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CCC: 0377-8282/2010
DOI: 10.1358/dof.2010.35.8.1537905

THE CUTTING EDGE OF CHEMISTRY

A PHARMA MATTERS REPORT – JANUARY-MARCH 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

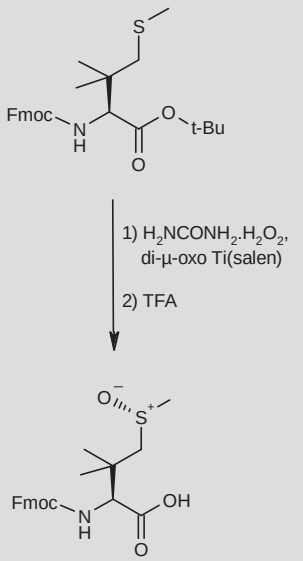
Soaking up polytheonamide B synthesis

Polytheonamides A and B (PA and PB) were first isolated from the coral reef sponge *Theonella swinhoei*, a well-known source of novel natural products with physiological activity. What makes PB particularly interesting is that it forms monovalent cation-selective transmembrane channels by penetrating vectorially into the biological membrane, forming a single-molecule channel and remaining in the membrane (1, 2). Its extraordinary cytotoxicity against mouse P388 leukemia cells (EC_{50} = 79 pM) can be attributed to these functional properties.

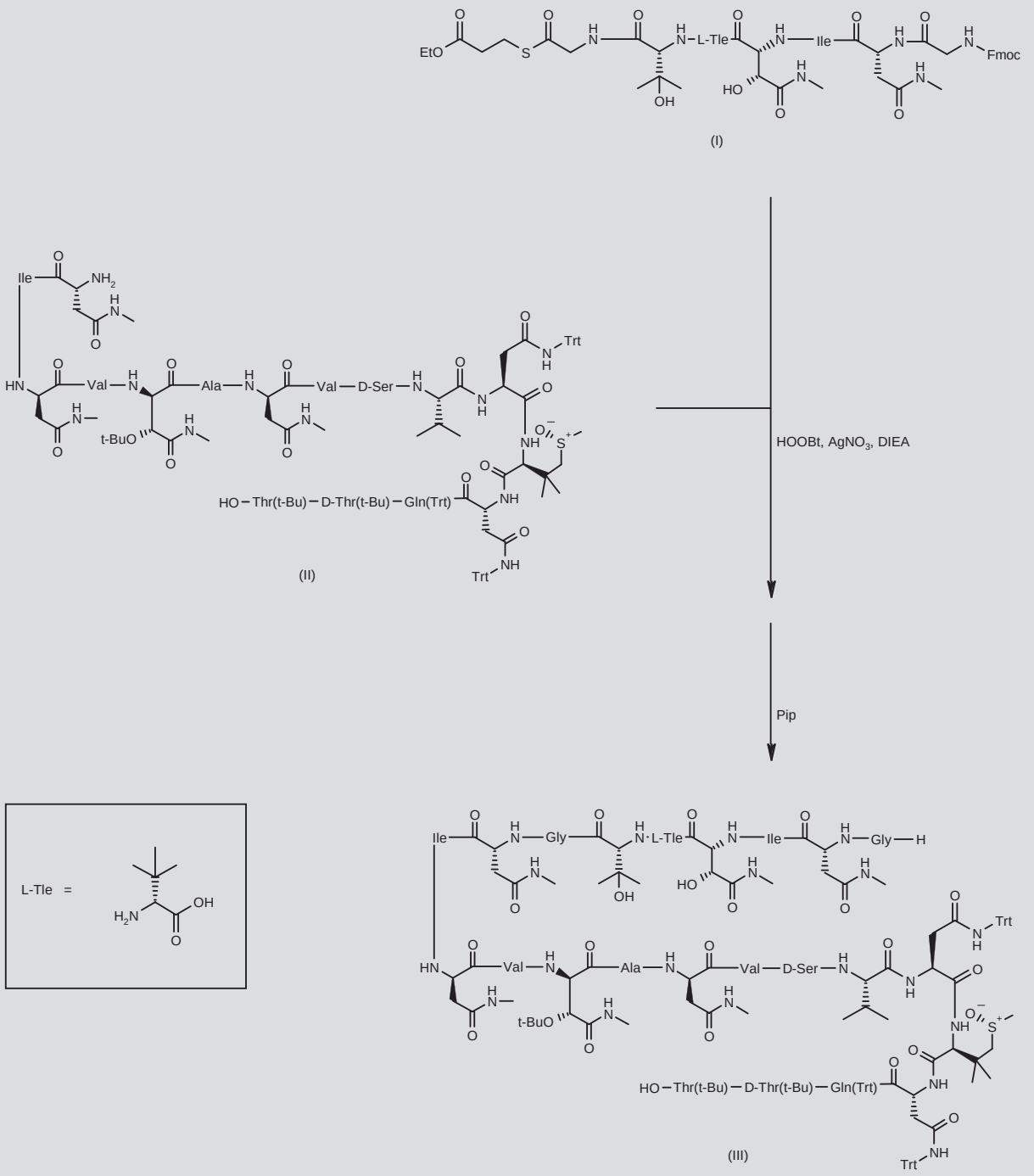
Researchers have assumed that an unidentified symbiotic microorganism present in *T. swinhoei* is responsible for the biosynthesis of polytheonamides. As such, the total synthesis of PB has represented a challenge. Scientists at The University of Tokyo have performed the first total synthesis of PB (3) . In detail, the team designed a four-stage synthesis. The first step is the obtention of 8 of the 13 nonproteinogenic amino acid monomers present in PB that required synthetic preparation. The second stage is the preparation of four designed peptide fragments by solid-phase synthesis using Fmoc rather than Boc chemistry. The third stage involves the assembly of the four peptide fragments adequately derivatized as thioesters to be used in the Ag^+-mediated amide formation (Ajinomoto conditions) selected as the method of coupling. The fourth and final step involves global deprotection under controlled acidic conditions.

This strategy not only has made it much more straightforward to synthesize such a significant compound as PB, but could allow chemists to construct other polypeptide drugs for testing against a range of disorders. The authors also point out: *"The synthetic material now available will allow studies of the relationships between its conformational properties, channel functions and cytotoxicity."* Indeed, they conclude: *"This attempt to gain precise atom-by-atom control of the structure will provide the first chemical basis for systematically correlating its molecular structure and biological function."*

Example: Preparation of Nonproteinogenic Amino Acid



Synthesis Scheme for Polytheonamide B: Peptide Fragment Assembly



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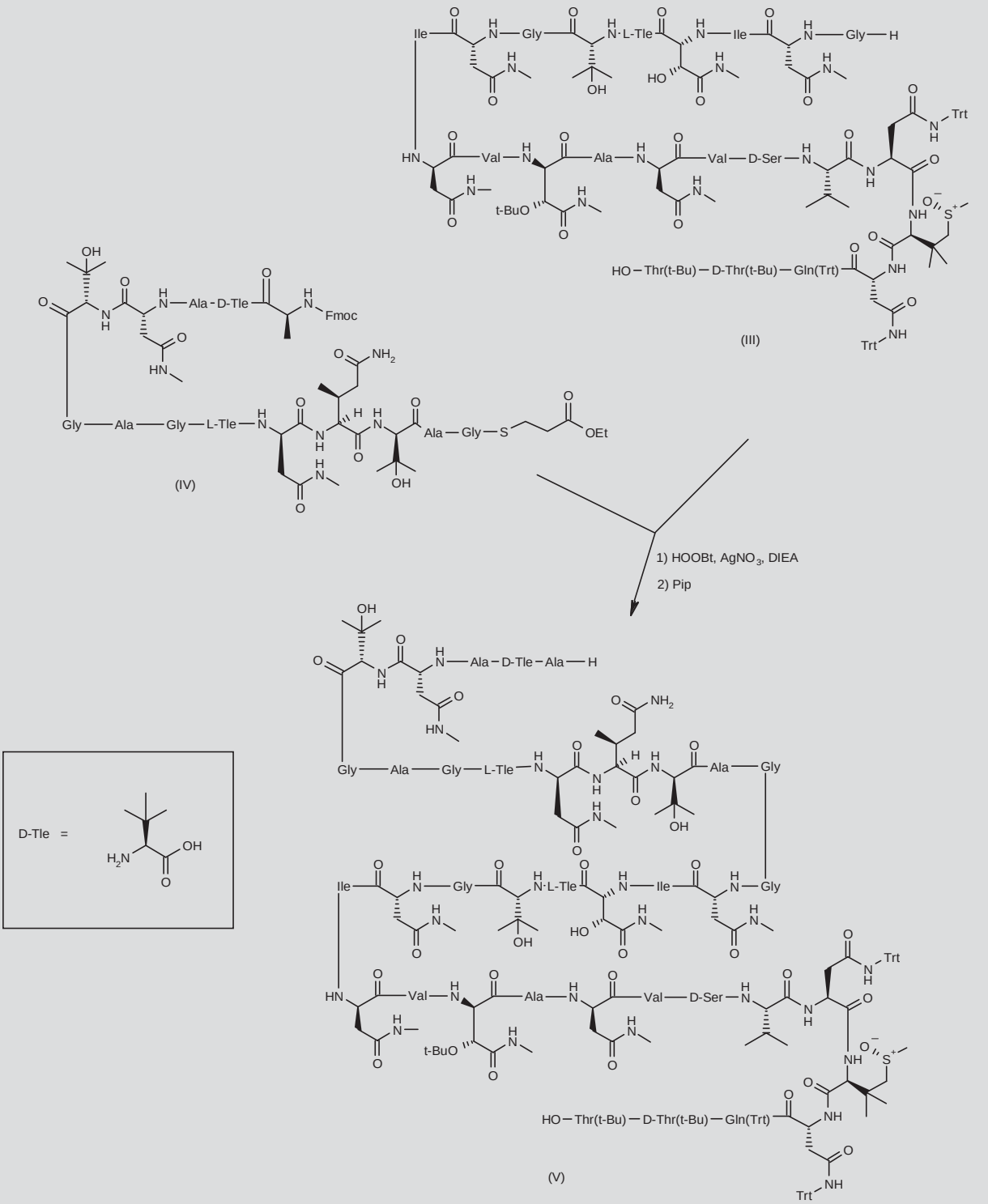
Synthesis Scheme for Polytheonamide B: Peptide Fragment Assembly (Cont.)



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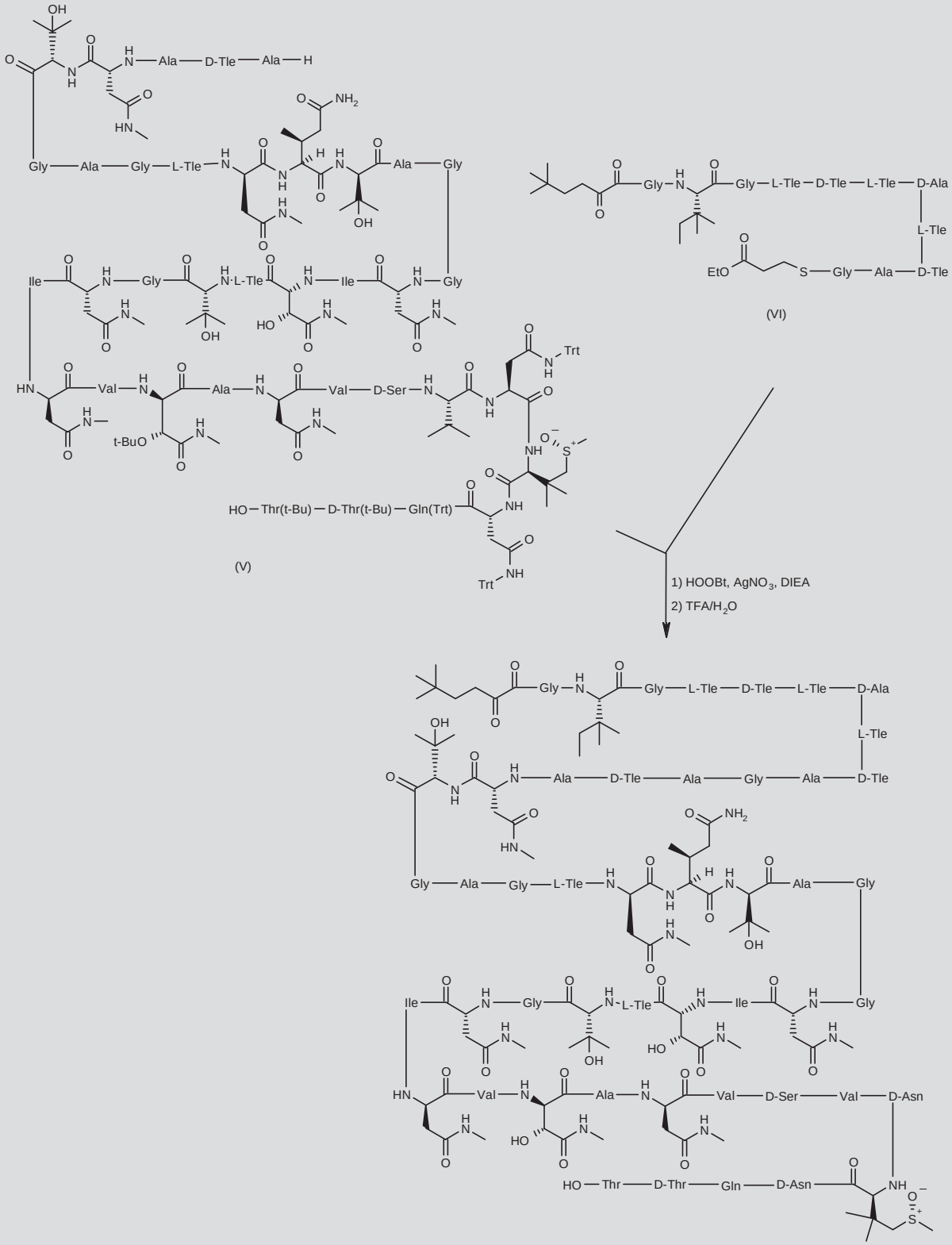
Synthesis Scheme for Polytheonamide B: Peptide Fragment Assembly (Cont.)



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 emphasize this point once again. For instance, a series of 2-arylbenzoxazoles from Merck & Co. offers hope for treating dyslipidemia and atherosclerosis, while arthritis is the target of Almirall's new (iso)nicotinic acids. A promising skeleton from Novartis is also featured in this issue and offers a new lead for immunosuppression.

Hypolipidemic benzoxazoles

Merck & Co. scientists have developed a series of 2-arylbenzoxazoles that block cholesteryl ester transfer protein (CETP) and therefore might be useful in treating lipoprotein disorders and atherosclerosis. Their structure–activity studies on the impact of varying the substitution on the benzoxazole moiety suggest that substitution at the 5- and 7-positions is beneficial to CETP inhibition. The most potent compound of the series has an IC_{50} of 28 nM.

Therapeutic Group: Treatment of Lipoprotein Disorders; Treatment of Disorders of the Coronary Arteries and Atherosclerosis

Studied Mechanism of Action: Cholesteryl Ester Transfer Protein (CETP) Inhibitors

Source: Smith, C.J.; Ali, A.; Chen, L.; Hammond, M.L.; et al. 2-Arylbenzoxazoles as CETP inhibitors: Substitution of the benzoxazole moiety. Bioorg Med Chem Lett 2010, 20(1): 346

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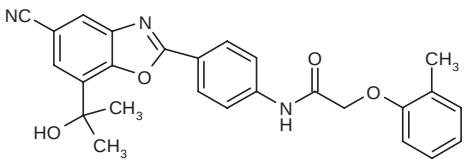


Anti-inflammatory amino(iso)nicotinic acids

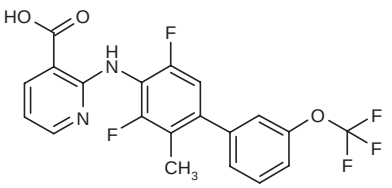
Arthritis is the focus of novel, patented dihydroorotate dehydrogenase (DHOdehase) inhibitors from Almirall that are orally active and could be suitable for treating autoimmune conditions such as rheumatoid arthritis. The potent amino(iso)nicotinic acid derivatives represent a new scaffold for DHOdehase inhibitors, a biaryl nicotinic acid derivative showing an IC_{50} of 6 nM against human DHOdehase (featured molecule). Structure–activity studies and optimization of the series led to one particular compound (chemical structure undisclosed) with potent in vitro activity against human, rat and mouse DHOdehase (IC_{50} = 0.037, 0.034 and 0.07 μM, respectively) compared with that of teriflunomide (IC_{50} = 1.5, 0.033 and 1.1 μM, respectively). The compound also inhibits the proliferation of human peripheral blood mononuclear cells more effectively and has demonstrated efficacy in reducing inflammation, as measured by paw volume, in a rat model.

Therapeutic Group: Antiarthritic Drugs

Studied Mechanism of Action: Dihydroorotate Dehydrogenase (DHOdehase) Inhibitors

Source: Erra, M.; Sanahuja, J.; Fonquerna, S.; Navarro, E.; et al. Best in class DHODH inhibitors: Evolution of clinical compounds. 239th ACS Natl Meet (March 21-25, San Francisco) 2010, Abst MEDI 461

Integrity Entry Number: 691251



Imidazo[1,2-*a*]pyrazine anticancer drugs

Aurora kinase A (ARK-1) and aurora kinase B (ARK-2) are enzymes belonging to a family of three mitotic serine/threonine-protein kinases that are critical regulators of mitosis, overexpressed in tumors, and thus have been longstanding targets for anticancer compounds. Merck & Co. has recently disclosed novel dual inhibitors of aurora kinases A and B based on an imidazo[1,2-*a*]pyrazine scaffold. Lead optimization allowed for the identification of progression candidates, although they showed poor oral bioavailability.

Therapeutic Group: Oncolytic Drugs

Studied Mechanism of Action: Aurora Kinase A (ARK-1) Inhibitors; Aurora Kinase B (ARK-2) Inhibitors

Source: Kerekes, A.D.; Esposite, S.J.; Doll, R.J.; Yu, T.; et al. Aurora kinase inhibitors based on the imidazolopyrazine core: Fluorine incorporation improves oral absorption and exposure. 239th ACS Natl Meet (March 21-25, San Francisco) 2010, Abst MEDI 146; Yu, T.; Tagat, J.R.; Zhang, Y.; Xiao, Y.; et al. Discovery of Aurora kinase inhibitors based on 3,6,8-trisubstituted imidazo[1,2-*a*]pyrazine scaffold. 239th ACS Nat Meet (March 21-25, San Francisco) 2010, Abst MEDI 145

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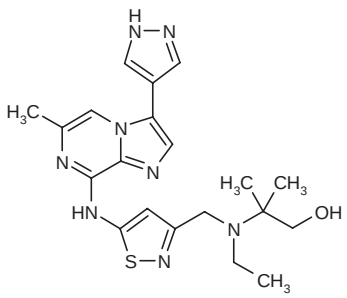

Pyrazoles avoid rejection

Employing a high-throughput screening and hit-to-lead optimization approach on lysophospholipid $S1P_1$ receptor agonists initially derived from the monoterpene (+)-3-carene, research at Novartis led to the discovery of a pyrazole scaffold displaying selective $S1P_1$ receptor agonist properties, excellent metabolism and pharmacokinetic properties and efficacy in animals models of autoimmune diseases.

Therapeutic Group: Immunosuppressants; Treatment of Transplant Rejection

Studied Mechanism of Action: Lysophospholipid $S1P_1$ Receptor Agonists

Source: Zécri, F.J.; Albert, R.; Landrum, G.; Hinterding, K.; et al. Pyrazole derived from (+)-3-carene; a novel potent, selective scaffold for sphingosine-1-phosphate (S1P1) receptor agonists. Bioorg Med Chem Lett 2010, 20(1): 35; Zécri, F.J.; Albert, R.; Baenteli, R.; Landrum, G.; et al. Discovery and optimization of multiple scaffolds of selective S1P1 receptor agonists. 239th ACS Natl Meet (March 21-25, San Francisco) 2010, Abst MEDI 31

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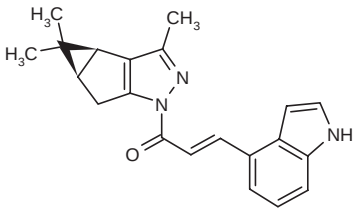

Inhibiting osteoarthritis with (pyridin-4-yl)-*2H*-tetrazoles

The treatment of osteoarthritis is a major target of modern drug discovery, and finding inhibitors of matrix metalloproteinase MMP-13 (collagenase 3) represents a promising approach. Pfizer has disclosed potent and highly selective MMP-13 inhibitors. The orally bioavailable compounds were built on a (pyridin-4-yl)-*2H*-tetrazole scaffold. In a preclinical rat model of osteoarthritis, one particular compound was shown to reduce levels of type II collagen neoepitope (TIINE), a biomarker of cartilage degradation, hence suggesting potential for cartilage protection.

Therapeutic Group: Treatment of Osteoarthritis

Studied Mechanism of Action: MMP-13 (Collagenase 3) Inhibitors

Source: Schnute, M.E.; O'Brien, P.M.; Nahra, J.; Morris, M.; et al. Discovery of (pyridin-4-yl)-2H-tetrazole as a novel scaffold to identify highly selective matrix metalloproteinase-13 inhibitors for the treatment of osteoarthritis. Bioorg Med Chem Lett 2010, 20(2): 576

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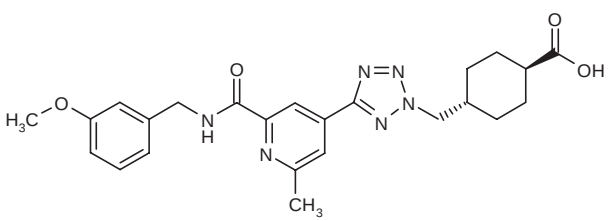


Featured Scaffold

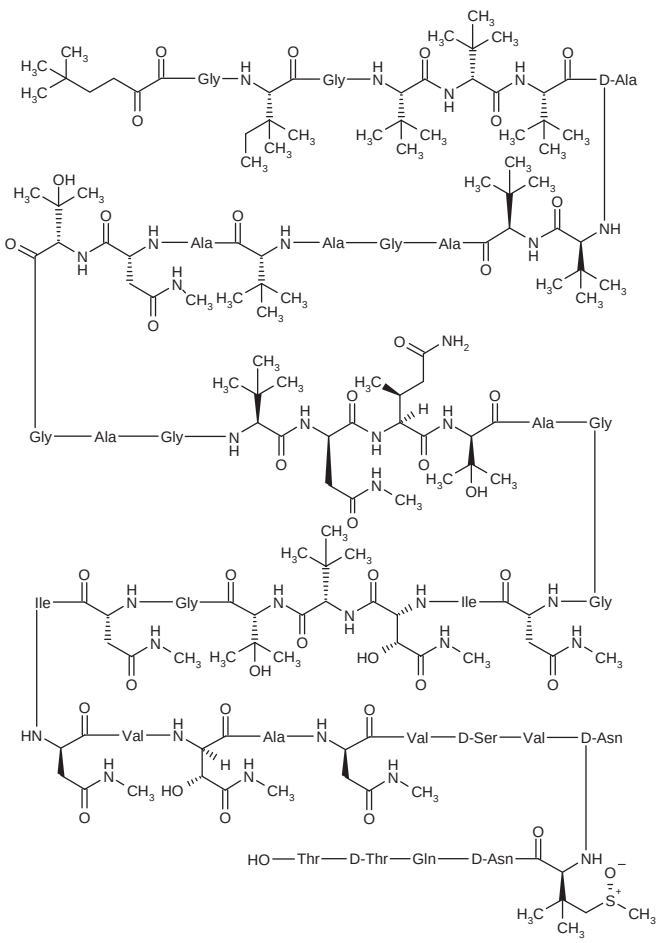
Tubular scaffolding

Polytheonamide B is the largest nonribosomal peptide known, consisting of 48 amino acid residues with an alternating D- and L-configuration, most of which are nonproteinogenic. These structural properties led to the peptide folding in a tubular β-helix stabilized by inter-residue hydrogen bonds and with all the side chains oriented outside the helix. These features indicate that PB forms single-molecule transmembrane channels that permeate monovalent cations and may contribute to its strong cytotoxicity.

Therapeutic Group: Oncolytic Drugs

Source: Inoue, M.; Shinohara, N.; Tanabe, S.; Takahashi, T. et al. Total synthesis of the large non-ribosomal peptide polytheonamide B. Nat Chem 2010, 2: 280

Integrity Entry Number: 691631



NEW MOLECULAR MECHANISMS OF ACTION

The mode of action of any product is key to understanding how to improve on any given design and discover more potent leads with fewer side effects. In this issue, we highlight the mode of action of agents for cancer, psoriasis, osteoarthritis and trypanosomiasis.

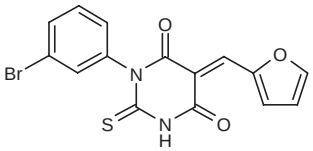
FORMIN HOMOLOGY 2 (FH2) DOMAIN INHIBITORS

Main Related Conditions: Cancer

Organization: University of Chicago (US)

Drug Name: SMIFH-2

Integrity Entry Number: 680540



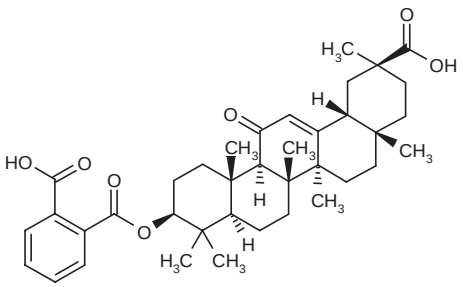
EPIDERMAL RETINOL DEHYDROGENASE 2 (RDH-E2) INHIBITORS

Main Related Conditions: Cancer; Photodamage; Psoriasis

Organization: York Pharma

Drug Name: YP-017

Integrity Entry Number: 461640

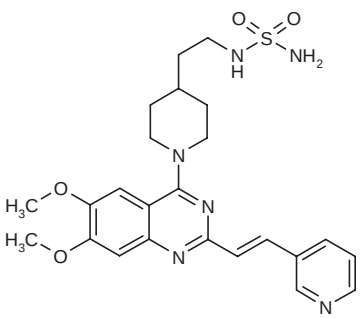


PLASMA-CELL MEMBRANE GLYCOPROTEIN PC-1 (NPP 1) INHIBITORS

Main Related Conditions: Osteoarthritis

Organization: Pfizer

Integrity Entry Number: 662883

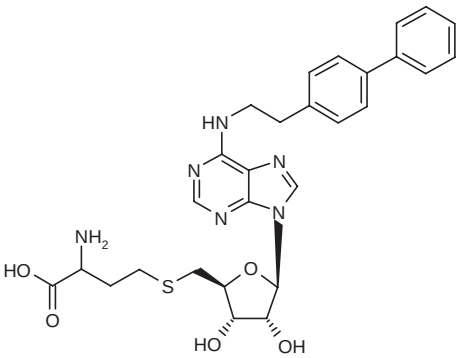


DNA METHYLTRANSFERASE 3b2 (Dnmt3b2) INHIBITORS

Main Related Conditions: Cancer

Organization: MethylGene

Integrity Entry Number: 661690

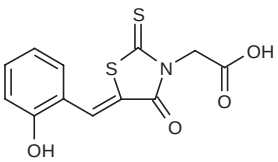


T. BRUCEI DOLICHOL-PHOSPHATE MANNOSE SYNTHASE (DPM SYNTHASE) INHIBITORS

Main Related Conditions: Trypanosomiasis (African sleeping sickness)

Organization: University of East Anglia (GB); University of St. Andrews (GB)

Integrity Entry Number: 663132

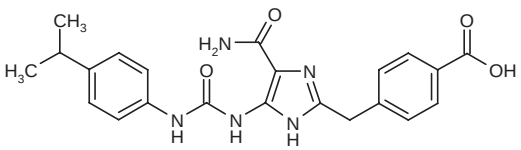


ECTONUCLEOTIDE PYROPHOSPHATASE/PHOSPHODIESTERASE 2 (E-NPP2; AUTOTAXIN) INHIBITORS

Main Related Conditions: Cancer

Organization: Merck KGaA

Integrity Entry Number: 657579



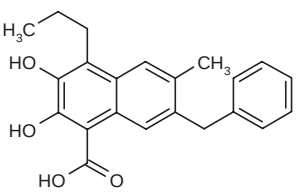
L-LACTATE DEHYDROGENASE A INHIBITORS

Main Related Conditions: Cancer

Organization: Johns Hopkins University (US)

Drug Name: FX-11

Integrity Entry Number: 685682



THE STARTING LINE

The Starting Line pinpoints new molecular entities (NMEs) ready to progress into the R&D arena, providing information on pharmacological activity, originator and chemical structures of key compounds. The development of drugs for cancer and CNS disorders continues to increase and a selection of novel, biologically active molecules selected from the current scientific literature and meetings are presented.

Organization: GlaxoSmithKline

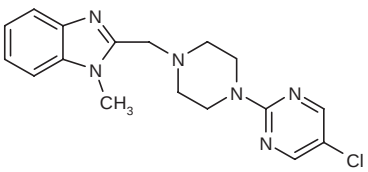
Drug Name: GSK-1331268

Condition: Schizophrenia

Mechanism of Action: $mGlu_2$ Agonists

Literature: D'Alessandro, P.L.; Corti, C.; Roth, A.; Ugolini, A.; et al. The identification of structurally novel, selective, orally bioavailable positive modulators of mGluR2. Bioorg Med Chem Lett 2010, 20(2): 759

Integrity Entry Number: 682950



Organization: deCODE Genetics

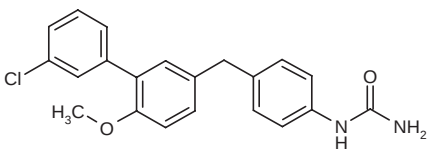
Drug Name: D-159687

Condition: Cognitive disorders

Mechanism of Action: Phosphodiesterase PDE4D Inhibitors

Literature: Burgin, A.B.; Magnusson, O.T.; Singh, J.; Witte, P.; Staker, B.L.; Bjornsson, J.M.; Thorsteinsdottir, M.; Hrafnsdottir, S.; Hagen, T.; Kiselyov, A.S.; Stewart, L.J.; Gurney, M.E. Design of phosphodiesterase 4D (PDE4D) allosteric modulators for enhancing cognition with improved safety. Nat Biotechnol 2010, 28(1): 63

Integrity Entry Number: 683992



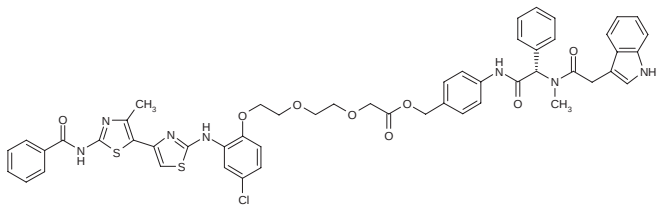
Organization: University of California, Oakland (US)

Condition: Cystic fibrosis

Mechanism of Action: CFTR Channel Activators; ΔF508-CFTR Correctors

Literature: Mills, A.D.; Yoo, C.; Butler, J.D.; Yang, B.; Verkman, A.S.; Kurth, M.J. Design and synthesis of a hybrid potentiator - Corrector agonist of the cystic fibrosis mutant protein DeltaF508-CFTR. Bioorg Med Chem Lett 2010, 20(1): 87

Integrity Entry Number: 683771



Organization: Roche

Drug Name: RO-85

Condition: Urinary incontinence; Pain

Mechanism of Action: $P2X_3$ Receptor Antagonists

Literature: Brotherton-Pleiss, C.E.; Dillon, M.P.; Ford, A.P.; Gever, J.R.; Carter, D.S.; Gleason, S.K.; Lin, C.J.; Moore, A.G.; Thompson, A.W.; Villa, M.; Zhai, Y. Discovery and optimization of RO-85, a novel drug-like, potent, and selective P2X3 receptor antagonist. Bioorg Med Chem Lett 2010, 20(3): 1031

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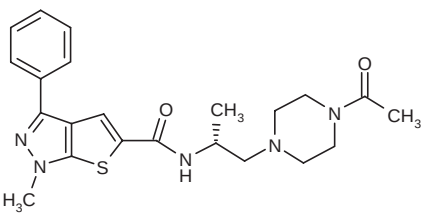

Organization: Intellikine; Merck Serono

Drug Name: SW-30

Condition: Arthritis; Cancer

Mechanism of Action: Phosphatidylinositol 3-Kinase δ (PI3Kδ) Inhibitors

Literature: Williams, O.; Houseman, B.T.; Kunkel, E.J.; Aizenstein, B.; Hoffman, R.; Knight, Z.A.; Shokat, K.M. Discovery of dual inhibitors of the immune cell PI3Ks p110delta and p110gamma: A prototype for new anti-inflammatory drugs. Chem Biol (Lond) 2010, 17(2): 123; Berndt, A.; Miller, S.; Williams, O.; Le, D.D.; et al. The p110delta structure: Mechanisms for selectivity and potency of new PI(3)K inhibitors. Nat Chem Biol 2010, 6(2): 117

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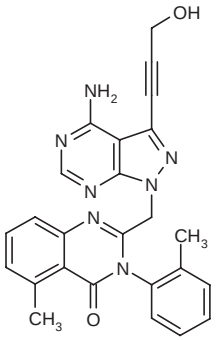

Organization: Merck & Co.

Drug Name: MK-6892

Condition: Atherosclerosis; Lipoprotein disorders

Mechanism of Action: Nicotinic Acid (Niacin; GPR109A; HM74A) Receptor Agonists

Literature: Shen, H.C.; Ding, F.-X.; Raghavan, S.; Deng, Q.; et al. Discovery of a biaryl cyclohexene carboxylic acid (MK-6892): A potent and selective high affinity niacin receptor full agonist with reduced flushing profiles in animals as a preclinical candidate. J Med Chem 2010, 53(6): 2666

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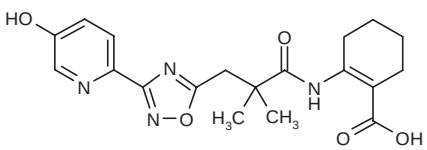

Organization: AngioChem

Drug Name: ANG-1007

Condition: Cancer, brain

Mechanism of Action: DNA-Intercalating Drugs

Literature: Che, C.; Yang, G.; Thiot, C. New angiopep-modified doxorubicin (ANG1007) and etoposide (ANG1009) chemotherapeutics with increased brain penetration. J Med Chem 2010, 53(7): 2814; Yang, G.; Che, C.; Thiot, C.; Lacoste, M.-C.; et al. Development of new cytotoxic etoposide and doxorubicin derivatives using the EPiC platform for increased brain penetration. 239th ACS Natl Meet (March 21-25, San Francisco) 2010, Abst MEDI 247M; Demeule, M.; Regina, A.; Yang, G.; Che, C.; et al. New Angiochem-modified doxorubicin with increased brain penetration and efficacy against brain tumors. Proc Am Assoc Cancer Res (AACR) 2010, 51: 3578

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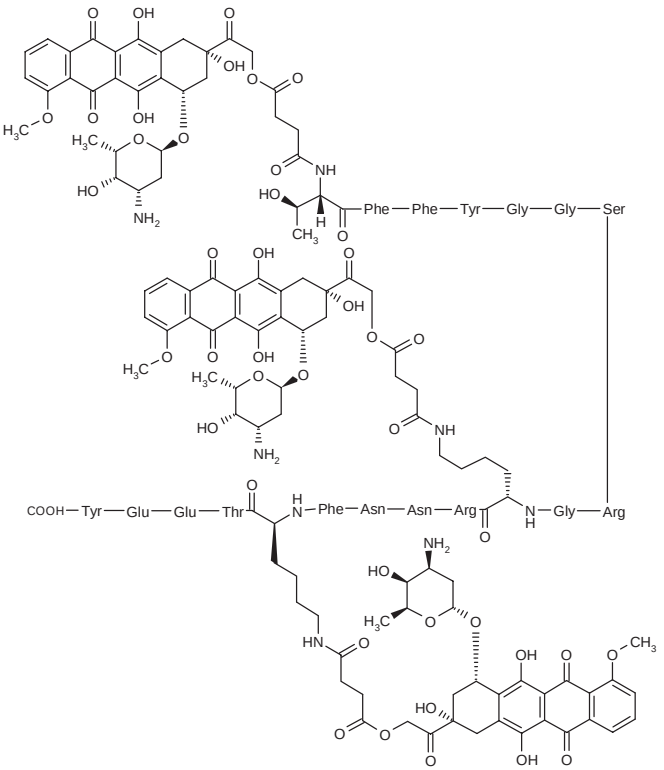


Organization: Merck & Co.; Ligand

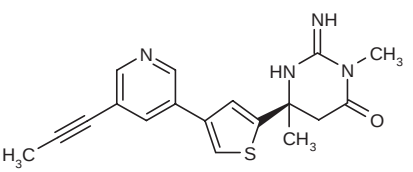
Drug Name: SCH-1359113

Condition: Dementia, Alzheimer's type

Mechanism of Action: β-Secretase 1 Inhibitors

Literature: Stamford, A.W.; Babu, S.; Caldwell, J.; Chen, X.; et al. Discovery of small molecule, orally active and brain penetrant BACE1 inhibitors. 239th ACS Natl Meet (March 21-25, San Francisco) 2010, Abst MEDI 290; Cumming, J.N.; Misiaszek, J.; Iserloh, U.; Mazzola, R.D.; et al. Novel iminopyrimidinone beta-Secretase inhibitors: Part 1. P1-P3 SAR. 239th ACS Natl Meet (March 21-25, San Francisco) 2010, Abst MEDI 531

Integrity Entry Number: 689946



Organization: Novartis

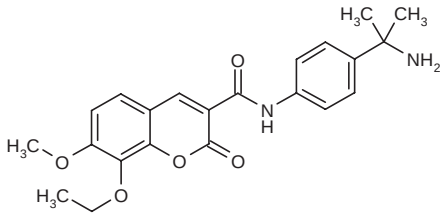
Drug Name: NIBR-785

Condition: Immunosuppression; Multiple sclerosis; Transplant rejection

Mechanism of Action: Lysophospholipid $S1P_1$ Receptor Agonists

Literature: Zecri, F.J.; Albert, R.; Baenteli, R.; Landrum, G.; et al. Discovery and optimization of multiple scaffolds of selective S1P1 receptor agonist. 239th ACS Natl Meet (March 21-25, San Francisco) 2010, Abst MEDI 31

Integrity Entry Number: 689798



Organization: Johnson & Johnson

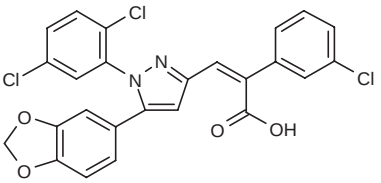
Drug Name: JNJ-26273364

Condition: Pancreatitis

Mechanism of Action: Cholecystokinin CCK_1 (CCK-A) Receptor Antagonists

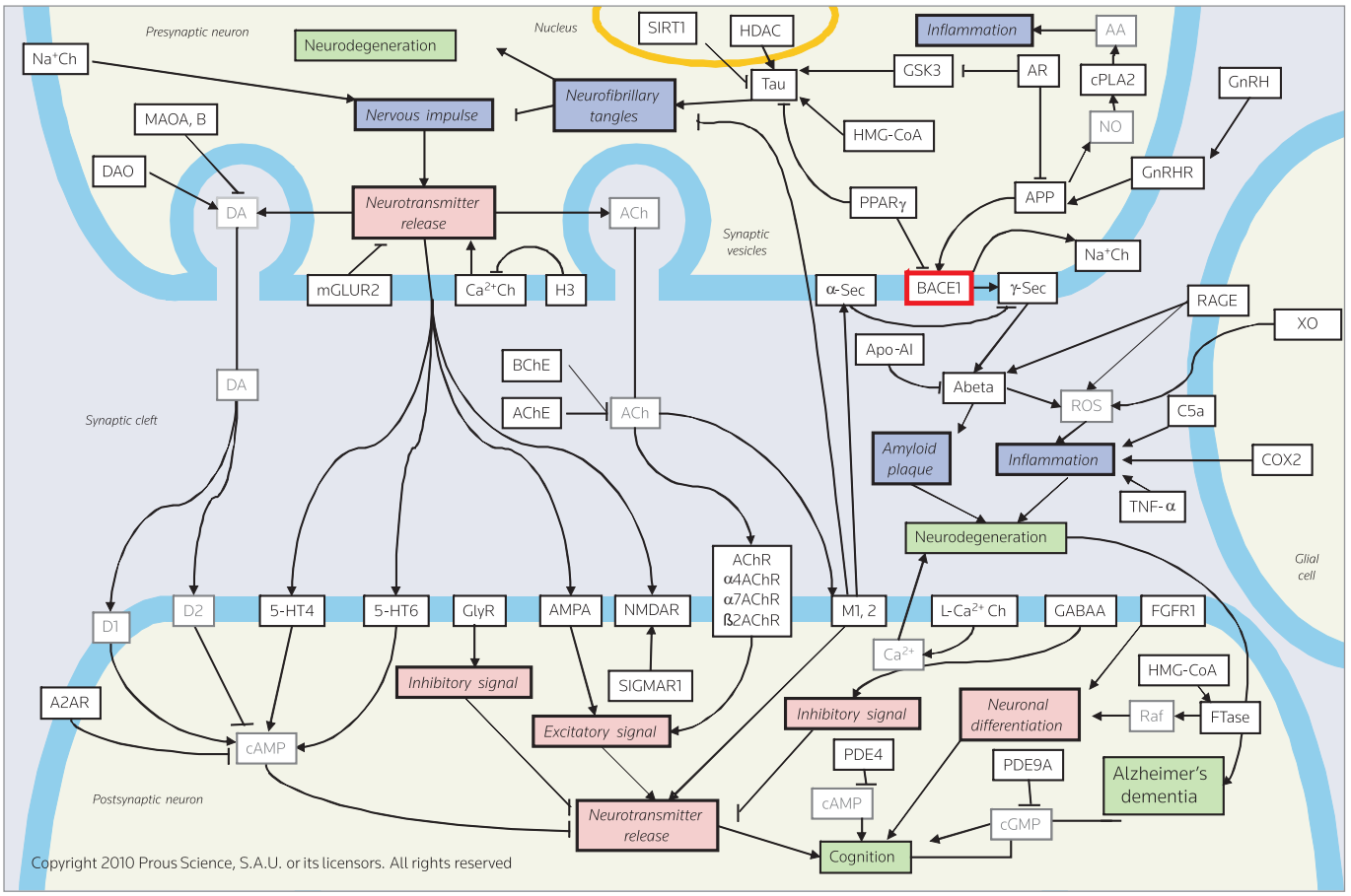
Literature: Gomeza, L.; Wua, J.; Mania, N.S.; Basub, S.; Moravekb, J.; Breitenbuchera, J.G. Carboxylation reaction of a highly functionalized vinylic anion: A case of unexpected stability and reactivity. Tetrahedron Lett 2010, 51(7): 1110; Guy Breitenbucher, J.; McClure, K.; Gomez, L.; Sehon, C.; et al. Value of Free-Wilson Analysis in the discovery of CCK-1 receptor antagonists for the treatment of pancreatitis. 239th ACS Natl Meet (March 21-25, San Francisco) 2010, Abst MEDI 540

Integrity Entry Number: 400482



ALZHEIMER'S DEMENTIA TARGET LANDSCAPE

Thomson Reuters Integrity^{SM} provides an interactive view of the targets and associated drugs in the CNS arena. In this issue, we offer a snapshot of the Targetscape for Alzheimer's disease, the indication targeted by the Merck & Co. NME SCH-1359113. The target for this drug –β-secretase 1 (BACE1)– is outlined in red in this Targetscape.



REFERENCES

1. Hamada, T., Matsunaga, S., Fujiwara, M. et al. *Solution structure of polytheonamide B, a highly cytotoxic nonribosomal polypeptide from marine sponge*. J Am Chem Soc 2010, Epub ahead of print.
2. Iwamoto, M., Shimizu, H., Muramatsu, I., Oiki, S. *A cytotoxic peptide from a marine sponge exhibits ion channel activity through vectorial-insertion into the membrane*. FEBS Lett 2010, Epub ahead of print.
3. Inoue, M., Shinohara, N., Tanabe, S. et al. *Total synthesis of the large nonribosomal peptide polytheonamide B.* Nat Chem 2010, *2*(4): 280-5.