

Highlights of the Society for Medicines Research Trends in Medicinal Chemistry meeting, held December 2002, in London, United Kingdom.

Perspectives into the Diversity of the U.K. Pharmaceutical Industry

by *SMR Committee*

The Trends in Medicinal Chemistry meeting was held by the Society for Medicines Research in London in December 2002 and highlighted compounds in early development and new discoveries which may lead to disease treatment in the near future.

The meeting opened with a presentation from Dr. Neil Press, Novartis (Horsham) on adenosine A3 receptor antagonists. A3 receptors are localized on eosinophils and may be important in chemotaxis and apoptosis of these cells, which are key inflammatory cells in asthma. The identification of selective antagonist ligands for the A3 receptor should help elucidate their biological significance. High throughput screening had identified aminothiazoles as hits and optimization gave [1], which is highly potent at human A3 (0.4 nM) and selective versus other adenosine receptors (>10,000 nM on A1, A2a, A2b). Compound [1] was active in a brown Norway rat model where a fall in blood pressure was blocked by the A3 agonist 2Cl-IB-

Summary

The Society for Medicines Research held a highly popular meeting in London in December 2002 entitled Trends in Medicinal Chemistry. The meeting was intended to alert researchers to some of the current areas of interest in the pharmaceutical industry either by highlighting some compounds in early development or exploring new discoveries likely to lead to new approaches to diseases treatment in the near future. © 2003 Prous Science. All rights reserved.

NECA. No effects were seen with the A2 agonist NECA. Though not as potent on A3 receptors, the aminothiazole [2], CGS 2466, was described as having an interesting profile blocking a range of receptors and enzymes that might be involved in inflammation. In addition to affinity at adenosine A3 and A2a receptors, the affinity of CGS 2466 compared well with that of Ariflo on PDE4D and of SB203580 on p38 MAPK.

Another G-protein-coupled receptor provided the topic for Dr. Verity Sabin of Celltech who described their work on P2Y2 receptor agonists. This approach may be useful in diseases with excess secretions, such as cystic fibrosis, chronic bronchitis and dry eye. The researchers had taken UTP and conducted SAR using carbostyryl replacements to the base, as in [3]. Methyl scanning around the car-

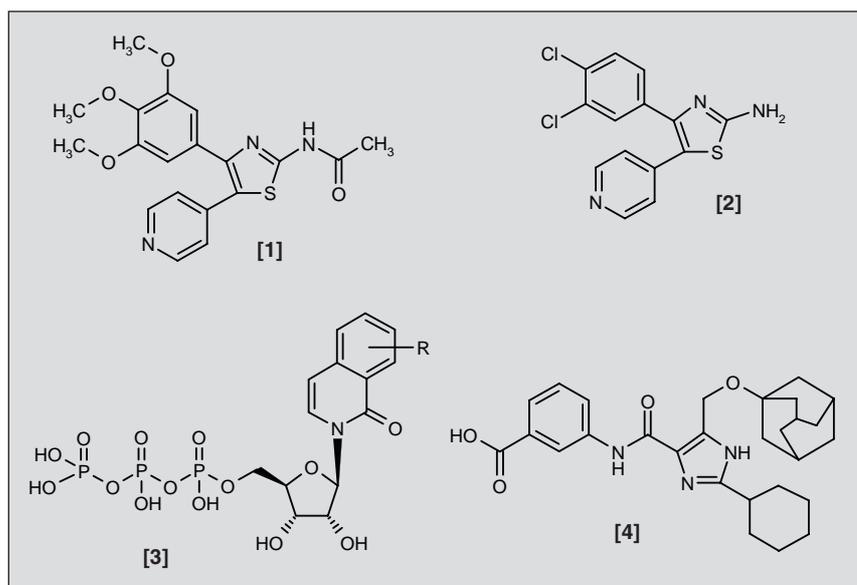
bostyryl ring showed the 7- and 8-positions tolerated substitution. The R = 7-F analog was a selective agonist for P2Y2 and had much improved stability in HBECs *in vitro* compared with the natural agonist, UTP. Stability was similar to a leading compound INS365, which has recently completed a phase III trial for dry eye disease.

A novel concept to neuromuscular block was described by Dr. Ronnie Palin from Organon. This overview provided an interesting contrast to conventional medicinal chemistry drug discovery efforts. Muscle relaxants are very useful in a variety of surgical applications. The concept was to induce rapid reversal of the current muscle relaxant rocuronium bromide by complexing the drug in a modified cyclodextrin (CD), thus removing it from the nicotinic acetylcholine receptor and avoiding the need for the con-

comitant use of muscarinic acetylcholine (ACh) receptor antagonists, such as atropine. Chemistry to modify CDs was highly challenging, but Organon succeeded in producing a thiopropionate derivative, Org25969, that showed exceptionally high affinity (K_a 10^7 per mole) for the hydrophobic drug rocuronium bromide. In rhesus monkeys, Org25969 produced 90% reversal in 1 min and is now in phase I trials.

An approach to reducing gastric acid secretion with gastrin receptor antagonists was described by Dr. Barret Kalindjian of the James Black Institute. The design was based on the minimum tetra-peptide fragment of gastrin that is required for biological activity. Modeling the linear tetra-peptide suggested that two aryl rings, 5–7 Å apart, and a dipole might be important. Dibenzobicyclo[2.2.0]octane derivatives were made to mimic this model, which had nM affinity at CCK2. This series had poor *in vivo* dog effects, so less lipophilic alternatives were sought. The imidazole [4] had a logD of 2.7, was active in dog with an ID_{50} of 0.5 mg/kg and had 27% oral bioavailability.

The theme of the meeting shifted to cardiovascular therapy with a report by Dr. Mike Palmer of Pfizer's research into endothelin A (ET_A) antagonists. Endothelin is a 21 amino acid peptide in three forms: ET-1, ET-2 and ET-3. ET-1 is the predominant form, a rigid and hydrophobic molecule. There are two receptors, ET_A and ET_B , but the role of the latter is unclear. While there is a mixed receptor antagonist already on the market (bosentan from Actelion) there is no currently approved selective ET_A -selective antagonist. Nevertheless, there is a lot of competitive activity in the area, and atrasentan is currently in phase III trials for prostate cancer. There is also a wide range of structural types in other phases of development. Pfizer's approach started with the template of BMS 193,884, and used high-throughput, library screening and *de novo* design to come up with a number of



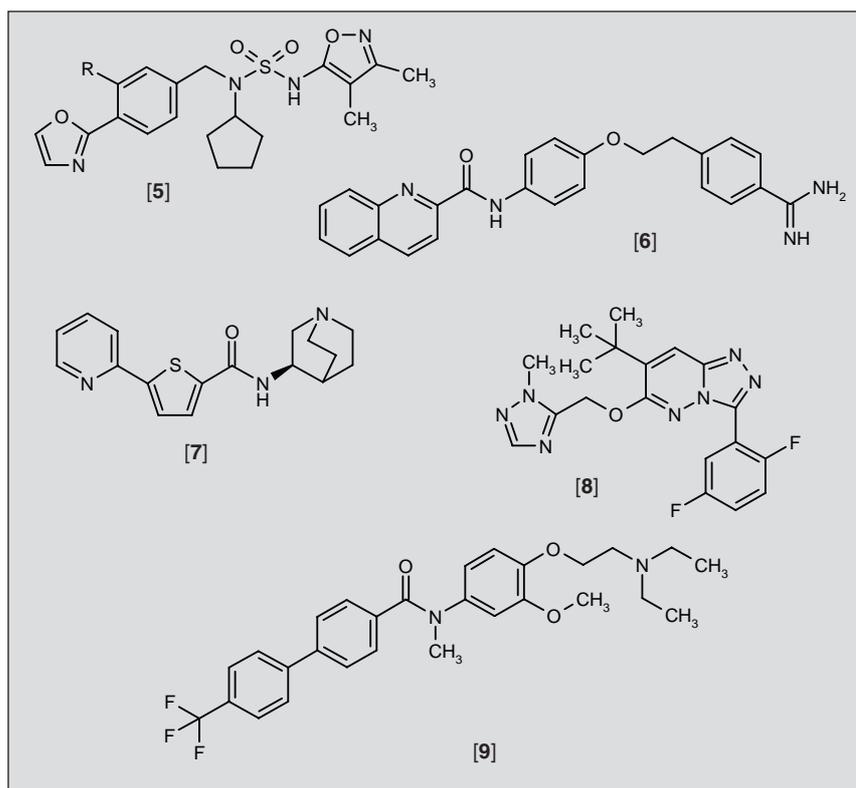
hits based on sulfonamide, sulfonyl urea and sulfamide structural classes. The sulfamide class was preferred and lead optimization led to UK 419,106 [5; R=H]. Biological activity was measured using human recombinant ET_A receptors in CHO cells. Despite a promising activity profile, this lead had poor pharmacokinetic properties due to rapid cytochrome p450 3A4 metabolism (opening of oxazole ring). While replacement of the oxazole ring with alternative heterocycles failed to improve half-life, steric hindrance of metabolism through substitution at the ortho position was effective. Finally, UK 444,040 [5; R=CH₂-(N-pyrrolidone)] was identified, with affinity for ET_A of 1 nM, selectivity over ET_B of around three orders of magnitude and a half-life of over 2 h *in vitro* and a predicted *in vivo* half-life in humans of 8 h. Functional efficacy was determined in human umbilical cord vein (HUV); a correlation of HUV pK_B and radioligand binding ET_A pK_i was established in this model, and UK 444,040 was shown to have a K_B of 137 nM. With this potency it was estimated that the compound would need good pharmacokinetic parameters for developability. In fact, a high clearance rate in rats (*i.v.*) precluded clinical work on this compound, although it represents a promising series for further optimization.

This presentation was followed by a recollection by Dr. Garry Pairaudeau of AstraZeneca's work on tryptase inhibitors, particularly in regard to lead generation, for use in lung diseases. Tryptase is a protease enzyme in the same family as thrombin, trypsin and factor Xa, but unlike these others it is only active as a tetramer. It was thought to be important in fibroblast proliferation, and as a result play a role in airway remodeling. The first approach used high-throughput screening, which produced 1200 active hits, but after eliminating alkylating agents, repeating assays and resynthesizing compounds to greater purity, none of these turned out to be of further interest! A second start to the program was based on a poorly selective thrombin inhibitor. Selectivity was bred into the molecule through designing compounds which spanned from the enzyme active site across to another binding site on an adjacent subunit. Tryptase is the only enzyme in the serine protease family to benefit from this additional form of binding because it is active as a tetramer. Compounds such as [6] were inhibitors of tryptase at 30 nM, with over 100-fold selectivity. Further improvements in potency could be achieved through substitution of the middle aryl ring with chlorine; however, the main problem was that the amidine group was resistant to

modification, and led to poor bioavailability. The only suitable replacement was a benzylamine, but this was rapidly metabolized by amine oxidases. The final blow was dealt by the finding that fibroblast proliferation was not dependent on tryptase, and the program was abandoned.

This biotechnology sector start-up company, Astex Technology, which has yet to deliver compounds into pre-clinical development, have an interesting approach to discovering novel drugs. Paul Wyatt described their approach, which focuses on the specialist methods available to Astex. The company is based on x-ray crystallography and drug design expertise. It is using known structures of receptors and enzymes to predict affinities for certain small molecule fragments in binding pockets, which are then confirmed by experiment. The affinity of the biomolecule for certain fragments can then be used to build a larger molecule composed of more than one of these fragments with much greater affinity. Because of the early stage of the discovery programs at Astex, the speaker was not able to present any structures in his talk. Active programs at Astex include p38 kinase inhibitors for inflammatory diseases, and CDK2 inhibitors for cancer, which are currently in the lead optimization stage.

The final session of the meeting had a predominantly CNS theme and predominantly featured work on ion channels. Dr. Richard Baker (Lilly) asked the question: Will selective neuronal nicotinic receptor ligands make useful drugs? There is keen interest in this family of ligand-gated ion channels triggered by the endogenous ligand, ACh. Despite the complicated picture caused by multiple α and β subunit combinations to give the pentameric structure (16 different subunits have been found in mammals), they are, as a class, known to be chemically tractable, e.g., nicotine is a nonspecific ligand. Several subunit combinations are found localized in the CNS and appear to modulate specific events, such as the release of a single neurotransmitter,



and clearly they represent drug targets worth investigating. It is only by identifying truly subtype-selective compounds that their biological roles will be discovered. Thus, to answer his own question, Dr. Baker gave an overview of the current public state of knowledge covering known subtype combinations, their possible biological significance, pharmacology/assay issues, details of some natural and synthetic ligands and an update on the current understanding of the ligand-receptor interactions that will help rational drug design. This latter point has taken on new momentum with the publication of the first x-ray structure of a molluscan 'nAChR-like' ACh binding protein (Nature 2001, 411: 269-76). Not all the subtype combinations have been defined yet. Some that appear to be of interest are $\alpha 4\beta 2$ —confined to the CNS, $\alpha 4\beta 4$ —highly localized in brain, $\alpha 7$ —the only homomeric channel and implicated in schizophrenia—and $\alpha 3\beta 4$, which is in the periphery and is implicated in gastrointestinal action. There is much interest in the $\alpha 7$ subtype. Natural products that interact with this ion channel include α -bun-

garotoxin and methyllycaconitine. Synthetic agonist ligands are typified by the generic structure of a bridgehead basic nitrogen heterocycle linked to an extended aromatic system by an amide or an amide isostere, e.g., [7], which has an IC_{50} of 0.58 nM, a brain/plasma ratio of 0.29 and a half-life of 2 h. No biological effects were seen with selective $\alpha 7$ agonists *in vivo*, however, in a battery of behavioral assays. The $\alpha 7$ knockout mouse is also known to exert a near normal phenotype. Dr. Baker's view was that only clinical trials with subtype-specific neuronal nicotinic receptor ligands would answer the question he posed.

The GABA-A receptor family poses a similarly complicated picture to the nicotinic receptors and was the subject of the presentation by Dr. Leslie Street (Merck Sharp and Dohme, Harlow). These are also pentameric receptors that gate chloride ions. The subunit composition is made from co-assembly from a family of 16 genes ($\alpha 1-6$, $\beta 1-3$, $\gamma 1-3$, $\delta, \epsilon, \pi, \rho$) and there are a variety of allosteric sites that lead to modulation of GABA activity

upon binding specific ligands, e.g., benzodiazepines, which give rise to an anxiolytic effect. There is a need to identify nonsedating anxiolytic agents. The increasing understanding of the pharmacological relevance of GABA-A receptor subtypes, using genetically modified mice, for example, with a diazepam-insensitive 1 subtype, suggests that this might be possible. Dr. Street described compounds that have been designed to work through the $\alpha 2$ - and $\alpha 3$ -containing GABA-A receptor subtypes. The $\alpha 2/\alpha 3$ subtypes are found in the amygdala, septum and locus coeruleus and are thus considered to be of relevance to anxiety. Using radioligand binding assays (tritiated flumazenil), the SAR of a series of triazolopyridazines was investigated. These compounds, e.g., [8], have low nanomolar affinity and no efficacy at the 1 subtype. Anxiolytic activity is seen *in vivo* in behavioral models, e.g., elevated plus maze, there is no sedating activity observed and the compounds display anticonvulsant properties.

The final presentation focused on a relatively newly discovered G protein-coupled receptor target. Dr. David Witty (GlaxoSmithKline) described the discovery of potent, selective antagonists of the human melanin-concentrating hormone receptor, 11CBy.

The neuropeptide, melanin-concentrating hormone (MCH) is implicated in signaling cascades related to the stress axis, as well as being involved in feeding. The discovery in 1999 that the receptor for MCH was a G-protein-coupled receptor, 11CBy, and hence a member of a chemically tractable protein family, provided an opportunity to investigate the therapeutic utility of antagonists for CNS disorders such as anxiety and depression, in addition to investigating the use in feeding disorders. The lead compound described was forthcoming from a biphenyl carboxamide series. Extensive modification and probing gave SB568849 [9] which has a pK_b of 7.7 at the 11CBy receptor. In DMPK studies [9] was shown to be 80% orally bioavailable, with a clearance of 16 ml/mg/kg and brain/blood ratio of 1:1. Greater than 30-fold selectivity was observed against a panel of receptors, including some 5-HT subtypes.

This was the sixth Trends in Medicinal Chemistry meeting organized by the Society for Medicines Research. They continue to be popular and this one was very well attended, attracting an audience of 130. In all, 10 different organizations were represented, and it was pleasing to see two new ones included that had not previously given presentations at these meetings.

The range of topics gave an interesting perspective into the diversity of research topics and into research strategies adopted by a significant section of those that make up the U.K. pharmaceutical industry. It perhaps comes as no surprise that studies on G-protein-coupled receptors provided the theme of half of the presentations.

Prous Science has collaborated with the Society to make the symposium available, free of charge, in a Webcast format (<http://www.prous.com/trends>). Visitors to the Webcast can hear each speaker's voice synchronized with the complete set of slides, graphics and photographs.

The SMR Committee organizes conferences on behalf of the Society for Medicines Research four times a year. These one-day conferences are of a multidisciplinary nature, therapeutically focused and normally staged in or around London. Details about forthcoming meetings can be obtained from: SMR Secretariat, 20/22 Queensberry Place, London SW72DZ, U.K. Tel: +44 171 581-8333; Fax: +44 171 823-9409; e-mail: smr@iob.org; URL: <http://www.socmr.org>.

INEX: 2002 RESULTS, 2003 MILESTONES

On March 12, 2003, Inex Pharmaceuticals Corp. summarized the progress made in 2002 and looked towards milestones it anticipates for 2003.

In December, positive results were reported from a pivotal phase II/III trial in which **Onco TCS (vincristine sulfate)** achieved a 24% response rate in 102 non-Hodgkin's lymphoma (NHL) patients who had relapsed after receiving an average of 4 prior treatment regimens before being enrolled. Interim results from a phase II trial of Onco TCS in newly diagnosed, previously untreated aggressive NHL patients showed that Onco TCS in

combination with other chemotherapeutic drugs achieved a 100% response rate in 69 patients. Follow-up data will be presented later in 2003. The Onco TCS clinical development program was expanded to nine phase II clinical trials in 2002, with the addition of trials in relapsed Hodgkin's disease and relapsed acute lymphoblastic leukemia. In 2003, Inex plans to file an NDA for the treatment of relapsed aggressive NHL in the third quarter, complete the reacquisition of product rights from Elan, and establish a marketing partnership for Onco TCS.

The program for **Topotecan TCS** (topotecan hydrochloride), Inex's second product, continued to make progress under the sponsorship of

partner GlaxoSmithKline, resulting in milestone payments of USD 2 million to Inex. In 2003, GSK intends to file an Investigational New Drug application (IND) to begin clinical trials of Topotecan TCS.

Preclinical data were reported showing that Inex's proprietary **liposomal transmembrane carrier systems (TCS)** for drug delivery improve the antitumor activity of the approved cancer drugs vincristine, vinblastine and vinorelbine.

Finally, Inex also reports that it intends to select a new product candidate from its **targeted chemotherapy** technology platform to become the company's third product in development.