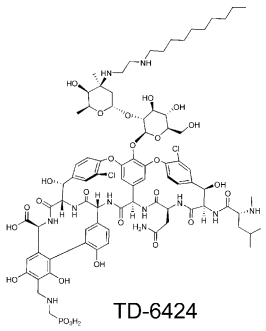
Semi-Synthetic Glycopeptide Antibacterials

Bioorg. Med. Chem. Lett. 13 (2003) 4165

J. Kevin Judice and John L. Pace*

Theravance, Inc., 901 Gateway Blvd., South San Francisco, CA 94080, USA



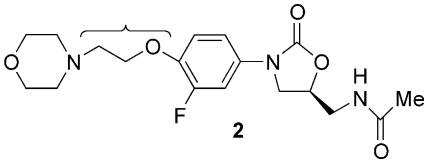
Influence of Ethylene-Oxy Spacer Group on the Activity of Linezolid: Synthesis of Potent Antibacterials Possessing a Thiocarbonyl Group

Bioorg. Med. Chem. Lett. 13 (2003) 4169

N. Selvakumar,* Mohammed A. Raheem, Manoj Kumar Khera, Trideep V. Rajale, Magadi Sitaram Kumar, Sreenivas Kandepu, Jagattaran Das, R. Rajagopalan, Javed Iqbal and Sanjay Trehan

Anti-infectives Discovery Group, Discovery Research, Dr. Reddy's Laboratories Ltd., Miyapur, Hyderabad 500 049, India

The introduction of ethylene-oxy spacer group in linezolid, subsequent SAR studies with different heterocycles and conversion of some of the compounds to their thiocarbonyl counterparts resulted in certain interesting antibacterial compounds.



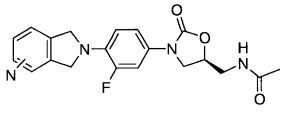
Synthesis and Antibacterial Activity of Pyrroloaryl-Substituted Oxazolidinones

Bioorg. Med. Chem. Lett. 13 (2003) 4173

Steven D. Paget,* Barbara D. Foleno, Christine M. Boggs, Raul M. Goldschmidt, Dennis J. Hlasta, Michele A. Weidner-Wells, Harvey M. Werblood, Ellyn Wira, Karen Bush and Mark J. Macielag

Johnson & Johnson Pharmaceutical Research & Development, L.L.C., Route 202, PO Box 300, Raritan, NJ 08869, USA

A novel series of oxazolidinones containing a pyrroloaryl substituent was synthesized and screened against a representative panel of susceptible and resistant Gram-positive bacteria. Several members of this series were found to have antibacterial activity comparable to or better than linezolid.



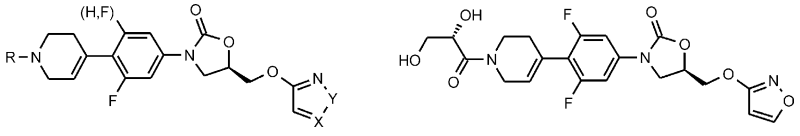
New Classes of Antibacterial Oxazolidinones with C-5, Methylene *O*-Linked Heterocyclic Side Chains

Bioorg. Med. Chem. Lett. 13 (2003) 4179

Michael B. Gravestock,[a,*] David G. Acton,[b] Michael J. Betts,[b] Michael Dennis,[b] Glenn Hatter,[b] Alexandra McGregor,[b] Michael L. Swain,[b] R. Geoffrey Wilson,[b] Lisa Woods[b] and Alan Wookey[b]

[a]*AstraZeneca R&D Boston, Infection Discovery, 35 Gatehouse Park, Waltham, MA 02451, USA*
[b]*AstraZeneca, Cancer and Infection Discovery, Alderley Park, Macclesfield, Cheshire SK10 4TG, UK*

Novel potent oxazolidinone antibacterials with heterocyclic C-5 side chains are described.



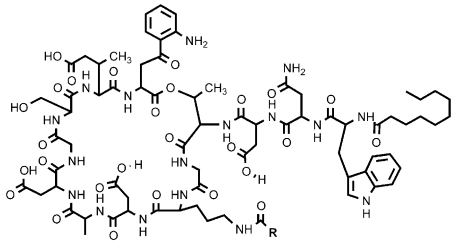
Bioorg. Med. Chem. Lett. 13 (2003) 4187

Synthesis and Biological Activity of *N*-Acylated Ornithine Analogues of Daptomycin

Jason Hill, James Siedlecki, Ian Parr,* Michael Morytko, Xiang Yu, Yanzhi Zhang, Jared Silverman, Nicole Controneo, Valerie Laganas, Tongchuan Li, Jan-Ji Lai, Dennis Keith, George Shimer and John Finn

Cubist Pharmaceuticals Inc., 65 Hayden Ave, Lexington, MA 02421, USA

N-Acylated ornithine analogues of daptomycin were synthesized and tested for their antibacterial efficacy.



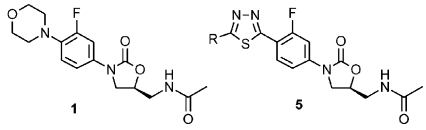
Bioorg. Med. Chem. Lett. 13 (2003) 4193

The Synthesis and Antibacterial Activity of 1,3,4-Thiadiazole Phenyl Oxazolidinone Analogues

Lisa M. Thomasco,* Robert C. Gadwood, Elizabeth A. Weaver, Jason M. Ochoada, Charles W. Ford, Gary E. Zurenko, Judith C. Hamel, Douglas Stapert, Judy K. Moerman, Ronda D. Schaadt and Betty H. Yagi

Discovery-Chemistry and Discovery-Infectious Diseases, Pharmacia Corporation, 7000 Portage Road, Kalamazoo, MI 49001, USA

Replacement of the morpholine C-ring of linezolid **1** with a 1,3,4-thiadiazolyl ring leads to oxazolidinone analogues **5** having potent antibacterial activity against both gram-positive and gram-negative organisms. Conversion of the C5 acetamide group to a thioacetamide further increases the potency of these compounds.



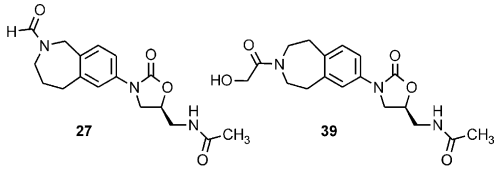
Bioorg. Med. Chem. Lett. 13 (2003) 4197

Synthesis and Biological Evaluation of Benzazepine Oxazolidinone Antibacterials

Paul D. Johnson,[a,*] Paul A. Aristoff,[a] Gary E. Zurenko,[b] Ronda D. Schaadt,[b] Betty H. Yagi,[b] Charles W. Ford,[b] Judith C. Hamel,[b] Douglas Stapert[b] and Judy K. Moerman[b]

[a]*Discovery-Chemistry, Pharmacia Corporation, 7000 Portage Road, Kalamazoo, MI 49001, USA*
[b]*Discovery-Infectious Diseases, Pharmacia Corporation, 7000 Portage Road, Kalamazoo, MI 49001, USA*

Novel benzazepine oxazolidinones were synthesized as potential antibacterial agents. Compounds **27** and **39** displayed in vitro Gram-positive antibacterial activity comparable to linezolid against clinically relevant organisms.

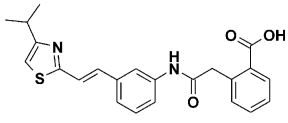


Bioorg. Med. Chem. Lett. 13 (2003) 4201

MexAB-OprM-Specific Efflux Pump Inhibitors in *Pseudomonas aeruginosa*. Part 1: Discovery and Early Strategies for Lead Optimization

Kiyoshi Nakayama,[a,*] Yohei Ishida,[a] Masami Ohtsuka,[a] Haruko Kawato,[a] Ken-ichi Yoshida,[a] Yoshihiro Yokomizo,[a] Shigeru Hosono,[a] Toshiharu Ohta,[a] Kazuki Hoshino,[b] Hiroko Ishida,[b] Kumi Yoshida,[b] Thomas E. Renau,[c] Roger Léger,[c] Jason Z. Zhang,[c] Ving J. Lee[c] and William J. Watkins[c]

[a]*Medicinal Chemistry Research Laboratory, Daiichi Pharmaceutical Co., Ltd., 1-16-13, Kitakasai, Edogawa, Tokyo 134-8630, Japan*
[b]*New Product Research Laboratories I, Daiichi Pharmaceutical Co., Ltd., 1-16-13, Kitakasai, Edogawa, Tokyo 134-8630, Japan*
[c]*Essential Therapeutics, Inc., 850 Maude Avenue, Mountain View, CA 94043, USA*

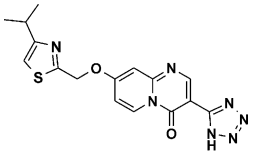


Bioorg. Med. Chem. Lett. 13 (2003) 4205

MexAB-OprM Specific Efflux Pump Inhibitors in *Pseudomonas aeruginosa*. Part 2: Achieving Activity In Vivo Through the Use of Alternative Scaffolds

Kiyoshi Nakayama,[a,*] Yohei Ishida,[a] Masami Ohtsuka,[a] Haruko Kawato,[a] Ken-ichi Yoshida,[a] Yoshihiro Yokomizo,[a] Toshiharu Ohta,[a] Kazuki Hoshino,[b] Tsuyoshi Otani,[b] Yuichi Kurosaka,[b] Kumi Yoshida,[b] Hiroko Ishida,[b] Ving J. Lee,[c] Thomas E. Renau[c] and William J. Watkins[c]

[a]*Medicinal Chemistry Research Laboratory, Daiichi Pharmaceutical Co., Ltd., 1-16-13, Kitakasai, Edogawa, Tokyo 134-8630, Japan*
[b]*New Product Research Laboratories I, Daiichi Pharmaceutical Co., Ltd., 1-16-13, Kitakasai, Edogawa, Tokyo 134-8630, Japan*
[c]*Essential Therapeutics, Inc., 850 Maude Avenue, Mountain View, CA 94043, USA*



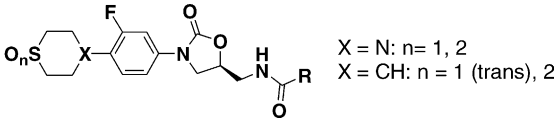
Bioorg. Med. Chem. Lett. 13 (2003) 4209

New Antibacterial Tetrahydro-4(2*H*)-thiopyran and Thiomorpholine *S*-Oxide and *S*,*S*-Dioxide Phenyloxazolidinones

Upinder Singh,[a] B. Raju,[a] Stuart Lam,[a] Joseph Zhou,[a] Robert C. Gadwood,[b] Charles W. Ford,[b] Gary E. Zurenko,[b] Ronda D. Schaadt,[b] Sara E. Morin,[b] Wade J. Adams,[b] Janice M. Friis,[b] Maria Courtney,[b] Joe Palandra,[b] Corinne J. Hackbarth,[a] Sara Lopez,[a] Charlotte Wu,[a] Kathleen H. Mortell,[a] Joaquim Trias,[a] Zhengyu Yuan,[a] Dinesh V. Patel[a] and Mikhail F. Gordeev[a,*]

[a]*Vicuron Pharmaceuticals Inc., 34790 Ardentech Court, Fremont, CA 94555, USA*
[b]*Pharmacia Corporation, 301 Henrietta St., Kalamazoo, MI 49007, USA*

A series of new leads have been identified, including orally active compounds with enhanced potency against fastidious gram-negatives.



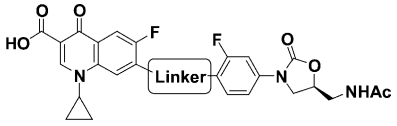
Bioorg. Med. Chem. Lett. 13 (2003) 4213

Novel Oxazolidinone–Quinolone Hybrid Antimicrobials

Mikhail F. Gordeev,[a,*] Corinne Hackbarth,[a] Michael R. Barbachyn,[b] Lee S. Banitt,[b] James R. Gage,[b] Gary W. Luehr,[a] Marcela Gomez,[a] Joaquim Trias,[a] Sara E. Morin,[b] Gary E. Zurenko,[b] Christian N. Parker,[b] Jonathan M. Evans,[b] Richard J. White[a] and Dinesh V. Patel[a]

[a]*Vicuron Pharmaceuticals Inc., 34790 Ardentech Ct., Fremont, CA 94555, USA*
[b]*Pharmacia Co., 7000 Portage Rd., Kalamazoo, MI 49001, USA*

Antimicrobial compounds incorporating oxazolidinone and quinolone pharmacophore substructures have been designed and evaluated. Representative analogues display an improved potency versus linezolid against gram-positive and fastidious gram-negative pathogens, including ciprofloxacin and linezolid-resistant strains.

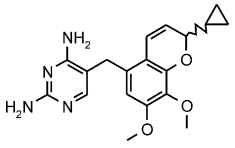


Bioorg. Med. Chem. Lett. 13 (2003) 4217

Iclaprim, a Novel Diaminopyrimidine with Potent Activity on Trimethoprim Sensitive and Resistant Bacteria

Peter Schneider,* Stephen Hawser and Khalid Islam

Arpida Ltd, Dammstrasse 36, CH-4142 Muenchenstein, Switzerland



Iclaprim

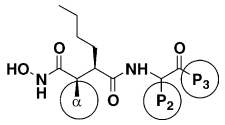
Bioorg. Med. Chem. Lett. 13 (2003) 4223

α-Substituted Hydroxamic Acids as Novel Bacterial Deformylase Inhibitor-Based Antibacterial Agents

R. Jain,[a] A. Sundram,[a] S. Lopez,[a] G. Neckermann,[b] C. Wu,[a] C. Hackbarth,[a] D. Chen,[a] W. Wang,[a] N. S. Ryder,[b] B. Weidmann,[b] D. Patel,[a] J. Trias,[a] R. White[a] and Z. Yuan[a,*]

[a]*Vicuron Pharmaceuticals (formerly Versicor Inc), 34790 Ardentech Court, Fremont, CA 94555, USA*
[b]*Novartis Institutes for Biomedical Research, Inc, 100 Technology Square, Cambridge, MA 02139, USA*

Analogues of 2-*R*-butyl succinic acid containing PDF inhibitors were prepared and SAR were explored at the metal chelating site α-position and the P_2'/P_3' position.



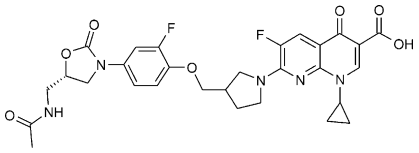
Bioorg. Med. Chem. Lett. 13 (2003) 4229

Structure–Activity Relationship in the Oxazolidinone–Quinolone Hybrid Series: Influence of the Central Spacer on the Antibacterial Activity and the Mode of Action

Christian Hubschwerlen,* Jean-Luc Specklin, Daniel K. Baeschlin, Yves Borer, Sascha Haefeli, Christine Sigwalt, Susanne Schroeder and Hans H. Locher

Morphochem AG, Schwarzwaldallee 215, CH 4058 Basel, Switzerland

Appropriate selection of the spacer led to the identification of oxazolidinone–quinolone hybrids with a balanced dual mode of action and with antibacterial activities that overcame all types of resistance in clinically relevant Gram-positive pathogens.



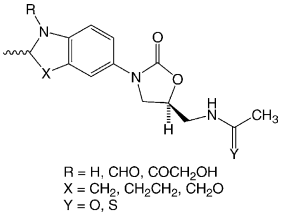
Bioorg. Med. Chem. Lett. 13 (2003) 4235

The Effect of Remote Chirality on the Antibacterial Activity of Indolinyl, Tetrahydroquinolyl and Dihydrobenzoxazinyl Oxazolidinones

Fred L. Ciske, Michael R. Barbachyn,* Michael J. Genin, Kevin C. Grega, Chi Sing Lee, Lester A. Dolak, Eric P. Seest, William Watt, Wade J. Adams, Janice M. Friis, Charles W. Ford and Gary E. Zurenko

Pfizer, 7000 Portage Road, Kalamazoo, MI 49001, USA

The design, synthesis, and antibacterial activity profile of a series of new oxazolidinones are discussed.

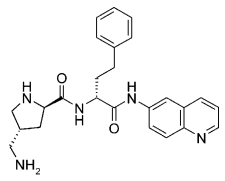


Bioorg. Med. Chem. Lett. 13 (2003) 4241

The Relationship between Physicochemical Properties, In Vitro Activity and Pharmacokinetic Profiles of Analogues of Diamine-Containing Efflux Pump Inhibitors

William J. Watkins,* Yakira Landaverry, Roger Léger, Renée Litman, Thomas E. Renau, Nicole Williams, Rose Yen, Jason Z. Zhang, Suzanne Chamberland, Deidre Madsen, David Griffith, Vrushali Tembe, Keith Huie and Michael N. Dudley

Essential Therapeutics, Inc., 850 Maude Ave., Mountain View, CA 94043, USA



Bioorg. Med. Chem. Lett. 13 (2003) 4245

Array Synthesis of Novel Lipodepsipeptide

James Siedlecki, Jason Hill, Ian Parr,* Xiang Yu, Michael Morytko, Yanzhi Zhang, Jared Silverman, Nicole Controneo, Valerie Laganas, Tongchuan Li, Jianshi Li, Dennis Keith, George Shimer and John Finn

Cubist Pharmaceuticals Inc, 65Hayden Av, Lexington, MA 02421, USA

Synthetic array technology was utilized to rapidly synthesize and analyze a diverse set of reductive alkylation analogues of daptomycin. Analysis of the array suggested the use of polar functionality such as sulfonamides or amide or polar spaces such as piperazine would beneficially affect activity.