Bioorg. Med. Chem. Lett. 13 (2003) 161

Small, Low Nanomolar, Noncovalent Thrombin Inhibitors Lacking a Group to Fill the 'Distal Binding Pocket'

Philip E. J. Sanderson,[a,*] Kellie J. Cutrona,[a] Dona L. Dyer,[a] Julie A. Krueger,[b] Lawrence C. Kuo,[c] S. Dale Lewis,[b] Bobby J. Lucas[b] and Youwei Yan[c]

[a]*Department of Medicinal Chemistry, Merck Research Laboratories, West Point, PA 19486, USA*
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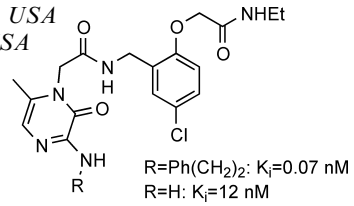
[c]*Department of Structural Biology, Merck Research Laboratories, West Point, PA 19486, USA*

A unique series of low molecular weight, potent, noncovalent thrombin inhibitors which lack a group to fill the 'distal binding pocket' are described.



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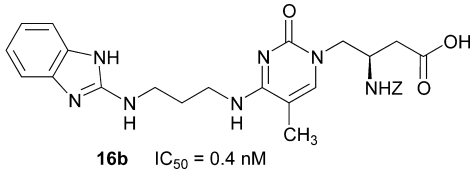
Highly Potent and Selective $\alpha_V\beta_3$-Receptor Antagonists: Solid-Phase Synthesis and SAR of 1-Substituted 4-Amino-1H-pyrimidin-2-ones

Christian Zechel,[a,*] Gisela Backfisch,[b] Jürgen Delzer,[b] Hervé Geneste,[b] Claudia Graef,[a] Wilfried Hornberger,[b] Andreas Kling,[b,*] Udo E. W. Lange,[a] Arnulf Lauterbach,[a] Werner Seitz[a] and Thomas Subkowski[a]

[a]*BASF AG, D-67056 Ludwigshafen, Germany*
[b]*Abbott GmbH & Co. KG, D-67008 Ludwigshafen, Germany*

Solid-phase synthesis and SAR of $\alpha_V\beta_3$-receptor antagonists based on an amino-pyrimidinone scaffold are described. Efficacy in functional cellular assays is demonstrated for selected examples.



16b IC_{50} = 0.4 nM

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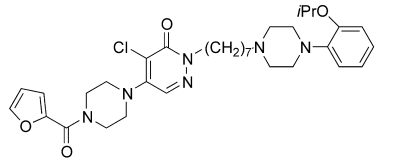
α_1-Adrenoceptor Antagonists. 5. Pyridazinone-arylpiperazines. Probing the Influence on Affinity and Selectivity of Both *ortho*-Alkoxy Groups at the Arylpiperazine Moiety and Cyclic Substituents at the Pyridazinone Nucleus

Laura Betti,[a] Monia Floridi,[b] Gino Giannaccini,[a] Fabrizio Manetti,[c,*] Giovannella Strappaghetti,[b,*] Andrea Tafi[c] and Maurizio Botta[c]

[a]*Dipartimento di Psichiatria, Neurobiologia, Farmacologia e Biotecnologie, Università di Pisa, Via Bonanno 6, 56126, Pisa, Italy*
[b]*Istituto di Chimica e Tecnologia del Farmaco, Università di Perugia, Via del Liceo 1, 06123 Perugia, Italy*
[c]*Dipartimento Farmaco Chimico Tecnologico, Università degli Studi di Siena, Via Aldo Moro, 53100 Siena, Italy*



K_i: α_1-AR = 0.052 nM; α_2-AR = 0.56 nM; 5–HT_{1A} = 0.80 nM

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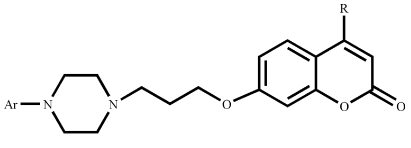
New Arylpiperazine Derivatives with High Affinity for α_{1A}, D_2 and 5-HT_{2A} Receptors

J. C. González-Gómez,[a] L. Santana,[a,*] E. Uriarte,[a] J. Brea,[b] M. Villazón,[b] M. I. Loza,[b] M. De Luca,[b] M. E. Rivas,[b] G. Y. Montenegro[b] and J. A. Fontenla[b]

[a]*Department of Organic Chemistry, Faculty of Pharmacy, University of Santiago, Campus Sur s/n, E-15782 Santiago de Compostela, Spain*
[b]*Department of Pharmacology, Faculty of Pharmacy, University of Santiago, Campus Sur s/n, E-15782 Santiago de Compostela, Spain*

The synthesis and pharmacological evaluation of new coumarin-arylpiperazines is reported. The new compounds showed high affinity over all considered receptors α_1, D_2 and 5-HT_{2A}.



R = Me, OMe
Ar = Ph, "o"-OMe-Ph, 2-Pyridyl, 2-Pyrimidyl

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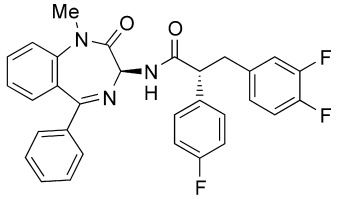
A New Series of Potent Benzodiazepine γ-Secretase Inhibitors

Ian Churcher,[a,*] Kate Ashton,[a] John W. Butcher,[b] Earl E. Clarke,[c] Timothy Harrison,[a] Huw D. Lewis,[c] Andrew P. Owens,[a] Martin R. Teall,[a] Susie Williams[a] and Jonathan D. J. Wrigley[c]

[a]*Department of Medicinal Chemistry, The Neuroscience Research Centre, Merck, Sharp and Dohme Research Laboratories, Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR, UK*
[b]*Department of Medicinal Chemistry, Merck Research Laboratories, PO Box 4, Sumneytown Pike, West Point, PA 19486, USA*
[c]*Department of Biochemistry and Molecular Biology, The Neuroscience Research Centre, Merck, Sharp and Dohme Research Laboratories, Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR, UK*



The structure–activity relationships of a series of γ-secretase inhibitors are discussed.

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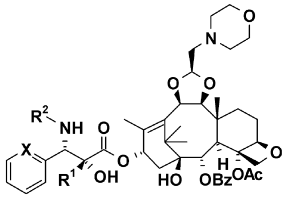
New Highly Active Taxoids from 9β-dihydrobaccatin-9,10-acetals. Part 3

Yasuyuki Takeda,[a] Toshiharu Yoshino,[a] Kouichi Uoto,[a] Jun Chiba,[a] Takashi Ishiyama,[a] Michio Iwahana,[b] Takeshi Jimbo,[b] Noriko Tanaka,[c] Hirofumi Terasawa[b] and Tsunehiko Soga[a,*]

[a]*Medicinal Chemistry Research Laboratory, Daiichi Pharmaceutical Co., Ltd., Tokyo R&D Center, 16-13 Kita-Kasai 1-Chome, Edogawa-ku, Tokyo 134-8630, Japan*
[b]*New Product Research Laboratories III, Daiichi Pharmaceutical Co., Ltd., Tokyo R&D Center, 16-13 Kita-Kasai 1-Chome, Edogawa-ku, Tokyo 134-8630, Japan*
[c]*New Product Research Laboratories II, Daiichi Pharmaceutical Co., Ltd., Tokyo R&D Center, 16-13 Kita-Kasai 1-Chome, Edogawa-ku, Tokyo 134-8630, Japan*



Novel water-soluble and orally active taxane analogues were synthesized. Cytotoxicity of synthetic compounds was greater than those of paclitaxel and docetaxel, especially against resistant cancer cell lines expressing P-glycoprotein. In addition, some compounds showed potent antitumor effects against B16 melanoma BL6 in vivo by both iv and po administration.

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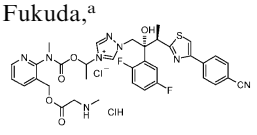
Design, Synthesis and Antifungal Activity of a Novel Water Soluble Prodrug of Antifungal Triazole

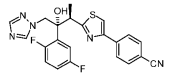
Jun Ohwada,[a] Masao Tsukazaki,[a] Tadakatsu Hayase,[a] Nobuhiro Oikawa,[a] Yoshiaki Isshiki,[a] Hiroshi Fukuda,[a] Eisaku Mizuguchi,[a] Masahiro Sakaitani,[a] Yasuhiko Shiratori,[a] Toshikazu Yamazaki,[b] Shigeyasu Ichihara,[c] Isao Umeda[a,*] and Nobuo Shimma[a]

[a]*Department of Chemistry, Nippon Roche Research Center, 200 Kajiwara, Kamakura, Kanagawa 247-8530, Japan*
[b]*Department of Mycology, Nippon Roche Research Center, 200 Kajiwara, Kamakura, Kanagawa 247-8530, Japan*
[c]*Department of Preclinical Science, Nippon Roche Research Center, 200 Kajiwara, Kamakura, Kanagawa 247-8530, Japan*



RO0098557 (1)

A highly potent water soluble triazole antifungal prodrug, RO0098557 (**1**), has been identified from its parent, the novel antifungal agent RO0094815 (**2**). The prodrug includes a triazolium salt linked to an aminocarboxyl moiety, which undergoes enzymatic activation followed by spontaneous chemical degradation to release **2**. Prodrug **1** showed high chemical stability and water solubility and exhibited strong antifungal activity against systemic candidiasis and aspergillosis as well as pulmonary aspergillosis in rats.



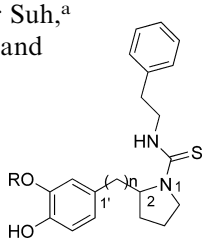
RO0094815 (2)

Bioorg. Med. Chem. Lett. 13 (2003) 197

Synthesis of 2-Substituted-Pyrrolidinethiourea Derivatives and Their Antagonist Effect on Vanilloid Receptor

Hyeung-geun Park,[a,*] Mi-kyung Park,[a] Ji-yeon Choi,[a] Sea-hoon Choi,[a] Jihye Lee,[a] Young-ger Suh,[a] Uhtaek Oh,[a] Jeewoo Lee,[a] Hee-Doo Kim,[b] Young-Ho Park,[c] Yeon Su Jeong,[c] Jin Kyu Choi[c] and Sang-sup Jew[a,*]

[a]*Research Institute of Pharmaceutical Sciences and College of Pharmacy, Seoul National University, Seoul 151-742, South Korea*
[b]*College of Pharmacy, Sookmyung Women's University, Seoul 140-742, South Korea*
[c]*AmorePacific R&D Center, Youngin-Si, Kyounggi-do 449-900, South Korea*



n = 0, 2 R = H, Me

Among the prepared pyrrolidine derivatives, **4b** ($n = 2$, $R = Me$, $IC_{50} = 3\ \mu M$) showed antagonist activity against the vanilloid receptor in a $^{45}Ca^{2+}$-influx assay.

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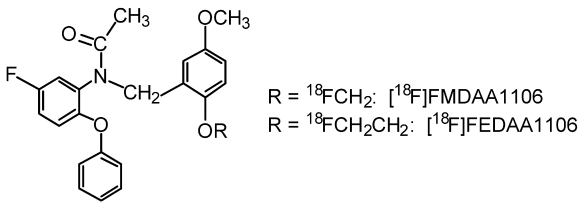
[^{18}F]FMDAA1106 and [^{18}F]FEDAA1106: Two Positron-Emitter Labeled Ligands for Peripheral Benzodiazepine Receptor (PBR)

Ming-Rong Zhang,[a,b,*] Jun Maeda,[a,b] Kenji Furutsuka,[a,b] Yuichiro Yoshida,[a,b] Masanao Ogawa,[a,b] Tetsuya Suhara[a,c] and Kazutoshi Suzuki[a]

[a]*Department of Medical Imaging, National Institute of Radiological Sciences, 4-9-1 Anagawa, Inage-ku, Chiba 263-8555, Japan*
[b]*SHI Accelerator Service Co. Ltd., 5-9-11 Kitashinagawa, Shinagawa-ku, Tokyo 141-8686, Japan*
[c]*CREST, Japan Sciences and Technology Corporation, 4-1-8 Honmachi, Kawaguchi 332-0012, Japan*

[^{18}F]FMDAA1106 and [^{18}F]FEDAA1106, two potent radioligands for peripheral benzodiazepine receptors (PBR), were designed and synthesized. Ex vivo autoradiograms of rat brains revealed that they had high specific bindings in the olfactory bulb, the region with the highest PBR density in the brain.



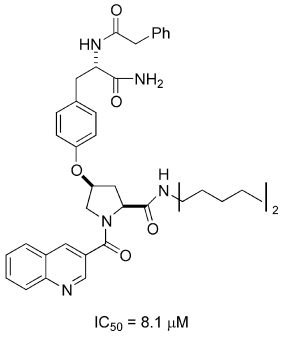
Bioorg. Med. Chem. Lett. 13 (2003) 205

Identification of TNF-α Inhibitors from a Split-Pool Library Based on a Tyrosine-Proline Peptidomimetic Scaffold

Randy W. Jackson,* John C. Tabone and J. Jeffry Howbert

Department of Chemistry, Celltech R&D, Inc., 1621 220th Street SE, Bothell, WA 98021, USA

The identification of novel TNF-α inhibitors from a split-pool combinatorial library based on a 4-aryloxyproline scaffold is described.



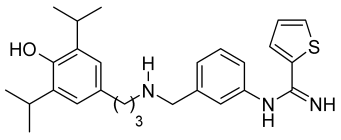
Bioorg. Med. Chem. Lett. 13 (2003) 209

Novel Inhibitors of Neuronal Nitric Oxide Synthase with Potent Antioxidant Properties

Serge Auvin,[a,*] Michel Auguet,[b] Edith Navet,[a] Jeremiah J. Harnett,[a] Isabelle Viossat,[b] Jocelyne Schulz,[b] Dennis Bigg[a] and Pierre-E. Chabrier[b]

[a]*Department of Medicinal Chemistry, Beaufour-Ipsen Research Laboratories, Institut Henri Beaufour, 5, Avenue du Canada, 91966 Les Ulis Cedex, France*
[b]*Department of Biology, Beaufour-Ipsen Research Laboratories, Institut Henri Beaufour, 5, Avenue du Canada, 91966 Les Ulis Cedex, France*

A series of hybrid compounds possessing nNOS inhibitory and antioxidant properties have been synthesized. Compound **8d** displayed the greatest dual potency.



8d

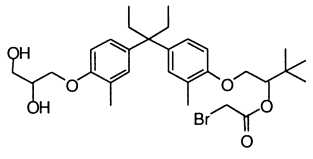
Bioorg. Med. Chem. Lett. 13 (2003) 213

Affinity Labeling of the Nuclear Vitamin D Receptor with Nonsteroidal Alkylating Agents

Ana Fernández-Gacio, Carlos Fernández-Marcos, Narasimha Swamy and Rahul Ray*

Bioorganic Chemistry and Structural Biology, Section in Endocrinology, Diabetes and Metabolism, Department of Medicine, Boston University School of Medicine, 85 East Newton Street, Boston, MA 02118, USA

Synthesis of an affinity alkylating nonsteroidal mimic of 1α,25-dihydroxyvitamin D$_3$, and affinity labeling of the VDR-ligand binding domain with this analogue is reported.



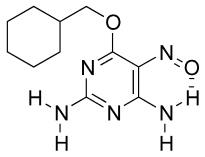
Bioorg. Med. Chem. Lett. 13 (2003) 217

4-Alkoxy-2,6-diaminopyrimidine Derivatives: Inhibitors of Cyclin Dependent Kinases 1 and 2

Veronique Mesguiche,[a] Rachel J. Parsons,[a] Christine E. Arris,[b] Johanne Bentley,[b] F. Thomas Boyle,[c] Nicola J. Curtin,[b] Thomas G. Davies,[d] Jane A. Endicott,[d] Ashleigh E. Gibson,[a] Bernard T. Golding,[a] Roger J. Griffin,[a] Philip Jewsbury,[c] Louise N. Johnson,[d] David R. Newell,[b] Martin E. M. Noble,[d] Lan Z. Wang[b] and Ian R. Hardcastle[a,*]

[a]*Northern Institute of Cancer Research and Department of Chemistry, Bedson Building, University of Newcastle, Newcastle upon Tyne NE1 7RU, UK*
[b]*Northern Institute of Cancer Research, Medical School, Framlington Place, Newcastle upon Tyne NE2 4HH, UK*
[c]*AstraZeneca Pharmaceuticals, Alderley Park, Cheshire SK10 4TG, UK*
[d]*Laboratory of Molecular Biophysics and Department of Biochemistry, University of Oxford, Oxford OX1 3QU, UK*

The synthesis and evaluation of 21 compounds as potential inhibitors of cdks 1 and 2 is described and the structure–activity relationships relating to NU6027 (IC_{50} vs cdk1/cyclinB1 = 2.9 ± 0.1 μM and IC_{50} vs cdk2/cyclinA3 = 2.2 ± 0.6 μM) are reported.



NU6027

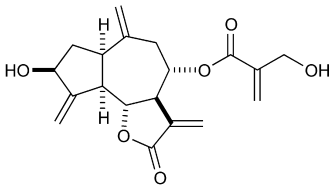
Bioorg. Med. Chem. Lett. 13 (2003) 223

Anti-Hyperlipidemic Sesquiterpenes and New Sesquiterpene Glycosides from the Leaves of Artichoke (*Cynara scolymus* L.): Structure Requirement and Mode of Action

Hiroshi Shimoda,[a] Kiyofumi Ninomiya,[a] Norihisa Nishida,[b] Tomoe Yoshino,[b] Toshio Morikawa,[a] Hisashi Matsuda[a] and Masayuki Yoshikawa[a,*]

[a]*Kyoto Pharmaceutical University, Misasagi, Yamashina-ku, Kyoto 607-8412, Japan*
[b]*Research and Development Division, Morishita Jintan Co. Ltd., 1-1-30 Tamatsukuri, Chuo-ku, Osaka 540-8566, Japan*

The methanolic extract from the leaves of artichoke (*Cynara scolymus* L.) was found to suppress serum triglyceride elevation in olive oil-loaded mice. Through bioassay-guided separation, sesquiterpenes (cynaropicrin, aguerin B, and grosheimin) were isolated as the active components together with new sesquiterpene glycosides (cynarascolosides A–C). The oxygen functional groups at the 3- and 8-positions and *exo*-methylene moiety in α-methylene-γ-butyrolactone ring were found to be essential for the anti-hyperlipidemic activity of guaiane-type sesquiterpene. In addition, inhibition of gastric emptying was clarified to be partly involved in anti-hyperlipidemic activity.



cynaropicrin

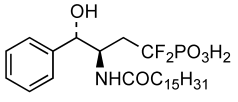
Bioorg. Med. Chem. Lett. 13 (2003) 229

Synthesis of Non-Competitive Inhibitors of Sphingomyelinases with Significant Activity

Tsutomu Yokomatsu,[a,*] Tetsuo Murano,[a] Takeshi Akiyama,[a] Junichi Koizumi,[a] Shiroshi Shibuya,[a] Yoshiaki Tsuji,[b] Shinji Soeda[b] and Hiroshi Shimeno[b,*]

[a]*School of Pharmacy, Tokyo University of Pharmacy & Life Science, 1432-1 Horinouchi, Hachioji, Tokyo 192-0392, Japan*
[b]*Faculty of Pharmaceutical Sciences, Fukuoka University, 8-9-1 Nanakuma, Jonan-ku, Fukuoka 841-0180, Japan*

A novel series of difluoromethylene phosphonate analogues of *N*-palmitoyl sphingosin-1-phosphate has been prepared. The study identified a non-competitive inhibitor **A** (IC_{50} = 3.3 μM, K_i = 1.6 μM) for Mg^{2+}-dependent N-SMase from bovine brain microsomes.



A

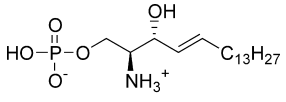
Bioorg. Med. Chem. Lett. 13 (2003) 237

Syntheses of Sphingosine-1-phosphate Stereoisomers and Analogues and Their Interaction with EDG Receptors

Hyun-Suk Lim, Yong-Seok Oh, Pann-Ghill Suh and Sung-Kee Chung*

Division of Molecular and Life Sciences, Pohang University of Science and Technology, Pohang 790-784, South Korea

The syntheses and biological activities of S1P stereoisomers and analogues are reported.



D-*erythro* S1P

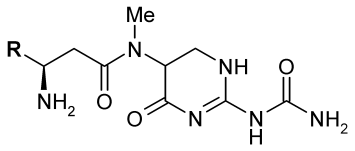
Bioorg. Med. Chem. Lett. 13 (2003) 241

Dihydropyrimidinones—A New Class of Anti-Staphylococcal Antibiotics

Michael Brands, Rainer Endermann, Reinhold Gahlmann, Jochen Krüger* and Siegfried Raddatz

BAYER AG, Business Group Pharma, Research, D-42096 Wuppertal, Germany

New derivatives of the natural dipeptide antibiotic TAN-1057 A, B were synthesized. The optimization program revealed analogues of the natural product which showed good anti-staphylococcal activity in vitro and in vivo. Furthermore, selected compounds displayed an improved toxicological profile compared to TAN-1057 A, B.



Bioorg. Med. Chem. Lett. 13 (2003) 247

β-Homolysine Oligomers: A New Class of Trojan Carriers

C. García-Echeverría* and Stephan Ruetz

Oncology Research, Novartis Pharma Inc., CH-4002 Basel, Switzerland

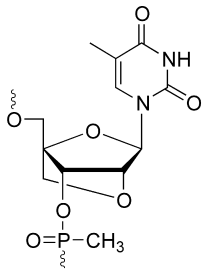
We describe the design, synthesis and cell-membrane translocation properties of a series of β-peptides with the general sequence fluorescin-Adoa-(β-homolysine)$_n$-NH_2, $n = 5$–8 and Adoa = 8-amino-3,6-diaxaoctanoic acid. These oligomers are able to cross the cytoplasmic membrane and accumulate in the nucleus of mammalian cells.

Bioorg. Med. Chem. Lett. 13 (2003) 253

Methylphosphonate LNA: A Locked Nucleic Acid with a Methylphosphonate Linkage

Anne Lauritsen,[a] Britta M. Dahl,[a] Otto Dahl,[a] Birte Vester[b] and Jesper Wengel[c,*]

[a]*Department of Chemistry, University of Copenhagen, Universitetsparken 5, DK-2100 Copenhagen, Denmark*
[b]*Department of Biochemistry and Molecular Biology, Nucleic Acid Center, University of Southern Denmark, Campusvej 55, DK-5230 Odense M, Denmark*
[c]*Department of Chemistry, Nucleic Acid Center, University of Southern Denmark, Campusvej 55, DK-5230 Odense M, Denmark*



Methylphosphonate LNA (T^{L}_{Me})

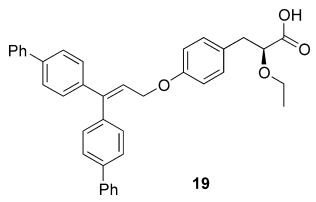
Bioorg. Med. Chem. Lett. 13 (2003) 257

Design and Synthesis of Novel PPARα/γ/δ Triple Activators Using a Known PPARα/γ Dual Activator as Structural Template

John P. Mogensen,* Lone Jeppesen, Paul S. Bury, Ingrid Pettersson, Jan Fleckner, Jan Nehlin, Klaus S. Frederiksen, Tatjana Albrektsen, Nanni Din, Steen B. Mortensen, L. Anders Svensson, Karsten Wassermann, Erik M. Wulff, Lars Ynddal and Per Sauerberg

Novo Nordisk A/S, Novo Nordisk Park, 2760 Måløv, Denmark

Using a known dual PPARα/γ activator (**5**) as a structural template, SAR evaluations led to the identification of triple PPARα/γ/δ activators (**18**–**20**) with equal potency and efficacy on all three receptors.



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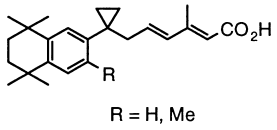
Bioorg. Med. Chem. Lett. 13 (2003) 261

Retinoic Acid Receptor Ligands Based on the 6-Cyclopropyl-2,4-hexadienoic Acid

Luc J. Farmer,* Lin Zhi, Susan Jeong, William W. Lamph, Deborah L. Osburn, Glenn Croston, Karen S. Flatten, Rich A. Heyman and Alex M. Nadzan

Discovery Research, Ligand Pharmaceuticals, Inc., 10275 Science Center Drive, San Diego, CA 92121, USA

A series of novel cyclopropanyl methyl hexadienoic acid retinoids was prepared. The most potent compounds showed either selective activity as RXR agonists or pan-agonists on the RAR and the RXR isoforms.



R = H, Me

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The Preparation of (*S*)-Aspartate Semi-Aldehyde Appropriate for Use in Biochemical Studies

Sarah J. Roberts,[a,b] Jonathan C. Morris,[b,*] Renwick C.J. Dobson[a] and Juliet A. Gerrard[a,*]

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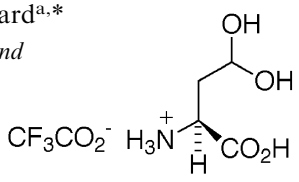
[b]*Department of Chemistry, University of Canterbury, Christchurch, New Zealand*

Two three-step syntheses of *(S)*-aspartate semi-aldehyde from diprotected aspartic acid are reported. *(S)*-Aspartate semi-aldehyde prepared in this manner has proved appropriate as a substrate for detailed enzyme studies.



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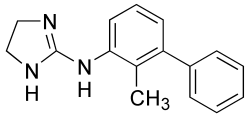
Discovery of a Series of (4,5-Dihydroimidazol-2-yl)-biphenylamine 5-HT$_7$ Agonists

Vinod Parikh,* Willard M. Welch* and Anne W. Schmidt

Pfizer Global Research and Development, Eastern Point Road, Groton, CT 06340, USA

A series of new 2-aminoimidazoline derivatives was prepared for 5HT$_7$ receptors.



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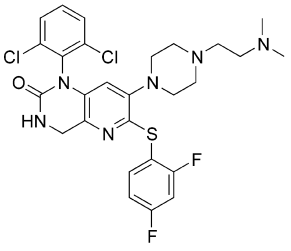
p38 MAP Kinase Inhibitors. Part 1: Design and Development of a New Class of Potent and Highly Selective Inhibitors Based on 3,4-Dihydropyrido[3,2-*d*]pyrimidone Scaffold

Swaminathan R. Natarajan,[a,*] David D. Wisnoski,[a] Suresh B. Singh,[a] John E. Stelmach,[a] Edward A. O'Neill,[b] Cheryl D. Schwartz,[b] Chris M. Thompson,[b] Catherine E. Fitzgerald,[b] Stephen J. O'Keefe,[b] Sanjeev Kumar,[c] Cornelis E. C. A. Hop,[c] Dennis M. Zaller,[b] Dennis M. Schmatz[b] and James B. Doherty[a]

[a]*Department of Medicinal Chemistry, Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065, USA*
[b]*Department of Inflammation Research, Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065, USA*
[c]*Department of Drug Metabolism, Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065, USA*



30 IC_{50} = 600 pM

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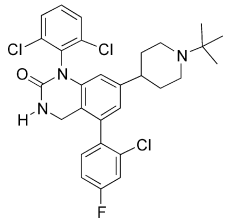
Design and Synthesis of Potent, Orally Bioavailable Dihydroquinazolinone Inhibitors of p38 MAP Kinase

John E. Stelmach,[a,*] Luping Liu,[a] Sangita B. Patel,[a] James V. Pivnichny,[a] Giovanna Scapin,[a] Suresh Singh,[a] Cornelis E. C. A. Hop,[b] Zhen Wang,[b] John R. Strauss,[c] Patricia M. Cameron,[d] Elizabeth A. Nichols,[d] Stephen J. O'Keefe,[d] Edward A. O'Neill,[d] Dennis M. Schmatz,[d] Cheryl D. Schwartz,[d] Chris M. Thompson,[d] Dennis M. Zaller[d] and James B. Doherty[a]

[a]*Department of Medicinal Chemistry, Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065, USA*
[b]*Department of Drug Metabolism, Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065, USA*
[c]*Department of Comparative Medicine, Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065, USA*
[d]*Department of Inflammation/Rheumatology, Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065, USA*



15i
p38 IC_{50}= 0.2nM

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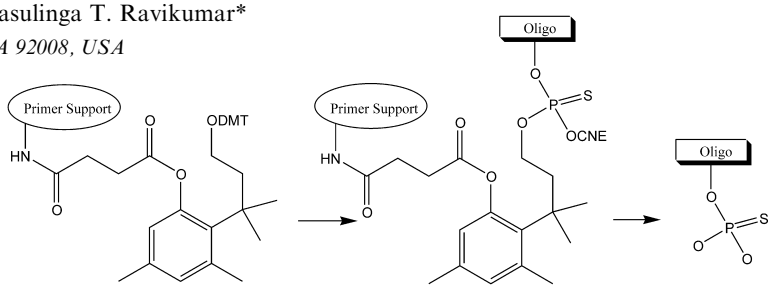
A Novel Solid Support for Synthesis of Oligonucleotide 3′-Phosphorothioate Monoesters

Zacharia S. Cheruvallath, Douglas L. Cole and Vasulinga T. Ravikumar*

Isis Pharmaceuticals, 2292 Faraday Avenue, Carlsbad, CA 92008, USA

A new reagent immobilized on solid support allowing for solid-phase synthesis of oligonucleotides with a 3′-terminal phosphorothioate monoester is described. The support is compatible with phosphoramidite chemistry for automated oligonucleotide synthesis. Final deprotection with ammonia under standard conditions leads to oligonucleotide 3′-terminal phosphorothioate monoester (3′-TPT).



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Development of a Presynaptic 5-HT_{1A} Antagonist

Ronald J. Mattson,[a,*] John D. Catt,[a] Charles P. Sloan,[a] Qi Gao,[d] Richard B. Carter,[b] Anthony Gentile,[a] Cathy D. Mahle,[c] F. Fatima Matos,[d] Rachel McGovern,[a] Cam P. VanderMaelen[e] and Frank D. Yocca[a]

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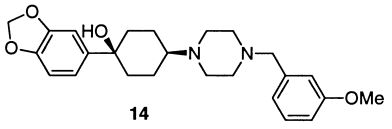
[b]*CoCensys, Inc., Irvine, CA 92718, USA*
[c]*Bayer Pharmaceutical Research Center, West Haven, CT, USA*
[d]*Pfizer Global Research and Development, Groton, CT, USA*
[e]*Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT 06877, USA*

A new 5-HT_{1A} silent antagonist **14**, antagonizes the effects of agonists on reciprocal forepaw treading behavior, on neuronal firing in the rat dorsal raphé, and on 5-HT_{1A} release in the raphé and hippocampus. While **14**, alone, was inactive in the social interaction paradigm, it completely reversed the social interaction activity of the serotonergic compounds; buspirone, **1**, and **2**.



14

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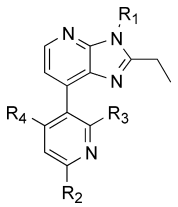
CRF Ligands Via Suzuki and Negishi Couplings of 3-Pyridyl Boronic Acids or Halides with 2-Benzyloxy-4-chloro-3-nitropyridine

Argyrios G. Arvanitis,[a,*] Charles R. Arnold,[a] Lawrence W. Fitzgerald,[b] William E. Frietze,[a] Richard E. Olson,[a] Paul J. Gilligan[a] and David W. Robertson[a]

[a]*Discovery Chemistry-Wilmington, Bristol-Myers Squibb Company, Experimental Station, Wilmington, DE 19880, USA*
[b]*CNS Diseases Research, Bristol-Myers Squibb Company, Experimental Station, Wilmington, DE 19880, USA*

A series of imidazo[4,5-*b*]pyridines with a 7-(3-pyridyl) substituent is described as high affinity CRF receptor ligands. Analogues were synthesized via palladium-catalyzed coupling of 3-pyridyl zinc or boronic aids.



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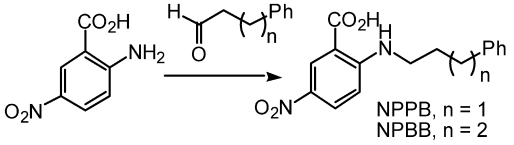
The Synthesis of NPPB and NPBB by Reductive Amination and the Effects of these Compounds on K^+ Channels of the Alga *Nitella hookeri*

Kristian R. Giles,[a,b] Mark Humphries,[b] Andrew Abell[b] and Ashley Garrill[a,*]

[a]*Department of Plant and Microbial Sciences, University of Canterbury, Private Bag 4800, Christchurch, New Zealand*
[b]*Department of Chemistry, University of Canterbury, Private Bag 4800, Christchurch, New Zealand*

A new synthesis of the ion channel inhibitors NPPB and NPBB using a simple reductive amination sequence is presented. The synthesised compounds were found to reduce channel amplitude of a K^+ channel present in cytoplasmic droplets of *Nitella hookeri*.



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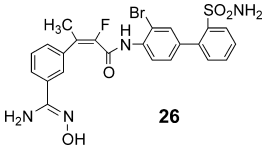
Design and Synthesis of Factor Xa Inhibitors and Their Prodrugs

Yonghong Song,[a,*] Lane Clizbe,[a] Chhaya Bhakta,[a] Willy Teng,[a] Paul Wong,[b] Brian Huang,[b] Katherine Tran,[b] Uma Sinha,[b] Gary Park,[b] Andrea Reed,[b] Robert M. Scarborough[a] and Bing-Yan Zhu[a]

[a]*Department of Medicinal Chemistry, Millennium Pharmaceuticals, Inc., 256 East Grand Ave., South San Francisco, CA 94080, USA*
[b]*Department of Biology, Millennium Pharmaceuticals, Inc., 256 East Grand Ave., South San Francisco, CA 94080, USA*

In addition to our previously reported fluoro acrylamides Xa inhibitors **2** and **3**, a series of potent and novel cyclic diimide amidine compounds has been identified. In efforts to improve their oral bioavailability, replacement of the amidine group with methyl amidrazone gives compounds of moderate potency (**14**, $IC_{50} = 0.028\,\mu M$). In the amidoxime prodrug approach, the amidoxime compounds show good oral bioavailability in rats and dogs. High plasma level of prodrug **26** and significant concentration of active drug **26a** were obtained upon oral administration of prodrug **26** in rats.



26

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Synthesis and Evaluation of Phosphoramidate Amino Acid-Based Inhibitors of Sialyltransferases

Lisa J. Whalen, Kerry A. McEvoy and Randall L. Halcomb*

University of Colorado, Department of Chemistry and Biochemistry, UCB 215, Boulder, CO 80309-0215, USA

The synthesis and evaluation of several phosphoramidate analogues of CMP-*N*-acetylneuraminic acid are reported.