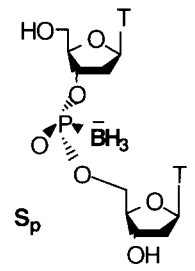
Conformational Studies of Dithymidine Borano-monophosphate Diastereoisomers

Bioorg. Med. Chem. **1997**, *5*, 787

Hong Li, Faqing Huang and Barbara Ramsay Shaw*
Department of Chemistry, Duke University, Durham, NC 27708, U.S.A.

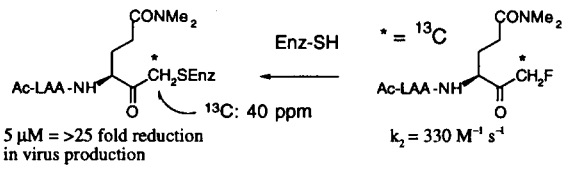
The boranophosphate ester nucleotides are isoelectronic and isostructural analogues of the normal phosphodiester nucleic acids. Substitution of the non-bridging oxygen in the phosphodiester with a borane group leads to chirality of the boranophosphate moiety but induces minimal conformational changes.



In Vitro and Ex Vivo Inhibition of Hepatitis A Virus 3C Proteinase by a Peptidyl Monofluoromethyl Ketone

Bioorg. Med. Chem. **1997**, *5*, 797

Tina S. Morris,[a] Sven Frormann,[b] Shirley Shechosky,[c] Christopher Lowe,[b] Manjinder S. Lall,[b] Verena Gauss-Müller,[d] Robert H. Purcell,[a] Suzanne U. Emerson,[a] John C. Vederas,[b,*] and Bruce A. Malcolm[c,*]
[a]*Hepatitis Viruses Section, National Institute of Allergies and Infectious Diseases, National Institutes of Health, Bethesda, MD 20892-0740, U.S.A.*
[b]*Department of Chemistry, University of Alberta, Edmonton, Alberta, T6G 2G2 Canada*
[c]*Department of Biochemistry, University of Alberta, Edmonton, Alberta, T6G 2H7 Canada; and*
[d]*Institute of Medical Microbiology, Medical University of Lübeck, 23538 Lübeck, Germany*



α1-Adrenoceptor Subtype Selectivity: Molecular Modelling and Theoretical Quantitative Structure–Affinity Relationships

Bioorg. Med. Chem. **1997**, *5*, 809

P. G. De Benedetti,[a,*] F. Fanelli,[a] M. C. Menziani,[a] M. Cocchi,[a] R. Testa,[b] and A. Leonardi[b]
[a]*Dipartimento di Chimica, Università di Modena, Via Campi 183, 41100 Modena, Italy and* [b]*Farmaceutical R&D Division Recordati S.p.A., via Civitali 1, 20148 Milano, Italy*

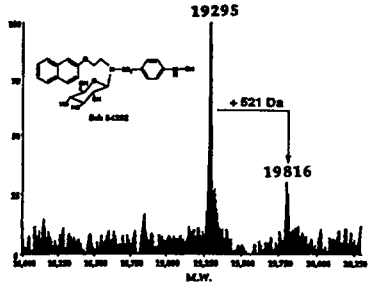
This study constitutes a preliminary rationalization, at the molecular level, of antagonist selectivity towards the three cloned α1-adrenergic receptor subtypes. The results of the theoretical structural/dynamics analysis of the isolated receptors are consistent with the theoretical quantitative structure–affinity relationships obtained from the antagonist-receptor interaction models corroborating the hypothesis that subtype selectivity seems to be mainly guided by the dynamic complementarity (induced fit) between ligand and receptor.

Detection and Structural Characterization of Ras Oncoprotein–Inhibitors Complexes by Electrospray Mass Spectrometry

Bioorg. Med. Chem. **1997**, *5*, 817

A. K. Ganguly,* B. N. Pramanik,* E. C. Huang, S. Liberles, L. Heimark, Y. H. Liu, A. Tsarbopoulos, R. J. Doll, A. G. Taveras, S. Remiszewski, M. E. Snow, Y. S. Wang, B. Vibulbhan, D. Cesarz, J. E. Brown, J. del Rosario, L. James, P. Kirschmeier and V. Girijavallabhan
Schering–Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, NJ 07033, U.S.A.

The ternary noncovalent complexes of the oncogenic ras protein with GDP and SCH 54292 or SCH 54341 were detected by electrospray ionization MS, with observed molecular weights of 19,816 and 19,570 Da, respectively. The protein–drug binding topography was determined by LC–ESI–MS enzymatic mapping following selective chemical modification of the ras complex lysine residues.



Stereochemistry of Yeast Δ^{24}-Sterol Methyl Transferase

Bioorg. Med. Chem. **1997**, *5*, 821

Adriana P. Acuna-Johnson, Allan C. Oehlschlager,* Aldona M. Pierce, Harold D. Pierce, Jr, and Eva K. Czyzewska
Department of Chemistry, Simon Fraser University, Burnaby, British Columbia, V5A 1S6 Canada

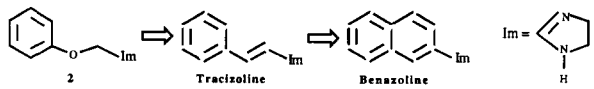
A 24(*S*)-methyl-25-thiasterol sulfonium intermediate analogue inhibits yeast 24-SMT more than the 24(*R*) analogue suggesting that methyl donation to Δ^{24} occurs from the *si* face.

Imidazoline Receptors: Qualitative Structure–Activity Relationships and Discovery of Tracizoline and Benazoline. Two Ligands with High Affinity and Unprecedented Selectivity

Bioorg. Med. Chem. **1997**, *5*, 833

Maria Pigini,[a] Pascal Bousquet,[b] Angelo Carotti,[c] Monique Dontenwill,[b] Mario Giannella,[a] Roberta Moriconi,[b] Alessandro Piergentili,[a] Wilma Quaglia,[a] Seyed K. Tayebati,[a] and Livio Brasili[d]
[a]*Dipartimento di Scienze Chimiche, Università di Camerino, Via S. Agostino 1, 62032 Camerino (MC), Italy;* [b]*Laboratoire de Pharmacologie Cardiovasculaire et Rénale, Université Louis Pasteur, CNRS URA 589, Faculté de Médecine, 11 rue Humann, 67000 Strasbourg, France;* [c]*Dipartimento Farmaco-Chimico, Università di Bari, Via E. Orabona 4, 70125 Bari, Italy; and* [d]*Dipartimento di Scienze Farmaceutiche, Università di Modena, Via Campi 183, 41100 Modena, Italy*

Starting from compound 2, isosteric substitution and conformational restriction lead to the discovery of Tracizoline and Benazoline, two I_2 imidazoline receptor ligands with high affinity and unprecedented selectivity with respect to both α_1- and α_2-adrenergic receptors.

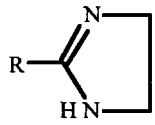


2-D and 3-D Modelling of Imidazoline Receptor Ligands: Insights into Pharmacophore

Bioorg. Med. Chem. **1997**, *5*, 843

A. Carrieri,[a] L. Brasili,[b] F. Leonetti,[a] M. Pigini,[c] M. Giannella,[c] P. Bousquet,[d] and A. Carotti[a,*]
[a]*Dipartimento Farmaco-Chimico, Università di Bari,* [b]*Università di Modena,* [c]*Università di Camerino,* [d]*Universitè Louis Pasteur, Strasbourg*

Molecular determinants for high imidazoline (I_2) and α_2 receptor affinity and I_2/α_2 selectivity have been detected on a large series of 2-substituted imdazolines by means of 2-D and 3-D QSAR methods. 3-D models with good fitting and predictive ability have been obtained.



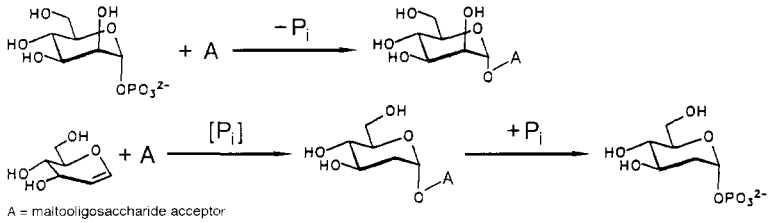
R = 2′-Naphthyl, ***Benazoline***
R = ***trans*-styryl, *Tracizoline***

Further Syntheses Employing Phosphorylase

Bioorg. Med. Chem. **1997**, *5*, 857

Britta Evers and Joachim Thiem*
Institut für Organische Chemie, Universität Hamburg, Martin-Luther-King-Platz 6, D-20146 Hamburg, Germany

With phosphorylase 2-deoxy-glucosyl or mannosyl residues were tranferred to maltooligosaccharides, and 2-deoxy-glucosyl phosphate was obtained using a recyclable primer.

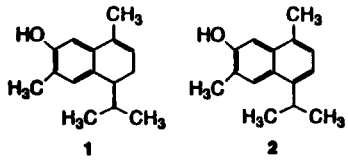


Antioxidative Constituents in *Heterotheca inuloides*

Bioorg. Med. Chem. **1997**, *5*, 865

Hiroyuki Haraguchi,[a,*] Harumi Ishikawa,[a] Yolanda Sanchez,[b] Tetsuya Ogura,[b] Yumi Kubo[c] and Isao Kubo[c]
[a]Faculty of Engineering, Fukuyama University, Gakuen-cho, Fukuyama 729–02, Japan, [b]Departamento de Quimica, Universidad Autonoma de Guadalajara, Guadalajara, Mexico and [c]Department of Environmental Science, Policy and Management, University of California, Berkeley, CA 94720-3112, U.S.A.

Sesquiterpenoids, 7-hydroxy-3,4-dihydrocadalin (**1**) and 7-hydroxycadalin (**2**), and flavonoids, quercetin, kaempferol and their glycosides, isolated from *Heterotheca inuloides*, a Mexican medicinal plant showed potent antioxidative activity against livermicrosomal and mitochondrial peroxidation. Especially, the terpene (**1**) protected mitochondrial enzyme activity against oxidative stress.

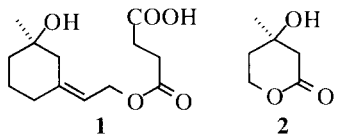


Feasibility of an Immunoassay for Mevalonolactone

Bioorg. Med. Chem. **1997**, *5*, 873

Thomas A. Spencer,[a] Dawn S. Clark,[a] Gary A. Johnson,[a] Sandra K. Erickson[b] and Linda K. Curtiss[c]
[a]Department of Chemistry, Dartmouth College, Hanover, NH 03755, U.S.A. [b]Department of Medicine, Veterans Administration Medical Center and University of California, San Francisco, CA 94121, U.S.A. and [c]The Scripps Research Institute, La Jolla, CA 92037, U.S.A.

Haptens (e.g., *R,S*-**1**) structurally resembling mevalonolactone (**2**) have been used to produce antibodies that bind *R,S*-**2** and *R*-**2** at pH 4.0, demonstrating the feasibility of an immunochemical approach to quantitation of mevalonic acid in biological samples.

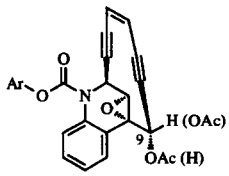


Structure–Activity Relationships of Cyclic Enediynes Related to Dynemicin A—I. Synthesis and Antitumor Activity of 9-Acetoxy Enediynes Equipped with Aryl Carbamate Moieties

Bioorg. Med. Chem. **1997**, *5*, 883

Ryoichi Unno,[a,*] Hisashi Michishita,[a] Hideaki Inagaki,[a] Yoko Suzuki,[a] Yutaka Baba,[a] Takahito Jomori,[a] Toshio Nishikawa[b] and Minoru Isobe[b]
[a]Drug Discovery Research Department, Sanwa Kagaku Kenkyusho Co. Ltd, 363, Shiosaki, Hokusei-cho, Inabe-gun, Mie 511-04, Japan [b]Laboratory of Organic Chemistry, School of Agricultural Sciences, Nagoya University, Furho-cho, Chikusa, Nagoya 464-01, Japan

The 9-acetoxy enediyne compounds, simple dynemicin A analogues equipped with various aryl carbamate moieties, were synthesized and evaluated for DNA-cleaving ability, in vitro cytotoxicity, and in vivo antitumor activity. Both **6a** and **6f** were found to show significant activities against P388 leukemia and Meth A sarcoma in mice, in spite of having IC_{50} values in the micromolar range.



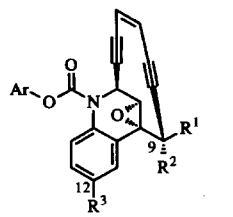
6a : Ar = Ph
6f : Ar = 4-Cl-Ph

Structure–Activity Relationships of Cyclic Enediynes Related to Dynemicin A—II. Synthesis and Antitumor Activity of 9- and 12-Substituted Enediynes Equipped with Aryl Carbamate Moieties

Bioorg. Med. Chem. **1997**, *5*, 903

Ryoichi Unno,[a,*] Hisashi Michishita,[a] Hideaki Inagaki,[a] Yoko Suzuki,[a] Yutaka Baba,[a] Takahito Jomori,[a] Masatoshi Moku,[b] Toshio Nishikawa[b] and Minoru Isobe[b]
[a]Drug Discovery Research Department, Sanwa Kagaku Kenkyusho Co, Ltd 363, Shiosaki, Hokwei-cho, Inabe-gun, Mie 511-04, Japan [b]Laboratory of Organic Chemistry, School of Agricultural Sciences, Nagoya University, Furho-cho, Chikusa-ku, Nagoya 464-01, Japan

Novel enediyne compounds, simple dynenucin A analogues equipped with aryl carbamate moieties, were synthesized and evaluated for DNA-cleaving ability, in vitro cytotoxicity, and in vivo antitumor activity, The 9-deoxy compound **6a** showed a significant activity against P388 leukemia in mice. We found that the size and character of the substituents ($R^1$and R^2) at the C9 position critically influenced both the stability and antitumor activity of the enediyne compounds.

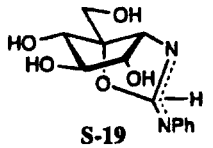


6a : Ar = 4-Cl-Ph, $R^1 = R^2 = R^3 = H$

Synthesis and Biological Evaluation of Potent Glycosidase Inhibitors: *N*-Phenyl Cyclic Isourea Derivatives of 5-Amino- and 5-Amino-*C*-(hydroxymethyl)-1,2,3,4-cyclopentanetetraols

Bioorg. Med. Chem. **1997**, *5*, 921

Chikara Uchida, Hiroshi Kimura and Seiichiro Ogawa*
Department of Applied Chemistry, Faculty of Science and Technology, Keio University, Hiyoshi, Kohoku-ku, Yokohama, 223 Japan



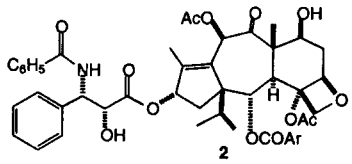
S-19
IC_{50} 7.6×10^{-9} M

Twenty-four 5-amino and 5-amino-*C*-(hydroxymethyl)-1,2,3,4-cyclopentanetetraols and the corresponding *N*-phenyl cyclic isourea derivatives were prepared and tested for inhibitory activity against six glycosidases. Structures mimic of putative transistion state glucosyl cation for hydrolysis 1L-(1,2,4,5/3) isomer **L-4** and its isourea derivatives **S-19** have been shown to possess strong activity against baker's yeast α-glucosidase.

Synthesis and Biological Activity of A-*nor*-Paclitaxel Analogues

Bioorg. Med. Chem. **1997**, *5*, 941

Mahendra D. Chordia,[a] David G. I. Kingston,[a,*] Ernest Hamel,[b,*] Chii M. Lin,[b] Byron H. Long,[c] Craig A. Fairchild,[c] Kathy A. Johnston[c] and William C. Rose[c]
[a]*Department of Chemistry, Virginia Polytechnic Institute and State University, Blacksburg, VA 24061-0212, U.S.A*
[b]*Laboratory of Drug Discovery Research and Development, Developmental Therapeutics Program, Division of Cancer Treatment, Diagnosis and Centers, National Cancer Institute, Frederick Cancer Research and Development Center, Frederick, MD 21702, U.S.A*
[c]*Bristol-Myers Squibb Pharmaceutical Research Institute, P.O. Box 4000, Princeton, NJ 05843, U.S.A.*



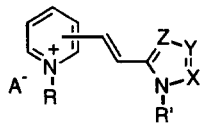
2

A number of paclitaxel analogues of general structure **2** have been prepared (Ar = substituted phenyl). Most of the compounds synthesized were less active than paclitaxel, but one analogue was equivalent to paclitaxel in a tubulin-assembly assay, and another analogue was more cytotoxic than paclitaxel in two different cell lines of the NCI screen.

Molecular Modeling of (*E*)-1-Alkyl-4(3)-[2-(1*H*-azolyl)-Vinyl]-pyridinium Salts and Evaluation of their Behavior towards Choline Acetyltransferase

Bioorg. Med. Chem. **1997**, *5*, 949

Ermitas Alcalde,[a,*] Ana Barat,[b] Pilar Goya,[c] Ana Martinez,[c] Galo Ramirez,[b] Tomás Roca[a] and Isabel Rozas[c]
[a]*Laboratorio de Química Orgánica, Facultad de Farmacia, E-08028 Barcelona, Spain*
[b]*Centro de Biología Molecular, CSIC-UAM, E-28049 Madrid, Spain*
[c]*Instituto de Química Médica, CSIC, E-28006 Madrid, Spain*



A new type of extended π-system aza-analogue of (*E*)-4-[2-(1-naphthylvinyl]-1-substituted pyridinium salts (**NVP**$^+$) has been designed and its inhibitory activity towards choline acetyltransferase (ChAT) has been evaluated in vitro.

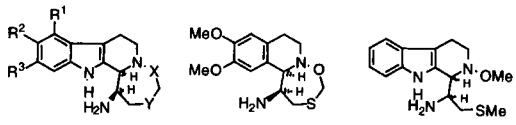
Antiviral and Tumor Cell Antiproliferative SAR Studies on Tetracyclic Eudistomins—II

Bioorg. Med. Chem. **1997**, *5*, 955

Jan H. van Maarseveen,[a] Hans W. Scheeren,[a] Erik De Clercq,[b] Jan Balzarini[b] and Chris G. Kruse[c,*]
[a]*Department of Organic Chemistry, University of Nijmegen, Toernooiveld, 6525 ED, Nijmegen, The Netherlands;*
[b]*Rega Institute, Katholieke Universiteit Leuven, Minderbroedersstraat 10, B-3000 Leuven, Belgium and*
[c]*Solvay Pharmaceuticals Research Laboratories, P.O.B. 900, 1380 DA, Weesp, The Netherlands*

In a search for the minimum pharmacophore the biological activity of the following tetracyclic eudistomin derivatives have been evaluated.

Naturally eudistomins: X=O, Y=S.
Synthetic analogs: X=O, Y=CH_2 and X=CH_2, Y=S

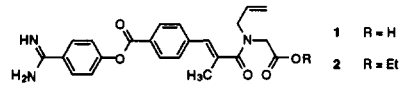


New Serine Protease Inhibitors with Leukotriene B_4 (LTB_4) Receptor Binding Affinity

Bioorg. Med. Chem. **1997**, 5, 971

Yoshisuke Nakayama, Kazuhiko Senokuchi, Katsuhito Sakaki, Masashi Kato, Toru Maruyama, Toru Miyazaki, Hidenori Ito, Hisao Nakai* and Masanori Kawamura
Minase Research Institute, Ono Pharmaceutical Co., Ltd, Shimamoto, Mishima, Osaka 618, Japan

A series of amidine-containing trypsin-like serine protease inhibitors such as **1** and **2** was found to exhibit leukotriene B4 (LTB_4) receptor affinity. The structure–activity relationships are described.



Synthesis and Antitumor Activity of Water-Soluble Enediyne Compounds Related to Dynemicin A

Bioorg. Med. Chem. **1997**, 5, 987

Ryoichi Unno,[a,*] Hisashi Michishita,[a] Hideaki Inagaki,[a] Yoko Suzuki,[a] Yutaka Baba,[a] Takahito Jomori,[a] Toshio Nishikawa[b] and Minoru Isobe[b]
[a]Drug Discovery Research Department, Sanwa Kagaku Kenkyusho Co., Ltd, 363, Shiosaki, Hokusei-cho, Inabe-gun, Mie 511-04, Japan [b]Laboratory of Organic Chemistry, School of Agricultural Sciences, Nagoya University, Furho-cho, Chikusa-ku, Nagoya 464-01, Japan

The water-soluble enediyne compounds, simple dynemicin A analogues, were synthesized and evaluated for in vitro cytotoxicity and in vivo antitumor activity. We found that the compounds with *tert*-amines showed not only the enhanced in vivo antitumor activity but also the decreased toxicity especially in the form of HCl salts.