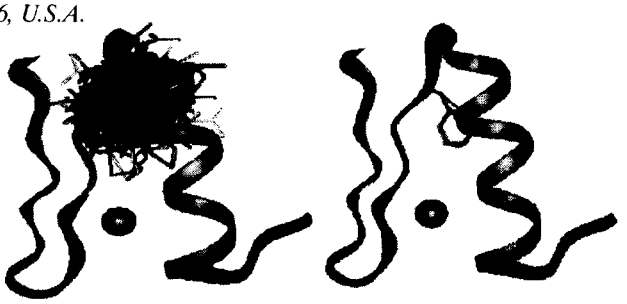
Computational Screening of Combinational Libraries

Bioorg. Med. Chem. **1996**, *4*, 631

Qiang Zheng* and Donald J. Kyle
Scios Nova, Inc., 820 West Maude Avenue, Sunnyvale, CA 94086, U.S.A.

A new computational method is applied for the first time, to predict the most stable amino acid substitution, along with its native conformation. The method differs from the existing ones in that it simultaneously screens an entire library of 190 random conformations, 10 for each of the 19 natural amino acids. The method can be modified to study ligand–host systems.

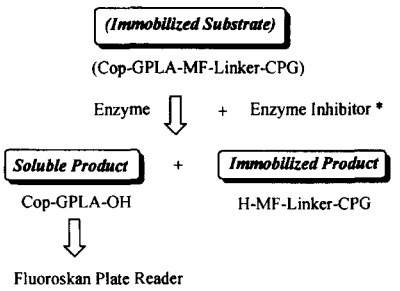


Lead Development: Validation and Application of High Throughput Screening for Determination of Pharmacokinetic Parameters for Enzyme Inhibitors

Bioorg. Med. Chem. **1996**, *4*, 639

Jasbir Singh,[a]* Jim Soloweij,[b] Martin Allen,[a] Loran Killar[c] and Mark Ator[b]
Departments of [a]Medicinal Chemistry, [b]Enzyme and Receptor Biochemistry, and [c]Pharmacology, Sterling Winthrop Pharmaceutical Research Division, 1250 S. Collegeville Road, Collegeville, PA 19426-0900, U.S.A.

An approach utilizing robotics (automation) for the rapid and reliable determination of protease inhibitor concentration in rat plasma samples is described. The bioassay protocol using an immobilized peptide substrate allows high sample throughput, compatible with parallel synthesis/SAR development strategy.

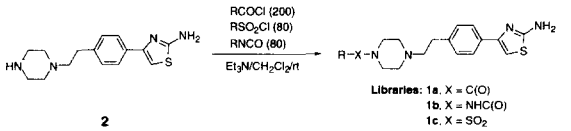


Parallel-Compound Synthesis: Methodology for Accelerating Drug Discovery

Bioorg. Med. Chem. **1996**, *4*, 645

Christopher N. Selway* and Nicholas K. Terrett
Discovery Chemistry Department, Pfizer Central Research, Sandwich, Kent CT13 9NJ, U.K.

The potential of parallel-compound synthesis to rapidly prepare analogues of a chemical lead and provide structure–activity relationship information is exemplified in two therapeutic areas: antiviral agents (herpes simplex virus) and neurokinin-2 receptor antagonists. For example, libraries of amides, sulphonamides, and ureas (libraries **1a–c**) were readily prepared from the piperidine **2** by parallel synthesis.

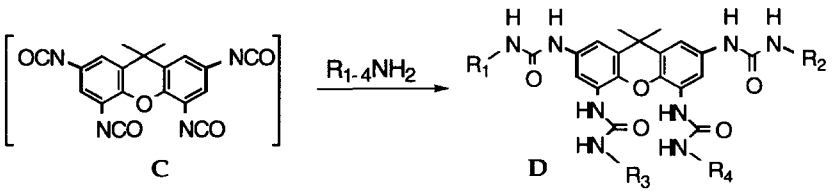


Solution-Phase Generation of Tetraurea Libraries

Bioorg. Med. Chem. **1996**, *4*, 655

Gerald W. Shipps, Jr., Urs P. Spitz and Julius Rebek, Jr.*
Department of Chemistry, Massachusetts Institute of Technology, 77 Massachusetts Avenue, Cambridge, MA 02139, U.S.A.

The tetraisocyanate **C** is generated in situ and reacted with a variety of amines to form ensembles of tetraureas (**D**). This solution-phase approach cleanly forms the expected compounds.



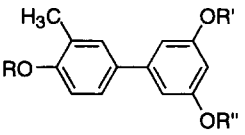
The Design and Synthesis of Substituted Biphenyl Libraries

Bioorg. Med. Chem. **1996**, *4*, 659

Michael R. Pavia,[a]* Michael P. Cohen,[a] Garrett J. Dilley,[a] Gloria R. Dubuc,[a] Tracy L. Durgin,[a] Frank W. Forman,[a] Mark E. Hediger,[a] Guy Milot,[a] Timothy S. Powers,[a] Irving Sucholeiki,[a] Shulan Zhou[a] and David G. Hangauer[b]

[a]*Sphinx Pharmaceuticals, A Division of Eli Lilly and Company, 840 Memorial Drive, Cambridge, MA 01239, U.S.A.*
[b]*Department of Medicinal Chemistry, State University of New York at Buffalo, C439 Cooke Hall, Buffalo, NY 14260, U.S.A.*

A novel scaffold system for the generation of diversity libraries has been designed which allows for rapid modification not only of functional groups, but their spatial arrangements as well. The biphenyl scaffold allows for display of three or four diverse functional groups in a wide variety of spatial arrangements depending on the substitution pattern selected.



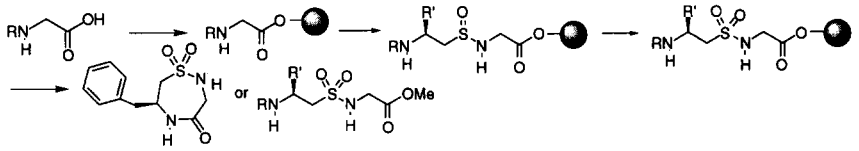
Molecular Diversity of Peptidomimetics: Approaches to the Solid-Phase Synthesis of Peptidosulfonamides

Bioorg. Med. Chem. **1996**, *4*, 667

Dries B. A. de Bont, Wilna J. Moree and Rob M. J. Liskamp*

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

The solid-phase synthesis via sulfinylation followed by oxidation of peptidosulfonamides (R′ = H, CH_2Ph, $(CH_2)_4N(H)Cbz$) and a cyclo-peptidosulfonamide (R′ = CH_2Ph) is described.

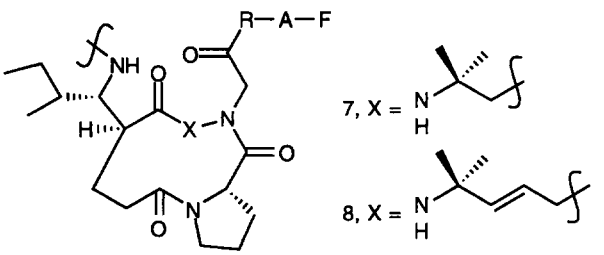


Sculpted Immunogens; B-Cell Epitope Optimization Using Constrained Secondary Structure Libraries

Bioorg. Med. Chem. **1996**, *4*, 673

Jan Urban,[a] Maher Qabar,[a] Charles Sia,[b] Michel Klein[b] and Michael Kahn[a,c,]*

[a]*Molecumetics, Ltd, 2023 120th Avenue N.E., Suite 400, Bellevue, Washington 98005, U.S.A.* [b]*Connaught Laboratories, 1755 Steeles Avenue West, Willowdale, Ontario, Canada M2R 3T4, and* [c]*Department of Pathobiology, University of Washington, Seattle, Washington 98195, U.S.A.*



Bioorg. Med. Chem. **1996**, *4*, 677

Identification of GIYWHHY as a Novel Peptide Substrate for Human $p60^{c\text{-}src}$ Protein Tyrosine Kinase

Qiang Lou, Margaret E. Leftwich and Kit S. Lam

Arizona Cancer Center and Department of Medicine, Microbiology and Immunology, University of Arizona College of Medicine, Tucson, AZ 85724, U.S.A.

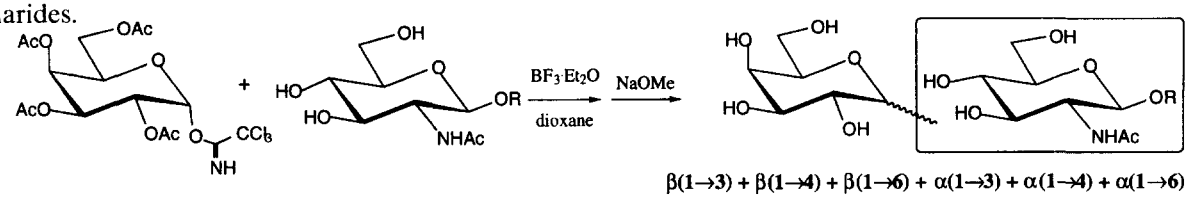
We have designed and synthesized a secondary 'one-bead, one-compound' combinatorial peptide library based on the -Ile-Tyr- dipeptide motif (XIYXXXX, where X = all 19 eukaryotic amino acids except for cysteine). A novel peptide, GIYWHHY, was identified as a specific and potent substrate for $p60^{c\text{-}src}$ protein tyrosine kinase.

Towards Oligosaccharide Libraries: A Study of the Random Galactosylation of Unprotected *N*-Acetylglucosamine

Bioorg. Med. Chem. **1996**, *4*, 683

Yili Ding, Jill Labbe, Osamu Kanie and Ole Hindsgaul*
Department of Chemistry, University of Alberta, Edmonton, Alberta, Canada T6G 2G2

A single reaction of an unprotected β-D-GlcNAc glycoside in dioxane yielded all six possible Gal-GlcNAc disaccharides.



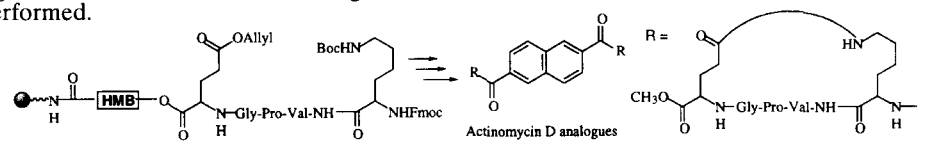
β(1→3) + β(1→4) + β(1→6) + α(1→3) + α(1→4) + α(1→6)

A Convergent Solid-Phase Synthesis of Actinomycin Analogues—Towards Implementation of Double-Combinatorial Chemistry

Bioorg. Med. Chem. **1996**, *4*, 693

Glenn Tong and John Nielsen*
The Technical University of Denmark, Department of Organic Chemistry, Building 201, DK-2800, Lyngby, Denmark

Actinomycin antibiotics bind to nucleic acids via both intercalation and hydrogen bonding. In our search for a novel class of nucleic acid binders, a highly convergent, solid-phase synthetic strategy has been developed and modeled upon natural actinomycins. This method includes Fmoc solid-phase peptide synthesis, solid-phase side-chain to side-chain cyclization, chemoselective cleavage and segment condensation. The final segment condensation allows, for the first time, double-combinatorial chemistry to be performed.



Affinity Purification of von Willebrand Factor Using Ligands Derived from Peptide Libraries

Bioorg. Med. Chem. **1996**, *4*, 699

Ping Y. Huang,[a] George A. Baumbach,[b] Christopher A. Dadd,[b] Joseph A. Buettner,[b] Barbara L. Masecar,[b] Marc Hentsch,[a] David J. Hammond[b] and Ruben G. Carbonell[a,*]
[a]*Department of Chemical Engineering, North Carolina State University, Raleigh, NC 27695-7905, U.S.A.*
[b]*Bayer Corporation, Pharmaceutical Division, Post Office Box 507, Clayton, NC 27520, U.S.A.*

A peptide RVRSFY was found to bind specifically to von Willebrand Factor by screening of a phage peptide library. It can be used as a ligand for the purification of vWF from complex mixtures by affinity chromatography.

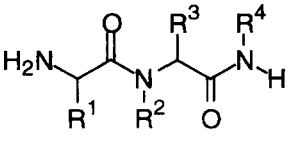
The Synthesis of Peptidomimetic Combinatorial Libraries Through Successive Amide Alkylations

Bioorg. Med. Chem. **1996**, *4*, 709

Barbara Dörner, Gregory M. Husar, John M. Ostresh and Richard A. Houghten*
Torrey Pines Institute for Molecular Studies, 3550 General Atomics Court, San Diego, CA 92121, U.S.A.

The peptidomimetic combinatorial library has four diversity positions (R^1–R^4) and is composed of 57,500 compounds.

R^1. 50 L-, D, and unnatural amino acids
R^2. Five alkyl groups (methyl, ethyl, allyl, benzyl, and naphthylmethyl)
R^3. 46 L-, D-, and unnatural amino groups
R^4. Five alkyl groups (methyl, ethyl, allyl, benzyl, and naphthylmethyl)

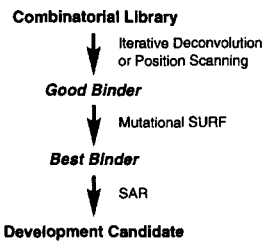


'Mutational SURF': A Strategy for Improving Lead Compounds Identified from Combinatorial Libraries

Bioorg. Med. Chem. **1996**, *4*, 717

Susan M. Freier,[a,*] Danielle A. M. Konings,[b] Jacqueline R. Wyatt[a] and David J. Ecker[a]
[a]ISIS Pharmaceuticals, 2292 Faraday Avenue, Carlsbad, CA 92008, U.S.A. [b]Department of Molecular, Cellular and Developmental Biology, University of Colorado, Boulder, CO 80309, U.S.A.

A procedure, called mutational SURF, for improving the activity of lead compounds identified from combinatorial libraries is described. Model calculations suggest mutational SURF is an efficient procedure for improving the success rate of iterative deconvolutions or position scanning.



A Solution-Phase Strategy for the Synthesis of Chemical Libraries Containing Small Organic Molecules: A Universal and Dipeptide Mimetic Template

Bioorg. Med. Chem. **1996**, *4*, 727

Soan Cheng,[a] Christine M. Tarby,[a] Daniel D. Comer,[a] John P. Williams,[a] Lynn H. Caporale,[a] Peter L. Myers[a] and Dale L. Boger[b]*
[a]CombiChem, Inc., 9050 Camino Santa Fe, San Diego, CA 92121, U.S.A. and [b]Department of Chemistry, The Scripps Research Institute, 10666 North Torrey Pines Road, La Jolla, CA 92037, U.S.A.

A general approach to the solution phase, parallel synthesis of chemical libraries, which allows the preparation of multi-milligram quantities of each individual member, is exemplified with both a universal and dipeptide mimetic template. In each step of the sequence, the reactants, unreacted starting material, reagents and their byproducts are removed by simple liquid/liquid or liquid/solid extractions providing the desired intermediates and final compounds in high purities ($\geq$90–100%) independent of the reaction yields and without deliberate reaction optimization.