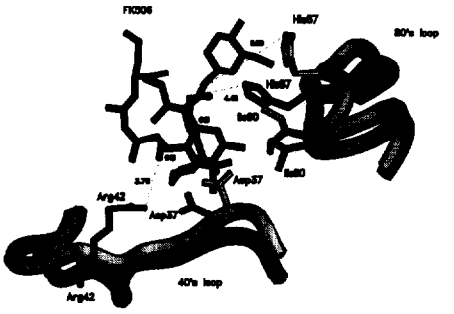
Modeling the Interaction Between FK506 and FKBP12: a Mechanism for Formation of the Calcineurin Inhibitory Complex

Bioorg. Med. Chem. **1997**, *5*, 217

Michael T. G. Ivery and Larry Weiler
Department of Chemistry, University of British Columbia, 2036 Main Mall Vancouver, British Columbia, Canada V6T 1Z1

Modeling of structures of FK506 and FKBP12 has been used to identify structural changes that occur in both molecules on formation of their complex and a mechanism for formation of the calcineurin inhibitory complex proposed.

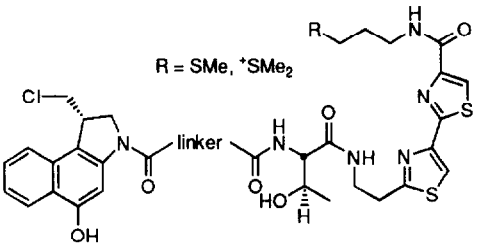


CC-1065/Duocarmycin and Bleomycin A_2 Hybrid Agents: Lack of Enhancement of DNA Alkylation by Attachment to Noncomplementary DNA Binding Subunits

Bioorg. Med. Chem. **1997**, *5*, 233

Dale L. Boger* and Nianhe Han
Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, U.S.A.

The preparation and evaluation of hybrid agents containing the *C*-terminus DNA binding domain of bleomycin linked to an analogue of the CC-1065/duocarmycin DNA alkylation subunits are described.

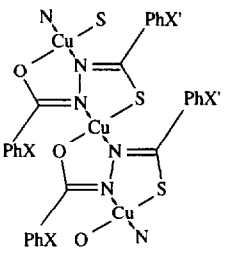


Antitumor Activity Studies of Newly Synthesized *N*-Salicyloyl-*N'*-(*p*-hydroxybenzthioyl)hydrazine and its Copper(II) Complex both in vivo and in vitro

Bioorg. Med. Chem. **1997**, *5*, 245

N. K. Singh,[a,*] Nagendra Singh,[a] G. C. Prasad,[b] A. Sodhi[c] and Anju Shrivastava[c]
[a]Department of Chemistry, Banaras Hindu University, Varanasi 221 005, India, [b]Department of Shalya Shalakya, Institute of Medical Sciences, B.H.U., Varanasi, [c]Department of Biotechnology, Faculty of Science, B.H.U., Varanasi, India

A new ligand *N*-salicyloyl-*N'*-(*p*-hydroxybenzthioyl)hydrazine (H_2STPH) and its Cu^{II} complex [Cu(SPTH)] were prepared and characterized by analytical and physicochemical studies. In vivo antitumor activity of [Cu(STPH)] has been tested against breast tumor in C_3H/J strain mice and in vitro on P-815 (murine mastocytoma) and K-562 (human erythroleukemia) cells.



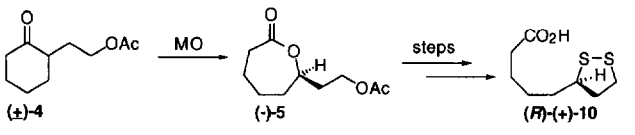
[Cu (ST PH)], X = OH, X ' = p-OH

The Synthesis of (*R*)-(+)-Lipoic Acid using a Monooxygenase-Catalysed Biotransformation as the Key Step

Bioorg. Med. Chem. **1997**, *5*, 253

B. Adger,[a] M. T. Bes,[b] G. Grogan,[b] R. McCague,[a] S. Pedragosa-Moreau,[b] S. M. Roberts,[c] R. Villa,[b] P. W. H. Wan[c] and A. J. Willetts[b]
[a]Chiroscience Ltd, Science Park, Cambridge CB4 4WE, U.K.
[b]Department of Biological Sciences and [c]Department of Chemistry, University of Exeter, Exeter EX4 4QD, U.K.

A monooxygenase enzyme is employed in the kinetic resolution of the ketone (±)-(**4**) to provide optically active lactone (−)-(**5**), an intermediate to naturally occurring lipoic acid.

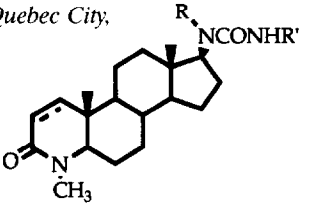


Bioorg. Med. Chem. **1997**, *5*, 305

Synthesis and In Vitro Study of 17β-[*N*-Ureylene-*N*,*N'*-disubstituted]-4-methyl-4-aza-5α-Androstan-3-ones as Selective Inhibitors of Type I 5α-Reductase

Mettilda Lourdusamy, Jean Côté, S. Laplante, Fernand Labrie and Shankar M. Singh*
Medicinal Chemistry Division, Laboratory of Molecular Endocrinology, CHUL Research Center, Quebec City, Québec, Canada, G1W 4G2

The synthesis and in vitro activity are described.

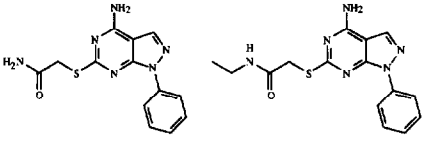


Bioorg. Med. Chem. **1997**, *5*, 311

1-Phenylpyrazolo[3,4-*d*]pyrimidines as Adenosine Antagonists: the Effects of Substituents at C4 and C6

Mary Chebib and Ronald J. Quinn
Queensland Pharmaceutical Research Institute, Griffith University, Brisbane 4111 Australia

For high affinity at A_1 and A_{2a} adenosine receptors the distal amide should be separated from the C6 thiol by only one carbon. Compared with a thiol at C4, both thiomethyl and amino resulted in increased affinity at both receptors.



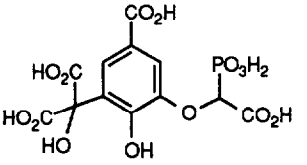
A_1 K_i 12.1 nM A_{2a} K_i 44.9 nM.

Bioorg. Med. Chem. **1997**, *5*, 323

New Aromatic Inhibitors of EPSP Synthase Incorporating Hydroxymalonates as Novel 3-Phosphate Replacements

Ajit Shah,[a] Jose L. Font,[a] Michael J. Miller,[a] Joel E. Ream,[a] Mark C. Walker[a] and James A. Sikorski[b,*]
[a]Ceregen and [b]Monsanto Corporate Research, Units of Monsanto Company, 700 Chesterfield Parkway North, St. Louis, MO 63198 U.S.A.

Aromatic analogues of the EPSP synthase reaction substrate, product, and tetrahedral intermediate were synthesized from 3,4-dihydroxybenzoic acid, containing a 3-hydroxymalonate in place of the normal 3-phosphate group. These molecules help define the scope and limitations of incorporating 3-hydroxymalonates as 3-phosphate replacements in this system.

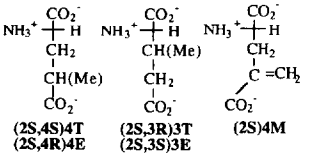


9, K_i (apparent) = 0.57 ± 0.06 μM

Bioorg. Med. Chem. **1997**, *5*, 335

Conformational Analysis of Glutamic Acid Analogues as Probes of Glutamate Receptors using Molecular Modelling and NMR Methods. Comparison with Specific Agonists

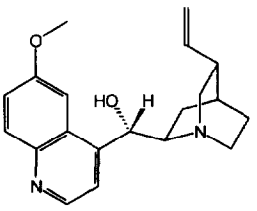
N. Todeschi,[a] J. Gharbi-Benarous,[a,b] F. Acher,[a] V. Larue,[a] J.-P. Pin,[c] J. Bockaert,[c] R. Azerad[a] and J.-P. Girault[a,*]
[a]Université René Descartes-Paris V, Laboratoire de Chimie et Biochimie Pharmacologique et Toxicologique (URA 400 CNRS), 45 rue des Saints-Pères, 75270 Paris Cedex 06, France; [b]Université Denis Diderot-Paris VII, UFR Chimie, 2 Place Jussieu, F-75251 Paris Cedex 05, France; [c]Centre CNRS-INSERM de Pharmacologie-Endocrinologie, UPR 9023 Mécanisme Moléculaires des Communications Cellulaires, rue de la Cardonille, 34094 Montpellier Cedex 5, France



Conformational Analysis of the Antimalarial Agent Quinidine

Bioorg. Med. Chem. **1997**, *5*, 353

Thais H. A. Silva,[a] Alaíde B. Oliveira[a] and Wagner B. De Almeida[b,*]
[a]Departamento de Produtos Farmacêuticos, Faculdade de Farmácia, UFMG; [b]Laboratório de Química Computacional e Modelagem Molecular (LQC-MM), Departamento de Química, ICEx, UFMG, Belo Horizonte, MG, CEP 31.270-901, Brazil



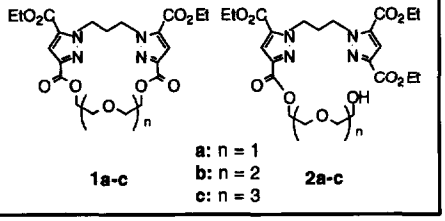
The potential energy surface for quinidine has been comprehensively investigated using molecular mechanics and quantum mechanical semiempirical AM1 and PM3 methods. The coexistence of different conformers is discussed for the first time in the literature based on the calculated transition state structures.

Selective Carriers of Norepinephrine and Ammonium Ions: Ionophoric Properties and Molecular Modelling Studies of Diester Crown Compounds Containing a 1,3-Bis(1*H*-pyrazol-1-yl)propane Unit

Bioorg. Med. Chem. **1997**, *5*, 363

María Isabel Rodríguez-Franco,* Marta Fierros, Ana Martínez, Pilar Navarro and Santiago Conde
Instituto de Química Médica (C.S.I.C.), Juan de la Cierva 3, 28006-Madrid, Spain

Crowns and podands containing a dipyrazolic unit show interesting norepinephrine and ammonium transport rates. A molecular modelling study has been used to elucidate the crown and ammonium cation complexes.

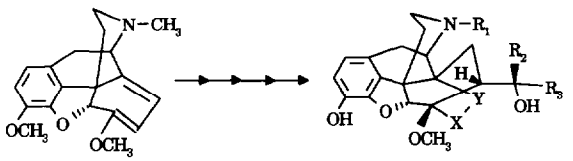


New Nepenthone and Thevinone Derivatives

Bioorg. Med. Chem. **1997**, *5*, 369

János Marton,[a] Csaba Simon,[a] Sándor Hosztafi,[a] Zoltán Szabó,[a] Árpád Márki,[b] Anna Borsodi[b] and Sándor Makleit[c,*]
[a]Alkaloida Chemical Company Ltd., P.O. Box 1, Tiszavasvári, H-4440 Hungary; [b]Institute of Biochemistry, Biological Research Center, Hungarian Academy of Sciences, Post Office Box 521, Szeged, Hungary; [c]Department of Organic Chemistry, Lajos Kossuth University, Post Office Box 20, Debrecen, H-4010 Hungary

New N-substituted (20*R*)- and (20*S*)-phenyl-6,14-etheno-morphinan derivatives were synthesized. The biochemical investigation of these compounds showed that the affinities of these derivatives to the δ-opioid receptors were high, but the selectivity was low. μ-Opioid receptor specificity was observed in two cases.

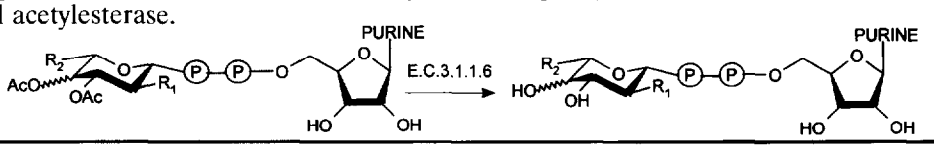


Convenient Chemoenzymatic Synthesis of β-Purine-diphosphate Sugars (GDP-fucose-analogues)

Bioorg. Med. Chem. **1997**, *5*, 383

Gabi Baisch and Reinhold Öhrlein*
Central Research Laboratories CIBA AG, Schwarzwaldallee 211, CH-4002 Basle, Switzerland

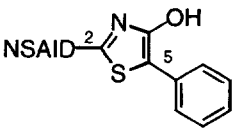
A versatile high-yielding synthesis of nucleotide–diphosphate sugars is presented. Chemically synthesized peracetylated β-fucose-1-phosphate derivatives were coupled to purine monophosphates via imidazolide activation. Complete deacetylations of the resulting purine–diphosphate sugars were achieved by treatment with commercial acetylesterase.



Conversion of Cyclooxygenase Inhibitors into Hydroxythiazole 5-Lipoxygenase Inhibitors

Bioorg. Med. Chem. **1997**, *5*, 393

Francis A. J. Kerdesky, Clint D. W. Brooks,* Keren I. Hulkower, Jennifer B. Bouska and Randy L. Bell
Immunoscience Research, D-47K, AP-10, Abbott Laboratories, 100 Abbott Park Road, Abbott Park, IL 60064-3500, U.S.A.



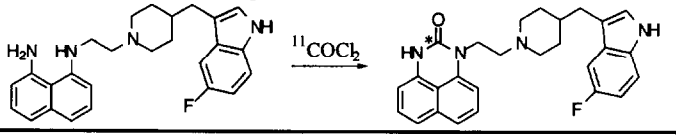
NSAID cyclooxygenase inhibitors such as naproxen, ibufenac, ibuprofen, and butibufen were transformed into 5-LO inhibitors by conversion to 4-hydroxythiazoles.

Synthesis of [^{11}C]RPR-72840A and its Evaluation as a Radioligand for the Serotonin Reuptake Site in Positron Emission Tomography

Bioorg. Med. Chem. **1997**, *5*, 397

D. Roeda,[a,*] B. Tavitian,[b] C. Coulon,[b] F. David,[a] F. Dollé,[a] C. Fuseau,[a] A. Jobert[b] and C. Crouzel[a]
[a]CEA and [b]INSERM U334, Service Hospitalier Frédéric Joliot, 4 Place du Général Leclerc, 91401 Orsay Cedex, France

The 5-HT reuptake inhibitor RPR-82740A was labelled with ^{11}C. [^{11}C]RPR-72840A was evaluated as a tracer for in vivo imaging with PET of the 5-HT reuptake site in baboon.

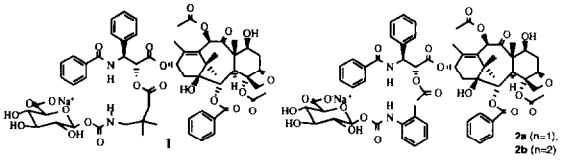


Synthesis and Biological Activity of β-Glucuronyl Carbamate-Based Prodrugs of Paclitaxel as Potential Candidates for ADEPT

Bioorg. Med. Chem. **1997**, *5*, 405

Dries B. A. de Bont,[a] Ruben G. G. Leenders,[a] Hidde J. Haisma,[b] Ida van der Meulen-Muileman[b] and Hans W. Scheeren[a,*]
[a]Department of Organic Chemistry, NSR Center for Molecular Structure, Design, and Synthesis, University of Nijmegen, Toernooiveld, 6525 ED, Nijmegen, The Netherlands; [b]Department of Medicinal Oncology, Academic Hospital Vrije Universiteit, De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands

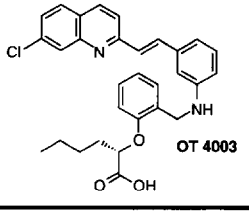
The synthesis of prodrugs **1** and **2a,b** is described. Enzyme catalyzed hydrolysis of the glucuronic acid moiety of **1** or **2b** results in the liberation of the parent drug paclitaxel via γ or δ lactam formation with half-lives of 45 min and 2 h. The prodrugs **1** and **2b** are two orders of magnitude less toxic than paclitaxel.



Discovery of OT4003, a Novel, Potent, and Orally Active cys-LT$_1$ Receptor Antagonist

Bioorg. Med. Chem. **1997**, *5*, 415

Ole Tværmose-Nielsen,[a] Schneur Rachlin,[a] Heinz Dannacher,[a] Fredrik Björkling,[a,*] Dorte Kirstein,[b] Erik Bramm,[c] Christian Kærgaard Nielsen,[c] Jens Thing Mortensen[d] and Lise Binderup[b]
Departments of [a]Chemistry, [b]Biochemistry, [c]Pharmacology, and [d]Toxicology, Leo Pharmaceutical Products, Industriparken 55, DK-2750 Ballerup, Denmark

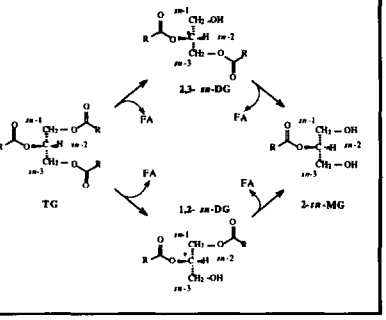


OT4003 was found to be a potent and selective inhibitor of [^{3}H]LTD$_4$ specific binding to guinea pig lung membranes (IC_{50} 2.4 ± 1.0 nM), and also a potent, orally active antagonist of LTD$_4$ induced bronchoconstriction in guinea pigs (ED_{50} 0.14 mg/kg; 4 h pretreatment). OT4003 was prepared using a short convergent synthesis, including an enzymatic resolution step.

In Vivo and In Vitro Studies on the Stereoselective Hydrolysis of Tri- and Diglycerides by Gastric and Pancreatic Lipases

Bioorg. Med. Chem. **1997**, *5*, 429

Frédéric Carrière,[a] Ewa Rogalska,[a] Claire Cudrey,[a] Francine Ferrato,[a] René Laugier[b] and Robert Verger[a,*]
[a]*Laboratoire de Lipolyse Enzymatique UPR 9025–CNRS. 31, chemin Joseph Aiguier, 13402 Marseille, France and* [b]*INSERM U-260, Boulevard Jean Moulin, 13006 Marseille, France*



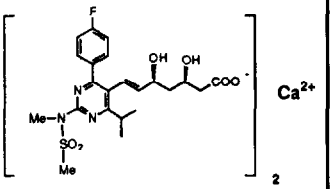
The stereoselectivity of dog gastric and dog pancreatic lipases was investigated both in vitro, under simulated physiological conditions, and in vivo, during the digestion of a liquid test meal.

Synthesis and Biological Activity of Methanesulfonamide Pyrimidine- and *N*-Methanesulfonyl Pyrrole-Substituted 3,5-Dihydroxy-6-heptenoates, a Novel Series of HMG-CoA Reductase Inhibitors

Bioorg. Med. Chem. **1997**, *5*, 437

Masamichi Watanabe,[a,*] Haruo Koike,[b] Teruyuki Ishiba,[b] Tetsuo Okada,[a] Shujiro Seo[a] and Kentaro Hirai[a]
[a]*Shionogi Research Laboratories, Shionogi and Company, Ltd., Fukushima-ku, Osaka 553, Japan;* [b]*Chemical Process Development Dept., Manufacturing Division, Shionogi & Co., Ltd., 1–3, Kuise Terajima 2-chome, Amagasaki, Hyogo 660, Japan*

The synthesis and biological evaluation of **3a** (S-4522) is described.



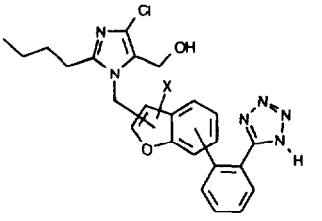
3a (S-4522)

The Conformation and Activity Relationship of Benzofuran Derivatives as Angiotensin II Receptor Antagonists

Bioorg. Med. Chem. **1997**, *5*, 445

Sung-eun Yoo,* Seung-Heui Lee, Soo-Kyung Kim and Sung-Hou Lee
Korea Research Institute of Chemical Technology, P.O. Box 107 Yusong, DaeDeog Science Town, TaeJon, Korea

We have synthesized various benzofuran derivatives and studied the relationship between the conformation and the angiotensin II receptor and antagonistic activity.



X= H or Br