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Transition Metal Complexes with HIV/AIDS Inhibitory Properties

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ABSTRACT

The management of HIV in the human body has been a major research area in the quest to find either the cure or the preventative scientific measure. The quest to manage the virus has been successful using some organic molecules that target one or more of the stages of the replication cycle of HIV rendering it inhibited to continue infecting other host cells. However, the approach is now moving to use of transition metal complexes to manage the HIV infection in the host cells and this review highlights the relevant contributions of such as HIV/AIDS inhibitors. There have been increasing number of reports on the trends for transition metal complexes with anticancer and antimicrobial activity hence this probed the need of such a review. Complexes of vanadium, manganese, iron, copper, cobalt, nickel, zinc, ruthenium, platinum and gold have been reported to be active against HIV-1 virus. The complexes discussed in this review showed anti-viral activity compared to the vehicle control.

1. Introduction

Transition metal complexes exhibit quite a variety of applications ranging from catalysis to materials synthesis, photochemistry, and biological systems. They also display diverse chemical, optical and magnetic properties. They can enhance the electrochemical reactivity of important biomolecules and can promote the electron-transfer reactions of biomolecular systems. Transition metals show variable oxidation states and can interact with several negatively charged molecules. Transition metal can also interact with neutral molecules, such as NH_3 in cis-platin. This activity of transition metals showed potential in the development of metal-based drugs with promising pharmacological application and it offers unique therapeutic opportunities. Transition metal complexes are used as drugs to treat several human diseases like carcinomas, lymphomas, infection control, anti-inflammatory, diabetes, and neurological disorders [1]. Gold (III), platinum (II), ruthenium (II, III, IV), iron (II) and vanadium (IV) complexes for anti-cancer, anti-HIV treatments and as enzyme inhibitors for potential therapeutic applications have been reported [2,3]. The anticancer activity of cisplatin and other closely related platinum compounds arises from their ability to damage DNA in cancer cells, leading to cell death. Compounds containing platinum with a 4^+ charge (non- toxic) must be converted to platinum 2^+ compounds using a directed fine beam of (laser) light before they kill cells. The bicyclam AMD3100 (a potent anti-HIV agent) has an unusual mechanism of action being active at the fusion/uncoating step. The transition metals complexes therefore hold a great promise as other sources of therapeutic drugs and this review intends to look at their role in HIV/AIDS with emphasis on their inhibitory properties.

2.Trends for metal complexes with anti-AIDS activity

Medicinal inorganic chemistry [4] is a field of increasing prominence as metal-based compounds offer possibilities for the design of therapeutic agents not readily available to organic compounds. The wide range of coordination numbers and geometries, accessible redox states, thermodynamic and kinetic characteristics, and the intrinsic properties of the cationic metal ion and ligand itself offer the medicinal chemist a wide spectrum of reactivities that can be exploited.

2.1 Anti-HIV Vanadium complexes

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Vanadium is a physiologically essential element that can be found in both anionic and cationic forms with oxidation states ranging from -1 to +5. This versatility contributes to the unique properties of vanadium compounds, in particular, its complexes with oxidation states +4 and +5 exert pleiotropic effects in cells such as modulation of cell's redox potential [5], affect enzymatic phosphorylation [6], and catalyze the generation of reactive oxygen species [7].

R. Wai-Yin Sun et al [3] reported on Vanadium complexes that exhibit potent anti-HIV properties toward infected immortalized T-cells. However, the instability of vanadium (IV) complexes under physiological conditions was frequently encountered.

To address the problem of instability, porphyrinato ligand was employed to stabilize VO^{2+}. Porphyrins have a rigid square planar scaffold that could prohibit the demetalation reaction.

The oxovanadium (IV) porphyrins **1a**–**e** (Figure 1) are stable in glutathione containing solutions. Their inhibitory effects on HIV-1 replication in Hut/CCR5 cells were evaluated. All these complexes showed anti-viral activities compared to the vehicle control solution (A vehicle control is a solution used such as saline or mineral oil, as a vehicle for an experimental compound in a study), whereas the water-soluble analogue **1a** containing aminosulfonyl functional groups exhibited the highest potency at the 5 μM level with over 97% inhibition.

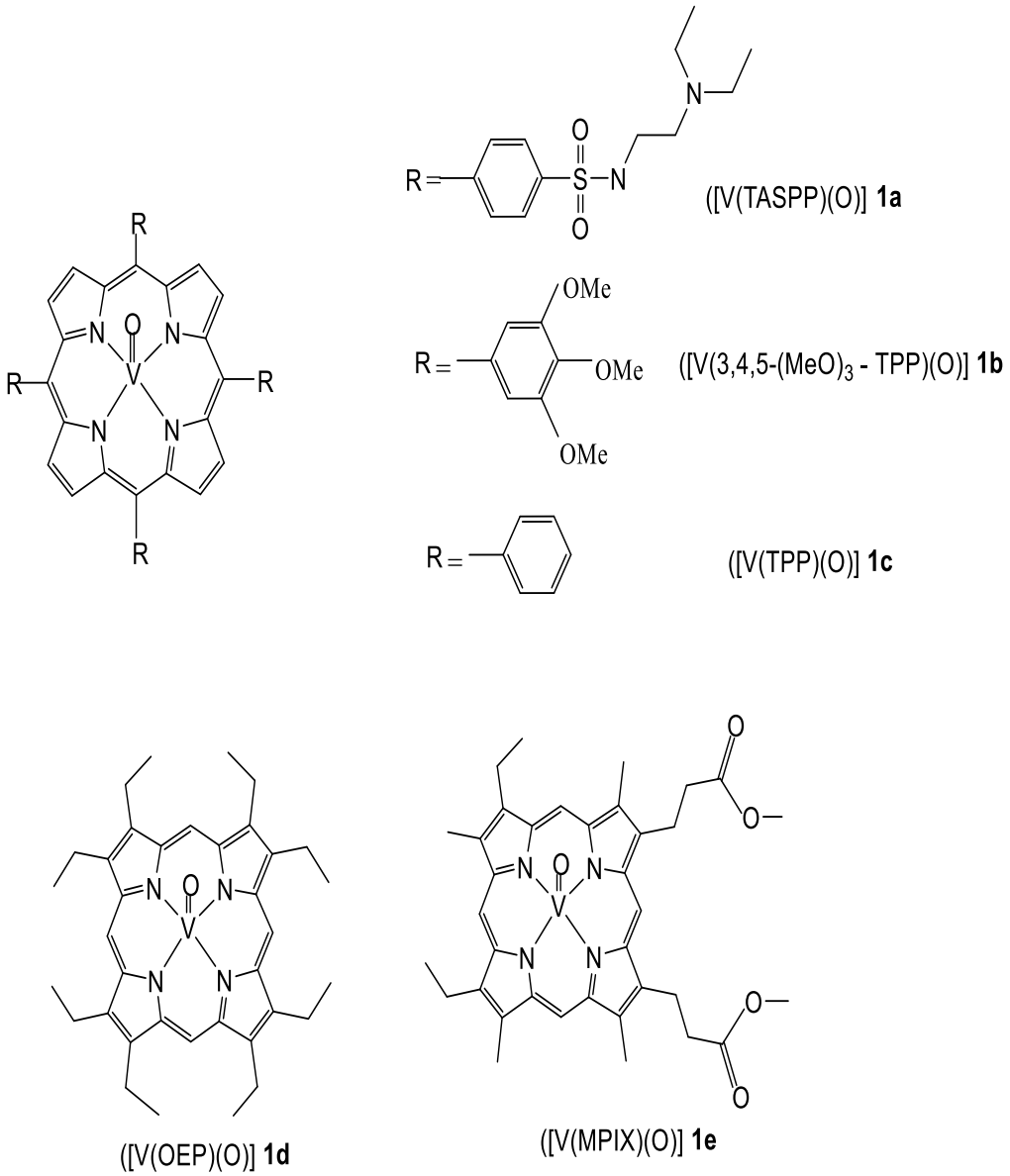


Figure 1. Oxovanadium(IV) porphyrin complexes [8].

HIV-1 reverse transcriptase (RT) is one of the major targets for anti-HIV drugs, and binding of vanadium complexes to RT has been reported [8]. The result of the computational study of structure **1a** showed marked activity against HIV-1 by blocking the entrance of the virus to its targeted host cells (*e.g.* Hut/CCR5).

D 'Cruz et al [9] investigated the potential utility of oxovanadium in combination with thiourea non-

nucleoside inhibitors (NNIs) of HIV-1 reverse transcriptase (RT) for the development of an effective dual-function anti-HIV spermicide shown in figure 2. The NNIs that are currently used to treat HIV-1infection inhibit virus replication by blocking HIV-1 reverse

transcriptase. Two rationally designed substituted phenyl ring containing pyridyl-thiourea NNIs, N-[2-(2-chlorophenethyl)]-N´-[2-(5-bromopyridyl)-thiourea) **2** and N-[2-(2-methoxyphenethyl)]-N´-[2-(pyridyl)-thiourea **3** that exhibited sub-nanomolarIC_{50} values against the drug-sensitive, drug-resistant, and multidrug-resistant strains of HIV-1, were complexed with oxovanadium. The oxovanadium–thiourea [OVT]NNIs, $C_{29}H_{27}Br_2Cl_2N_6O_2S_2V$ **4**, and $C_{31}H_{35}N_6O_4S_2V$ **5**, were synthesized by reacting $VOSO_4$, a V^{IV} compound, with the corresponding deprotonated thiourea NNI compounds as ligands. Each OVT-NNI was composed of two thiourea molecules as ligands with central vanadium in oxidation state V.

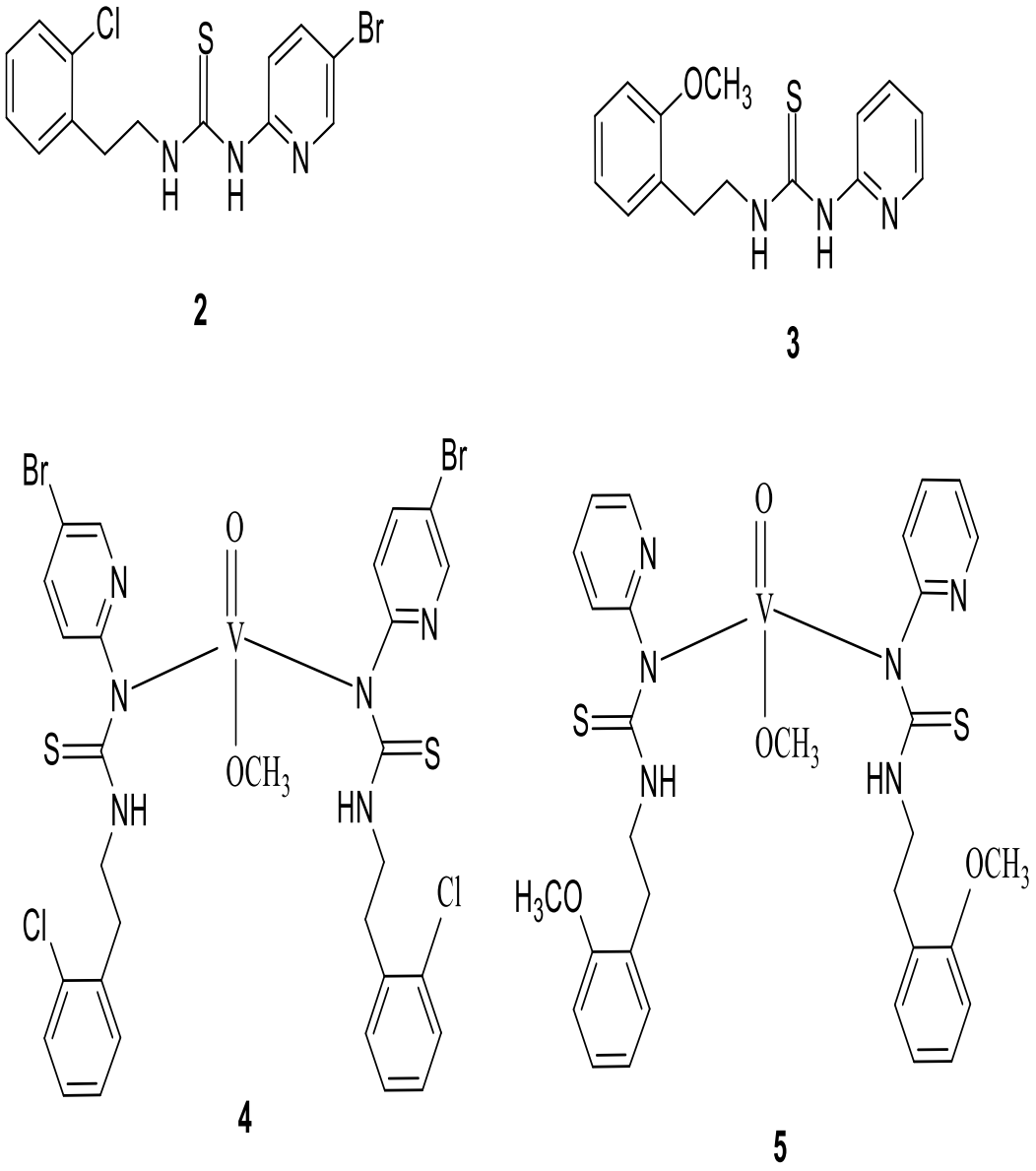


Figure 2. Structures of thiourea NNIs and oxovanadium(V)-thiourea NNIs. The thiourea NNIs **2** and **3** are composed of a chloro (**1**) or methoxy (**2**) substituted phenyl ring, an ethyl linker, a thiourea moiety, and a bromo-substituted (**1**) or unsubstituted (**2**) pyridyl group. The corresponding OVT-NNIs (**4** and **5**) with a square pyramidal geometry are linked to central vanadium (V) via nitrogen atoms with the oxo ligand (O^{2-}) in the axial position. The above structures for OVT-NNIs (**4** and **5**) represent the most probable structures, but not the only ones possible based on the data [9].

Elemental analysis showed that each OVT-NNI used two thiourea molecules as ligands. The new OVT-NNIs as well as their thiourea NNI ligands were evaluated for (i) anti-HIV activity using the cell-free recombinant RT inhibition assays, (ii) cellular HIV replication assays, (iii) spermicidal activity against human sperm by computer-assisted sperm analysis (CASA), and (iv) cytotoxicity against normal human female genital tract epithelial cell using MTT (3-(4, 5-dimethylthiazol- 2-yl)-2, 5-diphenyltetrazolium bromide) dye-reduction

assays. Similar to thiourea NNIs **2** and **3**, the OVT-NNIs **4** and **5**,exhibited potent anti-HIV activity with sub-micromolar $IC_{50[p24]}$ values (0.08 and 0.128 μM, respectively) and sub-micromolar $IC_{50[RT]}$ values (2.1 and 0.87 μM, respectively).Notably, OVT-NNIs were spermicidal against human sperm at low micro molar concentrations (IC_{50} = 34 and 55 μM, respectively) and induced rapid sperm immobilization ($T_{1/2}$ = 12 and 240 s) when compared with their respective thiourea NNI ligands (EC_{50} > 400 μM and $T_{1/2}$ >180 min). Moreover, OVT-NNIs displayed high selectivity indices against normal female genital tract epithelial cells (IC_{50} values > 250 μM) when compared to the detergent-type spermicide, nonoxynol-9, which was cytotoxic at spermicidal concentrations (IC_{50} values 32–64 μM). It appeared from this study that despite the tetrahedral geometry of the ‘‘bent sandwich” structures of vanadocenes or the square pyramidal geometry/‘‘butterfly” structures of oxovanadium (IV) and OVT-NNIs, the rapidity of vanadium (IV/V)-mediated spermicidal activity was dependent on the neutrality of these complexes. Because the neutral complexes of oxovanadium (IV/V) are rapid spermicidal agents, it is likely that these neutral complexes are rapidly transported across the sperm cell membranes.

2.2 Anti-HIV Manganese complexes

Bacchi et al [10] reported on the findings of a study that focused on two ligands, the (2Z)-2-hydroxy-4-oxo-4-(3,5-benzyloxy)phenylbut-2-enoic acid (H_2L^1, L-708,906, Figure 3a), which exemplifies the diketo acid (DKA) family of inhibitors, and the (Z)-3-hydroxy-1-phenyl-3-(1H-1,2,4-triazol-3-yl)prop-2-en-1-one (H_2L^2), designed as a model of S-1360 (Figure 3b), two DKA HIV-1 IN inhibitors, and, in particular, on their Mg^{2+} and Mn^{2+} complexes. Analysis of the biological results suggests that these compounds can act as complexes in their active form. Moreover, the electronic properties of the aromatic framework influence the metal-chelating ability of the pharmacophore and, consequently, the activity. Therefore, the difference in activities may be related to the complexes they preferentially form in solution.

Another relevant point that emerged from this study was that H_2L^2 preferentially chelates with only one metal ion through the keto-enol fragment, while the triazolic moiety is excluded by coordination at least at normal physiological conditions. This was confirmed by spectroscopic and potentiometric measurements and by X-ray diffraction analysis on $[Mn(HL^2)_2(CH_3OH)_2].2CH_3OH$. However, the triazolic moiety is involved in a complex web of hydrogen bonds both in the structure of the ligand and in the structure of the Mn^{2+} complex; in analogy, it could be involved in extensive interactions with IN and/or DNA. Therefore, at least for this ligand, a two-metal binding model could be reformulated: inhibition of IN by diketo acid-like inhibitors strictly requires the chelation of at least one metal ion within the catalytic core. It can be thought that the selectivity displayed by DKAs for strand transfer could not derive by the fact that inhibitors need both metal ions to bind strongly to the enzyme. It is plausible that chelation involves, in the first instance, only one metal and that binding of the inhibitor to the protein is possible only after the conformational changes occurring with 3′-processing, which would allow the accommodation of the ligand within the catalytic core. That also explained the importance of the aromatic substituents of the inhibitors since the hydrophobic portion is fundamental in orientating the drug within the protein active site.

The ligands H_2L^1 and H_2L^2 and their complexes **6**-**9** were tested for their ability to inhibit 3′- processing and strand transfer catalytic activities by oligonucleotide-based assays.

Inhibition of strand transfer activities in vitro assays for complexes **6**-**9** were also evaluated by using either Mn^{2+} or Mg^{2+}. All tested compounds showed anti-IN activity in the nanomolar/micromolar range. In particular, as far as the inhibitory activities of the ligands are concerned, H_2L^1 (IC_{50}, strand transfer = 0.5± 0.3 μM; 3′-processing = 9 ± 2 μM) was 100-fold more potent than H_2L^2 (IC_{50}, strand transfer = 43± 7 μM; 3′-processing > 100 μM). H_2L^2 was about 70-fold less potent than its parent compound S-1360 (IC_{50} = 0.6 ± 1 μM against strand transfer); it has an activity similar to the previously studied H_2L (IC_{50}, 3′-processing > 333; strand transfer = 69 ±4 μM). These data further confirm the fundamental role of the hydrophobic substituent of the chelating moiety, and that the substitution of the diketo acid functionality with a triazolic ring does not affect the activity.The complexes **6**-**9** retained an activity profile analogous to the corresponding free ligands, with IC_{50} values for inhibition of strand transfer ranging from 0.15 to 1.6 μM for **6** and **7**, and from 19 to 49 μM for **8** and **9**, respectively. Interestingly, with IC_{50} values of 0.15±0.03 and 3±0.01 μM (strand transfer and 3′-processing, respectively) the manganese complex **7** proved to be the most potent compound, with 6-fold greater potency than its magnesium congener **6** (IC_{50s} = 0.9 ± 0.5 and 52 ±18 μM, for strand transfer and 3′-processing). A similar “metal dependent” behavior was also shown by **8** and **9**.

Complexes **6** and **7**, as well as **8** and **9**, inhibit IN in similar concentration range, when tested in the presence of either Mg or Mn ions in the reaction buffer. When tested in the presence of Mg ions in the reaction buffer, **6** and **7** show an increase in potency, whereas a slight decrease in inhibition activity for **8** and **9** was observed. These results could be related to the selectivity of the free ligands vs the metal, resulting in different equilibria

in the medium.

The concentration of Mg^{2+} in vitro and in vivo therefore makes plausible the hypothesis that the free ligands could also act as complexes in their active form, as they could coordinate ions in solution before interaction at their putative binding site. Human immunodeficiency

virus type I reverse transcriptase (RT) possesses distinct DNA polymerase and RNase H sites, whereas integrase (IN) uses the same active site to perform 3′-end processing and strand transfer of the provirus DNA.These four enzymatic activities are essential for viral replication and require metal ions. Two Mg^{2+} ions are present in the RT polymerase site, and one or two Mg^{2+} ions are required for the catalytic activities of RNase H and IN.

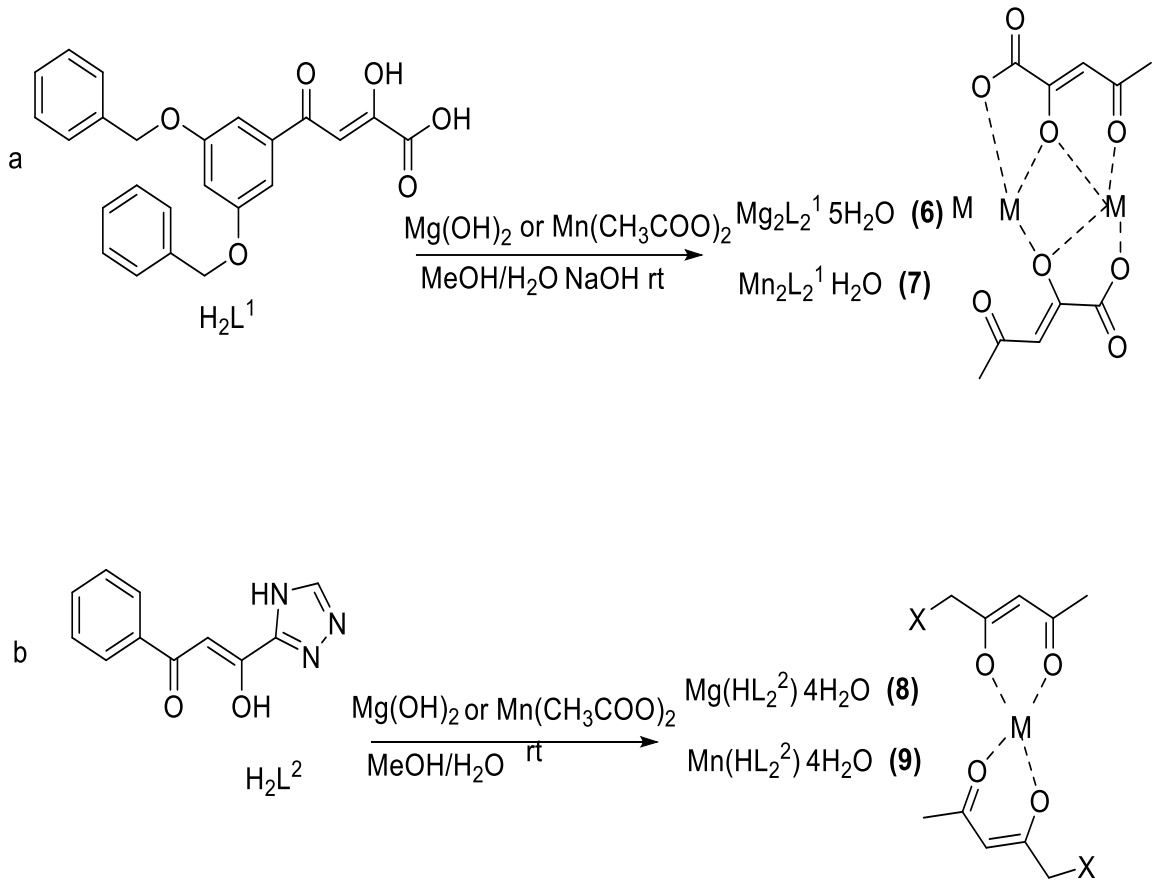


Figure 3. Synthesis of (a) Complexes **6** and **7** with Ligand H_2L^1 and (b) **8** and **9** with Ligand H_2L^2.[10].

Didierjean et al[11] tested the possibility of inhibition of the RT polymerase and RNase H as well as the IN 3′-end processing and transfer activities of purified enzymes by a series of 3,7-dihydroxytropolones designed to target two Mg^{2+} ions separated by ~3.7 Å. The 3, 7-dihydroxytropolones, was used as it inhibits inositol monophosphates by binding theMg^{2+} ions of the catalytic site, thus preventing binding of the substrate.

The RT polymerase and IN 3′processing and strand transfer activities were inhibited at submicromolar concentrations, while the RNase H activity was inhibited in the low micromolar range. In all cases, the lack of inhibition by tropolones and O-methylated 3,7-ihydroxytropolones was consistent with the active molecules binding the metal ions in the active site.

In addition, inhibition of the DNA polymerase activity was shown to depend on the Mg^{2+} concentration. Furthermore, selective inhibitors were identified for several of the activities tested, leaving some potential for the design of improved inhibitors. However, all tested compounds exhibited cellular toxicity that presently limits their applications [11].

2.3 Anti-HIV Iron complexes

Van Asbeck et al [12] reported how iron is involved in the replication of HIV and how iron chelation may interfere in the process to stop viral replication by inhibition of reverse transcriptase or protease activity. There are several possibilities as to how iron is involved in human immunodeficiency virus (HIV) replication. Nuclear factor kappa B (NF-kB) activation, regulating proviral transcription, can be influenced by iron through the production of reactive oxygen species. Sappey et al [13] did show that iron chelation using 5 mM DF or 60 mM deferiprone (L1) inhibited NF-kB activation and the

subsequent replication of HIV-1, as measured by p24 antigen production and reverse transcriptase (RT) measurements in peripheral mononuclear blood cells (PBMC) and other cell types. Another route that influences HIV replication through iron chelation, is through DNA synthesis inhibition by inactivation of iron-dependent ribonucleotide reductase (RR). It is known that non-heme iron is important for the function of RR which is involved in DNA synthesis by reducing ribonucleotides to deoxyribonucleotides [14]. Direct oxidative viral RNA DNA attack is another strategy used in targeting iron chelators against HIV-1. This could be achieved by bleomycin (BLM), a cytostatic agent with the ability to form a complex with DNA and RNA. Chelation may stop iron from viral metabolism; however, chelation may also help in catalysis of reactive oxygen species used by the viral constituents. In combination with existing antivirals, iron chelation could add to improve the treatment of HIV-disease. Hecht [15] observed that BLM binds to Fe^{2+}, and in oxidative environments an electron will be donated to an oxygen atom, this resulting in the formation of a BLM-Fe(III) complex and the generation of reactive oxygen species which can attack DNA and RNA by hydrogen abstraction. A significant inhibition of P24 production by BLM using human PBL and monocyte-derived macrophages, two cell types mostly infected with HIV-1 was also reported by Georgiou et al [16].

They also noted that bleomycin did not affect proliferation or viability of human lymphocytes and macrophages in clinically relevant concentrations, suggesting that BLM attacks the virus directly.

2.4 Anti-HIV Copper complexes

Kalstrom et al [17] on their studies of metal-catalyzed

oxidation of proteins reported that the HIV protease is potently inhibited by copper in an oxygen-independent reaction. Inhibition by copper alone requires the presence of cysteine residues in the protease. However, even a synthetic protease lacking cysteine residues could be inactivated by copper when dithiothreitol was added as an exogenous thiol. The Cu^{2+} ion itself inhibits the protease, but the work of Kalstrom et al[25] elegantly showed that this involves oxidation of cysteine by Cu^{2+} ion. They also noted that the simple Cu^{2+} cation is inactive as an antiviral agent because it cannot penetrate cells or the viral envelope to reach the protease. It was logically concluded that ligands, such as dithiothreitol facilitated the delivery of the complex to the viral target.

The synthesis and characterization of metal complexes with organic bioactive ligands of those with derivatives of sterically hindered o-diphenols (SHD), is one of the promising areas of the search for potential chemotherapeutic agents. Loginova et al [18] reported synthesis and characterization of Co(II), Ni(II) complexes with one of the sulphurous derivatives of SHD, that is 4,6-di-tert-butyl-3-[(2-hydroxyethyl)thio]benzene-1,2-diol (L) which acts as a bidentate O,S-coordinated ligand and yields Co(II) and Ni(II) complexes of the stoichiometry ML_2 which is characterized by square planar geometry. Anti-HIV activities of the ligand and its metal (II) complexes were found to decrease in the sequence $CuL_2 > CoL_2 \sim NiL_2 >$ HL. In the light of the spectral data, magnetic moment and analytical results the mode of bonding in the metal (II) complexes could be represented as shown above (Figure 4). The free ligand and its metal (II) complexes were tested for their anti-HIV activities in cell-based assays (Table 1 below). To evaluate the inhibitory activity of these compounds the MTC/EC_{50} ratio was used, permitting to judge about the broadness of the antivirus activity range and about the degree of toxicity of the compounds tested. All tests were compared with azidothymidine (AZT) as the positive control carried out at the same time under identical conditions.

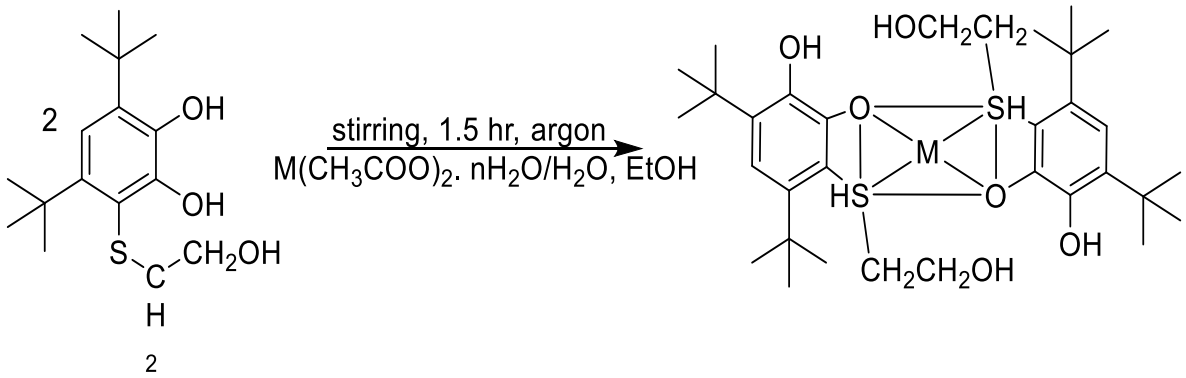


Figure 4. Mode of bonding in the metal (II) complexes [18].

The data obtained demonstrate a very low ligand activity and its high cytotoxicity, while its complexation with metal (II) ions results in a noticeable activity growth along with a decrease in cytotoxicity, as can be seen from comparing the maximal tolerable concentration (MTC) values for the metal complexes and the ligand (Table 1).

Table 1. Anti-HIV activities for the ligand and their metal (II) complexes [18].

Compound	MTC (μg mL^{-1})	MTC/EC_{50}		
		MTT	TBDE	IIF
L	4.0	1.09	1.74	1.01
CuL_2	9.0	8.36	5.14	2.49
CoL_2	13.5	4.07	3.57	3.91
NiL_2	14.0	2.86	2.78	n.a
$Cu(CH_3COO)_2$	1.5	n.a	n.a	n.a
$Co(CH_3COO)_2$	8.0	n.a	n.a	n.a
$Ni(CH_3COO)_2$	3.0	n.a	n.a	n.a
AZT	4.5	28.5	22.5	22.5

It was CuL_2 complex that showed the highest anti-HIV activity among the compounds tested; according to the MTC/EC_{50} value, it may be characterized as a rather active compound, although ranking significantly below AZT. As seen from Table 1, anti-HIV activities of the metal (II) complexes synthesized do not correlate with the toxicity of the metal (II) ions against the viral species tested, as the starting metal salts have demonstrated no anti-HIV activity.

The HIV inhibitory activity of all new compounds was tested. The EC_{50} values showed that all tested compounds were more potent than Atevirdine. Moreover, the benzoimidazolylpyrrole derivative ***(B)*** (EC_{50}= 9 x 10^{-6} μM) had higher therapeutic index than the Telaprevir (VX-950), the standard. The HIV-1 RT inhibitory activity showed that all of the tested compounds showed significant potency but none of them showed higher activity than Atevirdine. The HCV NS3-4A protease inhibitor activity of the tested compounds revealed that the complex formation had great positive effect on the bioactivity, where the Fe-complex **11** was the most potent compound with higher therapeutic index than VX-950, the standard. Also, the cytotoxicity of the synthesized compounds on hepatocyte cell line, showed that Cu-complex **14** was the most potent compound with potency nearly to that of the standard [19]. Antiviral and toxicity data were reported as compound concentration required to inhibit the virus induced cell killing by 50% (EC_{50}). The compounds ***(A)***, ***(B)***, ***(C)***, **10**-**17** were tested for RT inhibitory activity against purified recombinant HIV-1 RT using the cell-free Quan-T-RT assay system (Amersham Corp., Arlington Heights, IL), which utilizes the scintillation proximity assay (SPA) principle. $IC_{50[RT]}$ values (concentration at which the compound inhibits recombinant RT by 50%) were calculated by comparing the measurements to untreated sample.

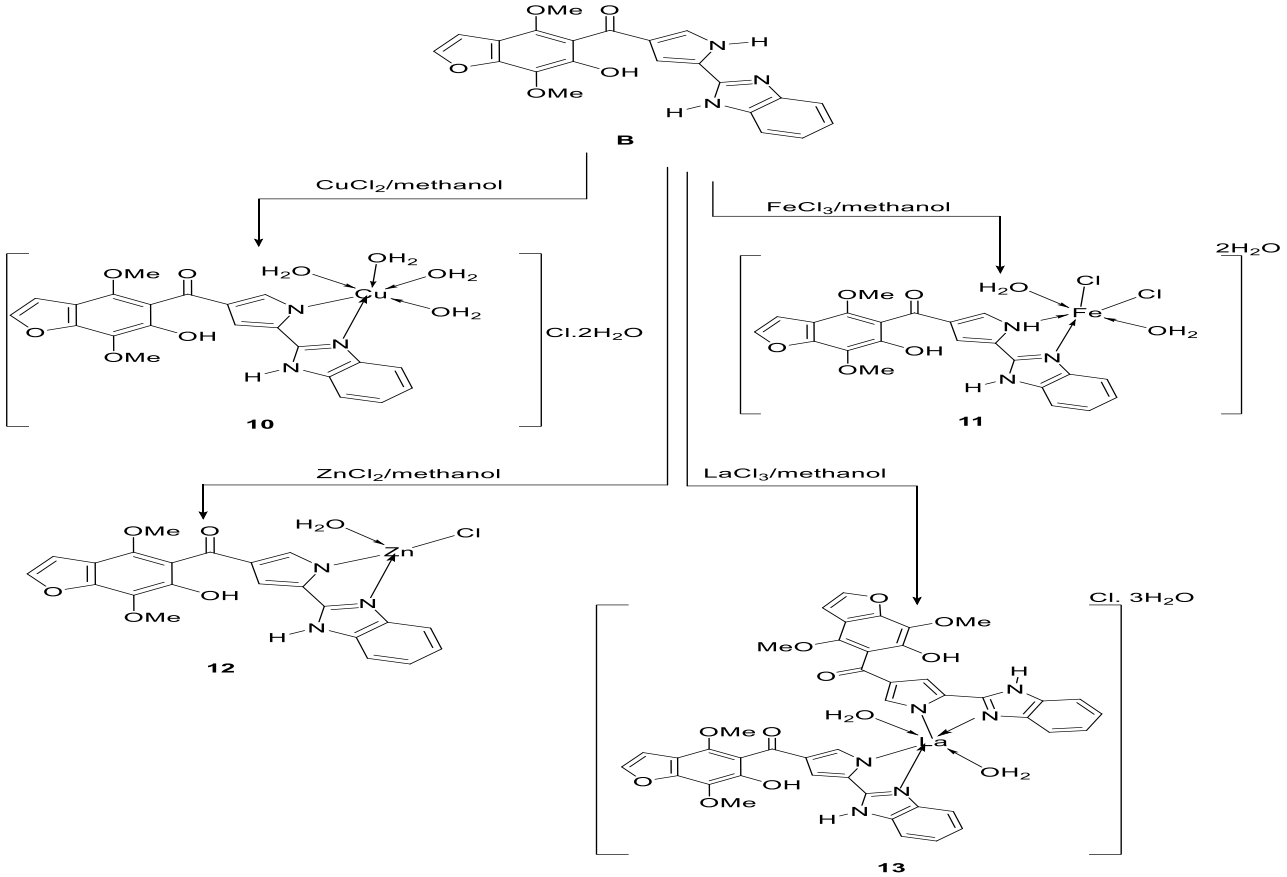


Figure 5. The synthesis of metal complexes **10** - **13** by coordination of compound ***(B)*** to $CuCl_2$, $FeCl_3$, $ZnCl_2$, and $LaCl_3$, respectively [19].

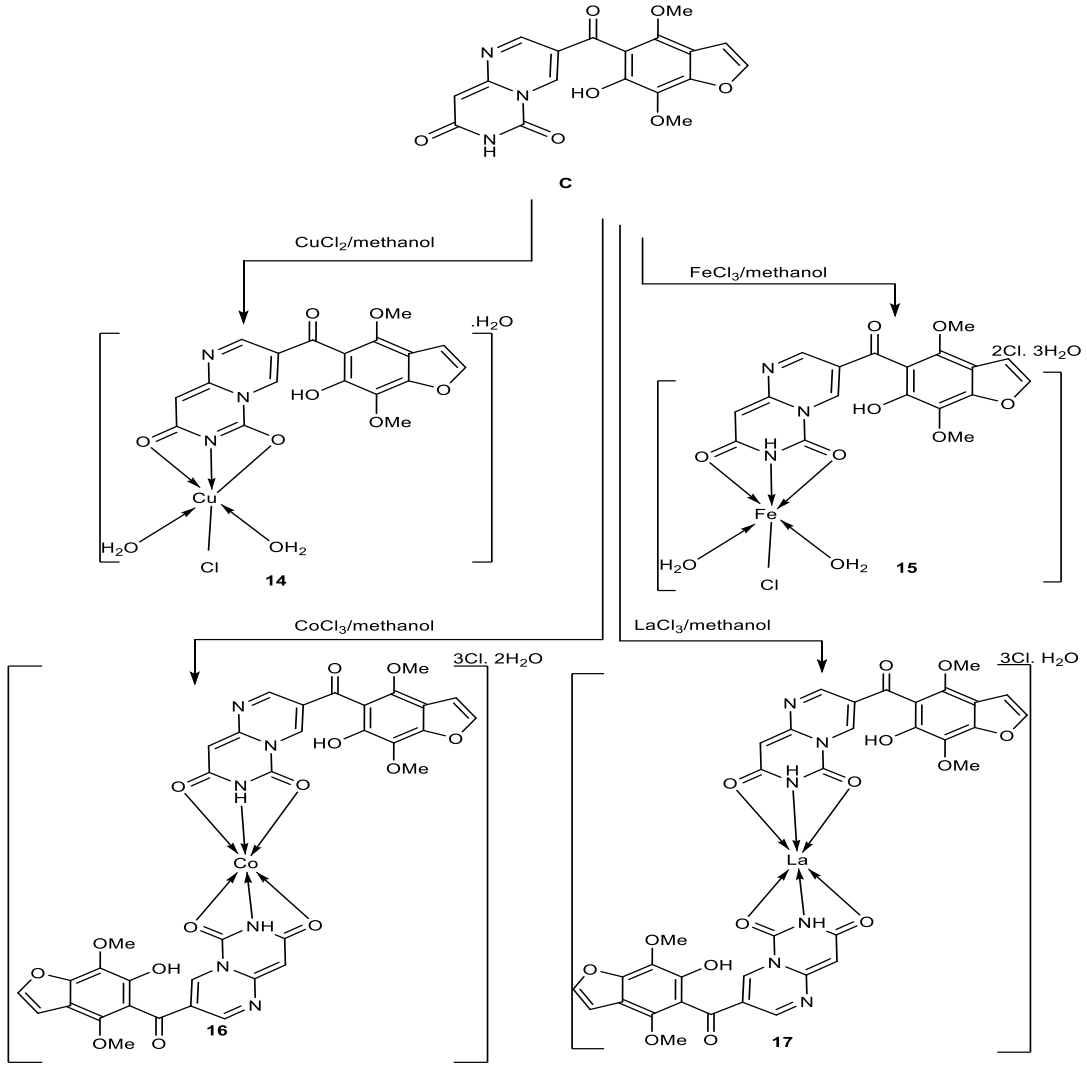


Figure 6: Synthesis of metal complexes **14 - 17** by coordination of ***(C)*** to $CuCl_2$, $FeCl_3$, $CoCl_2$ and $LaCl_3$, [19].

Results of HIV and HIV-RT inhibitory activity of the tested compounds and Atevirdine, the standard drug used, were evaluated (c.f. Table 2). The EC_{50} values listed in Table 2 showed that, the parent compound ***(A)*** (EC_{50}=2.0 x 10^{-6}), the free ligands ***(B)*** (EC_{50}= 9 x 10^{-6} µM) and ***(C)*** (EC_{50} = 10 x 10^{-6} µM) are more potent than Atevirdine (EC_{50} = 10 x 10^{-4} µM). Moreover, the benzimidazolylpyrrol derivative ***(B)*** has much better therapeutic index (TI= 110,000) than the standard drug (TI= 100,000). On the other hand, the complexes **10-17** and Atevirdine have comparable potency. Also, the complexes **10** (TI= 52, 665) and **17** (TI=56, 234) presented relative interesting therapeutic index. Studying the bioactivity of new synthesized compounds indicated that the coordination of ***(B)*** and ***(C)*** to atransition metal ion to form the complexes **10-17** decrease the potency relatively.

Screening of HIV-1 reverse transcriptase inhibition of the synthesized compounds showed that the starting material, furochromone derivative ***(A)***, was the most potent compound with lowest IC_{50} (17 µM). This potency was correlated by high HIV activity. Also, compound ***(B)*** showed high potency against HIV-1 reverse transcriptase inhibition activity with IC_{50} = 34.12 µM, that was paralleled by its potent HIV activity, as the therapeutic index.

This feature made compound ***(B)*** very interesting candidate for in vivo study.

Furthermore, compound ***(C)*** showed high activity toward HIV-1 reverse transcriptase inhibition with IC_{50}= 40.31 µM. Upon coordination of compound ***(B)*** and ***(C)*** to transition metal ions as Cu(II), Fe(III), Zn(II), Co (II) or La(II) to form the complexes **10-17**, the HIV-1 reverse transcriptase inhibition activity decreased which was also paralleled by HIV inhibitory activity reduction. From the above screening of HIV-1 reverse transcriptase inhibitory activity with the HIV activity, the synthesized compounds showed high efficacy in inhibition of HIV reverse transcriptase enzyme which is the enzyme responsible for viral replication. The activity of the potent complexes may be due to intercalation of the metals with the DNA of the virus and hence inhibit its replication. Also, the activity indicates that the complexes have a suitable molecular size and stereochemistry so that metal ions can bind to the enzyme at its active site.

Table 2. The HIV inhibitory activity and HIV- reverse transcriptase inhibition with therapeutic windows of the tested compounds ***(A)***, ***(B)***, ***(C)***, **10-17** and standard [19].

Cpds #	EC50[d]/µM[a]	$IC_{50[RT]}$/µM[b]	Therapeutic index[c]
(A)	2.0×10^{-6}	17.53	32 567
(B)	9.0×10^{-6}	34.12	110 000
(C)	10.0×10^{-6}	40.31	45 786
10	6.8×10^{-4}	87.98	52 665
11	7.1×10^{-4}	90.17	12 768
12	8.5×10^{-4}	92.27	23 498
13	5.5×10^{-4}	82.27	43 498
14	3.1×10^{-4}	80.16	22 567
15	5.4×10^{-4}	90.31	44 324
16	6.5×10^{-4}	96.18	23 458
17	2.1×10^{-4}	78.67	56 234
Atervidine	10.0×10^{-4}	10.00	100 000

[a] Compound concentration required to inhibit the virus induced cell killing by 50%. [b] Compound concentration required to achieve 50% inhibition of recombinant HIV-RT activity. [c] A therapeutic index is the lethal dose of a drug for 50% of the population (LD50) divided by the minimum effective dose for 50% of the population (ED_{50}). (LD_{50}) is the dose required to kill half the members of the tested population. (ED_{50}) is the dosage that produces a desired effect in half the test. [d] EC_{50} & IC_{50} values were estimated by logistic regression analysis. One-way ANOVA ($P < 0.01$) was used to test treatment difference in EC_{50} & IC_{50}. After significant factor by ANOVA individual group differences were analyzed using Holm-Sidak's procedure for multiple comparisons versus control.

García-Gallego et al [20] reported the synthesis and characterization of a sulfonate-containing N-donor ligand in its acid and sodium salt forms and its corresponding metal (Ni, Co, Cu and Zn) complexes in order to combine the potential cooperative effect between the sulfonate groups and the metal center in the treatment of HIV-infected MT-2 cells. The ligands are $Na_2[(DES)MeN(CH_2)_2NMe(DES)]\cdot 2H_2O$(**18**) and $[(DES)MeN^+H(CH_2)_2N^+HMe(DES)]\cdot H_2O$ (**19**),and its corresponding metal complexes, $[\{(DES)MeN(CH_2)_2NMe(DES)\}\text{-}\ M(H_2O)_2]\cdot nH_2O$ [M = Ni (**20**), Co (**21**), Cu (**22**) and Zn (**23**)] as shown on Figure 7 below. (DES = diethanesulfonate).

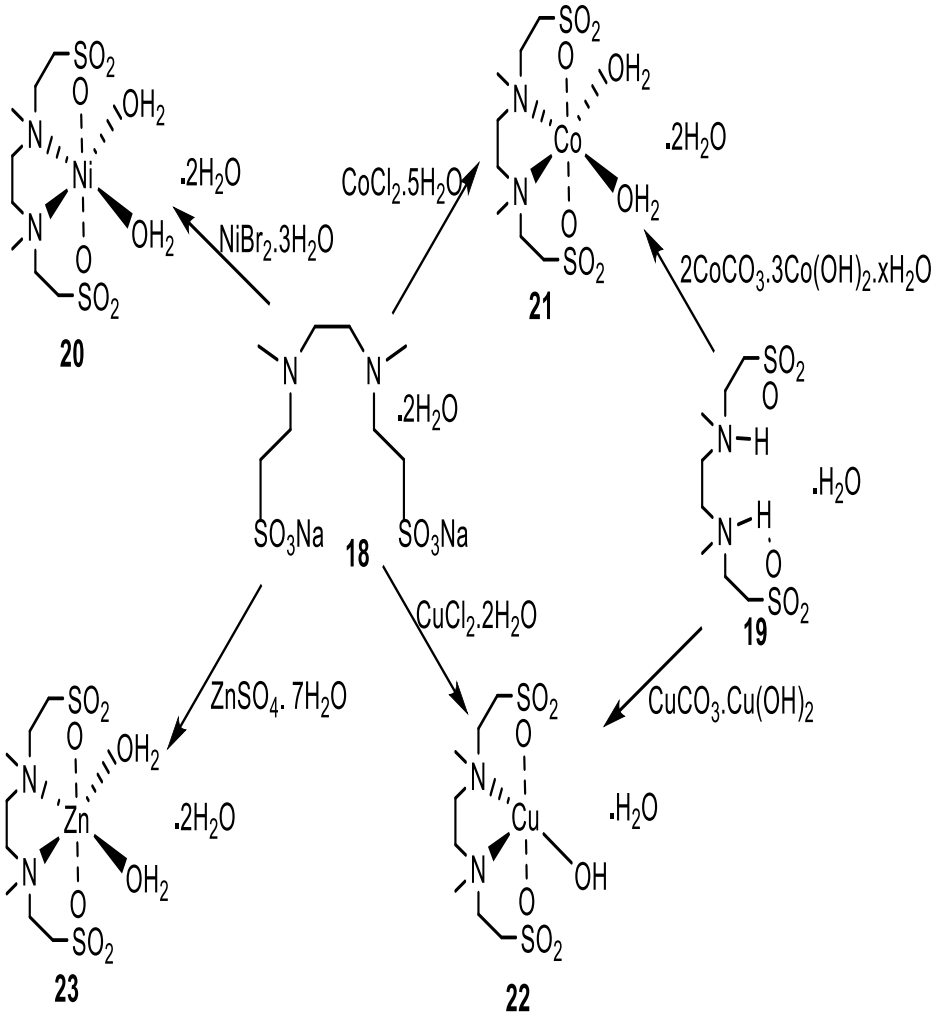


Figure 7. Synthesis of compounds **20-23** by starting from **18** or **19** [20].

It is worth highlighting that the aminosulfonato ligand in its sodium salt form **18**, as the core of the metallic complexes, was not toxic and showed no inhibitory effects against HIV, either in pre-infected or post-infected MT-2 cells. Treatment with nickel and cobalt complexes inhibited HIV replication by around 50% in both pre- and post-infected cells. In the case of the copper complex, 70% inhibition in the pre-infected cells and more than 50% in the post-infected cells were observed.

Because complexes **20**–**22** showed anti-HIV activity in the pre-infected cell experiment, this feature may be indicative of fusion inhibitor activity. However, when the treatment was administrated after cell infection, compounds **20**–**22** were also found to be capable of inhibiting HIV replication, which indicates that they may also act in subsequent steps of the replicative cycle. This dual behavior may be considered the greatest characteristic of these compounds as they combine HIV preventive and therapeutic behavior in a single molecule. In this sense, this family of complexes may be considered as promising new lead compounds for the development of targeted anti-virals.

Lebon et al [21] showed that the copper (II) complex of N1-(4-methyl-2-pyridyl)-2,3,6-trimethoxybenzamide interacts with the active site of the enzyme leading to competitive inhibition of HIV-1protease. On the other hand, N2-pyridine–amide ligands and oxazinane carboxamide ligands were found to be poor chelators of the cupric ion under the enzymatic assay conditions. In these cases, the observed inhibition was attributed to released cupric ions which react with cysteine residues on the surface of the protease.

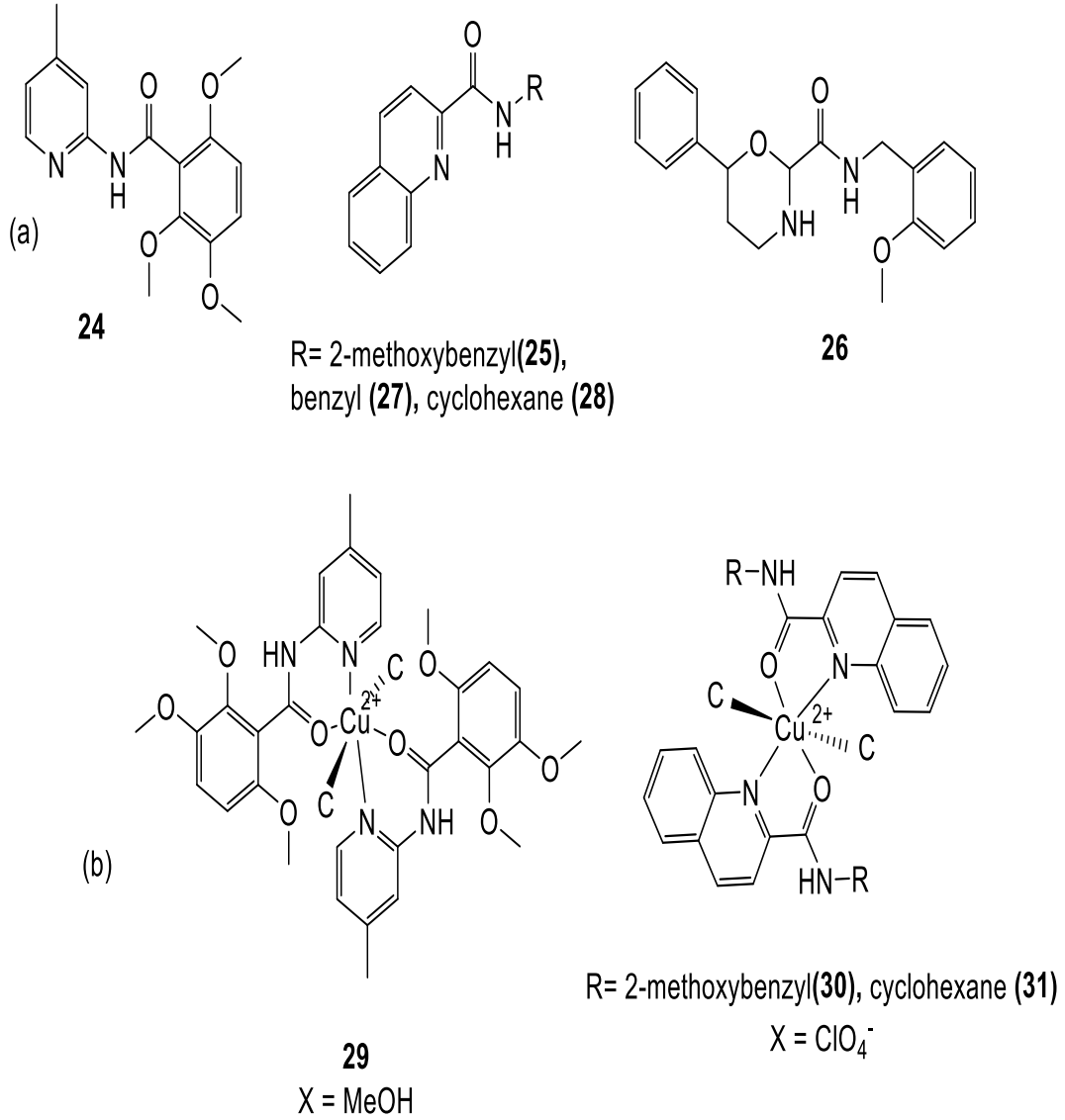
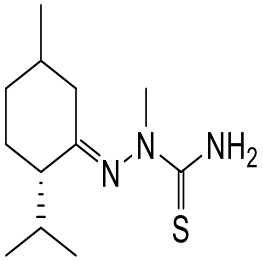


Figure 8: (a) Structure of the pyridine-amide and oxazinane carboxamide ligands studied, (b) crystallographic structure of complexes **29**, **30**, and **31** [21].

The copper ion present in the complex **29** is properly positioned to chelate the structural catalytic water molecule that initiates the proteolytic reaction. The mutant protease was inhibited (> 20%) in the presence of 1.7-2μM of the complex whereas no inhibitory effect was observed on other complexes of copper with N2-pyridine –amide ligands and oxazinane carboxamide ligands. Antiretroviral Activity of Thiosemicarbazone

Metal Complexes (See Figure 9) ([bis(citronellalthio-semicarbazonato) nickel(II)] **33**, and [aqua(pyridoxalthiosemicarbazonato) copper(II)] chloride monohydrate **34**was reported by Pelosi et al [22].

Both compounds exhibited antiviral properties against HIV but not against human T-cell leukemia viruses type 1 and 2 (HTLVs). In particular, the copper complex shows the most potent anti-HIV activity by acting at the post-entry steps of the viral cycle.



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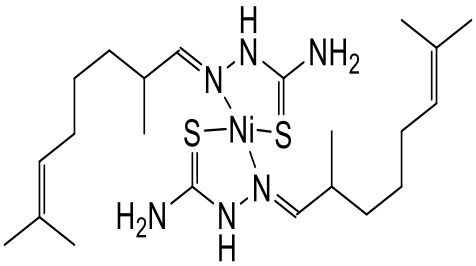

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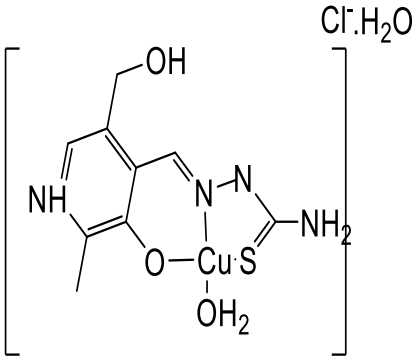

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Figure 9. General formulas for S,S-menthone thiosemicarbazone **32**, [bis(N,S-citronellalthio-semicarbazonato)nickel(II)] **33**, and [aqua(O,N,S-pyridoxalthiosemicarbazonato)copper(II)] chloride monohydrate **34** [22].

The compounds were first tested for their ability to enter cells by diffusion. From the log P_{ow} parameter, the nickel derivative **33** appears to be more prone to diffuse through the cell membrane, while the copper derivative, being charged, is in principle less prone to passive diffusion. Nevertheless, it is the copper complex **34** that presents the better results.

In fact, it inhibits HIV-1 replication in primary T cells and in cell line culture, displaying its antiviral activity during the early post entry step of HIV-1 replication. At the highest concentration (50 μg/mL), compound **32** exhibited the highest antiviral activity (HIV-1 reduction by 75%) whereas compound **33'**s reduction percentage was 80%.

2.5 Anti-HIV Zinc complexes

The anti-HIV-1 activity of zinc complex of Baicalin (BA), a flavonoid compound extracted and purified from the Chinese medicinal plants *Scutellaria baicalensis* Georgi, (BA–Zn) in vitro was reported by Wang et al [23] (See Figure 10). Baicalin is one of the leading natural products used for the chemotherapy of HIV infection [24], is reported to interfere with the interaction of HIV-1 envelope with HIV-1 co-receptors on cell surface and block HIV-1 entry into target cells [25].

Zinc is indispensable for the maintenance of optimal cell functions as an essential nutrient. Zinc ions have mitogenic effect on the lymphocyte proliferative response in healthy controls as well as in HIV-1 positive asymptomatic individuals in vitro Zinc treatment of PHA stimulated the peripheral blood mononuclear cells (PBMC) derived from HIV-1 positive individuals significantly enhanced[^{3}H] thymidine incorporation and the apoptotic percentage of PBMC was decreased [26]. The zinc complex of baicalin (BA–Zn) showed lower cytotoxicity and higher anti-HIV-1 activity compared with those of BA in vitro. The 50% cytotoxicity concentration (CC_{50s}) of BA–Zn and BA were 221.52

and 101.73 μM, respectively. The cytotoxicity of BA–Zn was observed at 1.2-fold lower than that of BA. The HIV-1 induced syncytium formation was observed to be inhibited by BA and BA–Zn. The EC_{50s} of this BA–Zn complex (29.08 μM) and RT production (31.17 μM) were lower than those of BA (43.27 and 47.34 μM, respectively).BA–Zn was more effective than BA in inhibiting the activities of recombinant RT and HIV-1 entry into host cells on inhibiting HIV-1 induced syncytium formation.

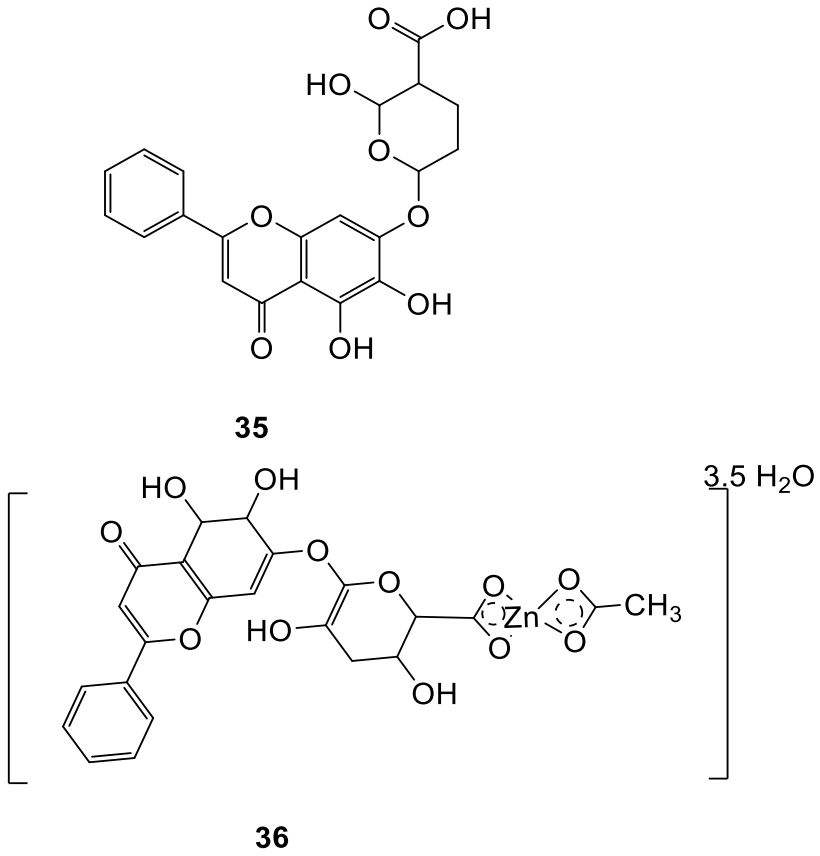


Figure 10. The molecular structures of baicalin (BA) **35** and zinc complex of baicalin (BA–Zn) **36** [23].

Table 3. The summary of cytotoxicity and anti-HIV-1 activities of BA and BA–Zn in C8166 cells [23].

Compounds	Cytotoxicity (CC_{50}, μM)	Anti-HIV-1 activities (EC_{50}, μM)		
		Syncytia	**p24**	**RT**
BA	101.73 ± 3.49	43.27 ± 3.85	41.94 ± 15.01	47.34 ± 6.92
BA–Zn	221.52 ± 1.13	29.08 ± 0.60	70.35 ± 7.23	31.17 ± 10.46

In this study BA–Zn was shown to be a novel HIV-1 inhibitor with better anti-HIV-1 activities than BA. Coupling with zinc did not change the target of BA on HIV-1 RT. Moreover, the EC_{50} of BA–Zn on inhibiting recombinant HIV-1 RT activity was more than two fold lower than that of BA. When dimerized and complexed with zinc, the anti-HIV-1 activity and cytotoxicity of cyclam (1,4,8,11-tetraazacyclotetradecane) were increased and decreased, respectively. This suggest that configurational selectivity of the zinc complex of cyclam and the zinc complex of the bis-tetraazamacrocycle xylyl-bicyclam played a major role in the recognition of HIV-1coreceptor CXCR4, which was relevant to the anti-HIV-1 activity of the compounds. BA was one of the HIV-1NNRTIs. All of the NNRTIs interacted with an allosterical non-substrate binding site on RT. The configuration of BA–Zn may be more adaptable than that of BA for binding with the allosterical site.

Haraguchi et al [27] on their research on inhibition of HIV-1 infection by zinc group metal compounds

examined 37 metal compounds for their inhibitory activities against infection with HIV-1 and found that zinc group metal compounds, namely, zinc acetate ($(CH_3COO)_2Zn·2H_2O$), zinc chloride ($ZnCl_2$), zinc nitrate ($Zn(NO_3)_2·6H_2O$), cadmium acetate ($(CH3COO)_2Cd·2H_2O$) and mercury chloride ($HgCl_2$), inhibited the expression of HIV-1 antigensin C8166 cells (Figure 11A) whilst other32 metal compounds hardly affectedHIV-1 infection at non-cytotoxic concentrations. Cadmium and mercury compounds at 1-10 µg/ml (shown in Figure 11B) and zinc compounds at 100 µg/ml strongly inhibited HIV-1 infection, although the cadmium, mercury and zinc compounds had severe cytotoxities at 100, 100 and 1000 µg/ml, respectively. Their IC_{50s} for inhibition of HIV-1infection were calculated to be 8, 8, 13, 0.18 and 0.12 µg/ml, respectively. These compounds more specifically inhibited HIV-1 transcription than cellular RNA synthesis, while they did not inhibit HIV-1-induced syncytium formation and HIV-1 viral DNA synthesis following HIV-1 infection. The metal compounds may owe their anti-HIV-1 effects to inhibition of HIV-1 DNA to RNA transcription, rather than inhibition of the adsorption, penetration or reverse transcription step of HIV-1 infection.

It is obvious that cadmium or mercury, because of their toxic potential, cannot be used clinically. Zinc, however, is an essential element and is detected in serum at about 1 µg/ml. It is possible that metal complexes may be found with higher anti-HIV-1 potency and/or lower toxicity than those reported by Haraguchi et al [27], and that this lead may yield useful drug candidates for the treatment of HIV-1 infections.

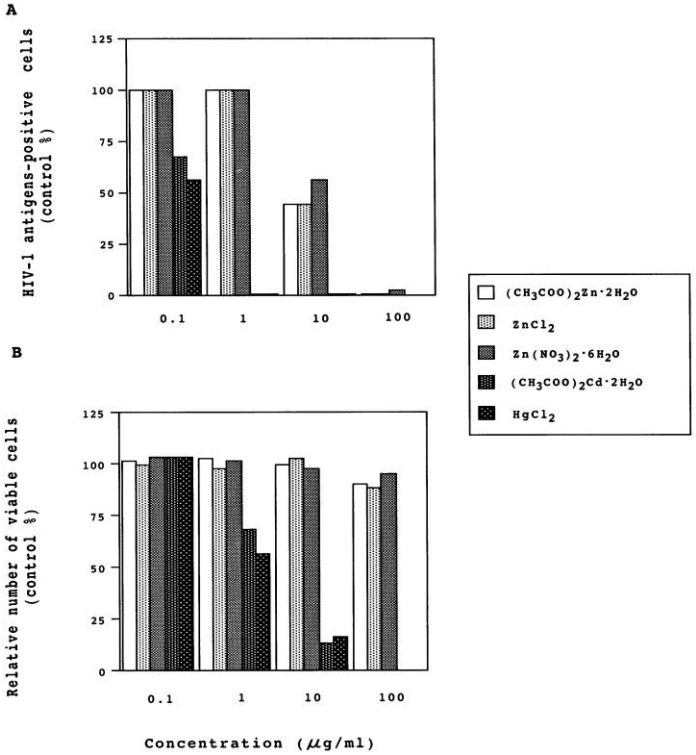


Figure 11. Anti-HIV-1 activities and cytotoxities of metal compounds [27].

C8166 cells were infected with HIV-1 and cultured in the presence of metal compounds. After incubation for 4 days, the percentage of HIV-1 antigen-positive C8166 cells was determined by IFA (A). The viability of C8166 cells was determined by the trypan blue dye exclusion test after incubation with the metal compounds for 4 days (B). Ross et al [28] synthesized four novel zinc (II) complexes (See Figure 12) with hexyl-Me_2-cyclam (HMC; 3,14-dimethyl-2,6,13,17-tetraazatricyclo docosane), **37**,and naphthyl-hexyl-Me_2-cyclam (NHMC; 2,13-bis(1-naphthylmethyl)-5,16-dimethyl-2,6,13,17-tetraazatricyclo docosane), **38**, as ligands. The X-ray crystallographic data for Zn(II)–HMC diacetate, **39** showed that zinc is six-coordinate in a distorted octahedral environment bound to four equatorial N atoms from the macrocycle and two axial acetato O atoms. The 14-membered metallo-macrocycle adopts a *trans*-III (RRSS) configuration with two six-membered rings in chair forms and two five-membered rings in *gauche* forms. In the chloride Zn(II)–HMC complex **40**, zinc appears to be 5-coordinate with square-pyramidal geometry. Interestingly, the chloro Zn(II)–NHMC complex **41** crystallized in a *trans*-I configuration containing 4-coordinate tetrahedral zinc bound to three cyclam ring N atoms, a possible model for intermediates formed during the uptake and release of metals by cyclams. The ligand **37** and the zinc complex **39** (Figure 13) were active towards viral strains HIV-1 (III_B) (IC_{50} values of 10.51 ± 0.23 and 3.50 ± 0.33 µM, respectively), and HIV-2 (ROD) (IC_{50} values of 133.78 ± 14.10 and >110.67 µM, respectively). 2D [1H, 13C] and [1H, 15N].

2.6 Anti-HIV Ruthenium complexes

Ruthenium based complexes as protein kinases and HIV-1 reverse transcriptase inhibitors has been reported by Che et al [2]. This chemotherapeutic activity is found in staurosporine. Staurosporine is a nonspecific protein kinase inhibitor. Its potency has been realized by replacing the carbohydrate unit of staurosporine with various ruthenium fragments (See Figure 14).

A non-toxic mixed-valent tetranuclear ruthenium oxo oxalato cluster (Figure 15) which exhibits anti-viral activities toward R5-and X4-tropic HIV-1 and cytoprotective activity toward HIV-1 infected cells was also reported by Wong et al [29]. This ruthenium complex was evaluated for its anti-viral activity toward R5-tropic HIV-1(BaL) infection/replication and compared to vehicle control (AZT), it exhibited promising anti-HIV-1 activity with over 98% inhibition of viral replication.

The dose dependent manner of its anti-HIV activity has been demonstrated (i.e., 65% inhibition at 0.5 µM and 98% inhibition at 50 µM). To confirm whether the complex was endowed with selective anti-viral activity instead of killing the host cells, the cell viabilities of

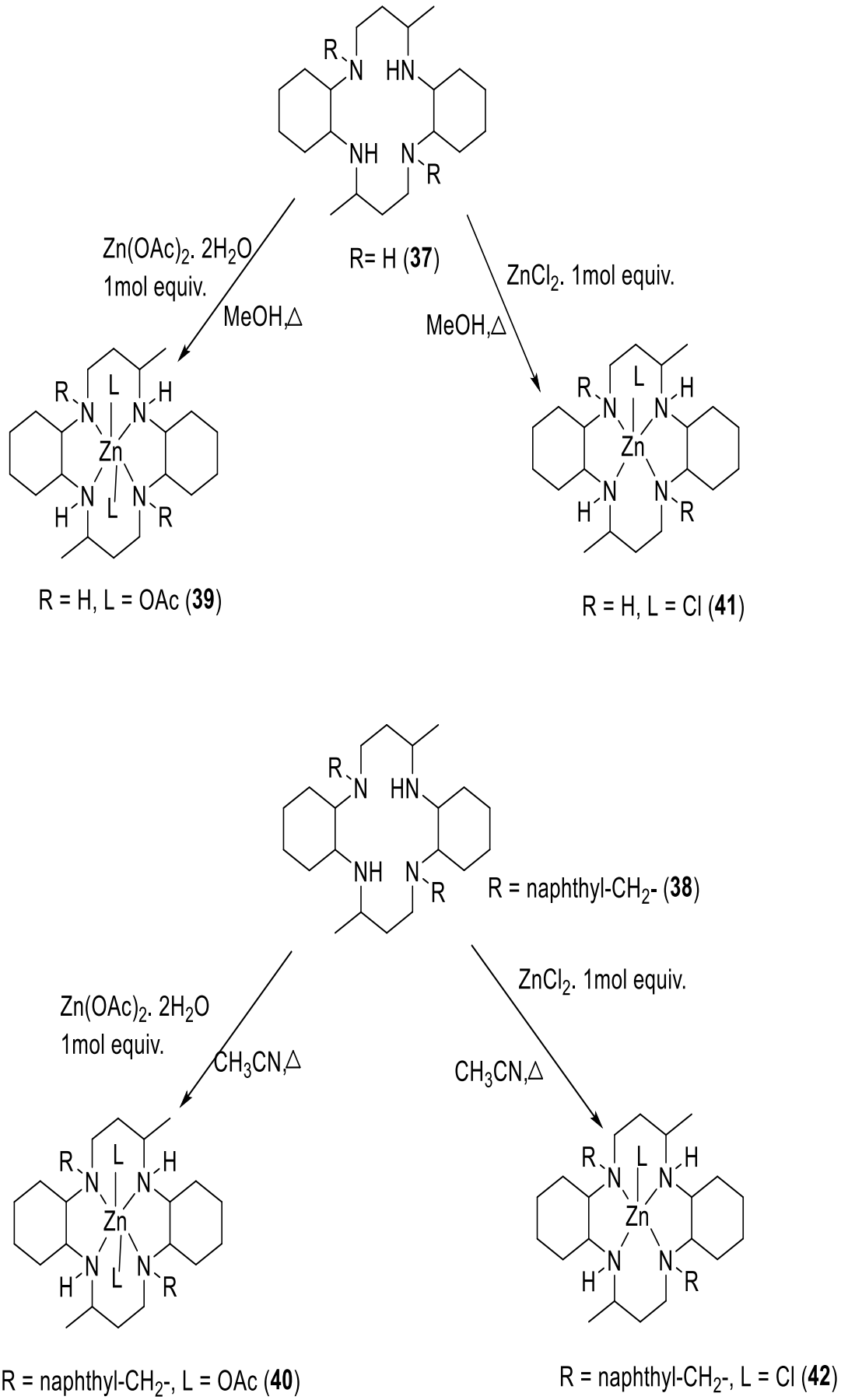


Figure 12. General preparative route to zinc macrocyclic complexes binding displaying octahedral and square-pyramidal geometries, according to axial ligand(s) [28].

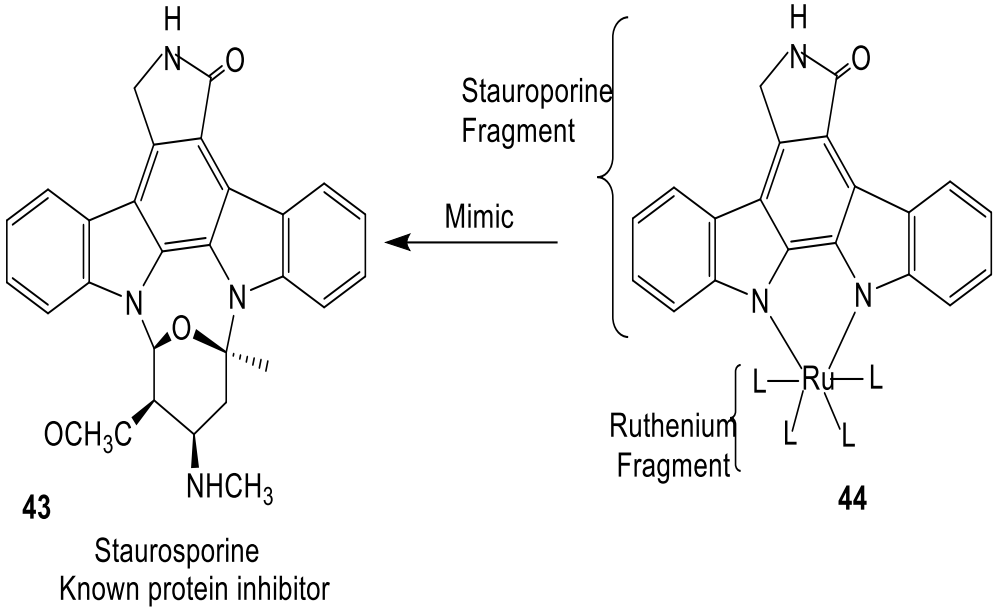


Figure 14. Structural amendment to include ruthenium in staurosporine compound [2].

Hut/CCR5, GHOST/CXCR4, and PBMCs were determined in parallel by MTT assay. The result above showed that it did not exert significant acute toxicity to the host cells, with >90% of cell survival being registered at a concentration up to 50 μM. To delineate the possible anti-HIV mechanism, the inhibitory activity of the complex toward HIV-1 reverse transcriptase (RT), one of the major targets for anti-HIV-1 agents, was evaluated and quantified by the ELISA method. Results showed that it could reduce the HIV-1 RT activity by half at nanomolar concentration, with IC_{50} =1.9 nM. Notably, the observed anti-HIV RT activity of the complex is more effective than the commonly used HIV-1 RT inhibitor, AZT-TP (IC_{50} = 68 nM) by more than 10-fold. It appears that RT can be a possible target for the complex to execute its anti-HIV activity.

2.7 Anti-HIV Platinum complexes

Virucidal agents, defined here as compounds that directly interact with or affect HIV virions, lower the infectivity of the virions for the host cell. Most of the compounds classified as virucidal are in fact surfactants. These are compounds that reduce the interfacial tension between two immiscible phases. This is due to the molecule containing two localized regions, one being hydrophilic in nature and the other hydrophobic. These compounds can be either ionic or nonionic and owe their virucidal properties to disrupting membrane integrity. Virucides destroy virus particles on contact. They differ from virustatic drugs which inhibit growth and/or reproduction of viruses without killing them in that they (virucidal agents) act directly and rapidly by lysing viral membranes on contact [30]

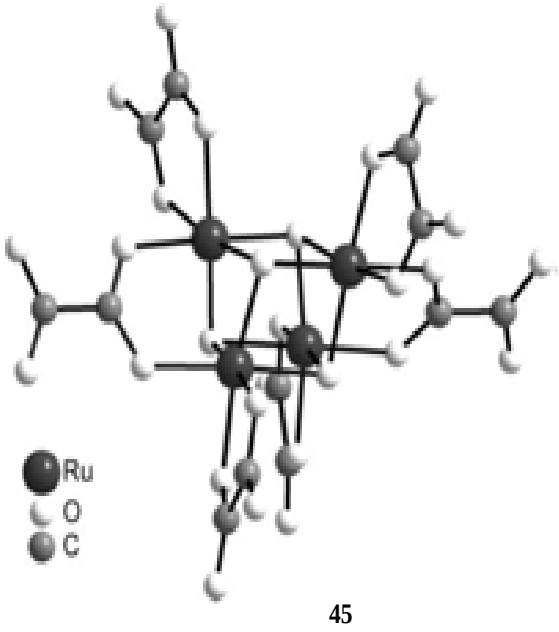


Figure 15. Ball and stick representation of a mixed-valent ruthenium-oxo oxalato cluster [29].

or by binding to virus coat proteins. Attention has been directed towards the possible use of these agents for preventing the sexual transmission of human immunodeficiency virus (HIV) infection [31]. Vzorov et al [32] investigated platinum compounds, especially those containing N-donor aromatic ligands as anti-HIV virucidal agents.

After screening over 70 related agents, including N-donor aromatic ligands and metal precursors, they identified a novel class of platinum(II) complexes with 2-pyridyl-1,2,4-triazine derivatives and Pt(II) formulations with these derivatives (ptt compounds) resulted in highest anti-HIV activity. The maximum

activity was observed when the agents were added immediately post-infection. The ptt agents did not block cell fusion activity of HIV-1 Env proteins in cells bearing CD4X4 or CD4R5 receptors, indicating a lack of interaction with the HIV envelope protein. The ptt compounds exhibited low toxicity for human epithelial cells and are thus promising candidates for use as microbicides or antiviral agents against HIV.

The results showed the importance of the ligand and especially its peripheral charge. The complex with the neutral ligand was inactive and relatively toxic, whereas the negative complex with the negative ligand, 3-(2-pyridyl)-1,2,4-triazine group, has been shown to be active and relatively non-toxic. Likewise, the negative ptt complexes with either one or two negative aromatic ligands were active and relatively non-toxic. This trend for ptt compounds is best described with two such active species shown in Figure 18 illustrating agents containing the ferene ligand, which is rendered dinegative by possessing two aromatic sulfonated furan rings and an analogous agent containing the "desulfonated" derivative of ferene. The latter complex, which has one neutral ligand, also shown in Figure 16, had low activity (Figure 17) and was relatively toxic to cells. In contrast, the negatively charged agents with ferene had high activity (Figure 17)and low toxicity.

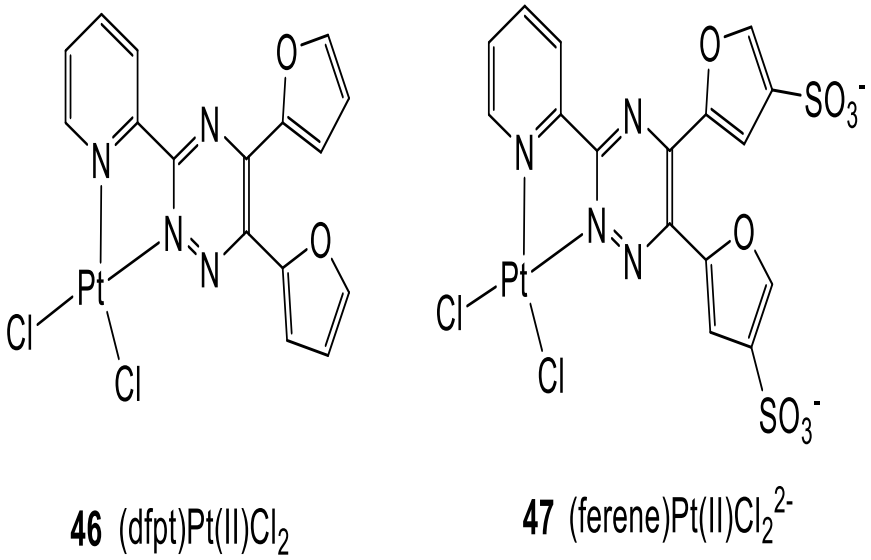


Figure 16. Proposed structures of three related and representative platinum (II) complexes with 2-pyridyl-1,2,4-triazine derivatives and Pt(II) formulations with these derivatives (ptt compounds) tested in the study [32].

Al-Masoudi et al [33] reported on anti-HIV activity of some new complexes of metal ions of 3-methyl-6,7-diphenyl-2-thiolumazine and 2-thiouracil (**49-53** in Figure 18).

All the complexes were assayed for their anti-HIV-1 and HIV-2 activity by examination of their inhibition of HIV-induced cytopathogenicity in MT-4 cells. 3-methyl-2-thiolumazine (MDPhTL) was selected for the coordination with various metals. $VO(MDPhTL)2H_2O$ was found to be the most active inhibitor against HIV-2 in cell culture (EC_{50} ≥18.95 μg/mL, selectivity index (SI) = 3), as well as $CuCl_2(MDPhTL)H_2O$ and $PtCl_2(MDPhTL)H_2O$ being EC_{50} ≥7.12 μg/mL and >2.23 μg/mL, but no selectivity was observed (SI <1), respectively against HIV-1 and HIV-2, which provide a good lead for designing and discovery of new high potent HIV NNRTIs by a structure-based molecular modification.

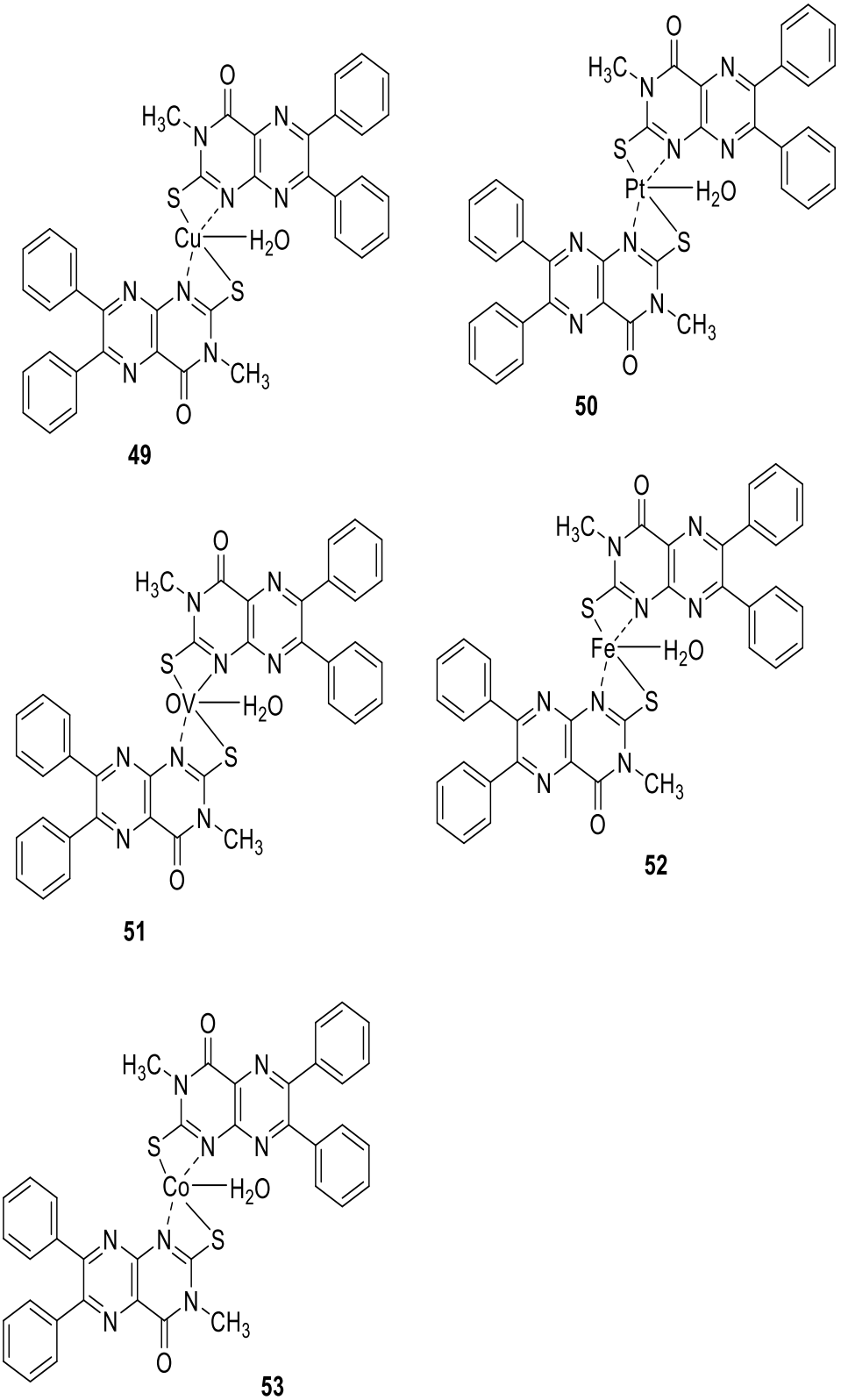


Figure 18. Complexes of Cu (II), Pt (II), VO (II), Fe (II), and Co (II) with 3-methyl-6,7-diphenyl-2-thiolumazine [33].

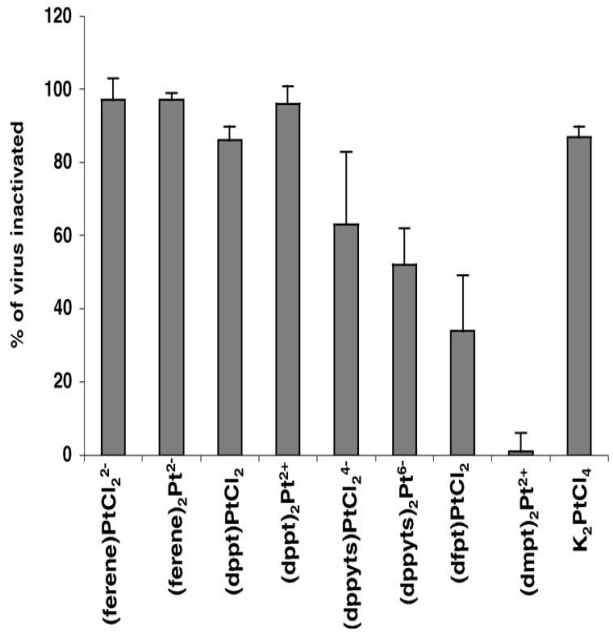
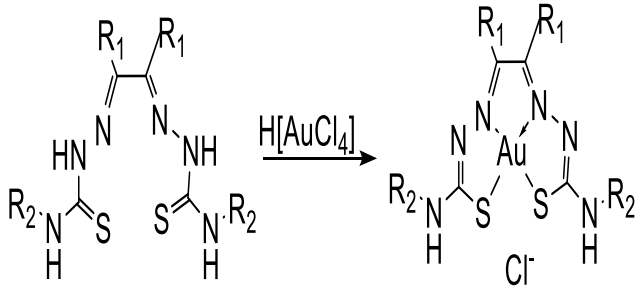


Figure 17. Inhibitory activity of ptt's against HIV-1 infection [32].

2.8 Anti-HIV Gold complexes

New technique, called virostatics, which involves the use of anti-HIV agents that work through the combination of a drug directly inhibiting virus production (viro) e.g. didanosine and the other indirectly inhibiting virus replication by reducing cellular proliferation (static) e.g. hydroxyurea (HU) have been investigated by Fonteh and co-workers[34]. They explored this technique by using four bis(thiosemicarbazonate)gold (III) complexes(54–57 in Figure 19) with a general formula [Au(L)]Cl {L=L1, glyoxal-bis(N4-methylthiosemicarbazone); L2, glyoxal-bis(N4-ethylthiosemicarbazone); L3, diacetyl-bis(N4-methylthiosemicarbazone); L4, diacetyl-bis(N4-ethylthiosemicarbazone)} and screened for activity against the human immunodeficiency virus (HIV). The resultant gold (III) complexes are relatively stable in the biological milieu.



R1 = H, R2 = Me (**54**); R1 = H, R2 = Et (**55**)
R1 = Me, R2 = Me (**56**); R1 = Me, R2 = Et (**57**)

Figure 19. Bis(thiosemicarbazones) L1–L4 and their respective complexes 54–57 [34].

Ligands have an important role in the synthesis of gold based compounds because their complexation to metals not only gives rise to stable compounds, but in some cases leads to better biological activities and/or reduced toxicities [35]. Thiosemicarbazones (Tscs) ligands and their complexes have been observed to have some important biological activity [36] including antiviral activity [37]. Gold (III) compounds are easily reducible by biologically occurring reductants such as thiols, these may reduce gold (III) to gold (I) [38]. Stable gold (III) complexes with anti-HIV activity exist [39], with their stability related to the ligand choice. The use of hard donor ligands such as N and O produces relatively stable gold (III) compounds. Tscs are compounds of mixed donor atoms (N, S) and their resultant gold (III) complexes are relatively stable in the biological milieu.
Complex 56 inhibited viral infection of TZM-bl cells by 98% (IC50=6.8±0.6 μM) at anon-toxic concentration of 12.5 μM while complex 57 inhibited infection of those cells by 72 and 98% (IC50=5.3±0.4 μM) at concentrations of 6.25 and 12.5 μM respectively. The mechanism of inhibition of infection in TZM-bl cells was presumably as a result of the cytostatic or anti-proliferative activity that was observed for complex 57 in real time cell electronic sensing(RT-CES)and carboxyflourescein succinimidyl ester (CFSE) analysis. Treatment of T lymphocytes from HIV infected individuals with 57 decreased CD4+ T cell p=0.0049) as demonstrated by multi-parametric flow cytometry without suppressing cytokine production. The ligands (L1–L4) showed some anti-viral activity, this was an indication of the importance of coordinating gold in these experimental drugs. Complexes 56 and 57 were shown to have ideal lipophilicity values that were similar when shake flask (0.97±0.5 and 2.42±0.6) and in silico prediction (0.8 and 1.5) methods were compared.
The activity and drug-like properties of complexes 56 and 57 suggested that these novel metal-based compounds could be combined with virus inhibitory drugs to work as cytostatic agents in the emerging class of anti-HIV drugs such as virostatics.

Although an exact mechanism of anti-HIV activity is yet to be elucidated, gold-based compounds have demonstrated effective antiviral activity in biochemical assays (See Figure 20). Mphahlele et al [40] demonstrated that gold (III) complexes may be potent oxidisers of HIV-1 RT and integrase enzymes and may impact the outcome of direct biochemical assays. In this study, gold (III) complexes were evaluated in HIV-1 polymerase and HIV-1 integrase biochemical assays. The KAuCl4 and HAuCl4 gold (III) tetrachlorides showed IC50's of 0.947 and 0.983 μMin the HIV-1 RT assay. While seven other selected gold (III) complexes showed IC50's starting from 0.461 to 8.796 μM. The gold (III) tetrachlorides were also observed to inhibit

integrase enzymatic activity with more than 80% inhibition observed with one dose evaluation of 10 μM of the potential drugs. RT inhibition was seen to decrease with a reducer present (10 mM DTT) and also against the M184V HIV-1 RT mutant cells. However, none of the gold (III) complexes were effective inhibitors in cell-based antiviral assays (SI values (SI values <5.95). Taken together, the findings of this study demonstrated that gold (III) complexes modify HIV-1 enzyme activity in direct biochemical assays, most likely through protein oxidation.

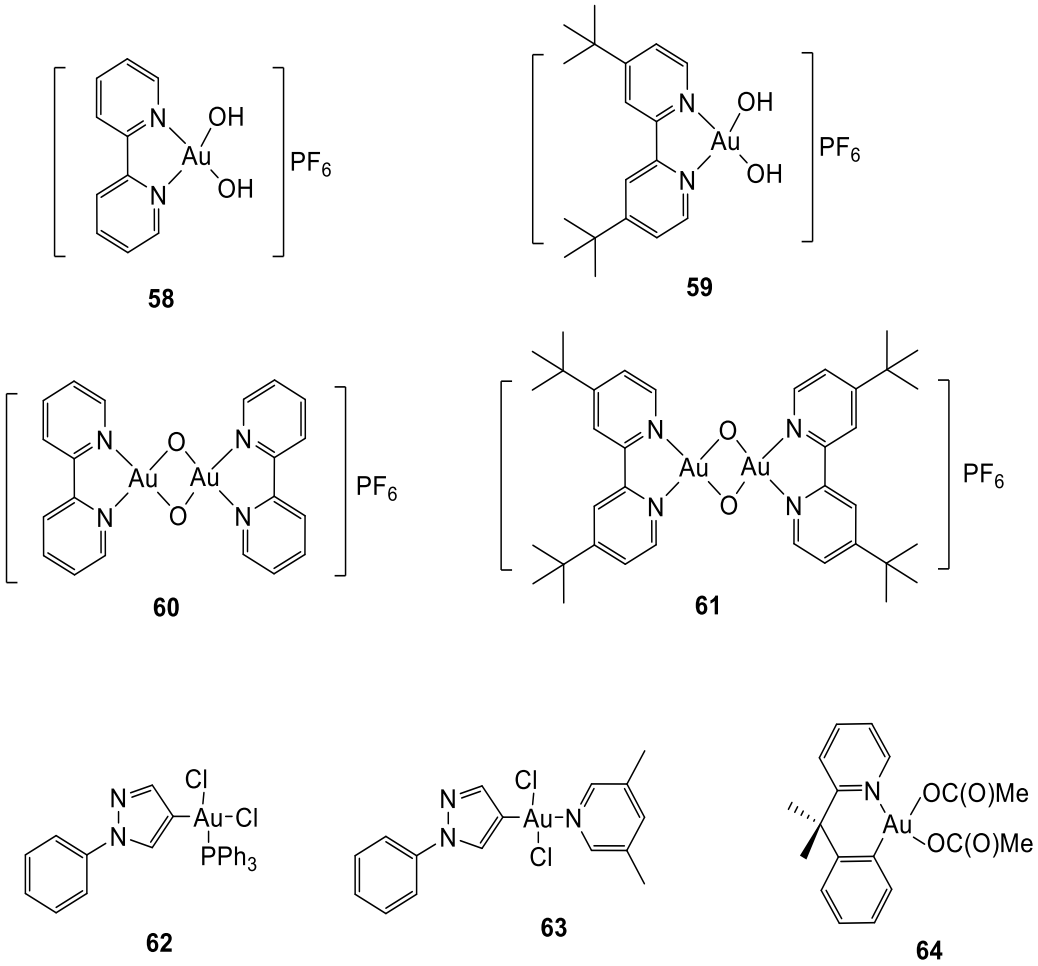


Figure 20. Schematic representation of the seven gold (III) compounds identified as having inhibitory activity towards HIV-1 reverse transcriptase in direct enzyme assays. Compounds **58**–**61** are coordination complexes while compounds **62**–**64** are organometallic compounds [40].

3. Conclusion

The role of transitional metals in HIV/AIDS research is mainly in development of drugs. In this study the anti-HIV transition metal complexes were reviewed. The unique redox and spectroscopic properties result in metal ions and their complexes having potential medicinal applications that could be complementary to organic compounds. Recent achievements in the development of metal-based therapeutics demonstrate that this is a potentially prosperous area for inorganic chemistry as well as microbiology and have stimulated considerable interest in the science community. Challenges faced when developing these drugs is the toxicity due to some of these transition metals. Thus, continuous efforts are needed to overcome the challenge.

Future clinical success will benefit from targets which are highly specific for HIV/AIDS cells. The rapidly expanding knowledge of their cellular characteristics offers many new opportunities for drugs that show low systemic toxicity and efficiently tackle the problem of drug resistance. The different examples mentioned in this review offer a promising start. Finally, the advent of medicinal bio organometallic chemistry and technology has further expanded the toolbox of the medicinal inorganic chemist. The nature of the research will rely ever more heavily on interdisciplinary collaboration, but many exciting discoveries and applications almost certainly lie ahead.

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