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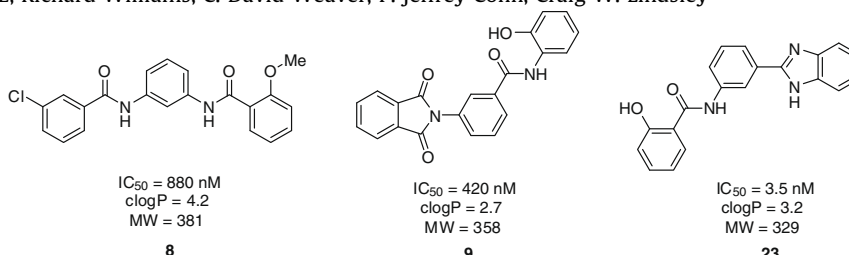
Contents

ARTICLES

Synthesis and SAR of novel, non-MPEP chemotype mGluR5 NAMs identified by functional HTS

pp 6502–6506

Ya Zhou, Alice L. Rodriguez, Richard Williams, C. David Weaver, P. Jeffrey Conn, Craig W. Lindsley*

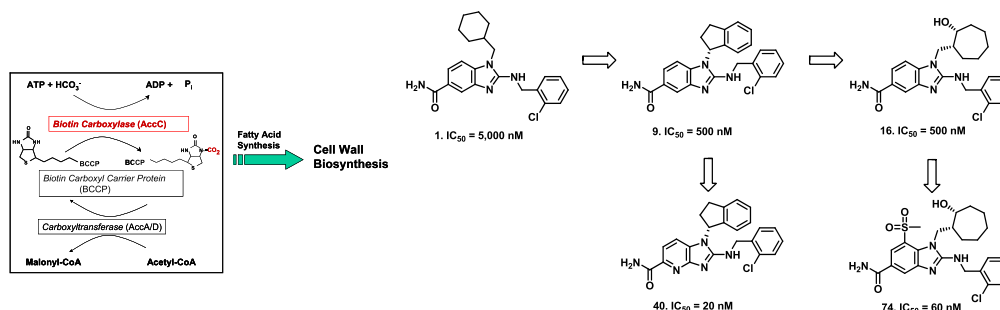


This Letter describes the discovery and SAR of three novel series of mGluR5 non-competitive antagonists/negative allosteric modulators (NAMs) not based on manipulation of an MPEP/MTEP chemotype identified by a functional HTS approach. This work demonstrates fundamentally new mGluR5 NAM chemotypes with submicromolar potencies, and further examples of a mode of pharmacology 'switch' to provide PAMs with a non-MPEP scaffold.

Discovery and optimization of antibacterial AccC inhibitors

pp 6507–6514

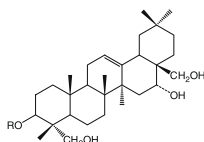
Cliff C. Cheng*, Gerald W. Shipps Jr., Zhiwei Yang, Binyuan Sun, Noriyuki Kawahata, Kyle A. Soucy, Aileen Soriano, Peter Orth, Li Xiao, Paul Mann, Todd Black



Four new cytotoxic oligosaccharidic derivatives of 12-oleanene from *Lysimachia heterogenea* Klatt

pp 6515–6518

Xin-an Huang*, Yong-ju Liang, Xiao-ling Cai, Xiao-quan Feng, Chuan-hai Zhang, Li-wu Fu, Wen-di Deng



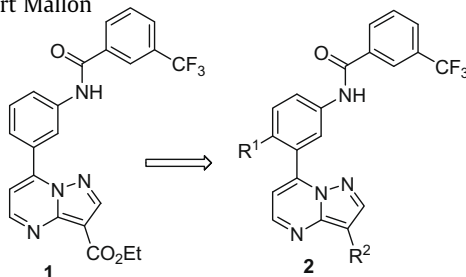
- 1 R = H-
- 2 R = β -D-Glu"--(1 \rightarrow 2)- α -L-Ara'-
- 3 R = β -D-Xyl"--(1 \rightarrow 2)- β -D-Glu"--(1 \rightarrow 2)- α -L-Ara'-
- 4 R = β -D-Glu"--(1 \rightarrow 4)-[β -D-Glu"--(1 \rightarrow 2)]- α -L-Ara'-
- 5 R = β -D-Xyl"--(1 \rightarrow 2)- β -D-Glu"--(1 \rightarrow 4)-[β -D-Glu"--(1 \rightarrow 2)]- α -L-Ara'-



Non-hinge-binding pyrazolo[1,5-*a*]pyrimidines as potent B-Raf kinase inhibitors

pp 6519–6523

Dan M. Berger ^{*}, Nancy Torres, Minu Dutia, Dennis Powell, Greg Ciszewski, Ariamala Gopalsamy, Jeremy I. Levin, Kyung-Hee Kim, Weixin Xu, James Wilhelm, YongBo Hu, Karen Collins, Larry Feldberg, Steven Kim, Eileen Frommer, Donald Wojciechowicz, Robert Mallon

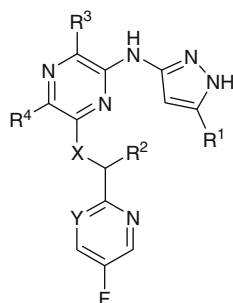


Optimization of initial lead compound **1** provided a series of pyrazolo[1,5-*a*]pyrimidines **2** as potent B-Raf kinase inhibitors.

Discovery of pyrazol-3-ylamino pyrazines as novel JAK2 inhibitors

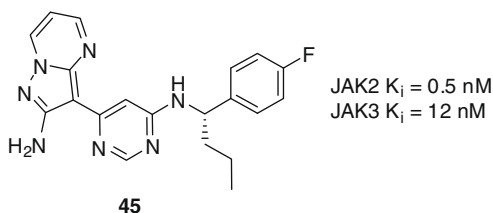
pp 6524–6528

Stephanos Ioannidis ^{*}, Michelle L. Lamb, Audrey M. Davies, Lynsie Almeida, Mei Su, Geraldine Bebernitz, Minwei Ye, Kirsten Bell, Marat Alimzhanov, Michael Zinda

**2-Aminopyrazolo[1,5-*a*]pyrimidines as potent and selective inhibitors of JAK2**

pp 6529–6533

Mark W. Ledebor ^{*}, Albert C. Pierce ^{*}, John P. Duffy, Huai Gao, David Messersmith, Francesco G. Salituro, Suganthini Nanthakumar, Jon Come, Harmon J. Zuccola, Lora Swenson, Dina Shlyakter, Sudipta Mahajan, Thomas Hooch, Bin Fan, Wan-Jung Tsai, Elaine Kolaczowski, Scott Carrier, James K. Hogan, Richard Zessis, S. Pazhanisamy, Youssef L. Bennani

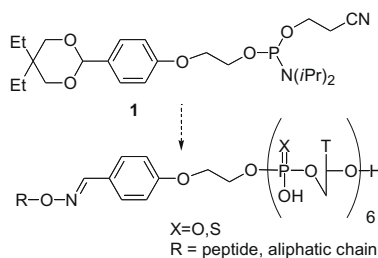


The discovery and structure based optimization of a novel series of 2-amino-pyrazolo[1,5-*a*]pyrimidines of potent and selective inhibitors of JAK2 is described.

**Efficient conjugation of oligonucleotides through aromatic oxime formation**

pp 6534–6537

Pierre Murat, Nicolas Spinelli, Pascal Dumy, Eric Defrancq ^{*}



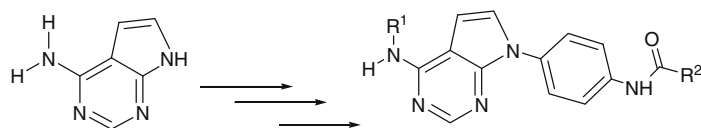
The efficient preparation of oligonucleotide conjugates via the formation of aromatic oxime linkage is reported and is found as efficient as the formation of conjugates through the formation of aliphatic oxime linkage.



Synthesis of pyrrolo[2,3-*d*]pyrimidine derivatives and their antiproliferative activity against melanoma cell line

pp 6538–6543

Myung-Ho Jung, Hwan Kim, Won-Kyoung Choi, Mohammed I. El-Gamal, Jin-Hun Park, Kyung Ho Yoo, Tae Bo Sim, So Ha Lee, Daejin Baek, Jung-Mi Hah, Jung-Hyuck Cho, Chang-Hyun Oh *

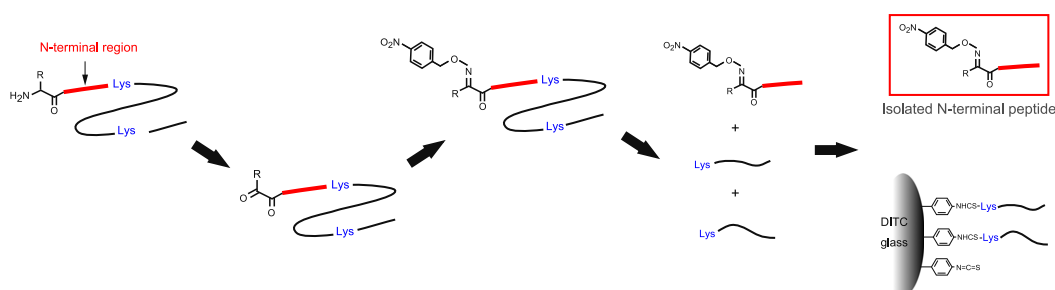


Synthesis of a new series of diarylureas and amides having pyrrolo[2,3-*d*]pyrimidine scaffold is described. Their in vitro antiproliferative activities against A375 human melanoma cell line and HS 27 fibroblast cell line were tested and the effect of substituents on pyrrolo[2,3-*d*]pyrimidine was investigated. The newly synthesized compounds, except *N*-acetyl derivatives (**Id**, **Ie**, and **Im**), generally showed superior or similar activity against A375 to Sorafenib. Among all of these derivatives, compounds **Iq** and **Ir** having imidazole and morpholine moieties, respectively, showed the most potent antiproliferative activity against A375.

A method for terminus proteomics: Selective isolation and labeling of N-terminal peptide from protein through transamination reaction

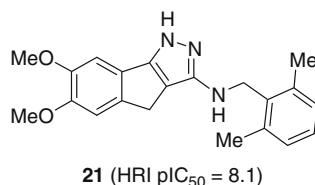
pp 6544–6547

Kazuhiro Sonomura, Hiroki Kuyama, Ei-ichi Matsuo, Susumu Tsunasawa, Osamu Nishimura *

**Discovery of the first known small-molecule inhibitors of heme-regulated eukaryotic initiation factor 2 α (HRI) kinase**

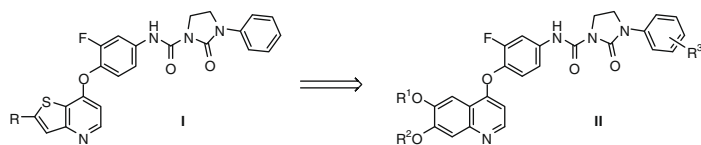
pp 6548–6551

Mark D. Rosen *, Craig R. Woods, Steven D. Goldberg, Michael D. Hack, A.Dawn Bounds, Young Yang, Pamela C. Wagaman, Victor K. Phuong, Angela P. Ameriks, Terrance D. Barrett, Kimon C. Kanelakis, Jui Chang, Nigel P. Shankley, Michael H. Rabinowitz

***N*-(4-(6,7-Disubstituted-quinolin-4-yloxy)-3-fluorophenyl)-2-oxo-3-phenylimidazolidine-1-carboxamides: A novel series of dual c-Met/VEGFR2 receptor tyrosine kinase inhibitors**

pp 6552–6556

Michael Mannion, Stéphane Raeppele *, Stephen Claridge, Nancy Zhou, Oscar Saavedra, Ljubomir Isakovic, Lijie Zhan, Frédéric Gaudette, Franck Raeppele, Robert Déziel, Normand Beaulieu, Hannah Nguyen, Ian Chute, Carole Beaulieu, Isabelle Dupont, Marie-France Robert, Sylvain Lefebvre, Marja Dubay, Jubrail Rahil, James Wang, Hélène Ste-Croix, A. Robert Macleod, Jeffrey M. Besterman, Arkadii Vaisburg

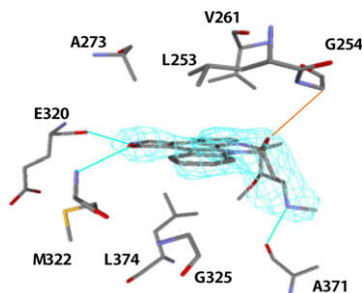


A series of *N*-(4-(6,7-disubstituted quinolin-4-yloxy)-3-fluorophenyl)-2-oxo-3-phenylimidazolidine-1-carboxamides (**II**) targeting c-Met and VEGFR2 tyrosine kinases, based on our previous 2-substituted thieno[3,2-*b*]pyridine series (**I**), was designed and synthesized. The new compounds were potent against these two enzymes with IC₅₀ values in the low nanomolar range in vitro, possessed favorable pharmacokinetic profiles and showed high efficacy in vivo in several human tumor xenograft models in mice.

Structural basis for the inhibitor recognition of human Lyn kinase domain

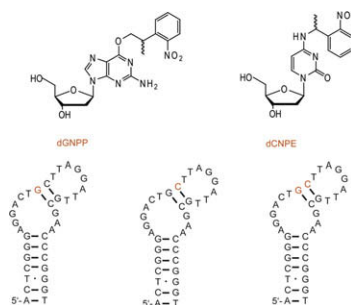
pp 6557–6560

Nao Miyano, Takayoshi Kinoshita, Ryoko Nakai, Yasuyuki Kirii, Koichi Yokota, Toshiji Tada *

**From selection to caged aptamers: Identification of light-dependent ssDNA aptamers targeting cytohesin**

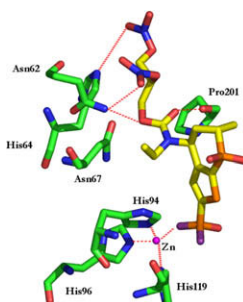
pp 6561–6564

Günter Mayer *, Andrea Lohberger, Sabine Butzen, Monika Pofahl, Michael Blind, Alexander Heckel *

**Nitric oxide-donating carbonic anhydrase inhibitors for the treatment of open-angle glaucoma**

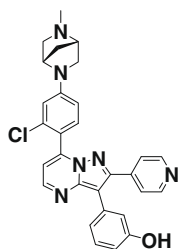
pp 6565–6570

Rebecca M. Steele *, Francesca Benedini, Stefano Biondi, Valentina Borghi, Laura Carzaniga, Francesco Impagnatiello, Daniela Miglietta, Wesley K. M. Chong, Ranjan Rajapakse, Alessandro Cecchi, Claudia Temperini, Claudiu T. Supuran *

**Discovery of highly potent and selective type I B-Raf kinase inhibitors**

pp 6571–6574

Xiaolun Wang *, Dan M. Berger, Edward J. Salaski, Nancy Torres, Yongbo Hu, Jeremy I. Levin, Dennis Powell, Donald Wojciechowicz, Karen Collins, Eileen Frommer

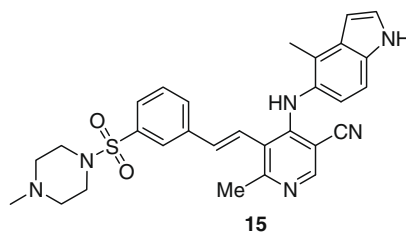


B-Raf enzyme $IC_{50} < 0.32$ nM
 A375 $IC_{50} < 10$ nM

A series of pyrazolo[1,5- α]pyrimidine analogs has been prepared and found to be extremely potent and selective B-Raf inhibitors.

Synthesis and PKC θ inhibitory activity of a series of 5-vinyl phenyl sulfonamide-3-pyridinecarbonitriles

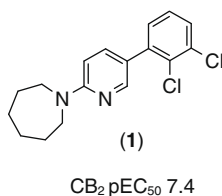
pp 6575–6577

Jaechul Shim ^{*}, Clark Eid, Julie Lee, Erica Liu, Divya Chaudhary, Diane H. Boschelli

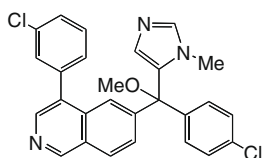
A series of vinyl phenyl sulfonamide-3-pyridinecarbonitriles were prepared and evaluated as PKC θ inhibitors. Optimization resulted in the identification of compound **15** with an IC₅₀ value of 0.44 nM for the inhibition of PKC θ with 150-fold selectivity over PKC δ .

2-Amino-5-aryl-pyridines as selective CB₂ agonists: Synthesis and investigation of structure–activity relationships

pp 6578–6581

Robert J. Gleave ^{*}, Paul J. Beswick, Andrew J. Brown, Gerard M. P. Giblin, Carl P. Haslam, David Livermore, Andrew Moses, Neville H. Nicholson, Lee W. Page, Brian Slingsby, Martin E. Swarbrick**Isoquinoline-based analogs of the cancer drug clinical candidate tipifarnib as anti-*Trypanosoma cruzi* agents**

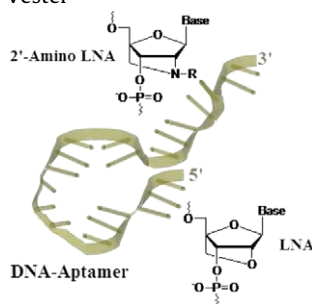
pp 6582–6584

Naveen Kumar Chennamaneni, Jenifer Arif, Frederick S. Buckner, Michael H. Gelb ^{*}

Isoquinoline-based inhibitors of *Trypanosoma cruzi* lanosterol 14 α -demethylase are prepared and shown to block the growth of the amastigote life cycle state of the parasite in the sub-nanomolar range.

**Aptamers as a model for functional evaluation of LNA and 2'-amino LNA**

pp 6585–6587

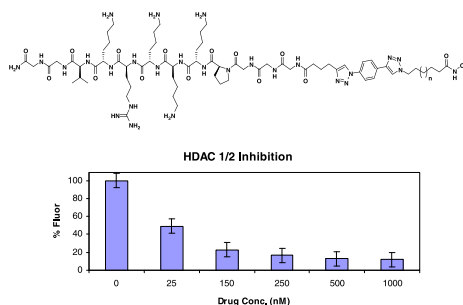
Frank J. Hernandez, Neerja Kalra, Jesper Wengel, Birte Vester ^{*}

Incorporation of a single LNA modification into an aptamer confers a significant improvement of affinity, and incorporation of 2'-amino LNA provides options for further derivatisation.

Design and synthesis of novel histone deacetylase inhibitor derived from nuclear localization signal peptide

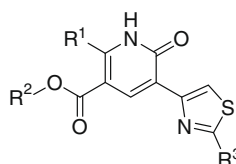
pp 6588–6590

Joshua C. Canzoneri, Po C. Chen, Adegboyega K. Oyelere *

**Design and synthesis of 6-oxo-1,6-dihydropyridines as CDK5 inhibitors**

pp 6591–6594

Matthew R. Kaller *, Wenge Zhong, Charles Henley, Ella Magal, Thomas Nguyen, David Powers, Robert M. Rzasa, Weiya Wang, Xiaoling Xiong, Mark H. Norman

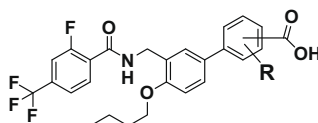


A series of 6-oxo-1,6-dihydropyridines were prepared and found to have potent CDK5 inhibition.

Novel biphenylcarboxylic acid peroxisome proliferator-activated receptor (PPAR) δ selective antagonists

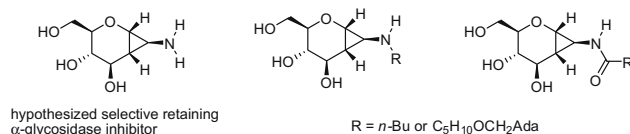
pp 6595–6599

Jun-ichi Kasuga, Seiichi Ishida, Daisuke Yamasaki, Makoto Makishima, Takefumi Doi, Yuichi Hashimoto, Hiroyuki Miyachi *

The discovery of new series of PPAR δ antagonists are described.**Synthesis and evaluation of *D*-gluco-pyranocyclopropyl amines as potential glucosidase inhibitors**

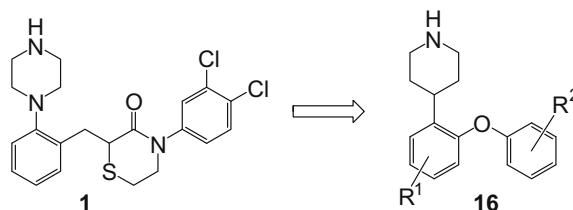
pp 6600–6603

Martijn D. P. Risseuw, Richard J. B. H. N. van den Berg, Wilma E. Donker-Koopman, Gijs A. van der Marel, Johannes M. F. G. Aerts, Mark Overhand *, Herman S. Overkleeft *



Discovery and pharmacological characterization of aryl piperazine and piperidine ethers as dual acting norepinephrine reuptake inhibitors and 5-HT_{1A} partial agonists

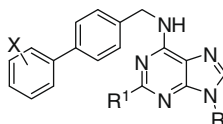
pp 6604–6607

David L. Gray ^{*}, Wenjian Xu, Brian M. Campbell, Amy B. Dounay, Nancy Barta, Susan Boroski, Lynne Denny, Lori Evans, Nancy Stratman, Al Probert

The discovery of piperidine diphenyl ethers (**16**) which combine norepinephrine reuptake inhibition (NRI) with 5-HT_{1A} partial agonist activity is described. Potent and selective leads were discovered starting from high-throughput screening hits including **1**.

Biaryl purine derivatives as potent antiproliferative agents: Inhibitors of cyclin dependent kinases. Part I

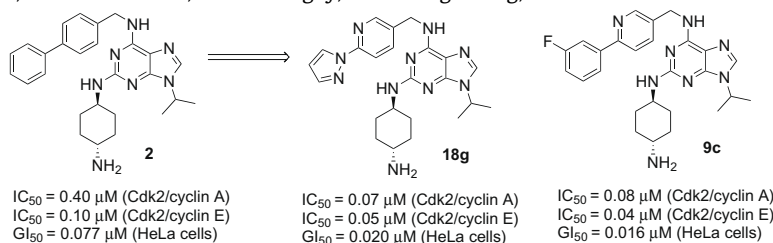
pp 6608–6612

Michael P. Trova, Keith D. Barnes ^{*}, Curt Barford, Travis Benanti, Mark Bielaska, Lori Burry, John M. Lehman, Christine Murphy, Harold O'Grady, Denise Peace, Susan Salamone, Jennifer Smith, Patricia Snider, Joseph Toporowski, Steven Tregay, Alison Wilson, Michael Wyle, Xiaozhang Zheng, Thomas D. Friedrich

Purines incorporating biarylmethylamino substituents at the C-6 position demonstrated inhibition of cyclin dependent kinases and potent antiproliferative activity.

Heterobiaryl purine derivatives as potent antiproliferative agents: Inhibitors of cyclin dependent kinases. Part II

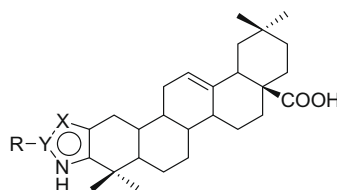
pp 6613–6617

Michael P. Trova, Keith D. Barnes ^{*}, Luis Alicea, Travis Benanti, Mark Bielaska, Joseph Bilotta, Brian Bliss, Thuy Nguyen Duong, Simon Haydar, R. Jason Herr, Yu Hui, Matthew Johnson, John M. Lehman, Denise Peace, Matthew Rainka, Patricia Snider, Susan Salamone, Steven Tregay, Xiaozhang Zheng, Thomas D. Friedrich

Biaryl purine derivatives such as **2** have demonstrated inhibition of cyclin dependent kinases and potent antiproliferative activity. Replacement of the C-6 biarylmethylamino group with heterobiarylmethylamino groups has afforded compounds such as **18g** and **9c** with significantly improved in vitro activity.

Synthesis and biological evaluation of heterocyclic ring-substituted maslinic acid derivatives as novel inhibitors of protein tyrosine phosphatase 1B

pp 6618–6622

Wen-Wei Qiu, Qiang Shen, Fan Yang, Bo Wang, Hui Zou, Jing-Ya Li, Jia Li ^{*}, Jie Tang ^{*}

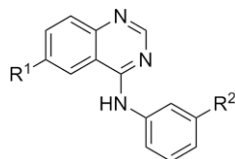
A series of heterocyclic ring-substituted maslinic acid derivatives were prepared and subsequently evaluated on PTP1B, TCPTP and related PTPs in order to increase PTP1B inhibitory activity and especially selectivity for PTP1B over TCPTP.



Discovery and SAR of 6-substituted-4-anilinoquinazolines as non-competitive antagonists of mGlu₅

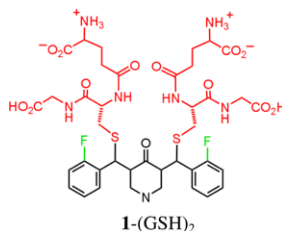
pp 6623–6626

Andrew S. Felts, Sam A. Saleh, Uyen Le, Alice L. Rodriguez, C. David Weaver, P. Jeffrey Conn, Craig W. Lindsley, Kyle A. Emmitte *

**1** R¹ = Br; R² = Cl mGlu₅ IC₅₀ = 256 nM**13** R¹ = Cl; R² = Br mGlu₅ IC₅₀ = 124 nM**32** R¹ = F; R² = Br mGlu₅ IC₅₀ = 96 nM**Curcumin analog cytotoxicity against breast cancer cells: exploitation of a redox-dependent mechanism**

pp 6627–6631

Aiming Sun *, Yang J. Lu, Haipeng Hu, Mamoru Shoji, Dennis C. Liotta, James P. Snyder *

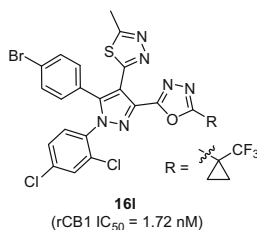


The glutathione conjugates of curcumin analogs represent a promising new series of stable and soluble anti-tumor pro-drugs.

Pentacycle derivatives as cannabinoid CB1 receptor ligands

pp 6632–6636

Suk Ho Lee, Hee Jeong Seo, Min Ju Kim, Suk Youn Kang, Sung-Han Lee, Kwangwoo Ahn, MinWoo Lee, Ho-Kyun Han, Jeongmin Kim, Jinhwa Lee *

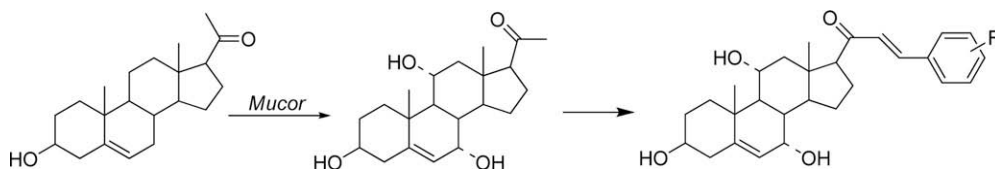


We have identified novel pentacycles series of small molecule cannabinoid-1 ligands that show potency comparable to that of known rCB1 antagonists. Among various analogues tested, 2-(5-(4-bromophenyl)-1-(2,4-dichlorophenyl)-4-(5-methyl-1,3,4-thiadiazol-2-yl)-1H-pyrazol-3-yl)-5-(1-(trifluoromethyl)cyclopropyl)-1,3,4-oxadiazole (**16l**) demonstrated highly favorable binding affinity for rCB1 receptor.

**Synthesis of 3β, 7α, 11α-trihydroxy-pregn-21-benzylidene-5-en-20-one derivatives and their cytotoxic activities**

pp 6637–6639

Li-Hong Shan, Hong-Min Liu *, Ke-Xue Huang, Gui-Fu Dai, Chen Cao, Rui-Jing Dong



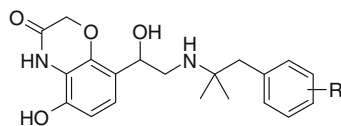
The synthesis and cytotoxic activities evaluation of a series of 3β, 7α, 11α-trihydroxy-pregn-21-benzylidene-5-en-20-one derivatives were described.



Use of 5-hydroxy-4H-benzo[1,4]oxazin-3-ones as β_2 -adrenoceptor agonists

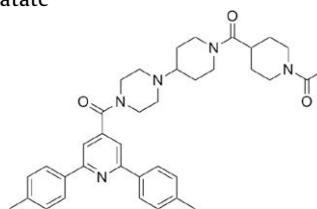
pp 6640–6644

Christoph Hoenke, Thierry Bouyssou, Christofer S. Tautermann, Klaus Rudolf, Andreas Schnapp, Ingo Konetzki *

 β_2 -Adrenoceptor agonists with different substituents R were prepared and investigated in vitro and in vivo.**(4-Piperidinyl)-piperazine: A new platform for acetyl-CoA carboxylase inhibitors**

pp 6645–6648

Tomomichi Chonan *, Takahiro Oi, Daisuke Yamamoto, Miyoko Yashiro, Daisuke Wakasugi, Hiroaki Tanaka, Ayumi Ohoka-Sugita, Fusayo Ito, Hiroko Koretsune, Akira Hiratate

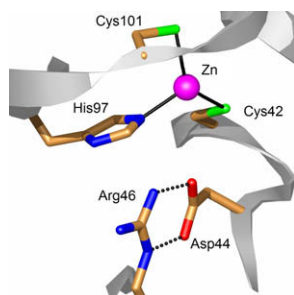
**31**human ACC1 IC_{50} = 101 nM
human ACC2 IC_{50} = 23 nM

Novel disubstituted (4-piperidinyl)-piperazine derivatives as ACC1/2 non-selective inhibitors were synthesized and evaluated.

**Carbonic anhydrase inhibitors. Characterization and inhibition studies of the most active β -carbonic anhydrase from *Mycobacterium tuberculosis*, Rv3588c**

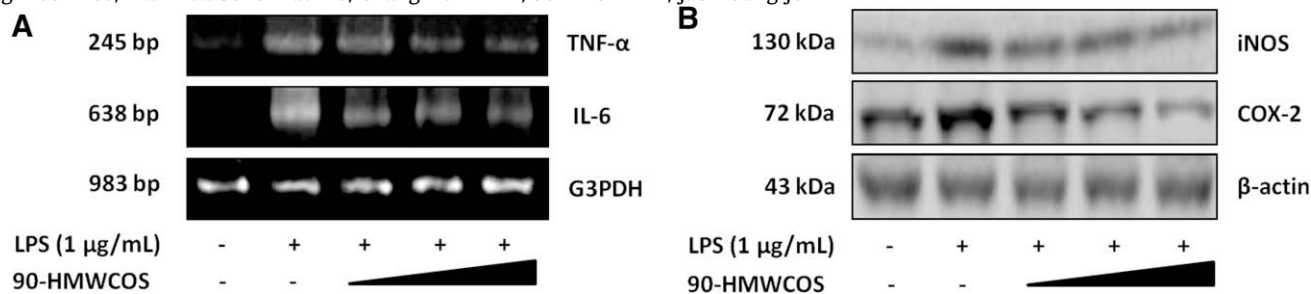
pp 6649–6654

Fabrizio Carta, Alfonso Maresca, Adrian Suarez Covarrubias, Sherry L. Mowbray, T. Alwyn Jones, Claudiu T. Supuran *

**Factors affecting anti-inflammatory effect of chito oligosaccharides in lipopolysaccharides-induced RAW264.7 macrophage cells**

pp 6655–6658

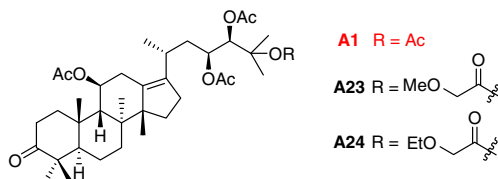
Sang-Hoon Lee, Mahinda Senevirathne, Chang-Bum Ahn, Se-Kwon Kim, Jae-Young Je *

90-HMWCOS exhibited anti-inflammatory effect via down-regulation of transcriptional and translational expression levels of TNF- α , IL-6 and iNOS and COX-2.

Anti-HBV agents. Part 3: Preliminary structure–activity relationships of tetra-acylalisol A derivatives as potent hepatitis B virus inhibitors

pp 6659–6665

Quan Zhang, Zhi-Yong Jiang, Jie Luo, Yun-Bao Ma, Ji-Feng Liu, Rui-Hua Guo, Xue-Mei Zhang, Jun Zhou, Wei Niu, Fei-Fei Du, Li Li, Chuan Li, Ji-Jun Chen^{*}



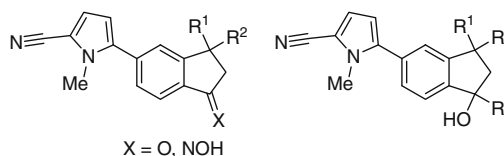
Thirty-two tetra-acylated alisol A derivatives were synthesized and evaluated for their anti-HBV activities and cytotoxicities in vitro. Among them, compounds A1, A23, and A24 exhibited high activities against secretion of HBV surface antigen with IC₅₀ values of 0.0048, 0.0044, and 0.014 mM, respectively, HBV e antigen with IC₅₀ values of 0.011, 0.012, and 0.018 mM, respectively, and remarkable selective index values of SI_{HBsAg} >333, SI_{HBeAg} >145; SI_{HBsAg} = 209, SI_{HBeAg} = 77; and SI_{HBsAg} >200, SI_{HBeAg} >156, respectively. Additional studies in rats showed that compound A1 has favorable pharmacokinetic prosperities for further development purpose, with elimination half-time (t_{1/2}) of 1.63 h and oral bioavailability (F) of 40.9%.



5-Aryl indanones and derivatives as non-steroidal progesterone receptor modulators

pp 6666–6669

Jeffrey C. Kern^{*}, Eugene Terefenko, Eugene Trybulski, Thomas J. Berrodin, Jeffrey Cohen, Richard C. Winneker, Matthew R. Yudt, Zhiming Zhang, Yuan Zhu, Puwen Zhang

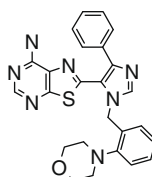


Progesterone receptor agonists and antagonists with low nanomolar in vitro potency are reported.

Novel thienopyrimidine and thiazolopyrimidine kinase inhibitors with activity against Tie-2 in vitro and in vivo

pp 6670–6674

Richard W. A. Luke^{*}, Peter Ballard, David Buttar, Leonie Campbell, Jon Curwen, Steve C. Emery, Alison M. Griffen, Lorraine Hassall, Barry R. Hayter, Cliff D. Jones, William McCoull, Martine Mellor, Mike L. Swain, Julie A. Tucker



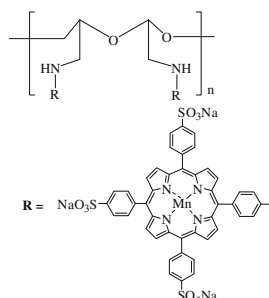
pTie-2 Cell IC₅₀ = 440 nM

The SAR and improvement in potency against Tie-2 of novel thienopyrimidine and thiazolopyrimidine kinase inhibitors are reported. These compounds have moderate potency in cellular assays of Tie-2 inhibition, good physical properties, DMPK, and show evidence of in vivo inhibition of Tie-2.

Synthesis and in vitro and in vivo evaluation of manganese(III) porphyrin–dextran as a novel MRI contrast agent

pp 6675–6678

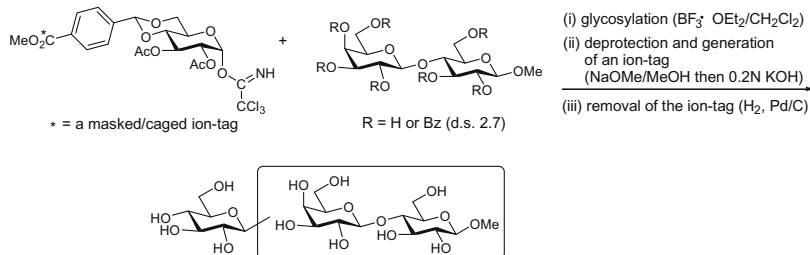
Zhi Zhang, Rui He, Kun Yan, Qian-ni Guo, Yun-guo Lu, Xu-xia Wang, Hao Lei^{*}, Zao-ying Li^{*}



The synthesis and evaluation of Mn porphyrin–dextran as MRI contrast agents are reported.

Use of ionically tagged glycosyl donors in the synthesis of oligosaccharide libraries

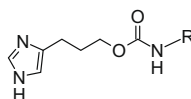
pp 6679–6681

Eun Ju Kim ^{*}, Gary R. Gray

Preparation of oligosaccharide libraries using ionically tagged glycosyl donors.

**Histamine H_3 and H_4 receptor affinity of branched 3-(1H-imidazol-4-yl)propyl N-alkylcarbamates**

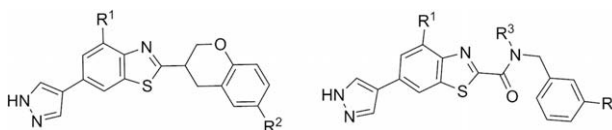
pp 6682–6685

Dorota Łażewska, Małgorzata Więcek, Xavier Ligneau, Tim Kottke, Lilia Weizel, Roland Seifert, Walter Schunack, Holger Stark, Katarzyna Kieć-Kononowicz ^{*}

Branched 3-(1H-imidazol-4-yl)propyl alkylcarbamates were investigated at the human histamine H_3 receptor (CHO-K1 or HEK-293 cells). A trend for a stereoselectivity at human H_3R was observed for the chiral α -branched ligands. Selected compounds were also tested at the human histamine H_4 receptor (Sf9 cells).

Benzothiazoles as Rho-associated kinase (ROCK-II) inhibitors

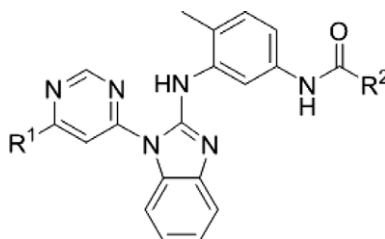
pp 6686–6690

Yan Yin, Li Lin, Claudia Ruiz, Michael D. Cameron, Jennifer Pocas, Wayne Grant, Thomas Schröter, Weimin Chen, Derek Duckett, Stephan Schürer, Philip LoGrasso, Yangbo Feng ^{*}

ROCK inhibitors have been developed from 2-chromanyl- and 2-carboxamido-benzothiazoles. SAR studies and lead optimizations are described, which result in novel ROCK-II inhibitors with sub-nanomolar IC_{50}s and good kinase selectivity.

Discovery of pyrimidine benzimidazoles as Src-family selective Lck inhibitors. Part II

pp 6691–6695

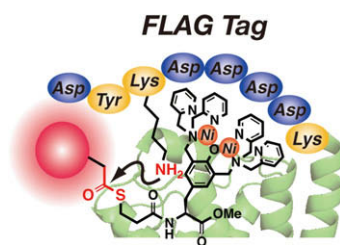
Guobao Zhang ^{*}, Pingda Ren, Nathanael S. Gray, Taebo Sim, Xia Wang, Yi Liu, Jianwei Che, Weitong Dong, Shin-Shay Tian, Mark L. Sandberg, Tracy A. Spalding, Russell Romeo, Maya Iskandar, Zhiliang Wang, H.Martin Seidel, Donald S. Karanewsky, Yun He ^{*}

A series of 4-amino-6-benzimidazole-pyrimidines were designed and synthesized as potent Lck inhibitors.

FLAG-tag selective covalent protein labeling via a binding-induced acyl-transfer reaction

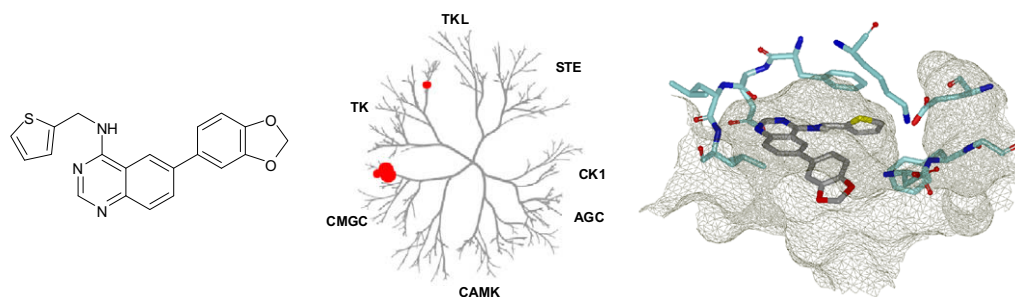
pp 6696–6699

Hiroshi Nonaka, Sho-hei Fujishima, Sho-hei Uchinomiya, Akio Ojida, Itaru Hamachi *

**Evaluation of substituted 6-arylquinazolin-4-amines as potent and selective inhibitors of cdc2-like kinases (Clk)**

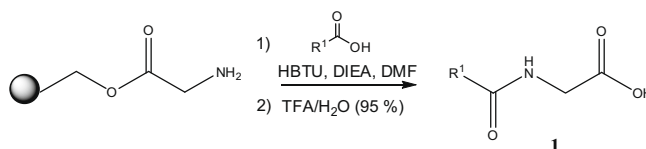
pp 6700–6705

Bryan T. Mott, Cordelle Tanega, Min Shen, David J. Maloney, Paul Shinn, William Leister, Juan J. Marugan, James Inglese, Christopher P. Austin, Tom Misteli, Douglas S. Auld, Craig J. Thomas *

**Solid phase synthesis of acylglycine human metabolites**

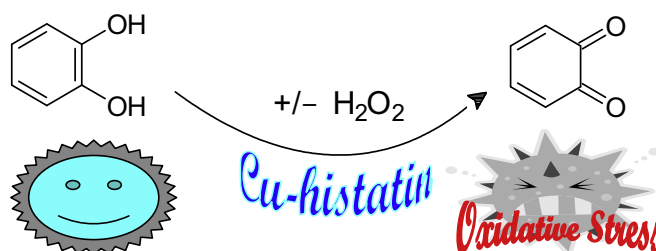
pp 6706–6708

Rolando Perez-Pineiro *, Ying Wei Dong, David S. Wishart *

The efficient solid phase synthesis of acylglycine human metabolites **1** is reported.**A plausible role of salivary copper in antimicrobial activity of histatin-5—Metal binding and oxidative activity of its copper complex**

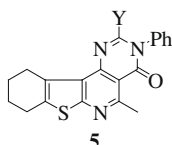
pp 6709–6712

William M. Tay, Ahmed I. Hanafy, Alexander Angerhofer, Li-June Ming *



A facile synthesis and biological activity of novel tetrahydrobenzo[4,5']thieno[3',2':5,6]pyrido[4,3-d]pyrimidin-4(3H)-ones

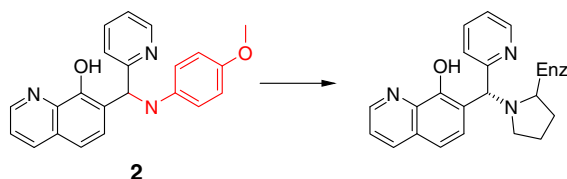
pp 6713–6716

Qingyun Ren, Yong-Ju Liang, Hongwu He^{*}, Liwu Fu^{*}, Yucheng Gu

The synthesis and biological activity of 2-substituted-8,9,10,11-tetrahydrobenzo[4,5']thieno[3',2':5,6]pyrido[4,3-d]pyrimidin-4(3H)-ones **5** are described. The biological evaluation showed that some compounds have antifungal activity against *Botrytis cinerea* at 50 mg/L and some of them were effective to both KB cells and KBv200 cells.

Discovery of covalent inhibitors for MIF tautomerase via cocrystal structures with phantom hits from virtual screening

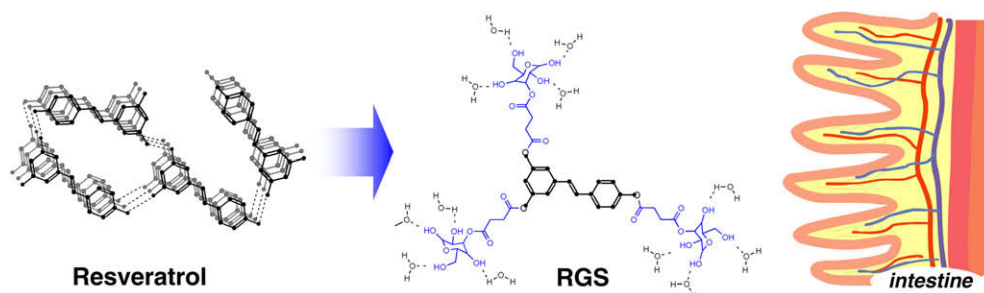
pp 6717–6720

Larry R. McLean^{*}, Ying Zhang, Hua Li, Ziyu Li, Ulrike Lukasczyk, Yong-Mi Choi, Zuoning Han, Joy Prisco, Jeremy Fordham, Joseph T. Tsay, Stephan Reiling, Roy J. Vaz, Yi Li^{*}

Virtual screen hits were shown to be covalent inhibitors by biochemical and X-ray crystallographic studies.

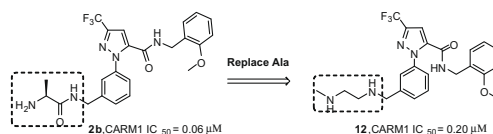
Soluble polyphenols: Synthesis and bioavailability of 3,4',5-tri(α-D-glucose-3-O-succinyl) resveratrol

pp 6721–6724

Lucia Biasutto, Ester Marotta, Alice Bradaschia, Mauro Fallica, Andrea Mattarei, Spiridione Garbisa, Mario Zoratti^{*}, Cristina Paradisi

1,2-Diamines as inhibitors of co-activator associated arginine methyltransferase 1 (CARM1)

pp 6725–6732

Eric Therrien, Guillaume Larouche, Sukhdev Manku, Martin Allan, Natalie Nguyen, Sylvia Styhler, Marie-France Robert, Anne-Christine Goulet, Jeffrey M. Besterman, Hannah Nguyen, Amal Wahhab^{*}

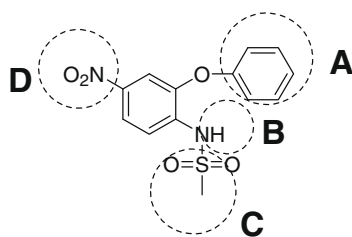
Cpd	N. AUC (PO) μM·h/(mg/Kg)	N. AUC (IV) μM·h/(mg/Kg)	Cl (IV) (L/h)/kg	V _d (IV) L/kg	t _{1/2} (IV) hours	% F
2b	0.01	0.04	86	33.6	0.07	-
12	0.07	2.1	1.2	1.4	2.1	4

We have identified the *N*¹-benzyl-*N*²-methylethane-1,2-diamine unit as a substitute for the (*S*)-alanine benzylamide moiety for the design of co-activator associated arginine methyltransferase 1 (CARM1) inhibitors. The potency of these inhibitors is in the same order of magnitude as their predecessors and their clearance, volume of distribution, and half lives were greatly improved.

Lead optimization of COX-2 inhibitor nimesulide analogs to overcome aromatase inhibitor resistance in breast cancer cells

pp 6733–6735

Bin Su, Shiuan Chen *

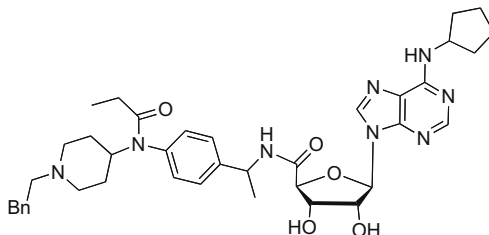


A series of COX-2 selective inhibitor nimesulide derivatives were synthesized as agents to suppress the proliferation of aromatase inhibitor-resistant breast cancer cells.

Design, synthesis and biological evaluation of a bivalent μ opiate and adenosine A1 receptor antagonist

pp 6736–6739

Smitha C. Mathew, Nandita Ghosh, Youlet By, Aurélie Berthault, Marie-Alice Virolleaud, Louis Carrega, Gaëlle Chouraqui, Laurent Commeiras, Jocelyne Condo, Mireille Attolini, Anouk Gaudel-Siri, Jean Ruf, Jean-Luc Parrain *, Jean Rodriguez *, Régis Guieu *

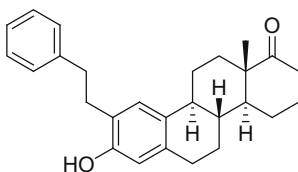


The synthesis and biological activity of a new hetero-bivalent ligand that has antagonist properties on both A₁ adenosine and μ opiate receptors with a K_i of 0.8 ± 0.05 and 0.7 ± 0.03 μ M, respectively, are described.

Structure-based design, synthesis and in vitro characterization of potent 17 β -hydroxysteroid dehydrogenase type 1 inhibitors based on 2-substitutions of estrone and D-homo-estrone

pp 6740–6744

Gabriele Möller, Dominga Deluca, Christian Gege, Andrea Rosinus, Dorota Kowalik, Olaf Peters, Peter Droescher, Walter Elger, Jerzy Adamski *, Alexander Hillisch



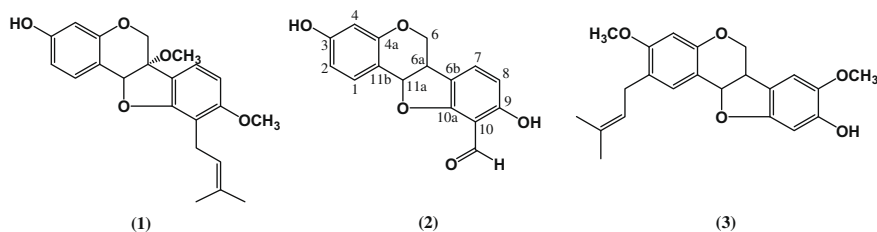
The development of 17 β -HSD1 inhibitor (e.g., 2-phenethyl-D-homo-estrone with IC₅₀ of 15 nM in vitro) is reported.



Cytotoxic and PTP1B inhibitory activities from *Erythrina abyssinica*

pp 6745–6749

Phi Hung Nguyen, Thi Van Thu Le, Phuong Thien Thuong, Trong Tuan Dao, Derek Tantoh Ndinteh, Joseph Tanyi Mbafor, Keon Wook Kang, Won Keun Oh *

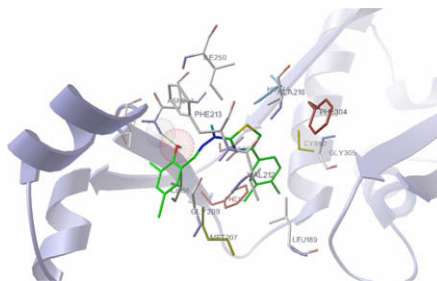


Three new (**1–3**) and 12 known (**4–15**) pterocarpan derivatives were isolated from the stem bark of *Erythrina abyssinica* (Leguminosae). All of the isolates were evaluated for their inhibitory effects on protein tyrosine phosphatase-1B (PTP1B), as well as their growth inhibition on MCF-7, MCF-7/TAMR, MCF-7/ADR and MDA-MB-231 breast cancer cell lines.

Design, synthesis and biological evaluation of novel thiazole derivatives as potent FabH inhibitors

pp 6750–6754

Peng-Cheng Lv, Kai-Rui Wang, Ying Yang, Wen-Jun Mao, Jin Chen, Jing Xiong, Hai-Liang Zhu *

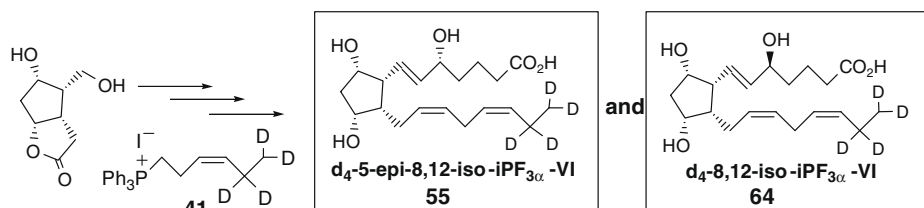


Docking results, along with the data of *Escherichia coli* FabH inhibitory activity assay indicated that compounds **11** and **18** would be potential inhibitors of *E. coli* FabH with potent antibacterial activity.

A new approach to the synthesis of polyunsaturated deuterated isoprostanes: Total synthesis of d₄-5-*epi*-8,12-iso-iPF_{3α}-VI and d₄-8,12-iso-iPF_{3α}-VI

pp 6755–6758

Chih-Tsung Chang, Pranav Patel, Vivek Gore, Wen-Liang Song, John A. Lawson, William S. Powell, Garret A. FitzGerald, Joshua Rokach *

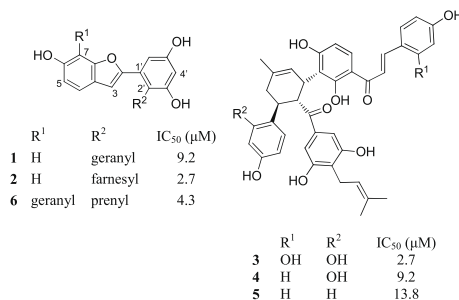


d₄-5-*epi*-8,12-iso-iPF_{3α}-VI **55** and d₄-8,12-iso-iPF_{3α}-VI **64** were synthesized using a new strategy to prepare the volatile D₄ synthons. **55** and **64** were subsequently used to quantify iPs in urine.

Protein tyrosine phosphatase 1B inhibitors isolated from *Morus bombycis*

pp 6759–6761

Duc Manh Hoang, Tran Minh Ngoc, Nguyen Tien Dat, Do Thi Ha, Young Ho Kim, Hoang Van Luong, Jong Seog Ahn *, KiHwan Bae *

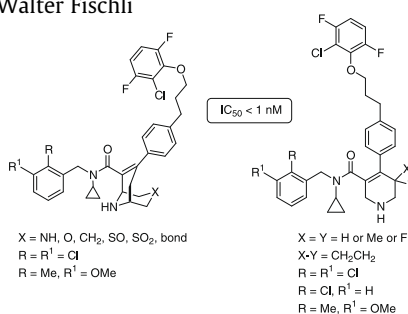


Inhibitory constituents against protein tyrosine phosphatase 1B from *Morus bombycis*.

New classes of potent and bioavailable human renin inhibitors

pp 6762–6765

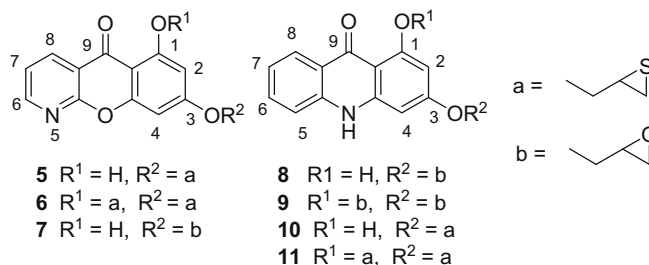
L'uboš Remeň *, Olivier Bezençon *, Sylvia Richard-Bildstein, Daniel Bur, Lars Prade, Olivier Corminboeuf, Christoph Boss, Corinna Grisostomi, Thierry Sifferlen, Panja Strickner, Patrick Hess, Stéphane Delahaye, Alexander Treiber, Thomas Weller, Christoph Binkert, Beat Steiner, Walter Fischli



Oxiranylmethoxy or thiiranylmethoxy-azaxanthenes and -acridone analogues as potential topoisomerase I inhibitors

pp 6766–6769

Hee-Ju Cho, Mi-Ja Jung, Youngjoo Kwon *, Younghwa Na *

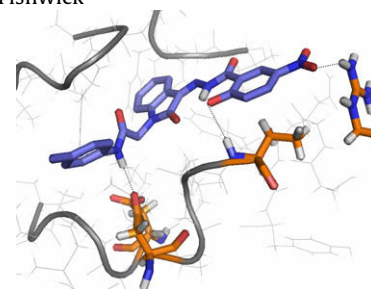


Discovery of novel non-peptide inhibitors of BACE-1 using virtual high-throughput screening

pp 6770–6774

N. Yi Mok, James Chadwick, Katherine A. B. Kellett, Nigel M. Hooper *, A. Peter Johnson *, Colin W. G. Fishwick *

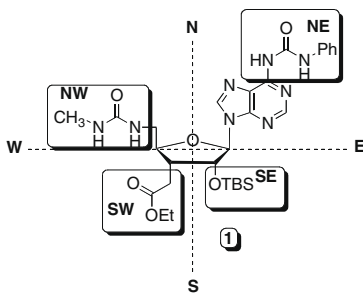
A novel series of isatin-based inhibitors of β -secretase (BACE-1) have been identified using a virtual high-throughput screening approach. Structure–activity relationship studies revealed structural features important for inhibition. Docking studies suggest these inhibitors may bind within the BACE-1 active site through H-bonding interactions involving the catalytic aspartate residues.



Preliminary SAR analysis of novel antiproliferative $N^6,5'$ -bis-ureidoadenosine derivatives

pp 6775–6779

Matt A. Peterson *, Marcelio Oliveira, Michael A. Christiansen, Christopher E. Cutler



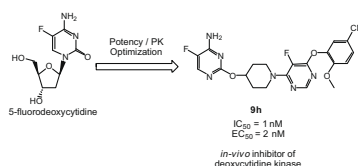
Analogs of lead antiproliferative agent **1** were prepared and tested for activities against the NCI 60 panel of human cancers. Variants in all four canonical quadrants were tested. The 2'-O-TBS, 5'-N-methylurea, and N^6 -phenylurea were necessary for optimal activity.



5-Fluorocytosine derivatives as inhibitors of deoxycytidine kinase

pp 6780–6783

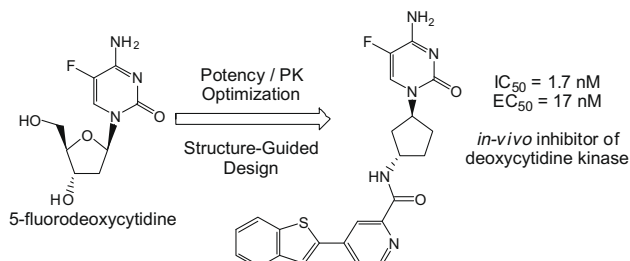
James E. Tarver, Theodore C. Jessop, Marianne Carlsen, David J. Augeri, Qinghong Fu, Jason P. Healy, Alexander Heim-Riether, Amy Xu, Jerry A. Taylor, Min Shen, Philip E. Keyes, S. David Kimball, Xuan-Chuan Yu, Maricar Miranda, Qingyun Liu, Jonathan C. Swaffield, Amr Nouraldeen, Alan G. E. Wilson, Rick Finch, Kanchan Jhaver, Ann Marie DiGeorge Foushee, Steve Anderson, Tamas Oravec, Kenneth G. Carson *



Lead optimization and structure-based design of potent and bioavailable deoxycytidine kinase inhibitors

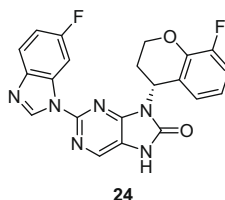
pp 6784–6787

Theodore C. Jessop^{*}, James E. Tarver, Marianne Carlsen, Amy Xu, Jason P. Healy, Alexander Heim-Riether, Qinghong Fu, Jerry A. Taylor, David J. Augeri, Min Shen, Terry R. Stouch, Ronald V. Swanson, Leslie W. Tari, Michael Hunter, Isaac Hoffman, Philip E. Keyes, Xuan-Chuan Yu, Maricar Miranda, Qingyun Liu, Jonathan C. Swaffield, S. David Kimball, Amr Nouraldean, Alan G. E. Wilson, Ann Marie DiGeorge Foushee, Kanchan Jhaver, Rick Finch, Steve Anderson, Tamas Oravec, Kenneth G. Carson

**2-Benzimidazolyl-9-(chroman-4-yl)-purinone derivatives as JAK3 inhibitors**

pp 6788–6792

Andrew G. Cole^{*}, Adolph C. Bohnstedt, Vidyadhar Paradkar, Celia Kingsbury, Jorge G. Quintero, Haengsoon Park, Yingchun Lu, Ming You, Irina Neagu, David J. Diller, Jeffrey J. Letourneau, Yuefei Shao, Ray A. James, Christopher M. Riviello, Koc-Kan Ho, Tsung H. Lin, Bojing Wang, Kenneth C. Appell, Matthew Sills, Elizabeth Quadros, Earl F. Kimble, Michael H. J. Ohlmeyer, Maria L. Webb



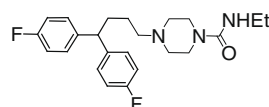
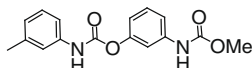
A novel class of 2-benzimidazolylpurinone-based JAK3 inhibitors with excellent kinase activity is described. Compound **24** demonstrates good oral bioavailability and in vivo efficacy in an acute mechanistic mouse model.

Mining biologically-active molecules for inhibitors of fatty acid amide hydrolase (FAAH): Identification of phenmedipham and amperozide as FAAH inhibitors

pp 6793–6796

Fabien Vincent^{*}, Margaret T. Nguyen, Daniel E. Emerling, Michael G. Kelly, Matthew A. J. Dunton^{*}

Phenmedipham
hFAAH $IC_{50} = 377 \text{ nM}$

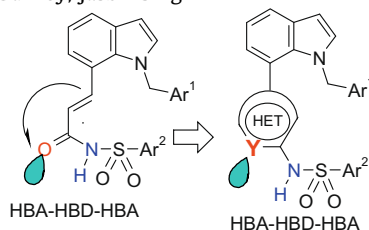


Amperozide
hFAAH $IC_{50} = 1.34 \text{ }\mu\text{M}$

**Heterocyclic 1,7-disubstituted indole sulfonamides are potent and selective human EP₃ receptor antagonists**

pp 6797–6800


Georgeta Hategan, Alexandre M. Polozov, Wayne Zeller, Hua Cao, Rama K. Mishra, Alex S. Kiselyov, Jose Ramirez, Gufrún Halldorsdottir, Þorkell Andrésson, Mark E. Gurney, Jasbir Singh^{*}



We have developed a pharmacophore model for the EP₃ receptor antagonists based on its endogenous ligand PGE₂. This ligand-based design yielded a series of novel peri-substituted [4.3.0] bicyclic aromatics featuring 1-alkylaryl 7-heterocyclic sulfonamide substituents. The synthesized molecules are potent antagonists of human EP₃ receptor in vitro and show inhibition of rat platelets aggregation. Optimized derivatives display high selectivity over IP, FP, and other EP receptor panels.



*Corresponding author

 Supplementary data available via ScienceDirect

COVER

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

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