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# THE CUTTING EDGE OF CHEMISTRY

## A PHARMA MATTERS REPORT - NOVEMBER 2011

*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.*

**CONTENTS**



### ORGANIC SYNTHESIS SCHEME SHOWCASE

#### Reshaping Roche's nutlins synthesis

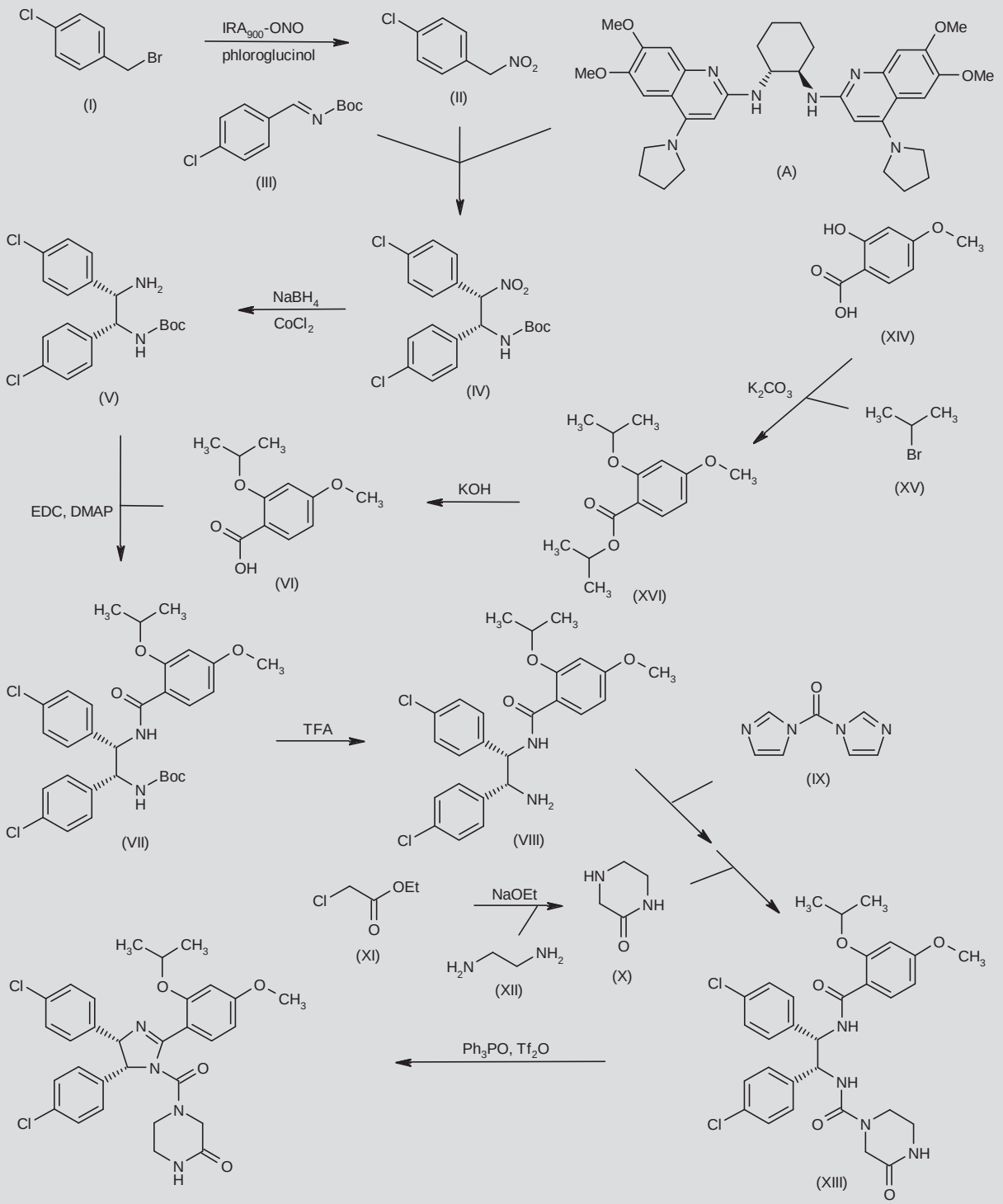
The nutlins are *cis*-imidazoline analogues that were first identified at Hoffmann-La Roche by screening of a chemical library. These small molecules inhibit the interaction of the tumor suppressor p53 and its negative regulator p53-binding protein Mdm2, which is overexpressed in many forms of cancer. This restarts programmed cell death, or apoptosis, in cancer cells, thus preventing uncontrolled tumor growth.

Of the first three members of the series, nutlin-3, *cis*-4-[4,5-bis(4-chlorophenyl)-2-(2-isopropoxy-4-methoxyphenyl)-4,5-dihydro-1*H*-imidazol-1-ylcarbonyl]piperazin-2-one, has become the focus of much recent research (1). The levorotatory enantiomer is 10-fold more potent in cellular assays than its dextrorotatory counterpart. Its efficacy has been extensively proven in vitro and in vivo, alone and in combination with other cancer chemotherapeutics. (–)-Nutlin-3 remains a paradigmatic probe for cell biology research (2).

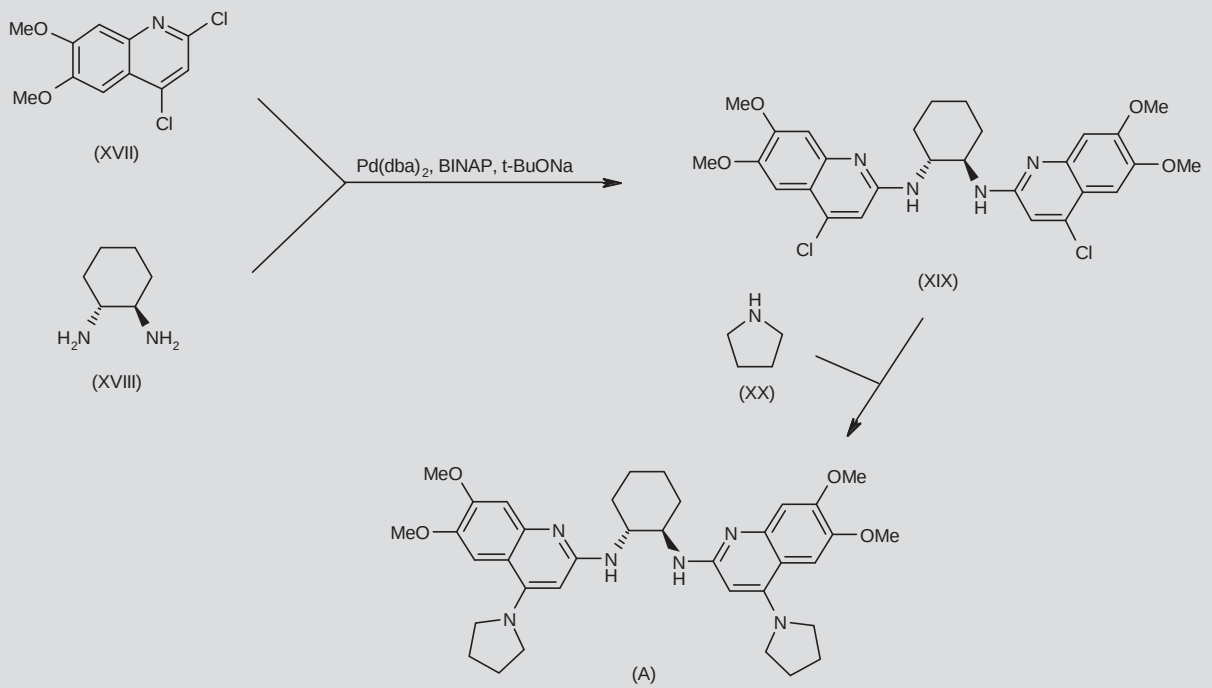
Further development and structure–activity relationship (SAR) studies will rely on the development of novel and more efficient synthetic approaches to the parent compound. The eutomer has been accessed by preparing the racemate and subsequently resolving it by supercritical chiral high-performance liquid chromatography (HPLC) (3). The synthesis now developed by Tyler Davis and Jeffrey Johnston of Vanderbilt University in Nashville, Tennessee, paves the way into the enantioselective arena of nutlin synthesis (4).

The chemists succeeded in developing the first highly diastereo- and enantioselective additions of aryl nitromethanes to aryl aldimines, which they applied to the synthesis of (–)-nutlin-3. The approach involved identifying and optimizing an electron-rich chiral bis(amidine) catalyst for the key aza-Henry transformation, accomplished by screening a range of possible candidates developed in earlier work by the team. Importantly, the team notes that catalytic enantioselective aza-Henry reactions with aryl nitromethanes had remained elusive, with two earlier attempts offering only low enantio- and diastereoselectivity despite the high stereoselection seen with other nitroalkanes.

**Synthesis Scheme for Nutlin (Part 1)**



**Synthesis Scheme for Nutlin (Part 2)**




The Davis and Johnston synthesis has provided access to thus far unavailable spectroscopic and analytical data on (–)-nutlin-3. They suggest that their reaction scheme should expand the repertory of nutlin-type probes and potentially fuel the development of a practical synthesis for drug development. The key stilbene *cis*-diamine intermediate might act as the fulcrum for the syntheses of analogues.

Testament to the importance of this intriguing class of compounds, with their ability to remedy broken apoptosis pathways, is that one member of the *cis*-imidazoline family (5), the Roche compound RG-7112, is currently undergoing phase I clinical trials (6).

*Integrity Entry Number*: 360069

## SCAFFOLDS ON THE MOVE

Novel chemical scaffolds with biological activity underpin major advances in medicinal chemistry. In this issue, a wide range of new skeletons illustrate newly synthesized or natural product-derived templates that can lay the groundwork for the discovery of new therapeutic agents.

### Brain-penetrating scaffold for Alzheimer's disease research

A functional high-throughput screening allowed for the identification of VU-0108370 as a novel indole scaffold with weak activity against the acetylcholine muscarinic $M_1$ receptor. SAR studies around the initial hit suggested that both the oxazole-amide and the *N*-benzyl group are essential for activity. The most potent compound in the series, the brain-penetrant $M_1$ receptor positive allosteric modulator ML-169, is being further studied in preclinical models of Alzheimer's disease and schizophrenia.

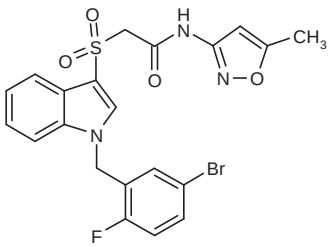
*Therapeutic Group*: Treatment of Alzheimer's Dementia; Pharmacological Tools

*Mechanism of Action*: Muscarinic Acetylcholine M1 Allosteric Modulators

*Source*: Reid, P.R.; Bridges, T.M.; Sheffler, D.J.; et al. Discovery and optimization of a novel, selective and brain penetrant M(1) positive allosteric modulator (PAM): The development of ML169, an MLPCN probe. Bioorg Med Chem Lett 2011, 21(9): 2697

*Organization*: Vanderbilt University

*Integrity Entry Number*: 735039



**A cage for HIV protease**

Researchers at AstraZeneca have reported the first pentacycloundecane (PCU) peptide-based HIV protease inhibitors. The bulky cage-like PCU structure should contribute to enhanced activity and delayed biodegradation, and it was expected to be well accommodated in the S1 and S1′ sub-binding sites of HIV protease. Indeed, a new compound with low nanomolar activity was identified. PCU-EAIS, a conjugate of the natural HIV protease substrate peptide FEAIS, was active against drug-resistant wild-type C South African HIV protease. The work could trigger wider development of cage peptide inhibitors against many other proteases already identified as therapeutic targets.

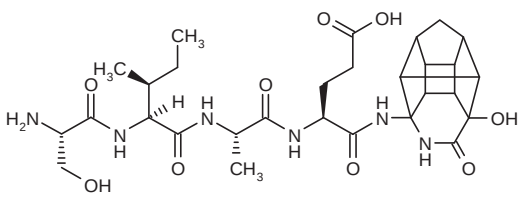
*Therapeutic Group*: Anti-HIV Agents

*Mechanism of Action*: HIV Protease Inhibitors

*Source*: Makatini, M.M.; Petzold, K.; Sriharsha, S.N.; et al. Pentacycloundecane-based inhibitors of wild-type C-South African HIV-protease. Bioorg Med Chem Lett 2011, 21(8): 2274

*Organization*: AstraZeneca

*Integrity Entry Number*: 735017



**Accidental antiobesity drugs**

A serendipitous discovery by scientists at Novo Nordisk has led to a new class of agonists with submicromolar potency for melanocortin $MC_1$ and $MC_4$ receptors. The cyclophane-containing compounds, resulting from an unexpected side reaction, exhibit certain selectivity over the $MC_3$ and $MC_5$ receptors and have demonstrated in vivo efficacy as therapeutic drugs for obesity.

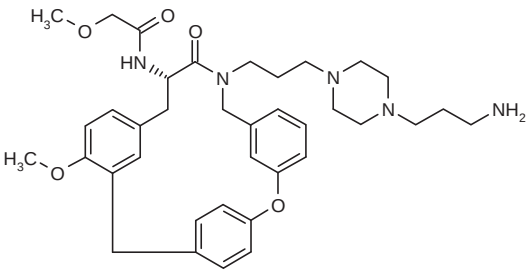
*Therapeutic Group*: Antiobesity Drugs

*Mechanism of Action*: Melanocortin MC1 Receptor Agonists

*Source*: Conde-Frieboes, K.; Ankersen, M.; Breinholt, J.; Hansen, B.S.; Raun, K.; Thogersen, H.; Wulff, B.S. Serendipitous discovery of a new class of agonists for the melanocortin 1 and 4 receptors and a new class of cyclophanes. Bioorg Med Chem Lett 2011, 21(5): 1459

*Organization*: Novo Nordisk

*Integrity Entry Number*: 734040



**Pegging inflammation on novel imidazoquinolines**

Imidazoquinolines represent a novel structural class of microsomal prostaglandin E synthase 1 (MPGES-1) inhibitors for antiinflammatory applications, according to researchers at Dainippon Sumitomo Pharma. MPGES-1 has recently attracted interest as a target for the treatment of various inflammatory disorders, given its connection with cyclooxygenase-2 (COX-2) and proinflammatory stimuli. SAR studies around the initial hit revealed that a hydroxyl group at the C4 position of the imidazoquinoline scaffold was key to high activity and identified a lead with subnanomolar potency and a suitable profile against cytochrome P450 inhibition.

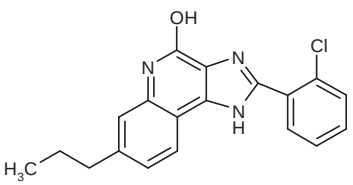
*Therapeutic Group*: Treatment of Inflammation

*Mechanism of Action*: Microsomal Prostaglandin E Synthase 1 (MPGES-1) Inhibitors

*Source*: Shiro, T.; Nagata, H.; Kakiguchi, K.; Inoue, Y.; Masuda, K.; Tobe, M. Synthesis and SAR study of imidazoquinolines as a novel structural class of mPGES-1 inhibitors. 241st ACS Natl Meet (March 27-30, Anaheim) 2011, Abst MEDI 60

*Organization*: Dainippon Sumitomo Pharma

*Integrity Entry Number*: 730549



**Pinning down the role of $P2Y_{14}$**

The exact role of the $P2Y_{14}$ receptor is still undetermined, and agonists or antagonists so far have been limited to nucleotide derivatives. Now, Merck Frosst has reported the synthesis and SAR of two classes of non-nucleotide $P2Y_{14}$ receptor antagonists. Compounds with either a dihydropyridopyrimidine or a naphthoic acid core have been identified that exhibit low nanomolar potency for the receptor. Leads from each series are endowed with a pharmacokinetic profile suitable for in vivo studies, which would contribute to the elucidation of the physiological function of $P2Y_{14}$.

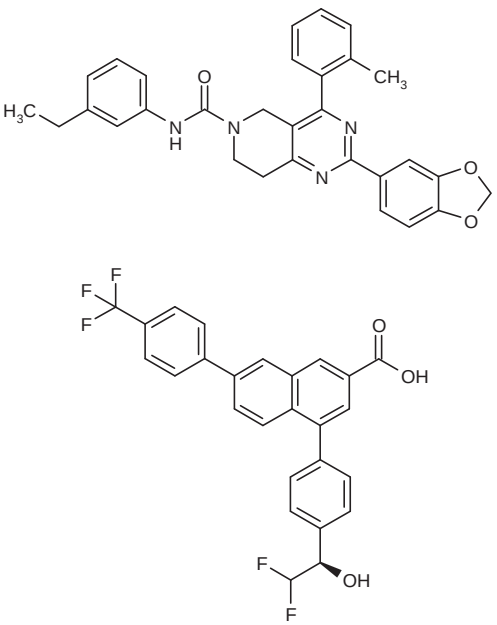
*Therapeutic Group*: Immunomodulators; Pharmacological Tools

*Mechanism of Action*: P2Y14 Receptor Antagonists

*Source*: Guay, D.; Beaulieu, C.; Belley, M.; et al. Synthesis and SAR of pyrimidine-based, non-nucleotide P2Y14 receptor antagonists. Bioorg Med Chem Lett 2011, 21(10): 2832; Gauthier, J.Y.; Belley, M.; Deschenes, D.; et al. The identification of 4,7-disubstituted naphthoic acid derivatives as UDP-competitive antagonists of P2Y14. Bioorg Med Chem Lett 2011, 21(10): 2836

*Organization*: Merck Frosst

*Integrity Entry Numbers*: 735337; 662279



**First and second series against inflammation**

AstraZeneca has identified two novel series of formylpeptide receptor FPR1 (fMLP) antagonists. The compounds were identified as new chemical starting points through high-throughput screening of the company's collection of 800,000 compounds. Representative of each series are small molecules based on methionine benzimidazole and diamide structures. As FPR1 is involved in the inflammatory response, antagonizing it might have potential application in the treatment of inflammatory disorders. Activity of leads from both series was confirmed in human neutrophils, making the leads in vitro validation tools to further study the target receptor.

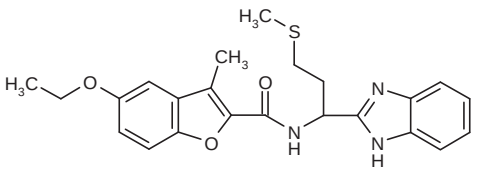
*Therapeutic Group*: Treatment of Inflammation

*Mechanism of Action*: Formylpeptide Receptor FPR1 Antagonists

*Source*: Unitt, J.; Fagura, M.; Phillips, T.; et al. Discovery of small molecule human FPR1 receptor antagonists. Bioorg Med Chem Lett 2011, 21(10): 2991

*Organization*: AstraZeneca

*Integrity Entry Number*: 735360



**Unexpected skeletons for arthritis and lupus**

Pfizer researchers have identified and optimized a series of compounds that act as interleukin-1 receptor-associated kinase 4 (IRAK-4) inhibitors as promising leads in this area. The compounds have an indolo[2,3-*c*]quinoline skeleton and are the unexpected result of research into the Toll-like receptor signaling mediated by the serine/threonine-protein kinase IRAK-4. The team explains that downstream signaling from IRAK-4 results in increased production of TNF-α and IFN-α, thought to be important in rheumatoid arthritis and lupus, respectively.

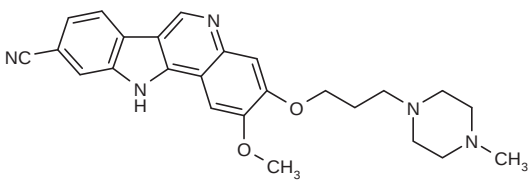
*Therapeutic Group*: Treatment of Rheumatoid Arthritis; Agents for Systemic Lupus Erythematosus

*Mechanism of Action*: Interleukin-1 Receptor-Associated Kinase 4 (IRAK-4) Inhibitors

*Source*: Tumey, L.N.; Rao, V.; Bhagirath, N.; et al. Identification and optimization of a series of indolo[2,3-c]quinoline IRAK4 inhibitors. 241st ACS Natl Meet (March 27-30, Anaheim) 2011, Abst MEDI 3

*Organization*: Pfizer

*Integrity Entry Number*: 725270



**Two-pronged antiviral attack against HIV**

Scientists at the University of Minnesota and the National Institutes of Health have identified 3-hydroxypyrimidine-2,4-diones as a scaffold that can inhibit HIV integrase. The new molecular scaffold contains an *N*-hydroxyimide functionality and can inhibit both reverse transcriptase and integrase in HIV. The team describes how the compound was designed rationally based on 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymine (HEPT) non-nucleoside reverse transcriptase inhibitors (NNRTIs). Alongside the existing benzyl group, the *N*-hydroxyimide feature satisfies the major structural requirements for integrase binding, while not interfering with the interaction with reverse transcriptase, the team adds. The dual inhibition of two critical HIV enzymes bodes well for activity against the virus.

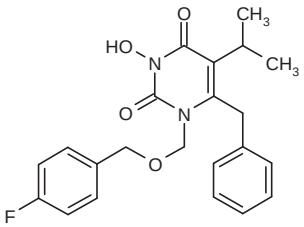
*Therapeutic Group*: Anti-HIV Agents

*Mechanism of Action*: HIV Integrase Inhibitors; Reverse Transcriptase Inhibitors

*Source*: Tang, J.; Maddali, K.; Metifiot, M.; Sham, Y.Y.; Vince, R.; Pommier, Y.; Wang, Z. 3-Hydroxypyrimidine-2,4-diones as an inhibitor scaffold of HIV integrase. J Med Chem 2011, 54(7): 2282

*Organization*: National Institutes of Health (NIH); University of Minnesota

*Integrity Entry Number*: 735971



## NEW MOLECULAR MECHANISMS OF ACTION

The mode of action of any product is key to understanding how to improve compound design and how to find more potent leads with fewer potential side effects. We showcase a range of fascinating compounds in this issue.

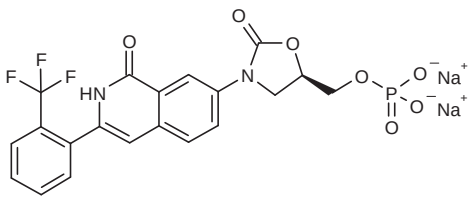
MICROTUBULE-ASSOCIATED PROTEIN 4 (MAP-4) INHIBITORS

*Main Related Conditions*: Cancer

*Organization*: Chugai Pharmaceutical

*Drug Name*: Phosphate-CH-4938056

*Integrity Entry Number*: 698007

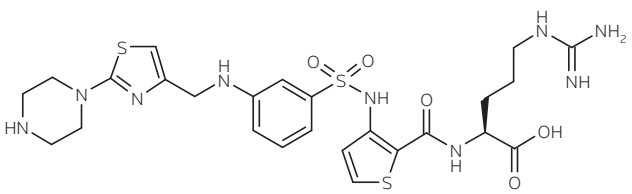


NEUROPILIN-1 (*NRP1*) ANTAGONISTS

*Main Related Conditions*: Viral Infection; Cancer; Neurodegeneration; Immunological Disorders

*Organization*: Ark Therapeutics

*Integrity Entry Number*: 725342

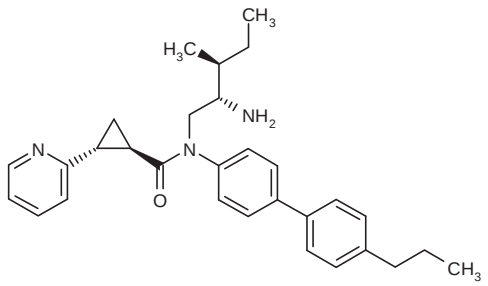


G PROTEIN-COUPLED RECEPTOR GPR88 AGONISTS

*Main Related Conditions*: Cognitive Disorders; Psychiatric Disorders; Obesity; Diabetes

*Organization*: Bristol-Myers Squibb; Lexicon Pharmaceuticals

*Integrity Entry Number*: 728409

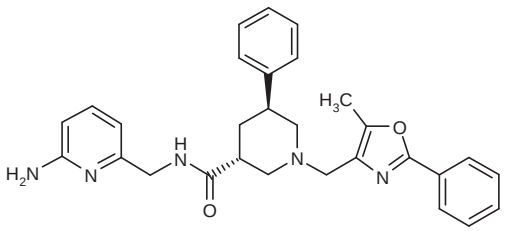


PHOSPHODIESTERASE PDE8B INHIBITORS

*Main Related Conditions*: Diabetes

*Organization*: Pfizer

*Integrity Entry Number*: 729739



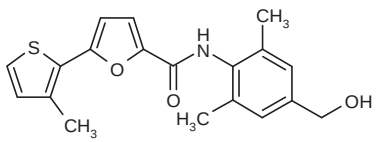
LYSOPHOSPHOLIPID $S1P_4$ RECEPTOR ANTAGONISTS

*Main Related Conditions*: Thrombosis

*Organization*: Scripps Research Institute

*Drug Name*: CYM-50374

*Integrity Entry Number*: 732675

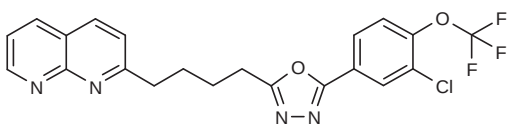


SUCCINATE RECEPTOR 1 (*SUCNR1*, *GPR91*) ANTAGONISTS

*Main Related Conditions*: Agents for Diabetic Nephropathy; Treatment of Hypertension

*Organization*: Advinus Therapeutics; Merck &Co.

*Integrity Entry Number*: 732686



## THE STARTING LINE

*The Starting Line* pinpoints new molecular entities (NMEs) ready to progress into the R&D arena. In this issue we look at some highlights from the 242nd ACS National Meeting (August 28-September 1, Denver).

*Organization*: Merck & Co.

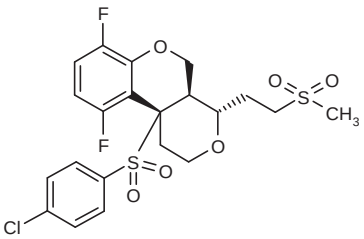
*Product*: GSI-1

*Condition*: Dementia of the Alzheimer's Type

*Mechanism of Action*: gamma-Secretase Inhibitors

*Literature*: Wu, W.-L.; Asberom, T.; Bara, T.; et al. Discovery of a potent and selective gamma-secretase inhibitor for the treatment of Alzheimer's disease. 242nd ACS Natl Meet (August 28-September 1, Denver) 2011, Abst MEDI 30

*Integrity Entry Number*: 742718



*Organization*: Pfizer

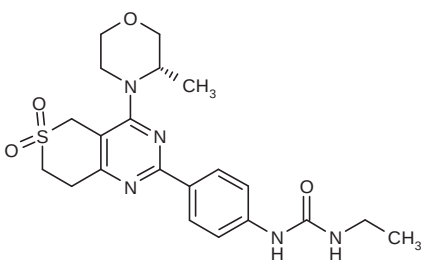
*Product:* PF-051399962

*Condition*: Cancer

*Mechanism of Action*: Mammalian Target of Rapamycin (mTOR) Inhibitors

*Literature*: Liu, K.K.-C.; Bailey, S.; Li, C.; Dinh, D.; Zou, A.; Li, J.; Yu, X.-H.; Wells, P.A. Potent and selective cyclic sulfones as mTOR selective inhibitors. 242nd ACS Natl Meet (August 28-September 1, Denver) 2011, Abst MEDI 37

*Integrity Entry Number*: 742783



*Organization*: Takeda

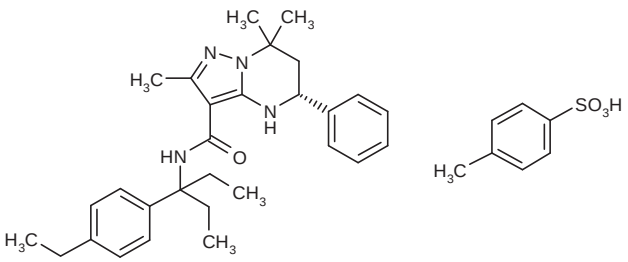
*Product*: TAK-075

*Condition*: Osteopetrosis

*Mechanism of Action*: Calcium-Sensing Receptor (CaS) Antagonists

*Literature*: Yoshida, M.; Mori, A.; Morimoto, S.; et al. Novel and potent calcium sensing receptor antagonists: Discovery of TAK-075 as an orally active bone anabolic agent. 241st ACS Natl Meet (March 27-30, Anaheim) 2011, Abst MEDI 265; Yoshida, M.; Mori, A.; Morimoto, S.; Kotani, E.; Oka, M.; Notoya, K.; Makino, H.; Ono, M.; Shirasaki, M.; Tada, N.; Fujita, H.; Ban, J.; Ikeda, Y.; Kawamoto, T.; Goto, M.; Kimura, H.; Baba, A.; Yasuma, T. Novel and potent calcium-sensing receptor antagonists: Discovery of (5R)-N-[1-ethyl-1-(4-ethylphenyl)propyl]-2,7,7-trimethyl-5-phenyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine-3-carboxamide monotosylate (TAK-075) as an orally active bone anabolic agent. Bioorg Med Chem 2011, 19(6): 1881

*Integrity Entry Number*: 726114



*Organization*: RaQualia

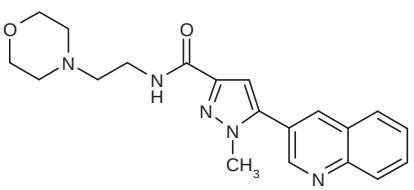
*Product*: RQ-00202065

*Condition*: Inflammatory Bowel Disease

*Mechanism of Action*: 5-HT2B Receptor Antagonists

*Literature*: Ohashi, Doi, K.; Ferens, D.; Takahashi, N.; et al. Investigation of roles of 5-HT2B receptors on colonic compliance in the anaesthetized rat. Dig Dis Week (May 7-10, Chicago) 2011, MO1320

*Integrity Entry Number*: 730548



*Organization*: Beth Israel Deaconess Medical Center; Boston University School of Medicine; Harvard Medical School; University of Texas at Dallas

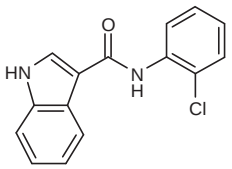
*Product*: LDN-0187608

*Condition*: Dementia of the Alzheimer's Type; Multiple Sclerosis

*Mechanism of Action*: KL Expression Enhancers

*Literature*: Abraham, C.R.; King, G.; Glicksman, M.; Sloane, J.A.; Kuro-O, M.; Chen, C.-D. Klotho enhancers as novel neuroprotective therapeutics for Alzheimer's disease and white matter degeneration. 10th Int Conf Alzheimer Parkinson Dis (AD/PD) (March 09-13, Barcelona) 2011, Abst 1754

*Integrity Entry Number*: 724456



*Organization*: Torrent Pharmaceuticals

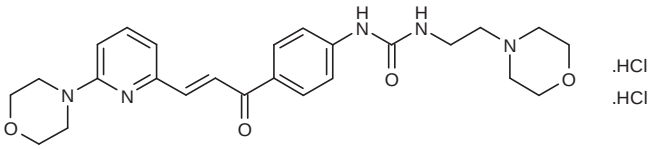
*Product*: TRC-051384

*Condition*: Ischemic Stroke

*Mechanism of Action*: Heat Shock 70 kDa Protein (HSP70) Inducers

*Literature*: Mohanan, A.; Deshpande, S.; Jamadarkhana, P.G.; Kumar, P.; Gupta, R.C.; Chauthaiwale, V.; Dutt, C. Delayed intervention in experimental stroke with TRC051384 - A small molecule HSP70 inducer. Neuropharmacology 2011, 60(6), 991

*Integrity Entry Number*: 731810



*Organization*: Zalicus

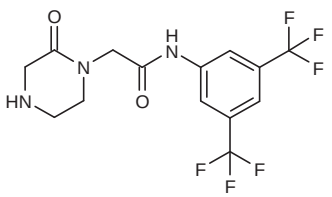
*Product*: Z-123212

*Condition*: Pain

*Mechanism of Action*: Ca(v)3.2 Channel Blockers; Na(v)1.7 Sodium Channel Blockers; Na(v)1.8 Sodium Channel Blockers

*Literature*: Hildebrand, M.E.; Smith, P.L.; Bladen, C.; et al. A novel slow-inactivation-specific ion channel modulator attenuates neuropathic pain. Pain 2011, 152(4), 833

*Integrity Entry Number*: 725828



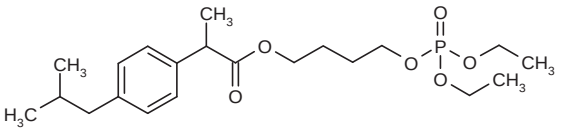
*Organization*: Medicon

*Product*: MDC-917

*Condition*: Cancer; Rheumatoid Arthritis

*Literature*: Xie, G.; Sun, Y.; Nie, T.; Mackenzie, G.G.; Huang, L.; Kopelovich, L.; Komninou, D.; Rigas, B. Phospho-ibuprofen (MDC-917) is a novel agent against colon cancer: Efficacy, metabolism, and pharmacokinetics in mouse models. J Pharmacol Exp Ther 2011, 337(3): 876; Huang, L.; Mackenzie, G.; Ouyang, N.; Sun, Y.; Xie, G.; Johnson, F.; Komninou, D.; Rigas, B. The novel phospho-non-steroidal anti-inflammatory drugs, OXT-328, MDC-22 and MDC-917, inhibit adjuvant-induced arthritis in rats. Br J Pharmacol 2011, 162(7): 1521

*Integrity Entry Number*: 732542



*Organization*: Bristol-Myers Squibb

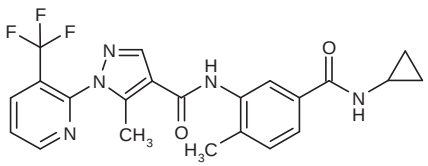
*Product*: BMS-626531

*Condition*: Arthritis

*Mechanism of Action*: TNF-alpha Production Inhibitors; MAPK p38 Inhibitors

*Literature*: Dyckman, A.J.; Li, T.; Hynes, J.; et al. Discovery of BMS-626531, a potent and selective inhibitor of p38alpha MAP kinase as a clinical candidate for the treatment of inflammatory diseases. 242nd ACS Natl Meet (August 28-September 1, Denver) 2011, Abst MEDI 7

*Integrity Entry Number*: 633421



*Organization*: Johnson & Johnson

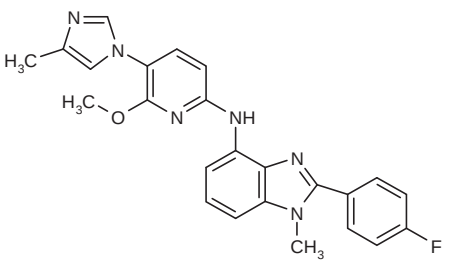
*Product*: JNJ-42601572

*Condition*: Dementia of the Alzheimer's Type

*Mechanism of Action*: beta-Amyloid (Abeta) Production Inhibitors; gamma-Secretase Modulators

*Literature*: Bischoff, F.; Gijsen, H.; Berthelot, D.; et al. Discovery of JNJ-42601572, a gamma-secretase modulator with potent, central activity in mouse and dog. 242nd ACS Natl Meet (August 28-September 1, Denver) 2011, Abst MEDI 3

*Integrity Entry Number*: 707328



## DOWNSIZING PHARMA AND UPGRADING COLLABORATIONS

The pharmaceutical industry is changing rapidly as the larger companies downsize and close sites to cut costs in response to the current economic climate. However, with such changes come new opportunities for the smaller biotechnology and discovery companies, which are already becoming increasingly important in the global sphere. As the likes of AstraZeneca, Pfizer and Novartis now rely less and less on in-house development, the shift is now toward a more innovative environment, where academia and small biotech companies can interact openly.

Collaborations between large pharma companies and these smaller enterprises, and even university departments and their spin-off companies, can help cut the overall risk exposure for the companies and lower investment costs significantly by allowing them to focus on developing only those drugs emerging from small laboratories that already show a great deal of clinical promise. Indeed, long gone are the blockbusters of the 1970s and 1980s, and many of those old stalwarts of the industry are ready to fall off-patent.

Already, GlaxoSmithKline, Pfizer and others have committed to biotech incubators to harvest the fruits of such collaborations. Mark Pepys of University College London recently told the journal *Nature* that: "All the drug companies are looking for a new model." Pepys is a professor of medicine and is himself collaborating with GlaxoSmithKline. Meanwhile, Pfizer announced on June 8, 2011, that it would be working with eight research institutions from the Boston area to search for novel drug candidates. The five-year deal would amount to USD 100 million, significantly less than the upkeep costs of a stand-alone R&D center. The announcement was the third by Pfizer since November 2010.

Martin Lehr, writing in the Osage University Partners Blog, suggests that the recent flurry of collaborative activity "can be attributed to a pharma-wide strategic initiative aimed at addressing a fundamental problem shared among all major pharma companies: a marked decline in revenue growth due to a lack of new innovative products and weak R&D productivity." The spin-offs and investors are also building the new industry model from their own foundations. Stevenage Bioscience Catalyst Campus, for instance, is being built as a unique bioscience community that will foster collaboration between small biotech and life sciences companies and start-ups, and give them access to the expertise, networks and scientific facilities that are more commonly associated with Big Pharma. Critical to the success of such initiatives is the notion of "open innovation". The developers of the campus suggest that such a focus will position the U.K. bioscience sector at the forefront of worldwide discovery.

However, it is still very early in the life cycle of open innovation, and some observers believe that we are still several years away from seeing any significant drugs emerge from the new relationships. Nevertheless, small companies have been collaborating with academia and spin-offs for a while: some drugs start surfacing from these relationships, and we can find some examples in this issue of *The Cutting Edge of Chemistry*.

Starting in 2006, the joint effort between Merck and Advinus in the area of metabolic diseases recently produced a *SUCNR1* antagonist preclinical candidate. The compound, featured in the *New Molecular Mechanisms of Action* section, represents a new mode of action for the treatment of hypertension and nephropathy in diabetes.

The Merck–Advinus collaboration time span from start to disclosure falls pretty much within the expected gap for drug development. With that in mind, we might want to keep a close eye at similarly early-started collaborations, such as the one between Astellas and Kyoto University in immunoregulation, which kicked off in 2007.

Another related example is Z-123212, disclosed by Zalicus. The compound has been developed in collaboration with the University of Calgary. This calcium and sodium channel blocker, presented in *The Starting Line*, has potential as a nonopioid analgesic.

Also within *The Starting Line* section of this issue, the oncolytic drug MDC-917 likewise arose from a collaborative effort, in this case between a spin-off company, Medicon, and Stony Brook University, New York.

The industry is unlikely to ever return to the heyday of regular billion dollar blockbusters pouring down the pipeline. Instead, the new collaborations between Big Pharma and highly innovative spin-offs and academia have the potential to open up new profit streams in the areas of post-genomic discovery and personalized medicine, and in nontraditional areas revealed by an aging population.

Further to this article, Thomson Reuters has produced a report commemorating the 2011 International Year of Chemistry, titled *"The Changing Role of Chemistry in Drug Discovery"*. The report explores many of the themes of this article in greater depth, with the input from several key pharmaceutical industry players. It examines how life in drug discovery has changed over the last 10 years and how it will continue to change and adapt in the future. With data taken from *Integrity* to support the findings, the report comments on trends, such as the relative rise of biologics to new chemical entities and the growing importance of drug repurposing. It also examines how the role of the chemist is changing, the skills that chemists will need, and where the chemists of the future will work.

Contact us at integritysupport@thomsonreuters.com to request the "*The Changing Role of Chemistry in Drug Discovery*" report.

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