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Guest Editorial

Of Medicinal Chemistry, *Pharmaceutical Sciences*, and *Pharmaceutical Science Communications*

This issue of the *Journal of Pharmacy and Pharmacology* comprises nineteen refereed reviews and original articles which reflect the variety of work presented at the 2nd Bath International Symposium on Medicinal Chemistry. The symposium was held at the University of Bath, September 25–27, 1994 and was an FCMG, RSC Symposium and a satellite meeting of the 13th International Congress on Medicinal Chemistry organized by EFMC in Paris. The oral and poster presenters were invited to contribute communications based upon their slides or posters. The aim was to mark this 2nd Bath International Symposium with a bound, refereed volume reflecting the studies which were reported.

It was originally intended that the Rapid Communications of Oxford journal *Pharmaceutical Science Communications* would process these manuscripts (editor P N Shaw, guest editor I S Blagbrough) with publication in early 1995, after rapid submission and refereeing of the manuscripts (December 1994–January 1995). However, due to the vagaries of commercial publishing, *Pharmaceutical Science Communications* was closed in early 1995, with these twenty papers refereed, amended by the authors, edited, and ready to print. Joseph Chamberlain, the editor of the newly founded publication *Pharmaceutical Sciences*, was approached to enquire whether that journal would consider publishing these papers. It soon became apparent that though the work was appropriate for *Pharmaceutical Sciences*, it would not be possible to publish the papers rapidly due to the pressure created by a significant number of original articles already submitted to that journal. Nevertheless, following significant page number expansion in this sister journal, *Journal of Pharmacy and Pharmacology*, it has been possible to publish this special issue. We are indebted to Dr Chamberlain and his staff for their help and dedication to this special issue.

This special issue opens with two reviews from presenters of oral contributions. Samanen and co-workers at SmithKline Beecham, King of Prussia, describe their chemical approaches to improve the oral bioavailability of peptides and peptoids. In particular, the development of orally active GPIIb/IIIa antagonists based upon RGDS tetrapeptide for platelet fibrinogen receptor antagonists is explored. The other review complements the study of peptide oral bioavailability, as Begley, from King's College London, has focussed upon the blood-brain barrier. Begley details the principles for targeting peptides and other drugs to the central nervous system (CNS). Strategies for increasing the uptake of drugs include: increasing plasma half-life, improving passive penetration with increasing lipophilicity, taking advantage of active transport, and reducing turnover and drug/peptide efflux from the CNS.

The first of the original papers from Todd and co-workers describes a simple procedure for the production of magnetizable solid-phase support beads based on the extrusion of agarose/iron oxide mixtures. Amine derivatized beads were used to adsorb nucleic acids from aqueous solution and to separate DNA/RNA mixtures. Magnetizable solid-phase support beads are a novel material for the purification of biological macromolecules. In this paper, ion-exchange ligands with affinity for nucleic acids are bound to biologically inert agarose; covalent cross-linking was achieved using epichlorohydrin. There were several papers contributed from overseas research groups. The international collaboration between the Universities of Bristol and of Michigan is represented by the paper from Derrick et al. Their work on potential irreversible ligands for opioid receptors, to determine the mechanisms of opioid actions, describes cinnamoyl derivatives of β-naltrexamine. The cinnamoylamido functional group on β-naltrexamine acts as a Michael acceptor forming a covalent bond to the protein receptor-complex.

The industrial contributions are from Fisons plc (Astra Charnwood) on P2T-purinoceptor antagonists and from Organon on α-glucosidase I inhibition. The Fisons research group (Tomkinson et al) report a QSAR study of 2-substituted ATP analogues as part of their research programme developing novel, potent and selective P2T-purinoceptor antagonists of ADP-induced platelet aggregation in-vitro. From their molecular modelling studies, these workers propose a receptor model containing a narrow lipophilic cleft which is occupied by the adenine 2-substituent. Organon, in collaboration with the Glycobiology Institute at the University of Oxford, report (van den Broek et al) a series of *N*-decyl-1-deoxynojirimycins, monosaccharides with antiviral (HIV-1) and immunosuppressive activity. These α-glucosidase I inhibitors, especially the *N*-7-oxadecyl compound, reduced adjuvant-induced arthritis in rats, and they are therefore candidates for treating auto-immune diseases such as rheumatoid arthritis.

The enzyme inhibition theme is continued in the work of Littlechild and colleagues at Exeter. McHarg & Littlechild report their studies with inhibitors of phosphoglycerate kinase (PGK) for the potential treatment of cardiovascular and respiratory disorders. A variety of fluoro-phosphonates, designed and prepared by Blackburn and co-workers, incorporating the CF_2 moiety as a non-scissile, isosteric and isoelectronic replacement for oxygen in a phosphonate, improving the physicochemical parameters of the phosphonate, were tested against yeast PGK. The binding site is discussed using the high-resolution crystal structure of porcine PGK. In the paper from Dalby & Littlechild, studies with type I aldolases have been aimed at isozyme specificity with respect to the design of specific enzyme inhibitors. Fructose intolerance, haemolytic anaemia, malaria and other parasite-borne disease states such as sleeping sickness

are associated with natural mutations in aldolases. Molecular modelling and X-ray crystallographic data are used to investigate the structural properties of these enzymes.

Antimalarials are also the subject of the studies by Adams & Berman from the University of Cape Town. The kinetics of the reaction between ferriprotoporphyrin IX (haemin) and the potent sesquiterpene endoperoxide antimalarial artesunate are consistent with a three-step, two-intermediate mechanism leading to a degraded tetrapyrrole ring system. As malaria affects 200 million people, with 1 million deaths annually, the emergence of chloroquine-resistant strains of the malarial parasite is a major problem in world health. Artemisinin, a novel sesquiterpene endoperoxide isolated from an ancient Chinese herbal remedy, has become the most important antimalarial since quinine. As the parasite metabolizes haemoglobin, it is likely that the site of action of quinolines and artemisinins is haemin.

Metabolism and toxicity in man are the concerns of Woodland, Buckberry, and colleagues. Woodland and co-workers report the MS-MS determination of the fragmentation patterns of substituted 1,2,3-benzotriazin-4-ones, extensively found in herbicides, insecticides, and nematocides, with established toxic sequelae if gaining access to the human food-chain. Adcock et al report their continuing studies on mammalian C-S lyases. Specifically, C-S lysis of 13 synthetic L-cysteine *S*-conjugates was examined with aspartate aminotransferase and alanine aminotransferase from porcine heart. The aberrant metabolism (toxification) by enzyme degradation along the glutathione pathway may be significant when cysteine conjugates form Schiff bases with pyridoxal phosphate-dependent enzymes.

Drug metabolism leading to the formation of an active metabolite is the subject of one of the three papers from Nicholls, Smith, and co-workers at the University of Wales. The dianilino sulphone, dapsone, introduced in the 1940s, remains an important anti-leprotic agent, and, more recently, has found use in the treatment of *Pneumocystis carinii* pneumonia in patients with AIDS. The most serious side effects include agranulocytosis and, more commonly, methaemoglobinaemia and haemolysis. Biotransformation is by hepatic P450 enzyme oxidation to a hydroxylamine metabolite, whose biosynthesis was inhibited by cimetidine, a known inhibitor of hepatic P450 isozymes. This active metabolite of dapsone is responsible for the observed blood dyscrasia (Ahmadi et al) as well as for the methaemoglobinaemia.

A comprehensive synthetic study on potential protein kinase C (PKC) inhibitors is reported by the same research group (Wilson et al). Amine-substituted tetracycles, containing a bicyclic [3.3.1] nonane fused to naphthalene, as mimics of the microbial metabolite staurosporine, have been prepared. Despite the close fit on superposition of staurosporine, these tetracycles did not inhibit PKC, and the unsaturated γ-lactam of staurosporine is an important binding motif together with the protonated amine on the sugar boat-conformer.

Smith, Nicholls and colleagues also report (Barrell et al) their continuing studies on the design and synthesis of potential aromatase inhibitors, as part of their Cancer Research Campaign funded programme. 3-Substituted pyrrolidine-2,5-diones, based upon ring contracted aminoglutethimides, reversible P450 aromatase inhibitors (used clinically), were prepared by functional group interconversions on preformed succinimides (pyrrolidine-2,5-diones). The 3-(prop-2-ynyl) compound was a reversible enzyme inhibitor, but no time-dependent (irreversible) inhibition of human placental P450 aromatase was observed.

There are five contributions from the "home team" at the University of Bath. Three of these are in the general area of peptides/peptoids and molecular modelling. Walford working with Campbell and Horwell at Parke-Davis report the preparation of dipeptoid mimetics for the tetrapeptide cholecystokinin, CCK(30-33). Cyclopropylphenylalanines were prepared by a modification of Schollkopf's bislactim ether approach, using a chiral diketopiperazine template. The diastereoselective synthesis afforded analogues with good binding affinities for the CCK-A and CCK-B receptors. Conformational studies indicated a β-turn within the peptide backbone. Pouton and co-workers report (Sahm) their continuing studies on B16 murine melanoma cells expressing native MC1 melanocortin receptor. The binding affinities and biological activities of linear and cyclic melanocortins (α-melanocyte-stimulating hormone analogues), cyclized by disulphide bridging, were assessed; D-Phe7 increased both affinity and activity of the cyclic compound. Molecular modelling studies of β-turns in cyclic melanotropin are also reported (Chan et al) by the same research group.

Moya & Blagbrough report their efficient syntheses of polyamine and polyamine amide voltage-sensitive calcium-channel blockers, based upon native funnel web spider toxin from *Agelenopsis aperta*, American funnel web spider. This is part of their studies on natural and synthetic polyamines, and polyamine amides as selective blockers of cation channels. Blagbrough and colleagues also report aspects of their work on competitive antagonists for the cation channel gated by nicotine and acetylcholine, preliminary synthetic studies of methyllycaconitine (MLA) are disclosed in Coates et al. These are rapid syntheses of AE-bicyclic analogues of MLA, the most potent and selective nicotinic acetylcholine-receptor antagonist yet discovered. The approach is based upon a double Mannich reaction to generate suitably functionalized unsymmetrical *N*-substituted piperidines. The methylsuccinimidobenzoates were prepared from isatoic anhydride and then condensation with methylsuccinic anhydride.

We wish to thank all our colleagues who contributed their work to this special issue. We are indebted to the many colleagues who refereed the manuscripts so rapidly in order to allow the preparation of this collection of papers on drug metabolism and medicinal chemistry.

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