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Monitor: molecules and profiles

Monitor provides an insight into the latest developments in drug discovery through brief synopses of recent presentations and publications together with expert commentaries on the latest technologies. There are two sections: *Molecules* summarizes the chemistry and the pharmacological significance and biological relevance of new molecules reported in the literature and on the conference scene; *Profiles* offers commentary on promising lines of research, emerging molecular targets, novel technology, advances in synthetic and separation techniques and legislative issues.

Molecules

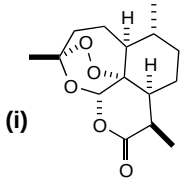
Novel anti-protozoal parasite agents

There are several protozoal parasites that cause devastating diseases in humans. Over the past decade, intense research efforts have been directed towards several nonalkaloidal trioxanes. This system offers an alternative to quinoline and antifolate malarial drugs, to which the *Plasmodium falciparum* parasite has become largely resistant [1].

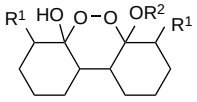
Infected red blood cells are under a high degree of endogenous oxidative stress and various physiological events come into play to relieve this stress, primarily in the provision of substrates for reduction in a process known as the hexose monophosphate shunt (HMS) [2,3]. Based on the observation that HMS activity in infected cells is increased up to 24-fold, Howarth and collaborators suggested that the introduction of an alternative reductive target compound (ARTC) into the system would prompt the uptake of the compound by the infected red blood cell. If this ARTC could also contain a moiety able to kill the parasite, it should be possible to produce new effective compounds. Howarth has demonstrated the plausibility of their hypothesis in a previous paper [4] and the same group has now expanded this concept, claiming that the principle could be applied to all protozoal parasites that, during some stage of their life-cycle, occupy cells of the host [5]. They state that a peroxide-based molecule that acts against the malarial parasite *P. falciparum,* should also act against the *Trypanosoma brucei, Trypanosoma cruzi,* and *Leishmania infantum* parasites, because all of them occupy cells of the host during their life-cycle. To prove their hypothesis, they synthesized two series of simple compounds, containing a peroxide unit (loosely related to the artemisinin trioxane substructure) (**i–iii**).

All of the compounds were assayed *in vitro* against the *P. falciparum* Ghana, *T. brucei* TB-1, *T. cruzi* TC-1, and *L. infantum* L1 strains and their cytotoxicity was measured on the cell line MRC-5. All compounds proved to be active against the protozoal parasites tested.

Though their activity is weak compared with other compounds currently used,



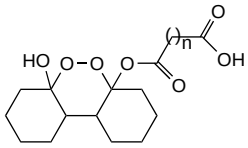
(i) Artemisinin



(ii)

R = H, Me 1 a-c

a R^1 = H R^2 = H
b R^1 = Me R^2 = H
c R^1 = H R^2 = Me



n = 1-4 2 a-d

(iii)

they are active against all tested parasites, therefore indicating that the HMS and the use of ARTCs might provide a route for the delivery of active anti-protozoal parasite compounds. Eventually, this approach could lead to a pan-antiprotozoal drug.

1 Peters, W. (1987) *Chemotherapy and drug resistance in malaria* (2nd edn), Academic Press
2 Atamna, H. *et al.* (1994) Hexose-monophosphate shunt activity in intact *Plasmodium falciparum*-infected erythrocytes and in free parasites. *Mol. Biochem. Parasitol.* 67, 79–89
3 Beutler, E. (1994) G6PD deficiency. *Blood,* 84, 3613–3636
4 Howarth, J. *et al.* (2001) Redox systems as conduits for antimalarial compounds. *J. Antimicrob. Chemother.* 47, 122–124
5 Howarth, J. et al. (2003) 1,4-Dihydroxy-2,3-dioxatricyclo[8.4.0.0^{4,9}]tetradecane and derivatives with *in vitro* activity against *Plasmodium falciparum*, *Trypanosoma brucei*, *Trypanosoma cruzi*, and *Leishmaniasis infantum*. *Bioorg. Med. Chem. Lett.* 13, 2013–2015

Daniela Barlocco
University of Milan
Viale Abruzzi 42
Milano 20131, Italy
tel: +39 02 5031 7515
fax: +39 02 5031 57565
e-mail: daniela.barlocco@unimi.it

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