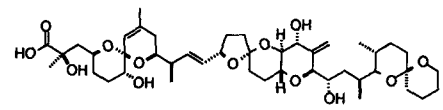
Inhibition of the Ser–Thr Phosphatases PP1 and PP2A by Naturally Occurring Toxins

Bioorg. Med. Chem. **1997**, *5*, 1739

James E. Sheppeck, II, Carla-Maria Gauss and A. Richard Chamberlin*
Department of Chemistry, University of California at Irvine, Irvine, CA 92697, U.S.A.

The okadaic acid class of naturally occurring toxins is a structurally diverse group of molecules that inhibit the protein phosphatases PP1 and PP2A. Studies providing information about the mode of binding between the toxins and the phosphatases contribute to an overall understanding of the signal transduction pathways in which the phosphatases are involved.



Okadaic acid
(dinoflagellates)

A Molecular Modeling Analysis of the Binding Interactions Between the Okadaic Acid Class of Natural Product Inhibitors and the Ser–Thr Phosphatases, PP1 and PP2A

Bioorg. Med. Chem. **1997**, *5*, 1751

Carla-Maria Gauss,[a] James E. Sheppeck, II,[a] Angus C. Nairn[b] and Richard Chamberlin[a,]*
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[b]*The Rockefeller University, 1230 York Avenue, New York, NY 10021, U.S.A.*

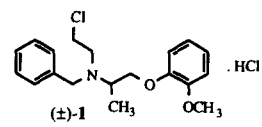
We have proposed computer-generated models of the catalytic subunits of the serine–threonine protein phosphatases PP1 and PP2A complexed with their endogenous substrate phospho-DARPP-32, and several known naturally occurring inhibitors.

Synthesis and α-Adrenoceptor Blocking Activity of the Enantiomers of Benzyl-(2-chloroethyl)-[2-(2-methoxyphenoxy)-1-methylethyl]amine Hydrochloride

Bioorg. Med. Chem. **1997**, *5*, 1775

Dario Giardinà,[a] Mauro Crucianelli,[a] Gabriella Marucci,[a] Piero Angeli,[a] Carlo Melchiorre[b] and Luciano Antolini[c]
[a]*Department of Chemical Sciences, University of Camerino, 62032 Camerino, Italy*
[b]*Department of Pharmaceutical Sciences, University of Bologna, 40126 Bologna, Italy*
[c]*Department of Chemistry, University of Modena, 41100 Modena, Italy*

The (*R*)-(+)-**1** enantiomer displayed a biphasic inhibition mechanism of rat vas deferens α_1-adrenoceptors similar to that of racemic **1**.



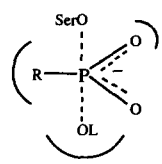
(±)-**1**

Structure–Activity Studies of the Inhibition of Serine β-Lactamases by Phosphonate Monoesters

Bioorg. Med. Chem. **1997**, *5*, 1783

Naixin Li, Jubrail Rahil, Margaret E. Wright and R.F. Pratt*
Department of Chemistry, Wesleyan University, Middletown, CT 06459, U.S.A.

Rates of inhibition of β-lactamases by a new series of phosphonate monoesters suggest interaction between the enzyme and the leaving group.



Bioorg. Med. Chem. **1997**, *5*, 1789

E-64 Analogues as Inhibitors of Cathepsin B. On the Role of the Absolute Configuration of the Epoxysuccinyl Group

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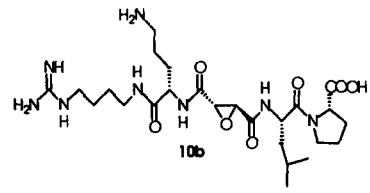
[a]*Max-Planck-Institut fur Biochemie, 82152 Martinsried, Germany*
[b]*Institut fur Physiologische Chemie, Physikalische Biochemie und Zellbiologie, Ludwig-Maximilians-Universität, 80336 München, Germany*
[c]*Department of Biochemistry and Molecular Biology, Josef Stefan Institute, 61111 Ljubljana, Slovenia*

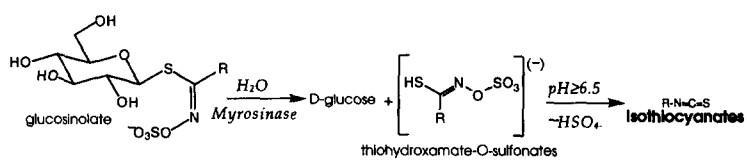
A comparative analysis of inhibition of cathepsin B by (2*S*,3*S*) and (2*R*,3*R*) trans-epoxysuccinyl compounds revealed differentiated configurational preferences of the E-64- and CA030-type inhibitors. Correspondingly, bis-peptidyl derivatives of trans-epoxysuccinic acid (**10b**) with the potential ability to interact with both the *S* and *S'* subsites do not fulfil the expectations in terms of increased potency and selectivity.



Bioorg. Med. Chem. **1997**, *5*, 1799

Myrosinase-Generated Isothiocyanate from Glucosinolates: Isolation, Characterization and In Vitro Antiproliferative Studies

O. Leoni,[a] R. Iori,[a] S. Palmieri,[a] E. Esposito,[b] E. Menegatti,[b] R. Cortesi[b] and C. Nastruzzi[b,*]
[a]*Istituto Sperimentale per le Colture Industriali MiRAAF, Via di Corticella 133, I-40129 Bologna, Italy*
[b]*Dipartimento di Scienze Farmaceutiche, Università di Ferrara, Via Fossato di Mortara 19, I-44100 Ferrara, Italy*

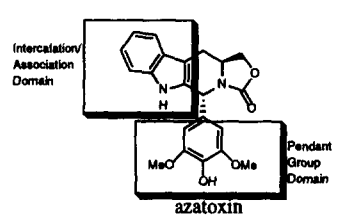


Bioorg. Med. Chem. **1997**, *5*, 1807

Structure–Activity Relationship for DNA Topoisomerase II-Induced DNA Cleavage by Azatoxin Analogues

Jose S. Madalengoitia, Jetze J. Tepe, Karl A. Werbovetz, Erich K. Lehnert and Timothy L. Macdonald*
Department of Chemistry, University of Virginia, Charlottesville, VA 22901, U.S.A.

Eighteen analogues were synthesized and evaluated for their ability to induce topoisomerase II-mediated DNA strand breaks in vitro. Substitution at the 8-, 9-, and 10-positions of the DNA intercalation/association domain enhanced activity, whereas, any variation in the pendant group domain of our model resulted in decreased topoisomerse II activity.

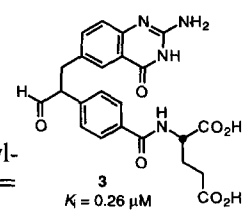


Bioorg. Med. Chem. **1997**, *5*, 1817

10-Formyl-5,8,10-trideazafolic Acid (10-Formyl-TDAF): A Potent Inhibitor of Glycinamide Ribonucleotide Transformylase

Dale L. Boger,[a,*] Nancy-Ellen Haynes,[a] Paul A. Kitos,[b] Mark S. Warren,[c] Joseph Ramcharan,[c] Ariane E. Marolewski[c] and Stephen J. Benkovic[c,*]
[a]*Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, U.S.A.*
[b]*Department of Biochemistry, University of Kansas, Lawrence, KS 66045, U.S.A.*
[c]*Department of Chemistry, Pennsylvania State University, University Park, PA 16802, U.S.A.*

The preparation and evaluation of 10-formyl-5,8,10-trideazafolic acid (**3**, 10-formyl-TDAF) as a potent inhibitor of glycinamide ribonucleotide transformylase (K_i = 0.26 ± 0.05 μM) is detailed.



Bioorg. Med. Chem. **1997**, *5*, 1831

Functionalized Analogues of 5,8,10-Trideazafolate as Potential Inhibitors of GAR Tfase or AICAR Tfase

Dale L. Boger,[a,*] Nancy-Ellen Haynes,[a] Mark S. Warren,[b] Lata T. Gooljarsingh,[b] Joseph Ramcharan,[b] Paul A. Kitos[c] and Stephen J. Benkovic[b,*]
[a]*Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, U.S.A.*
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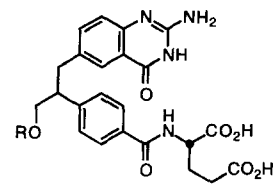
[c]*Department of Biochemistry, University of Kansas, Lawrence, KS 66045, U.S.A.*

A series of TDAF-based analogues of 10-formyl-tetrahydrofolic acid are examined in efforts to explore the formyl transfer region of GAR Tfase and AICAR Tfase.

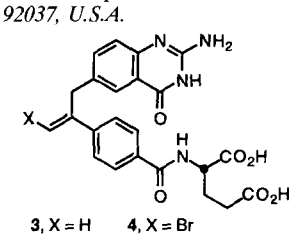


Bioorg. Med. Chem. **1997**, *5*, 1839

Functionalized Analogues of 5,8,10-Trideazafolate: Development of an Enzyme-Assembled Tight Binding Inhibitor of GAR Tfase and a Potential Irreversible Inhibitor of AICAR Tfase

Dale L. Boger,[a,*] Nancy-Ellen Haynes,[a] Mark S. Warren,[b] Joseph Ramcharan,[b] Paul A. Kitos[c] and Stephen J. Benkovic[b,*]
[a]*Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, U.S.A.*
[b]*Department of Chemistry, Pennsylvania State University, University Park, PA 16802, U.S.A.*
[c]*Department of Biochemistry, University of Kansas, Lawrence, KS 66047, U.S.A.*

The preparation and evaluation of ***15*** along with a set of inhibitors ***3*** and ***4*** of GAR and AICAR Tfase based on the TDAF core which contain an sp^2 C-10 carbon atom replacing N-10 of the natural cofactor are detailed. Both **3** and **4** were found to be simple competitive inhibitors of GAR Tfase and AICAR Tfase while **15** may provide an enzyme-assembled tight binding inhibitor of GAR Tfase by virtue of reaction with the substrate GAR at the active site and may inactivate AICAR Tfase by virtue of alkylation of an active site residue.

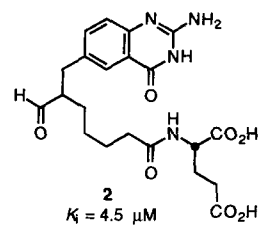


Bioorg. Med. Chem. **1997**, *5*, 1847

Abenzyl 10-Formyl-trideazafolic Acid (Abenzyl 10-Formyl-TDAF): An Effective Inhibitor of Glycinamide Ribonucleotide Transformylase

Dale L. Boger,[a,*] Nancy-Ellen Haynes,[a] Mark S. Warren,[b] Joseph Ramcharan,[b] Ariane E. Marolewski,[b] Paul A. Kitos[c] and Stephen J. Benkovic[b,*]
[a]*Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, U.S.A.*
[b]*Department of Chemistry, Pennsylvania State University, University Park, PA 16802, U.S.A.*
[c]*Department of Biochemistry, University of Kansas, Lawrence, KS 66047, U.S.A.*

The preparation and evaluation of *N*-[7-(2-amino-3,4-dihydro-4-oxo-quinazolin-6-yl)-6-formyl-1-oxo-heptyl]-L-glutamic acid (2-abenzyl-10-formyl-trideazafolic acid) as an inhibitor of GAR Tfase (K_i = 4.5 ± 0.3 μM) and AICAR Tfase (K_i = 42 ± 11 μM) are detailed.



Bioorg. Med. Chem. **1997**, *5*, 1853

Multisubstrate Analogue Based on 5,8,10-Trideazafolate

Dale L. Boger,[a,*] Nancy-Ellen Haynes,[a] Mark S. Warren,[b] Joseph Ramcharan,[b] Paul A. Kitos[c] and Stephen J. Benkovic[b,*]
[a]*Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, U.S.A*
[b]*Department of Chemistry, Pennsylvania State University, University Park, PA 16802, U.S.A.*
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The preparation and evaluation of the multisubstrate analogue **3** based on the 5,8,10-trideazafolate core for GAR and AICAR Tfase inhibition is detailed.