Graphical Abstracts

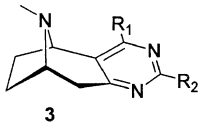
Bioorg. Med. Chem. 10 (2002) 1197

An Analysis of the Binding of Cocaine Analogues to the Monoamine Transporters Using Tensor Decomposition 3-D QSAR

Michael Appell,[a] William J. Dunn III,[a] Maarten E.A. Reith,[b] Larry Miller[c] and Judith L. Flippen-Anderson[d]

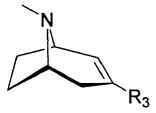
[a]*Department of Medicinal Chemistry & Pharmacognosy, University of Illinois at Chicago, 833 S. Wood, Chicago, IL 60612, USA*
[b]*Department of Biomedical and Therapeutic Sciences, University of Illinois College of Medicine, PO Box 1649, Peoria, IL 61656, USA*
[c]*Pharmacia, 4901 Searle Parkway, Skokie, IL 60077, USA*
[d]*Laboratory for the Structure of Matter, Code 6030, Naval Research Laboratory, 4555 Overlook Ave. SW, Washington, DC 20375-5000, USA*

Series of rigid and semi-rigid tropane analogues was designed using tensor decomposition 3-D QSAR. The compounds were synthesized and their affinities for the monoamine transporters were determined.



3

3a; R_1=H, R_2=C_6H_5
3b; R_1=H, R_2=NH_2
3c; R_1=H, R_2=CH_3
3d; R_1=R_2=H
3e; R_1=R_2=C_6H_5



4

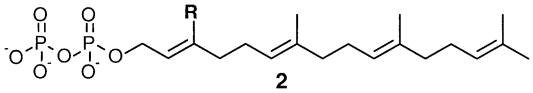
4a; R_3=1-naphthyl
4b; R_3=2-naphthyl

Bioorg. Med. Chem. 10 (2002) 1207

Coupling of Isoprenoid Triflates with Organoboron Nucleophiles: Synthesis and Biological Evaluation of Geranylgeranyl Diphosphate Analogues

YongQi Mu,[a] Lisa M. Eubanks,[b] C. Dale Poulter[b] and Richard A. Gibbs[a]

[a]*Department of Pharmaceutical Sciences, College of Pharmacy and Allied Health Professions, Wayne State University, 528 Shapero Hall, Detroit, MI 48202, USA*
[b]*Department of Chemistry, Henry Eyring Building, University of Utah, Salt Lake City, UT 84112, USA*



2

a: **R**=vinyl (3-vGGPP)
b: **R**=cyclopropyl (3-cpGGPP)
c: **R**=*tert*-butyl (3-tbGGPP)
d: **R**=phenyl (3-PhGGPP)

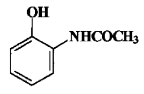
Bioorg. Med. Chem. 10 (2002) 1221

Acetamidoquinone and Acetamidohydroxy Derivatives as Inhibitors for Both Dihydroxyacetamido Epoxidase and Dehydrogenase

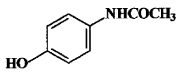
Chris G. Whiteley

Department of Biochemistry and Microbiology, Rhodes University, Grahamstown, South Africa

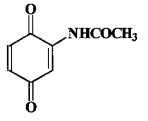
A series of substituted acetamidoquinones and acetamidophenols has been synthesised and shown to competitively inhibit both dihydroxyacetamido epoxidase and dihydroxyacetamido dehydrogenase. The most powerful inhibitor (K_i=4 nM) was 5-bromo-2-acetamido-1,4-benzoquinone. Both enzymes were purified by standard chromatographic procedures from *Streptomyces*.



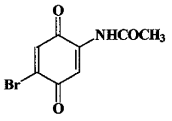
2-Acetamidophenol



4-Acetamidophenol



2-Acetamido-1,4-benzoquinone



5-Bromo-2-acetamido-1,4-benzoquinone

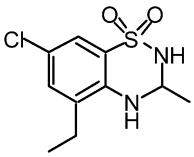
Bioorg. Med. Chem. 10 (2002) 1229

5′-Alkyl-benzothiadiazides: A New Subgroup of AMPA Receptor Modulators with Improved Affinity

Dean Phillips,[a] Jennifer Sonnenberg,[a] Amy C. Arai,[c] Rishi Vaswani,[b] Peter O. Krutzik,[b] Thomas Kleisli,[b] Markus Kessler,[c] Richard Granger,[b] Gary Lynch[b] and A. Richard Chamberlin[a]

[a]*Department of Chemistry, University of California, Irvine, CA 92697, USA*
[b]*Department of Psychiatry, University of California, Irvine, CA 92697, USA*
[c]*Department of Pharmacology, Southern Illinois University School of Medicine, Springfield, IL 62702, USA*

Benzothiadiazides, such as cyclothiazide and IDRA-21, are known to increase synaptic transmission through modulation of AMPA receptor activity. We discovered that a simple alkyl substitution to the IDRA-21 (shown) structure gave pronounced effects compared to the parent compound. This paper discusses its discovery and structure–activity relationships of several analogues.

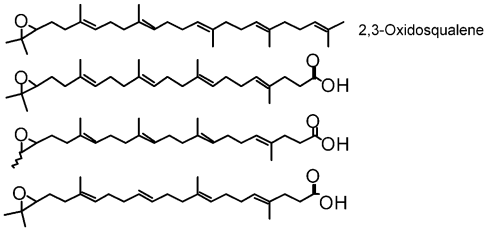


Bioorg. Med. Chem. 10 (2002) 1249

Polyene Substrates with Unusual Methylation Patterns to Probe the Active Sites of Three Catalytic Antibodies

Geun Tae Kim, Marion Wenz, Jong Il Park, Jens Hasserodt and Kim D. Janda

Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, USA



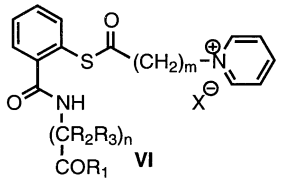
Bioorg. Med. Chem. 10 (2002) 1263

Synthesis and Biological Properties of Amino Acid Amide Ligand-Based Pyridinioalkanoyl Thioesters as Anti-HIV Agents

Yongsheng Song,[a] Atul Goel,[b] Venkatesha Basrur,[b] Paula E.A. Roberts,[c] Judy A. Mikovits,[c] John K. Inman,[d] Jim A. Turpin,[e] William G. Rice[a] and Ettore Appella[b]

[a]*Achillion Pharmaceuticals, Inc., 300 George Street, New Haven, CT O6511, USA*
[b]*Laboratory of Cell Biology, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, USA*
[c]*Laboratory of Antiviral Drug Mechanisms, SAIC Frederick, Frederick, MD 21702, USA*
[d]*Laboratory of Immunology, National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD 20892, USA*
[e]*Infectious Disease Research Department, Southern Research Institute, 431 Aviation Way, Frederick, MD 21702, USA*

Synthesis and antiviral activity of pyridinioalkanoyl thioesters (VI) is described.

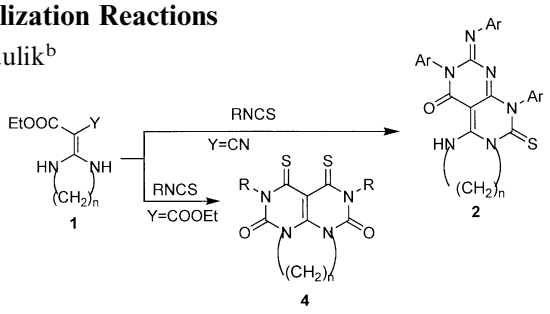


Bioorg. Med. Chem. 10 (2002) 1275

A Convenient Synthesis and Hepatoprotective Activity of Imidazo[1,2-*c*]pyrimido[5,4-*e*]pyrimidine, Tetraazaacenaphthene and Tetraazaphenalene from Cyclic Ketene Aminals Through Tandem Addition-Cyclization Reactions

Vishnu J. Ram,[a] Atul Goel,[a] Sanjay Sarkhel[b] and Prakas R. Maulik[b]

[a]*Division of Medicinal Chemistry, Central Drug Research Institute, Lucknow 226 001, India*
[b]*Molecular and Structural Biology Division, Central Drug Research Institute, Lucknow 226 001, India*



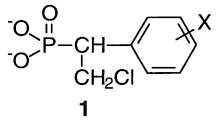
Bioorg. Med. Chem. 10 (2002) 1281

Novel Irreversible Butyrylcholinesterase Inhibitors: 2-Chloro-1-(substituted-phenyl)ethylphosphonic Acids

Nanjing Zhang and John E. Casida

Environmental Chemistry and Toxicology Laboratory, Department of Environmental Science, Policy and Management, University of California, Berkeley, CA 94720-3112, USA

The title compounds (**1**) [X = H, NO_2, $(CH_3)_2N$ or $(CH_3)_3N^+$ at the 3- or 4-position] were synthesized and their structural features related to hydrolytic stability and inhibitory mechanisms for BChE. Dissociation of chloride is proposed as the first and rate-limiting step both in the hydrolysis and by analogy in phosphorylation of BChE by **1** bound at the active site.



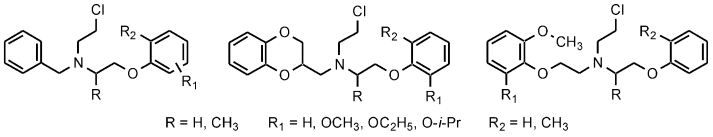
Bioorg. Med. Chem. 10 (2002) 1291

Structure–Activity Relationships Among Novel Phenoxybenzamine-Related β-Chloroethylamines

Dario Giardinà,[a] Mauro Crucianelli,[a] Piero Angeli,[a] Michela Buccioni,[a] Ugo Gulini,[a] Gabriella Marucci,[a] Gianni Sagratini[a] and Carlo Melchiorre[b]

[a]*Department of Chemical Sciences, University of Camerino, Italy*
[b]*Department of Pharmaceutical Sciences, University of Bologna, Italy*

Some components of the series evidenced the heterogeneity of α_1-adrenoceptors functionally active in the epididymal portion of CD rat vas deferens.



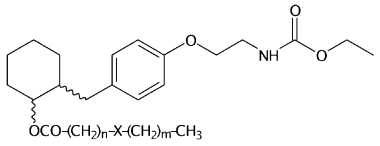
Bioorg. Med. Chem. 10 (2002) 1305

Fatty Acid Esters of Juvenoid Alcohols as Insect Hormonogen Agents (Juvenogens)

Zdeněk Wimmer,[a] David Šaman,[b] Jelena Kuldová,[c] Ivan Hrdý[c] and Blanka Bennettová[d]

[a]*Department of Natural Products, Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, Flemingovo náměstí 2, CZ-16610 Prague 6, Czech Republic*
[b]*Department of Nuclear Magnetic Resonance Spectroscopy, Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, Flemingovo náměstí 2, CZ-16610 Prague 6, Czech Republic*
[c]*Insect Chemical Ecology Unit, Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, Flemingovo náměstí 2, CZ-16610 Prague 6, Czech Republic*
[d]*Institute of Entomology, Academy of Sciences of the Czech Republic, Branišovská 31, CZ-37005 České Budějovice, Czech Republic*

A series of 8 new juvenogens (**3**–**10**) was prepared starting from a pair of isomeric insect juvenile hormone bioanalogues (**1** and **2**). The juvenogens **3**–**10** were tested for their effect on reproduction of blowfly *Neobellieria* (*Sarcophaga*) *bullata* and for the juvenilizing activity on termite *Prorhinotermes simplex*.



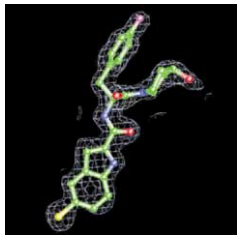
Bioorg. Med. Chem. 10 (2002) 1313

The 1.76 Å Resolution Crystal Structure of Glycogen Phosphorylase B Complexed with Glucose, and CP320626, a Potential Antidiabetic Drug

Nikos G. Oikonomakos,[a] Spyros E. Zographos,[a] Vicky T. Skamnaki[a] and Georgios Archontis[b]

[a]*Institute of Biological Research and Biotechnology, The National Hellenic Research Foundation, 48 Vas. Constantinou Avenue, Athens 11635, Greece*
[b]*Department of Physics, University of Cyprus, Box 20537, CY1678, Nicosia, Cyprus*

The binding of a potential antidiabetic drug to glycogen phosphorylase b in the crystal at 1.76 Å resolution is reported.

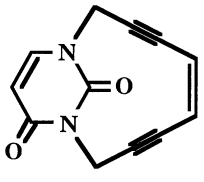


Bioorg. Med. Chem. 10 (2002) 1321

A Novel Approach Towards Studying Non-Genotoxic Enediynes as Potential Anticancer Therapeutics

Gholam Hossein Hakimelahi,[a] Gassan Sh. Gassanov,[a] Ming-Hua Hsu,[a] Jih Ru Hwu[a] and Shahram Hakimelahi[b]

[a]*Institute of Chemistry, Academia Sinica, Taipei, Taiwan 115, ROC*
[b]*Department of Cell Biology, Faculty of Medicine, University of Alberta, Edmonton, Alberta, Canada T6G 2H7*

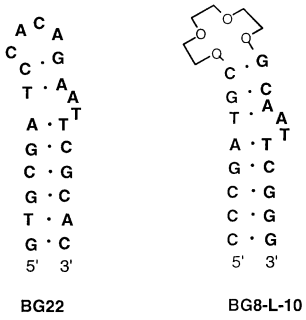


Bioorg. Med. Chem. 10 (2002) 1329

Recognition of Bulged DNA by a Neocarzinostatin Product via an Induced Fit Mechanism

Catherine F. Yang,[a] Patricia J. Jackson,[a] Zhen Xi[b] and Irving H. Goldberg[b]

[a]*Department of Chemistry, Rowan University, Glassboro, NJ 08028, USA*
[b]*Department of Biological Chemistry and Molecular Pharmacology, Harvard Medical School, Boston, MA 02115, USA*



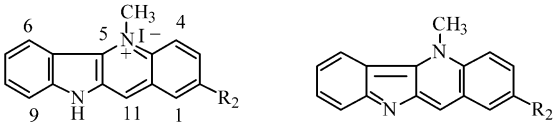
Bioorg. Med. Chem. 10 (2002) 1337

Substituted Indoloquinolines as New Antifungal Agents

Seth Y. Ablordeppey,[a] Pingchen Fan,[a] Shouming Li,[a] Alice M. Clark[b] and Charles D. Hufford[b]

[a]*Florida A&M University, College of Pharmacy and Pharmaceutical Sciences, Tallahassee, FL 32307, USA*
[b]*The National Center for Natural Products Research, Research Institute of Pharmaceutical Sciences, and Department of Pharmacognosy, The School of Pharmacy, University of Mississippi, University, MS 38677, USA*

Substitution at the 2-position of the 5-alkylated quindoline {indolo[3,2-*b*]quinoline} ring has resulted in more potent and broader spectrum of antifungal activity.



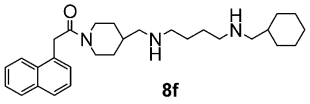
Bioorg. Med. Chem. 10 (2002) 1347

Discovery of Diaminobutane Derivatives as Ca^{2+}-Permeable AMPA Receptor Antagonists

Yoshiyuki Yoneda, Tetuya Mimura, Keiichi Kawagoe, Takanori Yasukouchi, Toshiaki Tatematu, Masayuki Ito, Masaki Saito, Masunobu Sugimura, Fusako Kito and Shinichi Kawajiri

Medicinal Chemistry Research Laboratory, Daiichi Pharmaceutical Co., Ltd., 16-13, Kitakasai 1-Chome, Edogawa-ku, Tokyo 134-8630, Japan

Compound **8f** showed selective Ca^{2+}-permeable AMPA receptor antagonist activity and neuroprotective effects in transient global ischemia models in gerbils.



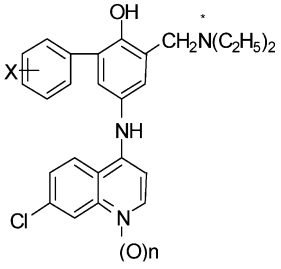
Bioorg. Med. Chem. 10 (2002) 1361

QSAR Studies on Antimalarial Substituted Phenyl Analogues and Their N^{ω}-Oxides

Vijay K. Agrawal,[a] Ruchi Sharma[a] and Padmakar V. Khadikar[b]

[a]*QSAR Laboratories, Department of Chemistry, A.P.S. University, Rewa 486 003, India*
[b]*Research Division, Laxmi Pest and Fumigation Pvt. Ltd. 3, Khatipura, Indore 452 007, India*

QSAR study on a series of substituted phenyl analogues and their N^{ω}-oxides were made using various combinations of electronic and topological descriptors. Based on the proposed models, the antimalarial action mechanism was discussed showing that metabolic action is similar to that of peroxide compounds.



Bioorg. Med. Chem. 10 (2002) 1367

3-D-QSAR Analysis of *N*-(3-Acyloxy-2-benzylpropyl)-*N*′-dihydroxytetrahydrobenzazepine and Tetrahydroisoquinoline and *N*-(3-Acyloxy-2-benzylpropyl)-*N*′-(4-hydroxy-3-methoxybenzyl) Thioureas Analogues as Potent Vanilloid Receptor Ligands

Ki H. Kim

Department of Structural Biology, Abbott Laboratories, Abbott Park, IL 60064-6100, USA

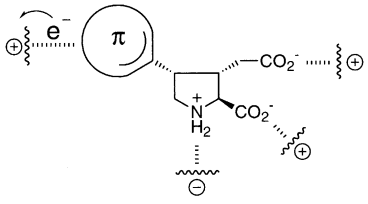
3-D-Quantitative structure–activity relationships of *N*-(3-acyloxy-2-benzylpropyl)-*N*′-dihydroxytetrahydro-benzazepine and tetrahydroisoquinoline and *N*-(3-acyloxy-2-benzylpropyl)-*N*′-(4-hydroxy-3-methoxybenzyl) thiourea analogues as potent vanilloid receptor ligands were investigated using the CoMFA and the COMSIA methods.

Bioorg. Med. Chem. 10 (2002) 1373

Molecular Orbital Calculation for the Model Compounds of Kainoid Amino Acids, Agonists of Excitatory Amino Acid Receptors. Does the Kainoid C4-Substituent Directly Interact with the Receptors?

Kimiko Hashimoto,[a] Takatoshi Matsumoto,[b] Kensuke Nakamura,[c] Shu-ichi Ohwada,[a] Tatsuro Ohuchi,[a] Manabu Horikawa,[a] Katsuhiro Konno[d] and Haruhisa Shirahama[a]

[a]*Department of Chemistry, Faculty of Science, Hokkaido University, Sapporo 060-0810, Japan*
[b]*Department of Synthetic Organic Chemistry, Faculty of Pharmaceutical Sciences, Nagoya City University, 3-1 Tanabe-dori, Mizuho-ku, Nagoya 467-8603, Japan*
[c]*Institute of Medical Molecular Design, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan*
[d]*Institute of Biosciences of Rio Claro, São Paulo State University, Rio Claro, SP 13506-900, Brazil*

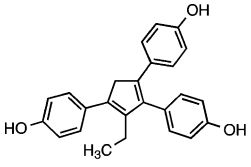


Bioorg. Med. Chem. 10 (2002) 1381

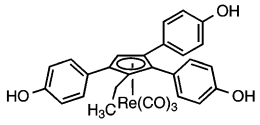
Aryl Cyclopentadienyl Tricarbonyl Rhenium Complexes: Novel Ligands for the Estrogen Receptor with Potential Use as Estrogen Radiopharmaceuticals

Eric S. Mull, Viswajanani J. Sattigeri, Alice L. Rodriguez and John A. Katzenellenbogen

Department of Chemistry, University of Illinois, Urbana, IL 61801, USA



cyclopentadiene, RBA = 4.9



cyclopentadiene rhenium tricarbonyl complex, RBA = 23

[estradiol RBA = 100]

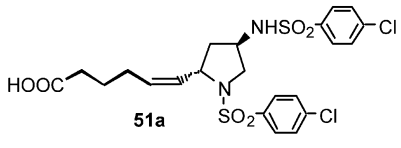
Bioorg. Med. Chem. 10 (2002) 1399

Synthesis and Biological Activity of 1-Phenylsulfonyl-4-Phenylsulfonylaminopyrrolidine Derivatives as Thromboxane A_2 Receptor Antagonists

Hiroshi Marusawa, Hiroyuki Setoi, Akihiko Sawada, Akio Kuroda, Jiro Seki, Yukio Motoyama and Hirokazu Tanaka

Exploratory Research Laboratories, Fujisawa Pharmaceutical Co., Ltd. 5-2-3 Tokodai, Tsukuba-shi, Ibaraki 300-2698, Japan

The synthesis and biological activity of novel 1-phenylsulfonyl-4-phenylsulfonylamino-pyrrolidine analogues as thromboxane A_2 receptor antagonist are described. In these compounds, **51a** displayed excellent efficacy in inhibiting U-46619-induced rat aortic strip contraction.



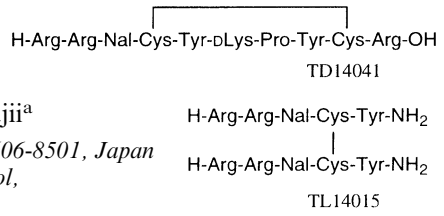
51a

Bioorg. Med. Chem. 10 (2002) 1417

Certification of the Critical Importance of L-3-(2-Naphthyl)alanine at Position 3 of a Specific CXCR4 Inhibitor, T140, Leads to an Exploratory Performance of Its Downsizing Study

Hirokazu Tamamura,[a] Akane Omagari,[a] Kenichi Hiramatsu,[a] Shinya Oishi,[a] Hiromu Habashita,[a] Taisei Kanamoto,[b] Kazuyo Gotoh,[b] Naoki Yamamoto,[c] Hideki Nakashima,[d] Akira Otaka[a] and Nobutaka Fujii[a]

[a]*Graduate School of Pharmaceutical Sciences, Kyoto University, Sakyo-ku, Kyoto 606-8501, Japan*
[b]*Department of Microbiology and Immunology, Kagoshima University Dental School, Sakuragaoka, Kagoshima 890-8544, Japan*
[c]*Tokyo Medical and Dental University, School of Medicine, Bunkyo-ku, Tokyo 113-8519, Japan*
[d]*St. Marianna University, School of Medicine, Miyamae-ku, Kawasaki 216-8511, Japan*



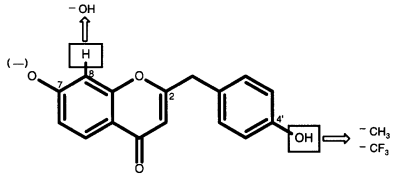
Bioorg. Med. Chem. 10 (2002) 1427

Binding of 1-Benzopyran-4-one Derivatives to Aldose Reductase: A Free Energy Perturbation Study

Giulio Rastelli,[a] Luca Costantino,[a] M. Cristina Gamberini,[a] Antonella Del Corso,[b] Umberto Mura,[b] J. Mark Petrash,[c] Anna Maria Ferrari[a] and Sara Pacchioni[a]

[a]*Dipartimento di Scienze Farmaceutiche, Universita di Modena e Reggio Emilia, Via Campi, 183, 41100 Modena, Italy*
[b]*Dipartimento di Fisiologia e Biochimica, Università di Pisa, Via S. Maria, 55, 56100 Pisa, Italy*
[c]*Department of Ophthalmology and Visual Sciences, Washington University, School of Medicine, St. Louis, MI 63110, USA*

Free energy perturbation simulations combined with the synthesis and biological evaluation of 1-benzopyran-4-one inhibitors of aldose reductase are presented.



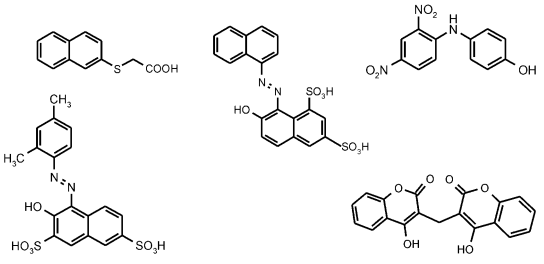
Bioorg. Med. Chem. 10 (2002) 1437

Discovery of New Inhibitors of Aldose Reductase from Molecular Docking and Database Screening

Giulio Rastelli, Anna Maria Ferrari, Luca Costantino and Maria Cristina Gamberini

Dipartimento di Scienze Farmaceutiche, Università di Modena e Reggio Emilia, Via Campi 183, 41100 Modena, Italy

Docking screening of the NCI database of compounds identified novel inhibitors of aldose reductase. Synthesis and optimization of inhibitory activity was undertaken for the class of the nitro derivatives.

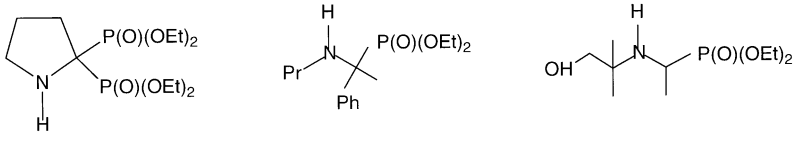


Bioorg. Med. Chem. 10 (2002) 1451

Synthesis and ^{31}P NMR Characterization of New Low Toxic Highly Sensitive pH Probes Designed for In Vivo Acidic pH Studies

Sophie Martel,[a] Jean-Louis Clément,[a] Agnès Muller,[b] Marcel Culcasi[a,c] and Sylvia Pietri[a]

[a]*Laboratoire Structure et Réactivité des Espèces Paramagnétiques, CNRS-UMR 6517 Universités d'Aix-Marseille I & III, Marseille, France*
[b]*Laboratoire de Physiologie Cellulaire, CNRS-UMR 5074 Faculté de Pharmacie, Montpellier, France*
[c]*SARL OXYLAB, Martigues, France*



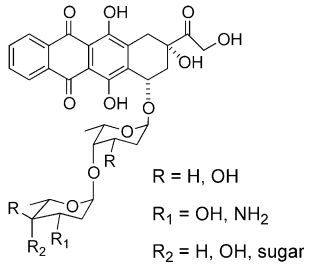
3 **5** **9**

Novel Anthracycline Oligosaccharides: Influence of Chemical Modifications of the Carbohydrate Moiety on Biological Activity

Bioorg. Med. Chem. 10 (2002) 1459

A. Cipollone,[a] M. Berettoni,[a] M. Bigioni,[a] M. Binaschi,[a] C. Cermele,[a] E. Monteagudo,[a] L. Olivieri,[a] D. Palomba,[a] F. Animati,[a] C. Goso[a] and C. A. Maggi[b]

[a]*Menarini Ricerche, via Tito Speri 10, 00040 Pomezia, Italy*
[b]*Menarini Ricerche, via Sette Santi 3, 50131 Firenze, Italy*

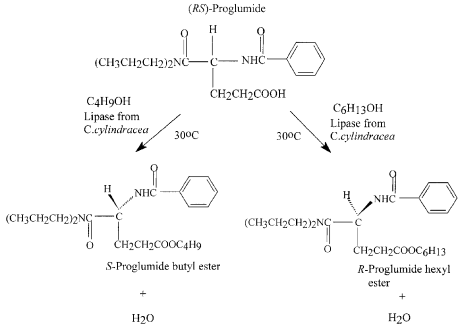


Resolution of (*RS*)-Proglumide Using Lipase from *Candida cylindraceae*

Bioorg. Med. Chem. 10 (2002) 1471

R. V. Muralidhar,[a] R. R. Chirumamilla,[a] V. N. Ramachandran,[a] R. Marchant[b] and P. Nigam[a]

[a]*School of Biomedical Sciences, University of Ulster at Coleraine, N. Ireland BT52 1SA, UK*
[b]*School of Environmental Sciences, University of Ulster at Coleraine, N. Ireland BT52 1SA, UK*



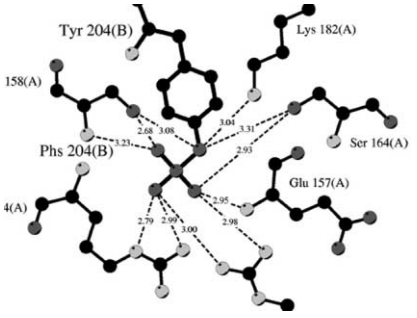
Experimental and Calculated Shift in pK_a upon Binding of Phosphotyrosine Peptide to the SH2 Domain of p56^{lck}

Bioorg. Med. Chem. 10 (2002) 1477

Nico J. de Mol, Malcolm B. Gillies and Marcel J. E. Fischer

Department of Medicinal Chemistry, Utrecht Institute for Pharmaceutical Sciences, Faculty of Pharmacy, Utrecht University, PO Box 80082, 3508TB Utrecht, The Netherlands

The preferred ionisation state of the tyrosine phosphate group for binding to the p56^{lck} SH2 domain is −2. Several positively charged residues in the phosphate binding pocket are responsible for this.



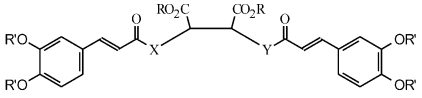
QSAR of HIV-1 Integrase Inhibitors by Genetic Function Approximation Method

Bioorg. Med. Chem. 10 (2002) 1483

Mahindra T. Makhija and Vithal M. Kulkarni

Pharmaceutical Division, Department of Chemical Technology, University of Mumbai, Matunga, Mumbai 400 019, India

A QSAR study was performed on a series of HIV-1 integrase inhibitors belonging to the class of catechols and noncatechols. The results obtained indicate that anti-integrase activity is a function of electronic, spatial, and thermodynamic parameters.

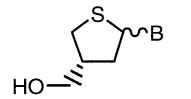


Bioorg. Med. Chem. 10 (2002) 1499

Synthesis and Biological Evaluation of Novel Thioapio Dideoxynucleosides

Hyung Ryong Moon,[a] Hea Ok Kim,[b] Sang Kook Lee,[a] Won Jun Choi,[a] Moon Woo Chun[c] and Lak Shin Jeong[a]

[a]*College of Pharmacy, Ewha Womans University, Seoul 120-750, Republic of Korea*
[b]*Division of Chemistry and Molecular Engineering, Seoul National University, Seoul 151-742, Republic of Korea*
[c]*College of Pharmacy, Seoul National University, Seoul 151-742, Republic of Korea*



B = pyrimidines and purines

Design, synthesis and biological activity of thioapio dideoxynucleosides are described.

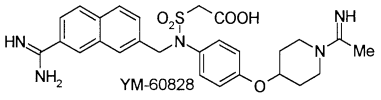
Bioorg. Med. Chem. 10 (2002) 1509

The Discovery of YM-60828: A Potent, Selective and Orally-Bioavailable Factor Xa Inhibitor

Fukushi Hirayama,[a] Hiroyuki Koshio,[a] Naoko Katayama,[a] Hiroyuki Kurihara,[a] Yuta Taniuchi,[b] Kazuo Sato,[c] Nami Hisamichi,[a] Yumiko Sakai-Moritani,[a] Tomihisa Kawasaki,[a] Yuzo Matsumoto[a] and Isao Yanagisawa[a]

[a]*Institute for Drug Discovery Research, Yamanouchi Pharmaceutical Co., Ltd., 21 Miyukigaoka, Tsukuba, Ibaraki 305-8585, Japan*
[b]*Clinical Development Department, Yamanouchi Pharmaceutical Co., Ltd., 3-17-1 Hasune, Itabashi, Tokyo 174-8612, Japan*
[c]*Project Coordination Department, Yamanouchi Pharmaceutical Co., Ltd., 3-17-1 Hasune, Itabashi, Tokyo 174-8612, Japan*

N-[(7-Amidino-2-naphthyl)methyl]aniline derivatives were prepared and evaluated for inhibitory activity against factor Xa in vitro and ex vivo. This study led to discovery of a potent and orally-bioavailable factor Xa inhibitor YM-60828.



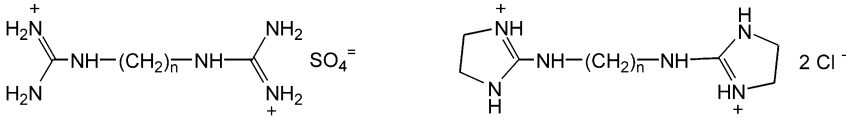
YM-60828

Bioorg. Med. Chem. 10 (2002) 1525

I_2-Imidazoline Binding Site Affinity of a Structurally Different Type of Ligands

Christophe Dardonville,[a] Isabel Rozas,[a,c] Luis F. Callado[b] and J. Javier Meana[b]

[a]*Instituto de Química Médica (CSIC), Juan de la Cierva, 3, 28006-Madrid, Spain*
[b]*Departamento de Farmacología, Universidad del Pais Vasco/EHU, 48940-Leioa, Bizkaia, Spain*
[c]*Department of Chemistry, Trinity College Dublin, Dublin 2, Ireland*



n= 6, 8, 9, 12

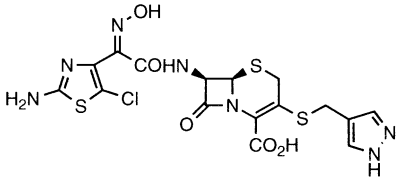
Bioorg. Med. Chem. 10 (2002) 1535

Orally Active Cephalosporins. Part 4: Synthesis, Structure–Activity Relationships and Oral Absorption of Novel 3-(4-Pyrazolylmethylthio)cephalosporins with Various C-7 Side Chains

Hirofumi Yamamoto,[a] Yoshiteru Eikyu,[a] Shinya Okuda,[a] Kohji Kawabata,[a] Hisashi Takasugi,[a] Hirokazu Tanaka,[a] Satoru Matsumoto,[b] Yoshimi Matsumoto[b] and Shuichi Tawara[b]

[a]*Medicinal Chemistry Research Laboratories, Fujisawa Pharmaceutical Co., Ltd., 2-1-6, Kashima, Yodogawa-ku, Osaka 532-8514, Japan*
[b]*Medicinal Biology Research Laboratories, Fujisawa Pharmaceutical Co., Ltd., 2-1-6, Kashima, Yodogawa-ku, Osaka 532-8514, Japan*

A series of 3-(4pyrazolylmethylthio)cephalosporins with various C-7 side chains was synthesized and evaluated for antibacterial activity and oral absorption. Among them, FR192752 (**40a**) exhibited potent activity against both Gram-positive and Gram-negative bacteria including *Haemophilus influenzae* and PRSP and high oral absorption in rats



FR192752 (**40a**)

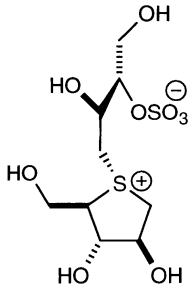
Bioorg. Med. Chem. 10 (2002) 1547

Absolute Stereostructure of Potent α-Glucosidase Inhibitor, Salacinol, with Unique Thiosugar Sulfonium Sulfate Inner Salt Structure from *Salacia reticulata*

Masayuki Yoshikawa,[a] Toshio Morikawa,[a] Hisashi Matsuda,[a] Genzoh Tanabe[b] and Osamu Muraoka[b]

[a]*Kyoto Pharmaceutical University, Misasagi, Yamashina-ku, Kyoto 607-8412, Japan*
[b]*School of Pharmaceutical Sciences, Kinki University, 3-4-1 Kowakae, Higashi-osaka, Osaka 577-8502, Japan*

A most potent α-*glucosidase* inhibitor named salacinol has been isolated from an antidiabetic Ayurvedic traditional medicine, *Salacia reticulata* WIGHT, through bioassay-guided separation. The absolute stereostructure of salacinol was determined on the basis of chemical and physicochemical evidence, which included the alkaline degradation of salacinol to 1-deoxy-4-thio-D-arabinofuranose and the X-ray crystallographic analysis, to be the unique spiro-like configuration of the inner salt comprised of 1-deoxy-4-thio-D-arabinofuranosyl sulfonium cation and 1′-deoxy-D-erythrosyl-3′-sulfate anion. Salacinol showed potent inhibitory activities on several α-glucosidases, such as maltase, sucrase, and isomaltase, and the inhibitory effects on serum glucose levels in maltose- and sucrose-loaded rats (in vivo) were found to be more potent than that of acarbose, a commercial α-glucosidase inhibitor.



salacinol

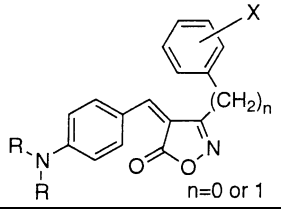
Bioorg. Med. Chem. 10 (2002) 1555

Novel Non-Steroidal/Non-Anilide Type Androgen Antagonists with an Isoxazolone Moiety

Toshiyasu Ishioka,[a] Asako Kubo,[b] Yukiko Koiso,[a] Kazuo Nagasawa,[a] Akiko Itai[b] and Yuichi Hashimoto[a]

[a]*Institute of Molecular and Cellular Biosciences, The University of Tokyo, 1-1-1 Yayoi, Bunkyo-ku, Tokyo, 113-0032, Japan*
[b]*Institute of Medicinal Molecular Design, Key Molecular Inc., 4-24-5 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan*

3-Substituted (*Z*)-4-(4-*N*,*N*-dialkylaminophenylmethylene-5(4*H*)-isoxazolones and related compounds have been designed and prepared as candidates for structurally novel androgen antagonists. Several compounds showed potent anti-androgenic activity.

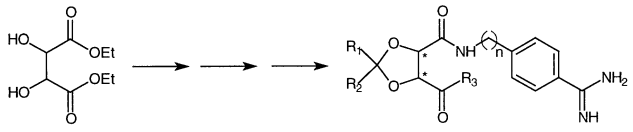


Bioorg. Med. Chem. 10 (2002) 1567

Synthesis of Potential Thrombin Inhibitors. Incorporation of Tartaric Acid Templates as P2 Proline Mimetics

Anders Dahlgren,[a] Jonas Brånalt,[b] Ingemar Kvarnström,[a] Ingemar Nilsson,[b] Djordje Musil[c] and Bertil Samuelsson[d]

[a]*Department of Chemistry, Linköping University, S-581 83 Linköping, Sweden*
[b]*AstraZeneca R&D, Medicinal Chemistry, S-431 83 Mölndal, Sweden*
[c]*AstraZeneca R&D, Structural Chemistry Laboratory, S-481 83 Mölndal, Sweden*
[d]*Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, S-106 91 Stockholm, Sweden*



(*R*,*R*) or (*S*,*S*)

R_1 = R_2 = H or R_1 = H, R_2 = Me or R_1 = R_2 = Me.
R_3 = amines.
Configuration at *: (*R*,*R*) or (*S*,*S*).
n = 1,2.

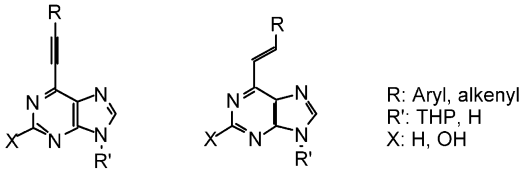
Potential thrombin inhibitors synthesized from tartaric acid.

Bioorg. Med. Chem. 10 (2002) 1581

Antioxidant Activity of Synthetic Cytokinin Analogues: 6-Alkynyl- and 6-Alkenylpurines as Novel 15-Lipoxygenase Inhibitors

Anders Bråthe,[a] Geir Andresen,[a] Lise-Lotte Gundersen,[a] Karl E. Malterud[b] and Frode Rise[a]

[a]*Department of Chemistry, University of Oslo, PO Box 1033, Blindern, N-0315 Oslo, Norway*
[b]*School of Pharmacy, University of Oslo, PO Box 1068, Blindern, N-0316 Oslo, Norway*



R: Aryl, alkenyl
R': THP, H
X: H, OH

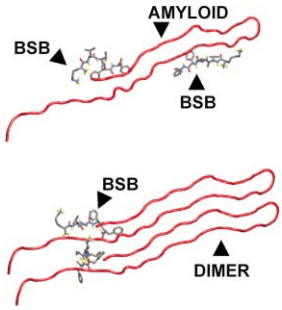
Bioorg. Med. Chem. 10 (2002) 1587

Mapping of Possible Binding Sequences of Two Beta-Sheet Breaker Peptides on Beta Amyloid Peptide of Alzheimer's Disease

Csaba Hetényi,[a] Tamás Körtvélyesi[b,c] and Botond Penke[a]

[a]*Department of Medical Chemistry, University of Szeged, Dóm tér 8, H-6720 Szeged, Hungary*
[b]*Department of Physical Chemistry, University of Szeged, PO Box 105, H-6720 Szeged, Hungary*
[c]*Department of Biomedical Engineering, Boston University, 44 Cummington St, Boston, MA 02215, USA*

Binding sequences of beta-sheet breaker (BSB) peptides on amyloid (Aβ) peptide of Alzheimer's disease were identified by computational docking method. Good agreement with experimental data was achieved. Possible binding positions of BSBs on the dimer (aggregated) form of Aβ were also selected.



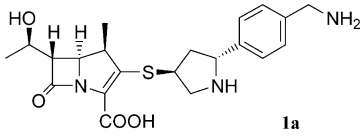
Bioorg. Med. Chem. 10 (2002) 1595

Structure–Activity Relationships of 1β-Methyl-2-(5-phenylpyrrolidin-3-ylthio)carbapenems

Hiroki Sato, Hiroki Sakoh, Takashi Hashihayata, Hideaki Imamura, Norikazu Ohtake, Aya Shimizu, Yuichi Sugimoto, Shunji Sakuraba, Rie Bamba-Nagano, Koji Yamada, Terutaka Hashizume and Hajime Morishima

Banyu Tsukuba Research Institute, Banyu Pharmaceutical Co., Ltd., Okubo-3, Tsukuba 300-2611, Ibaraki, Japan

The detailed structure–activity relationships of **1a** and related compounds was investigated.



1a

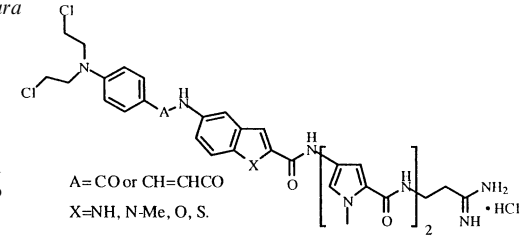
Bioorg. Med. Chem. 10 (2002) 1611

Benzoyl and Cinnamoyl Nitrogen Mustard Derivatives of Benzoheterocyclic Analogues of the Tallimustine: Synthesis and Antitumour Activity

Pier Giovanni Baraldi,[a] Romeo Romagnoli,[a] Maria Giovanna Pavani,[a] Maria del Carmen Nunez,[a] John P. Bingham[b] and John A. Hartley[b]

[a]*Dipartimento di Scienze Farmaceutiche, Università di Ferrara, Via Fossato di Mortara 17/19, 44100 Ferrara, Italy*
[b]*CRC Drug-DNA Interactions Research Group, Department of Oncology, Royal Free and University College Medical School, 91 Riding House Street, London W1W 7BS, UK*

A series of benzoyl and cinnamoyl nitrogen mustards tethered to different benzoheterocycles and to oligopyrroles structurally related to netropsin consisting of two pyrrole-amide units and terminating with an amidine moiety have been synthesised and a structure–activity relationship determined



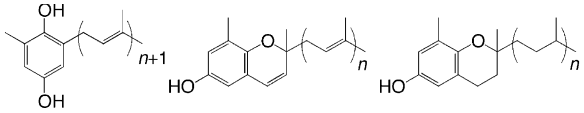
Bioorg. Med. Chem. 10 (2002) 1619

Powerful Antioxidative Agents Based on Garcinoic Acid from *Garcinia Kola*

Kenji Terashima, Yoshiaki Takaya and Masatake Niwa

Faculty of Pharmacy, Meijo University, Tempaku, Nagoya 468-8503, Japan

Structure–antioxidative activity relationship of garcinoic acid analogues ($n = 0, 1, 2, 3$) are discussed.



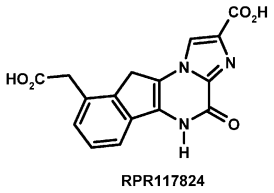
Bioorg. Med. Chem. 10 (2002) 1627

9-Carboxymethyl-5*H*,10*H*-imidazo[1,2-*a*]indeno[1,2-*e*]pyrazin-4-one-2-carbocylic Acid (RPR117824): Selective Anticonvulsive and Neuroprotective AMPA Antagonist

Serge Mignani, Georg Andrees Bohme, Guillaume Birraux, Alain Boireau, Patrick Jimonet, Dominique Damour, Arielle Genevois-Borella, Marc-Williams Debono, Jeremy Pratt, Marc Vuilhorgne, Florence Wahl and Jean-Marie Stutzmann

Aventis Pharma S.A., Centre de Recherche de Paris, 13 quai Jules Guesde, B.P. 14, 94403 Vitry-sur-Seine Cedex, France

The synthesis and biological evaluation of original 9-carboxymethyl-5*H*,10*H*-imidazo[1,2-*a*]-indeno[1,2-*e*] pyrazin-4-one-2-carboxylic acid **RPR117824** is described.



RPR117824

Bioorg. Med. Chem. 10 (2002) 1639

Novel Tn Antigen-Containing Neoglycopeptides: Synthesis and Evaluation as Anti Tumor Vaccines

Laura Cipolla, Maria Rescigno, Antonella Leone, Francesco Peri, Barbara La Ferla and Francesco Nicotra

Department of Biotechnology and Biosciences, Università degli Studi di Milano-Bicocca, P.za della Scienza 2, 20126 Milan, Italy

Three different neoglycopeptides were synthesized, containing one or two B cell epitopes and a T cell epitope. The three neoglycopeptides were tested in vitro as antitumor vaccines.