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# Bioorganic & Medicinal Chemistry Letters

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## Bioorganic & Medicinal Chemistry Letters Volume 20, Issue 8, 2010

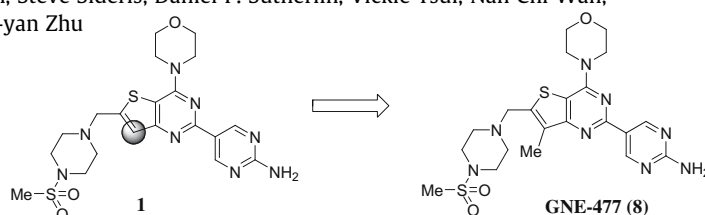
### Contents

#### ARTICLES

##### Identification of GNE-477, a potent and efficacious dual PI3K/mTOR inhibitor

pp 2408–2411

Timothy P. Heffron\*, Megan Berry, Georgette Castanedo, Christine Chang, Irina Chuckowree, Jennafer Dotson, Adrian Folkes, Janet Gunzner, John D. Lesnick, Cristina Lewis, Simon Mathieu, Jim Nonomiya, Alan Olivero, Jodie Pang, David Peterson, Laurent Salphati, Deepak Sampath, Steve Sideris, Daniel P. Sutherlin, Vickie Tsui, Nan Chi Wan, Shumei Wang, Susan Wong, Bing-yan Zhu

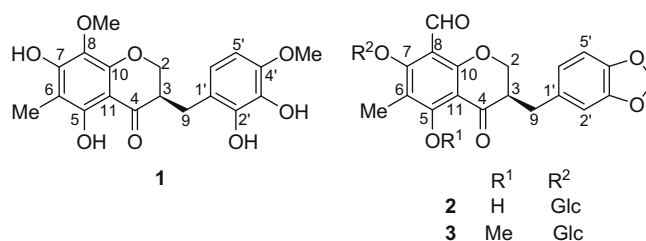


Efforts to identify potent small molecule inhibitors of PI3 kinase and mTOR led to the evaluation of tetrasubstituted thienopyrimidines. These molecules generally have reduced in vivo clearance relative to the trisubstituted thienopyrimidines culminating in the identification of **GNE-477 (8)**.

##### Homoisoflavonoid derivatives from the roots of *Ophiopogon japonicus* and their in vitro anti-inflammation activity

pp 2412–2416

Tran Manh Hung, Cao Van Thu, Nguyen Tien Dat, Sung-Woo Ryoo, Jeong Hyung Lee, Jin Cheol Kim, Minkyun Na, Hyun-Ju Jung, KiHwan Bae\*, Byung Sun Min\*

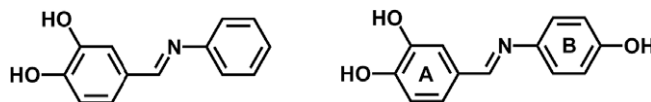


Three new homoisoflavonoids (**1–3**) were isolated from the roots of *Ophiopogon japonicus* (Liliaceae) and investigated by their effects on the release of the inflammatory chemokine eotaxin, stimulated by IL-4 and the combination of IL-4 and TNF- $\alpha$  in BEAS-2B cells.

##### Antioxidant and antiproliferative activities of hydroxyl-substituted Schiff bases

pp 2417–2420

Li-Xia Cheng, Jiang-Jiang Tang, Hui Luo, Xiao-Ling Jin, Fang Dai, Jie Yang, Yi-Ping Qian, Xiu-Zhuang Li, Bo Zhou\*



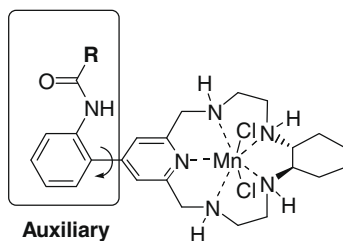
Eight hydroxyl-substituted Schiff bases were synthesized and bio-evaluated for their antioxidant and antiproliferative activities. Structure–activity relationship analysis indicates that *o*-diphenolic groups and 4-hydroxyl group attached to the aromatic B ring contribute critically to the activities.



## Synthesis and SOD activity of manganese complexes of substituted pyridino pentaaza macrocycles that contain axial auxiliary

pp 2421–2424

Hakyoung Lee, Wonchoul Park, Dongyeol Lim\*



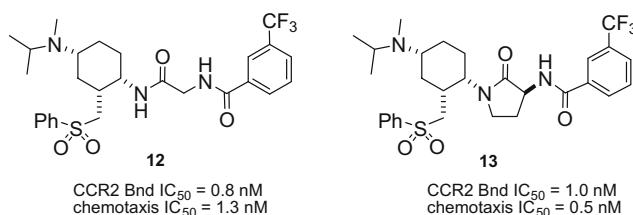
The synthesis and SOD-like activity of new manganese(II) complex of substituted pyridino pentaaza macrocyclic ligands are reported.



### $\gamma$ -Lactams as glycinamide replacements in cyclohexane-based CC chemokine receptor 2 (CCR2) antagonists

**pp 2425-2430**

Robert J. Cherney\*, Ruowei Mo, Dayton T. Meyer, Matthew E. Voss, Michael G. Yang, Joseph B. Santella III, John V. Duncia, Yvonne C. Lo, Gengjie Yang, Persymphonie B. Miller, Peggy A. Scherle, Qihong Zhao, Sandhya Mandlekar, Mary Ellen Cvijic, Joel C. Barrish, Carl P. Decicco, Percy H. Carter

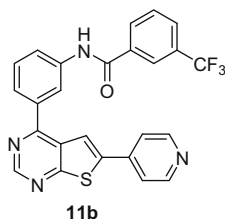


We describe the design, synthesis, and evaluation, of  $\gamma$ -lactams as glycinamide replacements within a series of di- and trisubstituted cyclohexane CCR2 antagonists.

### B-Raf kinase inhibitors: Hit enrichment through scaffold hopping

pp 2431–2434

Ariamala Gopalsamy\*, Mengxiao Shi, Yongbo Hu, Frederick Lee, Larry Feldberg, Eileen Frommer, Steven Kim, Karen Collins, Donald Wojciechowicz, Robert Mallon

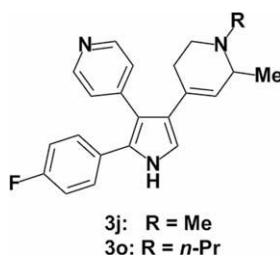


Scaffold hopping strategy was employed to replace the HTS hit scaffold pyrazolo[1,5-*a*]pyrimidine. This strategy led to the identification of additional lead compound **11b** with enhanced enzyme and cellular potency, while maintaining good selectivity over a number of kinases.

## Tetrahydropyridine derivatives with inhibitory activity on the production of proinflammatory cytokines: Part 2

pp 2435-2437

Akira Nakao\*, Nobuyuki Ohkawa, Takayoshi Nagasaki, Takashi Kagari, Hiromi Doi, Takaichi Shimozato, Shigeru Ushiyama, Kazumasa Aoki



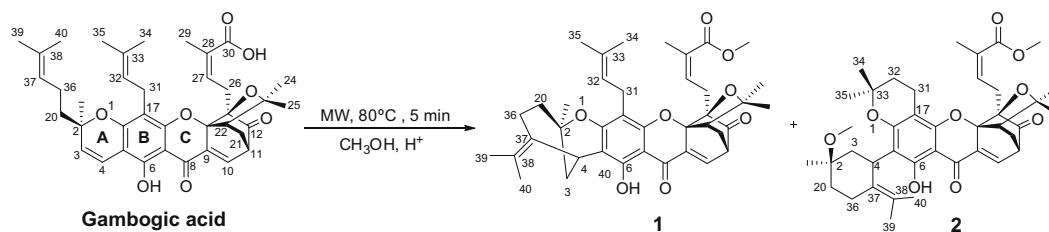
The synthesis of the proinflammatory cytokine production inhibitor **3o** (TNF $\alpha$  IC<sub>50</sub> = 0.44  $\mu$ M) and **3j** (TNF $\alpha$  ID<sub>50</sub> = 1.42 mg/kg) are reported.



### Spectacular modification of Gambogic acid on microwave irradiation in methanol: Isolation and structure identification of two products with potent anti-tumor activity

pp 2438–2442

Xiaojian Wang, Na Lu, Qian Yang, Qinsheng Dai, Lei Tao, Xiaoke Guo, Qinglong Guo\*, Qidong You\*



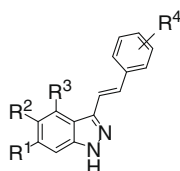
Treatment of gambogic acid with methanol in acidic condition under microwave irradiation led to the formation of two new products bearing spectacular A ring systems with promising anti-tumor effect.



### Synthesis and evaluation of alkenyl indazoles as selective Aurora kinase inhibitors

pp 2443–2447

Stéphanie Blanchard\*, Anthony D. William, Angeline C.-H. Lee, Anders Poulsen, Ee Ling Teo, Weiping Deng, Noah Tu, Evelyn Tan, Kay Lin Goh, Wai Chung Ong, Chee Pang Ng, Kee Chuan Goh, Zahid Bonday, Eric T. Sun

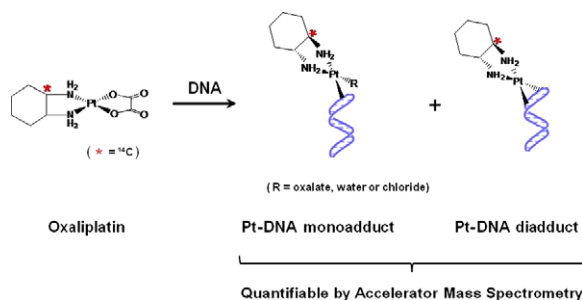


A series of alkenyl indazole derivatives were prepared and evaluated as selective Aurora inhibitors.

### Towards biomarker-dependent individualized chemotherapy: Exploring cell-specific differences in oxaliplatin–DNA adduct distribution using accelerator mass spectrometry

pp 2448–2451

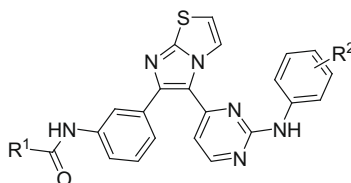
Sang Soo Hah\*, Paul T. Henderson, Kenneth W. Turteltaub



### Imidazo[2,1-b]thiazoles: Multitargeted inhibitors of both the insulin-like growth factor receptor and members of the epidermal growth factor family of receptor tyrosine kinases

pp 2452–2455

Steve D. Fidanze\*, Scott A. Erickson, Gary T. Wang, Robert Mantei, Richard F. Clark, Bryan K. Sorensen, Nwe Y. Bamaung, Peter Kovar, Eric F. Johnson, Kerren K. Swinger, Kent D. Stewart, Qian Zhang, Lora A. Tucker, William N. Pappano, Julie L. Wilsbacher, Jieyi Wang, George S. Sheppard, Randy L. Bell, Steven K. Davidsen, Robert D. Hubbard



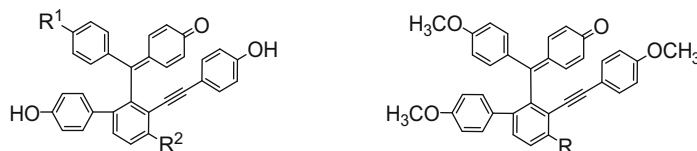
The design and enzyme activities of a novel class of imidazo[2,1-b]thiazoles is presented.



**Antimicrobial selaginellin derivatives from *Selaginella pulvinata***

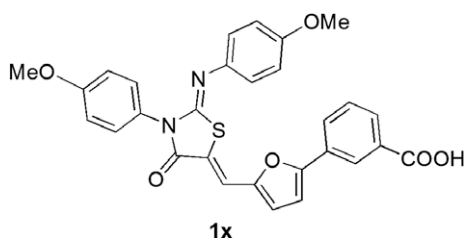
pp 2456–2460

Yuan Cao, Ji-Jun Chen, Ning-Hua Tan, Lukas Oberer, Trixie Wagner, Yong-Ping Wu, Guang-Zhi Zeng, He Yan, Qiang Wang\*

Selaginellin derivatives from *Selaginella pulvinata* with good antimicrobial activity.**Design, synthesis, and antibiofilm activity of 2-arylimino-3-aryl-thiazolidine-4-ones**

pp 2461–2464

Bin Pan, Ren-Zheng Huang, Shi-Qing Han\*, Di Qu, Ming-Li Zhu, Ping Wei, Han-Jie Ying

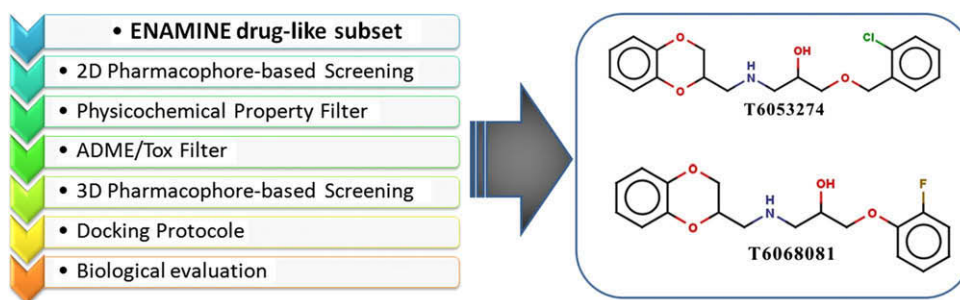


The minimal inhibitory concentration (MIC), minimal bactericidal concentration (MBC) and antibiofilm concentration assay of **1x** were 6.25  $\mu$ M, 25  $\mu$ M and 6.25  $\mu$ M against *Staphylococcus epidermidis*, respectively.

**The development and validation of a novel virtual screening cascade protocol to identify potential serotonin 5-HT<sub>7</sub>R antagonists**

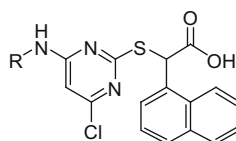
pp 2465–2468

Rafał Kurczab, Mateusz Nowak, Zdzisław Chilmonczyk, Ingebrigt Sylte, Andrzej J. Bojarski\*

**Rational design of a pirinixic acid derivative that acts as subtype-selective PPAR $\gamma$  modulator**

pp 2469–2473

Theresa M. Thieme, Ramona Steri, Ewgenij Proschak, Alexander Paulke, Gisbert Schneider, Manfred Schubert-Zsilavecz\*



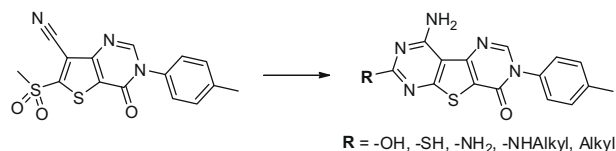
A series of pirinixic acid derivatives were synthesized and evaluated as subtype-selective peroxisome proliferator-activated receptor (PPAR $\gamma$ ) agonists and modulator by in vitro transactivation of human PPARs.



**A-ring modifications on the triazafluorenone core structure and their mGluR1 antagonist properties**

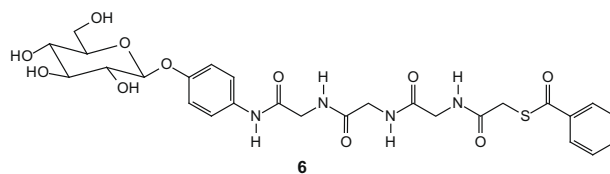
pp 2474–2477

T. K. Sasikumar\*, Li Qiang, Duane A. Burnett, William J. Greenlee, Cheng Li, Mariagrazia Grilli, Rosalia Bertorelli, Gianluca Lozza, Angelo Reggiani

**A novel D-glucose derivative radiolabeled with technetium-99m: Synthesis, biodistribution studies and scintigraphic images in an experimental model of Ehrlich tumor**

pp 2478–2480

André Luís Branco de Barros, Valbert Nascimento Cardoso, Luciene das Graças Mota, Elaine Amaral Leite, Mônica Cristina de Oliveira, Ricardo José Alves\*

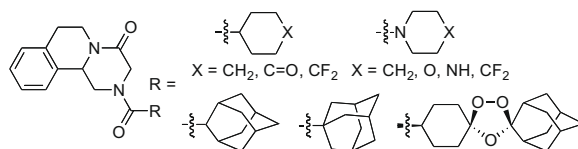


A D-glucose analogue was synthesized; its biodistribution studies and scintigraphic images were performed.

**Praziquantel analogs with activity against juvenile *Schistosoma mansoni***

pp 2481–2484

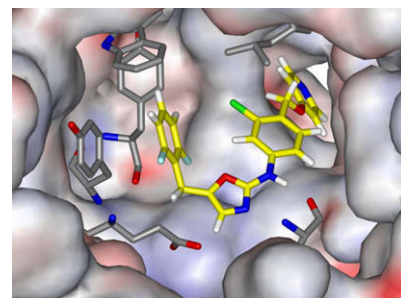
Yuxiang Dong, Jacques Chollet, Mireille Vargas, Nuha R. Mansour, Quentin Bickle, Yazen Alnouti, Jiangeng Huang, Jennifer Keiser, Jonathan L. Vennerstrom\*

**Eastern extension of azoles as non-nucleoside inhibitors of HIV-1 reverse transcriptase; cyano group alternatives**

pp 2485–2488

Cheryl S. Leung, Jacob G. Zeevaert, Robert A. Domaoal, Mariela Bollini, Vinay V. Thakur, Krasimir A. Spasov, Karen S. Anderson\*, William L. Jorgensen\*

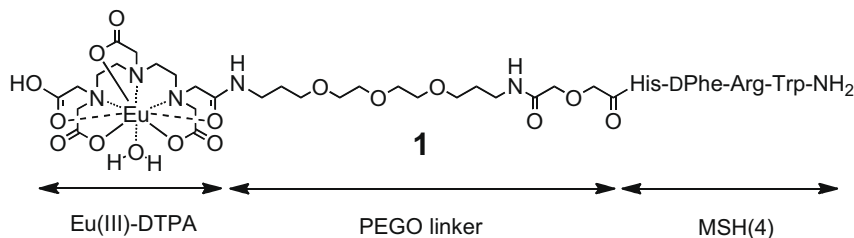
Synthesis, assaying, and computational results are reported for new anti-HIV agents that exhibit high potency and low cytotoxicity. Extension into an eastern channel in the HIV-1 reverse transcriptase binding site is investigated.



### Synthesis and characterization of a Eu-DTPA-PEGO-MSH(4) derivative for evaluation of binding of multivalent molecules to melanocortin receptors

pp 2489–2492

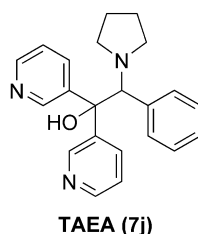
Liping Xu, Josef Vagner, Ramesh Alleti, Venkataramanarao Rao, Bhumasamudram Jagadish, David L. Morse, Victor J. Hruby, Robert J. Gillies, Eugene A. Mash\*



### Discovery of triarylethanamine inhibitors of the Kv1.5 potassium channel

pp 2493–2496

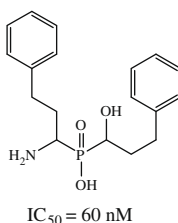
Douglas C. Beshore\*, Nigel J. Liverton, Charles J. McIntyre, Christopher F. Claiborne, Brian Libby, J. Christopher Culberson, Joseph J. Salata, Christopher P. Regan, Joseph J. Lynch, Laszlo Kiss, Robert H. Spencer, Stephanie A. Kane, Rebecca B. White, Suzie Yeh, George D. Hartman, Christopher J. Dinsmore



### Identification of very potent inhibitor of human aminopeptidase N (CD13)

pp 2497–2499

Renata Grzywa, Józef Oleksyszyn, Guy S. Salvesen, Marcin Drąg\*

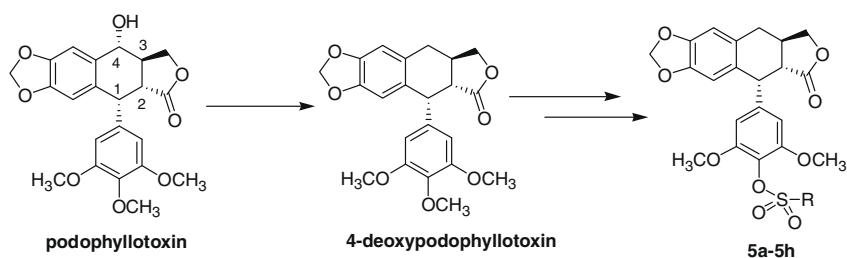


New potent human aminopeptidase N (CD13) inhibitor (IC<sub>50</sub> = 60 nM) is reported.

### Natural products-based insecticidal agents 5. Design, semisynthesis and insecticidal activity of novel 4'-substituted benzenesulfonate derivatives of 4-deoxypodophyllotoxin against *Mythimna separata* Walker in vivo

pp 2500–2502

Hui Xu\*, Juan-Juan Wang

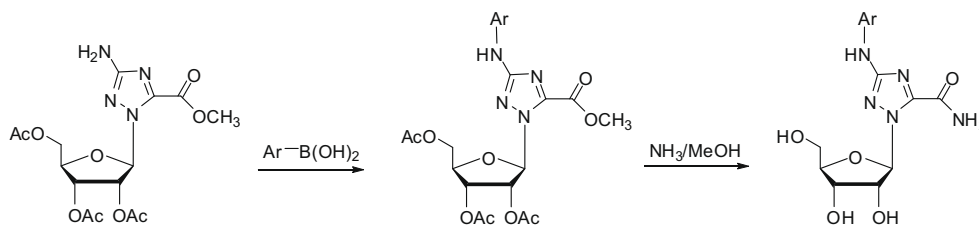


Some 4'-substituted benzenesulfonates of 4-deoxypodophyllotoxin exhibited the potent insecticidal activity.

**N-Aryltriazole ribonucleosides with potent antiproliferative activity against drug-resistant pancreatic cancer**

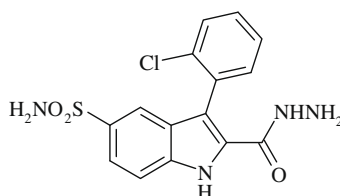
pp 2503–2507

Yang Liu, Yi Xia, Yuting Fan, Alain Maggiani, Palma Rocchi, Fanqi Qu, Juan L. Iovanna, Ling Peng\*

**Carbonic anhydrase inhibitors. The  $\beta$ -carbonic anhydrases from the fungal pathogens *Cryptococcus neoformans* and *Candida albicans* are strongly inhibited by substituted-phenyl-1H-indole-5-sulfonamides**

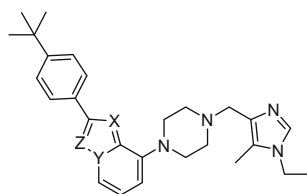
pp 2508–2511

Özlen Güzel, Alfonso Maresca, Rebecca A. Hall, Andrea Scozzafava, Antonio Mastrolorenzo, Fritz A. Mühlischlegel, Claudiu T. Supuran\*

 $K_i = 640 \text{ nM}$  (hCA I);  $K_i = 38.8 \text{ nM}$  (hCA II);  $K_i = 8.0 \text{ nM}$  (Can2);  $K_i = 45 \text{ nM}$  (CaNce103).**Synthesis and biological evaluation of piperazinyl heterocyclic antagonists of the gonadotropin releasing hormone (GnRH) receptor**

pp 2512–2515

Matthew D. Vera, Joseph T. Lundquist IV, Murty V. Chengalvala, Joshua E. Cottom, Irene B. Feingold, Lloyd M. Garrick, Daniel M. Green, Diane B. Hauze, Charles W. Mann, John F. Mehlmann, John F. Rogers, Linda Shanno, Jay E. Wrobel, Jeffrey C. Pelletier\*

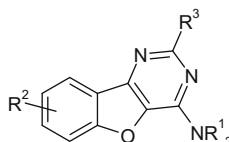
 $X = \text{N(H)}, \text{O}, \text{S}; Y = \text{C}, \text{N}; Z = \text{N(H)}, \text{O}, \text{S}$ 

A series of bicycloheterocyclic replacements for the previously described benzimidazole template were prepared and tested for GnRH activity.

**Identification and hit-to-lead exploration of a novel series of histamine H4 receptor inverse agonists**

pp 2516–2519

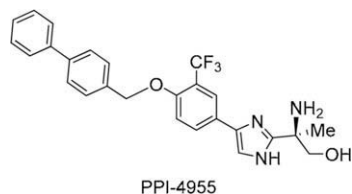
Sue Cramp\*, Hazel J. Dyke, Christopher Higgs, David E. Clark, Matthew Gill, Pascal Savy, Neil Jennings, Steve Price, Peter M. Lockey, Dennis Norman, Soraya Porres, Francis Wilson, Alison Jones, Nigel Ramsden, Raffaella Mangano, Dan Leggate, Marie Andersson, Richard Hale



The hit-to-lead exploration of a series of novel, potent and selective series of histamine H4 receptor inverse agonists originating from a virtual screening approach is described.

## Exploration of amino alcohol derivatives as novel, potent, and highly selective sphingosine-1-phosphate receptor subtype-1 agonists pp 2520–2524

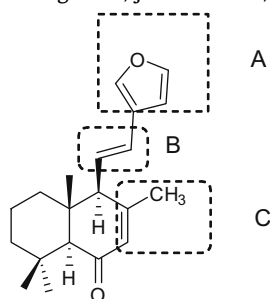
Ghotas Evindar\*, Sylvie G. Bernier, Elisabeth Doyle, Malcolm J. Kavarana, Alexander L. Satz, Jeanine Lorusso, Heather S. Blanchette, Ashis K. Saha, Gerhard Hannig, Barry A. Morgan, William F. Westlin



Identification of a selectivity enhancing moiety has allowed for discovery of pro-drug PPI-4955 (**21b**), a potent and selective sphingosine-1-phosphate receptor-1 agonist, with excellent dose responsiveness and pharmacodynamic properties.

## Synthesis, cytotoxic activity and structure–activity relationships of hedychenone analogues pp 2525–2528

P. Prabhakar Reddy, Aditya G. Lavekar, K. Suresh Babu, R. Ranga Rao, J. Shashidhar, G. Shashikiran, J. Madhusudana Rao\*



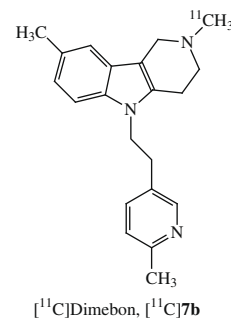
A series of analogues have been synthesized by modification of the furanoid ring, double bond and the vinylic methyl functionality of this natural product lead. All the compounds were tested for their in vitro cytotoxic activity against human cancer cell lines.



## [<sup>11</sup>C]Dimebon, radiosynthesis and lipophilicity of a new potential PET agent for imaging of Alzheimer's disease and Huntington's disease pp 2529–2532

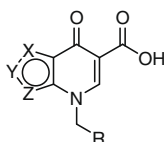
Mingzhang Gao, Min Wang, Gary D. Hutchins, Qi-Huang Zheng\*

Radiosynthesis and lipophilicity of [<sup>11</sup>C]Dimebon, a new potential PET agent for imaging of Alzheimer's disease and Huntington's disease, are first reported.



## Heterocyclic fused pyridone carboxylic acid M<sub>1</sub> positive allosteric modulators pp 2533–2537

Scott D. Kuduk\*, Christina N. Di Marco, Ronald K. Chang, William J. Ray, Lei Ma, Marion Wittmann, Matthew A. Seager, Kenneth A. Koeplinger, Charles D. Thompson, George D. Hartman, Mark T. Bilodeau

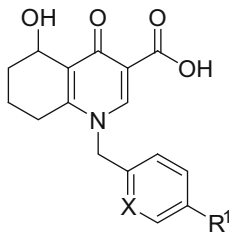


The phenyl ring in a series of quinolone carboxylic acid M<sub>1</sub> positive allosteric modulators was replaced with a variety of heterocycles in order to reduce protein plasma binding and enhance CNS exposure.



**Hydroxy cycloalkyl fused pyridone carboxylic acid M<sub>1</sub> positive allosteric modulators****pp 2538–2541**

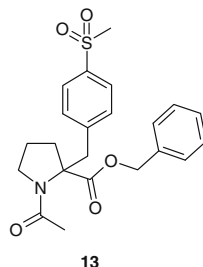
Scott D. Kuduk\*, Robert M. DiPardo, Douglas C. Beshore, William J. Ray, Lei Ma, Marion Wittmann, Matthew A. Seager, Kenneth A. Koeplinger, Charles D. Thompson, George D. Hartman, Mark T. Bilodeau



Incorporation of hydroxycycloalkyl fused pyridone carboxylic acids in lieu of quinolone carboxylic acids enhance free fraction without increased susceptibility to P-glycoprotein transport.

**Benzyl prolinates as novel selective KCC2 blockers****pp 2542–2545**

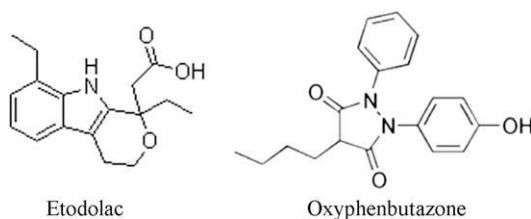
Cécile Pégurier\*, Nathalie Bosman, Philippe Collart, Marie-Laure Delporte, Karine Leclercq, Sébastien Lengelé, Ananda Kumar Kanduluru, Stéphane Meunier, Nathalie Pacico, Lakshmana Rao Vadali, Alain Wagner, Christian Wolff, Laurent Provins



The benzyl proline **13** has been identified as a potent KCC2 blocker with selectivity versus NKCC1 and favorable ADME properties. It was evaluated in an in vivo model of epilepsy, the audiogenic mouse seizure test.

**Chemopreventive activities of etodolac and oxyphenbutazone against mouse skin carcinogenesis****pp 2546–2548**

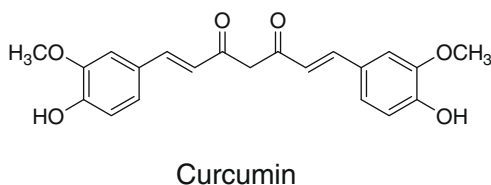
Govind J. Kapadia\*, Magnus A. Azuine, Yuuko Shigeta, Nobutaka Suzuki, Harukuni Tokuda



Inhibition of mouse skin cancer by non-steroidal anti-inflammatory drugs, etodolac and oxyphenbutazone is reported.

**Curcumin derivatives inhibit testicular 17 $\beta$ -hydroxysteroid dehydrogenase 3****pp 2549–2551**

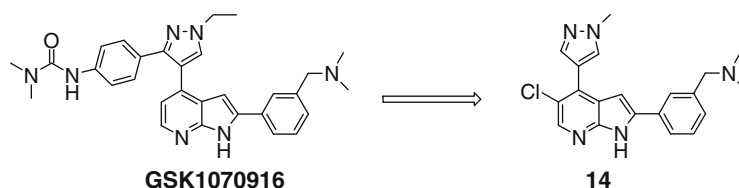
Guo-Xin Hu, Guang Liang, Yanhui Chu, Xiaokun Li, Qing-Quang Lian\*, Han Lin, Yi He, Yadong Huang, Dianne O. Hardy, Ren-Shan Ge\*



**Discovery of a new series of Aurora inhibitors through truncation of GSK1070916**

pp 2552–2555

Jesus R. Medina\*, Seth W. Grant, Jeffrey M. Axten, William H. Miller, Carla A. Donatelli, Mary Ann Hardwicke, Catherine A. Oleykowski, Qiaoyin Liao, Ramona Plant, Hong Xiang

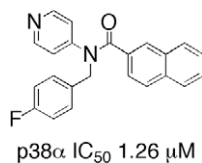


The SAR results from this investigation will be presented with an emphasis on the impact structural changes have on the cellular phenotype.

**Amide-based inhibitors of p38 $\alpha$  MAP kinase. Part 1: Discovery of novel *N*-pyridyl amide lead molecules**

pp 2556–2559

Gregory R. Luedtke, Kurt Schinzel, Xuefei Tan\*, Richland W. Tester, Imad Nashashibi, Yong-jin Xu, Sundeep Dugar, Daniel E. Levy\*, Joon Jung

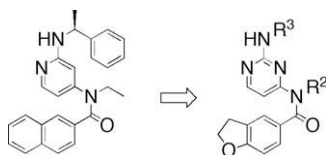


A novel series of *N*-pyridyl amide p38 $\alpha$  kinase inhibitors is described. The proposed binding modes of the initial hits were evaluated against SAR findings to provide rationale for further development of this structural class.

**Amide-based inhibitors of p38 $\alpha$  MAP kinase. Part 2: Design, synthesis and SAR of potent *N*-pyrimidyl amides**

pp 2560–2563

Richland Tester, Xuefei Tan\*, Gregory R. Luedtke, Imad Nashashibi, Kurt Schinzel, Weiling Liang, Joon Jung, Sundeep Dugar, Albert Licican, Jocelyn Tabora, Daniel E. Levy\*, Steven Do

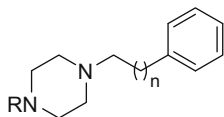


Identification and optimization of a new class of *N*-pyrimidyl amide based p38 $\alpha$  MAP kinase inhibitors is described. The lead structure was derived from a previously reported class of pyridine-based amides. p38 $\alpha$  activity (enzymatic/cellular) and CYP3A4 data for the new series are presented.

**The effect of the pyridyl nitrogen position in pyridylpiperazine sigma ligands**

pp 2564–2565

Lidiya Stavitskaya, Michael J. Seminerio, Marilyn M. Matthews-Tsourounis, Rae R. Matsumoto, Andrew Coop\*

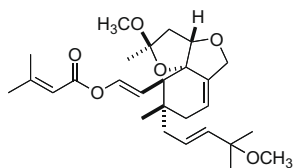
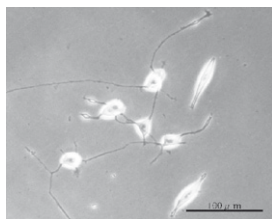


- 1** R = 4-pyridyl, n = 1
- 2** R = 4-pyridyl, n = 2
- 3** R = 3-pyridyl, n = 1
- 4** R = 3-pyridyl, n = 2
- 5\*** R = 2-pyridyl, n = 1
- 6\*** R = 2-pyridyl, n = 2

**NGF-potentiating vibsane-type diterpenoids from *Viburnum sieboldii***

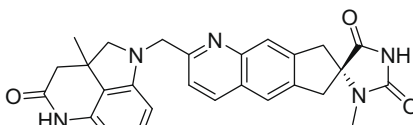
pp 2566–2571

Miwa Kubo, Yoshiko Kishimoto, Kenichi Harada, Hideaki Hioki, Yoshiyasu Fukuyama\*

**Identification of potent, highly constrained CGRP receptor antagonists**

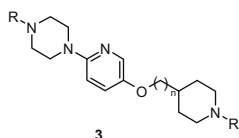
pp 2572–2576

Craig A. Stump\*, Ian M. Bell, Rodney A. Bednar, John F. Fay, Steven N. Gallicchio, James C. Hershey, Richard Jelley, Constantine Kreatsoulas, Eric L. Moore, Scott D. Mosser, Amy G. Quigley, Shane A. Roller, Christopher A. Salvatore, Steven S. Sharik, Cory R. Theberge, C. Blair Zartman, Stefanie A. Kane, Samuel L. Graham, Harold G. Selnick, Joseph P. Vacca, Theresa M. Williams

**19**  $K_i = 0.52$  nM**2,5-Disubstituted pyridines as potent GPR119 agonists**

pp 2577–2581

Yulin Wu\*, Judith D. Kuntz, Andrew J. Carpenter\*, Jing Fang, Howard R. Sauls, Daniel J. Gomez, Carina Ammala, Yun Xu, Shane Hart, Sarva Tadepalli

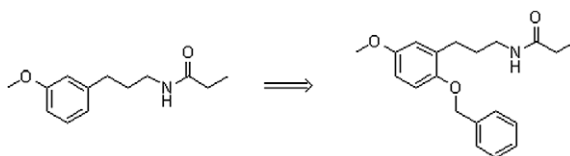
**3**

A series of 2-piperazinyl-5-alkoxypyridines (**3**) were synthesized and screened against human GPR119 receptor. Through SAR analysis, compounds containing 2-alkylsulfonylpiperazinyl-5-alkoxypyridines were discovered and found to be potent agonists of the human GPR119 receptor.

**Synthesis of substituted *N*-[3-(3-methoxyphenyl)propyl] amides as highly potent MT<sub>2</sub>-selective melatonin ligands**

pp 2582–2585

Yueqing Hu, Maurice K. C. Ho, King H. Chan, David C. New, Yung H. Wong\*

**1b****2b**MT<sub>2</sub>  $K_i = 7.07$  nMMT<sub>2</sub>  $K_i = 0.55$  pM

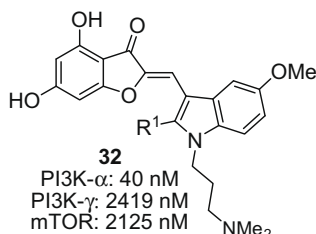
A benzyloxy substituent incorporated at C6 position of the 3-methoxyphenyl ring dramatically enhanced the melatonin MT<sub>2</sub>-binding affinity.



### Novel benzofuran-3-one indole inhibitors of PI3 kinase- $\alpha$ and the mammalian target of rapamycin: Hit to lead studies

pp 2586–2590

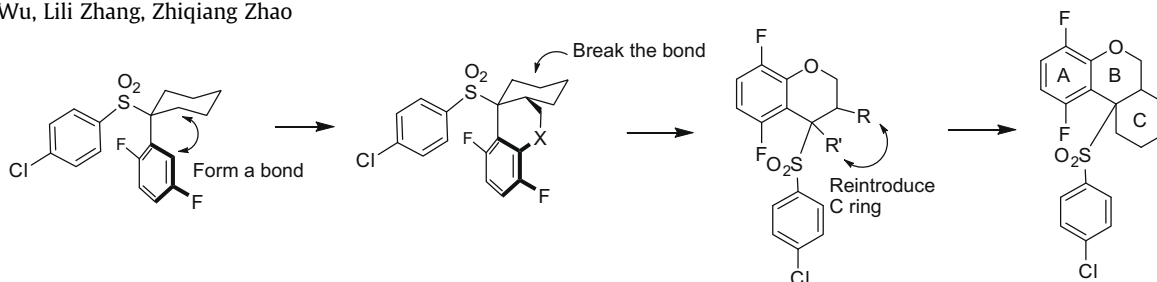
Matthew G. Bursavich, Natasja Brooijmans, Lawrence Feldberg, Irwin Hollander, Stephen Kim, Sabrina Lombardi, Kaapjoo Park, Robert Mallon, Adam M. Gilbert\*



### Design and synthesis of tricyclic sulfones as $\gamma$ -secretase inhibitors with greatly reduced Notch toxicity

pp 2591–2596

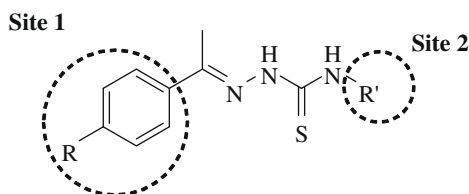
Ruo Xu\*, David Cole, Ted Asberom, Tom Bara, Chad Bennett, Duane A. Burnett, John Clader, Martin Domalski, William Greenlee, Lynn Hyde, Hubert Josien, Hongmei Li, Mark McBriar, Brian McKittrick, Andrew T. McPhail, Dmitri Pissarnitski, Li Qiang, Murali Rajagopalan, Thavalakulamgar Sasikumar, Jing Su, Haiqun Tang, Wen-Lian Wu, Lili Zhang, Zhiqiang Zhao



### Substituted hydrazinecarbothioamide as potent antitubercular agents: Synthesis and quantitative structure–activity relationship (QSAR)

pp 2597–2600

Supriya Singh, Pintu K. Mandal, Nagendra Singh, Anup K. Misra, Shubhra Singh, Vinita Chaturvedi, Sudhir Sinha, Anil K. Saxena\*

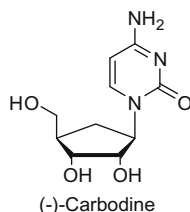


A series of novel substituted hydrazinecarbothioamides was synthesized and evaluated for anti-TB activity. Three most active compounds viz. **1**, **6** and **12** were found to exhibit minimum inhibitory concentration (MIC) of 0.4  $\mu$ g/mL whereas four compounds viz. **3**, **5**, **10** and **11** showed comparatively lesser activity with MIC value of 0.8  $\mu$ g/mL against *Mycobacterium tuberculosis* strain. A highly significant QSAR equation explaining 81.8% variance is described.

### (–)-Carbodine: Enantiomeric synthesis and in vitro antiviral activity against various strains of influenza virus including H5N1 (avian influenza) and novel 2009 H1N1 (swine flu)

pp 2601–2604

Jagadeeshwar R. Rao, Ashok K. Jha, Ravindra K. Rawal, Ashoke Sharon, Craig W. Day, Dale L. Barnard, Donald F. Smee, Chung K. Chu\*

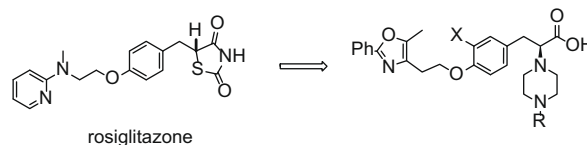


Enantiomerically pure cyclopentyl cytosine [(–)-carbodine] exhibited potent antiviral activity against H5N1 (avian) and novel H1N1 (swine) flu.

**(S)-3-(4-(2-(5-Methyl-2-phenyloxazol-4-yl)ethoxy)phenyl)-2-(piperazin-1-yl)propanoic acid compounds: Synthesis and biological evaluation of dual PPAR $\alpha/\gamma$  agonists**

pp 2605–2608

Xinbo Zhou, Wei Chen, Cheng Xu, Shiyong Fan, Yunde Xie, Wu Zhong, Lili Wang, Song Li\*

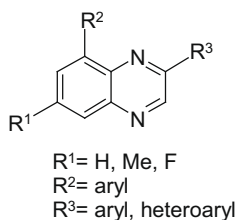


A series of novel, potent PPAR $\alpha/\gamma$  dual agonists were synthesized and appraised. Compound **2b** was chosen for further in vivo evaluation in the *db/db* mice, rosiglitazone were used for comparison.

**Discovery and SAR of potent, orally available 2,8-diaryl-quinoxalines as a new class of JAK2 inhibitors**

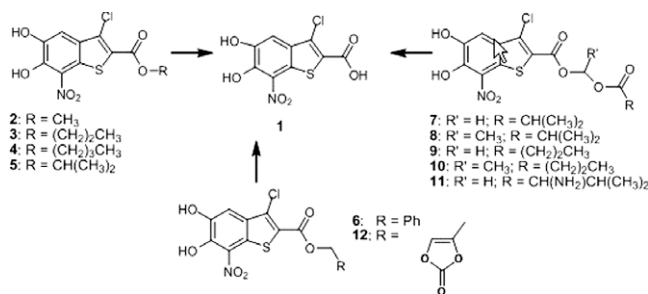
pp 2609–2613

Carole Pissot-Soldermann\*, Marc Gerspacher, Pascal Furet, Christoph Gaul, Philipp Holzer, Clive McCarthy, Thomas Radimerski, Catherine H. Regnier, Fabienne Baffert, Peter Drucekes, Gisele A. Tavares, Eric Vangrevelinghe, Francesca Blasco, Giorgio Ottaviani, Flavio Ossola, Julien Scesa, Janitha Reetz

**Design, synthesis and in vitro/in vivo evaluation of orally bioavailable prodrugs of a catechol-O-methyltransferase inhibitor**

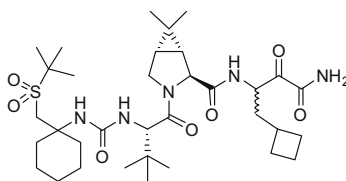
pp 2614–2616

Jarkko Rautio\*, Jukka Leppänen, Marko Lehtonen, Krista Laine, Mikko Koskinen, Jarmo Pystynen, Jouko Savolainen, Mikko Sairanen

**The introduction of P4 substituted 1-methylcyclohexyl groups into Boceprevir®: A change in direction in the search for a second generation HCV NS3 protease inhibitor**

pp 2617–2621

Frank Bennett\*, Yuhua Huang, Siska Hendrata, Raymond Lovey, Stephane L. Bogen, Weidong Pan, Zhuyan Guo, Andrew Prongay, Kevin X. Chen, Ashok Arasappan, Srikanth Venkatraman, Francisco Velazquez, Latha Nair, Mousumi Sannigrahi, Xiao Tong, John Pichardo, Kuo-Chi Cheng, Viyyoor M. Girijavallabhan, Anil K. Saksena, F. George Njoroge

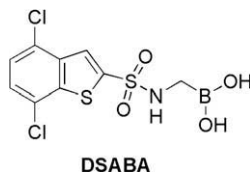


**52**  $K_i^* = 3 \text{ nM}$ ;  $EC_{90} = 80 \text{ nM}$   
 Monkey AUC=3.2uM.h (3mpk)

#### 4,7-Dichloro benzothien-2-yl sulfonylaminomethyl boronic acid: First boronic acid-derived beta-lactamase inhibitor with class A, C, and D activity

pp 2622–2624

Qiang Tan\*, Aimie M. Ogawa, Ronald E. Painter, Young-Whan Park, Katherine Young, Frank P. DiNinno

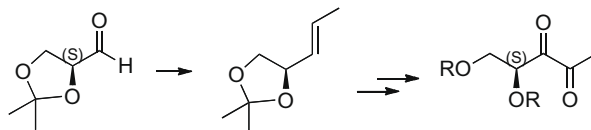


4,7-Dichloro-1-benzothien-2-yl sulfonylaminomethyl boronic acid (DSABA) is reported as the first boronic acid-based class D beta-lactamase inhibitor, also with class A and C activity.

#### Synthesis and bioluminescence-inducing properties of autoinducer (S)-4,5-dihydroxypentane-2,3-dione and its enantiomer

pp 2625–2628

Manikandan Kadirvel, William T. Stimpson, Souad Moumene-Afffi, Biljana Arsic, Nicola Glynn, Nigel Halliday, Paul Williams, Peter Gilbert, Andrew J. McBain, Sally Freeman, John M. Gardiner\*



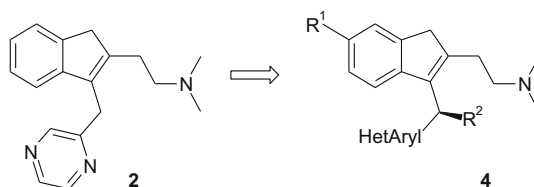
Synthesis of both enantiomers of autoinducer DPD (shown (S), R = H) along with their ester bioprecursors (R = Bz, Ac) & biological assays.



#### Selectivity profiling of novel indene H<sub>1</sub>-antihistamines for the treatment of insomnia

pp 2629–2633

Bin-Feng Li, Wilna J. Moree\*, Jinghua Yu, Timothy Coon, Said Zamani-Kord, Siobhan Malany, Kayvon Jalali, Jianyun Wen, Hua Wang, Chun Yang, Samuel R. J. Hoare, Robert E. Petroski, Ajay Madan, Paul D. Crowe, Graham Beaton\*



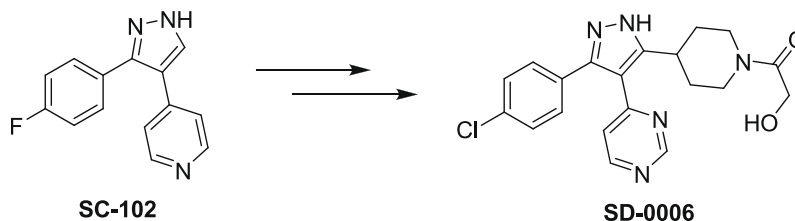
Structure–activity relationships were conducted around a lead H<sub>1</sub>-antihistamine **2**, to identify selective analogs with the potential for reduced biotransformation through the CYP2D6 pathway. A number of candidate compounds were identified from the general structure **4** using the appropriate combination of electron rich heterocycles, the presence of a chiral center and 6-substitution in the indene core.



#### Identification of SD-0006, a potent diaryl pyrazole inhibitor of p38 MAP kinase

pp 2634–2638

John K. Walker\*, Shaun R. Selness, Rajesh V. Devraj, Michael E. Hepperle, Win Naing, Huey Shieh, Ravi Kurambail, Syaulan Yang, Daniel L. Flynn, Alan G. Benson, Dean M. Messing, Tom Dice, Tina Kim, R. J. Lindmark, Joseph B. Monahan, Joseph Portanova

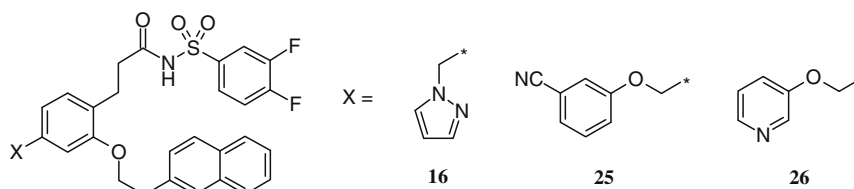


Starting from the novel screening lead, SC-102, synthesis and structure activity relationships are provided highlighting the progression to and identification of the potent p38 MAP kinase inhibitor SD-0006.

**Discovery of novel *N*-acylsulfonamide analogs as potent and selective EP3 receptor antagonists**

pp 2639–2643

Masaki Asada\*, Tetsuo Obitsu, Atsushi Kinoshita, Yoshihiko Nakai, Toshihiko Nagase, Isamu Sugimoto, Motoyuki Tanaka, Hiroya Takizawa, Ken Yoshikawa, Kazutoyo Sato, Masami Narita, Shuichi Ohuchida, Hisao Nakai, Masaaki Toda

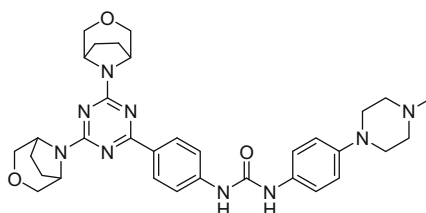


Identification of novel *N*-acyl 3,4-difluorobenzenesulfonamide analogs as potent and selective EP3 receptor antagonists and their in vivo efficacy with respect to the PGE<sub>2</sub>-induced uterine contraction in pregnant rats are reported.

**Discovery of 2-ureidophenyltriazines bearing bridged morpholines as potent and selective ATP-competitive mTOR inhibitors**

pp 2644–2647

Arie Zask\*, Jeroen C. Verheijen, David J. Richard, Joshua Kaplan, Kevin Curran, Lourdes Toral-Barza, Judy Lucas, Irwin Hollander, Ker Yu

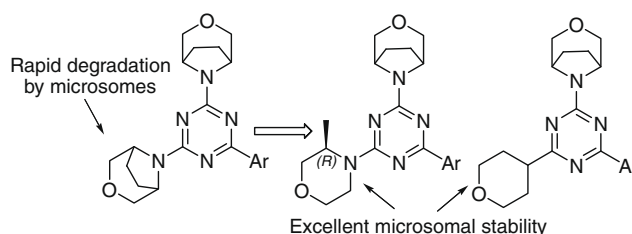


Incorporation of bridged morpholines in monocyclic triazine PI3K/mTOR inhibitors gave compounds with increased mTOR selectivity relative to the corresponding morpholine analogs leading to compounds which suppressed mTOR biomarkers in vivo and possessed excellent efficacy in a murine xenograft model.

**2-Arylureidophenyl-4-(3-oxa-8-azabicyclo[3.2.1]octan-8-yl)triazines as highly potent and selective ATP competitive mTOR inhibitors: Optimization of human microsomal stability**

pp 2648–2653

Jeroen C. Verheijen\*, David J. Richard, Kevin Curran, Joshua Kaplan, Ker Yu, Arie Zask

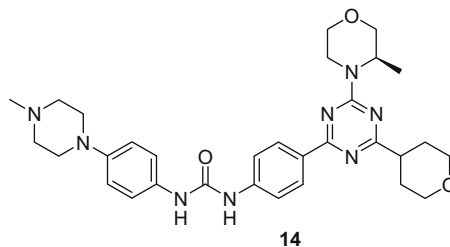


Isosteric replacement of one of the 3,5-ethylene-bridged morpholines in triazine mTOR inhibitors led to significant improvements in human microsomal stability, resulting in a compound that selectively suppressed mTOR biomarkers in vivo and possessed excellent efficacy in a murine xenograft model.

**Triazines incorporating (*R*)-3-methylmorpholine are potent inhibitors of the mammalian target of rapamycin (mTOR) with selectivity over PI3K $\alpha$** 

pp 2654–2657

David J. Richard\*, Jeroen C. Verheijen, Ker Yu, Arie Zask

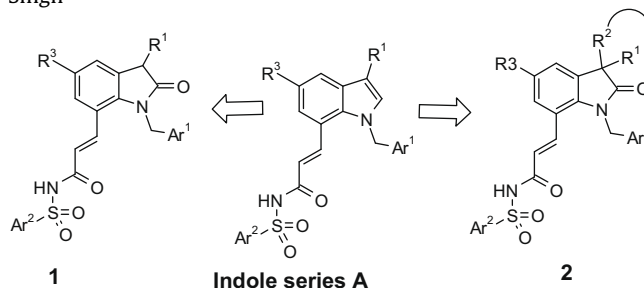


Potent inhibitors of the mammalian target of rapamycin (mTOR) which contain the triazine scaffold and the (*R*)-3-methyl morpholine moiety have been identified. Such compounds also displayed excellent cellular activity and good selectivity over the related lipid kinase PI3K $\alpha$ .

**1,7-Disubstituted oxyindoles are potent and selective EP<sub>3</sub> receptor antagonists**

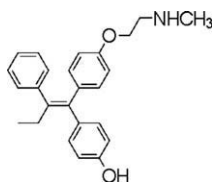
pp 2658–2664

Nian Zhou, Alexandre M. Polozov, Matthew O'Connell, James Burgeson, Peng Yu, Wayne Zeller, Jun Zhang, Emmanuel Onua, Jose Ramirez, Gudrun A. Palsdottir, Gudrun V. Halldorsdottir, Thorkell Andresson, Alex S. Kiselyov, Mark Gurney, Jasbir Singh\*

**Endoxifen is a new potent inhibitor of PKC: A potential therapeutic agent for bipolar disorder**

pp 2665–2667

Shoukath M. Ali, Ateeq Ahmad, Syed Shahabuddin, Moghis U. Ahmad, Saifuddin Sheikh, Imran Ahmad\*

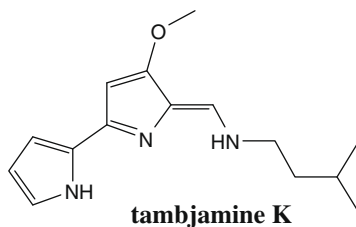


A novel synthesis of endoxifen and its PKC inhibitory activity is reported.

**A new cytotoxic tambjamine alkaloid from the Azorean nudibranch *Tambja ceutae***

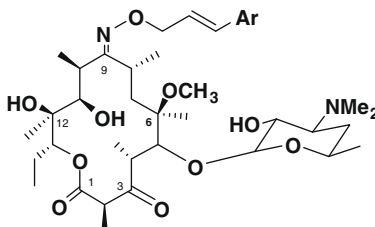
pp 2668–2670

Marianna Carbone, Carlo Irace, Francesca Costagliola, Francesco Castelluccio, Guido Villani, Gonalo Calado, Vinicius Padula, Guido Cimino, J. Lucas Cervera, Rita Santamaria, Margherita Gavagnin\*

**Synthesis and antibacterial activity of new 9-O-arylpropenyloxime ketolides**

pp 2671–2674

Ghilsoo Nam\*, Yang Soo Kim, Kyung Il Choi

**9-O-Arylpropenyloxime ketolides**

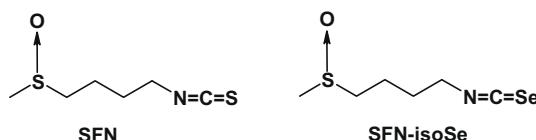
New 9-O-arylpropenyloxime ketolides were synthesized and evaluated their antibacterial activities against clinically isolated gram-positive strains. The SAR is discussed.



**Enhanced Nrf2-dependent induction of glutathione in mouse embryonic fibroblasts by isoselenocyanate analog of sulforaphane**

pp 2675–2679

Sans W. Emmert, Dhimant Desai, Shantu Amin, John P. Richie Jr.\*

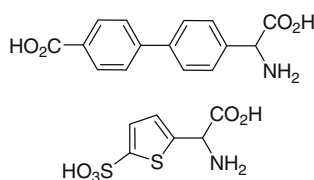


SFN-isoSe, an isosteric selenium analog of naturally occurring sulforaphane (SFN), is a potent inducer of the Nrf2/ARE pathway and may represent a more effective chemoprotective agent in vivo.

**Conformationally-restricted amino acid analogues bearing a distal sulfonic acid show selective inhibition of system x<sub>c</sub><sup>-</sup> over the vesicular glutamate transporter**

pp 2680–2683

Jean-Louis G. Etoga, S. Kaleem Ahmed, Sarjubhai Patel, Richard J. Bridges, Charles M. Thompson\*



block approx. 75% uptake of system x<sub>c</sub><sup>-</sup>

**OTHER CONTENTS****Corrigenda**

pp 2684–2685

\*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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