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# Bioorganic & Medicinal Chemistry Letters

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## Bioorganic & Medicinal Chemistry Letters Volume 20, Issue 19, 2010

### Contents

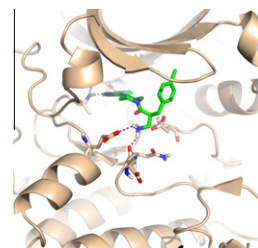
#### ARTICLES

##### Discovery of pyrrolopyrimidine inhibitors of Akt

pp 5607–5612

James F. Blake\*, Nicholas C. Kallan, Dengming Xiao, Rui Xu, Josef R. Bencsik, Nicholas J. Skelton, Keith L. Spencer, Ian S. Mitchell, Richard D. Woessner, Susan L. Gloor, Tyler Risom, Stefan D. Gross, Matthew Martinson, Tony H. Morales, Guy P. A. Vigers, Barbara J. Brandhuber

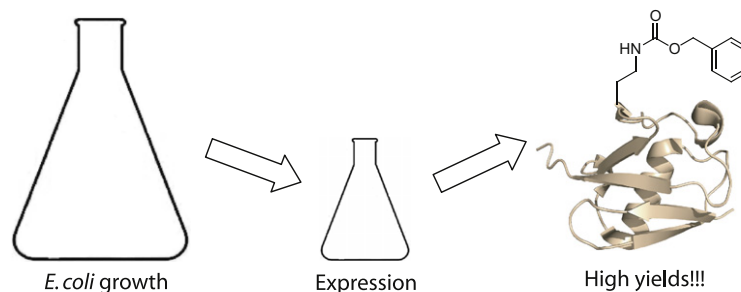
The discovery and optimization of a series of pyrrolopyrimidine based protein kinase B (Pkb/Akt) inhibitors discovered via HTS and structure based drug design is reported. The compounds demonstrate potent inhibition of all three Akt isoforms and knockdown of phospho-PRAS40 levels in LNCaP cells and tumor xenografts.



##### Condensed *E. coli* cultures for highly efficient production of proteins containing unnatural amino acids

pp 5613–5616

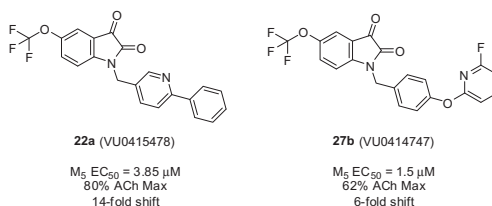
Jia Liu, Carlos A. Castañeda, Bryan J. Wilkins, David Fushman, T. Ashton Cropp\*



##### Heterobiaryl and heterobiaryl ether derived M<sub>5</sub> positive allosteric modulators

pp 5617–5622

Thomas M. Bridges, J. Phillip Kennedy, Corey R. Hopkins, P. Jeffrey Conn, Craig W. Lindsley\*

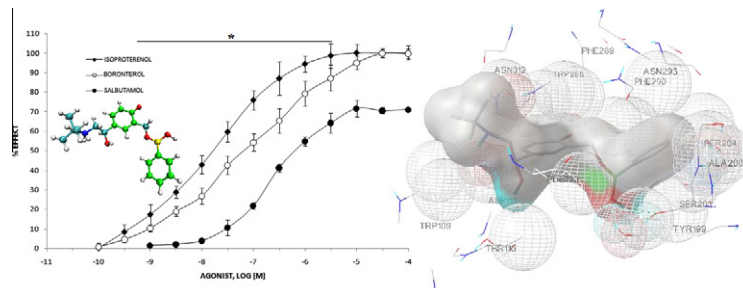


This Letter describes a chemical lead optimization campaign directed at VU0238429, the first M<sub>5</sub>-preferring positive allosteric modulator (PAM), discovered through analog work around VU0119498, a pan G<sub>q</sub> mAChR M<sub>1</sub>, M<sub>3</sub>, M<sub>5</sub> PAM. An iterative parallel synthesis approach was employed to incorporate basic heterocycles to improve physicochemical properties.

**Design, synthesis and in vitro evaluation of (R)-4-(2-(tert-butylamino)-1-hydroxyethyl)-2-(hydroxymethyl)phenyl hydrogen phenylboronate: A novel salbutamol derivative with high intrinsic efficacy on the  $\beta_2$  adrenoceptor**

pp 5623–5629

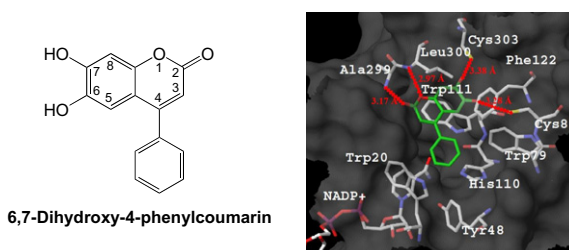
Marvin A. Soriano-Ursúa\*, José Correa-Basurto, Ignacio Valencia-Hernández, Marcos A. Amezcua-Gutiérrez, Itzia I. Padilla-Martínez, José G. Trujillo-Ferrara\*



**6,7-Dihydroxy-4-phenylcoumarin as inhibitor of aldose reductase 2**

pp 5630–5633

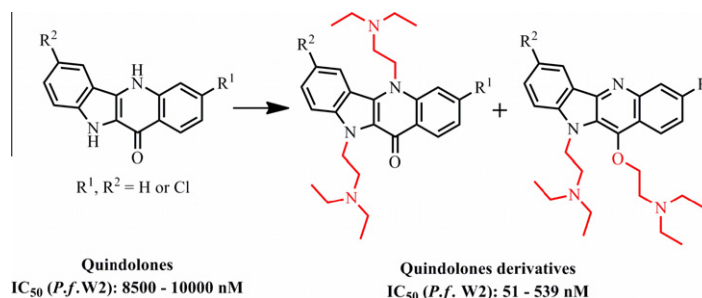
Atsushi Kato\*, Kaori Kobayashi, Kayo Narukawa, Yuka Minoshima, Isao Adachi, Shuichi Hirono, Robert J. Nash



**Bis-alkylamine quindolone derivatives as new antimalarial leads**

pp 5634–5637

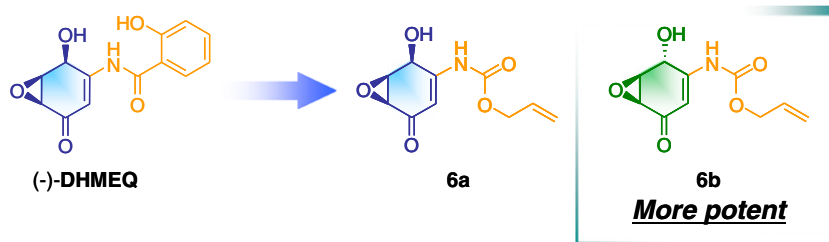
João Lavrado, Kaamil Gani, Pedro A. Nobre, Sofia A. Santos, Paula Figueiredo, Dinora Lopes, Virgílio do Rosário, Jiri Gut, Philip J. Rosenthal, Rui Moreira, Alexandra Paulo\*



**A new NF- $\kappa$ B inhibitor based on the amino-epoxyquinol core of DHMEQ**

pp 5638–5642

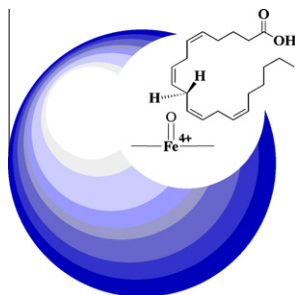
Tsuyoshi Saitoh, Chika Shimada, Masatoshi Takeiri, Mitsuhiro Shiino, Shigeru Ohba, Rika Obata, Yuichi Ishikawa, Kazuo Umezawa, Shigeru Nishiyama\*



**Effect of unsaturation in fatty acids on the binding and oxidation by myeloperoxidase: Ramifications for the initiation of atherosclerosis**

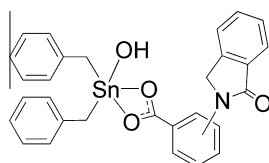
pp 5643–5648

Amanda L. Clark, Kathryn Mansfield Matera\*

**2-, 3-, and 4-(1-Oxo-1*H*-2,3-dihydroisoindol-2-yl)benzoic acids and their corresponding organotin carboxylates: Synthesis, characterization, fluorescent, and biological activities**

pp 5649–5652

Shuang-Lian Cai, Yong Chen, Wen-Xia Sun, Hui Li, Yun Chen\*, Shi-Shan Yuan\*

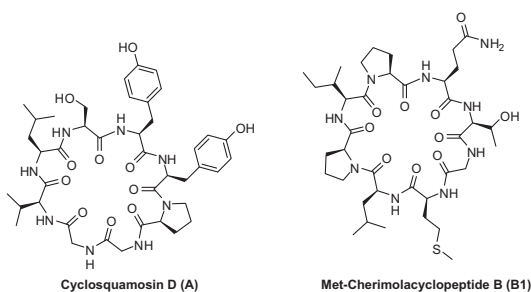


Synthesis of organotin complexes  $\text{Sn}(\text{OH})(\text{bz})_2\text{L}$  (bz = benzyl, HL = 2-, 3-, or 4-(1-oxo-1*H*-2,3-dihydroisoindol-2-yl)benzoic acid) and the evaluation of their antifungal and antibacterial activity is reported.

**Parallel synthesis and anti-inflammatory activity of cyclic peptides cyclosquamosin D and Met-cherimolacyclopeptide B and their analogs**

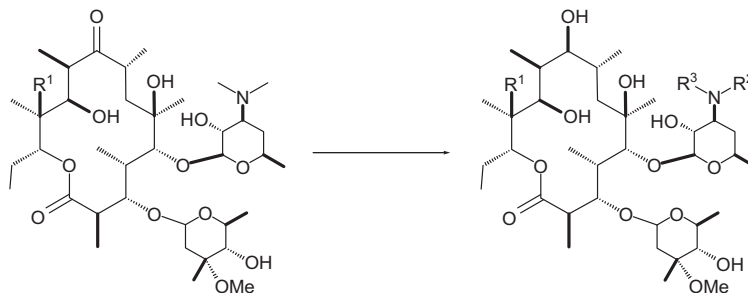
pp 5653–5657

Afef Dellai, Igor Maricic, Vipin Kumar, Sergey Arutyunyan, Abderrahman Bouraoui, Adel Nefzi\*

**9-Dihydroerythromycins as non-antibiotic motilin receptor agonists**

pp 5658–5661

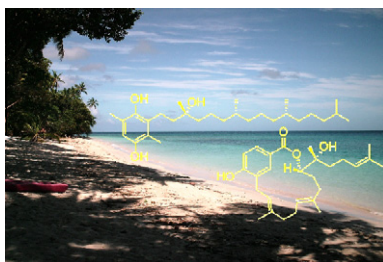
Yaoquan Liu\*, Yong Li, Yue Chen, Hao Zheng, Mark Claypool, David C. Myles, Christopher W. Carreras



**Unusual antimalarial meroditerpenes from tropical red macroalgae**

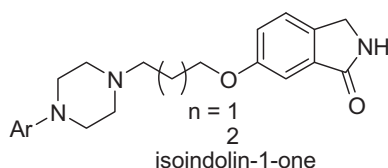
pp 5662–5665

E. Paige Stout, Jacques Prudhomme, Karine Le Roch, Craig R. Fairchild, Scott G. Franzblau, William Aalbersberg, Mark E. Hay, Julia Kubanek\*

**6-Alkoxyisoindolin-1-one based dopamine D<sub>2</sub> partial agonists as potential antipsychotics**

pp 5666–5669

David A. Favor\*, James J. Powers, Andrew D. White, Lawrence W. Fitzgerald, Vincent Groppi, Kevin A. Serpa

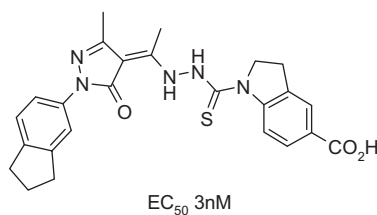


A series of 6-alkoxyisoindolin-1-ones are presented as potential antipsychotics. The in vitro pharmacological profile includes D<sub>2</sub> partial agonism (30–55%), 5-HT<sub>1A</sub> partial agonism (60–90%), and 5-HT<sub>2A</sub> antagonism. Selected compounds in this series displayed good in vivo activity and potency.

**Novel indoline-1- or 3,4-dihydroquinoline-1(2H)-substituted carbothiohydrazides as TPO receptor agonists**

pp 5670–5672

Peng Cho Tang\*, He Jun Lu, Yi Qian Chen, Hao Zheng, Peng Song, Li Wang, Qiang Qin, Ai Shen Gong

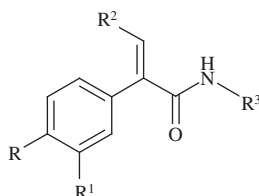


Novel series of carbohydrazides as small molecule TPO receptor agonists are reported.

**2,3-Disubstituted acrylamides as potent glucokinase activators**

pp 5673–5676

Achyutharao Sidduri\*, Joseph S. Grimsby, Wendy L. Corbett, Ramakanth Sarabu, Joseph F. Grippo, Jianping Lou, Robert F. Kester, Mark Dvorozniak, Linda Marcus, Cheryl Spence, Jagdish K. Racha, David J. Moore

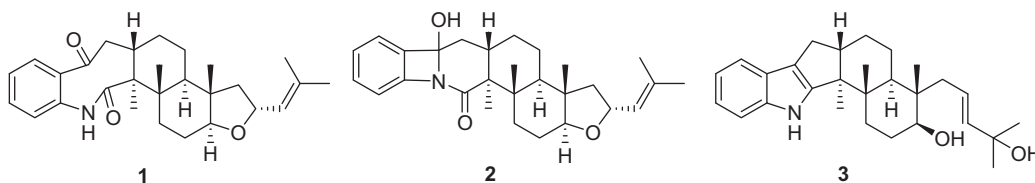


The phenylacetamide **1** represents the archtypical glucokinase activator (GKA) in which only the *R*-isomer is active. In order to probe whether the chiral center could be replaced, we prepared a series of olefins **2** and show in the present work that these compounds represent a new class of GKAs. Surprisingly, the SAR of the new series paralleled that of the saturated derivatives with the exception that there was greater tolerance for larger alkyl and cycloalkyl groups at R<sup>2</sup> region in comparison to the phenylacetamides. In normal Wistar rats, the 2,3-disubstituted acrylamide analog **10** was well absorbed and demonstrated robust glucose lowering effects.

**Indoloditerpenes from an algiculous isolate of *Aspergillus oryzae***

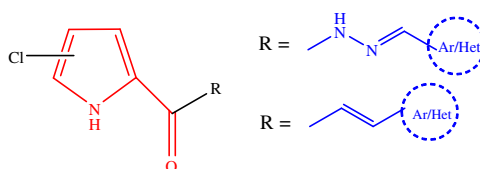
pp 5677–5680

Ming-Feng Qiao, Nai-Yun Ji\*, Xiang-Hong Liu, Ke Li, Qing-Mei Zhu, Qin-Zhao Xue

**Synthesis and evaluation of novel chloropyrrole molecules designed by molecular hybridization of common pharmacophores as potential antimicrobial agents**

pp 5681–5685

Rajesh A. Rane, Vikas N. Telvekar\*

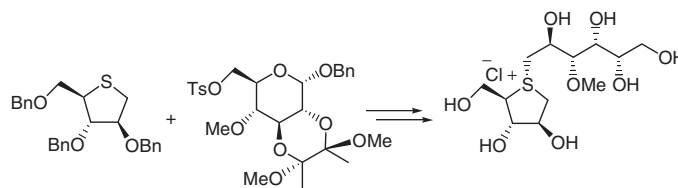


In an attempt to identify new potential lead as antimicrobial agent, 31 novel chloropyrrole derivatives of aryl hydrazones and chalcones incorporating common pharmacophore of pyoluteorin derivatives were synthesized.

**Probing the active-site requirements of human intestinal N-terminal maltase glucoamylase: The effect of replacing the sulfate moiety by a methyl ether in ponkoranol, a naturally occurring  $\alpha$ -glucosidase inhibitor**

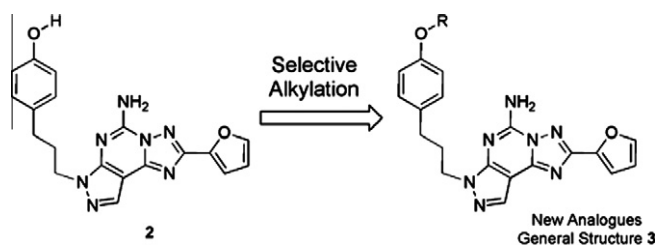
pp 5686–5689

Razieh Eskandari, Kyra Jones, David R. Rose, B. Mario Pinto\*

**Synthesis and evaluation of 1,2,4-triazolo[1,5-c]pyrimidine derivatives as  $A_{2A}$  receptor-selective antagonists**

pp 5690–5694

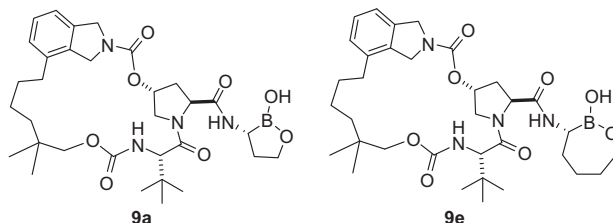
Bidhan A. Shinkre, T. Santhosh Kumar, Zhan-Guo Gao, Francesca Deflorian, Kenneth A. Jacobson\*, William C. Trenkle\*



**Novel macrocyclic HCV NS3 protease inhibitors derived from  $\alpha$ -amino cyclic boronates**

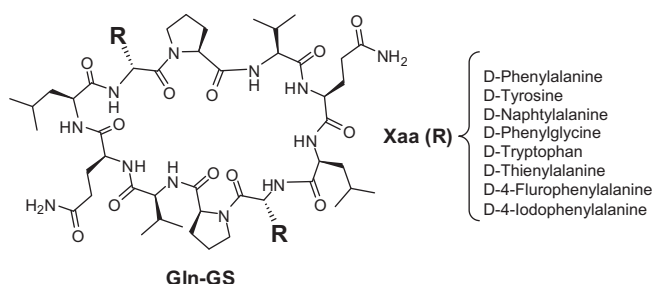
pp 5695–5700

Xianfeng Li\*, Yong-Kang Zhang, Yang Liu, Charles Z. Ding, Yasheen Zhou, Qun Li, Jacob J. Plattner, Stephen J. Baker, Suoming Zhang, Wieslaw M. Kazmierski\*, Lois L. Wright, Gary K. Smith, Richard M. Grimes, Renae M. Crosby, Katrina L. Creech, Luz H. Carballo, Martin J. Slater, Richard L. Jarvest, Pia Thommes, Julia A. Hubbard, Maire A. Convery, Pamela M. Nassau, William McDowell, Tadeusz J. Skarzynski, Xuelei Qian, Dazhong Fan, Liang Liao, Zhi-Jie Ni, Lewis E. Pennicott, Wuxin Zou, Jon Wright

**On resin amino acid side chain attachment strategy for the head to tail synthesis of new glutamine containing gramicidin-S analogs and their antimicrobial activity**

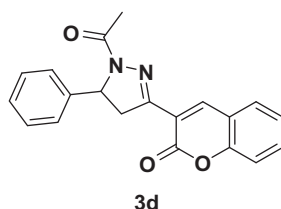
pp 5701–5704

Safa Derbal, Mary Hensler, Weiqin Fang, Victor Nizet, Kamel Ghedira, Adel Nefzi\*

**Synthesis and molecular docking study of novel coumarin derivatives containing 4,5-dihydropyrazole moiety as potential antitumor agents**

pp 5705–5708

Xin-Hua Liu, Hui-Feng Liu, Jin Chen, Yang Yang, Bao-An Song, Lin-Shan Bai, Jing-Xin Liu, Hai-Liang Zhu\*, Xing-Bao Qi

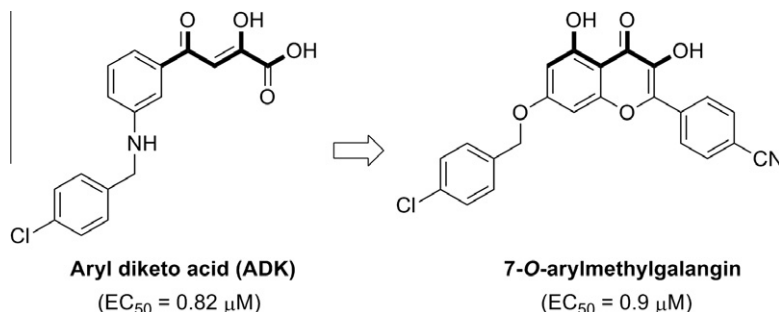


Novel coumarin derivatives containing 4,5-dihydropyrazole moiety as potential telomerase inhibitors were synthesized. The bioassay tests showed that compound **3d** exhibited potentially high activity against human gastric cancer cell SGC-7901 with the  $IC_{50}$  value was  $2.69 \pm 0.60$   $\mu$ g/mL.

**7-O-Arylmethylgalangin as a novel scaffold for anti-HCV agents**

pp 5709–5712

Hyo Seon Lee, Kwang-su Park, Chaewoon Lee, Bokhui Lee, Dong-Eun Kim, Youhoon Chong\*

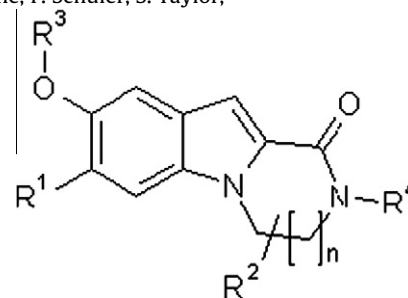


**Discovery of potent and selective histamine H<sub>3</sub> receptor inverse agonists based on the 3,4-dihydro-2H-pyrazino[1,2-a]indol-1-one scaffold**

pp 5713–5717

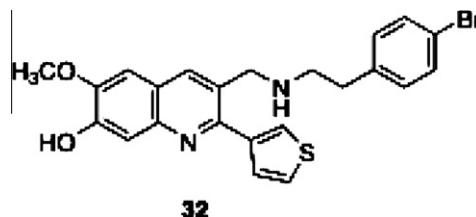
H. G. F. Richter\*, C. Freichel, J. Huwyler, T. Nakagawa, M. Nettekoven, J.-M. Plancher, S. Raab, O. Roche, F. Schuler, S. Taylor, C. Ullmer, R. Wiegand

A novel series of potent and selective histamine H<sub>3</sub> receptor inverse agonists has been discovered. Several analogues showed excellent physicochemical properties, low CYP450 inhibition potential and high stability in liver microsomes.

**Synthesis and SAR of 2-aryl-3-aminomethylquinolines as agonists of the bile acid receptor TGR5**

pp 5718–5721

Mark R. Herbert, Dana L. Siegel, Lena Staszewski, Charmagne Cayanan, Urmi Banerjee, Sangeeta Dhamija, Jennifer Anderson, Amy Fan, Li Wang, Peter Rix, Andrew K. Shiau, Tadimeti S. Rao, Stewart A. Noble, Richard A. Heyman, Eric Bischoff, Mausumee Guha, Ayman Kabakibi, Anthony B. Pinkerton\*

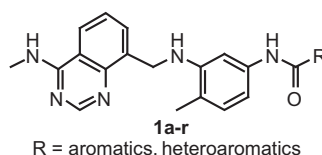


Optimization of a screening hit from uHTS led to the discovery of TGR5 agonist **32**, which was shown to have activity in a rodent model for diabetes.

**Synthesis of aminoquinazoline derivatives and their antiproliferative activities against melanoma cell line**

pp 5722–5725

Junsang Lee, Bong Soo Nam, Hwan Kim, Chang-Hyun Oh, So Ha Lee, Seung Joo Cho, Tae Bo Sim, Jung-Mi Hah, Dong Jin Kim, Jinsung Tae\*, Kyung Ho Yoo\*

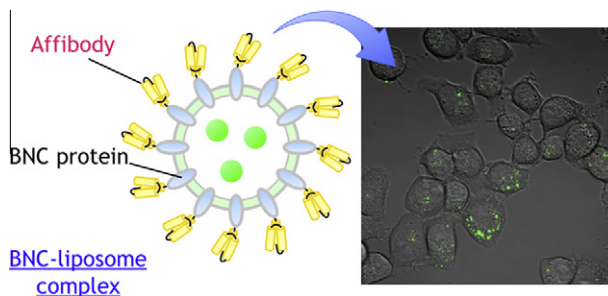


The synthesis of a novel series of aminoquinazoline derivatives **1a-r** and their antiproliferative activities against A375 human melanoma cell line were described. Among them, six compounds showed superior antiproliferative activities to Sorafenib as a reference compound. In particular, the representative compound **1q** bearing chromen-4-one moiety exhibited excellent antiproliferative activity (IC<sub>50</sub> = 0.006 μM) and good selectivity over HS27 fibroblast cell line.

**Affibody-displaying bionanocapsules for specific drug delivery to HER2-expressing cancer cells**

pp 5726–5731

Takuya Shishido, Hiroaki Mieda, Sang Youn Hwang, Yuya Nishimura, Tsutomu Tanaka, Chiaki Ogino, Hideki Fukuda, Akihiko Kondo\*

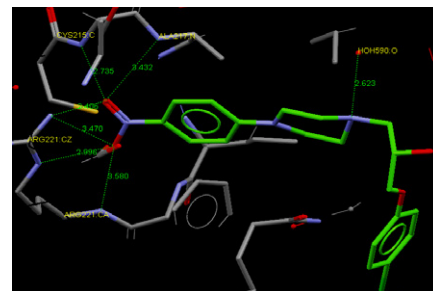
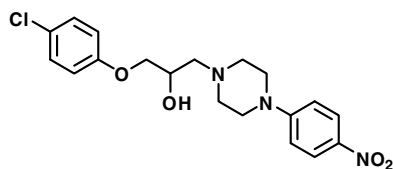


### Design, synthesis and docking studies on phenoxy-3-piperazin-1-yl-propan-2-ol derivatives as protein tyrosine phosphatase 1B inhibitors

pp 5732–5734

Swati Gupta, Gyanendra Pandey, Neha Rahuja, Arvind K. Srivastava, Anil K. Saxena\*

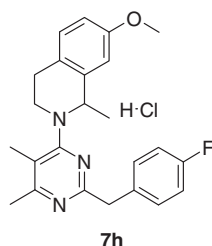
Interaction of the **5b** (green) with the amino acids in the active site of PTP1B (PDB ID 2F70).



### Novel pyrimidines as acid pump antagonists (APAs)

pp 5735–5738

Young Ae Yoon, Chan Sun Park, Myung Hun Cha, Hyunho Choi, Jae Young Sim, Jae Gyu Kim\*

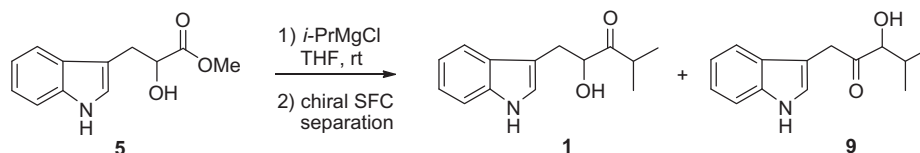


The synthesis of the potent acid pump antagonist **7h** ( $IC_{50}$  = 52 nM) is reported.

### A concise, total synthesis and antibacterial evaluation of 2-hydroxy-1-(1H-indol-3-yl)-4-methylpentan-3-one

pp 5739–5742

Son T. Nguyen\*, Michelle M. Butler, Laszlo Varady, Norton P. Peet, Terry L. Bowlin



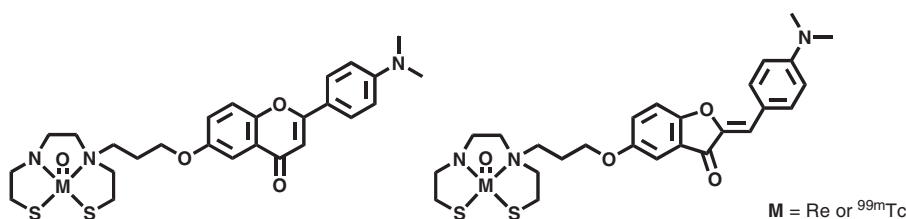
Treatment of racemic 2-hydroxy-3-(1H-indol-3-yl)propionic acid methyl ester (**5**) with isopropyl magnesium chloride provided the title compound **1** and its isomer, 3-hydroxy-1-(1H-indol-3-yl)-4-methylpentan-2-one (**9**). Both enantiomers (>96% ee) of each component were obtained via semi-preparative chiral supercritical fluid chromatography (SFC). In contrast to previous reports, these compounds, as well as their acetate derivatives, were not active or very weakly active against 16 bacterial strains, including *Escherichia coli*, *Bacillus subtilis* and *Staphylococcus aureus*.



### <sup>99m</sup>Tc/Re complexes based on flavone and aurone as SPECT probes for imaging cerebral β-amyloid plaques

pp 5743–5748

Masahiro Ono\*, Ryoichi Ikeoka, Hiroyuki Watanabe, Hiroyuki Kimura, Takeshi Fuchigami, Mamoru Haratake, Hideo Saji, Morio Nakayama\*

M = Re or <sup>99m</sup>Tc

Two <sup>99m</sup>Tc complexes based on flavone and aurone were tested as potential probes for imaging of cerebral β-amyloid plaques.

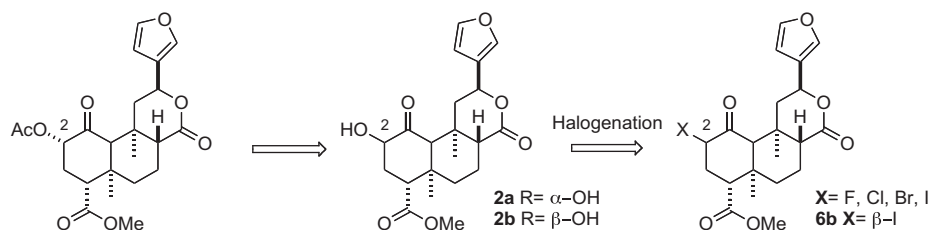




**Synthesis and biological evaluation of C-2 halogenated analogs of salvinorin A**

pp 5749–5752

David Y.W. Lee\*, Lu Yang, Wei Xu, Gang Deng, Lin Guo, Lee-Yuan Liu-Chen

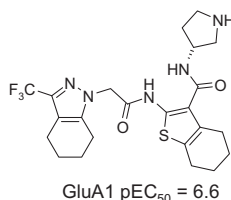


We have carried out the synthesis and biological evaluation of C-2 halogenation analogs of salvinorin A. KOPR binding and functional studies reveal  $\beta$  isomer in general binds better than  $\alpha$  isomer and affinity to the kappa receptor increases with atomic radius ( $I > Br > Cl > F$ ) with the exception of iodinated analog **6b**, which is a partial agonist with  $E_{max}$  of 46% of U50,488H.

**A novel series of positive modulators of the AMPA receptor: Discovery and structure based hit-to-lead studies**

pp 5753–5756

Craig Jamieson\*, Stephanie Basten, Robert A. Campbell, Iain A. Cumming, Kevin J. Gillen, Jonathan Gillespie, Bert Kazemier, Michael Kiczun, Yvonne Lamont, Amanda J. Lyons, John K. F. Maclean, Elizabeth M. Moir, John A. Morrow, Marianthi Papakosta, Zoran Rankovic, Lynn Smith

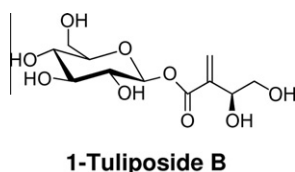


Starting from an HTS hit, the evolution of lead compound **22**, a positive allosteric modulator of the AMPA receptor is described using structure based drug design.

**Structure–activity relationships of tulipalines, tuliposides, and related compounds as inhibitors of MurA**

pp 5757–5762

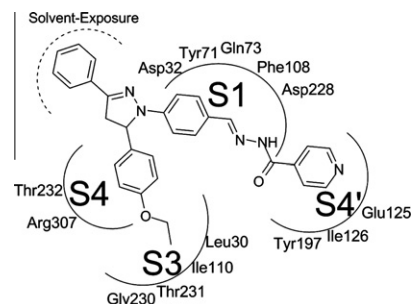
Thomas Mendgen, Therese Scholz, Christian D. Klein\*

**Identification of a sub-micromolar, non-peptide inhibitor of  $\beta$ -secretase with low neural cytotoxicity through in silico screening**

pp 5763–5766

Weijun Xu, Gang Chen, Weiliang Zhu\*, Zhili Zuo\*

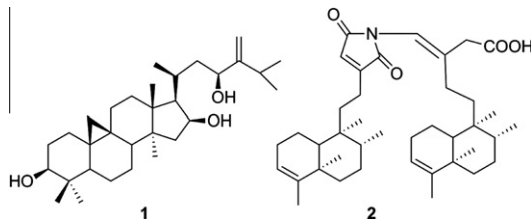
Twenty compounds identified via in silico were tested in BACE-1 FRET assays and methylthiazolotetrazolium (MTT) cytotoxicity experiment. Two compounds: **2** and **15** demonstrated IC<sub>50</sub> values of 0.53 and 9.4  $\mu$ M in addition to low toxic effect to the neuroblastoma cells.



### Cytotoxic cycloartane triterpene and rare isomeric bisclerodane diterpenes from the leaves of *Polyalthia longifolia* var. *pendula*

pp 5767–5771

Konen V. Sashidhara\*, Suriya P. Singh, Ruchir Kant, Prakas R. Maulik, Jayanta Sarkar, Sanjeev Kanojiya, K. Ravi Kumar



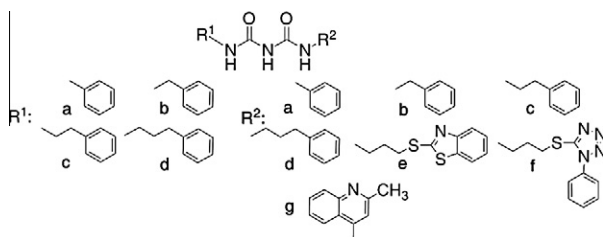
Two new compounds named Longitriol (**1**) and Longimide A (**2**) together with previously known Longimide B (**3**) were isolated from the leaves of *Polyalthia longifolia* var. *pendula*. Compounds **1** and **2** were tested in vitro against four human cancer cell lines and found to be most active against cervical carcinoma cell lines with IC<sub>50</sub> value of 10.03 and 4.12 µg/mL, respectively.



### Synthesis and cytotoxicity of some biurets against human breast cancer T47D cell line

pp 5772–5775

Shamileh Fouladdel, Ali Khalaj, Neda Adibpour\*, Ebrahim Azizi



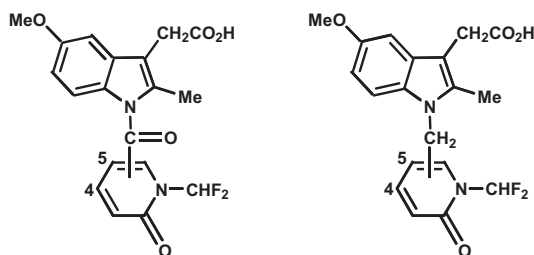
Design, synthesis and cytotoxicity of several biurets substituted at N and N' with different combination of R<sup>1</sup> and R<sup>2</sup> groups on human breast cancer T47D cell line are described.



### Synthesis and biological evaluation of indomethacin analogs possessing a *N*-difluoromethyl-1,2-dihydropyrid-2-one ring system: A search for novel cyclooxygenase and lipoxygenase inhibitors

pp 5776–5780

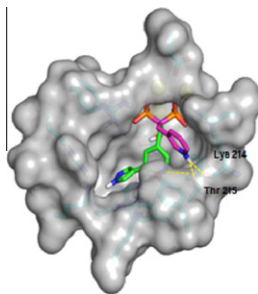
Morshed A. Chowdhury, Zhangjian Huang, Khaled R. A. Abdellatif, Ying Dong, Gang Yu, Carlos A. Velázquez, Edward E. Knaus\*



### Novel bisphosphonate inhibitors of the human farnesyl pyrophosphate synthase

pp 5781–5786

Joris W. De Schutter, Serge Zaretsky, Sarah Welbourn, Arnim Pause, Youla S. Tsantrizos\*

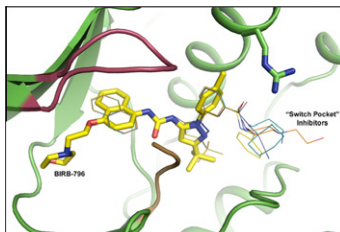


A structure-based approach was pursued in designing novel bisphosphonate active site inhibitors of the human farnesyl pyrophosphate synthase (hFPPS) that compete for binding with both IPP and risnedronate.

**Biochemical and biophysical characterization of unique switch pocket inhibitors of p38 $\alpha$** 

pp 5787–5792

Steven L. Swann\*, Philip J. Merta, Lemma Kifle, Duncan Groebe, Kathy Sarris, Philip J. Hajduk, Chaohong Sun



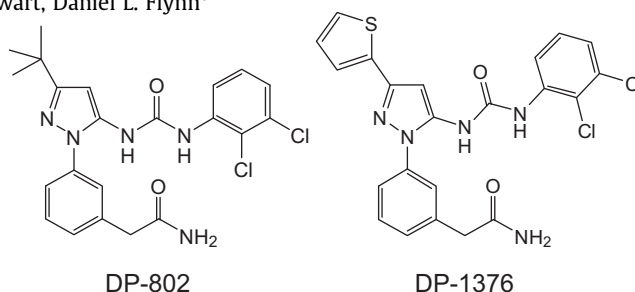
Herein we describe the identification and characterization of a class of molecules that are believed to extend into a region of p38 known as the 'switch pocket'. Although these molecules lack a canonical hinge binding motif, they show  $K_i$  values as low as 100 nM against p38 $\alpha$ . It is also clear that molecules that interact with this region of the protein demonstrate different binding kinetics than a canonical ATP mimetic, as well as a wide range of kinome profiles. Thus, the switch pocket presents new opportunities for kinome selectivity which could result in unique biochemical responses and offer new opportunities in the field of kinase drug discovery.

**Switch control pocket inhibitors of p38-MAP kinase. Durable type II inhibitors that do not require binding into the canonical ATP hinge region**

pp 5793–5798

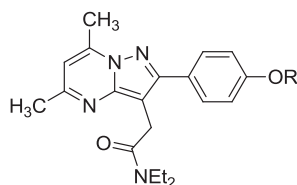
Yu Mi Ahn, Michael Clare, Carol L. Ensinger, Molly M. Hood, John W. Lord, Wei-Ping Lu, David F. Miller, William C. Patt, Bryan D. Smith, Lakshminarayana Vogeti, Michael D. Kaufman, Peter A. Petillo, Scott C. Wise, Jan Abendroth, Lawrence Chun, Robin Clark, Michael Feese, Hidong Kim, Lance Stewart, Daniel L. Flynn\*

Switch control pocket inhibitors of p38- $\alpha$  kinase are described. X-ray crystallography reveals a unique mode of binding to the switch control pocket residues arginine 67 or arginine 70.

**Pyrazolo[1,5-a]pyrimidine acetamides: 4-Phenyl alkyl ether derivatives as potent ligands for the 18 kDa translocator protein (TSPO)**

pp 5799–5802

Aaron Reynolds, Raphy Hanani, David Hibbs, Annelaure Damont, Eleonora Da Pozzo, Silvia Selleri, Frédéric Dollé, Claudia Martini, Michael Kassiou\*

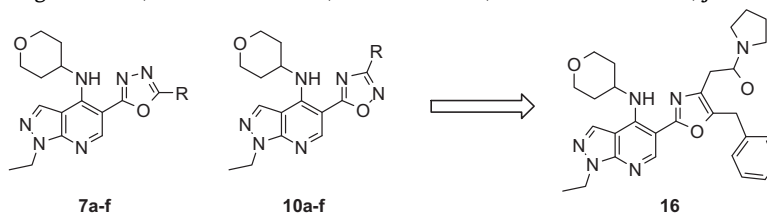


The synthesis of pyrazolo[1,5-a]pyrimidine acetamides, in vitro receptor binding and their ability to increase pregnenolone biosynthesis is reported.

**Pyrazolopyridines as potent PDE4B inhibitors: 5-Heterocycle SAR**

pp 5803–5806

Charlotte J. Mitchell\*, Stuart P. Ballantine, Diane M. Coe, Caroline M. Cook, Christopher J. Delves, Mike D. Dowle, Chris D. Edlin, J. Nicole Hamblin, Stuart Holman, Martin R. Johnson, Paul S. Jones, Sue E. Keeling, Michael Kranz, Mika Lindvall, Fiona S. Lucas, Margarete Neu, Yemisi E. Solanke, Don O. Somers, Naimisha A. Trivedi, Joanne O. Wiseman

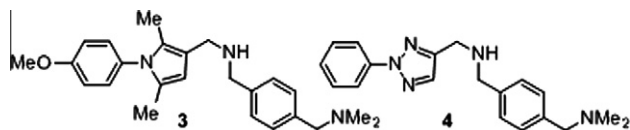


Several series of pyrazolo[3,4-b]pyridine-5-heterocycles have been identified as potent inhibitors of PDE4B. Molecular modelling and X-ray crystallography on early analogues **7a-f** and **10a-f** led to the design of pyrazolo[3,4-b]pyridine-5-oxazole **16**, which shows sub-nM potency against PDE4B. The crystal structure of **16** bound to PDE4B is also described.

**Novel pyrrole- and 1,2,3-triazole-based 2,3-oxidosqualene cyclase inhibitors**

pp 5807–5810

Takumi Watanabe\*, Yoji Umezawa, Yoshikazu Takahashi, Yuzuru Akamatsu



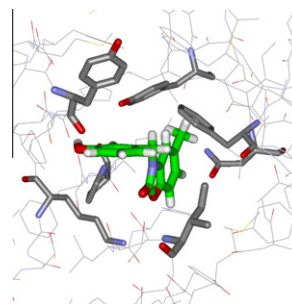
Pyrrole- and 1,2,3-triazole-based 2,3-oxidosqualene cyclase (OSC) inhibitors **3** and **4** were discovered by conducting a virtual screening, a docking study based on the crystallographic structure of OSC, and biological assays. A preliminary structure–activity–relationship study of **3** was also conducted.

**Optimization of *N*-benzyl-benzoxazol-2-ones as receptor antagonists of macrophage migration inhibitory factor (MIF)**

pp 5811–5814

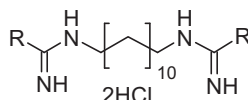
Alissa A. Hare, Lin Leng, Sunilkumar Gandavadi, Xin Du, Zoe Cournia, Richard Bucala\*, William L. Jorgensen\*

Substituted benzoxazol-2-ones are reported as antagonists of the signaling by macrophage migration inhibitory factor (MIF). One of the potent analogues is shown to attenuate MIF-dependent ERK1/2 phosphorylation in human synovial fibroblasts.

**Reverse-benzamidine antimalarial agents: Design, synthesis, and biological evaluation**

pp 5815–5817

Olivier Berger, Sharon Wein, Jean-Frederic Duckert, Marjorie Maynadier, Siham El Fangour, Roger Escale, Thierry Durand, Henri Vial, Yen Vo-Hoang\*



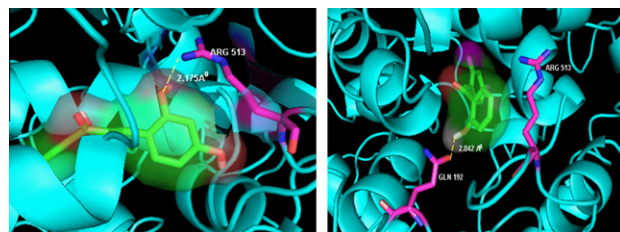
The antimalarial potencies and the RSA of bis-*N*-alkylamidines and a new series of reverse-benzamidine derivatives are reported.

**Fluorinated 2'-hydroxychalcones as garcinol analogs with enhanced antioxidant and anticancer activities**

pp 5818–5821

Subhash Padhye, Aamir Ahmad, Nikhil Oswal, Prasad Dandawate, Rukhsana A. Rub, Jyoti Deshpande, K. Venkateswara Swamy, Fazlul H. Sarkar\*

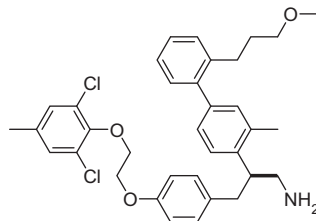
A series of hydroxyl- and fluoro-substituted 2'-hydroxychalcones have been synthesized as garcinol analogs and structurally characterized. The compounds were evaluated for their SOD activities and molecular docking studies were performed on them in COX-2 protein cavity. The fluorinated compounds were found to be more potent than their hydroxyl counterparts indicating the influence of metabolically stable C–F bonds towards bioavailability. The difluoro derivatives were found to be most effective against human pancreatic BxPC-3 cancer cells which possess up-regulated COX-2 expression as well as against a human breast cancer BT-20 cells with triple negative phenotype.



**Identification of a new biaryl scaffold generating potent renin inhibitors**

pp 5822–5826

Patrick Lacombe\*, Renée Aspiotis, Christopher Bayly, Austin Chen, Daniel Dubé, Réjean Fortin, Michel Gallant, Hélène Juteau, Suzanna Liu, Dan McKay, Patrick Roy, Tom Wu

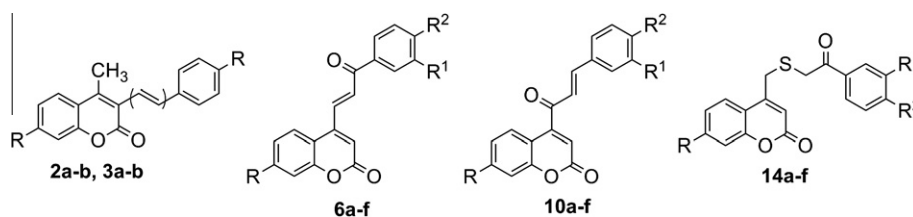


The discovery and SAR of a series of potent renin inhibitors possessing a novel biaryl scaffold are described herein. Molecular modeling revealed that the cyclopropylamide spacer present in our lead compound can be replaced by a simple, substituted aromatic ring such as a toluene. The resulting compounds exhibit subnanomolar renin IC<sub>50</sub> and good oral bioavailability in rats.

**Synthesis and biological evaluation of novel coumarin-based inhibitors of Cdc25 phosphatases**

pp 5827–5830

Sergio Valente, Emilie Bana, Elodie Viry, Denyse Bagrel, Gilbert Kirsch\*

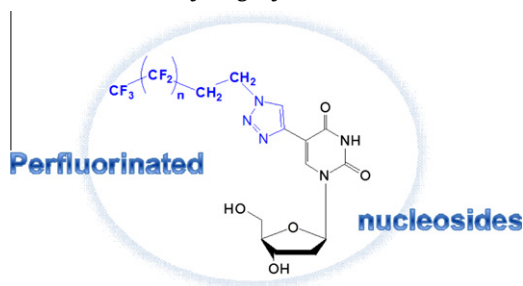


Novel coumarin-based Cdc25 phosphatases inhibitors.

**Design, synthesis, and anticancer activities of novel perfluoroalkyltriazole-appended 2'-deoxyuridines**

pp 5831–5834

Sun Min Park, Heeju Yang, Song-Kyu Park, Hwan Mook Kim, Byeang Hyeon Kim\*

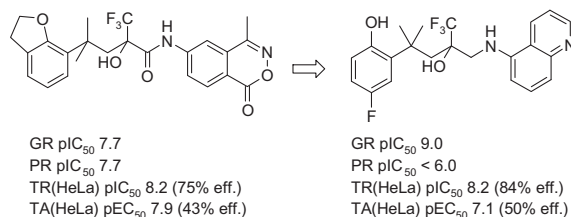


Novel synthesized perfluoroalkyltriazole-appended nucleosides exhibit anticancer activities against several cancer cell lines.

**Discovery of quinolines as selective glucocorticoid receptor agonists**

pp 5835–5838

Stefan Jaroch\*, Markus Berger, Christoph Huwe, Konrad Krolkiewicz, Hartmut Rehwinkel, Heike Schäcke, Norbert Schmees, Werner Skuballa

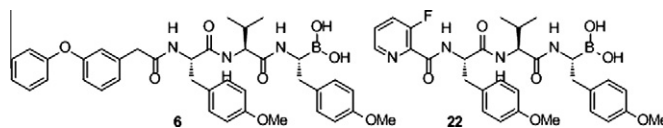


The dissociated glucocorticoid receptor (GR) agonist ZK 216348 (**1**) is rendered GR-selective by replacing the methylbenzoxazine moiety with quinolines. Compounds were shown to be efficacious in vitro in reporter gene and cell assays, along with reduced activity in a transactivation assay, hinting at an improved therapeutic window over corticosteroids.

**Structure–activity relationship of boronic acid derivatives of tyropeptin: Proteasome inhibitors**

pp 5839–5842

Takumi Watanabe\*, Hikaru Abe, Isao Momose, Yoshikazu Takahashi, Daishiro Ikeda, Yuzuru Akamatsu

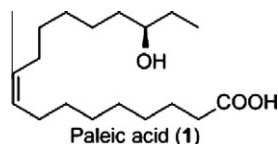


The structure–activity relationship of the boronic acid derivatives of tyropeptin, a proteasome inhibitor, was studied. Among 41 derivatives, 3-phenoxyphenylacetamide **6** and 3-fluoro picolinamide **22** displayed the most potent inhibitory activity toward chymotryptic activity of proteasome and cytotoxicity, respectively.

**The synthesis of paleic acid, an antimicrobial agent effective against *Mannheimia* and *Pasteurella*, and its structurally related derivatives**

pp 5843–5846

Takumi Watanabe\*, Ikuko Kurata, Chigusa Hayashi, Masayuki Igarashi, Ryuichi Sawa, Yoshikazu Takahashi, Yuzuru Akamatsu



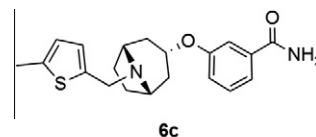
A synthetic route to paleic acid **1**, antimicrobial agent effective against *Mannheimia haemolytica* and *Pasteurella multocida*, has been established. The procedure was also applied to the preparation of structurally related analogs, which were used in structure–activity relationship studies for antibacterial activity.

**Discovery of 8-azabicyclo[3.2.1]octan-3-yloxy-benzamides as selective antagonists of the kappa opioid receptor. Part 1**

pp 5847–5852

Todd A. Brugel\*, Reed W. Smith, Michael Balestra, Christopher Becker, Thalia Daniels, Tiffany N. Hoerter, Gerard M. Koether, Scott R. Throner, Laura M. Panko, James J. Folmer, Joseph Cacciola, Angela M. Hunter, Ruifeng Liu, Philip D. Edwards, Dean G. Brown, John Gordon, Norman C. Ledonne, Mark Pietras, Patricia Schroeder, Linda A. Sygowski, Lee T. Hirata, Anna Zacco, Matthew F. Peters

Discovery and SAR studies of a novel series of potent and selective kappa opioid receptor antagonists containing an 8-azabicyclo[3.2.1]octane core is described. Analog **6c** was shown to successfully inhibit kappa agonist-induced rat diuresis in vivo.

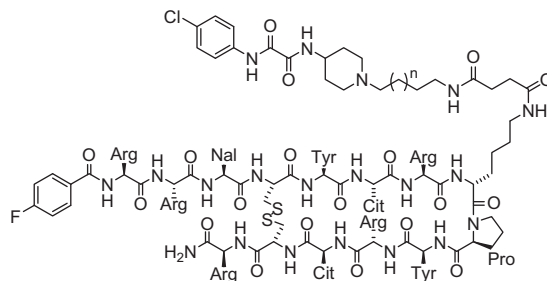


$\kappa$  GTP $\gamma$ S IC<sub>50</sub> = 20 nM  
 $\mu$  GTP $\gamma$ S IC<sub>50</sub> = 722 nM  
 $\delta$  GTP $\gamma$ S IC<sub>50</sub> = 8310 nM

**CD4 mimics targeting the HIV entry mechanism and their hybrid molecules with a CXCR4 antagonist**

pp 5853–5858

Tetsuo Narumi, Chihiro Ochiai, Kazuhisa Yoshimura, Shigeyoshi Harada, Tomohiro Tanaka, Wataru Nomura, Hiroshi Arai, Taro Ozaki, Nami Ohashi, Shuzo Matsushita, Hirokazu Tamamura\*

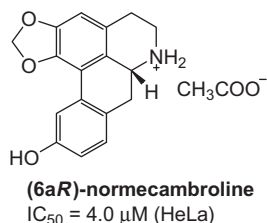


SAR studies of CD4 mimics and their conjugation with a CXCR4 antagonist are reported.

**Chemical investigation of drug-like compounds from the Australian tree, *Neolitsea dealbata***

pp 5859–5863

Trong D. Tran, Ngoc B. Pham, Gregory Fechner, Ronald J. Quinn\*

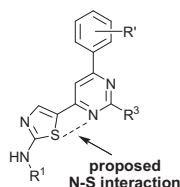


A new aporphine alkaloid, (6aR)-normecambroline (**1**), was identified from the bark of *Neolitsea dealbata*. This compound inhibited selectively against HeLa cells with an IC<sub>50</sub> of 4.0 μM.

**Utilization of a nitrogen–sulfur nonbonding interaction in the design of new 2-aminothiazol-5-yl-pyrimidines as p38α MAP kinase inhibitors**

pp 5864–5868

Shuqun Lin, Stephen T. Wroblewski\*, John Hynes Jr., Sidney Pitt, Rosemary Zhang, Yi Fan, Arthur M. Doweiko, Kevin F. Kish, John S. Sack, Mary F. Malley, Susan E. Kiefer, John A. Newitt, Murray McKinnon, James Trzaskos, Joel C. Barrish, John H. Dodd, Gary L. Schieven, Katerina Leftheris

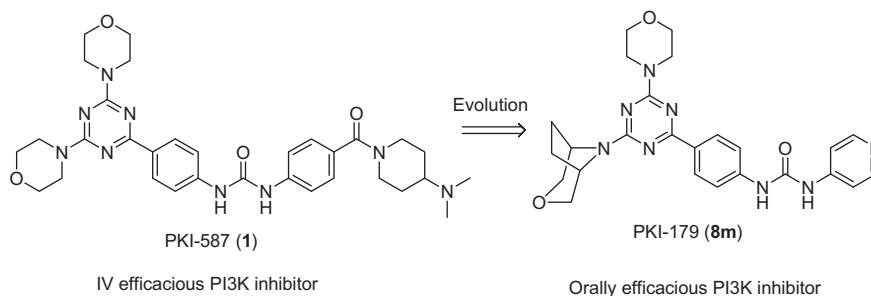


An intramolecular nitrogen–sulfur nonbonding interaction has been used in the design of a novel series of 2-aminothiazol-5-yl-pyrimidines as p38α MAP kinase inhibitors.

**PKI-179: An orally efficacious dual phosphatidylinositol-3-kinase (PI3K)/mammalian target of rapamycin (mTOR) inhibitor**

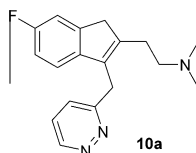
pp 5869–5873

Aranapakam M. Venkatesan\*, Zecheng Chen\*, Osvaldo Dos Santos, Christoph Dehnhardt, Efren Delos Santos, Semiramis Ayral-Kaloustian, Robert Mallon, Irwin Hollander, Larry Feldberg, Judy Lucas, Ker Yu, Inder Chaudhary, Tarek S. Mansour

**Identification of a novel selective H<sub>1</sub>-antihistamine with optimized pharmacokinetic properties for clinical evaluation in the treatment of insomnia**

pp 5874–5878

Wilna J. Moree\*, Bin-Feng Li, Said Zamani-Kord, Jinghua Yu, Timothy Coon, Charles Huang, Dragan Marinkovic, Fabio C. Tucci, Siobhan Malany, Margaret J. Bradbury, Lisa M. Hernandez, Jianyun Wen, Hua Wang, Samuel R. J. Hoare, Robert E. Petroski, Kayvon Jalali, Chun Yang, Aida Sacaan, Ajay Madan, Paul D. Crowe, Graham Beaton\*

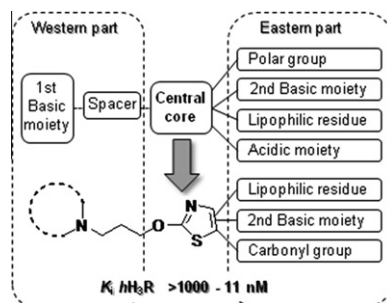


Several indenes with high affinity for the H<sub>1</sub> receptor and appropriate selectivity versus off-targets were assessed for metabolism profile and in vivo properties. Compound **10a** displayed a diversified metabolism profile, showed equivalent efficacy in a rat EEG/EMG model to a previously identified clinical candidate, and a potentially superior pharmacokinetic profile as determined from a human microdose study.

### Azole derivatives as histamine H<sub>3</sub> receptor antagonists, Part I: Thiazol-2-yl ethers

pp 5879–5882

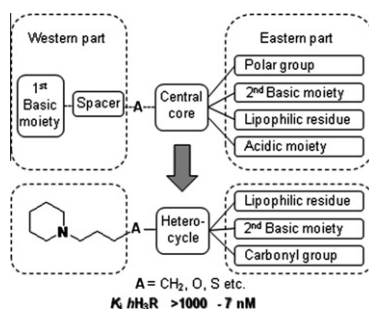
M. Walter, Y. von Coburg, K. Isensee, K. Sander, X. Ligneau, J.-C. Camelin, J.-C. Schwartz, H. Stark\*



### Azole derivatives as histamine H<sub>3</sub> receptor antagonists, Part 2: C–C and C–S coupled heterocycles

pp 5883–5886

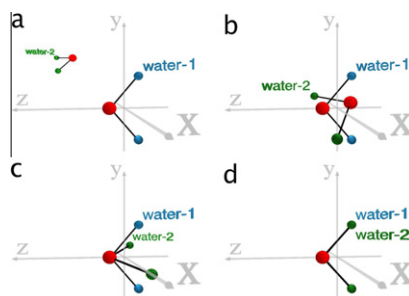
M. Walter, K. Isensee, T. Kottke, X. Ligneau, J.-C. Camelin, J.-C. Schwartz, H. Stark\*



### Molecular alignment using multipole moments

pp 5887–5890

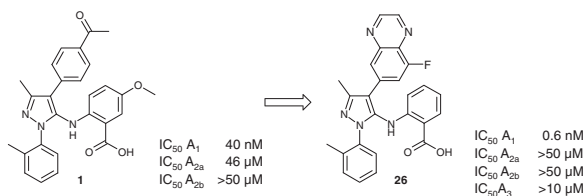
Loris Moretti\*, W. Graham Richards



### Identification and optimization of substituted 5-aminopyrazoles as potent and selective adenosine A1 receptor antagonists

pp 5891–5894

Nils Griebenow\*, Lars Bäracker, Heinrich Meier, Dirk Schneider, Nicole Teusch, Klemens Lustig, Raimund Kast, Peter Kolkhof



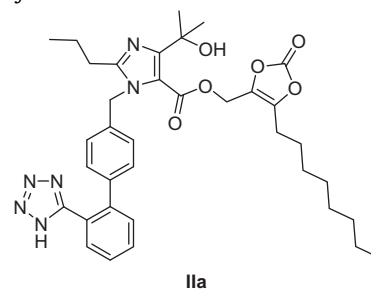


**Novel amides and esters prodrugs of olmesartan: Synthesis, bioconversion, and pharmacokinetic evaluation**

pp 5895–5899

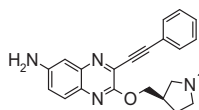
Jin-Hun Park, Jeong-Soo Chang, Mohammed I. El-Gamal, Won-Kyoung Choi, Woong San Lee, Hye Jin Chung, Hyun-Il Kim, Young-Jin Cho, Bong Sang Lee, Hong-Ryeol Jeon, Yong Sup Lee, Young Wook Choi, Jaehwi Lee, Chang-Hyun Oh\*

Compound **IIa** was found to be well absorbed from rat gastrointestinal tract and rapidly converted into olmesartan. After oral administration of **IIa**, the  $C_{max}$  and AUC values of olmesartan were significantly greater than those observed after oral administration of olmesartan medoxomil. Compound **IIa** is proposed to be an effective prodrug for olmesartan with improved oral bioavailability.

**Identification of 2,3,6-trisubstituted quinoxaline derivatives as a Wnt2/β-catenin pathway inhibitor in non-small-cell lung cancer cell lines**

pp 5900–5904

Sang-Bum Lee, Young In Park, Mi-Sook Dong\*, Young-Dae Gong\*

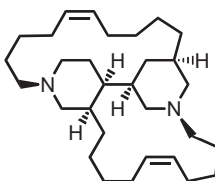


The 1434 small molecules were screened and identified 13 number of the 2,3,6-trisubstituted quinoxaline derivatives (>1 μM) that were able to inhibit the Wnt/β-catenin signal pathway and cell proliferation.

**Neopetrosiamine A, biologically active bis-piperidine alkaloid from the Caribbean sea sponge *Neopetrosia proxima***

pp 5905–5908

Xiaomei Wei, Karinel Nieves, Abimael D. Rodríguez\*

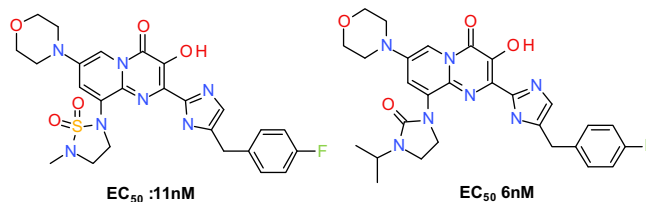


The discovery of a new 3-alkylpiperidine alkaloid with strong biological properties is reported.

**Design of a series of bicyclic HIV-1 integrase inhibitors. Part 2: Azoles: Effective metal chelators**

pp 5909–5912

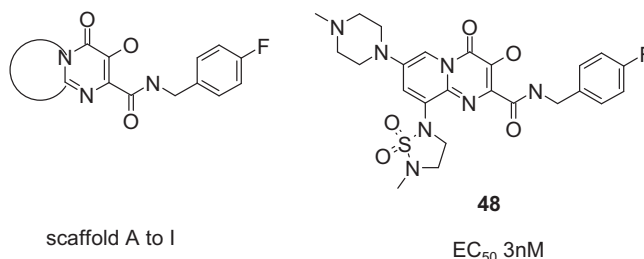
Giang Le, Nick Vandegraaff, David I. Rhodes, Eric D. Jones, Jonathan A. V. Coates, Neerarat Thienthong, Lisa J. Winfield, Long Lu, Xinming Li, Changjiang Yu, Xiao Feng, John J. Deadman\*



**Design of a series of bicyclic HIV-1 integrase inhibitors. Part 1: Selection of the scaffold**

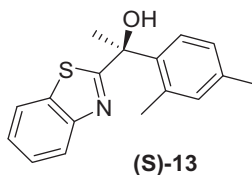
pp 5913–5917

Eric D. Jones, Nick Vandegraaff, Giang Le, Neil Choi, William Issa, Katherine Macfarlane, Neeranat Thienthong, Lisa J. Winfield, Jonathan A. V. Coates, Long Lu, Xinming Li, Xiao Feng, Changjiang Yu, David I. Rhodes, John J. Deadman\*

**Discovery of a class of calcium sensing receptor positive allosteric modulators; 1-(benzothiazol-2-yl)-1-phenylethanols**

pp 5918–5921

Magnus Gustafsson, Jacob Jensen, Sine M. Bertozzi, Erika A. Currier, Jian-Nong Ma, Ethan S. Burstein, Roger Olsson\*



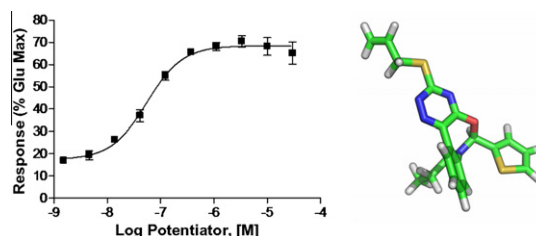
pEC<sub>50</sub> 8.0 ± 0.1, %Eff. 83 ± 5

1-(Benzothiazol-2-yl)-1-(4-chlorophenyl)ethanol (**1**) was identified as a positive allosteric modulator (PAM) of the CaSR in a functional cell-based assay. This compound belongs to a class of compounds that is structurally distinct from other known positive allosteric modulators e.g., the phenylalkylamines cinacalcet, a modified analog (**13**) potently suppressed parathyroid hormone (PTH) release in rats, consistent with its profile as a PAM of CaSRs.

**3D-QSAR CoMFA study of benzoxazepine derivatives as mGluR<sub>5</sub> positive allosteric modulators**

pp 5922–5924

Edward W. Lowe Jr., Alysia Ferrebee, Alice L. Rodriguez, P. Jeffrey Conn, Jens Meiler\*



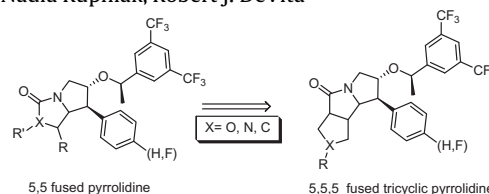
Positive allosteric modulation of the metabotropic glutamate receptor subtype 5 was studied by conducting a comparative molecular field analysis on 118 benzoxazepine derivatives. The model with the best predictive ability retained significant cross-validated correlation coefficients of  $q^2 = 0.58$  ( $r^2 = 0.81$ ) yielding a standard error of 0.20 in pEC<sub>50</sub> for this class of compounds. The subsequent contour maps highlight the structural features pertinent to the bioactivity values of benzoxazepines.

**Fused tricyclic pyrrolizinones that exhibit pseudo-irreversible blockade of the NK<sub>1</sub> receptor**

pp 5925–5932

Gregori J. Morriello\*, Gary Chicchi, Tricia Johnson, Sander G. Mills, Julie DeMartino, Marc Kurtz, K. L. C. Tsao, Song Zheng, Xinchun Tong, Emma Carlson, Karen Townson, Alan Wheeldon, Susan Boyce, Neil Collinson, Nadia Rupniak, Robert J. DeVita

Previously, we had disclosed a novel class of hNK<sub>1</sub> antagonists based on the 5,5-fused pyrrolidine core. These compounds displayed subnanomolar hNK<sub>1</sub> affinity along with good efficacy in a gerbil foot-tapping (GFT) model, but unfortunately they had low to moderate functional antagonist (IP-1) activity. To elaborate on the SAR of this class of hNK<sub>1</sub> compounds and to improve functional activity, we have designed and synthesized a new class of hNK<sub>1</sub> antagonist with a third fused ring. Compared to the 5,5-fused pyrrolidine class, these 5,5,5-fused tricyclic hNK<sub>1</sub> antagonists maintain subnanomolar hNK<sub>1</sub> binding affinity with highly improved functional IP-1 activity (<10% SP remaining). A fused tricyclic methyl, hydroxyl geminally substituted pyrrolizinone (compound **20**) had excellent functional IP (<2% SP remaining), hNK<sub>1</sub> binding affinity, off-target selectivity, pharmacokinetic profile and in vivo activity. Complete inhibition of agonist activity was observed at both 0 and 24 h in the gerbil foot-tapping model with an ID<sub>50</sub> of 0.02 mpk at both 0 and 24 h, respectively.

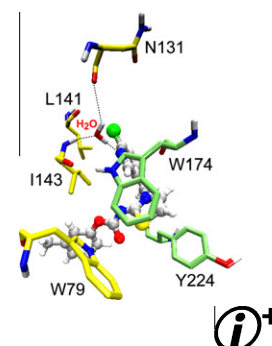


**Structural features of phenoxy-carbonylimino neonicotinoids acting at the insect nicotinic receptor**

pp 5933–5935

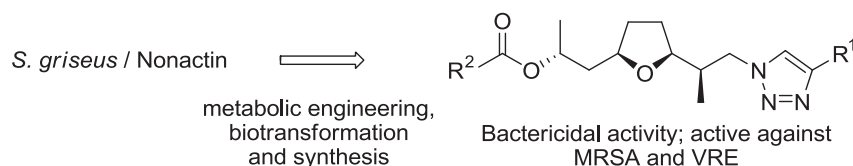
Ikuya Ohno, Motohiro Tomizawa, Nozomi Miyazu, Gohito Kushibiki, Kumiko Noda, Yasunori Hasebe, Kathleen A. Durkin, Taiji Miyake, Shinzo Kagabu\*

A structure–activity relationship study of phenoxy-carbonylimino neonicotinoids leads to establish in silico binding site interaction model featuring that the phenoxy ring of neonicotinoids undergoes a T-shape aromatic interaction with the loop D tryptophan indole plane of the insect nicotinic receptor.

**Natural product derivatives with bactericidal activity against Gram-positive pathogens including methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecalis***

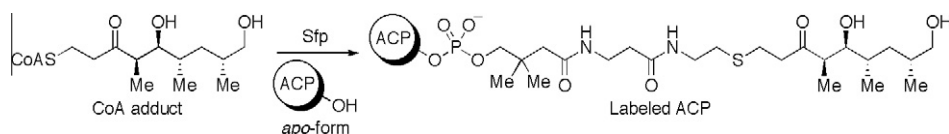
pp 5936–5938

Joshua B. Phillips, Adrienne E. Smith, Brian R. Kusche, Bradley A. Bessette Jr., P. Whitney Swain III, Stephen C. Bergmeier, Mark C. McMills, Dennis L. Wright, Nigel D. Priestley\*

**A general scheme for synthesis of substrate-based polyketide labels for acyl carrier proteins**

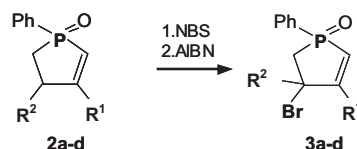
pp 5939–5942

Erick K. Leggans, David L. Akey, Janet L. Smith, Robert A. Fecik\*

**Preparation and characterization of novel 4-bromo-3,4-dimethyl-1-phenyl-2-phospholene 1-oxide and the analogous phosphorus heterocycles or phospho sugars**


pp 5943–5946

Manabu Yamada, Mitsuji Yamashita\*, Takuya Suyama, Junko Yamashita, Kazuhide Asai, Taishi Niimi, Nobuhisa Ozaki, Michio Fujie, Kasthuraiah Maddali, Satoki Nakamura, Kazunori Ohnishi

(a: R<sup>1</sup> = R<sup>2</sup> = H, b: R<sup>1</sup> = CH<sub>3</sub>, R<sup>2</sup> = H, c: R<sup>1</sup> = R<sup>2</sup> = CH<sub>3</sub>, d: R<sup>1</sup> = C<sub>2</sub>H<sub>5</sub>, R<sup>2</sup> = H)

4-Bromo-3,4-dimethyl-1-phenyl-2-phospholene 1-oxide (**3c**) was first synthesized from 3,4-dimethyl-1-phenyl-2-phospholene 1-oxide (**2c**) by a bromo-radical substitution reaction occurred at C-4 position by NBS and AIBN. The novel phospho sugar analogue exerted high anti-proliferative effect on U937 cells evaluated by MTT in vitro methods and was much more efficient than that of Gleevec®, which is known as a molecule targeting chemotherapeutic agent.

\*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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