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# Bioorganic & Medicinal Chemistry Letters

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## Bioorganic & Medicinal Chemistry Letters Volume 20, Issue 15, 2010

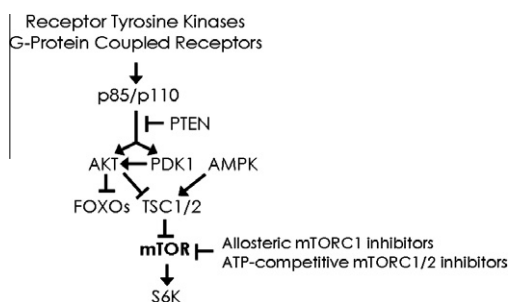
### Contents

#### BMCL DIGEST

#### Allosteric and ATP-competitive kinase inhibitors of mTOR for cancer treatment

pp 4308–4312

Carlos García-Echeverría

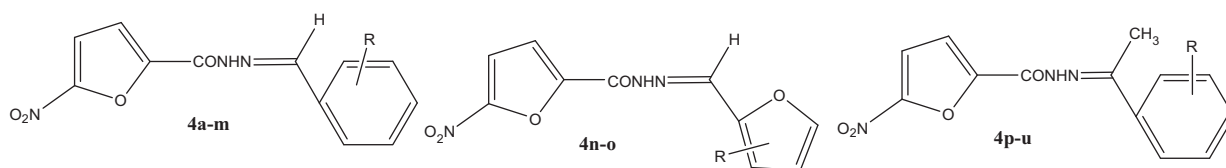


#### REGULAR ARTICLES

#### 5-Nitro-2-furoic acid hydrazones: Design, synthesis and in vitro antimycobacterial evaluation against log and starved phase cultures

pp 4313–4316

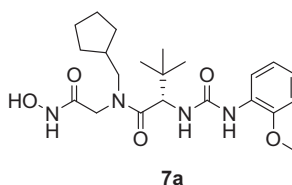
Dharmarajan Sriram\*, Perumal Yogeeswari, Devambatla Ravi Kumar Vyas, Palaniappan Senthilkumar, Pritesh Bhat, Madala Srividya



#### Peptide deformylase inhibitors with retro-amide scaffold: Synthesis and structure–activity relationships

pp 4317–4319

Seung Kyu Lee, Kwang Hyun Choi, Sang Jae Lee, Se Won Suh, B. Moon Kim, Bong Jin Lee\*



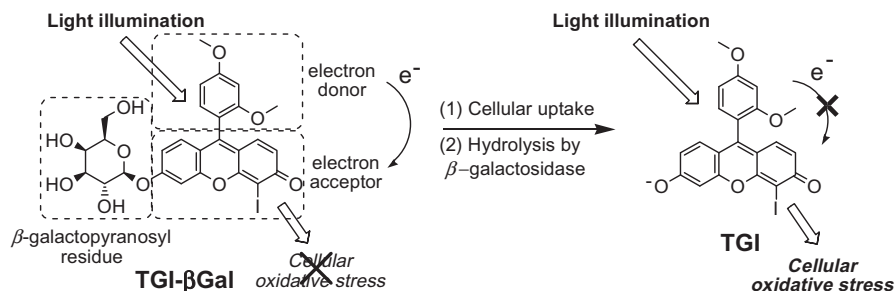
The synthesis and structure–activity relationship studies of peptide deformylase inhibitor **7a** are reported.



### Development of enzyme-activated photosensitizer based on intramolecular electron transfer

pp 4320–4323

Takatoshi Yogo, Yasuteru Urano, Mako Kamiya, Kiminari Sano, Tetsuo Nagano\*

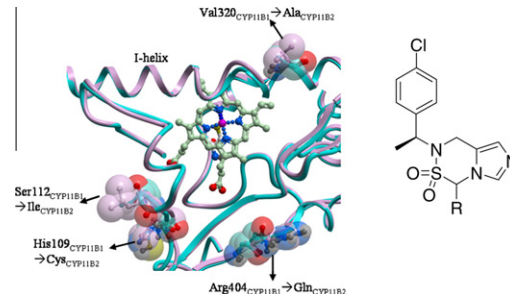


### The discovery of potent inhibitors of aldosterone synthase that exhibit selectivity over 11-β-hydroxylase

pp 4324–4327

Christopher M. Adams\*, Chii-Whei Hu, Arco Y. Jeng, Rajeshri Karki, Gary Ksander, Dan LaSala, Jennifer Leung-Chu, Guiqing Liang, Qian Liu, Erik Meredith, Chang Rao, Dean F. Rigel, Jie Shi, Sherri Smith, Clayton Springer, Chun Zhang

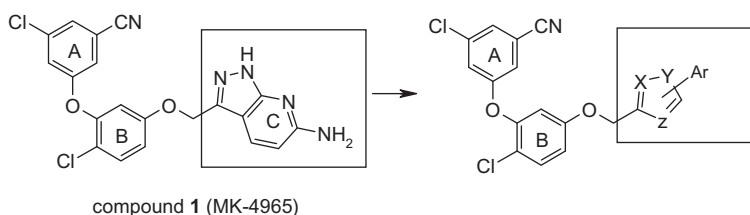
Aldosterone, the final component of the renin–angiotensin–aldosterone system, plays an important role in the pathophysiology of hypertension and congestive heart failure. Aldosterone synthase (CYP11B2) catalyzes the last three steps of aldosterone biosynthesis, and as such appears to be a target for the treatment of these disorders. A sulfonamide-imidazole scaffold has proven to be a potent inhibitor of CYP11B2. Furthermore, this scaffold can achieve high levels of selectivity for CYP11B2 over CYP11B1, a key enzyme in the biosynthesis of cortisol.



### Biaryl ethers as potent allosteric inhibitors of reverse transcriptase and its key mutant viruses: Aryl substituted pyrazole as a surrogate for the pyrazolopyridine motif

pp 4328–4332

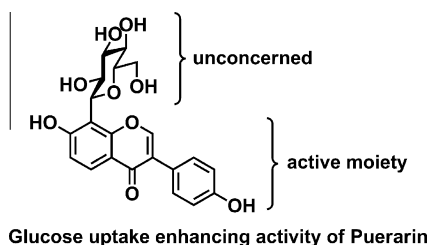
Dai-Shi Su\*, John J. Lim, Elizabeth Tinney, Thomas J. Tucker, Sandeep Saggarr, John T. Sisko, Bang-Lin Wan, Mary Beth Young, Kenneth D. Anderson, Deanne Rudd, Vandna Munshi, Carolyn Bahnck, Peter J. Felock, Meiquing Lu, Ming-Tain Lai, Sinoeun Touch, Gregory Moyer, Daniel J. DiStefano, Jessica A. Flynn, Yuexia Liang, Rosa Sanchez, Rebecca Perlow-Poehnelt, Mike Miller, Joe P. Vacca, Theresa M. Williams, Neville J. Anthony



### Glucose uptake enhancing activity of puerarin and the role of C-glucoside suggested from activity of related compounds

pp 4333–4336

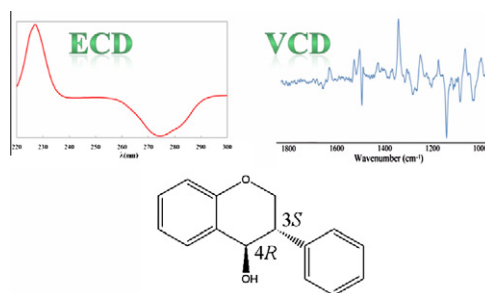
Eisuke Kato\*, Jun Kawabata



**Absolute configuration determination of isoflavan-4-ol stereoisomers**

pp 4337–4341

Mihyang Kim, Dongho Won, Jaehong Han\*

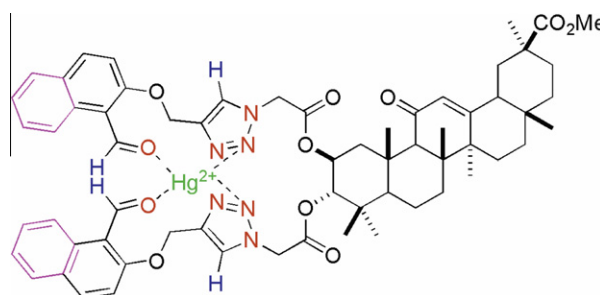


Absolute configurations of isoflavan-4-ol stereoisomers have been studied by ECD, VCD, and the modified Mosher method.

**Synthesis and binding ability of 1,2,3-triazole-based triterpenoid receptors for recognition of Hg<sup>2+</sup> ion**

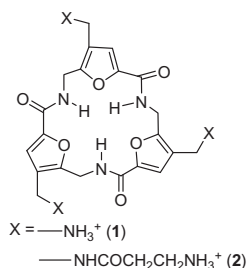
pp 4342–4345

Jun Hu, Meng Zhang, Li B. Yu, Yong Ju\*

A novel type of receptors based on 1,2,3-triazole glycyrrhetic acid derived from natural triterpenoid molecules has been synthesized via click chemistry and they showed high selectivity and affinity for Hg<sup>2+</sup> ion by both the 1,2,3-triazole rings and aldehyde groups.**Furan based cyclic homo-oligopeptides bind G-quadruplex selectively and repress c-MYC transcription**

pp 4346–4349

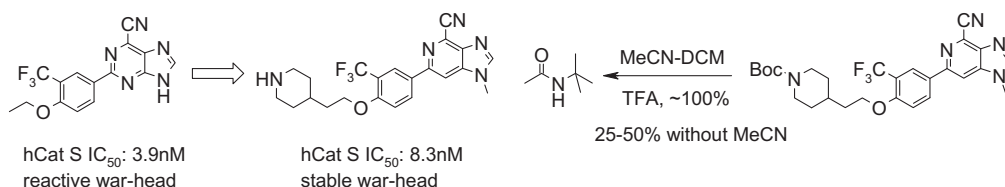
Tani Agarwal, Saumya Roy, Tushar Kanti Chakraborty\*, Souvik Maiti\*

**6-Phenyl-1H-imidazo[4,5-c]pyridine-4-carbonitrile as cathepsin S inhibitors**

pp 4350–4354

Jiaqiang Cai\*, Mark Baugh, Darcey Black, Clive Long, D. Jonathan Bennett, Maureen Dempster, Xavier Fradera, Jonathan Gillespie, Fiona Andrews, Sylviane Boucharens, John Bruin, Kenneth S. Cameron, Iain Cumming, William Hamilton, Philip S. Jones, Allard Kaptein, Emma Kinghorn, Maurice Maidment, Iain Martin, Ann Mitchell, Zoran Rankovic, John Robinson, Paul Scullion, Joost C.M. Uitdehaag, Paul Vink, Paul Westwood, Mario van Zeeland, Leon van Berkum, Martijn Bastiani, Tommi Meulemans

6-Phenyl-1H-imidazo[4,5-c]pyridine-4-carbonitrile derivatives were identified as selective human cathepsin S inhibitors with a stable thiol trapping nitrile war-head. A novel TFA based Boc deprotection method is also described. This new method uses acetonitrile as a co-solvent to remove *t*-butyl cation related side reactions by an in situ 'Ritter' reaction.

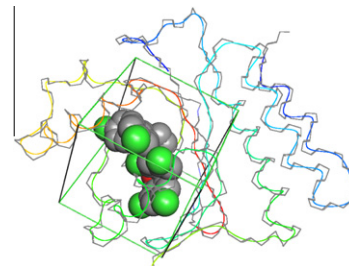


### LuxR-dependent quorum sensing: Computer aided discovery of new inhibitors structurally unrelated to *N*-acylhomoserine lactones

pp 4355–4358

Laurent Soullère\*, Mohamad Sabbah, Fanny Fontaine, Yves Queneau, Alain Doutheau

A docking-based virtual screening was used within the ligand binding sites of LuxR-type proteins to screen a chemical library of 2344 compounds. Biological evaluation of hit candidates on LuxR-dependent quorum sensing led to the discovery of six new inhibitors. Notably, calmidazolium was identified as one of the most potent AHL-structurally unrelated LuxR inhibitors.

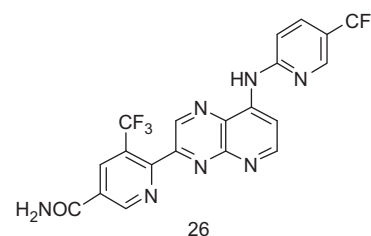


### Pyrido[2,3-*b*]pyrazines, discovery of TRPV1 antagonists with reduced potential for the formation of reactive metabolites

pp 4359–4363

Kevin J. Hodgetts\*, Charles A. Blum, Timothy Caldwell, Rajagopal Bakthavatchalam, Xiaozhang Zheng, Scott Capitosti, James E. Krause, Daniel Cortright, Marci Crandall, Beth Ann Murphy, Susan Boyce, A. Brian Jones, Bertrand L. Chenard

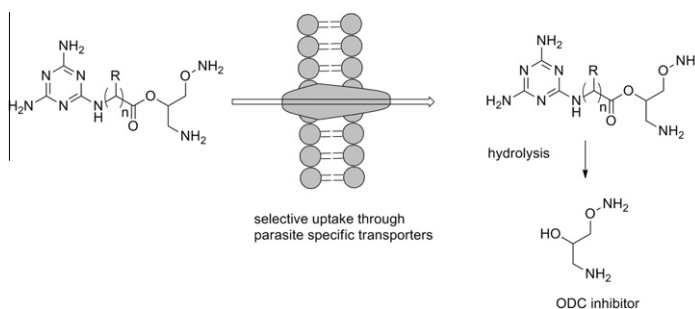
The transient receptor potential cation channel, subfamily V, member 1 (TRPV1) is a non-selective cation channel that can be activated by a wide range of noxious stimuli, including capsaicin, acid, and heat. Blockade of TRPV1 activation by selective antagonists is under investigation in an attempt to identify novel agents for pain treatment. During pre-clinical development, the 1,8-naphthyridine **2** demonstrated unacceptably high levels of irreversible covalent binding. Replacement of the 1,8-naphthyridine core by a pyrido[2,3-*b*]pyrazine led to the discovery of compound **26** which was shown to have significantly lower potential for the formation of reactive metabolites. Compound **26** was characterized as an orally bioavailable TRPV1 antagonist with moderate brain penetration. In vivo, **26** significantly attenuated carrageenan-induced thermal hyperalgesia (CITH) and dose-dependently reduced complete Freund's adjuvant (CFA)-induced chronic inflammatory pain after oral administration.



### Selective delivery of 2-hydroxy APA to *Trypanosoma brucei* using the melamine motif

pp 4364–4366

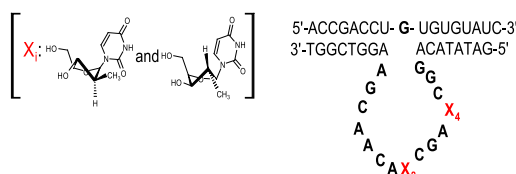
Nina Klee, Pui Ee Wong, Beatriz Baragaña, Farah El Mazouni, Margaret A. Phillips, Michael P. Barrett, Ian H. Gilbert\*



### 10-23 DNAzyme modified with (2'*R*)- and (2'*S*)-2'-deoxy-2'-*C*-methyluridine in the catalytic core

pp 4367–4370

Laura Robaldo, Javier M. Montserrat, Adolfo M. Iribarren\*



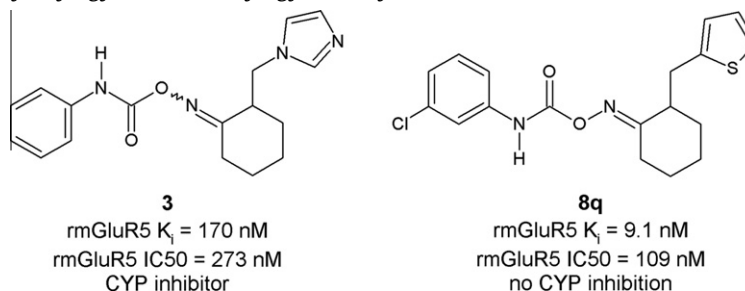
2'-Deoxy-2'-*C*-methyl nucleosides were incorporated at T positions of the catalytic core of a 10-23 DNAzyme directed against estrogen receptor  $\alpha$  ARNm. Comparison against DNAzymes modified with LNA-T was also performed.



**Carbamoyloximes as novel non-competitive mGlu5 receptor antagonists**

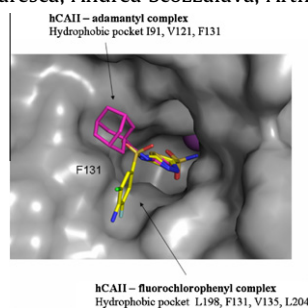
pp 4371–4375

János Galambos, Gábor Wágner, Katalin Nógrádi, Attila Bielik, László Molnár, Amrita Bobok, Attila Horváth, Béla Kiss, Sándor Kolok, József Nagy, Dalma Kurkó, Mónika L. Bak, Mónika Vastag, Katalin Sághy, István Gyertyán, Krisztina Gál, István Greiner, Zsolt Szombathelyi, György M. Keserü, György Domány\*

**Carbonic anhydrase inhibitors. The X-ray crystal structure of human isoform II in adduct with an adamantyl analogue of acetazolamide resides in a less utilized binding pocket than most hydrophobic inhibitors**

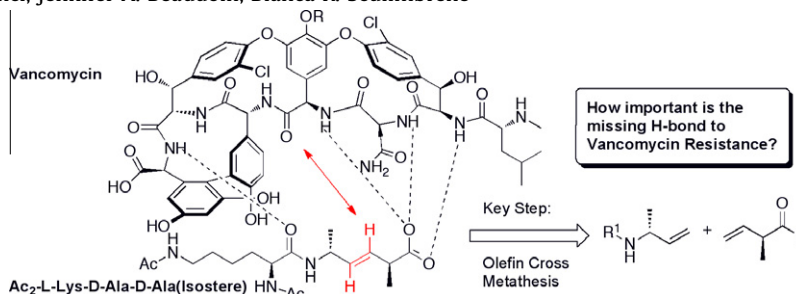
pp 4376–4381

Balendu Sankara Avvaru, Jason M. Wagner, Alfonso Maresca, Andrea Scozzafava, Arthur H. Robbins, Claudiu T. Supuran\*, Robert McKenna\*

**Synthesis of a D-Ala-D-Ala peptide isostere via olefin cross-metathesis and evaluation of vancomycin binding**

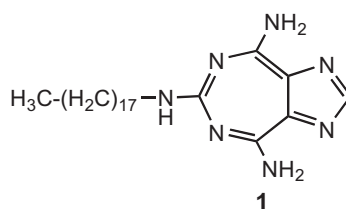
pp 4382–4385

Ryan K. Quinn, Amelia L. Cianci, Jennifer A. Beaudoin, Bianca R. Sculimbrene\*

**A novel, broad-spectrum anticancer compound containing the imidazo[4,5-e][1,3]diazepine ring system**

pp 4386–4389

Min Xie, Ravi K. Ujjinamatada, Mariola Sadowska, Rena G. Lapidus, Martin J. Edelman, Ramachandra S. Hosmane\*

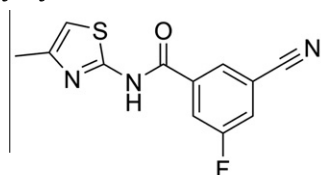


Synthesis and broad-spectrum anticancer activity of a novel heterocyclic compound **1** containing the title imidazo[4,5-e][1,3]diazepine ring system have been reported. The compound shows potent in vitro antitumor activity with low micromolar IC<sub>50</sub>'s against prostate, lung, breast, and ovarian cancer cell lines tested.

### 3-Cyano-5-fluoro-*N*-arylbenzamides as negative allosteric modulators of mGlu<sub>5</sub>: Identification of easily prepared tool compounds with CNS exposure in rats

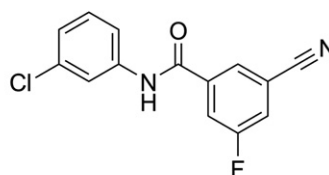
pp 4390–4394

Andrew S. Felts, Stacey R. Lindsley, Jeffrey P. Lamb, Alice L. Rodriguez, Usha N. Menon, Satyawar Jadhav, Carrie K. Jones, P. Jeffrey Conn, Craig W. Lindsley, Kyle A. Emmitte\*



**8** mGlu<sub>5</sub> IC<sub>50</sub> = 59 nM

rat brain/plasma ratio = 4.1 : 1



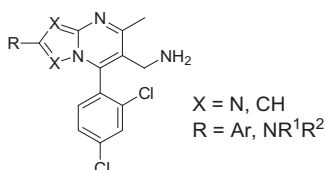
**27** mGlu<sub>5</sub> IC<sub>50</sub> = 45 nM

rat brain/plasma ratio = 1.4 : 1

### Synthesis and SAR of azolopyrimidines as potent and selective dipeptidyl peptidase-4 (DPP4) inhibitors for type 2 diabetes

pp 4395–4398

Robert P. Brigance\*, Wei Meng\*, Abera Fura, Thomas Harrity, Aiyang Wang, Robert Zahler, Mark S. Kirby, Lawrence G. Hamann



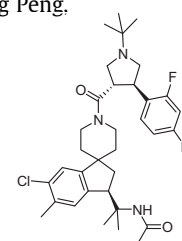
A series of azolopyrimidines were prepared and evaluated in vitro and in vivo for DPP4 activity.

### Spiroindane based amides as potent and selective MC4R agonists for the treatment of obesity

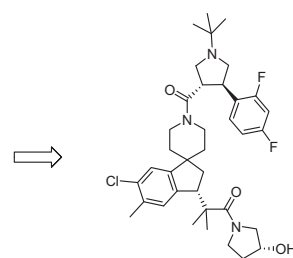
pp 4399–4405

Shuwen He\*, Zhixiong Ye, Peter H. Dobbelaar, Iyassu K. Sebat, Liangqin Guo, Jian Liu, Tianying Jian, Yingjie Lai, Christopher L. Franklin, Raman K. Bakshi, James P. Dellureficio, Qingmei Hong, David H. Weinberg, Tanya MacNeil, Rui Tang, Alison M. Strack, Constantin Tamvakopoulos, Qianping Peng, Randy R. Miller, Ralph A. Stearns, Howard Y. Chen, Airu S. Chen, Tung M. Fong, Matthew J. Wyvratt Jr., Ravi P. Nargund

We report a series of potent and selective MC4R agonists based on spiroindane amide privileged structures for potential treatments of obesity. Among the synthetic methods used, Method C allows rapid synthesis of the analogs. The series of compounds can afford high potency on MC4R as well as good rodent pharmacokinetic profiles. Compound **1r** (MK-0489) demonstrates MC4R mediated reduction of food intake and body weight in mouse models. Compound **1r** is efficacious in 14-day diet-induced obese (DIO) rat models.



**1r** (MK-0489)  
h-MC4R EC<sub>50</sub> 4.6 nM (109%act.)

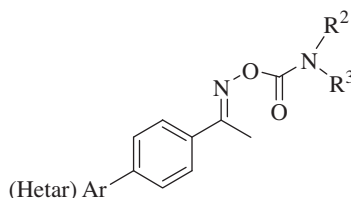


**35s**  
h-MC4R EC<sub>50</sub> 0.25 nM (98%act.)

### A new group of oxime carbamates as reversible inhibitors of fatty acid amide hydrolase

pp 4406–4411

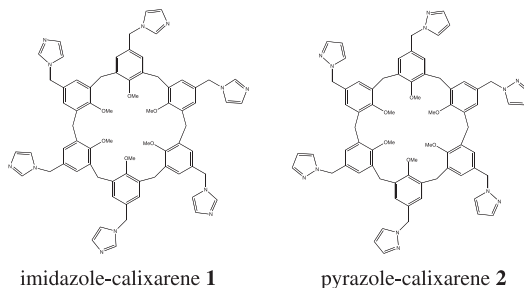
Sonia Gattinoni, Chiara De Simone, Sabrina Dallavalle, Filomena Fezza, Raffaella Nannei, Natalia Battista, Patrizia Minetti, Gianandrea Quattrocchi, Antonio Caprioli, Franco Borsini, Walter Cabri, Sergio Penco, Lucio Merlini\*, Mauro Maccarrone\*



**Enhancement of transcriptional activity of mutant p53 tumor suppressor protein through stabilization of tetramer formation by calix[6]arene derivatives**

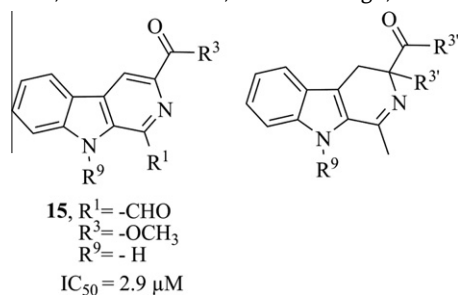
pp 4412–4415

Rui Kamada, Wataru Yoshino, Takao Nomura, Yoshiro Chuman, Toshiaki Imagawa, Takanori Suzuki, Kazuyasu Sakaguchi\*

**Synthesis and evaluation of  $\beta$ -carboline derivatives as inhibitors of human immunodeficiency virus**

pp 4416–4419

Keyur G. Brahmbhatt, Nafees Ahmed, Sudeep Sabde, Debashis Mitra\*, Inder Pal Singh, Kamlesh K. Bhutani\*

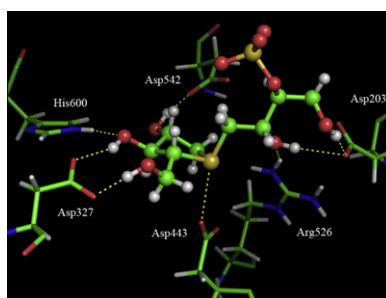


A series of  $\beta$ -carboline derivatives were prepared and evaluated for anti-HIV activity in human CD4<sup>+</sup> T cell line CEM-GFP, infected with HIV-1 NL<sub>4.3</sub>. 1-Formyl- $\beta$ -carboline-3-carboxylic acid methyl ester (**15**) showed  $IC_{50}$  of 2.9  $\mu M$ .

**Docking and SAR studies of salacinol derivatives as  $\alpha$ -glucosidase inhibitors**

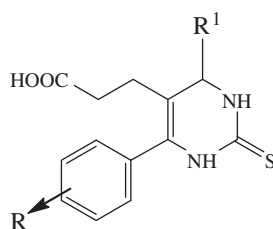
pp 4420–4423

Shinya Nakamura\*, Kazunori Takahira, Genzoh Tanabe, Toshio Morikawa, Mika Sakano, Kiyofumi Ninomiya, Masayuki Yoshikawa, Osamu Muraoka, Isao Nakanishi

**Synthesis and anti-inflammatory activity of some 3-(4,6-disubstituted-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl) propanoic acid derivatives**

pp 4424–4426

Santosh N. Mokale\*, Sandeep S. Shinde, Rupali D. Elgire, Jaiprakash N. Sangshetti, Devanand B. Shinde

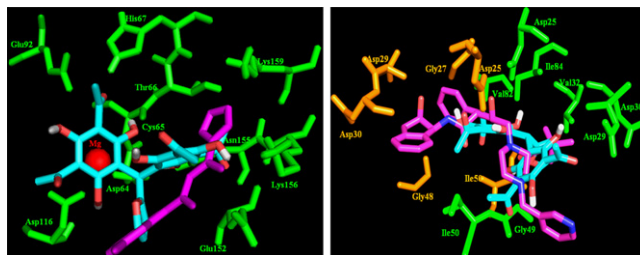


A new series of 3-(4,6-disubstituted-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl) propanoic acid derivatives has been synthesized and evaluated for their anti-inflammatory activity using rat paw edema method. Most of the compounds from the series show anti-inflammatory activity comparable to diclofenac.

### Active site binding modes of dimeric phloroglucinols for HIV-1 reverse transcriptase, protease and integrase

pp 4427–4431

Pawan Gupta, Rajender Kumar, Prabha Garg\*, Inder Pal Singh



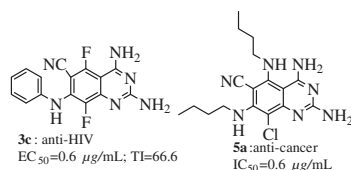
Compound **5** exhibited good binding interactions into the both active site of (a) IN (1QS4) and (b) PR (1HSG). This compound may be dual inhibitor acting against both IN and PR.



### Synthesis of highly functionalized 2,4-diaminoquinazolines as anticancer and anti-HIV agents

pp 4432–4435

Sheng-Jiao Yan, Han Zheng, Chao Huang, Yu-Yun Yan, Jun Lin\*



The novel 2,4-diaminoquinazolines **3–5** were easily prepared based on the reaction of polyhaloisophthalonitriles with guanidine carbonate. The anticancer and anti-HIV activities of **3–5** were evaluated in vitro. Compound **5a** was the most potent derivative against the five tumor cell lines with an  $IC_{50}$  value lower than  $2.5 \mu\text{g/mL}$ , and **3c** showed the most potent anti-HIV-1 activity with  $EC_{50}$  values of 0.6 and  $1.6 \mu\text{g/mL}$ , and  $TI$  values of  $>59.6$  and  $66.6$ , respectively.

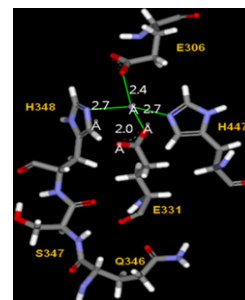


### In silico studies on the substrate specificity of an L-arabinose isomerase from *Bacillus licheniformis*

pp 4436–4439

Ponnandy Prabhu, Marimuthu Jeya, Jung-Kul Lee\*

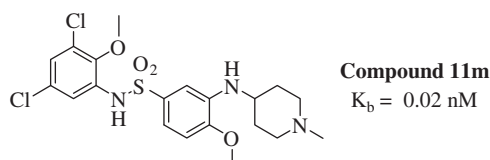
Based on in silico studies, the residue at position 346 has been proposed to be responsible for the unique substrate specificity of L-arabinose isomerase from *Bacillus licheniformis*.



### Synthesis and pharmacological evaluation of aryl aminosulfonamide derivatives as potent 5-HT<sub>6</sub> receptor antagonists

pp 4440–4443

Ramakrishna V.S. Nirogi\*, Anand V. Daulatabad, G. Parandhama, Shaikh Mohammad, K.R. Sastri, Anil K. Shinde, P.K. Dubey



Design, synthesis, SAR and Pharmacokinetic profile of a novel series of Aryl aminosulfonamides as potent 5-HT<sub>6</sub> receptor antagonists is presented. The lead compound was active in animal model of cognition.

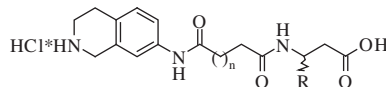




**Derivatives of tetrahydroisoquinoline: Synthesis and initial evaluation of novel non-peptide antagonists of the  $\alpha_{1\text{IB}}\beta_3$ -integrin**

pp 4444–4446

Andrei A. Krysko\*, Olga L. Krysko, Tatyana A. Kabanova, Sergei A. Andronati, Vladimir M. Kabanov

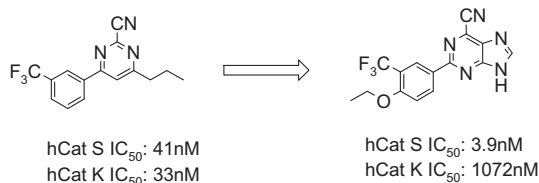


The synthesis of the novel fibrinogen receptor antagonists.

**2-Phenyl-9H-purine-6-carbonitrile derivatives as selective cathepsin S inhibitors**

pp 4447–4450

Jiaqiang Cai\*, D. Jonathan Bennett, Zoran Rankovic, Maureen Dempster, Xavier Fradera, Jonathan Gillespie, Iain Cumming, William Finlay, Mark Baugh, Sylviane Boucharens, John Bruin, Kenneth S. Cameron, William Hamilton, Jennifer Kerr, Emma Kinghorn, George McGarry, John Robinson, Paul Scullion, Joost C.M. Uitdehaag, Mario van Zeeland, Dominique Potin, Laurent Sanier, Andre Fouquet, Francois Chevallier, Hortense Deronzier, Cecile Dorleans, Eric Nicolai

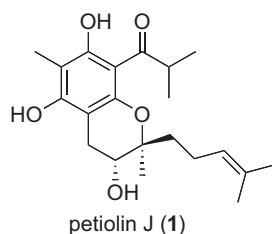


2-Phenyl-9H-purine-6-carbonitrile derivatives were designed as selective human cathepsin S inhibitors through P2 optimization and transition state stabilization by an intramolecular H-bond.

**Petiolins J–M, prenylated acylphloroglucinols from *Hypericum pseudopetiolatum* var. *kiusianum***

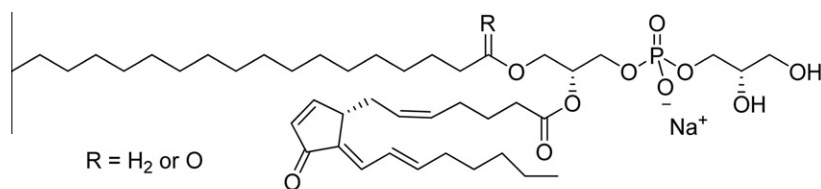
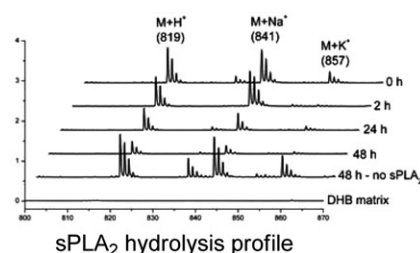
pp 4451–4455

Naonobu Tanaka, Mio Otani, Yoshiki Kashiwada, Yoshihisa Takaishi, Azusa Shibazaki, Tohru Gono, Motoo Shiro, Jun'ichi Kobayashi\*

**Prostaglandin phospholipid conjugates with unusual biophysical and cytotoxic properties**

pp 4456–4458

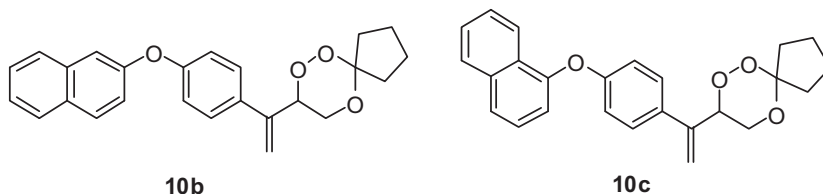
Palle J. Pedersen, Sidsel K. Adolph, Thomas L. Andresen, Mogens W. Madsen, Robert Madsen, Mads H. Clausen\*

15-deoxy- $\Delta^{12,14}$ -PGJ<sub>2</sub> phospholipid conjugates

### 6-(4'-Aryloxy-phenyl)vinyl-1,2,4-trioxanes: A new series of orally active peroxides effective against multidrug-resistant *Plasmodium yoelii* in Swiss mice

pp 4459–4463

Chandan Singh\*, Ved Prakash Verma, Niraj Krishna Naikade, Ajit Shankar Singh, Mohammad Hassam, Sunil. K. Puri

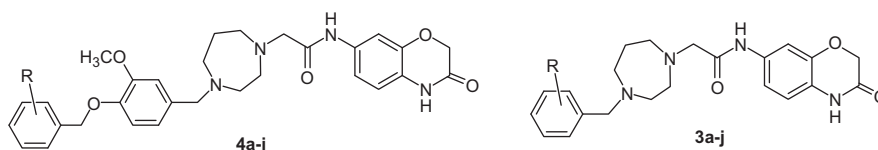


A new series of 6-(4'-aryloxy-phenyl)vinyl-1,2,4-trioxanes **10a–d**, **11a–d**, and **12a–d** have been synthesized and evaluated for their antimalarial activity against multidrug-resistant *Plasmodium yoelii* in Swiss mice by oral route. Trioxanes **10b** and **10c**, the two most active compounds of the series, provided 100% protection to the infected mice at 48 mg/kg  $\times$  4 days.

### Synthesis of 2-(4-substituted benzyl-1,4-diazepan-1-yl)-N-(3,4-dihydro-3-oxo-2H-benzo[b][1,4]oxazin-7-yl)-acetamides and their positive inotropic evaluation

pp 4464–4467

Kun Yang, Liang-Peng Sun, Ji-Yong Liu, Xun Cui\*, Hu-Ri Piao\*



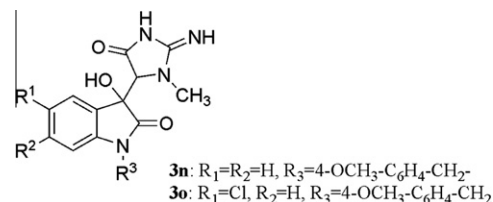
Two series of 2-(4-substituted benzyl-1,4-diazepan-1-yl)-N-(3,4-dihydro-3-oxo-2H-benzo[b][1,4]oxazin-7-yl)acetamides (**3a–j** and **4a–j**) were synthesized and their positive inotropic activity were evaluated by measuring left atrium stroke volume on isolated rabbit heart preparations.

### Synthesis and in vitro evaluation of N-alkyl-3-hydroxy-3-(2-imino-3-methyl-5-oxoimidazolidin-4-yl)-indolin-2-one analogs as potential anticancer agents

pp 4468–4471

Narsimha Reddy Penthala, Thirupathi Reddy Yerramreddy, Nikhil Reddy Madadi, Peter A. Crooks\*

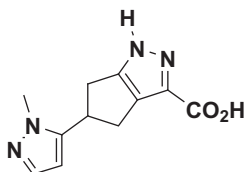
A series of novel 3-hydroxy-3-(2-imino-3-methyl-5-oxoimidazolidin-4-yl)indolin-2-one analogs (**3**) have been synthesized under microwave irradiation and conventional heating methods. These analogs were evaluated for their in vitro cytotoxicity against a panel of 57 human tumor cell lines. Compound **3o** had  $GI_{50}$  values of 190 nM and 750 nM against A549/ATTC non-small cell lung cancer and LOX IMVI melanoma cell lines, respectively, and both **3n** and **3o** exhibited  $GI_{50}$  values ranging from 2 to 5  $\mu$ M against CCRF-CEM, HL-60(TB), K-562, MOLT-4, and RPMI-8226 leukemia cell lines. These results indicate that N-4-methoxybenzyl-3-hydroxy-(2-imino-3-methyl-5-oxo-4-yl)indolin-2-one analogs may be useful leads for anticancer drug development.



### GPR109a agonists. Part 2: Pyrazole-acids as agonists of the human orphan G-protein coupled receptor GPR109a

pp 4472–4474

Jason E. Imbriglio\*, Sookhee Chang, Rui Liang, Subharekha Raghavan, Darby Schmidt, Abby Smenton, Scott Tria, Thomas O. Schrader, Jae-Kyu Jung, Craig Esser, Tom G. Holt, Michael S. Wolff, Andrew K.P. Taggart, Kang Cheng, Ester Carballo-Jane, M. Gerard Waters, James R. Tata, Steven L. Colletti



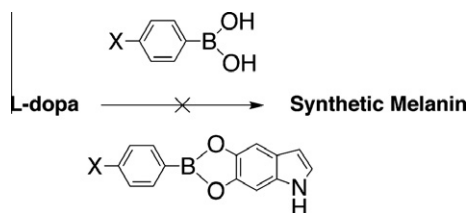
5-Alkyl and aryl-pyrazole-acids have been identified as a new class of selective, small-molecule, agonists of the human orphan G-protein-coupled receptor GPR109a, a high affinity receptor for the HDL-raising drug nicotinic acid.



**Aryl boronic acid inhibition of synthetic melanin polymerization**

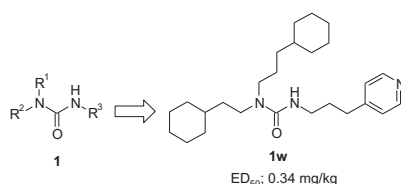
pp 4475–4478

Jason M. Belitsky\*

**Synthesis and pharmacological evaluation of 1,1,3-substituted urea derivatives as potent TNF- $\alpha$  production inhibitors**

pp 4479–4482

Hiroshi Enomoto\*, Ayako Sawa, Hiroshi Suhara, Noriyoshi Yamamoto, Hiroyuki Inoue, Chikako Setoguchi, Fumio Tsuji, Masahiro Okamoto, Yoshimasa Sasabuchi, Masato Horiuchi, Masakazu Ban



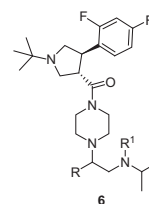
The synthesis of the urea derivatives were performed rapidly in a one-pot manner using a manual synthesizer. Several compounds containing hydrophobic substituents at R<sup>1</sup> and R<sup>2</sup> showed potent inhibitory activities against TNF- $\alpha$  production.

**Optimization of privileged structures for selective and potent melanocortin subtype-4 receptor ligands**

pp 4483–4486

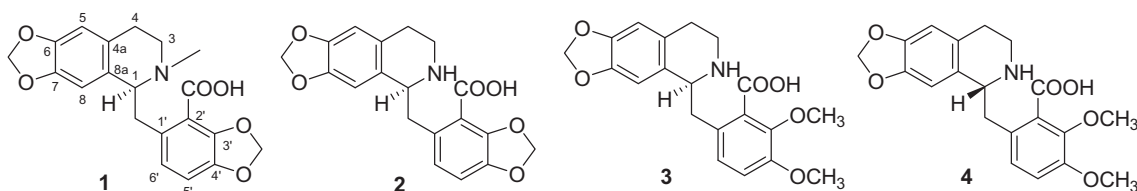
Qingmei Hong\*, Raman K. Bakshi, James Dellureficio, Shuwen He, Zhixiong Ye, Peter H. Dobbelaar, Iyassu K. Sebat, Liangqin Guo, Jian Liu, Tianying Jian, Rui Tang, Rubana N. Kalyani, Tanya MacNeil, Aurawan Vongs, Charles I. Rosenblum, David H. Weinberg, Qingping Peng, Constantin Tamvakopoulos, Randy R. Miller, Ralph A. Stearns, Doreen Cashen, Willian J. Martin, Airu S. Chen, Joseph M. Metzger, Howard Y. Chen, Allison M. Strack, Tung M. Fong, Euan MacIntyre, Lex H.T. Van der Ploeg, Matthew J. Wyvratt, Ravi P. Nargund

Design, syntheses and structure–activity relationships of piperazine privileged structures containing MC4R agonist compounds **6** were described. The most potent derivatives were low nM MC4R selective full agonists. Several compounds from the series had modest pharmacokinetic properties.

**Benzylisoquinoline alkaloids from the tubers of *Corydalis ternata* and their cytotoxicity**

pp 4487–4490

Ki Hyun Kim, Il Kyun Lee, Cheng Jie Piao, Sang Un Choi, Jei Hyun Lee, Yeong Shik Kim, Kang Ro Lee\*



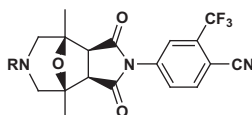
Chemical investigation of the tubers of *Corydalis ternata* resulted in the isolation and characterization of four new benzylisoquinoline alkaloids, *epi*-coryximine (**1**) and coryternatines A–C (**2–4**), along with 10 known alkaloids.



### Design and synthesis of 4-[3,5-dioxo-11-oxa-4,9-diazatricyclo[5.3.1.0<sup>2,6</sup>]undec-4-yl]-2-trifluoromethyl-benzonitriles as androgen receptor antagonists

pp 4491–4495

Hai-Yun Xiao\*, Aaron Balog, Ricardo M. Attar, David Fairfax, Linda B. Fleming, Christian L. Holst, Gregory S. Martin, Lana M. Rossiter, Jing Chen, Mary-Ellen Cvjic, Janet Dell-John, Jieping Geng, Marco M. Gottardis, Wen-Ching Han, Andrew Nation, Mary Obermeier, Cheryl A. Rizzo, Liang Schweizer, Thomas Spires Jr. Jr., Weifang Shan, Ashvinikumar Gavai, Mark E. Salvati, Gregory Vite

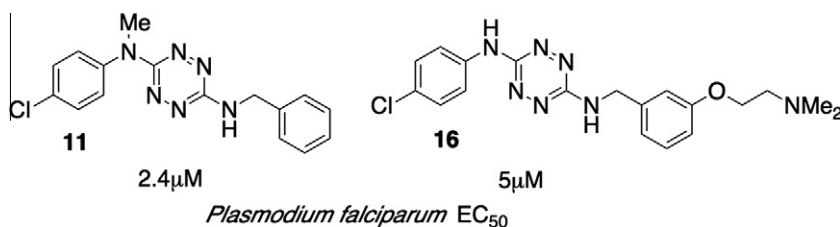


A novel series of 4-[3,5-dioxo-11-oxa-4,9-diazatricyclo[5.3.1.0<sup>2,6</sup>]undec-4-yl]-2-trifluoromethyl-benzonitriles has been synthesized. The ability of these compounds to act as antagonists of the androgen receptor was investigated and several were found to have potent activity in vitro and in vivo.

### Antimalarial 3-arylamino-6-benzylamino-1,2,4,5-tetrazines

pp 4496–4498

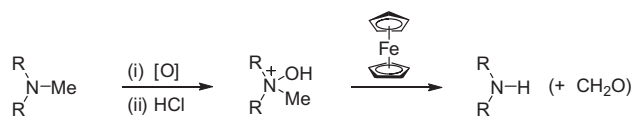
Duong Nhu, Sandra Duffy, Vicky M. Avery, Andrew Hughes, Jonathan B. Baell\*



### N-Demethylation of N-methyl alkaloids with ferrocene

pp 4499–4502

Gaik B. Kok, Peter J. Scammells\*



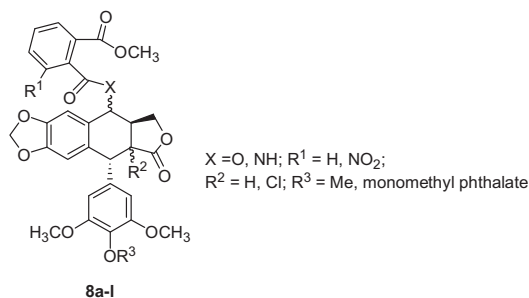
Ferrocene has been found to be a convenient and efficient catalyst for the N-demethylation of a number of opiate and tropane N-methyl alkaloids.



### Natural products-based insecticidal agents 6. Design, semisynthesis, and insecticidal activity of novel monomethyl phthalate derivatives of podophyllotoxin against *Mythimna separata* Walker in vivo

pp 4503–4506

Hui Xu\*, Xiao-Qiang He

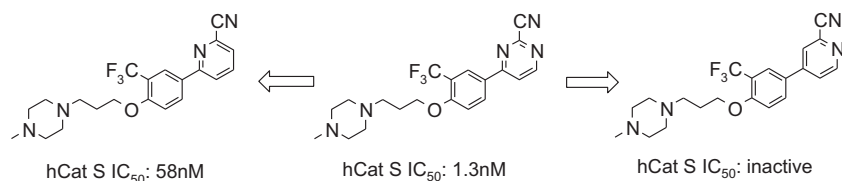


Trans-lactone, 4β-substitution, 2β-chlorine substitution, and 4'-methoxy group were the important structural properties of podophyllotoxins for good insecticidal activity.

**4-(3-Trifluoromethylphenyl)-pyrimidine-2-carbonitrile as cathepsin S inhibitors: N3, not N1 is critically important**

pp 4507–4510

Jiaqiang Cai\*, Xavier Fradera, Mario van Zeeland, Maureen Dempster, Kenneth S. Cameron, D. Jonathan Bennett, John Robinson, Lucy Popplestone, Mark Baugh, Paul Westwood, John Bruin, William Hamilton, Emma Kinghorn, Clive Long, Joost C.M. Uitdehaag

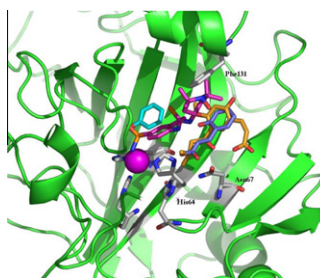


The N3 nitrogen of the pyrimidine-2-carbonitrile based cathepsin cysteine protease inhibitors is critically important. An 'in situ double activation' mechanism was postulated to explain these results. A novel expanded S2 binding pocket for human cathepsin S enzyme was also identified.

**Coumarins incorporating hydroxy- and chloro-moieties selectively inhibit the transmembrane, tumor-associated carbonic anhydrase isoforms IX and XII over the cytosolic ones I and II**

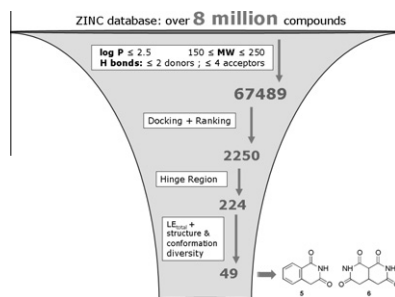
pp 4511–4514

Alfonso Maresca, Claudiu T. Supuran\*

**NF-κB inducing kinase (NIK) inhibitors: Identification of new scaffolds using virtual screening**

pp 4515–4520

Jérémie Mortier, Bernard Masereel, Caroline Remouchamps, Corinne Ganeff, Jacques Piette, Raphaël Frederick\*

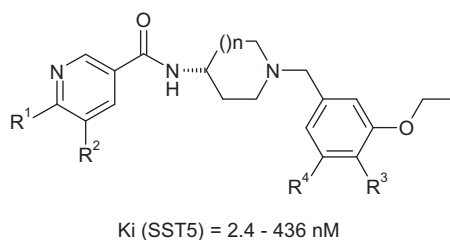


Virtual screening led to the identification of two molecular fragments (5 and 6) as NIK inhibitors.

**Piperidinyl-nicotinamides as potent and selective somatostatin receptor subtype 5 antagonists**

pp 4521–4525

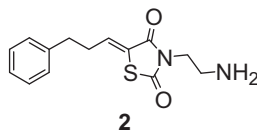
André Alker, Alfred Binggeli, Andreas D. Christ, Luke Green, Hans Peter Maerki, Rainer E. Martin, Peter Mohr\*



### Discovery of 3-(2-aminoethyl)-5-(3-phenyl-propylidene)-thiazolidine-2,4-dione as a dual inhibitor of the Raf/MEK/ERK and the PI3K/Akt signaling pathways

pp 4526–4530

Qianbin Li, Jingde Wu, Hui Zheng, Kai Liu, Tai L. Guo, Yuying Liu, Scott T. Eblen, Steven Grant, Shijun Zhang\*



The identification of 3-(2-aminoethyl)-5-(3-phenyl-propylidene)-thiazolidine-2,4-dione as a dual inhibitor of the Raf/MEK/ERK and PI3K/Akt signaling pathways is reported.

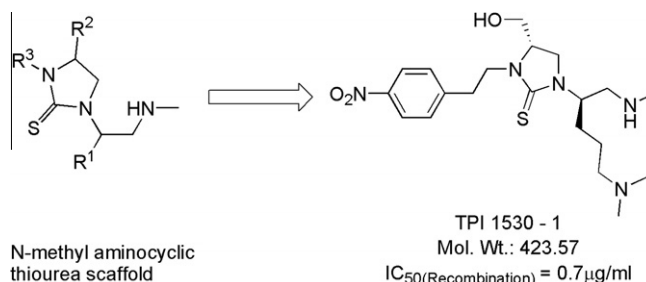


### Small molecule functional analogs of peptides that inhibit $\lambda$ site-specific recombination and bind Holliday junctions

pp 4531–4534

Dev K. Ranjit, Marc C. Rideout, Adel Nefzi, John M. Ostresh, Clemencia Pinilla, Anca M. Segall\*

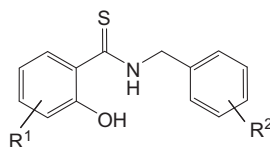
Combinatorial libraries were screened to identify a non-peptide analog of a peptide inhibitor of a DNA recombination reaction; like the peptide, 1530-1 acts by stabilizing the Holliday junction intermediate.



### N-Benzylsalicylthioamides as novel compounds with promising antimycotic activity

pp 4535–4538

Eva Petrílková\*, Karel Waisser, Vladimír Buchta, Petr Jílek, Marcela Vejsová



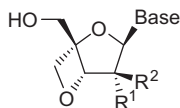
N-Benzylsalicylthioamides exhibit an in vitro antifungal activity against fluconazole-susceptible as well as the fluconazole-resistant fungal strains.



### Synthesis and anti-HCV activity of 3',4'-oxetane nucleosides

pp 4539–4543

Wonsuk Chang, Jinfa Du, Suguna Rachakonda, Bruce S. Ross, Serge Convers-Reignier, Wei T. Yau, Jean-Francois Pons, Eisuke Murakami, Haiying Bao, Holly Micolochick Steuer, Phillip A. Furman, Michael J. Otto, Michael J. Sofia\*



Base: cytosine or adenine  
R<sup>1</sup>, R<sup>2</sup>: H, F, Me, or OMe

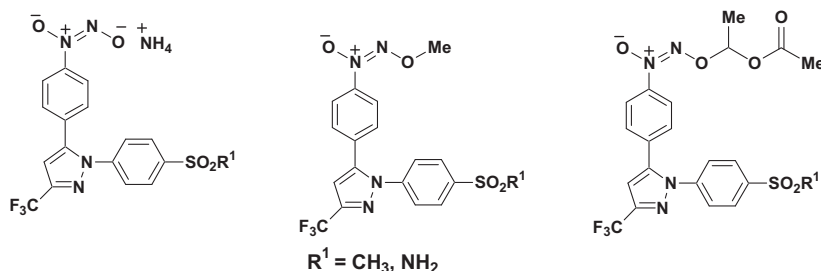
A series of 3'-O,4'-C-methylene cytidine and adenosine nucleosides were prepared and evaluated for their inhibition of HCV RNA replication.



**Celecoxib prodrugs possessing a diazen-1-ium-1,2-diolate nitric oxide donor moiety: Synthesis, biological evaluation and nitric oxide release studies**

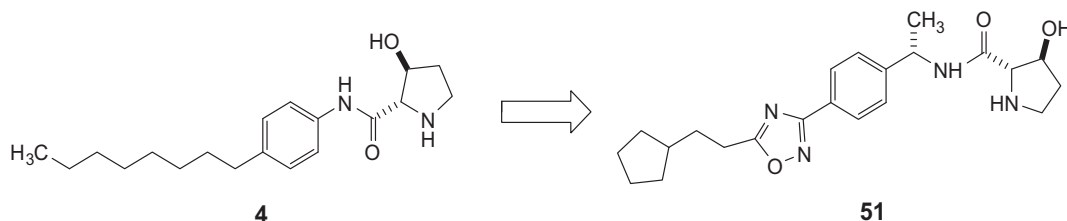
pp 4544–4549

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

**Discovery of novel sphingosine kinase-1 inhibitors. Part 2**

pp 4550–4554

Yibin Xiang\*, Bradford Hirth, John L. Kane Jr., Junkai Liao, Kevin D. Noson, Christopher Yee, Gary Asmussen, Maria Fitzgerald, Christine Klaus, Michael Booker



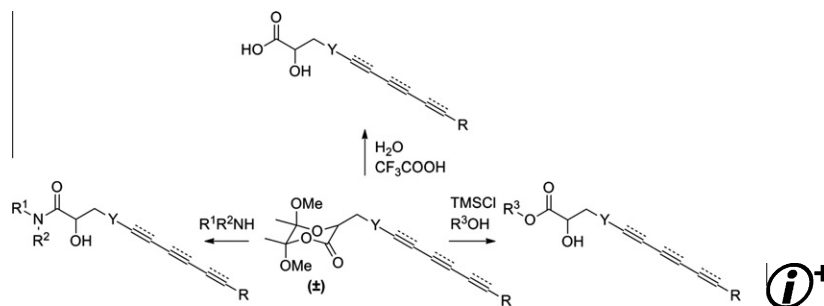
Working off the previously discovered sphingosine kinase-1 (SK1) inhibitor **4**, structural optimization resulted in identification of a new series of analogs exemplified by compound **51** which have improved aqueous solubility and ADME properties while maintain or enhance enzyme potency. The lead **51** has also demonstrated modest oral bioavailability in a rat PK study.

**Synthesis and activity of polyacetylene substituted 2-hydroxy acids, esters, and amides against microbes of clinical importance**

pp 4555–4557

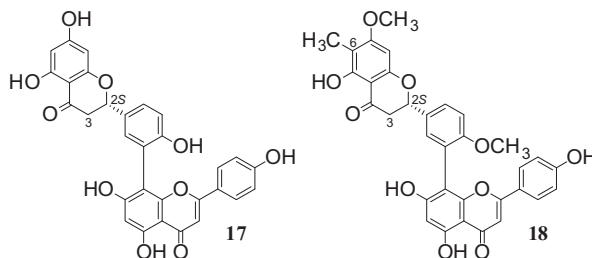
Stella Kyi, Nalin Wongkattiya, Andrew C. Warden, Michael S. O'Shea, Margaret Deighton, Ian Macreadie, Florian H.M. Graichen\*

A series of novel polyacetylene substituted 2-hydroxy acids and derivatives were prepared and characterized. Twenty one of these novel compounds were tested against 10 microbes of clinical importance and several of them showed good antimicrobial activity, in particular against *Pseudomonas aeruginosa*.

**β-Secretase (BACE-1) inhibitory effect of biflavonoids**

pp 4558–4560

Hiroaki Sasaki, Kazuhiko Miki, Kaoru Kinoshita, Kiyotaka Koyama, Lia D. Juliawaty, Sjamsul A. Achmad, Euis H. Hakim, Miyuki Kaneda, Kunio Takahashi\*

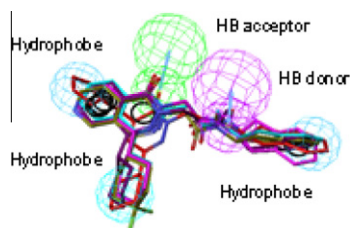


Amentoflavone-type biflavonoids, 2,3-dihydroamentoflavone **17** and 2,3-dihydro-6-methylginkgetin **18** exhibited potent β-secretase (BACE-1) inhibitory effects with IC<sub>50</sub> values of 0.75 and 0.35 μM, respectively.

### Identification of novel $\alpha 7$ nAChR positive allosteric modulators with the use of pharmacophore in silico screening methods

pp 4561–4565

Anna Maria Capelli\*, Laura Castelletti, Cristian Salvagno, Beatrice Oliosi, Elisa Di Lenarda, Caterina Virginio, Andrew Lightfoot, James N.C. Kew, Simon Teague



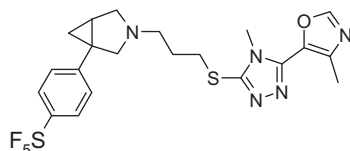
The identification of novel  $\alpha 7$  nAChR allosteric positive modulators using pharmacophore methods is reported.



### A specific and direct comparison of the trifluoromethyl and pentafluoro sulfanyl groups on the selective dopamine $D_3$ antagonist 3-([4-methyl-5-(4-methyl-1,3-oxazol-5-yl)-4H-1,2,4-triazol-3-yl]thio)propyl)-1-phenyl-3-azabicyclo[3.1.0]hexane template

pp 4566–4568

Fabrizio Micheli\*, Daniele Andreotti, Simone Braggio, Anna Checchia

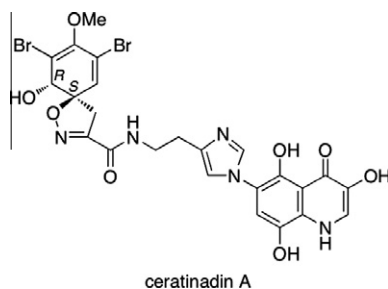


The comparison of selective DA  $D_3$  antagonists with different functional groups is reported.

### Ceratinadins A–C, new bromotyrosine alkaloids from an Okinawan marine sponge *Pseudoceratina* sp.

pp 4569–4572

Yuji Kon, Takaaki Kubota, Azusa Shibasaki, Tohru Gono, Jun'ichi Kobayashi\*

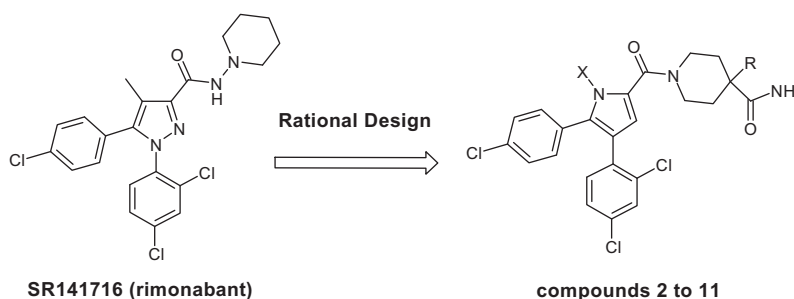


### Rational design of a novel peripherally-restricted, orally active $CB_1$ cannabinoid antagonist containing a 2,3-diarylpyrrole motif

pp 4573–4577

Laurent Hortala, Murielle Rinaldi-Carmona, Christian Congy, Laurent Boulu, Freddy Sadoun, Gérard Fabre, Olivier Finance, Francis Barth\*

A rational design approach around a new pyrrole core with modulation of the topological polar surface area allowed the identification of the potent, selective and peripherally-restricted  $CB_1$  antagonist **11** [X =  $-(CH_2)_3NHSO_2Me$ ; R = (4,4-difluoropiperidyl)] with a  $IC_{50}$  ( $hCB_1$ ) = 1.4 nM.

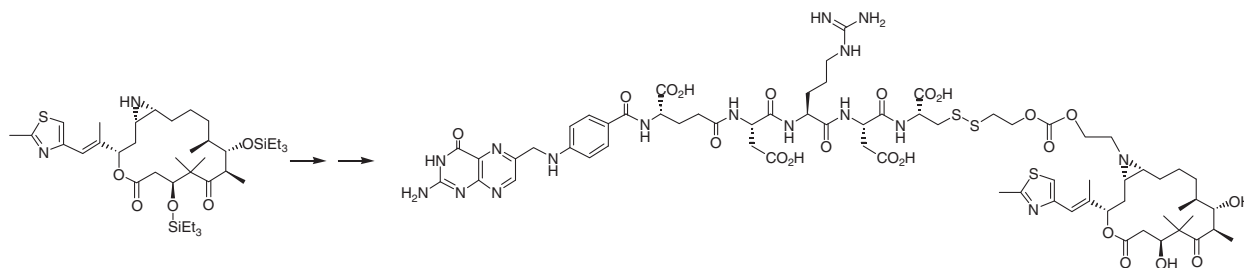




**Regioselective synthesis of folate receptor-targeted agents derived from epothilone analogs and folic acid**

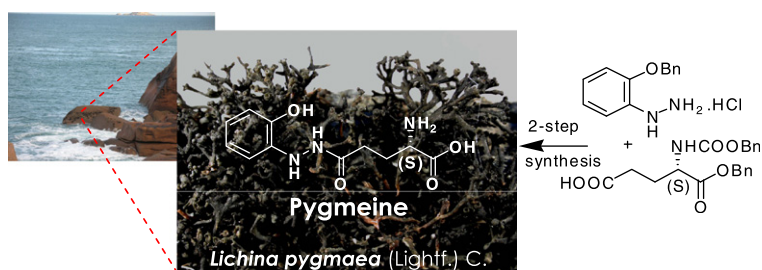
pp 4578–4581

Iontcho R. Vlahov\*, Gregory D. Vite, Paul J. Kleindl, Yu Wang, Hari Krishna R. Santhapuram, Fei You, Stephen J. Howard, Soong-Hoon Kim, Francis F.Y. Lee, Christopher P. Leamon

**A novel aryl-hydrazide from the marine lichen *Lichina pygmaea*: Isolation, synthesis of derivatives, and cytotoxicity assays**

pp 4582–4586

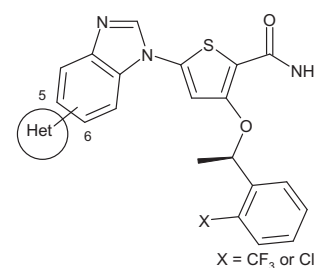
Catherine Roullier, Marylène Chollet-Krugler\*, Pierre van de Weghe, Françoise Lohézic-Le Devehat, Joël Boustie

**Heteroaryl-linked 5-(1H-benzimidazol-1-yl)-2-thiophenecarboxamides: Potent inhibitors of polo-like kinase 1 (PLK1) with improved drug-like properties**

pp 4587–4592

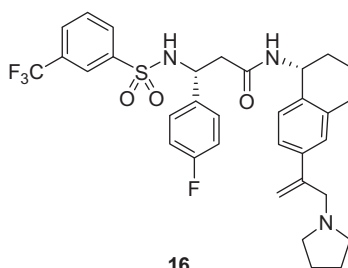
Tara R. Rheault\*, Kelly H. Donaldson, Jennifer G. Badiang-Alberti, Ronda G. Davis-Ward, C. Webb Andrews, Ramesh Bambal, Jeffrey R. Jackson, Mui Cheung

Potent inhibitors of PLK1 with acceptable solubility, mouse iv clearance, and reduced CYP450 inhibition were identified. Drug-like properties were improved using a heteroaryl ring as a functional handle for manipulation of inhibitors' physiochemical and DMPK properties.

**Aryl sulfonamides containing tetralin allylic amines as potent and selective bradykinin B1 receptor antagonists**

pp 4593–4597

Qingyian Liu\*, Wenyuan Qian, Aiwen Li, Kaustav Biswas, Jian Jeffrey Chen, Christopher Fotsch, Nianhe Han, Chester Yuan, Leyla Arik, Gloria Biddlecome, Eileen Johnson, Gondi Kumar, Dianna Lester-Zeiner, Gordon Y. Ng, Randall W. Hungate, Benny C. Askew



16

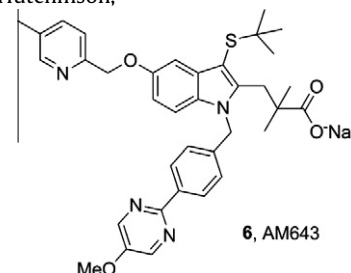
SAR studies led to the discovery of tetralin allylic amines as potent and selective bradykinin B1 receptor antagonists (hB1 IC<sub>50</sub> = 1.3 nM for compound **16**).

**5-Lipoxygenase-activating protein inhibitors. Part 3: 3-[3-*tert*-Butylsulfanyl-1-[4-(5-methoxy-pyrimidin-2-yl)-benzyl]-5-(5-methyl-pyridin-2-ylmethoxy)-1*H*-indol-2-yl]-2,2-dimethyl-propionic acid (AM643)—A potent FLAP inhibitor suitable for topical administration**

pp 4598–4601

Nicholas Stock\*, Christopher Baccei, Gretchen Bain, Charles Chapman, Lucia Correa, Janice Darlington, Christopher King, Catherine Lee, Daniel S. Lorrain, Pat Prodanovich, Angelina Santini, Kevin Schaab, Jilly F. Evans, John H. Hutchinson, Peppi Prasit

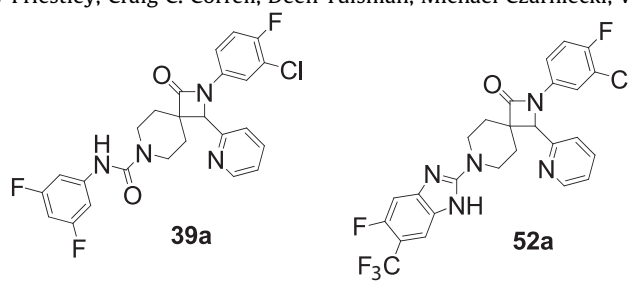
Dermal application of the potent FLAP inhibitor, **6** (AM643) using a prototypical vehicle in a murine ear arachidonic acid model showed significant reduction in the concentrations of leukotrienes in mouse skin with concomitant reduction in ear swelling.



**T-type calcium channel blockers: spiro-piperidine azetidines and azetidinones—optimization, design and synthesis**

pp 4602–4606

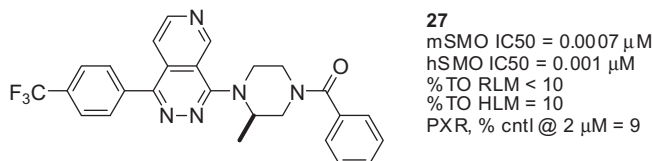
Elizabeth M. Smith\*, Steve Sorota\*, Hyunjin M. Kim, Brian A. McKittrick, Terry L. Nechuta, Chad Bennett, Chad Knutson, Duane A. Burnett, Jane Kieselgof, Zheng Tan, Diane Rindgen, Terry Bridal, Xiaoping Zhou, Yu-Ping Jia, Zoe Dong, Debbie Mullins, Xiaoping Zhang, Tony Priestley, Craig C. Correll, Deen Tulshian, Michael Czarniecki, William J. Greenlee



**Addressing PXR liabilities of phthalazine-based hedgehog/smoothened antagonists using novel pyridopyridazines**

pp 4607–4610

Jacob A. Kaizerman, Wade Aaron, Songzhu An, Richard Austin, Matt Brown, Angela Chong, Tom Huang, Randall Hungate, Ben Jiang, Michael G. Johnson, Gary Lee, Brian S. Lucas, Jessica Orf, Mingqing Rong, Maria M. Toteva, Dineli Wickramasinghe, Guifen Xu, Qiuping Ye, Wendy Zhong, Dustin L. McMinn\*

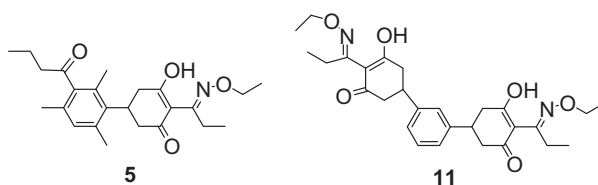


Pyridopyridazine antagonists of the hedgehog signaling pathway are described. Designed to optimize our previously described phthalazine smoothened antagonists, a representative compound, **27**, eliminates a PXR liability while retaining potency and in vitro metabolic stability. Moreover, the compound has improved efficacy in a hedgehog/smoothened signaling mouse pharmacodynamic model.

**Dimeric cyclohexane-1,3-dione oximes inhibit wheat acetyl-CoA carboxylase and show anti-malarial activity**

pp 4611–4613

Theola Louie, C. Dean Goodman, Georgina A. Holloway, Geoffrey I. McFadden, Vanessa Mollard, Keith G. Watson\*

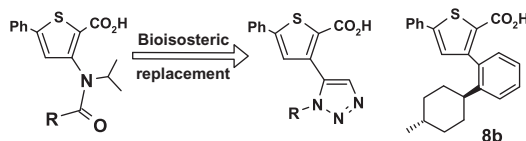


A variety of acetyl-CoA carboxylase inhibitors were tested against malaria with butoxydim **5** and the dimeric 1,3-cyclohexanedione **11** showing activity in the *Plasmodium berghei* mouse model.

**Cyclic amide bioisosterism: Strategic application to the design and synthesis of HCV NS5B polymerase inhibitors**

pp 4614–4619

Hanbiao Yang\*, Robert T. Hendricks\*, Nidhi Arora, Dov Nitzan, Calvin Yee, Matthew C. Lucas, Yanli Yang, Amy Fung, Sonal Rajyaguru, Seth F. Harris, Vincent J.P. Leveque, Julie Q. Hang, Sophie Le Pogam, Deborah Reuter, Gisele A. Tavares

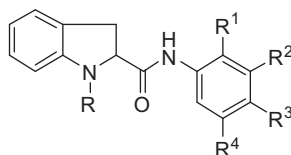


Conformational modeling has been successfully applied to the design of cyclic bioisosteres used to replace a conformationally rigid amide bond in a series of thiophene carboxylate inhibitors of HCV NS5B polymerase. Select compounds were equipotent with the original amide series. Single-point mutant binding studies, in combination with inhibition structure–activity relationships, suggest this new series interacts at the Thumb-II domain of NS5B. Inhibitor binding at the Thumb-II site was ultimately confirmed by solving a crystal structure of **8b** complexed with NS5B.

**Structure–activity relationship of indoline-2-carboxylic acid *N*-(substituted)phenylamide derivatives**

pp 4620–4623

Jae-Hwan Kwak, Yoseob Kim, Hyunjeong Park, Jae-Yong Jang, Keun Kuk Lee, Wonhui Yi, Jeong-Ah Kwak, Song-Gyu Park, Hwanmook Kim, Kiho Lee, Jong Soon Kang, Sang-Bae Han, Bang Yeon Hwang, Jin Tae Hong, Jae-Kyung Jung, Youngsoo Kim, Jungsook Cho, Heesoon Lee\*

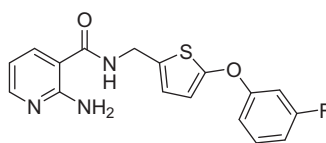


A series of indoline-2-carboxylic acid *N*-(substituted)phenylamide derivatives were synthesized to explore their inhibitory activities of NF- $\kappa$ B and they were also evaluated for cytotoxicity against various cancer cell lines for SAR.

**Synthesis and evaluation of novel antifungal agents-quinoline and pyridine amide derivatives**

pp 4624–4626

Kazutaka Nakamoto\*, Itaru Tsukada, Keigo Tanaka, Masayuki Matsukura, Toru Haneda, Satoshi Inoue, Norio Murai, Shinya Abe, Norihiro Ueda, Mamiko Miyazaki, Naoaki Watanabe, Makoto Asada, Kentaro Yoshimatsu, Katsura Hata



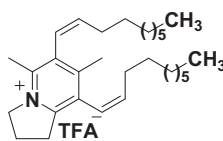
**10b** MIC = 0.05  $\mu$ g/ml  
(*C. albicans*)  
MIC=0.78  $\mu$ g/ml  
(*A. fumigatus*)

The synthesis of potent antifungal quinoline amide, azaindole amide and pyridine amides and its evaluation are reported.

**Anibamine, a natural product CCR5 antagonist, as a novel lead for the development of anti-prostate cancer agents**

pp 4627–4630

Xueping Zhang, Kendra M. Haney, Amanda C. Richardson, Eden Wilson, David A. Gewirtz, Joy L. Ware, Zandra E. Zehner, Yan Zhang\*



**Anibamine**

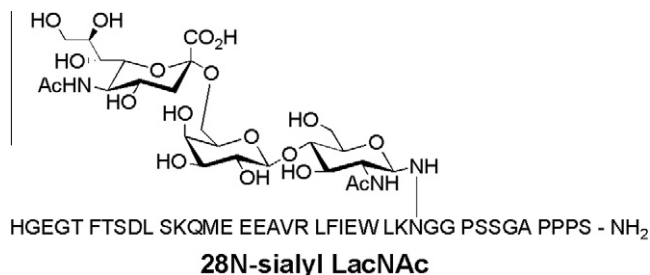
Anibamine produces significant inhibition of prostate cancer cell proliferation at micromolar to submicromolar concentrations and inhibits prostate tumor growth in mice.



### Identification of glycosylated exendin-4 analogue with prolonged blood glucose-lowering activity through glycosylation scanning substitution

pp 4631–4634

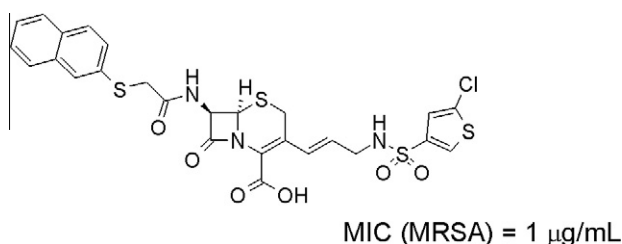
Taichi Ueda\*, Takaomi Ito, Kazuyoshi Tomita, Hiroko Togame, Masataka Fumoto, Kenji Asakura, Takeo Oshima, Shin-Ichiro Nishimura, Kohji Hanasaki



### Propenylamide and propenylsulfonamide cephalosporins as a novel class of anti-MRSA $\beta$ -lactams

pp 4635–4638

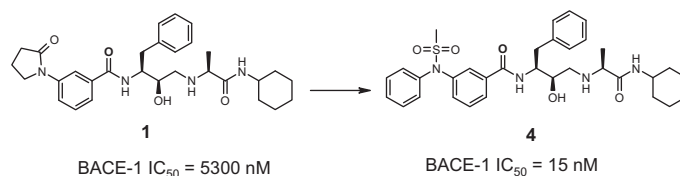
Jens Pohlmann\*, Natalya I. Vasilevich, Andrei I. Glushkov, Laurenz Kellenberger, Stuart Shapiro, Patrick Caspers, Malcolm G.P. Page, Franck Danel



### BACE-1 hydroxyethylamine inhibitors using novel edge-to-face interaction with Arg-296

pp 4639–4644

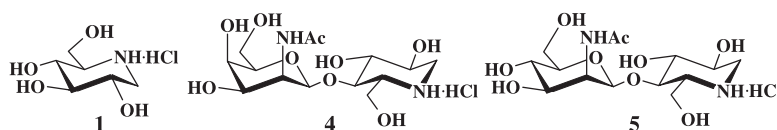
Brian Clarke, Leanne Cutler, Emmanuel Demont\*, Colin Dingwall, Rachel Dunsdon, Julie Hawkins, Colin Howes, Ishrut Hussain, Graham Maile, Rosalie Matico, Julie Mosley, Alan Naylor, Alistair O'Brien, Sally Redshaw, Paul Rowland, Virginie Soleil, Kathrine J. Smith, Sharon Sweitzer, Pam Theobald, David Vesey, Daryl S. Walter, Gareth Wayne



### Deoxynojirimycin and its hexosaminyll derivatives bind to natural killer cell receptors rNKR-P1A and hCD69

pp 4645–4648

Giorgio Catelani\*, Felicia D'Andrea, Alessio Griselli, Lorenzo Guazzelli, Petra Němcová, Karel Bezouška, Karel Křenek, Vladimír Křen\*

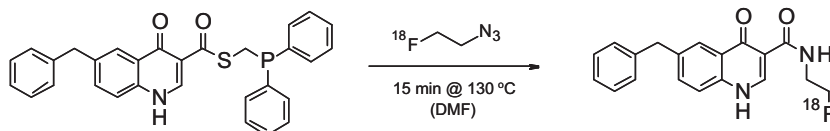


Binding affinity ( $-\log IC_{50}$ ) values toward NK cells activation receptors: for NKR-P1A receptor 5.0 (**1**), 5.5 (**4**), and 6.5 (**5**); for CD69 receptor 3.2 (**1**), 3.3 (**4**) and 4.5 (**5**)

### Use of 2-[<sup>18</sup>F]fluoroethylazide for the Staudinger ligation – Preparation and characterisation of GABA<sub>A</sub> receptor binding 4-quinolones

pp 4649–4652

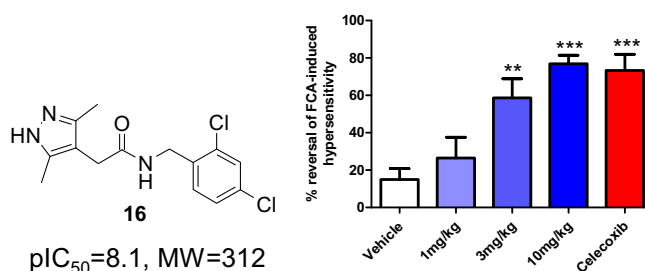
Alessandra Gaeta, John Woodcraft, Stuart Plant, Julian Goggi, Paul Jones, Mark Battle, William Trigg, Sajinder K. Luthra, Matthias Glaser\*



### Structure–activity relationships and in vivo activity of (1*H*-pyrazol-4-yl)acetamide antagonists of the P2X<sub>7</sub> receptor

pp 4653–4656

Paul J. Beswick, Andy Billinton, Laura J. Chambers, David K. Dean, Elena Fonfria, Robert J. Gleave, Stephen J. Medhurst, Anton D. Michel, Andrew P. Moses, Sadhana Patel, Shilina A. Roman, Sue Roomans, Stefan Senger, Alexander J. Stevens, Daryl S. Walter\*

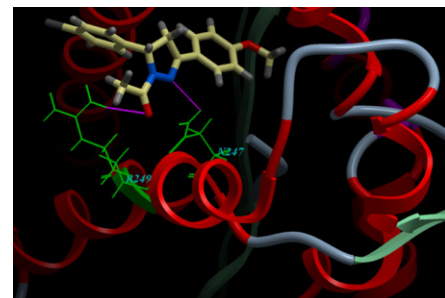


### Design, synthesis, and structure–activity relationships of pyrazole derivatives as potential FabH inhibitors

pp 4657–4660

Peng-Cheng Lv, Juan Sun, Yin Luo, Ying Yang, Hai-Liang Zhu\*

Fifty-six 1-acetyl-3,5-diphenyl-4,5-dihydro-(1*H*)-pyrazole derivatives were synthesized and developed as potent inhibitors of FabH. *Escherichia coli* FabH inhibitory assay was undertaken and the results suggested that compounds **12** and **13** were potent *E. coli* FabH inhibitors.

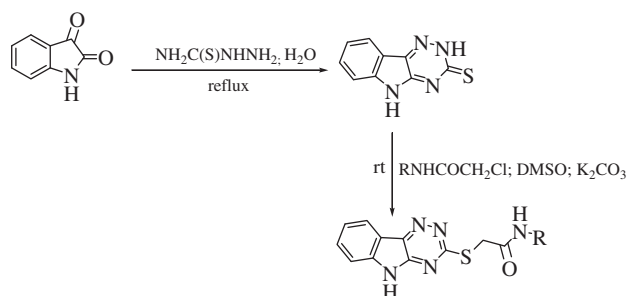


### Synthesis, antidepressant evaluation and QSAR studies of novel 2-(5*H*-[1,2,4]triazino[5,6-*b*]indol-3-ylthio)-*N*-(substituted phenyl)acetamides

pp 4661–4664

Suhas M. Shelke, Sharad H. Bhosale\*

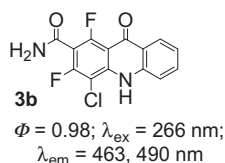
Eighteen derivatives of 2-(5*H*-[1,2,4]triazino[5,6-*b*]indol-3-ylthio)-*N*-substituted acetamides were synthesized, evaluated for antidepressant activity by tail suspension test and results obtained were subjected to QSAR analysis.



### Synthesis of polyhalo acridones as pH-sensitive fluorescence probes

pp 4665–4669

Chao Huang, Sheng-Jiao Yan, Yan-Mei Li, Rong Huang, Jun Lin\*



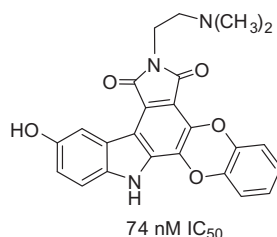
Polyhalo isophthalonitriles were reacted with substituted anilines and subsequently cyclocondensed in the presence of sulfuric acid to give polyhalo acridones. These polyhalo acridones were proven to be useful as pH-sensitive fluorescent probes for a wide range of acidic and basic conditions.



### Synthesis and biological evaluation of novel benzodioxinocarbazoles (BDCZs) as potential anticancer agents

pp 4670–4674

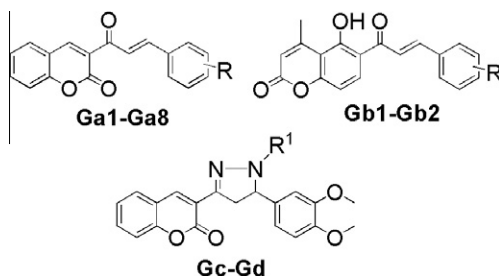
Nathalie Ayerbe, Sylvain Routier\*, Isabelle Gillaizeau, Carmen Maieranu, Daniel-Henry Caignard, Alain Pierré, Stéphane Léonce, Gérard Coudert\*



### Synthesis of novel $\alpha$ -pyranochalcones and pyrazoline derivatives as *Plasmodium falciparum* growth inhibitors

pp 4675–4678

Gajanan Wanare\*, Rahul Aher, Neha Kawathekar, Ravi Ranjan, Naveen Kumar Kaushik, Dinkar Sahal



The synthesis and antimalarial activity of the potential  $\alpha$ -pyranochalcones and novel active chromeno-pyrazolines is reported.

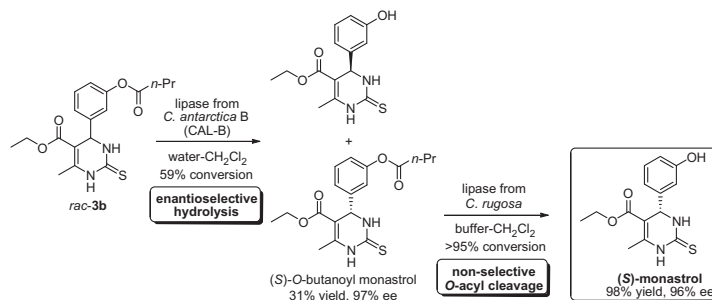


### Enantioselective biocatalytic synthesis of (S)-monastrol

pp 4679–4682

Maria Alfaro Blasco, Silvia Thumann, Jürgen Wittmann, Athanassios Giannis, Harald Gröger\*

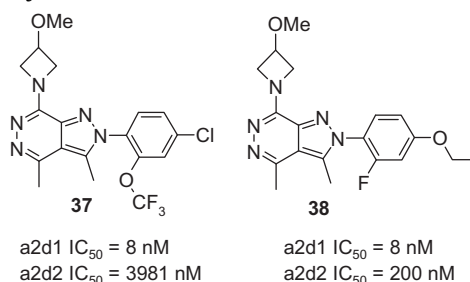
The first enantioselective biocatalytic synthesis of (S)-monastrol has been developed via an unexpected and unusual enzymatic pathway as suitable route. Whereas attempts for a direct hydrolysis of racemic monastrol were not successful, formation of racemic O-butanoyl monastrol and subsequent enantioselective hydrolysis furnished O-butanoyl (S)-monastrol with 97% ee. Cleavage of the O-butanoyl moiety then gave the desired (S)-monastrol with 96% ee.



**Pyrazolopyridazine alpha-2-delta-1 ligands for the treatment of neuropathic pain**

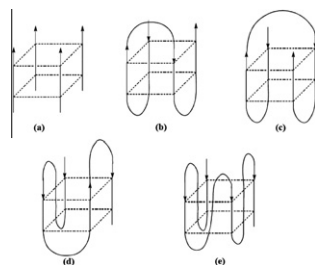
pp 4683–4688

James W. Myatt\*, Mark P. Healy, Gianpaolo S. Bravi, Andrew Billinton, Christopher N. Johnson, Kim L. Matthews, Karamjit S. Jandu, Wenjing Meng, Anne Hersey, David G. Livermore, Clement B. Douault, Jason Witherington, Rino A. Bit, James E. Rowedder, Jason D. Brown, Nick M. Clayton

**Conformational organizations of G-quadruplexes composed of d(G<sub>4</sub>T<sub>n</sub>)<sub>3</sub>G<sub>4</sub>**

pp 4689–4692

Wan Chi Wong, Jinyi Zhuang, Selina Ling Ling Ng, Lilian Li Lin New, Shuhui Hiew, Juanjuan Guo, Zhaoqi Yang\*, Tianhu Li

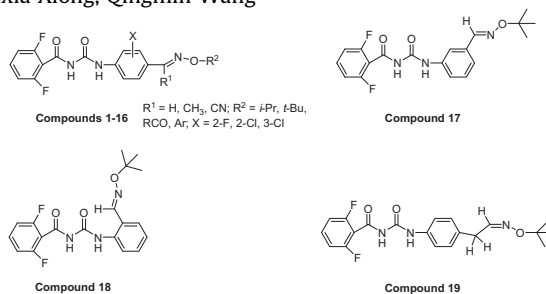


In this study, a series of oligonucleotides with four repeat guanines sequence d(G<sub>4</sub>T<sub>n</sub>)<sub>3</sub>G<sub>4</sub> (*n* = 1–6) were designed and the length of loop affect the polymorphism of G-quadruplex was investigated.

**Synthesis, larvicidal activity, and SAR studies of new benzoylphenylureas containing oxime ether and oxime ester group**

pp 4693–4699

Ranfeng Sun, Yongqiang Li, Maoyun Lü, Lixia Xiong, Qingmin Wang\*

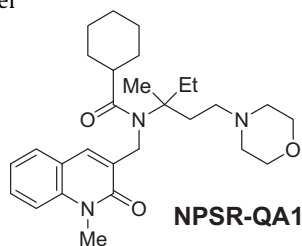


A series of new structural benzoylphenylureas were designed and synthesized and their structure–activity relationships were studied.

**Synthesis and evaluation of a new series of Neuropeptide S receptor antagonists**

pp 4700–4703

Jeffrey Y. Melamed\*, Amy E. Zartman, Nathan R. Kett, Anthony L. Gotter, Victor N. Uebele, Duane R. Reiss, Cindra L. Condra, Christine Fandozzi, Laura S. Lubbers, Blake A. Rowe, Georgia B. McGaughey, Martin Henault, Rino Stocco, John J. Renger, George D. Hartman, Mark T. Bilodeau, B. Wesley Trotter

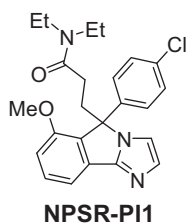


Medicinal chemistry efforts have identified a quinolinone class of potent NPSR antagonists that readily cross the blood–brain barrier. Optimization efforts resulted in the identification of a potent NPSR antagonist which dose-dependently and specifically inhibited [<sup>125</sup>I]-NPS binding in the CNS when administered to rats.

**Tricyclic imidazole antagonists of the Neuropeptide S Receptor**

pp 4704–4708

B. Wesley Trotter\*, Kausik K. Nanda, Peter J. Manley, Victor N. Uebele, Cindra L. Condra, Anthony L. Gotter, Karsten Menzel, Martin Henault, Rino Stocco, John J. Renger, George D. Hartman, Mark T. Bilodeau

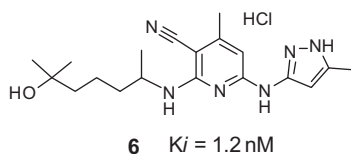


A new structural class of potent antagonists of the Neuropeptide S Receptor (NPSR) is reported. **NPSR-PI1** demonstrates potent in vitro NPSR antagonism and central exposure in vivo.

**3-Cyano-6-(5-methyl-3-pyrazoloamino)pyridines: Selective Aurora A kinase inhibitors**

pp 4709–4711

Ryoichi Ando, Hiroshi Ikegami, Makoto Sakiyama, Shinsuke Ooike, Masayuki Hayashi, Yasuhiro Fujino, Daisuke Abe, Hideo Nakamura, Tadashi Mishina, Harutoshi Kato, Yumiko Iwase, Hideo Tomozane, Masahiko Morioka\*

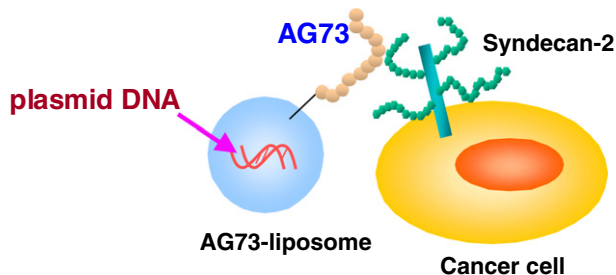


Compound **6** exhibited a potent Aurora A kinase inhibitory activity ( $K_i = 1.2 \text{ nM}$ ) and was effective in antitumor mice model at a dose of 30 mg/kg po qd.

**Cancer cell specific gene delivery by laminin-derived peptide AG73-labeled liposomes**

pp 4712–4714

Hiroshi Iijima, Yoichi Negishi, Daiki Omata, Motoyoshi Nomizu, Yukihiko Aramaki\*

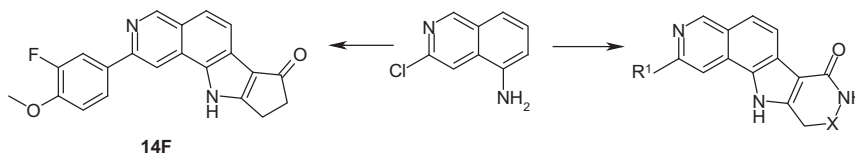


Liposome labeled with AG73, which is a laminin-derived peptide and a ligand for syndecan-2, is found to be a superior non-viral vector for the gene delivery to syndecan-2 overexpressing cancer cells.

**In vivo and in vitro SAR of tetracyclic MAPKAP-K2 (MK2) inhibitors. Part I**

pp 4715–4718

Laszlo Revesz\*, Achim Schlapbach, Reiner Aichholz, Roland Feifel, Stuart Hawtin, Richard Heng, Peter Hiestand, Wolfgang Jahnke, Guido Koch, Markus Kroemer, Henrik Möbitz, Clemens Scheufler, Juraj Velcicky, Christine Huppertz

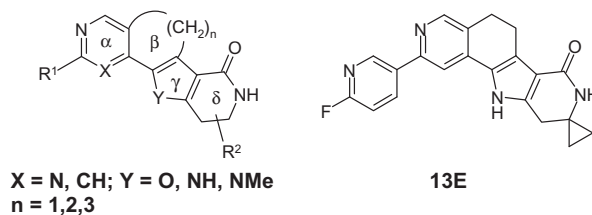


The synthesis and SAR of tetracyclic MK2 inhibitors is reported. Tetracyclic lactams showed good selectivity profiles and potently inhibited TNF $\alpha$  release from hPBMCs. Tetracyclic ketone **14F** was orally bioavailable and inhibited the LPS induced release of TNF $\alpha$  in mice.



**In vivo and in vitro SAR of tetracyclic MAPKAP-K2 (MK2) inhibitors. Part II****pp 4719–4723**

Laszlo Revesz\*, Achim Schlapbach, Reiner Aichholz, Janet Dawson, Roland Feifel, Stuart Hawtin, Amanda Littlewood-Evans, Guido Koch, Markus Kroemer, Henrik Möbitz, Clemens Scheufler, Juraj Velcicky, Christine Huppertz



The synthesis and SAR of tetracyclic MK2 inhibitors is reported. Spirocyclopropyl- and spiroazetidine groups attached to the  $\delta$ -ring produced potent MK2-inhibitors with oral activity in the acute LPS-induced TNF $\alpha$  release model in mice. Compound **13E** showed significant reduction of swelling and histological scores in two chronic arthritis models upon oral administration.

\*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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