established synthetic routes.The ferrocenes allow the use of a large variety of detection techniques like UV/Visible absorption spectroscopy, atomic spectroscopy, atomic absorption spectroscopy (AAS), inductively coupled plasma (ICP) excitation with optical emission spectroscopy (OES) or mass spectrometry (MS), electron impact or electrospray ionization (ESI) MS, and the electrochemical detection (ECD) techniques that include voltammetry or amperometry.

The role of the length of the methylene spacer between the two nitrogens in chloroquine analogues has been shown to have an influence on efficacy in chloroquine resistant strains of *P. falciparum*. Aminoquinolines with short (2-3 carbons) and long (10–12 carbons) methylene side chains are equipotent against chloroquine-sensitive, chloroquineresistant, and multidrug-resistant strains of *P. falciparum*. Whilst aminoquinolines with side chains of intermediate length (4–8 carbons) showed efficacy against chloroquinesensitive strains of *P. falciparum*, they showed a significant decrease in efficacy against chloroquine-resistant strains of *P.Falciparum*. In the chloroquine-sensitive D10 strain, the longer the methylene spacer, the lower the efficacy. It may be that the changes in lipophilicity and *pKa* values and other physicochemical effects of the incorporation of the ferrocenyl moiety into chloroquine are the primary factor in the enhanced efficacy of ferroquine.

As published as a patent application in 2006 (Maurel & Cudennec, 2009), some manganese based organometallic complexes having Mn-SOD like activities, pharmaceutical compositions and dietetic products for use in oxidative stress, including cancer and inflammatory conditions, were also designed. Many human diseases are associated with the overproduction of oxygen free radicals that inflict cell damage (Rafique et al, 2010). Primary reactive oxygen species (ROS) such as superoxide radical, hydrogen peroxide, hydroxyl radicals, and ortho-quinone derivatives of catecholamines exert their cellular effects by modifying DNA, lipids, and proteins to form secondary electrophiles (Zhang & Lippard, 2003). Damage caused by the primary and secondary ROS contributes to the pathogenesis of important human diseases. In particular, one consequence of oxidative metabolism is the generation of superoxide radicals (O_2^{-}.) which mediate extensive damage to the cellular components of living organisms. The molecular dismutation of O_2^{-}. to hydrogen peroxide (H_2O_2) and oxygen (O_2) is catalysed by superoxide dismutases (SODs).These enzymes are

suggested to form the first line of the cell's defence against oxygen damage. Indeed, mice defective for SOD do not survive and reduction of functional capabilities of this enzyme generates an high increase of oxidative stress in connection with strong mitochondrial disabilities of cells. Fe-containing SODs (FeSOD) are largely confined to prokaryotes and the Cu/Zn enzymes (Cu/ZnSOD) predominantly to eukaryotes. Mn-containing SODs (MnSOD) are universally present. In eukaryotes MnSODs are localised in the mitochondria, while the Cu/ZnSODs reside in the cytosol. SODs from various sources are currently of great interest as potential therapeutic treatments for oxidative damage. SOD has function against certain inflammatory processes (In particular, deficiency in Mn-SOD is supposed to have some significance in the development of rheumatoid arthritis). SOD has also function against inflammatory processes in alcohol-induced liver damage. Additional potential therapeutic effects for SOD include: (i) prevention of oncogenesis, tumour promotion and invasiveness, and UV-induced damage; (ii) protection of cardiac tissue against post-ischemia reperfusion damage; (iii) antiinflamatory effect; (iv) reducing the cytotoxic and cardiotoxic effects of anticancer drugs; (v) endothelial disorders; (vi) degenerative diseases; (vii) coagulation disorders, and; (viii) improving the longevity of living cells. Currently bovine Cu/ZnSOD is being utilised for the treatment of inflamed tendons in horses and for treating osteoarthritis in man. It has been shown that the mitochondrial antioxidant enzyme manganese-containing superoxide dismutase (MnSOD) functions as a tumor suppressor gene and that reconstitution of MnSOD expression in several human cancer cell lines leads to reversion of malignancy.

The use of SOD in therapy is limited by its short plasma half-life (clearance by the kidney) and inability to penetrate cell membranes (i.e., extracellular activity only) (Guo & Sadler, 1999). Low molecular mass mimics of SOD are therefore of much potential pharmaceutical interest. For example, a variety of Mn- and Fe-based porphyrins and macrocyclic complexes exhibit SOD mimic activity.

Among metal complexes (Cu, Fe, Mn) capable of catalyzing dismutation of the superoxide anion, those of manganese are a current focus for developing SOD mimics as drugs because of the low in vivo toxicity of this metal ion (Zhang & Lippard, 2003). Mn(II) and Mn(III) macrocycles appear to be particularly promising (Guo & Sadler, 1999). For example, a manganese (II) complex with bis (cyclohexylpyridine)-substituted macrocyclic ligand has been designed as a functional mimic of SOD which was reported to have a significant of inflammation and reperfusion injury (Aston et al., 2001, Rafique et al, 2010). This complex has remarkably high kinetic and thermodynamic stability with regard to dissociation, is oxidatively stable as well and is excreted intact with no dissociation in vivo This stability profile shows that this is a catalytically active SOD mimic. Manganese complexes have also been used to treat cell and tissue oxidative injuries by acting as superoxide anion scavenger. Nitrogen containing macrocyclic complexes of Manganese (II) have shown anti microbial activity. An octahedral geometry for these complexes has been confirmed by spectroscopic analysis. Many manganese complexes have been screened against a number of pathogenic fungi and bacteria to evaluate their growth and potential. Another example to the therapeutic effects of manganese complexes is Mn(III)5,10,15,20-tetrakis(4-benzoic acid)-porphyrin, which can protect against neurodegeneration and is therefore of potential interest for the treatment of brain diseases such as Parkinson and Alzheimer diseases (Meng et al, 2009). Results from systematic modification of the porphyrin ligand demonstrate that placement of four positively charged ortho-(N-alkyl) pyridyl groups (alkyl: methyl and ethyl) in the meso positions of

porphyrin can strongly facilitate the disproportion of O_2^{-}., owing to favorable electrostatic contributions. SC-52608 (Fig 15) is another complex, able to scavenge superoxide and therefore effectively protect the regionally ischemic and reperfused myocardium from injury. Both complexes reduced oxidative stress injury in vivo and they have high stability and catalytic efficacy (Guo & Sadler, 1999; Zhang & Lippard, 2003). In the search for a lipophilic manganese SOD mimic, a dinuclear manganese(III) complex of biliverdin IX dimethyl ester was discovered to have such activity. In this example O_{2-} . dismutation is effected by a Mn(III)/Mn(IV) redox couple. In addition, the manganese complex does not bind to NO and reacts very slowly with H_2O_2, demonstrating specificity towards O_{2-}.

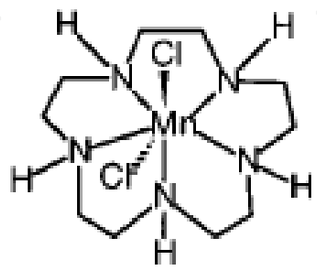


Fig. 15. Molecular structure of SC-52608 (Guo & Sadler, 1999)

The incorporation of manganese into the structure of antioxidants like pyran, pyridine, benzopyran and quinoline i.e., kojic acid, 6-hydroxynicotinic acid, 7-hydroxyflavone, 8-hydroxyquinoline and 8-hydroxyquinoline ethylenediamine, made the complexes possessed the SOD activity and increased radical scavenging activity of antioxidants as expected (Vajgupta et al, 2003). Manganese atom is therefore the essential part for SOD action. 7-hydroxyflavone complex was promising, since it exhibited potent radical scavenging ability and suppressed the MAP-induced hypermotility without reducing the locomotor activity in normal condition, and also improved the impaired learning and memory in transient ischemic mice.

A new approach involves modelling the pharmacological properties of established drugs with organometallic fragments (Ott et al, 2009). The metallocyclic peptide, bacitracin, has an interesting SOD activity. The Mn(II)–bacitracin complex (Piacham et al, 2006) (Fig 16, 17) is potentially useful as an effective agent against oxidative stress (for O_2^{-}. scavenging). On the other hand, probably this Mn(II)–bacitracin may be involved in the respiratory burst mechanism of white blood cells that could enhance bacterial killing by synergistic process to convert superoxide radical into hydrogen peroxide which is used by enzyme myeloperoxidase to convert normally unreactive halide ions into reactive hypohalous acids that are toxic to bacteria. Also its antibiotic mechanism could be useful for bacterial and oxidative stress treatments.

Bacitracin provides strong affinity to divalent metal ions such as Zn(II), Cu(II), Co(II), and Mn(II) in the formation of 1:1 complex. Structural characterization of metallobacitracin showed that it is composed of a cyclic heptapeptide and a short N-terminal sequence containing a thiazoline ring (Fig 17). The divalent metals interact with the cyclic and the linear peptides to form a strong bending structure that encapsulates the metal inside the coordination sphere. It is interesting to note that the established order of binding affinity of the transition metal ions was found to be inversely correlated with the observed SOD

activity reported in this work. The order of metal binding affinity and SOD activity is Cu(II) > Ni(II) > Co(II) ≈Zn(II) >Mn(II) (Brabec & Novakova, 2006) and Mn(II) > Cu(II) > Co(II) > Ni(II), respectively. However, it should be noted that the negative correlation is valid for Mn(II), Co(II), and Ni(II) but not Cu(II).

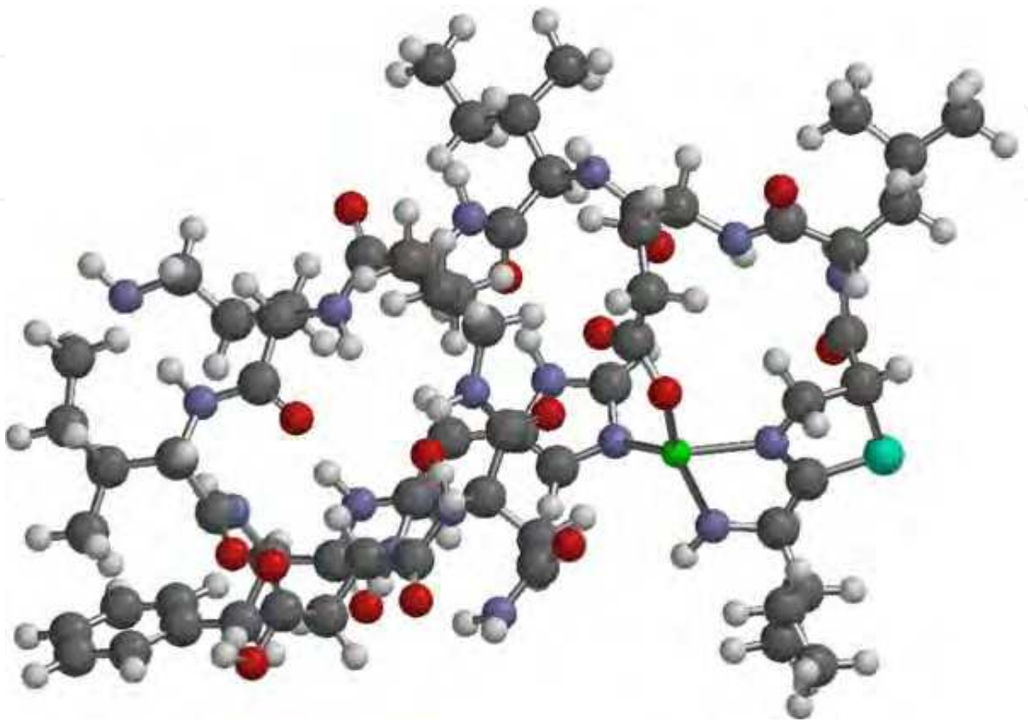


Fig. 16. Molecular modeling of Mn(II)-bacitracin complex (Piacham et al, 2006)

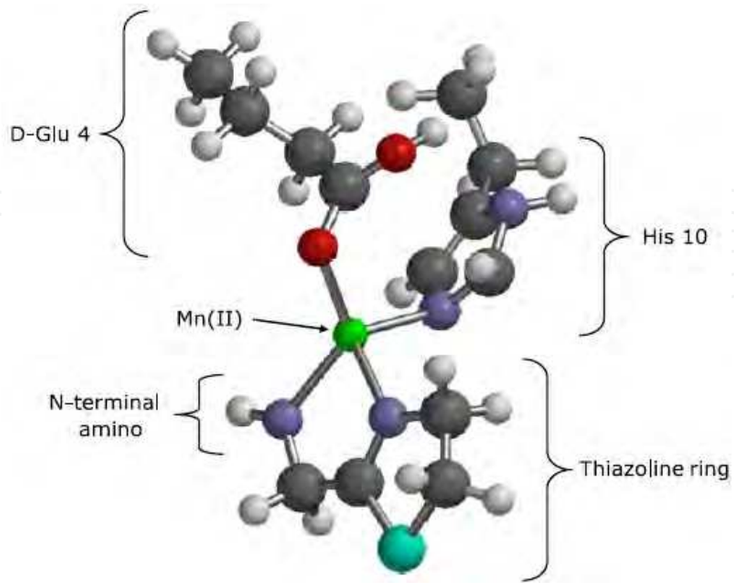


Fig. 17. Mn(II) ligand models derived from metallobacitracin complexes (Piacham et al, 2006)

It is possible that the observed trend, in which Cu(II)–bacitracin did not follow the order of increasing SOD activity with decreasing metal binding affinity, is because Cu(II) takes on a different coordination chemistry from the other divalent metal ions in which Cu(II) forms a tetragonally distorted geometry with two coordinated nitrogens and two coordinated oxygens, particularly, His-10 imidazole nitrogen, thiazoline nitrogen, Glu-4 carboxylate oxygen, and Asp-11 carboxylate oxygen. Proton NMR studies established that Co(II) is coordinated to three nitrogens and one oxygen, namely, His-10 imidazole nitrogen, thiazoline nitrogen, Ile-1 amino nitrogen, and Glu-4 carboxylate oxygen. For the construction of the molecular models of metallobacitracin, it was assumed that Mn(II) and Ni(II) adopt a similar coordination chemistry to that of Co(II) because they all have a vacant d shell.

Cobalt–aspirin complexes are investigated as potential cytostatics (Ott et al, 2009). Aspirin (acetylsalicylic acid) belongs to the family of nonsteroidal antirheumatics (NSAR), which have anti-inflammatory and pain-relieving effects The pharmacological effects of NSARs stem from the inhibition of enzymes in the cyclooxygenase family (COX). Besides the role of NSARs in inflammatory processes, they also seem to be involved in tumor growth. NSARs have thus come into focus as potential cytostatics. It may be possible to improve anti-tumor activity in the case of aspirin by binding it to an organometallic fragment. A hexacarbonyldicobalt–aspirin complex (Fig 18), is shown to inhibit COX activity differently from aspirin. Whereas the effect of aspirin stems from the acetylation of a serine residue in the active center of COX, Co-Aspirin complex does not attack this side chain, but acetylates several other sites instead. This may block access to the active center of the enzyme, resulting in a different activity spectrum for the drug. Experiments with zebra fish embryos showed that in contrast to aspirin, Co-Aspirin inhibits both cell growth and the formation of small blood vessels (angiogenesis). Tumors are dependent on newly formed blood vessels for their nutrients and can be starved out by the inhibition of angiogenesis. In addition, Co-Aspirin modulates other tumor-relevant metabolic pathways. For example, it activates the enzyme caspase, which is involved in processes that lead to apoptosis (programmed cell death).

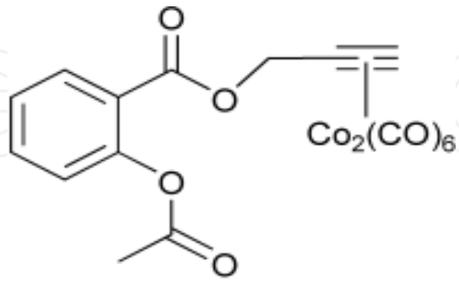


Fig. 18. The structure of hexacarbonyldicobalt–aspirin complex (Ott et al, 2009)

Sadler and coworkers (Meggers, 2007) investigated the binding of metal complexes of 1,4,8,11-tetraazacyclotetradecane (cyclam) macrocycles to the CXCR4 coreceptor and lysozyme as a model protein. In such metallocyclam complexes, the metal is supposed to function by controlling the conformation and configuration of the macrocycle. Additional

direct coordinative bonds with the target protein can be formed with the vacant axial coordination sites. One of the most potent members of this family is the xylyl-bicyclam AMD3100 (Fig 19), a CXCR4 receptor inhibitor, which is in clinical trials for the treatment of AIDS. The anti-HIV activity correlates with its binding to the coreceptor protein CXCR4. CXCR4 is a chemokine receptor that transduces signals of its endogenous ligand, CXCL12/stromal cell-derived factor-1 (SDF-1) (Tamamura et al, 2006). CXCR4 is classified into 7TMGPCR and plays a physiologically critical role by the action of CXCL12 in the migration of progenitors during embryologic development of the cardiovascular, hemopoietic, central nervous systems, etc. In addition, CXCR4 was previously identified as a coreceptor that is used by X4-HIV-1 in its entry into T cells and has recently been proven to be involved in several problematic diseases, including HIV infection, metastasis of several types of cancer, leukemia cell progression, rheumatoid arthritis. Thus, CXCR4 is thought to be a great therapeutic target to overcome these diseases, and several inhibitors directed against CXCR4 have been developed to date. Research performed on AMD3100 analogs have revealed that if it is complexed with certain metals it will increase the bonding affinity to CXCR4 by causing the cyclam rings to take on a folded cis configuration (Snell, 2005). When Zn(II)–xylyl-bicyclam binds with acetate, it undergoes a configuration change and becomes *cis* folded. The cyclam ring can function as a tetradentate coordination ring for transition metals, and it has been shown that chelation of such metal ions by the macrocyclic rings of AMD3100 alters its binding affinity to the CXCR4 receptor (Gerlach et al, 2003). Thus, the Zn^{2+} complex of AMD3100 binds with a 10-fold higher affinity to the receptor as compared to AMD3100 alone and has an up to 6-fold increased potency as an anti-HIV agent. Zn^{2+} is located in the center of the cyclam ring, coordinating the four nitrogens in a planar fashion. Since Zn^{2+} does not coordinate in a square planar conformation, it either obtains a square pyramidal or an octahedral geometry with one or two vacant coordination sites. Zn^{2+} has the option to make strong interactions with both histidine and cysteine residues, as well as acidic residues such as aspartates. The CXCR4 receptor does not contain any free extracellular cysteines; however, the main interaction points for AMD3100 are two aspartates, and furthermore, several histidine residues are located in TM-III, TM-V, and TM-VII (TM: transmembrane domain) pointing toward the main ligand binding crevice (Figure 20). Thus, metal ion coordination could either improve the binding mode of AMD3100 to one or more of the two aspartates, Asp171 and Asp262, or it could pick up interaction with one or more of the His residues that potentially could serve as partners in the coordination of Zn^{2+} bound by the bicyclam.

The level of anti-HIV activity expressed by these metal complexes were Zn>Ni>Cu>Co>Pd in decreasing order. The affinity of AMD3100, a symmetrical nonpeptide antagonist composed of two 1,4,8,11-tetraazacyclotetradecane (cyclam) rings connected through a 1,4-dimethylene(phenylene) linker to the CXCR4 chemokine receptor was increased 7, 36, and 50-fold, respectively, by incorporation of Cu^{2+}, Zn^{2+}, or Ni^{2+} into the cyclam rings of the compound. The rank order of the transition metal ions correlated with the calculated binding energy between free acetate and the metal ions coordinated in a cyclam ring. Construction of AMD3100 substituted with only a single Cu^{2+} or Ni^{2+} ion demonstrated that the increase in binding affinity of the metal ion substituted bicyclam is achieved through an enhanced interaction of just one of the ring systems.

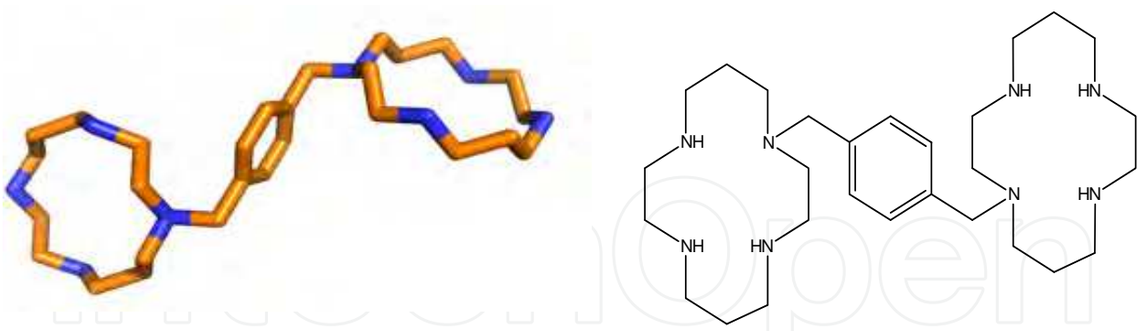


Fig. 19. The 3D (a) and 2D (b) structure of AMD3100 (New Indications for AMD-3100, In: Drug Discovery Opinion, 2008; (Snell, 2005)]

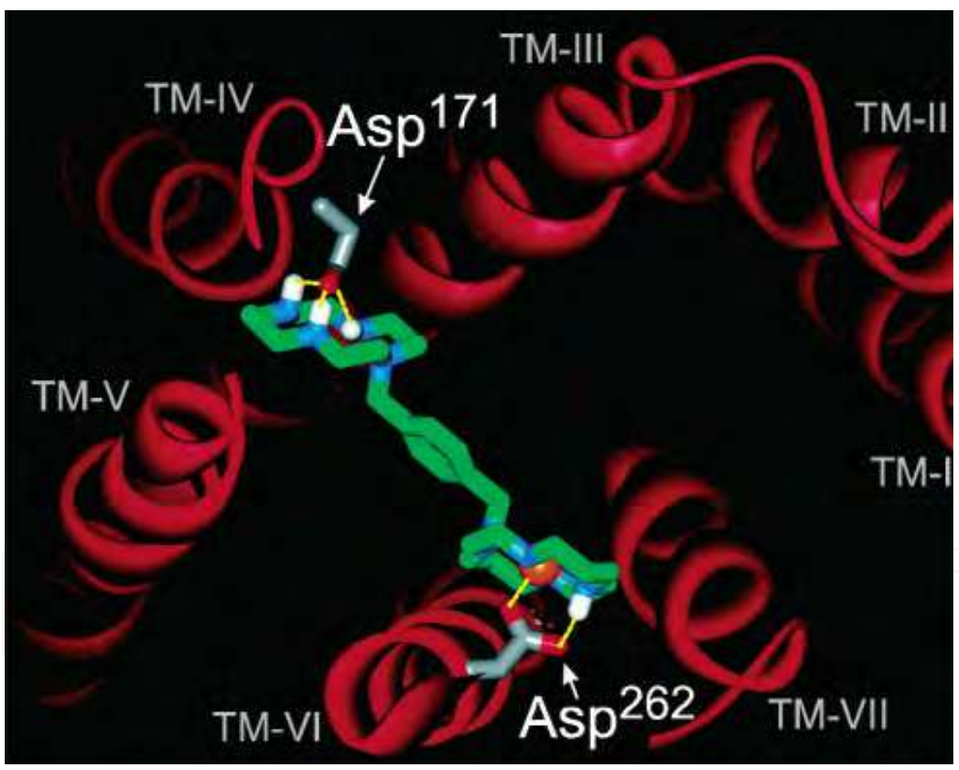


Fig. 20. Molecular model of the main ligand-binding pocket of the CXCR4 receptor with AMD3100(Zn) manually docked into favorable interactions with Asp171 in TM-IV and Asp262 in TM-VI. The receptor model is built over the rhodopsin model of Palcewski et al (Palczewski et al, 2000). The conformation of AMD3100 is based on structural requirements of high antiviral effects of AMD3100 and the crystallographic X-ray structure of 6,6'-spirobis- (1,4,8,11-tetraazacyclotetradecane)-dinickel(II)tetraperchlorate, obtained from the Cambridge Structural Database (Gerlach et al, 2003).

Several low molecular weight nonpeptide compounds having the dipicolylamine-zinc(II) complex structure were also identified as potent and selective antagonists of the chemokine receptor CXCR4 (Tamamura et al, 2006). These compounds showed strong inhibitory activity against CXCL12 binding to CXCR4, and one of them (which has two sets of the [bis(pyridin-2-ylmethyl) amino]methylene unit with zinc(II) complexation at the para-position of benzene) exhibited significant anti-HIV activity.

The use of organometallic complexes are also investigated in the treatment of leishmania. The drugs for treating cutaneous lesions, or, in the case of visceral leishmaniasis (kala-azar), caused by the species L. donovani or L. infantum have traditionally been pentavalent antimonials, aromatic diamidines and fungicides such as amphotericine B (Mesa-Valle et al, 1996). However, these are extremely toxic and cause a great number of side effects. Many recent efforts have been made to synthesize and evaluate alternative compounds for treating these parasites. In the last few years, certain metal complexes have proven anti-tumoral against such protozoan parasites as Trypanosoma cruzi, T. rhodesiense and L. donovani. One property that the tumor cells share with the trypanosomatids is rapid multiplication. Three organometallic complexes which have previously shown in vitro activity against the promastigote forms of L. donovani and have also shown a similar activity against the amastigote like forms, are Cis-Pt(DDH)(Ac.19 2,5-Dihydroxi-benzensulphonic)$_2$ and those of Rh(I): Rh(CO)$_2$Cl(5Cl-2-Methylbenzothiazole), Rh(CO)$_2$Cl(2-Aminobenzothiazole) were investigated by Mesa-Valle et al. (Mesa-Valle et al, 1996). In vitro toxicity of the complexes for the cells of the strain J-774 and the effect exerted on the parasite's biosynthesis of macromolecules were investigated. Only the Rh(I)(CO)$_2$Cl(2-Aminobenzothiazole) complex induced substantial toxicity in the cells. The Rh(I)(CO)$_2$Cl(5-Cl-2-Methylbenzothiazole) complex inhibited DNA, RNA, and protein synthesis. The best candidate, given its slight toxicity for mammal cells and its high activity against Leishmania by inhibiting the synthesis of macromolecules, is found as the complex Rh(I):Rh(CO)$_2$Cl(5-Cl-2-Methylbenzothiazole). Croft et al. investigated the effect of 27 Platinum, Rhodium and Iridium drug complexes against Leishmania donovani amastigotes in mouse peritoneal macrophages in vitro (Croft et al, 1992). Rh(III)-mepacrine, Ir(III) pyrrolidine dithiocarbamate and Ir(III) diethyl dithiocarbamate which showed antileishmanial activity had ED_{50} values of less than 1 μM. The two Iridium complexes produced, respectively, a 50% and 39% suppression of L. donovani amastigotes in the liver of BALB/c mice following the subcutaneous administration of 200 mg/kg for 5 consecutive days. Ultrastructural studies suggest that the amastigote kinetoplast-mitochondrion complex is the primary site of action of the Ir and Rh complexes. Ir-(cycloocta-1,5-diene)-pentamidine tetraphenylborate which has previously been studied on promastigote forms of Leishmania, was investigated for its antileishmanial properties on Leishmania donovani and Leishmania major mouse models, compared with pentamidine used as reference compound in the year 2000 (Loiseau, et al, 2000). In vitro, the iridium complex had the same IC_{50} value on intracellular forms of Leishmania as pentamidine (15 μM). In vivo, the compound could not be injected intravenously due to the DMSO excipient so that the treatments were performed intraperitoneally or subcutaneously. On the L. donovani LV9/Balb/C mouse model, the iridium complex was not toxic after intraperitoneal treatment at 232 mg/kg/day x 5 or

147 μmoles/kg/day x 5, whereas all the mice died within five days when treated at the same dose with pentamidine isethionate. However, only 23% of parasite suppression was observed with the iridium complex. On a L. major MON 74/Balb/C mouse model, susceptible to intravenously administered pentamidine at 6.7 μmoles/kg/day x 5 (54% of parasite suppression), the iridium complex exhibited 32% of parasite suppression after a treatment at 76 μmoles/kg/day x 5 administered subcutaneously. Transmission electron microscopy of amastigotes from infected and treated mice show aggregation of ribosomal material, distension of the nuclear membrane and kDNA depolymerization. The mechanism of action therefore involves several targets: membranes, ribosomes and kDNA. The researchers recommend the Iridium complex as a suitable candidate to be encapsulated in drug carriers such as liposomes or nanoparticles.

Organometallic complexes of Pt, Rh, Ir, Pd, Os, have been synthesized and their trypanocidal activity was studied in vitro and in vivo by Loiseau (Loiseau et al, 1992). Among these, the Ir-(cycloocta-1,5-diene)-pentamidine complex, showed in vitro activity at 60 μg/L on Tripanosoma brucei brucei. Moreover, all infected mice were cured by this compound subcutaneously administered in a single dose at 0.5 mg/kg (0.317 μmol/kg). In the same conditions, pentamidine cured all the mice at 5 μmol/kg. Ir-(cycloocta-1,5-diene)-pentamidine (or P1995) was 16 fold more efficient than pentamidine. Since the chemotherapeutic index of this molecule was 7.5 fold higher than those of pentamidine, the authors recommend P1995 to be considered as a potential trypanocidal drug of the future.

Scientists are looking for alternative approaches for the treatment of diabetes. Several trace elements, such as vanadium and zinc, exert insulin-mimetic effects in in vitro and in vivo systems (Hiromura & Sakurai, 2008). The complexes of these metals and small organic compounds (ligands) improved glucose utilization in both diabetic model animals and human diabetic patients . Both vanadyl and zinc complexes enhanced glucose uptake into the adipocytes without the addition of any hormones. Under the same experimental conditions, these complexes inhibited epinephrine-induced free fatty acid (FFA) release. Because of this insulin-mimetic activity, oxovanadium(IV) (vanadyl) and zinc(II) (zinc) complexes are proposed to be potent antidiabetic agents for both type 1 and type 2 Diabetes Mellitus therapy. New types of insulin-mimetic vanadyl and zinc complexes such as Bis(allixinato)oxovanadium(IV), [VO(alx)2], bis(allixinato)zinc(II) [$Zn(alx)_2$], bis(thioallixin-*N*-methyl)zinc(II) [$Zn(tanm)_2$] (Fig 21), were developed as the potent activators of the insulin signaling pathway. Although these complexes activate Akt/PKB, their critical action sites are slightly different from each other. Different action sites of the metal complexes may depend on the chemical characteristic of the vanadyl and zinc metal ions. The characteristic of ligand is important for the passing through the plasma membrane. $VO(alx)_2$, $Zn(alx)_2$, and $Zn(tanm)_2$ also play unique roles in cells; $VO(alx)_2$ regulates the activation of the FoxO1, while $Zn(alx)_2$ and $Zn(tanm)_2$ regulate the activation of HSL (hormone-sensitive lipase), resulting in the suppression of free fatty acid release. The common mechanism of action of $VO(alx)_2$, $Zn(alx)_2$, and $Zn(tanm)_2$ is their effect on the insulin signaling pathway; this in turn regulates gene transcription and suppresses lipolysis signaling.

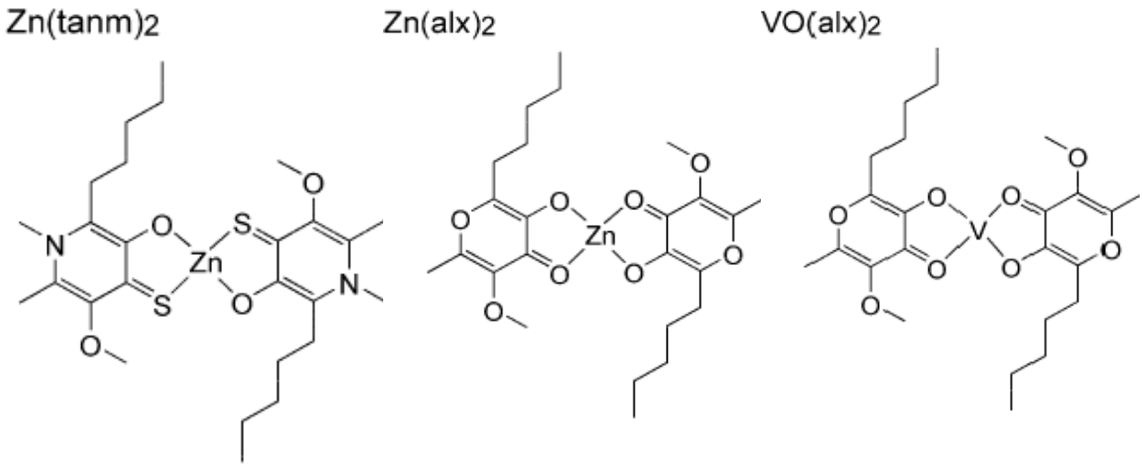


Fig. 21. The molecular structures of $VO(alx)_2$, $Zn(alx)_2$, and $Zn(tanm)_2$ (Hiromura & Sakurai, 2008)

Another application of organometallic complexes is antiinflammatory therapy. Numerous Cu(II) complexes of NSAIDs with enhanced anti-inflammatory activity and reduced gastrointestinal (GI) toxicity compared with their uncomplexed parent drug, were developed (Hiromura & Sakurai, 2008). No Cu(II) anti-inflammatory drug is currently available for oral human use, although an ethanolic gel-base of Cu-salicylate (Alcusal®) is available for topical temporal relief of pain and inflammation in humans (Weder et al, 2002). A Cu(II) dimer of indomethacin (IndoH_/1- (4-chlorobenzoyl)-5-methoxy-2-methyl-1H-Indole-3-acetic acid) with low toxicity is commercially available in Australasia, South East Asia and South Africa in a variety of oral pharmaceutical dosage forms for veterinary use. These low toxicity Cu drugs are of enormous interest, because many of today's anti-inflammatory drug therapies, including the NSAIDs, remain either largely inadequate and/or are associated with problematic side effects, e.g. renal insufficiency and failure, GI ulceration, bleeding or perforation ('NSAID gastropathy'), exacerbation of hypertension and congestive heart failure (CHF). Sorenson reported that Cu(II)-complexes of these antiinflammatory drugs were more active in animal models than either their parent inorganic Cu(II) salt or the parent NSAID . The pharmacological activity was proposed to be due to the inherent physico-chemical properties of the complex itself rather than just that of its constituents, since the amount of Cu(II) in such complexes does not correlate with anti-inflammatory activity. Sorenson reported that a salicylate complex of Cu(II) was ≈30 times more effective than aspirin as an anti-inflammatory agent. In two previous reviews, Sorenson reported over 140 Cu(II) complexes with anti-inflammatory activity. However, limited information is available on the nature of the Cu complexes of NSAIDs in biological matrices and in pharmaceutical formulations. SOD activity, redox behavior, lipophilicity and stability constants may be useful parameters in evaluating the biological activity of these Cu compounds.

The proposed curative properties of Cu-based nonsteroidal anti-inflammatory drugs (NSAIDs) have led to the development of numerous Cu(II) complexes of NSAIDs with enhanced anti-inflammatory activity (Trinchero et al, 2004) Crystalline complexes, Cu(II)–

NSAID (ibuprofen, naproxen, tolmetin, and diclofenac), with a carboxylic function have been studied by means of infrared and Raman spectroscopy. All NSAIDs bind to the metal through the carboxylate group. The spectroscopic data support the formation of dimeric $[Cu_2L_4(H_2O)_2]$ complexes in which the COO^- group behaves as a bridging bidentate ligand. The preparation and properties of the Cu(II) complex $Cu(SAS)_2.H_2O$ are reported for the antiinflammatory drug Salsalate (SAS) (Underhill et al, 1989). The complex is reported to exhibit an increased superoxide dismutase activity compared with the parent drug molecule in the nitroblue tetrazolium assay. Weder and friends synthesized Cu(II) indomethacin complexes (Weder et al, 1999).

Drugs belonging to the non-steroidal anti-inflammatory drug group (NSAID) are not only used as anti-inflammatory and analgesic agents, but also exhibit chemopreventive and chemosuppressive effects on various cancer cell lines (Roy et al, 2006). They exert their anticancer effects by inhibiting both at the protein level and/or at the transcription level. Cu(II) complexes of these NSAIDs show better anti-cancer effects than the bare drugs. UV-Visible spectroscopy was used to characterize the complexation between Cu(II) and two NSAIDs belonging to the oxicam group, piroxicam and meloxicam, both of which exhibit anticancer properties. For the first time, this study shows that, Cu(II)-NSAID complexes can directly bind with the DNA backbone, and the binding constants and the stoichiometry or the binding site sizes have been determined. Thermodynamic parameters from van't Hoff plots showed that the interaction of these Cu(II)-NSAID complexes with ctDNA is an entropically driven phenomenon. Circular dichroism spectroscopy showed that the binding of these Cu(II)-NSAIDs with ctDNA result in DNA backbone distortions which is similar for both Cu(II)-piroxicam and Cu(II)-meloxicam complexes. Competitive binding with a standard intercalator like ethidium bromide (EtBr) investigated by circular dichroism spectroscopy as well as fluorescence measurements indicate that the Cu(II)-NSAID complexes could intercalate in the DNA.

Inspired from Sorenson's studies, new investigations on formation and synthesis of Cu(II) complexes with antiinflammatory drugs were carried out as well as Zn(II) complexes, where some of them are ternary complexes (Anılanmert et al, 2010). The formation conditions and constants of Cu(II)-tryptophan-aspirin and Zn(II)-tryptophan-aspirin ternary complexes in aqueous solutions were determined using potentiometric method to provide chemical data for the synthesis, considering the synergistic capability of aspirin, the antiinflammatory activity of Cu(II), the synergistic effect of tryptophan-aspirin combination in migraine and in diseases which cause immune activation, the stronger analgesic, antiinflammatory and antithrombotic effect of Cu(II)-aspirinate and Zn(II)-aspirinate than aspirin, decreased gastrointestinal toxicity of Cu(II)-aspirinate and Zn(II)-aspirinate than aspirin, the stronger analgesic and antiinflammatory effects of some Cu(II)-amino acid complexes than Cu(II)-aspirinate and the increased bioavailability of Zn(II)-amino acid complexes. The effects of leucine in cancer, wound healing and regulation of glucose in blood, anticancer activity and healing activity of Cu(II) on radiation effects, antiinflammatory effects of Cu(II)-aspirin and Cu(II)-amino acid compounds, sinergistic activity of aspirin and its anticancer effect which was proved in recent years are known (Anılanmert, 2006). Under the light of these effects, the formation of Cu(II)-leucine-aspirin was also investigated using potentiometric and spectrophotometric method. The anticancer action and wound healing effect on skin cancers

topically and through injection into tumours should be investigated in the future. These ternary complexes have only been investigated using potentiometry, UV and IR spectrometry, synthesis studies are going on, yet no in vitro and in vivo study is performed, however they are recommended to be investigated for the above therapeutic effects.

3. Conclusion

In this chapter, clinical uses of organometallic complexes and some prominent studies on new therapeutic complexes were mentioned. Developments in explorations of organometallic compounds, in various therapeutic areas continue to be an active and productive area of research. Increasingly powerful tools, notably spectroscopic techniques like time-resolved infrared are used for identifying and structurally characterizing the solid complex, optical spectroscopic and potentiometric methods are used for monitoring intermediates and species in solution. Besides these preclinical and clinical studies are significantly enhancing our knowledge and understanding of the structure and mechanistic aspects of the therapeutic organometallic complexes.

4. References

Abu-Surrah, A.S., Kettunen, M., Leskelä, M., Al-Abed, Y. (2008), Platinum and Palladium Complexes Bearing New (1R,2R)-(-)-1,2-Diaminocyclohexane (DACH)-Based Nitrogen Ligands: Evaluation of the Complexes Against L1210 Leukemia, *Zeitschrift für anorganische und allgemeine Chemie*, Vol.634, No.14, (October 2008), 2655-2658, 1521-3749 DOI: 10.1002/zaac.200800281

Abu-Surrah, A.S., Kettunen, M. (2006), Platinum Group Antitumor Chemistry: Design and development of New Anticancer Drugs Complementary to Cisplatin, *Current Medicinal Chemistry*, Vol.13, 1337-1357, 0929-8673/06.

Allardyce, C. S., Dyson, P.J. (2006) Medicinal Properties of Organometallic Compounds, In: *Bioorganometallic Chemistry (Topics in Organometallic Chemistry)*, Gerard Simonneaux, Volume 17, pp.177-210, Springer-Verlag, 10 3-540-33047-9 , Berlin, Heidelberg DOI:10.1007/3418_001.

Anga, W. H., Casini, A., Sava, G., Dyson, P.J., (2011), Organometallic ruthenium-based antitumor compounds with novel modes of action, *Journal of Organometallic Chemistry,* Vol. 696, No.5, (March 2011), pp. 989-999, 0022-328X.

Anilanmert, B., Pekin, M., Apak, R. (2010), Investigation of the Formation of Copper(II)-Tryptophane-Aspirin Ternary Complexes, *Asian Journal of Chemistry*, Vol.22, No.10, (November-December 2010), 8060-8072, 0970-7077.

Anilanmert, B. (2006), *Determination of the stability constants of the ternary complexes that tryptophan-aspirin, leucine-aspirin ligands and Cu(II) and Zn(II) metals form, using potentiometric method*, doctorate thesis, Marmara University Institute of Health Sciences, 2006, Istanbul.

Antonarakis, E.S., Emadi, A., (2010), Ruthenium-based chemotherapeutics: are they ready for prime time?, *Cancer Chemotherapy and Pharmacology*, Vol.66, No.1, (March 2010), pp.1–9, 1432-0843.

Aston, K. Rath, N., Naik,A., Slomczynska, U., Schall,O. F., Riley, D.P.: Computer-Aided Design (CAD) of Mn(II) Complexes: Superoxide Dismutase Mimetics with Catalytic Activity Exceeding the Native Enzyme, Inorg. Chem. 2001, 40, 1779-1789, 0020-1669

Bharti, S.K., Singh, S.K. (2009) Recent Developments In The Field of Anticancer Metallopharmaceuticals, *International Journal of PharmTech Research*, Vol.1, No.4, (October-December 2009), pp. 1406-1420, 0974-4304.

Blackie, M.A.L., Chibale, K. (2008), Metallocene Antimalarials: The Continuing Quest, *Metal-Based Drugs*, Vol. 2008, Article ID 495123, doi:10.1155/2008/495123, 1687-5486.

Brabec V, Nováková O. DNA binding mode of ruthenium complexes and relationship to tumor cell toxicity. *Drug Resistance Updates*, Vol.9, No.3, (June 2006), pp. 111-22, 1368-7646.

Clarke, M.J., Zhu, F., Frasca, D.R., (1999) Non-Platinum Chemotherapeutic Metallopharmaceuticals, *Chemical Reviews*, Vol. 99, No.9, (July 1999), pp.2511-2533, 1520-6890.

Clarke, M.J. (2003) Ruthenium metallopharmaceuticals, *Coordination Chemistry Reviews,* Vol.236, No.1-2, (January 2010), pp.209-233, 0010-8545.

Croft, S.L., Neal, R.A., Craciunescu, D.G., Certad-Fombona, G. (1992), The activity of platinum, iridium and rhodium drug complexes against Leishmania donovani., *Tropical Medicine and Parasitology*, Vol. 43, No.1, (March 1992), pp.24-28, 0035-9203.

Dabrowiak, J.C. (2009), *Metals in Medicine*, pp.191-214, John Wiley and Sons, Ltd., Ist. Ed., West Sussex, 978-0-470-68196-1.

Dittrich, C., Hochhaus, A., Schaad, S., Salama, C., Jaehde, U., Jakupec, M. A., Hauses, M.,Gneist, M., Keppler, B. K. (2005) Phase I and pharmacokinetic study of the oral tris-(8-quinolinolato) gallium(III) complex (FFC11, KP46) in patients with solid tumors - a study of the CESAR Central European Society for Anticancer Drug Research – EWIV, *Journal of Clinical Oncology*, *Proceedings of ASCO Annual M*eeting. (June 2005), Vol 23, No. 16S, Part I of II, June 1 Supplement, pp.3205, 0732-183X.

Lentz, F., Drescher, A., Lindauer, A., Henke, M., Hilger, R.A., Hartinger, C.G., Scheulen, M.E., Dittrich, C., Keppler, B.K., Jaehde, U. (2009), Pharmacokinetics of a novel anticancer ruthenium complex (KP1019, FFC14A) in a phase I dose-escalation study, *Anti-Cancer Drugs*, Vol.20, No.2, (February 2009), pp. 97-103, 1473-5741.

Guo, Z., Sadler, P.J. (1999), Metals in Medicine *Angewandte Chemistry International Edition*, Vol.38, No.11, (June 1999), pp. 1512 – 1531, 1521-3773.

Gerlach, L.O., Jakobsen, J.S., Jensen, K.P., Rosenkilde, M.R., Skerlj, R.T., Ryde, U., Bridger, G.J., Schwartz, T.W. (2003), Metal Ion Enhanced Binding of AMD3100 to Asp262 in the CXCR4 Receptor, *Biochemistry,* Vol. 42, No.3, (January 2003),pp. *710-717*, 1520-4995.

Hanif, M. (2010) *From Biomolecules to Organometallic Compounds with Tumor- Inhibiting Properties*, Supervisor: O. Univ.-Prof. Dr. Bernhard K. Kepler, Vienna.

Hannon, M.J., (2007), Metal-based anticancer drugs: From a past anchored in platinum chemistry to a post-genomic future of diverse chemistry and biology, *Pure and Applied Chemistr*y, Vol.79, No.12, (January 2007), pp.2243–2261, 1365-3075.

Hiromura, M., Sakurai, H. (2008), Action mechanism of metallo-allixin complexes as antidiabetic agents, *Pure and Applied Chemistry,* Vol.80, No.12, pp. 2727–2733.

Jaouen, G., Top, S., Vessieres, A., (2006), Chap 3, Organometallics targeted to specific biological sites: The development of new therapies, In: *Bioorganometallics: Biomolecules, Labeling, Medicine,* Ed. Jaouen, G., pp 65-95, Wiley-VCH, 9783527607693, Weinheim.

Katsaros, N., Anagnostopoulou, A. (2002) Rhodium and its compounds as potential agents in cancer treatment., *Critical Reviews in Oncology/ Hematology*, Vol.42, No.3, (June 2002), pp. 297-308, 2002, 1040-8428.

Lee, S., Hille, A., Frias, C., Kater, B., Bonitzki, B., Wolf, S., Scheffler, H., Prokop, A., Gust, R. (2010), [NiII(3-OMe-salophene)]: A Potent Agent with Antitumor Activity, *Journal of Medicinal Chemistry*, Vol.53, No.16, (July 2010), pp 6064–6070, 1520-4804.

Liu, Z., Habtemariam, A., Pizarro, A.M., Fletcher, S.A., Kisova, A., Vrana, O., Salassa, L., Bruijnincx, P.C.A., Clarkson, G.J., Brabec, V., Sadler, P.J. (2011), Organometallic Half-Sandwich Iridium Anticancer Complexes, *Journal of Medicinal Chemistry,* Vol.*54*, No.8, (April 2011), pp.3011– 3026, 1520-4804.

Llorca, C.S.(2005): *New mono- and dinuclear ruthenium complexes containing the 3,5-bis(2-pyridyl)pyrazole ligand, synthesis, characterization and applications*, PhD dissertation, 84-689-2580-2, Girona.

Loiseau, P.M., Mbongo, N., Bories, C., Boulard, Y., Craciunescu, D.G. (2000), In vivo antileishmanial action of Ir-(COD)-pentamidine tetraphenylborate on Leishmania donovani and Leishmania major mouse models, *Parasite*, Vol. 7, No.2, (June 2000), pp.103-108, 1776-1042.

Loiseau, P.M., Craciunescu, D.G., Doadrio-Villarejo, J.C., Certad-Fombona, G., Gayral, P.(1992), Pharmacomodulations on new organometallic complexes of Ir, Pt, Rh, Pd, Os: in vitro and in vivo trypanocidal study against Trypanosoma brucei brucei., *Tropical Medicine and Parasitology*, Vol.43, No.2, (June 1992), pp.110-114, 0003-4983.

Maurel, J.C., Cudennec, C.A., (2009) *Manganese based organometallic complexes, pharmaceutical compositions and dietetic products*, Assignees: MEDESIS PHARMA S.A., IPC8 Class: AA61K3156FI, USPC Class: 514169, Publication date: 10/01/2009, Patent application number: 20090247492.

Meggers, E. (2007), Exploring biologically relevant chemical space with metal complexes, *Current Opinion in Chemical Biology*, Vol.11, No. 3, (June, 2007), pp. 287-292, 1367-5931.

Meng, X., Leyva, M.L., Jenny, M., Gross, I., Benosman, S., Fricker, B., Harlepp, S., He´braud, P., Boos, A., Wlosik, P., Bischoff, P., Sirlin, C., Pfeffer, M., Loeffler, J., Gaiddon, C. (2009) A Ruthenium-Containing Organometallic Compound Reduces Tumor Growth through Induction of the Endoplasmic Reticulum Stress Gene CHOP, *Cancer Research*, Vol.69 , No.13, (July 2009), 5458-5466, 1538-7445.

Mesa-Valle, C.M., Moraleda-Lindez,V., Craciunescu, D., Osuna, A. (1996), Antileishmanial action of organometallic complexes of Pt(II) and Rh(I), *Chemotherapy*, Vol. 91, No.5, (September/October 1996), pp. 625-633, 0009-3157.

New Indications for AMD-3100, In: *Drug Discovery Opinion, DDO Limited, Consultancy for Biotech and Pharma,* 2008, Available from: http://drugdiscoveryopinion.com/2008/08/new-indications-for-amd-3100/

Ogawa, K., Mukai, T., Asano, D., Kawashima, H., Kinuya, S., Shiba, K., Hashimoto, K., Mori, H., Saji, H., (2007), Therapeutic effects of a 186Re-complex-conjugated bisphosphonate for the palliation of metastatic bone pain in an animal model. *Journal of Nuclear Medicine,* Vol. 48, No.1, (January 2007), pp. 122-127, 2159-662X.

Ott, I., Gust R. (2007) Non platinum metal complexes as anti-cancer drugs, *Archive der Pharmazie*, Vol.340, No.3, (March 2007), pp.117-26, 0365-6233

Ott, I., Kircher, B., Bagowski, C.P., Vlecken, D.H.W., Ott, E.B., Will, J., Bensdorf, K., Sheldrick, W.S., Gust, R. (2009) Modulation of the Biological Properties of Aspirin by Formation of a Bioorganometallic Derivative *Angewandte Chemie International Edition*, Vol. 48, No. 6, (January 2009), pp. 1160–1163, 1521-3773

Palczewski, K., Kumasaka, T., Hori, T., Behnke, C. A., Motoshima, H., Fox, B. A., Le, T. I, Teller, D. C., Okada, T., Stenkamp, R. E. , Yamamoto, M., and Miyano, M. (2000) Crystal structure of rhodopsin: A G protein-coupled receptor, *Science*, Vol. 289 , No.5480, (August 2000), pp.739-745, 0036-8075.

Piacham, T., Isarankura-Na-Ayudhya, C., Nantasenamat, C., Yainoy, S., Ye, L., Bülow, L., Prachayasittikul, V. (2006) Metalloantibiotic Mn(II)-bacitracin complex mimicking manganese superoxide dismutase. *Biochemical and Biophysical Research Communications*, Vol.341, No. 4, (March 2006), pp.925-930, 0006-291X.

Rademaker-Lakhai, J.M., van den Bongard, D., Pluim, D., Beijnen, J.M., Schellens, J. H. M. (2004) A Phase I and Pharmacological Study with Imidazolium-trans-DMSO-imidazole-tetrachlororuthenate, a Novel Ruthenium Anticancer Agent, *Clinical Cancer Research*, Vol.10, No.11, (June 2004), pp. 3717-3727, 1557-3265.

Rafique, S., Idrees, M., Nasim, A., Akbar, H., Athar, A. (2010) Transition metal complexes as potential therapeutic Agents *Biotechnology and Molecular Biology Reviews*, Vol. 5, No. 2 (April 2010), pp.38-45, 1538-2273.

Roy S., Banerjee R., Sarkar, M. (2006), Direct binding of Cu(II)-complexes of oxicam NSAIDs with DNA backbone, *Journal of Inorganic Biochemistry*, Vol.100, No.8, (August 2006), pp.1320-1331, 0162-0134.

Rudrangi, S.R.S., Bontha, V.K., Bethi, S., Reddy, V., (2010), Ferrocenes: Legendary Magıc Bullets In Organometallic Chemistry-An Overview, *International Journal of Pharma Research and Development*, Vol.2, No.8, (October 2010), pp.53-61, 0974-9446, Publication Ref No.: IJPRD/2010/PUB/ARTI/VOV-2/ISSUE-8/OCT/008

Sannella, A.R., Casini, A., Gabbiani, C., Messori, L., Bilia, A.R., Vincieri, F.R., Majori, G., Severini, C. (2008), New uses for old drugs. Auranofin, a clinically established antiarthritic metallodrug, exhibits potent antimalarial effects in vitro: mechanistic and pharmacological implications. *FEBS Letters*, Vol.582, No.6, (March 2008), pp.844–847, 0014-5793.

Sekhon, B.S., (2010), Metalloantibiotics and antibiotic mimics - an overview, *Journal of Pharmaceutical Education and Research*, Vol. 1, No. 1, (June 2010), pp.1-20, 0976 – 8238.

Snell, T.L. (2005), Synthesis and Characterization of Cross-Bridged AMD3100 Analogs, *Centaurus*, Vol. 13, pp.27-31, (May 2005), 0008-8994.

Tamamura, H., Ojida, A., Ogawa, T., Tsutsumi, H., Masuno, H., Nakashima, H., Yamamoto, N., Hamachi, I., Fujii, N., (2006), Identification of a New Class of Low Molecular Weight Antagonists against the Chemokine Receptor CXCR4 Having the Dipicolylamine-Zinc(II) Complex Structure, *Journal of Medicinal Chemistry*, Vol.49, No.11, (June 2006), pp. 3412-3415, 1520-4804.

Timerbaev, A.R., (2009), Advances in developing tris(8-quinolinolato)gallium(III) as ananticancer drug: critical appraisal and prospects., *Metallomics,* Vol.1, No.3, (April 2009), pp.193-198, 1756-5901.

T. Schilling, K. B. Keppler, M. E. Heim, G. Niebch, H. Dietzfelbinger, J. Rastetter, A. R. Hanauske (1995), Clinical phase I and pharmacokinetic trial of the new titanium complex budotitane, *Investigational New Drugs* , Vol. 13, No.4, (December 1995), pp.327-332, 1573-0646.

Top, S., Vessières, A., Cabestaing, C., Laios, I., Leclercq, G., Provot, C., Jaouen, G. (2001), Studies on organometallic selective estrogen receptor modulators. (SERMs) Dual activity in the hydroxy-ferrocifen series, *Journal of Organometallic Chemistry,* Vol. 637–639, (December 2001), pp.500-506, 2001, 0022-328X.

Trinchero, A., Bonora, S., Tinti, A., Fini, G. (2004), Spectroscopic behavior of copper complexes of nonsteroidal anti-inflammatory drugs, *Biopolymers*, Special Issue: Selected Papers from the 10th European Conference on the Spectroscopy of Biological Molecules (ECSBM 2003), Vol.74, No.1-2, (October, 2004), pp.120–124, 1097-0102.

Underhill, A.E., Bury, A., Odling, R.J., Fleet, M.B., Stevens, A., Gomm, P.S. (1989), Metal complexes of antiinflammatory drugs. Part VII: Salsalate complex of copper(II) , *Journal of Inorganic Biochemistry*, Vol.37, No.1, (September 1989), pp. 1-5, 0162-0134.

Vajragupta, O., Boonchoong, P., Sumanont, Y., Watanabe, H., Wongkrajang, Y., Kammasud, N. (2003), Manganese-Based Complexes of Radical Scavengers as Neuroprotective Agents, *Bioorganic Medicinal Chemistry*, Vol.11, No.10, (May 2003), pp.2329–2337, 0968-0896.

Valvassori, S.S., Cristiano, M.P., Cardoso, D.C., Santos, G.D., Martins, M.R., Quevedo, J., da Paula, M.M.S. (2006) Pharmacological Activity of Ruthenium Complexes trans-$[RuCl_2(L)_4]$ (L = Nicotinic or i-Nicotinic acid) on Anxiety and Memory in Rats, *Neurochemical Research,* Vol.31, No.12, (December, 2006), pp.1457-1462, 0364-3190.

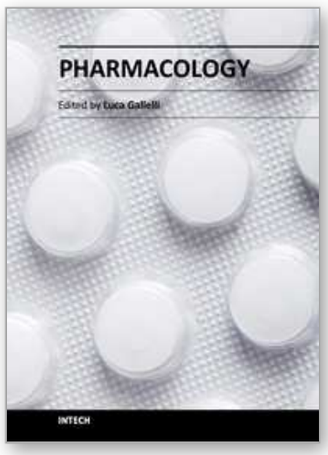
Weder, J.E., Dillon, C.T., Hambley, T.W., Kennedy, B.J, Lay, P.A., Biffin, J.R., Regtop, H.L., Davies, N.M. (2002), Copper complexes of non-steroidal anti-inflammatory drugs: an opportunity yet to be realized, *Coordination Chemistry Reviews*, Vol.232, No.1-2, (October, 2002), pp.95-126, 0010-8545.

Weder, J.E., Hambley, T.W., Kennedy, B.J., Lay, P.A., MacLachlan, D., Bramley, R., Delfs, C.D., Murray, K.S., Moubaraki, B., Warwick, B., Biffin, J.R., Regtop, H.L. (1999),

Anti-Inflammatory Dinuclear Copper(II) Complexes with Indomethacin. Synthesis, Magnetism and EPR Spectroscopy. Crystal Structure of the *N*,*N*-Dimethylformamide, *Adduct Inorganic Chemistry,* Vol.38 , No.8, (April 1999), pp.1736–1744, 1520-510X.

Zhang, C.X., Lippard, S.J. (2003) New metal complexes as potential therapeutics *Current Opinion in Chemical Biology,* Vol.7, No.4, (August, 2003),.481-489, 1367-5931.

Zhao, G., Lin, H. (2005), Metal complexes with aromatic N-containing ligands as potential agents in cancer tretment. *Current Medicinal Chemistry- Anticancer Agents.* Vol.5, No.2, (March 2005), 137-147, 1568-0118.



Pharmacology
Edited by Dr. Luca Gallelli

ISBN 978-953-51-0222-9
Hard cover, 720 pages
Publisher InTech
Published online 14, March, 2012
Published in print edition March, 2012

The history of pharmacology travels together to history of scientific method and the latest frontiers of pharmacology open a new world in the search of drugs. New technologies and continuing progress in the field of pharmacology has also changed radically the way of designing a new drug. In fact, modern drug discovery is based on deep knowledge of the disease and of both cellular and molecular mechanisms involved in its development. The purpose of this book was to give a new idea from the beginning of the pharmacology, starting from pharmacodynamic and reaching the new field of pharmacogenetic and ethnopharmacology.

How to reference
In order to correctly reference this scholarly work, feel free to copy and paste the following:

Beril Anilanmert (2012). Therapeutic Organometallic Compounds, Pharmacology, Dr. Luca Gallelli (Ed.), ISBN: 978-953-51-0222-9, InTech, Available from: http://www.intechopen.com/books/pharmacology/therapeutic-organometallic-compounds-

INTECH
open science | open minds

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

© 2012 The Author(s). Licensee IntechOpen. This is an open access article distributed under the terms of the Creative Commons Attribution 3.0 License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

IntechOpen

IntechOpen