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LOOKING AHEAD

Highlights of the Society for Medicines Research Symposium held December 2, 2004, in London, United Kingdom.

Trends in Medicinal Chemistry 2004

by Richard E. Armer and Phillip M. Cowley

Summary

On December 2, 2004, the Society for Medicines Research held the seventh *Trends in Medicinal Chemistry* one-day meeting. The meeting brought together speakers from Europe representing both academia and industry and provided an overview of some of the latest approaches being taken in a range of therapeutic areas such as oncology, antiinfectives, CNS disease and reproductive medicine.

The Society for Medicines Research meeting *Trends in Medicinal Chemistry* was held December 2, 2004 in London, United Kingdom. Representatives from nine organizations gathered to discuss some of the latest research in oncology, antiinfectives, CNS disease and reproductive medicine.

CCR5 antagonists for HIV therapy

Dr. Tony Wood (Pfizer, Sandwich, U.K.) gave the opening presentation describing the drug discovery program that led to the identification of **UK-427857**, a prototype CCR5 antagonist with excellent potency against lab-adapted and primary virus strains, as a clinical candidate for the treatment of HIV. Dr. Wood's presentation opened by outlining the medical need for new HIV therapies and the genetic and mechanistic rationale for the use of CCR5 antagonists in HIV treatment.

Screening and analogue testing led to the identification of **UK-107543** (Fig. 1) and provided some initial structure–activity relationship (SAR) information of the series. While UK-107543 displayed high affinity in the MIP-1β radioligand binding assay (IC_{50} 0.6 μM), antiviral activity was found to be poor in early analogues, ascribed at least in part to their lipophilic nature. The SAR information provided through analogue testing suggested that one of the aryl units in UK-107543 could be replaced by an amide, and this strategy, combined with conformational restriction, led to the identification of **UK-382055** (Fig. 1), which showed potent antiviral activity across a number of primary isolates.

Unfortunately, **UK-382055** also showed 99% inhibition of the I_{Kr} channel at 1 μM concentration leading to safety concerns over potential QT_c prolongation. Initial attempts to improve selectivity over I_{Kr} were focused on reducing lipophilicity of the molecule by introducing polar replacements for the cyclobutyl moiety of UK-382055. While this approach successfully reduced activity at I_{Kr}, the resulting compounds suffered from poor permeability and low bioavailability.

Focus returned to a series of triazole analogues, which had earlier been discarded because of poor antiviral activity. Incorporation of aspects of the SAR from the benzimidazole series realized compounds that combined good antiviral activity with acceptable pharmacokinetics. Further optimization led to the identification of **UK-427857** (Fig. 1), a potent antiviral agent with pharmacokinetics consistent with 100 mg b.i.d. dosing. The compound showed an excellent safety profile, and clinical data showed that the compound is able to reduce viral load.

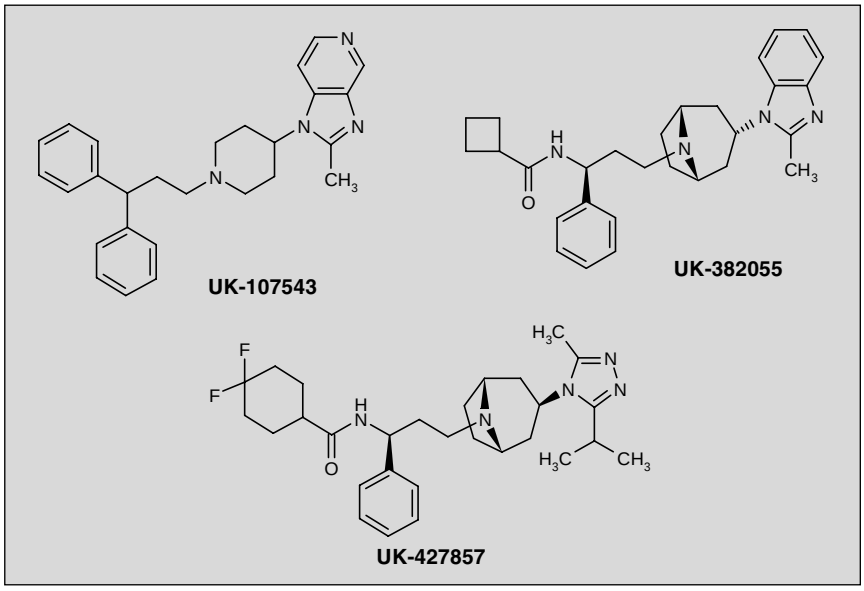


Fig. 1. CCR5 antagonists for HIV therapy.

High-concentration screening: Integrated lead generation

Dr. Jeremy Burrows (AstraZeneca, Alderley Park, U.K.) presented the use of high-concentration screening strategies as an evolving approach in lead generation. High-throughput screening (HTS) at a concentration of 10 μM is an established technology throughout the industry in the search for potent "hits" of a biological target. HTS therefore relies heavily on the quality of the compound collection and relies on the assumption that potent hits are present in the screening collection. Despite the successes of HTS, numerous targets have failed to yield attractive chemical start points.

Dr. Burrows stated that some targets or target classes are labeled "chemically intractable" because either the nature of the target is incompatible with the properties achievable with a drug-like molecule or because there are no potent compounds for that target class in HTS collections. He warned that generalization based on target classification was dangerous, using the identification of small molecule CCR5 receptor antagonists to illustrate his point. Antagonism of the CCR5 receptor involves blocking the interaction of ~7.8 kDa peptide agonists with a seven transmembrane G-protein–coupled receptor, an example of a protein–protein interaction often seen to be impossible to prevent with a small molecule. However, analysis of the receptor identified a pocket that can be occupied by a small molecule, and screening has been successful.

Approaches being taken at the moment include the use of "lead-like libraries" and high-concentration screening. The latter approach relies on finding small, weak binding fragments, ideally with structural information being incorporated. Fragment screening approaches can include biochemical screening (for example, simply using the existing screening assay in high-concentration mode) or biophysical and structure-based methods such as NMR, X-ray, mass spectrometry or surface plasmon resonance. Having identified fragments, optimization may involve fragment linking, fragment merging or fragment growing. Linking two active fragments can have superadditive effects in terms of potency, but is only possible with biostructural data or a great deal of luck.

Analysis of historical data from optimization projects led to three metrics for hits showing a significant difference between hits that led to development candidates and hits that were not optimizable. The recommended metrics for hits or fragments are as follows:

- Potency per atom (pIC_{50}/number of non-H atoms) > 0.2
- Potency difference to clogD (pIC_{50} – clogD) > 2
- Potency difference to human serum protein binding (pIC_{50} – logK) > 1

A high-concentration screening library has been generated within Astra Zeneca by selecting privileged fragments against a range of key target families, in addition to compounds from the building block store and compound collection. These were filtered to remove compounds with clogP > 3.5 or molecular weight > 300 and compounds with undesirable chemical functionality. Inclusion of molecular recognition features and diversity analysis led to a collection of 2,000 compounds (29% acids, 32% neutral, 35% bases and 4% zwitterions). The mean molecular weight of the library was 220, the mean clogP was 1.6, the mean clogD was 0 and the mean polar surface area was 60 A^2. The library is stored at 100 mM in DMSO solution. Use of this screening collection was shown to be yielding benefits in terms of progressible hit fragments across a range of target classes.

8-Fluoroimidazo[1,2-*a*]-pyridine: A versatile core for subtype selective $GABA_A$/BZ receptor ligands

Dr. Alexander Humphries (Merck Sharp and Dohme, Terlings Park, U.K.) described a medicinal chemistry program aimed at developing selective primary γ-aminobutyric acid A/benzodiazepine ($GABA_A$/BZ) receptor ligands as nonsedating anxiolytics. The $GABA_A$ receptor complex incorporates a Cl– ion-channel and plays a crucial role in controlling brain excitability. As with many other ligand-gated ionophores, the structure of the complex is pentameric, generally comprising two α subunits (selected from $\alpha_{1\text{-}6}$), coassembled with two β subunits

(from β_{1-3}) and a single γ subunit (from γ_{1-3}). In addition to the two GABA binding sites, the complex possesses a number of allosteric receptors that modulate the effect of GABA binding. Therapeutically, the most important of these is the site of action of classical BZs such as **diazepam**. This "BZ receptor" is expressed on $GABA_A$ complexes in situations where an α_1, α_2, α_3 or α_5 unit is interfaced with a γ_2 unit. Hence, the four subtypes of the BZ receptor are named after their α subunit.

Diazepam is well known for its potent anxiolytic and anticonvulsant properties, although these are accompanied by side effects such as memory loss and sedation. All of these properties are the result of nonselective agonist activity at all four α subtypes of the BZ receptor, and it is only recently that transgenic and pharmacological advances have provided insights into the functional differentiation of the subtypes. For example, it is now generally accepted that agonist activity at α_1 receptors is the principal cause of sedation, although the contribution of α_2- versus α_3-containing BZ receptors to the anxiolytic and anticonvulsant activity of diazepam has been the subject of some controversy.

The aim of the project was to maximize α_2 and/or α_3 activity while removing α_1 and α_5 activity to minimize sedative and cognitive side effects, respectively. The lead for the project was a competitor compound, **NS-2710** (Fig. 2), which displays anxiolysis in a rat model but with a narrow window over sedative side effects because of high affinity and moderate efficacy at α_1 receptors. Modification of the core heterocycle in NS-2710 and further optimization led to compound **[1]** (Fig. 2), which displayed high affinity for both α_1 and α_3 receptors. Importantly, while the compound showed good efficacy at α_3 receptors, it displayed no positive efficacy at α_1 receptors. This selective efficacy strategy was employed to avoid sedative side effects. Unfortunately, compound [1] and other analogues from this imidazopyridine series showed high clearance and low bioavailability.

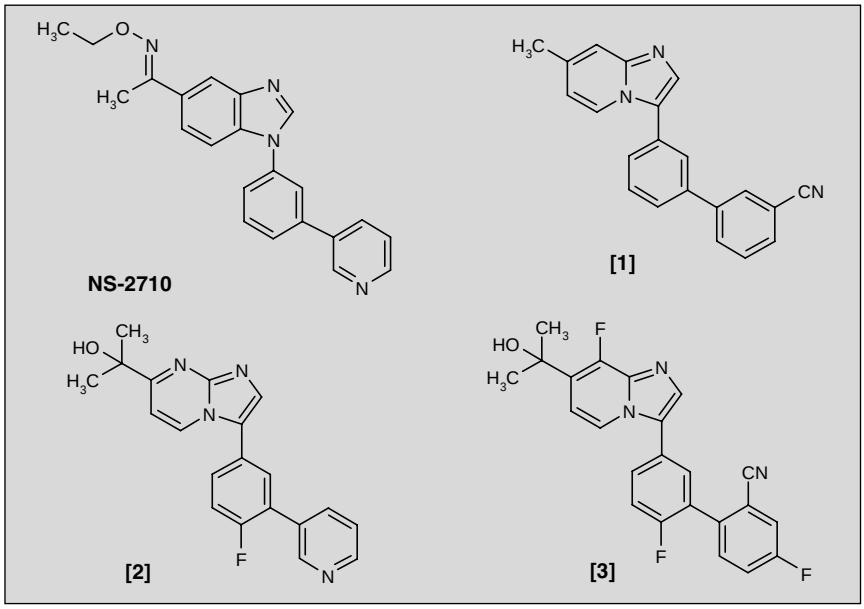


Fig. 2. $GABA_A$ BZ site receptor partial agonists.

Replacement of the imidazopyridine core in compound **[1]** with an imidazopyrimidine and optimization led to the identification of compound **[2]** (Fig. 2). Again, the compound showed high affinity for α_1 (K_i = 1.4 nM) and α_3 (K_i = 4.0 nM) receptors with 6% and 57% efficacy, respectively, consistent with the selective efficacy strategy. The compound had an acceptable pharmacokinetic profile, but further improvement was sought.

Exploration of an 8-fluoroimidazopyridine core led to the identification of compound **[3]** (Fig. 2), which maintained selective efficacy for the α_3 receptor and had an excellent pharmacokinetic profile. The compound served as a useful tool to probe the significance of α_3 receptors in anxiolysis. Compound [3] was shown to induce anxiolytic-like effects in the rat plus maze and similar effects to diazepam in a squirrel monkey CER paradigm. These results demonstrated that a selective α_3 agonist acts as a potent anxiolytic, contrary to the conclusions drawn from previously published experiments with transgenic mice, which suggested that α_2 agonist activity was essential for anxiolysis.

Hedgehog proteins and the foundation of small molecule modulators

Dr. Andy Boyd (Evotec OAI, Abingdon, U.K.) presented the discovery of small molecule modulators of hedgehog (Hh) proteins. The Hh family of proteins play an essential role in embryonic development. There are a series of protein ligands for the receptor including: Sonic (SHh), Indian (IHh) and Desert (DHh), which show very high interspecies homology from species as diverse as *Drosophila* and man. The Hh protein receptor, Patched-1 (Ptch-1), is a transmembrane protein with a structure reminiscent of that found in ion channels. Ptch-1 inhibits Smoothened (Smo), a receptor structurally similar to G-protein–coupled receptors. Upon binding of an Hh protein ligand to Ptch-1, the normally inhibited Smo is disinhibited, and it activates the nuclear transcription factor Gli-1 via a signaling cascade.

The three Hedgehog ligands, SHh, IHh and DHh, are morphogens that have different roles in embryogenesis.

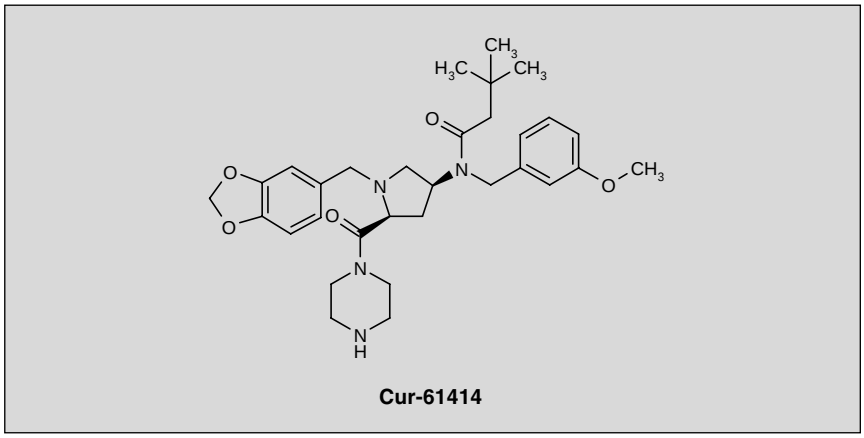


Fig. 3. Small molecule modulator of hedgehog proteins.

Thus, IHh affects cartilage and bone development, SHh influences neuronal development in the CNS and DHh regulates peripheral neuronal development.

Mutations that activate the Hh pathway produce basal cell carcinoma and medulloblastoma, a cancer that is rare but invariably fatal. In addition, Hh proteins are overexpressed by and stimulate proliferation of tumor cells in pancreatic and gastrointestinal tumors.

The Hh pathway is essential for the formation of normal nerves in the central and peripheral nervous system. It has been shown that treatment with an Hh protein accelerates the restoration of nerve function in models of trauma and disease. This indicates that the Hh pathway may have a potential therapeutic effect in treating certain neurological disorders (e.g., stroke, Parkinson's disease, spinal cord injury and diabetic neuropathy). While two complex natural products, jervine and cyclopamine, act upon the Hh pathway, tractable, small molecule modulators of this pathway have been lacking.

HTS using a cell-based reporter assay was initiated at Curis with the aim of identifying Hh antagonists. This led to the identification of several classes of antagonists including amino prolines (WO 2001026644) and quinazolinones (WO 2001019800), which have been the subject of patent applications.

Optimization of the amino proline series led to the identification of **Cur 61414** (Fig. 3) as a development compound. Efficient enentioselective routes have been established and all four possible stereoisomers profiled. Compounds with *cis*-stereochemistry were found to be much more active than *trans*-oriented compounds.

6-Position–substituted tetrahydroquinolines: Potent antagonists for the FSH receptor

Dr. Nicole van Straten (NV Organon, Oss, the Netherlands) introduced Organon's follicle-stimulating hormone (FSH) receptor antagonist program and its potential use as a new method of oral contraception. FSH belongs to the gonadotropins, a class of glycoprotein hormones involved in human reproduction. Stimulation of the G-protein–coupled FSH receptor leads to the production of estradiol, which in turn plays a pivotal role in oocyte maturation. On the other hand, inhibition of the FSH receptor will disturb follicle development and thus prevent ovulation. It is anticipated, therefore, that low-molecular-weight antagonists for the FSH receptor may yield a promising new method of nonsteroidal oral contraception devoid of CNS side effects.

6-Amino–substituted tetrahydroquinolines were identified from an agonist HTS approach aimed at identifying oral FSH agonists for use in IVF cycles. Simple substitution of the 6-amino group gave 6-amino–substituted tetrahydroquinolines with antagonistic activity for the FSH receptor that are capable of inhibiting the signal transduction pathway of the FSH receptor, with potencies in the micromolar to nanomolar range. The compounds were not, however, competitive with FSH in binding experiments. A representative example, **Org-43260** (Fig. 4), was further profiled in proof-of-principle assays.

Org-43260 inhibits the FSH receptor on a rat granulosa cell line and shows inhibition of follicle growth in an *ex vivo* mouse follicle culture assay. It was established that FSH receptor antagonistic activity resided in one enantiomer. Finally, Org-43260 showed a reasonable bioavailability after oral administration in the rat (50 mg kg^{-1}) of 19%, was negative in an

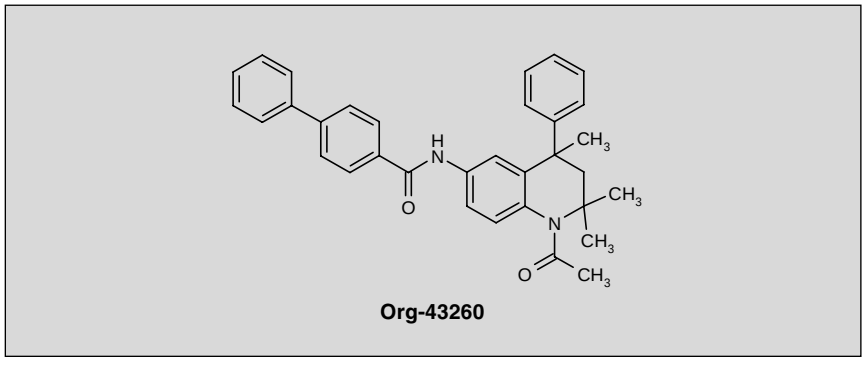


Fig. 4. Antagonist for the follicle-stimulating hormone receptor.

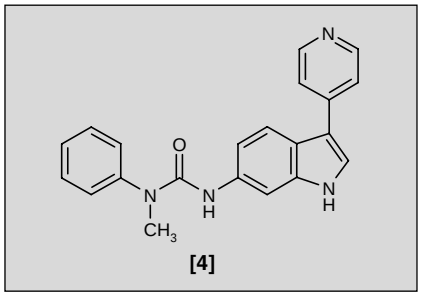
Ames test and showed little or no off-target activity in the NovaScreen panel.

Design of novel IMPDH II inhibitors

Dr. Andy Ratcliffe (UCB Pharma, Granta Park, Cambridge, U.K.) presented UCB's approach to identifying potent and orally available inhibitors of Inosine 5′-monophosphate dehydrogenase II (IMPDH II) for the treatment of autoimmune diseases. IMPDH is a key enzyme in the *de novo* synthesis pathway of guanine nucleotides. Two isoforms of the enzyme have been identified and designated type I and type II. Proliferating cells depend heavily on continued access to a pool of guanine nucleotides, and in order to meet this demand IMPDH II is upregulated.

Mycophenolic acid (MPA) is a potent, uncompetitive reversible inhibitor of both IMPDH I and II, which in the form of a prodrug is approved for transplant rejection. However, the reported gastrointestinal toxicity of MPA has resulted in the search for alternative IMPDH II inhibitors with improved therapeutic windows for treatment in autoimmune diseases such as psoriasis, systemic lupus erythematosus and rheumatoid arthritis.

Toward this end, several oxazole-based IMPDH II inhibitors have been reported and progressed to clinical studies. The approach initially taken at UCB was to utilize oxazole leads from the literature such as **VX-497** and **BMS-337197** as chemical start points and to try and introduce different scaffolds into the conserved oxazole structures seen in these two compounds. This approach was successful; however, it soon became apparent that there was a potential liability in the oxazole group of these compounds, as they lead to oxidative glutathione conjugates both *in vitro* and *in vivo*, presumably via formation of a reactive intermediate oxazole product. The project then switched to identify nonoxazole-based inhibitors using a high-concentration (50 μM) fragment screening approach. Soluble designed fragments were screened and the 4-pyridyl group identified as a potential oxazole replacement. Subsequent optimization led to indole **[4]** (Fig. 5) with 84 nM inhibition of IMPDH II and good drug likeness characteristics. Unfortunately, this compound and close analogues were shown to be potent inhibitors of CYP3A4, preventing their further progression.



[4]

Fig. 5. Novel inosine 5′-monophosphate dehydrogenase II inhibitor.

ROCK and Rho'll—From focused library to Rho-kinase inhibitors

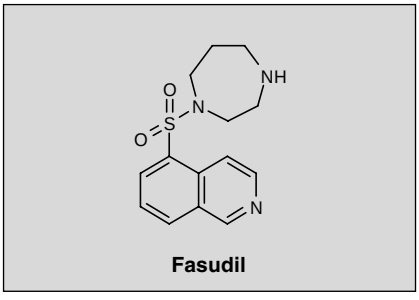
Dr. Roger Crossley (Biofocus, Saffron Walden, U.K.) gave and eloquent overview of Biofocus' approach to identifying Rho kinase inhibitors. Rho kinase α (ROK, ROCK2) is a serine/threonine kinase that is activated by association with the small GTP-binding protein Rho. ROK is implicated in the pathogenesis of a number of indications. *In vitro* and *in vivo* studies with first-generation ROK inhibitors have shown beneficial effects in models of cardiovascular disease, stroke, cancer, glaucoma, erectile dysfunction, and nerve growth and repair. **Fasudil** (Fig. 6), a kinase inhibitor with some selectivity for ROK, is marketed in Japan by Asahi Kasei for the treatment of vasospasm and has recently been shown to be effective in the treatment of stable angina in clinical trials with a relatively low side effect profile. Inhibition of ROK, therefore, has a multiplicity of potentially useful therapeutic outcomes with no apparent target-related safety issues in humans and hence is an increasingly interesting therapeutic target.

Biofocus has for a number of years now been producing and marketing focused screening libraries directed at kinases. Use of such libraries provides a highly cost-effective and efficient means of developing lead series following screening exercises. A selection of these libraries were identified as having the potential to hit Rho-kinase and were screened *in vitro*. Hits were identified and an optimization program undertaken at Biofocus. **BF-66852** (K_i ROKα = 80 nM) demonstrated good selectivity over related kinase targets and excellent selectivity over a broad screening selectivity panel of targets. The series possesses good physicochemical properties and demonstrated oral exposure in animal PK models. Patents from this work are due to be published in early 2005.

Multiple 5-HT approaches to novel antidepressants

Dr. Simon Ward (GlaxoSmithKline, Harlow, U.K.) gave a review of GlaxoSmithKline's approaches to identifying more rapidly acting antidepressants by combining 5-HT_1 activity with activity at the serotonin transporter. Extensive preclinical and clinical data links the enhancement of serotonergic neurotransmission with the antidepressant action of both the newer class of selective serotonin reuptake inhibitors (SSRIs) as well as the older classes of monamine oxidase inhibitors and tricyclic antidepressants.

Considerable research has also been carried out to investigate other 5-HT targets associated with depression, and studies involving combination treatments with selective serotonin reuptake inhibitors and 5-HT_1 receptor ligands have been carried out in the



Fasudil

Fig. 6. A kinase inhibitor with some selectivity for ROK.

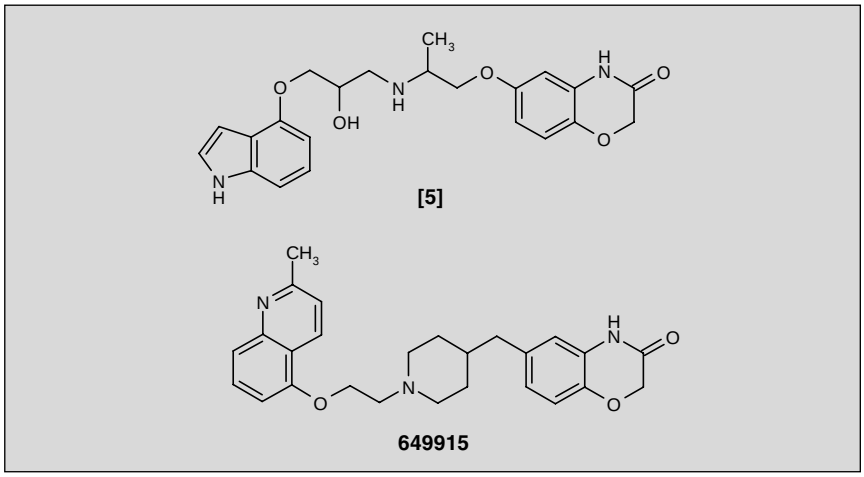


Fig. 7. Antidepressants combining 5-HT_1 activity with activity at the serotonin transporter.

clinic. The ongoing hypothesis is currently that the relatively long period of onset of action of SSRIs (3–4 weeks) is driven by initial counterproductive activation of 5-HT_1 subtypes due to excess levels of 5-HT produced by SSRI action. This activation gives rise to reduced 5-HT–mediated cell firing and also 5-HT release, which is reversed upon receptor desensitization following chronic SSRI use, giving rise to the delayed efficacy. The aim of this approach, therefore, was to build various compounds with SSRI and differing 5-HT_1 activities to give a new equally efficacious antidepressant with more rapid onset of action.

Starting from the HTS hit **[5]** (Fig. 7) with affinity for the 5-HT_{1A} receptor, a chemical series was developed that displays a range of affinities across the 5-HT_1 receptor subtypes and the serotonin transporter. Compound [5] had good potency at the 5-HT_{1A} (pK_i 9.1) receptor and serotonin transporter (SERT; pK_i 7.3) but also had unwanted high affinity for the β_2 receptor (pK_i 9.2). Removal of the chiral centers in compound [5] yielded a compound with good selectivity over β_2 while retaining activity at 5-HT_{1A} and SERT. Incorporation of a piperidine spacer group gave compounds with similar activity profiles, but the metabolic stability was poor because of rapid oxidation mediated by aldehyde oxidase. Subsequent optimization led to **649915** (Fig. 7) with pK_is of 8.6, 8.0 and 8.8 against 5-HT_{1A}, B and D, respectively, and pKi of 8.2 at SERT. 649915 demonstrated 40% oral bioavailability in the rat, penetrated the brain and demonstrated inhibitory activity in a 5-HT_{1A} agonist-induced hyperlocomotion model in the rat when dosed orally at 10 mg/kg. In an animal social interaction study, 649915 showed more rapid onset of action (7 days) than SSRIs (21 days) when dosed orally at 1 and 3 mg/kg. Subsequent SAR work identified other compounds with interesting profiles worthy of further investigation such as 7-fluoro and 7-chloro 649915, which retain good potency at 5-HT_{1A} and SERT, have good oral bioavailability and improved half-life over 649915 but are now selective (ca. 100-fold) over 5-HT_{1B} and 5-HT_{1D} receptors.

Steroid sulfatase inhibitors

Prof. Barry Potter (Sterix, Ipsen and University of Bath, U.K.) gave the final presentation of the day with an exciting discussion of the discovery and initial human activity of **STX-64** (Fig. 8) in multidrug-resistant breast cancer. Breast carcinoma is the most common form of female cancer. Many breast tumors are initially hormone-dependent, with estrogens playing a pivotal role in supporting their growth and development. An established form of intervention for women with hormone-dependent breast cancer (HDBC) is to treat with antiestrogens or aromatase inhibitors. Although these antiendocrine agents are proven to be effective in general, there is increasing evidence to suggest that a concomitant inhibition of steroid sulfatase (STS), which converts estrone (E1) sulfate to E1 and also dehydroepiandrosterone (DHEA) sulfate to DHEA, will further attenuate estrogenic stimulation in HDBC. Sterix discovered **E1-3-*O*-sulfamate** (EMATE) as the first potent, orally active, irreversible STS inhibitor, but the compound is highly estrogenic in rodents. Sterix therefore designed and synthesized nonsteroidal and nonestrogenic candidates showing comparable or even superior potency. A series of tricyclic sulfamates was produced whose SARs led to the discovery of the promising **STX-64** (667COUMATE), which inhibits STS activity in a time- and concentration-dependent manner with an IC_{50} of 8 nM and behaves as an active site-directed inhibitor. *In vivo*, administration of STX-64 inhibited rat liver STS activity by 93% (10 mg/kg, p.o.) and E1S-stimulated growth of uteri in ovariectomized rats, and caused regression of E1S-stimulated tumor growth in an NMU-induced mammary tumor model in a dose-dependent manner. Importantly, in contrast to EMATE, STX-64 was nonestrogenic.

STX-64 showed no significant and irreversible toxic effects in rats, and when administered orally had a bioavailability of 95%. This latter finding is attributed to the protection of STX-64 from metabolic degradation through sequestration into red blood cells as a result of binding to carbonic anhydrase

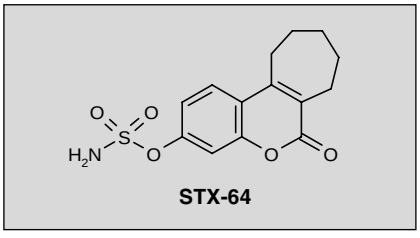


Fig. 8. Steroid sulfatase inhibitor.

II. STX-64 is the first STS inhibitor to enter clinical trial for treating postmenopausal women with HDBC and appears to be well tolerated as a potent inhibitor of STS activity, as measured in peripheral blood lymphocytes or in tumor tissue samples. Preliminary phase I trial results indicate that inhibition of STS constitutes a promising additional form of antiendocrine therapy for the treatment of HDBC, with early results indicating efficacy in both tamoxifen- and aromatase-resistant patients.

Conclusion

This was the seventh Trends in Medicinal Chemistry Meeting organized by the Society for Medicines Research. The meeting proved again to be a popular one, with nine different organizations represented. The range of topics gave an interesting perspective into the diversity of research and into the research strategies adopted within the various organizations. The meeting is available in a webcast format at the following URL: http://www.prous.com/trends04.

Richard E. Armer and Phillip M. Cowley are Conference Organizers and Committee Members of the Society for Medicines Research. The SMR Committee organizes conferences on behalf of the Society for Medicines Research four times a year. SMR symposia focus on research related to the discovery and development of new medicines and are usually held in London. Details about forthcoming meetings can be obtained from the SMR website: www.smr.org.uk or from: SMR Secretariat (secretariat@smr.org.uk).

TAK-652 SHOWS POTENT *IN VITRO* ANTI-HIV-1 ACTIVITY AND A SAFE PROFILE IN HUMANS

Scientists from Takeda have synthesized and tested a novel, small-molecule, orally available chemokine CCR5 antagonist **TAK-652**. This compound prevented the binding of RANTES, MIP-1α and MIP-1β to CCR5-expressing cells (IC_{50} = 3.1, 2.3 and 2.3 nM, respectively), blocked the binding of MCP-1 to CCR2b-expressing cells (IC_{50} = 5.9 nM), showed slight inhibition of ligand binding to CCR3- and CCR4-expressing cells and had no effect on ligand binding to CCR1- and CCR7-expressing cells. It inhibited the replication of R5 HIV-1 laboratory strains and six R5 HIV-1 clinical isolates, including reverse transcriptase- and protease inhibitor-resistant mutants in PBMCs (EC_{50} = 0.061 and 0.25 nM, respectively). TAK-652 was also effective against recombinant HIV-1 strains with seven different subtypes (A-G) of envelope protein (IC_{50} = 1.0 nM), while the addition of human serum decreased its activity five-fold. A double-blind, placebo-controlled, single oral dose (25–100 mg) study in healthy male volunteers demonstrated that TAK-652 was effectively absorbed, safe, well tolerated and reached plasma concentrations of 7 ng/ml 24 hours after administration (25 mg). A notable pharmacological profile and potent anti-HIV activity indicate that TAK-652 is a promising therapeutic candidate that could prevent HIV entry.

TAK-652 was also analyzed for its interactions *in vitro* with other antiretroviral drugs including zidovudine, lamivudine, efavirenz, indinavir and enfuvirtide (T-20). Single drugs or combinations of drugs were added to PBMCs infected with two different HIV-1 R5 clinical isolates, followed by 7-day incubation and measurement of HIV-1 p24 antigen at the end of the treatment. The analysis of data indicated that firstly, TAK-652 produced no toxicity in PBMCs at concentrations as high as 100 nM. Secondly, it was very effective against both HIV-1(R5-01) and HIV-1(R5-18) isolates (IC_{50} = 0.17 and 0.44 nM, respectively). Finally, TAK-652 produced favorable interactions with already existing antiretroviral agents, and combination indices indicated the presence of synergistic or additive actions. The researchers hope to advance TAK-652 into clinical evaluation.