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# Bioorganic & Medicinal Chemistry Letters

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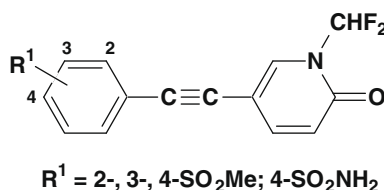
## Bioorganic & Medicinal Chemistry Letters Vol. 19, No. 3, 2009

### Contents

#### ARTICLES

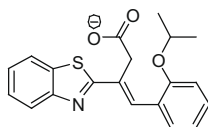
- Synthesis of 1-(methanesulfonyl- and aminosulfonylphenyl)acetylenes that possess a 2-(*N*-difluoromethyl-1,2-dihydropyridin-2-one) pharmacophore: Evaluation as dual inhibitors of cyclooxygenases and 5-lipoxygenase with anti-inflammatory activity** pp 584–588

Morshed Alam Chowdhury, Khaled R. A. Abdellatif, Ying Dong, Moshfiquir Rahman, Dipankar Das, Mavanur R. Suresh, Edward E. Knaus\*



- Discovery of novel inhibitors of *Trypanosoma cruzi* trans-sialidase from in silico screening** pp 589–596

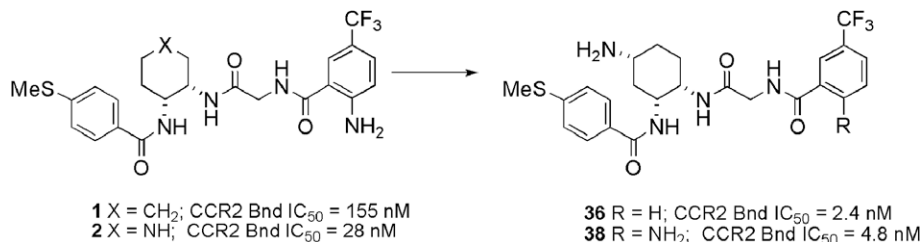
João Neres\*, Mark L. Brewer, Laura Ratier, Horacio Botti, Alejandro Buschiazzi, Philip N. Edwards, Paul N. Mortenson, Michael H. Charlton, Pedro M. Alzari, Alberto C. Frasch, Richard A. Bryce\*, Kenneth T. Douglas



Novel inhibitors of *Trypanosoma cruzi* trans-sialidase, discovered from in silico screening, are reported.

- Discovery of trisubstituted cyclohexanes as potent CC chemokine receptor 2 (CCR2) antagonists** pp 597–601

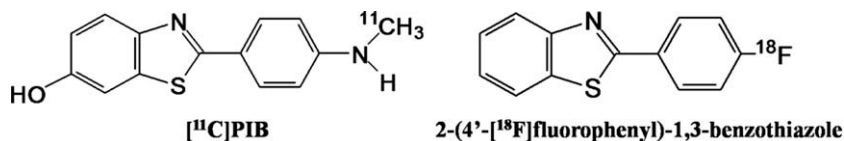
Robert J. Cherney\*, John B. Brogan, Ruowei Mo, Yvonne C. Lo, Gengjie Yang, Persymphonie B. Miller, Peggy A. Scherle, Bruce F. Molino, Percy H. Carter, Carl P. Decicco



### Synthesis of $^{18}\text{F}$ -labelled 2-(4'-fluorophenyl)-1,3-benzothiazole and evaluation as amyloid imaging agent in comparison with $[^{11}\text{C}]\text{PIB}$

pp 602–605

K. Serdons\*, T. Verduyck, D. Vanderghinste, J. Cleynhens, P. Borghgraef, P. Vermaelen, C. Terwinghe, F. Van Leuven, K. Van Laere, H. Kung, G. Bormans, A. Verbruggen

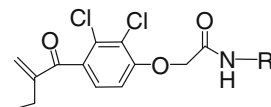


2-(4'- $[^{18}\text{F}]$ fluorophenyl)-1,3-benzothiazole was synthesized as derivative of  $[^{11}\text{C}]\text{PIB}$  to overcome the limitations associated with the short half-life of the carbon-11 label and was biologically evaluated in comparison with PIB.

### Amide derivatives of ethacrynic acid: Synthesis and evaluation as antagonists of Wnt/ $\beta$ -catenin signaling and CLL cell survival

pp 606–609

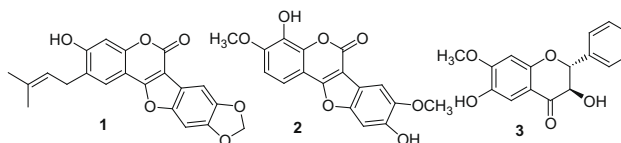
Guangyi Jin, Desheng Lu, Shiyin Yao, Christina C. N. Wu, Jerry X. Liu, Dennis A. Carson, Howard B. Cottam\*



### Osteogenic activity of constituents from *Butea monosperma*

pp 610–613

Rakesh Maurya\*, Dinesh K. Yadav, Geetu Singh, Biju Bhargavan, P. S. Narayana Murthy, Mahendra Sahai, Man Mohan Singh



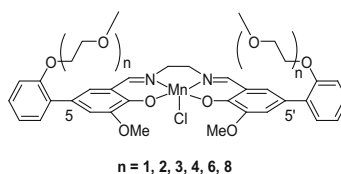
Three new compounds named buteaspermin A (1), buteaspermin B (2) and buteaspermanol (3), along with 19 known compounds were isolated from the stem bark of *Butea monosperma*. Five of these compounds 7, 10–13 showed promising osteogenic activity.



### Effect of the oligo(ethylene glycol) group on the antioxidant activity of manganese salen complexes

pp 614–617

Wonchoul Park, Dongyeol Lim\*



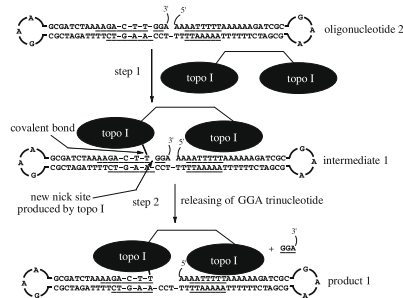
The SOD activities of oligo(ethylene glycol) derivatives of manganese salen complexes were similar and slightly more potent than the standard compound EUK-134. Their catalase-like activity was lower than that of EUK-134 in the initial conversion rate; however, some analogs exhibited a better catalytic turnover number.



**Nick-containing oligonucleotides as human topoisomerase I inhibitors**

pp 618–623

Sock Teng Chua, Ngee Mien Quek\*, Ming Li, Magdeline Tao Tao Ng, Weixing Yuan, May Ling Chua, Juanjuan Guo, Li Eng Koh, Ruijuan Ye, Tianhu Li\*

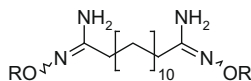


Here, we report oligonucleotides with various lengths that contain nick and topoisomerase I-binding sites as human topoisomerase I inhibitors.

**Design and synthesis of amidoxime derivatives for orally potent C-alkylamidine-based antimalarial agents**

pp 624–626

Mahama Ouattara, Sharon Wein, Séverine Denoyelle, Stéphanie Ortial, Thierry Durand, Roger Escalé, Henri Vial, Yen Vo-Hoang\*

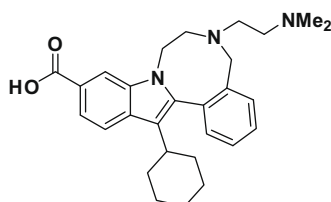


Specific *O*-substitutions of amidoximes are needed to design orally potent *C*-alkylamidine-based antimalarial agents.

**Tetracyclic indole inhibitors of hepatitis C virus NS5B-polymerase**

pp 627–632

Ian Stansfield\*, Caterina Ercolani, Angela Mackay, Immacolata Conte, Marco Pompei, Uwe Koch, Nadia Gennari, Claudio Giuliano, Michael Rowley, Frank Narjes

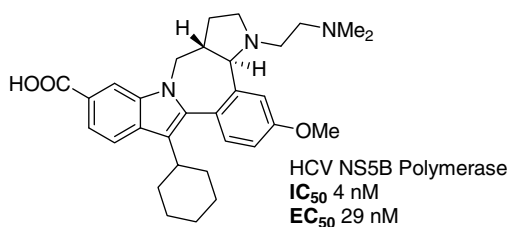


The evolutionary path is reported to conformationally constrained indole inhibitors of HCV NS5B-polymerase. Biochemical and cell-based potency was achieved, coupled with attractive DMPK properties—leading ultimately to the identification of a pre-clinical candidate with an excellent predicted human pharmacokinetic profile.

**Discovery of pentacyclic compounds as potent inhibitors of hepatitis C virus NS5B RNA polymerase**

pp 633–638

Jörg Habermann\*, Elena Capitò, Maria del Rosario Rico Ferreira, Uwe Koch, Frank Narjes

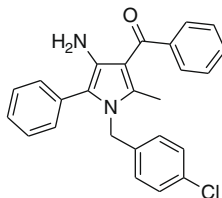


The synthesis and SAR of pentacyclic indoles as potent inhibitors of HCV NS5B polymerase is reported.

### Synthesis and characterization of a peripherally restricted CB<sub>1</sub> cannabinoid antagonist, URB447, that reduces feeding and body-weight gain in mice

pp 639–643

Jesse LoVerme, Andrea Duranti, Andrea Tontini, Gilberto Spadoni, Marco Mor, Silvia Rivara, Nephi Stella, Cong Xu, Giorgio Tarzia\*, Daniele Piomelli\*



URB447

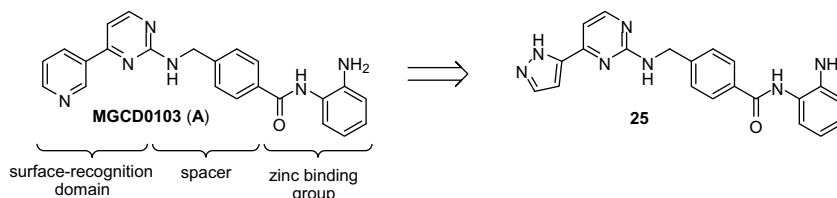
Synthesis and in vivo pharmacology of the first mixed CB<sub>1</sub> antagonist/CB<sub>2</sub> agonist, URB447, which reduces food intake in rats with a peripheral mechanism, are reported.



### SAR and biological evaluation of analogues of a small molecule histone deacetylase inhibitor N-(2-aminophenyl)-4-((4-(pyridin-3-yl)pyrimidin-2-ylamino)methyl)benzamide (MGCD0103)

pp 644–649

Stéphane Raeppe\*, Nancy Zhou, Frédéric Gaudette, Silvana Leit, Isabelle Paquin, Guillaume Larouche, Oscar Moradei, Sylvie Fréchette, Ljubomir Isakovic, Daniel Delorme, Marielle Fournel, Ann Kalita, Aihua Lu, Marie-Claude Trachy-Bourget, Pu Theresa Yan, Jianhong Liu, Jubrail Rahil, James Wang, Jeffrey M. Besterman, Koji Murakami, Zuomei Li, Arkadii Vaisburg

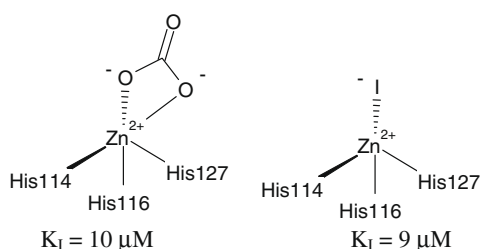


Analogues of the clinical compound **MGCD0103 (A)** were designed, synthesized, and evaluated in multiple in vitro assays. Lead molecule of the series, compound **25** showed significant anti-tumor activity in vivo in different mouse tumor xenograft models upon oral dosing.

### Carbonic anhydrase inhibitors: Inhibition studies of a coral secretory isoform with inorganic anions

pp 650–653

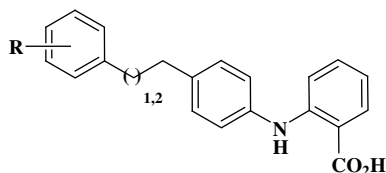
Anthony Bertucci, Alessio Innocenti, Didier Zoccola\*, Andrea Scozzafava, Denis Allemand, Sylvie Tambutti, Claudiu T. Supuran\*



### The synthesis and structure–activity relationship of substituted N-phenyl anthranilic acid analogs as amyloid aggregation inhibitors

pp 654–657

Lloyd J. Simons, Bradley W. Caprathe, Michael Callahan, James M. Graham, Takenori Kimura, Yingjie Lai, Harry LeVine III, William Lipinski, Annette T. Sakkab, Yoshikazu Tasaki, Lary C. Walker, Tomoyuki Yasunaga, Yuyang Ye, Nian Zhuang, Corinne E. Augelli-Szafran\*

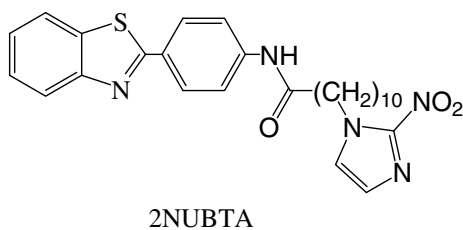


It is believed that  $\beta$ -amyloid aggregation is an important event in the development of Alzheimer's disease. In the course of our studies to identify  $\beta$ -amyloid aggregation inhibitors, a series of N-phenyl anthranilic acid analogs were synthesized and studied for  $\beta$ -amyloid inhibition activity. The synthesis, structure–activity relationship, and in vivo activity of these analogs are discussed.

**Synthesis and biological evaluation of radioiodinated 2NUBTA as a cerebral ischemia marker**

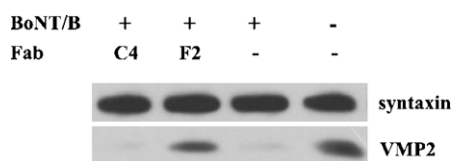
pp 658–661

Taiwei Chu\*, Zejun Li, Xiangyun Wang

**Selection and characterization of a human monoclonal neutralizing antibody for *Clostridium Botulinum* neurotoxin serotype B**

pp 662–664

Heyue Zhou, Bin Zhou, Sabine Pellett, Eric A. Johnson, Kim D. Janda\*

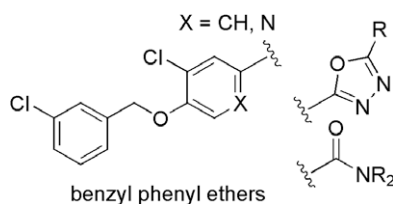


A human neutralizing antibody was selected from a naïve phage display library that specifically binds Botulinum neurotoxin serotype B. Biochemical studies provide evidence for its therapeutic potential and further development.

**Discovery and SAR of benzyl phenyl ethers as inhibitors of bacterial phenylalanyl-tRNA synthetase**

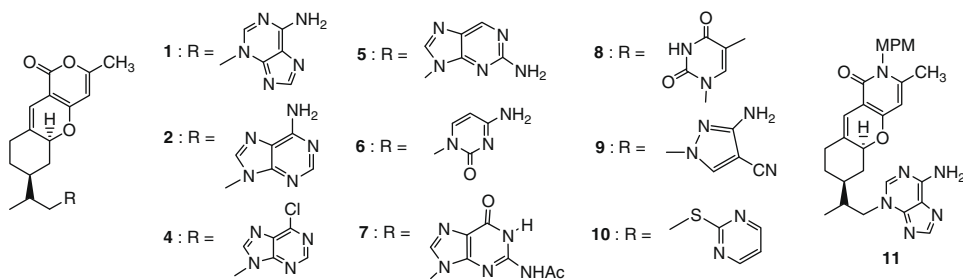
pp 665–669

Justin I. Montgomery\*, Peter L. Toogood, Kim M. Hutchings, Jia Liu, Lakshmi Narasimhan, Timothy Braden, Michael R. Dermeyer, Angela D. Kulynych, Yvonne D. Smith, Joseph S. Warmus, Clarke Taylor

**Syntheses of tricyclic pyrones and pyridinones and protection of Aβ-peptide induced MC65 neuronal cell death**

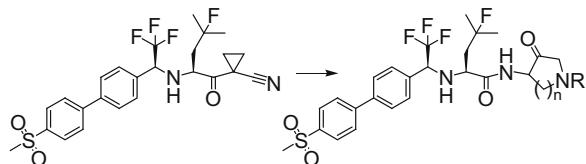
pp 670–674

Sandeep Rana, Hyun-Seok Hong, Lydia Barrigan, Lee-Way Jin, Duy H. Hua\*



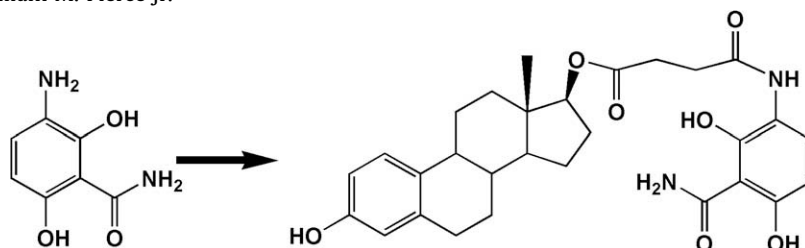
### Investigation of ketone warheads as alternatives to the nitrile for preparation of potent and selective cathepsin K inhibitors pp 675–679

Michael J. Boyd\*, Sheldon N. Crane, Joël Robichaud, John Scheigetz, W. Cameron Black, Nathalie Chauret, Qingping Wang, Frédéric Massé, Renata M. Oballa



### Bone selective effect of an estradiol conjugate with a novel tetracycline-derived bone-targeting agent pp 680–683

Jason R. Neale, Natali B. Richter, Kevyn E. Merten, K. Grant Taylor, Sujun Singh, Leonard C. Waite, Nicole K. Emery, Ned B. Smith, Jian Cai, William M. Pierce Jr. \*



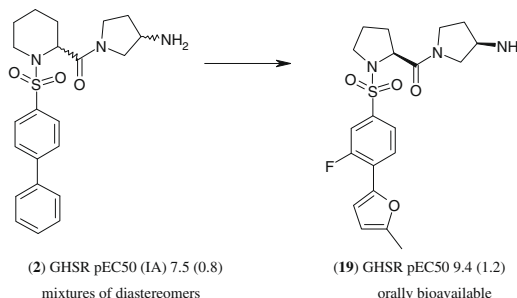
A novel bone-targeting agent containing elements of the tricarbonylmethane system of ring A of tetracycline was developed and conjugated to estradiol, resulting in a bone-targeted estrogen.



### Aryl sulphonyl amides as potent agonists of the growth hormone secretagogue (ghrelin) receptor pp 684–687

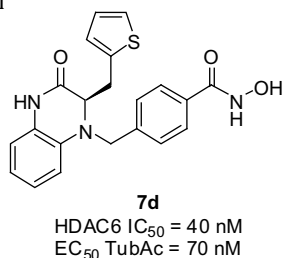
Jason Witherington\*, Lee Abberley, Benjamin R. Bellenie, Rio Boatman, Katharine Collis, David K. Dean, Alessandra Gaiba, N. Paul King, Nicola Shuker, Jon G. A. Steadman, Andrew K. Takle, Gareth Sanger, Sharon Butler, Fiona McKay, Alison Muir, Kim Winborn, Robert W. Ward, Tom D. Heightman

As part of an on-going lead optimisation effort, a cross screening exercise identified an aryl sulphonyl amide hit that was optimised to afford a highly potent series of ghrelin receptor agonists that displayed evidence of systemic exposure following oral administration.



### Novel HDAC6 isoform selective chiral small molecule histone deacetylase inhibitors pp 688–692

David V. Smil\*, Sukhdev Manku, Yves A. Chantigny, Silvana Leit, Amal Wahhab, Theresa P. Yan, Marielle Fournel, Christiane Maroun, Zuomei Li, Anne-Marie Lemieux, Alina Nicolescu, Jubrail Rahil, Sylvain Lefebvre, Anthony Panetta, Jeffrey M. Besterman, Robert Déziel

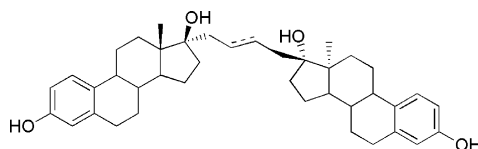


A number of potent (IC<sub>50</sub> = 10–200 nM) and highly selective HDAC6 inhibitors are reported.

**Estradiol dimers as a new class of steroid sulfatase reversible inhibitors**

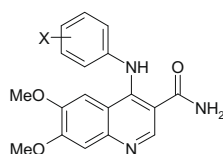
pp 693–696

Diane Fournier, Donald Poirier\*

**Identification of 3-amido-4-anilinoquinolines as potent and selective inhibitors of CSF-1R kinase**

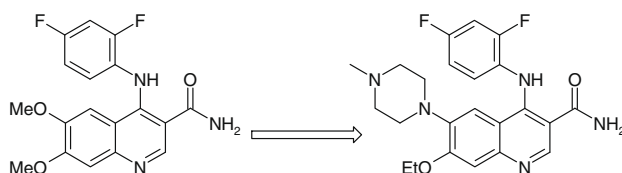
pp 697–700

David A. Scott\*, Carrie L. Balliet, Donald J. Cook, Audrey M. Davies, Thomas W. Gero, Charles A. Omer, Srinivasu Poondru, Maria-Elena Theoclitou, Boris Tyurin, Michael J. Zinda

**3-Amido-4-anilinoquinolines as CSF-1R kinase inhibitors 2: Optimization of the PK profile**

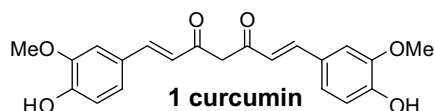
pp 701–705

David A. Scott\*, Kirsten J. Bell, Cheryl T. Campbell, Donald J. Cook, Les A. Dakin, David J. Del Valle, Lisa Drew, Thomas W. Gero, Maureen M. Hattersley, Charles A. Omer, Boris Tyurin, Xiaolan Zheng

**Curcumin is a potent DNA hypomethylation agent**

pp 706–709

Zhongfa Liu\*, Zhiliang Xie, William Jones, Ryan E. Pavlovicz, Shujun Liu, Jianhua Yu, Pui-kai Li, Jiayuh Lin, Jame R. Fuchs, Guido Marcucci, Chenglong Li, Kenneth K. Chan



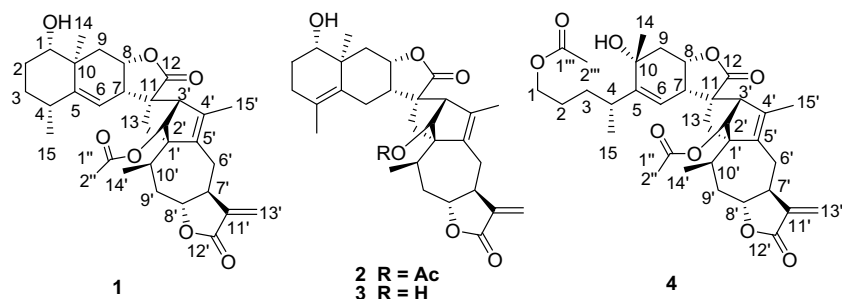
A potent dietary DNA methylation inhibitor, curcumin **1** ( $EC_{50}$  = 30 nM) and its hypomethylation activity on MV4-11 cells (15–20% decrease in global DNA methylation) is reported.



**Japonicones A–D, bioactive dimeric sesquiterpenes from *Inula japonica* Thunb.**

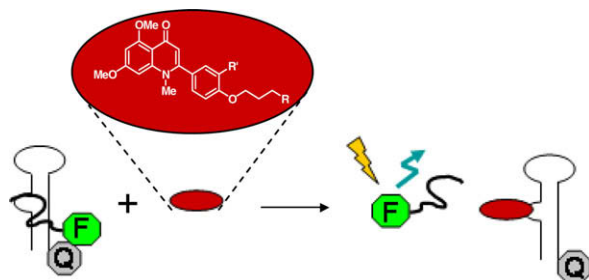
pp 710–713

Jiang Jiang Qin, Hui Zi Jin, Jian Jun Fu, Xiao Jia Hu, Yan Wang, Shi Kai Yan\*, Wei Dong Zhang\*

**Synthesis and biological evaluation of 2-phenylquinolones targeted at Tat/TAR recognition**

pp 714–717

Giuseppe Manfroni, Barbara Gatto\*, Oriana Tabarrini, Stefano Sabatini, Violetta Cecchetti, Giulia Giarretta, Cristina Parolin, Claudia Del Vecchio, Arianna Calistri, Manlio Palumbo, Arnaldo Fravolini

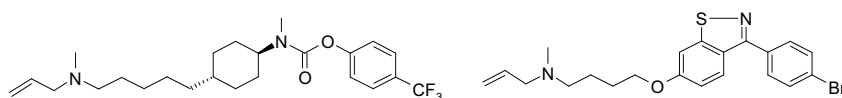


Fluorescence quenching analysis demonstrates that 2-phenylquinolone derivatives efficiently inhibit Tat/TAR recognition.

**Oxidosqualene cyclase from *Saccharomyces cerevisiae*, *Trypanosoma cruzi*, *Pneumocystis carinii* and *Arabidopsis thaliana* expressed in yeast: A model for the development of novel antiparasitic agents**

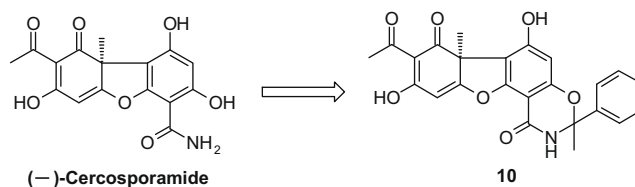
pp 718–723

Gianni Balliano\*, Henrietta Dehmlow\*, Simonetta Oliaro-Bosso, Matilde Scaldaferrì, Silvia Taramino, Franca Viola, Giulia Caron, Johannes Aebi, Jean Ackermann

**(–)-Cercosporamide derivatives as novel antihyperglycemic agents**

pp 724–726

Akihiro Furukawa\*, Tsuyoshi Arita, Susumu Satoh, Kazushi Araki, Masanori Kuroha, Jun Ohsumi



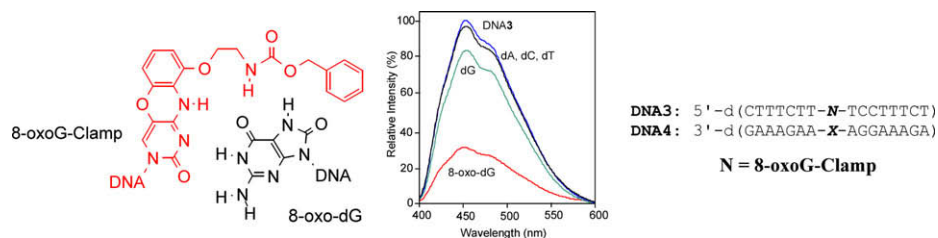
The syntheses of (–)-Cercosporamide derivatives and their plasma glucose lowering effects are reported.



**Selective fluorescence quenching of the 8-oxoG-clamp by 8-oxodeoxyguanosine in ODN**

pp 727–730

Tamer Nasr, Zhichun Li, Osamu Nakagawa, Yosuke Taniguchi, Sayaka Ono, Shigeki Sasaki \*

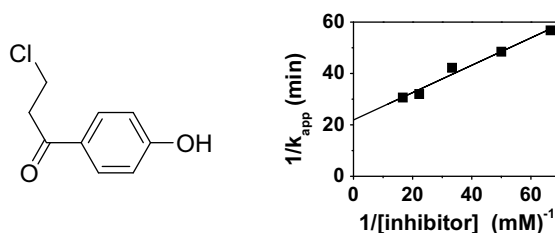


The 8-oxoG-clamp, a specific fluorescence probe for 2'-deoxy-8-oxoguanosine (8-oxo-dG) in solutions, was incorporated into the ODN, which was shown to be a selective fluorescence probe for 8-oxo-dG in DNA.

**Inactivation of GABA transaminase by 3-chloro-1-(4-hydroxyphenyl)propan-1-one**

pp 731–734

Yun-Hai Tao, Hui-Bi Xu, Xiang-Liang Yang \*

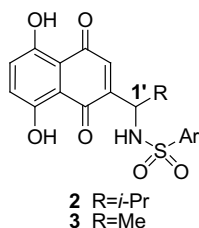


3-Chloro-1-(4-hydroxyphenyl)propan-1-one (**9**) was found to inactivate potently the enzyme in a time-dependent manner.

**Synthesis and biological activity of novel shikonin analogues**

pp 735–737

Wenjing Wang, Mei Dai, Caihua Zhu, Jiangang Zhang, Liping Lin, Jian Ding \*, Wenhua Duan \*



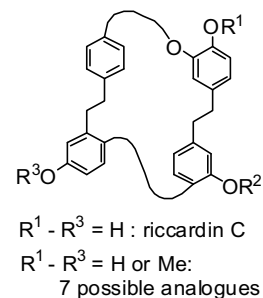
A series of shikonin analogues have been synthesized, these new analogues showed substantial in vitro antitumor activity.

**Synthesis of riccardin C and its seven analogues. Part 1: The role of their phenolic hydroxy groups as LXR $\alpha$  agonists**

pp 738–741

Hideaki Hioki, Naoki Shima, Kota Kawaguchi, Kenich Harada, Miwa Kubo, Tomoyuki Esumi, Tomoko Nishimaki-Mogami, Jun-ichi Sawada, Toshihiro Hashimoto, Yoshinori Asakawa, Yoshiyasu Fukuyama \*

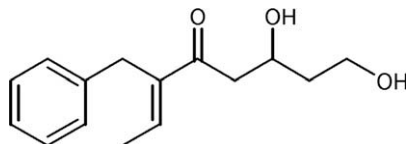
Riccardin C and its 7 analogues were synthesized. The structure–activity relationship of these compounds indicated that all hydroxy groups in riccardin C are essential for its binding to LXR $\alpha$ .



### Benzylidihydroxyoctenone, a novel anticancer agent, induces apoptosis via mitochondrial-mediated pathway in androgen-sensitive LNCaP prostate cancer cells

pp 742–744

Hong Sang Moon, Haeyoung Lim, Sangik Moon, Ha Lim Oh, Young-Tae Kim, Min Kyoung Kim, Chul-Hoon Lee \*

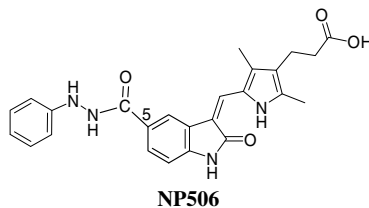


The chemical structure and nomenclature of F3-2-5, (E)-3-benzyl-6,8-dihydroxyoct-2-en-4-one.

### 5-Substituted pyrido[2,3-d]pyrimidine, an inhibitor against three receptor tyrosine kinases

pp 745–750

Naparat Kammasud, Chantana Boonyarat, Kingkan Sanphanya, Maleeruk Utsintong, Satoshi Tsunoda, Hiroaki Sakurai, Ikuo Saiki, Isabelle André, David S. Grierson, Opa Vajragupta \*

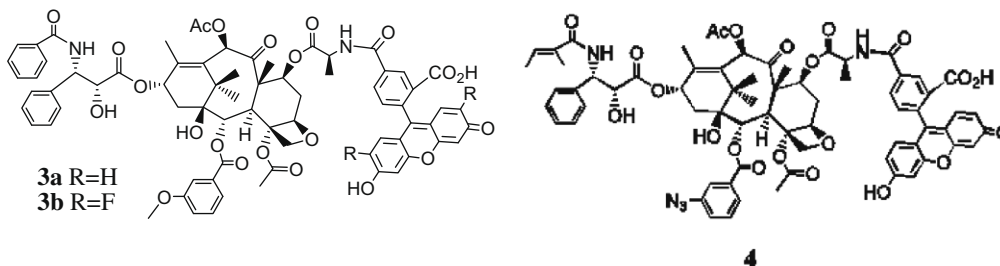


The introduction of the phenyl hydrazide motif to the position 5 of the pyrido[2,3-d]pyrimidine scaffold in NP506 led to the inhibitory effect in two signaling pathway: inhibition of AKT activation in the phosphatidylinositol 3'-kinase (PI3K)/AKT signaling pathway and the inhibition of ERK and JNK activation in MAPK pathway.

### Synthesis and biological activities of high affinity taxane-based fluorescent probes

pp 751–754

Xuan Li, Isabel Barasoain, Ruth Matesanz, J. Fernando Díaz \*, Wei-Shuo Fang \*

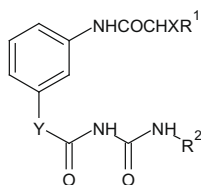


Three fluorescent probes **3a**, **3b**, and **4** have been synthesized through conjugation of fluorescein and difluorescein groups to the 7-OH of C-2 modified paclitaxel and cephalomannine derivatives with very high affinity to microtubules. All these probes exhibited potent tubulin assembly promotion and tumor cell killing activities.

### Synthesis and activity evaluation of benzoylurea derivatives as potential antiproliferative agents

pp 755–758

Dan-Qing Song, Yue-Ming Wang, Na-Na Du, Wei-Ying He, Ke-Liang Chen, Gui-Fang Wang, Peng Yang, Lian-Zong Wu, Xue-Bo Zhang, Jian-Dong Jiang \*



X = Cl, Br; R<sup>1</sup> = H, CH<sub>3</sub>; Y = CH<sub>2</sub>, CH=CH;

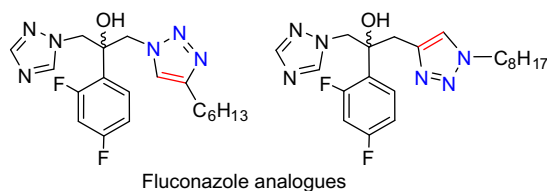
R<sup>2</sup> = methyl, phenyl, 3,4,5-trimethoxyphenyl, 3,4-methylenedioxyphenyl, 2-pyridyl



**Synthesis and antifungal activity of 1,2,3-triazole containing fluconazole analogues**

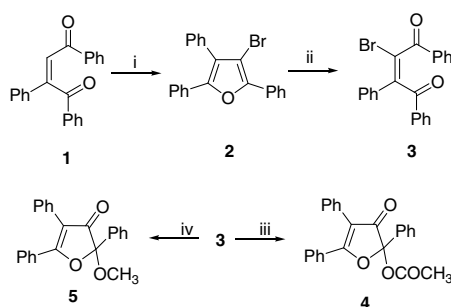
pp 759–763

Nilkanth G. Aher, Vandana S. Pore\*, Nripendra N. Mishra, Awanit Kumar, Praveen K. Shukla, Aanchal Sharma, Manoj K. Bhat

**Preliminary investigations on the synthesis and antitumor activity of 3(2H)-furanones**

pp 764–765

J. P. Rappai, V. Raman, P. A. Unnikrishnan, S. Prathapan\*, S. K. Thomas, C. S. Paulose

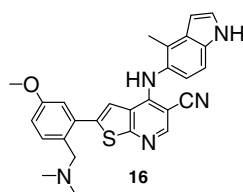


Synthesis and antitumor activity of two triaryl-3(2H)-furanones is reported.

**Second generation 4-(4-methyl-1H-indol-5-ylamino)-2-phenylthieno[2,3-b]pyridine-5-carbonitrile PKC $\theta$  inhibitors**

pp 776–769

Biqi Wu, Diane H. Boschelli\*, Julie Lee, Xiaoke Yang, Divya Chaudhary

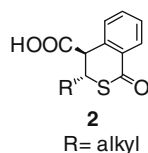


The 4-(4-methyl-1H-indol-5-ylamino)thieno[2,3-b]pyridine-5-carbonitrile **16** had an IC<sub>50</sub> of 16 nM for the inhibition of PKC $\theta$  activity.

**1-Oxo-3-substitute-isothiochroman-4-carboxylic acid compounds: Synthesis and biological activities of FAS inhibition**

pp 770–772

Xiaokui Wang, Guoming Zhao, Yao Chen, Xiaowei Xu, Wu Zhong, Lili Wang, Song Li\*

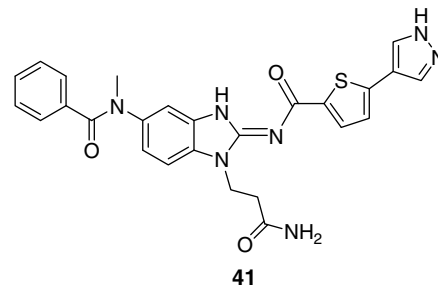


The synthesis and biological activity of a new series of compounds **2** are described.

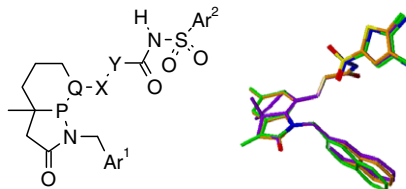
**Discovery of potent inhibitors of interleukin-2 inducible T-cell kinase (ITK) through structure-based drug design** pp 773–777

Brian N. Cook\*, Jörg Bentzien, Andre White, Peter A. Nemoto, Ji Wang, Chuk C. Man, Fariba Soleymanzadeh, Hnin Hnin Khine, Mohammed A. Kashem, Stanley Z. Kugler Jr., John P. Wolak, Gregory P. Roth, Stéphane De Lombaert, Steven S. Pullen, Hidenori Takahashi

This work describes the discovery of ITK inhibitors through structure-based design where high-resolution crystal structural information was used to optimize interactions within the kinase specificity pocket of the enzyme to improve both potency and selectivity.


**Peri-substituted hexahydro-indolones as novel, potent and selective human EP<sub>3</sub> receptor antagonists** pp 778–782

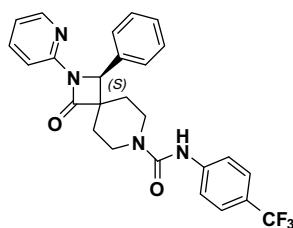
Matthew O'Connell, Wayne Zeller, James Burgeson, Rama K. Mishra, Jose Ramirez, Alex S. Kiselyov, Porkell Andrésson, Mark E. Gurney, Jasbir Singh\*



A series of peri-substituted [4.3.0] bicyclic non-aromatic heterocycles have been identified as potent and selective hEP<sub>3</sub> receptor antagonists. These molecules adopt a hair-pin conformation that overlaps with the endogenous ligand PGE<sub>2</sub> and fits into an internally generated EP<sub>3</sub> pharmacophore model. Optimized compounds show good metabolic stability and improved solubility over their corresponding bicyclic aromatic analogues.

**Spiro-piperidine azetidinones as potent TRPV1 antagonists** pp 783–787

Dong Xiao\*, Anandan Palani, Robert Aslanian, Brian A. McKittrick, Andrew T. McPhail, Craig C. Correll, P. Tara Phelps, John C. Anthes, Diane Rindgen

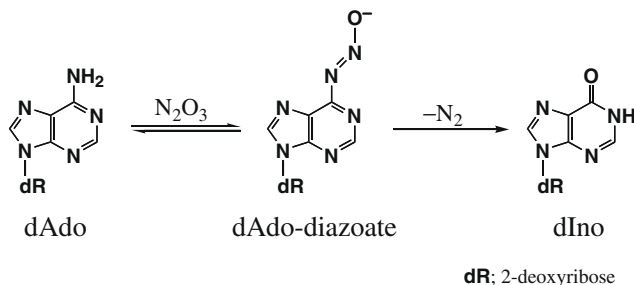


IC<sub>50</sub> (caps) = 13 ± 1.1 nM  
 IC<sub>50</sub> (PMA) = 8.5 ± 3.4 nM  
 rat AUC (0-6 h, po) @ 10mpk:  
 2500ng.h/ml  
 iv T<sub>1/2</sub> = 2.5 h; BA = 45%

A potent TRPV1 antagonist with good rat pharmacokinetic profile was discovered.

**Formation of diazoate intermediate upon nitrous acid and nitric oxide treatment of 2'-deoxyadenosine** pp 788–791

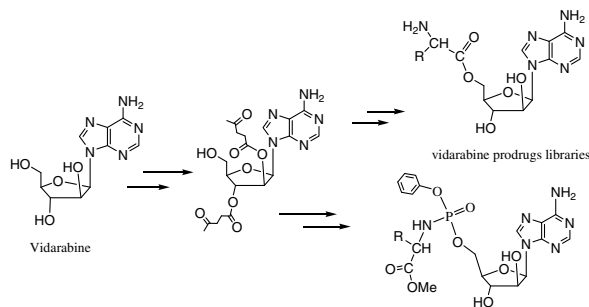
Toshinori Suzuki\*, Kiyoshi Iwakura, Yasuhide Takashima, Naoki Kasajima, Michiyo Inukai



**Design and synthesis of vidarabine prodrugs as antiviral agents**

pp 792–796

Wei Shen<sup>\*</sup>, Jae-Seung Kim, Phillip E. Kish, Jie Zhang, Stefanie Mitchell, Brian G. Gentry, Julie M. Breitenbach, John C. Drach, John Hilfinger

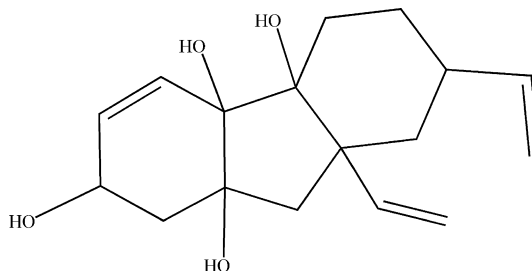


The synthesis of vidarabine prodrugs and their antiviral activities is reported.

**HY253, a novel compound isolated from *Aralia continentalis*, induces apoptosis via cytochrome c-mediated intrinsic pathway in HeLa cells**

pp 797–799

Ha Lim Oh, Haeyoung Lim, Younghee Park, Yoongho Lim, Hyun Chul Koh, Youl-Hee Cho, Chul-Hoon Lee<sup>\*</sup>

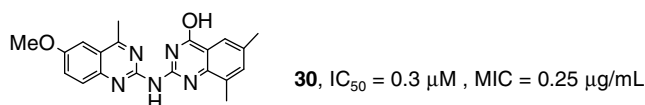


The chemical structure of HY253, 7,8a-divinyl-2,4a,4b,5,6,7,8,8a,9,9a-decahydro-1H-fluorene-2,4a,4b,9a-tetraol.

**Quinazolin-2-ylamino-quinazolin-4-ols as novel non-nucleoside inhibitors of bacterial DNA polymerase III**

pp 800–802

Joseph Guiles<sup>\*</sup>, Xicheng Sun, Ian A. Critchley, Urs Ochsner, Ming Tregay, Kim Stone, Jennifer Bertino, Louis Green, Rob Sabin, Frank Dean, H. Garry Dallmann, Charles S. McHenry, Nebojsa Janjic



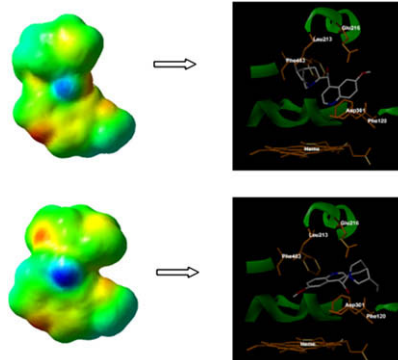
A novel series of quinazolin-2-ylamino-quinazolin-4-ols as a new class of DNA polymerase III inhibitors was identified. The synthesis, structure–activity relationships and functional activity are described.

**Insight into the effects of chiral isomers quinidine and quinine on CYP2D6 inhibition**

pp 803–806

Chunzhi Ai, Yan Li, Yonghua Wang, Yadong Chen, Ling Yang<sup>\*</sup>

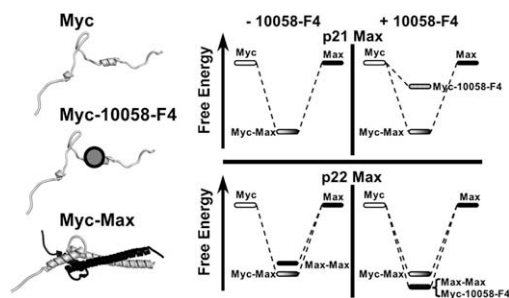
The different modes of the stereoisomers bound to CYP2D6 are resulted from the different molecular electrostatic potential surface.



### Small-molecule perturbation of competing interactions between c-Myc and Max

pp 807–810

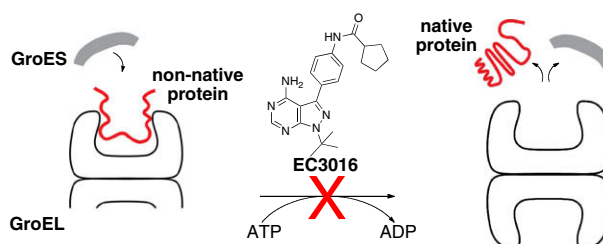
Ariele Viacava Follis, Dalia I. Hammoudeh, Andrew T. Daab, Steven J. Metallo\*



### A small molecule inhibitor selective for a variant ATP-binding site of the chaperonin GroEL

pp 811–813

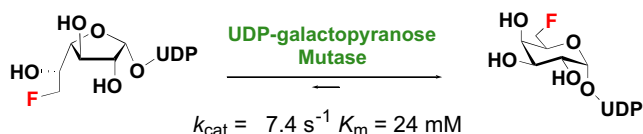
Eli Chapman\*, George W. Farr, Krystyna Furtak, Arthur L. Horwich



### Probing UDP-galactopyranose mutase binding pocket: A dramatic effect on substitution of the 6-position of UDP-galactofuranose

pp 814–816

Guillaume Eppe, Pauline Peltier, Richard Daniellou, Caroline Nugier-Chauvin, Vincent Ferrières\*, Stéphane P. Vincent\*

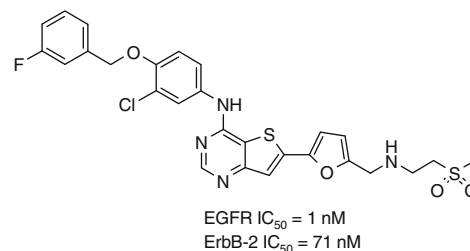


### Thienopyrimidine-based dual EGFR/ErbB-2 inhibitors

pp 817–820

Tara R. Rheault\*, Thomas R. Caferro, Scott H. Dickerson, Kelly H. Donaldson, Michael D. Gaul, Aaron S. Goetz, Robert J. Mullin, Octerloney B. McDonald, Kimberly G. Petrov, David W. Rusnak, Lisa M. Shewchuk, Glenn M. Spehar, Anne T. Truesdale, Dana E. Vanderwall, Edgar R. Wood, David E. Uehling

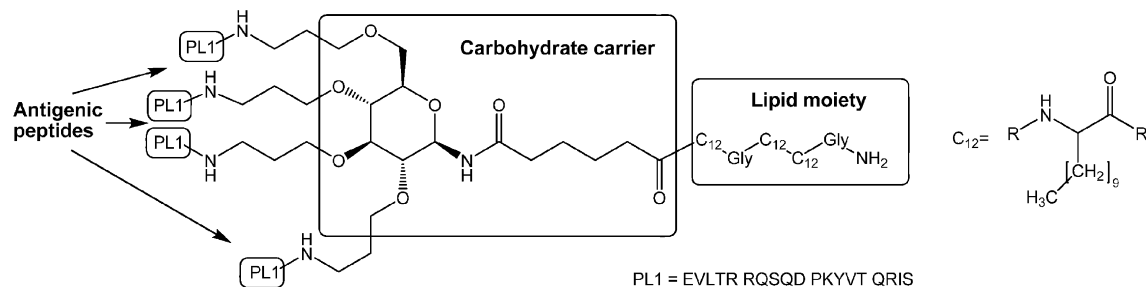
Two new series of potent and selective dual EGFR/ErbB-2 kinase inhibitors derived from novel thienopyrimidine cores have been identified. Isomeric thienopyrimidine cores were evaluated as isosteres for a 4-anilinoquinazoline core and several analogs containing the thieno[3,2-d]pyrimidine core showed anti-proliferative activity with IC<sub>50</sub> values less than 1 μM against human tumor cells in vitro.



**Synthesis of a *Streptococcus pyogenes* vaccine candidate based on the M protein PL1 epitope**

pp 821–824

Pavla Simerska\*, Hao Lu, Istvan Toth

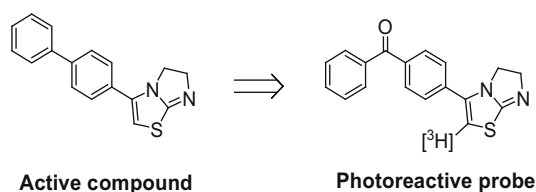


A complex vaccine candidate against group A streptococcus incorporating carrier, adjuvant and the antigen was synthesised using carbohydrate chemistry and solid-phase peptide methods.

**Synthesis and evaluation of photoreactive probes to elucidate iodide efflux in thyrocytes**

pp 825–827

S  verine Derbr  , Nathalie Lecat-Guillet, Florence Pillon, Yves Ambroise\*

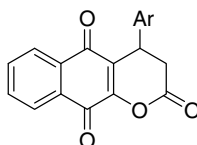


The synthesis of a radiolabeled photoreactive probe to elucidate the mechanism of transmembrane iodide fluxes in the thyroid gland is reported.

**New potential inhibitors of DNA topoisomerase. Part II: Design and synthesis of  $\alpha$ -lapachone derivatives under microwave irradiation**

pp 828–830

Ping Wei, Xiaohong Zhang, Shuijiang Tu\*, Shu Yan, Hanjie Ying, Pingkai Ouyang\*

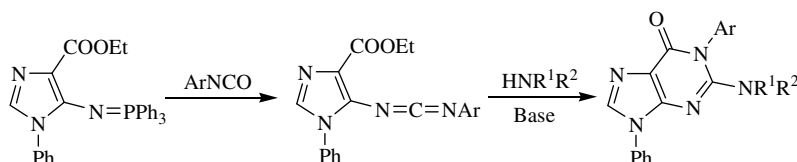


The synthesis of  $\alpha$ -lapachone derivatives as new potential inhibitors of DNA topoisomerase II is reported.

**Efficient synthesis and biological evaluation of 1,2,9-trisubstituted 1,9-dihydro-6H-purin-6-ones**

pp 831–833

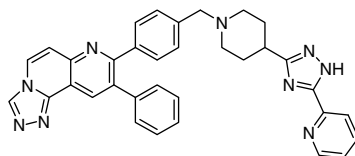
Nian-Yu Huang, Yong-Ju Liang, Ming-Wu Ding\*, Li-Wu Fu\*, Hong-Wu He



**Allosteric inhibitors of Akt1 and Akt2: Discovery of [1,2,4]triazolo[3,4-f][1,6]naphthyridines with potent and balanced activity**

pp 834–836

Yiwei Li\*, Jun Liang, Tony Siu, Essa Hu, Michael A. Rossi, Stanley F. Barnett, Deborah Defeo-Jones, Raymond E. Jones, Ronald G. Robinson, Karen Leander, Hans E. Huber, Sachin Mittal, Nicholas Cosford, Peppi Prasit

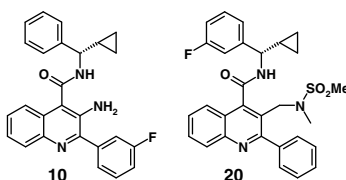


Akt1 IC<sub>50</sub> = 4.0 nM  
 Akt2 IC<sub>50</sub> = 10.0 nM  
 Cell Akt1 EC<sub>50</sub> = 17.0 nM  
 Cell Akt2 EC<sub>50</sub> = 107.6 nM

**New quinoline NK<sub>3</sub> receptor antagonists with CNS activity**

pp 837–840

Paul W. Smith\*, Paul A. Wyman, Peter Lovell, Caroline Goodacre, Halina T. Serafinowska, Antonio Vong, Frank Harrington, Sean Flynn, Daniel M. Bradley, Rod Porter, Sara Coggon, Graham Murkitt, Kirsten Searle, David R. Thomas, Jeannette M. Watson, William Martin, Zining Wu, Lee A. Dawson

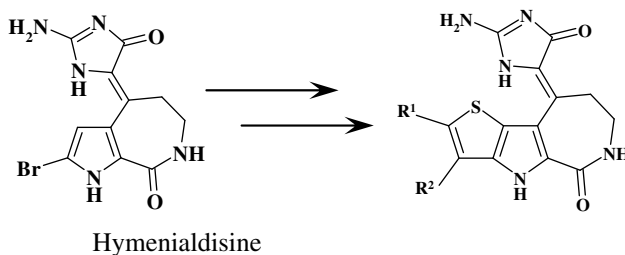


SAR investigation in the quinoline series of NK<sub>3</sub> antagonists led to identification of 3-amino quinoline **10** (GSK172981) and sulfonamide **20** (GSK256471). Both compounds are high affinity, potent NK<sub>3</sub> receptor antagonists which produce excellent NK<sub>3</sub> receptor occupancy in an ex vivo binding study in gerbil cortex.

**Synthesis and CHK1 inhibitory potency of Hymenialdisine analogues**

pp 841–844

Jean-Gilles Parmentier, Bernard Portevin, Roy M. Golsteyn, Alain Pierré, John Hickman, Philippe Gloanec, Guillaume De Nanteuil\*

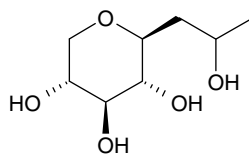


Thieno[3,2-*b*]pyrroloazepinones analogues of Hymenialdisine were prepared and found to be potent inhibitors of CHK1.

**Synthesis of Pro-Xylane™: A new biologically active C-glycoside in aqueous media**

pp 845–849

Alexandre Cavezza, Christophe Boule, Amélie Guéguiniat, Patrick Pichaud, Simon Trouille, Louis Ricard, Maria Dalko-Csiba\*



Pro-Xylane™

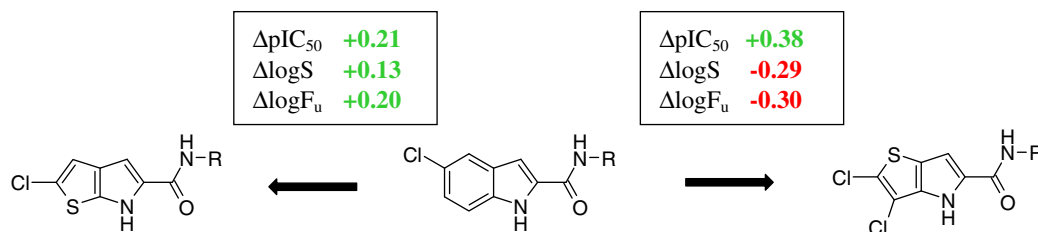
The scope and limitation of Lubineau's reaction were evaluated for the synthesis of C-glycosides. Further transformation of side chain carbonyl was also achieved. Optimization of these two steps was investigated in xylose case. Some of the compounds were shown to stimulate sulfated glycosaminoglycans (GAGs) synthesis. Pro-Xylane™ was identified as the best activator of GAGs biosynthesis.



**Matched molecular pair analysis of activity and properties of glycogen phosphorylase inhibitors**

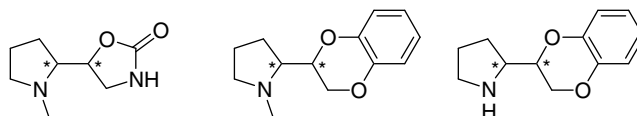
pp 850–853

Alan M. Birch, Peter W. Kenny\*, Iain Simpson, Paul R. O. Whittamore

**5-(2-Pyrrolidinyl)oxazolidinones and 2-(2-pyrrolidinyl)benzodioxanes: Synthesis of all the stereoisomers and  $\alpha 4\beta 2$  nicotinic affinity**

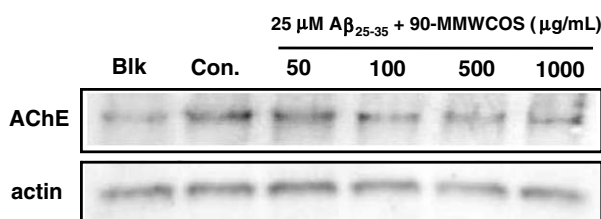
pp 854–859

Marco Pallavicini\*, Cristiano Bolchi, Matteo Binda, Antonio Cilia, Francesco Clementi, Rossana Ferrara, Laura Fumagalli, Cecilia Gotti, Milena Moretti, Alessandro Pedretti, Giulio Vistoli, Ermanno Valoti

**Chitoooligosaccharides suppress the level of protein expression and acetylcholinesterase activity induced by  $A\beta_{25-35}$  in PC12 cells**

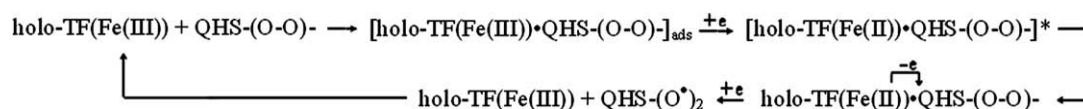
pp 860–862

Sang-Hoon Lee, Jin-Sook Park, Se-Kwon Kim\*, Chang-Bum Ahn, Jae-Young Je\*

A 90-MMWCOS (MW 1000–5000Da) suppressed the level of AChE protein expression and AChE activity induced by  $A\beta_{25-35}$  in PC12 cell lines.**Electrochemical activity of holotransferrin and its electrocatalysis-mediated process of artemisinin**

pp 863–866

Huai-Hong Cai, Jiye Cai, Pei-Hui Yang\*

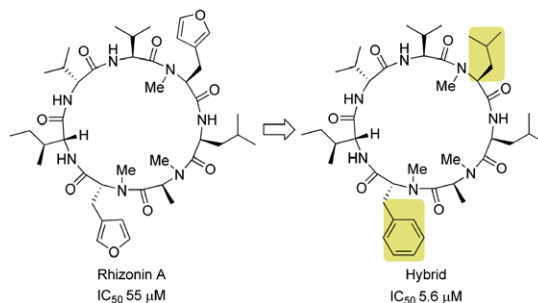


A sequential two-step process is proposed to explain holotransferrin-mediated electrocatalytic reduction of artemisinin. Holotransferrin (holo-TF) initially interacts with artemisinin (QHS) to form an adduct  $[\text{holo-TF(Fe(III))}\cdot\text{QHS-(O-O)-}]_{\text{ads}}$ , subsequently, holo-TF(Fe(III)) obtains one electron and then forms an intermediate adduct  $[\text{holo-TF(Fe(II))}\cdot\text{QHS-(O-O)-}]^*$ , which induces the cleavage of the peroxide bond in artemisinin and then generates  $\text{QHS-(O)}_2^*$  free radicals.

### Structure-based hybridization of the bioactive natural products rhizonin A and ternatin leading to a selective fat-accumulation inhibitor against 3T3-L1 adipocytes

pp 867–869

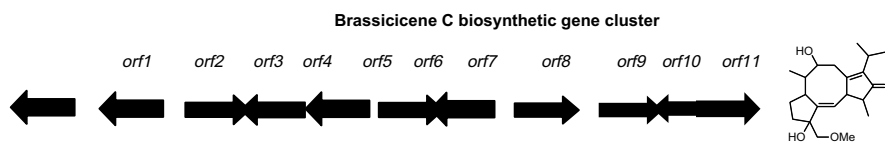
Kenichiro Shimokawa, Kaoru Yamada, Daisuke Uemura\*



### Identification and functional analysis of brassicene C biosynthetic gene cluster in *Alternaria brassicicola*

pp 870–874

Atsushi Minami\*, Naoto Tajima, Yusuke Higuchi, Tomonobu Toyomasu, Takeshi Sassa, Nobuo Kato, Tohru Dairi\*

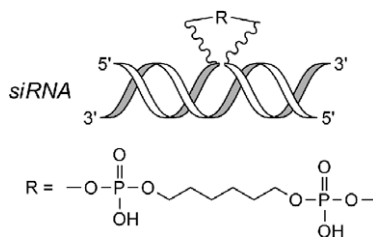


The biosynthetic gene cluster of brassicene C was identified in *Alternaria brassicicola* strain ATCC 96836 from genome database search.

### Effect of incorporation of alkyl linkers into siRNAs on RNA interference

pp 875–877

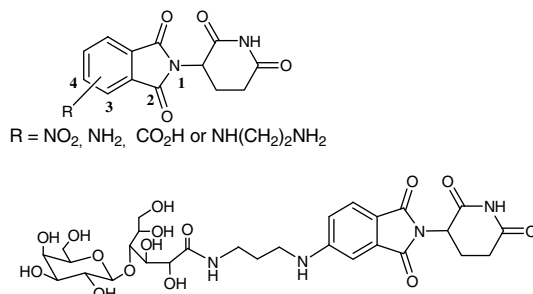
Yoshihito Ueno\*, Kayo Yoshikawa, Yoshiaki Kitamura, Yukio Kitade\*



### Preliminary biological evaluations of new thalidomide analogues for multiple sclerosis application

pp 878–881

Christiane Contino-Pépin\*, Audrey Parat, Sandrine Périno, Christine Lenoir, Michel Vidal, Hervé Galons, Stephen Karlik, Bernard Pucci\*

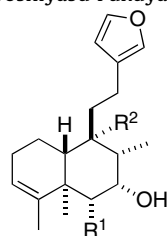


Synthesis and biological assessments in vitro (on EAhy926 cells) and in vivo (EAE model) of new thalidomide analogues.

**Novel NGF-potentiating diterpenoids from a Brazilian medicinal plant, *Ptychopetalum olacoides***

pp 882–886

Wanxia Tang, Miwa Kubo, Kenichi Harada, Hideaki Hioki, Yoshiyasu Fukuyama\*



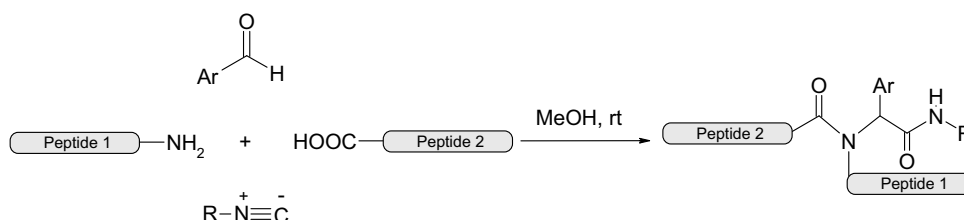
1 R<sup>1</sup> = OH, R<sup>2</sup> = CH<sub>3</sub>  
 2 R<sup>1</sup> = H, R<sup>2</sup> = CH<sub>2</sub>OH

Among four novel clerodane-type diterpenoids **1–4** isolated from *Ptychopetalum olacoides*, **1** and **2** were found to significantly enhance neurite-outgrowth of NGF-differentiated PC12 cells at 0.1–50 μM.

**Synthesis of novel Gn-RH analogues using Ugi-4MCR**

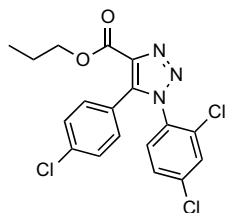
pp 887–890

Armin Arabanian, Mahdiah Mohammadnejad, Saeed Balalaie\*, Jürgen H. Gross

**Synthesis and CB1 cannabinoid receptor affinity of 4-alkoxycarbonyl-1,5-diaryl-1,2,3-triazoles**

pp 891–893

Hong Shu, Sari Izenwasser, Dean Wade, Edwin D. Stevens, Mark L. Trudell\*



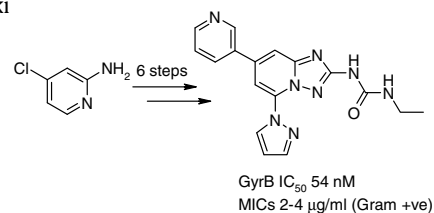
A series of 4-alkoxycarbonyl-1,5-diaryl-1,2,3-triazoles were synthesized regioselectively using click chemistry and evaluated at CB1 cannabinoid receptors. The *n*-propyl ester (*K*<sub>i</sub> = 4.6 nM) exhibited the most potent affinity of the series.

**DNA gyrase (GyrB)/topoisomerase IV (ParE) inhibitors: Synthesis and antibacterial activity**

pp 894–899

Stephen P. East\*, Clara Bantry White, Oliver Barker, Stephanie Barker, James Bennett, David Brown, E. Andrew Boyd, Christopher Brennan, Chandana Chowdhury, Ian Collins, Emmanuelle Convers-Reignier, Brian W. Dymock, Rowena Fletcher, David J. Haydon, Mihaly Gardiner, Stuart Hatcher, Peter Ingram, Paul Lancett, Paul Mortenson, Konstantinos Papadopoulos, Carol Smee, Helena B. Thomaides-Brears, Heather Tye, James Workman, Lloyd G. Czaplowski\*

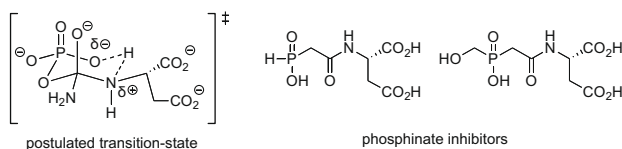
The synthesis and antibacterial activities of three chemotypes of DNA supercoiling inhibitors based on imidazo[1,2-*a*]pyridine and [1,2,4]triazolo[1,5-*a*]pyridine scaffolds that target the ATPase subunits of DNA gyrase and Topoisomerase IV (GyrB/ParE) is reported. The most potent scaffold was selected for optimization leading to a series with potent Gram-positive antibacterial activity and a low resistance frequency.



**Submicromolar phosphinic inhibitors of *Escherichia coli* aspartate transcarbamoylase**

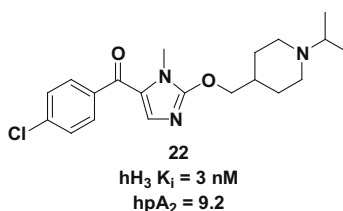
pp 900–902

Laëtitia Coudray, Evan R. Kantrowitz, Jean-Luc Montchamp\*

**Novel imidazole-based histamine H<sub>3</sub> antagonists**

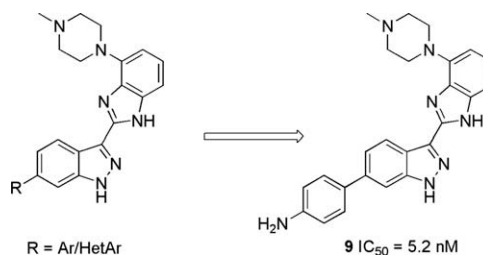
pp 903–907

Jill A. Jablonowski\*, Kiev S. Ly, Michael Bogenstaetter, Curt A. Dvorak, Jamin D. Boggs, Lisa K. Dvorak, Brian Lord, Kirsten L. Miller, Curt Mazur, Sandy J. Wilson, Timothy W. Lovenberg, Nicholas I. Carruthers

A novel series of imidazole containing histamine H<sub>3</sub> receptor ligands were investigated and found to be potent functional antagonists with appreciable brain uptake.**2-(6-Phenyl-1H-indazol-3-yl)-1H-benzo[d]imidazoles: Design and synthesis of a potent and isoform selective PKC- $\zeta$  inhibitor**

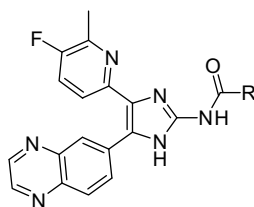
pp 908–911

John I. Trujillo\*, James R. Kiefer\*, Wei Huang, Atli Thorarensen, Li Xing, Nicole L. Caspers, Jacqueline E. Day, Karl J. Mathis, Kuniko K. Kretzmer, Beverley A. Reitz, Robin A. Weinberg, Roderick A. Stegeman, Ann Wrightstone, Lori Christine, Robert Compton, Xiong Li

The design and synthesis of a potent and isoform selective PKC $\zeta$  (9, IC<sub>50</sub> = 5.2 nM, 10- to 20,000-fold selective over other PKC isoforms, 200-fold selective over CDK-2) inhibitor is reported.**2-Aminoimidazoles inhibitors of TGF- $\beta$  receptor 1**

pp 912–916

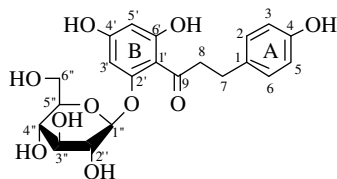
Dominique Bonafoux\*, Claudio Chuaqui, P. Ann Boriack-Sjodin, Chris Fitch, Gretchen Hankins, Serene Josiah, Cheryl Black, Gregg Hetu, Leona Ling, Wen-Cherng Lee\*

Acylated 2-amidoimidazoles were identified as potent and selective inhibitor of TGF- $\beta$ R1 that offer a superior pharmacokinetic profile compared to unsubstituted or alkylated 2-aminoimidazoles.

## Synthesis and biological evaluation of phloridzin analogs as human concentrative nucleoside transporter 3 (hCNT3) inhibitors

pp 917–921

Amol Gupte, John K. Buolamwini\*



Phloridzin

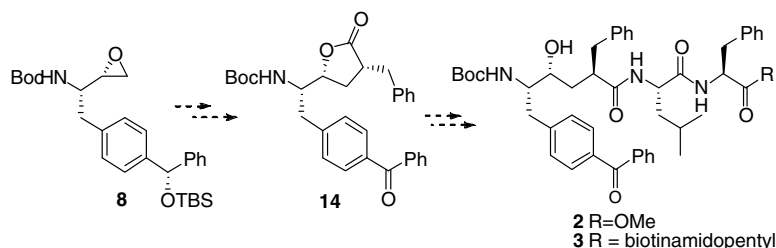
The synthesis and [ $^3\text{H}$ ]-uridine uptake investigation of the structure–activity relationship of new phloridzin analogs at the human concentrative nucleoside transporter 3 (hCNT3) is reported.



## Stereo-controlled synthesis of novel photoreactive $\gamma$ -secretase inhibitors

pp 922–925

Guangli Yang, Ye Ingrid Yin, Jiong Chun, Christopher C. Shelton, Ouathék Ouerfelli, Yue-Ming Li\*

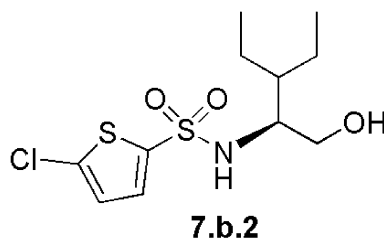


Synthesis of a photoreactive dipeptide isostere at the P1 position.

## (S)-N-(5-Chlorothiophene-2-sulfonyl)- $\beta$ , $\beta$ -diethylalaninol a Notch-1-sparing $\gamma$ -secretase inhibitor

pp 926–929

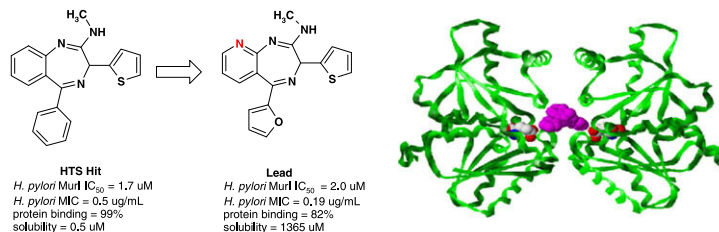
Derek C. Cole\*, Joseph R. Stock, Anthony F. Kreft, Madelene Antane, Suzan H. Aschmies, Kevin P. Atchison, David S. Casebier, Thomas A. Comery, George Diamantidis, John W. Ellingboe, Boyd L. Harrison, Yun Hu, Mei Jin, Dennis M. Kubrak, Peimin Lu, Charles W. Mann, Robert L. Martone, William J. Moore, Aram Oganessian, David R. Riddell, June Sonnenberg-Reines, Shaiu-Ching Sun, Erik Wagner, Zheng Wang, Kevin R. Woller, Zheng Xu, Hua Zhou, J. Steven Jacobsen



## Potent and selective inhibitors of *Helicobacter pylori* glutamate racemase (Murl): Pyridodiazepine amines

pp 930–936

Bolin Geng\*, Gregory Basarab, Janelle Comita-Prevoir, Madhusudhan Gowravaram, Pamela Hill, Andrew Kiely, James Loch, Lawrence MacPherson, Marshall Morningstar, George Mullen, Ekundayo Osimboni, Alexander Satz, Charles Eyermann, Tomas Lundqvist

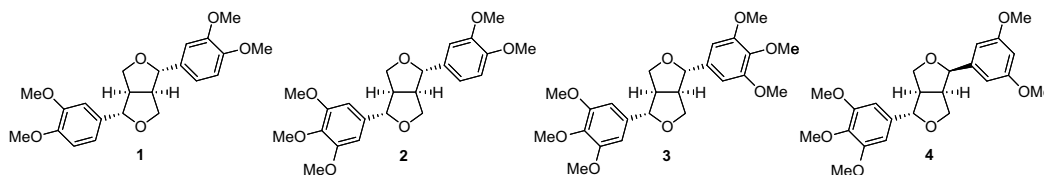


An SAR study of a screening hit generated a series of pyridodiazepine amines as inhibitors of *Helicobacter pylori* glutamate racemase (Murl) showing highly selective anti-*H. pylori* activity, marked improved solubility, and reduced plasma protein binding. X-ray co-crystal E-I structures were obtained. These uncompetitive allosteric inhibitors bind at the Murl dimer interface.

**In vitro anti-inflammatory activity of lignans isolated from *Magnolia fargesii***

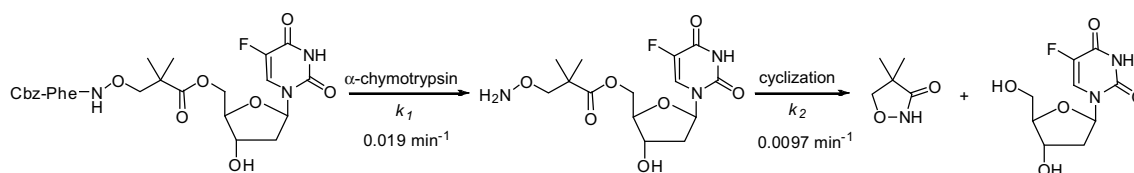
pp 937–940

Jae Yeon Kim, Hyo Jin Lim, Da Yeon Lee, Ji Sun Kim, Do Hee Kim, Hwa Jin Lee, Hee Doo Kim, Raok Jeon, Jae-Ha Ryu\*

Lignans from *Magnolia fargesii* inhibit the production of NO, PGE<sub>2</sub> and expression of iNOS and COX-2 by activated microglia.**3-Aminoxypropionate-based linker system for cyclization activation in prodrug design**

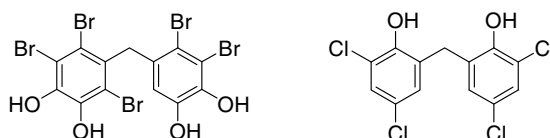
pp 941–944

Yiyu Ge, Xinghua Wu, Dazhi Zhang, Longqin Hu\*

**Synthesis and antimicrobial activities of halogenated bis(hydroxyphenyl)methanes**

pp 945–948

Ki-Bong Oh, Ji Hye Lee, Jong Wook Lee, Kyung-Mi Yoon, Soon-Chun Chung, Heung Bae Jeon, Jongheon Shin, Hyi-Seung Lee\*

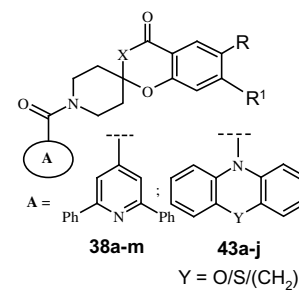


The synthesis and bioactivity of halophenols are described.

**Synthesis of spiro[chroman-2,4'-piperidin]-4-one derivatives as acetyl-CoA carboxylase inhibitors**

pp 949–953

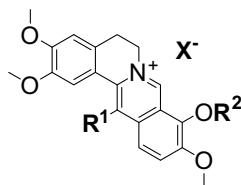
Pundlik Shinde, Sanjay K. Srivastava, Rajendra Odedara, Davinder Tuli, Siralee Munshi, Jitendra Patel, Shitalkumar P. Zambad, Rajesh Sonawane, Ramesh C. Gupta\*, Vijay Chauthaiwale, Chaitanya Dutt

A number of spiro[chroman-2,4'-piperidin]-4-one derivatives (**38a–m** and **43a–j**) have been designed, synthesized and screened for in vitro ACC inhibition. In vivo studies of compound **38j** has been carried out.

## Synthesis and structure–activity relationships of novel, substituted 5,6-dihydrodibenzo[*a,g*]quinolizinium P2X<sub>7</sub> antagonists

pp 954–958

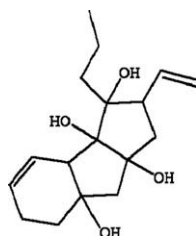
Ga Eun Lee, Ho-Sung Lee, So Deok Lee, Jung-Ho Kim, Won-Ki Kim, Yong-Chul Kim\*



## HY251, a novel cell cycle inhibitor isolated from *Aralia continentalis*, induces G<sub>1</sub> phase arrest via p53-dependent pathway in HeLa cells

pp 959–961

Ha Lim Oh, Haeyoung Lim, Youl-Hee Cho, Hyun Chul Koh, Hojung Kim, Yoongho Lim, Chul-Hoon Lee\*

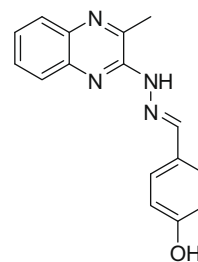
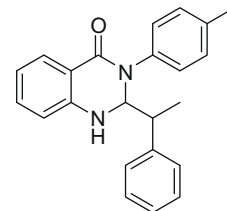
The chemical structure of HY251 3-propyl-2-vinyl-1,2,3,3a,3b,6,7,7a,8,8a-decahydrocyclopenta[*a*]indene-3,3a,7a,8a-tetraol.

## Positive allosteric modulators of the metabotropic glutamate receptor subtype 4 (mGluR4). Part II: Challenges in hit-to-lead

pp 962–966

Richard Williams, Colleen M. Niswender, Qingwei Luo, Uyen Le, P. Jeffrey Conn, Craig W. Lindsley\*

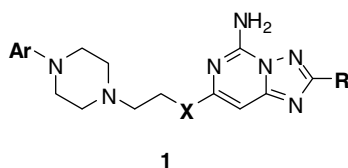
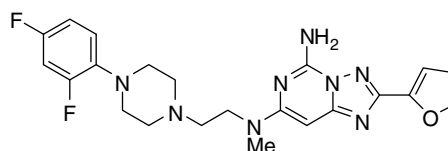
The synthesis and SAR of two mGluR4 positive allosteric modulator leads **6** and **7** is described. VU001171 (**6**) represents the most potent (EC<sub>50</sub> = 650 nM), efficacious (141% Glu Max) and largest fold shift (36-fold) of any mGluR4 PAM ever described. However, this work highlights the challenges in hit-to-lead for mGluR4 PAMs, with multiple confirmed HTS hits displaying little or no tractable SAR.

VU001171, **6**VU0092145, **7**

## Potent and selective adenosine A<sub>2A</sub> receptor antagonists: 1,2,4-Triazolo[1,5-*c*]pyrimidines

pp 967–971

Bernard R. Neustadt\*, Hong Liu, Jinsong Hao, William J. Greenlee, Andrew W. Stamford, Carolyn Foster, Leyla Arik, Jean Lachowicz, Hongtao Zhang, Rosalia Bertorelli, Silva Fredduzzi, Geoffrey Varty, Mary Cohen-Williams, Kwokei Ng

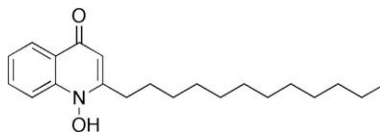
**1****16g** A<sub>2A</sub> Ki = 1.0nM, A<sub>1</sub>/A<sub>2A</sub> = 1580 X

Synthetic methodology was developed for a series of 1,2,4-triazolo[1,5-*c*]pyrimidines of type **1**. These compounds, exemplified by **16g**, showed potent and selective adenosine A<sub>2A</sub> antagonist activity, as well as oral activity in a rodent model of Parkinson's disease.

**Type II NADH dehydrogenase of the respiratory chain of *Plasmodium falciparum* and its inhibitors**

pp 972–975

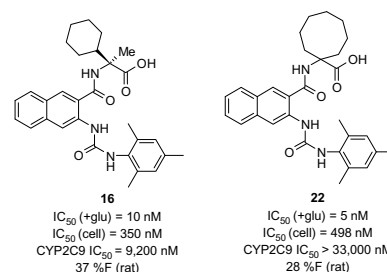
Carolyn K. Dong, Vishal Patel, Jimmy C. Yang, Jeffrey D. Dvorin, Manoj T. Duraisingh, Jon Clardy, Dyann F. Wirth \*

**Anthranilimide-based glycogen phosphorylase inhibitors for the treatment of type 2 diabetes: 1. Identification of 1-amino-1-cycloalkyl carboxylic acid headgroups**

pp 976–980

Steven M. Sparks \*, Pierette Banker, David M. Bickett, H. Luke Carter, Daphne C. Clancy, Scott H. Dickerson, Kate A. Dwornik, Dulce M. Garrido, Pamela L. Golden, Robert T. Nolte, Andrew J. Peat, Lauren R. Sheckler, Francis X. Tavares, Stephen A. Thomson, Liping Wang, James E. Weiel

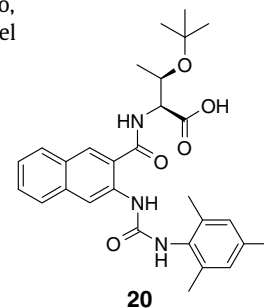
Optimization of the amino acid residue within a series of anthranilimide-based glycogen phosphorylase inhibitors is described. These studies culminated in the identification of anthranilimides **16** and **22** which displayed potent in vitro inhibition of GP $\alpha$  in addition to reduced inhibition of CYP2C9 and excellent pharmacokinetic properties.

**Anthranilimide-based glycogen phosphorylase inhibitors for the treatment of Type 2 diabetes: 2. Optimization of serine and threonine ether amino acid residues**

pp 981–985

Steven M. Sparks \*, Pierette Banker, David M. Bickett, Daphne C. Clancy, Scott H. Dickerson, Dulce M. Garrido, Pamela L. Golden, Andrew J. Peat, Lauren R. Sheckler, Francis X. Tavares, Stephen A. Thomson, James E. Weiel

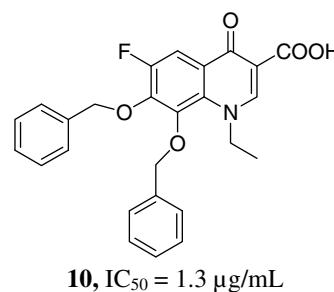
Optimization of the amino acid residue of a series of anthranilimide based glycogen phosphorylase inhibitors is described leading to the identification of serine and threonine ether analogs. *t*-Butylthreonine analog **20** displayed potent in vitro inhibition of GP $\alpha$ , low potential for P450 inhibition, and excellent pharmacokinetic properties.

**Synthesis, in vitro antitrypanosomal and antibacterial activity of phenoxy, phenylthio or benzyloxy substituted quinolones**

pp 986–989

Xiang Ma \*, Weicheng Zhou \*, Reto Brun

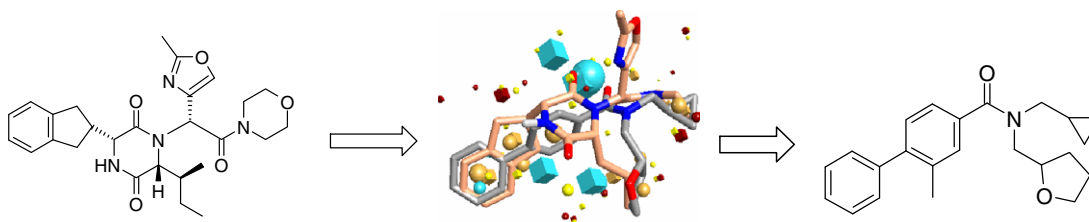
A series of quinolones based novel molecules was synthesized and evaluated as antitrypanosomal agents. Compound **10** has shown significant in vitro activity against *Trypanosoma cruzi*.





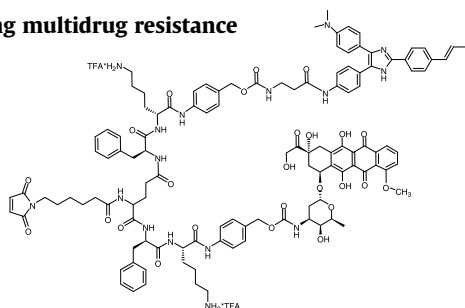
## Discovery and optimization of highly ligand-efficient oxytocin receptor antagonists using structure-based drug design pp 990–994

Benjamin R. Bellenie\*, Nicholas P. Barton, Amanda J. Emmons, Jag P. Heer, Cristian Salvagno



## Development of dual-acting prodrugs for circumventing multidrug resistance pp 995–1000

Khalid Abu Ajaj, Felix Kratz\*

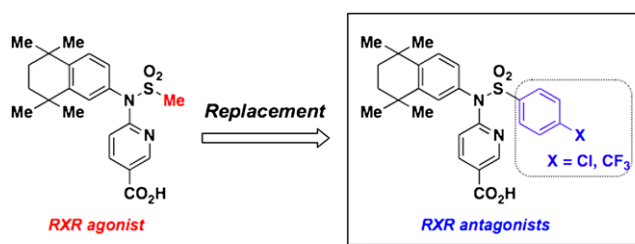


We have developed a novel dual-acting maleimide-bearing prodrug that incorporates the anticancer agent doxorubicin and an inhibitor of the P-glycoprotein efflux pump that is over-expressed in multidrug resistant tumor cells. Additionally, the prodrug contains a 1,6-self-immolative spacer coupled to the dipeptide Phe-Lys that acts as a substrate for cathepsin B. The prodrug, once bound through its maleimide moiety to the cysteine-34 group of human serum albumin, was cleaved by cathepsin B and in tumor homogenates demonstrating a release of the anticancer agent doxorubicin and the inhibitor.



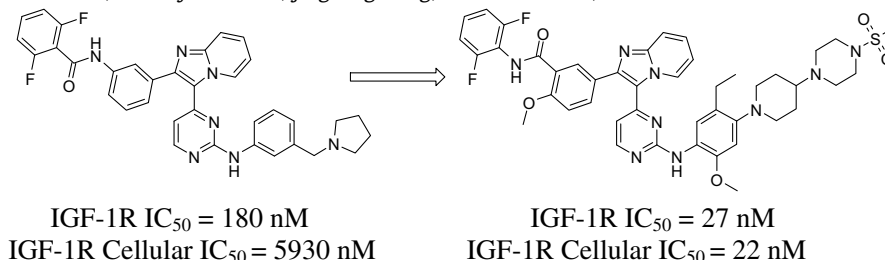
## Replacing alkyl sulfonamide with aromatic sulfonamide in sulfonamide-type RXR agonists favors switch towards antagonist activity pp 1001–1003

Ken-ichi Morishita, Nobumasa Yakushiji, Fuminori Ohsawa, Kayo Takamatsu, Nobuyasu Matsuura, Makoto Makishima, Masatoshi Kawahata, Kentaro Yamaguchi, Akihiro Tai, Kenji Sasaki, Hiroki Kakuta\*



## Discovery and optimization of imidazo[1,2-a]pyridine inhibitors of insulin-like growth factor-1 receptor (IGF-1R) pp 1004–1008

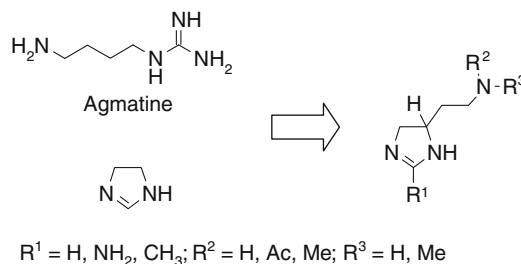
Kyle A. Emmitte\*, Brian J. Wilson, Erich W. Baum, Holly K. Emerson, Kevin W. Kuntz, Kristen E. Nailor, James M. Salovich, Stephon C. Smith, Mui Cheung, Roseanne M. Gerding, Kirk L. Stevens, David E. Uehling, Robert A. Mook Jr., Ganesh S. Moorthy, Scott H. Dickerson, Anne M. Hassell, M. Anthony Leesnitzer, Lisa M. Shewchuk, Arthur Groy, Jason L. Rowand, Kelly Anderson, Charity L. Atkins, Jingsong Yang, Peter Sabbatini, Rakesh Kumar



**New analogues of agmatine with higher affinity to imidazoline receptors**

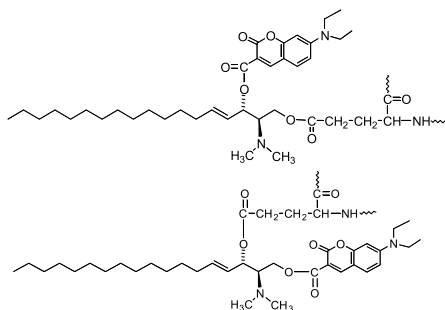
pp 1009–1011

Adam P. Treder, Ryszard Andruszkiewicz\*, Włodzimierz Zgoda, Celeste Ford, Alan L. Hudson

The synthesis and  $\alpha_2$ ,  $\text{I}_1$ , and  $\text{I}_2$  receptors' affinity studies of new agmatine analogues are reported.**N,N-Dimethylsphingosine conjugates of poly-L-glutamic acid: Synthesis, characterization, and initial biological evaluation**

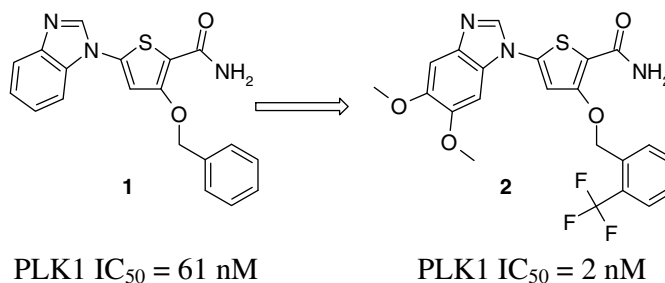
pp 1012–1017

Sukhen C. Ghosh, Edmond Auzenne, Mojgan Khodadadian, David Farquhar, Jim Klostergaard\*

**Discovery of thiophene inhibitors of polo-like kinase**

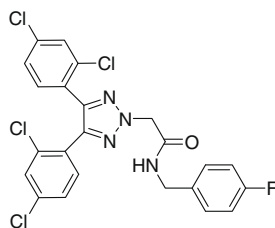
pp 1018–1021

Kyle A. Emmitte\*, C. Webb Andrews, Jennifer G. Badiang, Ronda G. Davis-Ward, Hamilton D. Dickson, David H. Drewry, Holly K. Emerson, Andrea H. Epperly, Daniel F. Hassler, Victoria B. Knick, Kevin W. Kuntz, Timothy J. Lansing, James A. Linn, Robert A. Mook Jr., Kristen E. Nailor, James M. Salovich, Glenn M. Spehar, Mui Cheung

**1,2,3-Triazole derivatives as new cannabinoid CB1 receptor antagonists**

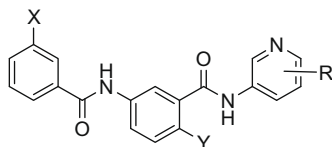
pp 1022–1025

Duen-Ren Hou\*, Safiul Alam, Ting-Chun Kuan, Mani Ramanathan, Tsung-Pang Lin, Ming-Shiu Hung\*

Development of new 1,2,3-triazoles as effective and selective CB1 receptor antagonists ( $\text{IC}_{50}$  =  $11.6 \pm 3.4$  nM;  $\text{CB}_2/\text{CB}_1 > 1000$ ) is reported.

**Identification of amidoheteroaryls as potent inhibitors of mutant (V600E) B-Raf kinase with in vivo activity****pp 1026–1029**

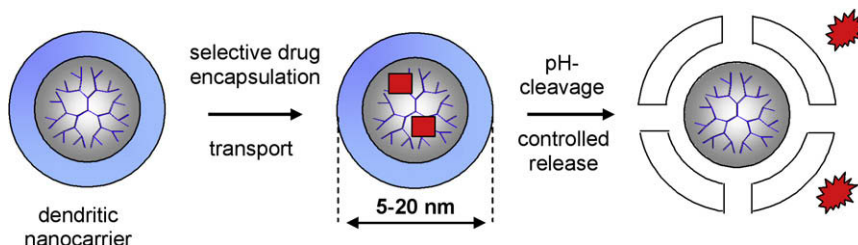
Paul D. Lyne\*, Brian Aquila, Donald J. Cook, Les A. Dakin, Jay Ezhuthachan, Stephanos Ioannidis, Timothy Pontz, Mei Su, Qing Ye, Xiaolan Zheng, Michael H. Block, Scott Cowen, Tracy L. Deegan, John W. Lee, David A. Scott, Dominique Custeau, Lisa Drew, Srinivasu Poondru, Minhui Shen, Allan Wu



Potent amidoheteroaryls inhibitors of V600E B-Raf with in vivo activity.

**Development of pH-responsive core-shell nanocarriers for delivery of therapeutic and diagnostic agents****pp 1030–1034**

Shangjie Xu, Ying Luo, Ralph Graeser, André Warnecke, Felix Kratz, Peter Hauff, Kai Licha, Rainer Haag\*

**OTHER CONTENTS****Retraction notice****p 1035****Instructions to contributors****p I**

\*Corresponding author

Supplementary data available via ScienceDirect

**COVER**

Overlay of high resolution co-crystal structures of *R*-**22**-ADP (cyan) and **1**-ADP (green) bound in an allosteric binding site of the mitotic kinesin KSP. [Roecker, A. J.; Coleman, P. J.; Mercer, S. P.; Schreier, J. D.; Buser, C. A.; Walsh, E. S.; Hamilton, K.; Lobell, R. B.; Tao, W.; Diehl, R. E.; South, V. J.; Davide, J. P.; Kohl, N. E.; Yan, Y.; Kuo, L. C.; Li, C.; Fernandez-Metzler, C.; Mahan, E. A.; Prueksaritanont, T.; Hartman, G. D. *Bioorg. Med. Chem. Lett.* **2007**, 17, 5677.]

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