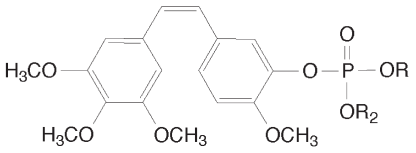
Bioorg. Med. Chem. Lett. 13 (2003) 1505

Synthesis, In Vitro, and In Vivo Evaluation of Phosphate Ester Derivatives of Combretastatin A-4

Mallinath B. Hadimani,[a] Jianyi Hua,[b] M. Devan Jonklaas,[a] Raymond J. Kessler,[a] Yezhou Sheng,[b] Adrian Olivares,[a] Rajendra P. Tanpure,[a] Aimee Weiser,[a] Jianxing Zhang,[a] Klaus Edvardsen,[b,*] Robert R. Kane[a,*] and Kevin G. Pinney[a,*]

[a]*Department of Chemistry & Biochemistry and Center for Drug Discovery, Baylor University, Waco, TX 76798-7348, USA*

[b]*Department of Cell and Molecular Biology, University of Lund, Lund, Sweden*



CA4P $R_1=R_2=Na$

this study R_1= alkyl or aryl; R_2=alkyl or Na

Combretastatin A-4 disodiumphosphate (CA4P), a prodrug formulation of the natural product combretastatin A-4 (CA4), is currently in clinical investigation for the treatment of cancer. In vivo, CA4P is rapidly enzymatically converted to CA4, a potent inhibitor of tubulin polymerization (IC_{50} = 1–2 μM), and rapidly causes bloodflow shutdown in tumor tissues. A variety of alkyl and aryl di- and triesters of CA4P have been synthesized and evaluated as potential CA4 prodrugs and/or stable CA4P analogues.

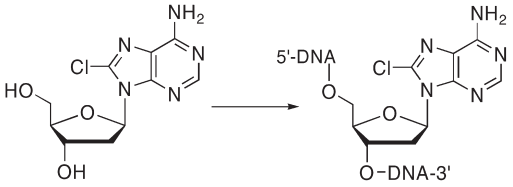
Bioorg. Med. Chem. Lett. 13 (2003) 1509

Effects of 8-Chlorodeoxyadenosine on DNA Synthesis by the Klenow Fragment of DNA Polymerase I

Lisa S. Chen, Michael H. Bahr and Terry L. Sheppard*

Department of Chemistry and The Robert H. Lurie Comprehensive Cancer Center, Northwestern University, 2145 Sheridan Road, Evanston, IL 60208-3113, USA

8-Chloro-2′-deoxyadenosine (8-Cl-dAdo) was incorporated into DNA oligonucleotides to determine its effects on DNA synthesis by Klenow DNA polymerase.



Bioorg. Med. Chem. Lett. 13 (2003) 1513

Phosphate Ester Serum Albumin Affinity Tags Greatly Improve Peptide Half-Life In Vivo

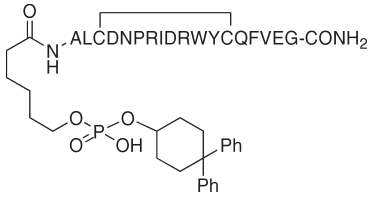
Kerry Zobel,[a] Michael F. T. Koehler,[a,b,*] Maureen H. Beresini,[c] Lisa D. Caris[c] and Daniel Combs[d]

[a]*Department of Protein Engineering, Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080, USA*

[b]*Department of Bioorganic Chemistry, Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080, USA*

[c]*Department of BioAnalytical Research and Development, Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080, USA*

[d]*Department of Clinical and Experimental Pharmacology, Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080, USA*



A novel series of phosphate ester based small molecule tags with high affinity for serum albumin reduce clearance and increase the circulating half life of bioactive peptides administered to rabbits.

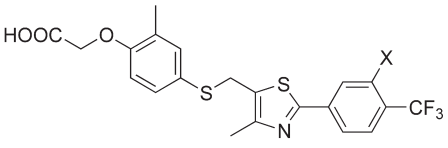
Bioorg. Med. Chem. Lett. 13 (2003) 1517

Novel Selective Small Molecule Agonists for Peroxisome Proliferator-activated Receptor δ (PPARδ)-synthesis and Biological Activity

Marcos L. Sznaidman, Curt D. Haffner,[b] Patrick R. Maloney,[b] Adam Fivush,[b] Esther Chao, Donna Goreham, Michael L. Sierra,[a] Christelle LeGrumelec,[a] H. Eric Xu,[b] Valerie G. Montana,[b] Millard H. Lambert,[b] Timothy M. Willson,[b] William R. Oliver, Jr.[b] and Daniel D. Sternbach[b,*]

[a]*GlaxoSmithKline, Five Moore Drive, Research Triangle Park, NC 27709-3398, USA.*

[b]*GlaxoSmithKline, Centre de Recherches, 25 Avenue du Québec, 91951 Les Ulis Cedex, France*



7k (GW501516), X = H, PPARδ EC_{50} = 1.1 nM

7l (GW0742), X = F, PPARδ EC_{50} = 1.0 nM

We report the synthesis and biological activity of a new series of small molecule agonists of the human Peroxisome Proliferator-Activated Receptor δ (PPARδ). Several hits were identified from our original libraries containing lipophilic carboxylic acids. Optimization of these hits by structure-guided design led to **7k** (GW501516) and **7l** (GW0742), which shows an EC_{50} of 1.1 nM against PPARδ with 1000 fold selectivity over the other human subtypes.

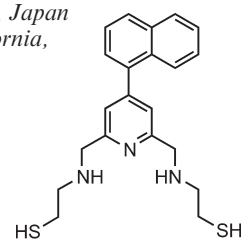
Bioorg. Med. Chem. Lett. 13 (2003) 1523

A Novel Metal-Chelating Inhibitor of Protein Farnesyltransferase

Akiyuki Hamasaki,[a] Hayato Naka,[b] Fuyuhiko Tamanoi,[c] Kazuo Umezawa[b] and Masami Otsuka[a,*]

[a]*Graduate School of Pharmaceutical Sciences, Kumamoto University, 5-1 Oe-honmachi, Kumamoto 862-0973, Japan*
[b]*Faculty of Science and Technology, Keio University, 3-14-1 Hiyoshi, Kohoku-ku, Yokohama 223-0061, Japan*
[c]*Department of Microbiology and Molecular Genetics, Molecular Biology Institute, University of California, Los Angeles, CA 90095-1489, USA*

A metal-chelating compound **2** was designed and synthesized. Compound **2** showed inhibitory activity against farnesyltransrferase and induced morphological change in K-ras-NRK cells.



2

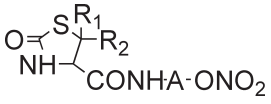
Bioorg. Med. Chem. Lett. 13 (2003) 1527

Synthesis and Collateral Dilator Activity of Nitroxyalkylamides Having Direct or Latent Sulfhydryl Moieties

Sadao Ishihara,[a,*] Fujio Saito,[b] Yasuo Ohhata,[a] Marie Kanai,[a] Hiroshi Mizuno,[a] Michio Fujisawa,[a] Ryosuke Yorikane[a] and Hiroyuki Koike[a]

[a]*Research Laboratories, Sankyo Co., Ltd., Hiromachi, Shinagawa-ku Tokyo 140, Japan*
[b]*Chemtech Labo., Inc., Hiromachi, Shinagawa-ku Tokyo 140, Japan*

To develop an orally active, long-acting nitrate that does not induce tolerance, nitroxyalkyl compounds were prepared and their activities evaluated by the use of carotid collaterals in anesthetized dogs. A compound having a favorable pharmacological profile, that is, long-lasting collateral vasodilatation, little hypotension, and lack of nitrate tolerance, was chosen for further evaluation.



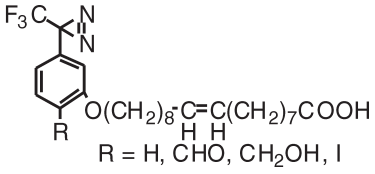
Bioorg. Med. Chem. Lett. 13 (2003) 1531

Efficient Synthesis of 3-Trifluoromethylphenyldiazirinyl Oleic Acid Derivatives and Their Biological Activity for Protein Kinase C

Makoto Hashimoto,[a,*] Kensuke Nabeta[a] and Kentaro Murakami[b,*]

[a]*Department of Bioresource Science, Obihiro University of Agriculture and Veterinary Medicine, Inada-cho, Obihiro 080-8555, Hokkaido, Japan*
[b]*Department of Biology, University of Vermont, 307 Marsh Life Sciences Building, Burlington, Vermont 05405-0086, USA*

3-Trifluoromethylphenyldiazirine based oleic acids derivatives are synthesized and subjected to biological activity for protein kinase C.



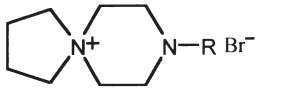
Bioorg. Med. Chem. Lett. 13 (2003) 1535

Unique Spirocyclopiperazinium Salt I: Synthesis and Structure–Activity Relationship of Spirocyclopiperazinium Salts as Analgesics

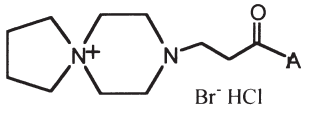
Feng-Li Gao, Xin Wang, Hong-Mei Zhang, Tie-Ming Cheng and Run-Tao Li*

School of Pharmaceutical Sciences, Peking University, Beijing 100083, PR China

Two series of unique spiropiperazinium derivatives were synthesized. Among them, **7f** (R = allyl, X = Br) and **10c** (Ar = C_6H_4–OH-*p*) showed excellent in vivo analgestic activity.



7a-n



10a-h

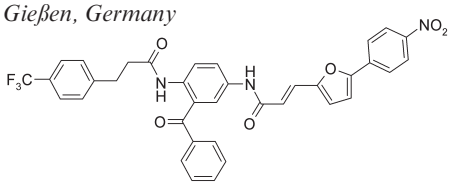
Bioorg. Med. Chem. Lett. 13 (2003) 1539

Structure–Activity Relationships of Novel Anti-Malarial Agents. Part 6: *N*-(4-Arylpropionylamino-3-benzoylphenyl)-[5-(4-nitrophenyl)-2-furyl]acrylic Acid Amides

Jochen Wiesner,[b] Katharina Fucik,[a] Katja Kettler,[a] Jacek Sakowski,[a] Regina Ortmann,[a] Hassan Jomaa[b] and Martin Schlitzer[a,*]

[a]*Department für Pharmazie - Zentrum für Pharmaforschung, Ludwig-Maximilians Universität München, Butenandtstraße 5-13, D-81377 München, Germany*
[b]*Biochemisches Institut der Universitätsklinik Gießen, Friedrichstraße 24, D-35249 Gießen, Germany*

We have demonstrated that the *p*-trifluoromethylphenylpropionylamino residue at the 2-position of the core structure leads to an active benzophenone-type anti-malarial agent. The attempt to improve water solubility by introduction of an amino group into the α-position of the arylpropionyl residue resulted in decreased activity.



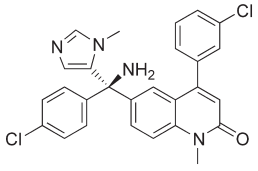
Bioorg. Med. Chem. Lett. 13 (2003) 1543

5-Imidazolyl-quinolinones, -quinazolinones and -benzo-azepinones as Farnesyltransferase Inhibitors

Patrick Angibaud,[a,*] Xavier Bourdrez,[a] Ann Devine,[b] David W. End,[b] Eddy Freyne,[c] Yannick Ligny,[a] Philippe Muller,[a] Geert Mannens,[d] Isabelle Pilatte,[a] Virginie Poncelet,[a] Stacy Skrzat,[b] Gerda Smets,[c] Jacky Van Dun,[c] Pieter Van Remoortere,[e] Marc Venet[a] and Walter Wouters[c]

[a]*Medicinal Chemistry Department, Johnson & Johnson Pharmaceutical Research & Development, Campus de Maigremont BP615, 27106 Val de Reuil, France*
[b]*Oncology Drug Discovery, Johnson & Johnson Pharmaceutical Research & Development, L.L.C. Welsh and McKean Roads, Spring-House, PA 19477-0776, USA*
[c]*Oncology Discovery Research, Johnson & Johnson Pharmaceutical Research & Development, Turnhoutseweg 30 B-2340, Belgium*
[d]*Preclinical Pharmacokinetics, Johnson & Johnson Pharmaceutical Research & Development, Turnhoutseweg 30 B-2340, Belgium*
[e]*Drug Evaluation, Johnson & Johnson Pharmaceutical Research & Development, Turnhoutseweg 30 B-2340, Belgium*

The synthesis and inhibiting potency of farnesyltransferase inhibitors closely related to R115777 is reported.



R115777

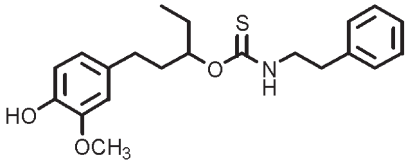
Bioorg. Med. Chem. Lett. 13 (2003) 1549

Chain-Branched Acyclic Phenethylthiocarbamates as Vanilloid Receptor Antagonists

JungWha Yoon,[a] HyeYoung Choi,[a] Hyun Joo Lee,[a] Chong Hyun Ryu,[a] Hyeung-geun Park,[b] Young-ger Suh,[b] Uhtaek Oh,[b] Yeon Su Jeong,[c] Jin Kyu Choi,[c] Young-Ho Park[c] and Hee-Doo Kim[a,*]

[a]*College of Pharmacy, Sookmyung Women's University, 53-12, Chungpa-dong, Yongsan-ku, Seoul 140-742, South Korea*
[b]*College of Pharmacy, Seoul National University, Seoul 151-742, South Korea*
[c]*AmorePacific R & D Center, Youngin-Si, Kyounggi-do 449-900, South Korea*

Chain-branched phenethylthiocarbamates were synthesized, and their antagonistic effect against vanilloid receptor tested.



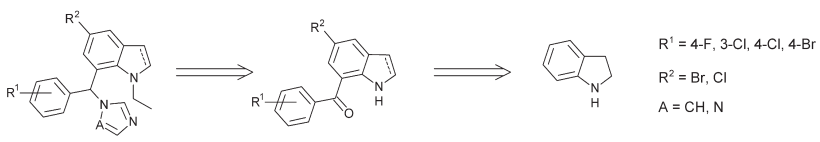
Bioorg. Med. Chem. Lett. 13 (2003) 1553

Preparation and Pharmacological Profile of 7-(α-Azolylbenzyl)-1*H*-indoles and Indolines as New Aromatase Inhibitors

Pascal Marchand,[a,*] Marc Le Borgne,[a] Martina Palzer,[b] Guillaume Le Baut[a] and Rolf W. Hartmann[b]

[a]*Laboratoires de Chimie Organique et de Chimie Thérapeutique, UFR des Sciences Pharmaceutiques, 1 rue Gaston Veil, 44035 Nantes Cedex, France*
[b]*Fachrichtung 12.1 Pharmazeutische und Medizinische Chemie, Universität des Saarlandes, PO Box 15 11 50, D-66041 Saarbrücken, Germany*

New series of 7-(α-azolylbenzyl)-1*H*-indoles and indolines are synthesized via a key-acylation step of indole derivatives in the presence of the suitable benzonitriles and $BCl_3/AlCl_3$. Their biological evaluation towards P450 arom and P450 17α is also reported.



R^1 = 4-F, 3-Cl, 4-Cl, 4-Br
R^2 = Br, Cl
A = CH, N

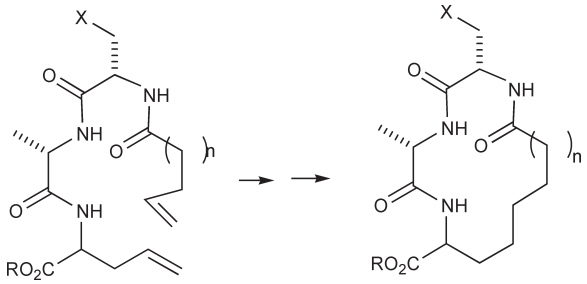
Bioorg. Med. Chem. Lett. 13 (2003) 1557

Macrocyclic Inhibitors of the Bacterial Cell Wall Biosynthesis Enzyme Mur D

James R. Horton,[a] Julieanne M. Bostock,[b] Ian Chopra,[b] Lars Hesse,[b] Simon E. V. Phillips,[b] David J. Adams,[b] A. Peter Johnson[a] and Colin W. G. Fishwick[a,*]

[a]*Departments of Chemistry, University of Leeds, Leeds, LS2 9JT, UK*
[b]*Biochemistry and Molecular Biology, University of Leeds, Leeds, LS2 9JT, UK*

The computer-aided design and subsequent metathesis-based synthesis of a new class of inhibitors to the bacterial peptidoglycan biosynthesis enzyme MurD is described. An assessment of the affinity of these new inhibitors for MurD is also presented.



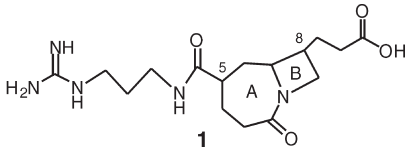
Bioorg. Med. Chem. Lett. 13 (2003) 1561

Nonpeptide RGD Antagonists: A Novel Class of Mimetics, the 5,8-Disubstituted 1-Azabicyclo[5.2.0]nonan-2-one Lactam

Erika Bourguet,[a] Jean-Louis Banères,[a] Joseph Parello,[a] Xavier Lusinchi,[b] Jean-Pierre Girard[a,*] and Jean-Pierre Vidal[a]

[a]*Laboratoire de Chimie Biomoléculaire et Interactions Biologiques, Unité Mixte de Recherche CNRS 5074, Université Montpellier I, Faculté de Pharmacie, 15 Av. C. Flahault, BP 14491, 34093 Montpellier Cedex 5, France*
[b]*Institut de Chimie des Substances Naturelles du CNRS, Gif-sur-Yvette, France*

The 1-azabicyclo[5.2.0]nonan-2-one lactam **1** adequately substituted on both cycles A and B as scaffolds mimics the conformationally constrained β-turn of the tripeptide RGD signaling motif of fibronectin. Using an in vitro *assay*, we establish that *trans* diastereoisomer **1b** dissociates a soluble fibronectin–integrin $\alpha_5\beta_1$ complex at concentrations comparable to those of a linear RGDS peptide as a competitor.



1

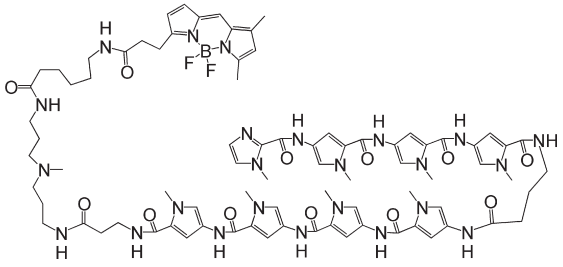
Bioorg. Med. Chem. Lett. 13 (2003) 1565

Controlling the Intracellular Localization of Fluorescent Polyamide Analogues in Cultured Cells

Kathleen S. Crowley,* Dennis P. Phillion, Scott S. Woodard, Barbara A. Schweitzer, Megh Singh, Hossein Shabany, Barry Burnette, Paul Hippenmeyer, Monique Heitmeier and James K. Bashkin*

Pharmacia Corporation, 700 Chesterfield Parkway North, Chesterfield, MO 63198, USA

The intracellular distribution of polyamides in mammalian cells is reported.



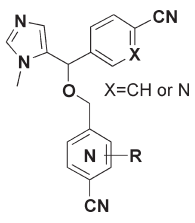
Bioorg. Med. Chem. Lett. 13 (2003) 1571

Discovery of Potent Imidazole and Cyanophenyl Containing Farnesyltransferase Inhibitors with Improved Oral Bioavailability

Yunsong Tong,* Nan-Horng Lin, Le Wang, Lisa Hasvold, Weibo Wang, Nicholas Leonard, Tongmei Li, Qun Li, Jerry Cohen, Wen-Zhen Gu, Haiying Zhang, Vincent Stoll, Joy Bauch, Kennan Marsh, Saul H. Rosenberg and Hing L. Sham

R47B, AP10, Global Pharmaceutical R&D, Abbott Laboratories, 100 Abbott Park Road, Abbott Park, IL 60064-6101, USA

A pyridyl moiety was introduced into a previously developed series of farnesyltransferase inhibitors containing imidazole and cyanophenyl, resulting in potent inhibitors with improved pharmacokinetics.



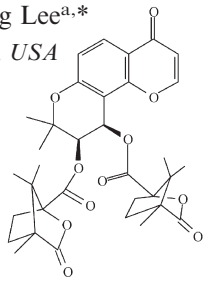
Bioorg. Med. Chem. Lett. 13 (2003) 1575

Anti-HIV Agents. Part 55: 3′*R*,4′*R*-Di-(*O*)-(−)-camphanoyl-2′,2′-dimethyldihydropyrano[2,3-*f*]chromone (DCP), a Novel Anti-HIV Agent

Donglei Yu,[a] Arnold Brossi,[a] Nicole Kilgore,[b] Carl Wild,[b] Graham Allaway[b] and Kuo-Hsiung Lee[a,*]

[a]*Natural Products Laboratory, School of Pharmacy, University of North Carolina, Chapel Hill, NC 27599, USA*
[b]*Panacos Pharmaceuticals, Inc., 217 Perry Parkway, Gaithersburg, MD 20877, USA*

The synthesis and anti-HIV activity of 3′*R*,4′*R*-di-(*O*)-(−)-camphanoyl-2′,2′-dimethyldihydropyrano[2,3-*f*]-chromone (DCP) **2** ($EC_{50} = 6.78\times10^{-4}$ μM) are reported.



2 $EC_{50}=6.78\times10^{-4}$ μM

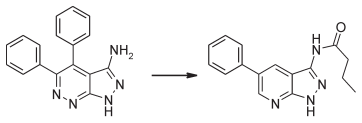
Bioorg. Med. Chem. Lett. 13 (2003) 1577

5-Aryl-pyrazolo[3,4-*b*]pyridines: Potent Inhibitors of Glycogen Synthase Kinase-3 (GSK-3)

Jason Witherington,* Vincent Bordas, Stephen L. Garland, Deirdre M. B. Hickey, Robert J. Ife, John Liddle, Martin Saunders, David G. Smith and Robert W. Ward

Department of Medicinal Chemistry, Neurology Centre of Excellence for Drug Discovery, GlaxoSmithKline Research Limited, New Frontiers Science Park, Third Avenue, Harlow, Essex CM19 5AW, UK

A novel series of pyrazolo[3,4-*b*]pyridines has been identified as potent inhibitors of Glycogen Synthase Kinase-3 (GSK-3).



IC_{50} 250 nM IC_{50} 56 nM

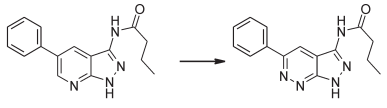
Bioorg. Med. Chem. Lett. 13 (2003) 1581

5-Aryl-pyrazolo[3,4-*b*]pyridazines: Potent Inhibitors of Glycogen Synthase Kinase-3 (GSK-3)

Jason Witherington,* Vincent Bordas, David Haigh, Deirdre M. B. Hickey, Robert J. Ife, Anthony D. Rawlings, Brian P. Slingsby, David G. Smith and Robert W. Ward

Department of Medicinal Chemistry, Neurology Centre of Excellence for Drug Discovery, GlaxoSmithKline Research Limited, New Frontiers Science Park, Third Avenue, Harlow, Essex CM19 5AW, UK

Introduction of a nitrogen atom into the 6-position of a series of pyrazolo[3,4-*b*]pyridines led to a dramatic improvement in the potency of GSK-3 inhibition. Rationalisation of the binding mode suggested participation of a putative structural water molecule, which was subsequently confirmed by X-ray crystallography.



IC_{50} 56 nM IC_{50} 4 nM

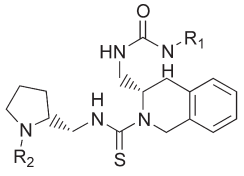
Bioorg. Med. Chem. Lett. 13 (2003) 1585

New Scaffolds in the Development of Mu Opioid-Receptor Ligands

Daniel Pagé,[a,*] Natalie Nguyen,[a] Sylvain Bernard,[a] Martin Coupal,[b] Mylène Gosselin,[b] Julie Lepage,[b] Lynda Adam[b] and William Brown[a]

[a]*Department of Chemistry, AstraZeneca R&D Montreal, 7171 Frederick-Banting, Saint-Laurent, Quebec, Canada H4S 1Z9*
[b]*Department of Molecular Pharmacology, AstraZeneca R&D Montreal, 7171 Frederick-Banting, Saint-Laurent, Quebec, Canada H4S 1Z9*

A new class of μ selective receptor ligands has been developed. Modified tetrahydroisoquinoline derivatives bearing basic pyrrolidine moieties through thiourea linkers were shown to exhibit good binding affinity. Alkylation of the pyrrolidine ring with benzyl derivatives having polar groups with hydrogen-bonding abilities enhanced the μ binding affinity up to 1.1 nM.



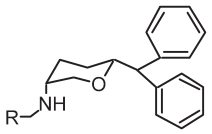
Bioorg. Med. Chem. Lett. 13 (2003) 1591

Design, Synthesis, and Activity of Novel *cis*- and *trans*-3,6-Disubstituted Pyran Biomimetics of 3,6-Disubstituted Piperidine as Potential Ligands for the Dopamine Transporter

Shijun Zhang,[a] Maarteen E. A. Reith[b] and Aloke K. Dutta[a,*]

[a]*Department of Pharmaceutical Sciences, Wayne State University, Detroit, MI 48202, USA*
[b]*University of Illinois, College of Medicine, Department of Biomedical and Therapeutic Sciences, Peoria, IL 61605, USA*

Novel design of 3,6-disubstituted pyran derivatives as potential dopamine transporter inhibitor and development of their efficient stereospecific synthesis route.



Bioorg. Med. Chem. Lett. 13 (2003) 1597

The Selective Inhibition of Phosphatases by Natural Toxins: The Anhydride Domain of Tautomycin Is Not a Primary Factor in Controlling PP1/PP2A Selectivity

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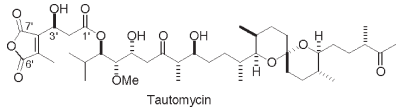
Analogues of the PP1/PP2A inhibitor tautomycin were prepared by modifying the C1′–C7′ anhydride moiety. All retain activity and constancy in IC_{50} ratios.



Tautomycin

Bioorg. Med. Chem. Lett. 13 (2003) 1601

A New Model of the Tautomycin–PP1 Complex That is Not Analogous to the Corresponding Okadaic Acid Structure

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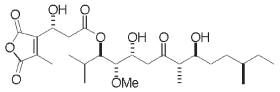
A revised model of PP1–tautomycin (TM) complex suggests that this toxin does not bind in a conformation analogous to its structural cousin okadaic acid (OA), as has been assumed, but instead more resembles the mode of binding adopted by calyculin. This model rationalizes the unexpected potency of a truncated TM analogue **2** lacking the bicyclic ketal common to TM and OA.



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