

MEETING REPORTS

*Highlights of the Society for Medicines Research Symposium
held December 8, 2005, in London, United Kingdom.*

Recent Disclosures of Clinical Drug Candidates

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Dr. Robert Carling (Merck Sharp and Dohme, Harlow, UK) gave the opening presentation at the Society for Medicines Research meeting held December 8, 2005, in London, United Kingdom. He described the drug discovery program that led to the identification of a selective GABA_A $\alpha_2\alpha_3$ binding site agonist clinical candidate for the treatment of anxiety.

γ -Aminobutyric acid (GABA) is the major inhibitory transmitter in the CNS, and its inhibitory action is mainly mediated through the GABA_A receptor complex, which incorporates a Cl⁻ ion channel. As with many other ligand-gated ionophores, the structure of the complex is pentameric, generally comprising two α -subunits (selected from α_{1-6}), co-assembled with two β -subunits (from β_{1-3}) and a single γ -subunit (from γ_{1-3}). In addition to the two primary GABA binding sites, the complex possesses a number of allosteric receptors that modulate the effect of

Summary

On December 8, 2005, the Society for Medicines Research held a one-day meeting in London, United Kingdom, entitled *Recent Disclosures of Clinical Drug Candidates*. The meeting brought together speakers from Europe representing the pharmaceutical industry and provided an overview of some of the latest approaches being taken in a range of therapeutic areas such as oncology, inflammation, CNS disease and reproductive medicine. © 2006 Prous Science. All rights reserved.

GABA binding. Therapeutically, the most important of these is the site of action of classical benzodiazepines such as **diazepam**. This “benzodiazepine (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 differenti-

ation 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. 1), which displays anxiolysis in a rat model but with a narrow window over sedative side effects due to high affinity and moderate efficacy at α_1 receptors. Modification of the core heterocycle in NS-2710 and further optimization led to compound

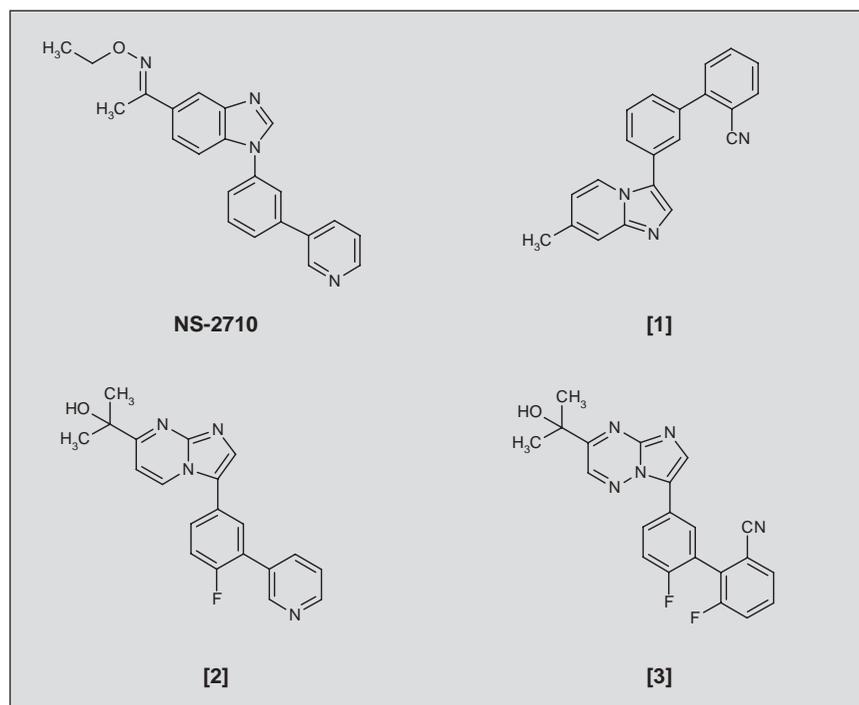


Fig. 1. GABA_Aα₂/α₃ binding site agonists.

[1] (Fig. 1), which displayed high affinity for both α₁ and α₃ receptors. Importantly, while the compound showed good efficacy at α₃ receptors, it displayed no positive efficacy at α₁ receptors. This selective efficacy strategy was employed to avoid sedative side effects. Unfortunately, **[1]** and other analogues from this imidazopyridine series showed high clearance and low bioavailability.

Replacement of the imidazopyridine core in **[1]** with an imidazopyrimidine and optimization led to the identification of compound **[2]** (Fig. 1). Again the compound showed high affinity for α₁ (K_i = 4.5 nM) and α₃ (K_i = 3.6 nM) receptors with 0% and 54% efficacy, respectively, consistent with the selective efficacy strategy. The compound had an acceptable pharmacokinetic profile, but further improvement was sought.

Exploration of an imidazotriazine core led to the identification of compound **[3]** (Fig. 1), which maintained selective efficacy for the α₃ receptor and had an excellent pharmacokinetic profile. The compound served as a

useful tool to probe the significance of α₃ receptors in anxiolysis. Compound **[3]** was shown to induce anxiolytic-like effects in the rat plus maze and similar effects to diazepam in the conditioned emotional response test of anxiolytic activity using the squirrel monkey. The results demonstrated that a selective α₃ agonist acts as a potent anxiolytic, contrary to the conclusions drawn from previously published experiments with transgenic mice, which suggested that α₂ agonist activity was essential for anxiolysis. The compound was selected as a clinical candidate and showed a clean profile in toxicology studies. First-in-human studies indicated reasonable oral exposure, and at a single dose of 1.5 mg in a PET study, 50% receptor occupancy in the brain was observed 24 hours postdose.

Novel pyrimidine cannabinoid CB₂ receptor agonists for the treatment of inflammatory pain

Dr. Gerard Giblin (GlaxoSmithKline, Harlow, UK) presented GlaxoSmithKline's CB₂ receptor agonist program aimed at the treatment of

inflammatory pain. The CB₂ receptor is one of two G-protein-coupled receptor-based cannabinoid receptors. The CB₁ receptor is present mainly in the CNS, whereas the CB₂ receptor is found predominantly in the periphery on inflammatory cells. The aim of the program was to identify potent and selective full agonists of the CB₂ receptor for the treatment of pain associated with osteoarthritis and rheumatoid arthritis with good selectivity over CB₁ receptors to avoid any psychoactive side effects. The efficacy of the candidate should be at least as good as cyclooxygenase-2 inhibitors but with GI/CV safety advantages and suitable for once- or twice-daily dosing.

The initial screening hit, **173271X** (Fig. 2), was a 1.2 μM partial agonist (52% efficacy) with good selectivity over CB₁ receptors. Replacement of the labile ester group and the potentially metabolically labile furan lead to analogues with almost full agonist efficacy and potency in the 50 nM range exemplified by **GW-833972X** (Fig. 2; CB₂ EC₅₀ = 60 nM [94% intrinsic activity], CB₁ EC₅₀ > 10,000 nM). **GW-833972X** also demonstrated 30% bioavailability in the rat but with a high clearance level and low half-life (0.8 h). It inhibited Freund's complete adjuvant-induced hypersensitivity and paw edema at 3 mg/kg i.p. in the rat but was also a potent inhibitor of multiple CYP450s *in vitro* at less than 1 μM.

Further optimization of **GW-833972X** to improve the absorption, distribution, metabolism, excretion and toxicology properties produced **GW-842166X** (Fig. 2), which is a potent, highly selective and full agonist of the CB₂ receptor (CB₂ EC₅₀ = 50 nM [96% intrinsic activity], CB₁ EC₅₀ > 30,000 nM). The compound had 25–60% bioavailability in both rats and dogs, which was formulation dependent because of low solubility issues and clearance values of <10% of liver blood flow rate in both species, giving rise to half-lives of 3 and 10 hours in the rat and dog, respectively. **GW-842166X** showed

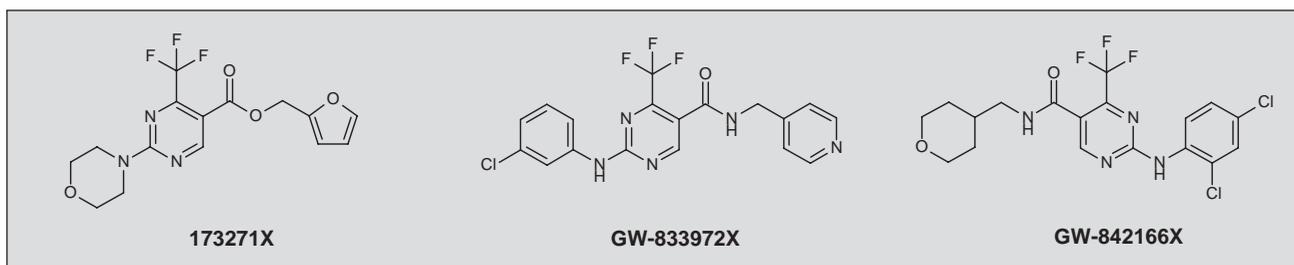


Fig. 2. Novel pyrimidine cannabinoid CB₂ receptor agonists.

potent analgesic activity in reversing established FCA-induced hyperalgesia with an ED₅₀ of 0.1 mg/kg p.o. (full reversal at 0.3 mg/kg p.o.), and this effect was not lost upon chronic dosing for 5 days at 1 mg/kg p.o. t.i.d. The compound is currently in phase I studies.

Small-molecule NEP inhibitors for the treatment of sexual dysfunction

Dr. David Pryde (Pfizer, Sandwich, UK) described a medicinal chemistry program aimed at developing selective neutral endopeptidase inhibitors for the treatment of female sexual arousal disorder. Rapidly acting compounds with short half-lives suitable for *prn* dosing were the objective of the program. Potent, mono-carboxylic acid small-molecule (Target MW < 400, logD -0.5 <> +1) glutaramide inhibitors based on the existing Pfizer compound **candoxatrilat** (Fig. 3) were optimized to **UK-414495** (Fig. 3). This compound exhibited all the desired properties, with excellent selectivity over other related endopeptidases and an EC₅₀ value of 36 nM in a rabbit *in vivo* model of genital blood flow. Rat PK showed rapid absorption and low clearance. The compound was predict-

ed to have a bioavailability of 80% to 100% and half-life of 4–20 hours in humans, with an efficacious dose of 75 mg; however, unacceptable toxicity in dogs due to putative formation of reactive acyl glucuronide intermediates was observed.

The formation of acyl glucuronide metabolites of **UK-414495** was confirmed in a hepatocyte study, with higher levels being observed in the dog. The acyl glucuronide metabolite of UK-414495 was also shown to be very unstable because of intramolecular cyclization occurring to give cyclic imide intermediates and respective breakdown products. This property of UK-414495 was attributed to the relatively low pK_a of the amide NH, and new analogues with nonaromatic amide substituents were identified with a higher pK_a and improved acyl glucuronide stability. Of these analogues, **UK-447841** (Fig. 3) was selected as a replacement clinical candidate. UK-447841 showed excellent selectivity over other related endopeptidases and an EC₅₀ value of 3.6 nM in a rabbit *in vivo* model of genital blood flow. Rat PK showed rapid absorption and low clearance and it was predicted to have a bioavailability of 70% and a

half-life of 3–12 hours in humans, with an efficacious dose of 25–100 mg. First-in-human studies showed high levels of oral exposure and linear kinetics with 3–800 mg doses. Absorption was rapid (T_{max} < 1 h) and half-life of 7–10 hours.

Discovery of a novel series of potent, orally active histamine H₃ receptor antagonists

Dr. David Wilson (GlaxoSmithKline, Harlow, UK) described the discovery of a new antagonist chemotype for the histamine H₃ receptor. The H₃ receptor is one of four histamine receptors and is highly expressed in cognitive areas of the brain. H₃ antagonists have been demonstrated to enhance cognition in a number of preclinical rodent models and thus have potential for the treatment of a number of CNS diseases such as dementia. The early prototypical H₃ antagonists contained a histamine moiety that led to a number of developability issues (Fig. 4A). More recently, several nonimidazole H₃ antagonists have started to appear in the literature (Fig. 4B).

Following a focused screen based on the phenoxypropyl amine pharma-

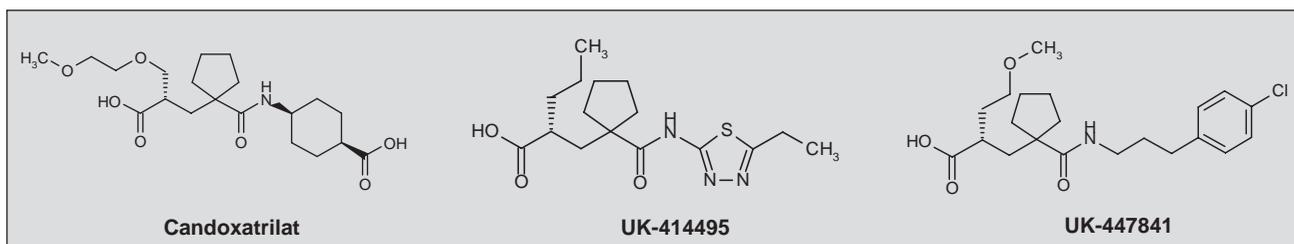


Fig. 3. Small-molecule NED inhibitors.

cophore, compound [4] (Fig. 4C) was identified as a novel H₃ lead. Conformational restraint led to the identification of [5] (Fig. 4C). The observation that, in contrast to the known phenoxypropyl-containing H₃ antagonists, the propyl amine side chain could be extended led to the hypothesis that the molecule might be binding in a reverse mode. To test this hypothesis, [7] (Fig. 4C) was synthesized and was indeed a potent novel H₃ chemotype.

Utilizing an *in vivo* screening cascade that consisted of a pharmacody-

namic model (RAMH-induced drinking assay) and cortical *ex vivo* binding led to the identification of **GSK-189254** (Fig. 5). Important structure-activity relationship findings to emerge from this work were that the cyclobutyl moiety was critical for high potency and that the left-hand side of the molecule could be utilized to obtain the desired physicochemical properties that were essential for robust *in vivo* performance.

GSK-189254 demonstrates robust performance in a number of cognition

models. Microdialysis studies have also demonstrated that the compound increases histamine levels in the brain.

Sugammadex: The first selective relaxant binding agent for reversal of neuromuscular block

Dr. Ton Bom (Organon, Newhouse, Scotland) presented an excellent lecture on **sugammadex** (Org-25969) (Fig. 6), the first selective relaxant binding agent for the reversal of neuromuscular block. **Tubocurarine** was introduced in 1944 as the first neuro-

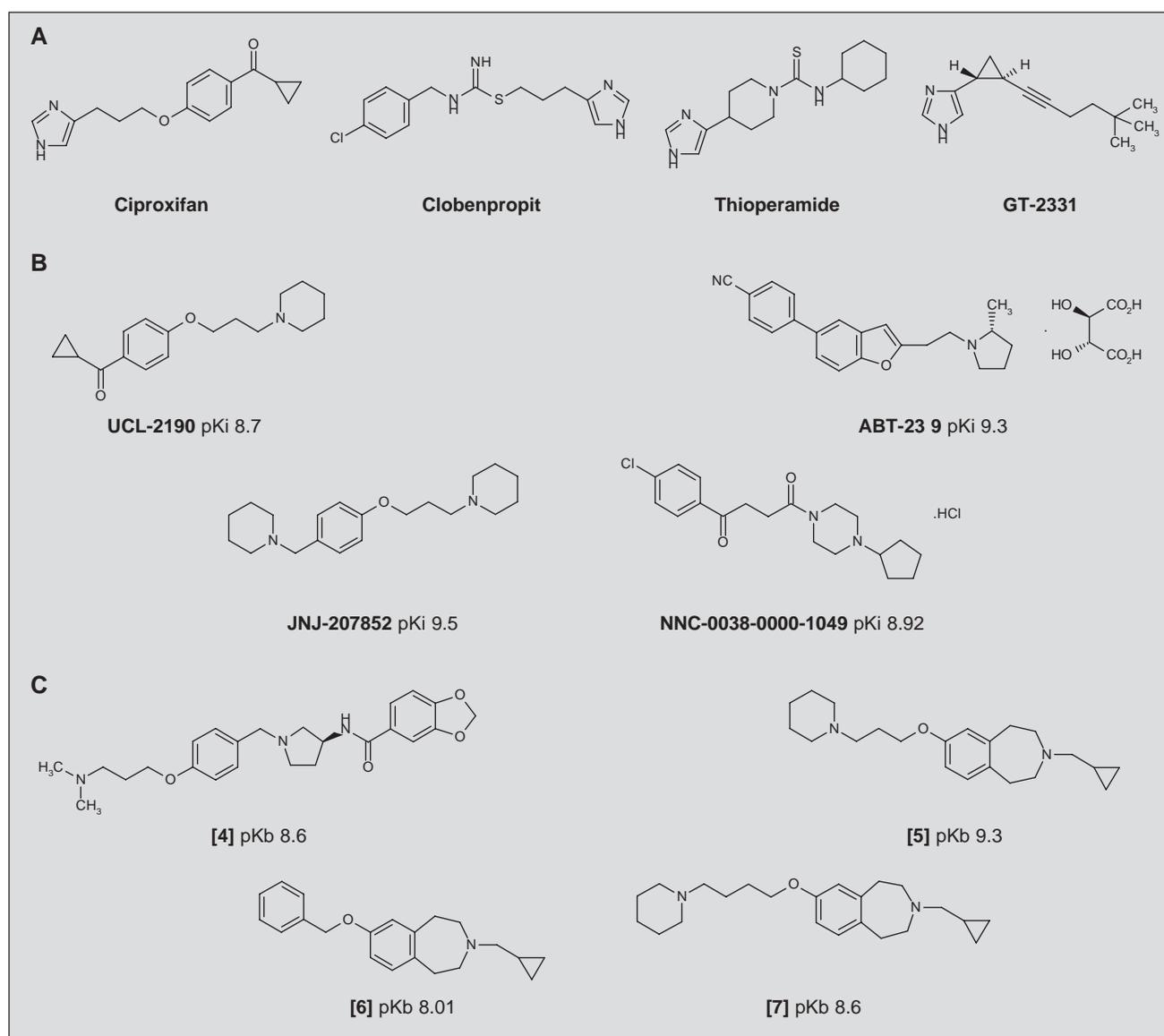


Fig. 4. H₃ antagonists developed before and after 1999. **A.** Prototypical H₃ antagonists pre-1999. **B.** Nonimidazole antagonists post-1999. **C.** Novel H₃ leads.

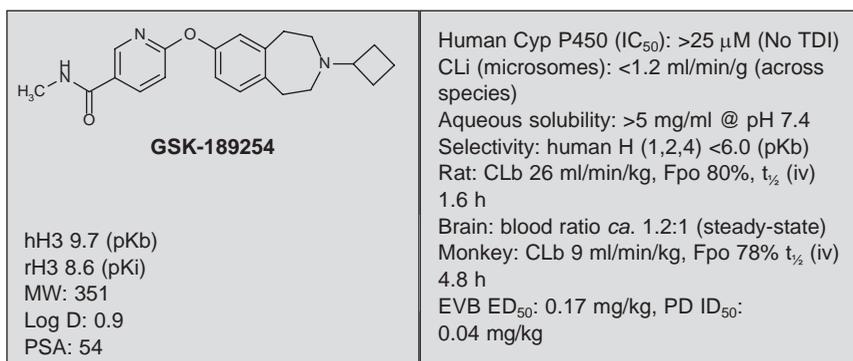


Fig. 5. H₃ antagonist.

muscular blocking agent, and since this time there has been a great deal of interest in identifying nondepolarizing muscle relaxants that display a short duration of action and lack cardiovascular and pulmonary side effects. Despite this interest, progress to these newer agents has been somewhat limited. Traditionally, acetylcholinesterase inhibitors, often in combination with muscarinic antagonists, are employed. These approaches have a major limitation, however, in that they can only be employed once spontaneous recovery from the neuromuscular block has started. Not only are these approaches ineffective at profound muscle block, but they also raise acetylcholine levels in the heart, airways and intestinal tract.

Following an observation from an *in vitro* tissue bath experiment in 1997, it was discovered that steroidal neuromuscular blocking agents (**rocuronium**, Fig. 7; **vecuronium**) could be dissolved in cyclodextrins. Cyclodextrin provides a cavity for the hydrophobic part of the steroid and thus increases its aqueous solubility.

This led to the hypothesis of a cyclodextrin that could completely encapsulate the blocker, thus removing it from the systemic circulation and resulting in an instantaneous reversal of muscle block. A large number of modified cyclodextrins were designed and synthesized, followed by extensive *in vitro* and *in vivo* testing.

Initial work focused on optimizing the cyclodextrin ring size, which led to the identification of the eight-membered cyclodextrin as being most optimal. The initial result prompted postulation that although the steroidal part of **rocuronium** fit well into the cavity of the γ -cyclodextrin, the cavity was not deep enough to fully encapsulate the hydrophobic portion or the charged amine moiety. The later part of the design phase focused on derivatization of the sugar side chains in order to incorporate negatively charged groups that would be able to complex with the charged amine. From the synthesis and screening of more than 200 modified cyclodextrins, **Org-25969** was identified.

Following intravenous infusion, **sugammadex** causes a rapid complexation of **rocuronium** in the blood. This complexation leads to a concentration resulting in rocuronium entering the blood from the surrounding tissue. Data obtained from the clinic indicate complete recovery from rocuronium-induced neuromuscular block within 3 minutes (the spontaneous recovery time is ~50 min). Data presented from the phase II studies demonstrate that even very profound muscle block can be rapidly reversed. Importantly, sugammadex is also very

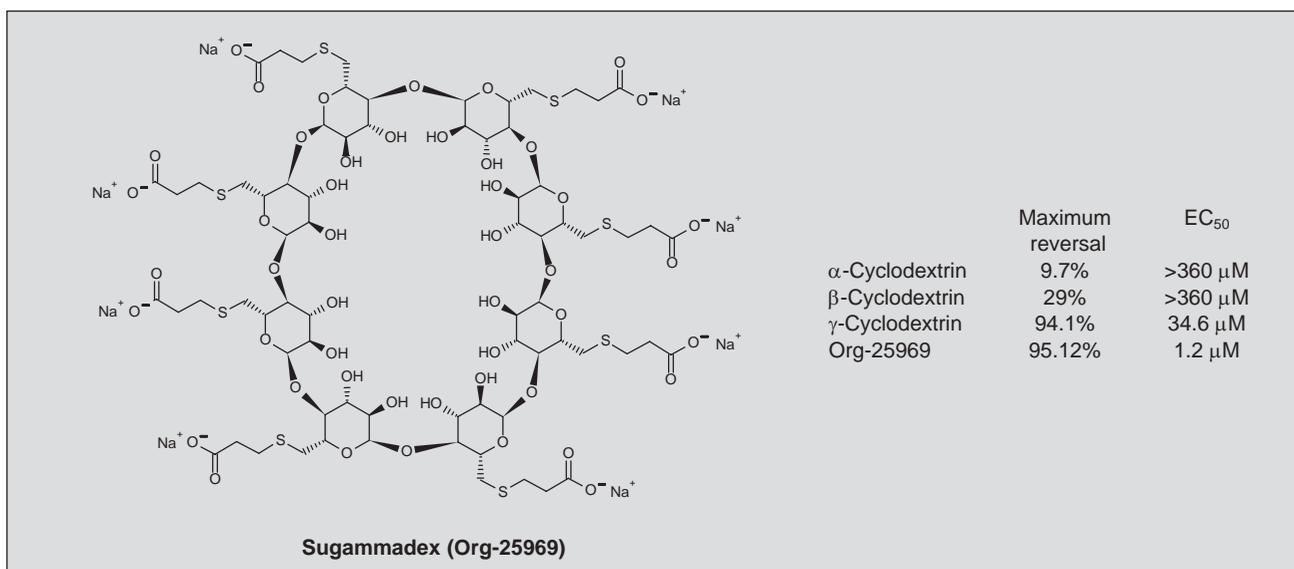


Fig. 6. First selective relaxant binding agent for reversal of neuromuscular block.

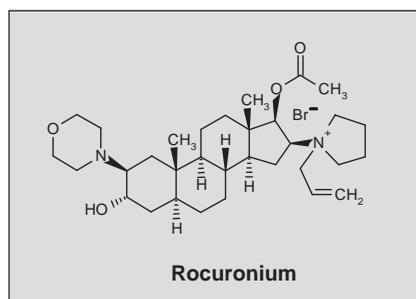


Fig. 7. Steroidal neuromuscular blocking agent.

selective and does not bind to any nonsteroidal neuromuscular blocking agents. Phase III clinical trials are presently running in both the United States and Europe.

AZD-2171: From design to the clinic

Dr. Laurent Hennequin (AstraZeneca, Reims, France) presented a case history of **AZD-2171** (Fig. 8), currently in phase II studies for advanced malignancies. Inhibition of vascular endothelial growth factor (VEGF)-signaling is an attractive, well-established antitumor target, given its pivotal role in the regulation of tumor angiogenesis and vascular permeability. VEGF signals through the endothelial cell receptors VEGF-R1 (Flt-1) and VEGF-R2 (KDR) by inducing receptor homo- or heterodimerization and stimulating intrinsic tyrosine kinase activity. VEGF has been shown to be directly implicated in a number of processes such as

endothelial proliferation, and endothelial cell migration and adhesion, and as a survival factor for the newly formed vasculature. Many approaches have been taken to affect VEGF signaling, ranging from receptor blocking or ligand sequestration by monoclonal antibodies, but researchers at AstraZeneca decided to target inhibition of the tyrosine kinase signaling.

The first clinical candidate to be identified was **AZD-6474** (Fig. 9), a dual VEGF/EGF kinase inhibitor. It has been proposed that this pharmacology might be an attractive profile, as it should decrease vascular permeability and inhibit cell proliferation while promoting apoptosis. Clinical data on AZD-6474 was also presented where clear effects were observed on tumor regression

Having identified **AZD-6474**, researchers at AstraZeneca went in search of a selective VEGF-R2 inhibitor. The observation that the aniline nitrogen could be replaced by oxygen was a key discovery, as it afforded excellent selectivity versus epidermal growth factor receptor. Subsequent work focused on identifying a potent bioisosteric replacement for the phenol moiety, which led to the discovery of the second clinical candidate, **AZD-2171**.

AZD-2171 displays excellent selectivity over other kinases, good preclinical pharmacokinetics in rats and dogs (Fpo 60% and 70%, respec-

tively) and superior inhibition of cell growth compared with other VEGF receptor inhibitors currently in clinical evaluation. Clinical data presented demonstrated that AZD-2171 has a pharmacokinetic profile to support once-daily dosing, and, importantly, the clinical response data suggest potential for broad antitumor activity.

Discovery of indacaterol for the treatment of asthma and COPD

The selective β_2 agonist salbutamol was first launched for the treatment of asthma in 1969 and has remained a standard treatment. Similar drugs were later introduced, but it was not until 1990 that the "long-acting" β_2 agonists **salmeterol** and **formoterol** provided a significant addition to the class. In fact, formoterol was made available in Japan in 1986, but was not introduced to the Western world until 1990, in Switzerland by Novartis.

Salbutamol, salmeterol and formoterol dominate the β -agonist therapy of airway disorders; asthma and chronic obstructive pulmonary disease. Yet, the Novartis group believes there are therapeutic improvements to be made, specifically in the areas of duration of action and speed of onset.

Dr. Alexandre Trifilieff (Novartis, Basel, Switzerland) described the profile of the currently available drugs and pointed to salbutamol's rapid onset but short duration (<5 min and 3–6 hours, respectively). Salmeterol, while active

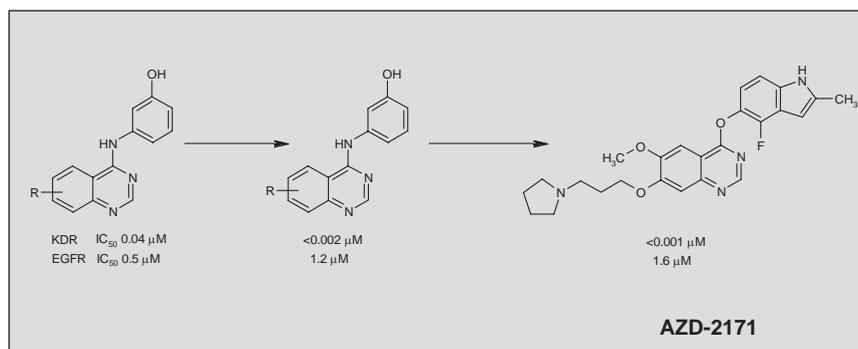


Fig. 8. Development of AZD-2171.

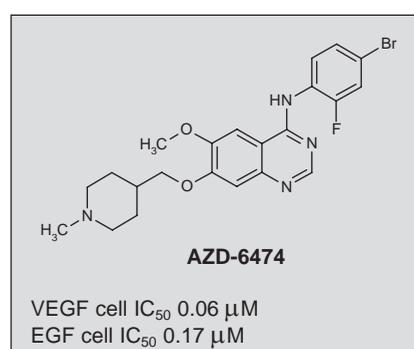


Fig. 9. Dual VEGF/EGF kinase inhibitor.

for 12 hours, has a relatively slow onset (>20 min) and formoterol, while having a rapid onset (<5 min) and a long duration, could be improved by extension of the latter to 24 hours.

The result of Novartis' further development of these drugs is **indacaterol** (Fig. 10), a single enantiomeric compound with high intrinsic efficacy, a fast onset and a duration of action suitable for once-daily dosing. In addition, it is easier to formulate, and side effects are reduced compared with earlier products.

Although **indacaterol** is slightly less potent than **formoterol** in some preclinical models, it is more efficacious than **salmeterol** and has a faster onset of action. However, when examined in the anesthetized primate, it is not only longer acting (inhibition of methacholine-induced bronchospasm) but is less prone to induce tachycardia.

Many of these properties have since been confirmed in phase II clinical trials, where the drug has been shown to be active when given by inhalation in the range 100–400 μg . The onset of action is within the required 5 minutes and the duration, especially at the top dose, is in the region of 24 hours. The results are derived from small trials and have yet to be substantiated in phase III studies, but the signs are that the project objectives have been met. The hope that the drug has a lower impact upon the cardiovascular system has yet to be confirmed.

Discovery of UCB-34714: A new pyrrolidone derivative with antiepileptic properties

Epilepsy remains an under-treated and little understood disorder, partly through a paucity of potent and selective agents and partly because it is not a single entity; it is rather, a collection of about 40 separate diseases. Despite their lack of specificity and side effect profiles, first-generation products such as **phenytoin** and **phenobarbitone** are still widely used, although newer products such as **gabapentin** and **topiramate** are gaining favor.

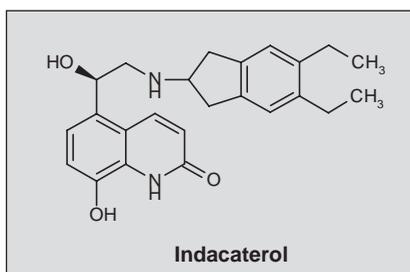


Fig. 10. Novel inhaled 24-hour β_2 adrenoceptor agonist.

One such second-generation product is **Keppra (levetiracetam; Fig. 11)** a second-generation antiepileptic drug that acts through an entirely novel mechanism. Like the disorder, the target through which levetiracetam exerts its activity is also little understood. Named SV2A, it is a protein binding site found in nerve synapses, where it may be involved with the translocation of synaptic vesicles and the exocytosis of neurotransmitters. Levetiracetam is the only approved antiepileptic drug to work through this mechanism.

Even so, argued Dr. Benoit Kenda (UCB, Belgium), more efficacious treatments are urgently required; 30–35% of all patients are resistant to current therapy. And the company's approach has been to extend the properties of the lead compound.

Levetiracetam is built upon a pyrrolidone acetamide scaffold. Exploration of the stereochemistry showed that the *S*-enantiomer was always the more effective and structure–activity relationship studies showed that the primary carboxamide

moiety was essential for receptor affinity. After these preliminary findings, an extensive lead exploration program was launched in which the starting structure was examined piecemeal, broken down, extended and reduced until **levetiracetam** emerged as four new chemical entities. From these, the most biologically satisfactory molecule proved to be **brivaracetam** (Fig. 11).

The *in vivo* measure of preclinical efficacy was that of amygdala kindling in rats (Matagne et al. *Epilepsia* 2003, 44(Suppl. 9): 260), and **brivaracetam** was shown to reduce seizure severity at 21–212 mg/kg (following intraperitoneal injection). **Levetiracetam**'s effective dose range was up to 1700 mg/kg, and it failed to meet the same level of efficacy as the newer compound. Brivaracetam was also more effective in models of corneal kindling in mice and hippocampal kindling in rats, and while the therapeutic ratio was, on occasions, lower than that of levetiracetam, it was never in the range that might suggest an adverse therapeutic ratio.

Brivaracetam is some 10-fold more active than its predecessor, the clinically approved **levetiracetam**. The drug is freely orally bioavailable in preclinical models, and it promises an additional benefit for the therapy of neuropathic pain.

Brivaracetam is currently undergoing phase II evaluation after a successful phase I program, where the maximum tolerated single dose was 1000 mg and more than 800 mg fol-

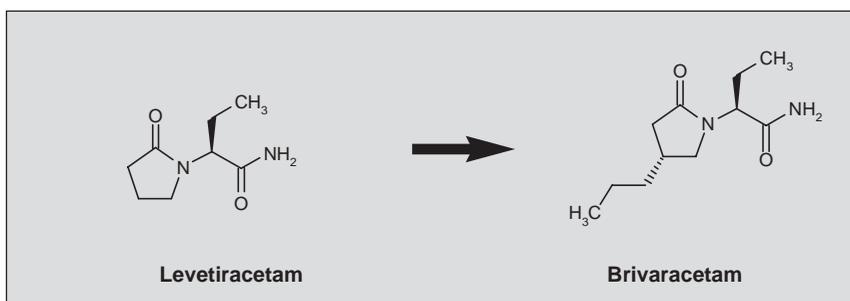


Fig. 11. Second-generation antiepileptic drugs.

lowing 2-week daily administration. The most frequent adverse effects were all CNS-related: dizziness, somnolence, fatigue, euphoria and disorientation. They were dose-related, had a fast onset and resolved within 24 hours. There were no changes in laboratory parameters or vital signs. Examined in patients with photosensitive epilepsy, proof-of-concept studies have shown that brivaracetam is effective at 10–80 mg p.o. and always more active than **levetiracetam**. It is currently being evaluated for the treatment of refractory patients with par-

tial-onset seizures as well as in neuropathic pain.

Conclusion

This was the first *Recent Disclosures of Clinical Drug Candidates* meeting organized by the Society for Medicines Research. The meeting proved to be very popular. Several pharmaceutical companies provided a fascinating illustration of the strength of research and the diversity of research strategies used to discover and develop new medicines.

Richard Armer, Peter Warne and Jason Witherington 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).