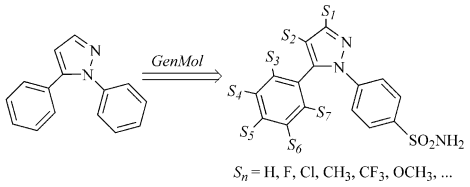
Bioorg. Med. Chem. Lett. 12 (2002) 267

Estimation of Binding Affinities for Celecoxib Analogues with COX-2 via Monte Carlo-Extended Linear Response

Steven S. Wesolowski and William L. Jorgensen*

Department of Chemistry, Yale University, New Haven, CT 06520-8107, USA

Monte Carlo-extended linear response calculations for celecoxib analogues with the COX-2 enzyme provide a promising screen for optimization of COX-2 inhibitors.



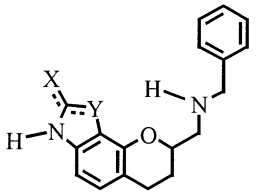
Bioorg. Med. Chem. Lett. 12 (2002) 271

New Generation Dopaminergic Agents. Part 8: Heterocyclic Bioisosteres that Exploit the 7-OH-2-(Aminomethyl)chroman D_2 Template

Richard E. Mewshaw,* Rulin Zhao, Xiaojie Shi, Karen Marquis, Julie A. Brennan, Hossein Mazandarani, Joseph Coupet and Terrance H. Andree

Global Chemical Sciences and CNS Disorders Departments, Wyeth-Ayerst Research Laboratories, PO Box 42528, Philadelphia, PA 19101-2528, USA

Based on their phenolic prototype, the 2-trifluoromethyl-benzimidazole (**5**) and benzimidazol-2-one (**6**) analogues were prepared and observed to have high affinity for the D_2 receptor.



5 X = CF_3 Y = N
6 X = O Y = NH

Bioorg. Med. Chem. Lett. 12 (2002) 275

5-Bromo (or Chloro)-6-azido-5,6-dihydro-2′-deoxyuridine and -thymidine Derivatives with Potent Antiviral Activity

Rakesh Kumar*

Department of Medical Microbiology and Immunology, Faculty of Medicine, University of Alberta, Edmonton, Canada T6G 2H7

Synthesis, antiviral, and cytotoxic activities of 5-bromo (or chloro)-6-azido-5,6-dihydro-2′-deoxyuridine (**4**,**5**) and -thymidine (**6**,**7**) are reported. Compounds **4** and **5** exhibited antiherpes activity against HSV-1, HSV-2, HCMV, and VZV.

Bioorg. Med. Chem. Lett. 12 (2002) 279

The C_{19} Position of 25-Hydroxyvitamin D_3 Faces Outward in the Vitamin D Sterol-Binding Pocket of Vitamin D-Binding Protein

James K. Addo, Narasimha Swamy and Rahul Ray*

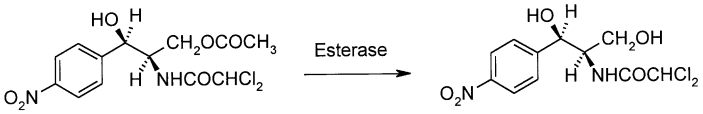
Bioorganic Chemistry & Structural Biology, Section in Endocrinology, Diabetes and Metabolism, Department of Medicine, Boston University School of Medicine, Boston, MA 02118, USA

Bioorg. Med. Chem. Lett. 12 (2002) 283

Isolation of 3′-*O*-Acetylchloramphenicol: A Possible Intermediate in Chloramphenicol Biosynthesis

Frank Groß,[a,b] Elizabeth A. Lewis,[c] Mahmood Piraee,[a] Karl-Heinz van Pée,[b] Leo C. Vining[a] and Robert L. White[c,*]

[a]*Department of Biology, Dalhousie University, Halifax, Nova Scotia, Canada B3H 4J1*
[b]*Institut für Biochemie, Technische Universität Dresden, D-01062 Dresden, Germany*
[c]*Department of Chemistry, Dalhousie University, Halifax, Nova Scotia, Canada B3H 4J3*



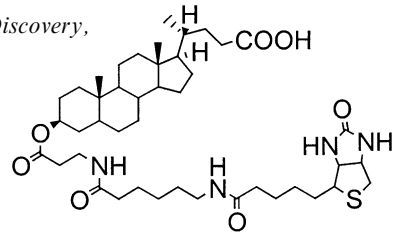
Bioorg. Med. Chem. Lett. 12 (2002) 287

Biotinylated Lithocholic Acids for Affinity Chromatography of Mammalian DNA Polymerases α and β

Madoka Watanabe,[a] Shinya Hanashima,[a] Yoshiyuki Mizushina,[b] Hiromi Yoshida,[b] Masahiko Oshige,[a] Kengo Sakaguchi[a] and Fumio Sugawara[a,*]

[a]*Department of Applied Biological Science, Frontier Research Center for Genoic Drug Discovery, Tokyo University of Science, Noda, Chiba 278-8510, Japan*
[b]*Laboratory of Food & Nutritional Sciences, Department of Nutritional Science, High Technology Research Center, Kobe-Gakuin University, Nishi-ku, Kobe, Hyogo 651-2180, Japan*

Biotinylated lithocholic acids have been synthesized. The compounds inhibited mammalian DNA polymerases α and β.



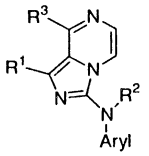
Bioorg. Med. Chem. Lett. 12 (2002) 291

Synthesis and Evaluation of Imidazo[1,5-*a*]pyrazines as Corticotropin Releasing Hormone Receptor Ligands

Richard A. Hartz,[a,*] Paul J. Gilligan,[a,*] Kausik K. Nanda,[a] Andrew J. Tebben,[a] Larry W. Fitzgerald[b] and Keith Miller[b]

[a]*DuPont Pharmaceuticals Company, Chemical and Physical Sciences, Experimental Station, PO Box 80500, Wilmington, DE 19880, USA*
[b]*DuPont Pharmaceuticals Company, CNS Diseases Research, 500 S Ridgeway Ave., Glenolden, PA 19036, USA*

A novel series of imidazo[1,5-*a*]pyrazines was synthesized and evaluated as corticotropin releasing hormone (CRH) receptor ligands.

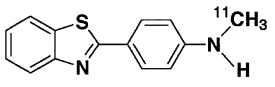


Bioorg. Med. Chem. Lett. 12 (2002) 295

A Lipophilic Thioflavin-T Derivative for Positron Emission Tomography (PET) Imaging of Amyloid in Brain

Chester A. Mathis,[a,*] Brian J. Bacskai,[b] Stephen T. Kajdasz,[b] Megan E. McLellan,[b] Matthew P. Frosch,[c] Bradley T. Hyman,[b] Daniel P. Holt,[a] Yanming Wang,[a] Guo-Feng Huang,[a] Manik L. Debnath[d] and William E. Klunk[d]

[a]*PET Facility, Department of Radiology, University of Pittsburgh, Pittsburgh, PA 15213, USA*
[b]*Alzheimer's Research Unit, Massachusetts General Hospital, Charlestown, MA 02129, USA*
[c]*Department of Pathology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115, USA*
[d]*Department of Psychiatry, University of Pittsburgh, Pittsburgh, PA 15213, USA*



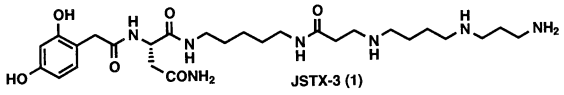
Bioorg. Med. Chem. Lett. 12 (2002) 299

An Efficient and Versatile Synthesis of Acylpolyamine Spider Toxins

Ken-ichi Nihei,[a] Massuo J. Kato,[a] Tetsuo Yamane,[b,d] Mario S. Palma[c,d] and Katsuhiro Konno[c,d,*]

[a]*Institute of Chemistry, University of São Paulo, São Paulo, SP 05508-900, Brazil*
[b]*Laboratory of Molecular Toxinology, Institute Butantan, São Paulo, SP 05503-900, Brazil*
[c]*Center of Study of Social Insects, Department of Biology, Institute of Biosciences of Rio Claro, São Paulo State University, Rio Claro, SP 13506-900, Brazil*
[d]*Center for Applied Toxinology, CEPID/FAPESP, São Paulo, SP 05468-901, Brazil*

An efficient and versatile method for the synthesis of acylpolyamine spider toxins such as JSTX-3 (**1**) is described.



Bioorg. Med. Chem. Lett. 12 (2002) 303

The DNA Phosphate Backbone is Not Involved in Catalysis of the Duocarmycin and CC-1065 DNA Alkylation Reaction

Yves Ambroise and Dale L. Boger*

Department of Chemistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, USA

Methylphosphonate modified oligonucleotides **8**–**12** were alkylated by duocarmycin SA at rates indistinguishable from the parent deoxyoligonucleotide **7**.

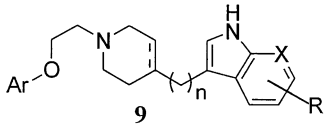
Bioorg. Med. Chem. Lett. 12 (2002) 307

Studies Toward the Discovery of the Next Generation of Antidepressants. Part 2: Incorporating a 5-HT$_{1A}$ Antagonist Component into a Class of Serotonin Reuptake Inhibitors

Richard E. Mewshaw,* Kristin L. Meagher, Ping Zhou, Dahui Zhou, Xiaojie Shi, Rosemary Scerni, Deborah Smith, Lee E. Schechter and Terrance H. Andree

Global Chemical Sciences and Neuroscience Departments, Wyeth-Ayerst Research Laboratories, PO Box 42528, Philadelphia, PA 19101-2528, USA

The design and synthesis of a novel series of indole derivatives (**9**) having dual 5-HT transporter reuptake and 5-HT$_{1A}$ antagonist activity are described.



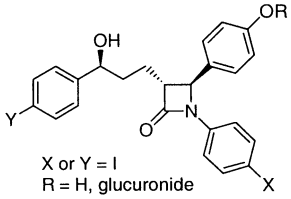
Bioorg. Med. Chem. Lett. 12 (2002) 311

Synthesis of Iodinated Biochemical Tools Related to the 2-Azetidinone Class of Cholesterol Absorption Inhibitors

Duane A. Burnett,* Mary Ann Caplen, Martin S. Domalski, Margaret E. Browne, Harry R. Davis, Jr. and John W. Clader

Schering-Plough Research Institute, 2015 Galloping Hill Road MS 2800, Kenilworth, NJ 07033-0539, USA

The discoveries of Sch 48461 and Sch 58235 and their novel pharmacology of inhibition of cholesterol absorption have prompted efforts to determine their biological mechanism of action (MOA). To this end, a series of radioiodinated analogues with good to excellent in vivo activity have been designed and synthesized as single enantiomers. They are structurally consistent with the allowable SAR of the 2-azetidinone class of cholesterol absorption inhibitors.



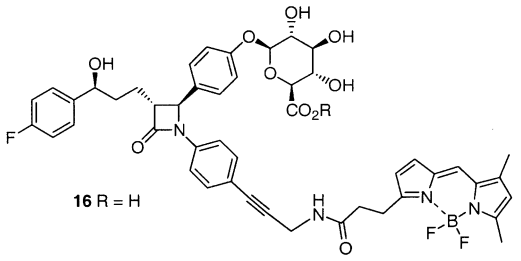
Bioorg. Med. Chem. Lett. 12 (2002) 315

Synthesis of Fluorescent Biochemical Tools Related to the 2-Azetidinone Class of Cholesterol Absorption Inhibitors

Duane A. Burnett,* Mary Ann Caplen, Margaret E. Browne, Hongrong Zhau, Scott W. Altmann, Harry R. Davis, Jr. and John W. Clader

Schering-Plough Research Institute, 2015 Galloping Hill Road MS 2800, Kenilworth, NJ 07033-0539, USA

Fluorescent analogues of the cholesterol absorption inhibitor (CAI), Sch 58235, have been designed and synthesized as single enantiomers. Biological testing reveals that they are potent CAIs and are suitable tools for the investigation of the azetidinone CAI mechanism of action (MOA).

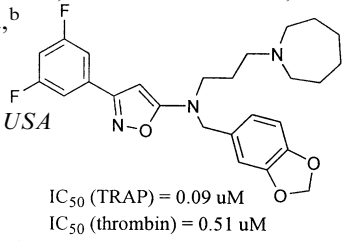


Bioorg. Med. Chem. Lett. 12 (2002) 319

Discovery of a Nonpeptidic Small Molecule Antagonist of the Human Platelet Thrombin Receptor (PAR-1)

Philippe G. Nantermet,[a,*] James C. Barrow,[a] George F. Lundell,[a] Janetta M. Pellicore,[a] Kenneth E. Rittle,[a] MaryBeth Young,[a] Roger M. Freidinger,[a] Thomas M. Connolly,[b] Cindra Condra,[b] Jerzy Karczewski,[b] Rodney A. Bednar,[b] Stanley L. Gaul,[b] Robert J. Gould,[b] Kris Prendergast[c] and Harold G. Selnick[a]

[a]*Department of Medicinal Chemistry, Merck Research Laboratories, West Point, PA 19486, USA*
[b]*Department of Pharmacology, Merck Research Laboratories, West Point, PA 19486, USA*
[c]*Department of Molecular Design and Diversity, Merck Research Laboratories, West Point, PA 19486, USA*



The synthesis and biological evaluation of a series of nonpeptidic small molecule antagonists of the human platelet thrombin receptor (PAR-1) are described.

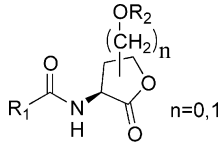
Bioorg. Med. Chem. Lett. 12 (2002) 325

Synthesis of New 3- and 4-Substituted Analogues of Acyl Homoserine Lactone Quorum Sensing Autoinducers

J. A. Olsen,[a] R. Severinsen,[a] T. B. Rasmussen,[b] M. Hentzer,[b] M. Givskov[b] and J. Nielsen[a,*]

[a]*Department of Chemistry, Bld. 207, Technical University of Denmark, 2800 Kgs. Lyngby, Denmark*
[b]*Molecular Microbiology, BioCentrum-DTU, Bld. 301, Technical University of Denmark, 2800 Kgs. Lyngby, Denmark*

Synthesis of 3- and 4-substituted autoinducer analogues and screening for their ability to activate and inhibit a *Vibrio fischeri* LuxI/LuxR-derived quorum sensing reporter system are reported.

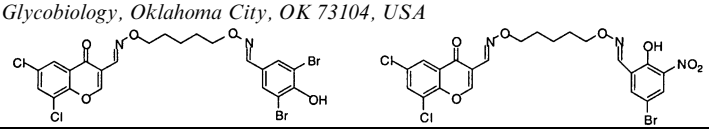


Bioorg. Med. Chem. Lett. 12 (2002) 329

Tyrosylprotein Sulfotransferase Inhibitors Generated by Combinatorial Target-Guided Ligand Assembly

John W. Kehoe,[a] Dustin J. Maly,[b] Dawn E. Verdugo,[b] Joshua I. Armstrong,[b] Brian N. Cook,[b] Ying-Bin Ouyang,[d] Kevin L. Moore,[d,e] Jonathan A. Ellman[b] and Carolyn R. Bertozzi[a,b,c,*]

[a]*Department of Molecular and Cell Biology, University of California, Berkeley, CA 94720, USA*
[b]*Department of Chemistry, University of California, Berkeley, CA 94720, USA*
[c]*Howard Hughes Medical Institute, University of California, Berkeley, CA 94720, USA*
[d]*Cardiovascular Biology Research Program, Oklahoma Medical Research Foundation, Department of Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, OK 73104, USA*
[e]*Oklahoma Center for Medical Glycobiology, Oklahoma City, OK 73104, USA*



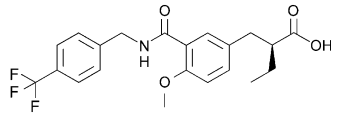
Bioorg. Med. Chem. Lett. 12 (2002) 333

Enantio-Dependent Binding and Transactivation of Optically Active Phenylpropanoic Acid Derivatives at Human Peroxisome Proliferator-Activated Receptor Alpha

Hiroyuki Miyachi,* Masahiro Nomura, Takahiro Tanase, Masahiro Suzuki, Koji Murakami and Katsuya Awano

Discovery Research Laboratories, Kyorin Pharmaceutical Co., Ltd., 2399-1 Mitarai, Nogi-machi, Shimotsuga-gun, Tochigi 329-0114, Japan

Optically active phenylpropanoic acid derivatives [(*S*)-**5**, and (*R*)-**5**] were prepared and their affinities for peroxisome proliferator-activated receptor (PPAR)α and PPARγ were evaluated.



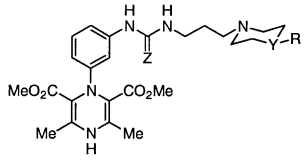
Bioorg. Med. Chem. Lett. 12 (2002) 337

Novel Dihydropyrazine Analogues as NPY Antagonists

Sing-Yuen Sit,[a,*] Yazhong Huang,[a] Ildiko Antal-Zimanyi,[b] Sally Ward[b] and Graham S. Poindexter[a]

[a]*Department of Neuroscience/Genitourinary Drug Discovery Chemistry, Bristol-Myers Squibb Pharmaceutical Research Institute, 5 Research Parkway, Wallingford, CT 06492-7660, USA*
[b]*Neuroscience/Genitourinary Drug Discovery Biology, Bristol-Myers Squibb Pharmaceutical Research Institute, 5 Research Parkway, Wallingford, CT 06492-7660, USA*

Efficient synthesis of 2,6-dimethyl dihydropyrazine analogues of 2,6-dimethyl dihydropyridine NPY antagonist was developed.



Dihydropyrazine analogues of **2a-2g**

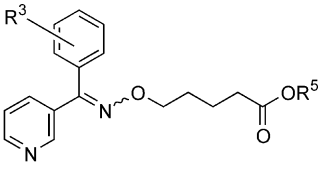
Bioorg. Med. Chem. Lett. 12 (2002) 341

Approach to Dual-Acting Platelet Activating Factor (PAF) Receptor Antagonist/Thromboxane Synthase Inhibitor (TxSI) Based on the Link of PAF Antagonists and TxSIs

Masakazu Fujita,* Taketsugu Seki, Haruaki Inada, Kazuhiro Shimizu, Akane Takahama and Tetsuro Sano

Omiya Research Laboratory, Nikken Chemicals Co., Ltd., Kitabukuro-cho, Saitama-shi, Saitama 330-0835, Japan

A series of compounds (**22**–**36**) which possess dual-acting PAF antagonist/TxSI have been generated by the approach of linking the known PAF antagonists and TxSIs, such as Ridogrel (**1**).



22-36

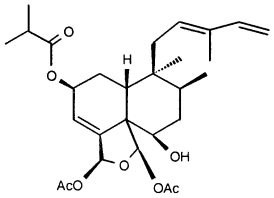
Bioorg. Med. Chem. Lett. 12 (2002) 345

Antitumor Agents. Part 212: Bucidarasins A–C, Three New Cytotoxic Clerodane Diterpenes from *Bucida buceras*

Ken-ichiro Hayashi,[a] Yuka Nakanishi,[a] Kenneth F. Bastow,[a] Gordon Cragg,[b] Hiroshi Nozaki[c] and Kuo-Hsiung Lee[a,*]

[a]*Natural Products Laboratory, School of Pharmacy, University of North Carolina, Chapel Hill, NC 27599, USA*
[b]*Developmental Therapeutics Program, National Cancer Institute, Bethesda, MD 20892, USA*
[c]*Department of Biochemistry, Okayama University of Science, 1-1 Ridai-cho, Okayama City 700-0005, Japan*

Bucidarasins A–C were isolated as the cytotoxic active principles from *Bucida buceras*. These new clerodane diterpenes showed potent cytotoxic activities against human tumour cell lines with IC_{50} values of 0.5–1.9 μM.



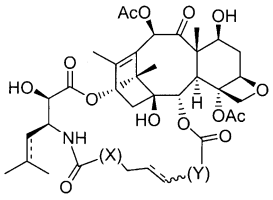
Bioorg. Med. Chem. Lett. 12 (2002) 349

Design, Synthesis and Biological Activity of Novel C2–C3′ N-Linked Macrocyclic Taxoids

Iwao Ojima,[a,*] Xudong Geng,[a] Songnian Lin,[a] Paula Pera[b] and Ralph J. Bernacki[b]

[a]*Department of Chemistry, State University of New York at Stony Brook, NY 11794-3400, USA*
[b]*Department of Experimental Therapeutics, Rosewell Park Cancer Institute, Elm and Carton Streets, Buffalo, NY 14263, USA*

Novel cytotoxic macrocyclic taxoids with various linkers connecting the C2 and C3′ N positions of taxoid framework are reported.



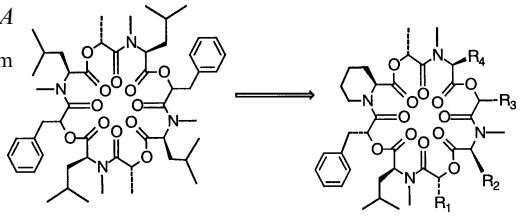
Bioorg. Med. Chem. Lett. 12 (2002) 353

Generation of a Small Library of Cyclodepsipeptide PF1022A Analogues Using a Cyclization-Cleavage Method with Oxime Resin

Byung H. Lee,* Fred E. Dutton, David P. Thompson and Eileen M. Thomas

Discovery Research, Pharmacia Animal Health, Kalamazoo, MI 49001, USA

N-Methyloctadepsipeptides attached to an oxime resin were cyclized by heating them in refluxing ethyl acetate for 2 days to give cyclodepsipeptide PF1022A analogues. Using this method, we generated a small library of PF1022A analogues (**2**), several of which possessed anthelmintic activity, based on an in vitro assay.



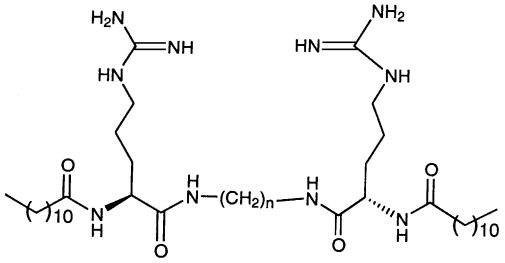
PF1022A (**1**) (**2**)

Bioorg. Med. Chem. Lett. 12 (2002) 357

Sequestration of Bacterial Lipopolysaccharide by Bis(Args) Gemini Compounds

Sunil David,[a,*] Lourdes Pérez[b] and M. Rosa Infante[b]

[a]*Molecular Biosciences, 4043 Haworth Hall, University of Kansas, Lawrence, KS 66044, USA*
[b]*Department of Surfactant Technology, CID (CSIC), J. Girona 18-26, 0834 Barcelona, Spain*



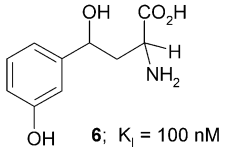
Bioorg. Med. Chem. Lett. 12 (2002) 361

2-Amino-4-[3′-hydroxyphenyl]-4-hydroxybutanoic Acid; A Potent Inhibitor of Rat and Recombinant Human Kynureninase

Harold A. Walsh, Pauline L. Leslie, Karen C. O'Shea and Nigel P. Botting*

School of Chemistry, University of St Andrews, St Andrews, Fife KY16 9ST, UK

The synthesis of a novel and potent inhibitor of human kynureninase is described.



6; K_I = 100 nM

Bioorg. Med. Chem. Lett. 12 (2002) 365

Binding of Aminoglycoside Antibiotics with Modified A-site 16S rRNA Construct Containing Non-Nucleotide Linkers

Jeffrey B.-H. Tok,* Wilson Wong and Nyla Baboolal

Department of Chemistry & Natural Sciences, York College and Graduate Center of the City University of New York, 94-20 Guy R. Brewer Blvd., Jamaica, NY 11451, USA

The design and synthesis of synthetically modified cyclic A-site 16S rRNA construct is reported. The binding characteristics of several members of the aminoglycoside antibiotics with this novel class of synthetically modified A-site 16S rRNA constructs were subsequently investigated.

Bioorg. Med. Chem. Lett. 12 (2002) 371

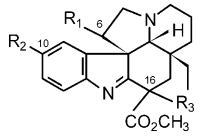
Cytotoxicity of 6,16-Disubstituted Analogues of (−)-Vincadifformine

Guy Lewin,[a,*] Reynald Hocquemiller,[a] Corinne Schaeffer,[b] Pierre-Hervé Lambert,[b] Stéphane Léonce[b] and Alain Pierré[b]

[a]*Laboratoire de Pharmacognosie (BIOCIS, UPRES-A 8076 CNRS), Faculté de Pharmacie, av. J.B. Clément, 92296 Châtenay-Malabry Cedex, France*
[b]*Institut de Recherches Servier, 11 rue des Moulineaux, 92150 Suresnes, France*

Eight analogues of (−)-16*R*-chloro-1-dehydro-6*S*-bromovincadifformine were synthesized and evaluated for cytotoxicity in L1210 cell culture. Modulation at C6, C10 and C16 displays structure–activity relationships.

R_1 = Br, OAc, OBz
R_2 = H, Br, NO_2
R_3 = Cl, NO_2



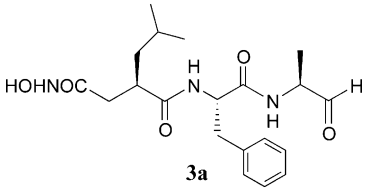
Bioorg. Med. Chem. Lett. 12 (2002) 375

Design and Synthesis of Dual Inhibitors for Matrix Metalloproteinase and Cathepsin

Minoru Yamamoto,[a] Shoji Ikeda,[a,*] Hirosato Kondo[a] and Shintaro Inoue[b]

[a]*Chemistry Group R&D Laboratories, Nippon Organon K.K., 1-5-90 Tomobuchi-Cho, Miyakojima-Ku, Osaka, Japan*
[b]*Basic Science Laboratory, Kanebo Ltd., 5-3-28 Kotobuki-Cho, Odawara, Kanagawa, Japan*

A dual inhibitor (**3a**) exhibited potent inhibitory activity, IC_{50} 25 nM against MMP-1 and 15 nM against cathepsin L.



3a

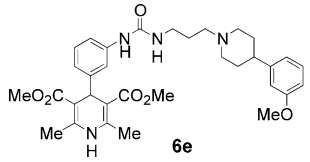
Bioorg. Med. Chem. Lett. 12 (2002) 379

Dihydropyridine Neuropeptide Y Y_1 Receptor Antagonists

Graham S. Poindexter,* Marc A. Bruce, Karen L. LeBoulluec, Ivo Monkovic, Scott W. Martin, Eric M. Parker, Larry G. Iben, Rachel T. McGovern, Astrid A. Ortiz, Jennifer A. Stanley, Gail K. Mattson, Michael Kozlowski, Meredith Arcuri and Ildiko Antal-Zimanyi

Pharmaceutical Research Institute, Bristol-Myers Squibb Co., 5 Research Parkway, Wallingford, CT 06492-7660, USA

Structure–activity studies around the *C*-3 ester and N-terminal portions of a dihydropyridine chemotype lead to the identification of **6e** as a potent and selective NPY Y_1 receptor antagonist.



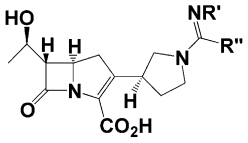
6e

Bioorg. Med. Chem. Lett. 12 (2002) 383

Synthesis and Antibacterial Evaluation of Novel 2-[*N*-Imidoylpyrrolidinyl] Carbapenems

Kouji Hattori,* Akira Yamada, Satoru Kuroda, Toshiyuki Chiba, Masayoshi Murata and Kazuo Sakane

Medicinal Chemistry Research Laboratories, Fujisawa Pharmaceutical Co. Ltd, 1-6, Kashima 2-Chome, Yodogawa-Ku, Osaka, Japan

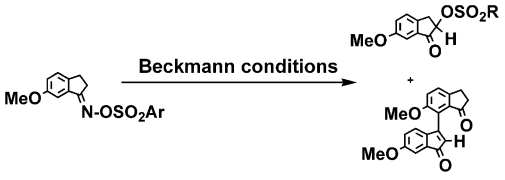


Bioorg. Med. Chem. Lett. 12 (2002) 387

Interesting Reaction of the Indanone Oximes Under Beckmann Rearrangement Conditions

Yasuhiro Torisawa,* Takao Nishi and Jun-ichi Minamikawa

Process Research Laboratory, Second Tokushima Factory, Otsuka Pharmaceutical Co., Ltd, Kawauchi-cho, Tokushima 771-0182, Japan



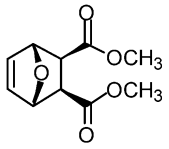
Bioorg. Med. Chem. Lett. 12 (2002) 391

The First Two Cantharidin Analogues Displaying PP1 Selectivity

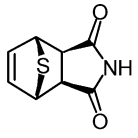
Adam McCluskey,[a,*] Mirella A. Keane,[a] Cecilia C. Walkom,[a] Michael C. Bowyer,[b] Alistair T. R. Sim,[c] David J. Young[d] and Jennette A. Sakoff[e]

[a]*Medicinal Chemistry Group, School of Biological and Chemical Sciences, The University of Newcastle, University Drive, Callaghan, Newcastle, NSW 2308, Australia*
[b]*School of Science & Technology, Central Coast Campus, The University of Newcastle, PO Box 127, NSW, Australia*
[c]*Discipline of Medical Biochemistry, Faculty of Medicine and Health Sciences, The University of Newcastle, University Drive, Callaghan, Newcastle, NSW 2308, Australia*
[d]*Faculty of Science and Technology, Griffith University, Brisbane, QLD 4111, Australia*
[e]*Department of Medical Oncology, Newcastle Mater Misericordiae Hospital, NSW 2298, Australia*

Compounds **3** and **6** represent the first selective inhibitors of the Ser/Thr protein phosphatase, PP1



3



6

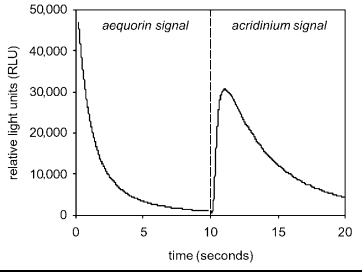
Bioorg. Med. Chem. Lett. 12 (2002) 395

Dual Analyte Detection Using Tandem Flash Luminescence

Maciej Adamczyk,* Jeffrey A. Moore and Kevin Shreder

Department of Chemistry (9NM), Abbott Diagnostics Division, Abbott Laboratories, Abbott Park, IL 60064-6016, USA

A heterogeneous, dual analyte-binding assay which makes use of the flash luminescence from both aequorin and an acridinium-9-carboxamide label is presented. The signal generating species were triggered both differentially and sequentially using Ca^{2+} followed by basic peroxide.



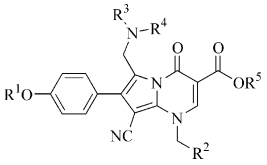
Bioorg. Med. Chem. Lett. 12 (2002) 399

Initial Structure–Activity Relationship Studies of a Novel Series of Pyrrolo[1,2-*a*]pyrimid-7-ones as GnRH Receptor Antagonists

Yun-Fei Zhu,* R. Scott Struthers, Patrick J. Connors, Jr., Yinghong Gao, Timothy D. Gross, John Saunders, Keith Wilcoxen, Greg J. Reinhart, Nicholas Ling and Chen Chen*

Neurocrine Biosciences, Inc., 10555 Science Center Drive, San Diego, CA 92121, USA

Initial SAR studies of 1-aminomethyl-2-aryl-3-cyano-pyrrolo[1,2-*a*]pyrimid-7-one-6-carboxylates as human GnRH receptor antagonists were discussed. The best compound from the series had 25 nM (K_i) binding affinity.



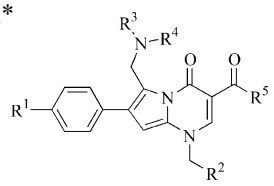
Bioorg. Med. Chem. Lett. 12 (2002) 403

A Novel Synthesis of 2-Arylpyrrolo[1,2-*a*]pyrimid-7-ones and Their Structure–Activity Relationships as Potent GnRH Receptor Antagonists

Yun-Fei Zhu,* Keith Wilcoxen, John Saunders, Zhiqiang Guo, Yinghong Gao, Patrick J. Connors, Jr., Timothy D. Gross, Fabio C. Tucci, R. Scott Struthers, Greg J. Reinhart, Qiu Xie and Chen Chen*

Neurocrine Biosciences, Inc., 10555 Science Center Drive, San Diego, CA 92121, USA

A novel synthesis of 2-aryl-pyrrolo[1,2-*a*]pyrimid-7-ones was disclosed. These compounds were further modified to afford a series of potent GnRH antagonists, exhibiting K_i values as low as 1.1 nM.



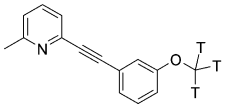
Bioorg. Med. Chem. Lett. 12 (2002) 407

[^{3}H]-M-MPEP, a Potent, Subtype-Selective Radioligand for the Metabotropic Glutamate Receptor Subtype 5

Fabrizio Gasparini,[a,*] Hendrik Andres,[b] Peter Josef Flor,[a] Micheline Heinrich,[a] Werner Inderbitzin,[a] Kurt Lingenhöhl,[a] Hanspeter Müller,[a] Veronica Cecilia Munk,[a] Kyla Omilusik,[a] Christine Stierlin,[a] Natacha Stoehr,[a] Ivo Vranesic[a] and Rainer Kuhn[a]

[a]*Nervous System Research, Novartis Pharma AG, 4002 Basel, Switzerland*
[b]*DMPK/Isotope Laboratory, Novartis Pharma AG, 4002 Basel, Switzerland*

The identification of a novel potent, subtype-selective antagonist of the metabotropic glutamate receptor 5 (mGluR-5) is reported. The radiolabeling with tritium of the novel derivative and the in vitro characterization of the binding properties to membranes of cells expressing the human mGluR5 are also described.



13, [^{3}H]-M-MPEP
(2-methyl-6-((3-methoxyphenyl) ethynyl)-pyridine)

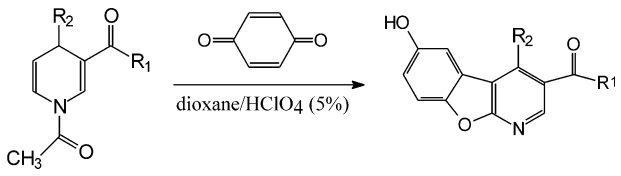
Bioorg. Med. Chem. Lett. 12 (2002) 411

Synthesis and First Biological Evaluation of 1-Aza-9-oxafluorenes as Novel Lead Structures for the Development of Small-Sized Cytostatics

Kristin Brachwitz and Andreas Hilgeroth*

Institute of Pharmaceutical Chemistry, Department of Pharmacy, Martin-Luther-University, Halle-Wittenberg, Wolfgang-Langenbeck-Str. 4, 06120 Halle, Germany

Facile synthesis leads to first 1-aza-9-oxafluorenes as novel class of tricyclic cytostatic agents with higher activities than other tricyclic carboline compounds.



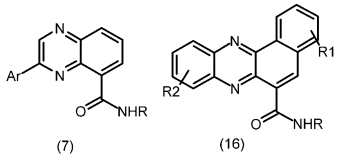
Bioorg. Med. Chem. Lett. 12 (2002) 415

Structure–Activity Relationships for Analogues of the Phenazine-Based Dual Topoisomerase I/II Inhibitor XR11576

Shouming Wang,[a,*] Warren Miller,[a] John Milton,[a] Nigel Vicker,[a] Alistair Stewart,[b] Peter Charlton,[b] Prakash Mistry,[b] David Hardick[a] and William A. Denny[c]

[a]*Department of Medicinal Chemistry, Xenova Ltd., 957 Buckingham Avenue, Slough, Berkshire SL1 4NL, UK*
[b]*Department of Pharmacology, Xenova Ltd., 957 Buckingham Avenue, Slough, Berkshire SL1 4NL, UK*
[c]*Auckland Cancer Society Research Centre, Faculty of Medical and Health Sciences, The University of Auckland, Private Bag 92019, Auckland, New Zealand*

As part of a programme to identify further analogues of the dual topo I/II inhibitor XR11576, we describe here the syntheses and SAR studies of various 'minimal' and 3,4-benzofused phenazine chromophores of the phenazine template of Xr11576.



Bioorg. Med. Chem. Lett. 12 (2002) 419

A Neural Network Based Virtual Screening of Cytochrome P450 3A4 Inhibitors

László Molnár and György M. Keserű*

Computer Assisted Drug Discovery, Gedeon Richter Ltd., PO Box 27, H-1475 Budapest, Hungary

A virtual high throughput screening test to identify potential CP450 3A4 inhibitors has been developed. Our feedforward neural net classified 91.7% of the inhibitors and 88.9% of the non-inhibitor compounds correctly.

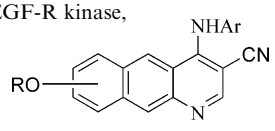
Bioorg. Med. Chem. Lett. 12 (2002) 423

4-Anilino-3-cyanobenzo[*g*]quinolines as Kinase Inhibitors

Nan Zhang,[a,*] Biqi Wu,[a] Allan Wissner,[a] Dennis W. Powell,[a] Sridhar K. Rabindran,[b] Constance Kohler[b] and Frank Boschelli[b]

[a]*Chemical Sciences, Wyeth-Ayerst Research, Pearl River, NY 10965, USA*
[b]*Discovery Oncology, Wyeth-Ayerst Research, Pearl River, NY 10965, USA*

A series of 4-anilino-3-cyanobenzo[*g*]quinolines was prepared as potent kinase inhibitors. Compared with their bicyclic 4-anilino-3-cyanoquinoline analogues, the tricyclic 4-anilino-3-cyanobenzo[*g*]quinolines are less active against EGF-R kinase, equally active against MAPK kinase (MEK), and more active against Src kinase. Several of these kinase inhibitors show potent growth inhibitory activity in tumor cells.



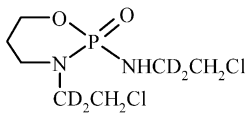
Bioorg. Med. Chem. Lett. 12 (2002) 427

Studies on the Side-Chain Hydroxylation of Ifosfamide and Its Bromo Analogue

Konrad Misiura,[a,*] Ryszard W. Kinas[a] and Halina Kuśnierczyk[b]

[a]*Department of Bioorganic Chemistry, Centre of Molecular and Macromolecular Studies, Polish Academy of Sciences, Sienkiewicza 112, 90-363 Łódź, Poland*
[b]*Department of Tumour Immunology, Institute of Immunology and Experimental Therapy, Polish Academy of Sciences, R. Weigla 12, 53-114 Wrocław, Poland*

Deutero-substituted derivatives of ifosfamide (IF-d_4) and its bromo analogue were synthesised. It was shown that kinetic isotope effect operates during microsomal hydroxylation of IF-d_4. Deutero-substituted derivatives are more active against L1210 leukaemia in mice than unlabelled compounds, suggesting a negative role of side-chain hydroxylation metabolic pathways in the anticancer activity of ifosfamine and its analogues.



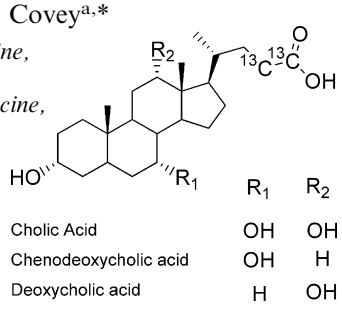
Bioorg. Med. Chem. Lett. 12 (2002) 433

A Simple Efficient Synthesis of [23,24]-$^{13}C_2$-Labeled Bile Salts as NMR Probes of Protein–Ligand Interactions

Gregory P. Tochtrop,[a,b] Gregory T. DeKoster,[b] David P. Cistola[b] and Douglas F. Covey[a,*]

[a]*Department of Molecular Biology & Pharmacology, Washington University School of Medicine, St. Louis, MO 63110, USA*
[b]*Department of Biochemistry & Molecular Biophysics, Washington University School of Medicine, St. Louis, MO 63110, USA*

The synthesis and evaluation of [23,24]-$^{13}C_2$-labeled bile salts as NMR probes for interactions between bile salts and human ileal bile acid binding protein (I-BABP) are reported. The NMR data demonstrate distinct binding environments for two bile salts, and also show structural proximity between bound bile salt side chains.



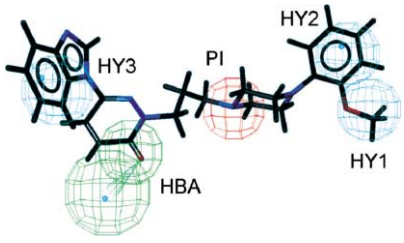
	R_1	R_2
Cholic Acid	OH	OH
Chenodeoxycholic acid	OH	H
Deoxycholic acid	H	OH

Bioorg. Med. Chem. Lett. 12 (2002) 437

α_1-Adrenoceptor Antagonists. Rational Design, Synthesis and Biological Evaluation of New Trazodone-like Compounds

Laura Betti,[a] Maurizio Botta,[b] Federico Corelli,[b] Monia Floridi,[c] Paola Fossa,[d] Gino Giannaccini,[a] Fabrizio Manetti,[b,*] Giovannella Strappaghetti[c,*] and Stefano Corsano[c]

[a]*Dipartimento di Psichiatria, Neurobiologia, Farmacologia e Biotecnologie, Università di Pisa, Via Bonanno 6, 56126 Pisa, Italy*
[b]*Dipartimento Farmaco Chimico Tecnologico, Università degli Studi di Siena, Via Aldo Moro, 53100 Siena, Italy*
[c]*Istituto di Chimica e Tecnologia del Farmaco, Università di Perugia, Via del Liceo 1, 06123 Perugia, Italy*
[d]*Dipartimento di Scienze Farmaceutiche, Università di Genova, Viale Benedetto XV 3, 16132 Genova, Italy*



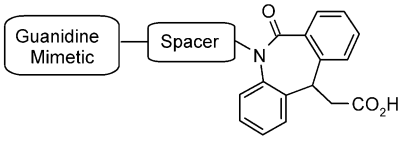
Bioorg. Med. Chem. Lett. 12 (2002) 441

Synthesis and SAR of *N*-Substituted Dibenzazepinone Derivatives as Novel Potent and Selective $\alpha_V\beta_3$ Antagonists

Andreas Kling,[a,*] Gisela Backfisch,[a] Jürgen Delzer,[a] Hervé Geneste,[a] Claudia Graef,[a] Uta Holzenkamp,[a] Wilfried Hornberger,[a] Udo E. W. Lange,[b] Arnulf Lauterbach,[a] Helmut Mack,[a] Werner Seitz[b] and Thomas Subkowski[a]

[a]*Knoll GmbH, D-67008 Ludwigshafen, Germany*
[b]*BASF AG, D-67056 Ludwigshafen, Germany*

A series of novel potent and highly selective $\alpha_V\beta_3$ antagonists based on an *N*-substituted dibenzazepinone scaffold is described. SAR involving spacer and guanidine pharmacophore was established, and efficacy for selected compounds shown in cellular assays.



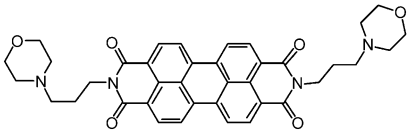
Bioorg. Med. Chem. Lett. 12 (2002) 447

Perylene Diimide G-Quadruplex DNA Binding Selectivity is Mediated by Ligand Aggregation

Sean M. Kerwin,* Grace Chen, Jonathan T. Kern and Pei Wang Thomas

Division of Medicinal Chemistry, College of Pharmacy, The University of Texas at Austin, Austin, TX 78712, USA

The G-quadruplex DNA binding preference of perylene diimide ligands is pH-dependent. Only at pH where the ligands are extensively aggregated is the apparent G-quadruplex DNA binding selectivity high.



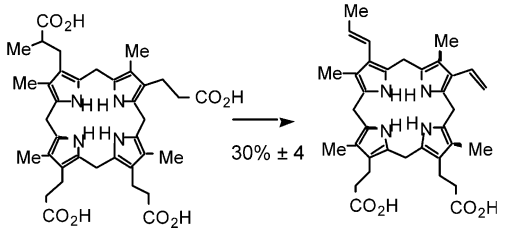
Bioorg. Med. Chem. Lett. 12 (2002) 451

Metabolism of Analogues of Coproporphyrinogen-III with Modified Side Chains: Implications for Binding at the Active Site of Coproporphyrinogen Oxidase

Timothy D. Lash,* Todd A. Kaprak, Lan Shen and Marjorie A. Jones

Department of Chemistry, Illinois State University, Normal, IL 61790-4160, USA

Coproporphyrinogen-III analogues with methyl units appended to the A or B ring propionate groups are shown to be moderate to poor substrates for coproporphyrinogen oxidase, a critical enzyme in the heme biosynthetic pathway; these results provide new insights into the binding specificity of this poorly understood enzyme.



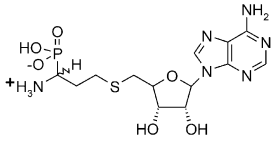
Bioorg. Med. Chem. Lett. 12 (2002) 457

Synthesis of an α-Aminophosphonate Nucleoside as an Inhibitor of *S*-Adenosyl-L-Homocysteine Hydrolase

Jennifer A. Steere, Peter B. Sampson and John F. Honek*

Department of Chemistry, University of Waterloo, Waterloo, Ontario, Canada N2L 3G1

A phosphonic acid analogue of *S*-adenosyl-L-homocysteine was prepared by a novel method and was found to inactivate *S*-adenosyl-L-homocysteine hydrolase in a time-dependent manner.



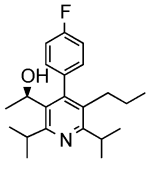
Bioorg. Med. Chem. Lett. 12 (2002) 461

Discovery of 5-Hydroxyalkyl-4-phenylpyridines as a New Class of Glucagon Receptor Antagonists

Gaetan H. Ladouceur,[a,]* James H. Cook,[a] Elizabeth M. Doherty,[a] William R. Schoen,[a] Margit L. MacDougall[b] and James N. Livingston[b]

[a]*Department of Chemistry Research, Bayer Research Center, 400 Morgan Lane, West Haven, CT 06516, USA*
[b]*Department of Diabetes and Obesity Research, Bayer Research Center, 400 Morgan Lane, West Haven, CT 06516, USA*

5-Hydroxyalkyl-4-phenylpyridines have been identified as a novel class of glucagon antagonists with potential utility for the treatment of diabetes. A lead structure with moderate activity was discovered through a high throughput screening assay. Structure–activity relationships led to the discovery of a potent antagonist.



IC_{50} = 0.11 μM

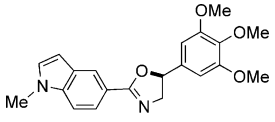
Bioorg. Med. Chem. Lett. 12 (2002) 465

Synthesis and Biological Evaluation of 2-Indolyloxazolines as a New Class of Tubulin Polymerization Inhibitors. Discovery of A-289099 as an Orally Active Antitumor Agent

Qun Li,* Keith W. Woods, Akiyo Claiborne, Stephen L. Gwaltney II, Kenneth J. Barr, Gang Liu, Laura Gehrke, R. Bruce Credo, Yu Hua Hui, Jang Lee, Robert B. Warner, Peter Kovar, Michael A. Nukkala, Nicolette A. Zielinski, Stephen K. Tahir, Michael Fitzgerald, Ki H. Kim, Kennan Marsh, David Frost, Shi-Chung Ng, Saul Rosenberg and Hing L. Sham

Cancer Research, Abbott Laboratories, Abbott Park, IL 60064-6101, USA

A-289099 mimics combrestatin A4 and is active against the MDR+ cancer cell lines.



A-289099
IC_{50} = 8.6 nM (HCT-15)

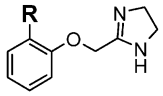
Bioorg. Med. Chem. Lett. 12 (2002) 471

α_1-Adrenoceptor Agonists: The Identification of Novel α_{1A} Subtype Selective 2′-Heteroaryl-2-(phenoxymethyl)imidazolines

Michael J. Bishop,* Kevin A. Barvian, Judd Berman, Eric C. Bigham, Deanna T. Garrison, Michael J. Gobel, Stephen J. Hodson, Paul E. Irving, James A. Liacos, Frank Navas III, David L. Saussy, Jr. and Jason D. Speake

GlaxoSmithKline Research and Development, 5 Moore Drive, Research Triangle Park, NC 27709 USA

Novel 2′-heteroaryl-2-(phenoxymethyl)imidazolines have been identified as potent agonists of the human α_1-adrenoreceptors in vitro. α_{1A} Subtype selective agonists have been identified.



R = Heteroaryl groups

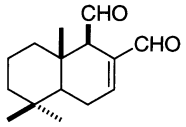
Bioorg. Med. Chem. Lett. 12 (2002) 477

Protective Effects of Polygodial and Related Compounds on Ethanol-Induced Gastric Mucosal Lesions in Rats: Structural Requirements and Mode of Action

Hisashi Matsuda, Yutana Pongpiriyadacha, Toshio Morikawa, Yousuke Kashima, Kyoko Nakano and Masayuki Yoshikawa*

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

The MeOH ext. from the leaves of *Tasmannia lanceolata* was found to potently inhibit ethanol-induced gastric lesions in rats. Through bioassay-guided separation, polygodial, polygodial 12α-acetal, and polygodial 12β-acetal, and methyl isodrimeninol were isolated as the active constituents. Among them, polygodial showed very potent gastroprotective effects (ED_{50} = 0.028 mg/kg, po) and the dialdehyde or diacetal structure was found to be essential for the strong activity. Since the gastroprotection of polygodial was attenuated by pretreatment with indomethacin, *N*-ethylmaleimide, N^G-nitro-L-arginine methyl ester and ruthenium red, endogenous prostaglandins, sulfhydryl compounds, nitric oxide and vannilloid receptors may be involved in the protective activity.



polygodial

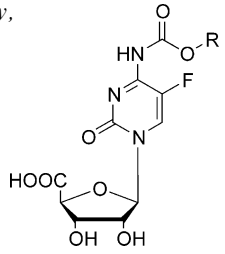
Bioorg. Med. Chem. Lett. 12 (2002) 483

Synthesis and Biological Activity of the New 5-Fluorocytosine Derivatives, 5′-Deoxy-*N*-alkyloxycarbonyl-5-fluorocytosine-5′-carboxylic Acid

Kwan-Hee Kim,* Ji-Young Kim, Keyong-Ho Lee, Moon-Jong Noh, Youn-Chul Kim and Ho-Jin Park

Biomedical Research Institute, Kolon Central Research Park, 207-2 Mabuk-Ri, Guseong-Eup, Yongin-City, Kyunggi-Do 449-797, Republic of Korea

A series of 5-fluorocytosine derivatives, 5′-deoxy-*N*-alkyloxycarbonyl-5-fluorocytosine-5′-carboxylic acid, were synthesized and evaluated for their antitumour activity.

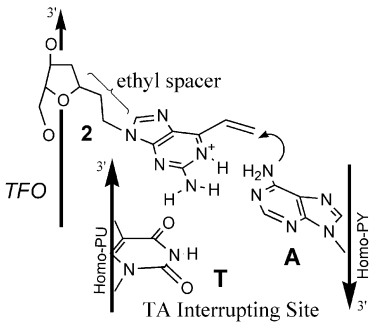


Bioorg. Med. Chem. Lett. 12 (2002) 487

Selective Cross-Linking to the Adenine of the TA Interrupting Site within the Triple Helix

Fumi Nagatsugi, Yoshihisa Matsuyama, Minoru Maeda and Shigeki Sasaki*

Graduate School of Pharmaceutical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan

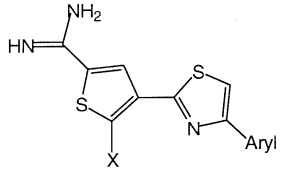


Bioorg. Med. Chem. Lett. 12 (2002) 491

Design and Synthesis of 4,5-Disubstituted-thiophene-2-amidines as Potent Urokinase Inhibitors

M. Jonathan Rudolph,* Carl R. Illig, Nalin L. Subasinghe, Kenneth J. Wilson, James B. Hoffman, Troy Randle, David Green, Chris J. Molloy, Richard M. Soll, Frank Lewandowski, Marie Zhang, Roger Bone, John C. Spurlino, Ingrid C. Deckman, Carl Manthey, Celia Sharp, Diane Maguire, Bruce L. Grasberger, Renée L. DesJarlais and Zhao Zhou

3-Dimensional Pharmaceuticals Inc., 665 Stockton Drive, Exton, PA 19341, USA

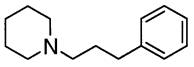


Bioorg. Med. Chem. Lett. 12 (2002) 497

N-Arylalkylpiperidines as High-Affinity Sigma-1 and Sigma-2 Receptor Ligands: Phenylpropylamines as Potential Leads for Selective Sigma-2 Agents

Dean Y. Maeda,[a] Wanda Williams,[b] Wes E. Kim,[a] Linn N. Thatcher,[a] Wayne D. Bowen[b] and Andrew Coop[a,*]

[a]*Department of Pharmaceutical Sciences, University of Maryland School of Pharmacy, 20 North Pine Street, Baltimore, MD 21201, USA*
[b]*Laboratory of Medicinal Chemistry National Institute of Diabetes, Digestive, and Kidney Diseases Building 8, Room B1-23, Bethesda, MD 20892, USA*



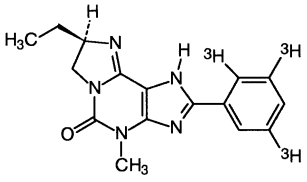
Bioorg. Med. Chem. Lett. 12 (2002) 501

[^{3}H]8-Ethyl-4-methyl-2-phenyl-(8*R*)-4,5,7,8-tetrahydro-1*H*-imidazo[2,1-*i*]-purin-5-one ([^{3}H]PSB-11), a Novel High-Affinity Antagonist Radioligand for Human A_3 Adenosine Receptors

Christa E. Müller,* Martina Diekmann, Mark Thorand and Vita Ozola

Pharmaceutical Institute, University of Bonn, Kreuzbergweg 26, D-53115 Bonn, Germany

The preparation and preliminary evaluation of [^{3}H]PSB-11 is described



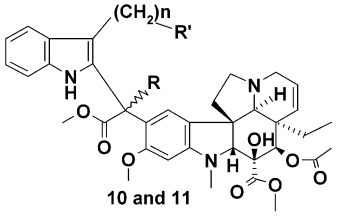
Bioorg. Med. Chem. Lett. 12 (2002) 505

New Method of Synthesis of *Vinca* Alkaloid Derivatives

Jacques Fahy,* Valérie Thillaye du Boullay and Dennis C. H. Bigg

Division de Chimie Médicinale V, Centre de Recherche Pierre Fabre, 81106 Castres, France

Vinblastine and vinorelbine analogues have been synthesised by reacting new versatile electrophilic vindoline derivatives with various 3-substituted indoles. The resulting compounds **10**–**11** have been evaluated for their antimitotic properties, but exhibited less potent activities in comparison with the standard binary *Vinca* alkaloids.

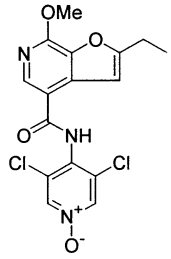


Bioorg. Med. Chem. Lett. 12 (2002) 509

7-Methoxyfuro[2,3-*c*]pyridine-4-carboxamides as PDE4 Inhibitors: A Potential Treatment for Asthma

George M. Buckley, Nicola Cooper, Richard J. Davenport, Hazel J. Dyke, Fiona P. Galleway, Lewis Gowers, Alan F. Haughan, Hannah J. Kendall, Christopher Lowe, John G. Montana, Janet Oxford, Joanna C. Peake, C. Louise Picken, Marianna D. Richard, Verity Sabin, Andrew Sharpe* and Julie B. H. Warneck

Celltech R & D, Granta Park, Great Abington, Cambridge CB1 6GS, UK



The synthesis and pharmacological profile of a novel series of 7-methoxy-furo[2,3-*c*]pyridine-4-carboxamides is reported.