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# Bioorganic & Medicinal Chemistry Letters

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## Bioorganic & Medicinal Chemistry Letters Volume 20, Issue 17, 2010

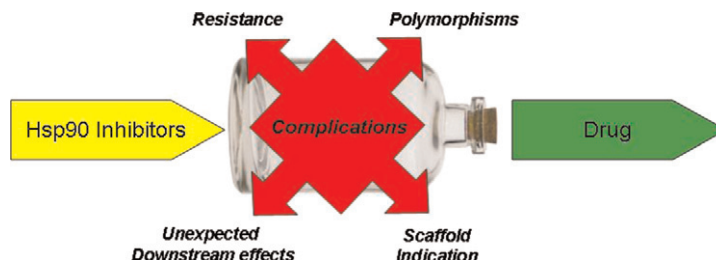
### Contents

#### BMCL DIGEST

##### Hsp90 inhibition: Elimination of shock and stress

pp 4983–4987

Adam S. Duerfeldt, Brian S. J. Blagg\*

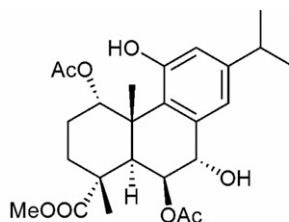


#### REGULAR ARTICLES

##### Antimicrobial phenolic abietane diterpene from *Lycopus europaeus* L. (Lamiaceae)

pp 4988–4991

Niko Radulović\*, Marija Denić, Zorica Stojanović-Radić



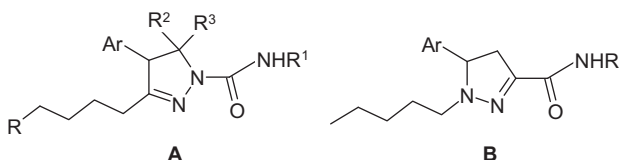
*Staphylococcus aureus* (MIC=22 µg/mL)  
*Aspergillus fumigatus* (MIC=89 µg/mL)



##### Two distinct classes of novel pyrazolinecarboxamides as potent cannabinoid CB<sub>1</sub> receptor agonists

pp 4992–4998

Jos H. M. Lange\*, Amos Attali, Martina A. W. van der Neut, Henri C. Wals, Arie Mulder, Hicham Zilaout, Ate Duursma, Hans H. M. van Aken, Bernard J. van Vliet

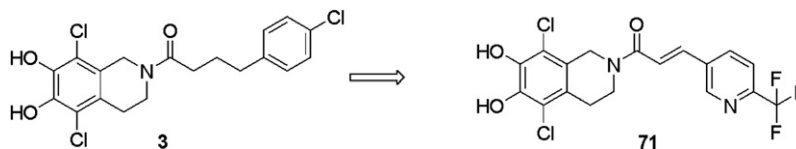


The synthesis and SAR of two novel CB<sub>1</sub> receptor agonist classes A and B are described.

### Synthesis of novel tetrahydroisoquinoline bronchodilators

pp 4999–5003

Maria F. Dalence-Guzmán, Jörgen Toftered, Viveca Thornqvist Oltner, David Wensbo, Martin H. Johansson\*

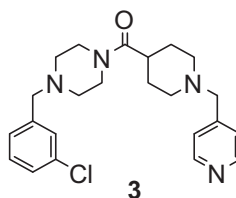


The discovery and synthesis of bronchodilator **71** using a functional tissue assay is described.

### The synthesis and structure–activity relationship of 4-benzimidazolyl-piperidinylcarbonyl-piperidine analogs as histamine H<sub>3</sub> antagonists

pp 5004–5008

Pauline C. Ting\*, Joe F. Lee, Margaret M. Albanese, Jie Wu, Robert Aslanian, Leonard Favreau, Cymbelene Nardo, Walter A. Korfmacher, Robert E. West, Shirley M. Williams, John C. Anthes, Maria A. Rivelli, Michel R. Corboz, John A. Hey

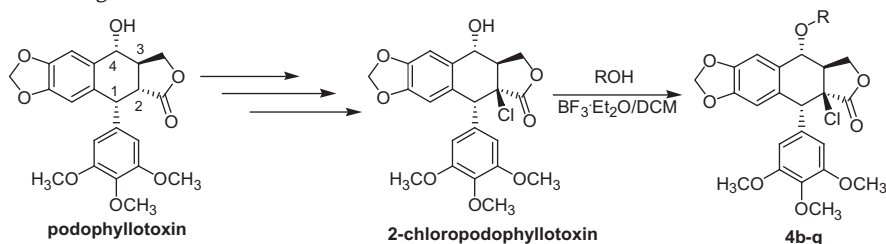


A structure–activity relationship study of the lead piperazinylcarbonylpiperidine compound **3** has resulted in the identification of 4-benzimidazolyl-piperidinylcarbonyl-piperidine **6h** as a histamine-3 (H<sub>3</sub>) receptor antagonist. Additional optimization of **6h** led to the identification of compounds **11i–k** with K<sub>i</sub> < 0.5 nM and good in vivo activity.

### Natural products-based insecticidal agents 7. Semisynthesis and insecticidal activity of novel 4 $\alpha$ -alkyloxy-2-chloropodophyllotoxin derivatives against *Mythimna separata* Walker in vivo

pp 5009–5012

Hui Xu\*, Xiao Xiao, Qing-tian Wang



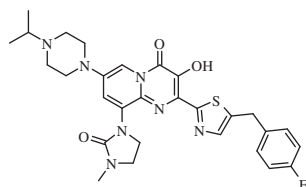
Some derivatives exhibited more promising and pronounced insecticidal activity than toosendanin, a commercial insecticide derived from *Melia azedarach*. It was clearly demonstrated that the length of straight-chain or branched-chain alkyloxy, and heteroatom-containing cycloalkyloxy at the C-4 position of 2-chloropodophyllotoxin were very important for the insecticidal activity.



### Discovery of potent HIV integrase inhibitors active against raltegravir resistant viruses

pp 5013–5018

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

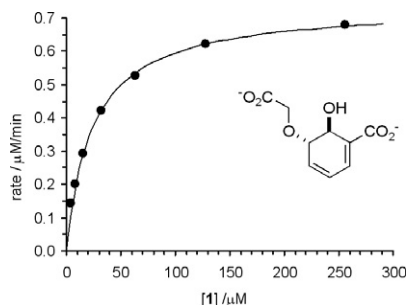


33 EC <sub>50</sub> HIV (WT-integrase)	6.8nM
EC <sub>50</sub> HIV (WT -integrase +50% NHS)	8.5nM
EC <sub>50</sub> HIV (QHGS -integrase)	21nM
EC <sub>50</sub> HIV (NHEQ -integrase)	8.9nM

**A stable analog of isochorismate for the study of MenD and other isochorismate-utilizing enzymes**

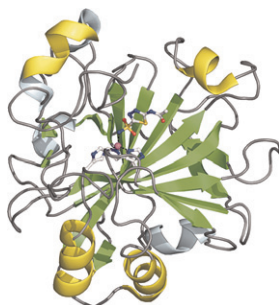
pp 5019–5022

Maohai Fang, Blaine M. Langman, David R. J. Palmer\*

**Crystal structure of the C183S/C217S mutant of human CA VII in complex with acetazolamide**

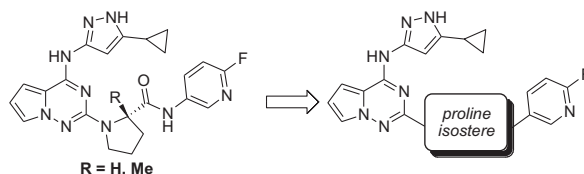
pp 5023–5026

Anna Di Fiore, Emanuela Truppo, Claudiu T. Supuran, Vincenzo Alterio, Nina Dathan, Fatemeh Botorabi, Seppo Parkkila, Simona Maria Monti\*, Giuseppina De Simone\*

**Proline isosteres in a series of 2,4-disubstituted pyrrolo[1,2-f][1,2,4]triazine inhibitors of IGF-1R kinase and IR kinase**

pp 5027–5030

Anthony J. Sampognaro\*, Mark D. Wittman, Joan M. Carboni, Chiehying Chang, Ann F. Greer, Warren W. Hurlburt, John S. Sack, Dolatrai M. Vyas

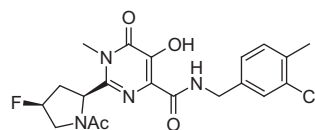


Analogues utilizing proline isosteres in IGF-1R/IR inhibitors are disclosed. X-ray co-crystallography of selected analogues reveals information key to target potency.

**Development of 2-pyrrolidinyl-N-methyl pyrimidones as potent and orally bioavailable HIV integrase inhibitors**

pp 5031–5034

Marco Ferrara\*, Fabrizio Fiore, Vincenzo Summa, Cristina Gardelli



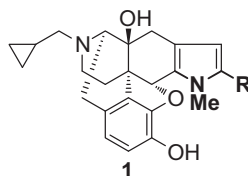
**13** Spread CIC<sub>95</sub> (50% NHS) = 46 nM

The identification of the promising agent against HIV-1 **13** is reported.

**Synthesis of pyrrolomorphinan derivatives as  $\kappa$  opioid agonists**

pp 5035–5038

Hideaki Fujii, Yoshihiro Ida, Shinichi Hanamura, Yumiko Osa, Toru Nemoto, Mayumi Nakajima, Ko Hasebe, Kaoru Nakao, Hidenori Mochizuki, Hiroshi Nagase\*

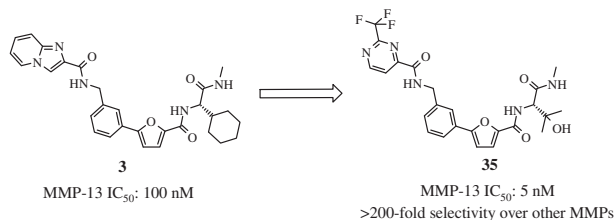


Pyrrolomorphinans **1** were synthesized to examine whether the pyrrole ring might be an accessory site in the  $\kappa$  receptor selective antagonist, nor-binaltorphimine.

**SAR studies of non-zinc-chelating MMP-13 inhibitors: Improving selectivity and metabolic stability**

pp 5039–5043

Donghong Amy Gao\*, Zhaoming Xiong\*, Alexander Heim-Riether, Laura Amodeo, E. Michael August, Xianhua Cao, Leonard Ciccarelli, Brandon K. Collins, Kyle Harrington, Kathleen Haverty, Melissa Hill-Drzewi, Xiang Li, Shuang Liang, Steluta Mariana Margarit, Neil Moss, Nelamangala Nagaraja, John Proudfoot, Rene Roman, Sabine Schlyer, Lana Smith Keenan, Steven Taylor, Bernd Wellenzohn, Dieter Wiedenmayer, Jun Li, Neil A. Farrow

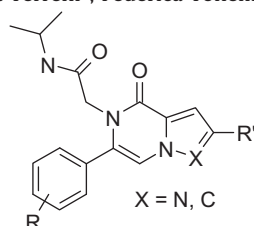


SAR studies to improve the selectivity and metabolic stability of a class of recently discovered non-Zn-chelating MMP-13 inhibitors are reported.

**Pyrrolo[1,2-*a*]pyrazine and pyrazolo[1,5-*a*]pyrazine: Novel, potent, and selective series of Vasopressin<sub>1b</sub> receptor antagonists**

pp 5044–5049

Roberto Arban, Federica Bianchi, Alberto Buson, Susanna Cremonesi, Romano Di Fabio, Gabriella Gentile\*, Fabrizio Micheli, Alessandra Pasquarello, Alfonso Pozzan, Luca Tarsi, Silvia Terreni\*, Federica Tonelli

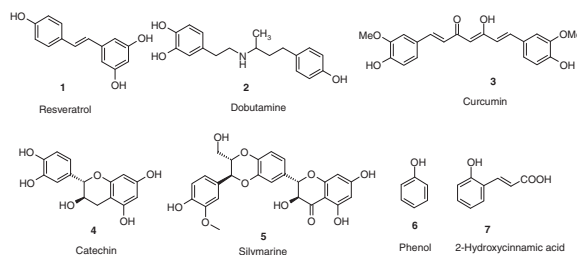


Novel series of pyrrole-pyrazinone and pyrazole-pyrazinone have been identified as potent and selective Vasopressin<sub>1b</sub> receptor antagonists. Exploration of the substitution pattern around the core of these templates allowed generation of compounds with high inhibitory potency at Vasopressin<sub>1b</sub> receptor including examples that showed good selectivity with respect to Vasopressin<sub>1a</sub>, Vasopressin<sub>2</sub>, and Oxytocin receptors subtype.

**Carbonic anhydrase inhibitors. Antioxidant polyphenols effectively inhibit mammalian isoforms I–XV**

pp 5050–5053

Alessio Innocenti, İlhami Gülçin, Andrea Scozzafava, Claudiu T. Supuran\*

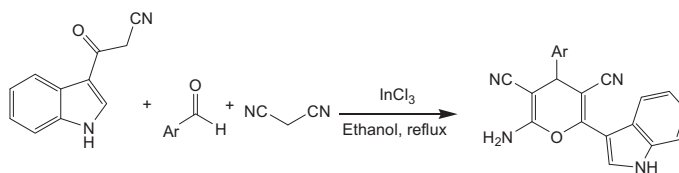


K<sub>S</sub> of 380 nM–12.02  $\mu$ M against CA I–CA XV.

**InCl<sub>3</sub> mediated one-pot multicomponent synthesis, anti-microbial, antioxidant and anticancer evaluation of 3-pyranyl indole derivatives**

pp 5054–5061

Neelakandan Vidhya Lakshmi, Prakasam Thirumurugan, K. M. Noorulla, Paramasivan. T. Perumal\*

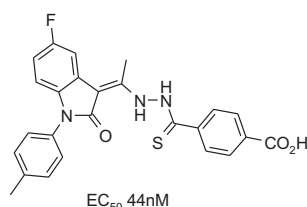


A simple and convenient method for the one-pot three-component synthesis of 3-pyranyl indoles has been accomplished by tandem Knoevenagel–Michael reaction of 3-cyanoacetyl indole, various aromatic aldehydes and malononitrile catalyzed by InCl<sub>3</sub> in ethanol under reflux conditions. The newly synthesized 3-pyranyl indoles were evaluated for anti-microbial, antioxidant, and anticancer activities. Some of the compounds are showed good anticancer activity against MCF-7 breast cancer cell lines on comparison with of standards drugs.

**Synthesis and biological evaluation of oxindolin-3-ylidene ethyl benzothiohydrazides as non-peptide TPO mimics**

pp 5062–5064

Peng Cho Tang\*, He Jun Lu, Yi Qian Chen, Sheng Lan Wang, Hao Zheng, Li Wang

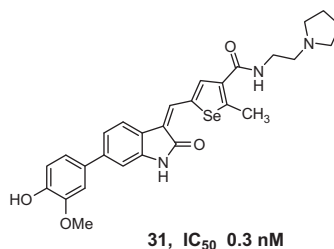


Oxindolin-3-ylidene ethyl benzothiohydrazides as small molecule c-mpl agonists is reported.

**Synthesis of selenophene derivatives as novel CHK1 inhibitors**

pp 5065–5068

Pao-Chiung Hong\*, Li-Jung Chen, Tzu-Yun Lai, Huei-Yu Yang, Shih-Jan Chiang, Yann-Yu Lu, Ping-Kuei Tsai, Hung-Yi Hsu, Win-Yin Wei, Chu-Bin Liao

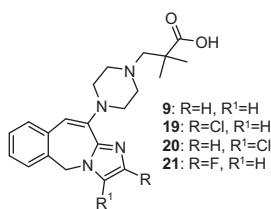


A series of selenophene derivatives (i.e., **31**) are reported as potent inhibitors of CHK1 kinase.

**Novel imidazobenzazepine derivatives as dual H<sub>1</sub>/5-HT<sub>2A</sub> antagonists for the treatment of sleep disorders**

pp 5069–5073

Massimo Gianotti\*, Corrado Corti, Sonia Delle Fratte, Romano Di Fabio, Colin P. Leslie, Francesca Pavone, Laura Piccoli, Luigi Stasi, Mark J. Wigglesworth



Application of a zwitterionic approach successfully delivered a class of high quality leads, 3-[4-(3-R<sup>1</sup>-2-R-5H-imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]-2,2-dimethylpropanoic acids (e.g., **9**, **19**, **20**, and **21**), characterized by potent and balanced H<sub>1</sub>/5-HT<sub>2A</sub> receptor antagonist activities and good developability profiles.

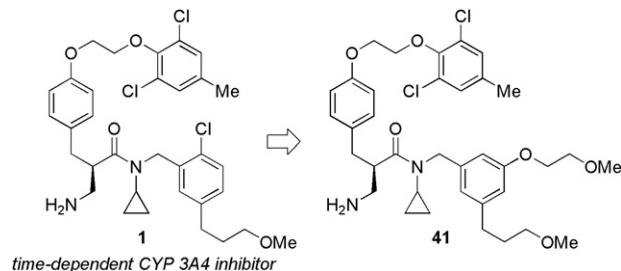


### Addressing time-dependent CYP 3A4 inhibition observed in a novel series of substituted amino propanamide renin inhibitors, a case study

pp 5074–5079

Austin Chen\*, Daniel Dubé, Laurence Dubé, Sébastien Gagné, Michel Gallant, Mireille Gaudreault, Erich Grimm, Robert Houle, Patrick Lacombe, Sébastien Laliberté, Suzanna Liu, Dwight MacDonald, Bruce Mackay, David Martin, Dan McKay, David Powell, Jean-François Lévesque\*

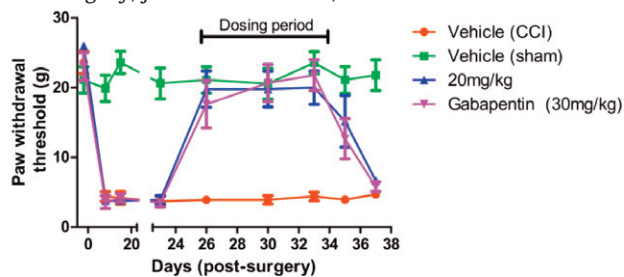
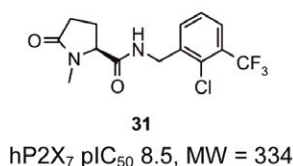
The identification of a possible culprit responsible for compound (**1**)'s time-dependent CYP 3A4 inhibition as well as suitable solution are described therein.



### Discovery and structure–activity relationships of a series of pyroglutamic acid amide antagonists of the P2X<sub>7</sub> receptor

pp 5080–5084

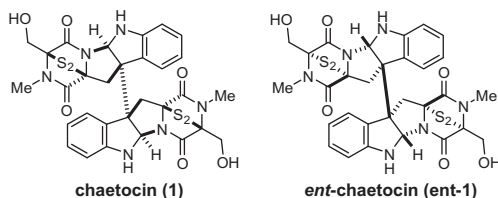
Muna H. Abdi, Paul J. Beswick, Andy Billinton, Laura J. Chambers, Andrew Charlton, Sue D. Collins, Katharine L. Collis, David K. Dean, Elena Fonfria, Robert J. Gleave, Clarisse L. Lejeune, David G. Livermore, Stephen J. Medhurst, Anton D. Michel, Andrew P. Moses, Lee Page, Sadhana Patel, Shilina A. Roman, Stefan Senger, Brian Slingsby, Jon G. A. Steadman, Alexander J. Stevens, Daryl S. Walter\*



### Unnatural enantiomer of chaetocin shows strong apoptosis-inducing activity through caspase-8/caspase-3 activation

pp 5085–5088

Yuou Teng, Katsuya Iuchi, Eriko Iwasa, Shinya Fujishiro, Yoshitaka Hamashima, Kosuke Dodo, Mikiko Sodeoka\*

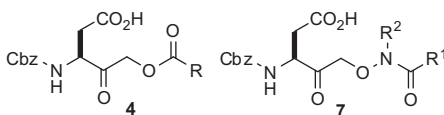


The unnatural enantiomer of chaetocin (*ent*-chaetocin) was more potent than chaetocin, and was found to induce apoptosis through the caspase-8/caspase-3 activation pathway.

### Inhibition of interleukin-1 $\beta$ converting enzyme (ICE or caspase 1) by aspartyl acyloxyalkyl ketones and aspartyl amidooxyalkyl ketones

pp 5089–5094

Paul Galatsis\*, Bradley Caprathe, Dennis Downing, John Gilmore, William Harter, Sheryl Hays, Catherine Kostlan, Kristin Linn, Elizabeth Lunney, Kim Para, Anthony Thomas, Joseph Warmus, Hamish Allen, Kenneth Brady, Robert Talanian, Nigel Walker



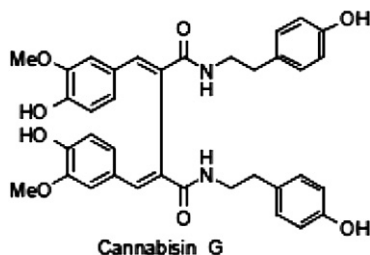
Acyloxyalkyl, **4**, and amidooxyalkyl, **7**, ketones based on aspartic acid have been prepared. These two series provide an improved understanding of the binding requirements for the hydrophobic prime side of ICE.



**Concise synthesis of Cannabisin G**

pp 5095–5098

Dawei Li, Wenling Li, Qian Wang, Zhaoqi Yang\*, Zijie Hou\*

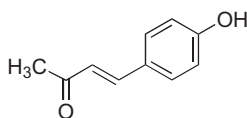


Cannabisin G (**1**), a naturally occurring lignanamide, was synthesized in 45% overall yield starting from 3-*tert*-butyl ethyl ferulate (**6**). An oxidative coupling by potassium ferricyanide in an alkaline media serves as the key step to construct the biphenylbutadiene skeleton of **1** with high regioselectivity.

**Structure-based engineering of benzalacetone synthase**

pp 5099–5103

Yoshihiko Shimokawa, Hiroyuki Morita, Ikuro Abe\*

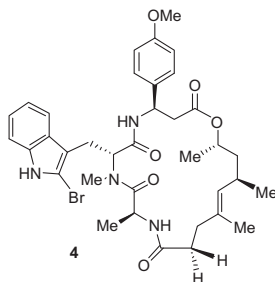


Structure-based engineering of benzalacetone synthase from *Rheum palmatum* is reported.

**Synthesis and biological evaluation of new jasplakinolide (jaspamide) analogs**

pp 5104–5107

Arun K. Ghosh\*, Zachary L. Dawson, Deuk Kyu Moon, Ruoli Bai, Ernest Hamel

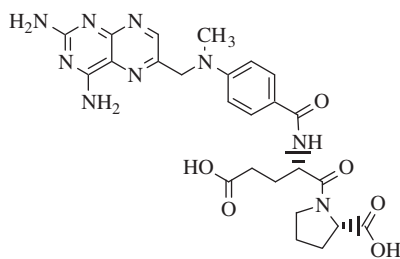


Eight new jasplakinolide derivatives were synthesized and evaluated for antitumor activity by measuring their ability to interfere with the actin cytoskeleton. Simplified derivative **4** is essentially as active as natural jasplakinolide.

**Development of methotrexate proline prodrug to overcome resistance by MDA-MB-231 cells**

pp 5108–5112

Zhiqian Wu\*, Anandkumar Shah, Namrata Patel, Xudong Yuan

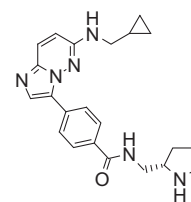


Pro-MTX

### Discovery of imidazo[1,2-*b*]pyridazine derivatives as IKK $\beta$ inhibitors. Part 1: Hit-to-lead study and structure–activity relationship

Hiroki Shimizu\*, Shinji Tanaka, Tadashi Toki, Isao Yasumatsu, Toshihiko Akimoto, Kaoru Morishita, Tomonori Yamasaki, Takanori Yasukochi, Shin Iimura

We developed the HTS-hit imidazo[1,2-*b*]pyridazine derivatives and acquired some potent compounds such as **8e**. These compounds showed potent IKK $\beta$  inhibitory activity and high kinase selectivity. The structure–activity relationship was revealed and the interaction model of imidazo[1,2-*b*]pyridazine compound with IKK $\beta$  was constructed.



compound **8e**

IKK $\beta$ : IC<sub>50</sub> 0.055  $\mu$ M

IKK $\alpha$ : IC<sub>50</sub> 40  $\mu$ M

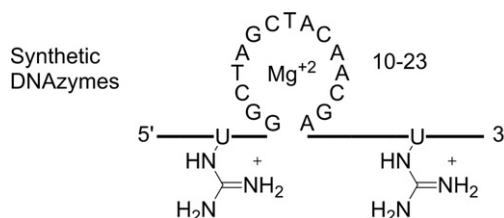
CDK2, GSK3 $\beta$ , PDK1,

JNK3, p38  $\alpha$ : IC<sub>50</sub> >100  $\mu$ M

pp 5113–5118

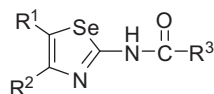
### Introduction of guanidinium-modified deoxyuridine into the substrate binding regions of DNAzyme 10–23 to enhance target affinity: Implications for DNAzyme design

Curtis H. Lam, David M. Perrin\*



### Synthesis of a series of novel 2,4,5-trisubstituted selenazole compounds as potential PLTP inhibitors

Cui Ling, Zhibing Zheng, Xian Cheng Jiang, Wu Zhong\*, Song Li



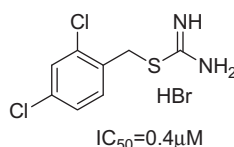
pp 5123–5125

The synthesis of 2,4,5-trisubstituted selenazoles and evaluation for their PLTP inhibitory activities are reported.



### S-Benzylisothiurea derivatives as small-molecule inhibitors of indoleamine-2,3-dioxygenase

Kenji Matsuno, Kazushige Takai, Yoshinobu Isaka, Yuka Unno, Masayuki Sato, Osamu Takikawa, Akira Asai\*



pp 5126–5129

Synthesis and structure–activity relationship of S-benzylisothiurea analogues as small-molecule inhibitors of indoleamine-2,3-dioxygenase are described.

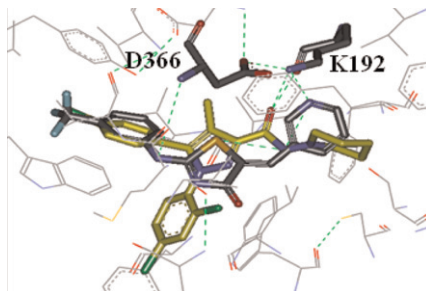




**Discovery of cannabinoid-1 receptor antagonists by virtual screening**

pp 5130–5132

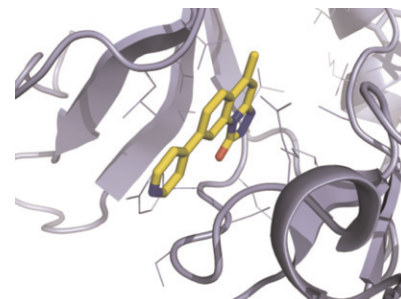
Gil Nam Lee, Kwang Rok Kim, Sung-Hoon Ahn, Myung Ae Bae, Nam Sook Kang\*

**Discovery of a novel class of triazolones as Checkpoint Kinase inhibitors—Hit to lead exploration**

pp 5133–5138

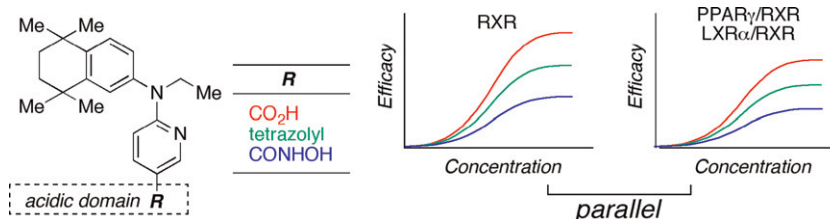
Vibha Oza\*, Susan Ashwell, Patrick Brassil, Jason Breed, Chun Deng, Jay Ezhuthachan, Heather Haye, Candice Horn, James Janetka, Paul Lyne, Nicholas Newcombe, Ludo Otterbien, Martin Pass, Jon Read, Sian Roswell, Mei Su, Dorin Toader, Dingwei Yu, Yan Yu, Anna Valentine, Peter Webb, Ann White, Sonya Zabudoff, Xiaolan Zheng

Checkpoint Kinase-1 (Chk1, CHK1, CHEK1) is a Ser/Thr protein kinase that mediates cellular responses to DNA-damage. A novel class of Chk1 inhibitors, triazoloquinolones/triazolones (TZ's) was identified by high throughput screening. The optimization of these hits to provide a lead series is described.

**Modification at the acidic domain of RXR agonists has little effect on permissive RXR-heterodimer activation**

pp 5139–5142

Shuji Fujii, Fuminori Ohsawa, Shoya Yamada, Ryosuke Shinozaki, Ryosuke Fukai, Makoto Makishima, Shuichi Enomoto, Akihiro Tai, Hiroki Kakuta\*

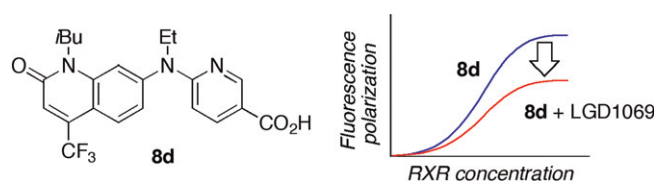


Modification at the acidic domain of RXR agonists has little or no effect on permissive RXR-heterodimer activation. This information may be useful for creating RXR agonists with improved absorption, distribution, metabolism, and excretion (ADME) characteristics.

**Fluorescent retinoid X receptor ligands for fluorescence polarization assay**

pp 5143–5146

Shoya Yamada, Fuminori Ohsawa, Shuji Fujii, Ryosuke Shinozaki, Makoto Makishima, Hirotaka Naitou, Shuichi Enomoto, Akihiro Tai, Hiroki Kakuta\*



Fluorescent retinoid X receptor (RXR) agonist 6-[ethyl-(1-isobutyl-2-oxo-4-trifluoromethyl-1,2-dihydroquinolin-7-yl)amino]-nicotinic acid (**8d**) was synthesized by modification of the lipophilic domain of general RXR agonists. Compound **8d** showed fluorescence polarization (FP) in the presence of RXR and the FP was reduced in the presence of an RXR agonist, LGD1069.

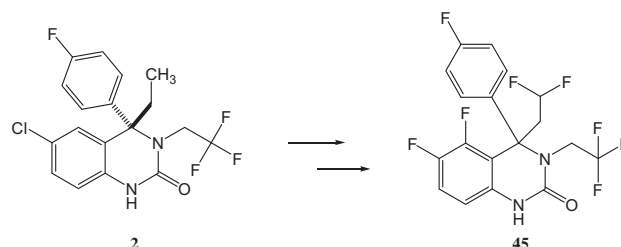


**Discovery and expanded SAR of 4,4-disubstituted quinazolin-2-ones as potent T-type calcium channel antagonists**

pp 5147–5152

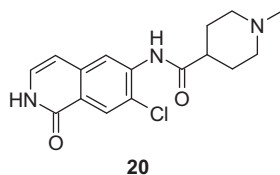
Kelly-Ann S. Schlegel\*, Zhi-Qiang Yang, Thomas S. Reger, Youheng Shu, Rowena Cube, Kenneth E. Rittle, Phung Bondiskey, Mark G. Bock, George D. Hartman, Cuyue Tang, Jeanine Ballard, Yuhsin Kuo, Thomayant Prueksaritanont, Cindy E. Nuss, Scott M. Doran, Steven V. Fox, Susan L. Garson, Richard L. Kraus, Yuxing Li, Victor N. Uebele, John J. Renger, James C. Barrow

The discovery and synthesis of 4,4-disubstituted quinazolinones as T-type calcium channel antagonists is reported. Based on lead compounds **2** and **3**, a focused SAR campaign driven by the optimization of potency, metabolic stability, and pharmacokinetic profile identified **45** as a potent T-type  $\text{Ca}^{2+}$  channel antagonist with minimized PXR activation. In vivo, **45** suppressed seizure frequency in a rat model of absence epilepsy and showed significant alterations of sleep architecture after oral dosing to rats as measured by EEG.

**Substituted 2H-isoquinolin-1-ones as potent Rho-kinase inhibitors: Part 2, optimization for blood pressure reduction in spontaneously hypertensive rats**

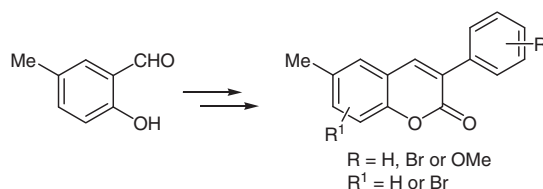
pp 5153–5156

John D. Ginn\*, Todd Bosanac, Rhonda Chen, Charles Cywin, Eugene Hickey, Mohammed Kashem, Steven Kerr, Stanley Kugler, Xiang Li, Anthony Prokopowicz III, Sabine Schlyer, James D. Smith, Michael R. Turner, Frank Wu, Erick R. R. Young

**New halogenated 3-phenylcoumarins as potent and selective MAO-B inhibitors**

pp 5157–5160

Maria João Matos\*, Dolores Viña, Patricia Janeiro, Fernanda Borges, Lourdes Santana, Eugenio Uriarte

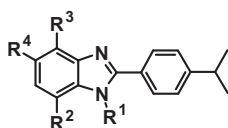


New series of bromo-6-methyl-3-phenylcoumarin derivatives, with bromo atom in both different benzene rings of the skeleton, and with or without different number of methoxy substituent at the 3-phenyl ring, were synthesized. The methoxy substituents were introduced, in this new scaffold, in the *meta* and/or *para* positions of the 3-phenyl ring. The synthesized compounds **3–7** were evaluated as MAO-A and B inhibitors.

**Penta-substituted benzimidazoles as potent antagonists of the calcium-sensing receptor (CaSR-antagonists)**

pp 5161–5164

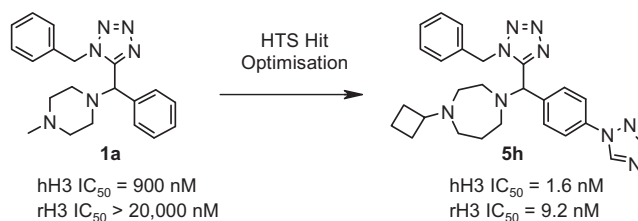
Marc Gerspacher\*, Eva Altmann, René Beerli, Thomas Buhl, Ralf Endres, Rainer Gamse, Jacques Kameni-Tcheudji, Michaela Kneissel, Karl Heinz Krawinkler, Martin Missbach, Alfred Schmidt, Klaus Seuwen, Sven Weiler, Leo Widler



**Discovery of substituted benzyl tetrazoles as histamine H3 receptor antagonists**

pp 5165–5169

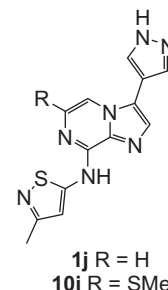
Adam J. Davenport\*, Christopher C. Stimson, Massimo Corsi, Darshan Vaidya, Edward Glenn, Timothy D. Jones, Sarah Bailey, Mark J. Gemkow, Ulrike Fritz, David J. Hallett

**Discovery of imidazo[1,2-*a*]pyrazine-based Aurora kinase inhibitors**

pp 5170–5174

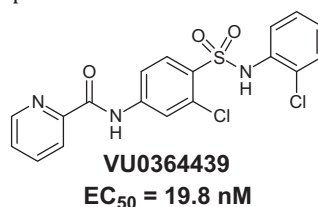
David B. Belanger\*, Patrick J. Curran, Alan Hruza, Johannes Voigt, Zhaoyang Meng, Amit K. Mandal, M. Arshad Siddiqui, Andrea D. Basso, Kimberly Gray

The synthesis and structure–activity relationships (SAR) of novel, potent imidazo[1,2-*a*]pyrazine-based Aurora kinase inhibitors are described. The X-ray crystal structure of imidazo[1,2-*a*]pyrazine Aurora inhibitor **1j** is disclosed. Compound **10i** was identified as good lead compound with an attractive in vitro DMPK profile.

**Synthesis and SAR of novel, 4-(phenylsulfamoyl)phenylacetamide mGlu<sub>4</sub> positive allosteric modulators (PAMs) identified by functional high-throughput screening (HTS)**

pp 5175–5178

Darren W. Engers, Patrick R. Gentry, Richard Williams, Julie D. Bolinger, C. David Weaver, Usha N. Menon, P. Jeffrey Conn, Craig W. Lindsley, Colleen M. Niswender\*, Corey R. Hopkins\*

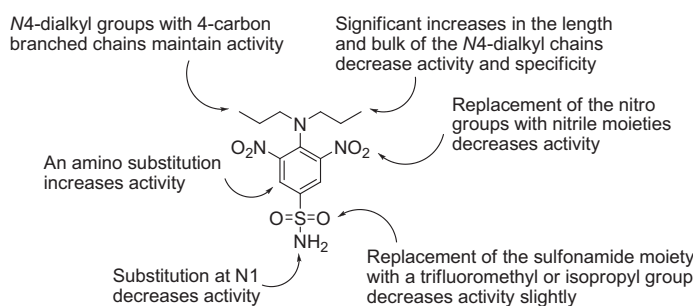


Herein we disclose the synthesis and SAR of a series of 4-(phenylsulfamoyl)phenylacetamide compounds as mGlu<sub>4</sub> positive allosteric modulators (PAMs) that were identified via a functional HTS. An iterative parallel approach to these compounds culminated in the discovery of VU0364439 (**11**) which represents the most potent (19.8 nM) mGlu<sub>4</sub> PAM reported to date.

**Synthesis and evaluation of oryzalin analogs against *Toxoplasma gondii***

pp 5179–5183

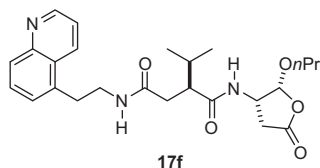
Molla M. Endeshaw, Catherine Li, Jessica de Leon, Ni Yao, Kirk Latibeaudiere, Kokku Premalatha, Naomi Morrisette, Karl A. Werbovetz\*



### Succinic acid amides as P2–P3 replacements for inhibitors of interleukin-1 $\beta$ converting enzyme (ICE or caspase 1)

pp 5184–5190

Paul Galatsis\*, Bradley Caprathe, John Gilmore, Anthony Thomas, Kristin Linn, Susan Sheehan, William Harter, Catherine Kostlan, Elizabeth Lunney, Charles Stankovic, John Rubin, Kenneth Brady, Hamish Allen, Robert Talanian

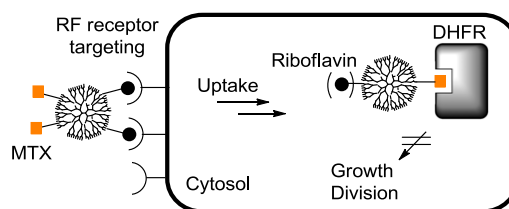


Succinic acid amides have been found to be effective P2–P3 scaffold replacements. ICE inhibitors based on this framework were synthesized and evaluated and the in vivo active ICE inhibitor **17f** is reported.

### Design of riboflavin-presenting PAMAM dendrimers as a new nanoplatform for cancer-targeted delivery

pp 5191–5194

Thommy P. Thomas, Seok Ki Choi, Ming-Hsin Li, Alina Kotlyar, James R. Baker Jr.\*



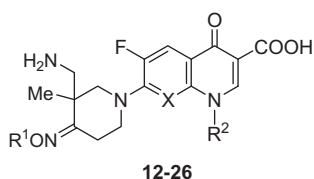
This communication describes the design and in vitro biological evaluation of novel generation 5 PAMAM dendrimers conjugated with riboflavin as a targeting ligand.



### Synthesis and in vitro antibacterial activity of novel fluoroquinolone derivatives containing substituted piperidines

pp 5195–5198

Yun Chai, Mingliang Liu\*, Bo Wang, Xuefu You, Lianshun Feng, Yibin Zhang, Jue Cao, Huiyuan Guo

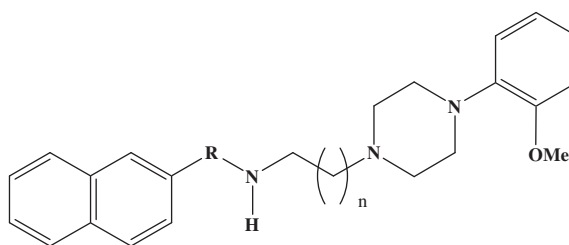


We report herein the synthesis of novel 7-(4-alkoxyimino-3-aminomethyl-3-methylpiperidin-1-yl) fluoroquinolone derivatives **12–26**. All of the title compounds have good potency in inhibiting the growth of *Staphylococcus aureus* and *Staphylococcus epidermidis* including MRSE (MIC: 0.125–4  $\mu\text{g/mL}$ ).

### Synthesis and in vitro binding studies of piperazine-alkyl-naphthamides: Impact of homology and sulphonamide/carboxamide bioisosteric replacement on the affinity for 5-HT<sub>1A</sub>, $\alpha_{2A}$ , D4.2, D3 and D2L receptors

pp 5199–5202

Mélissa Résimont, Jean-François Liégeois\*

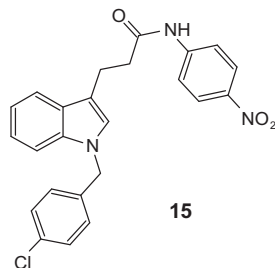


A series of piperazine-alkyl-naphthamides ( $R = \text{CO}$  or  $\text{SO}_2$ ;  $n = 1–5$ ) was prepared and tested for their affinity for 5-HT<sub>1A</sub>,  $\alpha_{2A}$ , D4.2, D3 and D2L receptors. Homology and sulphonamide/carboxamide isosteric replacement differentially affect the binding affinity for these receptors.

**Synthesis of *N*-aryl-3-(indol-3-yl)propanamides and their immunosuppressive activities**

pp 5203–5206

Francis Giraud, Pascal Marchand\*, Delphine Carbonnelle, Michael Sartor, François Lang, Muriel Duflos

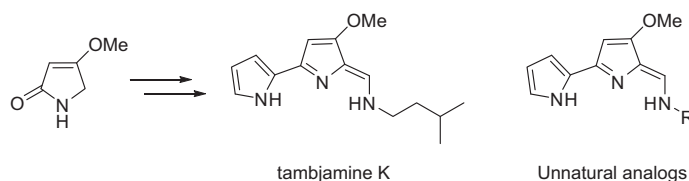


*N*-Aryl-3-(indol-3-yl)propanamides were synthesized and their immunosuppressive activities were evaluated. Compound **15** exhibited a significant inhibitory activity on murine splenocytes proliferation assay in vitro and on mice delayed-type hypersensitivity (DTH) assay in vivo.

**Total synthesis and biological evaluation of tambjamine K and a library of unnatural analogs**

pp 5207–5211

Leslie N. Aldrich, Sydney L. Stoops, Brenda C. Crews, Lawrence J. Marnett, Craig W. Lindsley\*

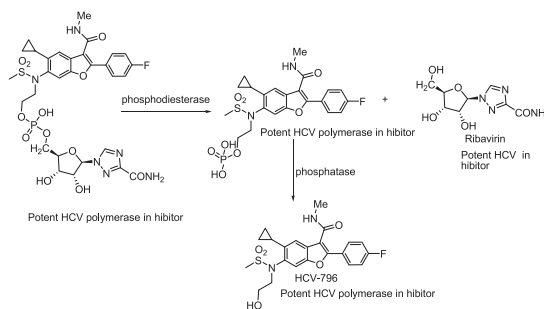


The first total synthesis of tambjamine K and a library of unnatural analogs is reported. Unnatural analogs were shown to be more potent in viability, proliferation, and invasion assays than the natural product in multiple cancer cell lines, with minimal to no cytotoxicity on non-transformed cell lines.

**Design and synthesis of HCV agents with sequential triple inhibitory potentials**

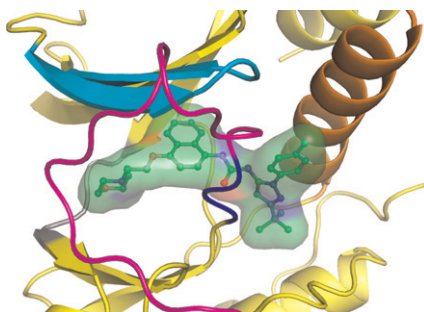
pp 5212–5216

Tianmin Zhu, Mahdi B. Fawzi, Michael Flint, Fangming Kong, Jan Szeliga, Russ Tsao, Anita Y. M. Howe, Weitao Pan\*

**X-ray crystal structure of JNK2 complexed with the p38 $\alpha$  inhibitor BIRB796: Insights into the rational design of DFG-out binding MAP kinase inhibitors**

pp 5217–5220

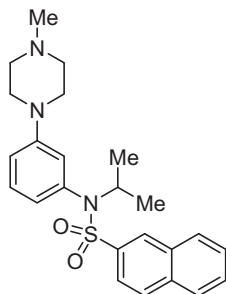
Andreas Kuglstatter\*, Manjiri Ghate, Stan Tsing, Armando G. Villaseñor, David Shaw, Jim W. Barnett, Michelle F. Browner



### Synthesis and SAR of (piperazin-1-yl-phenyl)-arylsulfonamides: A novel series of atypical antipsychotic agents

pp 5221–5224

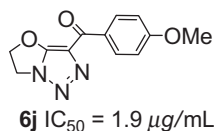
Chul Min Park\*, So Young Kim, Woo Kyu Park, Jung Hwan Choi, Churl Min Seong



### An efficient one-pot synthesis of heterocycle-fused 1,2,3-triazole derivatives as anti-cancer agents

pp 5225–5228

Sheng-Jiao Yan, Yong-Jiang Liu, Yu-Lan Chen, Lin Liu, Jun Lin\*



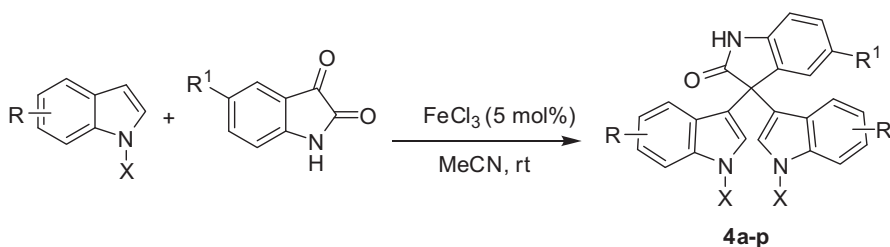
A series of heterocycle-fused 1,2,3-triazoles were easily prepared by the 1,3-dipolar cycloaddition in a one-pot reaction and evaluated in vitro against a panel of human tumor cell lines. 1,3-Oxazoheterocycle fused 1,2,3-triazoles were more potent against the tumor cell lines. 4-Methoxyphenyl substituted 1,3-oxazoheterocycle fused 1,2,3-triazole **6j** was found to be the most potent derivative with IC<sub>50</sub> values lower than 1.9 μg/mL against A431 cell line.



### Synthesis of 3,3-diindolyl oxyindoles efficiently catalysed by FeCl<sub>3</sub> and their in vitro evaluation for anticancer activity

pp 5229–5231

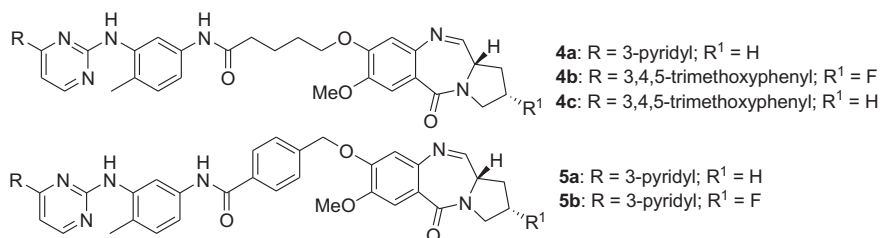
Ahmed Kamal\*, Y. V. V. Srikanth, M. Naseer A. Khan, Thokhir Basha Shaik, Md. Ashraf



### Synthesis and biological evaluation of anilino substituted pyrimidine linked pyrrolobenzodiazepines as potential anticancer agents

pp 5232–5236

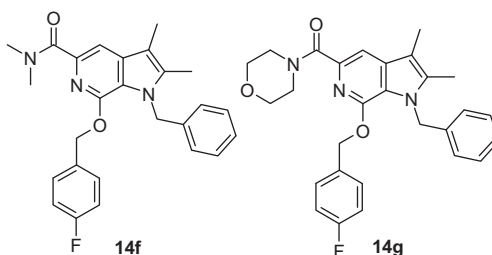
Ahmed Kamal\*, J. Surendranadha Reddy, M. Janaki Ramaiah, E. Vijaya Bharathi, D. Dastagiri, M. Kashi Reddy, S. N. C. V. L. Pushpavalli, Manika Pal-Bhadra\*



**Novel 1*H*-pyrrolo[2,3-*c*]pyridines as acid pump antagonists (APAs)**

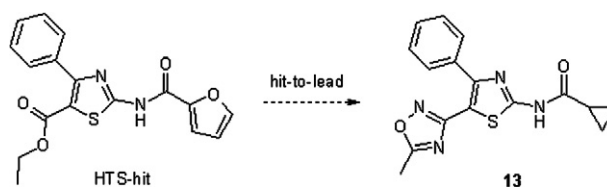
pp 5237–5240

Young Ae Yoon, Dong Hoon Kim, Byoung Moon Lee, Tae Kyun Kim, Myung Hun Cha, Jae Young Sim, Jae Gyu Kim\*

The synthesis of the potent acid pump antagonists **14f** and **14g** ( $IC_{50}$  = 28 and 29 nM) is reported.**Hit-to-lead optimization of a series of carboxamides of ethyl 2-amino-4-phenylthiazole-5-carboxylates as novel adenosine  $A_{2A}$  receptor antagonists**

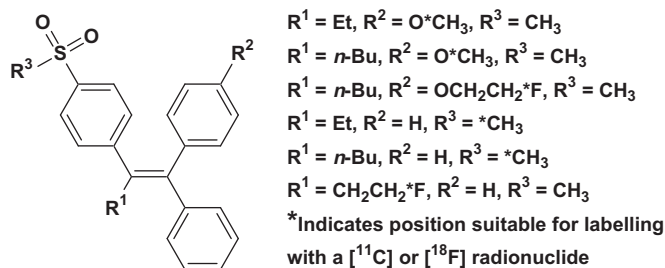
pp 5241–5244

Anette Graven Sams\*, Gitte Kobberøe Mikkelsen, Mogens Larsen, Lars Torup, Lise Tøttrup Brennum, Tenna Juul Schrøder, Benny Bang-Andersen

**Triaryl (Z)-olefins suitable for radiolabeling with carbon-11 or fluorine-18 radionuclides for positron emission tomography imaging of cyclooxygenase-2 expression in pathological disease**

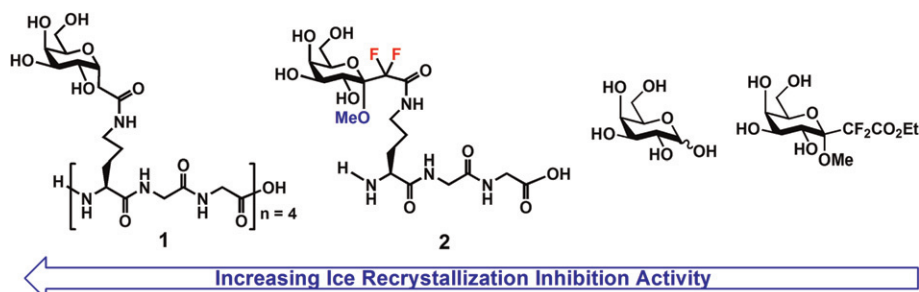
pp 5245–5250

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

**Assessing the ability of a short fluorinated antifreeze glycopeptide and a fluorinated carbohydrate derivative to inhibit ice recrystallization**

pp 5251–5254

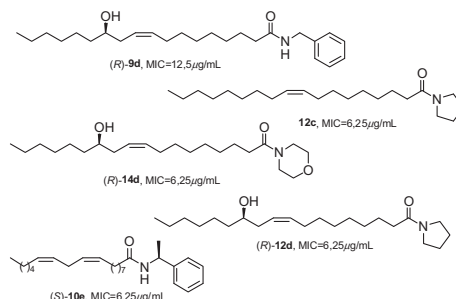
Jennifer L. Chaytor, Robert N. Ben\*



### Synthesis and antituberculosis activity of new fatty acid amides

pp 5255–5257

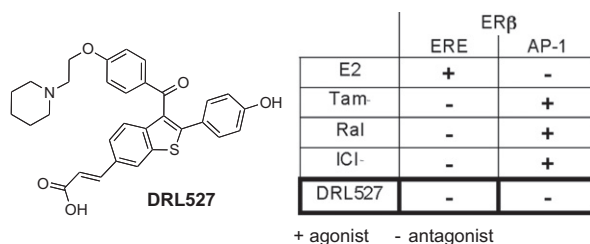
Caroline Da Ros Montes D'Oca, Tatiane Coelho, Tamara Germani Marinho, Carolina Rosa Lopes Hack, Rodrigo da Costa Duarte, Pedro Almeida da Silva, Marcelo Gonçalves Montes D'Oca\*



### A mutant selective anti-estrogen is a pure antagonist on EREs and AP-1 response elements

pp 5258–5261

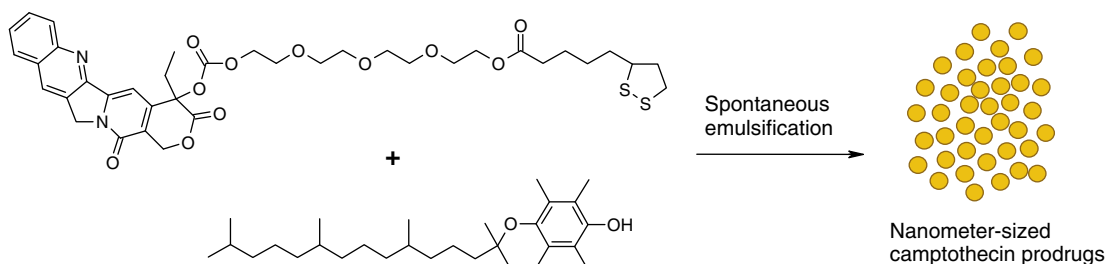
Disha Jain, John T. Koh\*



### Oxidative stimuli-responsive nanoprodrug of camptothecin kills glioblastoma cells

pp 5262–5268

Bong-Seop Lee, Aruna K. Nalla, Ilana R. Stock, Talia C. Shear, Keith L. Black, John S. Yu\*

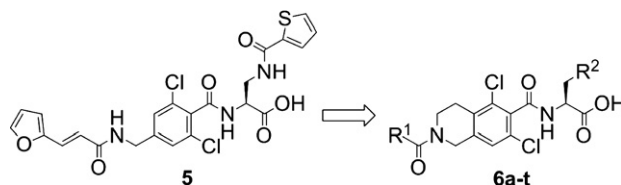


Nanometer-sized camptothecin prodrugs were prepared from camptothecin prodrug molecules and α-tocopherol by using spontaneous emulsification.

### Discovery of tetrahydroisoquinoline (THIQ) derivatives as potent and orally bioavailable LFA-1/ICAM-1 antagonists

pp 5269–5273

Min Zhong\*, Wang Shen, Kenneth J. Barr, Jennifer P. Arbitrario, Michelle R. Arkin, Minna Bui, Teresa Chen, Brian C. Cunningham, Marc J. Evanchik, Emily J. Hanan, Ute Hoch, Karen Huen, Jennifer Hyde, Jeffery L. Kumer, Teresa Lac, Chris E. Lawrence, Jose R. Martell, Johan D. Oslob, Kumar Paulvannan, Saileta Prabhu, Jeffrey A. Silverman, Jasmin Wright, Chul H. Yu, Jiang Zhu, W. Mike Flanagan



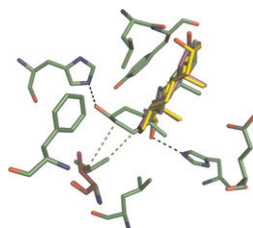
The discovery of a novel series of tetrahydroisoquinoline (THIQ) derivatives as potent and orally bioavailable LFA-1/ICAM-1 antagonists is described.



**Factorizing the role of a critical leucine residue in the binding of substrate to human 20 $\alpha$ -hydroxysteroid dehydrogenase (AKR1C1): Molecular modeling and kinetic studies of the Leu308Val mutant enzyme**

pp 5274–5276

Urmi Dhagat, Satoshi Endo, Midori Soda, Akira Hara, Ossama El-Kabbani\*

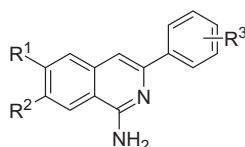


Structure of AKR1C1

**Synthesis, in vitro and in vivo evaluation of 3-arylisquinolinamines as potent antitumor agents**

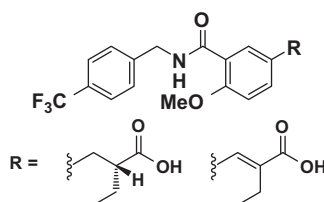
pp 5277–5281

Su Hui Yang, Hue Thi My Van, Thanh Nguyen Le, Daulat Bikram Khadka, Suk Hee Cho, Kyung-Tae Lee, Hwa-Jin Chung, Sang Kook Lee, Chang-Ho Ahn, Young Bok Lee\*, Won-Jea Cho\*

**Novel Notch-sparing  $\gamma$ -secretase inhibitors derived from a peroxisome proliferator-activated receptor agonist library**

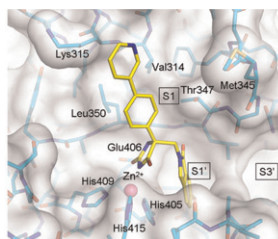
pp 5282–5285

Motonori Kurosumi, Yoshino Nishio, Satoko Osawa, Hisayoshi Kobayashi, Takeshi Iwatsubo, Taisuke Tomita, Hiroyuki Miyachi\*

Screening of our library of peroxisome proliferator-activated receptor (PPAR) agonists yielded several phenylpropanoic acid-derived  $\gamma$ -secretase inhibitors (GSIs).**Biaryl substituted hydantoin compounds as TACE inhibitors**

pp 5286–5289

Wensheng Yu\*, Ling Tong, Seong Heon Kim, Michael K. C. Wong, Lei Chen, De-Yi Yang, Bandarpalle B. Shankar, Brian J. Lavey, Guowei Zhou, Aneta Kosinski, Razia Rizvi, Dansu Li, Robert J. Feltz, John J. Piwinski, Kristin E. Rosner, Neng-Yang Shih, M. Arshad Siddiqui, Zhuyan Guo, Peter Orth, Himanshu Shah, Jing Sun, Shelby Umland, Daniel J. Lundell, Xiaoda Niu, Joseph A. Kozlowski,

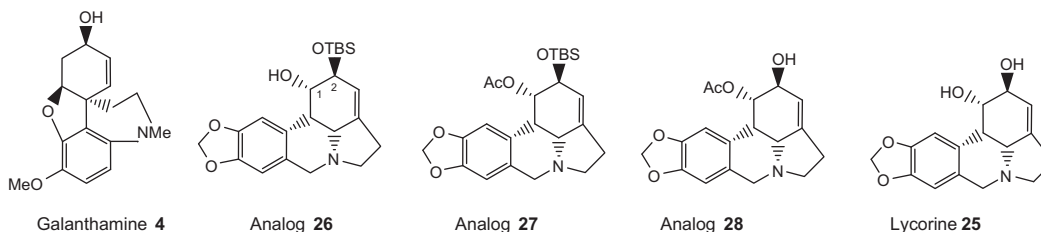


A series of biaryl substituted hydantoin TACE inhibitors is disclosed. Many compounds in this series exhibit sub-nanomolar TACE activities and good rat PK.

### Structure–activity studies on acetylcholinesterase inhibition in the lycorine series of Amaryllidaceae alkaloids

pp 5290–5294

James McNulty\*, Jerald J. Nair, Jessamyn R. L. Little, John D. Brennan, Jaume Bastida



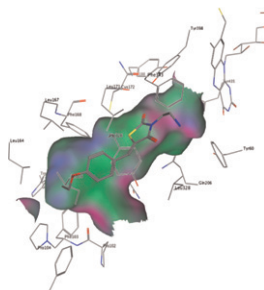
The synthesis of differentially functionalized analogs of the Amaryllidaceae alkaloid lycorine, accessed via a concise chemoselective silylation strategy, is described uncovering two of the most potent inhibitors of acetylcholinesterase (AChE) identified to date in this series. Important elements of this novel pharmacophore were elucidated through structure–activity relationship (SAR) studies.



### Identification of novel monoamine oxidase B inhibitors by structure-based virtual screening

pp 5295–5298

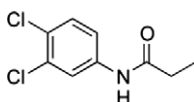
Werner J. Geldenhuys, Altaf S. Darvesh, Max O. Funk, Cornelis J. Van der Schyf, Richard T. Carroll\*



### Preliminary studies of 3,4-dichloroaniline amides as antiparasitic agents: Structure–activity analysis of a compound library in vitro against *Trichomonas vaginalis*

pp 5299–5301

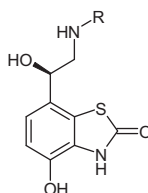
Padraick J. Dornbush, Cynric Cho, Elizabeth S. Chang, Lu Xu, Wade A. Russu, Lisa A. Wrischnik, Kirkwood M. Land\*



### A physical properties based approach for the exploration of a 4-hydroxybenzothiazolone series of $\beta_2$ -adrenoceptor agonists as inhaled long-acting bronchodilators

pp 5302–5307

David Beattie, Michelle Bradley, Andrew Brearley, Steven J. Charlton, Bernard M. Cuenoud, Robin A. Fairhurst\*, Peter Gedeck, Martin Gosling, Diana Janus, Darryl Jones, Christine Lewis, Clive McCarthy, Helen Oakman, Rowan Stringer, Roger J. Taylor, Andrew Tuffnell



**Using an in vitro cytotoxicity assay to aid in compound selection for in vivo safety studies**

pp 5308–5312

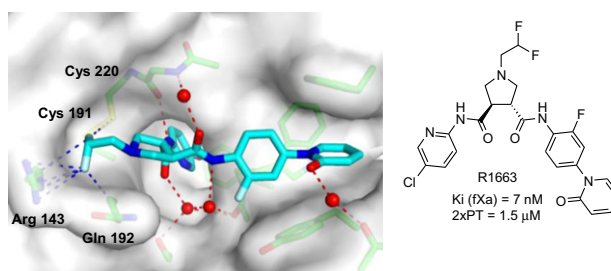
Nigel Greene\*, Michael D. Aleo, Shirley Louise-May, David A. Price\*, Yvonne Will

[THLE LC <sub>50</sub> bucket	# Cmpds Toxic@10μM (Total: 155)	# Cmpds Clean@10μM (Total: 57)
<10μM	8	0
10–25μM	7	3
25–50μM	20	0
50–100μM	19	3
>100μM	101	51

**Discovery of a factor Xa inhibitor (3R,4R)-1-(2,2-difluoro-ethyl)-pyrrolidine-3,4-dicarboxylic acid 3-[(5-chloro-pyridin-2-yl)-amide] 4-[[2-fluoro-4-(2-oxo-2H-pyridin-1-yl)-phenyl]-amide] as a clinical candidate**

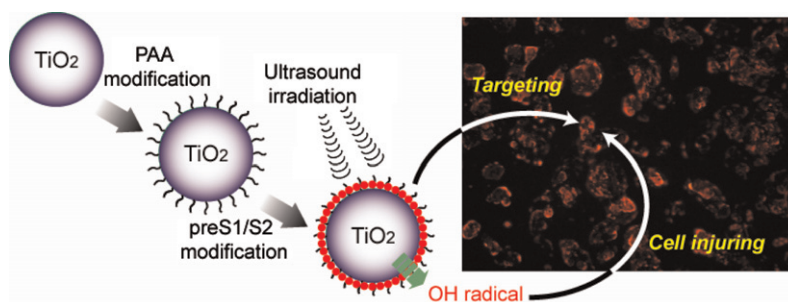
pp 5313–5319

Lilli Anselm, David W. Banner, Jörg Benz, Katrin Groebke Zbinden, Jacques Himber, Hans Hilpert, Walter Huber, Bernd Kuhn, Jean-Luc Mary, Michael B. Otteneder, Narendra Panday, Fabienne Ricklin, Martin Stahl, Stefan Thomi, Wolfgang Haap\*

**Construction of protein-modified TiO<sub>2</sub> nanoparticles for use with ultrasound irradiation in a novel cell injuring method**

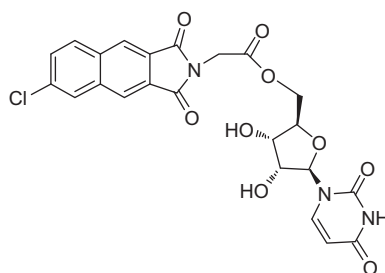
pp 5320–5325

Chiaki Ogino, Naonori Shibata, Ryosuke Sasai, Keiko Takaki, Yusuke Miyachi, Shun-ichi Kuroda, Kazuaki Ninomiya, Nobuaki Shimizu\*

**Labeling of nucleosides with fluorescent 6-chloro-2,3-naphthalimide**

pp 5326–5328

A. R. Katritzky\*, S. Ozcan, E. Todadze



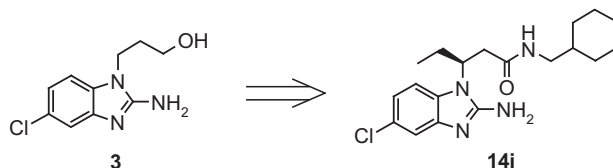
The synthesis and fluorescence properties of new highly fluorescent nucleosides are reported.



**Fragment-based discovery and optimization of BACE1 inhibitors**

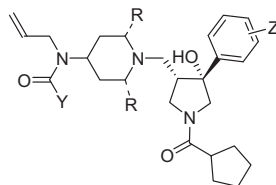
pp 5329–5333

James Madden\*, Jenny R. Dod, Robert Godemann, Joachim Kraemer, Myron Smith, Marion Biniszekiewicz, David J. Hallett, John Barker, Jane D. Dyekjaer, Thomas Hestekamp


**Studies on the structure–activity relationship of 1,3,4-tetra-substituted pyrrolidine embodied CCR5 receptor antagonists. Part 2: Discovery of highly potent anti-HIV agents**

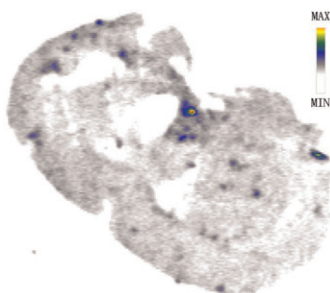
pp 5334–5336

Ben Li, Eric Dale Jones, Enkun Zhou, Li Chen, Dean Cameron Baylis, Shanghai Yu, Miao Wang, Xing He, Jonathan Alan Victor Coates, David Ian Rhodes, Gang Pei, John Joseph Deadman\*, Xin Xie\*, Dawei Ma\*


**Preparation of classical  $\text{Re}^{99\text{m}}\text{Tc}(\text{CO})_3^+$  and novel  $^{99\text{m}}\text{Tc}(\text{CO})_2(\text{NO})^{2+}$  cores complexed with flavonol derivatives and their binding characteristics for  $\text{A}\beta_{(1-40)}$  aggregates**

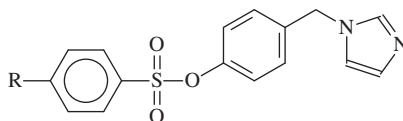
pp 5337–5344

Yang Yang, Lin Zhu, Mengchao Cui, Ruikun Tang, Huabei Zhang\*


**Synthesis and biochemical evaluation of a range of (4-substituted phenyl)sulfonate derivatives of 4-hydroxybenzyl imidazole-based compounds as potent inhibitors of  $17\alpha$ -hydroxylase/ $17,20$ -lyase ( $\text{P450}_{17\alpha}$ ) derived from rat testicular microsomes**

pp 5345–5348

Caroline P. Owen, Imran Shahid, Wai-Yee Lee, Sabbir Ahmed\*



R=various substituted sulfonyl derivatives, e.g.,  $\text{CH}_3$ ,  $\text{C}_2\text{H}_5$ ,  $\text{C}_3\text{H}_7$ ,  $\text{C}_4\text{H}_9$ ,  $\text{C}_5\text{H}_{11}$ ,  $\text{CF}_3$ , F and Ph

We report the synthesis and evaluation of a series of potent inhibitors of  $\text{P450}_{17\alpha}$ .

## pp 5349–5352

The chemical structure of compound 10 is a complex molecule. It features a coumarin core with a 3,4-dihydroxyphenyl group at the 2-position and a 3,4-dihydroxyphenyl group at the 3-position. The coumarin is linked via an ester bond to a sugar moiety (a pyranose ring). The sugar is further linked via an ester bond to a side chain containing a fluorinated phenyl group and a carboxylic acid group.

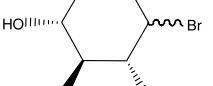


## pp 5353–5356

\*C1CN(S(=O)(=O)C1)COC2=CC=CC=C2  
(R)-24

## pp 5357–5359

$\text{Man}\alpha 1 \rightarrow 2 \text{Man}\alpha 1 \rightarrow 6 \text{Man}\alpha 1 \rightarrow 3 \text{Man}\alpha 1 \rightarrow 6 \text{Man}\beta 1 \rightarrow 4 \text{GlcNAc}\beta 1 \rightarrow 4 \text{GlcNAc}\beta 1$   
 $\text{Glc}\alpha 1 \rightarrow 3 \text{Glc}\alpha 1 \rightarrow 3 \text{Man}\alpha 1 \rightarrow 2 \text{Man}\alpha 1 \rightarrow 2 \text{Man}\alpha 1 \rightarrow 3 \text{Glc}_2 \text{Man}_9 \text{GlcNAc}_2$



bromoconduritol	IC <sub>50</sub>
cleavage-1	261.6 μM
cleavage-2	41.0 μM

Chemical structure of a branched oligosaccharide with two potential cleavage sites for glucosidase II. The structure shows a core fucose attached to a GlcNAc residue, which is linked to a mannose residue. The mannose residue is further linked to a glucose residue. The glucose residue has two potential cleavage sites for glucosidase II: one at the GlcNAc1-3Man linkage (cleavage-1) and another at the GlcNAc1-3Glc linkage (cleavage-2).

## pp 5360–5362

 <sup>+</sup> 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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