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# Bioorganic & Medicinal Chemistry Letters

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## Bioorganic & Medicinal Chemistry Letters Vol. 19, No. 2, 2009

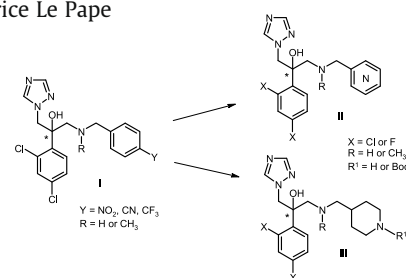
### Contents

#### ARTICLES

#### Synthesis and structure–activity relationships of 2-phenyl-1-[(pyridinyl- and piperidinylmethyl)amino]-3-(1*H*-1,2,4-triazol-1-yl)propan-2-ols as antifungal agents pp 301–304

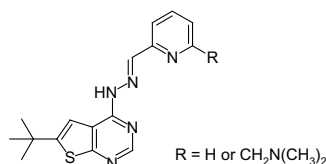
Francis Giraud, Rémi Guillon, Cédric Logé\*, Fabrice Pagniez, Carine Picot, Marc Le Borgne, Patrice Le Pape

Synthesis and SAR studies of modified 1-benzylamino-2-phenyl-3-(1*H*-1,2,4-triazol-1-yl)propan-2-ols as antifungal agents, allowed identification of new derivatives with MIC<sub>80</sub> values ranging from 1410.0 to 23.0 ng mL<sup>−1</sup> on the *Candida albicans* strain.



#### Discovery of novel thieno[2,3-*d*]pyrimidin-4-yl hydrazone-based inhibitors of Cyclin D1-CDK4: Synthesis, biological evaluation, and structure–activity relationships pp 305–308

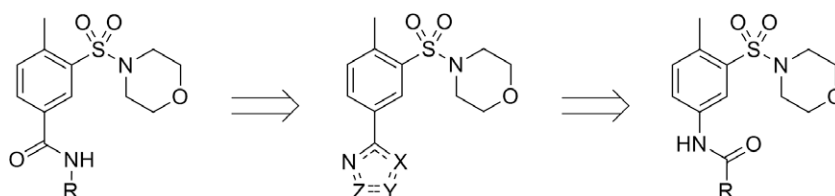
Takao Horiuchi\*, Jun Chiba, Kouichi Uoto, Tsunehiko Soga



New analogues of thieno[2,3-*d*]pyrimidin-4-yl hydrazone compounds as Cyclin D1/CDK4 inhibitors have been synthesized and evaluated their enzyme inhibitory activity and antiproliferative activity. The potency, selectivity profile, and structure–activity relationship trends of this class of compounds are discussed.

#### CB<sub>2</sub> selective sulfamoyl benzamides: Optimization of the amide functionality pp 309–313

Allan J. Goodman\*, Christopher W. Ajello, Karin Worm, Bertrand Le Bourdonnec, Markku A. Savolainen, Heather O'Hare, Joel A. Cassel, Gabriel J. Stabley, Robert N. DeHaven, Christopher J. LaBuda, Michael Koblisch, Patrick J. Little, Bernice L. Brogdon, Steven A. Smith, Roland E. Dolle

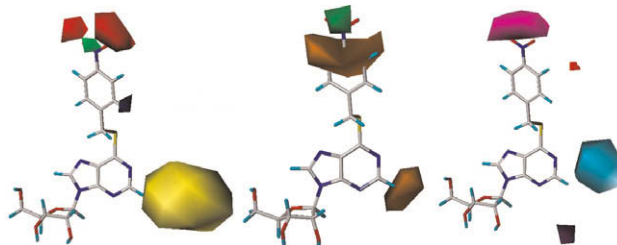


Isosteric replacement of the amide linkage was investigated. Reversal of the amide functionality led to a series of highly selective CB<sub>2</sub> receptor agonists.

**CoMFA and CoMSIA 3D-QSAR studies on  $S^6$ -(4-nitrobenzyl)mercaptapurine riboside (NBMPR) analogs as inhibitors of human equilibrative nucleoside transporter 1 (hENT1)**

pp 314–318

Amol Gupte, John K. Buolamwini\*

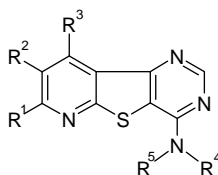


The 3D-QSAR studies involving CoMFA (comparative molecular field analysis) and CoMSIA (comparative molecular similarity indices analysis) on NBMPR analogs developed as human equilibrative nucleoside transporter (hENT1) inhibitors is reported.

**Synthesis and evaluation of pyrido-thieno-pyrimidines as potent and selective Cdc7 kinase inhibitors**

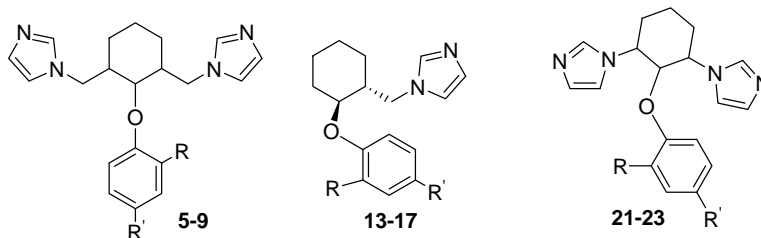
pp 319–323

Chunlin Zhao\*, Christian Tovar, Xuefeng Yin, Qui Xu, Ivan T. Todorov, Lyubomir T. Vassilev\*, Li Chen


**Aryloxy cyclohexyl imidazoles: A novel class of antileishmanial agents**

pp 324–327

Nagarapu Srinivas, Shraddha Palne, Nishi, Suman Gupta, Kalpana Bhandari\*

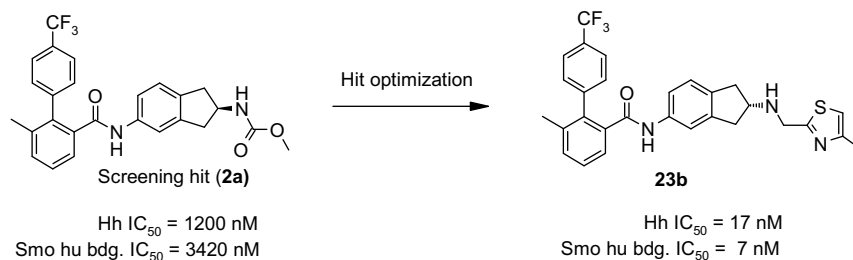


A series of aryloxy cyclohexane-based mono and bis imidazoles were synthesized and evaluated both in vitro and in vivo against *Leishmania donovani*. All the 13 compounds displayed very promising in vitro activity while one compound showed significant in vivo activity.


**Identification and structure–activity relationships of *ortho*-biphenyl carboxamides as potent Smoothed antagonists inhibiting the Hedgehog signaling pathway**

pp 328–331

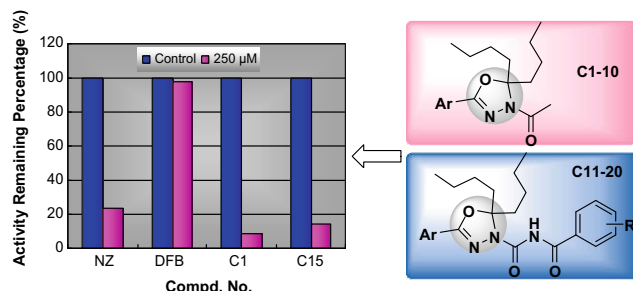
Stefan Peukert\*, Rishi K. Jain, Adrian Geisser, Yingchuan Sun, Rui Zhang, Aaron Bourret, Adam Carlson, Jennifer DaSilva, Arun Ramamurthy, Joseph F. Kelleher



**1,3,4-Oxadiazoline derivatives as novel potential inhibitors targeting chitin biosynthesis: Design, synthesis and biological evaluation**

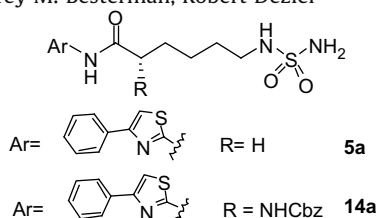
pp 332–335

Shaoyong Ke, Fengyi Liu, Ni Wang, Qing Yang\*, Xuhong Qian\*

**Sulfamides as novel histone deacetylase inhibitors**

pp 336–340

Amal Wahhab\*, David Smil, Alain Ajamian, Martin Allan, Yves Chantigny, Eric Therrien, Natalie Nguyen, Sukhdev Manku, Silvana Leit, Jubrail Rahil, Andrea J. Petschner, Ai-Hua Lu, Alina Nicolescu, Sylvain Lefebvre, Samuel Montcalm, Marielle Fournel, Theresa P. Yan, Zuomei Li, Jeffrey M. Besterman, Robert Déziel

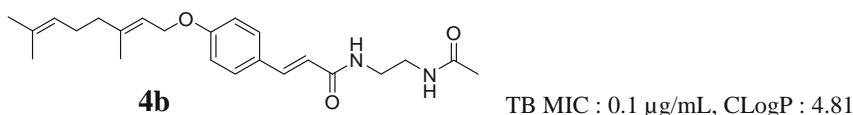


The sulfamide moiety has been utilized to design novel HDAC inhibitors. The potency and selectivity of these inhibitors were influenced both by the nature of the scaffold, and the capping group. Linear long-chain-based analogs were primarily HDAC6-selective, while analogs based on the lysine scaffold resulted in potent HDAC1 and HDAC6 inhibitors.

**Synthesis and evaluation of a novel series of pseudo-cinnamic derivatives as antituberculosis agents**

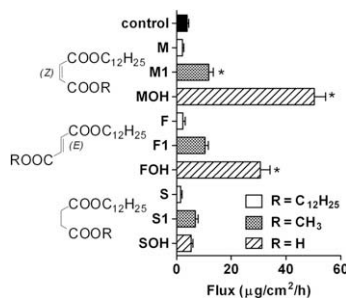
pp 341–343

Georges Koumba Yoya, Florence Bedos-Belval, Patricia Constant, Hubert Duran, Mamadou Daffé, Michel Baltas\*

**Dicarboxylic acid esters as transdermal permeation enhancers: Effects of chain number and geometric isomers**

pp 344–347

Michal Novotný, Alexandr Hrabálek, Barbora Janůšová, Jakub Novotný, Kateřina Vávrová\*



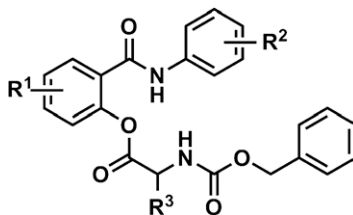
Transdermal permeation enhancers based on dicarboxylic acid esters were studied.



### Salicylanilide esters of *N*-protected amino acids as novel antimicrobial agents

pp 348–351

Aleš Imramovský\*, Jarmila Vinšová\*, Juana Monreal Ferriz, Vladimír Buchta, Josef Jampílek



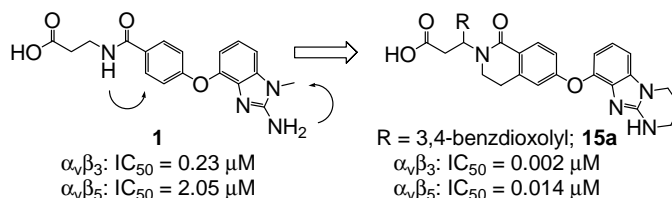
Synthesis of new highly antimicrobial active salicylanilide esters of *N*-protected amino acids is described.



### Synthesis and initial evaluation of novel, non-peptidic antagonists of the $\alpha_v$ -integrins $\alpha_v\beta_3$ and $\alpha_v\beta_5$

pp 352–355

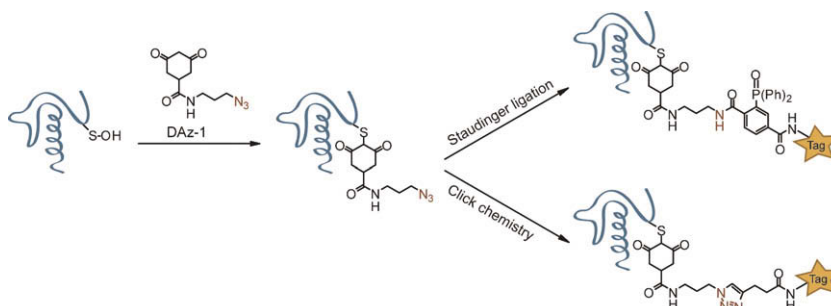
Jeffrey J. Letourneau\*, Jinqi Liu, Michael H. J. Ohlmeyer, Chris Riviello, Yajing Rong, Hong Li, Kenneth C. Appell, Shalini Bansal, Biji Jacob, Angela Wong, Maria L. Webb



### Facile synthesis and biological evaluation of a cell-permeable probe to detect redox-regulated proteins

pp 356–359

Young Ho Seo, Kate S. Carroll\*

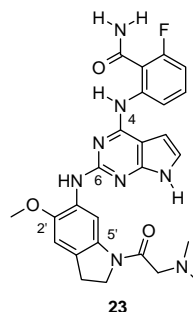


### Optimization of 4,6-bis-anilino-1*H*-pyrrolo[2,3-*d*]pyrimidine IGF-1R tyrosine kinase inhibitors towards JNK selectivity

pp 360–364

Stanley D. Chamberlain, Anikó M. Redman, Joseph W. Wilson, Felix Deanda, J. Brad Shotwell, Roseanne Gerding, Huangshu Lei, Bin Yang, Kirk L. Stevens, Anne M. Hassell, Lisa M. Shewchuk, M. Anthony Leesnitzer, Jeffery L. Smith, Peter Sabbatini, Charity Atkins, Arthur Groy, Jason L. Rowand, Rakesh Kumar, Robert A. Mook Jr., Ganesh Moorthy, Samarjit Patnaik\*

The SAR of C5' functional groups with terminal basic amines at the C6 aniline of 4,6-bis-anilino-1*H*-pyrrolo[2,3-*d*]pyrimidines is reported. Examples demonstrate potent inhibition of IGF-1R in enzymatic and cellular assays with 1000-fold selectivity over JNK1 and 3.



IGF-1R Enzyme IC<sub>50</sub> 1 nM  
 JNK1 Enzyme IC<sub>50</sub> 1585 nM  
 Phospho IGF-1R Cellular IC<sub>50</sub> 56 nM

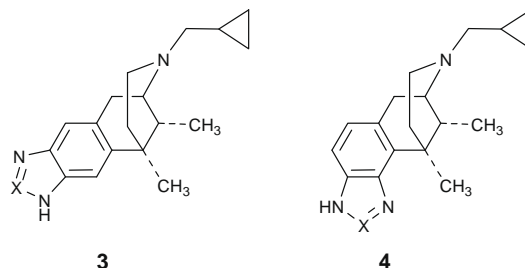
23



### Redefining the structure–activity relationships of 2,6-methano-3-benzazocines. Part 7: Syntheses and opioid receptor properties of cyclic variants of cyclazocine

pp 365–368

Mark P. Wentland\*, Qun Lu, Rakesh Ganorkar, Shao-Zhong Zhang, Sunjin Jo, Dana J. Cohen, Jean M. Bidlack

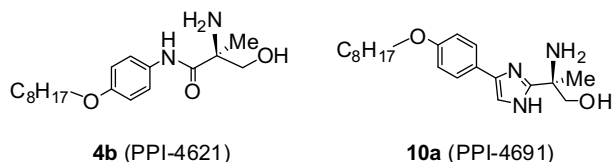


Members of a novel series of 7,8- and 8,9-fused triazole and imidazole analogues of cyclazocine display very high affinity for opioid receptors.

### Synthesis and evaluation of alkoxy-phenylamides and alkoxy-phenylimidazoles as potent sphingosine-1-phosphate receptor subtype-1 agonists

pp 369–372

Ghotas Evindar\*, Sylvie G. Bernier, Malcolm J. Kavarana, Elisabeth Doyle, Jeanine Lorusso, Michael S. Kelley, Keith Halley, Amy Hutchings, Albion D. Wright, Ashis K. Saha, Gerhard Hannig, Barry A. Morgan, William F. Westlin

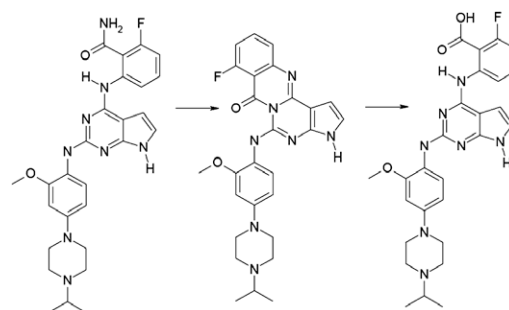


Discovery of two potent and selective sphingosine-1-phosphate receptor agonist chemotypes, alkoxy-phenylamide and alkoxy-phenylimidazole, with potent in vivo oral activity in mouse.

### Optimization of a series of 4,6-bis-anilino-1H-pyrrolo[2,3-d]pyrimidine inhibitors of IGF-1R: Elimination of an acid-mediated decomposition pathway

pp 373–377

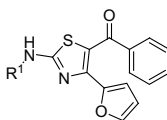
Stanley D. Chamberlain, Anikó M. Redman, Samarjit Patnaik, Keith Brickhouse, Yen-Chiat Chew, Felix Deanda, Roseanne Gerding, Huangshu Lei, Ganesh Moorthy, Mark Patrick, Kirk L. Stevens, Joseph W. Wilson, J. Brad Shotwell\*



### Synthesis of 2-amino-5-benzoyl-4-(2-furyl)thiazoles as adenosine A<sub>2A</sub> receptor antagonists

pp 378–381

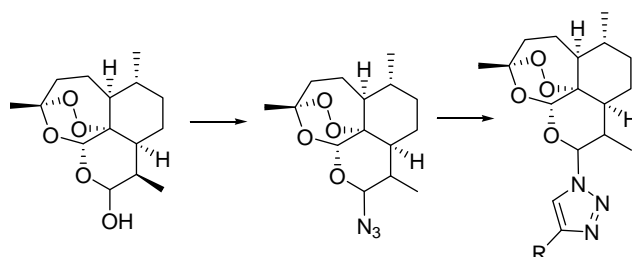
Andrew G. Cole\*, Tara M. Stauffer, Laura L. Rokosz, Axel Metzger, Lawrence W. Dillard, Wenguang Zeng, Ian Henderson

The discovery and synthesis of a series of 2-amino-5-benzoyl-4-(2-furyl)thiazoles as adenosine A<sub>2A</sub> receptor antagonists are reported.

### Synthesis of 10-substituted triazolyl artemisinins possessing anticancer activity via Huisgen 1,3-dipolar cycloaddition

pp 382–385

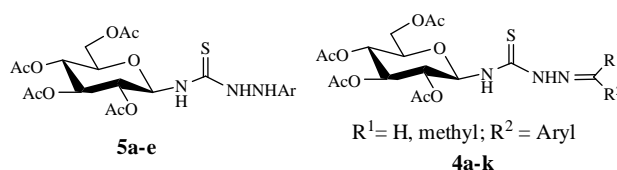
Sungsik Cho, Sangtae Oh, Yumi Um, Ji-Hee Jung, Jungyeob Ham, Woon-Seob Shin\*, Seokjoon Lee\*



### Syntheses and evaluation of glucosyl aryl thiosemicarbazide and glucosyl thiosemicarbazone derivatives as antioxidant and anti-dyslipidemic agents

pp 386–389

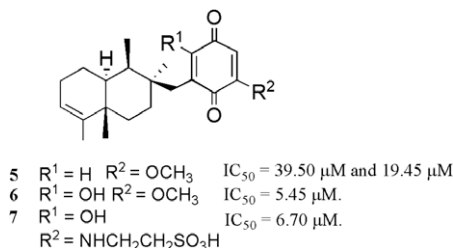
Samir Ghosh, Anup Kumar Misra\*, Gitika Bhatia, M. M. Khan, A. K. Khanna



### A novel sesquiterpene quinone from Hainan sponge *Dysidea villosa*

pp 390–392

Yan Li, Yu Zhang, Xu Shen\*, Yue-Wei Guo\*

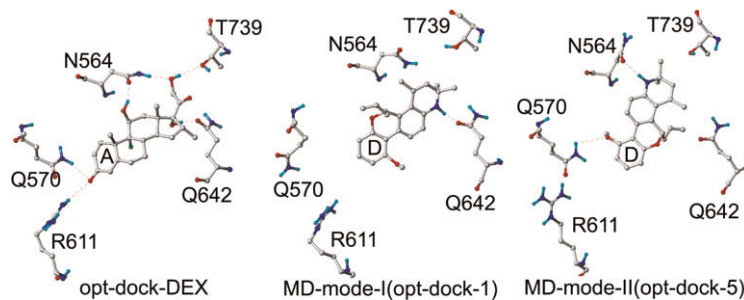


One new sesquiterpene Quinone **5**, together with two known analogues **6** and **7**, had been isolated from the Hainan sponge *Dysidea villosa* with a rare further rearranged drimane skeleton. Compound **7** exhibited the strongest hPTP1B inhibitory activity with an  $IC_{50}$  value of 6.70  $\mu M$ , **6** had significant cytotoxic activity against Hela cell line with an  $IC_{50}$  value of 5.45  $\mu M$ , and new compound **5** showed moderate PTP1B inhibitory activity and cytotoxicity with  $IC_{50}$  values of 39.50 and 19.45  $\mu M$ , respectively.

### Combining 3D-QSAR, docking, molecular dynamics and MM/PBSA methods to predict binding modes for nonsteroidal selective modulator to glucocorticoid receptor

pp 393–396

Yong Xu, Tao Zhang\*, Minbo Chen



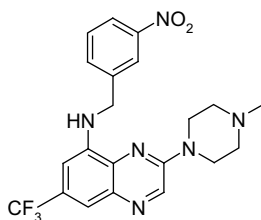
The AL-438 binding mode in GR ligand binding domain is predicted.



**Discovery of a novel series of quinoxalines as inhibitors of c-Met kinase**

pp 397–400

John Porter\*, Simon Lumb, Fabien Lecomte, James Reuberson, Anne Foley, Mark Calmiano, Kelly le Riche, Helen Edwards, Jean Delgado, Richard J. Franklin, Jose M. Gascon-Simorte, Alison Maloney, Christoph Meier, Mark Batchelor

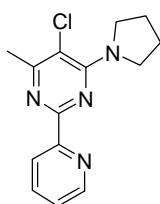


The SAR of a series of quinoxaline inhibitors of c-Met kinase is reported.

**Synthesis and evaluation of 2-pyridyl pyrimidines with in vitro antiplasmodial and antileishmanial activity**

pp 401–405

Chitalu C. Musonda, Gavin A. Whitlock\*, Michael J. Witty, Reto Brun, Marcel Kaiser



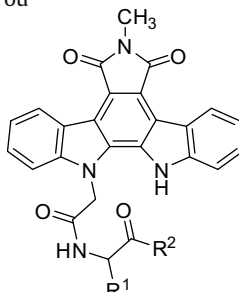
*L. donovani* IC<sub>50</sub> 0.53 μM  
clogP 2.9

A series of 2-pyridyl pyrimidines has been shown to possess potent in vitro activity against leishmania parasites.

**Design and synthesis of N-methylmaleimide indolocarbazole bearing modified 2-acetamino acid moieties as Topoisomerase I inhibitors**

pp 406–409

Zhiyu Li, Fuming Zhai, Li Zhao, Qinglong Guo, Qidong You\*

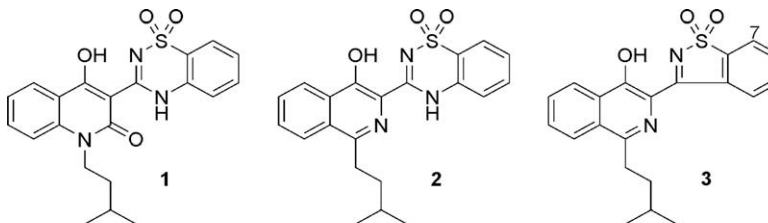


The preparation and evaluation of a novel class of TOPO I inhibitors based on indolocarbazole scaffold are reported.

**3-Hydroxyisoquinolines as inhibitors of HCV NS5b RNA-dependent RNA polymerase**

pp 410–414

Robert T. Hendricks\*, Stacey R. Spencer, James F. Blake, Jay B. Fell, John P. Fischer, Peter J. Stengel, Vincent J. P. Leveque, Sophie LePogam, Sonal Rajyaguru, Isabel Najera, John A. Josey, Steven Swallow



NS5b IC<sub>50</sub>: 1.1 μM

NS5b IC<sub>50</sub>: 51 μM

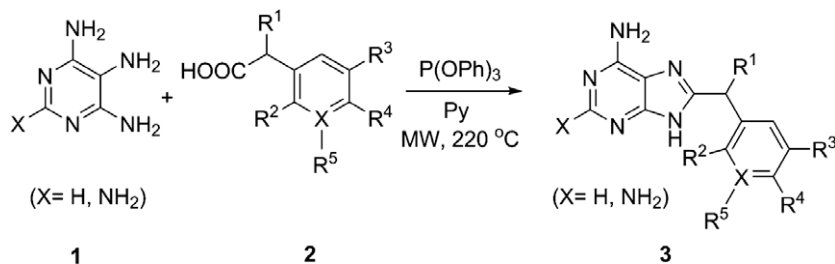
NS5b IC<sub>50</sub>: 4.5 μM

New isoquinoline-based non-nucleoside inhibitors (**2**, **3**) of HCV NS5b RNA-dependent RNA-polymerase are described. Their syntheses and structure–activity relationships are detailed, along with enzyme and cellular activities.

**Microwave-assisted one step synthesis of 8-arylmethyl-9H-purin-6-amines**

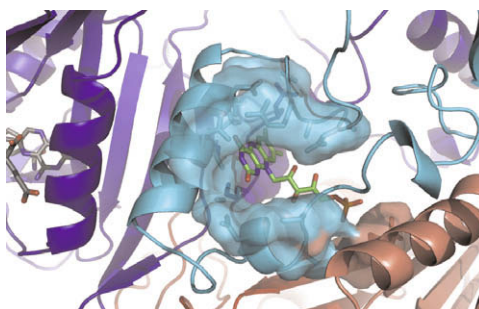
pp 415–417

Hui Tao, Yanlong Kang, Tony Taldone, Gabriela Chiosis\*

**Novel non-active site inhibitor of *Cryptosporidium hominis* TS-DHFR identified by a virtual screen**

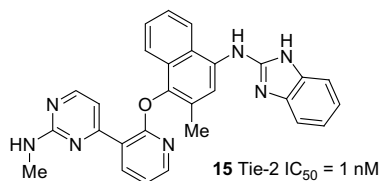
pp 418–423

W. Edward Martucci, Marina Udier-Blagovic, Chloe Atreya, Oladapo Babatunde, Melissa A. Vargo, William L. Jorgensen, Karen S. Anderson\*

**Pyridyl-pyrimidine benzimidazole derivatives as potent, selective, and orally bioavailable inhibitors of Tie-2 kinase**

pp 424–427

Victor J. Cee\*, Alan C. Cheng, Karina Romero, Steve Bellon, Christopher Mohr, Douglas A. Whittington, Annette Bak, James Bready, Sean Caenepeel, Angela Coxon, Holly L. Deak, Jenne Fretland, Yan Gu, Brian L. Hodous, Xin Huang, Joseph L. Kim, Jasmine Lin, Alexander M. Long, Hanh Nguyen, Philip R. Olivieri, Vinod F. Patel, Ling Wang, Yihong Zhou, Paul Hughes, Stephanie Geuns-Meyer

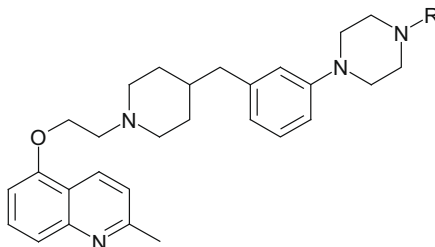


The optimization of a nonselective scaffold into **15**, a potent inhibitor of Tie-2 kinase with selectivity against VEGFR2 kinase, is reported.

**Studies on a series of potent, orally bioavailable, 5-HT<sub>1</sub> receptor ligands—Part II**

pp 428–432

Simon E. Ward\*, Peter Eddershaw, Sean T. Flynn, Laurie Gordon, Peter J. Lovell, Susan H. Moore, Claire M. Scott, Paul W. Smith, Kevin M. Thewlis, Paul A. Wyman



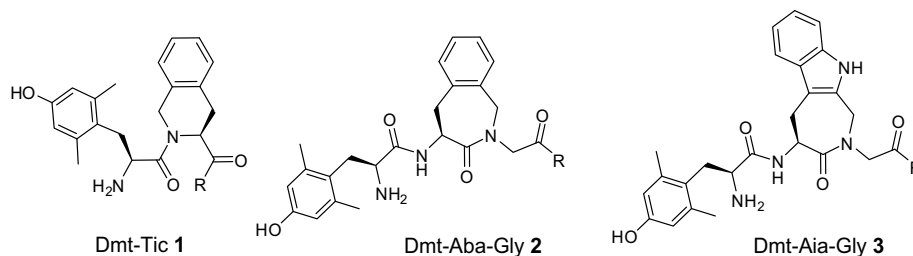
SAR studies on a series of substituted phenyl piperazines and piperidines are described. Several examples are disclosed as potent 5-HT<sub>1</sub> receptor ligands and their PK profiles presented.



**Conformationally constrained opioid ligands: The Dmt-Aba and Dmt-Aia versus Dmt-Tic scaffold**

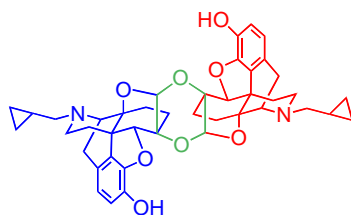
pp 433–437

Steven Ballet, Debby Feytens, Rien De Wachter, Magali De Vlaeminck, Ewa D. Marczak, Severo Salvadori, Chris de Graaf, Didier Rognan, Lucia Negri, Roberta Lattanzi, Lawrence H. Lazarus, Dirk Tourwé\*, Gianfranco Balboni

**Synthesis of novel twin drug consisting of 8-oxaendoethanotetrahydromorphides with a 1,4-dioxane spacer and its pharmacological activities:  $\mu$ ,  $\kappa$ , and putative  $\varepsilon$  opioid receptor antagonists**

pp 438–441

Hideaki Fujii, Akio Watanabe, Toru Nemoto, Minoru Narita, Kan Miyoshi, Atsushi Nakamura, Tsutomu Suzuki, Hiroshi Nagase\*

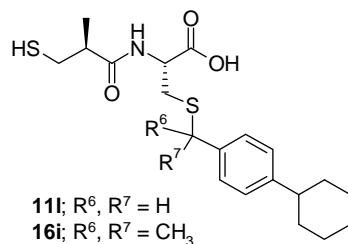


Novel dimeric morphinan derivative with a 1,4-dioxane spacer was synthesized, and showed  $\mu$ ,  $\kappa$ , and putative  $\varepsilon$  opioid receptor antagonist activities.

**Synthesis and biological evaluation of *N*-mercaptoacylcysteine derivatives as leukotriene  $A_4$  hydrolase inhibitors**

pp 442–446

Hiroshi Enomoto\*, Yuko Morikawa, Yurika Miyake, Fumio Tsuji, Maki Mizuchi, Hiroshi Suhara, Ken-ichi Fujimura, Masato Horiuchi, Masakazu Ban

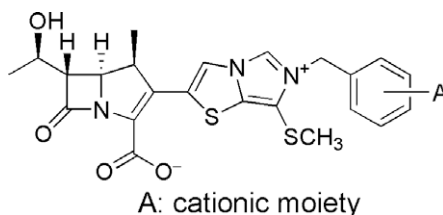


The design, synthesis, and biological evaluation of a new class of *N*-mercaptoacyl-L-cysteine derivatives as leukotriene  $A_4$  ( $LTA_4$ ) hydrolase inhibitors are reported. Modification at the *para*-substituent of the phenyl ring of *S*-benzyl-L-cysteine moiety improved  $LTA_4$  hydrolase inhibitory activity as well as selectivity over ACE. In particular, compounds **11i** and **16i** having cyclohexyl group exhibited superior features about the two enzymes.

**Synthesis of novel di- and tricationic carbapenems with potent anti-MRSA activity**

pp 447–450

Takahisa Maruyama\*, Yasuo Yamamoto, Yuko Kano, Mizuyo Kurazono, Eiki Shitara, Katsuyoshi Iwamatsu, Kunio Atsumi\*

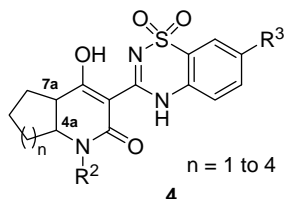


A new series of 1 $\beta$ -methyl carbapenems possessing a 6,7-disubstituted imidazo[5,1-*b*]thiazol-2-yl group was prepared. Among them, introduction of cationic benzyl moiety to the 6 position of imidazo[5,1-*b*]thiazole resulted in excellent anti-MRSA activity.

**5,6-Dihydro-1H-pyridin-2-ones as potent inhibitors of HCV NS5B polymerase**

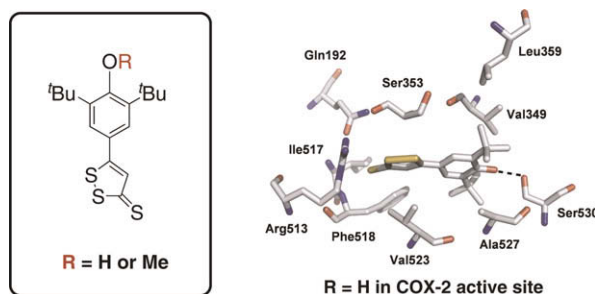
pp 451–458

Frank Ruebsam\*, Chinh V. Tran, Lian-Sheng Li, Sun Hee Kim, Alan X. Xiang, Yuefen Zhou, Julie K. Blazel, Zhongxiang Sun, Peter S. Dragovich, Jingjing Zhao, Helen M. McGuire, Douglas E. Murphy, Martin T. Tran, Nebojsa Stankovic, David A. Ellis, Alberto Gobbi, Richard E. Showalter, Stephen E. Webber, Amit M. Shah, Mei Tsan, Rupal A. Patel, Laurie A. LeBrun, Huiying J. Hou, Ruhi Kamran, Maria V. Sergeeva, Darian M. Bartkowski, Thomas G. Nolan, Daniel A. Norris, Leo Kirkovsky

**Synthesis and evaluation of dithiolethiones as novel cyclooxygenase inhibitors**

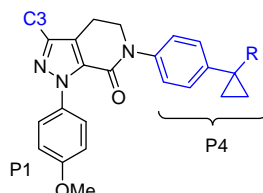
pp 459–461

Shannon D. Zanatta, David T. Manallack, Bevyn Jarrott, Spencer J. Williams\*

**Highly efficacious factor Xa inhibitors containing  $\alpha$ -substituted phenylcycloalkyl P4 moieties**

pp 462–468

Jennifer X. Qiao\*, Sarah R. King, Kan He, Pancras C. Wong, Alan R. Rendina, Joseph M. Luettgen, Baomin Xin, Robert M. Knabb, Ruth R. Wexler, Patrick Y. S. Lam



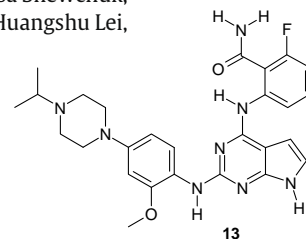
We previously disclosed a series of highly potent FXa inhibitors bearing  $\alpha$ -substituted ( $\text{CH}_2\text{NR}^1\text{R}^2$ ) phenylcyclopropyl P4 moieties in the pyrazolodihydropyridone core system. Herein, we describe our continuous SAR efforts in this series. Effects of the C-3 substitution of the pyrazolodihydropyridone core and the  $\alpha$ -substitution (R group) of the cyclopropyl ring on FXa binding affinity (FXa  $K_i$ ), human plasma anticoagulant activity (PT  $\text{EC}_{50}$ ) and permeability are discussed. A set of compounds obtained from optimization of the R group and the C-3 substituent were orally bioavailable in dogs. Furthermore, representative compounds were highly efficacious in the rabbit arteriovenous shunt thrombosis model ( $\text{EC}_{50}$ s = 29–81 nM).

**Discovery of 4,6-bis-anilino-1H-pyrrolo[2,3-d]pyrimidines: Potent inhibitors of the IGF-1R receptor tyrosine kinase**

pp 469–473

Stanley D. Chamberlain, Joseph W. Wilson, Felix Deanda, Samarjit Patnaik, Anikó M. Redman, Bin Yang, Lisa Shewchuk, Peter Sabbatini, M. Anthony Leesnitzer, Arthur Groy, Charity Atkins, Roseanne Gerding, Anne M. Hassell, Huangshu Lei, Robert A. Mook Jr., Ganesh Moorthy, Jason L. Rowand, Kirk L. Stevens, Rakesh Kumar, J. Brad Shotwell\*

A series of 4,6-bis-anilino-1H-pyrrolo[2,3-d]pyrimidines are evaluated as IGF-1R inhibitors. Reported examples demonstrate nanomolar potencies in in vitro enzyme and cellular assays as well as promising in vivo pharmacokinetics in rat.

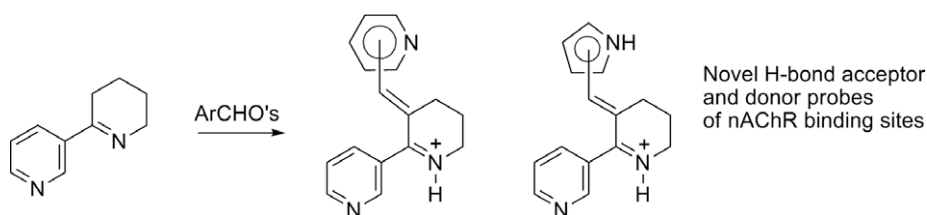


IGF-1R Enzyme  $\text{IC}_{50}$  2 nM  
Phospho IGF-1R Cellular  $\text{IC}_{50}$  109 nM

**Synthesis of H-bonding probes of  $\alpha 7$  nAChR agonist selectivity**

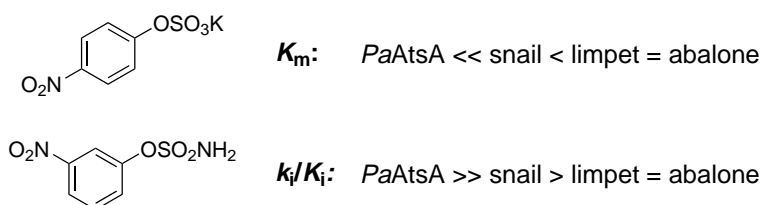
pp 474–476

Jingyi Wang, Roger L. Papke, Nicole A. Horenstein\*

**Aryl sulfamates are broad spectrum inactivators of sulfatases: Effects on sulfatases from various sources**

pp 477–480

Pavla Bojarová, Spencer J. Williams\*

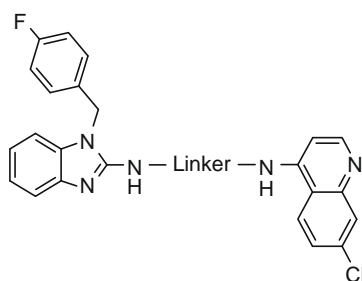


Aryl sulfamates were identified as versatile active-site directed inactivators for a range of sulfatases. They are promising tools for analysis of sulfatase-related processes and for the treatment of associated dysfunctions in vivo.

**Chloroquine–astemizole hybrids with potent in vitro and in vivo antiparasmodial activity**

pp 481–484

Chitalu C. Musonda, Gavin A. Whitlock\*, Michael J. Witty, Reto Brun, Marcel Kaiser

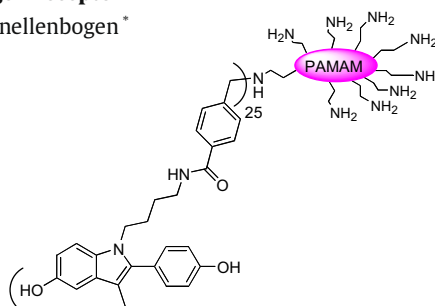


A series of novel hybrids of CQ and astemizole have been shown to possess potent in vitro and in vivo antiparasmodial activity.

**Tethered indoles as functionalizable ligands for the estrogen receptor**

pp 485–488

Bridget G. Trogden, Sung Hoon Kim, Shuyi Lee, John A. Katzenellenbogen\*

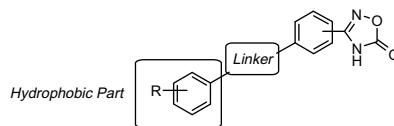


We report the synthesis of *N*-substituted-2-phenylindoles as estrogen receptor ligands. Optimal tether lengths were explored for creating a PAMAM-conjugated indole ligand.

**Novel non-carboxylic acid retinoids: 1,2,4-Oxadiazol-5-one derivatives**

pp 489–492

Julie Charton\*, Rebecca Deprez-Poulain, Nathalie Hennuyer, Anne Tailleux, Bart Staels, Benoit Deprez

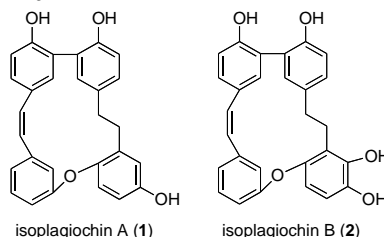


We have successfully obtained 1,2,4-oxadiazol-5-one bioisoteres of Am580 or Tazarotene-like retinoids. In particular compound **4** displays an EC<sub>50</sub> of 26 nM on RAR-β.

**Antimitotic activity of two macrocyclic bis(bibenzylyls), isoplagiochins A and B from the Liverwort *Plagiochila fruticosa***

pp 493–496

Hiroshi Morita\*, Yuichiro Tomizawa, Tomoe Tsuchiya, Yusuke Hirasawa, Toshihiro Hashimoto, Yoshinori Asakawa\*

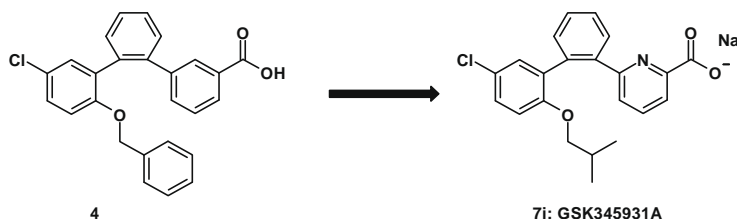


Two bis(bibenzylyls), isoplagiochins A (**1**) and B (**2**) have been isolated by the guidance of inhibitory effect of tubulin polymerization from the liverwort *Plagiochila fruticosa* (Plagiochilaceae). Isoplagiochins A and B inhibited the polymerization of tubulin at IC<sub>50</sub> 50 and 25 μM, respectively. Furthermore structure–activity relationship based on their conformations was discussed.

**Discovery of GSK345931A: An EP<sub>1</sub> receptor antagonist with efficacy in preclinical models of inflammatory pain**

pp 497–501

Adrian Hall\*, Susan H. Brown, Christopher Budd, Nicholas M. Clayton, Gerard M. P. Giblin, Paul Goldsmith, Thomas G. Hayhow, David N. Hurst, Alan Naylor, D. Anthony Rawlings, Tiziana Scoccitti\*, Alexander W. Wilson, Wendy J. Winchester

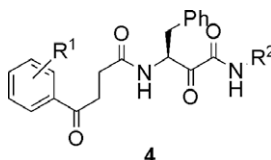


This paper details the discovery and characterization of GSK345931 (**7i**) from the lead compound **4**.

**Design and synthesis of 4-aryl-4-oxobutanoic acid amides as calpain inhibitors**

pp 502–507

Yong Zhang, Seo Yoon Jung, Changbae Jin, Nam Doo Kim, Ping Gong, Yong Sup Lee\*

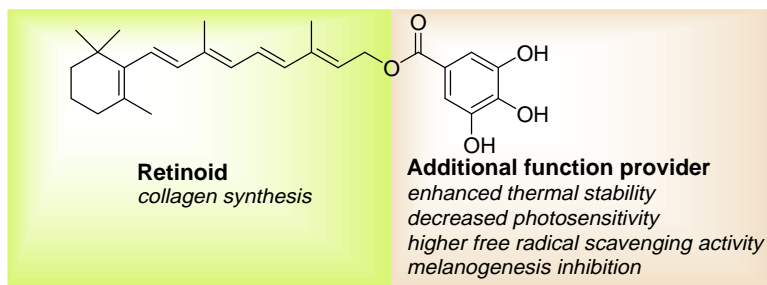


Aryl-4-oxobutanoic acid amide derivatives **4** were designed as acyclic variants of μ-calpain inhibitory chromone and quinolinone derivatives. Of the compounds synthesized, **4c-2**, which possesses a 2-methoxymethoxy group at the phenyl ring and a primary amide at the warhead region of the inhibitor most potently inhibited μ-calpain (IC<sub>50</sub> = 0.34 μM). Our findings suggest that the 4-aryl-4-oxobutanoic acid amide derivatives should be considered a new family of μ-calpain inhibitors.

**Synthesis and in vitro biological activity of retinyl polyhydroxybenzoates, novel hybrid retinoid derivatives**

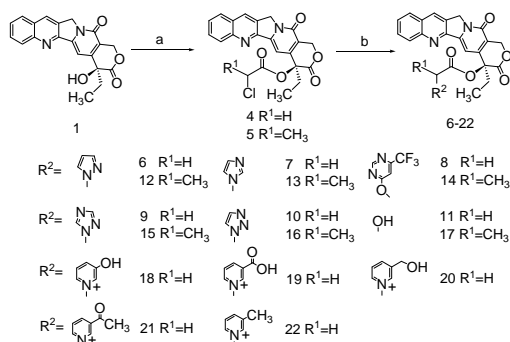
pp 508–512

Sungbum Kim, Youngmin Kim, Younggyu Kong, Hyojung Kim, Jahyo Kang\*

**Synthesis and antitumor activity of novel 20s-camptothecin analogues**

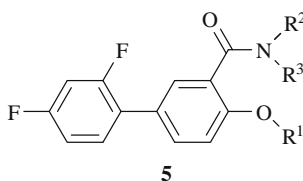
pp 513–515

Qingyong Li\*, Hongyan Lv, Yuangang Zu\*, Zhenhuan Qu, Liping Yao, Lin Su, Chen Liu, Limin Wang

**Synthesis and biological evaluation of amide derivatives of diflunisal as potential anti-inflammatory agents**

pp 516–519

Guang-Xiang Zhong\*, Jin-Qing Hu, Kun Zhao, Lu-Lu Chen, Wei-Xiao Hu, Ming-You Qiu

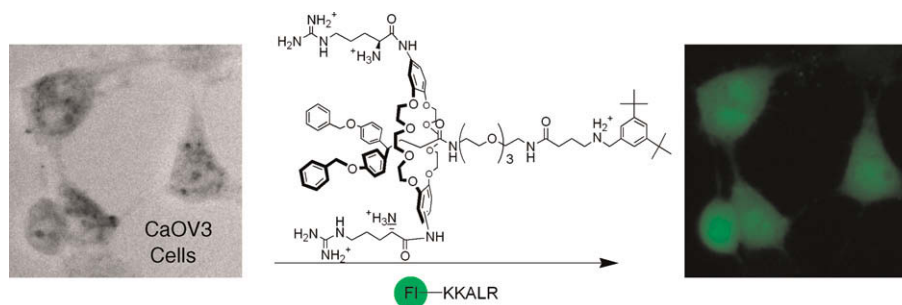


Twenty-one amide derivatives of diflunisal were synthesized starting in three steps. Compound **5m** possesses an excellent anti-inflammatory activity and a good analgesic activity, maybe a potential anti-inflammatory agent.

**Host-rotaxanes with oligomeric axles are intracellular transport agents**

pp 520–523

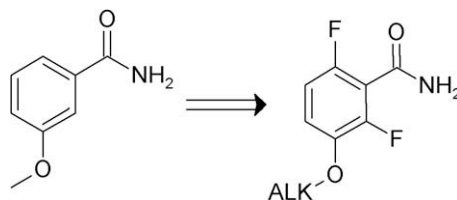
Jing Zhu, Molly McFarland-Mancini, Angela F. Drew, David B. Smithrud\*



**Antibacterial alkoxybenzamide inhibitors of the essential bacterial cell division protein FtsZ**

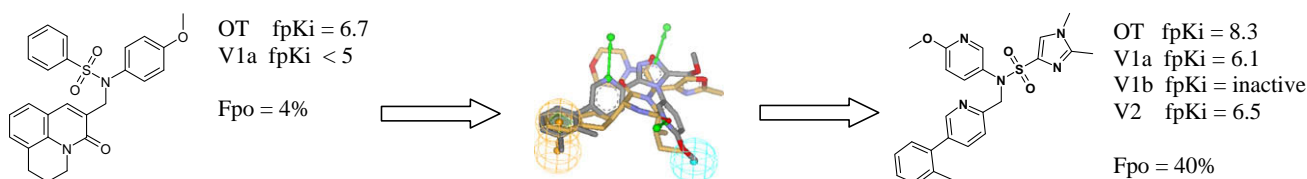
pp 524–527

Lloyd G. Czaplowski, Ian Collins, E. Andrew Boyd, David Brown, Stephen P. East, Mihaly Gardiner, Rowena Fletcher, David J. Haydon, Vincent Henstock, Peter Ingram, Clare Jones, Caterina Noula, Leanne Kennison, Chris Rockley, Valerie Rose, Helena B. Thomaides-Brears, Rebecca Ure, Mark Whittaker, Neil R. Stokes \*

**Discovery and optimisation of a potent and selective tertiary sulfonamide oxytocin antagonist**

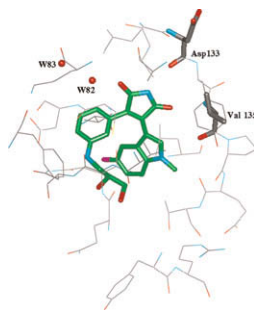
pp 528–532

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

**Identification of small molecules that inhibit GSK-3 $\beta$  through virtual screening**

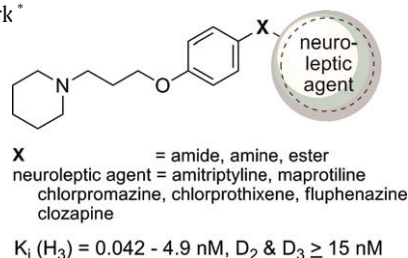
pp 533–537

Nam Sook Kang, Gil Nam Lee, Chi Hyun Kim, Myung Ae Bae, Ikyon Kim, Young Sik Cho \*

**Potential utility of histamine H<sub>3</sub> receptor antagonist pharmacophore in antipsychotics**

pp 538–542

Y. von Coburg, T. Kottke, L. Weizel, X. Ligneau, H. Stark \*



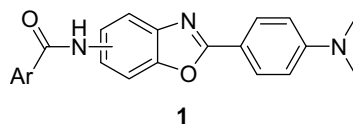
New multiple target drugs based on marketed neuroleptics have been designed, prepared and profiled maintaining dopamine hD<sub>2</sub>/hD<sub>3</sub> receptor affinities, reducing histamine hH<sub>1</sub> receptor affinities and introducing high affinity at histamine hH<sub>3</sub> receptors (H<sub>3</sub>R). hD<sub>1</sub>/hD<sub>5</sub> binding was heterogeneously shifted. The addition of an H<sub>3</sub>R pharmacophore to different typical and atypical neuroleptics by amide, amine or ester linkages resulted in a new profile of potential antipsychotics with low nanomolar to subnanomolar H<sub>3</sub>R affinities.



### Synthesis of 5- and 6-substituted 2-(4-dimethylaminophenyl)-1,3-benzoxazoles and their in vitro and in vivo evaluation as imaging agents for amyloid plaque

pp 543–545

Sven H. Hausner, David Alagille, Andrei O. Koren, Louis Amici, Julie K. Staley, Kelly P. Cosgrove, Ronald M. Baldwin, Gilles D. Tamagnan \*

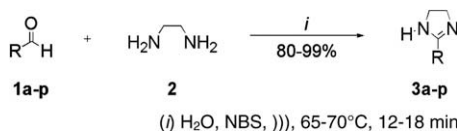


A series of novel 5- and 6-substituted 2-(4-dimethylaminophenyl)-1,3-benzoxazoles were synthesized and their potential as imaging probes for Alzheimer's Disease (AD) related amyloid plaque was evaluated in vitro and in vivo.

### Ultrasound promoted synthesis of 2-imidazolines in water: A greener approach toward monoamine oxidase inhibitors

pp 546–549

Gabriela da S. Sant' Anna, Pablo Machado, Patricia D. Sauzem, Fernanda A. Rosa, Maribel A. Rubin, Juliano Ferreira, Helio G. Bonacorso, Nilo Zanatta, Marcos A. P. Martins \*

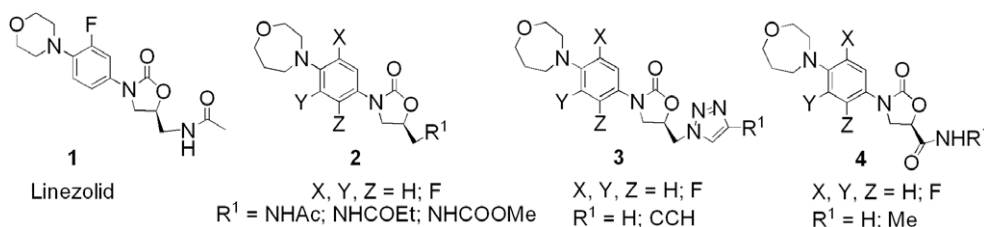


A series of sixteen 2-imidazolines (**3**) has been synthesized from the reaction of **1** and **2** by ultrasound irradiation with NBS in an aqueous medium in high yields (80–99%). The compound **3** ability to inhibit the activity of the A and B isoforms of monoamine oxidase (MAO) was investigated.

### Synthesis and structure–activity studies of novel homomorpholine oxazolidinone antibacterial agents

pp 550–553

Ji-Young Kim \*, Frederick E. Boyer, Allison L. Choy, Michael D. Huband, Paul J. Pagano, J. V. N. Vara Prasad



The synthesis and SAR of a novel series of oxazolidinones in which the morpholine C-ring of linezolid was replaced with homomorpholine are reported.

## OTHER CONTENTS

### Errata

pp 554–555

### Corrigendum

p 556

### Instructions to contributors

p I

\*Corresponding author

Supplementary data available via ScienceDirect

**COVER**

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

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ISSN 0960-894X