

Special Section

**David W. Robertson Memorial Issue**

Guest Editor: Albert Robichaud

*Chemical and Screening Sciences, Wyeth Research, Princeton, NJ 08543, USA*

**Contents**

David W. Robertson, In Memoriam

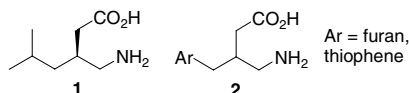
pp 2327–2328

**SPECIAL SECTION COMMUNICATIONS**

**Heteroaromatic side-chain analogs of pregabalin**

pp 2329–2332

Robert M. Schelkun, Po-wai Yuen,\* David J. Wustrow, Jack Kinsora,  
Ti-Zhi Su and Mark G. Vartanian



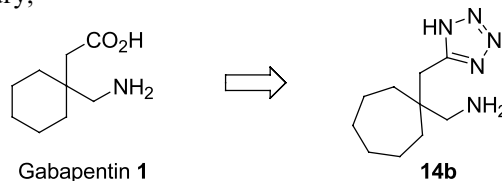
As part of a program to identify the scope of substituents recognized by the  $\alpha_2\text{-}\delta$  protein, a series of heteroaromatic analogs, **2**, of pregabalin, **1**, has been identified that possess anticonvulsant activity in the DBA/2 mouse model. The methods of synthesis and preliminary pharmacology are discussed herein.

**Carboxylate bioisosteres of gabapentin**

pp 2333–2336

Carmen E. Burgos-Lepley, Lisa R. Thompson, Clare O. Kneen, Simon A. Osborne,  
Justin S. Bryans, Thomas Capiris, Nirmala Suman-Chauhan, David J. Dooley,  
Cindy M. Donovan, Mark J. Field, Mark G. Vartanian, Jack J. Kinsora,  
Susan M. Lotarski, Ayman El-Kattan, Karen Walters, Madhu Cherukury,  
Charles P. Taylor, David J. Wustrow and Jacob B. Schwarz\*

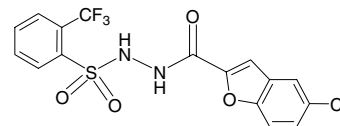
Ring expansion and acid replacement with tetrazole furnished a compound with a similar pattern of activity to gabapentin.



**The design and synthesis of human branched-chain amino acid aminotransferase inhibitors for treatment of neurodegenerative diseases**

pp 2337–2340

Lain-Yen Hu,\* Peter A. Boxer, Suzanne R. Kesten, Huangshu J. Lei, David J. Wustrow, David W. Moreland, Liming Zhang, Kay Ahn, Todd R. Ryder, Xiaohong Liu, John R. Rubin, Kelly Fahnoe, Richard T. Carroll, Satavisha Dutta, Douglass C. Fahnoe, Albert W. Probert, Robin L. Roof, Michael F. Rafferty, Catherine R. Kostlan, Jeffrey D. Scholten, Molly Hood, Xiao-Dan Ren, Gerald P. Schielke, Ti-Zhi Su, Charles P. Taylor, Anil Mistry, Patrick McConnell, Charles Hasemann and Jeffrey Ohren

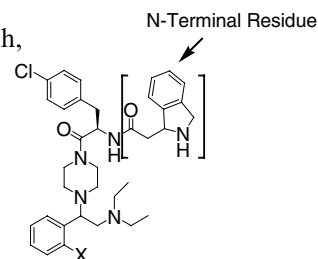


The SAR and pharmacological profile of a series of BCATc inhibitors is described.

**Synthesis and structure–activity relationships of novel dipeptides and reduced dipeptides as ligands for melanocortin subtype-4 receptor**

pp 2341–2346

Qing Shi,\* Paul L. Ornstein, Karin Briner, Timothy I. Richardson, Macklin B. Arnold, Ryan T. Backer, Jennifer L. Buckmaster, Emily J. Canada, Christopher W. Doecke, Larry W. Hertel, Nick Honigschmidt, Hansen M. Hsiung, Saba Husain, Steve L. Kuklish, Michael J. Martinelli, Jeffrey T. Mullaney, Thomas P. O'Brien, Matt R. Reinhard, Roger Rothhaar, Jikesh Shah, Zhipei Wu, Chaoyu Xie, John M. Zgombick and Matthew J. Fisher



The synthesis and SAR studies on the N-terminal residue of the 'address element' are reported.

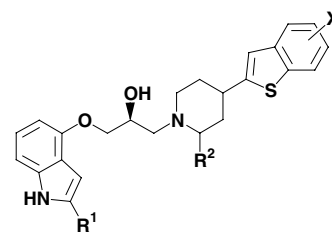
**Advances toward new antidepressants beyond SSRIs: Part 5**

pp 2347–2351

**1-Aryloxy-3-piperidinylpropan-2-ols with dual 5-HT<sub>1A</sub> receptor antagonism/SSRI activities**

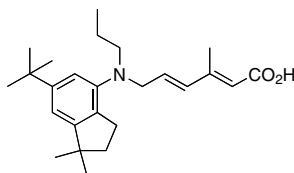
Kumiko Takeuchi,\* Todd J. Kohn, Nicholas A. Honigschmidt, Vincent P. Rocco, Patrick G. Spinazze, Susan K. Hemrick-Luecke, Linda K. Thompson, David C. Evans, Kurt Rasmussen, Deanna Koger, David Lodge, Laura J. Martin, Janice Shaw, Penny G. Threlkeld and David T. Wong

A series of 1-aryloxy-3-piperidinylpropan-2-ols possessing potent dual 5-HT<sub>1A</sub> receptor antagonism and serotonin reuptake inhibition was discovered. 1-(1*H*-Indol-4-yloxy)-3-(4-benzo[*b*]thiophen-2-ylpiperidinyl)propan-2-ols exhibited selective and high affinities at the 5-HT<sub>1A</sub> receptor and serotonin reuptake site in vitro. In vivo evaluation of this series of compounds demonstrated elevated extracellular serotonin levels from the basal and quick recovery of neuron firing that was presumably suppressed by the initial acute activation of 5-HT<sub>1A</sub> somatodendritic autoreceptors.


**Aza-retinoids as novel retinoid X receptor-specific agonists**

pp 2352–2356

Luc J. Farmer,\* Kristen S. Marron, Stacie S. Canan Koch, C. K. Hwang, E Adam Kallel, Lin Zhi, Alex M. Nadzan, Dave W. Robertson and Youssef L. Bennani\*

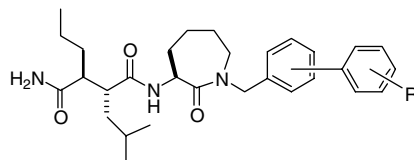


A new structurally simple series of potent lipophilic aza-retinoid RXR agonists has been developed. SAR studies for the *N*-alkyl-azadienoic acids described here demonstrate that the RXR activity profile is sensitive to the *N*-alkyl chain length. Further, we have expanded the work to include azadienoic acids, which exhibited many accessible conformations leading to a better understanding of the SAR around the series.

**Synthesis and evaluation of succinoyl-caprolactam  $\gamma$ -secretase inhibitors**

pp 2357–2363

Lorin A. Thompson,\* Ann Y. Liauw, Mercy M. Ramanjulu, Padmaja Kasireddy-Polam, Stephen E. Mercer, Thomas P. Maduskuie, Marcie Glicksman, Arthur H. Roach, Jere E. Meredith, Rui-Qin Liu, Andrew P. Combs, Jeffrey N. Higaki, Barbara Cordell, Dietmar Seiffert, Robert C. Zaczek, David W. Robertson and Richard E. Olson

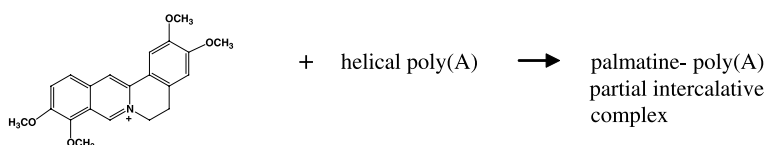


The synthesis, evaluation, and structure–activity relationships of a series of succinoyl lactam inhibitors of the Alzheimer's disease  $\gamma$ -secretase are described.

**REGULAR COMMUNICATIONS****RNA specific molecules: Cytotoxic plant alkaloid palmatine binds strongly to poly(A)**

pp 2364–2368

Prabal Giri, Maidul Hossain and Gopinatha Suresh Kumar\*

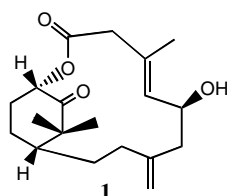


Palmatine, the plant alkaloid, binds strongly to single stranded (ss) poly(A) by mechanism of partial intercalation, leading to its usefulness in inhibition of gene expression in eukaryotic cells.

**Cespitulactones A and B, new diterpenoids from *Cespitularia taeniata***

pp 2369–2372

Ya-Ching Shen,\* Ching-Jen Ho, Yao-Haur Kuo and Yun-Sheng Lin



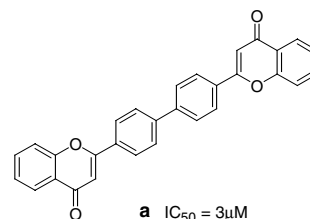
Two new diterpenoids, designated cespitulactones A (**1**) and B, were isolated from *Cespitularia taeniata* collected in Taiwan.

**Synthesis of phospholipase A<sub>2</sub> inhibitory biflavonoids**

pp 2373–2375

Jianjun Chen, Hyeun Wook Chang,\* Hyun Pyo Kim and Haeil Park\*

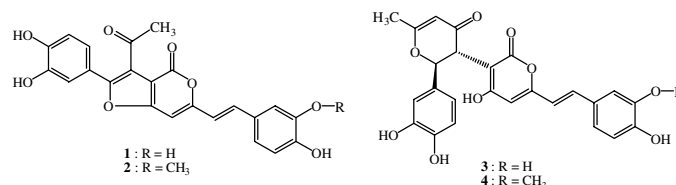
A series of C–C biflavones was designed to investigate the relationship between structural array of a different flavone–flavone subunit linkage and the inhibitory activity against phospholipase A<sub>2</sub> (PLA<sub>2</sub>). Among six classes of C–C biflavones designed, four classes of C–C biflavones, which have flavone–flavone subunit linkages at A ring–A ring, A ring–B ring, B ring–B ring, and B ring–C ring, were synthesized. The synthetic biflavones exhibited somewhat different inhibitory activities against sPLA<sub>2</sub>-IIA. Among them, the biflavone **a** having a C–C 4'–4' linkage showed comparable inhibitory activity with that of the natural biflavonoid, ochonaflavone, and 7-fold stronger activity than that of amentoflavone. Further chemical modification is being carried out in order to obtain the chemically optimized biflavonoids.



**Hispidin analogs from the mushroom *Inonotus xeranticus* and their free radical scavenging activity**

pp 2376–2379

In-Kyoung Lee and Bong-Sik Yun\*

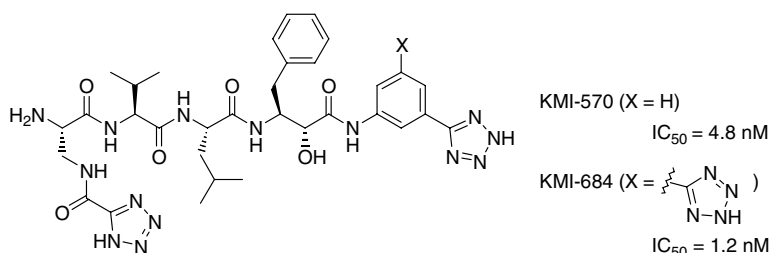


Three new free radical scavengers (**1**, **2**, and **4**) were isolated from the methanolic extract of the fruiting bodies of *Inonotus xeranticus* (Hymenochaetaceae), along with the known compound davallialactone (**3**). Their structures were established as hispidin analogs by extensive NMR spectral data. Compounds **3** and **4** displayed significant scavenging activity against the superoxide radical anion, ABTS radical cation, and DPPH radical, while **1** and **2** exhibited potent antioxidant effect only against ABTS radical cation.

**Design and synthesis of potent  $\beta$ -secretase (BACE1) inhibitors with P<sub>1</sub>' carboxylic acid bioisosteres**

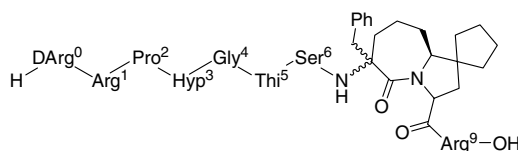
pp 2380–2386

Tooru Kimura, Yoshio Hamada, Monika Stochaj, Hayato Ikari, Ayaka Nagamine, Hamdy Abdel-Rahman, Naoto Igawa, Koushi Hidaka, Jeffrey-Tri Nguyen, Kazuki Saito, Yoshio Hayashi and Yoshiaki Kiso\*

**Bradykinin antagonists modified with dipeptide mimetic  $\beta$ -turn inducers**

pp 2387–2390

Maria C. Alcaro, Valerio Vinci, Anna M. D'Ursi, Mario Scrima, Mario Chelli, Sandro Giuliani, Stefania Meini, Marcello Di Giacomo, Lino Colombo and Anna Maria Papini\*

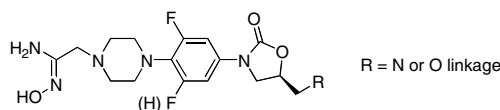


A structure–activity relationship study of Icatibant analogues modified with dipeptide mimetic  $\beta$ -turn inducers is reported.

**Synthesis and antibacterial activity of novel oxazolidinones bearing *N*-hydroxyacetamidine substituent**

pp 2391–2395

Mohamed Takhi,\* C. Murugan, M. Munikumar, K. M. Bhaskarreddy, Gurpreet Singh, K. Sreenivas, M. Sitaramkumar, N. Selvakumar, J. Das, Sanjay Trehan and Javed Iqbal

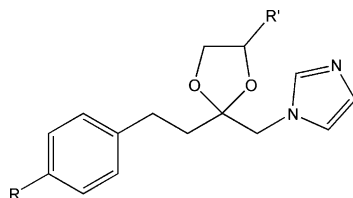


The synthesis of oxazolidinones possessing *N*-hydroxyacetamidine group on piperazine scaffold and their in vitro antibacterial activity profile are disclosed herein.

**Anti-*Plasmodium* activity of imidazole–dioxolane compounds**

pp 2396–2406

Jason Z. Vlahakis, Robert T. Kinobe, Kanji Nakatsu, Walter A. Szarek\* and Ian E. Crandall\*



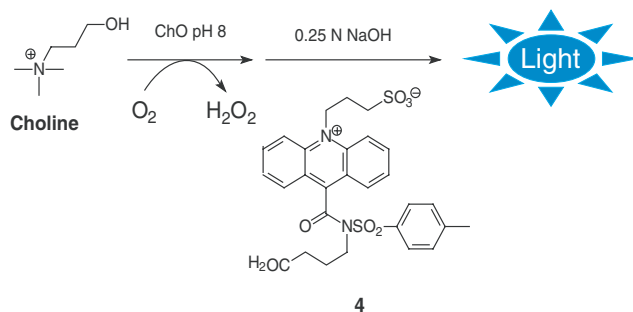
A series of imidazole–dioxolane compounds were assayed for inhibitory activity in *Plasmodium falciparum* cultures.

**Rapid high-throughput detection of peroxide with an acridinium-9-carboxamide:**

pp 2407–2410

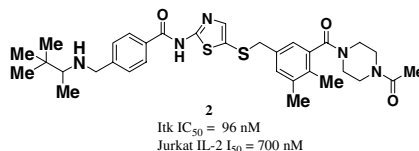
**A homogeneous chemiluminescent assay for plasma choline**

Maciej Adamczyk,\* R. Jeffrey Brashear and Phillip G. Mattingly

**Discovery and SAR of 2-amino-5-[(thiomethyl)aryl]thiazoles as potent and selective Itk inhibitors**

pp 2411–2415

Jagabandhu Das,\* Chunjian Liu,\* Robert V. Moquin, James Lin, Joseph A. Furch, Steven H. Spergel, Kim W. McIntyre, David J. Shuster, Kathleen D. O'Day, Becky Penhallow, Chen-Yi Hung, Steven B. Kanner, Tai-An Lin, John H. Dodd, Joel C. Barrish and John Wityak

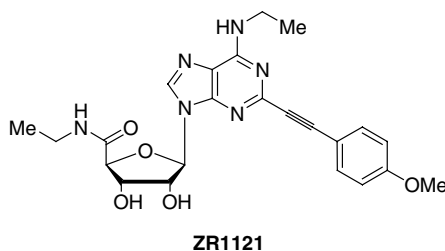


A series of structurally novel aminothiazole based small molecule inhibitors of Itk were prepared to elucidate their structure–activity relationships (SARs), selectivity, and cell activity in inhibiting IL-2 secretion in a Jurkat T-cell assay. Compound **2** is identified as a potent and selective Itk inhibitor which inhibits anti-TCR antibody induced IL-2 production in mice in vivo.

**N<sup>6</sup>-Ethyl-2-alkynyl NECAs, selective human A<sub>3</sub> adenosine receptor agonists**

pp 2416–2418

Ran Zhu, Cynthia R. Frazier, Joel Linden and Timothy L. Macdonald\*



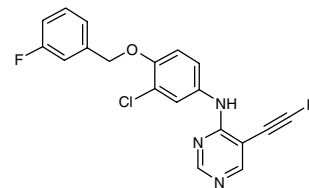
A new adenosine analogue ZR1121 is reported. Compared with currently widely used hA<sub>3</sub> agonists IB MECA and Cl-IB MECA, this compound has similar activity and about 100 times higher hA<sub>3</sub>/hA<sub>1</sub> selectivity.

**Alkynyl pyrimidines as dual EGFR/ErbB2 kinase inhibitors**

pp 2419–2422

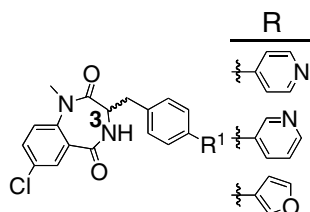
Alex G. Waterson,\* Kirk L. Stevens, Michael J. Reno, Yue-Mei Zhang, Eric E. Boros, Frederic Bouvier, Abdullah Rastagar, David E. Uehling, Scott H. Dickerson, Bryan Reep, Ochterloney B. McDonald, Edgar R. Wood, David W. Rusnak, Krystal J. Alligood and Sharon K. Rudolph

Anilinoalkynylpyrimidines were prepared and evaluated as dual EGFR/ErbB2 kinase inhibitors. A preference was found for substituted phenyl and heteroaromatic rings attached to the alkyne. In addition, the presence of a potential hydrogen bond donor appended to this ring was favored. Selected molecules in the series demonstrated some activity against human tumor cell lines.

**Identification of cytotoxic, T-cell-selective 1,4-benzodiazepine-2,5-diones**

pp 2423–2427

Tasha M. Francis, Thomas B. Sundberg, Joanne Cleary, Todd Groendyke, Anthony W. Pipari, Jr. and Gary D. Glick\*

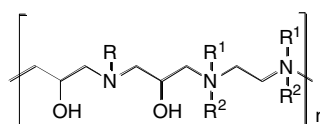


A 1,4-benzodiazepine-2,5-dione (BZD) library was evaluated for lymphotoxic members. When the C3 substituent contains an electron-rich heterocycle, the resulting BZDs have sub-micromolar potency and are selective for T-cells.

**Synthesis of lipopolyhydroxylalkyleneamines for gene delivery**

pp 2428–2432

Qun Li, Guisheng Zhang, Joie Marhefka, Marina V. Kameneva and Dexi Liu\*



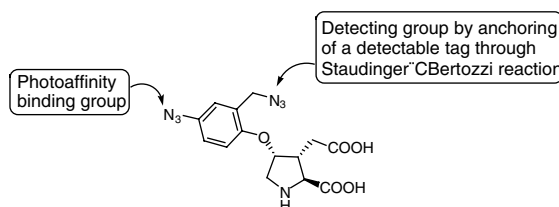
$R^1, R^2 = \text{H or } \text{CH}_3$   
 $R = \text{Methyl, Hexyl, Octadecyl, Dodecyl, 4-Dodecylphenyl}$   
 $n = 5-10$

A series of new lipopolyhydroxylalkyleneamines was synthesized and their activity in gene delivery was characterized.

**Synthesis of a bis-azido analogue of acromelic acid for radioisotope-free photoaffinity labeling and biochemical studies**

pp 2433–2436

Pi Sun, Guang Xing Wang,\* Kyoji Furuta and Masaaki Suzuki

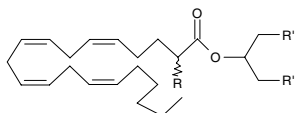


A novel bis-azido-containing acromelic acid analogue with the aromatic  $\text{N}_3$  acting as a photoaffinity group and the alkyl  $\text{N}_3$  group acting as a detecting group was designed and synthesized as a potential radioisotope-free biochemical probe for studies on kainoid receptors.

**$\alpha$ -Methylated derivatives of 2-arachidonoyl glycerol: Synthesis, CB1 receptor activity, and enzymatic stability**

pp 2437–2440

Teija Parkkari,\* Mikko Myllymäki, Juha R. Savinainen, Susanna M. Saario,  
Joel A. Castillo-Meléndez, Jarmo T. Laitinen, Tapio Nevalainen,  
Ari M.P. Koskinen and Tomi Järvinen

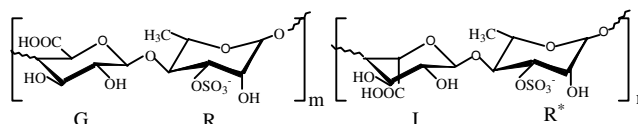


- 1a R=(R)-methyl, R'=R''=OH  
1b R=(S)-methyl, R'=R''=OH  
2a R=(R)-methyl, R'=OH, R''=F  
2b R=(S)-methyl, R'=OH, R''=F  
3a R=(R)-methyl, R'=R''=F  
3b R=(S)-methyl, R'=R''=F

**In vitro antioxidant activity of acetylated and benzoylelated derivatives of polysaccharide extracted from *Ulva pertusa* (Chlorophyta)**

pp 2441–2445

Huimin Qi, Quanbin Zhang,\* Tingting Zhao, Rugui Hu, Kun Zhang and Zhien Li



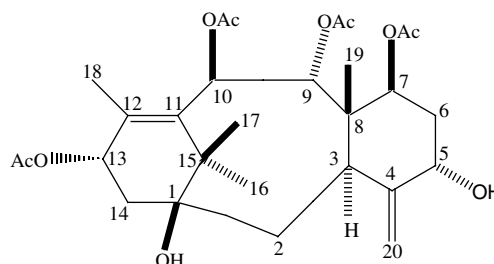
Acetylated and benzoylelated ulvans were prepared and their in vitro antioxidant activities were determined.

**Taxoid from the needles of the Himalayan yew *Taxus wallichiana* with cytotoxic and immunomodulatory activities**

pp 2446–2449

Sunil K. Chattopadhyay,\* Anirban Pal, Prakas R. Maulik, Tanpreet Kaur,  
Ankur Garg and Suman Preet S. Khanuja

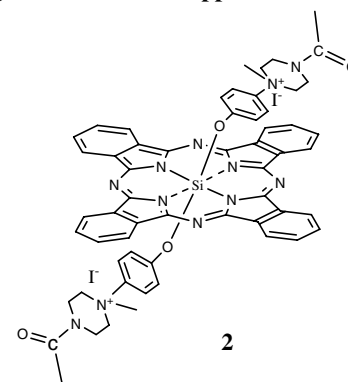
From the needles of *Taxus wallichiana*, a taxoid was isolated, characterized and its cytotoxic and immunomodulatory activities were evaluated.

**Preparation and in vitro photodynamic activities of novel axially substituted silicon (IV) phthalocyanines and their bovine serum albumin conjugates**

pp 2450–2453

Xiong-Jie Jiang, Jian-Dong Huang,\* Yu-Jiao Zhu, Fen-Xiang Tang,  
Dennis K. P. Ng and Jian-Cheng Sun

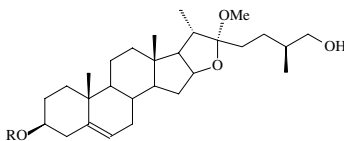
The new silicon (IV) phthalocyanine **2** was found to be essentially non-aggregated and strongly fluorescent in water. The compound and its non-covalent bovine serum albumin conjugate (2-BSA) exhibited extremely high photodynamic activities toward B16 melanoma cancer cell line with IC<sub>50</sub> values down to 33 and 38 nM, respectively.



**Synthesis and antitumor activity of icogenin and its analogue**

pp 2454–2458

Shujie Hou, Peng Xu, Liang Zhou, Dequan Yu and Pingsheng Lei\*

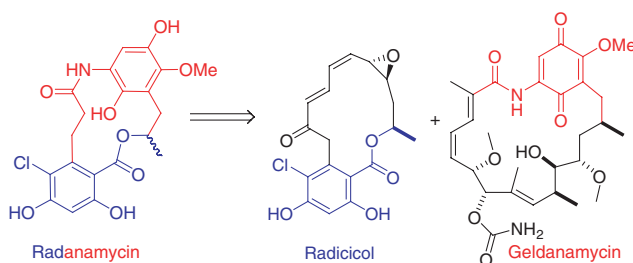


Icogenin: R =  $\alpha$ -L-rhamnopyranosyl-(1  $\rightarrow$  2)-[  $\beta$ -D-glucopyranosyl(1  $\rightarrow$  3)]- $\beta$ -D-glucopyranosyl (**1**). The designed analogue of icogenin: R =  $\alpha$ -L-rhamnopyranosyl-(1  $\rightarrow$  2)-[ $\beta$ -D-glucopyranosyl(1  $\rightarrow$  3)]- $\alpha$ -D-glucopyranosyl (**2**).

**Radanamycin, a macrocyclic chimera of radicicol and geldanamycin**

pp 2459–2462

Mingwen Wang, Gang Shen and Brian S. J. Blagg\*



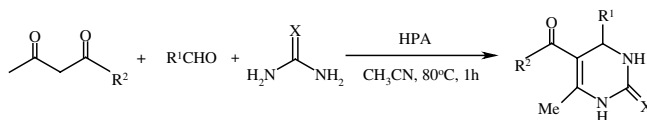
A chimera of radicicol and geldanamycin has been prepared and evaluated against MCF-7 breast cancer cells.

**A practical and green approach towards synthesis of dihydropyrimidinones:**

pp 2463–2466

Using heteropoly acids as efficient catalysts

Ezzat Rafiee\* and Hadi Jafari

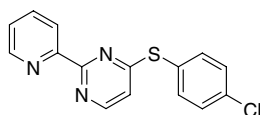


One-pot synthesis of dihydropyrimidinones catalyzed by heteropoly acids as efficient, inexpensive, easily available and environmentally friendly catalysts. High to excellent yields, short reaction times and compatibility with various functional groups are features of this new procedure.

**Structure–activity relationship of thiopyrimidines as mGluR5 antagonists**

pp 2467–2469

Lance G. Hammerland, Martin Johansson, Jonas Malmström, Jan P. Mattsson, Alexander B. E. Minidis,\* Karolina Nilsson, Alecia Peterson, David Wensbo, Andreas Wållberg\* and Krister Österlund



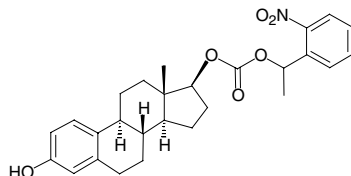
Structure–activity relationship investigation of thiopyrimidines as mGluR5 antagonists.



**Caged gene-inducer spatially and temporally controls gene expression and plant development in transgenic Arabidopsis plant**

pp 2470–2474

Ken-ichiro Hayashi,\* Kazuya Hashimoto, Naoyuki Kusaka, Atsushi Yamazoe, Hidehiro Fukaki, Masao Tasaka and Hiroshi Nozaki\*

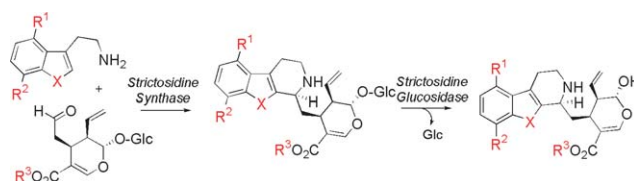


Two caged steroids were synthesized as caged gene-inducers and applied to transgenic plants harboring steroid-inducible gene activation systems. Light could control the spatial and temporal expression of transgene and plant development.

**Substrate specificity of strictosidine synthase**

pp 2475–2478

Elizabeth McCoy, M. Carmen Galan and Sarah E. O'Connor\*



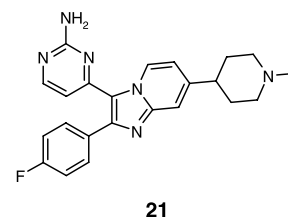
The substrate requirements for strictosidine synthase are systematically and quantitatively examined and the enzymatically generated compounds are processed by the second enzyme in this natural product biosynthetic pathway.

**Synthesis and SAR studies of very potent imidazopyridine antiprotozoal agents**

pp 2479–2483

Tefaye Biftu,\* Dennis Feng, Michael Fisher, Gui-Bai Liang, Xiaoxia Qian, Andrew Scribner, Richard Dennis, Shuliang Lee, Paul A. Liberator, Chris Brown, Anne Gurnett, Penny S. Leavitt, Donald Thompson, John Mathew, Andrew Misura, Samantha Samaras, Tamas Tamas, Joseph F. Sina, Kathleen A. McNulty, Crystal G. McKnight, Dennis M. Schmatz and Matthew Wyvrat

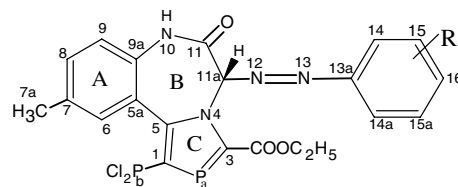
Compounds **10a** (IC<sub>50</sub> 110 pM) and **21** (IC<sub>50</sub> 40 pM) are the most potent inhibitors of *Eimeria tenella* cGMP-dependent protein kinase activity reported to date and are efficacious in the in vivo antiparasitic assay when administered to chickens at 12.5 and 6.25 ppm levels in the feed. However, both compounds are positive in the Ames microbial mutagenesis assay which precludes them from further development as antiprotozoal agents in the absence of negative lifetime rodent carcinogenicity studies.

**21****Studies on synthesis and evaluation of quantitative structure–activity relationship of 10-methyl-6-oxo-5-arylo-6,7-dihydro-5H-[1,3]azaphospholo[1,5-d][1,4]benzodiazepin-2-phospho-3-ethoxycarbonyl-1-phosphorus dichlorides**

pp 2484–2491

Ashok Kumar,\* Pratibha Sharma, V. K. Gurram and Nilesh Rane

A series of [1,3]azaphospholo [1,5-d][1,4] benzodiazepin-3-ethoxycarbonyl-1-phosphorus dichlorides have been synthesized. Their chemical structures are confirmed by spectral and elemental analysis data. These synthesized compounds are subjected to antimicrobial activity using ampicillin and clotrimazole as reference antibiotic drugs. Quantitative structure–activity relationship (QSAR) investigations are applied to find the correlation between evaluated biological activities and physicochemical descriptors. Significant correlations are obtained between biological activity and the polarizability parameter (MR) of the compounds studied.

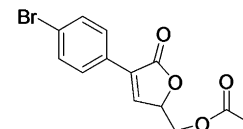


### Investigation of the mechanism of action of 3-(4-bromophenyl)-5-acyloxymethyl-2,5-dihydrofuran-2-one against *Candida albicans* by flow cytometry

pp 2492–2495

Luís A. Vale-Silva,\* Vladimír Buchta, Doris Vokurková and Milan Pour

Preliminary investigations on the mechanism of action of 3-(4-bromophenyl)-5-acyloxymethyl-2,5-dihydrofuran-2-one against *Candida albicans* by flow cytometry, using PI, DiBAC<sub>4</sub> (3), and FUN-1, and determination of the kinetics of growth inhibition are reported.

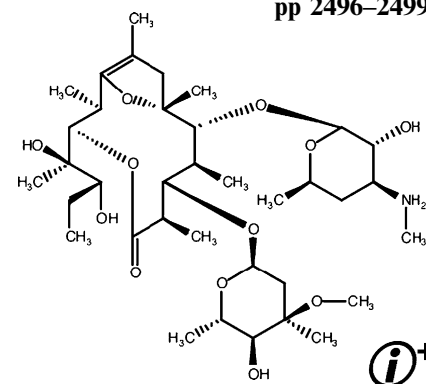


### Three-dimensional solution structure of EM703 with potent promoting activity of monocyte-to-macrophage differentiation

pp 2496–2499

Hiroaki Gouda,\* Toshiaki Sunazuka, Kiminari Yoshida, Akihiro Sugawara, Yusuke Sakoh, Satoshi mura and Shuichi Hirono

The three-dimensional structural features of EM703, which might be important for its potent promoting activity of monocyte-to-macrophage differentiation, are reported.

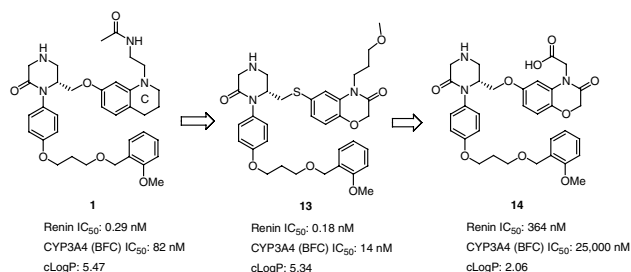


### Ketopiperazine-based renin inhibitors: Optimization of the “C” ring

pp 2500–2504

Daniel D. Holsworth,\* Cuiman Cai, Xue-Min Cheng, Wayne L. Cody, Dennis M. Downing, Noe Erasga, Chitase Lee, Noel A. Powell, Jeremy J. Edmunds, Michael Stier, Mehran Jalaie, Erli Zhang, Pat McConnell, Michael J. Ryan, John Bryant, Tingsheng Li, Aparna Kasani, Eric Hall, Rajendra Subedi, Mohammad Rahim and Samarendra Maiti

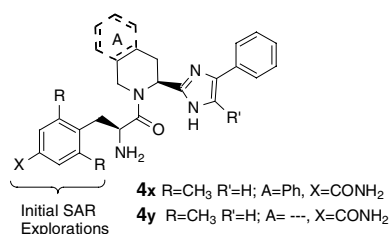
A series of ketopiperazine-based renin inhibitors designed to interact in the S<sub>3</sub> sub-pocket of the renin protein were evaluated for renin inhibitory activity. The investigation revealed that linear and sterically small side chain substituents are preferred in the S<sub>3</sub> sub-pocket for optimal renin inhibition. Polar groups in the S<sub>3</sub> sub-pocket were not well tolerated and caused a reduction in renin inhibitory activity. Further, compounds with clogP's 3 demonstrated a dramatic reduction in CYP3A4 inhibitory activity.



### Identification of potent phenyl imidazoles as opioid receptor agonists

pp 2505–2508

Henry J. Breslin,\* Chaozhong Cai, Tamara A. Miskowski, Santosh V. Coutinho, Sui-Po Zhang, Pamela Hornby and Wei He

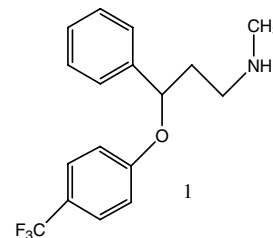


**The spermicidal and antitrichomonas activities of SSRI antidepressants**

pp 2509–2512

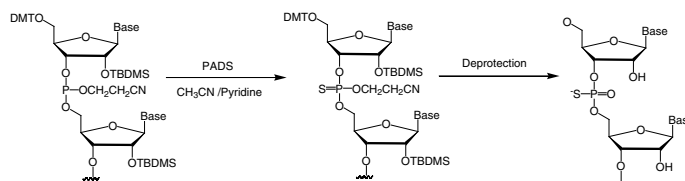
V. S. Kiran Kumar S. T., Vishnu Lal Sharma,\* Pratibha Tiwari, Divya Singh, Jagdamba Prasad Maikhuri, Gopal Gupta and Man Mohan Singh

The study investigated spermicidal and antitrichomonas activities of selective serotonin reuptake inhibitor (SSRI) antidepressants with a view to generate new lead for development of dual-function spermicidal microbicides, which is an urgent global need. Fluoxetine-HCl (**1**) was found to be most promising among the SSRIs studied.

**Development of siRNA for therapeutics: Efficient synthesis of phosphorothioate RNA utilizing phenylacetyl disulfide (PADS)**

pp 2513–2517

Vasulinga T. Ravikumar,\* Mark Andrade, Recaldo L. Carty, Amy Dan and Steve Barone

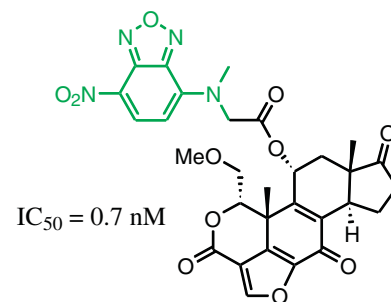


Efficient synthesis of phosphorothioate RNA (PS-RNA) is demonstrated by using phenylacetyl disulfide (PADS) in a mixture of pyridine and acetonitrile (1:1, v/v) for 3 min. Sulfurization is achieved with >99.8% stepwise efficiency. This reagent also performs well during synthesis of RNA containing PS:PO mixed backbone.

**Synthesis of fluorescent derivatives of wortmannin and demethoxyviridin as probes for phosphatidylinositol 3-kinase**

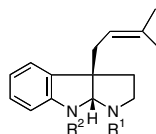
pp 2518–2521

José-Luis Giner,\* Karen A Kehbein, James A. Cook, Michele C. Smith, Chris J. Vlahos and John A. Badwey

**Antibacterial activity of (–)-deoxypseudophrynaminol versus its racemate and derivatives**

pp 2522–2524

Andrew V. Dix, Carly M. Meseck, Adam J. Lowe and Miguel O. Mitchell\*

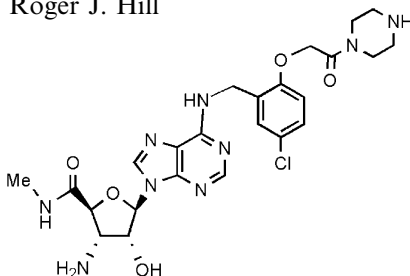


(–)-(3a*S*,8a*S*)-Deoxypseudophrynaminol ( $R^1 = \text{CH}_3$ ,  $R^2 = \text{H}$ ) has 43-fold greater antibacterial potency than the racemate at 40  $\mu\text{g/mL}$  against *Staphylococcus aureus*. When  $R^1 = \text{CO}_2\text{CH}_3$  and  $R^2 = \text{prenyl}$ , there is no antibacterial activity, but there is weak antibacterial activity when  $R^1 = \text{CH}_3$  and  $R^2 = \text{prenyl}$ .



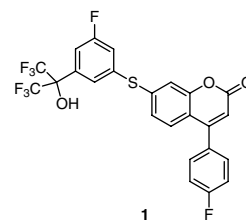
**The synthesis of highly potent, selective, and water-soluble agonists at the human adenosine A<sub>3</sub> receptor pp 2525–2527**

Michael P. DeNinno,\* Hiroko Masamune, Lois K. Chenard, Kenneth J. DiRico, Cynthia Eller, John B. Etienne, Jeanene E. Tickner, Scott P. Kennedy, Delvin R. Knight, Jimmy Kong, Joseph J. Oleynek, W. Ross Tracey and Roger J. Hill

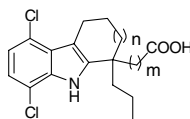
**Substituted coumarins as potent 5-lipoxygenase inhibitors****pp 2528–2531**

Erich L. Grimm,\* Christine Brideau, Nathalie Chauret, Chi-Chung Chan, Daniel Delorme, Yves Ducharme, Diane Ethier, Jean-Pierre Falguyret, Richard W. Friesen, Jocelyne Guay, Pierre Hamel, Denis Riendeau, Chantal Soucy-Breau, Philip Tagari and Yves Girard

A novel series of substituted coumarin derivatives has been synthesized. SAR studies in this series led to the identification of inhibitor **1**.

**Design and synthesis of 2,3,4,9-tetrahydro-1*H*-carbazole and 1,2,3,4-tetrahydro-cyclopenta[*b*]indole derivatives as non-nucleoside inhibitors of hepatitis C virus NS5B RNA-dependent RNA polymerase****pp 2532–2534**

Ariamala Gopalsamy,\* Mengxiao Shi, Gregory Ciszewski, Kaapjoo Park, John W. Ellingboe, Mark Orlowski, Boris Feld and Anita Y. M. Howe

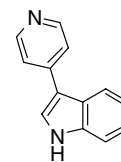


A novel class of HCV NS5B RNA dependent RNA polymerase inhibitors containing 2,3,4,9-tetrahydro-1*H*-carbazole and 1,2,3,4-tetrahydro-cyclopenta[*b*]indole scaffolds and their structure–activity relationship are described.

**Low molecular weight indole fragments as IMPDH inhibitors****pp 2535–2538**

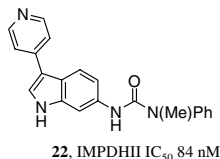
Rebekah E. Beevers, George M. Buckley, Natasha Davies, Joanne L. Fraser, Francis C. Galvin, Duncan R. Hannah,\* Alan F. Haughan, Kerry Jenkins, Stephen R. Mack, William R. Pitt, Andrew J. Ratcliffe, Marianna D. Richard, Verity Sabin, Andrew Sharpe and Sophie C. Williams

The study of non-oxazole containing indole fragments as inhibitors of inosine monophosphate dehydrogenase (IMPDH) is described. The synthesis and in vitro inhibitory values for IMPDH II are discussed.

**5**, IMPDHII IC<sub>50</sub> 1.15 μM

**Novel indole inhibitors of IMPDH from fragments: Synthesis and initial structure–activity relationships** pp 2539–2542

Rebekah E. Beevers, George M. Buckley, Natasha Davies, Joanne L. Fraser, Francis C. Galvin, Duncan R. Hannah,\* Alan F. Haughan, Kerry Jenkins, Stephen R. Mack, William R. Pitt, Andrew J. Ratcliffe, Marianna D. Richard, Verity Sabin, Andrew Sharpe and Sophie C. Williams



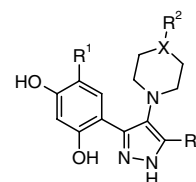
The elaboration of previously reported indole fragments as inhibitors of inosine monophosphate dehydrogenase (IMPDH) is described. The synthesis, in vitro inhibitory values for IMPDH II, PBMC proliferation and physicochemical properties are discussed.

**4-Amino derivatives of the Hsp90 inhibitor CCT018159**

pp 2543–2548

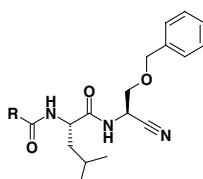
Xavier Barril, Mandy C. Beswick, Adam Collier, Martin J. Drysdale,\* Brian W. Dymock, Alexandra Fink, Kate Grant, Robert Howes, Allan M. Jordan, Andrew Massey, Allan Surgenor, Joanne Wayne, Paul Workman and Lisa Wright

Novel piperazinyl, morpholino and piperidyl derivatives of the pyrazole-based Hsp90 inhibitor CCT018159 have been prepared and the observed SAR explained by X-ray co-crystallography with Human Hsp90. The most potent of the new compounds has an IC<sub>50</sub> of less than 600 nM against the enzyme and demonstrates low micromolar inhibition of tumour cell proliferation.

**Dipeptide nitrile inhibitors of cathepsin K**

pp 2549–2554

Eva Altmann,\* Reiner Aichholz, Claudia Betschart, Thomas Buhl, Jonathan Green, René Lattmann and Martin Missbach

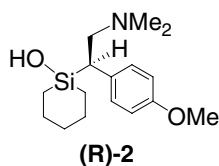


A series of dipeptidyl nitriles as inhibitors of cathepsin K have been explored starting from lead structure **1** (Cbz–Leu–NH–CH<sub>2</sub>–CN, IC<sub>50</sub> = 39 nM). Attachment of non-natural amino acid side chains in P1 and modification of the P3 subunit led to inhibitors with higher potency and improved pharmacokinetic properties.

**(R)-Sila-venlafaxine: A selective noradrenaline reuptake inhibitor for the treatment of emesis**

pp 2555–2558

Graham A. Showell,\* Matthew J. Barnes, Jürgen O. Daiss, John S. Mills, John G. Montana, Reinhold Tacke and Julie B. H. Warneck



The in vitro profile and in vivo anti-emetic activity of the selective noradrenaline reuptake inhibitor (R)-2 are reported.



**OTHER CONTENTS****Corrigendum****p 2559****Summary of instructions to authors****p I**

\*Corresponding author

①\* Supplementary data available via ScienceDirect

**COVER**

Reagents and Conditions (Fm = 9-fluorenylmethyl): (a) HATU, DIEA, DMF, rt; (b) 25% piperidine in DMF, repeat; (c) caprolactam, PyBOP, DIEA, DMF, rt, repeat; (d) Boronic acid, Pd(PPh<sub>3</sub>)<sub>4</sub>, THF, 2 M Na<sub>2</sub>CO<sub>3</sub>, 60 °C, 16 h; (e) 50% TFA/DCM, rt. [Thompson, L. A.; Liauw, A. Y.; Ramanjulu, M. M.; Kasireddy-Polam, P.; Mercer, S. E.; Maduskuie, T. P.; Glicksman, M.; Roach, A. H.; Meredith, J. E.; Liu, R-Q.; Combs, R. C.; Higaki, J. N.; Cordell, B.; Seiffert, D.; Zaczek, R. C.; Robertson, D. W. Olson, R. E. *Bioorg. Med. Chem. Lett.* **2006**, 16, 2357.]



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