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# Bioorganic & Medicinal Chemistry Letters

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## Bioorganic & Medicinal Chemistry Letters Vol. 19, No. 21, 2009

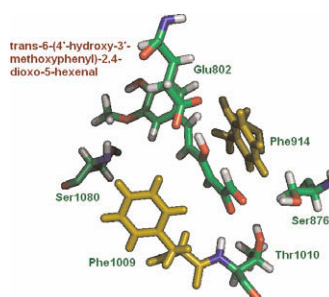
### Contents

#### ARTICLES

##### Insights into the inhibition of xanthine oxidase by curcumin

pp 5990–5993

Liang Shen, Hong-Fang Ji \*



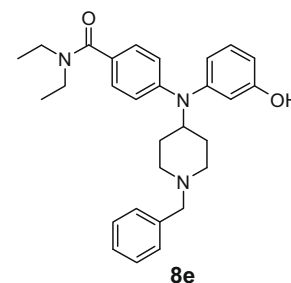
Molecular docking simulations indicated that parent curcumin binds weakly to xanthine oxidase, while its degradation products exhibit effective inhibitory activities.

##### *N,N*-Diethyl-4-[(3-hydroxyphenyl)(piperidin-4-yl)amino] benzamide derivatives: The development of diaryl amino piperidines as potent $\delta$ opioid receptor agonists with in vivo anti-nociceptive activity in rodent models

pp 5994–5998

Paul Jones, Andrew M. Griffin \*, Lars Gawell, Rico Lavoie, Daniel Delorme, Edward Roberts, William Brown, Christopher Walpole, Wenhau Xiao, Jamie Boulet, Maryse Labarre, Martin Coupal, Joanne Butterworth, Stephane St-Onge, Lejla Hodzic, Dominic Salois

Phenolic diaryl amino piperidines were found to have excellent agonist potency at the delta opioid receptor. Compound **8e** displays in vivo anti-nociceptive activity in two rodent models.

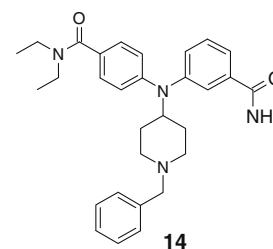


##### Delta agonist hydroxy bioisosteres: The discovery of 3-((1-benzylpiperidin-4-yl){4-[(diethylamino)carbonyl]phenyl}amino)benzamide with improved delta agonist activity and in vitro metabolic stability

pp 5999–6003

Andrew M. Griffin \*, William Brown, Christopher Walpole, Martin Coupal, Lynda Adam, Mylene Gosselin, Dominic Salois, Pierre-Emmanuel Morin, Marie Roumi

The primary amide was found to be a suitable replacement for the hydroxy group in a series of delta agonists. Compound **14** displayed potent agonism and improved metabolic stability.

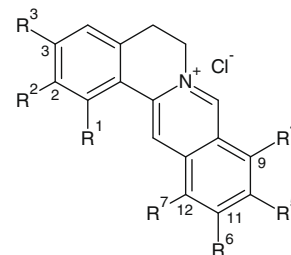


### Synthesis and biological evaluation of berberine analogues as novel up-regulators for both low-density-lipoprotein receptor and insulin receptor

pp 6004–6008

Yan-Xiang Wang, Yu-Ping Wang, Hao Zhang, Wei-Jia Kong, Ying-Hong Li, Fei Liu, Rong-Mei Gao, Ting Liu, Jian-Dong Jiang<sup>\*</sup>, Dan-Qing Song<sup>\*</sup>

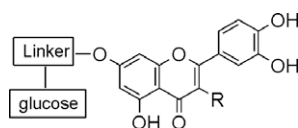
The goal of this study is to look for compounds with one-drug-multiple-target characteristic against metabolic syndrome. Berberine (BBR) derivatives were designed, synthesized and evaluated for their activity of up-regulating both LDLR and InsR mRNA expression.



### Glucose-containing flavones—their synthesis and antioxidant and neuroprotective activities

pp 6009–6013

Seung Hwan Kim, Ch. Naveen Kumar, Hyoung Ja Kim, Dong Han Kim, Jungsook Cho, Changbae Jin, Yong Sup Lee<sup>\*</sup>



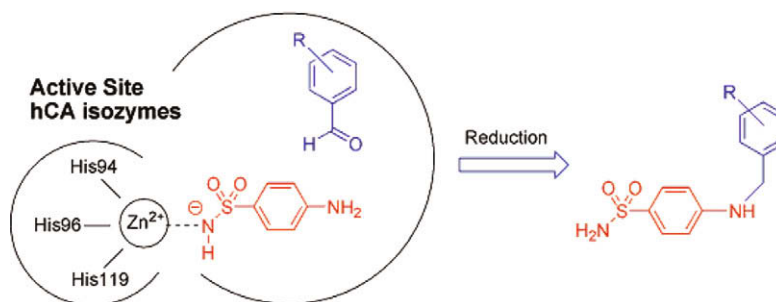
3a~f, R = OCH<sub>3</sub> or H

The attachment of glucoside was performed at the position of C-7 of quercetin 3-methyl ether (1) and luteolin (2) through glycosidic bond or ether linkage to increase water solubility. Among the synthesized, compounds 3b and 3c showed most potent protection in neuronal cells with IC<sub>50</sub> values of 7.33 and 5.34 μM, respectively, which are nearly equal to those of parent compounds 1 and 2 (IC<sub>50</sub> = 3.50 and 3.75 μM, respectively).

### Carbonic anhydrase II-induced selection of inhibitors from a dynamic combinatorial library of Schiff's bases

pp 6014–6017

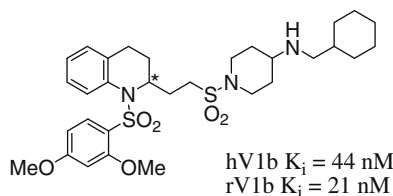
Gihane Nasr, Eddy Petit, Claudiu T. Supuran<sup>\*</sup>, Jean-Yves Winum, Mihail Barboiu<sup>\*</sup>



### Tetrahydroquinoline sulfonamides as vasopressin 1b receptor antagonists

pp 6018–6022

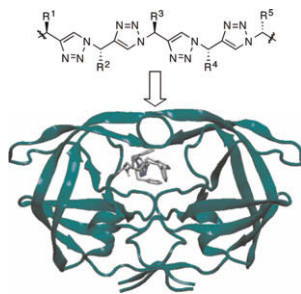
Jack D. Scott<sup>\*</sup>, Michael W. Miller, Sarah W. Li, Sue-Ing Lin, Henry A. Vaccaro, Liwu Hong, Deborra E. Mullins, Mario Guzzi, Jay Weinstein, Robert A. Hodgson, Geoffrey B. Varty, Andrew W. Stamford, Tin-Yau Chan, Brian A. McKittrick, William J. Greenlee, Tony Priestley, Eric M. Parker



**Evaluation of triazolamers as active site inhibitors of HIV-1 protease**

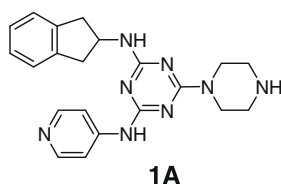
pp 6023–6026

Andrea L. Jochim, Stephen E. Miller, Nicholas G. Angelo, Paramjit S. Arora \*

Design of nonpeptidic  $\beta$ -strand mimetics as protease inhibitors is reported.**Triazine and pyrimidine based ROCK inhibitors with efficacy in spontaneous hypertensive rat model**

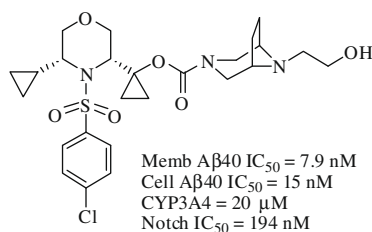
pp 6027–6031

Koc-Kan Ho \*, James R. Beasley, Laura Belanger, Darcey Black, Jui-Hsiang Chan, David Dunn, Bing Hu, Anthony Klon, Steven G. Kultgen, Michael Ohlmeyer, Susan M. Parlato, Peter C. Ray, Quynhchi Pham, Yajing Rong, Andrew L. Roughton, Tiffany L. Walker, Jane Wright, Kai Xu, Yan Xu, Limei Zhang, Maria Webb

A series of triazine and pyrimidine based ROCK inhibitors is described. An initial binding mode was established based on a homology model and the proposed interactions are consistent with the observed SAR. Compounds from the series are potent in a cell migration assay and possess a favorable kinase selectivity. In vivo activity was demonstrated for compound **1A** in a spontaneous hypertensive rat model.**Novel orally active morpholine *N*-arylsulfonamides  $\gamma$ -secretase inhibitors with low CYP 3A4 liability**

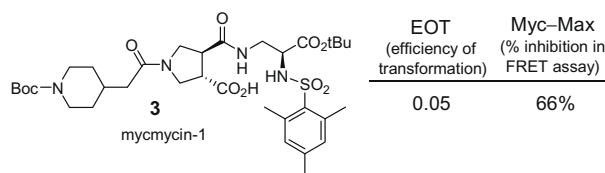
pp 6032–6037

Hubert Josien \*, Thomas Bara, Murali Rajagopalan, John W. Clader, William J. Greenlee, Leonard Favreau, Lynn A. Hyde, Amin A. Nomeir, Eric M. Parker, Lixin Song, Lili Zhang, Qi Zhang

The design of a new class of *N*-arylsulfonamide  $\gamma$ -secretase inhibitors based on the introduction of a morpholine core is reported. Compounds devoid of CYP 3A liability and active orally in a Tg CRND8 mice model of Alzheimer's disease were obtained.**Small molecule inhibitors of Myc/Max dimerization and Myc-induced cell transformation**

pp 6038–6041

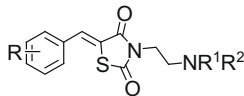
Jin Shi, James S. Stover, Landon R. Whitby, Peter K. Vogt, Dale L. Boger \*



**Structure–activity relationship (SAR) studies of 3-(2-amino-ethyl)-5-(4-ethoxy-benzylidene)-thiazolidine-2,4-dione: Development of potential substrate-specific ERK1/2 inhibitors**

pp 6042–6046

Qianbin Li, Adnan Al-Ayoubi, Tailiang Guo, Hui Zheng, Aurijit Sarkar, Tri Nguyen, Scott T. Eblen, Steven Grant, Glen E. Kellogg, Shijun Zhang \*

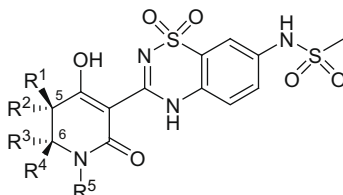


Preliminary structure–activity relationship studies of 3-(2-amino-ethyl)-5-(4-ethoxy-benzylidene)-thiazolidine-2,4-dione, a putative substrate-specific ERK1/2 inhibitor, is reported.


**5,5'- and 6,6'-Dialkyl-5,6-dihydro-1H-pyridin-2-ones as potent inhibitors of HCV NS5B polymerase**

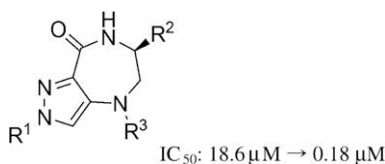
pp 6047–6052

David A. Ellis, Julie K. Blazel, Chinh V. Tran, Frank Ruebsam, Douglas E. Murphy \*, Lian-Sheng Li, Jingjing Zhao, Yuefen Zhou, Helen M. McGuire, Alan X. Xiang, Stephen E. Webber, Qiang Zhao, Qing Han, Charles R. Kissinger, Matthew Lardy, Alberto Gobbi, Richard E. Showalter, Amit M. Shah, Mei Tsan, Rupal A. Patel, Laurie A. LeBrun, Ruhi Kamran, Darian M. Bartkowski, Thomas G. Nolan, Daniel A. Norris, Maria V. Sergeeva, Leo Kirkovsky


**Synthesis and structure–activity relationships of pyrazolodiazepine derivatives as human P2X<sub>7</sub> receptor antagonists**

pp 6053–6058

Ju-Yeon Lee, Juan Yu, Won Je Cho, Hyojin Ko, Yong-Chul Kim \*

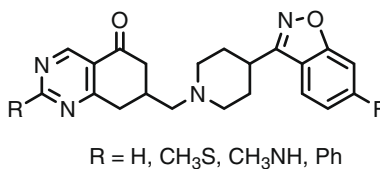


Novel and potent antagonists of P2X<sub>7</sub> receptors were developed through optimization of a weak lead compound identified from a potential privileged structure-based library.


**Synthesis and binding affinity of potential atypical antipsychotics with the tetrahydroquinazolinone motif**

pp 6059–6062

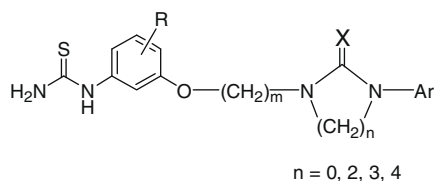
Laura Carro, Enrique Raviña, Eduardo Domínguez, José Brea, María I. Loza, Christian F. Masaguer \*



**Design and efficient synthesis of novel arylthiourea derivatives as potent hepatitis C virus inhibitors**

pp 6063–6068

Iou-Jiun Kang, Li-Wen Wang, Sheng-Ju Hsu, Chung-Chi Lee, Yen-Chun Lee, Yen-Shian Wu, Andrew Yueh\*, Jing-Chyi Wang, Tsu-An Hsu, Yu-Sheng Chao, Jyh-Haur Chern\*

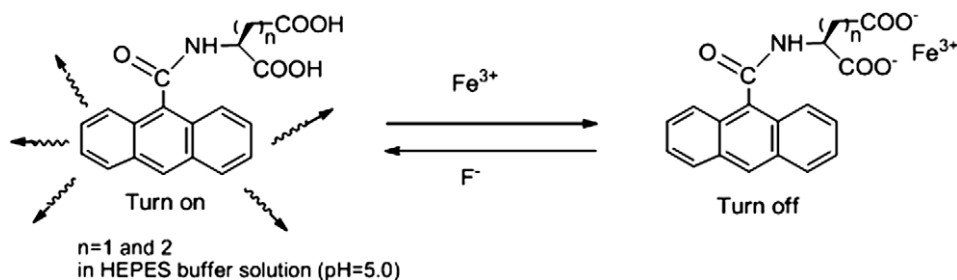


Synthesis and SAR for a series of novel arylthiourea derivatives as potent hepatitis C virus inhibitors are reported.

**Facile synthesis of anthracene-appended amino acids as highly selective and sensitive fluorescent  $\text{Fe}^{3+}$  ion sensors**

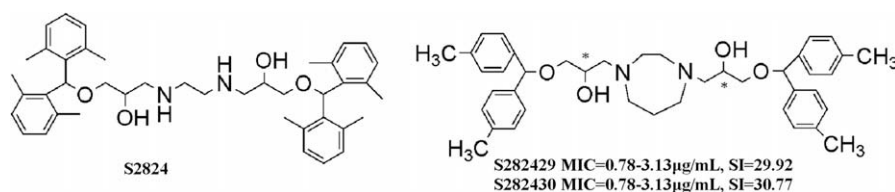
pp 6069–6073

Chuda Raj Lohani, Joung-Min Kim, Keun-Hyeung Lee\*

**Synthesis and evaluation of (S,S)-N,N'-bis-[3-(2,2',6,6'-tetramethylbenzhydryloxy)-2-hydroxy-propyl]-ethylenediamine (S2824) analogs with anti-tuberculosis activity**

pp 6074–6077

Xuelian Zhang, Yanwei Hu, Shudan Chen, Rusong Luo, Jun Yue, Ying Zhang, Wenhui Duan, Honghai Wang\*

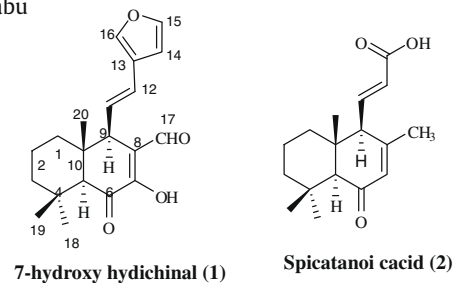


Thirty analogs of (S,S)-N,N'-bis-[3-(2,2',6,6'-tetramethylbenzhydryloxy)-2-hydroxy-propyl]-ethylenediamine were synthesized and tested antituberculosis activity. Two compounds in this series showed highly active against drug-resistant strains.

**Phytochemical investigation of labdane diterpenes from the rhizomes of *Hedychium spicatum* and their cytotoxic activity**

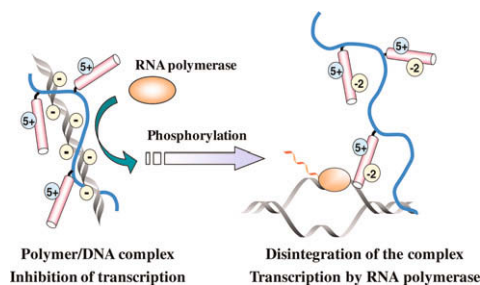
pp 6078–6081

P. Prabhakar Reddy, R. Ranga Rao, J. Shashidhar, B. S. Sastry, J. Madhusudana Rao, K. Suresh Babu\*

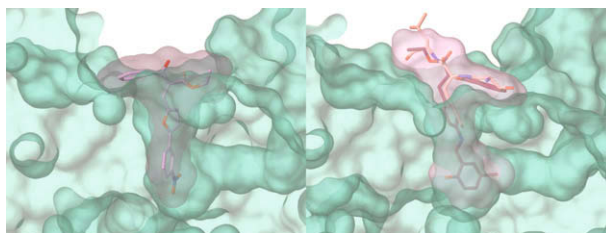
Phytochemical investigation of rhizomes of the *Hedychium spicatum* yielded two new labdane diterpenes (**1**, **2**) along with six known compounds (**3**–**8**). Cytotoxic activity of the isolates was studied against THP-1 (human acute monocytic leukemia), HL-60 (human promyelocytic leukemia), A-375 (human malignant melanoma) and A-549 (human lung carcinoma) cell lines.

**Cellular signal-specific peptide substrate is essential for the gene delivery system responding to cellular signals**

pp 6082–6086

Jeong-Hun Kang<sup>\*</sup>, Riki Toita, Tetsuro Tomiyama, Jun Oishi, Daisuke Asai, Takeshi Mori, Takuro Niidome, Yoshiki Katayama<sup>\*</sup>**A dynamic target-based pharmacophoric model mapping the CD4 binding site on HIV-1 gp120 to identify new inhibitors of gp120–CD4 protein–protein interactions**

pp 6087–6091

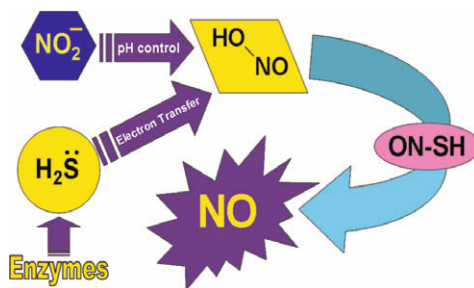
Fabiana Caporuscio, Andrea Tafi, Emmanuel González, Fabrizio Manetti, José A. Esté, Maurizio Botta<sup>\*</sup>

Two novel chemical scaffolds targeting the HIV-1 gp120 Phe43 cavity and able to interfere with gp120–CD4 protein–protein interactions were identified by structure-based in silico screening.

**Hydrogen sulfide induces nitric oxide release from nitrite**

pp 6092–6094

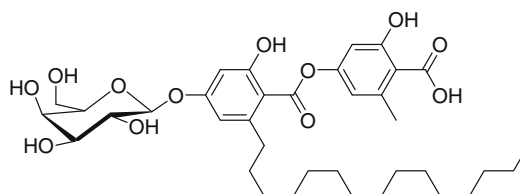
Loris Grossi



Hydrogen sulfide displays a role as cofactor of the nitrite in the NO release, which depends on the pH of the medium.

**Isolation of the protein tyrosine phosphatase 1B inhibitory metabolite from the marine-derived fungus *Cosmospora* sp. SF-5060**

pp 6095–6097

Changon Seo, Jae Hak Sohn, Hyuncheol Oh<sup>\*</sup>, Bo Yeon Kim, Jong Seog Ahn<sup>\*</sup>

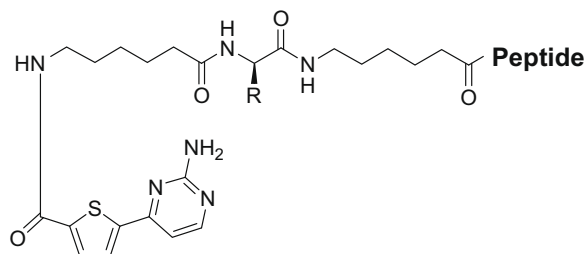
Bioassay-guided investigation on the EtOAc extract of cultures of the marine-derived fungus *Cosmospora* sp. SF-5060 afforded a potent tyrosine phosphatase 1B (PTP1B) inhibitory metabolite, aquastatin A.



**Effect of the structure of adenosine mimic of bisubstrate-analog inhibitors on their activity towards basophilic protein kinases**

pp 6098–6101

Erki Enkvist, Marie Kriisa, Mart Roben, Grete Kadak, Gerda Raidaru, Asko Uri \*

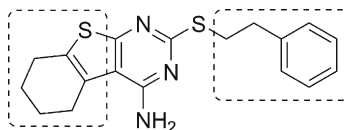


Testing of conjugates of a series of adenosine mimics with arginine-rich peptides as inhibitors of protein kinases revealed a compound with subnanomolar inhibitory potency.

**Analogs of a 4-aminothieno[2,3-*d*]pyrimidine lead (QB13) as modulators of P-glycoprotein substrate specificity**

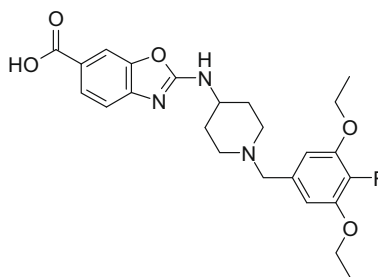
pp 6102–6105

Hans-Georg Häcker, Antje de la Haye, Katja Sterz, Gregor Schnakenburg, Michael Wiese, Michael Gütschow \*

**Benzoxazole piperidines as selective and potent somatostatin receptor subtype 5 antagonists**

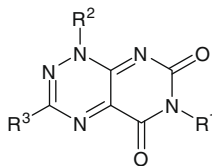
pp 6106–6113

Rainer E. Martin \*, Peter Mohr, Hans Peter Maerki, Wolfgang Guba, Christoph Kuratli, Olivier Gavelle, Alfred Binggeli, Stefanie Bendels, Rubén Alvarez-Sánchez, André Alker, Liudmila Polonchuk, Andreas D. Christ

**Pyrimido[5,4-*e*][1,2,4]triazine-5,7(1*H*,6*H*)-dione derivatives: Their cytoprotection effect from rotenone toxicity and preliminary DMPK properties**

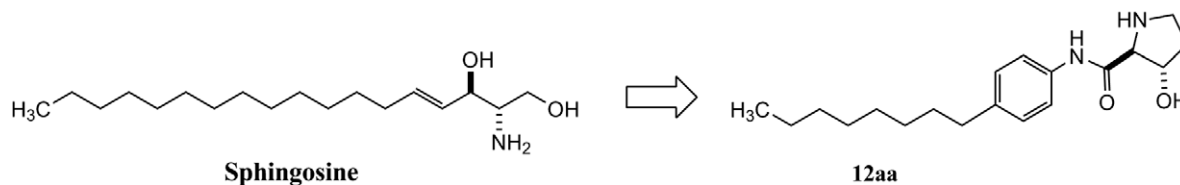
pp 6114–6118

Yuefen Zhou \*, Gang Liu, Jinhua Chen, P. S. Murali Mohan Reddy, Il Sang Yoon, Menghua Zhang, Bin Zhang, Jack R. Barber, Shi Chung Ng



**Discovery of novel sphingosine kinase 1 inhibitors**

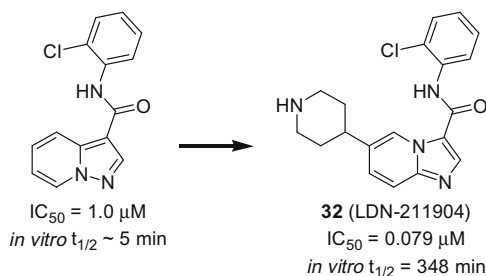
pp 6119–6121

Yibin Xiang<sup>\*</sup>, Gary Asmussen, Michael Booker, Bradford Hirth, John L. Kane Jr., Junkai Liao, Kevin D. Noson, Christopher Yee

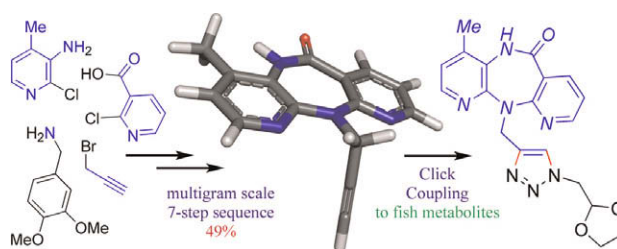
Potent and novel sphingosine kinase 1 (SK1) inhibitor (12aa) have been discovered through a series of modifications of sphingosine, the substrate of this enzyme.

**Structure–activity relationship study of EphB3 receptor tyrosine kinase inhibitors**

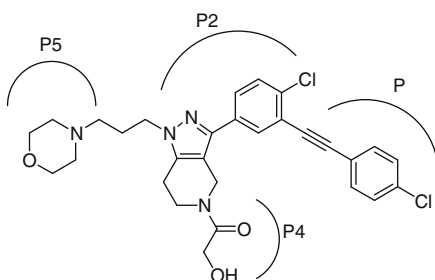
pp 6122–6126

Lixin Qiao, Sungwoon Choi, April Case, Thomas G. Gainer, Kathleen Seyb, Marcie A. Glicksman, Donald C. Lo, Ross L. Stein, Gregory D. Cuny<sup>\*</sup>**Efficient synthesis of nevirapine analogs to study its metabolic profile by click fishing**

pp 6127–6130

Sylvain Bernard, Daniel Defoy, Yves L. Dory<sup>\*</sup>, Klaus Klarskov<sup>\*</sup>**Pyrazole-based cathepsin S inhibitors with arylalkynes as P1 binding elements**

pp 6131–6134

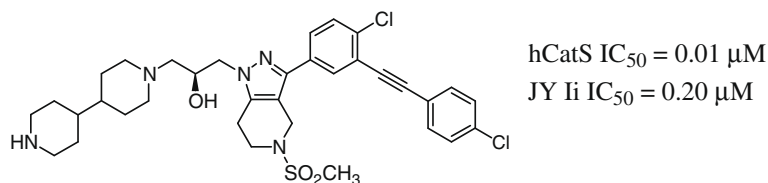
Michael K. Ameriks<sup>\*</sup>, Frank U. Axe, Scott D. Bembenek, James P. Edwards, Yin Gu, Lars Karlsson, Mike Randal, Siquan Sun, Robin L. Thurmond, Jian Zhu



**Pyrazole-based arylalkyne cathepsin S inhibitors. Part II: Optimization of cellular potency**

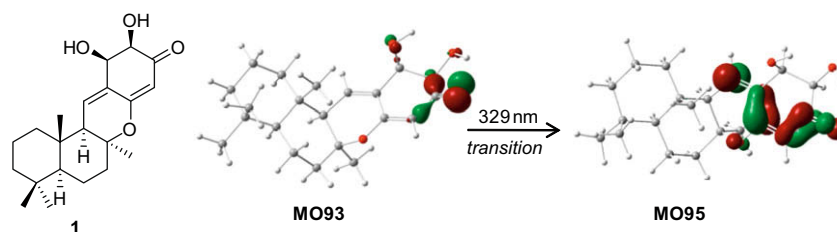
pp 6135–6139

Michael K. Ameriks<sup>\*</sup>, Hui Cai, James P. Edwards, Damara Gebauer, Elizabeth Gleason, Yin Gu, Lars Karlsson, Steven Nguyen, Siquan Sun, Robin L. Thurmond, Jian Zhu

**Puupehanol, a sesquiterpene-dihydroquinone derivative from the marine sponge *Hyrtios* sp.**

pp 6140–6143

Wen-Hui Xu, Yuanqing Ding, Melissa R. Jacob, Ameeta K. Agarwal, Alice M. Clark, Daneel Ferreira, Zong-Suo Liang, Xing-Cong Li<sup>\*</sup>

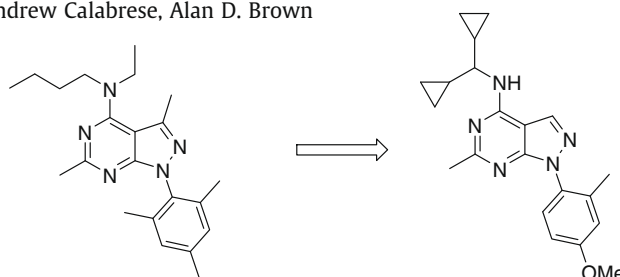


Puupehanol (1), a new sesquiterpene-dihydroquinone derivative, was isolated from the marine sponge *Hyrtios* sp., along with the known antifungal compounds puupehenone (2) and chloropuupehenone (3).

**Optimising metabolic stability in lipophilic chemical space: The identification of a metabolically stable pyrazolopyrimidine CRF-1 receptor antagonist**

pp 6144–6147

Duncan C. Miller<sup>\*</sup>, Wolfgang Klute, Andrew Calabrese, Alan D. Brown

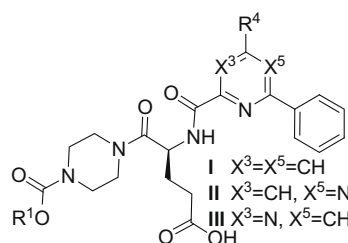


Balancing potency and metabolic stability in a target which favours lipophilic ligands is a considerable challenge. Here we describe two strategies employed to achieve this balance in a series of pyrazolopyrimidine CRF antagonists: moderation of lipophilicity, and incorporation of a metabolically stable lipophilic group.

**Piperazinyl-glutamate-pyrimidines as potent P2Y<sub>12</sub> antagonists for inhibition of platelet aggregation**

pp 6148–6156

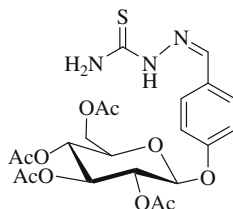
John J. Parlow<sup>\*</sup>, Mary W. Burney, Brenda L. Case, Thomas J. Girard, Kerri A. Hall, Ronald R. Hiesch, Rita M. Huff, Rhonda M. Lachance, Deborah A. Mischke, Stephen R. Rapp, Rhonda S. Woerndle, Michael D. Ennis



Piperazinyl-glutamate-pyrimidines were prepared with oxygen, nitrogen, and sulfur substitution at the 4-position (R<sup>4</sup>) of the pyrimidine leading to highly potent P2Y<sub>12</sub> antagonists.

**Discovery of 4-functionalized phenyl-O- $\beta$ -D-glycosides as a new class of mushroom tyrosinase inhibitors**

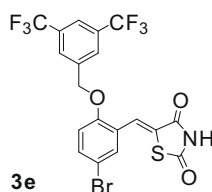
pp 6157–6160

Wei Yi, Rihui Cao <sup>\*</sup>, Huan Wen, Qin Yan, Binhua Zhou, Lin Ma, Huacan Song <sup>\*</sup>**9a**  $IC_{50}=0.31\pm0.12\ \mu M$ 

A series of 4-functionalized phenyl-O- $\beta$ -D-glycosides were designed, synthesized and evaluated as tyrosinase inhibitors. Compound **9a** was found to be the most potent inhibitor.

**Thiazolidinedione derivatives as PTP1B inhibitors with antihyperglycemic and antiobesity effects**

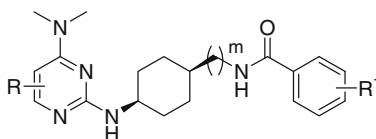
pp 6161–6165

Bharat Raj Bhattarai, Bhooshan Kafle, Ji-Sun Hwang, Deegendra Khadka, Sun-Myung Lee, Jae-Seung Kang, Seung Wook Ham, Inn-Oc Han, Hwangseo Park <sup>\*</sup>, Hyeonjin Cho <sup>\*</sup>**3e**

Compound **3e** inhibited PTP1B, improved glucose tolerance, suppressed weight gain, and improved blood parameters in a mouse model system.

**Pyrimidine-based antagonists of h-MCH-R1 derived from ATC0175: In vitro profiling and in vivo evaluation**

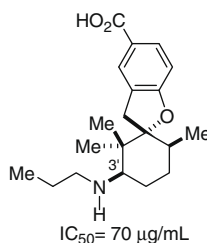
pp 6166–6171

Graeme Semple <sup>\*</sup>, Thuy-Anh Tran, Bryan Kramer, Debbie Hsu, Sangdon Han, Juyi Choi, Pureza Vallar, Martin D. Casper, Ning Zou, Erin K. Hauser, William Thomsen, Kevin Whelan, Dipanjan Sengupta, Michael Morgan, Yoshinori Sekiguchi, Kosuke Kanuma, Shigeyuki Chaki, Andrew J. Grottick

A series of pyrimidine analogues derived from ATC0175 were potent antagonists of human MCH-R1 in vitro with improved receptor selectivity. One example was shown to inhibit food intake and decrease body weight in a chronic study. However observed effect was most likely not due to interaction with the MCH-R1.

**New inhibitors of the complement system inspired in K76-COOH. A SAR study of filifolinol derivatives through modifications of the C3' position**

pp 6172–6175

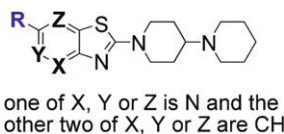
Enrique L. Larghi <sup>\*</sup>, María A. Operto, Rene Torres, Teodoro S. Kaufman <sup>\*</sup> $IC_{50}=70\ \mu g/mL$ 

The synthesis of new analogs of K76-COOH, as complement inhibitors, employing filifolinol as starting material suggest that the nature and stereochemistry of the C3' substituent may be important for the biological activity.

**Synthesis and structure–activity relationships of 2-(1,4'-bipiperidin-1'-yl)thiazolopyridine as H<sub>3</sub> receptor antagonists**

pp 6176–6180

Ashwin U. Rao <sup>\*</sup>, Anandan Palani, Xiao Chen, Ying Huang, Robert G. Aslanian, Robert E. West Jr., Shirley M. Williams, Ren-Long Wu, Joyce Hwa, Christopher Sondey, Jean Lachowicz

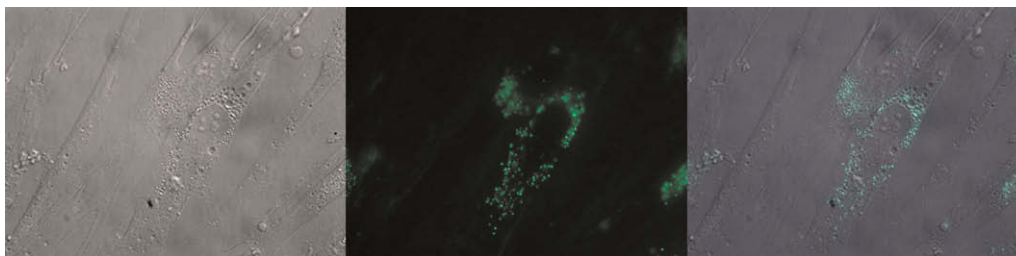


A series of 2-(1,4'-bipiperidin-1'-yl)thiazolopyridines was discovered as novel non-imidazole histamine H<sub>3</sub> receptor antagonists. The synthesis and structure–activity relationships for these new thiazolopyridine antagonists are described.

**Cellular localization and allele-selective inhibition of mutant huntingtin protein by peptide nucleic acid oligomers containing the fluorescent nucleobase [bis-*o*-(aminoethoxy)phenyl]pyrrolocytosine**

pp 6181–6184

Jiaxin Hu, David W. Dodd, Robert H. E. Hudson <sup>\*</sup>, David R. Corey <sup>\*</sup>

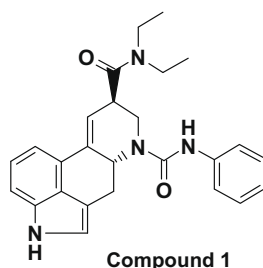


Modified PNAs enter cells and inhibit expression of huntingtin.

**Special ergolines are highly selective, potent antagonists of the chemokine receptor CXCR3: Discovery, characterization and preliminary SAR of a promising lead**

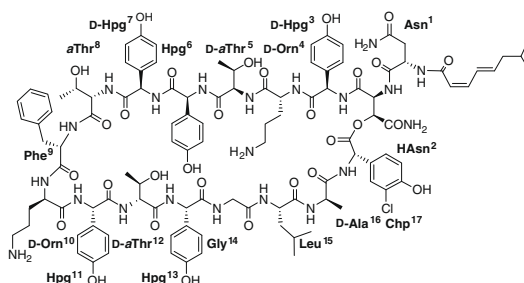
pp 6185–6188

Gebhard Thoma <sup>\*</sup>, Rolf Baenteli, Ian Lewis, Trixie Wagner, Lukas Oberer, Wolfgang Blum, Fraser Glickman, Markus B. Streiff, Hans-Guenter Zerwes

**Functional and biochemical analysis of a key series of ramoplanin analogues**

pp 6189–6191

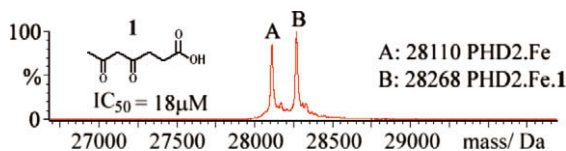
Xiao Fang, Joonwoo Nam, Dongwoo Shin, Yosup Rew, Dale L. Boger <sup>\*</sup>, Suzanne Walker <sup>\*</sup>



## 2-Oxoglutarate analogue inhibitors of prolyl hydroxylase domain 2

pp 6192–6195

Jasmin Mecinović, Christoph Loenarz, Rasheduzzaman Chowdhury, Christopher J. Schofield \*



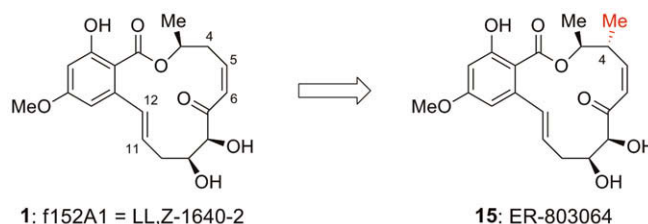
2-Oxoglutarate analogues were evaluated as inhibitors of the human oxygen sensing enzyme prolyl hydroxylase domain 2 and screened for binding by non-denaturing electrospray ionization mass spectrometry.



## Discovery of a potent, metabolically stabilized resorcylic lactone as an anti-inflammatory lead

pp 6196–6199

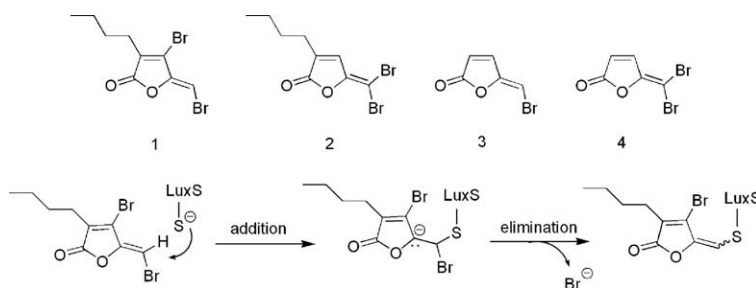
H. Du, T. Matsushima, M. Spyvee, M. Goto, H. Shirota, F. Gusovsky, K. Chiba, M. Kotake, N. Yoneda, Y. Eguchi, L. DiPietro, J.-C. Harmange, S. Gilbert, X.-Y. Li, H. Davis, Y. Jiang, Z. Zhang, R. Pelletier, N. Wong, H. Sakurai, H. Yang, H. Ito-Igarashi, A. Kimura, Y. Kuboi, Y. Mizui, I. Tanaka, M. Ikemori-Kawada, Y. Kawakami, A. Inoue, T. Kawai, Y. Kishi, Y. Wang \*



## A naturally occurring brominated furanone covalently modifies and inactivates LuxS

pp 6200–6204

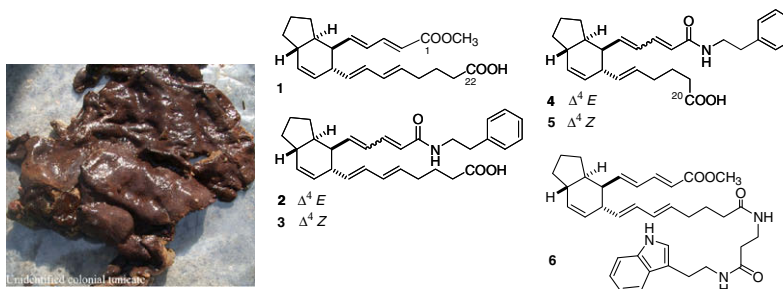
Tianzhu Zang, Bobby W. K. Lee, Lisa M. Cannon, Kathryn A. Ritter, Shujia Dai, Dacheng Ren, Thomas K. Wood, Zhaohui Sunny Zhou \*



## Bicyclic $\alpha,\omega$ -dicarboxylic acid derivatives from a colonial tunicate of the family Polyclinidae

pp 6205–6208

Baoquan Bao, Hung The Dang, Ping Zhang, Jongki Hong, Chong-O. Lee, Hee Young Cho, Jee H. Jung \*

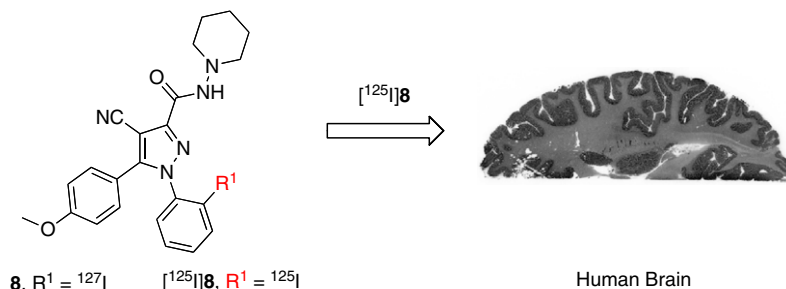


Unique bicyclic  $\alpha,\omega$ -dicarboxylic acid derivatives were isolated from a marine colonial tunicate and their biological evaluations were performed.

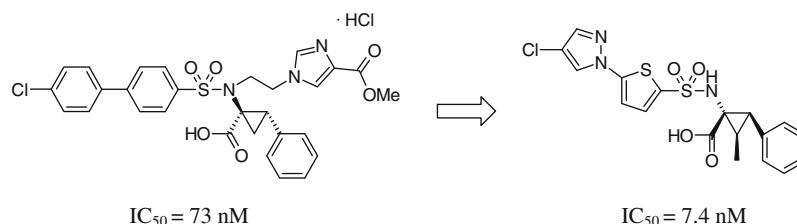


**Synthesis and in vitro autoradiographic evaluation of a novel high-affinity radioiodinated ligand for imaging brain cannabinoid subtype-1 receptors**

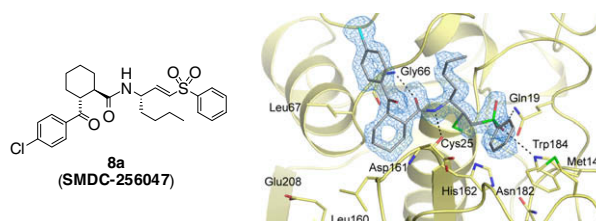
pp 6209–6212

Sean R. Donohue <sup>\*</sup>, Katarina Varnäs, Zhisheng Jia, Balázs Gulyás, Victor W. Pike, Christer Halldin**Synthesis and SAR of 2-phenyl-1-sulfonylaminocyclopropane carboxylates as ADAMTS-5 (Aggrecanase-2) inhibitors**

pp 6213–6217

Makoto Shiozaki <sup>\*</sup>, Hiroto Imai, Katsuya Maeda, Tomoya Miura, Katsutaka Yasue, Akira Suma, Masahiro Yokota, Yosuke Ogoshi, Julia Haas, Andrew M. Fryer, Ellen R. Laird, Nicole M. Littmann, Steven W. Andrews, John A. Josey, Takayuki Mimura, Yuichi Shinozaki, Hiromi Yoshiuchi, Takashi Inaba <sup>\*</sup>**Novel non-peptidic vinylsulfones targeting the S2 and S3 subsites of parasite cysteine proteases**

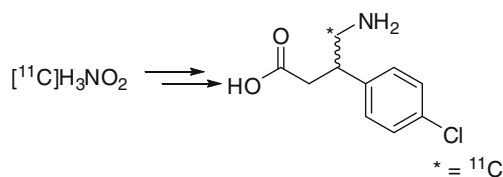
pp 6218–6221

Clifford Bryant, Iain D. Kerr, Moumita Debnath, Kenny K. H. Ang, Joseline Ratnam, Rafaela S. Ferreira, Priyadarshini Jaishankar, DongMei Zhao, Michelle R. Arkin, James H. McKerrow, Linda S. Brinen, Adam R. Renslo <sup>\*</sup>

We describe here the identification of non-peptidic vinylsulfones that inhibit parasite cysteine proteases in vitro and inhibit the growth of *Trypanosoma brucei brucei* parasites in culture. A high resolution (1.75 Å) co-crystal structure of **8a** bound to cruzain reveals how the non-peptidic P2/P3 moiety in such analogs bind the S2 and S3 subsites of the protease, effectively recapitulating important binding interactions present in more traditional peptide-based protease inhibitors and natural substrates.

**Synthesis of (R,S)-[4-<sup>11</sup>C]baclofen via Michael addition of nitromethane labeled with short-lived <sup>11</sup>C**

pp 6222–6224

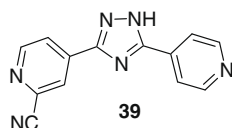
Koichi Kato <sup>\*</sup>, Ming-Rong Zhang, Kazutoshi Suzuki

within 20min, 36.4±1.8%conversion

### Discovery of 3-(3-cyano-4-pyridyl)-5-(4-pyridyl)-1,2,4-triazole, FYX-051-a xanthine oxidoreductase inhibitor for the treatment of hyperuricemia

pp 6225–6229

Takahiro Sato <sup>\*</sup>, Naoki Ashizawa, Koji Matsumoto, Takashi Iwanaga, Hiroshi Nakamura, Tsutomu Inoue, Osamu Nagata



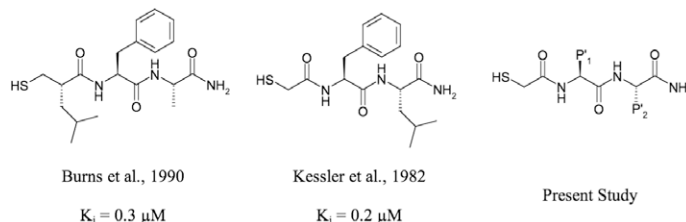
A series of 3,5-dipyridyl-1,2,4-triazole derivatives was synthesized and evaluated as xanthine oxidoreductase inhibitors. The best compound (FYX-051, compound **39**) exhibits extremely potent effects in lowering the serum UA levels in vivo, a weak CYP3A4-inhibitory activity, and a better pharmacokinetic profile.



### Inhibitor profiling of the *Pseudomonas aeruginosa* virulence factor LasB using *N*-alpha mercaptoamide template-based inhibitors

pp 6230–6232

George R. Cathcart, Brendan F. Gilmore, Brett Greer, Pat Harriott, Brian Walker <sup>\*</sup>

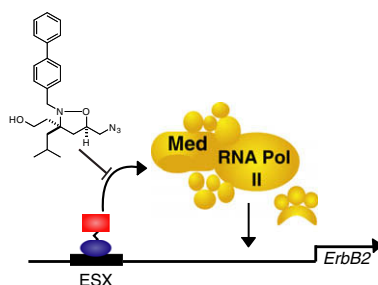


The synthesis and screening of a library of mercaptoamide containing dipeptides directed against *Pseudomonas elastase*, a key enzyme in biofilm formation and virulence.

### Inhibition of ErbB2(Her2) expression with small molecule transcription factor mimics

pp 6233–6236

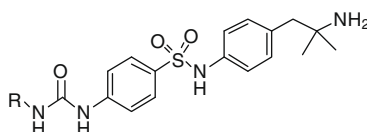
Lori W. Lee, Christopher E. C. Taylor, Jean-Paul Desaulniers, Manchao Zhang, Jonas W. Højfeldt, Quintin Pan, Anna K. Mapp <sup>\*</sup>



### Discovery and optimization of novel 4-[(aminocarbonyl)amino]-*N*-[4-(2-aminoethyl)phenyl]benzenesulfonamide ghrelin receptor antagonists

pp 6237–6240

Alexander Pasternak <sup>\*</sup>, Stephen D. Goble, Reynalda K. deJesus, Donna L. Hreniuk, Christine C. Chung, Michael R. Tota, Paul Mazur, Scott D. Feighner, Andrew D. Howard, Sander G. Mills, Lihu Yang

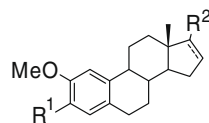


This Letter describes optimization of ghrelin receptor antagonists and inverse agonists starting from a screening hit.

**Synthesis, antiproliferative, and pharmacokinetic properties of 3- and 17-double-modified analogs of 2-methoxyestradiol**

pp 6241–6244

Gregory E. Agoston, Jamshed H. Shah, Lita Suwandi, Arthur D. Hanson, Xiaoguo Zhan, Theresa M. LaVallee, Victor Pribluda, Anthony M. Treston \*

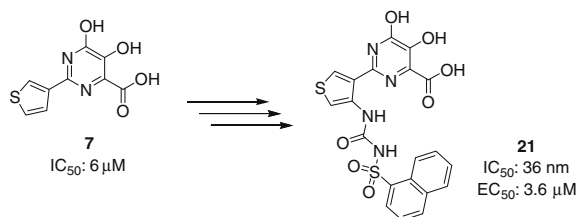


A series of doubly modified analogs of 2-methoxyestradiol were designed, synthesized and evaluated for antiproliferative, antiangiogenic, estrogenic and pharmacokinetic properties.

**2-(3-Thienyl)-5,6-dihydroxypyrimidine-4-carboxylic acids as inhibitors of HCV NS5B RdRp**

pp 6245–6249

Barbara Pacini \*, Salvatore Avolio, Caterina Ercolani, Uwe Koch, Giovanni Migliaccio, Frank Narjes, Laura Pacini, Licia Tomei, Steven Harper



A series of 2-(3-thienyl)-5,6-dihydroxypyrimidine-4-carboxylic inhibitors of the hepatitis C virus (HCV) NS5B polymerase enzyme are reported. Extensive SAR around the thiophene moiety led to the identification of the sulfonyl urea substituent as optimal in the HCV replicon assay. Mutations that confer resistance to these compounds are described.

\*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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