

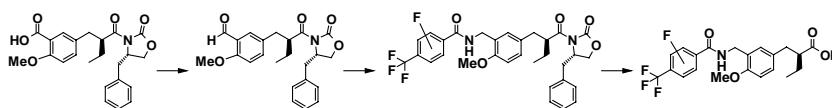
## Contents

### ARTICLES

**Concise and efficient asymmetric synthesis of (*S*)-2-ethylphenylpropanoic acid derivatives: Dual agonists for human peroxisome proliferator-activated receptor  $\alpha$  and  $\delta$**

pp 771–774

Jun-ichi Kasuga, Yuichi Hashimoto and Hiroyuki Miyachi\*

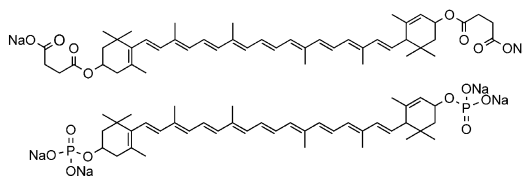


Optically active (*S*)-2-ethylphenylpropanoic acid derivatives, dual agonists for human peroxisome proliferator-activated receptor (PPAR)  $\alpha$  and  $\delta$ , were efficiently prepared.

**The synthesis and aqueous superoxide anion scavenging of water-dispersible lutein esters**

pp 775–781

Geoff Nadolski, Arturo J. Cardounel, Jay L. Zweier and Samuel F. Lockwood\*

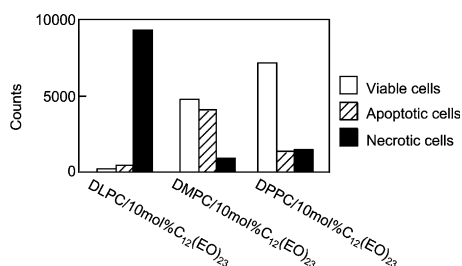


Novel water-dispersible lutein esters were prepared, which demonstrated potent, direct superoxide scavenging ability in an in vitro isolated human neutrophil assay.

**Two methylene groups in phospholipids distinguish between apoptosis and necrosis for tumor cells**

pp 782–785

Hideaki Nagami, Koji Nakano, Hideaki Ichihara, Yoko Matsumoto and Ryuichi Ueoka\*



It was found that two methylene groups in phospholipids having the same head group could clearly distinguish between apoptosis and necrosis for human leukemia cells.

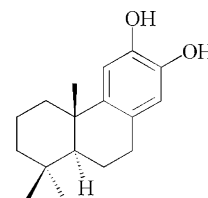


**Isolation, synthesis, and anti-tumor activities of a novel class of podocarpic diterpenes**

pp 786–789

Yi Xiong, Kuiwu Wang, Yuanjiang Pan,\* Hongxiang Sun and Jue Tu

A novel unusual 17-carbon diterpenoid, named (+)-7-deoxynimbidiol, was isolated from the stalks of *Celastrus hypoleucus* (Oliv.) Warb., and its racemate and derivatives were synthesized. When their anti-tumor activities were evaluated, compounds **2**, **11**, and **2b** were found to have potency against the cultured human-tumor cell lines HeLa, A549, CNE, and MCF in vitro. The SAR (structure–activity relationship) was discussed.

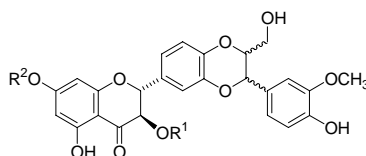


(+)–7-deoxynimbidiol

**Microbial transformation of silybin by *Trichoderma koningii***

pp 790–793

Hyun Jung Kim, Hae-Suk Park and Ik-Soo Lee\*



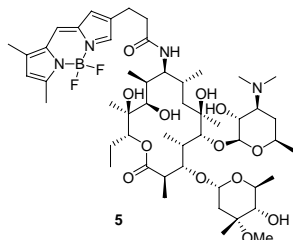
silybin 3-*O*- $\beta$ -D-glucopyranoside (**3**, **5**): R<sup>1</sup> =  $\beta$ -D-glucopyranosyl, R<sup>2</sup> = H  
 silybin 7-*O*- $\beta$ -D-glucopyranoside (**4**, **6**): R<sup>1</sup> = H, R<sup>2</sup> =  $\beta$ -D-glucopyranosyl

Biotransformation of silybin diastereomers with *Trichoderma koningii* gave two pairs of glucosylated derivatives, silybin 3-*O*- $\beta$ -D-glucopyranosides (**3** and **5**) and silybin 7-*O*- $\beta$ -D-glucopyranosides (**4** and **6**).

**Design, synthesis, and biological evaluation of BODIPY®–erythromycin probes for bacterial ribosomes**

pp 794–797

Jing Li, In Ho Kim, Eric D. Roche, Doug Beeman, A. Simon Lynch, Charles Z. Ding\* and Zhenkun Ma

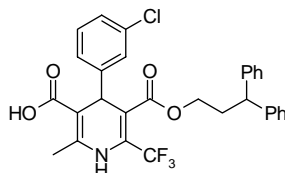


BODIPY®–erythromycin probes of bacterial ribosomes were designed, synthesized, and evaluated. The synthetic fluorescent probe **5** was successfully adapted in our ultra high-throughput screening (uHTS) for identifying novel ribosome inhibitors.

**Structure–activity relationship study of 1,4-dihydropyridine derivatives blocking N-type calcium channels**

pp 798–802

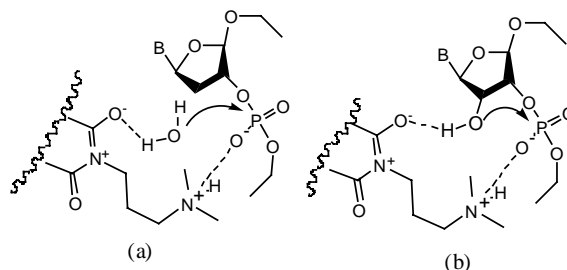
Takashi Yamamoto, Seiji Niwa, Seiji Ohno, Tomoyuki Onishi, Hiroyuki Matsueda, Hajime Koganei, Hisayuki Uneyama, Shin-ichi Fujita, Tomoko Takeda, Morikazu Kito, Yukitsugu Ono, Yuki Saitou, Akira Takahara, Seinosuke Iwata and Masataka Shoji\*



The structure–activity relationship studies of 1,4-dihydropyridine-3-carboxylic acid derived N-type calcium channel blockers were reported. As a consequence of this study, we found orally active 4-(3-chloro-phenyl)-2-methyl-6-trifluoromethyl-1,4-dihydropyridine-3,5-dicarboxylic acid 5-(3,3-diphenylpropyl) ester (**21b**).

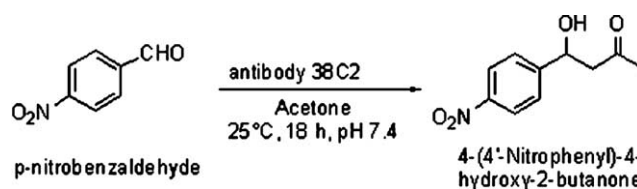
**Hydrolysis of plasmid DNA and RNA by amino alkyl naphthalimide as metal-free artificial nuclease**

pp 803–806

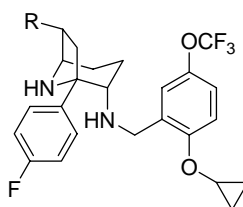
Qing Yang,\* Jianqiang Xu, Yuanshe Sun, Zhigang Li,  
Yonggang Li and Xuhong Qian\***Enhancing the synthetic utility of aldolase antibody 38C2**

pp 807–810

Kalyani Mondal, Namakkal G. Ramesh, Ipsita Roy and Munishwar N. Gupta\*

**Synthesis and structure–activity relationships of 8-azabicyclo[3.2.1]octane benzylamine NK<sub>1</sub> antagonists**

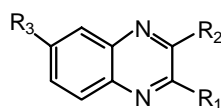
pp 811–814

Christopher G. Thomson,\* Emma Carlson, Gary G. Chicchi, Janusz J. Kulagowski,  
Marc M. Kurtz, Christopher J. Swain, Kwei-Lan C. Tsao and Alan Wheeldon

A series of 8-azabicyclo[3.2.1]octane benzylamine hNK<sub>1</sub> antagonists has been explored. Substitution with acidic moieties at the 6-*exo* position leads to high affinity hNK<sub>1</sub> antagonists which are selective over the hERG channel.

**Synthesis and antiprotozoal activity of some new synthetic substituted quinoxalines**

pp 815–820

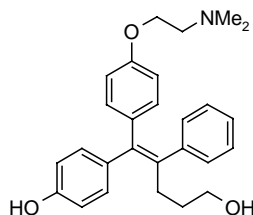
Xu Hui, Julie Desrivot, Christian Bories, Philippe M. Loiseau, Xavier Franck,  
Reynald Hocquemiller and Bruno Figadère\*

A series of substituted quinoxalines (29 compounds) was synthesized and evaluated against several protozoa. Some of them showed promising antileishmanial activity against *Leishmania donovani*.

**Structure-guided synthesis of tamoxifen analogs with improved selectivity for the orphan ERR $\gamma$** 

pp 821–824

Esther Y. H. Chao, Jon L. Collins, Stéphanie Gaillard, Aaron B. Miller, Liping Wang,  
 Lisa A. Orband-Miller, Robert T. Nolte, Donald P. McDonnell,  
 Timothy M. Willson and William J. Zuercher\*

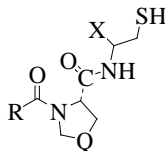


The design and synthesis of 4-hydroxytamoxifen (4-OHT) derivatives with improved binding selectivity for the orphan ERR $\gamma$  are described.

**Synthesis and pharmacochemical study of novel polyfunctional molecules combining anti-inflammatory, antioxidant, and hypocholesterolemic properties**

pp 825–829

Christos M. Doulgkeris, Dimitrios Galanakis, Angeliki P. Kourounakis, Karyofyllis C. Tsiakitzis,  
 Antonios M. Gavalas, Phaedra T. Eleftheriou, Panagiotis Victoratos, Eleni A. Rekka and  
 Panos N. Kourounakis\*

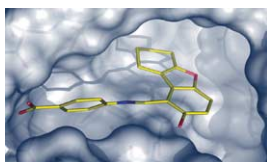


R = Indomethacin or naproxen residue; Q = CH<sub>2</sub>, CHOH or (CH<sub>2</sub>)<sub>2</sub>; X = H or COOC<sub>2</sub>H<sub>5</sub>.

**From genome to drug lead: Identification of a small-molecule inhibitor of the SARS virus**

pp 830–833

Andrea J. Dooley, Nice Shindo, Barbara Taggart, Jewn-Giew Park and Yuan-Ping Pang\*

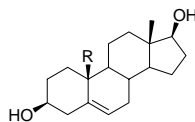


A small-molecule inhibitor of SARS-CoV, exhibiting an EC<sub>50</sub> of 23  $\mu$ M in cell-based assays, was identified by virtual screening against a computer model of a SARS-CoV cysteine proteinase.

**Androstenediol analogs as ER- $\beta$ -selective SERMs**

pp 834–838

Timothy A. Blizzard,\* Candido Gude, Jerry D. Morgan II, Wanda Chan,  
 Elizabeth T. Birzin, Marina Mojena, Consuelo Tudela, Fang Chen, Kristin Knecht,  
 Qin Su, Bryan Kraker, Ralph T. Mosley, Mark A. Holmes, Nandini Sharma,  
 Paula M. D. Fitzgerald, Susan P. Rohrer and Milton L. Hammond



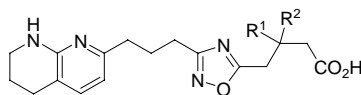
3 - 28

A series of 19-substituted androstenediol derivatives was prepared. Some of the novel analogs were surprisingly potent and selective ligands for ER- $\beta$ .

**Convergent, parallel synthesis of a series of  $\beta$ -substituted 1,2,4-oxadiazole butanoic acids as potent and selective  $\alpha_v\beta_3$  receptor antagonists**

pp 839–844

Mark L. Boys,\* Lori A. Schretzman, Nizal S. Chandrakumar, Michael B. Tollefson, Scott B. Mohler, Victoria L. Downs, Thomas D. Penning, Mark A. Russell, John A. Wendt, Barbara B. Chen, Heather G. Stenmark, Hongwei Wu, Dale P. Spangler, Michael Clare, Bipin N. Desai, Ish K. Khanna, Maria N. Nguyen, Tiffany Duffin, V. Wayne Engleman, Mary Beth Finn, Sandra K. Freeman, Melanie L. Hanneke, Jeffery L. Keene, Jon A. Klover, G. Allen Nickols, Maureen A. Nickols, Christina N. Steininger, Marisa Westlin, William Westlin, Yi X. Yu, Yaping Wang, Christopher R. Dalton and Sarah A. Norring



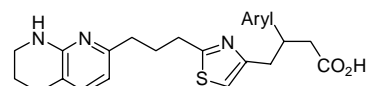
Synthesis of a series of potent and selective  $\alpha_v\beta_3$  antagonists containing a 1,2,4-oxadiazole core is reported.

**Synthesis of 2,5-thiazole butanoic acids as potent and selective  $\alpha_v\beta_3$  integrin receptor antagonists with improved oral pharmacokinetic properties**

pp 845–849

John A. Wendt,\* Hongwei Wu, Heather G. Stenmark, Mark L. Boys, Victoria L. Downs, Thomas D. Penning, Barbara B. Chen, Yaping Wang, Tiffany Duffin, Mary Beth Finn, Jeffery L. Keene, V. Wayne Engleman, Sandra K. Freeman, Melanie L. Hanneke, Kristen E. Shannon, Maureen A. Nickols, Christina N. Steininger, Marissa Westlin, Jon A. Klover, William Westlin, G. Allen Nickols and Mark A. Russell

A series of 2,5 thiazole containing compounds are described, which are potent antagonists of the integrin  $\alpha_v\beta_3$  and show selectivity relative to the other integrins, such as  $\alpha_{IIb}\beta_3$  and  $\alpha_v\beta_6$ . These analogs were demonstrated to have high bioavailability relative to other relative heterocyclic analogs.

**Conformation stability and organization of mefloquine molecules in different environments**

pp 850–853

Agnieszka Skórska,\* Jan liwiński and Barbara J. Oleksyn

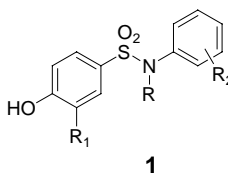


A comparison of three crystal structures of mefloquine in three different crystalline environments is reported.

**Substituted 4-hydroxyphenyl sulfonamides as pathway-selective estrogen receptor ligands**

pp 854–858

Joseph P. Sabatucci,\* Mark A. Ashwell, Eugene Trybulski, Mary-Margaret O'Donnell, William J. Moore, Douglas C. Harnish and Christopher C. Chadwick

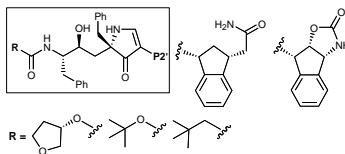


We describe here a series of 4-hydroxyphenyl sulfonamide estrogen receptor (ER) ligands that selectively inhibit NF- $\kappa$ B transcriptional activity but are devoid of conventional estrogenic activity.

**Design, synthesis, and biological evaluation of monopyrrolinone-based HIV-1 protease inhibitors possessing augmented P2' side chains**

pp 859–863

Amos B. Smith, III,\* Adam K. Charnley, Hironori Harada, Jason J. Beiger, Louis-David Cantin, Craig S. Kenesky, Ralph Hirschmann, Sanjeev Munshi, David B. Olsen, Mark W. Stahlhut, William A. Schleif and Lawrence C. Kuo

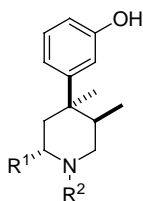


A series of monopyrrolinone-based HIV-1 protease inhibitors were synthesized and evaluated for activity against wild-type and mutant forms of the virus. X-ray cocrystal structures provide insight into their potent activity.

**Synthesis and structure–activity relationships of a new series of 2 $\alpha$ -substituted *trans*-4,5-dimethyl-4-(3-hydroxyphenyl)piperidine as  $\mu$ -selective opioid antagonists**

pp 864–868

Bertrand Le Bourdonnec,\* Allan J. Goodman, Mathieu Michaut, Hai-Fen Ye, Thomas M. Graczyk, Serge Belanger, Robert N. DeHaven and Roland E. Dolle

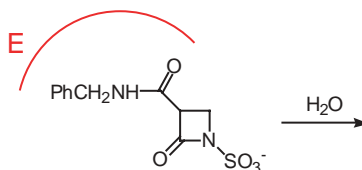


The synthesis and SAR studies of a series of 2 $\alpha$ -substituted *trans*-4,5-dimethyl-4-(3-hydroxyphenyl)piperidines as novel  $\mu$ -opioid receptor antagonists are reported.

**Synthesis and reactivity with  $\beta$ -lactamases of a monobactam bearing a retro-amide side chain**

pp 869–871

S. A. Adediran, J.-F. Lohier, D. Cabaret, M. Wakselman\* and R. F. Pratt\*

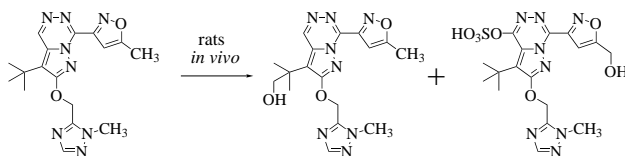


The monobactam sodium 3-benzylcarbamoyl-2-oxo-1-azetidinesulfonate, bearing a retro (vs classical  $\beta$ -lactam)-amide side chain, has been synthesized and the kinetics of its reaction with typical  $\beta$ -lactamases studied. The new compound is generally a poorer substrate than the analogous compound with a normal side chain but its formation of a transiently stable complex with a class C  $\beta$ -lactamase sustains the retro-amide side-chain concept.

**Pharmacokinetics and metabolism studies on (3-*tert*-butyl-7-(5-methylisoxazol-3-yl)-2-(1-methyl-1*H*-1,2,4-triazol-5-ylmethoxy) pyrazolo[1,5-*d*][1,2,4]triazine, a functionally selective GABA $_A$   $\alpha 5$  inverse agonist for cognitive dysfunction**

pp 872–875

Philip Jones,\* John R. Attack, Matthew P. Braun, Brian P. Cato, Mark S. Chambers, Desmond O'Connor, Susan M. Cook, Sarah C. Hobbs, Robert Maxey, Helen J. Szekeres, Nicola Szeto, Keith A. Wafford and Angus M. MacLeod

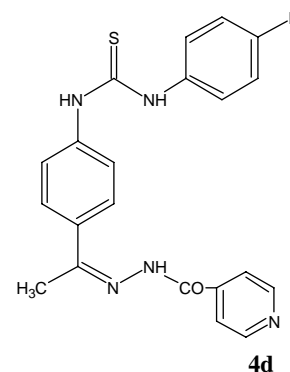


Metabolism of the GABA $_A$   $\alpha 5$  inverse agonist is reported.

**Synthesis and in vitro antitubercular activity of some  
1-[(4-sub)phenyl]-3-(4-{1-[(pyridine-4-carbonyl)hydrazono]ethyl}phenyl)thiourea**  
Dharmarajan Sriram,\* Perumal Yogeeswari and Kasinathan Madhu

pp 876–878

Various isonicotinyl hydrazones were prepared by reacting isonicotinyl hydrazide [INH] with 1-(4-acetylphenyl)-3-[(4-sub)phenyl]thiourea and were tested for their antimycobacterial activity. 1-(4-Fluorophenyl)-3-(4-{1-[(pyridine-4-carbonyl)hydrazono]ethyl}phenyl)thiourea (**4d**) was found to be the most potent compound with a minimum inhibitory concentration of 0.49  $\mu$ M against *Mycobacterium tuberculosis* H<sub>37</sub>R<sub>v</sub> and INH-resistant *M. tuberculosis*.

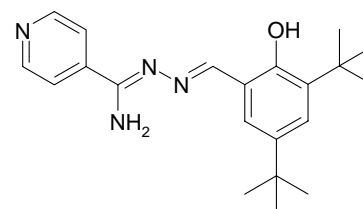


**Discovery of a potent phenolic *N*<sup>1</sup>-benzylidene-pyridinecarboxamidrazone selective  
against Gram-positive bacteria**

pp 879–883

Daniel L. Rathbone,\* Katy J. Parker, Michael D. Coleman,  
Peter A. Lambert and David C. Billington

The discovery of a potent phenolic *N*<sup>1</sup>-benzylidene-pyridinecarboxamidrazone is presented, which has a pronounced selectivity for Gram-positive bacteria over Gram-negative microorganisms and activity against various drug-resistant Gram-positive bacteria.

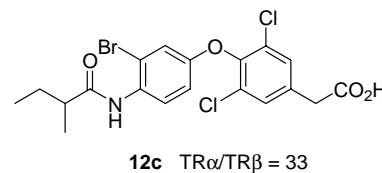


**Thyroid receptor ligands. Part 4: 4'-amido bioisosteric ligands selective for the thyroid  
hormone receptor beta**

pp 884–886

Yi-Lin Li, Chris Litten, Konrad F. Koehler, Karin Mellström, Neeraj Garg,  
Ana Maria Garcia Collazo, Mathias Färnegård, Marlena Grynfarb,  
Bolette Husman, Johnny Sandberg and Johan Malm\*

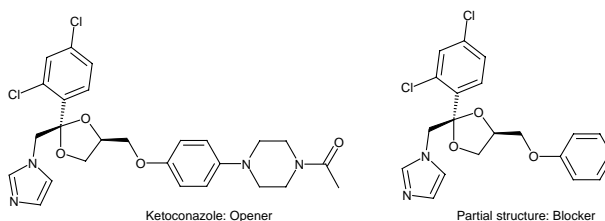
Based on the examination of the X-ray crystallographic structures of the LBD of TR $\alpha$  and TR $\beta$  in complex with KB-141 (**2**), a number of novel 4'-hydroxy bioisosteric thyromimetics were prepared. Optimal affinity and  $\beta$ -selectivity (33 times) was found with a medium size alkyl substituted amido group; *iso*-butyl (**12c**). It can be concluded that bioisosteric replacements of the 4'-hydroxy position represent a new promising class of TR $\beta$ -selective synthetic thyromimetics.



**Partial structures of ketoconazole as modulators of the large conductance calcium-activated potassium  
channel (BK<sub>Ca</sub>)**

pp 887–890

Eoin C. Power,\* C. Robin Ganellin and David C. H. Benton

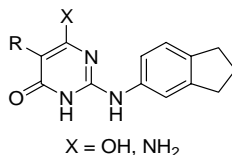


A series of partial structures of ketoconazole has been synthesized and tested on the large conductance calcium-activated potassium channel.

**Novel non-nucleobase inhibitors of *Staphylococcus aureus* DNA polymerase IIIIC**

pp 891–896

Yannick Rose,\* Stéphane Ciblat,\* Ranga Reddy, Adam C. Belley, Evelyn Dietrich, Dario Lehoux, Geoffrey A. McKay, Hugo Poirier, Adel Rafai Far and Daniel Delorme

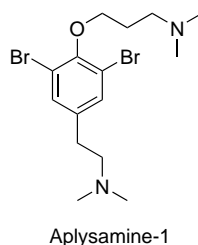


The preparation and biological evaluation of 5-substituted-6-hydroxy-2-(anilino)pyrimidinones as a new class of DNA polymerase IIIIC inhibitors, required for the replication of chromosomal DNA in Gram-positive bacteria, are described. These new dGTP competitive inhibitors displayed good levels of in vitro inhibition and antibacterial activity against *Staphylococcus aureus*. A new class of dATP competitive inhibitors, 6-substituted-2-amino-5-alkyl-pyrimidin-4-ones, whose antibacterial activity was unaffected by serum, were identified.

**Aplysamine-1 and related analogs as histamine H<sub>3</sub> receptor antagonists**

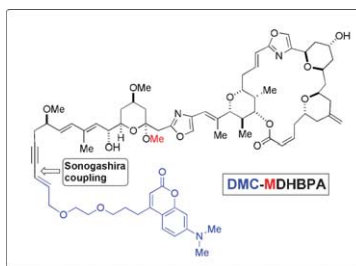
pp 897–900

Devin M. Swanson,\* Sandy J. Wilson, Jamin D. Boggs, Wei Xiao, Richard Apodaca, Ann J. Barbier, Timothy W. Lovenberg and Nicholas I. Carruthers

**Design and total synthesis of a fluorescent phorboxazole a analog for cellular studies**

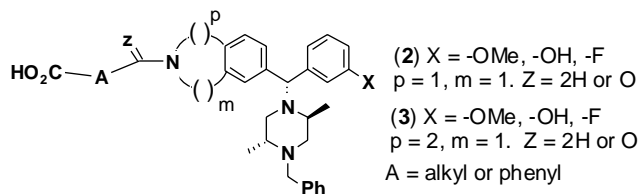
pp 901–904

Jiehao Chen, Lu Ying, T. Matthew Hansen, Mary M. Engler, Chi Sing Lee, James J. La Clair and Craig J. Forsyth\*

**Highly potent and selective zwitterionic agonists of the  $\delta$ -opioid receptor. Part 1**

pp 905–910

Donald S. Middleton,\* Graham N. Maw, Clare Challenger, Alan Jessiman, Patrick S. Johnson, William A. Million, Carly L. Nichols, Jenny A. Price and Michael Trevethick



A series of potent and selective zwitterionic  $\delta$ -opioid agonists (2) and (3) are described.



**Synthesis of 1-(3',4',5'-trimethoxy) phenyl naphtho[2,1-b]furan as a novel anticancer agent**

pp 911–914

Vandana Srivastava, Arvind S. Negi,\* J. K. Kumar, Uzma Faridi, Brijesh S. Sisodia, M. P. Darokar, Suaib Luqman and S. P. S. Khanuja

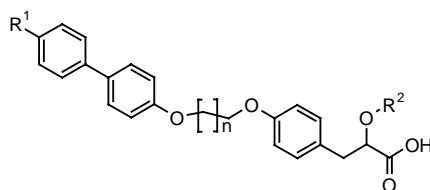


3',4',5'-Trimethoxy benzoyl-naphthalene 2-*O*-acetic acid (**5**) underwent base catalysed intramolecular condensation to yield exclusively 1-(3',4',5'-trimethoxy) phenyl naphtho[2,1-*b*]furan **8**, which has been characterised by spectroscopy. The reaction has been further extended to two more similar compounds **6** and **7** to get aryl naphtho[2,1-*b*]furans **9** and **10**, respectively. These aryl naphthofurans (**8** and **9**) showed significant anticancer activity against various human cancer cell lines in the in vitro MTT assay.

**Design, synthesis, and evaluation of 2-alkoxydihydrocinnamates as PPAR agonists**

pp 915–919

Ying Lu, Zongru Guo,\* Yanshen Guo, Jun Feng and Fengming Chu

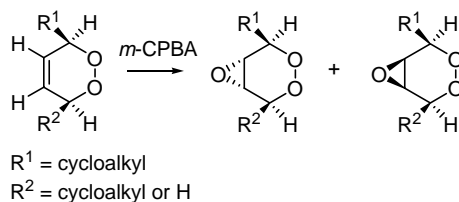


A series of 2-alkoxydihydrocinnamates as PPAR $\gamma$  and PPAR $\alpha$  dual agonists with substituted biphenyl tailpiece were synthesized and tested for their functional activity in vitro.

**Novel endoperoxides: Synthesis and activity against *Candida* species**

pp 920–922

Peter Macreadie, Thomas Avery, Ben Greatrex, Dennis Taylor and Ian Macreadie\*

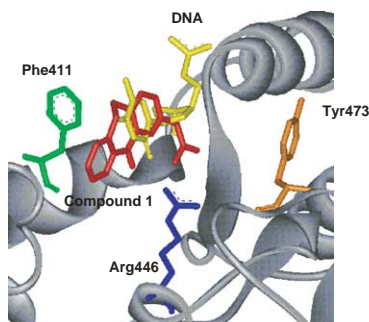


A series of novel endoperoxides were synthesised and tested for inhibitory activity against *Candida* growth. Despite structural similarities, their activity varied considerably. Several endoperoxides demonstrated potential for development as antifungal agents.

**Inhibition of DNA helicases with DNA-competitive inhibitors**

pp 923–927

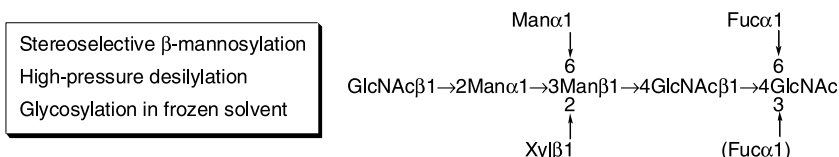
Sandy Dubaele, Wolfgang Jahnke, Joseph Schoepfer, Jean Fuchs and Patrick Chène\*



### Synthesis of complex-type glycans derived from parasitic helminths

pp 928–933

Jun Nakano, Hiromichi Ohta and Yukishige Ito\*



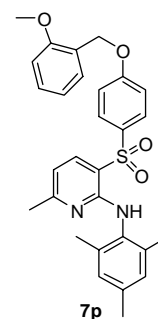
Synthesis of branched complex-type glycans derived from helminth glycoproteins is described.

### Synthesis and evaluation of 2-anilino-3-phenylsulfonyl-6-methylpyridines as corticotropin-releasing factor<sub>1</sub> receptor ligands

pp 934–937

Richard A. Hartz,\* Argyrios G. Arvanitis, Charles Arnold, Joseph P. Rescinito, Kimberly L. Hung, Ge Zhang, Harvey Wong, David R. Langley, Paul J. Gilligan and George L. Trainor

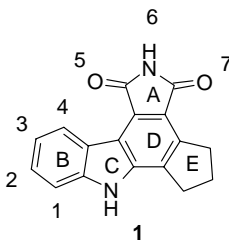
A novel series of 2-anilino-3-phenylsulfonyl-6-methylpyridines was synthesized and evaluated as corticotropin-releasing factor receptor ligands.



### Synthesis and structure–activity relationships of novel poly(ADP-ribose) polymerase-1 inhibitors

pp 938–942

Ming Tao,\* Chung Ho Park, Ron Bihovsky, Gregory J. Wells, Jean Husten, Mark A. Ator and Robert L. Hudkins



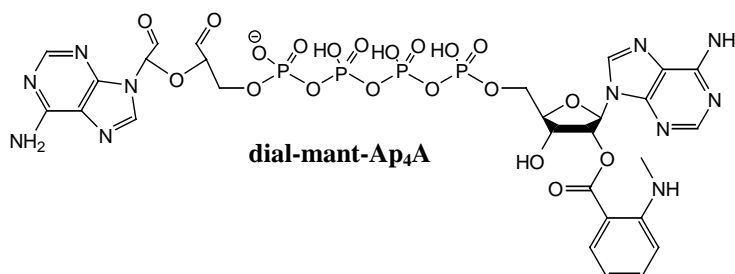
Pyrrolocarbazole **1** was identified as a potent PARP-1 inhibitor ( $IC_{50} = 36$  nM) from our internal database. The synthesis and SAR optimization around this template with the aid of modeling studies led to the identification of the truncated imide.

### Novel fluorescent labelled affinity probes for diadenosine-5',5'''- $P^1$ , $P^4$ -tetraphosphate (Ap<sub>4</sub>A)-binding studies

pp 943–948

Michael Wright and Andrew D. Miller\*

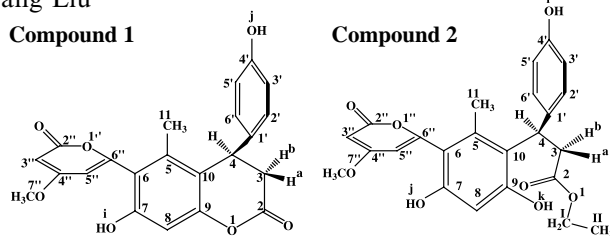
Synthesis and initial testing of two novel fluorescent labelled affinity probes designed for use in diadenosine-5',5'''- $P^1$ , $P^4$ -tetraphosphate (Ap<sub>4</sub>A)-binding studies, dial-mant-Ap<sub>4</sub>A and azido-mant-Ap<sub>4</sub>A.



**Isolation, structure elucidation, antioxidative and immunomodulatory properties of two novel dihydrocoumarins from *Aloe vera***

pp 949–953

Xiu-feng Zhang, Hong-mei Wang, Yuan-li Song, Li-hua Nie, Lan-fen Wang,  
Bin Liu, Ping-ping Shen and Yang Liu \*

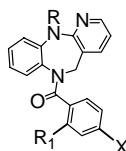


Only the isolated compound **1** is probably beneficial in regulating the ROS levels by scavenging ROS and promoting immunomodulatory activity.

**Pyridobenzodiazepines: A novel class of orally active, vasopressin  $V_2$  receptor selective agonists**

pp 954–959

Amedeo A. Failli,\* Jay S. Shumsky, Robert J. Steffan, Thomas J. Caggiano,  
David K. Williams, Eugene J. Trybulski, Xiaoping Ning, Yeungwai Lock,  
Tarak Tanikella, David Hartmann, Peter S. Chan and C. H. Park



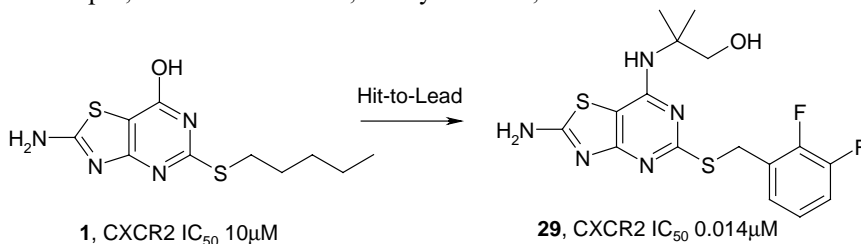
X = pyrazole, triazole

The synthesis and structure–activity relationships (SAR) of a novel class of potent, orally active, non-peptidic vasopressin  $V_2$  receptor selective agonists are described.

**Hit-to-Lead studies: The discovery of potent, orally bioavailable thiazolopyrimidine CXCR2 receptor antagonists**

pp 960–963

Andrew Baxter,\* Anne Cooper, Elizabeth Kinchin, Kerry Moakes, John Unitt and Alan Wallace

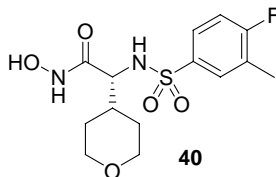


A Hit-to-Lead optimisation programme was carried out on a high throughput screening hit, the thiazolopyrimidine **1**, resulting in the discovery of the potent, orally bioavailable CXCR2 antagonist **29**.

**The discovery of a potent and selective lethal factor inhibitor for adjunct therapy of anthrax infection**

pp 964–968

Yusheng Xiong,\* Judyann Wiltsie, Andrea Woods, Jian Guo, James V. Pivnichny, Wei Tang,  
Alka Bansal, Richard T. Cummings, Barry R. Cunningham, Arthur M. Friedlander,  
Cameron M. Douglas, Scott P. Salowe, Dennis M. Zaller, Edward M. Scolnick,  
Dennis M. Schmatz, Kenneth Bartizal, Jeffrey D. Hermes, Malcolm MacCoss and Kevin T. Chapman

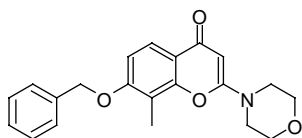


This paper reports the synthesis and SAR of LF inhibitors. Compound **40** is potent against LF ( $IC_{50}$  54 nM) and efficacious in animals studies against anthrax spore challenges.

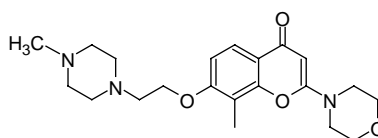
### Analysis of anti-PDE3 activity of 2-morpholinochromone derivatives reveals multiple mechanisms of anti-platelet activity

pp 969–973

Belinda M. Abbott and Philip E. Thompson\*



Platelet aggregation inhibitor  
v. PDE3  $IC_{50} = 0.6 \mu M$

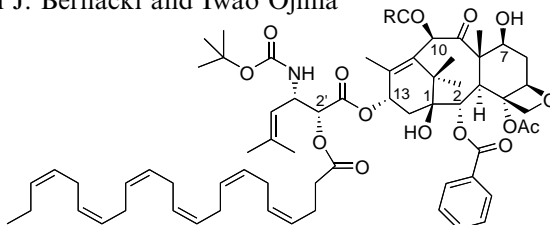


Platelet aggregation inhibitor  
Inactive v. PDE3

### Syntheses and evaluation of novel fatty acid-second-generation taxoid conjugates as promising anticancer agents

pp 974–977

Larissa Kuznetsova, Jin Chen, Liang Sun, Xinyuan Wu, Antonella Pepe, Jean M. Veith, Paula Pera, Ralph J. Bernacki and Iwao Ojima\*



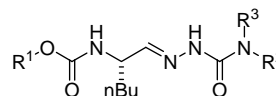
The syntheses and exceptional antitumor activities of a series of novel fatty acid-second-generation taxoid conjugates against human tumor xenografts are reported.

### Semicarbazone-based inhibitors of cathepsin K, are they prodrugs for aldehyde inhibitors?

pp 978–983

Kim K. Adkison, David G. Barrett, David N. Deaton,\* Robert T. Gampe, Anne M. Hassell, Stacey T. Long, Robert B. McFadyen, Aaron B. Miller, Larry R. Miller, J. Alan Payne, Lisa M. Shewchuk, Kevin J. Wells-Knecht, Derril H. Willard, Jr. and Lois L. Wright

Starting from potent aldehyde inhibitors with poor drug properties, derivatization to semicarbazones led to the identification of a series of semicarbazone-based cathepsin K inhibitors with greater solubility and better pharmacokinetic profiles than their parent aldehydes. Furthermore, a representative semicarbazone inhibitor attenuated bone resorption in an ex vivo rat calvarial bone resorption model. However, based on enzyme inhibition comparisons at neutral pH, semicarbazone hydrolysis rates, and  $^{13}C$  NMR experiments, these semicarbazones probably function as prodrugs of aldehydes.

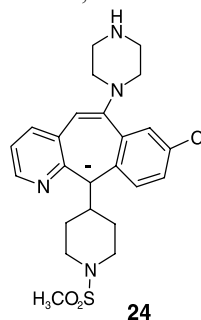


### Enhanced FTase activity achieved via piperazine interaction with catalytic zinc

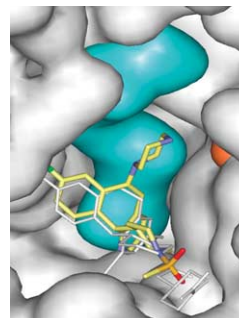
pp 984–988

F. George Njoroge,\* Bantha Vibulbhan, Patrick Pinto, Corey Strickland, W. Robert Bishop, Amin Nomeir and Vivyoor Girijavallabhan

Novel potent, orally bioavailable Ftase inhibitor targeting catalytic zinc is presented.



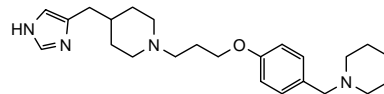
24  
Ftase  $IC_{50} = 0.007 \mu M$



**Reduction of CYP450 inhibition in the 4-[(1*H*-imidazol-4-yl)methyl]piperidine series of histamine H<sub>3</sub> receptor antagonists**

pp 989–994

Michael Berlin,\* Pauline C. Ting, Wayne D. Vaccaro, Robert Aslanian, Kevin D. McCormick, Joe F. Lee, Margaret M. Albanese, Mwangi W. Mutahi, John J. Piwinski, Neng-Yang Shih, Luli Duguma, Daniel M. Solomon, Wei Zhou, Rosy Sher, Leonard Favreau, Matthew Bryant, Walter A. Korfmacher, Cymbelene Nardo, Robert E. West, Jr., John C. Anthes, Shirley M. Williams, Ren-Long Wu, H. Susan She, Maria A. Rivelli, Michel R. Corboz and John A. Hey



A novel series of histamine H<sub>3</sub> receptor antagonists based on the 4-[(1*H*-imidazol-4-yl)methyl]piperidine template displaying low CYP2D6 and CYP3A4 inhibitory profiles has been identified.

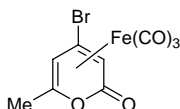
$K_i$  (H<sub>3</sub>, gp) = 3 nM  
 $pA_2$  = 8.6  
 $IC_{50}$  (CYP2D6) = 14  $\mu$ M  
 $IC_{50}$  (CYP3A4) > 30  $\mu$ M

 **$\eta^4$ -Pyrone iron(0)carbonyl complexes as effective CO-releasing molecules (CO-RMs)**

pp 995–998

Ian J. S. Fairlamb,\* Anne-Kathrin Duhme-Klair, Jason M. Lynam, Benjamin E. Moulton, Ciara T. O'Brien, Philip Sawle, Jehad Hammad and Roberto Motterlini\*

10.8  $\mu$ M of CO released in 1 h (from 60  $\mu$ M of complex).



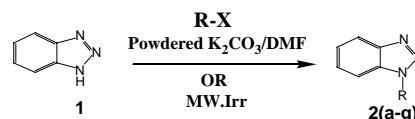
$IC_{10}$  = 132  $\mu$ M  
 (value at which 10% of cells are not viable - tested in cultured RAW264.7 murine macrophages - low toxicity)

**Microwave-assisted synthesis of *N*-alkylated benzotriazole derivatives: Antimicrobial studies**

pp 999–1004

S. Nanjunda Swamy, Basappa, G. Sarala, B. S. Priya, S. L. Gaonkar, J. Shashidhara Prasad and K. S. Rangappa \*

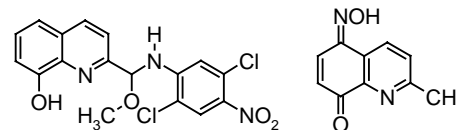
Synthesis and characterization of *N*-alkylated benzotriazole derivatives **2(a–g)** bearing pharmaceutically important bioactive substituents and their antimicrobial studies in vitro are described. The syntheses of the compounds were achieved by *N*-alkylation of the benzotriazole with different bioactive alkyl halides in presence of powdered  $K_2CO_3$  in DMF solution and by microwave irradiation method with good yield compared to conventional method. The crystal structure analysis shows that compound 4'-benzotriazol-1-yl-methyl-biphenyl-2-carbonitrile **2a** crystallizes in the space group P1 with cell parameters  $a$  = 8.526 (3) Å,  $b$  = 12.706 (3) Å,  $c$  = 7.966 (2) Å,  $\alpha$  = 100.89 (2)°,  $\beta$  = 101.63 (3)°,  $\gamma$  = 102.20(2)°, volume = 801.7(4) Å<sup>3</sup>,  $Z$  = 2 and the final  $R$  factor is 0.0559 for 6130 reflections with 218 parameters and zero restraint. This structure exhibits intermolecular hydrogen bonding. Compounds **2e**, **2a** showed significant antimicrobial activity.

**Intermolecular interactions in the crystal structures of potential HIV-1 integrase inhibitors**

pp 1005–1009

Katarzyna Majerz-Maniecka,\* Robert Musiol, Wojciech Nitek, Barbara J. Oleksyn, Jean-Francois Mouscadet, Marc Le Bret and Jaroslaw Polanski

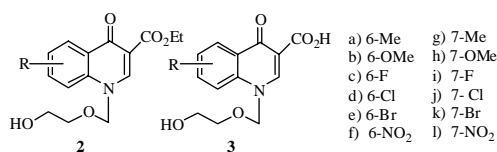
2-[(2,5-dichloro-4-nitro-phenylamino)-methoxy-methyl]-8-hydroxy-quinoline **1** and 2-methyl-quinoline-5,8-dione-5-oxime **2** were obtained as potential HIV-1 integrase inhibitors. They were synthesized and analyzed by X-ray crystallography. Semiempirical theoretical calculations of energy preferred conformations were also carried out. The crystal structures of both compounds are stabilized via hydrogen bonds and  $\pi$ - $\pi$  stacking interactions. The planarity of compound **1** is caused by intramolecular hydrogen bonds.



**Synthesis and anti-HSV-1 activity of quinolonic acyclovir analogues**

pp 1010–1013

Bianca d'A. Lucero, Claudia Regina B. Gomes, Izabel Christina de P. P. Frugulhetti, Letícia V. Faro, Lise Alvarenga, Maria Cecília B. V. de Souza,\* Thiago M. L. de Souza and Vitor F. Ferreira

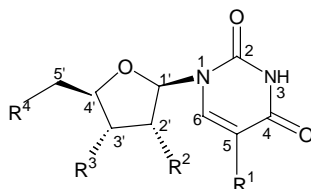


Several new acyclonucleosides, 1-[(2-hydroxy-ethoxy)methyl]-3-carbethoxy-4(1*H*)quinolones (**2a–l**) and 1-[(2-hydroxy-ethoxy)methyl]-4(1*H*)quinolone-3-carboxylic acids (**3a–j** and **3l**), were synthesized and evaluated against herpes simplex virus type 1 (HSV-1).

**3D-QSAR studies on antitubercular thymidine monophosphate kinase inhibitors based on different alignment methods**

pp 1014–1020

V. Aparna, J. Jeevan, M. Ravi, G. R. Desiraju\* and B. Gopalakrishnan\*

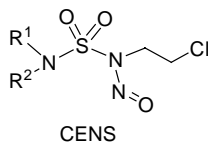


Robust and predictive 3D-QSAR models were developed for dTMP derivatives inhibiting TMP kinase. Three different alignment methods were used and compared with active site residues to explore the nature of substituent.

**Kinetic investigation on aqueous decomposition of 2-chloroethylnitrososulfamide**

pp 1021–1027

Achour Seridi, Mekki Kadri,\* Mohamed Abdaoui, Jean-Yves Winum\* and Jean-Louis Montero



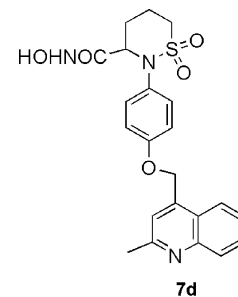
The kinetics of aqueous decomposition of three 2-chloroethylnitrososulfamide are reported.

**Conversion of potent MMP inhibitors into selective TACE inhibitors**

pp 1028–1031

Robert J. Cherney,\* Bryan W. King, John L. Gilmore, Rui-Qin Liu, Maryanne B. Covington, James J.-W. Duan and Carl P. Decicco

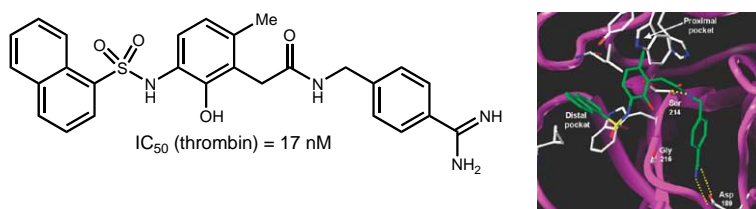
Novel sultam hydroxamates with potent MMP activity were transformed into potent TACE inhibitors, lacking MMP activity. From this effort, compound **7d** was identified as a potent TACE inhibitor ( $IC_{50} = 3.7$  nM) that lacked MMP-1, -2, -9, and -13 activity.



**7d**  
TACE  $IC_{50} = 3.7$  nM

**Phenolic P<sub>2</sub>/P<sub>3</sub> core motif as thrombin inhibitors—Design, synthesis, and X-ray co-crystal structure** pp 1032–1036

Stephen Hanessian,\* Eric Therrien, Willem A. L. van Otterlo, Malken Bayraktarian, Ingemar Nilsson,\* Ola Fjellström and Yafeng Xue



Prototypical thrombin inhibitors were synthesized based on a trisubstituted phenol as a core motif. A naphthylsulfonamide analogue showed excellent antithrombin activity. An X-ray co-crystal structure showed the expected interactions.

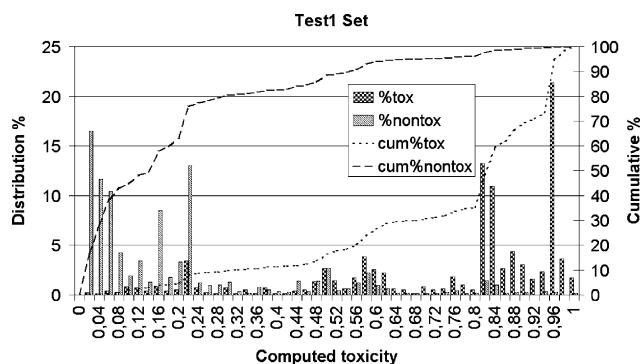
**A neural network based classification scheme for cytotoxicity predictions:**

pp 1037–1039

**Validation on 30,000 compounds**

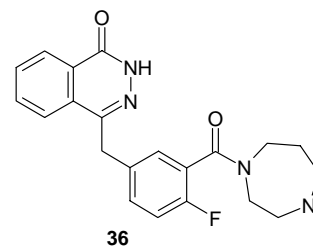
László Molnár, György M. Kesercü,\* Ákos Papp, Zsolt Lőrincz, Géza Ambrus and Ferenc Darvas

A neural network based classification approach using cytotoxicity data measured for 30,000 compounds has been developed to predict cytotoxicity.

**Phthalazinones 2: Optimisation and synthesis of novel potent inhibitors of poly(ADP-ribose)polymerase** pp 1040–1044

Xiao-ling Cockcroft,\* Krystyna J. Dillon, Lesley Dixon, Jan Drzewiecki, Frank Kerrigan, Vincent M. Loh, Jr., Niall M. B. Martin, Keith A. Menear\* and Graeme C. M. Smith

The discovery of novel and cellularly potent PARP-1 inhibitors is described. Compound **36** is effective in specific killing of BRCA2-deficient tumour cells.

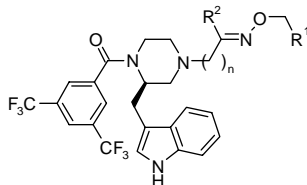


$IC_{50} = 7.0 \text{ nM}$ ,  $PF_{50} = 12.6$ ,  $t_{1/2} = 60 \text{ min}$

**Piperazinyl oxime ethers as NK-1 receptor antagonists**

pp 1045–1048

Adri van den Hoogenband, Jan H. van Maarseveen, Andrew C. McCreary, Arie T. Mulder, Guus J. M. van Scharrenburg, Herman H. van Stuivenberg, Theo J. J. Zethof, Barbara Zijta and Wouter I. Iwema Bakker\*

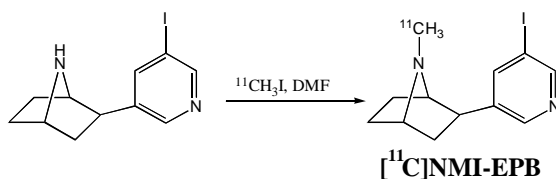


The synthesis and SAR for a new class of centrally active NK-1 receptor antagonists are described. The new compounds all have a piperazinyl oxime ether functionality. Several new compounds have high affinity for the NK-1 receptor and show good antagonistic activity in the gerbil foot-tapping assay.

**A novel nicotinic acetylcholine receptor antagonist radioligand for PET studies**

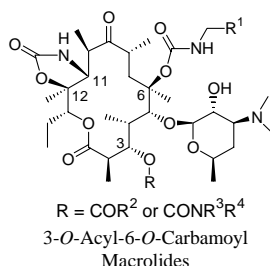
pp 1049–1053

Yu-Shin Ding,\* Kun-eek Kil, Kuo-Shyan Lin, Wei Ma,  
Yasuno Yokota and Ivy F. Carroll

**Synthesis and antibacterial activity of 3-*O*-acyl-6-*O*-carbamoyl erythromycin A derivatives**

pp 1054–1059

Bin Zhu,\* Brett A. Marinelli, Darren Abbanat, Barbara D. Foleno, Todd C. Henninger,  
Karen Bush and Mark J. Macielag

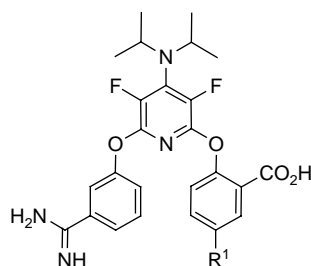


A series of 3-*O*-acyl-6-*O*-carbamoyl erythromycin A derivatives has been synthesized. The best compounds in this series possess potent in vitro antibacterial activity against erythromycin-susceptible and erythromycin-resistant bacteria.

**The discovery of fluoropyridine-based inhibitors of the factor VIIa/TF complex—Part 2**

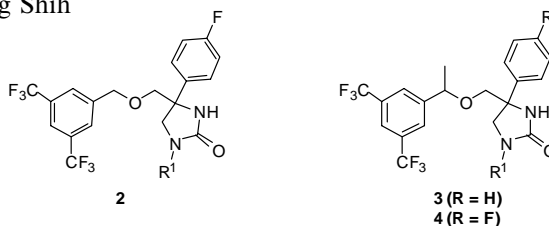
pp 1060–1064

Jeffrey T. Kohrt,\* Kevin J. Filipski, Wayne L. Cody, Cuiman Cai, Danette A. Dudley,  
Chad A. Van Huis, J. Adam Willardsen, Lakshmi S. Narasimhan, Erli Zhang,  
Stephen T. Rapundalo, Kamlai Saiya-Cork, Robert J. Leadley and Jeremy J. Edmunds

**Cyclic urea derivatives as potent NK<sub>1</sub> selective antagonists. Part II: Effects of fluoro and benzylic methyl substitutions**

pp 1065–1069

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

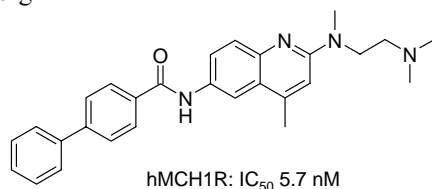




**6-Acylamino-2-amino-4-methylquinolines as potent melanin-concentrating hormone 1 receptor antagonists: Structure–activity exploration of eastern and western parts**

pp 1070–1075

Trond Ulven, Paul Brian Little, Jean-Marie Receveur, Thomas M. Frimurer, Øystein Rist, Pia K. Nørregaard and Thomas Högberg\*

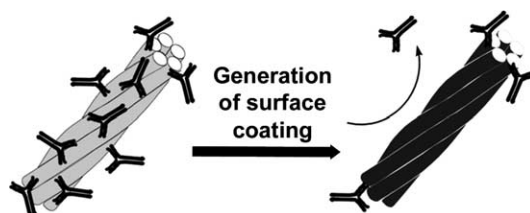


Further SAR investigations of the previously disclosed 2-aminoquinoline MCH1R antagonists resulted in identification of a novel biphenylcarboxamide antagonist.

**Inhibiting protein–amyloid interactions with small molecules: A surface chemistry approach**

pp 1076–1079

Petra Inbar and Jerry Yang\*

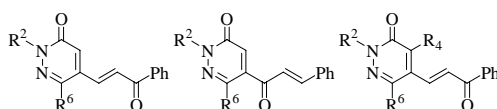


Anti-amyloid IgGs bind to the fibrillar form of Alzheimer's-related Aβ peptides. Molecules that bind and coat the surface of Aβ fibrils significantly inhibit these IgG–amyloid interactions.

**Pyridazines part 41: Synthesis, antiplatelet activity and SAR of 2,4,6-substituted 5-(3-oxo-3-phenylprop-1-en-1-yl)- or 5-(3-phenylprop-2-en-1-yl)pyridazin-3(2H)-ones**

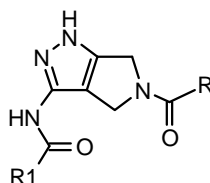
pp 1080–1083

Abel Crespo, Caroline Meyers, Alberto Coelho, Matilde Yáñez, Nuria Fraiz, Eddy Sotelo, Bert U. W. Maes, Reyes Laguna, Ernesto Cano, Guy L. F. Lemièrre and Enrique Raviña\*

**3-Amino-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazoles: A new class of CDK2 inhibitors**

pp 1084–1090

Paolo Pevarello,\* Daniele Fancelli, Anna Vulpetti, Raffaella Amici, Manuela Villa, Valeria Pittalà, Paola Vianello, Alexander Cameron, Marina Ciomei, Ciro Mercurio, James R. Bischoff, Fulvia Roletto, Mario Varasi and Maria Gabriella Brasca



We recently reported about the synthesis, expansion, and biological characterization of a new bicyclic scaffold toward potent Aurora-A kinase inhibitors. Here we report the expansion of the same class with the aim of achieving potent and selective CDK inhibitors.

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

\*Corresponding author

①<sup>+</sup> Supplementary data available via ScienceDirect**COVER**

Superposition of the X-ray crystal structures of 8 (white) and CVS1695 (magenta) in complexes with thrombin. [Hanessian, S.; Therrien, E.; van Otterlo, W. A. L.; Bayrakdarian, M.; Nilsson, I.; Fjellström, O.; Xue, Y. *Bioorg. Med. Chem. Lett.* **2006**, 16, 1036.]



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