

Nitroprusside and Other Cyanoferrate Complexes: A Brief Review on Biological Activity Aspects

Nitroprussiato e Outros Complexos Cianoferratos: Uma Breve Revisão sobre Aspectos da Atividade Biológica

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Research on cyanoferrate complexes has been motivated by their interplay in biological systems and potential pharmacological activity with low toxicity, a simple synthetic route, and low cost. The importance of cyanoferrate for research in medicinal chemistry began with using nitroprusside in cardiac surgeries due to its effect as a vasodilator agent. This compound has gained importance over the years due to the discovery of the various physiological functions of nitric oxide. Despite the great relevance of nitroprusside in medicine, the class of pentacyanoferrate only advanced a little in this area until the emergence of cyanoferrate complexes containing ligands with antituberculosis activity. These compounds have been the target of several studies that have helped develop new metallopharmaceuticals. Herein, our article briefly reviews the main discoveries about these compounds and extends the discussion to other examples of cyanoferrates with potential pharmacological activity against several diseases, such as cancer, cardiac disturbances, parasitic diseases, and tuberculosis.

Keywords: Cyanoferrate; cancer; cardiac disorders; parasites; tuberculosis.

1. Introduction

Metals are a group of elements that have been gaining notoriety due to a wide range of applications for therapeutic purposes and as diagnostic agents. Research focused on therapies for various diseases uses these elements primarily as metal complexes or coordination compounds that are a class of chemical substances essentially composed of a central metal ion coordinated to ligands, which may be organic or inorganic. Owing to their broad therapeutic applications, they have also been referred to as metallopharmaceuticals. The remarkable pharmacological potential of this group of substances arises from the numerous possibilities of controlling kinetic and thermodynamic properties through the choice of the metal oxidation state, of their geometry, and of the electronic character of the ligands.¹⁻⁴

The prominence of the therapeutic use of metallopharmaceuticals becomes evident when d-block metal ions are applied to major public health problems, such as the use of cisplatin (cis-diamminedichloroplatinum(II)), employed in cancer treatment since 1978. With the advent of cisplatin in this type of therapy, numerous obstacles emerged, including high toxicity, lack of selectivity, and cellular resistance, which limited its clinical use. Driven to overcome these challenges, significant efforts have been devoted to the search for new metallic centers for this kind of therapy, with platinum-, ruthenium-, gold-, and titanium-based metallopharmaceuticals standing out in various phases of clinical studies. The use of metallopharmaceuticals in modern medicine is not restricted to their anticancer potential, as the literature also reports applications of metal complexes as antiviral, antiparasitic, antimicrobial agents, as well as anti-inflammatory agents. In addition, the literature highlights major advances in the use of complexes formed by radioactive metals as reliable agents for diagnosis and therapeutic target tracking.¹⁻⁴

Research on cyano iron complexes has gained attention due to their interplay in biological systems and potential pharmacological activity with low toxicity, simple synthetic route, and low cost.⁵⁻⁸ The strong backbonding interactions between the metal $d\pi$ orbitals and the π orbitals of the cyano ligands reflect the stability exhibited by these complexes, both in the solid state and in aqueous solution.⁹ Moreover, the relative inertia of the cyano iron complexes makes them good candidates as drugs since they can reach their target site without substituting the ligands.⁵⁻⁸

The importance of cyanoferrates for research in medicinal chemistry began with using sodium

nitroprusside (SNP, $\text{Na}_2[\text{Fe}(\text{CN})_5\text{NO}] \cdot 2\text{H}_2\text{O}$) in cardiac surgeries due to its effect as a vasodilator agent.¹⁰ SNP has gained importance over the years due to the discovery of the various physiological functions of nitric oxide such as vasodilation, immune responses, neurotransmission, apoptosis.^{11–17} Despite the great relevance of nitroprusside in medicine, the class of pentacyanoferrate complexes only advanced a little in this area until the emergence of cyanoferrate complexes containing ligands with antituberculosis activity as well as less intensely; researches were reported on cyano iron complexes that present activity against other diseases such as leishmaniasis, Chagas disease, and cancer.^{5,18–20}

The selection of co-ligands and the number of cyano ligands around the metal center allows the design of the complex and, consequently, the fine-tuning of its photochemical properties, reduction potentials, and solubility in aqueous solution.⁸ Therefore, molecules with potential pharmacological activity in the metal coordination sphere make the iron cyanide complexes candidates for application in medicinal chemistry.^{5,18–20}

In this review, we highlight some examples of cyanoferrates with pharmacological applications such as hypotensive effect, anticancer action, anti-tuberculosis, and antiparasitic activity.

2. Therapeutic Applications and Toxicological Challenges of SNP as a Nitric Oxide Donor

Frequently, in treatments for acute myocardial infarction and cardiomyopathy, SNP is regularly prescribed, and it can also be used in cardiac surgeries.^{21–23} Its biological effects have been ascribed to its action as a NO donor in inducing vasodilation, which was examined through both in vitro (aortic rings) and in vivo (Wistar rats) experiments.^{24–26} Friederich, Jeffrey A. and collaborators suggested that, despite the chemical inertness of SNP under non-biological conditions, its in vivo action would occur through a degradation reaction at the vascular level, in which the $[\text{Fe}(\text{CN})_5\text{NO}]^{2-}$ ion binds to oxyhemoglobin, promoting the release of cyanide, methemoglobin, and nitric oxide (NO).^{27–31}

Cyanide is also released from the metal coordination sphere due to the trans-labilizing effect of NO in the $[\text{Fe}(\text{CN})_5\text{NO}]^{2-}$ species. Researchers³² have studied the mechanism of the thermal decomposition of the one-electron reduction product of the complex $[\text{Fe}(\text{CN})_5\text{NO}]^{2-}$, which was found to contain a mixture equilibrium of complex ions $[\text{Fe}(\text{CN})_4\text{NO}]^{2-}$ and $[\text{Fe}(\text{CN})_5\text{NO}]^{3-}$. At pH values lower than 8, the predominant species observed is $[\text{Fe}(\text{CN})_4\text{NO}]^{2-}$, which is formed by the instantaneous release of cyanide from the $[\text{Fe}(\text{CN})_5\text{NO}]^{3-}$ species. However, at basic pH values between 9 and 10, the slow decomposition of the mentioned species occurs through

first-order processes, with a rate constant of approximately 10^{-5} s^{-1} (pH 6–10), associated with NO dissociation.³² At pH 7.0 it is formed the intermediate species $[\text{Fe}(\text{CN})_4(\text{NO})_2]^{2-}$, which induces the release of HNO (N_2O , in sequence) and produces $[\text{Fe}(\text{CN})_5\text{NO}]^{2-}$ or releasing CN^- yielding $[\text{Fe}(\text{CN})_2(\text{NO})_2]^{2-}$.³²

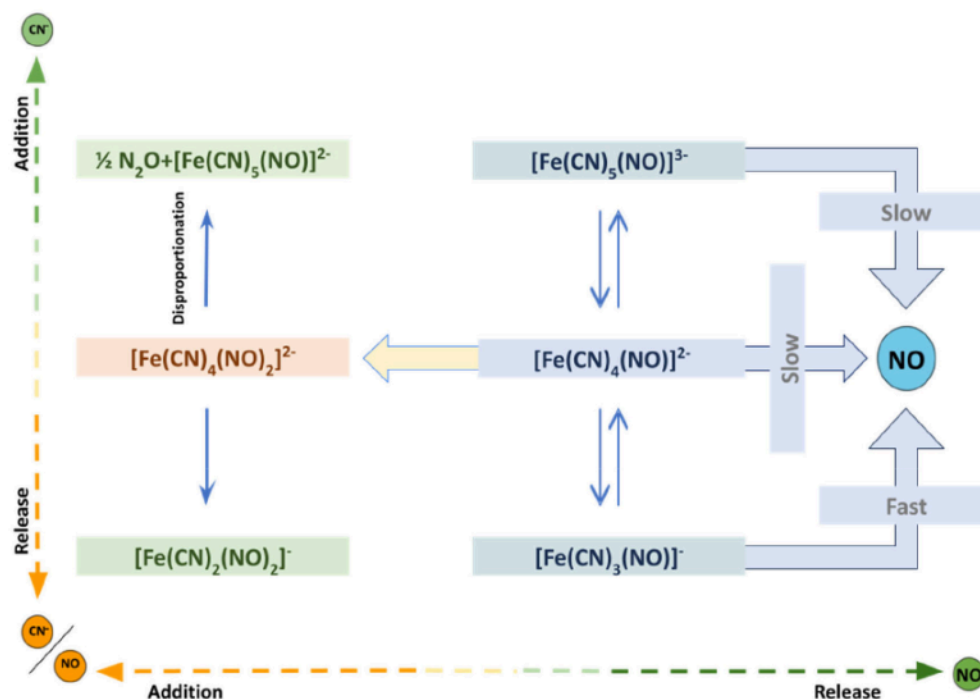
At a pH of 4, decomposition increases by two orders of magnitude, which leads to the release of cyanides from the ions $[\text{Fe}(\text{CN})_4\text{NO}]^{2-}$ and the rapid release of NO.³³ It is worth noting other possible decomposition products, including hexacyanoferrate(II), dissociated cyanide, and Prussian Blue-type precipitates, as described by Roncaroli *et al.* in 2005.³²

Cyanide is also released from the metal coordination sphere, which can be toxic to the patient since it inhibits oxidative phosphorylation and leads to metabolic acidosis (Scheme 1).³⁴ The yielding of the non-toxic thiocyanate species from the reaction of the cyanide with thiosulfate ($\text{S}_2\text{O}_3^{2-}$) has led to doctors administering nitroprusside to the patient with that reagent.¹⁰ NO acts on guanylate cyclase in vascular smooth muscle as a potent vasodilator, increasing the intracellular production of one of the messengers for the activation of protein kinase G, cyclic guanosine monophosphate (cGMP). That protein acts through the activation of phosphatases that inactivate the myosin light chains responsible for muscle contraction. Thus, in consequence, vascular smooth muscle relaxation allows the vessels to dilate.^{35–37}

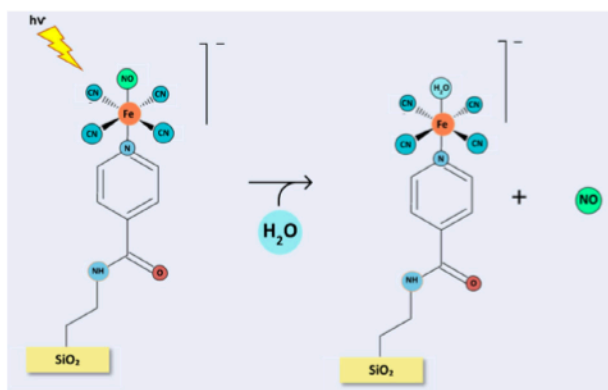
Scientists have made significant progress towards eliminating the cytotoxicity of cyanide released from SNP in biological systems. Drug delivery systems such as nanoparticles, Prussian blue-based nanoparticles, metal-organic frameworks (MOFs), and surface functionalization with specific molecules such as folic acid, proteins, and antibodies have been synthesized to increase drug efficiency and reduce toxic responses of the SNP.³⁸ These SNP-containing drug deliveries have been studied for the treatment of various diseases, including bacterial infection, glaucoma, cardiovascular diseases, and cancer.^{39–42}

Another exciting idea is to combine the concept of drug delivery with the removal of labile cyanide from the coordination sphere to reduce the toxicity of the SNP.⁴³ Ordeley and co-authors have developed a method of immobilizing $[\text{Fe}(\text{CN})_4(\text{L})\text{NO}]$ on modified mesoporous silica spheres, which has led to the creation of NO-releasing materials.⁴³ The researchers observed that in the presence of cysteine, the nitrosyl complex releases NO with a prolonged kinetic process; besides, CN^- anion liberation from the metal center was not noted.⁴³ The Group also observed NO liberation after light irradiation on the material and the consequent addition of one molecule of water in the coordination sphere (Scheme 2).⁴³ These findings have important implications for developing safe and effective NO-releasing materials in biological applications.

Other studies have shown some benefits of SNP in cardiopulmonary disorders as a possible alternative agent



Scheme 1. Reactions between nitroprusside and thiol



Scheme 2. NO liberation after light irradiation on the material

to adenosine in patients with intermediate lesions.⁴⁴ Lloyd and co-workers observed that patients with severe low-grade aortic stenosis treated with SNP experienced improvements in left ventricular measurements.⁴⁵ A study by Ripeckyj and co-workers in 2020 showed the positive effect of SNP in cardiopulmonary resuscitation (CPR) in large animals. SNP and CPR use lead to increased coronary perfusion and carotid blood flow. This study shows non-selective pulmonary vasodilation as a potential mechanism for hemodynamic benefits.⁴⁶

SNP has also been evaluated as a possible drug for treating mental pathologies. Its action mechanism is indirect since it acts as an anxiolytic, a condition directly associated with schizophrenia.⁴⁷ Several studies in rodents show the anxiolytic effect of SNP when given in high doses.⁴⁸⁻⁵⁰ However, due to the high load, sedation occurs as a side effect, and the anxiolytic properties of SNP disappear after subchronic application.⁵¹ Thus, Papageorgoulis and

co-workers demonstrated that repeated short-term, but not acute, low-dose SNP application produced anxiolytic behavior without the manifestation of undesirable effects.⁵¹ The studies shown in this section explicitly demonstrate the benefits of SNP in treating various cardiopulmonary disorders and mental pathologies; however, it also has possible toxic effects. In this report, we cited some examples of nitrosyl cyano iron complexes that can be an alternative to SNP as NO-donors to combat those diseases.

3. Antiparasitic Effect

Iron cyanide complexes exhibit a unique activity in treating parasites within their biological properties. Several studies show that these compounds exhibit remarkable properties for treating pathologies such as Chagas disease, leishmaniasis, and malaria.^{18,19,52-54}

Between 1999 and 2000⁵⁵⁻⁵⁷, Venturini and co-workers conducted two experiments using NO donors, including SNP, to evaluate their inhibitory activity against the *Trypanosoma cruzi* parasite, the etiological agent of Chagas disease, and *Plasmodium falciparum*, a parasite of the most dangerous form of malaria.⁵⁵⁻⁵⁷ The researchers observed that these compounds were effective in inhibiting the growth of the parasites in both cases.⁵⁵⁻⁵⁷ Furthermore, NO released from complexes inhibits Cruzipain, a cysteine protease that helps parasites avoid the adaptive immune system response by interfering with the functions of the immunoglobulins of the immunoglobulin G subclasses.⁵⁸ Besides, similar is the mechanism of action of the NO against *Plasmodium falciparum* since it inhibits falcipain, which also is a

cysteine protease involved in different processes of the erythrocyte cycle of the malaria parasite, such as hydrolysis of erythrocyte invasion, erythrocyte rupture, and hydrolysis of host hemoglobin.⁵⁹ In both cases, SNP acts against cruzipain and falcipain through S-nitrosylation, inhibiting the life cycles of the parasites, *T. cruzi*, and *P. falciparum*, respectively.^{55,56} Besides, NO released from SNP can react with O_2^- radical, producing the toxic species peroxynitrite.²⁶ Nitrosyl complexes can also act as nitroxyl (HNO) donors in the biological environment.^{31,53} The antiparasitic effect of this type of complex can be partly attributed to the nitroxyl effect against the promastigote form of the parasite *Leishmania major*.⁵³

Amorim and co-workers, in 2017, conducted a study in which they compared the anti-tuberculosis properties of the iron complex containing isoniazid (INH), the $[Fe(CN)_5(INH)]^{3-}$ with its possible anti-*Leishmania* activity.¹⁸ The correlation was realized because both organisms present the type II biosynthesis (FASII) of the fatty acids that constitute their structure. This biochemical process is interrupted by the action of pentacyano(isoniazid) ferrate(II), which inhibits the enzyme responsible for signaling the synthesis.^{18,45} The study demonstrated that $[Fe(CN)_5(INH)]^{3-}$ effectively reduced the proliferation of promastigote forms of three *L. braziliensis* strains. This complex also decreased the proliferation of amastigotes of the three strains isolated of *L. braziliensis* within the macrophages. Moreover, the toxicity tests revealed a very favorable profile for $[Fe(CN)_5(INH)]^{3-}$ according to the evaluation of the cell lineages or primary cultivation cells.^{10,9}

4. Anticancer Activity Of SNP

As far as we know, articles that report the anticancer activity of cyanoferrates are not abundant. However, some studies report the antineoplastic effect of SNP, which is ascribed to its ability to release NO in the biological environment.⁶⁰ Researchers have enlightened the mechanism of action of the NO in processes such as growth and death cellular by using NO-donors.^{61,62} They have suggested that nitric oxide plays opposite functions in biological systems, such as apoptosis and neogenesis, which seem to depend on levels of NO produced by cells.⁶³⁻⁶⁶

Sumitani and co-authors demonstrated that the death of NA cells (an epithelial cancer cell line) *in vitro* by $Na_2[Fe(CN)_5(NO)]$ could be related to NO release in a biological environment. The authors noted high levels of NO_2^- (product of NO) in the culture medium containing NA cells and SNP.^{60,67} These researchers showed that SNP induces apoptotic cell death via modulation of ERK activity in several cell types.⁶⁰

Another study demonstrated a synergistic effect on combating cancer cells using hyperthermia and SNP.²⁰ The authors showed that hyperthermia and Nitric oxide, released from SNP, induce oxidative stress, caspase activation, DNA

fragmentation, and mitochondrial depolarization. Besides, hyperthermia and SNP lead to necrotic and caspase-dependent apoptotic death of cancer cells.²⁰

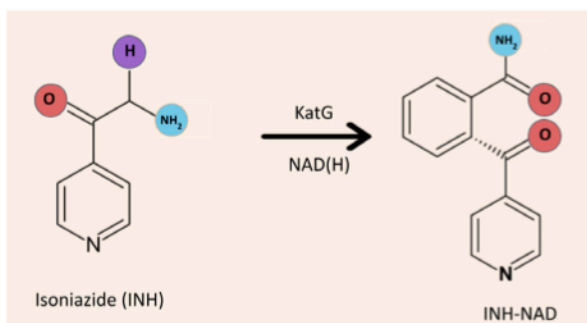
Kurimoto and co-authors researched the effect of NO on the growth and radiosensitivity of cultured glioma cells.⁶⁸ The researchers observed that S-nitroso-N-acetylpenicillamine (a known NO-donor) and SNP inhibited the growth of the glioma cells. The data indicated that NO mediates the inhibition of cellular growth effect since it was declined by the presence of hemoglobin, a scavenger of NO.⁶⁸ Besides, they noted radiosensitization when the malignant glioma cells were irradiated in the presence of NO-donors, an effect that was also attributed to the liberation of NO in the biological medium.⁶⁸ On the other hand, studies have shown that NO can also stimulate cancer cell growth. It is worth noting that NO can have a dual effect on cancer cell growth, depending on factors such as NO flux, release rate, and cell type.^{63,69} In other words, nitric oxide in low concentrations can stimulate the proliferation of cancer cells,⁶⁴⁻⁶⁷ while higher concentrations can inhibit the proliferation of cancer cells and induce apoptosis.^{63,65,70-72} Therefore, the use of NO-donors such as SNP should consider the rate of NO release in the cellular medium to lead to a better interpretation of the data.

5. Antituberculosis Activity

The resistance of the bacterium *Mycobacterium tuberculosis* that causes tuberculosis to traditional drugs has been observed by researchers in recent decades.⁵⁹ The strategy developed by Souza was to combine these drugs, mainly isoniazid (INH) and rifampicin, with the fragment $[Fe(CN)_5]$, resulting in efficient anti-tuberculosis agents.^{5,59,73,74} This highlights the importance of research related to treatments to combat this disease.

According to the literature, INH functions as a prodrug, activated by an electron transfer reaction catalyzed by the enzyme catalase-peroxidase (KatG). This process generates various reactive oxygen species and reactive organic radicals capable of efficiently attacking *M. tuberculosis* bacteria. The action of isoniazid occurs by forming the isonicotinic acyl radical. That species reacts with NAD(H) to form the NAD-isoniazid adduct, an efficient inhibitor of the InhA enzyme ($K_d = 0.4$ nM), directly related to the biosynthesis of mycolic acid (fatty acid in the cell wall of *M. tuberculosis*). Therefore, isoniazid is a very effective therapeutic drug for extended periods (Scheme 3).^{5,59,73,74} However, it was observed that 50% of isoniazid-resistant isolates have mutations in the katG gene. This gene is a bifunctional enzyme with broad-spectrum catalase and peroxidase activity, which acts by oxidizing several electron donors, including NAD(H), necessary for drug activation.^{5,59,73,74}

The complex $[Fe(CN)_5(INH)]^{2-}$ proposed by Sousa and co-authors (Figure 1),⁵⁹ can act as an alternative antituberculosis drug since the oxidation-reduction reactions



Scheme 3. The simplified mechanism of action of isoniazid

of the organic ligand usually require metallic enzymes. Therefore, intramolecular electron transfer reactions promoted by a metal complex coordinated to isoniazid would produce an alternative route for ligand oxidation. It was demonstrated that the complex $[\text{Fe}(\text{CN})_5(\text{INH})]^{2-}$ showed activity against strains resistant to the isoniazid ligand, which indicated that this compound would be a potential antituberculosis agent. The initial results led the researchers to invest in synthesizing a series of complexes with similar structures to achieve better results or to seek to understand their mechanism of bactericidal action.⁵⁹ This resembles the thioamide-pyridine antituberculosis prodrugs, whose mechanism was poorly understood.

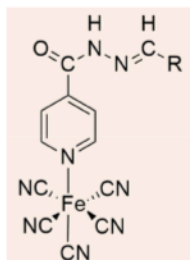
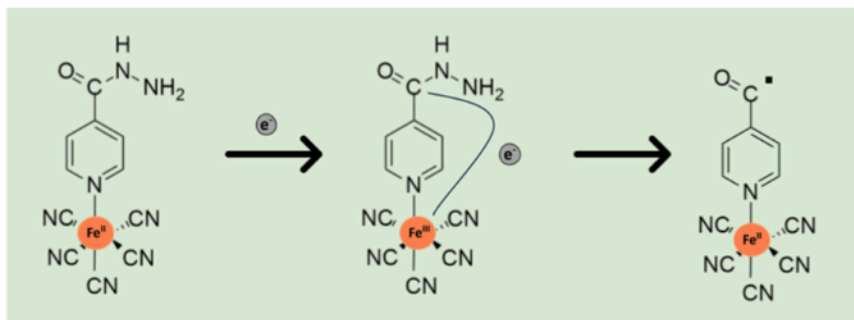


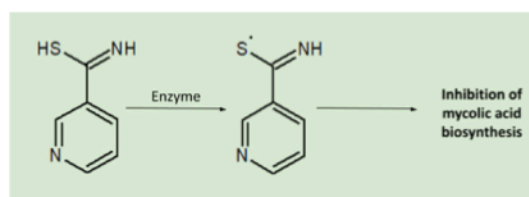
Figure 1. Structure of the derivatives of the complex $[\text{Fe}^{\text{III}}(\text{CN})_5(\text{INH})]^{2-}$, R = Ph (phenyl); CH_3 -4-Ph; CH_3 -O-4-Ph; F-4-Ph; Fur-2-yl

Researchers have showcased that its mechanism of action for treating multidrug-resistant tuberculosis occurs through activation by enzymatic electron transfer.⁵⁹ The authors of the work investigated the electron transfer reaction in an interaction between the complex $[\text{Fe}(\text{CN})_5(\text{H}_2\text{O})]^{2-}$ and thionicotinamide, which was observed to convert the ligand to the 3-cyanopyridine species coordinate to a Fe^{II}



Scheme 5. Mechanism of activation of isoniazid in the complex ion $[\text{Fe}^{\text{II}}(\text{CN})_5(\text{INH})]^{3-}$

metallic center.⁵⁹ The authors suggested that this study could aid the design of new thiocarbonyl-containing drugs against resistant strains of *Mycobacterium tuberculosis* by a self-activation mechanism.⁵⁹ In addition, scientists have also explored the synthesis of derivatives of the complex $[\text{Fe}(\text{CN})_5(\text{INH})]^{2-}$ with substituents that increase electronic density to enhance the inhibition of the MtInhA enzyme. Compound $\text{Na}_4[\text{Fe}(\text{CN})_5(\text{pyrazine-2-hydroxamic acid})]$ attracts attention due to its reaction with H_2O_2 , which produces pyrazinoic acid and HNO . Additionally, that compound appears to have extraordinary vasodilation properties with the added benefit of having lower toxicity than SNP.⁷⁵ These findings hold promise for developing more effective treatments for this deadly disease (Scheme 4).⁵



Scheme 4. Summarized action mechanism of the thionicotinamide (thiol)

6. Mechanism of Antituberculosis Action of $\text{Na}_3[\text{Fe}(\text{CN})_5(\text{INH})]$

The proposal of the synthesis of the iron complex $\text{Na}_3[\text{Fe}(\text{CN})_5(\text{INH})]$ had as a premise to make the oxidation process of this ligand more accessible. The iron in the complex has an oxidation potential that can be easily activated in a biological environment, thereby oxidizing the isoniazid ligand and forming its activated species.⁴⁵ This active species can inhibit the enoyl-[acyl transporter protein] reductase enzyme (InhA) of *Mycobacterium tuberculosis* without the need for activation by catalase-peroxidase KatG.⁷⁵ Therefore, it was suggested that the $[\text{Fe}(\text{CN})_5(\text{INH})]^{3-}$ complex would have an action against strains of *Mycobacterium tuberculosis*, whose INH resistance mechanism involves mutations in the katG gene (Rv1908c) (Scheme 5).^{76,77}

Once autoxidation occurs, inhibition of the InhA enzyme by the $[\text{Fe}^{\text{II}}(\text{CN})_5(\text{INH})]^{3-}$ complex would be possible.

Souza *et al.*⁷³ demonstrated the possibility of the formation of the radical $[\text{Fe}^{\text{II}}(\text{CN})_5(\text{INH})]^{3-}$ through the reaction with peroxide and superoxide. However, as discussed above, this intramolecular transfer mechanism is not possible in the intracellular environment of macrophages due to the high oxidation potential value of the metallic center of the complex, which would hinder the formation of the iron(III) species and, therefore, the subsequent transfer of Ligand-metal electrons. The same author had already observed the importance of the redox potential of the metallic center for the antituberculosis activity of complexes containing INH.⁷⁴ The researcher observed that only the complex $[\text{Fe}(\text{CN})_5(\text{INH})]^{3-}$ was able to inhibit this enzyme since the ruthenium complex, $[\text{Ru}(\text{CN})_5(\text{INH})]^{3-}$, has a much higher $E_{1/2}$ of the redox process of the metallic center than the iron complex.⁷⁴ Other ruthenium complexes containing the INH ligand also showed antituberculous activity with MIC values similar to the $[\text{Fe}(\text{CN})_5(\text{INH})]^{3-}$ complex. These complexes also showed potential oxidation values close to those of the $[\text{Fe}(\text{CN})_5(\text{INH})]^{3-}$ complex, suggesting a similar mechanism of action (Table 1).⁷⁶

Table 1. MIC (J774A.1) and $E_{1/2}$ MIII/II data for compounds Ru(II) and Fe(II) and free INH against the resistant strain, H37Rv.⁷⁶

Compounds	MIC ($\mu\text{g mL}^{-1}$) H37Rv	$E_{1/2} \text{M}^{\text{III/II}}$ (V)*
Isoniazid (INH)	0.07	–
$[\text{Ru}(\text{NH}_3)_5(\text{INH})]^{2+}$	0.60	0.16
$t\text{-}[\text{Ru}(\text{NH}_3)_4(\text{SO}_2)(\text{INH})]^{2+}$	0.88	0.29
$[\text{Fe}^{\text{II}}(\text{CN})_5(\text{INH})]^{3-}$	1.56	0.30

*Epa vs. SCE: pH 7.0, $l = 0.10 \text{ mol L}^{-1}$

However, Abadi and co-authors⁷⁶ showed that both the INH ligand and the complex did not show activity against Mycobacterium tuberculosis colonies with katG(S315T) mutation, suggesting that the activity of these compounds would be dependent on non-mutant katG. In other words, the mutation in the katG gene causes resistance to both the ligand and the complex, suggesting that the mechanism of action of both compounds against Mycobacterium tuberculosis could be identical. This hypothesis was reinforced by results related to treating macrophages containing the mutant strain with the complex that showed no action against the bacteria.⁷⁶ This result indicates that the intracellular host environment is not sufficient to trigger the self-activation mechanism of the complex. In summary, it can be concluded that the ligand and the complex require the katG enzyme to exert their antituberculosis action. Based on the information provided, it is reasonable to conclude that this compound may not be effective against drug-resistant strains of tuberculosis. However, recent results indicate its low toxicity compared to free isoniazid⁷⁸ and greater efficiency in combined therapies with other drugs.⁷⁹ Thus, this complex remains a viable candidate for research as a drug against tuberculosis.

7. Conclusion

SNP is one of the most essential metallopharmaceuticals used in medicine. However, as has been seen, its toxic effect due to cyanide dissociation has led researchers to develop new nitrosyl cyano complexes. Herein, we showed some examples of cyano nitrosyl complexes that could replace nitroprusside as vasodilating agents. Besides, we showed some examples of cyanoferrates containing drugs as ligands that are very promising for combating various diseases such as cancer, tuberculosis, and parasitic infections. Finally, we consider that the data presented supports the conclusion that this class of complexes has great potential as metallopharmaceuticals.

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Juan Camilo Rojas Sterling: Writing original draft, *Maria I. Z. Soares:* Writing-review & editing, *Gian Vitor Rodrigues:* Investigation; *Victoria C. R. Colmenares:* Writing-review & editing; *Diego B. Felix:* Writing-review & editing, *Emanuela da Conceição:* Writing-review & editing; *Marilândia P. Ananias:* Conceptualization and *José Clayton Melo Pereira:* Conceptualization, Writing-review & editing, Project administration.

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