

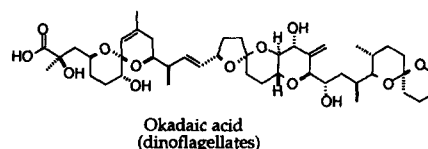
Inhibition of the Ser-Thr Phosphatases PP1 and PP2A by Naturally Occurring Toxins

Bioorg. Med. Chem. 1997, 5, 1739

James E. Sheppeck, II, Carla-Maria Gauss and A. Richard Chamberlin*

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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.



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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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

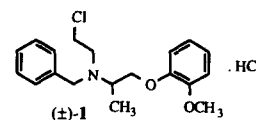
Dario Giardinà,^a Mauro Crucianelli,^a Gabriella Marucci,^a Piero Angeli,^a Carlo Melchiorre^b and Luciano Antolini^c

^aDepartment of Chemical Sciences, University of Camerino, 62032 Camerino, Italy

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^cDepartment 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.



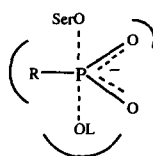
Structure-Activity Studies of the Inhibition of Serine β -Lactamases by Phosphonate Monoesters

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.



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

Bioorg. Med. Chem. 1997, 5, 1789

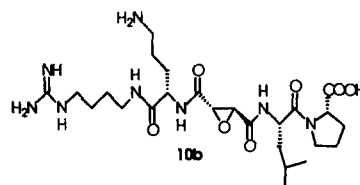
Norbert Schaschke,^a Irmgard Assfalg-Machleidt,^b Werner Machleidt,^b Dushan Turk,^c and Luis Moroder^{a,*}

^aMax-Planck-Institut für Biochemie, 82152 Martinsried, Germany

^bInstitut für Physiologische Chemie, Physikalische Biochemie und Zellbiologie, Ludwig-Maximilians-Universität, 80336 München, Germany

^cDepartment 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.



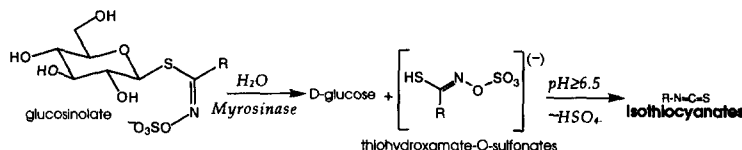
Myrosinase-Generated Isothiocyanate from Glucosinolates: Isolation, Characterization and In Vitro Antiproliferative Studies

Bioorg. Med. Chem. 1997, 5, 1799

O. Leoni,^a R. Iori,^a S. Palmieri,^a E. Esposito,^b E. Menegatti,^b R. Cortesi^b and C. Nastruzzi^{b,*}

^aIstituto Sperimentale per le Colture Industriali MiRAAF, Via di Corticella 133, I-40129 Bologna, Italy

^bDipartimento di Scienze Farmaceutiche, Università di Ferrara, Via Fossato di Mortara 19, I-44100 Ferrara, Italy



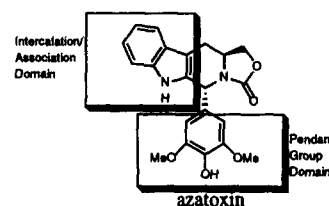
Structure-Activity Relationship for DNA Topoisomerase II-Induced DNA Cleavage by Azatoxin Analogues

Bioorg. Med. Chem. 1997, 5, 1807

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 topoisomerase II activity.



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

Bioorg. Med. Chem. 1997, 5, 1817

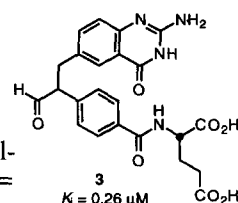
Dale L. Boger,^{a,*} Nancy-Ellen Haynes,^a Paul A. Kitos,^b Mark S. Warren,^c Joseph Ramcharan,^c Ariane E. Marolewski^c and Stephen J. Benkovic^{c,*}

^aDepartment of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, U.S.A.

^bDepartment of Biochemistry, University of Kansas, Lawrence, KS 66045, U.S.A.

^cDepartment 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 ($K_i = 0.26 \pm 0.05 \mu\text{M}$) is detailed.



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

Bioorg. Med. Chem. 1997, 5, 1831

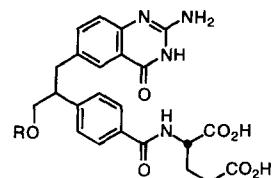
Dale L. Boger,^{a,*} Nancy-Ellen Haynes,^a Mark S. Warren,^b Lata T. Gooljarsingh,^b Joseph Ramcharan,^b Paul A. Kitos^c and Stephen J. Benkovic^{b,*}

^aDepartment of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, U.S.A.

^bDepartment of Chemistry, Pennsylvania State University, University Park, PA 16802, U.S.A.

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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.



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

Bioorg. Med. Chem. 1997, 5, 1839

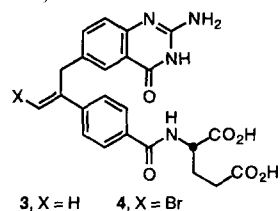
Dale L. Boger,^{a,*} Nancy-Ellen Haynes,^a Mark S. Warren,^b Joseph Ramcharan,^b Paul A. Kitos^c and Stephen J. Benkovic^{b,*}

^aDepartment of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, U.S.A.

^bDepartment of Chemistry, Pennsylvania State University, University Park, PA 16802, U.S.A.

^cDepartment 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.



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

Bioorg. Med. Chem. 1997, 5, 1847

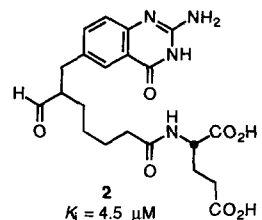
Dale L. Boger,^{a,*} Nancy-Ellen Haynes,^a Mark S. Warren,^b Joseph Ramcharan,^b Ariane E. Marolewski,^b Paul A. Kitos^c and Stephen J. Benkovic^{b,*}

^aDepartment of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, U.S.A.

^bDepartment of Chemistry, Pennsylvania State University, University Park, PA 16802, U.S.A.

^cDepartment 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 ($K_i = 4.5 \pm 0.3 \mu\text{M}$) and AICAR Tfase ($K_i = 42 \pm 11 \mu\text{M}$) are detailed.



Multisubstrate Analogue Based on 5,8,10-Trideazafolate

Bioorg. Med. Chem. 1997, 5, 1853

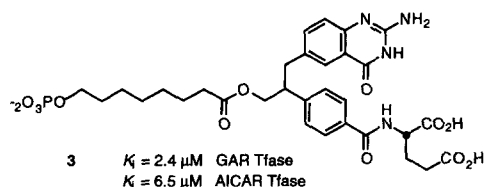
Dale L. Boger,^{a,*} Nancy-Ellen Haynes,^a Mark S. Warren,^b Joseph Ramcharan,^b Paul A. Kitos^c and Stephen J. Benkovic^{b,*}

^aDepartment of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, U.S.A.

^bDepartment of Chemistry, Pennsylvania State University, University Park, PA 16802, U.S.A.

^cDepartment of Biochemistry, University of Kansas, Lawrence, KS 66045, U.S.A.

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.

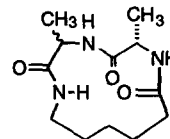


Effect of Stereochemistry on the Transport of Aca-Linked β -Turn Peptidomimetics Across a Human Intestinal Cell Line

Bioorg. Med. Chem. 1997, 5, 1859

Kiyoshi Tamura,^a Konstantinos A. Agrios,^b David Vander Velde,^b Jeffrey Aubé^{*,b} and Ronald T. Borchardt^{*,a}
Departments of ^aPharmaceutical Chemistry and ^bMedicinal Chemistry, The University of Kansas, Lawrence, KS 66045-2506, U.S.A.

The transport properties of a pair of stereoisomeric β -turn mimics were examined using the in vitro Caco-2 transwell system.



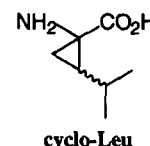
Libraries of Opiate and Anti-opiate Peptidomimetics Containing 2,3-Methanoleucine

Bioorg. Med. Chem. 1997, 5, 1867

Kevin Burgess,^{a,*} Wen Li,^a D. Scott Linthicum,^b Qing Ni,^c David Pledger,^b Richard B. Rothman^c and Aroonsiri Shitangkoon^a

^aDepartments of Chemistry and ^bVeterinary Pathobiology, Texas A&M University, College Station, TX 77843-3255, U.S.A.

^cClinical Psychopharmacology Section, DIR, NIDA, NIH, 4940 Eastern Drive, P.O. Box 5180, Baltimore, MD 21224, U.S.A.



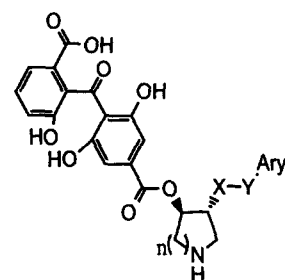
Synthesis and Protein Kinase C Inhibitory Activities of Balanol Analogues with Modification of 4-Hydroxybenzamido Moiety

Bioorg. Med. Chem. 1997, 5, 1873

Hong Hu,^{*} Jose S. Mendoza, Christopher T. Lowden, Lawrence M. Ballas and William P. Janzen

Sphinx Pharmaceuticals, A Division of Eli Lilly & Company, 4615 University Drive Durham, NC 27707, U.S.A.

A series of racemic balanol analogues with modification of 4-hydroxybenzamido moiety of balanol have been synthesized and evaluated for their inhibitory activities against human protein kinase C (PKC) isozymes. The study suggested the requirement of a free 4-hydroxyl group and an amide linkage of the benzamido moiety for an optimal PKC inhibition. The conformation associated with the 4-hydroxybenzamido moiety seemed to be critical for PKC inhibition.



Embodying a Stable α -Helical Protein Structure through Efficient Chemical Ligation via Thioether Formation

Bioorg. Med. Chem. 1997, 5, 1883

Shiroh Futaki,^{a,*} Tomoko Ishikawa,^a Mineo Niwa,^a Kouki Kitagawa^b and Takeshi Yagami^c

^aInstitute for Medicinal Resources, The University of Tokushima, Tokushima 770, Japan

^bNiigata College of Pharmacy, Niigata 950-21, Japan

^cNational Institute of Health Sciences, Tokyo 158, Japan

A versatile approach was developed which enables the creation of artificial functional proteins having an arbitrary combination and arrangement of helices.

