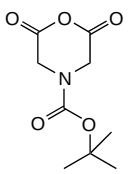
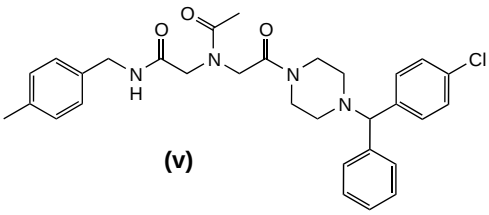


(iv)



(v)

nonpeptidic bradykinin antagonists with moderate potency highlights the potential of these agents and further work in this area is merited.

3 Salvino, J.M. *et al.* (1993) Design of potent non-peptide competitive antagonists of the human bradykinin B2 receptor. *J. Med. Chem.* 36, 2583–2584

4 Stewart, J.M. *et al.* (1999) Bradykinin antagonists: present progress and future prospects. *Immunopharmacology* 43, 155–161

5 Lam, Y.L. *et al.* (2004) Solution-phase combinatorial synthesis of nonpeptide bradykinin antagonists. *Bioorg. Med. Chem.* 12, 3543–3552

Paul Edwards

paul.edwards@santhera.com

TARGETS AND MECHANISMS

Metalloantimalarials

Metal ions have a long history as medicinal agents, having been used for the treatment of numerous infectious diseases, including parasitic diseases such as trypanosomiasis. Many early metal-containing drugs made use of highly toxic heavy metals such as arsenic and mercury. Consequently, these types of compounds lost favour because of unacceptably high levels of drug toxicity. Later, advances in organic synthesis and the related flowering of organic medicinal chemistry resulted in the almost total eclipse of metallodrugs. In recent years, interest in metal complexes as potential medicinal agents has begun to increase and this is now a relatively small, but rapidly growing, field. Modern approaches generally seek to improve the cellular uptake, selectivity and biocompatibility of the metal complex, often using metal ions that occur naturally in biological systems.

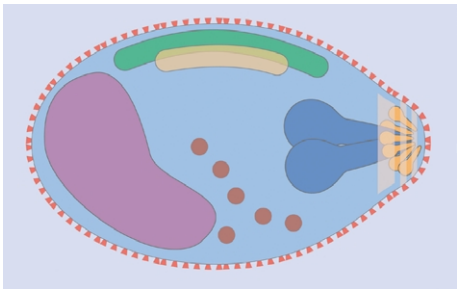


Image of a merozoite (part of the *Plasmodium* life cycle in humans) reproduced from archive.bmn.com/supp/part/bannister.html (see *Trends in Parasitology* 19, 209-213)

In recent years, there have been a number of reports on metal complexes with *in vitro* or *in vivo* antimalarial activity, including a ferrocene-containing analogue of chloroquine (ferroquine), which has advanced quite far down the road of drug development [1]. Now, another interesting metal complex has been reported by Ocheskey *et al.* [2] that has significant *in vitro* antimalarial activity. The complex is a gallium(III) complex of a hexadentate chelating ligand containing a pair of quinoline rings. This complex is a significant improvement on a previous gallium complex lacking the quinoline groups. Its biological activity is ~30-fold greater. Interestingly, it appears to have a similar mechanism of action to chloroquine, despite only a slight resemblance to this drug (the presence of quinoline rings). It is active against chloroquine-resistant parasites. Although this complex has far weaker activity than ferroquine, the large improvement in activity relative to its gallium(III) predecessor suggests that further significant improvements in activity could be possible. In addition, the study indicates that the relatively unexplored field of metalloantimalarials is likely to enjoy increased attention in the future and could be a fruitful area of investigation.

1 Biot, C. (2004) Ferroquine: a new weapon in the fight against malaria. *Curr. Med. Chem.* 3, 135–147

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Timothy J. Egan

tegan@science.uct.ac.za

Predicting hERG channel activity: a two-state model

During the 1990s, several high-profile drugs were withdrawn from the market because of sudden, cardiac-linked mortalities. The problem with these compounds was that, despite not being targeted at the heart, they induced cardiac arrhythmias; specifically, long QT syndrome (LQTS) with an increased propensity to develop the potentially fatal ventricular tachycardia known as Torsade de Pointes (TdP). In almost all cases, the molecular basis for drug-induced LQTS is interaction with a cardiac ion channel known as hERG (human ether-a-go-go related gene). Consequently, recent years have seen intense efforts by the pharmaceutical industry to develop methods that will enable the assessment of hERG channel blockade by potential drug compounds as early as possible in the drug discovery process [1,2].

Computational approaches towards understanding and predicting hERG blockade activity fall into two broad classes – structure-based and ligand-based. A recent example of the structure-based approach has been reported by Rajamani *et al.* [3]. Building on the information provided by site-directed mutagenesis studies, two homology models of the hERG channel were constructed in the belief that accounting for the flexibility of the channel might be important. One model was intended to represent the fully open state of the channel, and the other a partially open state. A set of 32 hERG ligands was then docked into the models and the best solution for each ligand energy minimized using the OPLS-AA (optimized potentials for liquid simulations-all atom) force field in conjunction with a continuum solvent model. During this optimization, all protein residues within 8 Å of the ligand were allowed to move. Following this, the final conformation of the ligand was extracted and minimized in isolation using the same conditions. From these calculations, the difference in computed electrostatic and van der Waals energies between the free and

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bound state of each ligand (Δele and Δvdw, respectively) was obtained. These two descriptors were then used to derive quantitative-SAR (QSAR) models predicting the experimental binding affinities of the ligands for the hERG channel.

It was found that a good QSAR model could only be obtained when the Δele and Δvdw values for each ligand were those computed from the hERG model to which it preferred to bind. That is, if, for a particular ligand, the sum of Δele and Δvdw was lowest (most favorable) for the open state, then the descriptors would be derived from that state rather than the partially open state, and vice versa. It was also shown that the binding modes of the compounds produced by the docking and optimization protocol were in general agreement with findings of site-directed mutagenesis experiments and with previously-derived pharmacophore models. The ability of the methods described by Rajamani *et al.* [3] to predict affinity and binding mode for several hERG blocking compounds – five outliers were omitted from the training set – suggests that this approach could be useful for guiding the synthesis of compounds with reduced hERG affinity. Further validation of this approach by its application to previously unseen compounds would be of much interest.

1 Fermini, B. and Fossa, A.A. (2003) The impact of drug-induced QT interval prolongation on drug discovery and development. *Nat. Rev. Drug Discov.* 2, 439–447
2 Finlayson, K. *et al.* (2004) Acquired QT interval prolongation and HERG: implications for drug discovery and development. *Eur. J. Pharmacol.* 500, 129–142
3 Rajamani, R. *et al.* (2005) A two-state homology model of the hERG K+ channel: application to ligand binding. *Bioorg. Med. Chem. Lett.* 15, 1737–1741

David Clark
david.clark@argentadiscovery.com

1359-6446/05/$ – see front matter PII: S1359-6446(05)03485-9