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MEETING REPORT

RECENT DISCLOSURES OF CLINICAL CANDIDATES

HIGHLIGHTS OF THE SOCIETY FOR MEDICINES RESEARCH SYMPOSIUM HELD DECEMBER 10TH 2009 AT THE NATIONAL HEART AND LUNG INSTITUTE, LONDON, UK

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SUMMARY

This Society for Medicines Research symposium was held on December 10th, 2009, at the National Heart and Lung Institute, London, U.K. The meeting, organized by David Fox and Diane Coe, showcased the discovery and early development of recent agents that have made it through to the clinic. The program included a wide variety of mechanistic approaches covering disease areas ranging from pain and endometriosis through to cancer, allergic rhinitis and pulmonary arterial hypertension. The meeting also included the 2009 SMR Award lecture, which described the discovery and clinical development of Januvia™ (sitagliptin), a new and innovative treatment for diabetes.

The first lecture of the symposium was given by Dr. Chris Murray (Astex Therapeutics) on the development of the heat shock protein HSP90 inhibitor AT-13387 using a fragment-based drug discovery approach. HSP90 is a molecular chaperone protein that directs the folding of polypeptides into functional configurations affecting stabilization and activation. Many of the proteins are oncogenes regulating tumor growth, survival and activation. As a consequence, inhibition of the pathway would have potential as an anticancer therapy.

A fragment screening campaign (1) was conducted using the *N*-terminal domain of HSP90 and 1,500 fragments (MW < 250 Da) to find compounds which bound to the ATPase active site. Multiple hit series were identified, but hit-to-lead efforts were focused on the fragment **1** (Fig. 1), although the fragment was only weakly active and had poor ligand efficiency, the x-ray crystal structure indicated a suboptimal substituent in a lipophilic pocket and a key conformational twist around the amide. Superimposition of the natural product radicicol on the x-ray crystal structure also suggested that introduction of an additional phenol group would be tolerated.

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Replacement of the methoxy group with small alkyl groups resulted in a 100-fold increase in potency due to the superior contact with the lipophilic pocket (**1** K_d = 790 μM; **2** K_d = 8.6 μM). Tertiary amide groups were synthesized, as these preserved the key conformational twist, and the isoindoline **3** was 30-fold more potent than the corresponding diethylamide **2**. Introduction of the additional phenol, resulting in the resorcinol **4**, gave a further enhancement in potency (K_d = 0.54 nM; ligand efficiency [LE] = 0.57), with the compound showing good cellular activity with a confirmed mechanism of action. Unfortunately, **4** had high plasma clearance with a plasma half-life of < 1 h and lead optimization was focused on improving the in vivo properties.

Basic substituents were introduced onto the isoindoline group with the aim of improving the volume of distribution. Although some of the modifications resulted in compounds with hERG activity, it was possible to obtain potent compounds with low hERG activity, and the compound AT-13387 (**5**) was selected as a clinical candidate (Fig. 2). AT-13387 demonstrated activity against a wide range of cancer cell lines, and treatment for 24 h in vitro resulted in suppression of client proteins for up to 7 days after removal of the inhibitor. Pharmacokinetic/dynamic profiling showed retention of AT-13387 in the tumor only and sustained effects on biomarkers following a single dose. The extended tumor pharmacodynamic effect could be a consequence of tumor-specific retention of the compound and sustained inhibition of HSP90. The compound also demonstrated efficacy in a number of different xenografts in nude mice, with significant tumor growth delay. AT-13387 is currently in phase I clinical trials for the treatment of tumors known to be dependent on HSP90 client proteins.

The next presentation was by Dr. David Fox (Pfizer Global R&D), who described the discovery program that has led to a second-genera-

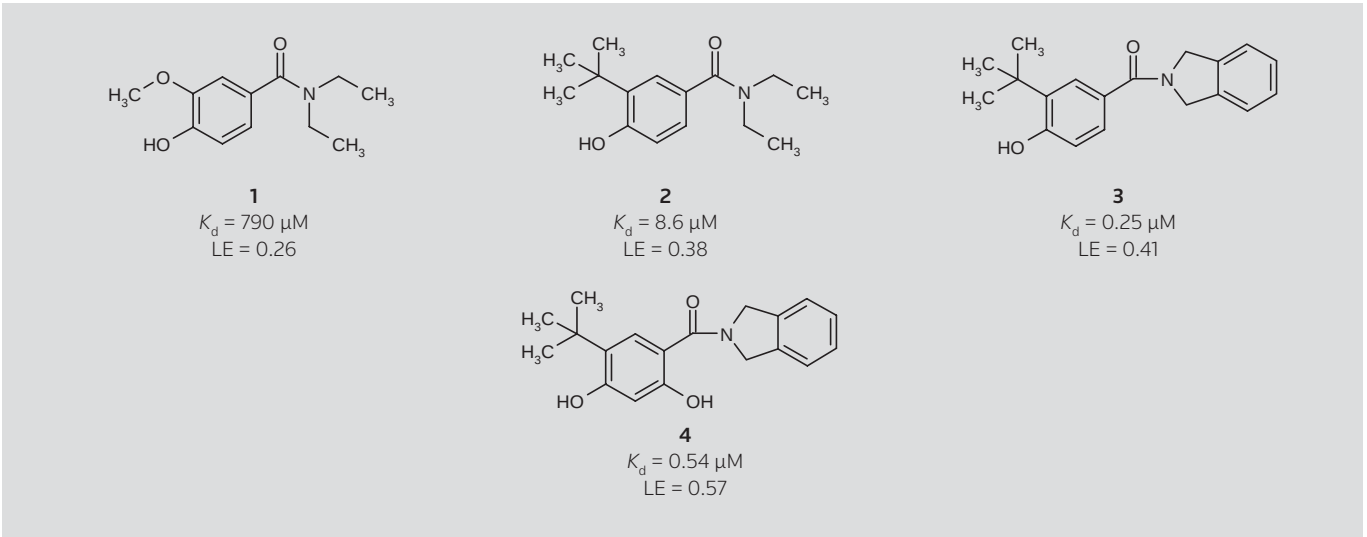


Figure 1.

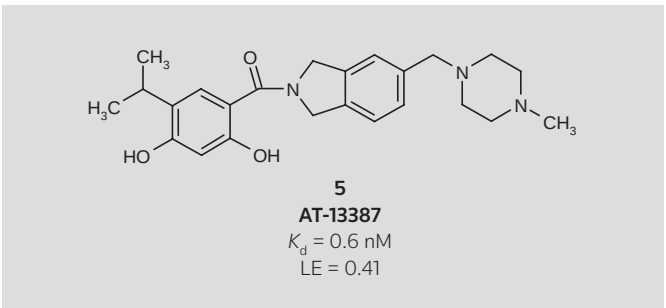


Figure 2.

tion series of selective phosphodiesterase PDE5 inhibitors for cardiovascular conditions (*2*). The talk began by outlining the important role played by the second messenger cGMP in the cardiovascular system, notably the role it plays in vascular smooth muscle relaxation and reducing platelet aggregation. The phosphodiesterase family of metalloenzymes, responsible for the breakdown of cyclic nucleotides, was then highlighted as a key feature of the cGMP pathway. PDE5 in particular, through its localization in vascular smooth muscle and platelets, and its specificity for cGMP (over cAMP), is an important target for drug intervention. The program established a number of broad criteria that would need to be met in order to fulfill the requirements for a versatile and effective agent for cardiovascular conditions. Among these was the importance of once-daily dosing potential, with low overall dose size to maximize the opportunities for combination therapy. In addition, safety and tolerance were recognized as key features for successful therapy. When surveying the clinical agents that were available at the start of the project (sildenafil, vardenafil, tadalafil), it was concluded that none represented a suitable starting point for a program that would deliver the exacting requirements that had been set out. The potential to deliver a once-daily agent from the sildenafil and vardenafil templates was considered to be unlikely, and the PDE11 activity of tadalafil was a concern at the time, since the role and possible toxicological liabilities associated with PDE11 inhibition had not been well established at this stage.

As a result, the project initiated a high-throughput screen in an attempt to identify new proprietary series that could form the basis of a second-generation agent. Dr. Fox then went on to present an analysis of the relationship between pharmacological selectivity and pharmacokinetic profile, and how the two needed to be considered alongside one another when seeking to minimize off-target pharmacological effects, which are often driven by peak drug exposure during the dosing period (C_{max}). In this particular program, a wealth of clinical data with sildenafil suggested that as long as a low peak-to-trough ratio was achieved (as would be expected for an agent with a long half-life), selectivity for PDE5 over PDE6 as low as 30-fold would be sufficient to avoid the visual disturbances associated with PDE6 inhibition. The hit-to-lead program also kept a close eye on molecular weight and lipophilicity (as expressed by clogP and logD) in order to ensure there was sufficient headroom for further optimization during the candidate identification stage. The parameter *ligand efficiency* (LE; a measure of the free binding energy per heavy atom) was used throughout to monitor progress and lead quality.

The talk then described one arm of the hit-to-lead program, where a potent but severely flawed hit, **6**, was transformed into a low-molecular-weight, structurally attractive lead series through a sequence of two parallel chemistry libraries. The outcome is illustrated in Figure 3.

The first library, based on a series of 2,4-diaminoquinazolines, sought to replace the nitro group, which according to x-ray co-crystal structures played a key role in binding through a bridged hydrogen bonding interaction with a backbone glutamine residue in the active site of the target enzyme. Furthermore, this library was designed to deliver lead compounds in a lipophilicity range around two orders of magnitude lower than the original hit. Compound **7** was identified in the first library, and this represented an excellent

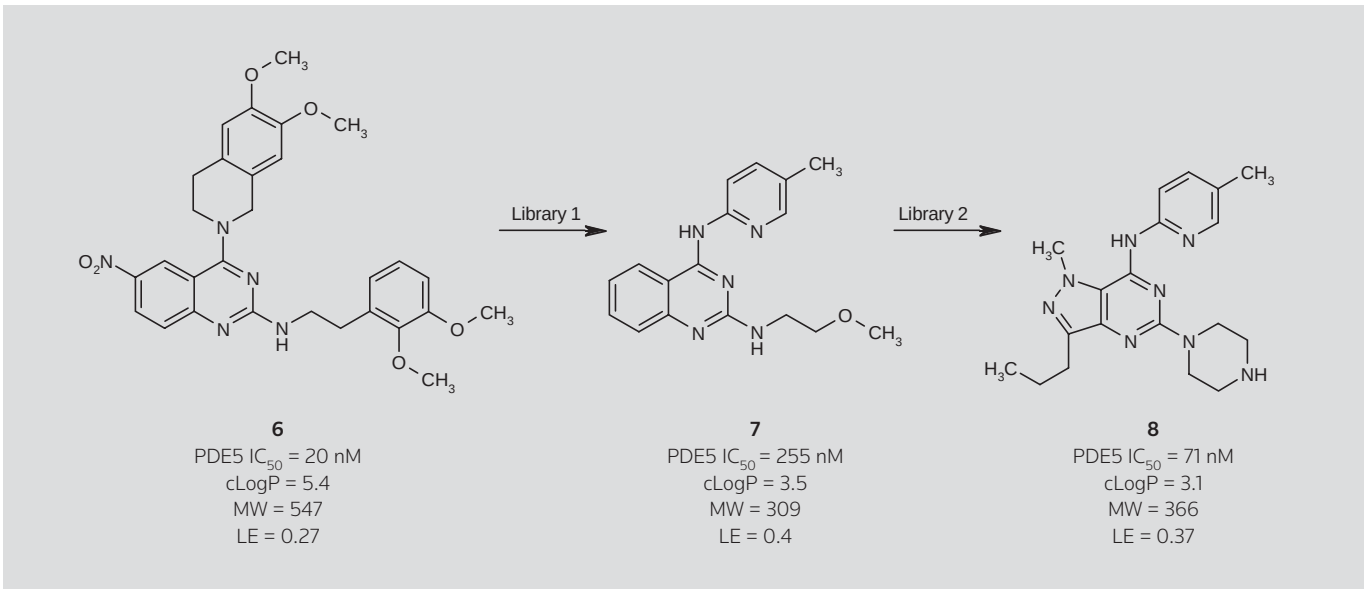


Figure 3.

springboard for a follow-up library that would look to build upon the discovery of aminopyridines as suitable substituents at the C4 position of the quinazoline. A key objective for this second library was to identify an alternative central template that would present increased scope for synthetic manipulation. Compound **8** emerged directly from this second library, and presented the project with the basis of a lead optimization program. x-Ray crystallographic analysis of the ligand–enzyme complex and use of homology models for the selectivity targets became an important part of the subsequent strategy. Notably, it became clear that the aminopyridine substituent was playing a key role in delivering the bridged hydrogen bonding interaction with the backbone glutamine residue, and extension of the N^1-pyrazole substituent would drive an improvement in PDE5 potency and selectivity over PDE10 (compound **9**; Fig. 4).

A breakthrough in potency and selectivity was achieved when an amide substituent was introduced at the C3 position of the pyrazole ring and removal of the basic center at C5 led to **10**, which successfully combined pharmacology and long half-life with the potential for good transcellular absorption. Unfortunately, this compound could not be advanced to clinical development as a result of cardiac contractility effects seen in dog safety studies. In response, a related C3 acidic series was introduced, which delivered subnanomolar

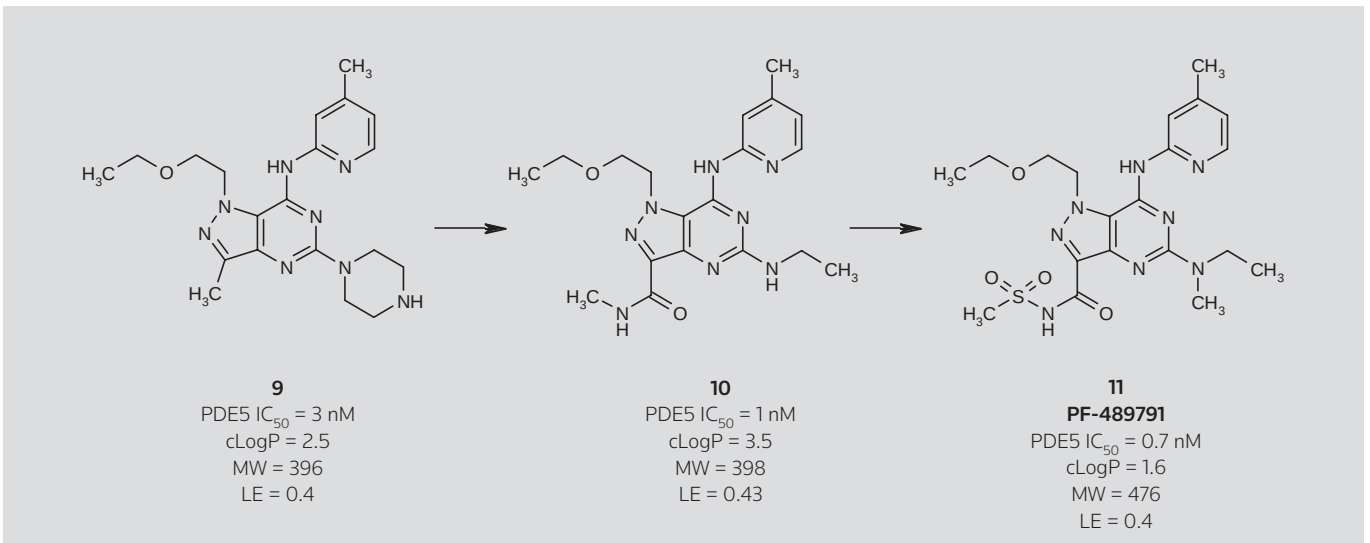


Figure 4.

potency for PDE5 and > 30-fold selectivity over related PDEs. The presence of the polar acidic group was expected to circumvent the safety findings associated with the neutral amide series. Although the parent series of carboxylic acids suffered from low and variable bioavailability in rats (presumably through glucuronidation), the *N*-acylsulfonamide **11** maintained the excellent pharmacological profile seen with the carboxylic acids, but now demonstrated a pharmacokinetic profile consistent with the project objectives. Importantly, compound **11** (PF-489791) avoided the cardiac contractility effects seen with **10**, and was selected for clinical evaluation. In the first-in-human single oral dosing studies, PF-489791 demonstrated an excellent pharmacokinetic profile, with dose-proportional increases in C_{max} and AUC, and a half-life of 12-14 h. PF-489791 is currently in phase II trials for pulmonary arterial hypertension.

The morning session of the meeting concluded with a presentation from Dr. Simon Hodgson (GlaxoSmithKline) on the optimization of a dual histamine H_1/H_3 receptor antagonist for the treatment of allergic rhinitis. Allergic rhinitis is a common disease, and although many symptoms, e.g., rhinorrhea and itching, are controlled via H_1, the major symptom of nasal congestion is not adequately controlled. Histamine H_3 receptors are widely expressed in the central nervous system (CNS) and peripheral nerve endings, and mediate the inhibition of neurotransmitter release. It is thought that activation of the H_3 receptor on the presynaptic terminals of sympathetic neurons reduces noradrenaline release, resulting in vasodilatation and nasal congestion. In principle, blocking the H_3 receptor would therefore be of benefit for the treatment of allergic rhinitis. Dr. Hodgson outlined the three options for a poly-pharmacological approach: add-on therapy, fixed-dose combinations or poly-pharmacology in a single molecule. Although the third option provides initial design challenges, the development of such an entity is more straightforward, and the remainder of the talk focused on this approach.

The target profile for the molecule included potent and balanced activity at H_1 and H_3 receptors, good oral drug properties, no off-target effects and minimal brain penetration. The H_1 and H_3 pharmacophores are quite different, however, and cross-screening resulted in a new lead, **12** (Fig. 5). The lead molecule was optimized using a square-array approach investigating 10 amines and 20 substituted aryl groups to **13**. The array approach resulted in some clear SAR conclusions –H_3 affinity was mainly a consequence of the amine RHS groups, while H_1 affinity was controlled by critical interactions at both ends of the molecule. Examples from the initial work include the molecules **14** and **15**; although these compounds had the desired balanced potency at H_1 and H_3 receptors, both demonstrated poor oral bioavailability in the rat and high CNS penetration.

To address the issue of CNS penetration, a number of analogues containing a carboxylic acid group were synthesized. The acid was better tolerated at the pendant left-hand side, resulting in retention of the balanced pharmacology, e.g., compound **16** (Fig. 6). The presence of the acid group had the desired effect on CNS penetration; however, the oral bioavailability of **16** was poor in both rats and dogs. Modification to an all-carbon linking group to the acid circumvented this issue, delivering **17**, with good oral bioavailability. Unfortunately, the compound was metabolized in human, rat and dog hepatocytes to the corresponding phenol **18**. The phenol fired an in silico genotoxicity alert and was positive in a mouse lymphoma assay in the presence and absence of S9, which prevented further progression of the molecule. Modification of the piperazine to a piperidine obviates the potentially problematic metabolite, and **19** (Fig. 7) was identified as a candidate molecule. Compound **19** showed good potency in in vitro H_1 and H_3 receptor assays, > 100-fold selectivity across a broad screen of targets, good oral bioavailability in rats and dogs, in vivo efficacy in guinea pig models and the required safety profile. The compound was evaluated in humans as single and repeated (7 days)

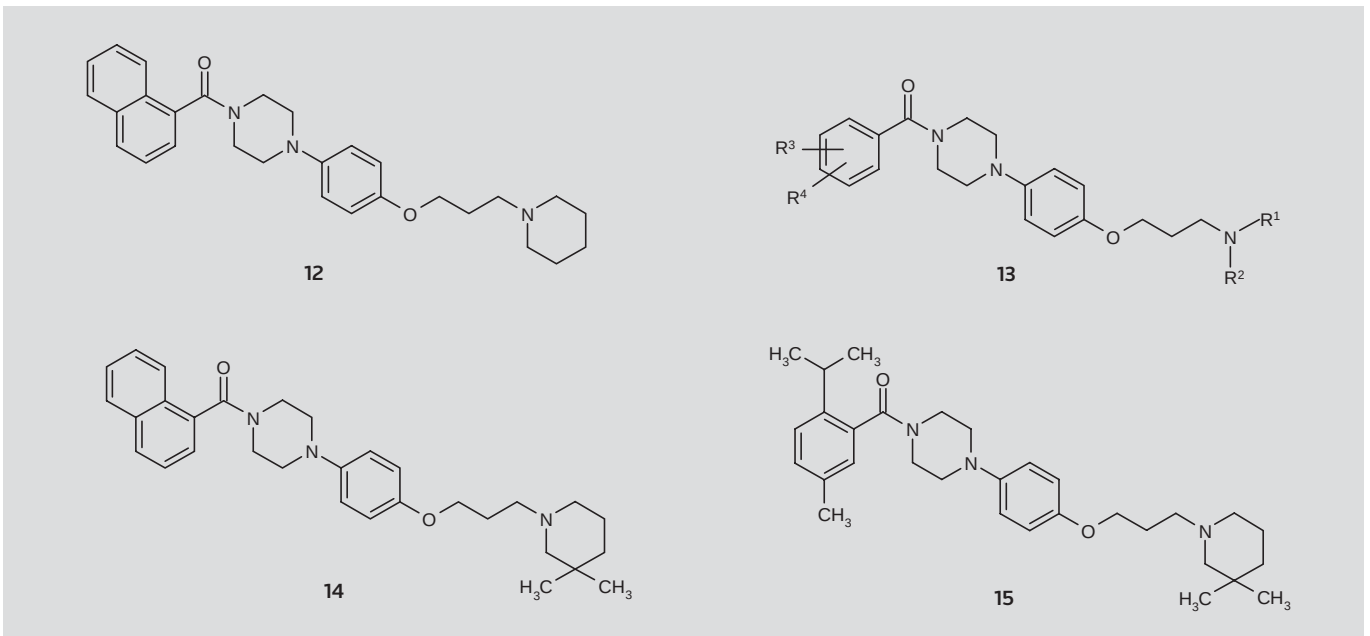
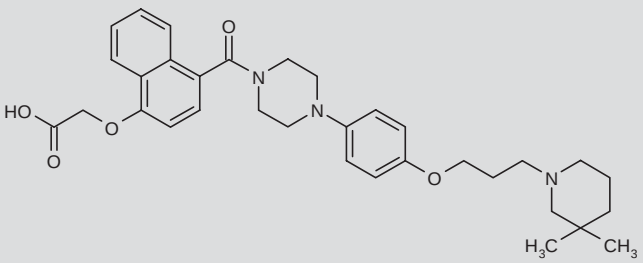
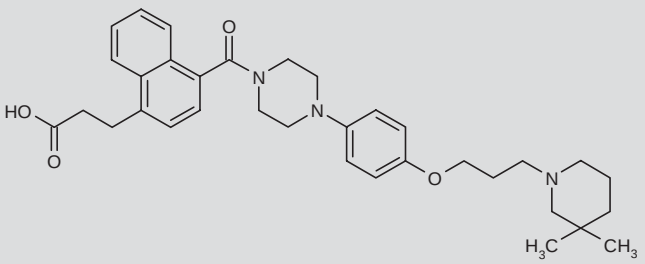


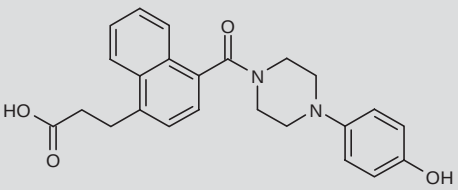
Figure 5.



16
hH_1 = 7.9 (FLIPR)
hH_3 = 8.3 (GTPγS)
Poor oral bioavailability (rat & dog)

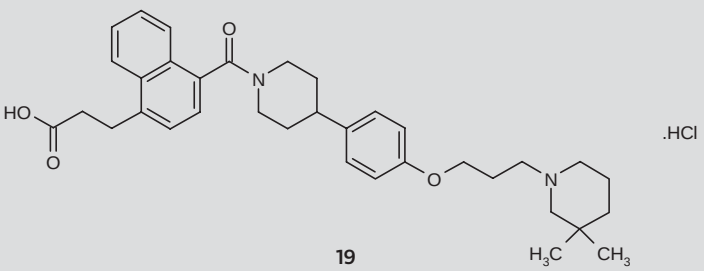


17
hH_1 = 8.34 (FLIPR)
hH_3 = 8.41 (GTPγS)
> 50% oral bioavailability (rat & dog)



18

Figure 6.



19
hH_1 = 8.1 (pP2, CHO)
hH_3 = 7.8 (pKb, GTPγS)
> 50% oral bioavailability (rat & dog)
Blood:brain ratio = 0.07
hERG = 4.95 (pIC_{50}, patch clamp)

Figure 7.

doses of 12, 20, 50 and 100 mg. In these clinical studies, **19** demonstrated a good safety profile and pharmacokinetics and pharmacodynamics consistent with a low oral dose administered once daily.

The 2009 SMR Award for outstanding achievement in the drug discovery and development of Januvia™ (sitagliptin) was presented by the SMR chairman Dr. Rob Williams to Dr. Emma Parmee (Merck & Co.). After receiving the award, Dr. Parmee gave a presentation outlining the history of Januvia™, a first-in-class dipeptidyl peptidase 4 (DPP IV) inhibitor for the treatment of type 2 diabetes. Diabetes is a global epidemic, and despite the availability of a range of treatments, significant unmet medical needs remain. DPP IV is a proline-selective serine dipeptidase, and inhibitors of DPP IV have been shown to increase circulating levels of glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) both in animal models and in the clinic, resulting in improved glucose tolerance.

The starting point for the program centered on two thiazolides, **20** and **21** (Fig. 8), in-licensed from Probiodrug. However, development was discontinued, as both compounds showed unacceptable toxicity profiles in rats and dogs. The two isomers showed identical inhibition of DPP IV in vitro and in vivo, but **21** was 10-fold more toxic. The difference in toxicity profiles resulted in the hypothesis that the effects were not mechanism-related but a consequence of off-target

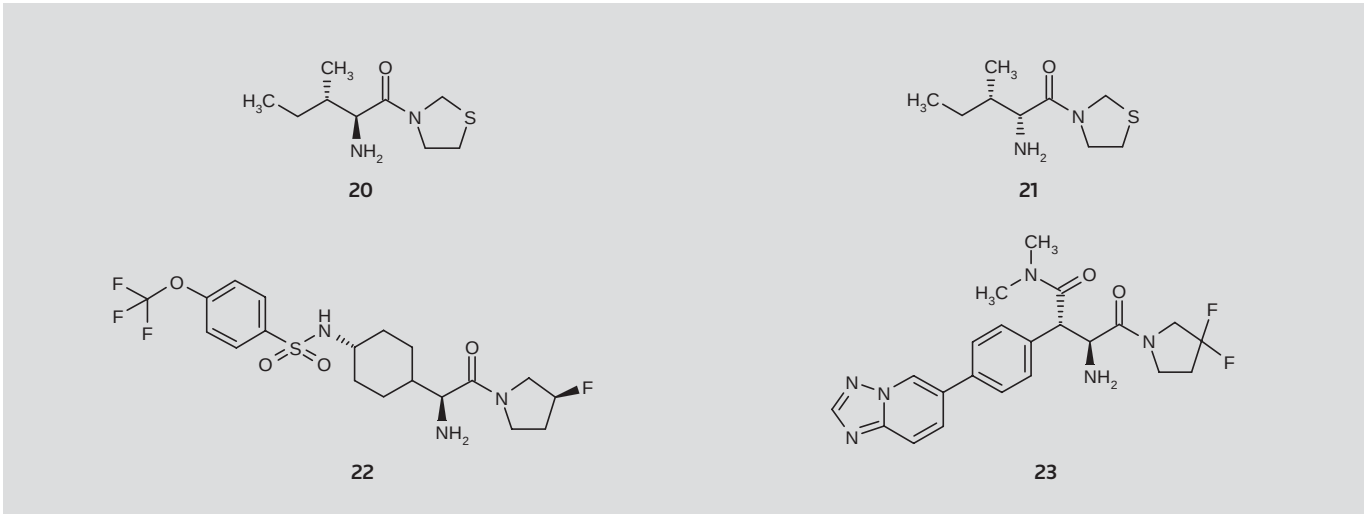


Figure 8.

inhibition. Screening against a panel of related dipeptidases showed that **20** and **21** had activity against DP8 which differed by 10-fold (3).

After this investigative work, an internal program was initiated to develop a potent DPP IV inhibitor with > 1,000-fold selectivity over the related proline peptidases, especially DP8 and DP9. The first series investigated was based on cyclohexylglycine-derived inhibitors, culminating in the identification of the fluoropyrrolidine derivative **22**, with a DPP IV IC_{50} of 36 nM, good to excellent oral bioavailability and a half-life of 4-12 h in preclinical species (4). Unfortunately, the compound had low micromolar affinity for DP8 and DP9 and its progression was stopped. After Januvia™ had been identified, further work on the α-amino acid series was carried out, resulting in a "back-up" compound, **23**.

Dr. Parmee then described the hits obtained from a high-throughput screen, the β-aminoacyl amide **24** and the piperazine **25** (Fig. 9). The β-aminoacyl amide series was optimized to provide a potent and highly selective DPP IV inhibitor, **26**. Unfortunately, the compound had very low oral bioavailability in rats (F < 1%) due to poor absorption and high clearance, and could not be progressed; however, the structure–activity relationship (SAR) from the series was incorporated into the piperazine series to produce a hybrid series, **27**. The main issue with the new series was low oral bioavailability as a consequence of extensive metabolism. To circumvent this problem, a range of heterocycles were investigated as replacements for the piperazine group. The conclusion of this area of work was the selection of the triazolopiperazine group, e.g., **28**. Further optimization of the substituent on the triazolopiperazine motif and adjustment of the fluorine substitution on the phenyl ring resulted in **29**, the compound which become Januvia™.

A highly efficient synthesis of **29** has recently been published; the new route reduces the total waste generated per kilogram of drug substance produced in comparison to the first-generation route, and eliminates aqueous waste streams (5).

In terms of clinical studies on Januvia™ a 100-mg once-daily monotherapy was selected for phase III studies. The compound was well tolerated, with a low incidence of hypoglycemia, and showed a significant improvement in the side effect profile when compared to other agents. The compound also showed improved glycemic control in studies when used in combination with metformin. The monotherapy and a fixed-dose combination with metformin, Janumet™, were approved by the FDA in 2006 and 2007, respectively.

Dr. Karl Gibson (Pfizer Global R&D) began the final session with a review of the discovery of PF-2413873, a progesterone receptor antagonist for the treatment of endometriosis. Dr. Gibson began by providing the audience with a background to the disease, highlighting the key role played by estradiol in the menstrual cycle, the role played by the same hormone in ectopic endometriosis, and the shortcomings of existing treatments. He then went on to describe how the steroidal progesterone receptor antagonist mifepristone (RU-486) was shown 20 years ago to block the proliferative action of estradiol on the endometrium in primates (6), and more recently, has been shown to treat surgically implanted endometriosis in a primate model of the disease. This effect, which involves blockade of the progesterone receptor, is termed functional estrogen antagonism and does not lower estradiol levels. As a result, it avoids the reduction in bone mineral density observed with treatment using gonadotrophin-releasing hormone (GnRH) analogues. The biochemical processes associated with progesterone receptor activation were then outlined, in particular how steroid agonist binding induces a conformational change in the receptor, which then triggers dimerization and translocation, followed by recruitment of coactivator proteins. Binding of these to DNA leads to recruitment of the remainder of the transcription machinery, leading to changes in gene expression and subsequent cellular response. With steroidal antagonists the conformational change associated with agonist binding is prevented, and an alternative conformational change is elicited, which results in an interaction with corepressor peptides, which bind to DNA and inhibit gene transcription.

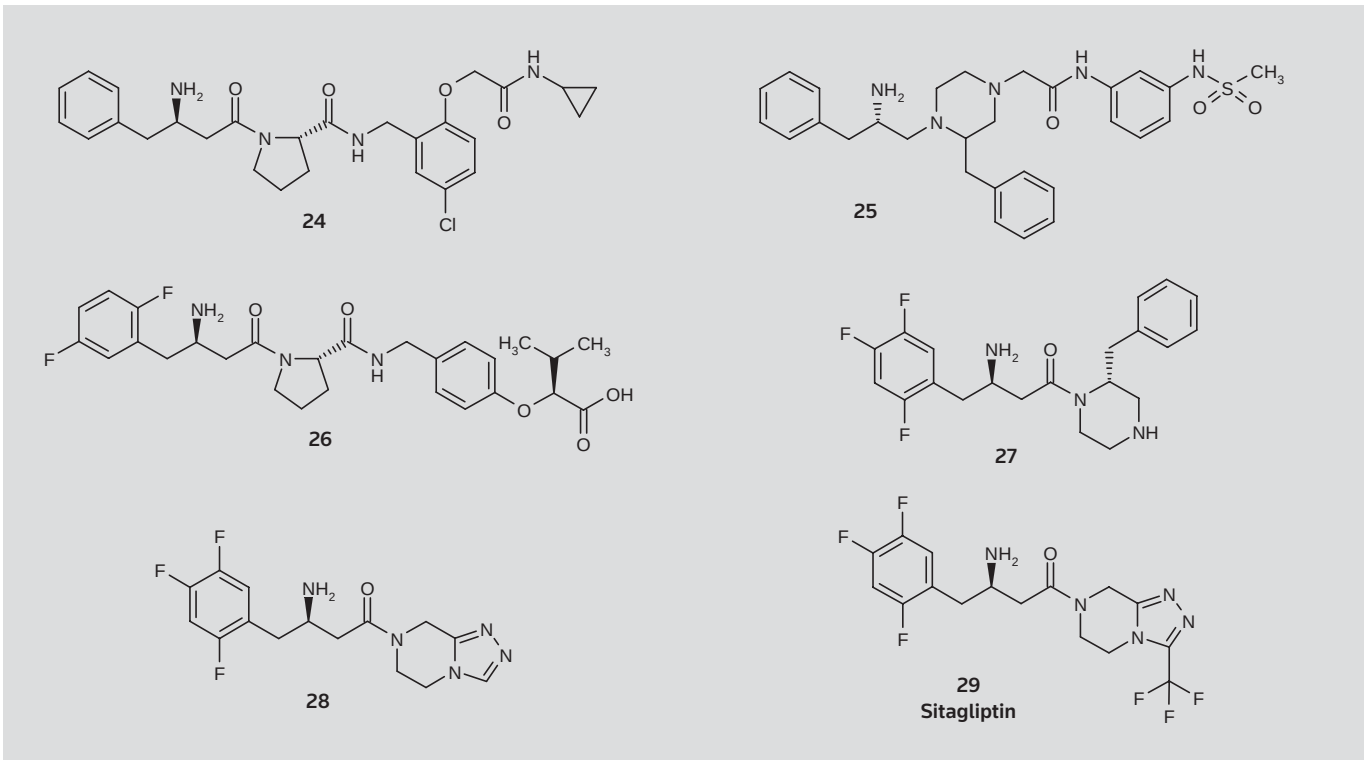


Figure 9.

The remainder of the talk focused on the medicinal chemistry program to identify a selective, nonsteroidal progesterone receptor antagonist which, it was hoped, would have advantages over a steroidal program in terms of drug complexity and patentability. The major challenge associated with the program was to achieve sufficient selectivity over closely related nuclear hormone receptors (e.g., glucocorticoid, mineralocorticoid and androgen receptors). The steroidal agonists for these receptors all share a ketone group in the steroid A-ring, which forms a key hydrogen bond with a protonated arginine residue. An important structural feature in all existing nonsteroidal ligands for nuclear hormone receptors is the presence of an aryl nitrile group, which, according to structural studies, mimics the ketone group in steroidal ligands. Given the clear importance of this group for activity, it was decided to preserve it in all subsequent designs. It was also recognized that the binding environment was lipophilic and the compounds needed to be of a certain size in order to span the regions occupied by the natural ligands. In order to ensure the project maintained good drug-like properties throughout the course of the program, a parameter termed *lipophilicity efficiency* was tracked (this is determined by subtracting the logD of the compound from the pIC_{50}). This provides an estimate of how much of the activity of a compound is a result of specific interactions rather than nonspecific lipophilicity-driven binding. This approach to design and decision-making (also termed ligand lipophilicity efficiency, or LLE) has since been published by Leeson et al. (7). The lead matter for the program emerged from a high-throughput screen where only hits that contained an aryl nitrile group were followed up. Of these, a series of cyanophenoxypyrazoles (e.g., compound **30**; Fig. 10) was selected for lead optimization on the basis of their similarity to a series of HIV reverse transcription inhibitors, for which the synthetic technology and compound safety were well established.

Although it was believed that the lead compound was sufficiently large to span the regions occupied by steroidal ligands, it was highly lipophilic and still had only modest potency and poor selectivity over androgen receptors. The synthetic route to the lead was highly versatile and enabled changes at all four positions of the pyrazole ring to be introduced readily. As a result, it was found that an amide substituent attached to the pyrazole nitrogen delivered significant improvements in LLE and selectivity (compound **31**). Further optimization was achieved through modification of the alkyl groups flanking the aryl ether. Notably, the introduction of cyclopropyl (Fig. 11) led to compound **32**, PF-2367982, which showed an improvement in metabolic stability (in human hepatocytes) while maintaining good potency and high LLE.

Despite an attractive pharmacological profile, the pharmacokinetic behavior of PF-2367982 was disappointing, with a short plasma half-life predicted based on variable clearance and a very low volume of distribution. The lack of concordance between in vitro and in vivo pharmacokinetics in rats suggested a nonhepatic clearance route, and it appeared that the compound underwent amide hydrolysis. Ultimately, a sulfone group was identified as a robust replacement for the amide, and redistribution of the lipophilicity around the pyrazole ring to the phenyl ring enabled potency, stability and selectivity to be optimized, leading to the identification of the clinical candidate PF-2413873 (compound **33**). Although the compound is poorly soluble in buffer, it does show improved solubility in simulated

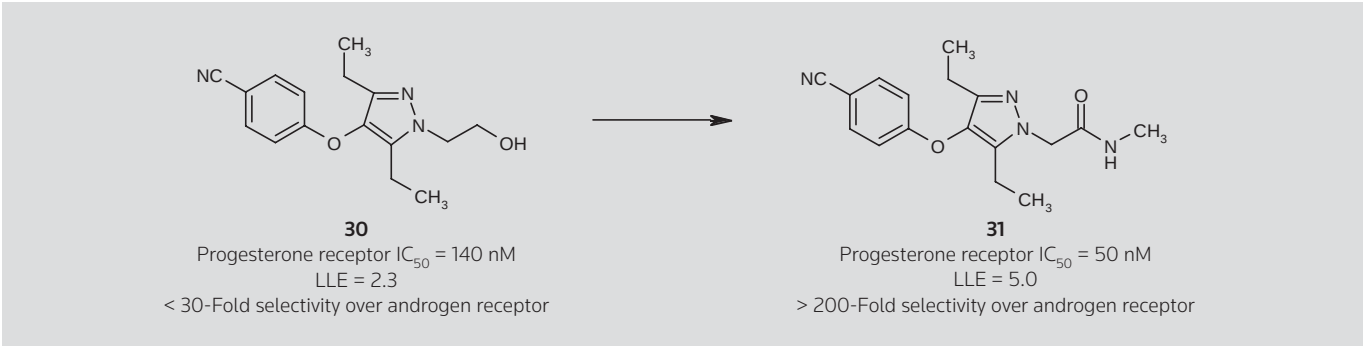


Figure 10.

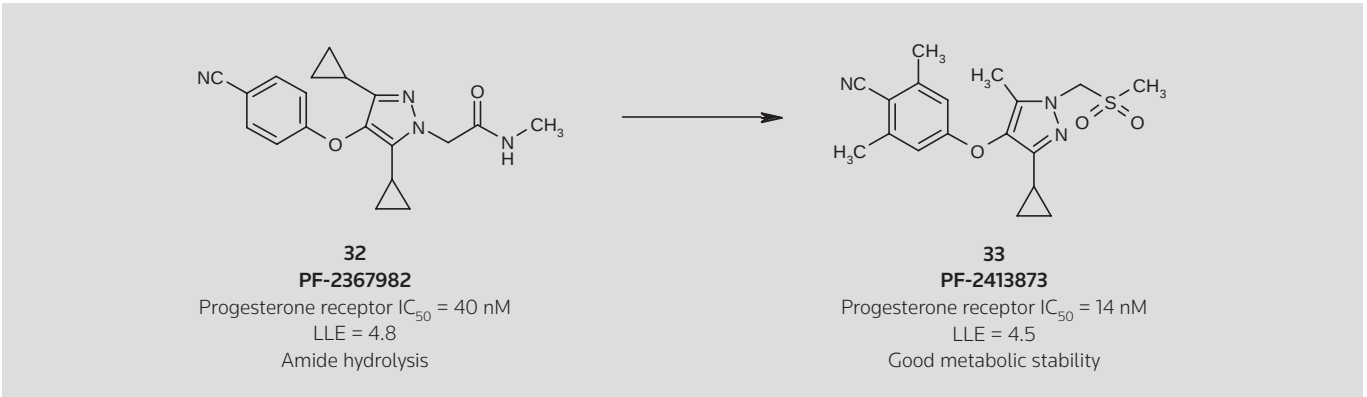
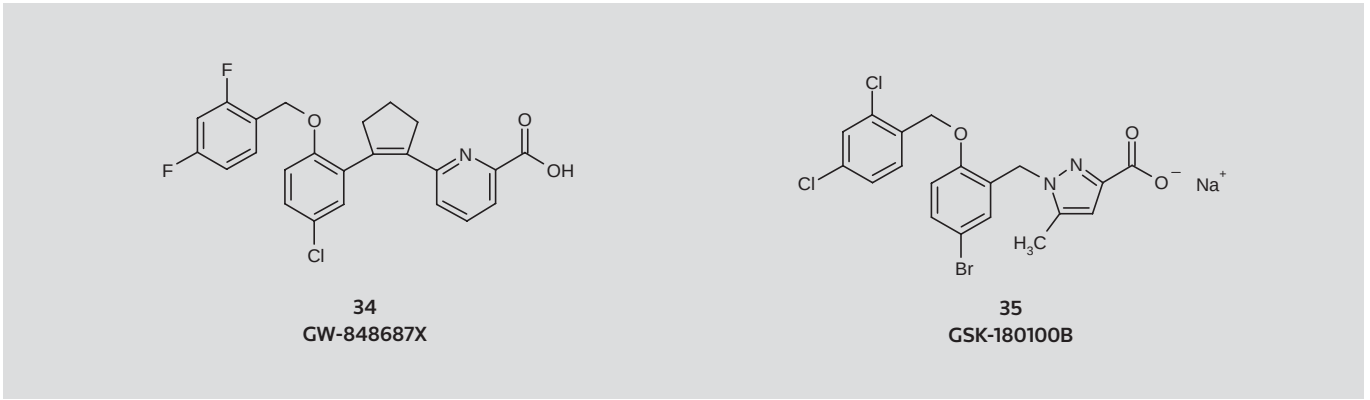


Figure 11.

gastric media, particularly fed media, where the presence of bile acid salts appears to have a favorable effect. In preclinical pharmacokinetic studies, PF-2413873 shows high clearance/low bioavailability in rats and low clearance/high bioavailability in dogs, and a higher volume of distribution compared with PF-2367982. Importantly, there was good concordance from in vitro to in vivo data within each species. This pharmacokinetic profile was borne out in phase I clinical studies, where the compound was well tolerated and displayed a plasma half-life of around 40 h. Dr. Gibson finished the talk with a description of the pharmacology of PF-2367982. It behaves as a competitive antagonist of the progesterone receptor but, surprisingly for an antagonist, appears to suppress nuclear translocation through modulation of the interaction of the progesterone receptor with coregulators. The in vivo pharmacology was also described, with PF-2413873 being at least as effective as RU-486 in blocking endometrial growth in cynomolgus monkeys at reasonable free drug exposures.

The final talk of the day was given by Dr. Mairi Gibson (GSK), detailing the discovery of second-generation prostanoid EP_1 receptor antagonists for the treatment of pain. The presentation began with an account of the key role played by the prostanoid PGE_2 in pain conditions, such as rheumatoid arthritis or pain associated with tissue injury. PGE_2 exerts its physiological effects through the activation of four G protein-coupled receptors (GPCRs), $EP_{1\text{-}4}$, with the EP_1 receptor strongly associated with inflammation, pain and fever. Indeed, antagonists of the EP_1 receptor have shown potential as treatments for visceral pain, overactive bladder and cerebral ischemia (8). In seeking a selective EP_1 antagonist, the project team sought an agent that would be effective in both acute and chronic models of pain with an ED_{50} value of ≤ 5 mg/kg. In addition, the compound would need to have potency and pharmacokinetics suitable for once- or twice-daily dosing, and would need to exhibit significant brain penetration to access EP_1 receptors in the CNS. The first clinical candidate identified by the team was the cyclopentenyl derivative GW-848687X (compound **34**; Fig. 12) (9), but it became clear during the course of the development program that this compound had insurmountable shortcomings that would need to be addressed by the back-up program. In particular, there was evidence for cytochrome P450 induction with GW-848687X in animal models of pain, with reduced exposure on days 4 and 5 in a 5-day rat joint pain study compared with earlier time points. In addition, the series had been associated with light instability issues, presumably as a result of an electrocyclic rearrangement involving the cyclopentenyl ring.

In order to address these issues, an alternative heterocyclic lead series was pursued, exemplified by the pyrazole GSK-180100B (compound **35**). This compound showed promise in that it avoided the reduction in exposure on chronic dosing seen with its predecessor. However, it had low CNS penetration and was not effective in the rat joint pain model. In an attempt to improve the CNS penetration of the compound, and thereby improve in vivo efficacy, the pyrazole



34
GW-848687X

35
GSK-180100B

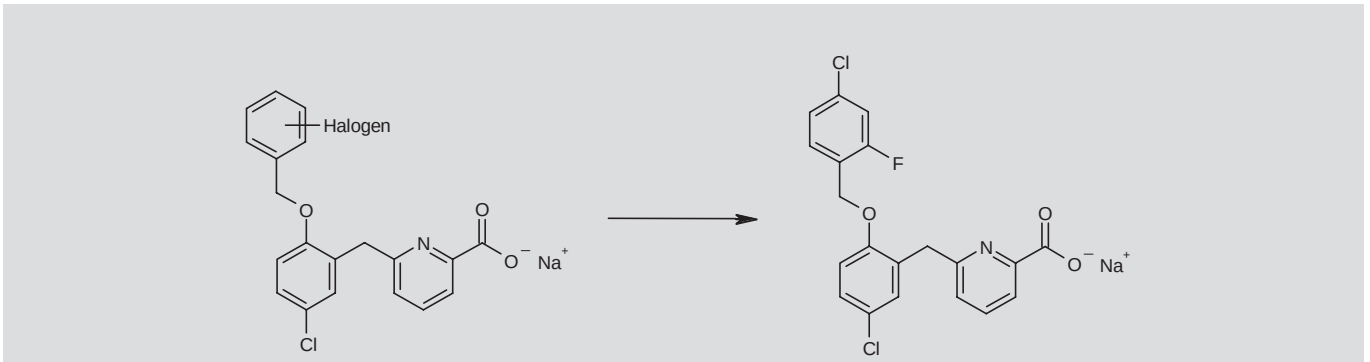
Figure 12.

ring was replaced with a pyridyl ring (Fig. 13). The activity and brain:blood ratio of members of this series were optimized by introducing a range of halo-substituted *O*-benzyl substituents. This led to the identification of GSK-269984A (compound **36**), which combined an excellent in vitro pharmacological profile with good pharmacokinetics and a brain:blood ratio of 0.39. Crucially, GSK-269984A showed full reversal of hypersensitivity at 10 mg/kg in the rat joint pain model, with no reduction in efficacy over the course of the 5 days. Dr. Gibson went on to describe how the synthetic route needed to be adapted to deliver material to support further preclinical studies, highlighting as the key step a Suzuki coupling with a benzyl chloride intermediate.

During the course of the pharmacokinetic evaluation of GSK-269984A it became clear that the compound carried a significant pharmacokinetic risk, with predictions to man from rat being acceptable, but dog and cynomolgus monkey data predicting low bioavailability. To confound the situation further, in vitro to in vivo translation within each species was poor. As a result, the project team took the decision to advance the compound to a microdose study in humans to resolve the pharmacokinetic uncertainty. The i.v. arm of this study indicated a plasma half-life of 8.5 h, sufficiently long to underwrite the subsequent oral study, which itself served to confirm the findings from the rat pharmacokinetic study. Indeed, GSK-269984A was shown to have an oral bioavailability of 80-90% and an oral half-life of 10.5 h, and therefore met the project objectives. The talk concluded with a summary of the pros and cons of the microdose strategy in drug discovery, emphasizing the low cost and minimal bulk required to reach a clinical decision point, but also noting the loss of time that can be incurred by placing a full development program on hold.

DISCLOSURES

Diane Coe (GlaxoSmithKline) and David Fox (Pfizer Global R&D) are members of the Society for Medicines Research (SMR) Committee which organizes conferences on behalf of the SMR. Details of forthcoming meetings can be obtained from the SMR Secretariat: 840 Melton Road, Thrumaston, Leicester, LE4 8BN, UK. Tel: +44 (0)116 269 1048; Fax: +44 (0)116 264 0141; E-mail: secretariat@smr.org.uk; URL: http://www.smr.org.uk.



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GSK-269984A

Figure 13.

REFERENCES

1. Murray, C.W., Rees, D.C. *The rise of fragment-based drug discovery*. Nat Chem 2009, 1(3): 187-92.
2. Palmer, M. J., Bell, A.S., Fox, D.N.A., Brown, D.G. *Design of second generation phosphodiesterase 5 inhibitors.* Curr Top Med Chem 2007, 7(4): 405-19.
3. Lankas, G.R., Leiting, R., Roy, R.S. et al. *Dipeptidyl peptidase IV inhibition for the treatment of type 2 diabetes: Potential importance of selectivity over dipeptidyl peptidases 8 and 9.* Diabetes 2005, 54(10): 2988-94.
4. Caldwell, C.G., Chen, P., He, J. et al. *Fluoropyrimidine amides as dipeptidyl peptidase IV inhibitors.* Bioorg Med Chem Lett 2004, 14(5): 1265-8.
5. Hansen, K.B., Hsiao, Y., Xu, F. et al. *Highly efficient asymmetric synthesis of sitagliptin*. J Am Chem Soc 2009, 131(25): 8798-804.
6. Wolf, J.P., Hsiu, J.G., Anderson, T.L., Ulmann, A., Baulieu, E.E., Hodgen, G.D. *Noncompetitive antiestrogenic effect of RU 486 in blocking the estrogen-stimulated luteinizing hormone surge and the proliferative action of estradiol on endometrium in castrate monkeys.* Fertil Steril 1989, 52(6): 1055-60.
7. Leeson, P.D., Springthorpe, B. *The influence of drug-like concepts on decision-making in medicinal chemistry.* Nat Rev Drug Discov 2007, 6(11): 881-90.
8. Hall, A., Billinton, A., Giblin, G.M.P. *EP1 antagonists for the treatment of inflammatory pain.* Curr Opin Drug Discov Devel 2007, 10(5): 597-612.
9. Giblin, G.M.P., Bit, R.A., Brown, S.H. et al. *The discovery of 6-[2-(5-chloro-2-{[(2,4-difluorophenyl)methyl]oxy}phenyl)-1-cyclopenten-1-yl]-2-pyridinecarboxylic acid, GW848687X, a potent and selective prostaglandin EP1 receptor antagonist for the treatment of inflammatory pain.* Bioorg Med Chem Lett 2007, 17(2): 385-9.