2015

Interesting Properties of p-, d-, and f-Block Elements When Coordinated With Dipicolinic Acid and Its Derivatives as Ligands: Their Use as Inorganic Pharmaceuticals

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Original Publication Citation

Celestine, M. J., Bullock, J. L., Boodram, S., Rambaran, V. H., & Holder, A. A. (2015). Interesting properties of p-, d-, and f-block elements when coordinated with dipicolinic acid and its derivatives as ligands: Their use as inorganic pharmaceuticals. *Reviews in Inorganic Chemistry, 35*(2), 57-67. doi:10.1515/revic-2014-0004

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Interesting properties of p-, d-, and f-block elements when coordinated with dipicolinic acid and its derivatives as ligands: their use as inorganic pharmaceuticals

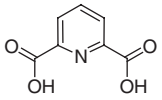
Abstract: This is a review of the literature concerning the interesting properties of p-, d-, and f-block elements when coordinated with 2,6-pyridinedicarboxylic acid (dipicolinic acid, H_2dipic) and its derivatives as ligands, with a focus on their use as inorganic pharmaceuticals. Some of the complexes reported were used as insulin-like, bioimaging contrasting agents, antimicrobial agents, and anticancer agents.

Keywords: bacteria; cancer; complexes; dipicolinic acid; insulin.

DOI 10.1515/revic-2014-0004
Received April 30, 2014; accepted July 26, 2014; previously published online September 13, 2014

Introduction

The review focuses on the interesting properties of p-, d-, and f-block elements when coordinated with 2,6-pyridinedicarboxylic acid (dipicolinic acid, H_2dipic) and its derivatives as ligands, with a focus on their use as inorganic pharmaceuticals. 2,6-Pyridinedicarboxylic acid (dipicolinic acid, H_2dipic), **I**, is a widely used building block in coordination and supramolecular chemistry (Froidevaux et al. 2000, Muller et al. 2001, Hunag et al. 2003, Storm and Luning 2003, Haino et al. 2005). It is a versatile, strong, nitrogen-oxygen, multimodal donor ligand, which forms stable complexes with diverse metal ions, sometimes in unusual oxidation states (Renaud et al. 1997a,b, Jackson et al. 2001, Devereux et al. 2002, Ouali et al. 2002, Kapoor et al. 2005, Tse et al. 2006, Kirillova et al. 2007).



I

The crystal structure of dipicolinic acid was first solved by Takusagawa et al. (1973). Lately, the pharmacological studies on dipicolinic acid have been given pertinent attention because of its low toxicity and amphophilic nature. Dipicolinic acid is also present in natural systems as a product of oxidative degradation of vitamins, coenzymes, and alkaloids, to name a few (Siddiqi et al. 2010). Furthermore, it is constituent of fulvic acid, and is an intermediate during L-tryptophan degradation as well as a precursor for the NAD enzyme (Siddiqi et al. 2010). Dipicolinic acid and its derivatives are now being featured as ligands in coordination complexes that have medicinal uses. The readers are encouraged to read reviews and articles for information regarding the solution chemistry of dipicolinic acid, its derivatives, and its coordination complexes (Buglyo et al. 2005, Smee et al. 2009, Kirillov and Shul'pin 2013). Please see the following review "Pyrazinecarboxylic acid and analogs: Highly efficient co-catalysts in the metal-complex-catalysed oxidation of organic compounds" (Kirillov and Shul'pin 2013). In this report, the reviews and featured articles have been published on the following topics: antidiabetic effects of a series of vanadium dipicolinate complexes in rats with streptozotocin (STZ)-induced diabetes (Willsky et al. 2011); how environment affects drug activity: localization, compartmentalization, and reactions of a vanadium insulin-enhancing compound,

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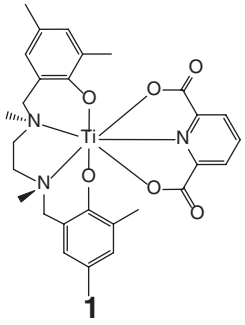
dipicolinatooxidovanadium(V) (Crans et al. 2011); and metal speciation in health and medicine represented by iron and vanadium (Crans et al. 2013).

Titanium

The chelate stabilization of a titanium(IV) (Ti^{IV})-salan alkoxide by ligand exchange with dipicolinic acid was reported to form the redox inactive, heptacoordinate complex **1**. This was found to be stable in both silica gel and aqueous media (Immel et al. 2012). The complex was reported to be highly toxic toward cervix carcinoma, HeLa S3, hepatocarcinoma, and Hep G2 cancer cell lines. It was also found to have an enhanced antitumor efficacy in a mouse cervical cancer model (Immel et al. 2012).



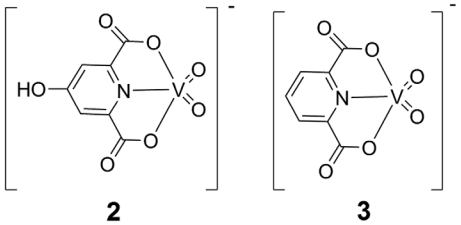
1

The relative efficacy of complex **1** was compared to another derivative in an *in vivo* model of cervical cancer; 18 C3 tumor-bearing mice received the complexes in a low-dose regime over multiple applications and their relative tumor inhibitory effects were monitored. Impressively, mice that were administered doses of complex **1** exhibited a significant reduction in tumor size. These data were well received, although a reduction of tumor growth was previously reported using a high-dose treatment with Ti^{IV} halo-salan alkoxides. The $dipic^{2-}$ stabilized complex **1**, in contrast to the Ti^{IV} halo-salan alkoxides, was well tolerated and showed an improved efficacy at lower doses (30 mg kg^{-1}).

Vanadium

For many years, it has been reported that vanadium-containing complexes have insulin-like properties both *in vivo* and *in vitro*. The synthesis and characterization of new vanadium complexes with insulin-like properties were reported (Crans et al. 2003a). The three new complexes were related to the (dipicolinato)dioxidovanadium(V) complex: (4-hydroxy-2,6-pyridinedicarboxylato)dioxidovanadium(V), (diaqua)(4-hydroxy-2,6-pyridinedicarboxylato) oxidovanadium(IV), and (4-amino-2,6-pyridinedicarboxylato)dioxidovanadium(V). The complex (4-hydroxy-2,6-pyridinedicarboxylato)oxidovanadium(V) was investigated in greater detail with regard to the chemistry, structure, kinetics, and insulin-like properties in rats with STZ-induced diabetes (Crans et al. 2003a). An oral administration of $[VO_2(dipic\text{-}OH)]^-$ was found to be effective in lowering both the hyperglycemia and hyperlipidemia of diabetes. This was the first report concerning the effective lowering of diabetic hyperlipidemia by a vanadium(V) (V^V) coordination complex (Crans et al. 2003a).

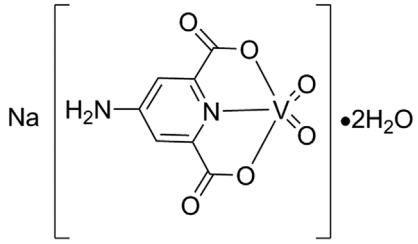
Recently, there was a report of a new insulin-like V^V complex, the (4-hydroxypyridine-2,6-dicarboxylato) oxovanadate(V) anion **2** (Crans et al. 2003b). The complex was designed based on the desire to make a compound with more favorable chemical and insulin-like properties than the analogous (pyridine-2,6-dicarboxylato) oxovanadate(V) anion **3**. The aqueous solution studies were carried out on complex **2**, where the complex was found to be more stable at a neutral pH and had a different lability pattern than complex **3**. The effect of complexes **2** and **3** anions on various biological systems including cell culture, yeast, and STZ-induced diabetic rats were investigated. The growth of myoblast cells (L6) was inhibited by both complexes **2** and **3** anions (Crans et al. 2003b). Since the complexes have limited stability at a neutral pH, yeast growth (pH range from 3.0 to 7.0) was employed as an adjunct cell model. The effect of the complex **3** anion on the inhibition of yeast cell growth was found to be pH dependent. The authors reported that these studies supported the hypothesis that the complex **2** anion would be more active as an insulin-like agent because of its greater stability at a neutral pH (Crans et al. 2003b). The studies involving the effect of complex **2** anion on hyperglycemia in rats with STZ-induced diabetes were also carried out. Complex **2** anion was found to lower the diabetic hyperglycemia and joined the ranks of the few V^V complexes that have been shown to have insulin-like properties in a diabetic animal model system (Crans et al. 2003b).



2 **3**

The evaluation of the insulin-like character of a V^V complex in STZ-induced diabetic rats was investigated. The

STZ-induced diabetic rats were orally administrated with sodium 4-amino-2,6-dipicolinatodioxidovanadium(V) dihydrate **4** (Li et al. 2009). The complex was administered through an aqueous solution at a concentration of 0.1 mg ml^{-1} for 20 days; then, the concentration was increased to 0.3 mg ml^{-1} for the following 20 days. At the end of the studies, sodium complex **4** statistically significantly reduced the levels of blood glucose ($p<0.01$), serum total cholesterol ($p<0.01$), triglycerides ($p<0.01$), and the activities of serum aspartate amino transferase ($p<0.05$) and alkaline phosphatase ($p<0.01$) compared to untreated diabetic animals (Li et al. 2009). After treatment with 0.3 mg ml^{-1} sodium complex **4**, the oral glucose tolerance was improved in diabetic animals ($p<0.01$). In addition, the daily intake of elemental vanadium was markedly decreased in sodium 4-amino-2,6-dipicolinatodioxidovanadium(V) dihydrate-treated diabetic rats compared to vanadyl sulfate-treated diabetic rats, which suggested that the antidiabetic activity of the element vanadium was elevated after being modified with the coordinated organic ligand (Li et al. 2009). These results suggested that sodium complex **4** was more effective than vanadyl sulfate at alleviating the symptoms of diabetes (Li et al. 2009).



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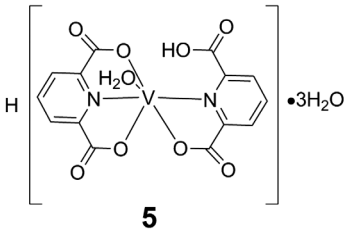
The aqueous vanadium(III) (V^{III}) speciation chemistry of two dipicolinate-containing complexes (where the oxidation states of the vanadium metal center were +3, +4, and +5) and the insulin-like effects were carried out on a chronic animal model system (Buglyo et al. 2005). The characterization of the V^{III} species was carried out at a low ionic strength to reflect physiological conditions. It required an evaluation of the hydrolysis of V^{III} at 0.20 M KCl. The aqueous V^{III} complexes with 2,6-pyridinedicarboxylic acid (H_2dipic) and 4-hydroxy-2,6-pyridinedicarboxylic acid (H_2dipic-OH) as ligands (where the complexes and their systems were designated as V^{III}-dipic and V^{III}-dipic-OH) were characterized and the complexes were observed from pH 2 to 7 at 0.2 M KCl (Buglyo et al. 2005). The V^{III}-dipic system formed stable 1:2 complexes, whereas the V^{III}-dipic-OH system formed stable 1:1 complexes. A comparison of these complexes with the V-pic system demonstrated that a second ligand has a lower affinity for the V^{III} species, presumably reflecting the bidentate coordination of the second $dipic^{2-}$ anion to the V^{III} species. The thermodynamic stability of the $[V^{III}(dipic)_2]^-$ complex was compared to the stability of the corresponding vanadium(IV) (V^{IV}) and V^{V} complexes. Surprisingly, the V^{III} complexes were found to be more stable than anticipated (Buglyo et al. 2005). An oral administration of $H[V^{III}(dipic)_2(H_2O)]\cdot 3H_2O$ **5**, $[V^{IV}O(dipic)(H_2O)_2]\cdot 2H_2O$, and $NH_4[VVO_2(dipic)]$, along with the positive control, $VOSO_4$, significantly lowered diabetic hyperglycemia in rats with STZ-induced diabetes (Buglyo et al. 2005).



5

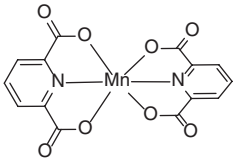
The STZ-induced diabetic rats treated with the V^{III}- and V^{IV}-containing complexes had blood glucose levels that were statistically different from those of the diabetic group (Buglyo et al. 2005). The animals treated with the V^{V} complex had the lowest blood glucose levels of the treated diabetic animals, which were statistically different from those of the diabetic group at all time points. Among the diabetic animals, the complexation to the dipicolinic acid ligand increased the serum levels of vanadium after the administration of the V^{V} and V^{IV} complexes but not after the administration of the V^{III} complex when data are normalized to the ingested dose of vanadium (Buglyo et al. 2005). Due to the fact that the vanadium complexes with different oxidation states have different biological properties, it was implied that redox processes must be important factors for the biological action of vanadium-containing complexes. The authors of these studies observed that the V^{V} complex was the most effective insulin-like agent, in contrast to previous studies in which the V^{IV} complex with maltol as a ligand was the most effective. The authors concluded that the effectiveness of coordinated vanadium was both ligand and oxidation state dependent (Buglyo et al. 2005).

Three vanadium complexes of chlorodipicolinic acid (4-chloro-2,6-dipicolinic acid) in oxidation states (+3, +4, and +5) were prepared and their properties were characterized across the various oxidation states. Additionally, the series of hydroxylamido, methylhydroxylamido, dimethylhydroxylamido, and diethylhydroxylamido complexes were prepared from the chlorodipicolinatodioxidovanadium(V) complex (Smee et al. 2009). The

chemical properties of the chlorodipicolinate compounds are discussed and correlated with their insulin-enhancing activity in STZ-induced diabetic Wistar rats (Smee et al. 2009). The effect of the chlorosubstitution on lowering diabetic hyperglycemia was evaluated and the differences were found depending on the compounds' oxidation state, as was similarly observed for the vanadium-containing-dipicolinate complexes (Buglyo et al. 2005). However, a linear correlation of oxidation states with efficacy was not observed, which suggests that the differences in the mode of action are not simply an issue of redox equivalents. More importantly, the results obtained contrasted the previous observation with the vanadium-picolinate complexes, where the halogen substituents increased the insulin-enhancing properties of the complex (Takino et al. 2001).

Manganese

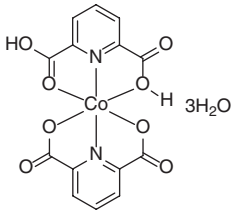
A manganese complex, $[Mn(dipic)_2]\cdot 6H_2O$ **6**, was tested for its antimicrobial activity (Tolga Çolak et al. 2009). In *in vitro* antibacterial and antifungal activities, the complex was tested with the use of the agar well diffusion method by minimal inhibition concentration (MIC) (Tolga Çolak et al. 2009). It was concluded that the complex was very effective against Gram-positive bacteria and fungi but ineffective against Gram-negative bacteria (Tolga Çolak et al. 2009).



6

Cobalt

The syntheses of Co(II) and Co(III) dipicolinate complexes were reported via solid-state X-ray characterization of $[Co(H_2dipic)(dipic)]\cdot 3H_2O$ **7** and $[Co(dipic)(\mu\text{-dipic})Co(H_2O)_5]\cdot 2H_2O$ **8**, respectively, in which two new coordination modes were observed (Yang et al. 2002). Solution studies show a high stability of the Co(III) complex, whereas the Co(II) complexes undergo pH-dependent ligand exchange in the presence of excess ligand (Yang et al. 2002). The $[Co(dipic)_2]^{2-}$ anion was found to be effective in reducing the hyperlipidemia of diabetes using oral administered aqueous solutions to rats with STZ-induced diabetes (Yang et al. 2002).



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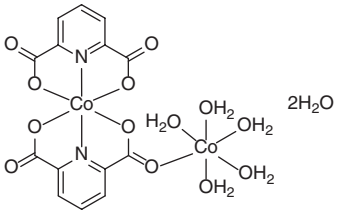

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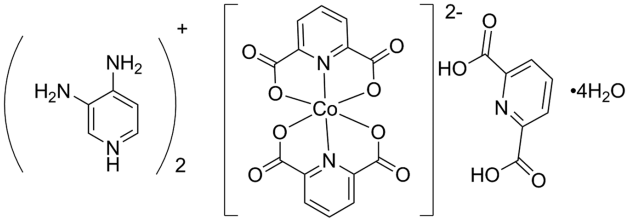
In another report by Azadbakht et al., $(H_2dap)[Co(dipic)_2]\cdot H_2dipic\cdot 4H_2O$ **9** (where dap=3,4-diaminopyridine) was screened for its antimicrobial activities against *Bacillus cereus* (ATCC 11778), *Bacillus subtilis* (ATCC 12711), *Staphylococcus aureus* (ATCC 25923), *Escherichia coli* (ATCC 25922), and *Pseudomonas aeruginosa* (ATCC 27853). However, the screening data revealed that compound **9** exhibited only inhibitory results against *S. aureus* (MIC >14 mg cm^{-3}). This finding was of great interest because it seemed to show conflict toward the well-known antimicrobial characteristic of the pure dipic ligand toward a broad spectrum of bacteria (Chauvin et al. 2006, Gaillard et al. 2013).

The confirmation of this observation was done via a comparison of independent data reported by Derikvand et al. (2012), Siddiqi et al. (2010), and Soleimani (2011). It is seen that the dipicolinic acid complexes show a varied resistance to bacterial growth. These data were further supported from the data retrieved from the antifungal studies of Siddiqi et al. (2010) and also showed similar inhibitory results for the complexes containing dipicolinic acid as a ligand. It was therefore the general conclusion from these results that showed the overall structure of the tested compounds to be the principal factor influencing the antimicrobial activity.

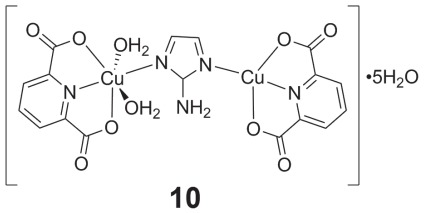


9

Copper

Complexes **10** and **11** were tested for their ability to bind to DNA, and it was seen that there was π-π stacking

between the ligands of the complex and the base pairs of DNA (Tabatabaee et al. 2013). A new Cu(II) complex, [Cu(Hdipic)(H_2dipic)]OH^-·2H_2O **12**, was tested for its antimicrobial properties (Derikvand et al. 2012). Complex **12** was reported to have moderate inhibitory effects on *B. subtilis*, *B. cereus*, and *S. aureus* but had no effect on Gram-negative bacteria (Derikvand et al. 2012).



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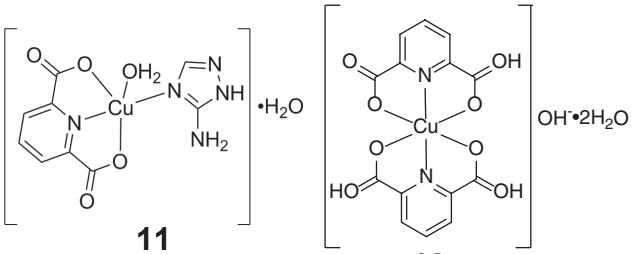


11 **12**

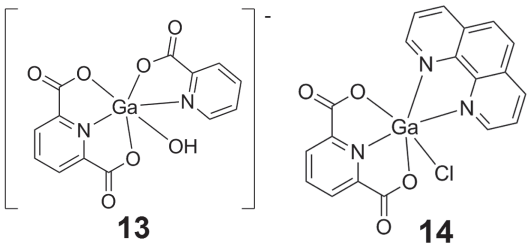
Zinc

The ternary complex formation of some potent insulin-like zinc(II) complexes of bidentate ligands, maltol and 3-hydroxy-1,2-dimethyl-pyridinone with (O,O), 2-picolinic acid and 6-methylpicolinic acid with (N,O), and the tridentate dipicolinic acid with (O,N,O) coordination modes, was studied in aqueous solutions by pH potentiometry and spectroscopic [UV-visible, circular dichroism (CD), and electrospray ionization-mass spectrometry (ESI-MS)] methods in the presence of critical cell constituents such as reduced L-glutathione (GSH) and adenosine 5′-triphosphate (ATP) (Enyedy et al. 2008). The results showed that the formation of the ternary complexes was hindered in the case of dipicolinic acid, especially with ATP, while it was favored with the bidentate ligands in the physiological pH range (Enyedy et al. 2008). The driving force of the formation of mixed-ligand species was found to be a more enhanced coordination of GSH and ATP as second ligands in the ternary complexes than in their binary ones due to steric and electrostatic reasons. The mitochondrial dehydrogenase activity of the Zn(II) complexes, as an indirect indicator for the glucose intake, was measured on Mono Mac and 3T3-L1 adipocyte cell lines (Enyedy et al. 2008). The activity of the complexes up to ~10–100 μM concentration was in the range of the effect of 0.75–1.5 μM insulin, while at higher concentration it was broken down due to the sensitivity of the cells and toxicity of the complexes (Enyedy et al. 2008).

Two ternary Zn(II) complexes with 1,10-phenanthroline (phen) as the main ligand and a carboxylate-containing ligand [dipicolinate ($dipic^{2-}$) or L-threoninate (L-Thr)] as the subsidiary ligand were prepared and characterized by elemental analysis, Fourier transform infrared (FTIR), UV-visible, fluorescence spectroscopy, X-ray diffraction, molar conductivity, and electrospray ionization mass spectrometry (Chin et al. 2012). X-ray structure analysis showed that both [Zn(phen)(dipic)(H_2O)]·H_2O and [Zn(phen)(L-Thr)(H_2O)Cl]·2H_2O have octahedral geometry about the Zn(II) metal center. Both complexes were found to inhibit topoisomerase I and had better anticancer activity than cisplatin against nasopharyngeal cancer cell lines HK1 and HONE-1 with concentrations causing 50% inhibition of cell proliferation (IC_{50} values) in the low micromolar range (Chin et al. 2012). The complex [Zn(phen)(L-Thr)(H_2O)Cl]·2H_2O had the highest therapeutic index for HK1 with a concentration of 1.3 μM. Both Zn(II) complexes were found to induce apoptosis. Changing the subsidiary ligand in the Zn(II) complexes affected the UV fluorescence spectral properties of the coordinated phen ligand, the binding affinity for some DNA sequences, nucleobase sequence selective binding, the phase at which cell cycle progression was arrested for treated cancer cells, and their therapeutic index (Chin et al. 2012).

Gallium

Two gallium(III) complexes (**13** and **14**) have been synthesized with the first ligand being dipicolinic acid and the second being either 2-picolinic acid or phen (Kong and Sun 2009). The two gallium(III) complexes were reported to have antimicrobial activities against *S. aureus*, *E. coli*, and *B. subtilis*. The highest inhibitions were reported against *S. aureus* for both complexes when compared to the activity of the free ligands (Kong and Sun 2009).



13 **14**

Ruthenium

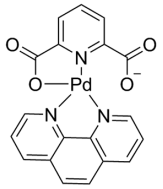
Ruthenium(II)-arene complexes of general formulas $[(\eta^6\text{-}p\text{-cymene})Ru(L^{1-3})Cl_2]$ (where L^{1-3}=3-acetylpyridine), 4-acetylpyridine, and 2-amino-5-chloropyridine)), correspondingly, $[(\eta^6\text{-}p\text{-cymene})Ru(HL^{4,5})Cl_2]$ (where HL^4 and HL^5 are isonicotinic acid and nicotinic acid, respectively), and $[(\eta^6\text{-}p\text{-cymene})Ru(HL^{6-9})Cl]$ (where H_2L^{6-9}=2,3-pyridinedicarboxylic acid, 2,4-pyridinedicarboxylic acid, 2,5-pyridinedicarboxylic acid, and 2,6-pyridinedicarboxylic acid), were prepared by the reaction of $[(\eta^6\text{-}p\text{-cymene})_2RuCl_2]_2$ with the corresponding ligand in 1:2 molar ratio in isopropanol (Grguric-Sipka et al. 2010). The complexes were characterized by elemental analysis, mass spectrometry, IR and nuclear magnetic resonance (NMR) spectroscopies, and X-ray crystallography, where appropriate (Grguric-Sipka et al. 2010). The complexes revealed a low antiproliferative activity in six investigated tumor cell lines (HeLa, B16, FemX, MDA-MB-361, MDA-MB-453, and LS-174) (Grguric-Sipka et al. 2010).

Rhodium

Several rhodium(II) complexes belonging to the general structure $[Rh(CO)_2(dipic\text{-}L)]$ [where L=dithiocarbamate (dtc) and xanthate derivatives] were synthesized and assayed as cytostatic and antitumor agents *in vitro* against KB cells and *in vivo* against P388 leukemia, Ehrlich ascites carcinoma, sarcoma 180 ascites, and ADJ/PC6A solid tumors. The assays against five *Trypanosoma* strains were also performed. Among the new compounds, the $[Rh(CO)_2(dipic\text{-}dtc)]$ appeared to be active in all biological systems without showing evident nephrotoxicity (Sengupta et al. 1983, Craciunescu et al. 1991).

Palladium

The palladium(II) complexes have been highly sought after in the realm of therapeutic anticancer drug development because of the similarities in bioactivities and coordination behavior between palladium(II) and platinum(II) complexes. Although the principle mechanism of its antitumor property is not yet known, it is confirmed that some species of the aromatic heterocycles can stack with nucleobases and then enhance the complex formation with DNA, which is the target in the chemotherapy of tumor. An example of such a heterocyclic complex is $[Pd(phen)(Hdipic^-)]\cdot 4H_2O$ **15**, as reported by Wang and Okabe (2005).



15

The interaction of $[Pd^{II}(dipic)Cl]^-$ with AMP, inosine-5′-monophosphate (IMP), and reduced GSH was studied kinetically as a function of [L] (L=AMP, IMP, GSH) and $[Cl^-]$ and temperatures (10–35°C) at pH 4.0 (Chatterjee et al. 2005). It was seen that the $[Pd^{II}(dipic)Cl]^-$ anion complexes first go through aquation replacing the chloride ligand (Chatterjee et al. 2005). The aqua palladium(II) complexes were reported to bind to weak nucleophiles such as AMP and IMP (Chatterjee et al. 2005).

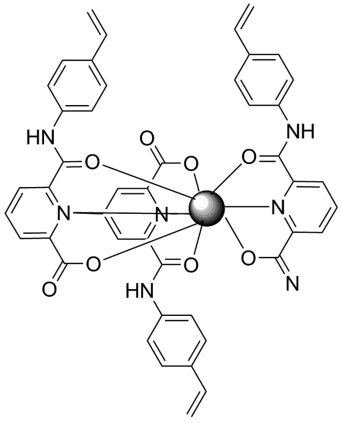
Tin

A series of diorganotin dipicolinates were synthesized and their antitumor activities against two human tumor cell lines MCF-7, a mammary tumor, and WiDr, a colon carcinoma, were determined (Gielen et al. 1991, Costa et al. 2005). All complexes synthesized were only moderately active in both cell lines tested. Among the series of synthesized complexes, $n\text{-}Bu_2Sn(2\text{-}O_2C\text{-}C_5H_4N\text{-}3\text{-}OH)_2$ was the most active of the series (ID_{50} values=96 and 337 ng ml^{-1} in MCF-7 and WiDr, respectively). All synthesized complexes showed less activity compared to similar previously synthesized complexes, such as di-*n*-butyltin-bis(3-methoxysalicylate), as characterized by ID_{50} values of 44 and 82 ng ml^{-1} against MCF-7 and WiDr, respectively (Bouâlam et al. 1991).

Yttrium

The highly selective separation of yttrium and lanthanides is of interest for the design of radiopharmaceuticals for the treatment of illness such as cancer and rheumatism,

and in the past decade, much interest has been taken in yttrium detection in biological applications (Horovitz 1999, Okamoto and Fukuzumi 2004). Chauvin et al. (2006) have demonstrated that imprinting a polymer with neutral [Y(**16**)$_3$] [where **16**=6-(4-vinylphenylcarbamoyl) pyridine-2-carboxylic acid] complexes, followed by acid demetallation, leads to resins highly selective for Y^{III} and heavy Ln^{III} ions (Chauvin et al. 2006). The obtained ion-imprinting effect stems from the rigid geometry imposed by the three dipicolinate-based ligand strands, which are maintained upon polymerization with styrene and divinylbenzene. The ion-imprinted polymer based on complex **16** was particularly efficient at extracting yttrium and has a sizeable capacity (8.9±0.2 mg g^{-1} resin) and a fast rate of extraction ($t_{1/2}$=1.7 min) (Chauvin et al. 2006). Complex **16** showed high selectivity for yttrium and lanthanide cations when compared against alkali and alkaline earth metals opening the potential for its use in the production of highly pure ^{90}Y and radiolanthanides for medicinal application and for the trace analysis of radiochemicals in food and the environment.



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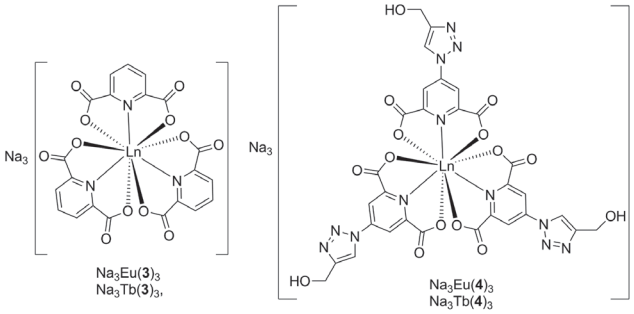
Lanthanides

Gaillard et al. (2013) have recently developed a "click" approach to synthesize dipicolinic acid derivatives for lanthanide chelates, which take advantage of the intrinsic efficiency of the copper-catalyzed azide-alkyne cycloaddition (CuAAC) reaction. The simple dipicolinic acid $Na_3Eu(\mathbf{17})_3$ and $Na_3Tb(\mathbf{17})_3$ complexes were used for the comparison for Eu^{3+} and Tb^{3+} 4-triazolyl-DPA complexes against $Na_3Eu(\mathbf{18})_3$, $Na_3Tb(\mathbf{18})_3$, $Eu(\mathbf{19})_3$, $Tb(\mathbf{19})_3$, $Eu(\mathbf{20})_3$, and $Tb(\mathbf{20})_3$ bearing a hydroxymethyl, a chlorine, and a trimethyl ammonium appendage, respectively. These 4-triazolyl-DPAs have shown promising results under two-photon excitation (TPE) and three-photon excitation (THPE). The nanoparticles containing the lanthanide complexes were obtained by a classic reverse emulsion process involving tetraethyl orthosilicate (TEOS), NP-5 surfactant [polyoxyethylene (**5**) nonylphenyl ether], and ammonia. The photophysical properties of NP-(**17**)$_3$ to NP-(**20**)$_3$ showed two distinguishable types of NPs. No significant luminescence was observed for NP-(**17**)$_3$ and NP-(**18**)$_3$, indicating a poor incorporation of the rare-earth complexes into the silica matrix. Conversely, the complexes bearing the ammonium moieties [NP-Eu(**19**)$_3$, NP-Tb(**19**)$_3$, and NP-Eu(**20**)$_3$] were more easily embedded into the silica nanoparticles, owning to their enhanced capability to interact with the silica network, due to the interactions between the ammonium moieties and the deprotonated silanol groups. The treatment of NP-Eu(**19**)$_3$-NH_2 with an excess of homobifunctional polyethylene glycol (PEG) yielded luminescent PEGylated NPs NP-Eu(**19**)$_3$-PEG-NHS. The presence of the -NHS termini on the NP's surface allows for the bioconjugation of these nano-objects with biomolecules, potentially leading to the applications of specified biolabeling and bioimaging (Gaillard et al. 2013).

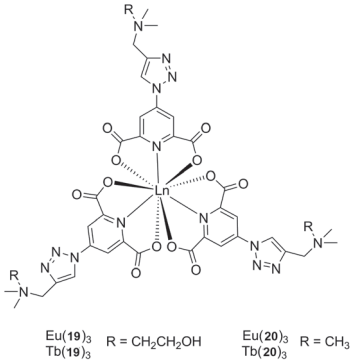


$Na_3Eu(\mathbf{3})_3$
$Na_3Tb(\mathbf{3})_3$,

17

$Na_3Eu(\mathbf{4})_3$
$Na_3Tb(\mathbf{4})_3$

18



$Eu(\mathbf{19})_3$ R = CH_2CH_2OH
$Tb(\mathbf{19})_3$

19

$Eu(\mathbf{20})_3$ R = CH_3
$Tb(\mathbf{20})_3$

20

The functionalized tris-dipicolinate europium(III) complexes have been reported to show two-photon absorption but exhibit weak stability in aqueous solutions due to the ligand substitution by water molecules, which radically

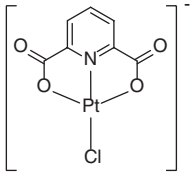
decreases the luminescence quantum yield and lifetime of the complexes (Chauvin et al. 2004, Picot et al. 2008).

$$[\mathrm{Ln(DPA)_3}]^{3-} \overset{\mathrm{H_2O}}{\rightleftharpoons} [\mathrm{Ln(DPA)_2(H_2O)_x}]^{-} + \mathrm{DPA}^{2-}$$

Tris-dipicolinate europium complexes $[Eu(dipic)_3]^{3-}$ (**21**) where the dipicolinic acid was functionalized by donor-π-conjugated moieties (Kong and Sun 2009, Grguric-Sipka et al. 2010), and further decorated with hydrosolubilizing PEG end-groups (**22**), were synthesized by Picot et al. (2008). These novel europium complexes fulfilled all of the requirements for use in biomedical imaging application: (i) water solubility, (ii) intense emission, (iii) long luminescence lifetime, and (iv) significant two-photon absorption. Philippot et al. (2011) utilized a one-step method based on the spray drying of sol-gel solutions involving silicon alkoides as precursors of silica NPs to incorporate and further stabilize similar lanthanide complexes in aqueous media. The best water dispersion and chemical stability of the Eu complexes embedded in silica NPs were obtained using an 8TMOS+1BTTPOHD silica matrix composition [where TMOS=tetramethoxysilane and BTTPOHD=1,16-bis(trimethoxysilyl)-4,7,10,13-tetraoxahexadecane]. Luminescence lifetimes remained constant upon dilution and similar values were obtained to those measured in the solid state, confirming the presence of nondissociated Eu complexes. High luminescent intensity and good photostability were registered for NPs slightly doped with Eu complexes (5 wt.%) by two-photon microscopy. The BTTPOHD moiety contained a PEG moiety further increasing the biocompatibility of these doped NPs, thus increasing the possibility of their potential application as stable biolabels for two-photon luminescence imaging (Philippot et al. 2011).

Platinum

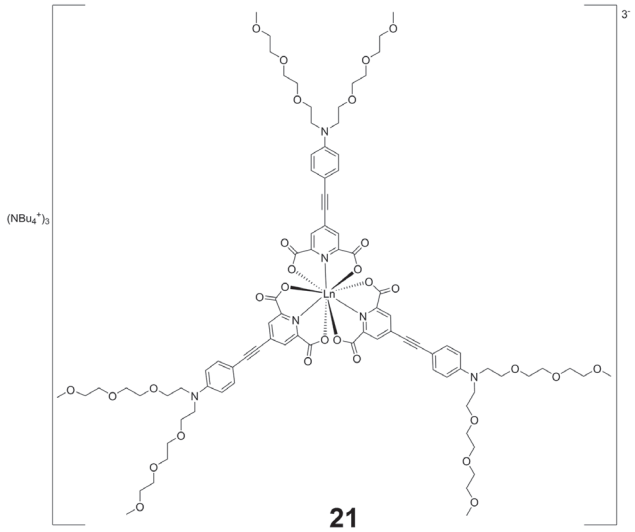
Due to the success of cisplatin, there have been many studies conducted on its derivatives to enhance carcinoma cell death while leaving the noncancerous cells intact (Chatterjee et al. 2005). The complex [Pt(dipic)Cl]$^-$ **23** was tested against breast (MCF-7), lung (NCI-H460), and central nervous system (CNS) (SF-268) cancer cells where the inhibition toward all three cell lines was reported (Chatterjee et al. 2005). The growth inhibition of 50% of the cell populations was perceived as 0.57, 0.50, and 0.70 mM for MCF-7, NCI-H460, and SF-268, respectively (Chatterjee et al. 2005). The efficacy of complex **23** was seen to be less than that of cisplatin (Chatterjee et al. 2005).



23

Bismuth

The incorporation of the acidic Bi(III) ion with ligands bearing N-O donor atoms produced a wide selection of pharmaceutically active complexes (e.g., complex **24**), which have been extensively used for the treatment of a broad spectrum of gastrointestinal disorders. The derivatives of dipicolinic acid have produced interesting motifs that exhibit relatively good stabilities in aqueous



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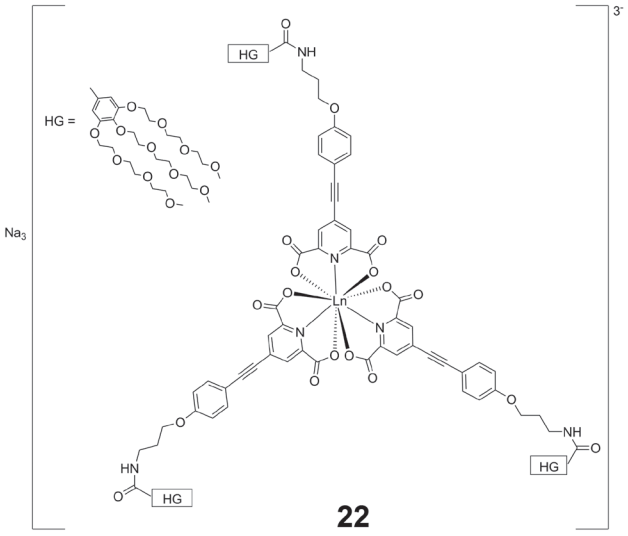
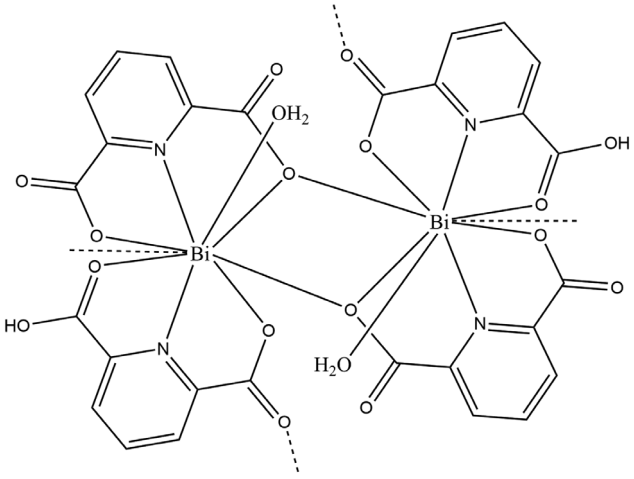


22

environments and high solubilities in slightly acidic conditions (Anjaneyulu et al. 2010, 2011).



24

Conclusion

In conclusion, the complexes with dipicolinic acid and its derivatives as ligands were reported to have effects that ranged from antibacterial and anticancer agents to having insulin-like properties. The different complexes were reported to have the ability to inhibit the growth of Gram-positive bacteria and fungi, to cause apoptosis in cancerous cells, to use as a bioimaging agent, or to reduce the blood glucose levels in STZ-induced diabetic rats.

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Bionotes

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