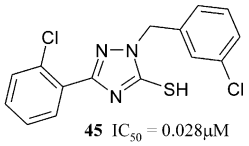
Hit-to-Lead Studies: The Discovery of Potent, Orally Bioavailable Triazolethiol CXCR2 Receptor Antagonists

Bioorg. Med. Chem. Lett. 13 (2003) 2625

Andrew Baxter,* Colin Bennion, Janice Bent, Kerry Boden, Steve Brough, Anne Cooper, Elizabeth Kinchin, Nicholas Kindon, Tom McInally, Mike Mortimore, Bryan Roberts and John Unitt

AstraZeneca R&D Charnwood, Bakewell Road, Loughborough LE11 5RH, UK

A Hit-to-Lead programme was carried out resulting in the discovery of the potent, orally bioavailable CXCR2 antagonist **45**.



45 $IC_{50} = 0.028\mu M$

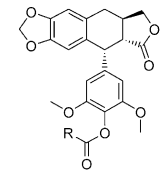
Antitumor Activity of Unsaturated Fatty Acid Esters of 4′-Demethyldeoxypodophyllotoxin

Bioorg. Med. Chem. Lett. 13 (2003) 2629

Young-Jae You, Yong Kim, Nguyen-Hai Nam and Byung-Zun Ahn*

College of Pharmacy, Chungnam National University, Taejon 305-764, South Korea

Unsaturated fatty acid esters of 4′-demethyldeoxypodophyllotoxin (DDPT) were prepared and tested for antitumor activity. The esters showed more potent in vivo antitumor activity despite the lower in vitro activity than DDPT. Especially, the ester of all-*cis*-11,14-eicosadienoic acid was much better in antitumor activity than VP-16 (IR, 83% vs 60%) without loss of body weight.



RCOOH: unsaturated fatty acid

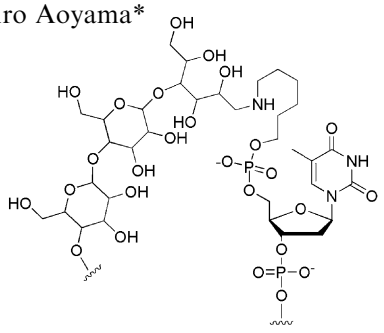
Facile Preparation of DNA-Tagged Carbohydrates

Bioorg. Med. Chem. Lett. 13 (2003) 2633

Shinsuke Sando, Kazuki Matsui, Yusuke Niinomi, Nobuhiko Sato and Yasuhiro Aoyama*

Department of Synthetic Chemistry and Biological Chemistry, Graduate School of Engineering, Kyoto University, Kyoto 606-8501, Japan

A simple and convenient method to conjugate carbohydrate with DNA-tag is reported.



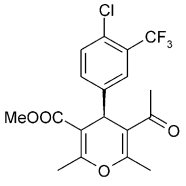
4-Phenyl-4H-pyrans as IK_{Ca} Channel Blockers

Bioorg. Med. Chem. Lett. 13 (2003) 2637

Klaus Urbahns,[a,*] Ervin Horváth,[b] Johannes-Peter Stasch[c] and Frank Mauler[b]

[a]*Institute of Medicinal Chemistry, Pharma Research Center, Bayer AG, D-42096 Wuppertal, Germany*
[b]*Institute of CNS Research, Pharma Research Center, Bayer AG, D-42096 Wuppertal, Germany*
[c]*Institute of Cardiovascular Research, Pharma Research Center, Bayer AG, D-42096 Wuppertal, Germany*

4-Phenyl-4H-pyrans have been identified as potent and specific IK_{Ca} channel blockers. Their synthesis and structure–activity relationships are described. A selected derivative, *rac*-**11**, reduces the infarct volume in a rat subdural hematoma model of traumatic brain injury after iv administration.



rac-**11**, IC_{50} = 8 nM

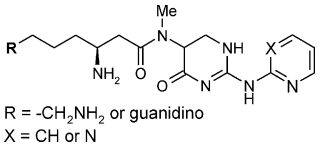
Bioorg. Med. Chem. Lett. 13 (2003) 2641

Pyrimidinone Antibiotics—Heterocyclic Analogues with Improved Antibacterial Spectrum

Michael Brands,* Yolanda Cancho Grande, Rainer Endermann, Reinhold Gahlmann, Jochen Krüger and Siegfried Raddatz

BAYER AG, Business Group Pharma, Research, D-42096 Wuppertal, Germany

We report the synthesis and pharmacological evaluation of new derivatives of the natural dipeptide antibiotic TAN 1057 A,B containing heterocycles either in the β-amino acid side chain or as mimics of the urea function. In the course of this program we identified novel analogues that display activity towards a broader panel of Gram-positive bacteriae.



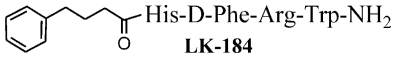
Bioorg. Med. Chem. Lett. 13 (2003) 2647

Sub-Nanomolar hMC1R Agonists by End-Capping of the Melanocortin Tetrapeptide His-D-Phe-Arg-Trp-NH_2

L. N. Koikov,[a,*] F. H. Ebetino,[b] M. G. Solinsky,[b] D. Cross-Doersen[b] and J. J. Knittel[a]

[a]*College of Pharmacy, University of Cincinnati, Cincinnati, OH 45267, USA*
[b]*Procter and Gamble Pharmaceuticals, Mason, OH 45040, USA*

Of the 23 R′-X-His-D-Phe-Arg-Trp-NH_2 (X = CO, SO_2) tested at the human (h)MC1, hMC3, and hMC4 receptors (R), the most potent MC1R agonist (EC_{50} 0.01 nM) is LK-184 (**19**). Its MC1R versus MC3/4R selectivity is ca. 1:500. SAR and a generalized hMCR model is discussed.

(19) 

LK-184

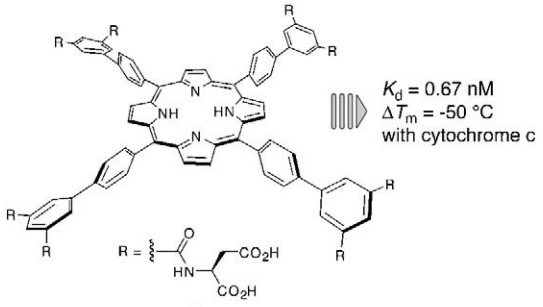
Bioorg. Med. Chem. Lett. 13 (2003) 2651

Tetrabiphenylporphyrin-Based Receptors for Protein Surfaces Show Sub-nanomolar Affinity and Enhance Unfolding

Toshihiro Aya and Andrew D. Hamilton*

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

A family of tetrabiphenylporphyrin-based receptors has been synthesized. Receptor **7** showed sub-nanomolar affinity (K_d = 0.67 nM) in binding to the surface of cytochrome *c*. In addition, a stoichiometric amount of the receptor **7** caused a lowering of the T_m of cytochrome *c* from 85 to 35 °C.



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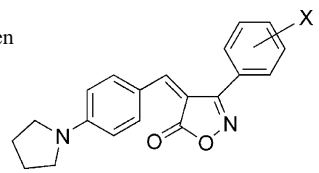
Bioorg. Med. Chem. Lett. 13 (2003) 2655

Anti-Androgens with Full Antagonistic Activity Toward Human Prostate Tumor LNCaP Cells with Mutated Androgen Receptor

Toshiyasu Ishioka, Aya Tanatani, Kazuo Nagasawa and Yuichi Hashimoto*

Institute of Molecular & Cellular Biosciences, The University of Tokyo, 1-1-1 Yayoi, Bunkyo-ku, Tokyo 113-0032, Japan

(*Z*)-4-(4-Pyrrolidinophenylmethylene)-3-phenyl-5(4*H*)-isoxazolones have been developed as full androgen antagonists, which are active towards LNCaP cells expressing point-mutated, constitutively active androgen receptor.



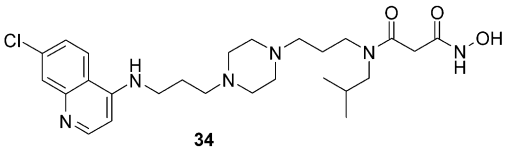
Bioorg. Med. Chem. Lett. 13 (2003) 2659

Design, Synthesis and Antimalarial Activity of Novel, Quinoline-Based, Zinc Metallo-Aminopeptidase Inhibitors

Marion Flipo,[a] Isabelle Florent,[b] Philippe Grellier,[b] Christian Sergheraert[a] and Rebecca Deprez-Poulain[a,*]

[a]*UMR CNRS 8525, Institut Pasteur et Institut de Biologie de Lille, Université de Lille 2, Lille, France*
[b]*USM 0504 'Biologie fonctionnelle des protozoaires', Département 'Régulations, Développement, Diversité Moléculaire', Muséum National d'Histoire Naturelle, FR CNRS 63 Paris, France*

A new series of antimalarials consisting in 45 potential inhibitors of PfA-M1 is described.



34

IC_{50} (PfA-M1) = 0.854 μM

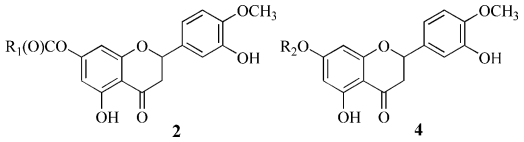
Bioorg. Med. Chem. Lett. 13 (2003) 2663

Hypocholesterolemic Activity of Hesperetin Derivatives

Tae-Sook Jeong,[a] Eun Eai Kim,[b] Chul-Ho Lee,[a] Jung-Hoon Oh,[a] Surk-Sik Moon,[c] Woo Song Lee,[a] Goo-Taeg Oh,[a] Sangku Lee[a,*] and Song-Hae Bok[a,b]

[a]*Korea Research Institute of Bioscience and Biotechnology, 52 Oun, Yusong, Taejon 305-333, Republic of Korea*
[b]*Bionutrigen Company, Ltd., 52 Oun, Taejon 305-333, Republic of Korea*
[c]*Department of Chemistry, Kongju National University, Kongju 314-701, Republic of Korea*

A series of hesperetin 7-*O*-esters **2** and hesperetin 7-*O*-ethers **4** were prepared and evaluated as hypocholesterolemic agents.



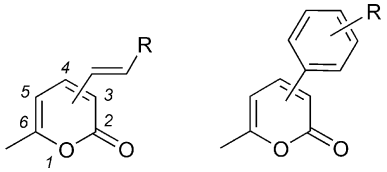
2 **4**

Bioorg. Med. Chem. Lett. 13 (2003) 2667

Suzuki Cross-Coupling Approaches to the Synthesis of Bioactive 3-Substituted and 5-Substituted-4-methoxy-6-methyl-2-pyrones

Lester R. Marrison,[a] Julia M. Dickinson[a] and Ian J. S. Fairlamb[b,*]

[a]*Department of Chemistry and Materials, John Dalton Building, The Manchester Metropolitan University, Chester Street, Manchester M1 5GD, UK*
[b]*Department of Chemistry, University of York, Heslington, York YO10 5DD, UK*



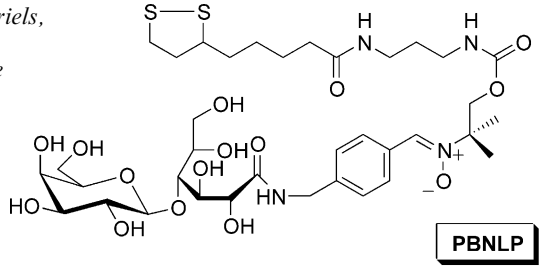
Bioorg. Med. Chem. Lett. 13 (2003) 2673

Synthesis and Antioxidant Efficiency of a New Amphiphilic Spin-Trap Derived from PBN and Lipoic Acid

G. Durand,[a] A. Polidori,[a,*] J. P. Salles,[b] M. Prost,[c] P. Durand[c] and B. Pucci[a,*]

[a]*Laboratoire de Chimie BioOrganique et des Systèmes Moléculaire Vectoriels, Faculté des Sciences, 33 rue Louis Pasteur, 84000 Avignon, France*
[b]*Targeting System Pharma, 830 chemin de vergon, 13510 Eguilles, France*
[c]*Centre Européen de Recherches et d'Analyses, 3 rue des mardors, 21560 Couternon, France*

The synthesis of a new amphiphilic antioxidant derived from both α-phenyl-*N*-*tert*-butyl nitrone (PBN) and lipoic acid is reported. The PBNLP induces a protection of erythrocytes against exogenous free radicals higher than PBN and lipoic acid alone and than their water-soluble derivatives in admixtures.



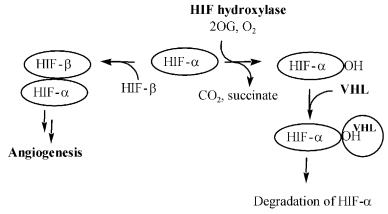
PBNLP

Bioorg. Med. Chem. Lett. 13 (2003) 2677

2-Oxoglutarate Analogue Inhibitors of HIF Prolyl Hydroxylase

David R. Mole,[a] Imre Schlemminger,[b] Luke A. McNeill,[b] Kirsty S. Hewitson,[a] Christopher W. Pugh,[a] Peter J. Ratcliffe[a] and Christopher J. Schofield[b]

[a]*Wellcome Trust Centre for Human Genetics, Roosevelt Drive, Oxford OX3 7BN, UK*
[b]*Oxford Centre for Molecular Sciences, Dyson Perrins Laboratory, South Parks Road, Oxford OX1 3QY, UK*



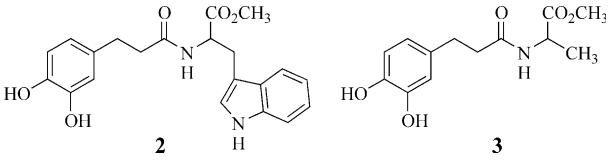
Bioorg. Med. Chem. Lett. 13 (2003) 2681

Anti-atherogenic Effects of 3,4-Dihydroxy Hydrocinnamides

Sangku Lee,[a] Chul-Ho Lee,[a] Jung-Hoon Oh,[a] Eun Eai Kim,[b] Yang-Kyu Choi,[a] Eun-Hee Kim,[a] Woo Song Lee,[a] Song-Hae Bok[a,b] and Tae-Sook Jeong[a,*]

[a]*Korea Research Institute of Bioscience and Biotechnology, 52 Oun, Yusong, Daejon 305-333, South Korea*
[b]*Bionutrigen Company, Ltd., 52 Oun, Daejon 305-333, South Korea*

3,4-Dihydroxy hydrocinnamides **2** and **3** exhibited anti-atherogenic effects in cholesterol-fed rabbits.

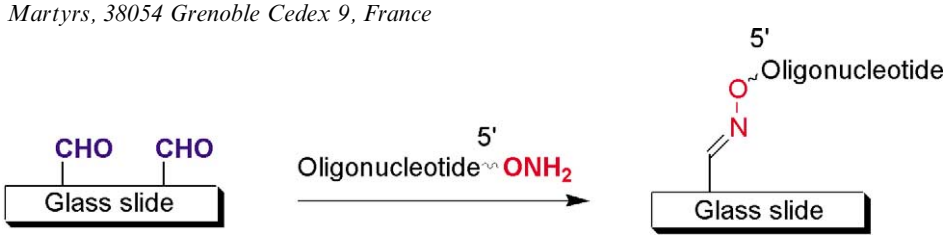


Bioorg. Med. Chem. Lett. 13 (2003) 2683

Oxime Bond Formation for the Covalent Attachment of Oligonucleotides on Glass Support

Eric Defrancq,[a,*] Antoine Hoang,[b] Françoise Vinet[b] and Pascal Dumy[a]

[a]*LEDSS, UMR CNRS 5616, Université Joseph Fourier, BP 53, 38041 Grenoble Cedex 9, France*
[b]*LETI-CEA-Grenoble 17, rue des Martyrs, 38054 Grenoble Cedex 9, France*

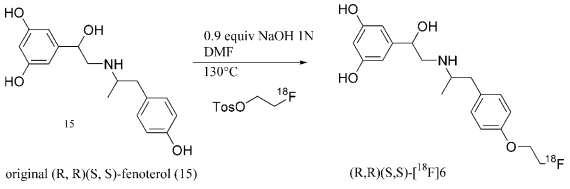


Bioorg. Med. Chem. Lett. 13 (2003) 2687

Synthesis and Preliminary Evaluation of (*R*,*R*)(*S*,*S*) 5-(2-(2-[4-(2-[^{18}F]fluoroethoxy)phenyl]-1-methylethylamino)-1-hydroxyethyl)-benzene-1,3-diol ([^{18}F]FEFE) for the In Vivo Visualisation and Quantification of the β2-Adrenergic Receptor Status in Lung

Esther Schirrmacher,[a,*] Ralf Schirrmacher,[a] Oliver Thews,[b] Wolfgang Dillenburg,[b] Andreas Helisch,[c] Ignatz Wessler,[d] Roland Buhl,[e] Sabine Höhnemann,[a] Hans-Georg Buchholz,[c] Peter Bartenstein,[c] Hans-Jürgen Machulla[f] and Frank Rösch[a]

[a]*Institute of Nuclear Chemistry, University of Mainz, Fritz Strassmann-Weg 2, D-55128 Mainz, Germany*
[b]*Institute of Physiological Chemistry, University of Mainz, Mainz, Germany*
[c]*Department of Nuclear Medicine, University of Mainz, Mainz, Germany*
[d]*Institute of Pharmacology, University of Mainz, Mainz, Germany*
[e]*III. Medical Clinic, University of Mainz, Mainz, Germany*
[f]*Section Radiopharmaceutical Chemistry, University of Tuebingen, Tuebingen, Germany*



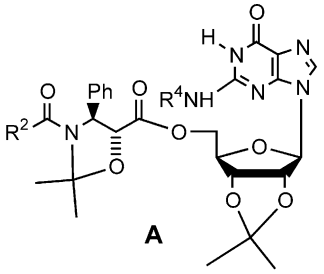
Bioorg. Med. Chem. Lett. 13 (2003) 2693

The Design and Synthesis of Guanosine Compounds with In Vitro Activity against the Colon Cancer Cell Line SW480: Non-Taxane Derived Mimics of Taxol?

Joshua Howarth,[a,*] Padraic Kenny,[a] Susan McDonnell[b] and Aine O'Connor[b]

[a]*School of Chemical Sciences, Dublin City University, Dublin 9, Ireland*
[b]*School of Biotechnology, Dublin City University, Dublin 9, Ireland*

We have synthesized four compounds, based on protected guanosine coupled to taxol isoserine side chain, of type **A**. These molecules show in vitro anti-cancer activity against the colon cancer cell line SW480 that their constituent parts do not.



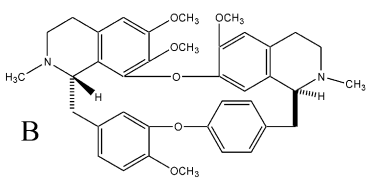
Bioorg. Med. Chem. Lett. 13 (2003) 2699

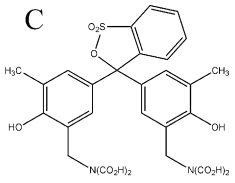
Search Compounds with Antimicrobial Activity by Applying Molecular Topology to Selected Quinolones

S. Mut-Ronda,[a] M. T. Salabert-Salvador,[a] M. J. Duart[b] and G. M. Antón-Fos[c,*]

[a]*Unidad de Investigación de Diseño de Fármacos y Conectividad Molecular, Departamento de Química Física, Universidad de Valencia, Valencia, Spain*
[b]*Departamento de Fisiología, Farmacología y Toxicología, Universidad Cardenal Herrera-CEU, Moncada, Spain*
[c]*Departamento de Química, Bioquímica y Biología Molecular, Universidad Cardenal Herrera-CEU, Moncada, Spain*

Molecular topology was used to obtain the Xylenol Orange (B) and [(±)-2-(2,4,5,7-tetranitro-9-fluorenyllideneaminooxy)] propionic acid (C) with antimicrobial activity.





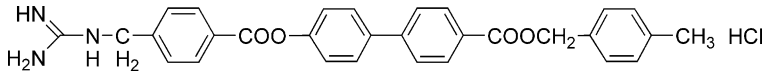
Bioorg. Med. Chem. Lett. 13 (2003) 2703

A Specific Anti-*Helicobacter pylori* Agent NE2001: Synthesis and Its Effect on the Growth of *H. pylori*

Ni Cheng,[a] Jian-Shu Xie,[b] Min-Yue Zhang,[a] Chang Shu[a] and De-Xu Zhu[a,*]

[a]*State Key Laboratory of Pharmaceutical Biotechnology, Department of Biochemistry, Nanjing University, Nanjing 210093, PR China*
[b]*Shanghai East Best Biopharmaceutical Enterprises Co., Ltd., Shanghai, PR China*

A novel anti-*Helicobacter pylori* agent NE2001 was synthesized and its effect on the *H. pylori* was examined.



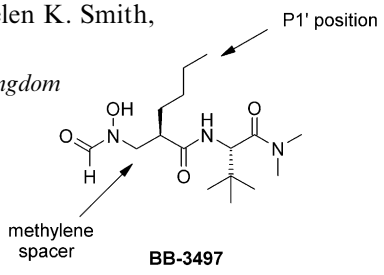
Bioorg. Med. Chem. Lett. 13 (2003) 2709

Structure–Activity Relationships of the Peptide Deformylase Inhibitor BB-3497: Modification of the Methylene Spacer and the P1′ Side Chain

Stephen J. Davies,* Andrew P. Ayscough, R. Paul Beckett, Ryan A. Bragg, John M. Clements, Sheila Doel, Christine Grew, Steven B. Launchbury, Gemma M. Perkins, Lisa M. Pratt, Helen K. Smith, Zoë M. Spavold, S. Wayne Thomas, Richard S. Todd and Mark Whittaker

British Biotech Pharmaceuticals Limited, Watlington Road, Oxford OX4 6LY, United Kingdom

Structural modifications to the peptide deformylase inhibitor BB-3497 are described



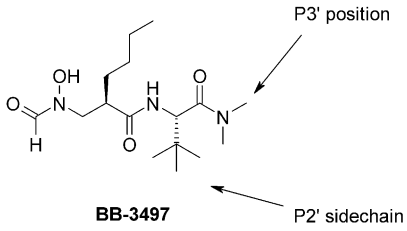
Bioorg. Med. Chem. Lett. 13 (2003) 2715

Structure–Activity Relationships of the Peptide Deformylase Inhibitor BB-3497: Modification of the P2′ and P3′ Side Chains

Stephen J. Davies,* Andrew P. Ayscough, R. Paul Beckett, John M. Clements, Sheila Doel, Lisa M. Pratt, Zoë M. Spavold, S. Wayne Thomas and Mark Whittaker

British Biotech Pharmaceuticals Limited, Watlington Road, Oxford OX4 6LY, UK

Structural modifications to the peptide deformylase inhibitor BB-3497 are described, highlighting the initial SAR around this lead for modifications to both the P2′ and P3′ side chains.



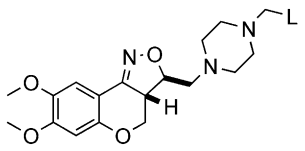
Bioorg. Med. Chem. Lett. 13 (2003) 2719

Synthesis of 3a,4-Dihydro-3*H*-[1]benzopyrano[4,3-*c*]isoxazoles, Displaying Combined 5-HT Uptake Inhibiting and α_2-Adrenoceptor Antagonistic Activities: A Novel Series of Potential Antidepressants

J. Ignacio Andrés,[a,*] Jesús Alcázar,[a] José M. Alonso,[a] Rosa M. Alvarez,[a] José M. Cid,[a] Ana I. De Lucas,[a] Javier Fernández,[a] Sonia Martínez,[a] Carmen Nieto,[a] Joaquín Pastor,[a] Margot H. Bakker,[b] Ilse Biesmans,[b] Lieve I. Heylen[b] and Anton A. Megens[b]

[a]*Johnson & Johnson Pharmaceutical Research & Development, Division of Janssen-Cilag, Medicinal Chemistry Department, Jarama s/n, 45007 Toledo, Spain*
[b]*Johnson & Johnson Pharmaceutical Research & Development, Division of Janssen Pharmaceutica N.V., Turnhoutseweg 30, B2340 Beerse, Belgium*

The synthesis and preliminary pharmacological activity of a series of novel 3-piperazinylmethyl-3a,4-dihydro-3H-[1]benzopyrano[4,3-*c*]isoxazoles as novel dual 5-HT reuptake inhibitors and α2-adrenoceptor antagonists are described.



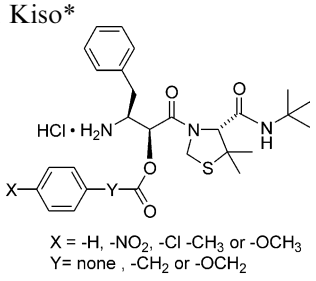
Bioorg. Med. Chem. Lett. 13 (2003) 2727

Effect of the Acyl Groups on *O*→*N* Acyl Migration in the Water-Soluble Prodrugs of HIV-1 Protease Inhibitor

Yoshio Hamada, Hikaru Matsumoto, Tooru Kimura, Yoshio Hayashi and Yoshiaki Kiso*

Department of Medicinal Chemistry, Center for Frontier Research in Medicinal Science, Kyoto Pharmaceutical University, Yamashina-ku, Kyoto 607-8412, Japan

To understand the effects of the acyl groups on the migration rate in the water-soluble prodrugs of HIV-1 protease inhibitors based on *O*→*N* intramolecular acyl migration reaction, we synthesized and evaluated phenoxyacetyl-type, phenylacetyl-type and benzoyl-type prodrugs.



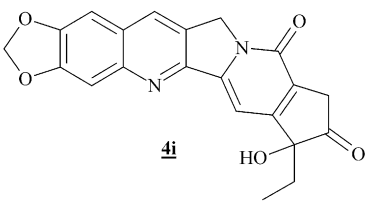
Bioorg. Med. Chem. Lett. 13 (2003) 2731

Synthesis and Pharmacological Evaluation of Novel Non-lactone Analogues of Camptothecin

Patrick Hautefaye,[a] Bernard Cimetière,[a] Alain Pierré,[a] Stéphane Léonce,[a] John Hickman,[a] William Laine,[b] Christian Bailly[b] and Gilbert Lavielle[a,*]

[a]*Institut de Recherches Servier, 125 Chemin de Ronde, 78290 Croissy sur Seine, France*
[b]*Laboratoire de Pharmacologie Antitumorale du Centre Oscar Lambert, INSERM U-524, IRCL, Place de Verdun, 59045 Lille, France*

Novel non-lactone analogues of camptothecin are potent inhibitors of topoisomerase I and exhibit cytotoxic activities.

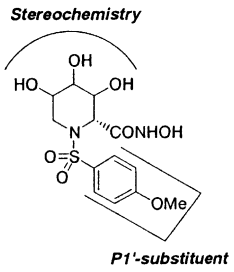


Bioorg. Med. Chem. Lett. 13 (2003) 2737

Structure–Activity Relationships of Azasugar-Based MMP/ADAM Inhibitors

Hideki Moriyama,[a,b] Takahiro Tsukida,[a,b,*] Yoshimasa Inoue,[b] Hirosato Kondo,[b] Kohichiro Yoshino[b] and Shin-Ichiro Nishimura[c,*]

[a]*Japan Bioindustry Association, Hokkaido Collaboration Center, N-21, W-12, Kita-Ku, Sapporo 001-0021, Japan*
[b]*R&D Laboratories, Nippon Organon K.K., 1-5-90, Tomobuchi-cho, Miyakojima-ku, Osaka 534–0016, Japan*
[c]*Division of Biological Sciences, Graduate School of Science, Hokkaido University, N-21, W-12, Kita-Ku, Sapporo 001-0021, Japan*



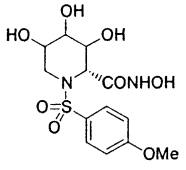
Bioorg. Med. Chem. Lett. 13 (2003) 2741

Design, Synthesis and Evaluation of Novel Azasugar-Based MMP/ADAM Inhibitors

Hideki Moriyama,[a,b] Takahiro Tsukida,[a,b,*] Yoshimasa Inoue,[b] Hirosato Kondo,[b] Kohichiro Yoshino[b] and Shin-Ichiro Nishimura[c,*]

[a]*Japan Bioindustry Association, Hokkaido Collaboration Center, N-21, W-12, Kita-Ku, Sapporo 001-0021, Japan*
[b]*R&D Laboratories, Nippon Organon K.K., 1-5-90, Tomobuchi-cho, Miyakojima-ku, Osaka 534-0016, Japan*
[c]*Division of Biological Sciences, Graduate School of Science, Hokkaido University, N-21, W-12, Kita-Ku, Sapporo 001-0021, Japan*

In this report, we demonstrate novel MMP/ADAM inhibitor based on azasugar scaffold.



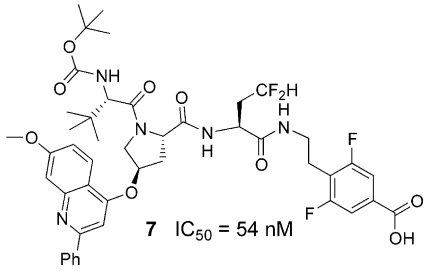
Bioorg. Med. Chem. Lett. 13 (2003) 2745

Novel, Potent Phenethylamide Inhibitors of the Hepatitis C Virus (HCV) NS3 Protease: Probing the Role of P2 Aryloxyprolines with Hybrid Structures

Federica Orvieto, Uwe Koch, Victor G. Matassa and Ester Muraglia*

Medicinal Chemistry Department, IRBM-MRL Rome, V. Pontina Km 30,600, 00040 Pomezia, Rome, Italy

Synthesis of HCV NS3 protease/NS4A inhibitors led to **7** (IC_{50} 54 nM). Molecular modeling suggests that this potent tripeptide inhibitor exploits interactions in the S1′, S1, S2, S3 and S4 sites of the protease.



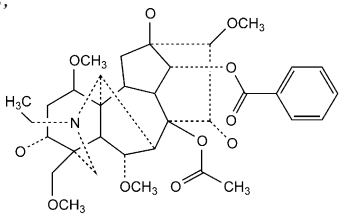
Bioorg. Med. Chem. Lett. 13 (2003) 2749

Topological Virtual Screening: A Way to Find New Anticonvulsant Drugs from Chemical Diversity

L. Bruno-Blanch,[a] J. Gálvez[b] and R. García-Domenech[b,*]

[a]*Medicinal Chemistry Laboratory, Biological Sciences Department, Faculty of Exact Sciences, National University of La Plata, 47 and 115 Street, B1900AVV, La Plata, Argentina*
[b]*Molecular Connectivity and Drug Design Research Unit, Physical Chemistry Department, Faculty of Pharmacy, University of Valencia, Avda. V.A. Estellés, s/n, CP-46100-Burjassot, Valencia, Spain*

A topological virtual screening test is presented, which is capable of identifying new drug leaders with anticonvulsant activity. On the basis of this model, 41 new structures with anticonvulsant activity have been identified.

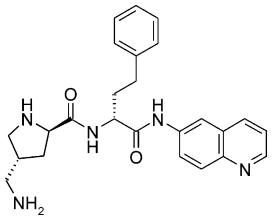


Bioorg. Med. Chem. Lett. 13 (2003) 2755

Conformationally-Restricted Analogues of Efflux Pump Inhibitors that Potentiate the Activity of Levofloxacin in *Pseudomonas aeruginosa*

Thomas E. Renau,[a,*] Roger Léger,[a] Lubov Filonova,[a] Eric M. Flamme,[a] Michael Wang,[a] Rose Yen,[a] Deidre Madsen,[a] David Griffith,[a] Suzanne Chamberland,[a] Michael N. Dudley,[a] Ving J. Lee,[a] Olga Lomovskaya,[a] William J. Watkins,[a] Toshiharu Ohta,[b] Kiyoshi Nakayama[b] and Yohei Ishida[b]

[a]*Essential Therapeutics, Inc., 850 Maude Avenue, Mountain View, CA 94043, USA*
[b]*New Product Research Laboratories I, Daiichi Pharmaceutical Co. Ltd., 1-16-13, Kita-Kasai, Edogawa, Tokyo 134-8630, Japan*

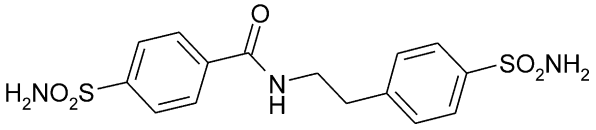


Bioorg. Med. Chem. Lett. 13 (2003) 2759

Carbonic Anhydrase Inhibitors: X-ray Crystallographic Structure of the Adduct of Human Isozyme II with a Bis-Sulfonamide—Two Heads Are Better Than One?

Angela Casini, Francesco Abbate, Andrea Scozzafava and Claudiu T. Supuran*

Università degli Studi di Firenze, Polo Scientifico, Dipartimento di Chimica, Laboratorio di Chimica Bioinorganica, Via della Lastruccia, 3, Rm. 188, I-50019 Sesto Fiorentino (Firenze), Italy

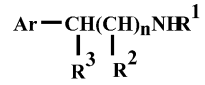


Bioorg. Med. Chem. Lett. 13 (2003) 2765

Carbonic Anhydrase Activators. The Selective Serotonin Reuptake Inhibitors Fluoxetine, Sertraline and Citalopram Are Strong Activators of Isozymes I and II

Angela Casini,[a] Silvio Caccia,[b] Andrea Scozzafava[a] and Claudiu T. Supuran[a,*]

[a]*Università degli Studi di Firenze, Dipartimento di Chimica, Laboratorio di Chimica Bioinorganica, Rm. 188, Via della Lastruccia 3, I-50019 Sesto Fiorentino (Firenze), Italy*
[b]*Istituto di Ricerche Farmacologiche Mario Negri, via Eritrea 62, 20157 Milan, Italy*



4

Ar = aromatic/heterocyclic group

$R^1 = R^2 = H, Me$

$R^3 = H, OH, COOH$

n = 1, 2, 3

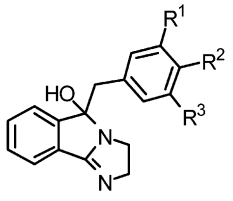
Bioorg. Med. Chem. Lett. 13 (2003) 2769

The Imidazo[2,1-*a*]isoindole System. A New Skeletal Basis for Antiplasmodial Compounds

Esther del Olmo,[a,*] Marlon García Armas,[b] Mª Inés Ybarra,[c] Josè Luis López,[a] Patricia Oporto,[d] Alberto Giménez,[d] Eric Deharo[e] and Arturo San Feliciano[a]

[a]*Departamento de Química Farmacéutica, Facultad de Farmacia, 37007-Salamanca, Spain*
[b]*Universidad Privada Antenor Orrego, Trujillo, Peru*
[c]*Universidad de Tucumán, Tucumán, Argentina*
[d]*Instituto de Investigaciones Fármaco Bioquímicas, UMSA, La Paz, Bolivia*
[e]*Institut de Recherche pour le Développement CP 9214, La Paz, Bolivia*

The in vitro antiplasmodial and the ferriprotoporphyrin IX biomineralization activities of some imidazo[2,1-*a*]isoindole and related compounds are reported.



Bioorg. Med. Chem. Lett. 13 (2003) 2773

Prediction of hERG Potassium Channel Affinity by Traditional and Hologram QSAR Methods

György M. Keserü*

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

Discriminant analysis of 68 compounds with reported hERG K + channel affinity resulted in a traditional QSAR model that classified 83% of actives and 87% of inactives correctly. The HQSAR model predicted patch-clamp IC_{50} values with reasonable accuracy and was found to be useful in discrimination studies evaluating large datasets.

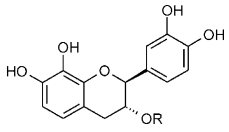
Bioorg. Med. Chem. Lett. 13 (2003) 2777

Novel 3-*O*-Acyl Mesquitol Analogues as Free-Radical Scavengers and Enzyme Inhibitors: Synthesis, Biological Evaluation and Structure–Activity Relationship

R. Jagadeeshwar Rao,[a] Ashok K. Tiwari,[b] U. Sampath Kumar,[a] S. Venkat Reddy,[a] Amtul Z. Ali[b] and J. Madhusudana Rao[a,*]

[a]*Natural Products Laboratory, Division of Organic Chemistry I, Indian Institute of Chemical Technology, Hyderabad-500 007, India*
[b]*Division of Pharmacology, Indian Institute of Chemical Technology, Hyderabad-500 007, India*

A series of aliphatic and aromatic acyl esters of novel isomer of mesquitol were synthesized which showed strong free-radical scavenging, xanthine oxidase and alpha glucosidase inhibitory activities. The structure–activity relationship is discussed.

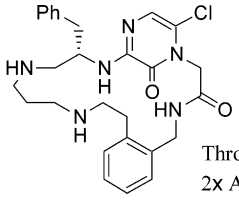


Bioorg. Med. Chem. Lett. 13 (2003) 2781

Design and Synthesis of Potent and Selective Macrocyclic Thrombin Inhibitors

Philippe G. Nantermet,[a,*] James C. Barrow,[a] Christina L. Newton,[a] Janetta M. Pellicore,[a] MaryBeth Young,[a] S. Dale Lewis,[b] Bobby J. Lucas,[b] Julie A. Krueger,[b] Daniel R. McMasters,[c] Youwei Yan,[d] Lawrence C. Kuo,[d] Joseph P. Vacca[a] and Harold G. Selnick[a]

[a]*Department of Medicinal Chemistry, Merck Research Laboratories, West Point, PA 19486, USA*
[b]*Department of Biological Chemistry, Merck Research Laboratories, West Point, PA 19486, USA*
[c]*Department of Molecular Systems, Merck Research Laboratories, West Point, PA 19486, USA*
[d]*Department of Structural Biology, Merck Research Laboratories, West Point, PA 19486, USA*



Thrombin K_i = 0.09 nM
2x APTT = 470 nM

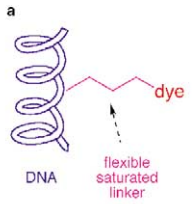
Bioorg. Med. Chem. Lett. 13 (2003) 2785

Oligonucleotides with Strongly Fluorescent Groups π-Conjugated to a Nucleobase: Syntheses, Melting Temperatures, and Conformation

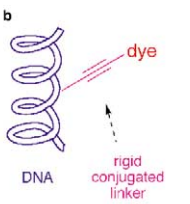
Guan-Sheng Jiao and Kevin Burgess*

Department of Chemistry, PO Box 30012, Texas A & M University, College Station, TX 77842-3012, USA

Phosphoramidite **1** was prepared, incorporated into oligonucleotides, and these were studied via thermal denaturation and circular dichroism.



usual approach to dye-lebelled primers annealed to template for DNA sequencing



target approach for this work

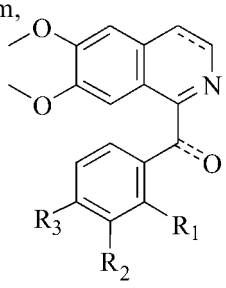
Bioorg. Med. Chem. Lett. 13 (2003) 2789

Antiplatelet Activity of Benzylisoquinoline Derivatives Oxidized by Cerium(IV) Ammonium Nitrate

Reen-Yen Kuo, Fang-Rong Chang, Chin-Chun Wu, Ramesh Patnam, Wei-Ya Wang, Ying-Chi Du and Yang-Chang Wu*

Graduate Institute of Natural Products, Kaohsiung Medical University, Kaohsiung 807, Taiwan

Oxidation of 1-benzyl-3,4-dihydroisoquinolines with cerium(IV) ammonium nitrate (CAN) yielded the mixture of corresponding 1-benzylisoquinolines and 1-benzoylisoquinolines (a–c-type). The selective oxidation of c-type derivatives can be achieved by using MeCN as solvent. In the antiplatelet assays, compounds belonging to a- and b-type showed stronger inhibitory effects than aspirin in the PAF or Col induced platelet aggregation.



	R_1	R_2	R_3
1(a-c)	Cl	H	H
2(a-c)	H	Cl	H
3(a-c)	H	H	Cl
4(a-c)	Br	H	H
5(a-c)	H	Br	H
6(a-c)	H	H	Br
7(a-c)	OMe	H	H
8(a-c)	H	OMe	H
9(a-c)	H	H	OMe

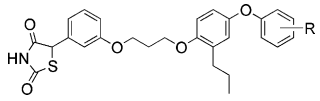
Bioorg. Med. Chem. Lett. 13 (2003) 2795

5-Aryl Thiazolidine-2,4-diones: Discovery of PPAR Dual α/γ Agonists as Antidiabetic Agents

Ranjit C. Desai,[a,*] Wei Han,[a] Edward J. Metzger,[a] Jeffrey P. Bergman,[a] Dominick F. Gratale,[a] Karen L. MacNaul,[b] Joel P. Berger,[b] Thomas W. Doebber,[b] Kwan Leung,[c] David E. Moller,[b] James V. Heck[a] and Soumya P. Sahoo[a,*]

[a]*Department of Medicinal Chemistry, Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065-0900, USA*
[b]*Department of Metabolic Disorders, Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065-0900, USA*
[c]*Department of Drug Metabolism, Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065-0900, USA*

A novel series of potent, orally efficacious dual PPAR α/γ agonists was identified.



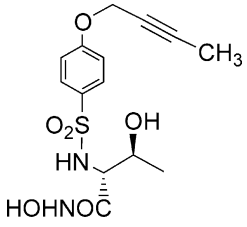
Bioorg. Med. Chem. Lett. 13 (2003) 2799

Acetylenic TACE Inhibitors. Part 1. SAR of the Acyclic Sulfonamide Hydroxamates

J. I. Levin,[a,*] J. M. Chen,[a] K. Cheung,[a] D. Cole,[a] C. Crago,[a] E. Delos Santos,[a] X. Du,[a] G. Khafizova,[a] G. MacEwan,[a] C. Niu,[a] E. J. Salaski,[a] A. Zask,[a] T. Cummons,[b] A. Sung,[b] J. Xu,[a] Y. Zhang,[c] W. Xu,[c] S. Ayral-Kaloustian,[a] G. Jin,[a] R. Cowling,[a] D. Barone,[d] K. M. Mohler,[d] R. A. Black[d] and J. S. Skotnicki[a]

[a]*Wyeth Research, 401 N. Middletown Rd., Pearl River, NY 10965, USA*
[b]*Wyeth Research, PO Box CN-8000, Princeton, NJ 08543, USA*
[c]*Wyeth Research, 200 Cambridge Park Drive, Cambridge, MA 02140, USA*
[d]*Immunex Corporation, Seattle, WA 98101, USA*

Compound **5j**, a potent and selective inhibitor of TACE, in vitro and in vivo, has been identified.



5j

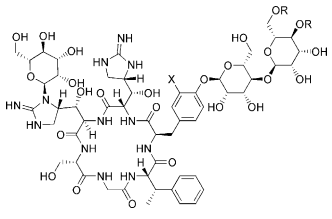
Bioorg. Med. Chem. Lett. 13 (2003) 2805

Synthesis and Evaluation of Ether and Halogenated Derivatives of Mannopeptimycin Glycopeptide Antibiotics

Phaik-Eng Sum,[a,*] David How,[a] Nancy Torres,[a] Peter J. Petersen,[b] Joseph Ashcroft,[a] Edmund I. Graziani,[a] Frank E. Koehn[a] and Tarek S. Mansour[a]

[a]*Chemical Sciences, Wyeth Research, Pearl River, NY 10965, USA*
[b]*Infectious Disease, Wyeth Research, Pearl River, NY 10965, USA*

A number of novel 6-*O* and 4-*O*-ether derivatives of mannopeptimycin glycopeptide and halogenated derivatives (X = I, Br) were synthesized for SAR. Many of the more lipophilic ether derivatives showed potent in vitro antibacterial activity against VRE, MRSA, and PRSP.

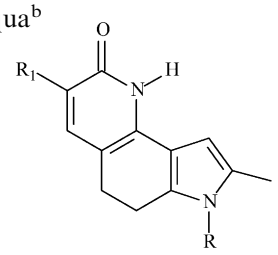


Bioorg. Med. Chem. Lett. 13 (2003) 2809

Pyrrolo[2,3-*h*]quinolinones: Synthesis and Photochemiotherapic Activity

Paola Barraja,[a] Patrizia Diana,[a] Antonino Lauria,[a] Alessandra Montalbano,[a] Anna Maria Almerico,[a] Gaetano Dattolo,[a] Girolamo Cirrincione,[a,*] Giampietro Viola[b] and Francesco Dall'Acqua[b]

[a]*Dipartimento Farmacochimico, Tossicologico e Biologico Università degli Studi, Via Archirafi 32, 90123 Palermo, Italy*
[b]*Dipartimento di Scienze Farmaceutiche Università degli Studi, Via Marzolo 5, 35131 Padova, Italy*



Derivatives of the new ring system pyrrolo[2,3-*h*]quinolinones were synthesized and evaluated as photochemotherapic agent. Two derivatives showed cytotoxic activity at submicromolar level.