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Metal Complexes and Medicine: A Successful Combination

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Abstract: Since the start of our independent research at the Department of Chemistry of the University of Zurich in 2009, our group has been, among other topics, working on the use of metal complexes in medicinal chemistry. In this short review article, we highlight our recent achievements in the use of such compounds to fight the parasitic disease schistosomiasis.

Keywords: Bioorganometallic chemistry · Medicinal inorganic chemistry · Medicinal organometallic chemistry · Schistosomiasis

Gilles Gasser *was born and raised in Neuchâtel (Switzerland). After his graduation in chemistry at the University of Neuchâtel in 2000, Gilles worked for one year for the chemical company Lonza in Visp (Switzerland). He then joined the laboratories of Prof. Helen Stoeckli-Evans at the University of Neuchâtel to undertake a PhD thesis in supramolecular chemistry. He was awarded his PhD in 2004. After post-doctoral stays at Monash University (Australia) with Prof. Leone Spiccia in bioinorganic chemistry and at the Ruhr-University Bochum (Germany) with Prof. Nils Metzler-Nolte in bioorganometallic chemistry, Gilles was given the opportunity to start his independent research career at the University of Zurich, first as Swiss National Science Foundation (SNSF) Ambizione fellow (2009) and then as a SNSF Assistant Professor (2010). Gilles is a recipient of several awards including the Jean Landry Award of the University of Neuchâtel for Excellence during his Diploma Thesis, the Jürg Engi Award of the University of Neuchâtel for the student with the best marks in organic chemistry (2000), the Syngenta Award for the best PhD thesis in Chemistry of the University of Neuchâtel (2004), an Alexander von Humboldt fellowship (2007) and the Werner Prize (2015).*

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1. Introduction

Thanks notably to the pioneering work of Alfred Werner at the University of Zurich in the field of coordination chemistry, the use of metal complexes as reaction catalysts could be significantly advanced during the 20th century.[1] Another less obvious field which has undoubtedly profited from the research performed by Alfred Werner is medicinal chemistry.[2] Although metal ions/metal complexes have been employed in medicine since ancient times, the use of structurally defined metal complexes in this field mostly appeared at the beginning of the 20th century with the discovery by Ehrlich, in collaboration with Sahachiro Hata, of the arsenic-containing organometallic complex Arsphenamine (also called Salvarsan or Compound 606, see Fig. 1) as an agent against syphilis.[3] This compound, whose exact structure was only unveiled in 2005,[4] was used against this infection disease until the discovery of penicillin.[5,6] Since then, many other metal complexes have been found to be useful in medicinal chemistry.[7–10] As surprisingly as it can be seen for the non-expert in the field, complexes of Fe, Sn, Bi, Lu, Hg, Sb, Pt, Au or As, for example, have been or are approved for the treatment of a range of conditions in medicine. The majority of the readers of this article have most probably used in the not-so-distant past the orange mercury-containing compound Merbromin (notably marketed as Mercurochrome) as a topical antiseptic (Fig. 1) although mercury is only perceived by the general public as a toxic heavy metal. Even more surprising is the case of As_2O_3, which was used, among others, by the Borgia family as a homicidal agent in the 15th and 16th centuries, but which is approved by the FDA for the treatment of relapsed acute promyelocytic leukemia under the trade name Trisenox. Finally, the metal gold, which is mostly associated with luxury, has also found application in medicinal chemistry. Three Au(I) complexes, namely Auranofin (Fig. 1), Aurothiomalate and Aurothiosulfate are approved drugs for the treatment of rheumatoid arthritis. Nonetheless, the most relevant examples in the field of medicinal chemistry are undoubtedly the platinum-based anticancer drugs Cisplatin, Oxaliplatin and Carboplatin (Fig. 1). These metal complexes are currently used in more than 50% of the chemotherapeutic treatments, often in combination with other drugs.

Despite the impressive success of these metal-based drugs, and more generally of drugs in all fields of medicine, there is undoubtedly still an important need for the development of new drugs to either treat incurable conditions or to improve the current available treatments which, for example, can lead to severe side-effects (*i.e.* treatment with Cisplatin). When we started our independent research at the University

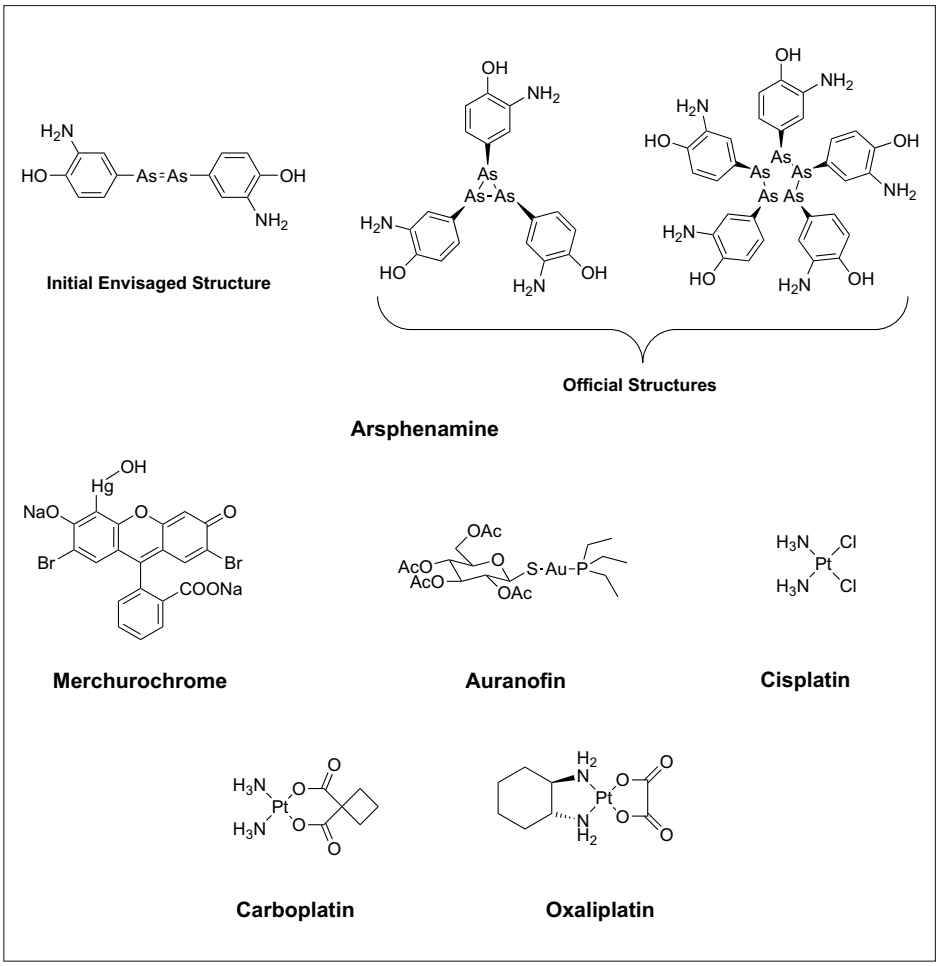


Fig. 1. Structures of metal complexes used in medicinal chemistry.

of Zurich, our group decided to primarily focus its attention on two diseases, namely cancer and schistosomiasis. While the former disease does not need to be presented, the latter is, very surprisingly, unknown to the general public. Schistosomiasis, also known as bilharziasis, is a parasitic disease which is responsible for 207 million infections each year in tropical and subtropical regions of sub-Saharan Africa, Asia and America.[11] In fact, it is the second most prevalent parasitic disease in the world after malaria. The number of deaths associated with this disease significantly varies depending on the studies (between 11'700 and 280'000).[12–14] More specifically, schistosomiasis is caused by parasitic worms (schistosomes) with a complex life cycle.[15] There are five species of schistosomes (*i.e. S. haematobium*, *S. intercalatum*, *S. japonicum*, *S. mansoni*, and *S. mekongi*), which are accountable for human infections leading either to intestinal or urogenital schistosomiasis.[16] This disease is often associated with liver damage resulting in swelling of the abdomen of the person affected. While this disease can be treated at present, with the organic drug Praziquantel (PZQ, Fig. 2), the therapeutic situation is far from ideal. Reduced susceptibility to PZQ has been reported, suggesting that this drug could become (much less) effective in the future.[17–19] This fact is extremely worrying since there is no current alternative to PZQ. In fact, since PZQ was marketed in 1984, no new drug has entered the market to fight this disease,[20] while the number of chemotherapeutic treatments against this disease gradually increased from 12.4 million people in 2006 to over 42.1 million people treated in 2012.[21,22] It is anticipated that this number will further increase in the future.[21,22] These distressing facts were the reasons for the start of our program on the evaluation of novel organometallic complexes as novel antischistosomal drug candidates.[11]

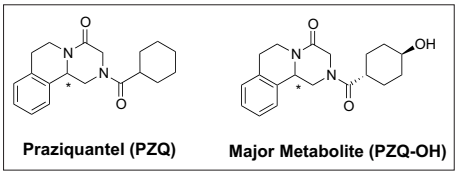


Fig. 2. Structures of the antischistosomal drug Praziquantel (PZQ) and of its metabolite PZQ-OH. *chiral carbon atom.

The concept that we have decided to employ to provide new lead structures in this field of research is based on the pioneering work of the groups of the French scientists Jaouen, Brocard and Biot. Those researchers demonstrated that the addition of a ferrocenyl moiety into the structure of two known organic drugs, namely the anticancer compound Tamoxifen and the antimalarial Chloroquine, to give the so-called organometallic complexes Ferrocifens and Ferroquine, respectively, allowed for novel, additional mode of actions compared to the parent organic drugs (Fig. 3).

More specifically, the Ferrocifens were shown to bind to the estrogen receptor similarly to Tamoxifen.[23,24] This competitive binding represses estradiol-mediated DNA transcription in the tumor tissue and is therefore responsible for the anticancer activity of Tamoxifen.[25] However, very interestingly, the Ferrocifen with n = 4 (Fig. 3) was also found to be active against breast cancer cell lines lacking this estrogen receptor (*i.e.* ER(–) cell line), contrary to Tamoxifen, which is inactive on this cell line. This discovery was extremely exciting for two reasons: 1) one third of the breast cancer patients do not express this receptor, rendering hormone therapy inefficient; 2) the expression of the estrogen receptor sometimes becomes down-regulated under Tamoxifen treatment, turning the drug ineffective. This interesting observation was explained by the specific presence of the organometallic moiety. Indeed, a redox activation was found to be responsible for the observed cytotoxicity in ER(–) cancer cells.[26] As shown in Scheme 1, the active metabolite hydroxyferrocifen can be readily oxidized to give a quinone methide intermediate.[26] This quinine methide can be then attacked by nucleophiles such as glutathione and nucleobases. This leads to the general toxicity and mutagenic potential of this compound. This mode of action was further confirmed when the researchers could prepare and biologically evaluate the ruthenocene analogue of the active Ferrocifen (see Fig. 3 – this compound will be called Ruthenocifen in this review article). These two complexes are isostructural but, compared to Ferrocifen, Ruthenocifen is not redox active. Hence, as expected, Ruthenocifen was found to be active only on ER(+) breast cancer cells but not on ER(–) cell lines.[27]

In the case of the antimalarial drug candidate Ferroquine, the presence of the ferrocene moiety was found to enable drug resistance to be overcome. Indeed, Ferroquine is active against chloroquine-resistant parasitic strains. One of the explanations for this observation is again redox chemistry. In addition to having a similar mode of action to Chloroquine, Ferroquine can also produce reactive oxidative species (ROS), which kill the parasites resistant to Chloroquine.[28,29] As for the Ferrocifens,

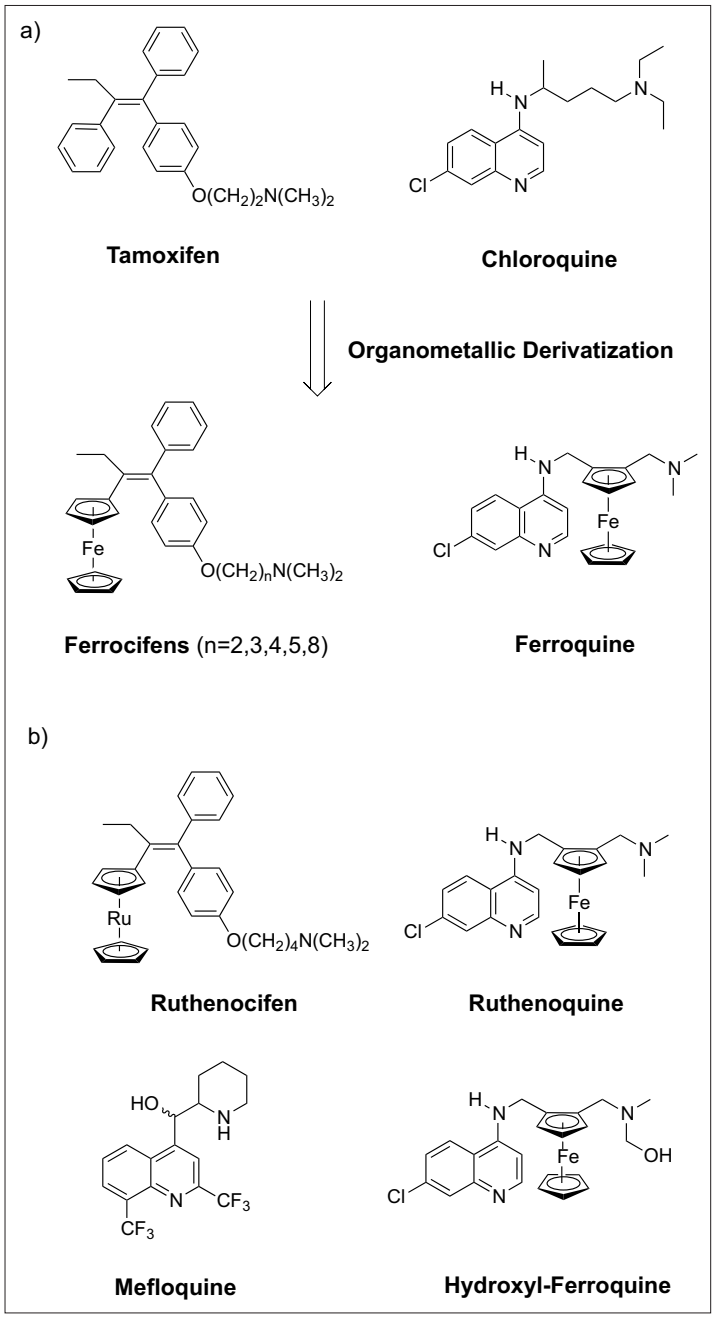


Fig. 3. a) Structures of Tamoxifen, Ferrocifens, Chloroquine and Ferroquine; b) Structures of a ruthenocene analogue of a Ferrocifen (Ruthenocifen), Ruthenoquine, Mefloquine and Hydroxyl-Ferroquine.

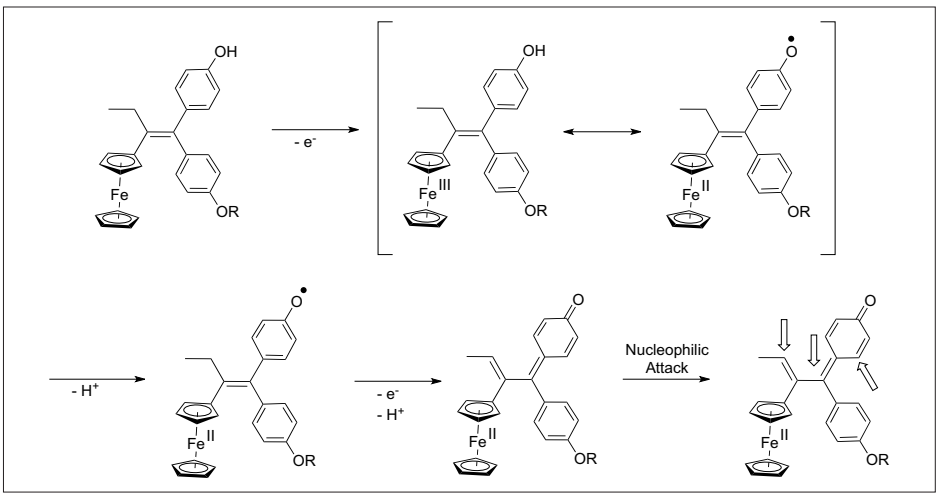
the replacement of the ferrocenyl moiety by a ruthenocene unit to give Ruthenoquine (Fig. 3) led to a decreased potency due to the absence of redox chemistry of the latter. Of important note, Ferroquine is the most advanced organometallic compound in industrial phase (Sanofi owns the rights for this drug candidate). This drug candidate should enter into phase IIb clinical trials this year.[30–32]

With this concept in mind, our group prepared and evaluated a series of organometallic compounds in collaboration with the group of Prof. Jennifer Keiser at the Swiss Tropical and Public Health Institute in Basel. In this short review, we present our recent achievements in this field of research. Of note, this topic was recently reviewed by our group and we invite the reader of this article to refer to this review for a more detailed description of the use of organometallic compounds to fight schistosomiasis.[11]

2. Organometallic-based Antischistosomal Drug Candidates

Obviously, the first idea which came to our mind was to derivatize PZQ with ferrocene. Thus, as shown in Fig. 4, we prepared and characterized 18 ferrocenyl derivatives of PZQ. As anticipated, using LC-MS techniques, these compounds were found to be extremely stable in human plasma. However, the bioactivity of these complexes was found to be relatively disappointing. Out of the 18 ferrocenyl derivatives in our hands, only four compounds were found to have an antischistosomal activity at 30 μg/mL *in vitro* against *S. mansoni*.[33]

We then evaluated the antischistosomal potential of two new chromium tricarbonyl derivatives of PZQ (**1** and **2**, Fig. 4).[34] One of the rationales behind the choice of this derivatization was that PZQ is, *in vivo,* rapidly metabolized to the much less active metabolite PZQ-OH (Fig. 2). We were hoping that this organometallic derivatization would reduce this conversion. Of note, as discussed in more detail in our recent articles, the amount of chromium used in our studies is far below the threshold of intrinsic toxicity of this metal.[11,34,35] The first biological results were found to be extremely promising. Both organometallic compounds were found to have a remarkable antischistosomal activity (0.25 μM for **1** and 0.27 μM for **2**), comparable to the parent organic drug PZQ (0.1 μM). Also, both compounds showed a promising selectivity for parasites since they had mainly no activity on the cervical cancer (HeLa) and non-cancerous (MRC-5) cell lines (IC_{50} >100 μM).[34]



Scheme 1. Redox activation of Ferrocifens as proposed by Jaouen *et al*. The ferrocenyl moiety serves as a 'redox antenna', following oxidation and proton abstraction, a quinone methide is formed, which is readily attacked by nucleophiles at the positions indicated by arrows. Scheme taken with permission from ref. [25]. Copyright American Chemical Society.

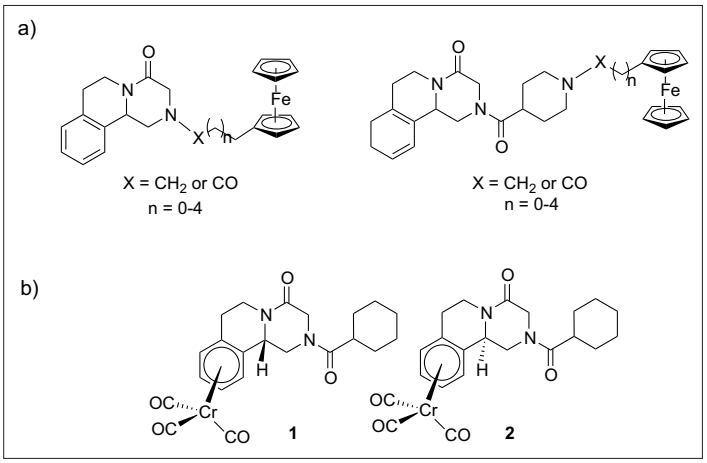


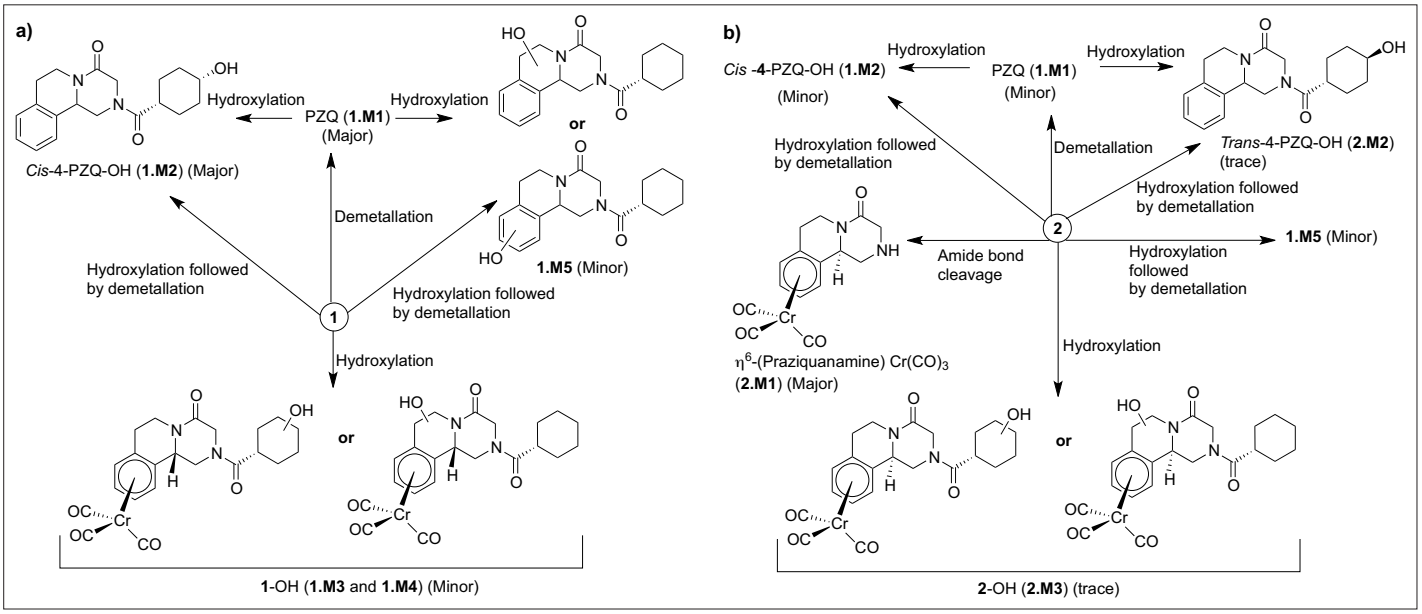
Fig. 4. a) Structures of a) ferrocenyl derivatives[33] and b) of chromium tricarbonyl derivatives[34] of the antischistosomal drug praziquantel.

These promising results encouraged us to explore in more detail the (metabolic) behavior of these organometallic compounds. First of all, we could demonstrate that these complexes were stable for 24 h at 37 °C in human plasma.[34] We could also show, using human liver microsomes, that their metabolic profile was, surprisingly, relatively different to PZQ and to one another (Scheme 2).[35] On one hand, **1** is primarily demetallated to PZQ or hydroxylated to *cis*-4-PZQ-OH. On the other hand, only minor demetallation and hydroxylation were observed for **2**. The major metabolite of **2** was identified as [(η^6-praziquanamine)Cr(CO)$_3$]. This metabolite is formed after cleavage of the cyclohexanoyl moiety.[35]

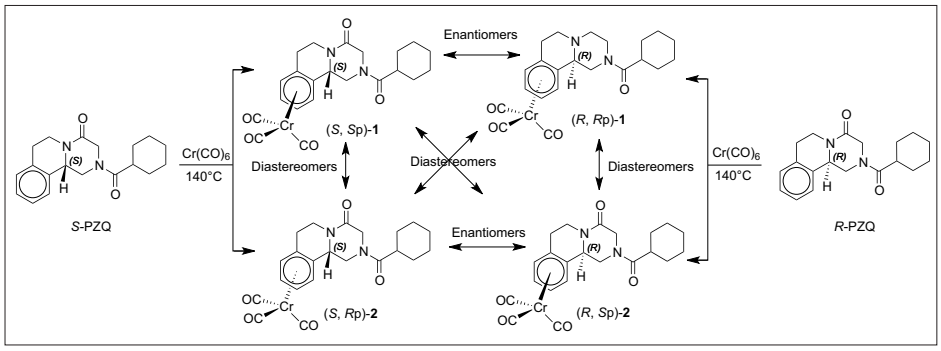
Another important study that we undertook to gain more insight into the mode of action of these organometallic compounds was to assess if the enantiomers/diastereoisomers of compounds **1** and **2** had similar biological activity. Indeed, PZQ is given to infected persons as a racemic mixture although only one of its enantiomers ((*R*)-PZQ) has an antischistosomal activity *in vitro*. In addition, this enantiomer is assumed to have fewer adverse events than the (*S*)-PZQ enantiomer.[36] With this in mind, we prepared and evaluated the *in vitro* antischistosomal activity against adult *S. mansoni* of the optically pure (η^6-PZQ)Cr(CO)$_3$ derivatives (R,R_p)-**1**, (S,S_p)-**1**, (S,R_p)-**2** and (R,S_p)-**2** (Scheme 3). Interestingly, only the two complexes containing the active PZQ ((*R*)-PZQ), namely (R,R_p)-**1** and (R,S_p)-**2** were found to be active. This observation, although not a definitive proof, suggests that the (*R*)-enantiomers of (η^6-PZQ)Cr(CO)$_3$ have the same target as PZQ.

With all this information available, we then evaluated the *in vivo* potential of these two compounds. For this purpose, a racemic mixture of compounds **1** and **2** (*i.e.* as for PZQ) was given to mice harboring adult *S. mansoni*. Unfortunately, contrary to expectations, relatively low total worm burden reductions of 24% and 29%, respectively, were obtained with single doses of 400 mg/kg of **1** and **2**. For comparison purposes, PZQ reached a total worm burden reduction of 96% with the same dosage.[35] These relatively disappointing results could be explained by distribution problems or protein binding.[11,35]

Another route that our group has been exploring to discover novel lead antischistosomal drug candidates is drug-repurposing. This strategy is based on the use of an already known and/or an approved drug to treat a (completely) different disease.[37] In collaboration with Prof. Christophe Biot and Prof. Jennifer Keiser, we evaluated the potential of the organometallic antimalarial drug candidates discussed above, namely Ferroquine and Ruthenoquine (Fig. 3) as antischistosomal agents.[38] For comparison purposes, Hydroxyl-Ferroquine and the known antimalarial drugs Chloroquine and Mefloquine were employed as reference compounds (Fig. 3). The rationale behind the choice of such derivatives is that the parasites in both malaria and schistosomiasis are blood-feeding and that they share the heme degradation pathway.[11] These facts could imply that drug candidates could have similar targets.[39] Unfortunately, our *in vivo* experiments revealed only a weak antischistosomal activity of these organometallic compounds. The highest total worm burden reduction was observed for the antimalarial drug candidate Ferroquine (19.4% and 35.6% when treated with 200 and 800 mg/kg, respectively).[38] Despite these relatively disappointing results, we strongly believe that other organometallic drug candidates, notably those already studied for their antiparasitic activity, should be evaluated as antischistosomal agents.



Scheme 2. Metabolic profiles of the chromium tricarbonyl complexes **1** and **2** (see Fig. 4 for the structures of **1** and **2**). Scheme taken with permission from ref. [35]. Copyright American Chemical Society.



Scheme 3. Synthesis of the optically pure $(\eta^6\text{-PZQ})Cr(CO)_3$ derivatives starting from *S*-PZQ and *R*-PZQ. Scheme taken with permission from ref. [35]. Copyright American Chemical Society.

3. Conclusions

It is difficult to predict if an organometallic complex will be used one day to treat schistosomiasis. However, we strongly believe that it would be a mistake to overlook such compounds as potential antischistosomal drug candidates, especially considering the great promise that Ferroquine is bringing to the field of malaria and, more generally to the field of medicinal organometallic chemistry. Since our last publication on this subject, our group has been actively working to unveil novel lead compounds. Very recently, in preliminary experiments, we could demonstrate that a novel ferrocenyl complex had a high activity *in vivo* and, importantly, did not engender any toxic effects on mice. These results hold great promise and will be published in the near future.

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