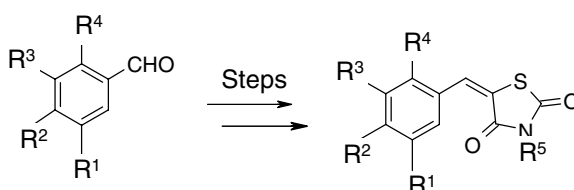


## Contents

### ARTICLES

**Synthesis of O-prenylated and O-geranylated derivatives of 5-benzylidene-2,4-thiazolidinediones and evaluation of their free radical scavenging activity as well as effect on some phase II antioxidant/detoxifying enzymes** pp 1149–1154

Sk. Ugir Hossain and Sudin Bhattacharya\*



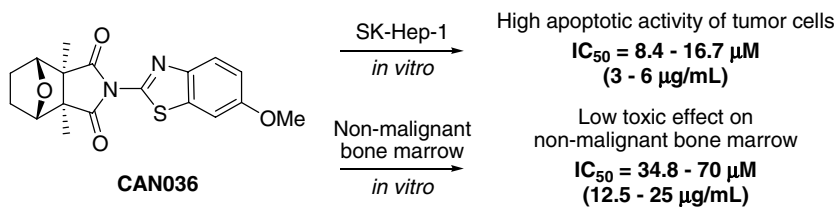
Several 2,4-thiazolidinedione compounds were synthesized as free radical scavenger and phase II detoxifying/antioxidant enzymes inducer.



**Synthesis and structure evaluation of a novel cantharimide and its cytotoxicity on SK-Hep-1 hepatoma cells**

pp 1155–1159

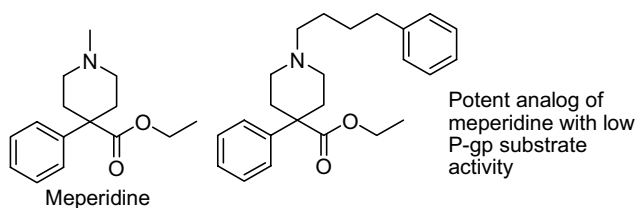
Stanton Hon Lung Kok, Chung Hin Chui, Wing Sze Lam, Jien Chen, Fung Yi Lau, Raymond Siu Ming Wong, Gregory Yin Ming Cheng, Paul Bo San Lai, Thomas Wai Tong Leung, Michael Wing Yiu Yu, Johnny Cheuk On Tang\* and Albert Sun Chi Chan\*



**Opioids and efflux transporters. Part 1: P-Glycoprotein substrate activity of N-substituted analogs of meperidine**

pp 1160–1162

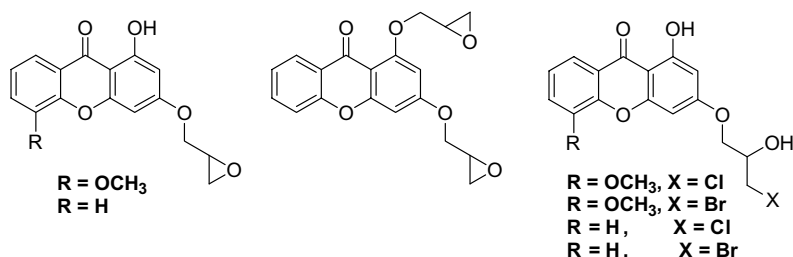
Susan L. Mercer, Hazem E. Hassan, Christopher W. Cunningham, Natalie D. Eddington and Andrew Coop\*



### Synthesis of new xanthone analogues and their biological activity test—Cytotoxicity, topoisomerase II inhibition, and DNA cross-linking study

pp 1163–1166

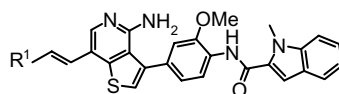
Sangwook Woo, Ji Jung, Chongsoon Lee, Youngjoo Kwon\* and Younghwa Na\*



### Discovery of thienopyridines as Src-family selective Lck inhibitors

pp 1167–1171

Lily Abbott, Patrick Betschmann, Andrew Burchat, David J. Calderwood, Heather Davis, Peter Hrnčiar, Gavin C. Hirst,\* Biqin Li, Michael Morytko, Kelly Mullen and Bryant Yang



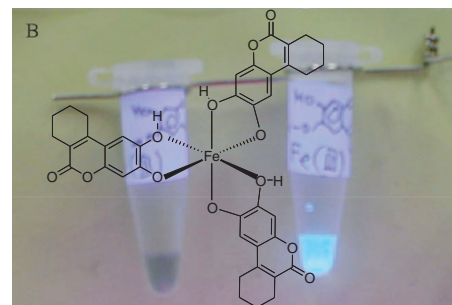
We describe the identification, SAR, and in vivo pharmacology of a new series of Src-family selective Lck inhibitors. These thienopyridines were designed to access the unique residues in the extended hinge region of Lck.

### A new visual screening assay for catalytic antibodies with retro-aldol retro-Michael activity

pp 1172–1175

Marina Shamis, Carlos F. Barbas, III and Doron Shabat\*

A black precipitate that is formed of three molecules of 3,4-cyclohexenoesculletin per ion of iron III is applied for visual detection of retro-aldol retro-Michael catalytic activity.

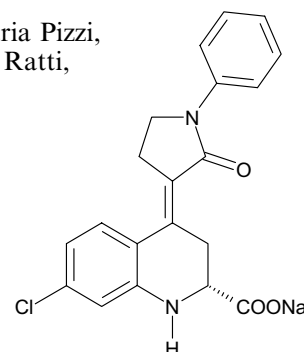


### Chiral tetrahydroquinoline derivatives as potent anti-hyperalgesic agents in animal models of sustained inflammation and chronic neuropathic pain

pp 1176–1180

Romano Di Fabio,\* Giuseppe Alvaro, Barbara Bertani, Daniele Donati, Domenica Maria Pizzi, Gabriella Gentile, Giorgio Pentassuglia, Simone Giacobbe, Simone Spada, Emiliangelo Ratti, Mauro Corsi, Mauro Quartaroli, Robert J. Barnaby and Giovanni Vitulli

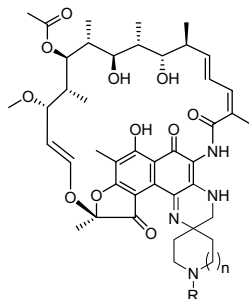
Chiral tetrahydroquinolines have been prepared by an asymmetric Mannich-type condensation reaction as in vivo potent anti-hyperalgesic agents in different animal models of chronic pain.



**Synthesis and antibacterial evaluation of a novel series of rifabutin-like spirorifamycins**

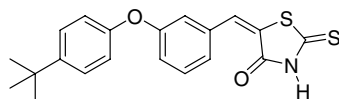
pp 1181–1184

In Ho Kim, Keith D. Combrink, Zhenkun Ma, Katrina Chapo, Dalai Yan, Paul Renick, Timothy W. Morris, Mark Pulse, Jerry W. Simecka and Charles Z. Ding\*

**Synthesis and evaluation of aryl thioxothiazolidinone inhibitors of ADAMTS-5 (Aggrecanase-2)**

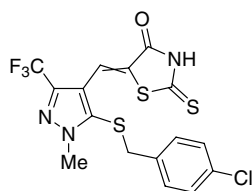
pp 1185–1188

Matthew G. Bursavich,\* Adam M. Gilbert, Sabrina Lombardi, Katy E. Georgiadis, Erica Reifenberg, Carl R. Flannery and Elisabeth A. Morris

ADAMTS-5 IC<sub>50</sub>: 1.7 μM**5-((1H-Pyrazol-4-yl)methylene)-2-thioxothiazolidin-4-one inhibitors of ADAMTS-5**

pp 1189–1192

Adam M. Gilbert,\* Matthew G. Bursavich, Sabrina Lombardi, Katy E. Georgiadis, Erica Reifenberg, Carl R. Flannery and Elisabeth A. Morris



ADAMTS-5 IC<sub>50</sub>: 1.1 μM  
ADAMTS-4 IC<sub>50</sub>: 44 μM

**Novel pyridinyl and pyrimidinylcarbazole sulfonamides as antiproliferative agents**

pp 1193–1196

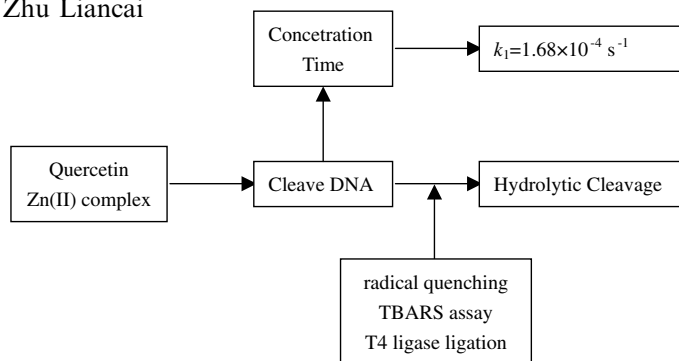
Laixing Hu, Zhuo-rong Li, Yue-ming Wang, Yanbin Wu, Jian-Dong Jiang\* and David W. Boykin\*

Carbazole sulfonamides **II** showed potent antiproliferative activity.

**Hydrolytic cleavage of DNA by quercetin zinc(II) complex**

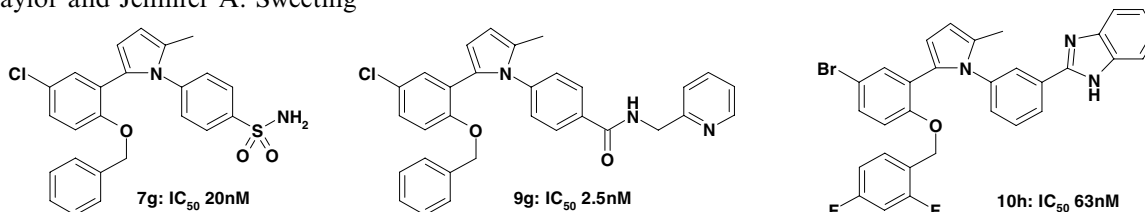
pp 1197–1199

Tan Jun,\* Wang Bochu\* and Zhu Liancai

**Discovery of novel, non-acidic 1,5-biaryl pyrrole EP<sub>1</sub> receptor antagonists**

pp 1200–1205

Adrian Hall,\* Stephen Atkinson, Susan H. Brown, Iain P. Chessell, Anita Chowdhury, Gerard M. P. Giblin, Paul Goldsmith, Mark P. Healy, Karamjit S. Jandu, Matthew R. Johnson, Anton D. Michel, Alan Naylor and Jennifer A. Sweeting

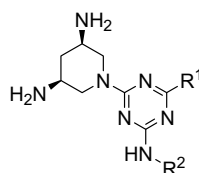


The discovery and SAR of novel non-acidic 1,5-biaryl pyrrole derivatives is described. Several new motifs were discovered that were found to be effective replacements for the carboxylic acid in a series of EP<sub>1</sub> receptor antagonists.

**Synthesis and SAR of 3,5-diamino-piperidine derivatives: Novel antibacterial translation inhibitors as aminoglycoside mimetics**

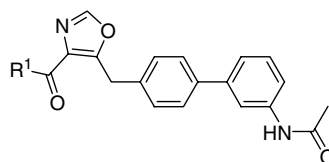
pp 1206–1210

Yuefen Zhou, Vlad E. Gregor, Benjamin K. Ayida, Geoffrey C. Winters, Zhongxiang Sun, Douglas Murphy, Greg Haley, Dwight Bailey, Jamie M. Froelich, Sarah Fish, Stephen E. Webber, Thomas Hermann and Daniel Wall\*

**Discovery and preliminary evaluation of 5-(4-phenylbenzyl)oxazole-4-carboxamides as prostacyclin receptor antagonists**

pp 1211–1215

Marc-Raleigh Brescia,\* Laura L. Rokosz, Andrew G. Cole, Tara M. Stauffer, John M. Lehrach, Douglas S. Auld, Ian Henderson and Maria L. Webb



The synthesis and evaluation of 5-(4-phenylbenzyl)oxazole-4-carboxamides as prostacyclin receptor antagonists is reported.



**In vitro selection of RNA aptamer against *Escherichia coli* release factor 1**

pp 1216–1220

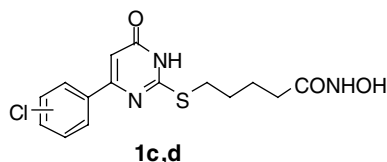
Shinsuke Sando,\* Atsushi Ogawa, Teruyuki Nishi, Masayoshi Hayami and Yasuhiro Aoyama\*

We successfully selected RNA aptamers against *Escherichia coli* release factor 1, allowing an enhanced nonsense suppression at the amber (UAG) stop codon.

**Discovery of uracil-based histone deacetylase inhibitors able to reduce acquired antifungal resistance and trailing growth in *Candida albicans***

pp 1221–1225

Antonello Mai,\* Dante Rotili, Silvio Massa, Gerald Brosch, Giovanna Simonetti, Claudio Passariello and Anna Teresa Palamara\*

**Simple criterion for selection of flavonoid compounds with anti-HIV activity**

pp 1226–1232

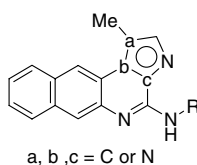
Veljko Veljkovic,\* Jean-François Mouscadet, Nevena Veljkovic, Sanja Glisic and Zeger Debyser

Flavonoid compounds represent an important natural source of antiretrovirals for AIDS therapy due to their significant anti-HIV-1 activity and low toxicity. Here we propose a simple theoretical criterion to discriminate active from inactive flavonoids that is suitable for rapid in silico screening of flavonoid libraries, and selection and optimization of lead compounds with anti-HIV-1 activity.

**Synthesis and biological evaluation of 4-amino derivatives of benzimidazoquinoxaline, benzimidazoquinoline, and benzopyrazoloquinazoline as potent IKK inhibitors**

pp 1233–1237

Francis Beaulieu,\* Carl Ouellet, Edward H. Ruediger, Makonen Belema, Yuping Qiu, Xuejie Yang, Jacques Banville, James R. Burke, Kurt R. Gregor, John F. MacMaster, Alain Martel, Kim W. McIntyre, Mark A. Pattoli, F. Christopher Zusi and Dolatrai Vyas



**Synthesis, characterization, antibacterial activity, and interaction with DNA of the vanadyl-enrofloxacin complex**

pp 1238–1242

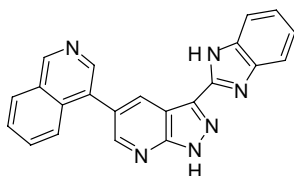
Eleni K. Efthimiadou, Nikos Katsaros, Alexandra Karaliota and George Psomas\*

The synthesis, characterization, antimicrobial activity and interaction with calf-thymus DNA of the mononuclear vanadyl complex with the second-generation quinolone enrofloxacin are reported.

**Synthesis of 3-(1*H*-benzimidazol-2-yl)-5-isoquinolin-4-ylpyrazolo[1,2-*b*]pyridine, a potent cyclin dependent kinase 1 (CDK1) inhibitor**

pp 1243–1245

Shenlin Huang,\* Ronghui Lin, Yang Yu, Yanhua Lu, Peter J. Connolly, George Chiu, Shengjian Li, Stuart L. Emanuel and Steven A. Middleton

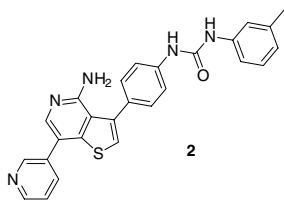


A novel compound 3-(1*H*-benzimidazol-2-yl)-5-isoquinolin-4-ylpyrazolo[1,2-*b*]pyridine was discovered to be a potent CDK1 inhibitor. An efficient chemistry was developed for the synthesis, with key steps including Pd(II) catalyzed Stille coupling reaction and sulfur(0) induced benzimidazole formation. The effects on VEGFR-2 kinase and tumour cell proliferation are also described.

**Thienopyridine urea inhibitors of KDR kinase**

pp 1246–1249

H. Robin Heyman,\* Robin R. Frey, Peter F. Bousquet, George A. Cunha, Maria D. Moskey, Asma A. Ahmed, Niru B. Soni, Patrick A. Marcotte, Lori J. Pease, Keith B. Glaser, Melinda Yates, Jennifer J. Bouska, Daniel H. Albert, Candace L. Black-Schaefer, Peter J. Dandliker, Kent D. Stewart, Paul Rafferty, Steven K. Davidsen, Michael R. Michaelides and Michael L. Curtin

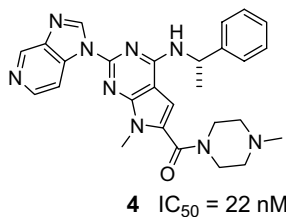


The evaluation of KDR kinase inhibitor **2** (IC<sub>50</sub> = 9 nM) and related analogs is reported.

**Development of new pyrrolopyrimidine-based inhibitors of Janus kinase 3 (JAK3)**

pp 1250–1253

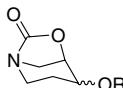
Michael P. Clark,\* Kelly M. George, Roger G. Bookland, Jack Chen, Steven K. Laughlin, Kumar D. Thakur, Wenlin Lee, Jan R. Davis, Ed J. Cabrera, Todd A. Brugel, John C. VanRens, Matthew J. Laufersweiler, Jennifer A. Maier, Mark P. Sabat, Adam Golebiowski, Vijay Easwaran, Mark E. Webster, Biswanath De and George Zhang

**4** IC<sub>50</sub> = 22 nM

**Bicyclic carbamates as inhibitors of papain-like cathepsin proteases**

pp 1254–1259

Robert Epple,\* Hugo D. Urbina, Ross Russo, Hong Liu, Daniel Mason, Badry Bursulaya, Christine Tumanut, Jun Li and Jennifer L. Harris

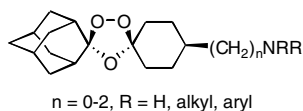


The discovery, SAR, and MoA investigation of a novel non-peptidic protease inhibitor scaffold are described.

**Weak base dispiro-1,2,4-trioxolanes: Potent antimalarial ozonides**

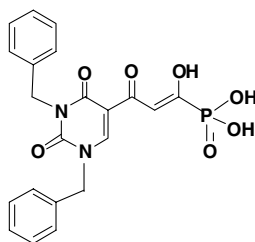
pp 1260–1265

Yuanqing Tang, Yuxiang Dong, Sergio Wittlin, Susan A. Charman, Jacques Chollet, Francis C. K. Chiu, William N. Charman, Hugues Matile, Heinrich Urwyler, Arnulf Dorn, Saroj Bajpai, Xiaofang Wang, Maniyan Padmanilayam, Jean M. Karle, Reto Brun and Jonathan L. Vennerstrom\*

**A novel diketo phosphonic acid that exhibits specific, strand-transfer inhibition of HIV integrase and anti-HIV activity**

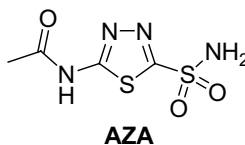
pp 1266–1269

Guochen Chi, Vasu Nair,\* Elena Semenova and Yves Pommier

**Identification of arylsulfonamides as Aquaporin 4 inhibitors**

pp 1270–1273

Vincent J. Huber,\* Mika Tsujita, Maya Yamazaki, Kenji Sakimura and Tsutomu Nakada



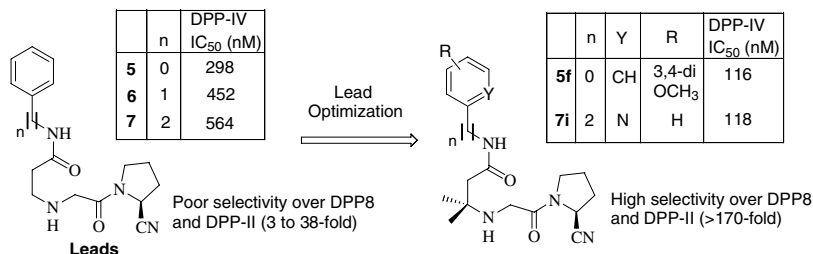
A series of carbonic anhydrase inhibitors, including AZA, have been found to inhibit AQP4 mediated water transport in an in vitro functional assay. AZA has an apparent IC<sub>50</sub> = 0.9 μM against human AQP4-M23.



### 3-[2-((2S)-2-Cyano-pyrrolidin-1-yl)-2-oxo-ethylamino]-3-methyl-butamide analogues as selective DPP-IV inhibitors for the treatment of type-II diabetes

pp 1274–1279

Mohane Selvaraj Coumar, Chung-Nien Chang, Chiung-Tong Chen, Xin Chen, Chia-Hui Chien, Ting-Yueh Tsai, Jai-Hong Cheng, Hsin-Yi Wu, Chia-Hung Han, Ssu-Hui Wu, Yu-Wen Huang, Tsu Hsu, Li-Jen Hsu, Yu-Sheng Chao, Hsing-Pang Hsieh\* and Weir-Torn Jiaang\*



### High-throughput screening affords novel and selective trypanothione reductase inhibitors with anti-trypanosomal activity

pp 1280–1283

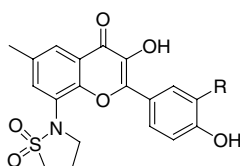
Derek C. Martyn, Deuan C. Jones, Alan H. Fairlamb and Jon Clardy\*

Trypanothione reductase (TR) was screened against 134,500 compounds. Four chemotypes were selective for TR over human glutathione reductase. The in vitro activity of 13 purchased compounds against TR and *Trypanosoma brucei* is summarized.

### 3-Hydroxychromones as cyclin-dependent kinase inhibitors: Synthesis and biological evaluation

pp 1284–1287

Jinho Lee,\* Taesik Park, Shinwu Jeong, Kyoung-Hee Kim and Changyong Hong

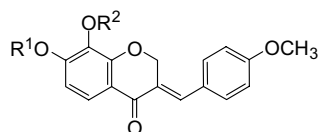


A novel series of 3-hydroxychromones were prepared and found to be CDK inhibitors. Isothiaszolidine 1,1-dioxide analogues showed potent CDK1 and CDK2 inhibitory activities and inhibited proliferation of EJ, HCT116, SW620, and MDA MB468 cancer cells.

### Synthesis, structural revision, and antioxidant activities of antimutagenic homoisoflavonoids from *Hoffmannosseggia intricata*

pp 1288–1290

Vidavalur Siddaiah, Muchchintala Maheswara, Chunduri Venkata Rao, Somepalli Venkateswarlu and Gottumukkala V. Subbaraju\*



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

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

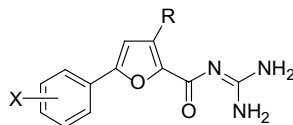
Intricatin (2) has been revised into 3 and antioxidant activity results are reported.



**3-Substituted-(5-arylfuran-2-ylcarbonyl)guanidines as NHE-1 inhibitors**

pp 1291–1295

Sunkyung Lee, Taemi Kim, Byung Ho Lee, Sung-eun Yoo, Kyunghye Lee and Kyu Yang Yi\*

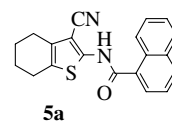


The synthesis and evaluation as NHE-1 inhibitors of 3-substituted-(5-arylfuran-2-ylcarbonyl)guanidines is described.

***N*-(3-Cyano-4,5,6,7-tetrahydro-1-benzothien-2-yl)amides as potent, selective, inhibitors of JNK2 and JNK3**

pp 1296–1301

Richard M. Angell, Francis L. Atkinson, Murray J. Brown, Tsu Tshen Chuang, John A. Christopher,\* Maria Cichy-Knight, Allison K. Dunn, Kendra E. Hightower, Susanna Malkakorpi, James R. Musgrave, Margarete Neu, Paul Rowland, Robyn L. Shea, Jeffery L. Smith, Donald O. Somers, Sonia A. Thomas, Gladstone Thompson and Ruolan Wang



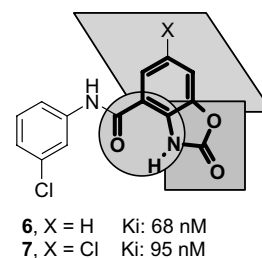
The identification and exploration of a novel, potent and selective series of *N*-(3-cyano-4,5,6,7-tetrahydro-1-benzothien-2-yl)amide inhibitors of JNK2 and JNK3 kinases is described. Compounds **5a** and **11a** were identified as potent inhibitors of JNK3 (pIC<sub>50</sub> 6.7 and 6.6, respectively), with essentially equal potency against JNK2 (pIC<sub>50</sub> 6.5). Selectivity within the mitogen-activated protein kinase (MAPK) family, against JNK1, p38α and ERK2, was observed for the series. X-ray crystallography of **5e** and **8a** in JNK3 revealed a unique binding mode, with the 3-cyano substituent forming an H-bond acceptor interaction with the hinge region of the ATP-binding site.

**Rational design, synthesis, and structure–activity relationship of benzoxazolones: New potent mglu5 receptor antagonists based on the fenobam structure**

pp 1302–1306

Simona M. Ceccarelli,\* Georg Jaeschke, Bernd Buettelmann, Jörg Huwyler, Sabine Kolczewski, Jens-Uwe Peters, Eric Prinssen, Richard Porter, Will Spooren and Eric Vieira

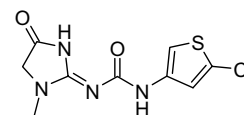
A novel class of potent and stable mGlu5 receptor antagonists was developed by combining information from a high-throughput screening campaign with the structure of the known anxiolytic fenobam.

**Synthesis and biological evaluation of fenobam analogs as mGlu5 receptor antagonists**

pp 1307–1311

Georg Jaeschke,\* Richard Porter, Bernd Büttelmann, Simona M. Ceccarelli, Wolfgang Guba, Bernd Kuhn, Sabine Kolczewski, Jörg Huwyler, Vincent Mutel, Jens-Uwe Peters, Theresa Ballard, Eric Prinssen, Eric Vieira, Jürgen Wichmann and Will Spooren

Optimization of affinity and microsomal stability led to identification of the potent, metabolically stable fenobam analog **4l**. Robust in vivo efficacy of **4l** was demonstrated in four different models of anxiety. Additionally, a ligand based pharmacophore alignment of fenobam and MPEP is proposed.

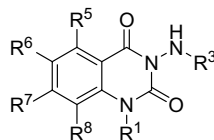


**4l**  
 K<sub>i</sub> (<sup>3</sup>H-MPEP): 78 nM  
 FLIPR: 436 nM

**Structure–activity relationships of 3-aminoquinazolin-2(1H)-ones, a new class of bacterial type-2 topoisomerase (DNA gyrase and topo IV) inhibitors**

pp 1312–1320

Tuan P. Tran,\* Edmund L. Ellsworth, Joseph P. Sanchez, Brian M. Watson, Michael A. Stier, H. D. Hollis Showalter, John M. Domagala, Martin A. Shapiro, E. Themis Joannides, Stephen J. Gracheck, Dai Q. Nguyen, Paul Bird, Judy Yip, Anurag Sharadendu, Chan Ha, Saeed Ramezani, Xiujuan Wu and Rajeshwar Singh

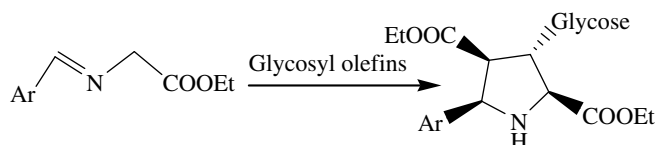


The syntheses and antibacterial SAR of the 3-aminoquinazolin-2(1H)-ones are reported.

**Diastereoselective synthesis of glycosylated prolines as  $\alpha$ -glucosidase inhibitors and organocatalyst in asymmetric aldol reaction**

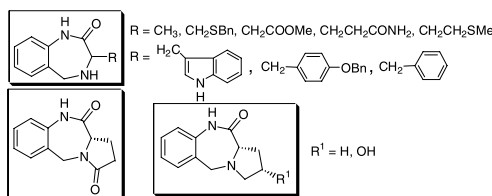
pp 1321–1325

Jyoti Pandey, Namrata Dwivedi, Nimisha Singh, A. K. Srivastava, A. Tamarkar and R. P. Tripathi\*


**Amino acid-based enantiomerically pure 3-substituted 1,4-benzodiazepin-2-ones: A new class of anti-ischemic agents**

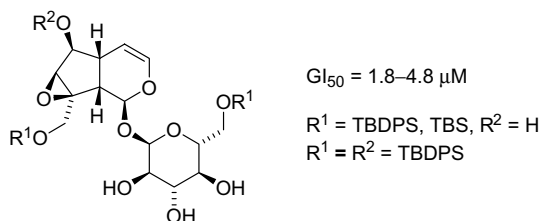
pp 1326–1331

Jitendra Kumar Mishra, Puja Garg, Preeti Dohare, Ashutosh Kumar, Mohammad Imran Siddiqi, Madhur Ray and Gautam Panda\*


**Novel antiproliferative analogs of the *Taq* DNA polymerase inhibitor catalpol**

pp 1332–1335

Carlos R. Pungitore, Leticia G. León, Celina García, Víctor S. Martín, Carlos E. Tonn and José M. Padrón\*

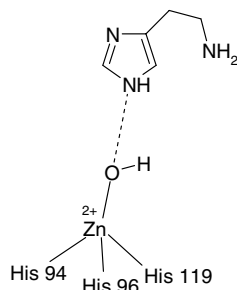


A series of new silylated catalpol analogs inhibit in a dose-dependent manner the proliferation of a panel of diverse human cancer cell lines through G<sub>0</sub>/G<sub>1</sub> phase arrest.

**Carbonic anhydrase activators: An activation study of the human mitochondrial isoforms VA and VB with amino acids and amines**

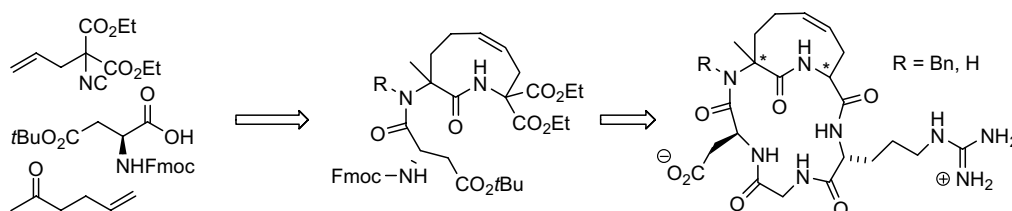
pp 1336–1340

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


**Synthesis and biological evaluation of new conformationally biased integrin ligands based on a tetrahydroazoninone scaffold**

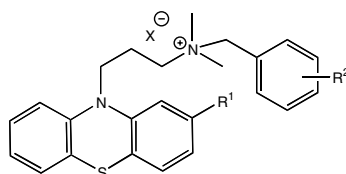
pp 1341–1345

Luca Banfi,\* Andrea Basso, Gianluca Damonte, Federico De Pellegrini, Andrea Galatini, Giuseppe Guanti, Ilaria Monfardini, Renata Riva and Carlo Scapolla


**Synthesis and antitubercular activity of quaternized promazine and promethazine derivatives**

pp 1346–1348

Aaron B. Bate, Jay H. Kalin, Eric M. Fooksman, Erica L. Amorose, Cristofer M. Price, Heather M. Williams, Michael J. Rodig, Miguel O. Mitchell,\* Sang Hyun Cho, Yuehong Wang and Scott G. Franzblau



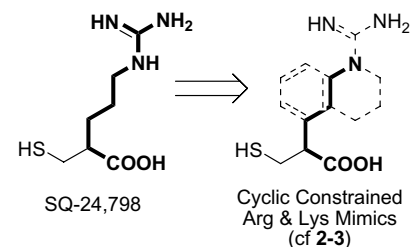
Quaternized promazine derivatives **4b** ( $R^1 = CF_3$ ,  $R^2 = 4\text{-Cl}$ ;  $X = Cl$ ) and **4c** ( $R^1 = CF_3$ ;  $R^2 = 3\text{-Cl}$ ;  $X = Cl$ ) inhibit actively growing and non-replicating *Mycobacterium tuberculosis* at  $<4$  and  $<8 \mu M$ , respectively.

**3-Mercaptopropionic acids as efficacious inhibitors of activated thrombin activatable fibrinolysis inhibitor (TAFIa)**

pp 1349–1354

Imadul Islam, Judi Bryant, Karen May, Raju Mohan, Shendong Yuan, Lorraine Kent, John Morser, Lei Zhao, Ron Vergona, Kathy White, Marc Adler, Marc Whitlow and Brad O. Buckman\*

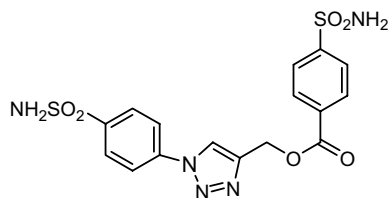
A novel series of cyclic potent, selective, small molecule, thiol-based inhibitors of activated Thrombin Activatable Fibrinolysis Inhibitor (TAFIa) are described. Inhibition of TAFIa with (rac)**2a** resulted in dose dependent acceleration of human plasma clot lysis in vitro and was efficacious as an adjunct to tPA in an in vivo rabbit jugular vein thrombolysis model.



**Anti-mycobacterial activity of a bis-sulfonamide**

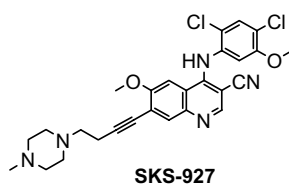
pp 1355–1357

Brendan L. Wilkinson, Laurent F. Bornaghi, Anthony D. Wright,  
Todd A. Houston\* and Sally-Ann Poulsen\*


**Inhibition of Src kinase activity by 7-ethynyl-4-phenylamino-3-quinolinecarbonitriles:  
Identification of SKS-927**

pp 1358–1361

Diane H. Boschelli,\* Ana Carolina Barrios Sosa, Jennifer M. Golas and Frank Boschelli

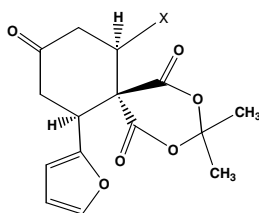


Of a series of 7-ethynyl-3-quinolinecarbonitriles, the most potent Src inhibitory activity was observed with SKS-927.

**Synthesis and HIV-1 integrase inhibitory activity of spiroundecane(ene) derivatives**

pp 1362–1368

Elvira E. Shults,\* Elena A. Semenova, Allison A. Johnson, Svetlana P. Bondarenko,  
Irina Y. Bagryanskaya, Yuri V. Gatilov, Genrikh A. Tolstikov and Yves Pommier\*

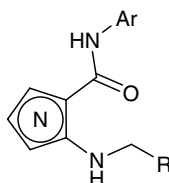


X = furan-2-yl, indol-3-yl, Ph, 4-MeOC<sub>6</sub>H<sub>4</sub>, C<sub>6</sub>H<sub>5</sub>, 4-Br-C<sub>6</sub>H<sub>4</sub>, 2-Cl-C<sub>6</sub>H<sub>4</sub>,  
4-MeO-3-OH-C<sub>6</sub>H<sub>3</sub>, 3-MeO-4-MeO-C<sub>6</sub>H<sub>3</sub>, 2-Me-4-MeO-C<sub>6</sub>H<sub>3</sub>, 2-MeO-3-MeO-C<sub>6</sub>H<sub>3</sub>.

***ortho*-Substituted azoles as selective and dual inhibitors of VEGF receptors 1 and 2**

pp 1369–1375

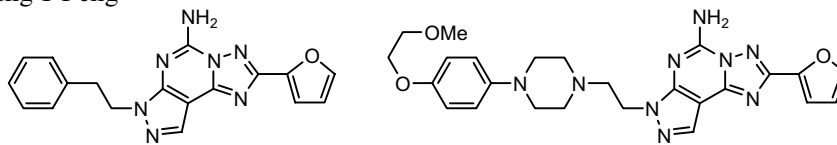
Alexander S. Kiselyov, Evgueni L. Piatnitski, Alexander V. Samet, Victor P. Kisliy  
and Victor V. Semenov\*



A novel series of potent *ortho*-substituted azole derivatives active against kinases VEGFR-1 and VEGFR-2 is described. Both specific and dual ATP-competitive inhibitors of VEGFR-2 were identified.

### Potent, selective, and orally active adenosine A<sub>2A</sub> receptor antagonists: Arylpiperazine derivatives of pyrazolo[4,3-*e*]-1,2,4-triazolo[1,5-*c*]pyrimidines pp 1376–1380

Bernard R. Neustadt,\* Jinsong Hao, Neil Lindo, William J. Greenlee, Andrew W. Stamford, Deen Tulshian, Ennio Ongini, John Hunter, Angela Monopoli, Rosalia Bertorelli, Carolyn Foster, Leyla Arik, Jean Lachowicz, Kwokei Ng and Kung-I Feng



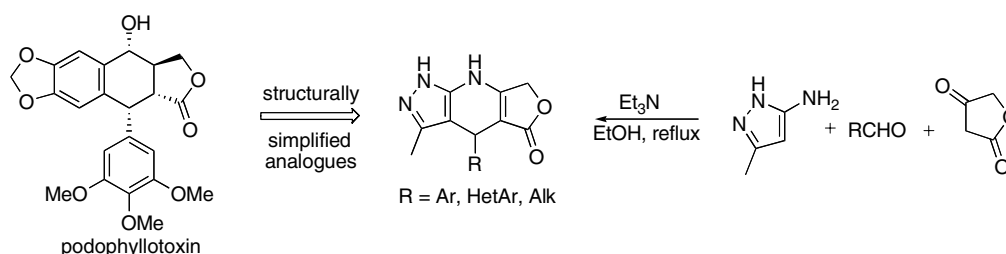
SCH 58261

SCH 420814 A<sub>2A</sub> Ki = 1.1 nM, A<sub>1</sub>/A<sub>2A</sub> = 1340 X

Starting from the known adenosine A<sub>2A</sub> antagonist SCH 58261, SAR-guided structural optimization led to SCH 420814, which is a potent and selective A<sub>2A</sub> antagonist, with good pharmacokinetics and excellent oral activity in rodent models of Parkinson's disease.

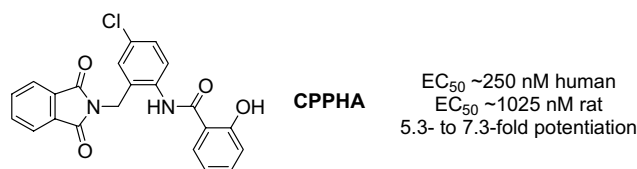
### Structural simplification of bioactive natural products with multicomponent synthesis: Dihydropyridopyrazole analogues of podophyllotoxin pp 1381–1385

Igor V. Magedov,\* Madhuri Manpadi, Elena Rozhkova, Nikolai M. Przheval'skii, Snezna Rogelj, Scott T. Shors, Wim F. A. Steelant, Severine Van slambrouck and Alexander Kornienko\*



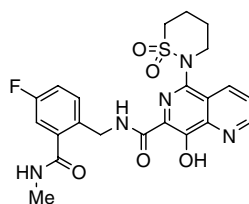
### Challenges in the development of mGluR5 positive allosteric modulators: The discovery of CPPHA pp 1386–1391

Zhijian Zhao,\* David D. Wisnoski, Julie A. O'Brien, Wei Lemaire, David L. Williams, Marlene A. Jacobson, Marion Wittman, Sookhee N. Ha, Herve Schaffhauser, Cyrille Sur, Doug J. Pettibone, Mark E. Duggan, P. Jeffrey Conn, George D. Hartman and Craig W. Lindsley



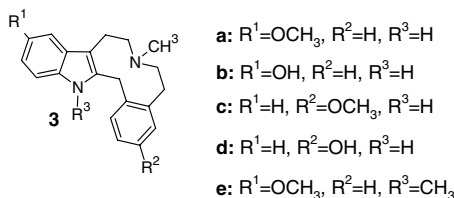
### A potent and orally active HIV-1 integrase inhibitor pp 1392–1398

Melissa S. Egbertson,\* H. Marie Moritz, Jeffrey Y. Melamed, Wei Han, Debra S. Perlow, Michelle S. Kuo, Mark Embrey, Joseph P. Vacca, Matthew M. Zrada, Amanda R. Cortes, Audrey Wallace, Yvonne Leonard, Daria J. Hazuda, Michael D. Miller, Peter J. Felock, Kara A. Stillmock, Marc V. Witmer, William Schleif, Lori J. Gabryelski, Gregory Moyer, Joan D. Ellis, Lixia Jin, Wei Xu, Matthew P. Braun, Kellem Kassahun, Nancy N. Tsou and Steven D. Young



### Dopamine/serotonin receptor ligands. Part 15: Oxygenation of the benz-indolo-azecine LE 300 leads to novel subnanomolar dopamine D<sub>1</sub>/D<sub>5</sub> antagonists pp 1399–1402

Christoph Enzensperger, Susann Kilian, Marit Ackermann, Anne Koch, Kristin Kelch and Jochen Lehmann\*

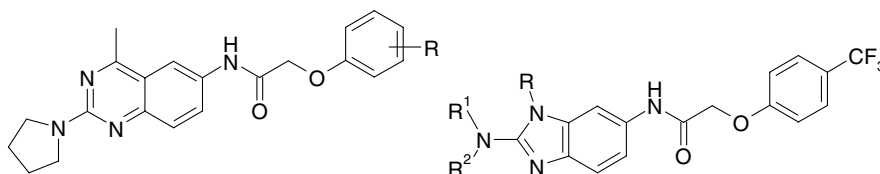


To explore SAR, the synthesis of novel azecine-styled dopamine antagonists and screening was performed at all human-cloned dopamine receptor subtypes. The benz-indolo-azecine with the highest affinity for D<sub>5</sub> until now, turned out to be **3e** K<sub>i</sub> = 0.23 nM.

### Quinazoline and benzimidazole MCH-1R antagonists

pp 1403–1407

Rosa Arienzo, Sue Cramp, Hazel J. Dyke,\* Peter M. Lockey, Dennis Norman, Alan G. Roach, Phil Smith, Melanie Wong and Stephen P. Wren



The discovery, synthesis, evaluation and structure–activity relationships of a series of quinazolines and benzimidazoles as MCH-1R antagonists are described.

### A molecular modeling analysis of novel non-hydroxamate inhibitors of TACE

pp 1408–1412

James E. Sheppeck, II,\* Andrew Tebben,\* John L. Gilmore, Anle Yang, Zelda R. Wasserman, Carl P. Decicco and James J.-W. Duan

We have developed a number of hydroxamate and non-hydroxamate inhibitors of TACE that possess the selective quinolinemethoxy P1' group. Using the X-ray co-crystal structure of our hydroxamate IK682 and TACE, and a co-crystal structure of a pyrimidinetrione in MMP-8, we have developed a highly plausible pharmacophore model of how our pyrimidinetrione and hydantoin inhibitors bind to TACE.

### Discovery of novel hydantoins as selective non-hydroxamate inhibitors of tumor necrosis factor- $\alpha$ converting enzyme (TACE)

pp 1413–1417

James E. Sheppeck, II,\* John L. Gilmore, Anle Yang, Xiao-Tao Chen, Chu-Biao Xue, John Roderick, Rui-Qin Liu, Maryanne B. Covington, Carl P. Decicco and James J.-W. Duan

We have discovered novel hydantoins that are drug-like, non-hydroxamate inhibitors of the matrix metalloprotease TACE with nM potency. Synthesis and SAR of these inhibitors is described as well as their selectivity against other MMPs.

## Synthesis and evaluation of novel chromogenic aminopeptidase substrates for microorganism detection and identification

pp 1418–1421

Arthur L. James, John D. Perry, Annette Rigby and Stephen P. Stanforth\*



## Discovery of 2-iminobenzimidazoles as a new class of trypanothione reductase inhibitor by high-throughput screening

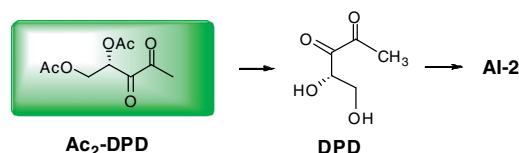
pp 1422–1427

Georgina A. Holloway, Jonathan B. Baell, Alan H. Fairlamb, Patrizia M. Novello, John P. Parisot, John Richardson, Keith G. Watson and Ian P. Street\*

A high-throughput screening campaign of a library of 100,000 lead-like compounds identified 2-iminobenzimidazoles (I) as a novel class of trypanothione reductase inhibitors. These 2-iminobenzimidazoles display potent trypanocidal activity against *Trypanosoma brucei rhodesiense*, do not inhibit closely related human glutathione reductase and have low cytotoxicity against mammalian cells.

**Ac<sub>2</sub>-DPD, the bis-(*O*)-acetylated derivative of 4,5-dihydroxy-2,3-pentanedione (DPD) is a convenient stable precursor of bacterial quorum sensing autoinducer AI-2** pp 1428–1431

Marine Frezza, Laurent Soulère, Damien Balestrino, Michel Gohar, Christian Deshayes, Yves Queneau, Christiane Forestier and Alain Doutheau\*



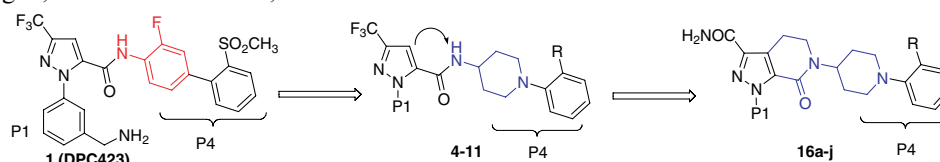
Ac<sub>2</sub>-DPD induces bioluminescence in *Vibrio harveyi* and β-galactosidase activity in *Salmonella enterica* Typhimurium, and inhibits biofilm formation in *Bacillus cereus*. Its biological activity is most likely due to in situ hydrolysis into DPD. Ac<sub>3</sub>-DPD can thus be considered as a stable and storable precursor of DPD.



### Pyrazole-based factor Xa inhibitors containing *N*-arylpiperidinyl P4 residues

pp 1432–1437

Jennifer X. Qiao,\* Xuhong Cheng, Joanne M. Smallheer, Robert A. Galembo, Spencer Drummond, Donald J. P. Pinto, Daniel L. Cheney, Kan He, Pancras C. Wong, Joseph M. Luetggen, Robert M. Knabb, Ruth R. Wexler and Patrick Y. S. Lam

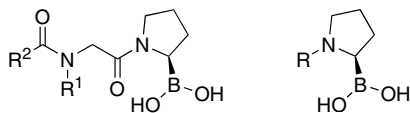


The synthesis, SAR, pharmacokinetic profile, and modeling studies of both monocyclic and fused pyrazoles containing substituted *N*-arylpiperidinyl P4 moieties that are potent and selective factor Xa inhibitors will be discussed. Fused pyrazole analog **16a**, with a 2'-methylsulfonylphenyl piperidine P4 group, was shown to be the best compound in this series (FXa  $K_i$  = 0.35 nM) based on potency, selectivity, and pharmacokinetic profile.

**Synthesis and structure–activity relationship of *N*-acyl-Gly-, *N*-acyl-Sar- and *N*-blocked-boroPro inhibitors of FAP, DPP4, and POP**

pp 1438–1442

Thuy Tran, Clifford Quan, Conrad Yap Edosada, Mark Mayeda, Christian Wiesmann, Dan Sutherlin and Beni B. Wolf\*

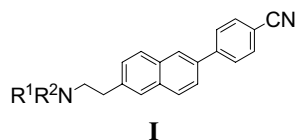


The structure–activity relationship of various *N*-acyl-Gly-, *N*-acyl-Sar-, and *N*-blocked-boroPro derivatives against three prolyl peptidases (FAP, DPP4, and POP) was explored.

**4-[6-(2-Aminoethyl)naphthalen-2-yl]benzonitriles are potent histamine H<sub>3</sub> receptor antagonists with high CNS penetration**

pp 1443–1446

Lawrence A. Black,\* Diana L. Nersesian, Padam Sharma, Yi-Yin Ku, Youssef L. Bennani, Kennan C. Marsh, Thomas R. Miller, Timothy A. Esbenshade, Arthur A. Hancock and Marlon Cowart

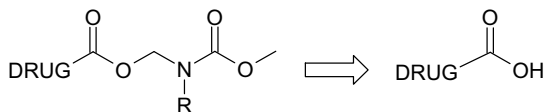


The synthesis and SAR of a series of naphthylethylamines **I** as histamine H<sub>3</sub> receptor antagonists with a high brain to plasma concentration ratio is reported.

***N*-Alkyl-*N*-alkyloxycarbonylaminomethyl (NANAOCAM) prodrugs of carboxylic acid containing drugs**

pp 1447–1450

Susruta Majumdar and Kenneth B. Sloan\*



*N*-Alkyl-*N*-alkyloxycarbonylaminomethyl and *N*-aryl-*N*-alkyloxycarbonylaminomethyl derivatives of carboxylic acids hydrolyse to the parent carboxylic acid both chemically and thereby serving as useful prodrugs of carboxylic acid containing drugs.

**Novel membrane-localizing TEMPO derivatives for measurement of cellular oxidative stress at the cell membrane**

pp 1451–1454

Shizuka Ban, Hidehiko Nakagawa,\* Takayoshi Suzuki and Naoki Miyata\*

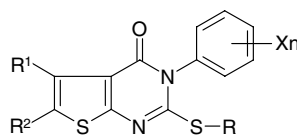
We designed and synthesized membrane-localizing TEMPO derivatives and demonstrated that a synthesized probe **1** localized and detected oxidative stress in the cell membrane in an activated macrophage-like cell line.



**Structure–activity relationship analysis of a novel necroptosis inhibitor, Necrostatin-5**

pp 1455–1465

Ke Wang, Jinfeng Li, Alexei Degterev, Emily Hsu, Junying Yuan and Chengye Yuan\*

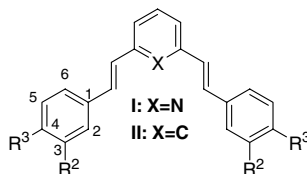


Structural effect of substituents on Nec-5, a new class of small molecule inhibitors of necroptosis, was described. Significant influence was found in structural variation of R, R<sup>1</sup>, R<sup>2</sup>, and Xn in the parent molecule.

**Bis-styrylpyridine and bis-styrylbenzene derivatives as inhibitors for Aβ fibril formation**

pp 1466–1470

Seong Rim Byeon, Ji Hoon Lee, Ji-Hoon Sohn, Dong Chan Kim, Kye Jung Shin, Kyung Ho Yoo, Inhee Mook-Jung, Won Koo Lee and Dong Jin Kim\*



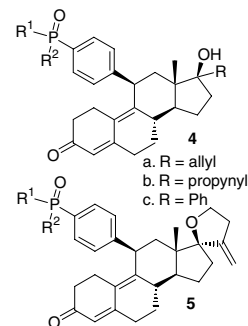
The new bis-styrylpyridine and bis-styrylbenzene derivatives were designed and synthesized. Most of them showed excellent inhibitory activities for Aβ fibril formation at IC<sub>50</sub> of 0.1–2.7 μM which is comparable to curcumin (IC<sub>50</sub> of 0.8 μM). In particular, **I-7** and **II-2** exhibited the best combination of inhibitory activity and compound cytotoxicity.

**Discovery of novel phosphorus-containing steroids as selective glucocorticoid receptor antagonist**

pp 1471–1474

Weiqin Jiang,\* James J. Fiordeliso, George Allan, Olivia Linton, Pamela Tannenbaum, Jun Xu, Peifang Zhu, Joseph Gunnet, Keith Demarest, Scott Lundeen and Zhihua Sui

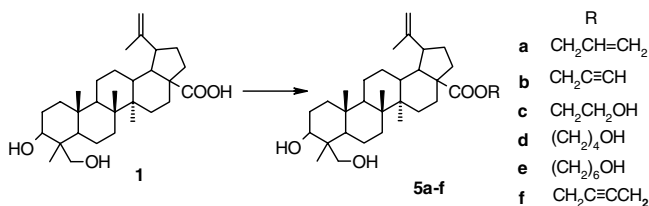
The synthesis and biological activities of the glucocorticoid receptor antagonists **4** and **5** are reported.

**Synthesis and cytotoxic activity of 17-carboxylic acid modified 23-hydroxy betulinic acid ester derivatives**

pp 1475–1478

Yi Bi, Jinyi Xu, Xiaoming Wu,\* Wencai Ye, Shengtao Yuan and Luyong Zhang

The derivatives **5a–f** of 23-hydroxy betulinic acid have better cytotoxicity than 23-hydroxy betulinic acid and betulinic acid in vitro. And they are also more potent than 23-hydroxy betulinic acid in vivo. The research results have been applied. China Patent: CN 10040277.2, 2006.



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

\*Corresponding author

①\* Supplementary data available via ScienceDirect

**COVER**

Typical snapshot of **7b** bound to HIV-RT from an MC simulation. Carbon atoms of **7b** are gold; from the left, Tyr181, Tyr188, Phe227, Leu100, Lys101; Trp229 at the top, Val106 at the bottom. H-bond with Lys101 O on right. Some residues in front including Glu138 have been removed for clarity. The water on N5 is also H-bonded to a carboxylate O of Glu138. [Thakur, V. T.; Kim, J. T.; Hamilton, A. D.; Bailey, C. M.; Domaoal, R. A.; Wang, L.; Anderson, K. S.; Jorgensen, W. L. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5664.]

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