SMRx

The Newsletter for the Society for Medicines Research

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AGM Approves New 2001 Committee for the SMR

by Malcolm Duckworth

The AGM on 30 November 2000 approved a number of changes to the SMR committee for 2001. There were considerably more than in previous years and it is worth detailing the background to why this was. The rules of the SMR, prior to November 2000, stipulated a committee of four officers (chairman, vice-chairman, honorary treasurer and honorary secretary) plus nine other elected members. The composition of the committee is also important. The SMR has always favoured a balanced committee comprising roughly equal representation from the academic community and industry, with a mix of scientific disciplines (medicinal chemists, pharmacologists, clinicians, etc.) that reflects the membership, and some representation from regions outside the south-east of England.

Over the previous years, the composition of the committee had veered away from these stated aims and it was the 2000 SMR committee's goal to redress the imbalance that had built up. Incidentally, a rule change was passed at the AGM that now allows for up to 13 elected members in addition to the officers.

Most appointments to the committee are for four years; thus, several positions became vacant because of natural retirement. The retirements included that of the vice-chairman, Dr Irene Francois, a medicinal chemist by training with senior management experience in large pharma and biotech, now with Rademacher Group, Dr Jeremy Gilmore, a senior medicinal chemist with Lilly and Dr Pam Greengrass, a senior pharmacologist from Pfizer. Increased work demands and industry mergers also meant that the SMR had to cope with resignations during 2000. These were Dr Roger Horton, a senior pharmacologist at St George's Hospital Medical School, London; Dr Ray Jupp, a molecular biologist and senior manager at Aventis; Dr Patricia Heath, a clinician with Celltech Chiroscience; and finally Dr Geoff Stemp, a senior medicinal chemist at SmithKline Beecham. Dr Stemp latterly held the position of honorary treasurer for two years and had served on the committee for a total of six years. It was against this background that the SMR set about rebuilding its committee to continue the business of running the society.

The new vice-chairman (chairman-elect) is Dr Peter Gallagher, a senior medicinal chemist at Lilly (Windlesham). Peter has been a long-standing member of the SMR and served on the committee during the 1990s, until 1996. He is thus very familiar with the society, and will take up the chairman's role in December 2001. Taking over the role of honorary treasurer is Dr Mark Giembycz, a pharmacologist from the National Heart and Lung Institute, London. During 2000, four members were co-opted on to the committee and stood for election at the AGM, at which time they were elected to serve for four years.

They were Professor Nick Carter, a professor in the Medical Genetics Unit from St George's Hospital Medical School, London; Dr Kate Brown, a biochemist from Imperial College, London; Dr Ian Morris, a pharmacologist from the University of Manchester; and Dr Trevor Hansel, Medical Director of the NHLI Clinical Studies Unit, Royal Brompton Hospital, London. Three further vacancies were filled by Dr Robert Williams, a pharmacologist and now director of pre-clinical development for Prolifix Ltd, Dr Dale Jackson, a biologist and deputy head of the department of experimental medicine at AstraZeneca, and Professor Clive Page, professor of pharmacology from King's College London.

The full SMR committee for 2001 is as follows:

- Dr David Cavalla (Arachnova) chairman (and next vice-chairman);
- Dr Peter Gallagher (Lilly) vice-chairman (chairman-elect);
- Dr Malcolm Duckworth (Glaxo SmithKline) honorary secretary;
- Dr Mark Giembycz (National Heart and Lung Institute) honorary treasurer;
- Dr Kate Brown (Imperial College of Science and Technology);
- Professor Nick Carter (St George's Hospital Medical School);
- Dr Trevor Hansel (National Heart and Lung Institute);
- Dr Simon Hodgson (Glaxo SmithKline);
- Dr Dale Jackson (AstraZeneca);
- Dr Ian Morris (University of Manchester);
- Professor Clive Page (King's College London);
- Dr Alan M Palmer (Vernalis); and
- Dr Robert Williams (Prolifix).•

SMR Award-winning Drug Becomes a Money-spinner for Lilly

Antischizophrenic olanzapine, marketed under the name of Zyprexa, is now rivalling Prozac as the biggest earner in Lilly's stables. Prozac sales are declining in the face of generic competition outside the US, while generic Prozac should be available on the US drug market from August this year. Lilly lost a crucial patent case in August last year in which the court rejected the company's method-of-use patent for Prozac. In the third quarter of 2000, Zyprexa sales rose by 28% to US$645 million, while Prozac's sales fell slightly to $680 million.

Zyprexa is sold in the US, Mexico, Brazil and South Africa for the treatment of acute mania with bipolar disorder. It recently received an approvable letter from the FDA to maintain a treatment response in schizophrenics. Lilly is also developing a mix of olanazapine with fluoxetine for

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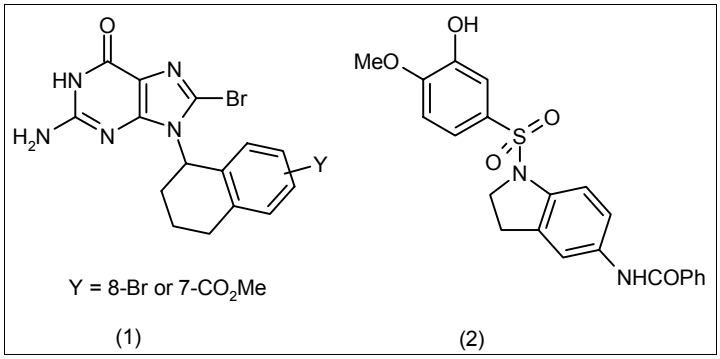
Trends in Medicinal Chemistry

by Malcolm Duckworth

The Society for Medicines Research held a one-day Trends in Medicinal Chemistry meeting on 30 November 2000, fittingly at the Research and Development site of GlaxoWellcome in Stevenage. As in previous years, the meeting proved to be highly popular and attracted over 140 registrants. The overall intention of the meeting was to alert researchers to emerging areas of chemistry and novel classes of compounds for a range of enzyme and receptor targets likely to lead to new approaches to disease treatment.

The symposium opened with a description by Dr Hazel Hunt (Celltech Chiroscience, Cambridge) of a novel class of phosphodiesterase (PDE) inhibitors. PDE enzymes are responsible for the hydrolysis of ubiquitous second messengers cAMP and cGMP to inactive AMP and GMP, respectively. Inhibition of PDE enzymes results in an accumulation of cyclic nucleotides, which leads to a modulation of the activation state of a number of biological pathways. The selective inhibition of a specific PDE isoenzyme has been an objective of the pharmaceutical industry for many years. Selective PDE3, PDE4 and PDE5 inhibitors are well documented and exemplified by drugs already launched as well as many compounds undergoing clinical evaluation.



PDE7 inhibitors from Celltech

PDE enzymes can be classified into 11 isoenzyme families based on substrate specificity and sensitivity to endogenous and exogenous regulators, but physiological roles have not been defined for all of them (e.g., PDE8-11). PDE7 is a cAMP-specific enzyme which has been shown to be insensitive to most standard PDE inhibitors, such as the PDE4 inhibitor, rolipram. Human PDE7 mRNA exists as two splice variants: PDE7A1 is widely distributed and PDE7A2 exists in skeletal muscle, heart and kidney, but active PDE7A protein has been detected primarily in T-cells. Recently, the presence of PDE7 in airway epithelial cells has also been reported. This distribution suggests that selective PDE7 inhibitors may have utility in T-cell mediated diseases and disorders of the airways.

Hut78 cells have been shown to produce PDE7 and can be used in screening. Two series of selective inhibitors were described. The guanine series (1) have low μM IC_{50}s and show little activity against isoenzymes 3 and 4. The SAR investigation showed that an 8-bromoguanine was preferred and a range of substituents were tolerated in the aromatic ring of the tetrahydronaphthalene, with 8-Br (1μM) and 7-CO_2Me (1.4μM) being the optimum. A second series of sulphonamides (2) produced submicromolar selective compounds but, for intellectual-property reasons, the structures of the most potent compounds could not be revealed. The SAR investigations showed that replacement of the sulphonamide linkage with amides, amines or ureas reduced inhibitory potency. The 3-OH, 4-OMe combination was one of the best and was used to investigate substitution in the indoline ring. The indoline could be replaced with a tetrahydroquinoline. Substituents at the 5 position of the indoline were preferred with -NHCOPh (2) giving a compound with an IC_{50} = 0.36μM and a selectivity of tenfold over other isoenzymes. Three undisclosed compounds (63597, 63627,

63705) were slightly more potent and selective. No comment was made on the biological effect of the compounds on T-cells.

The symposium included two talks on the design of selective ligands for the adenosine receptors. Adenosine is involved in an enormous range of physiological processes and mediates its biological activity via the family of P1 purinergic receptors. This family consists of four G-protein coupled 7-transmembrane receptor sub-types (A_1, A_{2a}, A_{2b} and A_3) and the identification of selective ligands for these subtypes has been the objective of various research groups. Much effort has been devoted to define the pharmacology and tissue distribution of the various receptors, and thus deduce any possible disease indications. The design of selective ligands to accelerate the biological understanding of this receptor family is an important part of the of the target validation process.

Dr Rick Cousins (GlaxoWellcome, Stevenage) gave the first of the talks. He described studies towards the preparation of novel purinyl-based structures and the strategies used in their synthesis. Particular attention was given to illustrate how modifications of the ribose moiety and substituents on adenosine generated potent selective purinergic receptor agonists. Array methodology was used to introduce a variety of lipophilic amine substituents into the adenosine ring at positions 2 and 6. The D-ribose ring was retained throughout. A series of potent A_{2a} agonists (typified by (3)) was identified, with subnanomolar binding affinities *in vitro* (measured against human receptors in a CHO cell line) and selectivities over A_1 and A_3 greater than 100. No comment was made for affinity or selectivity at A2b receptors.

New anti-ischaemic agents

The second talk on adenosine receptor ligands was given by Dr Lars Knutsen (Vernalis, Winnersh). The majority of the work described was carried out at Novo Nordisk. The novel adenosine A_1 agonists NNC 21-0136 and NNC 21-0147 constitute new biological leads as anti-ischaemic agents with neuroprotective effect in both global and focal rodent ischaemia models.

These compounds are potential drug candidates for stroke since they possess diminished cardiovascular effects in rats when compared to reference A_1 agonists such as *N*-cyclopentyladenosine and *R*-phenylisopropyladenosine. The presentation revealed the screening plan and brief SAR for this new series of P1 agonists. In the NNC 21-0136 series one SAR was observed for the affinity of these nucleosides to the rat brain A_1 receptor, but another SAR for the diminished cardiovascular effects. The SAR of 9-cyclo-pentylpurines was investigated. The purine 6- and 9-position SAR revealed that compounds such as NNC 53-0016 (456nM at A3) were an extension of an earlier *N*-alkoxyadenosine series of A_3 agonists. These latest compounds also possess cytokine modulating properties (down regulation of TNF-alpha gene expression) and some examples were found to be novel, potent inhibitors of phosphodiesterase type IV.

Dr Laurent Hennequin (AstraZeneca, Reimes, France) described the ongoing work that has led to the design of selective inhibitors of VEGF (vascular endothelial growth factor) receptor tyrosine kinase, as potential angiogenesis inhibitors. These will be important because pathological angiogenesis has been associated with a variety of disease states including diabetic retinopathy, psoriasis, cancer and rheumatoid arthritis. VEGF is a key mediator of angiogenesis implicated in tumour blood vessel formation, a prerequisite for the growth and metastasis of solid tumours. Inhibition of VEGF receptor-associated tyrosine kinase (RTK) activity should abolish VEGF signalling. At the molecular level, VEGF is a ligand for two VEGF RTKs: Flt-1 and KDR. Screening against these target enzymes — and in a whole cell assay — VEGF-driven proliferation of human umbilical vein vascular endothelial cells (HUVECs), as well as the selectivity profile in a panel of kinases led to the identification of ZD4190, an aminoquinazoline inhibitor of KDR activity amenable to oral administration.

Homology models of the ATP binding site showed a key N1 H-bond interaction. *In-vivo* activity in disease models (human xenografts) was seen with tumour growth from a variety of tissues: colon, lung, breast, prostate and ovary, at 100mg/kg/d. Pharmacokinetic studies showed that while the compound had an acceptable $t_{1/2}$ (~1.5h) and good bioavailability (F% >80) in the rat, bioavailability was much lower (F% <20) in dog and monkey. Analysis of the physicochemical properties, however, showed that the solubility at pH 7.4 was only 0.7μM and thus, ZD4190 was dropped. Improved solubility was found by introducing an alternative alkoxyamino substituent to give

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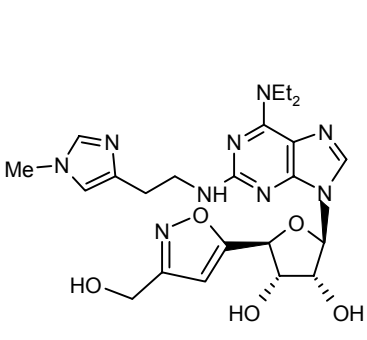

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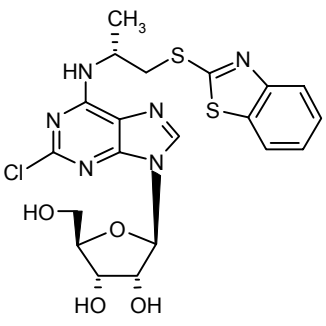

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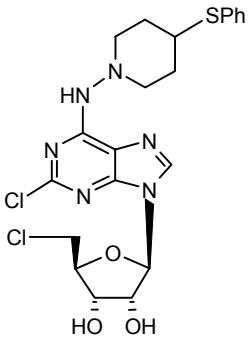

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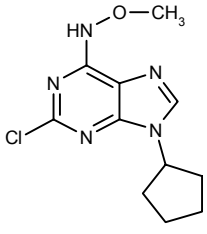

NNC 53-0016

Purinergic receptor selective agonists from Glaxo Wellcome and Novo Nordisk have potential in a number of indications including ischemia

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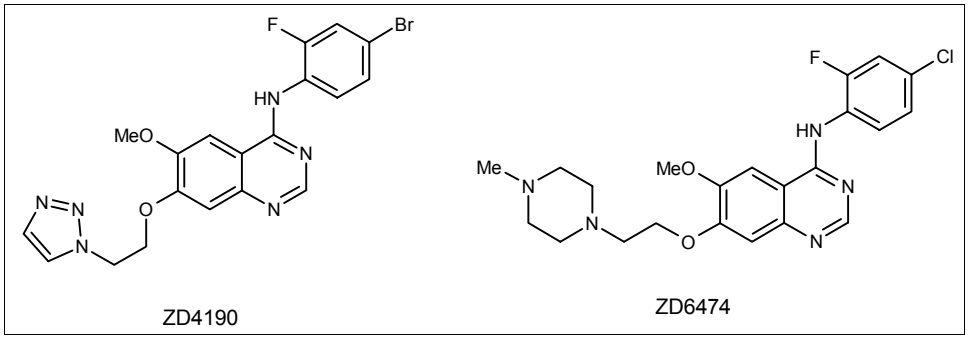


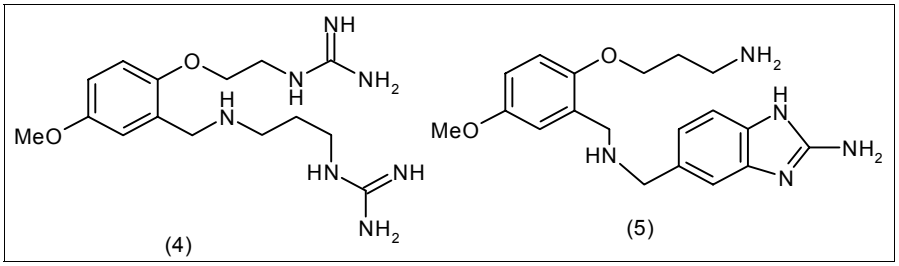
Selective inhibitors of VEGF (vascular endothelial growth factor) receptor tyrosine kinase, as potential angiogenesis inhibitors

ZD6474, which had solubility >500µM at pH 7.4. Good bioavailability was observed in rat and dog. There was no sacrifice of activity against tumour growth. The compound is in Phase-I clinical trials.

Targeting RNA as a drug target is a concept that has been around for some time, and the antisense approach to RNA has been the subject of considerable effort over a number of years. Dr Justin Bower (RiboTargets, Cambridge) gave an interesting overview of the current position and demonstrated that small-molecule inhibitors of RNA-protein interactions are now realistic targets. The position has changed because the intricacies of RNA tertiary structure have recently been revealed. Using high-resolution NMR and X-ray crystallographic data, RiboTargets is focusing on the development of small molecule inhibitors of RNA for anti-infective targets. Dr Bower described work in two areas.

First, he showed some progress in the HIV area. TAR is a structured RNA element found at the 5' end of all HIV-1 viral transcripts. Upon binding the transcription factor protein Tat, the processivity of transcription is enhanced, leading to full-length viral transcripts and ultimately viral protein. Blocking this Tat/TAR interaction has been shown to prevent viral protein synthesis. Using high-resolution NMR ternary complexes, the development of a novel series of Tat/TAR inhibitors (4), based on a known lead ALX0019, was achieved. Compounds were assayed in a fluorescence-based assay with RNA as the acceptor and the free peptide as the donor. The initial compounds possessed a substituted guanidine which was successfully replaced by an aminobenzimidazole (5) using 'SAR by NMR', with no loss of potency.

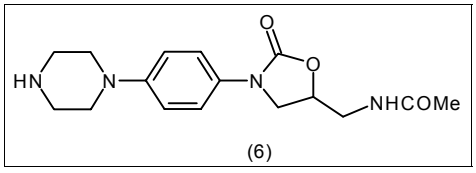
The second example for demonstrating small-molecule RNA-protein inhibitors was in the antibacterial area. The bacterial ribosome has long been a target of interest for novel anti-bacterial agents. Many natural-product antibiotics of significant clinical importance have been shown to interact at the ribosomal RNA (rRNA) level, including macrolides, aminoglycosides, streptogramins and tetracyclines. Most recently the non-natural oxazolidinone antibiotics have also been shown to act at the level of rRNA. Until recently, rational structure based design on rRNA has been hampered by the availability of high-resolution structural data; however, the recent publication of high-resolution X-ray structures of fragments of rRNA, and indeed of the 50S and 30S subunits, are set to revolutionise this area. RiboTargets developed an *in-silico* virtual screening technology (RiboDock™) which is capable of high-throughput docking against RNA/protein targets. Efforts targeting the thiostrepton binding sight on the 50S subunit were described. 1.2 million vitrual structures were docked of which 0.1% were virtual hits. One hundred and ninety-seven compounds could be purchased, of which 13 had acceptable activity in GTPase-activating region (GAR) binding assay at 50µM. Of these, three had acceptable activity and specificity in a bacterial translation assay. One of these, RBT1161 (no structure given) had comparable activity (20.5µM) with an oxazolidinone (6) (11µM). Both are prokaryote specific. RBT1161 has MIC of 11.8µg/ml against MRSA. The whole process for identification of the lead took six to eight weeks.



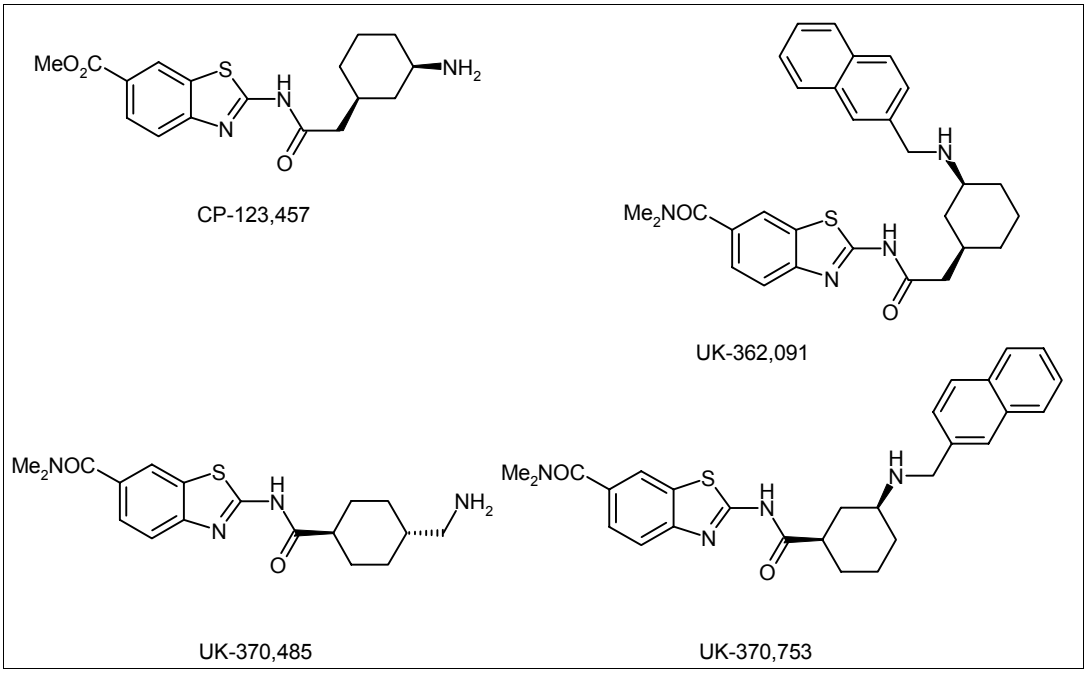
Novel Tat/TAR inhibitors for HIV

More anti-infectives

Continuing the anti-infectives theme, Dr Andy Bell (Pfizer, Sandwich) gave a presentation on the design of inhibitors for protein N-Myristoyl transferase (NMT), an enzyme found in all eukaryotic cells, which catalyses the transfer of the rare C_{14} fatty acid, myristic acid, to the N-terminal glycine of its substrate proteins. The need is for a fungicidal agent rather than a fungistatic. In collaboration with Millennium, gene knock-out experiments in yeast and *Candida* have shown NMT to be an essential enzyme, and that temperature-sensitive dependent shut-off leads to cidality; therefore, NMT is an attractive antifungal target. Despite extensive elegant efforts, particularly by the Searle group, only weakly antifungal NMT inhibitors have been identified to date. It was hypothesised that the weakness of antifungal activity of previous NMT inhibitors could be due to their large peptidomimetic nature and, consequently, Pfizer decided to look for alternative starting-points through a high through-



Virtual screening produced a novel antibacterial template with activity similar to this oxazolidinone



Pfizer's novel antifungals

put screen of their compound file. CP-123,457 was identified as an inhibitor of *Candida albicans* NMT (IC_{50} = 1.4μM) and it proved amenable to rapid follow-up by parallel synthesis. They were able to replace the potentially vulnerable ester functionality and achieve increased enzyme potency.

Lipophilicity was increased by derivatising the primary amine and although enzyme potency was reduced with small alkyl groups, reductive amination with aryl aldehydes gave several analogues with increased enzyme potency, for example, UK-362,091 (IC_{50}= 11nM, Log D=3.4) and antifungal activity, with a fungicidal mechanism of action. Several other primary amines, for example UK-370,485 (IC_{50}=42nM) were made.

A crystal structure of the binary complex of *Candida albicans* NMT with UK-370,485 was determined (2Å) to reveal a tight network of hydrogen bonds around the primary amino group that suggested a possible mechanism for the myristoylation of substrate proteins.

Additional isothermal calorimetry experiments were used to investigate the thermodynamics of the binding to the enzyme. The experiments suggested that a ternary complex was involved involving myristoyl-CoA, and that UK-370,485 binds with a strong enthalpic contribution with loss of entropy on binding. Despite their excellent enzyme potency, the primary amine series was felt to be too polar for good cellular penetration (Log D=-0.8 to 0). Alkylation of the amine, as in UK-362,091 gave UK-370,753 (IC_{50} = 86nM, MIC 0.09μg/ml) which is more active antifungally than versus the enzyme. It has a fungicidal mode of action.

Computational chemistry

In contrast to presentations on synthetic compounds, Dr Colin Edge (SmithKline Beecham, Harlow) described computational chemistry approaches that have been taken to enhance screening collections. He showed that compounds designed and marketed for human disorders differ in their physical properties from antibacterial drugs.

Analysis of physical properties of marketed drug sets allows the devising of simple rules, similar to the 'Rule of 5' proposed by Lipinski et al., which delimit the boundaries of property space for certain therapeutic classes. A set of rules were devised for antibacterials: molecular weights should be in the range 300–600; MlogP <3 (Moriguchi LogP was chosen over cLogP because it is more robust despite being less accurate, it has fewer fiddle factors and is a simple summation of atomic contributions), H-bond donors <10 and acceptors <15. The drug sets were also broken down into constituent functional groups in an attempt to make a drug-like scoring system. The most common fragment of CNS drugs is a tertiary amine, whereas for antibacterials, polar groups appear most. The rules and scoring system have been used to buy compounds to enhance the SB collection and design combinatorial libraries which are focused towards particular therapeutic classes.

Dr Francis Wilson (Roche, Welwyn Garden City) talked on the design and synthesis of inhibitors to combat hepatitis-C. Hepatitis-C virus (HCV) is the cause of the majority of cases of transfusion-associated hepatitis and a significant proportion of community-acquired hepatitis worldwide. Infection by HCV can lead to a range of clinical conditions including an asymptomatic carrier state, severe chronic active hepatitis, cirrhosis and, in some cases, hepato-cellular carcinoma. Current estimates show ~300 million chronically infected worldwide. The virus possesses a chymotrypsin-like serine proteinase, NS3, which has protease and helicase function. The protease typically cleaves after a cysteine. The first-generation electrophile-based inhibitors designed by Roche were aldehyde and boronic acids which had hepatotoxicity issues. Rat hepatocyte cultures were used to profile compounds for potential hepatotoxicity.

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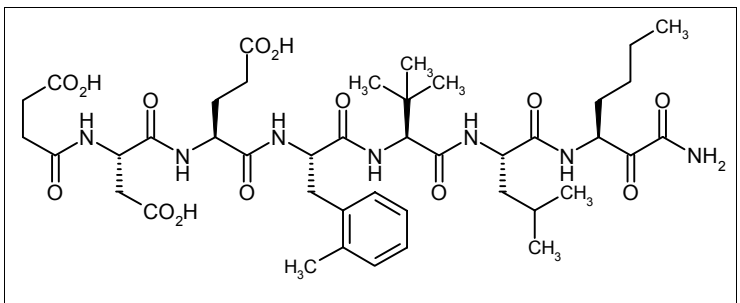

Ro 36-3810/000

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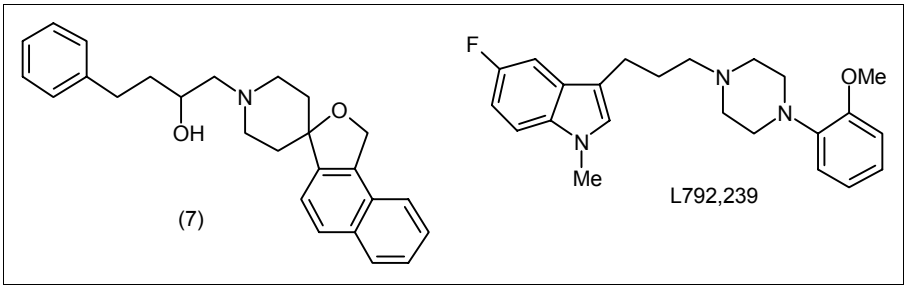
Replacement of a boronic acid with the alpha-keto amide (for example, Ro 36-3810/000) gave a hepatocyte penetrant compound (IC_{50} 4nM) that causes less of a rise in liver enzymes than the boronic acids. The key issue, however, is insufficient selectivity over other serine proteases (for example, chymotrypsin, elastase).

New work on anti-depressants

There is a clear need for an antidepressant compound with a faster onset of therapeutic action. Dr Monique van Niel (Merck Sharpe & Dohme, Harlow) described research designed to generate such compounds. They are designed to have dual activity against the 5-HT_{1A} receptor and the 5-HT neurotransmitter (re-uptake) transporter (5-HTT) and should increase the amount of 5-HT released in synapses of the brain. The hypothesis is based on clinical observations that suggested a greater proportion of patients with depression responded when the 5-HT depletion in rat (function), displacement of tritiated MPPF to determine 5-HT_{1A} receptor occupancy in mouse cortex (function), and *in-vivo* dialysis in rat hippocampus to measure 5-HT efflux. SAR on a series of amino alcohols, based on a compound from Eli Lilly, were described, which led to (7). The S enatiomer at the secondary alcohol centre was preferred. The compound had reasonably high clearance, good bioavailability and a brain to blood distribution ratio of 3: 5. Unfortunately, these compounds had some α_{1A} adrenoceptor affinity.

A second series, based on a lead from Bristol Myers Squibb, led to L792, 239. L792, 239 has high affinity at 5-HT_{1A} receptors (1.3nM) and the re-uptake site (0.1nM) and an intrinsic activity of 35%. *In-vivo* microdialysis experiments on this compound, which measured the amount of 5-HT efflux, indicated that levels were equal to those obtained using a combination of fluoxetine and the



Combined 5-HT uptake and 5HT_{1A} receptor blockers from Merck

HT_{1A} partial agonist pindolol was co-administered with a selective serotonin re-uptake inhibitor (SSRI), compared with those receiving only SSRIs, and that a reduced treatment time was needed to obtain a sustained response.

The assumption is that elevated levels of 5-HT are a contributing factor. Merck generated relevant biological data using the following systems: cloned 5-HT_{1A} receptors (Hela cells) (binding), 5-HTT (HEK cells) (binding), agonist-induced GTPγS binding (function), inhibition of PCA-induced 5-HT_{1A} antagonist WAY 100,635; thus, in line with expectations. Alternative series of compounds are also being investigated.

In summary, this was a popular, well-organised meeting with the nine speakers representing nine different pharmaceutical organisations. In addition to the continuing work on well-established classes of targets, new and exciting opportunities were presented based on new information from genomic and structural sources, in addition to approaches based on good clinical observation.•

Animal rights debate rises to new pitch

The plight of Huntingdon Life Sciences (HLS) in finding financial backers to take on a debt of £22.6 million from the Royal Bank of Scotland (RBS) has raised the temperature of debate concerning animal rights in Britain to a new height. The eventual saviour for the drug safety company came from an anonymous US source, but the story is not likely to end there.

The potential loss of 1,200 jobs and damage to the credibility of the UK as a science base gave rise to high-level support of the beleaguered company on a scale not hitherto seen. Anti-vivisectionist action against HLS has escalated after the company became the specified target of a campaign to close it down within three years in 1999. The campaigners have vowed to continue and to track down and expose HLS' new backers and put presure on them to pull out.

During the immediate build up to the expiry of the loan from the RBS, a number of prominent government ministers posited the importance of animal testing for determining drug safety. Health Minister Lord Hunt said 'animal research remains absolutely essential to the discovery of medicines as well as the assessment of safety and efficacy of new treatments'.

Home Office Minister Mike O'Brien said the new deal sent out an important message to protesters. 'It is wholly unacceptable for criminal elements, posing as protesters, to attempt to stop legitimate business,' he said.

Science Minister Lord Sainsbury said science jobs would have gone abroad had the company closed. He was closely involved in negotiations that led to the deal and has condemned the often violent protests.

Pressure is building on the government for a change in the law to allow the names and addresses of shareholders and directors to be kept secret in future. Equally, there is growing recognition that the response of various British financial institutions in giving in to anti-vivisectionist intimidation has further encouraged it.

The episode has highlighted the role of government in legislating for animal tests in the interests of public safety, and HLS has sought to tackle the issue head on by arguing that it is fulfilling a statutory requirement for the public good.•

Medicinal Chemistry at Manchester

By Professor Ian Morris

The more I work in medicinal chemistry, the more I realise that I cannot offer a good definition of the field for a university environment. A facile answer would be to quote the editorial policy of the *Journal of Medicinal Chemistry*, but in reality the subject varies from one academic centre to another. In the 1970s and 1980s most UK medicinal chemistry labs were heavily biased to analogue synthesis with attendant QSAR and perhaps some bio-assays. The drug industry had no such boundaries. It had to be multidisciplinary to move from target validation and lead optimisation through delivery and formulation, pharmacokinetics and pharmacodynamics, to drug usage.

At the University of Manchester in the late 1980s 'Med Chem' was redirected to ensure that it broke through the boundaries of traditional synthetic pharmaceutical chemistry. Recognising that biological and high-level instrumental techniques would have an increasing impact on medicinal chemistry, we sought to build a truly interdisciplinary environment in which to work and train our pharmaceutical researchers of the future. The natural setting for this to develop in Manchester was the department of pharmacy, now the school of pharmacy and pharmaceutical sciences. Pharmacy has always been a multidisciplinary profession, reflected in the teaching — and hence research complements — of schools of pharmacy. Building on the established synthetic medicinal chemistry base, we then developed support for structural studies of drug: receptor interactions through high-field NMR methods and molecular modelling. We also were in the vanguard of UK pharmacy schools to bring in molecular biologists, initially in over-expression and mutagenesis in bacterial vectors, but now including mammalian systems. This move was supported, also in the late 1980s, by increasing our effort in enzyme and protein chemistry and biochemistry. Nucleic acid work in the 1980s and early 1990s was primarily DNA-directed, but recently we have increasingly added RNA as an attractive drug target (several clinically useful antibiotics target RNA

Manchester University's main building on Stopford Road

and there are few, if any, RNA repair mechanisms).

By the mid-1990s it was clear that biological input to drug design would increase. To take this on board we have substantially increased our biological-targets activity, primarily in cancer, by recruiting with MRC support a team of cell, molecular and tumour biologists. This then reinforced our existing collaborations with the Paterson Institute for Cancer Research just up the road, and the school of biological sciences, even closer. Advances in computer power have made further development of molecular modelling essential, and we have just expanded our current strength by adding a computational chemistry group. Many areas of pharmacy will benefit from being in a position to capitalise on the huge computational power and new quantitative methods of the near future. Having such a computation base in the working environs of drug science (kinetics, delivery, distribution, diagnostics as well as drug design) will seed additional applications. All the above developments are still underpinned by strong synthetic chemistry, including organics, peptides, modified oligos and even novel metal complexes.

Pharmacy is a pipeline subject, transferring materials and technology from drug design and discovery right through to human use. Hence all of the above must be translated into molecules suitable for several forms of testing. It is this integrated research philosophy which distinguishes the approach of a school of pharmacy from the individual excellence in any of the contributing fields carried out in a specialist department, such as biochemistry or chemistry. That being said, we profit enormously by working with colleagues in other parts of the scientific community in Manchester and beyond, who can provide specialist expertise and exciting opportunities. For example, while we have in-house mass spectrometry for relatively routine LC-MS and MALDITOF applications, for more demanding applications we work with the departments of chemistry in the University of Manchester and in UMIST. We also have many productive collaborations with the chemistry department. Similarly, for gene therapy work we are closely allied with others in the faculty of medicine and the Paterson Institute. Our collaborators include major universities, institutes and industries in the UK, as well as centres of excellence abroad, for example in the US, Japan, Russia and France.

Within the school the synthetic and biochemical skills in medicinal chemistry have spawned partnerships with drug delivery to

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develop novel molecular diagnostics and delivery systems, resulting in several patents. We have also in the recent past worked with the pharmacokinetics group and Glaxo-Wellcome to look at the molecular features controlling paracellular absorption in the GI tract.

In terms of specific research, we have major programmes in: cancer (supported by MRC, CRC and AICR), cystic fibrosis (CF Trust), and in developing generalised approaches to new molecular materials and methods for diagnostics (with a BBSRC/DTI LINK programme and EPSRC support).

Our established programmes on rational drug design in antiparasitics are primarily against trypanosomes and malaria (Wellcome Trust and WHO). New programmes being established in RNA and ribosomal targets (Wellcome Trust) will rely heavily on our abilities and facilities in high-field NMR and molecular biology, combined with synthesis and computation.

The future looks exciting, as we are equipped and staffed to be in a good position to work with biologists and clinicians on new targets emerging from the various genome projects. However, a clear academic strategy is necessary as lead generation is now clearly well in the hands of the industry with combinatorial and high-through-put screens. Identification and choice of novel targets, some perhaps too 'risky' for commerce, and development of new, general approaches are useful roles for a modern, academic Medicinal Chemistry Centre. Application of the 'medicinal chemist's' skills to new areas, such as novel materials and molecular diagnostics, may be others.•

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treatment-resistant depression, which should be submitted for approval in the first half of 2002.

The discoverers of olanzapine, Drs David Tupper, Terrence Hotten and Nick Moore of Lilly (UK), won the 1999 SMR Award for Drug Design and Discovery (see *SMR newsletter*, January 2000).

Commercial success is not a basis upon which the award is decided, and indeed the winner is normally decided before the drug has matured in the marketplace. Nevertheless, the SMR award winners have generally been drugs of medical importance, as well as significant research achievements. The full list of winners since the award was established includes many substantial milestones in the annals of drug discovery:

- 1983 Mr Peter Doyle (Beecham) *Augmentin;*
- 1985 Dr David Jack (Glaxo) *Salbutamol;*
- 1987 Prof John Stenlake (University of Strathclyde) *Atracurium;*
- 1989 Prof Sir James Black, in association with Dr Albert Crowther and Prof Robin Ganellin (ICI and SK&F) *Beta-blockers* and *H2 antagonists;*
- 1991 Drs Dutta, Furr and Hutchinson (ICI) *Zoladex;*
- 1993 Dr Ken Richardson (Pfizer) *Fluconazole;*
- 1995 Prof Pat Humphrey (Glaxo) *Sumatriptan;*
- 1997 Drs Duncan, Redshaw and Roberts (Roche) *Saquinavir.*

The 2001 SMR award for drug discovery is due to be presented at the SMR Case Histories meeting on 6 December 2001.

Other SMR meetings planned for this year are:

- **Smoking-related Lung Disease (COPD): Prospects for New Drug Therapy**, Wednesday, 14 March 2001;
- **Improving Medicines through Drug Delivery**, Thursday, 5 July 2001;
- **Sodium Channels in Disease**, Thursday, 27 September 2001.

All these symposia are to be held at the National Heart and Lung Institute, Kensington, London. •

SMR Notes

DIARY

8–9 March 2001. Angiogenesis, Paris. Contact: euroconf@pasteur.fr.

25–27 March 2001. Third Junior Academics Meeting on the Molecular Mechanisms of Exocytosis and Endocytosis, Edinburgh. Contact: M.Cousin@ed.ac.uk.

8–11 April 2001. British Neuroscience Association National Meeting, Harrogate. Contact: harrogate2001@bna.org.uk.

1 May 2001. Bench to Bedside: Myocardial Dysfunction. Organised by the Royal Society of Medicine in London. Contact: natalie.barter@rsm.ac.uk.

6–11 May 2001. Thirteenth Noordwijkerhout — Trends in Drug Research, Amsterdam. Contact: timmermn@chem.vu.nl.

9–12 June 2001. Heart Failure 2001, Barcelona. Contact: webmaster@escardio.org.

NEW MEMBERS

Axxima Pharmaceuticals AGU: G. Elben; *University of Bath:* B.V.L. Taylor; *Biofocus Plc:* M.J. Slater; *Centre for Applied Microbiology & Research:* E. Bush; *Glaxo Wellcome:* A. Hall, H. Chaignot, K.S. Jandu; *Synthonics at Greenwich University:* P. Barraclough, W.R. King; Inpharmatica Ltd.: E. Chan; *Eli Lilly & Company:* M.P. Mazanetz; *Prolifix Ltd:* R.J. Williams; *SmithKline Beecham:* S. Aitken, A. Forrest, D. Hamprecht, R.M. Day, P. Brown, R. Novelli, S. Pardoe, S. Rahman, S.J. Ratcliffe.

NEWSLETTER PRODUCTION

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