Graphical Abstracts

Inhibition of HIV Tat–TAR Interactions by an Antisense Oligo-2′-*O*-methylribonucleoside Methylphosphonate

Bioorg. Med. Chem. Lett. 13 (2003) 1845

Tomoko Hamma,[a,c] Anthony Saleh,[a] Ikramul Huq,[b] Tariq M. Rana[b] and Paul S. Miller[a,*]

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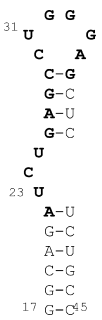
[b]*Department of Biochemistry and Molecular Pharmacology, University of Massachusetts Medical School, 364 Plantation St., Worcester, MA 01605, USA*
[c]*Division of Basic Science, Fred Hutchinson Cancer Research Center, 1100 Fairview Avenue North Mail Stop A3-015, Seattle, WA 98109, USA*

Anti-TAR RNA oligo-2′-*O*-methylribonucleotide methylphosphonate, **1676**, binds to TAR at 37 °C with a K_d in the low nM concentration range; inhibits Tat–TAR complex formation; and inhibits expression of a chloramphenicol reporter gene under control of the HIV LTR in HeLa HL3T1 cells in culture.



Synthesis and Biological Evaluation of Some Novel 4′-Thio-L-ribonucleosides with Modified Nucleobase Moieties

Bioorg. Med. Chem. Lett. 13 (2003) 1849

Vjera Pejanović,[a,*] Zdenka Stokić,[a] Biljana Stojanović,[a] Vesna Piperski,[a] Mirjana Popsavin[b] and Velimir Popsavin[b]

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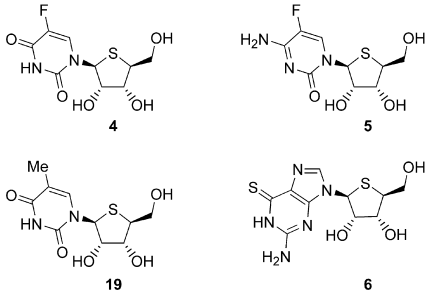
[b]*Department of Chemistry, Faculty of Sciences, University of Novi Sad, Trg D. Obradovica 3, 21000 Novi Sad, Yugoslavia*

The synthesis and biological evaluation of L-4′-thionucleosides **4**–**6** and **19** is reported.



Synthesis and Biological Evaluation of New UDP-GalNAc Analogues for the Study of Polypeptide-α-GalNAc-transferases

Bioorg. Med. Chem. Lett. 13 (2003) 1853

Patricia Busca,[a] Véronique Piller,[b] Friedrich Piller[b] and Olivier R. Martin[a,*]

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[b]*Centre de Biophysique Moléculaire, CNRS UPR 4301, 45071 Orléans, France*

The synthesis of the 3-*O*-, 4-*O*- and 6-*O*-methylated UDP-GalNAc analogues is reported. These modified glycosyl donors were not substrates for the bovine polypeptide-α-GalNAc transferase T1 and were weak inhibitors of this enzyme.

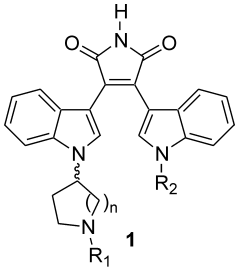
Acyclic *N*-(azacycloalkyl)bisindolylmaleimides: Isozyme Selective Inhibitors of PKCβ

Bioorg. Med. Chem. Lett. 13 (2002) 1857

Margaret M. Faul,[a,*] James R. Gillig,[b] Michael R. Jirousek,[c] Lawrence M. Ballas,[d] Theo Schotten,[e] Astrid Kahl[e] and Michael Mohr[e]

[a]*Global Chemical Process Research and Development Division, Lilly Research Laboratories, A Division of Eli Lilly and Company, Indianapolis, IN 46285, USA*
[b]*Discovery Chemistry Research and Technologies, Lilly Research Laboratories, A Division of Eli Lilly and Company, Indianapolis, IN 46285, USA*
[c]*La Jolla Laboratories, Pfizer Global Research and Development, San Diego, CA, USA*
[d]*Sphinx Laboratories, Research Triangle Park, NC, USA*
[e]*Lilly Forschung, A Division of Eli Lilly and Company, Hamburg, Germany*

The synthesis and structure–activity relationship (SAR) trends of a new class of *N*-(azacycloalkyl)bisindolylmaleimides **1**, acyclic derivatives of staurosporine, will be described and a comparison to the natural product provided.



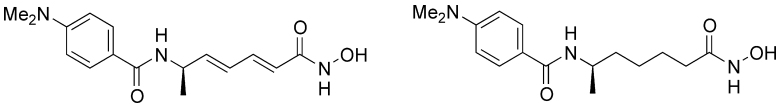
Bioorg. Med. Chem. Lett. 13 (2003) 1861

Amide Analogues of TSA: Synthesis, Binding Mode Analysis and HDAC Inhibition

K. Van Ommeslaeghe,[a] G. Elaut,[c] V. Brecx,[a] P. Papeleu,[c] K. Iterbeke,[a] P. Geerlings,[b] D. Tourwé[a,*] and V. Rogiers[c]

[a]*Department of Organic Chemistry, Vrije Universiteit Brussel, Pleinlaan 2, B-1050 Brussels, Belgium*
[b]*Department of General Chemistry, Vrije Universiteit Brussel, Pleinlaan 2, B-1050 Brussels, Belgium*
[c]*Department of Toxicology, Vrije Universiteit Brussel, Pleinlaan 2, B-1050 Brussels, Belgium*

New amide bond analogues of the histone deacetylase inhibitor TSA were prepared. The incorporation of an (*R*)-methyl group and a diene structure did not improve the inhibitory potency. The results are interpreted with the help of molecular modelling of the binding mode to a model of the active site of the HDLP protein.

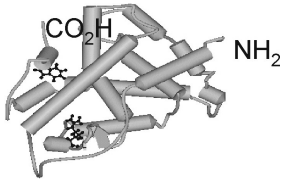


Bioorg. Med. Chem. Lett. 13 (2003) 1865

Binding Mode of 6ECDCA, a Potent Bile Acid Agonist of the Farnesoid X Receptor (FXR)

Gabriele Costantino, Antonio Macchiarulo, Antonio Entrena-Guadix, Emidio Camaioni and Roberto Pellicciari*

Dipartimento di Chimica e Tecnologia del Farmaco, Università di Perugia, Via del Liceo 1, 06123 Perugia, Italy



Bioorg. Med. Chem. Lett. 13 (2003) 1869

Density Functional Theory Calculations for Resveratrol

Huai Cao,[a,*] Xulin Pan,[a] Cong Li,[b] Chun Zhou,[a] Fengyi Deng[a] and Taohong Li[a]

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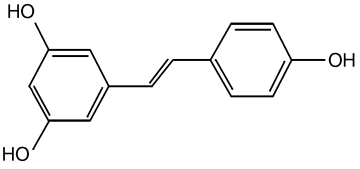
[b]*Department of Applied Chemistry, Yunnan University, Kunming 650091, People's Republic of China*

The results from the density functional theory (DFT) calculation elucidate the reaction mechanism of the resveratrol inhibiting some radicals.



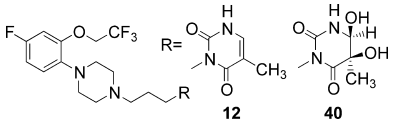
Bioorg. Med. Chem. Lett. 13 (2003) 1873

Synthesis, Pharmacology and Pharmacokinetics of 3-(4-Aryl-piperazin-1-ylalkyl)-uracils as Uroselective α_{1A}-Antagonists

F. J. Lopez,* L. Arias, R. Chan, D. E. Clarke, T. R. Elworthy, A. P. D. W. Ford, A. Guzman, S. Jaime-Figueroa, J. R. Jasper, D. J. Morgans, Jr., F. Padilla, A. Perez-Medrano, C. Quintero, M. Romero, L. Sandoval, S. A. Smith, T. J. Williams and D. R. Blue

Roche Bioscience, 3431 Hillview Ave, Palo Alto, CA 94304, USA

Compound **12** and its metabolite **40** are uroselective α_{1A}-adrenoceptor antagonists.



12 **40**

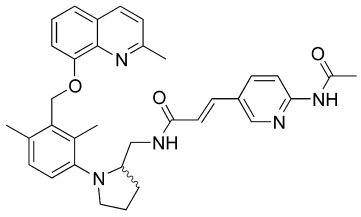
Bioorg. Med. Chem. Lett. 13 (2003) 1879

Design and Synthesis of Novel Pyrrolidine-Containing Bradykinin Antagonists

Jung Lee,* Charles Reynolds, Michele C. Jetter, Mark A. Youngman, Dennis J. Hlasta, Scott L. Dax, Dennis J. Stone, Sui-Po Zhang and Ellen E. Codd

Drug Discovery, Johnson & Johnson Pharmaceutical Research & Development, Welsh & McKean Roads, PO Box 776, Spring House, PA 19477-0776, USA

The design and synthesis of novel pyrrolidine-containing bradykinin antagonists are described.

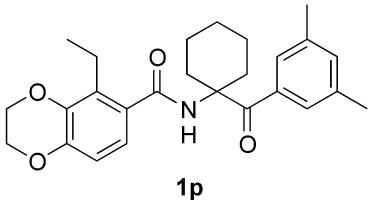


Bioorg. Med. Chem. Lett. 13 (2003) 1883

Optimization of α-Acylaminoketone Ecdysone Agonists for Control of Gene Expression

Colin M. Tice,* Robert E. Hormann, Christine S. Thompson, Jennifer L. Friz, Caitlin K. Cavanaugh and Jessica A. Saggers

RHeoGene, PO Box 949, 727 Norristown Road, Spring House, PA 19477-0949, USA



1p

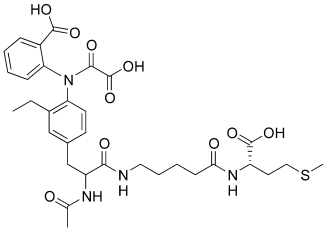
Bioorg. Med. Chem. Lett. 13 (2003) 1887

Potent, Selective Inhibitors of Protein Tyrosine Phosphatase 1B

Zhili Xin,[a,*] Thorsten K. Oost,[b] Cele Abad-Zapatero,[b] Philip J. Hajduk,[b] Zhonghua Pei,[a] Bruce G. Szczepankiewicz,[a] Charles W. Hutchins,[b] Steve J. Ballaron,[a] Mike A. Stashko,[a] Tom Lubben,[a] James M. Trevillyan,[a] Mike R. Jirousek[a] and Gang Liu[a,*]

[a]*Metabolic Disease Research, Global Pharmaceutical Research and Development, Abbott Laboratories, Abbott Park, IL 60064-6098, USA*
[b]*Advanced Technology, Global Pharmaceutical Research and Development, Abbott Laboratories, Abbott Park, IL 60064-6098, USA*

The discovery of potent PTP1B inhibitor **19** with selectivity over TCPTP is reported.



19 K_i = 76 nM (PTP1B), K_i = 380 nM (TCPTP)

Bioorg. Med. Chem. Lett. 13 (2003) 1891

N-Isonicotinoyl-(L)-4-aminophenylalanine Derivatives as Tight Binding VLA-4 Antagonists

George A. Doherty,[a,*] Ginger X. Yang,[a] Edite Borges,[a] Sharon Tong,[a] Ermengilda D. McCauley,[b] Kelly M. Treonz,[b] Gail Van Riper,[b] Stephen Pacholok,[b] Qian Si,[b] Gloria C. Koo,[b] Kashmira Shah,[b] Richard A. Mumford[b] and William K. Hagmann[a]

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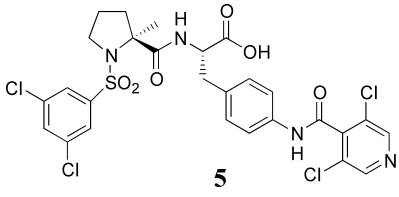
[b]*Department of Immunology and Rheumatology Research, Merck Research Laboratories, Rahway, NJ 07065, USA*

A series of isonicotinoyl-(L)-aminophenylalanine derivatives was prepared and evaluated as VLA-4 antagonists. These compounds exhibit subnanomolar binding affinity to activated and unactivated states of VLA-4 and significant off-rates. The best compound reported **5** shows activity in reducing eosinophil trafficking in an OVA asthma model even though it is highly protein bound and rapidly cleared from the plasma. The interplay between off-rate, protein binding and pharmacokinetics is discussed.



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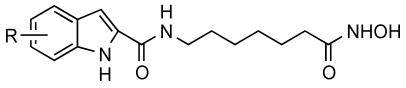
Bioorg. Med. Chem. Lett. 13 (2003) 1897

Indole Amide Hydroxamic Acids as Potent Inhibitors of Histone Deacetylases

Yujia Dai,* Yan Guo, Jun Guo, Lori J. Pease, Junling Li, Patrick A. Marcotte, Keith B. Glaser, Paul Tapang, Daniel H. Albert, Paul L. Richardson, Steven K. Davidsen and Michael R. Michaelides

Cancer Research, Abbott Laboratories, Dept. R47J, Bldg. AP10, 100 Abbott Park Road, Abbott Park, IL 60064-6100, USA

A series of indole amide-based hydroxamic acids is disclosed as potent HDAC inhibitors.



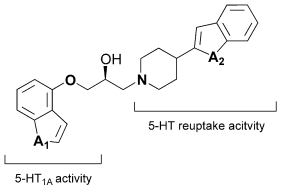
Bioorg. Med. Chem. Lett. 13 (2003) 1903

Advances Toward New Antidepressants Beyond SSRIs: 1-Aryloxy-3-piperidinylpropan-2-ols with Dual 5-HT_{1A} Receptor Antagonism/SSRI Activities. Part 1

Kumiko Takeuchi,* Todd J. Kohn, Nicholas A. Honigschmidt, Vincent P. Rocco, Patrick G. Spinazze, Daniel J. Koch, David L. Nelson, D. Bradley Wainscott, Laura J. Ahmad, Janice Shaw, Penny G. Threlkeld and David T. Wong

Lilly Research Laboratories, A Division of Eli Lilly and Company, Indianapolis, IN 46285, USA

A series of 1-aryloxy-3-piperidinylpropan-2-ols possessing potent dual 5-HT_{1A} receptor antagonism and serotonin reuptake inhibition was discovered. 1-(1*H*-Indol-4-yloxy)-3-(4-benzo[*b*]thiophen-2-ylpiperidinyl)propan-2-ols exhibited selective and high affinity at the 5-HT1A receptor and serotonin reuptake inhibition at nanomolar concentrations for dual activities.



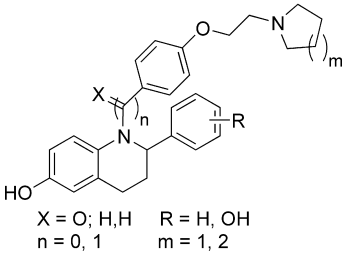
Bioorg. Med. Chem. Lett. 13 (2003) 1907

Tetrahydroquinoline-Based Selective Estrogen Receptor Modulators (SERMs)

Owen B. Wallace,* Kenneth S. Lauwers, Scott A. Jones and Jeffrey A. Dodge

Discovery Chemistry Research and Technologies, Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN 46285, USA

The synthesis of a series of 6-hydroxy-tetrahydroquinoline-based estrogen receptor ligands is disclosed. Binding affinity and inhibition of MCF-7 breast adenocarcinoma cell proliferation is discussed.



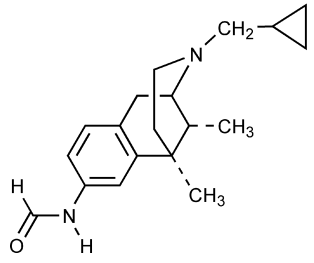
Bioorg. Med. Chem. Lett. 13 (2003) 1911

Redefining the Structure–Activity Relationships of 2,6-Methano-3-benzazocines. Part 2: 8-Formamidocyclazocine Analogues

Mark P. Wentland,[a,]* Xufeng Sun,[a] Yingchun Ye,[a] Rongliang Lou[a] and Jean M. Bidlack[b]

[a]*Department of Chemistry, Rensselaer Polytechnic Institute, Troy, NY 12180, USA*
[b]*Department of Pharmacology and Physiology, School of Medicine and Dentistry, University of Rochester, Rochester, NY 14642, USA*

High affinity binding for μ and κ opioid receptors has been observed in analogues of cyclazocine, ethylketocyclazocine and naltrexone where the prototypic (of opiates) phenolic OH group was replaced with a formamide (–NHCHO) group.



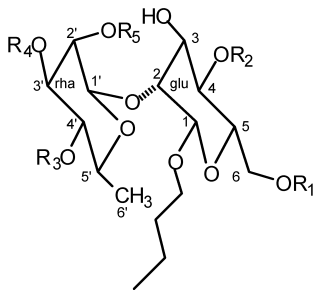
Bioorg. Med. Chem. Lett. 13 (2003) 1915

Polyacylated Neohesperidosides From *Geranium caespitosum*: Bacterial Multidrug Resistance Pump Inhibitors

Frank R. Stermitz,[a,*] Kevin K. Cashman,[a] Kathleen M. Halligan,[a] Cécile Morel,[a] George P. Tegos[b] and Kim Lewis[b]

[a]*Department of Chemistry, Colorado State University, Fort Collins, CO 80523 USA*
[b]*Department of Biology, Northeastern University, Boston, MA 02155 USA*

Tetra- and pentaacyl esters of butyl neohesperidoside inhibit *Staphylococcus aureus* MDR efflux pumps.



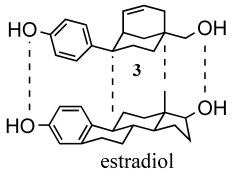
Bioorg. Med. Chem. Lett. 13 (2003) 1919

A Novel Estrogen Receptor Ligand Template

Robert Sibley,* Holia Hatoum-Mokdad, Robert Schoenleber, Laszlo Musza, William Stirtan, Diana Marrero, William Carley, Hong Xiao and Jacques Dumas

Bayer Research Center, Bayer Corporation, Pharmaceutical Division, 400 Morgan Lane, West Haven, CT 06516, USA

Three synthetic routes towards a novel estrogen receptor ligand template based on a rigid bicyclo-[3.3.1]-nonene core have been investigated. The successful route employs Diels–Alder ring formation followed by trans-annular cyclization through an enolate intermediate. The prototype compound **3** exhibits potent binding at the ERβ receptor with promising selectivity against ERα, and is an agonist in MCF-7 cells.



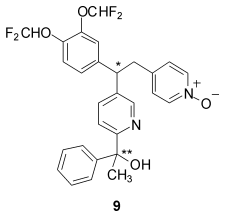
Bioorg. Med. Chem. Lett. 13 (2003) 1923

Substituted 2-Pyridinemethanol Derivatives as Potent and Selective Phosphodiesterase-4 Inhibitors

Yves Ducharme,* Richard W. Friesen, Marc Blouin, Bernard Côté, Daniel Dubé, Diane Ethier, Richard Frenette, France Laliberté, Joseph A. Mancini, Paul Masson, Angela Styhler, 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 activity of a novel series of PDE4 inhibitors is reported. SAR studies in this series led to the identification of optimized inhibitor **9**.



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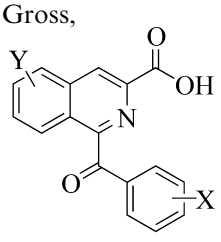
Bioorg. Med. Chem. Lett. 13 (2003) 1927

6,7-Dihydroxyisoquinoline-3-carboxylic Acids are Potent Inhibitors on the Binding of Insulin-Like Growth Factor (IGF) to IGF-Binding Proteins: Optimization of the 1-Position Benzoyl Side Chain

Yun-Fei Zhu, Keith Wilcoxen, Timothy Gross, Patrick Connors, Nathalie Strack, Raymond Gross, Charles Q. Huang, James R. McCarthy, Qiu Xie, Nicholas Ling and Chen Chen*

Department of Medicinal Chemistry and Department of Peptide Chemistry, Neurocrine Biosciences, Inc., 10555 Science Center Drive, San Diego, CA 92121, USA

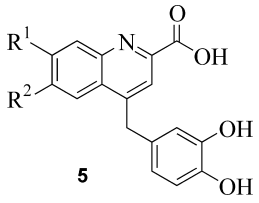


Bioorg. Med. Chem. Lett. 13 (2003) 1931

Quinoline-Carboxylic Acids are Potent Inhibitors that Inhibit the Binding of Insulin-Like Growth Factor (IGF) to IGF-Binding Proteins

Yun-Fei Zhu, Xiao-Chuan Wang, Patrick Connors, Keith Wilcoxen, Yinghong Gao, Raymond Gross, Nathalie Strack, Timothy Gross, James R. McCarthy, Qiu Xie, Nicholas Ling and Chen Chen*

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



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Bioorg. Med. Chem. Lett. 13 (2003) 1935

Antifungal Activity of a *Candida albicans* GGTase I Inhibitor-Alanine Conjugate. Inhibition of Rho1p Prenylation in *C. albicans*

Krishna K. Murthi,[a,*] Susan E. Smith,[b] Arthur F. Kluge,[a] Gustave Bergnes,[a] Patrick Bureau[a] and Vivian Berlin[b]

[a]*GPC Biotech, Inc., Departments of Chemistry, 610 Lincoln Street, Waltham, MA 02451, USA*
[b]*GPC Biotech, Inc., Department of Yeast Genetics, 610 Lincoln Street, Waltham, MA 02451, USA*

An alanine conjugate of a *Candida albicans* geranylgeranyl transferase I inhibitor was synthesized to facilitate its uptake into the fungal cell. The antifungal activity of CaGGTase-Ala conjugate is demonstrated. It is also shown that the CaGGTase-Ala conjugate affects prenylation of endogenous Rho1p, but has no effect on prenylation of endogenous Ras1p.

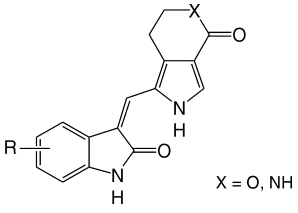
Bioorg. Med. Chem. Lett. 13 (2003) 1939

Novel Pyrrolyllactone and Pyrrolyllactam Indolinones as Potent Cyclin-Dependent Kinase 2 Inhibitors

Xiaoyuan Li,* Ping Huang, Jingrong Jean Cui, Jennifer Zhang and Cho Tang*

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

The discovery of a novel series of pyrrolyllactone and pyrrolyllactam indolinones as potent CDK2 inhibitors is reported.

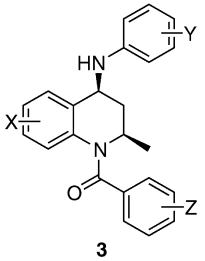


Bioorg. Med. Chem. Lett. 13 (2003) 1943

Synthesis and SAR of *cis*-1-Benzoyl-1,2,3,4-tetrahydroquinoline Ligands for Control of Gene Expression in Ecdysone Responsive Systems

Howard C. Smith,[a] Caitlin K. Cavanaugh,[a] Jennifer L. Friz,[a] Christine S. Thompson,[a] Jessica A. Saggers,[a] Enrique L. Michelotti,[b] Javier Garcia[b] and Colin M. Tice[a,*]

[a]*RHeoGene, PO Box 949, 727 Norristown Road, Spring House, PA 19477-0949, USA*
[b]*Rohm and Haas Company, PO Box 904, 727 Norristown Road, Spring House, PA 19477-0904, USA*



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