



Pergamon

N-Ferrocenylmethyl, *N'*-Methyl-2-substituted Benzimidazolium Iodide Salts with In Vitro Activity Against the *Leishmania infantum* Parasite Strain L1

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Abstract—Herein, we disclose results of our research into a class of benzimidazolium compounds active against the *Leishmania infantum* parasite strain L1. We have discovered that *N*-ferrocenylmethyl, *N'*-methyl-2-aryl (or styryl) benzimidazolium iodide salts show in vitro activity against this strain.

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The World Health Organisation (WHO) lists three diseases caused by kinetoplastids as being of primary importance in tropical and subtropical regions of the world; African trypanosomiasis, the leishmaniasis and Chagas disease.¹ Chemotherapy for clinical disease and prophylaxis in animals remains a primary concern. Since most available drugs have been in use for more than 40 years and are toxic while resistance to most of the primary chemotherapeutic agents has increased, it is imperative that new classes of compounds, potential drugs, are designed, synthesised, and tested.

Leishmaniasis is an old but largely unknown disease. Today, this disease affects 12 million people in 88 countries. The majority of cases are in developing countries, especially in the poorest and most remote communities. Unacknowledged and uncontrolled, this treatable disease continues to claim lives in remote areas. The parasite is transmitted by a sand fly living in tropical and temperate regions. The disease affects animals such as rodents and dogs, as well as humans.

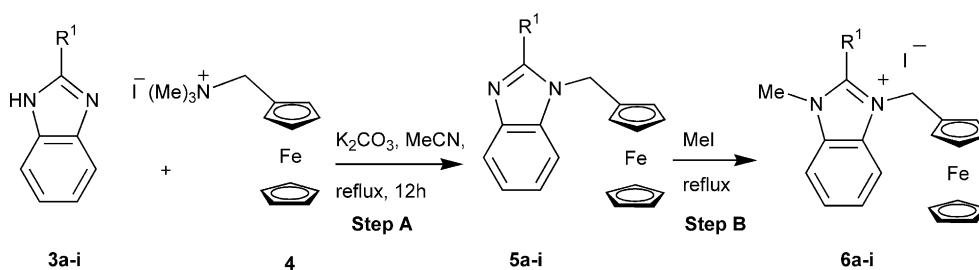
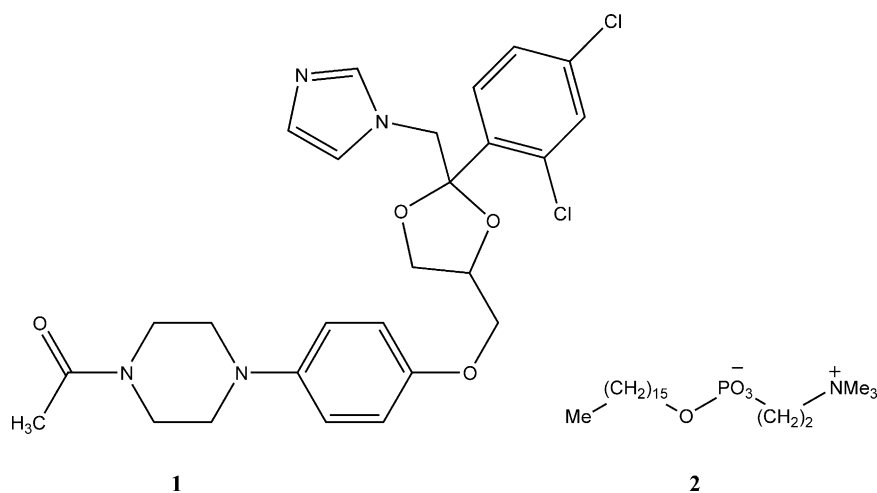
In humans the disease exists in different forms depending on the type of parasite and the immunity of the infected person. Thus it may present as simple skin ulcers, or in a progressive form that may permanently

disfigure those infected, or as visceral leishmaniasis which invades the whole body.

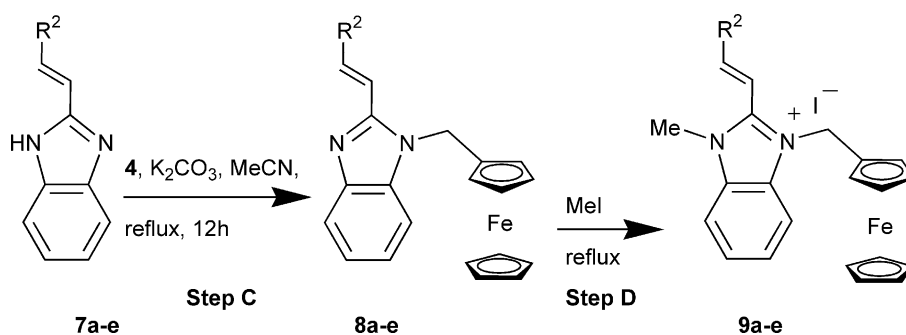
Classical treatment of leishmaniasis involves the antimony based drug, amphotericin B (ampho-B). However, with increasing resistance of the parasite to this drug new treatments are required. There are few leading experimental drugs, ketoconazole **1** an inhibitor of cytochrome P450² and miltefone (or hexadecylphosphocholine) **2**³ are two of the more promising. Ketoconazole is based on an azole group and through our investigations into novel azoles as anion receptors we had produced a series of benzimidazoles and corresponding iodide salts.⁴ This, coupled to our modest success in the use of *N*-ferrocenylmethyl, *N'*-methyl-2-substituted benzimidazolium iodide salts against the malaria parasite strain NF54 in vitro,⁵ warranted testing these same compounds against the *Leishmania infantum* parasite strain L1 in vitro. It should be noted that these molecules also bear similarity to recent work by Brocard based on the fact that the parasite needs iron for its development inside the red blood cell. Brocard and coworkers decided to try a simple strategy: combine poison (chloroquine) and bait (ferrocene) in the same molecule. They inserted a ferrocenyl group into the side chain of chloroquine, thus producing a hybrid compound called ferroquine that is much more potent in mice than chloroquine.⁶

The compounds **5a-i**, **6a-i**, **8a-e** and **9a-e** were synthesised according to Schemes 1 and 2, and the general

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Scheme 1.



Scheme 2.

synthetic methods are given in refs 7 and 8. The results are given in Tables 1 and 2.

From Tables 1 and 2, it can immediately be seen that 10 out of the 28 compounds tested by the WHO show activity against the *L. infantum* parasite strain L1, with IC_{50} 's in the range <0.5 to $>6.25 \mu\text{M}$. Although the most active compounds **9a** and **9c** are at least 25 times less active than the current drug of choice PX-6518

these compounds based on *N*-ferrocenylmethyl, *N'*-methyl-2-substituted benzimidazoles and benzimidazolium iodide salts are clearly interesting lead compounds with possibilities for development as drugs active against the *L. infantum* parasite strain L1. We are currently investigating these possibilities and likely modes of action of such compounds. This family of compounds also appears to have antibacterial and anti-cancer activity which we are currently assessing.

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