Graphical Abstracts

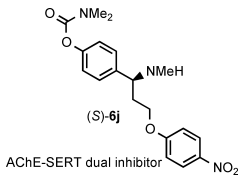
Bioorg. Med. Chem. 11 (2003) 1935

Design, Synthesis and Structure–Activity Relationships of Dual Inhibitors of Acetylcholinesterase and Serotonin Transporter as Potential Agents for Alzheimer's Disease

Narihiro Toda,[a] Keiko Tago,[a] Shinji Marumoto,[a] Kazuko Takami,[a] Mayuko Ori,[a] Naho Yamada,[a] Kazuo Koyama,[b] Shunji Naruto,[b] Kazumi Abe,[c] Reina Yamazaki,[c] Takao Hara,[c] Atsushi Aoyagi,[c] Yasuyuki Abe,[c] Tsugio Kaneko[c] and Hiroshi Kogen[a,*]

[a]*Exploratory Chemistry Research Laboratories, Sankyo Co., Ltd., 1-2-58 Hiromachi, Shinagawa-ku, Tokyo 140-8710, Japan*
[b]*Research Information Department, Sankyo Co., Ltd., 1-2-58 Hiromachi, Shinagawa-ku, Tokyo 140-8710, Japan*
[c]*Neuroscience and Immunology Research Laboratories, Sankyo Co., Ltd., 1-2-58 Hiromachi, Shinagawa-ku, Tokyo 140-8710, Japan*

Compound (*S*)-**6j** exhibited potent inhibitory activities against acetylcholinesterase and serotonin transporter. Furthermore, (*S*)-**6j** showed inhibitory potencies against both in mice brain following oral administration.



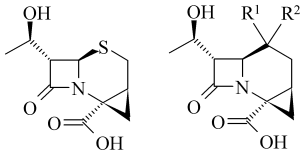
Bioorg. Med. Chem. 11 (2003) 1957

Synthesis of (3,4) β-Methylenecepham and (3,4) β-Methylene-carbacepham Via Intramolecular Carbene Addition to Double Bond

Anna Korda* and Jerzy Winiarski

Institute of Organic Chemistry, Polish Academy of Sciences, Kasprzaka 44/52, 01-224 Warsaw, Poland

The key step of the synthesis included presumed generation of the carbene species from the oxalimide substrate effected by triethylphosphite and its intramolecular addition to the double bond. In preliminary screening, two of the synthesised compounds exhibited modest antibacterial activity at 1.5–2.0 mg/mL against a number of bacterial strains.



b: $R^1 = R^2 = COOEt$
c: $R^1 = COMe$, $R^2 = COOEt$
d: $R^1 = R^2 = COMe$

Bioorg. Med. Chem. 11 (2003) 1969

Pyridoacridine Alkaloids Inducing Neuronal Differentiation in a Neuroblastoma Cell Line, from Marine Sponge *Biemna fortis*

Shunji Aoki,[a] Hong Wei,[a] Kouhei Matsui,[a] Rachmaniar Rachmat[b] and Motomasa Kobayashi[a,*]

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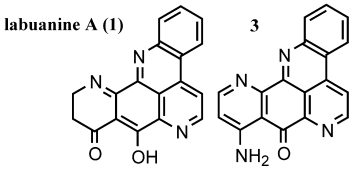
[b]*Research and Development Centre for Oceanology, LIPI, JL. Pasir Putih I, Ancol Timur, Jakarta 11048, Indonesia*

Labuanine A (**1**), a novel pyridoacridine alkaloid and three known related compounds **2**–**4** were isolated from marine sponge *Bienna fortis* as neuronal differentiation inducers against a murine neuroblastoma cell line, Neuro 2A.



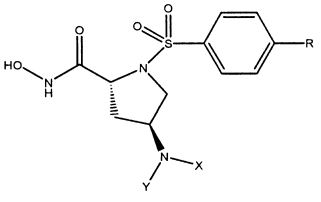
Bioorg. Med. Chem. 11 (2003) 1975

A Quantitative Structure–Activity Relationship Study of Hydroxamate Matrix Metalloproteinase Inhibitors Derived from Funtionalized 4-Aminoprolines

S.P. Gupta,[a,*] Dalip Kumar[a] and S. Kumaran[b]

[a]*Department of Chemistry, Birla Institute of Technology and Science, Pilani-333031, India*
[b]*Department of Pharmacy, Birla Institute of Technology and Science, Pilani-333031, India*

A quantitative structure–activity relationship study has been made on several series of functionalized 4-aminoproline derived hydroximates acting as matrix matelloproteinase inhibitors to indicate the beneficial role of some substituents and atoms in the molecules.



Bioorg. Med. Chem. 11 (2003) 1983

Structural Studies of [2′,6′-Dimethyl-L-tyrosine[1]]endomorphin-2 Analogues: Enhanced Activity and *cis* Orientation of the Dmt-Pro Amide Bond

Yoshio Okada,[a,b,*] Yoshio Fujita,[a] Takashi Motoyama,[a] Yuko Tsuda,[a,b] Toshio Yokoi,[a,b] Tingyou Li,[b] Yusuke Sasaki,[c] Akihiro Ambo,[c] Yunden Jinsmaa,[d] Sharon D. Bryant[d] and Lawrence H. Lazarus[d]

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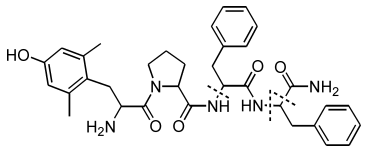
[b]*High Technology Research Center, Kobe Gakuin University, Nishi-ku, Kobe 651-2180, Japan*
[c]*Department of Biochemistry, Tohoku Pharmaceutical University, 4-1, Komatsushima 4-chome, Aoba-ku, Sendai 981-8558, Japan*
[d]*Peptide Neurochemistry, LCBRA, National Institutes of Environmental Health Sciences, Research Triangle Park, NC 27709, USA*



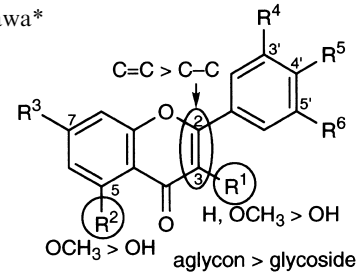
Bioorg. Med. Chem. 11 (2003) 1995

Structural Requirements of Flavonoids for Nitric Oxide Production Inhibitory Activity and Mechanism of Action

Hisashi Matsuda, Toshio Morikawa, Shin Ando, Iwao Toguchida and Masayuki Yoshikawa*

Kyoto Pharmaceutical University, Misasagi, Yamashina-ku, Kyoto 607-8412, Japan

To clarify the structure–activity relationships of flavonoids for NO production inhibitory activity, we examined 73 flavonoids. Among them, apigenin (IC_{50} = 7.7 μM), diosmetin (8.9 μM), and tetra-*O*-methylluteolin (2.4 μM), and hexa-*O*-methylmyricetin (7.4 μM) were found to show potent inhibitory activity, and several structural requirements of flavonoids for the activity were clarified: (1) the activities of flavones were stronger than those of corresponding flavonols; (2) the glycoside moiety reduced the activity; (3) the activities of flavones were stronger than those of corresponding flavanones; (4) methylation of the 3, 5, or 4′-hydroxyl group enhanced the activity, etc. In addition, potent NO production inhibitors were found to inhibit induction of iNOS without iNOS enzymatic inhibitory activity.



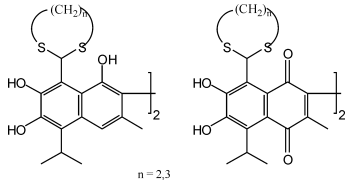
Bioorg. Med. Chem. 11 (2003) 2001

New Thioderivatives of Gossypol and Gossypolone, as Prodrugs of Cytotoxic Agents

Vi-Thuy Dao,[a] Michael K. Dowd,[b] Christiane Gaspard,[a] Marie-Thérèse Martin,[a] Julie Hémez,[a] Olivier Laprévote,[a] Michel Mayer[a] and Robert J. Michelot[a,*]

[a]*Institut de Chimie des Substances Naturelles, CNRS, 91198 Gif sur Yvette, France*
[b]*United State Department of Agriculture, Southern Regional Research Center, New Orleans Louisiana 70179, USA*

The syntheses of new dithiane or dithiolane derivatives of gossypol and gossypolone are reported. These derivatives could be proposed as prodrugs targeted against tumor cells surrounded by high concentrations of nitric oxide.



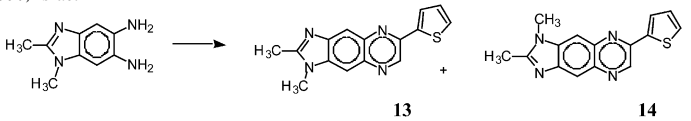
Bioorg. Med. Chem. 11 (2003) 2007

Tricyclic Quinoxalines as Potent Kinase Inhibitors of PDGFR Kinase, Flt3 and Kit

Aviv Gazit,[a] Kevin Yee,[b] Andrea Uecker,[c] Frank-D. Böhmer,[c] Tobias Sjöblom,[d] Arne Östman,[d] Johannes Waltenberger,[e] Gershon Golomb,[f] Shmuel Banai,[g] Michael C. Heinrich[b] and Alexander Levitzki[a,*]

[a]*Department of Biological Chemistry, The Alexander Silberman Institute of Life Sciences, The Hebrew University of Jerusalem, Givat Ram, Jerusalem 91904, Israel*
[b]*Department of Hematology and Medical Oncology, Oregon Health and Science University Cancer Institute and Portland Veteran's Affairs Medical Center, Portland, OR 97239, USA*
[c]*Research Unit 'Molecular Cell Biology', Klinikum der Friedrich-Schiller-Universität Jena, Drackendorfer Str.1, D-07747 Jena, Germany*
[d]*The Ludwig Institute for Cancer Research, Box 595, S-751 24 Uppsala, Sweden*
[e]*Department of Internal medicine II,Ulm University Medical Center, Robert Koch Strasse 8,D89081, Germany*
[f]*School of Pharmacy, The Hebrew University of Jerusalem, Ein Karem, Jerusalem, 91904, Israel*
[g]*Department of Cardiology, Bikur Cholim Hospital POB. 492 Jerusalem 91004, Israel*

The imidazolo quinoxalines **13** and **14** are potent and selective PDGFR kinase inhibitors where **13** is 20-fold more potent than **14**. Compound **13** is highly potent inhibitor of PDGFR signaling, non-toxic and with balanced solubility properties, making it a good drug candidate.

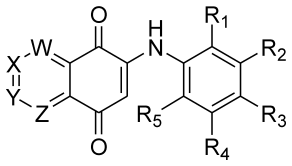


Bioorg. Med. Chem. 11 (2003) 2019

QSAR Study of Quinolinediones with Inhibitory Activity of Endothelium-Dependent Vasorelaxation by CoMSIA

Hea-Young Park Choo,[a,*] Suyoung Choi,[a] Chung-Kyu Ryu,[a] Hwa-Jung Kim,[a] In Young Lee,[b] Ae Nim Pae[b] and Hun Yeong Koh[b]

[a]*School of Pharmacy, Ewha Womans University, Seoul 120-750, South Korea*
[b]*Biochemicals Research Center, Korea Institute of Science and Technology, PO Box 131, Cheongryang, Seoul 130-650, South Korea*



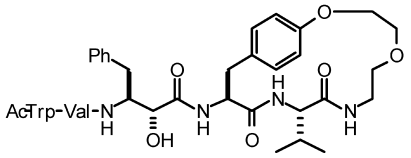
The 3D QSAR study of quinolinediones which showed potent inhibitory effect on the acetylcholine induced vasorelaxation was conducted by CoMSIA.

Bioorg. Med. Chem. 11 (2003) 2025

Design and Synthesis of Broad-Based Mono- and Bi- Cyclic Inhibitors of FIV and HIV Proteases

Chi Ching Mak,[a] Ashraf Brik,[a] Danica L. Lerner,[b] John H. Elder,[b] Garrett M. Morris,[b] Arthur J. Olson[b] and Chi-Huey Wong[a,*]

[a]*Department of Chemistry and the Skaggs Institute for Chemical Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, USA*
[b]*Department of Molecular Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, USA*



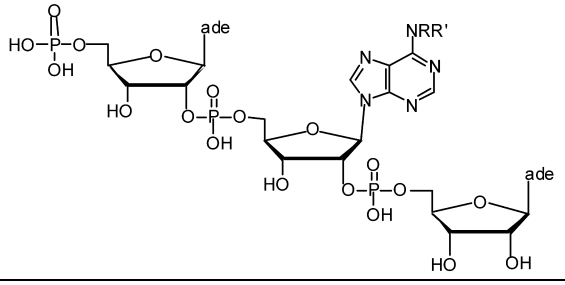
IC_{50} 5 nM (HIV-WT)
IC_{50} 45 nM (FIV-WT)
good antiviral activity for FIV

Bioorg. Med. Chem. 11 (2003) 2041

Probing the Activation Site of Ribonuclease L with New N^6-Substituted 2′,5′-Adenylate Trimers

Ursula Münch,[a,b] Ling Chen,[a,b] Suzanne F. Bayly[a,b] and Paul F. Torrence[a,b,*]

[a]*Section on Biomedical Chemistry, Laboratory of Medicinal Chemistry, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD 20892-0805, USA*
[b]*Department of Chemistry, Northern Arizona University, Flagstaff, AZ 86011-5698, USA*



p5'A2'p5'A$^{NRR'}$2'p5'A

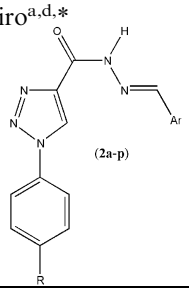
2-5A trimers, functionally modified at the central adenylate, were synthesized by post-synthetic conversion and their ability to bind to and to activate RNase L was evaluated.

Bioorg. Med. Chem. 11 (2003) 2051

Antiplatelet Properties of Novel *N*-Substituted-phenyl-1,2,3-triazole-4-acylhydrazone Derivatives

Anna C. Cunha,[a] Juliana M. Figueiredo,[a] Jorge L. M. Tributino,[a] Ana L. P. Miranda,[a] Helena C. Castro,[a,b] Russolina B. Zingali,[b] Carlos A. M. Fraga,[a,d] Maria Cecília B. V. de Souza,[c] Vitor F. Ferreira[c] and Eliezer J. Barreiro[a,d,*]

[a]*Laboratório de Avaliação e Síntese de Substâncias Biotivas (LASSBio, Faculdade de Farmácia, Universidade Federal do Rio de Janeiro, PO Box 68006, 21944-971, Rio de Janeiro, RJ, Brazil*
[b]*Laboratório de Hemostase e Venenos (LabHemoVen), Departamento de Bioquímica Médica, Instituto de Ciências Biomédicas, Universidade Federal do Rio de Janeiro, Rio de Janeiro, RJ, Brazil*
[c]*Departamento de Química Orgânica, Instituto de Química, Universidade Federal Fluminense, Niterói, RJ, Brazil*
[d]*Instituto de Química, Universidade Federal do Rio de Janeiro, Rio de Janeiro, RJ, Brazil*



The design, synthesis, and antiplatelet properties of new *N*-substituted-phenyl-1,2,3-triazole-4-acylhydrazone derivatives (**2a**–**p**) is reported.

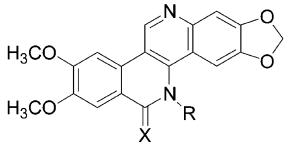
Bioorg. Med. Chem. 11 (2003) 2061

5*H*-Dibenzo[*c*,*h*]1,6-naphthyridin-6-ones: Novel Topoisomerase I-Targeting Anticancer Agents with Potent Cytotoxic Activity

Alexander L. Ruchelman,[a] Sudhir K. Singh,[a] Abhijit Ray,[a] Xiao Hua Wu,[b] Jin-Ming Yang,[b] Tsai-Kun Li,[c] Angela Liu,[c] Leroy F. Liu[b,c] and Edmond J. LaVoie[a,c,*]

[a]*Department of Pharmaceutical Chemistry, Rutgers, The State University of New Jersey, Piscataway, NJ 08854-8020, USA*
[b]*The Cancer Institute of New Jersey, New Brunswick, NJ 08901, USA*
[c]*Department of Pharmacology, The University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School, Piscataway, NJ 08854, USA*

X = O; R = $CH_2CH_2N(CH_3)_2$; $CHCH_3CH_2N(CH_3)_2$; $CH_2CH_2N(C_4H_8)$; $CH_2CH_2N(CH_2CH_2)_2NCH_3$; CH_2(–$CHOCH_2$ CH_2CH_2–); $CH_2(CH_2)_2N(CH_3)_2$; $CH_2(CH_2)_2CH_3$; CH_2(–$CHO(CH_2)_3$–); CH_2CH_2OH; $CH_2CH_2OCH_2CH_2OH$; $CH(CH_2OH)CH_2N(CH_3)_2$; $CH_2CHOHCH_2OH$; X = H, H; R = $CH_2CH_2N(CH_3)_2$; $CHCH_3CH_2N(CH_3)_2$



X = O; X = H, H

Bioorg. Med. Chem. 11 (2003) 2075

Allosteric Interactions and QSAR: On the Role of Ligand Hydrophobicity

Corwin Hansch,[a,*] Rajni Garg,[b] Alka Kurup[a] and Suresh Babu Mekapati[a]

[a]*Department of Chemistry, Pomona College, 645 North College Avenue, Claremont, CA 91711, USA*
[b]*Chemistry Department, Clarkson University, Potsdam, NY 13699, USA*

$-\mathrm{Clog}P + \mathrm{Clog}P^2 \Rightarrow$ Allosteric Interaction
(Clog$P$ is octanol/water partition coefficient)

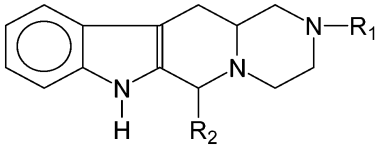
Bioorg. Med. Chem. 11 (2003) 2085

QSAR Studies in Substituted 1,2,3,4,6,7,12,12a-octahydropyrazino[2′,1′:6,1]pyrido[3,4-b]indoles—A Potent Class of Neuroleptics

Anil K. Saxena,[a,*] Siya Ram,[a] Mridula Saxena,[a] Nidhi Singh,[b] Philip Prathipati,[a] Padam C. Jain,[a] H.K. Singh[a] and Nitya Anand[a]

[a]*Central Drug Research Institute, Medicinal Cemistry Division, Cattar Manzil Palace Medicinal Chemistry Division, Lucknow-226001, India*
[b]*Pune University, S.G.R.S. College of Pharmacy, Pune-412301, India*

QSAR studies have been carried out on a series of substituted 1,2,3,4,6,7,12,12a-octahydropyrazino[2′,1′:6,1]pyrido[3, 4-b]indoles to identify the essential structural and physiochemical requirements for the neuroleptic activity.

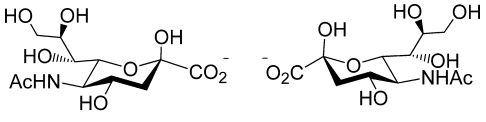


Bioorg. Med. Chem. 11 (2003) 2091

Directed Evolution of *N*-Acetylneuraminic Acid Aldolase to Catalyze Enantiomeric Aldol Reactions

Masaru Wada,[a] Che-Chang Hsu,[a] Dirk Franke,[a] Michael Mitchell,[a] Andreas Heine,[b] Ian Wilson[b] and Chi-Huey Wong[a,*]

[a]*Department of Chemistry and the Skaggs Institute for Chemical Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, USA*
[b]*Department of Molecular Biology and the Skaggs Institute for Chemical Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, USA*

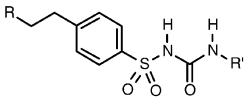


Bioorg. Med. Chem. 11 (2003) 2099

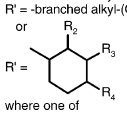
Hydroxyl-Substituted Sulfonylureas as Potent Inhibitors of Specific [^{3}H]Glyburide Binding to Rat Brain Synaptosomes

Ronald A. Hill,[a,*] Sonali Rudra,[a] Bo Peng,[a] David S. Roane,[a] Jeffrey K. Bounds,[a] Yang Zhang,[a] Ahmad Adloo[a] and Tiansheng Lu[b]

[a]*Division of Basic Pharmaceutical Sciences, College of Pharmacy, The University of Louisiana at Monroe, Monroe, LA 71209, USA*
[b]*Department of Chemistry, Louisiana State University, Baton Rouge, LA 70803, USA*



R' = -(CH$_2$)$_n$-OH
R' = -branched alkyl-OH
R' = -branched alkyl-(OH)$_2$
or



where one of
R$_2$, R$_3$, R$_4$ = *cis*- or *trans*-OH