

## Contents

### Publisher's Note

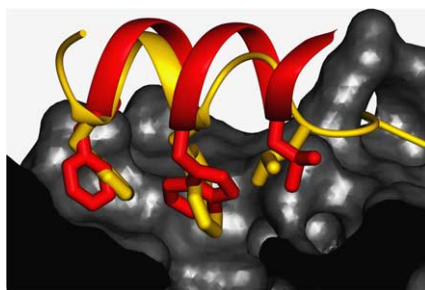
pp 9–10

### PERSPECTIVE

#### **$\beta$ -Peptides as inhibitors of protein–protein interactions**

pp 11–16

Joshua A. Kritzer, Olen M. Stephens, Danielle A. Guarracino, Samuel K. Reznik and Alanna Schepartz\*

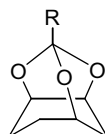


### REVIEW

#### **Natural and synthetic cage compounds incorporating the 2,9,10-trioxatricyclo[4.3.1.0<sup>3,8</sup>]decane type moiety**

pp 17–28

Elena Stanoeva, Weidong He and Norbert De Kimpe\*



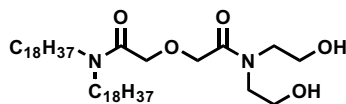
This review summarizes the natural occurrence, biological activities and synthetic approaches of the tetracyclic cage-like orthoesters with a 1,2,4-trioxygenated pattern of cyclohexane.

### ARTICLES

#### **Pore formation in and enlargement of phospholipid liposomes by synthetic models of ceramides and sphingomyelin**

pp 29–37

Robert Pajewski, Natasha Djedovič, Egan Harder, Riccardo Ferdani, Paul H. Schlesinger and George W. Gokel\*

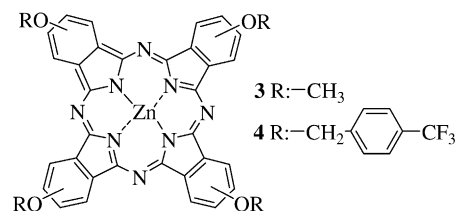


## Synthesis and photodynamic activity of zinc(II) phthalocyanine derivatives bearing methoxy and trifluoromethylbenzyloxy substituents in homogeneous and biological media

pp 39–46

E. Inés Yslas, Viviana Rivarola and Edgardo N. Durantini\*

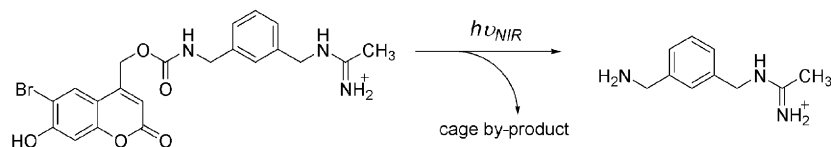
Two zinc(II) phthalocyanines bearing either four methoxy (ZnPc **3**) or trifluoromethylbenzyloxy (ZnPc **4**) substituents were synthesized and their photodynamic activity compared in both homogeneous medium containing photooxidizable substrate and in vitro on Hep-2 human larynx-carcinoma cell line. Although both sensitizers present similar behavior in organic solvent, a higher cell photoinactivation was found for ZnPc **3**.



## Photocontrol of nitric oxide production in cell culture using a caged isoform selective inhibitor

pp 47–57

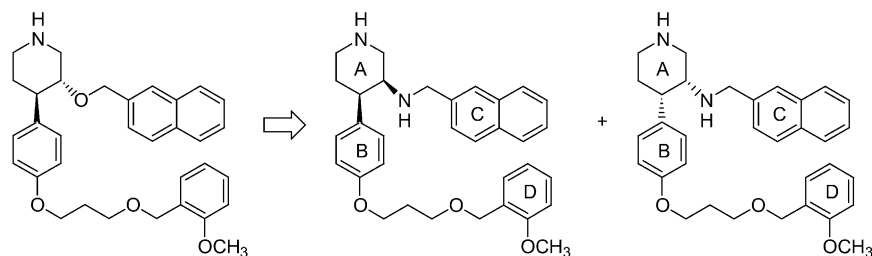
Basil Perdicakis, Heather J. Montgomery, Glenn L. Abbott, Dan Fishlock, Gilles A. Lajoie, J. Guy Guillemette and Eric Jervis\*



## The discovery and preparation of disubstituted novel amino-aryl-piperidine-based renin inhibitors

pp 59–68

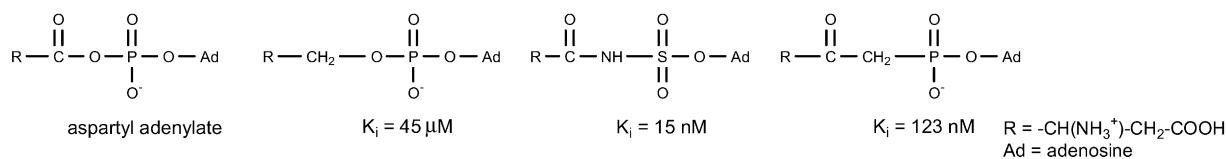
Wayne L. Cody,\* Daniel D. Holsworth, Noel A. Powell, Mehran Jalaie, Erli Zhang, Wei Wang, Brian Samas, John Bryant, Robert Ostroski, Michael J. Ryan and Jeremy J. Edmunds



## Synthesis and aminoacyl-tRNA synthetase inhibitory activity of aspartyl adenylate analogs

pp 69–75

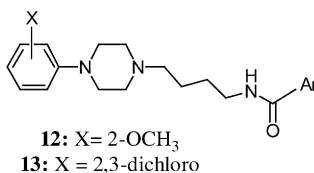
Stéphane Bernier, Pierre-Marie Akochy, Jacques Lapointe and Robert Chênevert\*



## Synthesis and in vitro binding of *N*-phenyl piperazine analogs as potential dopamine D<sub>3</sub> receptor ligands

pp 77–87

Wenhua Chu, Zhude Tu, Elizabeth McElveen, Jinbin Xu, Michelle Taylor,  
Robert R. Luedtke and Robert H. Mach\*

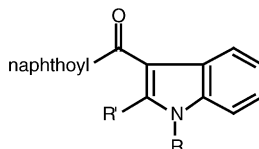


The synthesis of a series of *N*-(2-methoxyphenyl)piperazine and *N*-(2,3-dichlorophenyl)piperazine analogs and their in vitro binding affinities for dopamine D<sub>2</sub>, D<sub>3</sub>, D<sub>4</sub> are presented.

# Structure–activity relationships for 1-alkyl-3-(1-naphthoyl)indoles at the cannabinoid CB<sub>1</sub> and CB<sub>2</sub> receptors: steric and electronic effects of naphthoyl substituents. New highly selective CB<sub>2</sub> receptor agonists

**pp 89–112**

John W. Huffman,\* Gulay Zengin, Ming-Jung Wu, Jianzhong Lu, George Hynd, Kristen Bushell, Alicia L. S. Thompson, Simon Bushell, Cindy Tartal, Dow P. Hurst, Patricia H. Reggio, Dana E. Selley, Michael P. Cassidy, Jenny L. Wiley and Billy R. Martin

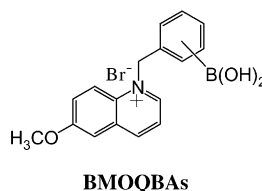


The synthesis and pharmacology of 47 1-alkyl-3-(1-naphthoyl)indoles (R = C<sub>3</sub>H<sub>7</sub> and C<sub>5</sub>H<sub>11</sub>, R' = H and CH<sub>3</sub>) is described. Naphthoyl substituents include 4- and 7-alkyl groups, plus 2, 4, 6, and 7-methoxy groups. Three of these compounds are highly selective CB<sub>2</sub> receptor agonists.

## Boronic acid fluorescent sensors for monosaccharide signaling based on the 6-methoxyquinolinium heterocyclic nucleus: progress toward noninvasive and continuous glucose monitoring

**pp 113–119**

Ramachandram Badugu, Joseph R. Lakowicz\* and Chris D. Geddes\*



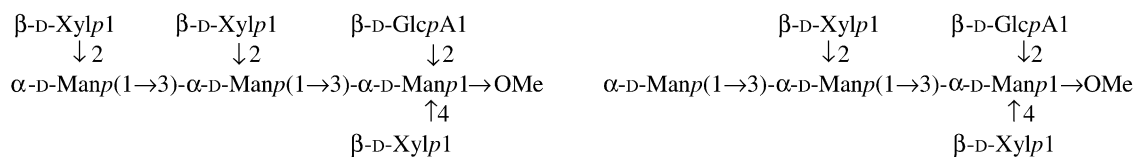
Glucose sensing probes based on 6-methoxyquinolinium boronic acid are potential candidates for the noninvasive and continuous glucose monitoring.



## Facile synthesis of the heptasaccharide repeating unit of *O*-deacetylated GXM of *C. neoformans* serotype B

**pp 121–130**

Wei Zhao and Fanzuo Kong\*

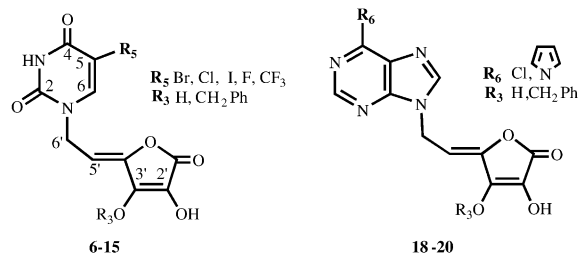


**The novel pyrimidine and purine derivatives of L-ascorbic acid: synthesis, one- and two-dimensional  $^1\text{H}$  and  $^{13}\text{C}$  NMR study, cytostatic and antiviral evaluation**

pp 131–139

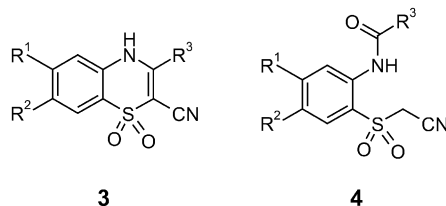
Tatjana Gazivoda, Miha Plevnik, Janez Plavec, Sandra Kraljević, Marijeta Kralj, Krešimir Pavelić, Jan Balzarini, Erik De Clercq, Mladen Mintas and Silvana Raić-Malić\*

Novel C-5 substituted pyrimidine (**6–15**) and purine (**18–20**) derivatives of L-ascorbic acid containing free hydroxy groups at C-2' or C-2' and C-3' positions of the lactone ring were synthesized and evaluated for their cytostatic and antiviral activities.


**Synthesis and pharmacological evaluation of 4*H*-1,4-benzothiazine-2-carbonitrile 1,1-dioxide and *N*-(2-cyanomethylsulfonylphenyl)acylamide derivatives as potential activators of ATP sensitive potassium channels**

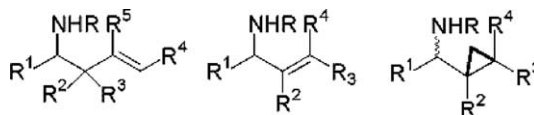
pp 141–155

Søren C. Schou, Holger C. Hansen, Tina M. Tagmose, Harrie C. M. Boonen, Anne Worsaae, Michael Drabowski, Philip Wahl, Per O. G. Arkhammar, Thora Bodvarsdottir, Marie-Hélène Antoine, Philippe Lebrun and John Bondo Hansen\*


**New antiestrogens from a library screen of homoallylic amides, allylic amides, and C-cyclopropylalkylamides**

pp 157–164

Jelena M. Janjic, Ying Mu, Christopher Kendall, Corey R. J. Stephenson, Raghavan Balachandran, Brianne S. Raccor, Ying Lu, Guangyu Zhu, Wen Xie, Peter Wipf and Billy W. Day\*

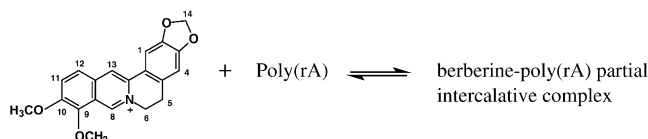


A new structural scaffold for antiestrogens was identified from the cell-based screening of a 67-member library of homoallylic amides, allylic amides, and C-cyclopropylalkylamides. Several derivatives had activity comparable to that of tamoxifen.

**Berberine, a strong polyriboadenylic acid binding plant alkaloid: spectroscopic, viscometric, and thermodynamic study**

pp 165–174

Ram Chandra Yadav, Gopinatha Suresh Kumar, Kakali Bhadra, Prabal Giri, Rangana Sinha, Sumana Pal and Motilal Maiti\*

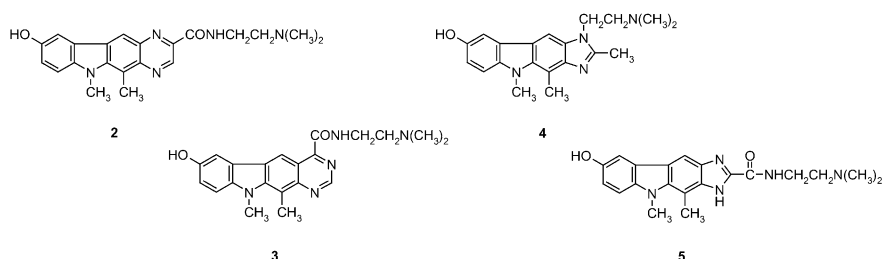


Berberine binds strongly to single stranded poly(rA) by mechanism of partial intercalation, leading to its usefulness for inhibition of gene expression in eukaryotic cells.

**Cytotoxic and antitumoral properties in a series of new, ring D modified, olivacine analogues**

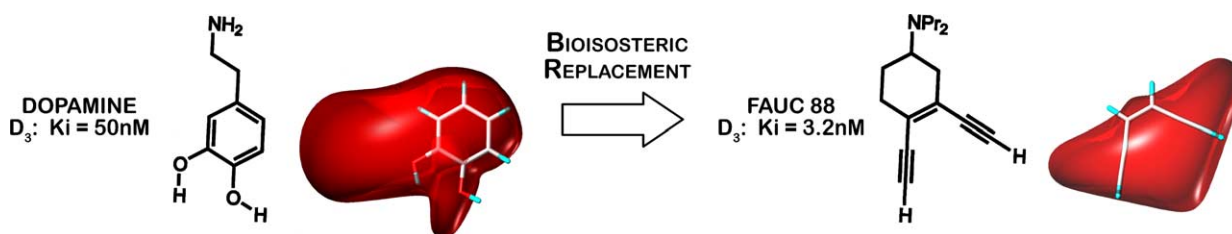
pp 175–184

Claude Guillonneau, Annette Nault, Eric Raimbaud, Stéphane Léonce, Laurence Kraus-Berthier, Alain Pierré and Solo Goldstein\*

**Fancy bioisosteres: synthesis and dopaminergic properties of the endiyne FAUC 88 as a novel non-aromatic D3 agonist**

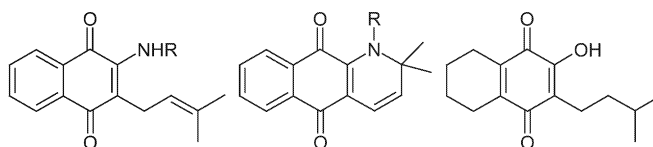
pp 185–191

Carola Lenz, Christian Haubmann, Harald Hübner, Frank Boeckler and Peter Gmeiner\*

**Molluscicidal activity of synthetic lapachol amino and hydrogenated derivatives**

pp 193–196

Tania M. S. Silva,\* Celso A. Camara, Ticiano P. Barbosa, André Z. Soares, Luciana C. da Cunha, Angelo C. Pinto and Maria D. Vargas



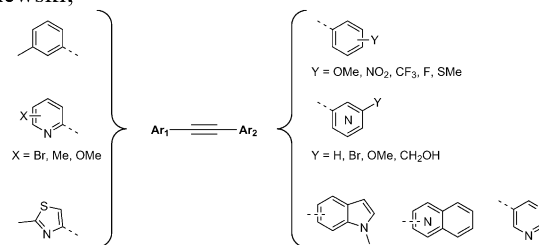
A series of new amino derivatives and a new partially hydrogenated derivative of the natural naphthoquinone lapachol were found to exhibit molluscicidal activity against *Biomphalaria glabrata*.

**Synthesis and receptor assay of aromatic–ethynyl–aromatic derivatives with potent mGluR5 antagonist activity**

pp 197–209

David Alagille, Ronald M. Baldwin, Bryan L. Roth, Jarda T. Wroblewski, Ewa Grajkowska and Gilles D. Tamagnan\*

Noncompetitive antagonists of the human metabotropic glutamate receptor subtype 5 (mGluR5) have been implicated as potential therapeutics for the treatment of a variety of nervous system disorders, including pain, anxiety, and drug addiction. To discover novel noncompetitive antagonists to the mGluR5, we initiated an SAR study around the known lead compounds MPEP and M-MPEP. Our results pointed out the critical role of the *para* position of the two aromatic rings, which leads to inactive products and permitted the discovery of potent mGluR5 antagonists (e.g., **16**, **25**, **28**, **34** IC<sub>50</sub> = 13.5, 11.9, 21, 15 nM, respectively).

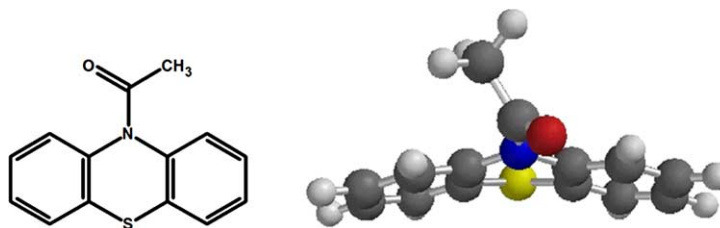


### Structure–activity relationships for inhibition of human cholinesterases by alkyl amide phenothiazine derivatives

pp 211–222

Sultan Darvesh,\* Robert S. McDonald, Andrea Penwell, Sarah Conrad, Katherine V. Darvesh, Diane Mataija, Geraldine Gomez, Angela Caines, Ryan Walsh and Earl Martin

A number of phenothiazine N-alkyl amide derivatives were synthesized in order to examine the structure–activity relationships for inhibition of human acetylcholinesterase and butyrylcholinesterase.

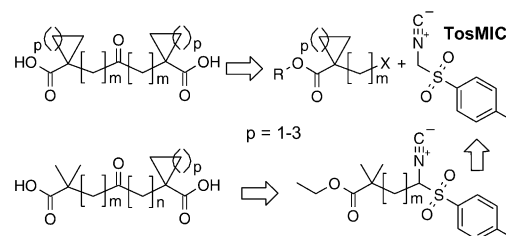


### $\alpha$ -Cycloalkyl-substituted $\omega$ -keto-dicarboxylic acids as lipid regulating agents

pp 223–236

Roel P. L. Bell, Dennis Verdijk, Mike Relou, Dennis Smith, Henk Regeling, Eelco J. Ebbers, Frank M. C. Leemhuis, Daniela C. Oniciu,\* Clay T. Cramer, Brian Goetz, Michael E. Pape, Brian R. Krause and Jean-Louis Dasseux

A series of cycloalkyl-substituted oxo-alkanedicarboxylic acids have been prepared by the TosMIC methodology departing from haloalkyl-substituted cycloalkylcarboxylic esters. cyclopropyl derivatives showed  $IC_{50}$  activity in the 0.3–1.0  $\mu$ M range on the de novo incorporation of radiolabeled acetate into lipids in primary cultures of rat hepatocytes, and they showed lipid-regulating properties when tested in vivo in female obese Zucker fatty rats.



### On the role of polarizability in QSAR

pp 237–255

Rajeshwar P. Verma, Alka Kurup and Corwin Hansch\*

The QSAR model for the polarizability effects on ligand–substrate interactions can be illustrated in terms of NVE (number of valence electrons) by Eq. I.

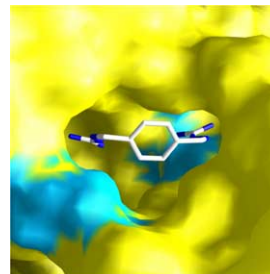
$$\log 1/C = a(NVE) \pm \text{constant} \quad (I)$$

### Identification and characterization of nonsubstrate based inhibitors of the essential dengue and West Nile virus proteases

pp 257–264

Vannakambadi K. Ganesh, Nik Muller, Ken Judge, Chi-Hao Luan, Radhakrishnan Padmanabhan and Krishna H. M. Murthy\*

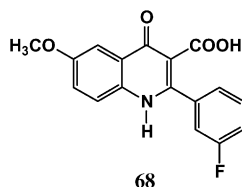
Using the structure of the dengue serine protease complexed with a protein inhibitor as a template, five inhibitory compounds were identified and characterized against Dengue and West Nile viral proteases.



### Synthesis and biological relationships of 3',6-substituted 2-phenyl-4-quinolone-3-carboxylic acid derivatives as antimitotic agents

pp 265–275

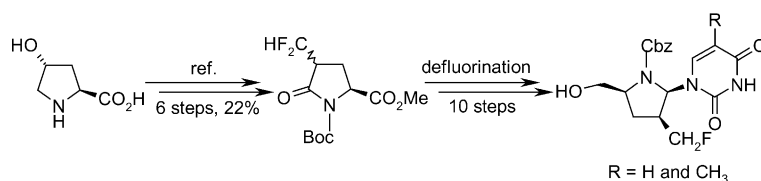
Ya-Yun Lai, Li-Jiau Huang, Kuo-Hsiung Lee, Zhiyan Xiao, Kenneth F. Bastow, Takao Yamori and Sheng-Chu Kuo\*



### Synthesis of 2',3'-dideoxy-2'-monofluoromethyl azanucleosides

pp 277–283

Xiao-Long Qiu and Feng-Ling Qing\*



## OTHER CONTENTS

Bioorganic & Medicinal Chemistry Reviews and Perspectives  
Contributors to this issue  
Instructions to contributors

pp 285–286  
p I  
pp III–VII

\*Corresponding author

Ⓛ<sup>+</sup> Supplementary data available via ScienceDirect

## COVER

Model illustrating how the rationally designed  $\beta$ -peptide **b53-1** might interact with its target, the oncoprotein hDM2. The mean solution structure of **b53-1** (red) was docked into the crystal structure of the hDM2 oncoprotein (gray surface) complexed to a peptide derived from p53 (gold). For clarity, some sidechains and part of the hDM2 surface were omitted. [Kritzer, J. A.; Stephens, O. M.; Guarracino, D. A.; Reznik, S. K.; Schepartz, A. *Bioorg. Med. Chem.* **2005**, *13*, 11–16].

© 2004 A. Schepartz. Published by Elsevier Ltd.

Indexed/Abstracted in: Beilstein, Biochemistry & Biophysics Citation Index, CANCERLIT, Chemical Abstracts, Chemistry Citation Index, Current Awareness in Biological Sciences/BIODISE, Current Contents: Life Sciences, EMBASE/Excerpta Medica, MEDLINE, PASCAL, Research Alert, Science Citation Index, SciSearch, TOXFILE



ISSN 0968-0896