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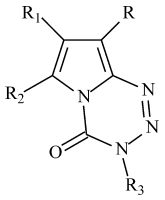
Pyrrolo[2,1-*d*][1,2,3,5]tetrazine-4(3H)-ones, a New Class of Azolotetrazines with Potent Antitumor Activity

Patrizia Diana, Paola Barraja, Antonino Lauria, Alessandra Montalbano, Anna Maria Almerico, Gaetano Dattolo and Girolamo Cirrincione*

Dipartimento Farmacochimico Tossicologico e Biologico, Università degli Studi di Palermo, Via Archirafi 32, 90123 Palermo, Italy

Pyrrolotetrazinones, obtained from the reaction of 2-diazopyrroles with isocyanates, showed in vitro antitumor activity with GI50 from micromolar to nanomolar concentrations.



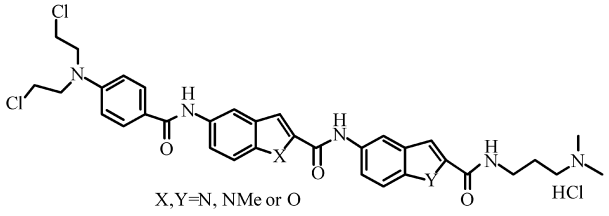
Bioorg. Med. Chem. 11 (2003) 2381

Benzoyl Nitrogen Mustard Derivatives of Benzoheterocyclic Analogues of Netropsin: Synthesis and Biological Activity

Pier Giovanni Baraldi,[a,*] Romeo Romagnoli,[a] Nicoletta Bianchi[b] and Roberto Gambari[b]

[a]*Dipartimento di Scienze Farmaceutiche, Università di Ferrara, Via Fossato di Mortara 17/19, 44100 Ferrara, Italy*
[b]*Dipartimento di Biochimica e Biologia Molecolare, Università di Ferrara, Via L. Borsari 46, 44100 Ferrara, Italy*

A series of benzoyl nitrogen mustards tethered to different benzoheterocycles dimers terminating with a dimethylaminopropyl moiety have been synthesised and a structure–activity relationship determined.



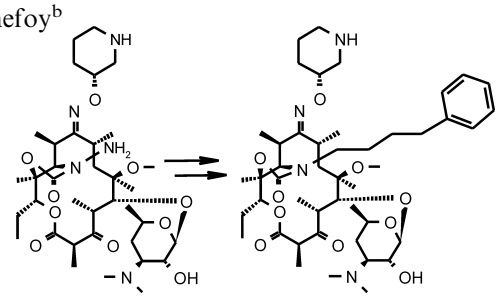
Bioorg. Med. Chem. 11 (2003) 2389

Synthesis of 9-Oxime-11,12-carbamate Ketolides through a Novel *N*-Deamination Reaction of 11,12-Hydrazonocarbamate Ketolide

Alexis Denis,[a,*] Jean-Marie Pejac,[a] François Bretin[a] and Alain Bonnefoy[b]

[a]*Medicinal Chemistry Department, Aventis Pharma 102 route de Noisy, Romainville, Cedex F-93235, France*
[b]*Anti-infective Diseases Group, Aventis Pharma 102 route de Noisy, Romainville Cedex, F-93235, France*

A series of 9-oxime-11,12-carbamate ketolides was synthesized through a 11,12-hydrazonocarbamate intermediate and deamination to give the corresponding carbamate. The N–N bond cleavage was achieved through an original new reaction using glycoaldehyde dimer. The new compounds display improved antibacterial activities against *Streptococcus pneumoniae* and *S. pyogenes* resistant to erythromycin.

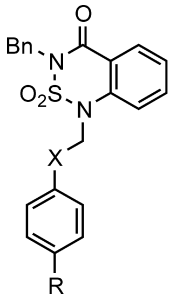


Bioorg. Med. Chem. 11 (2003) 2395

Benzothiadiazine Dioxides (BTD) Derivatives as Non-nucleoside Human Cytomegalovirus (HCMV) Inhibitors. Study of Structural Requirements for Biological Activity

Ana Martinez,[a,*] Carmen Gil,[a] Ana Castro,[a] Concepción Pérez,[a] Columbiana Prieto[b] and Joaquin Otero[b]

[a]*Instituto de Química Médica (CSIC), Juan de la Cierva 3, 28006 Madrid, Spain*
[b]*Unidad de Virologia, Servicio de Microbiologia, Hospital 'Doce de Octubre', 28041 Madrid, Spain*



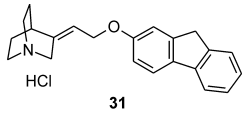
Bioorg. Med. Chem. 11 (2003) 2403

Syntheses and Biological Evaluation of Novel Quinuclidine Derivatives as Squalene Synthase Inhibitors

Tsukasa Ishihara,* Hirotoshi Kakuta, Hiroshi Moritani, Tohru Ugawa, Shuichi Sakamoto, Shin-ichi Tsukamoto and Isao Yanagisawa

Institute for Drug Discovery Research, Yamanouchi Pharmaceutical Co., Ltd., 21 Miyukigaoka, Tsukuba, Ibaraki 305-8585, Japan

Novel quinuclidine derivatives incorporating a tricyclic system were synthesized and evaluated for inhibitory activities against squalene synthase. (*Z*)-3-Ethylidenequinuclidine derivative **31** exhibited the most potent inhibitory activity and significantly reduced non-HDL cholesterol levels in hamsters following oral dosing.



31

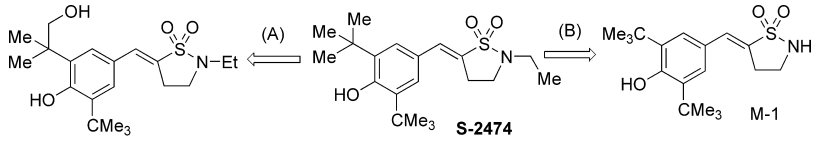
Bioorg. Med. Chem. 11 (2003) 2415

Synthesis and Activities of Oxidative Metabolites of the Anti-arthritic Drug Candidate S-2474

Masanao Inagaki,[a,*] Hirokuni Jyoyama,[a] Takashi Ono,[a] Katsutoshi Yamada,[a] Mika Kobayashi,[a] Takahiko Baba,[b] Akira Touchi,[b] Kouji Iwatani,[b] Tomoyuki Ohkawa,[b] Saichi Matsumoto[a] and Tatsuo Tsuri[a,*]

[a]*Discovery Research Laboratories, Shionogi & Co., Ltd., Fukushima-ku, Osaka 553-0002, Japan*
[b]*Developmental Research Laboratories, Shionogi & Co., Ltd., Futaba-cho, Toyonaka, Osaka 561-0825, Japan*

This study has clarified the primary, major metabolic pathways of antiarthritic drug candidate S-2474.



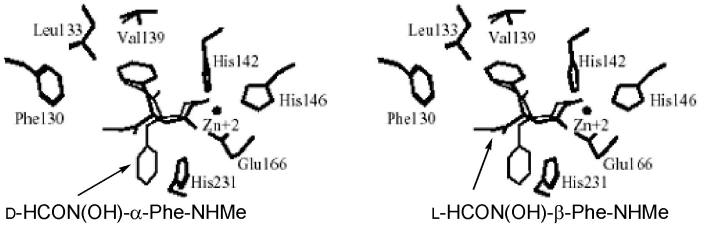
Metabolism of S-2474

Bioorg. Med. Chem. 11 (2003) 2421

Origin of the Stereospecificity in Binding Hydroxamates of α- and β-Phenylalanine Methylamide to Thermolysin Revealed by the X-ray Crystallographic Study

Seung-Jun Kim,[a] Dong H. Kim,[b,*] Jung Dae Park,[b] Joo-Rang Woo,[a] Yonghao Jin[b] and Seong Eon Ryu[a,*]

[a]*Center for Cellular Switch Protein Structure, Korea Research Institute of Bioscience and Biotechnology, 52 Euh-eun-dong, Yusong-gu, Deajeon 305-806, South Korea*
[b]*Center for Integrated Molecular Systems, Division of Molecular and Life Sciences, Pohang University of Science and Technology, San 31Hyoja-dong, Namku, Pohang 790-784, South Korea*

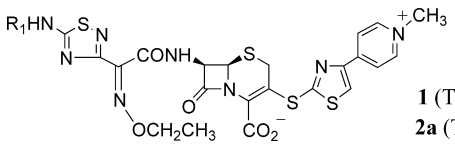


Bioorg. Med. Chem. 11 (2003) 2427

TAK-599, a Novel *N*-Phosphono Type Prodrug of Anti-MRSA Cephalosporin T-91825: Synthesis, Physicochemical and Pharmacological Properties

Tomoyasu Ishikawa,* Nobuyuki Matsunaga, Hiroyuki Tawada, Noritaka Kuroda, Yutaka Nakayama, Yukio Ishibashi, Mitsumi Tomimoto, Yukihiro Ikeda, Yoshihiko Tagawa, Yuji Iizawa, Kenji Okonogi, Shohei Hashiguchi* and Akio Miyake

Pharmaceutical Research Division, Takeda Chemical Industries, Ltd., 2-17-85 Jusohonmachi, Yodogawa-ku, Osaka 532-8686, Japan



1 (TAK-599); R_1=$PO(OH)_2$ (Acetic acid solvate)
2a (T-91825); R_1=H

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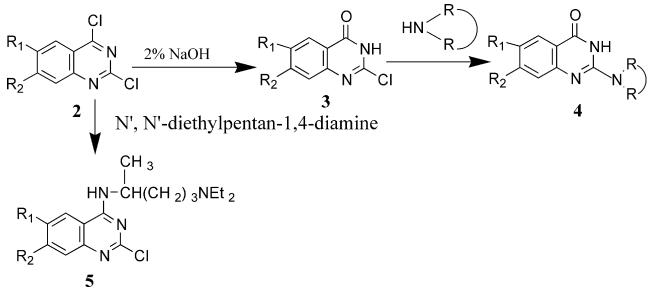
Synthesis and Antihyperglycemic Activity of Suitably Functionalized 3H-quinazolin-4-ones

Vishnu Ji Ram,[a,*] Farhanullah,[a]
Brajendra K. Tripathi[b] and Arvind K. Srivastava[b]

[a]*Division of Medicinal Chemistry, Central Drug Research Institute, Lucknow 226001, India*
[b]*Division of Biochemistry, Central Drug Research Institute, Lucknow 226001, India*

Synthesis and antihyperglycemic activity of 3H-quinazolin-4-ones are described.



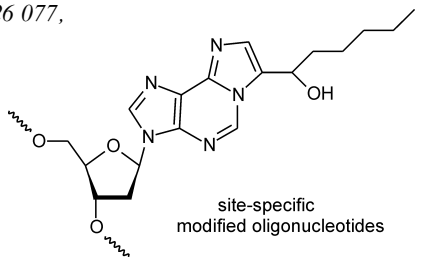
Bioorg. Med. Chem. 11 (2003) 2445

Site-Specific Incorporation of the 1-Hexanol-1,N^6-etheno-2′-deoxyadenosine Adduct into Oligodeoxyribonucleotides

Valdemir M. Carvalho,[a] Didier Gasparutto,[b] Paolo Di Mascio,[a] Marisa H. G. Medeiros[a] and Jean Cadet[b,*]

[a]*Departamento de Bioquímica, Instituto de Química, Universidade de São Paulo, CP 26 077, CEP 05513-970, São Paulo, Brazil*
[b]*Laboratoire Lésions des Acides Nucléiques, DRFMC/SCIB-FRE 2600, CEA/Grenoble, 38054 Grenoble Cedex 9, France*

Site-specifically modified oligonucleotides containing a hydrophobic 1,N^6-etheno-2′-deoxyadenosine adduct have been chemically synthesized. The integrity of the modified nucleoside in the DNA oligomers was confirmed by mass spectrometry measurements together with chromatographic analysis of the enzymatic hydrolysate.

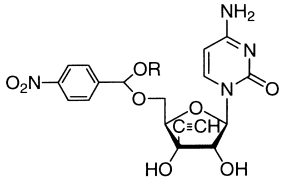


Bioorg. Med. Chem. 11 (2003) 2453

Synthesis of the Cyclic and Acyclic Acetal Derivatives of 1-(3-*C*-Ethynyl-β-D-*ribo*-pentofuranosyl)cytosine, a Potent Antitumor Nucleoside. Design of Prodrugs to be Selectively Activated in Tumor Tissues Via the Bio-Reduction–Hydrolysis Mechanism

Makoto Nomura,[a,b] Satoshi Shuto[a] and Akira Matsuda[a,*]

[a]*Graduate School of Pharmaceutical Sciences, Hokkaido University, Kita-12, Nishi-6, Kita-ku, Sapporo 060-0812, Japan*
[b]*Hanno Research Center, Taiho Pharmaceutical Co. Ltd., 1-27 Misugidai, Hanno, Saitama 357-8527, Japan*



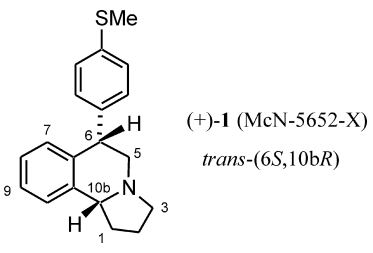
Bioorg. Med. Chem. 11 (2003) 2463

Structural Studies on McN-5652-X, a High-Affinity Ligand for the Serotonin Transporter in Mammalian Brain

Bruce E. Maryanoff,[a,*] David F. McComsey,[a] Rina K. Dukor,[b] Laurence A. Nafie,[b,c] Teresa B. Freedman,[c] Xiaolin Cao[c] and Victor W. Day[d]

[a]*Johnson & Johnson Pharmaceutical Research & Development, Spring House, PA 19477-0776, USA*
[b]*BioTools, Inc., 950 N. Rand Road; Unit 123, Wauconda, IL 60084, USA*
[c]*Department of Chemistry, Syracuse University, Syracuse, NY 13244-4100, USA*
[d]*Crystalytics Company, Lincoln, NE 68523, USA*

We have determined the solid-state structures of (+)-**1**·HClO4 and (+)-**1**·(+)-(2*R*,3*R*)-tartrate by X-ray diffraction to confirm the *trans* relative configuration and the 6*S*,10b*R* absolute configuration of (+)-**1**.

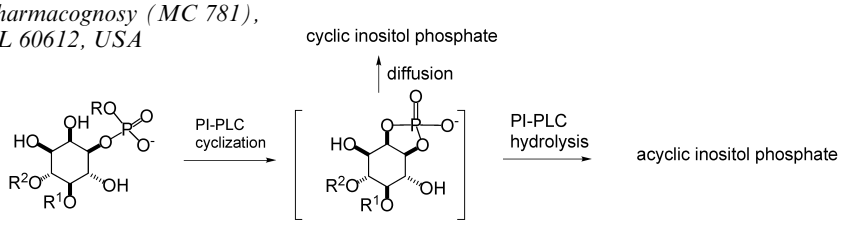


Bioorg. Med. Chem. 11 (2003) 2471

New Aspects of Formation of 1,2-Cyclic Phosphates by Phospholipase C-δ1

Yinghui Liu,[a] Karol S. Bruzik,[a,*] Bharath Ananthanarayanan[b] and Wonhwa Cho[b]

[a]*Department of Medicinal Chemistry and Pharmacognosy (MC 781), University of Illinois at Chicago, Chicago, IL 60612, USA*
[b]*Department of Chemistry, University of Illinois at Chicago, Chicago, IL 60612, USA*



RO = diacylglycerol, R^1 = H, PO_3^{2-}, R^2 = H, PO_3^{2-},

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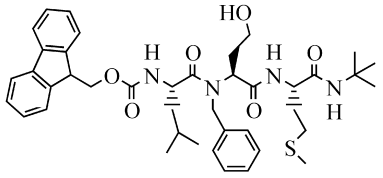
Synthesis and Activity of *N*-Benzyl Pseudopeptides HIV Protease Inhibitors

Mauro Marastoni,* Martina Bazzaro, Fabrizio Bortolotti and Roberto Tomatis

Dipartimento di Scienze Farmaceutiche e Centro di Biotecnologie, via Fossato di Mortara 17-19, Università di Ferrara, I-44100 Ferrara, Italy

The synthesis, antiviral activity and in vitro metabolic stability of *N*-benzyl pseudopeptides are reported.



Fmoc-Leu-N(Bzl)Hse-Met-NH-*t*Bu