Tetrahedron, **1993**, *49*, 3433

CONFORMATIONALLY CONSTRAINED NONPEPTIDE β–TURN MIMETICS OF ENKEPHALIN.

Benjamin Gardner●, Hiroshi Nakanishi* and Michael Kahn*+,
+Department of Pathobiology, University of Washington, Seattle, Washington 98195, *Molecumetics Institute, 2023 120th Avenue N.E., Bellevue, Washington 98005, and ●Department of Chemistry, University of Illinois at Chicago, Chicago, Illinois 60680

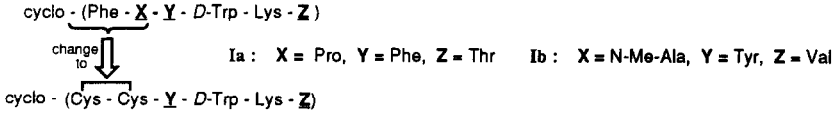
The design, synthesis and *in vitro* biological analysis of a family of conformationlly constrained nonpeptide mimetics incorporating a 4→1 β–turn prosthetic to examine the proposed biological significance of this conformer is described.

Tetrahedron, **1993**, *49*, 3449

APPROACHES TO PEPTIDOMIMETICS WHICH SERVE AS SURROGATES FOR THE *CIS* AMIDE BOND: NOVEL DISULFIDE-CONSTRAINED BICYCLIC HEXAPEPTIDE ANALOGS OF SOMATOSTATIN.

Stephen F. Brady*, William J. Paleveda, Jr., Byron H. Arison§, Richard Saperstein†, Edward J. Brady†, Karen Raynor¶, Terry Reisine¶, Daniel F. Veber, and Roger M. Freidinger, Department of Medicinal Chemistry, Merck Research Laboratories, West Point, PA 19486-0004, §Departments of Animal and Exploratory Drug Metabolism and †Membrane Biochemistry and Biophysics, Merck Research Laboratories, Rahway, NJ 07065-0900 ¶Department of Pharmacology, University of Pennsylvania School of Medicine, Philadelphia, PA 19104-6084

Proceeding from the highly potent somatostatin analogs **Ia** and **Ib**, we have replaced the -Phe-X- segment with -Cys-Cys-, thus implementing: 1) constraint of the amide bond to the *cis* geometry; 2) usage of disulfide as surrogate for phenyl. Synthesis, conformational properties and biological results are reported. Known *cis* amide bond mimetics are reviewed.

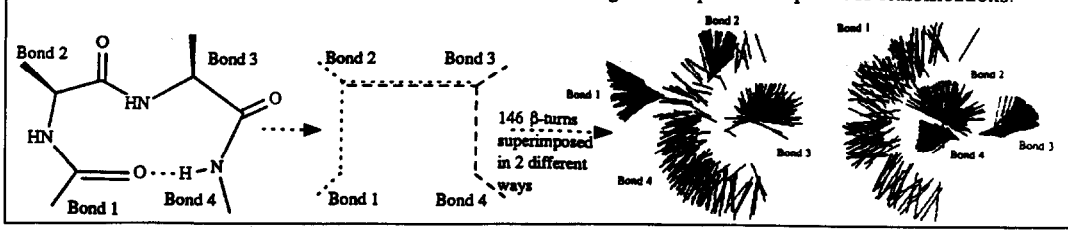


Tetrahedron, **1993**, *49*, 3467

β-TURN TOPOGRAPHY.

Jonathan B. Ball[1*], Richard A. Hughes[2], Paul F. Alewood[3] and Peter R. Andrews[3*]. [1]CSIRO McMaster Laboratory, Private Bag No.1, PO Glebe, NSW 2037, Australia; [2]Max-Planck-Institute for Psychiatry, Department of Neurochemistry, Am Klopferspitz 18a, 8033 Planegg-Martinsried, Federal Republic of Germany; [3]Centre for Drug Design and Development, University of Queensland, Queensland 4072, Australia;

Common topographical features were observed across a wide variety of β-turn types, leading to a new description for β-turns which is more relevant to molecular recognition aspects than previous classifications.

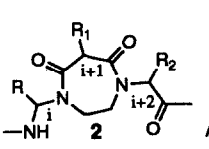


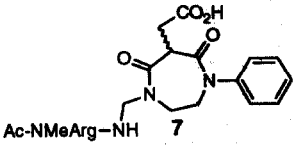
Tetrahedron, **1993**, *49*, 3479

The Use of γ-Turn Mimetics to Define Peptide Secondary Structure

James F. Callahan†*, Kenneth A. Newlander†, Joelle L. Burgess†, Drake S. Eggleston‡, Andrew Nichols, Angela Wong and William F. Huffman† Departments of Medicinal Chemistry†, Structural and Physical Chemistry‡, Pharmacology and Cellular Biochemistry, SmithKline Beecham Pharmaceuticals, 709 Swedeland Rd., P.O. Box 1539, King of Prussia, Pa 19406, USA

A novel γ-turn mimetic **2** has been prepared based on retro amide peptide design. Incorporation of this mimetic into linear peptide fibrinogen receptor antagonist **7** (GPIIb/IIIa receptor) affords the opportunity to test models of antagonist pharmacophore.



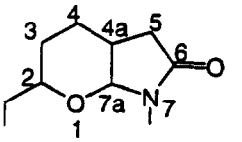


Tetrahedron, **1993**, *49*, 3489

DESIGN AND SYNTHESIS OF A BICYCLIC NON-PEPTIDE ß-BEND MIMETIC OF ENKEPHALIN

Bruce L. Currie, Department of Pharmaceutical Sciences, Chicago College of Pharmacy, John L. Krstenansky, Zhao-Lan Lin, Jiraporn Ungwitayatorn, Yu-Hwei Lee, Michelle del Rosario-Chow, Wen-Sing Sheu, and Michael E. Johnson, Department of Medicinal Chemistry and Pharmacognosy and Center for Pharmaceutical Biotechnology, College of Pharmacy, University of Illinois at Chicago, P.O. Box 6998 (m/c 781), Chicago IL 60680

Computer assisted molecular modeling studies have indicated that the bicyclic ring system shown can produce analogs that closely resemble the *functional group positioning of type I and I' peptide ß-bends.*



Tetrahedron, **1993**, *49*, 3501

THE REVERSE TURN AS A TEMPLATE FOR METAL COORDINATION

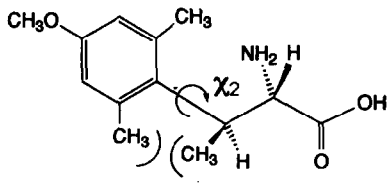
B. Imperiali,* and T. M. Kapoor
Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125.

The structural consequences of metal cation binding to three, Ac-Glu-Gly-Val-Pro-DSer-His-Thr-His-NH_2 (**1**), Ac-His-Gly-Val-Pro-DSer-His-Thr-His-NH_2 (**2**), and Ac-His-Gly-Val-Gly-Gly-His-Thr-His-NH_2 (**3**) are examined by ^1H NMR and CD. Evidence is provided to indicate that the structural preorganization provided by the constrained type II β-turn, in the core of the sequence, is an important determinant for effective metal complexation. Spectroscopic changes resultant on metal binding suggest the presence of a β-hairpin structure. In the absence of such a constraint, metal complexation is ineffective and defined structural changes are not observed.

Tetrahedron, **1993**, *49*, 3511

LOCALLY CONSTRAINED TYROSINE ANALOGUES WITH RESTRICTED SIDE CHAIN DYNAMICS

Ding Jiao, K. C. Russell and Victor J. Hruby*
Department of Chemistry
University of Arizona
Tucson, AZ 85721, U. S. A.



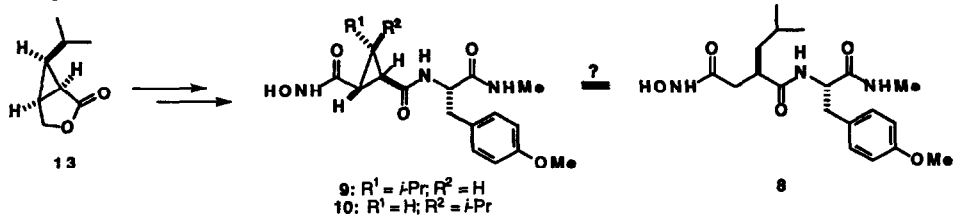
Restricted rotations around the χ_2 angle of constrained tyrosine analogues, with a $\Delta G^{\ddagger}$ = 14~20 kcal/mol, were studied by using variable temperature ^{1}H-NMR experiments. These tyrosine analogues may provide useful dynamic constraints for aromatic side chains in peptides and proteins.

Tetrahedron, **1993**, *49*, 3521

CYCLOPROPANES AS CONFORMATIONALLY RESTRICTED PEPTIDE ISOSTERES. DESIGN AND SYNTHESIS OF NOVEL COLLAGENASE INHIBITORS

Stephen F. Martin,* Christopher J. Oalmann, and Spiros Liras
Department of Chemistry and Biochemistry, The University of Texas, Austin, Texas 78712

The 1,2,3-trisubstituted cyclopropane derivatives **9** and **10** were prepared as conformationally constrained analogues of the collagenase inhibitor **8**. The syntheses of **9** and **10** featured elaboration of the chiral lactone **13**. A novel variant of the Weinreb protocol was developed in which amino acid derivatives were used as nucleophiles in reactions with lactone **13** to give dipeptide analogues directly.

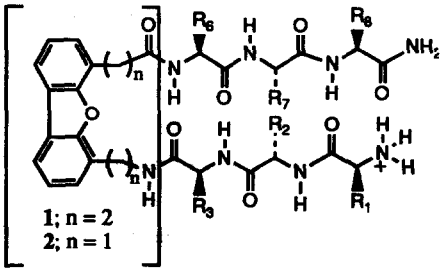


Tetrahedron, **1993**, *49*, 3533

THE DESIGN OF WATER SOLUBLE β-SHEET STRUCTURE BASED ON A NUCLEATION STRATEGY.

Humberto Díaz, Kwok Yin Tsang, Danny Choo and Jeffery W. Kelly *
Department of Chemistry, Texas A&M University, College Station, Texas 77843-3255

In an effort to develop small antiparallel β-sheet secondary structures in aqueous solutions, we have incorporated dibenzofuran-based amino acids into short polypeptides in order to stabilize the β-sheet secondary structure. This manuscript demonstrates that **1** in addition to a properly chosen sequence is required to obtain a well-defined β-sheet.



A HIERARCHICAL APPROACH TO PEPTIDOMIMETIC DESIGN

Tetrahedron, **1993**, *49*, 3547

Garland R. Marshall
Center for Molecular Design
Washington University, St. Louis, Missouri 63130

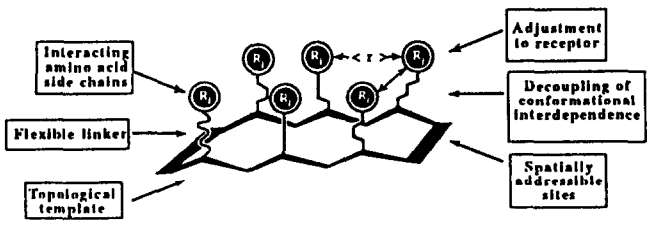
A review of current research, both from the author's laboratory as well as the literature, focused on development of peptidomimetics and utilizing structure-activity data on the parent peptide to determine the receptor-bound conformation as a guide to peptidomimetic design.

THE TASP CONCEPT: MIMETICS OF PEPTIDE LIGANDS, PROTEIN SURFACES AND FOLDING UNITS

Tetrahedron, **1993**, *49*, 3559

G. Tuchscherer*, B. Dörner*, U. Sila*, B. Kamber+, M. Mutter*

*Section de Chimie, Université de Lausanne, Rue de la Barre 2, CH-1005 Lausanne
+Ciba-Geigy AG, CH-4002 Basel, Switzerland



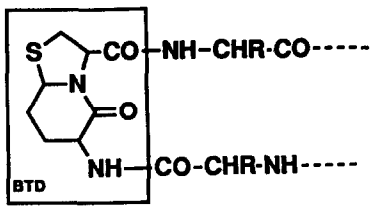
Topological templates (Figure) with selectively addressable functional sites for use in molecular recognition studies and a 4α-helix bundle Template Assembled Synthetic Protein (TASP) exhibiting structural motifs of MHC I are described.

Bicyclic Turned Dipeptide (BTD) as a β-Turn Mimetic; its Design, Synthesis and Incorporation into Bioactive Peptides

Tetrahedron, **1993**, *49*, 3577

Ukon Nagai*, Kazuki Sato, Rika Nakamura and Rika Kato
Mitsubishi-Kasei Institute of Life Sciences, Machida, Tokyo, JAPAN

BTD is a dipeptide mimetic with fixed β-turn conformation. It reverses the direction of chain propagation when incorporated into a polypeptide. The activity of BTD containing analogues of some bioactive peptides will also be mentioned.

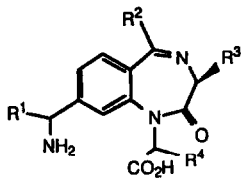


Protein β-Turn Mimetics I: Design, Synthesis, and Evaluation in Model Cyclic Peptides

Tetrahedron, **1993**, *49*, 3593

W.C. Ripka*, G.V. De Lucca*, A.C. Bach II, R. S. Pottorf and J.M. Blaney
Du Pont Merck Pharmaceutical Co. Experimental Station, Wilmington, DE 19880-0353

The benzodiazepine (BZD) peptidomimetic I has been substituted for the naturally occurring four amino acid beta-turn in cyclo-(Gly-Pro-dPhe-dAla)2 and shown by NMR structural analysis to retain the double beta turn conformation in the resulting cyclic octapeptide, cyclo-(Gly-Pro-dPhe-dAla-BZD). This supports the proposal that the benzodiazepine scaffold is a useful beta-turn mimetic that preserves both the geometry of the turn and the positioning of the sidechains.



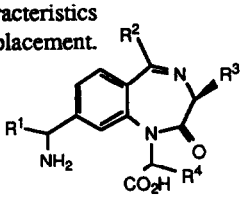
I BZD

Protein β-Turn Mimetics II: Design, Synthesis, and Evaluation in the Cyclic Peptide Gramicidin S

Tetrahedron, **1993**, *49*, 3609

W.C. Ripka*, G.V. De Lucca*, A.C. Bach II, R. S. Pottorf and J.M. Blaney
Du Pont Merck Pharmaceutical Co. Experimental Station, Wilmington, DE 19880-0353

The benzodiazepine (BZD) peptidomimetic I has been substituted for the naturally occurring four amino acid beta-turn in a Gramicidin S analog, cyclo-(Lys-Leu-dPhe-Val)2 and shown by NMR structural analysis to retain the double beta turn conformation in the resulting cyclic partial peptide, cyclo-(Lys-Leu-dPhe-Val-BZD). Additionally, the partial peptide incorporating the peptidomimetic has essentially equivalent biological activity as the original cyclic peptide. Both physical and biological characteristics of the BZD peptidomimetics support the role of this molecular unit as an effective beta-turn replacement.



I BZD

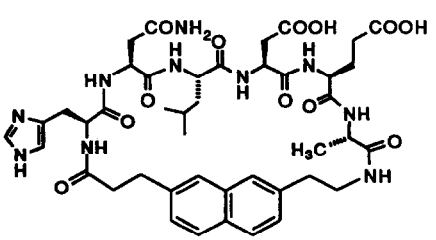
Tetrahedron, **1993**, *49*, 3629

Design, Synthesis, and Three-Dimensional Structural Characterization of a Constrained Ω-Loop Excised from Interleukin-1α

Ramakanth Sarabu*, Kathleen Lovey, Vincent S. Madison, David C. Fry, David N. Greeley, Charles M. Cook, and Gary L. Olson
Roche Research Center, Hoffmann-La Roche Inc., Nutley, New Jersey 07110

Abstract

The cyclic peptide **1**, containing a 2,7-disubstituted naphthalene spacer, was designed to mimic an exposed Ω-loop present in interleukin-1α, an important mediator of immune and inflammatory responses. The synthesis of this cyclic peptide was accomplished via solution phase fragment condensation methodology. The three dimensional characterization using 2D-NMR techniques revealed it to be an excellent mimic for the Ω-loop sequence 41-48 in interleukin -1α.



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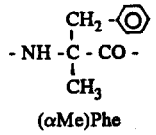
Tetrahedron, **1993**, *49*, 3641

BIOACTIVE AND MODEL PEPTIDES CHARACTERIZED BY THE (αMe)PHE RESIDUE

C. Toniolo, [a*] F. Formaggio, [a] M. Crisma, [a] G. Valle, [a] W.H.J. Boesten, [b] H.E. Schoemaker, [b] J. Kamphuis, [b] P.A. Temussi, [c] E.L. Becker, [d] and G. Précigoux [e]

[a]Biopolymer Res. Centre, CNR, Dept. Organic Chemistry, Univ. Padova, 35131 Padova, Italy; [b]DSM Res., Bio-organic Chemistry Section, 6160 MD Geleen, The Netherlands; [c]Dept. Chemistry, Univ. Naples, 80134 Naples, Italy; [d]Dept. Pathology, Univ. Connecticut, Health Center, Farmington, CT 06032, USA; [e]Lab. of Crystallography, Univ. Bordeaux I, 33405 Talence, France

Peptides based on the (αMe)Phe residue, promising sweeteners, chemoattractants, and candidates for molecular recognition studies, have been prepared and 3D-characterized.



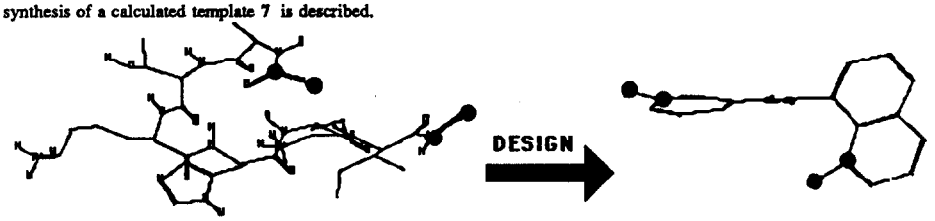
(αMe)Phe

Tetrahedron, **1993**, *49*, 3655

The Calculation and Synthesis of a Template Molecule

Stephen R. Wilson,* Wai K. Tam, Martin J. Di Grandi, and Weili Cui
Department of Chemistry, New York University, Washington Square
New York, NY 10003

A program called **DESIGN** is used to calculate templates by matching vectors from a database of carbon skeleta. The synthesis of a calculated template **7** is described.



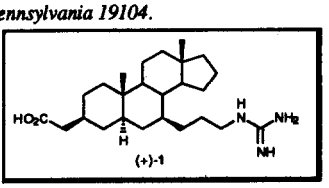
Tetrahedron, **1993**, *49*, 3665

The Versatile Steroid Nucleus: Design and Synthesis of a Peptidomimetic Employing this Novel Scaffold.

Ralph Hirschmann,* Paul A. Sprengeler, Tomomi Kawasaki, James W. Leahy, William C. Shakespeare, and Amos B. Smith, III*

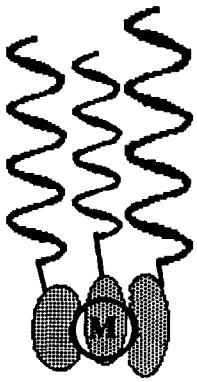
Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104.

The design and synthesis of peptidomimetic **1** employing the novel cyclopentanoperhydrophenanthrene skeleton is described. The large body of steroid literature allows for the introduction of diverse peptidal side chains with precise regio- and stereoselective control. Compound **1** binds to the fibrinogen receptor on blood platelets (GP IIb/IIIa), for which it was designed, with an IC_{50} of ca. 100 μM.



(+)-1

Tetrahedron, **1993**, *49*, 3677



BETWEEN THE SECONDARY STRUCTURE AND THE TERTIARY STRUCTURE FALLS THE GLOBULE: A PROBLEM IN DE NOVO PROTEIN DESIGN

Tomikazu Sasaki* and Marya Lieberman

Three-helix bundle proteins assembled on a tris-bipyridine metal complex permit us to study packing interactions of secondary structures in artificial and native proteins.