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MEDICINAL CHEMISTRY SELECTIONS FROM THE 237TH AMERICAN CHEMICAL SOCIETY NATIONAL MEETING & EXPOSITION

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ABSTRACT

The 237th American Chemical Society National Meeting & Exposition, held in Salt Lake City on March 22-26, 2009, featured oral and poster presentations on the latest innovations in the world of chemistry, broken down into 31 divisions. The variety of papers and posters presented in the medicinal chemistry division was vast and included early data on compounds to watch in the area of therapeutics, either because they are expected to progress through clinical trials, or because the understanding gained by identifying and synthesizing them and investigating them in preclinical and clinical studies will lead to other therapeutic compounds and strategies. Presented here are a selection of compounds in the early stages of investigation that have demonstrated activity encouraging further development.

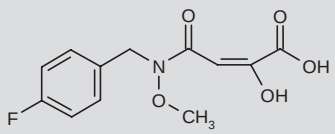
INTRODUCTION

Medicinal chemistry is just one of the areas covered at the National Meetings of the American Chemical Society (ACS), which also include programs on everything from agricultural and food chemistry to geochemistry and polymer chemistry. With such a wide array of areas, it is not surprising that the ACS has two national meetings each year, one in the spring and another in the fall.

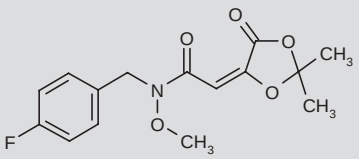
The ACS meetings are nevertheless known for the great quantity of information they provide on newly discovered, enhanced and tested pharmacological agents. In the medicinal chemistry division of the spring ACS meeting, 311 papers and posters were presented. What follows is a selection of compounds of particular interest, highlighting those with promising activity in vitro and/or in vivo or which have been selected for or are already in clinical development. They are organized by therapeutic area.

HIV

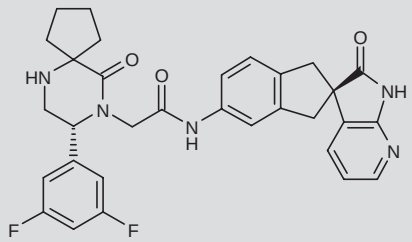
A series of novel amide ketoacid-based inhibitors of HIV integrase demonstrating oral antiviral activity was identified by Bristol-Myers Squibb in a hit-to-lead-to-clinical candidate process. Optimization of the initial hit compound (MW = 268; IC_{50} = 3 μM; EC_{50} = 100 μM) led to the identification of **BMS-538203**, which displayed a 50-fold improvement in activity in cell culture and a 2,000-fold improvement in antiviral activity compared to the lead compound (MW = 269; IC_{50} = 51 nM; K_i = 46 nM; half-life off-kinetics = 97 min; EC_{50} in the presence of 40% human serum = 320 nM; EC_{50} in the presence of 45 mg/mL human serum antigen = 277 nM; EC_{50} in the presence of 1.26 mg/L α_1-acid glycoprotein = 35 nM). When dosed orally using a prodrug delivery approach, the synthetic precursor **BMS-538158** displayed excellent exposure in rats, dogs and monkeys (bioavailability = 99%, 39% and 115%, respectively). The clearance (Cl), $t_{1/2}$ and volume at steady state (V_{ss}) of the prodrug were estimated to be



BMS-538203



BMS-538158



MK-3207

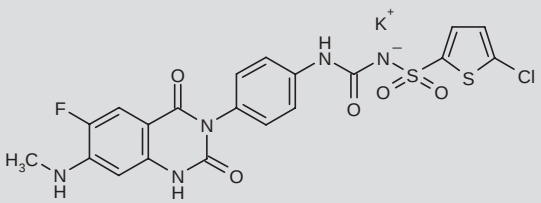
5.8, 2.9 and 3.3 mL/min/kg, 12.0, 9.0 and 5.0 h and 4.4, 0.7 and 0.6 L/kg, respectively, in rats, dogs and monkeys. BMS-538158 was selected for further clinical development in proof-of-concept studies based on its favorable predicted human clearance and volume of distribution (Vd_{ss}) profile (Cl = 2.19 mL/min/kg; Vd_{ss} = 0.23 L/kg) (1).

MIGRAINE

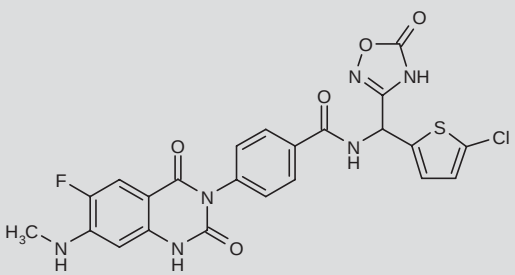
Merck Research Laboratories reported on the discovery of **MK-3207**, a new, highly potent, selective and orally bioavailable calcitonin gene-related peptide (CGRP) receptor antagonist (IC_{50} = 0.17 nM; hERG IP > 30 mM; L-type Ca^{2+} IC_{50} = 15 μM). The compound is the result of a rapid analogue synthesis strategy to identify alternatives to benzodiazepines and subsequent incorporation of a polar functionality in order to improve aqueous solubility and increase oral bioavailability (2). A phase II study of MK-3207 for the treatment of acute migraine was completed earlier this year (3).

ANTIPLATELET THERAPY

To improve on the $P2Y_{12}$ antagonist clopidogrel, investigators at Portola Pharmaceuticals identified a competitive, reversible, nonpurine inhibitor, **PRT-060128**, which is undergoing phase II evaluation. Work on identifying a second-generation inhibitor included a replacement for the sulfonylurea moiety, which led to a series of inhibitors with similar potency and pharmacokinetic characteristics. These nonsulfonylurea $P2Y_{12}$ inhibitors included the racemic **PRT-060392** (IC_{50} = 0.020 μM in a binding assay; IC_{50} = 4.04 μM for inhibition of platelet-rich plasma aggregation), with 10% bioavailability, a half-life of 9.8 h and an AUC of 49,130 ng.h/mL in animal studies. The (*S*)-isomer **PRT-060592** (IC_{50} = 0.021 μM in a binding assay) displayed dose-linear pharmacokinetics and negativity in the Ames test. PRT-060592 was three times more potent than the (*R*)-isomer **PRT-060674** but had lower exposure (4). These compounds have also been described in the patent literature (WO 2008036843).



PRT-060128



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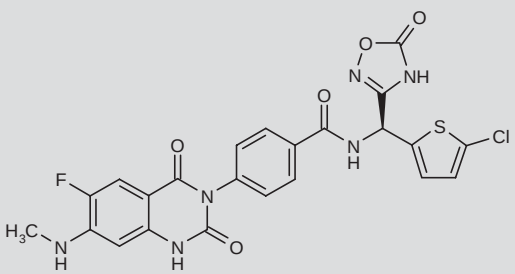

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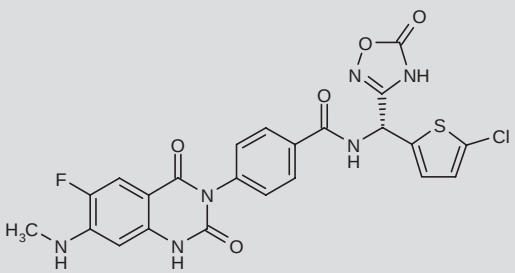


PRT-060674

HYPERTENSION

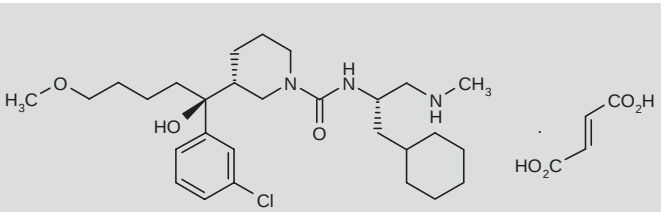
Low-molecular-weight alkylamine renin inhibitors with a novel scaffold have been identified by scientists at Vitae Pharmaceuticals using a proprietary structure-based drug design methodology for the development of antihypertensive drugs. Optimization of this scaffold resulted in the discovery of a lead compound (MW = 508;

IC_{50} = 0.47 nM against purified human renin) that displayed efficacy in an animal model of hypertension following oral administration. Further optimization led to the identification of compound **1** (IC_{50} = 0.5 nM against purified human renin, IC_{50} = 13 nM for inhibition of plasma renin activity) with > 1,000-fold selectivity over cathepsin D and E. This compound also showed activity in hypertensive rats following oral administration (5).

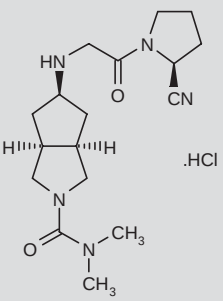
ENDOCRINE DISORDERS

Representatives from Shanghai Hengrui in Shanghai presented data on inhibitors of dipeptidyl peptidase IV (DDP4), a target in the treatment of type 2 diabetes, at the meeting. Among these was a series of azabicylooctane derivatives, including compounds **SHR-1039, SHR-1040** and **2**, with IC_{50} values against DPP4 of 0.009, 0.024 and 0.014 μM, respectively. Selectivity over DPP8 and DPP9 was also observed. In lean mice undergoing an oral glucose tolerance test, SHR-1039 reduced blood glucose excursions by 33.5% at a dose of 10 mg/kg. Oral administration of this dose to monkeys was associated with > 50% inhibition of DPP4 lasting 7 h ex vivo (6). Series of bicyclopyrrole and tricycloamine compounds were also prepared, with compounds **3** and **4** both having an IC_{50} value of 0.11 μM against DPP4. Although these compounds were less potent than the DPP4 inhibitor sitagliptin (IC_{50} = 0.050 μM), their in vitro activity was good and superior to that of other members of the series (7). SHR-1039 has also been claimed in the patent literature (WO 2008089636).

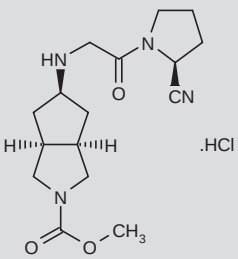
The discovery of **AMG-221**, which is in phase I clinical trials for the treatment of type 2 diabetes and metabolic syndrome, was described by Amgen. AMG-221 is an orally administered small molecule that acts as an inhibitor of 11-β-hydroxysteroid dehydrogenase type 1 (11-β-HSD1), an enzyme that regulates glucocorticoid action by converting inactive cortisone to active cortisol in the liver and adipose tissue. Unlike early 11-β-HSD1 inhibitors such as carbenox-



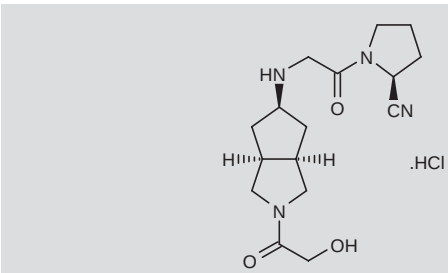
(**1**)



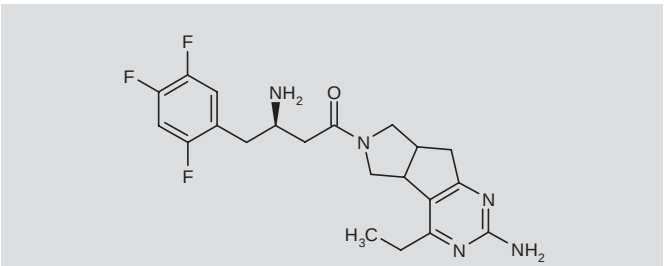
SHR-1039



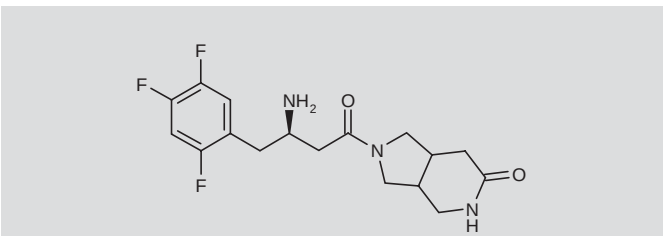
SHR-1040



(**2**)



(**3**)



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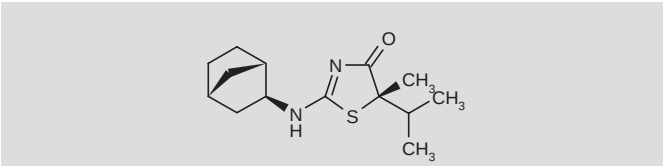
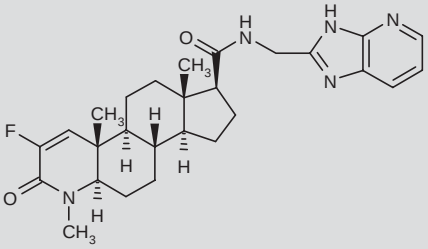


AMG-221

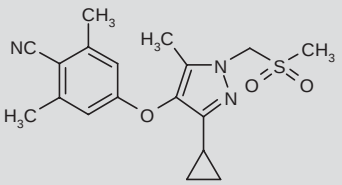
olone, which also displays antagonist activity against the electrolyte balance regulator 11-β-HSD2, AMG-221 has shown high potency and selectivity for 11-β-HSD1 both in vitro (K_i = 13 nM for 11-β-HSD1; IC_{50} = 10 nM against 11-β-HSD1; IC_{50} > 10 μM against 11-β-HSD2) and in vivo, where doses of 50 and 100 mg/kg/day p.o. b.i.d. for 13 days produced a reduction in insulin and glucose levels in diet-induced obese (DIO) mice (8).

Merck researchers described the discovery and synthesis of the novel selective androgen receptor (AR) modulator **MK-0773** (9). The compound was developed in an effort to overcome the adverse effects induced by other therapeutically active androgens, such as testosterone and dihydrotestosterone, including the promotion of hirsutism in women and prostate growth in men. The compound displayed a favorable pharmacological and pharmacokinetic profile (AR binding = 7.2 nM; TAMAR IP = 28 nM; TAMAR E_{max}/ R1881 = 0.60; VIRCON = 1.9% at 300 nM; bioavailability, $t_{1/2}$ and Cl = 99%, 4.2 h and 0.85 mL/min/kg, respectively, in dogs; water solubility = 0.77 mg/mL). MK-0773 is expected to offer beneficial myoanabolic effects with a significantly reduced risk of adverse effects (10). MK-0773 is currently being tested in a phase II clinical trial sponsored by Merck for the treatment of sarcopenia in women (estimated primary completion date October 2009) (11).

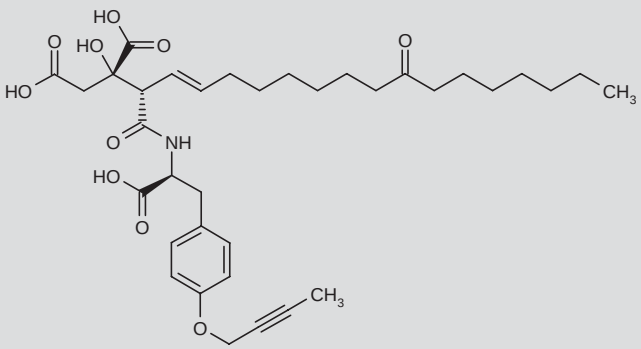
Lastly, Pfizer described the development of progesterone receptor (PR) antagonists for the treatment of endometriosis, which led to **PF-2413873** (PF-02413873), an agent currently in phase I clinical investigation. PF-2413873 (IC_{50} = 14 and 2.4 nM, respectively, in functional and binding assays) demonstrated 30-fold selectivity over mineralocorticoid receptors and > 100-fold selectivity over androgen/glucocorticoid receptors. Pharmacokinetic data were also presented, with clearance after i.v. administration of 84 and 4.6 mL/min/kg, respectively, in rats and dogs, respective $t_{1/2}$ values of 1.1 and 8.9 h, and an oral bioavailability in dogs of 94% (12). A phase I study of PF-2413873 in healthy young women is ongoing. The randomized, double-blind study is evaluating the tolerability, pharmacokinetics and effects on sex hormones of multiple doses of PF-2413873. Treatments include PF-2413873 20, 100, 500 and 1500 mg p.o. once daily for 14 days and placebo (13).



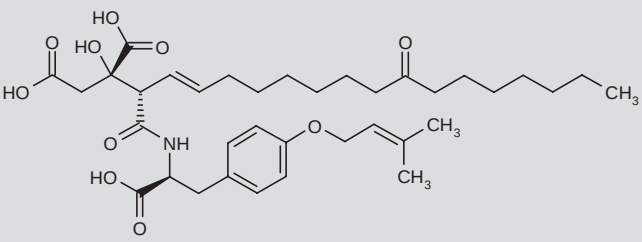
MK-0773



PF-2413873



NA-808



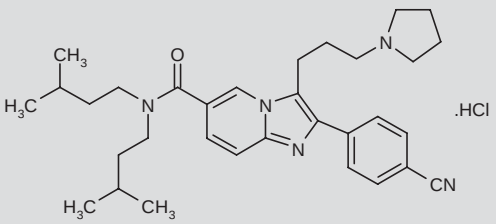
NA-255

HEPATITIS C

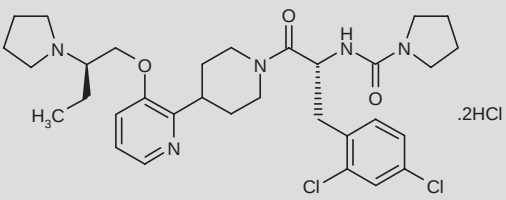
Scientists from Chugai Pharmaceutical disclosed the discovery of **NA-808**, a novel, host-targeting, anti-hepatitis C virus (HCV) agent that showed strong antireplicon activity and caused a significant reduction in HCV RNA in a human chimeric liver mouse model. NA-808 was identified through optimization of the lead compound **NA-255**, originally discovered by screening a library of natural products using an HCV replicon system. The target of NA-255 was identified as the host protein serine C-palmitoyltransferase, a key enzyme for the de novo synthesis of sphingolipids. The compounds work by disrupting the formation of the HCV replication complex on lipid rafts via inhibition of sphingolipid synthesis. NA-808 showed a broad spectrum of inhibitory activity against HCV genotypes 1 and 2 (IC_{50} = 2.2 and 6.5 nM, respectively). It also displayed a high barrier against the development of HCV resistance. In vitro NA-808 exhibited synergistic effects with PEG-interferon (14). NA-808 is currently in phase I development as an antiviral drug candidate for the treatment of chronic HCV infection.

METABOLIC DISORDERS

In a recent publication, Santhera Pharmaceuticals reported the discovery of two nonpeptide, orally bioavailable melanocortin MC_4 receptor antagonists that may be useful in treating cachexia, as the MC_4 receptor has been implicated in food intake and energy expen-



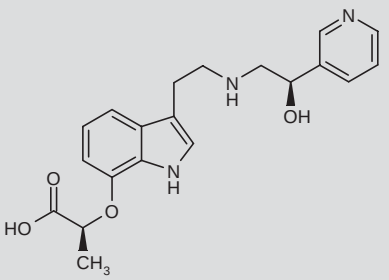
SNT-207707



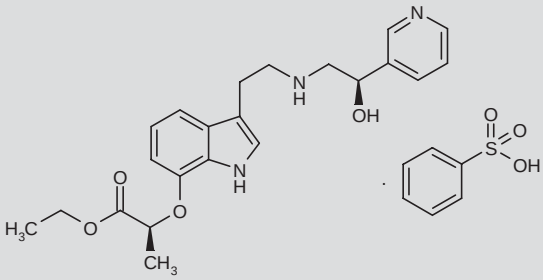
SNT-207858

diture. **SNT-207707** bound to the MC_4 receptor with an affinity of 8 nM and > 200-fold selectivity over MC_3 and MC_5 receptors. **SNT-207858** bound to the MC_4 receptor with an affinity of 22 nM and 170-fold selectivity versus MC_3 and 40-fold selectivity versus MC_5 receptors. A dose of 20 mg/kg s.c. of either of these agents significantly increased food intake during the lights-on phase. Oral administration of either agent also significantly and dose-dependently increased food intake in this model. In the C26 adenocarcinoma-induced cachexia model, once-daily oral administration of the compounds significantly reduced tumor-induced weight loss. Unlike vehicle-treated animals, most mice treated with SNT-207707 or SNT-207858 did not develop cachexia. Also, unlike vehicle-treated animals, treated mice had no loss, but rather slight gains in fat mass and lean body mass. Both agents also crossed the blood–brain barrier (15). Some of these data were also presented at the spring ACS meeting (16, 17). SNT-207858 has been described in the patent literature (WO 2009010299).

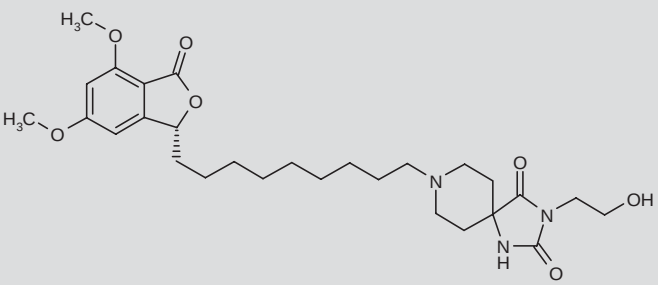
An effort to identify novel β_3-adrenoceptor (β3-AR) agonists for the treatment of obesity, diabetes and overactive bladder (OAB) led to the synthesis of a series of indol-7-yloxy derivatives and the discovery of **SM-296067** by Dainippon Sumitomo Pharma. SM-296067 showed good biological activity and high selectivity at the human β3-AR (EC_{50} = 97 nM) compared to human β1- and β2-ARs (EC_{50} nondetectable). The oral bioavailability of SM-296067 when administered as the prodrug form **SM-350300** (10 mg/kg) was estimated to be 49%, 59% and 24%, respectively, in rats, mice and cynomolgus monkeys. In fed and fasted dogs, the compound displayed a bioavailability of 21% and 47%, respectively. SM-350300 was also able to ameliorate pathological conditions in various rodent models of OAB. The increased selectivity of this compound compared to early β3-AR agonists already tested in clinical trials is expected to overcome the obstacle of adverse events such as tachycardia and muscle tremor (18).



SM-296067



SM-350300



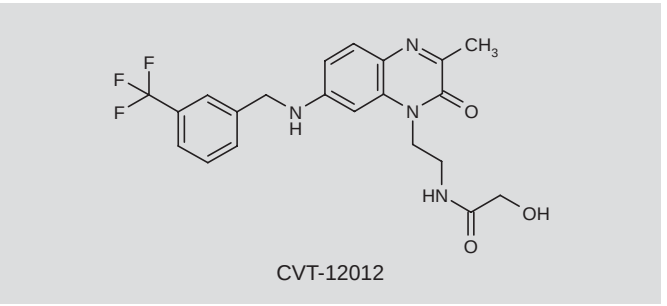
DNP-60502

The discovery of **DNP-60502**, a novel activator of AMP-activated protein kinase (AMPK) with potential use in the treatment of metabolic disorders, was detailed by Dainippon Sumitomo Pharma. AMPK is activated in response to cellular ATP depletion and plays a key role in cellular energy homeostasis by regulating glucose uptake and fatty acid oxidation in skeletal muscle. It is therefore considered a possible target for the treatment of diabetes and metabolic syndrome. DNP-60502 displayed good potency for AMPK activation in vitro (IC_{50} = 1.3 μM) and showed significant hypoglycemic effects in the obese insulin-resistant KKAy mouse (3 mg/kg p.o.) and in rats (10 mg/kg p.o.; bioavailability = 25%; C_{max} = 96 ng/mL). A significant hypolipidemic effect was also observed in hamsters fed a high-fat diet following administration of DNP-60502 3 and 10 mg/kg p.o. The compound may be developed as an antiobesity and antidiabetic drug (19). This compound has been described previously in the patent literature (WO 2008020607).

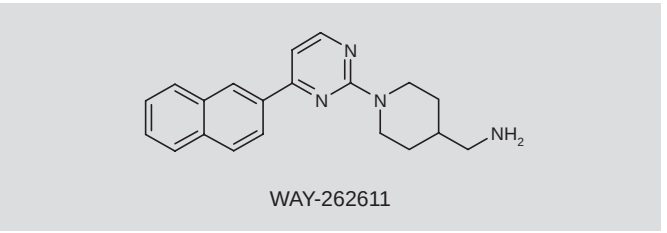
A screen of compounds by CV Therapeutics investigators led to the identification of unique inhibitors of stearoyl-CoA desaturase, a tar-

get for the treatment of obesity, metabolic syndrome and diabetes. Optimization of the lead compound led to improved potency but reduced bioavailability; this was overcome by important structural changes, resulting in **CVT-12012**. This compound had IC_{50} values of 38 and 6 nM, respectively, in rat microsomes and Hep G2 cells. Pharmacokinetic investigation yielded an AUC of 148 ng.h/mL, a clearance of 88.1 mL/min/kg, an elimination $t_{1/2}$ of 0.9 h and an oral bioavailability of 78%. After administration of a single dose of 5 mg/kg, liver concentrations were greater than plasma, adipose and muscle concentrations. Five days after treatment a decline in plasma and liver fatty acids was seen (20). CVT-12012 has also been claimed in the patent literature (US 20080255130).

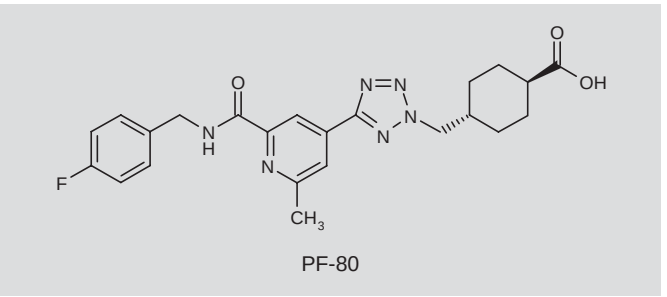
In order to target the Wnt β-catenin cellular messaging system to stimulate anabolic bone growth, Wyeth Research investigators overexpressed Wnt-3a and Dkk-1 in an osteosarcoma cell line with a TCF-response element luciferase reporter system to screen small molecules. A weak agonist was discovered and optimized, leading to **WAY-262611**, which demonstrated low micromolar cellular activity (TCF EC_{50} = 0.63 μM) without kinase activity (glycogen synthase kinase-3 beta IC_{50} > 100 μM). At 3 μM, inhibition of CYP3A4, CYP2C9 and CYP2D6 was 39%, 63% and 9%, respectively. Intravenous pharmacokinetic parameters in rats (2 mg/kg) included a plasma half-life of 8.2 h, AUC of 1029 ng.h/mL and clearance of 32 mL/min/kg. Following an oral dose of 10 mg/kg, $t_{1/2}$ was 5.6 h, t_{max} 4.76 h, C_{max} 277 ng/mL and AUC 3990 ng.h/mL (21). In a mouse calvaria model WAY-262611 significantly increased the trabecular bone formation rate compared to vehicle; the effects of WAY-262611 were not significant when *Dkk-1* knockout mice were used. In ovariectomized rats, the trabecular bone formation rate was dose-dependently and significantly increased by WAY-262611 given orally once daily for 28 days. WAY-262611 was also used as a template for structure–activity relationship studies to find more potent molecules (22). WAY-262611 has been claimed in the patent literature (WO 2009026326).



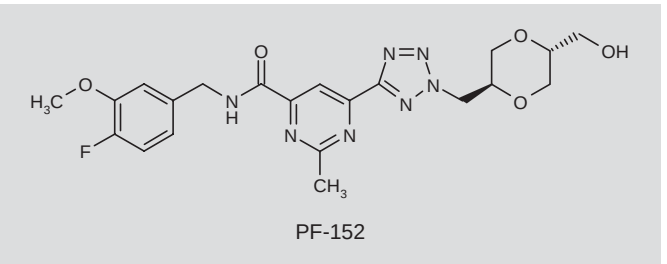
CVT-12012



WAY-262611



PF-80

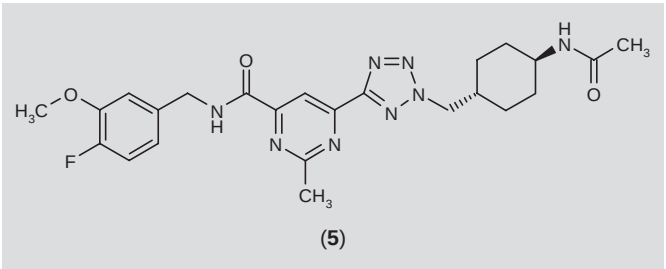


PF-152

IMMUNE-MEDIATED DISORDERS

The ACS meeting featured presentations on four inhibitors of matrix metalloproteinase MMP-13, a target for blocking the progression of osteoarthritis. These Pfizer compounds resulted from efforts to identify selective MMP-13 inhibitors that bind through the S1′ active-site pocket and are not dependent on inhibitor binding to the catalytic zinc. High-throughput screening and lead optimization, including the use of scaffold-hopping strategies and cartilage degradation biomarkers, led to the identification of inhibitors with > 1,000-fold selectivity and oral bioavailability. Among these was **PF-80**, with a K_i of 2.6 nM for MMP-13 and K_i values > 25 μM for other MMPs. PF-80 was orally available in rats and dogs, with a clearance of 14 mL/min/kg, an effective $t_{1/2}$ of 2.8 h and an oral bioavailability of 100% at 1 mg/kg in rats. The agent was also active in vivo at a dose of 50 mg/kg b.i.d. (23). Also identified was **PF-152**, with a clearance of 21.7 mL/min/kg, an effective $t_{1/2}$ of 0.7 h and an oral bioavailability of 54% in rats; these figures were 8.1 mL/min/kg, 1.6 h and 64%, respectively, in dogs. A dose of 5 mg/kg b.i.d. was also effective in a rat model of osteoarthritis. PF-152 was associated with declines in urinary type II collagen neoepitope, a biomarker of matrix metalloproteinase activity (24). A third compound (**5**) was also very selective for MMP-13, with a K_i of 0.6 nM, and was orally bioavailable in vivo (F = 44% in rats). A half-life of 1.02 h and a clearance of 10.7 mL/min/kg were measured in rats. Another compound (**6**) was again very selective for MMP-13, with a K_i of 4.97 nM. In rats it showed a $t_{1/2}$ of 1 h, a clearance of 9.7 mL/min/kg and an oral bioavailability of 62% (25). These compounds have been claimed in the patent literature (WO 2009016498).

The development of **PLX-3397** as a novel, orally active dual inhibitor of Fms (CSF-1-R) and Kit (SCFR) receptor tyrosine kinases for the treatment of autoimmune conditions was presented by Plexxikon. Fms and Kit regulate the activation of macrophages and mast cells, respectively, and are involved in the control of autoimmune processes manifested in diseases such as rheumatoid arthritis (RA) and multiple sclerosis (MS). PLX-3397 displayed potent and selective inhibition of both Fms and Kit, with good exposure in rodent and nonrodent models. Administration of PLX-3397 (50 mg/kg p.o. once daily) in the MOG–EAE (myelin oligodendrocyte glycoprotein–experimental allergic encephalomyelitis) animal model for human MS was associated



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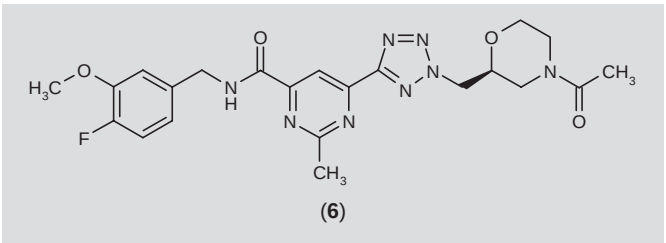


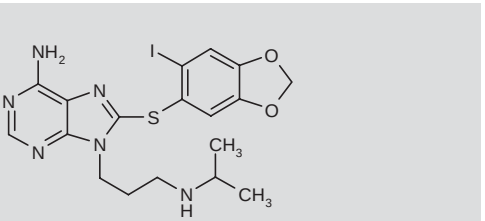
(**6**)

with a significant decrease (approximately 60%) in disease score, without any effect on body weight, by treatment day 10. The response to PLX-3397 in this model was found to be durable, without a rebound following treatment suspension, and the compound was also able to inhibit the progression of advanced disease when administered to the vehicle group. Histological analysis revealed that treatment with PLX-3397 abolished macrophage/microglial infiltration in the MOG–EAE model, thereby reducing inflammation. A reduction in bone erosion and associated pain was also observed and attributed to the inhibitory effect of the compound on osteoclasts. PLX-3397 may be potentially useful for the treatment of autoimmune/inflammatory conditions other than MS and RA, such as asthma, inflammatory bowel disease and lupus (26).

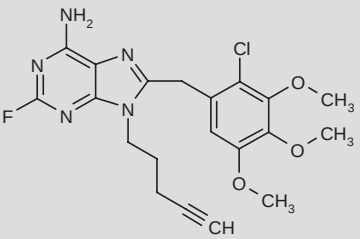
NEUROLOGICAL DISORDERS

Based on the hypothesis that heat shock protein HSP90 plays a compensatory role in maintaining and permitting the processes that lead to the disease phenotype in Alzheimer's disease (AD), as it appears to do in cancer, HSP90 inhibitors have been developed as possible treatments for AD. When investigated in the *Lrrk2* G2019S mutant mouse Parkinson's disease model at the Memorial Sloan-Kettering Cancer Center, the HSP90 inhibitor **PU-H71** was found to accumulate in the brain and rescue axonal growth, without inducing cytotoxicity in organs targeted by other HSP90 inhibitors. In vitro **PU-24FCl** reduced cellular levels of mutant tau, while another HSP90 inhibitor, **PU-DZ8**, was active in a rat model of Parkinson's disease. A number of newer compounds developed by a team from the Memorial Sloan-Kettering Cancer Center, Rockefeller University and Columbia University were discussed at the meeting, including **PU-DZ13** and **PU-HZ151** (K_i > 10 nM), which were very effective in reducing phosphorylated tau in vivo and had the additional beneficial effect of inducing HSP70 (27).

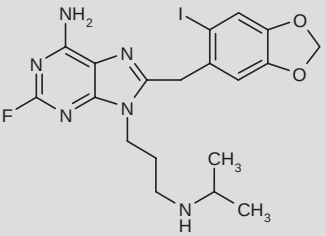
Presynaptic group III metabotropic glutamate receptors (mGlu) have been implicated in the pathology of central nervous system (CNS) conditions such as Parkinson's disease, anxiety and pain, and represent a potential therapeutic target for these pathologies. A virtual high-throughput screening of the $mGlu_4$ binding site led French scientists to identify a novel series of carboxyethylphosphinic acid compounds, a large number of which demonstrated the ability to activate $mGlu_4$. One such compound, **LSP-1-2111**, showed a marked preference for $mGlu_4$ and $mGlu_6$ versus other group III mGlu receptor subtypes (EC_{50} = 2.2, 1.7, 53 and 66 μM, respectively, for $mGlu_4$, $mGlu_6$, $mGlu_7$ and $mGlu_8$). LSP-1-2111 was further evaluated in an animal model of Parkinson's disease, where it was found to produce antiparkinsonian effects at 10-fold lower doses compared to previously known group III mGlu receptor agonists. The compound was able to reduce striatopallidal inhibitory postsynaptic currents in a



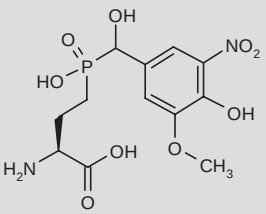
PU-H71



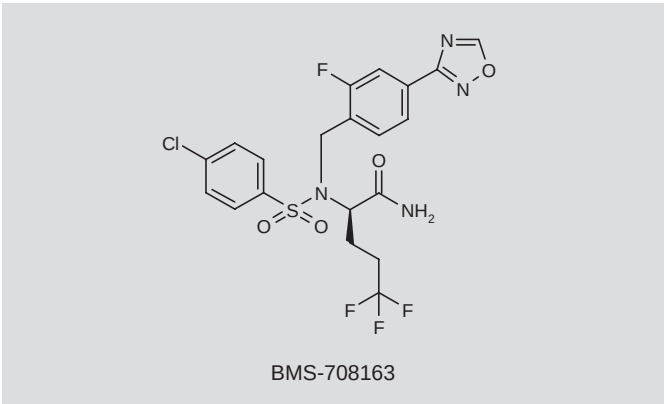
PU-24FCl

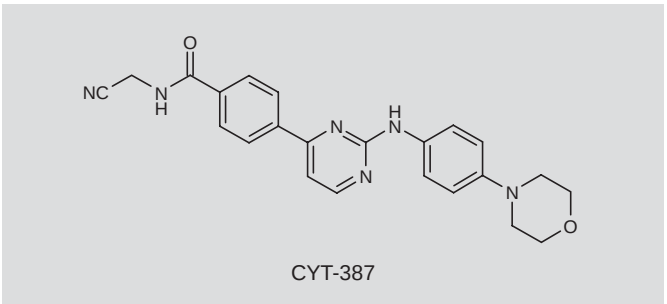


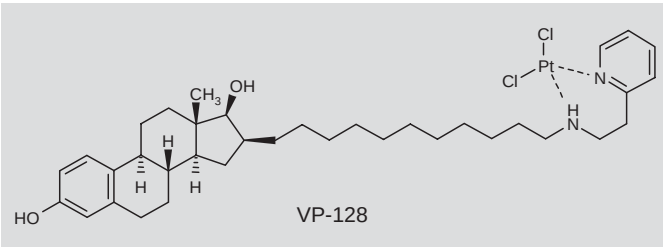
PU-DZ8

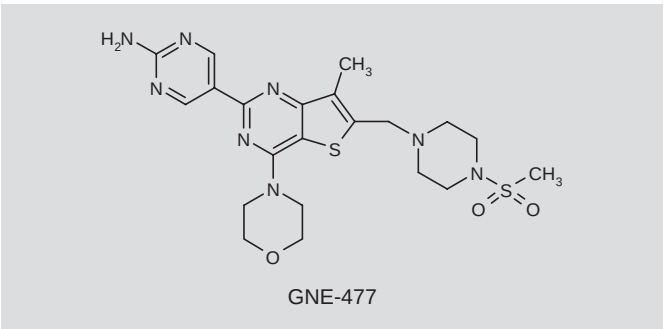


LSP-1-2111









dose-dependent manner in mice and reversed 6-hydroxydopamine-induced motor deficits in rats (28).

BMS-708163 (Bristol-Myers Squibb) is a γ-secretase inhibitor with selectivity towards Notch, making it a potential treatment for AD via interference with the formation of β-amyloid (Aβ) peptides. The agent's potency (IC_{50} = 0.3, 0.3 and 0.27 nM, respectively, against amyloid precursor protein [APP], $Aβ_{40}$ and $Aβ_{42}$) and selectivity over Notch (IC_{50} = 58 nM against mNotch; mNotch IC_{50}/APP IC_{50} = 193) were described at the congress. BMS-708163 was also found to significantly reduce Aβ in animal models and has entered phase I clinical investigation (29). A study of potential drug interactions in healthy volunteers has been completed (30) and another in healthy young and elderly Japanese volunteers evaluating safety, tolerability, pharmacokinetics and pharmacodynamics after 14 days of oral treatment is ongoing (31).

CANCER

The constitutively activating mutation in Janus kinase 2 (JAK2), JAK2(V617F), has been implicated in the dysregulation of the signal transducer and activator of transcription (STAT) signaling pathway, which is linked to the pathogenesis of chronic myeloproliferative neoplasms (MPNs), a group of hematological disorders including polycythemia vera, essential thrombocythemia and primary myelofibrosis. A medicinal chemistry program undertaken by Cytopia aiming to optimize a series of weakly active JAK2 inhibitors led to the identification of **CYT-387**, a small-molecule inhibitor of JAK2 with good potency, selectivity and oral bioavailability (32). In recently published data, inhibition of JAK1/JAK2 by CYT-387 was equipotent (IC_{50} = 11 and 18 nM, respectively) and 9-fold more potent compared to JAK3 (IC_{50} = 155 nM). CYT-387 was able to inhibit the growth of cell lines harboring the JAK2(V617F) mutation or a mutation in the thrombopoietin receptor MPL (IC_{50} = approx. 1500 and 200 nM, respectively). The compound induced dose-dependent decreases in STAT5 (IC_{50} = 400 nM) and STAT3 (IC_{50} = 2500 nM) phosphorylation in human erythroleukemia HEL cells. CYT-387 also inhibited the in vitro growth of erythroid colonies derived from polycythemia vera patients at low micromolar concentrations (IC_{50} < 0.5-4 μM). This inhibitory effect was significantly attenuated (by 2- to 4-fold) upon the addition of exogenous erythropoietin. It was concluded that CYT-387 displays potential for the treatment of mutant JAK-associated MPNs (33).

The possibility of using platinum therapy in treating breast cancer requires avoidance of toxicity, which may be accomplished by targeting the therapy to cancer cells via the estrogen receptor (ERα). To do this, investigators at the Université du Québec, Trois-Rivieres, attached a cisplatin derivative to estradiol, resulting in estradiol-platinum(II) hybrid molecules. In vitro cytotoxicity assays led to the selection of **VP-128** for further investigation. In vitro VP-128 was more effective in inducing apoptosis in human breast cancer MCF7 cells than cisplatin. VP-128 was also active against ERα-negative cells, and was more efficient than cisplatin in inhibiting the growth of a selection of breast and ovarian adenocarcinoma cell lines. In mice VP-128 suppressed the growth of hormone-dependent and -independent breast and ovarian cancer xenografts, demonstrating greater activity than cisplatin in hormone-dependent tumors and activity similar to cisplatin in breast and ovarian tumors derived from ERα-negative cells. No evidence of toxic side effects was seen with either agent in these experiments (34).

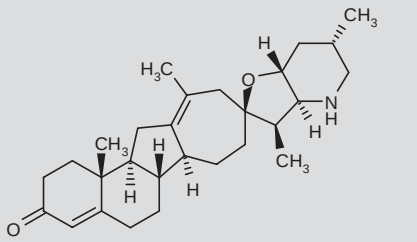
Phosphatidylinositol 3-kinase (PI3K) is implicated in the pathogenesis of a variety of tumor types and the identification of PI3K inhibitors with drug-like properties is therefore a goal of the pharmaceutical industry. Structure-guided design of an orally available inhibitor of PI3K activity, previously disclosed by Genentech and Piramed, led to the evolution of the thienopyrimidine series of PI3K inhibitors and the discovery of **GNE-477**, a compound with increased vitro activity

(IC_{50} = 2 nM for the p110α isoform of PI3K; EC_{50} = 280 nM for inhibition of human prostate cancer PC-3 cell proliferation; EC_{50} = 130 nM for human breast cancer MDA-MB-361 cell proliferation; K_{iapp} = 22 nM for mTOR). In vivo GNE-477 displayed activity in mice (50 mg/kg suspension; F = 98%, Cl = 14.8 mL/min/kg, $t_{1/2}$ = 3.7 h, Vd_{ss} = 2.0 L/kg), rats (5 mg/kg; F = 52%, Cl = 12.6 mL/min/kg, $t_{1/2}$ = 4.6 h, Vd_{ss} = 3.7 L/kg) and dogs (2 mg/kg; F = 90%, Cl = 5.0 mL/min/kg, $t_{1/2}$ = 6.1 h, Vd_{ss} = 2.1 L/kg). In a mouse prostate cancer xenograft model GNE-477 displayed activity at 1, 5 and 10 mg/kg and caused complete tumor suppression at 20 mg/kg (35). This compound has also been reported in the patent literature (WO 2007127175, WO 2008070740 and WO 2008073785).

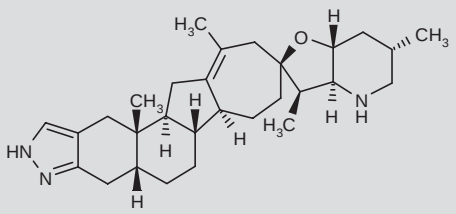
Cyclopamine, a natural product alkaloid from the plant *Veratrum*, has shown promising activity as an inhibitor of the hedgehog pathway, the aberrant signaling of which has been implicated in a variety of cancers. **IPI-269609**, a 7-membered D-ring semisynthetic analogue of cyclopamine, has demonstrated greater acid stability and better aqueous solubility compared to cyclopamine, while exhibiting equivalent biological activity against the hedgehog pathway. Efforts at Infinity Pharmaceuticals to improve activity led to the identification of A-ring fused heterocyclic analogues, including **7**, with 10-fold improved biological activity compared to cyclopamine (EC_{50} = 13 nM in C3H10 cells) (36). Efforts also led to the discovery of 7-membered A-ring lactam analogues, including **8**. This analogue displayed EC_{50} values in the range of 30-40 nM in C3H10 cells and an oral availability of approximately 100% in mice (5 mg/kg p.o.), rats (5 mg/kg p.o.) and cynomolgus monkeys (4 mg/kg p.o.), and 97% in beagle dogs (4 mg/kg p.o.). The $t_{1/2}$ and Cl were 3-6.5 h and 0.33-0.8 L/h/kg, respectively (37). **IPI-926**, a systemic hedgehog antagonist, was also identified through synthetic transformations of the A-ring (EC_{50} = 7-15 nM in C3H10 cells) (38). This compound displayed improved pharmaceutical properties and potency and a better pharmacokinetic profile relative to cyclopamine. A single oral dose of IPI-926 (< 4 mg/kg) to medulloblastoma B837Tx tumor-bearing mice inhibited GLI expression at 8 h. Daily administration of < 4 mg/kg p.o. resulted in tumor growth inhibition in the B837Tx model (39). IPI-926 is currently undergoing clinical evaluation (phase I) for the treatment of advanced and/or metastatic solid tumors (40).

Bristol-Myers Squibb disclosed data on the development of a novel class of inhibitors of insulin-like growth factor 1 receptor (IGF-I receptor), with optimization of a pyrrolo[1,2-*f*][1,2,4]triazine leading to the clinical candidate **BMS-754807** (K_i = 1.7 nM). BMS-754807 demonstrated selectivity for the IGF-I receptor in vitro, therapeutic activity in < 1 h at 2 mg/kg in rats, oral efficacy in in vivo tumor models and synergistic effects with cetuximab, and no cardiovascular effects in dogs at the maximum dose tested. Clearance in mice, monkeys, rats and dogs was 143, 46, 24 and 5.2 mL/min/kg, respectively, and oral bioavailability was 6%, 8%, 30% and 57%, respectively; oral bioavailability estimated for humans was 8-50%. Single and multiple oral doses have been evaluated in phase I studies and evaluation of BMS-754807 in cancer patients is ongoing (41). The combination of BMS-754807 and paclitaxel and carboplatin is being investigated in a phase I study currently enrolling patients with advanced or metastatic tumors. Multiple ascending doses are being assessed, with the aim of identifying recommended doses for phase II studies. The study is expected to conclude in December 2010 (42).

The synthesis and preclinical activity of Pfizer's mutant B-Raf inhibitor **PF-0419789** was described. Mutant B-Raf is a target in



IPI-269609



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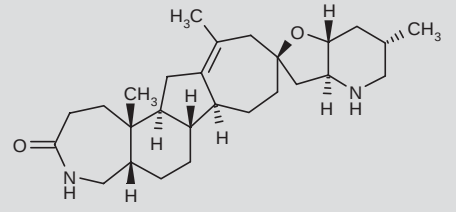

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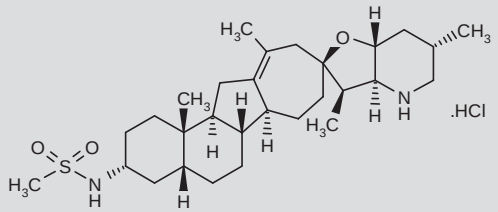
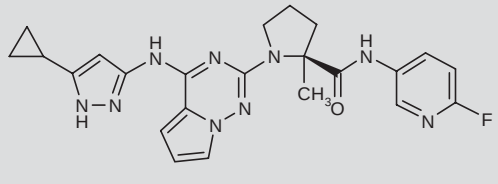
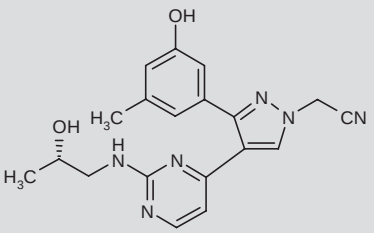


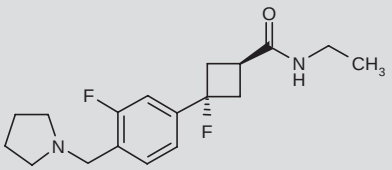
IPI-926



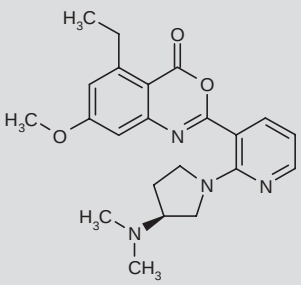
BMS-754807



PF-0419789



PF-03654746



AX-9657

melanoma, thyroid cancer and colorectal cancer, as well as other cancers. Efforts to develop a potent mutant B-Raf inhibitor starting with a phenolpyrazole lead led to PF-0419789, with a K_i value for mutant B-Raf of 1.07 nM and an IC_{50} for phosphorylated MEK of 19 nM. Following oral administration of 10 mg/kg in rats, a half-life of 2.6 h was measured, along with a bioavailability of 13% and a volume of distribution of 1.3 L/kg. In a colon tumor xenograft model, doses of 25, 50 and 100 mg/kg were associated with tumor growth inhibition of 62%, 80% and 86%, respectively (43). PF-0419789 has also been claimed in the patent literature (WO 2007105058).

PSYCHIATRIC DISORDERS

Histamine H_3 receptors regulate the release of histamine, a molecule that plays a major role in processes such as attention, learning and memory, and wakefulness. Pfizer's **PF-03654746**, a novel, potent and highly selective in vitro and ex vivo antagonist of the H_3 receptor (K_i = 2.3 and 37 nM, respectively, for human and rat receptors; ED_{50} = 2.2 mg/kg s.c.), was described at the meeting. The compound is expected to prove useful as a tool for the evaluation of the role of H_3 receptors in the treatment of conditions such as attention deficit hyperactivity disorder (ADHD), schizophrenia, AD and narcolepsy (44). The efficacy and safety of two doses of PF-03654746 in adults with ADHD were evaluated in a recently completed phase II study sponsored by Pfizer (45). The drug is also in phase I trials for cognition enhancement in schizophrenia and AD.

RESPIRATORY DISORDERS

Inhibition of neutrophil elastase (NE), a serine protease that degrades structural extracellular matrix proteins and promotes infiltration of activated neutrophils, is considered a potential therapeutic approach for the treatment of lung diseases. A serine hydrolase activity-based assay was developed by ActivX aiming to measure the cell permeability of novel small-molecule human NE inhibitors using the HL-60 human cell line, which exhibits characteristics similar to neutrophils. This approach permitted the evaluation of compound permeability across live cellular membranes and at different pH conditions (46). The assay, performed in collaboration with Kyorin Pharmaceutical, led to the identification of **AX-9657**, a potent (K_i = 5.1 nM; IC_{50} = 7 nM) and selective (apart from chymotrypsin) inhibitor of human NE. Intravenous infusion of the compound at a rate of 10 mg/kg/h over 1 h in rats revealed high distribution in the lung (lung/plasma ratio = 41.3). In a rat lung injury model AX-9657 (3 and 10 mg/kg/h) significantly reduced the hemoglobin content in bronchoalveolar lavage fluid following human NE-induced lung hemorrhage ($P < 0.01$). In a model of lipopolysaccharide-induced acute lung injury the compound (3 mg/kg/h) significantly reduced lung water content ($P < 0.05$). The results suggest that AX-9657 may be useful for the development of treatments for acute lung injury, cystic fibrosis, pulmonary fibrosis and chronic obstructive pulmonary disease through inhibition of excessive NE activity in the lung (47). AX-9657 has also been described in the patent literature (WO 2008036379).

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