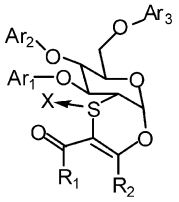
Bioorg. Med. Chem. Lett. 12 (2002) 2263

Design, Synthesis and Biological Activity of Carbohydrate-Containing Peptidomimetics as New Ligands for the Human Tachykinin NK-2 Receptor

Giuseppe Capozzi,[a] Sabrina Giannini,[a] Stefano Menichetti,[b] Cristina Nativi,[a,*] Alessandro Giolitti,[c] Riccardo Patacchini,[c] Enzo Perrotta,[c] Maria Altamura[c,*] and Carlo Alberto Maggi[c]

[a]*Dipartimento di Chimica Organica 'Ugo Schiff', Universita' di Firenze, via della Lastruccia, 13, I-50019 Sesto Fiorentino, Florence, Italy*
[b]*Dipartimento di Chimica Organica e Biologica, Universita' di Messina, Salita Sperone, 31, I-98166 Messina, Italy*
[c]*Menarini Ricerche S.p.A., Via dei Sette Santi 3, I-50131, Florence, Italy*



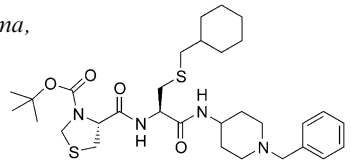
Bioorg. Med. Chem. Lett. 12 (2002) 2267

L-Cysteine Based N-type Calcium Channel Blockers: Structure–Activity Relationships of the C-Terminal Lipophilic Moiety, and Oral Analgesic Efficacy in Rat Pain Models

Takuya Seko,* Masashi Kato, Hiroshi Kohno, Shizuka Ono, Kazuya Hashimura, Yoshifumi Takenobu, Hideyuki Takimizu, Katsuhiko Nakai, Hitoshi Maegawa, Nobuo Katsube and Masaaki Toda

Minase Research Institute, Ono Pharmaceutical Co., Ltd., 3-1-1 Sakurai, Shimamoto, Mishima, Osaka 618-8585, Japan

The SAR study of L-cysteine based N-type calcium channel blockers are described. L-Cysteine derivative **9** was found to be potent and selective N-type calcium channel blocker with IC_{50} 0.33 μM in IMR-32 assay.



9 IC_{50} = 0.33 μM

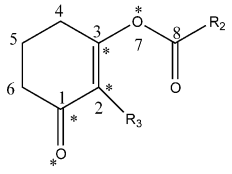
Bioorg. Med. Chem. Lett. 12 (2002) 2271

3D-QSAR Studies on 4-Hydroxyphenylpyruvate Dioxygenase Inhibitors by Comparative Molecular Field Analysis (CoMFA)

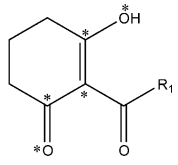
Meilan Huang,[a] Ding-Yah Yang,[b] Zhicai Shang,[a,*] Jianwei Zou[a] and Qingsen Yu[a]

[a]*Department of Chemistry, Zhejiang University, Hangzhou, Zhejiang 310027, People's Republic of China*
[b]*Department of Chemistry, Tunghai University, Taichung, 40704, Taiwan*

A comparative molecular field analysis (CoMFA) of alkanoic acid 3-oxo-cyclohex-1-enyl ester and 2-acylcyclohexane-1,3-dione derivatives of 4-hydroxyphenylpyruvate dioxygenase inhibitors has been performed to determine the factors required for the activity of these compounds.



Class 1



Class 2

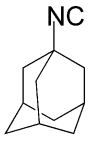
Bioorg. Med. Chem. Lett. 12 (2002) 2277

In Vivo Active Antimalarial Isonitriles

Chandan Singh,[a,*] Naveen Chandra Srivastav[a] and Sunil K. Puri[b]

[a]*Division of Medicinal Chemistry, Central Drug Research Institute, Lucknow-226001, India*
[b]*Division of Parasitology, Central Drug Research Institute, Lucknow-226001, India*

Antimalarial activity of easily accessible synthetic isonitriles has been reported.



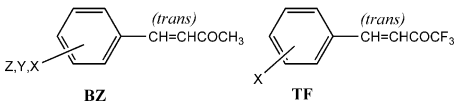
Bioorg. Med. Chem. Lett. 12 (2002) 2281

Quantum Chemical- and 3-D-QSAR (CoMFA) Studies of Benzalacetones and 1,1,1-Trifluoro-4-phenyl-3-buten-2-ones

Chisako Yamagami,[a,*] Noriko Motohashi[a] and Miki Akamatsu[b]

[a]*Kobe Pharmaceutical University, Motoyamakita-machi, Higashinadaku, Kobe 658-8558, Japan*
[b]*Graduate School of Agriculture, Koyto University, Kitashirakawa, Sakyoku, Kyoto 606-8502, Japan*

The inhibitory effect (IC_{50}) of the title compounds on UV-induced mutagenesis in *Escherichia coli* WP2*uvrA* was analyzed quantitatively by using various quantum chemical descriptors and also by the CoMFA method: both approaches provided results of similar quality.



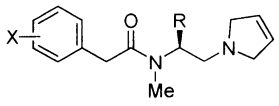
Bioorg. Med. Chem. Lett. 12 (2002) 2287

3-Pyrroline Containing Arylacetamides: A Novel Series of Remarkably Selective κ-Agonists

Qi-Yong Mou, Jie Chen, You-Cheng Zhu, De-He Zhou, Zhi-Qiang Chi and Ya-Qiu Long*

Shanghai Institute of Materia Medica, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences, 294 Taiyuan Road, Shanghai 200031, China

The synthesis and pharmacological evaluation of 3-pyrroline containing arylacetamides as highly selective κ-agonists was reported. The best such agent **1e** exhibited binding affinity to κ-receptor with K_i value of 5.72 nM and antinociceptive activity with ED_{50} value of 0.023 mg/kg.



1a-l

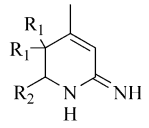
Bioorg. Med. Chem. Lett. 12 (2002) 2291

Design and Synthesis of Orally Bioavailable Inhibitors of Inducible Nitric Oxide Synthase. Part 1: Synthesis and Biological Evaluation of Dihydropyridin-2-imines

Yasufumi Kawanaka,[a,*] Kaoru Kobayashi,[b] Shinya Kusuda,[b] Tadashi Tatsumi,[b] Masanori Murota,[b] Toshihiko Nishiyama,[b] Katsuya Hisaichi,[b] Atsuko Fujii,[b] Keisuke Hirai,[b] Masao Naka,[b] Masaharu Komeno,[b] Hisao Nakai[b] and Masaaki Toda[b]

[a]*Fukui Research Institute, Ono Pharmaceutical Co., Ltd., Technoport, Yamagishi, Mikuni, Sakai, Fukui 913-8538, Japan*
[b]*Minase Research Institute, Ono Pharmaceutical Co., Ltd., Shimamoto, Mishima, Osaka 618-8585, Japan*

The dihydropyridin-2-imines, **1**, **5**, **9** and **10** were identified as potent inhibitors of inducible nitric oxide.



1: R_1=R_2=H; **5**: R_1=Me, R_2=H;
9: R_1=H, R_2=n-Pr; **10**: R_1=H, R_2=Allyl

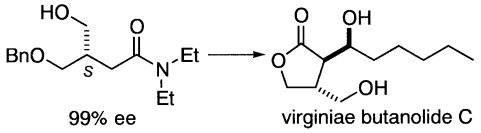
Bioorg. Med. Chem. Lett. 12 (2002) 2295

Preparation of Chiral 4-Benzyloxymethyldihydrofuran-2-one Using Lipase-Catalyzed Kinetic Resolution: Synthesis of (−)-Virginiae Butanolide C (VB C)

Kunihiko Takabe,[a,*] Nobuyuki Mase,[a] Hidetoshi Matsumura,[a] Takehiro Hasegawa,[a] Yasuhiro Iida,[a] Hisashi Kuribayashi,[a] Kenji Adachi,[a] Hidemi Yoda[a] and Masato Ao[b]

[a]*Department of Molecular Science, Faculty of Engineering, Shizuoka University, 3-5-1 Johoku, Hamamatsu 432-8561, Japan*
[b]*Nagoya Municipal Industrial Institute, 3-4-41 Rokuban, Atsuta-ku, Nagoya 456-0058, Japan*

The synthesis of highly stereocontrolled virginiae butanolide C is reported.

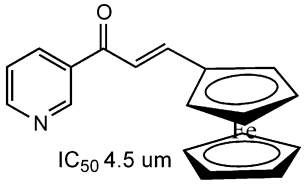


Bioorg. Med. Chem. Lett. 12 (2002) 2299

Antimalarial Activity of Ferrocenyl Chalcones

Xiang Wu,[a] Prapon Wilairat[b] and Mei-Lin Go[a,*]

[a]*Department of Pharmacy, National University of Singapore, 18, Science Drive 4, 117543, Singapore*
[b]*Department of Biochemistry, Mahidol University, Rama VI Road, Bangkok 10400, Thailand*

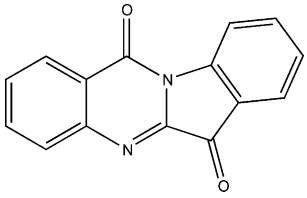


Bioorg. Med. Chem. Lett. 12 (2002) 2303

Novel Indolo[2,1-*b*]quinazoline Analogues as Cytostatic Agents: Synthesis, Biological Evaluation and Structure–Activity Relationship

Vedula M. Sharma,[a,*] P. Prasanna,[a] K. V. Adi Seshu,[a] B. Renuka,[a] C. V. Laxman Rao,[a] G. Sunil Kumar,[a] C. Prasad Narasimhulu,[a] P. Aravind Babu,[a] R. C. Puranik,[a] D. Subramanyam,[a] A. Venkateswarlu,[a] Sriram Rajagopal,[b] K. B. Sunil Kumar,[b] C. Seshagiri Rao,[b] N. V. S. Rao Mamidi,[b] Dhanvanthri S. Deevi,[b] R. Ajaykumar[b] and R. Rajagopalan[b]

[a]*Discovery Chemistry (Natural Products), Dr. Reddy's Research Foundation, Miyapur, Hyderabad - 500 050, India*
[b]*Discovery Biology, Dr. Reddy's Research Foundation, Miyapur, Hyderabad - 500 050, India*



A novel series of indoloquinazolines were synthesized and tested for anticancer activity in various human cancer cell lines. The most potent compounds were further tested in the hollow fibre assay followed by xenograft studies in nude mice to assess the anticancer property.

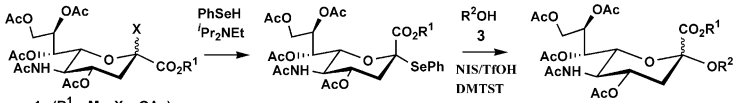
Bioorg. Med. Chem. Lett. 12 (2002) 2309

Use of Phenyl 2-α-Selenoglycosides of *N*-Acetylneuraminic Acid as a Glycosyl Donor for the Glycosylation Reactions

Kiyoshi Ikeda,* Yuji Sugiyama, Kiyoshi Tanaka and Masayuki Sato

School of Pharmaceutical Sciences, University of Shizuoka, Yada 52-1, Shizuoka 422-8526, Japan

Phenyl 2-α-selenoglycosides of Neu5Ac **2** were successfully prepared from the corresponding peracetylated chloro derivative of Neu5Ac **1** and phenylselenol in the presence of *N*,*N*-di-isopropylethylamine in excellent yields. The reaction of **2** with various alcohols was effectively catalyzed by NIS/TfOH or DMTST to produce a variety of glycosides in moderate yields. Selective activation of **2** over phenyl 2-α-thioglycoside of Neu5Ac **6** with $AgOTf/K_2CO_3$ was also achieved.



1a (R^1 = Me, X = OAc)
1b (R^1 = Me, X = Cl)
1c (R^1 = Bn, X = Cl)

2a (R^1 = Me) 4a (R^1 = Me, R^2 = -$CH_2C_6H_4$*p*-NO_2), 4b (R^1 = Bn, R^2 = -$CH_2C_6H_4$*p*-NO_2)
2b (R^1 = Bn) 4c (R^1 = Me, R^2 = -$CH_2CH_2NHC(O)OBn$), 4d (R^1 = Me, R^2 = -$CH_2C_6H_4$*p*-OMe)
4e (R^1 = Me, R^2 = -$CH_2CH(NHCO_2CH_2CCl_3)CO_2Bn$)
4f (R^1 = Me, R^2 = -6-*O*-Gal)

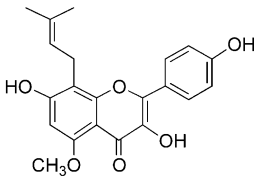
Bioorg. Med. Chem. Lett. 12 (2002) 2313

A Prenylated Flavonol, Sophoflavescenol: A Potent and Selective Inhibitor of cGMP Phosphodiesterase 5

Hye Joo Shin,[a] Hyoung Ja Kim,[a] Jong Hwan Kwak,[a] Hyung Ok Chun,[b] Je Hak Kim,[b] Hokoon Park,[a] Dong Hyun Kim[a] and Yong Sup Lee[a,*]

[a]*Division of Life Sciences, Korea Institute of Science & Technology, PO Box 131, Cheongryang, Seoul 130-650, Republic of Korea*
[b]*Institute of Science & Technology, Cheil Jedang Corporation, Majang, Ichon, Kyonggi-Do 467-810, Republic of Korea*

The inhibitory activities of kushenol H (**1**), kushenol K (**2**), kurarinol (**3**), sophoflavescenol (**4**) and kuraridine (**5**), obtained from *Sophora flavescens*, were tested against cGMP PDE5. Among them, sophoflavescenol (**4**) showed the most potent inhibitory activity (IC_{50} = 0.013 μM) against cGMP PDE5 with 31.5- and 196.2-fold selectivity over PDE3 and PDE4, respectively.



4, Sophoflavescenol

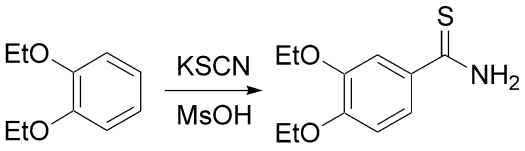
Bioorg. Med. Chem. Lett. 12 (2002) 2317

A Practical Synthesis of 3,4-Diethoxybenzthioamide Based on Friedel–Crafts Reaction with Potassium Thiocyanate in Methanesulfonic Acid

Shinji Aki,* Takafumi Fujioka, Masashi Ishigami and Jun-ichi Minamikawa

Process Research Laboratory, 2nd Tokushima Factory, Otsuka Pharmaceutical Co., Ltd., 224-18, Ebisuno, Hiraishi, Kawauchi-cho, Tokushima 771-0182, Japan

The synthesis of 3,4-diethoxybenzthioamide is reported.

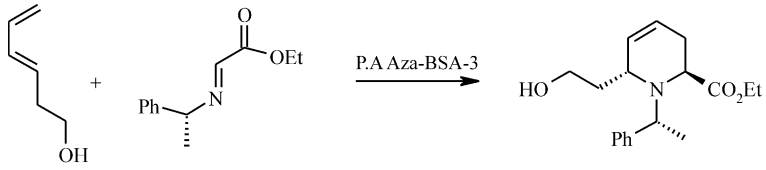


Bioorg. Med. Chem. Lett. 12 (2002) 2321

First Example of an Antibody-Catalyzed Aza Diels–Alder Reaction

Zhen-Dan Shi,[a] Bing-Hui Yang,[a] Yu-Lin Wu,[a] Ya-Juan Pan,[a] Yong-Yong Ji[b] and Ming Yeh[b]

[a]*State Key Laboratory of Bioorganic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, China*
[b]*Shanghai Institute of Cell Biology, Chinese Academy of Sciences, Shanghai 200031, China*



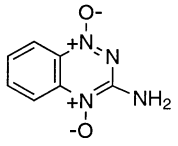
Bioorg. Med. Chem. Lett. 12 (2002) 2325

Oxidative DNA Base Damage by the Antitumor Agent 3-Amino-1,2,4-benzotriazine 1,4-Dioxide (Tirapazamine)

Delshanee Kotandeniya,[a] Brian Ganley[b] and Kent S. Gates[a,b,*]

[a]*Department of Chemistry, University of Missouri-Columbia, Columbia, MO 65211, USA*
[b]*Department of Biochemistry, University of Missouri-Columbia, Columbia, MO 65211, USA*

In this work, base excision repair enzymes that remove oxidatively damaged DNA bases, leaving behind easily detected strand breaks, were used to provide evidence that tirapazamine causes significant amount of damage to both purine and pyrimidine residues in double-stranded DNA.



Tirapazamine

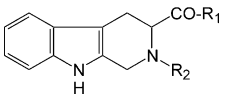
Bioorg. Med. Chem. Lett. 12 (2002) 2331

Synthesis and Thrombolytic Activity of Pseudopeptides Related to Fibrinogen Fragment

Yanfen Wu, Ming Zhao, Chao Wang and Shiqi Peng*

College of Pharmaceutical Chemistry, Peking University, Beijing 100083, PR China

The synthesis, bioactivity in vivo, stability to trypsin promotion hydrolysis and conformation for the pseudopeptides are reported, wherein R_1 = OH, R_2 = -Lys-Ala-Pro-Arg-Ala; or R_1 = -Ala-Arg-Pro-Ala-Lys-OH, R_2 = H



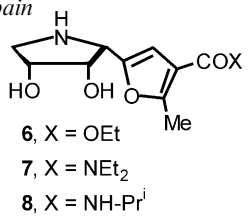
Bioorg. Med. Chem. Lett. 12 (2002) 2335

Synthesis of [(2*S*,3*S*,4*R*)-3,4-Dihydroxypyrrolidin-2-yl]-5-methylfuran-4-carboxylic Acid Derivatives: New Leads as Selective β-Galactosidase Inhibitors

Antonio J. Moreno-Vargas,[a] Raynald Demange,[b] José Fuentes,[a] Inmaculada Robina[a,*] and Pierre Vogel[b,*]

[a]*Departamento de Química Orgánica, Facultad de Química, Universidad de Sevilla, E-41071 Sevilla, Spain*
[b]*Institut de Chimie Moléculaire et Biologique, Ecole Polytechnique Fédérale de Lausanne, BCH, CH-1015 Lausanne-Dorigny, Switzerland*

The synthesis of selective β-galactosidase inhibitors is reported.



6, X = OEt
7, X = NEt_2
8, X = NH-Pr^i

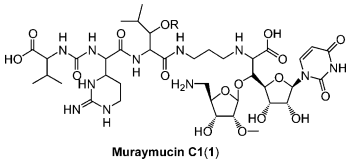
Bioorg. Med. Chem. Lett. 12 (2002) 2341

Muraymycins, Novel Peptidoglycan Biosynthesis Inhibitors: Semisynthesis and SAR of Their Derivatives

Yang-I Lin,* Zhong Li, Gerardo D. Francisco, Leonard A. McDonald, Rachel A. Davis, Guy Singh, Youjun Yang and Tarek S. Mansour

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

Sixteen muraymycin derivatives **2**–**17** were synthesized based on selective reactions of the primary and secondary amino groups of muraymycin C1 (**1**) with isocyanates and aldehydes. Disubstituted derivatives **3**–**9** demonstrated no activity (IC_{50}) against either MraY or MurG at $\leq 100\,\mu g/mL$ whereas mono substituted derivatives **11**–**17** demonstrated good inhibitory activity, well correlated with the lipophilicity of the substituent introduced. In particular, the activity of derivatives **13** and **14** was comparable to that of muraymycin C1 in this assay.



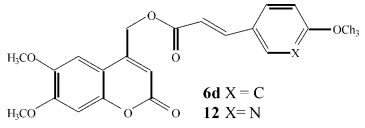
Bioorg. Med. Chem. Lett. 12 (2002) 2345

Preliminary Structure–Antiangiogenic Activity Relationships of 4-Senecioyloxymethyl-6,7-dimethoxycoumarin

Nguyen-Hai Nam,[a] Yong Kim,[a] Young-Jae You,[a] Dong-Ho Hong,[a,b] Hwan-Mook Kim[b] and Byung-Zun Ahn[a,*]

[a]*College of Pharmacy, Chungnam National University, Taejon 305-764, Republic of Korea*
[b]*Research Institute of Biosciences and Biotechnology, Taejon 305-600, Republic of Korea*

A systemic modification of a novel angiogenesis inhibitor 4-senecioyloxymethyl-6,7-dimethoxycoumarin (**1**) led to the findings of **6d** and **12** with 10-fold enhanced activity.



6d X = C
12 X = N

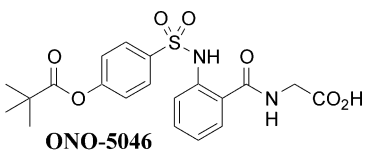
Bioorg. Med. Chem. Lett. 12 (2002) 2349

Clarification of Mechanism of Human Sputum Elastase Inhibition by a New Inhibitor, ONO-5046, Using Electrospray Ionization Mass Spectrometry

Yoshisuke Nakayama,[a] Yoshihiko Odagaki,[a,*] Setsuko Fujita,[a] Shozo Matsuoka,[b] Nobuyuki Hamanaka,[a] Hisao Nakai[a] and Masaaki Toda[a]

[a]*Medicinal Chemistry Research Laboratories, Minase Research Institute, Ono Pharmaceutical Co., Ltd., Shimamoto, Mishima, Osaka 618-8585, Japan*
[b]*Development Planning, Ono Pharmaceutical Co., Ltd., 2-1-5 Doshomachi, Chuo-ku, Osaka 541-8526, Japan*

Liquid chromatography electrospray ionization spectrometry to probe the nature of the covalent E–I complex was successfully applied to clarify the mechanism of human sputum elastase inhibition of a new inhibitor **ONO-5046**.



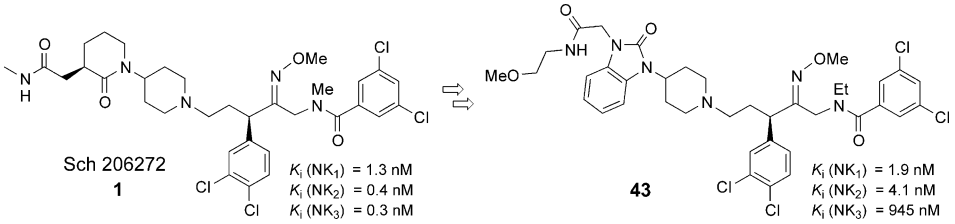
ONO-5046

Bioorg. Med. Chem. Lett. 12 (2002) 2355

Preparation of Oxime Dual NK_1/NK_2 Antagonists with Reduced NK_3 Affinity

Gregory A. Reichard,* Cheryl A. Grice, Neng-Yang Shih, James Spitler, Sapna Majmundar, Steven D. Wang, Sunil Paliwal, John C. Anthes and John J. Piwinski

Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, NJ 07033, USA



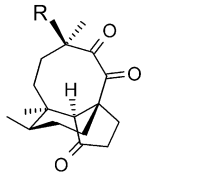
Bioorg. Med. Chem. Lett. 12 (2002) 2359

Design and Synthesis of Conformationally Restricted Eight-Membered Ring Diketones as Potential Serine Protease Inhibitors

Neil D. Pearson,[a] Drake S. Eggleston,[a] R. Curtis Haltiwanger,[b] Martin Hibbs,[a] Alison J. Laver[a] and Arun C. Kaura[c,*]

[a]*GlaxoSmithKline Pharmaceuticals, New Frontiers Science Park North, Third Avenue, The Pinnacles, Harlow, Essex CM19 5AG, UK*
[b]*GlaxoSmithKline Pharmaceuticals, Department of Physical and Structural Chemistry, PO Box 1539, King of Prussia, PA 19406, USA*
[c]*GlaxoSmithKline Pharmaceuticals, 1250 South Collegeville Road, PO Box 5089, Collegeville, PA 19426, USA*

Potential serine protease inhibitors **3** and **4** were prepared from mutilin and evaluated. X-ray crystallography confirmed structure of the acetamide **4**, which inhibited plasmin and urokinase in vitro.



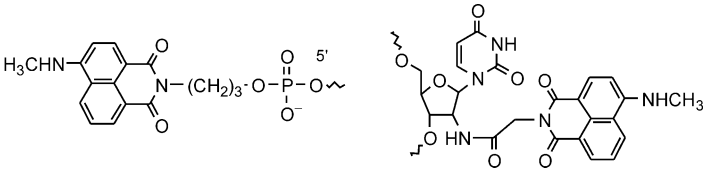
3 R = MeCONH; **4** R = Et

Bioorg. Med. Chem. Lett. 12 (2002) 2363

Synthesis of ODNs Containing 4-Methylamino-1,8-naphthalimide as a Fluorescence Probe in DNA

Kiyohiko Kawai,* Kazuhiro Kawabata, Sachiko Tojo and Tetsuro Majim*

The Institute of Scientific and Industrial Research (SANKEN), Osaka University, Mihogaoka 8-1, Ibaraki, Osaka 567-0047, Japan



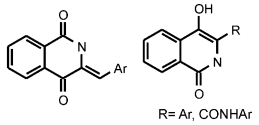
Bioorg. Med. Chem. Lett. 12 (2002) 2367

Novel Inhibitors of Plasminogen Activator Inhibitor-1: Development of New Templates From Diketopiperazines

Shouming Wang,[a,*] Julian Golec,[a] Warren Miller,[a] Sandra Milutinovic,[a] Adrian Folkes,[a] Susannah Williams,[a] Teresa Brooks,[b] Kevin Hardman,[b] Peter Charlton,[b] Stephen Wren[a] and John Spencer[a]

[a]*Department of Medicinal Chemistry, Xenova Ltd., 957 Buckingham Avenue, Slough SL1 4NL, Berkshire, UK*
[b]*Department of Pharmacology, Xenova Ltd., 957 Buckingham Avenue, Slough SL1 4NL, Berkshire, UK*

Several isoquinoline-based templates were identified from the studies of the conformational effects of the diketopiperazine structures for PAI-1 inhibition. Moderate to good activity was retained with the elimination of unattractive characteristics in the diketopiperazine template.



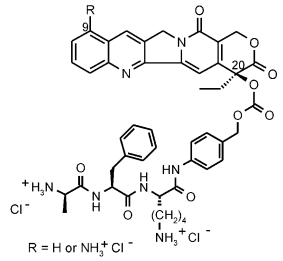
Bioorg. Med. Chem. Lett. 12 (2002) 2371

Novel 20-Carbonate Linked Prodrugs of Camptothecin and 9-Aminocamptothecin Designed for Activation by Tumour-Associated Plasmin

Franciscus M. H. de Groot, Guuske F. Busscher, René W. M. Aben and Hans W. Scheeren*

Department of Organic Chemistry, NSR-Center for Molecular Structure, Design and Synthesis, University of Nijmegen, Toernooiveld 1, 6525 ED Nijmegen, The Netherlands

Novel tripartate prodrugs of camptothecin and 9-aminocamptothecin are reported, in which a specific plasmin substrate has been coupled to the parent drugs via a 1,6-elimination spacer. Both prodrugs were stable in buffer, released parent drug upon incubation with plasmin, and showed decreased in vitro cytotoxicity.



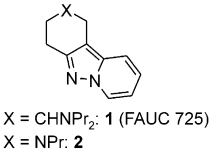
Bioorg. Med. Chem. Lett. 12 (2002) 2377

Fused Azaindole Derivatives: Molecular Design, Synthesis and In Vitro Pharmacology Leading to the Preferential Dopamine D3 Receptor Agonist FAUC 725

Stefan Löber, Harald Hübner and Peter Gmeiner*

Department of Medicinal Chemistry, Emil Fischer Center, Friedrich-Alexander University, Schuhstraße 19, D-91052 Erlangen, Germany

Molecular design based on the similarity of MEPs initiated the synthesis of the tricyclic test compounds **1** (FAUC 725) and **2**. **1** proved to be a highly potent and selective D3 agonist.



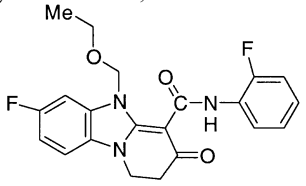
Bioorg. Med. Chem. Lett. 12 (2002) 2381

Potential Anxiolytic Agents. Part 4: Novel Orally-Active N^5-Substituted Pyrido[1,2-*a*]benzimidazoles with High GABA-A Receptor Affinity

Alfonzo D. Jordan,[a,*] Anil H. Vaidya,[a] Daniel I. Rosenthal,[a] Barry Dubinsky,[a] Cheryl P. Kordik,[a] Pauline J. Sanfilippo,[a] Wu-Nan Wu[b] and Allen B. Reitz[a]

[a]*Drug Discovery Division, Johnson & Johnson Pharmaceutical Research and Development, Welsh and McKean Roads, PO Box 776, Spring House, PA 19477-0776, USA*
[b]*Preclinical Development, Johnson & Johnson Pharmaceutical Research and Development, Welsh and McKean Roads, PO Box 776, Spring House, PA 19477-0776, USA*

The synthesis and SAR of a novel series of potent GABA-A receptor ligands are described. The most promising of these N^5-pyrido[1,2-*a*]benzimidazole (PBIs) derivatives is **24**, which has entered clinical trials.



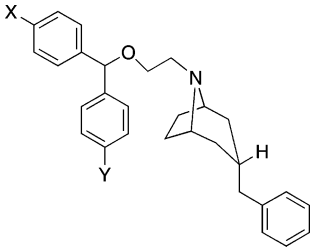
24

Bioorg. Med. Chem. Lett. 12 (2002) 2387

Synthesis and Dopamine Transporter Binding Affinities of 3α-Benzyl-8-(diarylmethoxyethyl)-8-azabicyclo[3.2.1]octanes

Amy L. Bradley,[a] Sari Izenwasser,[b] Dean Wade,[b] Cheryl Klein-Stevens,[c] Naijue Zhu[c] 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*
[c]*Department of Chemistry, Xavier University of Louisiana, New Orleans, LA 70125, USA*



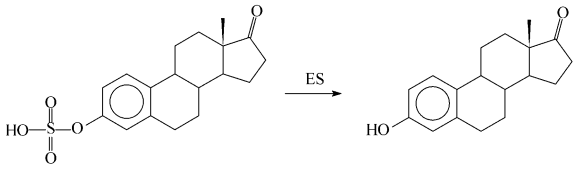
Bioorg. Med. Chem. Lett. 12 (2002) 2391

Inhibition of Estrone Sulfatase (ES) by Derivatives of 4-[(Aminosulfonyl)oxy] Benzoic Acid

Sabbir Ahmed,[a,*] Karen James[b] and Caroline P. Owen[a]

[a]*School of Chemical and Pharmaceutical Sciences, Kingston University, Penrhyn Road, Kingston upon Thames, Surrey KT1 2EE, UK*
[b]*Institute of Cancer Research, Sutton, Surrey, UK*

The inhibition of estrone sulfatase is investigated using esters of 4-aminosulfonated derivatives of benzoic acid.



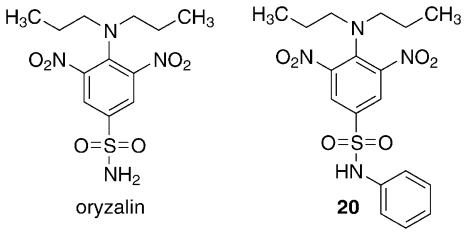
Bioorg. Med. Chem. Lett. 12 (2002) 2395

Antileishmanial Dinitroaniline Sulfonamides with Activity Against Parasite Tubulin

Gautam Bhattacharya, Manar M. Salem and Karl A. Werbovetz*

Division of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, The Ohio State University, 500 West 12th Avenue, Columbus, OH 43210, USA

The synthesis and evaluation of oryzalin analogues resulted in the identification of compounds with more potent activity against purified leishmanial tubulin and cultured *Leishmania* parasites than the lead molecule. Among these is **20**, which is 13.4-fold more active against *Leishmania donovani* axenic amastigotes than oryzalin.



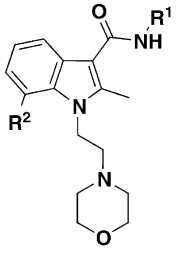
Bioorg. Med. Chem. Lett. 12 (2002) 2399

C-3 Amido-Indole Cannabinoid Receptor Modulators

John Hynes, Jr.,[a,*] Katerina Leftheris,[a] Hong Wu,[a] Chennagiri Pandit,[a] Ping Chen,[a] Derek J. Norris,[a] Bang-Chi Chen,[b] Rulin Zhao,[b] Peter A. Kiener,[c] Xiaorong Chen,[c] Lori A. Turk,[c] Vina Patil-Koota,[c] Kathleen M. Gillooly,[c] David J. Shuster[c] and Kim W. McIntyre[c]

[a]*Discovery Chemistry, Bristol-Myers Squibb, PO Box 4000, Princeton, NJ 08543-4000, USA*
[b]*Discovery Analytical Sciences, Bristol-Myers Squibb, PO Box 4000, Princeton, NJ 08543-4000, USA*
[c]*Immunology, Inflammation & Pulmonary Discovery, Bristol-Myers Squibb, PO Box 4000, Princeton, NJ 08543-4000, USA*

This communication describes the synthesis, SAR, and in vivo evaluation of a series of C-3 amido-indole derivatives as cannabinoid receptor 2 agonists for the treatment of inflammatory disorders. In vivo efficacy was demonstrated in a murine model of acute inflammation (**19a**, ED_{50} 5 mg/kg, iv).



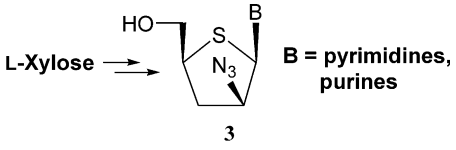
Bioorg. Med. Chem. Lett. 12 (2002) 2403

Synthesis and Biological Evaluation of Novel D-2′-Azido-2′,3′-dideoxyarabinofuranosyl-4′-thiopyrimidines and Purines

Hea Ok Kim,[a] Yong Hee Park,[b] Hyung Ryong Moon[b] and Lak Shin Jeong[b,*]

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

Synthesis of novel D-2′-azido-2′,3′-dideoxyarabinofuranosyl-4′-thiopyrimidines and purines is described.



Bioorg. Med. Chem. Lett. 12 (2002) 2407

Structure–Activity Relationship of Linear Peptide Bu-His-DPhe-Arg-Trp-Gly-NH_2 at the Human Melanocortin-1 and -4 Receptors: Arginine Substitution

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

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

A series of pentapeptides, based on Bu-His^6-DPhe^7-Arg^8-Trp^9-Gly^{10}-NH_2 and modified at the Arg^8 position, was prepared and pharmacologically characterized. Peptides containing either cyanoguanidine or acylguanidine, two substantially less basic arginine surrogates, were found to retain the agonist activity of the parent peptide at both hMC1R and hMC4R. This study unequivocally demonstrate that the positive charge of Arg^8 is not essential for efficient interactions of our peptides with both hMC1R and hMC4R.

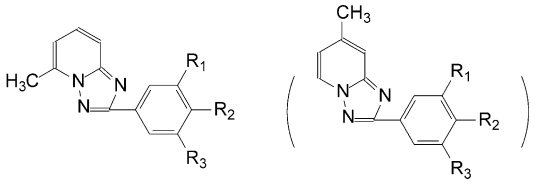
Bioorg. Med. Chem. Lett. 12 (2002) 2411

Non-Steroidal Pregnancy-Terminating Agents: Design, Synthesis and Structure–Activity Relationships of 2-Aryl-1,2,4-triazolo[1,5-*a*]pyridine

Tao Liu and Yongzhou Hu*

Zhejiang University, Department of Medicinal Chemistry, College of Pharmacy, Hangzhou 310031, PR China

The syntheses, the pregnancy-terminating activity relationships of compound (**5a**–**n**) are reported. The structure of these compounds is shown here. Compound **5b** and **5l** are found to be more potent than DL-111—a known drug has effective pregnancy-terminating activity in vitro. Further research shows they have the same activity as DL-111 in vivo. We also find that their oral anti-implantation are more excellent than similar drugs.



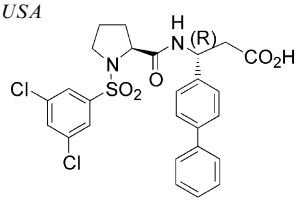
Bioorg. Med. Chem. Lett. 12 (2002) 2415

Substituted 3-Amino Biaryl Propionic Acids as Potent VLA-4 Antagonists

Ihor E. Kopka,[a,*] Linus S. Lin,[a] Richard A. Mumford,[b] Thomas Lanza, Jr.,[a] Plato A. Magriotis,[a] David Young,[a] Stephen E. DeLaszlo,[a] Malcolm MacCoss,[a] Sander G. Mills,[a] Gail Van Riper,[b] Ermengilda McCauley,[b] Kathryn Lyons,[c] Stella Vincent,[c] Linda A. Egger,[b] Usha Kidambi,[b] Ralph Stearns,[c] Adria Colletti,[c] Yohannes Teffera,[c] Sharon Tong,[a] Karen Owens,[a] Dorothy Levorse,[a] John A. Schmidt[b] and William K. Hagmann[a]

[a]*Department of Medicinal Chemistry, Merck Research Laboratories, PO Box 2000 RY 123-136, Rahway, NJ 07065, USA*
[b]*Department of Inflammation and Rheumatology Research, Merck Research Laboratories, Rahway, NJ 07065, USA*
[c]*Department of Drug Metabolism, Merck Research Laboratories, Rahway, NJ 07065, USA*

A series of substituted *N*-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl- and (L)-azetidyl-β-biaryl β-alanine derivatives was prepared as selective and potent VLA-4 antagonists. The 2,6-dioxygenated biaryl substitution pattern is important for optimizing potency. Oral bioavailability was variable and may be a result of binding to circulating plasma proteins.



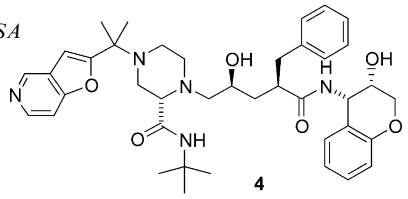
Bioorg. Med. Chem. Lett. 12 (2002) 2419

Indinavir Analogues with Blocked Metabolism Sites as HIV Protease Inhibitors with Improved Pharmacological Profiles and High Potency Against PI-Resistant Viral Strains

Yuan Cheng,[a,*] Fengqi Zhang,[a] Thomas A. Rano,[a] Zhijian Lu,[a] William A. Schleif,[b] Lori Gabryelski,[b] David B. Olsen,[c] Mark Stahlhut,[c] Carrie A. Rutkowski,[c] Jiunn H. Lin,[d] Lixia Jin,[d] Emilio A. Emini,[b] Kevin T. Chapman[a] and James R. Tata[a]

[a]*Department of Medicinal Chemistry, Merck Research Laboratories, Rahway, NJ 07065, USA*
[b]*Department of Viral Vaccine Research, Merck Research Laboratories, West Point, PA 19486, USA*
[c]*Department of Biological Chemistry, Merck Research Laboratories, West Point, PA 19486, USA*
[d]*Department of Drug Metabolism, Merck Research Laboratories, West Point, PA 19486, USA*

Indinavir analogues with blocked metabolism sites show highly improved pharmacokinetic profiles in animals.



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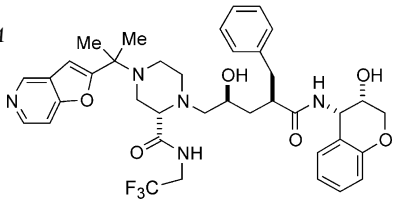
Bioorg. Med. Chem. Lett. 12 (2002) 2423

Synthesis and Activity of Novel HIV Protease Inhibitors with Improved Potency Against Multiple PI-Resistant Viral Strains

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

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

The modification of the carboxamide substituent in Indinavir analogues afforded a compound with substantially improved potency against multiply PI-resistant strains of HIV, as well as a more favorable in vivo pharmacokinetic profile.



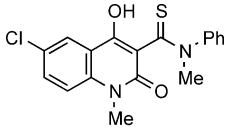
Bioorg. Med. Chem. Lett. 12 (2002) 2427

Quinoline-3-carbothioamides and Related Compounds as Novel Immunomodulating Agents

Takashi Tojo,[a] Glen W. Spears,[a] Kiyoshi Tsuji,[a,*] Hiroaki Nishimura,[a] Takashi Ogino,[a] Nobuo Seki,[c] Aiko Sugiyama[b] and Masaaki Matsuo[b]

[a]*Medicinal Chemistry Research Laboratories, Fujisawa Pharmaceutical Co., Ltd, 2-1-6, Kashima,Yodogawa-ku, Osaka 532-8514, Japan*
[b]*Research Information Management, Fujisawa Pharmaceutical Co., Ltd, 2-1-6, Kashima,Yodogawa-ku, Osaka 532-8514, Japan*
[c]*Exploratory Research Laboratories, Fujisawa Pharmaceutical Co., Ltd, 5-2-3, Tokodai, Tsukuba, Ibaraki 300-2698, Japan*

A series of quinoline-3-carbothioamides and their analogues was prepared. The optimal compound **9g** was highly effective in TNP-LPS induced T-cell independent antibody production, chronic graft-versus-host disease and autoimmune MRL/l mice.



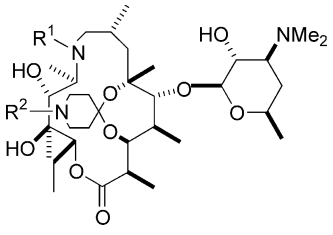
9g

Bioorg. Med. Chem. Lett. 12 (2002) 2431

Synthesis and SAR of Azalide 3,6-Ketal Aromatic Derivatives as Potent Gram-Positive and Gram-Negative Antibacterial Agents

Hengmiao Cheng,* John P. Dirlam, Carl B. Ziegler, Kristin M. Lundy, Shigeru F. Hayashi, Barbara J. Kamicker, Jason K. Dutra, Kirsten L. Daniel, Sheryl L. Santoro, David M. George, Camilla D. Bertsche, Subas M. Sakya and Melani Suarez-Contreras

Pfizer Global Research and Development, Groton Laboratories, Eastern Point Road, Groton, CT 06340, USA



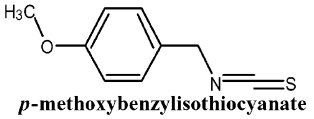
Bioorg. Med. Chem. Lett. 12 (2002) 2435

The Activity of *p*-Methoxybenzylisothiocyanate Against *Neisseria gonorrhoeae*, *Haemophilus ducreyi*, and Other Microorganisms

Henk Swart,* Sandra Van Dyk and Sarel F. Malan

Pharmaceutical Chemistry, Potchefstroomse Universiteit vir Christelike Hoër Onderwys, Private Bag X6001, Potchefstroom 2520, South Africa

The isolation and identification of *p*-methoxybenzylisothiocyanate from *Lepidium bonariense* and the MIC values of *p*-methoxybenzylisothiocyanate against *Neisseria gonorrhoeae*, *Haemophilus ducreyi*, and other micro-organisms. An in vitro cellular toxicity assay for *p*-methoxybenzylisothiocyanate is included.



***p*-methoxybenzylisothiocyanate**

Bioorg. Med. Chem. Lett. 12 (2002) 2439

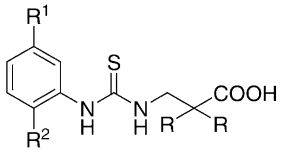
Thiourea-Based Gemfibrozil Analogues as HDL-Elevating Agents

Gary M. Coppola,[a,*] Robert E. Damon,[a] J. Bruce Eskesen,[a] Dennis S. France[a] and James R. Paterniti, Jr.[b]

[a]*Department of Metabolic and Cardiovascular Diseases, Novartis Institute for Biomedical Research, 556 Morris Avenue, Summit, NJ 07901, USA*

[b]*Amylin Pharmaceuticals, 9373 Towne Centre Drive, San Diego, CA 92121, USA*

A series of gemfibrozil analogues with a thiourea moiety embedded in the side chain was prepared and evaluated as HDL-elevating agents. Derivatives **9b**, **9c**, and **9d** were approximately as effective as gemfibrozil for HDL cholesterol elevation.



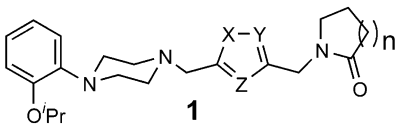
Bioorg. Med. Chem. Lett. 12 (2002) 2443

Arylpiperazine Substituted Heterocycles as Selective α_{1a} Adrenergic Antagonists

Haripada Khatuya, Richard H. Hutchings, Gee-Hong Kuo, Virginia L. Pulito, Linda K. Jolliffe, Xiaobing Li and William V. Murray*

Drug Discovery Research, Johnson & Johnson Pharmaceutical Research and Development LLC, 1000 Route 202, PO Box 300, Raritan, NJ 08869, USA

A series of arylpiperazine tethered heterocylic derivatives were synthesized as potent α_{1a}-AR antagonists, displaying binding affinity in the low nanomolar range.



1

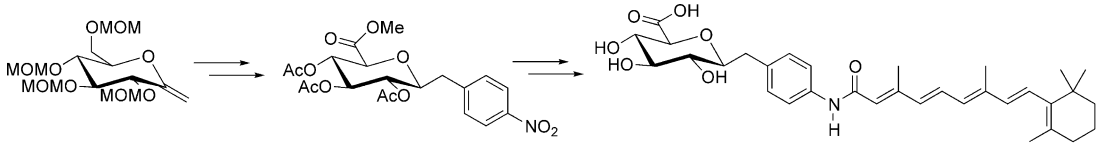
Bioorg. Med. Chem. Lett. 12 (2002) 2447

An Improved Synthesis of the *C*-linked Glucuronide of *N*-(4-Hydroxyphenyl)retinamide

Joel R. Walker,[a] Galal Alshafie,[b] Hussein Abou-Issa[b] and Robert W. Curley, Jr.[a,*]

[a]*Division of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, The Ohio State University, Columbus, OH 43210, USA*

[b]*Department of Surgery, College of Medicine, The Ohio State University, Columbus, OH 43210, USA*



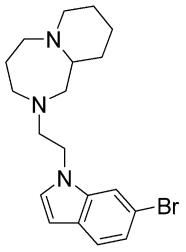
Bioorg. Med. Chem. Lett. 12 (2002) 2451

1-(Bicyclopiperazinyl)ethylindoles and 1-(Homopiperazinyl)ethyl-indoles as Highly Selective and Potent 5-HT$_7$ Receptor Ligands

Methvin B. Isaac,* Tao Xin, Anne O'Brien, David St-Martin, Angela Naismith, Neil MacLean, Julie Wilson, Lidia Demchyshyn, Ashok Tehim and Abdelmalik Slassi

NPS Pharmaceuticals Inc., 6850 Goreway Drive, Mississauga, ON, Canada L4V 1V7

A novel series of 1-(bicyclopiperazinyl)ethylindole and 1-(homopiperazinyl)ethyl-indole derivatives was synthesized and found to be potent and selective 5-HT$_7$ receptor ligands.



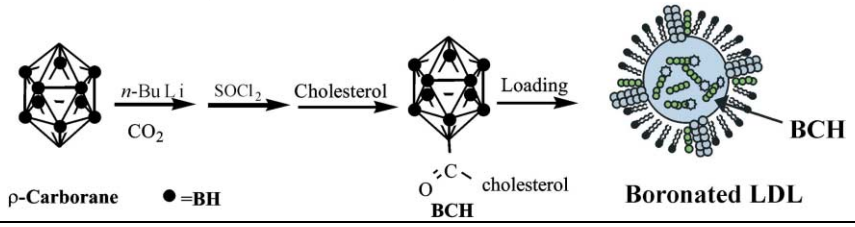
21
K_i (5HT$_7$)=3.0 nM

Bioorg. Med. Chem. Lett. 12 (2002) 2455

Synthesis of Cholesterol–Carborane Conjugate for Targeted Drug Delivery

Bingqing Ji,[a] Gina Peacock[b] and D. Robert Lu[a,*]

[a]*Department of Pharmaceutical and Biomedical Sciences, College of Pharmacy, University of Georgia, Athens, GA 30602, USA*
[b]*Department of Biopharmaceutical Sciences, School of Pharmacy, Shenandoah University, Winchester, VA 22655, USA*



Bioorg. Med. Chem. Lett. 12 (2002) 2459

A 5-Fluorodeoxyuridine Prodrug as Targeted Therapy for Prostate Cancer

Annastasiah Mhaka, Sam R. Denmeade, Wei Yao, John T. Isaacs and Saeed R. Khan*

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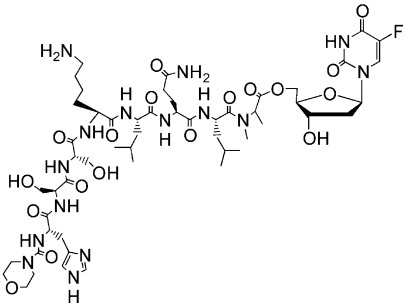
A method for targeted delivery of the cytotoxic agent 5-fluorodeoxyuridine (FudR) to sites of metastatic prostate cancer is described.



Bioorg. Med. Chem. Lett. 12 (2002) 2463

Non-Peptide $\alpha_v\beta_3$ Antagonists. Part 4: Potent and Orally Bioavailable Chain-Shortened RGD Mimetics

Paul J. Coleman,[a,*] Ben C. Askew,[a] John H. Hutchinson,[a] David B. Whitman,[a] James J. Perkins,[a] George D. Hartman,[a] Gideon A. Rodan,[b] Chih-Tai Leu,[b] Thomayant Prueksaritanont,[c] Carmen Fernandez-Metzler,[c] Kara M. Merkle,[c] Robert Lynch,[d] Joseph J. Lynch,[d] Sevgi B. Rodan[b] and Mark E. Duggan[a]

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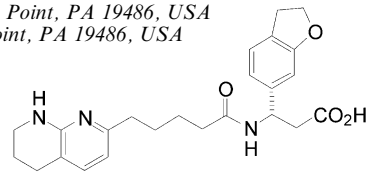
Potent non-peptidic $\alpha_v\beta_3$ antagonists have been prepared where deletion of an amide bond from an earlier series of linear RGD-mimetics provides a novel series of chain-shortened $\alpha_v\beta_3$ antagonists with significantly improved oral pharmacokinetics.



SPAV3 (IC_{50}) = 3.0 nM
Dog Pharmacokinetics:
F = 99%; Cl = 1.2 mL/min/kg

Bioorg. Med. Chem. Lett. 12 (2002) 2467

Tryptophanyl Phosphoramidates as Prodrugs of Synadenol and Its *E*-isomer: Synthesis and Biological Activity

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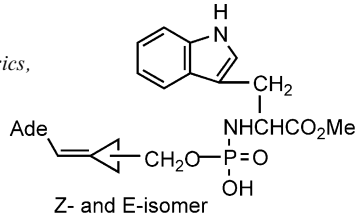
[a]*Barbara Ann Karmanos Cancer Institute, Wayne State University School of Medicine, Detroit, MI 48201-1379, USA.* [b]*Department of Pharmacology, Yale University School of Medicine, New Haven, CT 06510-8066, USA.* [c]*Department of Biologic and Materials Sciences, School of Dentistry, University of Michigan, Ann Arbor, MI 48019-1078, USA.* [d]*Department of Pediatrics, The University of Alabama at Birmingham, Birmingham, AL 35294, USA.* [e]*Experimental Retrovirology Section, Medicine Branch, Division of Clinical Sciences, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, USA.* [f]*Department of Internal Medicine II, Kumamoto University School of Medicine, Kumamoto 860, Japan*



Bioorg. Med. Chem. Lett. 12 (2002) 2471

Investigation of the PDZ Domain Ligand Binding Site Using Chemically Modified Peptides

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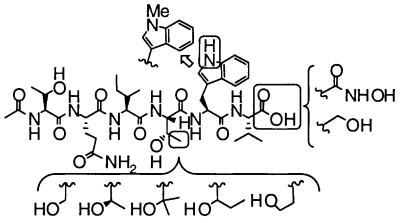
Chemically modified analogues to a tightly binding ligand for the second PDZ domain of MAGI-3 were synthesized and evaluated for their ability to compete with native ligand peptides. Modifications revealed the significance of the subpockets in the binding site in providing affinity to the PDZ domain.



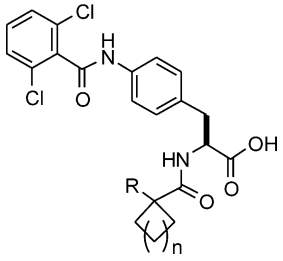
Bioorg. Med. Chem. Lett. 12 (2002) 2475

N-Cycloalkanoyl-L-Phenylalanine Derivatives as VCAM/VLA-4 Antagonists

Achyutharao Sidduri, Jefferson W. Tilley,* Kenneth Hull, Jian Ping Lou, Gerry Kaplan, Allen Sheffron, Li Chen, Robert Campbell, Robert Guthrie, Tai-Nan Huang, Nicholas Huby, Karen Rowan, Virginia Schwinge and Louis M. Renzetti

Roche Research Center, Hoffmann-La Roche Inc., 340 Kingsland Street, Nutley, NJ 07110, USA

A systematic structure–activity relationship investigation of the lead compound **1** resulted the identification of several *N*-[(substituted alkyl)cycloalkanoyl]-4-[((2,6-dichlorophenyl)carbonyl)amino]-L-phenylalanine derivatives as potent VCAM/VLA-4 antagonists. The data are consistent with a model of these compounds in which these alkanoylphenylalanines reside in a compact gauche (−) bioactive conformation.



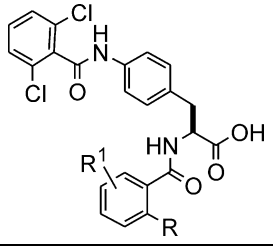
Bioorg. Med. Chem. Lett. 12 (2002) 2479

N-Aroyl-L-Phenylalanine Derivatives as VCAM/VLA-4 Antagonists

Achyutharao Sidduri,* Jefferson W. Tilley, Jian Ping Lou, Li Chen, Gerry Kaplan, Frank Mennona, Robert Campbell, Robert Guthrie, Tai-Nan Huang, Karen Rowan, Virginia Schwinge and Louis M. Renzetti

Roche Research Center, Hoffmann-La Roche Inc., 340 Kingsland Street, Nutley, NJ 07110, USA

A series of *N*-benzoyl-4-[(2,6-dichlorobenzoyl)amino]-L-phenylalanine derivatives was prepared in order to optimize the substitution on the *N*-benzoyl moiety for VCAM/VLA-4 antagonist activity. Disubstitution in the 2- and 6-positions is favored and a range of small alkyl and halogen are tolerated. A model of the bioactive conformation of these compounds is proposed.



Bioorg. Med. Chem. Lett. 12 (2002) 2483

Hepatobiliary Excretion of Dipyrrinone Sulfonates in Mrp2-Deficient (TR$^-$) Rats

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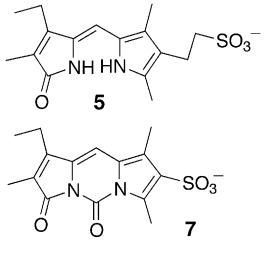
[b]*Department of Chemistry, University of Nevada, Reno, NV 89557-0020, USA*

Sulfonate **5** and the highly fluorescent analogue, **7**, were excreted rapidly in bile in rats following iv administration. Biliary excretion of **5** was not markedly impaired in Mrp2-deficient (TR$^-$) rats, but that of **7** was reduced. Both of these dipyrrinone organic anions can be cleared from blood and excreted rapidly in bile by Mrp2-independent mechanisms in the rat.



Bioorg. Med. Chem. Lett. 12 (2002) 2487

Bromotyrosine-Derived Natural and Synthetic Products as Inhibitors of Mycothiol-*S*-Conjugate Amidase

Gillian M. Nicholas,[a] Lisa L. Eckman,[a] Satyajit Ray,[a] Robert O. Hughes,[b] Jeffrey A. Pfefferkorn,[b,c] Sofia Barluenga,[b,c] K. C. Nicolaou[b,c] and Carole A. Bewley[a,*]

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