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THE CUTTING EDGE OF CHEMISTRY

A PHARMA MATTERS REPORT – APRIL 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

Long-sought lomaiviticin aglycone framed

Lomaiviticin A was first isolated in 2001 from the actinomycete *Micromonospora lomaivitiensis*, which was itself isolated from the marine ascidian *Polysyncraton lithostrotum* by Wyeth-Ayerst and University of Utah scientists (1). The skeleton represents a unique symmetric dimeric diazobenzo[*b*]fluorine glycoside that tests revealed to have antibiotic and antitumor activity, as well as DNA-damaging activity. Cytotoxicity against a number of cancer cell lines was determined and IC_{50} values of 0.01-143 nM were obtained.

The cytotoxicity profile of the compound is particularly intriguing because it differs markedly from that of two well-known chemotherapeutic agents: doxorubicin (Adriamycin®) and mitomycin C. Doxorubicin is thought to work by a mechanism involving DNA intercalation, and mitomycin C through DNA cross-linking. Lomaiviticin A exploits a different mechanism of interaction with DNA molecules associated with the diazobenzo[*b*]fluorine ring system that constitutes the aglycone part. Research suggests that the interaction occurs through the interaction of the molecule's azo groups with DNA molecules (1, 2).

Lomaiviticin A's novel mode of action and intriguing biological activity have, as with many such natural products, led to a great deal of effort being applied to design a route of total synthesis, and specifically for the aglycone part of the compound. Researchers have made several advances in the years since its discovery. In 2006, for instance, Nicolaou and colleagues in the U.S. carried out a stereocontrolled synthesis of a model core system for lomaiviticin A and B exploiting a Michael addition of a dimethyl malonate to a dimeric enone (3).

Zhang and colleagues succeeded in 2008 in a stereocontrolled assembly of the two-ring C3/C3' dideoxy core of lomaiviticin A and B (4). That same year, Krygowski et al. attained an enantioselective synthesis of the central four-ring system (5). In 2009, Nicolaou's team took another step toward the goal with a synthesis of the monomeric unit of the aglycone (6). Later that year, Herzon and colleagues published a synthesis of the fully glycosylated cyclohexenone ring (7).

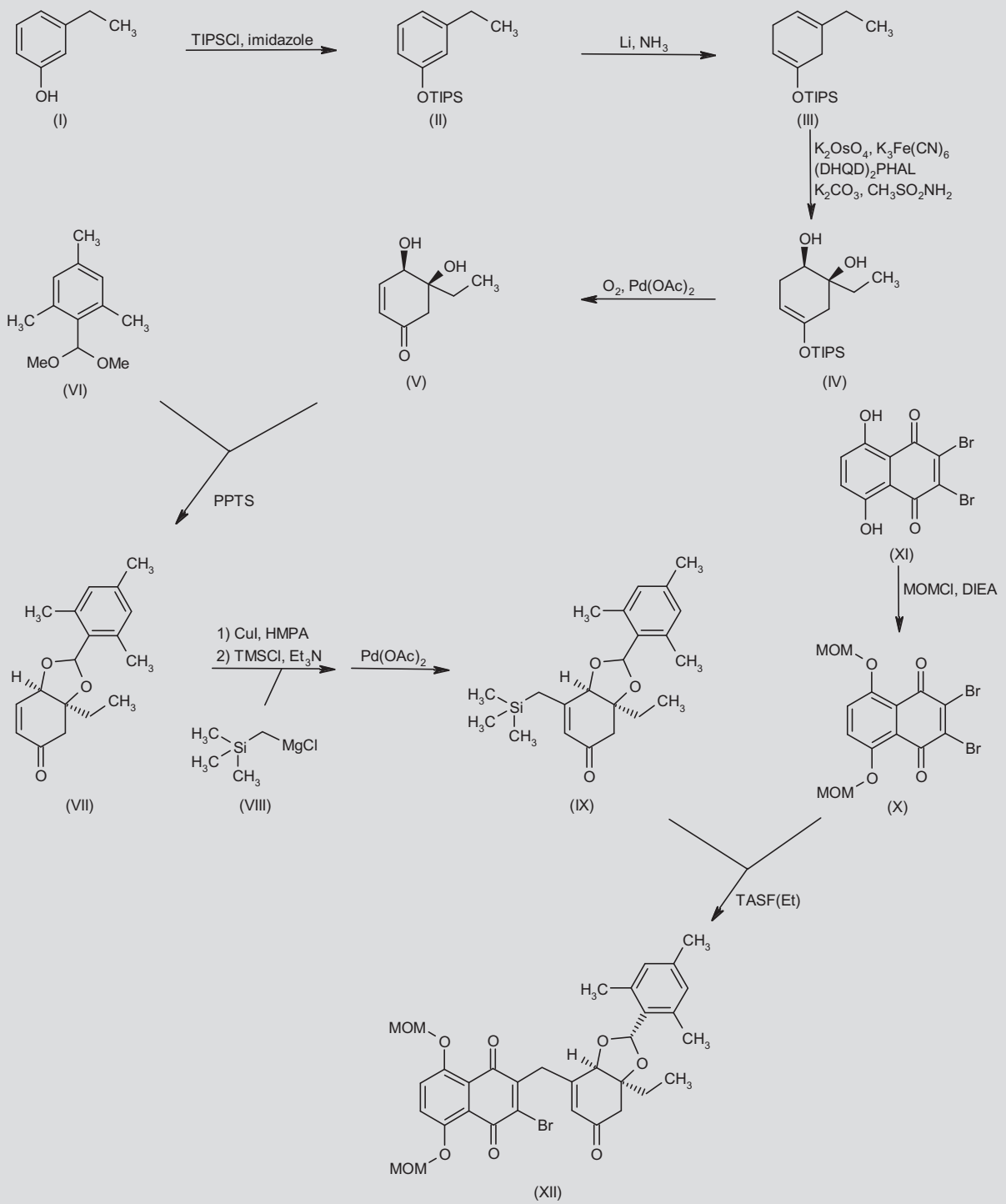
Shair and Morris then obtained the protected pyrrolosamine glycal of lomaiviticin A by a synthetic route involving epimerization of an L-threonine derivative (8), and in 2010, Shair published an enantioselective synthesis of the natural product's aglycone full carbon skeleton (9).

Herzon and coworkers completed the first synthesis of the aglycone of the lomaiviticins in just 11 steps (10). Their synthetic route has several highlights. The first is the preparation of the monomeric diazobenzo[*b*]fluorine ring system in eight steps using readily available starting materials. They point out that several of the steps can be carried out enantioselectively and in gram quantities. The scheme is also convergent and versatile, which means that it is primed for making derivatives. Secondly, they formed the dimer by building the necessary carbon–carbon bond under oxidative conditions, after having tested more than 1,500 different sets of reaction conditions.

Finally, Herzon's team reached the coupling product after a three-step sequence involving protection of the monomer, C–C bond formation through oxidative coupling by treatment with manganese tris(hexafluoroacetylacetonate), and lastly, deprotection.

The researchers explain that they obtained two coupling products in a ratio of 2 to 1, in which the desired dimer was the major component. Isolation of the protected dimer followed by deprotection under carefully optimized conditions led to the lomaiviticin agly-

Synthesis Scheme for Lomaiviticin A Aglycone (Part 1)



cone and an open-chain ketone isomer, which slowly converted to the cyclic counterpart.

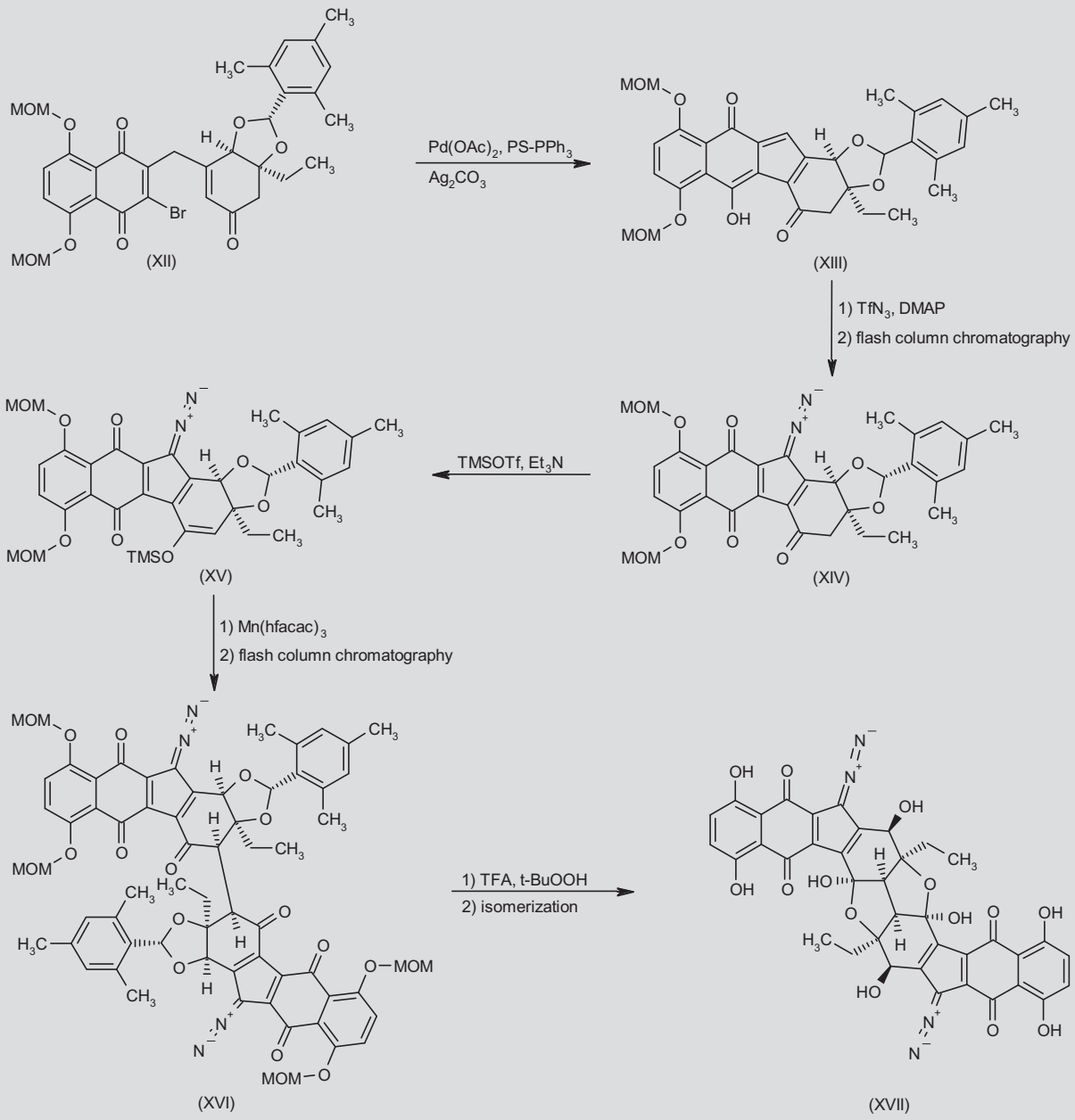
The researchers suggest that their synthetic route will facilitate additional biological testing of the lomaiviticins and their derivatives as putative anticancer drugs.

Integrity Entry Number: 676053

SCAFFOLDS ON THE MOVE

New chemical scaffolds are the basis of major advances in medicinal chemistry. In fact, the discovery of a new chemical skeleton with a clearly associated biological activity represents the starting point for the lead generation–lead optimization process. This article illustrates newly synthesized or natural product-derived templates that lay the groundwork for the discovery of new therapeutic agents.

Synthesis Scheme for Lomaiviticin A Aglycone (Part 2)



Indolinones identified for fibrotic disease and cancer

Scientists at Boehringer Ingelheim have used high-throughput screening to identify indolinones as inhibitors of the TGF-beta receptor type-1 (TGFR-1). They found a lead compound and a cluster of five derivatives with what they call double-digit nanomolar activity in their phosphorylation assay. The compounds could offer hope for more targeted treatment of fibrotic diseases and cancer, the team says. X-ray crystallography has guided subsequent investigation of the lead compound, and efficacy at the cellular level has been demonstrated. Moreover, extensive profiling against 232 human kinases shows little cross-reactivity, which bodes well for limited side effects.

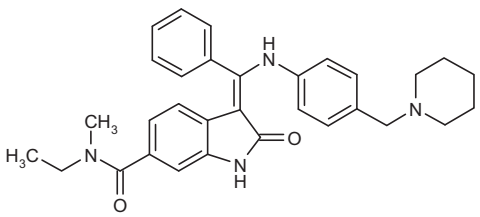
Therapeutic Group: Treatment of Fibrosis; Oncolytic Drugs

Mechanism of Action: Transforming Growth Factor (TGF)-beta Receptor Type I Inhibitors

Source: Roth, G.J.; Heckel, A.; Brandl, T.; et al. Design, synthesis, and evaluation of indolinones as inhibitors of the transforming growth factor beta receptor I (TGFbetaRI). J Med Chem 2010, 53(20): 7287

Organization: Boehringer Ingelheim

Integrity Entry Number: 713202



Effective inhibition of kinase achieved

Calcium/calmodulin-dependent protein kinase type II (CaMK-II) inhibitors represent a potentially useful approach for treating autoimmune diseases. Dainippon Sumitomo Pharma has now discovered a novel series of 5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidines containing a substituted phenyl sulfonamide. The lead compound in the series (depicted here) has 25 times the activity of the known inhibitor KN-93, and 100 times greater selectivity over CaMK-IV, myosin light chain kinase (MLCK), mitogen-activated protein kinase p38 α, serine/threonine-protein kinase c-Akt and protein kinase C (PKC) kinases.

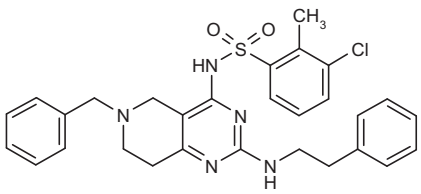
Therapeutic Group: Treatment of Autoimmune Diseases

Mechanism of Action: Calcium/Calmodulin-Dependent Protein Kinase Type II (CaMK-II) Inhibitors

Source: Asano, S.; Komiya, M.; Koike, N.; Koga, E.; Nakatani, S.; Isobe, Y. 5,6,7,8-Tetrahydropyrido[4,3-d]pyrimidines as novel class of potent and highly selective CaMKII inhibitors. Bioorg Med Chem Lett 2010, 20(22): 6696

Organization: Dainippon Sumitomo Pharma

Integrity Entry Number: 700970



Benzoxazole skeleton could target asthma and allergies

Researchers at Ewha Womans University are investigating 5-lipoxygenase (5-LO) inhibitors bearing a benzoxazole scaffold as a bioisostere for benzothiazoles. The enzyme 5-LO is an important target in asthma and allergies, as it is essential for leukotriene formation. The team investigated 14 compounds in the class, which proved active at fractional micromolar concentrations, and found that 2 compounds reduced airways hypersensitivity in mice.

Therapeutic Group: Antiallergy/Antiasthmatic Drugs

Mechanism of Action: 5-Lipoxygenase Inhibitors

Source: Song, H.; Oh, S.R.; Lee, H.K.; Han, G.; Kim, J.H.; Chang, H.W.; Doh, K.E.; Rhee, H.K.; Choo, H.Y. Synthesis and evaluation of benzoxazole derivatives as 5-lipoxygenase inhibitors. Bioorg Med Chem 2010, 18(21): 7580

Organization: Ewha Womans University

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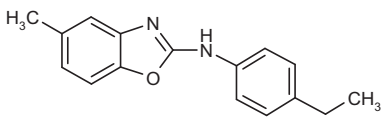


Trishomocubane selectivity for dopamine transporter

An unusual scaffold containing a trishomocubane unit is of interest to researchers at the University of Sydney searching for new drugs for Parkinson's disease and attention deficit hyperactivity disorder (ADHD). The team has found that the structures in the series of *N*-arylalkyl-8-aminopentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecanes can act as ligands for the dopamine transporter. This work is part of a wider search for trishomocubane derivatives with activity on the central nervous system.

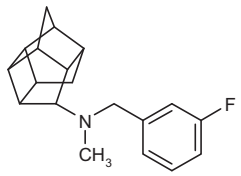
Therapeutic Group: Antiparkinsonian Drugs; Attention Deficit Hyperactivity Disorder (ADHD); Treatment of Substance Dependency

Mechanism of Action: Dopamine Transporter (DAT) Ligands

Source: Banister, S.D.; Moussa, I.A.; Beinat, C.; Reynolds, A.J.; Schiavini, P.; Jorgensen, W.T.; Kassiou, M. Trishomocubane as a scaffold for the development of selective dopamine transporter (DAT) ligands. Bioorg Med Chem Lett 2011, 21(1): 38

Organization: University of Sydney

Integrity Entry Number: 724471



Simplifying hepatitis C treatment

Current treatment for hepatitis C virus requires peginterferon alfa-2a/b and ribavirin, but research trends are turning toward small-molecule therapy targeting viral proteins. Scientists at Virobay have used an SPA (scintillation proximity assay) to carry out high-throughput screening for inhibitors of the RNA-directed RNA polymerase NS5B enzyme, which is involved in a key step of the viral life cycle. Among the hits was a quinolone derivative, with an IC_{50} of 1.15 μM against genotype 1b enzyme. Crystallography revealed that this structural type binds to the allosteric site-II (non-nucleoside inhibitor-site 2, NNI-2) of the enzyme.

Therapeutic Group: Anti-Hepatitis C Virus Drugs

Mechanism of Action: HCV NS5B Polymerase Inhibitors

Source: Kumar, D.V.; Rai, R.; Brameld, K.A.; et al. Quinolones as HCV NS5B polymerase inhibitors. Bioorg Med Chem Lett 2011, 21(1): 82

Organization: Virobay

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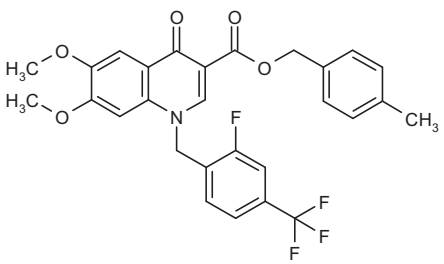


Fluorescent screening alights on glucocorticoid receptor antagonists

Researchers at Merck & Co. have used fluorescent screening to test almost 4 million compounds from Ligand and discovered a novel series of glucocorticoid receptor antagonists that are nonsteroidal in structure. Optimization of these compounds has now led to an improved profile and an orally available heterobiaryl sulfonamide. The compound is stable and selective for the receptor.

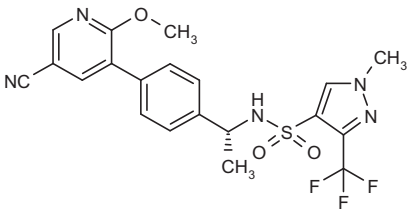
Therapeutic Group: Antidepressants; Anxiolytics; Treatment of Post-traumatic Stress Disorder (PTSD)

Mechanism of Action: Glucocorticoid Receptor (GR) Antagonists

Source: Brown, A.R.; Bosies, M.; Cameron, H.; et al. Discovery and optimization of a selective non-steroidal glucocorticoid receptor antagonist. Bioorg Med Chem Lett 2011, 21(1): 137

Organization: Merck & Co.; Ligand

Integrity Entry Number: 724433



GSK HTS and SAR for anxiety, depression drugs

High-throughput screening (HTS) of the GlaxoSmithKline (GSK) compound collection has led to the identification of a vasopressin V_{1B} receptor antagonist and other neighboring compounds. Structure–activity relationship (SAR) studies led to a group of thiazole sulfonamides with improved selectivity over V_{1A} and oxytocin receptors. The lead is targeted at novel treatments for anxiety and depression.

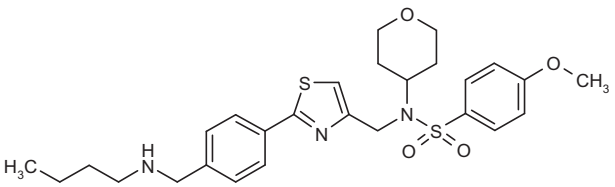
Therapeutic Group: Antidepressants; Anxiolytics

Mechanism of Action: Vasopressin (AVP) V1B Antagonists

Source: Smethurst, C.A.; Borthwick, J.A.; Gaines, S.; Watson, S.; Green, A.; Schulz, M.J.; Burton, G.; Buson, A.A.; Arban, R. The characterization of a novel V1b antagonist lead series. Bioorg Med Chem Lett 2011, 21(1): 92

Organization: GlaxoSmithKline

Integrity Entry Number: 724468



Enhanced cognitive effects with 5-HT_6 receptor ligands

A novel class of 5-HT_6 receptor ligands in the form of *N*[1]-arylsulfonyl-3-piperazinyl indole derivatives has been designed by the Indian company Suven Life Sciences, Ltd. These compounds demonstrate high-affinity antagonist activity at the receptor, with a lead compound exhibiting an IC_{50} of just 310 nM in a functional assay. The researchers explain that it shows enhanced cognitive effects when tested in laboratory rodents, thus highlighting its potential as a development candidate for the treatment of schizophrenia and Alzheimer's disease.

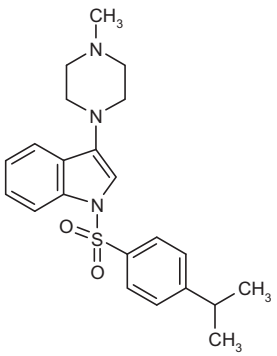
Therapeutic Group: Treatment of Alzheimer's Dementia; Antiobesity Drugs; Anxiolytics

Mechanism of Action: 5-HT6 Receptor Antagonists

Source: Nirogi, R.V.; Deshpande, A.D.; Kambhampati, R.; et al. Indole-3-piperazinyl derivatives: novel chemical class of 5-HT(6) receptor antagonists. Bioorg Med Chem Lett 2011, 21(1): 346

Organization: Suven Life Sciences

Integrity Entry Number: 724435



NEW MOLECULAR MECHANISMS OF ACTION

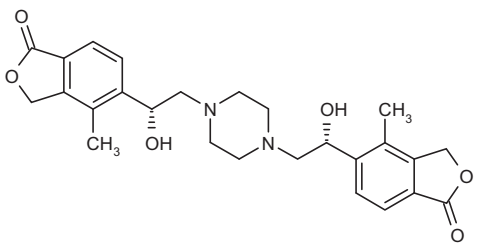
The mode of action of any product is key to understanding how to improve compound design and find more potent leads with fewer potential side effects. We showcase a range of fascinating compounds in this issue.

INWARDLY RECTIFYING POTASSIUM CHANNEL ($K_{ir}1.1$, ROMK) INHIBITORS

Main Related Conditions: Hypertension

Organization: Merck & Co.

Integrity Entry Number: 715564

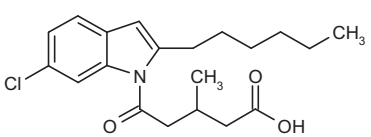


OXOEICOSANOID RECEPTOR 1 ANTAGONISTS

Main Related Conditions: Asthma; Chronic Obstructive Pulmonary Disease (COPD); Allergic Rhinitis; Fibrosis

Organization: Florida Institute of Technology; McGill University

Integrity Entry Number: 715289

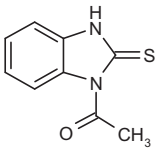


M. TUBERCULOSIS SALICYLATE SYNTHASE MbtI INHIBITORS

Main Related Conditions: Tuberculosis

Organization: Ecole Polytechnique Federale Lausanne; University of Minnesota

Integrity Entry Number: 724440



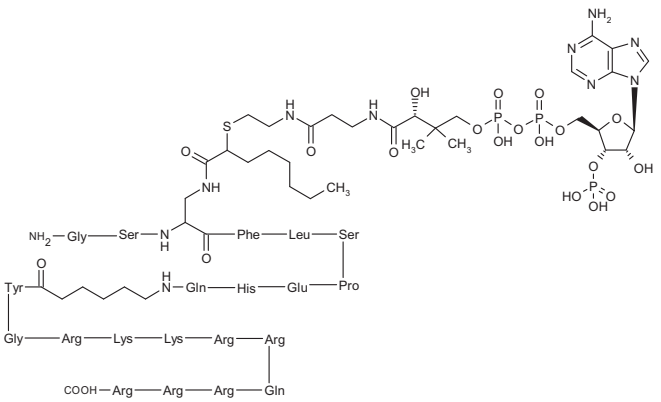
GHRELIN *O*-ACYLTRANSFERASE (GOAT) INHIBITORS

Main Related Conditions: Obesity; Type 2 Diabetes

Organization: Johns Hopkins University

Drug Name: GO-CoA-Tat

Integrity Entry Number: 714771

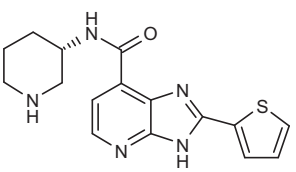


LYMPHOKINE-ACTIVATED KILLER T-CELL-ORIGINATED PROTEIN KINASE (PDZ-BINDING KINASE, *PBK*) INHIBITORS

Main Related Conditions: Cancer

Organization: OncoTherapy Science

Integrity Entry Number: 719752

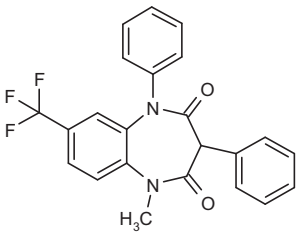


HIV CAPSID PROTEIN P24 (CA) ASSEMBLY INHIBITORS

Main Related Conditions: Anti-HIV Agents

Organization: Boehringer Ingelheim

Integrity Entry Number: 724427



THE STARTING LINE

The Starting Line pinpoints new molecular entities (NMEs) ready to progress into the R&D arena. A portion of this issue's pool is represented by drugs related to diabetes, atherosclerosis and cancer. Other conditions are Graves' disease and multiple sclerosis, the latter also being the topic of *The Finishing Line* in this issue.

Organization: Scripps Research Institute

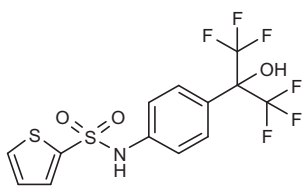
Drug Name: SR-3335

Condition: Type 2 diabetes

Mechanism of Action: ROR-alpha Inverse Agonists

Literature: Kumar, N.; Kojetin, D.J.; Solt, L.A.; Kumar, K.G.; Nuhant, P.; Duckett, D.R.; Cameron, M.D.; Butler, A.A.; Roush, W.R.; Griffin, P.R.; Burris, T.P. Identification of SR3335 (ML-176): A synthetic RORalpha selective inverse agonist. ACS Chem Biol 2011, 6(3): 218

Integrity Entry Number: 720960



Organization: AstraZeneca

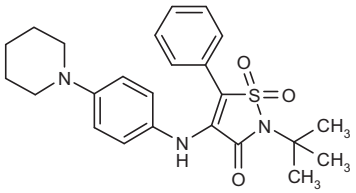
Drug Name: AZ-876

Condition: Atherosclerosis

Mechanism of Action: Liver X Receptor LXRalpha Agonists; Liver X Receptor LXRbeta Agonists

Literature: van der Hoorn, J.; Linden, D.; Lindahl, U.; Bekkers, M.; Voskuilen, M.; Nilsson, R.; Oscarsson, J.; Lindstedt, E.; Princen, H. Low dose of the liver X receptor agonist, AZ876, reduces atherosclerosis in APOE*3Leiden mice without affecting liver or plasma triglyceride levels. Br J Pharmacol 2011, 162(7): 1553

Integrity Entry Number: 722006



Organization: InVasc Therapeutics; Ohio State University

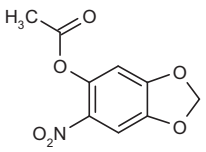
Drug Name: INV-403

Condition: Atherosclerosis

Mechanism of Action: CCL2 Expression Inhibitors; ICAM1 Expression Inhibitors; IKK2 (IKK-beta) Inhibitors; VCAM1 Expression Inhibitors

Literature: Ying, Z.; Kherada, N.; Kampfrath, T.; et al. A modified sesamol derivative inhibits progression of atherosclerosis. Arterioscler Thromb Vasc Biol 2011, 31(3): 536

Integrity Entry Number: 721867



Organization: Amgen

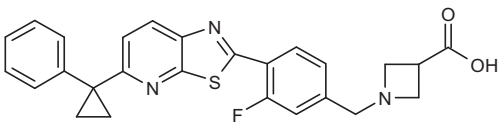
Drug Name: AMG-369

Condition: Multiple sclerosis

Mechanism of Action: Lysophospholipid S1P1 Receptor Agonists; Lysophospholipid S1P5 Receptor Agonists

Literature: Cee, V.J.; Frohn, M.; Lanman, B.A.; et al. Discovery of AMG 369, a thiazolo[5,4-b]pyridine agonist of S1P1 and S1P5. ACS Med Chem Lett 2011, 2(2): 107

Integrity Entry Number: 719718



Organization: Astellas Pharma

Drug Name: AS-1938909

Condition: Type 2 diabetes

Mechanism of Action: SH2 Domain-Containing Inositol Phosphatase (SHIP) Inhibitors

Literature: Suwa, A.; Kurama, T.; Yamamoto, T.; Sawada, A.; Shimokawa, T.; Aramori, I. Glucose metabolism activation by SHIP2 inhibitors via up-regulation of GLUT1 gene in L6 myotubes. Eur J Pharmacol 2010, 642(1-3): 177

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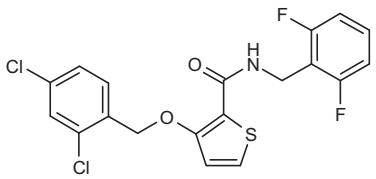

Organization: Genomics Inst. Novartis Res. Foundation; Scripps Research Institute; University of California, San Diego; University of Massachusetts

Drug Name: Longdaysin

Condition: Circadian rhythm disorder

Literature: Hirota, T.; Lee, J.W.; Lewis, W.G.; et al. High-throughput chemical screen identifies a novel potent modulator of cellular circadian rhythms and reveals CKIalpha as a clock regulatory kinase. PLoS Biol 2010, 8(12): e1000559

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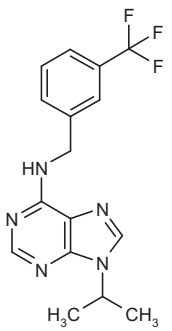


Organization: US Department of Health & Human Services

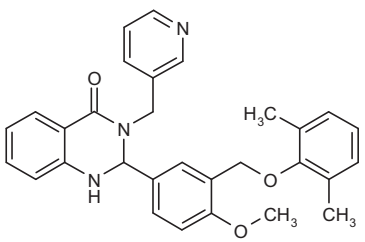
Drug Name: NCGC-00229600

Condition: Graves' disease

Mechanism of Action: Thyroid-Stimulating Hormone (Thyrotropin) Receptors (TSH-R) Inverse Agonists

Literature: Neumann, S.; Eliseeva, E.; McCoy, J.G.; Napolitano, G.; Giuliani, C.; Monaco, F.; Huang, W.; Gershengorn, M.C. A new small-molecule antagonist inhibits Graves' disease antibody activation of the TSH receptor. J Clin Endocrinol Metab 2011, 96(2): 548

Integrity Entry Number: 722712



Organization: University of British Columbia

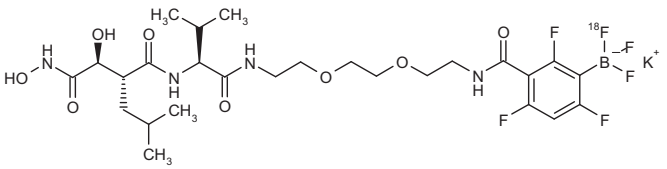
Drug Name: [^{18}F]-Marimastat-ArBF3

Condition: Cancer diagnostics

Mechanism of Action: Matrix Metalloproteinase Inhibitors

Literature: auf dem Keller, U.; Bellac, C.L.; Li, Y.; et al. Novel matrix metalloproteinase inhibitor [18F] marimastat-aryltrifluoroborate as a probe for in vivo positron emission tomography imaging in cancer. Cancer Res 2010, 70(19): 7562; Perrin, D.M.; Li, Y.; Bellac, C.; Ting, R.; et al. One-step aqueous 18F-labeling: Applications to imaging breast cancer. Int Chem Congr Pacific Basin Soc (December 15-20, Honolulu) 2010, Abst 41

Integrity Entry Number: 718051



Organization: Takeda

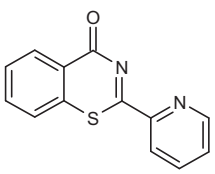
Drug Name: BTZO-1

Condition: Coronary artery disease

Mechanism of Action: Macrophage Migration Inhibitory Factor (MIF) Modulators

Literature: Kimura, H.; Sato, Y.; Tajima, Y.; et al. BTZO-1, a cardioprotective agent, reveals that macrophage migration inhibitory factor regulates ARE-mediated gene expression. Chem Biol (Lond) 2010, 17(12): 1282

Integrity Entry Number: 718049



Organization: CNRS; Universita degli Studi di Siena

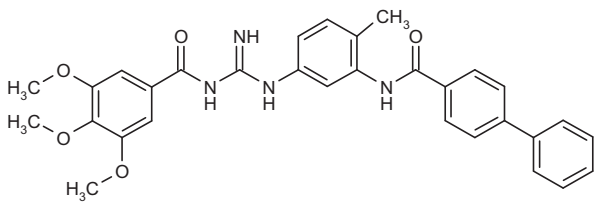
Drug Name: MRT-83

Condition: Cancer

Mechanism of Action: Hedgehog Signaling Inhibitors; SMO Receptor Antagonists

Literature: Roudaut, H.; Traiffort, E.; Gorojankina, T.; Vincent, L.; Faure, H.; Schoenfelder, A.; Mann, A.; Manetti, F.; Solinas, A.; Taddei, M.; Ruat, M. Identification and mechanism of action of the acylguanidine MRT-83, a novel potent smoothened antagonist. Mol Pharmacol 2010, 79(3): 453

Integrity Entry Number: 719651



THE FINISHING LINE

2010 finishing line for multiple sclerosis

Multiple sclerosis (MS) is believed to affect approximately 400,000 Americans and 2.1 million people worldwide, according to the National Multiple Sclerosis Society. As a chronic disorder occurring primarily in young adults with a virtually normal life expectancy, MS incurs significant economic, social and medical costs. A review of European cost-of-illness studies estimated the annual cost per patient in four countries using data from 1996 to 1999. The total cost in 2003 (including direct costs, out-of-pocket costs, informal care and indirect costs) was estimated to be EUR 18,716 in Italy, EUR 31,096 in Germany, EUR 25,625 in the U.K. and EUR 38,329 in Sweden (11).

The decade of the 1990s was an exciting era for MS patients and their physicians, as four different interferons and glatiramer acetate all obtained regulatory approval. These drugs have radically influenced the treatment of MS, and have in many cases changed the clinical course of the disease. Another significant achievement was the approval in 2010 of cladribine and fingolimod, the first oral treatments for MS (see the following section in this issue). However, in spite of the many advances made in a relatively short period of time, improvements are still required before the needs of MS patients can be fully addressed. While existing disease-modifying drugs may effectively slow the progression of relapsing–remitting MS to more disabling stages, the challenge remains to find therapies that are capable of halting disease progression altogether (12).

The market for MS therapeutics, valued at USD 7.3 billion (EUR 5.07 billion approximately) in 2009, is expected to grow to USD 9.7 billion (EUR 6.74 billion approximately) by the year 2014, mainly as a result of the upcoming approval and launch of new drugs with significant advantages over existing therapies (13).

The above facts are part of a fully-detailed overview of MS available in the *Disease Briefings* Knowledge Area of *Integrity*^{SM}, which provides dynamic executive summaries on the status of current and future trends in drug therapy. Apart from the specific content summarized above, other features such as *Targets for Therapeutic Intervention*, *Latest Headlines* obtained from *Thomson Reuters Drug News*, and more, are covered for MS and many other diseases.

The year 2010 marked the first launch for a number of new drugs and biologics, including several important innovations and therapeutic advances (Fig. 1). According to our records, 29 new chemical entities and biologics for therapeutic use reached their first markets in 2010. Following a growing tendency in recent years, at least 20 important line extensions (new formulations, new indications and/or

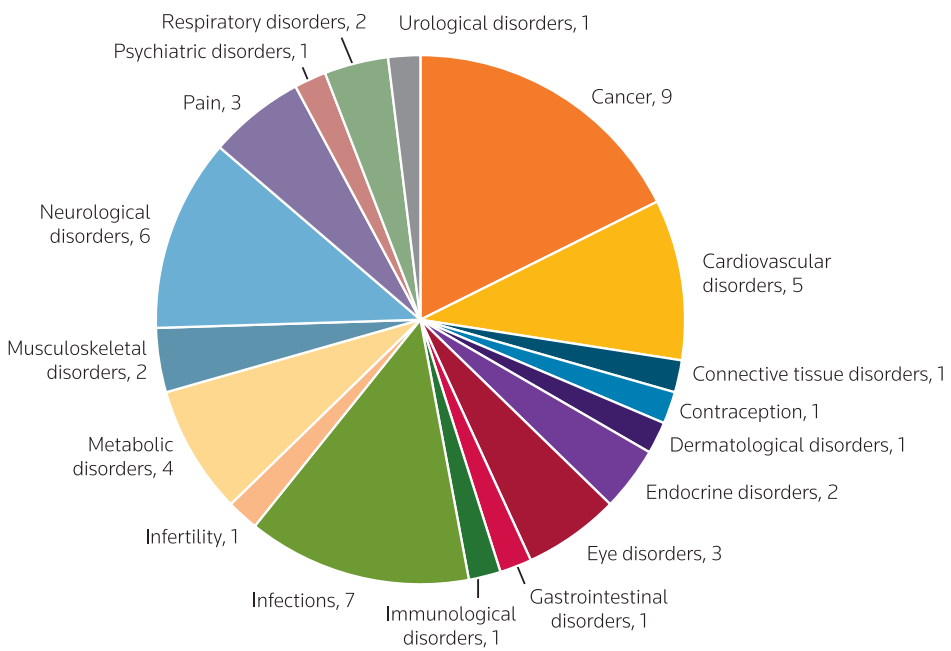


Figure 1. Distribution of 2010 new product intros by condition.

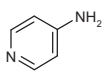
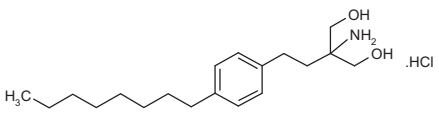
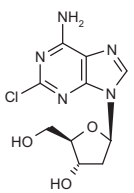
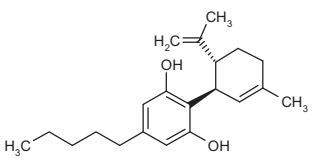
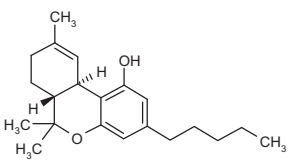
new combinations of previously marketed products) were introduced last year. Both figures are significantly lower than those registered in 2009, when 51 new chemicals and biologics and 24 line extensions were introduced for the first time.

During 2010, patients with MS (falling under the Neurological disorders category in Fig. 1) received good news on several fronts. *Fingolimod hydrochloride* (Gilenya®), a first-in-class lysophospholipid (S1P) receptor modulator, was approved and launched in the U.S. last year by Novartis (Tables I and II). It is indicated for the oral treatment of patients with relapsing forms of MS, to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability. Another orally active product, the immunomodulator *cladri-*

Table I. *New product intros – 2010.*

Trade name (country)	Company	Active ingredient	Indication
Ampyra™ (US)	Acorda Therapeutics; licensed from Elan	Dalfampridine, extended-release tablets, 10 mg	Treatment to improve walking in patients with multiple sclerosis (orphan drug)
Gilenya® (US)	Novartis	Fingolimod hydrochloride, capsules, 0.56 mg, equiv. to 0.50 mg fingolimod	Treatment of patients with relapsing forms of multiple sclerosis, to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability
Movectro® (AU)	Merck Serono	Cladribine, tablets, 10 mg	Treatment of relapsing–remitting multiple sclerosis for a maximum duration of 2 years
Sativex® (GB)	GW Pharmaceuticals; marketed by Bayer Schering Pharma	Nabiximols, oromucosal spray, 27 mg/mL dronabinol:25 mg/mL cannabidiol, delivering 2.7 mg dronabinol:2.5 mg cannabidiol/spray (100 μL)	Add-on treatment for symptom improvement in patients with moderate to severe spasticity due to multiple sclerosis who have not responded adequately to other antispasticity medications and who demonstrate clinically significant improvement in spasticity-related symptoms during an initial trial of therapy

Table II. *Chemical structures of new multiple sclerosis drugs launched in 2010.*

Integrity Entry Number	Generic name	Chemical structure
182600	Dalfampridine	
210392	Fingolimod hydrochloride	
113529	Cladribine	
70246	Cannabidiol (component of nabiximols)	
125566	Dronabinol (component of nabiximols)	

bine (Movectro®; Merck Serono), was launched for the first time in Australia for the treatment of relapsing–remitting MS. *Dalfampridine* (Ampyra™; Acorda/Elan), an orally active potassium channel blocker, was approved and launched in the U.S., where it is indicated to improve walking in patients with all four major types of MS. Prior to the launches of fingolimod and cladribine, there were no oral treatments for MS. The cannabinoid receptor agonist *nabiximols* (Sativex®; GW Pharmaceuticals) was approved and launched last year in the U.K. for a second MS-related indication: as an add-on treatment for symptom improvement in patients with moderate to severe spasticity due to MS. Nabiximols is a highly characterized extract of *Cannabis sativa* L. containing Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD) as its major chemical constituents. Important minor constituents are related cannabinoids and the non-cannabinoid components α- and *trans*-caryophyllenes. The product has been marketed since 2005 for the treatment of neuropathic pain in MS patients.

More information can be downloaded from *The Year's New Drugs & Biologics, 2010, Drugs of Today 2011, 47(1): 27*. Thomson Reuters' *Drugs of Today* is a monthly peer-reviewed journal providing information on drugs introduced to the global market.

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