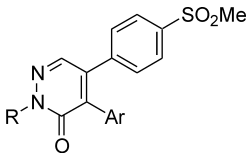
## Pyridazinones as Selective Cyclooxygenase-2 Inhibitors

*Bioorg. Med. Chem. Lett. 13 (2003) 597*

Chun Sing Li,* Christine Brideau, Chi Chung Chan, Chantal Savoie, David Claveau, Stella Charleson, Robert Gordon, Gillian Greig, Jacques Yves Gauthier, Cheuk K. Lau, Denis Riendeau, Michel Thérien, Elizabeth Wong and Petpiboon Prasit

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

Pyridazinone was found to be an excellent core template for selective COX-2 inhibitors.



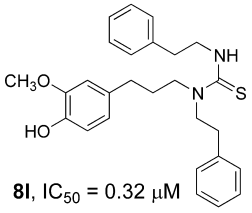

## Synthesis of *N*,*N*′,*N*″-Trisubstituted Thiourea Derivatives and Their Antagonist Effect on the Vanilloid Receptor

*Bioorg. Med. Chem. Lett. 13 (2003) 601*

Hyeung-geun Park,[a,*] Mi-kyung Park,[a] Ji-yeon Choi,[a] Sea-hoon Choi,[a] Jihye Lee,[a] Boon-saeng Park,[a] Myoung Goo Kim,[a] Young-ger Suh,[a] Hawon Cho,[a] Uhtaek Oh,[a] Jeewoo Lee,[a] Hee-Doo Kim,[b] Young-Ho Park,[c] Hyun-Ju Koh,[c] Kyung Min Lim,[c] Joo-Hyun Moh[c] and Sang-sup Jew[a,*]

[a]*Research Institute of Pharmaceutical Sciences and College of Pharmacy, Seoul National University, Seoul 151-742, South Korea*
[b]*College of Pharmacy, Sookmyung Women's University, Seoul 140-742, South Korea*
[c]*AmorePacific R & D Center, Youngin-Si, Kyounggi-do 449-900, South Korea*

Among the prepared *N*,*N*′,*N*″-trisubstituted thioureas, **8l** ($IC_{50} = 0.32$ μM) showed the highest antagonistic activity on the vanilloid receptor in a $^{45}Ca^{2+}$-influx assay.



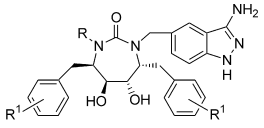

**8l**, $IC_{50}$ = 0.32 μM

## Synthesis, Antiviral Activity and Pharmacokinetics of P1/P1′ Substituted 3-Aminoindazole Cyclic Urea HIV Protease Inhibitors

*Bioorg. Med. Chem. Lett. 13 (2003) 605*

Robert F. Kaltenbach, III,[a,*] Mona Patel,[a] Robert E. Waltermire,[b] Gregory D. Harris,[b] Benjamin R. P. Stone,[b] Ronald M. Klabe,[a] Sena Garber,[a] Lee T. Bacheler,[a] Beverly C. Cordova,[a] Kelly Logue,[a] Matthew R. Wright,[a] Susan Erickson-Viitanen[a] and George L. Trainor[a]

[a]*Bristol-Myers Squibb Company, Experimental Station, Wilmington, DE 19880, USA*
[b]*Process R&D Department, Bristol-Myers Squibb Company, Process Research Facility, Deepwater, NJ 08023, USA*




R = Benzyl
R = *n*-Butyl

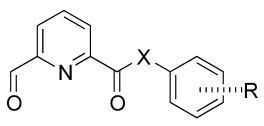
## Synthesis of 6-Formyl-pyridine-2-carboxylate Derivatives and Their Telomerase Inhibitory Activities

*Bioorg. Med. Chem. Lett. 13 (2003) 609*

Sang-sup Jew,[a,*] Boon-saeng Park,[a] Doo-yeon Lim,[a] Myoung Goo Kim,[a] In Kwon Chung,[b] Joo Hee Kim,[b] Chung Il Hong,[c] Joon-Kyum Kim,[c] Hong-Jun Park,[c] Jun-Hee Lee[c] and Hyeung-geun Park[a]

[a]*Research Institute of Pharmaceutical Sciences and College of Pharmacy, Seoul National University, Seoul 151-742, South Korea*
[b]*Department of Biology, College of Science, Yonsei University, Seoul 120-749, South Korea*
[c]*Chong Kun Dang Pharmaceutical Co., Seoul 152-070, South Korea*

Among the prepared 6-formyl-pyridine-2-carboxylate derivatives, **9p** (X = S, R = 3,4-$Cl_2$, $IC_{50} = 23$ μM) showed the highest telomerase inhibitory activity in TRAP assay and the significant in vivo tumor suppression activity.




X = O, N, S

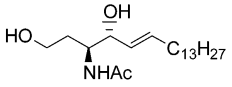
*Bioorg. Med. Chem. Lett. 13 (2003) 613*

## Synthesis of Non-Natural C2-*Homo*-ceramide and its Apoptotic Activity Against HL-60 Cells

Keiji Shikata, Hayato Niiro, Hideki Azuma, Taro Tachibana and Kenji Ogino*

*Department of Applied & Bioapplied Chemistry, Graduate School of Engineering, Osaka City University, Sugimoto 3-3-138, Sumiyoshi-ku, Osaka 558–8585, Japan*

Non-natural ceramide analogues, C2-*homo*-ceramide and C2-*homo*-dihydroceramide, were prepared from L-aspartic acid via L-*homo*-serine. The apoptotic activities of the synthesized ceramide analogues were examined in HL-60 human leukemia cells. C2-*homo*- and C2-*bishomo*-ceramide indicate low but considerable apoptotic activities in comparison with C2-ceramide.




**C2-Cer-1**

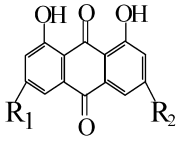
*Bioorg. Med. Chem. Lett. 13 (2003) 617*

## Determination of Active Components in Rhubarb and Study of Their Hydrophobicity by Micellar Electrokinetic Chromatography

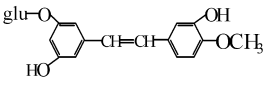
Xiaoyu Shang and Zhuobin Yuan*

*Department of Chemistry, Graduate School of the University of Science and Technology of China, Academia Sinica, Beijing 100039, PR China*

A (MEKC) method has been developed for the determination of six compounds in rhubarb. Hydrophobicity of solutes was studied. The $\Delta(\Delta G)$ derived from this method provide fundamental information on the interaction between solutes and micelle.




| | | |
|---|---|---|
| Aloe-emodin | $R_1$=H | $R_2$=$CH_2OH$ |
| Rhein | $R_1$=H | $R_2$=COOH |
| Emodin | $R_1$=OH | $R_2$=$CH_3$ |
| Physcion | $R_1$=$CH_3O$ | $R_2$=$CH_3$ |
| Chrysophanol | $R_1$=H | $R_2$=$CH_3$ |




Rhaponticin

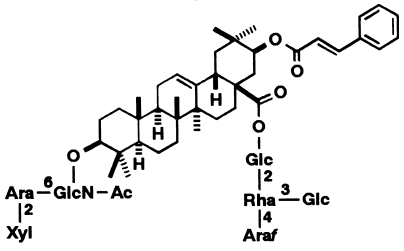
*Bioorg. Med. Chem. Lett. 13 (2003) 623*

## Enterolosaponins A and B, Novel Triterpene Bisdesmosides from *Enterolobium contortisiliquum*, and Evaluation for Their Macrophage-Oriented Cytotoxic Activity

Yoshihiro Mimaki,[a,*] Hiroshi Harada,[a] Chiseko Sakuma,[a] Mitsue Haraguchi,[b] Satoru Yui,[c] Tomoya Kudo,[c] Masatoshi Yamazaki[c] and Yutaka Sashida[a]

[a]*School of Pharmacy, Tokyo University of Pharmacy and Life Science, 1432-1, Horinouchi, Hachioji, Tokyo 192-0392, Japan*
[b]*Centro de Sanidade Animal, Instituto Biológico, Av. Conselheiro Rodrigues Aves, 1252, CEP 04014-002, São Paulo, SP, Brazil*
[c]*Faculty of Pharmaceutical Sciences, Teikyo University, 1091-1, Suarashi, Sagamiko, Tsukui-gun, Kanagawa 199-0195, Japan*

Two novel triterpene bisdesmosides, named enterolosaponin A (**1**) and B (**2**), were isolated from *Enterolobium contortisiliquum*. Enterolosaponin A (**1**) exhibited a highly selective cytotoxicity against BAC1.2F5 mouse macrophages.



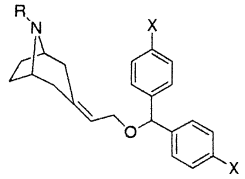

**Enterolosaponin A (1)**

*Bioorg. Med. Chem. Lett. 13 (2003) 629*

## Synthesis of Dopamine Transporter Selective 3-{2-(Diarylmethoxyethylidene)}-8-alkylaryl-8-azabicyclo[3.2.1]octanes

Amy L. Bradley,[a] Sari Izenwasser,[b] Dean Wade,[b] Shaine Cararas[a] and Mark L. Trudell[a,*]

[a]*Department of Chemistry, University of New Orleans, New Orleans, LA 70148, USA*
[b]*Department of Psychiatry, University of Miami School of Medicine, Miami, FL 33136, USA*




R = $CH_2CH_2CH_2Ph$, $CH_2Ph$
X = H, F

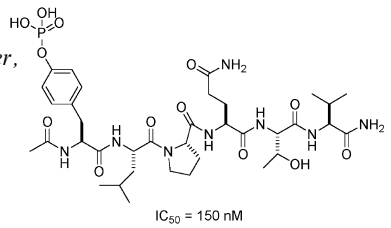
*Bioorg. Med. Chem. Lett. 13 (2003) 633*

## Identification of a High-Affinity Phosphopeptide Inhibitor of Stat3

Zhiyong Ren,[a] Larry A. Cabell,[b] Timothy S. Schaefer[a] and John S. McMurray[b,*]

[a]*Department of Neuro-Surgery, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030, USA*
[b]*Department of Neuro-Oncology, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030, USA*

Acetyl-Tyr ($PO_3H_2$)-Leu-Pro-Gln-Thr-Val-amide, selected from a screen of Stat3 docking sites, was found to be a potent inhibitor of dimerization and DNA binding.

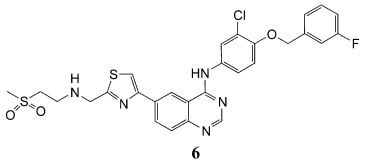



*Bioorg. Med. Chem. Lett. 13 (2003) 637*

## Discovery and Biological Evaluation of Potent Dual ErbB-2/EGFR Tyrosine Kinase Inhibitors: 6-Thiazolylquinazolines

Micheal D. Gaul, Yu Guo, Karen Affleck, G. Stuart Cockerill, Tona M. Gilmer, Robert J. Griffin, Stephen Guntrip, Barry R. Keith, Wilson B. Knight, Robert J. Mullin, Doris M. Murray, David W. Rusnak, Kathryn Smith, Sarva Tadepalli, Edgar R. Wood and Karen Lackey*

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

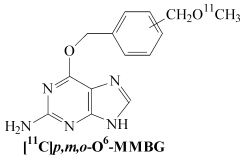



*Bioorg. Med. Chem. Lett. 13 (2003) 641*

## Synthesis and Preliminary Biological Evaluation of 6-*O*-[$^{11}$C]-[(methoxymethyl)benzyl]guanines, New Potential PET Breast Cancer Imaging Agents for the DNA Repair Protein AGT

Xuan Liu,[a] Qi-Huang Zheng,[a,*] Xiangshu Fei,[a] Ji-Quan Wang,[a] David W. Ohannesian,[b] Leonard C. Erickson,[b] K. Lee Stone[a] and Gary D. Hutchins[a]

[a]*Department of Radiology, Indiana University School of Medicine, Indianapolis, IN 46202, USA*
[b]*Department of Pharmacology and Toxicology, Indiana University School of Medicine, Indianapolis, IN 46202, USA*



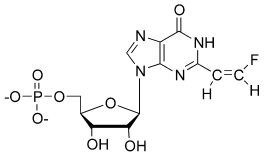

*Bioorg. Med. Chem. Lett. 13 (2003) 645*

## Inhibition of Inosine Monophosphate Dehydrogenase (IMPDH) by 2-[2-(*Z*)-Fluorovinyl]inosine 5′-Monophosphate

Vasu Nair* and Ramesh C. Kamboj

*Department of Pharmaceutical and Biomedical Sciences, The University of Georgia, Athens, GA 30602, USA*

Discovery of a potent inhibitor of inosine monophosphate dehydrogenase.



*Bioorg. Med. Chem. Lett. 13 (2003) 649*

## Structure–Activity Relationship of Linear Peptide Bu-His$^6$-DPhe$^7$-Arg$^8$-Trp$^9$-Gly$^{10}$-$NH_2$ at the Human Melanocortin-1 and -4 Receptors: DPhe$^7$ and Trp$^9$ Substitution

Waleed Danho,* Joseph Swistok, Adrian Wai-Hing Cheung, Grazyna Kurylko, Lucia Franco, Xin-Jie Chu, Li Chen and Keith Yagaloff

*Roche Research Center, Hoffmann-La Roche Inc., Nutley, NJ 07110, USA*

A series of pentapeptides, based on hMC4R pentapeptide agonist (Bu-His$^6$-DPhe$^7$-Arg$^8$-Trp$^9$-Gly$^{10}$-$NH_2$), was prepared in which either DPhe$^7$ or Trp$^9$ residue was systematically substituted. A number of interesting DPhe surrogates (D-Thi, D-3-$CF_3$Phe, D-2-Nal and D-3,4-diClPhe) as well as Trp surrogates (2-Nal and Bta) were identified in this study.

*Bioorg. Med. Chem. Lett. 13 (2003) 653*

## Protective Effect of Imidazolopyrazinone Antioxidants on Ischemia/Reperfusion Injury

Axelle Arrault,[a] Marlène Dubuisson,[b] Sonia Gharbi,[a] Cécile Marchand,[b] Tony Verbeuren,[c] Alain Rupin,[c] Alex Cordi,[c] Eliete Bouskela,[d] Jean-François Rees[b] and Jacqueline Marchand-Brynaert[a,*]

[a]*Unité de Chimie Organique et Médicinale, Université Catholique de Louvain, Bâtiment Lavoisier, Place Louis Pasteur 1, B-1348 Louvain-la-Neuve, Belgium*
[b]*Unité de Biologie Animale, Université Catholique de Louvain, Bâtiment Carnoy, Place Croix du Sud 4, B-1348 Louvain-la-Neuve, Belgium*
[c]*Institut de Recherches Servier, Rue des Moulineaux 11, F-92150 Suresnes, France*
[d]*Laboratorio de Pesquisas em Microcirculaçao, Universidade do estado do Rio de Janeiro, Rua Sao Francisco Xavier 524, 20550-013 Rio de Janeiro, Brazil*

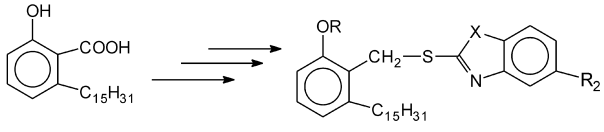
Coelenterazine analogues (bioluminescence substrates) are highly active in 'hamster cheek pouch' model of microvascular permeability.

*Bioorg. Med. Chem. Lett. 13 (2003) 657*

## Design, Synthesis and Biological Evaluation of Benzimidazole/ Benzothiazole and Benzoxazole Derivatives as Cyclooxygenase Inhibitors

R. Paramashivappa, P. Phani Kumar, P. V. Subba Rao and A. Srinivasa Rao*

*Vittal Mallya Scientific Research Foundation, PO Box #406, K. R. Road, Bangalore 560 004, India*



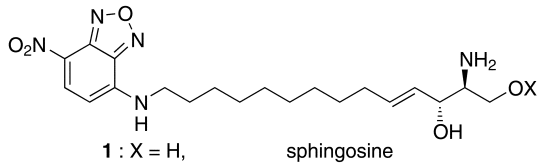

*Bioorg. Med. Chem. Lett. 13 (2003) 661*

## Synthesis of Fluorescence-Labeled Sphingosine and Sphingosine 1-Phosphate; Effective Tools for Sphingosine and Sphingosine 1-Phosphate Behavior

Toshikazu Hakogi,[a] Toshihiko Shigenari,[a] Shigeo Katsumura,[a] Takamitsu Sano,[b] Takayuki Kohno[b] and Yasuyuki Igarashi[b]

[a]*School of Science and Technology, Kwansei Gakuin University, Gakuen, Sanda, Hyogo 669-1337, Japan*
[b]*Graduate School of Pharmaceutical Sciences, Hokkaido University, Sapporo, Hokkaido 060-0812, Japan*

The synthesis of the fluorescence-labeled sphingosine and sphingosine 1-phosphate are reported.



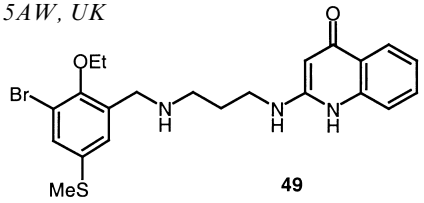
Bioorg. Med. Chem. Lett. 13 (2003) 665

## Optimisation of Aryl Substitution Leading to Potent Methionyl tRNA Synthetase Inhibitors with Excellent Gram-Positive Antibacterial Activity

Richard L. Jarvest,[a,*] John M. Berge,[a] Murray J. Brown,[a] Pamela Brown,[a] John S. Elder,[a] Andrew K. Forrest,[a] C. S. V. Houge-Frydrych,[a] Peter J. O'Hanlon,[a] David J. McNair,[a] Stephen Rittenhouse[b] and Robert J. Sheppard[a]

[a]*GlaxoSmithKline, New Frontiers Science Park, Third Avenue, Harlow, Essex CM19 5AW, UK*
[b]*GlaxoSmithKline, 1250 South Collegeville Road, Collegeville, PA 19426, USA*

Optimisation of the left-hand-side aryl moiety of a file compound screening hit against *Staphylococcus aureus* methionyl tRNA synthetase led to the identification of a series of potent nanomolar inhibitors. The best compounds showed excellent antibacterial activity against staphylococcal and enterococcal pathogens, including strains resistant to clinical antibiotics.



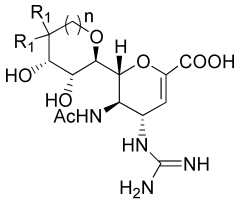

**49**

Bioorg. Med. Chem. Lett. 13 (2003) 669

## Synthesis and Anti-Influenza Evaluation of Orally Active Bicyclic Ether Derivatives Related to Zanamivir

Takeshi Masuda,[a] Satoshi Shibuya,[a] Masami Arai,[a] Shuku Yoshida,[b] Takanori Tomozawa,[b] Akiko Ohno,[b] Makoto Yamashita[b] and Takeshi Honda[a,*]

[a]*Medicinal Chemistry Research Laboratories, Sankyo Co., Ltd., 1-2-58 Hiromachi, Shinagawa-ku, Tokyo 140-8710, Japan*
[b]*Biological Research Laboratories, Sankyo Co., Ltd., 1-2-58 Hiromachi, Shinagawa-ku, Tokyo 140-8710, Japan*




**a**: $R_1$ = H, n = 1
**b**: $R_1$ = H, n = 0
**c**: $R_1$ = F, n = 1
**d**: $R_1$ = H, n = 2

Bioorg. Med. Chem. Lett. 13 (2003) 675

## Ganglioside Binding Pattern of CD33-Related Siglecs

Eugenia Rapoport,[a] Ilya Mikhalyov,[a] Jiquan Zhang,[b] Paul Crocker[b] and Nicolai Bovin[a,*]

[a]*Shemyakin and Ovchinnikov Institute of Bioorganic Chemistry RAS, ul. Miklukho-Maklaya 16/10, Moscow, 117997, Russia*
[b]*Wellcome Trust Biocentre at Dundee, School of Life Sciences, University of Dundee, Dundee DD1 5EH, UK*

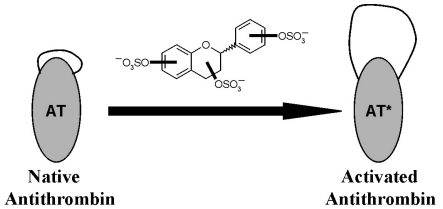
**Siglec-5** → GQ1b; **Siglec-7** → GD3, GQ1b, GT1b
**Siglec-8** → GD3; **Siglec-9** → GM3, GD3, GT1b; **Siglec-10** → GT1b

Bioorg. Med. Chem. Lett. 13 (2003) 679

## Exploring New Non-sugar Sulfated Molecules as Activators of Antithrombin

Gunnar T. Gunnarsson and Umesh R. Desai*

*Department of Medicinal Chemistry, Virginia Commonwealth University, 410 N. 12th Street, PO Box 980540, Richmond, VA 23298, USA*



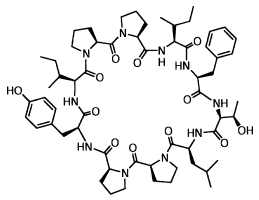
Bioorg. Med. Chem. Lett. 13 (2003) 685

## Antineoplastic Agents 390. Isolation and Structure of Phakellistatin 12 from a Chuuk Archipelago Marine Sponge[1]

George R. Pettit* and Rui Tan

*Cancer Research Institute and Department of Chemistry and Biochemistry, Arizona State University, PO Box 872404, Tempe, AZ 85287-2404, USA*

A new cancer cell-growth-inhibitory cyclodecapeptide, phakellistatin 12 (P388, $ED_{50}$ 2.8 μg/mL) has been isolated from the Western Pacific Ocean sponge, *Phakellia* sp.



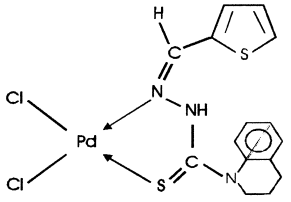
Bioorg. Med. Chem. Lett. 13 (2003) 689

## Synthesis, Spectral Studies and Screening for Amoebicidal Activity of New Palladium(II) Complexes Derived from Thiophene-2-carboxaldehyde Thiosemicarbazones

Shailendra, Neelam Bharti, Fehmida Naqvi and Amir Azam*

*Department of Chemistry, Jamia Millia Islamia, Jamia Nagar, New Delhi 110025, India*

Thiophene-2-carboxaldehyde thiosemicarbazone and their Pd(II) complexes have been synthesized and characterized by elemental analysis, IR, $^1H$ NMR, electronic spectra and thermogravimetric analysis. Assessment of antiamoebic activity against *Entamoeba histolytica* (strain *HM-1:1MSS*) resulted that all Pd(II) complexes were more active than their respective ligands and **2a** showed most promising activity among all the compounds.



**2a**

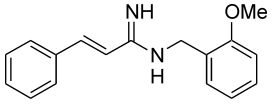
Bioorg. Med. Chem. Lett. 13 (2003) 693

## Novel $N^1$-(Benzyl)cinnamamidine Derived NR2B Subtype-Selective NMDA Receptor Antagonists

Neil R. Curtis,[a,*] Helen J. Diggle,[a] Janusz J. Kulagowski,[a] Clare London,[a] Sarah Grimwood,[b] Peter H. Hutson,[b] Fraser Murray,[b] Pawel Richards,[b] Alison Macaulay[c] and Keith A. Wafford[c]

[a]*Department of Medicinal Chemistry, Merck Sharp & Dohme Research Laboratories, The Neuroscience Research Centre, Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR, UK*
[b]*Department of Behavioural Neuroscience, Merck Sharp & Dohme Research Laboratories, The Neuroscience Research Centre, Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR, UK*
[c]*Department of Pharmacology, Merck Sharp & Dohme Research Laboratories, The Neuroscience Research Centre, Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR, UK*

Novel (*E*)-$N^1$-(benzyl)cinnamamidines (e.g., **1h**) were identified as NR2B subtype-selective NMDA receptor antagonists. Replacement of the styryl unit by 2-naphthyl was well tolerated.



**1h** $K_i$ 0.7 nM

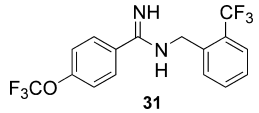
Bioorg. Med. Chem. Lett. 13 (2003) 697

## Orally Efficacious NR2B-Selective NMDA Receptor Antagonists

Christopher F. Claiborne,[a,*] John A. McCauley,[a,*] Brian E. Libby,[a] Neil R. Curtis,[b] Helen J. Diggle,[b] Janusz J. Kulagowski,[b] Stuart R. Michelson,[a] Kenneth D. Anderson,[a] David A. Claremon,[a] Roger M. Freidinger,[a] Rodney A. Bednar,[c] Scott D. Mosser,[c] Stanley L. Gaul,[c] Thomas M. Connolly,[c] Cindra L. Condra,[c] Bohumil Bednar,[c] Gary L. Stump,[d] Joseph J. Lynch,[d] Alison Macaulay,[e] Keith A. Wafford,[e] Kenneth S. Koblan[c] and Nigel J. Liverton[a]

[a]*Department of Medicinal Chemistry, Merck Research Laboratories, West Point, PA 19486, USA*
[b]*Department of Medicinal Chemistry, Merck Sharp & Dohme Research Laboratories, The Neuroscience Research Centre, Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR, UK*
[c]*Department of Molecular Pharmacology, Merck Research Laboratories, West Point, PA 19486, USA*
[d]*Department of Pharmacology, Merck Research Laboratories, West Point, PA 19486, USA*
[e]*Department of Pharmacology, Merck Sharp & Dohme Research Laboratories, The Neuroscience Research Centre, Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR, UK*

A novel series of benzamidines was synthesized and shown to exhibit NR2B-subtype selective NMDA antagonist activity. Compound **31** is orally active in a carrageenan-induced rat hyperalgesia model of pain and shows no motor coordination side effects.



**31**

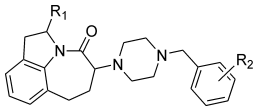
*Bioorg. Med. Chem. Lett. 13 (2003) 701*

## Design, Synthesis, and Discovery of 5-Piperazinyl-1,2,6,7-tetrahydro-5*H*-azepino[3,2,1-*hi*]indol-4-one Derivatives: A Novel Series of Mixed Dopamine $D_2/D_4$ Receptor Antagonist

He Zhao,* Xiaoyan Zhang, Kevin Hodgetts, Andrew Thurkauf, Jack Hammer, Jayaraman Chandrasekhar, Andrzej Kieltyka, Robbin Brodbeck, Stanislaw Rachwal, Renee Primus and Charles Manly

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

5-Piperazinyl-1,2,6,7-tetrahydro-5*H*-azepino[3,2,1-*hi*]indol-4-one derivatives were designed, synthesized, and identified as a new series of mixed dopamine $D_2/D_4$ receptor antagonists. This series featured a rigid tricyclic ring system as an important pharmacophore core structure for high binding affinity. Molecular modeling studies are also described.



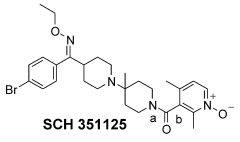
*Bioorg. Med. Chem. Lett. 13 (2003) 705*

## Biological Evaluation and Interconversion Studies of Rotamers of SCH 351125, an Orally Bioavailable CCR5 Antagonist

Anandan Palani,[a,*] Sherry Shapiro,[a] John W. Clader,[a] William J. Greenlee,[a] David Blythin,[a] Kathleen Cox,[b] Nicole E. Wagner,[c] Julie Strizki,[c] Bahige M. Baroudy[c] and Niya Dan[d]

[a]*Chemical Research, Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, NJ 07033, USA*
[b]*Drug Safety and Metabolism, Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, NJ 07033, USA*
[c]*Antiviral Research, Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, NJ 07033, USA*
[d]*Product Development, Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, NJ 07033, USA*

The separation and biological evaluation of rotamers as well as interconversion studies on rotamers of our clinical candidate SCH 351125 are described.

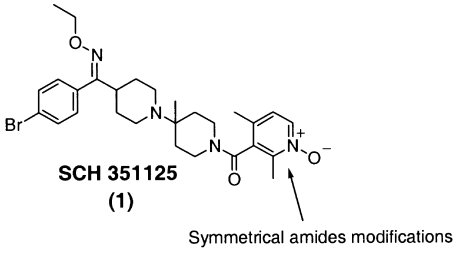



*Bioorg. Med. Chem. Lett. 13 (2003) 709*

## Oximino-Piperidino-Piperidine-Based CCR5 Antagonists. Part 2: Synthesis, SAR and Biological Evaluation of Symmetrical Heteroaryl Carboxamides

Anandan Palani,[a,*] Sherry Shapiro,[a] John W. Clader,[a] William J. Greenlee,[a] Susan Vice,[a] Stuart McCombie,[a] Kathleen Cox,[b] Julie Strizki[c] and Bahige M. Baroudy[c]

[a]*Chemical Research, Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, NJ 07033, USA*
[b]*Drug Safety and Metabolism, Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, NJ 07033, USA*
[c]*Antiviral Research, Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, NJ 07033, USA*



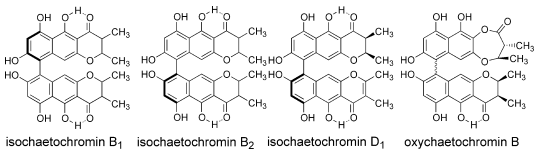

*Bioorg. Med. Chem. Lett. 13 (2003) 713*

## Four Novel Bis-(naphtho-γ-pyrones) Isolated from *Fusarium* Species as Inhibitors of HIV-1 Integrase

Sheo B. Singh,[a,*] Deborah L. Zink,[a] Gerald F. Bills,[b] Ana Teran,[b] Keith C. Silverman,[a] Russell B. Lingham,[a] Peter Felock[c] and Daria J. Hazuda[c]

[a]*Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065, USA*
[b]*CIBE, Merck Sharp & Dohme de Espana, S. A., Josefa Valcárcel 38, 28027 Madrid, Spain*
[c]*Merck Research Laboratories, West Point, PA 19486, USA*

Four novel naphtho-γ-pyrones and derivatives with coupled and strand transfer activity of HIV-1 integrase with $IC_{50}$ values ranging 1–12 μM have been described.



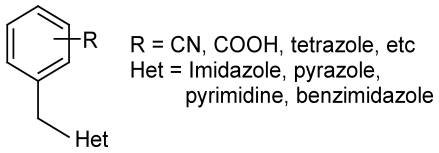
Bioorg. Med. Chem. Lett. 13 (2003) 719

## A Structure–Permeability Study of Small Drug-like Molecules

Thomas Fichert,[a] Mehran Yazdanian[b] and John R. Proudfoot[a,*]

[a]*Department of Medicinal Chemistry, Boehringer Ingelheim Pharmaceuticals Inc., 900 Ridgebury Road, PO Box 368, Ridgefield, CT 06877, USA*
[b]*Department of Pharmaceutics, Boehringer Ingelheim Pharmaceuticals Inc., 900 Ridgebury Road, PO Box 368, Ridgefield, CT 06877, USA*

A systematic structure–permeability relationship study on a set of small drug-like molecules with log D values in the range −2.5 to 3 and carrying a diverse array of functionality reveals that the compounds with log D greater than 0 and less than 3 are highly permeable. Surprisingly, several tetrazole derivatives were found to be substrates for efflux pump(s).



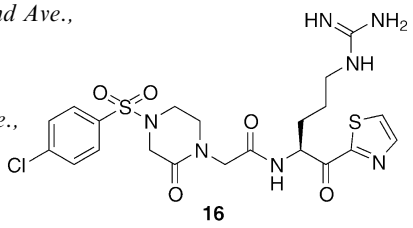

Bioorg. Med. Chem. Lett. 13 (2003) 723

## Design, Synthesis, and Structure–Activity Relationships of Unsubstituted Piperazinone-Based Transition State Factor Xa Inhibitors

Wenrong Huang,[a,*] Mary Ann Naughton,[a] Hua Yang,[a] Ting Su,[a] Suiko Dam,[b] Paul W. Wong,[b] Ann Arfsten,[b] Susan Edwards,[b] Uma Sinha,[b] Stanley Hollenbach,[c] Robert M. Scarborough[a] and Bing-Yan Zhu[a,*]

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

A series of novel transition state factor Xa inhibitors containing a variety of lactam ring systems as central templates was synthesized. Compound **16** displays $IC_{50}$ of 2 nM.




**16**

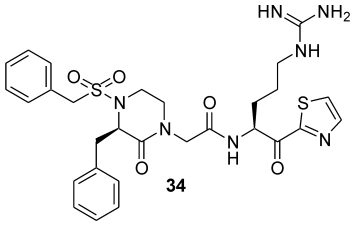
Bioorg. Med. Chem. Lett. 13 (2003) 729

## Design, Synthesis, and Structure–Activity Relationships of Substituted Piperazinone-Based Transition State Factor Xa Inhibitors

Ting Su,[a,*] Hua Yang,[a] Deborah Volkots,[a] John Woolfrey,[a] Suiko Dam,[b] Paul Wong,[b] Uma Sinha,[b] Robert M. Scarborough[a] and Bing-Yan Zhu[a,*]

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

A series of novel transition state factor Xa inhibitors containing substituted piperazinone as central templates was synthesized. Compound **34** displays $IC_{50}$ of 9.4 nM.




**34**

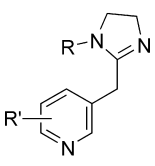
Bioorg. Med. Chem. Lett. 13 (2003) 733

## Binding of Nicotine and Homoazanicotine Analogues at Neuronal Nicotinic Acetylcholinergic (nACh) Receptors

G. Ferretti,[a,b] M. Dukat,[a] M. Giannella,[b] A. Piergentili,[b] M. Pigini,[c] W. Quaglia,[b] M. I. Damaj,[c] B. R. Martin[c] and R. A. Glennon[a,c,*]

[a]*Department of Medicinal Chemistry, Virginia Commonwealth University, Richmond, VA 23298, USA*
[b]*Dipartimento di Scienze Chimiche, Universita di Camerino, Camerino 62032, Italy*
[c]*Department of Pharmacology and Toxicology, Virginia Commonwealth University, Richmond, VA 23298, USA*

A series of homoazanicotine derivatives **3** was found to bind at α4β2 nACh receptors in a manner that appears to parallel that of their corresponding racemic nicotine counterparts.




**3**

Bioorg. Med. Chem. Lett. 13 (2003) 737

## Functional Expression and Characterization of EryA, the Erythritol Kinase of *Brucella Abortus*, and Enzymatic Synthesis of L-Erythritol-4-phosphate

Antonietta M. Lillo,[a] Charles N. Tetzlaff,[a] Félix J. Sangari[b] and David E. Cane[a,*]

[a]*Department of Chemistry, Brown University, Providence, RI 02912-9108, USA*
[b]*Departmento de Biología Molecular, Facultad de Medicina, Universidad de Cantabria, Unidad Asociada al Centro de Investigaciones Biologícas, CSIC, Cardenal Hererra Oria s/n, 39011 Santander, Spain*

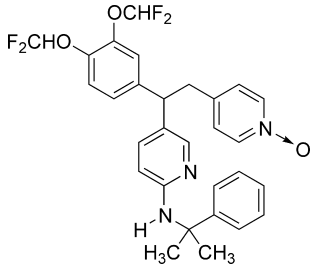
The *eryA* gene has been functionally expressed in *Escherichia coli*, and the resultant EryA was shown to catalyze the ATP-dependent conversion of erythritol (**1**) to L-erythritol-4-phosphate (**2,** L-E4P).

Bioorg. Med. Chem. Lett. 13 (2003) 741

## Substituted Aminopyridines as Potent and Selective Phosphodiesterase-4 Inhibitors

Bernard Côté,* Richard Frenette, Sylvie Prescott, Marc Blouin, Christine Brideau, Yves Ducharme, Richard W. Friesen, France Laliberté, Paul Masson, Angela Styhler and Yves Girard

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



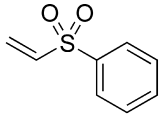

Bioorg. Med. Chem. Lett. 13 (2003) 745

## Lead Discovery of α,β-Unsaturated Sulfones from a Combinatorial Library as Inhibitors of Inducible VCAM-1 Expression

Liming Ni, X. Sharon Zheng, Patricia K. Somers, Lee K. Hoong, Russell R. Hill, Elaine M. Marino, Ki-Ling Suen, Uday Saxena and Charles Q. Meng*

*AtheroGenics, Inc., 8995 Westside Parkway, Alpharetta, GA 30004, USA*

α,β-Unsaturated sulfones have been discovered from a combinatorial library as leads for a new series of inhibitors of inducible VCAM-1 expression.

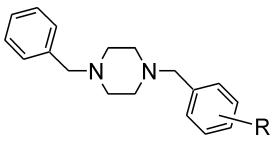



Bioorg. Med. Chem. Lett. 13 (2003) 749

## 1,4-Dibenzylpiperazines Possess Anticocaine Activity

Abby Foster,[a] Huifang Wu,[a] Weibin Chen,[a] Wanda Williams,[b] Wayne D. Bowen,[b] Rae R. Matsumoto[c] and Andrew Coop[a,*]

[a]*Department of Pharmaceutical Sciences, University of Maryland School of Pharmacy, 20 North Pine Street, Baltimore, MD 21201, USA*
[b]*Laboratory of Medicinal Chemistry National Institute of Diabetes, Digestive, and Kidney Diseases, Building 8, Room B1-23, Bethesda, MD 20892, USA*
[c]*Department of Pharmaceutical Sciences, University of Oklahoma Health Science Center College of Pharmacy, 1110 North Stonewall Avenue, Oklahoma City, OK 73117, USA*

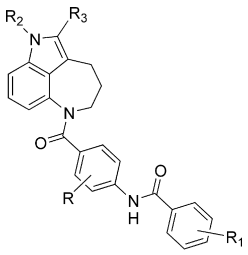


*Bioorg. Med. Chem. Lett. 13 (2003) 753*

## Synthesis and Biological Evaluation of Novel Indoloazepine Derivatives as Non-peptide Vasopressin V2 Receptor Antagonists

Jay M. Matthews,[a,*] Michael N. Greco,[a] Leonard R. Hecker,[a] William J. Hoekstra,[a] Patricia Andrade-Gordon,[a] Lawrence de Garavilla,[a] Keith T. Demarest,[b] Eric Ericson,[b] Joseph W. Gunnet,[b] William Hageman,[a] Richard Look,[b] John B. Moore[b] and Bruce E. Maryanoff[a]

[a]*Drug Discovery, Johnson & Johnson Pharmaceutical Research & Development,[†] Spring House, PA 19477-0776, USA*
[b]*Drug Discovery, Johnson & Johnson Pharmaceutical Research & Development, Raritan, NJ 08869, USA*



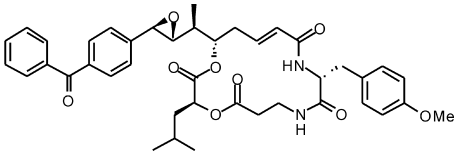
*Bioorg. Med. Chem. Lett. 13 (2003) 757*

## Cryptophycin Affinity Labels: Synthesis and Biological Activity of a Benzophenone Analogue of Cryptophycin-24

Ramdas Vidya,[a] MariJean Eggen,[a] Gunda I. Georg[a,*] and Richard H. Himes[b]

[a]*Department of Medicinal Chemistry, University of Kansas, Lawrence, KS 66045, USA*
[b]*Department of Molecular Biosciences, University of Kansas, Lawrence, KS 66045, USA*

A C16 side chain benzophenone analogue of cryptophycin-24 was synthesized and the β-isomer was found to be twice as active as cryptophycin-24 in an in vitro tubulin assembly assay.



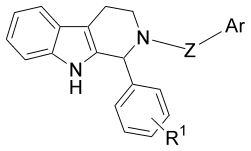
*Bioorg. Med. Chem. Lett. 13 (2003) 761*

## Synthesis and Biological Activities of Novel β-Carbolines as PDE5 Inhibitors

Zhihua Sui,* Jihua Guan, Mark J. Macielag, Weiqin Jiang, Yuhong Qiu, Patricia Kraft, Sheela Bhattacharjee, T. Matthew John, Elizabeth Craig, Donna Haynes-Johnson and Joanna Clancy

*Johnson & Johnson Pharmaceutical Research & Development L.L.C., 1000 Route 202, Raritan, NJ 08869, USA*

A series of $N^2$-furoyl and $N^2$pyrimidinyl β-carbolines was discovered to possess potent inhibitory activity against PDE5. During the synthesis we developed a tandem resin quenching protocol, which allowed us to synthesize large number of target compounds in a rapid fashion. Representative compounds exhibit superior selectivity versus other isozymes of PDEs, and demonstrated in vivo efficacy in increasing introcavernosal pressure in dogs.



Z = Furoyl, Pyrimidinyl

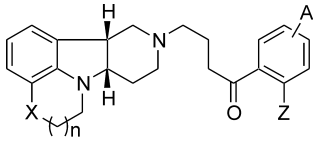
*Bioorg. Med. Chem. Lett. 13 (2003) 767*

## Novel, Highly Potent, Selective 5-$HT_{2A}$/$D_2$ Receptor Antagonists as Potential Atypical Antipsychotics

Taekyu Lee,[a,*] Albert J. Robichaud,[a] Kristopher E. Boyle,[a] Yimin Lu,[a] David W. Robertson,[a] Keith J. Miller,[b] Larry W. Fitzgerald,[b] John F. McElroy[b] and Brian L. Largent[b]

[a]*Discovery Chemistry, Bristol-Myers Squibb Company, Wilmington, DE 19880, USA*
[b]*CNS Diseases Research, Bristol-Myers Squibb Company, Wilmington, DE 19880, USA*

The syntheses and SAR of potent and selective 5-$HT_{2A}$/DA $D_2$ dual antagonists are reported.



X = S, C, O n = 1, 2