

# MEDICINES RESEARCH: CURRENT TRENDS AND CASE HISTORIES

## HIGHLIGHTS OF THE SOCIETY FOR MEDICINES RESEARCH SYMPOSIUM

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### ABSTRACT

This Society for Medicines Research symposium, sponsored by Peakdale Molecular and Pharmidex, was held on December 9, 2008, at the Queen Elizabeth II Conference Centre, Westminster, London, U.K. in association with and as part of Genesis 2008. The meeting, organized by Diane Coe, Richard Armer and Andrew Ratcliffe, focused on current trends and case histories in medicines research. Topics included exploiting the synthetic biology of natural products, the use of fragment-based NMR in drug discovery, and drug discovery and development programs in the areas of oncology, neurology, antivirals and urology.

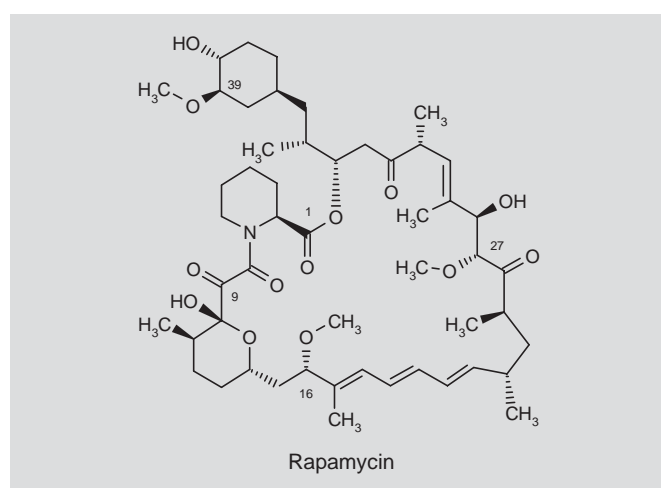
Despite today's climate of restructuring and merger and acquisition activity in the pharmaceutical industry, drug discovery research in the U.K. has remained high-class and cutting-edge, bringing new medicines to market.

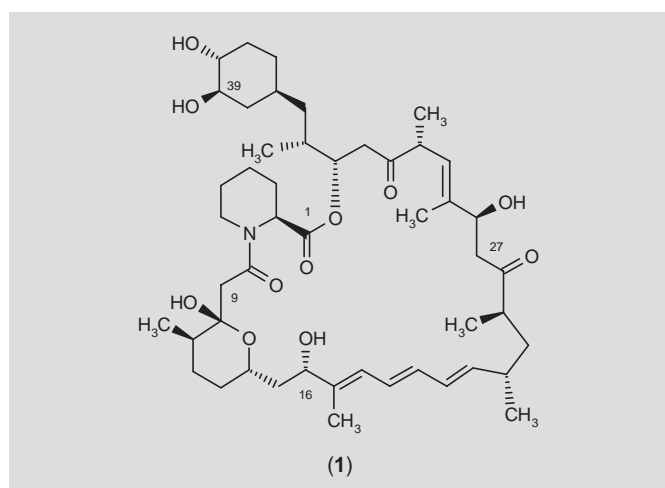
Dr. Ming-Qiang Zhang (Biotica Technology Ltd., Chesterford Research Park, Cambridge, U.K.) discussed synthetic biology as a novel emerging technology to further exploit the unique medicinal properties of macrocyclic natural products, in particular **rapamycin** (sirolimus) (1).

As a general class, macrocyclics represent a rich vein of clinically used immunosuppressants, anti-infectives and anticancer drugs. Although generally non-rule-of-5-compliant, they have the ability to undergo flip-flop conformational changes to promote intestinal permeability (2). In addition, their high level of structural preorganization allows binding to large surface areas without incurring an entropic penalty and loss in potency. They also often represent the smallest biomolecules involved in complex noncovalent molecular assemblies, the architecture of which is driven by the nature of the biological pathway.

However, the structural complexity of macrocycles, coupled with a shift towards rule-of-5 drug space, has resulted in limited exploitation by the synthetic medicinal chemistry community. As a test-

ament, the shortest de novo route to rapamycin, recently published by Ley and colleagues (3), comprises 35 steps, with <1% overall yield. As a consequence, semisynthetic methods represent the mainstay of generating analogues, but the range and diversity of functional group transformations is limited in scope. To address this deficiency, attention has turned to manipulation of biosynthetic routes. The biosynthesis of rapamycin is driven using a mixed type I polyketide synthase (PKS)/nonribosomal peptide synthetase (NRPS) system (4). On loading the system with the starter unit, 4,5-dihydroxycyclohex-1-enecarboxylic acid, PKS directs 14 successive polyketide chain extensions. Catalysis by NRPS then promotes an amidation reaction and insertion of L-pipecolic acid, before cleavage from the enzyme and macrocyclization to generate prerapamycin (**1**). Finally, through the action of post-PKS genes, which include methyltransferases and cytochrome P450 monooxygenases, prerapamycin is fully functionalized to rapamycin. Transformations include oxidation of C-9 to a C=O, insertion of an OMe at C-27, and O-methylation of C-16 and



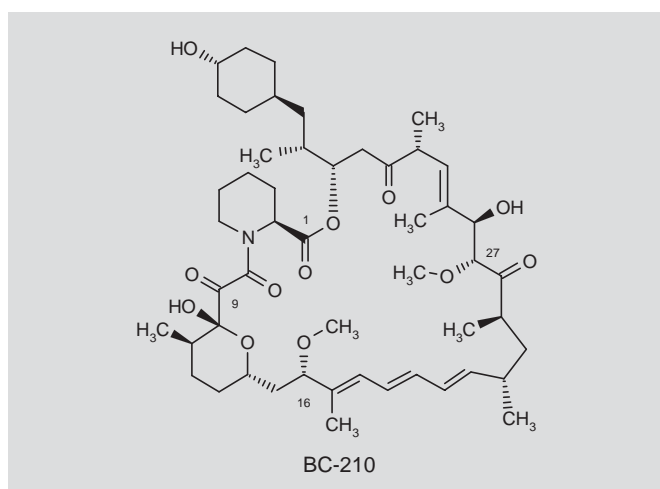
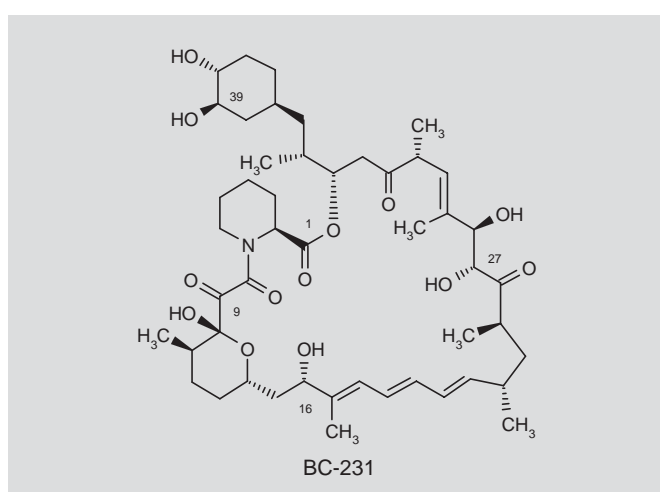
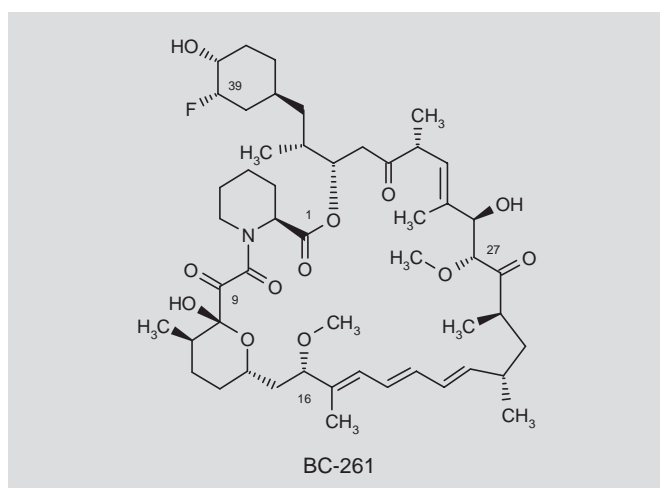


C-39 OH groups. Further studies have revealed that unique genes control these transformations, which can be manipulated. This, coupled with the observation that a genetically engineered *Streptomyces hygroscopicus* MG2-10 strain failed to produce rapamycin unless fed with the starter unit 4,5-dihydroxycyclohex-1-enecarboxylic acid, has paved the way for a combinatorial biosynthetic approach, in which novel and diverse analogues of rapamycin can be synthesized through judicious choice of post-PKS gene cassettes and starter acids on a scale that is both economic and environmentally friendly (4).

As part of the structure-activity relationships (SAR) generated from such analogues, the importance of the C-9 keto group in eliciting potent inhibition of mTOR, the serine/threonine kinase target of rapamycin, was confirmed in light of the significantly reduced activity of a number of C-9 CH<sub>2</sub> analogues.

The tumor suppressor protein/lipid PTEN phosphatase is part of the upstream signaling network of mTOR and negatively regulates its activity (1). Evaluation of analogues using two cancer cell lines, human prostate carcinoma DU 145 containing wild-type PTEN and human prostate adenocarcinoma PC-3 lacking PTEN, revealed a spectrum of anticancer activity. Although rapamycin shows a slight preference for inhibition of PTEN-deficient PC-3 cells ( $pIC_{50} = 7.68$ ) over wild-type PTEN DU 145 cells ( $pIC_{50} = 6.52$ ), potent inhibitors with far greater selectivity for either PC-3 or DU 145 cells could be identified. **BC-261** represents an analogue with greater potency for inhibition of PC-3 cells ( $pIC_{50} = 8.30$ ) over DU 145 cells ( $pIC_{50} = 5.42$ ). In contrast, **BC-231** appears to be more potent for DU 145 cells ( $pIC_{50} = 7.19$ ) compared to PC-3 cells ( $pIC_{50} = 4.26$ ). Both BC-261 and BC-231 hold promise as useful chemical biology tools to further explore and dissect the mTOR cancer axis, given that only about 10% of cancer patients respond to rapamycin therapy.

The drug metabolism and pharmacokinetic (DMPK) properties of rapamycin are less than ideal. Studies using Caco-2 cells showed that its intrinsic permeability is relatively low ( $P_{app} = 2$  nm/s), concomitant with significant efflux (B-A/A-B 458). Incubation in human liver microsomes (HLM) yields a  $t_{1/2}$  of 40 min, with O-demethylation of the C-39 OMe group identified as a major metabolic pathway. By feeding cyclohexanecarboxylic acid via the MG2-10 mutant strain, and allowing full post-PKS processing, **BC-210**, the des-C-39 MeO analogue of rapamycin, can be generated (4). Akin to rapamycin,

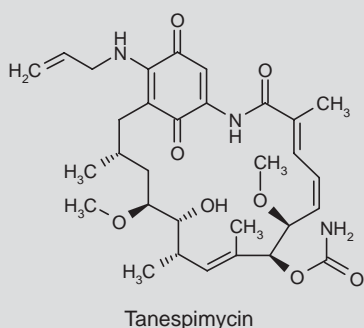
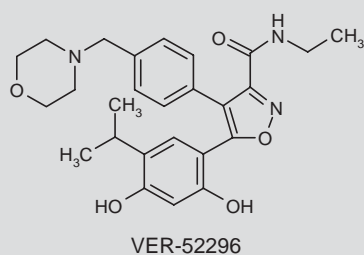


BC-210 elicits potent inhibition of mTOR kinase activity and cancer cell proliferation. However, compared to rapamycin, BC-210 demonstrates not only improved metabolic stability (HLM  $t_{1/2} = 59$  min), but more importantly a greatly enhanced Caco-2 profile, with an approximately 15-fold improvement in intrinsic permeability ( $P_{app} =$

29 nm/s) at the expense of an approximately 30-fold reduction in efflux activity (B-A/A-B 15) (4). As a consequence, i.v. dosing of BC-210 in mice leads to enhanced brain accumulation, which resulted in a significant reduction in brain tumors in an orthotopic human glioblastoma U-87 MG model, opening the way for rapamycin analogues to potentially treat glioblastoma multiforme or other neurodegenerative diseases.

Over the past 10 years there has been a rapid increase in the application and success of fragment-based screening as a complementary approach to traditional high-throughput screening (HTS) in generating chemically tractable hits (5). Fragments are low-molecular-weight entities, usually < 250 Da, with binding affinities ranging from millimolar to micromolar. Although high content screening can return fragments displaying low micromolar activity and extremely high ligand efficiency, it cannot reliably detect millimolar binders. The binding of such fragments is identified through biophysical methods that include protein–ligand NMR, surface plasmon resonance (SPR) or x-ray crystallography. Dr. Douglas Williamson (Vernalis Ltd., Granta Park, Great Abington, Cambridge, U.K.) described the use of a fragment-based drug design approach in the identification of **VER-52296** (6), a potent small-molecule inhibitor of heat shock protein 90 (Hsp90) currently undergoing phase I cancer trials in collaboration with Novartis.

Starting from commercially available compounds and through the application of a number of in silico filters, property calculations and generation of 2D 3-point pharmacophore fingerprints, Vernalis researchers have constructed a library of around 1,320 fragments, or SeeDs (Structural exploitation of experimental Drug starting points), primarily for use in NMR screening (7). Screening is performed in mixtures of 12 fragments, and active fragments are identified through NMR competitive binding experiments using a known competitive ligand. Active fragments are classified as bona fide hits

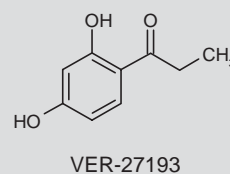
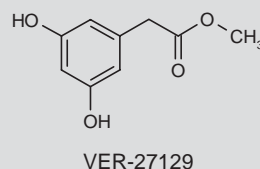
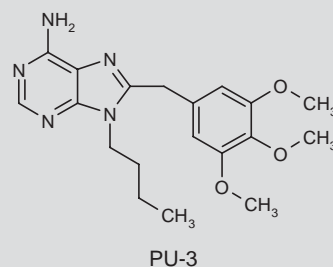


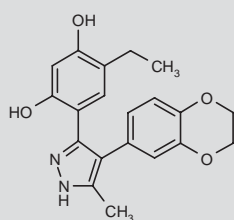
through a combination of further 2D NMR studies in conjunction with SPR. X-ray crystallography is then employed to aid fragment-to-lead and lead optimization strategies.

Hsp90 is a molecular chaperone that plays a fundamental role in controlling the function of many proteins associated with normal cell homeostasis. However, in human cancer Hsp90 is overexpressed and helps drive proliferation, angiogenesis, metastasis and survival of cancer cells. Encouraging early clinical trial data with the first-in-class inhibitor **tanespimycin** (17-AAG) has added impetus to the discovery and development of small-molecule Hsp90 inhibitors.

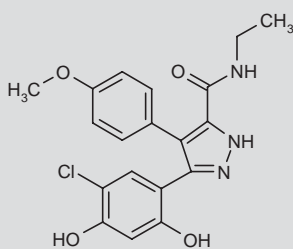
NMR screening of 729 fragments using **PU-3** as a competitive ligand delivered a 2.3% hit rate and led to the identification of a cluster of aromatic diols, such as **VER-27129** and **VER-27193**, that demonstrated  $IC_{50}$  values of 490 and 570  $\mu$ M, respectively, in a fluorescence polarization (FP)-based binding assay.

Keeping the aromatic diol functionality, substructure searching of commercially available compounds in tandem with a focused docking strategy on the x-ray structure of the *N*-terminal domain of human Hsp90 led to the identification of a more potent analogue, **VER-63579** (FP  $IC_{50}$  = 0.28  $\mu$ M). Crystallization of VER-63579 into Hsp90 allowed further structure-based optimization of binding potency, cellular activity and DMPK properties required to meet the target product profile. From this exercise, **VER-49009** emerged as an advanced compound, demonstrating an increase of an order of magnitude in FP binding potency ( $IC_{50}$  = 0.025  $\mu$ M) and submicromolar inhibition of the proliferation of human colon cancer HCT 116 cells ( $GI_{50}$  = 0.26  $\mu$ M) (8). Unfortunately, in other human cancer cell





VER-63579



VER-49009

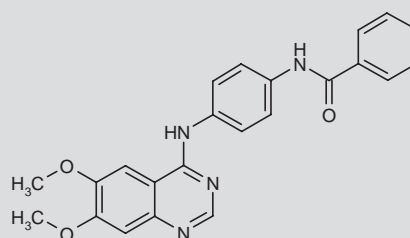


VER-50589

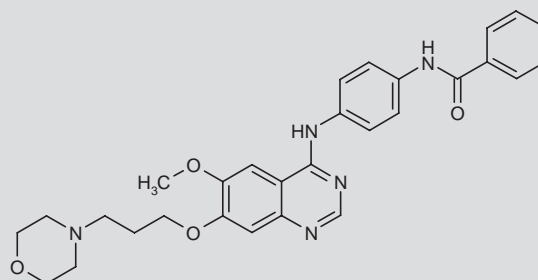
lines VER-49009 performed less efficiently in preventing proliferation, with  $GI_{50}$  values of 2.2 and 1.2  $\mu\text{M}$ , respectively, noted against PC-3 and DU 145 cells. Likewise, in U-87 MG cells the  $GI_{50}$  was 1.2  $\mu\text{M}$ . Further optimization revealed that a simple switch of the pyrazole core in VER-49009 to an isoxazole unit, as in **VER-50589**, resulted in a retention of binding potency ( $FP IC_{50} = 0.028 \mu\text{M}$ ) but an increase in cellular activity, with  $GI_{50}$  values of  $< 0.25 \mu\text{M}$  across all cancer cell lines tested. Investigation of the binding kinetics by SPR suggested that the differences in cellular activity may be associated with an approximately 10-fold slower off rate for VER-50589 compared to VER-49009, leading to higher cellular concentrations.

Maintaining the isoxazole core and introducing a solubilizing group, followed by further subtle modifications guided by x-ray structural information, led to the discovery of VER-52296 ( $FP IC_{50} = 0.021 \mu\text{M}$ ). Despite similar binding potency to VER-50589, VER-52296 showed superior cell growth inhibition (HCT 116  $GI_{50} = 0.016 \mu\text{M}$ ; PC-3  $GI_{50} = 0.006 \mu\text{M}$ ; DU 145  $GI_{50} = 0.005 \mu\text{M}$ ; U 87 MG  $GI_{50} = 0.008 \mu\text{M}$ ). In addition, the favorable DMPK properties of VER-52296 attained upon i.p. dosing to tumor-bearing mice, coupled with efficacy in a number of human tumor xenograft models, led to transition of the compound into development as an i.v. formulation.

Dr. Sam Butterworth (AstraZeneca Pharmaceuticals, Alderley Park, Macclesfield, Cheshire, U.K.) delivered the first case history presen-



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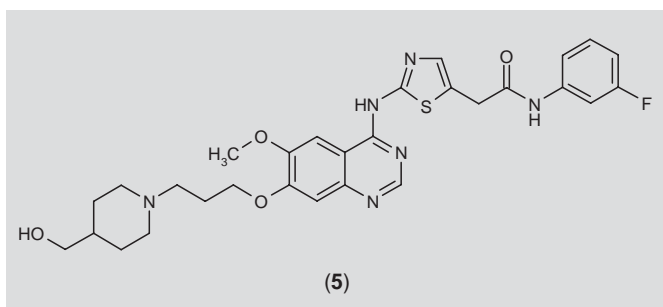
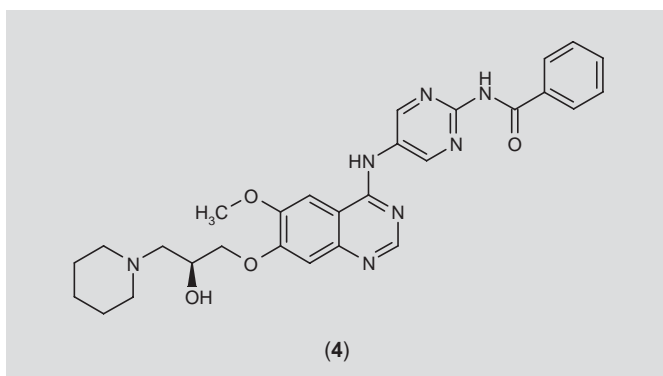
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tation describing the optimization of a series of aryl-substituted quinazolines as selective inhibitors of Aurora-B kinase for parenteral administration. The Aurora proteins are a small family of serine/threonine kinases that are expressed during mitosis and have been suggested to be attractive drug targets. Humans express three Aurora paralogues (Aurora-A, -B and -C) and two of these, Aurora-A and -B, are commonly overexpressed in tumor cells.

The starting point for the lead optimization effort was an aryl-substituted quinazoline (**2**) identified by screening of the AstraZeneca compound collection (9). Replacement of the methoxy group at the C-7 of the quinazoline with a 3-(1-morpholino)propoxy side-chain provided compound **3**, with good activity against both Aurora-A and -B (Aurora-A  $IC_{50} = 0.11 \mu\text{M}$  and Aurora-B  $IC_{50} = 0.13 \mu\text{M}$ ) and with improved cellular potency with respect to the initial hit compound. Although this compound proved to be a useful tool, its poor solubility (1.3  $\mu\text{g}/\text{mL}$ ) and high plasma protein binding (0.3% free) remained as issues to be addressed in the development of a clinical candidate.

Extensive lead optimization efforts were described: two key modifications were replacement of the central aniline ring and introduction of an enhanced solubilizing group at the end of the C-7 substituent. The replacement of the central aniline with a 5-pyrimidinyl group increased potency and reduced the lipophilicity of the compound, leading to increased levels of free drug measured in rat plasma. In parallel, replacement of the morpholine group in the C-7 substituent with the more basic piperidine, and incorporation of an OH group, led to the identification of compound **4**, demonstrating aqueous solubility approaching 0.8  $\text{mg}/\text{mL}$  (9).

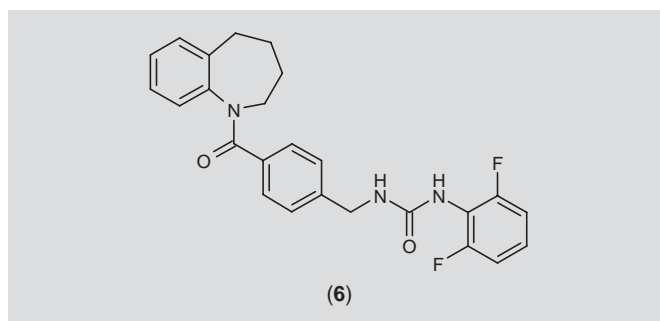
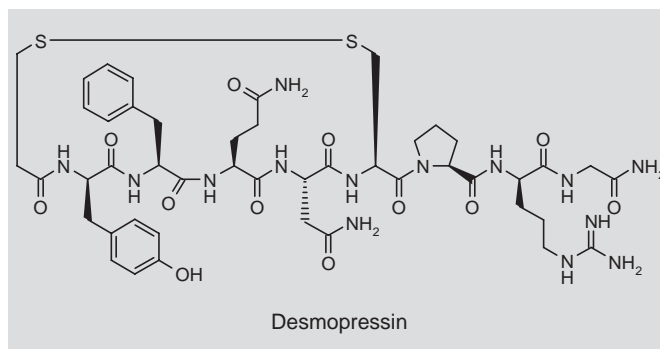
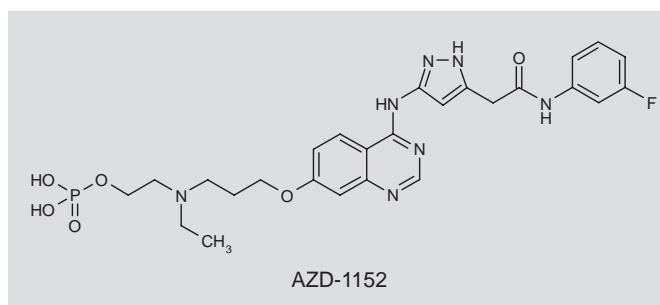
The aniline could also be successfully replaced by a five-membered heterocycle. The 2-aminothiazole (**5**) and 3-aminopyrazole analogues both retained affinity for the Aurora kinases and cellular



activity (10, 11). The pyrazole series was generally less lipophilic than the corresponding thiazoles, resulting in improvement in physico-chemical properties and a decrease in protein binding. However, for progression to the clinic it was necessary to identify a compound with aqueous solubility of > 10 mg/mL without resorting to the use of toxic vehicles. Further investigation showed that within the pyrazole series analogues designed as phosphate prodrugs delivered this threshold in addition to the desired rapid conversion to the parent drug in vivo (11).

A major breakthrough for the program was the determination that the mitotic defects described after exposure of cells to Aurora kinase inhibitors seem to be largely due to the inhibition of Aurora-B (12). This allowed the rapid selection of **AZD-1152** as a clinical candidate, which as its des-phosphate form gave 1,000-fold greater potency for Aurora-B ( $K_i < 0.001 \mu\text{M}$ ) than for Aurora-A ( $K_i = 1.4 \mu\text{M}$ ) (11). AZD-1152 showed no inhibition of the major cytochrome P450 isoforms and had no significant hERG inhibition ( $\text{IC}_{50} > 30 \mu\text{M}$ ). The compound is highly soluble (25 mg/mL, pH 9 buffer) and is completely and rapidly converted to the active drug following parenteral administration in rats. The compound was shown to be active in a range of tumor models and is currently in phase I/II trials (13).

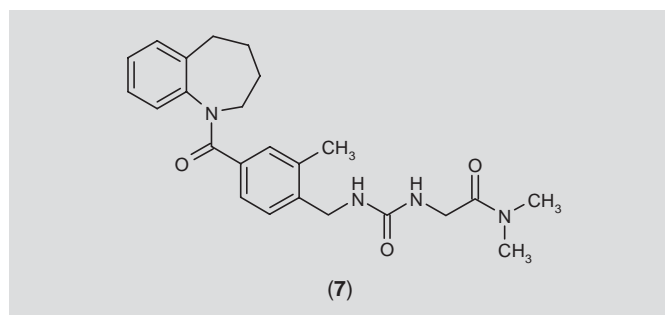
The second case history was given by Dr. Michael Roe (Vantia Ltd., Southampton Science Park, Southampton, U.K.) on the discovery of a vasopressin  $V_2$  receptor agonist. Arginine vasopressin (AVP) is a cyclic nonapeptide hormone released from the posterior pituitary that acts at two classes of receptors,  $V_1$  and  $V_2$ . Activation of  $V_2$  receptors stimulates an increase in water permeability in the collecting ducts of the kidney, with subsequent regulation of the aquaporin-2 (AQP-2) water channels. **Desmopressin**, the only commercially available  $V_2$  agonist, is effective as a treatment for diseases such as diabetes insipidus, enuresis and nocturia, where a reduction in urine



output is desired. However, as the peptidic nature of the compound limits its oral bioavailability, there exists the opportunity for an improved oral therapy.

Screening of libraries of 50,000 compounds targeting the vasopressin  $V_2$  and related oxytocin receptors identified compound **6** (human  $V_2$   $\text{EC}_{50} = 47 \text{ nM}$ ) (14). Although fully effective in a human in vitro assay, there was only a small response in the corresponding rat assay. As a consequence, the compound could not be further utilized as a pharmacological tool.

Introduction of small alkyl groups on the 3-position of the aryl linker improved potency in the human in vitro assay, and showed full and potent agonism in the rat receptor in vitro assay. Evaluation in the Brattleboro rat model, a model of diabetes insipidus, showed that the compound had activity when dosed i.v., but not orally. This observation was accounted for by limited aqueous solubility, and the next iteration of compounds focused on the incorporation of more hydrophilic groups. Replacement of the difluorophenyl motif with glycine derivatives resulted in the dimethylamide analogue (**7**), which retained similar levels of potency (human  $V_2$   $\text{EC}_{50} = 58 \text{ nM}$ ), but with significant improvement in aqueous solubility (177  $\mu\text{g/mL}$ ) (14).



To reduce the number of hydrogen bond donors, a number of cyclic proline analogues were prepared, from which the dimethylamide derivative **VA-106483** was the preferred compound, demonstrating a similar level of potency (human  $V_2$   $EC_{50}$  = 24 nM) and excellent solubility (7 mg/mL). Substitution of the proline ring or modification of the benzazepine ring failed to give compounds with superior in vivo profiles, and VA-106483 was selected as the clinical candidate (14). In the initial clinical study the compound was administered as a 1-h infusion and a dose-dependent increase in exposure was observed. A similar profile was also obtained following oral dosing, with an oral bioavailability of approximately 50%. The compound is effective in the clinic, with a dose-dependent duration of action, and is currently in phase II studies for nocturia.

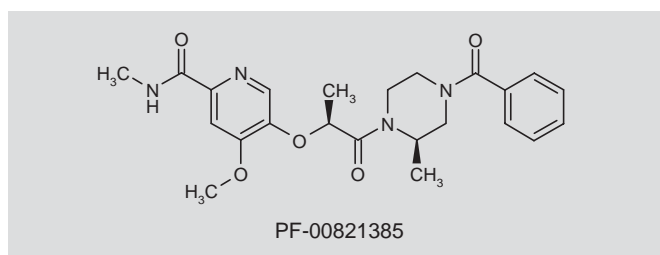
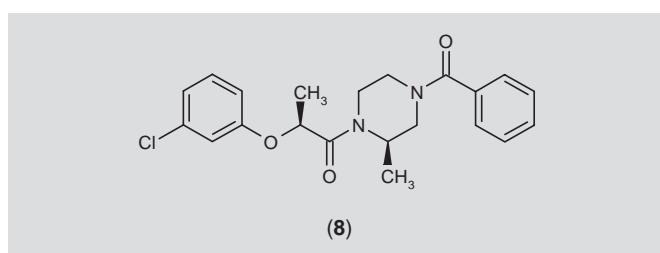
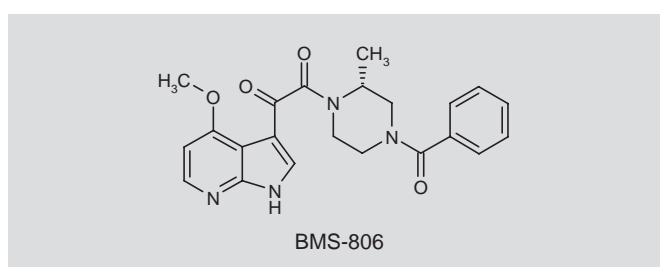
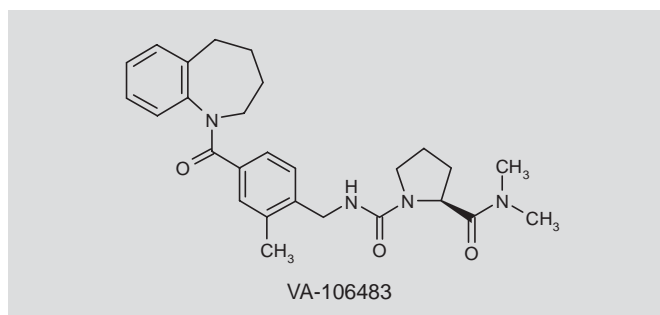
Thien Duc Tran (Pfizer Global Research and Development, Sandwich, Kent, U.K.) gave a talk on the design and synthesis of gp120-CD4 inhibitors for the treatment of HIV. The first step in HIV infection is the binding of the viral glycoprotein (gp120) to the cell-surface receptor CD4. Inhibition of this step is an attractive target for inhibition of HIV-1 infection. The first-generation molecule in this class, **BMS-806**, was progressed to a phase I study, which was subsequently terminated, although not due to mechanism-related safety issues.

The program at Pfizer had the goal of developing an oral agent tailored to a dose of < 500 mg b.i.d. The molecules had to have broad-spectrum activity against a range of HIV isolates, and a pharmacokinetic and safety profile comparable with other antiretroviral agents. A lead generation program was initiated, preparing a range of amides based on the (3*R*)-3-methyl-1-(phenylcarbonyl)piperazine core. The initial compound of interest contained the (2*R*)-2-[(3-chlorophenyl)oxy]propanamide motif (**8**).

Optimization of the aryl ring was undertaken with the aim of improving potency and lowering lipophilicity. From this strategy **PF-00821385** emerged as a clinical candidate, with potent in vitro activity ( $IC_{50}$  = 10 nM in a fusion assay), 100% absorption in rats and good aqueous solubility (10 mg/mL). Furthermore, the compound proved active against both CCR5- and CXCR4-tropic strains of HIV, with a dose of 200 mg b.i.d. predicted to achieve blood levels equivalent to the  $IC_{90}$  for > 70% of clade B isolates.

PF-00821385 was shown to be safe and well tolerated in a single-escalating-dose study in humans, with no dose-limiting adverse effects at doses of 3-1300 mg. However, the development of the compound is currently on hold.

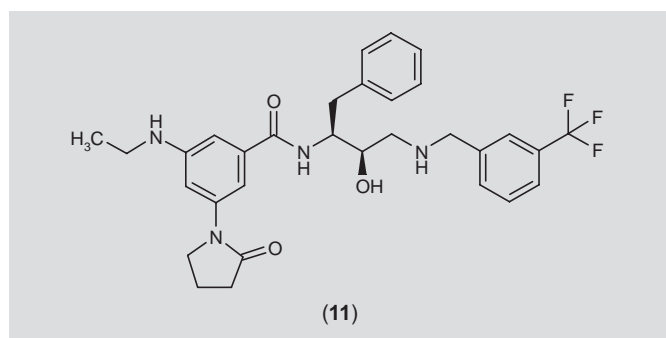
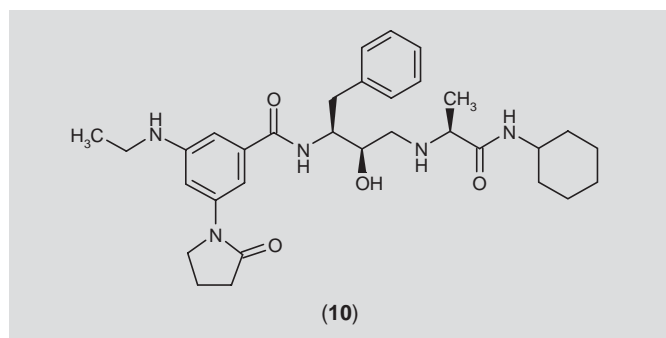
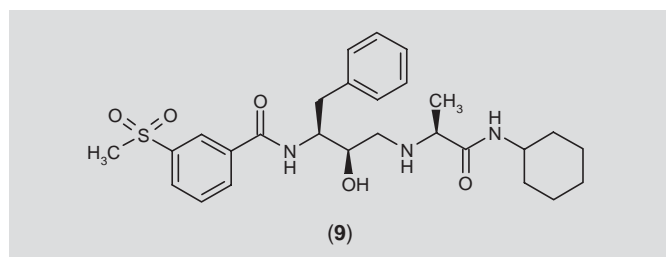
The final case history of the symposium was delivered by Emmanuel Demont (Immuno-Inflammation CEDD, GlaxoSmithKline, Steve-



nage, Hertfordshire, U.K.) on the discovery of orally active  $\beta$ -secretase (BACE1) inhibitors. Alzheimer's disease is characterized by the progressive formation of insoluble amyloid plaques and neurofibrillary tangles. These plaques are comprised of  $\beta$ -amyloid peptide generated from amyloid precursor protein (APP) in a process which involves BACE1. The inhibition of BACE1, an aspartyl protease, therefore has the potential to provide a disease-modifying therapy for Alzheimer's disease. The strategy for the design of inhibitors was based on the transition state-mimetic concept. This approach relies on replacement of the scissile amide bond with a stable mimetic of the putative transition state. The work described involved the use of hydroxyethylamine as the mimetic. Initially, a library of potential inhibitors was generated with the constraints of MW < 700 and no more than two amide bonds. From this work, compound **9** was identified with micromolar activity against BACE1 (15).

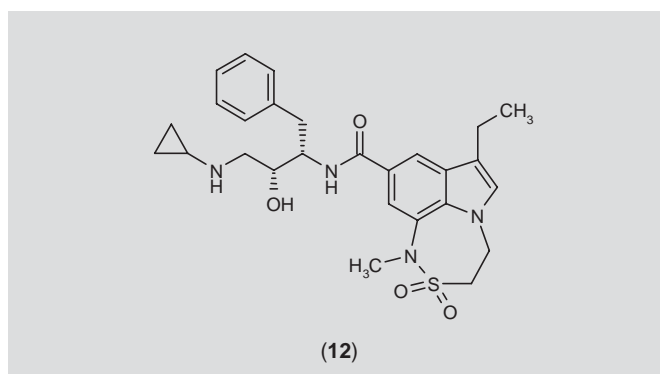
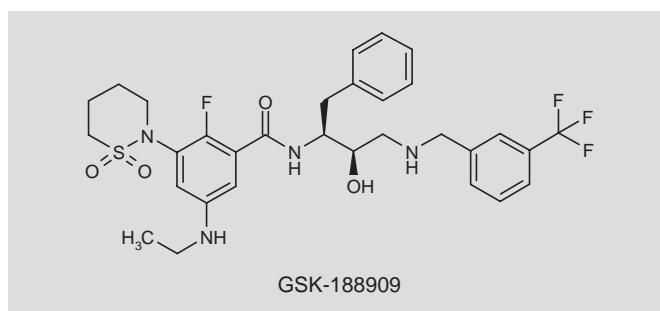
Despite an extensive effort, no significant improvement in potency could be found. However, the replacement of the methylsulfonyl with





the more lipophilic *n*-pentylsulfone resulted in a slight increase in potency, which allowed a co-crystal structure to be obtained with a human BACE1 construct. This crystal structure indicated that the sulfone formed an H-bond interaction with Asn-294, and that a substituent on the other *meta*-position would be able to access the unoccupied  $S_3$  pocket. After replacing the sulfone with the equipotent pyrrolidinone group, exploration of this strategy resulted in the discovery of **10**, showing an approximately 400-fold increase in potency against BACE1 ( $IC_{50}$  = 13 nM) (15).

The next stage in the lead optimization program was the truncation of the prime side of the molecules and reduction of the peptidic nature of the molecule (16). This work concluded with the introduction of the *meta*-substituted trifluoromethylaryl group, producing compound **11**, with an  $IC_{50}$  of 40 nM. As the program had optimized both the prime side of the molecule and the  $S_3$  pocket, efforts were directed at optimization of the motif found to H-bond to Asn-294 (17). Introduction of the 6-membered sultam as a replacement for the lactam resulted in a significant increase in potency in both the enzyme and cell-based assays. An additional increase in potency was obtained by the introduction of a fluoro substituent; the compound **GSK-188909** elicited selective nanomolar inhibition of BACE1 ( $IC_{50}$  = 4 nM), with a pharmacokinetic profile which allowed the effects of BACE1 inhibitors on amy-



loid production to be evaluated in an animal model of Alzheimer's disease. Oral dosing with 250 mg/kg of the compound in TASTPM mice, with or without prior dosing of a P-glycoprotein inhibitor, resulted in a significant decrease in  $\beta$ -amyloid peptide.

The final iteration of lead optimization described in the presentation centered on efforts to address the suboptimal pharmacokinetics (18). In vitro metabolism studies indicated that the main metabolic pathways constituted benzylic oxidation and dealkylation of the aniline substituent. Through molecular modeling, the issue of dealkylation was addressed by re-engineering the aniline functionality as part of a tricyclic system, which maintained the key interactions. The analogue had similar potency to the parent compound, and co-crystallization of the compound with the BACE1 construct confirmed the modeling hypotheses. Replacement of the benzyl group with the cyclopropyl group addressed the other major metabolic pathway and resulted in compound **12** ( $IC_{50}$  = 20 nM), with improved pharmacokinetics in rats ( $F$  = 17-22%).

As a thought-provoking topic, Dr. Dennis Smith (Pfizer Global Research and Development, Sandwich, Kent, U.K.) presented a personal view on whether a historical perspective was useful in predicting the future of drug discovery and development. Detailed analysis of drugs marketed in the 20th century points to four general sources. These include follow-on drugs from established chemical classes, first-in-class drugs, new uses for older therapeutic classes of drugs for intractable diseases and opportunistic so-called "inverse" ideas. Over the last 2 years, 40 small-molecule new chemical entities have received FDA approval. A breakdown of these drugs confirms that such sources are still being actively mined and likely to remain so in the future.

It was suggested that, in the case of drug development and regulatory approval, the landscape had significantly changed over the last

four decades. Propranolol, the first full  $\beta$ -adrenoceptor antagonist brought to the market in the 1960s for hypertension, was approved on the basis of clinical findings from 107 patients in uncontrolled studies that included monotherapy plus diuretic. In stark contrast, aliskiren, approved in 2007 as a first-in-class nonpeptide renin inhibitor for hypertension, required just over 7,000 patients. Clinical studies included monotherapy plus combinations with hydrochlorothiazide, a diuretic, or valsartan, an angiotensin II receptor antagonist. The significant differences in patient numbers are reflective of the current increase in safety demands and demonstration of patient benefit, leading to longer times and increase in cost of bringing drugs to market. It was recommended that to alleviate this situation phase III development should be shared with health-care organizations and government. Further changes that could impact drug discovery were presented, and include the use of pharmacokinetic/pharmacodynamic (PK/PD) models at project inception to assess the viability of concepts and definition of objectives. Analysis of the so-called "magic bullet" approach, in which a toxin is delivered by an antibody, was illustrated as a case in point. Antibody affinity is generally subnanomolar, whereas few small-molecule toxin drugs ever reach this level. As a consequence, for the toxin to be successfully delivered to the site of action, the  $V_{\max}$  of internalization must be high. It was suggested that in many cases this appeared overly optimistic. To date, only gemtuzumab, a monoclonal IgG<sub>4k</sub> antibody conjugated with calicheamicin, a very potent anticancer drug, has been approved for clinical use in refractory acute myeloid leukemia. It will be interesting to see whether additional antibody conjugates succeed in the market. In a similar vein it was also proposed that mathematical disease models were underutilized in assessing which mechanism when targeted could deliver the greatest impact on disease progression.

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