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THE CUTTING EDGE OF CHEMISTRY

A PHARMA MATTERS REPORT – APRIL-JUNE 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[SM], a unique database integrating biological, chemical and pharmacological data.

CONTENTS

ORGANIC SYNTHESIS SCHEME SHOWCASE

Cost-effective ketolide entry

An efficient large-scale synthesis of modithromycin (EDP-420), a first-in-class bridged bicyclic ketolide (bicyclolide) antibiotic drug candidate, offers a cost-effective entry point to these compounds in just 10 steps (1).

EDP-420 is a member of a new class of macrolides designed by Enanta Pharmaceuticals to circumvent the resistance problems now seen with traditional antibiotics, which are often ineffective against certain strains of respiratory pathogens.

EDP-420 is active against *Haemophilus influenzae*, atypical organisms such as *Chlamydia pneumoniae*, *Mycoplasma pneumoniae* and *Legionella pneumophila*, and even multidrug-resistant streptococci. Enanta has demonstrated safety and tolerability and presented pharmacokinetic results for the compound in healthy adults (2), with the conclusion that efficacy trials for respiratory tract infections should be pursued. EDP-420 has reached phase II clinical trials for the treatment of community-acquired pneumonia (CAP).

The 10-step synthesis to EDP-420 begins with inexpensive and commercially available erythromycin A 9-oxime, which is converted to the end product using triacetylation, palladium-catalyzed *O,O*-bis-allylation (bridge formation), acid-catalyzed sugar cleavage, oxime reduction, acetylation, osmium-catalyzed bridge olefin oxidative cleavage, Corey-Kim oxidation, oxime formation in the bridge, deprotection, and finally, purification to yield multikilogram quantities.

When scaling up from the discovery stage, two transformations required modification of the reaction conditions. The olefin oxidative cleavage, which had initially been carried out by ozonolysis, was finally performed employing sodium periodate and catalytic amounts of osmium tetroxide, conditions that adapted well to the equipment available at the pilot plant.

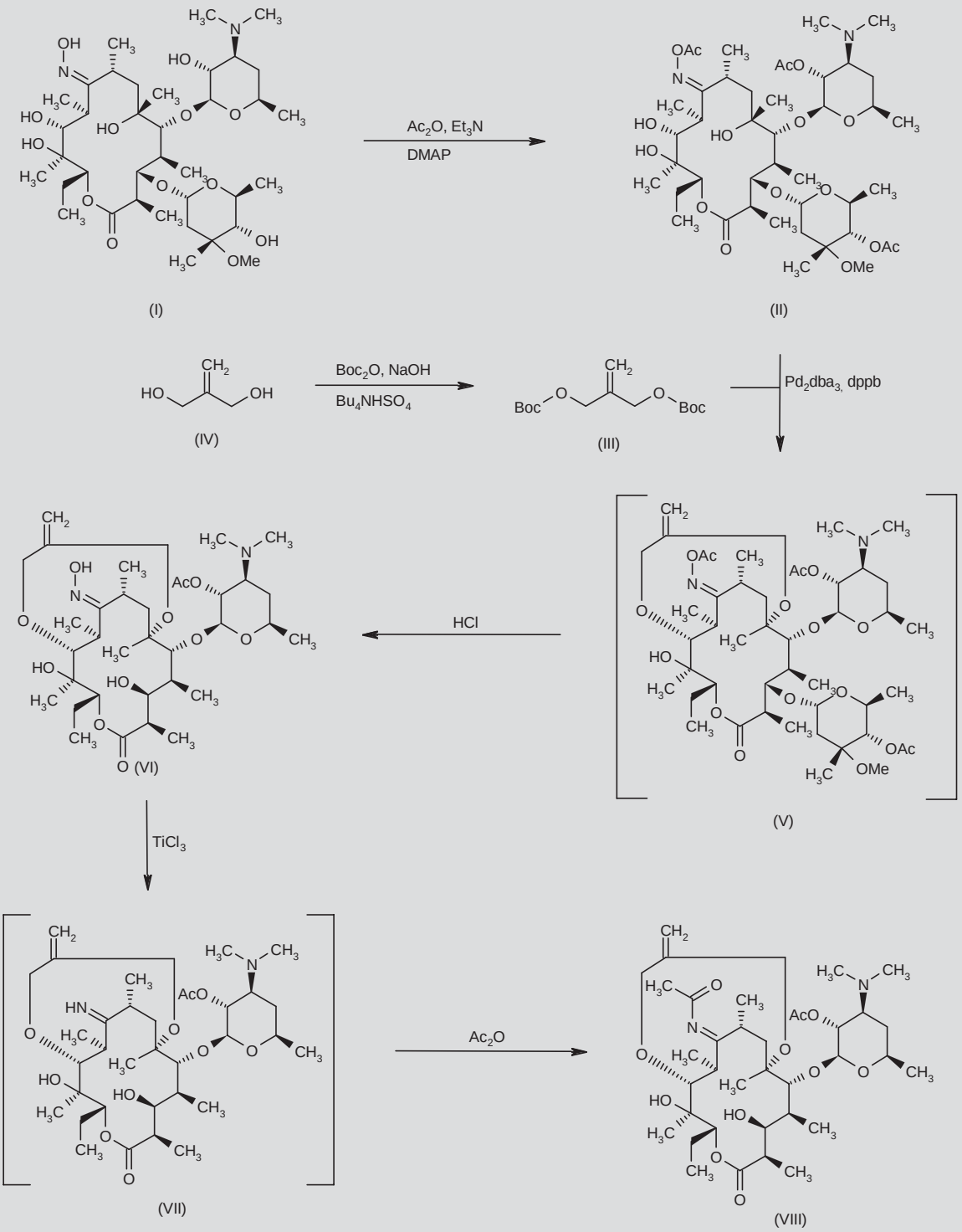
The ketolide formation was modified to circumvent the use of Dess-Martin periodinane at the multikilogram scale for cost and safety reasons. Hence, a screening for alternative reagents revealed that the Corey-Kim conditions provided satisfactory yields and selectivities after a convenient optimization of the *N*-chlorosuccinimide stoichiometry.

Integrity Entry Number: 347484

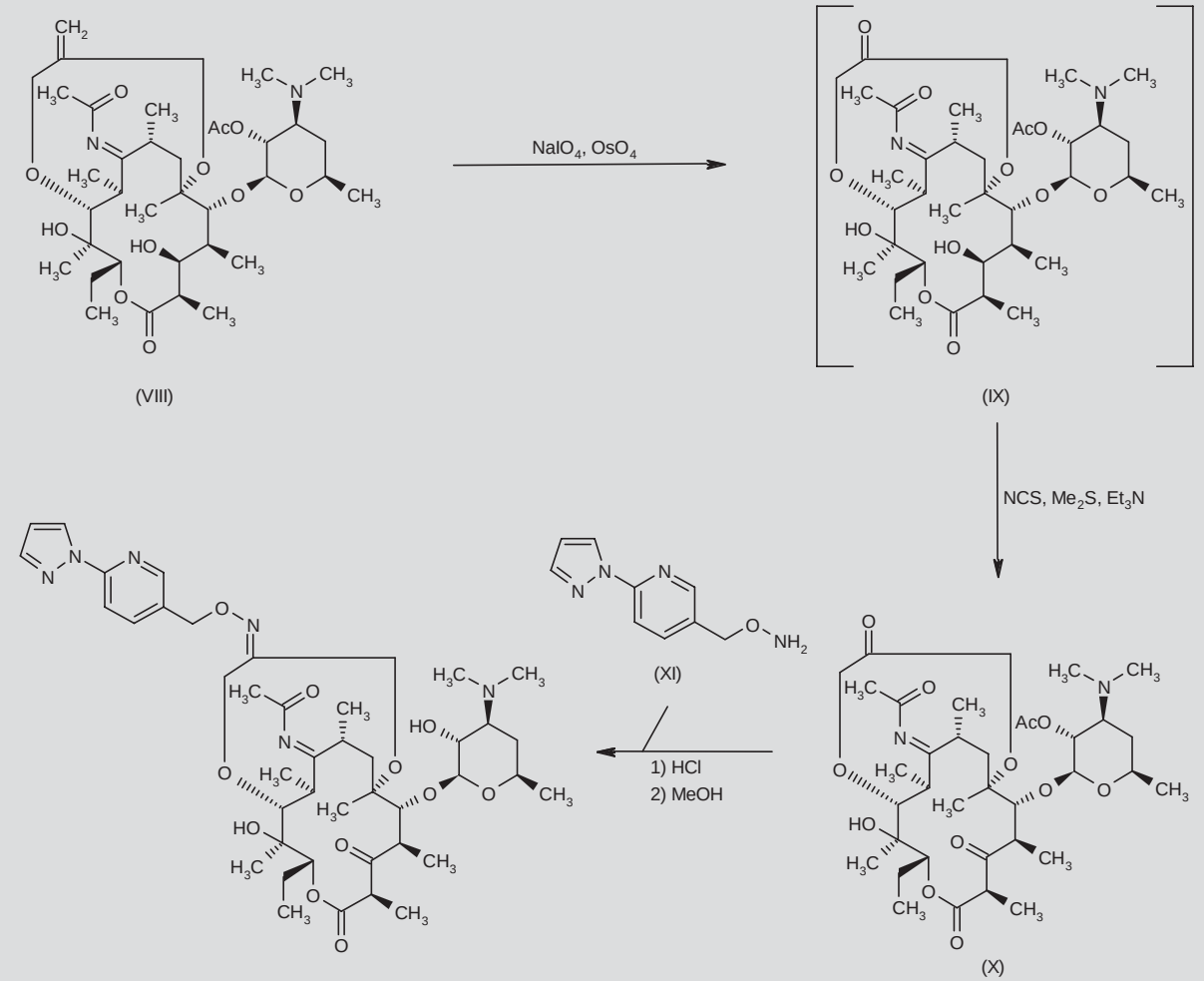
SCAFFOLDS ON THE MOVE: SILKWORMS AND THE FIGHT AGAINST MRSA

Anti-infectives, antidiabetic agents and antiobesity scaffolds are all featured in this edition of *The Cutting Edge of Chemistry*. A natural product skeleton from a marine source, almiramide, has potential against leishmaniasis, while Yale scientists' synthetic calixarene derivatives could prove useful in treating HIV. A range of phosphaisocoumarin analogues are being investigated for targeting pancreatic cholesterol esterase, while a skeleton linker modification gives Dainippon Sumitomo Pharma a new lead in regulating low-density lipoprotein. Merck & Co. targets obesity and diabetes with its malonyl-CoA decarboxylase inhibitors.

Synthesis Scheme for EDP-420 (Part 1)



Synthesis Scheme for EDP-420 (Part 2)



A group at Kitasato Institute in Tokyo, Japan, gives us the highlighted skeleton for this issue in the form of the nosokomycins, which are antibiotics with activity against methicillin-resistant *Staphylococcus aureus* (MRSA). Found to belong to the moenomycin family, they bear an unusual sesterterpenoid fragment. The team has used a rather novel biological approach to early-stage screening for activity that allowed them to quickly home in on the most active compounds. Rather than using a conventional agar diffusion assay based on paper disks, the team used live silkworm larvae.

In vivo studies are plagued with expense and ethical considerations, particularly at the primary discovery stage. The use of invertebrates rather than mammals addresses both considerations to some degree, and researchers have focused on *Caenorhabditis elegans* (a nematode worm), the fruit fly *Drosophila melanogaster* and silkworms.

Indeed, the Japanese researchers had previously demonstrated that a model of silkworm larvae infected with human pathogenic bacteria followed by injection with a test compound can reveal whether or not the test substance has antibiotic activity on the basis of survival of the larvae or otherwise (3, 4).

"Several companies in Japan are interested in the silkworm assay for evaluating or screening antibiotics," says team member Hiroshi Tomada, *"but it is still at the early stages of development. We believe that this silkworm system is good for predicting antibiotic efficacy in vivo, and reducing the number of animals for drug development."*

Featured Scaffold

Silky approach to antibiotics

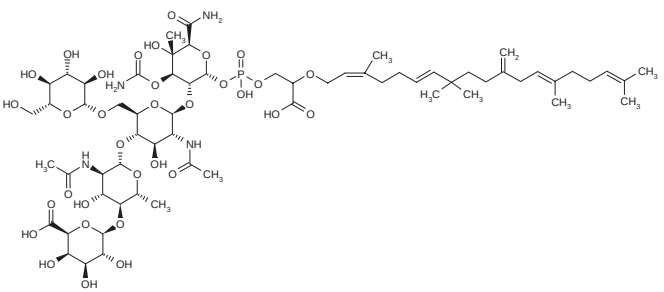
Two papers from the Kitasato Institute describe nosokomycins, antibiotics from the broth of *Streptomyces* sp. K04-0144. They are new members of the structurally rare moenomycin family, which bears an unusual sesterterpenoid moiety. Their identifying characteristic is the absence of the cyclopentenone ring present in the oligosaccharide moiety of moenomycin A. The team used a rather

new approach to detecting these compounds by screening microbial culture broths with an in vivo-mimetic assay employing silkworm larvae. Activity against MRSA was demonstrated at low doses.

Therapeutic Group: Antibiotics

Source: Uchida, R.; Iwatsuki, M.; Kim, Y.P.; Ohte, S.; Omura, S.; Tomoda, H. Nosokomycins, new antibiotics discovered in an in vivo-mimic infection model using silkworm larvae. I: Fermentation, isolation and biological properties. J Antibiot 2010, 63(4): 151; Uchida, R.; Iwatsuki, M.; Kim, Y.P.; Omura, S.; Tomoda, H. Nosokomycins, new antibiotics discovered in an in vivo-mimic infection model using silkworm larvae. II: Structure elucidation. J Antibiot 2010, 63(4): 157

Integrity Entry Number: 466456



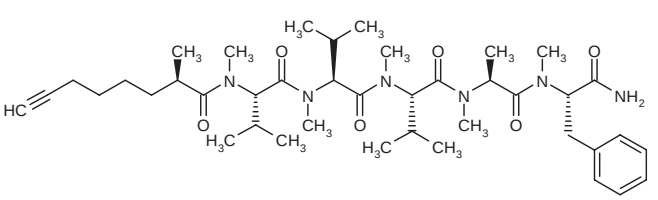
Lipopeptide lead for leishmaniasis

The protozoal disease leishmaniasis afflicts 12 million people worldwide each year and so represents a major target for new scaffolds. U.S. researchers have focused on almiramides A-C, extracted from marine cyanobacteria, as they have in vitro activity against the parasite. The scaffold is an *N*-methylated linear lipopeptide with an unsaturated terminus on the side chain that is a requirement for activity. Structure–activity optimization has led to a new compound from which several semisynthetic derivatives with fully methylated peptide backbones and improved selectivity indices have been obtained.

Therapeutic Group: Antileishmanials

Source: Sanchez, L.M.; Lopez, D.; Vesely, B.A.; Della Togna, G.; Gerwick, W.H.; Kyle, D.E.; Linington, R.G. Almiramides A-C: Discovery and development of a new class of leishmaniasis lead compounds. J Med Chem 2010, 53(10): 4187

Integrity Entry Number: 698465



New link for cholesterol-lowering compounds

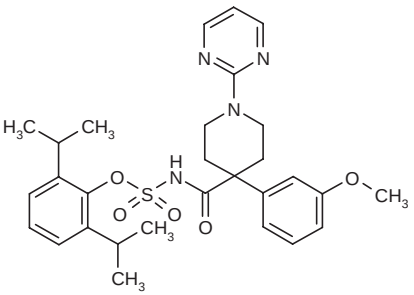
Dainippon Sumitomo Pharma describes the extension studies on a dual low-density lipoprotein receptor (LDL-R) upregulator and acyl-coenzyme A:cholesterol acyltransferase (ACAT) inhibitor. The replacement of the methylene urea linker in this lead with an acylsufonamide linker results in compounds that retain potent LDL-R upregulatory activity but reduced interference with ACAT even at 1 μM concentration. The sodium salt of an optimized compound reduced plasma total and LDL cholesterol levels in a hyperlipidemic animal model.

Therapeutic Group: Treatment of Lipoprotein Disorders

Studied Mechanism of Action: LDL-Receptor Up-Regulators

Source: Asano, S.; Ban, H.; Tsuboya, N.; Uno, S.; Kino, K.; Ioriya, K.; Kitano, M.; Ueno, Y. A novel class of antihyperlipidemic agents with low density lipoprotein receptor up-regulation via the adaptor protein autosomal recessive hypercholesterolemia. J Med Chem 2010, 53(8): 3284

Integrity Entry Number: 697434



Phosphaisocoumarins target cholesterol enzyme

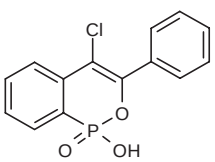
Pancreatic cholesterol esterase is a target in atherosclerosis and for the development of hypocholesterolemic agents. A team at Sun Yat-Sen University in China has prepared 45 isocoumarin phosphorus analogues, phosphaisocoumarins, and investigated inhibition of enzyme. Selected phosphaisocoumarins displayed a potent inhibitory effect against pancreatic cholesterol esterase, with IC_{50} values of 2-5 μM.

Therapeutic Group: Treatment of Lipoprotein Disorders

Studied Mechanism of Action: Cholesterol Esterase Inhibitors

Source: Li, B.; Zhou, B.; Lu, H.; Ma, L.; Peng, A.Y. Phosphaisocoumarins as a new class of potent inhibitors for pancreatic cholesterol esterase. Eur J Med Chem 2010, 45(5): 1955

Integrity Entry Number: 696200



Malonyl-CoA decarboxylase inhibition keeping hunger at bay

Merck & Co. discusses a new class of malonyl-CoA decarboxylase inhibitors with potential in treating type 2 diabetes and obesity, two conditions with the greatest risk of chronic disease and mortality.

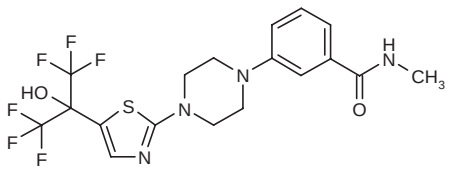
Research in mice has shown inhibition of the enzyme to lead to a reduction in food intake and body weight. In addition, acute treatment lowers blood glucose levels in a murine model of type 2 diabetes.

Therapeutic Group: Antiobesity Drugs; Antidiabetic Drugs

Studied Mechanism of Action: Malonyl-CoA Decarboxylase Inhibitors

Source: Tang, H.; Yan, Y.; Feng, Z.; De Jesus, R.K.; et al. Design and synthesis of a new class of MCD inhibitors with anti-obesity and anti-diabetic activities. 32nd Natl Med Chem Symp (June 6-9, Minneapolis-St. Paul) 2010, Abst 34

Integrity Entry Number: 698981



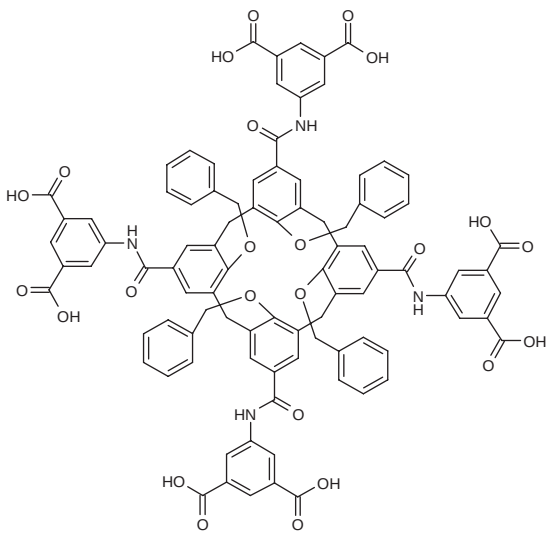
Molecular vase combats HIV and HCV

Yale University scientists report that tetrabutoxy-calix[4]arene derivatives had previously been shown to be useful oncolytic scaffolds, through inhibition of vascular endothelial growth factor receptor and platelet-derived growth factor receptor tyrosine kinases. They now suggest that a modified calixarene might be used as a dual antiviral strategy in treating HIV and hepatitis C virus (HCV). The mode of action is currently being investigated, but clues regarding structure–activity relationships suggest that interacting head groups may play a key role in the dual antiviral effect and that maintaining these at the broader rim of the calixarene cone is essential for activity.

Therapeutic Group: Anti-HIV Agents; Anti-Hepatitis C Virus Drugs

Source: Tsou, L.K.; Dutschman, G.E.; Gullen, E.A.; Telpoukhovskaia, M.; Cheng, Y.C.; Hamilton, A.D. Discovery of a synthetic dual inhibitor of HIV and HCV infection based on a tetrabutoxy-calix[4]arene scaffold. Bioorg Med Chem Lett 2010, 20(7): 2137

Integrity Entry Number: 694442



NEW MOLECULAR MECHANISMS OF ACTION

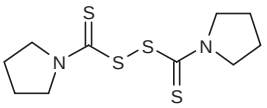
The mode of action of any product is key to understanding how to improve on any given design and how to find more potent leads with fewer potential side effects. We notice that in the discovery end of the pipeline for top Pharma companies the therapeutic areas with the greatest focus include inflammation, pain, diabetes, obesity and bacterial infections. In this issue, we highlight the mode of action of antimycobacterial agents for tuberculosis with methionine aminopeptidase 1A-inhibitory activity and of antidiabetic compounds involving inhibition of insulin-degrading enzyme.

E3 UBIQUITIN-PROTEIN LIGASE INHIBITORS

Main Related Conditions: Cancer, Breast

Organization: Cardiff University (GB); Barbara Ann Karmanos Cancer Institute (US)

Integrity Entry Number: 694234

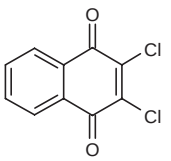


MYCOBACTERIUM TUBERCULOSIS METHIONINE AMINOPEPTIDASE 1A (METAP 1A) INHIBITORS; *M. TUBERCULOSIS* METHIONINE AMINOPEPTIDASE 1B (METAP 1B) INHIBITORS

Main Related Conditions: Tuberculosis

Organization: Johns Hopkins University School of Medicine (US); Texas Southern University (US)

Integrity Entry Number: 495652



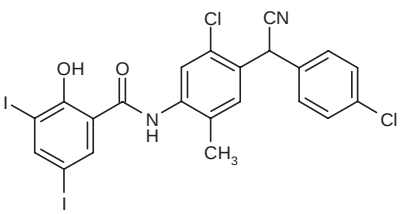
ONCHOCERCA VOLVULUS CHITINASE INHIBITORS

Main Related Conditions: Onchocerciasis

Organization: Scripps Research Institute (US)

Drug Name: Closantel

Integrity Entry Number: 689456



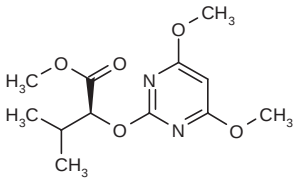
ENDOPLASMIN (GRP-94) INHIBITORS

Main Related Conditions: Systemic Lupus Erythematosus

Organization: University of Connecticut (US); Korea Research Institute of Chemical Technology (KR); Seoul National University (KR)

Drug Name: GPM-1

Integrity Entry Number: 691746



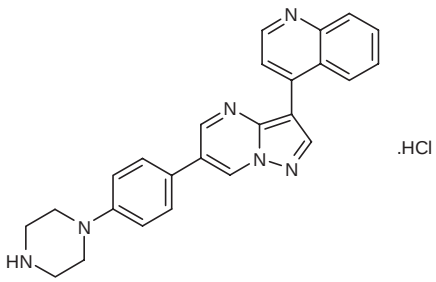
ACTIVIN RECEPTOR-LIKE KINASE 3 (ALK-3; BMPR-1A) INHIBITORS

Main Related Conditions: Ossification, extraskeletal; Colitis; Anemia

Organization: Massachusetts General Hospital (US); Stemgent; Brigham & Women's Hospital (US)

Drug Name: LDN-193189

Integrity Entry Number: 642052



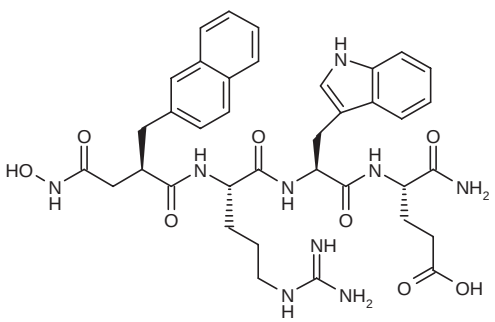
INSULIN-DEGRADING ENZYME (INSULYSIN; ABETA-DEGRADING PROTEASE) INHIBITORS

Main Related Conditions: Diabetes

Organization: Harvard College (US); Yale University (US); Brigham & Women's Hospital (US)

Drug Name: Ii-1

Integrity Entry Number: 668389



THE STARTING LINE: BIOLOGICS MORE PAINFUL THAN ORGANICS

The Starting Line pinpoints new molecular entities (NMEs) ready to progress into the R&D arena. This issue's focus is on pain and also looks at NMEs for other conditions, including cancer, asthma and trypanosomiasis.

Historically, small drug molecules produced using conventional organic synthesis techniques have been developed to treat pain. In recent years, drugs from biological sources have received growing interest within the pharmaceutical industry. In contrast to conventional drug synthesis, biologics are manufactured in a living system such as a microorganism, plant or animal cell, and are being developed by using a variety of techniques, including recombinant DNA expression.

Organically synthesized small molecules have been extremely successful, in part due to the well-defined chemical structure. In many cases, the crystal structure of a small molecule docking with its protein target can be obtained to reveal the underlying chemical mechanism of action and to guide modifications that can lead to more effective analogues. Moreover, chemical analysis and characterization of any components and the purity of a formulation are relatively accessible using standard laboratory techniques. In contrast, biologics represent a much more diffuse proposition and thus are far more difficult to determine using standard laboratory tests. After all, some of the components of biologic therapies may be unknown, as post-translational modifications of the biologic can often generate minor changes in the drug.

Additionally, the living systems used to produce biologics can be sensitive to minor changes in the conditions of the production process, potentially causing the final product to deviate from the known structure significantly, and thus altering the way in which it acts in the body. As such, the source and nature of the starting materials, as well as the manufacturing process, have to be extremely tightly controlled to ensure the drug is produced as expected.

In the area of pain, monoclonal antibodies (MAbs) are an emerging area of therapeutic research still very much in their infancy. It is rather telling that within *Thomson Reuters Integrity*[SM] there are some 230 drugs that are under active development for pain in human trials. Of these, the overwhelming majority are organically synthesized molecules, with no more than 5% classified as MAbs. All the latter act as anti-nerve growth factor drugs.

Thus far, no MAbs have been successfully launched for pain. In June 2010, the FDA requested that trials of the Pfizer drug tanezumab for the treatment of osteoarthritis pain be suspended, following some concerns on the worsening of osteoarthritis after taking the drug. In July 2010, trials of tanezumab were halted for two further indications. This drug is currently in clinical trials for other forms of pain and is being investigated with the aim of continuing. If launched, this will be the first biotech therapy approved for pain.

In this issue of *The Cutting Edge of Chemistry* we see three new molecular entities for the treatment of pain, none of which are biologics and all of which can be chemically synthesized. However, some observers suggest that one of the limiting factors in the development of biologics is mainly regulatory. If there were a smoother

route to approval for biologic drugs, would they become more widespread and provide innovative therapies for healthcare?

Organization: University of Dundee (GB); University of Toronto (CA); University of York (GB)

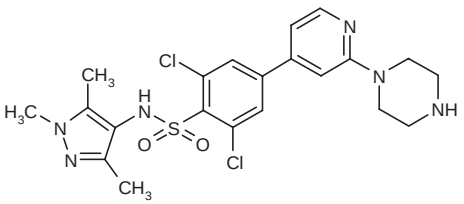
Drug Name: DDD-85646

Condition: Trypanosomiasis

Mechanism of Action: *N*-Myristoyltransferase Inhibitors

Literature: Frearson, J.A.; Brand, S.; McElroy, S.P.; et al. *N*-Myristoyltransferase inhibitors as new leads to treat sleeping sickness. Nature 2010, 464(7289): 728

Integrity Entry Number: 692017



Organization: Merck Frosst

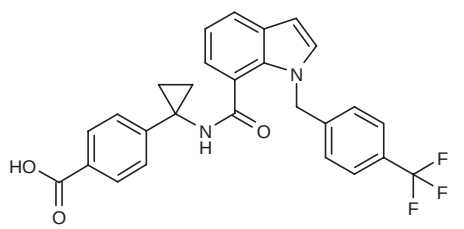
Drug Name: MF-766

Condition: Arthritis; Pain

Mechanism of Action: Prostanoid EP4 Antagonists

Literature: Colucci, J.; Boyd, M.; Berthelette, C.; Chiasson, J.-F.; et al. Discovery of 4-[1-[[[1-[4-(trifluoromethyl)benzyl]-1H-indol-7-yl]carbonyl]amino]cyclopropyl}benzoic acid (MF-766), a highly potent and selective EP4 antagonist for treating inflammatory pain. Bioorg Med Chem Lett 2010, 20(12): 3760; Boyd, M.; Frosst, M. The discovery highly potent and selective EP4 antagonists for the treatment of inflammatory pain. 32nd Natl Med Chem Symp (June 6-9, Minneapolis-St. Paul) 2010, Abst 35

Integrity Entry Number: 638300



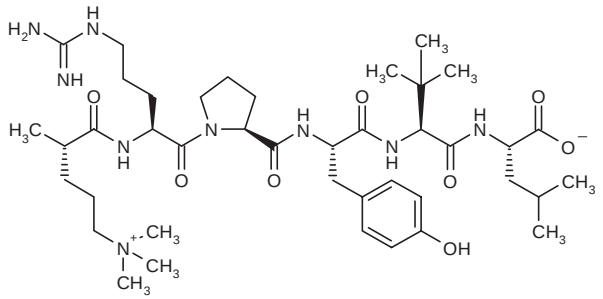
Organization: Argolyn Bioscience; Medical University of South Carolina (US)

Drug Name: ABS-212

Condition: Pain

Literature: Hughes, F.M.; Shaner, B.E.; May, L.A.; Zotian, L.; et al. Identification and functional characterization of a stable, centrally active derivative of the neurotensin (8-13) fragment as a potential first-in-class analgesic. J Med Chem 2010, 53(12): 4623

Integrity Entry Number: 695716



Organization: Amira Pharmaceuticals

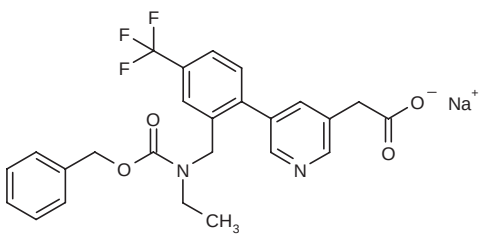
Drug Name: AM-206

Condition: Asthma; Chronic obstructive pulmonary disease (COPD); Rhinitis, allergic

Mechanism of Action: CRTH2 Receptor Antagonists

Literature: Stebbins, K.J.; Broadhead, A.R.; Baccei, C.S.; et al. Pharmacological blockade of the DP2 receptor inhibits cigarette smoke-induced inflammation, mucus cell metaplasia, and epithelial hyperplasia in the mouse lung. *J Pharmacol Exp Ther* 2010, 332(3): 764; Broadhead, A.; Stebbins, K.J.; Stock, N.S.; Coate, H.; et al. AM206, a novel CRTH2 selective antagonist, inhibits sneezing and nasal rubs in a mouse allergic rhinitis model. Am J Respir Crit Care Med 2010, 181(Abstracts Issue): A4047

Integrity Entry Number: 691897



Organization: Pfizer

Drug Name: WYE-103231

Condition: Pain; Pain, neuropathic

Mechanism of Action: Norepinephrine Reuptake Inhibitors

Literature: O'Neill, D.J.; Adedoyin, A.; Alfinito, P.D.; Bray, J.A.; et al. Discovery of novel selective norepinephrine reuptake inhibitors: 4-[3-aryl-2,2-dioxido-2,1,3-benzothiadiazol-1(3H)-yl]-1-(methylamino)butan-2-ols (WYE-103231). J Med Chem 2010, 53(11): 4511

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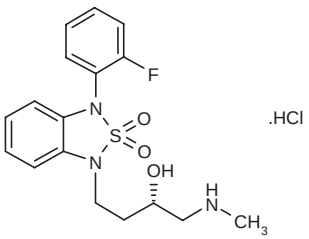


Organization: BIAL

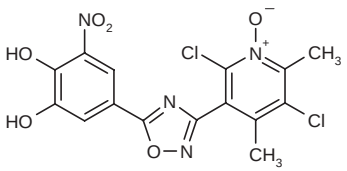
Drug Name: BIA-9-1067

Condition: Parkinson's disease

Mechanism of Action: COMT Inhibitors

Literature: Kiss, L.E.; Ferreira, H.S.; Torrão, L.; Bonifácio, M.J.; Palma, P.N.; Soares-da-Silva, P.; Learmonth, D.A. Discovery of a long-acting, peripherally selective inhibitor of catechol-*O*-methyltransferase. J Med Chem 2010, 53(8): 3396

Integrity Entry Number: 686182



Organization: Kyowa Hakko Kirin

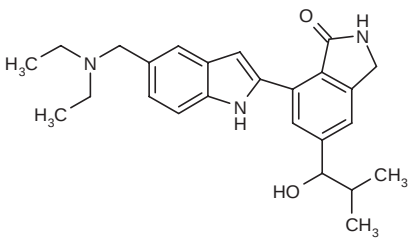
Drug Name: K-454

Condition: Cancer

Mechanism of Action: JAK2 Inhibitors; JAK3 Inhibitors

Literature: Atsumi, T.; Amishiro, N.; Yamamoto, J.; Nakazato, T.; et al. Discovery and development of novel isoindolinone derivatives as JAK inhibitors. 239th ACS Natl Meet (March 21-25, San Francisco) 2010, Abst MEDI 149

Integrity Entry Number: 476783



Organization: Nihon University (JP); Roswell Park Cancer Institute (US)

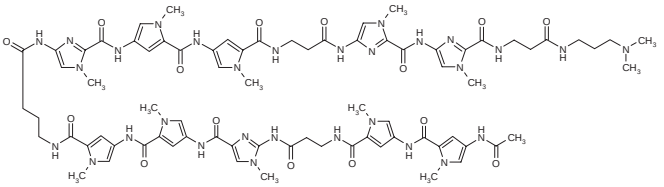
Drug Name: GB-1201

Condition: Ulcer, corneal

Mechanism of Action: TGFB1 Expression Inhibitors

Literature: Chen, M.; Matsuda, H.; Wang, L.; et al. Pretranscriptional regulation of Tgf-beta1 by PI polyamide prevents scarring and accelerates wound healing of the cornea after exposure to alkali. Mol Ther 2010, 18(3): 519

Integrity Entry Number: 690271



Organization: J-Pharma; Mitsubishi Tanabe Pharma

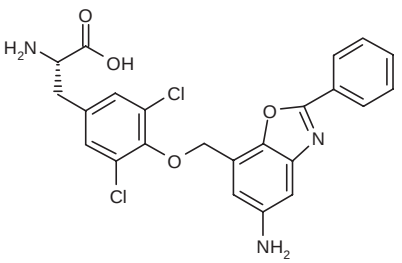
Drug Name: KYT-0353

Condition: Cancer

Mechanism of Action: Drugs Acting on Amino Acid Transporters

Literature: Oda, K.; Hosoda, N.; Endo, H.; et al. L-type amino acid transporter 1 inhibitors inhibit tumor cell growth. Cancer Sci 2010, 101(1): 173

Integrity Entry Number: 690239



Organization: Johnson & Johnson

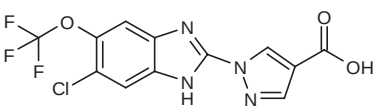
Drug Name: JNJ-42041935

Condition: Anemia

Mechanism of Action: Hypoxia-Inducible Factor Prolyl Hydroxylase Inhibitors

Literature: Rabinowitz, M.H.; Venkatesan, H.; Rosen, M.; Peltier, H.; et al. Structure based design and biological evaluation of benzimidazole HIF prolyl hydroxylase inhibitors for the treatment of anemia. 239th ACS Natl Meet (March 21-25, San Francisco) 2010, Abst MEDI 321

Integrity Entry Number: 689991



PAIN TARGETSCAPE

Thomson Reuters Integrity[SM] provides an interactive view of targets and associated drugs across all therapy areas. In this issue we offer a snapshot of the Targetscape for pain (see below). The monoclonal antibodies in development in the field of pain all act on the nerve growth factor target highlighted here.

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2. Jiang, L.J., Wang, M., Or, Y.S. *Pharmacokinetics of EDP-420 after ascending single oral doses in healthy adult volunteers.* Antimicrob Agents Chemother 2009, 53(5): 1786-92.
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