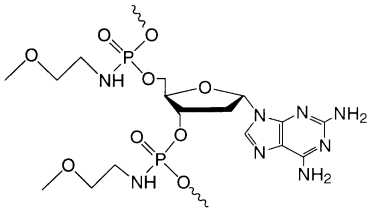
Bioorg. Med. Chem. Lett. 12 (2002) 1435

2-Amino-α-2′-deoxyadenosine Increased Duplex Stability of Methoxyethylphosphoramidate α-Oligodeoxynucleotides with RNA Target

Magali Naval, Thibaut Michel, Jean-Jacques Vasseur and Françoise Debart*

Laboratoire de Chimie Organique Biomoléculaire de Synthèse, UMR 5625 CNRS-UM II, CC 008, Université Montpellier II, Place Eugène Bataillon, 34095 Montpellier Cedex 05, France



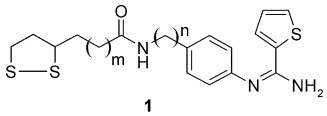
Synthesis of 3′-*H*-phosphonate of 2-amino-α-2′-deoxyadenosine and binding properties of methoxyethylphosphoramidate α-oligonucleotides containing 2-amino-α-2′-deoxyadenosine to their DNA and RNA targets were reported.

Bioorg. Med. Chem. Lett. 12 (2002) 1439

Novel Lipoic Acid Analogues that Inhibit Nitric Oxide Synthase

Jeremiah J. Harnett,[a,*] Michel Auguet,[b] Isabelle Viossat,[b] Christine Dolo,[a] Dennis Bigg[a] and Pierre-E. Chabrier[b]

[a]*Department of Medicinal Chemistry, Beaufour-Ipsen Research Laboratories, Institute Henri Beaufour, 5, Avenue du Canada, 91966 Les Ulis Cedex, France*
[b]*Department of Biology, Beaufour-Ipsen Research Laboratories, Institute Henri Beaufour, 5, Avenue du Canada, 91966 Les Ulis Cedex, France*



1

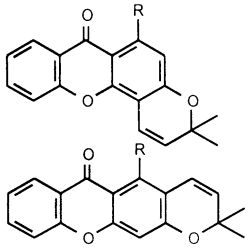
The design and synthesis of novel lipoic acid analogues is described. Arylthiophene amidine analogues of lipoic acid are both inhibitors of nitric oxide synthase and are metabolic antioxidants. Compound **1** is capable of protecting neuronal cells against glutamate cytotoxicity and preventing loss of intracellular glutathione.

Bioorg. Med. Chem. Lett. 12 (2002) 1443

Design and Synthesis of Some New Pyranoxanthenone Aminoderivatives with Cytotoxic Activity

George Kolokythas,[a] Ioannis K. Kostakis,[a] Nicole Pouli,[a] Panagiotis Marakos,[a,*] Alexios-Leandros Skaltsounis[b] and Harris Pratsinis[c]

[a]*Division of Pharmaceutical Chemistry, Department of Pharmacy, University of Athens, Panepistimiopolis-Zografou, Athens 15771, Greece*
[b]*Division of Pharmacognosy, Department of Pharmacy, University of Athens, Panepistimiopolis-Zografou, Athens 15771, Greece*
[c]*Laboratory of Cell Proliferation & Ageing, Institute of Biology, NCSR 'Democritos', 15310 Athens, Greece*



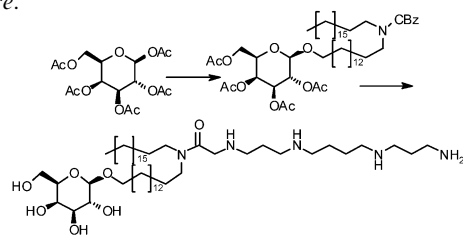
R= $CONHCH_2CH_2NR'R'$
$CH_2NHCH_2CH_2NR'R'$
NR'R'= NMe_2, NEt_2

Bioorg. Med. Chem. Lett. 12 (2002) 1447

Glycosidation of Alkylamino-alkan-1-ol. A Simple and Convenient Synthesis of Glycosylated Cationic Lipids

Christophe Jacopin, Marie-José Egron, Daniel Scherman and Jean Herscovici*

Laboratoire de Chimie Bioorganique et de Biotechnologie Moléculaire et Cellulaire. UMR 7001 CNRS-ENSCP-Aventis-Gencell. 11, rue Pierre et Marie Curie, 75231 Paris Cedex, France



Starting from long chain alkylamino-alkan-1-ol a series of amino glycolipids were synthesized. This procedure allow a short and convenient preparation of glycosylated cationic lipids for gene delivery.

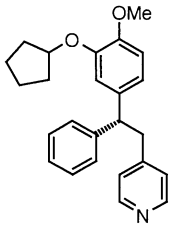
Bioorg. Med. Chem. Lett. 12 (2002) 1451

CDP840. A Prototype of a Novel Class of Orally Active Anti-Inflammatory Phosphodiesterase 4 Inhibitors

R. P. Alexander,[a,*] G. J. Warrellow,[a] M. A. W. Eaton,[a] E. C. Boyd,[a] J. C. Head,[a] J. R. Porter,[a] J. A. Brown,[a] J. T. Reuberson,[a] B. Hutchinson,[a] P. Turner,[a] B. Boyce,[a] D. Barnes,[a] B. Mason,[a] A. Cannell,[a] R. J. Taylor,[a] A. Zomaya,[a] A. Millican,[a] J. Leonard,[a] R. Morphy,[a] M. Wales,[b] M. Perry,[b] R. A. Allen,[b] N. Gozzard,[b] B. Hughes[b] and G. Higgs[b]

[a]*Department of Medicinal Chemistry, Celltech R&D Ltd., 208 Bath Road, Slough, Berkshire SL1 3WE, UK*
[b]*Department of Biology, Celltech R&D Ltd., 208 Bath Road, Slough, Berkshire SL1 3WE, UK*

The discovery, synthesis and biological activity of a novel series of triarylethane phosphodiesterase **4** inhibitors is described.



CDP840 (**29**)

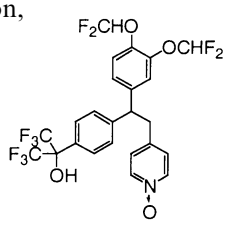
Bioorg. Med. Chem. Lett. 12 (2002) 1457

Discovery of L-791,943: A Potent, Selective, Non Emetic and Orally Active Phosphodiesterase-4 Inhibitor

Daniel Guay,* Pierre Hamel, Marc Blouin, Christine Brideau, Chi Chung Chan, Nathalie Chauret, Yves Ducharme, Zheng Huang, Mario Girard, Tom R. Jones, France Laliberté, Paul Masson, Malia McAuliffe, Hanna Piechuta, José Silva, Robert N. Young and Yves Girard

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

The synthesis and biological profiles of highly potent catechol derivatives as PDE4 inhibitors and the SAR study leading to the discovery of the metabolically stable inhibitor L-791,943 are reported.



L-791,943 (**11n**)

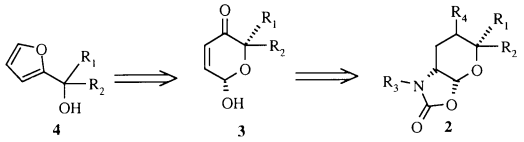
Bioorg. Med. Chem. Lett. 12 (2002) 1463

Novel Bicyclic Oxazolone Derivatives as Anti-Angiogenic Agents

Françoise M. Perron-Sierra,[a,*] Alain Pierré,[b] Mike Burbridge[b] and Nicolas Guilbaud[b]

[a]*Institut de Recherches Servier, 125 Chemin de Ronde, 78290 Croissy-sur-Seine, France*
[b]*Institut de Recherches Servier, 3 rue de la République, 92150 Suresnes, France*

Novel bicyclic tetrahydropyrano[3,2-*d*]oxazolones derivatives, analogues of Fumagillin, were synthesised via a stereocontrolled oxidative-rearrangement of furylcarbinols and subsequent treatment with the appropriate isocyanate. These compounds demonstrated potent antiangiogenic activity.



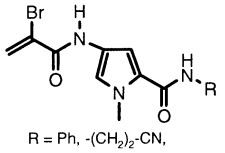
Bioorg. Med. Chem. Lett. 12 (2002) 1467

Cytotoxic Alpha-Bromoacrylic Derivatives of Low Molecular Weight

Italo Beria,[a,*] Marina Caldarelli,[a] Cristina Geroni,[b] Nicola Mongelli,[a] Benedetta Reinach,[c] Luisella Vignati[c] and Paolo Cozzi[a]

[a]*Chemistry Department, Pharmacia Discovery Research Oncology, Viale Pasteur 10, 20014 Nerviano, Milan, Italy*
[b]*External Research Department, Pharmacia Discovery Research Oncology, Viale Pasteur 10, 20014 Nerviano, Milan, Italy*
[c]*Global Drug Metabolism Department, Pharmacia Discovery Research Oncology, Viale Pasteur 10, 20014 Nerviano, Milan, Italy*

The design, synthesis, in vitro and in vivo activities of a series of α-bromoacrylic derivatives of low molecular weight (MW) are described and compared with those of α-bromoacrylic derivaties of distamycin-like frames.



R = Ph, -$(CH_2)_2$-CN, -$(CH_2)_2$-C(NH)NH2

Bioorg. Med. Chem. Lett. 12 (2002) 1473

Identification of Novel Antifungal Nonapeptides Through the Screening of Combinatorial Peptide Libraries Based on a Hexapeptide Motif

B. Kundu,[a,*] T. Srinivasan,[a] A. P. Kesarwani,[a] A. Kavishwar,[b] S. K. Raghuwanshi,[b] S. Batra[a] and P. K. Shukla[b]

[a]*Department of Medicinal Chemistry, Central Drug Research Institute, Lucknow-226 001, India*
[b]*Department of Medical Mycology, Central Drug Research Institute, Lucknow-226 001, India*

Four sets of mixture based nonapeptide libraries derived from an antifungal hexapeptide pharmacophore Arg-D-Trp-D-Phe-Ile-D-Phe-His-NH_2 (**II**) have been synthesized. The three C-terminal positions 7, 8 and 9 were subject to randomization using 19 genetically coded amino acids. They were then screened for their antifungal activity against *Candida albicans* and *Cryptococcus neoformans* in order to quantify inhibition at each step of the nonapeptide sublibrary deconvolution. The studies led to the identification of several novel nonapeptides with potent antifungal activity. Two of the nonapeptides exhibited approximately 17-fold increase in the activity in comparison to the lead hexapeptide motif His-D-Trp-D-Phe-Phe-D-Phe-Lys-NH_2 (**I**) against *C. albicans*.

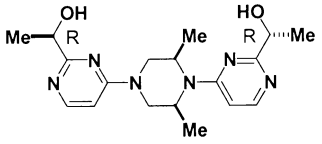
Bioorg. Med. Chem. Lett. 12 (2002) 1477

SAR and Species/Stereo-Selective Metabolism of the Sorbitol Dehydrogenase Inhibitor, CP-470,711

Margaret Y. Chu-Moyer,* William E. Ballinger, David A. Beebe, James B. Coutcher, Wesley W. Day, Jiancheng Li, Peter J. Oates and R. Matthew Weekly

Cardiovascular and Metabolic Diseases, Pfizer Global Research and Development, Groton Laboratories MS8220-3095, Eastern Point Road, Groton, CT 06340, USA

In vivo pharmacological and drug metabolism studies revealed that CP-470,711 (**1**) undergoes epimerization in rat, but not dog. In vitro studies suggest that **1** will not epimerize in humans.



1: CP-470,711

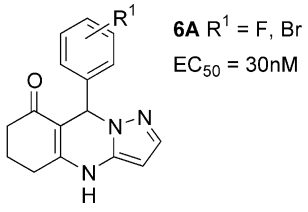
Bioorg. Med. Chem. Lett. 12 (2002) 1481

Structure–Activity Studies for a Novel Series of Tricyclic Dihydropyrimidines as K_{ATP} Channel Openers (KCOs)

Irene Drizin, Mark W. Holladay, Lin Yi, Henry Q. Zhang, Sujatha Gopalakrishnan, Murali Gopalakrishnan, Kristi L. Whiteaker, Steven A. Buckner, James P. Sullivan and William A. Carroll

Neuroscience Research, GPRD, Abbott Laboratories, 100 Abbott Park Road, Abbott Park, IL 60064-6101, USA

A novel series of tricyclic dihydropyrimidines was synthesized and evaluated for activity as K_{ATP} channel openers. The functional activity of several compounds, for example **6A** ($EC_{50} = 30$ nM) and its enantiomers exceeded cromakalim.



6A R^1 = F, Br
EC_{50} = 30nM

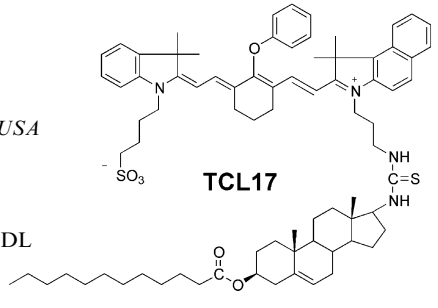
Bioorg. Med. Chem. Lett. 12 (2002) 1485

Tricarbocyanine Cholesteryl Laurates Labeled LDL: New Near Infrared Fluorescent Probes (NIRFs) for Monitoring Tumors and Gene Therapy of *Familial hypercholesterolemia*

Gang Zheng,[a,*] Hui Li,[a] Kathy Yang,[a] Dana Blessington,[b] Kai Licha,[c] Sissel Lund-Katz,[d] Britton Chance[b] and Jerry D. Glickson[a]

[a]*Department of Radiology, University of Pennsylvania, Philadelphia, PA 19104, USA*
[b]*Department of Biochemistry/Biophysics, University of Pennsylvania, Philadelphia, PA 19104, USA*
[c]*Institut fürDiagnostikforschung GmbH an der Freien Universität Berlin, 14050, Germany*
[b]*Department of Pediatric GI Nutrition, The Children's Hospital of Philadelphia, Philadelphia, PA 19104, USA*

The synthesis and selective internalization of a new NIRF by $HepG_2$ tumor overexpressing LDL receptors are reported.



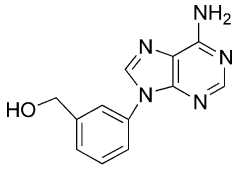
Bioorg. Med. Chem. Lett. 12 (2002) 1489

9-[(Hydroxymethyl)phenyl]adenines: New Aryladenine Substrates of Adenosine Deaminase[1]

Mohamed Brakta, Devangachinta Murthy, L'Ouverture Ellis and Shashikant Phadtare*

College of Pharmacy, Xavier University of Louisiana, New Orleans, LA 70125, USA

The aromatic adenine nucleoside analogues have been prepared and tested as substrates of adenosine deaminase (ADA). The 9-[[(*o*-hydroxymethyl)phenyl]methyl]adenine **5** and 9-[[(*m*-hydroxymethyl)phenyl]adenine **7** were deaminated quantitatively by ADA in 6–10 h.



7

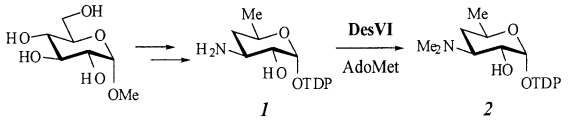
Bioorg. Med. Chem. Lett. 12 (2002) 1493

Synthesis of TDP-3-Amino-3,4,6-trideoxy-α-D-*xylo*-hexopyranose—The Immediate Precursor of TDP-α-D-desosamine

Cheng-Wei T. Chang[a,b] and Hung-wen Liu[a,b,*]

[a]*Division of Medicinal Chemistry, College of Pharmacy, and Department of Chemistry and Biochemistry, University of Texas, Austin, TX 78712, USA*
[b]*Department of Chemistry, University of Minnesota, Minneapolis, MN 55455, USA*

A synthetic pathway starting from methyl α-D-glucose to make the title compound (**1**) is described. Compound **1** could be converted to desosamine (**2**) by Des VI enzyme.



1 *2*

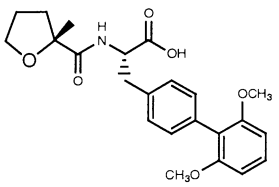
Bioorg. Med. Chem. Lett. 12 (2002) 1497

N-Tetrahydrofuroyl-(L)-Phenylalanine Derivatives as Potent VLA-4 Antagonists

Ginger X. Yang,[a,*] Linda L. Chang,[a] Quang Truong,[a] George A. Doherty,[a] Plato A. Magriotis,[a] Stephen E. de Laszlo,[a] Bing Li,[a] Malcolm MacCoss,[a] Usha Kidambi,[b] Linda A. Egger,[b] Ermengilda McCauley,[b] Gail Van Riper,[b] Richard A. Mumford,[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 Immunology and Rheumatology Research, Merck Research Laboratories, Rahway, NJ 07065, USA*

The synthesis, biological properties, and pharmacokinetic profile of tetrahydrofuranoyl such as **17** are reported.



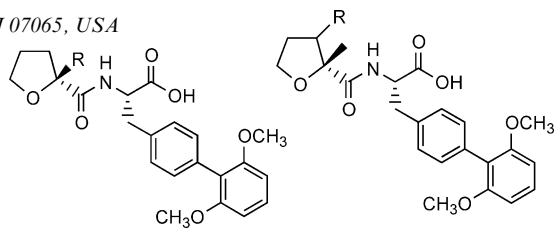
Bioorg. Med. Chem. Lett. 12 (2002) 1501

Substituted Tetrahydrofuroyl-1-phenylalanine Derivatives as Potent and Specific VLA-4 Antagonists

George A. Doherty,[a,*] Ginger X. Yang,[a] Edite Borges,[a] Linda L. Chang,[a] Malcolm MacCoss,[a] Sharon Tong,[a] Usha Kidambi,[b] Linda A. Egger,[b] Ermenegilda McCauley,[b] Gail Van Riper,[b] Richard A. Mumford,[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 Immunology & Rheumatology Research, Merck Research Laboratories, Rahway, NJ 07065, USA*

A series of substituted tetrahydrofuroyl-1-phenylalanine derivatives was prepared and evaluated as VLA-4 antagonists. Substitution of the α carbon of the tetrahydrofuran with aryl groups increased the specificity for VLA-4 versus $\alpha_4\beta_7$ while amide substitution increased the potency of the series without increasing the specificity. Substitution of the β carbon of the tetrahydrofuran with keto or amino groups slightly improved the specificity for VLA-4 versus $\alpha_4\beta_7$ but with a significant loss in binding affinity for VLA-4.



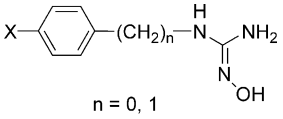
Bioorg. Med. Chem. Lett. 12 (2002) 1507

Electrochemical and Peroxidase Oxidation Study of *N′*-Hydroxyguanidine Derivatives as NO Donors

Tingwei Cai, Ming Xian and Peng George Wang*

Department of Chemistry, Wayne State University, Detroit, MI 48202, USA

Oxidation potentials of a series of *N*-substituted-*N′*-hydroxyguanidines and their NO release abilities under the oxidation of horseradish peroxidase/H_2O_2 were evaluated.



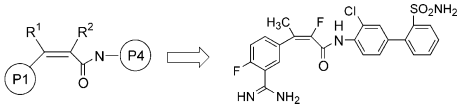
Bioorg. Med. Chem. Lett. 12 (2002) 1511

Design, Synthesis, and SAR of Substituted Acrylamides as Factor Xa Inhibitors

Yonghong Song,* Lane Clizbe, Chhaya Bhakta, Willy Teng, Wenhao Li, Yanhong Wu, Zhaozhong Jon Jia, Penglie Zhang, Lingyan Wang, Brandon Doughan, Ting Su, James Kanter, John Woolfrey, Paul Wong, Brian Huang, Katherine Tran, Uma Sinha, Gary Park, Andrea Reed, John Malinowski, Stan Hollenbach, Robert M. Scarborough and Bing-Yan Zhu

Millennium Pharmaceuticals, Inc., 256 East Grand Avenue, South San Francisco, CA 94080, USA

Substituted acrylamides were used as templates that bridge P1 and P4 moieties, resulting in a series of potent (sub-nanomolar) and selective factor Xa inhibitors. Compounds in this series show good in vivo efficacy in animal models.



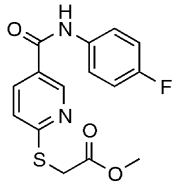
Bioorg. Med. Chem. Lett. 12 (2002) 1517

Nicotinanilides as Inhibitors of Neutrophil Chemotaxis

Neil S. Cutshall,[a,*] Kristin A. Kucera,[b] Rocky Ursino,[b] John Latham[b] and Nathan C. Ihle[a]

[a]*Department of Chemistry, Celltech R&D Inc., 1631 220th Street SE, Bothell, WA 98021, USA*
[b]*Department of Gene Function & Target Validation, Celltech R&D Inc., 1631 220th Street SE, Bothell, WA 98021, USA*

This communication describes the synthesis and SAR of a novel series of substituted nicotinanilides as potent modulators of GRO-α-driven human neutrophil chemotaxis. Compound **5b** was a potent inhibitor of chemotaxis ($IC_{50} = 42$ nM) and demonstrated high selectivity over the chemoattractant polypeptide *N*-formyl-methionyl-leucyl-phenylalanine ($IC_{50} > 40$ μM).



5b

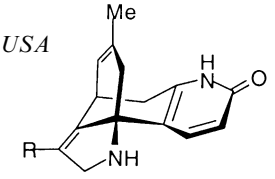
Bioorg. Med. Chem. Lett. 12 (2002) 1521

Synthesis of More Potent Analogues of the Acetylcholinesterase Inhibitor, Huperzine B

V. Rajendran,[a] Ashima Saxena,[b] Bhupendra P. Doctor[b] and Alan P. Kozikowski[a,*]

[a]*Drug Discovery Program, Department of Neurology, Georgetown University Medical Center, 3900 Reservoir Road NW, Washington, DC 20007-2197, USA*
[b]*Division of Biochemistry, Walter Reed Army Institute of Research, Silver Spring, MD 20910-7500, USA*

The synthesis and acetylcholinesterase inhibition activity of analogues of huperzine B are reported. These new racemic analogues show a better AChE inhibitory activity than the natural product huperzine B.



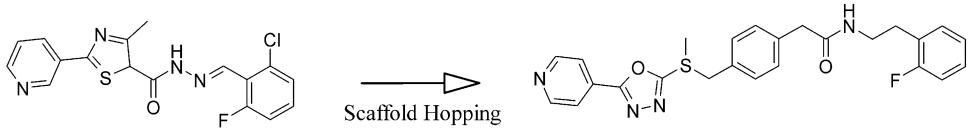
R = Et or Me

Bioorg. Med. Chem. Lett. 12 (2002) 1525

Scaffold Hopping and Optimization towards Libraries of Glycogen Synthase Kinase-3 Inhibitors

Lars Nærum, Leif Nørskov-Lauritsen* and Preben H. Olesen

Medicinal Chemistry Research, Novo Nordisk A/S, Novo Nordisk Park, DK-2760 Måløv, Denmark



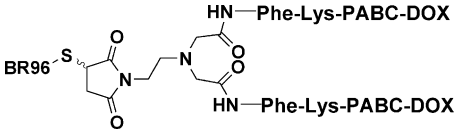
Bioorg. Med. Chem. Lett. 12 (2002) 1529

Doxorubicin Immunoconjugates Containing Bivalent, Lysosomally-Cleavable Dipeptide Linkages

Gene M. Dubowchik,[a,*] Shilpa Radia,[a] Harold Mastalerz,[a] Michael A. Walker,[a] Raymond A. Firestone,[a] H. Dalton King,[a] Sandra J. Hofstead,[a] David Willner,[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 immunoconjugates carrying 14 molecules of doxorubicin attached through bivalent, lysosomally-cleavable dipeptides linkers were prepared.



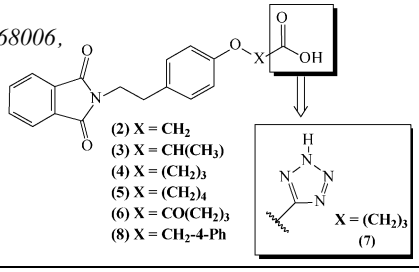
Bioorg. Med. Chem. Lett. 12 (2002) 1533

Novel Phthalimide Derivatives, Designed as Leukotriene D_4 Receptor Antagonists

Lídia M. Lima,[a,b] Fernanda C. F. de Brito,[a] Simone D. de Souza,[a] Ana L. P. Miranda,[a] Carlos R. Rodrigues,[a] Carlos A. M. Fraga[a,b] and Eliezer J. Barreiro[a,b,*]

[a]*LASSBio, Faculdade de Farmácia, Universidade Federal do Rio de Janeiro, PO Box 68006, Rio de Janeiro, 21944-970, RJ, Brazil*
[b]*Instituto de Química, Universidade Federal do Rio de Janeiro, Rio de Janeiro, 21949-900, RJ, Brazil*

The synthesis of novel phthalimide LTD_4 receptor antagonists **2**–**8** is reported.



Bioorg. Med. Chem. Lett. 12 (2002) 1537

CoMFA and HQSAR of Acylhydrazide Cruzain Inhibitors

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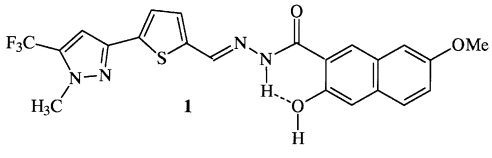
CoMFA and HQSAR methods were used to describe QSAR models for a series of acylhydrazide cruzain inhibitors structurally related to **1**.



Bioorg. Med. Chem. Lett. 12 (2002) 1543

Synthesis and Cytotoxicity of 2α-Amido Docetaxel Analogues

Wei-Shuo Fang,* Ying Liu, Hong-Yan Liu, Shao-Feng Xu, Liang Wang and Qi-Cheng Fang

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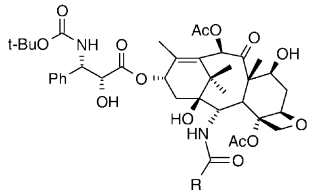
Different 2-amido docetaxel analogues were prepared and evaluated for their cytotoxicities. Among them, *m*-methoxy and *m*-chlorobenzoylamido analogues were most active but not superior to docetaxel and paclitaxel, and D-seco analogues were inactive. Change of 2-benzoate to 2-benzamide may not improve their activities to drug-resistant cell lines.



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