



Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl



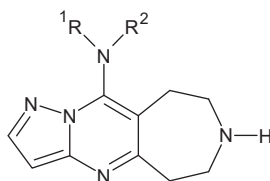
Bioorganic & Medicinal Chemistry Letters Volume 21, Issue 1, 2011

Contents

REGULAR ARTICLES

Novel 6,7,8,9-tetrahydro-5H-1,4,7,10a-tetraaza-cyclohepta[f]indene analogues as potent and selective 5-HT_{2C} agonists for the treatment of metabolic disorders pp 34–37

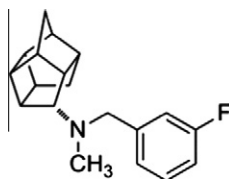
Heather Tye*, Stephan G. Mueller, Juergen Prestle, Stefan Scheuerer, Marcus Schindler, Bernd Nosse, Natacha Prevost, Christopher J. Brown, Alexander Heifetz, Clemens Moeller, Anna Pedret-Dunn, Mark Whittaker



A new class of potent and selective 5-HT_{2C} agonists for the treatment of metabolic disorders is described. Optimization of selectivity, permeability and hERG interaction is discussed.

Trishomocubane as a scaffold for the development of selective dopamine transporter (DAT) ligands pp 38–41

Samuel D. Banister, Iman A. Moussa, Corinne Beinat, Aaron J. Reynolds, Paolo Schiavini, William T. Jorgensen, Michael Kassiou*



DAT	$K_i = 1.2 \text{ nM}$
NET	$K_i > 10000 \text{ nM}$
SERT	$K_i > 10000 \text{ nM}$

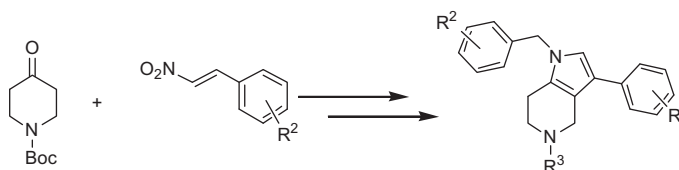
12

The in vitro affinity of a series of N-substituted N-methyl-8-aminopentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecanes for monoamine transporters DAT, NET, and SERT, is reported. Compound **12** was identified as a high affinity DAT ligand with excellent selectivity over the NET and SERT.



Novel tetrahydropyrido[3,2-c]pyrroles as 5-HT₇ antagonists pp 42–44

Dale A. Rudolph*, Curt A. Dvorak, Lisa Dvorak, Diane Nepomuceno, Pascal Bonaventure, Timothy W. Lovenberg, Nicholas I. Carruthers

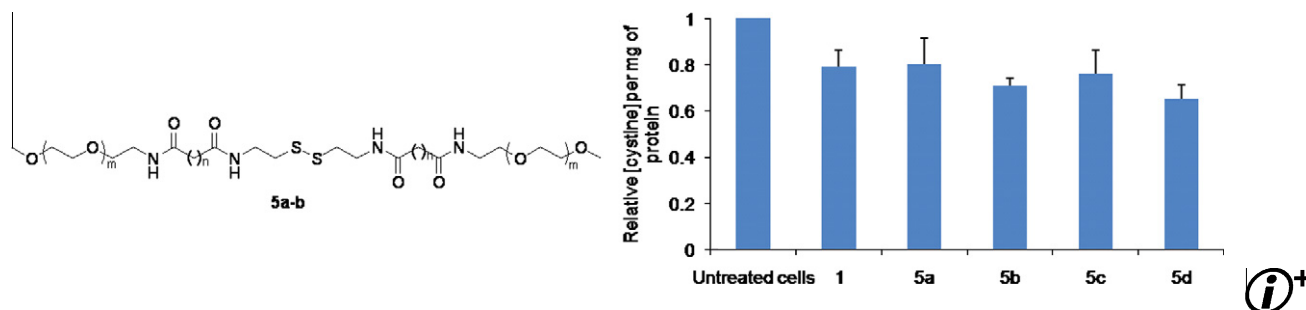


The synthesis and SAR for a novel series of tetrahydropyrido[3,2-c]pyrroles is described. Representative compounds are functional antagonists at the 5-HT₇ receptor and demonstrate activity in a rat pharmacodynamic model of 5-HT₇ activity.

PEGylated derivatives of cystamine as enhanced treatments for nephropathic cystinosis

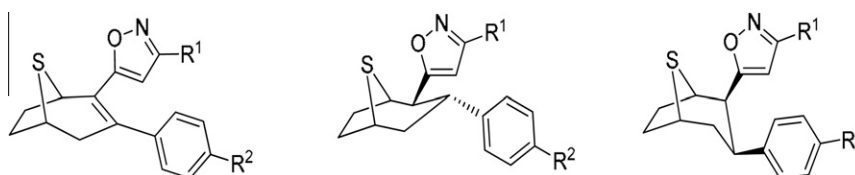
pp 45–47

Ziad Omran*, Graeme Kay, Alberto Di Salvo, Rachel M. Knott, Donald Cairns

**The synthesis and biological evaluation of 2-(3-methyl or 3-phenylisoxazol-5-yl)-3-aryl-8-thiabicyclo[3.2.1]octanes**

pp 48–51

Madhusudhan Purushotham, Anjaneyulu Sheri, Duy-Phong Pham-Huu, Bertha K. Madras, Aaron Janowsky, Peter C. Meltzer*

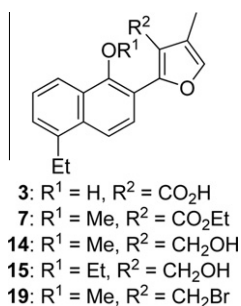


The 2-(3-methylisoxazol-5-yl)-3-aryl-8-thiabicyclo[3.2.1]octanes are potent and selective inhibitors of the Dopamine Transporter (DAT). Isoxazoles **6c** (3β-(4-fluorophenyl)) and **6d** (3β-(4-chlorophenyl)) inhibit the DAT (IC₅₀ = 7 nM) and are inactive at Serotonin Transporter inhibition (IC₅₀ >1000 nM).

Antitumor agents 279. Structure–activity relationship and in vivo studies of novel 2-(furan-2-yl)naphthalen-1-ol (FNO) analogs as potent and selective anti-breast cancer agents

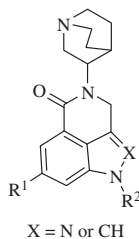
pp 52–57

Yizhou Dong, Kyoko Nakagawa-Goto, Chin-Yu Lai, Yoon Kim, Susan L. Morris-Natschke, Eva Y.-H. P. Lee*, Kenneth F. Bastow*, Kuo-Hsiung Lee*

**Novel serotonin type 3 receptor partial agonists for the potential treatment of irritable bowel syndrome**

pp 58–61

David D. Manning*, Christopher L. Cioffi, Alexander Usyatinsky, Kevin Fitzpatrick, Liaqat Masih, Cheng Guo, Zhenjun Zhang, Sok Hui Choo, M. Inthikhab Sikkander, Kristen N. Ryan, Jennifer Naginskaya, Carla Hassler, Svetlana Dobritsa, Jonathan D. Wierschke, William G. Earley, Amy S. Butler, Catherine A. Brady, Nicholas M. Barnes, Marlene L. Cohen, Peter R. Guzzo



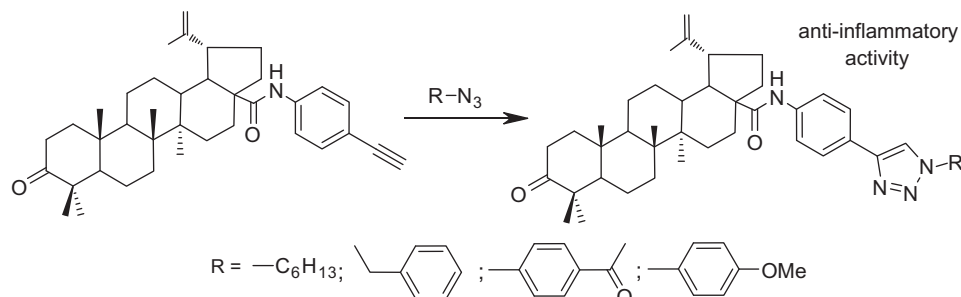
X = N or CH

Selective, low intrinsic activity 5-HT₃ receptor partial agonists with good oral activity are described.

Rapid access to new bioconjugates of betulonic acid via click chemistry

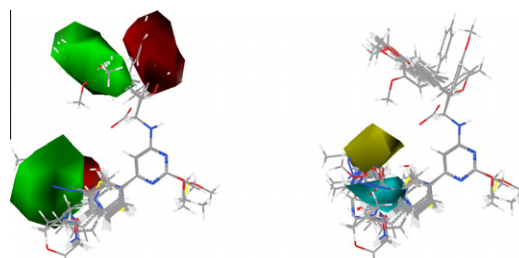
pp 62–65

Sergey F. Vasilevsky*, Anastasiya I. Govdi, Irina V. Sorokina, Tatyana G. Tolstikova, Dmitry S. Baev, Genrikh A. Tolstikov, Victor I. Mamatuyk, Igor V. Alabugin*

**Understanding DP receptor antagonism using a CoMSIA approach**

pp 66–75

Lan Mu, Joacy Aguiar, Ali Ardati, Bin Cao, Charles J. Gardner, Tim Gillespy, Keith Harris, Sungtaek Lim, Robert Marcus, Isabelle Morize, Ashfaq Parkar, David Stefany, Yi Li, Roy J. Vaz, Dragan A. Cirovic*

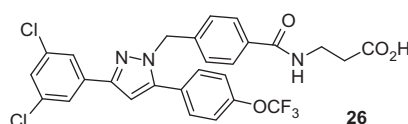


CoMSIA model of 2,6-substituted-4-monosubstituted aminopyrimidine antagonists of prostaglandin D₂ receptor (DP1) is reported. The utility of this QSAR model in chemical lead optimization is discussed.

Discovery of novel, potent, selective, and orally active human glucagon receptor antagonists containing a pyrazole core

pp 76–81

Dong-Ming Shen*, Edward J. Brady, Mari R. Candelore, Qing Dallas-Yang, Victor D.-H. Ding, William P. Feeney, Guoqiang Jiang, Margaret E. McCann, Steve Mock, Sajjad A. Qureshi, Richard Saperstein, Xiaolan Shen, Xinchun Tong, Laurie M. Tota, Michael J. Wright, Xiaodong Yang, Song Zheng, Kevin T. Chapman, Bei B. Zhang, James R. Tata, Emma R. Parmee

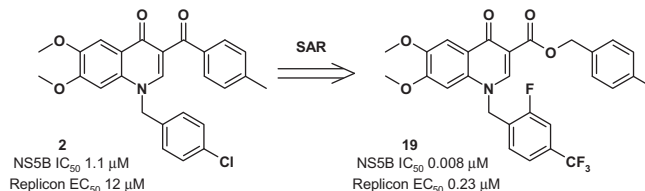


The discovery and SAR study of a novel 1,3,5-pyrazole series of human glucagon receptor antagonists represented by **26** are presented. Compound **26** was selective and orally active in several in vivo preclinical models of type II diabetes.

Quinolones as HCV NS5B polymerase inhibitors

pp 82–87

Dange V. Kumar, Roopa Rai*, Ken A. Brameld, John R. Somoza, Ravi Rajagopalan, James W. Janc, Yu M. Xia, Tony L. Ton, Michael B. Shaghafi, Huiyong Hu, Isabelle Lehoux, Nhat To, Wendy B. Young, Michael J. Green

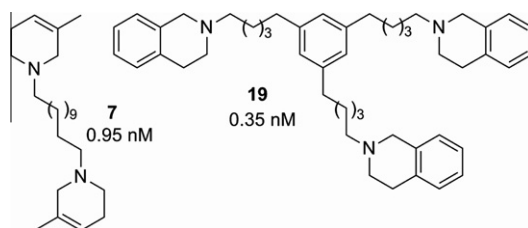


Hepatitis C virus (HCV) infection is treated with a combination of peginterferon alfa-2a/b and ribavirin. To address the limitations of this therapy, numerous small molecule agents are in development, which act by directly affecting key steps in the viral life-cycle. Herein we describe our discovery of quinolone derivatives, novel small-molecules that inhibit NS5b polymerase, a key enzyme of the viral life-cycle. Our SAR led us from keto-quinolones such as **2** to benzyl esters such as **19** with attractive enzyme inhibition and cell-based replicon activity. This class of compounds binds to an allosteric site of NS5B polymerase (NNI-2) as confirmed through a co-crystal structure of a representative compound to NS5B.

Novel bis-, tris-, and tetrakis-tertiary amino analogs as antagonists at neuronal nicotinic receptors that mediate nicotine-evoked dopamine release

pp 88–91

Zhenfa Zhang, Guangrong Zheng, Marharyta Pivavarchyk, A. Gabriela Deaciuc, Linda P. Dwoskin, Peter A. Crooks*

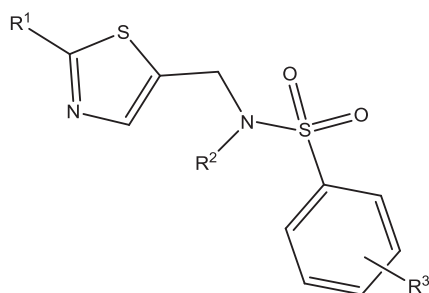


A series of tertiary amine analogs derived from lead azaaromatic quaternary ammonium salts has been designed and synthesized. The bis-tertiary amine analog **7** exhibited an IC_{50} of 0.95 nM, while the tris-tertiary amine analog **19** had an IC_{50} of 0.35 nM at nAChRs mediating nicotine-evoked dopamine release.

The characterization of a novel V1b antagonist lead series

pp 92–96

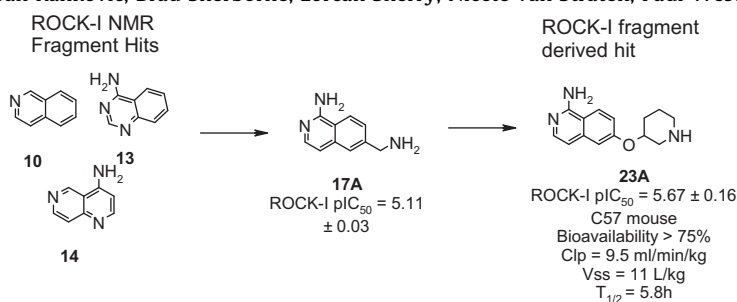
Chris A. Smethurst, Jennifer A. Borthwick*, Simon Gaines, Steve Watson, Andrew Green, Mark J. Schulz, George Burton, Alberto A. Buson, Roberto Arban



Fragment-based discovery of 6-substituted isoquinolin-1-amine based ROCK-I inhibitors

pp 97–101

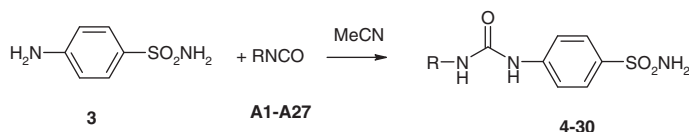
Peter Ray*, Jane Wright, Julia Adam, Johnathan Bennett, Sylviane Boucharens, Darcey Black, Andrew Cook, Angus R. Brown, Ola Epemolu, Dan Fletcher, Anders Haunso, Margaret Huggett, Phil Jones, Steven Laats, Amanda Lyons, Jordi Mestres, Jos de Man, Richard Morphy, Zoran Rankovic, Brad Sherborne, Lorcan Sherry, Nicole van Straten, Paul Westwood, Guido Z. R. Zaman



Inhibition of β -carbonic anhydrases with ureido-substituted benzenesulfonamides

pp 102–105

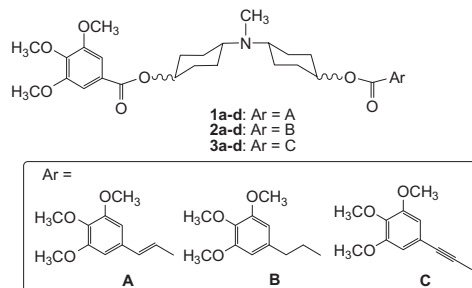
Fabio Pacchiano, Fabrizio Carta, Daniela Vullo, Andrea Scozzafava, Claudiu T. Supuran*



Inhibition of P-glycoprotein-mediated Multidrug Resistance (MDR) by *N,N*-bis(cyclohexanol)amine aryl esters: Further restriction of molecular flexibility maintains high potency and efficacy

pp 106–109

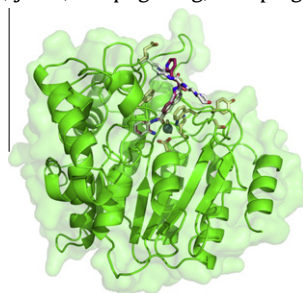
Cecilia Martelli, Silvia Dei, Catherine Lambert, Dina Manetti, Francesca Orlandi, Maria Novella Romanelli, Serena Scapechi, Milena Salerno, Elisabetta Teodori*



Application of p21 and klf2 reporter gene assays to identify selective histone deacetylase inhibitors for cancer therapy

pp 110–116

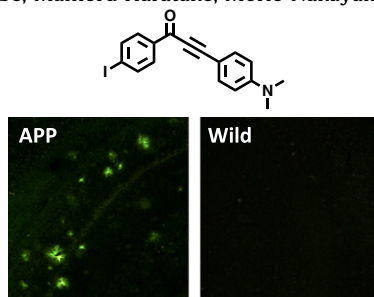
Jason C. Wong*, Lei Guo, Zhenghong Peng, Weixing Zhang, Nan Zhang, Wayne Lai, Zhenshan Zhang, Chao Zhang, Xiongwen Zhang, Shan Song, Desi Pan, Chuanming Xie, Jia Li, Zhiqing Ning, Xianping Lu, Yun He, Li Chen



Diphenylpropynone derivatives as probes for imaging β -amyloid plaques in Alzheimer's brains

pp 117–120

Masahiro Ono*, Hiroyuki Watanabe, Rumi Watanabe, Mamoru Haratake, Morio Nakayama*, Hideo Saji



A new series of diphenylpropynone (DPP) derivatives for use in vivo to image β -amyloid plaques in the brain of patients with Alzheimer's disease were synthesized and characterized.

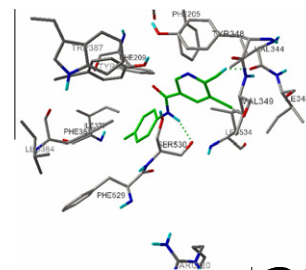


Design of novel *N*-phenylnicotinamides as selective cyclooxygenase-1 inhibitors

pp 121–124

Lei Shi, Zi-Lin Li, Ying Yang, Zhen-Wei Zhu, Hai-Liang Zhu*

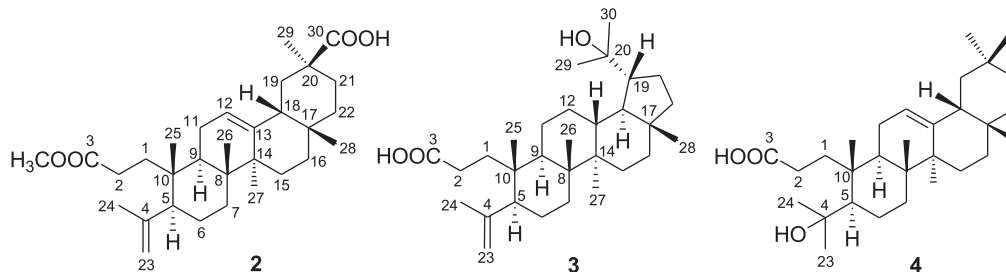
A series of *N*-phenylnicotinamides (**1–40**) were designed and evaluated in vitro for their COX inhibitory activities. Most of the synthesized compounds were proved to be potent and selective inhibitors of COX-1. Compound **28** showed the most potent COX-1 inhibitory activity (COX-1 IC₅₀ = 0.68 ± 0.07 μ M) and good selectivity (COX-2 IC₅₀ >100 μ M). This compound may be useful as a lead compound for superior COX-1 inhibitors. On the basis of the biological results, structure–activity relationships for the COX-1-inhibitory activities of the synthesized *N*-phenylnicotinamides were discussed concisely.



Ring A-*seco* triterpenoids with antibacterial activity from *Dysoxylum hainanense*

pp 125–129

Xiu-Feng He, Xiao-Ning Wang, Sheng Yin, Lei Dong, Jian-Min Yue*



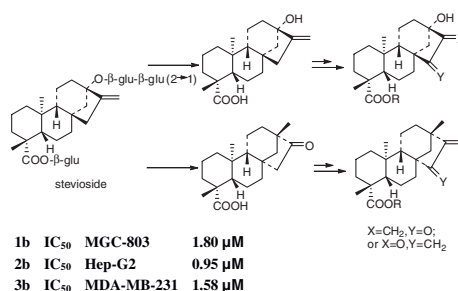
Five new ring A-*seco* triterpenoids, dysoxyhainic acids F–J (**1–5**), along with a known ring A-*seco* triterpenoid koetjapic acid (**6**) were isolated from the twigs and leaves of *Dysoxylum hainanense*. Compounds **2–4** and **6** exhibited significant antimicrobial activity against Gram-positive bacteria.



Synthesis and biological evaluation of novel *exo*-methylene cyclopentanone tetracyclic diterpenoids as antitumor agents

pp 130–132

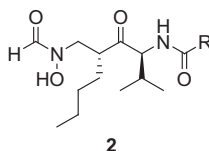
Jing Li, Dayong Zhang*, Xiaoming Wu



Peptide deformylase inhibitors with non-peptide scaffold: Synthesis and structure–activity relationships

pp 133–136

Seung Kyu Lee, Kwang Hyun Choi, Sang Jae Lee, Jong Sun Lee, Ji Yun Park, B. Moon Kim, Bong Jin Lee*



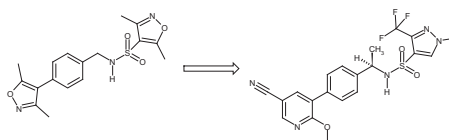
The synthesis and structure–activity relationship studies of peptide deformylase inhibitor **2** are reported.



Discovery and optimisation of a selective non-steroidal glucocorticoid receptor antagonist

pp 137–140

Angus R. Brown*, Michael Bosies, Helen Cameron, John Clark, Angela Cowley, Mark Craighead, Moira A. Elmore, Alistair Firth, Richard Goodwin, Susan Goutcher, Emma Grant, Morag Grassie, Simon J. A. Grove, Niall M. Hamilton, Hannah Hampson, Alison Hillier, Koc-Kan Ho, Michael Kiczun, Celia Kingsbury, Steven G. Kultgen, Peter T. A. Littlewood, Scott J. Lusher, Susan MacDonald, Lorraine McIntosh, Theresa McIntyre, Ashvin Mistry, J. Richard Morphy, Olaf Nimz, Michael Ohlmeyer, Jack Pick, Zoran Rankovic, Brad Sherborne, Alasdair Smith, Michael Speake, Gayle Spinks, Fiona Thomson, Lynn Watson, Mark Weston

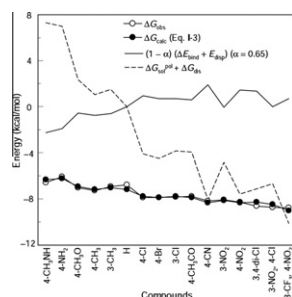


High-throughput screening of 3.87 million compounds delivered a novel series of non-steroidal GR antagonists. Subsequent rounds of optimisation allowed progression from a non-selective ligand with a poor ADMET profile to an orally bioavailable, selective, stable, glucocorticoid receptor antagonist.

Correlation analyses on binding affinity of substituted benzenesulfonamides with carbonic anhydrase using ab initio MO calculations on their complex structures (II)

pp 141–144

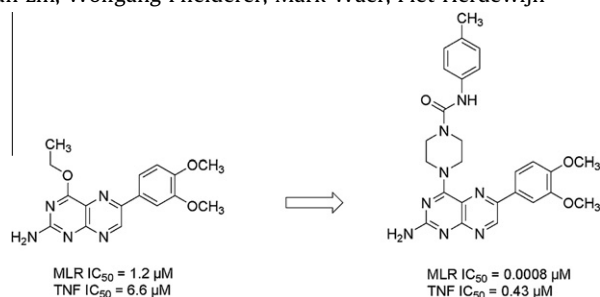
Yohei Munei, Kazunori Shimamoto, Masataka Harada, Tatsusada Yoshida, Hiroshi Chuman*



Synthesis and in vitro evaluation of 2-amino-4-N-piperazinyl-6-(3,4-dimethoxyphenyl)-pteridines as dual immunosuppressive and anti-inflammatory agents

pp 145–149

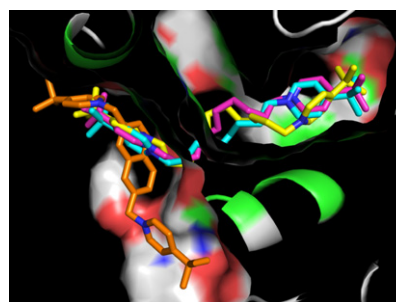
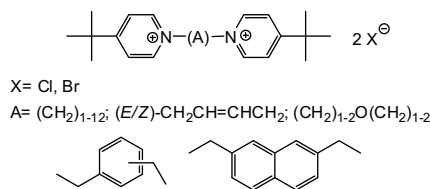
Steven De Jonghe, Arnaud Marchand, Ling-Jie Gao, Agnes Calleja, Eva Cuveliers, Ilse Sienaert, Jean Herman, Gavin Clydesdale, Hassane Sefrioui, Yuan Lin, Wolfgang Pfeleiderer, Mark Waer, Piet Herdewijn*



Preparation, in vitro screening and molecular modelling of symmetrical 4-tert-butylpyridinium cholinesterase inhibitors—Analogues of SAD-128

pp 150–154

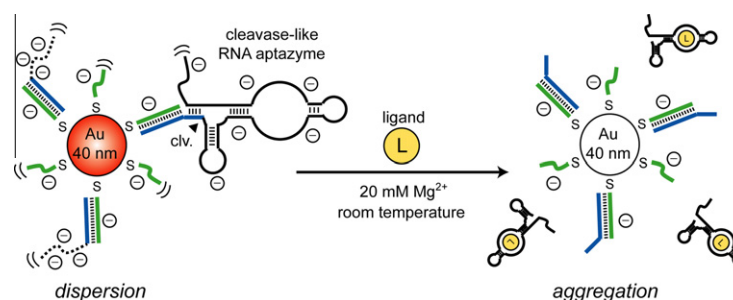
Kamil Musilek, Jan Roder, Marketa Komloova, Ondrej Holas, Martina Hrabanova, Miroslav Pohanka, Vlastimil Dohnal, Veronika Opletalova, Kamil Kuca, Young-Sik Jung*



RNA aptazyme-tethered large gold nanoparticles for on-the-spot sensing of the aptazyme ligand

pp 155–159

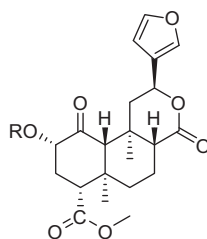
Atsushi Ogawa*



Synthesis and biological evaluation of new salvinorin A analogues incorporating natural amino acids

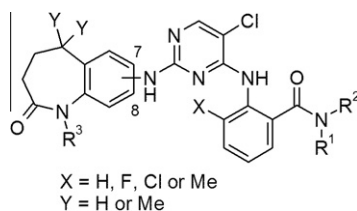
pp 160–163

Jakub Fichna, Kevin Lewellyn, Feng Yan, Bryan L. Roth, Jordan K. Zjawiony*

**Fused bicyclic derivatives of 2,4-diaminopyrimidine as c-Met inhibitors**

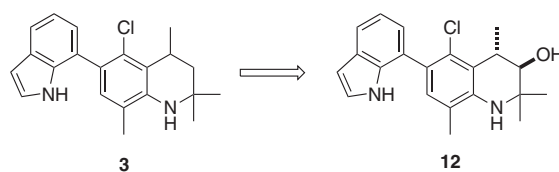
pp 164–167

Linda R. Weinberg*, Mark S. Albom, Thelma S. Angeles, Jean Husten, Joseph G. Lisko, Robert J. McHugh, Karen L. Milkiewicz, Seetha Murthy, Gregory R. Ott, Jay P. Therooff, Rabindranath Tripathy, Ted L. Underiner, Craig A. Zifcsak, Bruce D. Dorsey

**Tetrahydroquinoline glucocorticoid receptor agonists: Discovery of a 3-hydroxyl for improving receptor selectivity**

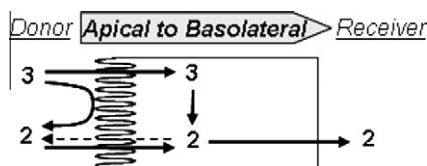
pp 168–171

Steven L. Roach*, Robert I. Higuchi, Andrew R. Hudson, Mark E. Adams, Peter M. Syka, Dale E. Mais, Jeffrey N. Miner, Keith B. Marschke, Lin Zhi

**MDCK cell permeability characteristics of a sulfenamide prodrug: Strategic implications in considering sulfenamide prodrugs for oral delivery of NH-acids**

pp 172–175

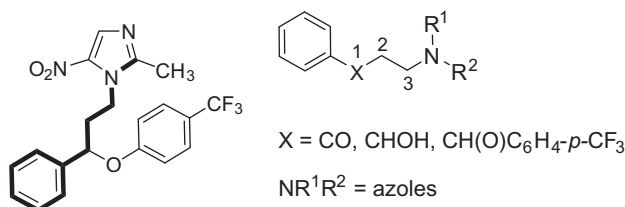
Victor R. Guarino*, Kwame Nti-Addae, Valentino J. Stella



Design and synthesis of 3-(azol-1-yl)phenylpropanes as microbicidal spermicides for prophylactic contraception

pp 176–181

Lalit Kumar, Amit Sarswat, Nand Lal, Ashish Jain, Sumit Kumar, S. T. V. S. Kiran Kumar, Jagdamba P. Maikhuri, Atindra K. Pandey, Praveen K. Shukla, Gopal Gupta, Vishnu L. Sharma*

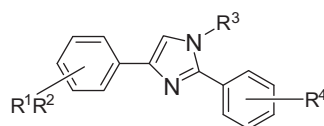


A series of 25 3-(azol-1-yl)phenylpropanes were evaluated for spermicidal, antitrichomonas and anticandida activities. Two compounds exhibited spermicidal, antitrichomonas and anticandida activities with good safety profile, warranting further lead optimization for furnishing a prophylactic vaginal contraceptive.

**Structure–activity relationships of 2,4-diphenyl-1H-imidazole analogs as CB2 receptor agonists for the treatment of chronic pain**

pp 182–185

Shu-Wei Yang*, Jennifer Smotryski, Julius Matasi, Ginny Ho, Deen Tulshian, William J. Greenlee, Rossella Brusa, Massimiliano Beltramo, Kathleen Cox



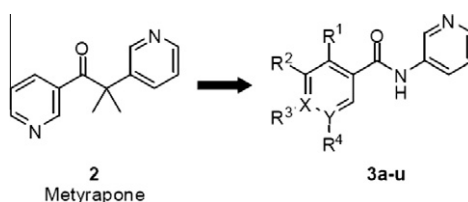
2,4-Diphenyl-1H-imidazole analogs

A series of 2,4-diphenyl-1H-imidazole analogs have been synthesized and displayed potent human CB2 agonist activity. Many of these analogs showed high functional selectivity over human CB1 receptors. The syntheses, structure–activity relationships, and selected pharmacokinetic data of these analogs are described.

N-(Pyridin-3-yl)benzamides as selective inhibitors of human aldosterone synthase (CYP11B2)

pp 186–190

Christina Zimmer, Marieke Hafner, Michael Zender, Dominic Ammann, Rolf W. Hartmann*, Carsten A. Vock*

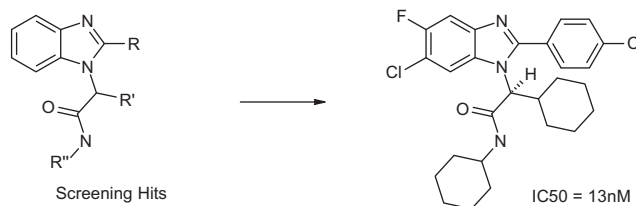


The synthesis of CYP11B2 inhibitors with pronounced selectivity against other steroidogenic CYP enzymes is reported.

**Discovery of novel and orally active FXR agonists for the potential treatment of dyslipidemia & diabetes**

pp 191–194

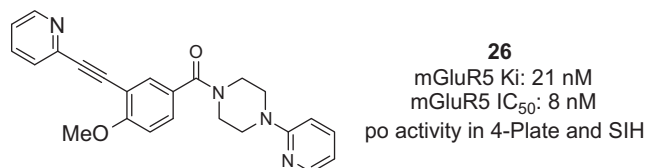
Hans G. F. Richter, Gregory M. Benson, Denise Blum, Evelyne Chaput, Song Feng, Christophe Gardes, Uwe Grether, Peter Hartman, Bernd Kuhn, Rainer E. Martin, Jean-Marc Plancher, Markus G. Rudolph, Franz Schuler, Sven Taylor, Konrad H. Bleicher*



3-(Pyridin-2-yl-ethynyl)benzamide metabotropic glutamate receptor 5 negative allosteric modulators: Hit to lead studies

pp 195–199

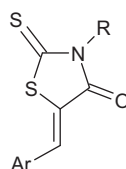
Adam M. Gilbert*, Matthew G. Bursavich, Sabrina Lombardi, Adedayo Adedoyin, Jason M. Dwyer, Zoe Hughes, Jeffrey C. Kern, Xavier Khawaja, Sharon Rosenzweig-Lipson, William J. Moore, Sarah J. Neal, Michael Olsen, Stacey J. Sukoff Rizzo, Dane Springer



In vitro evaluation of 5-arylidene-2-thioxo-4-thiazolidinones active as aldose reductase inhibitors

pp 200–203

Rosanna Maccari*, Antonella Del Corso, Marco Giglio, Roberta Moschini, Umberto Mura, Rosaria Ottanà

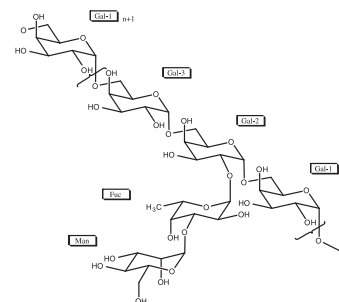


Structure of fomitellan A, a mannofucogalactan from the fruiting bodies of *Fomitella fraxinea*

pp 204–206

Soo-Muk Cho, Bong-Sik Yun*, Ick-Dong Yoo, Hiroyuki Koshino*

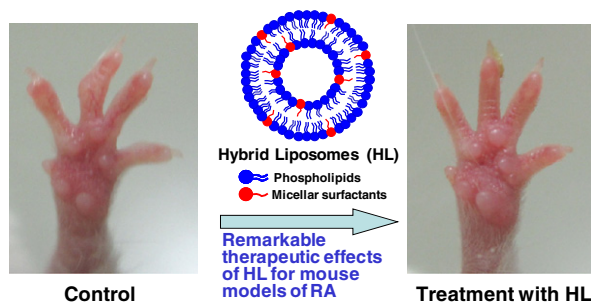
Chemical structure of fomitellan A, a polysaccharide with a mitogenic effect isolated from the fruiting bodies of *Fomitella fraxinea*, has been assigned as a mannofucogalactan with a repeating unit of penta-saccharide, which was composed of a (1→6)-linked D-galactopyranosyl backbone having a C-2 position substituted with disaccharide units of 3-O-D-mannopyranosyl-L-fucopyranosyl residue. The 1H and ^{13}C NMR signals of fomitellan A have been completely assigned by extensive NMR experiments.



Inhibitory effects of hybrid liposomes on the growth of synoviocyte causing rheumatoid arthritis

pp 207–210

Hideaki Ichihara, Motoki Hino, Taku Makizono, Masayo Umebayashi, Yoko Matsumoto, Ryuichi Ueoka*

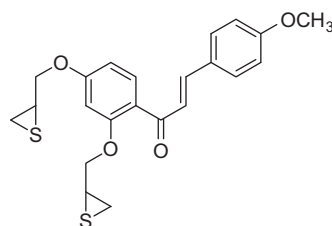


Remarkably high therapeutic effects without joint swelling were obtained in mouse models of RA treated with HL.

Synthesis and topoisomerase II inhibitory and cytotoxic activity of oxiranylmethoxy- and thiiranylmethoxy-chalcone derivatives

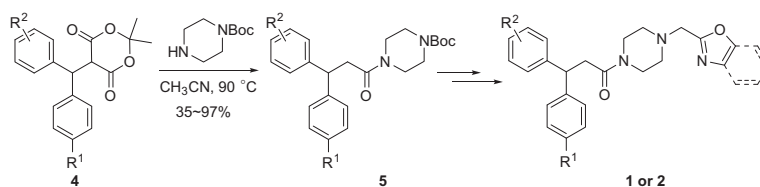
pp 211–214

Younghwa Na*, Jung-Min Nam

**Facile synthesis and biological evaluation of 3,3-diphenylpropanoyl piperazines as T-type calcium channel blockers**

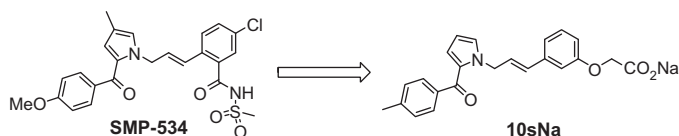
pp 215–219

Yeon-hee Choi, Du Jong Baek, Seon Hee Seo, Jae Kyun Lee, Ae Nim Pae, Yong Seo Cho*, Sun-Joon Min*

**Development of a new class of benzoylpyrrole-based PPAR α/γ activators**

pp 220–224

Kantaro Ushiroda, Katsunori Maruta, Makoto Kitoh, Kiyotaka Iwai, Jun Nagamine, Atsushi Tsuchida, Mutsuo Taiji, Ryu Nagata*

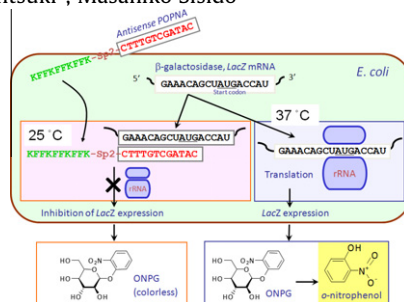


TGF- β signaling pathway inhibitor and potential anti-nephropathic agent SMP-534 was successfully converted to a new class of benzoylpyrrole-based PPAR α/γ activators as an anti-diabetic agent. Compound **10sNa** showed a favorable blood glucose-lowering effect without body weight gain.

Antisense effect of pyrrolidine-based oxy-peptide nucleic acids in *Escherichia coli*

pp 225–227

Mizuki Kitamatsu*, Shunsuke Kurami, Takashi Ohtsuki*, Masahiko Sisido



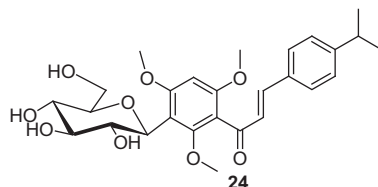
The antisense effect of the pyrrolidine-based oxy-peptide nucleic acid (POPNA) was equivalent to that of a Nielsen-type PNA. The POPNA could switch its antisense effect (*LacZ* activity) over a wide range of ambient temperatures.



Synthesis and antihyperglycemic activity of phenolic C-glycosides

pp 228–233

Preeti Rawat, Manmeet Kumar, Neha Rahuja, Daya Shankar Lal Srivastava, Arvind Kumar Srivastava, Rakesh Maurya*

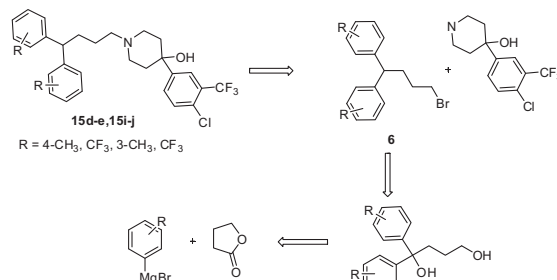


Various phenolic C-glycosides were evaluated for their in vitro and in vivo antihyperglycemic activity employing glucose uptake by rat muscle cell lines (L-6) and low dosed-streptozotocin-induced diabetic rats, respectively. The compound **24** lowered the blood glucose levels by 34.9% and 33.6% during 5 h and 24 h, respectively, at the dose of 25 mg/kg body weight which is comparable to standard antidiabetic drug metformin.

Synthesis and SAR study of diphenylbutylpiperidines as cell autophagy inducers

pp 234–239

Gang Chen, Hongguang Xia, Yu Cai, Dawei Ma*, Junying Yuan*, Chengye Yuan*

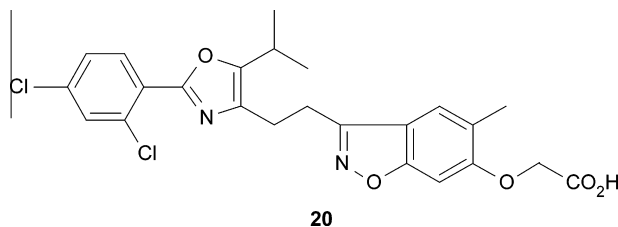


A novel type of diphenylbutylpiperidines as autophagy inducers has been synthesized via new route and some of them showed 10-fold greater activity comparable to lead compound.

**Synthesis of a novel human PPAR δ selective agonist and its stimulatory effect on oligodendrocyte differentiation**

pp 240–244

Shogo Sakuma*, Tsuyoshi Endo, Takashi Kanda, Hideki Nakamura, Satomi Yamasaki, Tomio Yamakawa

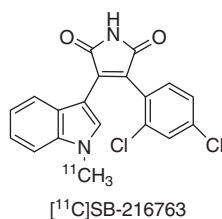


We have succeeded in synthesizing a novel PPAR δ selective agonist, compound **20**, characterized by a benzisoxazole ring. Compound **20** exhibited a potent hPPAR δ transactivation activity and high δ selectivity. Compound **20** stimulated oligodendrocyte differentiation of primary oligodendrocyte precursor cells in vitro, indicating that it may be an effective drug to treat demyelinating disorders, such as multiple sclerosis.

The first synthesis of [¹¹C]SB-216763, a new potential PET agent for imaging of glycogen synthase kinase-3 (GSK-3)

pp 245–249

Min Wang, Mingzhang Gao, Kathy D. Miller, George W. Sledge, Gary D. Hutchins, Qi-Huang Zheng*

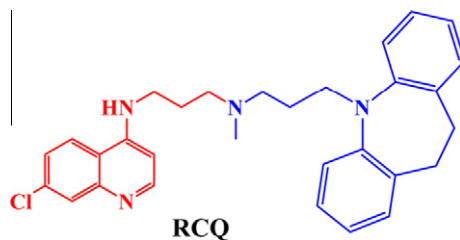


Radiosynthesis of [¹¹C]SB-216763, a new potential PET agent for imaging of glycogen synthase kinase (GSK-3), is first reported.

Molecular modeling and UV-vis spectroscopic studies on the mechanism of action of reversed chloroquine (RCQ)

pp 250–254

Vanessa A. Oteló, Antonio C. Sant'Ana, Dalva L. A. de Faria, Carla M. S. Menezes*

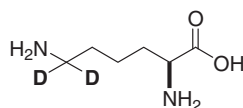


Molecular modeling and ultraviolet-visible spectroscopy (UV-vis) studies strongly suggest that the interaction between **RCQ** and heme is predominant through the quinoline moiety in a mechanism of action similar to that observed for chloroquine.

**Control of lysyl oxidase activity through site-specific deuteration of lysine**

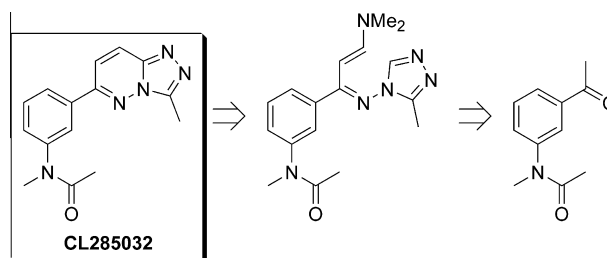
pp 255–258

Nikolay B. Pestov, Irina A. Okkelman, Vadim V. Shmanai, Alaksiej L. Hurski, Amato J. Giaccia, Mikhail S. Shchepinov*

**A new and efficient synthetic route for the anxiolytic agent CL285032**

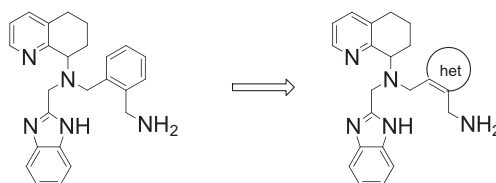
pp 259–261

Victor P. Ghidu, Marc A. Ilies, Tom Cullen, Robert Pollet, Magid Abou-Gharbia*

**Synthesis and SAR of novel CXCR4 antagonists that are potent inhibitors of T tropic (X4) HIV-1 replication**

pp 262–266

Renato Skerlj*, Gary Bridger, Ernie McEachern, Curtis Harwig, Chris Smith, Trevor Wilson, Duane Veale, Helen Yee, Jason Crawford, Krystyna Skupinska, Rossana Wauthy, Wen Yang, Yongbao Zhu, David Bogucki, Maria Di Fluri, Jonathon Langille, Dana Huskens, Erik De Clercq, Dominique Schols



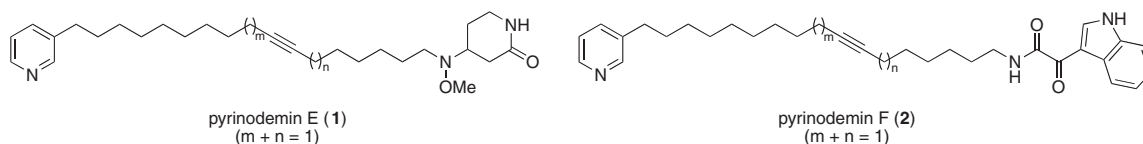
A SAR was developed for a novel series of heterocyclic containing compounds. Potent CXCR4 antagonists were identified based on anti-HIV-1 activity and Ca^{2+} flux inhibition that also displayed good pharmacokinetics.



Pyrinodemins E and F, new 3-alkylpyridine alkaloids from sponge *Amphimedon* sp.

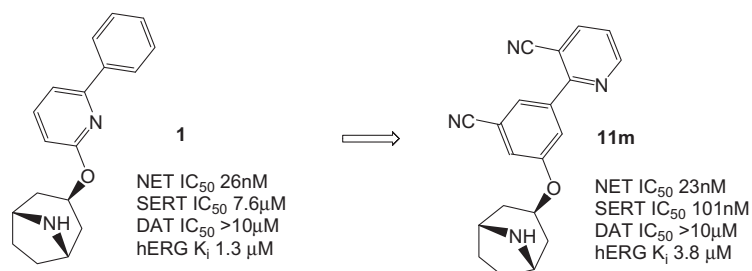
pp 267–270

Ken'ichi Kura, Takaaki Kubota, Jane Fromont, Jun'ichi Kobayashi*

**The identification, and optimisation of hERG selectivity, of a mixed NET/SERT re-uptake inhibitor for the treatment of pain**

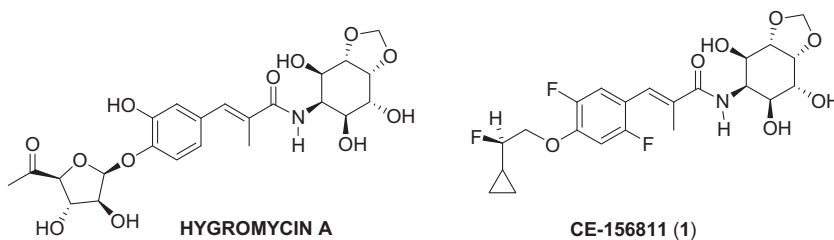
pp 271–275

Derek Angus, Matilda Bingham*, Dawn Buchanan, Neil Dunbar, Lindsay Gibson, Richard Goodwin, Anders Haunsø, Andrea Houghton, Margaret Huggett, Richard Morphy, Susan Napier*, Olaf Nimz, Joanna Passmore, Glenn Walker

**The discovery and structure–activity relationships leading to CE-156811, a difluorophenyl cyclopropyl fluoroether: A novel potent antibacterial analog derived from hygromycin A**

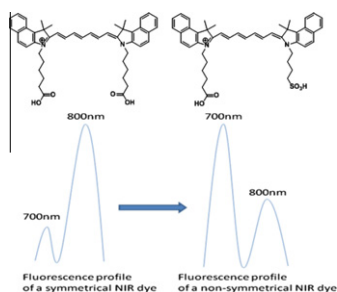
pp 276–279

Phuong T. Le*, Steven J. Brickner, Sarah K. Wade, Katherine Brighty, Rhonda Monahan, Gregory G. Stone, Dennis Girard, Steve Finegan, Joan Duignan, John Schafer, Meghan Maloney, Richard P. Zaniewski, Ann G. Connolly, Jennifer Liras, Jon Bordner, Ivan Samardjiev

**Synthesis and spectroscopy of near infrared fluorescent dyes for investigating dichromatic fluorescence**

pp 280–284

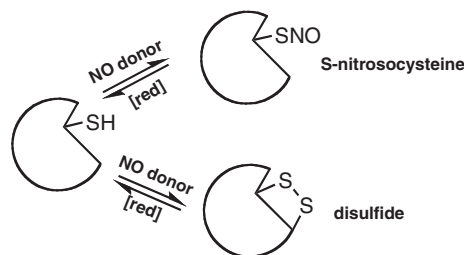
Mingfeng Bai, Samuel Achilefu*



Oxidative inactivation of the lymphoid tyrosine phosphatase mediated by both general and active site directed NO donors

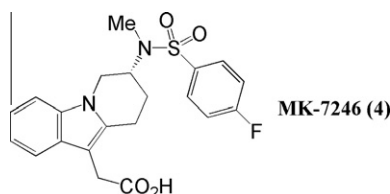
pp 285–287

Caitlin E. Karver, Vanessa F. Ahmed, Amy M. Barrios*

**Discovery of MK-7246, a selective CRTH2 antagonist for the treatment of respiratory diseases**

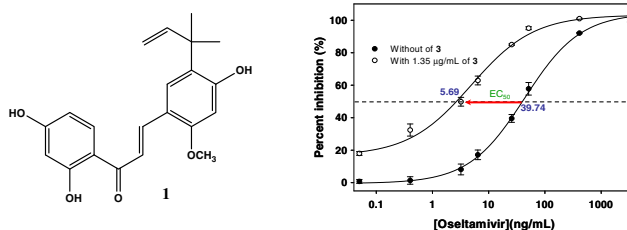
pp 288–293

Michel Gallant*, Christian Beaulieu, Carl Berthelette, John Colucci, Michael A. Crackower, Chad Dalton, Danielle Denis, Yves Ducharme, Richard W. Friesen, Daniel Guay, François G. Gervais, Martine Hamel, Robert Houle, Connie M. Krawczyk, Birgit Kosjek, Stephen Lau, Yves Leblanc, Ernest E. Lee, Jean-François Levesque, Christophe Mellon, Carmela Molinaro, Wayne Mullet, Gary P. O'Neill, Paul O'Shea, Nicole Sawyer, Susan Sillaots, Daniel Simard, Deborah Slipetz, Rino Stocco, Dan Sørensen, Vouy Linh Truong, Elizabeth Wong, Jin Wu, Helmi Zaghdane, Zhaoyin Wang

**Chalcones as novel influenza A (H1N1) neuraminidase inhibitors from *Glycyrrhiza inflata***

pp 294–298

Trong Tuan Dao, Phi Hung Nguyen, Hong Sik Lee, Eunhee Kim, Junsoo Park, Seong Il Lim, Won Keun Oh*

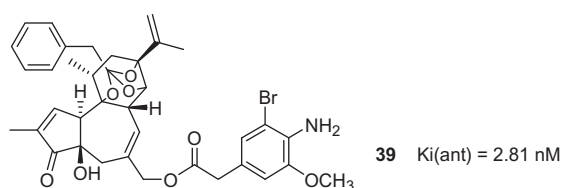


One new licochalcone G (1) and seven known (2–8) chalcones were isolated as inhibitory principles on influenza A virus from the acetone extract of *Glycyrrhiza inflata*. Compounds 3 and 6 without prenyl group showed strong inhibitory effects on various neuraminidases from influenza viral strains, H1N1 and H9N2, and more novel H1N1 (WT) and oseltamivir-resistant novel H1N1 (H274Y) expressed in 293T cells. In addition, the efficacy of oseltamivir with the presence of compound 3 (5 μM) was increased against H274Y neuraminidase.

**Receptor activity and conformational analysis of 5'-halogenated resiniferatoxin analogs as TRPV1 ligands**

pp 299–302

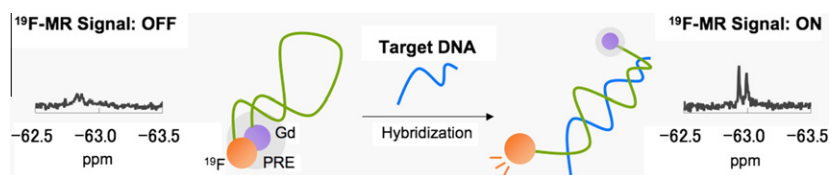
Kwang Su Lim, Dong Wook Kang, Yong Soo Kim, Myeong Seop Kim, Seul-Gi Park, Sun Choi, Larry V. Pearce, Peter M. Blumberg, Jeewoo Lee*



Signal turn-on probe for nucleic acid detection based on ^{19}F nuclear magnetic resonance

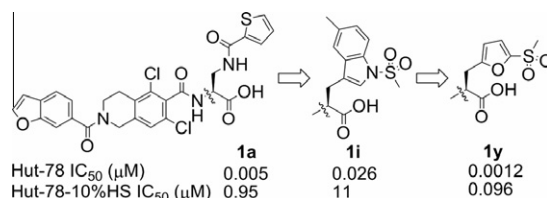
pp 303–306

Takashi Sakamoto, Yu-ki Shimizu, Jun Sasaki, Hikaru Hayakawa, Kenzo Fujimoto*

**Structure–activity relationship (SAR) of the α -amino acid residue of potent tetrahydroisoquinoline (THIQ)-derived LFA-1/ICAM-1 antagonists**

pp 307–310

Min Zhong*, Emily J. Hanan, Wang Shen, Minna Bui, Michelle R. Arkin, Kenneth J. Barr, Marc J. Evanchik, Ute Hoch, Jennifer Hyde, Jose R. Martell, Johan D. Oslob, Kumar Paulvannan, Sailata Prabhu, Jeffrey A. Silverman, Jasmin Wright, Chul H. Yu, Jiang Zhu, W. Mike Flanagan

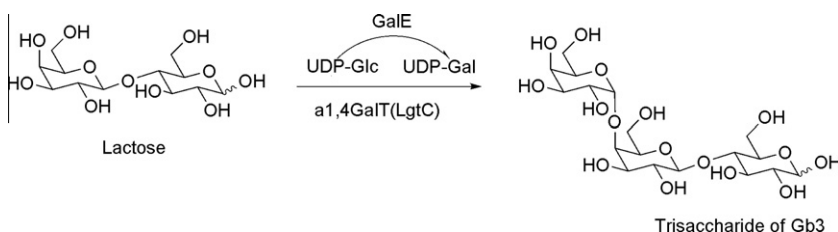


Structure–activity relationship (SAR) of the α -amino acid residue and identification of (*S*)-2,3-diaminopropanoic acid (DAP) replacements of potent tetrahydroisoquinoline (THIQ)-derived LFA-1/ICAM-1 antagonists are described.

Large scale enzymatic synthesis of oligosaccharides and a novel purification process

pp 311–314

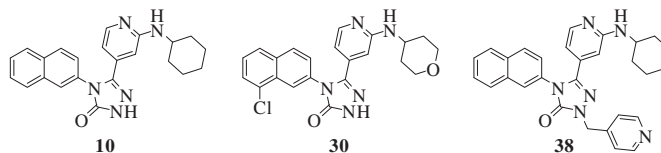
Guangyan Zhou*, Xianwei Liu, Doris Su, Lei Li, Min Xiao, Peng G. Wang*

**Highly selective c-Jun N-terminal kinase (JNK) 2 and 3 inhibitors with in vitro CNS-like pharmacokinetic properties prevent neurodegeneration**

pp 315–319

Gary D. Probst*, Simeon Bowers, Jennifer M. Sealy, Anh P. Truong, Roy K. Hom, Robert A. Galemme Jr., Andrei W. Konradi, Hing L. Sham, David A. Quincy, Hu Pan, Nanhua Yao, May Lin, Gergely Tóth, Dean R. Artis, Wes Zmolek, Karina Wong, Ann Qin, Colin Lorentzen, David F. Nakamura, Kevin P. Quinn, John-Michael Sauer, Kyle Powell, Lany Ruslim, Sarah Wright, David Chereau, Zhao Ren, John P. Anderson, Frédérique Bard, Ted A. Yednock, Irene Griswold-Prenner

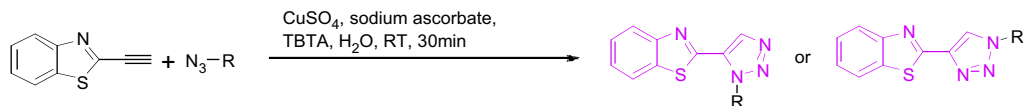
In this Letter, we describe the discovery of selective JNK2 and JNK3 inhibitors, such as **10**, that routinely exhibit >10-fold selectivity over JNK1 and >1000-fold selectivity over related MAPKs, p38 α and ERK2. Substitution of the naphthalene ring affords an isoform selective JNK3 inhibitor, **30**, with approximately 10-fold selectivity over both JNK1 and JNK2. A naphthalene ring penetrates deep into the selectivity pocket accounting for the differentiation amongst the kinases. Interestingly, the gatekeeper Met146 sulfide interacts with the naphthalene ring in a sulfur- π stacking interaction. Compound **38** ameliorates neurotoxicity induced by amyloid- β in human cortical neurons. Lastly, we demonstrate how to install propitious in vitro CNS-like properties into these selective inhibitors.



Development of benzothiazole ‘click-on’ fluorogenic dyes

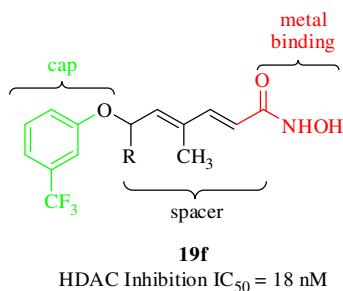
pp 320–323

Jianjun Qi, Ching-Hsuan Tung*

**Design and synthesis of aryl ether and sulfone hydroxamic acids as potent histone deacetylase (HDAC) inhibitors**

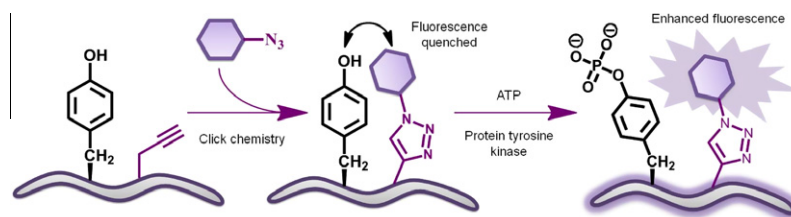
pp 324–328

Chittari Pabba*, Brian T. Gregg*, Douglas B. Kitchen, Zhen Jia Chen, Angela Judkins

**A facile, click chemistry-based approach to assembling fluorescent chemosensors for protein tyrosine kinases**

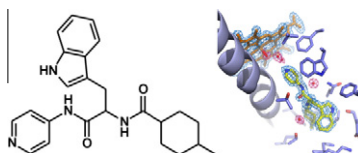
pp 329–331

Mohd Aizuddin Kamaruddin, Phuc Ung, Mohammed Iqbal Hossain, Boonyarin Jarasrassamee, William O'Malley, Philip Thompson, Denis Scanlon, Heung-Chin Cheng, Bim Graham*

**Reverse type I inhibitor of *Mycobacterium tuberculosis* CYP125A1**

pp 332–337

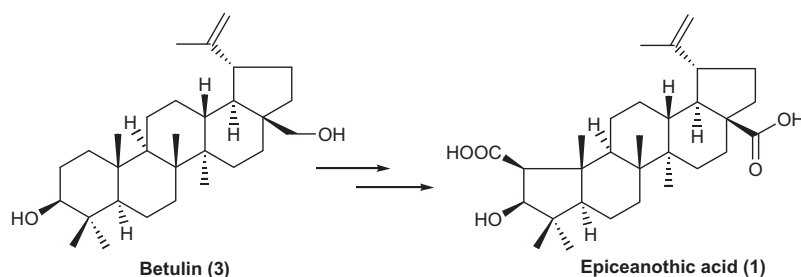
Hugues Ouellet, Petrea M. Kells, Paul R. Ortiz de Montellano, Larissa M. Podust*



Efficient synthesis and biological evaluation of epiceanothic acid and related compounds

pp 338–341

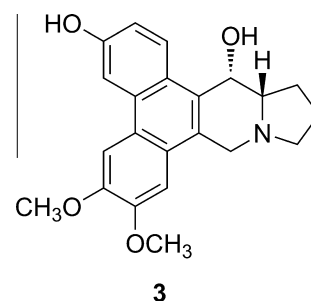
Pu Zhang, Li Xu, Keduo Qian, Jun Liu, Luyong Zhang, Kuo-Hsiung Lee*, Hongbin Sun*

**Asymmetric synthesis of phenanthroindolizidine alkaloids with hydroxyl group at the C14 position and evaluation of their antitumor activities**

pp 342–345

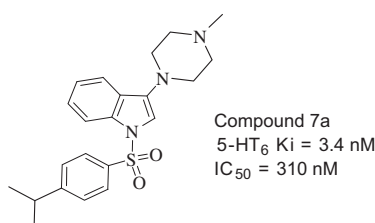
Takashi Ikeda*, Takashi Yaegashi, Takeshi Matsuzaki, Syusuke Hashimoto, Seigo Sawada

The asymmetric total synthesis of the strongly cytotoxic phenanthroindolizidine alkaloid **3** was achieved. Using the same route, various derivatives were also synthesized. Cytotoxicity of those synthetic compounds and the in vivo antitumor efficacy of selected compounds were evaluated.

**Indole-3-piperazinyl derivatives: Novel chemical class of 5-HT₆ receptor antagonists**

pp 346–349

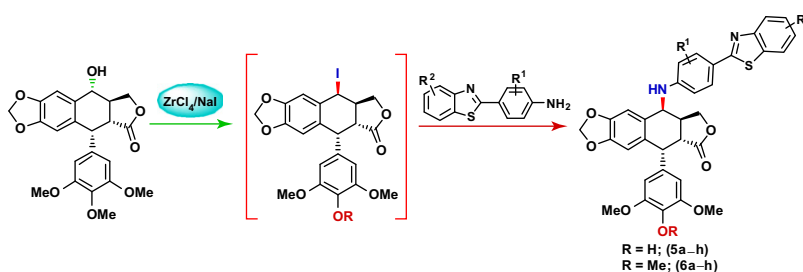
Ramakrishna V. S. Nirogi*, Amol D. Deshpande, Ramasastri Kambhampati, Rajesh Kumar Badange, Laxman Kota, Anand V. Daulatabad, Anil K. Shinde, Ishtiyaque Ahmad, Vishwottam Kandikere, Pradeep Jayarajan, P. K. Dubey

Design, synthesis and SAR of a novel series of *N*₁-arylsulfonyl-3-piperazinyl indole derivatives as 5-HT₆ receptor ligands are reported.**An efficient one-pot synthesis of benzothiazolo-4β-anilino-podophyllotoxin congeners: DNA topoisomerase-II inhibition and anticancer activity**

pp 350–353

Ahmed Kamal*, B. Ashwini Kumar, Paidakula Suresh, Nagula Shankaraiah, M. Shiva Kumar

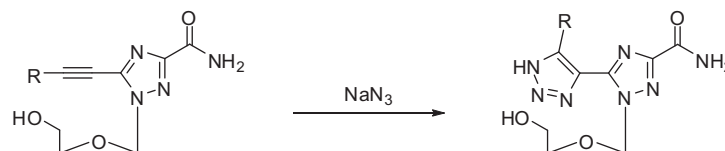
A facile one-pot zirconium tetrachloride and sodium iodide mediated iodination protocol has been applied for the synthesis of benzothiazolo-4β-anilino-podophyllotoxin (**5a–h**) and benzothiazolo-4β-anilino-4-*O*-demethylepipodophyllotoxin (**6a–h**) congeners. Some of these compounds have shown significant in vitro cytotoxicity on selected human cancer cell lines apart from DNA topoisomerase-II inhibition activity.



Bitriazolyl acyclonucleosides synthesized via Huisgen reaction using internal alkynes show antiviral activity against tobacco mosaic virus

pp 354–357

Menghua Wang, Ruizhi Zhu, Zhijin Fan, Yifeng Fu, Liang Feng, Jianhua Yao, Alain Maggiani, Yi Xia, Fanqi Qu, Ling Peng*

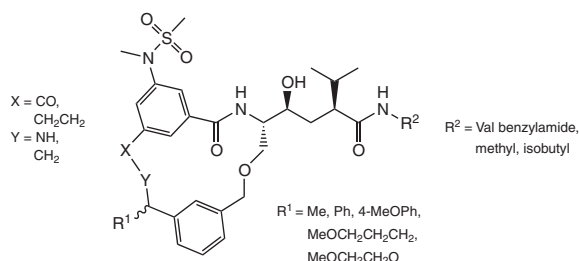


A family of novel bitriazolyl acyclonucleosides were synthesized via the Huisgen reaction by addition of NaN_3 onto the triazole nucleosides bearing internal alkynyl groups introduced at the 5-position of the triazole ring. Some of the synthesized compounds exhibited interesting antiviral activity against tobacco mosaic virus.

**Design and synthesis of potent macrocyclic renin inhibitors**

pp 358–362

Christian Sund*, Oscar Belda, Daniel Wikteliu, Christer Sahlberg, Lotta Vrang, Susanne Sedig, Elizabeth Hamelink, Ian Henderson, Tatiana Agback, Katarina Jansson, Neera Borkakoti, Dean Derbyshire, Anders Eneroth, Bertil Samuelsson

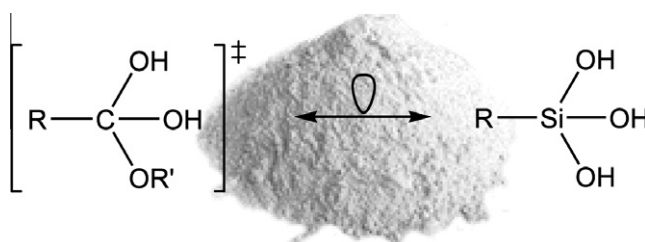


Eight 15–16-membered peptidomimetic macrocycles with the HE scaffold were synthesized and evaluated for their in vitro renin inhibitory activities.

Silanetriols as in vitro inhibitors for AChE

pp 363–365

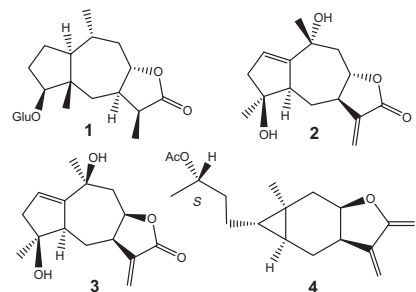
Martina Blunder, Natascha Hurkes, Stefan Spirk, Martina List, Rudolf Pietschnig*

**Antiproliferative and apoptotic sesquiterpene lactones from *Carpesium faberi***

pp 366–372

Xu-Wen Li, Liang Weng, Xue Gao, Yun Zhao, Fei Pang, Jian-Hui Liu, Hong-Feng Zhang, Jin-Feng Hu*

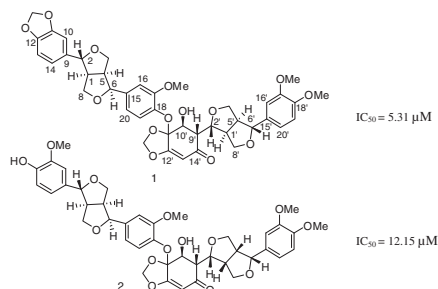
Four new (**1–4**) and 13 known sesquiterpene lactones together with two known diterpenes were isolated from *Carpesium faberi*. All isolated compounds were evaluated for their antiproliferative activities against MCF-7 human breast cancer cells using the MTT assay. The sesquiterpene lactones (except tomentosin **17**) possessing an α -methylene- γ -lactone moiety were found to have significant antiproliferative activities. The cell cycle-specific inhibition and apoptosis induced by selected compounds were investigated using flow cytometry (FCM).



Two dimeric lignans with an unusual α,β -unsaturated ketone motif from *Zanthoxylum podocarpum* and their inhibitory effects on nitric oxide production

pp 373–376

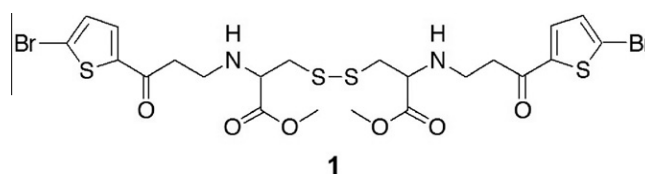
Xiao-Jiang Zhou, Xiao-Liang Chen, Xue-Song Li, Jia Su, Jiang-Bo He, Yue-Hu Wang, Yan Li, Yong-Xian Cheng*



Potent transglutaminase inhibitors, dithio β -aminoethyl ketones

pp 377–379

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

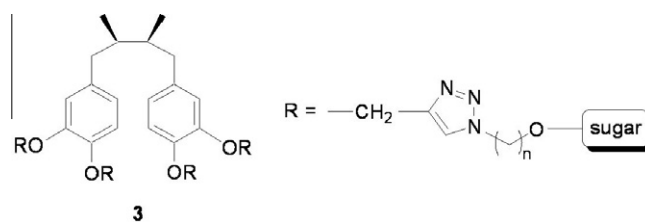


Potent transglutaminase inhibitors were obtained from disulfide compounds, cystamine, dimethyl cystine, and dimethyl homocystine. The disulfide bond and thiophene ring play an important role in inhibitory activity of synthesized aryl β -amino ketones.

Glycosylated nordihydroguaiaretic acids as anti-cancer agents

pp 380–382

Jih Ru Hwu*, Chuan-I Hsu, Ming-Hua Hsu, Yu-Chuan Liang, Ru Chih C. Huang*, Yuan C. Lee*



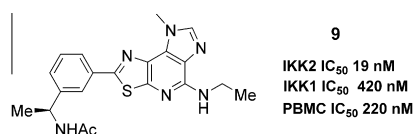
Perglycosylated nordihydroguaiaretic acids were synthesized through the Huiseng 1,3-dipolar cycloaddition reaction, which possessed good water solubility and activity against Hep3B cell line.



Imidazo[4,5-d]thiazolo[5,4-b]pyridine based inhibitors of IKK2: Synthesis, SAR, PK/PD and activity in a preclinical model of rheumatoid arthritis

pp 383–386

Alaric J. Dyckman*, Charles M. Langevine, Claude Quesnelle, James Kempson, Junqing Guo, Patrice Gill, Steven H. Spergel, Scott H. Watterson, Tianle Li, David S. Nirschl, Kathleen M. Gillooly, Mark A. Pattoli, Kim W. McIntyre, Laishun Chen, Murray McKinnon, John H. Dodd, Joel C. Barrish, James R. Burke, William J. Pitts



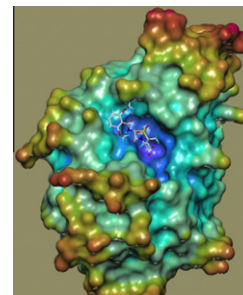
The synthesis, structure–activity relationships (SAR) and biological evaluation of thiazole based tricyclic inhibitors of IKK2 are described. Compound **9** was determined to be efficacious in a murine model for rheumatoid arthritis.

Modifications of the C6-substituent of penicillin sulfones with the goal of improving inhibitor recognition and efficacy

pp 387–393

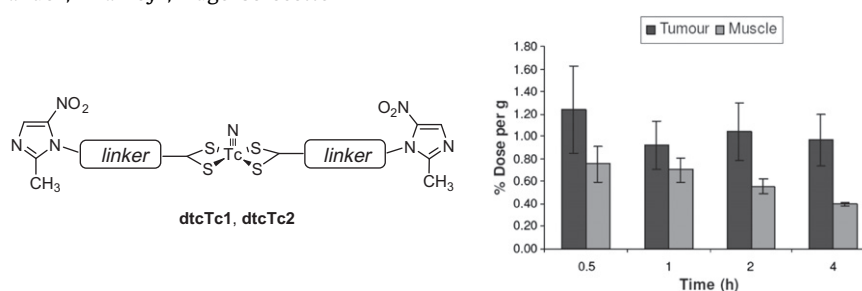
Micheal Nottingham, Christopher R. Bethel, Sundar Ram Reddy Pagadala, Emily Harry, Abishai Pinto, Zachary A. Lemons, Sarah M. Drawz, Focco van den Akker, Paul R. Carey, Robert A. Bonomo, John D. Buynak*

The importance of an H-bond donating substituent on the β -lactamase inhibitory activity was assessed through the synthesis and evaluation of a systematic series of 6 β -substituted penicillin sulfones.

**Synthesis and biological characterisation of novel dithiocarbamate containing 5-nitroimidazole ^{99m}Tc -complexes as potential agents for targeting hypoxia**

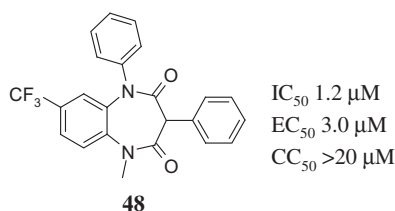
pp 394–397

Javier Giglio, Soledad Fernández, Ana Rey*, Hugo Cerecetto*

**Discovery of a 1,5-dihydrobenzo[b][1,4]diazepine-2,4-dione series of inhibitors of HIV-1 capsid assembly**

pp 398–404

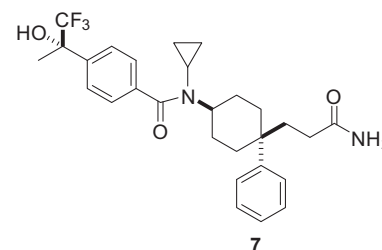
Lee D. Fader*, Richard Bethell, Pierre Bonneau, Michael Bös, Yves Bousquet, Michael G. Cordingley, René Coulombe, Patrick Deroy, Anne-Marie Faucher, Alexandre Gagnon, Nathalie Goudreau, Chantal Grand-Maître, Ingrid Guse, Oliver Hucke, Stephen H. Kawai, Jean-Eric Lacoste, Serge Landry, Christopher T. Lemke, Eric Malenfant, Stephen Mason, Sébastien Morin, Jeff O'Meara, Bruno Simoneau, Steve Titolo, Christiane Yoakim

**Synthesis and optimization of novel 4,4-disubstituted cyclohexylbenzamide derivatives as potent 11 β -HSD1 inhibitors**

pp 405–410

Daqing Sun*, Zhulun Wang, Seb Caille, Michael DeGraffenreid, Felix Gonzalez-Lopez de Turiso, Randall Hungate, Juan C. Jaen, Ben Jiang, Lisa D. Julian, Ron Kelly, Dustin L. McMinn, Jacob Kaizerman, Yosup Rew, Athena Sudom, Hua Tu, Stefania Ursu, Nigel Walker, Maren Willcockson, Xuelei Yan, Qiuping Ye, Jay P. Powers

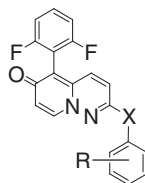
The synthesis and SAR of a series of 4,4-disubstituted cyclohexylbenzamide inhibitors of 11 β -HSD1 are described. Optimization rapidly led to potent, highly selective, and orally bioavailable inhibitors demonstrating efficacy in both rat and non-human primate ex vivo pharmacodynamic models.



Synthesis and biological activity of pyridopyridazin-6-one p38 MAP kinase inhibitors. Part 1

pp 411–416

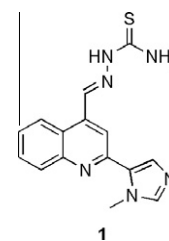
Robert M. Tynebor*, Meng-Hsin Chen, Swaminathan R. Natarajan, Edward A. O'Neill, James E. Thompson, Catherine E. Fitzgerald, Stephen J. O'Keefe, James B. Doherty

**A novel series of IKK β inhibitors part I: Initial SAR studies of a HTS hit**

pp 417–422

Timothy D. Cushing*, Vijay Baichwal, Karen Berry, Roland Billedeau, Viola Bordunov, Chris Broka, Mario Cardozo, Peng Cheng, David Clark, Stacie Dalrymple, Michael DeGraffenreid, Adrian Gill, Xiaolin Hao, Ronald C. Hawley, Xiao He, Juan C. Jaen, Sharada S. Labadie, Marc Labelle, Csaba Lehel, Pu-Ping Lu, Joel McIntosh, Shichang Miao, Camran Parast, Youngsook Shin, Eric B. Sjogren, Marie-Louise Smith, Francisco X. Talamas, George Tonn, Keith M. Walker, Nigel P. C. Walker, Holger Wesche, Chris Whitehead, Matt Wright, Michelle F. Browner

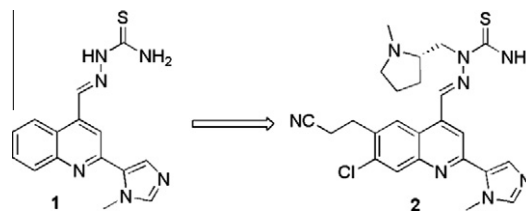
A novel series of thiosemicarbazides was discovered as potent inhibitors of IKK β .

**A novel series of IKK β inhibitors part II: Description of a potent and pharmacologically active series of analogs**

pp 423–426

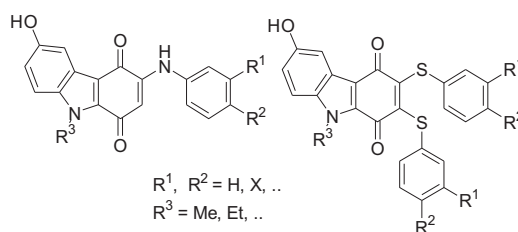
Timothy D. Cushing*, Vijay Baichwal, Karen Berry, Roland Billedeau, Viola Bordunov, Chris Broka, Michelle F. Browner, Mario Cardozo, Peng Cheng, David Clark, Stacie Dalrymple, Michael DeGraffenreid, Adrian Gill, Xiaolin Hao, Ronald C. Hawley, Xiao He, Sharada S. Labadie, Marc Labelle, Csaba Lehel, Pu-Ping Lu, Joel McIntosh, Shichang Miao, Camran Parast, Youngsook Shin, Eric B. Sjogren, Marie-Louise Smith, Francisco X. Talamas, George Tonn, Keith M. Walker, Nigel P. C. Walker, Holger Wesche, Chris Whitehead, Matt Wright, Juan C. Jaen

Compound **2** was the culmination of SAR efforts from HTS lead **1**. It has submicromolar potency in a HWB assay and efficacy in a CIA mouse model.

**Synthesis and antifungal evaluation of 6-hydroxy-1*H*-carbazole-1,4(9*H*)-diones**

pp 427–430

Chung-Kyu Ryu*, Seung-Yon Lee, Na Young Kim, Jung An Hong, Joo Hee Yoon, Aram Kim

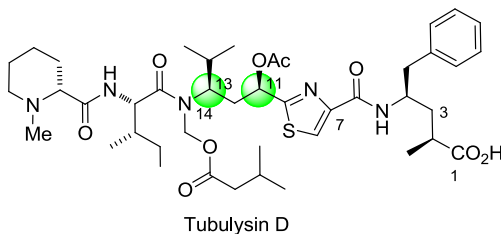


6-Hydroxy-1*H*-carbazole-1,4(9*H*)-diones were synthesized and tested for in vitro antifungal activity against fungi. Many of these tested compounds exhibited potent antifungal activity.

Synthesis and biological evaluation of tubulysin D analogs related to stereoisomers of tubuvaline

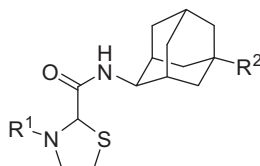
pp 431–434

Taku Shibue, Iwao Okamoto, Nobuyoshi Morita, Hiroshi Morita, Yusuke Hirasawa, Takahiro Hosoya, Osamu Tamura*

**Synthesis and 11 β hydroxysteroid dehydrogenase 1 inhibition of thiazolidine derivatives with an adamantyl group**

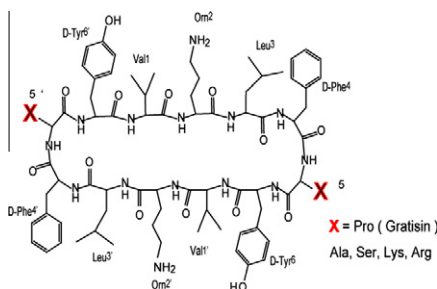
pp 435–439

Sung Wook Kwon, Seung Kyu Kang, Jae Hong Lee, Joo Hwan Bok, Chi Hyun Kim, Sang Dal Rhee, Won Hoon Jung, Hee Youn Kim, Myung Ae Bae, Jin Sook Song, Duck Chan Ha, Hyae Gyoung Cheon, Ki Young Kim*, Jin Hee Ahn*

**Novel gratisin derivatives with high antimicrobial activity and low hemolytic activity**

pp 440–443

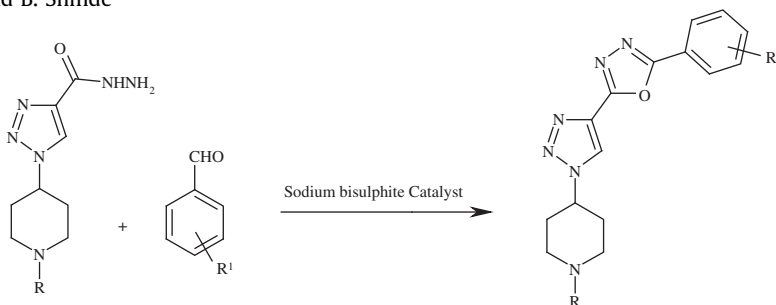
Makoto Tamaki*, Yukie Imazeki, Aya Shirane, Kenta Fujinuma, Mitsuno Shindo, Masahiro Kimura, Yoshiki Uchida

**Microwave assisted one pot synthesis of some novel 2,5-disubstituted 1,3,4-oxadiazoles as antifungal agents**

pp 444–448

Jaiprakash N. Sangshetti, Aniruddha R. Chabukswar, Devanand B. Shinde*

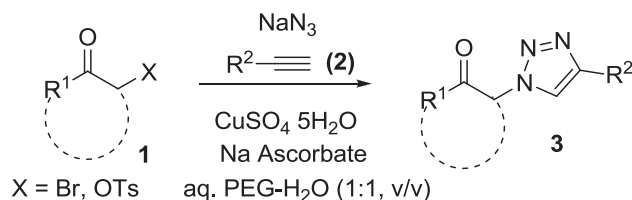
Sodium bisulfite has been reported first time for the synthesis of 2,5-disubstituted 1,3,4-oxadiazole using microwave and conventional method in ethanol–water. The yields obtained are in the range of 90–95% using microwave and 87–91% using conventional method. All the synthesized compounds (**8a–8s**) are novel and were evaluated for their in vitro antifungal activity.



Click chemistry inspired one-pot synthesis of 1,4-disubstituted 1,2,3-triazoles and their Src kinase inhibitory activity

pp 449–452

Dalip Kumar*, V. Buchi Reddy, Anil Kumar, Deendayal Mandal, Rakesh Tiwari, Keykavous Parang*



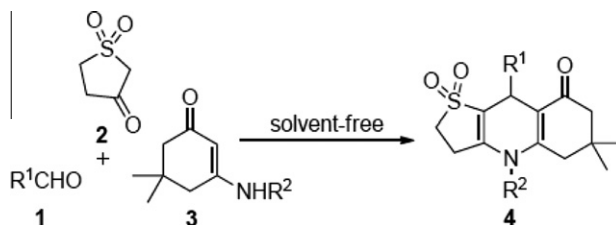
The synthesis and Src kinase inhibitory activity of two classes of 1,4-disubstituted 1,2,3-triazoles are reported.



Design and efficient synthesis of A-278637 derivatives as potential potassium channel opener

pp 453–455

Tuanjie Li, Xiaodong Feng, Changsheng Yao*, Chenxia Yu, Bei Jiang, Shujiang Tu

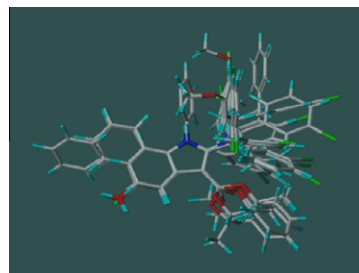
A series of thieno[3,2-*b*]quinoline derivatives designed based on A-278637 scaffold, were synthesized efficiently via one-pot three-component reaction under solvent-free and catalyst-free conditions. This work provides a new compound library with potential biological activity for biomedical screening.

CoMFA and CoMSIA studies on 5-hydroxyindole-3-carboxylate derivatives as 5-lipoxygenase inhibitors: Generation of homology model and docking studies

pp 456–462

P. Aparoy, G. K. Suresh, K. Kumar Reddy, P. Reddanna*

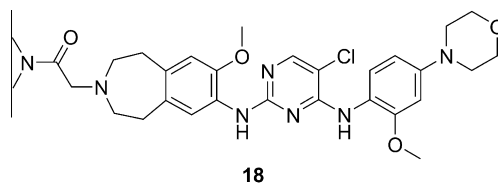
In this Letter, CoMFA and CoMSIA were performed on a series of 2-substituted 5-hydroxyindole-3-carboxylate derivatives as potent 5-LOX inhibitors. The data generated from the present study will further help design and validate novel and potent 5-LOX inhibitors.



Novel 2,3,4,5-tetrahydro-benzo[d]azepine derivatives of 2,4-diaminopyrimidine, selective and orally bioavailable ALK inhibitors with antitumor efficacy in ALCL mouse models

pp 463–466

Eugen F. Mesaros*, Jason P. Burke, Jonathan D. Parrish, Benjamin J. Dugan, Andrew V. Anzalone, Thelma S. Angeles, Mark S. Albom, Lisa D. Aimone, Matthew R. Quail, Weihua Wan, Lihui Lu, Zeqi Huang, Mark A. Ator, Bruce A. Ruggeri, Mangeng Cheng, Gregory R. Ott*, Bruce D. Dorsey

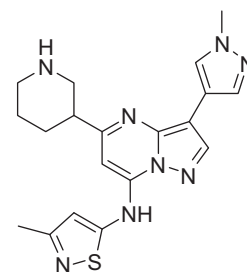
ALK $\text{IC}_{50} = 4 \text{ nM}$

Discovery of pyrazolo[1,5-*a*]pyrimidine-based CHK1 inhibitors: A template-based approach—Part 1

pp 467–470

Michael P. Dwyer*, Kamil Paruch, Marc Labroli, Carmen Alvarez, Kerry M. Keertikar, Cory Poker, Randall Rossman, Thierry O. Fischmann, Jose S. Duca, Vincent Madison, David Parry, Nicole Davis, Wolfgang Seghezzi, Derek Wiswell, Timothy J. Guzi

The synthesis and SAR development of a pyrazolo[1,5-*a*]pyrimidine-based structural series is described which led to the identification of potent, selective CHK1 inhibitors such as **17r**.

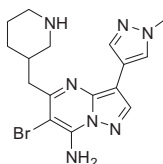


17r CHK1 IC₅₀ = 0.009 μM
CDK2 IC₅₀ = 40 μM

Discovery of pyrazolo[1,5-*a*]pyrimidine-based CHK1 inhibitors: A template-based approach—Part 2

pp 471–474

Marc Labroli*, Kamil Paruch, Michael P. Dwyer, Carmen Alvarez, Kartik Keertikar, Cory Poker, Randall Rossman, Jose S. Duca, Thierry O. Fischmann, Vincent Madison, David Parry, Nicole Davis, Wolfgang Seghezzi, Derek Wiswell, Timothy J. Guzi



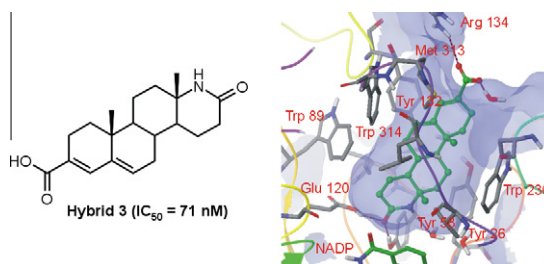
22j; CHK1 IC₅₀ = 0.007 μM, CDK2 = 2.4 μM

Previous efforts by our group have established pyrazolo[1,5-*a*]pyrimidine as a viable core for the development of potent and selective CDK inhibitors. As part of an effort to utilize the pyrazolo[1,5-*a*]pyrimidine core as a template for the design and synthesis of potent and selective kinase inhibitors, we focused on a key regulator in the cell cycle progression, CHK1. Continued SAR development of the pyrazolo[1,5-*a*]pyrimidine core at the C5 and C6 positions, in conjunction with previously disclosed SAR at the C3 and C7 positions, led to the discovery of potent and selective CHK1 inhibitors.

Discovery of a novel hybrid from finasteride and epristeride as 5α-reductase inhibitor

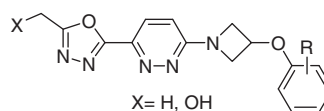
pp 475–478

Zhiyi Yao, Yingjun Xu, Minmin Zhang, Sheng Jiang, Marc C. Nicklaus, Chenzhong Liao*

**Biological activity and preclinical efficacy of azetidinyl pyridazines as potent systemically-distributed stearoyl-CoA desaturase inhibitors**

pp 479–483

Elise Isabel*, David A. Powell, W. Cameron Black, Chi-Chung Chan, Sheldon Crane, Robert Gordon, Jocelyne Guay, Sebastien Guiral, Zheng Huang, Joël Robichaud, Kathryn Skorey, Paul Tawa, Lijing Xu, Lei Zhang, Renata Oballa

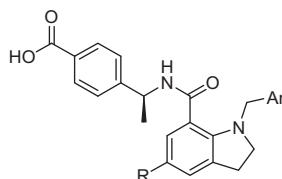


Potent and orally bioavailable azetidinyl pyridazines SCD inhibitors were identified. Preclinical in vivo data and synthesis of a radiolabeled ligand are reported.

A novel series of potent and selective EP₄ receptor ligands: Facile modulation of agonism and antagonism

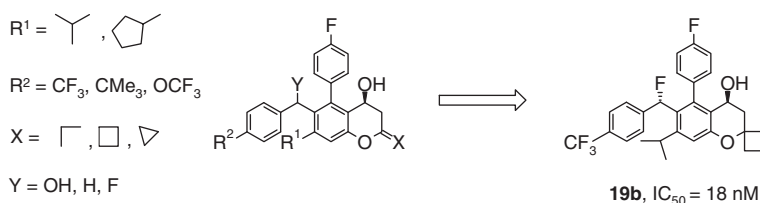
pp 484–487

Michael J. Boyd*, Carl Berthelette, Jean-François Chiasson, Patsy Clark, John Colucci, Danielle Denis, Yongxin Han, Jean-François Lévesque, Marie-Claude Mathieu, Rino Stocco, Alex Therien, Steve Rowland, Mark Wrona, Daigen Xu

**Chromanol derivatives—A novel class of CETP inhibitors**

pp 488–491

Alexandros Vakalopoulos*, Carsten Schmeck, Michael Thutewohl, Volkhart Li, Hilmar Bischoff, Klemens Lustig, Olaf Weber, Holger Paulsen, Harry Elias

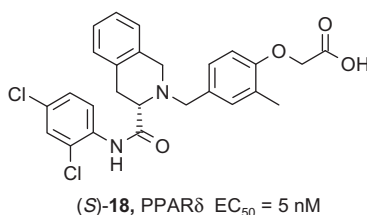


A novel chemical class of active cholesteryl ester transfer protein (CETP) inhibitors were prepared and an evaluation of the structure–activity relationships of these chromanols is described. Compound **19b** was identified as a potent CETP inhibitor with an excellent in vitro and PK-profile.

Discovery of isoindoline and tetrahydroisoquinoline derivatives as potent, selective PPAR δ agonists

pp 492–496

Christopher A. Luckhurst*, Linda A. Stein, Mark Furber, Nicola Webb, Marianne J. Ratcliffe, Gary Allenby, Sara Botterell, Wendy Tomlinson, Barrie Martin, Andrew Walding

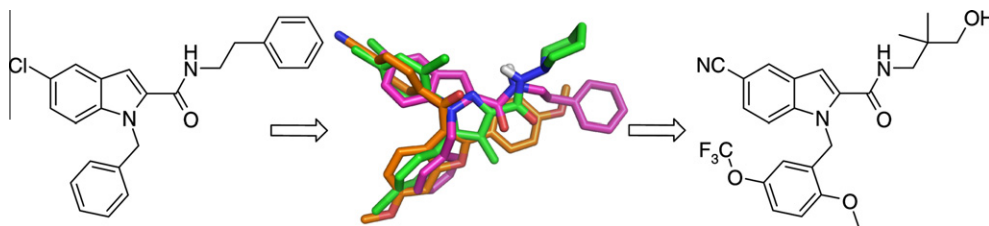


We describe the discovery of small molecule isoindoline and tetrahydroisoquinoline derivatives as agonists of human peroxisome proliferator-activated receptor δ (PPAR δ) that displayed excellent selectivity over the PPAR α and PPAR γ subtypes. Compound **18** demonstrated efficacy in upregulation of PDK4 in human primary myotubes, a biomarker for increased fatty acid oxidation.

The discovery of novel indole-2-carboxamides as cannabinoid CB₁ receptor antagonists

pp 497–501

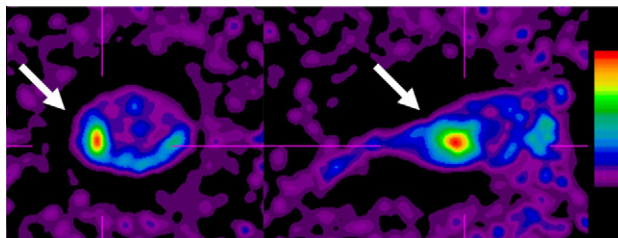
Phillip M. Cowley*, James Baker, David R. Barn, Kirsteen I. Buchanan, Ian Carlyle, John K. Clark, Thomas R. Clarkson, Maureen Deehan, Darren Edwards, Richard R. Goodwin, David Jaap, Yasuko Kiyoi, Chris Mort, Ronald Palin, Alan Prosser, Glenn Walker, Nick Ward, Grant Wishart, Trevor Young



Radiolabeling and preliminary biological evaluation of a $^{99m}\text{Tc}(\text{CO})_3$ labeled 3,3'-(benzylidene)-bis-(1*H*-indole-2-carbohydrazide) derivative as a potential SPECT tracer for in vivo visualization of necrosis

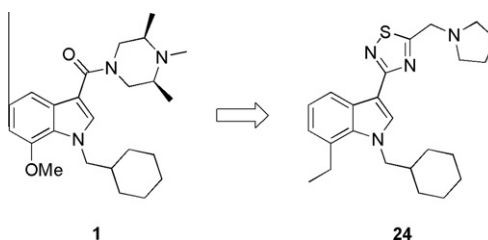
pp 502–505

Kristof Prinsen, Lixin Jin, Kathleen Vunckx, Marijke De Saint-Hubert, Lin Zhou, Jan Cleynhens, Johan Nuyts, Guy Bormans, Yicheng Ni, Alfons Verbruggen*


Design, synthesis, and structure–activity relationships of indole-3-heterocycles as agonists of the CB1 receptor

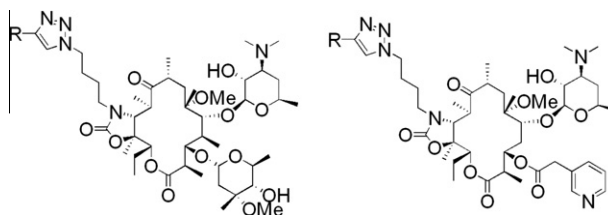
pp 506–509

Angus J. Morrison*, Julia M. Adam*, James A. Baker, Robert A. Campbell, John K. Clark, Jean E. Cottney, Maureen Deehan, Anna-Marie Easson, Ruth Fields, Stuart Francis, Fiona Jeremiah, Neil Keddle, Takao Kiyoi, Duncan R. McArthur, Karsten Meyer, Paul D. Ratcliffe, Jurgen Schulz, Grant Wishart, Kazuya Yoshiizumi


Synthesis and antibacterial activity of novel 4-aryl-[1,2,3]-triazole containing macrolides

pp 510–513

David Pereira*, Prabhavathi Fernandes

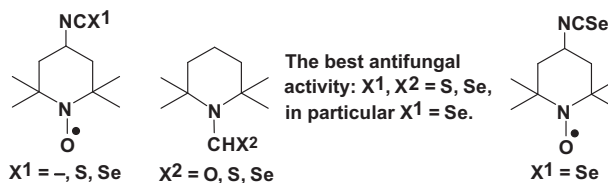


Two series of novel triazole containing 14-member macrolides having either a cladinose or a 3-pyridyl acetate group the 3-position of the macrolide ring were synthesized.

Reactions of nitroxides. Part X: Antifungal activity of selected sulfur and selenium derivatives of 2,2,6,6-tetramethylpiperidine

pp 514–516

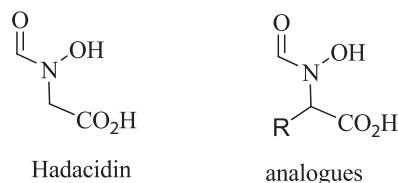
Jerzy Zakrzewski*, Maria Krawczyk



Evaluation of hadacidin analogues

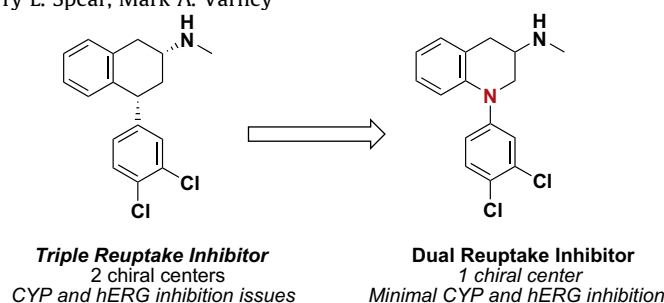
pp 517–519

Nidhi Tibrewal, Gregory I. Elliott*

**Discovery of 1-(3,4-dichlorophenyl)-N,N-dimethyl-1,2,3,4-tetrahydroquinolin-4-amine, a dual serotonin and dopamine reuptake inhibitor**

pp 520–523

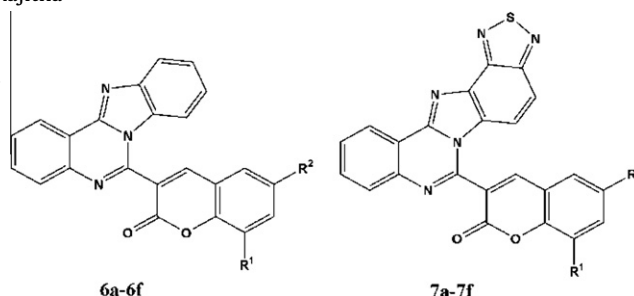
Liming Shao*, Jianguo Ma, Fengjiang Wang, Scott C. Malcolm, Michael C. Hewitt, Una C. Campbell, Nancy A. Spicer, Larry W. Hardy, Rudy Schreiber, Kerry L. Spear, Mark A. Varney

**3-[Benzimidazo- and 3-[benzothiadiazoleimidazo-(1,2-c)quinazolin-5-yl]-2H-chromene-2-ones as potent antimicrobial agents**

pp 524–527

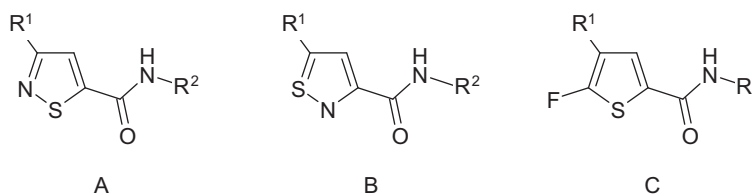
B. Suresh Kuarm, Y. Thirupathi Reddy, J. Venu Madhav, Peter A. Crooks, B. Rajitha*

A series of 3-[benzimidazo(1,2-c)quinazolin-5-yl]-2H-chromene-2-one (**6a–6f**) and 3-[benzothiadiazoleimidazo(1,2-c)quinazolin-5-yl]-2H-chromene-2-one (**7a–7f**) derivatives that incorporate a variety of substituents at the 6- and/or 8-positions of the coumarin moieties have been synthesized utilizing cellulose sulfuric acid as an efficient catalyst under both conventional heating and microwave irradiation procedures. These analogs were evaluated for their antimicrobial activity against *Bacillus subtilis*, *Staphylococcus aureus*, *Streptococcus pyogenes* (Gram-positive bacteria); *Escherichia coli*, *Klebsiella pneumonia*, *Salmonella typhimurium* (Gram-negative bacteria); and *Aspergillus niger*, *Candida albicans*, and *Aspergillus flavus* (Fungi). Two analogs, **6c** (a 6,8-dichloro analog; MIC_[SA] = 2.5 µg/mL; MIC_[ST] = 2.5 µg/mL) and **7d** (a 6,8-dibromo analog; MIC_[ST] = 2.5 µg/mL) were identified as potent antibacterial agents, and two analogs, **6b** (a 6-bromo analog; MIC_[AF] = 10 µg/mL) and **6d** (a 6,8-dibromo analog; MIC_[AF] = 15 µg/mL; MIC_[CA] = 15 µg/mL), were identified as potent antifungal agents. Based on the MIC data, analogs **6b**, **6c**, **6d**, and **7d** were identified as the most potent antimicrobial agents in the series.

**Thiophene and bioisostere derivatives as new MMP12 inhibitors**

pp 528–530

Matthew Badland*, Delphine Compère*, Karine Courté, Anne-Claude Dublanchet, Stéphane Blais, Ajith Manage, Guillaume Peron, Roger Wrigglesworth




pp 531–536

8 (single isomer): PPAR δ EC₅₀ = 3 nM

pp 537–541

10n
BACE-1 IC₅₀ = 10 nM
HEKSw IC₅₀ = 26 nM

pp 542–545



$R^1 = \text{CN}, R^2 = \text{CH}_3\text{C}=\text{CH}_2$ (**7**);
 $R^1 = \text{HCO}, R^2 = \text{HC}(\text{CH}_3)_2$ (**18**);
 $R^1 = \text{HCO}, R^2 = \text{CH}_3\text{C}=\text{CH}_2$ (**19**)



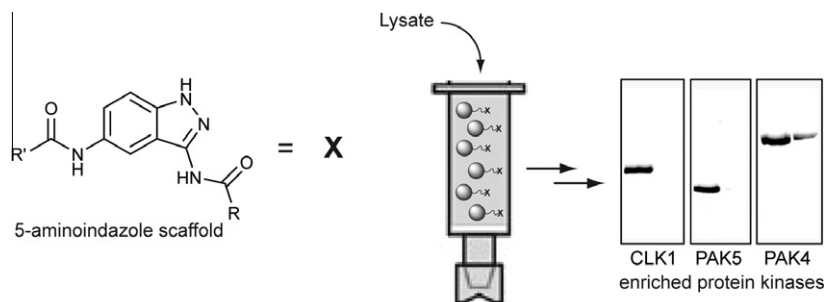
pp 546–549

15

Protein kinase affinity reagents based on a 5-aminoindazole scaffold

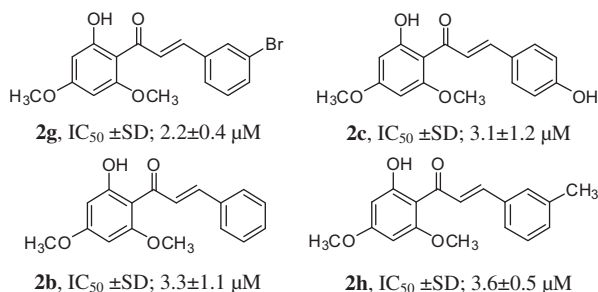
pp 550–554

Ratika Krishnamurthy, Amanda M. Brock, Dustin J. Maly*

**Chalcone-based inhibitors against hypoxia-inducible factor 1—Structure activity relationship studies**

pp 555–557

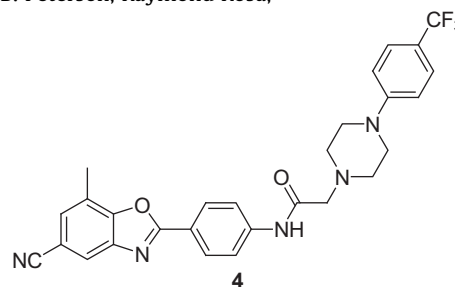
Balasubramanian Srinivasan, Thomas E. Johnson, Chengguo Xing*

**2-Arylbenzoxazoles as CETP inhibitors: Raising HDL-C in cynoCETP transgenic mice**

pp 558–561

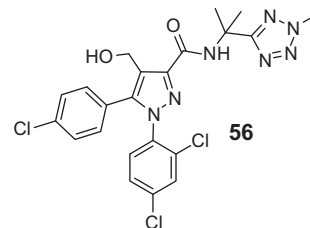
Florida Kallashi*, Doseop Kim, Jennifer Kowalchick, You Jung Park, Julianne A. Hunt, Amjad Ali, Cameron J. Smith, Milton L. Hammond, James V. Pivnichny, Xinchun Tong, Suoyu S. Xu, Matt S. Anderson, Ying Chen, Suzanne S. Eveland, Qiu Guo, Sheryl A. Hyland, Denise P. Milot, Anne-Marie Cumiskey, Melanie Latham, Laurence B. Peterson, Raymond Rosa, Carl P. Sparrow, Samuel D. Wright, Peter J. Sinclair

Compound **4** was found to be a potent inhibitor of CETP (CE IC₅₀ = 16 nM, TG IC₅₀ = 18 nM) with good pharmacokinetic properties and in vivo efficacy (ΔHDL-C = 24 mg/dL).

**Novel pyrazole-3-carboxamide derivatives as cannabinoid-1 (CB1) antagonists: Journey from non-polar to polar amides**

pp 562–568

Pradip K. Sasmal*, D. Srinivasa Reddy, Rashmi Talwar, B. Venkatesham, D. Balasubrahmanyam, M. Kannan, P. Srinivas, K. Shiva Kumar, B. Neelima Devi, Vikram P. Jadhav, Sanjoy K. Khan, Priya Mohan, Hira Chaudhury, Debnath Bhuniya, Javed Iqbal, Ranjan Chakrabarti



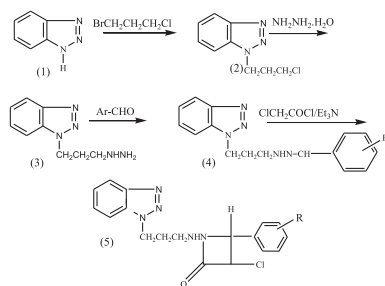
The synthesis and biological evaluation of novel pyrazole-3-carboxamide derivatives as CB1 antagonists are described. The in vivo proof of principle for weight loss is exemplified with compound **56** from this series.



Conventional and microwave assisted synthesis of 2-oxo-4-substituted aryl-azetidine derivatives of benzotriazole: A new class of biological compounds

pp 569–573

Adesh Dubey*, S. K. Srivastava, S. D. Srivastava

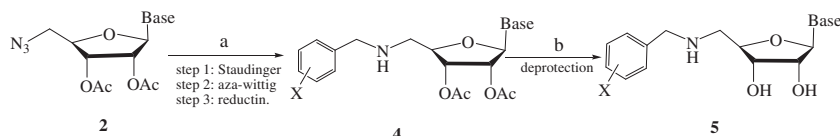


Some new kind of azetidinone derivatives of benzotriazole **5a–i** synthesized from *N*-[(benzylidene hydrazino)-propyl]-benzotriazole **4a–i**. The reaction was carried out by both conventional and microwave methods. Some azetidinone derivatives of benzotriazole displayed better antitubercular and antimicrobial activity.

Synthesis and biological activity of novel 5'-arylamino-nucleosides by microwave-assisted one-pot tandem Staudinger/aza-Wittig/reduction

pp 574–576

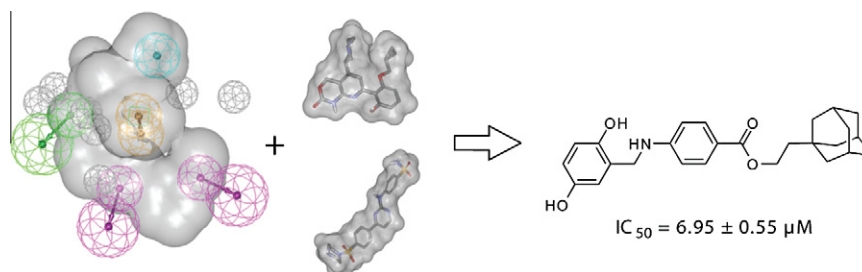
Hua Chen, Jianpeng Zhao, Yanan Li, Fengjuan Shen, Xiaoliu Li*, Qingmei Yin, Zhanbin Qin, Xinhao Yan, Yanfei Wang, Pingzhu Zhang, Jinchao Zhang



Discovery of a novel IKK-β inhibitor by ligand-based virtual screening techniques

pp 577–583

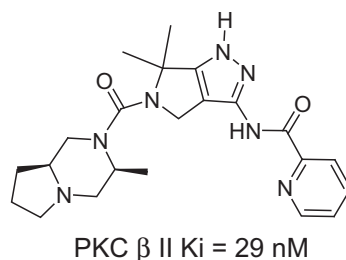
Stefan M. Noha, Atanas G. Atanasov, Daniela Schuster, Patrick Markt, Nanang Fakhruddin, Elke H. Heiss, Olivia Schrammel, Judith M. Rollinger, Hermann Stuppner, Verena M. Dirsch, Gerhard Wolber*



Identification of novel pyrrolopyrazoles as protein kinase C β II inhibitors

pp 584–587

Hui Li*, Yufeng Hong, Seiji Nukui, Jihong Lou, Sarah Johnson, Stephanie Scales, Iriny Botrous, Eileen Tompkins, Chunfeng Yin, Ru Zhou, Mingying He, Jordan Jensen, Djamel Bouzida, Gordon Alton, Jennifer Lafontaine*, Stephan Grant

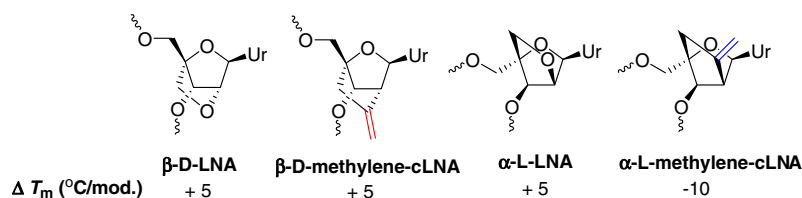


The discovery and initial SAR of a series of novel pyrrolopyrazole PKC β II inhibitors are reported.

Replacing the 2'-oxygen with an exocyclic methylene group reverses the stabilization effects of α -L-LNA

pp 588–591

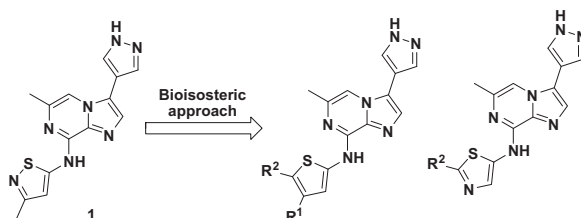
Punit P. Seth*, Charles R. Allerson, Andres Berdeja, Eric E. Swayze



Bioisosteric approach to the discovery of imidazo[1,2-a]pyrazines as potent Aurora kinase inhibitors

pp 592–598

Zhaoyang Meng*, Bheemashankar A. Kulkarni, Angela D. Kerekes, Amit K. Mandal, Sara J. Esposito, David B. Belanger, Panduranga Adulla Reddy, Andrea D. Basso, Seema Tevar, Kimberly Gray, Jennifer Jones, Elizabeth B. Smith, Ronald J. Doll, M. Arshad Siddiqui

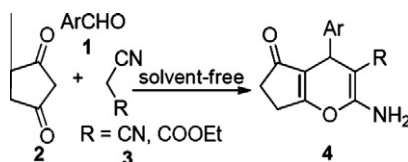


Our continued effort toward the development of the imidazo[1,2-a]pyrazine scaffold as Aurora kinase inhibitors is described. Bioisosteric approach was applied to optimize the 8-position of the core. Several new potent Aurora A/B dual inhibitors, such as **25k** and **25l**, were identified.

Design and an efficient synthesis of natural product-based cyclopenta[b]pyran derivatives with potential bioactivity

pp 599–601

Changsheng Yao, Bei Jiang, Tuanjie Li, Bingbin Qin, Xiaodong Feng, Honghong Zhang, Cuihua Wang, Shuijiang Tu*



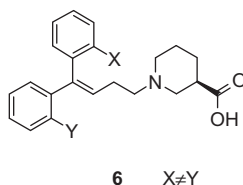
A series of 4-aryl-cyclopenta[b]pyran derivatives, designed based on natural product scaffold, were synthesized efficiently via multi-component reaction under solvent-free and catalyst-free conditions. This chemistry provides a new compound library with potential activity for biomedical screening.



Stereospecific synthesis and structure–activity relationships of unsymmetrical 4,4-diphenylbut-3-enyl derivatives of nipecotic acid as GAT-1 inhibitors

pp 602–605


Domenica A. Pizzi*, Colin P. Leslie*, Romano Di Fabio, Catia Seri, Giovanni Bernasconi, Michela Squaglia, Gennaro Carnevale, Alessandro Falchi, Elisabetta Greco, Laura Mangiarini, Michele Negri



Two complementary stereospecific syntheses of unsymmetrical 4,4-diphenylbut-3-enyl derivatives **6** ($X \neq Y$) are reported. Structure–activity relationships of compounds **6** at the GAT-1 transporter are presented with the optimal substitution pattern leading to potency (**6ac**, $X = \text{Me}$, $Y = \text{F}$, $\text{fp}K_i = 7.83$) comparable to the clinical standard tiagabine.

OTHER CONTENT**Corrigendum****p 606**

*Corresponding author

+ Supplementary data available via ScienceDirect**COVER**

Botulinum neurotoxins are the most deadly toxins known to man, approximately 10 million times more deadly than cyanide. Botulinum neurotoxins are classified by the US Centers for Disease Control (CDC) as bioterrorism agents. The etiological agent responsible for botulinum intoxication is a metalloprotease; as such this is a key therapeutic target. Currently, there are no approved pharmacological treatments for botulinum intoxication. Discovering molecules that could be used as a path forward for therapeutic development as botulinum protease inhibitors is tantamount. A benzylidene cyclopentenedione-based inhibitor was found to be the first affinity reagent to covalently modify the active site of botulinum neurotoxin A light chain metalloprotease. Its kinetic parameters are reported and such an approach for inhibition of this deadly neurotoxin. [Capková, K.; Hixon, M. S.; Pellett, S.; Barbieri, J. T.; Johnson, E. A.; Janda, K. D. *Bioorg. Med. Chem. Lett.* **2010**, 20, 206.]

Available online at www.sciencedirect.com

Indexed/Abstracted in: Beilstein, Biochemistry & Biophysics Citation Index, CANCERLIT, Chemical Abstracts, Chemistry Citation Index, Current Awareness in Biological Sciences/BIOBASE, Current Contents: Life Sciences, EMBASE/Excerpta Medica, MEDLINE, PASCAL, Research Alert, Science Citation Index, SciSearch, TOXFILE. Also covered in the abstract and citation database SCOPUS®. Full text available on ScienceDirect®

**ELSEVIER**

ISSN 0960-894X