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# Bioorganic & Medicinal Chemistry Letters

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## Bioorganic & Medicinal Chemistry Letters Volume 20, Issue 5, 2010

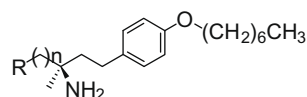
### Contents

#### ARTICLES

##### S1P receptor mediated activity of FTY720 phosphate mimics

pp 1485–1487

Klemens Högenauer\*, Klaus Hinterding, Peter Nussbaumer



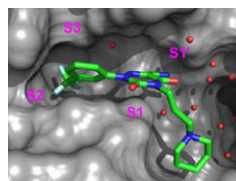
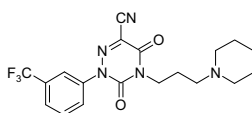
R = CO<sub>2</sub>H, P(O)(OH)<sub>2</sub>, SO<sub>3</sub>H, heterocycle  
n = 0–2

This work describes various carboxylic acids, phosphonic acids, sulfonic acids, tetrazoles as well as sulfonylhydantoin to act as agonists on the S1P<sub>1</sub> receptor.

##### Dioxo-triazines as a novel series of cathepsin K inhibitors

pp 1488–1490

Zoran Rankovic\*, Jiaqiang Cai\*, Xavier Fradera, Maureen Dempster, Ashvin Mistry, Ann Mitchell, Clive Long, Emma Hamilton, Angela King, Sylviane Boucharens, Craig Jamieson, Jonathan Gillespie, Iain Cumming, Joost Uitdehaag, Mario van Zeeland

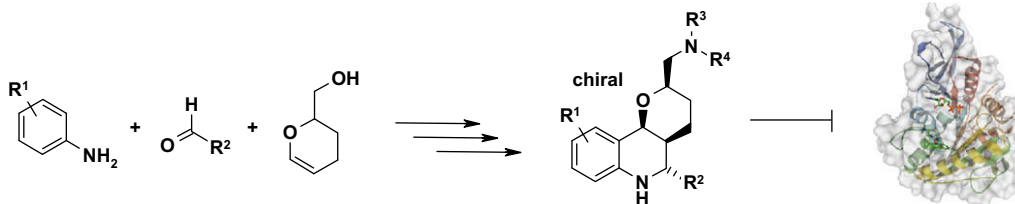


A series of potent and selective dioxo-triazine inhibitors of cathepsin K was identified from HTS.

##### The discovery and optimization of hexahydro-2H-pyrano[3,2-c]quinolines (HHPQs) as potent and selective inhibitors of the mitotic kinesin-5

pp 1491–1495

Kai Schiemann\*, Dirk Finsinger, Frank Zenke, Christiane Amendt, Thorsten Knöchel, David Bruge, Hans-Peter Buchstaller, Ulrich Emde, Wolfgang Stähle, Soheila Anzali

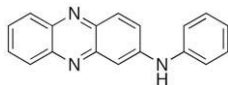


The synthesis, SAR, co-crystal structure and in vivo activity of hexahydro-2H-pyrano[3,2-c]quinolines (HHPQs) as potent and selective inhibitors of the mitotic kinesin-5 are described.

**Iodine scanning of a phenazine inhibitor of vacuolar sorting**

pp 1496–1499

Marci Surpin, Yunfan Zou, Chiyi Xiong, Natasha V. Raikhel, Michael C. Pirrung\*

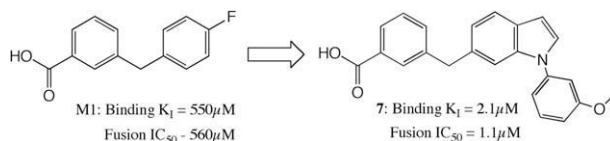


The synthesis and biological activity of N-phenylphenazin-2-amine and 4 iodinated derivatives is reported.

**Design, synthesis, and evaluation of indole compounds as novel inhibitors targeting Gp41**

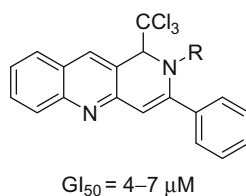
pp 1500–1503

Guangyan Zhou\*, Dong Wu, Evan Hermel, Edina Balogh, Miriam Gochin\*

**Antiproliferative activity of novel benzo[b][1,6]naphthyridines in human solid tumor cell lines**

pp 1504–1506

Simonas Rudys, Carla Ríos-Luci, Eduardo Pérez-Roth, Inga Cikotiene\*, José M. Padrón\*

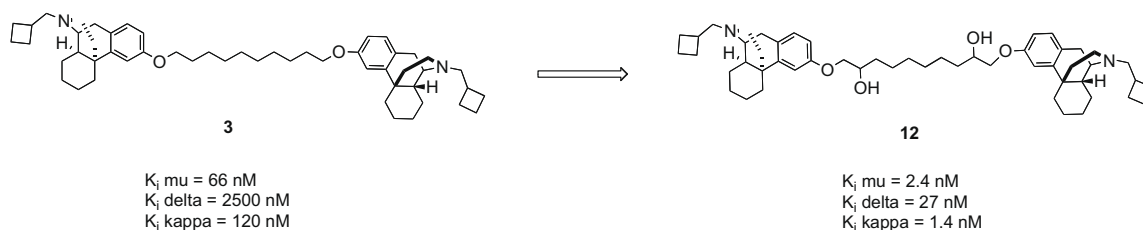


The synthesis and antiproliferative activity of novel 1,2-dihydro-3-phenyl-1-(trichloromethyl)benzo[b][1,6]naphthyridines is reported.

**Effect of linker substitution on the binding of butorphan univalent and bivalent ligands to opioid receptors**

pp 1507–1509

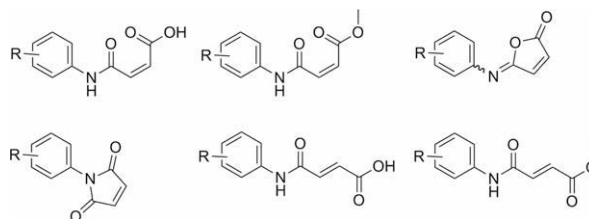
Brian S. Fulton\*, Brian L. Knapp, Jean M. Bidlack, John L. Neumeyer



**Derivatives of aryl amines containing the cytotoxic 1,4-dioxo-2-butenyl pharmacophore**

pp 1510–1515

Amitabh Jha\*, Chandrani Mukherjee, Ashok K. Prasad, Virinder S. Parmar, Manjula Vadaparti, Umashankar Das, Erik De Clercq, Jan Balzarini, James P. Stables, Anuraag Shrivastav, Rajendra K. Sharma, Jonathan R. Dimmock

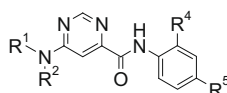


Cytotoxicity and QSAR studies on compounds containing the 1,4-dioxo-2-butenyl moiety viz. *N*-arylmaleamic acids, methyl *N*-arylmaleamates, *N*-arylisomaleimides, *N*-arylmaleimides, *N*-arylfumaramic acids, and methyl *N*-arylfumaramates are reported.

**Discovery of a novel series of potent S1P1 agonists**

pp 1516–1519

Stefano Crosignani\*, Agnes Bombrun, David Covini, Maurizio Maio, Delphine Marin, Anna Quattropani, Dominique Swinnen, Don Simpson, Wolfgang Sauer, Bernard Françon, Thierry Martin, Yves Cambet, Anthony Nichols, Isabelle Martinou, Fabienne Burgat-Charvillon, Delphine Rivron, Cristina Donini, Olivier Schott, Valerie Eligert, Laurence Novo-Perez, Pierre-Alain Vitte, Jean-François Arrighi

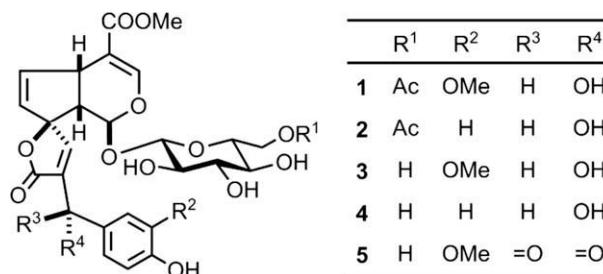


The discovery of a novel series of S1P1 agonists is described. Several single-digit nanomolar S1P1 agonists were discovered, and a selected compound was shown to be able to induce lymphopenia in mice after oral dosing.

**New anti-malarial phenylpropanoid conjugated iridoids from *Morinda morindoides***

pp 1520–1523

Satoru Tamura, Bruno Kilunga Kubata, Syamsurizal, Sawako Itagaki, Toshihiro Horii, Muzele Kalulu Taba, Nobutoshi Murakami\*

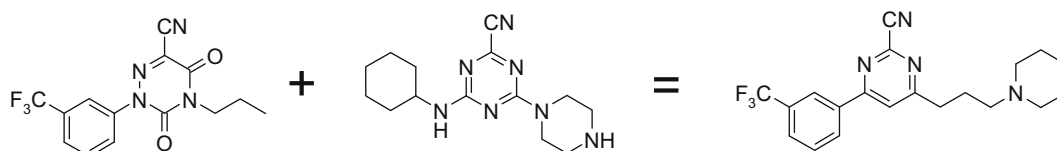


A new phenylpropanoid conjugated iridoid (**1**) together with four known congeners (**2–5**) was isolated from the leaves of *Morinda morindoides* as potent anti-malarial principles through bioassay-guided separation.

**Design and optimization of a series of novel 2-cyano-pyrimidines as cathepsin K inhibitors**

pp 1524–1527

Zoran Rankovic\*, Jiaqiang Cai\*, Jennifer Kerr, Xavier Fradera, John Robinson, Ashvin Mistry, Emma Hamilton, George McGarry, Fiona Andrews, Wilson Caulfield, Iain Cumming, Maureen Dempster, John Waller, Paul Scullion, Iain Martin, Ann Mitchell, Clive Long, Mark Baugh, Paul Westwood, Emma Kinghorn, John Bruin, William Hamilton, Joost Uitdehaag, Mario van Zeeland, Dominique Potin, Laurent Saniere, Andre Fouquet, François Chevallier, Hortense Deronzier, Cecile Dorleans, Eric Nicolai

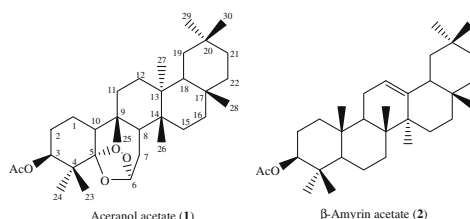


Morphing structural features of HTS-derived chemotypes led to the discovery of novel 2-cyano-pyrimidine inhibitors of cathepsin K with improved pharmacokinetic profile.

**Triterpene compounds isolated from *Acer mandshuricum* and their anti-inflammatory activity**

pp 1528–1531

Yan Ding, Chun Liang, Jun Ho Kim, Young-Mi Lee, Jae-Hee Hyun, Hee-Kyoung Kang,  
Jeong-Ah Kim, Byung Sun Min, Young Ho Kim\*

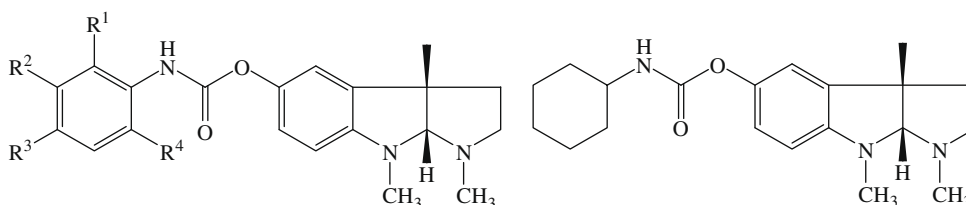


Bioassay-guided fractionation of the MeOH extract led to the isolation of six compounds, including one new triterpene (**1**). Compound **2** reduced the LPS-induced secretion of TNF- $\alpha$  in a RAW264.7 cell line.

**Synthesis of physostigmine analogues and evaluation of their anticholinesterase activities**

pp 1532–1534

Zha-Jun Zhan, Hong-Ling Bian, Jian-Wei Wang, Wei-Guang Shan\*

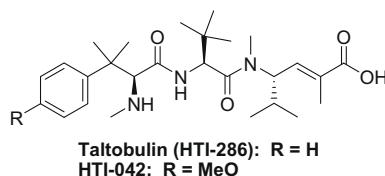


A series of physostigmine analogues, were prepared and evaluated for cholinesterase inhibition activities. Compound **17** especially exhibited significantly higher selectivity over BChE than phenserine, a compound currently on clinical trial. Discussion about the relationships between structure and activity of these derivatives was also presented.

**Absolute configurations of tubulin inhibitors taltobulin (HTI-286) and HTI-042 characterized by X-ray diffraction analysis and NMR studies**

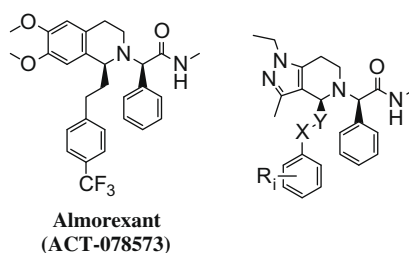
pp 1535–1538

Chuansheng Niu\*, Douglas M. Ho, Arie Zask, Semiramis Ayral-Kaloustian

**Novel pyrazolo-tetrahydropyridines as potent orexin receptor antagonists**

pp 1539–1542

Thierry Sifferlen\*, Christoph Boss\*, Emmanuelle Cottreel, Ralf Koberstein, Markus Gude, Hamed Aissaoui,  
Thomas Weller, John Gatfield, Catherine Brisbare-Roch, Francois Jenck

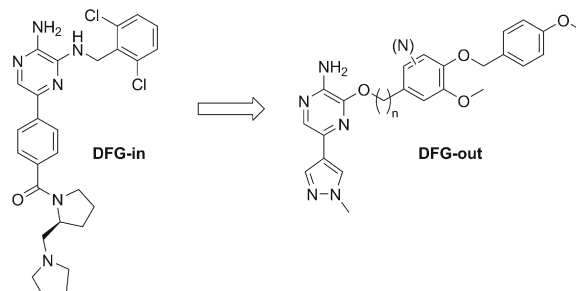


A novel series of dual orexin receptor antagonists was prepared by heteroaromatic five-membered ring system replacement of the dimethoxyphenyl moiety contained in the tetrahydroisoquinoline core skeleton of almorexant, a dual orexin receptor antagonist in phase 3 clinical development.

**Structure-based drug design enables conversion of a DFG-in binding CSF-1R kinase inhibitor to a DFG-out binding mode**

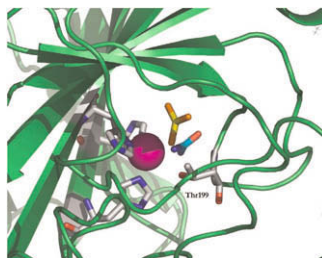
pp 1543–1547

Marvin J. Meyers\*, Matthew Pelc, Satwik Kamtekar, Jacqueline Day, Gennadiy I. Poda, Molly K. Hall, Marshall L. Michener, Beverly A. Reitz, Karl J. Mathis, Betsy S. Pierce, Mihir D. Parikh, Deborah A. Mischke, Scott A. Long, John J. Parlow, David R. Anderson, Atli Thorarensen

**Carbonic anhydrase inhibitors. Inhibition of transmembrane isoforms IX, XII, and XIV with less investigated anions including trithiocarbonate and dithiocarbamate**

pp 1548–1550

Alessio Innocenti, Andrea Scozzafava, Claudiu T. Supuran\*

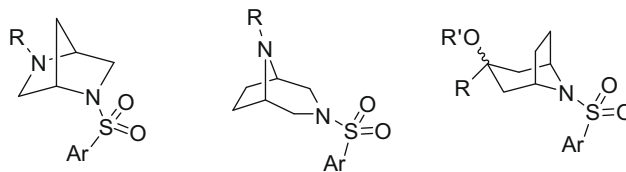


$\text{CS}_3^{2-}$ :  $K_i = 9.7 \mu\text{M}$  (CA IX);  $K_i = 120 \mu\text{M}$  (CA XII);  $K_i = 660 \mu\text{M}$  (CA XIV).

**Azabicyclic sulfonamides as potent 11 $\beta$ -HSD1 inhibitors**

pp 1551–1554

Unmesh Shah\*, Craig D. Boyle, Samuel Chackalamannil, Hana Baker, Timothy Kowalski, Julie Lee, Giuseppe Terracina, Lili Zhang



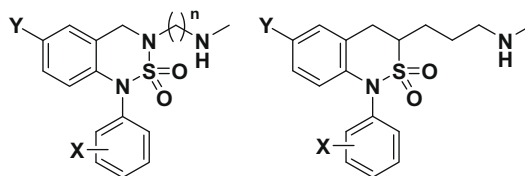
Ar = 4-*t*Bu-phenyl; R, R' = alkyl, cycloalkyl, etc.

Inhibition of 11 $\beta$ -HSD1 has demonstrated potential in the treatment of various components of metabolic syndrome. We wish to report herein the discovery of novel azabicyclic sulfonamide based 11 $\beta$ -HSD1 inhibitors. Highly potent compounds exhibiting inhibitory activities at both human and mouse 11 $\beta$ -HSD1 were identified. Several compounds demonstrated significant in vivo activity in the mouse cortisone challenge assay.

**Structure–activity relationships of norepinephrine reuptake inhibitors with benzothiadiazine dioxide or dihydrosulfostyryl cores**

pp 1555–1558

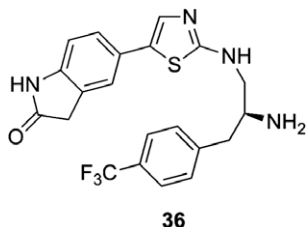
Andrew Fensome, Joel Goldberg\*, Casey C. McComas, Eugene J. Trybulski, Richard P. Woodworth, Darlene C. Deecher, Garth T. Whiteside, Puwen Zhang



**Azole-based inhibitors of AKT/PKB for the treatment of cancer**

pp 1559–1564

Qingping Zeng, John G. Allen\*, Matthew P. Bourbeau, Xianghong Wang, Guomin Yao, Seifu Tadesse, James T. Rider, Chester C. Yuan, Fang-Tsao Hong, Matthew R. Lee, Shiwen Zhang, Julie A. Lofgren, Daniel J. Freeman, Suijin Yang, Chun Li, Elizabeth Tominey, Xin Huang, Douglas Hoffman, Harvey K. Yamane, Christopher Fotsch, Celia Dominguez, Randall Hungate, Xiaoling Zhang

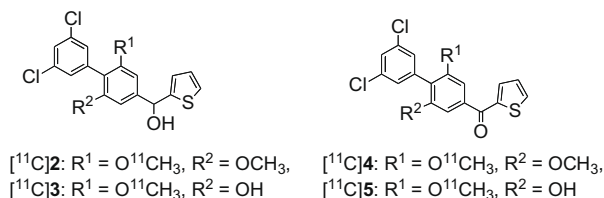


<b>36</b>	IC <sub>50</sub> , nM
AKT1	18.3±6.4
PKA	167±50
CDK2	185±96
pPRAS40	300±80

**Radiosynthesis of novel carbon-11-labeled triaryl ligands for cannabinoid-type 2 receptor**

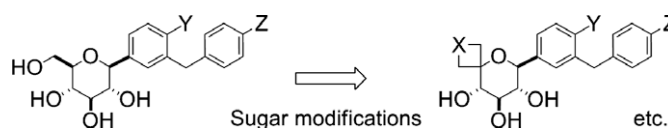
pp 1565–1568

Masayuki Fujinaga, Katsushi Kumata, Kazuhiko Yanamoto, Kazunori Kawamura, Tomoteru Yamasaki, Joji Yui, Akiko Hatori, Masanao Ogawa, Yuichiro Yoshida, Nobuki Nengaki, Jun Maeda, Ming-Rong Zhang\*

**C-Aryl glycoside inhibitors of SGLT2: Exploration of sugar modifications including C-5 spirocyclization**

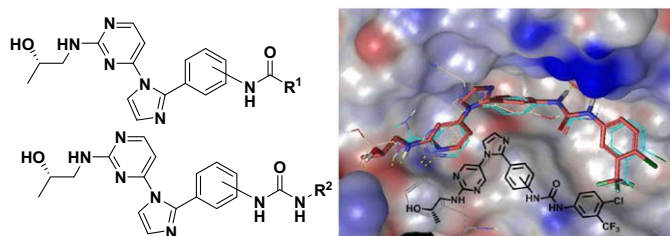
pp 1569–1572

Ralph P. Robinson\*, Vincent Mascitti, Carine M. Boustany-Kari, Christopher L. Carr, Patrick M. Foley, Emi Kimoto, Michael T. Leininger, Andre Lowe, Michelle K. Klenotic, James I. MacDonald, Robert J. Maguire, Victoria M. Masterson, Tristan S. Maurer, Zhuang Miao, Jigna D. Patel, Cathy Prévile, Matthew R. Reese, Li She, Claire M. Steppan, Benjamin A. Thuma, Tong Zhu

**Discovery and initial SAR of pyrimidin-4-yl-1H-imidazole derivatives with antiproliferative activity against melanoma cell lines**

pp 1573–1577

Junghun Lee, Hwan Kim, Hana Yu, Jae Yoon Chung, Chang-Hyun Oh, Kyung Ho Yoo, Taebo Sim, Jung-Mi Hah\*

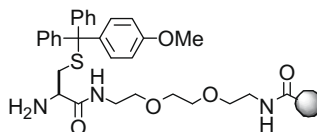


A series of pyrimidin-4-yl-1H-imidazol-2-yl derivatives **7**, **8**, **9** and their antiproliferative activities against A375 human melanoma cell line and WM3629 cell line were described.

**Biochemical analysis of cellular target of S-trityl-L-cysteine derivatives using affinity matrix**

pp 1578–1580

Makiko Shimizu, Hirosuke Ishii, Naohisa Ogo, Kenji Matsuno, Akira Asai\*

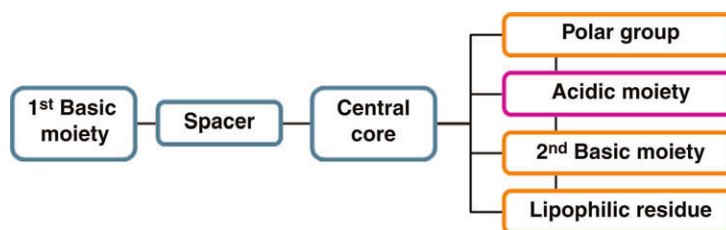


Synthesis of S-trityl-L-cysteine (STLC) analogue-immobilized affinity beads and biochemical analysis of the cellular target of STLC derivatives were reported.

**Acidic elements in histamine H<sub>3</sub> receptor antagonists**

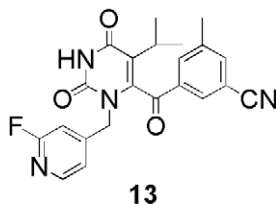
pp 1581–1584

Kerstin Sander, Yvonne von Coburg, Jean-Claude Camelin, Xavier Ligneau, Oliver Rau, Manfred Schubert-Zsilavecz, Jean-Charles Schwartz, Holger Stark\*

**N1-Heterocyclic pyrimidinediones as non-nucleoside inhibitors of HIV-1 reverse transcriptase**

pp 1585–1588

Michael L. Mitchell\*, Jong Chan Son, Ill Young Lee, Chong-Kyo Lee, Hae Soo Kim, Hongyan Guo, Jianhong Wang, Jaclyn Hayes, Michael Wang, Amber Paul, Eric B. Lansdon, James M. Chen, Gene Eisenberg, Romas Geleziunas, Lianhong Xu, Choung U. Kim

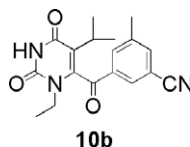


A series of N1-heterocyclic pyrimidinediones were evaluated as HIV-1 non-nucleoside reverse transcriptase inhibitors, resulting in the discovery of compound **13**.

**N1-Alkyl pyrimidinediones as non-nucleoside inhibitors of HIV-1 reverse transcriptase**

pp 1589–1592

Michael L. Mitchell\*, Jong Chan Son, Hongyan Guo, Yun-A Im, Eun Jung Cho, Jianhong Wang, Jaclyn Hayes, Michael Wang, Amber Paul, Eric B. Lansdon, James M. Chen, Doris Graupe, Gerry Rhodes, Gong-Xin He, Romas Geleziunas, Lianhong Xu, Choung U. Kim

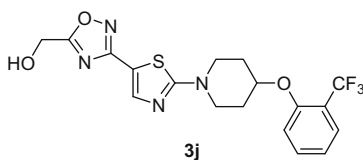


Evaluation of a series of N1-alkyl pyrimidinediones as HIV-1 non-nucleoside reverse transcriptase inhibitors identified compound **10b**, which represents the lead compound with pharmacokinetics and antiviral potency that may support once-daily dosing.

**SAR and optimization of thiazole analogs as potent stearyl-CoA desaturase inhibitors**

pp 1593–1597

Yeeman K. Ramtohl\*, Cameron Black, Chi-Chung Chan, Sheldon Crane, Jocelyne Guay, Sébastien Guiral, Zheng Huang, Renata Oballa, Li-Jing Xu, Lei Zhang, Chun Sing Li

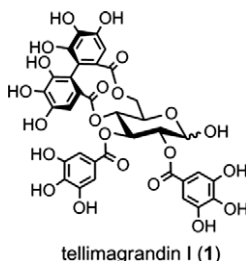


A potent and bioavailable SCD inhibitor, **3j** was identified from optimization of a lead thiazole compound and its in vivo SCD inhibition studies are described.

**Tellimagrandin I, HCV invasion inhibitor from Rosae Rugosae Flos**

pp 1598–1600

Satoru Tamura, Gang-Ming Yang, Natsuko Yasueda, Yoshiharu Matsuura, Yasumasa Komoda, Nobutoshi Murakami\*

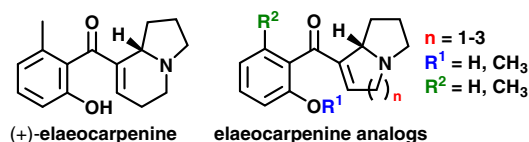


Tellimagrandin I (**1**) along with two relative tannins were disclosed as the HCV invasion inhibitors from Rosae Rugosae Flos by use of the model virus expressing the HCV envelopes E1 and E2.

**Synthesis and evaluation of opioid receptor-binding affinity of elaeocarpenine and its analogs**

pp 1601–1603

Haruaki Kurasaki, Iwao Okamoto, Nobuyoshi Morita, Osamu Tamura\*

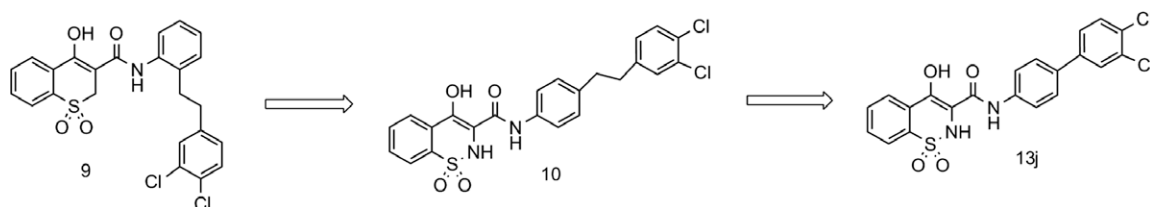


We report the first total synthesis of elaeocarpenine and its analogs and evaluation of their in vitro binding affinities to  $\mu$ -,  $\delta$ - and  $\kappa$ -opioid receptor subtypes.

**Selective inducible microsomal prostaglandin E<sub>2</sub> synthase-1 (mPGES-1) inhibitors derived from an oxicam template**

pp 1604–1609

Jane Wang\*, David Limburg, Jeff Carter, Gabriel Mbalaviele, James Gierse, Michael Vazquez



The design and synthesis of a series of potent and selective mPGES-1 inhibitors based on an oxicam template are described. Our SAR studies allowed us to optimize this series resulting in the identification of compound **13j** which demonstrated potent inhibition in both enzyme and cellular assay. This series of compounds illustrated good mPGES-1 inhibition along with good selectivity over COX-2 and 6-keto PGF<sub>1 $\alpha$</sub> .

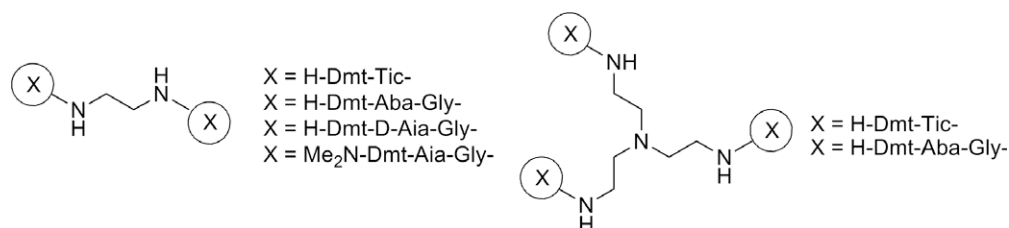




**Novel multiple opioid ligands based on 4-aminobenzazepinone (Aba), azepinoindole (Aia) and tetrahydroisoquinoline (Tic) scaffolds**

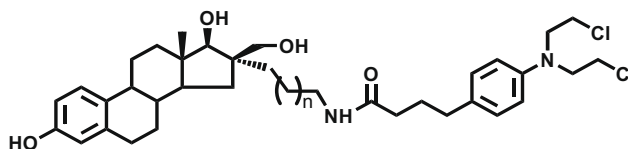
pp 1610–1613

Steven Ballet\*, Ewa D. Marczak, Debby Feytens, Severo Salvadori, Yusuke Sasaki, Andrew D. Abell, Lawrence H. Lazarus, Gianfranco Balboni, Dirk Tourwé

**Design, synthesis and biological evaluation of estradiol–chlorambucil hybrids as anticancer agents**

pp 1614–1618

Atul Gupta, Pijus Saha, Caroline Descôteaux, Valérie Leblanc, Éric Asselin, Gervais Bérubé\*

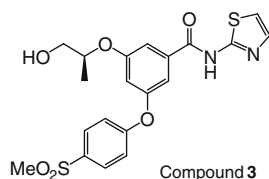


The synthesis of a series of estradiol–chlorambucil hybrids is reported. The hybrids showed significant in vitro anticancer activity when compared to chlorambucil on breast cancer cell lines.

**Metabolic activation of *N*-thiazol-2-yl benzamide as glucokinase activators: Impacts of glutathione trapping on covalent binding**

pp 1619–1622

Tomoharu Iino\*, Noriaki Hashimoto, Takuro Hasegawa, Masato Chiba, Jun-ichi Eiki, Teruyuki Nishimura

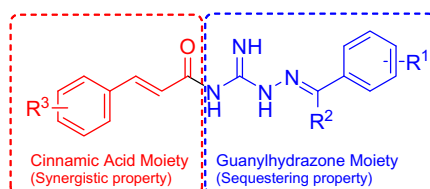


The in vitro covalent binding results that were observed during the course of evaluating the compound **3** for the treatment of type-2 diabetes are described.

**Novel molecular hybrids of cinnamic acids and guanylhyaones as potential antitubercular agents**

pp 1623–1625

Ranjeet Bairwa, Manoj Kakwani, Nilesh R. Tawari, Jaya Lalchandani, M. K. Ray, M. G. R. Rajan, Mariam S. Degani\*



Microwave assisted synthesis of 20 novel phenylacrylamide derivatives incorporating cinnamic acids and guanylhyaones and in vitro evaluation against *Mycobacterium tuberculosis* is described.

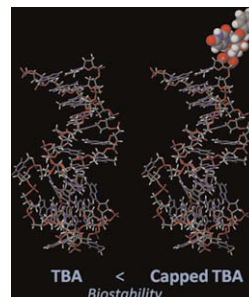


### Effect of 3'-end capping of aptamer with various 2',4'-bridged nucleotides: Enzymatic post-modification toward a practical use of polyclonal aptamers

pp 1626–1629

Yuuya Kasahara, Shunsuke Kitadume, Kunihiro Morihiro, Masayasu Kuwahara\*, Hiroaki Ozaki, Hiroaki Sawai, Takeshi Imanishi, Satoshi Obika

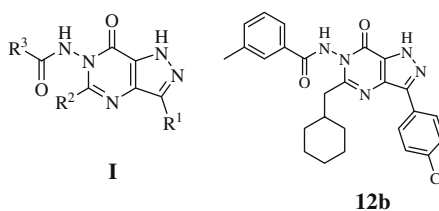
The capping of the 3'-ends of thrombin binding aptamers (TBAs) with bridged nucleotides increased the nuclease resistances and the stabilities in human serum. The binding abilities of the aptamers were not affected by the capping. The capping could be simply executed via a one step enzymatic process using 2',4'-bridged nucleoside 5'-triphosphate and terminal deoxynucleotidyl transferase.



### Novel 6-*N*-arylcarboxamidopyrazolo[4,3-*d*]pyrimidin-7-one derivatives as potential anti-cancer agents

pp 1630–1633

Vani N. Devegowda, Jung Hyun Kim, Ki-Cheol Han, Eun Gyeong Yang, Hyunah Choo, Ae Nim Pae, Ghilsoo Nam\*, Kyung Il Choi\*

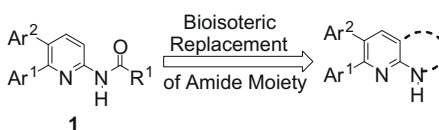


A library of 6-*N*-arylcarboxamidopyrazolo[4,3-*d*]pyrimidin-7-one derivatives (**I**) was synthesized and structure-anticancer activity relationships have been established for R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup>. The most active compound **12b** showed GI<sub>50</sub> value of 0.44 μM and 1.07 μM against cancer cell lines HT-29 and DU-145, respectively.

### Discovery of potent and selective bicyclic A<sub>2B</sub> adenosine receptor antagonists via bioisosteric amide replacement

pp 1634–1637

Paul Eastwood\*, Jacob Gonzalez, Sergio Paredes, Silvia Fonquerna, Arantxa Cardús, Juan Antonio Alonso, Arsenio Nueda, Teresa Domenech, Raquel F. Reinoso, Bernat Vidal

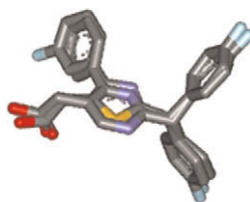


Several novel, potent and selective A<sub>2B</sub> adenosine receptor antagonists have been prepared in which the aryl-amide moiety of the lead series **1** was replaced by various bioisosteric bicyclic moieties.

### Exploration of SAR features by modifications of thiazoleacetic acids as CRTH2 antagonists

pp 1638–1641

Marie Grimstrup, Jean-Marie Receveur, Øystein Rist, Thomas M. Frimurer, Peter Aadal Nielsen, Jesper M. Mathiesen, Thomas Höglberg\*

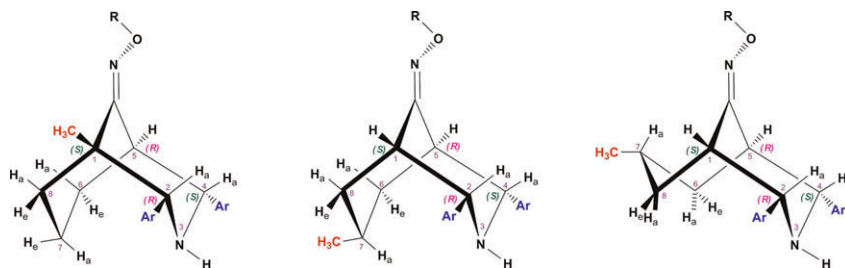


SAR data have been supported by key analogues of thiazoleacetic acids and modelling studies to arrive at potent and novel chemotypes of CRTH2 antagonists.

**Stereospecific synthesis of oximes and oxime ethers of 3-azabicycles: A SAR study towards antimicrobial agents**

pp 1642–1647

Paramasivam Parthiban, Paramasivam Rathika, Venkatachalam Ramkumar, Se Mo Son, Yeon Tae Jeong\*

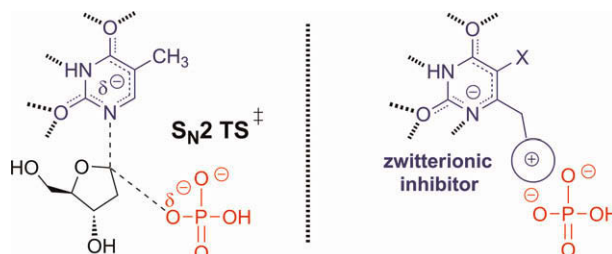


Libraries of 1- and 7-methyl-2,4-diaryl-3-azabicyclo[3.3.1]nonan-9-ones/oximes/O-methyloximes were synthesized and unambiguously characterized by 1D/2D NMR and single crystal XRD data. All the synthesized oximes and oxime ethers were evaluated for their in vitro antimicrobial activity.

**The role of phosphate in the action of thymidine phosphorylase inhibitors: Implications for the catalytic mechanism**

pp 1648–1651

Harsh V. Jain, Roshni Rasheed, Thomas I. Kalman\*

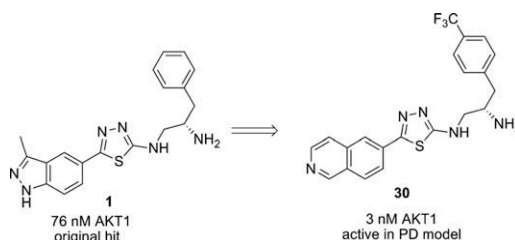


The inhibition of thymidine phosphorylase by AIFU was determined to follow uncompetitive kinetics with respect to inorganic phosphate, indicating that zwitterionic transition state analogs bind to the enzyme phosphate binary complex, consistent with an  $S_N2$ -type catalytic mechanism.

**2-Aminothiadiazole inhibitors of AKT1 as potential cancer therapeutics**

pp 1652–1656

Qingping Zeng, Matthew P. Bourbeau\*, G. Erich Wohlhieter, Guomin Yao, Holger Monenschein, James T. Rider, Matthew R. Lee, Shiwen Zhang, Julie Lofgren, Daniel Freeman, Chun Li, Elizabeth Tominey, Xin Huang, Douglas Hoffman, Harvey Yamane, Andrew S. Tasker, Celia Dominguez, Vellarkad N. Viswanadhan, Randall Hungate, Xiaoling Zhang



The development of a series of potent AKT1 inhibitors is reported.

**3-(Arylsulfonyl)-1-(azacyclyl)-1H-indoles are 5-HT<sub>6</sub> receptor modulators**

pp 1657–1660

Ronald C. Bernotas\*, Schuyler Antane, Rajesh Shenoy, Van-Duc Le, Ping Chen, Boyd L. Harrison, Albert J. Robichaud, Guo Ming Zhang, Deborah Smith, Lee E. Schechter

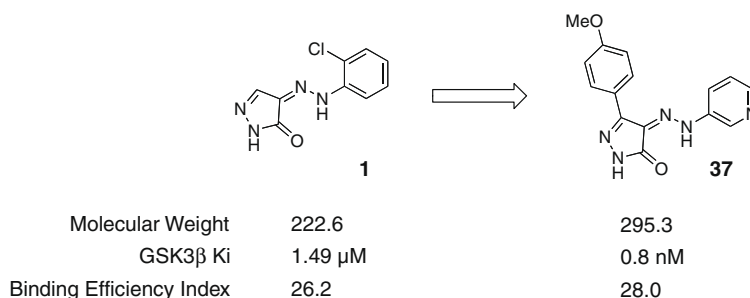


A series of 1-(azacyclyl)-3-arylsulfonyl-1H-indoles **6** was prepared as constrained 5-HT<sub>6</sub> modulators.

**3-Aryl-4-(arylhrazono)-1H-pyrazol-5-ones: Highly ligand efficient and potent inhibitors of GSK3 $\beta$** 

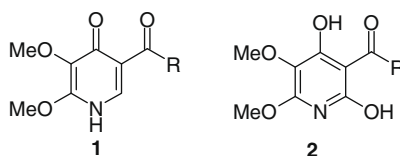
pp 1661–1664

Michael Arnost, Al Pierce, Ernst ter Haar, David Lauffer, Jaren Madden, Kirk Tanner, Jeremy Green\*

**Synthetic atpenin analogs: Potent mitochondrial inhibitors of mammalian and fungal succinate-ubiquinone oxidoreductase**

pp 1665–1668

Thomas P. Selby\*, Kenneth A. Hughes, James J. Rauh, Wayne S. Hanna

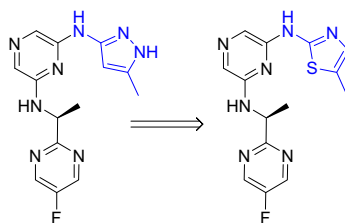


This Letter describes the synthesis of a series of synthetic atpenin analogs of formulae **1** and **2** as potential agricultural fungicides where some compounds showed potent mammalian and fungal mitochondrial complex II inhibition.

**Replacement of pyrazol-3-yl amine hinge binder with thiazol-2-yl amine: Discovery of potent and selective JAK2 inhibitors**

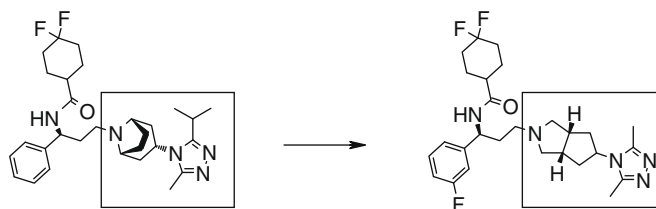
pp 1669–1673

Stephanos Ioannidis\*, Michelle L. Lamb, Lynsie Almeida, Huiping Guan, Bo Peng, Geraldine Beberntz, Kirsten Bell, Marat Alimzhanov, Michael Zinda

**Evaluation of a 3-amino-8-azabicyclo[3.2.1]octane replacement in the CCR5 antagonist maraviroc**

pp 1674–1676

Rémy C. Lemoine\*, Ann C. Petersen, Lina Setti, Thomas Baldinger, Jutta Wanner, Andreas Jekle, Gabrielle Heilek, André deRosier, Changhua Ji, David M. Rotstein

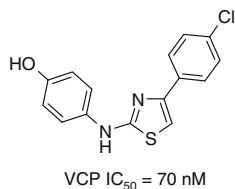


The bicyclic 5-amino-3-azabicyclo[3.3.0]octanes were shown to be effective replacements for the 3-amino-8-azabicyclo[3.2.1]octane found in the CCR5 antagonist maraviroc.

**2-Anilino-4-aryl-1,3-thiazole inhibitors of valosin-containing protein (VCP or p97)**

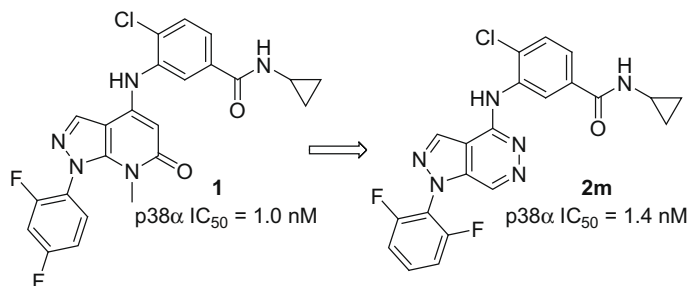
pp 1677–1679

Matthew G. Bursavich\*, Daniel P. Parker, J. Adam Willardsen, Zhong-Hua Gao, Thaylon Davis, Kirill Ostanin, Rosann Robinson, Ashley Peterson, Daniel M. Cimborá, Ju-Fen Zhu, Burt Richards

**Part 2: Structure–activity relationship (SAR) investigations of fused pyrazoles as potent, selective and orally available inhibitors of p38 $\alpha$  mitogen-activated protein kinase**

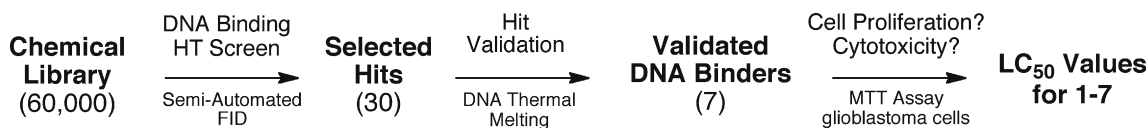
pp 1680–1684

Ryan P. Wurz\*, Liping H. Pettus, Bradley Henkle, Lisa Sherman, Matthew Plant, Kent Miner, Helen J. McBride, Lu Min Wong, Christiaan J. M. Saris, Matthew R. Lee, Samer Chmait, Christopher Mohr, Faye Hsieh, Andrew S. Tasker

**Semi-automated high-throughput fluorescent intercalator displacement-based discovery of cytotoxic DNA binding agents from a large compound library**

pp 1685–1688

LaTeca S. Glass, Aditi Bapat, Mark R. Kelley, Millie M. Georgiadis\*, Eric C. Long\*

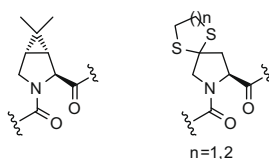


High-throughput fluorescent intercalator displacement (HT-FID) was adapted to the semi-automated screening of a commercial compound library leading to the discovery of cytotoxic DNA-targeted agents.

**Towards the second generation of Boceprevir: Dithianes as an alternative P2 substituent for 2,2-dimethyl cyclopropyl proline in HCV NS3 protease inhibitors**

pp 1689–1692

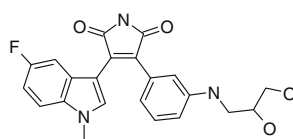
Latha G. Nair\*, Stephane Bogen, Sumei Ruan, Weidong Pan, Russel Pike, Xiao Tong, Kuo-Chi Cheng, Zhuyan Guo, Ronald J. Doll, F. George Njoroge



**Discovery of potent and bioavailable GSK-3 $\beta$  inhibitors**

pp 1693–1696

Leyi Gong\*, Don Hirschfeld, Yun-Chou Tan, J. Heather Hogg, Gary Peltz, Zafirra Avnur, Pete Dunten

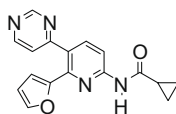
**34**

A series of maleimides was discovered with high potency and good selectivity for GSK-3 $\beta$ . The most potent compound **34** has an IC<sub>50</sub> of 0.6 nM for GSK-3 $\beta$ , over 100-fold selectivity against a panel of other kinases, and shows efficacy in rat osteoporosis models.

**Discovery of N-(5,6-diarylpyridin-2-yl)amide derivatives as potent and selective A<sub>2B</sub> adenosine receptor antagonists**

pp 1697–1700

Paul Eastwood\*, Jacob Gonzalez, Sergio Paredes, Arsenio Nueda, Teresa Domenech, Joan Alberti, Bernat Vidal

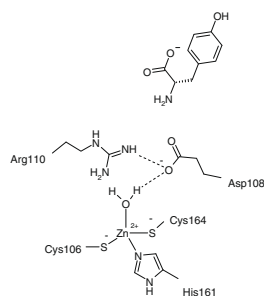
**9**: A<sub>2B</sub> K<sub>i</sub> = 4±1 nM

The potent and selective A<sub>2B</sub> adenosine receptor antagonist **9** was shown to have good oral bioavailability in the rat.

**Carbonic anhydrase activators: Activation of the  $\beta$ -carbonic anhydrase from the pathogenic yeast *Candida glabrata* with amines and amino acids**

pp 1701–1704

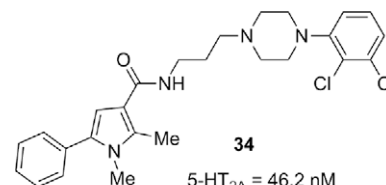
Alessio Innocenti, Worraanong Leewattanapasuk, Gheorghe Manole, Andrea Scozzafava, Fritz A. Mühlischlegel, Claudiu T. Supuran\*

**Arylpiperazine-containing pyrrole 3-carboxamide derivatives targeting serotonin 5-HT<sub>2A</sub>, 5-HT<sub>2C</sub>, and the serotonin transporter as a potential antidepressant**

pp 1705–1711

Suk Youn Kang, Eun-Jung Park, Woo-Kyu Park, Hyun Jung Kim, Daeyoung Jeong, Myung Eun Jung, Kwang-Seop Song, Suk Ho Lee, Hee Jeong Seo, Min Ju Kim, MinWoo Lee, Ho-Kyun Han, Eun-Jung Son, Ae Nim Pae, Jeongmin Kim, Jinhwa Lee\*

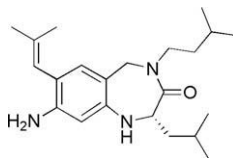
Arylpiperazine-containing pyrrole 3-carboxamide derivatives were synthesized and evaluated as novel antidepressant compounds. The various analogues were efficiently prepared and bio-assayed for binding to 5-HT<sub>2A</sub>, 5-HT<sub>2C</sub> receptor, and 5-HT transporter. Based on their in vitro and in vivo activities as well as selectivity over other neurotransmitter receptors and PK profiles, **34** was identified as a lead compound. Consequently, this pyrrole series of compounds appears to be promising enough to warrant further investigation.

**34**

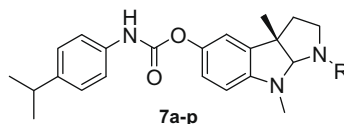
5-HT<sub>2A</sub> = 46.2 nM  
 5-HT<sub>2C</sub> = 12 nM  
 SERT = 61.7 nM

**LXXLL peptide mimetics as inhibitors of the interaction of vitamin D receptor with coactivators****pp 1712–1717**

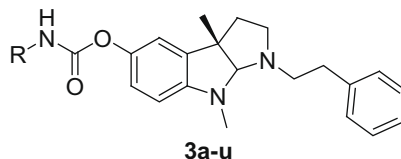
Yusuke Mita, Kosuke Dodo, Tomomi Noguchi-Yachide, Hiroyuki Miyachi, Makoto Makishima, Yuichi Hashimoto\*, Minoru Ishikawa\*

**Design, synthesis, evaluation and QSAR analysis of *N*<sup>1</sup>-substituted norcymserine derivatives as selective butyrylcholinesterase inhibitors****pp 1718–1720**

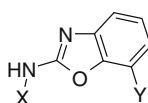
Jun Takahashi, Ichiro Hijikuro, Takeshi Kihara, Modachur G. Muruges, Shinichiro Fuse, Ryo Kunimoto, Yoshinori Tsumura, Akinori Akaike, Tetsuhiro Niidome, Yasushi Okuno, Takashi Takahashi, Hachiro Sugimoto\*

**Design, synthesis and evaluation of carbamate-modified (–)-*N*<sup>1</sup>-phenethylnorphysostigmine derivatives as selective butyrylcholinesterase inhibitors****pp 1721–1723**

Jun Takahashi, Ichiro Hijikuro, Takeshi Kihara, Modachur G. Muruges, Shinichiro Fuse, Yoshinori Tsumura, Akinori Akaike, Tetsuhiro Niidome, Takashi Takahashi, Hachiro Sugimoto\*

**2-Amino-aryl-7-aryl-benzoxazoles as potent, selective and orally available JAK2 inhibitors****pp 1724–1727**

Marc Gerspacher\*, Pascal Furet, Carole Pissot-Soldermann, Christoph Gaul, Philipp Holzer, Eric Vangrevelinghe, Marc Lang, Dirk Erdmann, Thomas Radimerski, Catherine H. Regnier, Patrick Chene, Alain De Pover, Francesco Hofmann, Fabienne Baffert, Thomas Buhl, Reiner Aichholz, Francesca Blasco, Ralf Endres, Jörg Trappe, Peter Drueckes

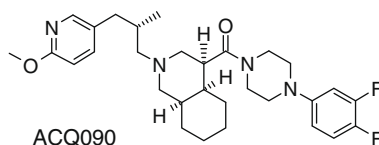


X = aryl  
Y = aryl, heteroaryl

**Decahydroisoquinoline derivatives as novel non-peptidic, potent and subtype-selective somatostatin  $ss_{t3}$  receptor antagonists**

pp 1728–1734

Thomas Troxler\*, Konstanze Hurth, Karl-Heinrich Schuh, Philippe Schoeffter, Daniel Langenegger, Albert Enz, Daniel Hoyer

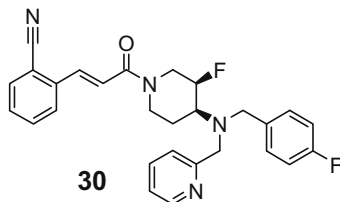


Starting from non-peptidic  $ss_{t1}$ -selective somatostatin receptor antagonists, first compounds with mixed  $ss_{t1}/ss_{t3}$  affinity were identified by directed structural modifications. Systematic optimization of these initial leads afforded novel, enantiomerically pure, highly potent and  $ss_{t3}$ -subtype selective somatostatin antagonists based on a (4*S*,4*aS*,8*aR*)-decahydro-isoquinoline-4-carboxylic acid core moiety. The representative compound ACQ090 can efficiently be synthesized and shows promising PK properties in rodents.

**Exploration of a new series of PAR1 antagonists**

pp 1735–1739

Bruno Planty, Chantal Pujol, Marie Lamothe\*, Catherine Maraval, Clemens Horn, Bruno Le Grand, Michel Perez

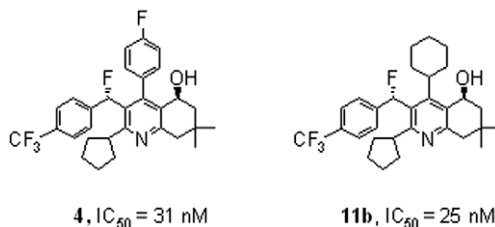


Two series of new PAR1 antagonists have been identified. The first incorporates a cinnamoylpiperidine motif and the second a cinnamoylpyridine pattern. The synthesis, biological activity and structure–activity relationship of these compounds are presented. In each series, one analog showed potent in vivo antithrombotic activity in a rat AV shunt model, with up to 53% inhibition at 1.25 mpk iv for compound **30**.

**Novel tetrahydroquinoline derived CETP inhibitors**

pp 1740–1743

Carsten Schmeck\*, Heike Gielen-Haertwig, Alexandros Vakalopoulos, Hilmar Bischoff, Volkhart Li, Gabriele Wirtz, Olaf Weber

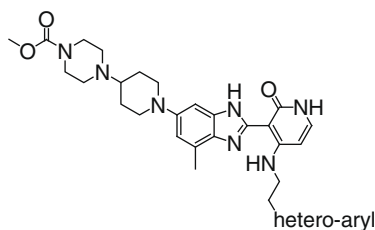


Variations in the 4-position of **4** led to novel CETP inhibitors. The cyclohexyl group was found to be a suitable replacement for the *p*F-phenyl substituent. Compound **11b** was identified as a potent CETP inhibitor with an excellent in vitro and PK-profile.

**SAR of PXR transactivation in benzimidazole-based IGF-1R kinase inhibitors**

pp 1744–1748

Kurt Zimmermann\*, Mark D. Wittman, Mark G. Saulnier, Upender Velaparthi, Xiaopeng Sang, David B. Frennesson, Charles Struzynski, Steven P. Seitz, Liqi He, Joan M. Carboni, Aixin Li, Ann F. Greer, Marco Gottardis, Ricardo M. Attar, Zheng Yang, Praveen Balimane, Lorell N. Discenza, Francis Y. Lee, Michael Sinz, Sean Kim, Dolatrai Vyas



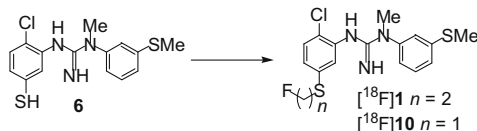
The SAR of PXR transactivation by 3-(benzimidazol-2-yl)-pyridine-2-one based ATP competitive inhibitors of Insulin-like Growth Factor 1 Receptor kinase (IGF-1R) is discussed. Compounds without PXR transactivation, with in vivo antitumor activity, reduced protein binding and improved oral exposure are presented.



### Synthesis and in vitro evaluation of $^{18}\text{F}$ -labelled *S*-fluoroalkyl diarylguanidines: Novel high-affinity NMDA receptor antagonists for imaging with PET

pp 1749–1751

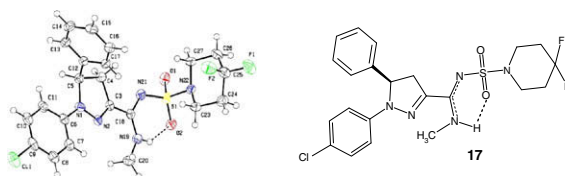
Edward G. Robins, Yongjun Zhao, Imtiaz Khan, Anthony Wilson, Sajinder K. Luthra, Erik Årstad\*



### Synthesis, SAR and intramolecular hydrogen bonding pattern of 1,3,5-trisubstituted 4,5-dihydropyrazoles as potent cannabinoid $\text{CB}_1$ receptor antagonists

pp 1752–1757

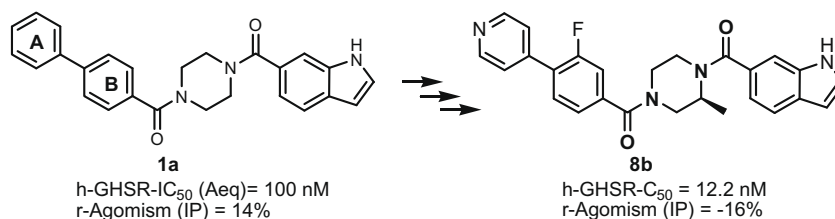
Jos H. M. Lange\*, Martina A. W. van der Neut, Arnold P. den Hartog, Henri C. Wals, Jan Hoogendoorn, Herman H. van Stuivenberg, Bernard J. van Vliet, Chris G. Kruse

Compound **17** was shown to elicit an unexpected intramolecular H-bonding pattern.

### Identification of piperazine-bisamide GHSR antagonists for the treatment of obesity

pp 1758–1762

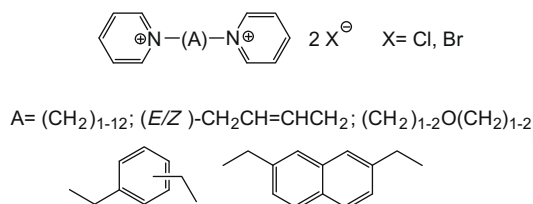
Ming Yu\*, Mike Lizarzaburu, Holger Beckmann, Richard Connors, Kang Dai, Katrin Haller, Cong Li, Lingming Liang, Michelle Lindstrom, Ji Ma, Alykhan Motani, Malgorzata Wanska, Alex Zhang, Leping Li, Julio C. Medina

Optimization of the initial growth hormone secretagogue receptor (GHSR) partial agonist **1a** provided the antagonistic tool compound **8b** that featured with improved potency, complete elimination of the partial agonist activity, and suitable PK profiles.

### Preparation and in vitro screening of symmetrical bispyridinium cholinesterase inhibitors bearing different connecting linkage—initial study for Myasthenia gravis implications

pp 1763–1766

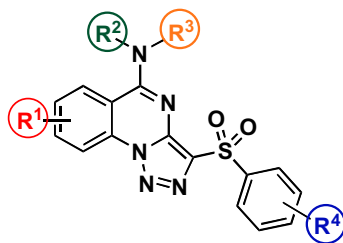
Kamil Musilek\*, Marketa Komloova, Vlasta Zavadova, Ondrej Holas, Martina Hrabanova, Miroslav Pohanka, Vlastimil Dohnal, Florian Nachon, Martin Dolezal, Kamil Kuca, Young-Sik Jung\*



### Development of improved inhibitors of wall teichoic acid biosynthesis with potent activity against *Staphylococcus aureus*

pp 1767–1770

Kyungae Lee, Jennifer Campbell, Jonathan G. Swoboda, Gregory D. Cuny, Suzanne Walker\*



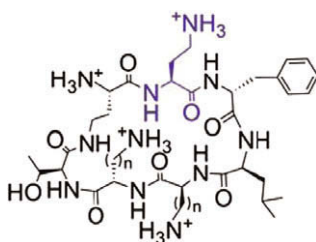
The synthesis and biological evaluation of a focused library of wall teichoic acid biosynthesis inhibitors is reported.



### Structure–activity relationships of bacterial outer-membrane permeabilizers based on polymyxin B heptapeptides

pp 1771–1775

Hirotohi Urakawa, Keiichi Yamada\*, Keiko Komagoe, Setsuko Ando, Hiroyuki Oku, Takashi Katsu, Ichiro Matsuo

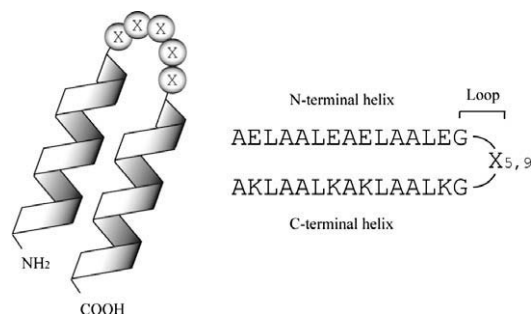
Dab<sup>2</sup> (Dab=L-2,4-Diaminobutyric acid) residue of Polymyxin B heptapeptide plays a critical role in permeation of the outer membrane of *Escherichia coli*.

### Selection of inhibitory peptides for Aurora-A kinase from a phage-displayed library of helix–loop–helix peptides

pp 1776–1778

Daisuke Fujiwara, Zhengmao Ye, Masaki Gouda, Koichi Yokota, Takeshi Tsumuraya, Ikuko Fujii\*

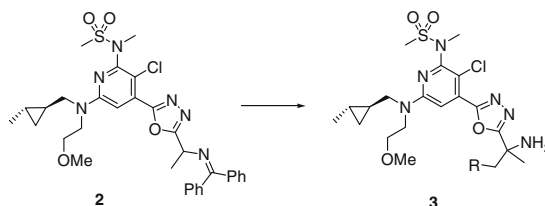
A phage-displayed library of the loop region in the de novo designed helix–loop–helix peptide was constructed and screened against Aurora-A kinase to provide the inhibitory peptides.



### Rapid P1 SAR of brain penetrant tertiary carbinamine derived BACE inhibitors

pp 1779–1782

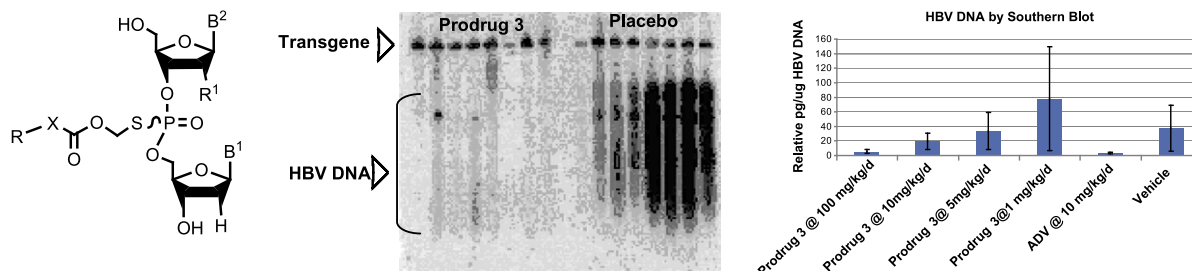
Hong Zhu, Mary B. Young, Philippe G. Nantermet, Samuel L. Graham, Dennis Colussi, Ming-Tain Lai, Beth Pietrak, Eric A. Price, Sethu Sankaranarayanan, Xiao-ping Shi, Katherine Tugusheva, Marie A. Holahan, Maria S. Michener, Jacquelynn J. Cook, Adam Simon, Daria J. Hazuda, Joseph P. Vacca, Hemaka A. Rajapakse\*

This Letter describes the one pot synthesis of tertiary carbinamine **3** and related analogs of brain penetrant BACE-1 inhibitors via the alkylation of the Schiff base intermediate **2**. Extensive SAR studies led to the identification of a potent BACE inhibitor which is twofold more potent in vitro compared to the lead compound. Significant lowering of CSF Aβ40 was observed in a cisterna magna ported rhesus monkey model with the administration of compound **3**.

**Orally bioavailable anti-HBV dinucleotide acyloxyalkyl prodrugs**

pp 1783–1786

John E. Coughlin, Seetharamaiyer Padmanabhan, Guangrong Zhang, Cassandra J. Kirk, Chandrika P. Govardhan, Brent E. Korba, Kathleen O'Loughlin, Carol E. Green, Jon Mirsalis, John D. Morrey, Radhakrishnan P. Iyer\*

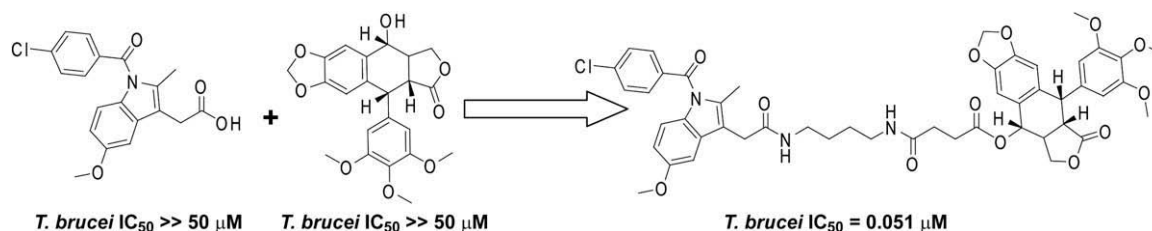


Novel acyloxyalkyl dinucleotide prodrugs have been developed as orally bioavailable anti-HBV agents.

**Podophyllotoxin analogues active versus *Trypanosoma brucei***

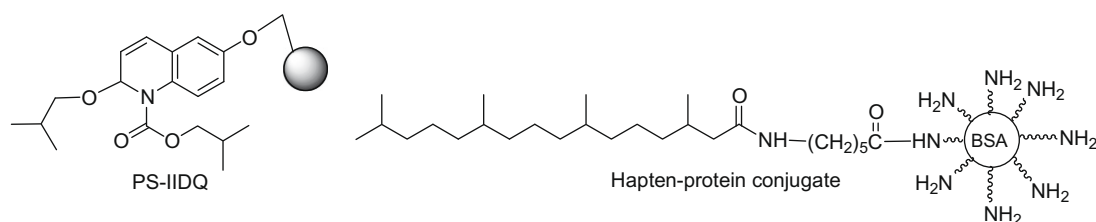
pp 1787–1791

Md. Jashim Uddin, David C. Smithson, Kristin M. Brown, Brenda C. Crews, Michele Connelly, Fangyi Zhu, Lawrence J. Marnett, R. Kiplin Guy\*

**Use of polystyrene-supported 2-isobutoxy-1-isobutoxycarbonyl-1,2-dihydroquinoline for the preparation of a hapten–protein conjugate for antibody development**

pp 1792–1795

Manisha Sathe, Mariliza Derveni, Marjorie Allen, David C. Cullen\*



Polystyrene supported 2-isobutoxy-1-isobutoxycarbonyl-1,2-dihydroquinoline (PS-IIDQ), a polymer-supported covalent coupling reagent, was successfully employed for the first time in the bioconjugation of an example hapten (phytanic acid derivative) to a protein (bovine serum albumin (BSA)) within the context of immunogen preparation for antibody development.

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\*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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