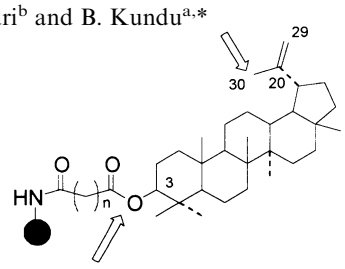
Solid-Phase Synthesis and Bioevaluation of Lupeol-Based Libraries as Antimalarial Agents

Bioorg. Med. Chem. Lett. 12 (2002) 2803

T. Srinivasan,[a] G. K. Srivastava,[a] A. Pathak,[a] S. Batra,[a] K. Raj,[a] Kshipra Singh,[b] S. K. Puri[b] and B. Kundu[a,*]

[a]*Medicinal Chemistry Division, Central Drug Research Institute, Lucknow-226 001, India*
[b]*Parasitology Division, Central Drug Research Institute, Lucknow-226 001, India*

The use of the triterpenoid lupeol as a scaffold for the synthesis of lupeol-based libraries is described. Lupeol was anchored to a solid support (Rink amide/Sieber Amide) through aliphatic dicarboxylic acid moieties, which also served as a site for introducing diversity. The resulting polymer linked 3β-*O* (resin-alkanoyl)-lup-20(29)-ene **3** was used to generate key intermediates 3β-*O* (resin-alkanoyl)-30-bromo-lup-20(29)-ene **4** and 3β-*O* (resin-alkanoyl)-30-amino-lup-20(29)-ene **6** for the generation of libraries based on disubstituted lupeol derivatives. A 96-member library was screened for its in-vitro antimalarial activity against *Plasmodium falciparum*.



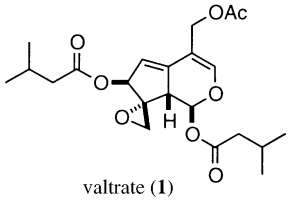
New Rev-Transport Inhibitor with Anti-HIV Activity from Valerianae Radix

Bioorg. Med. Chem. Lett. 12 (2002) 2807

Nobutoshi Murakami,[a] Ying Ye,[a] Motoyuki Kawanishi,[a] Shunji Aoki,[a] Nobuaki Kudo,[b] Minoru Yoshida,[b] Emi E. Nakayama,[c] Tatsuo Shioda[c] and Motomasa Kobayashi[a,*]

[a]*Graduate School of Pharmaceutical Sciences, Osaka University, 1-6 Yamada-oka, Suita, Osaka 565-0871, Japan*
[b]*Graduate School of Agriculture and Life Sciences, The University of Tokyo, Bunkyo-ku, Tokyo 113, Japan*
[c]*Research Institute for Microbial Diseases, Osaka University, 3-1 Yamada-oka, Suita, Osaka 565-0871, Japan*

Bioassay-guided separation by use of the fission yeast expressing the NES of Rev resulted in isolation of valtrate (**1**) as a new Rev-transport inhibitor from Valerianae Radix.



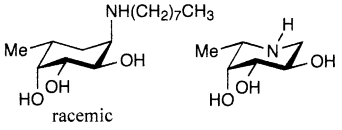
valtrate (**1**)

Convenient Synthesis and Evaluation of Enzyme Inhibitory Activity of Several *N*-Alkyl-, *N*-Phenylalkyl, and Cyclic Isourea Derivatives of 5a-Carba-α-DL-fucopyranosylamine

Bioorg. Med. Chem. Lett. 12 (2002) 2811

Seiichiro Ogawa,* Makiko Mori, Goichi Takeuchi, Fuminao Doi, Maiko Watanabe and Yuko Sakata

Department of Life Sciences and Informatics, Faculty of Science and Technology, Keio University, Hiyoshi, Kohoku-ku, Yokohama 223-8522, Japan



K_i = 16 nM ref. K_i = 31 nM

against α-L-fucosidase (bovine kidney)

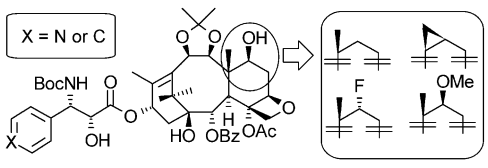
New Highly Active Taxoids from 9β-Dihydrobaccatin-9,10-acetals. Part 2

Bioorg. Med. Chem. Lett. 12 (2002) 2815

Takashi Ishiyama, Shin Iimura, Toshiharu Yoshino, Jun Chiba, Kouichi Uoto, Hirofumi Terasawa and Tsunehiko Soga*

Medicinal Chemistry Research Laboratory, Daiichi Pharmaceutical Co., Ltd., Tokyo R&D Center, 16-13 Kita-kasai 1-Chome Edogawa-ku, Tokyo 134-8630, Japan

The dramatic improvement of the activity of 9β-dihydro taxoids by modification of the 7 and/or 3′ positions is reported.



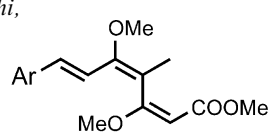
Bioorg. Med. Chem. Lett. 12 (2002) 2821

The First Synthesis and Antifungal Activities of 9-Methoxystrobilurin-type β-Substituted β-Methoxyacrylate

Hiromi Uchiro, Koh Nagasawa, Tomoya Kotake, Daiju Hasegawa, Aya Tomita and Susumu Kobayashi*

Faculty of Pharmaceutical Sciences, Tokyo University of Science, 12 Ichigayafunagawara-machi, Shinjuku-ku, Tokyo 162-0826, Japan

The first synthesis of 9-methoxystrobilurin-type β-substituted MOAs was successfully achieved. Antifungal activities of the synthesized compounds against several representative fungi were examined and superior antifungal properties of 9-methoxystrobilurin-type β-substituted MOAs compared with those of oudemansin-type analogue were clearly revealed.



Ar = Ph, α-Naphthyl, β-Naphthyl, Thienyl *etc.*

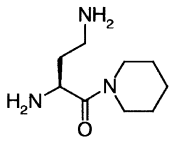
Bioorg. Med. Chem. Lett. 12 (2002) 2825

Development of Potent and Selective Dipeptidyl Peptidase II Inhibitors

Kristel Senten,[a] Pieter Van der Veken,[a] Gunther Bal,[a] Ingrid De Meester,[b] Anne-Marie Lambeir,[b] Simon Scharpé,[b] Brigitte Bauvois,[c] Achiel Haemers[a] and Koen Augustyns[a,*]

[a]*Department of Medicinal Chemistry, University of Antwerp (UIA), Universiteitsplein 1, B-2610 Antwerpen, Belgium*
[b]*Department of Medical Biochemistry, University of Antwerp (UIA), Universiteitsplein 1, B-2610 Antwerpen, Belgium*
[c]*Institut Curie, Pavillon Pasteur, Unité INSERM 365, 26, rue d'ULM, 75231 Paris Cedex 05, France*

The design and synthesis of a series of DPP II inhibitors are reported, in which the most potent and selective Dab-Pip has an $IC_{50} = 0.13$ μM and a 7600-fold selectivity with respect to DPP IV.



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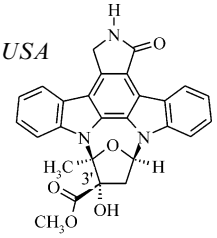
Bioorg. Med. Chem. Lett. 12 (2002) 2829

Synthesis and Kinase Inhibitory Activity of 3′-(*S*)-*epi*-K-252a

Diane E. Gingrich and Robert L. Hudkins

Department of Medicinal Chemistry, Cephalon, Inc., 145 Brandywine Parkway, West Chester, PA 19380, USA

The 3′-*epi* diastereomer of K-252a (**2**) was synthesized resulting in a 19 nM inhibitor of VEGFR2 and a 1 nM inhibitor of TrkA tyrosine kinase.



***epi*-2**

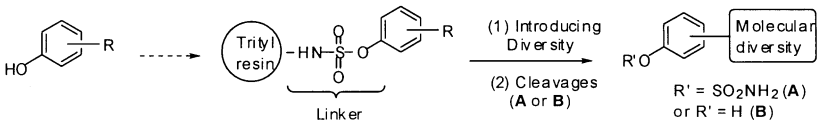
Bioorg. Med. Chem. Lett. 12 (2002) 2833

A Multidetachable Sulfamate Linker Successfully Used in a Solid-Phase Strategy to Generate Libraries of Sulfamate and Phenol Derivatives

Donald Poirier,* Liviu C. Ciobanu and Marie Bérubé

Medicinal Chemistry Division, Oncology and Molecular Endocrinology Research Center and Laval University, Centre Hospitalier Universitaire de Québec (CHUQ), Pavillon CHUL, 2705 Laurier Boulevard, Québec, Qc, Canada G1V 4G2

Four model libraries of enzyme inhibitors were rapidly synthesized in very good yields and purities.



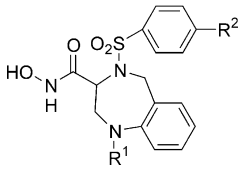
Bioorg. Med. Chem. Lett. 12 (2002) 2867

Benzodiazepine Inhibitors of the MMPs and TACE

Frances C. Nelson,[a,*] Efren Delos Santos,[a] Jeremy I. Levin,[a] James M. Chen,[a] Jerauld S. Skotnicki,[a] John F. DiJoseph,[b] Michele A. Sharr,[b] Amy Sung,[b] Loran M. Killar,[b] Rebecca Cowling,[a] Guixian Jin,[a] Catherine E. Roth[b] and J. Donald Albright[a]

[a]*Wyeth Research, 401 N. Middletown Road, Pearl River, NY 10965, USA*
[b]*Wyeth Research, PO Box CN8000, Princeton, NJ 08543, USA*

A series of benzodiazepine inhibitors of the MMPs and TACE has been developed. These compounds display an interesting selectivity profile and should be useful tools for exploring the biological relevance of such selectivity.



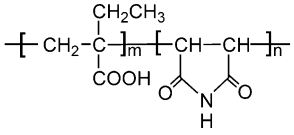
Bioorg. Med. Chem. Lett. 12 (2002) 2843

Synthesis of Poly(maleimide-co-2-ethylacrylic Acid) and Its Properties of Suppressing Metastasis and Growth of Carcinoma

Zhongliang Zhu, Lianjun Shi and Junlian Huang

Department of Macromolecular Science, The Key Laboratory of Molecular Engineering, Education Ministry of China, Fudan University, Shanghai 200433, People's Republic of China

A series of copolymers with different contents and composition is prepared using maleimide and 2-ethylacrylic acid as comonomer. This kind of copolymer shows low toxicity (LD_{50}: 601–798 mg/kg) and significant curative effect on Lewis lung carcinoma and S180.



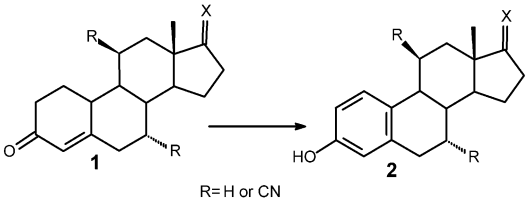
Bioorg. Med. Chem. Lett. 12 (2002) 2847

Synthesis of Nitrile Derivatives of Estrogens

Hasrat Ali and Johan E. van Lier*

CIHR Group in the Radiation Sciences, Faculty of Medicine, Université de Sherbrooke, Sherbrooke, QC, Canada J1H 5N4

The nature of the 11β-substituent strongly affects the conversion of 19-nortestosterone to estrogen derivatives.



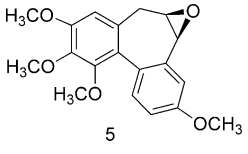
Bioorg. Med. Chem. Lett. 12 (2002) 2851

Antitumor Agents. Part 215: Antitubulin Effects of Cytotoxic B-Ring Modified Allocolchicinoids

Shiqing Han,[a] Ernest Hamel,[b] Kenneth F. Bastow,[a] Andrew T. McPhail,[c] Arnold Brossi[a] and Kuo-Hsiung Lee[a,*]

[a]*Natural Products Laboratory, School of Pharmacy, University of North Carolina at Chapel Hill, NC 27599, USA*
[b]*Screening Technologies Branch, Developmental Therapeutics Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute at Frederick, National Institutes of Health, Frederick, MD 21702, USA*
[c]*Department of Chemistry, Paul M. Gross Chemical Laboratory, Duke University, Durham, NC 27708, USA*

N-Acetylcolchinol methyl ether **1** served as the starting material to prepare the chloroacetamide (**3**) and epoxide (**5**) analogues. Both **3** and **5** were potent inhibitors of tubulin polymerization in vitro.



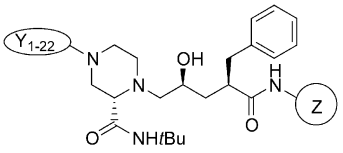
Bioorg. Med. Chem. Lett. 12 (2002) 2855

Combinatorial Library of Indinavir Analogues: Replacement for the Aminoindanol at P_2'

Subharekha Raghavan,[a,*] Zheng Yang,[a] Ralph T. Mosley,[a] William A. Schleif,[b] Lori Gabryelski,[b] David B. Olsen,[b] Mark Stahlhut,[b] Lawrence C. Kuo,[b] Emilio A. Emini,[b] Kevin T. Chapman[a] and James R. Tata[a]

[a]*Department of Medicinal Chemistry Merck Research Laboratories, Rahway, NJ 07065, USA*
[b]*Department of Antiviral Research Merck Research Laboratories, West Point, PA 19486, USA*

A combinatorial library of indinavir analogues was synthesized on the solid support to identify a replacement for the aminoindanol moiety at P_2'. 2,6-Dimethyl-4-hydroxy phenol was discovered to be a good replacement for aminoindanol.



Bioorg. Med. Chem. Lett. 12 (2002) 2859

Design, Synthesis and Evaluation of 4-Imidazolylflavans as New Leads for Aromatase Inhibition

Christelle Pouget, Catherine Fagnere, Jean-Philippe Basly, Gérard Habrioux and Albert José Chulia*

UPRES EA 1085, 'Biomolécules et cibles cellulaires tumorales', Faculté de Pharmacie, 2 rue du Docteur Marcland, 87025 Limoges cedex, France

Two 4-imidazolylflavans were synthesized and their stereochemistry was established by ^{1}H and ^{13}C NMR data. These compounds were tested for their activity to inhibit aromatase. It was observed that the introduction of an imidazolyl group at carbon 4 on flavan nucleus led to very potent molecules.

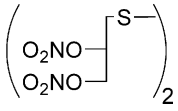
Bioorg. Med. Chem. Lett. 12 (2002) 2863

Neuroprotection Against Ischemic Brain Injury Conferred by a Novel Nitrate Ester

James N. Reynolds,[b] Brian M. Bennett,[b] Roland J. Boegman,[b] Khem Jhamandas,[b] Jodan D. Ratz,[b] Sergei I. Zavorin,[a] Dan Scutaru,[a] Adina Dumitrascu[a] and Gregory R. J. Thatcher[a,b,*]

[a]*Department of Chemistry, Queen's University, Kingston, ON, Canada K7L 3N6*
[b]*Department of Pharmacology and Toxicology, Queen's University, Kingston, ON, Canada K7L 3N6*

A novel nitrate is neuroprotective in the MCAO in vivo stroke model when administered post-ischemia.



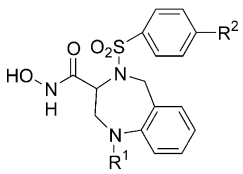
Bioorg. Med. Chem. Lett. 12 (2002) 2867

Benzodiazepine Inhibitors of the MMPs and TACE

Frances C. Nelson,[a,*] Efren Delos Santos,[a] Jeremy I. Levin,[a] James M. Chen,[a] Jerauld S. Skotnicki,[a] John F. DiJoseph,[b] Michele A. Sharr,[b] Amy Sung,[b] Loran M. Killar,[b] Rebecca Cowling,[a] Guixian Jin,[a] Catherine E. Roth[b] and J. Donald Albright[a]

[a]*Wyeth Research, 401 N. Middletown Road, Pearl River, NY 10965, USA*
[b]*Wyeth Research, PO Box CN8000, Princeton, NJ 08543, USA*

A series of benzodiazepine inhibitors of the MMPs and TACE has been developed. These compounds display an interesting selectivity profile and should be useful tools for exploring the biological relevance of such selectivity.

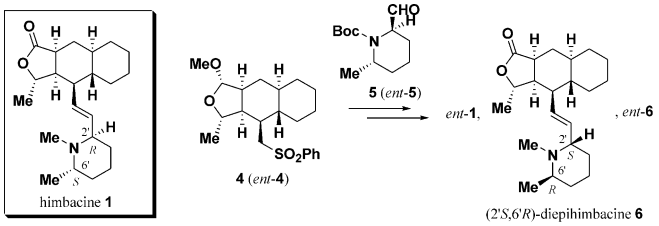


Bioorg. Med. Chem. Lett. 12 (2002) 2871

Synthesis and Muscarinic M_2 Subtype Antagonistic Activity of Unnatural *ent*-Himbacine and an Enantiomeric Pair of (2′*S*,6′*R*)-Diepihimbacine

Masanori Takadoi[a,*] and Shiro Terashima[b]

[a]*Discovery Research Laboratories, Kyorin Pharmaceutical Company Ltd., 2399-1 Nogi, Nogi-machi, Tochigi 329-0114, Japan*
[b]*Sagami Chemical Research Center, 2743-1 Hayakawa, Ayase, Kanagawa 252-1193, Japan*



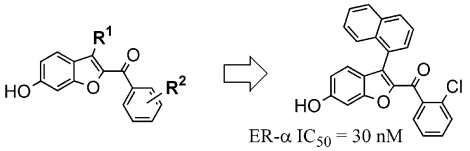
Bioorg. Med. Chem. Lett. 12 (2002) 2875

Solid-Phase Synthesis and Investigation of Benzofurans as Selective Estrogen Receptor Modulators

Roger A. Smith,[a,*] Jinshan Chen,[a] Mary M. Mader,[a] Ingo Muegge,[a] Ulrike Moehler,[a] Suresh Katti,[b] Diana Marrero,[b] William G. Stirtan,[b] Daniel R. Weaver,[c] Hong Xiao[c] and William Carley[c]

[a]*Department of Chemistry Research, Bayer Research Center, 400 Morgan Lane, West Haven, CT 06516, USA*
[b]*Department of Research Technologies, Bayer Research Center, 400 Morgan Lane, West Haven, CT 06516, USA*
[c]*Department of Cancer and Osteoporosis Research, Bayer Research Center, 400 Morgan Lane, West Haven, CT 06516, USA*

A library of benzofurans was prepared by solid-phase synthesis methods, and several analogues were identified as potent ligands for the estrogen receptors ER-α and ER-β, with some compounds having selectivity for ER-α. Analogues designed to more closely mimic Raloxifene were less effective. Certain benzofurans were effective in a bone pit assay, but were characterized as agonists in a MCF-7 breast tumor cell proliferation assay.



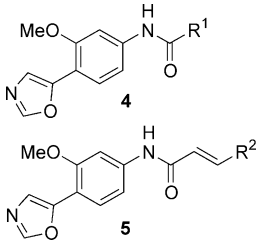
Bioorg. Med. Chem. Lett. 12 (2002) 2879

Novel Amide-Based Inhibitors of Inosine 5′-Monophosphate Dehydrogenase

Scott H. Watterson,* Chunjian Liu, T. G. Murali Dhar, Henry H. Gu, William J. Pitts, Joel C. Barrish, Catherine A. Fleener, Katherine Rouleau, N. Z. Sherbina, Diane L. Hollenbaugh and Edwin J. Iwanowicz

Bristol-Myers Squibb PRI, PO Box 4000, Princeton, NJ 08543-4000, USA

The preparation and in vitro biological evaluation of a series of novel amide-based small molecule inhibitors of inosine monophosphate dehydrogenase are described.



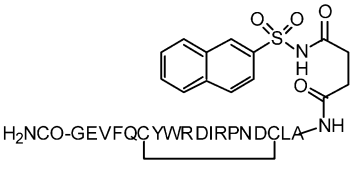
Bioorg. Med. Chem. Lett. 12 (2002) 2883

Albumin Affinity Tags Increase Peptide Half-Life In Vivo

Michael F. T. Koehler,[a,*] Kerry Zobel,[a] Maureen H. Beresini,[b] Lisa D. Caris,[b] Daniel Combs,[c] Brian D. Paasch[b] and Robert A. Lazarus[a]

[a]*Department of Protein Engineering, Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080, USA*
[b]*Department of BioAnalytical Research and Development, Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080, USA*
[c]*Department of Clinical and Experimental Pharmacology, Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080, USA*

Small molecule tags with high affinity for serum albumin reduce clearance and increase the circulating half-life of bioactive peptides administered to rabbits.



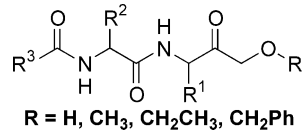
Bioorg. Med. Chem. Lett. 12 (2002) 2887

Novel Route to the Synthesis of Peptides Containing 2-Amino-1′-hydroxymethyl Ketones and Their Application as Cathepsin K Inhibitors

Rohan V. Mendonca,* Shankar Venkatraman and James T. Palmer

Celera, 180 Kimball Way, South San Francisco, CA 94080, USA

A new synthetic route to hydroxymethyl and alkoxymethyl ketones is reported.

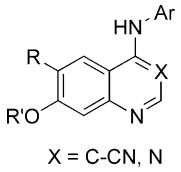


Bioorg. Med. Chem. Lett. 12 (2002) 2893

Syntheses and EGFR and HER-2 Kinase Inhibitory Activities of 4-Anilinoquinoline-3-carbonitriles: Analogues of Three Important 4-Anilinoquinazolines Currently Undergoing Clinical Evaluation as Therapeutic Antitumor Agents

Allan Wissner,* M. Brawner Floyd, Sridhar K. Rabindran, Ramaswamy Nilakantan, Lee M. Greenberger, Ru Shen, Yu-Fen Wang and Hwei-Ru Tsou

Chemical Sciences and Oncology and Immunoinflammatory Research, Wyeth Research, 401 N. Middletown Road, Pearl River, NY 10965, USA

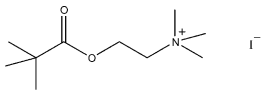


Bioorg. Med. Chem. Lett. 12 (2002) 2899

Molecular Modeling and Enzymatic Studies of the Interaction of a Choline Analogue and Acetylcholinesterase

Stefano Alcaro,[a,*] Luigi Scipione,[b] Francesco Ortuso,[a] Salvatore Posca,[b] Vincenzo Rispoli[a] and Domenicantonio Rotiroti[a]

[a]*Dipartimento di Scienze Farmacobiologiche, Università degli Studi 'Magna Græcia' di Catanzaro, Complesso 'Ninì Barbieri', I-88021 Roccelletta di Borgia (CZ), Italy*
[b]*Dipartimento di Studi di Chimica e Tecnologia delle Sostanze Biologicamente Attive, Università degli Studi 'La Sapienza' di Roma, P. le A. Moro, 5, 00185 Rome, Italy*



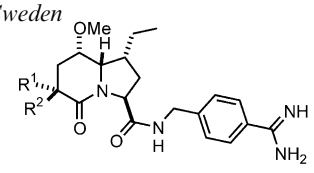
Pivaloyl-choline iodide **1** interactions with acetylcholinesterase (AChE) have been studied by theoretical and enzymatic methods. An integrated computational approach has clearly shown a substrate rather than inhibitory profile for **1**. Enzymatic experiments have also supported the same theoretical conclusion indicating that AChE was able to hydrolyze **1** to choline.

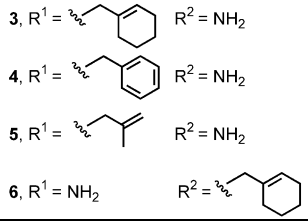
Bioorg. Med. Chem. Lett. 12 (2002) 2907

Targeting Thrombin and Factor VIIa: Design, Synthesis, and Inhibitory Activity of Functionally Relevant Indolizidinones

Stephen Hanessian,[a,*] Eric Therrien,[a] Kenneth Granberg[b] and Ingemar Nilsson[b]

[a]*Department of Chemistry, Université de Montréal, PO Box 6128, Station Centre-ville, Montréal, QC, Canada H3C 3J7*
[b]*AstraZeneca R&D Mölndal, Medicinal Chemistry, Mölndal, Sweden*



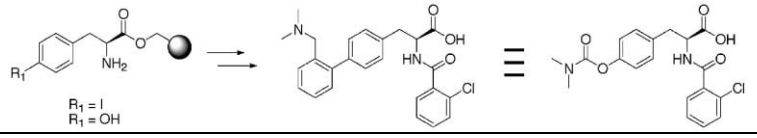


Bioorg. Med. Chem. Lett. 12 (2002) 2913

Solid-Phase Synthesis of Dual $\alpha_4\beta_1/\alpha_4\beta_7$ Integrin Antagonists: Two Scaffolds with Overlapping Pharmacophores

Georgette M. Castanedo,[a] Fredrick C. Sailes,[a] Nathan J. P. Dubree,[a] John B. Nicholas,[a] Lisa Caris,[b] Kevin Clark,[b] Susan M. Keating,[b] Maureen H. Beresini,[b] Henry Chiu,[c] Sherman Fong,[c] James C. Marsters, Jr.,[a] David Y. Jackson[a] and Daniel P. Sutherlin[a,*]

[a]*Department of Bioorganic Chemistry, Genentech, Inc., South San Francisco, CA 94080, USA*
[b]*Department of Pharmacology, Genentech, Inc., South San Francisco, CA 94080, USA*
[c]*Department of Immunology, Genentech, Inc., South San Francisco, CA 94080, USA*



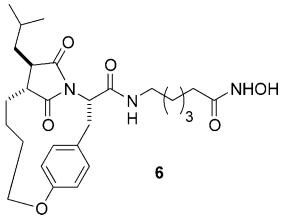
Bioorg. Med. Chem. Lett. 12 (2002) 2919

Succinimide Hydroxamic Acids as Potent Inhibitors of Histone Deacetylase (HDAC)

Michael L. Curtin,* Robert B. Garland, H. Robin Heyman, Robin R. Frey, Michael R. Michaelides, Junling Li, Lori J. Pease, Keith B. Glaser, Patrick A. Marcotte and Steven K. Davidsen

Cancer Research Area, Abbott Laboratories, Dept. 47J, Bldg. AP10, 100 Abbott Park Road, Abbott Park, IL 60064, USA

The evaluation of HDAC inhibitor **6** (IC_{50} 38 nM) and simplified succinimide hydroxamic acid analogues is reported.



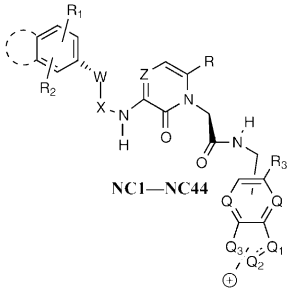
Bioorg. Med. Chem. Lett. 12 (2002) 2925

Non-covalent Thrombin Inhibitors Featuring P_3-heterocycles with P_1-Bicyclic Arginine Surrogates†

Jingrong Jean Cui, Gian-Luca Araldi, John E. Reiner, Komandla Malla Reddy, Scott J. Kemp, Jonathan Z. Ho, Daniel V. Siev, Lala Mamedova, Tony S. Gibson, John A. Gaudette, Nathaniel K. Minami, Susanne M. Anderson, Annette E. Bradbury, Thomas G. Nolan and J. Edward Semple*

Department of Medicinal Chemistry, Corvas International, Inc., 3030 Science Park Road, San Diego, CA 92121, USA

The design, synthesis and biological activity of achiral, non-covalent, orally bioavailable thrombin inhibitors **NC1**–**NC44** is disclosed that feature weakly basic bicyclic P_1-arginine mimics including indazoles, benzimidazoles, indoles, benzotriazoles and aminobenzisoxazoles.



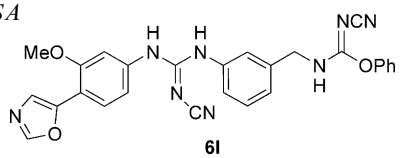
Bioorg. Med. Chem. Lett. 12 (2002) 2931

Novel Guanidine-Based Inhibitors of Inosine Monophosphate Dehydrogenase

Edwin J. Iwanowicz,* Scott H. Watterson, Chunjian Liu, Henry H. Gu, Toomas Mitt, Katerina Leftheris, Joel C. Barrish, Catherine A. Fleener, Katherine Rouleau, N. Z. Sherbina and Diane L. Hollenbaugh

Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ 08543-4000, USA

A series of novel guanidine-based inhibitors of IMPDH II was prepared and the structure–activity relationships (SARs) are described. Studies were focused on replacing a urea moiety, key to potent biological activity for a previously described chemical series. Compound **6l** was identified as a potent inhibitor of IMPDH II with an IC_{50}(16 nM) comparable to mycophenolic acid.



IMPDH II IC_{50} 0.016 μM

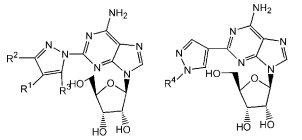
Bioorg. Med. Chem. Lett. 12 (2002) 2935

Structure–Affinity Relationships of the Affinity of 2-Pyrazolyl Adenosine Analogues for the Adenosine A_{2A} Receptor

Venkata P. Palle,[a,*] Elfatih O. Elzein,[a,*] Scott A. Gothe,[c] Zhihe Li,[b] Zhenhai Gao,[b] Stephanie Meyer,[b] Brent Blackburn[a,b] and Jeff A. Zablocki[a]

[a]*Department of Bioorganic Chemistry, CV Therapeutics, 3172 Porter Drive, Palo Alto, CA 94304, USA*
[b]*Department of Pharmacological Sciences, CV Therapeutics, 3172 Porter Drive, Palo Alto, CA 94304, USA*
[c]*Tripos, Inc., 601 Gateway Blvd. Suite 720, So. San Francisco, CA, USA*

The SAR of two series of A_{2A} adenosine agonists are reported.



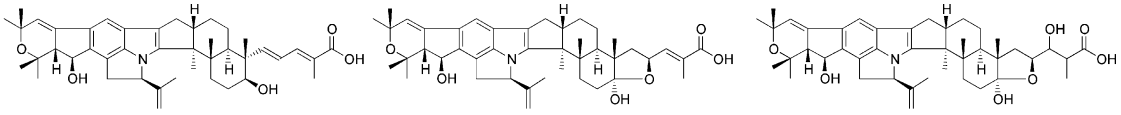
Bioorg. Med. Chem. Lett. 12 (2002) 2941

Nodulisporic Acid B, B_1, and B_2: A Series of 1′-Deoxy-nodulisporic Acids from *Nodulisporium* sp.

John G. Ondeyka,* Arlene M. Dahl-Roshak, Jan S. Tkacz, Deborah L. Zink, Michelle Zakson-Aiken, Wesley L. Shoop, Michael A. Goetz and Sheo B. Singh

Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065, USA

Discovery and biological activities of a series of 1′-deoxy-nodulisporic acid congeners nodulisporic acids B, B_1 and B_2 have been described.



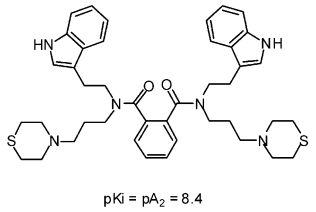
Bioorg. Med. Chem. Lett. 12 (2002) 2945

Successful Bridging from a Peptide to a Non Peptide Antagonist at the Human Tachykinin NK-2 Receptor

Maria Altamura, Franca Canfarini, Rose-Marie Catalioto, Antonio Guidi,* Franco Pasqui, Anna R. Renzetti, Antonio Triolo and Carlo A. Maggi

Menarini Ricerche S.p.A., Via dei Sette Santi 3, 50131 Florence, Italy

Novel non peptide antagonists at the hNK-2 receptor have been derived from a potent peptide antagonist.



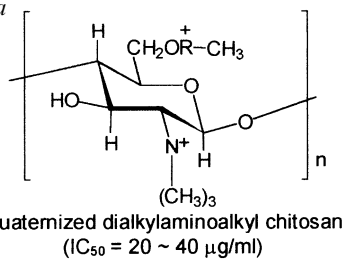
Bioorg. Med. Chem. Lett. 12 (2002) 2949

Cytotoxic Activity of Aminoderivatized Cationic Chitosan Derivatives

Jung-Kul Lee,[a] Hyun-Soo Lim[b] and Jung-Hoe Kim[c,*]

[a]*BioNgene Co., Ltd., 10-1, 1Ka Myungryun-Dong, Chongro-Ku, Seoul, 110-521, South Korea*
[b]*Division of Biotechnology and Chemical Engineering, Yosu National University, San 96-1 Dunduck-dong, Yeosu Jeollanam-Do, 550-749, South Korea*
[c]*Department of Biological Sciences, Korea Advanced Institute of Science and Technology, 307-1 Kusong-Dong, Yusong-Ku, Taejon-Si, 449-791, South Korea*

Chitosan derivatives were prepared by dialkylaminoalkylation and reductive amination followed by quaternization. Cytotoxic activity of the chitosan derivatives was investigated and a relationship between structure and activity is suggested.



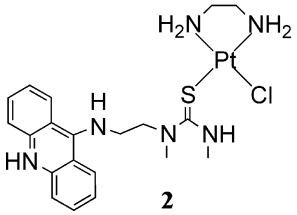
Bioorg. Med. Chem. Lett. 12 (2002) 2953

Cytotoxic Acridinylthiourea and Its Platinum Conjugate Produce Enzyme-Mediated DNA Strand Breaks

Jennifer M. Brow, Cynthia R. Pleatman and Ulrich Bierbach*

Department of Chemistry, Wake Forest University, Winston-Salem, NC 27109, USA

The novel acridinylthiourea, 1-[2-(acridin-9-ylamino)ethyl]-1,3-dimethylthiourea (**1**), has been identified as a dual topoisomerase I/II poison. As a carrier ligand in the DNA-directed platinum–acridine conjugate, **2**, acridine turns the metallodrug into a topoisomerase II poison.



2

Bioorg. Med. Chem. Lett. 12 (2002) 2957

Novel Substituted 4-Aminomethylpiperidines as Potent and Selective Human β_3-Agonists. Part 1: Aryloxypropanolaminomethylpiperidines

Robert J. Steffan,[a,*] Mark A. Ashwell,[a] William R. Solvibile,[a] Edward Matelan,[a] Elwood Largis,[b] Stella Han,[b] Jeffery Tillet[b] and Ruth Mulvey[b]

[a]*Chemical Sciences, Wyeth Research, 500 Arcola Rd, Collegeville, PA 19426, USA*
[b]*Cardiovascular/Metabolic Diseases, Wyeth Research, 500 Arcola Rd, Collegeville, PA 19426, USA*

The synthesis and SAR of a series of human β_3 adrenoreceptor agonists based on a template derived from a common pharmacophore coupled with 4-aminomethylpiperidine is described. Potent and selective agents were identified that were in vitro active in CHO cells expressing human β_3-AR ($EC_{50} = 49$ nM, IA = 1.1), and in vivo active in a transgenic mouse model.

Bioorg. Med. Chem. Lett. 12 (2002) 2963

Novel Substituted 4-Aminomethylpiperidines as Potent and Selective Human β_3-Agonists. Part 2: Arylethanolaminomethylpiperidines

Robert J. Steffan,[a,*] Mark A. Ashwell,[a] William R. Solvibile,[a] Edward Matelan,[a] Elwood Largis,[b] Stella Han,[b] Jeffery Tillet[b] and Ruth Mulvey[b]

[a]*Chemical Sciences, Wyeth Research, 500 Arcola Rd, Collegeville, PA 19426, USA*
[b]*Cardiovascular/Metabolic Diseases, Wyeth Research, 500 Arcola Rd, Collegeville, PA 19426, USA*

The synthesis and SAR of a series of β_3 adrenoreceptor agonists based on a novel template derived from 4-aminomethylpiperidine coupled with a common pharmacophore, arylethylamine, is described. This combination led to the identification of human β_3 adrenoreceptor agonists with in vivo activity in a transgenic mouse model.

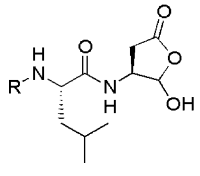
Bioorg. Med. Chem. Lett. 12 (2002) 2969

Acyl Dipeptides as Reversible Caspase Inhibitors. Part 1: Initial Lead Optimization

Steven D. Linton,* Donald S. Karanewsky, Robert J. Ternansky, Joe C. Wu, Brian Pham, Lalitha Kodandapani, Robert Smidt, Jose-Luis Diaz, Lawrence C. Fritz and Kevin J. Tomaselli

Idun Pharmaceuticals, Inc., 9380 Judicial Drive, San Diego, CA 92121, USA

Parallel synthesis was used to explore the SAR of a peptidomimetic caspase inhibitor. The most potent compound had nanomolar activity against caspases 1, 3, 6, 7, and 8.



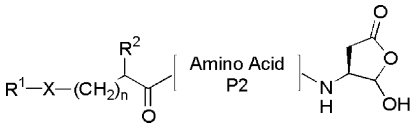
Bioorg. Med. Chem. Lett. 12 (2002) 2973

Acyl Dipeptides as Reversible Caspase Inhibitors. Part 2: Further Optimization

Steven D. Linton,[a,*] Donald S. Karanewsky,[a] Robert J. Ternansky,[a] Ning Chen,[a] Xian Guo,[a] Kathy G. Jahangiri,[a] Vincent J. Kalish,[a] Steven P. Meduna,[a] Edward D. Robinson,[a] Brett R. Ullman,[a] Joe C. Wu,[a] Brian Pham,[a] Lalitha Kodandapani,[a] Robert Smidt,[a] Jose-Luis Diaz,[a] Lawrence C. Fritz,[a] U. von Krosigk,[b] Silvio Roggo,[b] Albert Schmitz[b] and Kevin J. Tomaselli[a]

[a]*Idun Pharmaceuticals, Inc., 9380 Judicial Drive, San Diego, CA 92121, USA*
[b]*Novartis Pharma Ltd., Pharma Research, CH-4002 Basel, Switzerland*

A new structural class of broad spectrum caspase inhibitors was optimized for its activity against caspases 1, 3, 6, 7, and 8. The most potent compound had low nanomolar broad spectrum activity, in particular, single digit nanomolar inhibitory activity against caspase 8.



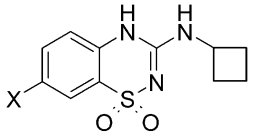
Bioorg. Med. Chem. Lett. 12 (2002) 2977

Synthesis and Evaluation of 7-Substituted-3-cyclobutylamino-4*H*-1,2,4-benzothiadiazine-1,1-dioxide Derivatives as K_{ATP} Channel Agonists

Andrew J. Peat,* Claire Townsend, Jennings F. Worley III, Scott H. Allen, Dulce Garrido, Robert J. Mertz, Jeffrey L. Pfohl, Christopher M. Terry, Jim F. Truax, Robert L. Veasey and Stephen A. Thomson

GlaxoSmithKline Research and Development, 5 Moore Drive, Research Triangle Park, NC 27709, USA

A series of 7-substituted-3-cyclobutylamino-4*H*-1,2,4-benzothiadiazine-1,1-dioxide derivatives has been synthesized and evaluated as K_{ATP} channel agonists using the inside-out excised patch clamp technique. The most active compounds were ~20-fold more potent than diazoxide in opening K_{ATP} channels. A linear relationship exists between the potency of the compound and the sigma value of the 7-substituent with electron-withdrawing groups exhibiting higher activity. These compounds may be useful in modulating insulin release from pancreatic β-cells and in diseases associated with hyperinsulinemia.



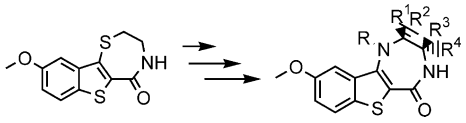
Bioorg. Med. Chem. Lett. 12 (2002) 2981

Novel Benzthiodiazepinones as Antiherpetic Agents: SAR Improvement of Therapeutic Index by Alterations of the Seven-Membered Ring

Harriet W. Hamilton,[a,*] Gisele Nishiguchi,[a] Susan E. Hagen,[a] John D. Domagala,[a] Peter C. Weber,[a] Stephen Gracheck,[a] Stefanie L. Boulware,[a] Eric C. Nordby,[a] Hidetsura Cho,[b] Takeshi Nakamura,[b] Satoru Ikeda[b] and Wataru Watanabe[b]

[a]*Departments of Chemistry and Infectious Diseases, Pfizer Global R&D, Ann Arbor, MI 48118, USA*
[b]*Departments of Chemical and Biological Research, Japan Tobacco Inc., Central Pharmaceutical Research Institute, Takatsuki, Osaka, Japan*

A series of novel benzthiodiazepinones was studied as antiherpetic agents. Significant improvements in potency and therapeutic index in a viral replication assay were realized over the starting molecule.



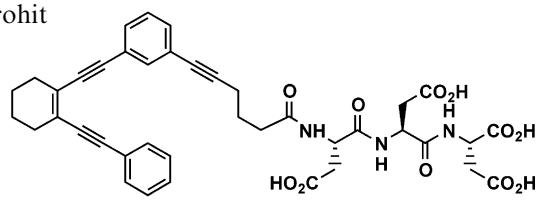
Bioorg. Med. Chem. Lett. 12 (2002) 2985

Protein Degradation with Photoactivated Enediyne-Amino Acid Conjugates

Gary Plourde, II, Ahmed El-Shafey, Farid S. Fouad, Ajay S. Purohit and Graham B. Jones*

Department of Chemistry, Northeastern University, 360 Huntington Ave., Boston, MA 02115, USA

A series of photoactivated enediynes was prepared, and successfully employed for the selective degradation of target proteins.



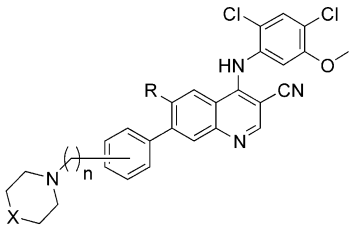
Bioorg. Med. Chem. Lett. 12 (2002) 2989

Substituted 4-Anilino-7-phenyl-3-quinolinecarbonitriles as Src Kinase Inhibitors

Dan Berger,[a,*] Minu Dutia,[a] Dennis Powell,[a] Allan Wissner,[a] Frenel DeMorin,[a] Yuri Raifeld,[a] Jennifer Weber[b] and Frank Boschelli[b]

[a]*Chemical Sciences, Wyeth Research, Pearl River, NY 10965, USA*
[b]*Discovery Oncology, Wyeth Research, Pearl River, NY 10965, USA*

A series of 4-anilino-7-phenyl-3-quinolinecarbonitriles with water-solubilizing groups attached via the C-7 phenyl ring was prepared as Src kinase inhibitors.



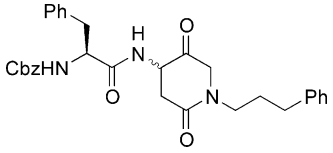
Bioorg. Med. Chem. Lett. 12 (2002) 2993

General Solid-Phase Method to Prepare Novel Cyclic Ketone Inhibitors of the Cysteine Protease Cruzain

Lily Huang and Jonathan A. Ellman

Center for New Directions in Organic Synthesis, Department of Chemistry, University of California, Berkeley, CA 94720, USA

A series of constrained ketone-based inhibitors has been developed that show low nanomolar K_i values. These ketone inhibitors showed promising activity towards cruzain, the cysteine protease implicated in Chagas' disease. This series of constrained inhibitors, which can be accessed quickly and efficiently using a solid-phase combinatorial strategy, should be applicable to other members of the cysteine protease class.



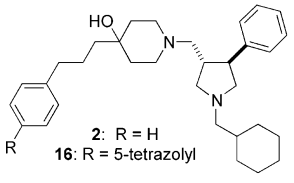
Bioorg. Med. Chem. Lett. 12 (2002) 2997

1,3,4-Trisubstituted Pyrrolidine CCR5 Receptor Antagonists. Part 3: Polar Functionality and Its Effect on Anti-HIV-1 Activity

Jeffrey J. Hale,[a,*] Richard J. Budhu,[a] Sander G. Mills,[a] Malcolm MacCoss,[a] Sandra L. Gould,[b] Julie A. DeMartino,[b] Martin S. Springer,[b] Salvatore J. Siciliano,[b] Lorraine Malkowitz,[b] William A. Schleif,[c] Daria Hazuda,[c] Michael Miller,[c] Joseph Kessler,[c] Renee Danzeisen,[c] Karen Holmes,[c] Janet Lineberger,[c] Anthony Carella,[c] Gwen Carver[c] and Emilio A. Emini[c]

[a]*Department of Medicinal Chemistry, Merck Research Laboratories, Rahway, NJ 07065, USA*
[b]*Department of Immunology Research, Merck Research Laboratories, Rahway, NJ 07065, USA*
[c]*Department of Antiviral Research, Merck Research Laboratories, West Point, PA 19486, USA*

Incorporation of acidic functional groups into a lead CCR5 antagonist **2** identified from a targeted combinatorial library resulted in compounds exemplified by **16** with enhanced anti-HIV-1 activity and attenuated L-type calcium channel affinity.



Bioorg. Med. Chem. Lett. 12 (2002) 3001

1,3,4-Trisubstituted Pyrrolidine CCR5 Receptor Antagonists. Part 4: Synthesis of N-1 Acidic Functionality Affording Analogues with Enhanced Antiviral Activity Against HIV

Christopher L. Lynch,[a,*] Jeffrey J. Hale,[a] Richard J. Budhu,[a] Amy L. Gentry,[a] Sander G. Mills,[a] Kevin T. Chapman,[a] Malcolm MacCoss,[a] Lorraine Malkowitz,[b] Martin S. Springer,[b] Sandra L. Gould,[b] Julie A. DeMartino,[b] Salvatore J. Siciliano,[b] Margaret A. Cascieri,[b] Anthony Carella,[c] Gwen Carver,[c] Karen Holmes,[c] William A. Schleif,[c] Renee Danzeisen,[c] Daria Hazuda,[c] Joseph Kessler,[c] Janet Lineberger,[c] Michael Miller[c] and Emilio A. Emini[c]

[a]*Department of Medicinal Chemistry, Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065, USA*
[b]*Department of Immunology Research, Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065, USA*
[c]*Department of Antiviral Research, Merck Research Laboratories, PO Box 4, West Point, PA 19486, USA*

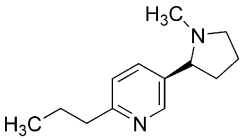
Bioorg. Med. Chem. Lett. 12 (2002) 3005

(−)6-*n*-Propylnicotine Antagonizes the Antinociceptive Effects of (−)Nicotine

Małgorzata Dukat,[a] Mohamed El-Zahabi,[a] Giovanni Ferretti,[a] M. Imad Damaj,[b] Billy R. Martin,[b] Richard Young[a] and Richard A. Glennon[a,b,*]

[a]*Department of Medicinal Chemistry, School of Pharmacy, Box 980540, Virginia Commonwealth University, Richmond, VA 23298-0540, USA*
[b]*Department of Pharmacology, School of Medicine, Virginia Commonwealth University, Richmond, VA 23298-0540, USA*

(−)6-Ethylnicotine is a nACh receptor agonist. However, its 6-*n*-propyl homologue (−)**4** binds at nACh receptors with similar affinity yet antagonizes the antinociceptive effects, but not the locomotor or stimulus effects, of (−)nicotine.



(−)4 Ki = 22 nM

Bioorg. Med. Chem. Lett. 12 (2002) 3009

Substituted 4-(2,2-Diphenylethyl)pyridine-*N*-oxides as Phosphodiesterase-4 Inhibitors: SAR Study Directed Toward the Improvement of Pharmacokinetic Parameters

Richard Frenette,* Marc Blouin, Christine Brideau, Nathalie Chauret, Yves Ducharme, Richard W. Friesen, Pierre Hamel, Tom R. Jones, France Laliberté, Chun Li, Paul Masson, Malia McAuliffe and Yves Girard

Merck Frosst Centre for Therapeutic Research, PO Box 1005, Pointe-Claire-Dorval, Québec, Canada H9R 4P8

A detailed SAR study directed toward the optimization of pharmacokinetic parameters for analogues of L-791,943 is reported. The introduction of a soft metabolic site on this structure permitted the identification of L-826,141 as a potent phosphodiesterase type 4 (PDE4) inhibitor showing a shorter half-life than L-791,943 in a variety of animal species and also in vivo efficacy in different models.