



Bioorganic & Medicinal Chemistry Letters Volume 20, Issue 3, 2010

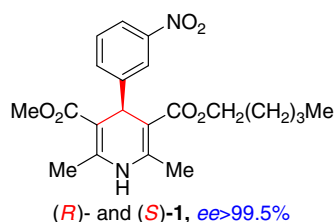
Contents

ARTICLES

Synthesis and biological activity of the calcium modulator (*R*) and (*S*)-3-methyl 5-pentyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate

pp 805–808

Bang-le Zhang*, Wei He, Xin Shi, Meng-lei Huan, Qiu-ju Huang, Si-yuan Zhou*



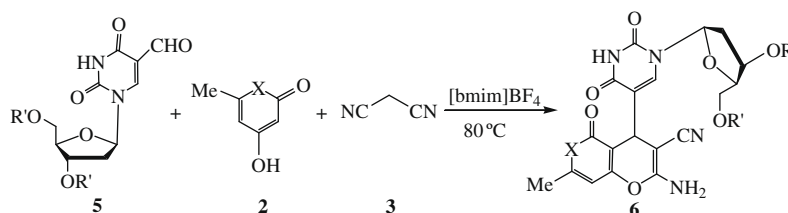
The synthesis of the calcium modulator (*R*) and (*S*)-1 in extremely high optical purities (ee >99.5%) is reported. (*S*)-1 was defined as active isomer which is more potent than (*R*)-1 both in rat cardiac and cerebral cortex membrane.



Practical and efficient synthesis of pyrano[3,2-*c*]pyridone, pyrano[4,3-*b*]pyran and their hybrids with nucleoside as potential antiviral and antileishmanial agents

pp 809–813

Xuesen Fan*, Dong Feng, Yingying Qu, Xinying Zhang, Jianji Wang, Philippe M. Loiseau, Graciela Andrei, Robert Snoeck, Erik De Clercq



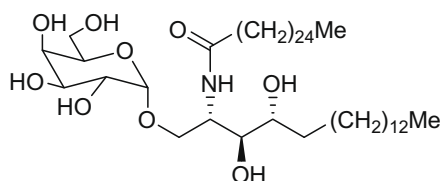
A highly practical and efficient preparation of pyrano[3,2-*c*]pyridone and pyrano[4,3-*b*]pyran derivatives was developed. As an application, a series of pyrimidine nucleoside-pyrano[3,2-*c*]pyridone or pyrano[4,3-*b*]pyran hybrids were obtained. They were evaluated as potential antiviral and antileishmanial agents and showed encouraging biological activities.



Syntheses and biological activities of KRN7000 analogues having aromatic residues in the acyl and backbone chains with varying stereochemistry

pp 814–818

Jeong-Ju Park, Ji Hyung Lee, Kyung-Chang Seo, Gabriel Bricard, Manjunatha M. Venkataswamy, Steven A. Porcelli, Sung-Kee Chung*



α -GalCer (KRN7000)

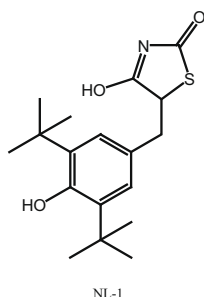
KRN7000 is an important ligand identified for CD1d protein of APC, and KRN7000/CD1d complex can stimulate NKT cells to release a broad range of bioactive cytokines. In an effort to understand the structure–activity relationships, 26 new KRN7000 analogues have been synthesized incorporating aromatic residue in the chains with varying stereochemistry, and their biological activities examined.



Structure-based design of a thiazolidinedione which targets the mitochondrial protein mitoNEET

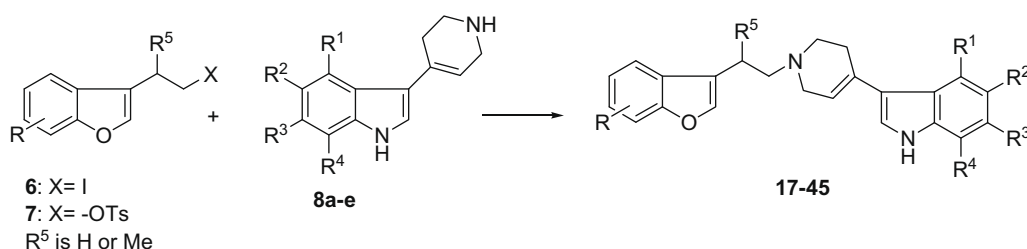
pp 819–823

Werner J. Geldenhuys, Max O. Funk, Kendra F. Barnes, Richard T. Carroll*

**Novel benzofuran derivatives with dual 5-HT_{1A} receptor and serotonin transporter affinity**

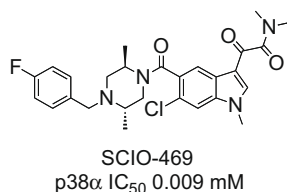
pp 824–827

Aranapakam M. Venkatesan*, O. Dos Santos, John Ellingboe, Deborah A. Evrard, Boyd L. Harrison, Deborah L. Smith, Rosemary Scerni, Geoffrey A. Hornby, Lee E. Schechter, Terrence H. Andree

**Design and synthesis of piperazine-indole p38 α MAP kinase inhibitors with improved pharmacokinetic profiles**

pp 828–831

Xuefei Tan*, Richland W. Tester, Gregory R. Luedtke, Sarvajit Chakravarty, Babu J. Mavunkel, John J. Perumattam, Qing Lu, Imad Nashashibi, Joon Jung, Jie Hu, Albert Licican, Ramona Almirez, Jocelyn Tabora, Vinh Tran, Maureen Laney, Daniel E. Levy*, Sundee Dugar

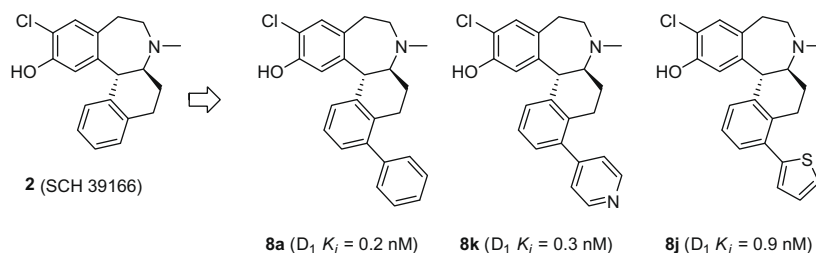


SAR studies of the p38 α MAP kinase inhibitor SCIO-469 focused on maintaining activity while improving pharmacokinetic properties. Advantages were noted for compounds bearing substituents on the benzylic methylene carbon.

Remote functionalization of SCH 39166: Discovery of potent and selective benzazepine dopamine D₁ receptor antagonists

pp 832–835

T. K. Sasikumar*, Duane A. Burnett, William J. Greenlee, Michelle Smith, Ahmad Fawzi, Hongtao Zhang, Jean E. Lachowicz

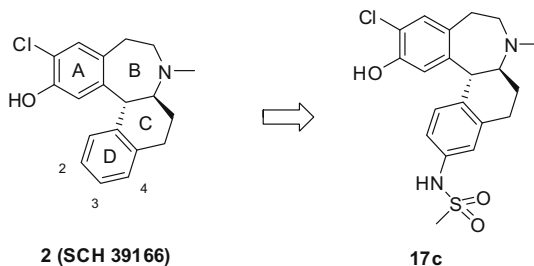


A series of highly potent dopamine D₁ antagonists have been discovered. All compounds showed excellent selectivity over other dopaminergic receptors. Compound **8j** showed a modestly improved PK profile than SCH 39166.

Discovery of new SCH 39166 analogs as potent and selective dopamine D₁ receptor antagonists

pp 836–840

Li Qiang*, T. K. Sasikumar, Duane A. Burnett, Jing Su, Haiqun Tang, Yuanzan Ye, Robert D. Mazzola Jr., Zhaoning Zhu, Brian A. McKittrick, William J. Greenlee, Ahmad Fawzi, Michelle Smith, Hongtao Zhang, Jean E. Lachowicz

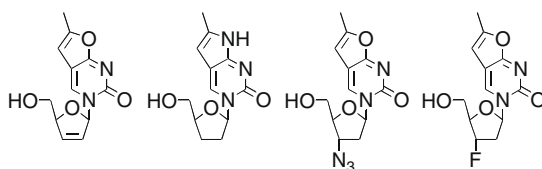


The D-ring functionalization of SCH 39166 is described. Compound **17c** was discovered to have subnanomolar D₁ activity and nearly 10-fold improvement of selectivity over D₂ compared to SCH 39166. It also showed a significant improvement of PK profile.

Synthesis of fluorescent nucleoside analogs as probes for 2'-deoxyribonucleoside kinases

pp 841–843

Yongfeng Li, Priti B. Soni, Lingfeng Liu, Xiao Zhang, Dennis C. Liotta, Stefan Lutz*

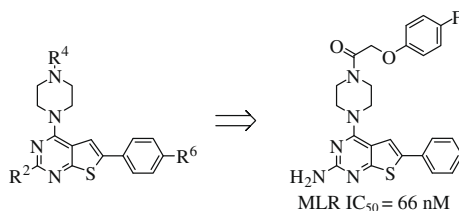


The preparation of fluorescent nucleoside analogs as molecular reporters for 2'-deoxynucleoside kinase activity is reported.

Synthesis, immunosuppressive activity and structure–activity relationship study of a new series of 4-N-piperazinyl-thieno[2,3-*d*]pyrimidine analogues

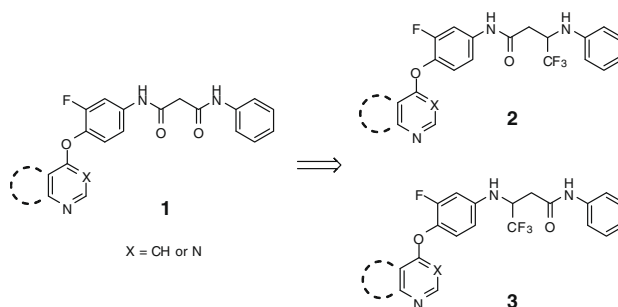
pp 844–847

Mi-Yeon Jang, Steven De Jonghe, Kristien Van Belle, Thierry Louat, Mark Waer, Piet Herdewijn*

**Identification of potent and selective VEGFR receptor tyrosine kinase inhibitors having new amide isostere headgroups**

pp 848–852

Frédéric Gaudette, Stéphane Raeppel*, Hannah Nguyen, Normand Beaulieu, Carole Beaulieu, Isabelle Dupont, A. Robert Macleod, Jeffrey M. Besterman, Arkadii Vaisburg

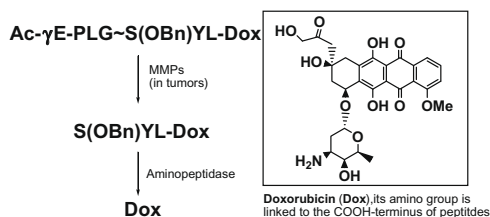


A novel series of analogues of malonamides **1**, previously known as dual c-Met/VEGFR2 inhibitors, in which one of the amide bonds was substituted by an amide isostere such as a trifluoroethylamine unit (regioisomers **2** and **3**) was prepared and evaluated for their enzymatic and cellular inhibition of VEGFR2 and c-Met enzymes. Some of these analogs (regioisomers **3**) were shown to be potent and selective inhibitors of VEGFR2 in the enzymatic assay and displayed significant effect against VEGFR-dependent angiogenic activity in cells.

Discovery of matrix metalloproteases selective and activated peptide–doxorubicin prodrugs as anti-tumor agents

pp 853–856

Zilun Hu*, Xiangjun Jiang, Charles F. Albright, Nilsa Graciani, Eddy Yue, Mingzhu Zhang, Shu-Yun Zhang, Robert Bruckner, Melody Diamond, Randine Dowling, Maria Rafalski, Swamy Yeleswaram, George L. Trainor, Steven P. Seitz, Wei Han

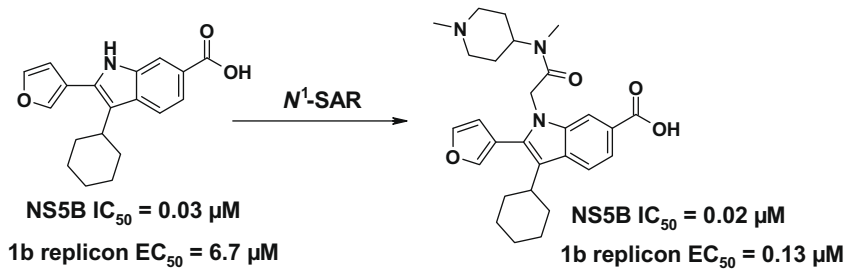


A series of MMP activated and selective peptide-doxorubicin prodrugs were discovered as efficacious antitumor agents.

N-Acetamideindolecarboxylic acid allosteric ‘finger-loop’ inhibitors of the hepatitis C virus NS5B polymerase: discovery and initial optimization studies

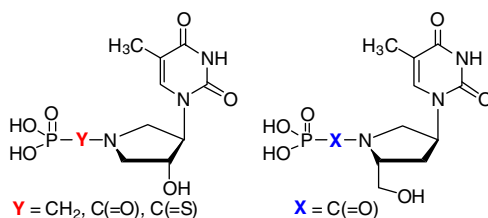
pp 857–861

Pierre L. Beaulieu*, Eric Jolicoeur, James Gillard, Christian Brochu, René Coulombe, Nathalie Dansereau, Jianmin Duan, Michel Garneau, Araz Jakalian, Peter Kühn, Lisette Lagacé, Steven LaPlante, Ginette McKercher, Stéphane Perrault, Martin Poirier, Marc-André Poupart, Timothy Stammers, Louise Thauvette, Bounkham Thavonekham, George Kukolj

**Structural diversity of nucleoside phosphonic acids as a key factor in the discovery of potent inhibitors of rat T-cell lymphoma thymidine phosphorylase**

pp 862–865

Petr Kočalka, Dominik Rejman*, Václav Vaněk, Markéta Rinnová, Ivana Tomečková, Šárka Králíková, Magdalena Petrová, Ondřej Páv, Radek Pohl, Miloš Buděšínský, Radek Liboska, Zdeněk Točík, Natalya Panova, Ivan Votruba*, Ivan Rosenberg*

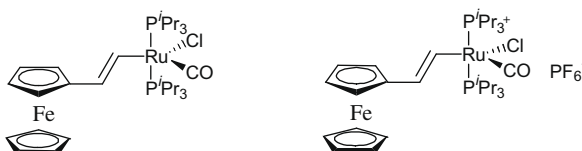


Potent inhibitors of the rat T-cell lymphoma thymidine phosphorylase with IC₅₀ values within 11–45 nM.

**Comparative biological evaluation of two ethylene linked mixed binuclear ferrocene/ruthenium organometallic species**

pp 866–869

Ingo Ott*, Konrad Kowalski*, Ronald Gust, Jörg Maurer, Philipp Mücke, Rainer F. Winter



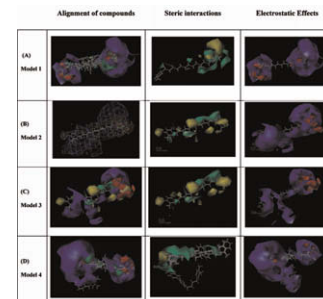
Mixed ferrocene/ruthenium bioorganometallics.

Predictive screening model for potential vector-mediated transport of cationic substrates at the blood–brain barrier choline transporter

pp 870–877

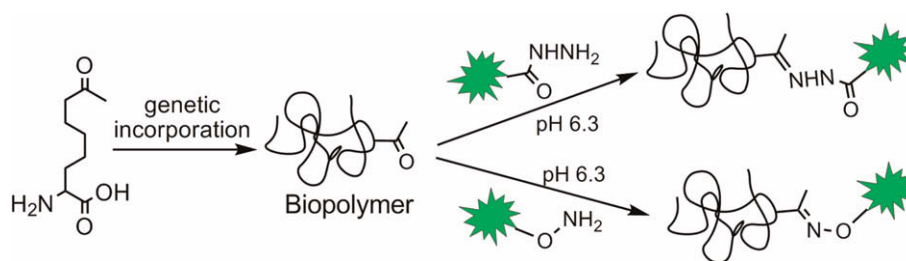
Werner J. Geldenhuys, Vamshi K. Manda, Rajendar K. Mittapalli, Cornelis J. Van der Schyf, Peter A. Crooks, Linda P. Dwoskin, David D. Allen, Paul R. Lockman*

A set of semi-rigid cyclic and acyclic bis-quaternary ammonium analogs, which were part of a drug discovery program aimed at identifying antagonists at neuronal nicotinic acetylcholine receptors, were investigated to determine structural requirements for affinity at the blood–brain barrier choline transporter (BBB CHT). This transporter may have utility as a drug delivery vector for cationic molecules to access the central nervous system. In the current study, a virtual screening model was developed to aid in rational drug design/ADME of cationic nicotinic antagonists as BBB CHT ligands. Four 3D-QSAR comparative molecular field analysis (CoMFA) models were built which could predict the BBB CHT affinity for a test set with an $r^2 < 0.5$ and cross-validated q^2 of 0.60, suggesting good predictive capability for these models. These models will allow the rapid in silico screening of binding affinity at the BBB CHT of both known nicotinic receptor antagonists and virtual compound libraries with the goal of informing the design of brain bioavailable quaternary ammonium analogs that are high affinity selective nicotinic receptor antagonists.

**Genetic incorporation of an aliphatic keto-containing amino acid into proteins for their site-specific modifications**

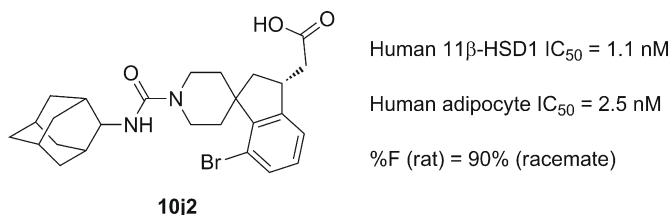
pp 878–880

Ying Huang, Wei Wan, William K. Russell, Pei-Jing Pai, Zhiyong Wang, David H. Russell, Wenshe Liu*

**Spirocyclic ureas: Orally bioavailable 11 β -HSD1 inhibitors identified by computer-aided drug design**

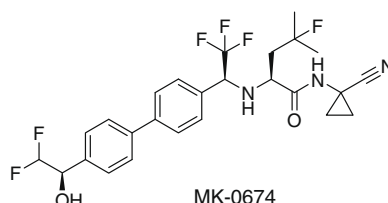
pp 881–886

Colin M. Tice*, Wei Zhao, Zhenrong Xu, Salvacion T. Cacatian, Robert D. Simpson, Yuan-Jie Ye, Suresh B. Singh, Brian M. McKeever, Peter Lindblom, Joan Guo, Paula M. Krosky, Barbara A. Kruk, Jennifer Berbaum, Richard K. Harrison, Judith J. Johnson, Yuri Bukhtiyarov, Reshma Panemangalore, Boyd B. Scott, Yi Zhao, Joseph G. Bruno, Linghang Zhuang, Gerard M. McGeehan, Wei He, David A. Claremon

**The discovery of MK-0674, an orally bioavailable cathepsin K inhibitor**

pp 887–892

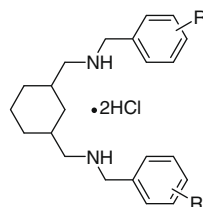
Elise Isabel*, Kevin P. Bateman, Nathalie Chauret, Wanda Cromlish, Sylvie Desmarais, Le T. Duong, Jean-Pierre Falgout, Jacques Yves Gauthier, Sonia Lamontagne, Cheuk K. Lau, Serge Léger, Tammy LeRiche, Jean-François Lévesque, Chun Sing Li, Frédéric Massé, Daniel J. McKay, Christophe Mellon, Deborah A. Nicoll-Griffith, Renata M. Oballa, M. David Percival, Denis Riendeau, Joël Robichaud, Gideon A. Rodan, Sevgi B. Rodan, Carmai Seto, Michel Thérien, Vouy Linh Truong, Gregg Wesolowski, Robert N. Young, Robert Zamboni, W. Cameron Black



Synthesis and antibacterial activity of benzyl-[3-(benzylamino-methyl)-cyclohexylmethyl]-amine derivatives

pp 893–895

Deepak Kumar, Seema Joshi, Rajesh K. Rohilla, Nilanjan Roy, Diwan S. Rawat*



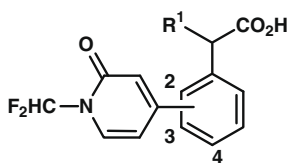
	MIC (μg/mL)				
R-4	<i>E. coli</i>	<i>P. aeruginosa</i>	<i>S. aureus</i>	<i>S. epidermidis</i>	
Et	NA	0.125	NA	0.25	
<i>n</i> -Pr	0.016	0.016	NA	0.016	
<i>n</i> -Bu	0.016	0.002	0.004	0.004	
<i>t</i> -Bu	0.002	0.004	0.016	0.008	

21 Examples

Phenylacetic acid regioisomers possessing a *N*-difluoromethyl-1,2-dihydropyrid-2-one pharmacophore: Evaluation as dual inhibitors of cyclooxygenases and 5-lipoxygenase with anti-inflammatory activity

pp 896–902

Gang Yu, Morshed A. Chowdhury, Khaled R. A. Abdellatif, Ying Dong, P. N. Praveen Rao, Dipankar Das, Carlos A. Velázquez, Mavanur R. Suresh, Edward E. Knaus*

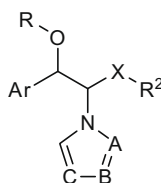


2-, 3- and 4-regioisomers
R¹ = H, Me

Discovery and SAR of small molecule PAR1 antagonists

pp 903–906

Ian Rilatt*, Etienne Mirabel, Bruno Le Grand, Michel Perez

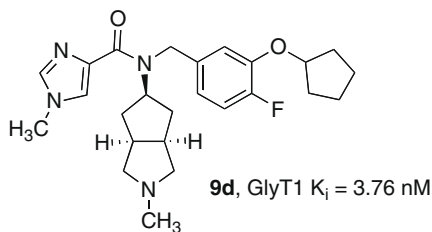


The development of novel small molecule inhibitors of PAR1 is described.

An octahydro-cyclopenta[c]pyrrole series of inhibitors of the type 1 glycine transporter

pp 907–911

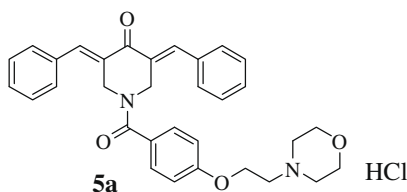
John A. Lowe III*, Shari L. DeNinno, Susan E. Drozda, Christopher J. Schmidt, Karen M. Ward, F. David Tingley III, Mark Sanner, Don Tunucci, James Valentine

The discovery of a potent, selective inhibitor of the type 1 glycine transporter, **9d**, is reported.

3,5-Bis(benzylidene)-1-[4-2-(morpholin-4-yl)ethoxyphenylcarbonyl]-4-piperidone hydrochloride: A lead tumor-specific cytotoxin which induces apoptosis and autophagy

pp 912–917

Umashankar Das, Hiroshi Sakagami, Qing Chu, Qintao Wang, Masami Kawase, Ponniah Selvakumar, Rajendra K. Sharma, Jonathan R. Dimmock*

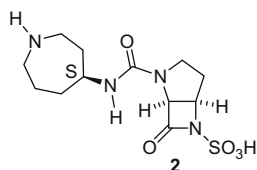


Various 3,5-bis(benzylidene)-1-[4-(2-aminoethoxy)phenylcarbonyl]-4-piperidone hydrochlorides demonstrate significant cytotoxic potencies with greater toxicity to tumors than normal cells. The lead molecule **5a** causes apoptosis and autophagy in different malignant cell lines.

Side chain SAR of bicyclic β -lactamase inhibitors (BLIs). 1. Discovery of a class C BLI for combination with imipenem

pp 918–921

Timothy A. Blizzard*, Helen Chen, Seongkon Kim, Jane Wu, Katherine Young, Young-Whan Park, Amy Ogawa, Susan Raghoobar, Ronald E. Painter, Nichelle Hairston, Sang Ho Lee, Andrew Misura, Tom Felcetto, Paula Fitzgerald, Nandini Sharma, Jun Lu, Sookhee Ha, Emily Hickey, Jeff Hermes, Milton L. Hammond

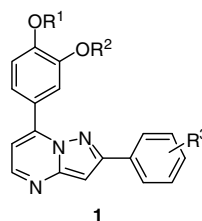
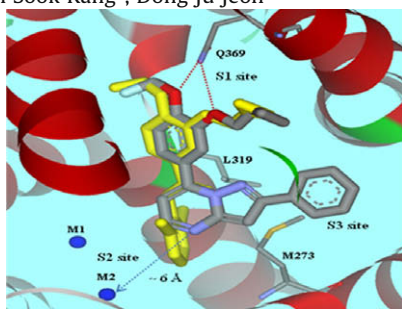


Bridged monobactam β -lactamase inhibitors were prepared and evaluated as potential partners for combination with imipenem to overcome class C β -lactamase mediated resistance. The (S)-azepine analog **2** was found to be effective in both in vitro and in vivo assays and was selected for preclinical development.

Design, synthesis, and evaluation of 2-aryl-7-(3',4'-dialkoxyphenyl)-pyrazolo[1,5-a]pyrimidines as novel PDE-4 inhibitors

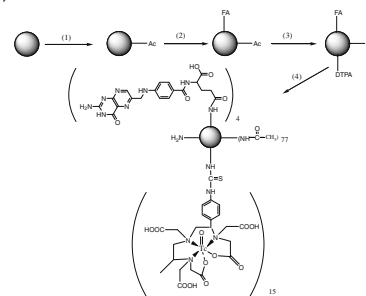
pp 922–926

Ikyon Kim, Jong Hwan Song, Chang Min Park, Joon Won Jeong, Hyung Rae Kim, Jin Ryul Ha, Zaesung No, Young-Lan Hyun, Young Sik Cho, Nam Sook Kang*, Dong Ju Jeon*

**Radiosynthesis and micro-SPECT imaging of ^{99m}Tc -dendrimer poly(amido)-amine folic acid conjugate**

pp 927–931

Yuanqing Zhang, Yanhong Sun, Xiaoping Xu, Hua Zhu, Liliang Huang, Xuezhu Zhang, Yujin Qi, Yu-Mei Shen*



^{99m}Tc radiolabeled acetylated (Ac) dendrimer poly(amido)amine (PAMAM) generation five (G5)-folic acid (FA)-2-(p-isothiocyanatobenzyl)-6-methyl-diethylenetriaminepentaacetic acid (1B4M DTPA) to form the conjugate of ^{99m}Tc -Ac-G5-FA-1B4M DTPA with quantitative radiochemical yield. Furthermore the radioactive conjugate is excellent in vitro/in vivo stability, rapid blood clearance and certain tumor accumulation which was further confirmed by micro-SPECT imaging study.



pp 932–934

Chemical structure of the metal-organic complex (1) and the R group. The complex consists of a central metal ion (M) coordinated by two bidentate ligands (N, N') and two monodentate ligands (O, O'). The R group is defined as a 4-((2-hydroxy-1-hydroxymethyl-2-oxoethyl)amino)phenyl group.

pp 935–938

R = —H; —OCH₃
n = 1, 2, 3, 4



pp 939–941

Etangien

pp 942–944

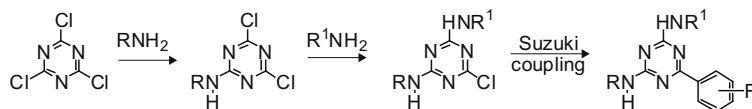
8



Synthesis and antimicrobial activity of 2-fluorophenyl-4,6-disubstituted [1,3,5]triazines

pp 945–949

Mona Saleh, Shaun Abbott, Valérie Perron, Caroline Lauzon, Christopher Penney, Boulos Zacharie*

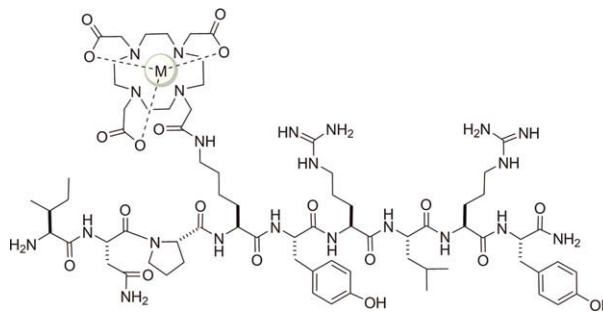


A number of low molecular weight fluorophenyl triazine molecules that show antimicrobial activity.

[Lys(DOTA)⁴]BVD15, a novel and potent neuropeptide Y analog designed for Y₁ receptor-targeted breast tumor imaging

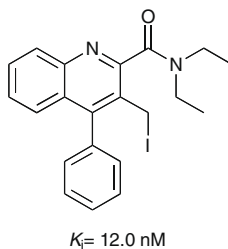
pp 950–953

Brigitte Guérin*, Véronique Dumulon-Perreault, Marie-Claude Tremblay, Samia Ait-Mohand, Patrick Fournier, Célène Dubuc, Simon Authier, François Bénard

[Lys(DOTA)⁴]BVD15, a potent NPY Y₁ analog suitable for radiolabeling with metallo positron emitters for PET imaging of breast cancer.**New iodinated quinoline-2-carboxamides for SPECT imaging of the translocator protein**

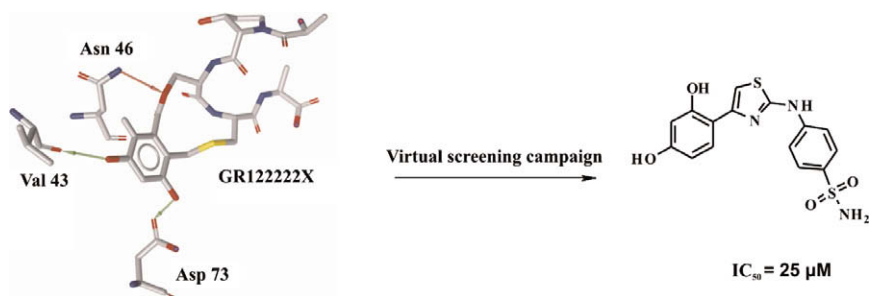
pp 954–957

Louise Stevenson, Adriana A. S. Tavares, Aurélie Brunet, Fiona I. McGonagle, Deborah Dewar, Sally L. Pimlott, Andrew Sutherland*

A new library of iodinated quinoline-2-carboxamides has been prepared and tested for affinity with the translocator protein (TSPO). *N,N*-Diethyl-3-iodomethyl-4-phenylquinoline-2-carboxamide was found to have excellent affinity with a *K_i* value of 12.0 nM.**In silico discovery of 2-amino-4-(2,4-dihydroxyphenyl)thiazoles as novel inhibitors of DNA gyrase B**

pp 958–962

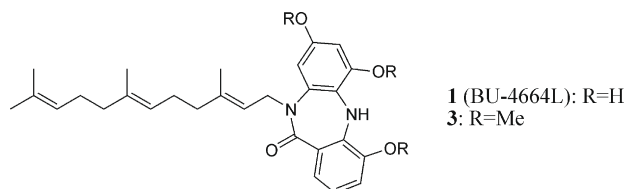
Matjaž Brvar, Andrej Perdih, Marko Oblak, Lucija Peterlin Mašič, Tom Solmajer*



Anti-invasive and anti-angiogenic activities of naturally occurring dibenzodiazepine BU-4664L and its derivatives

pp 963–965

Satoshi Miyana, Hiroaki Sakurai, Ikuo Saiki, Hiroyasu Onaka, Yasuhiro Igarashi*

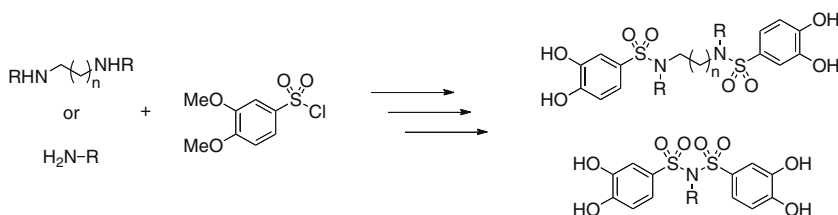


BU-4664L (**1**) was found to inhibit tumor cell invasion and angiogenesis by interrupting cellular motility. Compound **3** displayed the highest in vitro anti-angiogenic effect ($IC_{50} = 0.22 \mu M$).

Novel bis-arylsulfonamides and aryl sulfonimides as inactivators of plasminogen activator inhibitor-1 (PAI-1)

pp 966–970

Nadine C. El-Ayache, Shih-Hon Li, Mark Warnock, Daniel A. Lawrence, Cory D. Emal*

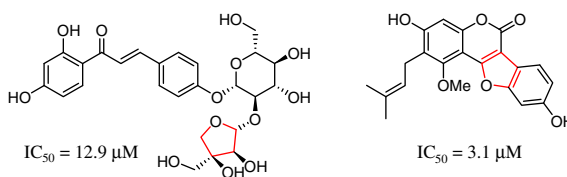


The synthesis and evaluation of potent and novel bis-arylsulfonamide and arylsulfonimide-based inhibitors of plasminogen activator inhibitor-1 (PAI-1) is described.

**Inhibition of neuraminidase activity by polyphenol compounds isolated from the roots of *Glycyrrhiza uralensis***

pp 971–974

Young Bae Ryu, Jang Hoon Kim, Su-Jin Park, Jong Sun Chang, Mun-Chual Rho, Ki-Hwan Bae, Ki Hun Park*, Woo Song Lee*

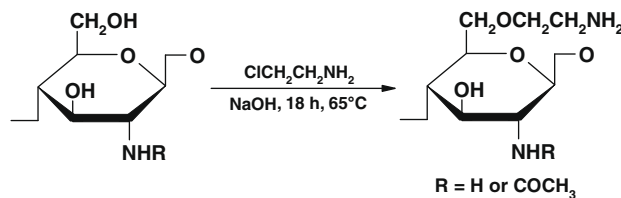


The efficacy of the neuraminidase inhibition appears to be relatively to present of five-membered ring in polyphenols.

**Synergistic effects between aminoethyl-chitosans and β -lactams against methicillin-resistant *Staphylococcus aureus* (MRSA)**

pp 975–978

Dae-Sung Lee, Young-Mog Kim, Myung-Suk Lee, Chang-Bum Ahn, Won-Kyo Jung*, Jae-Young Je*

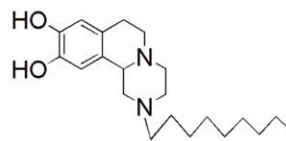
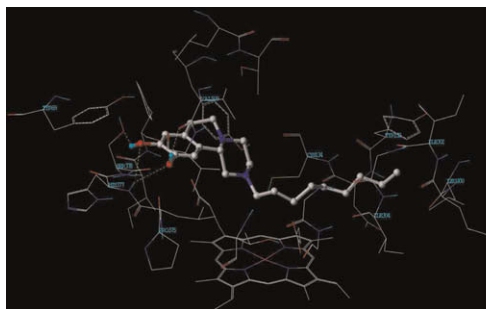


Two kinds of aminoethyl-chitosans (AEC), AEC90 and AEC50, having degrees of deacetylation of 90% and 50%, exhibited strong synergistic effects in combination with β -lactams against MRSA.

Synthesis and antifungal activities in vitro of novel pyrazino [2,1-a] isoquinolin derivatives

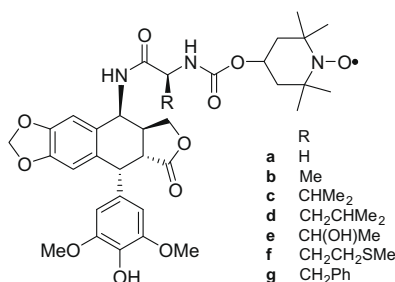
pp 979–982

Hui Tang, Canhui Zheng, Jiaguo Lv, Juan Wu, Yanan Li, Hui Yang, Bingyue Fu, Chuntong Li, Youjun Zhou*, Ju Zhu*

The mode of action of compound **13a** with the active site of CYP51 of *Candida albicans* is reported.**Novel semisynthetic spin-labeled derivatives of podophyllotoxin with cytotoxic and antioxidative activity**

pp 983–986

Jia-Qiang Zhang, Zhi-Wei Zhang, Ling Hui, Shi-Wu Chen*, Xuan Tian*

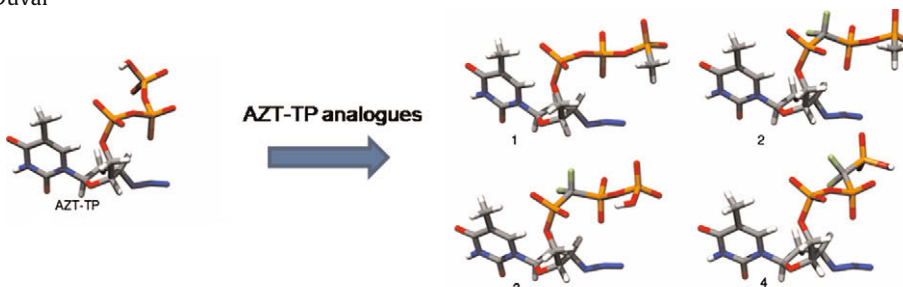


The synthesized compounds showed superior or comparable cytotoxicities and pronounced antioxidative activity compared to VP-16.

**Design, synthesis and studies of triphosphate analogues for the production of anti AZT-TP antibodies**

pp 987–990

Camille Roucairol, Stéphane Azoulay*, Marie-Claire Nevers, Jérôme Golebiowski, Christophe Créminon, Jacques Grassi, Alain Burger*, Danièle Duval

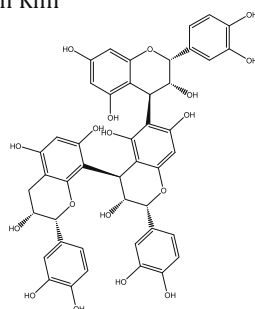


This Letter describes the design of stable triphosphate analogues of AZT using molecular modelling, their synthesis and their use for producing anti AZT-TP antibodies for developing an immunoassay for TDM.

**Identification of potential and selective collagenase, gelatinase inhibitors from *Crataegus pinnatifida***

pp 991–993

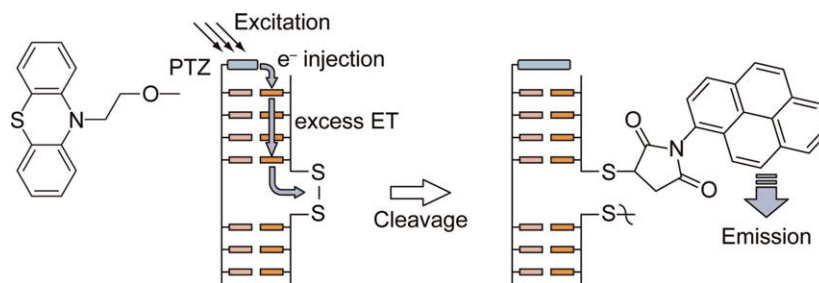
Hyung-In Moon, Tae-im Kim, Hyun-Soo Cho, Eung Kweon Kim*

Compound **3** showed collagenase, gelatinases A and B inhibitory activity (IC₅₀) at 0.34, 0.4 and 2.3 μM, respectively. The presence of an epicatechin-(4β→6) moiety may play an important role in collagenase and gelatinase inhibitory activities.

Fluorescent analysis of excess electron transfer through DNA

pp 994–996

Tadao Takada*, Chie Tanaka, Mitsunobu Nakamura, Kazushige Yamana*

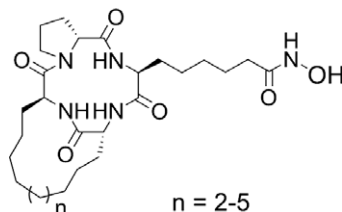


A new method for fluorescence analysis of excess electron transfer through DNA based on reductive cleavage of a disulfide bond and a thiol-specific fluorescent probe is described.

Bicyclic peptides as potent inhibitors of histone deacetylases: Optimization of alkyl loop length

pp 997–999

Nurul M. Islam, Tamaki Kato, Norikazu Nishino*, Hyun-Jung Kim, Akihiro Ito, Minoru Yoshida

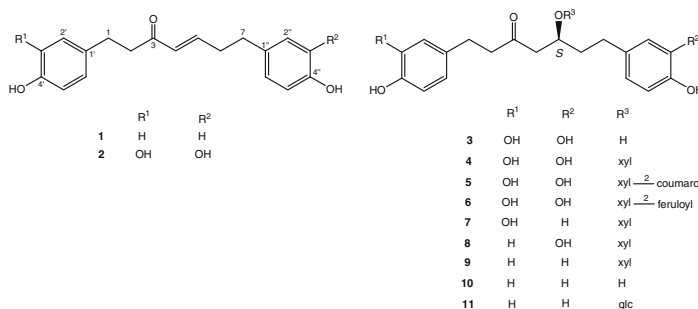


A series of bicyclic tetrapeptide hydroxamic acids were designed and synthesized as histone deacetylase (HDAC) inhibitors. Most of them were found to be potent inhibitors with remarkable selectivity among the HDACs. The *in vivo* activity depends on alkyl loop length.

Anti-influenza diarylheptanoids from the bark of *Alnus japonica*

pp 1000–1003

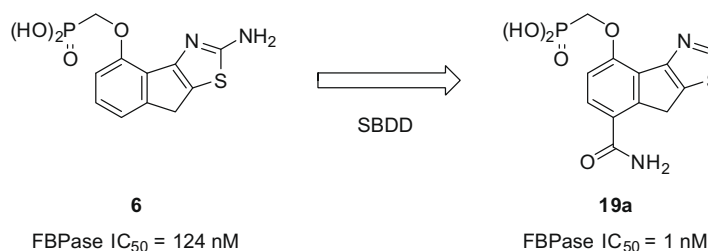
Nguyen Huu Tung, Hyuk-Joon Kwon, Jae-Hong Kim, Jeong Chan Ra, Yan Ding, Jeong Ah Kim, Young Ho Kim*



Structure-based drug design of tricyclic 8*H*-indeno[1,2-*d*][1,3]thiazoles as potent FBPase inhibitors

pp 1004–1007

Tomoharu Tsukada, Mizuki Takahashi, Toshiyasu Takemoto, Osamu Kanno, Takahiro Yamane, Sayako Kawamura, Takahide Nishi*

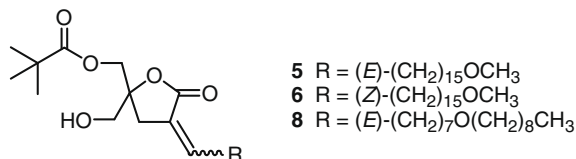


Our structure-based drug design efforts led to the finding of **19a** as potent FBPase inhibitor (FBPase IC₅₀ = 1 nM).

Polar 3-alkylidene-5-pivaloyloxymethyl-5'-hydroxymethyl- γ -lactones as protein kinase C ligands and antitumor agents

pp 1008–1012

Ji-Hye Kang, Yerim Kim, Shin-Hye Won, Song-Kyu Park, Chang Woo Lee, Hwan-Mook Kim, Nancy E. Lewin, Nicholas A. Perry, Larry V. Pearce, Daniel J. Lundberg, Robert J. Surawski, Peter M. Blumberg, Jeewoo Lee*

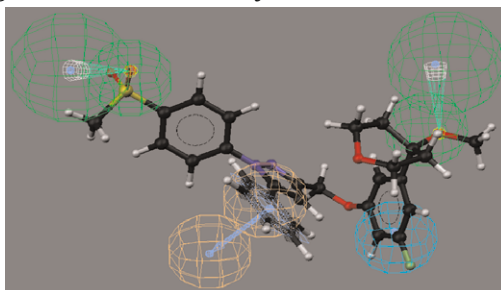


DAG-lactones **5**, **6** and **8** with an ether type of side chain showed high binding affinities in range of K_i = 3–5 nM and excellent antitumor profiles.

Pharmacophore modeling and virtual screening for designing potential 5-Lipoxygenase inhibitors

pp 1013–1018

P. Aparoy, K. Kumar Reddy, Suresh K. Kalangi, T. Chandramohan Reddy, P. Reddanna*

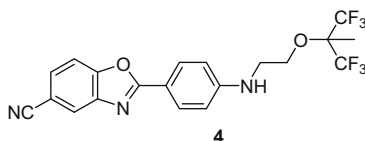


In this Letter, we identified pharmacophore model of the 5-LOX inhibitors. Then the best quantitative pharmacophore model generated was used as a 3D query to screen several commercial databases.

**2-Arylbenzoxazoles as CETP inhibitors: Substitution and modification of the α -alkoxyamide moiety**

pp 1019–1022

Julianne A. Hunt*, Silvia Gonzalez, Florida Kallashi, Milton L. Hammond, James V. Pivnichny, Xinchun Tong, Suoyu S. Xu, Matt S. Anderson, Ying Chen, Suzanne S. Eveland, Qiu Guo, Sheryl A. Hyland, Denise P. Milot, Carl P. Sparrow, Samuel D. Wright, Peter J. Sinclair

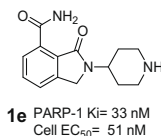


Compound **4** was found to be a potent (IC_{50} = 151 nM) and orally bioavailable inhibitor of CETP.

Discovery and SAR of substituted 3-oxoisindoline-4-carboxamides as potent inhibitors of poly(ADP-ribose) polymerase (PARP) for the treatment of cancer

pp 1023–1026

Viraj B. Gandhi*, Yan Luo, Xuesong Liu, Yan Shi, Vered Klinghofer, Eric F. Johnson, Chang Park, Vincent L. Giranda, Thomas D. Penning, Gui-Dong Zhu

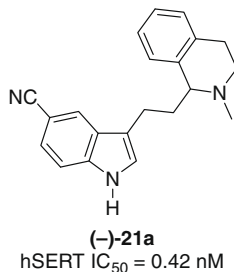


We have discovered a series of compounds with a 3-oxoisindoline-4-carboxamide core structure as potent PARP inhibitors. The highlight of the core is a conformational restriction of a benzamide by formation of a seven-membered hydrogen-bond with an oxindole carbonyl group, with compound **1e** identified as the most potent in vitro PARP-1 inhibitor.

Synthesis and hSERT activity of homotryptamine analogs. Part 6: [3+2] dipolar cycloaddition of 3-vinylindoles

pp 1027–1030

Lawrence R. Marcin*, Ronald J. Mattson, Qi Gao, Dedong Wu, Thaddeus F. Molski, Gail K. Mattson, Nicholas J. Lodge

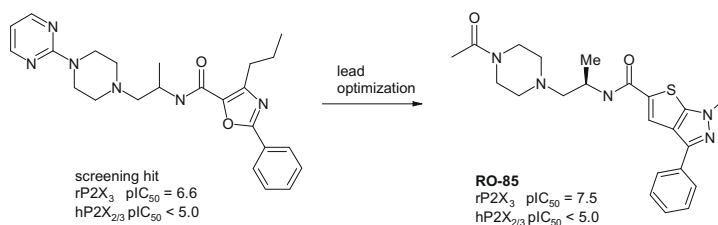


A series of ring constrained homotryptamine analogs was prepared in 5 steps from 1-tosyl-3-vinylindoles via [3+2] dipolar cycloaddition with cyclic nitrones. The final products, including **(-)-21a**, demonstrated potent and selective binding affinity for the human serotonin transporter (hSERT).

Discovery and optimization of RO-85, a novel drug-like, potent, and selective P2X₃ receptor antagonist

pp 1031–1036

Christine E. Brotherton-Pleiss*, Michael P. Dillon, Anthony P. D. W. Ford, Joel R. Gever, David S. Carter, Shelley K. Gleason, Clara J. Lin, Amy G. Moore, Anthony W. Thompson, Marzia Villa, Yansheng Zhai

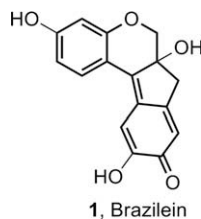


The discovery and optimization of RO-85, a novel drug-like, potent and selective P2X₃ antagonist is described.

Antitumor agents. 271: Total synthesis and evaluation of brazilein and analogs as anti-inflammatory and cytotoxic agents

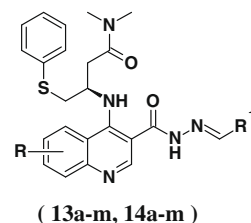
pp 1037–1039

Chiao-Ting Yen, Kyoko Nakagawa-Goto, Tsong-Long Hwang, Pei-Chi Wu, Susan L. Morris-Natschke, Wan-Chun Lai, Kenneth F. Bastow, Fang-Rong Chang, Yang-Chang Wu*, Kuo-Hsiung Lee*

**Design and synthesis of some new quinoline-3-carbohydrazone derivatives as potential antimycobacterial agents**

pp 1040–1044

Sumesh Eswaran, Airody Vasudeva Adhikari*, Nishith K. Pal, Imran H. Chowdhury

**R** = 8-CF₃, 6-F**R¹** = Aromatic/aliphatic group

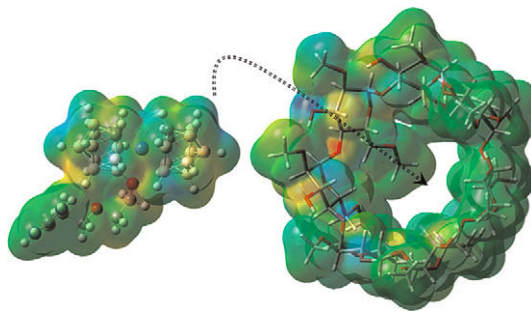
Synthesis of a new series of quinoline-3-carbohydrazones is presented together with the pharmacological profiles. Compounds **13e**, **13i**, **13k**, **14a**, **14c**, and **14i** emerged as the lead molecules with MIC ranging 0.625–5 µg/mL and did not show toxicity on Vero cells up to 62.5 µg/mL which are in comparable with the present first line anti tuberculosis drugs.



Solubilization and deaggregation of cobalt bis(dicarbollide) derivatives in water by biocompatible excipients

pp 1045–1048

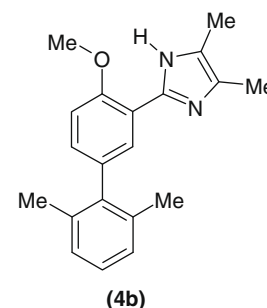
Jakub Rak, Robert Kaplánek*, Vladimír Král*

Scheme of cobalt bis(dicarbollide) derivative **2** and DIMEB.**Discovery of biaryl inhibitors of H⁺/K⁺ ATPase**

pp 1049–1054

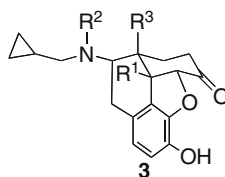
Neil Garton*, Nick Bailey, Mark Bamford, Emmanuel Demont, Irene Farre-Gutierrez, Gail Hutley, Gianpaolo Bravi, Paula Pickering

We report the identification of a novel biaryl template for H⁺/K⁺ ATPase inhibition. Evaluation of critical SAR features within the biaryl imidazole framework and the use of pharmacophore modelling against known imidazopyridine and azaindole templates suggested that the geometry of the molecule is key to achieving activity. Herein we present our work optimising the potency of the molecule through modifications and substitutions to each of the ring systems. In particular sub-micromolar potency is achieved with (**4b**) presumably through a proposed intramolecular hydrogen bond that ensures the required imidazole basic centre is appropriately located.

**Investigation of Beckett–Casy model 1: Synthesis of novel 16,17-*seco*-naltrexone derivatives and their pharmacology**

pp 1055–1058

Satomi Imaide, Hideaki Fujii, Akio Watanabe, Toru Nemoto, Mayumi Nakajima, Kaoru Nakao, Hidenori Mochizuki, Hiroshi Nagase*

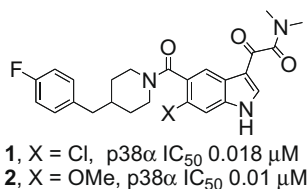


Novel 16,17-*seco*-naltrexone derivatives **3** were synthesized using 16–17 bond cleavage reaction of naltrexone as the key reaction to examine the Beckett–Casy model.

Piperidine-based heterocyclic oxalyl amides as potent p38 α MAP kinase inhibitors

pp 1059–1062

Babu J. Mavunkel, John J. Perumattam, Xuefei Tan*, Gregory R. Luedtke, Qing Lu, Don Lim, Darin Kizer, Sundeep Dugar, Sarvajit Chakravarty, Yong-jin Xu, Joon Jung, Albert Licican, Daniel E. Levy*, Jocelyn Tabora

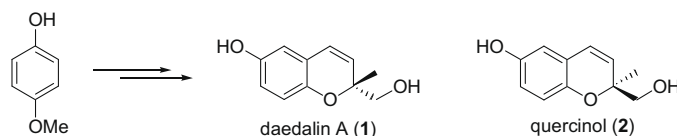


A new class of p38 α MAP kinase inhibitors based on 4-fluorobenzylpiperidine substituted heterocycles is described. Optimal features include a piperidine and an oxalyl amide separated by a [6,5] fused ring heterocycle.

Asymmetric syntheses of daedalin A and quercinol and their tyrosinase inhibitory activity

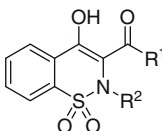
pp 1063–1064

Mitsuo Sekimoto, Yasunao Hattori, Keiji Morimura, Mitsuru Hirota, Hidefumi Makabe*

**Discovery of cyclicsulfonamide derivatives as 11 β -hydroxysteroid dehydrogenase 1 inhibitors**

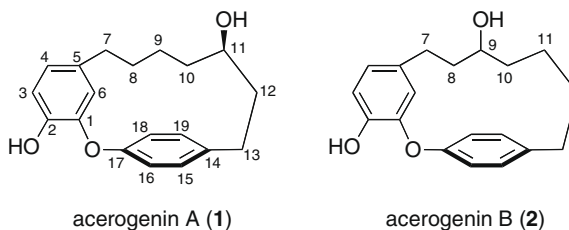
pp 1065–1069

Se Hoan Kim, Ravirala Ramu, Sung Wook Kwon, Su-Hee Lee, Chi Hyun Kim, Seung Kyu Kang, Sang Dal Rhee, Myung Ae Bae, Sung Hoon Ahn, Duck Chan Ha, Hye Gyeong Cheon, Ki Young Kim*, Jin Hee Ahn*

**Cyclic diarylheptanoids as Na⁺-glucose cotransporter (SGLT) inhibitors from *Acer nikoense***

pp 1070–1074

Hiroshi Morita*, Jun Deguchi, Yusuke Motegi, Seizo Sato, Chihiro Aoyama, Jiro Takeo, Motoo Shiro, Yusuke Hirasawa

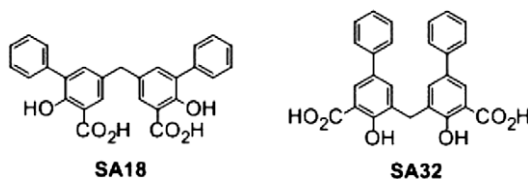


Two cyclic diarylheptanoids, acerogenins A (1) and B (2) have been isolated from the bark of *Acer nikoense* as inhibitors of Na⁺-glucose cotransporter (SGLT). Acetogenins A (1) and B (2) inhibited both isoforms, SGLT1 and SGLT2. Structure–activity relationship of acetogenin derivatives on inhibitory activity of SGLT as well as conformational analysis of 1 and 2 on the basis of *J*-resolved HMBC spectra and X-ray analysis were discussed.

Inhibition of IKK- β : A new development in the mechanism of the anti-obesity effects of PTP1B inhibitors SA18 and SA32

pp 1075–1077

Bharat Raj Bhattarai, Jeong-Hyeon Ko, Suja Shrestha, Bhooshan Kafle, Heeyeong Cho, Ju-Hee Kang*, Hyeongjin Cho*

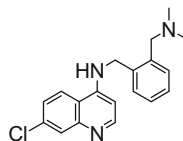


SA18 and SA32 inhibited IKK- β both in vitro and in vivo suggesting a novel mechanism of the anti-obesity effect by these compounds.

Synthesis and evaluation of phenylequine for antimalarial activity in vitro and in vivo

pp 1078–1080

Margaret A. L. Blackie, Vanessa Yardley, Kelly Chibale*

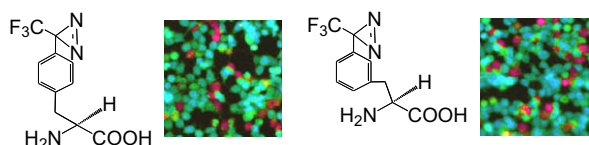


The synthesis and in vivo efficacy of phenylequine salts is reported (ED₅₀ of 0.81 in *Plasmodium yoelii*).

**Photoactive ligands probing the sweet taste receptor. Design and synthesis of highly potent diazirinyl D-phenylalanine derivatives**

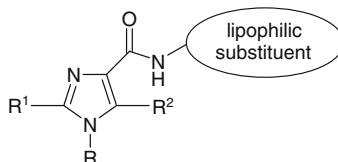
pp 1081–1083

Katsuyoshi Masuda, Ayako Koizumi, Takumi Misaka, Yasumaru Hatanaka, Keiko Abe, Takaharu Tanaka, Masaji Ishiguro, Makoto Hashimoto*

**Synthesis and SAR of novel imidazoles as potent and selective cannabinoid CB₂ receptor antagonists with high binding efficiencies**

pp 1084–1089

Jos H. M. Lange*, Martina A.W. van der Neut, Henri C. Wals, Gijs D. Kuil, Alice J. M. Borst, Arie Mulder, Arnold P. den Hartog, Hicham Zilaout, Wouter Goutier, Herman H. van Stuivenberg, Bernard J. van Vliet

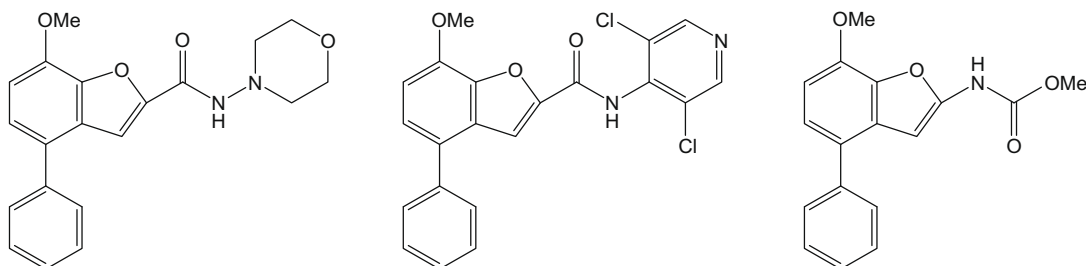


Imidazoles represent a novel chemotype of potent and selective CB₂ receptor antagonists.

**Synthetic studies on selective adenosine A_{2A} receptor antagonists: Synthesis and structure–activity relationships of novel benzofuran derivatives**

pp 1090–1093

Osamu Saku*, Mayumi Saki, Masako Kurokawa, Ken Ikeda, Takuya Takizawa, Noriaki Uesaka

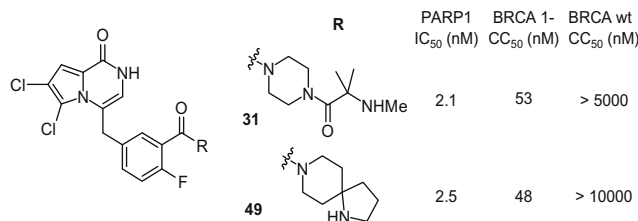


Novel benzofuran derivatives as potent and selective adenosine A_{2A} inhibitors were synthesized and evaluated.

Identification and SAR of novel pyrrolo[1,2-*a*]pyrazin-1(2*H*)-one derivatives as inhibitors of poly(ADP-ribose) polymerase-1 (PARP-1)

pp 1094–1099

Giovanna Pescatore*, Danila Branca, Fabrizio Fiore, Olaf Kinzel, Laura Llauger Bufi, Ester Muraglia, Federica Orvieto, Michael Rowley, Carlo Toniatti, Caterina Torrisi, Philip Jones

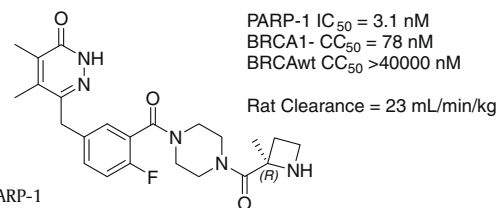


The discovery and optimization of a novel series of pyrrolo[1,2-*a*]pyrazin-1(2*H*)-one PARP inhibitors is reported, leading to potent inhibitors displaying excellent anti-proliferation activity in BRCA deficient cells.

Development of substituted 6-[4-fluoro-3-(piperazin-1-ylcarbonyl)benzyl]-4,5-dimethylpyridazin-3(2*H*)-ones as potent poly(ADP-ribose) polymerase-1 (PARP-1) inhibitors active in BRCA deficient cells

pp 1100–1105

Federica Ferrigno*, Danila Branca, Olaf Kinzel, Samuele Lillini, Laura Llauger Bufi, Edith Monteagudo, Ester Muraglia, Michael Rowley, Carsten Schultz-Fademrecht, Carlo Toniatti, Caterina Torrisi, Philip Jones

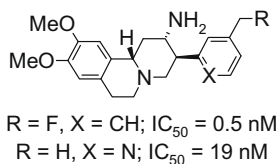


An extensive SAR exploration of the dimethylpyridazin-3(2*H*)-one scaffold led to the identification of potent PARP-1 inhibitors, capable of inhibiting the proliferation of BRCA-1 deficient cancer cells in the low nanomolar range, displaying >100-fold selectivity over the BRCA proficient cells, with clean off-target profiles and low clearance in rats.

Aryl- and heteroaryl-substituted aminobenzo[*a*]quinolizines as dipeptidyl peptidase IV inhibitors

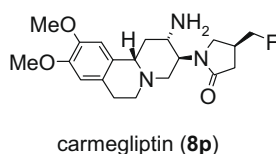
pp 1106–1108

Markus Boehringer, Holger Fischer, Michael Hennig, Daniel Hunziker, Joerg Huwyler, Bernd Kuhn, Bernd M. Loeffler, Thomas Luebbers, Patrizio Mattei*, Robert Narquizian, Elena Sebokova, Urs Sprecher, Hans Peter Wessel


Discovery of carmegliptin: A potent and long-acting dipeptidyl peptidase IV inhibitor for the treatment of type 2 diabetes

pp 1109–1113

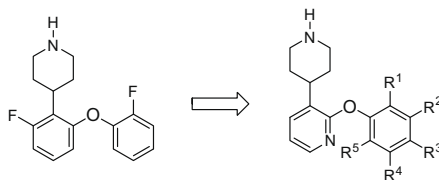
Patrizio Mattei*, Markus Boehringer, Patrick Di Giorgio, Holger Fischer, Michael Hennig, Joerg Huwyler, Buelent Koçer, Bernd Kuhn, Bernd M. Loeffler, Alexander MacDonald, Robert Narquizian, Etienne Rauber, Elena Sebokova, Urs Sprecher



Design, synthesis, and pharmacological evaluation of phenoxy pyridyl derivatives as dual norepinephrine reuptake inhibitors and 5-HT_{1A} partial agonists

pp 1114–1117

Amy B. Dounay*, Nancy S. Barta, Brian M. Campbell, Corey Coleman, Elizabeth M. Collantes, Lynne Denny, Satavisha Dutta, David L. Gray, Dongfeng Hou, Rathna Iyer, Samarendra N. Maiti, Daniel F. Ortwine, Al Probert, Nancy C. Stratman, Rajendra Subedi, Tammy Whisman, Wenjian Xu, Kim Zoski

**Molecular modeling study of 4-phenylpiperazine and 4-phenyl-1,2,3,6-tetrahydropyridine derivatives: A new step towards the design of high-affinity 5-HT_{1A} ligands**

pp 1118–1123

Sébastien Dilly, Amaury Graulich, Jean-François Liégeois*

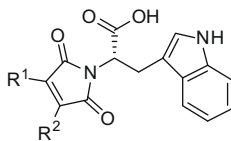


A conformational analysis of 4-phenylpiperazine (left) and 4-phenyl-1,2,3,6-tetrahydropyridine (right) derivatives demonstrates that the privileged almost planar orientation of the 4-substituted phenyl ring found in the latter is more favourable for 5-HT_{1A} affinity.

Design, synthesis, inhibitory activity, and binding mode study of novel DNA methyltransferase 1 inhibitors

pp 1124–1127

Takayoshi Suzuki*, Rikako Tanaka, Shohei Hamada, Hidehiko Nakagawa, Naoki Miyata*



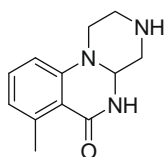
- 5: R¹ = R² = H
 6: R¹ = H, R² = CH₃
 7: R¹ = H, R² = Ph
 8: R¹ = CH₃, R² = CH₃

To identify novel non-nucleoside DNA methyltransferase (DNMT) inhibitors, we designed and synthesized a series of maleimide derivatives. Among this series, compounds 5–8 were found to be more potent DNMT1 inhibitors than RG108, a DNMT1 inhibitor reported previously by Siedlecki et al.

Tricyclic dihydroquinazolinones as novel 5-HT_{2C} selective and orally efficacious anti-obesity agents

pp 1128–1133

Saleem Ahmad*, Khehyong Ngu, Keith J. Miller, Ginger Wu, Chen-pin Hung, Sarah Malmstrom, Ge Zhang, Eva O'Tanyi, William J. Keim, Mary Jane Cullen, Kenneth W. Rohrbach, Michael Thomas, Thao Ung, Qinling Qu, Jinping Gan, Rangaraj Narayanan, Mary Ann Pelleymounter, Jeffrey A. Robl



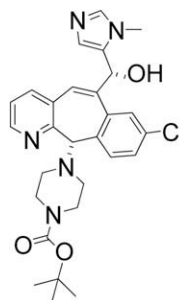
Compound (+)-2a

5-HT _{2C}	EC ₅₀	45 nM (IA = 1)
5-HT _{2B}	EC ₅₀	>10000 nM (IA = 0)
5-HT _{2A}	EC ₅₀	>10000 nM (IA = 0)

Discovery of C-imidazole azaheptapyridine FPT inhibitors

pp 1134–1136

Hugh Y. Zhu*, Alan B. Cooper, Jagdish Desai, George Njoroge, Paul Kirschmeier, W. Robert Bishop, Corey Strickland, Alan Hruza, Ronald J. Doll, Viyyoor M. Girijavallabhan

Compound **10a**

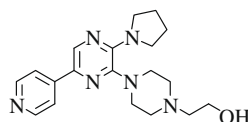
FPTase IC₅₀ = 0.38 nM
Soft Agar IC₅₀ = 0.5 nM

The discovery of C-linked imidazole azaheptapyridine bridgehead FPT inhibitors is described. This novel class of compounds are sub nM FPT enzyme inhibitors with potent cellular inhibitory activities. This series also has reduced hERG activity versus previous N-linked imidazole series. X-ray of compound **10a** bound to FTase revealed strong interaction between bridgehead imidazole 3N with catalytic zinc atom.

2,3-Diaminopyrazines as rho kinase inhibitors

pp 1137–1140

Alan J. Henderson*, Mark Hadden, Cheng Guo, Neema Douglas, Helene Decornez, Mark R. Hellberg, Andrew Rusinko, Marsha McLaughlin, Naj Sharif, Colene Drace, Raj Patil

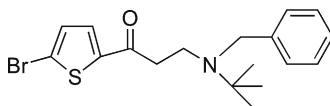
**38**

A series of 2,3-diaminopyrazines were synthesized and evaluated as rho kinase inhibitors. Compound **38** was found to have highly favorable in vitro properties, and demonstrated excellent efficacy in a monkey model of glaucoma.

Potent transglutaminase inhibitors, aryl β-aminoethyl ketones

pp 1141–1144

Shoichiro Ozaki, Etsuko Ebisui, Kozo Hamada, Jun-Ichi Goto, Akinobu Z. Suzuki, Akiko Terauchi, Katsuhiko Mikoshiba*

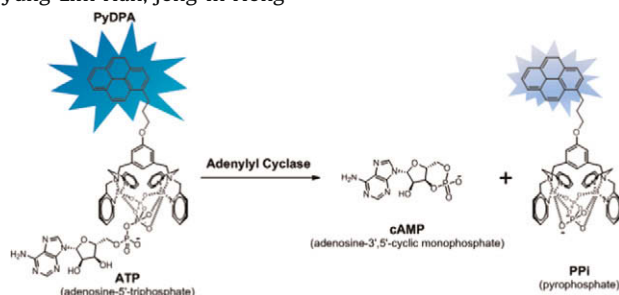


We report on potent inhibitors of tissue transglutaminase implicated in various diseases ranging from celiac disease and neurodegenerative disorders such as Alzheimer's, Huntington's, and Parkinson's diseases.

Label-free fluorescent real-time monitoring of adenylyl cyclase

pp 1145–1147

Hyun-Woo Rhee, Kyoung-Shim Kim, Pyung-Lim Han, Jong-In Hong*

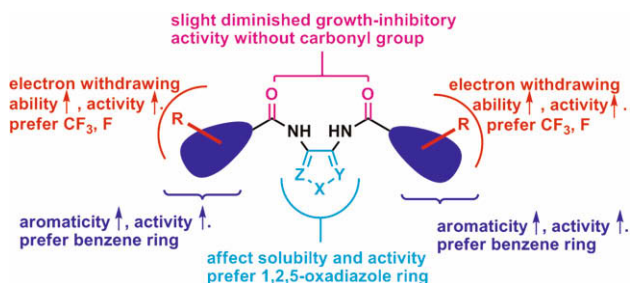


Using a synthetic fluorescent chemosensor (PyDPA) which binds strongly to the pyrophosphate group, we developed a label-free fluorescent real-time detection system for adenylyl cyclase.

Synthesis and structure–activity relationships of novel furazan-3,4-diamide analogs as potent anti-cancer agents

pp 1148–1152

Wen-Shan Li*, Shivaji V. More, Chie-Hong Wang, Ya Ching Jen, Ching-Fa Yao*, Tein-Fu Wang, Chin-Chun Hung, Shu-Chuan Jao

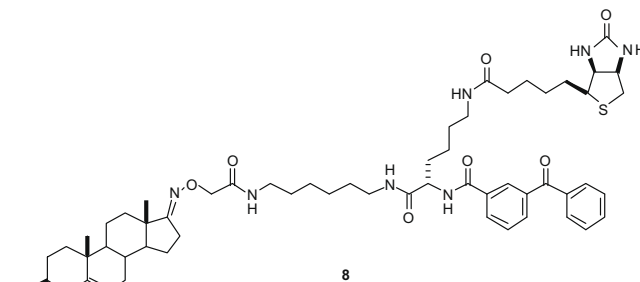


Schematic representation of structure–activity relationships based on diverse furazan-3,4-diamide analogs.

**Synthesis and application of a photoaffinity analog of dehydroepiandrosterone (DHEA)**

pp 1153–1155

Horacio F. Olivo*, Nury Perez-Hernandez, Dongmin Liu, Mary Iruthayanathan, Brianne O'Leary, Laurie L. Homan, Joseph S. Dillon*

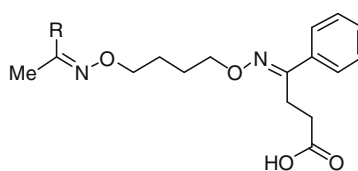


A novel analog of DHEA, carrying both benzophenone and biotin groups, retains the biological activity of DHEA and can be used for analysis and isolation of cellular DHEA binding sites.

**Design and synthesis of novel bis-oximinoalkanoic acids as potent PPAR α agonists**

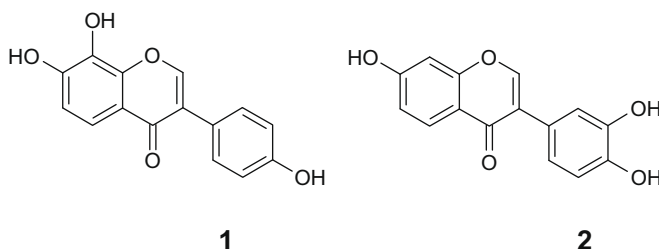
pp 1156–1161

Harikishore Pingali*, Mukul Jain, Shailesh Shah, Pandurang Zaware, Pankaj Makadia, Suresh Pola, Baban Thube, Darshit Patel, Pravin Patil, Priyanka Priyadarshini, Dinesh Suthar, Maanan Shah, Suresh Giri, Pankaj Patel

**9d**, R=4-methoxyphenyl**9m**, R=3-methoxy-4-methylphenylA novel class of selective PPAR α agonists containing bis-oximinoalkanoic acid was described. Selected compounds **9d** and **9m** showed excellent potency and high selectivity towards PPAR α in vitro and found to be effective in reducing serum triglycerides (TG) in vivo.**Natural *ortho*-dihydroxyisoflavone derivatives from aged Korean fermented soybean paste as potent tyrosinase and melanin formation inhibitors**

pp 1162–1164

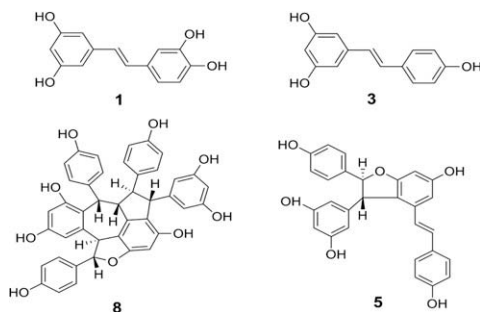
Jun-Seong Park*, Dong Hyun Kim, Jae Kyoung Lee, Jin Young Lee, Duck Hee Kim, Han Kon Kim, Hak-Ju Lee, Ho Cheol Kim

**1****2**Natural melanin formation inhibitors from aged Korean fermented soybean paste (**1–2**) are reported.

The antimicrobial activity of compounds from the leaf and stem of *Vitis amurensis* against two oral pathogens

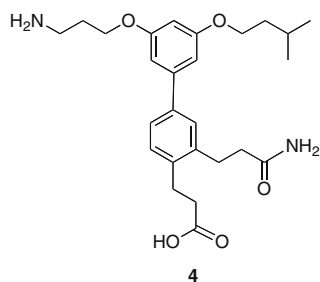
pp 1165–1168

NamHui Yim, Do Thi Ha, Trinh Nam Trung, Jin Pyo Kim, SangMyung Lee, MinKyeun Na, HyunJu Jung, Hyun Su Kim, Young Ho Kim, KiHwan Bae*

**Molecular design of small organic molecules based on structural information for a conformationally constrained peptide that binds to G-CSF receptor**

pp 1169–1172

Radwan El-Haggar, Ken Kamikawa*, Kazuya Machi, Zhengmao Ye, Yuko Ishino, Takeshi Tsumuraya, Ikuro Fujii*

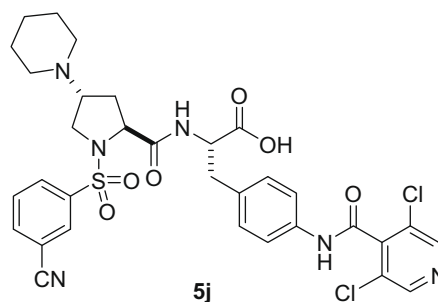


The synthesis of ligand **4** binds to G-CSF receptor is reported.

**Heterocycle-substituted proline dipeptides as potent VLA-4 antagonists**

pp 1173–1176

Thomas S. Reger*, Jasmine Zunic, Nicholas Stock, Bowei Wang, Nicholas D. Smith, Benito Munoz, Mitchell D. Green, Michael F. Gardner, Joyce P. James, Weichao Chen, Kenneth Alves, Qian Si, Kelly M. Treonze, Russell B. Lingham, Richard A. Mumford

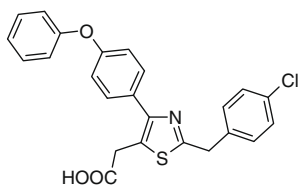


Compounds such as **5j** (IC_{50} = 0.11 nM) are potent inhibitors of VLA-4.

Novel selective thiazoleacetic acids as CRTH2 antagonists developed from in silico derived hits. Part 1

pp 1177–1180

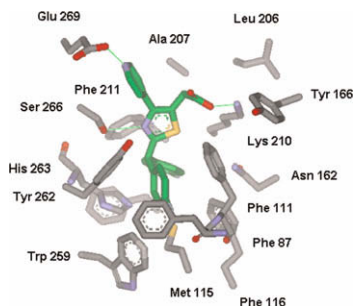
Øystein Rist, Marie Grimstrup, Jean-Marie Receveur, Thomas M. Frimurer, Trond Ulven, Evi Kostenis, Thomas Höglberg*



Novel selective thiazoleacetic acids as CRTH2 antagonists developed from in silico derived hits. Part 2

pp 1181–1185

Marie Grimstrup, Øystein Rist, Jean-Marie Receveur, Thomas M. Frimurer, Trond Ulven, Jesper M. Mathiesen, Evi Kostenis, Thomas Högberg*

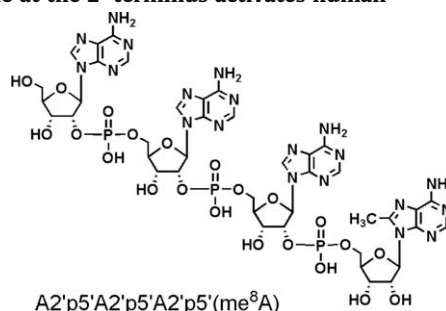


SAR has been established by exploring the eastern and western side of 5-thiazoleacetic acids supported by modeling and docking studies.

5'-O-Dephosphorylated 2',5'-oligoadenylate (2-5A) with 8-methyladenosine at the 2'-terminus activates human RNase L

pp 1186–1188

Kumi Nagaoka, Yoshiaki Kitamura, Yoshihito Ueno, Yukio Kitade*

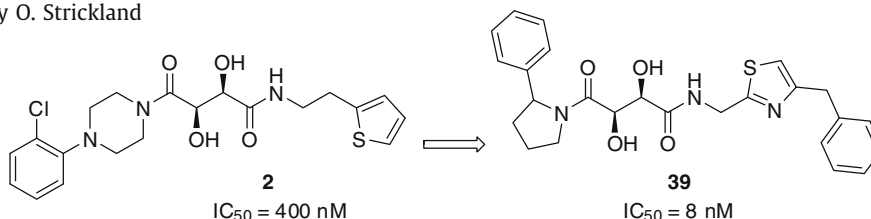


The 5'-phosphoryl group of 2-5A is reportedly necessary for the conformational change leading to RNase L activation. However, we found that 5'-O-dephosphorylated 2-5A tetramer analogs with 8-methyladenosine at the 2'-terminus were more effective as an activator of RNase L than the parent 2-5A tetramer. Introduction of 8-methyladenosine is thought to induce a dramatic shift of 2-5A in the binding site of RNase L.

The discovery of novel tartrate-based TNF- α converting enzyme (TACE) inhibitors

pp 1189–1193

Kristin E. Rosner*, Zhuyan Guo, Peter Orth, Gerald W. Shipps Jr., David B. Belanger, Tin Yau Chan, Patrick J. Curran, Chaoyang Dai, Yongqi Deng, Vinay M. Girijavallabhan, Liwu Hong, Brian J. Lavey, Joe F. Lee, Dansu Li, Zhidan Liu, Janeta Popovici-Muller, Pauline C. Ting, Henry Vaccaro, Li Wang, Tong Wang, Wensheng Yu, Guowei Zhou, Xiaoda Niu, Jing Sun, Joseph A. Kozlowski, Daniel J. Lundell, Vincent Madison, Brian McKittrick, John J. Piwinski, Neng -Yang Shih, M. Arshad Siddiqui, Corey O. Strickland

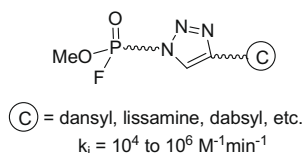


Synthesis and optimization of novel tartrate TACE inhibitors are described.

Inhibition of acetylcholinesterase by chromophore-linked fluorophosphonates

pp 1194–1197

Lilu Guo, Alirica I. Suarez, Michael R. Braden, John M. Gerdes, Charles M. Thompson*

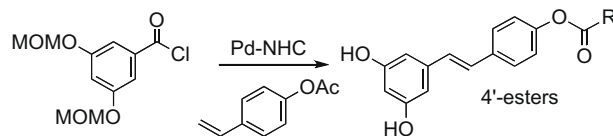


The synthesis and inhibition of AChE by a series of chromophore-linked fluorophosphonates is reported.

Synthesis of 4'-ester analogs of resveratrol and their evaluation in malignant melanoma and pancreatic cell lines

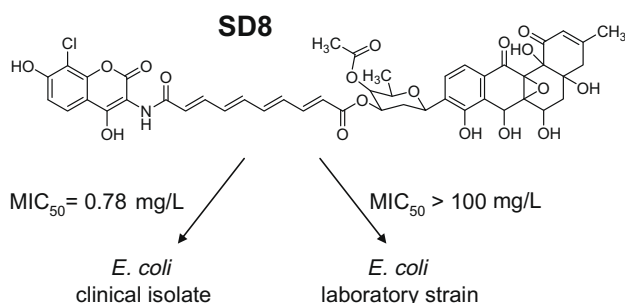
pp 1198–1201

Yong Wong, Gregory Osmond, Kenneth I. Brewer, Douglas S. Tyler, Merritt B. Andrus*

**Simocyclinone D8 turns on against Gram-negative bacteria in a clinical setting**

pp 1202–1204

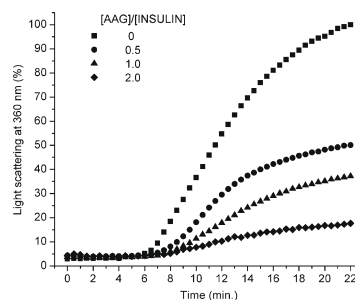
Sara N. Richter*, Ilaria Frasson, Manlio Palumbo, Claudia Sissi, Giorgio Palù

**Chaperone-like activity of the acute-phase component human serum α_1 -acid glycoprotein: Inhibition of thermal- and chemical-induced aggregation of various proteins**

pp 1205–1209

Ferenc Zsila*

The lipocalin protein plasma drug transporter α_1 -acid glycoprotein possesses chaperone-like activity evidenced by suppressing heat- and chemical-induced aggregation of various proteins.

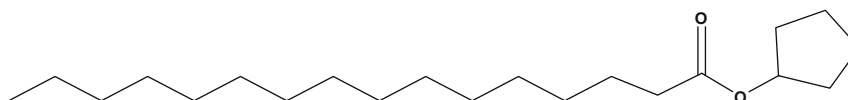


1

**Synthesis and biological evaluation of new potential inhibitors of *N*-acylethanolamine hydrolyzing acid amidase**

pp 1210–1213

Carmela Saturnino, Stefania Petrosino, Alessia Ligresti, Chiara Palladino, Giovanni De Martino, Tiziana Bisogno, Vincenzo Di Marzo*

**13**

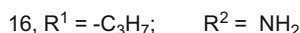
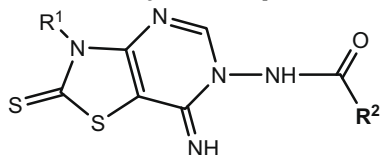
N-Acylethanolamine-hydrolyzing acid amidase (NAAA) specifically hydrolyzes *N*-palmitoylethanolamine, an anti-inflammatory mediator. We synthesized and screened several new compounds, and cyclopentylhexadecanoate (**13**) exhibited the highest inhibitory activity on NAAA.



Synthesis of novel 7-imino-2-thioxo-3,7-dihydro-2H-thiazolo [4,5-d] pyrimidine derivatives as adenosine A_{2A} receptor antagonists

pp 1214–1218

Pratibha Mehta Luthra*, Chandra Bhushan Mishra, Pawan Kumar Jha, Sandeep Kumar Barodia

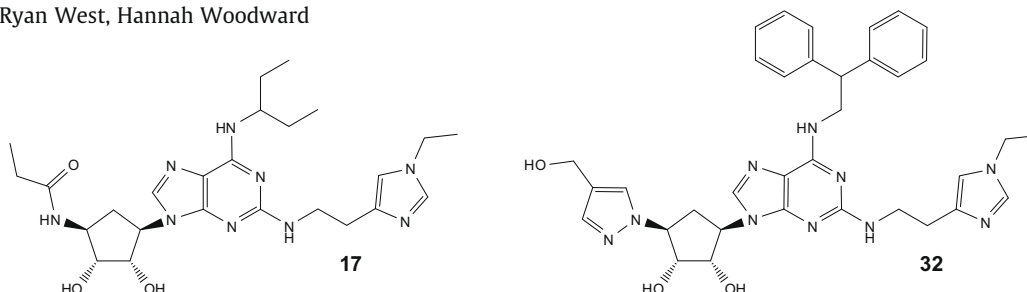


Novel bicyclic thiazolopyrimidine compounds (**15–26**) were synthesized and their in vitro binding studies and functional assay (cAMP determination) showed that compound (**16**) is a potent and selective A_{2A}R antagonist with strong binding affinity (K_i value = 0.0038 nM) towards A_{2A}R and higher selectivity (737-fold) versus A₁R.

**Synthesis and evaluation of two series of 4'-aza-carbocyclic nucleosides as adenosine A_{2A} receptor agonists**

pp 1219–1224

David Beattie, Andrew Brearley, Zarin Brown, Steven J. Charlton, Brian Cox, Robin A. Fairhurst*, John R. Fozard, Peter Gedeck, Paul Kirkham, Koremu Meja, Lana Nanson, James Neef, Helen Oakman, Gillian Spooner, Roger J. Taylor, Robert J. Turner, Ryan West, Hannah Woodward

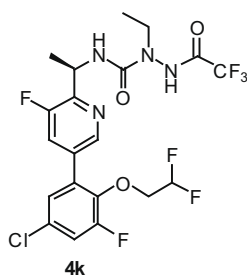


Two series of 4'-aza-carbocyclic nucleosides are described as adenosine A_{2A} receptor agonists.

Novel small molecule bradykinin B₁ receptor antagonists. Part 1: Benzamides and semicarbazides

pp 1225–1228

Marco Schaudt, Elsa Locardi, Gunther Zischinsky, Roland Stragies, Jochen R. Pfeifer, Christoph Gibson, Dirk Scharn, Uwe Richter, Holger Kalkhof, Klaus Dinkel, Karsten Schnatbaum*

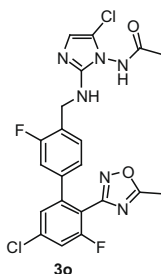


Benzamides and semicarbazides are introduced as new classes of bradykinin B₁ receptor antagonists. The best compounds feature excellent pharmacokinetic properties in the rat.

Novel small molecule bradykinin B₁ receptor antagonists. Part 2: 5-membered diaminoheterocycles

pp 1229–1232

Gunther Zischinsky, Roland Stragies, Marco Schaudt, Jochen R. Pfeifer, Christoph Gibson, Elsa Locardi, Dirk Scharn, Uwe Richter, Holger Kalkhof, Klaus Dinkel, Karsten Schnatbaum*

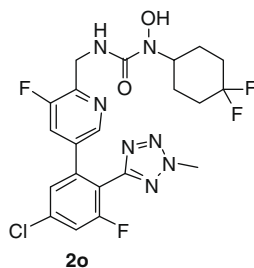


New bradykinin B₁ receptor antagonists based on 5-membered diaminoheterocycles with nanomolar activity are presented.

Novel small molecule bradykinin B₁ receptor antagonists. Part 3: Hydroxyurea derivatives

pp 1233–1236

Karsten Schnatbaum*, Marco Schaudt, Roland Stragies, Jochen R. Pfeifer, Christoph Gibson, Elsa Locardi, Dirk Scharn, Uwe Richter, Holger Kalkhof, Klaus Dinkel, Gunther Zischinsky

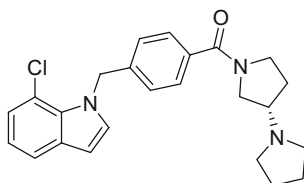


Hydroxy urea analogues have been developed as a new class of bradykinin B₁ receptor antagonists. Systematic optimization led to the identification of several antagonists with low-nanomolar activity and very high oral bioavailability in the rat.

Benzimidazole- and indole-substituted 1,3'-bipyrrolidine benzamides as histamine H₃ receptor antagonists

pp 1237–1240

Derek C. Cole*, Jonathan L. Gross, Thomas A. Comery, Suzan Aschmies, Warren D. Hirst, Cody Kelley, Ji-In Kim, Katie Kubek, Xiaoping Ning, Brian J. Platt, Albert J. Robichaud, William R. Solvibile, Joseph R. Stock, Gregory Tawa, Marla J. Williams, John W. Ellingboe

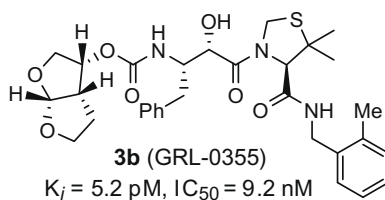


Using a focused screen of biogenic amine compounds a novel series of H₃R antagonists was identified. Preliminary SAR led to reduction of MW while increasing binding affinity and potency. Optimization of the physical properties of the series led to (S)-**6n**, with improved brain to plasma exposure and efficacy in both water intake and novel object recognition models.

Synthesis and biological evaluation of novel allophenylnorstatine-based HIV-1 protease inhibitors incorporating high affinity P2-ligands

pp 1241–1246

Arun K. Ghosh*, Sandra Gemma, Elena Simoni, Abigail Baldrige, D. Eric Walters, Kazuhiko Ide, Yasushi Tojo, Yasuhiro Koh, Masayuki Amano, Hiroaki Mitsuya

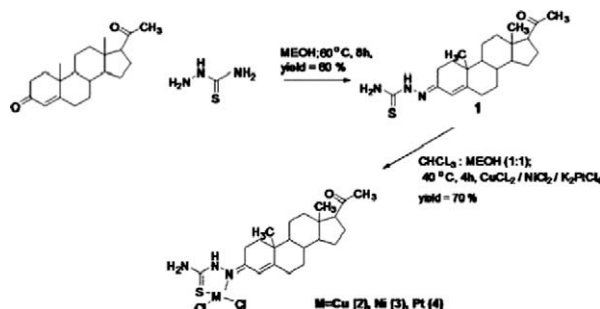


A series of novel HIV-1 protease inhibitors were designed and synthesized incorporating stereochemically defined and conformationally constrained cyclic ethers as P2-ligands into allophenylnorstatine based isostere. Inhibitor **3b** with a bis-THF P2-ligand has shown impressive potency.

Hybrid anticancer agents: Isothiocyanate–progesterone conjugates as chemotherapeutic agents and insights into their cytotoxicities

pp 1247–1251

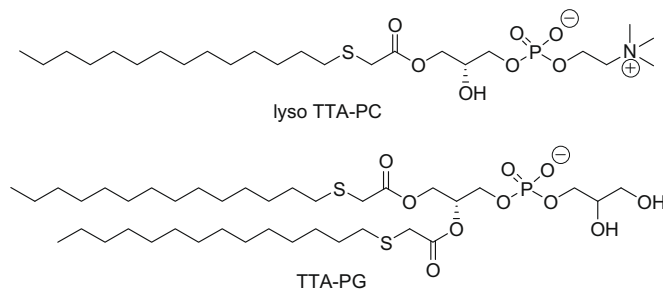
Shreelekha Adsule, Sanjeev Banerjee, Fakhara Ahmed, Subhash Padhye, Fazlul H. Sarkar*



Novel phospholipid analogues of pan-PPAR activator tetradecylthioacetic acid are more PPAR α selective

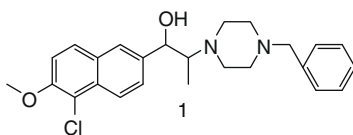
pp 1252–1255

Yushma Bhurruth-Alcor, Therese H. Rost, Michael R. Jorgensen, Rajender, Melanie Müller, Jon Skorve, Rolf K. Berge, Andrew D. Miller*

Phospholipid analogues of tetradecylthioacetic acid (TTA) are synthesized and shown to be potent, selective PPAR α agonists.**Synthesis and antidepressant activity of optical isomers of 2-(4-benzylpiperazin-1-yl)-1-(5-chloro-6-methoxynaphthalen-2-yl) propan-1-ol (SIP15056)**

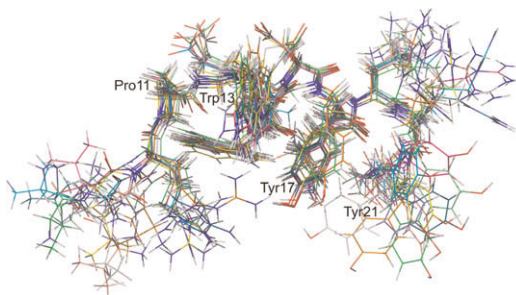
pp 1256–1259

Zhijie Weng, Jianqi Li*

Optical isomers of 2-(4-benzylpiperazin-1-yl)-1-(5-chloro-6-methoxynaphthalen-2-yl) propan-1-ol (**1**, SIP15056), which are multiple reuptake inhibitors of monoamine transmitters, were synthesized to evaluate their antidepressant activities and acute toxicities.**Solution structural investigation and conformation–activity relationship of BAM8-22 by NMR and molecular dynamics simulations**

pp 1260–1262

Guohua Lv, Shouliang Dong*

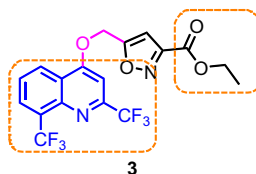


The solution conformation and dynamics features of BAM8-22 were investigated by NMR spectroscopy and MD simulations.

**Synthesis and antituberculosis activity of novel mefloquine-isoxazole carboxylic esters as prodrugs**

pp 1263–1268

Jialin Mao, Hai Yuan, Yuehong Wang, Baojie Wan, Dennis Pak, Rong He, Scott G. Franzblau*

MIC(MABA/LORA): 0.9/12.2 μ MIC₅₀ > 128 μ M

SI > 142.2/ >10.5

EC₉₀ = 4.1 μ M

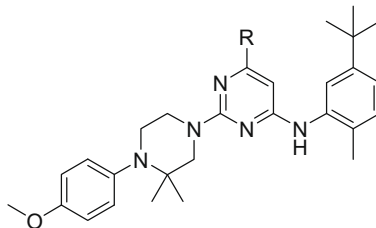
Prodrug or not ?



Piperazinyl pyrimidine derivatives as potent γ -secretase modulators

pp 1269–1271

Alexey Rivkin*, Sean P. Ahearn, Stephanie M. Chichetti, Yoona R. Kim, Chaomin Li, Andrew Rosenau, Sam D. Kattar, Joon Jung, Sanjiv Shah, Bethany L. Hughes, Jamie L. Crispino, Richard E. Middleton, Alexander A. Szewczak, Benito Munoz, Mark S. Shearman

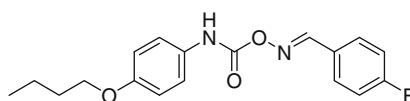


The development of a novel series of piperazinyl pyrimidines as γ -secretase modulators for potential use in the treatment of Alzheimer's disease is disclosed herein. Optimization of a screening hit provided a series of potent γ -secretase modulators with >180-fold in vitro selectivity over inhibition of Notch cleavage.

Oxime Carbamate—Discovery of a series of novel FAAH inhibitors

pp 1272–1277

S.Y. Sit*, Charles M. Conway, Kai Xie, Robert Bertekap, Clotilde Bourin, Kevin D. Burris



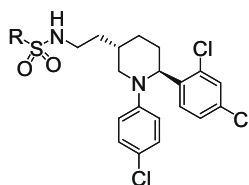
50 $IC_{50} = 2.2 \pm 0.9$ nM

The rationale behind the discovery and the biological evaluations of this novel class of FAAH inhibitors are presented. Both in vitro and in vivo results of selected targets are discussed, along with inhibition kinetics and molecular modeling studies.

**Diaryl piperidines as CB₁ receptor antagonists**

pp 1278–1283

Jack D. Scott*, Sarah W. Li, Hongwu Wang, Yan Xia, Charles L. Jayne, Michael W. Miller, Ruth A. Duffy, George C. Boykow, Timothy J. Kowalski, Brian D. Spar, Andrew W. Stamford, Samuel Chackalamannil, Jean E. Lachowicz, William J. Greenlee



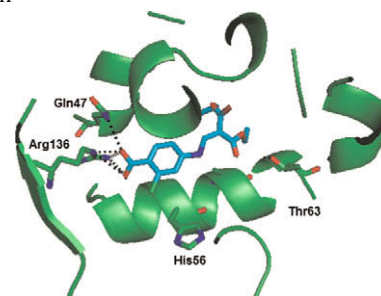
hCB₁ $K_i = 3$ –61 nM

A study of the effects of substituents on the selectivity of the binding of *N*-arylaminomethylene malonate inhibitors to DHODH

pp 1284–1287

Deborah Cowen, Paul Bedingfield, Glenn A. McConkey, Colin W. G. Fishwick*, A. Peter Johnson*

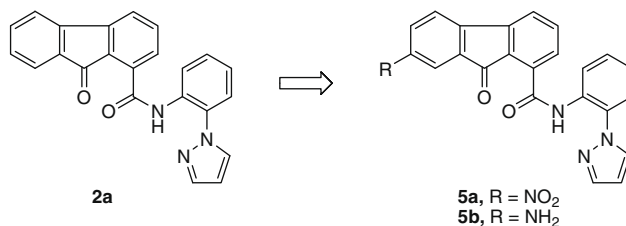
A series of mono- and di-substituted *N*-arylaminomethylene malonates have been used to probe the potential of utilizing additional H-bonding contacts in the ubiquinone binding channel, for selective inhibition between either human or *Plasmodium* DHODH. The resulting trends in measured affinity were rationalized using molecular docking.



Discovery of *N*-aryl-9-oxo-9*H*-fluorene-1-carboxamides as a new series of apoptosis inducers using a cell- and caspase-based high-throughput screening assay. 2. Structure–activity relationships of the 9-oxo-9*H*-fluorene ring

pp 1288–1292

William Kemnitzer, Nilantha Sirisoma, Songchun Jiang, Shailaja Kasibhatla, Candace Crogan-Grundy, Ben Tseng, John Drewe, Sui Xiong Cai*

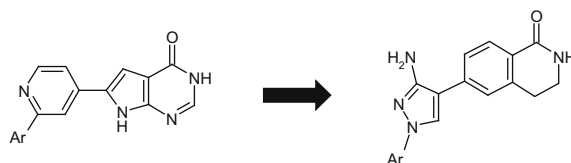


The synthesis and SAR of a group of apoptosis inducing 9-oxo-9*H*-fluorene-1-carboxamides with modifications at the 9-oxo-9*H*-fluorene ring are reported.

Novel 3-aminopyrazole inhibitors of MK-2 discovered by scaffold hopping strategy

pp 1293–1297

Juraj Velcicky*, Roland Feifel, Stuart Hawtin, Richard Heng, Christine Huppertz, Guido Koch, Markus Kroemer, Henrik Moebitz, Laszlo Revesz, Clemens Scheufler, Achim Schlapbach

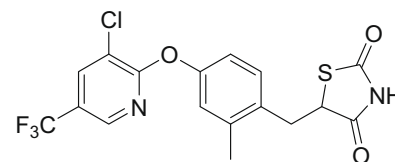


3-Aminopyrazole based MK2-inhibitors were discovered by scaffold hopping strategy. Optimized derivatives proved to inhibit intracellular phosphorylation of hsp27 as well as LPS-induced TNF α release in cells and in vivo.

Discovery of 5-aryloxy-2,4-thiazolidinediones as potent GPR40 agonists

pp 1298–1301

Changyou Zhou*, Cheng Tang, Eric Chang, Min Ge, Songnian Lin, Eric Cline, Carina P. Tan, Yue Feng, Yun-Ping Zhou, George J. Eiermann, Aleksandr Petrov, Gino Salituro, Peter Meinke, Ralph Mosley, Taro E. Akiyama, Monica Einstein, Sanjeev Kumar, Joel Berger, Andrew D. Howard, Nancy Thornberry, Sander G. Mills, Lihu Yang*



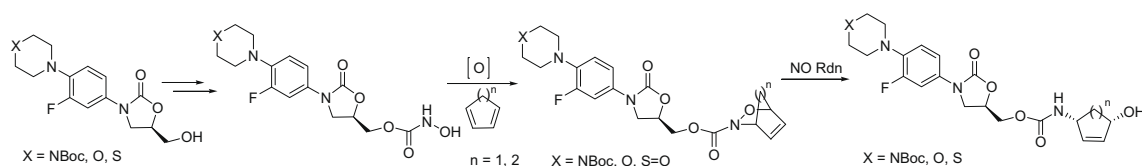
Compound C
hGPR40 EC₅₀ = 10 nM

Systematic structure–activity relationship (SAR) studies of a screening lead led to the discovery of a series of thiazolidinediones (TZDs) as potent GPR40 agonists. Among them, compound **C** demonstrated an acute mechanism-based glucose-lowering in an intraperitoneal glucose tolerance test (IPGTT) in lean mice, while no effects were observed in GPR40 knock-out mice.

Syntheses and antibacterial activity studies of new oxazolidinones from nitroso Diels–Alder chemistry

pp 1302–1305

Shanshan Yan, Marvin J. Miller*, Timothy A. Wenciewicz, Ute Möllmann



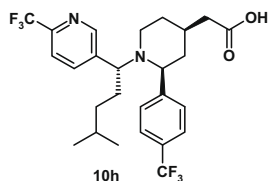
A series of novel oxazolidinone antibiotics having [2,2,1] and [2,2,2] bicyclic oxazine moieties at the C-5 side chain of the A-ring were synthesized by nitroso Diels–Alder reactions, from three linezolid analogs containing morpholine, piperazine and thiomorpholine, respectively, as the C-ring components. Subsequent N–O bond cleavage generated oxazolidinones with 4-amino cycloalk-2-en-1-ol substituents. The in vitro antibacterial activities of these oxazolidinone analogs were evaluated.



Piperidine-derived γ -secretase modulators

pp 1306–1311

Adrian Hall*, Richard L. Elliott, Gerard M. P. Giblin, Ishrut Hussain, James Musgrave, Alan Naylor, Rosemary Sasse, Beverley Smith

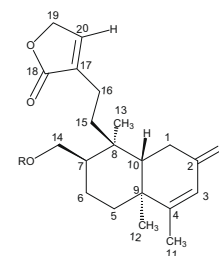


Compound **10h** was found to be a potent modulator in vitro and was found to decrease A β 42, increase A β 38 and have no effect on A β 40 levels. Furthermore, **10h** demonstrated excellent pharmacokinetic parameters in the mouse, rat and dog in addition to good CNS penetration in the mouse.

**Gomphostenins: Two new antimalarial compounds from the leaves of *Gomphostemma niveum***

pp 1312–1314

Manisha Sathe, M. P. Kaushik*



Gomphostenin **1** R = H
Gomphostenin-A **2** R = COCH₃

Phytochemical investigation of CHCl₃ extract of the *Gomphostemma niveum* leaves led to the isolation of two new diterpene, compound **1** and **2**. Their structures were elucidated by spectroscopic procedures and single crystal XRD. Compound **1** named as Gomphostenin **1** and structure was established as 8-ethyl (5*H*-furan-2-one, 14-hydroxy, 2-oxo 3, 20 *Z*(17) diene clerodane, while compound **2** named as Gomphostenin-A was found to be the acetyl derivative of compound **1** and revealed as 8-ethyl (5*H*-furan-2-one, 14-acetoxy, 2-oxo 3, 20 *Z*(17) diene clerodane. In vitro antimalarial activity against *Plasmodium falciparum* showed that compound **2** was more active than compound **1** and CHCl₃ extract as well; with IC₅₀ value of 3.4 μ g/mL

*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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