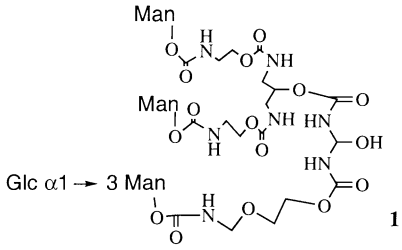
Bioorg. Med. Chem. Lett. 12 (2002) 1237

Synthesis of a Molecular Mimic of the Glc_1Man_9 Oligoside as Potential Inhibitor of Calnexin Binding to ΔF508 CFTR Protein

Slim Cherif,[a] Michael R. Leach,[b] David B. Williams[b] and Claude Monneret[a,*]

[a]*UMR 176 CNRS-Institut Curie, Section de Recherche, 26 rue d'Ulm, 75248 Paris Cedex 05, France*
[b]*Department of Biochemistry, University of Toronto, Toronto, Canada M5S 1A8*

The molecular mimic **1** was synthesized and evaluated for its ability to inhibit the binding of $[^3H]Glc_1Man_9GlcNAc_2$ to GST fused calnexin.



1

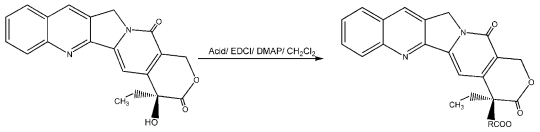
Bioorg. Med. Chem. Lett. 12 (2002) 1241

Novel Camptothecin Derivatives. Part 1: Oxyalkanoic Acid Esters of Camptothecin and Their In Vitro and In Vivo Antitumor Activity

Li-Xi Yang,[a,b,*] Xiandao Pan[a] and Hui-Juan Wang[a]

[a]*Radiobiology Laboratory, California Pacific Medical Center Research Institute, San Francisco, CA 94118, USA*
[b]*St. Mary's Medical Center, San Francisco, CA 94117, USA*

A series of oxyalkanoic acid esters of (20*S*)-camptothecin derivatives was prepared by the method of acylation.



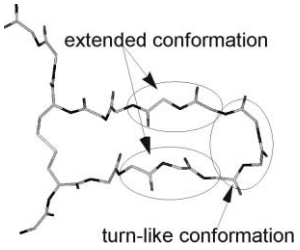
Bioorg. Med. Chem. Lett. 12 (2002) 1245

Structure–Activity Relationships for Mini Atrial Natriuretic Peptide by Proline-Scanning Mutagenesis and Shortening of Peptide Backbone

Kenji Sugase,[a,c] Yoshiaki Oyama,[b] Katsuhiko Kitano,[b] Hideo Akutsu[d,*] and Masaji Ishiguro[a,*]

[a]*Suntory Institute for Bioorganic Research, Shimamoto, Mishima 618-8503, Japan*
[b]*Suntory Biomedical Research Limited, Shimamoto, Mishima 618-8503, Japan*
[c]*Department of Chemistry and Biotechnology, Faculty of Engineering, Yokohama National University, Hodogaya-ku, Yokohama 240-8501, Japan*
[d]*Institute for Protein Research, Osaka University, Yamadaoka, Suita 565-0871, Japan*

Proline-scanning mutagenesis and the analogue peptides with shorter backbones were used to characterize the receptor-bound structure of mini atrial natriuretic peptide.

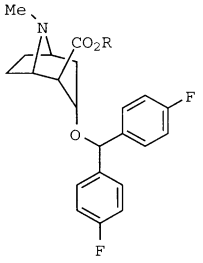


Bioorg. Med. Chem. Lett. 12 (2002) 1249

Enantioselective Synthesis of *S*-(+)-2β-Carboalkoxy-3α-[bis(4-fluorophenyl)methoxy]tropanes as Novel Probes for the Dopamine Transporter

Mu-Fa Zou,[a] Gregory E. Agoston,[a] Yuri Belov,[b] Theresa Kopajtic,[c] Jonathan L. Katz[c] and Amy Hauck Newman[a,*]

[a]*Medicinal Chemistry Section, National Institute on Drug Abuse-Intramural Research Program, NIH, Baltimore, MD 21224, USA*
[b]*ChromBA, State College, PA 16803, USA*
[c]*Psychobiology Section, National Institute on Drug Abuse-Intramural Research Program, NIH, Baltimore, MD 21224, USA*



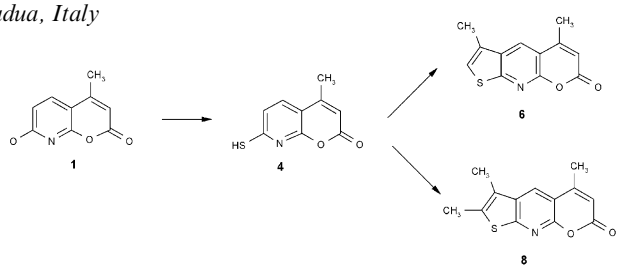
Bioorg. Med. Chem. Lett. 12 (2002) 1253

Synthesis, Photobiological Activity and Photoreactivity of Methyl-thieno-8-azacoumarins, Novel Bioisosters of Psoralen

Lisa Dalla Via,[a,*] Sebastiano Marciani Magno,[a,b] Paolo Rodighiero[b] and Ornella Gia[a,b]

[a]*Dipartimento di Scienze Farmaceutiche, Università di Padova, Padua, Italy*
[b]*Centro di Studio sulla Chimica del Farmaco e dei Prodotti Biologicamente attivi del CNR, via Marzolo 5, 35131 Padova, Italy*

The thieno-8-azacoumarin **6** and **8** were synthesised. Compound **6** showed a photocytotoxic ability higher with respect to that of the well-known drug 8-methoxypsoralen (8-MOP) in HL-60 cells. Interestingly, no skin phototoxicity appears.



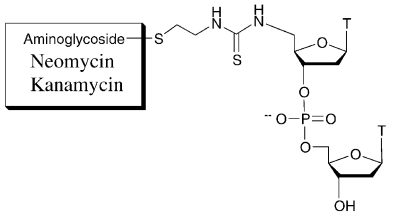
Bioorg. Med. Chem. Lett. 12 (2002) 1259

Synthesis of Aminoglycoside–DNA Conjugates

I. Charles, Liang Xue and Dev P. Arya*

Laboratory of Medicinal Chemistry, Department of Chemistry, Clemson University, Clemson, SC 29634, USA

The synthesis of a DNA dimer covalently linked to kanamycin and neomycin via thiourea linkage is presented.



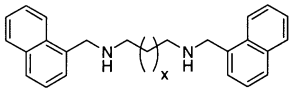
Bioorg. Med. Chem. Lett. 12 (2002) 1263

Induction of Apoptosis by Aryl-Substituted Diamines: Role of Aromatic Group Substituents and Distance Between Nitrogens

Mark R. Burns,* Solveig LaTurner, Josh Ziemer, Maralee McVean, Bruce Devens, C. Lance Carlson, Gerard F. Graminski, Scott M. Vanderwerf, Reitha S. Weeks and Jay Carreon

MediQuest Therapeutics, Inc., 4010 Stone Way North, Seattle, WA 98103, USA

A series of aromatic substituted diamines has been synthesized and characterized for their cytotoxic profiles against human breast and prostate tumor cell lines.



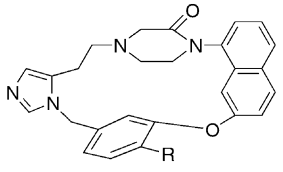
Bioorg. Med. Chem. Lett. 12 (2002) 1269

Potent Inhibitors of Farnesyltransferase and Geranylgeranyltransferase-I

Diem N. Nguyen,[a,*] Craig A. Stump,[a] Eileen S. Walsh,[b] Christine Fernandes,[b] Joseph P. Davide,[b] Michelle Ellis-Hutchings,[b] Ronald G. Robinson,[b] Theresa M. Williams,[a] Robert B. Lobell,[b] Hans E. Huber[b] and Carolyn A. Buser[b]

[a]*Department of Medicinal Chemistry, Merck Research Laboratories, West Point, PA 19486, USA*
[b]*Department of Cancer Research, Merck Research Laboratories, West Point, PA 19486, USA*

The SAR studies of a biaryl series led to the discovery of potent dual FPTase/GGPTase-I inhibitors.



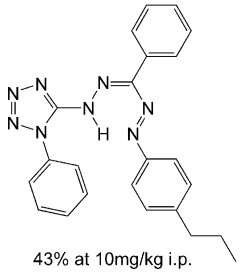
Bioorg. Med. Chem. Lett. 12 (2002) 1275

Design, Synthesis and Biological Activity of Novel Non-Peptidyl Endothelin Converting Enzyme Inhibitors, 1-Phenyl-tetrazole-formazan Analogues

Kazuto Yamazaki, Hirohiko Hasegawa, Kayo Umekawa, Yasuyuki Ueki, Naohito Ohashi and Masaharu Kanaoka*

Research Division, Sumitomo Pharmaceuticals Co., Ltd., 3-1-98 Kasugadenaka, Konohona-ku, Osaka 554-0022, Japan

The design and synthesis of the endothelin converting enzyme inhibitors (43% at 10 mg/kg ip) is reported.



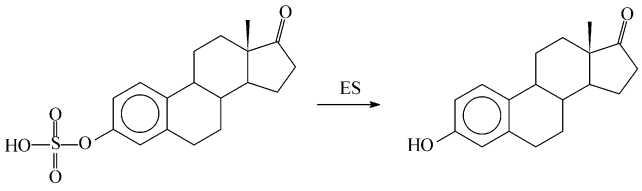
Bioorg. Med. Chem. Lett. 12 (2002) 1279

The Mechanism of the Irreversible Inhibition of Estrone Sulfatase (ES) Through the Consideration of a Range of Methane- and Amino-Sulfonate-Based Compounds

Sabbir Ahmed,[a,*] Karen James,[b] Caroline P. Owen,[a] Chirag K. Patel[a] and Luther Sampson[c]

[a]*School of Chemical and Pharmaceutical Sciences, Kingston University, Penrhyn Road, Kingston upon Thames, Surrey KT1 2EE, UK*
[b]*Institute of Cancer Research, Sutton, UK*
[c]*Novartis Pharma AG, CH-4002 Basel, Switzerland*

The mechanism of inhibition of the enzyme estrone sulfatase (ES) is considered together with the inhibitory activity of a range of sulfonate- and sulfamate-based compounds.



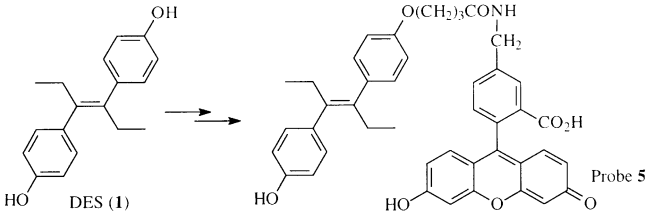
Bioorg. Med. Chem. Lett. 12 (2002) 1283

Synthesis of a Novel Fluorescent Probe for Estrogen Receptor

Maciej Adamczyk,* Rajarathnam E. Reddy and Zhiguang Yu

Department of Chemistry (9NM, Bldg AP20), Diagnostics Division, Abbott Laboratories, 100 Abbott Park Road, Abbott Park, IL 60064-6016, USA

A novel probe **5** was synthesized from diethylstilbestrol (DES, **1**), which is useful for probing estrogen receptor (ERα).



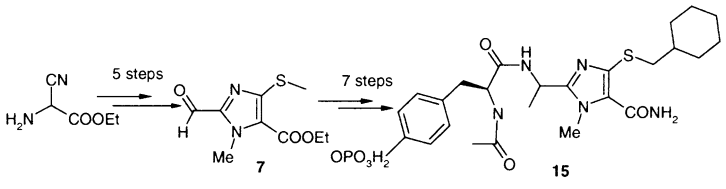
Bioorg. Med. Chem. Lett. 12 (2002) 1287

Imidazole-Based Ligands of the Src SH_2 Protein

Pierre Deprez,* Eliane Mandine, Annie Vermond and Dominique Lesuisse

Aventis Pharma, Paris Research Center, Medicinal Chemistry, 102 route de Noisy, 93235 Romainville Cedex, France

From the tetrafunctionalized imidazole **7**, the synthesis of the imidazole **15** is described and this compound is evaluated as Src SH2 binder.



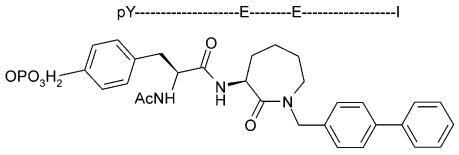
Bioorg. Med. Chem. Lett. 12 (2002) 1291

Discovery of Highly Potent Src SH_2 Binders: Structure–Activity Studies and X-ray Structures

Pierre Deprez,* Isabelle Baholet, Stéphane Burlet, Gudrun Lange, Remi Amengual, Bernard Schoot, Annie Vermond, Eliane Mandine and Dominique Lesuisse

Aventis Pharma, Paris Research Center, Medicinal Chemistry, 102 route de Noisy, 93235 Romainville Cedex, France

We identified RU 81843 which is one of the most potent SH2 binder known to date (9 nM vs 150 nM for pYEEI). X-Ray structure indicates that the caprolactam scaffold is able to efficiently deliver the biphenyl and pY substituents in the respective binding pockets, while also nicely interacting with the protein.



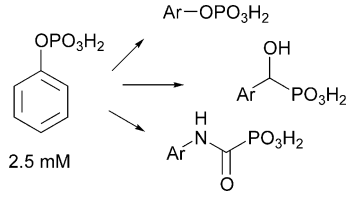
Bioorg. Med. Chem. Lett. 12 (2002) 1295

Small Ligands Interacting with the Phosphotyrosine Binding Pocket of the Src SH_2 Protein

Pierre Deprez,* Eliane Mandine, Dominique Gofflo, Stéphane Meunier and Dominique Lesuisse

Aventis Pharma, Paris Research Center, Medicinal Chemistry, 102 route de Noisy, 93235 Romainville Cedex, France

Small aromatic fragments bearing a phosphate, a hydroxy or an amido phosphonic acid moiety have been prepared through parallel synthesis. Their binding potencies towards Src SH_2 were compared to phenyl phosphate.



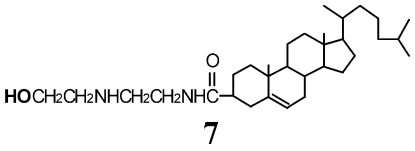
Bioorg. Med. Chem. Lett. 12 (2002) 1299

Comparative Study of Transfection Efficiency of Cationic Cholesterols Mediated by Liposomes-Based Gene Delivery

Seiji Hasegawa, Naohide Hirashima and Mamoru Nakanishi*

Graduate School of Pharmaceutical Sciences, Nagoya City University, Tanabe-dori, Mizuho-ku, Nagoya 467-8603, Japan

Liposomes with cationic cholesterol derivative **7** exhibited the highest transfection efficiency among related derivatives. Introduction of the hydroxy group facilitated the dissociation of DNA from lipoosmes, resulting in enhanced transfection efficiency.



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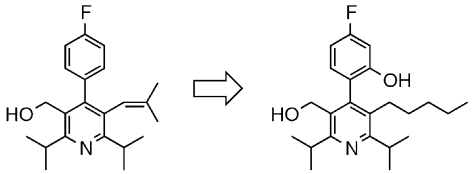
Bioorg. Med. Chem. Lett. 12 (2002) 1303

Optimization of the 4-Aryl Group of 4-Aryl-pyridine Glucagon Antagonists: Development of an Efficient, Alternative Synthesis

Roger A. Smith,[a,*] Donald L. Hertzog,[a] Martin H. Osterhout,[a] Gaetan H. Ladouceur,[a] Mary Korpusik,[a] Mark A. Bobko,[a] J. Howard Jones,[a] Kathleen Phelan,[a] Romulo H. Romero,[a] Thomas Hundertmark,[a] Margit L. MacDougall,[b] James N. Livingston[b] and William R. Schoen[a]

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

A narrow structure–activity relationship was established for the 4-aryl group in 4-aryl-pyridine glucagon antagonists. However, substitution with a 2′-hydroxy group gave a ca. 3-fold increase in activity. For efficient preparation of 2′-substituted phenylpyridines, a novel synthesis via pyrones and 4-methoxy-pyridines was developed.



IC_{50} = 7 μM IC_{50} = 0.19 μM

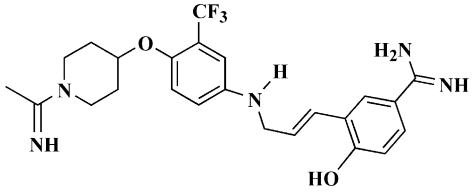
Bioorg. Med. Chem. Lett. 12 (2002) 1307

Design and Synthesis of Aminophenol-Based Factor Xa Inhibitors

Shung Wu, William J. Guilford,* Yuo-Ling Chou, Brian D. Griedel, Amy Liang, Steve Sakata, Kenneth J. Shaw, Lan Trinh, Wei Xu, Zuchun Zhao and Michael M. Morrissey

Discovery Research, Berlex Biosciences, 15049 San Pablo Avenue, PO Box 4099, Richmond, CA 94804-0099, USA

A novel potent and selective aminophenol scaffold for fXa inhibitors was developed from a previously reported benzimidazole-based naphthylamidine template. The aminophenol template is more synthetically accessible than the benzimidazole template which simplified the introduction of carboxylic acid groups. Substitution of a propenyl-*para*-hydroxy-benzamidine group on the aminophenol template produced selective sub-nanomolar fXa inhibitors. The potency of the inhibitors is partially explained with the aid of a trypsin complex crystal structure.



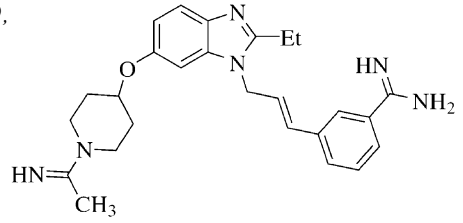
Bioorg. Med. Chem. Lett. 12 (2002) 1311

Benzimidazole-Based fXa Inhibitors with Improved Thrombin and Trypsin Selectivity

Kenneth J. Shaw, William J. Guilford,* Brian Griedel, Steve Sakata, Lan Trinh, Shung Wu, Wei Xu, Zuchun Zhao and Michael M. Morrissey

Medicinal Chemistry, Berlex Biosciences, 15049 San Pablo Avenue, PO Box 4099, Richmond, CA 94804-0099, USA

Optimization of the benzimidazole-based fXa inhibitors for selectivity versus thrombin and trypsin was achieved by substitution on the benzimidazole ring with a nitro group at C-4 and replacement of the naphthylamidine group with either a biphenylamidine or propenylbenzamidine group. Although both of the changes improved potency against fXa, selectivity versus trypsin was achieved by substitution of the propenylbenzamidine group.

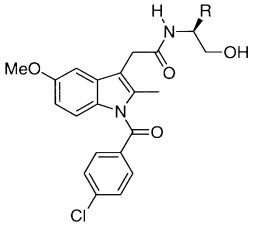


Bioorg. Med. Chem. Lett. 12 (2002) 1315

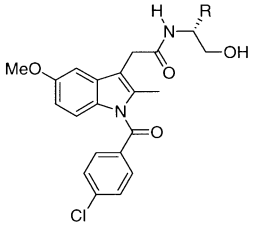
Enantiospecific, Selective Cyclooxygenase-2 Inhibitors

Kevin R. Kozak, Jeffery J. Prusakiewicz, Scott W. Rowlinson and Lawrence J. Marnett*

Departments of Biochemistry and Chemistry, Vanderbilt-Ingram Cancer Center and Center in Molecular Toxicology, Vanderbilt University School of Medicine, Nashville, TN 37232, USA



Nonselective COX Inhibitor



Selective COX-2 Inhibitor

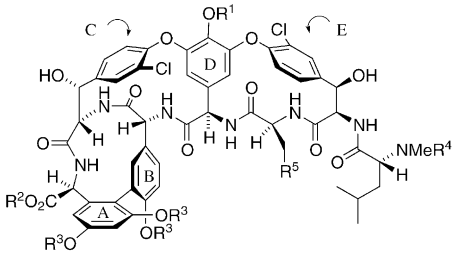
Bioorg. Med. Chem. Lett. 12 (2002) 1319

Synthesis and Evaluation of Vancomycin and Vancomycin Aglycon Analogues that Bear Modifications in the Residue 3 Asparagine

J. Jeffrey McAtee, Steven L. Castle, Qing Jin and Dale L. Boger*

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

The synthesis of several vancomycin analogues and their antimicrobial evaluation are reported, along with the peptide binding affinities (K_a) for L-Lys-D-Ala-D-Ala and L-Lys-D-Ala-D-Lac.



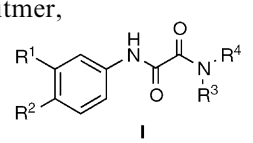
Bioorg. Med. Chem. Lett. 12 (2002) 1323

Novel Diamide-Based Inhibitors of IMPDH

Henry H. Gu,* Edwin J. Iwanowicz, Junqing Guo, Scott H. Watterson, Zhongqi Shen, William J. Pitts, T. G. Murali Dhar, Catherine A. Fleener, Katherine Rouleau, N. Z. Sherbina, Mark Witmer, Jeffrey Tredup and Diane Hollenbaugh

Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ 08543-4000, USA

A series of novel amide-based small molecule inhibitors of inosine monophosphate dehydrogenase is described.



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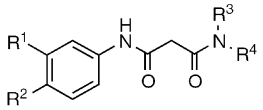

II