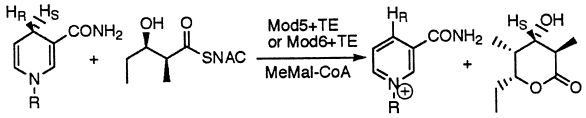
Bioorg. Med. Chem. Lett. 11 (2001) 1477

Erythromycin Biosynthesis. The 4-*pro-S* Hydride of NADPH is Utilized for Ketoreduction by Both Module 5 and Module 6 of the 6-Deoxyerythronolide B Synthase

Yifeng Yin,[a] Rajesh Gokhale,[b] Chaitan Khosla[b,c] and David E. Cane[a,*]

[a]*Department of Chemistry, Box H, Brown University, Providence, RI 02912-9108, USA*
[b]*Department of Chemical Engineering, Stanford University, Stanford, CA 94305-5025, USA*
[c]*Departments of Chemistry and Biochemistry, Stanford University, Stanford, CA 94305-5025, USA*

The stereochemistry of the ketoreductase-catalyzed reactions of modules 5 and 6 of the 6-deoxyerythronolide B synthase is reported.



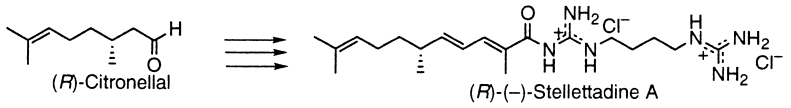
Bioorg. Med. Chem. Lett. 11 (2001) 1481

Synthesis and Absolute Configuration of Stellettadine A: A Marine Alkaloid That Induces Larval Metamorphosis in Ascidians

Dai Nozawa, Hirosato Takikawa and Kenji Mori*

Department of Chemistry, Faculty of Science, Science University of Tokyo, Kagurazaka 1-3, Shinjuku-ku, Tokyo 162-8601, Japan

Stellettadine A and its unnatural enantiomer were synthesized from the enantiomers of citronellal, and the natural alkaloid was shown to be *R*.



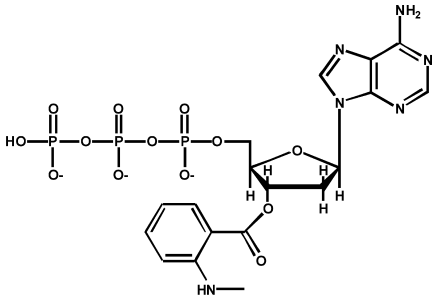
Bioorg. Med. Chem. Lett. 11 (2001) 1485

Active Site of an Aminoacyl–tRNA Synthetase Dissected by Energy-Transfer-Dependent Fluorescence

Tyzoon K. Nomanbhoy and Paul Schimmel*

The Skaggs Institute for Chemical Biology, The Scripps Research Institute, Beckman Center, 10550 North Torrey Pines Road, La Jolla, CA 92037, USA

The fluorescent nucleotide, *N*-methylanthraniloyl dATP (mdATP), is used in an energy-transfer-dependent fluorescence assay to investigate the active site of a specific aminoacyl–tRNA synthetase.



mdATP

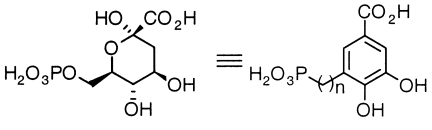
Bioorg. Med. Chem. Lett. 11 (2001) 1493

Aromatic Inhibitors of Dehydroquinate Synthase: Synthesis, Evaluation and Implications for Gallic Acid Biosynthesis

Sunil S. Chandran[a] and J. W. Frost[a,b,*]

[a]*Department of Chemistry, Michigan State University, East Lansing, MI 48823-1322, USA*
[b]*Department of Chemical Engineering, Michigan State University, East Lansing, MI 48823-1322, USA*

The synthesis and evaluation of novel aromatic inhibitors of the enzyme 3-dehydroquinate synthase are reported.



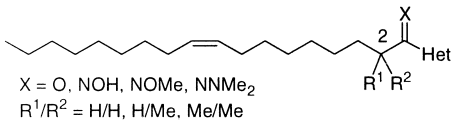
Bioorg. Med. Chem. Lett. 11 (2001) 1517

α-Keto Heterocycle Inhibitors of Fatty Acid Amide Hydrolase: Carbonyl Group Modification and α-Substitution

Dale L. Boger,* Hiroshi Miyauchi and Michael P. Hedrick

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

Two series of α-keto heterocycle inhibitors of FAAH which explore the importance of the electrophilic carbonyl and α-substitution are detailed.



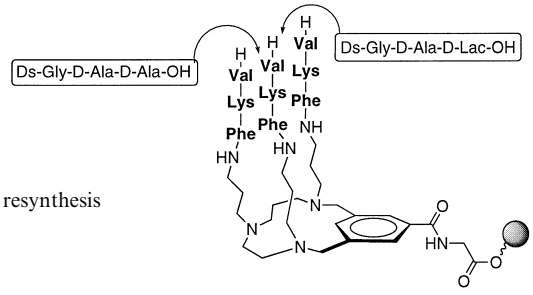
Bioorg. Med. Chem. Lett. 11 (2001) 1521

Bio-inspired Synthetic Receptor Molecules Towards Mimicry of Vancomycin

Menno C. F. Monnee, Arwin J. Brouwer, Linda M. Verbeek, André M. A. van Wageningen and Rob M. J. Liskamp*

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

Preparation of a 512-member synthetic receptor library followed by screening and resynthesis of selected members led to a bio-inspired mimic of vancomycin.

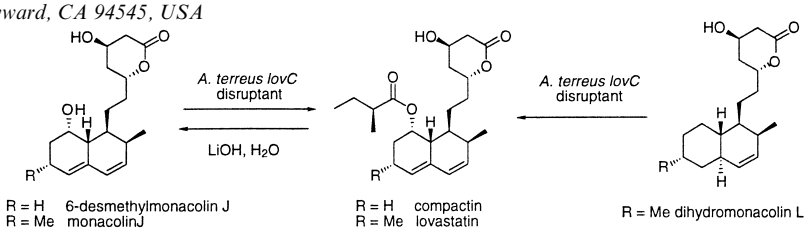


Bioorg. Med. Chem. Lett. 11 (2001) 1527

Conversion of Cyclic Nonaketides to Lovastatin and Compactin by a *lovC* Deficient Mutant of *Aspergillus terreus*

Karine Auclair,[a] Jonathan Kennedy,[b,c] C. Richard Hutchinson[b,c] and John C. Vederas[a,*]

[a]*Department of Chemistry, University of Alberta, Edmonton, Alberta, Canada T6G 2G2*
[b]*School of Pharmacy and Department of Bacteriology, University of Wisconsin, Madison, WI 53706, USA*
[c]*Kosan Biosciences Inc., 3832 Bay Center Place, Hayward, CA 94545, USA*

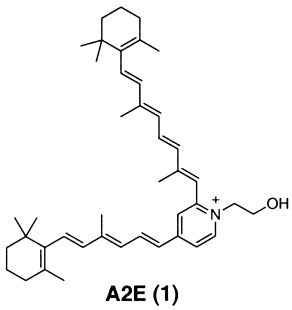


Bioorg. Med. Chem. Lett. 11 (2001) 1533

Fluorescent Pigments of the Retinal Pigment Epithelium and Age-Related Macular Degeneration

Shimon Ben-Shabat,[a] Craig A. Parish,[a] Masaru Hashimoto,[a] Jianghua Liu,[a] Koji Nakanishi[a,*] andJanet R. Sparrow[b,*]

[a]*Department of Chemistry, Columbia University, New York, NY 10027, USA*
[b]*Department of Ophthalmology, Columbia University, New York, NY 10032, USA*



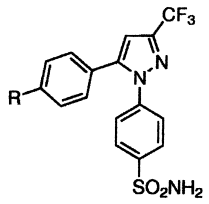
Bioorg. Med. Chem. Lett. 11 (2001) 1541

Rationale for the Observed COX-2/COX-1 Selectivity of Celecoxib from Monte Carlo Simulations

Melissa L. P. Price and William L. Jorgensen*

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

Computational studies have yielded an analysis of the contributions to the free energy difference between the binding of celecoxib to COX-1 and to COX-2. The energetic and structural results point to the Ile to Val mutation at residue 523 as the key contributor to COX-2 selectivity. The His to Arg change at residue 513 is less significant.



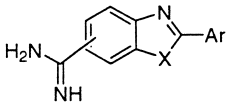
Bioorg. Med. Chem. Lett. 11 (2001) 1545

Amidino Benzimidazole Inhibitors of Bacterial Two-Component Systems

Michele A. Weidner-Wells, Kwasi A. Ohemeng, Van N. Nguyen, Stephanie Fraga-Spano, Mark J. Macielag, Harvey M. Werblood, Barbara D. Foleno, Glenda C. Webb, John F. Barrett and Dennis J. Hlasta*

Drug Discovery, The R. W. Johnson Pharmaceutical Research Institute, 1000 Route 202, Raritan, NJ 08869, USA

Novel benzimidazoles were identified as inhibitors of bacterial two-component systems with in vitro antibacterial activity. Modifications of the aryl group at C-2, the amidine moiety, and the heterocyclic core were investigated.



X = NH, NMe, O

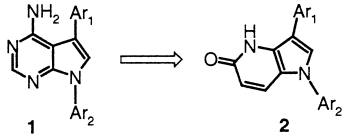
Bioorg. Med. Chem. Lett. 11 (2001) 1549

Cell Permeability as a Parameter for Lead Generation in the Protein Tyrosine Kinase Inhibition Field

Christos Papageorgiou,* Gian Camenisch and Xaver Borer

Novartis Pharma AG, WSJ350.3.14, CH-4002 Basel, Switzerland

Capitalizing on the properties of the protein tyrosine kinase inhibitors **1**, pyrrolopyridones **2** were designed and synthesized as potential leads for the development of novel compounds with improved cell permeability properties.



1 **2**

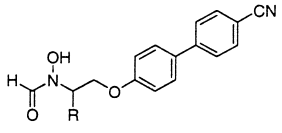
Bioorg. Med. Chem. Lett. 11 (2001) 1553

Biaryl Ether Retrohydroxamates as Potent, Long-Lived, Orally Bioavailable MMP Inhibitors

Michael R. Michaelides,* Joseph F. Dellaria, Jane Gong, James H. Holms, Jennifer J. Bouska, Jamie Stacey, Carol K. Wada, H. Robin Heyman, Michael L. Curtin, Yan Guo, Carole L. Goodfellow, Ildiko B. Elmore, Daniel H. Albert, Terrance J. Magoc, Patrick A. Marcotte, Douglas W. Morgan and Steven K. Davidsen

Cancer Research Area, Abbott Laboratories, Dept. 47J, Bldg. AP10, 100 Abbott Park Road, Abbott Park, IL 60064, USA

A series of biaryl ether retrohydroxates exhibiting potent MMP-2 inhibitory activity has been developed. Select compounds possess long $t_{1/2}$ (7 h) and high oral bioavailability (>95%).



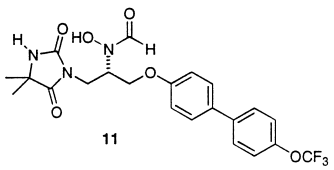
Bioorg. Med. Chem. Lett. 11 (2001) 1557

Discovery and Characterization of the Potent, Selective and Orally Bioavailable MMP Inhibitor ABT-770

Michael L. Curtin,* Alan S. Florjancic, H. Robin Heyman, Michael R. Michaelides, Robert B. Garland, James H. Holms, Douglas H. Steinman, Joseph F. Dellaria, Jane Gong, Carol K. Wada, Yan Guo, Ildiko B. Elmore, Paul Tapang, Daniel H. Albert, Terrance J. Magoc, Patrick A. Marcotte, Jennifer J. Bouska, Carole L. Goodfellow, Joy L. Bauch, Kennan C. Marsh, Douglas W. Morgan and Steven K. Davidsen

Cancer Research Area, Abbott Laboratories, Dept. 47J, Bldg. AP10, 100 Abbott Park Road, Abbott Park, IL 60064, USA

Modification of the biphenyl portion of MMP inhibitor **2a** gave analogue **2i** which is greater than 1000-fold selective against MMP-2 versus MMP-1. The stereospecific synthesis of both enantiomers of **2i** was achieved beginning with (*S*)- or (*R*)-benzyl glycidyl ether. The (*S*)-enantiomer, **11** (ABT-770), is orally bioavailable and efficacious in an in vivo model of tumor growth.



11

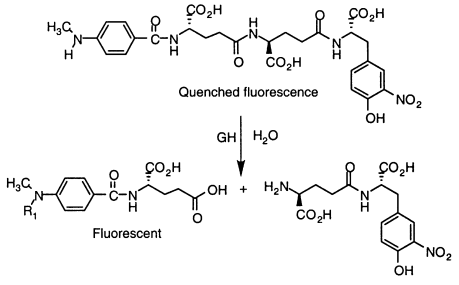
Bioorg. Med. Chem. Lett. 11 (2001) 1561

N-Me-*p*AB-Glu-γ-Glu-γ-Tyr(3-NO_2): An Internally Quenched Fluorogenic γ-Glutamyl Hydrolase Substrate

Jessica J. Pankuch and James K. Coward*

Departments of Chemistry and Medicinal Chemistry, University of Michigan, Ann Arbor, MI 48109-1055, USA

A γ-glutamyl tripeptide containing an internally quenched fluorophore has been synthesized and shown to be a substrate for rat γ-glutamyl hydrolase.



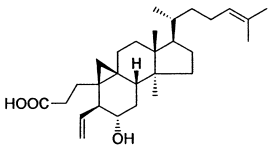
Bioorg. Med. Chem. Lett. 11 (2001) 1565

Cyclooxygenase-Inhibitory and Antioxidant Constituents of the Aerial Parts of *Antirhea acutata*

Dongho Lee,[a] Eun Jung Park,[a] Muriel Cuendet,[a] Franklin Axelrod,[b] Pedro I. Chavez,[c] Harry H. S. Fong,[a] John M. Pezzuto[a] andA. Douglas Kinghorn[a,*]

[a]*Program for Collaborative Research in the Pharmaceutical Sciences and Department of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, University of Illinois at Chicago, IL 60612, USA*
[b]*Department of Biology, University of Puerto Rico-Rio Piedras, San Juan, PR 00931, Puerto Rico*
[c]*College of Pharmacy-Glendale Campus, Midwestern University, Glendale, AZ 85308, USA*

Two new compounds, (6*S*)-hydroxy-29-*nor*-3,4-*seco*-cycloart-4(30),24-dien-3-oic acid (**1**) and 8-[1-(3,4-dihydroxyphenyl)-3-methyoxy-3-oxopropyl] epicatechin (**3**) were isolated by bioassay-guided fractionation from the aerial parts of *Antirhea acutata* (Rubiaceae). Compounds **1** and **3** showed moderate inhibitory activities in cyclooxygenase-1 and -2 assays (**1**, IC_{50} 43.7 and 4.7 μM, respectively), or in DPPH free-radical and cytochrome c reduction antioxidant assays (**3**, IC_{50} 29.1 and 16.3 μM, respectively).



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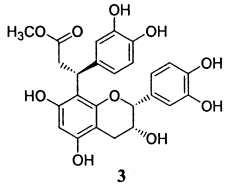


3

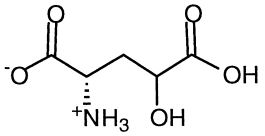
Bioorg. Med. Chem. Lett. 11 (2001) 1569

New Probes of the Agonist Binding Site of Metabotropic Glutamate Receptors

Anne-Sophie Bessis,[a] Jean Bolte,[b] Jean-Philippe Pin[c] and Francine Acher[a,*]

[a]*Laboratoire de Chimie et Biochimie Pharmacologiques et Toxicologiques, UMR8601-CNRS, Université René Descartes, 45 rue des Saints-Pères, 75270 Paris Cedex 06, France*
[b]*Laboratoire de Synthèse, Electrosynthèse et Etude de Systèmes d'Intérêt Biologique, UMR6504-CNRS, Université Blaise Pascal, 63177 Aubière Cedex, France*
[c]*Centre INSERM-CNRS de Pharmacologie-Endocrinologie, UPR9023-CNRS, 141 rue de la Cardonille, 34094 Montpellier Cedex 5, France*

The (2*S*,4*R*)- and (2*S*,4*S*)-4-hydroxyglutamates are agonists of $mGlu_{1a}R$, $mGlu_2R$, and $mGlu_{8a}R$. Activities are discussed on the basis of binding site models.



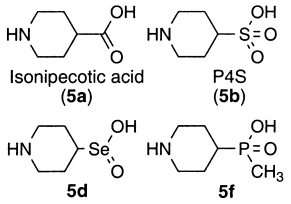
Bioorg. Med. Chem. Lett. 11 (2001) 1573

Bioisosteric Determinants for Subtype Selectivity of Ligands for Heteromeric $GABA_A$ Receptors

Bjarke Ebert,[a] Martin Mortensen,[a] Sally A. Thompson,[b] Jan Kehler,[a] Keith A. Wafford[b] andPovl Krogsgaard-Larsen[a,*]

[a]*The Centre for Drug Design and Transport, Departments of Pharmacology and Medicinal Chemistry, The Royal Danish School of Pharmacy, 2 Universitetsparken, DK-2100 Copenhagen, Denmark*
[b]*Department of Pharmacology, Merck Sharp and Dohme Research Laboratories, Terlings Park, Eastwick Road, Harlow CM20 2QR, Essex, UK*

The structure of the carboxyl bioisosteric groups is of major pharmacological importance. Whereas **5a** is a $GABA_A$ agonist, **5b** and **5d** are generally low-efficacy partial agonists, and **5f** is an antagonist.

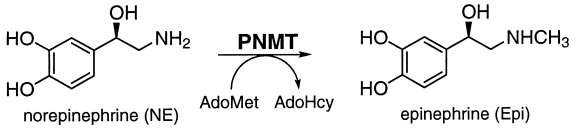


Bioorg. Med. Chem. Lett. 11 (2001) 1579

Phenylethanolamine *N*-Methyltransferase Kinetics: Bovine Versus Recombinant Human Enzyme

Gary L. Grunewald,[a,*] Michael J. McLeish[b] and Kevin R. Criscione[a]

[a]*Department of Medicinal Chemistry, University of Kansas, 4060 Malott Hall, 1251 Wescoe Hall Drive, Lawrence, KS 66045-7582, USA*
[b]*College of Pharmacy, University of Michigan, Ann Arbor, MI 48109, USA*



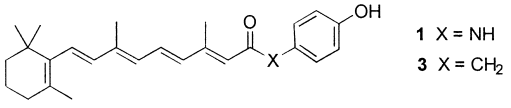
Bioorg. Med. Chem. Lett. 11 (2001) 1583

An Unhydrolyzable Analogue of *N*-(4-Hydroxyphenyl)retinamide: Synthesis and Preliminary Biological Studies

Kevin L. Weiss,[a] Galal Alshafie,[b] Jason S. Chapman,[c] Serena M. Mershon,[a] Hussein Abou-Issa,[b] Margaret Clagett-Dame[c] and Robert W. Curley, Jr.[a,*]

[a]*Division of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, The Ohio State University, Columbus, OH 43210, USA*
[b]*Department of Surgery, College of Medicine, The Ohio State University, Columbus, OH 43210, USA*
[c]*Department of Biochemistry, University of Wisconsin-Madison, Madison, WI 53706, USA*

The synthesis of the nonhydrolyzable analogue (**3**) of 4-HPR (**1**) is described as well as its antitumor activity, which is comparable to **1**.



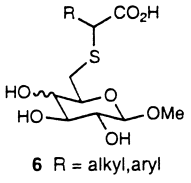
Bioorg. Med. Chem. Lett. 11 (2001) 1587

Synthesis of Novel Sialylmimetics as Biological Probes

Susan J. Bradley,[b] Ashmath Fazli,[b] Milton J. Kiefel[a,b] and Mark von Itzstein[a,b,*]

[a]*Centre for Biomolecular Science and Drug Discovery, Griffith University (Gold Coast Campus), PMB 50 Gold Coast Mail Centre, Queensland, 9726, Australia*
[b]*Department of Medicinal Chemistry, Monash University (Parkville Campus), 381 Royal Parade, Parkville, Victoria, 3052, Australia*

The synthesis of a range of sialylmimetics of the general structure **6** is described, and preliminary data describing their inhibition of rotaviral infection is presented.

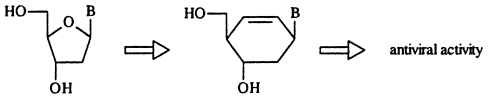


Bioorg. Med. Chem. Lett. 11 (2001) 1591

The Cyclohexene Ring as Bioisostere of a Furanose Ring: Synthesis and Antiviral Activity of Cyclohexenyl Nucleosides

Piet Herdewijn[a,*] and Erik De Clercq[b]

[a]*Laboratory of Medicinal Chemistry, K.U. Leuven, Rega Institute for Medical Research, Minderbroedersstraat 10, B-3000 Leuven, Belgium*
[b]*Laboratory of Antiviral Chemotherapy, K.U. Leuven, Rega Institute for Medical Research, Minderbroedersstraat 10, B-3000 Leuven, Belgium*

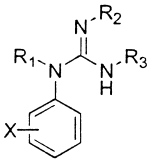


Bioorg. Med. Chem. Lett. 11 (2001) 1599

The Binding of Arylguanidines at 5-HT_3 Serotonin Receptors: A Structure–Affinity Investigation

Małgorzata Dukat,[a] Young-na Choi,[a] Milt Teitler,[b] Ann Du Pre,[b] Kathy Herrick-Davis,[b] Carol Smith[b] andRichard A. Glennon[a,*]

[a]*Department of Medicinal Chemistry, School of Pharmacy, Virginia Commonwealth University, Richmond, VA 23298-0540, USA*
[b]*Center for Neuropharmacology and Neuroscience, Albany Medical College, Albany, NY 12208, USA*



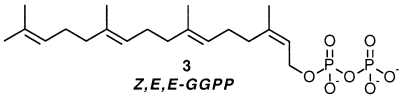
On the basis of comparative structure–affinity studies, arylguanidines and arylbiguanides are proposed to bind at 5-HT_3 receptors in such a manner that they likely share common aryl binding sites.

Bioorg. Med. Chem. Lett. 11 (2001) 1605

Synthesis and Evaluation of GGPP Geometric Isomers: Divergent Substrate Specificities of FTase and GGTase I

Todd J. Zahn,[a] Jessica Whitney,[a] Carolyn Weinbaum[b] and Richard A. Gibbs[a,*]

[a]*Department of Pharmaceutical Sciences, College of Pharmacy and AHP, Wayne State University, Detroit, MI 48202, USA*
[b]*Department of Pharmacology and Cancer Biology, Duke University Medical Center, Durham, NC 27710, USA*



GGTase I: IC_{50} = 100 nM
FTase: K_m = 21 nM; k_{rel} = 0.67

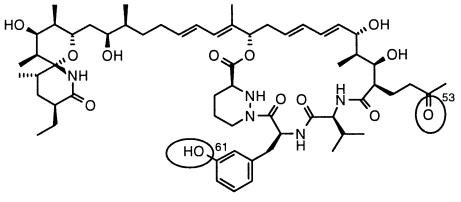
Bioorg. Med. Chem. Lett. 11 (2001) 1609

Synthesis of Derivatives of the Novel Cyclophilin-Binding Immunosuppressant Sanglifehrin A with Reduced Numbers of Polar Functions

Rolf Bänteli,* Jürgen Wagner and Gerhard Zenke

Novartis Pharma AG, CH-4002 Basel, Switzerland

The syntheses and the biological activities of 53-deoxo sanglifehrin A and 61-deoxy octahydrosanglifehrin A are described. Our results indicate that the 53-keto group is not necessary for immunosuppressive activity, while the 61 hydroxy group is required.



sanglifehrin A, **1**

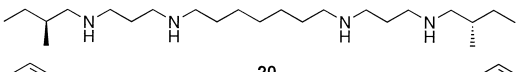
Bioorg. Med. Chem. Lett. 11 (2001) 1613

Novel Alkylpolyamine Analogues That Possess Both Antitrypanosomal and Antimicrosporidial Activity

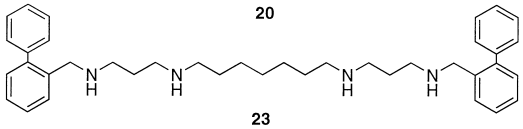
Yu Zou,[a] Zhiqian Wu,[a] Nilantha Sirisoma,[a] Patrick M. Woster,[a,*] Robert A. Casero, Jr.,[b] Louis M. Weiss,[c] Donna Rattendi,[d] Schennella Lane[d] and Cyrus J. Bacchi[d]

[a]*Department of Pharmaceutical Sciences, Wayne State University, Detroit, MI 48202, USA*
[b]*The Johns Hopkins Oncology Center, 424 N. Bond St., Baltimore, MD 21231, USA*
[c]*Albert Einstein College of Medicine, Bronx, NY 10461, USA*
[d]*Haskins Laboratories and Department of Biology, Pace University, New York, NY 10038, USA*

The synthesis and evaluation of a series of bis(alkyl)-polyamine analogues is described. These analogues were synthesized by a facile route, and evaluated as antiparasitic agents in vitro and in vivo. Compound **20** possesses significant antitrypanosomal activity in vitro, while analogue **23** is effective against *Microsporidia* in vitro, and is curative for microsporidiosis in a murine model of infection.



20



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