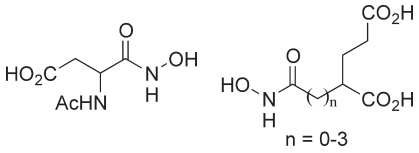
Bioorg. Med. Chem. Lett. 13 (2003) 2097

Synthesis and Biological Evaluation of Hydroxamate-Based Inhibitors of Glutamate Carboxypeptidase II

Doris Stoermer, Qun Liu, Monicia R. Hall, Juliet M. Flanary, Ajit G. Thomas, Camilo Rojas, Barbara S. Slusher and Takashi Tsukamoto*

Guilford Pharmaceuticals Inc., 6611 Tributary Street, Baltimore, MD 21224, USA



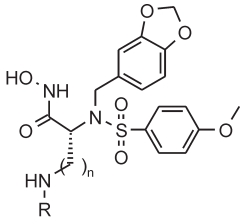
Bioorg. Med. Chem. Lett. 13 (2003) 2101

Novel Inhbitors of Procollagen C-Terminal Proteinase. Part 1: Diamino Acid Hydroxamates

N. G. J. Delaet,[a,*] L. A. Robinson,[a] D. M. Wilson,[a] R. W. Sullivan,[a] E. K. Bradley,[a] S. M. Dankwardt,[b] R. L. Martin,[b] H. E. Van Wart[b] and K. A. M. Walker[b]

[a]*CombiChem Inc., 4570 Executive Drive, San Diego, CA 92121, USA*
[b]*Roche Bioscience, Inflammatory Diseases Unit, 3401 Hillview Ave, Palo Alto, CA 94304, USA*

The parallel synthesis and SAR studies of diamino acid hydroxamate inhibitors of procollagen C-terminal proteinase are reported.



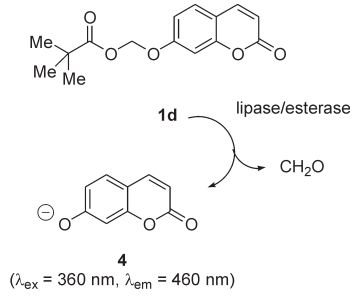
Bioorg. Med. Chem. Lett. 13 (2003) 2105

A Low Background High-Throughput Screening (HTS) Fluorescence Assay for Lipases and Esterases Using Acyloxymethylethers of Umbelliferone

Emmanuel Leroy, Nicolas Bensel and Jean-Louis Reymond*

Department of Chemistry & Biochemistry, University of Bern, Freiestrasse 3, 3012 Bern, Switzerland

Oxymethyl ethers of umbelliferone, for example **1d**, undergo a selective fluorogenic reaction with lipases and esterases.

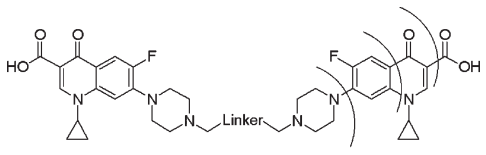


Bioorg. Med. Chem. Lett. 13 (2003) 2109

Structural Features of Piperazinyl-Linked Ciprofloxacin Dimers Required for Activity Against Drug-Resistant Strains of *Staphylococcus aureus*

Robert J. Kerns,[a,*] Michael J. Rybak,[b] Glenn W. Kaatz,[c] Flamur Vaka,[d] Raymond Cha,[b] Richard G. Grucz[b] and Veena U. Diwadkar[d]

[a]*Division of Medicinal and Natural Products Chemistry, The University of Iowa, Iowa City, IA 52242, USA*
[b]*Anti-Infective Research Laboratory, Department of Pharmacy Practice, Wayne State University, Detroit, MI 48202, USA*
[c]*John D. Dingell VAMC & Wayne State University School of Medicine, Detroit, MI 48201, USA*
[d]*Department of Pharmaceutical Sciences, Wayne State University, Detroit, MI 48202, USA*

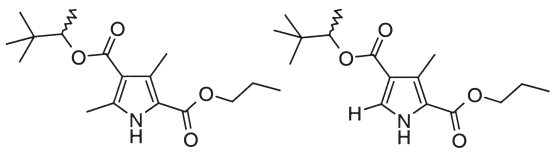


Bioorg. Med. Chem. Lett. 13 (2003) 2113

2,4-Dicarboxy-pyrroles as Selective Non-Competitive mGluR1 Antagonists: Further Characterization of 3,5-Dimethyl Pyrrole-2,4-dicarboxylic Acid 2-Propyl Ester 4-(1,2,2-Trimethyl-propyl) Ester and Structure–Activity Relationships

Fabrizio Micheli,* Romano Di Fabio,* Fabio Bordi, Palmina Cavallini, Paolo Cavanni, Daniele Donati, Stefania Faedo, Micaela Maffeis, Fabio Maria Sabbatini, Giorgio Tarzia and Maria Elvira Tranquillini

GlaxoSmithkline Medicine Research Centre, Via Fleming 4, 37135 Verona, Italy



1 19

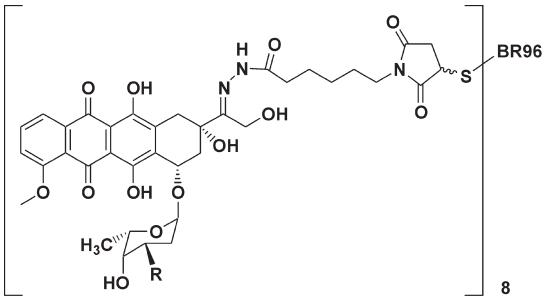
Bioorg. Med. Chem. Lett. 13 (2003) 2119

BR96 Conjugates of Highly Potent Anthracyclines

H. Dalton King,[a,*] Andrew J. Staab,[a] Kahnie Pham-Kaplita,[a] Derek Yurgaitis,[a] Raymond A. Firestone,[a] Shirley J. Lasch[b] and Pamela A. Trail[b]

[a]*Bristol-Myers Squibb Pharmaceutical Research Institute, PO Box 5100, Wallingford, CT 06492-7660, USA*
[b]*Bristol-Myers Squibb Pharmaceutical Research Institute, PO Box 4000, Princeton, NJ 08543-4000, USA*

BR96 conjugates of the highly potent antitumor agents 5-diacetoxypentyldoxorubicin and morpholinodoxorubicin were synthesized and found to be highly potent and antigen specific in vitro.



8

R = NH_2, $NH(CH_2)_4CH(OAc)_2$, N-Morpholino

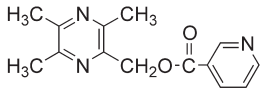
Bioorg. Med. Chem. Lett. 13 (2003) 2123

Synthesis of the Novel Liqustrazine Derivatives and Their Protective Effect on Injured Vascular Endothelial Cell Damaged by Hydrogen Peroxide

Xinyong Liu,[a,*] Rui Zhang,[a] Wenfang Xu,[a] Chaowu Li,[b] Quanqin Zhao[c] and Xingpo Wang[c]

[a]*Institute of Medicinal Chemistry, School of Pharmacy, No. 44 Wenhuaxi Road, Jinan 250012, China*
[b]*Qilu Hospital, Jinan 250012, China*
[c]*School of Chemistry and Engineer, Shandong University, Jinan 250012, China*

A series of new 2-acyloxymethyl-3,5,6-trimethylpyrazine derivatives was synthesized and their protective effects on the vascular endothelial cells were reported.



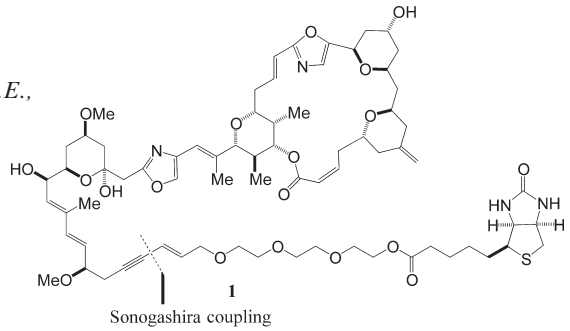
5a (**P**max=88.57%, C=0.1mmol.L^{-1})

Bioorg. Med. Chem. Lett. 13 (2003) 2127

Total Synthesis of a Biotinylated Derivative of Phorboxazole A Via Sonogashira Coupling

T. Matthew Hansen,, Mary M. Engler and Craig J. Forsyth*

Department of Chemistry, University of Minnesota, 207 Pleasant ST S.E., Minneapolis, MN 55455, USA



1

Sonogashira coupling

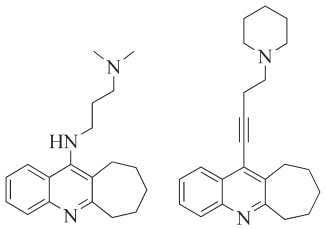
Bioorg. Med. Chem. Lett. 13 (2003) 2131

A New Class of Histamine H_3-Receptor Antagonists: Synthesis and Structure–Activity Relationships of 7,8,9,10-Tetrahydro-6H-cyclohepta[*b*]quinolines

Sean C. Turner,* Timothy A. Esbenshade, Youssef L. Bennani and Arthur A. Hancock

Neuroscience Research, Global Pharmaceutical Research and Development, Abbott Laboratories, 100 Abbott Park Road, Abbott Park, IL 60064, USA

The synthesis and biological evaluation of novel cycloheptaquinoline ligands of the human H_3 receptor are described.



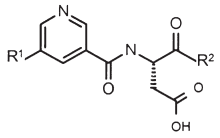
1 **2**

Bioorg. Med. Chem. Lett. 13 (2003) 2137

Nicotinyl Aspartyl Ketones as Inhibitors of Caspase-3

Elise Isabel,[a,*] W. Cameron Black,[a] Christopher I. Bayly,[a] Erich L. Grimm,[a] Marc K. Janes,[a] Daniel J. McKay,[a] Donald W. Nicholson,[a] Dita M. Rasper,[a] Johanne Renaud,[a] Sophie Roy,[a] John Tam,[a] Nancy A. Thornberry,[b] John P. Vaillancourt,[a] Steven Xanthoudakis[a] and Robert Zamboni[a]

[a]*Merck Frosst Centre for Therapeutic Research, Merck Frosst Canada & Co., PO Box 1005, Pointe-Claire-Dorval, Quebec, Canada H9R 4P8*
[b]*Merck Research Laboratories, Rahway, NJ 07065, USA*



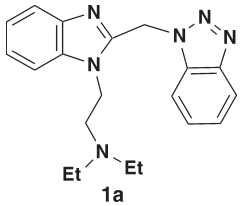
Bioorg. Med. Chem. Lett. 13 (2003) 2141

Fundamental Structure–Activity Relationships Associated with a New Structural Class of Respiratory Syncytial Virus Inhibitor

Kuo-Long Yu,[a] Yi Zhang,[a] Rita L. Civiello,[a] Kathleen F. Kadow,[b] Christopher Cianci,[b] Mark Krystal[b] and Nicholas A. Meanwell[a,*]

[a]*Department of Chemistry, The Bristol-Myers Squibb Pharmaceutical Research Institute, 5, Research Parkway, Wallingford, CT 06492, USA*
[b]*Department of Virology, The Bristol-Myers Squibb Pharmaceutical Research Institute, 5, Research Parkway, Wallingford, CT 06492, USA*

Structure–activity relationships surrounding the dialkylamino side chain of a series of benzotriazole-derived inhibitors of respiratory syncytial virus fusion based on the screening lead **1a** were examined. The results indicate that the topology of the side chain is important but the terminus element offers considerable latitude to modulate physical properties.



1a

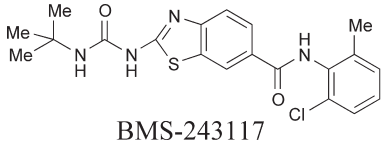
Bioorg. Med. Chem. Lett. 13 (2003) 2145

Molecular Design, Synthesis, and Structure–Activity Relationships Leading to the Potent and Selective P56^{lck} Inhibitor BMS-243117

Jagabandhu Das,* James Lin, Robert V. Moquin, Zhongqi Shen, Steven H. Spergel, John Wityak, Arthur M. Doweyko, Henry F. DeFex, Qiong Fang, Suhong Pang, Sidney Pitt, Ding Ren Shen, Gary L. Schieven and Joel C. Barrish

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

A series of structurally novel benzothiazole based small molecule inhibitors of p56^{lck} was prepared to elucidate their structure–activity relationships (SARs), selectivity, and cell activity in the T-cell proliferation assay. BMS-243117 is identified as a potent and selective Lck inhibitor with good cellular activity against T-cell proliferation.



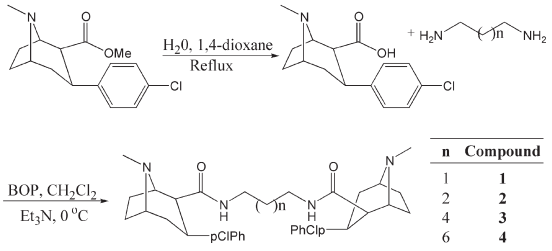
BMS-243117

Bioorg. Med. Chem. Lett. 13 (2003) 2151

Bivalent Biogenic Amine Reuptake Inhibitors

Keith Fandrick,[a] Xianqi Feng,[a] Aaron Janowsky,[b] Robert Johnson[b] and John R. Cashman[a,*]

[a]*Human BioMolecular Research Institute, 5310 Eastgate Mall, San Diego, CA 92121, USA*
[b]*Veterans Administration Hospital, Portland, OR 97201, USA*



n	Compound
1	**1**
2	**2**
4	**3**
6	**4**

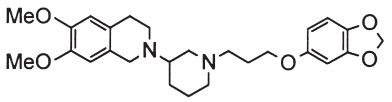
Bioorg. Med. Chem. Lett. 13 (2003) 2155

(±)-2-(3-Piperidyl)-1,2,3,4-tetrahydroisoquinolines as a New Class of Specific Bradycardic Agents

Hideki Kubota, Akio Kakefuda,* Toshihiro Watanabe, Yasuko Taguchi, Noe Ishii, Noriyuki Masuda, Shuichi Sakamoto and Shin-ichi Tsukamoto

Institute for Drug Discovery Research, Yamanouchi Pharmaceutical Co. Ltd., 21 Miyukigaoka, Tsukuba, Ibaraki 305-8585, Japan

A series of (±)-2-(3-piperidyl)-1,2,3,4-tetrahydroisoquinolines were prepared and their bradycardic activities were examined. Modifications on the benzyl moiety of the parent compound, **1**, led to the identification of compound **11e** as a potent and specific bradycardic agent.



11e

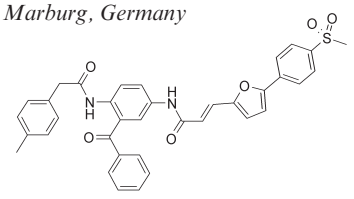
Bioorg. Med. Chem. Lett. 13 (2003) 2159

Structure–Activity Relationships of Novel Anti-Malarial Agents. Part 7: *N*-(3-Benzoyl-4-tolylacetylaminophenyl)-3-(5-aryl-2-furyl)acrylic Acid Amides with Polar Moieties

Jochen Wiesner,[c] Andreas Mitsch,[b] Hassan Jomaa[c] and Martin Schlitzer[a,*]

[a]*Department für Pharmazie, Zentrum für Pharmaforschung, Ludwig-Maximilians-Universität München, Butenandtstraße 5-13, D-81377 München, Germany*
[b]*Institut für Pharmazeutische Chemie, Philipps-Universität Marburg, Marbacher Weg 6, D-35032 Marburg, Germany*
[c]*Biochemisches Institut der Universität Gießen, Friedrichstraße 24, D-35249 Gießen, Germany*

We have described evidence that novel anti-malarial compounds based on 2,5-diaminobenzophenone farnesyltransferase inhibitors might benefit from the presence of a polar moiety with hydrogen bond acceptor properties at the arylfurylacryloyl partial structure. Here, we demonstrate that several moieties with hydrogen bond acceptor properties lead to improved anti-malarial activity in comparison to the nitro group described before.



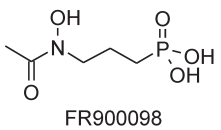
Bioorg. Med. Chem. Lett. 13 (2003) 2163

Acyloxyalkyl Ester Prodrugs of FR900098 with Improved In Vivo Anti-Malarial Activity

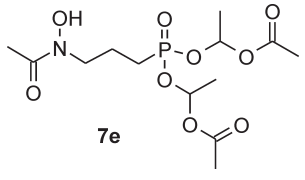
Regina Ortmann,[a] Jochen Wiesner,[b] Armin Reichenberg,[b] Dajana Henschker,[b] Ewald Beck,[b] Hassan Jomaa[b] and Martin Schlitzer[a,*]

[a]*Department für Pharmazie, Ludwig-Maximilians-Universität München, Butenandtstraße 5-13, D-81377 München, Germany*
[b]*Biochemisches Institut, Justus-Liebig-Universität Gießen, Friedrichstrasse 24, D-35392 Gießen, Germany*

FR900098, an inhibitor of 1-deoxy-D-xylulose 5-phosphate (DOXP) reductoisomerase, with increased efficacy in a murine malaria model is reported.



FR900098



7e

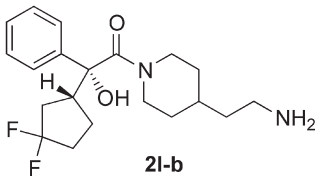
Bioorg. Med. Chem. Lett. 13 (2003) 2167

Muscarinic M_3 Receptor Antagonists with (2*R*)-2-[(1*R*)-3,3-Difluorocyclopentyl]-2-hydroxyphenylacetamide Structures. Part 2

Yoshio Ogino, Norikazu Ohtake,* Kensuke Kobayashi, Toshifumi Kimura, Toru Fujikawa, Takuro Hasegawa, Kazuhito Noguchi and Toshiaki Mase

Banyu Tsukuba Research Institute in collaboration with Merck Research Laboratories, Okubo-3, Tsukuba 300-2611, Ibaraki, Japan

A potent and orally bioavailable, M_2 sparing M_3 antagonist (**2l–b**) was identified by extensive modification of the amine part of (2*R*)-2-[(1*R*)-3,3-difluorocyclopentyl]-2-hydroxyphenylacetamide structures.



2l-b

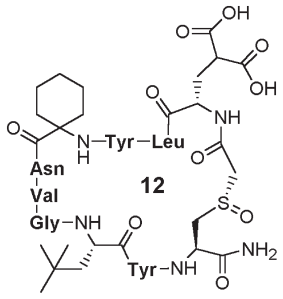
Bioorg. Med. Chem. Lett. 13 (2003) 2173

Potent Grb2–SH2 Domain Antagonists not Relying on Phosphotyrosine Mimics

Peng Li,[a] Manchao Zhang,[b] Ya-Qiu Long,[a] Megan L. Peach,[a] Hongpeng Liu,[b] Dajun Yang,[b] Marc Nicklaus[a] and Peter P. Roller[a,*]

[a]*Laboratory of Medicinal Chemistry, National Cancer Institute, National Institutes of Health, Frederick, MD 21702, USA*
[b]*School of Medicine, University of Michigan, Ann Arbor, MI 48109, USA*

Highly potent Grb2–SH2 domain antagonists were discovered by peptidomimetic modifications of the phage library-derived peptide **G1TE**. These agents circumvent the need for pTyr or pTyr mimics and exhibit high potency, such as ligand **12** ($IC_{50} = 75$ nM).



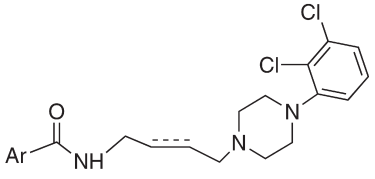
12

Bioorg. Med. Chem. Lett. 13 (2003) 2179

N-{4-[4-(2,3-Dichlorophenyl)piperazin-1-yl]butyl, Butenyl and Butynyl}arylcarboxamides as Novel Dopamine D_3 Receptor Antagonists

Amy Hauck Newman,[a,*] Jianjing Cao,[a] Christina J. Bennett,[a] Michael J. Robarge,[a] Rebekah A. Freeman[b] and Robert R. Luedtke[b]

[a]*Medicinal Chemistry Section, National Institute on Drug Abuse-Intramural Research Program, Baltimore, MD 21224, USA*
[b]*Department of Pharmacology and Neurosciences, University of North Texas Health Science Center, Fort Worth, TX 76107, USA*



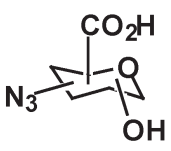
Bioorg. Med. Chem. Lett. 13 (2003) 2185

3-Azido-3-deoxy-glycopyranoside Derivatives as Scaffolds for the Synthesis of Carbohydrate-Based Universal Pharmacophore Mapping Libraries

Rakesh Jain, Muthoni Kamau, Chunguang Wang, Robert Ippolito, Huiming Wang, Richard Dulina, Jan Anderson, David Gange and Michael J. Sofia*

Intercardia Research Labs, 8 Cedar Brooke Drive, Cranbury, NJ 08512, USA

Six scaffolds, **1**–**6**, were prepared for use in generating combinatorial libraries. Each scaffold contains three sites for introducing chemical diversity, a carboxylic acid, a free hydroxyl group and azido group.



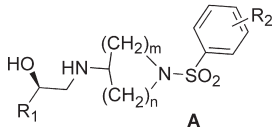
Bioorg. Med. Chem. Lett. 13 (2003) 2191

Cyclic Amine Sulfonamides as Linkers in the Design and Synthesis of Novel Human β_3 Adrenergic Receptor Agonists

Fuk-Wah Sum,[a,*] Victoria Wong,[a] Stella Han,[b] Elwood Largis,[b] Ruth Mulvey[b] and Jeff Tillett[b]

[a]*Chemical Sciences, Wyeth Research, Pearl River, NY 10965, USA*
[b]*Cardiovascular and Metabolic Diseases Research, Wyeth Research, Princeton, NJ 08543, USA*

Compounds A containing piperidine ($m=2$, $n=2$), pyrrolidine ($m=2$, $n=1$), and azetidine ($m=1$, $n=1$) sulfonamides as linkers were designed as novel human β_3 adrenergic receptor (β_3-AR) agonists. Several derivatives have been discovered to possess potent β_3-AR activity and good selectivity against β_1- and β_2-AR.



A

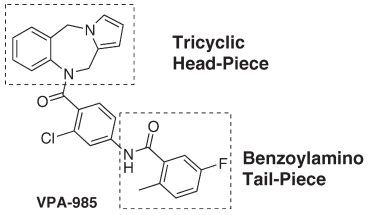
Bioorg. Med. Chem. Lett. 13 (2003) 2195

Structure–Activity Study of Novel Tricyclic Benzazepine Arginine Vasopressin Antagonists

Fuk-Wah Sum,[a,*] John Dusza,[a] Efren Delos Santos,[a] George Grosu,[a] Marvin Reich,[a] Xumei Du,[a] J. Donald Albright,[a] Peter Chan,[b] Joseph Coupet,[b] Xun Ru,[b] Hossein Mazandarani[b] and Trina Saunders[b]

[a]*Chemical Sciences, Wyeth Research, Pearl River, NY 10965, USA*
[b]*Cardiovascular and Metabolic Diseases Research, Wyeth Research, Princeton, NJ 08543, USA*

Novel tricyclic benzazepine derivatives based on modifications of VPA-985, an orally active arginine vasopressin (AVP) antagonist, have been designed and synthesized. Potent AVP antagonists of the rat V_{1a} and V_2 receptors were discovered.



VPA-985

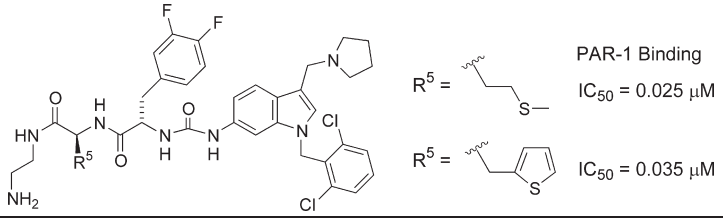
Bioorg. Med. Chem. Lett. 13 (2003) 2199

High-Affinity Thrombin Receptor (PAR-1) Ligands: A New Generation of Indole-Based Peptide Mimetic Antagonists with a Basic Amine at the C-terminus

Han-Cheng Zhang,* Kimberly B. White, David F. McComsey, Michael F. Addo, Patricia Andrade-Gordon, Claudia K. Derian, Donna Oksenberg and Bruce E. Maryanoff*

Drug Discovery, Johnson & Johnson Pharmaceutical Research & Development, Spring House, PA 19477-0776, USA

Indole-based peptide mimetics with a basic amine at the C-terminus were produced by new trityl resin-based methods and found to be excellent PAR-1 antagonists.



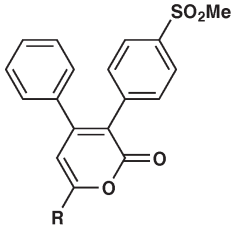
Bioorg. Med. Chem. Lett. 13 (2003) 2205

6-Alkyl, Alkoxy, or Alkylthio-Substituted 3-(4-Methanesulfonylphenyl)-4-phenylpyran-2-ones: A Novel Class of Diarylheterocyclic Selective Cyclooxygenase-2 Inhibitors

P. N. Praveen Rao, Mohsen Amini, Huiying Li, Amgad G. Habeeb and Edward E. Knaus*

Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Alberta, Canada T6G 2N8

Design, synthesis, and evaluation of a novel class of diarylheterocycles as selective cyclooxygenase-2 inhibitors (**10a**–**c**, **11a**–**c** and **12a**–**c**) are described.



10a-c, R = Me, Et, *i*-Pr
11a-c, R = OMe, OEt, O-*i*-Pr
12a-c, R = SMe, SEt, S-*i*-Pr

Bioorg. Med. Chem. Lett. 13 (2003) 2211

4-Amino-2-(aryl)-butylbenzamides and their Conformationally Constrained Analogues. Potent Antagonists of the Human Neurokinin-2 (NK_2) Receptor

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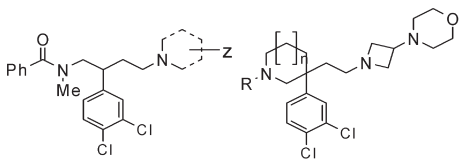
Two series of potent neurokinin-2 antagonists (**1**) and (**2**) are described.



(1)
Z = mono-or bicyclic ring

(2)
R = acyl or sulphonyl,
n = 1, 0

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Synthesis of Radiolabeled Biphenylsulfonamide Matrix Metalloproteinase Inhibitors as New Potential PET Cancer Imaging Agents

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1

1a, X=2-OMe
1b, X=3-OMe
1c, X=4-OMe
1d, X=2-F
1e, X=3-F
1f, X=4-F
1g, X=4-NO_2

Bioorg. Med. Chem. Lett. 13 (2003) 2223

Antitumor Agents. Part 218: Cappamensin A, a New In Vitro Anticancer Principle, from *Capparis sikkimensis*

Jiu-Hong Wu,[a] Fang-Rong Chang,[a] Ken-ichiro Hayashi,[a] Hiroaki Shiraki,[a] Chih-Chuang Liaw,[a] Yuka Nakanishi,[a] Kenneth F. Bastow,[a] Donglei Yu,[a] Ih-Sheng Chen[b] and Kuo-Hsiung Lee[a,*]

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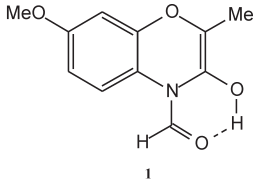
A novel inhibitor of in vitro tumor cell growth replication, cappamensin A (**1**), 3-hydroxy-7-methoxy-2-methylbenzo [6] morpholine-4-carbaldehyde, was isolated from the roots of *Capparis sikkimensis* subsp. *formosana* using bioactivity-guided fractionation.



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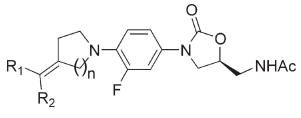
Bioorg. Med. Chem. Lett. 13 (2003) 2227

Synthesis and In Vitro Activity of New Methylenepiperidinyl and Methylenepyrrolidinyl Oxazolidinone Antibacterial Agents

Hye Yeon Kim, Jae Seok Lee, Joo Hwan Cha, Ae Nim Pae, Yong Seo Cho, Moon Ho Chang and Hun Yeong Koh*

Biochemicals Research Center, Korea Institute of Science and Technology, Cheongryang, Seoul 130-650, South Korea

We have prepared and evaluated the antibacterial activities of a series of substituted methylenepiperidinyl and methylenepyrrolidinyl oxazolidinones against several gram-positive strains including the resistant strains of Staphyloccus and Enterococcus, such as MRSA, CRSA, MSSA and VRE.



5. n = 1
6. n = 2

Bioorg. Med. Chem. Lett. 13 (2003) 2231

Discovery of a Potent and Selective Series of Pyrazole Bacterial Methionyl-tRNA Synthetase Inhibitors

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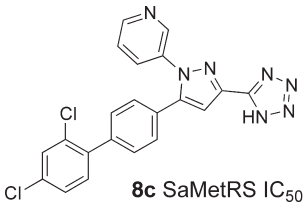
Starting with a micromolar lead identified from high-throughput screening, a series of pyrazoles were discovered with significantly improved potency on bacterial methionyl-tRNA synthetase and selectivity over human methionyl-tRNA synthetase.



Bioorg. Med. Chem. Lett. 13 (2003) 2235

Borrelidin Induces the Transcription of Amino Acid Biosynthetic Enzymes Via a *GCN4*-Dependent Pathway

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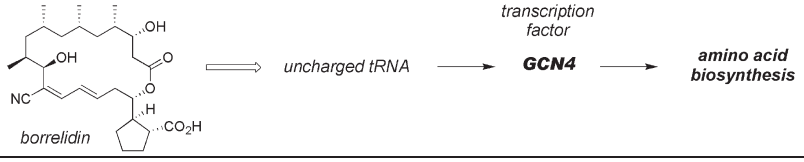
Global cellular profiling of messenger RNA levels has been used to provide insight into the effects of borrelidin on the eukaryotic model organism *Saccharomyces cerevisiae*. The most notable result of treatment with borrelidin is the induction of amino acid biosynthetic enzymes in a time-dependent fashion. We have ascertained that induction of this pathway involves the *GCN4* transcription factor. This conclusion was determined by treating a yeast strain lacking this gene and observing the absence of increased gene transcription under Gcn4p control.



Bioorg. Med. Chem. Lett. 13 (2003) 2239

Enantiotracin

Patrick G. McDougal and John H. Griffin*

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The enantiomer of the antibiotic bacitracin A was prepared by solid-phase total synthesis. *ent*-Bacitracin A was found to be equally potent to the natural enantiomer in in vitro susceptibility assays. This supports the notion that bacitracin exerts its antibacterial effects through interaction with bactoprenylpyrophosphate, an achiral ligand.