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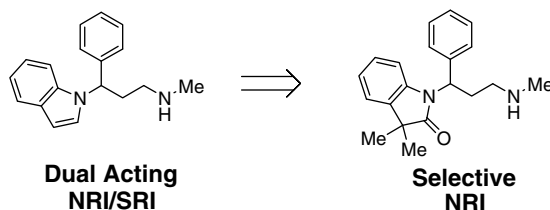
Bioorganic & Medicinal Chemistry Letters Vol. 18, No. 18, 2008

Contents

ARTICLES

Synthesis and activity of 1-(3-amino-1-phenylpropyl)indolin-2-ones: A new class of selective norepinephrine reuptake inhibitors pp 4929–4931

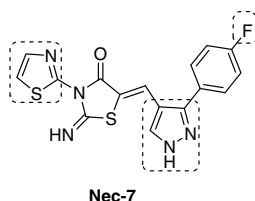
Casey C. McComas*, An T. Vu, Paige E. Mahaney, Stephen T. Cohn, Andrew Fensome, Michael A. Marella, Lisa Nogle, Eugene J. Trybulski, Fei Ye, Puwen Zhang, Peter Alfinito, Jenifer Bray, Grace Johnston, Elizabeth Koury, Darlene C. Deecher



A novel class of 1-(3-amino-1-phenylpropyl)indolin-2-ones displays potent norepinephrine reuptake inhibition while maintaining good selectivity (>100-fold) against the human serotonin and dopamine transporters.

Structure–activity relationship study of a novel necroptosis inhibitor, necrostatin-7 pp 4932–4935

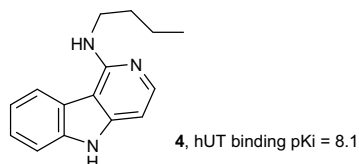
WeiHong Zheng, Alexei Degterev, Emily Hsu, Junying Yuan, Chengye Yuan*



Nec-7, a new necroptosis inhibitor and its structural modification.

N-Alkyl-5H-pyrido[4,3-b]indol-1-amines and derivatives as novel urotensin-II receptor antagonists pp 4936–4939

Yonghui Wang*, Zining Wu, Brian F. Guida, Sarah K. Lawrence, Michael J. Neeb, Ralph A. Rivero, Stephen A. Douglas, Jian Jin*

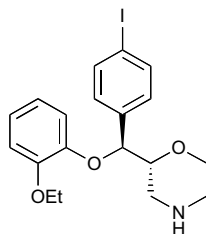


Synthesis, structure and activity relationships, functional and animal ortholog activities of a novel class of urotensin-II receptor antagonists are described.

New iodoreboxetine analogues for SPECT imaging of the noradrenaline transporter

pp 4940–4943

Nicola K. Jobson, Andrew R. Crawford, Deborah Dewar, Sally L. Pimlott, Andrew Sutherland*

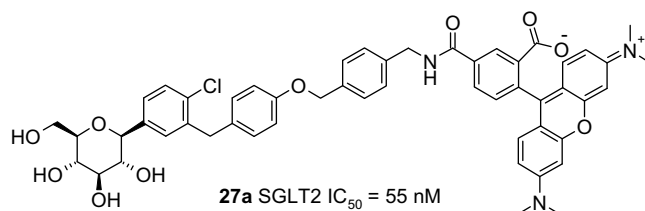
 $K_i = 53.8 \text{ nM}$

(2*S*,3*S*)- and (2*R*,3*R*)-iodoreboxetine analogues have been prepared in a stereoselective manner and biological testing against various mono-amine transporters have shown these compounds to be potent and selective for the noradrenaline transporter.

**Design and synthesis of fluorescent SGLT2 inhibitors**

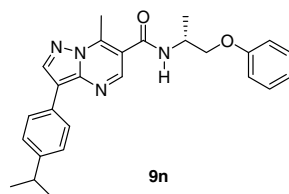
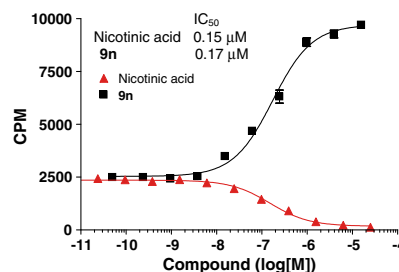
pp 4944–4947

Mark I. Lansdell*, Denise J. Burring, David Hepworth, Matthew Strawbridge, Emily Graham, Thierry Guyot, Mark S. Betson, James D. Hart

**27a** SGLT2 $IC_{50} = 55 \text{ nM}$ **Discovery of pyrazolopyrimidines as the first class of allosteric agonists for the high affinity nicotinic acid receptor GPR109A**

pp 4948–4951

Hong C. Shen*, Andrew K. P. Taggart, Larissa C. Wilsie, M. Gerard Waters, Milton L. Hammond, James R. Tata, Steven L. Colletti

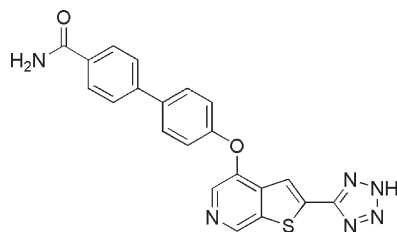
**9n**

Pyrazolopyrimidines were discovered as the first class of allosteric agonists for the high affinity nicotinic acid receptor GPR109A. In addition to its intrinsic activity, compound **9n** significantly enhances nicotinic acid binding to the receptor, thereby potentiating the functional efficacy of nicotinic acid.

Discovery of thieno[2,3-*c*]pyridines as potent COT inhibitors

pp 4952–4955

Dawn George*, Michael Friedman, Hamish Allen, Maria Argiriadi, Claude Barberis, Agnieszka Bischoff, Anca Clabbers, Kevin Cusack, Richard Dixon, Shannon Fix-Stenzel, Thomas Gordon, Bernd Janssen, Yong Jia, Maria Moskey, Christopher Quinn, Jose-Andres Salmeron, Neil Wishart, Kevin Woller, Zhengtian Yu



COT $IC_{50} = 0.01 \text{ }\mu\text{M}$
 COT cell $IC_{50} = 0.13 \text{ }\mu\text{M}$

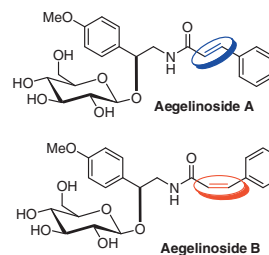
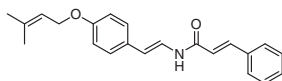
A series of thieno[2,3-*c*]pyridines were identified as potent inhibitors of COT kinase activity. Structural modifications exploring SAR resulted in the identification of inhibitors with improved enzyme potency and cellular activity.



Phenylethyl cinnamides: A new series of α -glucosidase inhibitors from the leaves of *Aegle marmelos*

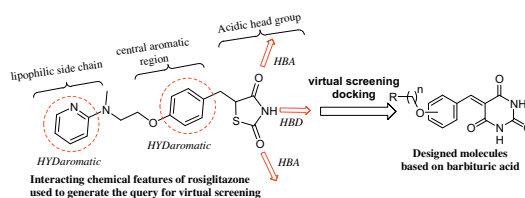
pp 4956–4958

Preecha Phuwapraisirisan*, Thanchanok Puksasook, Jonkolnee Jong-aramruang, Udom Kokpol

**New PPAR γ ligands based on barbituric acid: Virtual screening, synthesis and receptor binding studies**

pp 4959–4962

Sandeep Sundriyal, Bhoomi Viswanad, Poduri Ramarao, Asit K. Chakraborti, Prasad V. Bharatam*

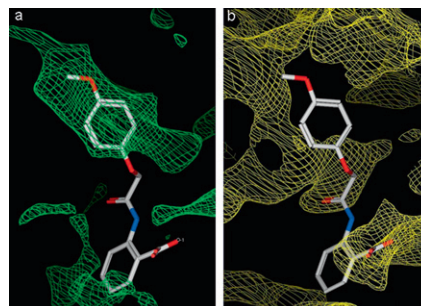


Barbituric acid was identified as a new acid head group for the design of novel PPAR γ ligands using virtual screening, synthesis and radio ligand binding analysis.

**Molecular modeling aided design of nicotinic acid receptor GPR109A agonists**

pp 4963–4967

Qiaolin Deng*, Jessica L. Frie, Daria M. Marley, Richard T. Beresis, Ning Ren, Tian-Quan Cai, Andrew K. P. Taggart, Kang Cheng, Ester Carballo-Jane, Junying Wang, Xinchun Tong, M. Gerard Waters, James R. Tata, Steven L. Colletti

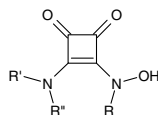


Application of molecular modeling to aid development of potent GPR109A agonists.

Synthesis of a 200-member library of squaric acid *N*-hydroxylamide amides

pp 4968–4971

Julie Charton*, Benoît P. Déprez, Rébecca F. Déprez-Poulain



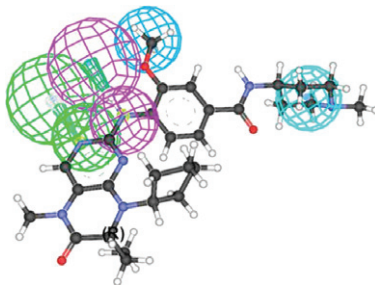
We report here the parallel synthesis of 200 compounds based on squaric acid template. The library was screened on the zinc metalloenzyme ADAMTS-5 and hits with IC₅₀ in the range of 1–50 μ M were identified.



Pharmacophore modeling and virtual screening for designing potential PLK1 inhibitors

pp 4972–4977

Hui-Yuan Wang, Zhi-Xing Cao, Lin-Li Li, Pei-Du Jiang, Ying-Lan Zhao, Shi-Dong Luo, Li Yang, Yu-Quan Wei, Sheng-Yong Yang*

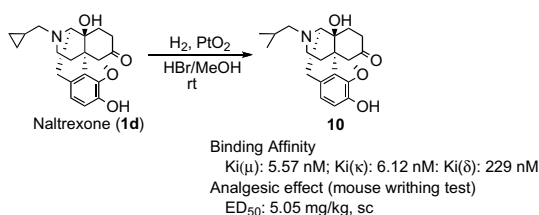


Pharmacophore model of PLK1 inhibitors was established. This model was then used as a 3D query to screen several chemical databases including Specs, NCI, Maybridge, and CNPD.

**Synthesis of *N*-isobutylnoroxymorphone from naltrexone by a selective cyclopropane ring opening reaction**

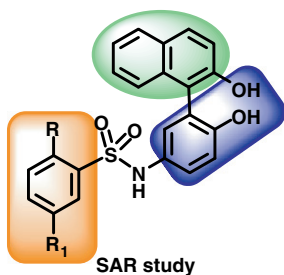
pp 4978–4981

Hideaki Fujii, Yumiko Osa, Marina Ishihara, Shinichi Hanamura, Toru Nemoto, Mayumi Nakajima, Ko Hasebe, Hidenori Mochizuki, Hiroshi Nagase*

**Synthesis and SAR study of *N*-(4-hydroxy-3-(2-hydroxynaphthalene-1-yl)phenyl)-arylsulfonamides: Heat shock protein 90 (Hsp90) inhibitors with submicromolar activity in an in vitro assay**

pp 4982–4987

Thota Ganesh*, Pahk Thepchatrri, Lian Li, Yuhong Du, Haian Fu, James P. Snyder, Aiming Sun

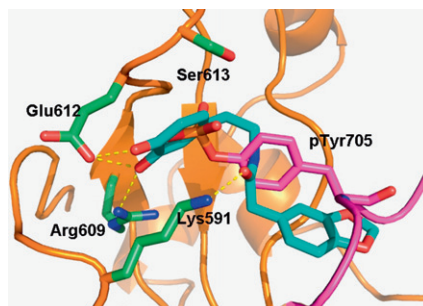


A versatile synthesis and SAR study of the sulfonamide scaffold are reported.

Discovery of the catechol structural moiety as a Stat3 SH2 domain inhibitor by virtual screening

pp 4988–4992

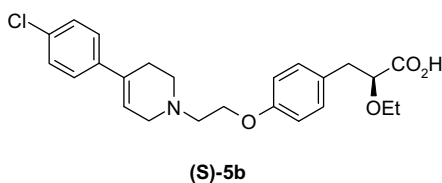
Wenshan Hao*, Yongbo Hu, Chuansheng Niu, Xinyi Huang, Chao-Pei Betty Chang, James Gibbons, Jun Xu



Design, synthesis, and evaluation of novel aryl-tetrahydropyridine PPAR α / γ dual agonists

pp 4993–4996

Eunkyung Kim, Chan Sun Park, Taedong Han, Myung-Ho Bae, Wonee Chong, Choong Hyun Lee, Young Ah Shin, Byung-Nak Ahn, Mi Kyung Kim, Chang Yell Shin, Moon Ho Son, Jin Kwan Kim, Ho Sang Moon, Hyun Joo Shim, Eun Jung Kim, Soon Hoe Kim, Joong In Lim, Chun Ho Lee *

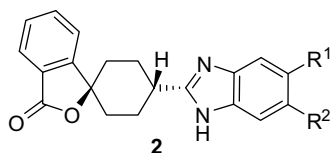


The synthesis of the potent PPAR α / γ dual agonist **(S)-5b** (EC_{50} = 1.73/0.64 μ M (α / γ)) is reported.

Syntheses and structure–activity relationships of novel, potent, and selective *trans*-2-[3-oxospiro-[isobenzofuran-1(3*H*),1'-cyclohexan]-4'-yl]benzimidazole NPY Y5 receptor antagonists

pp 4997–5001

Yoshio Ogino, Norikazu Ohtake *, Yoshikazu Nagae, Kenji Matsuda, Makoto Ishikawa, Minoru Moriya, Maki Kanesaka, Yuko Mitobe, Junko Ito, Tetsuya Kanno, Akane Ishihara, Hisashi Iwaasa, Tomoyuki Ohe, Akio Kanatani, Takehiro Fukami

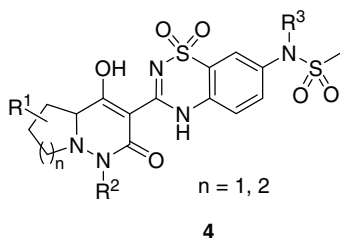


Structure–activity relationships of a novel 2-(substituted cyclohexyl)benzimidazole NPY Y5 receptor antagonists are described.

Hexahydro-pyrrolo- and hexahydro-1*H*-pyrido[1,2-*b*]pyridazin-2-ones as potent inhibitors of HCV NS5B polymerase

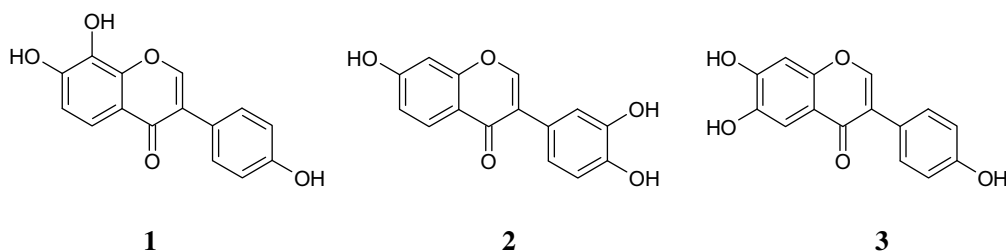
pp 5002–5005

Frank Ruebsam *, Zhongxiang Sun, Benjamin K. Ayida, Stephen E. Webber, Yuefen Zhou, Qiang Zhao, Charles R. Kissinger, Richard E. Showalter, Amit M. Shah, Mei Tsan, Rupal Patel, Laurie A. LeBrun, Ruhi Kamran, Maria V. Sergeeva, Darian M. Bartkowski, Thomas G. Nolan, Daniel A. Norris, Leo Kirkovsky

***ortho*-Dihydroxyisoflavone derivatives from aged Doenjang (Korean fermented soypaste) and its radical scavenging activity**

pp 5006–5009

Jun-Seong Park *, Hye Yoon Park, Dong Hyun Kim, Duck Hee Kim, Han Kon Kim

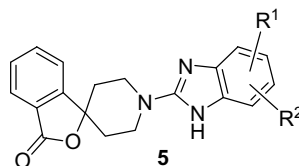


ortho-Dihydroxyisoflavone derivatives isolated from aged *Doenjang* (**1–3**) are reported.

Design, syntheses, and structure–activity relationships of novel NPY Y5 receptor antagonists: 2-{3-Oxospiro[isobenzofuran-1(3H),4'-piperidin]-1'-yl}benzimidazole derivatives

pp 5010–5014

Yoshio Ogino, Norikazu Ohtake*, Yoshikazu Nagae, Kenji Matsuda, Minoru Moriya, Takuya Suga, Makoto Ishikawa, Maki Kanesaka, Yuko Mitobe, Junko Ito, Tetsuya Kanno, Akane Ishihara, Hisashi Iwaasa, Tomoyuki Ohe, Akio Kanatani, Takehiro Fukami

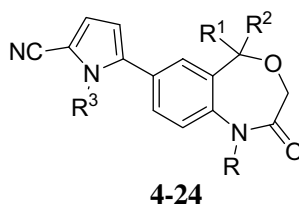


Structure–activity relationships of novel 2-(substituted piperidin-1-yl)benzimidazole NPY Y5 receptor antagonists are described.

1,5-Dihydro-benzo[e][1,4]oxazepin-2(1H)-ones containing a 7-(5'-cyanopyrrol-2-yl) group as nonsteroidal progesterone receptor modulators

pp 5015–5017

Jeffrey C. Kern, Eugene A. Terefenko, Andrew Fensome, Ray Unwalla, Jay Wrobel, Jeffrey Cohen, Yuan Zhu, Thomas J. Berrodin, Matthew R. Yudt, Richard C. Winneker, Zhiming Zhang, Puwen Zhang*

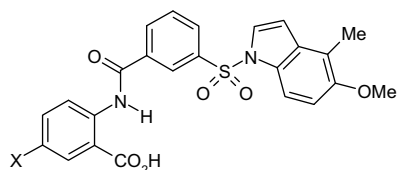


The functional activities of compounds **4–24** as progesterone receptor agonist or antagonist are modulated by the size and nature of R¹ and R² substituents.

Discovery of a novel class of PPARδ partial agonists

pp 5018–5022

Barry G. Shearer*, Hari S. Patel, Andrew N. Billin, James M. Way, Deborah A. Winegar, Millard H. Lambert, Robert X. Xu, Lisa M. Leesnitzer, Raymond V. Merrihew, Stephane Huet, Timothy M. Willson



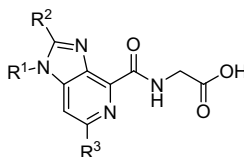
GSK1115 X = Cl
GSK7227 X = Me

The discovery and evaluation of a novel anthranilic acid class of PPARδ partial agonists is described.

Structure-guided design of substituted aza-benzimidazoles as potent hypoxia inducible factor-1α prolyl hydroxylase-2 inhibitors

pp 5023–5026

Mike Frohn*, Vellarkad Viswanadhan, Alexander J. Pickrell, Jennifer E. Golden, Kristine M. Muller, Roland W. Bürli, Gloria Biddlecome, Sean C. Yoder, Norma Rogers, Jennifer H. Dao, Randall Hungate, Jennifer R. Allen

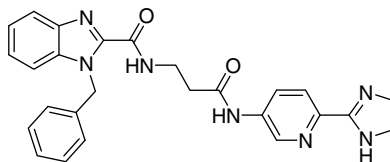


We report the structure-based design and synthesis of a novel series of aza-benzimidazoles as PHD2 inhibitors. These efforts resulted in compound **22**, which displayed highly potent inhibition of PHD2 function in vitro.

1-Benzylbenzimidazoles: The discovery of a novel series of bradykinin B₁ receptor antagonists

pp 5027–5031

Qin Guo, Jayaraman Chandrasekhar, David Ihle, David J. Wustrow, Bertrand L. Chenard, James E. Krause, Alan Hutchison, Dawn Alderman, Charles Cheng, Daniel Cortright, Daniel Broom, Mark T. Kershaw, Jean Simmermacher-Mayer, Yao Peng, Kevin J. Hodgetts*



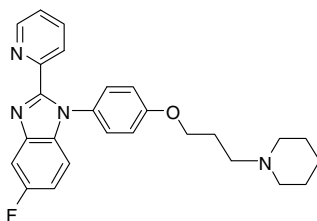
38g cBK B₁ EC₅₀ = 2 nM
rBK B₁ EC₅₀ = 0.8 nM

The design, synthesis, and structure–activity studies of a novel series of BK B₁ receptor antagonists based on a 1-benzylbenzimidazole chemotype are described. A number of compounds, for example, **38g**, with excellent affinity for the cynomolgus macaque and rat BK B₁ receptor were discovered.

Benzimidazole-substituted (3-phenoxypropyl)amines as histamine H₃ receptor ligands

pp 5032–5036

Robert Aslanian*, Xiaohong Zhu, Henry A. Vaccaro, Neng-Yang Shih, John J. Piwinski, Shirley M. Williams, Robert E. West Jr.

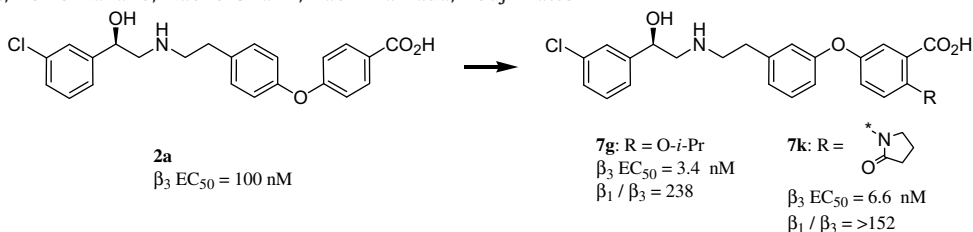


A series of non-imidazole histamine H₃ receptor antagonists based on the (3-phenoxypropyl)amine motif have been identified. Compound **8a** displays a good pharmacokinetic profile in the rat.

Discovery of novel series of benzoic acid derivatives containing biphenyl ether moiety as potent and selective human β₃-adrenergic receptor agonists: Part IV

pp 5037–5040

Yutaka Nakajima, Masashi Imanishi, Shinji Itou, Hitoshi Hamashima, Yasuyo Tomishima, Kenichi Washizuka, Minoru Sakurai, Shigeo Matsui, Emiko Imamura, Koji Ueshima, Takao Yamamoto, Nobuhiro Yamamoto, Hirofumi Ishikawa, Keiko Nakano, Naoko Unami, Kaori Hamada, Kouji Hattori*

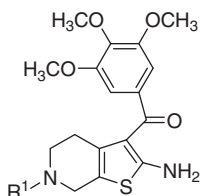


SAR study of phenoxybenzoic acid derivatives as β₃-AR agonist is described. Compounds **7g** and **7k**, exhibiting excellent β₃-AR activity and selectivity, were discovered.

Synthesis and biological evaluation of 2-amino-3-(3',4',5'-trimethoxybenzoyl)-6-substituted-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine derivatives as antimetabolic agents and inhibitors of tubulin polymerization

pp 5041–5045

Romeo Romagnoli*, Pier Giovanni Baraldi*, Maria Dora Carrion, Olga Cruz-Lopez, Carlota Lopez Cara, Manlio Tolomeo, Stefania Grimaudo, Antonietta Di Cristina, Maria Rosa Pipitone, Jan Balzarini, Sahar Kandil, Andrea Brancale, Taradas Sarkar, Ernest Hamel



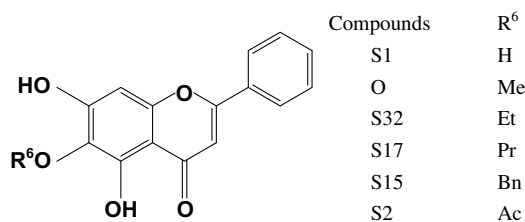
R¹ = alkyl, acyl, C(X)Yalkyl
with X = O or S and Y = O or NH.



Impacts of baicalein analogs with modification of the 6th position of A ring on the activity toward NF- κ B-, AP-1-, or CREB-mediated transcription

pp 5046–5049

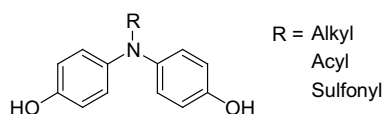
Sheng-Teng Huang, Yashang Lee, Elizabeth A. Gullen, Yung-Chi Cheng*

SAR and effect on the NF- κ B, AP-1, or CREB mediated transcription of baicalein analogs with modification of the 6th position of A ring.

Promising core structure for nuclear receptor ligands: Design and synthesis of novel estrogen receptor ligands based on diphenylamine skeleton

pp 5050–5053

Kiminori Ohta, Yuki Chiba, Takumi Ogawa, Yasuyuki Endo*

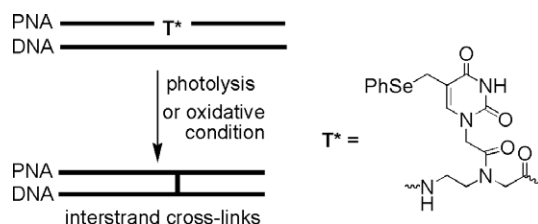


Novel diphenylamine-type estrogen receptor ligands were designed and synthesized, and showed moderate estrogenic activities. We propose that the diphenylamine skeleton may be a privileged core structure for various nuclear receptor ligands.

PNA/DNA interstrand cross-links from a modified PNA base upon photolysis or oxidative conditions

pp 5054–5057

Yongtae Kim, In Seok Hong*

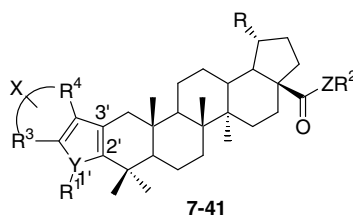


PNA/DNA interstrand cross-links were formed from modified PNA base upon photolysis or oxidative conditions.

Synthesis and cytotoxic activity of heterocyclic ring-substituted betulinic acid derivatives

pp 5058–5062

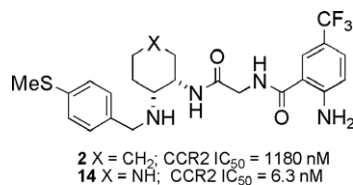
Vivek Kumar*, Nidhi Rani, Pawan Aggarwal, Vinod K. Sanna, Anu T. Singh, Manu Jaggi, Narendra Joshi, Pramod K. Sharma, Raghuvir Irchhaiya, Anand C. Burman

A new series of betulinic acid derivatives have been synthesized by introducing heterocyclic ring between C-2 and C-3 positions of betulinic acid. Compound **11** has showed IC₅₀ of 2.44, 2.5, and 2.7 μ g/ml on MIAPaCa, PA-1, and SW620 cancer cell lines, respectively. While compound **38** showed IC₅₀ of 0.67 μ g/ml on MIAPaCa cell line.

Synthesis and evaluation of *cis*-3,4-disubstituted piperidines as potent CC chemokine receptor 2 (CCR2) antagonists

pp 5063–5065

Robert J. Cherney*, David J. Nelson, Yvonne C. Lo, Gengjie Yang, Peggy A. Scherle, Heather Jezak, Kimberly A. Solomon, Percy H. Carter, Carl P. Decicco

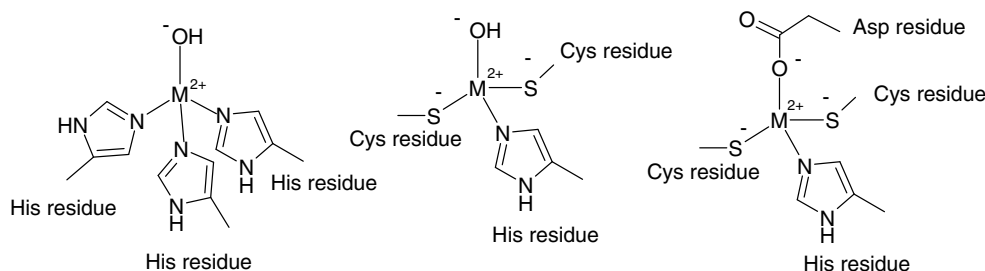


A series of *cis*-3,4-disubstituted piperidines was synthesized and evaluated as CC chemokine receptor 2 (CCR2) antagonists. Several derivatives have excellent binding, functional antagonism, and selectivity.

Carbonic anhydrase inhibitors: Inhibition of the β -class enzymes from the fungal pathogens *Candida albicans* and *Cryptococcus neoformans* with simple anions

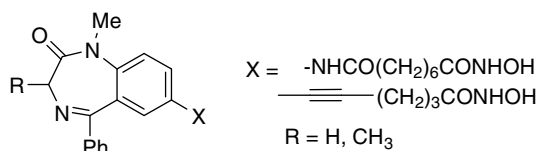
pp 5066–5070

Alessio Innocenti, Fritz A. Mühlischlegel, Rebecca A. Hall, Clemens Steegborn, Andrea Scozzafava, Claudiu T. Supuran*

**Design, synthesis and preliminary biological evaluation of new hydroxamate histone deacetylase inhibitors as potential antileukemic agents**

pp 5071–5074

L. Guandalini, C. Cellai, A. Laurenzana, S. Scapecchi, F. Paoletti*, M. N. Romanelli*

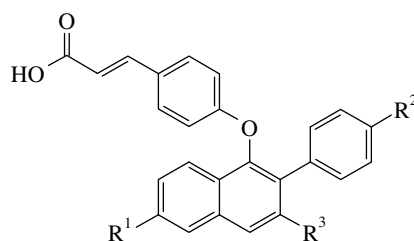


The design and evaluation of new HDAC-inhibitors carrying a 5-phenyl-benzo[e][1,4]diazepin-2-one nucleus are reported.

Synthesis of 3-alkyl naphthalenes as novel estrogen receptor ligands

pp 5075–5077

Jing Fang*, Adwoa Akwabi-Ameyaw, Jonathan E. Britton, Subba R. Katamreddy, Frank Navas III, Aaron B. Miller, Shawn P. Williams, David W. Gray, Lisa A. Orband-Miller, Jean Shearin, Dennis Heyer

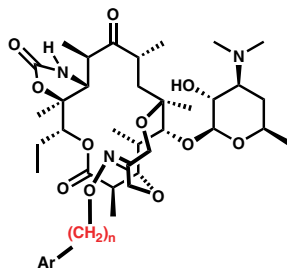


A novel series of 3-alkyl naphthalenes and their activity against estrogen receptor are reported.

Design, synthesis, and antibacterial activities of novel 3,6-bicyclopide oximes: Length optimization and zero carbon linker oximes

pp 5078–5082

Datong Tang*, Yonghua Gai, Alexander Polemeropoulos, Zhigang Chen, Zhe Wang, Yat Sun Or

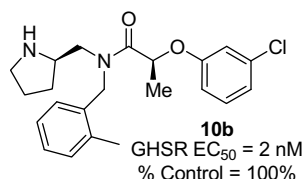


We designed and synthesized a series of novel 3,6-bicyclopide oximes, possessing linkers of varying lengths to the secondary binding site. The *E* isomers exhibited excellent antibacterial profiles against a broad spectrum of resistant pathogens.

Discovery and optimization of (*R*)-prolinol-derived agonists of the Growth Hormone Secretagogue receptor (GHSR)

pp 5083–5086

Weixu Zhai, Neil Flynn, Daniel A. Longhi, Joseph A. Tino, Brian J. Murphy, Dorothy Slusarchyk, David A. Gordon, Anna Pendri, Shuhao Shi, Robert Stoffel, Baoqing Ma, Michael J. Sofia, Samuel W. Gerritz*



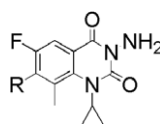
The discovery of single-digit nanomolar full agonists (e.g., **10b**) of the Growth Hormone Secretagogue receptor (GHSR) is reported, starting with a micromolar screening hit identified from a GPCR-targeted solid-phase library. The 'library pedigree' of this series greatly facilitated its rapid optimization.



Synthesis and antibacterial activity of the C-7 side chain of 3-aminoquinazolinones

pp 5087–5090

Kim M. Hutchings*, Tuan P. Tran, Edmund L. Ellsworth, Brian M. Watson, Joseph P. Sanchez, H. D. Hollis Showalter, Michael A. Stier, Martin Shapiro, E. Themis Joannides, Michael Huband, Dai Q. Nguyen, Samarendra Maiti, Tingsheng Li, Jyoti Tailor, George Thomas, Chan Ha, Rajeshwar Singh

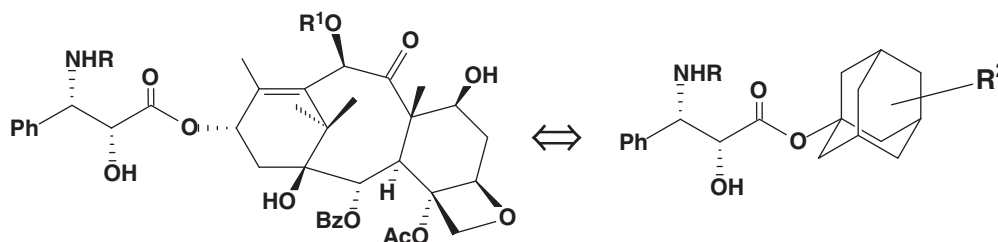


The synthesis and structure–activity relationship of a novel series of bacterial topoisomerase (3-aminoquinazolinones) inhibitors is described.

Design, synthesis, and bioactivity of putative tubulin ligands with adamantane core

pp 5091–5094

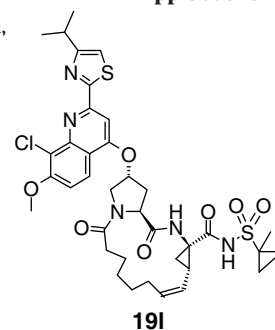
Olga N. Zefirova*, Evgeniya V. Nurieva, Heiko Lemcke, Andrei A. Ivanov, Dmitrii V. Shishov, Dieter G. Weiss, Sergei A. Kuznetsov, Nikolay S. Zefirov



Discovery of novel potent and selective dipeptide hepatitis C virus NS3/4A serine protease inhibitors

pp 5095–5100

Pierre Raboisson*, Tse-I Lin, Herman de Kock, Sandrine Vendeville, Wim Van de Vreken, David McGowan, Abdellah Tahri, Lili Hu, Oliver Lenz, Frederic Delouvroy, Dominique Surleraux, Piet Wigerinck, Magnus Nilsson, Åsa Rosenquist, Bertil Samuelsson, Kenneth Simmen

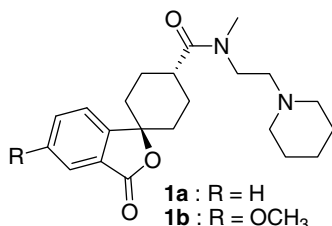


Lead Optimization performed on P3-truncated proline-containing macrocycles led to the identification selective and orally bioavailable dipeptide hepatitis C virus NS3/4A protease inhibitors, which has features attractive for further preclinical development.

Synthesis and evaluation of a spiro-isobenzofuranone class of histamine H₃ receptor inverse agonists

pp 5101–5106

Makoto Jitsuoka, Daisuke Tsukahara, Sayaka Ito, Takeshi Tanaka, Norihiro Takenaga, Shigeru Tokita, Nagaaki Sato*

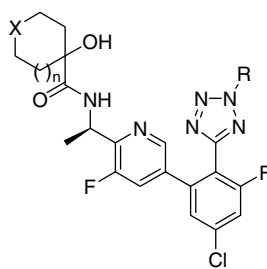


Spiro-isobenzofuranones derivatives **1a** and **1b** were discovered as potent and selective H₃ inverse agonists.

Bradykinin B₁ receptor antagonists: An α -hydroxy amide with an improved metabolism profile

pp 5107–5110

Scott D. Kuduk*, Ronald K. Chang, Robert M. DiPardo, Christina N. Di Marco, Kathy L. Murphy, Richard W. Ransom, Duane R. Reiss, Cuyue Tang, Thomayant Prueksaritanont, Douglas J. Pettibone, Mark G. Bock

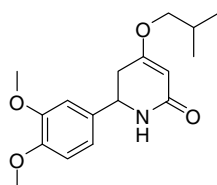


The design and synthesis of human bradykinin B₁ antagonists featuring *N*-methyl tetrazole and α -hydroxy amide moieties are disclosed.

Novel hypoglycemic dihydropyridones serendipitously discovered from O- versus C-alkylation in the synthesis of VMAT2 antagonists

pp 5111–5114

Yuli Xie, Anthony Raffo, Masanori Ichise, Shixian Deng, Paul E. Harris, Donald W. Landry*



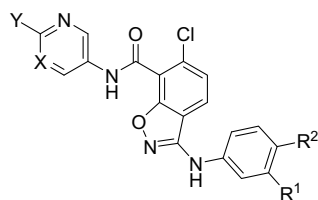
Compound **8**
45% decrease of AUC IPGTT at 2mg/kg

A novel hypoglycemic dihydropyridone was serendipitously discovered in the course of synthesizing VMAT2 antagonists.

Discovery of amido-benzisoxazoles as potent c-Kit inhibitors

pp 5115–5117

Roxanne K. Kunz*, Shannon Rumpf, Ning Chen, Dawei Zhang, Andrew S. Tasker, Roland Bürli, Randall Hungate, Violeta Yu, Yen Nguyen, Douglas A. Whittington, Kristin L. Meagher, Matthew Plant, Yanyan Tudor, Michael Schrag, Yang Xu, Gordon Y. Ng, Essa Hu

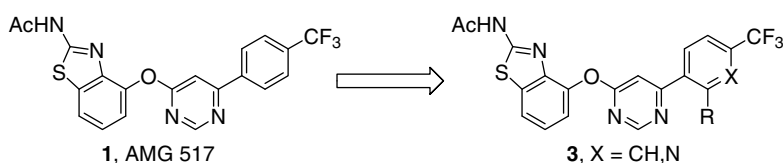


A novel series of 7-amido-3-(arylamino)-benzisoxazoles are herein disclosed as potent inhibitors of the receptor tyrosine kinase c-Kit, with IC₅₀ values in the nanomolar range.

Substituted aryl pyrimidines as potent and soluble TRPV1 antagonists

pp 5118–5122

Markian M. Stec*, Yunxin Bo, Partha P. Chakrabarti, Lillian Liao, Mqhele Ncube, Nuria Tamayo, Rami Tamir, Narendra R. Gavva, James J. S. Treanor, Mark H. Norman

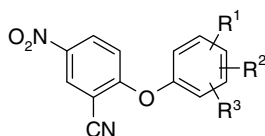


Analogues with various substituents at the R region of **3** were prepared to improve the solubility while maintaining the potent TRPV1 activity of clinical candidate AMG 517.

Synthesis and anti-CVB 3 evaluation of substituted 5-nitro-2-phenoxybenzonitriles

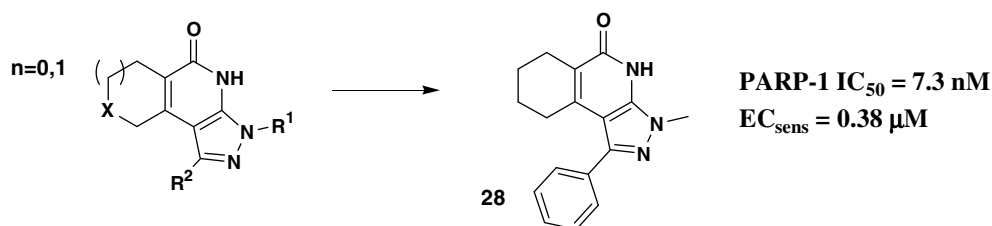
pp 5123–5125

Gerhard Pürstinger*, Armando M. De Palma, Günther Zimmerhofer, Simone Huber, Sophie Ladurner, Johan Neyts

**Identification of ring-fused pyrazolo pyridin-2-ones as novel poly(ADP-ribose)polymerase-1 inhibitors**

pp 5126–5129

Wilna J. Moree*, Phyllis Goldman, Anthony J. Demaggio, Erik Christenson, Dan Herendeen, John Eksterowicz, Edward A. Kesicki, David L. McElligott, Graham Beaton

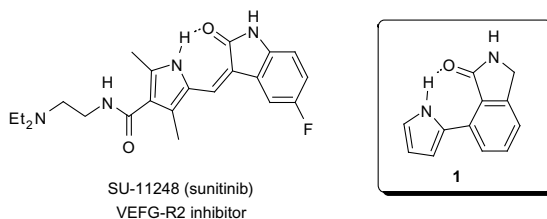


Potent PARP-1 inhibitors were identified in a tricyclic pyrazolo pyridine-2-one series with nanomolar binding affinity and submicromolar activity in a cell-based chemosensitization assay.

7-[1*H*-Indol-2-yl]-2,3-dihydro-isoindol-1-ones as dual Aurora-A/VEGF-R2 kinase inhibitors: Design, synthesis, and biological activity

pp 5130–5133

Terry V. Hughes*, Stuart L. Emanuel, Harold R. O'Grady, Peter J. Connolly, Catherine Rugg, Angel R. Fuentes-Pesquera, Prabha Karnachi, Richard Alexander, Steven A. Middleton



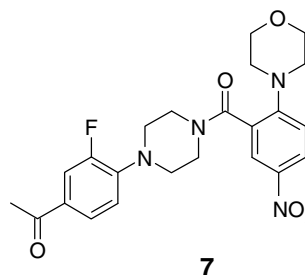
The design of a new kinase inhibitor scaffold **1** based on known VEGF-R2 kinase inhibitors is described. The series designed to be inhibitors of VEGF-R2 kinase were synthesized and found to potently inhibit VEGF-R2 and Aurora-A kinases. The structure-based design, synthesis, initial SAR, and in vivo efficacy of the series are discussed.

Discovery of benzoylpiperazines as a novel class of potent and selective GlyT1 inhibitors

pp 5134–5139

Emmanuel Pinard*, Daniela Alberati, Edilio Borroni, Holger Fischer, Dominik Hainzl, Synèse Jolidon, Jean-Luc Moreau, Robert Narquizian, Matthias Nettekoven, Roger D. Norcross, Henri Stalder, Andrew W. Thomas

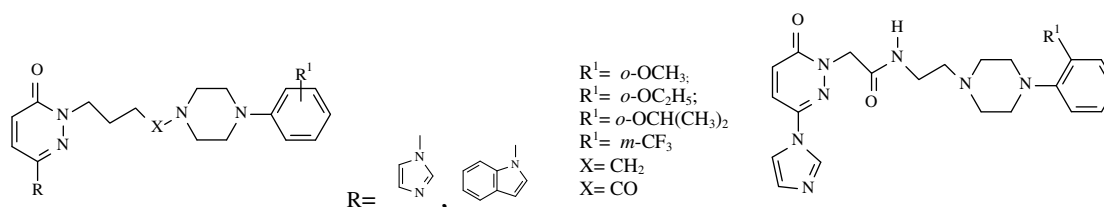
Screening of the Roche compound library led to the identification of the benzoylpiperazine **7** as a structurally novel GlyT1 inhibitor. The SAR which was developed in this series resulted in the discovery of highly potent compounds displaying excellent selectivity against the GlyT2 isoform, drug-like properties, and in vivo efficacy after oral administration.



Synthesis and biological affinity of new imidazo- and indol-arylpiperazine derivatives: Further validation of a pharmacophore model for α_1 -adrenoceptor antagonists

pp 5140–5145

Giovannella Strappaghetti*, Luciano Mastrini, Antonio Lucacchini, Gino Giannaccini, Laura Betti, Laura Fabbrini

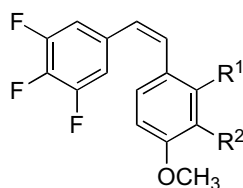


In continuing our search for selective α_1 -AR antagonists, new alkoxyarylpiperazinylalkylpyridazinone derivatives were designed and synthesized. The new compounds were tested for their affinity toward α_1 -AR, α_2 -AR, and toward 5-HT_{1A} receptors. The ability of these compounds to inhibit the serotonin transporters (SERT) was also determined.

Design, synthesis, biochemical, and biological evaluation of nitrogen-containing trifluoro structural modifications of combretastatin A-4

pp 5146–5149

John J. Hall, Madhavi Sriram, Tracy E. Strecker, Justin K. Tidmore, Christopher J. Jelinek, G. D. Kishore Kumar, Mallinath B. Hadimani, George R. Pettit, David J. Chaplin, Mary Lynn Trawick, Kevin G. Pinney*

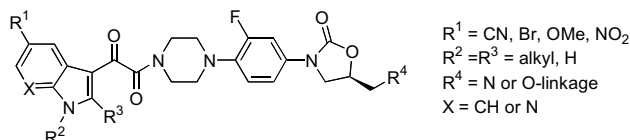


A series of nitrogen-containing fluoro combretastatin structural modifications have been synthesized and evaluated for potential anti-cancer activity.



Novel and potent oxazolidinone antibacterials featuring 3-indolylglyoxamide substituents**pp 5150–5155**

Mohamed Takhi *, Gurpreet Singh, C. Murugan, Nirvesh Thaplyyal, Soma Maitra, K. M. Bhaskarreddy, P. V. S. Amarnath, Arundhuti Mallik, T. Harisudan, Ravi Kumar Trivedi, K. Sreenivas, N. Selvakumar, Javed Iqbal



The synthesis and antibacterial activity of novel oxazolidinones possessing indolylglyoxamide moiety on piperazine scaffold have been disclosed.

OTHER CONTENTS**Erratum****p 5156****Summary of instructions to authors****p I**

*Corresponding author

 Supplementary data available via ScienceDirect

COVER

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

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