



Bioorganic & Medicinal Chemistry Letters Volume 21, Issue 9, 2011

Symposium-in-Print

Recent Advances in Medicinal Chemistry

Guest Editors: Brian S. J. Blagg, Douglas S. Johnson and Robert M. Garbaccio

Contents

EDITORIAL

Recent advances in medicinal chemistry

pp 2585–2586

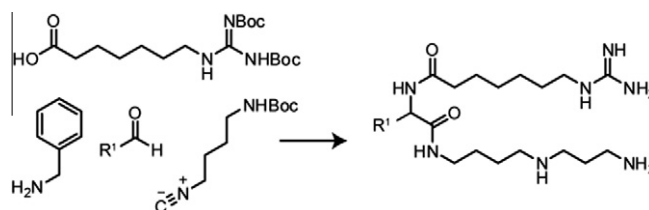
Dale L. Boger, Brian S. J. Blagg, Douglas S. Johnson, Robert M. Garbaccio

ARTICLES

Improved synthesis of 15-deoxyspergualin analogs using the Ugi multi-component reaction

pp 2587–2590

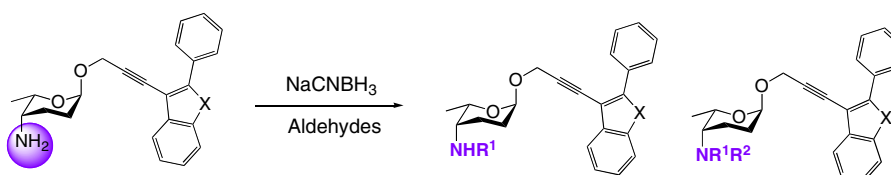
Christopher G. Evans, Matthew C. Smith, James P. Carolan, Jason E. Gestwicki*



Effect of carbohydrate amino group modifications on the cytotoxicity of glycosylated 2-phenylbenzo[b]thiophenes and 2-phenylbenzo[b]furans

pp 2591–2596

Wei Shi, Todd L. Lowary*



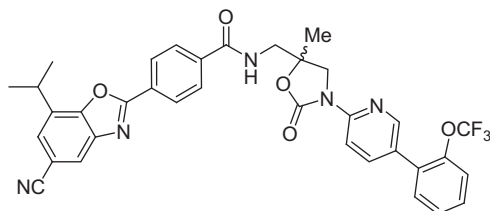
X = O, S, NTs



2-(4-Carbonylphenyl)benzoxazole inhibitors of CETP: Attenuation of hERG binding and improved HDLc-raising efficacy

pp 2597–2600

Ramzi F. Sweis*, Julianne A. Hunt, Peter J. Sinclair, Ying Chen, Suzanne S. Eveland, Qiu Guo, Sheryl A. Hyland, Denise P. Milot, Anne-Marie Cumiskey, Melanie Latham, Raymond Rosa, Larry Peterson, Carl P. Sparrow, Matt S. Anderson

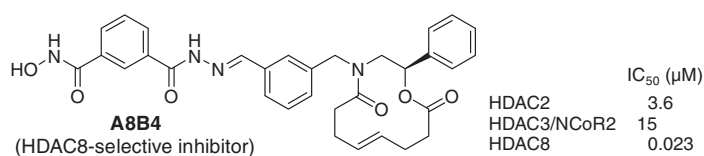


Compounds **7e** and **7f** were the first in this series of benzoxazoles found to be a potent inhibitors of CETP (IC_{50} = 22 and 18 nM), with robust in vivo efficacy (Δ HDLc = 33 and 27 mg/dL) and absent of any hERG binding liabilities.

Discovery of histone deacetylase 8 selective inhibitors

pp 2601–2605

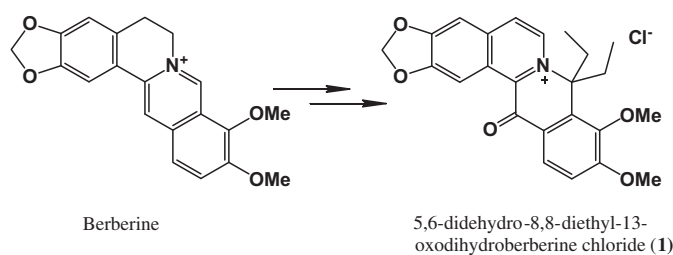
Weiping Tang*, Tuoping Luo, Edward F. Greenberg, James E. Bradner, Stuart L. Schreiber*



Potent antiprotozoal activity of a novel semi-synthetic berberine derivative

pp 2606–2610

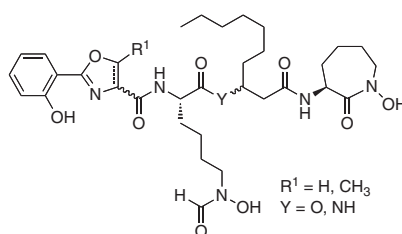
Mark Bahar, Ye Deng, Xiaohua Zhu, Shanshan He, Trupti Pandharkar, Mark E. Drew, Armando Navarro-Vázquez, Clemens Anklin, Roberto R. Gil, Raymond W. Doskotch, Karl A. Werbovets, A. Douglas Kinghorn*



Syntheses and studies of amamistatin B analogs reveals that anticancer activity is relatively independent of stereochemistry, ester or amide linkage and select replacement of one of the metal chelating groups

pp 2611–2615

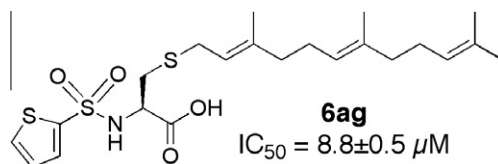
Chunrui Wu, Patricia A. Miller, Marvin J. Miller*



Probing the isoprenylcysteine carboxyl methyltransferase (Icmt) binding pocket: Sulfonamide modified farnesyl cysteine (SMFC) analogs as Icmt inhibitors

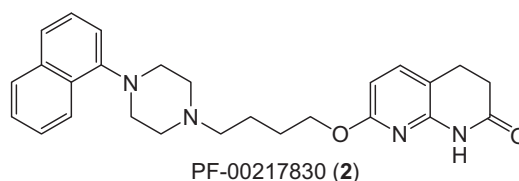
pp 2616–2620

Jaimeen D. Majmudar, Kalub Hahne, Christine A. Hrycyna*, Richard A. Gibbs*

**Discovery of PF-00217830: Aryl piperazine naphthyridinones as D₂ partial agonists for schizophrenia and bipolar disorder**

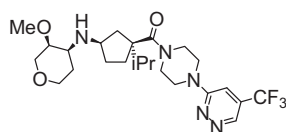
pp 2621–2625

Douglas S. Johnson*, Chung Choi, Lorraine K. Fay, David A. Favor, Joseph T. Repine, Andrew D. White, Hyacinth C. Akunne, Lawrence Fitzgerald, Kim Nicholls, Bradley J. Snyder, Steven Z. Whetzel, Liming Zhang, Kevin A. Serpa

**Discovery of ((1S,3R)-1-isopropyl-3-((3S,4S)-3-methoxy-tetrahydro-2H-pyran-4-ylamino)cyclopentyl)(4-(5-(trifluoromethyl)pyridazin-3-yl)piperazin-1-yl)methanone, PF-4254196, a CCR2 antagonist with an improved cardiovascular profile**

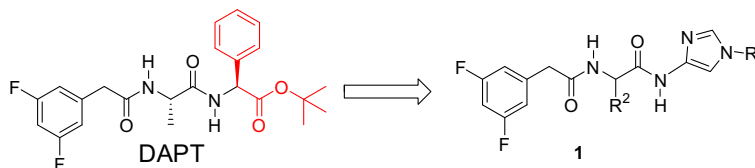
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Robert O. Hughes*, D. J. Rogier, Rajesh Devraj, Changsheng Zheng, Ganfeng Cao, Hao Feng, Michael Xia, Rajan Anand, Li Xing, Joseph Glenn, Ke Zhang, Maryanne Covington, Philip A. Morton, J. Matthew Hutzler, John W. Davis II, Peggy Scherle, Fred Baribaud, Anthony Bahinski, Zun-Li Mo, Robert Newton, Brian Metcalf, Chu-Biao Xue

Projected Human Dose 35 - 45 mg BID
CV-TI = 3800-fold**Diamide amino-imidazoles: A novel series of γ-secretase inhibitors for the treatment of Alzheimer's disease**

pp 2631–2636

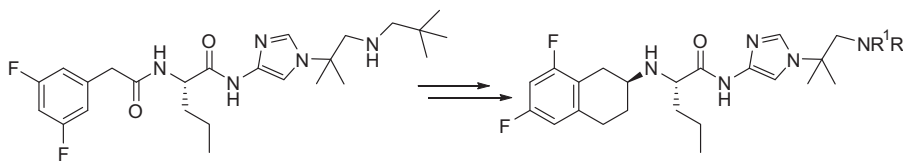
Michael A. Brodney*, David D. Auperin, Stacey L. Becker, Brian S. Bronk, Tracy M. Brown, Karen J. Coffman, James E. Finley, Carol D. Hicks, Michael J. Karmilowicz, Thomas A. Lanz, Dane Liston, Xingrong Liu, Barbara-Anne Martin, Robert B. Nelson, Charles E. Nolan, Christine E. Oborski, Christine P. Parker, Karl E. G. Richter, Nikolay Pozdnyakov, Barbara G. Sahagan, Joel B. Schachter, Sharon A. Sokolowski, Barbara Tate, Jeffrey W. Van Deusen, Douglas E. Wood, Kathleen M. Wood



Design, synthesis, and in vivo characterization of a novel series of tetralin amino imidazoles as γ -secretase inhibitors: Discovery of PF-3084014

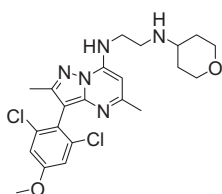
pp 2637–2640

Michael A. Brodney*, David D. Auperin, Stacey L. Becker, Brian S. Bronk, Tracy M. Brown, Karen J. Coffman, James E. Finley, Carol D. Hicks, Michael J. Karmilowicz, Thomas A. Lanz, Dane Liston, Xingrong Liu, Barbara-Anne Martin, Robert B. Nelson, Charles E. Nolan, Christine E. Oborski, Christine P. Parker, Karl E. G. Richter, Nikolay Pozdnyakov, Barbara G. Sahagan, Joel B. Schachter, Sharon A. Sokolowski, Barbara Tate, Douglas E. Wood, Kathleen M. Wood, Jeffrey W. Van Deusen, Lei Zhang


Discovery and evaluation of pyrazolo[1,5-a]pyrimidines as neuropeptide Y1 receptor antagonists

pp 2641–2645

David A. Griffith, Diane M. Hargrove, Tristan S. Maurer, Charles A. Blum, Stéphane De Lombaert, John K. Inthavongsay, Lee E. Klade, Christine M. Mack, Colin R. Rose, Martin J. Sanders, Philip A. Carpino*



2f, hY1R K_i = 1 nM, FLIPR IC_{50} = 7 nM, rY1R K_i = 3 nM

cElogD = 2.6

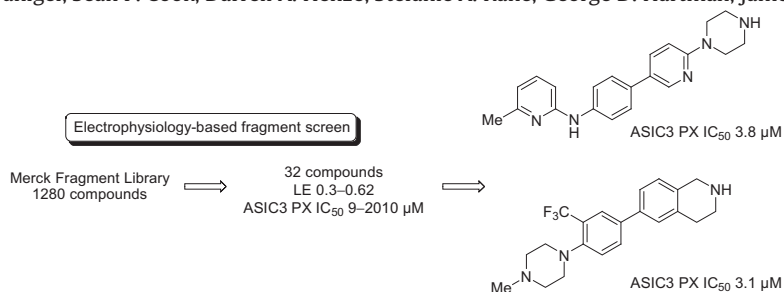
rat B/P = 0.13

A novel series of pyrazolo[1,5-a]pyrimidine derivatives was synthesized and evaluated as NPY Y1R antagonists. Oral administration of **2f** resulted in modest reductions of food intake in several rodent models.

High concentration electrophysiology-based fragment screen: Discovery of novel acid-sensing ion channel 3 (ASIC3) inhibitors

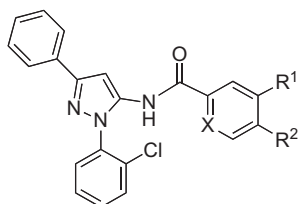
pp 2646–2649

Scott E. Wolkenberg*, Zhijian Zhao, James J. Mulhearn, Scott T. Harrison, John M. Sanders, Matthew J. Cato, Aneta Jovanovska, Jacqueline Panigel, Sean P. Cook, Darrell A. Henze, Stefanie A. Kane, George D. Hartman, James C. Barrow


Design and synthesis of substituted *N*-(1,3-diphenyl-1*H*-pyrazol-5-yl)benzamides as positive allosteric modulators of the metabotropic glutamate receptor subtype 5

pp 2650–2654

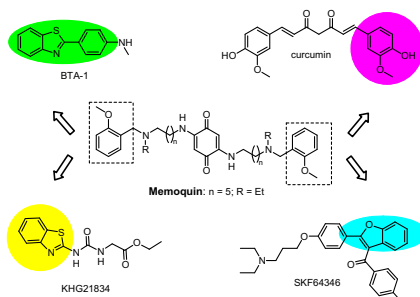
Mu-Fa Zou, Jianjing Cao, Alice L. Rodriguez, P. Jeffrey Conn, Amy Hauck Newman*



Multitargeted drugs discovery: Balancing anti-amyloid and anticholinesterase capacity in a single chemical entity

pp 2655–2658

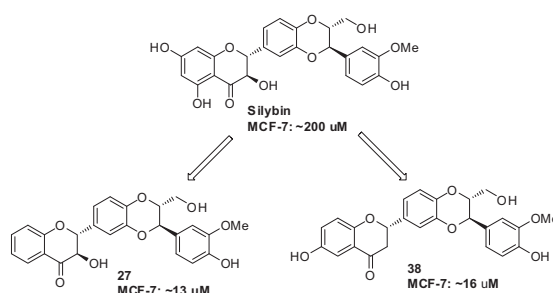
Maria Laura Bolognesi*, Manuela Bartolini, Andrea Tarozzi, Fabiana Morroni, Federica Lizzi, Andrea Milelli, Anna Minarini, Michela Rosini, Patrizia Hrelia, Vincenza Andrisano, Carlo Melchiorre



Identification and initial SAR of silybin: An Hsp90 inhibitor

pp 2659–2664

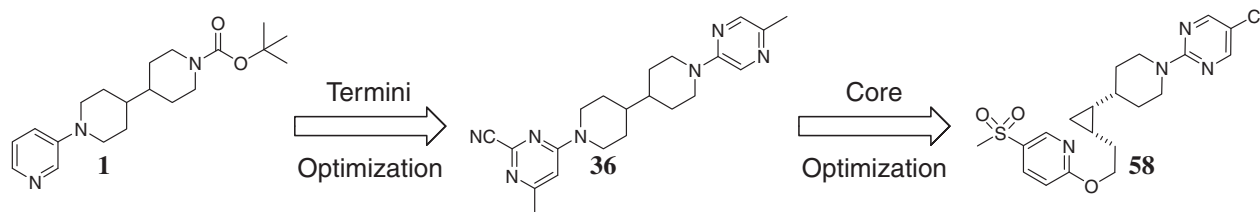
Huiping Zhao, Gary E. Brandt, Lakshmi Galam, Robert L. Matts, Brian S. J. Blagg*



Design of potent and selective GPR119 agonists for type II diabetes

pp 2665–2669

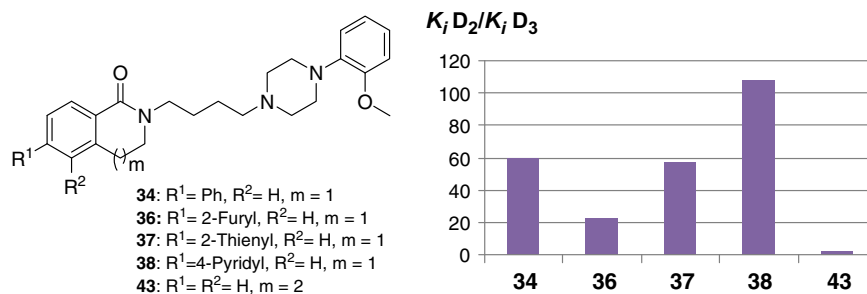
Jason W. Szewczyk*, John Acton, Alan D. Adams, Gary Chicchi, Stanley Freeman, Andrew D. Howard, Yong Huang, Cai Li, Peter T. Meinke, Ralph Mosely, Elizabeth Murphy, Rachel Samuel, Conrad Santini, Meng Yang, Yong Zhang, Kake Zhao, Harold B. Wood



Aromatic ring functionalization of benzolactam derivatives: New potent dopamine D₃ receptor ligands

pp 2670–2674

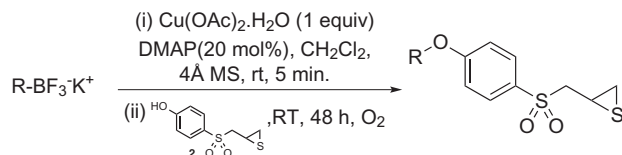
Raquel Ortega*, Harald Hübner, Peter Gmeiner, Christian F. Masaguer



Exploration of mild copper-mediated coupling of organotrifluoroborates in the synthesis of thiirane-based inhibitors of matrix metalloproteinases

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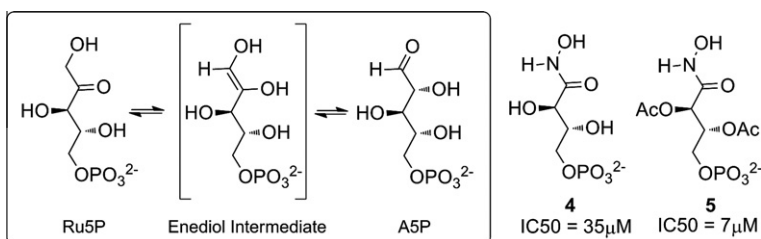
Sebastian A. Testero, Renee Bouley, Jed F. Fisher, Mayland Chang, Shahriar Mobashery*



Enediol mimics as inhibitors of the D-arabinose 5-phosphate isomerase (KdsD) from Francisella tularensis

pp 2679–2682

Alejandra Yep, Roderick J. Sorenson, Michael R. Wilson, H. D. Hollis Showalter, Scott D. Larsen, Paul R. Keller, Ronald W. Woodard*

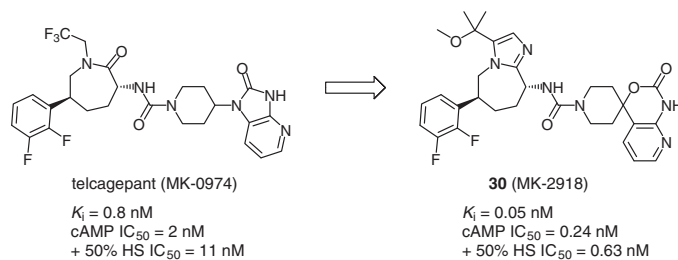


Orally bioavailable imidazoazepanes as calcitonin gene-related peptide (CGRP) receptor antagonists:

pp 2683–2686

Discovery of MK-2918

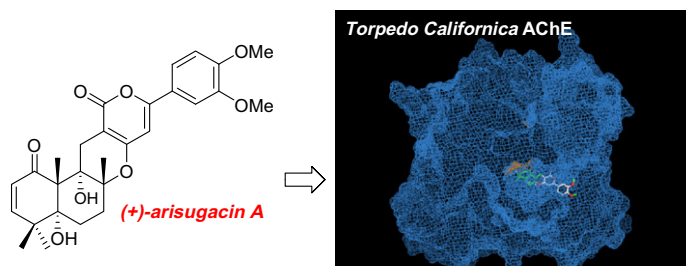
Daniel V. Paone*, Diem N. Nguyen, Anthony W. Shaw, Christopher S. Burgey, Craig M. Potteiger, James Z. Deng, Scott D. Mosser, Christopher A. Salvatore, Sean Yu, Shane Roller, Stefanie A. Kane, Harold G. Selnick, Joseph P. Vacca, Theresa M. Williams



(+)-Arisugacin A—Computational evidence of a dual binding site covalent inhibitor of acetylcholinesterase

pp 2687–2691

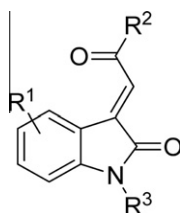
Ziyad F. Al-Rashid*, Richard P. Hsung*



Acylideneoxindoles: A new class of reversible inhibitors of human transglutaminase 2

pp 2692–2696

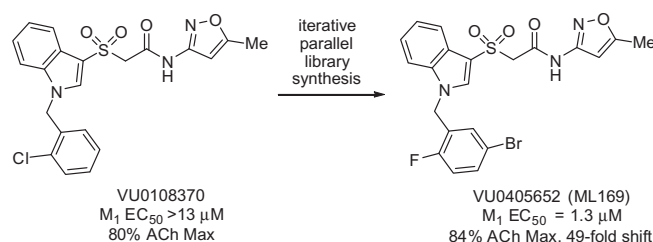
Cornelius Klöck, Xi Jin, Kihang Choi, Chaitan Khosla*, Peter B. Madrid, Andrew Spencer, Brian C. Raimundo, Paul Boardman, Guido Lanza, John H. Griffin*

**Discovery and optimization of a novel, selective and brain penetrant M₁ positive allosteric modulator (PAM): The development of ML169, an MLPCN probe**

pp 2697–2701

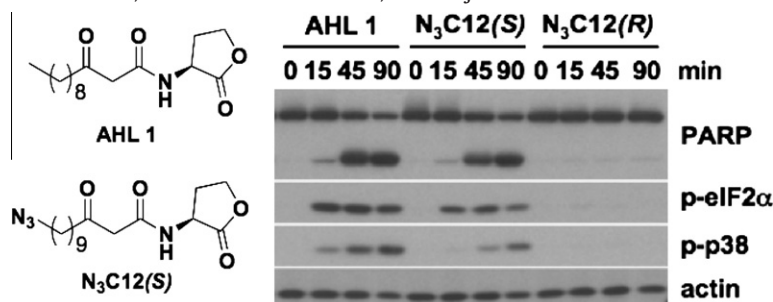
Paul R. Reid, Thomas M. Bridges, Douglas J. Sheffler, Hyekyung P. Cho, L. Michelle Lewis, Emily Days, J. Scott Daniels, Carrie K. Jones, Colleen M. Niswender, C. David Weaver, P. Jeffrey Conn, Craig W. Lindsley, Michael R. Wood*

This Letter describes a chemical lead optimization campaign directed at VU0108370, a weak M₁ PAM hit with a novel chemical scaffold from a functional HTS screen within the MLPCN. An iterative parallel synthesis approach rapidly established SAR for this series and afforded VU0405652 (ML169), a potent, selective and brain penetrant M₁ PAM with an in vitro profile comparable to the prototypical M₁ PAM, BQCA, but with an improved brain to plasma ratio.

**Synthesis of ‘clickable’ acylhomoserine lactone quorum sensing probes: Unanticipated effects on mammalian cell activation**

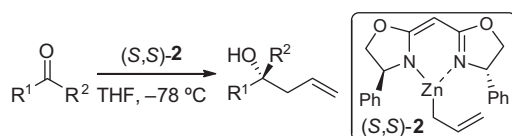
pp 2702–2705

Amanda L. Garner, Jing Yu, Anjali Kumari Struss, Colin A. Lowery, Jie Zhu, Sook Kyung Kim, Junguk Park, Alexander V. Mayorov, Gunnar F. Kaufmann, Vladimir V. Kravchenko, Kim D. Janda*

**Experimental and theoretical investigation of the scope of enantioselective ketone allylations employing Nakamura's allylzinc–bisoxazoline reagent**

pp 2706–2710

A. George Johnson, Brad M. Loertscher, Adam R. Moeck, Sam S. Matthews, Daniel H. Ess*, Steven L. Castle*



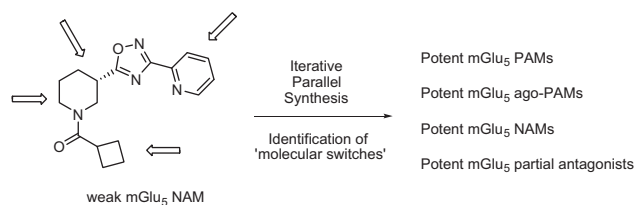
An investigation of the scope of enantioselective ketone allylations employing Nakamura's chiral allylzinc–bisoxazoline reagent is described, along with the development of a theoretical model to explain the results.



Discovery of molecular switches within the ADX-47273 mGlu₅ PAM scaffold that modulate modes of pharmacology to afford potent mGlu₅ NAMs, PAMs and partial antagonists

pp 2711–2714

Jeffrey P. Lamb, Darren W. Engers, Colleen M. Niswender, Alice L. Rodriguez, Daryl F. Venable, Jeffrey P. Conn, Craig W. Lindsley*

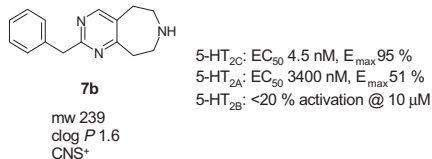


This Letter describes a chemical lead optimization campaign directed at a weak mGlu₅ NAM discovered while developing SAR for the mGlu₅ PAM, ADX-47273. An iterative parallel synthesis effort discovered multiple, subtle molecular switches that afford potent mGlu₅ NAMs, mGlu₅ PAMs as well as mGlu₅ partial antagonists.

Pyrimido[4,5-*d*]azepines as potent and selective 5-HT_{2C} receptor agonists: Design, synthesis, and evaluation of PF-3246799 as a treatment for urinary incontinence

pp 2715–2720

Mark D. Andrews*, Paul V. Fish*, Julian Blagg, Tiffini K. Brabham, Paul E. Brennan, Alison Bridgeland, Alan D. Brown, Peter J. Bungay, Kelly M. Conlon, Nicholas J. Edmunds, Kerry af Forselles, Colleen P. Gibbons, Martin P. Green, Giles Hanton, Mark Holbrook, Alan S. Jessiman, Karin McIntosh, Gordon McMurray, Carly L. Nichols, James A. Root, R. Ian Storer, Michael R. Sutton, Robin V. Ward, Dominique Westbrook, Gavin A. Whitlock

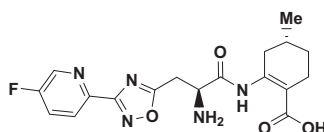


New pyrimido[4,5-*d*]azepines **7** are disclosed as potent 5-HT_{2C} receptor agonists. A preferred example, **7b** had minimal activation at either the 5-HT_{2A} or 5-HT_{2B} receptors combined with robust efficacy in a preclinical canine model of stress urinary incontinence. In addition, it proved to be critical to build an understanding of the translation between recombinant cell-based systems, native tissue preparations and in vivo preclinical models. This was a significant undertaking and proved to be crucial in compound selection.

The discovery of high affinity agonists of GPR109a with reduced serum shift and improved ADME properties

pp 2721–2724

Jason E. Imbriglio*, Daniel DiRocco, Rena Bodner, Subharekha Raghavan, Weichun Chen, Daria Marley, Craig Esser, Tom G. Holt, Michael S. Wolff, Andrew K. P. Taggart, M. Gerard Waters, James R. Tata, Steven L. Colletti



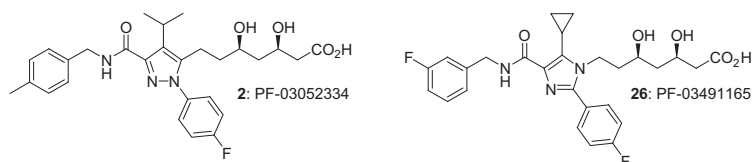
Amino-anthranilic acid derivatives have been identified as a new class of low serum shifted, high affinity full agonists of the human orphan G-protein-coupled receptor GPR109a with improved ADME properties.



Discovery of novel hepatoselective HMG-CoA reductase inhibitors for treating hypercholesterolemia: A bench-to-bedside case study on tissue selective drug distribution

pp 2725–2731

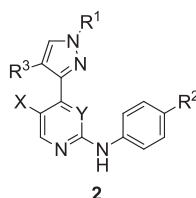
Jeffrey A. Pfefferkorn*, John Litchfield, Richard Hutchings, Xue-Min Cheng, Scott D. Larsen, Bruce Auerbach, Mark R. Bush, Chitase Lee, Noe Erasga, Daniel M. Bowles, David C. Boyles, Gina Lu, Catherine Sekerke, Valerie Askew, Jeffrey C. Hanselman, Lisa Dillon, Zhiwu Lin, Andrew Robertson, Karl Olsen, Carine Boustany, Karen Atkinson, Theunis C. Goosen, Vaishali Sahasrabudhe, Jonathan Chupka, David B. Duignan, Bo Feng, Renato Scialis, Emi Kimoto, Yi-An Bi, Yurong Lai, Ayman El-Kattan, Rebecca Bakker-Arkema, Paul Barclay, Erick Kindt, Vu Le, Jaap W. Mandema, Mark Milad, Bradley D. Tait, Robert Kennedy, Bharat K. Trivedi, Mark Kowala



Synthesis and SAR of 4-(pyrazol-3-yl)-pyridines as novel c-jun N-terminal kinase inhibitors

pp 2732–2735

Romain Noël, Youseung Shin, Xinyi Song, Yuanjun He, Marcel Koenig, Weimin Chen, Yuan Yuan Ling, Li Lin, Claudia H. Ruiz, Phil LoGrasso, Michael D. Cameron, Derek R. Duckett, Theodore M. Kamenecka*

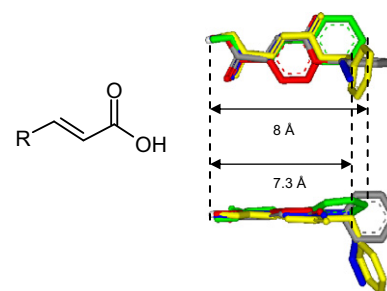


The design and synthesis of a novel series of c-jun N-terminal kinase (JNK) inhibitors is described. The development of the 4-(pyrazol-3-yl)-pyridine series was discovered from an earlier pyrimidine series of JNK inhibitors. Through the optimization of the scaffold **2**, several potent compounds with good in vivo profiles were discovered.

Structure–activity relationships of *trans*-substituted-propenoic acid derivatives on the nicotinic acid receptor HCA2 (GPR109A)

pp 2736–2739

J.P. D. van Veldhoven, C. C. Blad, C. M. Artsen, C. Klopman, D. R. Wolfram, M. J. Abdelkadir, J. R. Lane, J. Brussee, A. P. IJzerman*

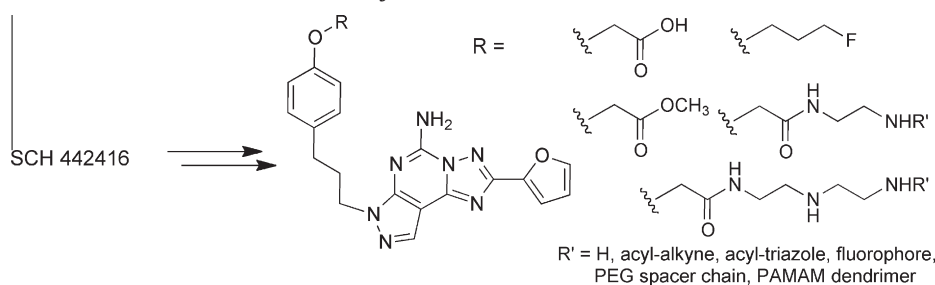


trans-Propenoic acid derivatives were synthesized and their activity on the HCA2 receptor (GPR109A) evaluated by structure–activity relationships and pharmacophore modeling.

**Molecular probes for the A_{2A} adenosine receptor based on a pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidin-5-amine scaffold**

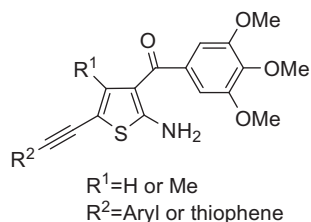
pp 2740–2745

T. Santhosh Kumar, Shilpi Mishra, Francesca Deflorian, Lena S. Yoo, Khai Phan, Miklos Kecskés, Angela Szabo, Bidhan Shinkre, Zhan-Guo Gao, William Trenkle, Kenneth A. Jacobson*

**Synthesis of novel antimetabolic agents based on 2-amino-3-aryl-5-(hetero)arylethynyl thiophene derivatives**

pp 2746–2751

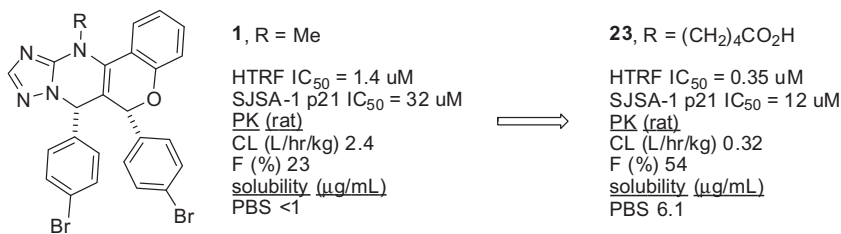
Romeo Romagnoli*, Pier Giovanni Baraldi*, Olga Cruz-Lopez, Manlio Tolomeo, Antonietta Di Cristina, Rosaria Maria Pipitone, Stefania Grimaudo, Jan Balzarini, Andrea Brancale, Ernest Hamel



Improvement of the synthesis and pharmacokinetic properties of chromenotriazolopyrimidine MDM2-p53 protein-protein inhibitors

pp 2752–2755

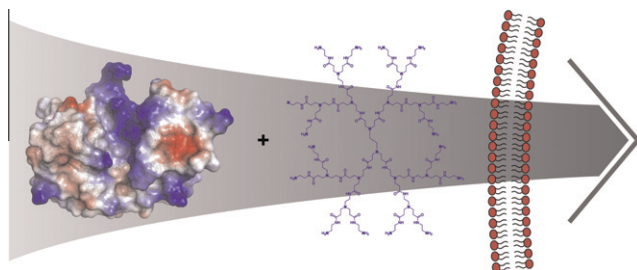
Hilary P. Beck*, Michael DeGraffenreid, Brian Fox, John G. Allen, Yosup Rew, Stephen Schneider, Anne Y. Saiki, Dongyin Yu, Jonathan D. Oliner, Kevin Salyers, Qiuping Ye, Steven Olson



Potential of ribonuclease cytotoxicity by a poly(amidoamine) dendrimer

pp 2756–2758

Gregory A. Ellis, Megan L. Hornung, Ronald T. Raines*



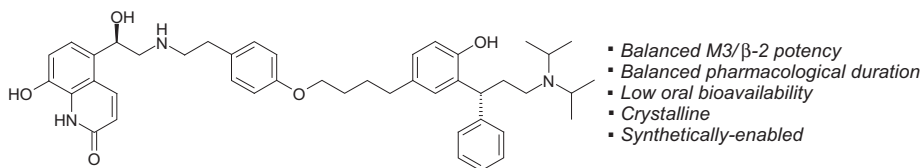
The toxicity of a cationic ribonuclease for cancer cells is increased by co-treatment with a cationic dendrimer.



Inhalation by design: Dual pharmacology β-2 agonists/M3 antagonists for the treatment of COPD

pp 2759–2763

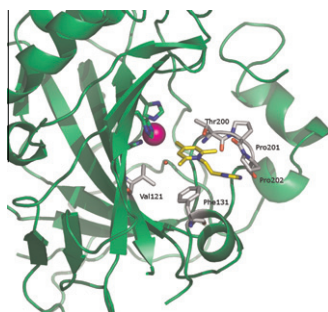
Lyn H. Jones*, Helen Baldock, Mark E. Bunnage, Jane Burrows, Nick Clarke, Michele Coghlan, David Entwistle, David Fairman, Neil Feeder, Craig Fulton, Laura Hilton, Kim James, Rhys M. Jones, Amy S. Kenyon, Stuart Marshall, Sandra D. Newman, Rachel Osborne, Sheena Patel, Matthew D. Selby, Emilio F. Stuart, Michael A. Trevethick, Karen N. Wright, David A. Price



An inhibitor-like binding mode of a carbonic anhydrase activator within the active site of isoform II

pp 2764–2768

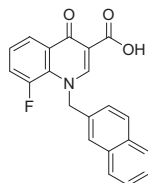
Khyati Dave, Marc A. Ilies*, Andrea Scozzafava, Claudia Temperini, Daniela Vullo, Claudiu T. Supuran*



Fused heterocyclic M₁ positive allosteric modulators

pp 2769–2772

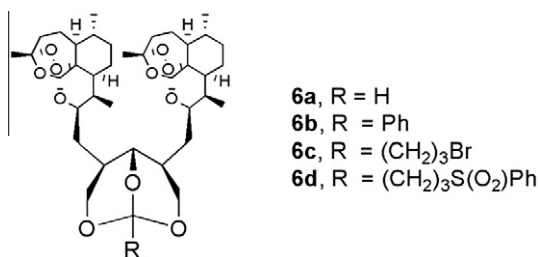
Scott D. Kuduk*, Christina N. Di Marco, Victoria Cofre, William J. Ray, Lei Ma, Marion Wittmann, Matthew A. Seager, Kenneth A. Koepflinger, Charles D. Thompson, George D. Hartman, Mark T. Bilodeau



Fused aromatics such as naphthalene were identified as highly potent and CNS penetrant M₁ positive allosteric modulators during an SAR study to replace the phenyl B-ring linkage.

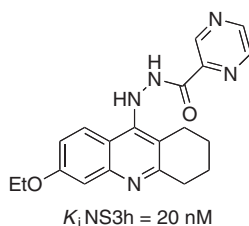
A single, low, oral dose of a 5-carbon-linked trioxane dimer orthoester plus mefloquine cures malaria-infected mice pp 2773–2775

Deuk Kyu Moon, Abhai Tripathi, David Sullivan, Maxime A. Siegler, Sean Parkin, Gary H. Posner*

**Discovery of potent nucleotide-mimicking competitive inhibitors of hepatitis C virus NS3 helicase**

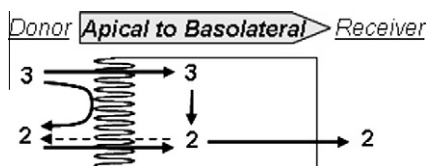
pp 2776–2779

Sandra Gemma, Stefania Butini, Giuseppe Campiani*, Margherita Brindisi, Samantha Zanolì, Maria Pia Romano, Pierangela Tripaldi, Luisa Savini, Isabella Fiorini, Giuseppe Borrelli, Ettore Novellino, Giovanni Maga

**Reprint of “MDCK cell permeability characteristics of a sulfenamide prodrug: Strategic implications in considering sulfenamide prodrugs for oral delivery of NH acids” [Bioorg. Med. Chem. Lett. 21 (2011) 172-175]**

pp 2780–2783

Victor R. Guarino*, Kwame Nti-Addae, Valentino J. Stella



*Corresponding author

 Supplementary data available via ScienceDirect

COVER

Overall view of the hCA II-**8** (in yellow) adduct. The protein is shown as ribbon, the Zn(II) ion is the violet sphere, with its three histidine ligands (His94, 96 and 119) in blue and green, whereas residues 121, 131, and 200–202 are shown in gray. [Khyati, D.; Ilies, M. A.; Scozzafava, A.; Temperini, C.; Vullo, D.; Supuran, C. T. *Bioorg. Med. Chem. Lett.* **2011**, 21, 2764.]

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