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MEETING REPORT

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SUMMARY

The 243rd American Chemical Society (ACS) National Meeting and Exposition took place in San Diego, California, attracting more than 18,000 delegates from the pharmaceutical and biotechnology industries, as well as academic experts. There were over 11,700 oral and poster presentations, covering a diverse range of topics from medicinal chemistry and synthetic methods, to health and environmental chemistry. This report summarizes research highlights on novel treatments for Alzheimer's disease, pain, metabolic disorders and infections.

Key words: Alzheimer's disease – Pain – Metabolic disorders – Infections – Cancer

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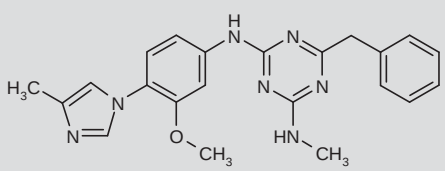
NOVEL THERAPIES FOR THE POTENTIAL TREATMENT OF ALZHEIMER'S DISEASE

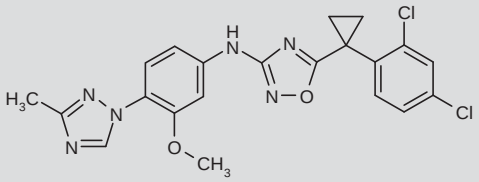
The discovery and development of novel bicyclic acylguanidines as orally active beta-secretase 1 inhibitors for the potential treatment of Alzheimer's disease (AD) was discussed by Johnny (Zhaoning) Zhu of Merck & Co. It was predicted that by 2015, the number of patients with AD will quadruple, emphasizing the need for more effective treatments. Early beta-secretase inhibitors possessed a hydroxylamine moiety, and while they were effective, they had poor blood–brain barrier (BBB) penetration. This hydroxylamine group was used as a platform for the design of BBB-penetrating compounds with an amidine structure bearing a weakly basic group. A fragment-based screen identified an initial beta-secretase 1 inhibitor that was reasonably potent (K_i = 57 nM) and displayed moderate acute cortex efficacy. Conformational analysis revealed that a conformationally restricted structure had higher potency at beta-secretase, giving a compound with a K_i value of 200 nM at beta-secretase 1. In silico studies found that the presence of water molecules prevented a more potent interaction with the enzyme. This led to a series of optimization strategies to give a lead compound that contained a fused pyrrolidine structure. This compound had the ability to disperse the water molecules in the active site, resulting in a K_i value of 2 nM and a cellular potency of 19 nM. Substitution of the pyrrolidine nitrogen identified compound BACEi-8 (presumed to be SCH-900478), which demonstrated inhibition of beta-secretase 1 and 2 (K_i = 5 and 2.7 nM, respectively). SCH-900478 showed good pharmacokinetics in rat, dog and monkey models in vivo, with AUC values of 0.3, 0.4 and 0.5 μM.h, respectively, oral C_{max} values of 0.1, 0.2 and 0.5 nM, respectively, and a $t_{1/2}$ of 1.1 hours in rats. SCH-900478 showed efficacy in a rat model, with a cortex ED_{50} of 41 mg/kg and a cerebrospinal fluid (CSF) plasma ED_{50} of 190 ng/mL. In cynomolgus monkeys, SCH-900478 (10 mg/kg p.o. at 4 hours) reduced CSF and cortex β-amyloid(40) ($A\beta_{40}$) levels by 35% and 58%, respectively. It was also shown in a 14-day monkey efficacy model that the compound reduced CSF and cortex $A\beta_{40}$ by over 90% compared to vehicle at doses over 100 mg/kg/day, and CSF and cortex soluble amyloid beta A4 protein (sAPPβ) by over 70% compared to vehicle at these doses.

Bristol-Myers Squibb's Lawrence Marcin discussed the company's program of bicyclic triazoles as gamma-secretase modulators for the potential treatment of AD. A high-throughput screening (HTS) identified aniline-derived heterocycles as gamma-secretase inhibitors with $A\beta_{42}$ IC_{50} values of < 1 μM, and one compound having $A\beta_{42}$ and $A\beta_{40}$ IC_{50} values of 180 nM and 3 μM, respectively. However, the presence of the aniline group was problematic, as it is known to cause mutagenesis. The hit compounds were optimized to identify **BMS-802299**, which had an $A\beta_{42}$ IC_{50} of 29 nM. BMS-802299 (30 and 100 mg/kg p.o. or s.c.) was evaluated in vivo in a mouse model and was found to reduce brain $A\beta_{42}$ levels in a dose-dependent manner in both dose groups, indicating that the route of administration did not affect the activity. The compound was also evaluated for ADME properties and found to be AMES negative; however, it had respective IC_{50} values of 0.69 and < 1 μM for cytochrome P450 3A4 and hERG inhibition. In order to overcome these ADME issues, further optimization revealed an aminotriazole compound to be the most effective. Modification of the triazole moiety to form an oxadiazole structure resulted in the most potent lead compound ($A\beta_{42}$ IC_{50} = 36 nM); it was determined that the oxadiazole core was responsible for the combination of good potency in a transgenic mouse model and brain penetration. **BMS-831929** (10, 30 and 100 mg/kg p.o.) was found to reduce $A\beta_{42}$ levels in transgenic mice and displayed an IC_{50} of 33 nM for $A\beta_{42}$. It had a high drug exposure level (EC_{50} = 2.5 μM), which resulted in its robust dose–response. This compound also had pharmacokinetic problems, as it was highly protein-bound and showed potent cytochrome P450 and hERG inhibition. Reverting back to evaluating the triazole core, **BMS-869780** was identified, which had an IC_{50} of 4.1 nM at $A\beta_{40}$ and demonstrated robust brain $A\beta_{42}$ reduction. It was also found to have an improved reduction in $A\beta_{42}$ levels compared with the known gamma-secretase inhibitor E-2012, and it was twofold more potent in wild-type mice compared with transgenic mice. ADME studies showed an oral bioavailability of 51%, 13% and 16%, respectively, in rats, dogs and monkeys, which revealed species-dependent oral bioavailability; the in vitro human $t_{1/2}$ was 51 minutes and the rat $t_{1/2}$ was 2.5 hours. However, further toxicity studies revealed the compound to be hepatotoxic, which led to the development of second-generation analogues of BMS-869780 that have addressed hepatotoxicity issues.

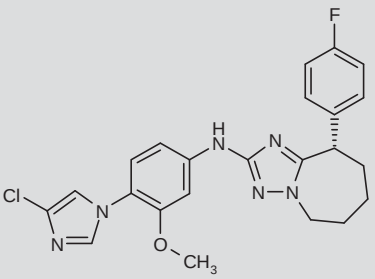
The development of novel prostanoid EP_2 receptor antagonists for the potential treatment of AD was discussed by Brian Fox (Amgen).



BMS-802299



BMS-831929



BMS-869780

HTS identified a compound with moderate affinity and antagonism for the EP_2 receptor in a number of species, including the human EP_2 receptor (IC_{50} = 48 nM). However, it was not selective over EP_3 and EP_4 receptors, and had poor microsomal stability and potent cytochrome P450 inhibition. An optimization strategy replaced the metabolically unstable methoxy group and altered the core structure to minimize oxidative metabolism. The pyridine moiety was replaced to reduce basicity and prevent cytochrome P450 inhibition. Replacement of the methoxy group with a chloro substituent and the presence of a methyl group alpha to the amine group resulted in enhanced selectivity, stability and affinity for the EP_2 receptor. Substituting the pyridine for a pyrimidine or pyridone group dramatically improved the selectivity of the compound and resolved the cytochrome P450 inhibition issues. This resulted in a lead compound that had moderate pharmacokinetic properties in mice, with clearance, half-life and volume of distribution values of 0.93 L/h/kg, 3.4 hours and 2.49 L/kg, respectively, for i.v. administration (1.0 mg/kg), and a C_{max} and bioavailability of 1.2 μM and 31%, respectively, for oral administration (5.0 mg/kg). The compound also demonstrated good CNS permeability, with brain/plasma ratios of 1 and 0.8, respectively, in mice and rats. The compound significantly increased Aβ phagocytosis and had a human EP_2 receptor IC_{50} of 8 nM.

TARGETING KCNQ CHANNELS FOR THE TREATMENT OF PAIN

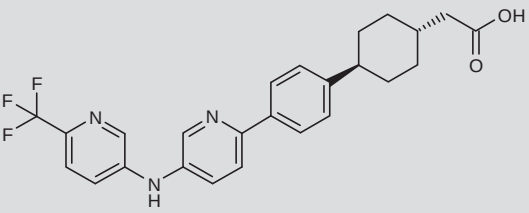
Chronic pain has a prevalence of approximately 100 million in the U.S., resulting in a cost of approximately USD 1 billion per year for

care and lost productivity. Brian Brown of Abbott Laboratories discussed the development of novel voltage-gated potassium channel KCNQ stimulators for the potential treatment of chronic pain. It was hypothesized that KCNQ2/3 selectivity may be able to improve the therapeutic index of the known KCNQ channel openers flupirtine and retigabine (Potiga™, Trobalt™). HTS identified a compound that demonstrated proof of concept by showing selectivity among KCNQ subtypes, with separation of effects between pain and side effect assays. The compound had an EC_{50} of 0.38 µM for KCNQ2/3 and 0.29 µM for KCNQ2 compared with other subtypes. It displayed good activity in a neuropathic pain assay, but was not suitable for further development due to poor drug-like properties. Further optimization led to the identification of 2-aminophthalazinone compounds, which showed selectivity for KCNQ2 subtypes and had improved pharmacokinetics. One compound showed an EC_{50} of 0.07 µM for KCNQ2/3 and acceptable pharmacokinetics in rats. The $t_{1/2}$ for i.v. administration was 0.5 hours, and the C_{max} and bioavailability for oral administration were 283 ng/mL and 21%, respectively. The compound had limited CNS exposure, which reduced side effect concerns, but still provided analgesic activity. In vivo, the compound displayed no adverse coordination effects in the edge test compared with retigabine. A second compound displayed an EC_{50} of 0.56 µM for KCNQ2/3. It also had good oral pharmacokinetics in rats, with a $t_{1/2}$, C_{max} and bioavailability of 3 hours, 1250 ng/mL and 65%, respectively. Although the compound had weaker KCNQ2/3 activity, similar in vivo efficacy results were observed for the two compounds due to the improved pharmacokinetic profile of the drug. This compound had a clean CEREP profile.

DGAT1 INHIBITORS FOR METABOLIC DISEASES

Jianliang Lu (Eli Lilly) reported on the discovery of a novel class of diacylglycerol *O*-acyltransferase 1 (DGAT1) inhibitors for the treatment of obesity and diabetes. The most active compound showed selective inhibition of DGAT1 (IC_{50} for human DGAT1 and DGAT2 = 75.7 and 100,000 nM, respectively; IC_{50} for mouse and rat DGAT1 = 100 and 142 nM, respectively). Pharmacokinetic studies in mice (5 mg/kg p.o.) and rats (10 mg/kg p.o.) showed respective C_{max} values of 499 and 5490 ng/mL, AUC of 396 and 4650 ng.h/mL, t_{max} of 0.25 and 0.33 hours, $t_{1/2}$ of 2.65 and 2.10 hours, and a bioavailability of 18.6% and 104%. Administration of this compound at 6 mg/kg/day for 14 days inhibited body weight gain (4.65%), food intake (11.36%) and fat mass (9.53%) in C57 mice; further reductions were seen at a dose of 60 mg/kg/day. It also decreased the level of plasma triglycerides in fasted male Sprague-Dawley rats (ED_{50} = 0.26 mg/kg); doses of 1, 3 and 10 mg/kg/day showed the most significant effect.

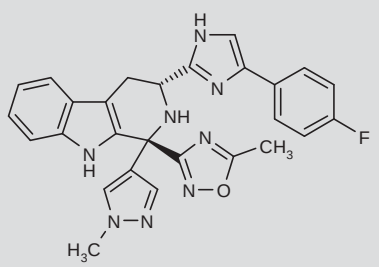
Michael Serrano-Wu (Novartis Institutes for BioMedical Research) discussed two different molecules that inhibit DGAT1 via different mechanisms. One compound showed a DGAT1 IC_{50} of 39 nM, a cell IC_{50} of 390 nM and a plasma C_{max} of 77 nM. It also showed a robust triglyceride-lowering effect in dogs. Another compound showed similar effects in rats and mice. The DGAT1 inhibitor **LCQ-908** is in clinical trials after showing robust pharmacodynamic effects in dogs and monkeys. The robustness of the preclinical triglyceride model was also confirmed in the first-in-human study of LCQ-908 in healthy volunteers, with postprandial triglycerides being suppressed. Familial chylomicronemia syndrome (FCS) currently has no effective treatment and a phase II clinical trial of LCQ-908 in FCS patients showed a reduction of plasma triglycerides of 38.4% from baseline after LCQ-908 treatment for 21 days.



LCQ-908

MK-4256 SELECTED FOR TYPE 2 DIABETES

Somatostatin sst_3 receptor antagonism has been suggested to be a potential mechanism for promoting glucose-dependent insulin secretion, which may be useful for the treatment of type 2 diabetes. Shuwen He (Merck Research Laboratories) presented structure–activity relationship (SAR) studies on a beta-carboline series of sst_3 receptor antagonists that led to lead compound **MK-4256**. This compound had a human sst_3 K_i of 0.5 nM and human sst_3 cAMP IC_{50} of 1.0 nM, as well as > 500-fold selectivity over other subtypes. MK-4256 demonstrated excellent pharmacokinetic data in mouse, dog and rhesus monkeys. In rats it showed a $t_{1/2}$ of 1.7 hours, C_{max} of 0.22 µM, clearance of 34 mL/min/kg and bioavailability of 42%; in dogs these results were 7.0 hours, 1.96 µM, 2.3 mL/min/kg and 53%, respectively, and in rhesus monkeys 7.2 hours, 1.4 µM, 3.1 mL/min/kg and 65%, respectively. Studies of brain penetration (1 mg/kg i.v.) revealed low brain/plasma relationship values (0.016 at 4 hours). When dosed in an oral glucose tolerance test model in mice, this sst_3 receptor antagonist showed outstanding efficacy, with an 85% reduction in net blood glucose AUC at 0.03 mg/kg (down to 100% reduction at 10 mg/kg), with low hypoglycemic risk. The com-

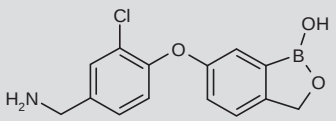


MK-4256

pound was more effective in wild-type but not *Sstr3* knockout mice at reducing blood glucose. MK-4256 was selected for further development for the treatment of type 2 diabetes.

ANACOR'S ROCK KINASE INHIBITORS

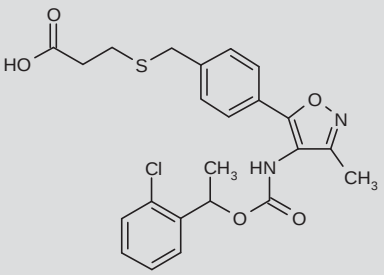
The use of rho-associated protein kinase (ROCK) inhibitors has been suggested as a potential therapy for a number of indications (e.g., hypertension, heart failure, stroke, AD, osteoporosis, cancer, asthma, glaucoma) because of its association with the control of the actin-myosin cytoskeleton, and smooth muscle contraction, cell migration and proliferation. Tsutomu Akama (Anacor Pharmaceuticals) investigated a series of novel benzoxaborole ROCK1/2 inhibitors. SAR studies on this series found that the 4-(aminomethyl)phenoxy group is important for enzyme inhibition. This led to the discovery of **AN-3485**, a benzoxaborazole that demonstrated potent inhibition of ROCK1/2 (ROCK1 and ROCK2 IC_{50} = 1.8 and 0.97 µM, respectively) and > 25-fold selectivity over other kinases in the AGC protein kinase family. Pharmacokinetics in mice showed a C_{max} value of 3.22 mg/mL, a clearance of 2210 mL/h/kg and an $AUC_{0-\infty}$ of 2.26 µg.h/mL when dosed at 5 mg/kg i.v. Oral administration (10 mg/kg) showed a C_{max} value of 1.45 mg/mL, AUC_{last} of 2.66 µg.h/mL and 59% bioavailability. AN-3485 demonstrated efficacy in lowering blood pressure after oral administration in spontaneously hypertensive rats. It also showed potent inhibition of cytokine release of peripheral blood mononuclear cells (PBMCs). These data support the potential use of AN-3485 or its analogues for inflammatory diseases.



AN-3485

AJINOMOTO'S LPA_1 RECEPTOR ANTAGONIST FOR FIBROTIC DISEASES

Lysophosphatidic acid (LPA) has been related to inflammatory processes, tissue fibrosis, and the proliferation and migration of tumor cells. Inhibition of this enzyme may therefore be a potential treatment for cardiovascular diseases, cancer, neuropathies, inflammation and fibrosis. Takashi Yamamoto (Ajinomoto Pharmaceuticals) described the SAR study of a series of 3-unsubstituted isoxazole derivatives as lysophospholipid LPA_1 receptor antagonists. SAR modifications of **KI-16425** led to isoxazole derivatives with low IC_{50} values for the human LPA_1 receptor. Further SAR identified a potent and selective LPA_1 receptor antagonist that exhibited an IC_{50} for the human receptor of 12 nM in a radioligand assay. The cellular

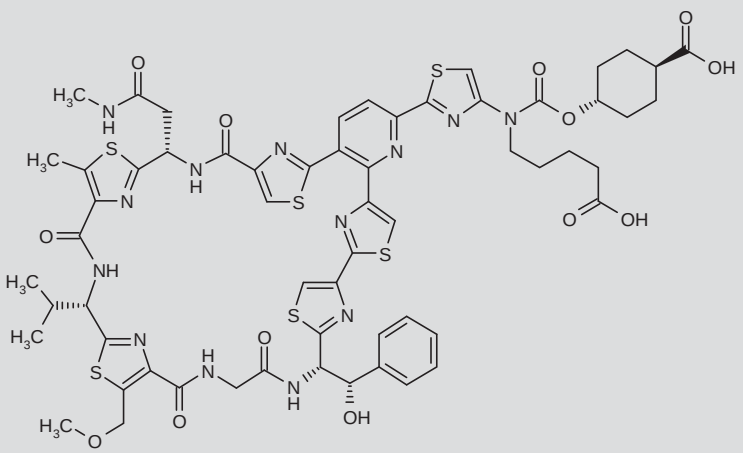


KI-16425

antagonist activity ($[Ca^{2+}]$ influx) IC_{50} was 60 nM for the human LPA_1 receptor in CHO cells (1400 nM for the human LPA_2 receptor). IC_{50} values for cytochrome P450 inhibition were found to be high (> 10 µM for 1A2, 2C9, 2C19 and 2D6, and 4.5 µM for 3A4). This compound also showed an excellent pharmacokinetic profile. In mice (3 mg/kg i.v.) and rats (5 mg/kg i.v.) it exhibited AUC values of 1.0 and 3.6 µM.h, respectively, and clearance values of 5.8 and 3.0 L/kg/h, respectively. Oral administration to mice (30 mg/kg) and rats (60 mg/kg) showed AUC values of 0.54 and 10.3 µM.h, respectively, and a $t_{1/2}$ of 0.25 hours in both species; C_{max} was 0.59 and 15.3 µM, respectively. After oral administration to mice, there was clear inhibition of LPA-stimulated histamine at 30 and 100 mg/kg. This compound could be a promising candidate for the treatment of fibrotic diseases such as idiopathic pulmonary fibrosis, systemic sclerosis, scleroderma and renal fibrosis associated with chronic kidney disease.

NOVARTIS' LFF-571 FOR THE TREATMENT OF *CLOSTRIDIUM DIFFICILE* INFECTION

Jennifer Leeds (Novartis) described the clinical progress of **LFF-571**, an elongation factor Tu inhibitor for the treatment of *C. difficile* infection. LFF-571 was identified as a semisynthetic metabolite of GE-2270A, which was optimized from a *Staphylococcus aureus* HTS, and was found to have potency against Gram-positive bacteria, including *S. aureus* and *Enterococcus faecalis*, as well as good aqueous solubility. In vitro studies in mutant bacterial strains found that LFF-571-resistant strains of *C. difficile*, *S. aureus*, *E. faecalis* and *Enterococcus faecium* were not cross-resistant with other antibiotics, such as methicillin, cefazolin and vancomycin. A randomized, double-blind, placebo-controlled phase I trial of single- and multiple-ascending doses of LFF-271 (25, 50, 100, 400 and 1000 mg) investigated the safety, tolerability and pharmacokinetics in healthy volunteers. The drug was found to be generally safe and well tolerated and had minimal systemic exposure in healthy volunteers and patients with *C. difficile* infection. Adverse events following multiple doses (25, 100 and 200 mg every 6 hours) were reported to be mild, with the exception of one occurrence of moderate skin laceration. A clinical proof-of-concept study was described, which assessed the clinical response rate of oral LFF-571 in *C. difficile* patients, as well as safety and tolerability. This multicenter, randomized, evaluator-blinded, active-controlled, parallel-group study involved the administration

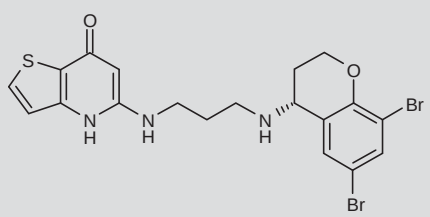


LFF-571

of LFF-571 (200 mg) or vancomycin (125 mg) 4 times daily for 10 days, with a follow-up of 43 days. Preliminary data from this study found that the agent was effective for the treatment of *C. difficile* infection. It was stated that enrollment in the trial had finished in January 2012, with results expected "soon". Subsequent studies will examine different doses and dose regimens.

CRESTONE'S *C. DIFFICILE* AGENT

Joseph Guiles (Cedarburg-Hauser Pharmaceuticals) discussed the development of **CRS-3123** (Crestone). Crestone aimed to develop drugs that lower the recurrence rate of *C. difficile* infection, with mechanisms of action that inhibit spore formation and toxin production, and lower the impact on beneficial anaerobes by developing a species-specific agent. Lead optimization focused on modification of the left and right sides of the molecule, which bind the methionine and hydrophobic pockets, respectively, of the *C. difficile* MetRS enzyme. Investigations into the Met-binding left side of the molecule found that conformational constraint improved antibacterial activity, and introduction of a thiophene moiety to the hydrophobic right side of the molecule further improved potency. It was determined that the (*R*)-enantiomer of CRS-3123 was the most potent, with a K_i of 20 pM and an MIC_{50} of 0.5 µg/mL, compared with the (*S*)-enantiomer, which had a K_i of 80,000 pM and an MIC_{50} of > 32 µg/mL. In vitro investigations revealed that (*R*)-CRS-3123 was selectively toxic to *C. difficile*, without having toxic effects on normal gut flora. In vivo, in a hamster model of *C. difficile* infection, CRS-3123 (5 mg/kg p.o. b.i.d. for 5 days) resulted in 90-100% survival for the duration of the study compared with vancomycin, which showed recurrence after day 15. Furthermore, the drug had no rounding effect on *C. difficile* sporulation. CRS-3123 had low oral bioavailability in vivo, which minimized systemic absorption. An IND was expected to be filed and a double-blind, randomized, placebo-controlled phase I study was expected to start in April 2012 to investigate the safety and pharmacokinetics of a single ascending dose of CRS-3123.



CRS-3123

GyrB AND ParE INHIBITORS

AstraZeneca's John Manchester described the company's program of novel azaindole-based inhibitors of of GyrB and ParE. An HTS and optimization program led to the identification of a beta-keto acid lead compound. This compound was found to have excellent potency against *Streptococcus pneumoniae* ParE and *S. aureus* GyrB, with IC_{50} values of approximately 1.8 and 1 nM, respectively, and it was also effective against *S. pneumoniae* (IC_{50} < 0.024 µM) and *S. aureus* (IC_{50} = 0.098 µM; fMIC = 0.46 µM). In vivo studies in mice showed that the compound had a plasma concentration lower than the MIC following intraperitoneal (i.p.) dosing. It also displayed good clearance in mice and rats and free levels of the drug (30 mg/kg) exceeded *S. aureus* MICs achieved in mice, with efficacy expected for doses ≥ 30 mg/kg. Preclinical studies in an *S. aureus* ARC516 immunocompetent mouse thigh model found that there was a dose-dependent reduction in bacterial load following a single i.p. dose (10-100 mg/kg). It was determined that stasis occurred between 30

and 60 mg/kg and an approximate 1.5-log kill was achieved in 24 hours at a dose of 100 mg/kg compared with untreated mice. The drug (100 mg/kg) was also found to have a similar potency to linezolid (Zyvox®; 160 mg/kg).

Pyrrolopyrimidine inhibitors of GyrB and ParE for the potential treatment of bacterial infections were described by Trius Therapeutics' John Finn. It was explained that inhibitors of ParE and GyrB are generally used for the treatment of Gram-positive infections and currently there are no drugs in clinical use that target these enzymes. The aim of Trius Therapeutics' program was to develop inhibitors of Gram-negative pathogens, including biodefense pathogens such as *Yersinia pestis* and *Francisella tularensis*. A structure-based drug design strategy led to the discovery of three compounds with good enzymatic potency. In *E. faecalis* and *F. tularensis* GyrB, initial compounds had K_i values of < 0.3 nM, and in *E. faecalis*, *F. tularensis* and *Escherichia coli* ParE, the compounds had K_i values in the range of 3.2-8.6, 1.1-1.7 and 0.59-4.6 nM, respectively. A virtual HTS screen and de novo design selected 50 further compounds to be advanced into crystallographic screening with *E. faecalis* GyrB, based on enzyme data. Four optimized compounds were selected for mechanism of action studies and it was found that some of the compounds displayed off-target activity, with one compound having MIC values of 32 and 8 μg/mL, respectively, against *S. aureus* and *E. coli*, while one compound that displayed on-target activity had MIC values of < 0.013 and 0.25 μg/mL, respectively, against *S. aureus* and *E. coli*. These compounds were found to have antibacterial activity against a range of commercial pathogens and biodefense pathogens, including *Y. pestis* (MIC = 8 μg/mL). It was stated that evaluating the mechanism of action is crucial, as in this study a number of compounds were found to have off-target activity. Structure-based drug design allowed expansion of GyrB and ParE inhibitors to Gram-negative bacteria by exploiting polar groups and charged molecules to aid solubility and decrease efflux.

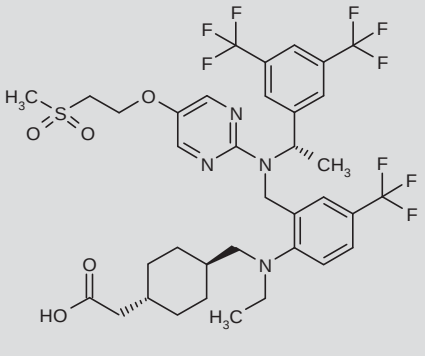
POTENTIAL THERAPIES FOR SCHIZOPHRENIA

Schizophrenia is a chronic, severe psychiatric disorder that affects approximately 1% of the population worldwide. This disease causes disability, and an increase in suicide attempts is observed in patients. Currently marketed antipsychotics treat the positive symptoms of schizophrenia, such as hallucinations and delusions, but have a lesser effect on negative or cognitive symptoms, including emotional blunting, social withdrawal and disorganized thought, and speech and memory deficits, respectively. The discovery of a novel class of amino-azabenzimidazolone metabotropic glutamate $mGlu_2$ receptor positive allosteric modulators was discussed by Joseph Pero (Merck & Co.). The optimization of this series led to an isoxazole derivative that selectively potentiated $mGlu_2$ receptors, with EC_{50} values of 29 and 75 nM, respectively, against human and rat $mGlu_2$ receptors in a fluorometric imaging plate reader (FLIPR) assay, compared with > 30,000 nM for human $mGlu_3$, $mGlu_4$, $mGlu_5$ and $mGlu_6$ receptors. In rats, the compound showed clearance and half-life values of 28 mL/min/kg and 2.3 hours, respectively, and a bioavailability of 72%; in dogs, the respective values were 7 mL/min/kg, 12 hours and 24%. The clearance and half-life values in humans were predicted to be 3-9 mL/min/kg and 11-18 hours, respectively. This compound had a clean safety profile and achieved CNS penetration. In an MK-801-induced hyperlocomotion assay, the compound demonstrated full efficacy at oral doses of 10 and 30 mg/kg.

Dalton King (Bristol-Myers Squibb) reported on a novel series of potent nicotinic acetylcholine receptor (nAChR) α7 partial agonists that culminated in the discovery of BMS-902483. In vitro, this compound selectively acts as a partial agonist of α7 nAChR, with an EC_{50} of 9.3 nM, compared with an IC_{50} of 480 nM for the $5\text{-}HT_3$ receptor and 100-fold selectivity over other nicotinic receptors. The compound had low protein binding activity and achieved brain penetration. BMS-902483 demonstrated efficacy in multiple animal models, including a mouse model of episodic memory. The compound also reversed MK-801-induced deficits and ketamine disruption in rat models of executive function and sensory deficit, respectively. A pharmacokinetic study showed good oral bioavailability in mice and dogs (59% and 38%, respectively), a high clearance (272, 266, 48.2 and 144 mL/min/kg, respectively, in mice, rats, dogs and monkeys) and V_{ss} (51.8, 22.7, 44.2 and 46.9 L/kg, respectively, in mice, rats, dogs and monkeys), and good absorption. BMS-902483 was selected as a clinical candidate, but its development was discontinued due to hepatotoxicity found in dogs in IND studies. Studies are being conducted on further compounds to avoid these toxic effects but maintain the favorable properties.

KOWA'S CETP INHIBITOR (–)-K-18597

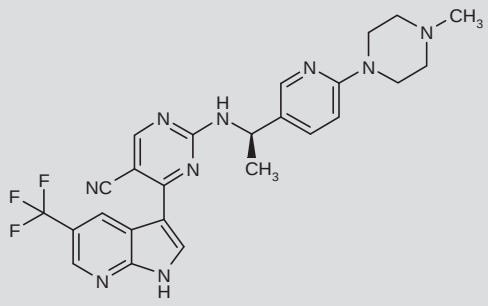
The inhibition of cholesteryl ester transfer protein (CETP) is being studied for the treatment of coronary heart disease. Koichi Yamazaki (Kowa) described SAR studies that led to the discovery of **(–)-K-18597**, which demonstrated CETP inhibition, with an IC_{50} of 0.9 μM, and exhibited a long duration of effect. This inhibition was enantiomer-dependent, as the (+)-enantiomer had less inhibitory activity (IC_{50} = 4.9 μM). In a 2-week study in hamsters, (–)-K-18597 (3 mg/day) and anacetrapib (MK-0859; Merck & Co.; 10 mg/day) decreased LDL cholesterol by 20% and 22%, respectively, and increased HDL cholesterol by 78% and 71%, respectively. (–)-K-18597 (3-30 mg/day), but not anacetrapib (10-30 mg/day), decreased plasma triglycerides and total liver cholesterol levels. Administration of (–)-K-18597 did not increase blood pressure and did not cause the release of aldosterone from human adenocarcinoma H295R cells.



(–)-K-18597

VERTEX'S PLK1 INHIBITORS FOR CANCER THERAPY

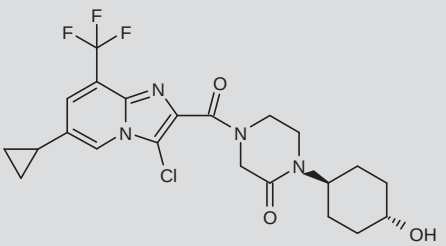
Serine/threonine-protein kinase PLK1 (polo-like kinase 1) is known to be a valid target for the treatment of cancer, as it is overexpressed in several human cancers. Joanne Pinder (Vertex Pharmaceuticals) presented a series of PLK1 inhibitors based on a pyrrolopyridine scaffold. The initial hit obtained by HTS showed good inhibition of PLK1, but poor selectivity over other polo-like kinases and poor pharmacokinetics. SAR studies from this compound led to **VRT-764527**, which maintained potent inhibition of PLK1 (K_i = 0.14 nM) and improved selectivity over other polo-like kinases (PLK2 and PLK3 K_i = 46 and 17 nM, respectively), and 100-fold selectivity over other kinases. VRT-764527 had good in vitro activity, microsomal stability and negligible hERG activity (24 μM). Pharmacokinetic properties in rats included a bioavailability of 28%, with clearance and half-life values of 36.4 mL/min/kg and 2.2 hours, respectively. In a xenograft model in nude mice, VRT-764527 (30-50 mg/kg b.i.d.) demonstrated dose-dependent efficacy, with a decrease in tumor volume to 62% and 45%, respectively, of control with doses of 40 and 50 mg/kg.



VRT-764527

IMIDAZOPYRIDINE COMPOUNDS FOR HEPATITIS C VIRUS

Non-structural protein 4B (NS4B) is a novel target for the treatment of hepatitis C virus (HCV) infection. A series of imidazopyridines substituted with a critical oxazolidinone moiety as potential antiviral agents for HCV were presented by Anna Banka (GlaxoSmithKline). These compounds were identified as inhibitors of the HCV replicon. Initial hits had poor dose-scalability and potent cytochrome P450 induction; however, SAR studies resulted in the identification of **GSK-853A**, which demonstrated inhibitory activities of 0.7 and 4.2 nM, respectively, against replicons 1A and 1B. The compound showed excellent pharmacokinetic properties across different species: the respective clearance, half-life (at 1 mg/kg i.v.) and bioavailability (at 5 mg/kg p.o.) values were 4.7 mL/min/kg, 1.8 hours and 37% in mice; 20 mL/min/kg, 4.2 hours and 90% in rats; 1.0 mL/min/kg, 13 hours and 80% in dogs; and 2.1 mL/min/kg, 4.9 hours and 120% in monkeys. GSK-853A also showed an increase in exposure compared with the initial hits. This series of compounds led to a potential development candidate.



GSK-853A

DISCLOSURES

The authors state no conflicts of interest.

The website for this meeting can be found at: http://portal.acs.org/portal/acs/corg/content?_nfpb=true&_pageLabel=PP_MULTICOLUMN_T5_33&node_id=644&use_sec=false&sec_url_var=region1&__uuid=643ffa5d-bc60-4065-b734-33d9262df6e8.