Bioorg. Med. Chem. **1996**, *4*, 2029

Properties of Triple Helix Formation with Oligodeoxyribonucleotides Containing 8-Oxo-2′-deoxyadenosine and 2′-Modified Nucleoside Derivatives

T. Ishibashi[a], H. Yamakawa[a], Q. Wang[a,b], S. Tsukahara[a], K. Takai[a], T. Maruyama[c] and H. Takaku[a]
[a]Department of Industrial Chemistry, Chiba Institute of Technology, Tsudanuma, Narashino, Chiba 275, Japan; [b]Department of Chemistry, Auburn University, Auburn, AL 36849-5312, U.S.A.; [c]Faculty of Pharmaceutical Sciences, Tokushima Bunri University, Yamashiro-cho, Tokushima 770, Japan

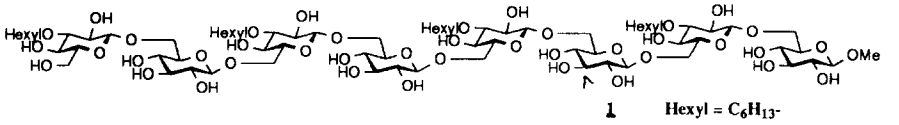
The 8-oxo-2′-deoxyadenosine substituted oligomers were shown to bind within the physiological pH range in a pH-independent fashion, without a compromise in specificity. In particular, the substitutions of three deoxycytidine resides with 8-oxo-2′-deoxyadenosine showed higher endonuclease inhibition than the substitution of either one or two deoxycytidine residues with 8-oxo-2′-deoxyadenosine. By contrast, the oligonucleotides containing 2′-modified nucleosides (Uf, Um, Uf-Cf, Um-Cm, dAOH-Uf, and dAOH-Um) bind in a pH-dependent manner to the target duplex.

Bioorg. Med. Chem. **1996**, *4*, 2035

An Efficient Synthesis of Methyl Tetra-*O*-hexyl Gentiooctaoside, An Octaosyl Analogue of ANP Receptor Antagonist HS-142-1

Y. Qiu, Y. Nakahara and T. Ogawa
The Institute of Physical and Chemical Research (RIKEN), Wako-shi, Saitama, Japan

A 3-*O* hexyl analogue (**1**) of the octaosyl component of fungal lipooligosaccharide HS-142-1, was stereo- and regioselectively synthesized as a potent antagonist for the tetrameric atrial natriuretic peptide (ANP) receptors.

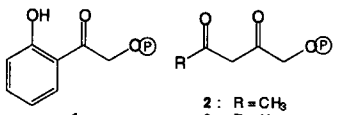


1 Hexyl = C_6H_{13}-

Bioorg. Med. Chem. **1996**, *4*, 2043

Slow Reversible Inhibitions of Rabbit Muscle Aldolase with Substrate Analogues: Synthesis, Enzymatic Kinetics and UV Difference Spectroscopy Studies

T. Gefflaut, C. Blonski and J. Périé*
Groupe de Chimie Organique Biologique, UMR 5623, Bât. IIR1, Université Paul Sabatier, 118 route de Narbonne, 31062 Toulouse Cedex, France



1 **2**: R = CH_3 **3**: R = H

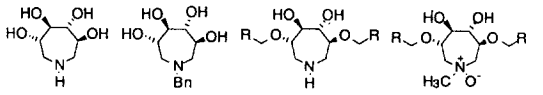
Ⓟ = $P(O)(OH)_2$

Bioorg. Med. Chem. **1996**, *4*, 2055

C_2-Symmetrical Tetrahydroxyazepanes as Inhibitors of Glycosidases and HIV/FIV Proteases

Xinhua Qian, Francisco Morís-Varas, Michael C. Fitzgerald, and Chi-Huey Wong*
Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, U.S.A.

Tetrahydroxyazepanes and derivatives inhibit different glycosidases and HIV and FIV proteases with K_i in the micromolar range.

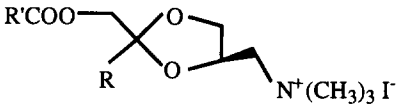


Synthesis, NMR Spectroscopy Study, and Antimuscarinic Activity of a Series of 2-(Acyloxymethyl)-1,3-dioxolanes

Bioorg. Med. Chem. **1996**, *4*, 2071

Luca Malmusi,[a] Adele Mucci,[b] Luisa Schenetti,[b] Ugo Gulini,[c] Gabriella Marucci[c] and Livio Brasili[a,*]
[a]*Dipartimento di Scienze Farmaceutiche and* [b]*Dipartimento di Chimica, Università degli Studi di Modena, Via Campi 183, 41100 Modena, Italy;* [c]*Dipartimento di Scienze Chimiche, Università degli Studi di Camerino, Via S. Agostino 1, 62032 Camerino (MC) Italy*

A series of 1,3-dioxolane-based ligands was synthesized and tested for antimuscarinic activity. The compounds display moderate to low affinity for the three receptor subtypes M_1–M_3, with some of them showing a significant selectivity for the M_3 subtype. Quantitative analysis of conformer populations was performed and it was shown that the exocyclic $CH_2N^+(CH_3)_3$ group is prevalently in a pseudo-axial orientation in the *cis* isomers and in a pseudo-equatorial orientation in the *trans* isomers.

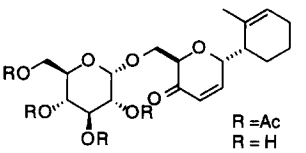


Hexose Keto-C-glycoside Conjugates: Design, Synthesis, Cytotoxicity, and Evaluation of Their Affinity for the Glucose Transporter Glut-1

Bioorg. Med. Chem. **1996**, *4*, 2081

Clara Uriel,[a] Marie-José Egron,[a] Monique Santarromana,[b] Daniel Scherman,[b] Kostas Antonakis[a] and Jean Herscovici[a]*
[a]*Laboratoire de Chimie Organique et Spectroscopique UMR 133 BP 8, 94801 Villejuif, France and* [b]*Centre De Biotechnologie UMR 133 CNRS-Rhône-Poulenc Rorer Crva Monod Bp 14, 94403 Vitry Sur Seine Cedex, France*

The design, synthesis, cytotoxicity, and biological evaluation of carbohydrate/C-glycoside conjugates are described. The study demonstrates that (1) carbohydrate and C-glycoside could be bonded at non anomeric position by the reaction of carbohydrate triflate with C-glycoside alkoxides in the presence of DMPU, and (2) there is a structure–activity relationship between the cytotoxicity of the conjugate and the nature of the carbohydrate residue.



Bioorg. Med. Chem. **1996**, *4*, 2091

Structure–Activity Relationships of 2-Aryl-2,5-dihydropyridazino[4,3-*b*]indol-3(3H)-ones at the Benzodiazepine Receptor

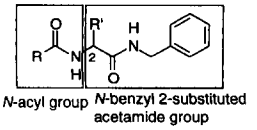
F. Palluotto,[a] A. Carotti,[a] G. Casini,[a] F. Campagna,[a,*] G. Genchi,[b] M. Rizzo,[c] and G. B. De Sarro[d]
[a]*Dipartimento Farmacochimico and* [b]*Dipartimento Farmacobiologico, Università di Bari, Italy;* [c]*Facoltà di Farmacia and* [d]*Dipartimento di Medicina Sperimentale e Clinica, Università di Reggio Calabria, Italy*

A large series of 2-aryl-2,5-dihydropyridazino[4,3-*b*]indol-3(3H)ones has been prepared and tested as central benzodiazepine receptor (BZR) ligands and potential (anti)convulsant agents. Stereoelectronic requirements for high receptor affinity were detected by means of 2-D and 3-D QSAR analyses.

Bioorg. Med. Chem. **1996**, *4*, 2105

The Anticonvulsant Activities of Functionalized *N*-Benzyl 2-Acetamidoacetamides. The Importance of the 2-Acetamido Substituent

Daeock Choi,[a] James P. Stables[b] and Harold Kohn[a]
[a]*Department of Chemistry, University of Houston, Houston, TX 77204-5641, U.S.A.;* [b]*Epilepsy Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Federal Building, Room 114, Bethesda, MD 20892-9020, U.S.A.*

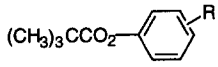


Bioorg. Med. Chem. **1996**, *4*, 2115

Non-peptidic Inhibitors of Human Neutrophil Elastase: The Design and Synthesis of Sulfonanilide-Containing Inhibitors

Katsuhiro Imaki, Takanori Okada, Yoshisuke Nakayama, Yuuki Nagao, Kaoru Kobayashi, Yasuhiro Sakai, Tetsuya Mohri, Takaaki Amino, Hisao Nakai* and Masanori Kawamura
Department of Medicinal Chemistry, Minase Research Institute, Ono Pharmaceutical Co., Ltd, Shimamoto, Mishima, Osaka 618, Japan

Synthesis, SAR and biological evaluation of pivaloyloxybenzene derivatives are described.



Bioorg. Med. Chem. **1996**, *4*, 2135

Synthesis and Structure–Activity Relationships of Cephalosporins, 2-Isocephems, and 2-Oxaisocephems with C-3′ or C-7 Catechol or Related Aromatics

Koichi Tsuji,[a,*] Hidetsugu Tsubouchi,[a] Koichi Yasumura,[b] Makoto Matsumoto[a] and Hiroshi Ishikawa[a]
[a]Microbiological Research Institute, Otsuka Pharmaceutical Co., Ltd, Kagasuno 463-10, Kawauchi-cho, Tokushima 771-01, Japan; [b]Fujii Memorial Research Institute, Otsuka Pharmaceutical Co., Ltd, Karasaki 1-11-1, Ohtsu 520-01, Japan

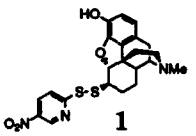
A series of cephalosporins, 2-isocephems, and 2-oxaisocephems and C-3′ or C-7 catechol or related aromatics have been prepared and evaluated for antibacterial activity.

Ligand Recognition in μ Opioid Receptor: Experimentally Based Modeling of μ Opioid Receptor Binding Sites and Their Testing by Ligand Docking

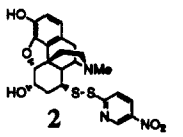
Bioorg. Med. Chem. **1996**, *4*, 2151

Takeshi Sagara,[a] Hiromu Egashira,[a] Mikako Okamura,[a] Ikuo Fujii,[b] Yasuyuki Shimohigashi,[c] and Ken Kanematsu[a,*]
[a]Institute of Synthetic Organic Chemistry, Faculty of Pharmaceutical Sciences, Kyushu University 62, Fukuoka 812-82, Japan; [b]Protein Engineering Research Institute, 6-2-3 Furuedai, Suita, Osaka 565, Japan; [c]Laboratory of Biochemistry, Department of Chemistry, Faculty of Science, Kyushu University 33, Fukuoka 812-81, Japan

For three-dimensional understanding of the mechanisms that control potency and selectivity of the ligand binding at the atomic level, we have analysed the feature of the opioid receptor–ligand interaction based on the receptor's 3-D model using the *S*-activated dihydromorphine derivative (ligands **1** and **2**).



1



2

Bioorg. Med. Chem. **1996**, *4*, 2167

Tachykinin NK-1 Receptor Probed with Constrained Analogues of Substance P

Sandrine Sagan,* Hubert Josien, Philippe Karoyan, Alié Brunissen, Gérard Chassaing and Solange Lavielle*
Laboratoire de Chimie Organique Biologique, CNRS URA 493, Université P. et M. Curie, 4, place Jussieu, 75005 Paris, France

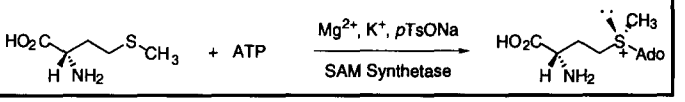
According to the binding potencies of constrained analogues of phenylalanine, the S_7 binding subsite of human NK-1 receptor is small, whereas the S_8, which can accommodate three coplanar nuclei, might probably reside in the extracellular loop. The discrepancies observed between affinity (K_i) and activity (EC_{50}) values for IPs production are not an artefact of CHO cells since a good correlation was found between EC_{50} for PI hydrolysis and those measured in guinea pig ileum bioassay.

Enzymatic Synthesis of *S*-Adenosyl-L-methionine on the Preparative Scale

Bioorg. Med. Chem. **1996**, *4*, 2179

Jeongho Park,[a] Junzhe Tai,[b] Charles A. Roessner[a] and A. Ian Scott[a,*]
[a]*Center for Biological NMR, Department of Chemistry, Texas A&M University, College Station, Texas 77843-3255, U.S.A.*
[b]*Department of Basic Courses Teaching, Yan Sian Agricultural College, Long Jing 133400, Ji Lin Province, China*

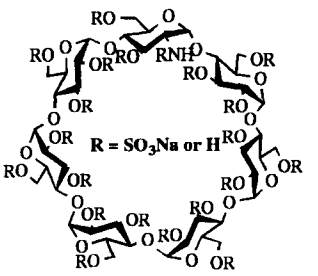
The problem of product inhibition of *E. coli* SAM synthetase was overcome either by construction of a recombinant strain in *E. coli* harboring yeast SAM synthetase or by including additives, such as βME, acetonitrile, urea, or *p*TsONa. The recombinant yeast SAM synthetase was used to generate SAM in situ for use in the multi-enzymatic synthesis of precorrin 2.



Bioorg. Med. Chem. **1996**, *4*, 2187

Synthesis and Biological Evaluation of 2-Amino-2-deoxy- and 6-Amino-6-deoxy-cyclomaltoheptaose Polysulfates as Synergists for Angiogenesis Inhibition

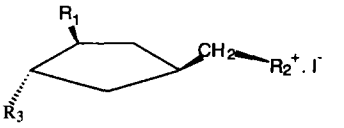
N. Sakairi,[a] H. Kuzuhara,[a,*] T. Okamoto[b] and M. Yajima[b]
[a]*The Institute of Physical and Chemical Research (RIKEN), Hirosawa, Wako-shi, Saitama 351-01, Japan;* [b]*Kaken Pharmaceutical Co. Ltd, 14 Shinomiya Minami Kawara-cho, Yamashina-ku, Kyoto 607, Japan*



Bioorg. Med. Chem. **1996**, *4*, 2193

Muscarinic Thioligands with Cyclopentane Nucleus

Alessandro Piergentili,[a] Maria Pigini,[a] Wilma Quaglia,[a] Seyed K. Tayebati,[a] Francesco Amenta,[b] Maurizio Sabbatini[b] and Mario Giannella[a,*]
[a]*Dipartimento di Scienze Chimiche, Università di Camerino, Via S. Agostino 1, 62032 Camerino, Italy;* [b]*Sezione di Anatomia Umana, Istituto di Farmacologia, Università di Camerino, Via Scalzino 5, 62032 Camerino, Italy*



Some thio- and the benzoyl-derivatives of deoxamuscarine were synthesized and tested as muscarinic agonists in binding and functional assays. The esterification of the hydroxy moiety increases the selectivity toward the M_2 subtype, while etherification heightens the M_3 selectivity.

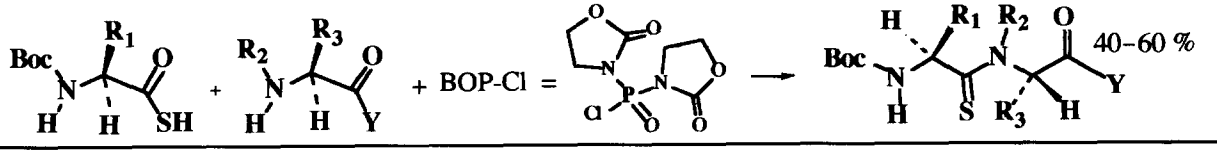
$R_1 = CH_3, SCH_3$
$R_2 = NMe_3, SMe_2$
$R_3 = OH, SCH_2C_6H_5, OSO_2CH_3, OSO_2C_6H_5, OCOC_6H_5, OCOCH_3, OCH_2CH_3, OCH_2C_6H_5$

Bioorg. Med. Chem. **1996**, *4*, 2201

Use of BOP-Cl in the Presence of Boc-Amino Monothioacids for the Thioacylation of Iminoacid Residues

Hoang-Thanh Le, Jean-François Gallard, Michel Mayer, Eric Guittet and Robert Michelot
Natural Products Chemistry Institute, C.N.R.S., Avenue de la Terrasse, 91198 Gif sur Yvette, France

Boc-amino monothioacids were coupled at moderate temperature (0 °C–RT) to imino acids residues (Pro, Sar) to give thiopeptides in fair yields and with a retained optical purity.

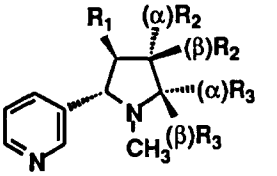


Bioorg. Med. Chem. **1996**, *4*, 2211

Quantitative Structure–Activity Relationships of Nicotine Analogues as Neuronal Nicotinic Acetylcholine Receptor Ligands

Ki Hwan Kim,* Nan-Horng Lin and David J. Anderson
Pharmaceutical Products Division, Abbott Laboratories, 100 Abbott Park Road, Abbott Park, IL 60064, U.S.A.

Quantitative structure–activity relationships of 34 pyrrolidine-modified nicotine agonists (**I**) are investigated for their binding affinity toward neuronal nicotinic acetylcholine receptor.



(I)

Bioorg. Med. Chem. **1996**, *4*, 2219

Nonenzymatic Sequence-Specific Cleavage of Duplex DNA via Triple-Helix Formation by Homopyrimidine Phosphorothioate Oligonucleotides

S. Tsukahara, J. Suzuki, K. Ushijima, K. Takai and H. Takaku
Department of Industrial Chemistry, Chiba Institute of Technology, Tsudanuma, Narashino, Chiba 275, Japan

The 3′-terminal phosphorothioate oligonucleotide-phenanthroline derivatives (Rp or Sp) were found to have cleavage activities of the same order as for the oligonucleotide phenanthroline (OP-17 mer). Furthermore, the OPSp-17 mer was intact after incubation in 10% fetal bovine serum for 24 h, whereas, the OPRp-17 mer was slightly more unstable than the OPSp-17 mer. However, the OP-17 mer was completely degraded. An increased resistance to nucleases has been observed by the introduction of phosphorothioate groups on the 3′-terminus of oligonucleotide-phenanthroline derivatives. This stabilization should help us to design much more efficient chemical recognition enzymes, which could be used as tools in cellular biology.

Bioorg. Med. Chem. **1996**, *4*, 2225

Chemoprevention of Carcinogen–DNA Binding: the Relative Role of Different Oxygenated Substituents on 4-Methylcoumarins in the Inhibition of Aflatoxin B_1–DNA Binding in vitro

Hanumantharao G. Raj,[a,*] Sangita Gupta,[b] Gopa Biswas,[a] Suddham Singh,[b] Amarjit Singh,[b] Amitabh Jha,[b] Kirpal S. Bisht,[b] Sanjay K. Sharma,[b] Subhash C. Jain[b] and Virinder S. Parmar[b]
[a]*Department of Biochemistry, V. P. Chest Institute;* [b]*Department of Chemistry, University of Delhi, Delhi-110 007, India*

Eighteen 4-methylcoumarins bearing methoxy/hydroxy/acetoxy/ethoxycarbonylmethyl/ethoxycarbonylethyl functionalities have been found to effectively inhibit the rat liver microsome-mediated aflatoxin B_1–DNA binding in vitro. The contribution of functionality on coumarin nucleus towards the inhibition of AFB_1–DNA binding is in the order acetoxy > hydroxy > methoxy, the ethoxycarbonylalkyl side chain has no effect on inhibition of aflatoxin B_1–DNA binding.