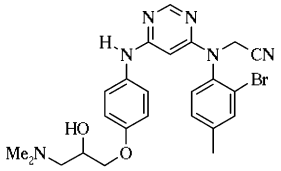
Bioorg. Med. Chem. Lett. 13 (2003) 2955

Cyclin-Dependent Kinase 4 Inhibitors as a Treatment for Cancer. Part 1: Identification and Optimisation of Substituted 4,6-Bis Anilino Pyrimidines

John F. Beattie, Gloria A. Breault,* Rebecca P. A. Ellston, Stephen Green, Philip J. Jewsbury, Catherine J. Midgley, Russell T. Naven, Claire A. Minshull, Richard A. Pauptit, Julie A. Tucker and J. Elizabeth Pease*

AstraZeneca, Alderley Park, Macclesfield, Cheshire SK10 4TG, UK

Development of potent and selective CDK4 inhibitors.



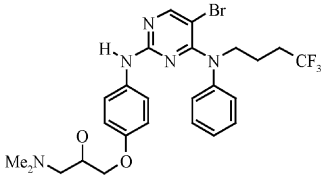
Bioorg. Med. Chem. Lett. 13 (2003) 2961

Cyclin-Dependent Kinase 4 Inhibitors as a Treatment for Cancer. Part 2: Identification and Optimisation of Substituted 2,4-Bis Anilino Pyrimidines

Gloria A. Breault,* Rebecca P. A. Ellston, Stephen Green, S. Russell James, Philip J. Jewsbury, Catherine J. Midgley, Richard A. Pauptit, Claire A. Minshull, Julie A. Tucker and J. Elizabeth Pease*

AstraZeneca, Alderley Park, Macclesfield, Cheshire SK10 4TG, UK

Development of potent and selective CDK4 inhibitors.



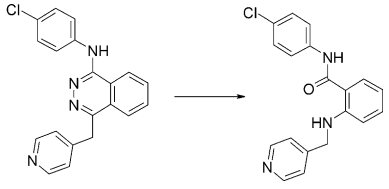
Bioorg. Med. Chem. Lett. 13 (2003) 2967

Identification of a New Chemical Class of Potent Angiogenesis Inhibitors Based on Conformational Considerations and Database Searching

Pascal Furet,[a,*] Guido Bold,[a] Francesco Hofmann,[a] Paul Manley,[a] Thomas Meyer[a] and Karl-Heinz Altmann[b]

[a]*Oncology Research, Novartis Pharma AG, CH-4002 Basel, Switzerland*
[b]*Corporate Research, Novartis Pharma AG, CH-4002 Basel, Switzerland*

The discovery of a new class of inhibitors of the kinase activity of the vascular endothelial growth factor tyrosine kinase receptors KDR and Flt-1 is described.

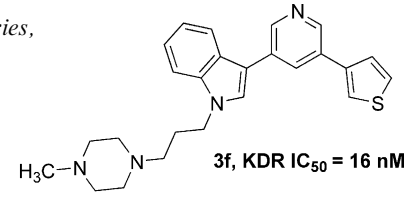


Bioorg. Med. Chem. Lett. 13 (2003) 2973

Discovery and Evaluation of 3-(5-Thien-3-ylpyridin-3-yl)-1*H*-indoles as a Novel Class of KDR Kinase Inhibitors

Mark E. Fraley,* Kenneth L. Arrington, Scott R. Hambaugh, William F. Hoffman, April M. Cunningham, Mary Beth Young, Randall W. Hungate, Andrew J. Tebben, Ruth Z. Rutledge, Richard L. Kendall, William R. Huckle, Rosemary C. McFall, Kathleen E. Coll and Kenneth A. Thomas

Departments of Medicinal Chemistry and Cancer Research, Merck Research Laboratories, West Point, PA 19486, USA



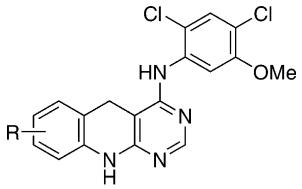
Bioorg. Med. Chem. Lett. 13 (2003) 2974

Inhibition of Src Kinase Activity by 4-Anilino-5,10-dihydropyrimido[4,5-*b*]quinolines

Diane H. Boschelli,[a,*] Dennis Powell,[a] Jennifer M. Golas[b] and Frank Boschelli[b]

[a]*Chemical and Screening Sciences, Wyeth Research, 401 N. Middletown Road, Pearl River, NY 10965, USA*
[b]*Oncology, Wyeth Research, 401 N. Middletown Road, Pearl River, NY 10965, USA*

4-(2,4-Dichloro-5-methoxy)anilino-5,10-dihydropyrimido[4,5-*b*]quinolines are potent inhibitors of Src kinase activity.



Bioorg. Med. Chem. Lett. 13 (2003) 2981

Synthesis of Three Enantiomeric Pairs of *scyllo*-Inositol Phosphate and Molecular Interactions Between All Possible Regioisomers of *scyllo*-Inositol Phosphate and Inositol 1,4,5-Trisphosphate 3-Kinase

Yong-Uk Kwon,[a] Jungkyun Im,[a] Gildon Choi,[b] Young-Soo Kim,[a] Kwan Yong Choi[b] and Sung-Kee Chung[a,*]

[a]*Department of Chemistry, Division of Molecular and Life Sciences, Pohang University of Science & Technology, Pohang 790-784, South Korea*
[b]*National Research Laboratory of Protein Folding and Engineering, Division of Molecular and Life Sciences, Pohang University of Science & Technology, Pohang 790-784, South Korea*

We herein describe the facile synthetic routes to three enantiomeric pairs of *scyllo*-inositol phosphate and the molecular interactions between 15 possible regioisomers of *scyllo*-inositol phosphate and inositol 1,4,5-trisphosphate 3-kinase.

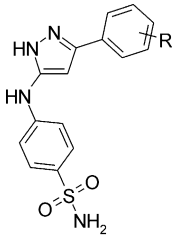
Bioorg. Med. Chem. Lett. 13 (2003) 2985

Anilinopyrazole as Selective CDK2 Inhibitors: Design, Synthesis, Biological Evaluation, and X-ray Crystallographic Analysis

Jun Tang,[a,*] Lisa M. Shewchuk,[b] Hideyuki Sato,[a] Masaichi Hasegawa,[a] Yoshiaki Washio[a] and Naohiko Nishigaki[a]

[a]*GlaxoSmithKline K. K. Tsukuba Research Laboratories, 43 Wadai Tsukuba, Ibaraki 300-4247, Japan*
[b]*GlaxoSmithKline Inc., Five Moore Drive, Research Triangle Park, NC 27709, USA*

A novel series of anilinopyrazoles has been designed based on the X-ray crystal structure analysis. Most compounds from this series not only show sub-nanomolar IC_{50} values for CDK2, but also demonstrate almost 1000-fold selectivity to other kinases including CDK1.



Anilinopyrazole 1

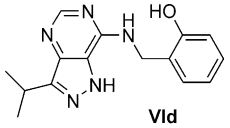
Bioorg. Med. Chem. Lett. 13 (2003) 2989

Pyrazolo[4,3-*d*]pyrimidines as New Generation of Cyclin-Dependent Kinase Inhibitors

Daniela Moravcová,[a] Vladimír Kryštof,[b] Libor Havlíček,[a] Jiří Moravec,[a] René Lenobel[b] and Miroslav Strnad[b,*]

[a]*Isotope Laboratory, Institute of Experimental Botany, Academy of Sciences of the Czech Republic, Vídeňská 1083, 14220 Prague 4, Czech Republic*
[b]*Laboratory of Growth Regulators, Palacký University and Institute of Experimental Botany, Šlechtitelů 11, 783 71 Olomouc, Czech Republic*

Substituted pyrazolo[4,3-*d*]pyrimidines are presented as novel inhibitors of CDK1/cyclin B, showing also antiproliferative activity on leukemic cell line K-562.



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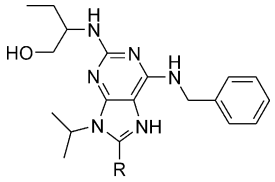
Bioorg. Med. Chem. Lett. 13 (2003) 2993

2,6,8,9-Tetrasubstituted Purines as New CDK1 Inhibitors

Jiří Moravec,[a] Vladimír Kryštof,[b] Jan Hanuš,[a] Libor Havlíček,[a] Daniela Moravcová,[a] Květoslava Fuksová,[a] Marek Kuzma,[c] René Lenobel,[b] Michal Otyepka[d] and Miroslav Strnad[b,*]

[a]*Isotope Laboratory, Institute of Experimental Botany, Academy of Sciences of the Czech Republic, Vídeňská 1083, 14220 Prague 4, Czech Republic*
[b]*Laboratory of Growth Regulators, Palacký University & Institute of Experimental Botany, Šlechtitelů 11, 783 71 Olomouc, Czech Republic*
[c]*Institute of Microbiology, Academy of Sciences of the Czech Republic, Vídeňská 1083, 14200 Prague 4, Czech Republic*
[d]*Department of Inorganic and Physical Chemistry, Palacký University, Tř. Svobody 26, 77146 Olomouc, Czech Republic*



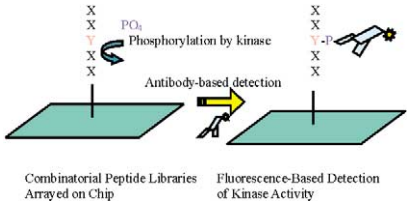
The additional group at C-8 of 2,6,9-trisubstituted purines decreases their CDK inhibitory activity, but the compounds still exert antiproliferative activity.

Bioorg. Med. Chem. Lett. 13 (2003) 2997

Combinatorial Peptide Microarrays for the Rapid Determination of Kinase Specificity

Mahesh Uttamchandani,[a] Elaine W. S. Chan,[b] Grace Y. J. Chen[a,b] and Shao Q. Yao[a,b,*]

[a]*Department of Biological Sciences, National University of Singapore, 3 Science Drive 3, Singapore 117543, Singapore*
[b]*Department of Chemistry, National University of Singapore, 3 Science Drive 3, Singapore 117543, Singapore*



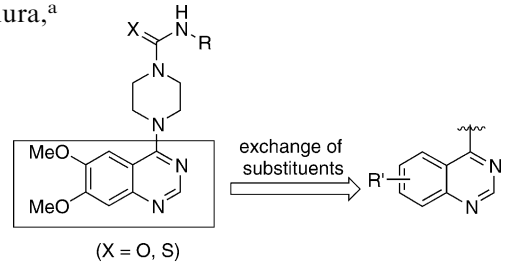
We report a rapid method for profiling of kinases using a strategy that couples the merits of combinatorics (in rapid diversity generation) with the throughput attainable using microarrays (in parallel screening).

Bioorg. Med. Chem. Lett. 13 (2003) 3001

Potent and Selective Inhibitors of Platelet-Derived Growth Factor Receptor Phosphorylation. Part 4: Structure–Activity Relationships for Substituents on the Quinazoline Moiety of 4-[4-(*N*-Substituted(thio)carbamoyl)-1-piperazinyl]-6,7-dimethoxyquinazoline Derivatives

Kenji Matsuno,[a,*] Takashi Seishi,[a] Takao Nakajima,[a] Michio Ichimura,[a] Neill A. Giese,[b] Jin-Chen Yu,[b] Shoji Oda[a] and Yuji Nomoto[a]

[a]*Kyowa Hakko Kogyo Co., Ltd., Pharmaceutical Research Institute, Shimotogari 1188, Nagaizumi-cho, Sunto-gun, Shizuoka 411-8731, Japan*
[b]*Millennium Pharmaceuticals, Inc., 256 E. Grand Avenue, South San Francisco, CA 94080, USA*

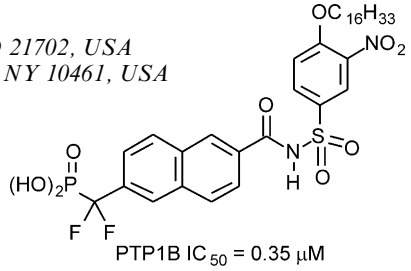


Bioorg. Med. Chem. Lett. 13 (2003) 3005

Acylsulfonamide-Containing PTP1B Inhibitors Designed to Mimic an Enzyme-Bound Water of Hydration

Ding-Guo Liu,[a] Yang Gao,[a] Johannes H. Voigt,[a] Kyeong Lee,[a] Marc C. Nicklaus,[a] Li Wu,[b] Zhong-Yin Zhang[b] and Terrence R. Burke, Jr.[a,*]

[a]*Laboratory of Medicinal Chemistry, CCR, NCI, NIH, NCI-Frederick, Frederick, MD 21702, USA*
[b]*Department of Molecular Pharmacology, Albert Einstein College of Medicine, Bronx, NY 10461, USA*



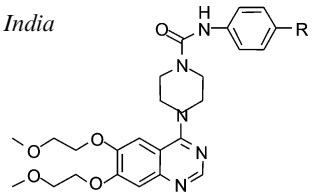
Bioorg. Med. Chem. Lett. 13 (2003) 3009

Topological Designing of 4-Piperazinylquinazolines as Antagonists of PDGFR Tyrosine Kinase Family

Padmakar V. Khadikar,[a,*] Anjali Shrivastava,[a] Vijay K. Agrawal[b] and Shachi Srivastava[b]

[a]*Research Division, Laxmi Fumigation and Pest Control Pvt. Ltd., 3 Khatipura, Indore-452 007, India*
[b]*QSAR and Computer Chemical Laboratories, A.P.S. University, Rewa-486 003, India*

Topological designing of a series of 4-piperazinylquinazolines as antagonists of platelet-derived growth factor receptor (PDGFR) tyrosine kinase family has been reported using a series of distance-based topological indices. Regression analysis of the data, using maximum R^2 method indicated that inhibitory activity, pIC_{50} (μm), in cellular PGDFR phosphorylation assay can be modelled excellently in multi-parametric model. The results are discussed critically using cross-validated parameters.



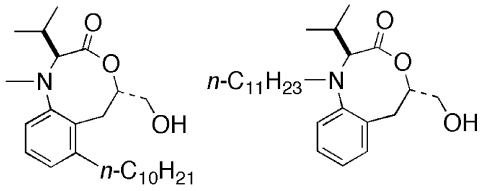
Bioorg. Med. Chem. Lett. 13 (2003) 3015

Synthesis and Binding Selectivity of 7- and 15-Decylbenzolactone-V8 for the C1 Domains of Protein Kinase C Isozymes

Yu Nakagawa,[a] Kazuhiro Irie,[a,*] Nobuhiro Yamanaka,[a] Hajime Ohigashi[a] and Ken-ichiro Tsuda[b]

[a]*Division of Food Science and Biotechnology, Graduate School of Agriculture, Kyoto University, Kyoto 606-8502, Japan*
[b]*Fundamental Research Laboratories NEC Corporation, 34 Miyukigaoka, Tsukuba 305-8501, Japan*

7- and 15-decylbenzolactone-V8 (**7**, **8**) were synthesized, and their conformation and binding affinities for synthetic C1 peptides of all PKC isozymes were examined.



7 **8**

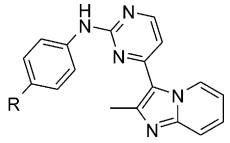
Bioorg. Med. Chem. Lett. 13 (2003) 3021

Imidazo[1,2-*a*]pyridines: A Potent and Selective Class of Cyclin-Dependent Kinase Inhibitors Identified Through Structure-Based Hybridisation

Malcolm Anderson, John F. Beattie, Gloria A. Breault,* Jason Breed, Kate F. Byth, Janet D. Culshaw, Rebecca P. A. Ellston, Stephen Green, Claire A. Minshull, Richard A. Norman, Richard A. Pauptit, Judith Stanway, Andrew P. Thomas* and Philip J. Jewsbury*

AstraZeneca, Alderley Park, Macclesfield, Cheshire SK10 4TG, UK

Comparison of the imidazo[1,2-*a*]pyridine and bisanilinopyrimidine binding modes and emerging structure–activity trends led to the development of potent and selective imidazo[1,2-*a*]pyridine inhibitors of CDK4 and CDK2.



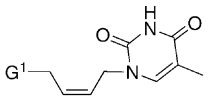
Bioorg. Med. Chem. Lett. 13 (2003) 3027

Improving the Selectivity of Acyclic Nucleoside Analogues as Inhibitors of Human Mitochondrial Thymidine Kinase: Replacement of a Triphenylmethoxy Moiety with Substituted Amines and Carboxamides

Ana-Isabel Hernández,[a] Jan Balzarini,[b] Fátima Rodríguez-Barrios,[c] Ana San-Félix,[a] Anna Karlsson,[d] Federico Gago,[c] María-José Camarasa[a] and María Jesús Pérez-Pérez[a,*]

[a]*Instituto de Química Médica (CSIC), Juan de la Cierva 3, E-28006 Madrid, Spain*
[b]*Rega Institute for Medical Research, Katholieke Universiteit Leuven, B-3000 Leuven, Belgium*
[c]*Departamento de Farmacología, Universidad de Alcalá, E-28871 Alcalá de Henares, Madrid, Spain*
[d]*Karolinska Institute, S-14186 Hudding/Stockholm, Sweden*

Replacement of the *O*-trityl moiety in **1** by a series of amines and carboxamides led to more selective and equally potent mitochondrial thymidine kinase inhibitors (i.e., compound **13**).



1 $G^1 = OC(Ph)_3$
13 $G^1 = N(CH_2Ph)_2$

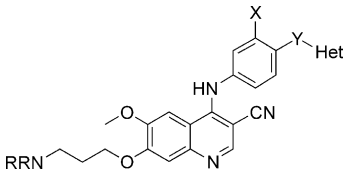
Bioorg. Med. Chem. Lett. 13 (2003) 3031

Synthesis and Evaluation of 4-Anilino-6,7-dialkoxy-3-quinolinecarbonitriles as Inhibitors of Kinases of the Ras-MAPK Signaling Cascade

Dan Berger,[a,*] Minu Dutia,[a] Dennis Powell,[a] Biqi Wu,[a] Allan Wissner,[a] Diane H. Boschelli,[a] M. Brawner Floyd,[a] Nan Zhang,[a] Nancy Torres,[a] Jeremy Levin,[a] Xuemei Du,[a] Donald Wojciechowicz,[b] Carolyn Discafani,[b] Constance Kohler,[b] Steven C. Kim,[b] Larry R. Feldberg,[b] Karen Collins[b] and Robert Mallon[b]

[a]*Chemical Sciences, Wyeth Research, Pearl River, NY 10965, USA*
[b]*Discovery Oncology, Wyeth Research, Pearl River, NY 10965, USA*

A series of 4-anilino-3-quinolinecarbonitriles was synthesized and evaluated against kinases of the Ras-MAPK signaling cascade.

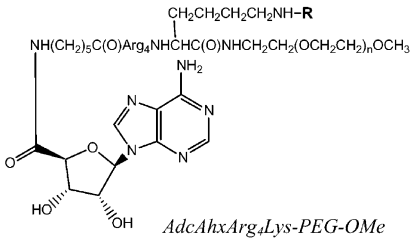


Bioorg. Med. Chem. Lett. 13 (2003) 3035

Liquid-Phase Synthesis of a Pegylated Adenosine–Oligoarginine Conjugate, Cell-Permeable Inhibitor of cAMP-Dependent Protein Kinase

Kaido Viht,[a] Kärt Padari,[b] Gerda Raidaru,[a] Juhan Subbi,[c] Indrek Tammiste,[c] Margus Pooga[d] and Asko Uri[a,*]

[a]*Institute of Organic and Bioorganic Chemistry, University of Tartu, 2 Jakobi St., 51014, Tartu, Estonia*
[b]*Institute of Zoology and Hydrobiology, University of Tartu, 46 Vanemuise St., 51014, Tartu, Estonia*
[c]*Institute of Chemical Physics and Biophysics, 23 Akadeemia St., 12618, Tallinn, Estonia*
[d]*Estonian Biocentre, Riia 23a, 51010 Tartu, Estonia*



AdcAhxArg$_4$Lys-PEG-OMe

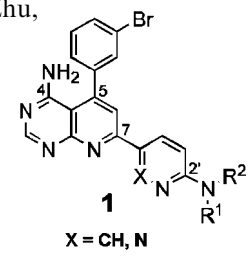
Bioorg. Med. Chem. Lett. 13 (2003) 3041

Adenosine Kinase Inhibitors: Polar 7-Substitutent of Pyridopyrimidine Derivatives Improving Their Locomotor Selectivity

Guo Zhu Zheng,* Yue Mao, Chih-Hung Lee, John K. Pratt, John R. Koenig, Richard J. Perner, Marlon D. Cowart, Gregory A. Gfesser, Steve McGaraughty, Katharine L. Chu, Chang Zhu, Haixia Yu, Kathy Kohlhaas, Karen M. Alexander, Carol T. Wismer, Joseph Mikusa, Michael F. Jarvis, Elizabeth A. Kowaluk and Andrew O. Stewart

Abbott Laboratories, Neuroscience Research, Bldg. AP9A LL, 100 Abbott Park Road, Abbott Park, IL 60064-6115, USA

We have discovered that polar 7-substituents of pyridopyrimidine derivatives affect not only whole cell AK inhibitory potency, but also selectivity in causing locomotor side effects in vivo animal models.



1

X = CH, N

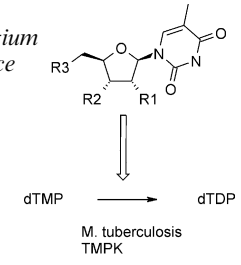
Bioorg. Med. Chem. Lett. 13 (2003) 3045

Thymidine and Thymidine-5′-*O*-monophosphate Analogues as Inhibitors of *Mycobacterium tuberculosis* Thymidylate Kinase

Veerle Vanheusden,[a] Philippe Van Rompaey,[a] Hélène Munier-Lehmann,[b] Sylvie Pochet,[c] Piet Herdewijn[d] and Serge Van Calenbergh[a,*]

[a]*Laboratory for Medicinal Chemistry (FFW), Ghent University, Harelbekestraat 72, B-9000 Gent, Belgium*
[b]*Laboratoires de Chimie Structurale des Macromolécules, Institut Pasteur, 75724 Paris Cedex 15, France*
[c]*Unité de Chimie Organique (URA2128), 75724 Paris Cedex 15, France*
[d]*Laboratory for Medicinal Chemistry, Rega Institute, Catholic University of Leuven, B-3000 Leuven, Belgium*

The design, synthesis and biological activity of thymidine analogues as inhibitors of *Mycobacterium tuberculosis* thymidine monophosphate kinase are described.



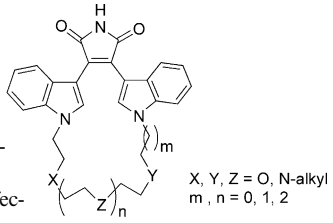
Bioorg. Med. Chem. Lett. 13 (2003) 3049

Macrocyclic Bisindolylmaleimides as Inhibitors of Protein Kinase C and Glycogen Synthase Kinase-3

Han-Cheng Zhang,[a,*] Kimberly B. White,[a] Hong Ye,[a] David F. McComsey,[a] Claudia K. Derian,[a] Michael F. Addo,[a] Patricia Andrade-Gordon,[a] Annette J. Eckardt,[a] Bruce R. Conway,[b] Lori Westover,[b] Jun Z. Xu,[b] Richard Look,[b] Keith T. Demarest,[b] Stuart Emanuel[b] and Bruce E. Maryanoff[a]

[a]*Drug Discovery, Johnson & Johnson Pharmaceutical Research & Development, Spring House, PA 19477-0776, USA*
[b]*Drug Discovery, Johnson & Johnson Pharmaceutical Research & Development, Raritan, NJ 08869-0602, USA*

A novel series of macrocyclic bisindolylmaleimides containing linkers with multiple heteroatoms was synthesized and found to be potent inhibitors (single digit nanomolar IC_{50}) for PKC-β and GSK-3β. The compounds showed good selectivity over PKC-α, -γ, -δ, -ε, -ζ, and 10 other protein kinases, and were effective in cell-based functional assays.



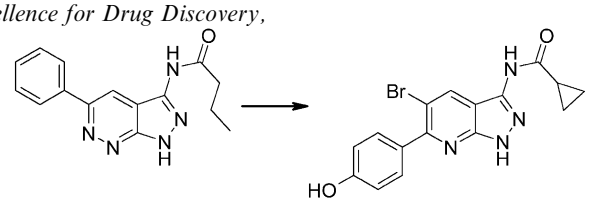
Bioorg. Med. Chem. Lett. 13 (2003) 3055

6-Aryl-pyrazolo[3,4-*b*]pyridines: Potent Inhibitors of Glycogen Synthase Kinase-3 (GSK-3)

Jason Witherington,* Vincent Bordas, Alessandra Gaiba, Neil S. Garton, Antoinette Naylor, Anthony D. Rawlings, Brian P. Slingsby, David G. Smith, Andrew K. Takle and Robert W. Ward

Department of Medicinal Chemistry, Neurology & GI Centre of Excellence for Drug Discovery, GlaxoSmithKline Research Limited, New Frontiers Science Park, Third Avenue, Harlow, Essex CM19 5AW, UK

Utilising X-ray crystallography data, a novel series of 6-aryl-pyrazolo[3,4-*b*]pyridines has been identified as potent inhibitors of Glycogen Synthase Kinase-3 (GSK-3).



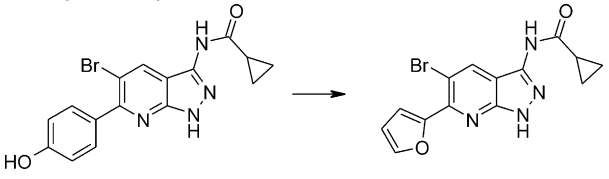
Bioorg. Med. Chem. Lett. 13 (2003) 3059

6-Heteroaryl-pyrazolo[3,4-*b*]pyridines: Potent and Selective Inhibitors of Glycogen Synthase Kinase-3 (GSK-3)

Jason Witherington,* Vincent Bordas, Alessandra Gaiba, Antoinette Naylor, Anthony D. Rawlings, Brian P. Slingsby, David G. Smith, Andrew K. Takle and Robert W. Ward

Department of Medicinal Chemistry, Neurology & GI Centre of Excellence for Drug Discovery, GlaxoSmithKline Research Limited, New Frontiers Science Park, Third Avenue, Harlow, Essex CM19 5AW, UK

Selectivity profiling of a series of 6-aryl-pyrazolo[3,4-*b*]pyridines, revealed significant inhibition of CDK-2. Optimisation of this nucleus to exploit nonconserved interations led to the identification of a potent and selective series of 6-heteroaryl-pyrazolo[3,4-*b*]pyridines.



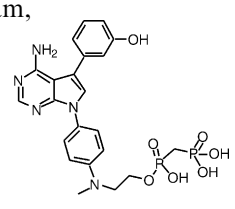
Bioorg. Med. Chem. Lett. 13 (2003) 3063

Bone-Targeted Src Kinase Inhibitors: Novel Pyrrolo- and Pyrazolopyrimidine Analogues

Raji Sundaramoorthi,* William C. Shakespeare, Terence P. Keenan, Chester A. Metcalf, III, Yihan Wang, Ukti Mani, Merry Taylor, Shuangying Liu, Regine S. Bohacek, Surinder S. Narula, David C. Dalgarno, Marie Rose van Schravandijk, Sheila M. Violette, Shuenn Liou, Susan Adams, Mary K. Ram, Jeffrey A. Keats, Manfred Weigele and Tomi K. Sawyer

ARIAD Pharmaceuticals, Inc. 26 Landsdowne Street, Cambridge, MA 02139-4234, USA

The chemistry, biology and drug design of bone-targeted inhibitors of Src kinase is discussed.

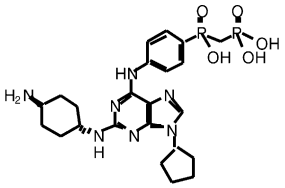


Bioorg. Med. Chem. Lett. 13 (2003) 3067

Bone-Targeted 2,6,9-Trisubstituted Purines: Novel Inhibitors of Src Tyrosine Kinase for the Treatment of Bone Diseases

Yihan Wang,* Chester A. Metcalf, III, William C. Shakespeare, Raji Sundaramoorthi, Terence P. Keenan, Regine S. Bohacek, Marie Rose van Schravendijk, Shiela M. Violette, Surinder S. Narula, David C. Dalgarno, Chad Haraldson, Jeffrey Keats, Shuenn Liou, Ukti Mani, Selvi Pradeepan, Mary Ram, Susan Adams, Manfred Weigele and Tomi K. Sawyer

ARIAD Pharmaceuticals, Inc., 26 Landsdowne Street, Cambridge, MA 02139-4234, USA

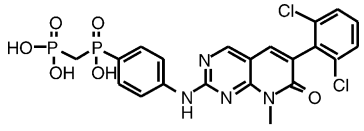


Bioorg. Med. Chem. Lett. 13 (2003) 3071

Bone-Targeted Pyrido[2,3-*d*]pyrimidin-7-ones: Potent Inhibitors of Src Tyrosine Kinase as Novel Antiresorptive Agents

Chi B. Vu, George P. Luke, Noriyuki Kawahata, William C. Shakespeare,* Yihan Wang, Raji Sundaramoorthi, Chester A. Metcalf, III, Terence P. Keenan, Selvi Pradeepan, Evelyn Corpuz, Taylor Merry, Regine S. Bohacek, David C. Dalgarno, Surinder S. Narula, Marie Rose van Schravendijk, Mary K. Ram, Susan Adams, Shuenn Liou, Jeffrey A. Keats, Shelia M. Violette, Wei Guan, Manfred Weigele and Tomi K. Sawyer

ARIAD Pharmaceuticals, Inc., 26 Landsdowne Street, Cambridge, MA 02139-4234, USA



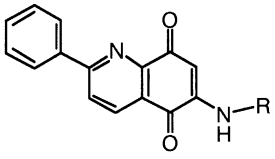
Bioorg. Med. Chem. Lett. 13 (2003) 3075

Design of Quinolinedione-Based Geldanamycin Analogues

Robert Hargreaves,[a] Cynthia L. David,[b] Luke Whitesell[b] and Edward B. Skibo[a,*]

[a]*Department of Chemistry and Biochemistry, Arizona State University, Tempe, AZ 85287-1604, USA*
[b]*Steele Memorial Children's Research Center, University of Arizona, Tucson, AZ 85724, USA*

Quinoline-5,8-dione-based compounds were designed from the structure of the geldanamycin-bound Hsp-90 active site.



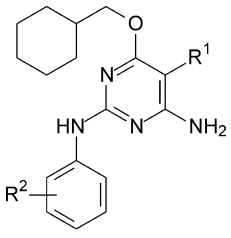
Bioorg. Med. Chem. Lett. 13 (2003) 3079

Structure-Based Design of 2-Arylamino-4-cyclohexylmethyl-5-nitroso-6-aminopyrimidine Inhibitors of Cyclin-Dependent Kinases 1 and 2

Kerry L. Sayle,[a] Johanne Bentley,[b] F. Thomas Boyle,[c] A. Hilary Calvert,[b] Yuzhu Cheng,[b] Nicola J. Curtin,[b] Jane A. Endicott,[d] Bernard T. Golding,[a] Ian R. Hardcastle,[a] Philip Jewsbury,[c] Veronique Mesguiche,[a] David R. Newell,[b] Martin E. M. Noble,[d] Rachel J. Parsons,[a] David J. Pratt,[d] Lan Z. Wang[b] and Roger J. Griffin[a,*]

[a]*Northern Institute for Cancer Research, School of Natural Sciences-Chemistry, Bedson Building, University of Newcastle, Newcastle Upon Tyne NE1 7RU, UK*
[b]*Northern Institute for Cancer Research, Medical School, Framlington Place, Newcastle upon Tyne NE2 4HH, UK*
[c]*AstraZeneca Pharmaceuticals, Alderley Park, Cheshire SK10 4TG, UK*
[d]*Laboratory of Molecular Biophysics and Department of Biochemistry, University of Oxford, Oxford OX1 3QU, UK*

A series of O^4-cyclohexylmethyl-5-nitroso-6-aminopyrimidines bearing 2-arylamino substituents was synthesised and evaluated for CDK1 and CDK2 inhibitory activity. Consistent with analogous studies with O^6-cyclohexylmethylpurines, 2-arylaminopyrimidines with a sulfonamide or carboxamide group at the 4′-position were potent inhibitors, with IC_{50} values against CDK2 of 1.1 ± 0.3 and 35 ± 8 nM, respectively. The crystal structure of the 4′-carboxamide derivative, in complex with phospho-Thr160 CDK2/cyclin A, confirmed the expected binding mode of the inhibitor, and revealed an additional interaction between the carboxamide function and an aspartate residue.



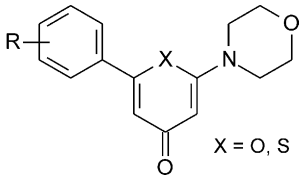
Bioorg. Med. Chem. Lett. 13 (2003) 3083

2,6-Disubstituted Pyran-4-one and Thiopyran-4-one Inhibitors of DNA-Dependent Protein Kinase (DNA-PK)

Jonathan J. Hollick,[a] Bernard T. Golding,[a] Ian R. Hardcastle,[a] Niall Martin,[b] Caroline Richardson,[b] Laurent J. M. Rigoreau,[a,b] Graeme C. M. Smith[b] and Roger J. Griffin[a,*]

[a]*Northern Institute for Cancer Research, School of Natural Sciences-Chemistry, Bedson Building, University of Newcastle, Newcastle Upon Tyne NE1 7RU, UK*
[b]*KuDOS Pharmaceuticals Limited, 327 Cambridge Science Park, Milton Road, Cambridge CB4 0WG, UK*

6-Aryl-2-morpholin-4-yl-4*H*-pyran-4-ones and 6-aryl-2-morpholin-4-yl-4*H*-thiopyran-4-ones were synthesised and evaluated as potential inhibitors of the DNA repair enzyme DNA-dependent protein kinase (DNA-PK). Several compounds in each series exhibited superior activity to the chromenone LY294002, and were of comparable potency to the benzochromenone NU7026 ($IC_{50} = 0.23$ μM). Importantly, members of both structural classes were found to be selective inhibitors of DNA-PK over related phosphatidylinositol 3-kinase-related kinase (PIKK) family members. A multiple-parallel synthesis approach, employing Suzuki cross-coupling methodology, was utilized to prepare libraries of thiopyran-4-ones with a range of aromatic groups at the 3′- and 4′-positions on the thiopyran-4-one 6-aryl ring. Screening of the libraries resulted in the identification of 6-aryl-2-morpholin-4-yl-4*H*-thiopyran-4-ones bearing naphthyl or benzo[*b*]thienyl substituents at the 4′-position, as potent DNA-PK inhibitors with IC_{50} values in the 0.2–0.4 μM range.



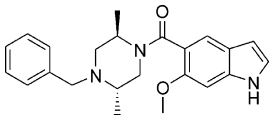
Bioorg. Med. Chem. Lett. 13 (2003) 3087

Indole-Based Heterocyclic Inhibitors of p38α MAP Kinase: Designing a Conformationally Restricted Analogue

Babu J. Mavunkel,[a] Sarvajit Chakravarty,[a] John J. Perumattam,[a] Gregory R. Luedtke,[a] Xi Liang,[a] Don Lim,[a] Yong-jin Xu,[a] Maureen Laney,[a] David Y. Liu,[b] George F. Schreiner,[a] John A. Lewicki[c] and Sundeep Dugar[a,*]

[a]*Scios Inc., 820 West Maude Avenue, Sunnyvale, CA 94086, USA*
[b]*FibroGen, Inc., 225 Gateway Blvd., South San Francisco, CA 94080, USA*
[c]*Osel Inc., 1800 Wyatt Drive, Suite 14, Santa Clara, CA 95054, USA*

p38α Mitogen Activated Protein Kinase (MAP kinase) is an intracellular soluble serine threonine kinase. p38a kinase is activated in response to cellular stresses, growth factors and cytokines such as interleukin-1 (IL-1) and tumor necrosis factor alpha (TNF-α). The central role of p38α activation in settings of both chronic and acute inflammation has led efforts to find inhibitors of this enzyme as possible therapies for diseases such as rheumatoid arthritis, where p38α activation is thought to play a causal role. Herein, we report structure–activity relationship studies on a series of indole-based heterocyclic inhibitors, that led to the design and identification of a new class of p38α inhibitors.



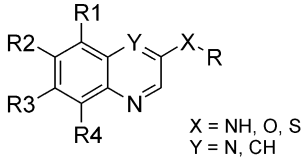
Bioorg. Med. Chem. Lett. 13 (2003) 3091

Potent Quinoxaline-Based Inhibitors of PDGF Receptor Tyrosine Kinase Activity. Part 1: SAR Exploration and Effective Bioisosteric Replacement of a Phenyl Substituent[1]

Michael R. Myers,* Wei He, Barbara Hanney, Natalie Setzer, Martin P. Maguire, Allison Zulli, Glenda Bilder, Helen Galzcinski, Dilip Amin, Saul Needle and Alfred P. Spada

Aventis Pharmaceuticals, Route 202/206, Bridgewater, NJ 08807, USA

Novel substituted 2-anilino- and 2-cycloalkylaminoquinoxalines have been found to be useful and selective inhibitors of PDGF-R autophosphorylation. Replacement of an anilino-substituent with substituted cyclohexylamino- or norbornylamino-substituents led to significant improvements in the pharmacokinetic profile of these analogues.



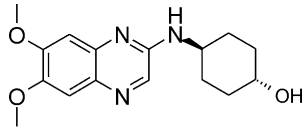
Bioorg. Med. Chem. Lett. 13 (2003) 3097

Potent Quinoxaline-Based Inhibitors of PDGF Receptor Tyrosine Kinase Activity. Part 2: The Synthesis and Biological Activities of RPR127963, an Orally Bioavailable Inhibitor[1]

Wei He,* Michael R. Myers, Barbara Hanney, Alfred P. Spada, Glenda Bilder, Helen Galzcinski, Dilip Amin, Saul Needle, Ken Page, Zaid Jayyosi and Mark H. Perrone

Aventis Pharmaceuticals, Route 202/206, Brigdewater, NJ 08807, USA

RPR127963 demonstrates an excellent pharmacokinetic profile in several species and was found to be efficacious in the prevention of restenosis in a Yucatan mini-pig model upon oral administration of 1–5 mg/kg. The in vitro selectivity profile and SAR of the highly optimized PDGF-R tyrosine kinase inhibitor are highlighted.



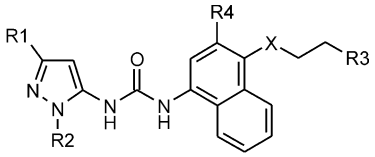
Bioorg. Med. Chem. Lett. 13 (2003) 3101

The Kinetics of Binding to p38 MAP Kinase by Analogues of BIRB 796

John Regan,[a,*] Christopher A. Pargellis,[b] Pier F. Cirillo,[a] Thomas Gilmore,[a] Eugene R. Hickey,[a] Gregory W. Peet,[b] Alfred Proto,[b] Alan Swinamer[a] and Neil Moss[a]

[a]*Departments of Medicinal Chemistry, Boehringer Ingelheim Pharmaceuticals, 900 Ridgebury Road, Ridgefield, CT 06877, USA*
[b]*Immunology and Inflammation, Boehringer Ingelheim Pharmaceuticals, 900 Ridgebury Road, Ridgefield, CT 06877, USA*

We demonstrate the rates of association and dissociation of binding for analogues of the potent p38 MAP kinase inhibitor, BIRB 796, are influenced by lipophilic and hydrogen bond interactions and low energy conformations of the compounds.



BIRB 796
R1 = *t*-butyl
R2 = 4-methylphenyl
R3 = morpholine
R4 = H
X = O

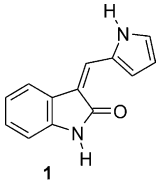
Bioorg. Med. Chem. Lett. 13 (2003) 3105

Mapping the Kinase Domain of Janus Kinase 3

Christopher Adams, David J. Aldous,* Shelley Amendola, Paul Bamborough, Colin Bright, Sarah Crowe, Paul Eastwood, Garry Fenton, Martyn Foster, Trevor K.P. Harrison, Sue King, Justine Lai, Christopher Lawrence, Jean-Philippe Letallec, Clive McCarthy, Neil Moorcroft, Kenneth Page, Sudha Rao, Jane Redford, Shazia Sadiq, Keith Smith, John E. Souness, Sukanthini Thurairatnam, Mark Vine and Barry Wyman

Aventis Pharmaceuticals, 1041 Route 202–206, PO Box 6800, Bridgewater, NJ 08807, USA

The utilization and impact of parallel synthesis on lead exploration around initial hit oxindole (**1**) are described. The emergent SAR, analogue design and functional impact will also be detailed.



1

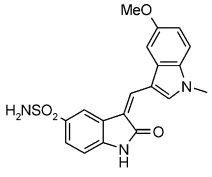
Bioorg. Med. Chem. Lett. 13 (2003) 3111

Potent Small Molecule Inhibitors of Spleen Tyrosine Kinase (SYK)

Justine Y.Q. Lai, Paul J. Cox,* Rajesh Patel, Shazia Sadiq, David J. Aldous, Sukanthini Thurairatnam, Keith Smith, Darren Wheeler, Savita Jagpal, Sofia Parveen, Gary Fenton, Trevor K. P. Harrison, Clive McCarthy and Paul Bamborough

Aventis Pharmaceuticals, Route 202/206, Brigdewater, NJ 08807, USA

A series of oxindoles demonstrating inhibition of the phosphorylation of biotinylated substrates by Syk and IgE/FcεRI triggered basophil cell degranulation has been identified. A study of the SAR around sulphonamide **31** (IC_{50} = 5 nM, EC_{50} = 1400 nM) led to the identification of amide **32** (IC_{50} = 145 nM, EC_{50} = 100 nM).



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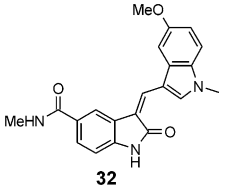

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