

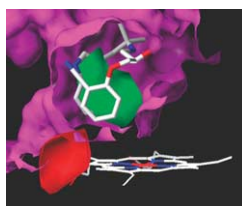
## Contents

### ARTICLES

**A 3D-QSAR model for CYP2D6 inhibition in the aryloxypropanolamine series**

pp 3816–3820

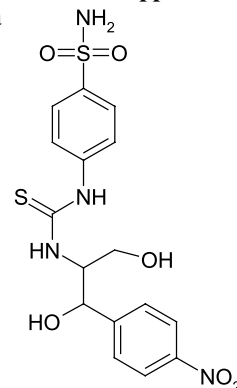
Roy J. Vaz,\* Akbar Nayeem, Kenneth Santone, Gamini Chandrasena and Ashvinikumar V. Gavai\*



**Carbonic anhydrase inhibitors: Design of thioureido sulfonamides with potent isozyme II and XII inhibitory properties and intraocular pressure lowering activity in a rabbit model of glaucoma**

pp 3821–3827

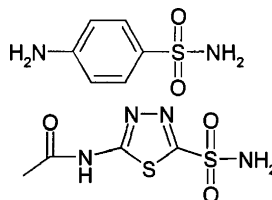
Francesco Mincione, Michele Starnotti, Emanuela Masini,\* Lucia Bacciottini, Chiara Scrivanti, Angela Casini, Daniela Vullo, Andrea Scozzafava and Claudiu T. Supuran\*



**Carbonic anhydrase inhibitors: Inhibition of the transmembrane isozyme XIV with sulfonamides**

pp 3828–3833

Isao Nishimori, Daniela Vullo, Alessio Innocenti, Andrea Scozzafava, Antonio Mastrolorenzo and Claudiu T. Supuran\*



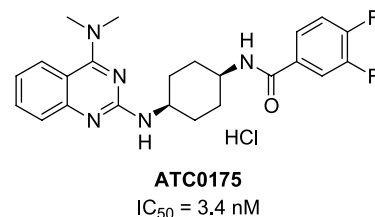


**Lead optimization of 4-(dimethylamino)quinazolines, potent and selective antagonists for the melanin-concentrating hormone receptor 1**

pp 3853–3856

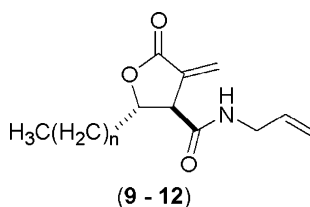
Kosuke Kanuma, Katsunori Omodera, Mariko Nishiguchi, Takeo Funakoshi, Shigeyuki Chaki, Graeme Semple, Thuy-Anh Tran, Bryan Kramer, Debbie Hsu, Martin Casper, Bill Thomsen and Yoshinori Sekiguchi\*

The synthesis and SAR of 4-(dimethylamino)quinazolines as melanin-concentrating hormone receptor 1 (MCH-R1) antagonists are reported, leading to the discovery of ATC0175.

**New  $\alpha$ -methylene- $\gamma$ -butyrolactones with antimycobacterial properties**

pp 3857–3859

Minerva A. Hughes, Jill M. McFadden and Craig A. Townsend\*



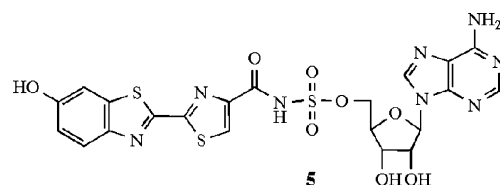
Synthesis and activity of new  $\alpha$ -methylene- $\gamma$ -butyrolactones against mycobacteria.

**Synthesis of an *N*-acyl sulfamate analog of luciferyl-AMP: A stable and potent inhibitor of firefly luciferase**

pp 3860–3864

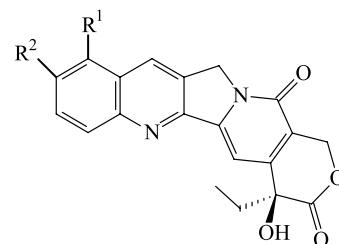
Bruce R. Branchini,\* Martha H. Murtiashaw, Jill N. Carmody, Emily E. Mygatt and Tara L. Southworth

We report here the multi-step synthesis and physical and enzymatic characterization of an *N*-acyl sulfamate analog of luciferyl-adenylate, 5'-*O*-[(*N*-dehydroluciferyl)-sulfamoyl]-adenosine (compound **5**). This represents the first example of a stable and potent ( $K_i$  = 340 nM) reversible inhibitor of firefly luciferase activity based on the structure of the natural acyl-adenylate intermediate.

**Radiosynthesis of carbon-11-labeled camptothecin derivatives as potential positron emission tomography tracers for imaging of topoisomerase I in cancers**

pp 3865–3869

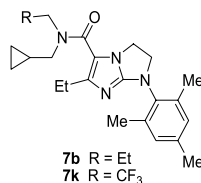
Mingzhang Gao, Kathy D. Miller, George W. Sledge and Qi-Huang Zheng\*



R<sup>1</sup>=O<sup>11</sup>CH<sub>3</sub>, R<sup>2</sup>=H, [<sup>11</sup>C]**5**  
R<sup>1</sup>=H, R<sup>2</sup>=O<sup>11</sup>CH<sub>3</sub>, [<sup>11</sup>C]**7**  
R<sup>1</sup>=NO<sub>2</sub>, R<sup>2</sup>=O<sup>11</sup>CH<sub>3</sub>, [<sup>11</sup>C]**9**  
R<sup>1</sup>=CH<sub>2</sub>N<sup>+</sup>(CH<sub>3</sub>)<sub>2</sub>, R<sup>2</sup>=OH, [<sup>11</sup>C]**11**

### Synthesis, structure–activity relationships, and anxiolytic activity of 7-aryl-6,7-dihydroimidazoimidazole pp 3870–3873 corticotropin-releasing factor 1 receptor antagonists

Xiaojun Han,\* Jodi A. Michne, Sokhom S. Pin, Kevin D. Burris, Lynn A. Balanda, Lawrence K. Fung, Tracey Fiedler, Kaitlin E. Browman, Matthew T. Taber, Jie Zhang and Gene M. Dubowchik\*

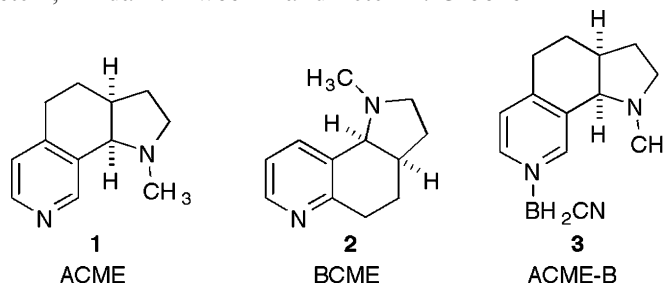


The synthesis and SAR of constrained dihydroimidazoimidazoles, and behavioral activity of compounds **7b** ( $K_i$  42 nM) and **7k** ( $K_i$  41 nM) in a mouse canopy model of anxiety, are reported.

### The characterization of a novel rigid nicotine analog with $\alpha 7$ -selective nAChR agonist activity and modulation of agonist properties by boron inclusion pp 3874–3880

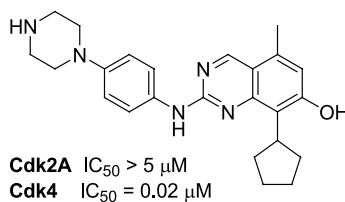
Roger L. Papke,\* Guangrong Zheng, Nicole A. Horenstein, Linda P. Dwoskin and Peter A. Crooks

The rigid nicotine analog ACME and its *N*-cyanoborane conjugate ACME-B are selective partial agonists of rat  $\alpha 7$  nicotinic receptors expressed in *Xenopus* oocytes, with no significant activation of either  $\alpha 3\beta 4$  or  $\alpha 4\beta 2$  receptors. ACME-B is both more potent and efficacious than ACME.



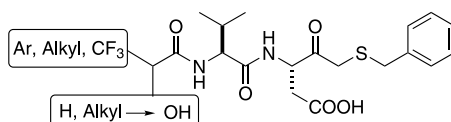
### 2-Aminoquinazoline inhibitors of cyclin-dependent kinases pp 3881–3885

Yadagiri Bathini, Inderjit Singh, Patricia J. Harvey, Paul R. Keller, Rajeshwar Singh, Ronald G. Micetich, David W. Fry, Ellen M. Dobrusin and Peter L. Toogood\*



### Lipophilic versus hydrogen-bonding effect in P<sub>3</sub> on potency and selectivity of valine aspartyl ketones as caspase 3 inhibitors pp 3886–3890

Christophe Mellon,\* René Aspiotis, Cameron W. Black, Christopher I. Bayly, Erich L. Grimm, André Giroux, Yongxin Han, Elise Isabel, Daniel J. McKay, Donald W. Nicholson, Dita M. Rasper, Sophie Roy, John Tam, Nancy A. Thornberry, John P. Vaillancourt, Steven Xanthoudakis and Robert Zamboni

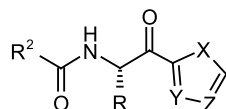


The evolution of capped valine aspartyl ketones as caspase 3 inhibitors is described in terms of the effect of hydrogen bonding and lipophilic interactions on potency and selectivity.

**Ketoheterocycle-based inhibitors of cathepsin K: A novel entry into the synthesis of peptidic ketoheterocycles**

pp 3891–3895

Francis X. Tavares,\* David N. Deaton, Aaron B. Miller, Larry R. Miller and Lois L. Wright

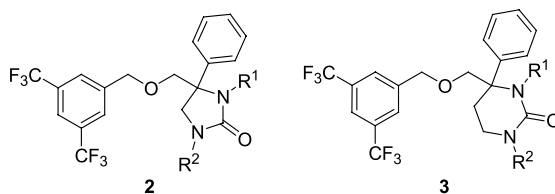


Ketoheterocyclic inhibitors of cathepsin K have been disclosed. SAR of potency enhancing P<sup>2</sup>–P<sup>3</sup> groups coupled with ketoheterocyclic warheads to provide cathepsin K inhibitors have been described. In addition, a novel route to access  $\alpha$ -ketothiazoles using a key thioamide functionality has been disclosed. The mild method employed allows for the presence of diverse functional groups, such as amide and carbamate functionalities, commonly found in protease inhibitors that have peptidomimetic scaffolds. This new method should provide a quick entry into functionally diverse protease inhibitors.

**Cyclic urea derivatives as potent NK<sub>1</sub> selective antagonists**

pp 3896–3899

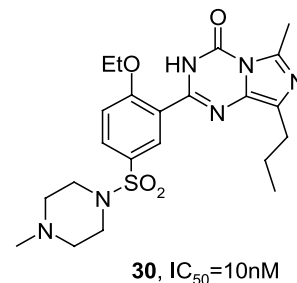
Ho-Jane Shue, Xiao Chen, Neng-Yang Shih,\* David J. Blythin, Sunil Paliwal, Ling Lin, Danlin Gu, John H. Schwerdt, Sapna Shah, Gregory A. Reichard, John J. Piwinski, Ruth A. Duffy, Jean E. Lachowicz, Vicki L. Coffin, Fei Liu, Amin A. Nomeir, Cynthia A. Morgan and Geoffrey B. Varty

**Comparison of different heterocyclic scaffolds as substrate analog PDE5 inhibitors**

pp 3900–3907

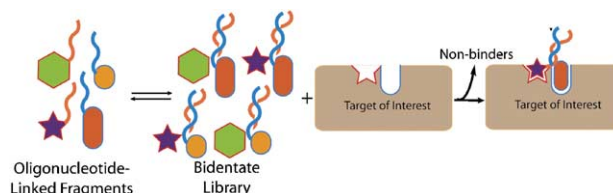
Helmut Haning,\* Ulrich Niewöhner, Thomas Schenke, Thomas Lampe, Alexander Hillisch and Erwin Bischoff

Several different heterocyclic systems were compared as PDE5 inhibitor scaffolds. In addition to the known 3*H*-imidazo[5,1-*f*][1,2,4]triazin-4-ones and pyrazolopyrimidinones, isomeric imidazo[1,5-*a*][1,3,5]triazin-4(3*H*)-ones (e.g., **30**) were also shown to be potent and selective PDE inhibitor scaffolds with in vivo activity. SAR trends were elucidated for sulfonamide derivatives with generality across different scaffolds.

**Self-assembly of bivalent protein-binding agents based on oligonucleotide-linked organic fragments**

pp 3908–3911

K. Ingrid Sprinz, Debarati M. Tagore and Andrew D. Hamilton\*

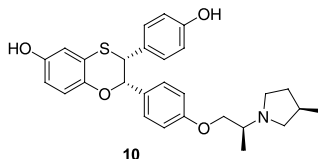


A library of bidentate fragments linked through an oligonucleotide duplex was tested for protein binding. Thermal denaturation experiments showed that the melting temperature, thus stability, of the bidentate binding ligand increased from 59 to 71°C in the presence of protein.

**Estrogen receptor ligands. Part 13: Dihydrobenzoxathiin SERAMs with an optimized antagonist side chain**

pp 3912–3916

Timothy A. Blizzard,\* Frank DiNinno, Helen Y. Chen, Seongkon Kim, Jane Y. Wu, Wanda Chan, Elizabeth T. Birzin, Yi Tien Yang, Lee-Yuh Pai, Edward C. Hayes, Carolyn A. DaSilva, Susan P. Rohrer, James M. Schaeffer and Milton L. Hammond

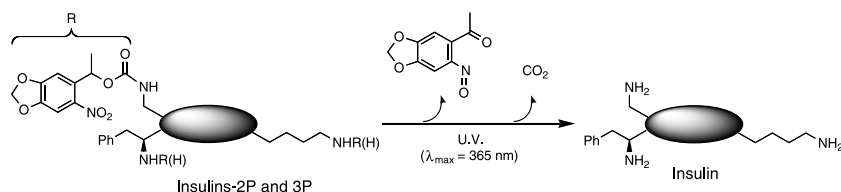


An optimized side chain for dihydrobenzoxathiin SERAMs was discovered and attached to four dihydrobenzoxathiin platforms. The novel SERAMs show exceptional estrogen antagonist activity in uterine tissue and an MCF-7 breast cancer cell assay.

**Synthesis and evaluation of photolabile insulin prodrugs**

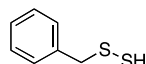
pp 3917–3920

Lian-Sheng Li, Jennie L. Babendure, Subhash C. Sinha,\* Jerrold M. Olefsky\* and Richard A. Lerner\*


**Generation of reactive oxygen species by a persulfide (BnSSH)**

pp 3921–3924

Tonika Chatterji, Kripa Keerthi and Kent S. Gates\*



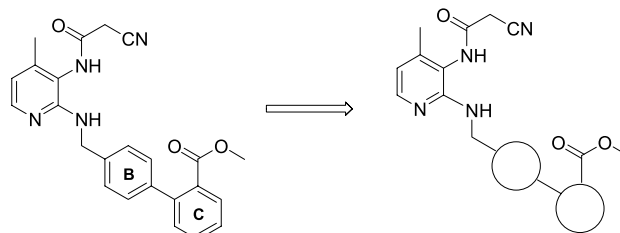
Hydropersulfides ( $RS_2SH$ ) have been implicated as important intermediates in cell-killing by the anticancer natural products leinamycin and varacin. Here experiments with synthetic benzyl hydrodisulfide (BnSSH) provide direct evidence that persulfides readily decompose to yield cytotoxic reactive oxygen species under physiologically relevant conditions.

**Bradykinin B<sub>1</sub> antagonists: SAR studies in the 2,3-diaminopyridine series**

pp 3925–3929

Scott D. Kuduk,\* Ronald K. Chang, Christina Ng, Kathy L. Murphy, Richard W. Ransom, Cuyue Tang, Thomayant Prueksaritanont, Roger M. Freidinger, Douglas J. Pettibone and Mark G. Bock

An SAR analysis of 2,3-diaminopyridine bradykinin B<sub>1</sub> antagonists was carried out and revealed that either of the aromatic rings comprising the biphenyl region could be effectively replaced with non-aromatic carbo- or heterocyclic rings.



**In vitro antiproliferative activity against human colon cancer cell lines of representative 4-thiazolidinones. Part I**

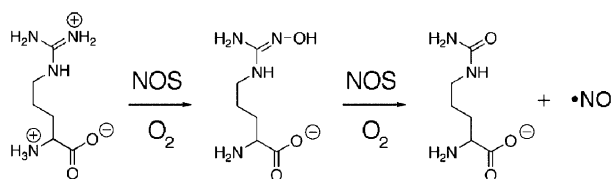
pp 3930–3933

Rosaria Ottanà, Stefania Carotti, Rosanna Maccari, Ida Landini, Giuseppe Chiricosta, Barbara Caciagli, Maria Gabriella Vigorita\* and Enrico Mini

**L-Arginine analogs as alternate substrates for nitric oxide synthase**

pp 3934–3941

Scott D. Luzzi and Michael A. Marletta\*

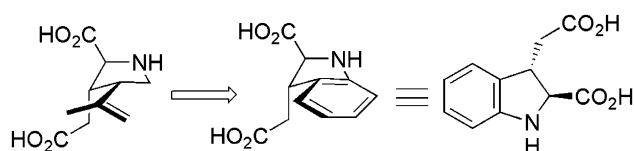


Synthetic *N*<sup>6</sup>-methyl-L-arginine and commercially available L-canavanine were evaluated as alternate substrates of inducible nitric oxide synthase.

**Indole- and indoline-based kainate analogues with antagonist activity at ionotropic glutamate receptors**

pp 3942–3947

Xiaohong Shou, Ricardo Miledi and A. Richard Chamberlin\*



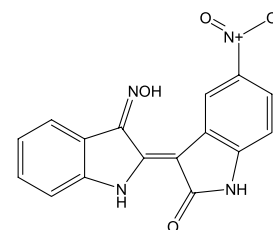
Conformationally constrained, indole/indoline-based analogues based on the well-known glutamate receptor agonist kainic acid were designed and synthesized. Screening for ionotropic glutamate receptor activity showed these compounds to be kainate receptor antagonists, rather than agonists.

**Induction of apoptosis by a novel indirubin-5-nitro-3'-monoxime, a CDK inhibitor, in human lung cancer cells**

pp 3948–3952

Jong-Won Lee, Myoung Ju Moon, Hye-Young Min, Hwa-Jin Chung, Eun-Jung Park, Hyen Joo Park, Ji-Young Hong, Yong-Chul Kim and Sang Kook Lee\*

A novel indirubin analog, indirubin-5-nitro-3'-monoxime, inhibited cell proliferation against various human cancer cells. Additional studies indicate that the mechanism of action of this analog against human lung cancer cells might be to arrest cell cycle progression at G<sub>2</sub>/M phase and induce apoptosis via p53- and mitochondria-dependent pathways.



### Synthesis and in vitro study of novel 7-*O*-acyl derivatives of Oroxylin A as antibacterial agents

pp 3953–3956

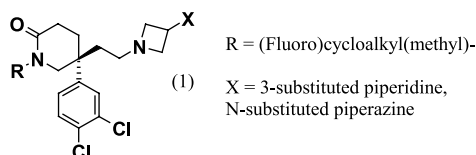
K. Suresh Babu, T. Hari Babu, P. V. Srinivas, B. S. Sastry, K. Hara Kishore, U. S. N. Murty and J. Madhusudana Rao\*

A series of 7-*O*-acyl derivatives of Oroxylin A were prepared and their antibacterial potential is reported.

### Structure–activity relationships of 1-alkyl-5-(3,4-dichlorophenyl)-5-[2-[3-(substituted)-1-azetidiny]-ethyl]-2-piperidones. Part 2: Improving oral absorption

pp 3957–3961

Donald S. Middleton,\* A. Roderick MacKenzie, Sandra D. Newman, Martin Corless, Andrew Warren, Allan P. Marchington and Barry Jones



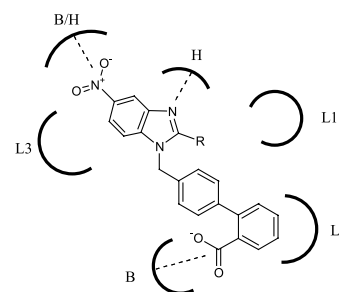
A series of potent NK<sub>2</sub> antagonists (1) with optimised physicochemistry for oral absorption and metabolic stability are described.

### Design, synthesis, and evaluation of novel substituted benzimidazole compounds as angiotensin II receptor antagonists

pp 3962–3965

Alka Bali, Yogita Bansal, M. Sugumaran, Jatinder Singh Saggu, P. Balakumar, Gurpreet Kaur, Gulshan Bansal,\* Ajay Sharma and Manjeet Singh

5-Nitrobenzimidazole coupled through a methylene linker to biphenyl carboxylic acid has been synthesized and evaluated for angiotensin II antagonism activity. On the basis of their higher activity over standard compounds, a binding profile for benzimidazole-based compounds has been proposed. Alkyl group at 2-position has also been optimized with respect to 5-substituent.

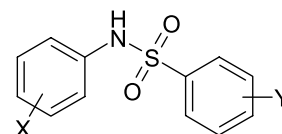


### Study on supramolecular complexing ability vis-à-vis estimation of pK<sub>a</sub> of substituted sulfonamides: Dominating role of Balaban index (*J*)

pp 3966–3973

Alexandru T. Balaban, Padmakar V. Khadikar,\* Claudiu T. Supuran, Abhilash Thakur and Mamta Thakur

The supramolecular complexing ability vis-à-vis pK<sub>a</sub> estimation of a large series of 43 sulfonamides was made using a series of molecular descriptors including topological indices. The set of topological indices chosen also contains Balaban (*J*) and a variety of Balaban type indices: *J*, *J*<sub>2</sub>, *J*<sub>m</sub>, *J*<sub>v</sub>, *J*<sub>c</sub>, and *J*<sub>p</sub>. The results have shown that the most discriminating Balaban index (*J*) in multi-parametric regression analysis combined with indicator parameters yields excellent models and also establishes the superiority of the *J* index over other Balaban type indices. The statistics are improved when one of the indicator parameters is replaced by molar volume. The results are discussed critically using a variety of statistics.



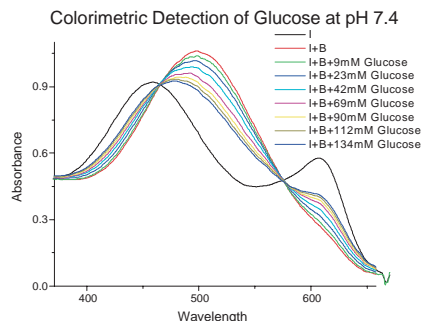


### A colorimetric titration method for quantification of millimolar glucose in a pH 7.4 aqueous phosphate buffer

pp 3974–3977

Serhan Boduroglu, Jouliana M. El Khoury, D. Venkat Reddy, Peter L. Rinaldi and Jun Hu\*

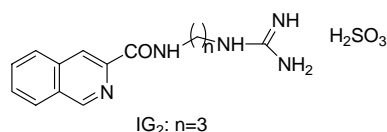
The unusually high binding affinity of 3-pyridinylboronic acid to sugars is reported.



### Synthesis and assay of isoquinoline derivatives as HIV-1 Tat–TAR interaction inhibitors

pp 3978–3981

Meizi He, Dekai Yuan, Wei Lin, Ruifang Pang, Xiaolin Yu and Ming Yang\*



Synthesis and biological evaluation of a series of isoquinoline derivatives are described. The compound IG<sub>2</sub> bearing guanidinium group-terminated side chain can block the HIV-1 Tat–TAR RNA interaction and exhibit the antiviral potency.

## OTHER CONTENTS

### Contributors to this issue

### Summary of instructions to authors 2005

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p III

\*Corresponding author

Supplementary data available via ScienceDirect

## COVER

Schematic of a bidentate biotin ligand binding two adjacent biotin sites on the tetrameric SA. Subunits (red, cyan, blue, and pink) binding biotin (green) through an amine-modified (yellow) DNA duplex. PDB code: streptavidin (1SWG). NDB code: duplex DNA (BDL084). [Sprinz, K. I.; Tagore, D. M.; Hamilton, A. D. *Bioorg. Med. Chem. Lett.* **2005**, 15, 3908.]

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