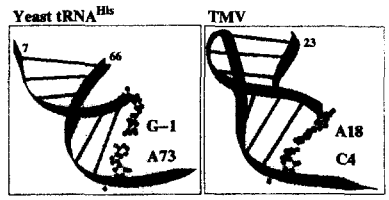
Strategy for RNA Recognition by Yeast Histidyl-tRNA Synthetase

Bioorg. Med. Chem. **1997**, *5*, 1001

Joëlle Rudinger, Brice Felden, Catherine Florentz and Richard Giegé*
UPR 9002 'Structure des Macromolécules Biologiques et Mécanismes de Reconnaissance', Institut de Biologie Moléculaire et Cellulaire du Centre National de la Recherche Scientifique, 15 rue René Descartes, F-67084 Strasbourg Cedex, France

Common rules accounting for aminoacylation of several tRNA and tRNA-like molecules by yeast histidyl-tRNA synthetase are examined. A nucleotide at position minus 1 facing the 'discriminator' base in $tRNA^{His}$ or its mimic in tRNA-like domains is the main histidine identity element.

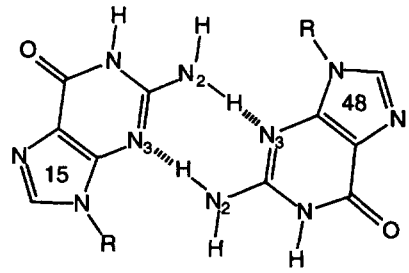


A Strategy of tRNA Recognition that Includes Determinants of RNA Structure

Bioorg. Med. Chem. **1997**, *5*, 1011

Christian S. Hamann and Ya-Ming Hou*
Department of Biochemistry and Molecular Pharmacology, Thomas Jefferson University, 233 South 10th Street, Philadelphia, PA 19107, U.S.A.

We provide evidence that a relationship between the N2:N3 pairing of G15:G48 and a mismatch at A13:A22 is important for aminoacylation of a tRNA with cysteine.

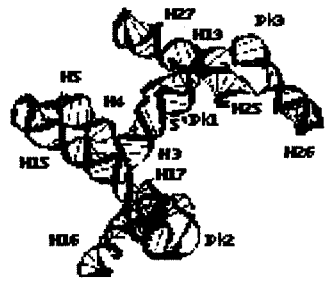


Context Dependent RNA–RNA Recognition in a Three-Dimensional Model of the 16S rRNA Core

Bioorg. Med. Chem. **1997**, *5*, 1021

Benoît Masquida, Brice Felden and Eric Westhof
Institut de Biologie Moléculaire et Cellulaire du CNRS-UPR 9002, 15 rue René Descartes F-67084 Strasbourg Cedex, France

A 3-D model of the core of the 16S rRNA of *Escherichia coli* has been built in agreement with all the available experimental data. The roles in assembly, initiation or elongation of the three pseudoknots in ribosomal dynamics are emphasized as well as their relative locations in the 30S subunit which are mediated by complex multiple-way junctions.

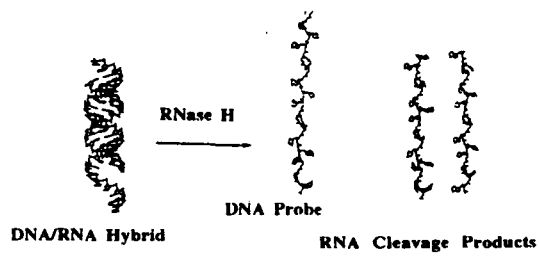


Modulation of RNase H Activity by Modified DNA Probes: Major Groove vs Minor Groove Effects

Bioorg. Med. Chem. **1997**, *5*, 1037

Andrew T. Daniher, Jin Xie, Shashank Mathur and James K. Bashkin*
Department of Chemistry, Washington University, St Louis, MO 63130, U.S.A.

DNA/RNA duplexes were formed using DNA probes designed to deliver metal complexes via either the major groove or the minor groove of the duplex. The duplexes were treated with *E. coli* RNase H. Modifications in the major groove produced the same RNA cleavage pattern as unmodified DNA probes. However, minor groove substituents inhibited RNA cleavage over a four-base region. Our results support enzyme binding in the minor groove of an DNA/RNA duplex.

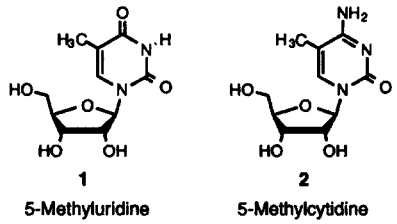


Recognition of RNA by Triplex Formation: Divergent Effects of Pyrimidine C-5 Methylation

Bioorg. Med. Chem. **1997**, *5*, 1043

Shaohui Wang, Yanzheng Xu and Eric T. Kool*
Department of Chemistry and Department of Biochemistry and Biophysics, University of Rochester, Rochester, NY 14627, U.S.A

The contrasting effects of addition of methyl groups to the C-5 position of uracil and cytosine on the binding of RNA sequences by triplex-forming circular RNA oligonucleotides are described.

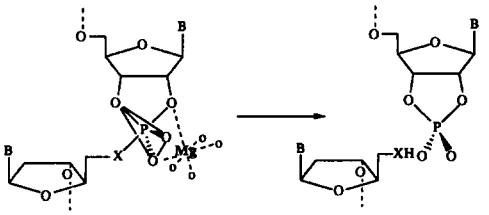


Application of a 5′-Bridging Phosphorothioate to Probe Divalent Metal and Hammerhead Ribozyme Mediated RNA Cleavage

Bioorg. Med. Chem. **1997**, *5*, 1051

Robert G. Kuimelis and Larry W. McLaughlin*
Department of Chemistry, Merkert Chemistry Center, Boston College, Chestnut Hill, MA 02167, U.S.A.

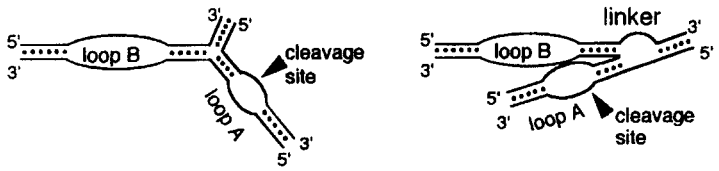
The synthesis and cleavage activity of a chimeric DNA/RNA oligonucleotide containing a 5′-bridging phosphorothioate linkage adjacent to a ribonucleotide in an otherwise all-DNA sequence is described.



Construction of Hairpin Ribozymes with a Three-Way Junction

Bioorg. Med. Chem. **1997**, *5*, 1063

Yasuo Komatsu, Miho Shirai, Shigeko Yamashita and Eiko Ohtsuka*
Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo 060, Japan

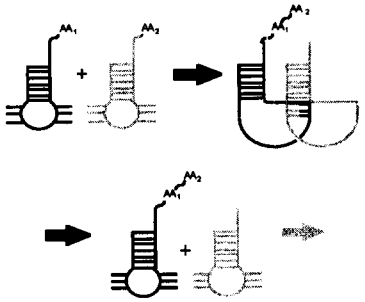


RNA–RNA Interactions Between Oligonucleotide Substrates for Aminoacylation

Bioorg. Med. Chem. **1997**, *5*, 1071

Barry S. Henderson and Paul Schimmel*
Department of Biology, Massachusetts Institute of Technology, Cambridge, MA 02139, U.S.A.

The design and characterization of complexes formed through lateral loop–loop base pairing between RNA hairpin substrates for amino-acylation is described. These studies demonstrate an experimental basis for microhelix association for peptide synthesis.

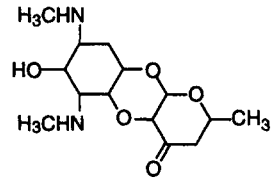


The Selection In Vivo and Characterization of an RNA Recognition Motif for Spectinomycin

Bioorg. Med. Chem. **1997**, *5*, 1081

George Thom and Catherine D. Prescott*
SmithKline Beecham Pharmaceuticals, Department of Molecular Recognition, 1250 South Collegeville Road, Post Office Box 5089, Collegeville, PA 19426-0989, U.S.A.

A novel in vivo approach is described for the selection of RNA fragments that confer resistance to the antibiotic spectinomycin. These RNA molecules are predicted to share structural features in common with the drug binding site on the intact 30S ribosomal subunit.



Post-SELEX Combinatorial Optimization of Aptamers

Bioorg. Med. Chem. **1997**, *5*, 1087

Bruce E. Eaton, Larry Gold,* Brian J. Hicke, Nebojša Janjić, Fiona M. Jucker, David P. Sebesta, Theodore M. Tarasow, Michael C. Willis and Dominic A. Zichi
NeXstar Pharmaceuticals, Inc., 2860 Wilderness Place, Boulder, CO 80301, U.S.A.

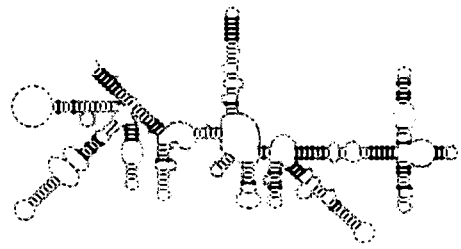
In vitro selection techniques provide a means of isolating nucleic acid ligands for binding to particular protein targets. Although most aptamers have quite high affinities for their target proteins, it has been shown that post-SELEX modification can result in further enhancement of binding affinity, as well as other desired properties. This has led to the current development of a more systematic approach to aptamer optimization using a combinatorial screening methodology.

In vitro Evolution Used to Define a Protein Recognition Site Within a Large RNA Domain

Bioorg. Med. Chem. **1997**, *5*, 1097

Amalia Sapag and David E. Draper*
Department of Chemistry, Johns Hopkins University, Baltimore, MD 21218, U.S.A.

Ribosomal protein S4 recognizes a large, 460 nucleotide domain of 16S ribosomal RNA. Thirty highly mutated sequences still recognizing S4 were selected, and contain compensatory base changes throughout the domain. S4 apparently requires proper folding of the entire domain to form its recognition site.

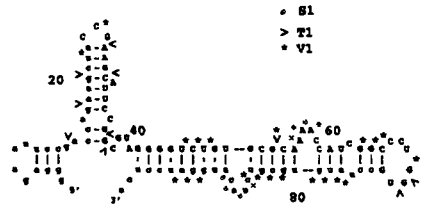


Interacting RNA Species Identified by Combinatorial Selection

Bioorg. Med. Chem. **1997**, *5*, 1107

Bongrae Cho,[a] David C. Taylor,[a] Hugh B. Nicholas, Jr[b] and Francis J. Schmidt[a,*]
[a]*Department of Biochemistry, University of Missouri-Columbia, Columbia, MO 65212, U.S.A. and* [b]*Pittsburgh Supercomputing Center, 4400 Fifth Avenue, Pittsburgh, PA 15213, U.S.A.*

Aptamer RNAs were selected from a random library for the ability to bind to a small RNA stem-loop. The selection scheme was designed to preclude isolation of aptamers with extensive Watson–Crick complementarity to the target RNA.



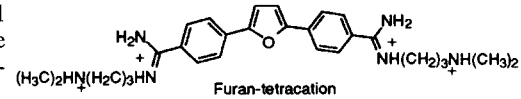
Modulation of the Rev–RRE Interaction by Aromatic Heterocyclic Compounds

Bioorg. Med. Chem. **1997**, *5*, 1149

Maria L. Zapp,[a,*] Donna W. Young,[a] Arvind Kumar,[b] Ravinder Singh,[c] David W. Boykin,[b] W. David Wilson[b] and Michael R. Green[c]

[a]*Department of Molecular Genetics and Microbiology and UMASS Cancer Center, University of Massachusetts Medical Center, Worcester, MA 01605, U.S.A.;* [b]*Department of Chemistry and Center for Biotechnology and Drug Design, Georgia State University, Atlanta, GA 30303, U.S.A. and* [c]*Howard Hughes Medical Institute, Program in Molecular Medicine, University of Massachusetts Medical Center, Worcester, MA 01605, U.S.A.*

A series of aromatic heterocycles were tested for their ability to inhibit the HIV-1 Rev–RRE interaction. In particular, a tetracationic diphenylfuran, AK.A, can selectively block binding of Rev to its high-affinity viral RNA binding site at concentrations as low as 0.1 μM. The molecular basis for the AK.A–RNA interaction, as well as the mode of RNA binding differs from previously described aminoglycoside Rev inhibitors.



Design and Analysis of Molecular Motifs for Specific Recognition of RNA

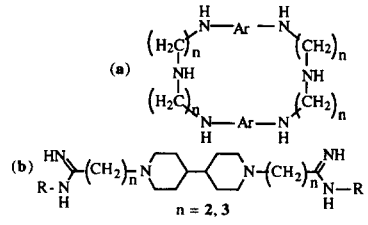
Bioorg. Med. Chem. **1997**, *5*, 1157

Ke Li,[a] M. Fernandez-Saiz,[a] C. Ted Rigl,[a] Arvind Kumar,[a] Kaliappa G. Ragunathan,[a] Adrian W. McConnaughie,[b] David W. Boykin,[a] Hans-Jörg Schneider[b] and W. David Wilson*[,a]

[a]*Department of Chemistry, Georgia State University, Atlanta, GA 30303, U.S.A.*

[b]*FR Organische Chemie, Universität des Saarlandes, D-66041 Saarbrücken, Germany*

A series of macrocyclic (a) and linear (b) polycations were synthesized and evaluated for differential binding to polymeric RNA and DNA duplexes, as well as for inhibition of HIV-1 RRE/Rev interaction in vitro.



Discovery of Selective, Small-Molecule Inhibitors of RNA Complexes—I. The Tat Protein/TAR RNA Complexes Required for HIV-1 Transcription

Bioorg. Med. Chem. **1997**, *5*, 1173

Houng-Yau Mei,[a,*] David P. Mack,[a,*] Adam A. Galan,[a] Nadia S. Halim,[a] Andrea Heldsinger,[d] Joseph A. Loo,[b] David W. Moreland,[c] Kristin A. Sannes-Lowery,[b] Lamia Sharmeen,[d] Hoa N. Truong,[a] and Anthony W. Czarnik[a]

[a]*BioOrganic Chemistry Section,* [b]*Analytical Research Section,* [c]*Biomolecular Structure and Drug Design Section, Department of Chemistry; and* [d]*Infectious Diseases Section, Department of Therapeutics, Parke-Davis Pharmaceutical Research, Division of Warner–Lambert Company, 2800 Plymouth Road, Ann Arbor, MI 48106, U.S.A.*

We report here a therapeutic program focusing on the inhibition of an HIV-1 Tat protein–TAR RNA interaction. High-throughput screening methodologies were established to identify in vitro Tat–TAR inhibitors. Cellular activities of the Tat–TAR inhibitors were examined in Tat-activated reporter gene assays and HIV-1 infection assays.

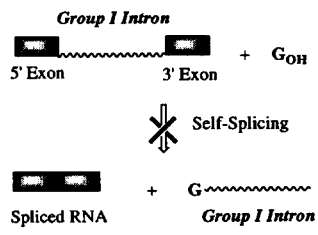
Discovery of Selective, Small-Molecule Inhibitors of RNA Complexes—II. Self-Splicing Group I Intron Ribozyme

Bioorg. Med. Chem. **1997**, *5*, 1185

Houng-Yau Mei,* Mei Cui, Shannon M. Lemrow and Anthony W. Czarnik

BioOrganic Chemistry Section, Department of Chemistry, Parke-Davis Pharmaceutical Research, Division of Warner–Lambert Company, 2800 Plymouth Road, Ann Arbor, MI 48106, U.S.A.

Self-splicing group I intron RNA was chosen as a potential therapeutic target. High-throughput screening methodologies have been developed to identify small organic molecules that regulate the activities of these catalytic introns.

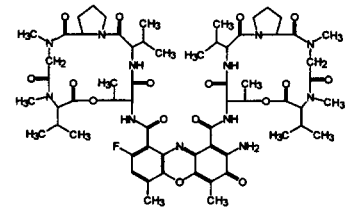


Selectivity of F8-Actinomycin D for RNA:DNA Hybrids and Its Anti-Leukemia Activity

Bioorg. Med. Chem. **1997**, *5*, 1197

Fusao Takusagawa, Ken T. Takusagawa, Robert G. Carlson, and Robert F. Weaver
Department of Biochemistry, University of Kansas, Lawrence KS 66045-2106, U.S.A.

Physical and biological characteristics of F8-Actinomycin D, studied by X-ray crystallography, molecular modeling, DNA/RNA binding measurement, RNA synthesis inhibitory activity and antitumor screen, indicate that the unique anti-leukemia selectivity of F8AMD might be caused by the agent binding to RNA:DNA hybrid.



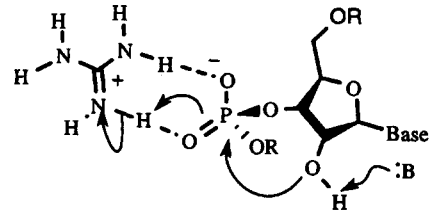
F8AMD

Using Guanidinium Groups for the Recognition of RNA and as Catalysts for the Hydrolysis of RNA

Bioorg. Med. Chem. **1997**, *5*, 1209

Denise M. Perreault, Larry A. Cabell and Eric V. Anslyn*
Department of Chemistry and Biochemistry, The University of Texas at Austin, TX 78712, U.S.A.

A series of artificial phosphodiesterases, which incorporate guanidinium groups positioned to mimic the hydrogen-bonding patterns found in natural enzymes and simple salts, are discussed.

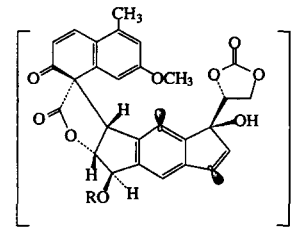


Effect of Ribonucleotide Substitution on Nucleic Acid Bulge Recognition by Neocarzinostatin

Bioorg. Med. Chem. **1997**, *5*, 1221

Lizzy S. Kappen, Zhen Xi and Irving H. Goldberg*
Department of Biological Chemistry and Molecular Pharmacology, Harvard Medical School, Boston, MA 02115, U.S.A.

To determine why bulged RNA structures are not as good substrates for cleavage by the enediyne antibiotic neocarzinostatin chromophore in the general base-catalyzed reaction as are DNA bulges, we have systematically substituted ribonucleotide residues in a DNA bulged structure (CCGATGCG·CGCAGTTCGG) (cleaved residue is underlined) known to be an excellent substrate and have studied them for cleavage efficiency, drug binding, and bulge-dependent drug product formation.



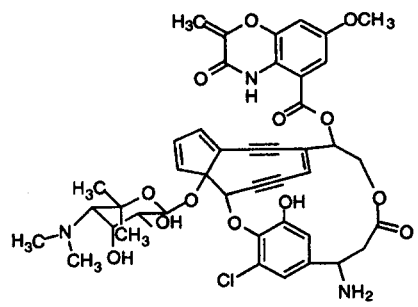
3

Selective Cleavages of tRNA^{Phe} with Secondary and Tertiary Structures by Enediyne Antitumor Antibiotics

Bioorg. Med. Chem. **1997**, *5*, 1229

Yukio Sugiura,* Ryuichi Totsuka, Michihiro Araki and Yasushi Okuno
Institute for Chemical Research, Kyoto University, Uji, Kyoto 611, Japan

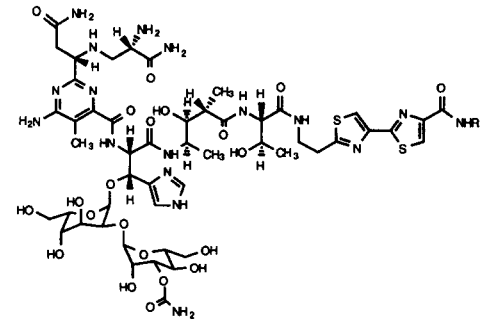
Site-selective cleavage for yeast tRNA^{Phe} by some enediyne antibiotics has been investigated in the absence and presence of Mg^{2+} ions. C-1027 and esperamicin specifically cleaved the RNA at the anticodon arm region.



On the Chemistry of RNA Degradation by Fe·Bleomycin

Bioorg. Med. Chem. **1997**, *5*, 1235

Chris E. Holmes,[a] Robert J. Duff,[a] Gijs A. van der Marel,[b] Jacques van Boom,[b] and Sidney M. Hecht[a,*]
[a]*Departments of Chemistry and Biology, University of Virginia, Charlottesville, VA 22901 U.S.A.;*
[b]*Department of Organic Chemistry, University of Leiden, Leiden, The Netherlands*



The chemistry of RNA cleavage by bleomycin is defined using two types of substrates.