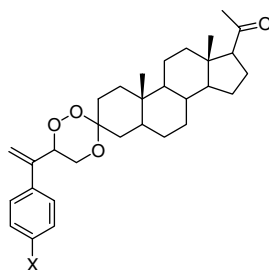


Contents

ARTICLES

- Orally active antimalarials: Synthesis and bioevaluation of a new series of steroid-based 1,2,4-trioxanes against multi-drug resistant malaria in mice** pp 4097–4101

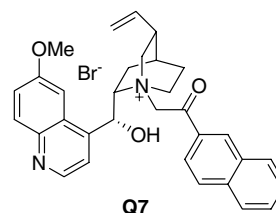
Chandan Singh,* Upasana Sharma, Gunjan Saxena and Sunil. K. Puri



- Synthesis and evaluation of amphiphilic cationic quinine-derived for antibacterial activity against methicillin-resistant *Staphylococcus aureus*** pp 4102–4106

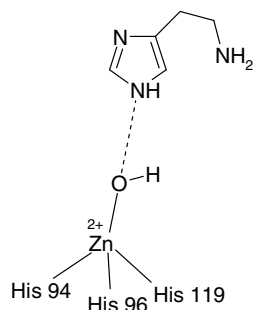
Jian Lv, Yunbo Qian, Tingting Liu and Yongmei Wang*

Several representative amphiphilic cationic quinine-derivatives have been synthesized and evaluated against methicillin-resistant *Staphylococcus aureus*. This is the first reported antibacterial activity of this class of compounds. In vitro the minimal inhibitory concentration values of the best compound **Q7** ranged from 0.4 to 1.6 $\mu\text{g/mL}$ ($\text{MBC} < 3.2 \mu\text{g/mL}$).



- Carbonic anhydrase activators: Activation of the human isoforms VII (cytosolic) and XIV (transmembrane) with amino acids and amines** pp 4107–4112

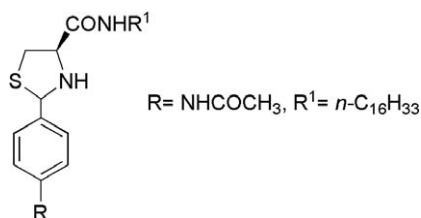
Daniela Vullo, Alessio Innocenti, Isao Nishimori, Andrea Scozzafava, Kai Kaila and Claudiu T. Supuran*



Synthesis and antiproliferative activity of thiazolidine analogs for melanoma

pp 4113–4117

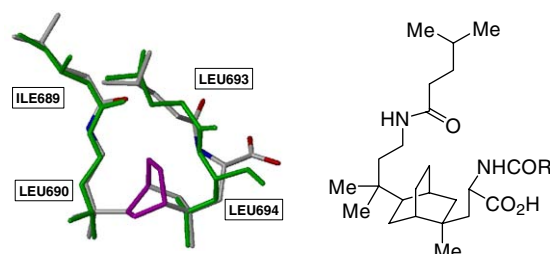
Wei Li, Yan Lu, Zhao Wang, James T. Dalton and Duane D. Miller*

**Bicyclo[2.2.2]octanes: Close structural mimics of the nuclear receptor-binding motif of steroid receptor coactivators**

pp 4118–4122

Hai-Bing Zhou, Margaret L. Collins, Jillian R. Gunther, John S. Comninos and John A. Katzenellenbogen*

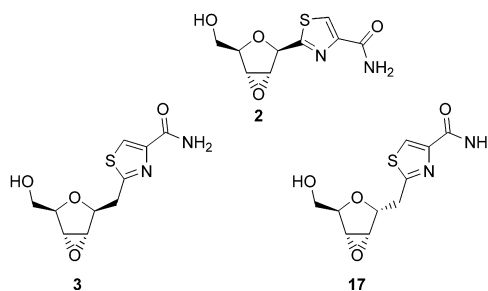
The design, synthesis, and initial inhibitory activity of a series of bicyclo [2.2.2]octanes that are close structural mimics of the two key leucine residues of this SRC sequence as bound in the hydrophobic groove of the estrogen receptor are reported. These bicyclic systems block the NR–SRC interaction with modest potency.

**Synthesis and antitumour activity of new tiazofurin analogues bearing a 2,3-anhydro functionality in the furanose ring**

pp 4123–4127

Mirjana Popsavin,* Saša Spaić, Miloš Svirčev, Vesna Kojić, Gordana Bogdanović and Velimir Popsavin

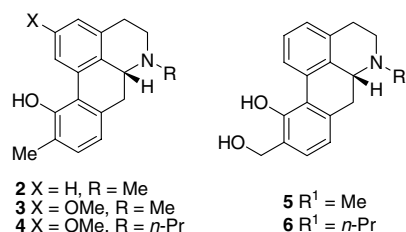
Novel tiazofurin derivatives, 2',3'-anhydro-tiazofurin (**2**) and the corresponding β -(**3**) and α -(**17**) homo-C-nucleosides, have been synthesized and evaluated for their in vitro antitumour activity.

**R-(–)-N-alkyl-11-hydroxy-10-hydroxymethyl- and 10-methyl-aporphines as 5-HT_{1A} receptor ligands**

pp 4128–4130

Yu-Gui Si, Matthew P. Gardner, Frank I. Tarazi, Ross J. Baldessarini and John L. Neumeyer*

Several *N*-substituted-11-hydroxy-10-hydroxymethyl- and 11-hydroxy-10-methylaporphines were synthesized and their binding affinities at dopamine D₁ and D₂ receptors and serotonin 5-HT_{1A} and 5-HT_{2A} receptors in rat forebrain tissue were evaluated. Tested compounds displayed moderate to high affinity to 5-HT_{1A} receptors but low affinity to D₁ and D₂ receptors.

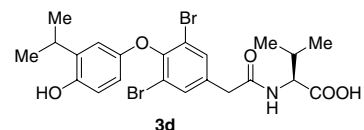


Thyroid receptor ligands. Part 8: Thyromimetics derived from N-acylated- α -amino acid derivatives displaying modulated pharmacological selectivity compared with KB-141

pp 4131–4134

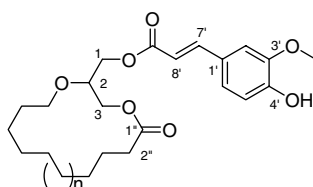
Neeraj Garg, Yi-Lin Li, Ana Maria Garcia Collazo, Chris Litten, Denis E. Ryono, Minsheng Zhang, Yolanda Caringal, Robert P. Brigance, Wei Meng, William N. Washburn, Peter Agback, Karin Mellström, Stefan Rehnmark, Mahmoud Rahimi-Ghadim, Thomas Norin, Marlena Grynfarb, Johnny Sandberg, Gary Grover and Johan Malm*

Based on the scaffold of the pharmacologically selective KB-141 (**2a**), N-acylated- α -amino acid derivatives were synthesized and tested in a TR-binding assay and a reporter cell assay. On the basis of TR β_1 -isoform selectivity and affinity to the reporter cell assay, **3d** was selected for further studies in the cholesterol-fed rat model. In this model **3d** revealed an improved therapeutic window between cholesterol and TSH lowering but decreased margins versus tachycardia compared with **2a**.

**Natural feruloyl monoglyceride macrocycles as protecting factors against free-radical damage of lipidic membranes**

pp 4135–4139

Brigida D'Abrosca, Antonio Fiorentino,* Severina Pacifico, Giuseppe Cefarelli, Piera Uzzo, Marianna Letizia and Pietro Monaco



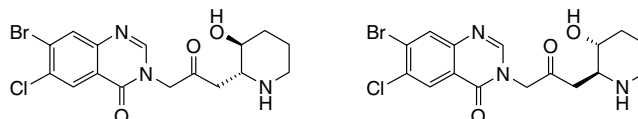
n = 10 - 21

Nine new antioxidant feruloyl monoglyceride (MGs) macrocycles have been isolated from the leaves of *Carex distachya*.

(2R,3S)-(+)- and (2S,3R)-(-)-Halofuginone lactate: Synthesis, absolute configuration, and activity against *Cryptosporidium parvum*

pp 4140–4143

Michael R. Linder, Anja R. Heckeroth, Michael Najdrowski, Arwid Dausgies, Dieter Schollmeyer and Christian Miculka*

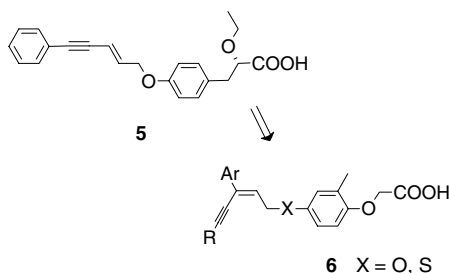


Preparation of trans-enantiomers of Halofuginone, determination of absolute configuration, activity of enantiomers against *C. parvum* in vitro and acute toxicity in vivo are reported.

**Novel selective PPAR δ agonists: Optimization of activity by modification of alkynylallylic moiety**

pp 4144–4149

Miroslav Havranek,* Per Sauerberg, John P. Mogensen, Pavel Kratina, Claus B. Jeppesen, Ingrid Pettersson and Pavel Pihera



6 X = O, S

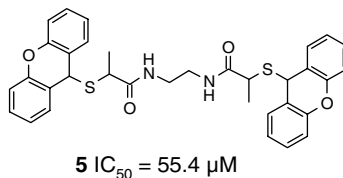
Selective PPAR δ agonists, **6**, were obtained by SAR study of structural changes of the PPARpan agonist **5**.



A novel arginine methyltransferase inhibitor with cellular activity

pp 4150–4153

Astrid Spannhoff, Rospita Machmur, Ralf Heinke, Patrick Trojer, Ingo Bauer, Gerald Brosch, Roland Schüle, Wolfgang Hanefeld, Wolfgang Sippl and Manfred Jung*

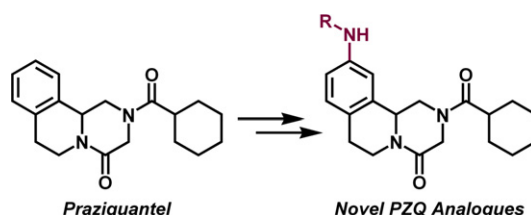


A new cell permeable arginine methyltransferase inhibitor by fragment based virtual screening.

**Praziquantel derivatives I: Modification of the aromatic ring**

pp 4154–4157

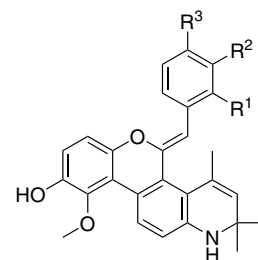
Fiona Ronketti, A. Venkata Ramana, Xia Chao-Ming, Livia Pica-Mattoccia, Donato Cioli and Matthew H. Todd*

**5(Z)-Benzylidene-1,2-dihydro-9-hydroxy-10-methoxy-2,2,4-trimethyl-5H-1-aza-6-oxa-chrysenes as non-steroidal glucocorticoid receptor modulators**

pp 4158–4162

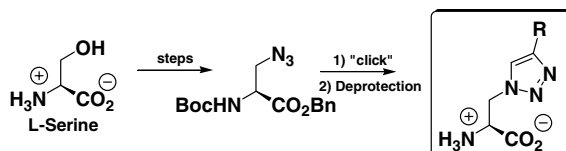
Robert J. Ardecky, Andrew R. Hudson,* Dean P. Phillips, John S. Tyhonas, Charlotte Deckhut, Thomas L. Lau, Yongkai Li, Esther A. Martinborough, Steven L. Roach, Robert I. Higuchi, Francisco J. Lopez, Keith B. Marschke, Jeffrey N. Miner, Donald S. Karanewsky, Andrés Negro-Vilar and Lin Zhi

A series of 5-benzylidene-1,2-dihydro-2,2,4-trimethyl-5H-1-aza-6-oxa-chrysenes were synthesized and profiled for their ability to act as selective glucocorticoid receptor modulators (SGRMs). The synthesis and structure–activity relationships for this series of compounds are presented.

**Design, synthesis, and biological activity of novel triazole amino acids used to probe binding interactions between ligand and neutral amino acid transport protein SN1**

pp 4163–4166

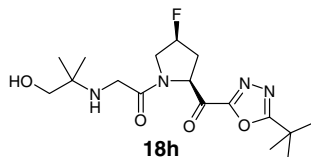
Mariusz Gajewski, Ben Seaver and C. Sean Esslinger*



Synthesis, SAR, and X-ray structure of novel potent DPPIV inhibitors: Oxadiazolyl ketones

pp 4167–4172

Ki Dong Koo, Min Jung Kim, Sungsub Kim, Kyoung-Hee Kim, Sang Yong Hong, Gwong-Cheung Hur, Hyeon Joo Yim, Geun Tae Kim, Hee Oon Han, O Hwan Kwon, Tae Sik Kwon, Jong Sung Koh* and Chang-Seok Lee*



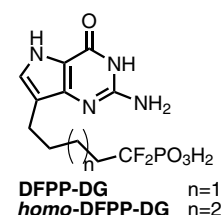
Compound **18h** showed excellent inhibitory activity against DPPIV, good selectivity over DPPII and DPPVIII, and showed good PK, PD profile.

Synthesis and biological evaluation of 9-deazaguanine derivatives connected by a linker to difluoromethylene phosphonic acid as multi-substrate analogue inhibitors of PNP

pp 4173–4177

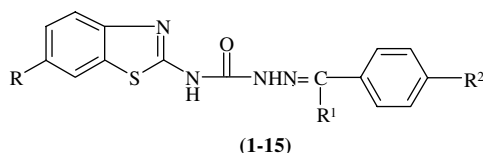
Sadao Hikishima, Mariko Hashimoto, Lucyna Magnowska, Agnieszka Bzowska and Tsutomu Yokomatsu*

DFPP-DG is a very potent PNP inhibitor with apparent inhibition constants of 4.4 and 8.1 nM versus calf-spleen and human erythrocyte PNPs, respectively. One of its analogues, **homo-DFPP-DG**, is even more potent versus human enzyme, with an apparent inhibition constant of 5.3 nM.

**Synthesis of benzothiazole semicarbazones as novel anticonvulsants—The role of hydrophobic domain**

pp 4178–4182

Nadeem Siddiqui,* Arpana Rana, Suroor A. Khan, Mashooq A. Bhat and Syed E. Haque

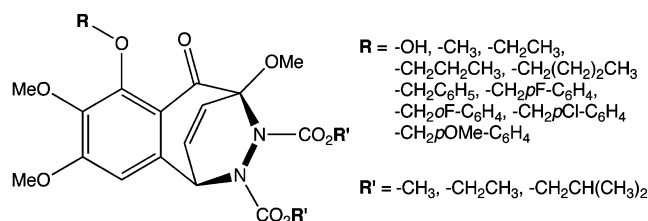


A series of 1,3-benzothiazol-2-yl semicarbazones (**1–15**) were prepared in satisfactory yield and evaluated for their anticonvulsant, neurotoxicity and other toxicity studies. All the synthesized compounds were in good agreement with elemental and spectral data. Majority of the compounds were active in MES screen. Selected compounds were checked for their lipophilic character.

Synthesis and in vitro protozoocidal activity of diazabicyclic benzotropolone derivatives

pp 4183–4186

Alexander Khrizman, Jason S. Moulthrop, Susan Little, Hayley Wharton, Vanessa Yardley and Guillermo Moyna*



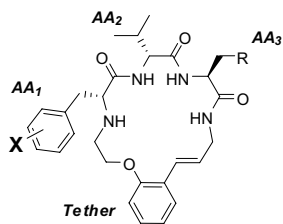
The synthesis and protozoocidal evaluation of a series of endocyclic hydrazines based on benzotropolone ethers is described.



Potent macrocyclic antagonists to the motilin receptor presenting novel unnatural amino acids

pp 4187–4190

Eric Marsault,* Kamel Benakli, Sylvie Beaubien, Carl Saint-Louis, Robert Déziel and Graeme Fraser

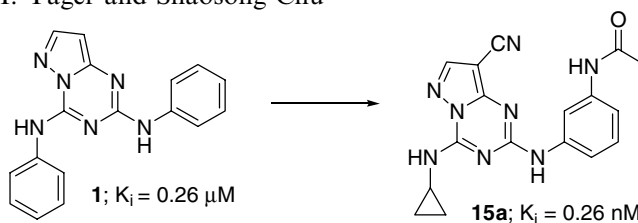


New macrocyclic peptidomimetics bearing novel unnatural amino acids are reported as potent motilin antagonist.

Structure-based design, synthesis, and study of pyrazolo[1,5-a][1,3,5]triazine derivatives as potent inhibitors of protein kinase CK2

pp 4191–4195

Zhe Nie,* Carin Perretta, Philip Erickson, Stephen Margosiak, Robert Almasy, Jia Lu, April Averill, Kraig M. Yager and Shaosong Chu*



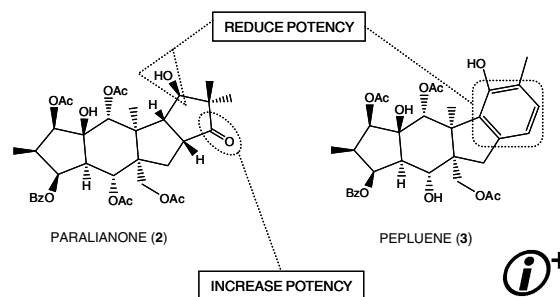
Structure-guided modifications to a series of pyrazolo[1,5-a][1,3,5]triazine derivatives provided pM inhibitors of protein kinase CK2 with low μM cytotoxic activity in cell-based assays with prostate and colon cancer cell lines.

Paraliane and pepluane diterpenes as anti-inflammatory agents: First insights in structure–activity relationships

pp 4196–4200

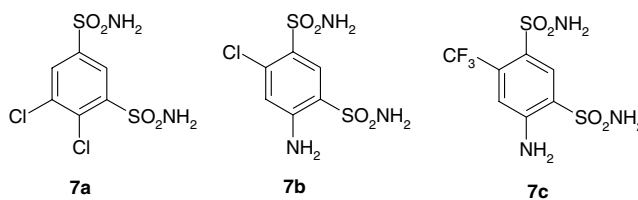
Elisa Barile, Ernesto Fattorusso, Armando Ialenti, Angela Ianaro and Virginia Lanzotti*

The isolation and structural characterization of paraliane and pepluane diterpenes are described. Preliminary pharmacological tests let us to draw structure–activity relationships on this incoming class of promising anti-inflammatory agents.

**Carbonic anhydrase inhibitors: Inhibition of human, bacterial, and archaeal isozymes with benzene-1,3-disulfonamides—Solution and crystallographic studies**

pp 4201–4207

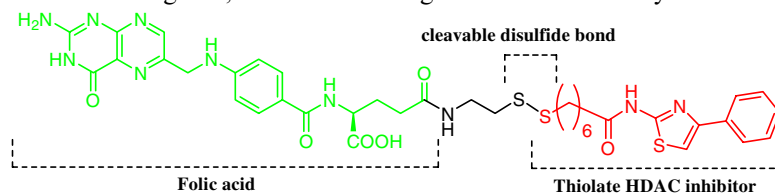
Vincenzo Alterio, Giuseppina De Simone,* Simona Maria Monti, Andrea Scozzafava and Claudiu T. Supuran*



Design, synthesis, and biological activity of folate receptor-targeted prodrugs of thiolate histone deacetylase inhibitors

pp 4208–4212

Takayoshi Suzuki,* Shinya Hisakawa, Yukihiro Itoh, Nobuaki Suzuki, Katsumasa Takahashi, Masatoshi Kawahata, Kentaro Yamaguchi, Hidehiko Nakagawa and Naoki Miyata*

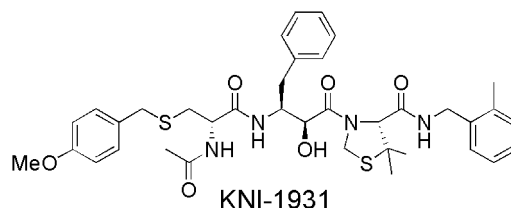


Aiming to develop selective anticancer drugs, we designed and synthesized three disulfides bearing a folate moiety as candidate folate receptor (FR)-targeted prodrugs of thiolate histone deacetylase inhibitors. One of the folate conjugates showed growth-inhibitory activity toward folate receptor-positive MCF-7 breast cancer cells.

Synthesis and antiviral property of allophenylnorstatine-based HIV protease inhibitors incorporating D-cysteine derivatives as P₂/P₃ moieties

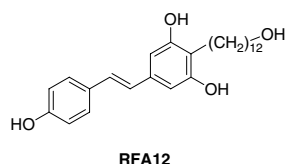
pp 4213–4217

Ei'ichi Ami, Koichiro Nakahara, Akihiko Sato, Jeffrey-Tri Nguyen, Koushi Hidaka, Yoshio Hamada, Shingo Nakatani, Tooru Kimura, Yoshio Hayashi and Yoshiaki Kiso*

**Dual bioactivity of resveratrol fatty alcohols: Differentiation of neural stem cells and modulation of neuroinflammation**

pp 4218–4222

Frédérique Hauss, Jiawei Liu, Alessandro Michelucci, Djalil Coowar, Eleonora Morga, Paul Heuschling and Bang Luu*

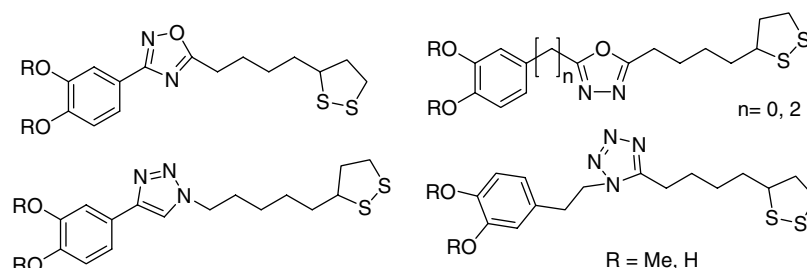


Synthesis of resveratrol fatty alcohols (RFAs), a new class of molecules acting simultaneously on neuroprotection and neuroregeneration is described. RFAs represent an innovative approach for the treatment of different neuropathies.

Design and synthesis of 1,2-dithiolane derivatives and evaluation of their neuroprotective activity

pp 4223–4227

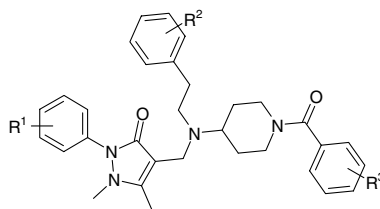
Maria Koufaki,* Christina Kiziridi, Faidra Nikoloudaki and Michael N. Alexis



Pyrazolone methylamino piperidine derivatives as novel CCR3 antagonists

pp 4228–4231

Cécile Pégurier,* Philippe Collart, Pierre Danhaive, Sabine Defays, Michel Gillard, Frédéric Gilson, Thierry Kogej, Patrick Pasau, Nathalie Van Houtvin, Marc Van Thuyne and BerendJan van Keulen

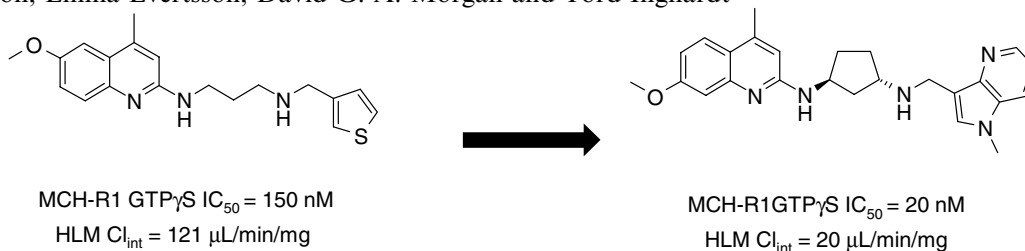


The discovery and optimization of a novel class of potent CCR3 antagonists is described. Details of synthesis and SAR are given.

Discovery of cyclopentane- and cyclohexane-*trans*-1,3-diamines as potent melanin-concentrating hormone receptor 1 antagonists

pp 4232–4241

Fabrizio Giordanetto,* Olle Karlsson, Jan Lindberg, Lars-Olof Larsson, Anna Linusson, Emma Evertsson, David G. A. Morgan and Tord Inghardt*

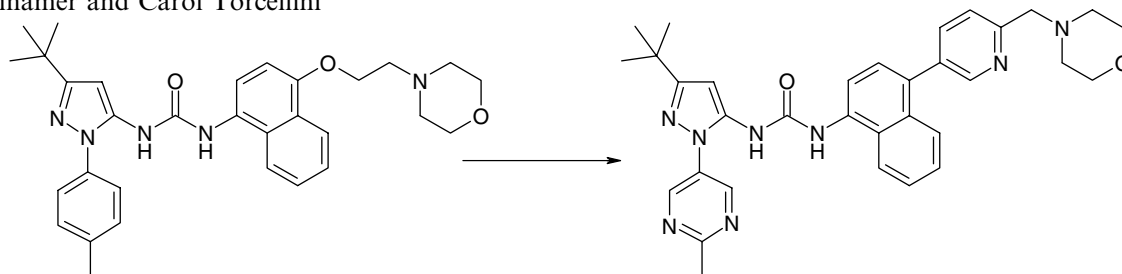


The optimization of a HTS-derived lead compound into a potent and metabolically stable MCH-R1 antagonist is presented.

New modifications to the area of pyrazole-naphthyl urea based p38 MAP kinase inhibitors that bind to the adenine/ATP site

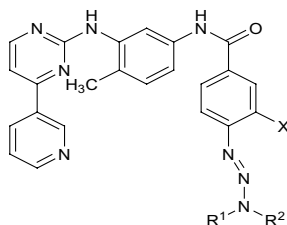
pp 4242–4247

Neil Moss,* Steffen Breitfelder, Raj Betageri, Pier F. Cirillo, Tazmeen Fadra, Eugene R. Hickey, Thomas Kirrane, Rachel R. Kroe, Jeffrey Madwed, Richard M. Nelson, Christopher A. Pargellis, Kevin C. Qian, John Regan, Alan Swinamer and Carol Torcellini

**Optimization of novel combi-molecules: Identification of balanced and mixed bcr-abl/DNA targeting properties**

pp 4248–4253

Zakaria Rachid, Athanasia Katsoulas, Christopher Williams, Anne-Laure Larroque, James McNamee and Bertrand J. Jean-Claude*

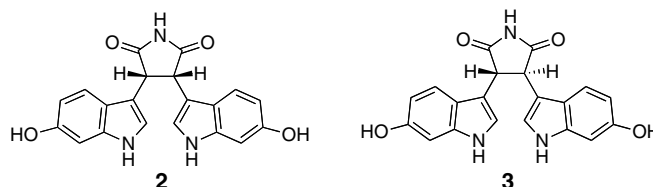


We designed and synthesized an optimized combi-molecule that induced approximately twofold stronger abl TK inhibitory activity than Gleevec and high levels of DNA damage in chronic myelogenous leukemic cells (CML).

Synthesis, determination of stereochemistry, and evaluation of new bisindole alkaloids from the myxomycete *Arcyria ferruginea*: An approach for Wnt signal inhibitor

pp 4254–4257

Kouken Kaniwa, Midori A. Arai, Xiaofan Li and Masami Ishibashi*



To determine the stereochemistry of dihydroarcyriarubin C (**1**), *cis*- (**2**) and *trans*-dihydroarcyriarubin C (**3**) were synthesized. Comparison of their NMR characteristics allowed the *trans* stereochemistry of **1** to be confirmed. The compound **2** showed moderate inhibition of Wnt signal transcription.

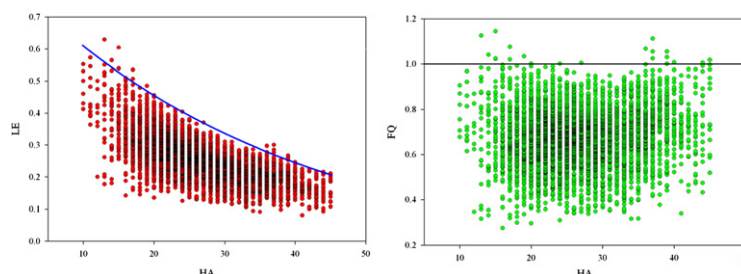


The role of molecular size in ligand efficiency

pp 4258–4261

Charles H. Reynolds,* Scott D. Bembenek and Brett A. Tounge

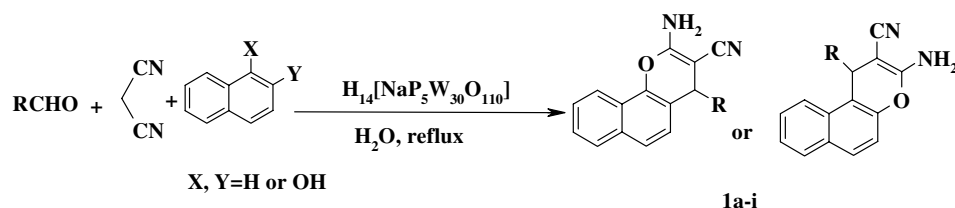
Average and maximal ligand efficiencies decrease as ligand size increases. We propose a method for scaling ligand efficiencies that removes this dependence on molecular size.



Aqua mediated synthesis of substituted 2-amino-4H-chromenes catalyzed by green and reusable Preyssler heteropolyacid

pp 4262–4265

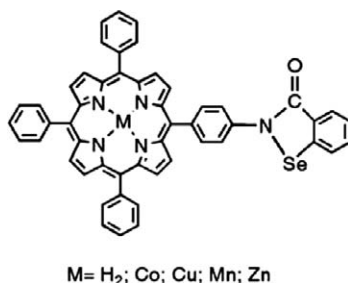
Majid M. Heravi,* Khadijeh Bakhtiari, Vahideh Zadsirjan, Fatemeh F. Bamoharram and Omid M. Heravi



Novel ebselen–porphyrin conjugates: Synthesis and nucleic acid interaction study

pp 4266–4270

Zhi Xue, An-Xin Hou,* Daniel Wei-Jing Kwong and Wai-Kwok Wong*

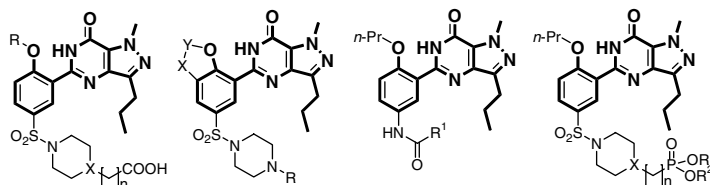


The synthesis and DNA interaction of novel ebselen–porphyrin conjugates is reported.

3D-QSAR studies on sildenafil analogues, selective phosphodiesterase 5 inhibitors

pp 4271–4274

Jakyung Yoo, Khac-Minh Thai, Dae-Kee Kim, Ju Young Lee and Hyun-Ju Park*

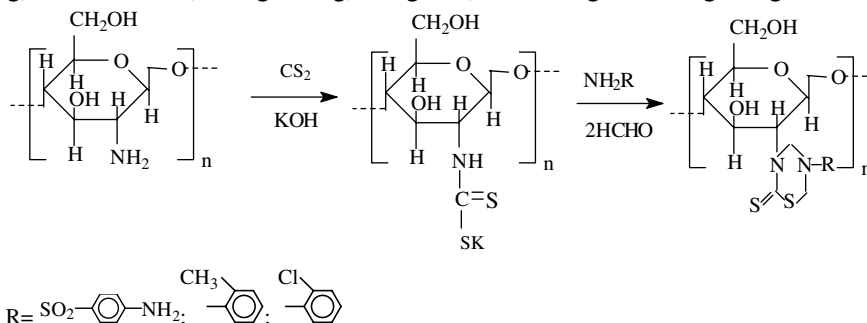


A series of sildenafil analogues have been prepared and their in vitro PDE5 inhibitory activities were evaluated. Herein, the results of 3D-QSAR (CoMFA and CoMSIA) analyses on these inhibitors are reported.

**Preparation of 1,3,5-thiadiazine-2-thione derivatives of chitosan and their potential antioxidant activity in vitro**

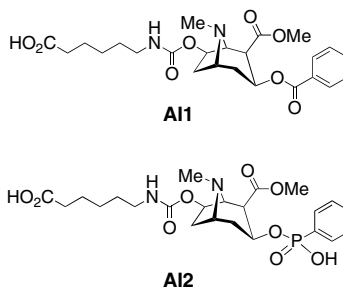
pp 4275–4279

Xia Ji, Zhimei Zhong, Xiaolin Chen, Rong Xing, Song Liu, Lin Wang and Pengcheng Li*

**Positional linker effects in haptens for cocaine immunopharmacotherapy**

pp 4280–4283

Akira Ino, Tobin J. Dickerson* and Kim D. Janda*

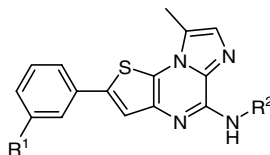


The synthesis of two new cocaine haptens designed to bury the drug deep within an antibody combining site are reported.

Synthesis and structure–activity relationship of imidazo(1,2-a)thieno(3,2-e)pyrazines as IKK-β inhibitors

pp 4284–4289

Makonen Belema,* Amy Bunker, Van N. Nguyen, Francis Beaulieu, Carl Ouellet, Yuping Qiu, Yunhui Zhang, Alain Martel, James R. Burke, Kim W. McIntyre, Mark A. Pattoli, Connie Dalosio, Kathleen M. Gillooly, Wendy J. Clarke, Patrick J. Brassil, F. Chris Zusi and Dolatrai M. Vyas

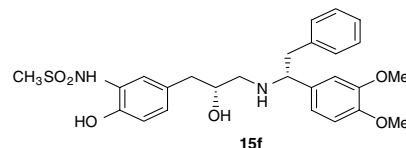


The identification of a potent series of IKK-β selective inhibitors based on an imidazothienopyrazine template and the oral efficacy of one such analog (**22j**) in the LPS-induced TNF-α release mouse model are described.

Arylpropanolamines: Selective β_3 agonists arising from strategies to mitigate phase I metabolic transformations

pp 4290–4296

W. N. Washburn,* T. W. Harper, G. Wu, J. D. Godfrey, P. McCann, R. Girotra, C. Shao, H. Zhang, A. Gavai, A. Mikkilineni, T. Dejneka, S. Ahmed, Y. Caringal, J. Hangeland, M. Zhang, P. T. W. Cheng, A. D. Russell, S. Skwish, D. A. Slusarchyk, G. T. Allen, B. H. Frohlich, B. E. Abboa-Offei, M. Cap, T. L. Waldron, R. J. George, B. Tesfamariam, K. E. Dickinson, A. A. Seymour and P. M. Sher



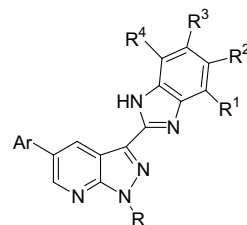
Utilization of N-substituted-4-hydroxy-3-methylsulfonanilidoethanolamines **1** as selective β_3 agonists is complicated by their propensity to undergo metabolic oxidative N-dealkylation, generating 0.01–2% of a very potent α_1 adrenergic agonist **2**. A summary of the SAR for this hepatic microsomal conversion precedes presentation of strategies to maintain the advantages of chemotype **1** while mitigating the consequences of N-dealkylation. This effort led to the identification of 4-hydroxy-3-methylsulfonanilidopropanolamines **15** for which the SAR for the unique stereochemical requirements for binding to the β adrenergic receptors culminated in the identification of the potent, selective β_3 agonist **15f**.

Synthesis and evaluation of pyrazolo[3,4-*b*]pyridine CDK1 inhibitors as anti-tumor agents

pp 4297–4302

Ronghui Lin,* Peter J. Connolly, Yanhua Lu, George Chiu, Shengjian Li, Yang Yu, Shenlin Huang, Xun Li, Stuart L. Emanuel, Steven A. Middleton, Robert H. Gruninger, Mary Adams, Angel R. Fuentes-Pesquera and Lee M. Greenberger

A series of 3,5-disubstituted pyrazolo[3,4-*b*]pyridine cyclin-dependent kinase (CDK) inhibitors was synthesized. These compounds showed potent and selective CDK inhibitory activities and inhibited in vitro cellular proliferation in cultured human tumor cells. Selected compounds were evaluated in an in vivo tumor xenograft model. The synthesis and biological evaluation of these pyrazolo[3,4-*b*]pyridines and related compounds are reported.

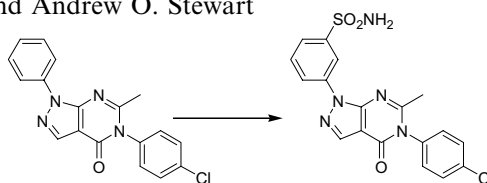


Rapid hit to lead evaluation of pyrazolo[3,4-*d*]pyrimidin-4-one as selective and orally bioavailable mGluR1 antagonists

pp 4303–4307

Xueqing Wang,* Teodozyi Kolasa, Odile F. El Kouhen, Linda E. Chovan, Candace L. Black-Shaefer, Frank L. Wagenaar, Jennifer A. Garton, Robert B. Moreland, Prisca Honore, Yau Yi Lau, Peter J. Dandliker, Jorge D. Brioni and Andrew O. Stewart

Hit to lead study of a series of novel and subtype-selective mGluR1 antagonists was discussed. Early ADME evaluation was key to guiding the SAR and generating orally bioavailable lead molecule.



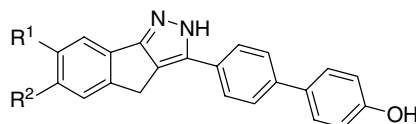
Keywords: mGluR1 antagonist, Hit to Lead, ADME



Synthesis and biological evaluation of 4'-(6,7-disubstituted-2, 4-dihydro-indeno[1,2-*c*]pyrazol-3-yl)-biphenyl-4-ol as potent Chk1 inhibitors

pp 4308–4315

Zhi-Fu Tao,* Gaoquan Li, Yunsong Tong, Zehan Chen, Philip Merta, Peter Kovar, Haiying Zhang, Saul H. Rosenberg, Hing L. Sham, Thomas J. Sowin and Nan-Horng Lin

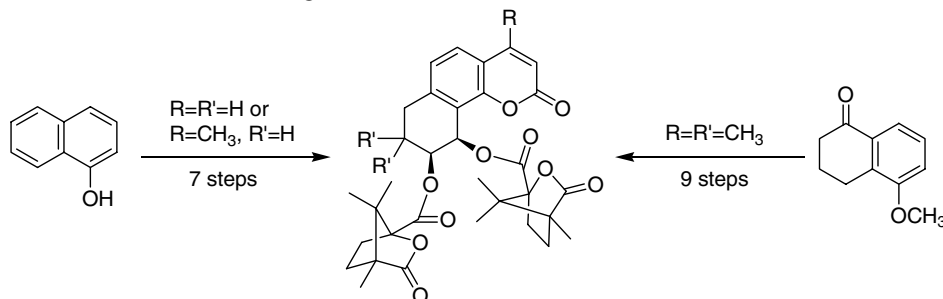


A series of potent tricyclicpyrazole-based Chk1 inhibitors were synthesized and their biological activities were evaluated.

Anti-AIDS agents 72. Bioisosteres (7-carbon-DCKs) of the potent anti-HIV lead DCK

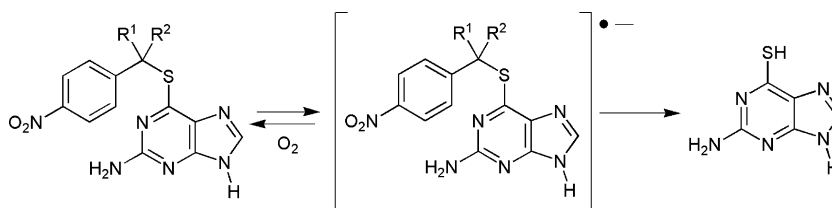
pp 4316–4319

Yang Wang, Shao-Xu Huang, Peng Xia,* Yi Xia, Zheng-Yu Yang, Nicole Kilgore, Susan L. Morris-Natschke and Kuo-Hsiung Lee*

**Hypoxia-driven elimination of thiopurines from their nitrobenzyl prodrugs**

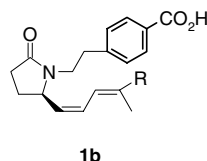
pp 4320–4322

Peter Thomson,* Matthew A. Naylor, Michael R. L. Stratford, Gemma Lewis, Sally Hill, Kantilal B. Patel, Peter Wardman and Peter D. Davis

**Discovery of novel prostaglandin analogs of PGE₂ as potent and selective EP₂ and EP₄ receptor agonists**

pp 4323–4327

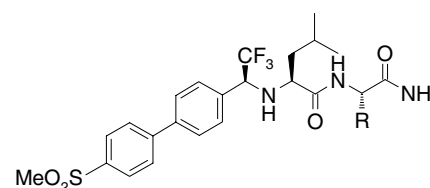
Yufang Xiao,* Gian Luca Araldi, Zhong Zhao, Nadia Brugger, Srinivasa Karra, David Fischer and Elizabeth Palmer

**Primary amides as selective inhibitors of cathepsin K**

pp 4328–4332

Serge Léger,* Christopher I. Bayly, W. Cameron Black, Sylvie Desmarais, Jean-Pierre Falgoutyret, Frédéric Massé, M. David Percival and Jean-François Truchon

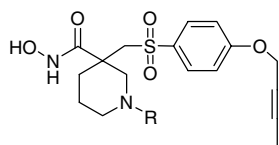
Many of the reported inhibitors of cathepsin K rely on an electrophilic functionality to interact with the nucleophilic cysteine residue found in the catalytic site of this class of enzymes. We report a novel series of cathepsin K inhibitors where a nitrile electrophile has been replaced with an α -substituted amide. Introduction of the benzyl substituent resulted in a 24-fold increase in potency over the unsubstituted amides. This series of compounds also showed excellent selectivity against the cathepsins B, L, and S. Mechanistic studies show that these compounds are slowly processed substrates of Cat K.



Design and synthesis of 3,3-piperidine hydroxamate analogs as selective TACE inhibitors

pp 4333–4337

Henry-Georges Lombart,* Eric Feyfant, Diane Joseph-McCarthy, Adrian Huang, Frank Lovering, LinHong Sun, Yi Zhu, Congmei Zeng, Yuhua Zhang and Jeremy Levin



Structure-based methods were used to design β -sulfone 3,3-piperidine hydroxamates as TACE inhibitors with the aim of improving selectivity for TACE versus MMP-13. Several compounds in this series were synthesized and evaluated in enzymatic and cell-based assays. These analogs exhibit excellent in vitro potency against isolated TACE enzyme and show good selectivity for TACE over the related metalloproteases MMP-2, -13, and -14.

Structure–activity studies of phenanthroindolizidine alkaloids as potential antitumor agents

pp 4338–4342

Wenli Gao, Scott Bussom, Susan P. Grill, Elizabeth A. Gullen, You-Cai Hu, Xueshi Huang, Sanbao Zhong, Conrad Kaczmarek, Julio Gutierrez, Samson Francis, David C. Baker,* Shishan Yu* and Yung-Chi Cheng*

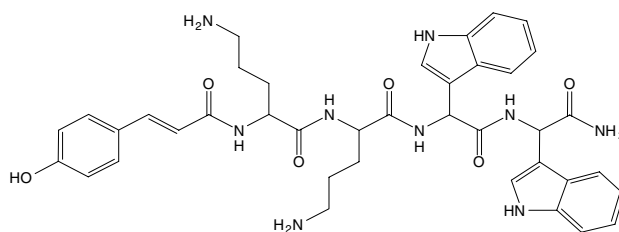
Compounds	R ¹	R ²	R ³	R ⁴	R ⁵	N ¹⁰
DCB-3500	OMe	OMe	OMe	H	H (S)	–
DCB-3501	OMe	OMe	OMe	OH (R)	H (S)	–
DCB-3503	OMe	OMe	OMe	OH (S)	H (S)	–
DCB-3506	OMe	OH	OMe	OH (S)	H (S)	–
PA-2 (Tylophoridine E)	H	OH	OMe	OH (S)	H (S)	–
PA-3 (Tylophoridine C)	H	OMe	OH	OH (S)	H (S)	N ⁺ –O [–]
PA-4 (Tylophoridine F)	H	OMe	OMe	OH (R)	H (S)	N ⁺ –O [–]
PA-5 [(R)-(+)-Deoxytylophorinidine]	H	OMe	OH	H	H (R)	–
PA-6 (Tylophorinine)	H	OMe	OMe	OH (R)	H (S)	–
PA-7 (Tylophorinidine)	H	OMe	OH	OH (S)	H (S)	–

Structure–activity relationships were explored based on a series of phenanthroindolizidine alkaloids synthesized or isolated. DCB-3503 and PA-7 (tylophorinidine) were determined to be the most active compounds against HepG2 tumor growth both in vitro and in vivo.

**Antimicrobial activity of rationally designed amino terminal modified peptides**

pp 4343–4346

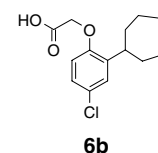
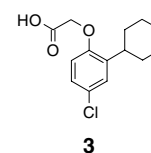
Gopal Singh Bisht, Diwan S. Rawat, Anil Kumar, Rita Kumar and Santosh Pasha*

**2-Cycloalkyl phenoxyacetic acid CRTh2 receptor antagonists**

pp 4347–4350

David A. Sandham,* Clive Aldcroft, Urs Baettig, Lucy Barker, David Beer, Gurdip Bhalay, Zarin Brown, Gerald Dubois, David Budd, Louise Bidlake, Emma Campbell, Brian Cox, Brian Everatt, David Harrison, Catherine J. Leblanc, Jodie Manini, Rachael Profit, Rowan Stringer, Katy S. Thompson, Katharine L. Turner, Morris F. Tweed, Christoph Walker, Simon J. Watson, Steven Whitebread, Jennifer Willis, Gareth Williams and Caroline Wilson

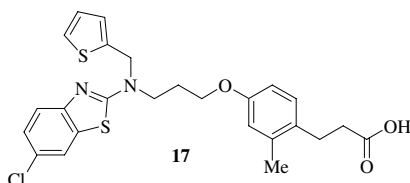
High throughput screening identified a phenoxyacetic acid scaffold **3** as a novel CRTh2 receptor antagonist chemotype. Optimisation furnished compound **6b**, which showed functional potency for inhibition of human eosinophil shape change and oral bioavailability in the rat.



Phenylpropanoic acid derivatives bearing a benzothiazole ring as PPAR δ -selective agonists

pp 4351–4357

Hiroki Fujieda, Shinya Usui, Takayoshi Suzuki, Hidehiko Nakagawa, Michitaka Ogura, Makoto Makishima and Naoki Miyata*



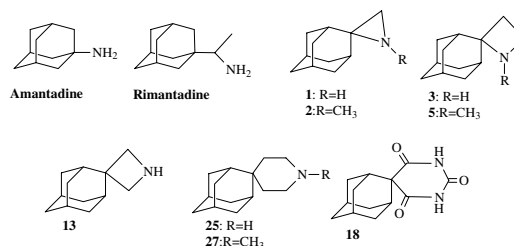
To find novel PPAR δ -selective agonists, we designed and synthesized a series of phenylpropanoic acid derivatives bearing a benzothiazole ring. Optimization of this series led to the identification of a potent and selective PPAR δ agonist **17**.

Design and synthesis of bioactive adamantane spiro heterocycles

pp 4358–4362

Nicolas Kolocouris,* Grigoris Zoidis, George B. Foscolos, George Fytas, S. Radhika Prathalingham, John M. Kelly, Lieve Naesens and Erik De Clercq

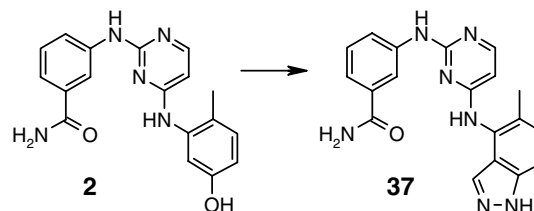
The prime target of this study was to examine the anti-influenza A virus and trypanocidal activity of spiro adamantane analogs **1**, **2**, **3**, **5**, **13**, **25**, **27** and **18** and to correlate their potency to the size of the heterocyclic ring.

**N-4-Pyrimidinyl-1H-indazol-4-amine inhibitors of Lck: Indazoles as phenol isosteres with improved pharmacokinetics**

pp 4363–4368

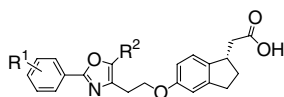
Paul Bamborough,* Richard M. Angell, Inder Bhamra, David Brown, James Bull, John A. Christopher, Anthony W. J. Cooper, Lynsey H. Fazal, Ilaria Giordano, Lucy Hind, Vipulkumar K. Patel, Lisa E. Ranshaw, Martin J. Sims, Philip A. Skone, Kathryn J. Smith, Emma Vickerstaff and Melanie Washington

2,4-Dianilino pyrimidines with a phenolic group at the 4-position are potent inhibitors of Lck tyrosine kinase enzyme activity, but they have poor pharmacokinetic properties. Analogues where the 4-position was replaced by 4-amino(5-methyl-1H-indazole) had comparable enzyme potency and improved pharmacokinetic properties.

**Indanylacetic acids as PPAR- δ activator insulin sensitizers**

pp 4369–4373

Philip Wickens,* Chengzhi Zhang, Xin Ma, Qian Zhao, John Amatruda, William Bullock, Michael Burns, Louis-David Cantin, Chih-Yuan Chuang, Thomas Claus, Miao Dai, Fernando Dela Cruz, David Dickson, Frederick J. Ehr Gott, Dongping Fan, Sarah Heald, Martin Hentemann, Christiana I. Iwuagwu, Jeffrey S. Johnson, Ellalahewage Kumarasinghe, David Ladner, Rico Lavoie, Sidney Liang, James N. Livingston, Derek Lowe, Steve Magnuson, Gretchen Mannelly, Ingo Mugge, Herbert Ogutu, Susan Pleasic-Williams, Robert W. Schoenleber, Jeff Shapiro, Tatiana Shelekhin, Laurel Sweet, Christopher Town and Manami Tsutsumi



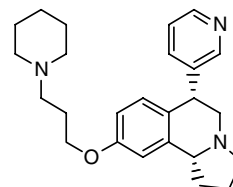
A novel series of indane acetic acid molecules are insulin sensitizers and have selectivity for PPAR- δ agonist activity over PPAR- α .

Pyrrolidino-tetrahydroisoquinolines bearing pendant heterocycles as potent dual H₃ antagonist and serotonin transporter inhibitors

pp 4374–4377

John M. Keith,* Leslie A. Gomez, Ann J. Barbier, Sandy J. Wilson, Jamin D. Boggs, Brian Lord, Curt Mazur, Leah Aluisio, Timothy W. Lovenberg and Nicholas I. Carruthers

A series of novel and potent 6-heteroaryl-pyrrolidino-tetrahydroisoquinolines with dual histamine H₃ antagonist/serotonin transporter inhibitor activity is described. In vitro and in vivo data are discussed.

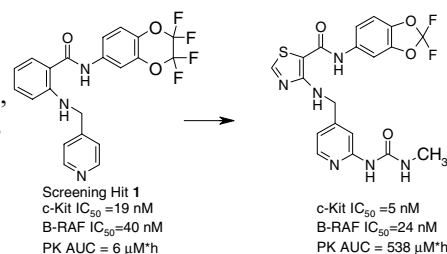


1d hH₃ K_i = 0.8 nM
hSERT K_i = 2 nM

SAR of a novel ‘Anthranilamide Like’ series of VEGFR-2, multi protein kinase inhibitors for the treatment of cancer

pp 4378–4381

Philip Wickens,* Harold Kluender, Julie Dixon, Catherine Brennan, Furahi Achebe, Antonella Bacchiocchi, Don Bankston, Donald Bierer, Michael Brands, Debbie Braun, Melissa S. Brown, Chih-Yuan Chuang, Jacques Dumas, Istvan Enyedy, Gloria Hofilena, Zhenqiu Hong, Tim Housley, Benjamin Jones, Uday Khire, Charles Kreiman, Ellalahewage Kumarasinghe, Timothy Lowinger, Ronda Ott-Morgan, Louise Perkins, Barton Phillips, Robert Schoenleber, William J. Scott, Ryan Sheeler, Anikó Redman, Xiuying Sun, Ian Taylor, Lei Wang, Scott Wilhelm, Xiaomei Zhang, Mingbao Zhang, Elizabeth Sullivan, Christopher Carter, Mark Miglarese and Joan Levy

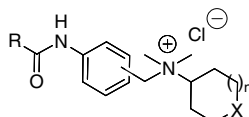


Novel series of anthranilamide type molecules that are active as inhibitors of B-Raf, c-Kit, and VEGFR-2 were identified.

Potent and selective CC-chemokine receptor-2 (CCR2) antagonists as a potential treatment for asthma

pp 4382–4386

Bharat Lagu,* Chrissy Gerchak, Meng Pan, Cuifen Hou, Monica Singer, Ravi Malaviya, Michele Matheis, Gil Olini, Druie Cavender and Michael Wachter

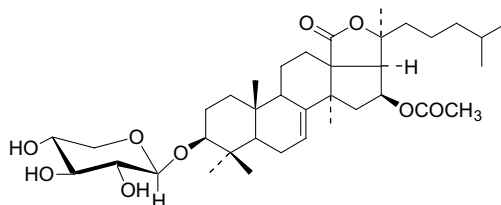


A number of compounds bearing a quaternary ammonium moiety were found to be antagonists with nanomolar binding affinity for the chemokine receptor-2. The structure–activity relationships in the series are described herein along with some detailed characterization of the interesting compounds.

Antifungal activity in triterpene glycosides from the sea cucumber *Actinopyga lecanora*

pp 4387–4391

Rajesh Kumar, Ashok Kumar Chaturvedi, Praveen Kumar Shukla and Vijai Lakshmi*



Isolation and structure elucidation of a novel triterpene glycoside, along with two known saponin and in vitro antifungal activity.

OTHER CONTENTS**Erratum****p 4392****Summary of instructions to authors****p I**

*Corresponding author

i* Supplementary data available via ScienceDirect

COVER

Typical snapshot of **7b** bound to HIV-RT from an MC simulation. Carbon atoms of **7b** are gold; from the left, Tyr181, Tyr188, Phe227, Leu100, Lys101; Trp229 at the top, Val106 at the bottom. H-bond with Lys101 O on right. Some residues in front including Glu138 have been removed for clarity. The water on N5 is also H-bonded to a carboxylate O of Glu138. [Thakur, V. T.; Kim, J. T.; Hamilton, A. D.; Bailey, C. M.; Domaoal, R. A.; Wang, L.; Anderson, K. S.; Jorgensen, W. L. *Bioorg. Med. Chem. Lett.* **2006**, 16, 5664.]

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