Trends in Medicinal Chemistry Meeting Report

The SMR held its Trends in Medicinal Chemistry meeting on 26 September 1996.

The first two talks focused on schizophrenia, a disease that affects 0.5% of the population, using approaches based on selective dopamine antagonism. Chris Johnson (SB) recounted his company's search for D3 receptor antagonists by describing the SAR investigations which led to the synthesis of a series of di-substituted pyrrole antagonists with excellent selectivity for the D3 receptor over the D2 receptor. This was postulated to be a result of a favourable interaction between the ligand and a tyrosine residue, present in the D3 but not D2 receptor. Boronic acid cross-coupling reactions allowed the synthesis of a wide range of aryl pyrroles the best of which are now being used to study further the nature of D3 receptors in the CNS.

Jan Kulagowski (Merck), on the other hand, concentrated on the D4 receptor, based on the observation that the anti-psychotic drug clozapine is selective for the D4 over the D2 receptor. A series of indole derivatives were developed which had good selectivity for the D4 receptor, but some of these compounds had undesirable cardiovascular effects. Replacement of the indole by an azaindole ring gave rise to the development candidate L-745,870, now in Phase II clinical trials. This compound has excellent selectivity and a clean in vitro profile, lacking the ion channel activity which had plagued earlier members of this series. L-745,870 has been shown to be well tolerated in Phase I clinical trials at doses of 10 and 25 mg/kg per day for 14 days.

Jenny Raphy (Parke-Davis) discussed the development of non-peptide neurokinin (NK) antagonists. In the case of NK3 antagonists, this process was aided by the use of a library of dipeptides, the most active of which formed the basis for traditional medicinal chemistry. The result of extensive exploration was PD 163416, which was found to have selectivity over NK1 and NK2 receptors. The compound has improved solubility over earlier analogues but its bioavailability is low (<10%).

Alan Stobie (Pfizer) presented preliminary results on investigations into the use of glycine antagonists for the treatment of stroke. The problem confronting the Pfizer group was achieving the correct balance of activity and CNS permeability. They achieved this by designing compounds which would have optimal pKa and logD values. Manipulation of these two properties led to the discovery of a series of hydroxyquinolin-2-ones which had the required aqueous solubility characteristics and CNS activity. Researchers at Pfizer are currently investigating other classes of glycine antagonists for use in the treatment of stroke.

Rod Porter (SB) presented on the discovery of SB 205209, a potent and selective 5HT1D/B agonist, now in Phase III clinical trials for the treatment of migraine. Initial lead compounds were amines, but suffered from rapid in vivo N-acetylation. Metabolic stability was achieved by the introduction of an N-methyl group to give SB 205209, a cyclic analogue of

tryptamine. SB 209509, also known as VML-251, is being developed by Vanguard Medica. Clinical trials have shown excellent responses with relief generally seen within two hours.

Allopregnanolone is an allosteric modulator of the GABAA receptor and Neil Hamilton from Organon described how this endogenous neurosteroid had been used as the starting-point for novel anaesthetics with improved onset, potency and side-effect profile. Organon used a steroid template in the the discovery of ORG 21465, a potent anaesthetic with a shorter duration of action. ORG 21465 could be prepared in eight steps in an overall yield of 25% from pregnanolone and has been selected for further development.

Prostaglandin (PGE2) is known to be hyperalgesic in that it does not actively cause pain when injected into tissue but sensitises nerves to other inflammatory mediators; this led Peter Warner (Zeneca) to investigate novel PGE2 antagonists as an alternative method of pain relief. The Zeneca team used a benzyl ether as a starting-point with moderate activity. This lead had two active metabolites which were identified and chemically modified to give PGE2 inhibitors with greater activity and metabolic stability. These compounds were seen to be devoid of cyclo-oxygenase activity and were effective in pain models.

Paul Rafferty (Knoll) described the development of novel anti-inflammatory benzylaminoalkyl imidazoles which inhibited macrophage activation. The imidazole derivative BTS-71312 was identified and is now in Phase II clinical trials. BTS-71312 does not inhibit either 5-lipoxygenase or cyclo-oxygenase enzymes but inhibits the release of PGE2 and leukotriene D4, and other mediators by an as yet unidentified mechanism.

The design and synthesis of bioavailable phosphodiesterase (PDE) inhibitors was discussed by Paul Cox (Rhone Poulenc Rorer). Selective inhibitors of PDE4 have been touted for the treatment of asthma for some time, as a result of the involvement of PDE4 in most inflammatory processes. RP 73401 was an early lead but suffered due to low bioavailability and extensive first pass metabolism. Several changes to RP 73401 were seen to have profound effects. Replacement of the cyclopentyl ring with tetrahydrofuran, oxidation of the pyridine to pyridine N-oxide and replacement of the phenyl ring with another pyridine N-oxide led to RPR-114597 having a bioavailability of 77% compared with less than 1% in RP 73401.

Simon Hodgson (Glaxo Wellcome) reported on a series of hydroxamate and hydroxyurea 5-lipoxygenase inhibitors of which 3323W was the most potent. Earlier analogues suffered from extensive metabolism in healthy volunteers, which was solved by fluorination of the terminal phenyl ring. The most active compound in this series (3323W) was found to be an inhib-itor of broncho-constriction and to block eosinophil influx, an effect not seen in leukotriene antagonists. It also has a long half-life and is active 24 hours after administration.

All in all, there were a number of lessons from a range of medicinal chemistry, with broad application. Credit is due to the content and delivery of the presentations.