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THE CUTTING EDGE OF CHEMISTRY

A PHARMA MATTERS REPORT – NOVEMBER 2010

This new section is a chemistry-oriented review providing insight into the latest synthesis schemes, scaffolds, mechanisms of action and new structures advancing drug discovery and development. This review takes a look at the new advances in chemistry transforming drug discovery and development, through expert insight and drawing on the strategic data from Thomson Reuters Integrity℠, a unique database integrating biological, chemical and pharmacological data. This report highlights content from Thomson Reuters Integrity℠ covering some of the major meetings in the last half of 2010, including the 240th ACS National Meeting, the 50th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), the 9th International Meeting of the International Society for the Study of Xenobiotics (ISSX) and the XXIst International Symposium on Medicinal Chemistry (ISMC).

CONTENTS

ORGANIC SYNTHESIS SCHEME SHOWCASE

More efficient synthesis offers hope of glucose control without insulin

Type 2 diabetes is a growing health problem worldwide and the condition is a sharp focus of much research in the pharmaceutical industry. The sodium/glucose cotransporter 2 (SGLT2) has been identified as a possible target for antidiabetic drugs. Inhibiting this protein would slow glucose reuptake in the kidneys and potentially allow control of hyperglycemia in a glucose-dependent manner, without recourse to modulating insulin.

A putative lead for drug discovery in this area emerged in the form of an *O*-aryl glucoside natural product known as phlorizin, a toxic dihydrochalcone polyphenol found in the bark of common fruit trees, such as pear, apple and cherry trees. Its toxicity is related to its nonselective ability to inhibit SGLT1 and SGLT2, which suggests that more selective derivatives might be useful in glucose transport inhibition.

Indeed, several structurally related *O*-aryl and *C*-aryl glucosides are currently in clinical trials. With a differential trait from other members of the *C*-aryl glucoside series, an ether bridge, compound 689201 in *Integrity* was discussed in the ORGN sessions of the 240th ACS National Meeting (1). Vincent Mascitti and Cathy Préville of Pfizer Global Research and Development in Groton, Connecticut, presented the evolution of the synthetic approach to the compound along the development pathway (also later outlined in *Org Lett* 2010, 12(13): 2940).

The team's original route (Fig. 1) relied on an acyclic Weinreb amide as an advanced versatile intermediate, which allowed for the convenient preparation of analogues in the early stages of development. However, with a 0.3% yield over 13 linear steps and a final HPLC separation of diastereomers, this approach was not well suited for large-scale synthesis according to the team.

A more efficient synthetic route is now envisaged (Fig. 2) for the compound, currently in phase II clinical trials. The new approach stands out for exploiting pseudo C2-symmetry in the identification of the diacetonide D-mannofuranose as starting material.

The aldehyde derived from this carbohydrate precursor undergoes addition with the convenient dithiane carbanion to afford a single diastereomer. From this point, the new stereoselective route offers a 26% yield over five linear steps, "which constitutes a major improvement over the original route", the team says.

The Pfizer team also pointed out that this same route provides a quick entry point to C1- and C5-substituted dioxabicyclo[3.2.1]octane-2,3,4-triols, which might also have useful biological activity.

Integrity Entry Number: 689201

SCAFFOLDS ON THE MOVE: THE NEAR AND FAAH OF ENDOCANNABINOID MANIPULATION

The manipulation of endocannabinoid degradation through fatty acid amide hydrolase (FAAH) inhibition was a focus of dis-

Figure 1. Synthesis Scheme for 689201

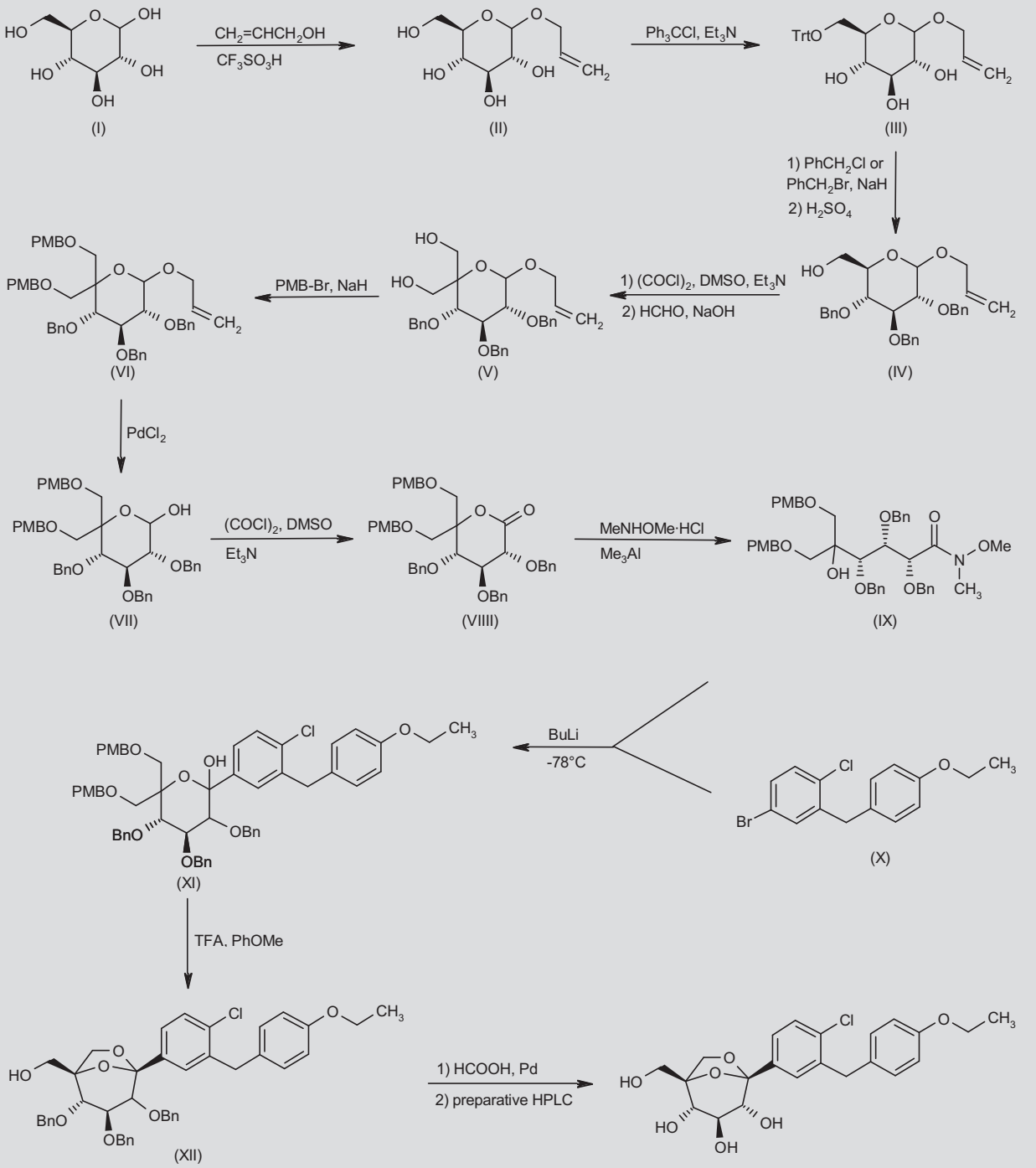
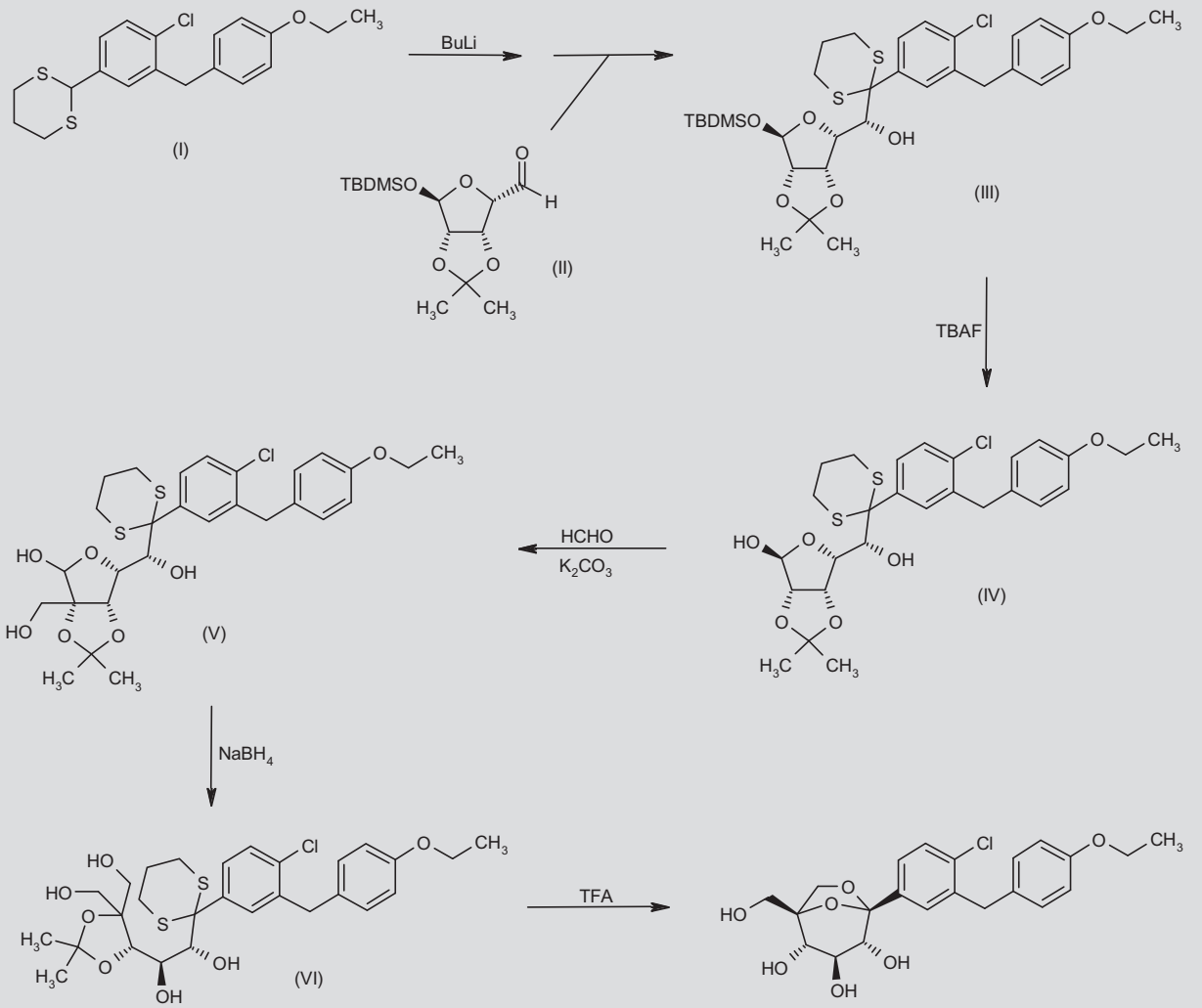


Figure 2. Synthesis Scheme for 689201



cussion at the 240th ACS National Meeting in August 2010. Cannabinoid CB_1 receptor agonists have already been approved by regulatory agencies for reducing nausea and pain in cancer and multiple sclerosis patients. Unfortunately, these agents have side effects, including dysphoria, dizziness and motor coordination problems.

FAAH is a member of the serine hydrolase family of enzymes that catabolizes the endogenous cannabinoid ligand (endocannabinoid) anandamide (AEA). AEA has been shown to produce analgesic effects in vivo, with none of the side effects observed when targeting the CB_1 receptor exogenously (2). Thus, FAAH inhibition could allow for a more selective approach to cannabinoid-mediated analgesia. The pharmacological profile of FAAH inhibitors can be different according to their mode of action. As a general observation, reversible FAAH inhibitors exhibit very satisfactory selectivity indexes. However, their efficacy is usually only partial, presumably because they are metabolized rapidly. In contrast, irreversible FAAH inhibition tends to correlate with high in vivo efficacy, although selectivity might be compromised, given that more than 200 serine hydrolases are encoded in the human proteome (3).

During the last ACS National Meeting session, three well-known pharmaceutical companies, Amgen, Johnson & Johnson and Pfizer, commented on their strategies for FAAH inhibition. The Pfizer team presented a series of piperidine ureas (Featured scaffold 1), and argued that they act irreversibly at the enzyme by covalently binding the nucleophilic serine 241 in the active site. Notably, the compounds were proven to exhibit outstanding selectivity over other serine hydrolases. A representative of this class, currently in phase II clinical trials, is PF-04457845 (640867). Johnson & Johnson similarly described the discovery of a novel class of piperidine urea FAAH inhibitors (Featured scaffold 2), exemplified by compound JNJ-40355003 (707111) in *Integrity*, and discussed structure–activity relationships (SAR), as well as results

in preclinical pain models. Finally, Amgen researchers aimed at the design of reversible non-covalent-binding FAAH inhibitors (Featured scaffold 3). By combining high-throughput screening and rational design with this mechanistic prerequisite, they identified a preliminary set of sterically constrained cyclic ureas. The mode of action was confirmed by co-crystallization studies. This starting point was subsequently refined by SAR studies, leading to the exemplified compound 656203 in *Integrity*.

Despite the fact that the three aforementioned series share a common trait, the arylurea moiety, it is perhaps not surprising that the best approach to FAAH inhibition is still a matter of debate.

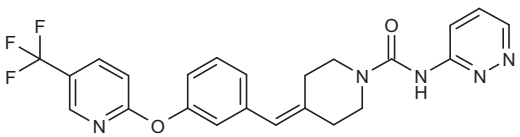
Featured scaffold 1

Therapeutic Group: Non-Opioid Analgesics

Source: Johnson, D. Discovery of PF-04457845, an irreversible FAAH inhibitor with exquisite selectivity. 240th ACS Natl Meet (August 22-26, Boston) 2010, Abst MEDI 500

Drug Name: PF-04457845

Integrity Entry Number: 640867



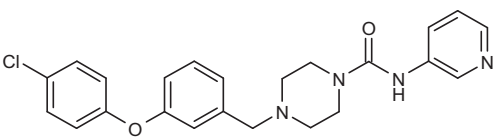
Featured scaffold 2

Therapeutic Group: Non-Opioid Analgesics

Source: Tichenor, M.S.; Keith, J.M.; Apodaca, R.L.; Xiao, W.; et al. Inhibitors of fatty acid amide hydrolase (FAAH): SAR and results in pre-clinical pain models. 240th ACS Natl Meet (August 22-26, Boston) 2010, Abst MEDI 499

Drug Name: JNJ-40355003

Integrity Entry Number: 707111

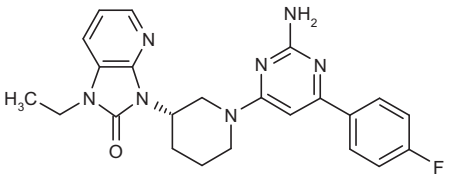


Featured scaffold 3

Therapeutic Group: Non-Opioid Analgesics

Source: Gustin, D.J.; Li, Y.; Hedberg, C.; Min, X.; et al. Discovery of a novel series of potent, non-covalent fatty acid amide hydrolase (FAAH) inhibitors through rational design. 240th ACS Natl Meet (August 22-26, Boston) 2010, Abst MEDI 498

Integrity Entry Number: 656203



Novel chemical scaffolds with biological activity underpin major advances in medicinal chemistry. Also showcased here are some of the latest scaffolds within drugs for a wide range of therapeutic areas.

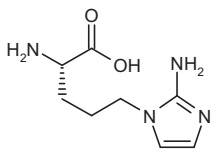
2-Aminoimidazole moiety offers arginase attack

An SAR analysis by David Christianson of the University of Pennsylvania and colleagues demonstrated that the 2-aminoimidazole group can target metal coordination and hydrogen bond interactions in the active site of arginase, a key metalloenzyme of the urea cycle. Targeting this enzyme, which converts L-arginine to L-ornithine and urea, is promising in the management of diseases in which L-arginine homeostasis goes awry, including asthma, cardiovascular diseases and erectile dysfunction. New arginase inhibitors should emerge from this work that exhibit alternative and improved pharmacokinetic profiles.

Therapeutic Group: Antiallergy/Antiasthmatic Drugs

Source: Ilies, M.; Di Costanzo, L.; North, M.L.; Scott, J.A.; Christianson, D.W. 2-Aminoimidazole amino acids as inhibitors of the binuclear manganese metalloenzyme human arginase I. J Med Chem 2010, 53(10): 4266

Integrity Entry Number: 698475



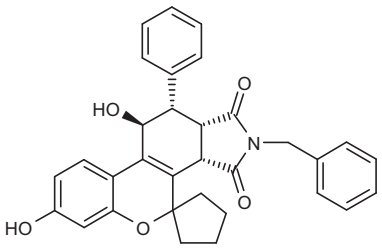
Nonsteroidal prostate therapy sidesteps resistance

A nonsteroidal benzopyran-containing androgen receptor antagonist could find utility in treating resistant forms of prostate cancer, according to researchers at Seoul National University. They carried out a medium-throughput screening exercise on 2,000 drug-like small molecules to identify the scaffold, which competes with the endogenous agonist dihydrotestosterone. The screen was a cell-based reporter gene assay and activity was confirmed by Western blot analysis, RT-PCR and in vitro cellular proliferation assay. The new lead holds promise for overcoming the problems of resistance seen with flutamide and bicalutamide in long-term use by sidestepping their well-known substructure.

Therapeutic Group: Prostate Cancer Therapy

Source: Oh, S.; Nam, H.J.; Park, J.; Beak, S.H.; Park, S.B. Development of a benzopyran-containing androgen receptor antagonist to treat antiandrogen-resistant prostate cancer. ChemMedChem 2010, 5(4): 529

Integrity Entry Number: 699824



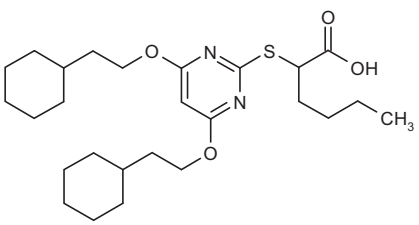
Painkillers show secret promise in Alzheimer's disease

Results from in vivo models suggest that the combined action of γ-secretase modulators and peroxisome proliferator-activated receptor PPAR-γ agonists has potential in the treatment of Alzheimer's disease. Researchers from Roche now disclose the first drug-like compounds that exhibit dual activity at the two targets. SAR studies around the initial hit, 2-[bis(phenethoxy)pyrimidine-2-ylthio]hexanoic acid, indicated that the carboxylic acid moiety is crucial for both activities, and that the initial butyl group at the stereocenter has the optimal length. The exemplified compound, with the phenyl ring substituted by a cyclohexyl ring, was the most active (IC_{50} $A\beta_{42}$ = 5.1 μM; EC_{50} PPAR-γ = 6.6 μM). Importantly, it was shown that it did not produce impairment of Notch processing and signaling over the tested concentration range (5-40 μM).

Therapeutic Group: Treatment of Alzheimer's Dementia

Source: Hieke, M.; Ness, J.; Steri, R.; et al. Design, synthesis, and biological evaluation of a novel class of gamma-secretase modulators with PPARgamma activity. J Med Chem 2010, 53(12): 4691

Integrity Entry Number: 701189



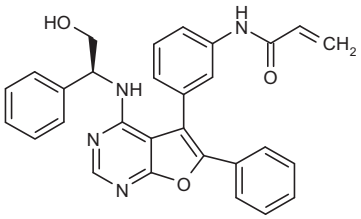
Small screen reveals novel cancer inhibitor

Researchers in China have rapidly synthesized a focused library of 350 furanopyrimidines and then screened them alternatively for Aurora and epidermal growth factor receptor (EGFR) kinase activity. Of three promising candidates, resynthesis confirmed one hit as a potent EGFR kinase inhibitor, while being devoid of Aurora kinase inhibition. Docking results with this hit suggest that the furanopyrimidine ring oxygen forms the required hinge binding interaction with the Met769 hinge residue, while the three phenyl rings form extensive hydrophobic interactions with the surrounding residues. Introduction of a Michael acceptor group gave rise to a marked improvement in activity. The novel lead thus obtained could hold promise in the development of an alternative cancer therapy for gefitinib-resistant EGFR-overexpressing tumors.

Therapeutic Group: Oncolytic Drugs

Source: Coumar, M.S.; Chu, C.Y.; Lin, C.W.; et al. Fast-forwarding hit to lead: Aurora and epidermal growth factor receptor kinase inhibitor lead identification. J Med Chem 2010, 53(13): 4980

Integrity Entry Number: 702179



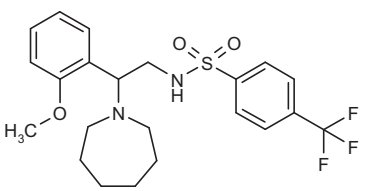
Potent substitution leads to potential antipsychotics

The identification of *N*-[2-(azepan-1-yl)-2-phenylethyl]benzenesulfonamides as novel inhibitors of glycine transporter GlyT1 offers new hope for antipsychotic agents for treating schizophrenia. Employing a pharmacophore-encoded virtual screening, a benzenesulfonamide was the most potent hit. Subsequent SAR studies revealed that this moiety provided the best balance between potency and solubility. Exchanging the piperidine ring in the hit by the homologous azepane ring represented a threefold increase in potency, while other modifications from the original (other ring sizes, ring truncation or heteroatom variation) proved detrimental for activity.

Therapeutic Group: Antipsychotic Drugs

Source: Varnes, J.G.; Forst, J.M.; Hoerter, T.N.; et al. Identification of N-(2-(azepan-1-yl)-2-phenylethyl)-benzenesulfonamides as novel inhibitors of GlyT1. Bioorg Med Chem Lett 2010, 20(16): 4878

Integrity Entry Number: 704339



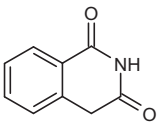
Rheumatoid arthritis inhibitors, in the NIK of time

Inhibition of serine/threonine-protein kinase NIK represents an important area of research in rheumatoid arthritis. Until now, however, very few NIK inhibitors have been reported. By applying a carefully designed set of sequential restrictions, scientists in Belgium narrowed down an initial small-molecule pool of 8 million compounds to a final set of 49 candidates for in vitro screening. Two new fragments, 4*H*-isoquinoline-1,3-dione and 2,7-naphthyridine-1,3,6,8-tetrone, were thus identified, exhibiting an IC_{50} of 51 and 90 μM, respectively, in a radiometric protein assay. Analogues of the former scaffold have previously been reported as having activity against other kinases. This work is still in progress and other analogues are being investigated for NIK activity.

Therapeutic Group: Treatment of Rheumatoid Arthritis

Source: Mortier, J.; Masereel, B.; Remouchamps, C.; Ganeff, C.; Piette, J.; Frederick, R. NF-kappaB inducing kinase (NIK) inhibitors: Identification of new scaffolds using virtual screening. Bioorg Med Chem Lett 2010, 20(15): 4515

Integrity Entry Number: 703714



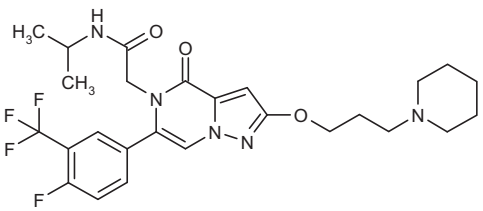
GSK finds behavioral antagonists

GlaxoSmithKline scientists in Italy have identified two new series of potent antagonists of the vasopressin V_{1B} receptor in their proprietary compound collection. The compounds have submicromolar potency and high selectivity. Neither the pyrrole-pyrazinone- nor the pyrazole-pyrazinone-type compounds interfere with V_{1A}, V_2 or oxytocin receptors, and all have good central nervous system penetration. A selected (3-trifluoromethyl-4-fluorophenyl)-substituted derivative from the pyrazole-pyrazinone series was further studied in vivo, exhibiting an encouraging pharmacokinetic profile and good CNS penetration in rats. The compounds could have potential in a range of diseases, such as behavioral problems, anxiety and depression.

Therapeutic Group: Anxiolytics; Antidepressants

Source: Arban, R.; Bianchi, F.; Buson, A.; et al. Pyrrolo[1,2-a]pyrazine and pyrazolo[1,5-a]pyrazine: Novel, potent, and selective series of vasopressin1b receptor antagonists. Bioorg Med Chem Lett 2010, 20(17): 5044

Integrity Entry Number: 708330



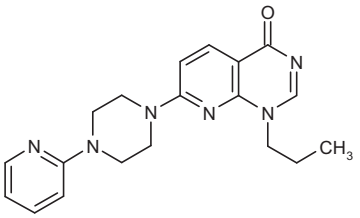
Treating Alzheimer's disease without anxiety

Researchers in Japan have used high-throughput screening to identify pyrido[2,3-*d*]pyrimidine-4(1*H*)-one derivatives as $GABA_A$ α5 receptor ligands. This receptor is highly expressed in the hippocampus and is thought to play a role in learning and memory. Ligands for the receptor might therefore demonstrate benefits in treating problems of cognition, such as those seen in Alzheimer's disease. These new modulators are promising not only because of their in vivo activity at low doses, but also because they show none of the anxiogenic or convulsant effects associated with other less selective compounds acting at $GABA_A$ α5 receptors.

Therapeutic Group: Treatment of Alzheimer's Disease

Source: Sugawara, M.; Danjo, T.; Nakajima, T.; Uchida, S.; et al. Pyrido[2,3-d]pyridine-4(1H)-ones: A novel class of GABA-A alfa5 receptor inverse agonists. Drugs Fut [21st Int Symp Med Chem (September 5-9, Brussels) 2010] 2010, 35(Suppl. A): Abst PC.380

Integrity Entry Number: 697329



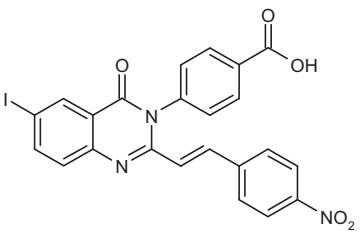
Selective antagonists for stroke and epilepsy

Quinazolin-4-one derivatives represent a novel class of noncompetitive NMDA NR2C/D subunit-selective receptor antagonists according to work in the U.S. and Denmark. The compounds contain the (*E*)-3-phenyl-2-styrylquinazolin-4(3*H*)-one backbone and inhibit recombinant NMDA receptor function, and were identified after completion of a fluorescence-based screen of 83,880 compounds. They could represent some of the first compounds for neurologic disorders that are more than tenfold selective for their NR2C/D-containing NMDA target receptor. The compounds therefore have potential in the treatment of stroke and epilepsy.

Therapeutic Group: Treatment of Stroke; Antiepileptic Drug

Source: Mosley, C.A.; Acker, T.M.; Hansen, K.B.; et al. Quinazolin-4-one derivatives: A novel class of noncompetitive NR2C/D subunit-selective N-methyl-D-aspartate receptor antagonists. J Med Chem 2010, 53(15): 5476

Integrity Entry Number: 705078



NEW MOLECULAR MECHANISMS OF ACTION

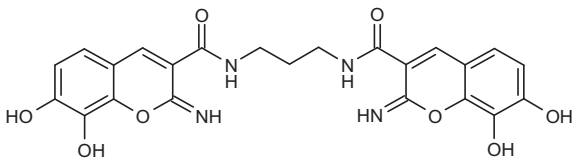
The mode of action of any product is key to understanding how to improve on any given design and how to find more potent leads with fewer potential side effects. GTPase inhibitors, bacterial regulators and drugs for ischemia and hyperlipidemia all feature new modes of action. We showcase a range of fascinating compounds in this issue.

DYNAMIN GTPASE INHIBITORS

Main Related Conditions: Infections

Organization: University of Newcastle (AU); University of Sydney (AU)

Integrity Entry Number: 698429



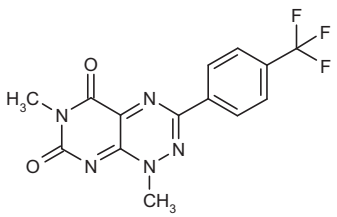
BACTERIAL TRANSCRIPTIONAL REGULATORY PROTEIN WAIR INHIBITORS

Main Related Conditions: Infection, bacterial

Organization: Kirin Holdings

Drug Name: Walrycin B

Integrity Entry Number: 699525

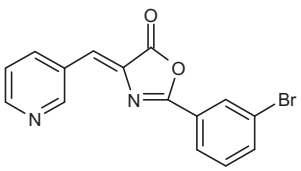


DEATH-ASSOCIATED PROTEIN KINASE INHIBITORS

Main Related Conditions: Ischemia

Organization: PharmaDesign; NB Health Laboratory (NBHL)

Integrity Entry Number: 695636

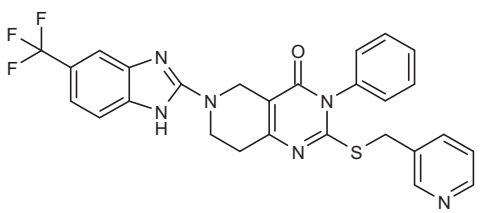


MONOACYLGLYCEROL *O*-ACYLTRANSFERASE 2 (MGAT2) INHIBITORS

Main Related Conditions: Hyperlipidemia; Diabetes; Obesity

Organization: Banyu

Integrity Entry Number: 707130

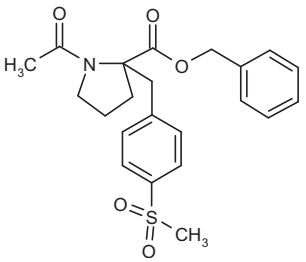


ELECTRONEUTRAL POTASSIUM-CHLORIDE COTRANSPORTER 2 (KCC2) INHIBITORS

Main Related Conditions: Epilepsy

Organization: UCB

Integrity Entry Number: 696970

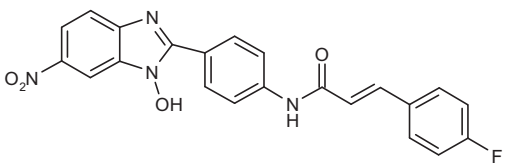


THERMOREGULATORY PROTEIN LCRF INHIBITORS

Main Related Conditions: Infection, bacterial

Organization: Paratek Pharmaceuticals

Integrity Entry Number: 449263



THE STARTING LINE

The Starting Line pinpoints new molecular entities (NMEs) ready to progress into the R&D area. This issue focuses on highlights from major conferences held during 2010.

Organization: Creighton University (US); Semmelweis University Medical School (HU); Temple University (US)

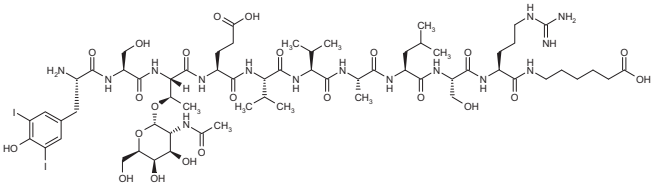
Drug Name: E1/Aca

Condition: Obesity

Mechanism of Action: Leptin Receptor (OBR) Agonists

Literature: Kovalszky, I.; Surmacz, E.; Scolaro, L.; et al. Leptin-based glycopeptide induces weight loss and simultaneously restores fertility in animal models. Diabetes Obes Metab 2010, 12(5): 393

Integrity Entry Number: 701707



Organization: Novartis

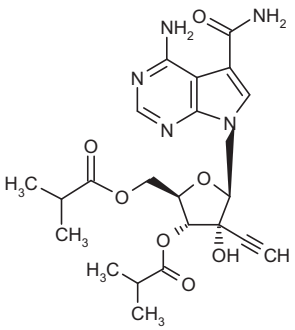
Drug Name: NITD-203

Condition: Infection, dengue virus

Mechanism of Action: Dengue Virus RNA-Directed RNA Polymerase (NS5) Inhibitors

Literature: Chen, Y.L.; Yin, Z.; Lakshminarayana, S.B.; et al. Inhibition of dengue virus RNA synthesis by an adenosine nucleoside. Antimicrob Agents Chemother 2010, 54(7): 2932; Chen, Y.L.; Yin, Z.; Duraiswamy, J.; et al. Inhibition of dengue virus by an ester prodrug of an adenosine analog. Antimicrob Agents Chemother 2010, 54(8): 3255

Integrity Entry Number: 701621



Organization: Lundbeck

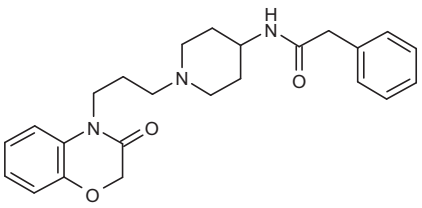
Drug Name: Lu-E51090

Condition: Dementia, Alzheimer's type; Schizophrenia

Mechanism of Action: Muscarinic M1 Receptor Agonists

Literature: Sams, A.G.; Hentzer, M.; Mikkelsen, G.K.; Larsen, K.; et al. Discovery of N-{1-[3-(3-oxo-2,3-dihydrobenzo[1,4]oxazin-4-yl)propyl]piperidin-4-yl}-2-phenylacetamide (Lu AE51090): An allosteric muscarinic M1 receptor agonist with unprecedented selectivity and procognitive potential. J Med Chem 2010, 53(17): 6386; Sams, A.G. et al. Discovery of LU AE51090, an allosteric muscarinic M1 agonist: Pro-cognitive potential alone and as add-on to antipsychotic treatment. Drugs Fut [21st Int Symp Med Chem (September 5-9, Brussels) 2010] 2010, 35(Suppl. A): Abst L.29

Integrity Entry Number: 704493



Organization: GlaxoSmithKline

Drug Name: GSK-299423

Condition: Infection, bacterial

Mechanism of Action: DNA Gyrase Inhibitors

Literature: Barfoot, C.W.; Brown, P.; Dabbs, S.; Davies, D.T.; Hennessy, A.J.; Miles, T.J. The design of efficient and selective routes to pyridyl analogues of 2,3-dihydro-1,4-benzodioxin-6-carbaldehyde. Tetrahedron Lett 2010, 51(38): 5038; Bax, B.D.; Chan, P.F.; Eggleston, D.S; Fosberry, A.; et al. Type IIA topoisomerase inhibition by a new class of antibacterial agents. Nature 2010, 466(7309): 935

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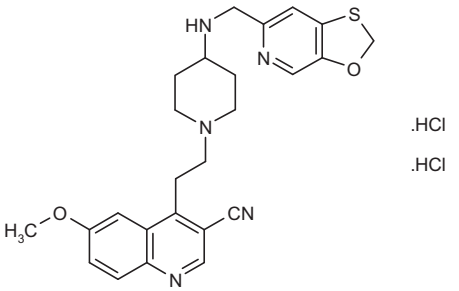


Organization: NeuroGenetic Pharmaceuticals

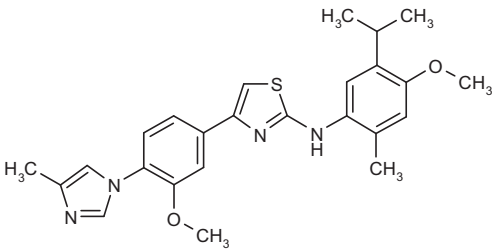
Drug Name: NGP-328

Condition: Dementia, Alzheimer's type

Mechanism of Action: Antiamyloidogenic Agents; gamma-Secretase Modulators

Literature: Cheng, S.; Comer, D.; Mao, L.; Pleynet, D.; et al. 2-Aminothiazoles derivatives as potent gamma-secretase modulators. 240th ACS Natl Meet (August 22-26, Boston) 2010, Abst MEDI 1

Integrity Entry Number: 706409



Organization: Pharmasset

Drug Name: PSI-353661

Condition: Hepatitis C (HCV)

Mechanism of Action: RNA-Directed RNA Polymerase (NS5B) Inhibitors

Literature: Sofia, M.J.; Bao, D.; Chang, W.; Chun, B.-K.; et al. Discovery of PSI-352938 and PSI-353661: Purine nucleotide prodrugs for the treatment of HCV. 240th ACS Natl Meet (August 22-26, Boston) 2010, Abst MEDI 19

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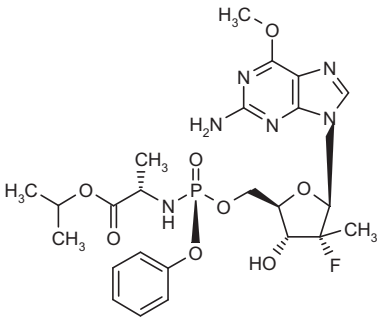


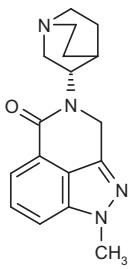
Organization: Albany Molecular Research (AMRI); Celentyx

Condition: Irritable bowel syndrome

Mechanism of Action: 5-HT3 Partial Agonists

Literature: Manning, D.D.; Cioffi, C.L.; Ryan, K.N.; Usyatinsky, A.; et al. Novel 5-HT3 receptor partial agonists for the potential treatment of irritable bowel syndrome. Drugs Fut [21st Int Symp Med Chem (September 5-9, Brussels) 2010] 2010, 35(Suppl. A): Abst PC.073

Integrity Entry Number: 707628



Organization: Array BioPharma; Genentech

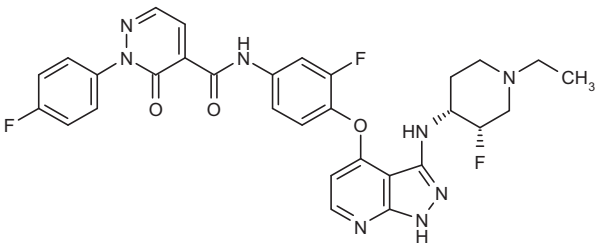
Drug Name: GNE-A

Condition: Cancer

Mechanism of Action: HGF Receptor (c-Met) Inhibitors

Literature: Liederer, B.M.; Baumgardner, M.; Dean, B.; et al. Investigation of metabolism in mice, rats, monkeys, dogs and humans of a novel met kinase inhibitor for species selection for preclinical toxicology studies. 9th Int ISSX Meet (September 4-8, Istanbul) 2010, Abst P347; Liederer, B.M.; Dinkel, V.; Gaudino, J.; Gopaul, S.; Le, H.; Liu, X.; Sutherlin, D.; Wong, S.; Khojasteh, C. Influence of fluorine substitution at the C-3 position on oxidative metabolism of N-ethylpiperidine analogs. 9th Int ISSX Meet (September 4-8, Istanbul) 2010, Abst P346; Liederer, B.M.; Berezhkovskiy, L.M.; Dean, B.; Dinkel, V.; et al. Preclinical profiling, prediction of human pharmacokinetics and pharmacokine tic-pharmacodynamic modeling of a potent and selective met kinase inhibitor. 9th Int ISSX Meet (September 4-8, Istanbul) 2010, Abst P427.

Integrity Entry Number: 707607



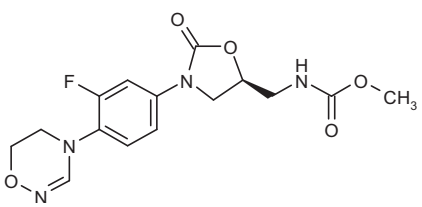
Organization: LegoChem Biosciences

Drug Name: LCB01-577

Condition: Tuberculosis

Literature: Oh, T.; Song, T.; Cho, Y.; Lee, H.; Woo, S.; et al. In vitro anti-tuberculous activity of new oxazolidinones against drug resistance tuberculosis. 50th Intersci Conf Antimicrob Agents Chemother (ICAAC) (September 12-15, Boston) 2010, Abst F1-2144

Integrity Entry Number: 708705



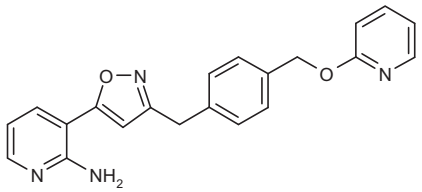
Organization: Eisai

Drug Name: E-1210

Condition: Infection, fungal

Literature: Miyazaki, M.; Horii, T.; Hata, K.; Watanabe, N. In vitro antigungal activity of E1210: A novel antifungal with activity against clinically important yeasts and moulds. 50th Intersci Conf Antimicrob Agents Chemother (ICAAC) (September 12-15, Boston) 2010, Abst F1-840; Watanabe, N.; Horii, T.; Miyazaki, M.; Hata, K. E1210, a new broad-spectrum antifungal, inhibits glycosylphosphatidylinositol (GPI) biosynthesis and effects Candida albicans cell characteristics. 50th Intersci Conf Antimicrob Agents Chemother (ICAAC) (September 12-15, Boston) 2010, Abst F1-841; Hata, K.; Miyazaki, M.; Horii, T.; Watanabe, N. Efficacy of E1210, a new broad-spectrum antifungal, in murine models of oropharyngeal candidiasis, disseminated candidiasis, and pulmonary aspergillosis. 50th Intersci Conf Antimicrob Agents Chemother (ICAAC) (September 12-15, Boston) 2010, Abst F1-842; Horii, T.; Okubo, M.; Miyazaki, M.; Hata, K.; et al. In vivo pharmacodynamic correlates of success for E1210 treatment of disseminated candidiasis. 50th Intersci Conf Antimicrob Agents Chemother (ICAAC) (September 12-15, Boston) 2010, Abst F1-843; Okubo, M.; Toritsuka, N.; Horii, T.; Hata, K.; et al. Preclinical pharmacokinetics and toxicology of E1210, a new broad-spectrum antifungal. 50th Intersci Conf Antimicrob Agents Chemother (ICAAC) (September 12-15, Boston) 2010, Abst F1-844

Integrity Entry Number: 666392



ONE TO WATCH

Detox with plastic antibodies

Plastic antibody nanoparticles could be synthesized to specifically target almost any blood-borne toxin, and so be used to create a detoxifying serum for removing bacterial toxins or the noxious agents in various venoms.

Plastic antibodies mimic natural antibodies by targeting molecules with high affinity by interaction of their complementary surfaces. They are usually made by molecular imprinting of a monomer solution containing small amounts of the target molecule during polymerization, which results in a polymer network pocked with complementary binding sites for the target.

Now, Kenneth Shea of the University of California, Irvine, and colleagues in the U.S. and Japan have published details of a novel nanoparticle (NP) plastic antibody (4). Their synthesis combines molecular imprinted polymer (MIP) plastic antibody production and monomer optimization strategy. "We have developed methods for synthesizing protein-sized polymer particles with a binding affinity and selectivity comparable to those of natural antibodies by combining MIP nanoparticle synthesis with a functional monomer optimization strategy", Shea explains. The first step involved testing a small library of nanoparticles that might have activity by virtue of their complementary structure relative to the biological target. "The affinity of each NP for the biological target is evaluated, and the composition of subsequent NP generations is adjusted to enhance the specificity", Shea and colleagues add. The nanoparticles are polymerized with the imprinting target, peptide or epitope to produce plastic antibodies with binding affinity, selectivity and particle size comparable to natural antibodies.

They have successfully demonstrated the detoxifying efficacy of this plastic antibody in living mice. The team demonstrated that their plastic antibodies can capture and clear a target peptide toxin, melittin, from the bloodstream, reducing mortality in the mice and significantly diminishing peripheral toxic symptoms. Shea adds that, "Coupled with their biocompatibility and nontoxic characteristics, plastic antibodies offer the potential for neutralizing a wide range of biomacromolecules in vivo."

REFERENCES

1. Preville, C., Mascitti, V. *Syntheses of dioxa-bicyclo [3.2.1] octane-2,3,4-triol derivative SGLT2 inhibitors*. 240th ACS Natl Meet (Aug 22-26, Boston) 2010, Abst ORGN 930.
2. Walker, J.M., Huang, S.M., Strangman, N.M., Tsou, K., Sañudo-Peña, M.C. *Pain modulation by release of the endogenous cannabinoid anandamide.* Proc Natl Acad Sci U S A 1999, 96(21): 12198-203.
3. Ahn, K., Stevens, R.C., Cravatt, B.F. et al. *Discovery and characterization of a highly selective FAAH inhibitor that reduces inflammatory pain.* Chem Biol 2009, 16(4): 411-20.
4. Hoshino, Y., Koide, H., Urakami, T., Kanazawa, H., Kodama, T., Oku, N., Shea, K.J. *Recognition, neutralization, and clearance of target peptides in the bloodstream of living mice by molecularly imprinted polymer nanoparticles: A plastic antibody*. J Am Chem Soc 2010, 132(19): 6644-5.