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Bioorganic & Medicinal Chemistry Letters

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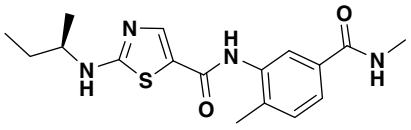
Contents

ARTICLES

The discovery of (*R*)-2-(*sec*-butylamino)-*N*-(2-methyl-5-(methylcarbamoyl)phenyl) thiazole-5-carboxamide (BMS-640994)—A potent and efficacious p38α MAP kinase inhibitor pp 1762–1767

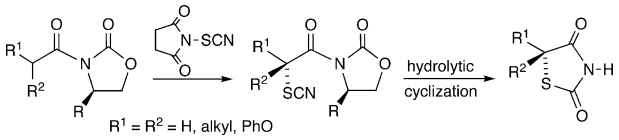
John Hynes Jr.,* Hong Wu, Sidney Pitt, Ding Ren Shen, Rosemary Zhang, Gary L. Schieven, Kathleen M. Gillooly, David J. Shuster, Tracy L. Taylor, XiaoXia Yang, Kim W. McIntyre, Murray McKinnon, Hongjian Zhang, Punit H. Marathe, Arthur M. Doweyko, Kevin Kish, Susan E. Kiefer, John S. Sack, John A. Newitt, Joel C. Barrish, John Dodd and Katerina Leftheris



SAR studies leading to the identification of the orally active anti-inflammatory agent BMS-640994 (**6e**) are disclosed.

Electrophilic α-thiocyanation of chiral and achiral *N*-acyl imides. A convenient route to 5-substituted and 5,5-disubstituted 2,4-thiazolidinediones pp 1768–1771

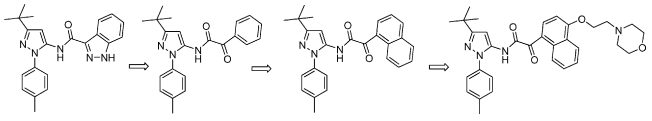
J. R. Falck,* Shuanhu Gao, Ravi Naga Prasad and Sreenivasulu Reddy Koduru



Electrophilic α-thiocyanation of *N*-acyl carboximides using *N*-thiocyanatosuccinimide and cyclization affords 2,4-thiazolidinediones in good yields. α-Thiocyanation of chiral carboximides proceeds with excellent diastereoselectivity, although partial racemization occurs during cyclization.

The design and synthesis of novel α-ketoamide-based p38 MAP kinase inhibitors pp 1772–1777

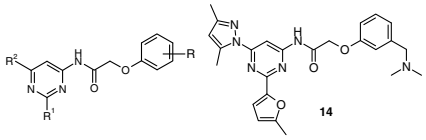
Antonio Garrido Montalban,* Erik Boman, Chau-Dung Chang, Susana Conde Ceide, Russell Dahl, David Dalesandro, Nancy G. J. Delaet, Eric Erb, Justin T. Ernst, Andrew Gibbs, Jeffrey Kahl, Linda Kessler, Jan Lundström, Stephen Miller, Hiroshi Nakanishi, Edward Roberts, Eddine Saiah, Robert Sullivan, Zhijun Wang and Christopher J. Larson



The design and synthesis of novel α-ketoamide-based p38 inhibitors is reported.

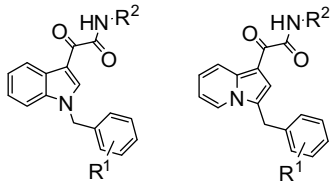
Synthesis of *N*-pyrimidinyl-2-phenoxyacetamides as adenosine A_{2A} receptor antagonists **pp 1778–1783**
Xiaohu Zhang,* Jaimie K. Rueter, Yongsheng Chen, Manisha Moorjani, Marion C. Lanier, Emily Lin, Raymond S. Gross, John E. Tellew, John P. Williams, Sandra M. Lechner, Stacy Markison, Tanya Joswig, Siobhan Malany, Mark Santos, Julio C. Castro-Palomino, María I. Crespo, Maria Prat, Silvia Gual, José-Luis Díaz, John Saunders and Deborah H. Slee

A series of *N*-pyrimidinyl-2-phenoxyacetamide adenosine A_{2A} antagonists is described. SAR studies led to compound **14** with excellent potency, selectivity, and efficacy in the rat haloperidol-induced catalepsy model for Parkinson's disease.

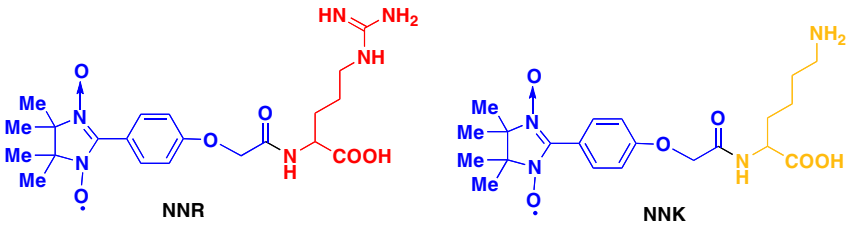


Indole- and indolizine-glyoxylamides displaying cytotoxicity against multidrug resistant cancer cell lines **pp 1784–1787**
David A. James,* Keizo Koya, Hao Li, Guiqing Liang, Zhiqiang Xia, Weiwen Ying, Yaming Wu and Lijun Sun

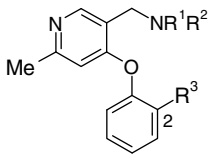
We report herein the SAR studies of a series of indole- **1** and indolizine-glyoxylamides **2** that demonstrate substantial in vitro anti-proliferative activities against cancer cell lines, including multidrug resistance (MDR) phenotypes. The in vitro cytotoxic effects have been demonstrated across a wide array of tumor types, including hematologic and solid tumor cell lines of various origins (e.g., leukemia, breast, colon, uterine).



Protective effect of nitronyl nitroxide–amino acid conjugates on liver ischemia–reperfusion induced injury in rats **pp 1788–1794**
Wei Bi,* Jianhui Cai, Ping Xue, Yanrong Zhang, Sanguang Liu, Xiang Gao, Meng Li, Zhibo Wang, Michèle Baudy-Floc'h, Sarah A. Green and Lanrong Bi*



[4-(Phenoxy)pyridin-3-yl]methylamines: A new class of selective noradrenaline reuptake inhibitors **pp 1795–1798**
Paul V. Fish,* Thomas Ryckmans, Alan Stobie and Florian Wakenhut

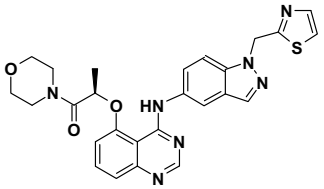


31: NR^1R^2 = NHMe; R^3= OPh
NRI, K_i 10 nM
SRI, K_i 823 nM
DRI, K_i 1910 nM

Pyridinyl phenyl ethers are disclosed as a new series of selective noradrenaline reuptake inhibitors (NRI). Structure–activity relationships established that potent NRI activity could be achieved by appropriate substitution at the 2-position of the phenoxy ring. Compound **31** demonstrated potent NRI activity combined with good selectivity over serotonin and dopamine reuptake, and no significant off-target pharmacology.

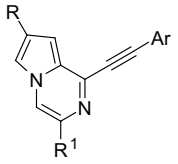
Neutral 5-substituted 4-indazolylaminoquinazolines as potent, orally active inhibitors of erbB2 receptor tyrosine kinase pp 1799–1803
Bernard Barlaam,* David G. Acton, Peter Ballard, Robert H. Bradbury, Darren Cross, Richard Ducray, Hervé Germain, Kevin Hudson, Teresa Klinowska, Françoise Magnien, Donald J. Ogilvie, Annie Olivier, Helen S. Ross, Robin Smith, Cath B. Trigwell, Michel Vautier and Lindsay Wright

We have identified a new series of C-5 substituted indazolylaminoquinazolines as potent erbB2 kinase inhibitors. The lead compound **22** showed excellent in vitro potency, good physical properties, acceptable oral pharmacokinetics in rat and dog, and low human in vitro clearance. It showed at least equivalent activity dose for dose compared to lapatinib in various erbB2- or EGFR-driven xenograft models after chronic oral administration.



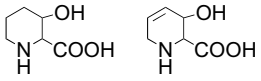
22

Phenylethynyl-pyrrolo[1,2-*a*]pyrazine: A new potent and selective tool in the mGluR5 antagonists arena pp 1804–1809
Fabrizio Micheli,* Barbara Bertani,* Andrea Bozzoli, Luca Crippa, Paolo Cavanni, Romano Di Fabio, Daniele Donati, Paola Marzorati, Giancarlo Merlo, Alfredo Paio, Lorenzo Perugini and Paola Zarantonello



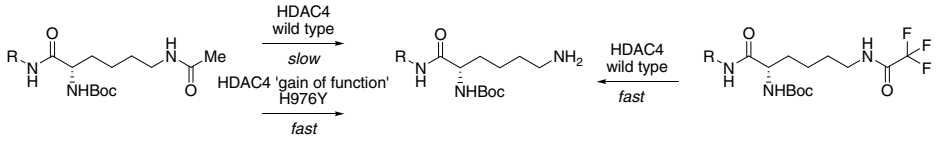
The synthesis of a new class of potent and selective mGluR5 antagonists are reported.

Synthesis of all stereoisomers of 3-hydroxypipecolic acid and 3-hydroxy-4,5-dehydropipecolic acid and their evaluation as glycosidase inhibitors pp 1810–1813
Chiaki Ohara, Ryouko Takahashi, Tatsunori Miyagawa, Yuichi Yoshimura, Atsushi Kato, Isao Adachi and Hiroki Takahata *



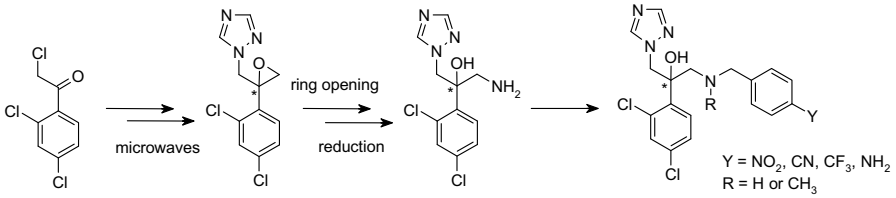
All stereoisomers

Probing the elusive catalytic activity of vertebrate class IIa histone deacetylases pp 1814–1819
Philip Jones,* Sergio Altamura, Raffaele De Francesco, Paola Gallinari, Armin Lahm, Petra Neddermann, Michael Rowley, Sergio Serafini and Christian Steinkühler



Bacteria preparations of HDAC4 have weak but measurable deacetylase activity, the low efficiency can be restored either by mutation of an active site histidine to tyrosine, or by the use of a non-acetylated lysine substrate.

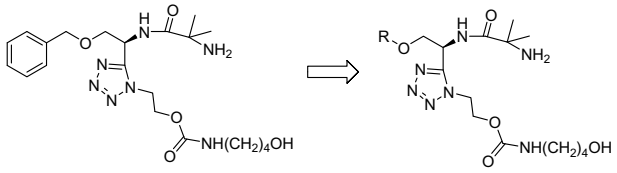
Design, synthesis, and evaluation of 1-(*N*-benzylamino)-2-phenyl-3-(1*H*-1,2,4-triazol-1-yl)propan-2-ols as antifungal agents pp 1820–1824
Francis Giraud, Cédric Logé, Fabrice Pagniez, Damien Crepin, Patrice Le Pape and Marc Le Borgne*



6a-c, **7a-c**, **8a** and **9a**

A series of 1-(*N*-benzylamino)-2-phenyl-3-(1*H*-1,2,4-triazol-1-yl)propan-2-ols were synthesized for their antifungal activity on two strains of *Candida albicans* and *Aspergillus fumigatus*. Synthesis and SAR studies that led to the most active compound **7b** are discussed with the help of molecular modeling.

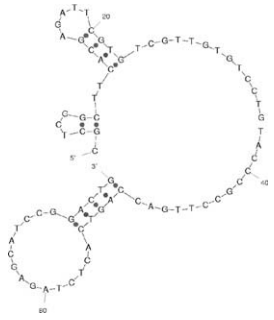
Design and synthesis of tetrazole-based growth hormone secretagogue: The SAR studies of the *O*-benzyl serine side chain pp 1825–1829
Jun Li,* Stephanie Y. Chen, Shiwei Tao, Haixia Wang, James J. Li, Steve Swartz, Christa Musial, Andres A. Hernandez, Neil Flynn, Brian J. Murphy, Blake Beehler, Kenneth E. Dickinson, Leah Giupponi, Gary Grover, Ramakrishna Seethala, Paul Sleph, Dorothy Slusarchyk, Mujing Yan, William G. Humphreys, Hongjian Zhang, William R. Ewing, Jeffrey A. Robl, David Gordon and Joseph A. Tino*



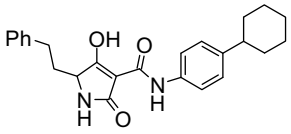
4-Aminopyrimidine tetrahydronaphthols: A series of novel vanilloid receptor-1 antagonists with improved solubility properties pp 1830–1834
Elizabeth M. Doherty,* Daniel Retz, Narender R. Gavva, Rami Tamir, James J. S. Treanor and Mark H. Norman

Combinatorial selection of a single stranded DNA thioaptamer targeting TGF-β1 protein pp 1835–1839
Jonghoon Kang, Myung Soog Lee, John A. Copland, III, Bruce A. Luxon and David G. Gorenstein*

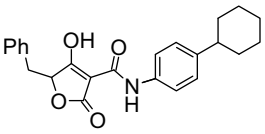
We have isolated a high affinity thioaptamer targeting TGF-β1. The '*thio*' effect is well described by our theoretical model.



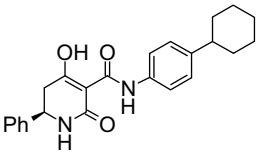
Design and structure–activity relationships of potent and selective inhibitors of undecaprenyl pyrophosphate synthase (UPPS): Tetramic, tetronic acids and dihydropyridin-2-ones **pp 1840–1844**
Stefan Peukert,* Yingchuan Sun, Rui Zhang, Brian Hurley, Mike Sabio, Xiaoyu Shen, Christen Gray, JoAnn Dzink-Fox, Jianshi Tao, Regina Cebula and Sompong Wattanasin



Tetramic acid (**1e**): IC_{50} = 0.16 μM



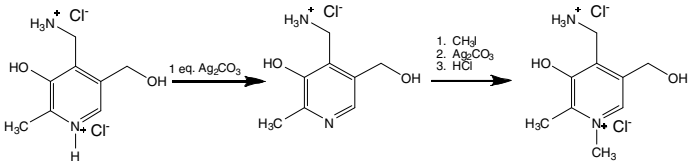
Tetronic acid (**3c**): IC_{50} = 0.5 μM



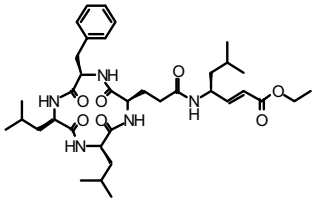
Dihydropyridin-2-one (**4b**): IC_{50} = 0.07 μM

***N*-Methylpyridoxamine: Novel canine vitamin B_6 urine metabolite** **pp 1845–1848**
Karen L. Ericson,* Vincent M. Maloney, J. Dennis Mahuren, Stephen P. Coburn and Thorsten P. Degenhardt

The urine of canines given daily dosage of pyridoxamine revealed an unidentified metabolite hypothesized to be *N*-methylpyridoxamine. Its identity was established by synthesis of *N*-methylpyridoxamine and comparison to the canine metabolite by HPLC. The synthetic compound was confirmed by IR, NMR, UV–vis, and emission spectroscopy. Although *N*-methylpyridoxamine is a significant canine pyridoxamine metabolite, relevance to vitamin B_6 metabolism in other species, including humans, is not yet determined.



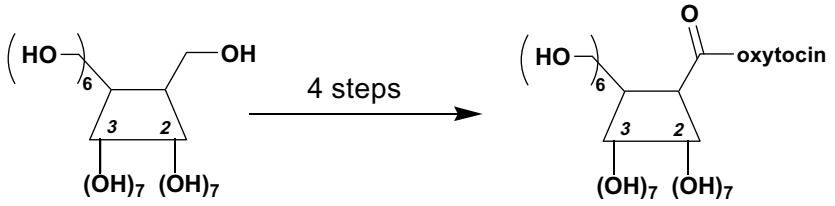
Vinyl ester-based cyclic peptide proteasome inhibitors **pp 1849–1854**
Anna Baldisserotto, Mauro Marastoni,* Stella Fiorini, Loretta Pretto, Valeria Ferretti, Riccardo Gavioli and Roberto Tomatis



c[Phe-Leu-Leu-Glu(Leu-VE)]

Synthesis and biological activity of vinyl ester cyclopeptide derivatives were reported. Some compounds showed good inhibition of the proteasome chymotrypsin-like activity.

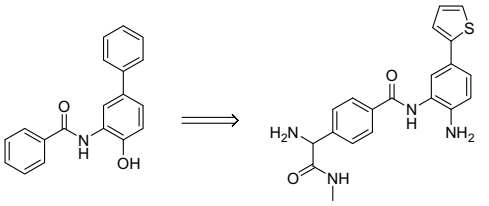
Synthesis and pharmacological evaluation of a new targeted drug carrier system: β-Cyclodextrin coupled to oxytocin **pp 1855–1858**
Carine Bertolla, Stéphanie Rolin, Brigitte Evrard, Lionel Pochet and Bernard Masereel*



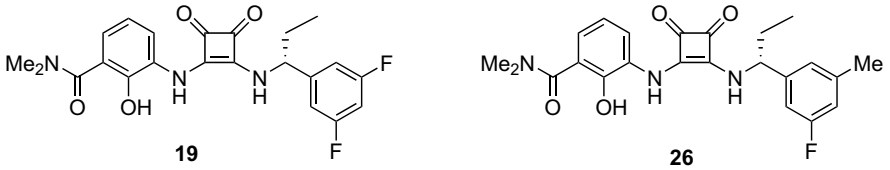
β-Cyclodextrin (β-CD) was monofunctionalized into its carboxylic derivative and then conjugated to the *N*-side of oxytocin. The conjugate partly preserves the activity of oxytocin and can be used as a drug carrier system for drug targeting the uterine in case of cancer or delivery.

Phenylglycine and phenylalanine derivatives as potent and selective HDAC1 inhibitors (SHI-1) **pp 1859–1863**
Kevin J. Wilson,* David J. Witter, Jonathan B. Grimm, Phieng Siliphaivanh, Karin M. Otte, Astrid M. Kral, Judith C. Fleming, Andreas Harsch, Julie E. Hamill, Jonathan C. Cruz, Melissa Chenard, Alexander A. Szewczak, Richard E. Middleton, Bethany L. Hughes, William K. Dahlberg, J. Paul Secrist and Thomas A. Miller

An HTS screening campaign identified a series of low molecular weight phenols that showed excellent selectivity (>100-fold) for HDAC1/HDAC2 over other Class I and Class II HDACs. Evolution and optimization of this HTS hit series provided HDAC1-selective (SHI-1) compounds with excellent anti-proliferative activity and improved physical properties. Dose-dependent efficacy in a mouse HCT116 xenograft model was demonstrated with a phenylglycine SHI-1 analog.



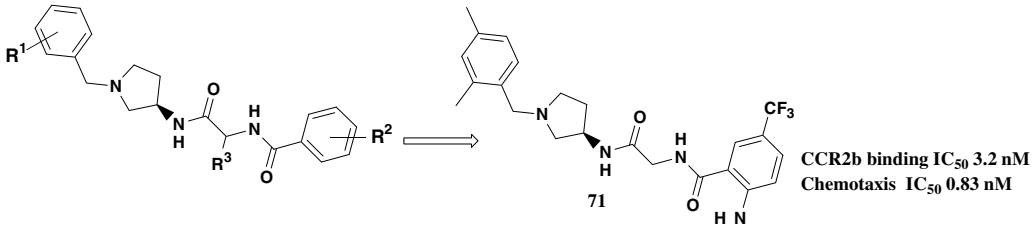
Synthesis and structure–activity relationships of new disubstituted phenyl-containing 3,4-diamino-3-cyclobutene-1,2-diones as CXCR2 receptor antagonists **pp 1864–1868**
Gaifa Lai,* J. Robert Merritt, Zhenmin He, Daming Feng, Jianhua Chao, Michael F. Czarniecki, Laura L. Rokosz, Tara M. Stauffer, Diane Rindgen and Arthur G. Taveras



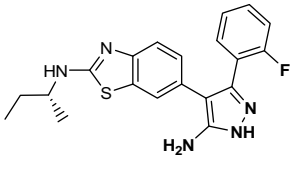
A series of 3,4- and 3,5-disubstituted phenyl-containing cyclobutenedione analogues were synthesized and evaluated as CXCR2 receptor antagonists. Two potent compounds **19** and **26** exhibited good oral pharmacokinetic profiles.

Potent antagonists of the CCR2b receptor. Part 3: SAR of the (*R*)-3-aminopyrrolidine series **pp 1869–1873**
Wilna J. Moree,* Ken-ichiro Kataoka, Michele M. Ramirez-Weinhouse, Tatsuki Shiota, Minoru Imai, Takaharu Tsutsumi, Masaki Sudo, Noriaki Endo, Yumiko Muroga, Takahiko Hada, Dewey Fanning, John Saunders, Yoshinori Kato, Peter L. Myers and Christine M. Tarby

SAR studies of a 3-amino pyrrolidine series led to the identification of potent CCR2b antagonists with low nanomolar activity in binding and functional assays as exemplified by compound **71**.



Benzothiazole based inhibitors of p38α MAP kinase **pp 1874–1879**
Chunjian Liu,* James Lin, Sidney Pitt, Rosemary F. Zhang, John S. Sack, Susan E. Kiefer, Kevin Kish, Arthur M. Doweyko, Hongjian Zhang, Punit H. Marathe, James Trzaskos, Murray Mckinnon, John H. Dodd, Joel C. Barrish, Gary L. Schieven and Katerina Leftheris



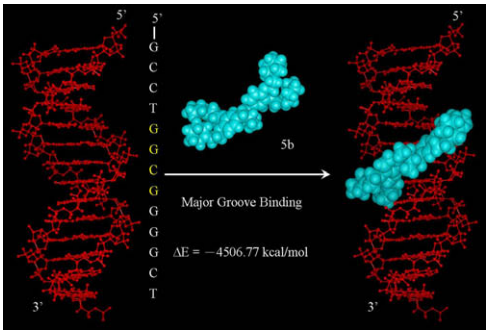
The rational design, synthesis, and SAR studies of a novel class of benzothiazole based inhibitors of p38α MAP kinase are described.

Induction of apoptosis of human tumor cells by hybrid liposomes including docosahexaenoic acid **pp 1880–1883**
Koichi Goto, Yoshihiro Tanaka, Yoko Matsumoto and Ryuichi Ueoka*

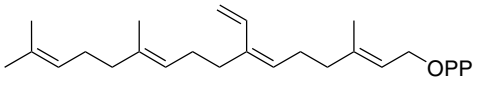
Hybrid liposomes composed of DMPC and Tween 80 including docosahexaenoic acid (DHA) markedly inhibited the growth of various human tumor cells through induction of apoptosis in vitro.

New nordihydroguaiaretic acid derivatives as anti-HIV agents **pp 1884–1888**
Jih Ru Hwu,* Ming-Hua Hsu and Ru Chih C. Huang*

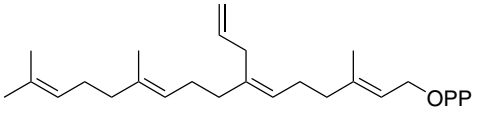
A series of new nordihydroguaiaretic acid derivatives were prepared and screened, which exhibited inhibitory activity against HIV.



Synthesis and evaluation of 3- and 7-substituted geranylgeranyl pyrophosphate analogs **pp 1889–1892**
Michelle Maynor, Sarah A. Scott, Emily L. Rickert and Richard A. Gibbs*

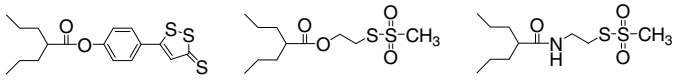


2d 7-vGGPP
IC_{50}=1000nM
weak inhibitor



2e 7-alGGPP
K_M=27nM
efficient substrate

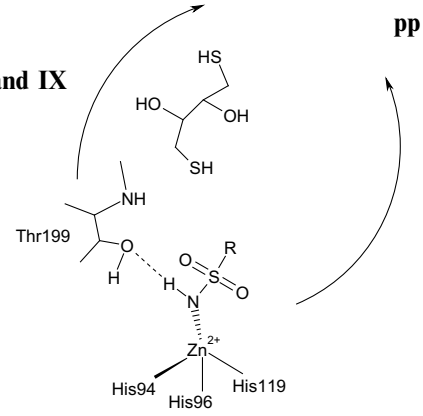
New sulfurated derivatives of valproic acid with enhanced histone deacetylase inhibitory activity **pp 1893–1897**
Elena Perrino, Graziella Cappelletti, Valerio Tazzari, Erminio Giavini, Piero Del Soldato and Anna Sparatore*



ACS 2 ACS 33 ACS 43

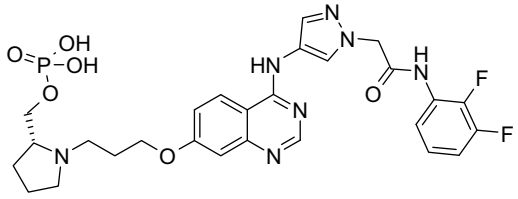
Carbonic anhydrase inhibitors: The very weak inhibitors dithiothreitol, β-mercaptoethanol, tris(carboxyethyl)phosphine and threitol interfere with the binding of sulfonamides to isozymes II and IX pp 1898–1903

Alessio Innocenti, Mika Hilvo, Andrea Scozzafava, Mikaela Lindfors, Henri R. Nordlund, Markku S. Kulomaa, Seppo Parkkila and Claudiu T. Supuran*



Synthesis and SAR of 1-acetanilide-4-aminopyrazole-substituted quinazolines: Selective inhibitors of Aurora B kinase with potent anti-tumor activity pp 1904–1909

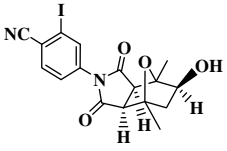
Kevin M. Foote,* Andrew A. Mortlock, Nicola M. Heron, Frédéric H. Jung, George B. Hill, Georges Pasquet, Madeleine C. Brady, Stephen Green, Simon P. Heaton, Sarah Kearney, Nicholas J. Keen, Rajesh Odedra, Stephen R. Wedge and Robert W. Wilkinson



Identification and optimization of a novel series of [2.2.1]-oxabicyclo imide-based androgen receptor antagonists pp 1910–1915

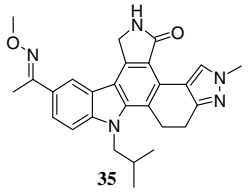
Mark E. Salvati,* Aaron Balog, Weifang Shan, Richard Rampulla, Soren Giese, Tom Mitt, Joseph A. Furch, Gregory D. Vite, Ricardo M. Attar, Maria Jure-Kunkel, Jieping Geng, Cheryl A. Rizzo, Marco M. Gottardis, Stanley R. Krystek, Jack Gougoutas, Michael A. Galella, Mary Obermeier, Aberra Fura and Gamini Chandrasena

A novel series of [2.2.1]-oxabicyclo imide-based compounds were identified as potent antagonists of the androgen receptor. Molecular modeling and iterative drug design were applied to optimize this series. The lead compound [3*aS*-(3*a*α,4β,5β,7β,7*a*α)]-4-(octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2*H*-isoindol-2-yl)-2-iodobenzonitrile was shown to have potent in vivo efficacy after oral dosing in the CWR22 human prostate tumor xenograph model.



Design and synthesis of dihydroindazolo[5,4-*a*]pyrrolo[3,4-*c*]carbazole oximes as potent dual inhibitors of TIE-2 and VEGF-R2 receptor tyrosine kinases pp 1916–1921

Reddeppareddy Dandu,* Allison L. Zulli, Edward R. Bacon, Ted Underiner, Candy Robinson, Hong Chang, Sheila Miknyoczki, Jennifer Grobelny, Bruce A. Ruggeri, Shi Yang, Mark S. Albom, Thelma S. Angeles, Lisa D. Aimone and Robert L. Hudkins



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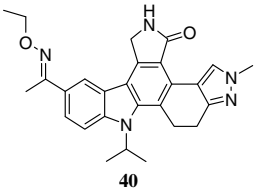
TIE-2 IC_{50} = 30 nM
VEGF-R2 IC_{50} = 7 nM

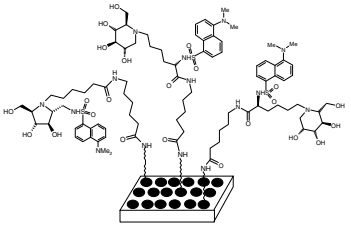


40

TIE-2 IC_{50} = 26 nM
VEGF-R2 IC_{50} = 4 nM

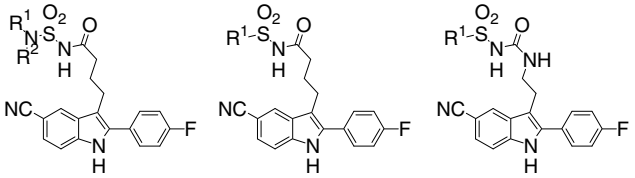
Glycosidase profiling with immobilised glycosidase-inhibiting iminoalditols—A proof-of-concept study **pp 1922–1925**
Andreas J. Steiner, Arnold E. Stütz, Tanja M. Wrodnigg,* Chris A. Tarling, Stephen G. Withers, Albin Hermetter and Hannes Schmidinger

The design of an iminoalditol chip and a proof-of-concept study by exposure of the microarray to β-glucosidase from *Agrobacterium* sp. is reported.

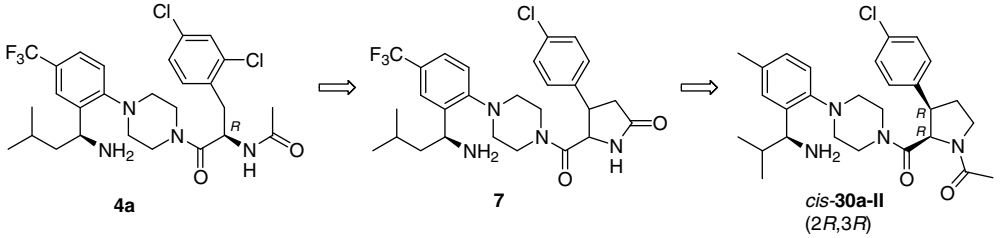


Carboxylic acid bioisosteres acylsulfonamides, acylsulfamides, and sulfonylureas as novel antagonists of the CXCR2 receptor **pp 1926–1930**
Michael P. Winters,* Carl Crysler, Nalin Subasinghe, Declan Ryan, Lynette Leong, Shuyuan Zhao, Robert Donatelli, Edward Yurkow, Marie Mazzulla, Lisa Boczon, Carl L. Manthey, Christopher Molloy, Holly Raymond, Lynne Murray, Laura McAlonan and Bruce Tomczuk

A series of novel acylsulfamide **1**, acylsulfonamide **2**, and sulfonylurea **3** bioisosteres of carboxylic acids were prepared as CXCR2 antagonists. Structure–activity relationships are reported for these series. One potent orally bioavailable inhibitor had excellent PK properties and was active in a lung injury model in hyperoxia-exposed newborn rats.

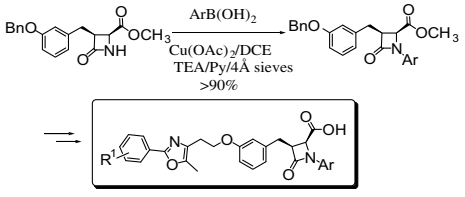


Design and synthesis of 3-arylpyrrolidine-2-carboxamide derivatives as melanocortin-4 receptor ligands **pp 1931–1938**
Joe A. Tran, Fabio C. Tucci, Melissa Arellano, Wanlong Jiang, Caroline W. Chen, Dragan Marinkovic, Beth A. Fleck, Jenny Wen, Alan C. Foster and Chen Chen*



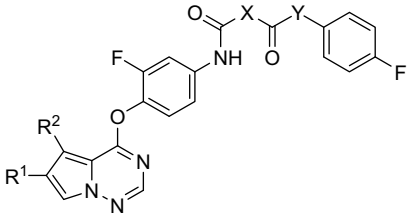
Discovery of azetidinone acids as conformationally-constrained dual PPARα/γ agonists **pp 1939–1944**
Wei Wang, Pratik Devasthale,* Dennis Farrelly, Liqun Gu, Thomas Harrity, Michael Cap, Cuixia Chu, Lori Kunselman, Nathan Morgan, Randy Ponticiello, Rachel Zebo, Litao Zhang, Kenneth Locke, Jonathan Lippy, Kevin O'Malley, Vinayak Hosagrahara, Lisa Zhang, Pathanjali Kadiyala, Chiehying Chang, Jodi Muckelbauer, Arthur M. Doweyko, Robert Zahler, Denis Ryono, Narayanan Hariharan and Peter T. W. Cheng

A novel class of azetidinone acid-derived dual PPARα/γ agonists has been synthesized for the treatment of diabetes and dyslipidemia. The preferred stereochemistry in this series for binding and functional agonist activity against both PPARα and PPARγ receptors was shown to be 3*S*,4*S*. Synthesis, in vitro and in vivo activities of compounds in this series are described. A high-yielding method for N-arylation of azetidinone esters is also described.

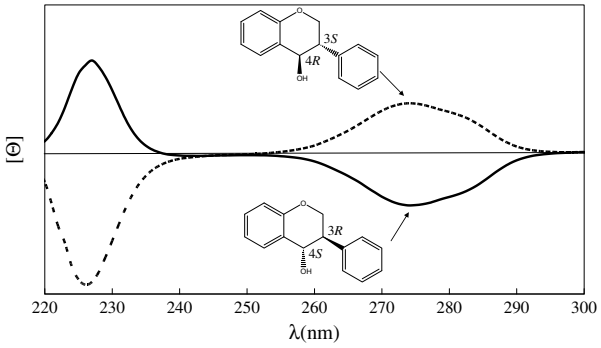


Identification of pyrrolo[2,1-*f*][1,2,4]triazine-based inhibitors of Met kinase **pp 1945–1951**
Gretchen M. Schroeder,* Xiao-Tao Chen, David K. Williams, David S. Nirschl, Zhen-Wei Cai, Donna Wei, John S. Tokarski, Yongmi An, John Sack, Zhong Chen, Tram Huynh, Wayne Vaccaro, Michael Poss, Barri Wautlet, Johnni Gullo-Brown, Kristen Kellar, Veeraswamy Manne, John T. Hunt, Tai W. Wong, Louis J. Lombardo, Joseph Fargnoli and Robert M. Borzilleri

A variety of pyrrolo[2,1-*f*][1,2,4]triazines were synthesized and evaluated as Met kinase inhibitors. Substitution at the pyrrolotriazine C-5 or C-6 position gave compounds with potent activity in the Met-driven GTL-16 human gastric carcinoma cell line.

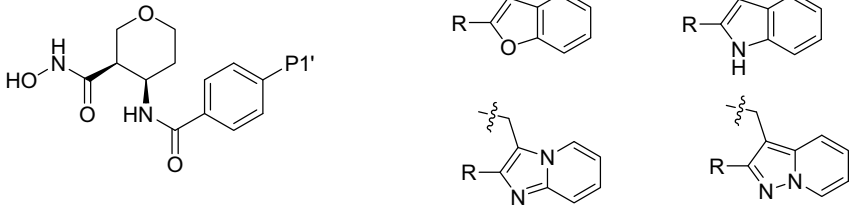


Absolute configurations of isoflavan-4-ol stereoisomers **pp 1952–1957**
Dongho Won, Bok-Kyu Shin, Suil Kang, Hor-Gil Hur, Mihyang Kim and Jaehong Han*



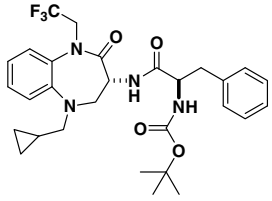
Potent, selective, orally bioavailable inhibitors of tumor necrosis factor-α converting enzyme (TACE): Discovery of indole, benzofuran, imidazopyridine and pyrazolopyridine P1′ substituents **pp 1958–1962**
Zhonghui Lu,* Gregory R. Ott,* Rajan Anand, Rui-Qin Liu, Maryanne B. Covington, Krishna Vaddi, Mingxin Qian, Robert C. Newton, David D. Christ, James Trzaskos and James J.-W. Duan

Selective inhibitors of TNF-α converting enzyme (TACE) with novel P1′ substituents.



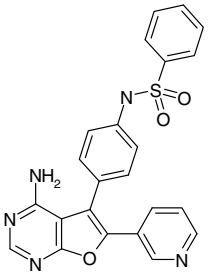
3-Amino-1,5-benzodiazepinones: Potent, state-dependent sodium channel blockers with anti-epileptic activity **pp 1963–1966**
Scott B. Hoyt,* Clare London, Matthew J. Wyvratt, Michael H. Fisher, Doreen E. Cashen, John P. Felix, Maria L. Garcia, Xiaohua Li, Kathryn A. Lyons, D. Euan MacIntyre, William J. Martin, Birgit T. Priest, McHardy M. Smith, Vivien A. Warren, Brande S. Williams, Gregory J. Kaczorowski and William H. Parsons

A series of 3-amino-1,5-benzodiazepinones were synthesized and evaluated as potential sodium channel blockers in a functional, membrane potential-based assay. One member of this series displayed subnanomolar, state-dependent sodium channel block, and was orally efficacious in a mouse model of epilepsy.

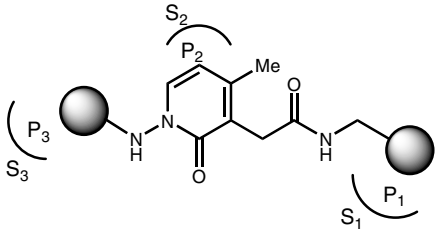


Rational design of 4-amino-5,6-diaryl-furo[2,3-*d*]pyrimidines as potent glycogen synthase kinase-3 inhibitors **pp 1967–1971**
Yasushi Miyazaki, Yutaka Maeda, Hideyuki Sato, Masato Nakano* and Geoffrey W. Mellor

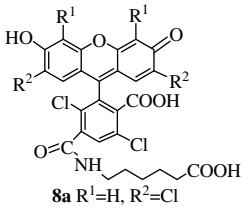
4-Amino-5,6-diaryl-furo[2,3-*d*]pyrimidines have been identified as inhibitors of glycogen synthase kinase-3β (GSK-3β). One representative derivative, 4-amino-5-(4-(benzenesulfonylamino)-phenyl)-6-(3-pyridyl)-furo[2,3-*d*]pyrimidine (**12**) exhibited potent GSK-3β inhibitory activity in low nanomolar level of IC_{50}. The binding mode was proposed from a docking study.



Design, synthesis, and thrombin-inhibitory activity of pyridin-2-ones as P_2/P_3 core motifs **pp 1972–1976**
Stephen Hanessian,* Daniel Simard, Malken Bayrakdarian, Eric Therrien, Ingemar Nilsson* and Ola Fjellström



Synthesis of chlorinated fluoresceins for labeling proteins **pp 1977–1979**
Min Tian, Xiang-Long Wu, Bin Zhang, Jian-Li Li and Zhen Shi*

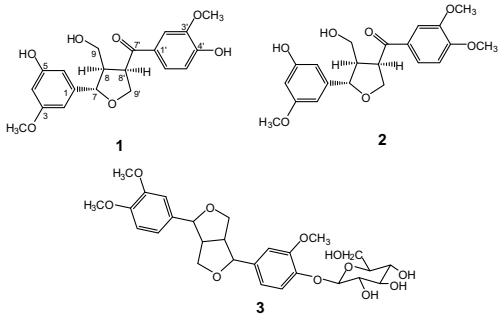


8a R^1=H, R^2=Cl
8b R^1=Cl, R^2=H

Two novel chlorinated fluoresceins 4,7,2′,7′-tetrachloro-6-(5-carboxypentyl)fluorescein (**8a**) and 4,7,4′,5′-tetrachloro-6-(5-carboxypentyl)fluorescein (**8b**) were synthesized, and these two chlorinated fluoresceins containing 6-aminohexanoic acid linker have been used to label the proteins.

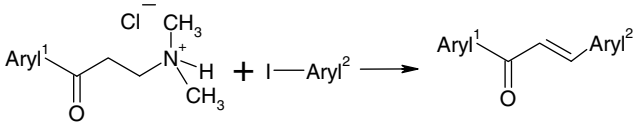
Lignans from the fruits of *Forsythia suspensa* **pp 1980–1984**
Xiang-Lan Piao, Moon Hee Jang, Jian Cui* and Xiangshu Piao*

Two new monoepoxylignans, forsythialan A (**1**) and B (**2**), were isolated from the methanol extract of the fruits of *Forsythia suspensa* Vahl, along with a known compound, phillyrin (**3**). Their structures were established by extensive spectroscopic analyses. The compounds **1** and **2** showed potent antioxidant effects against peroxynitrite-induced oxidative stress in renal epithelial cell.



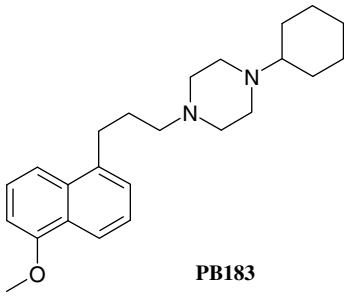
1 **2** **3**

A new Heck reaction modification using ketone Mannich bases as enone precursors: Parallel synthesis of anti-leishmanial chalcones pp 1985–1989
Christina Reichwald, Orly Shimony, Nina Sacerdoti-Sierra, Charles L. Jaffe and Conrad Kunick*

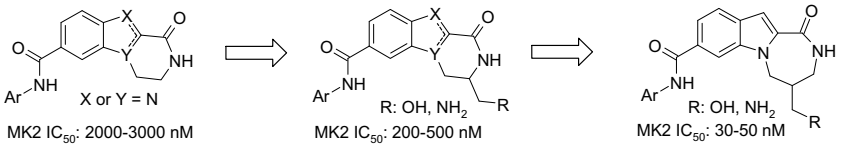


PB183, a sigma receptor ligand, as a potential PET probe for the imaging of prostate adenocarcinoma pp 1990–1993
Nicola Antonio Colabufo,* Carmen Abate, Marialessandra Contino, Carmela Inglese, Mauro Niso, Francesco Berardi and Roberto Perrone

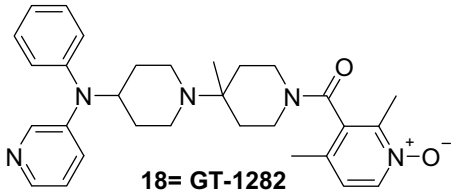
PB183, a PET probe suitable in prostate adenocarcinoma.



Synthesis and SAR studies of indole-based MK2 inhibitors pp 1994–1999
Zhaoming Xiong,* Donghong Amy Gao, Derek A. Cogan, Daniel R. Goldberg, Ming-Hong Hao, Neil Moss, Edward Pack, Chris Pargellis, Donna Skow, Thomas Trieselmann, Brian Werneburg and Andre White

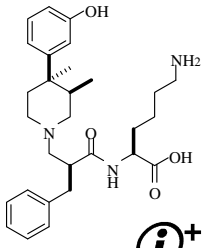


Reduced cardiac side-effect potential by introduction of polar groups: Discovery of NIBR-1282, an orally bioavailable CCR5 antagonist which is active in vivo pp 2000–2005
Gebhard Thoma,* Christian Beerli, Marc Bigaud, Christian Bruns, Nigel G. Cooke, Markus B. Streiff and Hans-Guenter Zerwes



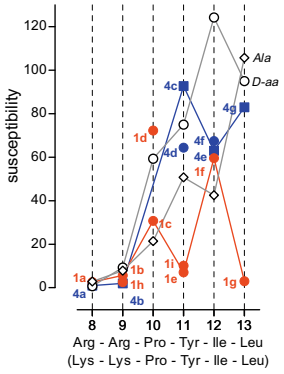
Novel *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidines as μ opioid receptor antagonists with improved opioid receptor selectivity profiles **pp 2006–2012**
Bertrand Le Bourdonnec,* William M. Barker, Serge Belanger, Daniel D. Wiant, Nathalie C. Conway-James, Joel A. Cassel, Timothy J. O'Neill, Patrick J. Little, Robert N. DeHaven, Diane L. DeHaven-Hudkins and Roland E. Dolle

The discovery and SAR studies of a series of *N*-substituted *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)-piperidines as novel μ opioid receptor antagonists, analogs of alvimopan, are reported.



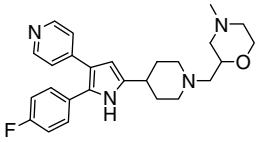
Peptide backbone modifications on the C-terminal hexapeptide of neurotensin **pp 2013–2018**
Jürgen Einsiedel, Harald Hübner, Maud Hervet, Steffen Härterich, Susanne Koschatzky and Peter Gmeiner*

Highly potent neurotensin receptor ligands and the generation of a pharmacophore model are reported.



***N*-Alkyl-4-piperidinyl-2,3-diarylpyrrole derivatives with heterocyclic substitutions as potent and broad spectrum anticoccidial agents** **pp 2019–2022**
Gui-Bai Liang,* Xiaoxia Qian, Dennis Feng, Michael Fisher, Tami Crumley, Sandra J. Darkin-Rattray, Paula M. Dulski, Anne Gurnett, Penny Sue Leavitt, Paul A. Liberator, Andrew S. Misura, Samantha Samaras, Tamas Tamas, Dennis M. Schmatz, Matthew Wyvratt and Tesfaye Biftu

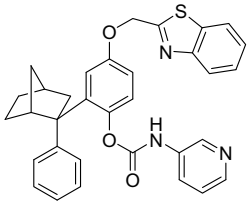
Diaryl-(4-piperidinyl)-pyrrole derivatives bearing cyclic amine substituents have been synthesized and evaluated as anticoccidial agents. Improvements in potency of Et-PKG inhibition and broad spectrum anticoccidial activities in feed have been achieved.



8c IC_{50} = 0.67 nM

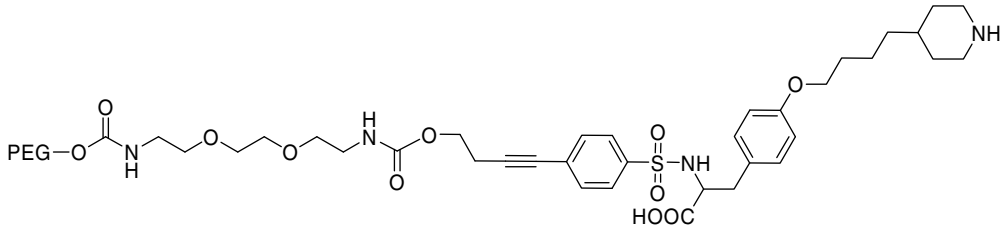
Substituted 2,2-bisaryl-bicycloheptanes as novel and potent inhibitors of 5-lipoxygenase activating protein **pp 2023–2027**
Dwight Macdonald,* Christine Brideau, Chi Chung Chan, Jean-Pierre Falgueyret, Richard Frenette, Jocelyne Guay, John H. Hutchinson, Hélène Perrier, Peptiboon Prasit, Denis Riendeau, Philip Tagari, Michel Thérien, Robert N. Young and Yves Girard

The discovery and SAR of a novel series of substituted 2,2-bisaryl-bicycloheptane inhibitors of 5-lipoxygense activating protein (FLAP) are herein described. One of the most potent compounds identified is compound **2** (FLAP IC50 = 2.8 nM) which blocks 89% of ragweed induced urinary LTE4 production in dogs (at an I.V. dose of 2.5 μg/kg/min). This compound inhibits calcium ionophore stimulated LTB_4 production in both human polymorphonuclear (PMN) leukocytes and human whole blood (IC_{50} = 2.0 and 33 nM, respectively).

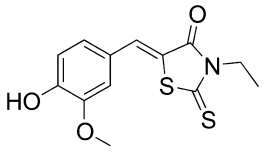


2

Synthesis and biological evaluation of PEG-tirofiban conjugates **pp 2028–2031**
Laurent Désaubry,* Stéphanie Riché, Patricia Laeuffer and Jean-Pierre Cazenave



Rhodanine derivatives as novel inhibitors of PDE4 **pp 2032–2037**
Mark W. Irvine,* Graham L. Patrick, Justin Kewney, Stuart F. Hastings and Simon J. MacKenzie

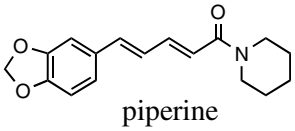


3i IC_{50}=0.74μM

The discovery, synthesis and in-vitro activity of a novel series of rhodanine based phosphodiesterase-4 inhibitors (e.g. **3i**) is described.

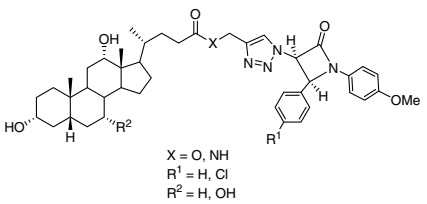
Protective effects of amide constituents from the fruit of *Piper chaba* on D-galactosamine/TNF-α-induced cell death in mouse hepatocytes **pp 2038–2042**
Hisashi Matsuda, Kiyofumi Ninomiya, Toshio Morikawa, Daisuke Yasuda, Itadaki Yamaguchi and Masayuki Yoshikawa*

From the fruit of *Piper chaba* (Piperaceae), a new amide constituent named piperchabamide E together with twenty known amide constituents and two aromatic constituents were isolated as hepatoprotective constituents. With regard to structure–activity relationships, the amide moiety and the 1,9-decadiene structure between the benzene ring and amide moiety was suggested to be important for strong inhibition of D-galactosamine (D-GalN)/tumor necrosis factor-α (TNF-α)-induced cell death of hepatocytes. Furthermore a principal amide constituent, piperine, dose-dependently inhibited increase in serum GPT and GOT levels at doses of 2.5–10 mg/kg (p.o.) in D-GalN/lipopolysaccharide-treated mice, and this inhibitory effect was suggested to depend on the reduced sensitivity of hepatocytes to TNF-α.

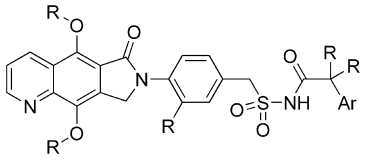


piperine

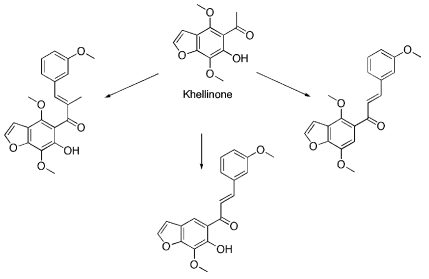
Synthesis and antimicrobial activity of β-lactam–bile acid conjugates linked via triazole **pp 2043–2047**
Namdev S. Vatmurge, Braja G. Hazra,* Vandana S. Pore, Fazal Shirazi, Pradnya S. Chavan and Mukund V. Deshpande



Structure–activity relationships and pharmacokinetic parameters of quinoline acylsulfonamides as potent and selective antagonists of the EP_4 receptor pp 2048–2054
Jason D. Burch,* Michel Belley, Réjean Fortin, Denis Deschênes, Mario Girard, John Colucci, Julie Farand, Alex G. Therien, Marie-Claude Mathieu, Danielle Denis, Erika Vigneault, Jean-François Lévesque, Sébastien Gagné, Mark Wrona, Daigen Xu, Patsy Clark, Steve Rowland and Yongxin Han*

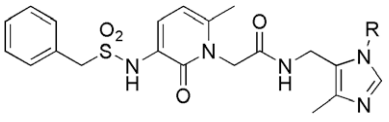


Synthesis and biological evaluation of chalcones as inhibitors of the voltage-gated potassium channel Kv1.3 pp 2055–2061
Julia Cianci, Jonathan B. Baell, Bernard L. Flynn, Robert, W. Gable, Jorgen A. Mould, Dharam Paul and Andrew J. Harvey*



Structure-based design of novel groups for use in the P1 position of thrombin inhibitor scaffolds. Part 2: *N*-acetamidoimidazoles pp 2062–2066
Richard C. A. Isaacs,* Mark G. Solinsky, Kellie J. Cutrona, Christina L. Newton, Adel M. Naylor-Olsen, Daniel R. McMasters, Julie A. Krueger, S. Dale Lewis, Bobby J. Lucas, Lawrence C. Kuo, Youwei Yan, J. J. Lynch and E. A. Lyle

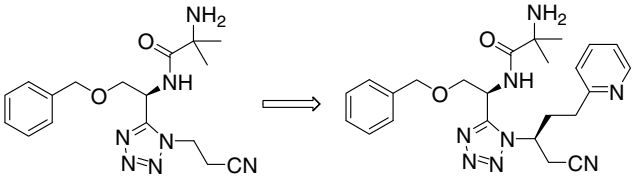
Alkylation of the N1 nitrogen of the imidazole P1 ligand of the pyridoneacetamide thrombin inhibitor **1** (RH) with various acetamide moieties furnished inhibitors (RCH_2CONHR') with significantly improved thrombin potency, trypsin selectivity, functional in vitro anticoagulant potency, and in vivo antithrombotic efficacy.



1

Optimization of 1*H*-tetrazole-1-alkanenitriles as potent orally bioavailable growth hormone secretagogues pp 2067–2072
Andrés S. Hernández,* Stephen G. Swartz, Dorothy Slusarchyk, Mujing Yan, R. Krishna Seethala, Paul Sleph, Gary Grover, Kenneth Dickinson, Leah Giupponi, Timothy W. Harper, W. Griffith Humphreys, Daniel A. Longhi, Neil Flynn, Brian J. Murphy, David A. Gordon, Scott A. Biller, Jeffrey A. Robl and Joseph A. Tino*

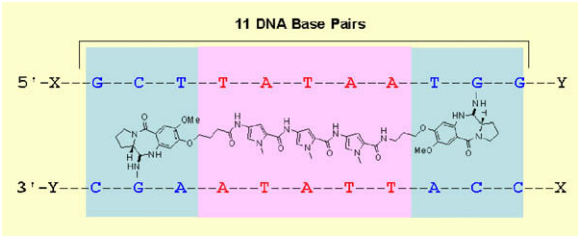
The 1*H*-tetrazole-1-alkanenitrile *SR*-**9g** exhibits a >10-fold in vivo potency enhancement over the lead nitrile **1** and has acceptable oral bioavailability in rats and dogs. An enantiospecific synthesis of 1*H*-tetrazole-1-alkanenitrile nitriles **9** has been developed.



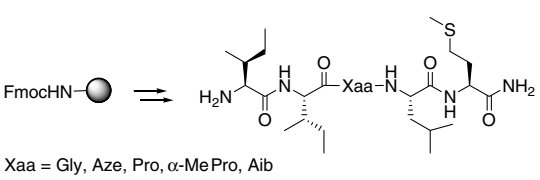
1 ***SR*-9g**

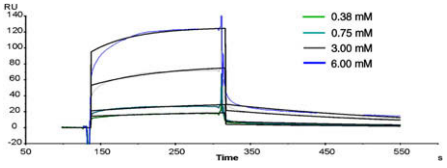
An asymmetric C8/C8′-tripyrrole-linked sequence-selective pyrrolo[2,1-*c*][1,4]benzodiazepine (PBD) dimer DNA interstrand cross-linking agent spanning 11 DNA base pairs **pp 2073–2077**
Arnaud C. Tiberghien, David A. Evans, Konstantinos Kiakos, Christopher R. H. Martin, John A. Hartley, David E. Thurston* and Philip W. Howard

A novel sequence-selective extended PBD dimer **4** has been synthesized that binds with high affinity to an interstrand cross-linking site spanning 11 DNA base pairs. Despite its molecular weight (984.07) and length, the molecule readily penetrates cellular and nuclear membranes to reach its DNA target.

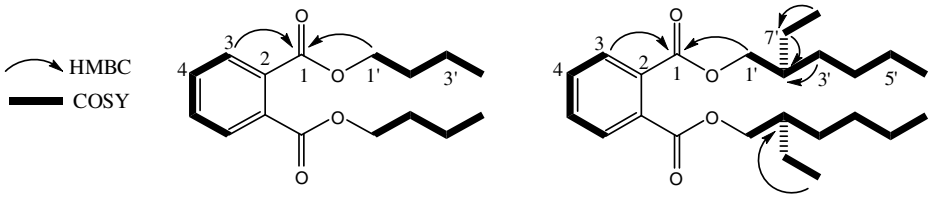


Synthesis and biological properties of β-turned $A\beta_{31-35}$ constrained analogues **pp 2078–2082**
M. Jesús Pérez de Vega,* José Luis Baeza, M. Teresa García-López, Miquel Vila-Perelló, Carmen Jiménez-Castells, Ana María Simón, Diana Frechilla, Joaquin del Río, Ricardo Gutiérrez-Gallego, David Andreu and Rosario González-Muñiz





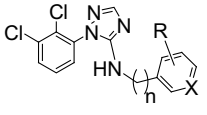
Cathepsin B inhibitory activities of phthalates isolated from a marine *Pseudomonas* strain **pp 2083–2088**
Van L. T. Hoang, Yong Li and Se-Kwon Kim*



Dibutyl phthalate Di-(2-ethylhexyl) phthalate

Dibutyl phthalate and di-(2-ethylhexyl) phthalate were isolated from the culture supernatant of a marine *Pseudomonas* sp. PB01 (GenBank Accession No. EU126129). Both of them showed dose-dependent cathepsin B inhibitions in vitro and inhibited pericellular cathepsin B with no acute cytotoxic effects.

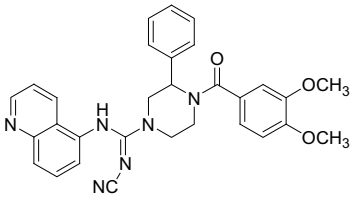
Synthesis and in vitro activity of 1-(2,3-dichlorophenyl)-*N*-(pyridin-3-ylmethyl)-1*H*-1,2,4-triazol-5-amine and 4-(2,3-dichlorophenyl)-*N*-(pyridin-3-ylmethyl)-4*H*-1,2,4-triazol-3-amine $P2X_7$ antagonists **pp 2089–2092**
Alan S. Florjancic,* Sridhar Peddi, Arturo Perez-Medrano, Biqin Li, Marian T. Namovic, George Grayson, Diana L. Donnelly-Roberts, Michael F. Jarvis and William A. Carroll*



A novel series of aminotriazole-based $P2X_7$ antagonists was synthesized. Most compounds showed greater potency at the human receptor although several analogs were discovered with potent activity (pIC_{50} 7.5) at both human and rat $P2X_7$.

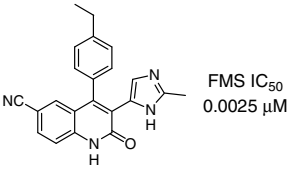
Synthesis and in vitro activity of *N*′-cyano-4-(2-phenylacetyl)-*N*-*o*-tolylpiperazine-1-carboximidamide $P2X_7$ antagonists **pp 2093–2096**
Michael J. Morytko, Patrick Betschmann, Kevin Woller, Anna Ericsson, Haipeng Chen, Diana L. Donnelly-Roberts, Marian T. Namovic, Michael F. Jarvis, William A. Carroll* and Paul Rafferty

A novel series of cyanoguanidine-piperazine $P2X_7$ antagonists was designed with compound **29** displaying potent activity (IC_{50} = 30–60 nM) at both rat and human $P2X_7$.



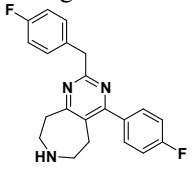
29

Synthesis and evaluation of novel 3,4,6-substituted 2-quinolones as FMS kinase inhibitors **pp 2097–2102**
Mark J. Wall, Jinsheng Chen, Sanath Meegalla, Shelley K. Ballentine, Kenneth J. Wilson, Renee L. DesJarlais, Carsten Schubert, Margery A. Chaikin, Carl Crysler, Ioanna P. Petrounia, Robert R. Donatelli, Edward J. Yurkow, Lisa Boczon, Marie Mazzulla, Mark R. Player, Raymond J. Patch, Carl L. Manthey, Christopher Molloy, Bruce Tomczuk and Carl R. Illig*



A series of 3,4,6-substituted 2-quinolones has been synthesized and evaluated as FMS inhibitors.

2-Alkyl-4-aryl-pyrimidine fused heterocycles as selective 5-HT_{2A} antagonists **pp 2103–2108**
Brock T. Shireman,* Curt A. Dvorak, Dale A. Rudolph, Pascal Bonaventure, Diane Nepomuceno, Lisa Dvorak, Kirsten L. Miller, Timothy W. Lovenberg and Nicholas I. Carruthers

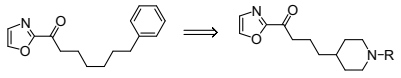


35g

5-HT_{2A} K_i =0.7 nM
5-HT_{2B} K_i =40 nM
5-HT_{2C} K_i =50 nM

The synthesis and SAR for a novel series of 2-alkyl-4-aryl-tetrahydro-pyrido-pyrimidines and 2-alkyl-4-aryl-tetrahydro-pyrimido-azepines are described. Representative compounds were shown to be subtype selective 5-HT_{2A} antagonists.

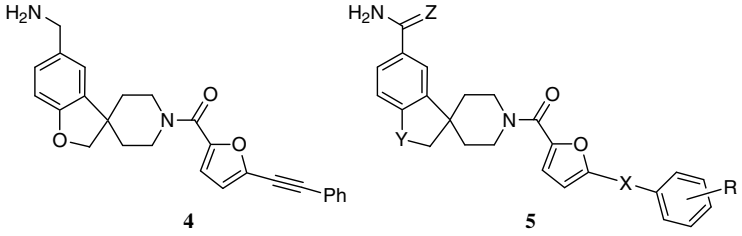
Novel ketooxazole based inhibitors of fatty acid amide hydrolase (FAAH) **pp 2109–2113**
Amy Timmons, Mark Seierstad, Rich Apodaca, Matt Epperson, Dan Pippel, Sean Brown, Leon Chang, Brian Scott, Michael Webb, Sandra R. Chaplan and J. Guy Breitenbucher*



1

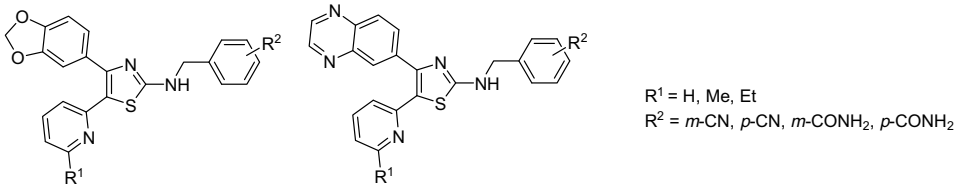
FAAH IC_{50} = 43 nM

Potent, nonpeptide inhibitors of human mast cell tryptase. Synthesis and biological evaluation of novel spirocyclic piperidine amide derivatives **pp 2114–2121**
Michael J. Costanzo,* Stephen C. Yabut, Han-Cheng Zhang, Kimberley B. White, Lawrence de Garavilla, Yuanping Wang, Lisa K. Minor, Brett A. Tounge, Alexander N. Barnakov, Frank Lewandowski, Cynthia Milligan, John C. Spurlino, William M. Abraham, Victoria Boswell-Smith, Clive P. Page and Bruce E. Maryanoff*

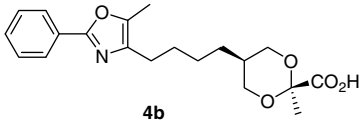


4 5

Synthesis and biological evaluation of 5-(pyridin-2-yl)thiazoles as transforming growth factor-β type1 receptor kinase inhibitors **pp 2122–2127**
Dae-Kee Kim,* Joon Hun Choi, Young Jae An and Ho Soon Lee



Discovery of a novel class of 1,3-dioxane-2-carboxylic acid derivatives as subtype-selective peroxisome proliferator-activated receptor α (PPARα) agonists **pp 2128–2132**
Tomiyoshi Aoki, Tetsuo Asaki,* Taisuke Hamamoto, Yukiteru Sugiyama, Shinji Ohmachi, Kenji Kuwabara, Kohji Murakami and Makoto Todo

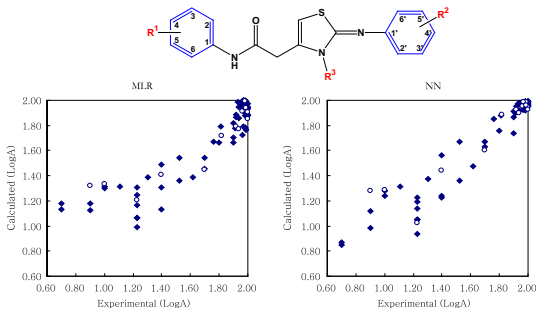


4b

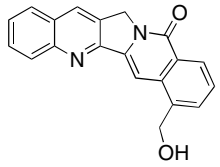
A new series of 1,3-dioxane-2-carboxylic acid derivatives was identified as potent and subtype-selective human PPARα agonists. Compound **4b** exhibits superior hypolipidemic activity in type 2 diabetic KK-A^{y} mice.

Quantitative structural–activity relationship (QSAR) study for fungicidal activities of thiazoline derivatives against rice blast **pp 2133–2142**
Jin Soo Song, Taesung Moon, Kee Dal Nam, Jae Kyun Lee, Hoh-Gyu Hahn, Eui-Ju Choi * and Chang No Yoon*

For the development of new fungicides from thiazoline derivatives against rice blast, the quantitative structural–activity relationship (QSAR) analyses were performed using multiple linear regression (MLR) and neural network (NN).

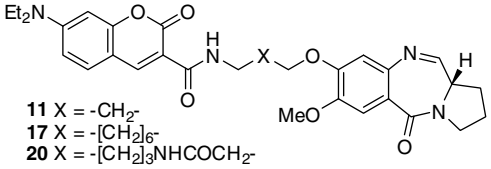


Synthesis and bioevaluation of 22-hydroxyacuminatine analogs **pp 2143–2146**
François Grillet, Barbora Baumlová, Grégoire Prévost, Jean-François Constant, Sophie Chaumeron, Dennis C. H. Bigg, Andrew E. Greene and Alice Kanazawa*



22-Hydroxyacuminatine

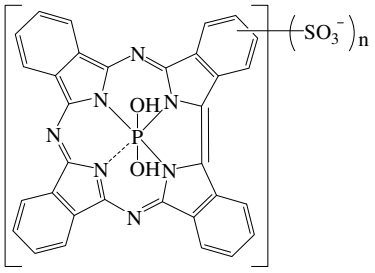
Fluorescent 7-diethylaminocoumarin pyrrolobenzodiazepine conjugates: Synthesis, DNA interaction, cytotoxicity and differential cellular localization **pp 2147–2151**
Geoffrey Wells, Marie Suggitt, Marissa Coffils, Mirza A. H. Baig, Philip W. Howard, Paul M. Loadman, John A. Hartley, Terence C. Jenkins and David E. Thurston*



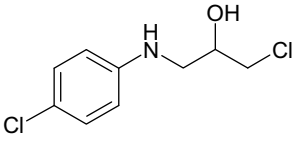
A series of three fluorescent PBD–coumarin conjugates with different linker architectures has been synthesized to probe correlations between DNA-binding affinity, cellular localization and cytotoxicity.

Photochemical DNA cleavage by novel water-soluble sulfonated dihydroxy phosphorus(V) tetrabenzotriazacorrole **pp 2152–2155**
Lei Huang, Cheng Zhong, Fushi Zhang* and Chen-Ho Tung*

The photosensitizing properties of a novel water-soluble phthalocyanine-like photosensitizer, sulfonated dihydroxy phosphorus(V) tetrabenzotriazacorrole {$P(OH)_2TBCS_n$}, were reported.

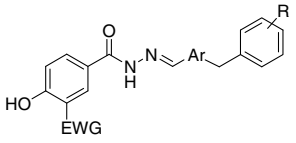


Synthesis and antimicrobial activity of 3-arylamino-1-chloropropan-2-ols **pp 2156–2161**
Ashok K. Prasad,* Pankaj Kumar, Ashish Dhawan, Anil K. Chhillar, Deepti Sharma, Vibha Yadav, Manish Kumar, Hirday N. Jha, Carl E. Olsen, Gainda L. Sharma and Virinder S. Parmar



A series of nine 3-arylamino-1-chloropropan-2-ols have been synthesized and screened for their anti-microbial activity. 1-Chloro-3-(4′-chlorophenylamino)-propan-2-ol exhibited more than 90% inhibition of growth of *Aspergillus fumigatus* at a concentration of 5.85 μg/ml; interestingly the compound did not show any toxicity up to a concentration of 4000 μg/ml.

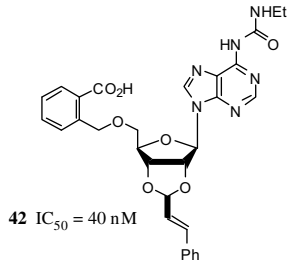
Discovery and SAR of hydrazide antagonists of the pituitary adenylate cyclase-activating polypeptide (PACAP) receptor type 1 (PAC_1-R) pp 2162–2166
Xenia Beebe,* Daria Darczak, Rachel A. Davis-Taber, Marie E. Uchic, Victoria E. Scott, Michael F. Jarvis and Andrew O. Stewart



Potent small molecule antagonists for the PAC_1-R have been discovered. Previously known antagonists for the PAC_1-R were slightly truncated peptide ligands. The hydrazides reported here are the first small molecule antagonists ever reported for this class B GPCR.

Adenosine analogues as inhibitors of $P2Y_{12}$ receptor mediated platelet aggregation pp 2167–2171
James G. Douglass, J. Bryan deCamp, Emilee H. Fulcher, William Jones, Sanjoy Mahanty, Anna Morgan, Dima Smirnov, José L. Boyer and Paul S. Watson*

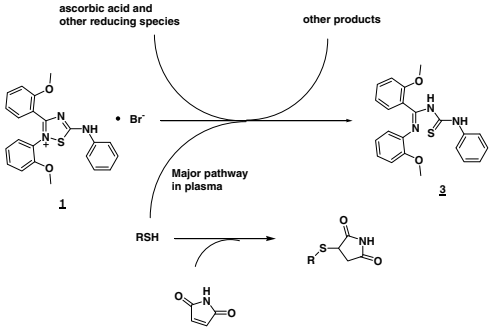
Modified adenosine derivatives may lead to the development of $P2Y_{12}$ antagonists that are potent, selective, and bind reversibly to the receptor. Analogues of 2′,3′-*trans*-styryl acetal-*N*6-ureido-adenosine monophosphate were prepared by modification of the 5′-position. The resulting analogues were tested for $P2Y_{12}$ antagonism in a platelet aggregation assay. Compound **42** was found to be the most potent with an IC_{50} value of 40 nM.



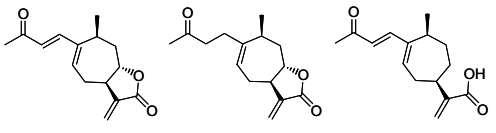
42 IC_{50} = 40 nM

Non-enzymatic reduction of a 1,2,4-thiadiazolium derivative pp 2172–2178
Fa Zhang,* Carmelita Estavillo, Margie Mohler and Jane Cai

2,3-Bis-(2-methoxy-phenyl)-5-phenylamino-[1,2,4]-thiadiazolium bromide (**1**), a 1,2,4-thiadiazolium derivative, was reduced to the corresponding imidoylthiourea, 1-[(2-methoxy-phenyl)-(2-methoxy-phenylimino)-methyl]-3-phenyl-thiourea (**3**), by some biological interesting reducing reagents including glutathione, cysteine, and ascorbic acid. The reduction also occurred in Sprague–Dawley rat and Yorkshire swine plasma. Chemical trapping studies suggested that thiol containing biological molecules existing in the plasma are mainly responsible for this reaction. A facile method for preparation of **3** from **1** was established by using 2-thioethanol as a reaction reagent as well as a solvent. Those new findings could shed light on the development of 1,2,4-thiadiazolium derivatives for their potential pharmaceutical applications.



Inhibition of lipopolysaccharide-induced inducible nitric oxide synthase and cyclooxygenase-2 expression by xanthanolides isolated from *Xanthium strumarium* pp 2179–2182
Jeong Hoon Yoon, Hyo Jin Lim, Hwa Jin Lee, Hee-Doo Kim, Raok Jeon and Jae-Ha Ryu*

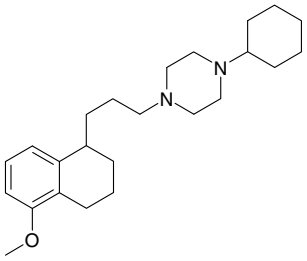


1 2 3

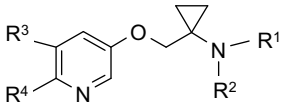
Three sesquiterpenoids from *Xanthium strumarium* (**1**, **2** and **3**) inhibited the production of NO (IC_{50} = 0.47, 11.2, 136.5 μM, respectively), expression of iNOS/COX-2 and degradation of I-κB-α in activated microglia.

Tritium radiolabelling of PB28, a potent sigma-2 receptor ligand: pharmacokinetic and pharmacodynamic characterization **pp 2183–2187**
Nicola Antonio Colabufo,* Carmen Abate, Marialessandra Contino, Carmela Inglese, Savina Ferorelli, Francesco Berardi and Roberto Perrone

The radiosynthesis and pharmacodymamic properties of the powerful sigma-2 agonist PB28 (K_d = 0.12 nM) are reported.

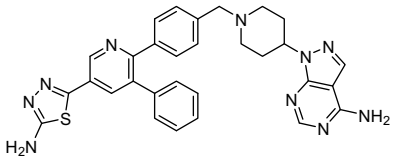


Preparation and affinity profile of novel nicotinic ligands **pp 2188–2193**
Yves Charton, Claude Guillonneau, Brian Lockhart, Pierre Lestage and Solo Goldstein*



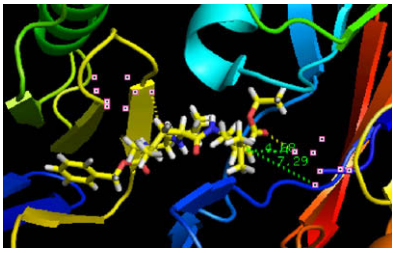
New nicotinic ligands with restricted conformational mobility induced by a cyclopropane ring are disclosed. Affinity studies indicated that these compounds are potent and selective α4β2 nicotinic ligands.

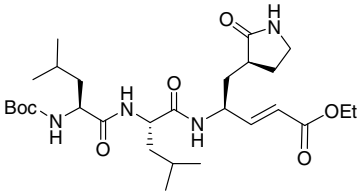
Optimization of 2,3,5-trisubstituted pyridine derivatives as potent allosteric Akt1 and Akt2 inhibitors **pp 2194–2197**
John C. Hartnett,* Stanley F. Barnett, Mark T. Bilodeau, Deborah Defeo-Jones, George D. Hartman, Hans E. Huber, Raymond E. Jones, Astrid M. Kral, Ronald G. Robinson and Zhicai Wu



Akt1 IC_{50} = 126 nM
Akt2 IC_{50} = 22 nM
Cell Akt1 IC_{50} = 621 nM
Cell Akt2 IC_{50} = 416 nM

Novel CADD-based peptidyl vinyl ester derivatives as potential proteasome inhibitors **pp 2198–2202**
Ke Mou, Bo Xu, Chao Ma, Xiaoming Yang, Xiaomin Zou, Yang Lü and Ping Xu*



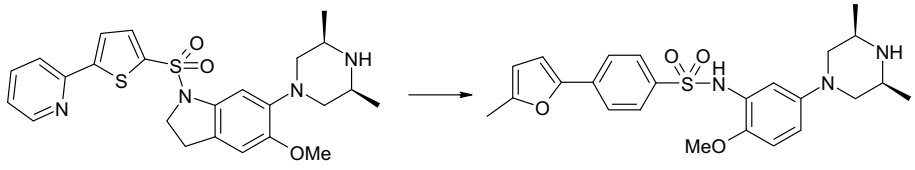


compound 27

A binding mode of peptidyl vinyl ester derivatives with proteasome catalytic-site was reported. Basing on this model, a novel series of potential proteasome inhibitors was designed, synthesized and assayed.

Potent achiral agonists of the growth hormone secretagogue (ghrelin) receptor. Part 2: Lead optimisation pp 2203–2205
Jason Witherington,* Lee Abberley, Michael A. Briggs, Katharine Collis, David K. Dean, Alessandra Gaiba, N. Paul King, Helmut Kraus, Nicola Shuker, Jon G. A. Steadman, Andrew K. Takle, Gareth Sanger, Graham Wadsworth, Sharon Butler, Fiona McKay, Alison Muir, Kim Winborn and Tom D. Heightman

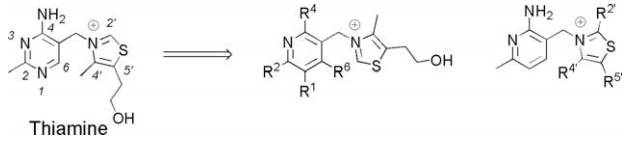
Systematic optimisation of a previously described series of poorly bioavailable ghrelin agonists has identified highly potent orally efficacious compounds.



(**1**) SB-791016, GHSR pEC50 9.8 (0.9)
poor systemic exposure

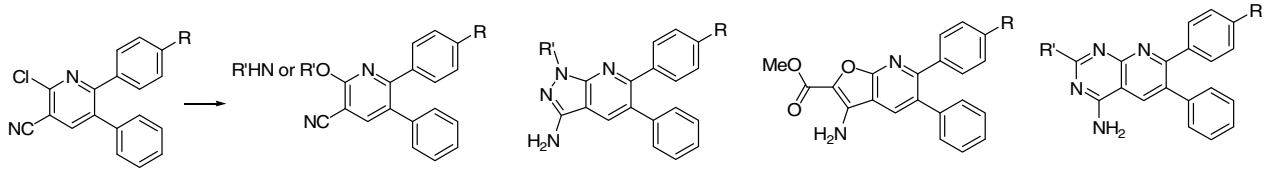
(**24**) GHSR pEC50 9.1 (1.0)
75% bioavailability in rats

Synthesis, in vitro and in vivo activity of thiamine antagonist transketolase inhibitors pp 2206–2210
Allen A. Thomas,* Y. Le Huerou, J. De Meese, Indrani Gunawardana, Tomas Kaplan, Todd T. Romoff, Stephen S. Gonzales, Kevin Condroski, Steven A. Boyd, Josh Ballard, Bryan Bernat, Walter DeWolf, May Han, Patrice Lee, Christine Lemieux, Robin Pedersen, Jed Pheneger, Greg Poch, Darin Smith, Francis Sullivan, Solly Weiler, S. Kirk Wright, Jie Lin, Barb Brandhuber and Guy Vigers

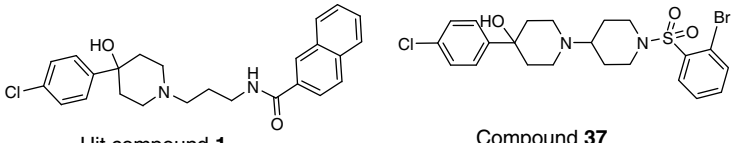


The synthesis, SAR, and in vivo activity of highly potent thiamine mimetics utilized as transketolase (TK) antagonists is presented.

Rapid assembly of diverse and potent allosteric Akt inhibitors pp 2211–2214
Zhicai Wu,* Ronald G. Robinson, Sheng Fu, Stanley F. Barnett, Deborah Defeo-Jones, Raymond E. Jones, Astrid M. Kral, Hans E. Huber, Nancy E. Kohl, George D. Hartman and Mark T. Bilodeau



Identification of novel series of human CCR1 antagonists pp 2215–2221
Yun Feng Xie, Ila Sircar, Kirk Lake, Mallareddy Komandla, Kathleen Ligsay, Jian Li, Kui Xu, Jason Parise, Lisa Schneider, Dingqiu Huang, Juping Liu, Naoki Sakurai, Miguel Barbosa and Rick Jack*

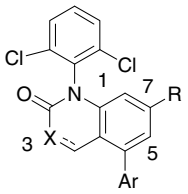


Hit compound **1**
IC_{50} (μM): 5.83 (Binding)
1.65 (FLIPR)

Compound **37**
IC_{50} (μM): 0.09 (Binding)
0.09 (FLIPR)
0.042 (Chemotaxis)

A hit-to-lead optimization process on the high throughput screening hit compound **1** resulted in the identification of several potent and selective CCR1 receptor antagonists. Compound **37** shows the best overall profile with IC_{50} values of <0.01 μM in binding and functional assays.

Synthesis and biological activity of quinolinone and dihydroquinolinone p38 MAP kinase inhibitors **pp 2222–2226**
Meng-Hsin Chen,* Patricia Fitzgerald, Suresh B. Singh, Edward A. O'Neill, Cheryl D. Schwartz, Chris M. Thompson, Stephen J. O'Keefe, Dennis M. Zaller and James B. Doherty



The synthesis and biological activities of some quinolinone and dihydroquinolinone p38 MAP kinase inhibitors are reported. Modifications to the dihydroquinolinone pharmacophore revealed that dihydroquinolinone may be replaced with a quinolinone pharmacophore and this modification led to enhanced p38α inhibitory activity. From a study of C-7 substituents with amino acid side chains, a very potent series of compounds in the p38α enzyme assays was identified. Translation of the in vitro activity into reasonable whole blood activity was improved in this latter series of compounds by judicious modification of the physical properties in appropriate regions of the lead.

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Corrigendum **pp 2227–2229**
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*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

COVER

Overlay of high resolution co-crystal structures of *R*-**22**-ADP (cyan) and **1**-ADP (green) bound in an allosteric binding site of the mitotic kinesin KSP. [Roecker, A. J.; Coleman, P. J.; Mercer, S. P.; Schreier, J. D.; Buser, C. A.; Walsh, E. S.; Hamilton, K.; Lobell, R. B.; Tao, W.; Diehl, R. E.; South, V. J.; Davide, J. P.; Kohl, N. E.; Yan, Y.; Kuo, L. C.; Li, C.; Fernandez-Metzler, C.; Mahan, E. A.; Prueksaritanont, T.; Hartman, G. D. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5677.]

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