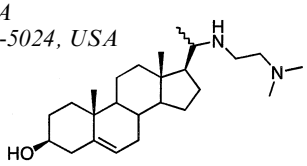
Bioorg. Med. Chem. 9 (2001) 1073

Structure–Activity Relationship of Aza-Steroids as PI-PLC Inhibitors

Wenge Xie,[a] Hairuo Peng,[a] Deog-Il Kim,[a] Mark Kunkel,[b] Garth Powis[b] and Leon H. Zalkow[a]

[a]*School of Chemistry and Biochemistry, Georgia Institute of Technology, Atlanta, GA 30332, USA*
[b]*Arizona Cancer Center, University of Arizona, 1515 North Campbell Avenue, Tucson, AZ 85724-5024, USA*

The 20α epimer (**8a2**) of 22,25-diazacholesterol, the most potent of a number of azasteroids tested (IC_{50} of 0.64 μM), was 50 times more potent than the epimeric 20β isomer (**8a1**) as a PIPLC inhibitor. The epimeric mixture (**8a**) of compounds **8a1** and **8a2** (1:1) exhibited selective growth inhibition effects in the NCI in vitro tumor cell screen with a GI_{50} MG-MID values of 5.75 μM for 54 human tumors.



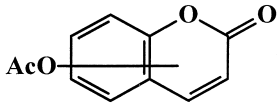
Bioorg. Med. Chem. 9 (2001) 1085

Mechanism of Biochemical Action of Substituted Benzopyran-2-ones. Part 8: Acetoxycoumarin: Protein Transacetylase Specificity for Aromatic Nuclear Acetoxy Groups in Proximity to the Oxygen Heteroatom

Hanumantharao G. Raj,[a] Ekta Kohli,[a] Rajeev Goswami,[b] Sanjay Goel,[a] Ramesh C. Rastogi,[b] Subhash C. Jain,[b] Jesper Wengel,[c] Carl E. Olsen[d] and Virinder S. Parmar[b]

[a]*Department of Biochemistry, V. P. Chest Institute, University of Delhi, Delhi 110 007, India*
[b]*Department of Chemistry, University of Delhi, Delhi 110 007, India*
[c]*Department of Chemistry, University of Southern Denmark, DK-5230 Odense M, Denmark*
[d]*Chemistry Department, Royal Veterinary and Agricultural University, DK-1871 Frederiksberg C, Copenhagen, Denmark*

The specificity for transacetylase action on various acetoxycoumarins demonstrates that the acetoxycoumarin having the acetoxy substituent nearest to the pyrone ring oxygen of the coumarin moiety is the best substrate for the transacetylase.



C-3,C-4, C-5, C-6, C-7 monoacetoxy or C-7, C-8 diacetoxycoumarin

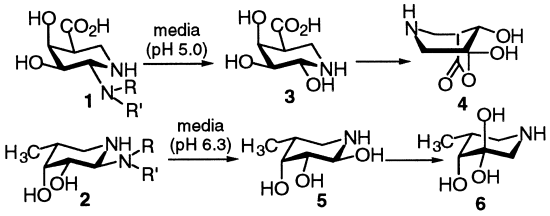
Bioorg. Med. Chem. 9 (2001) 1091

Glycosidase Inhibitors of *gem*-Diamine 1-*N*-iminosugars: Structures in Media of Enzyme Assays

Ken-ichiro Kondo, Hayamitsu Adachi, Eiki Shitara, Fukiko Kojima and Yoshio Nishimura

Institute of Microbial Chemistry, 3-14-23 Kamiosaki, Shinagawa-ku, Tokyo 141-0021, Japan

gem-Diamine 1-*N*-iminosugars (**1** and **2**) change the structures to **4** and **6** via **3** and **5**, respectively in media, and the products (**3**–**6**) as well as the parent compounds (**1**, **2**) potently inhibit glycosidases.



Bioorg. Med. Chem. 9 (2001) 1097

Inhibition of the HIV-1 Rev–RRE Complex Formation by Unfused Aromatic Cations

Ge Xiao, Arvind Kumar, Ke Li, C. Ted Rigl, Miroslav Bajic, Tina M. Davis, David W. Boykin* and W. David Wilson*

Department of Chemistry, Georgia State University, Atlanta, GA 30303, USA

A diphenylfuran lead compound was systematically varied and the ability of the new compounds to inhibit the formation of Rev–RRE and Tat–TAR complexes was assayed by gel-mobility shift experiments. In this series, DB340 was found to be the most active compound and also the most specific compound for inhibition of Rev–RRE complex formation.

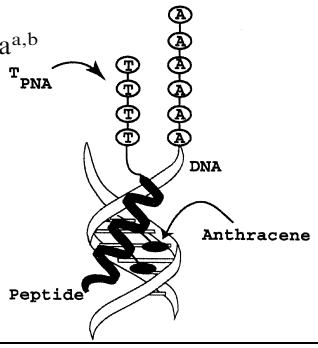
Bioorg. Med. Chem. 9 (2001) 1115

Construction of Peptide Conjugates with Peptide Nucleic Acids Containing an Anthracene Probe and Their Interactions with DNA

Ganesan Balasundaram,[a] Tsuyoshi Takahashi,[a] Akihiko Ueno[a] and Hisakazu Mihara[a,b]

[a]*Department of Bioengineering, Graduate School of Bioscience and Biotechnology, Tokyo Institute of Technology, Nagatsuta, Yokohama 226-8501, Japan*
[b]*Form and Function, PRESTO, Japan Science and Technology Corporation, Tokyo Institute of Technology, Nagatsuta, Yokohama 226-8501, Japan*

α-Helix peptides containing thymine PNA oligomers at the C-terminus were designed and synthesized. Two anthracene chromophores were used as probes and functional groups. Incorporation of thymine PNA oligomer into the designed peptide influenced the DNA binding property, especially with $[d(AT)_{10}dA_6]_2$ without changing the conformations of anthracene side chain and the peptide.



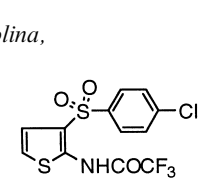
Bioorg. Med. Chem. 9 (2001) 1123

Synthesis and Antiviral/Antitumor Evaluation of 2-Amino- and 2-Carboxamido-3-arylsulfonylthiophenes and Related Compounds as a New Class of Diarylsulfones

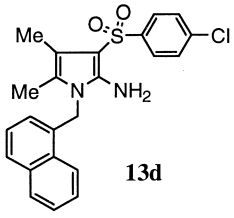
Chad E. Stephens,[a] Takita M. Felder[a], J. Walter Sowell, Sr.,[a] Graciela Andrei,[b] Jan Balzarini,[b] Robert Snoeck[b] and Erik De Clercq[b]

[a]*Division of Medicinal Chemistry, College of Pharmacy, University of South Carolina, Columbia, SC 29208, USA*
[b]*Rega Institute of Medical Research, Katholieke Universiteit Leuven, B-3000 Leuven, Belgium*

Certain title compounds have exhibited activity against HIV-1, CMV, VZV, and/or various human tumor cell lines. Compounds **8d** and **13d**, for example, inhibit CMV at concentrations < 1 μg/mL.



8d



13d

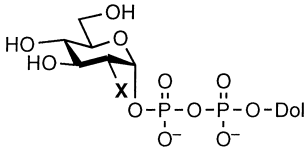
Bioorg. Med. Chem. 9 (2001) 1133

Substrate Specificity of *N*-Acetylglucosaminyl(diphosphodolichol) *N*-Acetylglucosaminyl Transferase, a Key Enzyme in the Dolichol Pathway

Vincent W.-F. Tai, Mary K. O'Reilly and Barbara Imperiali

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, MA 02139, USA

Unnatural dolichol diphosphate monosaccharides (X = F, OEt, $NHCOCF_3$, NH_2) were synthesized to probe the substrate specificity of *N*-acetylglucosaminyl(diphosphodolichol) *N*-acetylglucosaminyl transferase, also known as Enzyme II, from pig liver.

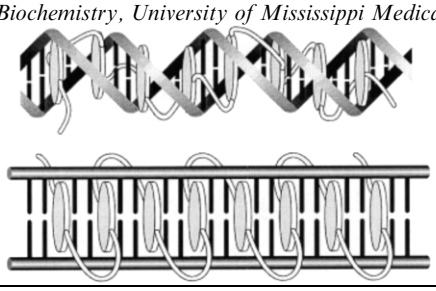


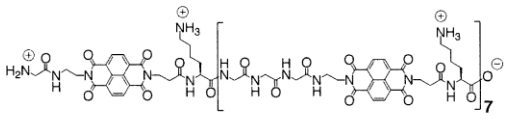
Bioorg. Med. Chem. 9 (2001) 1141

An *Octakis*-Intercalating Molecule

Meredith M. Murr,[a] Matthew T. Harting,[a] Vladimir Guelev,[a] Jinsong Ren,[b] Jonathan B. Chaires[b] and Brent L. Iverson[a,*]

[a]*Department of Chemistry and Biochemistry, The University of Texas at Austin, Austin, TX 78712, USA*
[b]*Department of Biochemistry, University of Mississippi Medical School, MS, USA*





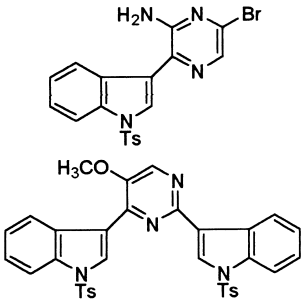
Bioorg. Med. Chem. 9 (2001) 1149

Synthesis and Cytotoxicity Evaluation of Novel Indolylpyrimidines and Indolylpyrazines as Potential Antitumor Agents

Biao Jiang, Cai-Guang Yang, Wen-Nan Xiong and Jun Wang

Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, P. R. China

The synthesis and cytotoxicity evaluation of novel indolylpyrimidines and indolylpyrazines as potential antitumor agents is reported.



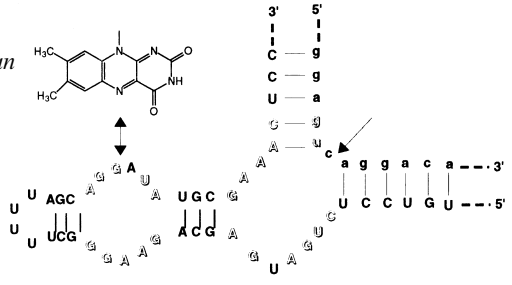
Bioorg. Med. Chem. 9 (2001) 1155

Coupling between Substrate Binding and Allosteric Regulation in Ribozyme Catalysis

Michihiro Araki, Mie Hashima, Yasushi Okuno and Yukio Sugiura

Institute for Chemical Research, Kyoto University, Uji, Kyoto 611-0011, Japan

The contribution of substrate binding to allosteric regulation in the rate process of ribozyme catalysis has been investigated.



Bioorg. Med. Chem. 9 (2001) 1165

Structure–Activity Relationships in 2,2-Diphenyl-2-ethylthioacetic Acid Esters: Unexpected Agonistic Activity in a Series of Muscarinic Antagonists

S. Scapecchi,[a] G. Marucci,[b] R. Matucci,[c] P. Angeli,[b] C. Bellucci,[a] M. Buccioni,[b] S. Dei,[a] F. Gualtieri,[a] D. Manetti,[a] M. N. Romanelli[a] and E. Teodori[a]

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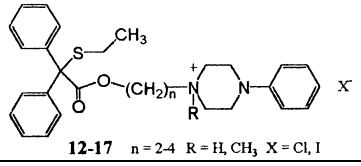
[b]*Dipartimento di Scienze Chimiche, Universita' di Camerino, Via S. Agostino 1, 62032 Camerino, Italy*
[c]*Dipartimento di Farmacologia Preclinica e Clinica, Università di Firenze, viale Pieraccini 6, 50139 Firenze, Italy*

A series of derivatives of 2,2-diphenyl-2-ethylthioacetic acid were synthetised and their antimuscarinic activity of M_{1-4} receptor subtype was evaluated by functional tests and binding experiments. One of the compounds obtained showed unexpected agonistic activity in functional experiments on M_2 receptors. Other compounds carrying a phenylpiperazine moiety (**12**–**17**) were prepared and found to be endowed with similar behaviour.

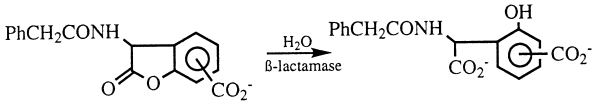


Bioorg. Med. Chem. 9 (2001) 1175

The Synthesis and Evaluation of Benzofuranones as β-Lactamase Substrates

S.A. Adediran,[a] D. Cabaret,[b] B. Drouillat,[b] R.F. Pratt[a] and M. Wakselman[b]

[a]*Department of Chemistry, Wesleyan University, Middletown, CT 06459, USA*
[b]*SIRCOB, ESA CNRS 8086, Université de Versailles, Bât. Lavoisier, 45, avenue des Etats Unis F-78075, Versailles, France*

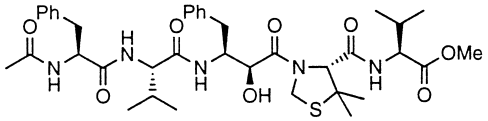


Bioorg. Med. Chem. 9 (2001) 1185

Structure–Activity Studies of FIV and HIV Protease Inhibitors Containing Allophenylnorstatine

Van-Duc Le,[a] Chi Ching Mak,[a] Ying-Chuan Lin,[b] John H. Elder[b] and Chi-Huey Wong[a]

[a]*Department of Chemistry and the Skaggs Institute for Chemical Biology, 10550 North Torrey Pines Road, La Jolla, CA 92037, USA*
[b]*Department of Molecular Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, USA*



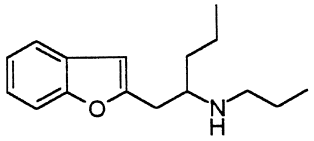
VLE776
HIV PR (IC_{50}) = 8 nM
FIV PR (IC_{50}) = 48 nM

Bioorg. Med. Chem. 9 (2001) 1197

Structure–Activity Studies Leading to (−)1-(Benzofuran-2-yl)-2-propylaminopentane, ((−)BPAP), a Highly Potent, Selective Enhancer of the Impulse Propagation Mediated Release of Catecholamines and Serotonin in the Brain

Fumio Yoneda,[a] Toshiaki Moto,[a] Masatoshi Sakae,[a] Hironori Ohde,[a] Berta Knoll,[b] Ildikó Miklya[b] and Joseph Knoll[b]

[a]*Research Institute, Fujimoto Pharmaceutical Corporation, Matsubara, Osaka 580-8503, Japan*
[b]*Department of Pharmacology, Semmelweis University of Medicine, POB 370, Budapest H-1445, Hungary*



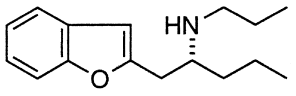
(-)BPAP

Bioorg. Med. Chem. 9 (2001) 1213

Enantioselective Synthesis and Absolute Configuration of (−)-1-(Benzofuran-2-yl)-2-propylaminopentane, ((−)-BPAP), a Highly Potent and Selective Catecholaminergic Activity Enhancer

Takahiro Oka,[a] Takuya Yasusa,[a] Takashi Ando,[a] Mayumi Watanabe,[a] Fumio Yoneda,[a] Toshimasa Ishida[b] and Joseph Knoll[c]

[a]*Research Institute, Fujimoto Pharmaceutical Corporation, 1-3-40, Nishiotsuka, Matsubara, Osaka 580-8503, Japan*
[b]*Osaka Universzity of Pharmaceutical Science, 4-20-1, Nasahara, Takatsuki, Osaka 569-1094, Japan*
[c]*Department of Pharmacology, Semmelweis University of Medicine, P.O.B. 370, Budapest H-1445, Hungary*



(*R*)-(-)-BPAP

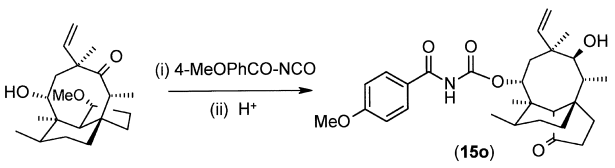
Bioorg. Med. Chem. 9 (2001) 1221

Pleuromutilins. Part 1: The Identification of Novel Mutilin 14-Carbamates

Gerald Brooks,[a] Wendy Burgess,[c] David Colthurst,[c] Jeremy D. Hinks,[c] Eric Hunt,[a] Michael J. Pearson,[c] Burdena Shea,[c] Andrew K. Takle,[a] Jennifer M. Wilson[c] and Gary Woodnutt[b]

[a]*SmithKline Beecham Pharmaceuticals Research and Development, Discovery Chemistry Europe, New Frontiers Science Park, Third Avenue, Harlow, Essex CM19 5AW, UK*
[b]*SmithKline Beecham Pharmaceuticals Research and Development, Microbiology Research, 1250 South Collegville Road, Collegville, PA 19426, USA*
[c]*SmithKline Beecham Pharmaceuticals Research and Development, Brockham Park, Betchworth, Surrey RH3 7AJ, UK*

A novel series of mutilin 14-carbamates have been identified, for example SB-222734 (**15o**), which have potent antibacterial activity against a number of clinically relevant bacterial pathogens.



(**15o**)

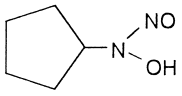
Bioorg. Med. Chem. 9 (2001) 1233

Synthesis of *N*-substituted *N*-nitrosohydroxylamines as Inhibitors of Mushroom Tyrosinase

Mitsuhiro Shiino,[a] Yumi Watanabe[a] and Kazuo Umezawa[b]

[a]*Laboratory of Chemistry, School of Medicine, Keio University, 4-1-1 Hiyoshi, Kohoku-ku, Yokohama 223-0061, Japan*
[b]*Department of Applied Chemistry, Faculty of Science and Technology, Keio University, 3-14-1 Hiyoshi, Kohoku-ku, Yokohama 223-0061, Japan*

A series of *N*-substituted *N*-nitrosohydroxylamines were synthesized and their inhibitory effects on mushroom tyrosinase were examined. Among them, *N*-cyclopentyl-*N*-nitrosohydroxylamine (**9**) was found to be the most potent inhibitor($IC_{50} = 0.6\,\mu M$).



9

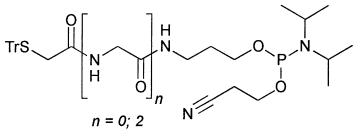
Bioorg. Med. Chem. 9 (2001) 1241

Synthesis and Application of a Novel, Crystalline Phosphoramidite Monomer with Thiol Terminus, Suitable for the Synthesis of DNA Conjugates

Zoltán Kupihár,[a] Zoltán Schmél,[b] Zoltán Kele,[a] Botond Penke[a] and Lajos Kovács[a]

[a]*Department of Medicinal Chemistry, Dóm tér 8, University of Szeged, H-6720 Szeged, Hungary*
[b]*Department of Pharmaceutical Analysis, Somogyi B. u. 4, University of Szeged, H-6720 Szeged, Hungary*

A new crystalline 5′-thiol modifier phosphoramidite monomer ($n = 2$), suitable for DNA synthesis, has been prepared. This monomer has been built into an oligonucleotide using the standard protocol. After cleavage, purification and removal of the trityl group with Ag^+, a free 5′-thiol terminal oligonucleotide has been obtained which was subsequently coupled to a cysteine derivative via a disulfide bridge to afford a conjugate.

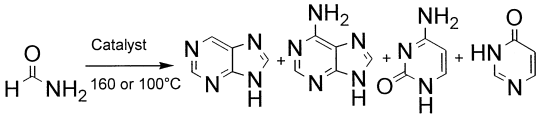


Bioorg. Med. Chem. 9 (2001) 1249

A Possible Prebiotic Synthesis of Purine, Adenine, Cytosine, and 4(3H)-Pyrimidinone from Formamide: Implications for the Origin of Life

Raffaele Saladino,[a] Claudia Crestini,[b] Giovanna Costanzo,[c] Rodolfo Negri[d] and Ernesto Di Mauro[c,d]

[a]*Dipartimento A.B.A.C., Università della Tuscia, 01100 Viterbo, Italy*
[b]*Dipartimento di Scienze e Tecnologie Chimiche, Università di Roma Tor Vergata, 00133 Rome, Italy*
[c]*Fondazione Istituto Pasteur, Fondazione Cenci Bolognetti c/o Dipartimento di Genetica e Biologia Molecolare, Università di Roma La Sapienza, 00185 Rome, Italy*
[d]*Centro di Studio per gli Acidi Nucleici, CNR, 00185 Rome, Italy*



Bioorg. Med. Chem. 9 (2001) 1255

Human DNA Topoisomerase I Inhibitory Activities of Synthetic Polyamines: Relation to DNA Aggregation

Alyona Sukhanova,[a] Jerome Dêvy,[a] Michel Pluot,[a] Jean-Claude Bradley,[b] Jean-Pierre Vigneron,[c] Jean-Claude Jardillier,[a] Jean-Marie Lehn[c] and Igor Nabiev[a]

[a]*EA2063, Université de Reims Champagne-Ardenne, 51100 Reims, France*
[b]*Department of Chemistry, Drexel University, Philadelphia, PA 19107, USA*
[c]*UPR 285, Collège de France, 75005 Paris, France*

Structure–function correlation of seven synthetic tetramines and hexamines in terms of their DNA aggregation abilities and human DNA topoisomerase I inhibition activities.

Bioorg. Med. Chem. 9 (2001) 1269

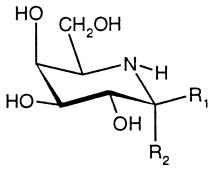
α- and β-Homogalactonojirimycins (α- and β-Homogalactostatins): Synthesis and Further Biological Evaluation

Olivier R. Martin,[a,*] Oscar M. Saavedra,[a] Fang Xie,[a] Li Liu,[a] Sylviane Picasso,[b] Pierre Vogel,[b] Haruhisa Kizu[c] and Naoki Asano[c]

[a]*Department of Chemistry, State University of New York, Binghamton, NY 13902-6016, USA*
[b]*Institut de Chimie Organique, Université de Lausanne, BCH, 1015 Lausanne, Switzerland*
[c]*Faculty of Pharmaceutical Sciences, Hokuriku University, Kanazawa 920-11, Japan*

The synthesis of α- and β-homogalactonojirimycins **3** and **4** and their activities as inhibitors of glycosidases are reported. Compound **3** is a good inhibitor of human lysosomal α-galactosidase A.

3 R_1 =H, R_2 = CH_2OH
4 R_1 = CH_2OH, R_2 =H

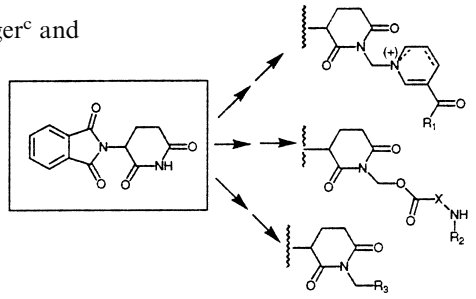


Bioorg. Med. Chem. 9 (2001) 1279

Synthesis and Immunological Activity of Water-Soluble Thalidomide Prodrugs

Sonja Hess,[a] Michaela A. Akermann,[a] Stephan Wnendt,[b] Kai Zwingenberger[c] and Kurt Eger[a]

[a]*University of Leipzig, Institute of Pharmacy, Pharmaceutical Chemistry, Brüderstrasse 34, D-04103 Leipzig, Germany*
[b]*Molecular Pharmacology Department, Grünenthal, Zieglerstrasse 8, D-52068 Aachen, Germany*
[c]*Medical Scientific Division, Grünenthal, Zieglerstrasse 8, D-52068 Aachen, Germany*



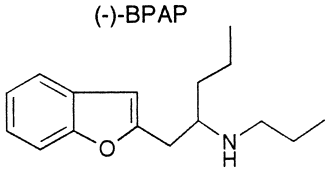
Bioorg. Med. Chem. 9 (2001) 1293

Theoretical Investigation of (−)1-(Benzofuran-2-yl)-2-propylaminopentane [(−)-BPAP] as a Hydroxyl Radical Scavenger

Sachiko Nakai and Fumio Yoneda

Fujimoto Pharmaceutical Corporation, 1-3-40 Nishi-Otsuka, Matsubara-shi, Osaka 580-8503, Japan

The chemical reactions between (−)-BPAP and •OH were studied using molecular orbital theory, with several simplified models.

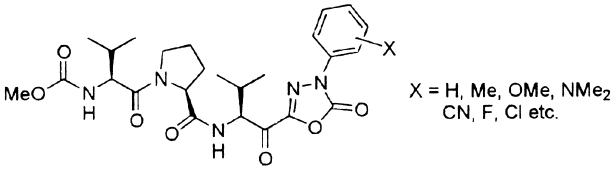


Bioorg. Med. Chem. 9 (2001) 1307

Design and Synthesis of New Orally Active Inhibitors of Human Neutrophil Elastase

Kazuyuki Ohmoto, Motohiro Okuma, Tetsuya Yamamoto, Hideomi Kijima, Tomohiko Sekioka, Kanji Kitagawa, Shigeki Yamamoto, Kenji Tanaka, Kazuhito Kawabata, Atsushi Sakata, Haruo Imawaka, Hisao Nakai and Masaaki Toda

Minase Research Institute, Ono Pharmaceutical Co., Ltd., Shimamoto, Mishima, Osaka 618-8585, Japan



Bioorg. Med. Chem. 9 (2001) 1325

A Multireceptorial Binding Reinvestigation on an Extended Class of σ Ligands: *N*-[ω-(Indan-1-yl and Tetralin-1-yl)alkyl] Derivatives of 3,3-Dimethylpiperidine Reveal High Affinities Towards σ_1 and EBP Sites

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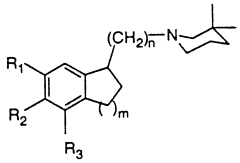
New and known *N*-[ω(indan-1-yl and tetralin-1-yl)alkyl] derivatives of 3,3-dimethylpiperidine were tested at σ_1 and σ_2 receptor, L-type Ca^{++} channel and EBP (Δ_8–Δ_7 sterol isomerase) site, showing high σ_1 affinity and moderate or low σ_2 affinity. 1-[4-(2,3-Dihydro-1*H*-inden-1-yl)butyl]-3,3-dimethylpiperidine (**26**) is the best mixed σ_1 and EBP ligand (apparent $K_i = 1.75$ and 1.54 nM, respectively) with a good selectivity versus σ_2 receptor (138- and 157-fold, respectively).



Bioorg. Med. Chem. 9 (2001) 1337

New Synthesis of (±)-α-CMBHC and Its Confirmation as a Metabolite of α-Tocopherol (Vitamin E)

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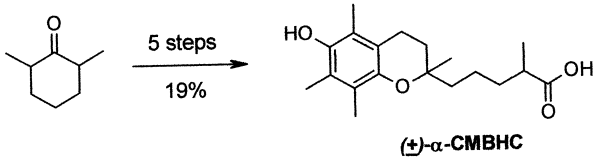

Bioorg. Med. Chem. 9 (2001) 1345

Lipase Catalysed Synthesis of Optically Enriched α-Haloamides

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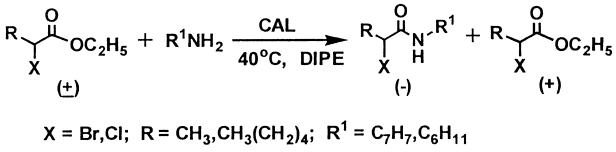
Lipase catalysed synthesis of optically enriched α-haloamides with concomitant optical enrichment of the starting α-haloesters is described. *Candida antarctica* lipase (CAL) was found to be a better catalyst over porcine pancreatic lipase (PPL) and *Candida cylindraceae* lipase (CCL). The effect of different organic solvents was also studied.



Bioorg. Med. Chem. 9 (2001) 1349

Synthesis and Structure–Affinity Relationships of 4-(5-Aryl-1,2,3,6-tetrahydropyridino)pyrimidine Derivatives as Corticotropin-Releasing Factor$_1$ Receptor Antagonists

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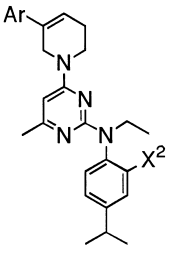
This paper describes the synthesis and structure–affinity relationships of 4-(5-aryl-1,2,3,6-tetrahydropyridino)pyrimidine derivatives as corticotropin-releasing factor$_1$ receptor antagonists.



Bioorg. Med. Chem. 9 (2001) 1357

Chemical Modification of Aryl-1,2,3,6-tetrahydropyridinopyrimidine Derivative to Discover Corticotropin-Releasing Factor$_1$ Receptor Antagonists: Aryl-1,2,3,6-tetrahydropyridino-purine, -3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine, -purin-8-one, and -7*H*-pyrrolo[2,3-*d*]pyrimidine Derivatives

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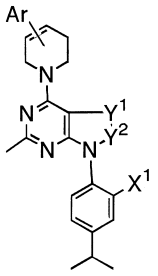

This paper describes the synthesis and structure–affinity relationships of aryl-1,2,3,6-tetrahydropyridino-purine, -3*H*-1,2,3-triazolo[4,5-*d*]pyridine, -purin-8-one, and -7*H*-pyrrolo[2,3-*d*]pyrimidine derivatives (Y^1–Y^2: N=C(H), N=N, N(Me)–C(O) and C(Me)=C(H or Me), respectively) as corticotropin-releasing factor$_1$ receptor antagonists.