EC Pharmacology and Toxicology Editor's Column - 2017

A Metal Complex Incorporating Some Drug Molecules as Ligands

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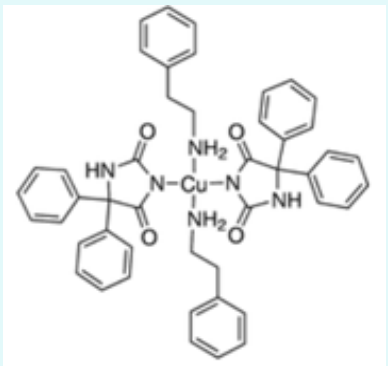
COLUMN ARTICLE

Thirteen years ago, without any pharmacological interests particularly, we have reported on preparations, electronic and crystal structures of a copper(II) complexes having 5,5-diphenylhydantoinate (phenytoinate; deprotonated phenytoin) and 2-phenylethylamine (phenethylamine) ligands (Figure 1) [1]. Before this paper, I (mainly supervised by the late Dr. Seiko Komorita at Osaka university, Japan) have systematically studied on copper(II) complexes of phenytoinate ligands [2-6]. These complexes afford various coordination geometries in the crystalline states by slight changes of steric hindrance or other structural features accompanying with changes of electronic sates (optical properties). For example, four-coordinated square planar [CuN_4] (reddish violet color) [1,4-6], distorted square planar [CuN_4] (blue violet color) [3,4], and five-coordinated square pyramidal [CuN_4O] (blue color) coordination environments were typically determined and found by X-ray crystallography. As for phenytoin or the related organic compounds of 5-substitued hydantoin derivatives and common imides such as succinimide, phthalimide, maleimide and so on, it should be noted that deprotonated nitrogen coordination atoms have pi-orbitals distributing perpendicular to the five-membered hydantoin ring, which resulted in formation of in - ([CuN_4]) plane pi-character of coordination bonds according to Komorita's studies. Such circumstance may be characteristic to monodentate ligands of deprotonated hydantoin derivatives. In contrast, phenethylamine binds to copper(II) ion through amino group.



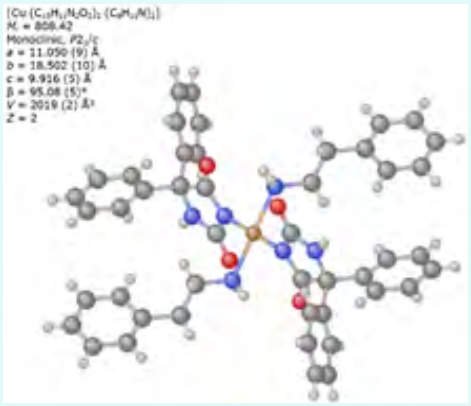


Figure 1: The copper(II) complex having phenytoin and phenethylamine ligands [1]; [left] chemical structure, [right] crystal structure.

Citation: Takashiro Akitsu. "A Metal Complex Incorporating Some Drug Molecules as Ligands". EC Pharmacology and Toxicology ECO.01 (2017): 16-18.

Phenytoin [7], which was firstly prepared and reported by Heinrich Biltz (German chemist) in 1908, is one of anti-seizure drugs preventing tonic-clonic seizures or partial seizures. It is also used for heart arrhythmias or neuropathic pain. Blood levels can be measured to determine the proper dose, although we purchased it from Wako, a chemical supplier in Japan, not as medical drugs but as test reagents, otherwise too much dose results in Stevens-Johnson syndrome or other side effects. It sometimes inhibits the voltage-gated sodium channels (associated with phenytoin sodium) in the human brain and suppresses abnormal excitation of the human brain, thereby exhibiting anticonvulsant action seriously.

Phenethylamine [8], a kind of alkaloid, is one of neurotransmitters which is prepared from decarboxylation of phenylalanine by enzymes. Colorless liquid phenethylamine even neat yields easily carbonate by carbon dioxide in atmosphere similar to other primary amines. There are many phenethylamine derivatives used for entactogens, hormone, stimulant, hallucinogen, anoretic drugs, bronchodilators, or antidepressants. The phenethylamine derivatives were substituted at amino group, phenyl group, and methylene moiety.

Thus, both organic ligands of the copper complex, namely phenytoin [7] and phenethylamine [8] (including their derivatives), are well known drug molecules as they are. However, shall we dare to think significance of metal complexes incorporating some drug molecules as ligands? Besides toxicity of heavy metal ions, accumulation of pharmacophores may lead to lose appropriate molecular recognition to proteins or suitable capability of chemical reactions. In the case of hydantoin, 3-position nitrogen is easy to release proton to exhibit acidity. Losing 3-position proton, sodium ion binding to 2-position C=O- group to be sodium phenytoinate (Dilatin). Coordination to copper(II) ion hinders pi-conjugation being important for them as well as metabolic turnover reactions. In the case of phenethylamine derivatives of mono-methyl-substituted amino group, at least, Epinephrine (Adrenaline), Phenylephrine, N-Methylphenethylamine, Methamphetamine, Ephedrine/Pseudoephedrine, Methcathinone, Mephedrone, MDMA, and MDMC cannot be kept their chemical structures.

In contrast to drug design, simple accumulation of functional moieties in a molecule may sometimes be a good strategy to obtain new materials regardless of interaction between these moieties. For example, one of the related optically active copper(II) complex, namely enantiomers or diastereomers of trans-[Cu(phenytoinate)2(1-phenylethylamine)2], [4] has both chiral (R- or S-1-phenylethlyamine) recognizing ligands and magnetic (paramagnetic, s=1/2) Cu(II) ion having an unpaired electron in a molecule. In this way, this feature may be a difficult aspect of (multi-functional) drugs especially for non-pharmaceutical chemists like me studying on organic/inorganic hybrid functional materials composed of functional parts or components.

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