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Literature Review

SYNTHESIS OF METAL-ORGANIC (COMPLEXES) COMPOUNDS COPPER(II)-IMIDAZOLE FOR ANTIVIRAL HIV CANDIDATE

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ABSTRACT

The human immunodeficiency virus (HIV) is viruses known as rotaviruses. Potential target for therapeutic is reverse transcriptase (RT), possesses an RNA-dependent DNA polymerase, DNA-dependent DNA polymerase and ribonuclease H fuctions. Imidazoles have high anti-HIV inhibitory activity, some derivates of imidazole reported drugs. 8-chloro-2,3-dihydroimidazole[1,2-b][1,4,2]benzodithi-azine-5,5-dioxides and 9-chloro-2,3,4-trihydropyri-mido[1,2-b][1,4,2]benzodithi-azine-6,6-dioxides. This compounds succesfully identified anti-HIV activity. Copper is a bio-essential element and copper complexes have been extensively utilized in metal mediated DNA cleavage for the generation of activated oxygen species. It has been reported that teraaza macrocyclic copper coordination compounds have anti-HIV activities. Studies have shown that these macrocyclic complexes can react with DNA in different binding fashions and exhibit effective nuclease activities. Complex compounds are compounds in which there is an atom that acts as the central atom and trotter group of molecules that can be either neutral or charged ions. Application a metal-organic (complex) compounds, especially copper metal and derivates of imidazole. So, in this study can explore new anti-HIV candidate.

Key words: *Complexes compound, copper, imidazole, antiviral, HIV*

ABSTRAK

Human immunodeficiency virus (HIV) adalah virus yang termasuk golongan rotavirus. Target potensial untuk terapi adalah reverse transcriptase (RT), memiliki sebuah DNA-dependent RNA polimerase, DNA-dependent DNA polimerase dan ribonuklease. Imidazol memiliki aktivitas penghambatan anti-HIV yang tinggi, beberapa turunan dari imidazol melaporkan obat. 8-kloro-2,3-dihydroimidazole [1,2-b] [1,4,2] benzodithi-azine-5,5-dioksida dan 9-chloro-2,3,4-trihydropyri-mido [1,2-b] [1,4,2] benzodithi-azine-6,6-dioksida. Ini senyawa aktivitas anti-HIV berhasil diidentifikasi. Tembaga adalah unsur dan tembaga kompleks bio-penting telah banyak digunakan dalam logam dimediasi pembelahan DNA untuk generasi spesies oksigen aktif. Telah dilaporkan bahwa senyawa koordinasi tembaga teraaza makrosiklik memiliki kegiatan anti-HIV. Penelitian telah menunjukkan bahwa kompleks makrosiklik dapat bereaksi dengan DNA di mode mengikat yang berbeda dan menunjukkan aktivitas nuklease yang sangat efektif. Senyawa kompleks adalah senyawa yang ada atom yang bertindak sebagai atom dan dikelilingi oleh molekul yang dapat berupa ion netral atau ion pengganti. Aplikasi logam-organik (kompleks) senyawa, terutama logam tembaga dan turunan dari imidazol. Jadi, pada studi ini dapat dipelajari kandidat anti-HIV baru.

Kata kunci: *Senyawa kompleks, tembaga, imidazole, antivirus, HIV*

INTRODUCTION

The human immunodeficiency virus is a number of class of viruses known as rotaviruses, was identifiend as the causative agent in the transmission and development of acquired immune deficiency syndrome (AIDS). The replicative cycle of HIV provides many potential targets for therapeutic intervation. Reverse transcriptase

(RT), possesses an RNA-dependent DNA polymerase, a DNA dependent DNA polymerase and ribonuclease H fuctions.[1]

Imidazoles have high anti-HIV inhibitory activity[2], some derivates of imidazole reported drugs. Imidazole a ring substituted and pirimidine ring for potent inhibitory activity against RT. These cmpund showed minimal cytotoxicity and are therefore suitable for antiviral development.

Complex compounds are compounds in which there is an atom that acts as the central atom and trotter group of molecules that can be either neutral or charged ions. This trotter group called ligands. Complex compounds formed are influenced by the nature of the ligand, which includes the alkalinity, bond, and chelate effects.

Copper is a bio-essential element and copper complexes have been extensively utilized in metal mediated DNA cleavage for the generation of activated oxygen species. It has been reported that tetraaza macrocyclic copper coordination compounds have anti-HIV activities.

This papers reviews about imidazole potency and copper for anti-HIV. So, in this study can explore drug from the mixture compound, metal-organic compound, especially Cu-imidazole complexes.

Imidazole Compound and Derivates

Brzozowski et al., (2006) prepared new compound with modifications on the imidazole [2]. We present the synthesis 8-chloro-2,3-dihydroimidazole[1,2b][1,4,2]

benzodithi-azine-5,5-dioxides and 9-chloro-2,3,4-trihydropyrimido[1,2b][1,4,2]

benzodithi-azine-6,6-dioxides (figure 1). Succesfully identified anti-HIV activity ECO_{50} 0.09 µM. This compounds showed minimal cytotoxicity and suitable for antiviral development. In the compounds, methyl group at position 7 showed the highest anti-HIV activity cause electron-donating. Compounds showed significant cytotoxicity in cell-based assays even though they were very effective in HIV-1 integrase-based assays.[2]

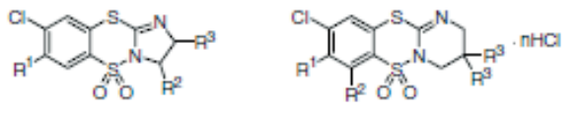
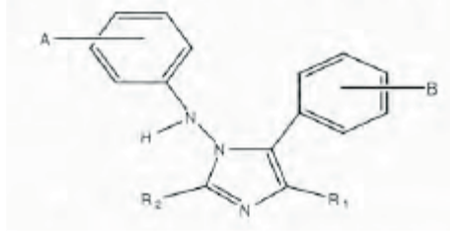


Figure 1. Modification of imidazole.[2]



Figures 2. 5-phenyl-1-phenylamino imidazole.[3]

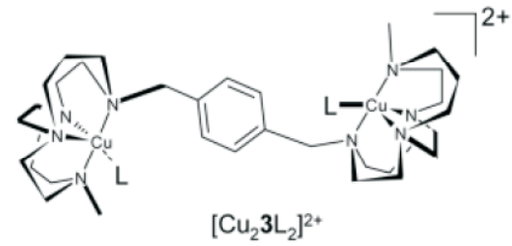
Anti-HIV of 5-phenyl-1-phenylamino-imidazole have been cytotoxicity data in QSAR study. In the QSAR study, imidazole derivate presence of hydrogen bond donor groups appears to be an important feature for reducing the cytotoxicity. Molecular size can also important for determining the cytotoxicity.[3]

In 2004, 1-[2-(alkylthio-1-imidazolyl)carbonyl]-4-[3-(isopropyl amino)-2-pydridyl] piperazines, the compound were tested for anti-HIV activity and had maximum precent of protection $2x10^{-5}M$.[1]

2-alkylthio-1-[4-(1-benzyl-2-athyl-4-nitro-1H-imidazole-5-yl)-piperazin-1-yl] ethanones and alkyl-[4-(1-benzyl-2-ethyl-4-nitro-1H-imidazol-5-yl)-piperazin-1yl) ketones, the newly synthesized compounds were assayed against HIV-1 and HIV-2 in MT-4 cells. The compounds were showed inhibition of HIV-1 (EC_{50} 0.45 µg mL^{-1}) and HIV-2 (0.50 µg mL^{-1}). The target is non-nucleoside reverse transcriptase inhibitor.[4]

Copper For Antiviral HIV Activity

Copper is a bio-essential element and copper complexes have been extensively utilized in metal-mediated DNA cleavage for the generation of activated oxygen species. It has been reported that teraaza macrocyclic copper coordination compounds have anti-HIV activities. Studies have shown that these macrocyclic complexes can react with DNA in different binding fashions and exhibit effective nuclease activities.[5]

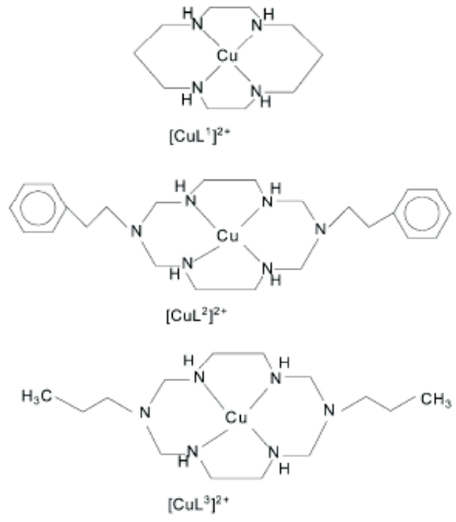


Figures 3. Macrocyclic copper(II) complexes.[5]

At 2010, copper(II) containing bis-macrocyclic $[Cu_2 3L_2]^{2+}$ has improved anti-HIV potency in vitro (EC_{50} 4.3 nM). The interaction of the metallodrug has been optimized by using ultra rigid chelator units that offer an equatorial site for coordination to the amino acid side chains of the protein.[6]

Cu_2-xylyl-bicyclam also exhibits anti-HIV activity. It was used Cu^{2+}-cyclam as a paramagnetic probe to investigate interactions of metal-locyclams with the model protein target in solution.[7]

Copper complexes were substrated competitive inhibitors for HIV-1 protease. For example, [bis-(2-pyridylcarbonyl)-amido] copper(II) nitrate dihydrate binds with an inhibiton constant of 480 µM. molecular modeling suggests that the catalytic water between Asp25 and Asp125 of HIV-1 protease is directly coordinated to the Cu(II) ion.[8]

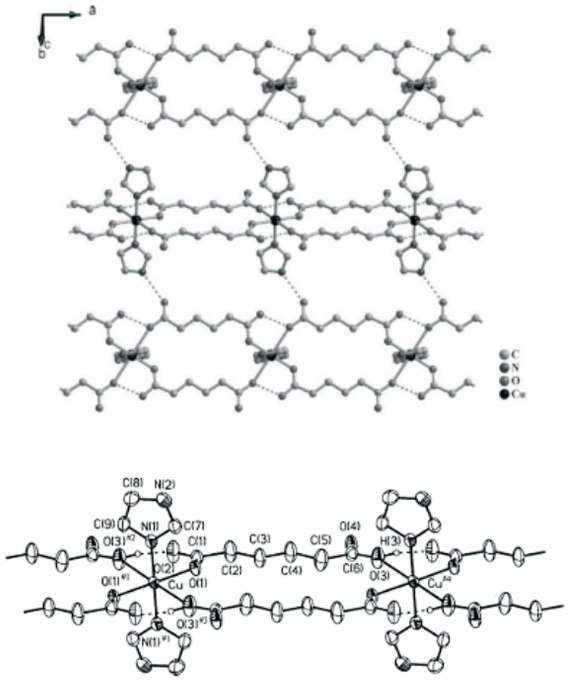


Figures 4. Copper(II) bis-macrocyclic.[8]

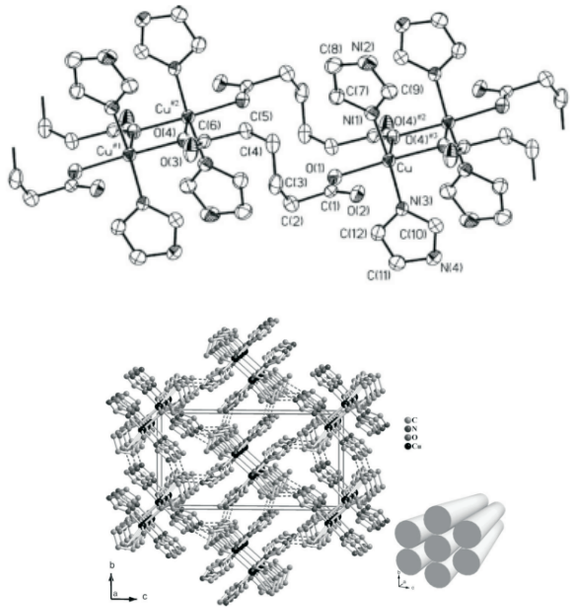
Complex Compounds of Cu(II)-Imidazole

Complex compounds copper(II) with monodentate ligand 1 imidazoles

Ying et al., Synthesis complex compounds of Cu(II) as the central atom with ligands that have a monodentate imidazole strutur octahedral geometry. Complex compound formed is $Cu(C_3N_2H_4)_2(HL)_2$ and $Cu(C_3N_2H_4)_{2L}$ with $C_3N_2H_4$ is an imidazole and HL is adipic acid. In the structure of the complex compounds occur hydrogen bonds between the NH---O into a compound supermolecule due to polymerization. In the complex compound $Cu(C_3N_2H_4)_{2L}$, Cu atom has five coordination centers of CuN_2O_3 pyramidal, then bind to ligands bridge ligand monodentate adipic acid so as to form a polymerization.[9]

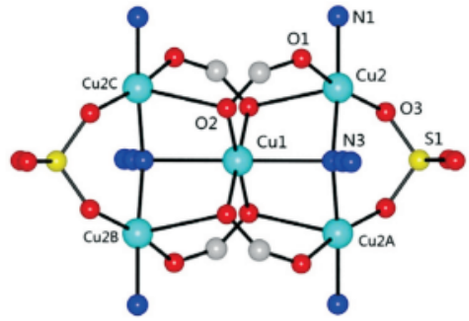


Figures 5. (a) Complex compound $Cu(C_3N_2H_4)_2(HL)_2$, (b) Hydrogen bonding structure.[9]

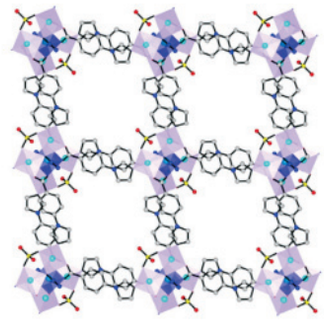


Figures 6. (a) Complex compound $Cu(C_3N_2H_4)_2L$, (b) Hydrogen bonding structure.[9]

In the year 2011 has been synthesized $[Cu_{5(}IBA)_{4(}N_3)_{2(}SO_4)_2]$.$4H_2O$ with HIBA is 4- (imidazol-1-yl) benzoate -acid by Liu. This complex compound has a symmetrical structure with an angle {Cu2, Cu2A, Cu2B, Cu2C} is 71.57° and 108.43°. Magnetic properties of complex compounds are ferromagnetic.[10]

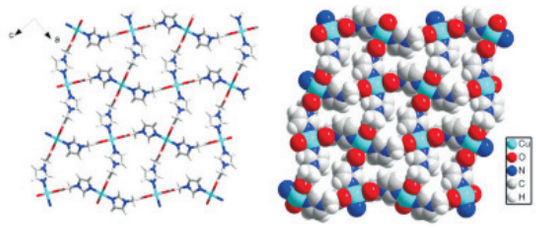


Figures 7. Complex compound $[Cu_5(IBA)_4(N_3)_2(SO_4)_2].4H_2O$.[10]



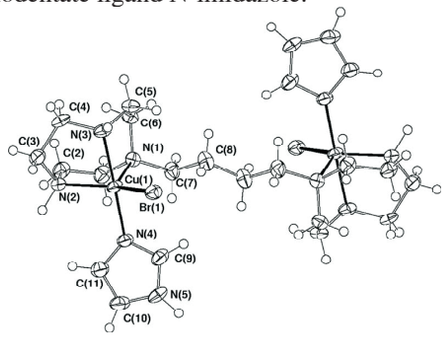
Figures 8. 2D structure $[Cu_5(IBA)_4(N_3)_2(SO_4)_2].4H_2O$ of hydrogen bonding effect. [10]

By Li et al., In 2013 have synthesized a complex compound used for heterogeneous catalysts. This is a complex compound $[Cu(IMA)_2]_n$, synthesized in methanol and ambient temperature. The catalytic properties of complex compounds is very good because it has the results (%) is high and the higher the stability of the compound.[11]



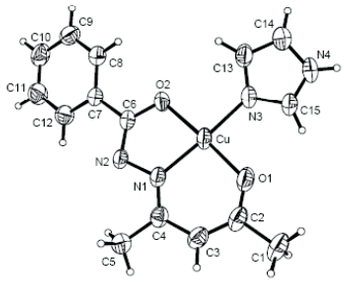
Figures 9. 2D Crystal structure of MOF with 4 coordination Cu^{2+}.[11]

$[Cu_2L^{but}(imidazole)_{2Br2}](ClO_4)_2$ have been successfully synthesized by Graham et al., In 2005 ago. The molecular structure above has cation $[Cu_2L^{but}(imidazole)_{2\ Br2}]^{2+}$ and perchlorate anions. L^{but} ligand is anticonformation so as to cause the complex compounds into centrosymmetry with bridge butane, Cu---Cu 8446 Å. Copper (II) as a coordination center, coordinating with the anions bromide dn monodentate ligand N-imidazole.[12]



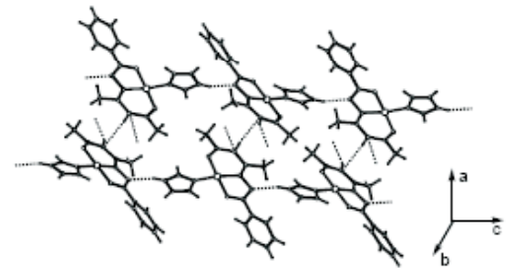
Figures 10. $[Cu_2L^{but}(imidazole)_2Br_2]\ (ClO_4)_2$ Compound.[12]

Complex compounds [Cu(bhac)(Himdz)] has a central atom Cu(II) as a coordination center, acetylacetone benzoilhidrazona tridentat ligand and monodentate ligands imidazole. These compounds can be formed due to metal ion coordination with enolate-O, imine-N and the deprotonated amide-O atom sixth and fifth ring chelate.[13]



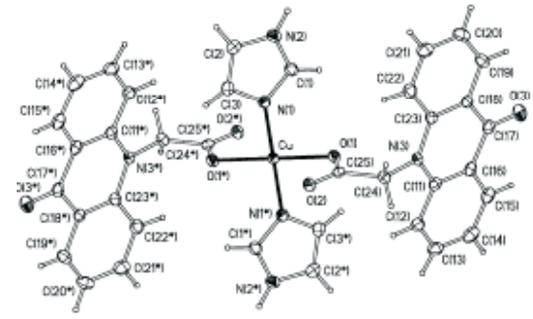
Figures 11. Complex compound [Cu(bhac)(Himdz)]. [13]

Then through intramolecular hydrogen bonds NH---N form a crystalline regularity, this is called polymerization. The effective magnetic moment of these compounds is 1.86 μB. Weak antiferromagnetic because their 2-apical equatorial, chloro and bridges asetato.[13]



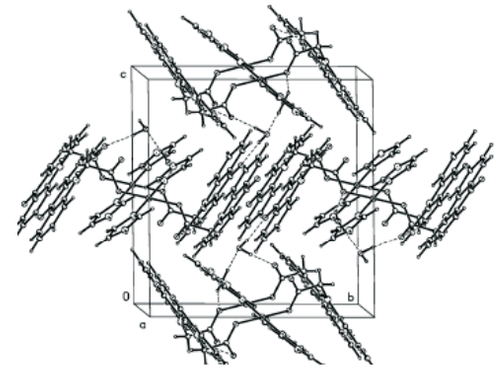
Figures 12. 2D structure of crystal [Cu(bhac)(Himdz)]. [13]

Synthesis of bis (9,10-dihydro-9 oxo-10-acrydinacetato) bis (imidazole) Copper (II)tetrahydrate.[14] Monomer crystal structure of $Cu(CMA)_{2(}Him)_2$ will react intermolecular hydrogen bond with water molecules.



Figures 13. Complex compound $Cu(CMA)_2(Him)_2$. [14]

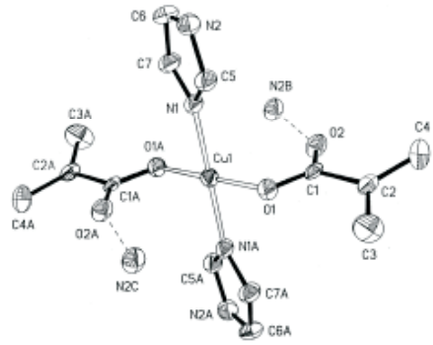
Cu complex compounds $(CMA)_{2(}Him)_2$ can bind hydrogen NH---O form a crystalline order as follows,



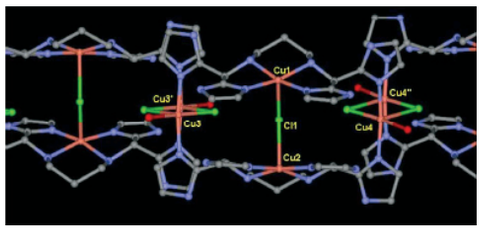
Figures 14. 2D crystal $Cu(CMA)_2(Him)_2$. [14]

In 2005, Song et al., Have managed to synthesize $[Cu_{4(}H_3L)(H_2L)CL_3(H_2O)_2]\ Cl_2.5H_2O$. This complex compound used as a ligand clorate ligands bridge connecting Cu-Cu so that a Cu-Cl-Cu. Furthermore, with

the intramolecular hydrogen bond is formed a polymer complex.[15]

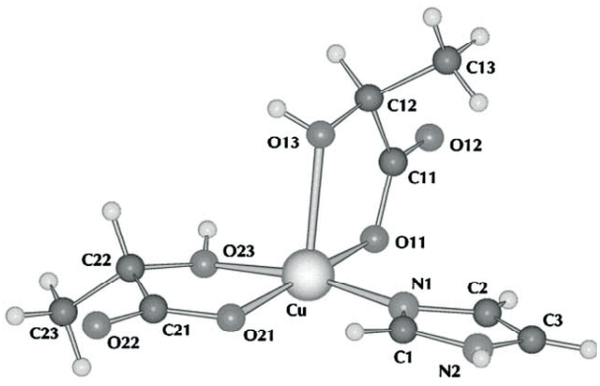


Figures 15. Complex compound $[Cu_4(H_3L)(H_2L)Cl_3(H_2O)_2]Cl_2.5H_2O$. [15]



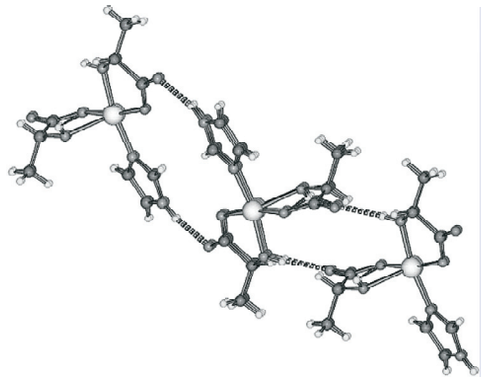
Figures 16. 1D polimer structure of complex compound $[Cu_4(H_3L)(H_2L)Cl_3(H_2O)_2]Cl_2.5H_2O$. [15]

Carbalo et al., 2004 perform synthesis of $[Cu(HL)_2(Im)]$ with the coordination geometry pyramide structure.[16]



Figures 17. Complex compound $[Cu(HL)_2(Im)]$. [16]

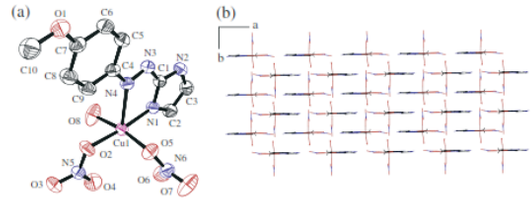
The complex compounds will undergo intramolecular hydrogen bonds form a continuous crystal. The crystals were formed as glasses with Cu(II) as the central atom.



Figures 18. Crystal $[Cu(HL)_2(Im)]$ showed 2D after hydrogen donding. [16]

Complex compounds copper (II) with a bidentate ligand 1 imidazoles

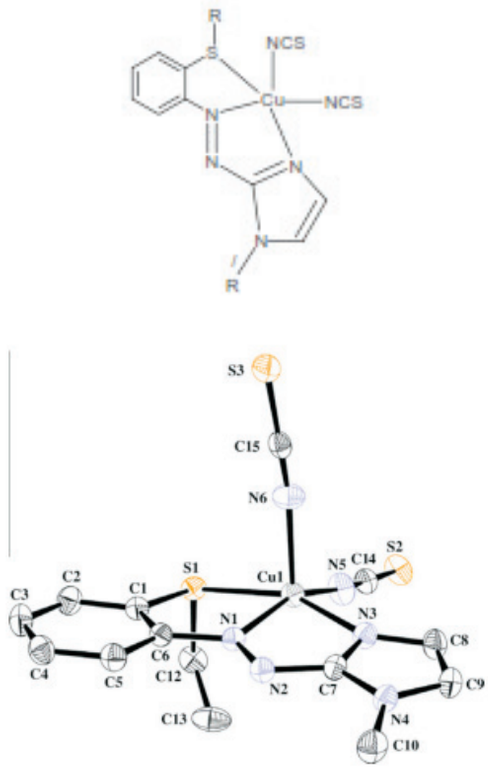
In 2010 Pramanik et al., Have succeeded in synthesizing complex compounds $[Cu(II)(L_2)(H_2O)(NO_3)_2]$ with the central atom Cu(II) which has a planar coordination giometry pyramid, nitrate as a monodentate ligand and two atoms N on imidazole freely donate an electron pair to form a common bond of Cu(II) which is referred to as a bidentate ligand. Furthermore, there is intramolecular hydrogen bond bond, the N atom of the imidazole with oxygen atoms from nitrate. So as to form a polymerization, namely a crystal.[17]



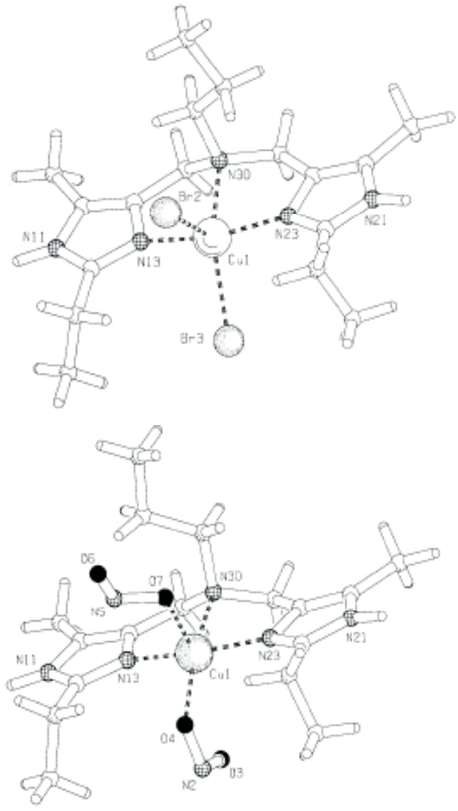
Figures 19. (a) Complex compound $[Cu(II)(L_2)(H_2O)(NO_3)_2]$, (b) Polymeri -zation. [17]

Complex compounds copper(II) by ligand tridentat 1 imidazoles

Sarker et al., 2010 has been to synthesize a complex compound with Cu(II) as the central atom, 1-alkyl-2-(o-tioalkil) fenilazoimidazol as ligands tridentat, and SCN as bridging ligand. Molecular formula is [CuII (SetaaiNMe) $(SCN)_2$]. Imidazole donated three pairs of free electrons to bind together with the atom Cu(II). SCN as ligands bridge will connect between the molecules form a complex compound supermolecule.[18]



Figures 20. (Left) Chemistry Structure, (Right) Design of molecule structure [Cu^{II}(SetaaiNMe)$(SCN)_2$]. [18]



Figures 21. Left [Cu(biap)Br_2] and right [Cu(biap)$(NO_2)_2$]. [19]

Baretta et al., 2000 managed to synthesize two complex compounds with imidazole as a ligand tridentate namely, [Cu(biap)Br_2] and [Cu(biap)$(NO_2)_2$]. Complex compounds [Cu(biap)Br_2] has the shape of trigonal geometry bipiramidal with Br_2 in apical position and 3 nitrogen of ligands and anions bromide in equarorial. Hydrogen bonding occurs in bromine and imdazol-NH atom in the molecule itself. Complex compounds [Cu(biap)$(NO_2)_2$] asymetric shape. Can be seen in the image below ions Cu(II) in a position squer pyramidal with two imidazole and 1 amine, nitroten together with the oxygen on the nitrite on the state of equatorial and equal.[19]

SUMMARY

Imidazoles have high anti-HIV inhibitory activity, some derivates of imidazole reported drugs. Imidazole a ring substituted and pirimidine ring for potent inhibitory activity against RT. Copper is a bio-essential element and copper complexes have been extensively utilized in metal mediated DNA cleavage for the generation of activated oxygen species. Copper can potential for anti-HIV, because copper have inhibitor activity for HIV-proteinase. Copper can interact with donor atoms on a biological target via the formation of coordinate bonds rather than a combination of weaker intermolecular force such as H-bonding and chelator. The chelator has high stability complex to retain the copper ion in vivo and exchangeable ligands must be present to allow coordination of amino acid side chains.

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