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Meeting Report

Highlights from the 236th American Chemical Society (ACS) National Meeting & Exposition

I. Izco-Basurko, P. Cole, D. Mormeneo
Prous Science, Provenza 388, 08025 Barcelona, Spain

CONTENTS

Abstract

The 236th American Chemistry Society (ACS) National Meeting and Exposition, held in Philadelphia during the third week of August, featured the latest advances in the identification and improvement of biomedical drugs, imaging agents and technologies. Impressive presentations and discussions were organized around the theme of "Chemistry for Health: Catalyzing Translational Research". This article provides a summary of investigations into some of the most interesting new pharmacological agents and tools under development. In addition to diagnostic agents and nanotechnology, this includes therapeutics for AIDS, pain and blood coagulation, as well as cardiovascular, endocrine, gastrointestinal, metabolic, inflammatory, neurologic, oncologic, psychopharmacologic, renal–urologic and respiratory drugs.

Introduction

The 236th National Meeting and Exposition of the American Chemical Society (ACS) brought together more than 13,800 attendees, with scientists, students and other visitors attending from around the world. Tremendous efforts are being made worldwide to improve the technologies and methodology for identifying new chemical entities and for optimization of drugs in terms of pharmacokinetics, potency and safety. Here we have highlighted some of the most interesting findings in treating multiple disorders, such as diabetes, thrombosis, cancer and schizophrenia, presented at the meeting.

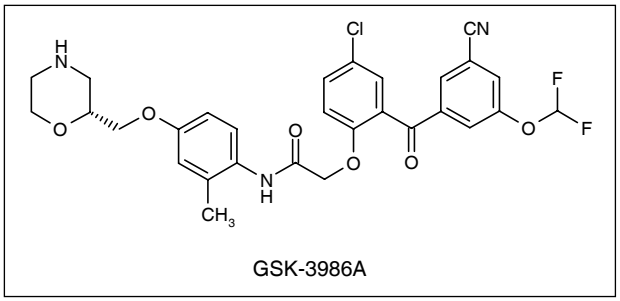
New therapeutic agents

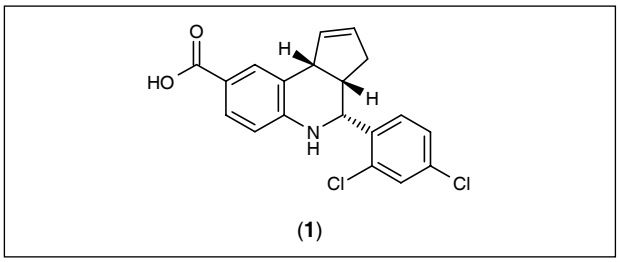
AIDS compounds

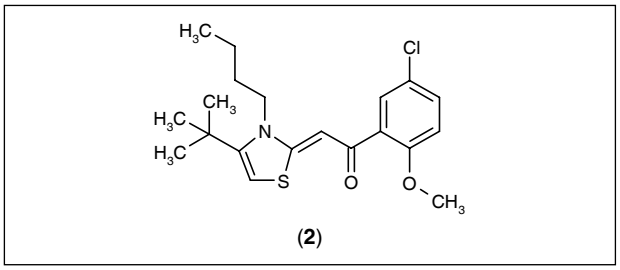
Investigators from GlaxoSmithKline found acceptable clinical efficacy in recent studies with the anti-HIV agent GW-8248X, a benzophenone non-nucleoside reverse transcriptase inhibitor (NNRTI), but adverse events and low aqueous solubility led to discontinuation of clinical investigation of the agent. They then sought an agent with similar potency and increased aqueous solubility via replacement of the sulfonamide and A-ring chlorine. Structure–activity relationship (SAR) efforts to optimize the A-ring showed that the chlorine can only be replaced with small, relatively nonpolar substituents to maintain potency. Of the leads resulting from these studies, **GSK-3986A** exhibited good activity against HIV, as well as improved hERG and aqueous solubility properties, and has progressed to rat dose-escalation studies. The activity of GSK-3986A was measured against a panel of HIV strains, including wild-type HIV-1 and the mutants K103N, Y181C and V106A (IC_{50} = 0.3, 0.3, 0.7 and 3.1 nM, respectively), showing much lower activity against hERG (IC_{50} = 29.8 μM). Pharmacokinetics have been investigated in rats (CL = 5 ml/min/kg, $t_{1/2}$ = 8.1 h, F = 28%) and dogs (CL = 17 ml/min/kg, $t_{1/2}$ = 5 h, F = 87%) (1).

Analgesic drugs (migraine, inflammatory and neuropathic pain)

Acting on reports that activation of the large-conductance, calcium-activated potassium channel $K_{Ca}1.1$ affects neuronal excitability and that agonists may be useful for treating migraine, Amgen investigators used high-throughput screening to identify a $K_{Ca}1.1$ agonist. SAR analyses of a novel class of tetrahydroquinoline analogues led to improved cellular potency and activity in electrophysiology studies. One compound (**1**) demonstrated a 10-fold improvement over the lead compound in potency in cellular assays. In vivo pharmacokinetic assessments showed a $t_{1/2}$ of 4.4 h and an oral bioavailability of 30% in rats. Assessment of ion channel selectivity yielded values of > 100 μM for $Na_v1.5$ and > 25 μM


GSK-3986A

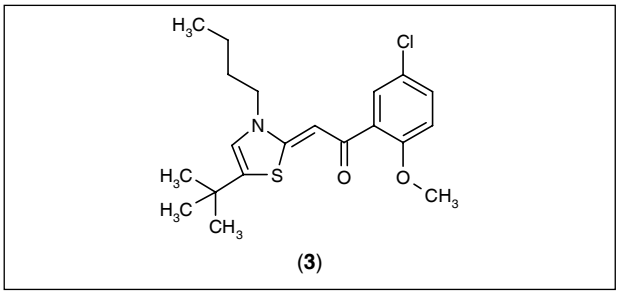

(**1**)


(**2**)

for $K_v1.1$, $K_v1.5$. and $K_v1.3$. Safety evaluation revealed an hERG IC_{50} of > 30 μM. $K_{Ca}1.1$ agonists may be an innovative way to treat migraine headaches (2).

Targeting the cannabinoid CB_2 receptor may provide analgesia without the adverse effects seen with CB_1 receptor agonism. Abbott has pursued the development of a series of thiazolylidene-ethanone derivatives as CB_2-selective agonists. SAR analyses identified two compounds, **2** and **3**, with nanomolar potency and good in vitro selectivity (**2**: K_i hCB_1 > 10,000 nM, K_i hCB_2 = 7.7 nM, K_i rCB_2 = 25.0 nM, EC_{50} hCB_2 = 67 nM; **3**: K_i hCB_1 > 10,000 nM, K_i hCB_2 = 7.6 nM, K_i rCB_2 = 1.0 nM, EC_{50} hCB_2 = 17 nM). In a pharmacokinetic study, i.p. administration of 10 μmol/kg yielded a bioavailability of 86% and 50% for compounds **2** and **3**, respectively. Both compounds demonstrated efficacy against capsaicin-induced secondary mechanical hyperalgesia in vivo. Research continues for optimization of pharmacokinetic and in vivo characteristics (3).

A series of 2,7-diaminothiazolo[5,4-*d*]pyrimidine derivatives were synthesized as transient receptor potential TRPV1 antagonists by Johnson & Johnson investigators for the treatment of neuroinflammatory diseases. For one such compound **4**, human and rat K_i values were 15 and 6 nM, respectively, and IC_{50} values were 21 nM against human TRPV1 and 7 nM against rat TRPV1. In rats, an oral dose of 10 mg/kg is associated with a clearance of 0.4 l/h/kg, a $t_{1/2}$ of 2.3 h and a C_{max} of 0.6 μM. The compound was also effective in rats with carrageenan-induced thermal hyperalgesia (4).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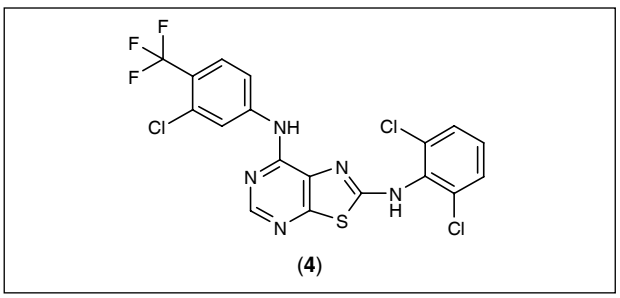
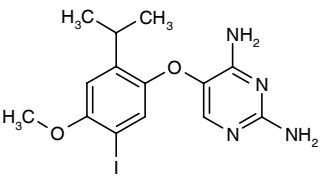
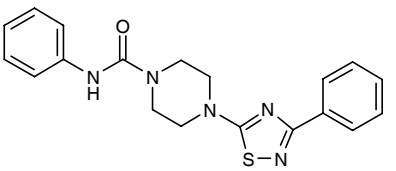

(**4**)

Researchers at Roche have developed novel dual $P2X_3$/$P2X_{2/3}$ purinergic receptor antagonists for the treatment of inflammatory and neuropathic pain. **RO-4** showed selective binding affinity for human $P2X_3$ and $P2X_{2/3}$ receptors (IC_{50} = 11 and 14 nM, respectively) over other P2X receptor subtypes. This compound has shown efficacy in preclinical inflammatory and neuropathic pain models. Similarly, RO-4 reduced mechanical allodynia in a model of rat bone cancer following twice-daily oral treatment at 100 mg/kg. RO-4 did not affect locomotor activity up to oral doses of 300 mg/kg. However, dose-dependent and dose-limiting emesis, as well as reduced food consumption, have been observed following oral dosing in dogs, which was suppressed by pretreatment with ondansetron. Further research led to the discovery of **RO-41**, a prodrug of RO-4, which was also an antagonist, with less potent activity against $P2X_3$ and $P2X_{2/3}$ receptors (IC_{50} = 21 and 50 nM, respectively) and less emetic potential than RO-4. Another compound, **RO-51**, also exhibited potent antagonist activity at $P2X_3$ and $P2X_{2/3}$ receptors (IC_{50} = 2 and 5 nM, respectively). These results suggest therapeutic potential for this mechanism of action in a number of pain conditions (5).

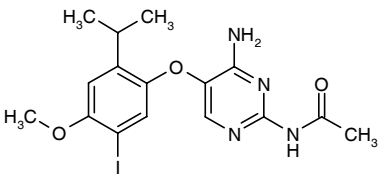
Research undertaken at Johnson & Johnson has resulted in the discovery of novel fatty acid amide hydrolase (FAAH) inhibitors with potential utility as analgesics. In particular, **JNJ-1661010** inhibited the human FAAH enzyme in vitro with an IC_{50} value of 33 nM. When orally administered at 3, 10 and 30 mg/kg, the compound dose-dependently increased the concentrations of the FAAH substrates anandamide, oleoylethanolamide and palmitoylethanolamide in rat brain (6). Further studies presented at the 12th World Congress of Pain held recently in Glasgow showed JNJ-1661010 to be effective in diverse pain models, attenuating tactile allodynia in a mild ther-



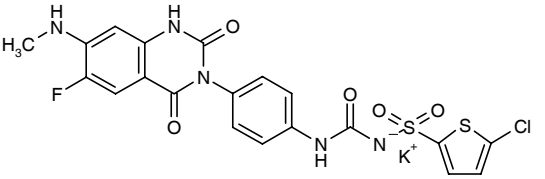
RO-4



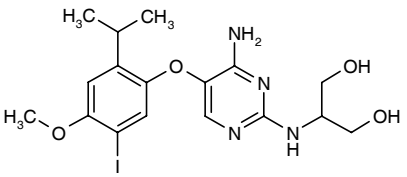
JNJ-1661010



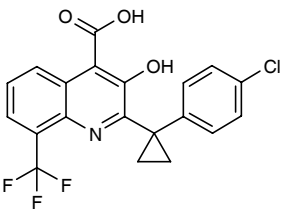
RO-41



PRT-060128



RO-51



PSI-421

mal injury model of acute tissue damage and a rat spinal nerve ligation model of neuropathic pain. Thermal hyperalgesia caused by carrageenan injection in the rat paw was also reduced by JNJ-1661010 treatment (7).

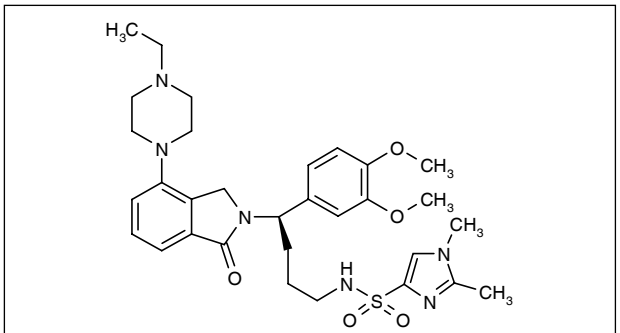
Blood coagulation (antiplatelet, thrombosis)

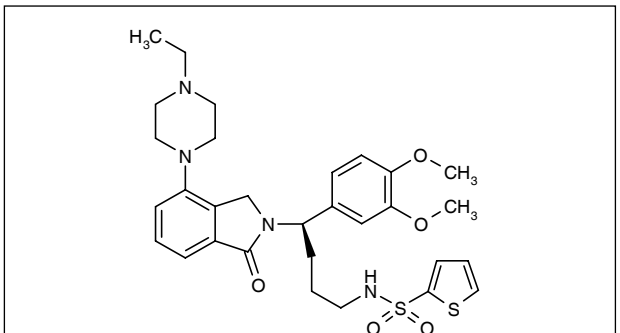
Researchers from Portola Pharmaceuticals disclosed the preclinical and clinical features of **PRT-060128**, a $P2Y_{12}$ inhibitor under development as an antiplatelet agent. PRT-060128 is characterized by a competitive and reversible mechanism of action. This agent is bioavailable following i.v. bolus or oral dosing, demonstrated an onset of action within seconds and a duration of effect of 6-12 h. PRT-060128 showed an IC_{50} of 20 nM in a binding assay and of 4 μM in a platelet-rich plasma aggregation assay. In an ex vivo aggregation evaluation in healthy subjects, i.v. PRT-060128 demonstrated complete, immediate and reversible inhibition of platelet aggregation. Effects on bleeding time after i.v. administration to healthy subjects were concentration-dependent and reversible. The compound also showed efficacy in patients not responding to clopidogrel, 14 of whom (N = 16) had potent antiplatelet responses. Superiority to clopidogrel was also seen in an animal tail transection model in which bleeding time was reduced by PRT-060128 (8). This compound is currently in phase II evaluation for the treatment of patients undergoing nonurgent percutaneous coronary intervention (PCI) (9).

A recently identified novel P-selectin inhibitor, **PSI-421** (Wyeth), showed improved aqueous solubility and pharmacokinetic properties, with oral efficacy in animal models of both arterial and venous injury. This compound inhibited P-selectin in vitro with an IC_{50} value of 225 μM. Additionally, oral treatment at 50 mg/kg reduced leukocyte rolling in cremasteric postcapillary venules of normal mice by 47% relative to vehicle. PSI-421 exhibited a good pharmacokinetic profile in mice, rats, dogs and nonhuman primates, with increased oral bioavailability and drug exposure compared to previous analogues. In the rat carotid artery balloon injury model, PSI-421 was able to significantly prevent neointimal lesions when given at 30 mg/kg p.o. Treatment with PSI-421 at 1 mg/kg p.o. before and after thrombosis resulted in greater vein lumen patency in a baboon deep vein thrombosis model (10).

Cardiovascular drugs (chronic heart failure)

Efforts at Johnson & Johnson to optimize a phthalimide-based urotensin-II receptor antagonist have led to the identification of **JNJ-39327041**, which displayed improved potency, ADME (absorption, distribution, metabolism and excretion) and safety. Such agents are potentially useful for metabolic and cardiovascular disorders such as renal failure, diabetes and chronic heart failure. An early compound demonstrated in vitro and in vivo potency but also displayed cytochrome P-450 (CYP450) inhibition and a poor ADME profile. Derivatives with lower molecular weight were prepared by replacing the *N*-(α-methylbenzyl) group. Elimination of one carbonyl led to isoindolinones, the most potent of which was **JNJ-**

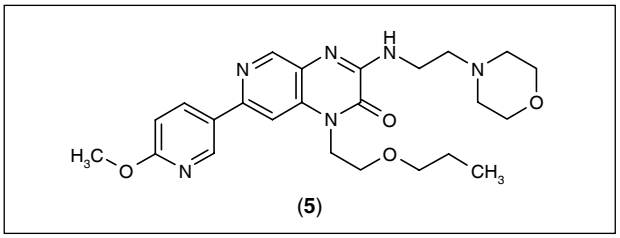

JNJ-39327041


JNJ-39319202

39319202. Further optimization of this series produced JNJ-39327041, with improved Lipinski parameters, lower CYP450 inhibition and a better in vitro ADME profile. IC_{50} values for rat and human urotensin-II were 22 and 50 nM, respectively, for JNJ-39327041 and 1.2 and 1.9 nM, respectively, for JNJ-39319202. K_i values for human urotensin-II binding were 24 and 4 nM for JNJ-39327041 and JNJ-39319202, respectively. For CYP450 2C19 and CYP450 3A4, IC_{50} values were > 10 μM for JNJ-39327041 and 8.6 and 0.92 μM, respectively, for JNJ-39319202 (11).

Endocrine drugs (diabetes, obesity)

Novel phosphodiesterase PDE5 inhibitors with a long duration of action have been synthesized at Pfizer after efforts were made to optimize a pyridopyrazinone scaffold to improve intrinsic solubility and microsomal stability. Focused on moving the nitrogen around the B-ring from the 1-position ("northern pyridines") to the 3- ("southeastern pyridines") and 4-positions ("southern pyridines"), the research found that solubility was significantly improved with the southern pyridines. The southeastern pyridines represented improved potency over the southern compounds, with compounds **5** and **6** demonstrating PDE5 IC_{50} values of 0.7 and 0.27 nM, respectively. Compounds **5** and **6** also displayed selectivity for PDE5 over PDE6 and PDE11, a solubility of 8.5 and > 45 μg/ml, respectively, and good pharmacokinetics, with improved clearance compared to the southern pyridines (12).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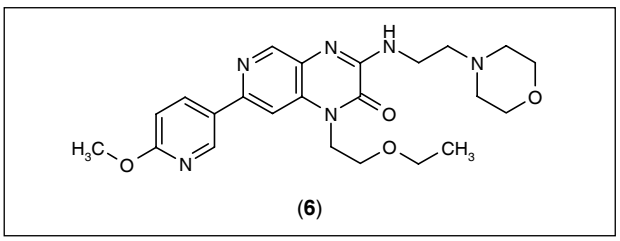
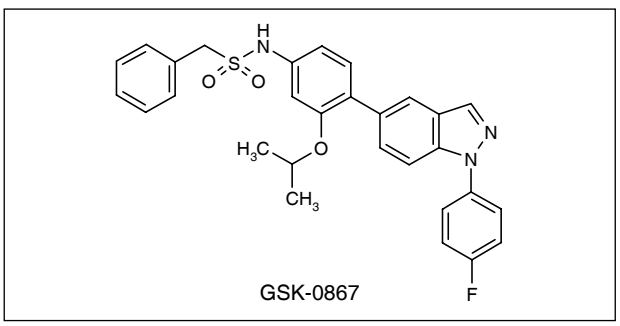
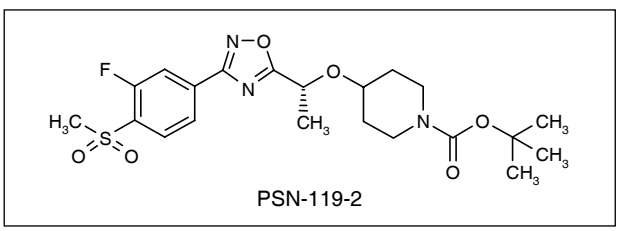
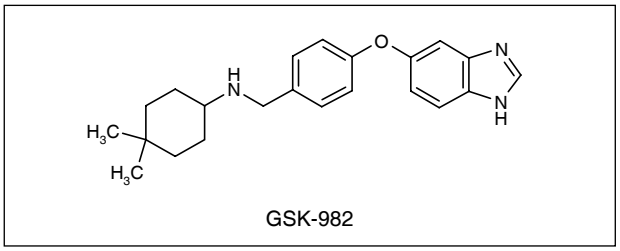

(**6**)


GSK-0867

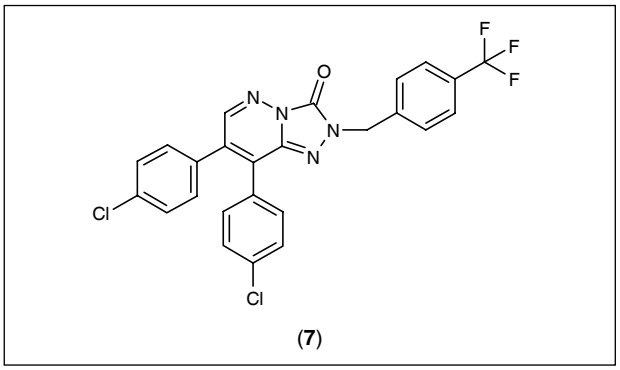

PSN-119-2

Researchers at GlaxoSmithKline have synthesized novel modulators of the glucocorticoid receptor (GR) that hold promise for the treatment of inflammatory disorders, diabetes and depression. Among these compounds, **GSK-0867** was found to bind to the GR with a pIC_{50} of 7.6 and behaved as an agonist in both transactivation assays (pEC_{50} < 5.2), and also in transrepression assays using NF-κB (pIC_{50} = 6.3). It also inhibited IL-6 release from primary human synovial fibroblasts (pIC_{50} = 7.7), but did not affect glycogen synthase production in primary human skeletal muscle cells (13).

Several modifications in the structure of PSN-632408 by researchers at Prosidion have led to the development of a more potent G protein-coupled receptor GPR119 agonist, **PSN-119-2**. In vitro, the compound was shown to stimulate insulin secretion in the HIT-T15 hamster insulinoma cell line (IC_{50} = 18 nM) and GLP-1 release in the GLUTag mouse enteroendocrine cell line (IC_{50} = 8 nM). Oral administration of PSN-119-2 at 10 or 30 mg/kg was associated with a decrease in glucose levels in rats, with-



GSK-982



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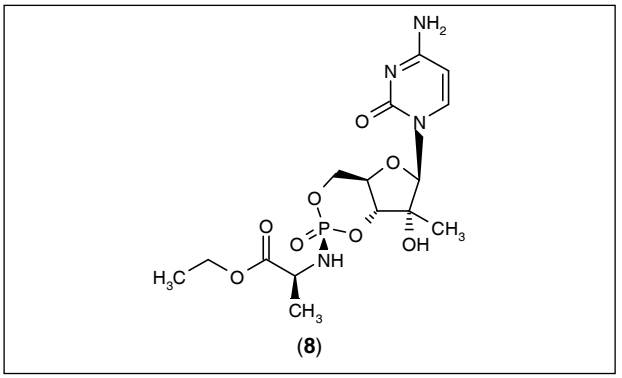

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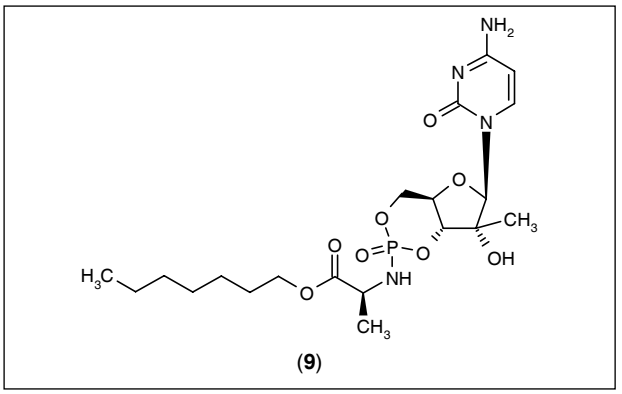


(**9**)

out causing hypoglycemia. Additionally, the compound significantly decreased food intake in a rat acute feeding model. These early results suggest the therapeutic potential of PSN-119-2 in the treatment of type 2 diabetes and obesity (14).

Efforts at GlaxoSmithKline to discover opioid receptor antagonists with the potential to treat obesity yielded **GSK-982**, which demonstrated relevant in vivo activity. A series of 5-phenoxybenzimidazoles were prepared with a wide range of substituted amines. Among these compounds was GSK-982 (μ fpK_i = 8.9, δ fpK_i = 8.4, κ fpK_i = 7.9), with a clearance of 35.2 ml/min/kg, a volume of distribution at steady state of 19.6 l/kg, a $t_{1/2}$ of 6.7 h, a bioavailability of 86% and brain/plasma ratios of 1.1 and 1.3, respectively, at 1.5 and 8 h. GSK-982 at 30 mg/kg reduced nocturnal feeding in lean Long Evans rats on standard chow and significantly and dose-dependently reduced 24-h food intake over 2 days in diet-induced obese Long Evans rats (15).

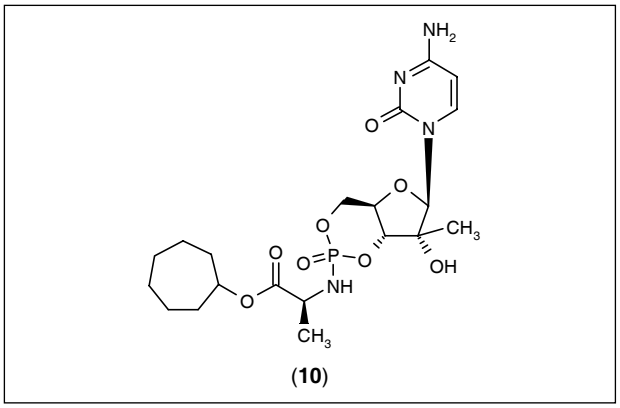
Researchers at Bristol-Myers Squibb have discovered a series of novel bicyclic triazolopyridazine cannabinoid CB_1 receptor antagonists with potential utility in treating obesity. Within this series of compounds, **7** demonstrated potent and selective binding to the CB_1 receptor (K_i = 2 nM) over CB_2 receptors (K_i > 13,000 nM). Pharmacokinetic studies following oral doses of 1, 3 and 10 mg/kg in rats showed good exposure in brain and plasma, as well as some degree of accumulation. In a rat model of weight loss, drug concentrations in plasma, brain and adipose tissue reached 2.6, 3 and 66 μM, respectively, after a dose of 10 mg/kg. A 45% reduction in the amount of cumulative kilocalories consumed was also observed. The compound induced weight loss, which was predominantly due to loss of fat (40%) rather than lean mass. Treatment did not significantly affect respiratory function or blood chemistry (16).

Gastrointestinal drugs (hepatitis C, inflammatory bowel disease, bowel dysfunction, cachexia and Helicobacter pylori infection)

Seeking to improve the efficacy of the hepatitis C virus (HCV) RNA polymerase (NS5B) inhibitor valopicitabine, investigators at Merck & Co. and the Istituto di Ricerche di Biologia Molecolare P. Angeletti developed 2'-methylcytidine prodrugs using a kinase-bypass approach (5'-phosphoramidate) to provide more efficient formation of the active triphosphate. Compounds **8**, **9**, **10**, **11**, **12** and **13** were associated with an AUC for formation of triphosphate in human hepatocytes over 2 h of 60, 115, 75, 158, 55 and 42 μM.h, respectively. In vivo efficacy after s.c. dosing was seen in hamsters administered 1.5 μmol of the compounds in polyethylene glycol (PEG), with triphosphate formation in liver over 6 h of 10.3, 2.6 and 6.8 nmol/g liver for compounds **10**, **11** and **12**, respectively, compared to < 0.2 nmol/g liver for valopicitabine (17).

Researchers from Boehringer Ingelheim have characterized Pim-2 kinase as a novel therapeutic target for inflammatory states, such as inflammatory bowel disease, and developed a new family of Pim-2 inhibitors. SAR studies on the cinnamic acid and homopiperazine fragments of a lead compound led to a first potent Pim-2 kinase inhibitor family of compounds (18).

The growth hormone secretagogue receptor (ghrelin) has been found to play a role in gastrointestinal disorders, including gastroparesis, opioid-induced bowel dysfunction and cancer-related cachexia. SAR analysis at Bristol-Myers Squibb and Elixir Pharmaceuticals led to modifica-



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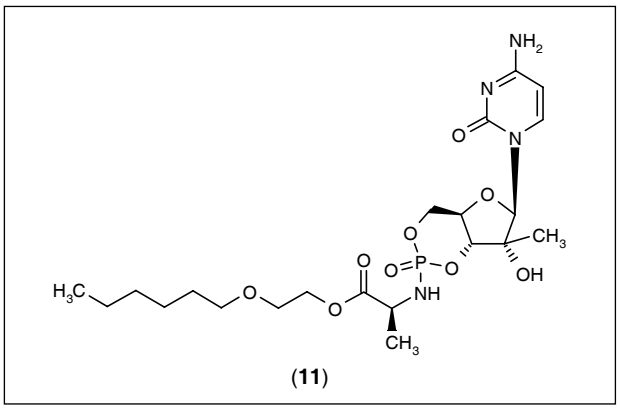

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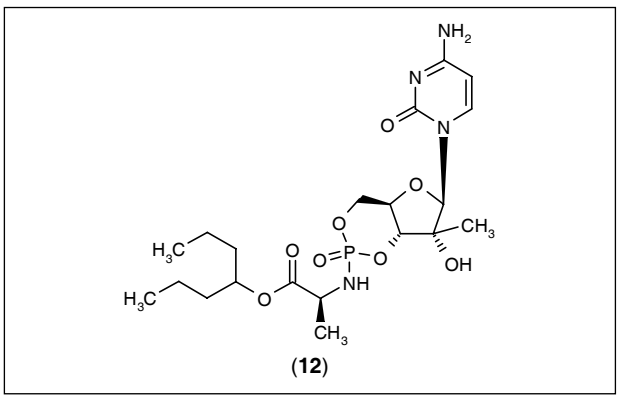

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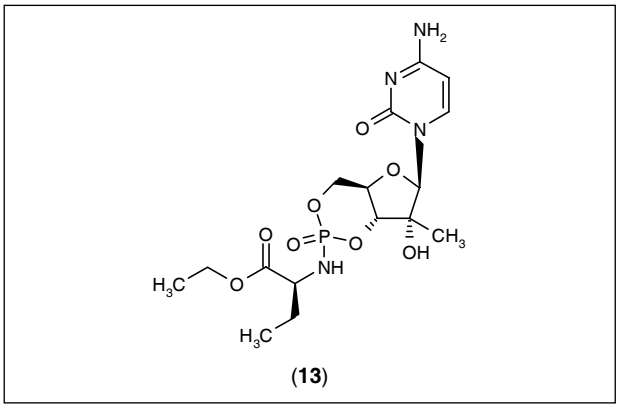

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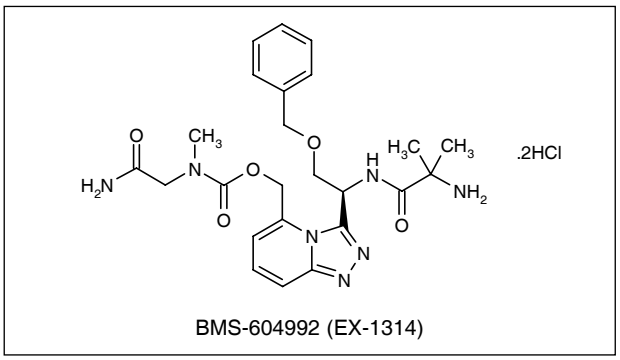
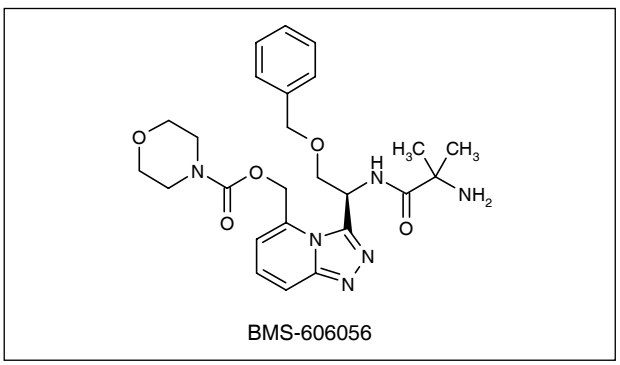


BMS-604992 (EX-1314)

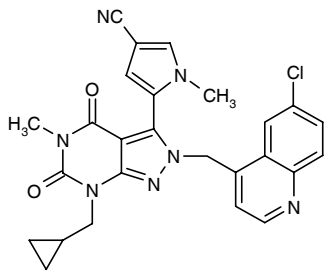


BMS-606056

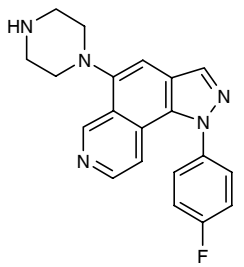
tion of the tetrazole-based BMS-317180, a first-generation ghrelin receptor agonist, resulting in a novel compound, **BMS-604992** (now referred to as EX-1314), with greater potency (K_i = 6 nM, EC_{50} = 0.3 nM) and less cardiac channel activity. BMS-604992 gave ED_{50} values of 2.5 μmol/kg i.v. in dogs and 0.002 μmol/kg i.v. in rats. Pharmacokinetic analysis in rats, cynomolgus monkeys and dogs led to a predicted human dose of 80-130 mg. Minimal ion channel inhibition was observed at 30 μM (19).

Another SAR analysis conducted by researchers at Bristol-Myers Squibb resulted in the identification of a potent triazolopyridine-based ghrelin receptor agonist, **BMS-606056** (K_i = 4 nM, EC_{50} = 0.2 nM). Investigation of cardiovascular liability and pharmacokinetics indicated superiority over other ghrelin receptor agonists. Oral bioavailability was 11%, 67% and 21%, respectively, in rats, dogs and cynomolgus monkeys, with respective $t_{1/2}$ values of 1.2, 1.9 and 2.1 h. BMS-606056 had an excellent profile in in vitro liability and toxicology panels and in other preclinical toxicity assessments, and increased endogenous growth hormone secretion in rats and dogs in vivo (20).

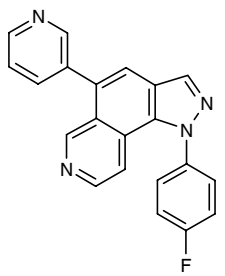
The synthesis and preclinical characteristics of inhibitors of *H. pylori* glutamate racemase (MurI), which may find utility in treating or preventing *H. pylori* infection, were described by AstraZeneca investigators. High-throughput screening of compounds led to the identification of highly specific low-micromolar inhibitors of *H. pylori* MurI. SAR analyses led to compounds with low-nanomolar potency and good antimicrobial activity. Compound **14** demonstrated an IC_{50} of 26 nM against *H. pylori* MurI and an MIC of 0.25 μg/ml. Pharmacokinetic analysis in mice yielded a clearance of 18 ml/min/kg, a $t_{1/2}$ of 1.6 h and a



(**14**)



UR-14102

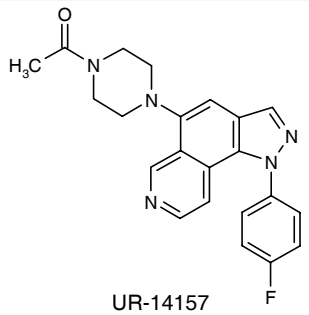


UR-14146

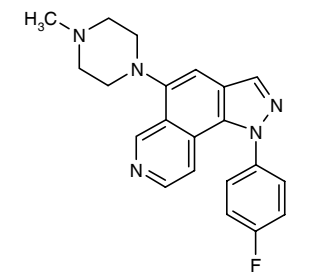
bioavailability of 7.5%. In dogs, these values were 1 mg/min/kg, 20 h and 70%, respectively (21).

Musculoskeletal and connective tissue agents (chronic inflammatory diseases)

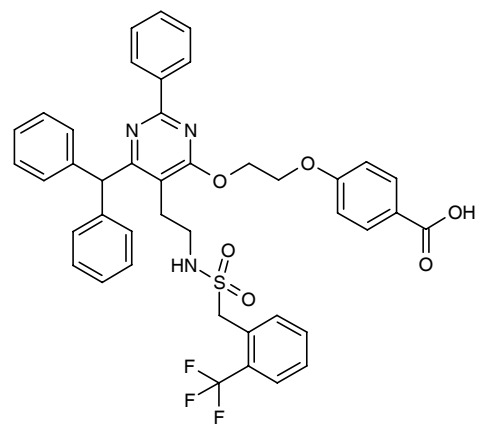
A series of p38 mitogen-activated protein (MAP) kinase inhibitors based on a novel tricyclic pyrazole scaffold have been synthesized at Palau Pharma, yielding several potent and active compounds that may be evaluated for the treatment of chronic inflammatory diseases. Second-generation inhibitors were generated by modification of the central ring of the tricyclic pyrazole scaffold through selective bromination and subsequent derivatization. The second-generation compounds were generally very potent in vitro (radiometric and cellular assays) and in vivo. Inhibition of lipopolysaccharide (LPS)-induced TNF-α production in BALB/c mice at 10 mg/kg p.o. reached 75.0%, 75.0%, 63.6% and 67.9%, respectively, with **UR-14102, UR-14146, UR-14157** and **UR-14159**.



UR-14157



UR-14159



(**15**)

These compounds also demonstrated good kinase selectivity, high solubility and low potential for CYP3A4 inhibition (22).

Selective cytosolic phospholipase $A_2\alpha$ ($cPLA_2\alpha$) inhibition may be a useful strategy for the treatment of inflammatory diseases, as it blocks the formation of arachidonic acid and downstream inflammatory mediators. Researchers at Wyeth have developed a compound (**15**) that blocked the in vitro formation of thromboxane B_2 (TxB_2), leukotriene B_4 (LTB_4), prostaglandin E_2 (PGE_2) and prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) with respective IC_{50} values of 0.11, 0.05, 0.12 and 0.12 μM. In vivo efficacy was demonstrated in acute inflammatory models in rats, such as carrageenan-induced paw edema and antigen-induced pulmonary inflammation, at i.p. doses of 10 and 25 mg/kg (23).

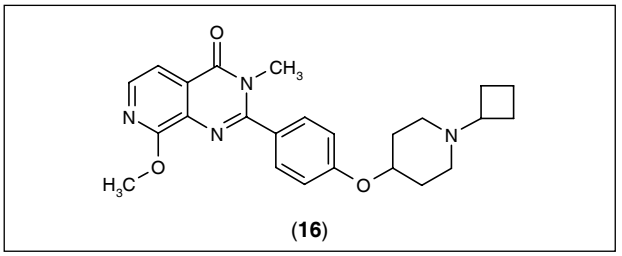
Neurological drugs (cognitive behavior, Alzheimer's disease, Parkinson's disease)

The histamine H_3 receptor is a presynaptic autoreceptor found mainly in the central nervous system (CNS) that modulates the release of several neurotransmitters, such as norepinephrine, dopamine, acetylcholine, serotonin and GABA. In previous experiments in animals, H_3 antagonists/inverse agonists have been shown to enhance wakefulness, improve attentive and cognitive behaviors and reduce feeding and body weight. Banyu Pharmaceuticals and Merck & Co. have recently synthesized a quinazolinone class of H_3 antagonists/inverse agonists, structural optimization of which led to the identification of compound **16**. In in vivo studies in rats **16** demonstrated good brain exposure and appropriate pharmacokinetics. In the histamine release assay, the minimum effective dose (MED) was 3 mg/kg p.o. (24).

Seoul National University investigators have developed a series of benzofuran analogues that inhibit β-amyloid (Aβ) aggregation, an effect which may block the formation of the amyloid plaques implicated in the pathophysiology of Alzheimer's disease. The analogues inhibited Aβ aggregation with IC_{50} values of < 5 μM. One compound, **DWK-1339**, demonstrated superiority over the others in in vivo studies, including an acute Alzheimer's disease model, and in in vitro tests, and was selected for further development. Evaluation of DWK-1339 tissue distribution yielded K_d (ml/g tissue) values of 23.91, 10.38, 18.23, 8.99 and 4.87 for liver, kidney, lung, heart and brain, respectively (25).

The α7 neuronal nicotinic acetylcholine receptors (nAChRs) have been implicated in cognitive processes, and receptor agonists may be useful for treating Alzheimer's disease and schizophrenia. Modification of agents acting on α4β2 nAChRs produced compounds with activity at α7 nAChRs, and optimization led to **A-859261**, an α7 nAChR agonist with high affinity and selectivity. Binding and functional activity studies revealed a K_i of 0.5 nM and an EC_{50} of 0.5 μM for A-859261. Pharmacokinetic assessments in rats, dogs and monkeys showed an excellent profile and the drug was found to enter the brain after i.p. administration to mice, with peak levels achieved in brain 15-45 min after a dose of 5 μmol/kg i.p. A-859261 was also active in in vivo models of memory consolidation (inhibitory avoidance), recognition memory (social recognition) and working memory (delayed match-to-sample) in mice, rats and monkeys, respectively (26).

The adenosine A_{2A} receptor antagonist **BIIB-014** (V-2006) is being developed by Biogen Idec and Vernalis as a treatment for Parkinson's disease and entered phase II trials in 2007. Previous data encouraging continued development of the agent include potent (K_i = 1.3 nM) antagonist activity at the adenosine A_{2A} receptor and selectivity (> 50-fold) for this receptor over other subtypes, as well as activity in the MPTP-induced model of parkinsonism in marmosets. Pharmacokinetic studies in animals revealed oral bioavailability, with metabolism by multiple CYP isoforms but negligible CYP inhibition. Phase I data from healthy young males showed rapid absorption (2-4 h) and a half-life of 11-26 h. Pharmacokinetics were altered in elderly subjects but these changes did not appear to be sufficient to warrant dose reduction (27).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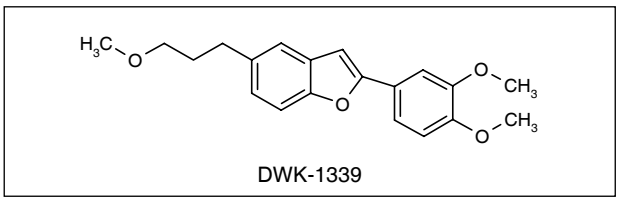
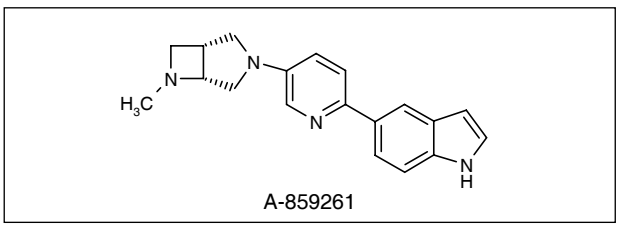
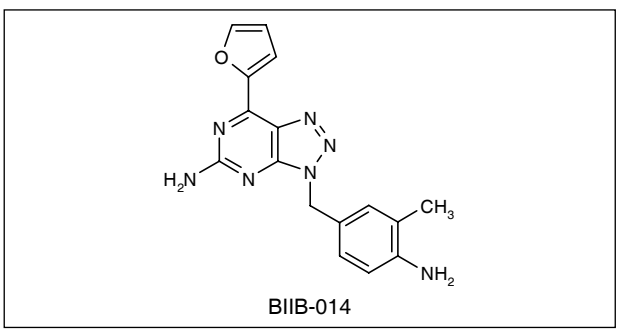
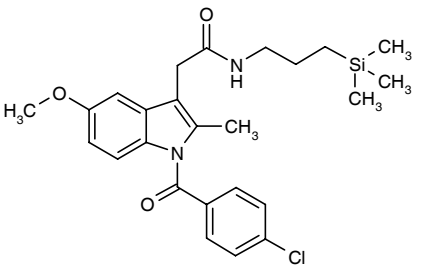

DWK-1339


A-859261

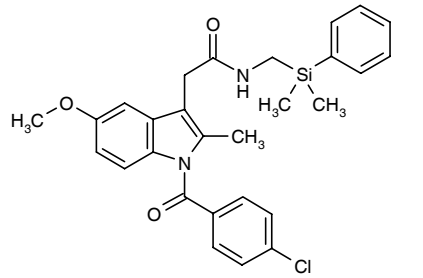

BIIB-014

Oncolytic drugs

The benefit of replacing carbon with silicon (organosilicon chemistry) in anticancer molecules has been explored by a team of investigators from the University of Wisconsin-Madison, SAFC Pharma and Silamed, which created a library of sila-indomethacin amide derivatives. When tested against human recombinant cyclooxygenase COX-1 and -2, the compounds proved to be selective for COX-2. Growth-inhibitory activity against MIA PaCa-2 human pancreatic carcinoma cells was seen at low micromolar concentrations. Two of these compounds, **RND-100** and **17**, had IC_{50} values of < 6.0 μM, while that for unmodified indomethacin was > 100 μM. The com-



RND-100

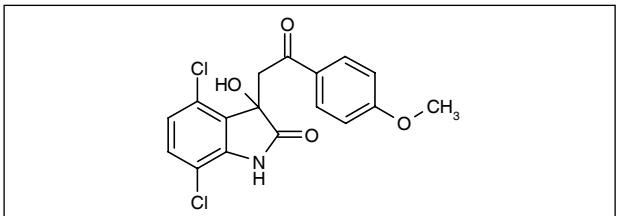


(**17**)

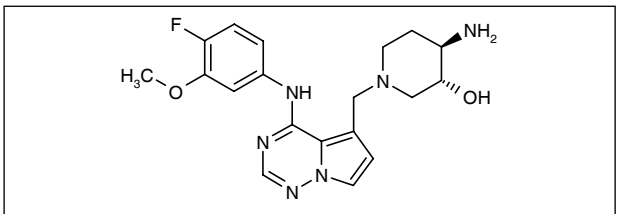
pounds were safe and well tolerated in vivo but were limited by solubility. The generation of a new series of polar sila amines is under way, and optimization of formulations of RND-100 and **17** may also be undertaken (28).

Recent studies have identified the EWS-FLI1 protein as a critical target in the Ewing's sarcoma family of tumors (ESFT). Based on this finding, Georgetown University researchers have synthesized a series of small-molecule EWS-FLI1 inhibitors that disrupt RNA helicase A (RHA) protein binding to EWS-FLI1. **YK-4-279** was chosen as the lead compound and was found to inhibit the growth of the ESFT cell lines TC32, ES925 and GUES1 with IC_{50} values of 0.9, 1 and 8 μM, respectively, and to induce apoptosis in TC32, ES925, TC71 and A4573 cells, whereas it was not active against nonmalignant cell lines (human foreskin keratinocytes or embryonic kidney HEK 293 cells) or other malignant cell lines (human endometrial cancer or pancreatic COLO 357 carcinoma cells). In vivo assays showed that YK-4-279 at 1.5 or 3 mg/dose i.p. decreased tumor volume and at the highest dose it improved survival of mice bearing ESFT xenografts. The interaction between RHA and EWS-FLI1 paves the way for developing novel therapeutic agents such as YK-4-279 for the treatment of ESFT (29).

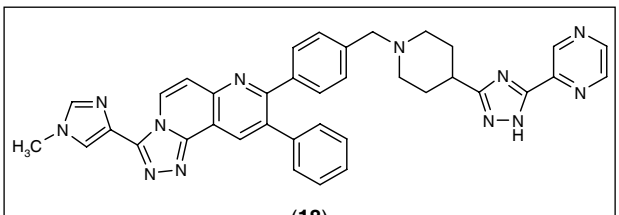
Seeking to target both EGFR (ErbB-1) and HER2 (erbB-2) receptor tyrosine kinases for oncolytic treatments, Bristol-Myers Squibb developed a series of pyrrolotriazine-based compounds. Optimization of a first-generation pan-HER kinase inhibitor led to the identification of **BMS-690858** (HER2 IC_{50} = 0.023 μM, EGFR IC_{50} = 0.017 μM), which was selected for in vivo evaluation. In a HER2-dependent N87 gastric tumor xenograft model, BMS-690858 reduced tumor growth, an effect that was also seen in the EGFR-dependent A549 lung tumor



YK-4-279



BMS-690858

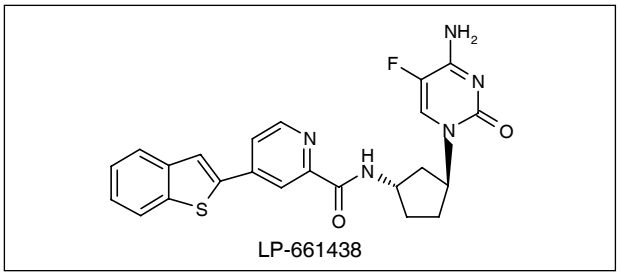


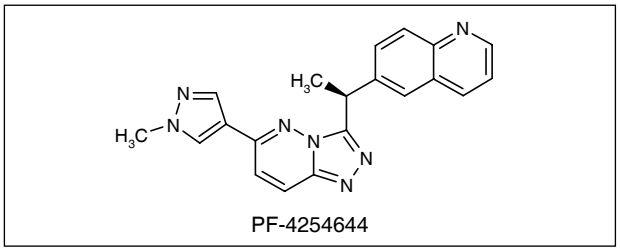
(**18**)

model. BMS-690858 was associated with excellent aqueous solubility and pharmacokinetics suitable for once- or twice-daily dosing (30).

Beginning with a compound that binds an allosteric pleckstrin homology domain-dependent site, Merck & Co. investigators identified other AKT inhibitors with the goal of developing a small molecule for cancer treatment. Optimization of the lead compound led to a dual AKT1/2 inhibitor that was evaluated in vivo, and further refinement with the goal of identifying a dual AKT1/2 inhibitor suitable for i.v. administration led to the identification of compound **18**, with IC_{50} values for AKT1, AKT2 and AKT3 of 0.5, 4.7 and 490 nM, respectively. EC_{50} values for inhibition of AKT phosphorylation were 2.9, 13 and > 5000 nM, respectively, for pAKT1, pAKT2 and pAKT3. Pharmacokinetic evaluation in dogs, rats and monkeys revealed characteristics appropriate for i.v. delivery, a low potential for drug–drug interactions and extensive binding to plasma proteins. In mice bearing ovarian A2780 tumors, AKT1/2 inhibition was seen in tumor tissues, and in another model a synergistic effect on ovarian xenograft growth was observed when the compound was combined with docetaxel (31).

Inhibition of deoxycytidine kinase may be useful for treating multiple diseases, as revealed by studies in knockout mice. Acting on this knowledge, investigators at Lexicon Pharmaceuticals sought agents capable of blocking the uptake of deoxycytidine by T lymphocytes in vitro and in vivo. As part of a de novo inhibitor design effort, cytidine-like analogues with the ribose ring replaced by a substituted cyclopentane were created. SAR analyses


LP-661438

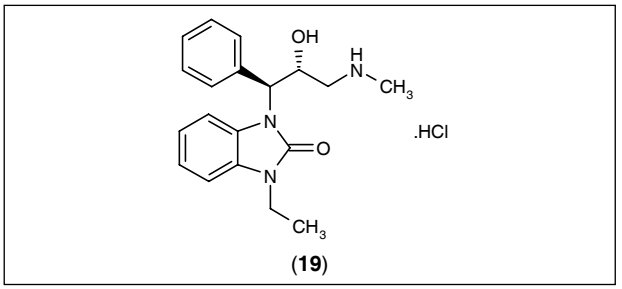

PF-4254644

showed that *m*-biphenyl amides had good potency and pharmacokinetics in mice. When the co-crystal structure of deoxycytidine kinase and a molecule from a separate chemical series revealed a new hydrophobic binding pocket formed by rearrangement of four amino acid side-chains, the design of a hybrid molecule containing select fragments from both chemical series appeared possible. One such hybrid molecule, **LP-661438**, proved to be a potent deoxycytidine kinase inhibitor (IC_{50} = 1.7 nM, EC_{50} = 17 nM) and inhibited the uptake of deoxycytidine by T lymphocytes in vitro and in vivo (32).

To utilize c-Met/HGF signaling as a target in cancer treatment and pathogenic studies, Pfizer investigators identified a class of potent and selective c-Met inhibitors, but these compounds proved to be susceptible to metabolism. Refinement of these compounds via structure-based design and medicinal chemistry lead optimization eventually led to **PF-4254644**, which demonstrated a c-Met K_i value of 10 nM and an IC_{50} of 6 nM for c-Met in A549 cells. Notable selectivity over 150 kinases was seen, along with good pharmacokinetics in rats and dogs and no CYP3A4 induction. PF-4254644 also inhibited human gastric carcinoma tumor growth in nude mice (33).

Psychopharmacological drugs (attention deficit hyperactivity disorder, depression, narcolepsy, schizophrenia)

Selective norepinephrine reuptake inhibitors (SNRIs) are marketed for the treatment of attention deficit hyperactivity disorder and major depressive disorder, and novel SNRIs are being sought. Wyeth has now reported the synthesis of a new class of 3-(3-amino-2-hydroxy-1-phenylpropyl)-1,3-dihydro-2*H*-benzimidazol-2-ones that were evaluated for specificity using the human norepinephrine transporter (hNET) and for selectivity using human serotonin (hSERT) and dopamine (hDAT) transporters. Compounds with potency in the hNET reuptake assay (IC_{50} = 3-60 nM) were identified, as were compounds with selectivity (> 100-fold) for hNET compared to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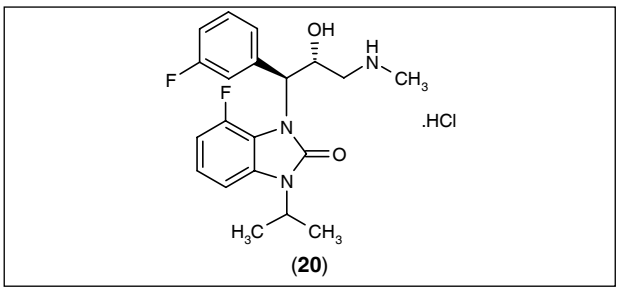
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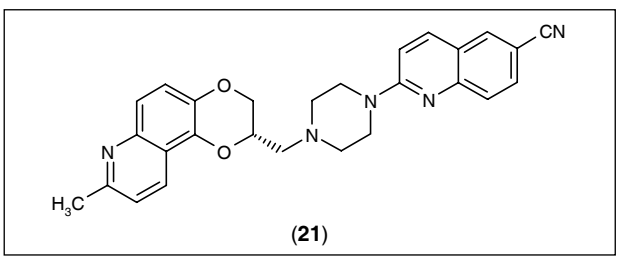

(**21**)

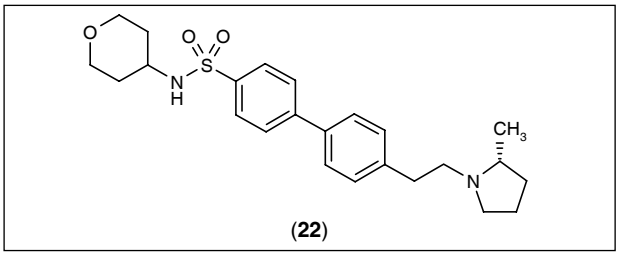
hSERT and hDAT. Two of the compounds, **19** and **20**, also demonstrated efficacy in ameliorating physiological dysfunction after oral administration in a rat model. For compound **19**, the hNET IC_{50} was 28 nM, with little or no inhibition of hSERT and hDAT at concentrations up to 1 and 10 μM, respectively. Compound **20** inhibited hNET with an IC_{50} of 7 nM, with 19% and 27% inhibition, respectively, of hSERT and hDAT. Both compounds displayed good oral bioavailability in rats (34).

Dual selective serotonin reuptake inhibitors (SSRIs)/5-HT_{1A} receptor antagonists may provide the antidepressant effect of SSRIs without the delay in efficacy thought to be due to stimulation of inhibitory 5-HT_{1A} autoreceptors. Wyeth has prepared analogues of one such molecule, including a series of novel 2-(piperazin-1-yl)quinolines. In in vitro binding and functional assays, one of these compounds, **21**, demonstrated a K_i of 13.8 nM for rat SERT transporter affinity, a K_i of 3.7 nM for human 5-HT_{1A} receptor affinity and an IC_{50} of 102 nM for 5-HT_{1A} receptor functional activity. In rats, administration of **21** rapidly and dose-dependently increased levels of 5-HT in the frontal cortex. In a rat model of schedule-induced polydipsia, the compound significantly decreased adjunctive drinking behavior, suggesting anti-obsessive–compulsive disorder-like activity. Pharmacokinetic characterization in rats yielded moderate clearance, volume of distribution and $t_{1/2}$ values, and acceptable oral bioavailability (35).

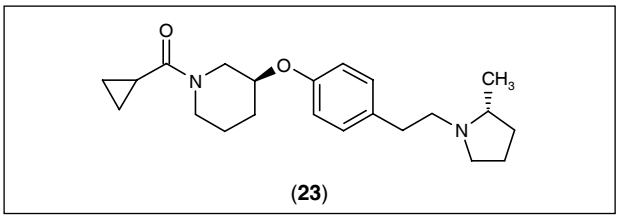
With the natural product conessine as the starting point, Arena Pharmaceuticals' investigators have produced several series of H_3 receptor antagonists/inverse agonists in the search for compounds that may be useful for treating narcolepsy or excessive daytime sleepiness. Compound **22** was characterized as follows: rat H_3 K_i = 2 nM, human H_3 K_i = 7 nM, > 500-fold selectivity for H_3 receptors, a $t_{1/2}$ in rats of 2.5 h, a t_{max} of 0.8 h and an oral bioavailability of 62%. At a dose of 3 mg/kg p.o., **22** demonstrated in vivo activity, with a wake effect of approximately 5 h. The profile of compound **23** was as follows: rat H_3 K_i = 1 nM, human H_3 K_i = 15 nM, > 500-fold selectivity for H_3 receptors, a $t_{1/2}$ in rats of 3.3 h, a t_{max} of 0.5 h and an oral bioavailability of 37%. At a dose of 1 mg/kg p.o., **23** demonstrated in vivo activity in a sleep study, with a wake effect of approximately 150 min, which was increased 50% compared to vehicle. A third compound, **24**, had the following characteristics: rat H_3 K_i = 1 nM, human H_3 K_i = 2 nM, > 1,000-fold selectivity for H_3 receptors, a $t_{1/2}$ in rats of 2.5 h, a t_{max} of 0.3 h and an oral bioavailability of 66%. In vivo activity was also seen with **24** in a rat dipsogenia model, inhibiting H_3 agonist-induced drinking in a dose-dependent manner. Efforts are under way to optimize compounds **23** and **24** (36).

Novel glycine transporter (GlyT1) inhibitors have been developed at Merck & Co. representing a promising approach for the treatment of schizophrenia. **DCCCyB** inhibited GlyT1 receptor in vitro (IC_{50} = 29 nM) and showed a good safety profile in dogs, with no cardiovascular effects at plasma levels up to 10 μM. Following single-dose administration in humans at 25 and 120 mg, DCCCyB showed dose-dependent intersubject variability in drug exposure and C_{max}. Additional PET studies established dose-dependent GlyT1 receptor occupancy with values between 41% and 80% at 120 mg (37).

Inhibition of cyclic nucleotide phosphodiesterase PDE10A may be a useful strategy for the treatment of schizophrenia, according to Pfizer researchers. The synthesis of a series of pyrazole derivatives led to the identification of **PF-2545920**, a compound that behaved as an efficient PDE10A ligand (K_i = 0.18 nM) and showed selectivity (> 1,000) over other PDE enzymes. PF-2545920 exhibited good brain penetration (brain/plasma ratio = 0.9). In vivo, PF-2545920 inhibited conditioned avoidance responding (CAR) and antagonized phencyclidine- and amphetamine-induced hyperactivity in rats (ED_{50} = 0.7, 1 and 4.4 mg/kg s.c., respectively). Following a single dose in humans, the compound was stable, with high oral bioavailability, a half-life of 14 h and a clearance of 4 ml/min/kg (38). A phase II trial is currently being conducted to evaluate the safety and efficacy of PF-254920 in reducing symptoms associated with schizophrenia compared with placebo (39), and a phase I trial is investigating the safety and tolerability of multiple doses of PF-2535920 in subjects with stable schizophrenia (40).



(**22**)



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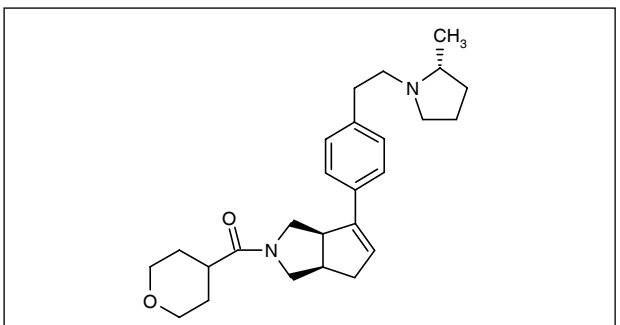
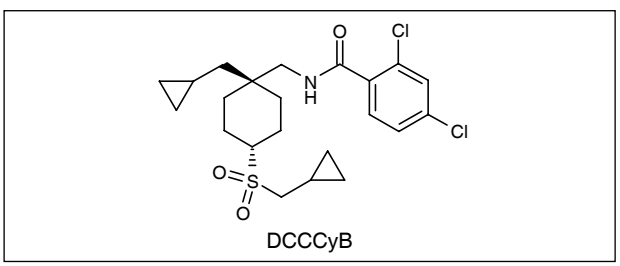
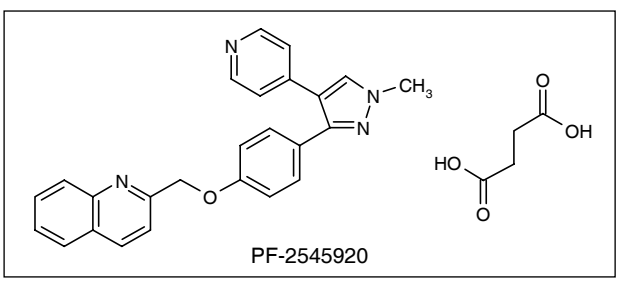


(**24**)



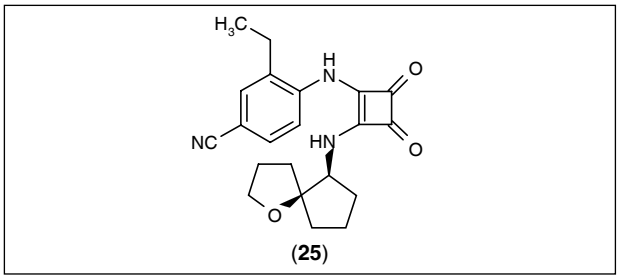
DCCCyB

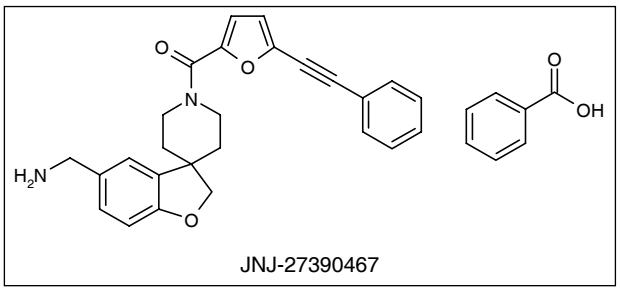


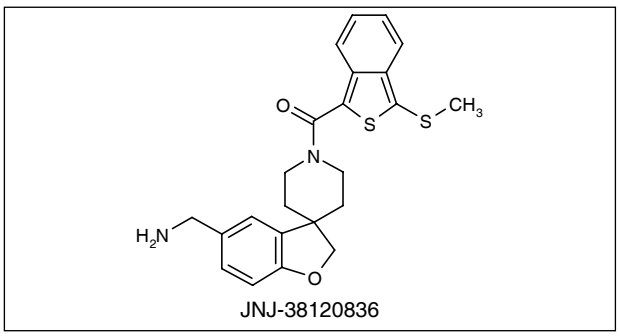
PF-2545920

Urologic drugs (overactive bladder)

Novel spirofuran potassium channel openers (KCOs) were identified by a team at Johnson & Johnson as part of a structure-based design program seeking treatments for overactive bladder. Compounds were tested for KCO activity with a cellular assay using a TE671 human medullablastoma cell line with a fluorescence imaging agent to measure changes in membrane potential. The most potent compound, **25**, was evaluated in a conscious rat model of overactive bladder, with animals surgically processed to develop bladder hypertrophy and instability


(**25**)


JNJ-27390467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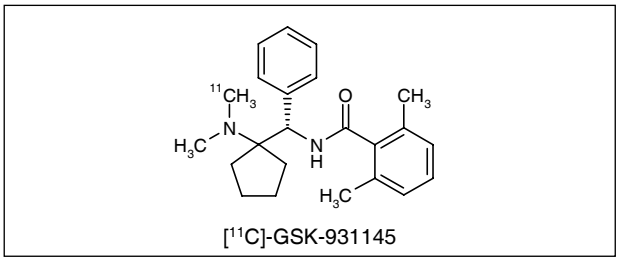
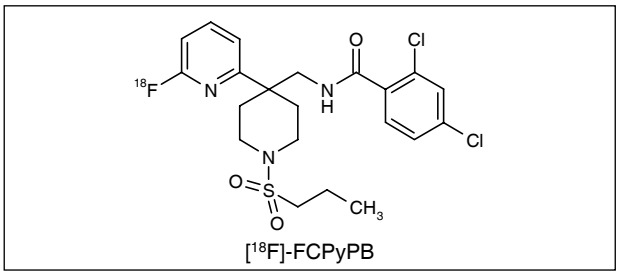
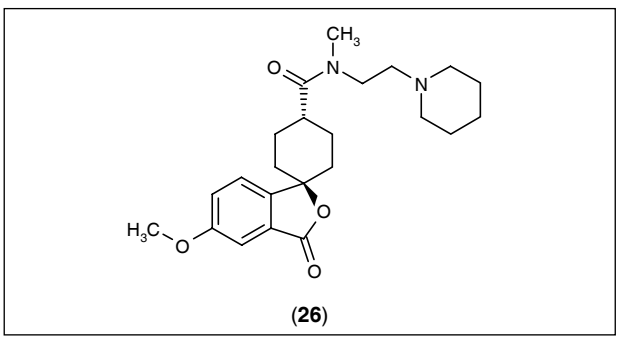

[^{11}C]-GSK-931145


[^{18}F]-FCPyPB


(**26**)

as a result of partial outlet obstruction. At an oral dose of 10 mg/kg, this compound was effective in reducing bladder hypersensitivity and urination frequency (41).

Respiratory drugs (asthma)

Johnson & Johnson investigators have described the development of spirocyclic piperidine amide derivatives, with **JNJ-27390467** identified as a potent and selective inhibitor of human mast cell tryptase. It is hoped that such agents can be used to treat inflammatory disorders. Pharmacokinetic data on JNJ-27390467 were encouraging and the agent was effective in animal models of asthma. SAR analysis of the *N*-acyl portion of JNJ-27390467 led to the identification of two other potent tryptase inhibitors, including **JNJ-38120836**, which had an IC_{50} < 10 nM, a K_i of 5.4 and excellent selectivity versus trypsin (42).

Novel diagnostic agents

Researchers at GlaxoSmithKline have attempted to identify glycine transporter GlyT1 inhibitors for the treatment of schizophrenia, focusing on non-glycine-based approaches after early glycine-based inhibitors displayed weak activity. This research is based on the idea that GlyT1 is involved in the regulation of synaptic glycine levels and NMDA receptors are co-localized with GlyT1; enhancing glycine levels at the NMDA site may improve the impaired NMDA function seen in schizophrenia. This led to the identification of GSK-931145, which demonstrated potency in in vivo models, inhibition of ex vivo uptake of glycine, anticonvulsant activity and a consistent brain free fraction across species. The compound was thus labeled to serve as a novel PET ligand for imaging of GlyT1 and demonstrated heterogeneous distribution in porcine brain according to GlyT1 distribution. **[^{11}C]-GSK-931145** may be useful for further investigating GlyT1 in schizophrenia and for developing GlyT1 inhibitors (43).

Futhermore, Merck & Co. identified another potent selective GlyT1 inhibitor as a potential PET tracer for clinical imaging of GlyT-1. **[^{18}F]-FCPyPB** bound with high affinity to GlyT1 (IC_{50} = 2 nM). Following injection into rhesus monkeys (2 mg/kg), [^{18}F]-FCPyPB accumulated in the cerebellum (K_d = 0.39 nM) (44).

Banyu Pharmaceuticals and Merck & Co. have recently synthesized a quinazolinone class of H_3 antagonists/inverse agonists that have demonstrated potential activity in neurological disorders in early preclinical assays. Further compound searching led to the identification of a spiro-isobenzofuranone class of H_3 antagonists/inverse agonists, exemplified by compound **26**, which was found to have potential utility as a clinical PET tracer for imaging human brain H_3 receptors (45).

PEG-coated nanoparticles as a novel transmucosal delivery technology

A team from Johns Hopkins University has found a way of delivering nanoparticles through human mucus, which may allow mucosal site drug delivery for a variety of indications. The team studied the quantitative transport rates of hundreds of nanoparticles of various sizes and surface chemistries in human cervicovaginal mucus. They found that large nanoparticles of 500 and 200 nm diffused through mucus nearly as fast as they moved through water when coated with low-molecular-weight polyethylene glycol (PEG). A high-molecular-weight PEG coating made nanoparticles more adhesive to mucus than they were without coating, and PEG densities were found to be important with reduced particle sizes. It was found that the spacings within the human mucus mesh were much larger than previously thought, and that fluid within the spacings of human mucus has a viscosity over 1,000 times lower than the bulk viscosity. Studies of therapy with PEG-coated nanoparticles in mouse lung and cervical cancer models are under way (46, 47).

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