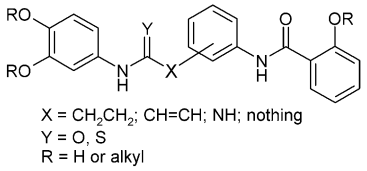
## Effect of Catechol Derivatives on Cell Growth and Lipoxygenase Activity

*Bioorg. Med. Chem. Lett. 13 (2003) 2435*

Julie Simpson, Rebecca Forrester, Michael J. Tisdale, David C. Billington and Daniel L. Rathbone*

*School of Life and Health Sciences, Aston University, Birmingham B4 7ET, UK*

Potent ($IC_{50}$ $10^{-6}$–$10^{-7}$ M) inhibition of the growth of murine colonic tumour cells in vitro was observed along with inhibition of 5-, 12- and 15-lipoxygenase in intact cells and inhibition of rabbit reticulocyte 15- lipoxygenase ($IC_{50}$ ~1 μM).



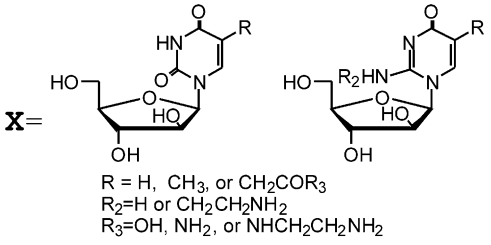

## Convenient Synthesis of Oligodeoxyribonucleotides Bearing Arabinofuranosyl Pyrimidine Derivatives and Its Duplex Formation with Complementary DNA

*Bioorg. Med. Chem. Lett. 13 (2003) 2441*

Hiroaki Ozaki,* Kiyohiro Nakajima, Kaoru Tatsui, Chieko Izumi, Masayasu Kuwahara and Hiroaki Sawai

*Department of Chemistry, Faculty of Engineering, Gunma University, 1-5-1 Tenjin-cho, Kiryu, Gunma 376-8515, Japan*

5'd(CGCTTCTXCCTGCCA)3'
3'd(GCGAAGAAGGACGGT)5'



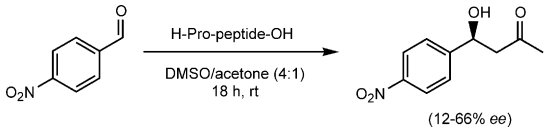

## Discovery of New Peptide-based Catalysts for the Direct Asymmetric Aldol Reaction

*Bioorg. Med. Chem. Lett. 13 (2003) 2445*

Jacob Kofoed,[a,b] John Nielsen[b] and Jean-Louis Reymond[a,*]

[a]*Department of Chemistry and Biochemistry, University of Berne, Freiestrasse 3, 3012 Berne, Switzerland*
[b]*Chemistry Department, The Royal Veterinary and Agricultural University, Thorvaldsensvej 40, 1871 Frederiksberg C, Denmark*

Small molecule peptides with N-terminal proline were found to catalyze the direct asymmetric aldol reaction between acetone and *p*-nitrobenzaldehyde with good activity and moderate enantioselectivity.

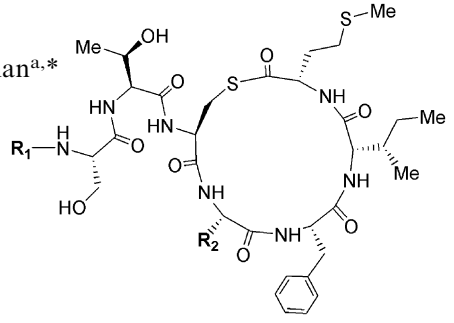



## Side-Chain-to-Tail Thiolactone Peptide Inhibitors of the Staphylococcal Quorum-Sensing System

*Bioorg. Med. Chem. Lett. 13 (2003) 2449*

R. John Scott,[a] Lu-Yun Lian,[c] S. Hanna Muharram,[b] Alan Cockayne,[b] Stewart J. Wood,[a] Barrie W. Bycroft,[a] Paul Williams[a,b] and Weng C. Chan[a,*]

[a]*School of Pharmaceutical Sciences, University of Nottingham, University Park, Nottingham NG7 2RD, UK*
[b]*Institute of Infection, Immunity & Inflammation, University of Nottingham, University Park, Nottingham NG7 2RD, UK*
[c]*Department of Biomolecular Sciences, University of Manchester Institute of Science & Technology, The Mill, Sackville Street, Manchester M60 1QD, UK*



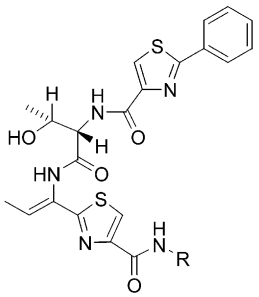
Bioorg. Med. Chem. Lett. 13 (2003) 2455

## Structure-Based Design of Agents Targeting the Bacterial Ribosome

Justin Bower,[a] Martin Drysdale,[a] Richard Hebdon,[b] Allan Jordan,[a,*] Georg Lentzen,[c] Natalia Matassova,[d] Alastair Murchie,[d] Jenifer Powles[c] and Stephen Roughley[a]

[a]*Department of Medicinal Chemistry, RiboTargets Ltd., Granta Park, Abington, Cambridge CB1 6GB, UK*
[b]*Department of Bacteriology, RiboTargets Ltd., Granta Park, Abington, Cambridge CB1 6GB, UK*
[c]*Department of Screening, RiboTargets Ltd., Granta Park, Abington, Cambridge CB1 6GB, UK*
[d]*Department of Assay Development, RiboTargets Ltd., Granta Park, Abington, Cambridge CB1 6GB, UK*

Structure-based drug design has been applied to the antibiotic thiostrepton. Knowledge of the interaction between the antibiotic and the bacterial ribosome has allowed the design and preparation of a library of compounds in an effort to overcome some of thiostreptons' limitations.

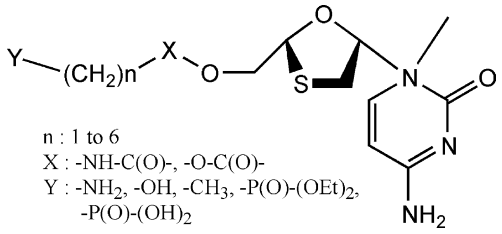


Bioorg. Med. Chem. Lett. 13 (2003) 2459

## Are 5′-*O*-Carbamate-2′,3′-dideoxythiacytidine New Anti-HIV and Anti-HBV Nucleoside Drugs or Prodrugs?

Carole Anastasi,[a,b] Patrick Vlieghe,[b] Olivier Hantz,[c] Olivier Schorr,[c] Christophe Pannecouque,[d] Myriam Witvrouw,[d] Erik De Clercq,[d] Pascal Clayette,[e,f] Nathalie Dereuddre-Bosquet,[e,f] Dominique Dormont,[e] Françoise Gondois-Rey,[g] Ivan Hirsch[g] and Jean-Louis Kraus[a,*]

[a]*Laboratoire de Chimie Biomoléculaire, INSERM U-382, IBDM, Université Méditerranée, Parc Scientifique de Luminy, 163 avenue de Luminy, case 901, 13288 Marseille Cedex 9, France*
[b]*Laboratoires LAPHAL, Avenue de Provence, B.P. 7, 13718 Allauch Cedex, France*
[c]*INSERM U-271, Unité de Recherche sur les Hépatites, le Sida et les Rétrovirus Humains, 151 cours A. Thomas, 69424 Lyon cedex 3, France*
[d]*Rega Institute for Medicinal Research, Katholieke Universiteit Leuven, B-3000 Leuven, Belgium*
[e]*CEA, Service de Neurovirologie, DSV/DRM, CRSSA, 60-68 avenue de la division Leclerc, B.P. 6, 92265 Fontenay aux Roses Cedex, France*
[f]*SPI-BIO, 2 rue du Buisson aux Fraises, Z.I. de la Bonde, 91741 Massy Cedex, France*
[g]*INSERM U-372, Unité de Pathogénie des Infections à Lentivirus, Parc Scientifique de Luminy, 163 avenue de Luminy, B.P 178, 13276 Marseille Cedex 9, France*




n : 1 to 6
X : -NH-C(O)-, -O-C(O)-
Y : $-NH_2$, -OH, $-CH_3$, $-P(O)-(OEt)_2$, $-P(O)-(OH)_2$

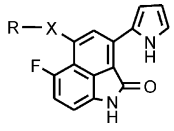
Bioorg. Med. Chem. Lett. 13 (2003) 2465

## 3,5,6-Trisubstituted Naphthostyrils as CDK2 Inhibitors

Jin-Jun Liu,[a,*] Apostolos Dermatakis,[a] Christine Lukacs,[a] Fred Konzelmann,[a] Yi Chen,[a] Ursula Kammlott,[a] Wanda Depinto,[b] Hong Yang,[b] Xuefeng Yin,[b] Yingsi Chen,[b] Andy Schutt,[b] Mary Ellen Simcox[b] and Kin-Chun Luk[a]

[a]*Department of Discovery Chemistry, Hoffmann-La Roche Inc., 340 Kingsland Street, Nutley, NJ 07110, USA*
[b]*Department of Oncology, Hoffmann-La Roche Inc., 340 Kingsland Street, Nutley, NJ 07110, USA*

A novel class of 3,5,6-trisubstituted naphthostyril analogues was designed and synthesized to study the structure–activity relationship for inhibition of cyclin-dependent kinase 2 (CDK2). These compounds, particularly molecules with side-chain modifications providing additional hydrogen bonding capability, were demonstrated to be potent CDK2 inhibitors with cellular activities consistent with CDK2 inhibition.




X = O, NH, C, S, S(=O), $SO_2$

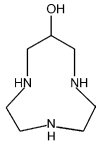
Bioorg. Med. Chem. Lett. 13 (2003) 2469

## Copper Complex of Hydroxyl-Substituted Triazamacrocyclic Ligand and Its Antitumor Activity

Feng Liang,[a] Chengtai Wu,[a,*] Huakuan Lin,[b] Tao Li,[c] Dongzhao Gao,[b] Zhaoyang Li,[d] Jun Wei,[d] Congyi Zheng[d] and Mengxiang Sun[d]

[a]*Department of Chemistry, Wuhan University, Wuhan 430072, PR China*
[b]*Department of Chemistry, Nankai University, Tianjin 300071, PR China*
[c]*Department of Ophthalmology, The Affiliated Tongji Hospital, Tongji Medical College of Huazhong University of Science and Technology, Wuhan 430030, PR China*
[d]*School of Life Sciences, Wuhan University, Wuhan 430072, PR China*

Antitumor activity evaluations of copper complex with triaza macrocyclic ligand were presented.



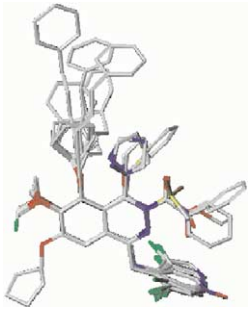
*Bioorg. Med. Chem. Lett. 13 (2003) 2473*

## Comparative Molecular Field Analysis (CoMFA) of Phthalazine Derivatives as Phosphodiesterase IV Inhibitors

Asit K. Chakraborti,* B. Gopalakrishnan, M. Elizabeth Sobhia and Alpeshkumar Malde

*Department of Medicinal Chemistry, National Institute of Pharmaceutical Education and Research (NIPER), Sector-67, S.A.S. Nagar 160 062, Punjab, India*

The CoMFA study of phthalazine derivatives of PDE IV inhibitors is reported.



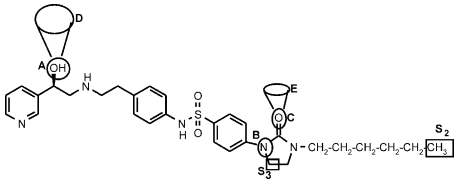
*Bioorg. Med. Chem. Lett. 13 (2003) 2481*

## Development of 3D-QSAR Models in Cyclic Ureidobenzenesulfonamides: Human $\beta_3$-Adrenergic Receptor Agonist

Sushil K. Kashaw, Lalit Rathi, Pradeep Mishra and Anil K. Saxena*

*Medicinal Chemistry Division, Central Drug Research Institute, Lucknow 226001, India*

3D-QSAR studies have been performed on ureidobenzene-sulfonamides to identify the essential structural and physico-chemical requirement in terms of common biophoric and secondary sites for binding and interacting with $\beta_3$-adrenoceptors.

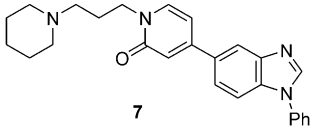


*Bioorg. Med. Chem. Lett. 13 (2003) 2485*

## Design and Synthesis of 1,5-Diarylbenzimidazoles as Inhibitors of the VEGF-Receptor KDR

Mark T. Bilodeau,* April M. Cunningham, Timothy J. Koester, Patrice A. Ciecko, Kathleen E. Coll, William R. Huckle, Randall W. Hungate, Richard L. Kendall, Rosemary C. McFall, Xianzhi Mao, Ruth Z. Rutledge and Kenneth A. Thomas

*Departments of Medicinal Chemistry and Cancer Research, Merck Research Laboratories, PO Box 4, West Point, PA 19486, USA*



7

KDR $IC_{50}$ = 25 nM
Cell $IC_{50}$ = 37 nM

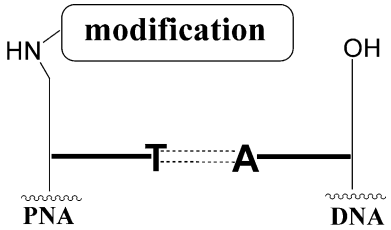
*Bioorg. Med. Chem. Lett. 13 (2003) 2489*

## Synthesis and DNA Binding Properties of Terminally Modified Peptide Nucleic Acids

Andriy Mokhir, Burkhard Zohm, Andreas Fuessl and Roland Kraemer*

*Anorganisch-Chemisches Institut, Karl-Ruprechts University of Heidelberg, Im Neuenheimer Feld 270, Heidelberg 69120, Germany*

PNA conjugates with terminal modifications having varying structure and charge were synthesized and their binding to DNA was studied.



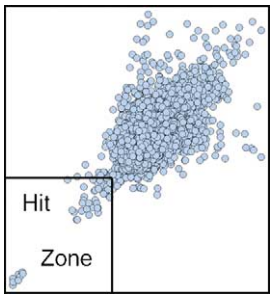
Bioorg. Med. Chem. Lett. 13 (2003) 2493

## High Throughput Screening Identifies Novel Inhibitors of *Escherichia coli* Dihydrofolate Reductase that are Competitive with Dihydrofolate

Michela Zolli-Juran,[a] Jonathan D. Cechetto,[a] Rebecca Hartlen,[a] Denis M. Daigle[b] and Eric D. Brown[a,b,*]

[a]*McMaster HTS Lab, Department of Biochemistry, McMaster University, Hamilton, ON, Canada L8N 3Z5*
[b]*Canadian Bacterial Diseases Network, Antimicrobial Research Centre, Department of Biochemistry, McMaster University, Hamilton, ON, Canada L8N 3Z5*

High throughput screening of 50,000 small molecules against dihydrofolate reductase.



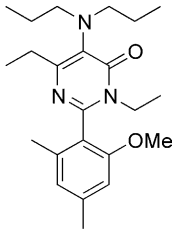

Bioorg. Med. Chem. Lett. 13 (2003) 2497

## 2-Aryl-3,6-dialkyl-5-dialkylaminopyrimidin-4-ones as Novel CRF-1 Receptor Antagonists

Kevin J. Hodgetts, Taeyoung Yoon, Jianhua Huang, Michael Gulianello, Andrzej Kieltyka, Renee Primus, Robbin Brodbeck, Stéphane De Lombaert and Darío Doller*

*Neurogen Corporation, 35 NE Industrial Road, Branford, CT 06405, USA*

The discovery, synthesis and structure–activity studies of a novel series of 2-arylpyrimidin-4-ones as CRF-1 receptor antagonists is described.




1, CRF-1 $K_i$ = 4 nM

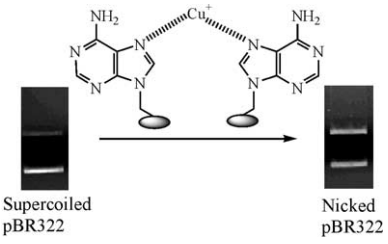
Bioorg. Med. Chem. Lett. 13 (2003) 2501

## DNA Strand Scission by a Cu(I)·Adenylated Polymeric Template: Preliminary Mechanistic and Recycling Studies

Sandeep Verma,[a,*] S. G. Srivatsan, Craig A. Claussen[b] and Eric C. Long[b]

[a]*Department of Chemistry, Indian Institute of Technology-Kanpur, Kanpur 208016 (UP), India*
[b]*Department of Chemistry, Indiana University Purdue University-Indianapolis, Indianapolis, IN 46202, USA*

Cleavage of model phosphate esters and supercoiled plasmid DNA by a Cu(I)·adenylated polymer template is reported.

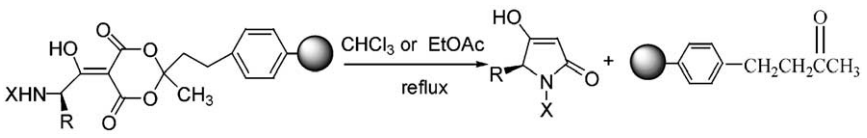



Bioorg. Med. Chem. Lett. 13 (2003) 2505

## A Facile Solid Phase Synthesis of Tetramic Acid

Zhanxiang Liu, Xiuxiu Ruan and Xian Huang*

*Department of Chemistry, Zhejiang University (Campus Xixi), Hangzhou, 310028, People's Republic of China*



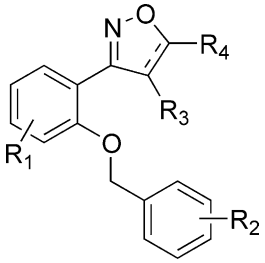
*Bioorg. Med. Chem. Lett. 13 (2003) 2509*

## 3-(2-Benzyloxyphenyl)isoxazoles and Isoxazolines: Synthesis and Evaluation as CFTR Activators

Robert E. Sammelson,[a,*] T. Ma,[b] Luis J. V. Galietta,[c] A. S. Verkman[b] and Mark J. Kurth[a]

[a]*Department of Chemistry, University of California, Davis, CA 95616-5295, USA*
[b]*Department of Medicine and Physiology, Cardiovascular Research Institute, University of California, San Francisco, CA 94143-0521, USA*
[c]*Laboratory of Molecular Genetics, Istituto Giannina Gaslini, 16148 Genova, Italy*

A novel class of activators for chloride conductance in the cystic fibrosis transmembrane conductance regulator is reported.

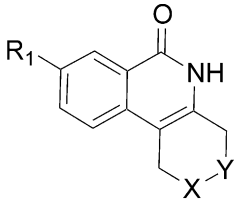



*Bioorg. Med. Chem. Lett. 13 (2003) 2513*

## Design and Synthesis of Poly(ADP-ribose)polymerase-1 (PARP-1) Inhibitors. Part 3: In Vitro Evaluation of 1,3,4,5-Tetrahydro-benzo[*c*][1,6]- and [*c*][1,7]-naphthyridin-6-ones

Dana Ferraris,* Rica Pargas Ficco, Thomas Pahutski, Susan Lautar, Shirley Huang, Jie Zhang and Vincent Kalish

*Guilford Pharmaceuticals Inc., 6611 Tributary Street, Baltimore, MA 21224, USA*




$R_1$ = H or F,
X = NR or $CH_2$

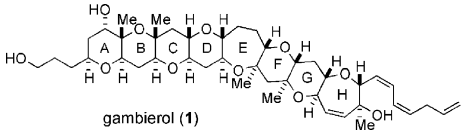
*Bioorg. Med. Chem. Lett. 13 (2003) 2519*

## Synthesis and Biological Evaluation of Gambierol Analogues

Haruhiko Fuwa,[a] Noriko Kainuma,[a] Masayuki Satake[b] and Makoto Sasaki[b,*]

[a]*Graduate School of Science, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan*
[b]*Graduate School of Life Sciences, Tohoku University, Tsutumidori-Amamiya, Aoba-ku, Sendai 981-8555, Japan*

Synthesis of the structural analogues of gambierol (**1**) and evaluation of their toxicity are reported.




gambierol (**1**)

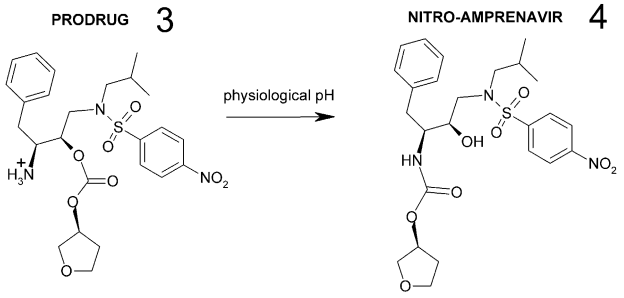
*Bioorg. Med. Chem. Lett. 13 (2003) 2523*

## Novel Prodrug Approach to Amprenavir-Based HIV-1 Protease Inhibitors Via O→*N Acyloxy* Migration of P1 Moiety

Wieslaw M. Kazmierski,* Patricia Bevans, Eric Furfine, Andrew Spaltenstein and Hanbiao Yang

*GlaxoSmithKline, 5 Moore Drive, Research Triangle Park, NC 27709, USA*

We have developed a new approach to prodrugs, which utilizes a pH-induced intramolecular O→*N* migration of an acyloxy group in carbonate moiety to free amino moiety. This method is exemplified by a facile rearrangement of highly water-soluble prodrug **3** to carbamate **4**, a close analogue of HIV-1 protease inhibitor Amprenavir. The O→*N acyloxy* migration is unprecedented in the context of prodrugs and it enables a high atom economy due to recycling of the 'pro' moiety.

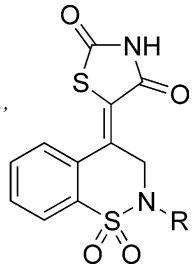


Bioorg. Med. Chem. Lett. 13 (2003) 2527

## Synthesis and In Vitro Evaluation of Novel Small Molecule Inhibitors of Bacterial Arylamine *N*-Acetyltransferases (NATs)

Edward W. Brooke,[b] Stephen G. Davies,[a,*] Andrew W. Mulvaney,[a] Minoru Okada,[c] Frédérique Pompeo,[b] Edith Sim,[b] Richard J. Vickers[a] and Isaac M. Westwood[a]

[a]*The Dyson Perrins Laboratory, University of Oxford, South Parks Road, Oxford OX1 3QY, UK*
[b]*Department of Pharmacology, University of Oxford, Mansfield Road, Oxford OX1 3QT, UK*
[c]*Chemistry Laboratories, Institute for Drug Discovery Research, Yamanouchi Pharmaceutical Company Ltd., 21 Miyukigoaka, Tsukuba, Ibaraki, 305-8585, Japan*



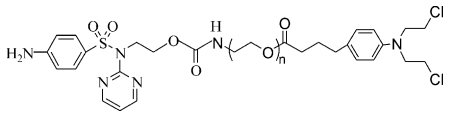
The synthesis and in vitro evaluation of a novel series of 5-substituted-(1,1-dioxo-2,3-dihydro-1H-1λ$^6$-benzo[e][1,2]thiazin-4-ylidene)-thiazolidine-2,4-dione analogues as competitive inhibitors of bacterial arylamine-*N*-acetyltransferases are reported.

Bioorg. Med. Chem. Lett. 13 (2003) 2531

## Synthesis of Poly(Ethylene Glycol) with Sulfadiazine and Chlorambucil End Groups and Investigation of Its Antitumor Activity

Zhongfan Jia, Haitao Zhang and Junlian Huang*

*The Key Laboratory of Molecular Engineering, Education Ministry of China, Department of Macromolecular Science, Fudan University, Shanghai 200433, People's Republic of China*



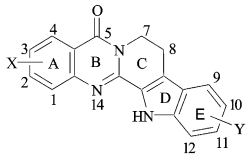
α-Amino-ω-hydroxyl-poly ethylene glycol) (PEG) with different molecular weight ($M_n$ = 2100, 4400, 7200) were synthesized and used as carrier for the combination of sulfadiazine and chlorambucil. In vivo, all these polymer drugs with sulfadiazine and chlorambucil at each end showed the higher antitumor activity against Lewis lung cancer than the same polymers but without the sulfadiazine. The best one is the sample with molecular weight of 2100.

Bioorg. Med. Chem. Lett. 13 (2003) 2535

## Effect of Structural Modification on the Inhibitory Selectivity of Rutaecarpine Derivatives on Human CYP1A1, CYP1A2, and CYP1B1

Ming-Jaw Don,[a] David F. V. Lewis,[b] Shu-Yun Wang,[a] Mei-Wen Tsai[a] and Yune-Fang Ueng[a,*]

[a]*National Research Institute of Chinese Medicine, 155-1 Li-Nong Street, Sec. 2, Taipei 112, Taiwan, ROC*
[b]*School of Biomedical and Life Sciences, University of Surrey, Guildford, Surrey GU2 7XH, UK*



Inhibitory selectivity of rutaecarpine derivatives on human CYP1 members is discussed.

1, X = Y = H
2, X = H, Y = 10-OMe
3, X = H, Y = 11-OMe
4, X = Y = H, 7,8 = Δ
5, X = 1-OMe, Y = H
6, X = 2-OMe, Y = H
7, X = 3-OMe, Y = H
8, X = 1,2-di-OMe, Y = H
9, X = 1,3-di-OMe, Y = H
10, X = 2,3-di-OMe, Y = H
11, X = 3,4-di-OMe, Y =H
12, X = 2-Cl, Y = H
13, X = 3-Cl, Y = H
14, X = 3-Br, Y = H

Bioorg. Med. Chem. Lett. 13 (2003) 2539

## Discovery of the First Series of Inhibitors of Human Papillomavirus Type 11: Inhibition of the Assembly of the E1–E2–Origin DNA Complex

Christiane Yoakim,[a,*] William W. Ogilvie,[a] Nathalie Goudreau,[a] Julie Naud,[a] Bruno Haché,[a] Jeff A. O'Meara,[a] Michael G. Cordingley,[b] Jacques Archambault[b] and Peter W. White[b]

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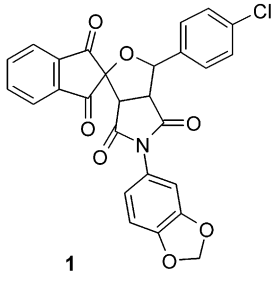

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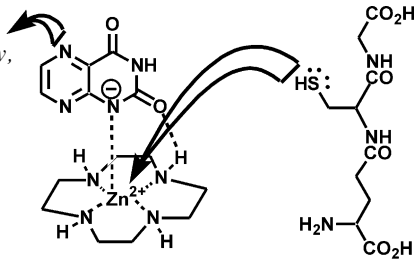
Bioorg. Med. Chem. Lett. 13 (2003) 2543

## Molecular Probe for Selective Detection of Thiols in Water of Neutral pH

Dong H. Kim* and Min Su Han

*Center for Integrated Molecular Systems and Department of Chemistry, Division of Molecular and Life Sciences, Pohang University of Science and Technology, San 31 Hyoja-dong, Pohang 790-784, South Korea*

Glutathione, a biologically important thiol-containing tripeptide is detected by $[Zn(cyclen)(lumazine)]^{+}$ in aqueous solution of neutral pH.



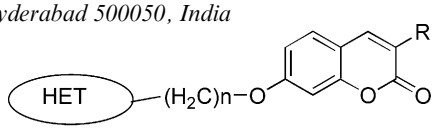
Bioorg. Med. Chem. Lett. 13 (2003) 2547

## Novel Coumarin Derivatives of Heterocyclic Compounds as Lipid-Lowering Agents

Gurram R. Madhavan,[a,*] Vadla Balraju,[a] Bejugam Mallesham,[a] Ranjan Chakrabarti[b] and Vidya B. Lohray[a]

[a]*Discovery Chemistry, Dr. Reddy's Discovery Research, Bollarum Road, Miyapur, Hyderabad 500050, India*
[b]*Discovery Biology, Dr. Reddy's Discovery Research, Bollarum Road, Miyapur, Hyderabad 500050, India*

Novel coumarin derivatives having different heterocycles (**5, 7a–i, 10 and 11**) and their triglyceride-lowering activities are reported.



R=NHAc, OEt, $CO_2Et$ or $CO_2H$ ; n=1 or 2.

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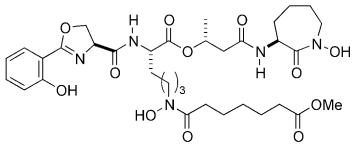
## Solid-Phase Synthesis of Methyl Carboxymycobactin T 7 and Analogues as Potential Antimycobacterial Agents

Amruta R. Poreddy,[a] Otto F. Schall,[a] Garland R. Marshall,[a,b] Colin Ratledge[c] and Urszula Slomczynska[a,*]

[a]*MetaPhore Pharmaceuticals, Inc., 1910 Innerbelt Business Center Drive, Saint Louis, MO 63114, USA*
[b]*Department of Biochemistry and Molecular Biophysics, Washington University School of Medicine, 660 South Euclid Avenue, Saint Louis, MO 63110, USA*
[c]*Department of Applied Biology, The University of Hull, Hull HU6 7RX, UK*

The solid-phase syntheses of methyl carboxymycobactin T 7 (**1a**) and its analogues are reported.



Methyl carboxymycobactin T 7 (**1a**)

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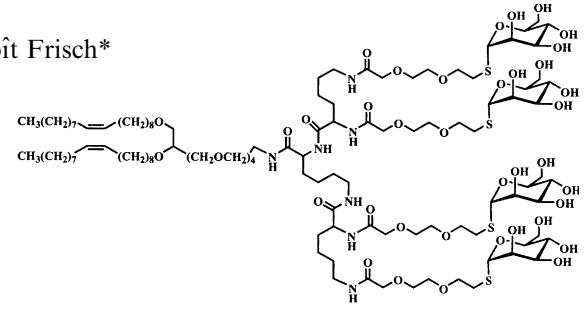
## Synthesis of an Amphiphilic Tetraantennary Mannosyl Conjugate and Incorporation Into Liposome Carriers

Socorro Espuelas, Philippe Haller, Francis Schuber and Benoît Frisch*

*Laboratoire de Chimie Bioorganique, UMR 7514 CNRS/ULP, Université Louis Pasteur, Faculté de Pharmacie, 74 route du Rhin, 67400-Illkirch, France*

We have synthesized a novel conjugate ($Man_4K_3DOG$) composed of a tetramannosyl head group connected, via a polyethylene glycol spacer, to a lipid moiety. This amphiphilic molecule was easily incorporated into the bilayers of liposomes. As expected from the clustering effect, such multivalent mannose residues when exposed on the surface of the vesicles showed much higher binding affinity for Concanavalin A than their monomannosyl analogue.



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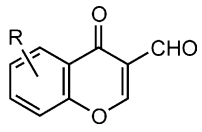
## Formylchromone Derivatives as a Novel Class of Protein Tyrosine Phosphatase 1B Inhibitors

Yi Sup Shim, Ki Chul Kim, Dae Yoon Chi, Keun-Hyeung Lee and Hyeongjin Cho*

*Department of Chemistry and Institute of Molecular Cell Biology, Inha University, 253 Yonghyun-dong, Nam-ku, Incheon 402-751, South Korea*

The chemical reactivities of formylchromone and its derivatives as inhibitors of protein tyrosine phosphatase PTP1B were studied. In an initial assessment of the structure–activity relationship, the most potent inhibitor showed an $IC_{50}$ of 4.3 μM and excellent selectivity against LAR.




Bioorg. Med. Chem. Lett. 13 (2003) 2565

## Ring Substituted Analogues of 5-Aminomethyl-10,11-dihydro-dibenzo[*a*,*d*]cycloheptene (AMDH): Potential Modes of Binding to the 5-$HT_{2A}$ Receptor

Srinivas Peddi,[a] Bryan L. Roth,[b] Richard A. Glennon[a] and Richard B. Westkaemper[a,*]

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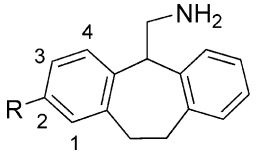
[b]*NIMH Psychoactive Drug Screening Program and Departments of Biochemistry and Psychiatry, Case Western Reserve University School of Medicine, Cleveland, OH 44106,USA*

The 5-$HT_{2A}$ receptor affinities of a parallel series of 2-substituted 5-aminomethyl-10,11-dihydro-dibenzo[*a*,*d*]cycloheptenes, 3-substituted 9-(aminomethyl)-9,10-dihydroanthracenes (AMDA) and 3-substituted DOB analogues suggests that the two tricyclic series of compounds bind to the receptor in different fashions from DOB analogues.



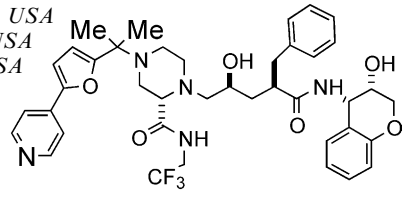

Bioorg. Med. Chem. Lett. 13 (2003) 2569

## HIV Protease Inhibitors with Picomolar Potency Against PI-Resistant HIV-1 by Extension of the $P_3$ Substituent

Joseph L. Duffy,[a,*] Thomas A. Rano,[a] Nancy J. Kevin,[a] Kevin T. Chapman,[a] William A. Schleif,[b] David B. Olsen,[c] Mark Stahlhut,[c] Carrie A. Rutkowski,[c] Lawrence C. Kuo,[d] Lixia Jin,[e] Jiunn H. Lin,[e] Emilio A. Emini[b] and James R. Tata[a]

[a]*Department of Basic Chemistry, Merck Research Laboratories, Rahway, NJ 07065, USA*
[b]*Department of Virus and Cell Biology, Merck Research Laboratories, West Point, PA 19486, USA*
[c]*Department of Biological Chemistry, Merck Research Laboratories, West Point, PA 19486, USA*
[d]*Department of Structural Biology, Merck Research Laboratories, West Point, PA 19486, USA*
[e]*Department of Drug Metabolism, Merck Research Laboratories, West Point, PA 19486, USA*

A biaryl pyridylfuran $P_3$ substituent on the hydroxyethylene isostere scaffold affords HIV protease inhibitors (PI's) with picomolar ($IC_{50}$) potency against the protease enzymes from PI-resistant HIV-1 strains.



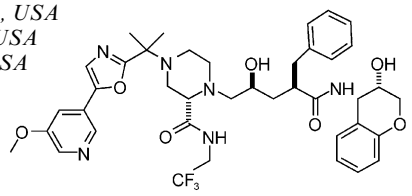

Bioorg. Med. Chem. Lett. 13 (2003) 2573

## The Design, Synthesis and Evaluation of Novel HIV-1 Protease Inhibitors with High Potency Against PI-Resistant Viral Strains

Fengqi Zhang,[a,*] Kevin T. Chapman,[a] William A. Schleif,[b] David B. Olsen,[c] Mark Stahlhut,[c] Carrie A. Rutkowski,[c] Lawrence C. Kuo,[d] Lixia Jin,[e] Jiunn H. Lin,[e] Emilio A. Emini[b] and James R. Tata[a]

[a]*Department of Basic Chemistry, Merck Research Laboratories, Rahway, NJ 07065, USA*
[b]*Department of Virus and Cell Biology, Merck Research Laboratories, West Point, PA 19486, USA*
[c]*Department of Biological Chemistry, Merck Research Laboratories, West Point, PA 19486, USA*
[d]*Department of Structural Biology, Merck Research Laboratories, West Point, PA 19486, USA*
[e]*Department of Drug Metabolism, Merck Research Laboratories, West Point, PA 19486, USA*

The modification of the carboxamide and the pyridyl substituents in indinavir analogues afforded a compound with excellent potency against multiply PI-resistant strains of HIV-1, as well as a more favorable in vivo pharmacokinetic profile.

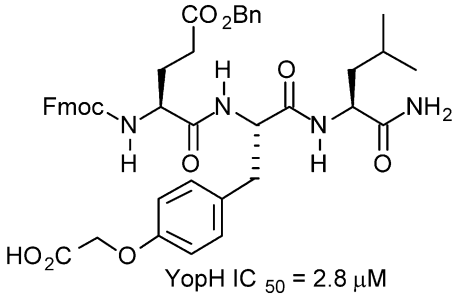


*Bioorg. Med. Chem. Lett. 13 (2003) 2577*

## Tripeptide Inhibitors of *Yersinia* Protein-Tyrosine Phosphatase

Kyeong Lee,[a] Yang Gao,[a] Zhu-Jun Yao,[a] Jason Phan,[b] Li Wu,[c] Jiao Liang,[c] David S. Waugh,[b] Zhong-Yin Zhang[c] and Terrence R. Burke, Jr.[a,*]

[a]*Laboratory of Medicinal Chemistry, CCR, NCI, NIH, NCI-Frederick, Frederick, MD 21702, USA*
[b]*Macromolecular Crystallography Laboratory, CCR, NCI, NIH, NCI-Frederick, Frederick, MD 21702, USA*
[c]*Department of Molecular Pharmacology, Albert Einstein College of Medicine, Bronx, NY 10461, USA*



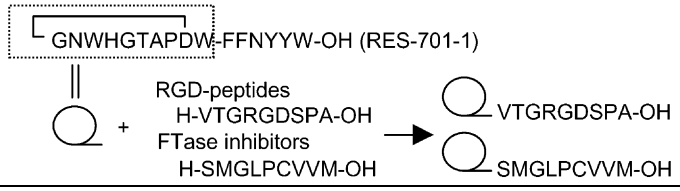

*Bioorg. Med. Chem. Lett. 13 (2003) 2583*

## Improvement of Biological Activity and Proteolytic Stability of Peptides by Coupling with a Cyclic Peptide

Kenji Shibata,[a] Toshiyuki Suzawa,[a] Shiro Soga,[b] Tamio Mizukami,[a] Koji Yamada,[b] Nobuo Hanai[a] and Motoo Yamasaki[a,*]

[a]*Tokyo Research Laboratories, Kyowa Hakko Kogyo Co., Ltd., 3-6-6, Asahi-machi, Machida-shi, Tokyo 194-8533, Japan*
[b]*Pharmaceutical Research Institute, Kyowa Hakko Kogyo Co., Ltd., 1188, Shimotogari, Nagaizumi-cho, Sunto-gun, Shizuoka 411-8731, Japan*

The cyclic moiety of an endothelin antagonist peptide RES-701-1 was coupled to some biologically active peptides to improve their activities and stabilities against proteolysis. Coupling of our cyclic peptide is proposed to be a novel conformation-stabilizing method for biologically active peptides.



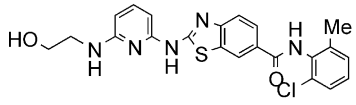

*Bioorg. Med. Chem. Lett. 13 (2003) 2587*

## Discovery of 2-Amino-heteroaryl-benzothiazole-6-anilides as Potent p56$^{lck}$ Inhibitors

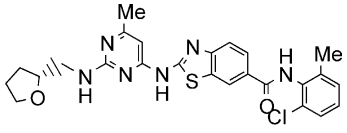
Jagabandhu Das,* Robert V. Moquin, James Lin, Chunjian Liu, Arthur M. Doweyko, Henry F. DeFex, Qiong Fang, Suhong Pang, Sidney Pitt, Ding Ren Shen, Gary L. Schieven, Joel C. Barrish and John Wityak

*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 (SAR), selectivity and cell activity in the T-cell proliferation assay. BMS-350751 (**2**) and BMS-358233 (**3**) are identified as potent Lck inhibitors with excellent cellular activities against T-cell proliferation.



**2** (BMS-350751)
Lck $IC_{50}$ = 0.5 nM
Lck $K_i$ = 900 pM
T-cell Prolif. $I_{50}$ = 475 nM



**3** (BMS-358233)
Lck $IC_{50}$ = 1 nM
Lck $K_i$ = 540 pM
T-cell Prolif. $I_{50}$ = 262 nM

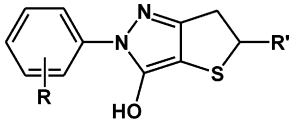
*Bioorg. Med. Chem. Lett. 13 (2003) 2591*

## 2-Phenyl-5,6-dihydro-2*H*-thieno[3,2-*c*]pyrazol-3-ol Derivatives as New Inhibitors of Bacterial Cell Wall Biosynthesis

Zhong Li, Gerardo D. Francisco, William Hu, Pornpen Labthavikul, Peter J. Petersen, Anatoly Severin, Guy Singh, Youjun Yang, Beth A. Rasmussen, Yang-I Lin,* Jerauld S. Skotnicki and Tarek S. Mansour

*Chemical Sciences and Infectious Diseases, Wyeth Research, Pearl River, NY 10965, USA*

Twenty five 2-phenyl-5,6-dihydro-2*H*-thieno[3,2-*c*]pyrazol-3-ol derivatives were synthesized for evaluation as new inhibitors of bacterial cell wall biosynthesis. Many of them demonstrated good inhibitory activity against *Staphylococcoccus aureus* MurB, MurC and MurD enzymes in vitro and antimicrobial activity against gram-positive bacteria including MRSA, VRE and PRSP. However, when they were tested in the presence of 4% bovine serum albumin, the MIC values increased to greater than 128 μg/mL against PRSP. None of the compounds demonstrated activity against gram-negative bacteria at MIC $<32$ μg/mL.



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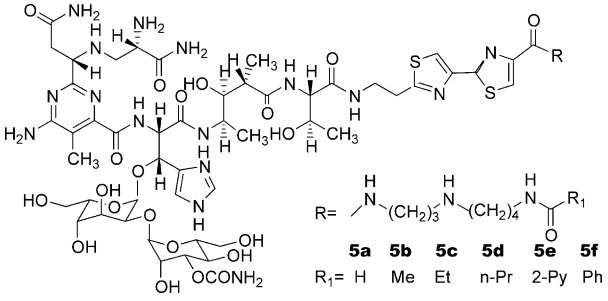
*Bioorg. Med. Chem. Lett. 13 (2003) 2595*

## Synthesis, Biological Evaluation and DNA Binding Properties of Novel Bleomycin Analogues

Zhi-Dong Xu, Min Wang, Su-Long Xiao, Chun-Li Liu and Ming Yang*

*National Research Laboratory of Natural and Biomimetic Drugs, Peking University, Beijing 100083, Peoples Republic of China*



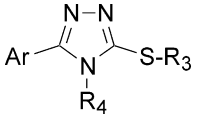

*Bioorg. Med. Chem. Lett. 13 (2003) 2601*

## 1,2,4-Triazolo Mercapto and Aminonitriles as Potent Antifungal Agents

Xavier Collin,[a,*] Armelle Sauleau[a] and Joël Coulon[b]

[a]*Department of Pharmaceutical Chemistry, Faculty of Pharmacy, avenue du Pr Léon Bernard, F-35043 Rennes Cedex, France*
[b]*Department of Microbial Biochemistry, LCPME UMR 7564 CNRS-UHP Nancy 1, Faculty of Pharmacy, 5 rue A. Lebrun, F-54001 Nancy Cedex, France*

A series of 3-mercapto-1,2,4-triazoles mono or disubstituted at 2,3 or 4-positions were synthesized. Antifungal activity is reported.




Ar = substituted phenyl groups
$R_3$ = cyanoalkyl or amidoalkyl groups
$R_4$ = free or protected amino function

*Bioorg. Med. Chem. Lett. 13 (2003) 2607*

## Synthesis and Activity of Novel Benzoxazole Derivatives of Mannopeptimycin Glycopeptide Antibiotics

Phaik-Eng Sum,[a,*] David How,[a] Nancy Torres,[a] Howard Newman,[a] Peter J. Petersen[b] and Tarek S. Mansour[a]

[a]*Chemical Sciences, Wyeth Research, Pearl River, NY 10965, USA*
[b]*Infectious Disease Research, Wyeth Research, Pearl River, NY 10965, USA*

Benzoxazoles of mannopeptimycin-β were synthesized via a novel procedure. Many of the derivatives showed enhanced antibacterial activity than the parent compound mannopeptimycin-β.