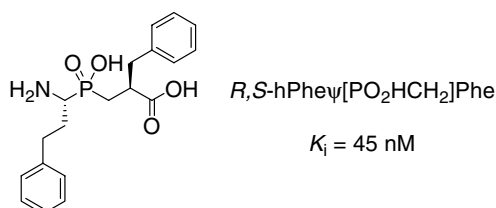


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Individual stereoisomers of phosphinic dipeptide inhibitor of leucine aminopeptidase pp 1550–1554

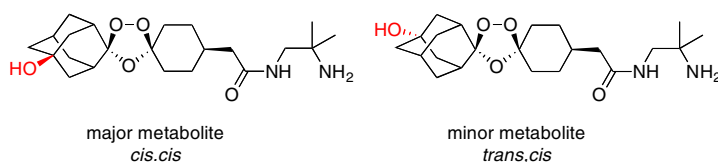
Artur Mucha,* Michael Lämmerhofer, Wolfgang Lindner, Małgorzata Pawełczak and Paweł Kafarski



First successful separation of all four stereoisomers of a phosphinic acid pseudodipeptide allowed to determine the inhibitory activity of the homophenylalanyl-phenylalanine analogue towards leucine aminopeptidase stereoselectively.

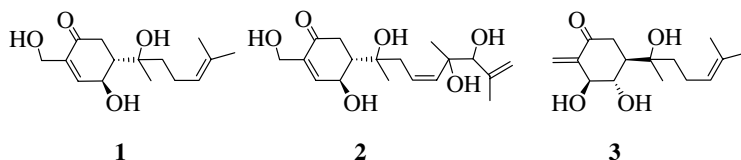
Characterization of the two major CYP450 metabolites of ozonide (1,2,4-trioxolane) OZ277 pp 1555–1558

Lin Zhou, André Alker, Armin Ruf, Xiaofang Wang, Francis C. K. Chiu, Julia Morizzi, Susan A. Charman, William N. Charman, Christian Scheurer, Sergio Wittlin, Yuxiang Dong, Daniel Hunziker and Jonathan L. Vennerstrom*



New cytotoxic saturated and unsaturated cyclohexanones from *Anthemis maritima* pp 1559–1562

Francesca Collu, Leonardo Bonsignore, Mariano Casu, Costantino Floris, Jürg Gertsch and Filippo Cottiglia*

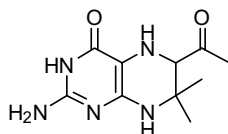


Three new compounds, antheminones A (1), B (2), and C (3) were isolated from the leaves of *Anthemis maritima*. These compounds exhibited significant antiproliferative activity against leukemia cells.

6-Acetyl-7,7-dimethyl-5,6,7,8-tetrahydropterin is an activator of nitric oxide synthases

pp 1563–1566

Colin J. Suckling,* Colin L. Gibson, Judith K. Huggan, Raghavendar R. Morthala, Brendan Clarke, Suma Kununthur, Roger M. Wadsworth, Simon Daff and Davide Papale

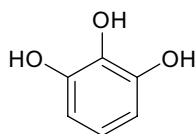


6-Acetyl-7,7-dimethyl-5,6,7,8-tetrahydropterin activates nitric oxide synthase in tissue, cell, and enzyme preparations as a substitute for the natural cofactor, tetrahydrobiopterin.

**Pyrogallol and its analogs can antagonize bacterial quorum sensing in *Vibrio harveyi***

pp 1567–1572

Nanting Ni, Gaurav Choudhary, Minyong Li and Binghe Wang*



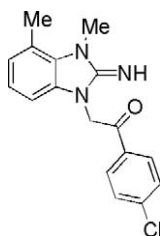
$$2 \text{ IC}_{50} = 2 \pm 1 \text{ } \mu\text{M}$$

Discovery of several pyrogallol compounds as single digit micromolar inhibitors of bacterial quorum sensing in *Vibrio harveyi*.

**Discovery of small molecule benzimidazole antagonists of the chemokine receptor CXCR3**

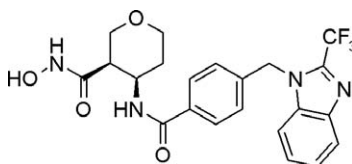
pp 1573–1576

Martin E. Hayes,* Grier A. Wallace, Pintipa Grongsaard, Agnieszka Bischoff, Dawn M. George, Wenyan Miao, Michael J. McPherson, Robert H. Stoffel, David W. Green and Gregory P. Roth

**Potent, exceptionally selective, orally bioavailable inhibitors of TNF- α Converting Enzyme (TACE):
Novel 2-substituted-1*H*-benzo[d]imidazol-1-yl)methyl)benzamide P1' substituents**

pp 1577–1582

Gregory R. Ott,* Naoyuki Asakawa, Zhonghui Lu, Rajan Anand, Rui-Qin Liu, Maryanne B. Covington, Krishna Vaddi, Mingxin Qian, Robert C. Newton, David D. Christ, James M. Trzaskos and James J.-W. Duan

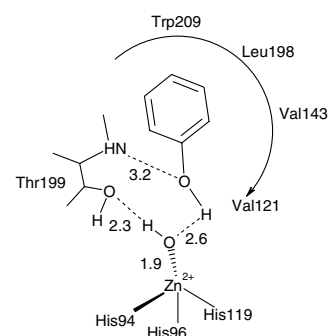


Novel ((2-substituted-1*H*-benzo[d]imidazol-1-yl)methyl)benzamides were found to be excellent P1' substituents in conjunction with unique constrained β -amino hydroxamic acid scaffolds for the discovery of potent, exceptionally selective inhibitors of TNF- α Converting Enzyme (TACE).

Carbonic anhydrase inhibitors: Interactions of phenols with the 12 catalytically active mammalian isoforms (CA I–XIV)

Alessio Innocenti, Daniela Vullo, Andrea Scozzafava and Claudiu T. Supuran*

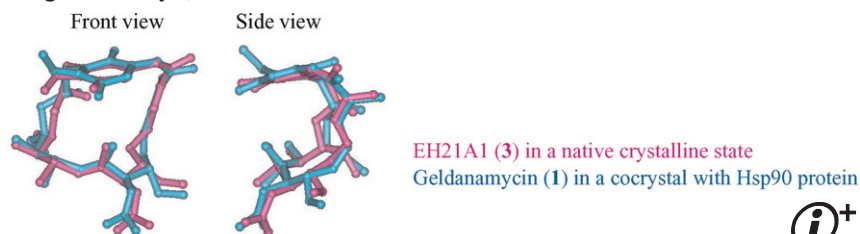
pp 1583–1587

**Conformational significance of EH21A1–A4, phenolic derivatives of geldanamycin, for Hsp90 inhibitory activity**

Hideyuki Onodera, Masami Kaneko, Yuichi Takahashi, Yumiko Uochi, Jun Funahashi, Takayuki Nakashima, Shiro Soga, Makoto Suzuki, Shunichi Ikeda, Yoshinori Yamashita, Endang S. Rahayu, Yutaka Kanda and Michio Ichimura*

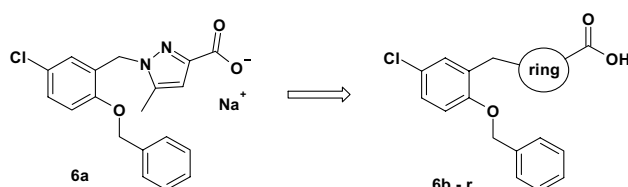
pp 1588–1591

EH21A1–A4, phenolic derivatives of geldanamycin were isolated from *Streptomyces* sp. Their native structures are similar to the active form of geldanamycin. The conformational character is a probable reason for their high affinity to Hsp90 protein.

**Novel methylene-linked heterocyclic EP₁ receptor antagonists**

Adrian Hall,* Rino A. Bit, Susan H. Brown, Anita Chowdhury, Gerard M. P. Giblin, David N. Hurst, Ian R. Kilford, Xiao Lewell, Alan Naylor and Tiziana Scoccitti

pp 1592–1597



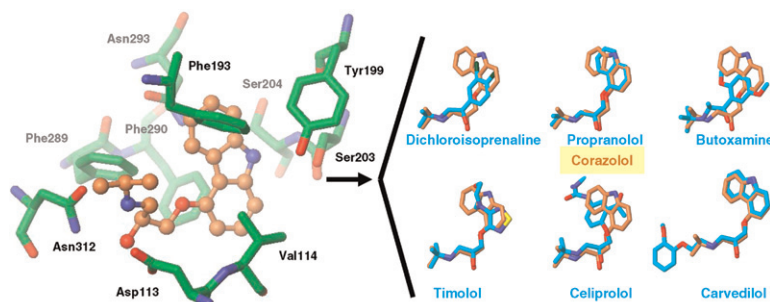
The synthesis and biological activity of a series of novel methylene-linked heterocyclic EP₁ receptor antagonists is described.

Use of the X-ray structure of the Beta2-adrenergic receptor for drug discovery

Sid Topiol* and Michael Sabio

pp 1598–1602

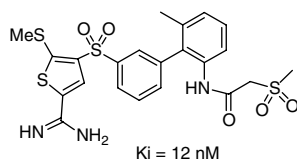
We explore the utility of the Beta2-adrenergic receptor's X-ray structure in drug design including high-throughput docking. Results validate the approach and project its usefulness in finding and designing novel compounds.



Biphenylsulfonyl-thiophene-carboxamidine inhibitors of the complement component C1s

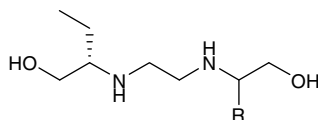
pp 1603–1606

Jeremy M. Travins, Farah Ali, Hui Huang, Shelley K. Ballentine, Ehab Khalil, Heather R. Hufnagel, Wenxi Pan, Joan Gushue, Kristi Leonard, Roger F. Bone, Richard M. Soll, Renee L. DesJarlais, Carl S. Crysler, Nisha Ninan, Jennifer Kirkpatrick, Maxwell D. Cummings, Norman Huebert, Christopher J. Molloy, Michael Gaul, Bruce E. Tomczuk and Nalin L. Subasinghe*

**Design, synthesis, and evaluation of novel ethambutol analogues**

pp 1607–1611

Raghunandan Yendapally and Richard E. Lee*



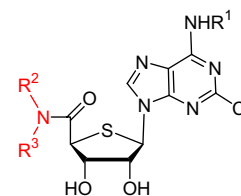
The synthesis, biological evaluation and structure–activity relationships of novel ethambutol analogues as anti-tuberculosis agents are reported.

Structure–activity relationships of 2-chloro-*N*⁶-substituted-4'-thioadenosine-5'-*N,N*-dialkyluronamides as human A₃ adenosine receptor antagonists

pp 1612–1616

Lak Shin Jeong,* Hyuk Woo Lee, Hea Ok Kim, Dilip K. Tosh, Shantanu Pal, Won Jun Choi, Zhan-Guo Gao, Amit R. Patel, Wanda Williams, Kenneth A. Jacobson and Hee-Doo Kim

Potent and selective A₃ adenosine receptor (AR) full antagonists with a nucleoside skeleton, of which the affinity and selectivity are independent of species, were discovered. Steric factors in the 5' region were important in binding of nucleosides to the human A₃AR.

**6a-r**

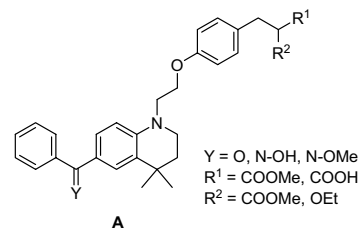
(R¹ = alkyl, cycloalkyl, or arylalkyl;
R², R³ = alkyl or cycloalkyl)

4,4-Dimethyl-1,2,3,4-tetrahydroquinoline-based PPARα/γ agonists. Part I: Synthesis and pharmacological evaluation

pp 1617–1622

Cécile Parmenon, Jérôme Guillard, Daniel-Henri Caignard, Nathalie Hennuyer, Bart Staels, Valérie Audinot-Bouchez, Jean-Albert Boutin, Catherine Dacquet, Alain Ktorza and Marie-Claude Viaud-Massuard*

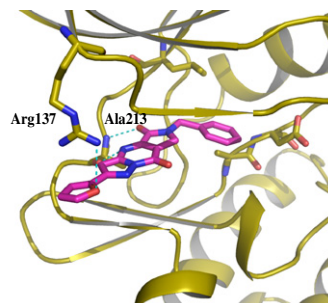
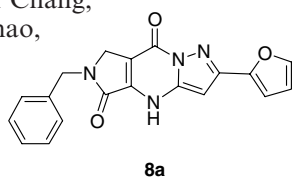
Type-2 diabetes (T2D) is a complex metabolic disease characterized by insulin resistance in the liver and peripheral tissues accompanied by a defect in pancreatic β-cell. Since their discovery three subtypes of Peroxisomes Proliferators Activated Receptors were identified namely PPARα, PPARγ and PPARβ/(δ). In this course, we were interested in designing novel PPARγ selective agonists and/or dual PPARα/γ agonists. Based on the typical topology of synthetic PPAR agonists, we focused our design approach on 4,4-dimethyl-1,2,3,4-tetrahydroquinoline as novel cyclic tail.



Aurora kinase A inhibitors: Identification, SAR exploration and molecular modeling of 6,7-dihydro-4*H*-pyrazolo-[1,5-*a*]pyrrolo[3,4-*d*]pyrimidine-5,8-dione scaffold

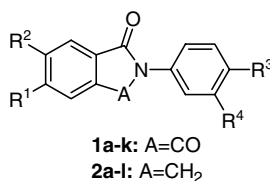
pp 1623–1627

Mohane Selvaraj Coumar, Jian-Sung Wu, Jiun-Shyang Leou, Uan-Kang Tan, Chung-Yu Chang, Teng-Yuan Chang, Wen-Hsing Lin, John T.-A. Hsu, Yu-Sheng Chao, Su-Ying Wu* and Hsing-Pang Hsieh*

**Isoindol-1,3-dione and isoindol-1-one derivatives with high binding affinity to β -amyloid fibrils**

pp 1628–1631

Hyu Ji Lee, Soo Jeong Lim, Seung Jun Oh, Dae Hyuk Moon, Dong Jin Kim, Jinsung Tae and Kyung Ho Yoo*

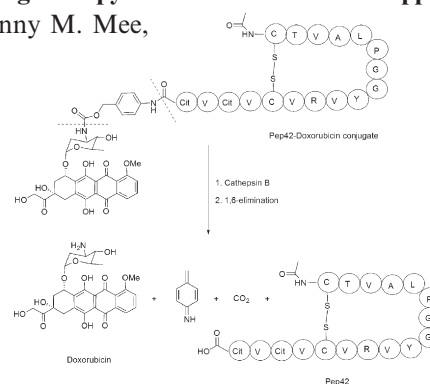


Based on the structural features of Indoprofen and PIB, a series of isoindol-1,3-diones **1a–k** and isoindol-1-ones **2a–l** were designed and synthesized. All the isoindolone derivatives showed very good binding affinities with K_i values in the subnanomolar range (0.42–0.94 nM) against aggregated A β 42 fibrils. Among them, several compounds exhibited excellent binding affinities (K_i = 0.42–0.49 nM) than those of Indoprofen (K_i = 0.52 nM) and PIB (K_i = 0.70 nM).

A cell-penetrating peptidic GRP78 ligand for tumor cell-specific prodrug therapy

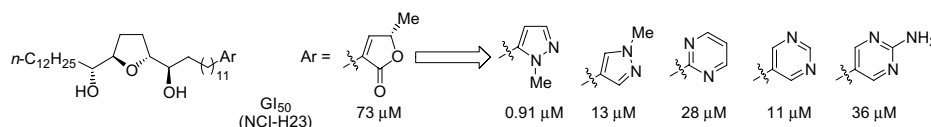
pp 1632–1636

Yoshiyuki Yoneda, Sebastian C. J. Steiniger, Kateřina Čapková, Jenny M. Mee, Ying Liu, Gunnar F. Kaufmann and Kim D. Janda*

**Synthesis of hybrid acetogenins, α,β -unsaturated- γ -lactone-free nitrogen-containing heterocyclic analogues, and their cytotoxicity against human cancer cell lines**

pp 1637–1641

Naoto Kojima, Tetsuya Fushimi, Naoyoshi Maezaki, Tetsuaki Tanaka* and Takao Yamori

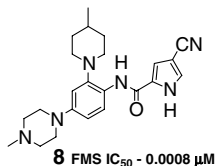


A series of nitrogen-containing heterocyclic analogues of solamin, a natural mono-THF acetogenin, have been synthesized and investigated for their cytotoxicity against 39 tumor cell lines.

Discovery of novel FMS kinase inhibitors as anti-inflammatory agents

pp 1642–1648

Carl R. Illig, Jinsheng Chen, Mark J. Wall, Kenneth J. Wilson, Shelley K. Ballentine, M. Jonathan Rudolph, Renee L. DesJarlais, Yanmin Chen, Carsten Schubert, Ioanna Petrounia, Carl S. Crysler, Christopher J. Molloy, Margery A. Chaikin, Carl L. Manthey, Mark R. Player, Bruce E. Tomczuk and Sanath K. Meegalla*

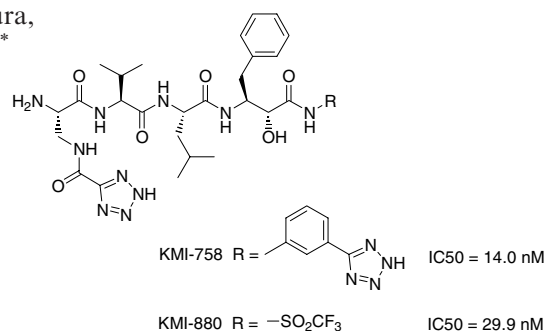


Discovery of a series of novel 2,4-disubstituted arylamides as potential anti-inflammatory agents is described. Compound **8** was utilized in an in vivo CIA model to evaluate the therapeutic potential of FMS inhibition.

BACE1 inhibitors: Optimization by replacing the P₁' residue with non-acidic moiety

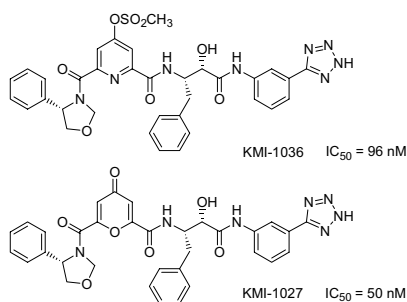
pp 1649–1653

Yoshio Hamada, Hamdy Abdel-Rahman, Abdellah Yamani, Jeffrey-Tri Nguyen, Monika Stochaj, Koushi Hidaka, Tooru Kimura, Yoshio Hayashi, Kazuki Saito, Shoichi Ishiura and Yoshiaki Kiso*

**Novel non-peptidic and small-sized BACE1 inhibitors**

pp 1654–1658

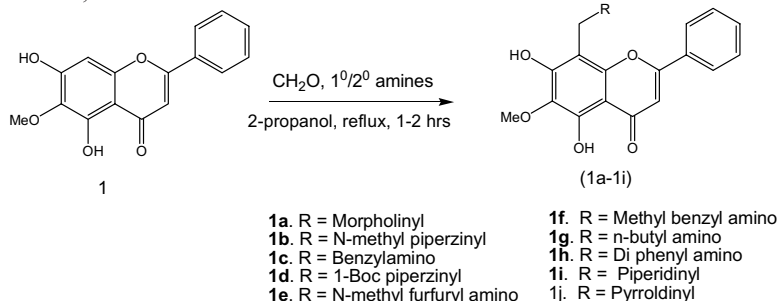
Yoshio Hamada, Hiroko Ohta, Naoko Miyamoto, Ryoji Yamaguchi, Abdellah Yamani, Koushi Hidaka, Tooru Kimura, Kazuki Saito, Yoshio Hayashi, Shoichi Ishiura and Yoshiaki Kiso*

**Synthesis and biological evaluation of novel 8-aminomethylated oroxylin A analogues as α-glucosidase inhibitors**

pp 1659–1662

T. Hari Babu, V. Rama Subba Rao, Ashok K. Tiwari, K. Suresh Babu, P. V. Srinivas, Amtul Z. Ali and J. Madhusudana Rao*

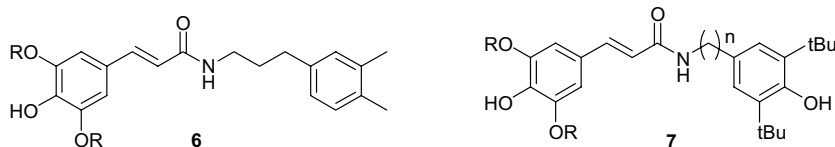
A series of 8-aminomethylated derivatives of oroxylin A were prepared by Mannich reaction and their α-glucosidase inhibition activities were studied.



Synthesis and antioxidant activities of 3,5-dialkoxy-4-hydroxycinnamamides

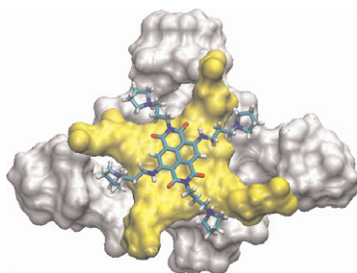
pp 1663–1667

Tae-Souk Kang, Hyang-Ok Jo, Woo-Kyu Park, Jong-Pyung Kim, Yasuo Konishi, Jae-Yang Kong, No-Sang Park and Young-Sik Jung*

**Tri- and tetra-substituted naphthalene diimides as potent G-quadruplex ligands**

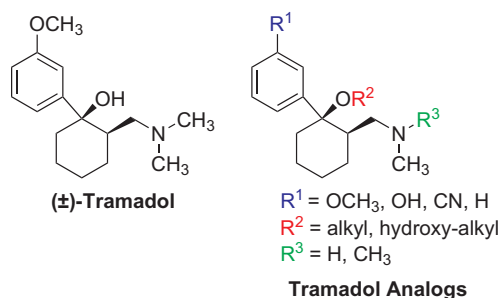
pp 1668–1673

Francisco Cuenca, Olga Greciano, Mekala Gunaratnam, Shozeb Haider, Deeksha Munnur, Rupesh Nanjunda, W. David Wilson and Stephen Neidle*

**In vitro and in vivo evaluation of *O*-alkyl derivatives of tramadol**

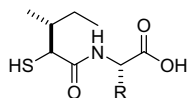
pp 1674–1680

Liming Shao,* Michael Hewitt, Thomas P. Jerussi, Frank Wu, Scott Malcolm, Paul Grover, Kevin Fang, Patrick Koch, Chris Senanayake, Nandkumar Bhongle, Seth Ribe, Roger Bakale and Mark Currie

**Thiol-based angiotensin-converting enzyme 2 inhibitors: P1' modifications for the exploration of the S1' subsite**

pp 1681–1687

David N. Deaton,* Kevin P. Graham, Jeffrey W. Gross and Aaron B. Miller



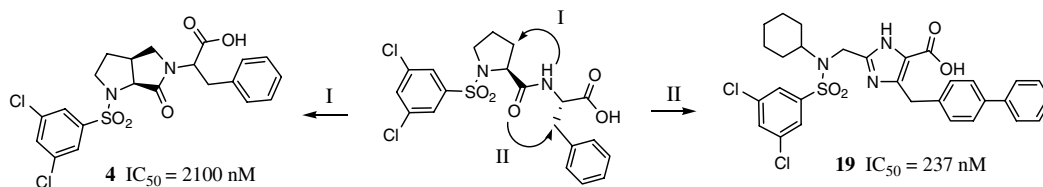
Explorations of the S1' subsite of ACE2 via modifications of the P1' methylene biphenyl moiety of thiol-based metalloprotease inhibitors led to improvements in ACE2 selectivity versus ACE and NEP, while maintaining potent ACE2 inhibition.



Constraining the amide bond in N-Sulfonylated dipeptide VLA-4 antagonists

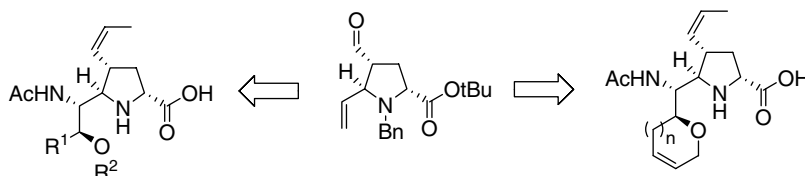
pp 1688–1691

Linda L. Chang,* Ginger X. Yang, Ermengilda McCauley, Richard A. Mumford, John A. Schmidt and William K. Hagmann

**Synthesis of potent pyrrolidine influenza neuraminidase inhibitors**

pp 1692–1695

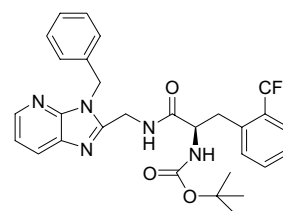
A. Chris Krueger,* Yibo Xu, Warren M. Kati, Dale J. Kempf, Clarence J. Maring, Keith F. McDaniel, Akhteruzzaman Molla, Debra Montgomery and William E. Kohlbrenner

**Imidazopyridines: A novel class of hNa_v1.7 channel blockers**

pp 1696–1701

Clare London,* Scott B. Hoyt, William H. Parsons, Brande S. Williams, Vivien A. Warren, Richard Tschirret-Guth, McHardy M. Smith, Birgit T. Priest, Erin McGowan, William J. Martin, Kathryn A. Lyons, Xiaohua Li, Bindhu V. Karanam, Nina Jochnowitz, Maria L. Garcia, John P. Felix, Brian Dean, Catherine Abbadie, Gregory J. Kaczorowski and Joseph L. Duffy

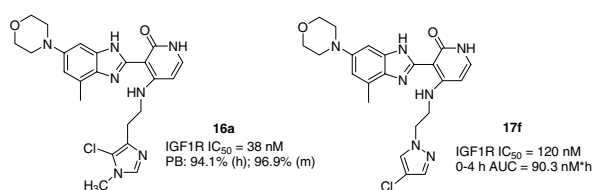
A series of imidazopyridines were evaluated as hNa_v1.7 blockers.

**2-(1*H*-Imidazol-4-yl)ethanamine and 2-(1*H*-pyrazol-1-yl)ethanamine side chain variants of the IGF-1R inhibitor BMS-536924**

pp 1702–1707

Mark G. Saulnier,* David B. Frennesson, Mark D. Wittman, Kurt Zimmermann, Upender Velaparthi, David R. Langley, Charles Struzynski, Xiaopeng Sang, Joan Carboni, Aixin Li, Ann Greer, Zheng Yang, Praveen Balimane, Marco Gottardis, Ricardo Attar and Dolatrai Vyas

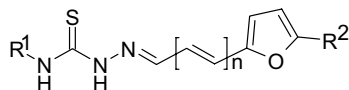
A series of IGF-1R inhibitors is disclosed, wherein the (*m*-chlorophenyl)-ethanol side chain of BMS-536924 (**1**) is replaced with a series of 2-(1*H*-imidazol-4-yl)ethanamine and 2-(1*H*-pyrazol-1-yl)ethanamine side chains. Some analogs show improved IGF-1R potency and oral exposure. Analogs from both series, **16a** and **17f**, show in vivo activity comparable to **1** in our constitutively activated IGF-1R Sal tumor model. This may be due to the improved protein binding in human and mouse serum for imidazole **16a** and the excellent oral exposure of pyrazole **17f**.



Thiosemicarbazones active against *Clostridium difficile*

pp 1708–1711

Cait Costello, Tarja Karpanen, Peter A. Lambert, Preena Mistry, Katy J. Parker, Daniel L. Rathbone,* Jiangmeng Ren, Laura Wheeldon and Tony Worthington

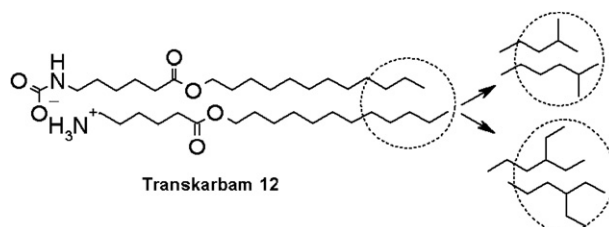


The synthesis and screening of a set of antimicrobial thiosemicarbazones is reported.

Transkarbams with terminal branching as transdermal permeation enhancers

pp 1712–1715

Jana Klimentová, Petr Kosák, Kateřina Vávrová,* Tomáš Holas, Jakub Novotný and Alexandr Hrabálek

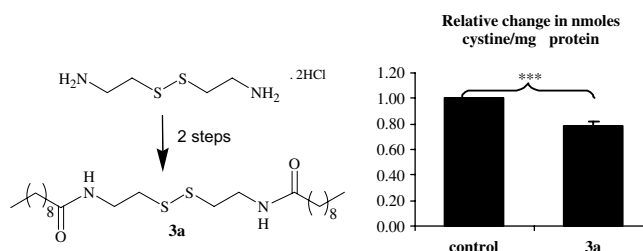


Series of Transkarbam 12 derivatives with terminal methyl or ethyl branching was prepared and their permeation-enhancing activity was compared to that of their linear analogues.

**A potential new prodrug for the treatment of cystinosis: Design, synthesis and in-vitro evaluation**

pp 1716–1719

Bridgeen McCaughan, Graeme Kay, Rachel M. Knott and Donald Cairns*



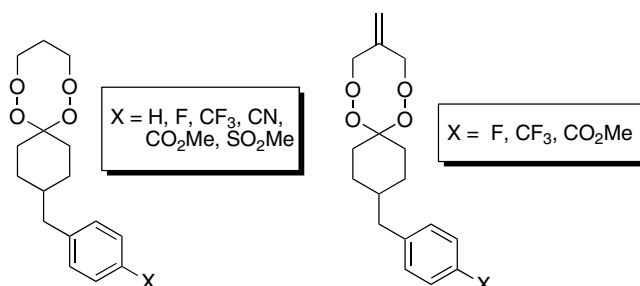
Prodrug **3a** has been shown to deplete levels of lysosomal cystine with negligible toxicity to cultured cells.

An efficient route into synthetically challenging bridged achiral 1,2,4,5-tetraoxanes with antimalarial activity

pp 1720–1724

Gemma L. Ellis, Richard Amewu, Charlotte Hall, Karen Rimmer, Steven A. Ward and Paul M. O'Neill*

Here we present an efficient route into the synthetically challenging bridged 1,2,4,5-tetraoxanes. These achiral derivatives display nanomolar antimalarial activity (IC_{50} = 40–100 nM).

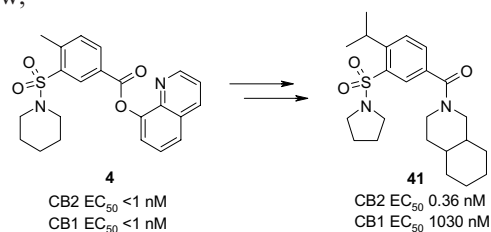


Arylsulfonamide CB2 receptor agonists: SAR and optimization of CB2 selectivity

pp 1725–1729

Monika Ermann,* Doris Riether,* Edward R. Walker, Innocent F. Mushi, James E. Jenkins, Beatriz Noya-Marino, Mark L. Brewer, Malcolm G. Taylor, Patricia Amouzegh, Stephen P. East, Brian W. Dymock, Mark J. Gemkow, Andreas F. Kahrs, Andreas Ebnet, Sabine Löbbe, Kathy O'Shea, Daw-Tsun Shih and David Thomson

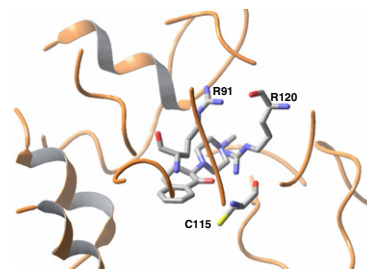
A high-throughput screening campaign resulted in the discovery of a highly potent dual cannabinoid receptor 1 (CB1) and 2 (CB2) agonist. Following a thorough SAR exploration, a series of selective CB2 full agonists were identified.

**2-Aminotetralones: Novel inhibitors of MurA and MurZ**

pp 1730–1734

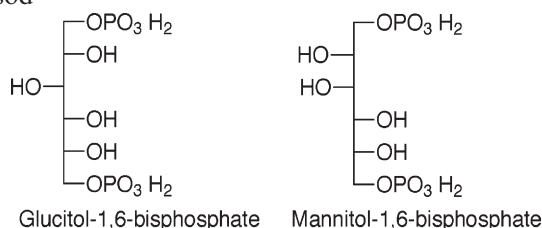
Colin J. Dunsmore, Keith Miller, Katy L. Blake, Simon G. Patching, Peter J. F. Henderson, James A. Garnett, William J. Stubbings, Simon E. V. Phillips, Deborah J. Palestrant, Joseph De Los Angeles, Jennifer A. Leeds, Ian Chopra and Colin W. G. Fishwick*

A new series of inhibitors of *Escherichia coli* MurA and *Staphylococcus aureus* MurA and MurZ having useful antibacterial properties are reported.

**Separate synthesis and evaluation of glucitol bis-phosphate and mannitol bis-phosphate, as competitive inhibitors of fructose bis-phosphate aldolases**

pp 1735–1737

Charles-Gabin Mabiala-Bassiloua, Magdalena Zwolinska, Helene Therisod, Jurgen Sygusch and Michel Therisod*



Glucitol and mannitol-1,6-bis-phosphate were separately synthesized and evaluated as inhibitors of various fructose bis-phosphate aldolases.

**OTHER CONTENTS**

Summary of instructions to authors

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i+ Supplementary data available via ScienceDirect

COVER

Overlay of Corazolol (aqua carbon atoms, ball and stick) and the top-ranked hits from docking a database of proprietary compounds into the X-ray structure of the β 2-Adrenergic receptor. Structures shown (grey carbon atoms, stick) are taken from the top-ranked 100 hits after removal of compounds with the traditional β -blocker alkyl motif. [Topiol, S.; Sabio, M. *Bioorg. Med. Chem. Lett.*, **2008**, 18, 1598].

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