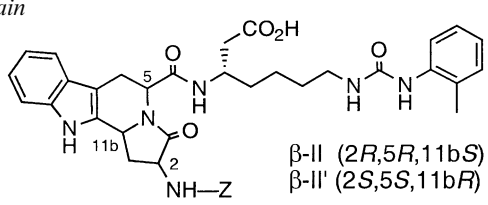
Effects of the Incorporation of IBTM β-Turn Mimetics Into the Dipeptoid CCK_1 Receptor Agonist PD 170292

Bioorg. Med. Chem. Lett. 12 (2002) 109

Mercedes Martín-Martínez,[a] Miriam Latorre,[b] M. Teresa García-López,[a] Edurne Cenarruzabeitia,[b] Joaquín Del Río[b] and Rosario González-Muñiz[a,*]

[a]*Instituto de Química Médica (CSIC), Juan de la Cierva 3, 28006 Madrid, Spain*
[b]*Departamento de Farmacología, Universidad de Navarra, Irunlarrea 1, 31008 Pamplona, Spain*

Replacement of the 2-Adoc-D-αMeTrp residue in the non-selective CCK_1 receptor agonist PD 170292 by the Z-(2*R*,5*R*,11b*S*)-IBTM skeleton, able to fix a type II β-turn-like conformation, led to a conformationally restricted dipeptoid analogue, namely **3a**, which exhibited a notable increase in the CCK_1 selectivity and antagonist properties.



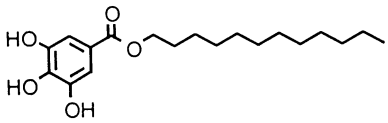
Anti-MRSA Activity of Alkyl Gallates

Bioorg. Med. Chem. Lett. 12 (2002) 113

Isao Kubo,* Ping Xiao and Ken'ichi Fujita

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

A series of alkyl gallates was found to show antibacterial activity against Gram-positive bacteria including methicillin resistant *Staphylococcus aureus* (MRSA) strains. For example, dodecyl gallate exhibited bactericidal activity against MRSA ATCC 33591 strain with an MBC of 74 μM. The time–kill curve study showed that dodecyl gallate is bactericidal against this MRSA strain and the activity comes in part from its ability to inhibit respiratory electron transport system. The length of the alkyl chain is not a major contributor but plays a role in eliciting the activity.



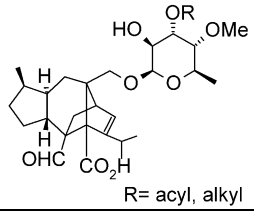
Antifungal Sordarins. Synthesis and Structure–Activity Relationships of 3′-*O*-Substituted Derivatives

Bioorg. Med. Chem. Lett. 12 (2002) 117

Enrique M. Arribas, Julia Castro, Ian R. Clemens, Juan C. Cuevas,* Jesús Chicharro, Mª Teresa Fraile, Silvestre García-Ochoa, Federico Gómez de las Heras and José R. Ruiz

GlaxoSmithKline, Research Department, Parque Tecnológico de Madrid, Severo Ochoa, 2. 28760 Tres Cantos, Madrid, Spain

A number of novel 3′-*O*-acyl and alkyl sordarins were synthesised. Antifungal activity is reported.



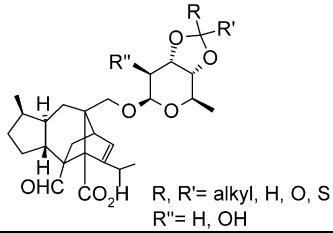
Antifungal Sordarins. Synthesis and Structure–Activity Relationships of 3′,4′-Fused Dioxolane and Dioxane Derivatives

Bioorg. Med. Chem. Lett. 12 (2002) 121

José M. Bueno, Juan C. Cuevas, José M. Fiandor,* Silvestre García-Ochoa and Federico Gómez de las Heras

GlaxoSmithKline, Research Department, Parque Tecnológico de Madrid, Severo Ochoa, 2. 28760 Tres Cantos, Madrid, Spain

A number of novel 3′,4′-fused sordarin derivatives were synthesised. Antifungal activity is reported.



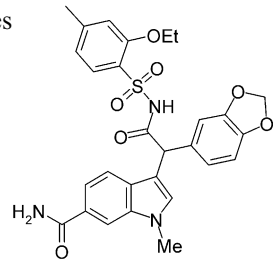
Bioorg. Med. Chem. Lett. 12 (2002) 125

The Design and Synthesis of a Novel Series of Indole Derived Selective ET_A Antagonists

David J. Rawson,* Kevin N. Dack, Roger P. Dickinson and Kim James

Department of Discovery Chemistry, Pfizer Central Research, Sandwich, Kent CT13 9NJ, UK

Conformational constraint has been used as the key design element in the identification of a series of potent and selective ET_A antagonists. The most potent antagonist, **32**, (ET_A IC_{50} = 0.55 nM) is 722-fold selective over the ET_B receptor.



32

ET_A IC_{50} = 0.55nM
$ET_{A/B}$ = 722

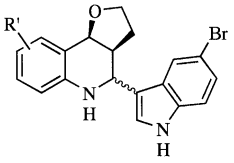
Bioorg. Med. Chem. Lett. 12 (2002) 129

Potent In Vitro Methicillin-Resistant *Staphylococcus aureus* Activity of 2-(1*H*-indol-3-yl)tetrahydroquinoline Derivatives

Michael Z. Hoemann,* Roger L. Xie, Richard F. Rossi, Sylvia Meyer, Alban Sidhu, Gregory D. Cuny and James R. Hauske

Sepracor Inc., 111 Locke Dr., Marlborough, MA 01752, USA

Novel antibacterial agents, 2-(1*H*-indol-3-yl)tetrahydroquinolines, were prepared using hetero Diels–Alder chemistry and found to be effective in vitro against methicillin-resistant *Staphylococcus aureus*.

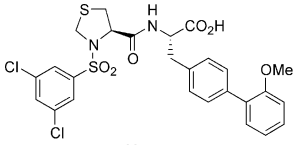


Bioorg. Med. Chem. Lett. 12 (2002) 133

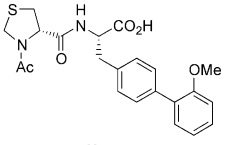
Specific and Dual Antagonists of $\alpha_4\beta_1$ and $\alpha_4\beta_7$ Integrins

Linus S. Lin,[a,*] Thomas Lanza, Jr.,[a] Ermenegilda McCauley,[b] Gail Van Riper,[b] Usha Kidambi,[b] Jin Cao,[b] Linda A. Egger,[b] Richard A. Mumford,[b] John A. Schmidt,[b] Malcolm MacCoss[a] and William K. Hagmann[a]

[a]*Department of Medicinal Chemistry, Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065, USA*
[b]*Department of Immunology and Rheumatology Research, Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065, USA*



10a
IC_{50} ($\alpha_4\beta_1$): 0.30 nM
IC_{50} ($\alpha_4\beta_7$): 306 nM



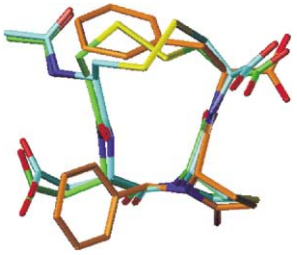
8b
IC_{50} ($\alpha_4\beta_1$): 0.20 nM
IC_{50} ($\alpha_4\beta_7$): 2.1 nM

Bioorg. Med. Chem. Lett. 12 (2002) 137

N-Acyl-L-phenylalanine Derivatives as Potent VLA-4 Antagonists that Mimic a Cyclic Peptide Conformation

Li Chen,* Jefferson Tilley, Richard V. Trilles, Weiya Yun, David Fry, Charles Cook, Karen Rowan, Virginia Schwinge and Robert Campbell

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



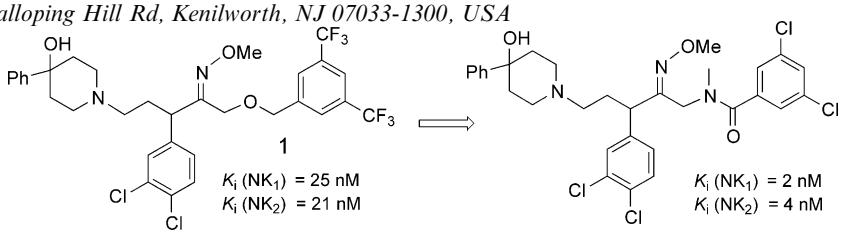
Bioorg. Med. Chem. Lett. 12 (2002) 141

Synthesis and Structure–Activity Relationships of Oxime Neurokinin Antagonists: Discovery of Potent Arylamides

Neng-Yang Shih,* Margaret Albanese, John C. Anthes, Nicholas I. Carruthers, Cheryl A. Grice, Ling Lin, Pietro Mangiaracina, Gregory A. Reichard, John Schwerdt, Vera Seidl, Shing-Chung Wong and John J. Piwinski

Schering-Plough Research Institute, 2015 Galloping Hill Rd, Kenilworth, NJ 07033-1300, USA

The structural modification of the benzylic ether region of oxime **1** has resulted in the identification of several novel aryl amides as selective or dual NK_1/NK_2 antagonists.



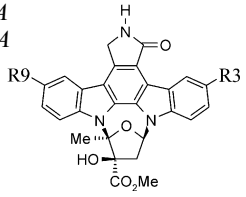
Bioorg. Med. Chem. Lett. 12 (2002) 147

Mixed Lineage Kinase Activity of Indolocarbazole Analogues

Chikara Murakata,[d] Masami Kaneko,[d] George Gessner,[b] Thelma S. Angeles,[b] Mark A. Ator,[b] Teresa M. O'Kane,[c] Beth Ann W. McKenna,[c] Beth Ann Thomas,[c] Joanne R. Mathiasen,[c] Michael S. Saporito,[c] Donna Bozyczko-Coyne[c] and Robert L. Hudkins[a,*]

[a]*Department of Medicinal Chemistry, Cephalon, Inc., 145 Brandywine Parkway, West Chester, PA 19380, USA*
[b]*Department of Biochemistry, Cephalon, Inc., 145 Brandywine Parkway, West Chester, PA 19380, USA*
[c]*Department of Neurobiology, Cephalon, Inc., 145 Brandywine Parkway, West Chester, PA 19380, USA*
[d]*Kyowa-Hakko Kogyo Co., Ltd., Tokyo, Japan*

The MLK1–3 activity for a series of analogues of the indolocarbazole K-252a is reported.



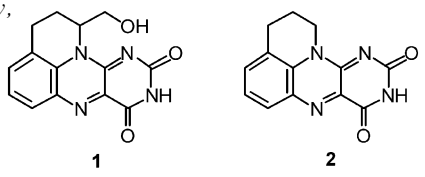
Bioorg. Med. Chem. Lett. 12 (2002) 151

An N1–Hydrogen Bonding Model for Flavin Coenzyme

Fengli Guo, Bryan H. Chang and Carmelo J. Rizzo*

Department of Chemistry and Center for Molecular Toxicology, Vanderbilt University, VU Station B 351822, Nashville, TN 37235-1822, USA

Flavin **1** has been synthesized as a model for hydrogen bonding to the N1-position of flavin coenzyme and its properties compared to **2**.



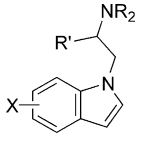
Bioorg. Med. Chem. Lett. 12 (2002) 155

Evaluation of Isotryptamine Derivatives at 5-HT_2 Serotonin Receptors

Jean Chang-Fong,[a] James Addo,[a] Małgorzata Dukat,[a] Carol Smith,[b] Nicholas A. Mitchell,[b] Katharine Herrick-Davis,[b] Milt Teitler[b] and Richard A. Glennon[a,*]

[a]*Department of Medicinal Chemistry, School of Pharmacy, Virginia Commonwealth University, Richmond, VA 23298, USA*
[b]*Center for Neuropharmacology and Neuroscience, Albany Medical College, Albany, NY 12208, USA*

Several isotryptamine derivatives, including 5,6-difluoro-α-methylisotryptamine (i.e., R = –H, R′ = $–CH_3$, X = 5,6-diF) — an agent previously reported to bind with 100-fold selectivity at 5-HT_{2C} receptors, failed to show enhanced selectivity for 5-HT_{2C} versus 5-HT_{2A} receptors.

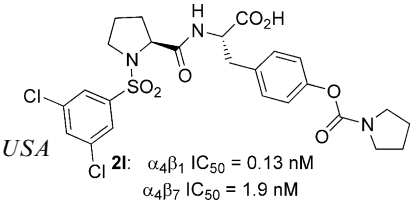


Bioorg. Med. Chem. Lett. 12 (2002) 159

The Discovery of Small Molecule Carbamates as Potent Dual $\alpha_4\beta_1/\alpha_4\beta_7$ Integrin Antagonists

Linda L. Chang,[a,*] Quang Truong,[a] Richard A. Mumford,[b] Linda A. Egger,[b] Usha Kidambi,[b] Kathryn Lyons,[c] Ermengilda McCauley,[b] Gail Van Riper,[b] Stella Vincent,[c] John A. Schmidt,[b] Malcolm MacCoss[a] and William K. Hagmann[a]

[a]*Department of Basic Medicinal Chemistry, Merck Research Laboratories, Rahway, NJ 07065, USA*
[b]*Department of Immunology and Rheumatology, Merck Research Laboratories, Rahway, NJ 07065, USA*
[c]*Department of Drug Metabolism, Merck Research Laboratories, Rahway, NJ 07065, USA*



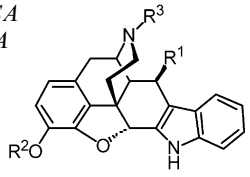
A series of (*N*-arylsulfonyl)-Pro-Tyr-carbamates, exemplified by **2l**, are potent dual $\alpha_4\beta_1/\alpha_4\beta_7$ integrin antagonists.

Bioorg. Med. Chem. Lett. 12 (2002) 165

Synthesis and Biological Activity of 8β-Substituted Hydrocodone Indole and Hydromorphone Indole Derivatives

Han Yu,[a] Thomas Prisinzano,[a] Christina M. Dersch,[b] Jamila Marcus,[b] Richard B. Rothman,[b] Arthur E. Jacobson[a] and Kenner C. Rice[a,*]

[a]*Laboratory of Medicinal Chemistry, NIDDK, National Institutes of Health, Bethesda, MD 20892, USA*
[b]*Clinical Psychopharmacology Section, NIDA, Addiction Research Center, Baltimore, MD 21224, USA*



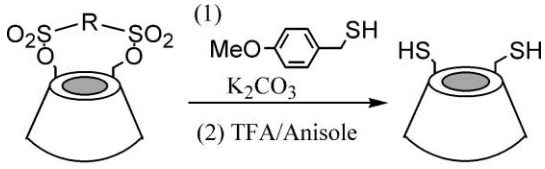
Bioorg. Med. Chem. Lett. 12 (2002) 169

Facile Synthesis of β-Cyclodextrin Dithiols

Jerry Yang* and David K. Leung

Department of Chemistry, Columbia University, New York, NY 10027, USA

Nucleophilic addition of 4-methoxy-α-toluenethiol to capped cyclodextrins followed by deprotection in TFA affords cyclodextrin dithiols in good yields with no disulfide formation and minimal purification.



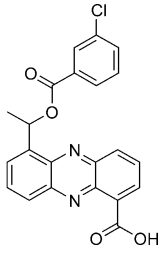
Bioorg. Med. Chem. Lett. 12 (2002) 171

Solid-Phase Synthesis of New Saphenamycin Analogues with Antimicrobial Activity

Jane B. Laursen, Peter C. de Visser, Henrik K. Nielsen, Knud J. Jensen and John Nielsen*

Department of Chemistry, Kemitorvet, Building 207, Technical University of Denmark, DK-2800 Kgs. Lyngby, Denmark

The synthesis of 12 new saphenamycin analogues modified at the benzoate moiety is reported. Screening for antimicrobial activity against *Bacillus subtilis* has revealed MIC values ranging from 0.07 to 3.93 μg/mL.



MIC = 0.07 μg/mL

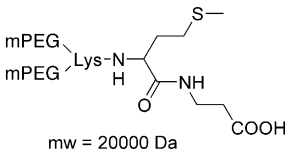
Bioorg. Med. Chem. Lett. 12 (2002) 177

An Improved Procedure for the Synthesis of Branched Polyethylene Glycols (PEGs) with the Reporter Dipeptide Met-βAla for Protein Conjugation

Andrea Guiotto,[a] Michela Pozzobon,[a] Chiara Sanavio,[a] Oddone Schiavon,[a] Piero Orsolini[b] and Francesco M. Veronese[a,*]

[a]*Dipartimento di Science Farmaceutiche, Via Marzolo 5, 35100 Padova, Italy*
[b]*DEBIO R.P., Route du Levant 146, CH 1920 Martigny, Switzerland*

A new procedure for the synthesis of the branched PEG_2Lys-Met-βAla-OH derivative is reported.



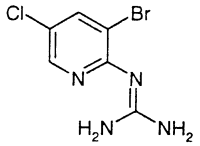
Bioorg. Med. Chem. Lett. 12 (2002) 181

Selective Urokinase-Type Plasminogen Activator (uPA) Inhibitors. Part 1: 2-Pyridinylguanidines

Christopher G. Barber,* Roger P. Dickinson and Valerie A. Horne

Department of Discovery Chemistry, Pfizer Global Research and Development, Sandwich, Kent CT13 9NJ, UK

The identification of 2-pyridinylguanidines (e.g., **27** and **28**) as selective inhibitors of urokinase-type plasminogen activator (uPA) is described. The X-ray crystal structure of **27** has been determined, and modelling has been used to predict binding in the enzyme active site.



27

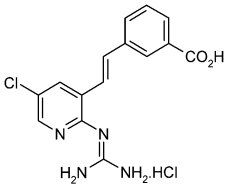
Bioorg. Med. Chem. Lett. 12 (2002) 185

Selective Urokinase-Type Plasminogen Activator (uPA) Inhibitors. Part 2: (3-Substituted-5-halo-2-pyridinyl)guanidines

Christopher G. Barber* and Roger P. Dickinson

Department of Discovery Chemistry, Pfizer Global Research and Development, Sandwich, Kent CT13 9NJ, UK

A series of (3-substituted-5-chloro-2-pyridinyl)guanidines have been designed with good potency and selectivity for urokinase-type plasmonogen activator (uPA). Compound **36** has a K_i of 0.17 μM and greater than 300-fold selectivity with respect to tPA and plasmin.



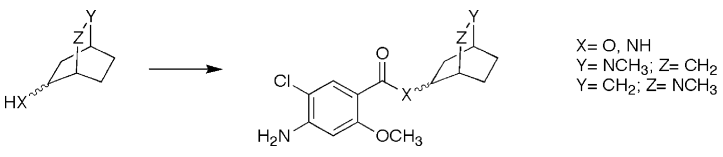
36

Bioorg. Med. Chem. Lett. 12 (2002) 189

Synthesis and Pharmacology of Isoquinuclidine Derivatives as 5-HT_3 Ligands

Isabel Iriepa,[a,*] Francisco J. Villasante,[a] Enrique Gálvez,[a] Luis Labeaga,[b] Ana Innerarity[b] and Aurelio Orjales[b]

[a]*Departamento de Química Orgánica, Universidad de Alcalá, Ctra. Madrid-Barcelona Km. 33,600, 28871 Alcalá de Henares, Madrid, Spain*
[b]*Departamento de Investigación, FAES, S.A., Máximo Aguirre 14, 48940 Leioa, Vizcaya, Spain*

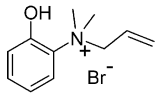


Bioorg. Med. Chem. Lett. 12 (2002) 193

Oxyaniliniums as Acetylcholinesterase Inhibitors for the Reversal of Neuromuscular Block

Simon J. A. Grove,[a] Jasmit Kaur,[a] Alan W. Muir,[b] Eleanor Pow,[b] Gary J. Tarver[a] and Ming-Qiang Zhang[a,*]

[a]*Department of Medicinal Chemistry, Organon Laboratories Ltd., Newhouse, Lanarkshire ML1 5SH, Scotland, UK*
[b]*Department of Pharmacology, Organon Laboratories Ltd., Newhouse, Lanarkshire ML1 5SH, Scotland, UK*



ED_{50} (i.v., cat): 0.50 μmol/kg
vs vecuronium bromide

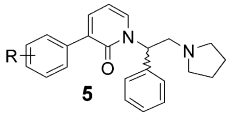
Bioorg. Med. Chem. Lett. 12 (2002) 197

3-Aryl Pyridone Derivatives. Potent and Selective Kappa Opioid Receptor Agonists

Graeme Semple,[a,*] Britt-Marie Andersson,[b] Vijay Chhajlani,[b] Jennie Georgsson,[a] Magnus Johansson,[a] Marcel Lindschoten,[a] Fritof Pontén,[a] Åsa Rosenquist,[a] Henrik Sörensen,[a] Lars Swanson[a] and Marianne Swanson[a]

[a]*Department of Medicinal Chemistry, AstraZeneca R&D Mölndal, S-431 83, Mölndal, Sweden*
[b]*Dept of Biochemistry and Cell Biology, AstraZeneca R&D Mölndal, S-431 83, Mölndal, Sweden*

A new series of 3-aryl pyridone based kappa opioid receptor agonists was designed and synthesised, based on an understanding of the kappa opioid receptor pharmacophore. New compounds were comparable to U-69,593 in receptor affinity, selectivity and functional agonist effect at the cloned human kappa opioid receptor.



5

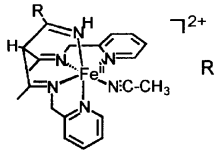
Bioorg. Med. Chem. Lett. 12 (2002) 201

DNA Cleavage by Pentadentate Iron(II) Complexes Containing Fluoro-Substituted Phenyl Groups

Hiromasa Kurosaki, Aoi Maruyama, Hiroyuki Koike, Naoko Kuroda, Yoshinobu Ishikawa and Masafumi Goto*

Faculty of Pharmaceutical Sciences, Kumamoto University, 5-1 Oe-honmachi, Kumamoto 862-0973, Japan

Four pentadentate iron(II) complexes with varied number of fluorine substitution, **2b**–**2e**, have been prepared and were employed for DNA cleavage reaction in the presence of hydrogen peroxide. Among them, **2e** has the highest activity toward degradation of plasmid pUC 19 DNA.



(2)

R = CH_3: **2a**
C_6H_5: **2b**
4F-C_6H_4: **2c**
3,4-F_2-C_6H_3: **2d**
C_6F_5: **2e**

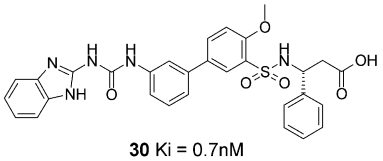
Bioorg. Med. Chem. Lett. 12 (2002) 205

Biphenyls as Potent Vitronectin Receptor Antagonists

Klaus Urbahns,[a,*] Michael Härter,[a] Markus Albers,[b] Delf Schmidt,[c] Beatrix Stelte-Ludwig,[d] Ulf Brüggemeier,[c] Andrea Vaupel[a] and Christoph Gerdes[d]

[a]*Institute of Medicinal Chemistry, Pharma Research Centre, Bayer AG, D-42096 Wuppertal, FRG*
[b]*Combinatorial Chemistry Group, Central Research, Bayer AG, D-51368 Leverkusen, FRG*
[c]*Institute of Molecular Screening Technologies, Pharma Research Centre, Bayer AG, D-42096 Wuppertal, FRG*
[d]*Institute of Cardiovascular Research, Pharma Research Centre, Bayer AG, D-42096 Wuppertal, FRG*

Identified from a combinatorial library based on a biphenyl moiety, **30** is a subnanomolar vitronectin receptor ($\alpha_V\beta_3$) antagonist with selectivity towards the related GPIIbIIIa receptor and functional activity on human smooth muscle cell migration.



30 Ki = 0.7nM

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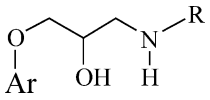
New Series of Aryloxypropanolamines with Both Human β_3-Adrenoceptor Agonistic Activity and Free Radical Scavenging Properties

Silvère Aubriot,[a] Edwige Nicolle,[a,*] Mireille Lattier,[b] Cécile Morel,[a] Wenhong Cao,[c] Kiefer W. Daniel,[c] Sheila Collins,[c] Gérard Leclerc[a] and Patrice Faure[b]

[a]*Département de Pharmacochimie Moléculaire, UMR-CNRS 5063, UFR de Pharmacie, Université Joseph Fourier, BP 138, F-38243 Meylan cedex, France*
[b]*Laboratoire du Stress Cardiovasculaire et des Pathologies Associées, EA 2937 UFR de Pharmacie, Université Joseph Fourier, F-38700 La Tronche, France*
[c]*Division of Biological Psychiatry, Duke University Medical Center, Box 3557 Durham, NC 27710, USA*



Aryloxypropanolamines **6**–**19** have been synthesized and were in vitro evaluated. Some compounds displayed both free radical scavenging properties and β_3-adrenergic activity.

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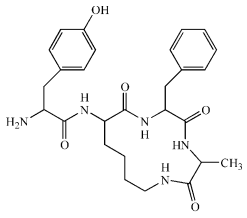
Synthesis and Biological Activities of YkFA Analogues: Effects of Position 4 Substitutions and Altered Ring Size on In Vitro Opioid Activity

John E. Burden,[a] Peg Davis,[b] Frank Porreca[b] and Arno F. Spatola[a,*]

[a]*Department of Chemistry, University of Louisville, Louisville, KY 40292, USA*
[b]*Department of Pharmacology, University of Arizona, Tucson, AZ 85721, USA*



YkFA

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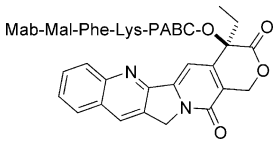
Synthesis of an Immunoconjugate of Camptothecin

Michael A. Walker,* Gene M. Dubowchik, Sandra J. Hofstead, Pamela A. Trail and Raymond A. Firestone

Bristol-Myers Squibb Pharmaceutical Research Institute, PO Box 5100, 5 Research Parkway, Wallingford, CT 06492, USA



The first immuniconjugate of camptothecin has been synthesized wherein the drug is attached to the tumor-recognizing antibody BR96 via a Cathepsin B cleavable linker.

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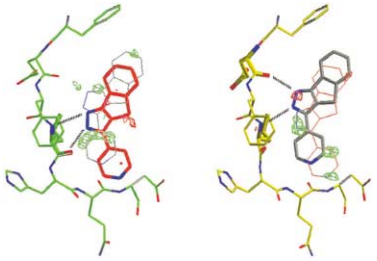
Structure-Based Design and Protein X-ray Analysis of a Protein Kinase Inhibitor

Pascal Furet,[a,*] Thomas Meyer,[a] André Strauss,[b] Sylvie Raccuglia[b] and Jean-Michel Rondeau*[,b]

[a]*Novartis Pharmaceuticals Inc., Oncology Research, CH-4002 Basel, Switzerland*
[b]*Novartis Pharmaceuticals Inc., Core Technologies, CH-4002 Basel, Switzerland*



We identified an inhibitor of the cell cycle kinases CDK1/2 by structure-based design. X-ray analysis of its complex with CDK2 revealed two distinct binding modes involving the two possible tautomeric forms of the compound.

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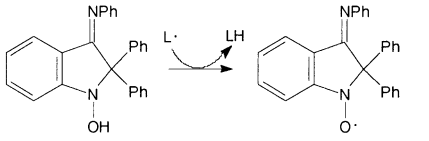
Theoretical Elucidation on Structure–Antioxidant Activity Relationships for Indolinonic Hydroxylamines

Hong-Yu Zhang[a,*] and Lan-Fen Wang[b]

[a]*Laboratory for Computational Biology, Shandong Provincial Research Center for Bioinformatic Engineering and Technique, Shandong University of Technology, Zibo 255091, PR China*
[b]*Department of Chemistry, Shandong Teachers' University, Jinan 250014, PR China*

Structure–antioxidant activity relationships for indolinonic hydroxylamines were elucidated by B3LYP/6-31G(d, p) calculations.



O-H BDE is ~ 10 kcal/mol lower than that of a-tocopherol

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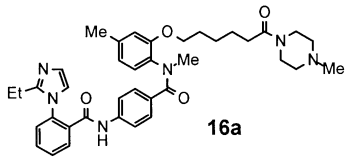
N-Methylbenzanilide Derivatives as a Novel Class of Selective V_{1A} Receptor Antagonists

Akio Kakefuda,[a,*] Junko Tsukada,[b] Toshiyuki Kusayama,[a] Atsuo Tahara[a] and Shin-ichi Tsukamoto[a]

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

A series of *N*-methylbenzanilide derivatives was prepared as selective V_{1A} antagonists. Structural modifications led to the identification of compounds which had high V_{1A} affinity and V_2/V_{1A} selectivity such as **16a.**



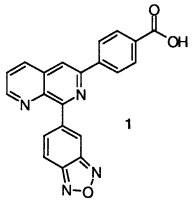
Bioorg. Med. Chem. Lett. 12 (2002) 233

Synthesis of 4-(8-benzo[1,2,5]oxadiazol-5-yl-[1,7]naphthyridine-6-yl)-benzoic Acid: a Potent and Selective Phosphodiesterase Type 4D Inhibitor

Rene Hersperger,[a,*] Janet Dawson[a] and Thomas Mueller[b]

[a]*Novartis Pharma AG, Arthritis & Bone Metabolism, CH-4002 Basel, Switzerland*
[b]*Novartis Pharma AG, Research Information Management, CH-4002 Basel, Switzerland*

The synthesis of a 6,8-disubstituted 1,7-naphthyridine **1** and its characterization as a potent and selective phosphodiesterase type 4D inhibitor ($IC_{50} = 1.5$nM) are described. The compound inhibited TNFα-release from human peripheral blood mononuclear cells and was orally active in a model of adjuvant-induced arthritis in rats.



1

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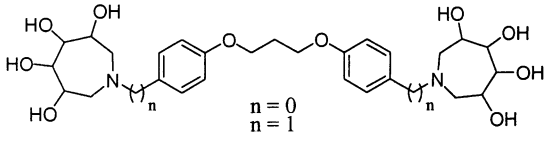
Polyhydroxylated Azepanes as New Motifs for DNA Minor Groove Binding Agents

Heather A. Johnson and Neil R. Thomas*

School of Chemistry, University of Nottingham, Nottingham, NG7 2RD, UK

The synthesis, DNA binding affinity and biological evaluation of bis-azepanes is reported.



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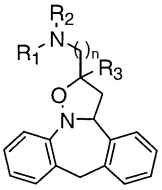
Synthesis and Structure–Activity Relationship of 2-(Aminoalkyl)-2,3,3a,8-tetrahydrodibenzo[*c*,*f*]isoxazolo[2,3-*a*]azepine Derivatives: A Novel Series of 5-$HT_{2A/2C}$ Receptor Antagonists. Part 1

J. Ignacio Andrés,[a,*] Jesús Alcázar,[a] José M. Alonso,[a] Adolfo Díaz,[a] Javier Fernández,[a] Pilar Gil,[a] Laura Iturrino,[a] Encarna Matesanz,[a] Theo F. Meert,[b] Anton Megens[c] and Victor K. Sipido[d]

[a]*Janssen-Cilag, Basic Research Centre, Jarama s/n, 45007 Toledo, Spain*
[b]*CNS Department, Janssen Research Foundation, B2340 Beerse, Belgium*
[c]*General in vivo Pharmacology, Janssen Research Foundation, B2340 Beerse, Belgium*
[d]*Medicinal Chemistry Department, Janssen Research Foundation, B2340 Beerse, Belgium*

The synthesis of a series of novel tetrahydrodibenzo[*c*,*f*]isoxazolo[2,3-*a*]azepine derivatives as 5-$HT_{2A/2C}$ antagonists is described. The mCPP activity of the synthesised compounds is also reported.



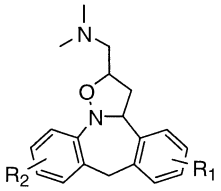
Bioorg. Med. Chem. Lett. 12 (2002) 249

Synthesis and Structure–Activity Relationship of 2-(Aminoalkyl)-2,3,3a,8-tetrahydrodibenzo[*c*,*f*]isoxazolo[2,3-*a*]azepine Derivatives: A Novel Series of 5-$HT_{2A/2C}$ Receptor Antagonists. Part 2

J. Ignacio Andrés,[a,*] Jesús Alcázar,[a] José M. Alonso,[a] Adolfo Díaz,[a] Javier Fernández,[a] Pilar Gil,[a] Laura Iturrino,[a] Encarna Matesanz,[a] Theo F. Meert,[b] Anton Megens[c] and Victor K. Sipido[d]

[a]*Janssen-Cilag, Basic Research Centre, Jarama s/n, 45007 Toledo, Spain*
[b]*CNS Department, Janssen Research Foundation, B2340 Beerse, Belgium*
[c]*General in vivo Pharmacology, Janssen Research Foundation, B2340 Beerse, Belgium*
[d]*Medicinal Chemistry Department, Janssen Research Foundation, B2340 Beerse, Belgium*

The synthesis of a series of substituted 2-(dimethylaminomethyl)-2,3,3a,8-tetrahydrodibenzo[*c*,*f*]isoxazolo [2,3-*a*]azepine derivatives as 5-HT2A/2C antagonists as well as their mCPP antagonistic activity is reported.



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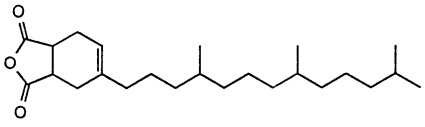
Cyclic Acid Anhydrides as a New Class of Potent, Selective and Non-Peptidic Inhibitors of Geranylgeranyl Transferase

Charles M. Marson,[a,*] Alphonso S. Rioja,[a] Greg Brooke,[b] R. Charles Coombes[b] and David M. Vigushin[b]

[a]*Department of Chemistry, University College London, Christopher Ingold Laboratories, 20 Gordon Street, London WC1H OAJ, UK*
[b]*Department of Cancer Medicine, 5th Floor MRC Cyclotron Building, Imperial College of Science, Technology and Medicine, Hammersmith Hospital Campus, Du Cane Road, London W12 ONN, UK*

Cyclic anhydride inhibitors selective for GGPTase-I are described.

GGPTase-I IC_{50} = 21 μM
FPTase IC_{50} > 1000 μM



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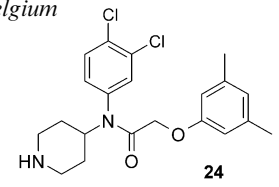
First Dual NK_1 Antagonists–Serotonin Reuptake Inhibitors: Synthesis and SAR of a New Class of Potential Antidepressants

Thomas Ryckmans,[a,*] Laurent Balançon,[a] Olivier Berton,[b] Christophe Genicot,[a] Yves Lamberty,[b] Benedicte Lallemand,[a] Patrick Pasau,[a] Nathalie Pirlot,[a] Luc Quéré[a] and Patrice Talaga[a]

[a]*Chemical Research, R&D, UCB Pharma SA, Chemin du Foriest, B-1420 Braine-l'Alleud, Belgium*
[b]*Preclinical CNS Research, R&D, UCB Pharma SA, Chemin du Foriest, B-1420 Braine-l'Alleud, Belgium*

Compounds combining NK_1 antagonism and serotonin reuptake inhibition are described, and potentially represent a new generation of antidepressants. Compound **24** displays good affinities for both the NK_1 receptor and the serotonin reuptake site (32 and 25 nM, respectively).



24

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Increase of the Adenallene Anti-HIV Activity in Cell Culture Using Its Bis(*t*BuSATE) Phosphotriester Derivative

David Egron,[a] Christian Périgaud,[a,*] Gilles Gosselin,[a] Anne-Marie Aubertin,[b] Hiroyuki Gatanaga,[c] Hiroaki Mitsuya,[c] Jiri Zemlicka[d] and Jean-Louis Imbach[a]

[a]*UMR CNRS 5625, Université Montpellier II, cc 008, Place E. Bataillon, 34095 Montpellier Cedex 5, France*
[b]*Institut de Virologie de la Faculté de Médecine de Strasbourg, U. INSERM 74, 3 rue Koeberlé, 67000 Strasbourg, France*
[c]*Experimental Retrovirology Section, Medicine Branch, Division of Clinical Sciences, NCI, NIH, Bethesda, MA 20892, USA*
[d]*Department of Chemistry, Barbara Ann Karmanos Cancer Institute, Wayne State University School of Medicine, Detroit, MI 48201-1379, USA*

The bis(*t*BuSATE) phosphotriester derivative of adenallene proved to be more effective than its parent nucleoside analogue in inhibiting HIV replication in cell culture experiments.