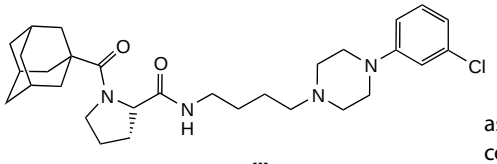
Monitor Editor: Matthew Thorne
m.thorne@elsevier.com

monitor

COMBINATORIAL CHEMISTRY

Arylpiperazine derivatives: biological evaluation of serotonin receptors

Long-chain arylpiperazines are a therapeutically interesting class of molecules that bind to several G-protein-coupled receptors (e.g. serotonin, dopamine and adrenoceptor) to produce various pharmacological responses. Within this therapeutic class, the serotonin, also known as 5-hydroxytryptamine (5-HT), receptors 5-HT_{1A} and 5-HT_{2A} have a role in the pathology of mental disorders such as anxiety and depression [1]. Multiple SAR studies performed with numerous generations of arylpiperazine derivatives suggest that 5-HT_{1A} and 5-HT_{2A} receptor affinity and selectivity depend on the *N*-1-aryl substituent, the terminal fragment (often an amide or imide) and the length of the alkyl spacer. Many different building blocks have been introduced into the amide pharmacophoric fragment. However, its role in the stabilization of the ligand–receptor complex is still unclear. To discover new, potent, serotonin receptor ligands and to further SAR studies, selected amino acid moieties were incorporated into the pharmacophoric group [2]. A small library of 72 compounds was synthesized on SynPhase™ lanterns (Mimotopes) and their binding profile to 5-HT_{1A} and 5-HT_{2A} receptors determined. A sub-set of this library, chosen on the basis of purity data, was screened in a radioligand-binding assay for 5-HT_{1A} and 5-HT_{2A} receptors. One of the most active compounds was **(i)**, which had a K_i for 5-HT_{1A} of 24 nM and exhibited 81-fold selectivity for 5-HT_{1A} over 5-HT_{2A}. The introduction of a diverse array of building blocks has extended the rational design of compounds within this target family, helping to accelerate the search for new central nervous system agents.



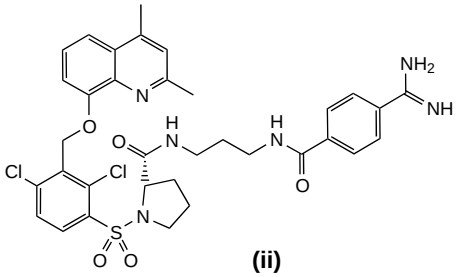
(i)

1 Jones, B.J. and Blackburn, T.P. (2002) The medical benefits of 5-HT research. *Pharmacol. Biochem. Behav.* 71, 555–568

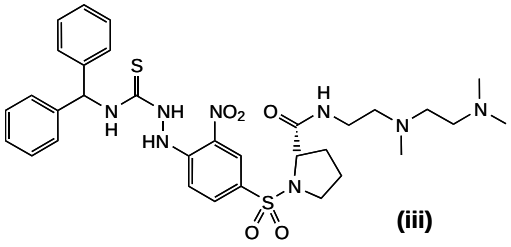
2 Zajdel, P. *et al.* (2004) A new class of arylpiperazine derivatives: the library synthesis on SynPhase lanterns and biological evaluation on serotonin 5-HT_{1A} and 5-HT_{2A} receptors. *J. Comb. Chem.* 6, 761–767

Nonpeptide bradykinin antagonists

Bradykinin is an autacoid (a physiologically active organic compound that is internally secreted) related to acute and chronic pain and inflammation. Of the two bradykinin (B) receptors known, B_1 and B_2, B_2 receptors are constitutively expressed on most cell types, whereas B_1 receptors are induced during inflammatory insults. Many of the reported antagonists for B_2 receptors are peptidic in nature and thus, because of the difficulties associated with the administration of peptidic compounds, nonpeptide bradykinin antagonists are of interest as novel anti-inflammatory



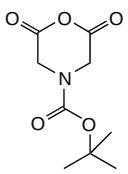
(ii)



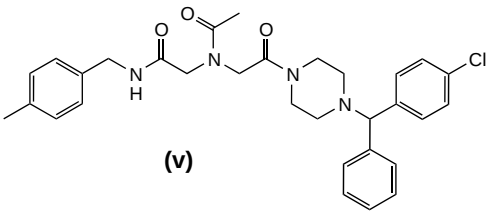
(iii)

therapeutics – recent examples include LF160687 **(ii)** and bradyzide **(iii)**. Although the structural features that are essential for a compound to have bradykinin antagonist activity have yet to be characterized conclusively, it is generally accepted that the antagonist should have a hydrophobic aromatic group and two groups that are basic in nature and are separated by 10 Å [3]; however, the presence of basic groups does not appear to be essential for activity [4]. In the search for new bradykinin antagonists, compounds containing a piperazine ring, three amide bonds and a lipophilic ring system have been designed [5]. A small library of 50 compounds was synthesized as single compounds in solution, starting from an iminodiacetic anhydride template **(iv)**. Each compound was then tested for its bradykinin-induced contractilities on guinea-pig ileum smooth muscle at a concentration of 0.1 μM. One of the most potent compounds obtained from this library was **(v)**, which displayed 46% inhibition in this assay. The production of

1359-6446/05/$ – see front matter PII: S1359-6446(05)03439-2



(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.

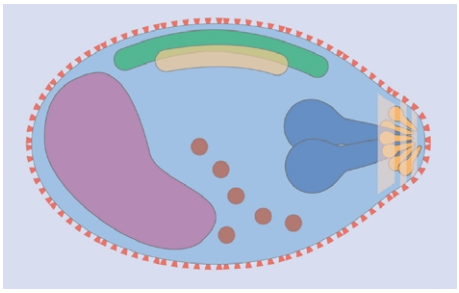


Image of a merozoite (part of the *Plasmodium* life cycle in humans) reproduced from archive.bmn.com/supp/part/bannister.html (see *Trends in Parasitology* 19, 209-213)

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

2 Ocheskey, J.A. *et al.* (2005) Metalloantimalarials: synthesis and characterization of a novel agent possessing activity against *Plasmodium falciparum*. *Chem. Commun.* 1622–1624

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

1359-6446/05/$ – see front matter PII: S1359-6446(05)03470-7