Biphenyl Derivatives as Novel Dual NK_1/NK_2-Receptor Antagonists

Bioorg. Med. Chem. Lett. 12 (2002) 2065

Robert Mah,[a,b,*] Marc Gerspacher,[a] Andreas von Sprecher,[a] Stefan Stutz,[b] Vincenzo Tschinke,[a,b] Gary P. Anderson,[c] Claude Bertrand,[d] Natarajan Subramanian[a] and Howard A. Ball[a]

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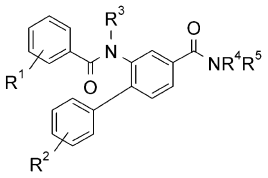
[c]*Department of Pharmacology, University of Melbourne, Parkville, 3052 VIC, Australia*
[d]*Inflammatory Disease Unit, Roche Biosciences, Palo Alto, CA, USA*



Apoptosis-Inducing Activity of Synthetic Intermediates of Halichlorine

Bioorg. Med. Chem. Lett. 12 (2002) 2069

Midori Itoh, Jun Kuwahara, Kohji Itoh,* Yu-ichi Fukuda, Mikiko Kohya, Mitsuru Shindo and Kozo Shishido

Institute for Medicinal Resources, University of Tokushima, Sho-machi 1-78, Tokushima 770-8505, Japan

Synthetic intermediates of halichlorine with the azaspiro core structure induced apoptosis of cultured human cell lines at micromolar concentrations. The novel biological activity was suggested to depend on the skeletal structure and silyloxymethyl functionality on the five-membered ring.

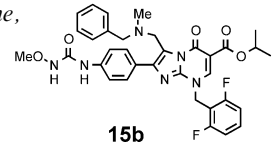
A New Class of Potent Nonpeptide Luteinizing Hormone-Releasing Hormone (LHRH) Antagonists: Design and Synthesis of 2-Phenylimidazo[1,2-*a*]pyrimidin-5-ones

Bioorg. Med. Chem. Lett. 12 (2002) 2073

Satoshi Sasaki,[a,*] Toshihiro Imaeda,[a] Yoji Hayase,[a] Yoshiaki Shimizu,[b] Shizuo Kasai,[b] Nobuo Cho,[a] Masataka Harada,[a] Nobuhiro Suzuki,[b] Shuichi Furuya[c] and Masahiko Fujino[a,b,c]

[a]*Pharmaceutical Research Division, Takeda Chemical Industries, Ltd., 10 Wadai, Tsukuba, Ibaraki 300-4293, Japan*
[b]*Pharmaceutical Research Division, Takeda Chemical Industries, Ltd., 17-85 Jusohonmachi 2-chome, Yodogawa-ku, Osaka 532-8686, Japan*
[c]*Strategic Product Planning Department, Takeda Chemical Industries, Ltd., 1-1 Doshomachi 4-chome, Chuo-ku, Osaka 540-8645, Japan*

A new class of nonpeptide luteinizing hormone-releasing hormone (LHRH) receptor antagonists, the 2-phenylimidazo[1,2-*a*]pyrimidin-5-ones, has been designed and synthesized. Compound **15b** showed a sub-nanomolar affinity and a nanomolar in vitro functional antagonism.



15b

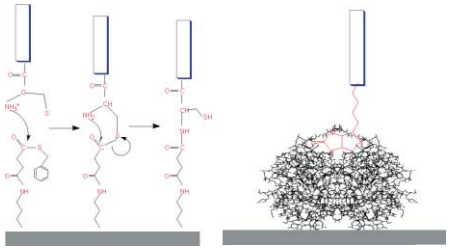
Developing Site-Specific Immobilization Strategies of Peptides in a Microarray

Bioorg. Med. Chem. Lett. 12 (2002) 2079

Marie-Laure Lesaicherre,[a] Mahesh Uttamchandani,[b] Grace Y. J. Chen[a,b] and Shao Q. Yao[a,b,*]

[a]*Department of Chemistry, National University of Singapore, 3 Science Drive 3, Singapore 117543, Singapore*
[b]*Department of Biological Sciences, National University of Singapore, 3 Science Drive 3, Singapore 117543, Singapore*

Specific immobilization of N-terminally cysteine-containing peptides on thioester slides and biotinylated peptides on avidin slides is reported.



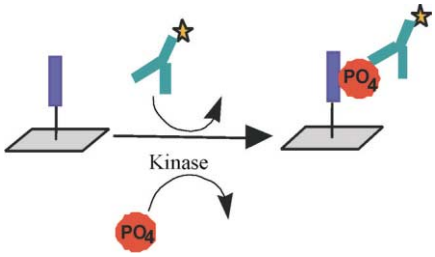
Bioorg. Med. Chem. Lett. 12 (2002) 2085

Antibody-Based Fluorescence Detection of Kinase Activity on a Peptide Array

Marie-Laure Lesaicherre,[a] Mahesh Uttamchandani,[b] Grace Y. J. Chen[a,b] and Shao Q. Yao[a,b,*]

[a]*Department of Chemistry, National University of Singapore, 3 Science Drive 3, Singapore, 117543, Singapore*
[b]*Department of Biological Sciences, National University of Singapore, 3 Science Drive 3, Singapore, 117543, Singapore*

We report a novel sensitive, specific and extremely fast fluorescence-based approach for quantitative detection of peptide phosphorylation on chip using fluorescently-labeled anti-phosphoserine and anti-phosphotyrosine antibodies.



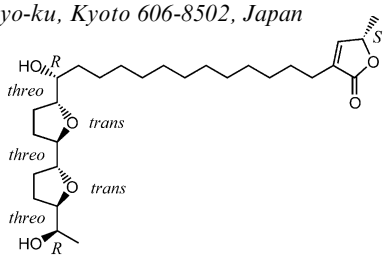
Bioorg. Med. Chem. Lett. 12 (2002) 2089

Essential Structural Factors of Acetogenins, Potent Inhibitors of Mitochondrial Complex I

Tomoko Motoyama, Hiromi Yabunaka and Hideto Miyoshi*

Division of Applied Life Sciences, Graduate School of Agriculture, Kyoto University, Sakyo-ku, Kyoto 606-8502, Japan

Synthesis and activity of a novel acetogenin, which has the shortest tail (i.e., a methyl group), is described.



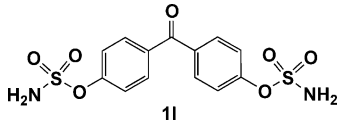
Bioorg. Med. Chem. Lett. 12 (2002) 2093

4,4′-Benzophenone-*O*,*O*′-disulfamate: A Potent Inhibitor of Steroid Sulfatase

Peter Nussbaumer,* Melitta Bilban and Andreas Billich

NOVARTIS Research Institute, Brunnerstrasse 59, A-1235 Vienna, Austria

With an IC_{50} value of 190 nM compound **1l** is the first small monocycle-based STS inhibitor coming close to the potency of the steroidal standard estrone sulfamate.



1l

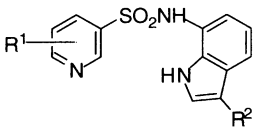
Bioorg. Med. Chem. Lett. 12 (2002) 2097

Synthesis and Biological Evaluation of *N*-(7-Indolyl)-3-pyridinesulfonamide Derivatives as Potent Antitumor Agents

Takashi Owa,* Hiroshi Yoshino, Tatsuo Okauchi, Tadashi Okabe, Yoichi Ozawa, Naoko Hata Sugi, Kentaro Yoshimatsu, Takeshi Nagasu, Nozomu Koyanagi and Kyosuke Kitoh

Tsukuba Research Laboratories, Eisai Co., Ltd., 5-1-3 Tokodai, Tsukuba, Ibaraki 300-2635, Japan

We herein report the synthesis and antitumor activity of E7070 analogues containing a 3-pyridinesulfonamide moiety. Of the compounds examined, ER-35745, a 6-amino-3-pyridinesulfonamide derivative, demonstrated significant oral efficacy against the HCT116 human colon carcinoma xenograft in nude mice.



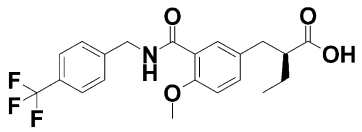
Bioorg. Med. Chem. Lett. 12 (2002) 2101

Efficient Asymmetric Synthesis of (*S*)-2-Ethylphenylpropanoic Acid Derivative, a Selective Agonist for Human Peroxisome Proliferator-Activated Receptor Alpha

Masahiro Nomura, Takahiro Tanase and Hiroyuki Miyachi*

Discovery Research Laboratories, Kyorin Pharmaceutical Co., Ltd., 2399-1 Mitarai, Nogi-machi, Shimotsuga-gun, Tochigi 329-0114, Japan

An optically active phenylpropanoic acid derivative, a selective agonist for hPPARα, was efficiently prepared by using Evans chiral oxazolidinone technique as a key step.



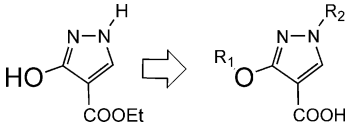
Bioorg. Med. Chem. Lett. 12 (2002) 2105

Synthesis and Hypoglycemic Evaluation of Substituted Pyrazole-4-carboxylic Acids

Bertrand Cottineau, Patrick Toto, Christophe Marot, Aline Pipaud and Jacques Chenault*

Institut de Chimie Organique et Analytique, Université d'Orléans, BP 6759, 45067 Orléans Cedex 2, France

The synthesis and the hypoglycemic activities of a series of substituted pyrazole-4-carboxylic acids is reported.



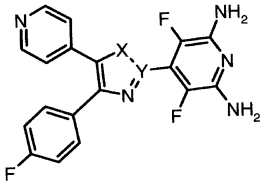
Bioorg. Med. Chem. Lett. 12 (2002) 2109

SAR of 2,6-Diamino-3,5-difluoropyridinyl Substituted Heterocycles as Novel p38 MAP Kinase Inhibitors

Laszlo Revesz,[a,*] Franco E. Di Padova,[a] Thomas Buhl,[a] Roland Feifel,[a] Hermann Gram,[a] Peter Hiestand,[a] Ute Manning,[a] Romain Wolf[a] and Alfred G. Zimmerlin[b]

[a]*Arthritis and Bone Research, Novartis Pharma AG, CH-4002 Basel, Switzerland*
[b]*Preclinical Safety, Novartis Pharma AG, CH-4002 Basel, Switzerland*

2,6-Diamino-3,5-difluoropyridinyl substituted pyridinylimidazoles, -pyrroles, -oxazoles, -thiazoles and -triazoles have been identified as novel p38α inhibitors. Imidazole **11** from this series showed good oral efficacy in the established adjuvant-induced arthritis and the collagen induced arthritis in rats with disease modifying properties.



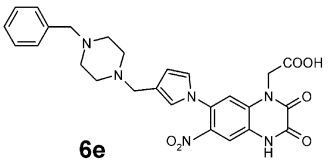
Bioorg. Med. Chem. Lett. 12 (2002) 2113

Pyrrolylquinoxalinediones Carrying a Piperazine Residue Represent Highly Potent and Selective Ligands to the Homomeric Kainate Receptor GluR5

W. Lubisch,* B. Behl, C. Henn, H. P. Hofmann, J. Reeb, F. Regner and M. Vierling

Department of CNS Discovery Research, Abbott GmbH & Co. KG, PO Box 210805, 67008 Ludwigshafen, Germany

Pyrrolylquinoxalinediones carrying aminoalkyl residues were evaluated for affinity to the recombinant, homomeric kainate receptors GluR5, GluR6 and GluR7. Most derivatives preferred binding to GluR5. In particular, the piperazine **6e** represents a highly potent and selective antagonist to GluR5.



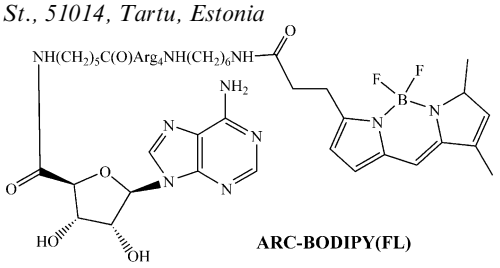
6e

Bioorg. Med. Chem. Lett. 12 (2002) 2117

Identification of the Ability of Highly Charged Nanomolar Inhibitors of Protein Kinases to Cross Plasma Membranes and Carry a Protein into Cells

Asko Uri,[a,*] Gerda Raidaru,[a] Juhan Subbi,[b] Kärt Padari[c] and Margus Pooga[d]

[a]*Institute of Organic and Bioorganic Chemistry, University of Tartu, 2 Jakobi St., 51014, Tartu, Estonia*
[b]*Institute of Chemical Physics and Biophysics, 23 Akadeemia St., 12618, Tallinn, Estonia*
[c]*Institute of Zoology and Hydrobiology, University of Tartu, 2 Jakobi St., 51014, Tartu, Estonia*
[d]*Estonian Biocentre, Riia 23a, 51010 Tartu, Estonia*



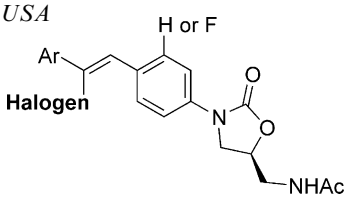
Bioorg. Med. Chem. Lett. 12 (2002) 2121

The Synthesis and Biological Evaluation of a Novel Series of Antimicrobials of the Oxazolidinone Class

Richard J. Sciotti,* Marina Pliushchev, Paul E. Wiedeman, Darlene Balli, Robert Flamm, Angela M. Nilius, Kennan Marsh, DeAnne Stolarik, Robert Jolly, Roger Ulrich and Stevan W. Djuric*

Abbott Laboratories, Infectious Disease Research, Department 47N, Abbott Park, IL 60064, USA

A novel series of antimicrobials of the oxazolidinone class is disclosed. These compounds are characterized relative to previously described analogues by a 'halostilbene-derived' pharmacophore and demonstrate enhanced antimicrobial activity against key Gram-positive pathogens when compared to Linezolid.



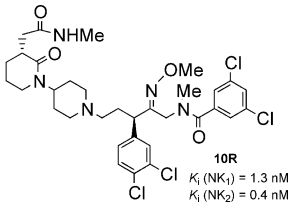
Bioorg. Med. Chem. Lett. 12 (2002) 2125

Identification of a Novel 1′-[5-((3,5-Dichlorobenzoyl)methylamino)-3-(3,4-dichlorophenyl)-4-(methoxyimino)pentyl]-2-oxo-(1,4′-bipiperidine) as a Dual NK_1/NK_2 Antagonist

Pauline C. Ting,* Joe F. Lee, Neng-Yang Shih, John J. Piwinski, John C. Anthes, Richard W. Chapman, Charles A. Rizzo, John A. Hey, Kwokei Ng and Amin A. Nomeir

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

A novel 2-oxo-(1,4′-bipiperidine) oxime **10R**, which is a potent dual NK_1/NK_2 inhibitor in vitro and in vivo and exhibits an improved pharmacokinetic profile, has been identified.



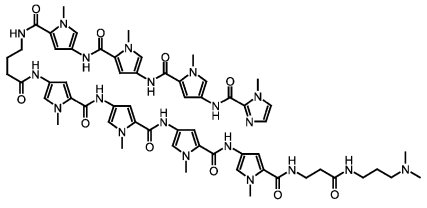
Bioorg. Med. Chem. Lett. 12 (2002) 2129

Rapid Solid-Phase Synthesis of DNA-Binding Pyrrole-Imidazole Polyamides

Peter O. Krutzik and A. Richard Chamberlin*

Department of Chemistry, University of California-Irvine, Irvine, CA 92697, USA

Polyamide synthesis times have been reduced by over 60% through application of azabenzotriazole activation and rapid Boc deprotection schemes.



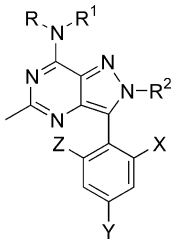
Bioorg. Med. Chem. Lett. 12 (2002) 2133

3-Aryl Pyrazolo[4,3-*d*]pyrimidine Derivatives: Nonpeptide CRF-1 Antagonists

Jun Yuan, Michael Gulianello, Stéphane De Lombaert, Robbin Brodbeck, Andrzej Kieltyka and Kevin J. Hodgetts*

Neurogen Corporation, 35 Northeast Industrial Road, Branford, CT 06405, USA

The synthesis of a series of 3-aryl pyrazolo[4,3-*d*]pyrimidines as potential corticotropin-releasing factor (CRF-1) antagonists is described. The effects of substitution on the aromatic ring, the amino group and the pyrazolo ring on CRF-1 receptor binding were investigated.



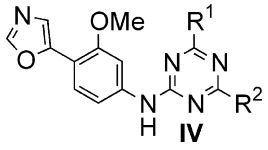
Bioorg. Med. Chem. Lett. 12 (2002) 2137

Rapid Synthesis of Triazine Inhibitors of Inosine Monophosphate Dehydrogenase

William J. Pitts,* Junqing Guo, T. G. Murali Dhar, Zhongqi Shen, Henry H. Gu, Scott H. Watterson, Mark S. Bednarz, Bang-Chi Chen, Joel C. Barrish, Donna Bassolino, Daniel Cheney, Catherine A. Fleener, Katherine A. Rouleau, Diane L. Hollenbaugh and Edwin J. Iwanowicz

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

A series of novel triazine-based small molecule inhibitors (IV) of inosine monophosphate dehydrogenase was prepared. The synthesis and the structure–activity relationships (SARs) derived from in vitro studies are described.



IV

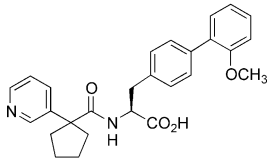
Bioorg. Med. Chem. Lett. 12 (2002) 2141

N-(Arylacetyl)-biphenylalanines as Potent VLA-4 Antagonists

Bing Li,[a,*] Stephen E. de Laszlo,[a] Theodore M. Kamenecka,[a] Ihor E. Kopka,[a] Philippe L. Durette,[a] Thomas Lanza, Jr.,[a] Malcolm MacCoss,[a] Sharon Tong,[a] Richard A. Mumford,[b] Ermengilda D. McCauley,[b] Gail Van Riper,[b] John A. Schmidt[b] and William K. Hagmann[a]

[a]*Department of Medicinal Chemistry, Merck Research Laboratories, Rahway, NJ 07065, USA*
[b]*Department of Inflammation and Rheumatology Research, Merck Research Laboratories, Rahway, NJ 07065, USA*

A series of potent *N*-(aralkyl-, arylcycloalkyl-, and heteroaryl-acyl)-4-biphenylalanine VLA-4 antagonists were prepared by rapid analogue methods employing solid phase chemistry. Further optimization led to several highly potent compounds (e.g., **27** $IC_{50} = 1$ nM), which had good rat pharmacokinetic properties, although most suffered from high plasma clearance rates.



27

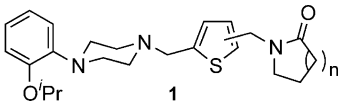
Bioorg. Med. Chem. Lett. 12 (2002) 2145

Novel Thiophene Derivatives for the Treatment of Benign Prostatic Hyperplasia

Haripada Khatuya, Virginia L. Pulito, Linda K. Jolliffe, Xiaobing Li and William V. Murray*

Johnson & Johnson Pharmaceutical Research and Development LLC, Drug Discovery Research, 1000 Route 202, PO Box 300, Raritan, NJ 08869, USA

The syntheses and biological activities of a novel series of 2,4- and 2,5-disubstituted thiophenes (**1**) are reported. These analogues have shown excellent affinity and selectivity against α_{1a}-adrenergic receptor subtypes.



1

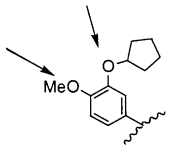
Bioorg. Med. Chem. Lett. 12 (2002) 2149

Improving Metabolic Stability of Phosphodiesterase-4 Inhibitors Containing a Substituted Catechol: Prevention of Reactive Intermediate Formation and Covalent Binding

Nathalie Chauret,* Daniel Guay,* Chun Li, Stephen Day, José Silva, Marc Blouin, Yves Ducharme, James A. Yergey and Deborah A. Nicoll-Griffith

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

Replacement of the methoxy and cyclopentyloxy substituents on the catechol moiety of PDE4 inhibitors resulted in the discovery of potential drug candidates where the formation of reactive metabolites that could covalently bind to microsomal proteins was significantly reduced or eliminated.



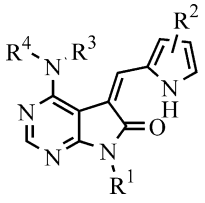
Bioorg. Med. Chem. Lett. 12 (2002) 2153

Rational Design of 4,5-Disubstituted-5,7-dihydro-pyrrolo[2,3-*d*]pyrimidin-6-ones as a Novel Class of Inhibitors of Epidermal Growth Factor Receptor (EGF-R) and Her2(p185^{erbB}) Tyrosine Kinases

Li Sun,* Jean Cui, Congxin Liang, Yong Zhou, Asaad Nemataalla, Xueyan Wang, Hui Chen, Cho Tang and James Wei*

SUGEN, Inc., 230 East Grand Avenue, South San Francisco, CA 94080, USA

A series of 4,5-disubstituted-5,7-dihydro-pyrrolo[2,3-*d*]pyrimidin-6-ones has been designed, synthesized as potent and selective inhibitors of the EGF-R kinase family.



Bioorg. Med. Chem. Lett. 12 (2002) 2159

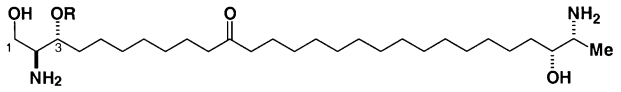
Antifungal Activity of Bifunctional Sphingolipids. Intramolecular Synergism within Long-Chain α,ω-bis-Aminoalcohols

Gillian M. Nicholas, Ronghua Li, John B. MacMillan and Tadeusz F. Molinski*

Department of Chemistry, University of California, Davis, CA 95616, USA

Oceanapiside R = β-D-glucopyranosyl-
Oceanin R = H

MIC 3-10μg/mL



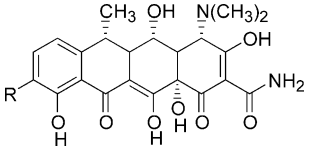
Bioorg. Med. Chem. Lett. 12 (2002) 2163

Synthesis and Biological Evaluation of 9-Substituted Tetracycline Derivatives

Darrell J. Koza[a,*] and Yaw A. Nsiah[b]

[a]*Department of Physical Sciences, Eastern Connecticut State University, Center for Antimicrobial Resistance, Goddard Hall, Willimantic, CT 06226, USA*
[b]*Department of Biology, Eastern Connecticut State University, Center for Antimicrobial Resistance, Goddard Hall, Willimantic, CT 06226, USA*

The synthesis of a new class of novel tetracycline derivatives via transition metal-based chemistry is reported.



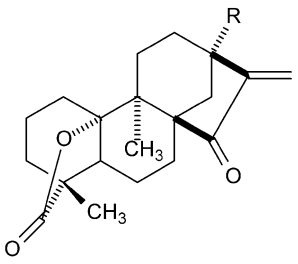
Bioorg. Med. Chem. Lett. 12 (2002) 2167

Antimalarial Compounds from *Parinari capensis*

Arina C. U. Uys,[a] Sarel F. Malan,[a,*] Sandra van Dyk[a] and Robyn L. van Zyl[b]

[a]*Pharmaceutical Chemistry, School of Pharmacy, Potchefstroom University for Christian Higher Education, Private Bag X6001, Potchefstroom 2520, South Africa*
[b]*Department of Pharmacy and Pharmacology, Faculty of Health Sciences, University of the Witwatersrand, 7 York Road, Parktown 2193, South Africa*

The isolation of three diterpene lactones from *Parinari capensis* and the antimalarial activity thereof (IC_{50} of 0.54, 0.67 and 1.57 μg/mL) is described.



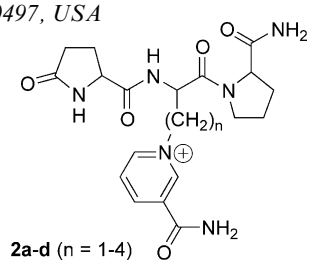
Bioorg. Med. Chem. Lett. 12 (2002) 2171

Design, Synthesis, and Biological Evaluation of Novel, Centrally-Acting Thyrotropin-Releasing Hormone Analogues

Katalin Prokai-Tatrai,[a,b] Pál Perjési,[a] Alevtina D. Zharikova,[a] Xiaoxu Li[a] and Laszlo Prokai[a,c,*]

[a]*Center for Drug Discovery, College of Pharmacy, University of Florida, Gainesville, FL 32610-0497, USA*
[b]*Center for Neurobiology of Aging, College of Medicine, University of Florida, Gainesville, FL 32610-0267, USA*
[c]*The McKnight Brain Institute of the University of Florida, Gainesville, FL 32610-0015, USA*

Solid-phase synthesis and analeptic effect evaluated after intravenous injection of their 1,4-dihydropyridine prodrug forms (**3a**–**d**) of novel TRH analogues (**2a**–**d**) having central pyridinium moiety are reported.



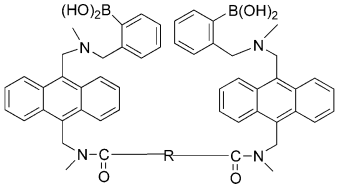
2a-d (n = 1-4)

Bioorg. Med. Chem. Lett. 12 (2002) 2175

Diboronic Acids as Fluorescent Probes for Cells Expressing Sialyl Lewis X

Wenqian Yang,[a] Shouhai Gao,[a] Xingming Gao,[a] Vishnu Vardhan Reddy Karnati,[a] Weijuan Ni,[a] Binghe Wang,[a,*] W. Borden Hooks,[b] John Carson[b] and Brent Weston[b]

[a]*Department of Chemistry, North Carolina State University, Raleigh, NC 27695-8204, USA*
[b]*Department of Pediatrics, University of North Carolina, Chapel Hill, NC 27599-7220, USA*



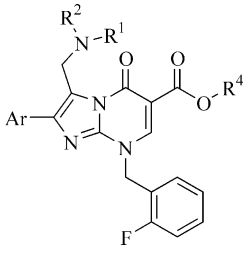
Bioorg. Med. Chem. Lett. 12 (2002) 2179

Synthesis and Initial Structure–Activity Relationships of a Novel Series of Imidazolo[1,2-*a*]pyrimid-5-ones as Potent GnRH Receptor Antagonists

Keith M. Wilcoxen,[a] Yun-Fei Zhu,[a,*] Patrick J. Connors, Jr.,[a] John Saunders,[a] Timothy D. Gross,[a] Yinghong Gao,[a] Greg J. Reinhart,[b] R. Scott Struthers[b] and Chen Chen[a,*]

[a]*Department of Medicinal Chemistry, Neurocrine Biosciences, Inc., 10555 Science Center Drive, San Diego, CA 92121, USA*
[b]*Department of Exploratory Discovery, Neurocrine Biosciences, Inc., 10555 Science Center Drive, San Diego, CA 92121, USA*

SAR studies of 2-arylimidazolo[1,2-*a*]pyrimid-5-ones resulted in the discovery of a series of potent nonpeptide human GnRH receptor antagonists (compound **10e**, $K_i = 7.5$ nM).

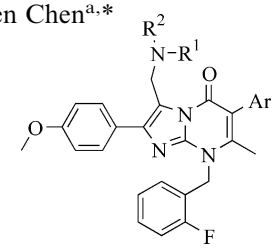


Bioorg. Med. Chem. Lett. 12 (2002) 2185

Design, Synthesis and Structure–Activity Relationships of Novel Imidazolo[1,2-*a*]pyrimid-5-ones as Potent GnRH Receptor Antagonists

Timothy D. Gross,[a] Yun-Fei Zhu,[a,*] John Saunders,[a] Keith M. Wilcoxen,[a] Yinghong Gao,[a] Patrick J. Connors, Jr.,[a] Zhiqiang Guo,[a] R. Scott Struthers,[b] Greg J. Reinhart[b] and Chen Chen[a,*]

[a]*Department of Medicinal Chemistry, Neurocrine Biosciences, Inc., 10555 Science Center Drive, San Diego, CA 92121, USA*
[b]*Department of Exploratory Discovery, Neurocrine Biosciences, Inc., 10555 Science Center Drive, San Diego, CA 92121, USA*



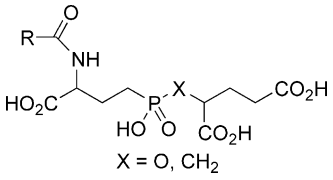
SAR studies of lead GnRH receptor antagonists resulted in the discovery of potent compound **10b** ($K_i = 4.6$ nM) in which the 7-position of the imidazolo[1,2-*a*]pyrimidone was substituted with a methyl, and the ester at the 6-position was replaced by the 3-methoxyphenyl group.

Bioorg. Med. Chem. Lett. 12 (2002) 2189

Phosphonate and Phosphinate Analogues of *N*-Acylated γ-Glutamylglutamate: Potent Inhibitors of Glutamate Carboxypeptidase II

Takashi Tsukamoto,[a,*] Juliet M. Flanary,[a] Camilo Rojas,[a] Barbara S. Slusher,[a] Nadya Valiaeva[b] and James K. Coward[b]

[a]*Guilford Pharmaceuticals Inc., 6611 Tributary Street, Baltimore, MD 21224, USA*
[b]*Departments of Chemistry and Medicinal Chemistry, University of Michigan, Ann Arbor, MI, 48109-1055, USA*

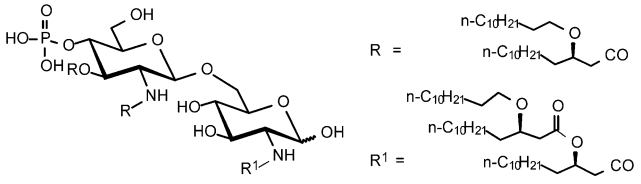


Bioorg. Med. Chem. Lett. 12 (2002) 2193

Lipid A Structures Containing Novel Lipid Moieties: Synthesis and Adjuvant Properties

Zi-Hua Jiang, Mimi V. Bach, Wladyslaw A. Budzynski, Mark J. Krantz, R. Rao Koganty* and B. Michael Longenecker

Biomira Inc., 2011-94 Street, Edmonton, Alberta, Canada T6N 1H1



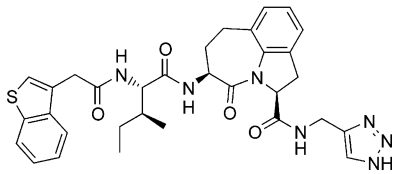
Bioorg. Med. Chem. Lett. 12 (2002) 2197

Discovery of Potent, Selective Human Granzyme B Inhibitors that Inhibit CTL Mediated Apoptosis

Christopher A. Willoughby,[a,*] Herbert G. Bull,[b] Margarita Garcia-Calvo,[b] Joanne Jiang,[b] Kevin T. Chapman[a] and Nancy A. Thornberry[b]

[a]*Department of Medicinal Chemistry, Merck Research Laboratories, Rahway, NJ 07065, USA*
[b]*Department of Endocrinology and Chemical Biology, Merck Research Laboratories, Rahway, NJ 07065, USA*

A novel class of small molecule human granzyme B inhibitors is reported. Compound **20** has a K_i of 7 nM against human granzyme B and blocks CTL mediated apoptosis with an IC_{50} of 3 μM.



20 K_i = 7 nM, IC_{50} = 3 μM

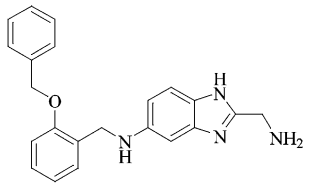
Bioorg. Med. Chem. Lett. 12 (2002) 2201

Design and Synthesis of Novel Inhibitors of Gelatinase B

Xueqing Wang,[a] Youngchool Choe,[b] Charles S. Craik[b] and Jonathan A. Ellman[a,*]

[a]*Center for New Directions in Organic Synthesis, Department of Chemistry, University of California, Berkeley, CA 94720, USA*
[b]*Pharmaceutical Chemistry, Program in Chemistry and Chemical Biology, University of California, San Francisco, CA 94143, USA*

A new method was developed to identify nonpeptidic metalloproteinase inhibitors with novel zinc binding groups. Application of this method to matrix metalloproteinase-9 resulted in the identification of aminomethyl benzimidazole analogue **7a** with an $IC_{50} = 13\ \mu M$.



7a

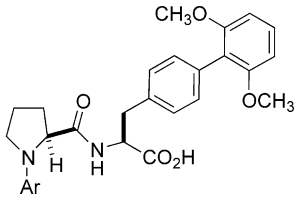
Bioorg. Med. Chem. Lett. 12 (2002) 2205

N-Aryl-prolyl-dipeptides as Potent Antagonists of VLA-4

Theodore M. Kamenecka,[a,*] Thomas Lanza, Jr.,[a] Stephen E. de Laszlo,[a] Bing Li,[a] Ermengilda D. McCauley,[b] Gail Van Riper,[b] Linda A. Egger,[c] Usha Kidambi,[c] Richard A. Mumford,[b] Sharon Tong,[a] Malcolm MacCoss,[a] John A. Schmidt[b] and William K. Hagmann[a]

[a]*Department of Medicinal Chemistry, Merck Research Laboratories, Rahway, NJ 07065, USA*
[b]*Department of Inflammation and Rheumatology Research, Merck Research Laboratories, Rahway, NJ 07065, USA*
[c]*Department of Pharmacology, Merck Research Laboratories, Rahway, NJ 07065, USA*

The design, synthesis, and biological evaluation of a series of *N*-arylprolyl-dipeptide derivatives as small molecule VLA-4 antagonists is described. *N*-Heteroaryl derivatives were best and exhibited subnanomolar activity against the integrin VLA-4.



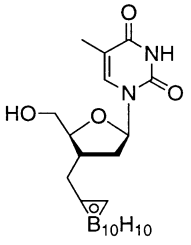
Bioorg. Med. Chem. Lett. 12 (2002) 2209

Synthesis and Biological Evaluation of 3′-Carboranyl Thymidine Analogues

Junhua Yan,[a] Charlotta Naeslund,[b] Ashraf S. Al-Madhoun,[c] Jianghai Wang,[c] Weihua Ji,[a] Guirec Y. Cosquer,[a] Jayaseharan Johnsamuel,[a] Stefan Sjöberg,[b] Staffan Eriksson[c] and Werner Tjarks[a,*]

[a]*College of Pharmacy, Ohio State University, Columbus, OH 43210, USA*
[b]*Department of Organic Chemistry, Institute of Chemistry, Uppsala University, Box 531, S-75121 Uppsala, Sweden*
[c]*Department of Veterinary Medical Chemistry, University of Agricultural Sciences, The Biomedical Centre, Box 575, S-75123 Uppsala, Sweden*

3′-Carboranyl thymidine analogues were synthesized and evaluated as substrates for human thymidine kinases 1 and 2.



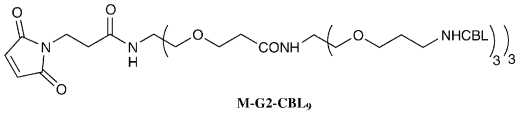
Bioorg. Med. Chem. Lett. 12 (2002) 2213

Syntheses of Dendritic Linkers Containing Chlorambucil Residues for the Preparation of Antibody–Multidrug Immunoconjugates

Chengzao Sun, Peter Wirsching* and Kim D. Janda*

Department of Chemistry, The Scripps Research Institute and the Skaggs Institute for Chemical Biology, 10550 N. Torrey Pines Road, La Jolla, CA 92037, USA

A novel dendritic molecule with nine chlorambucil (CBL) residues on the surface and a maleimide moiety at the core terminus was synthesized. This molecule is ready for attachment to single-chain Fv antibodies (scFvs) to form antibody–multidrug immunoconjugates.



M-G2-CBL$_9$

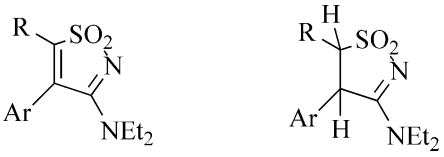
Bioorg. Med. Chem. Lett. 12 (2002) 2217

Isothiazole Dioxides: Synthesis and Inhibition of *Trypanosoma brucei* Protein Farnesyltransferase

Francesca Clerici,[a,*] Maria Luisa Gelmi,[a] Kohei Yokoyama,[b,c] Donato Pocar,[a] Wesley C. Van Voorhis,[d] Frederick S. Buckner[d] and Michael H. Gelb[b,c,*]

[a]*Istituto di Chimica Organica, Facoltà di Farmacia, Università di Milano, Via Venezian 21, 20133 Milan, Italy*
[b]*Department of Chemistry, University of Washington, Seattle, WA 98195, USA*
[c]*Department of Biochemistry, University of Washington, Seattle, WA 98195, USA*
[d]*Department of Medicine, University of Washington, Seattle, WA 98195, USA*

The synthesis and evaluation as *Trypanosoma brucei* protein farnesyltransferase inhibitors of several isothiazole dioxide derivatives are reported.



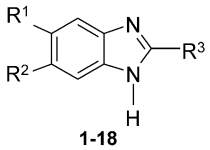
Bioorg. Med. Chem. Lett. 12 (2002) 2221

Synthesis and Antiparasitic Activity of 1*H*-Benzimidazole Derivatives

Juan Valdez,[a] Roberto Cedillo,[b] Alicia Hernández-Campos,[a] Lilián Yépez,[b] Francisco Hernández-Luis,[a] Gabriel Navarrete-Vázquez,[a] Amparo Tapia,[b] Rafael Cortés,[c] Manuel Hernández[c] and Rafael Castillo[a,*]

[a]*Departamento de Farmacia, Facultad de Química, UNAM, CU. México D.F. 04510, México*
[b]*Unidad de Investigación Medica en Enfermedades Infecciosas y Parasitarias, IMSS. México D.F. 06720, México*
[c]*Departamento de Biología Celular, CINVESTAV, IPN. México D.F. 07000, México*

Compounds **1**–**18** have been synthesized and tested in vitro against the protozoa *Giardia lamblia*, *Entamoeba histolytica* and the helminth *Trichinella spiralis*. Inhibition of rat brain tubulin polymerization was also measured and compared for each compound. Results indicate that most of the compounds tested were more active as antiprotozoal agents than Metronidazole and Albendazole. None of the compounds was as active as Albendazole against *T. spiralis*. Although only compounds **3**, **9** and **15** (2-methoxycarbonylamino derivatives) inhibited tubulin polymerization, these were not the most potent antiparasitic compounds.



1-18

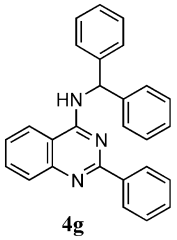
Bioorg. Med. Chem. Lett. 12 (2002) 2225

Identification of a Novel Partial Inhibitor of Dopamine Transporter Among 4-Substituted 2-Phenylquinazolines

Subramaniam Ananthan,[a,*] Surendra K. Saini,[a] Rashmi Khare,[a] Sarah D. Clayton,[a] Christina M. Dersch[b] and Richard B. Rothman[b]

[a]*Organic Chemistry Department, Southern Research Institute, Birmingham, AL 35255, USA*
[b]*Clinical Psychopharmacology Section, IRP, National Institute on Drug Abuse, Baltimore, MD 21224, USA*

The identification of a partial inhibitor of dopamine transporter **4g** is reported.



4g

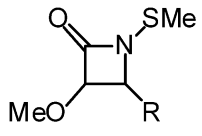
Bioorg. Med. Chem. Lett. 12 (2002) 2229

N-Thiolated β-Lactams: Novel Antibacterial Agents for Methicillin-Resistant *Staphylococcus aureus*

Edward Turos,[a,*] Timothy E. Long,[a] Monika I. Konaklieva,[a] Cristina Coates,[a] Jeung-Yeop Shim,[a] Sonja Dickey,[b] Daniel V. Lim[b] and Andrew Cannons[b]

[a]*Department of Chemistry, 4202 E. Fowler Avenue, University of South Florida, Tampa, FL 33620, USA*
[b]*Department of Biology, University of South Florida, Tampa, FL 33620, USA*

N-Methylthio-substituted β-lactams comprise a novel family of antibacterial agents that display high selectivity for MRSA as well as unusual SAR features and a mode of action.



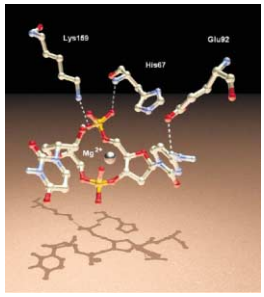
Bioorg. Med. Chem. Lett. 12 (2002) 2233

Binding Modes of Two Novel Dinucleotide Inhibitors of HIV-1 Integrase

Sven Guenther and Vasu Nair*

Department of Chemistry, The University of Iowa, Iowa City, IA 52242, USA

Insights into the binding modes on HIV-1 integrase of our novel dinucleotide inhibitors (pisodApdC and pdCpisodU) obtained using molecular docking experiments.

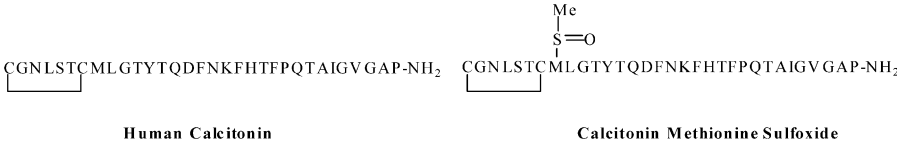


Bioorg. Med. Chem. Lett. 12 (2002) 2237

Convenient Synthesis of Human Calcitonin and Its Methionine Sulfoxide Derivative

Tiesheng Shi and and Dallas L. Rabenstein*

Department of Chemistry, University of California, Riverside, CA 92521, USA

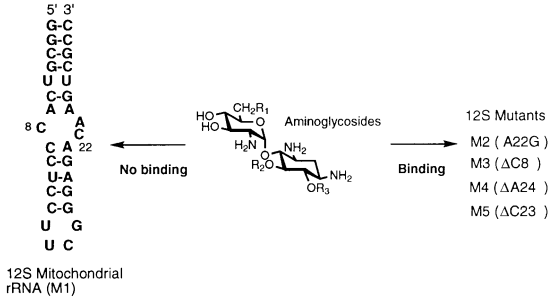


Bioorg. Med. Chem. Lett. 12 (2002) 2241

Decoding Region Bubble Size and Aminoglycoside Antibiotic Binding

Do Hyun Ryu and Robert R. Rando*

Department of Biological Chemistry and Molecular Pharmacology, Harvard Medical School, 45 Shattuck Street, Boston, MA 02115, USA

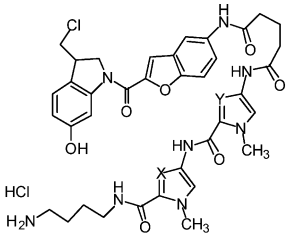


Bioorg. Med. Chem. Lett. 12 (2002) 2245

Sequence Selective Recognition of DNA by Hairpin Conjugates of a Racemic *seco*-Cyclopropaneindoline-2-benzofurancarboxamide and Polyamides

James L. Toth,[a] Carly A. Price,[a] Erik C. Madsen,[a] Heather L. Handl,[a] Stephen J. Hudson,[b] Richard B. Hubbard, III,[a,c] J. Phillip Bowen,[c] Konstantinos Kiakos,[d] John A. Hartley[d] and Moses Lee[a,*]

[a]*Department of Chemistry, Furman University, Greenville, SC 29613, USA*
[b]*Department of Biology, Furman University, Greenville, SC 29613, USA*
[c]*Department of Chemistry, University of Georgia, Athens, GA 30602, USA*
[d]*Department of Oncology, Royal Free University College Medical School, London W1W 7BS, UK*



1, X = Y = N
2, X = N, Y = CH
3, X = CH, Y = N
4, X = Y = CH