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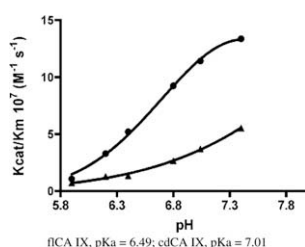
Bioorganic & Medicinal Chemistry Letters Vol. 19, No. 20, 2009

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ARTICLES

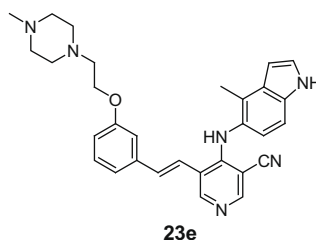
- The proteoglycan region of the tumor-associated carbonic anhydrase isoform IX acts as an intrinsic buffer optimizing CO₂ hydration at acidic pH values characteristic of solid tumors** pp 5825–5828

Alessio Innocenti, Silvia Pastorekova, Jaromir Pastorek, Andrea Scozzafava, Giuseppina De Simone, Claudiu T. Supuran *



- First generation 5-vinyl-3-pyridinecarbonitrile PKC θ inhibitors** pp 5829–5832

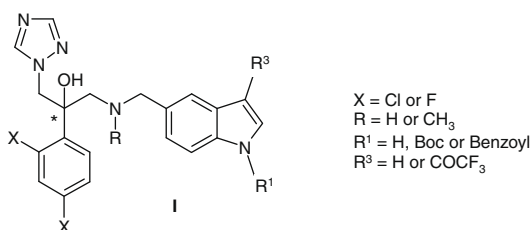
Chuansheng Niu *, Diane H. Boschelli, L. Nathan Tumey, Niala Bhagirath, Joan Subrath, Jaechul Shim, Yan Wang, Biqi Wu, Clark Eid, Julie Lee, Xiaoke Yang, Agnes Brennan, Divya Chaudhary



The synthesis of a series of 5-vinyl-3-pyridinecarbonitriles resulted in a potent PKC θ inhibitor **23e**, which had an IC₅₀ value of 4.7 nM for the inhibition of PKC θ with 11-fold selectivity over PKC δ .

- Design of new antifungal agents: synthesis and evaluation of 1-[(1H-indol-5-ylmethyl)amino]-2-phenyl-3-(1H-1,2,4-triazol-1-yl)propan-2-ols** pp 5833–5836

Rémi Guillon, Francis Giraud, Cédric Logé *, Marc Le Borgne, Carine Picot, Fabrice Pagniez, Patrice Le Pape

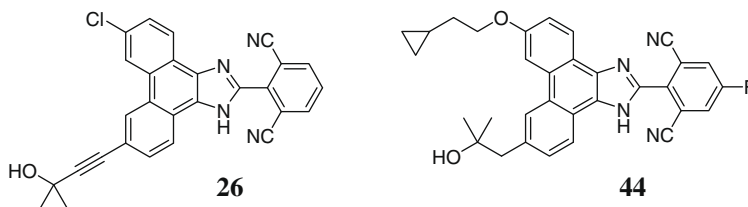


A series of 1-[(1H-indol-5-ylmethyl)amino]-2-phenyl-3-(1H-1,2,4-triazol-1-yl)propan-2-ols were synthesized and evaluated in vitro against *Candida albicans* and *Aspergillus fumigatus* strains. All the compounds exhibited potent MICs (<65 ng mL⁻¹) against *C. albicans* strain. The SAR studies behind the indole scaffold will be discussed.

Discovery of disubstituted phenanthrene imidazoles as potent, selective and orally active mPGES-1 inhibitors

pp 5837–5841

André Giroux^{*}, Louise Boulet, Christine Brideau, Anh Chau, David Claveau, Bernard Côté, Diane Ethier, Richard Frenette, Marc Gagnon, Jocelyne Guay, Sébastien Guiral, Joseph Mancini, Evelyn Martins, Frédéric Massé, Nathalie Méthot, Denis Riendeau, Joel Rubin, Daigen Xu, Hongping Yu, Yves Ducharme, Richard W. Friesen

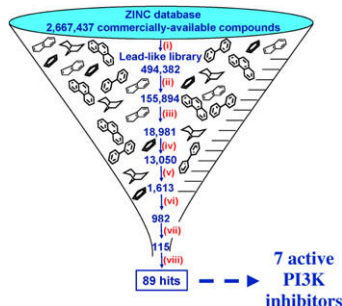


Phenanthrene imidazoles **26** and **44** have been identified as novel potent, selective, and orally active mPGES-1 inhibitors.

Phosphoinositide-3-kinase (PI3K) inhibitors: Identification of new scaffolds using virtual screening

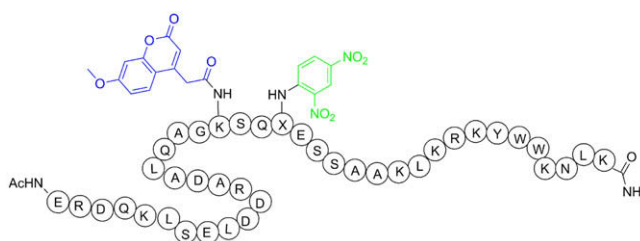
pp 5842–5847

Raphaël Frédéric^{*}, Claire Mawson, Jackie D. Kendall, Claire Chaussade, Gordon W. Rewcastle, Peter R. Shepherd, William A. Denny

**Synthetic substrate for application in both high and low throughput assays for botulinum neurotoxin B protease inhibitors**

pp 5848–5850

Nicholas T. Salzameda, Joseph T. Barbieri, Kim D. Janda^{*}

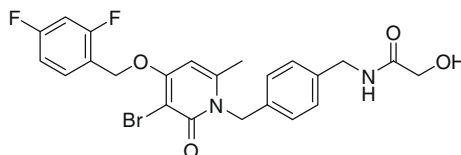


A FRET based synthetic substrate for the botulinum neurotoxin light chain B serotype utilized in both a high and low throughput assay for identification and characterization of inhibitors.

**Discovery of N-substituted pyridinones as potent and selective inhibitors of p38 kinase**

pp 5851–5856

Shaun R. Selness^{*}, Rajesh V. Devraj, Joseph B. Monahan, Terri L. Boehm, John K. Walker, Balekudru Devadas, Richard C. Durley, Ravi Kurumbail, Huey Shieh, Li Xing, Michael Hepperle, Paul V. Rucker, Kevin D. Jerome, Alan G. Benson, Laura D. Marrufo, Heather M. Madsen, Jeff Hitchcock, Tom J. Owen, Lance Christie, Michele A. Promo, Brian S. Hickory, Edgardo Alvira, Win Naing, Radhika Blevis-Bal

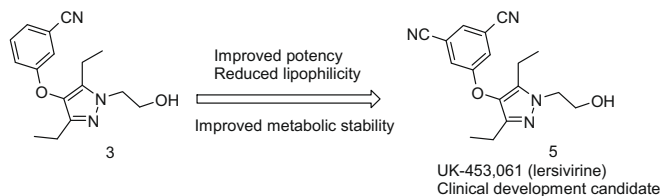


20, p38 α IC₅₀ = 46 nM

Pyrazole NNRTIs 4: Selection of UK-453,061 (lersivirine) as a Development Candidate

pp 5857–5860

Charles E. Mowbray ^{*}, Catherine Burt, Romuald Corbau, Simon Gayton, Michael Hawes, Manos Perros, Isabelle Tran, David A. Price, Faye J. Quinton, Matthew D. Selby, Paul A. Stupple, Rob Webster, Anthony Wood

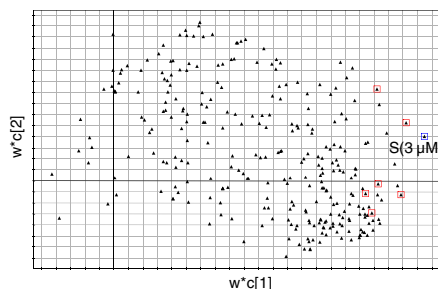


We prepared three discreet cohorts of potent non-nucleoside HIV reverse transcriptase inhibitors (NNRTIs) based on the recently reported 3-cyanophenoxypyrazole lead **2**. Several of these compounds displayed very promising anti-HIV activity in vitro, safety, pharmacokinetic and pharmaceutical profiles. We describe our analysis and conclusions leading to the selection of alcohol **5** (UK-453,061, lersivirine) for clinical development.

Small kinase assay panels can provide a measure of selectivity

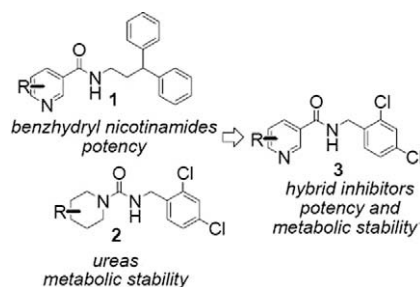
pp 5861–5863

Peter Brandt ^{*}, Annika Jenmalm Jensen, Jonas Nilsson

**Design and synthesis of substituted nicotinamides as inhibitors of soluble epoxide hydrolase**

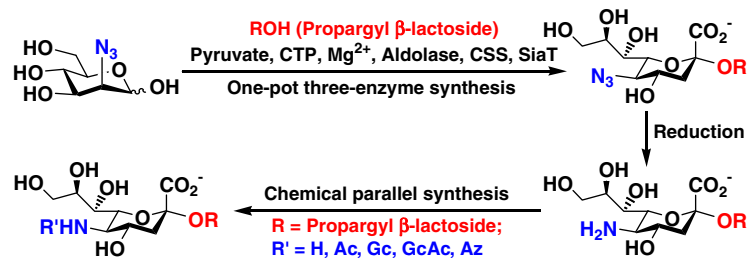
pp 5864–5868

Steven J. Taylor ^{*}, Fariba Soleymanzadeh, Anne B. Eldrup, Neil A. Farrow, Ingo Muegge, Alison Kukulka, Alisa K. Kabcenell, Stephane De Lombaert

**Parallel chemoenzymatic synthesis of sialosides containing a C5-diversified sialic acid**

pp 5869–5871

Hongzhi Cao, Saddam Muthana, Yanhong Li, Jiansong Cheng, Xi Chen ^{*}



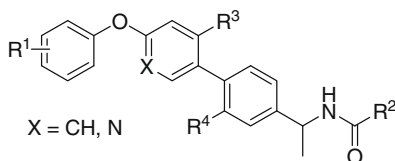
A convenient chemoenzymatic strategy for synthesizing sialosides containing a C5-diversified sialic acid is reported.



Potent biphenyl- and 3-phenyl pyridine-based inhibitors of acetyl-CoA carboxylase

pp 5872–5876

Tasir S. Haque^{*}, Ningning Liang, Rajasree Golla, Ramakrishna Seethala, Zhengping Ma, William R. Ewing, Christopher B. Cooper, Mary Ann Pelleymounter, Michael A. Poss, Dong Cheng

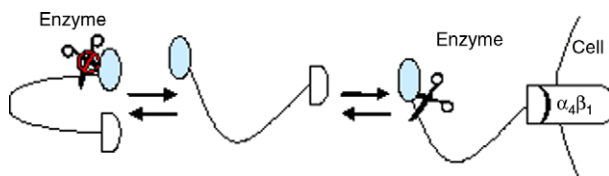


We report potent biphenyl- and 3-phenyl pyridine-based inhibitors of human acetyl-CoA carboxylase (ACC) enzymes 1 and 2.

Cell recognition enhanced enzyme hydrolysis of a model peptide–drug conjugate

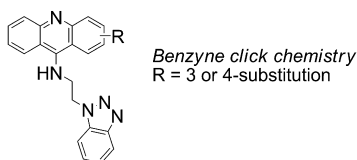
pp 5877–5879

Phanidhara R. Kotamraj, Xiaoling Li, Bhaskara Jasti, Wade A. Russu^{*}

**Synthesis and evaluation of 9-aminoacridines derived from benzyne click chemistry**

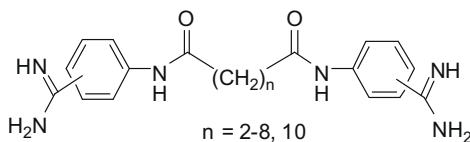
pp 5880–5883

Lesley A. Howell, Aaron Howman, Maria A. O'Connell, Anja Mueller, Mark Searcey^{*}

**Synthesis and SAR of alkanediamide-linked bisbenzamidines with anti-trypanosomal and anti-pneumocystis activity**

pp 5884–5886

Tien L. Huang^{*}, Jean Jacques Vanden Eynde, Annie Mayence, Margaret S. Collins, Melanie T. Cushion, Donna Rattendi, Indira Londono, Lakshman Mazumder, Cyrus J. Bacchi, Nigel Yarlett

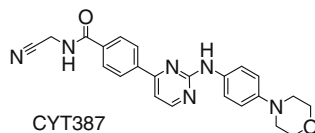


The synthesis and SAR of a series of alkanediamide-linked bisbenzamidines as potent inhibitors of *Trypanosoma brucei* and *Pneumocystis carinii* are described.

Phenylaminopyrimidines as inhibitors of Janus kinases (JAKs)

pp 5887–5892

Christopher J. Burns, David G. Bourke^{*}, Laura Andrau, Xianyong Bu, Susan A. Charman, Andrew C. Donohue, Emmanuelle Fantino, Michelle Farrugia, John T. Feutrell, Max Joffe, Marcel R. Kling, Margarita Kurek, Tracy L. Nero, Thao Nguyen, James T. Palmer, Ian Phillips, David M. Shackleford, Harrison Sikanyika, Michelle Styles, Stephen Su, Herbert Treutlein, Jun Zeng, Andrew F. Wilks

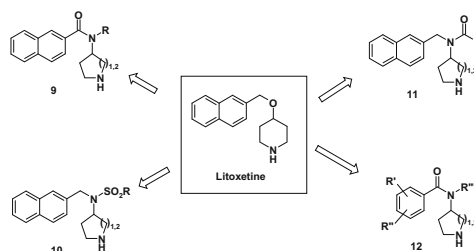


Details of SAR studies leading to CYT387, a potent and selective dual JAK1 and JAK2 inhibitor, are reported.

Design and optimisation of selective serotonin re-uptake inhibitors with high synthetic accessibility: Part 2

pp 5893–5897

Mark Andrews, Alan Brown^{*}, Jean-Yves Chiva, David Fradet, David Gordon, Mark Lansdell, Malcolm MacKenny

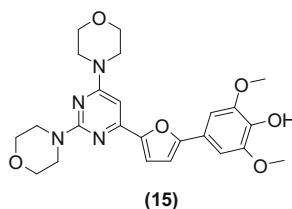


The reported selective serotonin re-uptake inhibitor (SSRI) litoxetine was used as the starting point in the design of a second wave of potent, selective SSRIs with high ease of synthetic accessibility.

Identification and optimisation of novel and selective small molecular weight kinase inhibitors of mTOR

pp 5898–5901

Keith A. Menear, Sylvie Gomez, Karine Malagu, Christine Bailey, Kristel Blackburn, Xiao-Ling Cockcroft, Sally Ewen, Alexandra Fundo, Armelle Le Gall, Gesine Hermann, Luisa Sebastian, Mihiro Sunose, Thomas Presnot, Eleanor Torode, Ian Hickson, Niall M. B. Martin, Graeme C. M. Smith, Kurt G. Pike^{*}

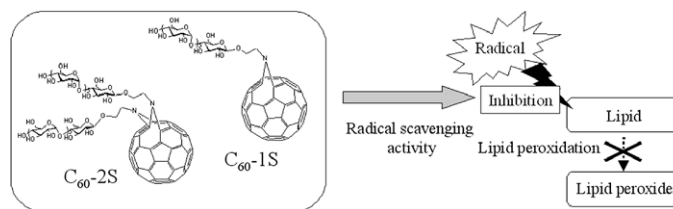


The discovery and optimisation of a novel series of inhibitors of mTOR kinase are described. Compound **15** has low nanomolar potency against mTOR kinase and is highly selective relative to PI3K α .

Antioxidant action of sugar-pendant C₆₀ fullerenes

pp 5902–5904

Masanori Horie, Akiko Fukuhara, Yoshiro Saito, Yasukazu Yoshida, Hiroe Sato, Hiromi Ohi, Makoto Obata, Yuji Mikata, Shigenobu Yano, Etsuo Niki^{*}

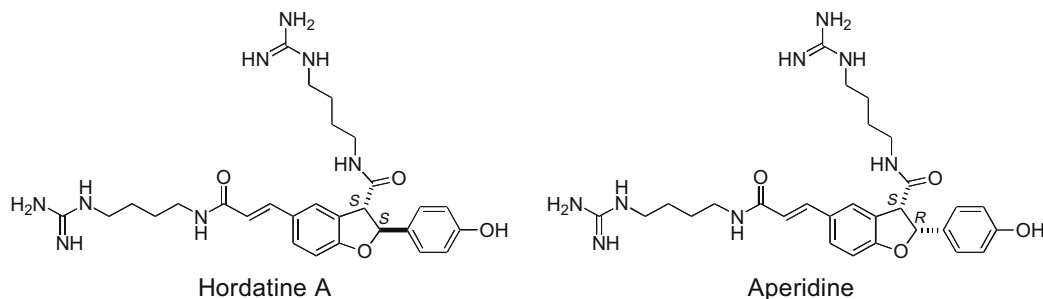


The sugar-pendant fullerene C₆₀ derivatives inhibited human plasma lipid peroxidation by scavenging radicals.

Structure–activity relationship study on α_1 adrenergic receptor antagonists from beer

pp 5905–5908

Toshiyuki Wakimoto ^{*}, Makoto Nitta, Kana Kasahara, Taketo Chiba, Ye Yiping, Kuniro Tsuji, Toshiyuki Kan, Haruo Nukaya, Masaji Ishiguro, Minako Koike, Yoshiaki Yokoo, Yoshihide Suwa

**Synthesis, SAR, and X-ray structure of tricyclic compounds as potent FBPase inhibitors**

pp 5909–5912

Tomoharu Tsukada, Mizuki Takahashi, Toshiyasu Takemoto, Osamu Kanno, Takahiro Yamane, Sayako Kawamura, Takahide Nishi ^{*}

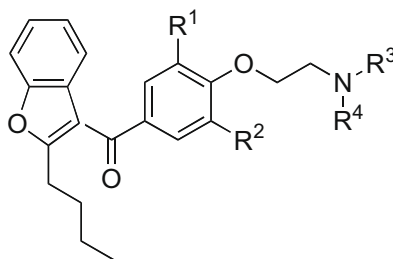


A novel series of tricyclic compounds were designed and synthesized as FBPase inhibitors. SAR studies in this series led to the finding of optimized inhibitors **8I** and **14b**.

Amiodarone and its putative metabolites fail to activate wild type hTAAR1

pp 5913–5914

Anita H. Lewin ^{*}, Hernán A. Navarro, Brian P. Gilmour

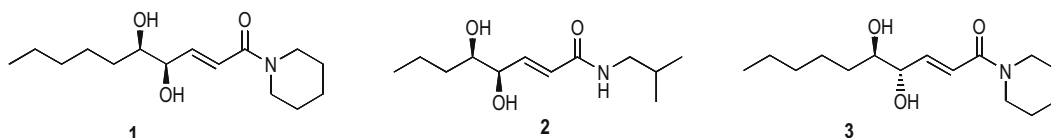


Although amiodarone and its metabolites are capable of stimulating rodent TAAR1, they fail to affect stably expressed unmodified hTAAR1 in vitro.

First stereoselective total synthesis and anticancer activity of new amide alkaloids of roots of pepper

pp 5915–5918

Ch. Srinivas, Ch. N. S. Sai Pavan Kumar, B. China Raju, V. Jayathirtha Rao ^{*}, V. G. M. Naidu, S. Ramakrishna, Prakash V. Diwan ^{*}

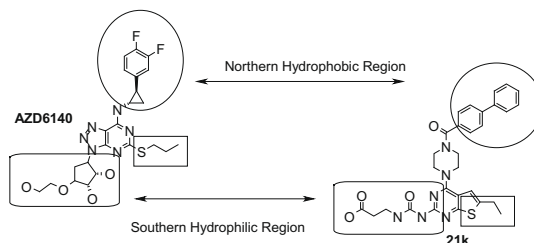


The first stereoselective total synthesis of new natural amide alkaloids **1–3** and their anti cancer activity is reported.

Thienopyrimidine-based P2Y₁₂ platelet aggregation inhibitors

pp 5919–5923

Steven W. Kortum ^{*}, Rhonda M. Lachance, Barbara A. Schweitzer, Gopichand Yalamanchili, Hayat Rahman, Michael D. Ennis, Rita M. Huff, Ruth E. TenBrink

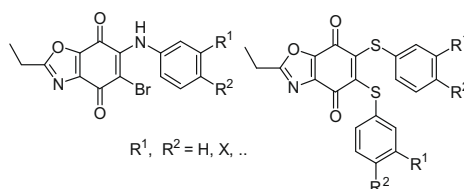


Herein we describe the design and synthesis of a novel series of potent thienopyrimidine P2Y₁₂ inhibitors and the negative impact protein binding has on the inhibition of platelet aggregation.

**Synthesis and antifungal activity of benzo[d]oxazole-4,7-diones**

pp 5924–5926

Chung-Kyu Ryu ^{*}, Ra-Young Lee, Na Young Kim, Yang Hui Kim, Ae Li Song

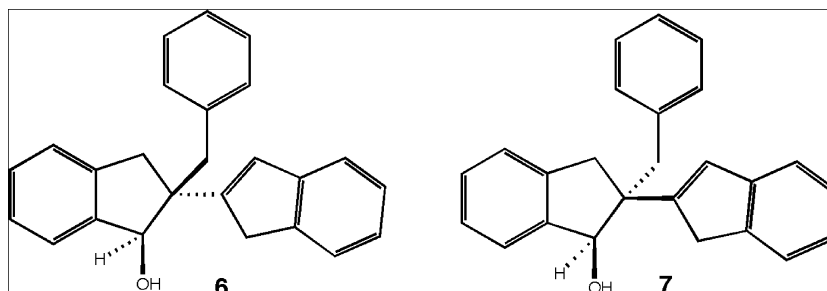


Benzo[d]oxazole-4,7-diones were synthesized and tested for in vitro antifungal activity against fungi. Many of these tested compounds exhibited potent antifungal activity.

Diastereoisomers of 2-benzyl-2, 3-dihydro-2-(1H-inden-2-yl)-1H-inden-1-ol: Potential anti-inflammatory agents

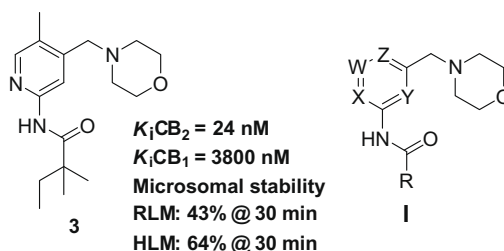
pp 5927–5930

Helen Sheridan ^{*}, John J. Walsh, Carina Cogan, Michael Jordan, Tom McCabe, Egle Passante, Neil H. Frankish

**Novel pyridine derivatives as potent and selective CB₂ cannabinoid receptor agonists**

pp 5931–5935

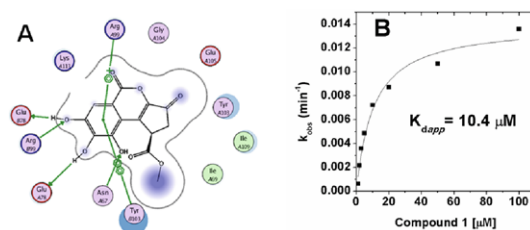
Guo-Hua Chu ^{*}, Christopher T. Saeui, Karin Worm, Damian G. Weaver, Allan J. Goodman, Robert L. Broadrup, Joel A. Cassel, Robert N. DeHaven, Christopher J. LaBuda, Michael Koblisch, Bernice Brogdon, Steve Smith, Bertrand Le Bourdonnec, Roland E. Dolle



A novel series of pyridine derivatives was synthesized and identified as potent and selective CB₂ agonists.

Selective inactivation of triosephosphate isomerase from *Trypanosoma cruzi* by brevifolin carboxylate derivatives isolated from *Geranium bellum* Rose pp 5936–5939

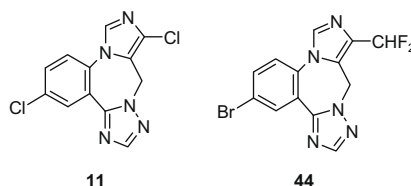
Juan Gayosso-De-Lucio, Martin Torres-Valencia, Arturo Rojo-Domínguez, Hugo Nájera-Peña, Beatriz Aguirre-López, José Salas-Pacheco, Claudia Avitia-Domínguez, Alfredo Téllez-Valencia *



Kinetic and molecular docking of highly selective inactivation of triosephosphate isomerase from *Trypanosoma cruzi* by brevifolin carboxylate derivatives is reported.

The discovery and unique pharmacological profile of R04938581 and R04882224 as potent and selective GABA_A $\alpha 5$ inverse agonists for the treatment of cognitive dysfunction pp 5940–5944

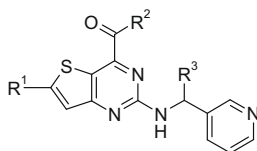
Henner Knust *, Guido Achermann, Theresa Ballard, Bernd Buettelmann, Rodolfo Gasser, Holger Fischer, Maria-Clemencia Hernandez, Frédéric Knoflach, Andreas Koblet, Heinz Stadler, Andrew W. Thomas, Gerhard Trube, Pius Waldmeier



Lead optimisation of the imidazo[1,5-a][1,2,4]-triazolo[1,5-d][1,4]benzodiazepine class led to the identification of two clinical leads [R04882224 (**11**) and R04938581 (**44**)] functioning as novel potent and selective GABA_A $\alpha 5$ inverse agonists. The unique pharmacological profiles and optimal pharmacokinetic profiles resulted in in vivo activity in selected cognition models.

Discovery and optimization of potent and selective functional antagonists of the human adenosine A_{2B} receptor pp 5945–5949

Simon T. Bedford, Karen R. Benwell, Teresa Brooks, Ijen Chen, Mike Comer, Sarah Dugdale, Tim Haymes, Allan M. Jordan *, Guy A. Kennett, Anthony R. Knight, Burkhard Klenke, Loic LeStrat, Angela Merrett, Anil Misra, Sean Lightowler, Anthony Padfield, Karine Poullennec, Mark Reece, Heather Simmonite, Melanie Wong, Ian A. Yule



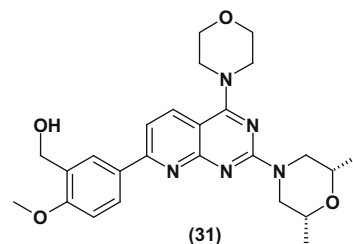
A novel class of antagonists of the human adenosine A_{2B} receptor is described. Offering interesting pharmacokinetic properties, these derivatives may prove useful in elucidating the role of adenosine A_{2B} receptors in a number of human disease conditions.



The discovery and optimisation of pyrido[2,3-d]pyrimidine-2,4-diamines as potent and selective inhibitors of mTOR kinase pp 5950–5953

Karine Malagu, Heather Duggan, Keith Menear, Marc Hummersone, Sylvie Gomez, Christine Bailey, Peter Edwards, Jan Drzewiecki, Frédéric Leroux, Mar Jimenez Quesada, Gesine Hermann, Stephanie Maine, Carrie-Anne Molyneaux, Armelle Le Gall, James Pullen, Ian Hickson, Lisa Smith, Sharon Maguire, Niall Martin, Graeme Smith, Martin Pass *

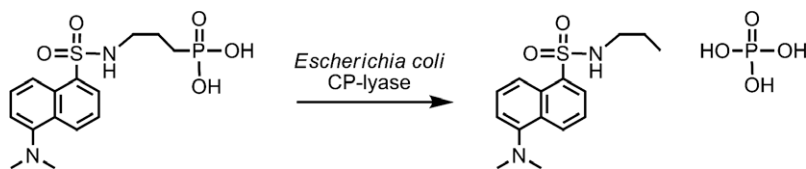
The discovery and optimization of a novel series of inhibitors of mTOR kinase are described. Compound **31**, KU-63794, has low nanomolar potency against mTOR kinase and is highly selective relative to other PI3K-related kinases.



A fluorescent substrate for carbon–phosphorus lyase: Towards the pathway for organophosphonate metabolism in bacteria

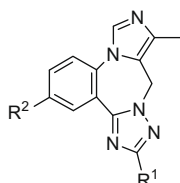
pp 5954–5957

Shu-Mei He, Yan Luo, Bjarne Hove-Jensen, David L. Zechel *

**Imidazo[1,5-a][1,2,4]-triazolo[1,5-d][1,4]benzodiazepines as potent and highly selective GABA_A α5 inverse agonists with potential for the treatment of cognitive dysfunction**

pp 5958–5961

Bernd Buettelmann *, Theresa M. Ballard, Rodolfo Gasser, Holger Fischer, Maria-Clemencia Hernandez, Frédéric Knoflach, Henner Knust, Heinz Stadler, Andrew W. Thomas, Gerhard Trube

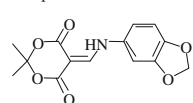


We have discovered a novel class of imidazo[1,5-a][1,2,4]-triazolo[1,5-d][1,4]benzodiazepines as a promising class of GABA_A α5 ligands which combine both high subtype binding selectivity with a marked inverse agonism. Two compounds (**10e** and **11f**) were found to be active in an in vivo model for cognitive improvement.

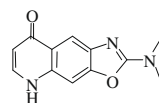
Synthesis and biological evaluation of new heterocyclic quinolinones as anti-parasite and anti-HIV drug candidates

pp 5962–5964

Albert Darque, Aurélien Dumètre, Sébastien Hutter, Gilles Casano, Maxime Robin, Christophe Pannecouque, Nadine Azas *

Compound **1k**

IC₅₀ *P. falciparum* (W2) = 10 μM
 Specificity Index *P. falciparum* (W2) = 25

Compound **2h**

IC₅₀ *P. falciparum* (W2) = 40 μM
 Specificity Index *P. falciparum* (W2) > 3.1

A series of quinolinones was synthesized by condensation of aminoheterocycle with Meldrum's acid derivatives (yield 90%), followed by thermal cyclization of the resulting synthetic intermediate (yield 58%). One intermediate compound (**1k**) and one final product (**2h**) display interesting antiparasitic activities.

**Discovery of highly potent novel antifungal azoles by structure-based rational design**

pp 5965–5969

Wenya Wang, Chunquan Sheng *, Xiaoying Che, Haitao Ji, Yongbing Cao, Zhenyuan Miao, Jianzhong Yao, Wannian Zhang *



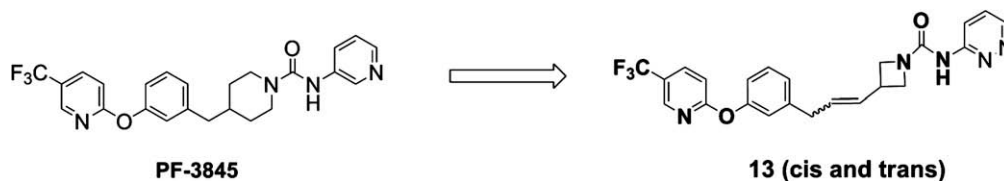
A series of new azoles with excellent in vitro antifungal activity were rational designed and synthesized.



Structure based design of novel irreversible FAAH inhibitors

pp 5970–5974

Jane L. Wang ^{*}, Scott J. Bowen, Barbara A. Schweitzer, Heather M. Madsen, Joseph McDonald, Matthew J. Pelc, Ruth E. Tenbrink, David Beidler, Atli Thorarensen




The design and synthesis a series of novel FAAH irreversible azetidine urea inhibitors from PF-3845 are described. Our SAR studies allowed us to optimize this series resulting in the identification of compounds **13** which were potent inhibitors of both human and rat enzyme. This series of compounds illustrated good hydrolase selectivity along with good rat PK properties.

OTHER CONTENTS**Instructions to contributors**

p I

*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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