Synthesis and Biological Evaluation of DNA Targeting Flexible Side-Chain Substituted β-Carboline Derivatives

Bioorg. Med. Chem. Lett. 11 (2001) 437

Sulong Xiao, Wei Lin, Chao Wang and Ming Yang*

National Research Laboratory of Natural and Biomimetic Drugs, Peking University, Beijing 100083, People's Republic of China

A series of 3-substituted-β-carboline derivatives was synthesized from L-tryptophan. The intercalating binding mode of these compounds with DNA, the effects of the flexible alkylamine side chain on the intercalating ability and their antitumor activity were studied, which agreed well with the molecular modeling results.

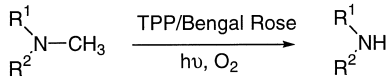
Photochemical *N*-Demethylation of Alkaloids

Bioorg. Med. Chem. Lett. 11 (2001) 443

Justin A. Ripper,[a] Edward R. T. Tiekink[b] and Peter J. Scammells[a,*]

[a]*School of Biological and Chemical Sciences, Deakin University, Geelong, Victoria 3217, Australia*
[b]*Department of Chemistry, The University of Adelaide, Adelaide 5005, Australia*

Certain alkaloids were observed to undergo *N*-demethylation processes under photochemical conditions. Tropine, acetyltropine, tropinone, and atropine were cleanly *N*-demethylated upon treatment with tetraphenylporphine (TTP), oxygen, and light. Dextromethorphan also underwent an *N*-demethylation reaction, but reacted further to afford an imine. In contrast, 14-acyloxycodeinones underwent a photochemically induced tandem *N*-demethylation–acyl migration.

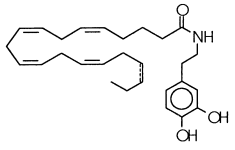


Synthesis and Biological Evaluation of Novel Amides of Polyunsaturated Fatty Acids with Dopamine

Bioorg. Med. Chem. Lett. 11 (2001) 447

Vladimir Bezuglov,[a,*] Mikhail Bobrov,[a] Natalia Gretskaya,[a] Alla Gonchar,[a] Galina Zinchenko,[a] Dominique Melck,[b] Tiziana Bisogno,[b] Vincenzo Di Marzo,[b] Dmitry Kuklev,[c] Jean-Claude Rossi,[d] Jean-Pierre Vidal[d] and Thierry Durand[d]

[a]*Shemyakin-Ovchinnikov Institute of Bioorganic Chemistry RAS, 16/10 Miklukho-Maklaya str., 117437 Moscow, Russia*
[b]*Istituto per la Chimica di Molecole di Interesse Biologico, C.N.R., Via Toiano 6, 80072, Arco Felice, Napoli, Italy*
[c]*Pacific Research Institute of Fisheries & Oceanography (TINRO), 4 Shevchenko str., 690600 Vladivostok, Russia*
[d]*Laboratoire de Chimie Biomoléculaire et Intéractions Biologiques associé au C.N.R.S., Université Montpellier I, Faculté de Pharmacie, 15 Av. Ch. Flahault, F-34060 Montpellier, France*



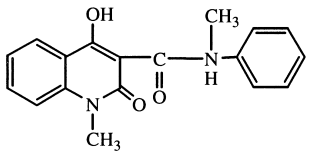
Amides of fatty acids from C18, C20, and C22 series with dopamine have been synthesized and their cannabimimetic properties were demonstrated.

Modified Synthesis and Antiangiogenic Activity of Linomide

Bioorg. Med. Chem. Lett. 11 (2001) 451

Saeed R. Khan,* Annastasiah Mhaka, Roberto Pili and John T. Isaacs

Johns Hopkins Oncology Center, Baltimore, MD 21205, USA



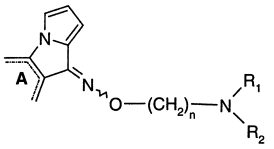
A modified procedure for the synthesis of Linomide is described. The synthesized drug was characterized and assessed for its in vivo antiangiogenic activity. In a murine angiogenesis assay Linomide treatment inhibited new blood vessel formation as documented by reduced microvessel area and blood volume.

Bioorg. Med. Chem. Lett. 11 (2001) 453

First Tricyclic Oximino Derivatives as 5-HT_3 Ligands

I. Baglin,[a] C. Daveu,[a] J. C. Lancelot,[a] R. Bureau,[a] F. Dauphin,[b] B. Pfeiffer,[c] P. Renard,[c] P. Delagrange[d] and S. Rault[a,*]

[a]*Centre d'Etudes et de Recherche sur le Médicament de Normandie, Université de Caen, 5 rue Vaubenard, 14032 Caen Cedex, France*
[b]*Université de Caen, UMR 6551 CNRS, Centre Cyceron, Boulevard Becquerel, BP 5229, 14074 Caen Cedex, France*
[c]*ADIR et CIE, 1 rue Carle Hébert, 92415 Courbevoie Cedex, France*
[d]*Institut de Recherches Internationales Servier, 6 place des Pléiades, 92415 Courbevoie Cedex, France*



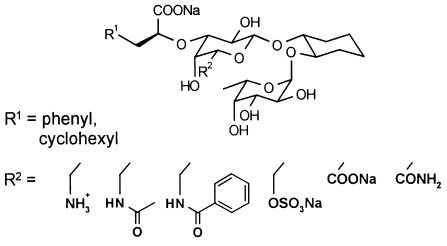
The design and the synthesis of a new type of 5-HT_3 ligands with subnanomolar affinity is described. The *O*-dialkylaminoethyl-oximino-thienopyrrolizine structure was deduced from molecular modeling studies by replacement of an amidine moiety by an oximino one.

Bioorg. Med. Chem. Lett. 11 (2001) 459

Synthesis of Sialyl Lewis^x Mimics. Modifications of the 6-Position of Galactose

Rolf Bänteli[a,*] and Beat Ernst[b]

[a]*Novartis Pharma AG, CH-4002 Basel, Switzerland*
[b]*Institute of Molecular Pharmacy, University of Basel, CH-4051 Basel, Switzerland*



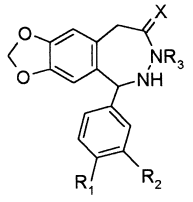
Seven sLe^x mimics where the -CH_2OH group of the galactose moiety is replaced by -$CH_2NH_3^+$, -CH_2NHAc, -CH_2NHBz, -CH_2OSO_3Na, -COONa and -$CONH_2$ have been prepared and tested for their binding affinity to E-selectin.

Bioorg. Med. Chem. Lett. 11 (2001) 463

Synthesis and Anticonvulsant Activity of Novel and Potent 1-Aryl-7,8-methylenedioxy-1,2,3,5-tetrahydro-4*H*-2,3-benzodiazepin-4-ones

Silvana Grasso,[a,*] Giovambattista De Sarro,[b] Angela De Sarro,[c] Nicola Micale,[a] Santina Polimeni,[a] Maria Zappalà,[a] Giulia Puia,[d] Mario Baraldi[d] and Carlo De Micheli[e]

[a]*Dipartimento Farmaco-Chimico, Università di Messina, Viale Annunziata, 98168 Messina, Italy*
[b]*Dipartimento di Medicina Sperimentale e Clinica, Università di Catanzaro, Via T. Campanella, 88100 Catanzaro, Italy*
[c]*Istituto di Farmacologia, Università di Messina, Policlinico Universitario, Torre Biologica, 98100 Messina, Italy*
[d]*Dipartimento di Scienze Farmaceutiche, Università di Modena, Via dei Campi 183, 41100 Modena, Italy*
[e]*Istituto di Chimica Farmaceutica, Università di Milano, Viale Abruzzi 42, 20121 Milano, Italy*



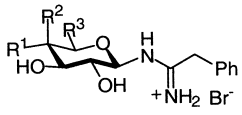
The synthesis and anticonvulsant activity of 1-aryl-7,8-methylenedioxy-1,2,3,5-tetrahydro-4*H*-2,3-benzodiazepin-4-ones (**4**) are reported.

Bioorg. Med. Chem. Lett. 11 (2001) 467

β-D-Glycosylamidines: Potent, Selective, and Easily Accessible β-Glycosidase Inhibitors

Wenfei Guo,[a] Jun Hiratake,[a,*] Koichi Ogawa,[b] Mikio Yamamoto,[b] Seung-Jin Ma[a] and Kanzo Sakata[a]

[a]*Institute for Chemical Research, Kyoto University, Uji, Kyoto 611-0011, Japan*
[b]*Research Institute, Nihon Shokuhin Kako Co., Ltd., 30 Tajima, Fuji, Shizuoka 417-8530, Japan*



1a: R^1 = OH, R^2 = H, R^3 = CH_2OH
1b: R^1 = H, R^2 = OH, R^3 = CH_2OH
1c: R^1 = OH, R^2 = H, R^3 = H

The synthesis and evaluation of β-D-glycosylamidines **1a**–**c** as potent and selective β-glycosidase inhibitors ($K_i = 0.1\ \mu M$) are reported.

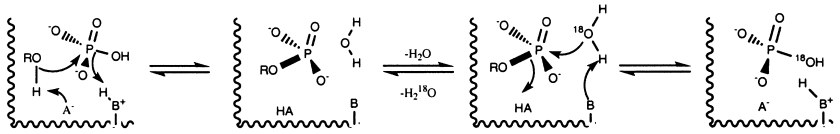
Bioorg. Med. Chem. Lett. 11 (2001) 471

Protein Phosphatase 1 Catalyses the Direct Hydrolytic Cleavage of Phosphate Monoester in a Ternary Complex Mechanism

Jonathan Sanvoisin and David Gani*

School of Chemistry, The Haworth Building, The University of Birmingham, Edgbaston, Birmingham, B15 2TT, UK

^{18}O-Exchange into inorganic phosphate requires the presence of a product alcohol.



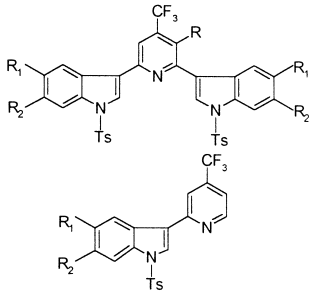
Bioorg. Med. Chem. Lett. 11 (2001) 475

Synthesis and Antitumor Evaluation of Novel Monoindolyl-4-trifluoromethylpyridines and Bisindolyl-4-trifluoromethylpyridines

Biao Jiang,* Xen-Nan Xiong and Cai-Guang Yang

Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, People's Republic of China

The synthesis and antitumor activity of the monoindolyl-4-trifluoromethylpyridines and bisindolyl-4-trifluoromethylpyridines are reported.



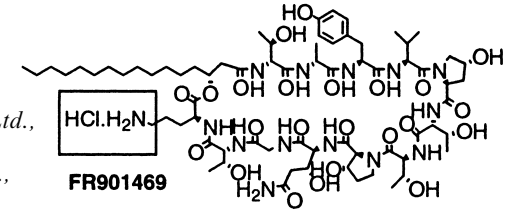
Bioorg. Med. Chem. Lett. 11 (2001) 479

Synthesis and Biological Activity of Novel Macrocyclic Antifungals: Acylated Conjugates of the Ornithine Moiety of the Lipopeptidolactone FR901469

David Barrett,[a,*] Akira Tanaka,[a] Keiko Harada,[a] Hidenori Ohki,[a] Etsuko Watabe,[b] Katsuyuki Maki[b] and Fumiaki Ikeda[b]

[a]*Medicinal Chemistry Research Laboratories, Fujisawa Pharmaceutical Co. Ltd., 2-1-6 Kashima, Yodogawa-ku, Osaka 532-8514, Japan*
[b]*Medicinal Biology Research Laboratories, Fujisawa Pharmaceutical Co. Ltd., 2-1-6 Kashima, Yodogawa-ku, Osaka 532-8514, Japan*

Ornithine-modified analogues of the macrocyclic natural product FR901469 were designed and evaluated as antifungal agents.



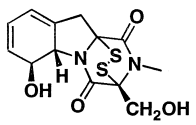
Bioorg. Med. Chem. Lett. 11 (2001) 483

Evidence for Gliotoxin–Glutathione Conjugate Adducts

Paul H. Bernardo,[a] Christina L. L. Chai,[a,*] Geoffrey J. Deeble,[a] Xue-Ming Liu[a] and Paul Waring[b]

[a]*Department of Chemistry, The Faculties, Australian National University, ACT 0200, Australia*
[b]*Division of Cell Biology and Immunology, John Curtin School of Medical Research, Australian National University, ACT 0200, Australia*

The equilibrium constant for the gliotoxin/glutathione pair was found to be 1200 M^{-1} at pH 7.0 at 25 °C. Under conditions where the reaction was quenched rapidly with the addition of acid, gliotoxin–glutathione adducts were detected.



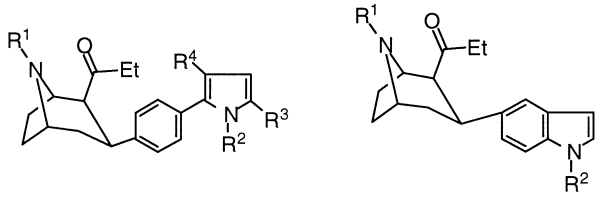
Gliotoxin

Bioorg. Med. Chem. Lett. 11 (2001) 487

Synthesis and Monoamine Transporter Affinity of 3β-(4-(2-Pyrrolyl)phenyl)-8-azabicyclo[3.2.1]octanes and 3β-(5-Indolyl)-8-azabicyclo[3.2.1]octanes

Huw M. L. Davies,[a,*] Pingda Ren,[a] Norman Kong,[a] Tammy Sexton[b] and Steven R. Childers[b]

[a]*Department of Chemistry, State University of New York at Buffalo, Buffalo, NY 14260-3000, USA*
[b]*Department of Physiology and Pharmacology, Wake Forest University School of Medicine, Winston-Salem, NC 27157, USA*



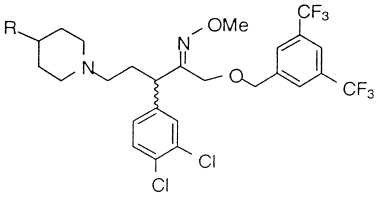
Bioorg. Med. Chem. Lett. 11 (2001) 491

Synthesis of Substituted 4(*Z*)-(Methoxyimino)pentyl-1-piperidines as Dual NK_1/NK_2 Inhibitors

Pauline C. Ting,* Joe F. Lee, John C. Anthes, Neng-Yang Shih and John J. Piwinski

Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, NJ 07033-1300, USA

A series of 4(*Z*)-(methoxyimino)pentyl-1-piperidines was prepared, and their biological activity as dual NK_1/NK_2 receptor antagonists determined. Analogues containing a substituted piperidinylpiperidine moiety displayed nanomolar potency for both the NK_1 and NK_2 receptors.



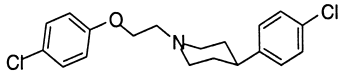
Bioorg. Med. Chem. Lett. 11 (2001) 495

Pharmacophore-Based Discovery, Synthesis, and Biological Evaluation of 4-Phenyl-1-arylalkyl Piperidines as Dopamine Transporter Inhibitors

Sukumar Sakamuri,[a,b] Istvan J. Enyedy,[a,c,d] Alan P. Kozikowski,[a,b] Wahiduz A. Zaman,[e] Kenneth M. Johnson[e] and Shaomeng Wang[a,c,d,*]

[a]*Drug Discovery Program, Georgetown University Medical Center, 3900 Reservoir Road, NW, Washington, DC 20007-2197, USA*
[b]*Department of Neurology, Georgetown University Medical Center, 3900 Reservoir Road, NW, Washington, DC 20007-2197, USA*
[c]*Department of Oncology, Georgetown University Medical Center, 3900 Reservoir Road, NW, Washington, DC 20007-2197, USA*
[d]*Department of Neuroscience, Georgetown University Medical Center, 3900 Reservoir Road, NW, Washington, DC 20007-2197, USA*
[e]*Department of Pharmacology and Toxicology, University of Texas Medical Branch, Galveston, TX 77555, USA*

Pharmacophore-based discovery and synthesis of a series of 4-phenyl-1-arylalkylpiperidines are discussed. These compounds were evaluated for their ability to inhibit uptake of dopamine (DA) into striatal nerve endings (synaptosomes). Their structure–activity relationship and functional antagonism studies are reported.



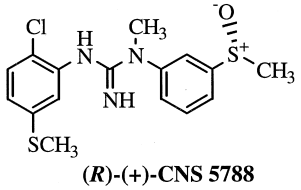
Bioorg. Med. Chem. Lett. 11 (2001) 501

Identification and Characterization of a Potential Ischemia-Selective *N*-Methyl-D-aspartate (NMDA) Receptor Ion-Channel Blocker, CNS 5788

Seetharamaiyer Padmanabhan,* Michael E. Perlman, Lu Zhang, Deke Moore, Dan Zhou, James B. Fischer, Graham J. Durant and Robert N. McBurney

Cambridge NeuroScience, Inc., 333 Providence Highway, Norwood, MA 02602, USA

Synthesis and in vitro and in vivo studies led to the characterization of a potential ischemia-selective and neuroprotective sulfoxide based ion-channel blocker **10**. The *R* enantiomer has been identified to be orally active and neuroprotective with minimum side effects



(*R*)-(+)-CNS 5788

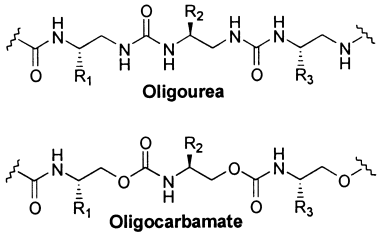
Bioorg. Med. Chem. Lett. 11 (2001) 505

Targeting RNA with Peptidomimetic Oligomers in Human Cells

Natarajan Tamilarasu, Ikramul Huq and Tariq M. Rana*

Department of Pharmacology, Robert Wood Johnson Medical School, and Molecular Biosciences Graduate Program at Rutgers State University, 675 Hoes Lane, Piscataway, NJ 08854, USA

Replication of human immunodeficiency virus type 1 (HIV-1) requires specific interactions of Tat protein with the *trans*-activation responsive region (TAR) RNA, a stem-loop structure located at the 5′-end of all HIV mRNAs. Here we report that two TAR RNA-binding peptidomimetics, oligourea and oligocarbamate, inhibit transcriptional activation by Tat protein in human cells with an IC_{50} of 0.5 and ~1.0 μM, respectively. Peptidomimetics that can target specific RNA structures provide novel molecules that can be used to control cellular processes involving protein–RNA interactions in vivo.

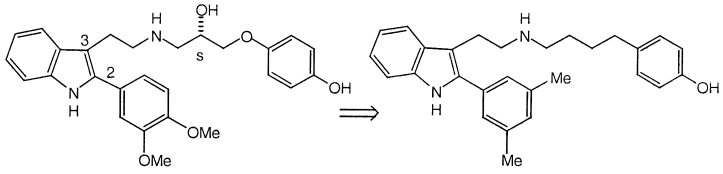


Bioorg. Med. Chem. Lett. 11 (2001) 509

Initial Structure–Activity Relationship of a Novel Class of Nonpeptidyl GnRH Receptor Antagonists: 2-Arylindoles

Lin Chu,[a,*] Jennifer E. Hutchins,[a] Ann E. Weber,[a] Jane-Ling Lo,[b] Yi-Tien Yang,[b] Kang Cheng,[b] Roy G. Smith,[b] Michael H. Fisher,[a] Matthew J. Wyvratt[a] and Mark T. Goulet[a]

[a]*Department of Medicinal Chemistry, Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065-0900, USA*
[b]*Department of Biochemistry and Physiology, Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065-0900, USA*

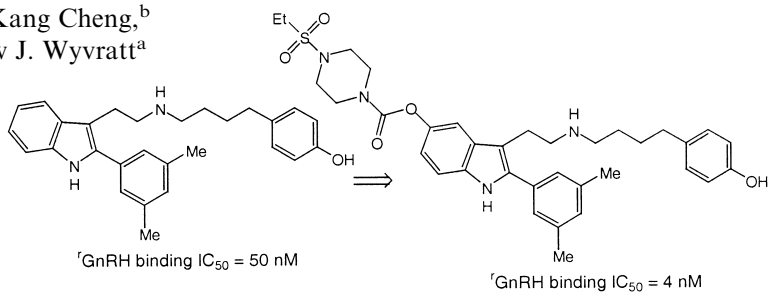


Bioorg. Med. Chem. Lett. 11 (2001) 515

SAR Studies of Novel 5-Substituted 2-Arylindoles as Nonpeptidyl GnRH Receptor Antagonists

Lin Chu,[a,*] Jane-Ling Lo,[b] Yi-Tien Yang,[b] Kang Cheng,[b] Roy G. Smith,[b] Michael H. Fisher,[a] Matthew J. Wyvratt[a] and Mark T. Goulet[a]

[a]*Department of Medicinal Chemistry, Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065-0900, USA*
[b]*Department of Biochemistry and Physiology, Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065-0900, USA*

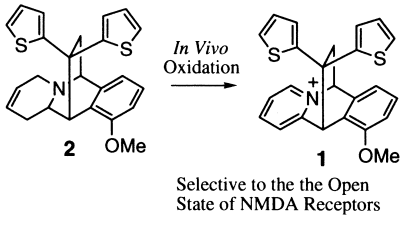


Bioorg. Med. Chem. Lett. 11 (2001) 519

4,5,9,10-Tetrahydro-1,4-ethanobenz[*b*]quinolizine as a Prodrug for Its Quinolizinium Cation as a Ligand to the Open State of the TCP-Binding Site of NMDA Receptors

Shigeki Sasaki,[a,c] Takahiro Kanda,[a] Nobuyasu Ishibashi,[a] Fumihiko Yamamoto,[a,c] Terushi Haradahira,[b,c] Takashi Okauchi,[d] Jun Meda,[d] Kazutoshi Suzuki[b] and Minoru Maeda[a,c,*]

[a]*Graduate School of Pharmaceutical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan*
[b]*National Institute of Radiological Sciences, 4-9-1 Anagawa, Inage-ku, Chiba 263-8555, Japan*
[c]*CREST, Japan Science and Technology Corporation, 4-1-8 Honmachi, Kawaguchi, Saitama 332-0012, Japan*
[d]*SHI Accelerator Service, 5-9-11 Kitashinagawa, Shinagawa-ku, Tokyo 141-8686, Japan*



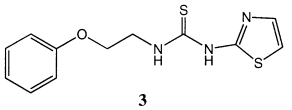
Bioorg. Med. Chem. Lett. 11 (2001) 523

Anti-HIV Activity of Aromatic and Heterocyclic Thiazolyl Thiourea Compounds

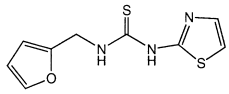
T. K. Venkatachalam,[a,b] Elise A. Sudbeck,[a,c] Chen Mao[a,c] and Fatih M. Uckun[a,d,*]

[a]*Drug Discovery Program, Parker Hughes Institute, St. Paul, MN 55113, USA*
[b]*Department of Chemistry, Parker Hughes Institute, St. Paul, MN 55113, USA*
[c]*Department of Structural Biology, Parker Hughes Institute, St. Paul, MN 55113, USA*
[d]*Department of Virology, Parker Hughes Institute, St. Paul, MN 55113, USA*

Thiazolyl thiourea derivatives **3** and **6** were shown to be potent anti-HIV agents, with $IC_{50}[HTLV_{IIIB}]$ values of $< 0.001\ \mu M$ and selectivity indices of >100,000. Compound **6** is active against NNRTI-resistant HIV-1 strains as well.



3



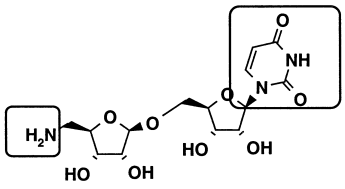
6

Bioorg. Med. Chem. Lett. 11 (2001) 529

Synthesis of Analogues of the *O*-β-D-Ribofuranosyl Nucleoside Moiety of Liposidomycins. Part 1: Contribution of the Amino Group and the Uracil Moiety upon the Inhibition of MraY

C. Dini,[a,*] N. Drochon,[a] S. Feteanu,[b] J. C. Guillot,[a] C. Peixoto[a] and J. Aszodi[a]

[a]*Medicinal Chemistry Department, Aventis Pharma, 102 route de Noisy, 93235 Romainville Cedex, France*
[b]*Infectious Disease Group, Aventis Pharma, 102 route de Noisy, 93235 Romainville Cedex, France*

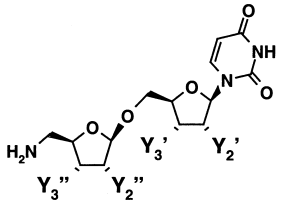


Bioorg. Med. Chem. Lett. 11 (2001) 533

Synthesis of Analogues of the *O*-β-D-Ribofuranosyl Nucleoside Moiety of Liposidomycins. Part 2: Role of the Hydroxyl Groups upon the Inhibition of MraY

C. Dini,[a,*] N. Drochon,[a] J. C. Guillot,[a] P. Mauvais,[b] P. Walter[a] and J. Aszodi[a]

[a]*Medicinal Chemistry Department, Aventis Pharma, 102 route de Noisy, 93235 Romainville Cedex, France*
[b]*Infectious Disease Group, Aventis Pharma, 102 route de Noisy, 93235 Romainville Cedex, France*



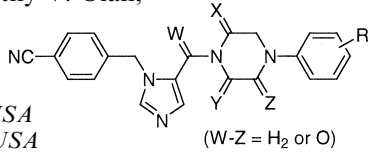
	Y2'	Y3'	Y2''	Y3''
III	**H**	OH	OH	OH
IV	OH	**H**	OH	OH
V	OH	OH	**H**	OH
VI	OH	OH	OH	**H**
VII	**H**	**H**	OH	OH

Bioorg. Med. Chem. Lett. 11 (2001) 537

Oxo-piperazine Derivatives of *N*-Arylpiperazinones as Inhibitors of Farnesyltransferase

Christopher J. Dinsmore,[a,*] Jeffrey M. Bergman,[a] Donna D. Wei,[a] C. Blair Zartman,[a] Joseph P. Davide,[b] Ian B. Greenberg,[b] Dongming Liu,[b] Timothy J. O'Neill,[b] Jackson B. Gibbs,[b] Kenneth S. Koblan,[b] Nancy E. Kohl,[b] Robert B. Lobell,[b] I-Wu Chen,[c] Debra A. McLoughlin,[c] Timothy V. Olah,[c] Samuel L. Graham,[a] George D. Hartman[a] and Theresa M. Williams[a]

[a]*Department of Medicinal Chemistry, Merck Research Laboratories, West Point, PA 19486, USA*
[b]*Department of Cancer Research, Merck Research Laboratories, West Point, PA 19486, USA*
[c]*Department of Drug Metabolism, Merck Research Laboratories, West Point, PA 19486, USA*



(W-Z = H_2 or O)

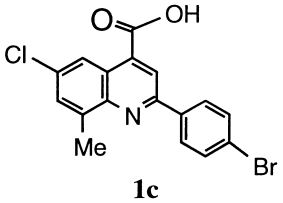
Bioorg. Med. Chem. Lett. 11 (2001) 541

A Series of Quinoline Analogues as Potent Inhibitors of *C. albicans* Prolyl tRNA Synthetase

Xiang Y. Yu,[a,*] Jason M. Hill,[a] Guixue Yu,[a] Yifeng Yang,[a] Arthur F. Kluge,[a] Dennis Keith,[a] John Finn,[a] Paul Gallant,[b] Jared Silverman[b] and Audrey Lim[b]

[a]*Department of Medicinal Chemistry, Cubist Pharmaceuticals, Inc., 24 Emily Street, Cambridge, MA 02139, USA*
[b]*Department of Biology, Cubist Pharmaceuticals, Inc., 24 Emily Street, Cambridge, MA 02139, USA*

A series of quinoline inhibitors of *C. albicans* prolyl tRNA synthetase was identified. The most potent analogue, 2-(4-bromo-phenyl)-6-chloro-8-methyl-4-quinolinecarboxylic acid, showed $IC_{50} = 5$ nM (Ca. ProRS) with high selectivity over the human enzyme.



1c

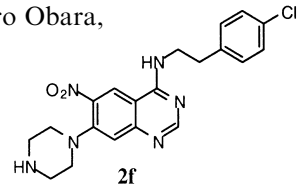
Bioorg. Med. Chem. Lett. 11 (2001) 545

Structure–Activity Relationships of Quinazoline Derivatives: Dual-Acting Compounds with Inhibitory Activities Toward Both TNF-α Production and T Cell Proliferation

Masanori Tobe, Yoshiaki Isobe, Hideyuki Tomizawa, Mitsuhiro Matsumoto, Fumihiro Obara, Takahiro Nagasaki and Hideya Hayashi*

Pharmaceuticals and Biotechnology Laboratory, Japan Energy Corporation, Toda-shi, Saitama 335-8502, Japan

Compound **2f** exhibited inhibitory activities toward both TNF-α production and T cell proliferation.



2f

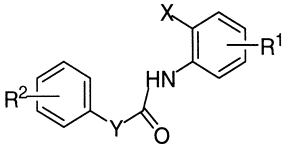
Bioorg. Med. Chem. Lett. 11 (2001) 549

Synthesis and Structure–Activity Relationship of Diarylamide Derivatives as Selective Inhibitors of the Proliferation of Human Coronary Artery Smooth Muscle Cells

Haruhisa Ogita, Yoshiaki Isobe, Haruo Takaku, Rena Sekine, Yuso Goto, Satoru Misawa and Hideya Hayashi*

Pharmaceuticals & Biotechnology Laboratory, Japan Energy Corporation, 3-17-35, Niizo-Minami, Toda-shi, Saitama 335-8502, Japan

A series of diarylamide derivatives were synthesized and evaluated for their inhibitory activities against the proliferation of human coronary artery smooth muscle cells (SMCs) and human coronary artery endothelial cells (ECs)



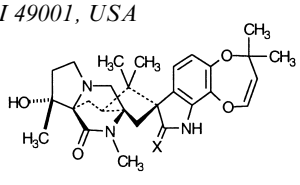
Bioorg. Med. Chem. Lett. 11 (2001) 553

Semi-Synthesis of 2-Deoxo- and 3-Epi-paraherquamide A

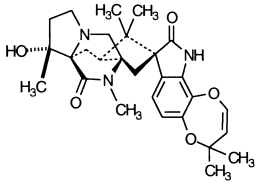
Byung H. Lee,* Michael F. Clothier and Sandra S. Johnson

Animal Health Discovery Research, Pharmacia Corp., Kalamazoo, MI 49001, USA

2-Deoxo- and 3-epi-paraherquamide A were synthesized from paraherquamide A. 2-Deoxoparaherquamide A has good activity against HC and TC in our jird model comparable to the parent compound while 3-epi-paraherquamide A showed no activity.



X = O, Paraherquamide A (**2**)
X = H_2, 2-Deoxoparaherquamide A (**3**)



3-Epi-Paraherquamide A (**4**)

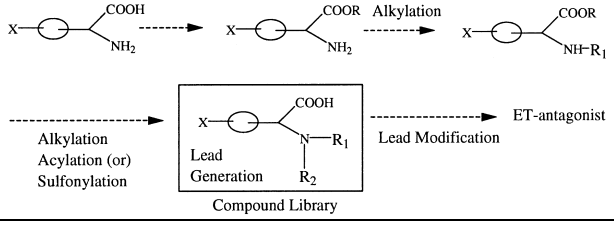
Bioorg. Med. Chem. Lett. 11 (2001) 555

Peptoids as Endothelin Receptor Antagonists

Falguni Dasgupta,* N. Gangadhar, M. Bruhaspathy, Ashwani K. Verma, Simi Sarin and Ashish K. Mukherjee

New Drug Discovery Research, Ranbaxy Laboratories Limited, A-1 Phase-1 Okhla Industrial Area, New Delhi-110020, India

Based on the structure–activity correlation of known short chain amino acids and the butenolides, a series of new peptoids as endothelin receptor antagonists has been synthesized. Screening of these novel compounds resulted in the discovery of ET antagonists with IC_{50}s in the low micromolar concentrations.



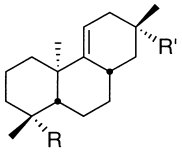
Bioorg. Med. Chem. Lett. 11 (2001) 559

Pimarane Cyclooxygenase 2 (COX-2) Inhibitor and its Structure–Activity Relationship

Young-Ger Suh,[a,*] Young-Ho Kim,[b] Mi-Hyoun Park,[b] Young-Hoon Choi,[a] Hye-Kyung Lee,[a] Ju-Yeon Moon,[a] Kyung-Hoon Min,[a] Dong-Yun Shin,[a] Jae-Kyung Jung,[a] Ok-Hui Park,[a] Ra-Ok Jeon,[d] Hyung-Sup Park[c] and Soon-Ah Kang[c]

[a]*College of Pharmacy, Seoul National University, San 56-1 Shinrim-Dong, Kwanak-Gu, Seoul 151-742, South Korea*
[b]*College of Pharmacy, Chungnam University, Taejon 305-764, South Korea*
[c]*College of Medicine, Ulsan University, Seoul 138-040, South Korea*
[d]*College of Pharmacy, Sookmyung Women's University, Seoul 140-742, South Korea*

A novel pimarane COX-2 inhibitor as well as its structure–activity relationship and molecular modelings are reported. Particularly, the linker extended analogues exhibited the significantly enhanced COX-2 inhibitory activities and selectivities.



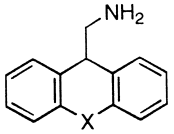
Bioorg. Med. Chem. Lett. 11 (2001) 563

Exploring the Relationship Between Binding Modes of 9-(Aminomethyl)-9,10-dihydroanthracene and Cyproheptadine Analogues at the 5-HT_{2A} Serotonin Receptor

Richard B. Westkaemper,[a,*] Scott P. Runyon,[a] Jason E. Savage,[b] Bryan L. Roth[b] and Richard A. Glennon[a]

[a]*Department of Medicinal Chemistry, School of Pharmacy, Virginia Commonwealth University, Richmond, VA 23298, USA*
[b]*Departments of Biochemistry and Psychiatry, Case Western Reserve University School of Medicine, Cleveland, OH 44106, USA*

The 5-HT_{2A} receptor affinities of a parallel series of 9-(aminomethyl)-9,10-dihydroanthracene and cyproheptadine analogues suggest that the two classes of compounds bind to the receptor in different fashions.



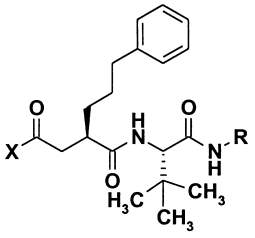
Bioorg. Med. Chem. Lett. 11 (2001) 567

Selectivity of Inhibition of Matrix Metalloproteases MMP-3 and MMP-2 by Succinyl Hydroxamates and their Carboxylic Acid Analogues is Dependent on P3′ Group Chirality

M. Jonathan Fray,[a,*] M. Frank Burslem[b] and Roger P. Dickinson[a]

[a]*Department of Discovery Chemistry, Pfizer Global Research and Development, Sandwich, Kent CT13 9NJ, UK*
[b]*Department of Discovery Biology, Pfizer Global Research and Development, Sandwich, Kent CT13 9NJ, UK*

Structure–activity relationships are described for a series of succinyl hydroxamic acids (X = NHOH) and their carboxylic acid analogues (X = OH) as inhibitors of matrix metalloproteases MMP-3 and MMP-2.



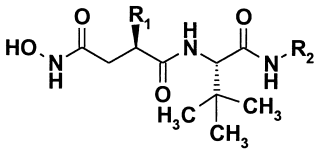
Bioorg. Med. Chem. Lett. 11 (2001) 571

Discovery of Potent and Selective Succinyl Hydroxamate Inhibitors of Matrix Metalloprotease-3 (Stromelysin-1)

M. Jonathan Fray* and Roger P. Dickinson

Department of Discovery Chemistry, Pfizer Global Research and Development, Sandwich, Kent CT13 9NJ, UK

Structure–activity relationships are described for a series of succinyl hydroxamic acids as potent and selective inhibitors of matrix metalloprotease-3 (stromelysin-1).

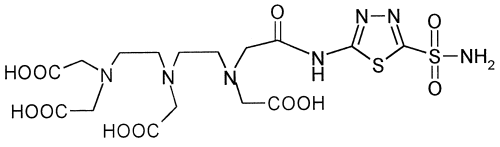


Bioorg. Med. Chem. Lett. 11 (2001) 575

Carbonic Anhydrase Inhibitors: Synthesis of Sulfonamides Incorporating dtpa Tails and of their Zinc Complexes with Powerful Topical Antiglaucoma Properties

Andrea Scozzafava,[a] Luca Menabuoni,[b] Francesco Mincione,[c] Giovanna Mincione[a] and Claudiu T. Supuran[a,*]

[a]*Università degli Studi, Laboratorio di Chimica Inorganica e Bioinorganica, Via Gino Capponi 7, I-50121, Firenze, Italy*
[b]*Ospedale San Giovanni di Dio, S. O. Oculistica, Via Torregalli 3, I-50123, Florence, Italy*
[c]*Università degli Studi, Institute of Ophthalmology, Viale Morgagni 85, I-50134, Firenze, Italy*

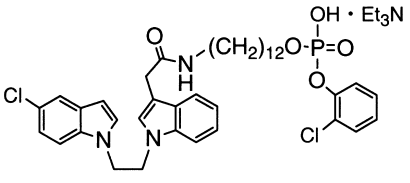


Bioorg. Med. Chem. Lett. 11 (2001) 583

Development of Novel Telomerase Inhibitors Based on a Bisindole Unit

Shigeki Sasaki,[a,*] Takeru Ehara,[a] Ikuhiro Sakata,[a] Yasuhiro Fujino,[b] Naozumi Harada,[b] Junko Kimura,[b] Hideo Nakamura[b] and Minoru Maeda[a]

[a]*Graduate School of Pharmaceutical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan*
[b]*Mitsubishi-Tokyo Pharmaceuticals, Inc., 1000 Kamoshida-cho, Aoba-ku, Yokohama 227-8502, Japan*



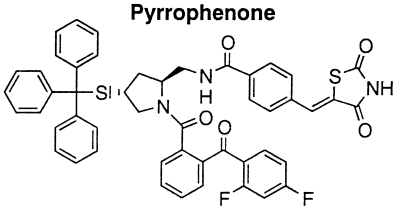
IC_{50}=2.5 μM

Bioorg. Med. Chem. Lett. 11 (2001) 587

Pyrrolidine Inhibitors of Human Cytosolic Phospholipase A_2. Part 2: Synthesis of Potent and Crystallized 4-Triphenylmethylthio Derivative 'Pyrrophenone'

Kaoru Seno,* Takayuki Okuno, Koichi Nishi, Yasushi Murakami, Katsutoshi Yamada, Shozo Nakamoto and Takashi Ono

Shionogi Research Laboratories, Shionogi & Co., Ltd., 12-4, Sagisu 5-Chome, Fukushima-ku, Osaka 553-0002, Japan



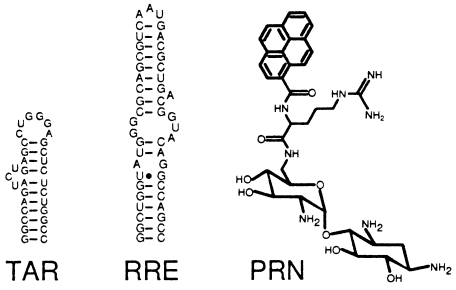
Bioorg. Med. Chem. Lett. 11 (2001) 591

Aminoglycoside Antibiotics, Neamine and Its Derivatives as Potent Inhibitors for the RNA–Protein Interactions Derived from HIV-1 Activators

Keita Hamasaki* and Akihiko Ueno

Department of Bioengineering, Graduate School of Bioscience and Biotechnology, Tokyo Institute of Technology, 4259 Nagatsuta, Yokohama 226-8501, Japan

Neamine derivatives which have an arginine (RN), a pyrene (PCN) and both pyrene and arginine (PRN) have been prepared and their binding toward the RNA fragments derived from HIV-1 activator region, TAR and RRE RNA was examined. Among them, PRN bound either TAR RNA or RRE RNA with equivalent binding affinities as Tat and Rev peptide, respectively.



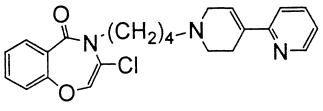
Bioorg. Med. Chem. Lett. 11 (2001) 595

New 5-HT_{1A} Receptor Agonists Possessing 1,4-Benzoxazepine Scaffold Exhibit Highly Potent Anti-Ischemic Effects

Katsuhide Kamei,[a,*] Noriko Maeda,[a] Ryoko Ogino,[a] Makoto Koyama,[a] Mika Nakajima,[a] Toshio Tatsuoka,[b] Tomochika Ohno[a] and Teruyoshi Inoue[b]

[a]*Suntory Biomedical Research Limited, 1-1-1, Wakayama-dai, Shimamoto-cho, Mishima-gun, Osaka 618-8503, Japan*
[b]*Suntory Limited, Mori Bldg. No. 31, 5-7-2, Kojimachi, Chiyoda-ku, Tokyo 102-8530, Japan*

A series of new 1,4-benzoxazepine derivatives was prepared and evaluated for binding affinity to 5-HT_{1A} receptor and neuroprotective effect in vivo.



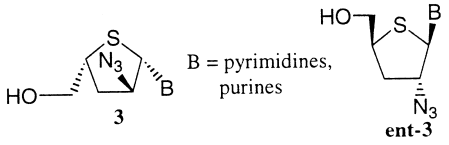
Bioorg. Med. Chem. Lett. 11 (2001) 599

Synthesis and Antiviral Activity of Novel D- and L-2′-Azido-2′,3′-dideoxyribofuranosyl-4′-thiopyrimidines and Purines

Hea Ok Kim,[a] Yun Ha Kim,[b] Hwal Suh[a] and Lak Shin Jeong[b,*]

[a]*College of Medicine, Yonsei University, Seoul 120-752, South Korea*
[b]*Laboratory of Medicinal Chemistry, College of Pharmacy, Ewha Women's University, Seoul 120-750, South Korea*

Synthesis and antiviral activity of novel D- and L-2′-azido-2′,3′-dideoxyribofuranosyl-4′-thiopyrimidines and purines are described.



Bioorg. Med. Chem. Lett. 11 (2001) 605

Controlled Drug Release: New Water-Soluble Prodrugs of an HIV Protease Inhibitor

Hikaru Matsumoto, Youhei Sohma, Tooru Kimura, Yoshio Hayashi and Yoshiaki Kiso*

Department of Medicinal Chemistry, Center for Frontier Research in Medicinal Science, Kyoto Pharmaceutical University, Yamashina-ku, Kyoto 607-8412, Japan

Highly water-soluble prodrugs with controlled release of a parent drug were synthesized. These prodrugs released the parent drug via an intramolecular cyclization reaction through an imide formation in physiological condition.