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MEETING REPORT

MEDICINAL CHEMISTRY HIGHLIGHTS FROM THE 239TH AMERICAN CHEMICAL SOCIETY NATIONAL MEETING & EXPOSITION

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SUMMARY

The American Chemical Society (ACS) organizes two meetings each year to accommodate the tremendous amount of research being done, with over 7,000 papers presented at each meeting. The theme for the 239th Meeting and Exposition was "Chemistry for a Sustainable World", with dedicated lectures and events, but all areas of research in chemistry were represented. The medicinal chemistry division of the congress included hundreds of posters and numerous symposia and general oral sessions. These have been reviewed to provide a selection of compounds with promising therapeutic activity or which have provided insight into therapeutic targets and potentially useful mechanisms of action. The ACS meetings provide the opportunity to glimpse these molecules in the early stages of development, allowing in some cases the first view of their pharmacological profiles.

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INTRODUCTION

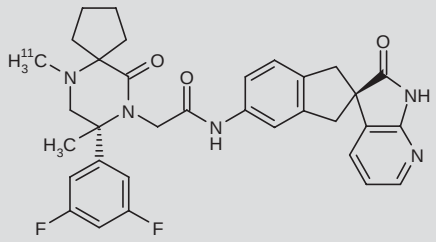
Anyone interested in getting an idea of the state of research in medicinal chemistry at a given time point could save a great deal of time and effort by focusing on the presentations given at one of the two national meetings held each year by the American Chemical Society (ACS). They would nevertheless be faced with the daunting task of trying to attend the great number of oral sessions while having a look at the hundreds of posters presented over the course of 5 days. Such an exhaustive exercise would yield, however, new information on drugs representing known and newer mechanisms of action for almost any disease of interest. A selection of these compounds is given below organized by therapeutic area, focusing on molecules which have displayed activity encouraging further investigation or the synthesis of which has provided the impetus for further research.

AIDS

In order to improve the antiviral activity and ADME properties of MPC-4326, a search at Myriad Pharmaceuticals for next-generation HIV maturation inhibitors led to the identification of **MPI-461359** and its preclinical evaluation. MPI-461359 proved highly potent in MT4 cytoprotection (EC_{50} = 23 nM) and peripheral blood mononuclear cell (PBMC) viral replication (EC_{50} = 7 nM) assays. MPI-461359 displayed selective inhibition of Gag processing, metabolic stability in liver microsomes from humans, monkeys and dogs, and no cytochrome P450 or hERG inhibition issues. Pharmacokinetic investigation in rats yielded low clearance with a good half-life, a low volume of distribution, very good oral bioavailability (35.8%) and amenability to solid-dosage formulation. Lastly, no drug-related toxicity was seen in rats treated with escalating doses for 28 days (1).

MIGRAINE

The first calcitonin gene-related peptide (CGRP) receptor antagonists have demonstrated efficacy in migraine. To explore this effect, Merck & Co. investigators sought a positron emission tomography (PET) tracer for the receptor to evaluate its occupancy by these antagonists in the central nervous system. Their efforts were highlighted in a poster and an oral presentation at the meeting.



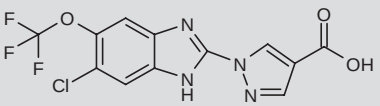
[11C]-MK-4232

[11C]-MK-4232 (K_i = 0.039 nM; K_d = 0.27 and 0.22 nM, respectively, for human and rhesus monkey CGRP receptors; human P-glycoprotein basolateral–apical/apical–basolateral transport ratio = 1.7) was advanced to phase I exploration after exhibiting many of the properties desirable for a PET tracer and displaying good uptake when characterized in rhesus monkeys (2). Standard uptake values at 80 min for [11C]-MK-4232 were 1.4 in cerebellum and 0.7 in white matter in rhesus monkeys, and the cerebrospinal fluid (CSF)/plasma ratio was 3.1. In brains of rhesus monkeys the uptake and high affinity of [11C]-MK-4232 for the CGRP receptor resulted in a large specific signal. Antagonists of the CGRP receptor were also found to block the uptake of [11C]-MK-4232 in rhesus monkey and human cerebellum and brainstem. [11C]-MK-4232 may therefore be a useful tool for examining the relationship between central CGRP receptor antagonism and migraine relief (3).

HEMATOLOGICAL AND BLOOD COAGULATION DISORDERS

The discovery of **TAK-442**, a tetrahydropyrimidin-2(1*H*)-one derivative that acts as an orally available, selective and direct competitive inhibitor of activated coagulation factor Xa (FXa), was described by scientists at Takeda. Chemical replacement of the imidazo[1,5-*c*]imidazol-3-one moiety with other lactam rings in a novel series of potent FXa inhibitors in order to enhance their physicochemical properties led to the identification of TAK-442, which exhibited improved stability in human liver microsomes. The compound displayed selective inhibitory activity against FXa over other serine proteases, such as thrombin, factor IXa, t-PA and trypsin (IC_{50} = 2.2, 1200, 4500, 44,000 and > 60,000 nM, respectively) and showed weak inhibitory activity against six cytochrome P450 isoforms at 10 μM. Pharmacokinetic profiling in monkeys revealed a steady-state volume of distribution of 579 mL/kg and clearance of 708 mL/h/kg following i.v. administration at 0.1 mg/kg. When dosed orally at 1 mg/kg it displayed an AUC of 760 mg.h/mL, a mean residence time of 6.96 h and an oral bioavailability of 52.5%. In vivo evaluation of the compound in rabbits revealed dose-dependent prevention of thrombosis following bolus and infusion administration (ID_{50} = 41 μg/kg). No effect on bleeding time was observed in the rabbit ear thrombosis model at 500 μg/kg (4).

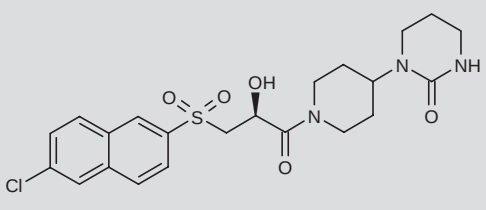
A series of potent hypoxia-inducible factor (HIF) prolyl hydroxylase inhibitors found to stabilize the HIF protein and stimulate erythropoietin (EPO) production in whole cell cultures was further explored at Johnson & Johnson using primary functional assays for prolyl hydroxylase inhibition and iron chelation to focus on mechanism-based inhibitors. These efforts led to the benzimidazole lead compound **JNJ-42041935**. Acute oral dosing of the agent at 100 μmol/kg in BALB/c mice was associated with a rapid increase in plasma EPO, while chronic dosing at the same dose for 5 days was associated with increases in hematocrit and hemoglobin levels at day 8. JNJ-42041935 could potentially be used to treat anemia (5).



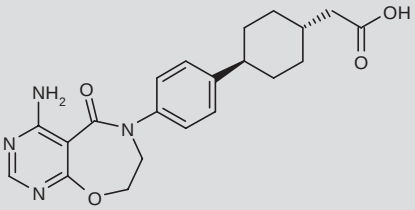
JNJ-42041935

ENDOCRINE DISORDERS

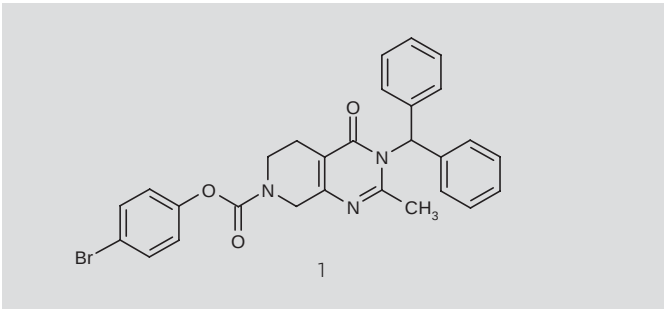
The discovery and preclinical pharmacology of Pfizer's **PF-4620110**, a novel diacylglycerol *O*-acyltransferase DGAT1 inhibitor proposed for the treatment of type 2 diabetes, were disclosed. PF-4620110 inhibited DGAT1 with an IC_{50} of 19 nM and exhibited selectivity over DGAT2 (IC_{50} > 10 μM) and the human estrogen receptor (IC_{50} > 30 μM). The compound displayed a stable lactam ring, exhibited no glucuronidation issues, demonstrated good photostability and tested negative for genotoxicity in the Ames test. It showed an oral bioavailability of 100% and a good safety profile in rats. No effects on heart rate were seen in cardiovascular studies and no significant adverse events were reported at any of the doses evaluated. In an animal model of diabetes (*db/db* mice) administration of PF-4620110 at 0.3, 3 and 15 mg/kg for 21 days resulted in a good response, with a significant reduction in the levels of hepatic triglycerides. The agent also stimulated the effects of glucagon-like peptide 1 (GLP-1) and the anorexigenic peptide YY (PYY) (6).



TAK-442



PF-4620110



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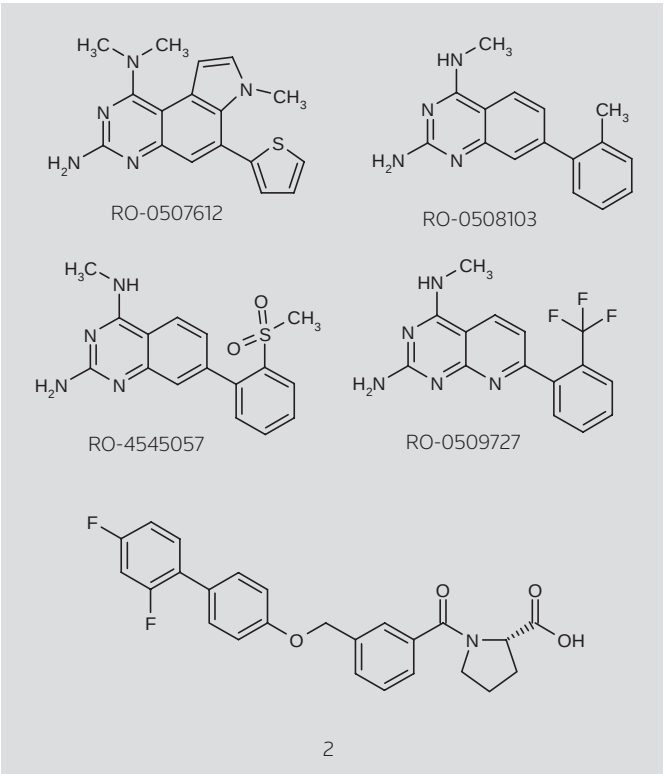
Merck & Co. researchers have identified a potent and orally active agonist of G protein-coupled receptor GPR119, a mechanism associated with increasing intracellular cyclic AMP (cAMP) and increased glucose-dependent insulin secretion from pancreatic β-cells and incretin secretion from endocrine cells of the gastrointestinal tract. Structure–activity relationship (SAR) studies of an initial lead led to the synthesis of a series of pyridopyrimidinone aryl carbamates, including compound **1**. Compound **1** (human EC_{50} = 86 nM for cAMP) was active at a dose of 3 mg/kg in mice undergoing an acute oral glucose tolerance test and, when combined with a GLP-1 analogue or a dipeptidyl peptidase 4 (DPP IV) inhibitor it showed an additive effect in lowering blood glucose in an oral glucose tolerance test in lean mice. Blood glucose was also effectively lowered in a 14-day study in a streptozotocin/diet-induced obesity model in mice, with subchronic activity at a dose of 30 mg/kg (7).

Researchers at Roche presented novel protein-tyrosine phosphatase PTP-1B inhibitors and described the discovery of orally active glycogen synthase (GS) activators for the treatment of type 2 diabetes. PTP-1B has been implicated in the regulation of insulin and leptin signaling and is therefore expected to represent a target for the development of antidiabetic and antiobesity therapeutics. A series of diaminopyrroloquinazolines such as **RO-0507612** were identified during high-throughput screening exhibited good cell-based potency and selectivity for PTP-1B, but displayed cytotoxicity and poor pharmacokinetics (PTP-1B IC_{50} = 22.4 μM; human liver microsome clearance 7.8 mL/min/kg). Further optimization of these compounds by removal of the pyrrole ring led to the identification of diaminoquinazolines that retained potency in PTP-1B assay systems and showed an improved safety profile. Representative compounds from this series, namely **RO-0508103** and **RO-4545057**, exhibited significant improvements in biological, physicochemical and pharmacokinetic parameters (PTP-1B IC_{50} = 2.3 and 1.39 μM, respectively; human liver microsome clearance values = 2.4 and 2.4 mL/min/kg body weight, respectively). The agents maintained selectivity for PTP-1B (9 of 10 PTPs) and exhibited in vivo activity in mouse models of obesity (diet-induced obesity and *ob/ob*) and diabetes (*db/db*). Oral administration of RO-4545057 (25 and 50 mg/kg) resulted in a significant acute reduction in glucose levels and an improvement in the oral glucose tolerance test (OGTT) in *db/db* mice (8). Further SAR exploration of diaminoquinazoline PTP-1B inhibitors led to the identification of a series of diaminopyridopyrimidine compounds which retained potency in PTP-1B assays and good pharmacokinetic profiles. A selected analogue, designated **RO-0509727**, exhibited potent and selective activity against



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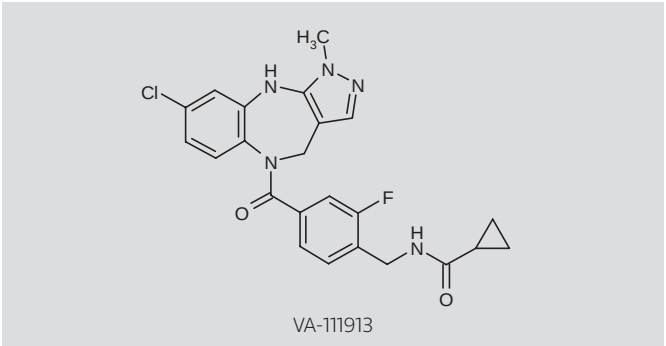
PTP-1B (IC_{50} = 0.5 μM). Pharmacokinetic evaluation in mice revealed an oral bioavailability value of 66%. Administration of RO-0509727 (50 mg/kg p.o.) to mice with diet-induced obesity correlated with a decrease in glucose AUC (9). Activation of the enzyme GS is also expected to represent a therapeutic option for the treatment of type 2 diabetes, as well as cardiovascular conditions. High-throughput screening led to the identification of a biphenyl-furanoic acid derivative with good physical properties but weak GS-activating activity. Lead optimization comprising a series of furan ring replacements, as well as distal phenyl ring, linker region and proline-like substitutions, resulted in the identification of compound **2**. The agent displayed physical and pharmacokinetic properties that supported its suitability for in vivo profiling (EC_{50} = 0.2 μM; bovine serum albumin shift = 3.77; human liver microsome clearance = 0 μL/min/mg; solubility = 399 μg/mL; pharmacokinetic parameters in rats: $t_{1/2}$ = 3.5 h; C_{max} = 1005 ng/mL; AUC = 5071 ng.h/mL; oral bioavailability = 75%). Administration at 75 mg/kg b.i.d. to *ob/ob* mice correlated with improved glucose tolerance and metabolic endpoints, as indicated by significantly reduced levels of fructosamine, triglycerides and free fatty acids, compared with values in vehicle-treated control animals (10).

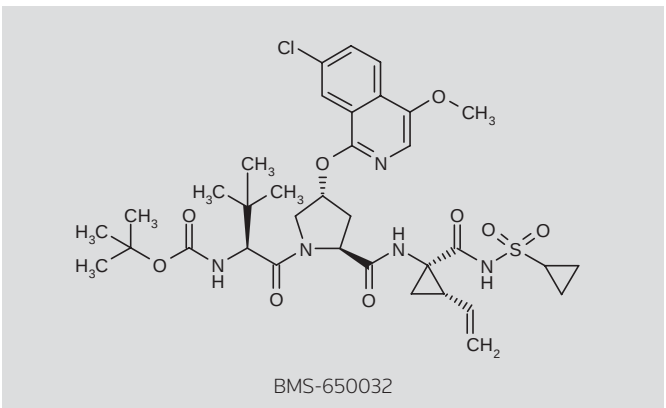
Vantia Therapeutics investigators also described the screening and SAR studies leading to their novel vasopressin receptor V_{1A} antagonist **VA-111913** (VT-913), which is in phase II development for the treatment of dysmenorrhea. The agent resulted from efforts to identify a vasopressin receptor antagonist that could inhibit contractions in uterine smooth muscle and uterine blood vessels. VA-111913 (radioligand binding K_i = 1.74 nM) inhibited vasopressin-induced uterine contractions in vitro at 100 nM and was evaluated in rat models.


VA-111913

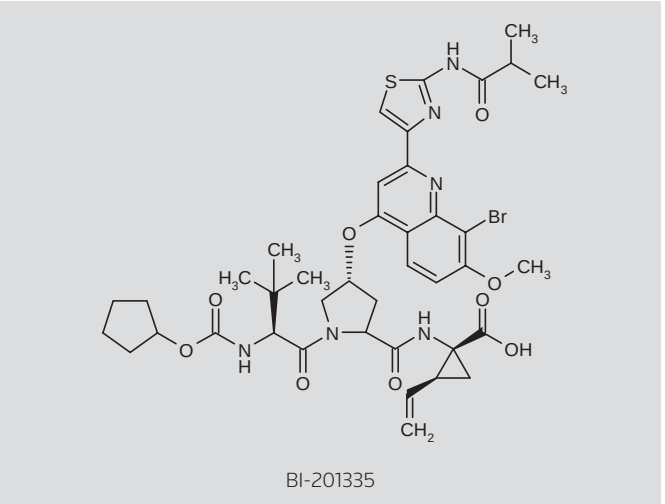
While blood pressure rose in animals injected with vasopressin (30 ng/kg), i.v. administration of VA-111913 10 ng/kg was associated with a decrease in systolic arterial pressure. Oral bioavailability was 44% in rats, and a $t_{1/2}$ of 234 min was measured. VA-111913 displayed selectivity for the V_{1A} receptor and was considered easy to synthesize (11).

HEPATITIS C

Bristol-Myers Squibb has advanced the hepatitis C virus (HCV) serine protease/NTPase/helicase NS3 inhibitor **BMS-650032** to clinical development after preclinical investigations gave encouraging results. The identification of the agent came after a previous serine protease/NTPase/helicase NS3 inhibitor, BMS-605339, entered clinical evaluation but was discontinued due to adverse events. BMS-650032 (EC_{50} = 4 nM) displayed respective oral bioavailabilities of 12%, 62% and 11% in rats, dogs and monkeys and respective $t_{1/2}$ values of 12, 1.1 and 1.3 h. In patients, a $t_{1/2}$ of 17 h was measured and no serious adverse events were observed in a 14-day trial (12).

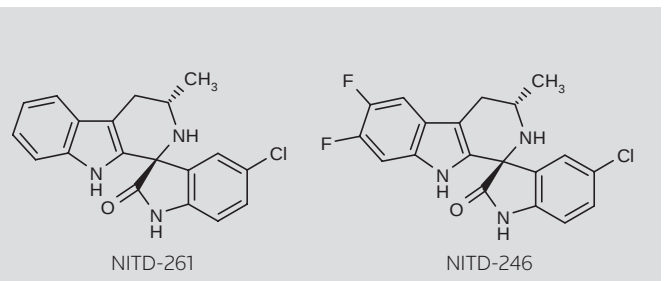

BMS-650032

Presentations at the meeting also included a description of the identification of the potent, specific and reversible peptidomimetic inhibitor of HCV serine protease NS3/NS4, **BI-201335**, from Boehringer Ingelheim. For genotypes 1a, 1b and 2a, K_{iapp} values for BI-201335 were 1.2, 2.8 and 21 nM, respectively, and EC_{50} values were 6.5, 3.1 and 47 nM, respectively. Pharmacokinetics in rats were predictive of good pharmacokinetics in humans, with favorable liver distribution, and combination with interferon alfa was effective at reducing the emergence of resistant replicons. Favorable pharmacokinetics have been observed in humans ($t_{1/2}$ approximately 22-31 h) (13).


BI-201335

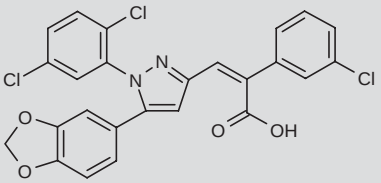
MALARIA

A new class of antimalarial compounds, the spirotetrahydro-β-carbolines, has been identified at Novartis from a whole cell screen on *Plasmodium falciparum*, with optimized compounds demonstrating in vivo efficacy. **NITD-261** (NF54 strain IC_{50} = 9.2 nM; K1 strain IC_{50} = 8.5 nM) displayed high metabolic clearance and CYP2C9 liability. **NITD-246** (NF54 strain IC_{50} = 0.2 nM; K1 strain IC_{50} = 0.2 nM) displayed increased potency with reduced clearance and moderate CYP2C9 liability. **NITD-609** was 10-fold more potent than NITD-261, with low clearance and moderate CYP2C9 liability. Evaluation of the plasma profiles of these agents in mice indicated that NITD-246 and NITD-609 could be given as single doses with long-lasting effects. NITD-609 demonstrated nanomolar IC_{50} values against laboratory-adapted drug-resistant *P. falciparum* strains and *P. falciparum* and *Plasmodium vivax* clinical isolates, and blood schizonticidal activity without liver schizonticidal activity or antibacterial, antifungal or other antiparasitic activity. In toxicological studies, NITD-609 displayed low cytotoxic and cardiotoxic potential, no signs of genotoxicity and was well tolerated in mice at doses up to 500 mg/kg. In vivo oral efficacy was seen with these compounds, with > 99% parasitemia reduction and prolongation of survival in mice at low doses. The mechanism of action and target remain to be elucidated (14).


NITD-261 NITD-246

GASTROINTESTINAL DISORDERS

Selective inhibitors of the cholecystokinin receptors CCK_1 and CCK_2 are expected to provide therapeutic options for the treatment of gastrointestinal conditions. Scientists at Johnson & Johnson reported

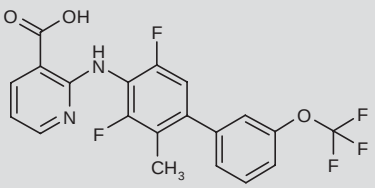


JNJ-26273364

the discovery of a novel series of CCK_1 receptor antagonists and disclosed information on SAR studies and Free-Wilson additivity analysis that led to the identification of **JNJ-26273364**, an optimized compound with high water solubility. Pharmacokinetic analysis of JNJ-26273364 in rats revealed a bioavailability of 100% and half-life of 3 h. The compound inhibited the release of amylase in the bile duct at oral doses of 0.3-10 μmol/kg. Following i.v. administration at 1 μmol/kg at 30 min after the onset of experimental pancreatitis, JNJ-26273364 inhibited the sulfated CCK octapeptide (CCK8S)-evoked release of pancreatic amylase into the serum. It also inhibited the CCK8S-induced gallbladder contraction in guinea pigs. The study supports the potential application of CCK receptor antagonists for the treatment of pancreatitis (15).

IMMUNE-MEDIATED DISORDERS

Researchers at Almirall described the discovery of a novel chemical class of dihydroorotate dehydrogenase (DHOdehase) inhibitors that are expected to be suitable as clinical candidates for the treatment of autoimmune conditions such as rheumatoid arthritis. Potent and orally bioavailable amino(iso)nicotinic acid derivatives, a new scaffold for DHOdehase inhibitors, were identified by SAR optimization. Compound **3**, a biaryl nicotinic acid derivative, exhibited an IC_{50} of 6 nM against human DHOdehase. Further SAR exploration led to the identification of nicotinic acid derivative **4**, which inhibited human DHOdehase with an IC_{50} of 11 nM. Optimization of the hydrophobic interaction with enzyme valine residues in order to improve potency resulted in the discovery of the isonicotinic acid derivative **5** and the nicotinic acid derivative **6** (IC_{50} = 45 and 23 nM, respectively). The best compound in this series, compound A (chemical structure undisclosed), revealed potent in vitro inhibitory activity against human, rat and mouse DHOdehase (IC_{50} = 0.037, 0.034 and 0.07 μM, respectively) compared with teriflunomide (IC_{50} = 1.5, 0.033 and 1.1 μM, respectively). Compound A inhibited the proliferation of human PBMCs with greater potency than teriflunomide (IC_{50} = 0.8 μM vs. 43 μM). Pharmacokinetic profiling of compound A in rats following oral administration at 10 mg/kg revealed an AUC of 1080 μg.h/mL and a half-life of 10 h. In a rat model of adjuvant-induced arthritis, oral administration of compound A at 10 mg/kg once daily to animals with established arthritis (from day 11 to 19 following disease induction) correlated with a reduction in paw volume (index of inflammation). Compound A did not exhibit hepatotoxic effects in mice at a dose of 100 mg/kg. This research led to the identification of a candidate for clinical development (16).



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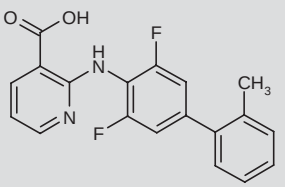

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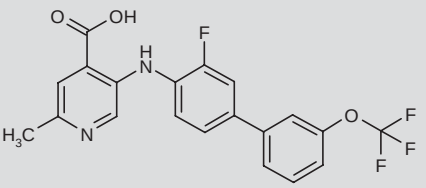

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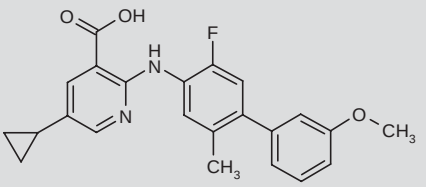

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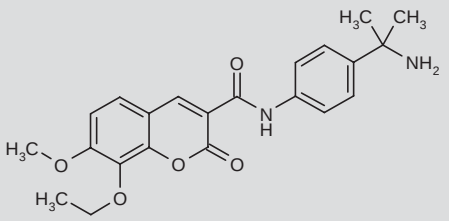
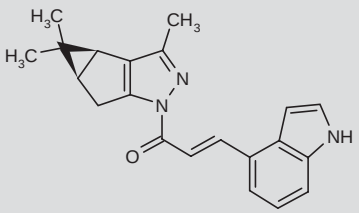
The optimization of lysophospholipid receptor $S1P_1$ agonists initially derived from monoterpene (+)-3-carene or 2-oxo-2*H*-chromene-3-carboxamide was described by Novartis investigators. The resulting compounds were selective and demonstrated excellent drug metabolism and pharmacokinetic properties and efficacy in relevant animal models, such as experimental autoimmune encephalomyelitis (EAE), a model for multiple sclerosis. Among compounds synthesized was **NIBR-785**, with EC_{50} values for human $S1P_1$, $S1P_3$, $S1P_4$ and $S1P_5$ of 2 (91% agonism), > 1000, > 1000 and 560 nM (43%), respectively. For **NIBR-713**, these values were 2 (90%), 995 (84%), 560 (28%) and 505 nM, respectively. For a third compound, **7**, the EC_{50} value for human $S1P_1$ was 0.3 nM (17).

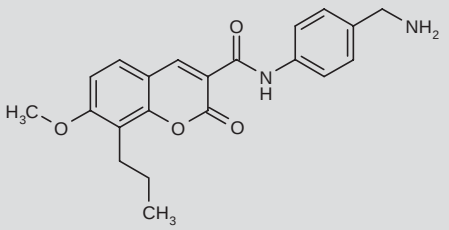
Lexicon Pharmaceuticals' sphingosine-1-phosphate lyase (SPL 1) inhibitor **LX-2931** is in clinical development as a treatment for autoimmune disorders, and a related compound, **LX-2932**, has been designated as its backup. LX-2931 was found to be potent, soluble, stable and easy to formulate. In vivo, the compound was associated with a 55-65% decline in circulating lymphocytes relative to vehicle control 18 h after administration of an oral dose of 100 mg/kg. LX-2932 was also associated with reduced levels of lymphocytes. In rats given LX-2931 30 mg/kg once daily for 3 days, levels of T cells in thymus and spleen increased and SPL 1 activity declined in lymphoid



NIBR-785



NIBR-713



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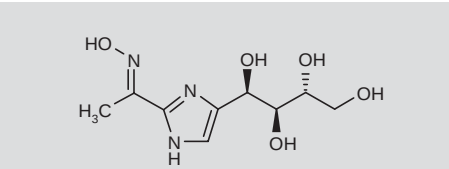
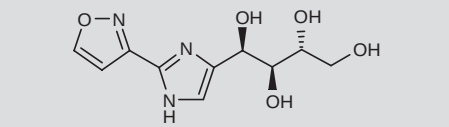
tissues. The lymphopenic effects of LX-2931 and LX-2932 were similar in primates. A low (5 mg/kg) dose of LX-2931 demonstrated efficacy in a collagen-induced arthritis model. Complete blood count data were consistent from mouse to man (18).

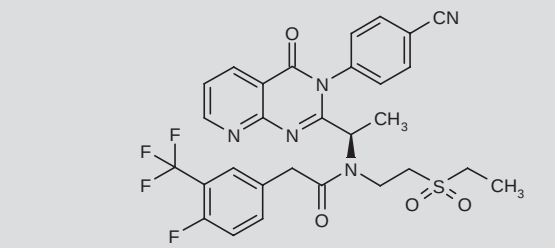
Amgen's AMG-487 is a potent, selective and orally bioavailable chemokine CXCR3 receptor antagonist, but it displayed potential for time-dependent inhibition of CYP enzymes responsible for its clearance. The company therefore sought other CXCR3 antagonists. A promising compound, **8**, bound CXCR3 with high affinity but displayed positive chromosomal aberration. Continued SAR studies led to the identification of compound **9**, which tested negative in the chromosomal aberration assay and inhibited [^{125}I]-IP-10 binding to CXCR3 with an IC_{50} of 12 nM in the presence of human serum. In mice, compound **9** inhibited cell migration into the lung following bleomycin challenge. A good pharmacokinetic profile was also revealed (19).



LX-2931



LX-2932



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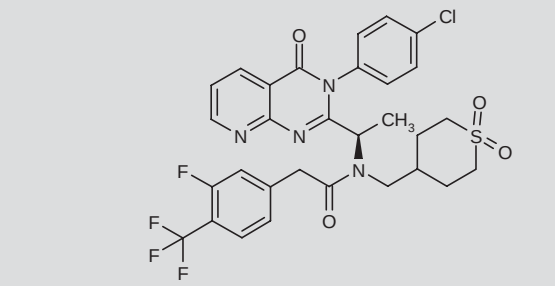

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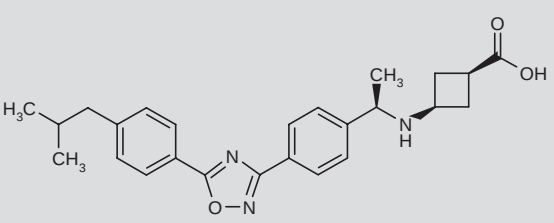
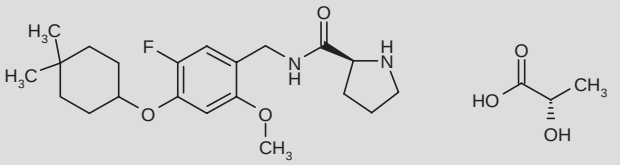
Preclinical data in support of the selection of Pfizer's **PF-991**, a lysophospholipid $S1P_1$ receptor agonist, for further development as a therapeutic candidate for the treatment of autoimmune disorders such as rheumatoid arthritis were disclosed at the meeting. Pharmacokinetic profiling of PF-991 in rats revealed a clearance of 6 mL/min/kg, a steady-state volume of distribution of 2.7 L/kg, a half-life of 5.2 h and high oral bioavailability (90%). In rats, lymphopenia (> 80%) was observed following administration of PF-991 at 10 mg/kg p.o. or 5 mg/kg i.v. In a rat model of collagen-induced arthritis, which resembles the features of rheumatoid arthritis in humans, treatment with the agent at 10 and 30 mg/kg correlated with 60% inhibition of the development of disease symptoms (20).



PF-991



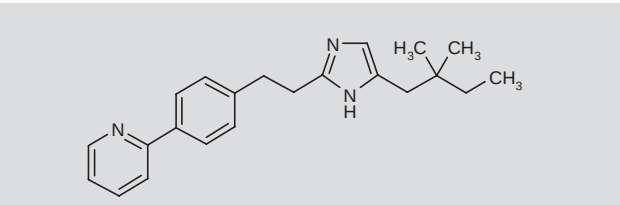
10

METABOLIC DISORDERS

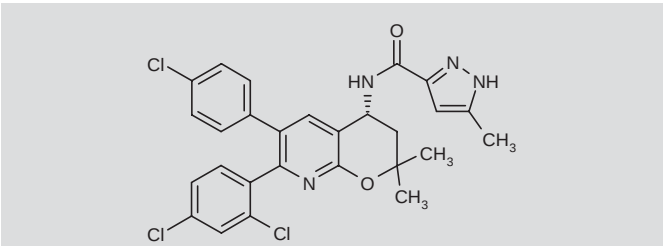
Pfizer researchers synthesized agonists targeting the 5-HT_{2C} receptor for obesity, first creating mixed 5-$HT_{2C/2B}$ receptor agonists. Less selective agents were hindered by safety issues, including cardiovascular, gastrointestinal and psychiatric adverse events. The investigators therefore sought compounds with binding < 10 nM and > 100-fold selectivity for 5-HT_{2C} relative to other receptors. Their efforts led to compound **10**, with K_i values of 0.9 nM for 5-HT_{2C}, 3940 nM for 5-HT_{2B} and 12.8 nM for 5-HT_{2A} receptors. An EC_{50} of 2.3 nM was measured for the 5-HT_{2C} receptor, with 95-100% agonist efficacy, whereas the EC_{50} for the 5-HT_{2B} receptor was > 10,000 nM. In vivo, compound **10** was associated with dose-related inhibition of nocturnal food intake, and chronic weight loss was seen in rats with diet-induced obesity. Oral bioavailability was predicted to be moderate in humans (approximately 40%) (21).

Efforts to exploit the bombesin BB_3 receptor as a target for the treatment of obesity led investigators at Merck & Co. to synthesize a series of BB_3 agonists containing a biarylethylimidazole pharmacophore, with SAR analyses leading to compound **11**, with promising in vivo activity. Compound **11**, displayed potent and selective binding affinity (IC_{50} = 18 and 5204 nM, respectively, for human BB_3 and BB_2 receptors) and functional agonist activity (EC_{50} = 53 nM; 99% activation). Pharmacokinetic variables in rats included an oral bioavailability of 21%, a $t_{1/2}$ of 5.89 h and an AUC of 0.579 μM.h. In mice treated with an oral dose of 60 mg/kg, the brain:plasma ratio was 0.93 at 1 h and 0.59 at 6 h. Compound suppressed acute food intake in wild-type but not BB_3 knockout mice and increased the metabolic rate and decreased body weight in mice with diet-induced obesity, but not in those lacking BB_3. An oral dose of 100 mg/kg b.i.d. was associated with reduced body weight in diet-induced obese mice. High brain BB_3 receptor occupancy was required for chronic agonist effects (22).

Despite setbacks in the development of cannabinoid CB_1 receptor inverse agonists for the treatment of obesity, Merck & Co. continued its efforts to identify new agents of this kind. SAR analysis of a lead compound hampered by off-target hERG inhibition led to the identification of **MK-5596** (IC_{50} = 1.0 and 1500 nM, respectively, for CB_1 and CB_2 receptors; K_i = 1.0 μM for the I_{Kr} channel), with the following pharmacokinetic parameters in rats: Cl_p = 4.5 mL/min/kg, Vd_{ss} = 3.0 L/kg, $t_{1/2}$ = 8.5 h, oral bioavailability = 91%. CNS penetration was achieved with desired brain levels established and maintained in rats. In vivo, body weight and food intake were reduced in diet-induced obese rats. Food intake and weight reductions seen in wild-type mice were not observed in CB_1 receptor knockout mice. A good safety margin was also determined in preclinical species. Further studies indicated that clearance would involve phase I and phase II metabolism, with unchanged parent in humans. These findings led to the selection of MK-5596 as a clinical candidate (23).

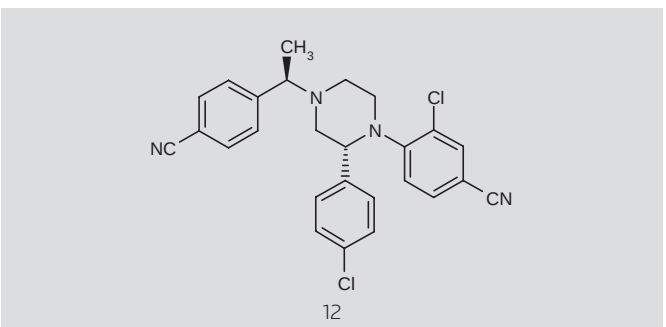


11



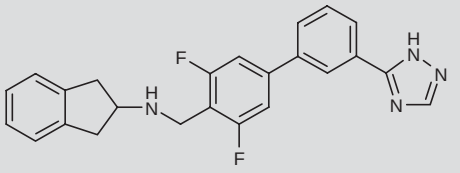
MK-5596

Merck & Co. also presented novel agents containing a 1,2-diarylpiperazine scaffold as potent cannabinoid CB_1 receptor antagonists. The selected candidate, compound **12**, exhibited high affinity and selectivity for the CB_1 over the CB_2 receptor. Respective pharmacokinetic profiling of **12** at 3 mg/kg in mice, rats and monkeys revealed $AUC_{(0\text{-}24)}$ values of 5.9, 5.9 and 2.5 μM.h and C_{max} values of 0.6, 0.57 and 0.21 μM. In rats and monkeys, the agent displayed a respective Cl of 9.8 and 5 mL/min/kg, a V_{ss} of 4.4 and 1.7 L/kg and a $t_{1/2}$ of 5.5 and 6.4 h. Its oral bioavailability in rats was considerably higher than in monkeys (55% vs. 9%). In functional assays, oral administration of **12** to mice with diet-induced obesity was equipotent to rimonabant regarding the reduction of food intake. The molecule was found to be more effective than rimonabant in longer-term feeding studies evaluating body weight and adiposity (24).



12

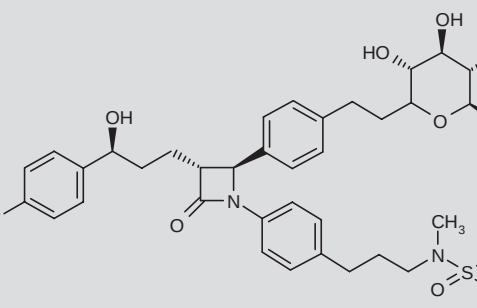
Scientists at GlaxoSmithKline (GSK) described the selection of **GSK-1521498**, a novel and potent μ opioid receptor inverse agonist, as a candidate clinical compound for the treatment of obesity. In preclinical studies, GSK-1521498 displayed selectivity for the μ opioid



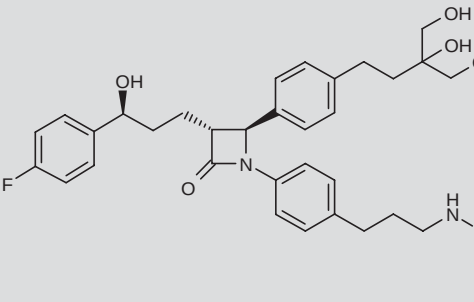
GSK-1521498

receptor (pK_i = 8.8) over the κ and δ opioid receptors (pK_i = 7.7 for both). The compound exhibited respective pIC_{50} values of 5.4, 5.3 and 5.7 against noradrenaline (NET), dopamine (DAT) and serotonin (SERT) transporters. Pharmacokinetic profiling in rats revealed an oral bioavailability of 40%, a half-life of 4.4 h and a time to maximum plasma concentration of 4 h (C_{max} = 2932 mg/mL). Following i.v. administration, the clearance of the agent was estimated to be 5.3 mL.min/kg (25).

Encouraged by the activity of ezetimibe, a team of investigators from Merck & Co. identified novel cholesterol absorption inhibitors targeting Niemann-Pick C1-like protein 1, the putative target of ezetimibe. Compound **13** showed protein binding activity (IC_{50} = 0.059 and 0.057 μM, respectively, for human and murine protein). In a mouse cholesterol absorption inhibition assay, ED_{50} values for plasma and liver were 72 and 93 μg/kg, respectively. A second compound, **14**, displayed an IC_{50} of 5 nM for binding to recombinant human protein and of 4 nM for brush border membrane vesicle protein. Acute efficacy comparable to ezetimibe was seen for **14** in rats and mice, and in cholesterol-fed hamsters chronic efficacy was comparable to ezetimibe with once-daily dosing. Compound **14** was not orally bioavailable in rats and oral bioavailability was low in dogs and rhesus monkeys. Other characteristics observed included a short duration of action, no CYP inhibition, low permeability, minimum off-target activities and negative Ames tests. Compound **14** has been selected for clinical development (26).



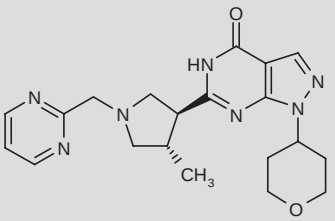
13



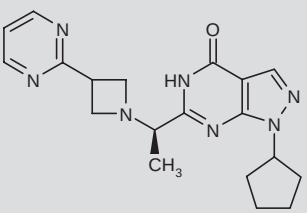
14

NEUROLOGICAL DISORDERS

The discovery of selective phosphodiesterase PDE9 inhibitors was reported at the congress by scientists at Pfizer. Among these, **PF-04447943** exhibited potent inhibitory activity against PDE9 (IC_{50} = 12 nM), with 100-fold selectivity over PDE1C and high water solubility. Functional data on the compound from studies performed in rats, monkeys and humans have previously been reported. A structurally diverse backup compound, **15**, was also identified. This agent displayed an IC_{50} of 32 nM against PDE9 and 30-fold selectivity over PDE1C. Pharmacokinetic profiling of **15** in rats and dogs revealed oral bioavailabilities of 63% and 71%, respectively, with respective half-lives of 1.1 and 4.4 h. The compound was well tolerated and demonstrated good brain penetrability and high water solubility. Administration of **15** to rats with scopolamine-induced cognitive deficits was associated with a reversal of behavioral symptoms, which suggests potential use for the treatment of Alzheimer's disease (27).

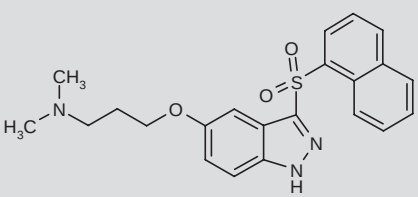


PF-04447943



15

Scientists at Pfizer also described the identification of **SAM-531** (WAY-262531), a selective, orally bioavailable 5-HT_6 receptor antagonist with potential utility in the treatment of cognitive disorders associated with schizophrenia and Alzheimer's disease. SAM-531 displayed high activity at the 5-HT_6 receptor, with K_i and IC_{50} values

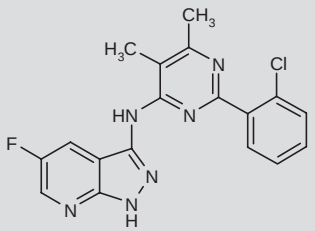


SAM-531

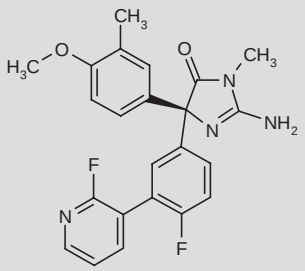
of 1.2 and 5.5 nM, respectively. Following administration of the compound to dogs and monkeys at 3 mg/kg p.o., the oral bioavailability was estimated to be 51% and 63%, respectively. Treatment with SAM-531 correlated with increases in the acetylcholine and glutamate levels and was associated with an enhancement in memory retention in a novel object recognition paradigm (28).

Interrupting the formation of β-amyloid (Aβ) by targeting β-secretase is one strategy being explored to treat Alzheimer's disease. Compounds with drug-like characteristics and β-secretase 1-inhibitory activity have been developed at Pfizer using structure-based design, medicinal chemistry SAR analysis and structure–pharmacokinetic parameter relationship analysis. Among these agents was **WAY-258131** (β-secretase 1 K_i = 0.02 μM, IC_{50} = 12 nM, EC_{50} = 24 nM; brain:plasma ratio = 0.05-0.20), which inhibited Aβ production in vivo upon oral dosing and reversed cognitive deficits. **WAY-264116** (β-secretase 1 IC_{50} = 297 nM, EC_{50} = 189 nM) lowered $Aβ_{40}$ in guinea pig plasma and cerebrospinal fluid, had an acute effect on contextual fear conditioning in mice, lowered plasma $Aβ_{40}$ following 1 month of chronic dosing, and reduced dense-core plaque load with 3-month dosing. The compound was also characterized by a brain:plasma ratio of > 0.6-1, an oral bioavailability of 89% and an hERG IC_{50} of 4.6 nM. Other molecules described were **WYE-106531** (β-secretase 1 IC_{50} = 23 nM, hERG IC_{50} > 30 μM; brain:plasma ratio = 0.31) and **W-Y** (β-secretase 1 IC_{50} = 55 nM; brain:plasma ratio = 0.04) (29). Another compound, **16** (β-secretase 1 IC_{50} = 0.10 μM; brain:plasma ratio = 0.4), was associated with acute reduction of central Aβ 3 h after s.c. dosing in wild-type mice (30).

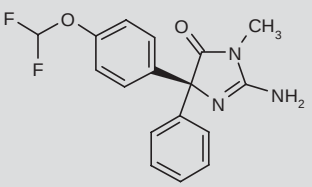
Scientists at Vertex Pharmaceuticals disclosed data on the identification of novel orally available inhibitors of glycogen synthase kinase-3 (GSK-3) which may represent potential candidates for the treatment of neurodegenerative diseases. Compound **17** was found to preferentially inhibit the autophosphorylation of the regulatory tyrosine residue in the GSK-3 kinase activation domain over GSK-3 serine/threonine kinase activity against substrates such as β-catenin. This selective inhibition of enzymatic activity could increase the safety window and provide potential therapeutic benefit. In vitro, in primary hippocampal neuron cultures (embryonic day 16), the compound was observed to promote neuronal plasticity and angiogenesis, as detected by an increase in the axonal and dendritic branching of cultured neurons. In vivo, in a rat middle cerebral artery occlusion (MCAO) model of stroke, administration of the agent at 0.5-1.5 mg/kg once daily starting at 24 h post-MCAO for a total of 14 days correlated with a significant recovery in behavioral impairment, which was associated with the detection of markers of neurogenesis, angiogenesis and plasticity and a concomitant inhibition of GSK-3



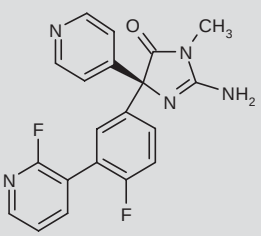
17



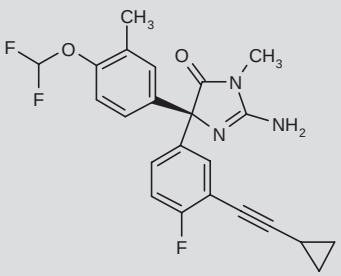
WAY-258131



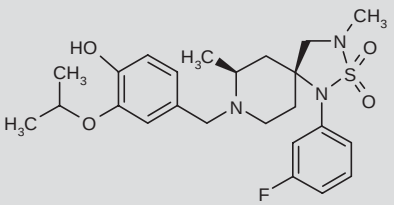
WAY-264116



W-Y



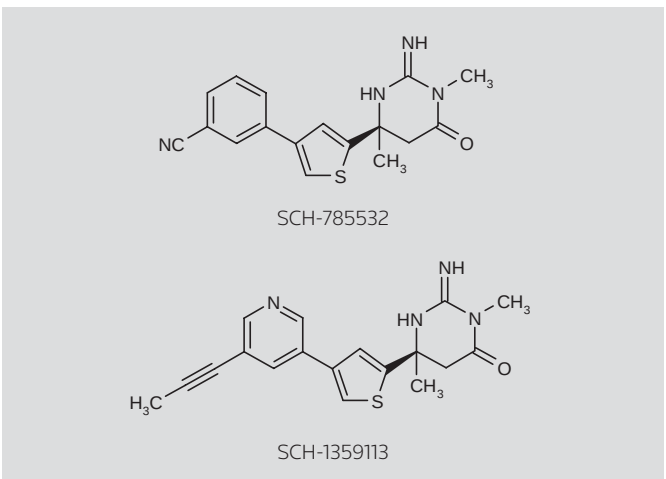
WYE-106531



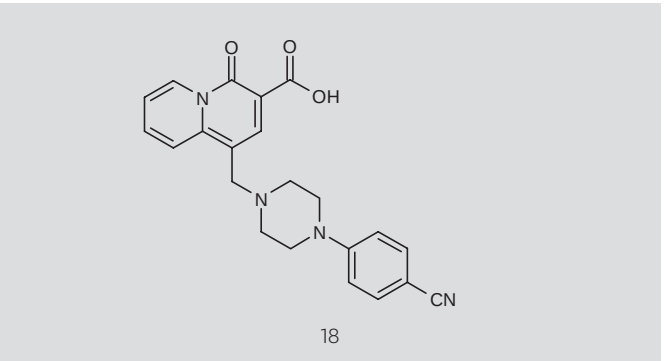
16

tyrosine autophosphorylation. No induction of β-catenin was observed. The study supports the development of partial GSK-3 inhibitors that could promote neuroregeneration following injury (31).

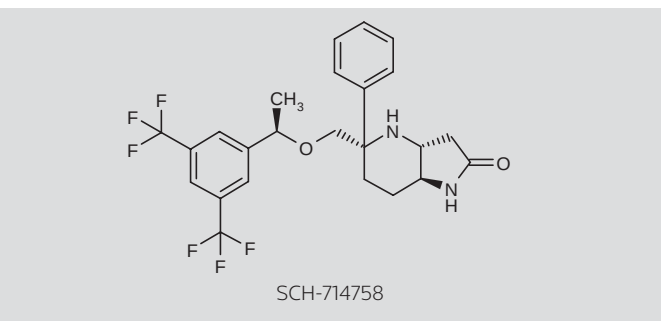
An effort was made to identify selective brain-penetrant inhibitors of β-secretase 1, which could affect the production of $A\beta_{40}$ and $A\beta_{42}$ related to Alzheimer's disease, by modification of a fragment-based screening hit guided by x-ray crystallography. These efforts led Schering-Plough (now Merck & Co.) and Ligand Pharmaceuticals researchers to the iminohydantoin β-secretase 1 inhibitor **SCH-785532** (β-secretase 1 K_i = 57 nM; cellular $A\beta_{40}$ IC_{50} = 68 nM; oral bioavailability in mice = 17%). In rats, administration of SCH-785532 resulted in a decrease in CSF $A\beta_{40}$, reflecting inhibition of CNS β-secretase 1. No effect on cortex $A\beta_{40}$ was observed at doses up to 100 mg/kg. A second compound, **SCH-1359113** (β-secretase 1 K_i = 7 nM; cellular $A\beta_{40}$ IC_{50} = 13 nM), demonstrated oral bioavailability of 90% (10 mg/kg) in the rat, with a C_{max} of 3.8 μM and an AUC of 20 μM.h. A dose of 3 mg/kg i.v. yielded a $t_{1/2}$ of 1.6 h. SCH-1359113 was associated with a decrease in CSF and cortex $A\beta_{40}$ in rats, and Aβ production in plasma, CSF and brain was also reduced in cynomolgus monkeys (32).



Scientists at Merck & Co. also reported the identification of novel quinolizidinone carboxylic acid scaffolds as a result of replacement of the quinolone ring system, leading to the generation of allosteric modulators of the muscarinic acetylcholine M_1 receptor. A selected positive allosteric modulator, compound **18**, exhibited selectivity for the M_1 receptor over the M_2-M_4 receptor subtypes. The agent displayed a lipophilicity index (logD) of 1.4 and increased water solubility. Protein binding affinities of 93.8% and 86.6%, respectively, were recorded for human and rat M_1 receptors. Pharmacokinetic profiling in rats revealed an oral bioavailability of 23%, clearance of 10 mL/min/kg and a half-life of 6.4 h. Enhanced CNS exposure was also observed. The molecule correlated with a reversal in scopolamine-induced cognitive deficits in vivo following chronic 14-day i.p. administration to rats at 30 min prior to behavioral testing. Selective allosteric muscarinic acetylcholine receptor M_1 modulators are expected to be useful for improving cognitive decline associated with Alzheimer's disease (33).

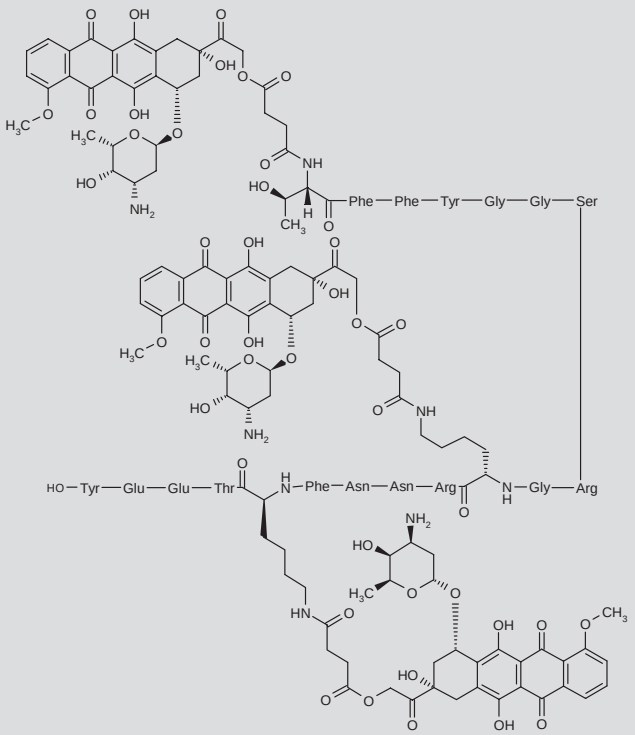


A new lead tachykinin NK_1 receptor antagonist was identified at Schering-Plough (now Merck & Co.) that does not possess the liability of in vivo degradation of a previous lead NK_1 antagonist. A successful agent may find utility for the treatment of nausea and vomiting, anxiety, depression, inflammation and pain. Investigations with the previous lead as a starting point led to fused bicyclic compounds such as **SCH-714758**, for which a diastereoselective synthesis was achieved. SCH-714758 (NK_1 K_i = 0.28 nM) displayed improvements in hERG inhibition, P450 inhibition and pharmacokinetics in vivo (34).

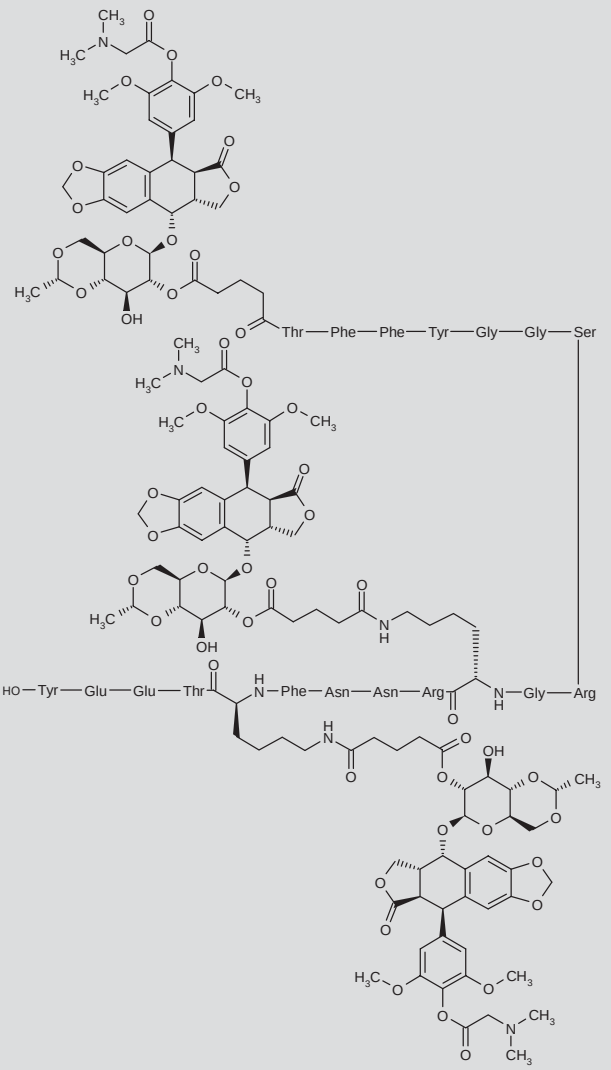


CANCER

New compounds with potential for treating brain cancer have been devised at Angiochem, using its Engineered Peptide Compounds (EPiC) platform, which previously gave rise to ANG-1005, an agent in phase I/II trials. **ANG-1007** consists of three doxorubicin molecules conjugated to one Angiopep-2 molecule, while **ANG-1009** consists of three etoposide molecules conjugated to one Angiopep-2 molecule. Doxorubicin and etoposide have anticancer activity but limited penetration into brain tissue. Respective in vitro IC_{50} values for ANG-1007 were 6.0, 4.6 and 7.3 nM in glioblastoma, hepatocarcinoma and lung carcinoma cells, all lower than those obtained with doxorubicin. ANG-1009 IC_{50} values in these cell lines were 330, 48 and 148 nM, respectively. The brain uptake of radiolabeled ANG-1007 and ANG-1009, as measured by in situ brain perfusion in CD-1 mice, was much higher than that of the parent drugs. Unlike their parent drugs, ANG-1007 and ANG-1009 displayed similar uptake in wild-type and P-glycoprotein knockout mice, and brain tissue distribution in normal brain tissue and brain tumor tissue was significantly higher with ANG-1007 and ANG-1009 than with the parent agents after an i.v. bolus injection. The in vivo efficacy of the agents is being evaluated (35).



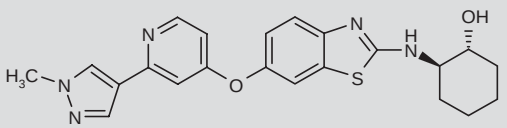
ANG-1007



ANG-1009

Scientists at Novartis described the discovery of a selective and orally bioavailable inhibitor of colony-stimulating factor 1 receptor (CSF-1-R), which is expected to suppress tumor-induced osteolysis. Compound **19** inhibited CSF-1-R with an IC_{50} value of 0.0009 μM. Pharmacokinetic evaluation of the compound in mice and rats (5 mg/kg i.v.), dogs (5 mg/kg p.o.) and cynomolgus monkeys (2 mg/kg i.v.) revealed a clearance of 4, 0.6, 6 and 2.2 mL/min/kg, respectively. Following oral administration at 20 mg/kg to mice and rats and 5 mg/kg to dogs and monkeys, the agent exhibited half-life values of 2.6, 8, 7 and 6.5 h, respectively, with C_{max} values of 1.7, 2.1, 0.8 and 1.5 μM/dose, respectively. Oral bioavailability in rats and dogs was estimated at 42%, whereas in mice and monkeys it reached 100%. Administration of **19** at 60 mg/kg p.o. once daily for 5 weeks correlated with a reduction in tumor-induced osteolysis in rodent models (36).

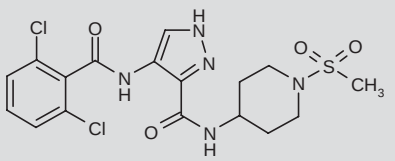
A structure-based drug discovery approach undertaken at Vernalis led to the identification of a series of indolylpyridone derivatives with inhibitory activity against the serine/threonine-protein kinase Chk1 in the low micromolar range. Inhibition of Chk1 is known to potentiate the antitumor effects of chemotherapeutic agents, such as gemcitabine, cisplatin and irinotecan. Optimization of the lead compound resulted in the discovery of **V-158411** (VER-158411), a small-molecule dual inhibitor of Chk1 and Chk2 (IC_{50} = 4.4 and 4.5 nM, respectively), which exhibited selectivity over other kinases, including Aurora kinase A and B and cyclin-dependent kinase 1 (CDK1) (IC_{50} = 25, 19 and > 50,000 nM, respectively). Treatment of cancer cells with V-158411 as a single agent for 72 h correlated with



19

inhibition of the proliferation of HT-29, HCT 116, NCI-H460, COLO 205, MDA-MB-231 and PC-3 cell lines, with mean GI_{50} values of 0.65, 3.98, 2.73, 1.58, 6.33 and 9.49 nM, respectively. In vitro coapplication of the compound (400 nM for 72 h) with cytotoxic agents such as gemcitabine, camptothecin, cisplatin and SN-38 in a range of colon, lung and prostate cancer cell lines resulted in potentiation of the cytotoxic activity of these agents, with a more pronounced effect (> 10-fold potentiation) seen in HT-29 colon cancer cells. Pharmacokinetic profiling of V-158411 (10 mg/kg i.v.) in dogs, rats and mice revealed $AUC_{(last)}$ values of 17,637, 6912 and 7099 ng.h/mL, respectively, with respective half-lives of 3.3, 3.3 and 2.9 h. The clearance rates were estimated at 9.6, 23 and 20 mL/min/kg, respectively, with respective volume of distribution values of 1.1, 2.4 and 3.3 L/kg. In nude mice bearing established COLO 205 xenografts, treatment with V-158411 (30 or 60 mg/kg i.v.) at 2 h after irinotecan administration (75 mg/kg i.p.) was found to potentiate the antitumor activity of irinotecan, without any additional systemic toxicity (37).

A fragment-based drug discovery approach at Astex Therapeutics for the development of orally available CDK inhibitors led to the identification of **AT-9311**, a potent and selective CDK1 and CDK2 inhibitor. In vitro, AT-9311 exhibited inhibitory activity against CDK2, with an IC_{50} value of 0.005 μM and selectivity over non-CDK kinases. In vivo oral administration of the compound at 50 mg/kg b.i.d. correlated with oncolytic effects in mice bearing HCT 116 xenografts. The agent displayed good tolerability in mice at a dose of 100 mg/kg b.i.d. Pharmacokinetic profiling revealed an oral bioavailability of 45% (38).

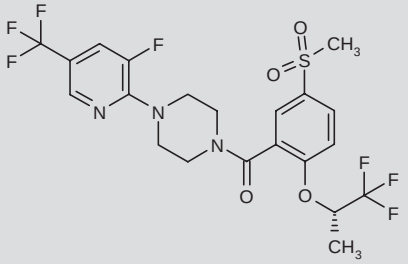


AT-9311

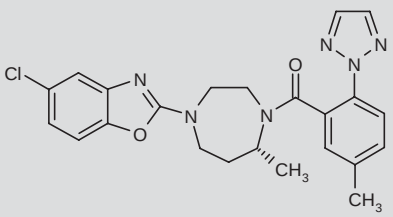
PSYCHIATRIC DISORDERS

Data on the discovery of **RG-1678** (Chugai, Roche), a novel, potent, selective and orally available inhibitor of the sodium- and chloride-dependent glycine transporter GlyT-1, were disclosed at the meeting. RG-1678 exhibited selectivity for GlyT-1 over GlyT-2 (EC_{50} = 0.03 and > 30 μM, respectively). Pharmacokinetic profiling in rats and cynomolgus monkeys revealed good oral bioavailability (78% and 56%, respectively), with respective half-life values of 58 and 6.4 h and V_{ss} values of 3.58 and 1.98 L/kg. Following i.v. administration, the mean clearance was estimated at 4.3 and 3.6 mL/min/kg in rats and monkeys, respectively. In rats, a high brain:plasma ratio of 0.7 was estimated and a robust increase in glycine levels in rat brain was observed following administration of RG-1678 at 10 mg/kg p.o. The predicted pharmacokinetic profile in humans indicated a clearance of 1 mL/min/kg, V_{ss} of 3.6 L/kg and half-life of 40 h (39).

Preclinical data on **MK-4305**, a potent dual orexin OX_1/OX_2 receptor antagonist, were presented by scientists at Merck & Co. Pharmacokinetic profiling of MK-4305 in rats and dogs revealed oral bioavailabilities of 20-30% and 56%, respectively, with respective half-lives of 0.5 and 3.3 h. The compound was cleared at rates of 44 and 4 mL/min/kg in rats and dogs, respectively, and exhibited good brain penetrability. MK-4305 was found to promote sleep in rats in a dose-dependent manner at 10, 30 and 100 mg/kg and correlated with an increase in both rapid eye movement (REM) and non-REM (NREM) sleep (40).



RG-1678



MK-4305

DISCLOSURES

The authors state no conflicts of interest.

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