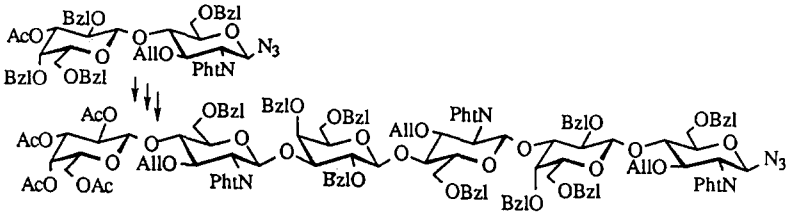
Glycosyl Azides as Building Blocks in Convergent Syntheses of Oligomeric Lactosamine and Lewis^x Saccharides

Bioorg. Med. Chem. **1997**, *5*, 1

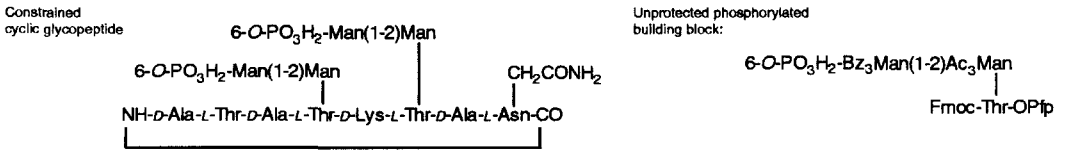
Wolfgang Bröder and Horst Kunz*
Institut für Organische Chemie, Johannes Gutenberg-Universität Mainz, Becher-Weg 18-20, D-55128 Mainz, Germany



Constrained Glycopeptide Ligands for MPRs. Limitations of Unprotected Phosphorylated Building Blocks

Bioorg. Med. Chem. **1997**, *5*, 21

Henrik Franzyk,[a] Mette K. Christensen,[a] Rikke M. Jørgensen,[a] Morten Meldal,[a] Henriette Cordes,[b] Søren Mouritsen[b] and Klaus Bock[a]
[a]Department of Chemistry, Carlsberg Laboratory, Gamle Carlsberg Vej 10, DK-2500 Valby, Copenhagen, Denmark; [b]Department of Basic Immunology, M & E, Lersø, Parkallé 40, DK-2100, Copenhagen, Denmark

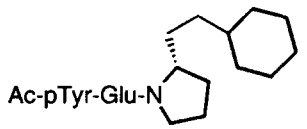


Design of Peptidomimetic Ligands for the pp60^{src} SH2 Domain

Bioorg. Med. Chem. **1997**, *5*, 41

Mark S. Plummer,[a] Elizabeth A. Lunney,[a] Kimberly S. Para,[a] Aurash Shahripour,[a] Charles J. Stankovic,[a] Christine Humblet,[a] James H. Fergus,[b] James S. Marks,[b] Roman Herrara,[b] Susan Hubbell,[c] Alan Saltiel[c] and Tomi K. Sawyer[c]
Departments of [a]Chemistry, [b]Biochemistry and [c]Signal Transduction, Parke-Davis Pharmaceutical Research, Division of Warner-Lambert Company, 2800 Plymouth Road, Ann Arbor, MI 48106, U.S.A.

Potent ligands of the Src SH2 domain, discovered through structure-based drug design efforts, with the general structure Ac-pTyr-Glu-NRR′ are disclosed.



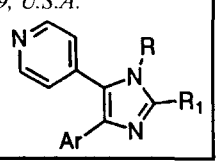
17 IC_{50} = 0.56 μM

Regulation of Stress-Induced Cytokine Production by Pyridinylimidazoles; Inhibition of CSBP Kinase

Bioorg. Med. Chem. **1997**, *5*, 49

Timothy F. Gallagher,*[a] George L. Seibel,[b] Shouki Kassis,[c] Jeffrey T. Laydon,[c] Mary Jane Blumenthal,[c] John C. Lee,[c] Dennis Lee,[a] Jeffrey C. Boehm,[a] Susan M. Fier-Thompson,[a] Jeffrey W. Abt,[a] Margaret E. Soreson,[a] Juanita M. Smietana,[a] Ralph F. Hall,[a] Ravi S. Garigipati,[a] Paul E. Bender,[a] Karl F. Erhard,[a] Arnold J. Krog,[a] Glenn A. Hofmann,[d] Peter L. Sheldrake,[e] Peter C. McDonnell,[f] Sanjay Kumar,[f] Peter R. Young[f] and Jerry L. Adams[a]
Departments of [a]Medicinal Chemistry, [b]Physical & Structural Chemistry, [c]Cellular Biochemistry, [d]Biomolecular Discovery, [e]Chemical Development and [f]Molecular Immunology, SmithKline Beecham Pharmaceuticals, King of Prussia, PA 19406-0939, U.S.A.

Members of three classes of pyridinylimidazoles are shown to bind to CSBP (p38). A subset of these compounds is evaluated for CSBP, ERK, PKA and PKCα activity. A pharmacophore and potential modes of binding for the pyridinylimidazoles to CSBP are presented.



Bioorg. Med. Chem. **1997**, *5*, 65

Cloning and Mutagenesis of the p110α Subunit of Human Phosphoinositide 3′-Hydroxykinase

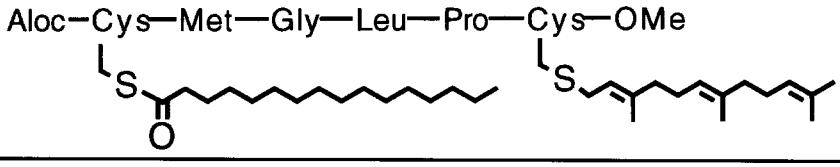
Steven M. Stirdivant, Janet Ahern, Robert R. Conroy, Stanley F. Barnett, Lynette M. Ledder, Allen Oliff and David C. Heimbrook
Department of Cancer Research, Merck Research Laboratories, West Point, PA 19486, U.S.A.

The cloning and characterization of the p110α catalytic subunit of human PI3K is reported. Expression of the wild-type p110α protein in CHO cells is sufficient to activate the serum response element derived from the promoter of c-*fos*, an immediate early gene product. In contrast, catalytically-impaired p110α mutants as well as the p85α subunit of PI3K were inactive in the *fos* assay.

Bioorg. Med. Chem. **1997**, *5*, 75

Synthesis of Characteristic Lipopeptides of the Human *N-Ras* Protein and their Evaluation as Possible Inhibitors of Protein Farnesyl Transferase

Paul Stöber, Michael Schelhaas, Edgar Nägele, Patrizia Hagenbuch, János Rétey* and Herbert Waldmann*
Universität Karlsruhe, Institut für Organische Chemie, Richard-Willstätter-Allee 2, D-76128 Karlsruhe, Germany

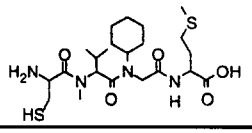


Synthesis and Biological Activity of Semipeptoid Farnesyltransferase Inhibitors

Bioorg. Med. Chem. **1997**, *5*, 85

Hadas Reuveni,[a] Alex Gitler,[a] Enrique Poradosu,[a] Chaim Gilon[b] and Alexander Levitzki[a,*]
Department of [a]Biological and [b]Organic Chemistry, The Institutes of [a]Life Sciences and [b]Chemistry, The Hebrew University of Jerusalem, Jerusalem 91904, Israel

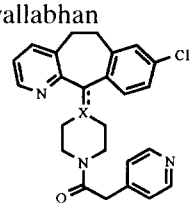
Structure–activity relationship studies of a semipeptoid family, derived from CVFM, led to a potent (in vitro IC_{50} = 1.2 nM) and selective inhibitor of Ras farnesyltransferase, named HR-11. The methyl ester derivative of HR-11 inhibits Ras farnesylation in intact cells with an IC_{50} = 10 μM and with no detectable inhibition of Rap1A/K-rev geranylgeranylation.



Antitumor 8-Chlorobenzocycloheptapyridines: a New Class of Selective, Nonpeptidic, Nonsulfhydryl Inhibitors of Ras Farnesylation

Bioorg. Med. Chem. **1997**, *5*, 93

A. K. Mallams, F. G. Njoroge, R. J. Doll,* M. E. Snow, J. J. Kaminski, R. R. Rossman, B. Vibulbhan, W. R. Bishop, P. Kirschmeier, M. Liu, M. S. Bryant, C. Alvarez, D. Carr, L. James, I. King, Z. Li, C.-C. Lin, C. Nardo, J. Petrin, S. W. Remiszewski, A. G. Taveras, S. Wang, J. Wong, J. Catino, V. Girijavallabhan and A. K. Ganguly
Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, NJ 07033, U.S.A.



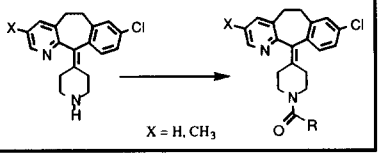
Compounds in the 8-chlorobenzocycloheptapyridine structural class are inhibitors of ras farnesyl protein transferase (FPT). These compounds are nonpeptidic, nonsulfhydryl and inhibit ras farnesylation in a cell assay. Some of these compounds inhibit human tumor growth in mice when given orally. A correlation of structure with biological activity and a comparison to a tetrapeptide FPT inhibitor is discussed.

Bioorg. Med. Chem. **1997**, *5*, 101

Discovery of Novel Nonpeptide Tricyclic Inhibitors of Ras Farnesyl Protein Transferase

F. George Njoroge,* Ronald J. Doll, Bancha Vibulbhan, Carmen S. Alvarez, W. Robert Bishop, Joanne Petrin, Paul Kirschmeier, Nicholas I. Carruthers, Jesse K. Wong, Margaret M. Albanese, John J. Piwinski, Joseph Catino, V. Girijavallabhan and Ashit K. Ganguly
Schering-Plough Research Institute, Departments of Chemistry and Tumor Biology, 2015 Galloping Hill Road, Kenilworth, NJ 07033, U.S.A.

A series of tricyclic amides has been prepared and evaluated as inhibitors of Farnesyl Protein Transferase (FPT). Compounds that have IC_{50} in the nanomolar range have been obtained.



Synthesis and Conformational Analysis of Peptide Inhibitors of Farnesyltransferase

Bioorg. Med. Chem. **1997**, *5*, 115

Gerardo Byk,*[a] Yves Lelievre,[b] Marc Duchesne,[b] François F. Clerc,[b] Daniel Scherman[a] and Jean Dominique Guitton[b]
[a]Rhône-Poulenc Rorer, UMR-133 RPR-CNRS and [b]Biotechnology Department 13, Quai Jules Guesde, B.P. 14, 94403 Vitry Sur Seine, France

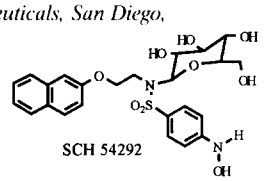
We have synthesized modified analogues of peptide CysValTicMet, a potent FTase inhibitor on isolated enzyme assays by different approaches. Stabilization toward amino-peptidases by amino terminal modification and/or increased cell internalisation by introduction of hydrophobic aliphatic chains, introduction of pseudopeptide or non natural amino acids for stabilization towards endopeptidases and transformation into prodrugs. Additionally, we have carried out comparative conformational analysis studies of selected molecules emerging from the present work and from our recently described peptidomimetic inhibitors of FTase, by molecular dynamics with a simulated annealing protocol.

Ras Oncoprotein Inhibitors: The Discovery of Potent, Ras Nucleotide Exchange Inhibitors and the Structural Determination of a Drug–Protein Complex

Bioorg. Med. Chem. **1997**, *5*, 125

A. G. Taveras,[a] S. Remiszewski,[a] R. J. Doll,[a] D. Cesarz,[a] J. del Rosario,[a] B. Vibulbhan,[a] B. Bauer,[a] J. E. Brown,[a] D. Carr,[a] J. Catino,[a] C. A. Evans,[a] V. Girijavallabhan,[a] E. C. Huang,[a] L. Heimark,[a] L. James,[a] P. Kirschmeier,[a] S. Liberles,[a] C. Nash,[a] L. Perkins,[a] B. N. Pramanik,[a] M. M. Senior,[a] M. E. Snow,[a] A. Tsarbopoulos,[a] Y.-S. Wang,[a] A. K. Ganguly,[a] R. Aust,[b] E. Brown,[b] D. Delisle,[b] S. Fuhrman,[b] T. Hendrickson,[b] C. Kissinger,[b] R. Love,[b] W. Sisson[b], E. Villafranca[b] and S. E. Webber[b]
[a]Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, NJ 07033, U.S.A.; [b]Agouron Pharmaceuticals, San Diego, CA 92121, U.S.A.

SCH 54292 inhibits oncogenic ras nucleotide exchange with an $IC_{50} = 0.7$ μM. NMR, mass spectrometry and molecular modeling indicate that this compound binds to a previously unknown binding site in the critical Switch-2 region of the ras protein without displacing GDP. The determined SCH-54292-ras-GDP complex is shown graphically.



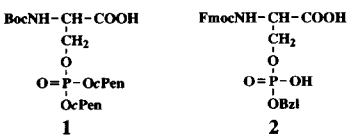
SCH 54292

Synthetic Study of Phosphopeptides Related to Heat Shock Protein HSP27

Bioorg. Med. Chem. **1997**, *5*, 135

Tateaki Wakamiya,[a,]* Ryusaku Togashi,[a] Takatoshi Nishida,[a] Kunio Saruta,[b] Jun-ichi Yasuoka,[b] Shoichi Kusumoto,[b] Saburo Aimoto,[c] Kumiko Yoshizawa Kumagaye,[d] Kiichiro Nakajima[d] and Kazuhiro Nagata[e]
[a]Department of Chemistry, Faculty of Science and Technology, Kinki University, Higashi-osaka, Osaka 577, Japan, [b]Department of Chemistry, Faculty of Science, Osaka University, Toyonaka, Osaka 560, Japan, [c]Institute for Protein Research, Osaka University, Suita, Osaka 565, Japan, [d]Peptide Institute, Protein Research Foundation, Minoh, Osaka 562, Japan, [e]Department of Cell Biology, Chest Disease Research Institute, Kyoto University, Kyoto 606-01, Japan

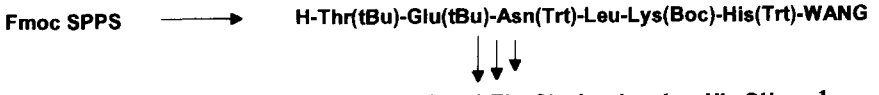
Phosphoamino acid derivatives **1** and **2** were utilized for synthesizing phosphopeptides related to HSP27.



Bioorg. Med. Chem. **1997**, *5*, 147

Combined Fmoc–Alloc Strategy for a General SPPS of Phosphoserine Peptides; Preparation of Phosphorylation-Dependent Tau Antisera

Gideon Shapiro,[a,*] Dieter Büchler, Claudio Dalvit, Peter Frey,[b] Maria del Carmen Fernandez, Berta Gomez-Lor, Esteban Pombo-Villar, Urs Stauss,[b] Robert Swoboda[b] and Caroline Waridel[b]
[a]*Preclinical Research, Sandoz Pharma Ltd, CH-4002 Basel, Switzerland*
[b]*Sandoz Research Institute Berne Ltd, CH-3007, Berne, Switzerland*

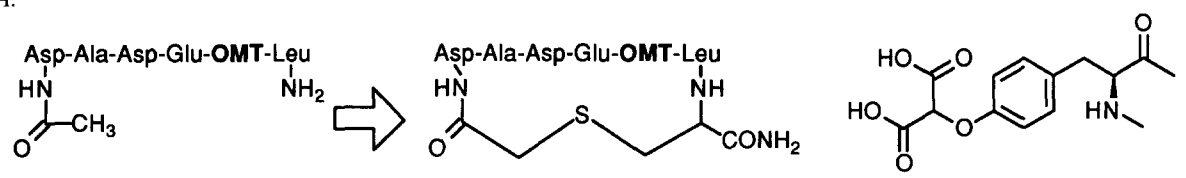


1

Bioorg. Med. Chem. **1997**, *5*, 157

Potent Inhibition of Protein-Tyrosine Phosphatase by Phosphotyrosine-Mimic Containing Cyclic Peptides

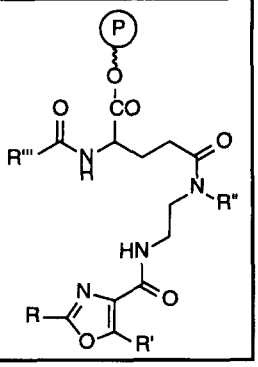
Miki Akamatsu,[a] Peter P. Roller,[a] Li Chen,[b] Zhong-Yin Zhang,[b] Bin Ye[a] and Terrence R. Burke, Jr[a,*]
[a]*Laboratory of Medicinal Chemistry, Division of Basic Sciences, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, U.S.A.;* [b]*Department of Molecular Pharmacology, Albert Einstein College of Medicine, Bronx, NY 10461, U.S.A.*



Bioorg. Med. Chem. **1997**, *5*, 165

Combinatorial Synthesis and Biological Evaluation of a Library of Small-Molecule Ser/Thr-Protein Phosphatase Inhibitors

P. Wipf, A. Cunningham, R. L. Rice and J. S. Lazo
Departments of Chemistry and Pharmacology, University of Pittsburgh, Pittsburgh, PA 15260, U.S.A.



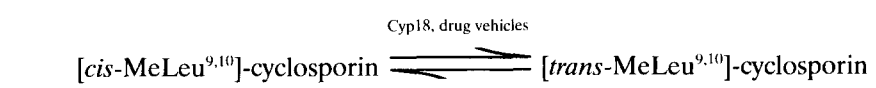
Based on functional groups present in natural product serine/threonine protein phosphatase inhibitors, we have designed a pharmacophore model and demonstrated the feasibility of a solid-phase combinatorial chemistry approach for the preparation of functional analogues. Preliminary biological testing of 18 structural variants exhibited a concentration-dependent inhibition in proliferation of MDA-MB-231 cells and flow cytometry data confirmed blockage in cell cycle progression at the G1 checkpoint.

Bioorg. Med. Chem. **1997**, *5*, 179

Modulation of Cyclosporin A/Cyclophilin Interactions by Drug Vehicles

Bernhard Janowski and Gunter Fischer
Max-Planck-Society, Research Unit Enzymology of the Peptide Bond, D-06120 Halle, Germany

Cremophor EL has been found to affect time-dependent inhibition of the peptidyl-prolyl *cis/trans* isomerase activity of cyclophilin by cyclosporin A.

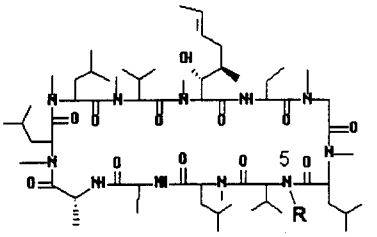


Bioorg. Med. Chem. **1997**, *5*, 187

Conformational Control of Cyclosporin through Substitution of the N-5 Position. A New Class of Cyclosporin Antagonists

Christos Papageorgiou,* Jörg Kallen, Julien France and Richard French
Sandoz Pharma Ltd, Preclinical Research, CH-4002 Basel, Switzerland

The regiospecific alkylation of cyclosporin A (**1**, CsA) yields derivatives **2–5** which, although they still bind to cyclophilin A (CypA), are not immunosuppressive. ^{1}H NMR studies with these CsA antagonists show that they exist in a single, all *trans* conformation which is not the bioactive one as determined by X-ray crystallographic analysis of the CypA/**3** complex.

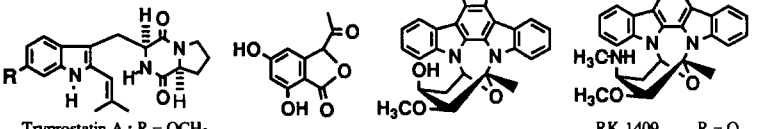


Bioorg. Med. Chem. **1997**, *5*, 193

Screening of Cell Cycle Inhibitors from Microbial Metabolites by a Bioassay Using a Mouse cdc2 Mutant Cell Line, tsFT210

Hiroyuki Osada,* Cheng-Bin Cui, Rie Onose and Fumio Hanaoka
The Institute of Physical and Chemical Research (RIKEN), Wako-shi, Saitama 351-01, Japan

A convenient and practical bioassay method was established for the screening of new mammalian cell cycle inhibitors, by which novel inhibitors, tryprostatins A, B and acetophthalidin, and so on, have been discovered from microbial metabolites.



Tryprostatin A : R = OCH_3
Tryprostatin B : R = H

Acetophthalidin

RK-286C

RK-1409 R = O
Staurosporine R = H_2

Bioorg. Med. Chem. **1997**, *5*, 205

Synthetic Inhibitors of Regulatory Proteins Involved in the Signaling Pathway of the Replication of Human Immunodeficiency Virus 1

Masami Otsuka,[a] Mikako Fujita,[a] Yukio Sugiura[a] Tadashi Yamamoto,[b] Jun-ichiro Inoue,[b,*] Toshio Maekawa[c] and Shunsuke Ishii[c]
[a]Institute for Chemical Research, Kyoto University, Uji, Kyoto 611, Japan; [b]Institute of Medical Science, University of Tokyo, Shirokane-dai, Minato-ku, Tokyo 108, Japan; [c]Tsukuba Life Science Center, The Institute of Physical and Chemical Research (RIKEN), Tsukuba, Ibaraki 305, Japan

Variously functionalized dimethylaminopyridine derivatives were prepared. These were inhibitory against NF-κB, HIV-EP1, Sp1, and E1A which mediate the expression of genes of HIV-1 directed by the long terminal repeat.