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# Bioorganic & Medicinal Chemistry Letters

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## Bioorganic & Medicinal Chemistry Letters Volume 20, Issue 23, 2010

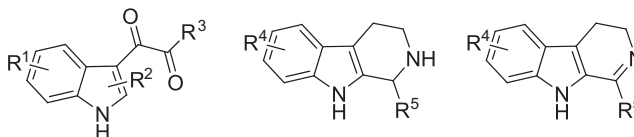
### Contents

#### ARTICLES

##### Synthetic analogs of indole-containing natural products as inhibitors of sortase A and isocitrate lyase

pp 6882–6885

Yeon-Ju Lee, Yu-Ri Han, Wanki Park, Seo-Hee Nam, Ki-Bong Oh\*, Hyi-Seung Lee\*



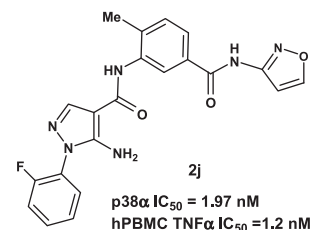
Synthetic analogs of natural products with enhanced activities against SrtA and ICL.

##### 5-Amino-pyrazoles as potent and selective p38 $\alpha$ inhibitors

pp 6886–6889

Jagabandhu Das\*, Robert V. Moquin, Alaric J. Dyckman, Tianle Li, Sidney Pitt, Rosemary Zhang, Ding Ren Shen, Kim W. McIntyre, Kathleen Gillooly, Arthur M. Doweiko, John A. Newitt, John S. Sack, Hongjian Zhang, Susan E. Kiefer, Kevin Kish, Murray McKinnon, Joel C. Barrish, John H. Dodd, Gary L. Schieven, Katerina Leftheris

The synthesis and structure–activity relationships (SAR) of p38 $\alpha$  MAP kinase inhibitors based on a 5-amino-pyrazole scaffold are described. These studies led to the identification of compound **2j** as a potent and selective inhibitor of p38 $\alpha$  MAP kinase with excellent cellular potency toward the inhibition of TNF $\alpha$  production. Compound **2j** was highly efficacious in vivo in inhibiting TNF $\alpha$  production in an acute murine model of TNF production. X-ray co-crystallography of a 5-amino-pyrazole analog **2f** bound to unphosphorylated p38 $\alpha$  is also disclosed.

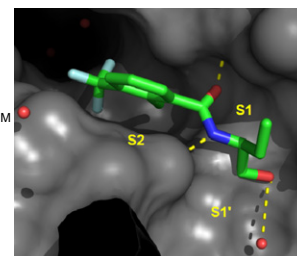
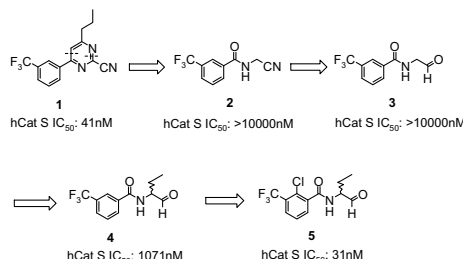


##### Trifluoromethylphenyl as P2 for ketoamide-based cathepsin S inhibitors

pp 6890–6894

Jiaqiang Cai\*, John Robinson, Simone Belshaw, Kathryn Everett, Xavier Fradera, Mario van Zeeland, Leon van Berkum, Peter van Rijsbergen, Lucy Popplestone, Mark Baugh, Maureen Dempster, John Bruin, William Hamilton, Emma Kinghorn, Paul Westwood, Jennifer Kerr, Zoran Rankovic, Wullie Arbuckle, D. Jonathan Bennett, Philip S. Jones, Clive Long, Iain Martin, Joost C. M. Uitdehaag, Tommi Meulemans

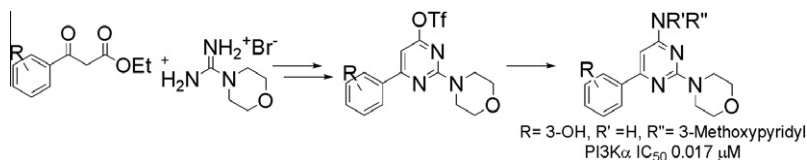
By using a small atom (Cl, F, or Me) to increase the torsion angle between the phenyl ring and the attached secondary amide, trifluoromethylphenyl motif was applied successfully as P2 for aldehyde/ketoamide-based cathepsin S inhibitors.



### Identification and structure–activity relationship of 2-morpholino 6-(3-hydroxyphenyl) pyrimidines, a class of potent and selective PI3 kinase inhibitors

pp 6895–6898

Sabina Pecchi\*, Paul A. Renhowe, Clarke Taylor, Susan Kaufman, Hanne Merritt, Marion Wiesmann, Kevin R. Shoemaker, Mark S. Knapp, Elizabeth Ornelas, Thomas F. Hendrickson, Wendy Fantl, Charles F. Voliva



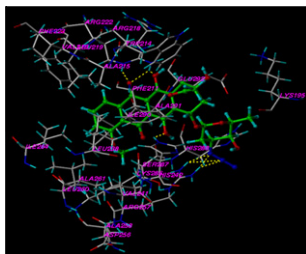
2-Morpholino pyrimidines inhibitors of PI3 kinase.



### Interaction of 3'-azido-3'-deamino daunorubicin with human serum albumin: Investigation by fluorescence spectroscopy and molecular modeling methods

pp 6899–6904

Yan Lu, Qingqin Feng, Fengling Cui\*, Weiwei Xing, Guisheng Zhang\*, Xiaojun Yao

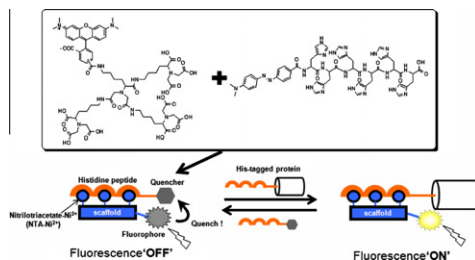


Site I is large enough to accommodate ADNR molecule and residues of HSA, ALA215, and HIS288 are in close proximity to ADNR suggesting the existence of hydrophobic interaction between them.

### Construction of a 'turn-on' fluorescent probe system for His-tagged proteins

pp 6905–6908

Atsushi Murata, Satoshi Arai, Su-In Yoon, Masao Takabayashi, Miwako Ozaki, Shinji Takeoka\*



A new type of a 'turn-on' fluorescent probe for His-tagged proteins was constructed using tetramethylrhodamine-conjugated nitrilotriacetate derivative and Dabcyl-conjugated hexahistidine peptide.

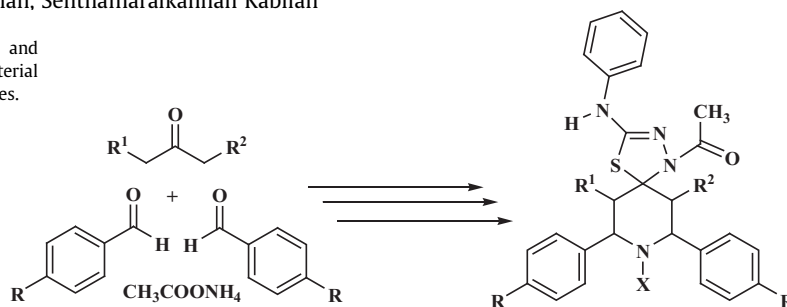


### Synthesis, antimicrobial evaluation and QSAR studies of novel piperidin-4-yl-5-spiro-thiadiazoline derivatives

pp 6909–6914

Seeman Umamatheswari, Bhaskar Balaji, Muthiah Ramanathan, Senthamarai Kannan Kabilan\*

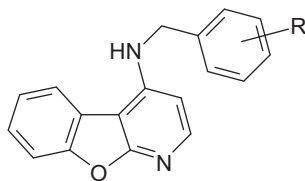
Series of spiro-thiadiazoline derivatives of piperidines were synthesized and characterised. All the compounds were evaluated for in vitro antibacterial potency by serial dilution method, which is explained through QSAR studies.



**Discovery and selectivity-profiling of 4-benzylamino 1-aza-9-oxafluorene derivatives as lead structures for IGF-1R inhibitors**

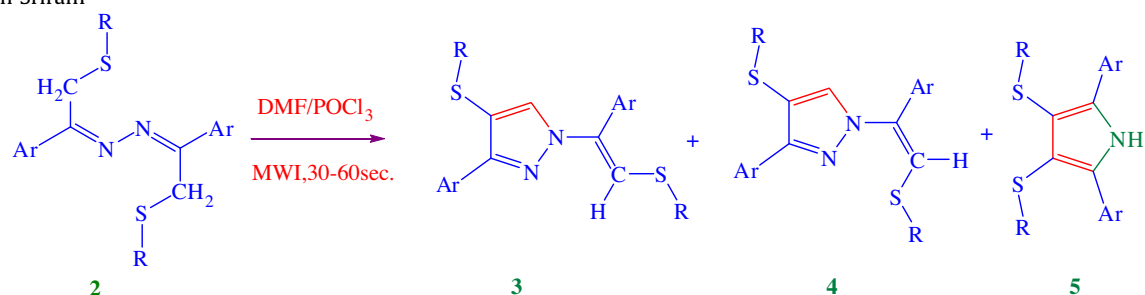
pp 6915–6919

Martin Krug, German Erlenkamp, Wolfgang Sippl, Christoph Schächtele, Frank Totzke, Andreas Hilgeroth\*

**Pyrazole derivatives from azines of substituted phenacyl aryl/cyclohexyl sulfides and their antimicrobial activity**

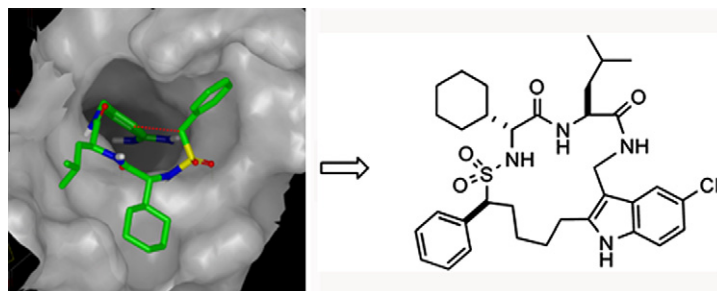
pp 6920–6924

Ramaian Manikannan, Ramaian Venkatesan, Shanmugam Muthusubramanian\*, Perumal Yogeeswari, Dharmarajan Sriram

**Design and synthesis of macrocyclic indoles targeting blood coagulation cascade Factor XIa**

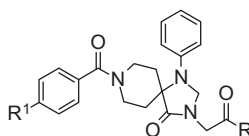
pp 6925–6928

Stephen Hanessian\*, Andreas Larsson, Tomas Fex, Wolfgang Knecht, Niklas Blomberg

**Spiroimidazolidinone NPC1L1 inhibitors. Part 2: Structure–activity studies and in vivo efficacy**

pp 6929–6932

Kobporn L. Howell\*, Robert J. DeVita\*, Margarita Garcia-Calvo, Roger D. Meurer, JeanMarie Lisnock, Herbert G. Bull, Daniel R. McMasters, Margaret E. McCann, Sander G. Mills

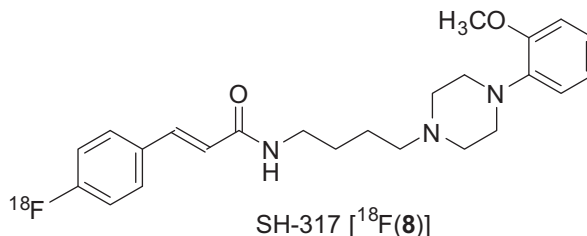


Ezetimibe (Zetia®), a cholesterol-absorption inhibitor (CAI) approved by the FDA for the treatment of hypercholesterolemia, is believed to target the intestine protein Niemann-Pick C1-Like 1 (NPC1L1) or its pathway. A spiroimidazolidinone NPC1L1 inhibitor identified by virtual screening showed moderate binding activity but was not efficacious in an in vivo rodent model of cholesterol absorption. Synthesis of analogs established the structure–activity relationships for binding activity, and resulted in compounds with in vivo efficacy, thereby providing proof-of-concept that non-β-lactams can be effective CAIs.

### Synthesis, biological evaluation and radiolabelling by $^{18}\text{F}$ -fluoroarylation of a dopamine $\text{D}_3$ -selective ligand as prospective imaging probe for PET

pp 6933–6937

S. B. Höfling, S. Maschauer, H. Hübner, P. Gmeiner, H.-J. Wester, O. Prante, M. R. Heinrich\*



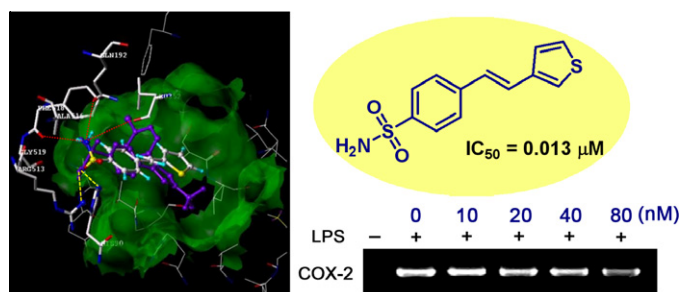
Radical  $^{18}\text{F}$ -fluoroarylation with fluorine-18-labelled arenediazonium chlorides has been successfully applied to the radiochemical synthesis of the dopamine  $\text{D}_3$ -selective ligand SH 317 ([ $^{18}\text{F}$ ]**8**). SH 317 has been evaluated as a new PET ligand candidate by in vivo experiments.



### Sulfonamide derivatives of styrylheterocycles as a potent inhibitor of COX-2-mediated prostaglandin $\text{E}_2$ production

pp 6938–6941

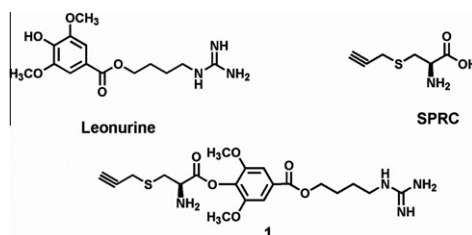
Chaemin Lim, Minhee Lee, Eun-Jung Park, Ran Cho, Hyen-Joo Park, Seong Jin Lee, Heeyeong Cho, Sang Kook Lee\*, Sanghee Kim\*



### Synthesis and biological evaluation of novel leonurine–SPRC conjugate as cardioprotective agents

pp 6942–6946

Chunhua Liu, Xianfeng Gu\*, Yi Zhun Zhu\*

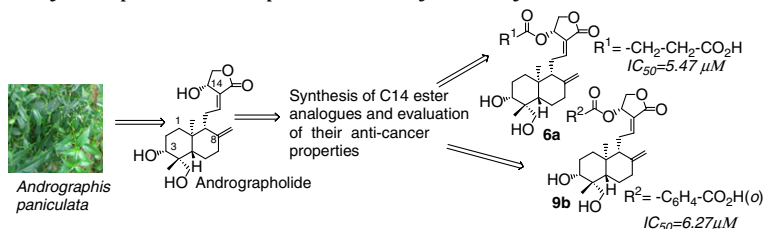


The synthesis and biological evaluation of novel leonurine–SPRC conjugate, 3,5-dimethoxy-4-(2-amino-3-prop-2-ynylsulfanyl-propionyl)-benzoic acid 4-guanidino-butyl ester (**1**) is reported in this Letter. It is designed to improve the pharmacology efficiency by combining leonurine with S-propargyl cysteine (SPRC), a cysteine analog, via a phenolic hydroxyl ester bond, which could be readily hydrolyzed to release bioactive leonurine and SPRC. Pharmacological evaluation has shown that **1** possesses potent cardioprotective effect against hypoxia-induced neonatal rat ventricular myocytes damage at lower molar concentration (10-fold less than leonurine required and 100-fold less than SPRC required). The mechanism is in partial related to improve hydrogen sulfide production, anti-oxidative stress and anti-apoptosis.

### Synthesis, cytotoxicity, and structure–activity relationship (SAR) studies of andrographolide analogues as anti-cancer agent

pp 6947–6950

Bimolendu Das, Chinmay Chowdhury\*, Deepak Kumar, Rupashree Sen, Rajneeta Roy, Padma Das, Mitali Chatterjee



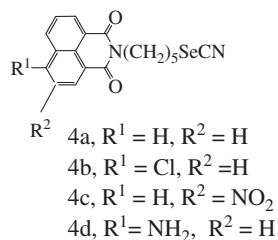
A series of analogues of andrographolide, prepared through chemo-selective functionalization at C14 hydroxy, have been evaluated for in vitro cytotoxicities against human leukemic cell lines. Two of the analogues (**6a**, **6b**) exhibited significant potency. Preliminary studies on structure–activity relationship (SAR) revealed that the  $\alpha$ -alkylidene- $\gamma$ -butyrolactone moiety of andrographolide played a major role in the activity profile. The structures of the analogues were established through spectroscopic and analytical data.



**Naphthalimide based novel organoselenocyanates: Finding less toxic forms of selenium that would retain protective efficacy**

pp 6951–6955

Somnath Singha Roy, Prosenjit Ghosh, Ugir Hossain Sk, Pramita Chakraborty, Jaydip Biswas, Syamsundar Mandal, Arin Bhattacharjee, Sudin Bhattacharya\*

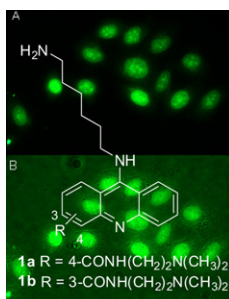


Synthesis, toxicity and the ability to modulate the antioxidant/detoxifying enzymes of some naphthalimide based organoselenocyanates is reported.

**Design and synthesis of threading intercalators to target DNA**

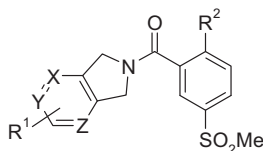
pp 6956–6959

Lesley A. Howell, Rosul Gulam, Anja Mueller, Maria A. O'Connell, Mark Searcey\*

**Discovery of benzoylisoindolines as a novel class of potent, selective and orally active GlyT1 inhibitors**

pp 6960–6965

Emmanuel Pinard\*, Daniela Alberati, Markus Bender, Edilio Borroni, Virginie Brom, Serge Burner, Holger Fischer, Dominik Hainzl, Remy Halm, Nicole Hauser, Synèse Jolidon, Judith Lengyel, Hans-Peter Marty, Thierry Meyer, Jean-Luc Moreau, Roland Mory, Robert Narquizian, Roger D. Norcross, Philipp Schmid, Roger Wermuth, Daniel Zimmerli



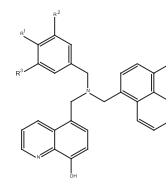
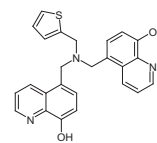
Benzoylisoindolines were discovered as a novel structural class of GlyT1 inhibitors. The SAR studies followed by the lead optimization effort focused primarily on addressing hERG liability and on improving oral activity resulted in the identification of potent GlyT1 inhibitors displaying excellent selectivity and in vivo profiles.

**N,N-Bis-(8-hydroxyquinoline-5-yl methyl)-benzyl substituted amines (HQNBA): Peroxisome proliferator-activated receptor (PPAR-γ) agonists with neuroprotective properties**

pp 6966–6968

Sébastien Madonna, Pamela Maher\*, Jean-Louis Kraus\*

N,N-Bis-(8-hydroxyquinoline-5-yl methyl)-benzyl substituted amines (HQNBA) are new peroxisome proliferator-activated receptor (PPAR-γ) agonists, which exert neuroprotective effects on lesioned HT22 cells.

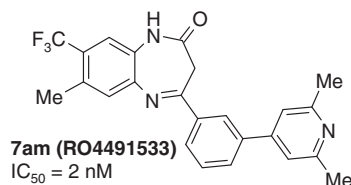
JLK1472  $R^1 = CH_3$   $R^2 = H$ JLK1486  $R^1 = CF_3$   $R^2 = H$ JLK1530  $R^1 = H$   $R^2 = CF_3$ 

JLK1535

### Synthesis and characterization of 1,3-dihydro-benzo[b][1,4]diazepin-2-one derivatives: Part 4. In vivo active potent and selective non-competitive metabotropic glutamate receptor 2/3 antagonists

pp 6969–6974

Thomas J. Woltering\*, Jürgen Wichmann, Erwin Goetschi, Frédéric Knoflach, Theresa M. Ballard, Jörg Huwyler, Silvia Gatti

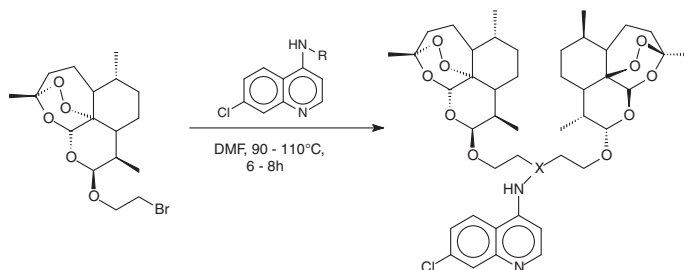


A series of 1,3-dihydro-benzo[b][1,4]diazepin-2-ones was finally developed into highly drug-like non-competitive group II mGluR antagonists. After oral administration of, for example, **7am** in vivo activity by reversal of the LY354740-induced hypolocomotion in rats and improvement of memory deficit in the DMTP task—also synergistically with donepezil—could be demonstrated.

### Artemisinin–quinoline hybrid-dimers: Synthesis and in vitro antiplasmodial activity

pp 6975–6977

Marli C. Lombard, David D. N'Da\*, Jaco C. Breytenbach, Peter J. Smith, Carmen A. Lategan

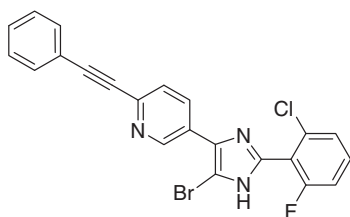


Novel artemisinin–quinoline dimers were synthesized upon reaction of 2-(10β-dihydroartemisinoxy)ethylbromide with different aminoquinoline moieties under specific conditions and were shown to have moderate in vitro antimalarial activity.

### Biarylimidazoles as inhibitors of microsomal prostaglandin E<sub>2</sub> synthase-1

pp 6978–6982

Tom Y. H. Wu, Hélène Juteau\*, Yves Ducharme, Richard W. Friesen, Sébastien Guiral, Lynn Dufresne, Hugo Poirier, Myriam Salem, Denis Riendeau, Joseph Mancini, Christine Brideau



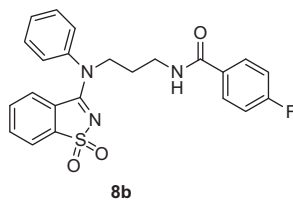
Assays	IC <sub>50</sub> (nM)
mPGES-1	1
A549 (2%/50% FBS)	13 / 160
HWBA	1600

Biarylimidazoles were prepared and evaluated as inhibitors of microsomal prostaglandin E<sub>2</sub> synthase-1.

### N-{3-[(1,1-dioxido-1,2-benzothiazol-3-yl)(phenyl)amino]propyl}benzamide analogs as potent Kv1.3 inhibitors. Part 1

pp 6983–6988

Curt D. Haffner\*, Stephen A. Thomson, Yu Guo, Lee T. Schaller, Sharon Boggs, Scott Dickerson, Jeff Gobel, Dan Gillie, J. Patrick Condreay

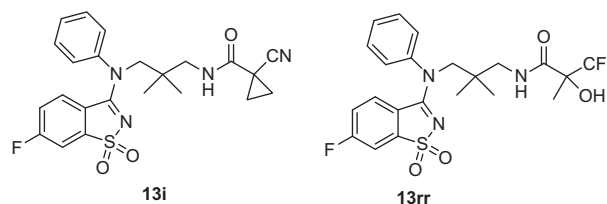


We report the synthesis and in vitro activity of a series of novel N-{3-[(1,1-dioxido-1,2-benzothiazol-3-yl)(phenyl)amino]propyl}benzamide analogs. These analogs showed potent inhibitory activity against Kv1.3. Several compounds, including compound **8b**, showed similar potency to the known Kv1.3 inhibitor PAP-1 when tested under the IonWorks patch clamp assay conditions.

### Substituted *N*-{3-[(1,1-dioxido-1,2-benzothiazol-3-yl)(phenyl)amino]propyl}benzamide analogs as potent Kv1.3 ion channel blockers. Part 2

pp 6989–6992

Curt D. Haffner\*, Stephen A. Thomson, Yu Guo, Kimberly Petrov, Andrew Larkin, Pierette Banker, Gregory Schaaf, Scott Dickerson, Jeff Gobel, Dan Gillie, J. Patrick Condreay, Chuck Poole, Tiffany Carpenter, John Ulrich

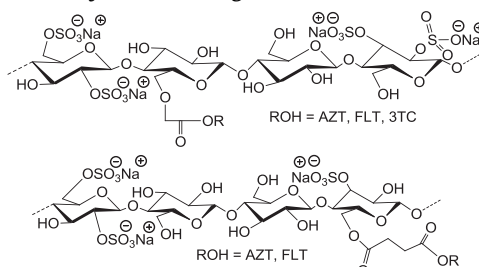


We report the synthesis and in vitro activity of a series of novel substituted *N*-{3-[(1,1-dioxido-1,2-benzothiazol-3-yl)(phenyl)amino]propyl}benzamide analogs. These analogs showed potent inhibitory activity against Kv1.3. Several demonstrated similar potency to the known Kv1.3 inhibitor PAP-1 when tested under the IonWorks patch clamp assay conditions. Two compounds, **13i** and **13rr**, were advanced further as potential tool compounds for in vivo validation studies.

### Synthesis, antiviral and contraceptive activities of nucleoside–sodium cellulose sulfate acetate and succinate conjugates

pp 6993–6997

Hitesh K. Agarwal, Anil Kumar, Gustavo F. Doncel\*, Keykavous Parang\*



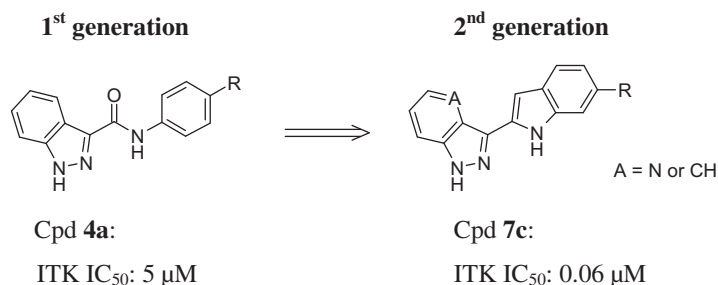
The synthesis and anti-HIV activities of two classes of conjugates between sodium cellulose sulfate succinate and sodium cellulose sulfate acetate as HIV-entry inhibitors and nucleoside reverse transcriptase inhibitors are reported.



### Identification of potent ITK inhibitors through focused compound library design including structural information

pp 6998–7003

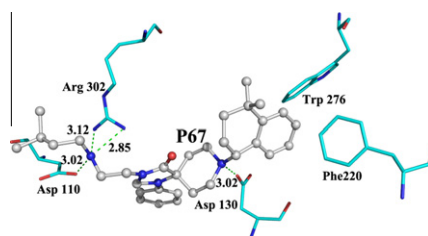
Matthias Herdemann, Isabelle Heit\*, Frank-Uwe Bosch, Gianluca Quintini, Claudia Scheipers, Alexander Weber\*



### 3D-QSAR, homology modeling, and molecular docking studies on spiropiperidines analogues as agonists of nociceptin/orphanin FQ receptor

pp 7004–7010

Ming Liu, Lin He, Xiaopeng Hu, Peiqing Liu, Hai-Bin Luo\*

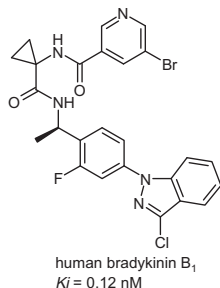


We studied 3D-QSAR and molecular mechanism of spiropiperidine analogues targeting nociceptin/orphanin FQ receptor (NOP). Molecular docking simulations reveal salt bridge, hydrogen-bonding, and hydrophobic interactions stabilize the most active agonist **P67** in the binding site pocket of NOP.

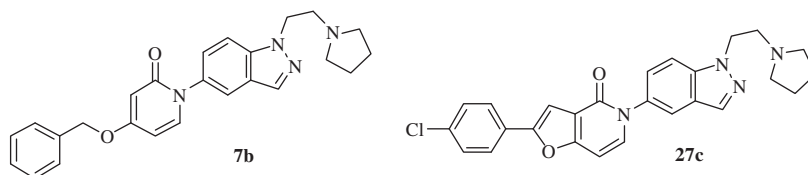


**Indazole derivatives as novel bradykinin B<sub>1</sub> receptor antagonists****pp 7011–7014**

Vera Bodmer-Narkevitch\*, Neville J. Anthony, Victoria Cofre, Samson M. Jolly, Kathy L. Murphy, Richard W. Ransom, Duane R. Reiss, Cuyue Tang, Thomayant Prueksaritanont, Douglas J. Pettibone, Mark G. Bock, Scott D. Kuduk

**5-(Pyridinon-1-yl)indazoles and 5-(furopyridinon-5-yl)indazoles as MCH-1 antagonists****pp 7015–7019**

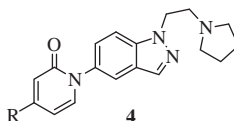
Matthew D. Surman\*, Emily E. Freeman, James F. Grabowski, Mark Hadden, Alan J. Henderson, Guowei Jiang, Xiaowu (May) Jiang, Michele Luche, Yuri Khmelnitsky, Steven Vickers, Jean Viggers, Sharon Cheetham, Peter R. Guzzo



The synthesis and SAR of 5-(pyridinon-1-yl)indazoles and 5-(furopyridinon-5-yl)indazoles as potent MCH-1 antagonists are described.

**Synthesis and SAR of 4-aryl-1-(indazol-5-yl)pyridin-2(1H)ones as MCH-1 antagonists for the treatment of obesity****pp 7020–7023**

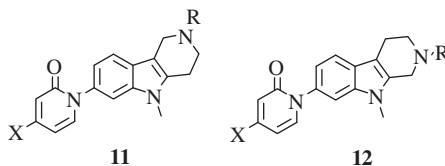
Mark Hadden\*, Dustin M. Deering, Alan J. Henderson, Matthew D. Surman, Michele Luche, Yuri Khmelnitsky, Steven Vickers, Jean Viggers, Sharon Cheetham, Peter R. Guzzo



The synthesis and SAR of 4-aryl-1-(indazol-5-yl)pyridin-2(1H)ones as MCH-1 antagonists are described.

**Tetrahydrocarboline analogs as MCH-1 antagonists****pp 7024–7028**

Alan J. Henderson\*, Dustin Deering, James F. Grabowski, Mark Hadden, Xiaowu Jiang, Yuri Khmelnitsky, Michele Luche, Matthew D. Surman, Sharon Cheetham, Steven Vickers, Jean Viggers, Peter R. Guzzo



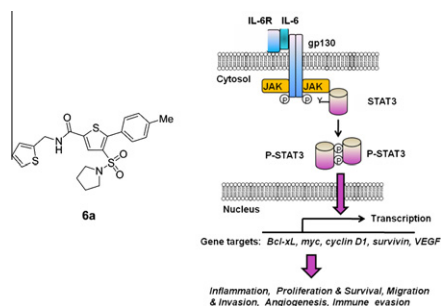
The synthesis and SAR of tetrahydrocarboline analogs as MCH-1 antagonists are described.

**A novel small-molecule inhibitor of IL-6 signalling**

pp 7029–7032

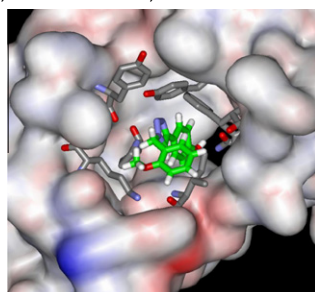
Giovanna Zinzalla, Mohammad R. Haque, B. Piku Basu, John Anderson, Samantha L. Kaye, Shozeb Haider, Fyeza Hasan, Dyeison Antonow, Samantha Essex, Khondaker M. Rahman, Jonathan Palmer, Daniel Morgenstern, Andrew F. Wilderspin, Stephen Neidle, David E. Thurston\*

Compound **6a** is a selective inhibitor of the IL-6/STAT3 signalling pathway.

**Receptor agonists of macrophage migration inhibitory factor**

pp 7033–7036

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



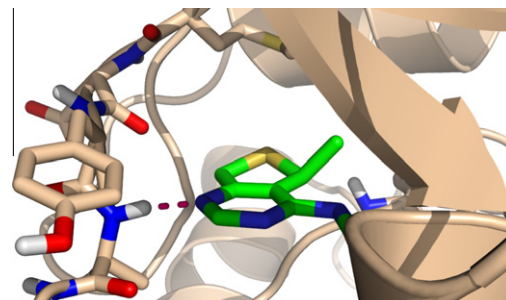
Substituted aryl-1,2,3-triazoles are reported as the first agonists of the binding of the cytokine macrophage migration inhibitory factor (MIF) to its receptor CD74. The contrasting behavior of MIF antagonists and agonists is also demonstrated in MIF-dependent ERK1/2 phosphorylation using human fibroblasts.

**Discovery of dihydrothieno- and dihydrofuroypyrimidines as potent pan Akt inhibitors**

pp 7037–7041

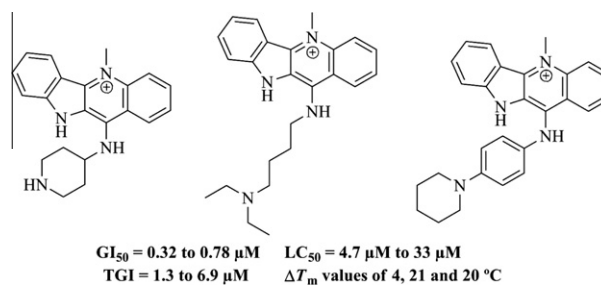
Josef R. Bencsik\*, Dengming Xiao, James F. Blake, Nicholas C. Kallan, Ian S. Mitchell, Keith L. Spencer, Rui Xu, Susan L. Gloor, Matthew Martinson, Tyler Risom, Richard D. Woessner, Faith Dizon, Wen-I Wu, Guy P. A. Vigers, Barbara J. Brandhuber, Nicholas J. Skelton, Wei Wei Prior, Lesley J. Murray

We report the discovery and synthesis of a novel series of dihydrothieno- and dihydrofuroypyrimidines as potent pan Akt inhibitors. A representative dihydrothieno compound was advanced into a PC3-NCI prostate mouse tumor model in which it demonstrated a dose-dependent reduction in tumor growth and stasis when dosed orally daily at 200 mg/kg.

**C-11 diamino cryptolepine derivatives NSC748392, NSC748393 and NSC748394: Anticancer profile and G-quadruplex stabilization**

pp 7042–7045

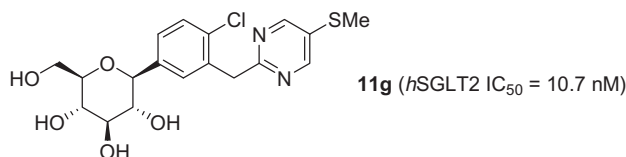
João Lavrado, Anthony P. Reszka, Rui Moreira, Stephen Neidle, Alexandra Paulo\*



**Pyrimidinylmethylphenyl glucoside as novel C-aryl glucoside SGLT2 inhibitors**

pp 7046–7049

Junwon Lee, Jong Yup Kim, Jungsub Choi, Sung-Han Lee, Jeongmin Kim, Jinhwa Lee\*

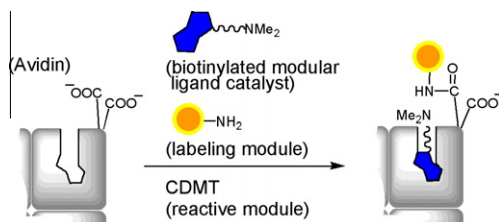


Novel C-aryl glucoside SGLT2 inhibitors containing pyrimidine motif were designed and synthesized for biological evaluation. Among various analogs tested, methylthiopyrimidine **11g** demonstrated best in vitro activity against *h*SGLT2 in this series to date.

**Labeling study of avidin by modular method for affinity labeling (MoAL)**

pp 7050–7053

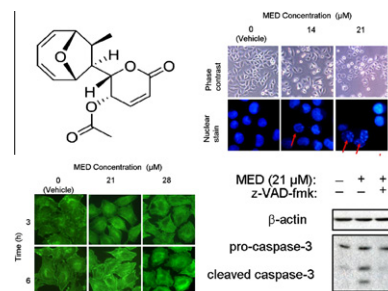
Shuichi Nakanishi, Hiroyuki Tanaka, Kazuhito Hioki, Kohei Yamada, Munetaka Kunishima\*

**Mycopoxydiene, a fungal polyketide, induces cell cycle arrest at the G2/M phase and apoptosis in HeLa cells**

pp 7054–7058

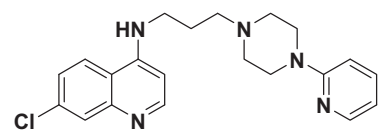
Jifeng Wang, Baobing Zhao, Wei Zhang, Xuan Wu, Ruoyu Wang, Yaojian Huang, Dong Chen, Kum Park, Bart C. Weimer\*, Yuemao Shen\*

Mycopoxydiene (MED) is a polyketide isolated from a marine fungus associated with mangrove forests. MED induced the reorganization of cytoskeleton in HeLa cells by promoting formation of actin stress fiber and inhibiting polymerization of tubulin. MED could induce cell cycle arrest at G2/M in HeLa cells. MED-associated apoptosis was characterized by the formation of fragmented nuclei, PARP cleavage, cytochrome c release, activation of caspase-3, and an increased proportion of sub-G1 cells. Additionally, MED activated MAPK pathways. It showed encouraging biological activities.

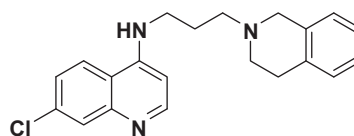
**Synthesis of new 4-aminoquinolines and quinoline–acridine hybrids as antimalarial agents**

pp 7059–7063

Ashok Kumar, Kumkum Srivastava, S. Raja Kumar, S. K. Puri, Prem M. S. Chauhan\*



**17**, MIC = 0.125 μg/mL  
Orally active at the dose 100 mg/kgx 4 days



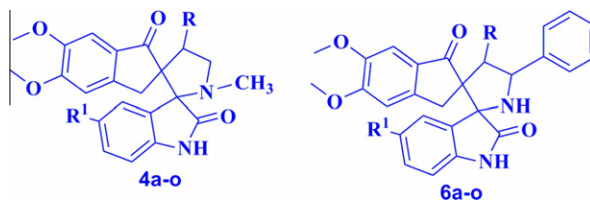
**21**, MIC = 0.031 μg/mL

New side chain modified 4-aminoquinolines and quinoline–acridine hybrids were synthesized and screened in vitro against NF 54 strain of *Plasmodium falciparum*. Compound **17** showed the curative response to all the treated mice infected with CQ-resistant N-67 strain of *Plasmodium yoelii* at the dose of 100 mg/kg for four days by oral route.

**Substituted spiro [2.3'] oxindolespiro [3.2'']-5,6-dimethoxy-indane-1''-one-pyrrolidine analogue as inhibitors of acetylcholinesterase**

pp 7064–7066

Mohamed Ashraf Ali\*, Rusli Ismail, Tan Soo Choon, Yeong Keng Yoon, Ang Chee Wei, Suresh Pandian, Raju Suresh Kumar, Hasnah Osman, Elumalai Manogaran

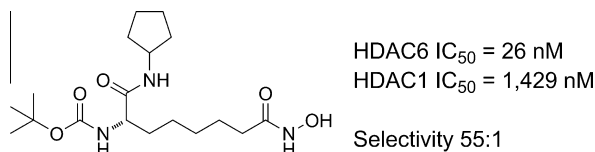


Compound **4k**, showed potent inhibitory activity against acetyl cholinesterase enzyme with  $IC_{50}$  0.10  $\mu$ M/L. Pyrrolidine analogues might be potential acetyl cholinesterase agents for AD.

**Inhibitors selective for HDAC6 in enzymes and cells**

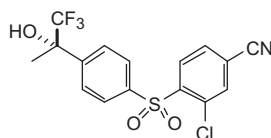
pp 7067–7070

Praveer K. Gupta, Robert C. Reid, Ligong Liu, Andrew J. Lucke, Steve A. Broomfield, Melanie R. Andrews, Matthew J. Sweet, David P. Fairlie\*

**The synthesis and SAR of novel diarylsulfone 11 $\beta$ -HSD1 inhibitors**

pp 7071–7075

Xuelei Yan\*, Zhulun Wang, Athena Sudom, Mario Cardozo, Michael DeGraffenreid, Yongmei Di, Pingchen Fan, Xiao He, Juan C. Jaen, Marc Labelle, Jinsong Liu, Ji Ma, Dustin McMinn, Shichang Miao, Daqing Sun, Liang Tang, Hua Tu, Stefania Ursu, Nigel Walker, Qiuping Ye, Jay P. Powers

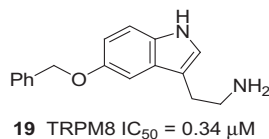


The synthesis and SAR of a series of diarylsulfone inhibitors of 11 $\beta$ -HSD1 are described. Optimization rapidly led to potent, selective, and orally bioavailable inhibitors demonstrating efficacy in a non-human primate ex vivo enzyme inhibition model.

**5-Benzyloxytryptamine as an antagonist of TRPM8**

pp 7076–7079

Jeff DeFalco\*, Daniel Steiger, Michelle Dourado, Daniel Emerling, Matthew A. J. Duncton\*



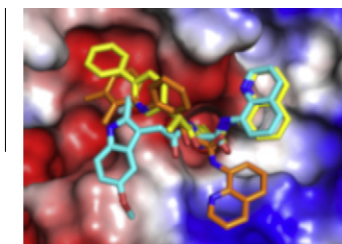
5-Benzyloxytryptamine **19** was found to be an antagonist of TRPM8. Related tryptamine derivatives showed diminished, or no activity at TRPM8.



**Antimalarial histone deacetylase inhibitors containing cinnamate or NSAID components**

pp 7080–7084

Nicole C. Wheatley, Katherine T. Andrews, Truc L. Tran, Andrew J. Lucke, Robert C. Reid, David P. Fairlie\*

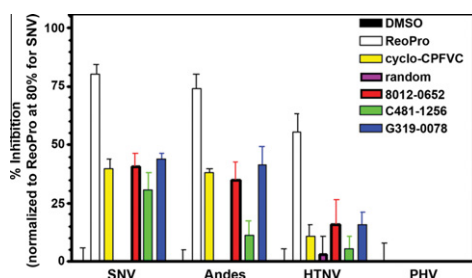


NSAID containing inhibitors docked into PfHDAC1 homology model.

**Small molecule inhibitors of hantavirus infection**

pp 7085–7091

Pamela R. Hall, Andrei Leitão, Chunyan Ye, Kathleen Kilpatrick, Brian Hjelle, Tudor I. Oprea, Richard S. Larson\*



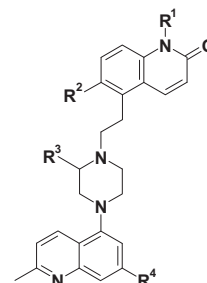
New entry inhibitors of hantaviruses that selectively target  $\beta_3$  integrin, utilized by Andes and Sin Nombre virus, were selected using LBVS and cell-based assays. These bioactive compounds are thought to bind the receptor at host cell plasma membrane, thus preventing viral entry at the cell surface.

**5-[2-[4-(2-Methyl-5-quinolinyl)-1-piperazinyl]ethyl]-2(1H)-quinolinones and 3,4-dihydro-2(1H)-quinolinones: Dual-acting 5-HT<sub>1</sub> receptor antagonists and serotonin reuptake inhibitors. Part 3**

pp 7092–7096

Steven M. Bromidge\*, Roberto Arban, Barbara Bertani, Manuela Borriello, Anna-Maria Capelli, Romano Di-Fabio, Stefania Faedo, Massimo Gianotti\*, Laurie J. Gordon, Enrica Granci, Alessandra Pasquarello, Simone K. Spada, Angela Worby, Laura Zonzini, Valeria Zucchelli

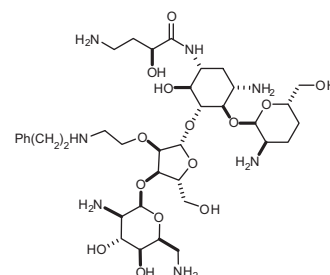
5-[2-[4-(2-Methyl-5-quinolinyl)-1-piperazinyl]ethyl]-2(1H)-quinolinones and 3,4-dihydro-2(1H)-quinolinones have been identified with different combinations of 5-HT<sub>1</sub> autoreceptor antagonist and hSerT potencies and excellent rat PK profiles. The availability of tool compounds with a range of profiles at targets known to play a key role in the control of synaptic 5-HT levels will allow exploration of different pharmacological profiles in a range of animal behavioral and disease models.

**Structure-based design, synthesis and A-site rRNA co-crystal complexes of novel amphiphilic aminoglycoside antibiotics with new binding modes: A synergistic hydrophobic effect against resistant bacteria**

pp 7097–7101

Stephen Hanessian\*, Kandasamy Pachamuthu, Janek Szychowski, Alexandre Giguère, Eric E. Swayze, Michael T. Migawa, Boris François, Jiro Kondo, Eric Westhof

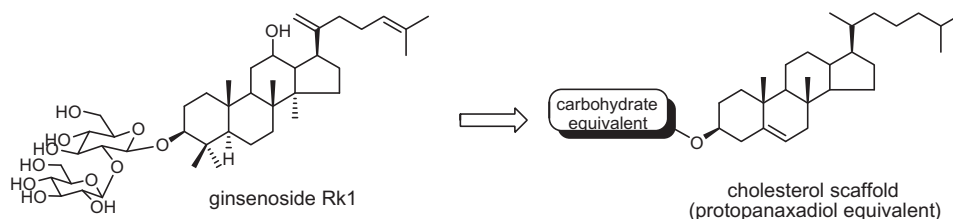
Incorporation of an hydrophobic (phenethylamino)ethyl ether at C2'' of N1-(HABA)-3',4'-dideoxyparomomycin led to a novel analog with an excellent antibacterial profile against a host of resistant bacteria.



**Cholesterol-derived novel anti-apoptotic agents on the structural basis of ginsenoside Rk1**

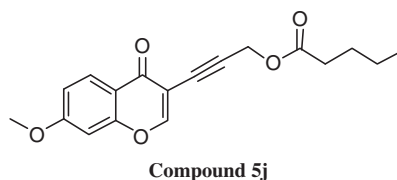
pp 7102–7105

Sujin Lee, Sony Maharjan, Kyeojin Kim, Nam-Jung Kim, Hyun-Jung Choi, Young-Guen Kwon\*, Young-Ger Suh\*

**Synthesis and in vitro antifungal activities of new 3-substituted benzopyrone derivatives**

pp 7106–7109

Zhiliang Lv, Chunquan Sheng, Yikai Zhang, Tiantian Wang, Jilu Feng, Hailing Sun, Hanyu Zhong, Mingfeng Zhang, Huan Chen, Ke Li\*

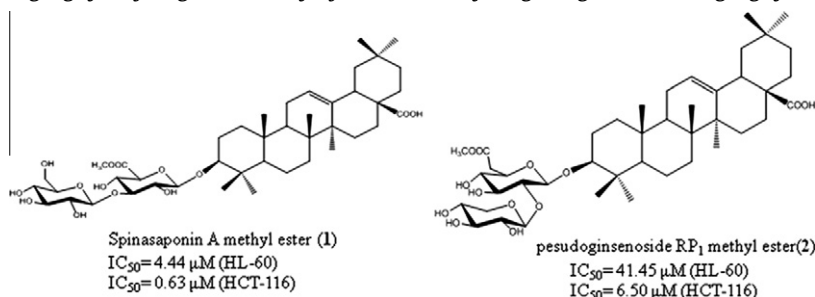


A series of benzopyrones, NOE-azole antifungal agent, was synthesized and evaluated the antifungal activity in vitro, most of which showed moderate activity. Compound **5j** (MIC<sub>80</sub> 1.5 µg/mL against *Trichophyton rubrum*) was the most potent one.

**Oleanane-type triterpenoids from *Panax stipuleanatus* and their anticancer activities**

pp 7110–7115

Chun Liang, Yan Ding, Huu Tung Nguyen, Jeong-Ah Kim, Hye-Jin Boo, Hee-Kyoung Kang, Mahn Cuong Nguyen, Young Ho Kim\*

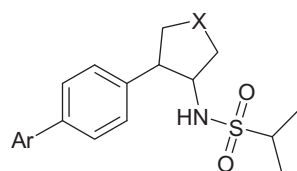


One newly (**1**) and 10 known oleanane-type triterpenoids were isolated from the methanol extract of *Panax stipuleanatus* rhizomes. Compounds **1** and **2** exhibited significant cytotoxic activity against two human cancer HL-60 and HCT-116 cell lines.

**N-Substituted pyrrolidines and tetrahydrofurans as novel AMPAR positive modulators**

pp 7116–7119

Kevin M. Thewlis\*, Laura Aldegheri, Mark H. Harries, Claudette Mookherjee, Beatrice Oliosi, Simon E. Ward

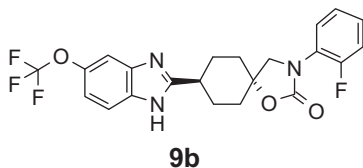


This work describes the synthesis and biological activity of a series of pyrrolidine and tetrahydrofuran analogues as AMPA receptor positive modulators. Ar = substituted phenyl or heterocycle.

**Design, synthesis and SAR of a novel series of benzimidazoles as potent NPY Y5 antagonists**

pp 7120–7123

Domenica Antonia Pizzi\*, Colin Philip Leslie, Angelica Mazzali, Catia Seri, Matteo Biagetti, Jonathan Bentley, Thorsten Genski, Romano Di Fabio, Stefania Contini, Fabio Maria Sabbatini, Laura Zonzini, Laura Caberlotto

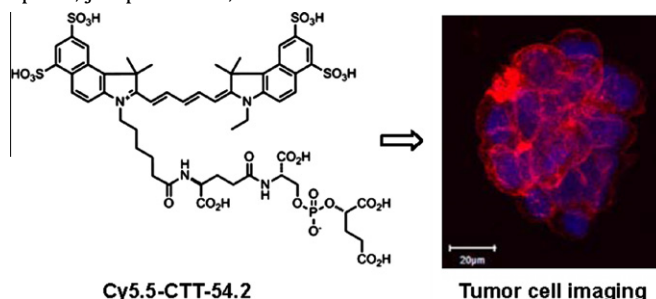


The synthesis and SAR of a series of potent NPY Y5 antagonists is reported. Optimisation led to the identification of compounds **9b** (fpK<sub>i</sub> = 9.2).

**A targeted low molecular weight near-infrared fluorescent probe for prostate cancer**

pp 7124–7126

Tiancheng Liu, Lisa Y. Wu, Mark R. Hopkins, Joseph K. Choi, Clifford E. Berkman\*



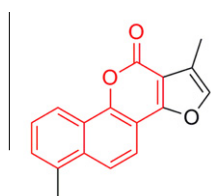
A novel near-infrared imaging probe was synthesized, which exhibited potent PSMA inhibitory activity (IC<sub>50</sub> = 0.55 nM) and PSMA-targeted imaging of prostate cancer cells in vitro.

**Neo-tanshinlactone inspired synthesis, in vitro evaluation of novel substituted benzocoumarin derivatives as potent anti-breast cancer agents**

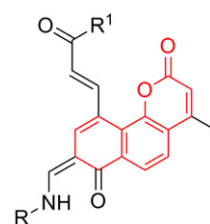
pp 7127–7131

Koneni V. Sashidhara\*, Jammikuntla N. Rosaiah, Manoj Kumar, Rishi Kumar Gara, Lakshma Vadithe Nayak, Kamini Srivastava, Hemant Kumar Bid, Rituraj Konwar

A small library of novel benzocoumarin derivatives based on naturally occurring neo-tanshinlactone scaffold was constructed and some of them showed better activity than the reference compound tamoxifen.



Neo-tanshinlactone  
(Naturally occurring)

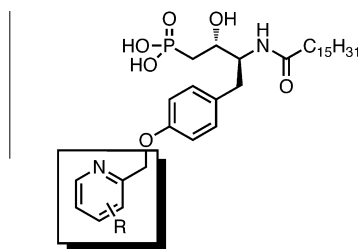


Neo-tanshinlactone analogues  
(Synthetic)

**Synthesis and structure–activity relationships of tyrosine-based inhibitors of autotaxin (ATX)**

pp 7132–7136

James E. East\*, Andrew J. Kennedy, Jose L. Tomsig, Alexandra R. De Leon, Kevin R. Lynch, Timothy L. Macdonald\*



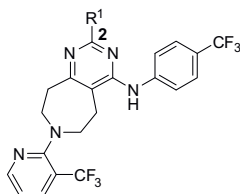
electron rich pyridyl region  
increases potency



**Discovery and synthesis of 6,7,8,9-tetrahydro-5H-pyrimido-[4,5-d]azepines as novel TRPV1 antagonists**

pp 7137–7141

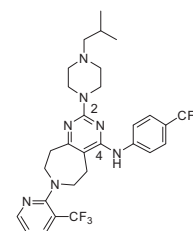
Natalie A. Hawryluk\*, Jeffrey E. Merit, Alec D. Lebsack, Bryan J. Branstetter, Michael D. Hack, Nadia Swanson, Hong Ao, Michael P. Maher, Anindya Bhattacharya, Qi Wang, Jamie M. Freedman, Brian P. Scott, Alan D. Wickenden, Sandra R. Chaplan, J. Guy Breitenbucher

**1,2-Diamino-ethane-substituted-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepines as TRPV1 antagonists with improved properties**

pp 7142–7146

Alec D. Lebsack\*, Jason C. Rech, Bryan J. Branstetter, Natalie A. Hawryluk, Jeffrey E. Merit, Brett Allison, Raymond Rynberg, Johnathan Buma, Michele Rizzolio, Nadia Swanson, Hong Ao, Michael P. Maher, Michelle Herrmann, Jamie Freedman, Brian P. Scott, Lin Luo, Anindya Bhattacharya, Qi Wang, Sandra R. Chaplan, Alan D. Wickenden, J. Guy Breitenbucher

A series of 1,2-diamino-ethane-substituted-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepines were synthesized and evaluated for improved physiochemical and pharmacokinetic properties while maintaining TRPV1 antagonist activity.

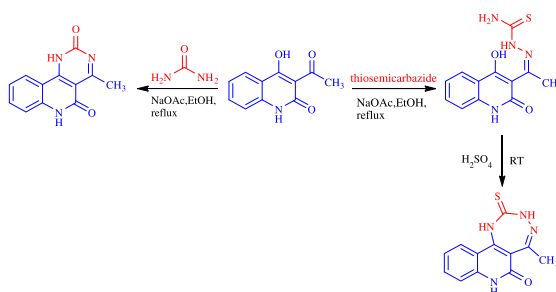


13  
hTRPV1 IC<sub>50</sub> = 11 ± 6 nM  
rTRPV1 IC<sub>50</sub> = 89 ± 43 nM

**Synthesis, antioxidant and toxicological study of novel pyrimido quinoline derivatives from 4-hydroxy-3-acyl quinolin-2-one**

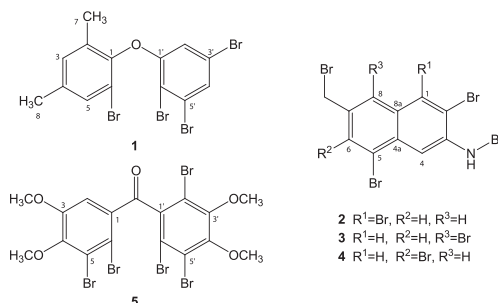
pp 7147–7151

Mathan Sankaran, Chandraprakash Kumarasamy, Uvarani Chokkalingam, Palathurai Subramaniam Mohan\*

**Highly brominated metabolites from marine red alga *Laurencia similis* inhibit protein tyrosine phosphatase 1B**

pp 7152–7154

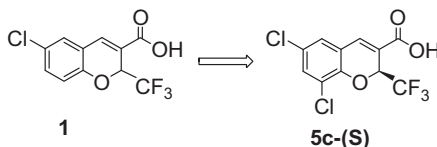
Jianchun Qin, Hua Su, Yamei Zhang, Jinming Gao, Lin Zhu, Xian Wu, Hongyu Pan\*, Xiang Li\*



**The novel benzopyran class of selective cyclooxygenase-2 inhibitors-part I: The first clinical candidate**

pp 7155–7158

Jane L. Wang\*, Jeffery Carter, James R. Kiefer, Ravi G. Kurumbail, Jennifer L. Pawlitz, David Brown, Susan J. Hartmann, Matthew J. Graneto, Karen Seibert, John J. Talley

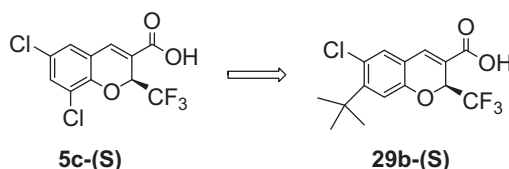


The design and synthesis of a series of potent and selective COX-2 inhibitors based on a benzopyran lead (**1**) is described. Our SAR studies allowed us to optimize this series resulting in the identification of clinical compound **5c-(S)**, which possesses superior in vivo efficacy in animal models of inflammation and pain.

**The novel benzopyran class of selective cyclooxygenase-2 inhibitors. Part 2: The second clinical candidate having a shorter and favorable human half-life**

pp 7159–7163

Jane L. Wang\*, David Limburg, Matthew J. Graneto, John Springer, Joseph Rogier Bruce Hamper, Subo Liao, Jennifer L. Pawlitz, Ravi G. Kurumbail, Timothy Maziasz, John J. Talley, James R. Kiefer\*, Jeffery Carter



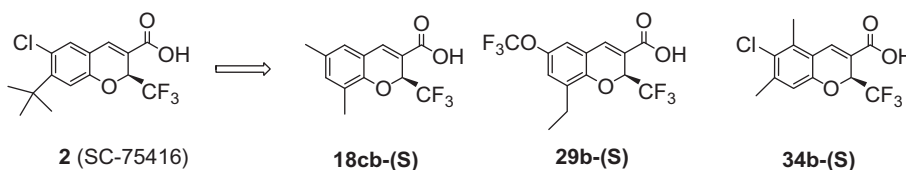
We describe our strategy to discover a selective inhibitor of COX-2 with a shorter human half-life compared with the previous clinical candidate SD-8381 (**5c-(S)**,  $t_{1/2}$  ~160 h). In this paper, we disclose a series of selective COX-2 inhibitors based on the benzopyran template that display potency against COX-2 in animal models of pain and inflammation. We also discussed the discovery of two COX-2 binding modes and utilizing the microsomal data as a filter leading to the discovery of clinical candidate **29b-(S)** (SC-75416), successfully advanced through a phase II efficacy trial.

**The novel benzopyran class of selective cyclooxygenase-2 inhibitors. Part III: The three microdose candidates**

pp 7164–7168

Jane L. Wang\*, Karl Aston, David Limburg, Cindy Ludwig, Ann E. Hallinan, Francis Koszyk, Bruce Hamper, David Brown, Matthew Graneto, John Talley, Timothy Maziasz, Jaime Masferrer, Jeffery Carter

Our objective described in this Letter was to discover selective inhibitors of COX-2 that were efficacious in animal models of inflammation and pain and that would exhibit acceptable pharmacokinetic properties allowing them to advance into clinical development, following SC-75416 (**2**), already in clinical trials. Since incorporation of metabolically labile moieties in this series provided a means for reducing their half-life, in this Letter we discuss the extension of this strategy and the application of a Phase I human microdose screening strategy to advance compounds for which allometric scaling had been marked by a high degree of uncertainty. Using this Phase I microdose screening strategy, we rapidly obtained human pharmacokinetic data for the three clinical agents **18c-(S)**, **29b-(S)**, and **34b-(S)** affording us the data to allow selection of appropriate candidates for further development.



\*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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