Graphical Abstracts

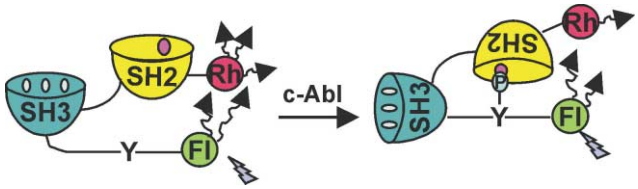
Bioorg. Med. Chem. Lett. 11 (2001) 3091

Fluorescent Monitoring of Kinase Activity in Real Time: Development of a Robust Fluorescence-based Assay for Abl Tyrosine Kinase Activity

Roseanne M. Hofmann,[a] Graham J. Cotton,[a] Emmanuel J. Chang,[a] Ephraim Vidal,[b] Darren Veach,[b] William Bornmann[b] and Tom W. Muir[a,*]

[a]*Laboratory of Synthetic Protein Chemistry, The Rockefeller University, New York, NY 10021, USA*
[b]*Organic Synthesis Core, Memorial Sloan-Kettering Cancer Institute, New York, NY 10021, USA*

A fluorescent biosensor for Abl kinase activity was developed.



Bioorg. Med. Chem. Lett. 11 (2001) 3095

Flavonoids: Structural Requirements for Antiproliferative Activity on Breast Cancer Cells

Christelle Pouget, Fabienne Lauthier, Alain Simon, Catherine Fagnere, Jean-Philippe Basly, Christiane Delage and Albert-José Chulia*

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

Several classes of flavonoids (flavones, flavanones, 2′-hydroxychalcones and flavan-4-ols) having a variety of substituents on A ring were investigated for their antiproliferative activity against MCF-7 human breast cancer cells. Structure–activity relationships of these compounds were discussed.

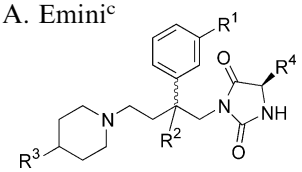
Bioorg. Med. Chem. Lett. 11 (2001) 3099

Discovery of Human CCR5 Antagonists Containing Hydantoins for the Treatment of HIV-1 Infection

Dooseop Kim,[a,*] Liping Wang,[a] Charles G. Caldwell,[a] Ping Chen,[a] Paul E. Finke,[a] Bryan Oates,[a] Malcolm MacCoss,[a] Sander G. Mills,[a] Lorraine Malkowitz,[b] Sandra L. Gould,[b] Julie A. DeMartino,[b] Martin S. Springer,[b] Daria Hazuda,[c] Michael Miller,[c] Joseph Kessler,[c] Renee Danzeisen,[c] Gwen Carver,[c] Anthony Carella,[c] Karen Holmes,[c] Janet Lineberger,[c] William A. Schleif[c] and Emilio A. Emini[c]

[a]*Department of Medicinal Chemistry, Merck Research Laboratories, RY 121-240, 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, West Point, PA 19486, USA*

A series of hydantoin derivatives has been discovered as highly potent nonpeptide antagonists for the human CCR5 receptor. The synthesis, SAR, and biological profiles of this class of antagonists are described.



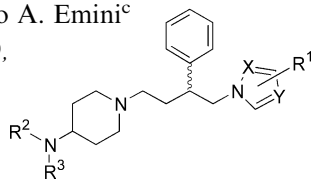
Bioorg. Med. Chem. Lett. 11 (2001) 3103

Design, Synthesis, and SAR of Heterocycle-Containing Antagonists of the Human CCR5 Receptor for the Treatment of HIV-1 Infection

Dooseop Kim,[a,*] Liping Wang,[a] Charles G. Caldwell,[a] Ping Chen,[a] Paul E. Finke,[a] Bryan Oates,[a] Malcolm MacCoss,[a] Sander G. Mills,[a] Lorraine Malkowitz,[b] Sandra L. Gould,[b] Julie A. DeMartino,[b] Martin S. Springer,[b] Daria Hazuda,[c] Michael Miller,[c] Joseph Kessler,[c] Renee Danzeisen,[c] Gwen Carver,[c] Anthony Carella,[c] Karen Holmes,[c] Janet Lineberger,[c] William A. Schleif[c] and Emilio A. Emini[c]

[a]*Department of Medicinal Chemistry, Merck Research Laboratories, RY 121-240, 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, West Point, PA 19486, USA*

The synthesis, SAR, and biological profiles of heterocycle-containing antagonists of the human CCR5 receptor are described.



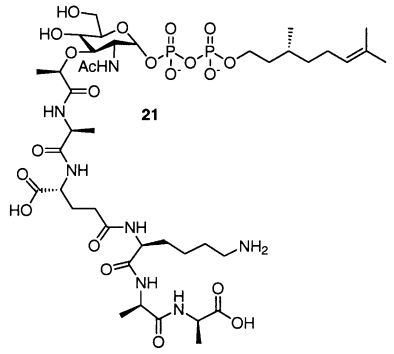
Bioorg. Med. Chem. Lett. 11 (2001) 3107

Synthesis of P^1-Citronellyl-P^2-α-D-pyranosyl Pyrophosphates as Potential Substrates for the *E. coli* Undecaprenyl-pyrophosphoryl-*N*-acetylglucoseaminyl Transferase MurG

Predrag Cudic, Douglas C. Behenna, Michael K. Yu, Ryan G. Kruger, Lawrence M. Szewczuk and Dewey G. McCafferty*

Johnson Research Foundation and the Department of Biochemistry and Biophysics, The University of Pennsylvania School of Medicine, Philadelphia, PA 19104-6059, USA

The synthesis and biological evaluation of P^1-citronellyl-P^2-α-D-pyranosyl pyrophosphates such as **21** are reported.



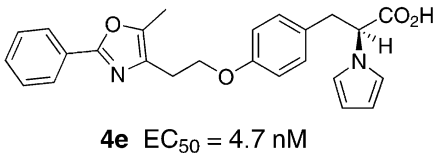
Bioorg. Med. Chem. Lett. 11 (2001) 3111

Synthesis and Biological Activity of L-Tyrosine-based PPARγ Agonists with Reduced Molecular Weight

Kevin G. Liu,[a,*] Millard H. Lambert,[a] Andrea H. Ayscue,[a] Brad R. Henke,[b] Lisa M. Leesnitzer,[a] William R. Oliver, Jr.,[b] Kelli D. Plunket,[a] H. Eric Xu,[a] Daniel D. Sternbach[b] and Timothy M. Willson[a,*]

[a]*Nuclear Receptor Discovery Research, GlaxoSmithKline, Research Triangle Park, NC 27709, USA*
[b]*Metabolic Diseases Drug Discovery, GlaxoSmithKline, Research Triangle Park, NC 27709, USA*

Pyrrole (**4e**) is identified as a potent PPARγ agonist synthesized in four steps from L-tyrosine methyl ester.



4e EC_{50} = 4.7 nM

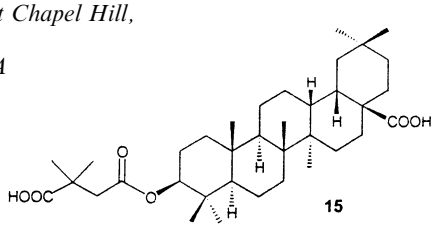
Bioorg. Med. Chem. Lett. 11 (2001) 3115

Synthesis and Anti-HIV Activity of Oleanolic Acid Derivatives

Yong-Ming Zhu,[a] Jing-Kang Shen,[a] Hui-Kang Wang,[b] L. Mark Cosentino[c] and Kuo-Hsiung Lee[b,*]

[a]*Shanghai Institute of Materia Medica, Chinese Academy of Sciences, 294 Taiyuan Road, Shanghai 200031, China*
[b]*Natural Products Laboratory, School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599-7360, USA*
[c]*Biotech Research Laboratories, 217 Perry Parkway, Gaithersburg, MD 20877, USA*

Thirteen oleanolic acid derivatives were prepared and evaluated for anti-HIV activity in H9 lymphocytes. Saturating the C_{12}–C_{13} double bond and converting the C_{17}-carboxyl group to an aminomethyl group led to compounds **13**–**15** and **19**–**20**, respectively, which showed improved anti-HIV activity. Compound **15** was the most potent derivative with EC_{50} = 0.0039 μg/mL and TI = 3570.



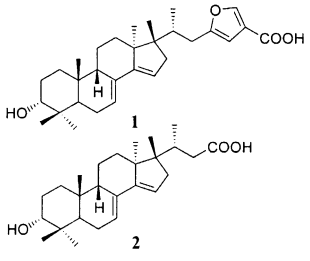
Bioorg. Med. Chem. Lett. 11 (2001) 3119

Two Novel Cytotoxic and Antimicrobial Triterpenoids from *Pseudolarix kaempferi*

Sheng-Ping Yang and Jian-Min Yue*

Institute of Materia Medica, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences, 294 Taiyuan Road, Shanghai, 200031, PR China

Two novel tritperpenoids, isopseudolarifurocic acids A (**1**) and B (**2**), were isolated from the bark of *Pseudolarix kaempferi*. Compounds **1** and **2** exhibited significant cytotoxic activities against several tumor cell lines. Compound **1** also showed most potent antimicrobial activities against both Gram-positive and Gram-negative bacteria.



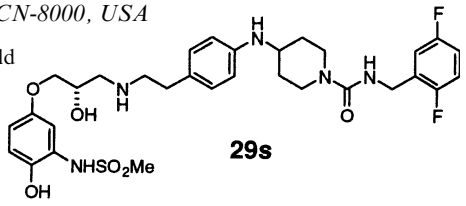
Bioorg. Med. Chem. Lett. 11 (2001) 3123

4-Aminopiperidine Ureas as Potent Selective Agonists of the Human β_3-Adrenergic Receptor

Mark A. Ashwell,[a,*] William R. Solvibile, Jr.,[a] Stella Han,[b] Elwood Largis,[b] Ruth Mulvey[b] and Jeffrey Tillet[b]

[a]*Chemical Sciences, Wyeth-Ayerst Research, PO Box CN-8000, USA*
[b]*Cardiovascular/Metabolic Diseases Research, Wyeth-Ayerst Research, PO Box CN-8000, USA*

Compound **29s** was identified as a potent (EC_{50} = 1 nM) and selective (greater than 400-fold over β_1- with no β_2-AR agonism) full β_3-AR agonist with in vivo activity in a transgenic mouse model of thermogenesis.



29s

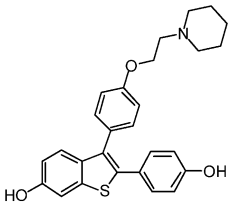
Bioorg. Med. Chem. Lett. 11 (2001) 3129

Activity of a Tamoxifen–Raloxifene Hybrid Ligand for Estrogen Receptors at an AP-1 Site

Ross V. Weatherman, David C. Carroll and Thomas S. Scanlan*

Departments of Pharmaceutical Chemistry and Cellular and Molecular Pharmacology, University of California — San Francisco, San Francisco, CA 94143-0446, USA

To test the effect of ligand flexibility on the selective transcriptional activities of ERα and ERβ from an AP-1 site, an analogue of raloxifene was made that removed the ketone and made the ligand more planar and conformationally more similar to 4-hydroxytamoxifen. It was found to be a much stronger activator an an AP-1 site with ERα than with ERβ.



Bioorg. Med. Chem. Lett. 11 (2001) 3133

Modelling Studies of the Active Site of Human Sorbitol Dehydrogenase: an Approach to Structure-Based Inhibitor Design of the Enzyme

Connie Darmanin and Ossama El-Kabbani*

Department of Medicinal Chemistry, Victorian College of Pharmacy, Monash University, 381 Royal Parade, Parkville, Victoria 3052, Australia

The design of novel sorbitol dehydrogenase inhibitors based on the model of the holoenzyme/WAY135 706 complex is reported.

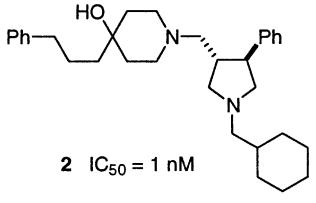
Bioorg. Med. Chem. Lett. 11 (2001) 3137

Combinatorial Synthesis of CCR5 Antagonists

Christopher A. Willoughby,[a,*] Scott C. Berk,[a] Keith G. Rosauer,[a] Silvia Degrado,[a] Kevin T. Chapman,[a] Sandra L. Gould,[b] Martin S. Springer,[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*

The synthesis of the combinatorial library of CCR5 antagonists is reported. Compound **2** was discovered, which has a 1 nM IC_{50} in a CCR5 binding assay and inhibits HIV-1 replication with an IC_{95} of 580 nM.



2 IC_{50} = 1 nM

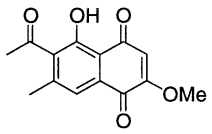
Bioorg. Med. Chem. Lett. 11 (2001) 3143

Discovery, Total Synthesis, HRV 3C-Protease Inhibitory Activity, and Structure–Activity Relationships of 2-Methoxystypandrone and Its Analogues

Sheo B. Singh,[a,*] Pia L. Graham,[b] Robert A. Reamer[a] and Michael G. Cordingley[b]

[a]*Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065, USA*
[b]*Merck Research Laboratories, West Point, PA 19486, USA*

Discovery, a new total synthesis employing Diels–Alder method, HRV 3C-protease inhibitory activity, and SAR of methoxystypandrone has been described.



Methoxystypandrone

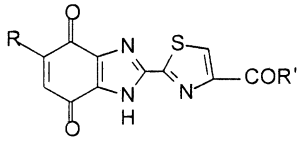
Bioorg. Med. Chem. Lett. 11 (2001) 3147

Synthesis and Antiproliferative Activity of Some Thiazolylbenzimidazole-4,7-diones

Laura Garuti,[a,*] Marinella Roberti,[a] Annalisa Pession,[b] Emanuela Leoncini[c] and Silvana Hrelia[c]

[a]*Department of Pharmaceutical Science, University of Bologna, via Belmeloro 6, I-40126 Bologna, Italy*
[b]*Department of Experimental Pathology, University of Bologna, via S. Giacomo, Bologna, Italy*
[c]*Department of Biochemistry "G. Moruzzi" University of Bologna, via Irnerio48, I-40126 Bologna, Italy*

Some thiazolylbenzimidazole-4,7-diones were synthesized and tested in vitro on tumor cell lines.
Two of them show a very good antiproliferative activity on K562 cells, others are active on SW620 cells.



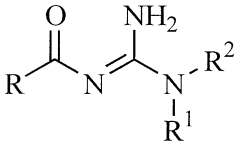
Bioorg. Med. Chem. Lett. 11 (2001) 3151

Solution-Phase, Parallel Synthesis and Pharmacological Evaluation of Acylguanidine Derivatives as Potential Sodium Channel Blockers

Seetharamaiyer Padmanabhan,* Ruth C. Lavin, Paresh M. Thakker, Jinqing Guo, Lu Zhang, Deke Moore, Michael E. Perlman, Cassandra Kirk, Deborah Daly, Kathy J. Burke-Howie, Teresa Wolcott, Suchitra Chari, David Berlove, James B. Fischer, William F. Holt, Graham J. Durant and Robert N. McBurney

CeNeS Pharmaceuticals Inc., 333 Providence Highway, Norwood, MA 02062, USA

A series of acylguanidines was prepared using solution-phase, parallel synthesis. These compounds were evaluated as potential sodium channel blockers through both in vitro and in vivo studies.



Bioorg. Med. Chem. Lett. 11 (2001) 3157

Biological Activity in Human Neutrophils of Di-tripeptides, Analogues of the Chemotactic fMLP

Giorgio Cavicchioni,[a,*] Marianna Turchetti[a] and Susanna Spisani[b]

[a]*Department of Pharmaceutical Sciences, Via Fossato di Mortara 17/19, University of Ferrara, 44100 Ferrara, Italy*
[b]*Department of Biochemistry and Molecular Biology, Via L.Borsari 46, University of Ferrara, 44100 Ferrara, Italy*

for-Met-Ser(for-Met-Leu-Phe)-Phe-OMe **1** and for-Met-Lys(for-Met-Leu-Phe)-Phe-OMe **2** were synthesized in order to investigate biological activities on human neutrophils of crosslinked di-tripeptides. Our results seem to highlight that the tested di-tripeptides (i) do not step up chemotaxis, (ii) can elicit superoxide anion production which is dependent on the nature of the residue at position 2, chosen in the tripeptide that is crosslinked to the fMLP-OMe.

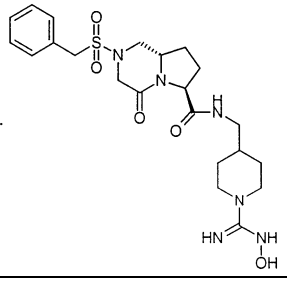
Bioorg. Med. Chem. Lett. 11 (2001) 3161

Novel Bicyclic Lactam Inhibitors of Thrombin: Potency and Selectivity Optimization through P1 Residues

Sophie Lévesque,[a,*] Yves St-Denis,[a] Benoit Bachand,[a] Patrice Préville,[a] Lorraine Leblond,[a] Peter D. Winocour,[a] Jeremy J. Edmunds,[b] J. R. Rubin[b] and M. Arshad Siddiqui[a]

[a]*Shire BioChem Inc., 275 Armand-Frappier Blvd., Laval, Québec, Canada H7V 4A7*
[b]*Pfizer Global Research and Development, Ann Arbor, MI 48105, USA*

Peptidomimetic inhibitors of thrombin lacking the important Ser195–carbonyl interaction have been prepared. The binding energy lost after the removal of the activated carbonyl was recaptured through a series of modifications of the P1 residues of the bicyclic lactam inhibitors. Selected substituted compounds displayed useful pharmacological profiles both in vitro and in vivo.



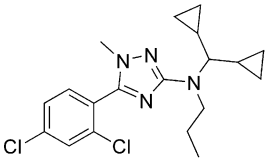
Bioorg. Med. Chem. Lett. 11 (2001) 3165

1-Alkyl-3-amino-5-aryl-1*H*-[1,2,4]triazoles: Novel Synthesis Via Cyclization of *N*-Acyl-*S*-methylisothioureas with Alkylhydrazines and Their Potent Corticotropin-Releasing Factor-1 (CRF_1) Receptor Antagonist Activities

Chen Chen,* Raymond Dagnino, Jr., Charles Q. Huang, James R. McCarthy and Dimitri E. Grigoriadis

Neurocrine Biosciences, Inc., 10555 Science Centre Drive, San Diego, CA 92121, USA

1-Alkyl-3-amino-5-aryl-1*H*-[1,2,4]triazoles exemplified by **7a** were synthesized via a novel cyclization of the *N*-acyl-*N*′,*N*′-dialkyl-*S*-methylisothiourea with an alkylhydrazine. Some of the triazoles were found to be potent CRF_1 receptor antagonists.



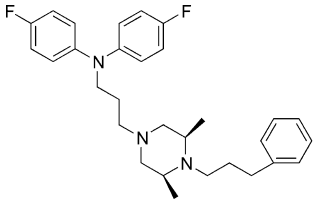
7a, K_i = 9 nM

Bioorg. Med. Chem. Lett. 11 (2001) 3169

[3-*cis*-3,5-Dimethyl-(1-piperazinyl)alkyl]-bis-(4′-fluorophenyl)amine Analogues as Novel Probes for the Dopamine Transporter

Jianjing Cao,[a] Stephen M. Husbands,[a] Theresa Kopajtic,[b] Jonathan L. Katz[b] and Amy Hauck Newman[a,*]

[a]*Medicinal Chemistry Section, National Institute on Drug Abuse — Intramural Research Program, 5500 Nathan Shock Drive, Baltimore, MD 21224, USA*
[b]*Psychobiology Section, National Institute on Drug Abuse — Intramural Research Program, 5500 Nathan Shock Drive, Baltimore, MD 21224, USA*



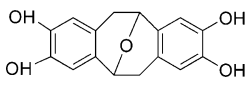
Bioorg. Med. Chem. Lett. 11 (2001) 3175

Synthesis and HIV-1 Integrase Inhibitory Activities of Catechol and Bis-Catechol Derivatives

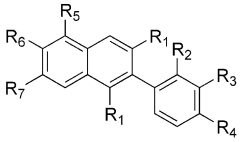
Romain Dupont,[a] Laurence Jeanson,[b] Jean-François Mouscadet[b] and Philippe Cotelle[a,*]

[a]*Laboratoire de Chimie Organique Physique, UPRESA CNRS 8009, Université des Sciences et Technologies de Lille, 59655 Villeneuve d'Ascq, France*
[b]*Laboratoire de Physicochimie et de Pharmacologie des Macromolécules Biologiques, UMR CNRS 8532, Institut Gustave Roussy, PRII, 39, rue Camille Desmoulins, 94805 Villejuif, France*

Fourteen catechol and bis-catechol derivatives have been synthesised and tested for their HIV-1 inhibitory activities. The six more active molecules have been tested for their antiviral activity and cytotoxicity. We have found that bis-catechols **1** and **2** are the most active HIV-1 integrase inhibitor whereas the best antiviral compound is **4**.



1



2-14

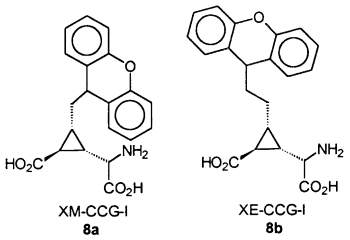
Bioorg. Med. Chem. Lett. 11 (2001) 3179

Design, Synthesis and Preliminary Evaluation of Novel 3′-Substituted Carboxycyclopropylglycines as Antagonists at Group 2 Metabotropic Glutamate Receptors

Roberto Pellicciari,[a,*] Gabriele Costantino,[a] Maura Marinozzi,[a] Antonio Macchiarulo,[a] Laura Amori,[a] Peter Josef Flor,[b] Fabrizio Gasparini,[b] Rainer Kuhn[b] and Stephan Urwyler[b]

[a]*Dipartimento di Chimica e Tecnologia del Farmaco, Università di Perugia, Via del Liceo 1, 06127 Perugia, Italy*
[b]*Novartis Pharma AG, Nervous System Research, Basel, Switzerland*

The two novel amino acids **8a** and **8b** were synthesized and evaluated as potential mGluR ligands. Compound **8b** is a submicromolar antagonist at group 2 mGluRs.



XM-CCG-I **8a** XE-CCG-I **8b**