



Bioorganic & Medicinal Chemistry Letters Vol. 19, No. 8, 2009

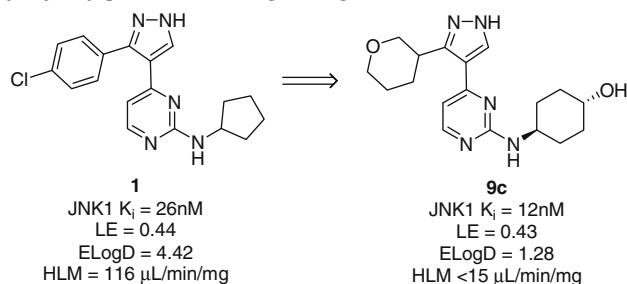
Contents

ARTICLES

Synthesis and SAR of 4-substituted-2-aminopyrimidines as novel c-Jun N-terminal kinase (JNK) inhibitors

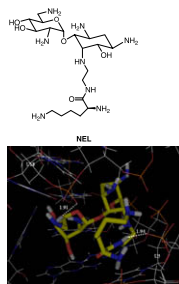
pp 2099–2102

Paul S. Humphries*, Jennifer A. Lafontaine*, Charles S. Agree, David Alexander, Ping Chen, Quyen-Quyen T. Do, Lilian Y. Li, Elizabeth A. Lunney, Ranjan J. Rajapakse, Karen Siegel, Sergei L. Timofeevski, Tianlun Wang, David M. Wilhite

**Synthesis and evaluation of novel neamine derivatives effectively targeting to RNA**

pp 2103–2106

Yanli Xu, Hongwei Jin, Zhenjun Yang, Liangren Zhang, Qi Wang, Manning Li, Lihe Zhang*

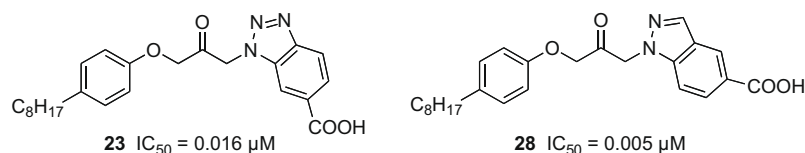


Modification on 5-hydroxyl group of neamine may provide a promising way for the development of potential candidates effectively targeting to RNAs.

**1-(5-Carboxyindol-1-yl)propan-2-ones as inhibitors of human cytosolic phospholipase $A_2\alpha$: Synthesis and properties of bioisosteric benzimidazole, benzotriazole and indazole analogues**

pp 2107–2111

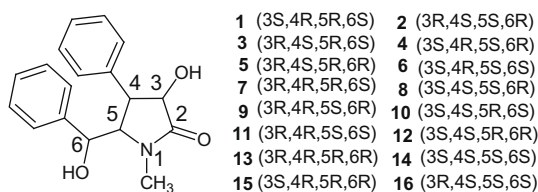
Stefanie Bovens, Martina Kaptur, Alwine Schulze Elfringhoff, Matthias Lehr*



Synthesis and activity in enhancing long-term potentiation (LTP) of clausenamide stereoisomers

pp 2112–2115

Zhiqiang Feng*, Xingzhou Li, Guojun Zheng, Liang Huang*

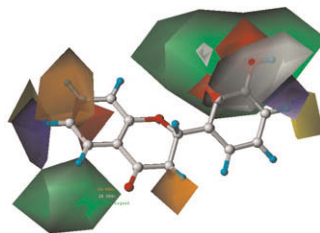


The synthesis and activity in enhancing LTP of 16 (8 pairs) optically pure stereoisomers of clausenamide with four chiral centers are reported.

Relationships between the structures of flavanone derivatives and their effects in enhancing Early growth response-1 gene expression

pp 2116–2120

Sunhee Lee, Yoonkyung Woo, Soon Young Shin, Young Han Lee*, Yoongho Lim*



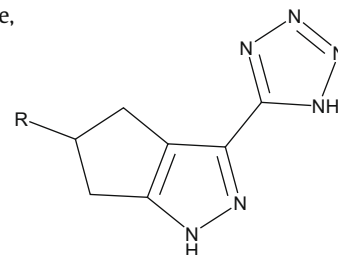
To identify the structural requirements that are pivotal in enhancing Early growth response-1 (Egr-1) expression, the quantitative relationships between the structural properties of flavanone derivatives and their increments of Egr-1 expression were elucidated.

**GPR109a agonists. Part 1: 5-Alkyl and 5-aryl-pyrazole-tetrazoles as agonists of the human orphan G-protein coupled receptor GPR109a**

pp 2121–2124

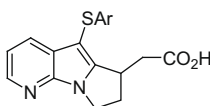
Jason E. Imbriglio*, Sookhee Chang, Rui Liang, Subharekha Raghavan, Darby Schmidt, Abby Smenton, Scott Tria, Thomas O. Schrader, Jae-Kyu Jung, Craig Esser, Andrew K. P. Taggart, Kang Cheng, Ester Carballo-Jane, M. Gerard Waters, James R. Tata, Steven L. Colletti

5-Alkyl and aryl-pyrazole-tetrazoles have been identified as a new class of selective, small-molecule, agonists of the human G-protein-coupled receptor GPR109a, a high affinity receptor for the HDL-raising drug nicotinic acid.

**Discovery of potent and selective DP1 receptor antagonists in the azaindole series**

pp 2125–2128

Yves Leblanc*, Patrick Roy, Claude Dufresne, Nicolas Lachance, Zhaoyin Wang, Gary O'Neill, Gillian Greig, Danielle Denis, Marie-Claude Mathieu, Deborah Slipetz, Nicole Sawyer, Nancy Tsou

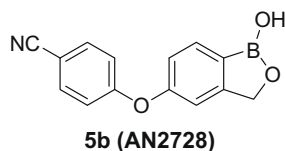


Potent and selective azaindole DP1 receptor antagonists were identified.

Discovery and structure–activity study of a novel benzoxaborole anti-inflammatory agent (AN2728) for the potential topical treatment of psoriasis and atopic dermatitis

pp 2129–2132

Tsutomu Akama*, Stephen J. Baker, Yong-Kang Zhang, Vincent Hernandez, Huchen Zhou, Virginia Sanders, Yvonne Freund, Richard Kimura, Kirk R. Maples, Jacob J. Plattner

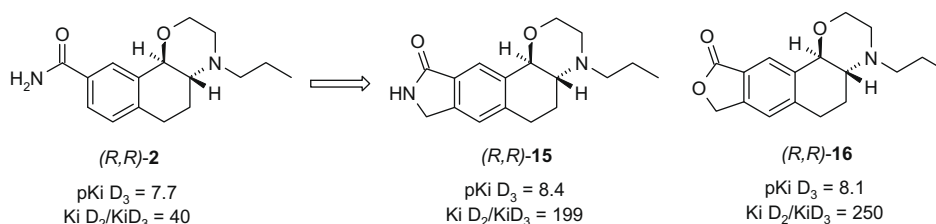


Anti-inflammatory activity and SAR of novel benzoxaborole derivatives are reported.

Modulations of the amide function of the preferential dopamine D₃ agonist (R,R)-S32504: Improvements of affinity and selectivity for D₃ versus D₂ receptors

pp 2133–2138

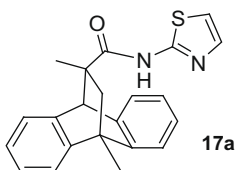
Jean-Louis Peglion*, Christophe Poitevin, Clotilde Mannoury La Cour, Delphine Dupuis, Mark J. Millan



Discovery of novel dihydro-9,10-ethano-anthracene carboxamides as glucocorticoid receptor modulators

pp 2139–2143

Bingwei V. Yang*, Wayne Vaccaro*, Arthur M. Doweyko, Lidia M. Doweyko, Tram Huynh, David Tortolani, Steven G. Nadler, Lorraine McKay, John Somerville, Deborah A. Holloway, Sium Habte, David S. Weinstein, Joel C. Barrish

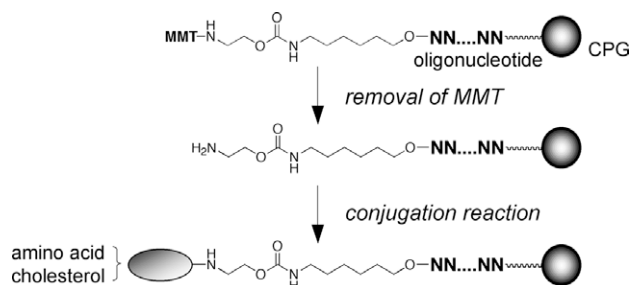


A series of dihydro-9,10-ethano-anthracene-11-carboxamides as novel glucocorticoid receptor modulators is reported. SAR exploration identified compounds from this series displaying a promising dissociation profile in discriminating between transrepression and transactivation activities. **17a** is a partial agonist of GR-mediated transactivation which elicits potent and efficacious transrepression in reporter gene assays. A hypothetical binding mode is provided which accounts for the induction of functional activity by a bridgehead methyl group.

Efficient synthesis of oligonucleotide conjugates on solid-support using an (aminoethoxycarbonyl)aminoethyl group for 5'-terminal modification

pp 2144–2147

Naoshi Kojima, Toshie Takebayashi, Akiko Mikami, Eiko Ohtsuka, Yasuo Komatsu*

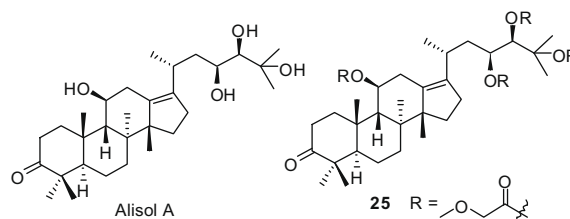


Anti-HBV agents. Part 2: Synthesis and in vitro anti-hepatitis B virus activities of alisol A derivatives

pp 2148–2153

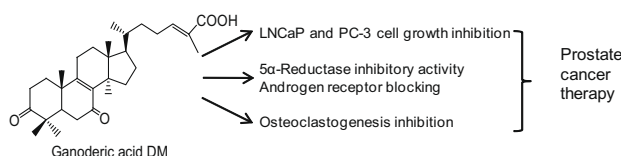
Quan Zhang, Zhi-Yong Jiang*, Jie Luo, Ji-Feng Liu, Yun-Bao Ma, Rui-Hua Guo, Xue-Mei Zhang, Jun Zhou, Ji-Jun Chen*

Chemical modifications were performed on hydroxyl groups at C-11,23,24,25 positions and C-13(17) double bond of alisol A for structure–activity relationship study. Forty-one derivatives of alisol A were synthesized and assayed for their in vitro anti-hepatitis B virus (HBV) activities and cytotoxicities. Of them, 14 compounds were active against HBV surface antigen (HBsAg) and HBV e antigen (HBeAg) secretion in HepG 2.2.15 cells, and the most promising compound 25 exhibited high activities against secretion of HBsAg ($IC_{50} = 0.028$ mM), HBeAg ($IC_{50} = 0.027$ mM) and remarkable selective indices ($SI_{HBsAg} > 90$, $SI_{HBeAg} > 93$).

**Ganoderic acid DM: Anti-androgenic osteoclastogenesis inhibitor**

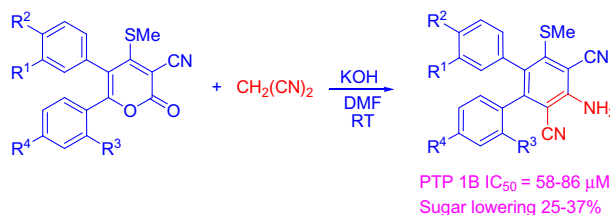
pp 2154–2157

Jie Liu, Jun Shiono, Kuniyoshi Shimizu, Akiko Kukita, Toshio Kukita, Ryuichiro Kondo*

**5,6-Diarylanthrano-1,3-dinitriles as a new class of antihyperglycemic agents**

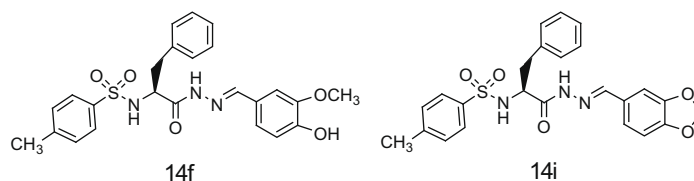
pp 2158–2161

Fateh V. Singh, Amrita Parihar, Sumit Chaurasia, Amar B. Singh, Salil P. Singh, Akhilesh K. Tamrakar, Arvind K. Srivastava, Atul Goel*

**Synthesis and antiviral activities of novel acylhydrazone derivatives targeting HIV-1 capsid protein**

pp 2162–2167

Baohé Tian, Meizi He, Shixing Tang, Indira Hewlett, Zhiwu Tan, Jiebo Li, Yinxue Jin, Ming Yang*

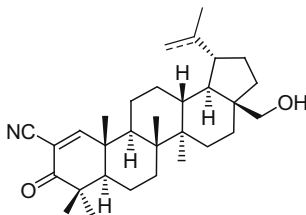


A variety of novel acylhydrazone derivatives were synthesized and tested for their antiviral activities as inhibitors of HIV-1 capsid assembly. Compounds **14f** and **14i** could inhibit HIV-1 capsid assembly strongly and displayed the most promising potency ($EC_{50} = 0.21$ and 0.17 μ M).

Synthesis and cytotoxicity of 2-cyano-28-hydroxy-lup-1-en-3-ones

pp 2168–2171

Ali Koohang, Nathan D. Majewski, Erika L. Szotek, Aye Aye Mar, David A. Eiznhamer, Michael T. Flavin, Ze-Qi Xu *

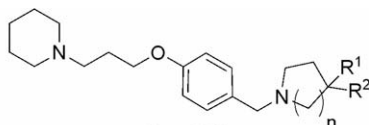


Incorporation of the 2-cyano-1-en-3-one functionality into the A-ring of betulin and dihydrobetulin converted the non-cytotoxic molecules to potent apoptosis-inducing antiproliferative agents.

Fluorinated non-imidazole histamine H₃ receptor antagonists

pp 2172–2175

K. Isensee, M. Amon, A. Galaparti, X. Ligneau, J.-C. Camelin, M. Capet, J.-C. Schwartz, H. Stark *

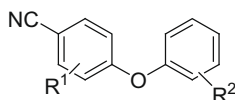
**5a-c, 5f-h**n = 1, 2; R¹ = F, Cl, Br; R² = F, HH₃ K_i = 0.068 - 0.278 nM, ED₅₀ = 0.23 - 7.4 mg/kg

Novel dibasic fluorinated non-imidazole histamine H₃ receptor antagonists were prepared with high affinities at hH₃ receptor in the nanomolar and subnanomolar concentration range and some with high antagonist in vivo potencies.

**Diphenyl ethers as androgen receptor antagonists for the topical suppression of sebum production**

pp 2176–2178

Lorna H. Mitchell *, Lain-Yen Hu, Maria Nguyen, Stephen Fakhoury, Yvonne Smith, Donna Iula, Catherine Kostlan, Matthew Carroll, Danielle Dettling, Daniel Du, David Pocalyko, Kimberly Wade, Bruce Lefker

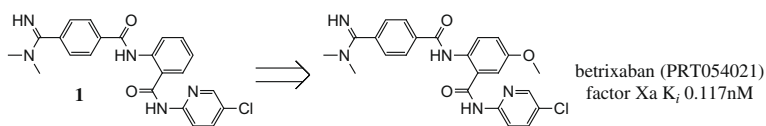


A series of diphenyl ethers was prepared and evaluated for androgen receptor antagonist activity in human androgen receptor binding and cellular functional assays. Analogs with potent in vitro activities were evaluated for topical in vivo efficacy in the Golden Syrian Hamster ear model. Several compounds showed reduction in wax esters in this validated animal model.

Discovery of betrixaban (PRT054021), N-(5-chloropyridin-2-yl)-2-(4-(N,N-dimethylcarbamimidoyl)benzamido)-5-methoxybenzamide, a highly potent, selective, and orally efficacious factor Xa inhibitor

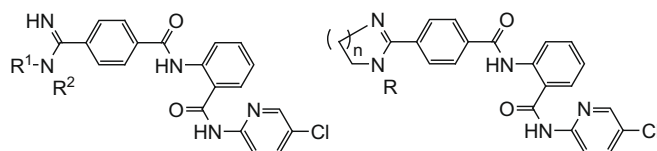
pp 2179–2185

Penglie Zhang, Wenrong Huang, Lingyan Wang, Liang Bao, Zhaozhong J. Jia *, Shawn M. Bauer, Erick A. Goldman, Gary D. Probst, Yonghong Song, Ting Su, Jingmei Fan, Yanhong Wu, Wenhao Li, John Woolfrey, Uma Sinha, Paul W. Wong, Susan T. Edwards, Ann E. Arfsten, Lane A. Clizbe, James Kanter, Anjali Pandey, Gary Park, Athiwat Hutchaleelaha, Joseph L. Lambing, Stanley J. Hollenbach, Robert M. Scarborough, Bing-Yan Zhu



Anthranilamide-based *N,N*-dialkylbenzamidines as potent and orally bioavailable factor Xa inhibitors: P4 SAR pp 2186–2189

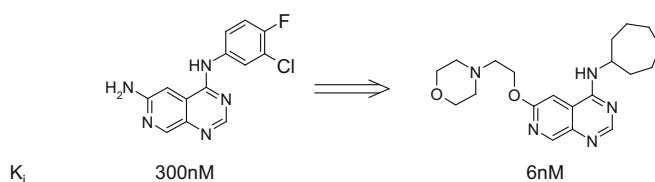
Penglie Zhang, Liang Bao, Jingmei Fan, Zhaozhong J. Jia*, Uma Sinha, Paul W. Wong, Gary Park, Athiwa Hutcheleela, Robert M. Scarborough, Bing-Yan Zhu



An anthranilamide-based benzamidine and its *N*-substituted analogs were designed and examined as factor Xa inhibitors, using the *N*-substituted benzamidines as unconventional S4 binding element. A group of *N,N*-dialkylbenzamidines have been discovered as potent factor Xa inhibitors with strong anticoagulant activity and promising oral PK profiles.

In vitro and in vivo SAR of pyrido[3,4-*d*]pyrimidin-4-ylamine based mGluR1 antagonists pp 2190–2194

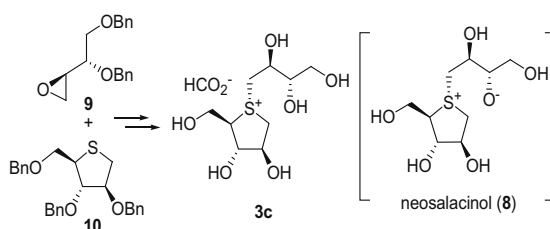
Simon J. Mantell*, Karl R. Gibson, Simon A. Osborne, Graham N. Maw, Huw Rees, Peter G. Dodd, Ben Greener, Gareth W. Harbottle, William A. Million, Cedric Poinard, Steven England, Pauline Carnell, Alison M. Betts, Russell Monhemius, Rebecca L. Prime



SAR and CNS penetration of a series of novel mgluR1 antagonists is described. The multiple of the unbound K_i in cerebrospinal fluid necessary to give morphine like analgesic effects in an electromyograph pinch model in rodents is given.

Facile synthesis of de-*O*-sulfated salacinols: Revision of the structure of neosalacinol, a potent α -glucosidase inhibitor pp 2195–2198

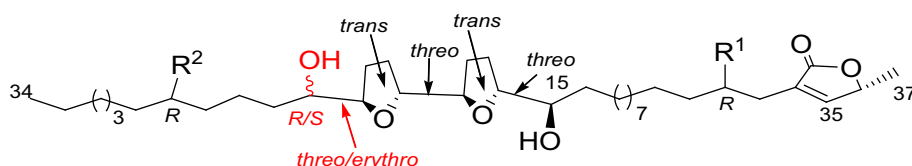
Genzoh Tanabe, Weijia Xie, Ai Ogawa, Changnian Cao, Toshie Minematsu, Masayuki Yoshikawa, Osamu Muraoka*



The structure of neosalacinol (**8**), a potent α -glucosidase inhibitor isolated recently from Ayurvedic medicine *Salacia oblonga*, was revised to salacinol de-*O*-sulfate (**3c**), by comparison of the spectroscopic properties of **8** with an authentic specimen synthesized by the coupling reaction of **9** and **10**.

Structure–activity relationships of diverse annonaceous acetogenins against human tumor cells pp 2199–2202

Haijun Yang*, Ning Zhang, Xiang Li, Jianwei Chen, Baochang Cai

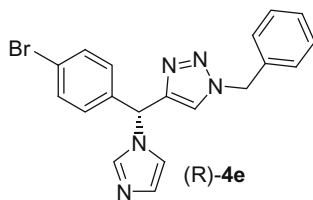


Twelve annonaceous acetogenins (ACGs) with different stereochemical structures and configuration were selected to test for their inhibitions on the growth of Hela, SMMC-7541, SGC-7901, MCF-7 and A-5408 tumor cell lines using MTT method. This was the first to simultaneously investigate effects of structural factors of stereochemical structures and configuration on cytotoxicities with structure–activity relationship.

Synthesis and biological evaluation of new enantiomerically pure azole derivatives as inhibitors of *Mycobacterium tuberculosis*

pp 2203–2205

Daniele Castagnolo, Marco Radi, Filippo Dessì, Fabrizio Manetti, Manuela Saddi, Rita Meleddu, Alessandro De Logu, Maurizio Botta*



MIC = 16 $\mu\text{g mL}^{-1}$

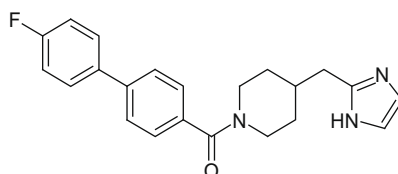
Mycobacterium tuberculosis

A series of novel enantiomerically pure azole derivatives was synthesised. The new compounds, bearing both an imidazole as well as a triazole moiety, were evaluated as antimycobacterial agents. One of them proved to have activity against *Mycobacterium tuberculosis* comparable to those of the classical antibacterial/antifungal drugs.

A new class of 5-HT_{2B} antagonists possesses favorable potency, selectivity, and rat pharmacokinetic properties

pp 2206–2210

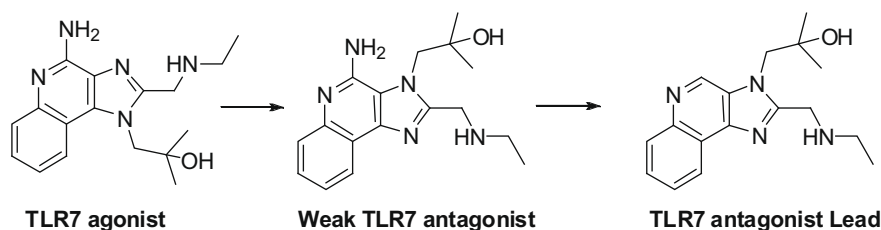
Neil Moss*, Younggi Choi, Derek Cogan, Adam Flegg, Andreas Kahrs, Pui Loke, Orietta Meyn, Raj Nagaraja, Spencer Napier, Ashley Parker, J. Thomas Peterson, Philip Ramsden, Christopher Sarko, Donna Skow, Josh Tomlinson, Heather Tye, Mark Whitaker



Regioisomerism-dependent TLR7 agonism and antagonism in an imidazoquinoline

pp 2211–2214

Nikunj M. Shukla, Matthew R. Kimbrell, Subbalakshmi S. Malladi, Sunil A. David*



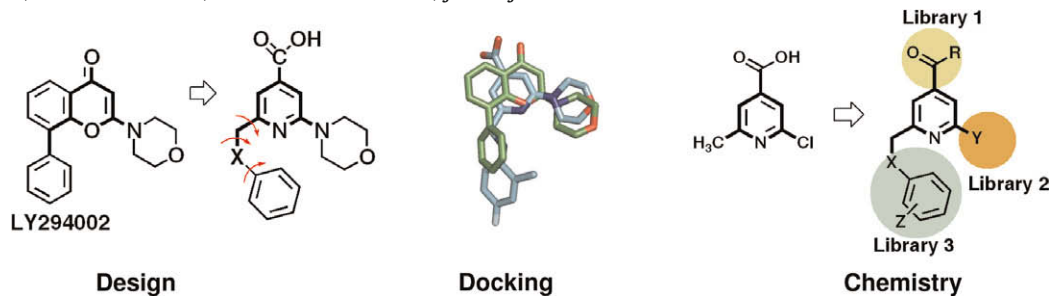
A regioisomer of a known TLR7 agonist was found to have TLR7 antagonistic activity.



Exploring the PI3K α and γ binding sites with 2,6-disubstituted isonicotinic derivatives

pp 2215–2219

Philip T. Cherian, Leonid N. Koikov, Matthew D. Wortman, James J. Knittel*

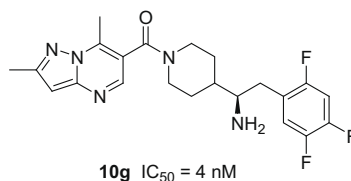


Using a homology model of PI3K α based of PI3K γ , a series of isonicotinic acid derivatives was designed and synthesized for studying the PI3K α and γ active sites.

Piperidiny-2-phenethylamino inhibitors of DPP-IV for the treatment of Type 2 diabetes

pp 2220–2223

John W. Benbow*, Kim A. Andrews, Jiri Aubrecht, David Beebe, David Boyer, Shawn Doran, Michael Homiski, Yu Hui, Kirk McPherson, Janice C. Parker, Judith Treadway, Maria VanVolkenberg, William J. Zembrowski

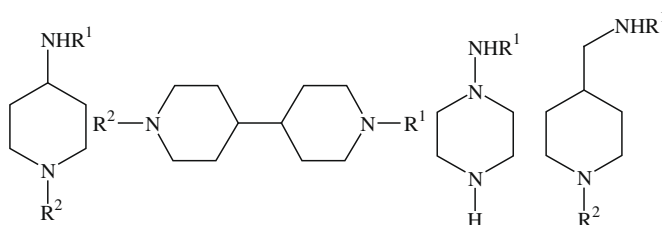


Utilizing parallel synthesis and a high-throughput in vitro micronucleus assay enabled the identification of **10g**, a highly DPP-IV selective compound with an acceptable human DPP-IV inhibition profile based on the rat PK/PD model and a projected human dose that was suitable for clinical development.

[³⁵S]GTPγS binding studies of amphiphilic drugs-activated Gi proteins: A caveat

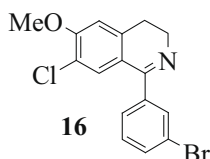
pp 2224–2229

Dina Manetti*, Lorenzo Di Cesare Mannelli, Silvia Dei, Luca Guandalini, Elisabetta Martini, Martina Banchelli, Carla Ghelardini

**1-Aryl-3,4-dihydroisoquinoline inhibitors of JNK3**

pp 2230–2234

John A. Christopher*, Francis L. Atkinson, Benjamin D. Bax, Murray J. B. Brown, Aurélie C. Champigny, Tsu Tshen Chuang, Emma J. Jones, Julie E. Mosley, James R. Musgrave

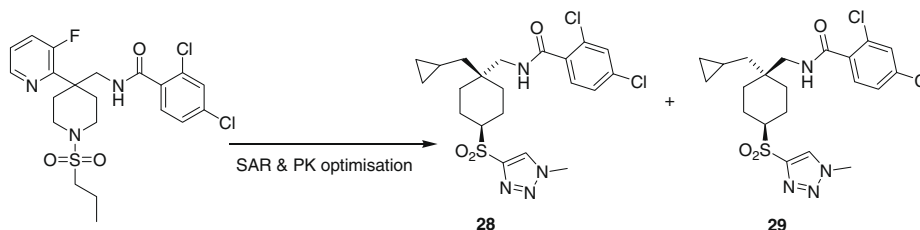


A series of 1-aryl-3,4-dihydroisoquinoline inhibitors of JNK3 are described. Compounds **20** and **24** are the most potent inhibitors (pIC₅₀ 7.3 and 6.9, respectively in a radiometric filter binding assay), with 10- and 1000-fold selectivity over JNK2 and JNK1, respectively, and selectivity within the wider mitogen-activated protein kinase (MAPK) family against p38α and ERK2. X-ray crystallography of **16** reveals a highly unusual binding mode where an H-bond acceptor interaction with the hinge region is made by a chlorine substituent.

Optimisation of a series of potent, selective and orally bioavailable GlyT1 inhibitors

pp 2235–2239

Joanne L. Thomson, Wesley P. Blackaby, Andrew S. R. Jennings, Simon C. Goodacre, Andrew Pike, Steve Thomas, Terry A. Brown, Alison Smith, Gopalan Pillai, Leslie J. Street, Richard T. Lewis*



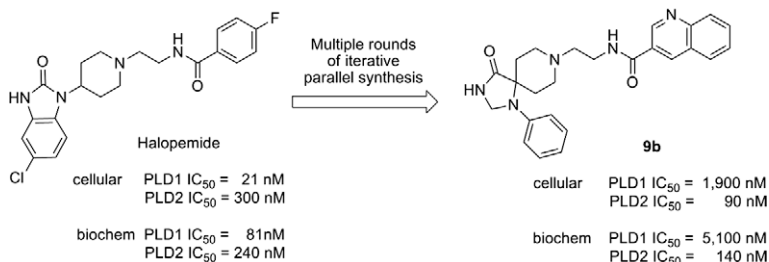
A series of heterocyclic sulfonamides have been developed which are potent and selective inhibitors of hGlyT1. SAR studies to optimise the in vitro and in vivo properties are described. Optimisation of the central scaffold resulted in cyclohexane sulfonones **28** and **29**, which have good PK properties and show promise for further development.

Design and synthesis of isoform-selective phospholipase D (PLD) inhibitors. Part II. Identification of the 1,3,8-triazaspiro[4,5]decan-4-one privileged structure that engenders PLD2 selectivity

pp 2240–2243

Robert Lavieri, Sarah A. Scott, Jana A. Lewis, Paige E. Selvy, Michelle D. Armstrong, H. Alex Brown, Craig W. Lindsley*

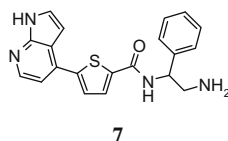
The synthesis and SAR of isoform-selective PLD inhibitors is described. By virtue of the installation of the 1,3,8-triazaspiro[4,5]decan-4-one privileged structure, inhibitors with up to an unprecedented 40-fold selectivity for PLD2 over PLD1 were developed. Interestingly, SAR for this series diverged considerably from earlier efforts, and also provided potent dual PLD1/2 inhibitors.



Discovery of 5-pyrrolopyridinyl-2-thiophenecarboxamides as potent AKT kinase inhibitors

pp 2244–2248

Mark A. Seefeld*, Meagan B. Rouse, Kenneth C. McNulty, Lihui Sun, Jizhou Wang, Dennis S. Yamashita, Juan I. Luengo, ShuYun Zhang, Elisabeth A. Minthorn, Nestor O. Concha, Dirk A. Heering



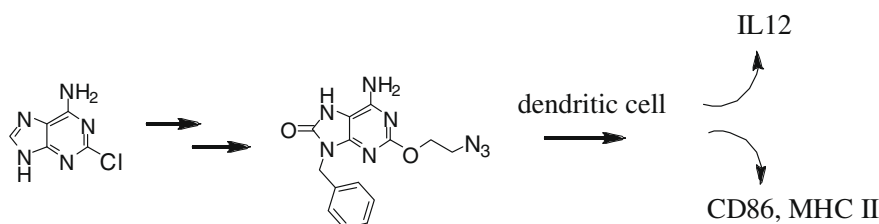
A pyrrolopyridinyl thiophene carboxamide **7** was discovered as a tractable starting point for a lead optimization effort in an AKT kinase inhibition program. SAR studies aided by a co-crystal structure of **7** in AKT2 led to the identification of AKT inhibitors with subnanomolar potency. Representative compounds showed antiproliferative activity as well as inhibition of phosphorylation of the downstream target GSK3β.



2-Azidoalkoxy-7-hydro-8-oxoadenine derivatives as TLR7 agonists inducing dendritic cell maturation

pp 2249–2251

Jimmy J. Weterings, Selina Khan, Gerbrand J. van der Heden van Noort, Cornelis J. M. Melief, Herman S. Overkleeft, Sjoerd H. van der Burg, Ferry Ossendorp, Gijsbert A. van der Marel*, Dmitri V. Filippov*



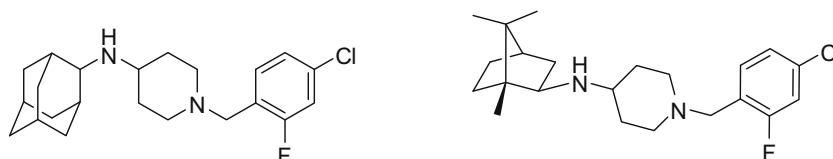
The synthesis of an array of 2-azidoalkoxy substituted 7-hydro-8-oxoadenines is described. The relation of the structure of these compounds and their ability to induce maturation of dendritic cells is evaluated.



Exploring a pocket for polycycloaliphatic groups in the CXCR3 receptor with the aid of a modular synthetic strategy

pp 2252–2257

Maikel Wijtmans, Dennis Verzijl, Cindy M. E. van Dam, Leontien Bosch, Martine J. Smit, Rob Leurs, Iwan J. P. de Esch*

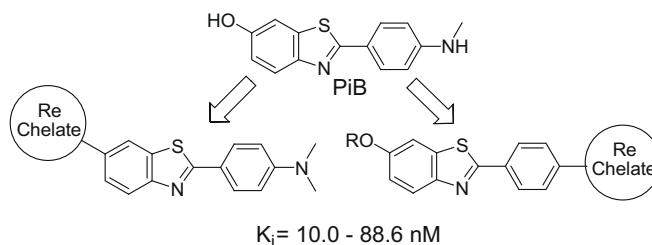


The strategic use of specific polycycloaliphatic groups in obtaining small antagonists for the CXCR3 receptor was investigated. 2-Adamantyl- and (iso)bornyl groups proved beneficial.



Synthesis and β -amyloid binding properties of rhenium 2-phenylbenzothiazoles

pp 2258–2262

Kuo-Shyan Lin^{*}, Manik L. Debnath, Chester A. Mathis, William E. Klunk**Tricyclic HIV integrase inhibitors V. SAR studies on the benzyl moiety**

pp 2263–2265

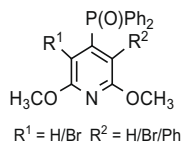
Haolun Jin^{*}, Sammy Metobo, Salman Jabri, Michael Mish, Rachael Lansdown, Xiaowu Chen, Manuel Tsiang, Matthew Wright, Choung U. Kim

| R | 3-Cl-4-F | 5-Cl-2,4-F |
|---------------------------|----------|------------|
| | | |
| IC ₅₀ | 52 nM | 39 nM |
| EC ₅₀ (10%FBS) | 3.5 nM | 6 nM |
| EC ₅₀ (HSP) | 12 nM | 17 nM |
| t _{1/2} (rat iv) | 1.36 hr | 1.38 hr |
| t _{1/2} (dog iv) | 7.13 hr | 16 hr |

SAR studies on the *para*-fluorobenzyl moiety of tricyclic HIV integrase inhibitors are discussed and lead compounds with potency and PK properties comparable to raltegravir were identified.

The preparation of 2,6-disubstituted pyridinyl phosphine oxides as novel anti-cancer agents

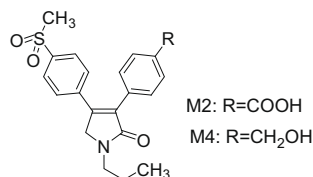
pp 2266–2269

Kim Hung Lam^{*}, Roberto Gambari, Marcus Chun Wah Yuen, Chi Wai Kan, Penni Chan, Lijin Xu, Weijun Tang, Chung Hin Chui, Gregory Yin Ming Cheng, Raymond Siu Ming Wong, Fung Yi Lau, Cindy Sze Wai Tong, Andrew Kit Wah Chan, Paul Bo San Lai, Stanton Hon Lung Kok, Chor Hing Cheng, Albert Sun Chi Chan^{*}, Johnny Cheuk On Tang^{*}

The preparation of 2,6-disubstituted pyridinyl phosphine oxides and their antitumor properties were reported.

**Synthesis and anti-inflammatory activity of the major metabolites of imrecoxib**

pp 2270–2272

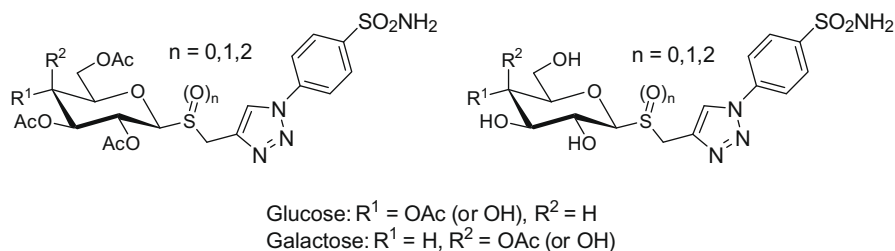
Zhiqiang Feng, Fengming Chu, Zongru Guo^{*}, Piaoyang Sun

The synthesis and anti-inflammatory activity of two moderately selective COX-2 inhibitors M2 and M4, as the major metabolites of imrecoxib, is reported.

Inhibition of carbonic anhydrase isozymes with benzene sulfonamides incorporating thio, sulfinyl and sulfonyl glycoside moieties

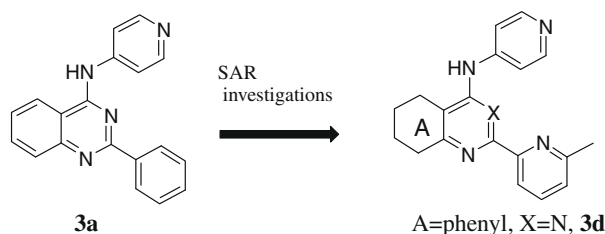
pp 2273–2276

Mathilde Singer, Marie Lopez, Laurent F. Bornaghi, Alessio Innocenti, Daniela Vullo, Claudiu T. Supuran*, Sally-Ann Poulsen*

**Design of novel quinazoline derivatives and related analogues as potent and selective ALK5 inhibitors**

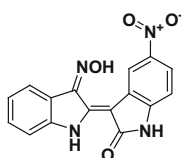
pp 2277–2281

F. Gellibert*, M.-H. Fouchet, V.-L. Nguyen, R. Wang, G. Krysa, A.-C. de Gouville, S. Huet, N. Dodic

Starting from quinazoline **3a**, we identified **3d** a potent and selective ALK5 inhibitor over p38MAP kinase suitable for oral administration.**Novel small molecule activators of β -catenin-mediated signaling pathway: structure–activity relationships of indirubins**

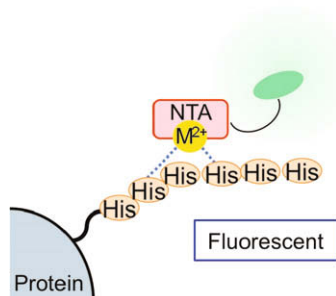
pp 2282–2284

Eun-Jung Park, Soo Jeong Choi, Yong-Chul Kim, Sang Hyung Lee, Seoung Woo Park, Sang Kook Lee*

Based on the β -catenin-driven Wnt activator of 6-bromoindirubin-3'-oxime (BIO), indirubin analogs were evaluated for β -catenin-mediated gene expression. A novel indirubin analog, indirubin-5-nitro-3'-oxime (INO), was considered a potential activator, and structure–activity studies were conducted with indirubins.**Turn-on fluorescent probe with visible light excitation for labeling of hexahistidine tagged protein**

pp 2285–2288

Mie Kamoto, Naoki Umezawa*, Nobuki Kato, Tsunehiko Higuchi*



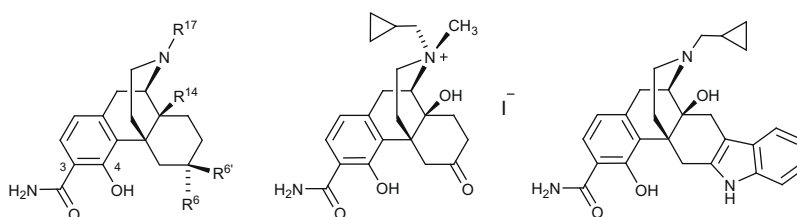
A novel fluorescein-based probe is reported. This molecule shows selective fluorescence enhancement on binding to a hexahistidine tag on the protein surface.



Syntheses of novel high affinity ligands for opioid receptors

pp 2289–2294

Mark P. Wentland*, Rongliang Lou, Qun Lu, Yigong Bu, Christoph Denhardt, Jin Jin, Rakesh Ganorkar, Melissa A. VanAlstine, Chengyun Guo, Dana J. Cohen, Jean M. Bidlack

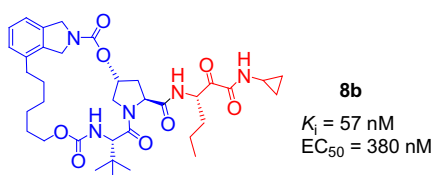


High binding affinity [K_i values (μ) = 0.072–1.3 nM] to opioid receptors is seen in a novel series of 3-desoxy-3-carboxamido-4-hydroxymorphinans where the carboxamide group is stabilized in the putative bioactive conformation.

Inhibitors of hepatitis C virus NS3/4A: α -Ketoamide based macrocyclic inhibitors

pp 2295–2298

Salvatore Avolio*, Keith Robertson, Josè Ignacio Martin Hernando, Jillian DiMuzio, Vincenzo Summa

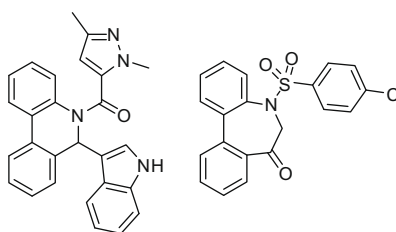


Design, synthesis and biological evaluation of a new series of hepatitis C virus (HCV) NS3/4A protease inhibitors bearing a P2-P4 macrocycle and a P1-P1' α -ketoamide warhead is described.

Inhibitors of potassium channels $K_v1.3$ and $IK-1$ as immunosuppressants

pp 2299–2304

Stefano Pegoraro, Martin Lang, Tobias Dreker, Jürgen Kraus, Svetlana Hamm, Cathal Meere, Juliane Feurle, Stefan Tasler*, Sylvia Prütting, Zerrin Kuras, Violeta Visan, Stephan Grissmer*

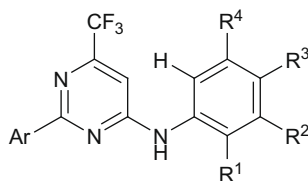


Applying vHTS based on a homology model, potent inhibitors of $K_v1.3$ and $IK-1$ were identified.

Discovery of substituted 4-anilino-2-arylpyrimidines as a new series of apoptosis inducers using a cell- and caspase-based high throughput screening assay. 2. Structure–activity relationships of the 2-aryl group

pp 2305–2309

Nilantha Sirisoma, Azra Pervin, Bao Nguyen, Candace Crogan-Grundy, Shailaja Kasibhatla, Ben Tseng, John Drewe, Sui Xiong Cai*

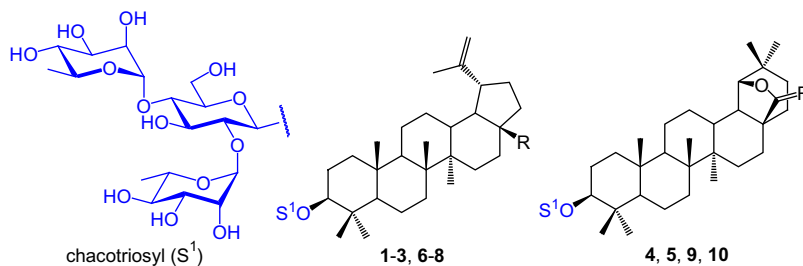


The synthesis and SAR studies of the 2-aryl group of 4-anilino-2-arylpyrimidines as novel apoptosis inducers are reported.

Synthesis, cytotoxicity, and haemolytic activity of chacotrioside lupane-type neosaponins and their germanicane-type rearrangement products

pp 2310–2314

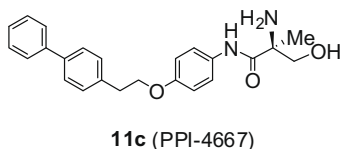
Charles Gauthier, Jean Legault, Marianne Piochon, Serge Lavoie, Samuel Tremblay, André Pichette*



Synthesis and evaluation of arylalkoxy- and biarylalkoxy-phenylamide and phenylimidazoles as potent and selective sphingosine-1-phosphate receptor subtype-1 agonists

pp 2315–2319

Ghotas Evindar*, Alexander L. Satz, Sylvie G. Bernier, Malcolm J. Kavarana, Elisabeth Doyle, Jeanine Lorusso, Nazbeh Taghizadeh, Keith Halley, Amy Hutchings, Michael S. Kelley, Albion D. Wright, Ashis K. Saha, Gerhard Hannig, Barry A. Morgan, William F. Westlin

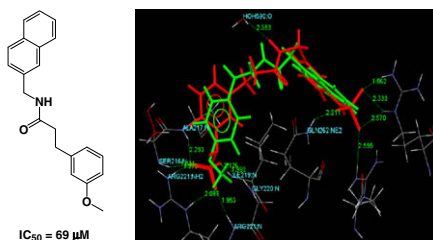


In pursuit of potent and selective sphingosine-1-phosphate receptor agonists, further SAR expansion on our previously reported scaffolds led to discovery of novel series of molecules with excellent in vitro and in vivo potency in both mouse and rat models.

Synthesis of protein tyrosine phosphatase 1B inhibitors: Model validation and docking studies

pp 2320–2323

Anil K. Saxena*, Gyanendra Pandey, Swati Gupta, Amar Bahadur Singh, Arvind K. Srivastava



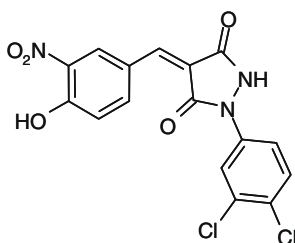
Structure of the most potent compound (3a) and its binding pose (in red colour) into the active site gorge of PTP-1B enzyme as compared to the X-ray crystal based binding pose of the control (PDB-ID: 2F70).

Structure of the most potent compound (3a) and its binding pose (in red colour) into the active site gorge of PTP-1B enzyme as compared to the X-ray crystal based binding pose of the control (PDB-ID: 2F70).

QSAR analysis of pyrazolidine-3,5-diones derivatives as Dyrk1A inhibitors

pp 2324–2328

Kyung Ah Koo, Nam Doo Kim, Yong Sog Chon, Min-Su Jung, Burm-Jong Lee, Jung Ho Kim, Woo-Joo Song*



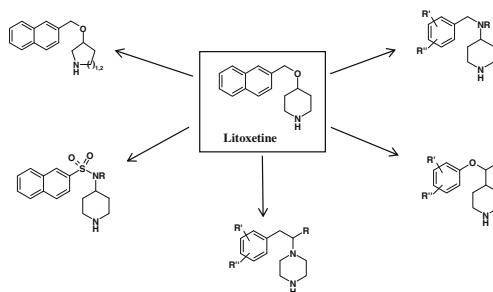
The QSAR analysis of 34 pyrazolidine-3,5-diones derivatives of HCD160 showed that the presence of the 3-nitro-4-hydroxyphenyl moiety enhanced the inhibition activity for Dyrk1A.



Design and optimization of selective serotonin re-uptake inhibitors with high synthetic accessibility Part 1

pp 2329–2332

Mark Andrews, Alan Brown*, Jean-Yves Chiva, David Fradet, David Gordon, Mark Lansdell, Malcolm MacKenny

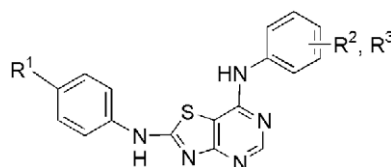


The reported selective serotonin Re-uptake Inhibitor (SSRI) litoxetine was used as the starting point in the design of a range of potent, selective SSRIs with high ease of synthetic accessibility.

Synthesis and evaluation of 2,7-diamino-thiazolo[4,5-d] pyrimidine analogues as anti-tumor epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors

pp 2333–2337

Ronghui Lin*, Sigmond G. Johnson, Peter J. Connolly, Steven K. Wetter, Eva Binnun, Terry V. Hughes, William V. Murray, Niranjana B. Pandey, Sandra J. Moreno-Mazza, Mary Adams, Angel R. Fuentes-Pesquera, Steven A. Middleton

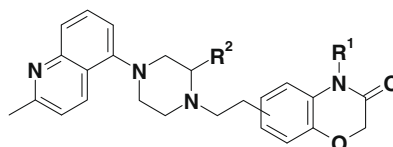


2,7-Diamino-thiazolo[4,5-d]pyrimidines analogues were synthesized as novel epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors. Representative compounds showed potent and selective EGFR inhibitory activities and inhibited in vitro cellular proliferation in EGFR-overexpressing human tumor cells. The synthesis and preliminary biological, physical, and pharmacokinetic evaluation of these thiazolopyrimidine compounds are reported.

8-[2-(4-Aryl-1-piperazinyl)ethyl]-2H-1,4-benzoxazin-3(4H)-ones: Dual-acting 5-HT_{1A/B/D} receptor antagonists and serotonin reuptake inhibitors—Part II

pp 2338–2342

Steven M. Bromidge*, Barbara Bertani, Manuela Borriello, Andrea Bozzoli, Stefania Faedo, Massimo Gianotti, Laurie J. Gordon, Matthew Hill, Valeria Zucchelli, Jeannette M. Watson, Laura Zonzini

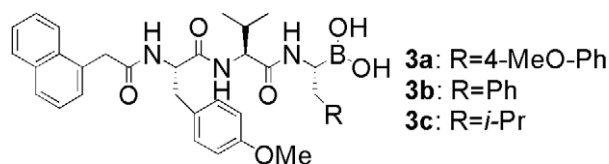


8-[2-(4-Aryl-1-piperazinyl)ethyl]-2H-1,4-benzoxazin-3(4H)-ones have been identified as highly potent 5-HT_{1A/B/D} receptor antagonists with and without additional SerT activity and a high degree of selectivity over hERG potassium channels. Modulation of the different target activities gave compounds with a range of profiles suitable for further in vivo characterization.

**Synthesis of boronic acid derivatives of tyropeptin: Proteasome inhibitors**

pp 2343–2345

Takumi Watanabe*, Isao Momose*, Masatoshi Abe, Hikaru Abe, Ryuichi Sawa, Yoji Umezawa, Daishiro Ikeda, Yoshikazu Takahashi, Yuzuru Akamatsu



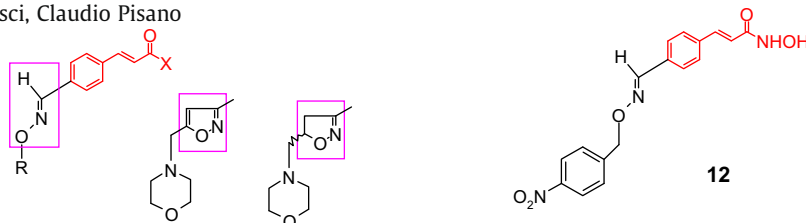
Synthesis of boronic acid derivatives (3a–c) of tyropeptin, proteasome inhibitors, are reported.



N-Hydroxy-(4-oxime)-cinnamide: A versatile scaffold for the synthesis of novel histone deacetylase (HDAC) inhibitors

pp 2346–2349

Giuseppe Giannini*, Mauro Marzi, Riccardo Pezzi, Tiziana Brunetti, Gianfranco Battistuzzi, Maria Di Marzo, Walter Cabri, Loredana Vesci, Claudio Pisano

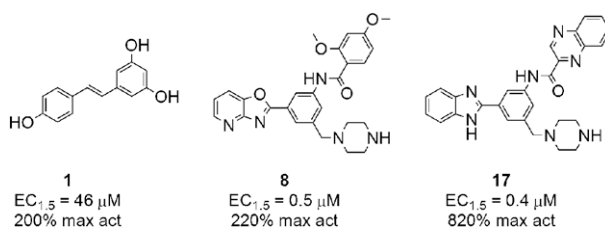


A small library of N-based scaffold derivatives has been described. SAR has been established for R, oxime moiety and X cinnamoyl-based HDAC inhibitors. Several 4-oxime derivatives demonstrated a promising inhibitory activity on HDAC6 and HDAC8 coupled to a good selectivity profile. Analogue **12** (ST2987) constitutes a promising lead compound for further optimization towards the identification of a clinical candidate.

**Discovery of oxazolo[4,5-b]pyridines and related heterocyclic analogs as novel SIRT1 activators**

pp 2350–2353

Jean E. Bemis*, Chi B. Vu, Roger Xie, Joseph J. Nunes, Pui Yee Ng, Jeremy S. Disch, Jill C. Milne, David P. Carney, Amy V. Lynch, Lei Jin, Jesse J. Smith, Siva Lavu, Andre Iffland, Michael R. Jirousek, Robert B. Perni

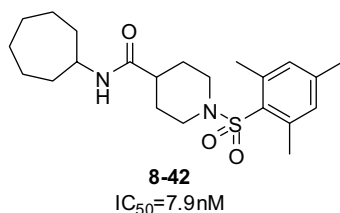


The identification and SAR of novel small molecule activators of SIRT1, which are structurally distinct and more potent than resveratrol (**1**), are described.

Discovery of potent non-urea inhibitors of soluble epoxide hydrolase

pp 2354–2359

Yuli Xie, Yidong Liu, Gangli Gong, Deborah H. Smith, Fang Yan, Alison Rinderspacher, Yan Feng, Zhengxiang Zhu, Xiangpo Li, Shi-Xian Deng, Lars Branden, Dušica Vidović, Caty Chung, Stephan Schürer, Christophe Morisseau, Bruce D. Hammock, Donald W. Landry*

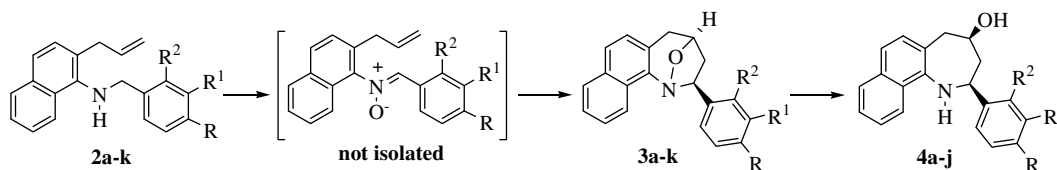


A class of potent non-urea inhibitors of soluble epoxide hydrolase was discovered via high throughput screening and SARs-guided modification.

Synthesis and in vitro activity of new tetrahydronaphtho[1,2-b]azepine derivatives against *Trypanosoma cruzi* and *Leishmania chagasi* parasites

pp 2360–2363

Alirio Palma*, Andrés Felipe Yépes, Sandra Milena Leal, Carlos Andrés Coronado, Patricia Escobar



OTHER CONTENTS**Corrigenda****pp 2364–2367****Instructions to contributors****p I**

*Corresponding author

+ Supplementary data available via ScienceDirect**COVER**

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

Available online at

 **ScienceDirect**
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

**ELSEVIER**

ISSN 0960-894X