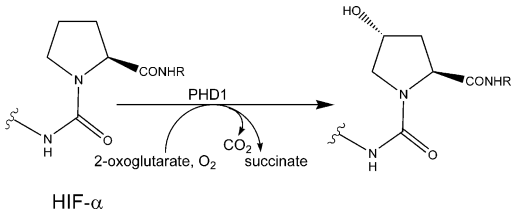
Graphical Abstracts

The Use of Dioxygen by HIF Prolyl Hydroxylase (PHD1)

Bioorg. Med. Chem. Lett. 12 (2002) 1547

Luke A. McNeill,[a] Kirsty S. Hewitson,[a] Jonathan M. Gleadle,[b] Louise E. Horsfall,[a] Neil J. Oldham,[a] Patrick H. Maxwell,[b,*] Christopher W. Pugh,[b,*] Peter J. Ratcliffe[b,*] and Christopher J. Schofield[a,*]

[a]*Oxford Centre for Molecular Sciences, Dyson Perrins Laboratory, South Parks Road, Oxford OX1 3QY, UK*
[b]*Wellcome Trust Centre for Human Genetics, Roosevelt Drive, Oxford OX3 7BN, UK*

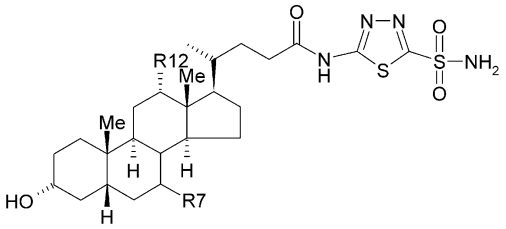


Carbonic Anhydrase Inhibitors. Preparation of Potent Sulfonamides Inhibitors Incorporating Bile Acid Tails

Bioorg. Med. Chem. Lett. 12 (2002) 1551

Andrea Scozzafava and Claudiu T. Supuran*

Università degli Studi di Firenze, Dipartimento di Chimica, Laboratorio di Chimica Bioinorganica, Rm. 188, Via della Lastruccia 3, I-50019 Sesto Fiorentino, Firenze, Italy



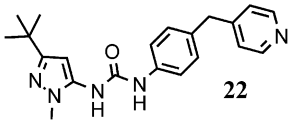
Synthesis and Pharmacological Characterization of a Potent, Orally Active p38 Kinase Inhibitor

Bioorg. Med. Chem. Lett. 12 (2002) 1559

Jacques Dumas,[a,*] Holia Hatoum-Mokdad,[a] Robert N. Sibley,[a] Roger A. Smith,[a] William J. Scott,[a] Uday Khire,[a] Wendy Lee,[a] Jill Wood,[a] Donald Wolanin,[a] Jeffrey Cooley,[a] Donald Bankston,[a] Aniko M. Redman,[a] Robert Schoenleber,[a] Yolanda Caringal,[a] David Gunn,[a] Romulo Romero,[a] Martin Osterhout,[a] Holger Paulsen,[a] Timothy J. Housley,[b] Scott M. Wilhelm,[b] John Pirro,[c] Du-Shieng Chien,[c] Gerald E. Ranges,[b] Alka Shrikhande,[b] Andrew Muzsi,[b] Elizabeth Bortolon,[b] Jean Wakefield,[b] Cynthia Gianpaolo Ostravage,[b] Ajay Bhargava[b] and Thuy Chau[b]

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

Pyrazolyl urea **22** is a potent and selective p38 kinase inhibitor in biochemical and cellular assays. This compound is orally active in two acute models of cytokine release and a chronic model of arthritis (murine collagen induced arthritis).



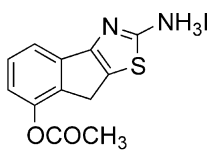
2-Aminothiazoles: A New Class of Agonist Allosteric Enhancers of A_1 Adenosine Receptors

Bioorg. Med. Chem. Lett. 12 (2002) 1563

Mahendra D. Chordia,[a,*] Lauren J. Murphree,[b] Timothy L. Macdonald,[a] Joel Linden[c] and Ray A. Olsson[a]

[a]*Department of Chemistry, University of Virginia, Charlottesville, VA 22901, USA*
[b]*Department of Pharmacology, University of Virginia, Charlottesville, VA 22901, USA*
[c]*Department of Medicine (Cardiology), University of Virginia, Charlottesville, VA 22901, USA*

Synthesis and biological activities of 2-aminothiazole derivatives as an allosteric enhancer for A1 adenosine receptor are reported.



6a EC_{50} = 0.3 μM

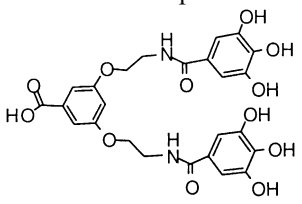
Bioorg. Med. Chem. Lett. 12 (2002) 1567

Synthesis and Biological Activity of Polygalloyl-Dendrimers as Stable Tannic Acid Mimics

S. Bart A. Halkes, Ioannis Vrasidas, Gilbert R. Rooijer, Albert J. J. van den Berg, Rob M. J. Liskamp and Roland J. Pieters*

Department of Medicinal Chemistry, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, PO Box 80082, 3508 TB Utrecht, The Netherlands

Dendrimers containing 2, 4, and 8 galloyl units were prepared and shown to be stable tannic acid mimics. They were tested for anti-oxidant activity and collagen cross-linking abilities.



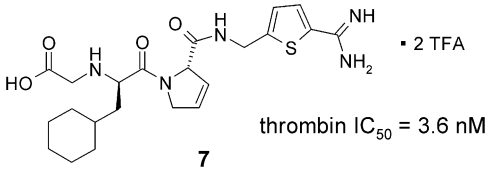
Bioorg. Med. Chem. Lett. 12 (2002) 1571

Solid-Phase Synthesis of Thrombin Inhibitors

Udo E. W. Lange and Christian Zechel*

BASF AG, D-67056 Ludwigshafen, Germany

The convergent solid-phase synthesis of thrombin inhibitors is reported. This synthesis permits the efficient generation of inhibitor libraries to optimize potency and selectivity.



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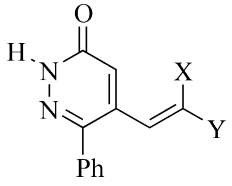
Bioorg. Med. Chem. Lett. 12 (2002) 1575

Pyridazines. Part 28: 5-Alkylidene-6-phenyl-3(2*H*)-pyridazinones, a New Family of Platelet Aggregation Inhibitors

Eddy Sotelo,[a] Nuria Fraiz,[b] Matilde Yáñez,[b] Reyes Laguna,[b] Ernesto Cano,[b] José Brea[b] and Enrique Raviña[a,*]

[a]*Departamento de Química Orgánica, Laboratorio de Química Farmacéutica, Universidad de Santiago de Compostela, 15782-Santiago de Compostela, Spain*
[b]*Departamento de Farmacología, Facultad de Farmacia, Universidad de Santiago de Compostela, 15782-Santiago de Compostela, Spain*

The synthesis and anti-platelet activities of several 5-alkylidene-6-phenyl-3(2*H*)-pyridazinones are described. The most active compounds are those that contain oxygenated functions (COOR, COMe) on the alkylidene fragment (**6a**, **6b**, and **6c**).



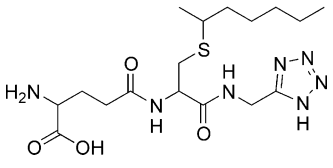
Bioorg. Med. Chem. Lett. 12 (2002) 1579

Inhibition of Glutathione *S*-Transferase in Rat Hepatocytes by a Glycine-Tetrazole Modified *S*-alkyl–GSH Analogue

Danny Burg,[a,*] Liesbeth Hameetman,[a] Dmitri V. Filippov,[b] Gijs A. van der Marel[b] and Gerard J. Mulder[a]

[a]*Division of Toxicology, Leiden/Amsterdam Center for Drug Research, Leiden University, PO Box 9502, 2300RA, Leiden, The Netherlands*
[b]*Division of Bio-Organic Synthesis, Leiden Institute of Chemistry, Leiden University, PO Box 9502, 2300RA, Leiden, The Netherlands*

The synthesis and evaluation of a novel tetrazoyl-modified GSH-conjugate analogue is reported.



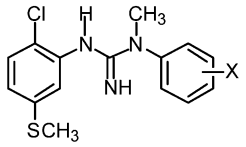
Bioorg. Med. Chem. Lett. 12 (2002) 1583

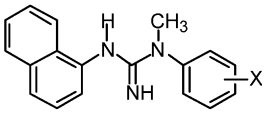
Synthesis and In Vitro Evaluation of *N*,*N*′-Diphenyl and *N*-Naphthyl-*N*′-phenylguanidines as *N*-Methyl-D-aspartate Receptor Ion-channel Ligands

Filip Dumont,* Abida Sultana and Rikki N. Waterhouse

Division of Functional Brain Mapping, Columbia University, 1051 Riverside Drive, New York, NY 10032, USA

A series of *N*,*N*′-diphenyl and *N*-naphthyl-*N*′-phenyl guanidine derivatives was synthesized as potential positron emission tomography (PET) ligands for the PCP site of the NMDA receptor. The affinity of the compounds was determined using in vitro receptor binding assays, and their log P values were estimated using HPLC analysis.





Bioorg. Med. Chem. Lett. 12 (2002) 1587

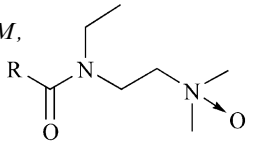
Synthesis and Preliminary Biochemical Assessment of Ethyl-Terminated Perfluoroalkylamine Oxide Surfactants

Yann Chaudier,[a] Francesca Zito,[b] Philippe Barthélémy,[a] David Stroebel,[b] Bruno Améduri,[c] Jean-Luc Popot[b,*] and Bernard Pucci[a,*]

[a]*Laboratoire de Chimie Bioorganique et des Systèmes Moléculaires Vectoriels, Faculté des Sciences, Université d'Avignon, 33 rue Louis Pasteur, F-84000 Avignon, France.* [b]*Laboratoire de Physico-Chimie Moléculaire des Membranes Biologiques, CNRS and Université Paris-7, UMR 7099, Institut de Biologie Physico-Chimique, 13 rue Pierre et Marie Curie, F-75005 Paris, France*

[c]*Laboratoire de Chimie Macromoléculaire, UMR CNRS 5076, ENSCM, 8 rue de l'Ecole Normale, F-34296 Montpellier Cedex 5, France*

The synthesis of ethyl-terminated perfluoroalkylamine oxide surfactants is reported. The efficiency of these new surfactants in maintaining membrane proteins soluble in aqueous solution was assayed.



R = $C_{11}H_{23}$-
$C_6F_{13}CH_2CH_2$-
$C_8F_{17}CH_2CH_2$-
$CH_3CH_2C_6F_{12}CH_2CH_2$-

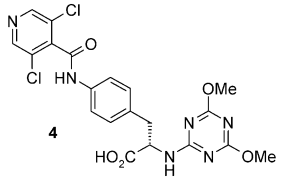
Bioorg. Med. Chem. Lett. 12 (2002) 1591

Discovery and Evaluation of *N*-(triazin-1,3,5-yl) Phenylalanine Derivatives as VLA-4 Integrin Antagonists

John R. Porter,* Sarah C. Archibald, Julien A. Brown, Kirstie Childs, David Critchley, John C. Head, Brian Hutchinson, Ted A. H. Parton, Martyn K. Robinson, Anthony Shock, Graham J. Warrellow and Alex Zomaya

Celltech R&D Ltd, 216 Bath Road, Slough SL1 4EN, UK

A series of triazinyl derivatives, such as **4**, that block the interaction of VLA-4 integrin with VCAM-1 are described.



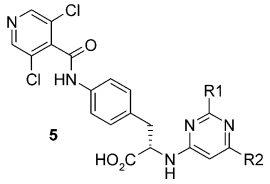
Bioorg. Med. Chem. Lett. 12 (2002) 1595

N-(Pyrimidin-4-yl) and *N*-(Pyridin-2-yl) Phenylalanine Derivatives as VLA-4 Integrin Antagonists

John R. Porter,* Sarah C. Archibald, Julien A. Brown, Kirstie Childs, David Critchley, John C. Head, Brian Hutchinson, Ted A. H. Parton, Martyn K. Robinson, Anthony Shock, Graham J. Warrellow and Alex Zomaya

Celltech R&D Ltd, 216 Bath Road, Slough SL1 4EN, UK

A series of pyridinyl and pyrimidyl analogues, such as **5**, that block the interaction of VLA-4 integrin with VCAM-1 are described.



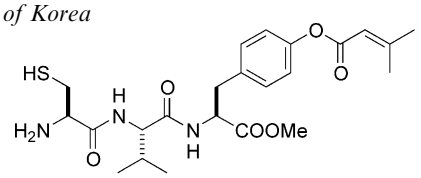
Bioorg. Med. Chem. Lett. 12 (2002) 1599

Development of Tripeptidyl Farnesyltransferase Inhibitors

Hee-Yoon Lee,[a,*] Jeong-Hun Sohn[a] and Byoung-Mog Kwon[b]

[a]*Center for Molecular Design and Synthesis, Department of Chemistry and School of Molecular Science(BK21), Korea Advanced Institute of Science and Technology, Daejon 305-701, Republic of Korea*
[b]*Korea Research Institute of Bioscience and Biotechnology, Daejon 305-333, Republic of Korea*

The first example of tripeptide inhibitors of farnesyltransferase with sub-micromolar inhibition activity was developed based on the fact that CVFM is not a substrate for farnesyltransferase.



Y$_3$ IC_{50} = 0.5 μM

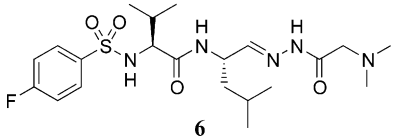
Bioorg. Med. Chem. Lett. 12 (2002) 1603

Exploration of Peptidyl Hydrazones as Water-Soluble Calpain Inhibitors

Masayuki Nakamura* and Jun Inoue

Research Laboratory, Senju Pharmaceutical Co., Ltd., 1-5-4 Murotani Nishiku, Kobe 651-2241, Japan

N,N-Dimethyl glycyl hydrazone **6** is a potent calpain inhibitor which possesses appropriate water-solubility and excellent in vitro metabolic stability.



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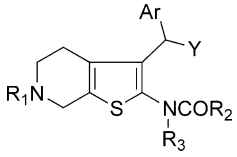
Bioorg. Med. Chem. Lett. 12 (2002) 1607

Synthesis and Bioactivities of Novel 4,5,6,7-Tetrahydrothieno[2,3-*c*]pyridines as Inhibitors of Tumor Necrosis Factor-α (TNF-α) Production

Masakazu Fujita,* Taketsugu Seki, Haruaki Inada and Naoko Ikeda

Omiya Research Laboratory, Nikken Chemicals Co., Ltd., 1-346, Kitabukuro-cho, Saitama-shi, Saitama 330-0835, Japan

Novel 4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine derivatives were synthesized and evaluated for their abilities to inhibit lipopolysaccharide (LPS)-stimulated production of TNF-α in rat whole blood. Several of these compounds exhibited potent inhibitory activity.



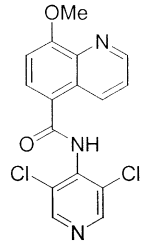
Bioorg. Med. Chem. Lett. 12 (2002) 1613

8-Methoxyquinoline-5-carboxamides as PDE4 Inhibitors: A Potential Treatment for Asthma

George M. Buckley,[a] Nicola Cooper,[a] Hazel J. Dyke,[a] Fiona P. Galleway,[a] Lewis Gowers,[a] Alan F. Haughan,[a] Hannah J. Kendall,[a] Christopher Lowe,[a] Robert Maxey,[a] John G. Montana,[a] Robert Naylor,[b] Janet Oxford,[a] Joanna C. Peake,[a] C. Louise Picken,[a] Karen A. Runcie,[a] Verity Sabin,[a] Andrew Sharpe[a,*] and Julie B. H. Warneck[a]

[a]*Celltech R&D, Granta Park, Great Abington, Cambridge CB1 6GS, UK*
[b]*Department of Pharmacology, University of Bradford, Bradford BD7 1DP, UK*

A series of bicyclic heteroaryl ring systems was considered as a replacement for the 3-cyclopentyloxy-4-methoxyphenyl moiety in rolipram resulting in the discovery of 8-methoxyquinoline-5-carboxamides as potent inhibitors of phosphodiesterase 4.



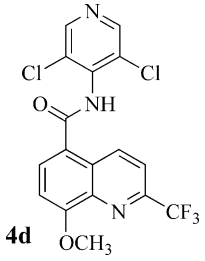
Bioorg. Med. Chem. Lett. 12 (2002) 1617

8-Methoxyquinolines as PDE4 Inhibitors

Motasim Billah,[c] George M. Buckley,[a] Nicola Cooper,[a] Hazel J. Dyke,[a] Robert Egan,[c] Ashit Ganguly,[c] Lewis Gowers,[a] Alan F. Haughan,[a] Hannah J. Kendall,[a] Christopher Lowe,[a] Michael Minnicozzi,[c] John G. Montana,[a] Janet Oxford,[a] Joanna C. Peake,[a] C. Louise Picken,[a] John J. Piwinski,[c] Robert Naylor,[b] Verity Sabin,[a,*] Neng-Yang Shih[c] and Julie B. H. Warneck[a]

[a]*Celltech Group plc, Granta Park, Abington, Cambridge CB1 6GS, UK*
[b]*Dept. of Pharmacology, University of Bradford, Bradford BD7 1DP, UK*
[c]*Schering-Plough Corporation, Galloping Hill Road, Kenilworth, NJ 07033-0530, USA*

The synthesis and pharmacological profile of a novel series of 2-substituted 8-methoxyquinolines is described. **4d** was found to be a potent inhibitor of PDE4.



4d

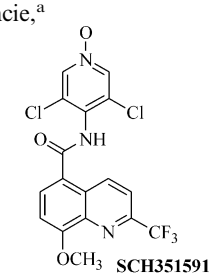
Bioorg. Med. Chem. Lett. 12 (2002) 1621

Synthesis and Profile of SCH351591, a Novel PDE4 Inhibitor

Motasim Billah,[c] Nicola Cooper,[a] Francis Cuss,[c] Richard J. Davenport,[a] Hazel J. Dyke,[a] Robert Egan,[c] Ashit Ganguly,[c] Lewis Gowers,[a] Duncan R. Hannah,[a] Alan F. Haughan,[a] Hannah J. Kendall,[a] Christopher Lowe,[a] Michael Minnicozzi,[c] John G. Montana,[a] Robert Naylor,[b] Janet Oxford,[a] Joanna C. Peake,[a] John J. Piwinski,[c] Karen A. Runcie,[a] Verity Sabin,[a,*] Andrew Sharpe,[a] Neng-Yang Shih[c] and Julie B. H. Warneck[a]

[a]*Celltech Group plc, Granta Park, Abington, Cambridge CB1 6GS, UK*
[b]*Department of Pharmacology, University of Bradford, Bradford BD7 1DP, UK*
[c]*Schering-Plough Corporation, Galloping Hill Road, Kenilworth, NJ 07033-0530, USA*

The syntheses and pharmacological profiles of some 2-trifluoromethyl-8-methoxyquinoline-5-carboxamides are described. **SCH351591** is a potent selective inhibitor of PDE4.



SCH351591

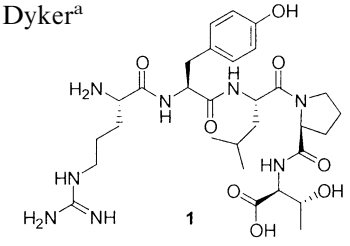
Bioorg. Med. Chem. Lett. 12 (2002) 1625

Syntheses of Depsipeptide Analogues of the Insect Neuropeptide Proctolin

Jürgen Scherkenbeck,[a,*] Andrew Plant,[a] Frank Stieber,[b] Peter Lösel[a] and Hubert Dyker[a]

[a]*Bayer AG, Central Research, 51368 Leverkusen, Germany*
[b]*Department of Chemistry, University of Dortmund, Germany*

Four depsipeptide analogues of the insect neuropeptide proctolin **1** have been prepared, containing a single ester linkage between Arg[1] and Tyr[2], Tyr[2] and Leu[3], and between Pro[4] and Thr[5], respectively. A didepsipentapeptide containing an ester linkage between Tyr[2] and Leu[3] and between Pro[4] and Thr[5], has also been prepared. The depsipeptide H-Arg-Tyr-Leu-Pro-ψ[CO–O]-Thr-OH (**4**) is the first example of a backbone-modified proctolin analogue which shows full myotropic activity.



1

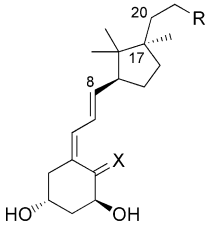
Bioorg. Med. Chem. Lett. 12 (2002) 1629

Vitamin D_3: Synthesis of *seco* C-9,11,21-*trisnor*-17-Methyl-1α, 25-dihydroxyvitamin D_3 Analogues

Yusheng Wu,[a] Katrien Sabbe,[a] Pierre De Clercq,[a] Maurits Vandewalle,[a,*] Roger Bouillon[b] and Annemieke Verstuyf[b]

[a]*Ghent University, Department of Organic Chemistry, Laboratory for Organic Synthesis, Krijgslaan 281 S4, B-9000 Gent, Belgium*
[b]*Laboratorium voor Experimentele Geneeskunde en Endocrinologie, K.U. Leuven, Onderwijs en Navorsing Gasthuisberg, Herestraat 49, B-3030 Leuven, Belgium*

The synthesis and biological activities of *seco* C-9,11,21-*trisnor*-17-methyl-1α,25-dihydroxyvitamin D_3 analogues (D-ring analogues) are described.



3 X = CH_2
4 X = H_2

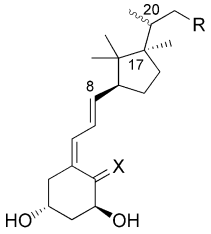
Bioorg. Med. Chem. Lett. 12 (2002) 1633

Vitamin D_3: Synthesis of *seco*-C-9,11-*bisnor*-17-Methyl-1α, 25-dihydroxyvitamin D_3 Analogues

Yusheng Wu,[a] Pierre De Clercq,[a] Maurits Vandewalle,[a,*] Roger Bouillon[b] and Annemieke Verstuyf[b]

[a]*Ghent University, Department of Organic Chemistry, Laboratory for Organic Synthesis, Krijgslaan 281 S4, B-9000 Gent, Belgium*
[b]*Laboratorium voor Experimentele Geneeskunde en Endocrinologie, K.U. Leuven, Onderwijs en Navorsing Gasthuisberg, Herestraat 49, B-3030 Leuven, Belgium*

The synthesis and biological properties of *seco*-C-9,11-bisnor-17-methyl-1α,25-dihydroxyvitamin D_3 novel D-ring analogues are described.



3 X = CH_2
4 X = H_2

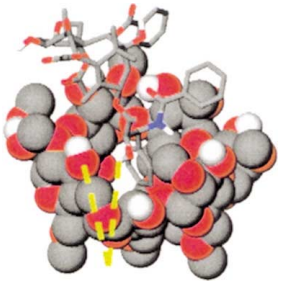
Bioorg. Med. Chem. Lett. 12 (2002) 1637

Preparation, Characterization, Molecular Modeling and In Vitro Activity of Paclitaxel–Cyclodextrin Complexes

Stefano Alcaro,[a] Cinzia Anna Ventura,[b] Donatella Paolino,[c] Danilo Battaglia,[a] Francesco Ortuso,[a] Luigi Cattel,[d] Giovanni Puglisi[c] and Massimo Fresta[a,*]

[a]*Department of Pharmacobiological Sciences, University 'Magna Græcia' of Catanzaro, Complesso 'Ninì Barbieri', I-88021 Roccelletta di Borgia (CZ), Italy*
[b]*Pharmaco-Chemical Department, University of Messina, Viale Annunziata, I-98168 Messina, Italy*
[c]*Department of Pharmaceutical Sciences, University of Catania, Viale Andrea Doria n. 6, I-95125 Catania, Italy*
[d]*Department of Drug Science and Technology, University of Torino, Via P. Giucia 9, I-10125 Turin, Italy*

Paclitaxel (**PTX**) was complexed with β-cyclodextrin (**1**), 2,6-dimethyl-β-cyclodextrin (**2**) and 2,3,6-trimethyl-β-cyclodextrin (**3**). **PTX**–CYD complexes were characterized both at the solid and liquid state. Experimental findings are in agreement with molecular modeling analysis, which showed different **PTX**–CYD interaction as a function of macrocyle methylation. The complexation of **PTX** within CYD cavity preserved the antitumoral activity.

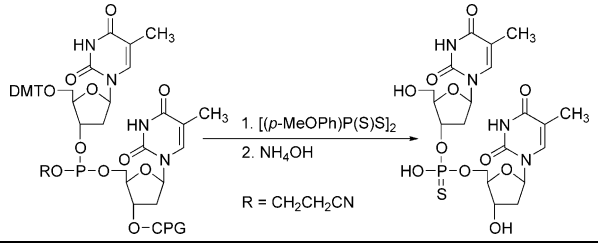


Bioorg. Med. Chem. Lett. 12 (2002) 1643

Synthesis of Oligodeoxyribonucleoside Phosphorothioates Using Lawesson's Reagent for the Sulfur Transfer Step

Jingyue Ju and Charles E. McKenna

Department of Chemistry, University of Southern California, Los Angeles, CA 90089-0744, USA



Bioorg. Med. Chem. Lett. 12 (2002) 1647

Drugs, Leads, and Drug-Likeness: An Analysis of Some Recently Launched Drugs

John R. Proudfoot*

Boehringer Ingelheim Pharmaceuticals Inc., Department of Medicinal Chemistry, 900 Ridgebury Road, PO Box 368, Ridgefield CT 06877, USA

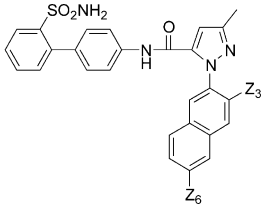
An analysis of the origins of recently launched drugs reveals that most were derived by modification of known drug structures or from lead structures obtained from the scientific literature. The drug structures are, in general, very closely related to their leads.

Bioorg. Med. Chem. Lett. 12 (2002) 1651

Design, Synthesis and Biological Activity of Novel Non-Amidine Factor Xa Inhibitors. Part 1: P_1 Structure–Activity Relationships of the Substituted 1-(2-Naphthyl)-1*H*-pyrazole-5-carboxylamides

Zhaozhong J. Jia,[a,*] Yanhong Wu,[a] Wenrong Huang,[a] Erick Goldman,[a] Penglie Zhang,[a] John Woolfrey,[a] Paul Wong,[b] Brian Huang,[b] Uma Sinha,[b] Gary Park,[b] Andrea Reed,[b] Robert M. Scarborough[a] and Bing-Yan Zhu[a,*]

[a]*Medicinal Chemistry Department, Millennium Pharmaceuticals, Inc., 256 East Grand Ave, South San Francisco, CA 94080, USA*
[b]*Biology Department, Millennium Pharmaceuticals, Inc., 256 East Grand Ave, South San Francisco, CA 94080, USA*



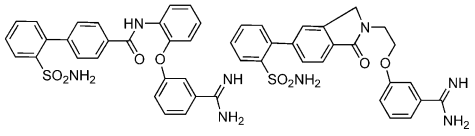
Potent non-benzamidine factor Xa inhibitors with excellent enzyme specificity and oral bioavailability were designed and prepared by employing substituted 2-naphthyl to displace the P_1 benzamidine moiety.

Bioorg. Med. Chem. Lett. 12 (2002) 1657

Design, Synthesis, and SAR of Monobenzamidines and Aminoisoquinolines as Factor Xa Inhibitors

Penglie Zhang,[a,*] Jingmei F. Zuckett,[a] John Woolfrey,[a] Katherine Tran,[b] Brian Huang,[b] Paul Wong,[b] Uma Sinha,[b] Gary Park,[b] Andrea Reed,[b] John Malinowski,[b] Stan Hollenbach,[b] Robert M. Scarborough[a] and Bing-Yan Zhu[a,*]

[a]*Department of Medicinal Chemistry, Millennium Pharmaceuticals, Inc., 256 E. Grand Avenue, South San Francisco, CA 94080, USA*
[b]*Department of Biology, Millennium Pharmaceuticals, Inc., 256 E. Grand Avenue, South San Francisco, CA 94080, USA*



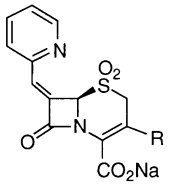
Diaryl ether and benzopyrrolidinone inhibitors of FXa, as well as the corresponding aminoisoquinoline compounds have been designed and synthesized.

Bioorg. Med. Chem. Lett. 12 (2002) 1663

Cephalosporin-Derived Inhibitors of β-Lactamase. Part 4: The C3 Substituent

John D. Buynak,* Lakshminarayana Vogeti, Venkata Ramana Doppalapudi, George Martin Solomon and Hansong Chen

Department of Chemistry, Southern Methodist University, Dallas, TX 75275-0314, USA



R = -H, -X, -S(O)$_n$-R', -CH=CHCONHR',

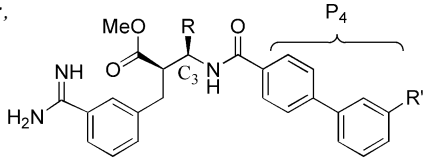
A series of unique, C3 substituted, cephalosporin-derived inhibitorsof β-lactamase was prepared and evaluated. It was possible to fine-tune the inhibitor to target either the class A penicillinases, the class C cephalosporinases, or to simultaneously inhibit both classes of serine hydrolase.

Bioorg. Med. Chem. Lett. 12 (2002) 1667

Optimization of the β-Aminoester Class of Factor Xa Inhibitors. Part 1: P_4 and Side-Chain Modifications for Improved In Vitro Potency

Mark Czekaj,* Scott I. Klein, Kevin R. Guertin,* Charles J. Gardner, Allison L. Zulli, Henry W. Pauls, Alfred P. Spada, Daniel L. Cheney, Karen D. Brown, Dennis J. Colussi, Valeria Chu, Robert J. Leadley and Christopher T. Dunwiddie

Drug Innovation and Approval, Aventis Pharmaceuticals, Route 202-206, Bridgewater, NJ 08807, USA



A systematic modification of the C_3 side-chain and a survey of P_4 variations of the β-aminoester class of fXa inhibitors is described. These changes have resulted in potent and selective inhibitors (R = Me, R′ = CH_2NH_2, K_i = 0.9 nM).

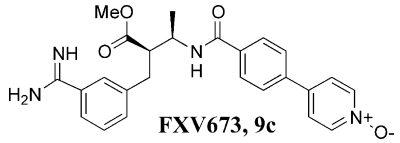
Bioorg. Med. Chem. Lett. 12 (2002) 1671

Optimization of the β-Aminoester Class of Factor Xa Inhibitors. Part 2: Identification of FXV673 as a Potent and Selective Inhibitor with Excellent In Vivo Anticoagulant Activity

Kevin R. Guertin,* Charles J. Gardner, Scott I. Klein, Allison L. Zulli, Mark Czekaj, Yong Gong, Alfred P. Spada, Daniel L. Cheney, Sebastian Maignan, Jean-Pierre Guilloteau, Karen D. Brown, Dennis J. Colussi, Valeria Chu, Christopher L. Heran, Suzanne R. Morgan, Ross G. Bentley, Christopher T. Dunwiddie, Robert J. Leadley and Henry W. Pauls*

Drug Innovation and Approval, Aventis Pharmaceuticals, Route 202-206, Bridgewater, NJ 08807, USA

Optimization of the β-aminoesters culminates in the clinical candidate, **FXV673**, a potent ($K_i = 0.4$ nM), selective and efficacious fXa inhibitor.



FXV673, 9c

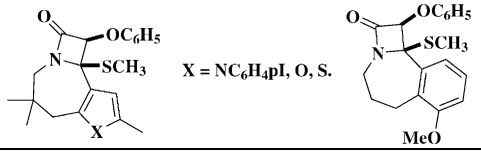
Bioorg. Med. Chem. Lett. 12 (2002) 1675

Synthesis of Novel Furo, Thieno, and Benzazetoazepines and Evaluation of Their Cytotoxicity

L. Roberto Martínez,[a,*] J. Gustavo Avila Zarraga,[b] Mª Esther Duran[a], Mª Teresa Ramírez Apam[a] and Roberto Cañas[a]

[a]*Instituto de Química, Universidad Nacional Autónoma de México, Circuito Exterior, Ciudad Universitaria, 04510 Coyoacán, México, D.F., Mexico*
[b]*Facultad de Química, Departamento de Orgánica, Universidad Nacional Autónoma de México, Circuito Interior, Ciudad Universitaria, 04510 Coyoacán, México, D.F., Mexico*

The synthesis of the title compounds was achieved using cyclic ketones as starting material. The observed cytotoxic activity depends of type ring fused to azetoazepine moiety.

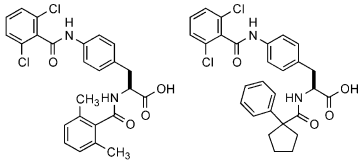


Bioorg. Med. Chem. Lett. 12 (2002) 1679

Focused Library Approach for Identification of New *N*-Acylphenylalanines as VCAM/VLA-4 Antagonists

Li Chen,* Richard Trilles, Dorota Miklowski, Tai-Nan Huang, David Fry, Robert Campbell, Karen Rowan, Virginia Schwinge and Jefferson W. Tilley

Roche Research Center, Hoffmann-La Roche Inc., 340 Kingsland Street, Nutley, NJ 07110, USA



IC_{50}: 1.2 nM 1.7 nM

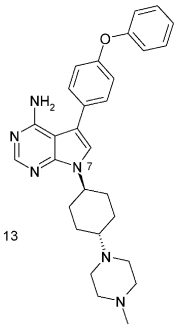
Bioorg. Med. Chem. Lett. 12 (2002) 1683

Pyrrolo[2,3-*d*]pyrimidines Containing Diverse N-7 Substituents as Potent Inhibitors of Lck

David J. Calderwood,* David N. Johnston, Rainer Munschauer and Paul Rafferty

Abbott Bioresearch Center, 100 Research Drive, Worcester, MA 01605-5314, USA

Optimization of the N-7 position resulted in compound **13**, a potent and orally active lck inhibitor.



13

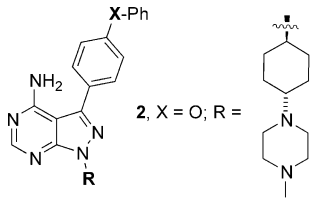
Bioorg. Med. Chem. Lett. 12 (2002) 1687

Pyrazolo[3,4-*d*]pyrimidines Containing an Extended 3-Substituent as Potent Inhibitors of Lck — a Selectivity Insight

Andrew F. Burchat, David J. Calderwood, Michael M. Friedman, Gavin C. Hirst,* Biqin Li, Paul Rafferty, Kurt Ritter and Barbara S. Skinner

Abbott Bioresearch Center, 100 Research Drive, Worcester, MA 01605-5314, USA

Compound **2** is a potent lck inhibitor that is orally active in models on T cell inhibition. The linker (**X**) plays a crucial role in driving kinase selectivity for lck, tie-2, and kdr.



Bioorg. Med. Chem. Lett. 12 (2002) 1691

Development of a Genetic Selection for Catalytic Antibodies

Jeff Gildersleeve, Jeff Janes, Helle Ulrich, Priscilla Yang, Carlos Barbas and Peter G. Schultz*

Department of Chemistry, The Scripps Research Institute, La Jolla, CA 92037, USA