Drugs of the Future 2010, 35(4): 339-348

CCC: 0377-8282/2010
DOI: 10.1358/dof.2010.35.4.1487189

THE CUTTING EDGE OF CHEMISTRY

A PHARMA MATTERS REPORT – 2009 REVIEW

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

The discovery of new chemical entities (NCEs) brings a series of scientific challenges, not only with regard to the pathophysiological model involved, but also from a chemistry perspective. In fact, the routes of synthesis of new bioactive compounds often need to be optimized in terms of yield or economic parameters. This is particularly important when a molecule needs to be prepared in batch when entering preclinical and clinical development stages.

This section describes especially difficult to synthesize end products and a new type of chemical reaction successfully applied in the preparation of a new compound. *Thomson Reuters Integrity℠* provides key organic synthesis information including preparation schemes and sourcing information on chemical intermediates.

Routes to osteoporosis drugs

Cathepsin K inhibitors are being developed as pharmaceutical treatments for osteoporosis and bone metastasis. Teams at GlaxoSmithKline (GSK) and Merck & Co. recently reported details of intriguing new syntheses for two drugs in this area.

SB-462795

Wang and colleagues at GSK discuss process development for the potent cathepsin K inhibitor SB-462795 in *Tetrahedron* 2009, 65(32): 6291. Strategically, the synthesis exploits a ring-closing metathesis (RCM) reaction to construct a seven-membered azepanone ring. The authors illustrate in detail how several tactical iterations evolved.

The main features of the route are: a chiral auxiliary-based aldol reaction involving a crotonate imide and a hydrazine-mediated auxiliary cleavage followed by a Curtius reaction to convert the resulting unsaturated carbonyl intermediate to an allylamine derivative. Additionally, the RCM reaction to generate the azepanone is a key feature.

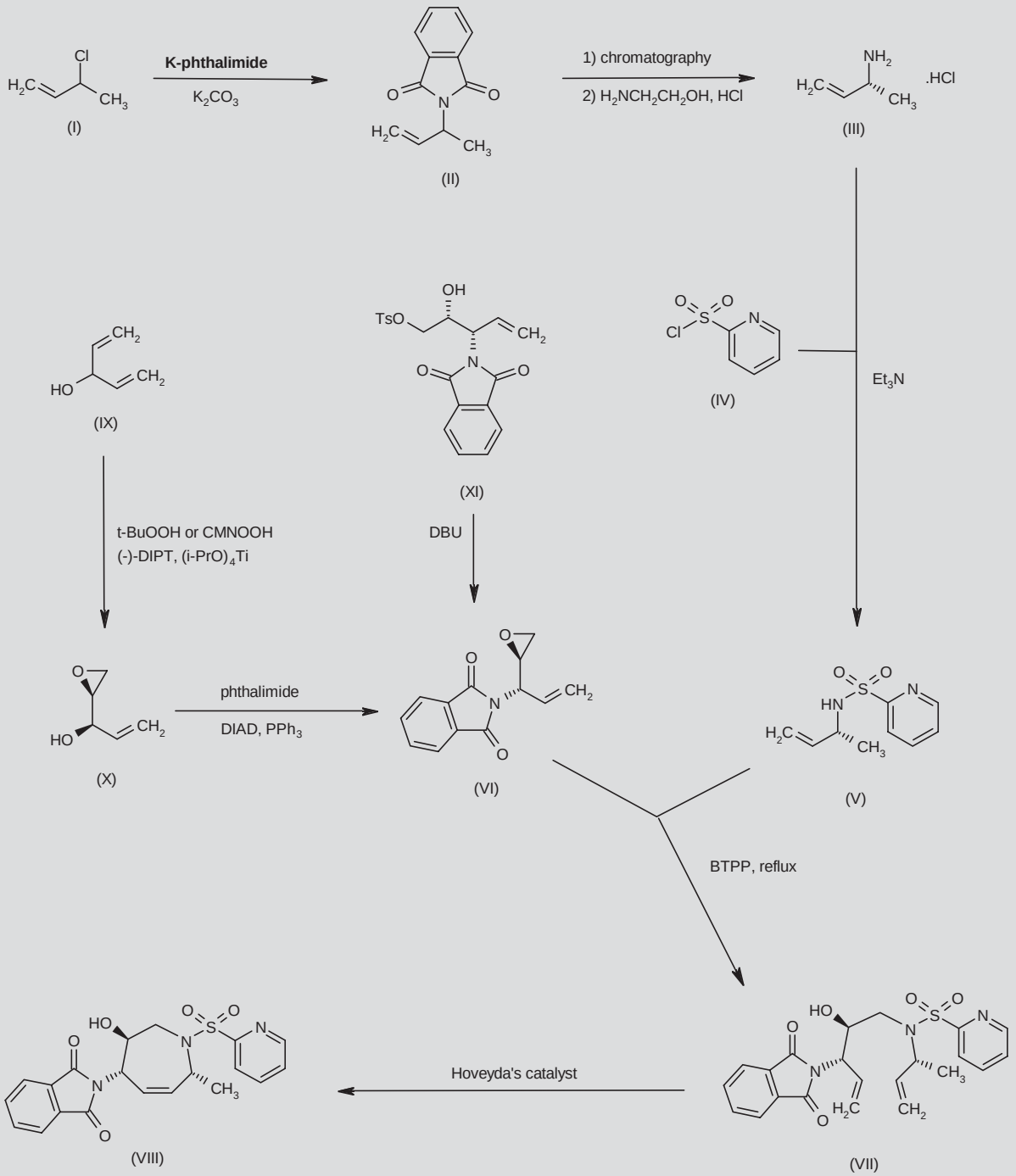
The GSK team was able to readily control the stereochemistry at C4 under thermodynamic equilibration conditions, but had significant isolation problems with the mixtures of isomers. This problem was solved in second-generation routes that control the C4 stereocenter from the outset. Other features of the routes include a practical purification of a crude epoxide precursor by selective epoxide opening using TsOH to give the "crystalline" monotosylate of a vicinal diol, an efficient epoxide-opening reaction by a sulfonamide catalyzed by BTPP, and an efficient RCM reaction. The final route is amenable to large-scale manufacturing, as demonstrated by the synthesis of more than 200 kg of SB-462795.

Odanacatib

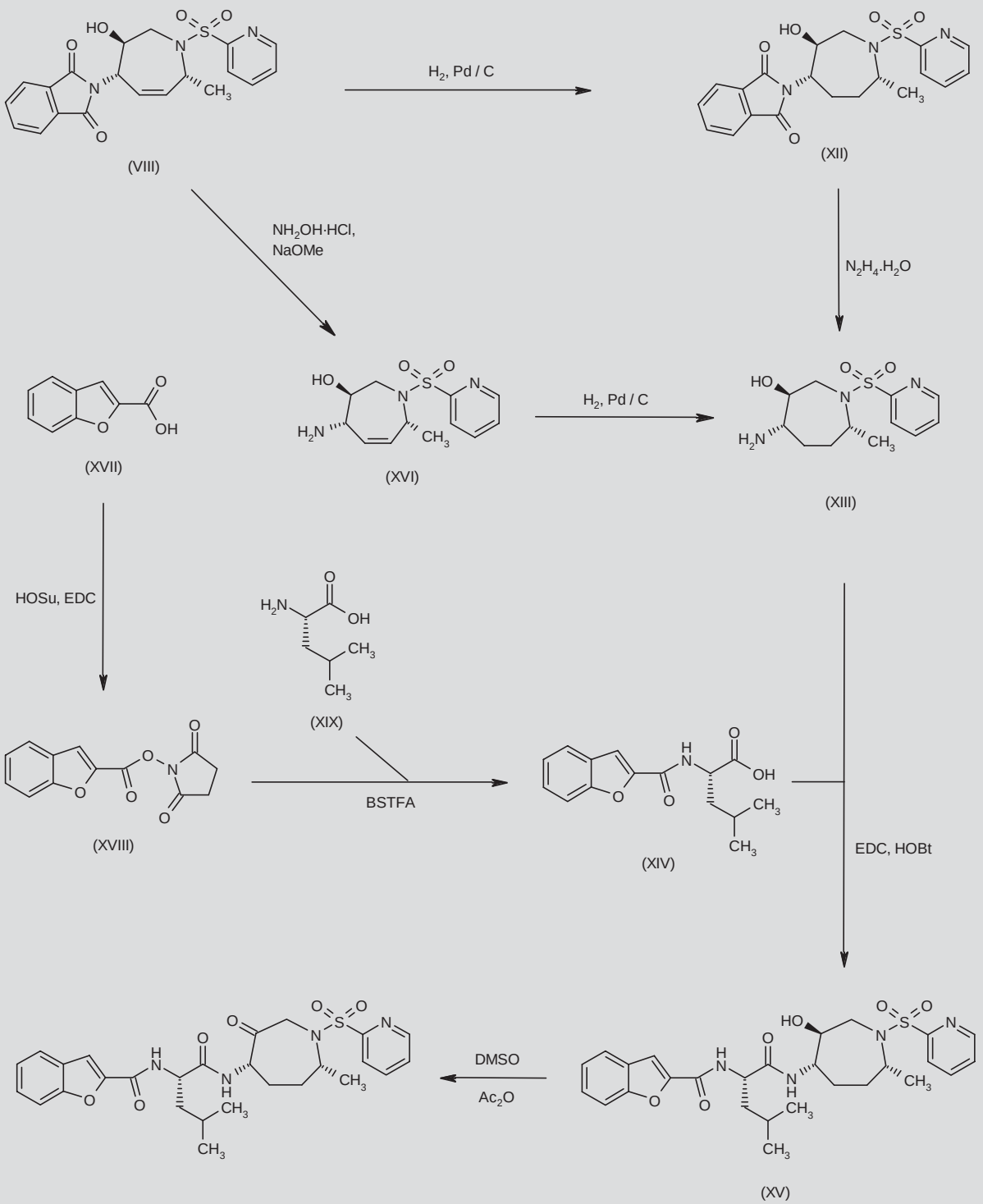
An enantioselective synthesis of a potent cathepsin K inhibitor, odanacatib (MK-0822), has been completed in just six steps with a 61% overall yield. Details are reported by O'Shea and colleagues at Merck & Co. in *J Org Chem* 2009, 74(4): 1605. The key step in their synthesis involves the novel stereospecific S_N2 triflate displacement of a chiral (*R*)-α-(trifluoromethyl)benzyl triflate with (*S*)-γ-fluoroleucine ethyl ester to generate the required (*S*)-α-(trifluoromethyl)benzyl amino stereocenter.

The researchers point out that under optimized conditions they can carry out the triflate displacement in high yield (95%) and with

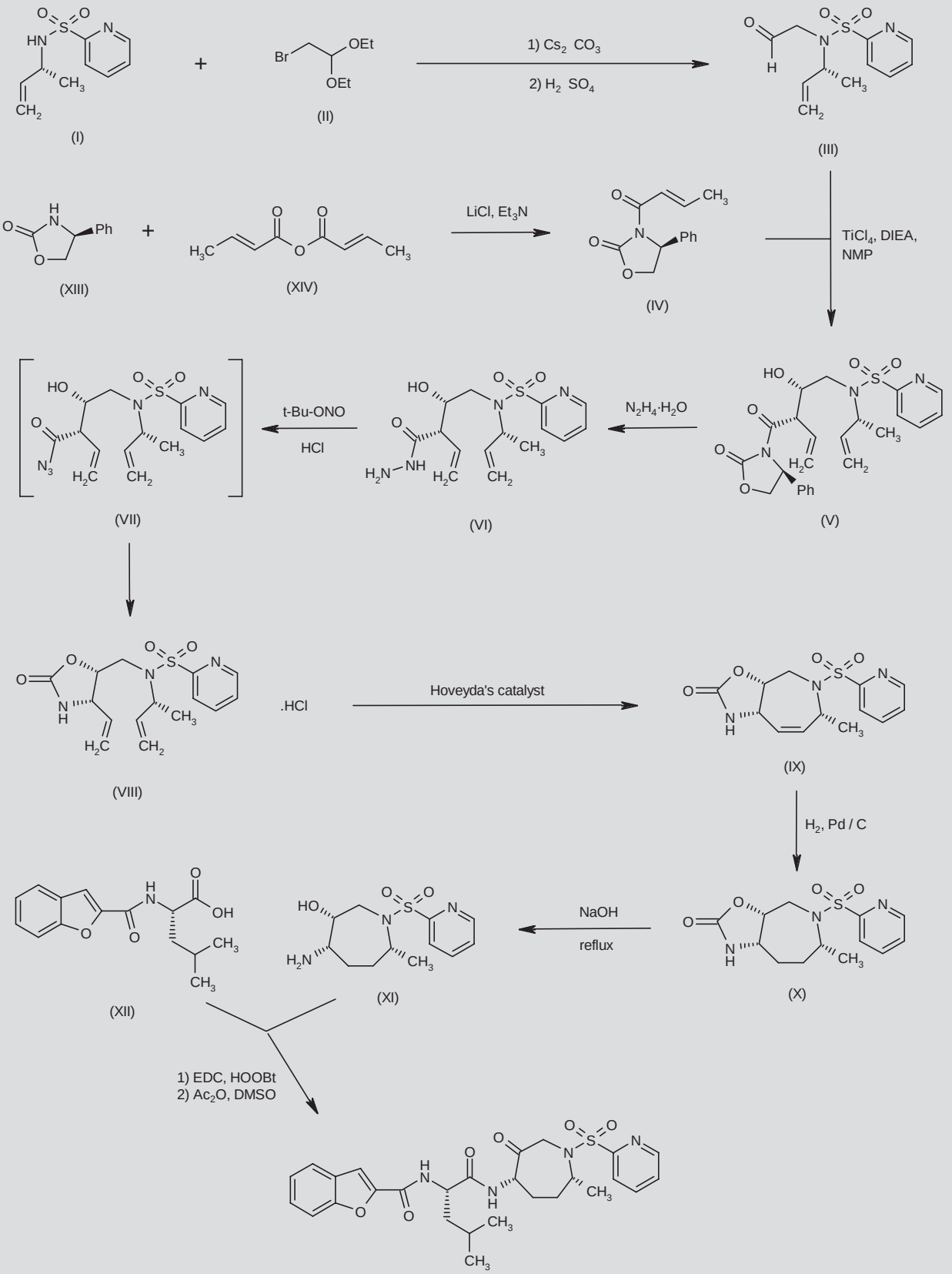
Synthesis Scheme for SB-462795 (Part 1)



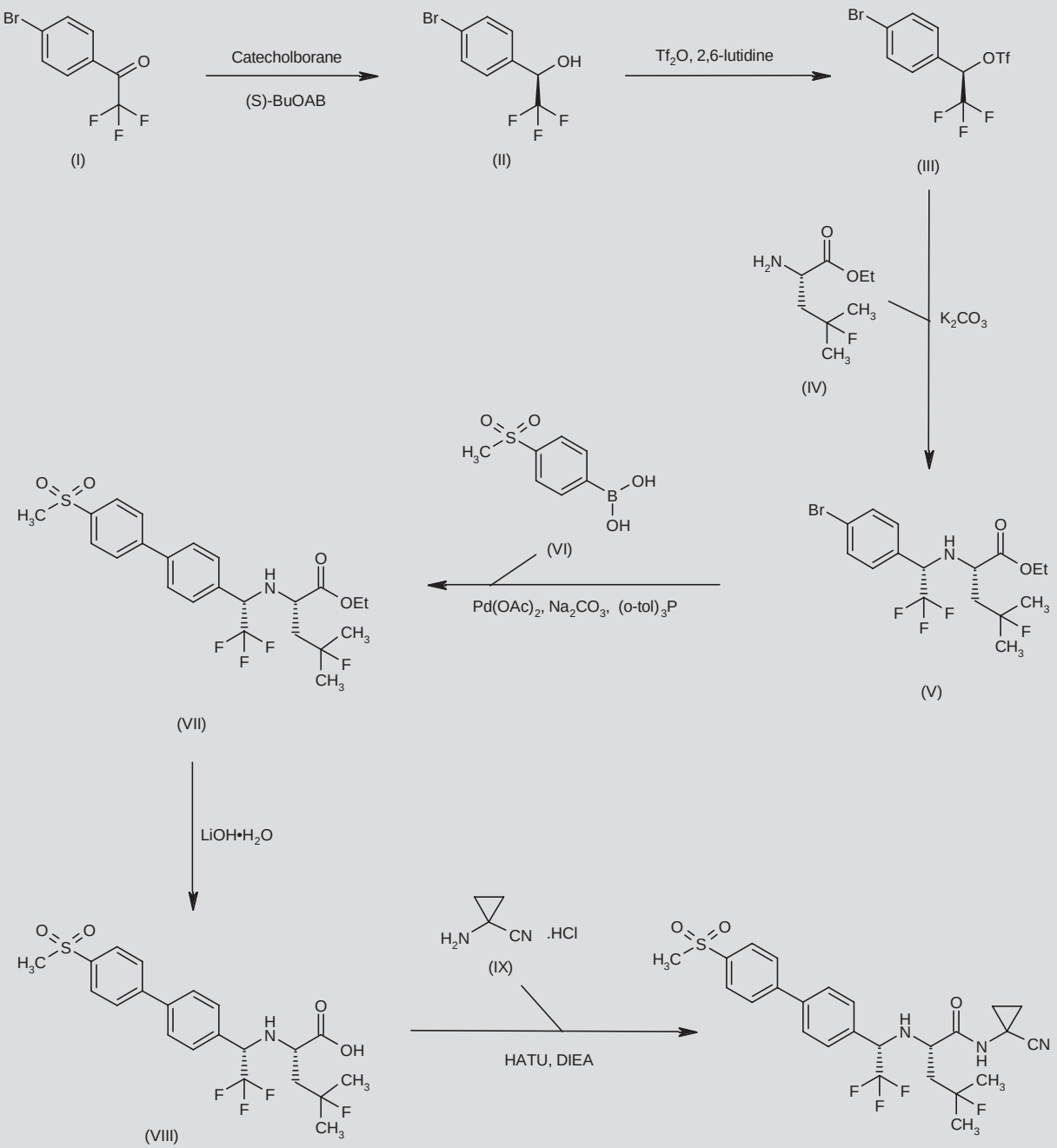
Synthesis Scheme for SB-462795 (Part 2)



Alternative Synthesis Scheme for SB-462795



Synthesis Scheme for Odanacatib



minimal loss of stereochemical integrity; they achieve 84% diastereoisomeric excess after coupling.

Importantly, they demonstrate that switching the 4-substituent on the phenyl ring from bromo to another aryl ring (present in the target structure) leads to decreased performance. Also, the use of dipolar aprotic solvents typically employed for S_N2-type displacements leads to decomposition of the triflate.

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 section illustrates newly synthesized or natural product-derived templates that can lay the groundwork for the discovery of new therapeutic agents.

Antipsychotic γ-lactam

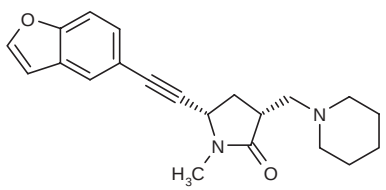
Researchers at Novartis have optimized a *cis*-γ-lactam scaffold discovered using high-throughput screening to obtain potent and selective nicotinic acetylcholine receptor α7 agonists for development as antipsychotic drugs and for the the treatment of cognition disorders. The new agonists have in vitro activity and selectivity and demonstrate good in vivo brain penetration in mice.

Therapeutic Group: Antipsychotic Drugs; Treatment of Cognition Disorders

Studied Mechanism of Action: Nicotinic AChR α7 Agonists

Source: Enz, A.; Feuerbach, D.; Frederiksen, M.U.; Gentsch, C.; Hurth, K.; Mueller, W.; Nozulak, J.; Roy, B.L. γ-Lactams – A novel scaffold for highly potent and selective α7 nicotinic acetylcholine receptor agonists. Bioorg Med Chem Lett 2009, 19(5): 1287

Integrity Entry Number: 654867



Stroke therapy

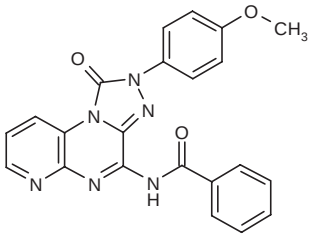
Italian academics have discovered a new class of human adenosine A_3 receptor antagonists with potential in the treatment of ischemic stroke. The team has worked with two series of 2-arylpyrido[2,3-*e*]-1,2,4-triazolo[4,3-*a*]pyrazin-1-one (PTP) derivatives, 4-oxo- or 4-amino-substituted PTPs. In both series, hydrogen bond acceptor substituents were introduced in the 2-phenyl ring and acyl or cycloalkyl residues were added to the 4-amino group. They saw promisingly high affinities for human A_3 receptors and selectivity over A_1 and A_2.

Therapeutic Group: Treatment of Ischemic Stroke

Studied Mechanism of Action: Adenosine A_3 Antagonists

Source: Colotta, V.; Lenzi, O.; Catarzi, D.; Varano, F.; Filacchioni, G.; Martini, C.; Trincavelli, L.; Ciampi, O.; Pugliese, A.M.; Traini, C.; Pedata, F.; Morizzo, E.; Moro, S. Pyrido[2,3-*e*]-1,2,4-triazolo[4,3-*a*]-pyrazin-1-one as a new scaffold to develop potent and selective human A3 adenosine receptor antagonists. Synthesis, pharmacological evaluation, and ligand-receptor modeling studies. J Med Chem 2009, 52(8): 2407

Integrity Entry Number: 661638



Calpain inhibitor optimization

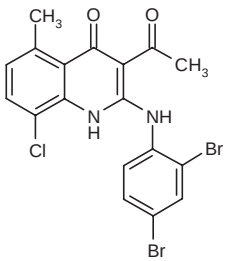
Alzheimer's disease and dementia are the targets of new calpain inhibitors found by screening the Korean Chemical Bank. 3-Acetyl-2-aminoquinolin-4-one derivatives emerged as μ-calpain inhibitors with higher specificity and efficacy than MDL-28170. The researchers discuss the influence of the size and charge properties of substitutions on the phenylamino ring as providing an opportunity for optimization.

Therapeutic Group: Treatment of Alzheimer's Dementia

Studied Mechanism of Action: μ-Calpain (Calpain-1) Inhibitors; Cathepsin B Inhibitors; Cathepsin L Inhibitors

Source: Kang, D.H.; Jun, K.Y.; Lee, J.P.; Pak, C.S.; Na, Y.; Kwon, Y. Identification of 3-acetyl-2-aminoquinolin-4-one as a novel, non-peptidic scaffold for specific calpain inhibitory activity. J Med Chem 2009, 52(9): 3093

Integrity Entry Number: 666769



Chalcones as MAO Inhibitors

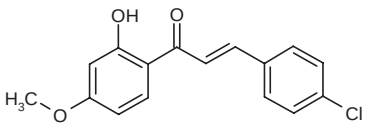
A series of chalcones with potential application as antiparkinsonian drugs and for treating cognition disorders were the focus of several academic researchers. They found compounds with the ability to selectively inhibit human monoamine oxidases (MAO) at concentrations in the micro- and nanomolar ranges. Docking studies reveal new insights into the inhibition mechanism and could assist in rational drug design of more potent and selective chalcone MAO inhibitors.

Therapeutic Group: Antiparkinsonian Drugs; Treatment of Cognition Disorders

Studied Mechanism of Action: MAO-B Inhibitors

Source: Chimenti, F.; Fioravanti, R.; Bolasco, A.; Chimenti, P.; Secci, D.; Rossi, F.; Yanez, M.; Orallo, F.; Ortuso, F.; Alcaro, S. Chalcones: A valid scaffold for monoamine oxidases inhibitors. J Med Chem 2009, 52(9): 2818

Integrity Entry Number: 666774



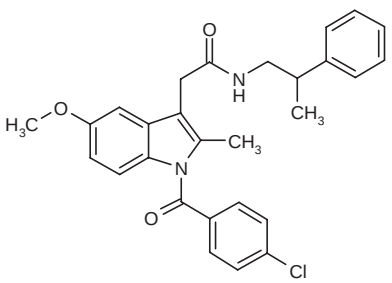
Sterol defeat for parasite

A new series of inhibitors of the sterol 14α-demethylase enzyme from *Trypanosoma cruzi* (TC), the cause of Chagas disease, has been found with an indomethacin-amide scaffold. The same structure is present in a class of cyclooxygenase-2-selective inhibitors, but in this case inhibits TCCYP51 and shows antiparasitic activity in cultured TC cells. The authors suggest that the mode of action may be through inhibition of sterol biosynthesis in the parasite.

Therapeutic Group: Antitrypanosomals

Source: Konkle, M.E.; Hargrove, T.Y.; Kleshchenko, Y.Y.; von Kries, J.P.; Ridenour, W.; Uddin, M.J.; Caprioli, R.M.; Marnett, L.J.; Nes, W.D.; Villalta, F.; Waterman, M.R.; Lepesheva, G.I. Indomethacin amides as a novel molecular scaffold for targeting *Trypanosoma cruzi* sterol 14α-demethylase. J Med Chem 2009, 52(9): 2846

Integrity Entry Number: 666791



FEATURED SCAFFOLD

Novel Notch approach to cancer – stapled peptides

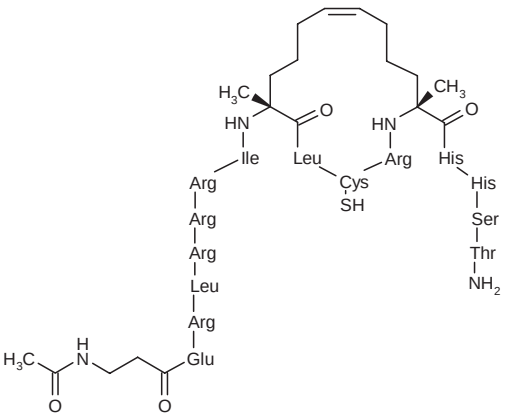
Synthetic, cell-permeable, stabilized α-helical peptides with potential anticancer properties have been discovered where other efforts have failed. The hydrocarbon-stapled peptide SAHM1 targets a critical protein–protein interface in the Notch transactivation complex. The researchers demonstrate high-affinity binding, which prevents assembly of the active transcriptional complex, resulting in direct inhibition of Notch signaling.

Therapeutic Group: Oncolytic Drugs

Studied Mechanism of Action: Notch Signaling Inhibitors

Source: Moellering, R.E.; Cornejo, M.; Davis, T.N.; Del Bianco, C.; Aster, J.C.; Blacklow, S.C.; Kung, A.L.; Gilliland, D.G.; Verdine, G.L.; Bradner, J.E. Direct inhibition of the NOTCH transcription factor complex. Nature 2009, 462(7270): 182

Integrity Entry Number: 679726



NEW MOLECULAR MECHANISMS OF ACTION

The elucidation of the human genome is facilitating the discovery of a wide array of new pharmacological targets, as well as the identification of new pathways for potential therapeutic intervention. This section includes recently disclosed new molecular mechanisms of action along with examples of associated modulators and the corresponding disease area of interest.

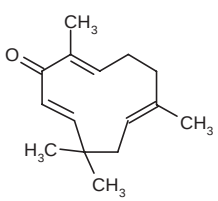
We can stress the importance of the discovery of new mechanisms of action leading to oncolytic drugs. This therapeutic area continues to be of utmost relevance, as can be seen in the number of new patents published in 2009, or by the fact that as much as 15% of patents available in *Thomson Reuters Integrity*SM are for compounds for the treatment of cancer. This shows that despite the R&D efforts invested in the discovery of better and safer drugs for cancer, there is still a strong unmet need compared with other pathologies.

NUCLEAR FACTOR, ERYTHROID DERIVED 2, LIKE 2 (Nrf2) ACTIVATORS

Main Related Conditions: Cancer

Drug Name: Zerumbone

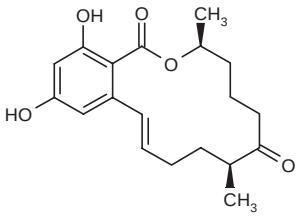
Integrity Entry Number: 310722



CARBONYL REDUCTASE [NADPH] 1 INHIBITORS

Main Related Conditions: Cancer

Integrity Entry Number: 659471

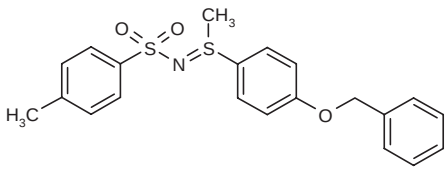


PIRIN INHIBITORS

Main Related Conditions: Cancer

Drug Name: NPD-123

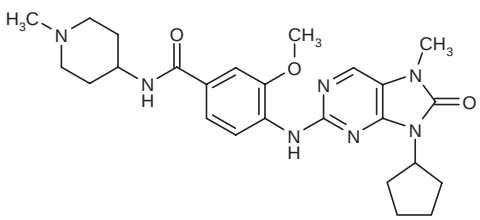
Integrity Entry Number: 681410



TTK INHIBITORS

Main Related Conditions: Cancer

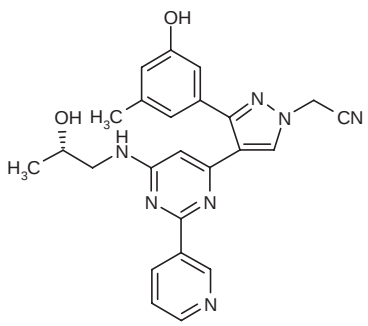
Integrity Entry Number: 654066



ROS INHIBITORS

Main Related Conditions: Cancer

Integrity Entry Number: 666682

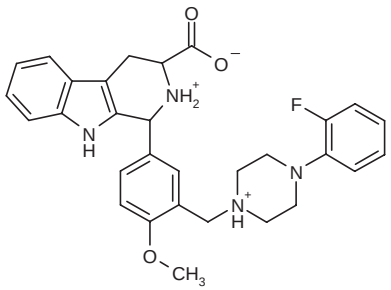


NICOTINIC ACID ADENINE DINUCLEOTIDE PHOSPHATE (NAADP) ANTAGONISTS

Main Related Conditions: Diabetes type 2

Drug Name: Ned-19

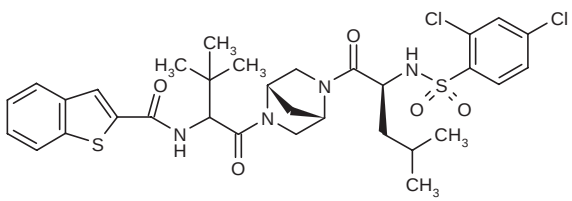
Integrity Entry Number: 654911



TRPV4 ANTAGONISTS

Main Related Conditions: Pain; Congestive heart failure; Overactive bladder; Osteoarthritis

Integrity Entry Number: 673385

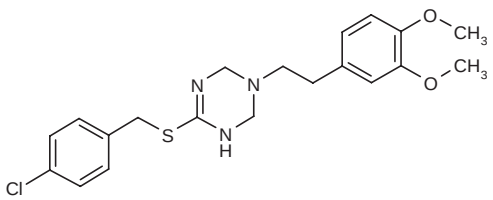


P20 INHIBITORS

Main Related Conditions: Bacterial infection

Drug Name: MAC-13243

Integrity Entry Number: 676726



THE STARTING LINE

A selection of new molecular entities (NMEs) ready to progress in the R&D arena, including pharmacological activity, originator and chemical structure of the compounds.

The fields of cancer and psychopharmacology seem to have been particularly active recently. In fact, more than half of the selected NMEs presented at recent conferences and in the literature pertain to these categories.

Organization: Università degli Studi di Milano (IT)

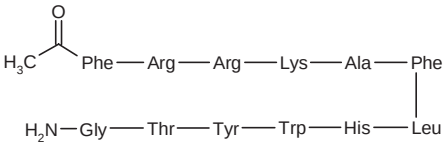
Drug Name: Plug-X

Condition: Cancer

Mechanism of Action: Antimitotic Drugs, Tubulin polymerization inhibitors

Literature: Pieraccini, S.; Saladino, G.; Cappelletti, G.; et al. In silico design of tubulin-targeted antimitotic peptides. Nat Chem 2009, 1(8): 642

Integrity Entry Number: 677889



Organization: Genentech

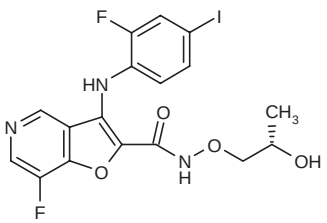
Drug Name: G-573

Condition: Cancer

Mechanism of Action: Mitogen-Activated Protein Kinase Kinase (MEK) Inhibitors

Literature: Choo, E.F.; Belvin, M.; Hoeflich, K; et al. Preclinical disposition and pharmacokinetics-pharmacodynamic modeling of biomarker response and tumor growth inhibition in xenograft mouse models with G-573, a MEK inhibitor. Drug Metab Rev 2009, 41(Suppl. 3): Abst 327 [16th North Am ISSX Meet (October 18-22, Baltimore) 2009]

Integrity Entry Number: 676787



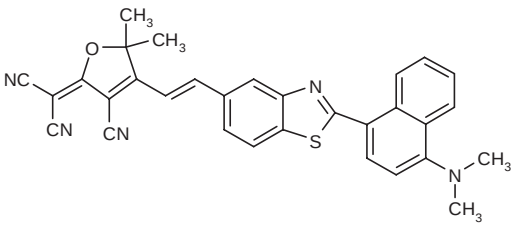
Organization: Massachusetts General Hospital; Massachusetts Institute of Technology; University of Pittsburgh (US)

Drug Name: RD-36

Condition: Dementia, Alzheimer's type

Literature: Neal, K.L.; Raymond, S.B.; Meek, S.T.; et al. Characterization of novel near-infrared organic compounds for imaging of amyloid aggregates in mouse models of Alzheimer's disease. 39th Annu Meet Soc Neurosci (October 17-21, Chicago) 2009, Abst 288.23

Integrity Entry Number: 676286



Organization: Merck & Co.

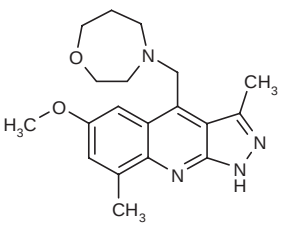
Drug Name: SCH-1518291

Condition: Diagnostics, Schizophrenia

Mechanism of Action: Phosphodiesterase PDE10A Inhibitors

Literature: Mullins, D.E.; Guzzi, M.F.; Lavey, C.; et al. Characterization of the in vivo binding properties of SCH 1518291, a potent and selective PDE10 inhibitor. 39th Annu Meet Soc Neurosci (October 17-21, Chicago) 2009, Abst 646.16

Integrity Entry Number: 676723



Organization: Pfizer

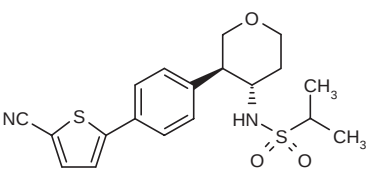
Drug Name: PF-4778574

Condition: Cognitive disorders, Schizophrenia

Mechanism of Action: AMPA Agonists

Literature: Shaffer, C.L.; Scialis, R.J.; Lotarski, S.; et al. Defining the mechanism-mediated exposure-response continuum of a novel AMPA receptor potentiator. 39th Annu Meet Soc Neurosci (October 17-21, Chicago) 2009, Abst 883.17

Integrity Entry Number: 677837



Organization: Abbott

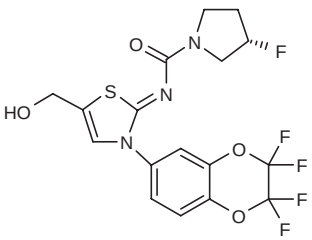
Drug Name: A-988056

Condition: Cognitive disorders, Psychosis

Mechanism of Action: Nicotinic α7 Positive Allosteric Modulators

Literature: Faghih, R.; Gfesser, G.A.; Malysz, J.; et al. Discovery of novel positive allosteric modulators of the α7 nicotinic acetylcholine receptor. 238th ACS Natl Meet (August 16-20, Washington) 2009, Abst MEDI 225

Integrity Entry Number: 669376



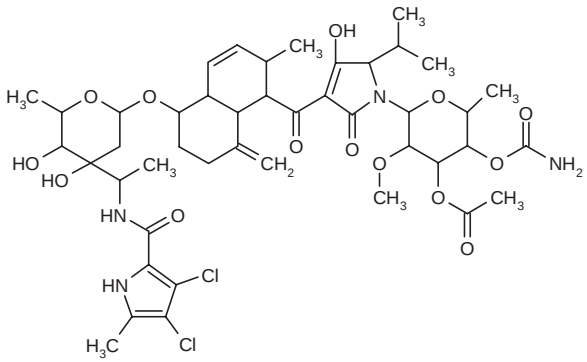
Organization: Microbial Chemistry Research Foundation (JP)

Drug Name: Amycolamicin

Condition: Bacterial infection

Literature: Igarashi, M.; Sawa, R.; Umekita, M.; et al. Amycolamicin: A novel antibiotic from *Streptomyces* sp. 49th Intersci Conf Antimicrob Agents Chemother (ICAAC) (September 12-15, San Francisco) 2009, Abst F1-1497

Integrity Entry Number: 676487



Organization: Amira Pharmaceuticals

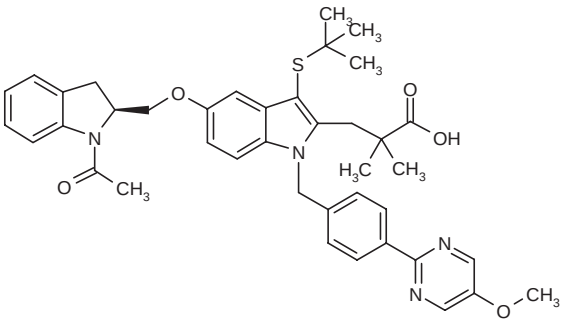
Drug Name: AM-679

Condition: Inflammatory disorders

Mechanism of Action: 5-Lipoxygenase-Activating Protein (FLAP) Inhibitor

Literature: Musiyenko, A.; Correa, L.; Stock, N.; Hutchinson, J.H.; Lorrain, D.S.; Bain, G.; Evans, J.F.; Barik, S. A novel 5-lipoxygenase-activating protein inhibitor, AM679, reduces inflammation in the respiratory syncytial virus-infected mouse eye. Clin Vaccine Immunol 2009, 16(11): 1654

Integrity Entry Number: 678370



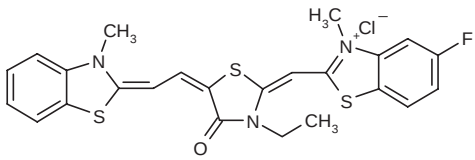
Organization: Hoshi University (JP); Swiss Tropical Institute (CH); Synstar Japan

Drug Name: SJL-01

Condition: Leishmaniasis

Literature: Yang, M.; Arai, C.; Bakar, A.; et al. Fluorinated rhodacyanine (SJL-01) possessing high efficacy for visceral leishmaniasis (VL). J Med Chem 2009 2010, 53(1): 368

Integrity Entry Number: 678333



Organization: NeuroMed Pharmaceuticals

Drug Name: NP-118809

Condition: Pain

Mechanism of Action: N-Type Calcium Channel ($Ca_V2.2$) Blocker

Literature: Zamponi, G.W.; Feng, Z.P.; Zhang, L.; Pajouhesh, H.; Ding, Y.; Belardetti, F.; Pajouhesh, H.; Dolphin, D.; Mitscher, L.A.; Snutch, T.P. Scaffold-based design and synthesis of potent N-type calcium channel blockers. Bioorg Med Chem Lett 2009, 19(22): 6467

Integrity Entry Number: 346687