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Contents

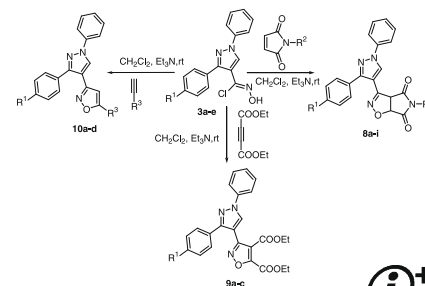
ARTICLES

Synthesis and antinociceptive activity of pyrazolyl isoxazolines and pyrazolyl isoxazoles

pp 3370–3373

K. Karthikeyan, T. Veenus Seelan, K. G. Lalitha, P. T. Perumal *

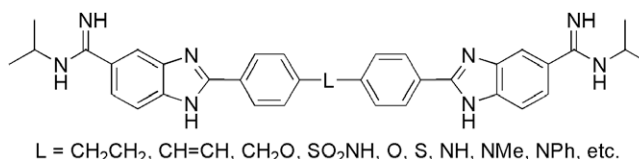
Pyrazolyl isoxazolines and isoxazoles were synthesised in moderate to good yields using 1,3-dipolar cycloaddition of pyrazole derived nitrile oxide with various dipolarophiles such as N-substituted maleimide, diethylacetylene dicarboxylate and phenylacetylene. The synthesized compounds were evaluated for antinociceptive activities. The 3-pyrazolyl-4,5-dicarboxy isoxazoles (**9a–c**) exhibited the maximum antinociceptive activity.



Optimization of the central linker of dicationic bis-benzimidazole anti-MRSA and anti-VRE agents

pp 3374–3377

Laixing Hu, Maureen L. Kully, David W. Boykin, Norman Abood *

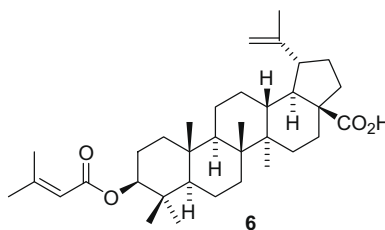


A series of bis-benzimidazole diamidine compounds containing different central linkers has been synthesized and evaluated for in vitro antibacterial activities, including MRSA and VRE bacterial strains.

Cancer preventive agents 9. Betulinic acid derivatives as potent cancer chemopreventive agents

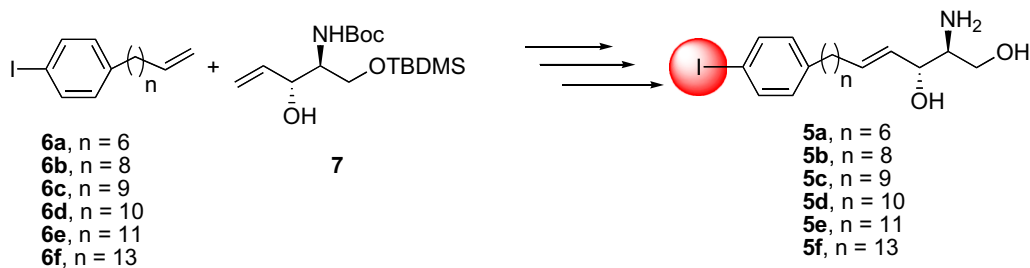
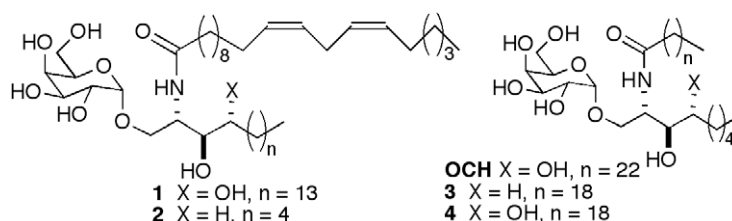
pp 3378–3381

Kyoko Nakagawa-Goto, Koji Yamada, Masahiko Taniguchi, Harukuni Tokuda, Kuo-Hsiung Lee *

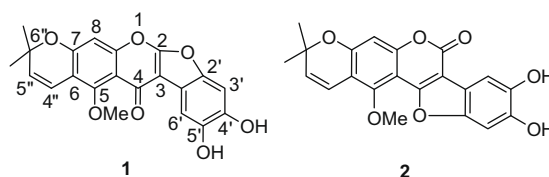


Iodophenyl tagged sphingosine derivatives: Synthesis and preliminary biological evaluation

pp 3382–3385

Wenchao Qu^{*}, Karl Ploessl, Hong Truong, Mei-Ping Kung, Hank F. Kung**Synthesis and evaluation of an acyl-chain unsaturated analog of the Th2 biasing, immunostimulatory glycolipid, OCH** pp 3386–3388Geetha Velmourougane, Ravinder Raju, Gabriel Bricard, Jin S. Im, Gurdial S. Besra, Steven A. Porcelli, Amy R. Howell^{*}**Hirtellanines A and B, a pair of isomeric isoflavonoid derivatives from *Campylotropis hirtella* and their immunosuppressive activities**

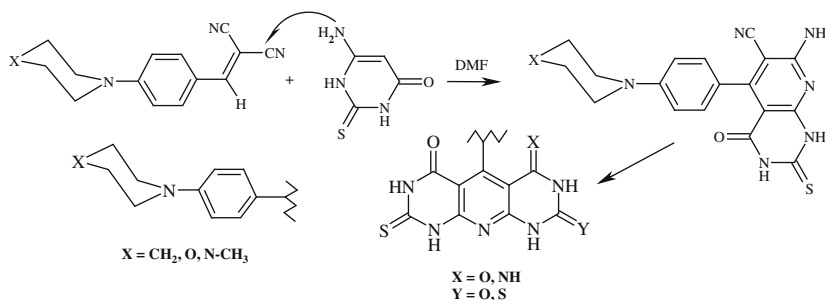
pp 3389–3391

Qing Yao Shou, Qing Tan, Zheng Wu Shen^{*}

A pair of isomeric isoflavonoid derivatives, Hirtellanines A (**1**) and B (**2**), has been isolated from the roots of *Campylotropis hirtella*. Hirtellanines A showed strong immunosuppressive activities.

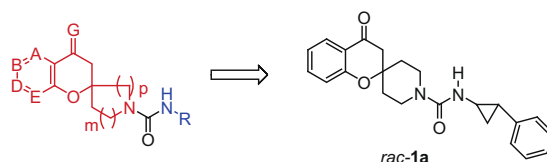
**Synthesis of 4-substituted pyrido[2,3-d]pyrimidin-4(1H)-one as analgesic and anti-inflammatory agents**

pp 3392–3397

Abdel-Rahman B. A. El-Gazzar^{*}, Hend N. Hafez

Discovery of spirocyclic secondary amine-derived trisubstituted ureas as highly potent, selective and bioavailable soluble epoxide hydrolase inhibitors pp 3398–3404

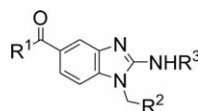
Hong C. Shen ^{*}, Fa-Xiang Ding, Siyi Wang, Suoyu Xu, Hsuan-shen Chen, Xinchun Tong, Vincent Tong, Kaushik Mitra, Sanjeev Kumar, Xiaoping Zhang, Yuli Chen, Gaochao Zhou, Lee-Yuh Pai, Magdalena Alonso-Galicia, Xiaoli Chen, Bei Zhang, James R. Tata, Joel P. Berger, Steven L. Colletti



Spirocyclic secondary amine-derived trisubstituted ureas were identified as highly potent, bioavailable and selective soluble epoxide hydrolase (sEH) inhibitors. Despite good oral exposure and excellent ex vivo target engagement in blood, one such compound, *rac-1a*, failed to lower blood pressure acutely in spontaneously hypertensive rats (SHRs). This study posed the question as to whether sEH inhibition provides a robust mechanism leading to a significant antihypertensive effect.

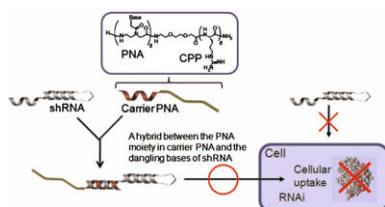
Substituted benzimidazoles: A novel chemotype for small molecule hKSP inhibitors pp 3405–3409

Brian R. Lahue ^{*}, Yao Ma, Gerald W. Shipp Jr., Wolfgang Seghezzi, Ronald Herbst



Carrier PNA for shRNA delivery into cells pp 3410–3413

Mizuki Kitamatsu ^{*}, Takanori Kubo, Rino Matsuzaki, Tamaki Endoh, Takashi Ohtsuki ^{*}, Masahiko Sisido

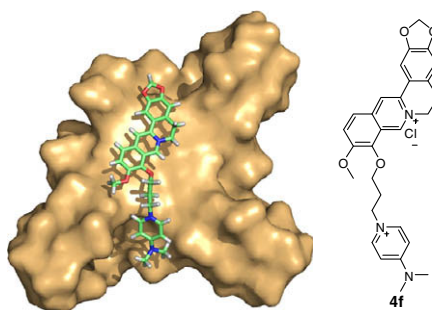


A peptide nucleic acid conjugated to a cell-penetrating peptide (carrier PNA) sequence-specifically binds to an shRNA bearing complementary dangling bases, and the carrier PNA delivers the shRNA effectively into cells.



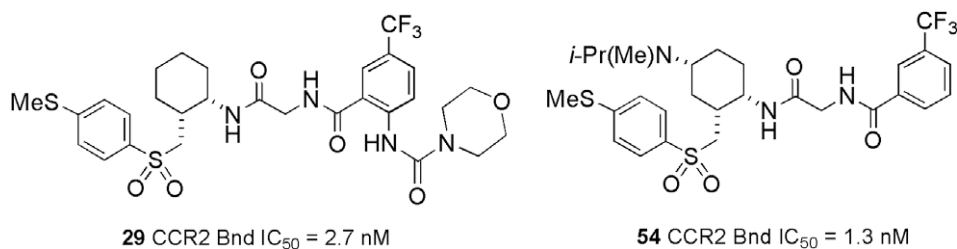
Synthesis and evaluation of 9-O-substituted berberine derivatives containing aza-aromatic terminal group as highly selective telomeric G-quadruplex stabilizing ligands pp 3414–3417

Yan Ma, Tian-Miao Ou, Jia-Heng Tan, Jin-Qiang Hou, Shi-Liang Huang, Lian-Quan Gu ^{*}, Zhi-Shu Huang ^{*}

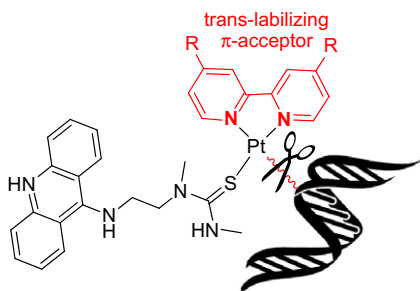


Novel sulfone-containing di- and trisubstituted cyclohexanes as potent CC chemokine receptor 2 (CCR2) antagonists pp 3418–3422

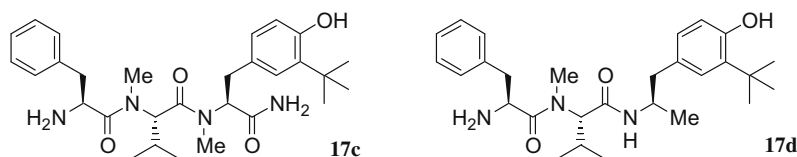
Robert J. Cherney^{*}, Ruowei Mo, Dayton T. Meyer, Matthew E. Voss, Yvonne C. Lo, Gengjie Yang, Persymphonie B. Miller, Peggy A. Scherle, Andrew J. Tebben, Percy H. Carter, Carl P. Decicco

**Synthesis and biological evaluation of platinum–acridine hybrid agents modified with bipyridine non-leaving groups** pp 3423–3425

Alexander R. Kheradi, Gilda Saluta, Gregory L. Kucera, Cynthia S. Day, Ulrich Bierbach^{*}

**Discovery of novel motilin antagonists: Conversion of tetrapeptide leads to orally available peptidomimetics** pp 3426–3429

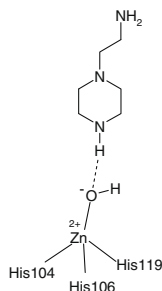
Naoki Taka^{*}, Hiroharu Matsuoka, Tsutomu Sato, Hitoshi Yoshino, Ikuhiro Imaoka, Haruhiko Sato, Ken-ichiro Kotake, Yoshikazu Kumagai, Kenshi Kamei, Ken-ichi Ozaki, Atsuko Higashida, Toshio Kuroki



Peptidomimetic motilin antagonists (**17c** and **17d**) were identified. Both compounds dose-dependently suppressed motilin-induced colonic and gastric motility in conscious dogs.

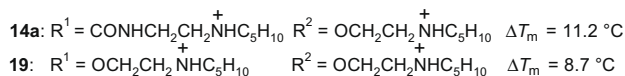
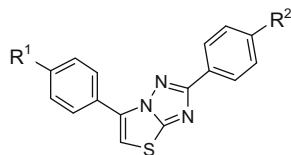
Carbonic anhydrase activators. Activation of the membrane-associated isoform XV with amino acids and amines pp 3430–3433

Alessio Innocenti, Mika Hilvo, Seppo Parkkila, Andrea Scozzafava, Claudiu T. Supuran^{*}

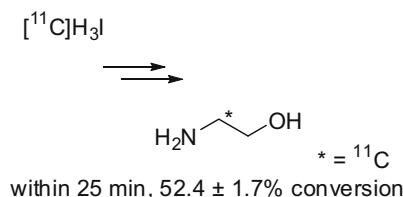


2,6-Diphenylthiazolo[3,2-*b*][1,2,4]triazoles as telomeric G-quadruplex stabilizers

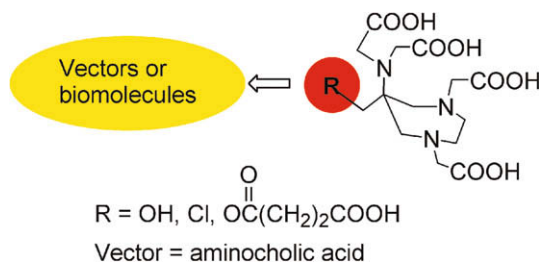
pp 3434–3438

Jamal El Bakali, Frédérique Klupsch, Aurore Guédin, Bertrand Brassart, Gaëlle Fontaine, Amaury Farce, Pascal Roussel, Raymond Houssin, Jean-Luc Bernier, Philippe Chavatte, Jean-Louis Mergny, Jean-François Riou^{*}, Jean-Pierre HénichartTwo of the title compounds (**14a**, **19**) bearing cationic side chains present high selectivity for telomeric G-quadruplex over duplex DNA.**Synthesis of ¹¹C-labeled 2-aminoethanol via a nitroaldol reaction using nitro[¹¹C]methane**

pp 3439–3441

Koichi Kato^{*}, Ming-Rong Zhang, Katsuyuki Minegishi, Kazutoshi SuzukiA practical and accessible method for the synthesis of 2-amino[2-¹¹C]ethanol is reported.**Fast and easy access to efficient bifunctional chelators for MRI applications**

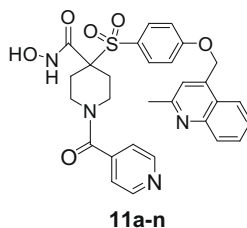
pp 3442–3444

Giuseppe Gugliotta, Mauro Botta, Giovanni Battista Giovenzana, Lorenzo Tei^{*}

Novel bifunctional ligands based on the AAZTA structure with different functional groups are reported. The Gd-complexes show optimal magnetic properties for Magnetic Resonance-Molecular Imaging applications.

**Synthesis and activity of quinolinylmethyl P1' α -sulfone piperidine hydroxamate inhibitors of TACE**

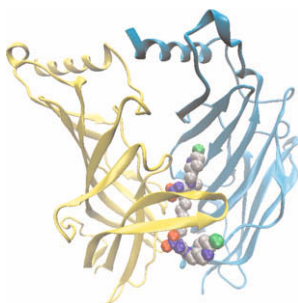
pp 3445–3448

Chunchun Zhang^{*}, Frank Lovering, Mark Behnke, Arie Zask, Vincent Sandanayaka, Linhong Sun, Yi Zhu, Weixin Xu, Yuhua Zhang, Jeremy I. LevinThe activity of a series of α -sulfone piperidine hydroxamate TACE inhibitors **11a-n** bearing a quinolinyl methyl P1' group was compared to α - and β -sulfone piperidine hydroxamates with a butynyloxy P1' group.

Bis-neonicotinoid insecticides: Observed and predicted binding interactions with the nicotinic receptor

pp 3449–3452

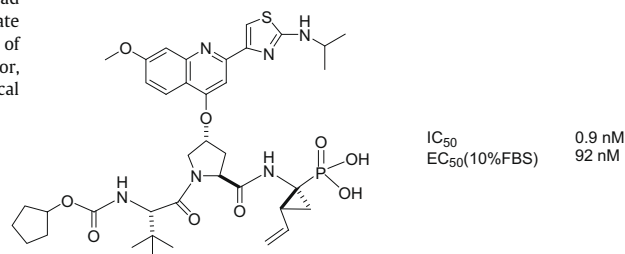
Ikuya Ohno, Motohiro Tomizawaa, Kathleen A. Durkin, John E. Casida, Shinzo Kagabu *

**Discovery of novel phosphonate derivatives as hepatitis C virus NS3 protease inhibitors**

pp 3453–3457

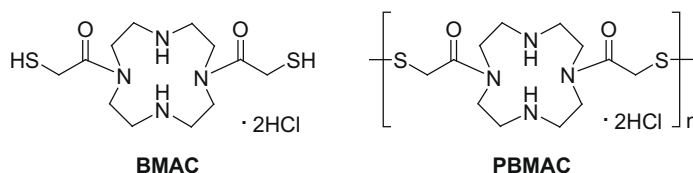
X. Christopher Sheng *, Hyung-Jung Pyun, Kleem Chaudhary, Jianying Wang, Edward Doerffler, Melissa Fleury, Darren McMurtrie, Xiaowu Chen, William E. Delaney IV, Choung U. Kim

The design and preparation of highly potent tricyclic HIV integrase inhibitors are reported. The lead compound has shown good oral bioavailability in both rat and dog. A novel class of phosphonate derivatives was designed to mimic the interaction of product-like carboxylate based inhibitors of HCV NS3 protease. A phosphonic acid was demonstrated to be a potent HCV NS3 protease inhibitor, and a potential candidate for treating HCV infection. The syntheses and preliminary biological evaluation of this phosphonate class of inhibitor are described.

**Linear disulfide-containing low polymer as efficient DNA cleavage reagent**

pp 3458–3460

Yong-Zhe Xiang, Yi-Le Liao, Ji Zhang *, Da-Wei Zhang, Shan-Yong Chen, Qiao-Sen Lu, Yu Zhang, Hong-Hui Lin *, Xiao-Qi Yu *



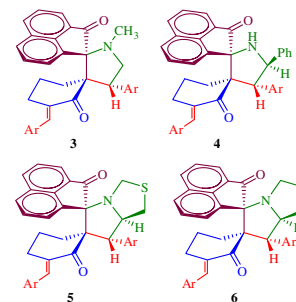
The disulfide bonds-containing polymer (PBMAC) can promote the cleavage of DNA more efficiently than its monomer (BMAC) under physiological conditions.

**An atom economic synthesis and antitubercular evaluation of novel spiro-cyclohexanones**

pp 3461–3465

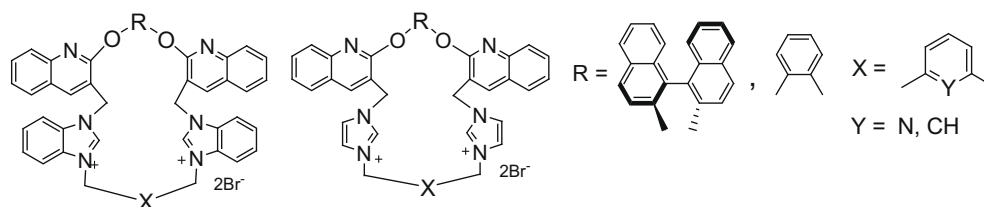
Raju Ranjith Kumar, Subbu Perumal *, S. C. Manju, Pritesh Bhatt, Perumal Yogeewari, Dharmarajan Sriram

Twenty eight spiro-cyclohexanones were synthesized via 1,3-dipolar cycloaddition of azomethine ylides to a series of 2,6-bis[(E)-arylmethylidene]cyclohexanones and were screened for their in vitro activity against *Mycobacterium tuberculosis* H37Rv (MTB) using agar dilution method. Two compounds, 4-(2,4-dichloro-phenyl)-5-phenylpyrrolo-(spiro[2.2']acenaphthene-1''-one)-spiro[3.2']-6'-(2,4-dichlorophenylmethylidene)-cyclohexanone (**4i**) and spiro-[5.2']acenaphthene-1''-one-spiro[6.2']-6'-(2,4-dichlorophenylmethylidene)-cyclohexanone-7-(2,4-dichlorophenyl)tetrahydro-1H-pyrrolo[1,2-c][1,3]thiazole (**5i**) display maximum activity in vitro with MIC of 0.4 µg/mL and were 4 and 15 times more potent than ethambutol and pyrazinamide, respectively.

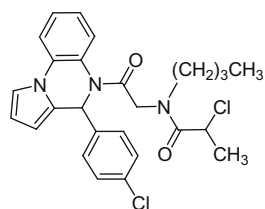


Synthesis and antibacterial activity of some novel imidazole-based dicationic quinolinophanes

pp 3466–3470

Perumal Rajakumar ^{*}, Rathinam Raja, Subramaniyan Selvam, Ramasamy Rengasamy, Subramani Nagaraj**Hit-to-lead optimization of pyrrolo[1,2-a]quinoxalines as novel cannabinoid type 1 receptor antagonists**

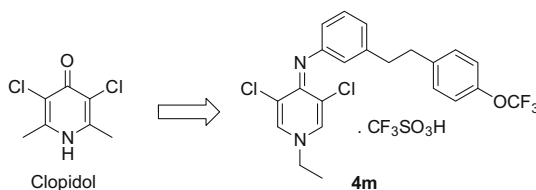
pp 3471–3475

György Szabó ^{*}, Róbert Kiss, Dóra Páyer-Lengyel, Krisztina Vukics, Judit Szikra, Andrea Baki, László Molnár, János Fischer, György M. Keserücompound **45** CB₁ K_i = 45 nM

Hit-to-lead optimization of a novel series of *N*-alkyl-*N*-[2-oxo-2-(4-aryl-4*H*-pyrrolo[1,2-*a*]quinoxaline-5-yl)-ethyl]-carboxylic acid amides, derived from a high throughput screening (HTS) hit, are described.

Design, synthesis and structure–activity relationships of (1*H*-pyridin-4-ylidene)amines as potential antimalarials

pp 3476–3480

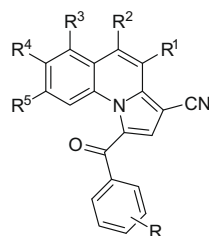
Tiago Rodrigues, Rita C. Guedes, Daniel J. V. A. dos Santos, Marta Carrasco, Jiri Gut, Philip J. Rosenthal, Rui Moreira ^{*}, Francisca Lopes

IC₅₀ = 9.73 μM (*P. falciparum* W2) IC₅₀ = 0.94 μM (*P. falciparum* W2)

(1*H*-Pyridin-4-ylidene)amines designed as clodolol isosteres were active against *Plasmodium falciparum* W2 (chloroquine-resistant) and FCR3 (atovaquone-resistant) strains in the low micromolar range.

**Discovery of 1-benzoyl-3-cyanopyrrolo[1,2-a]quinolines as a new series of apoptosis inducers using a cell- and caspase-based high-throughput screening assay. 2: Structure–activity relationships of the 4-, 5-, 6-, 7- and 8-positions**

pp 3481–3484

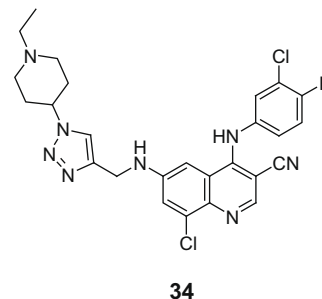
William Kemnitzer, Jared Kuemmerle, Songchun Jiang, Nilantha Sirisoma, Shailaja Kasibhatla, Candace Crogan-Grundy, Ben Tseng, John Drewe, Sui Xiong Cai ^{*}

The synthesis and SAR studies of the 4-, 5-, 6-, 7- and 8-positions of apoptosis inducing 1-benzoyl-3-cyanopyrrolo[1,2-*a*]quinolines are reported.

Selective inhibitors of tumor progression loci-2 (Tpl2) kinase with potent inhibition of TNF- α production in human whole blood pp 3485–3488

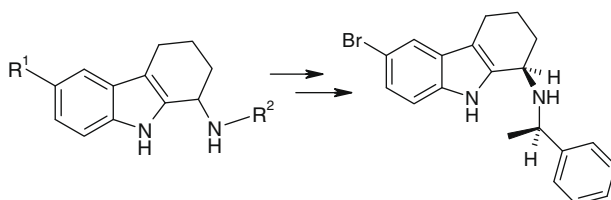
Junjun Wu ^{*}, Neal Green, Rajeev Hotchandani, Yonghan Hu, Jeffrey Condon, Adrian Huang, Neelu Kaila, Huan-Qiu Li, Satenig Guler, Wei Li, Steve Y. Tam, Qin Wang, Jeffrey Pelker, Suzana Marusic, Sang Hsu, J. Perry Hall, Jean-Baptiste Telliez, Junqing Cui, Lih-Ling Lin

Tpl2 (cot/MAP3K8) is an upstream kinase of MEK in the ERK pathway. It plays an important role in Tumor Necrosis Factor- α (TNF- α) production and signaling. We have discovered that 8-halo-4-(3-chloro-4-fluoro-phenylamino)-6-[(1*H*-[1,2,3]triazol-4-ylmethyl)-amino]-quinoline-3-carbonitriles (**4**) are potent inhibitors of this enzyme. In order to improve the inhibition of TNF- α production in LPS-stimulated human blood, a series of analogs with a variety of substitutions around the triazole moiety were studied. We found that a cyclic amine group appended to the triazole ring could considerably enhance potency, aqueous solubility, and cell membrane permeability. Optimization of these cyclic amine groups led to the identification of 8-chloro-4-(3-chloro-4-fluorophenylamino)-6-((1-(1-ethylpiperidin-4-yl)-1*H*-1,2,3-triazol-4-yl)methylamino)quinoline-3-carbonitrile (**34**). In a LPS-stimulated rat inflammation model, compound **34** showed good efficacy in inhibiting TNF- α production.



Substituted tetrahydrocarbazoles with potent activity against human papillomaviruses pp 3489–3492

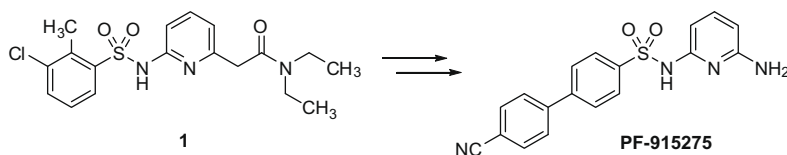
Kristjan S. Gudmundsson ^{*}, Paul R. Sebahar, Leah D'Aurora Richardson, John G. Catalano, Sharon D. Boggs, Andrew Spaltenstein, Phiroze B. Sethna, Kevin W. Brown, Robert Harvey, Karen R. Romines



Synthesis of a series of substituted 1-aminotetrahydrocarbazoles with potent activity against human papillomaviruses is described. Synthetic approaches allowing for variation of the substitution pattern are outlined and resulting changes in antiviral activity are highlighted.

N-(Pyridin-2-yl) arylsulfonamide inhibitors of 11 β -hydroxysteroid dehydrogenase type 1: Discovery of PF-915275 pp 3493–3497

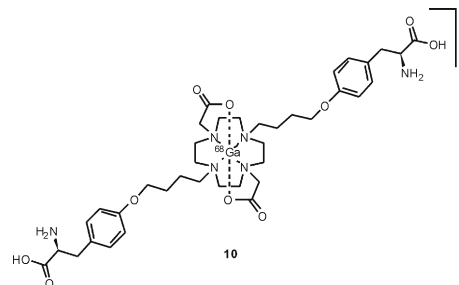
Michael Siu ^{*}, Theodore O. Johnson, Yong Wang, Sajiv K. Nair, Wendy D. Taylor, Stephan J. Cripps, Jean J. Matthews, Martin P. Edwards, Thomas A. Pauly, Jacques Ermolieff, Arturo Castro, Natilie A. Hosea, Amy LaPaglia, Andrea N. Fanjul, Jennifer E. Vogel



[⁶⁸Ga]Ga-DO₂A-(OBU-*L*-tyr)₂: Synthesis, ⁶⁸Ga-radiolabeling and in vitro studies of a novel ⁶⁸Ga-DO₂A-tyrosine conjugate as potential tumor tracer for PET pp 3498–3501

Carsten Burchardt, Patrick J. Riss ^{*}, Frederic Zoller, Simone Maschauer, Olaf Prante, Torsten Kuwert, Frank Roesch

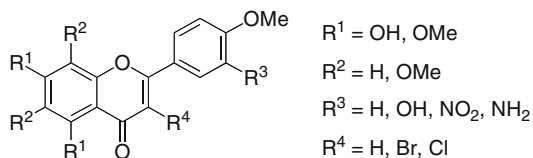
The novel ⁶⁸Ga-DO₂A-tyrosine derivative **10** shows specific uptake in F98-glioblastoma cells indicating high potential for imaging tumor metabolism by positron emission tomography (PET).



Semisynthesis and antiproliferative evaluation of a series of 3'-aminoflavones

pp 3502–3506

Jérôme Quintin, Didier Buisson, Sylviane Thoret, Thierry Cresteil, Guy Lewin *

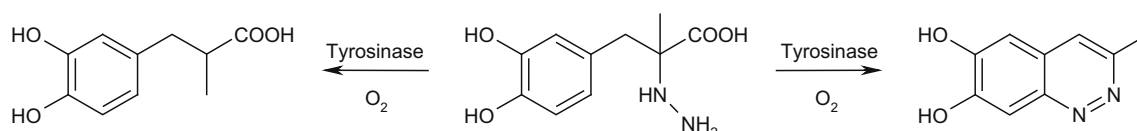


A series of 3'-aminoflavones 5,6,7,8-tetra or 5,7-dioxygenated on the A-ring was synthesized from tangeretin or naringin, two natural *Citrus* flavonoids, then evaluated for their antiproliferative and proapoptotic activities, and for the inhibition of tubulin assembly.

Oxidation of carbidopa by tyrosinase and its effect on murine melanoma

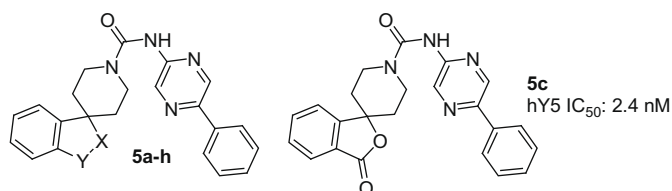
pp 3507–3510

Beata Gąsowska-Bajger, Bożena Frąckowiak-Wojtasek, Sabina Koj, Tomasz Cichoń, Ryszard Smolarczyk, Stanisław Szala, Hubert Wojtasek *

**Aryl urea derivatives of spiropiperidines as NPY Y5 receptor antagonists**

pp 3511–3516

Toshiyuki Takahashi, Yuji Haga, Toshihiro Sakamoto, Minoru Moriya, Osamu Okamoto, Katsumasa Nonoshita, Takunobu Shibata, Takuya Suga, Hirobumi Takahashi, Tomoko Hirohashi, Aya Sakuraba, Akira Gomori, Hisashi Iwaasa, Tomoyuki Ohe, Akane Ishihara, Yasuyuki Ishii, Akio Kanatani, Takehiro Fukami *

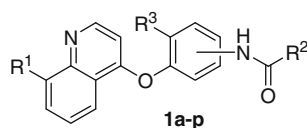


Aryl urea derivatives of a variety of spiropiperidines were tested for their NPY Y5 receptor binding affinities. Of the spiropiperidines so far examined, spiro[3-oxoisobenzofuran-1(3H),4'-piperidine] was a useful scaffold for producing orally active NPY Y5 receptor antagonists.

Aminoquinoline derivatives with antiproliferative activity against melanoma cell line

pp 3517–3520

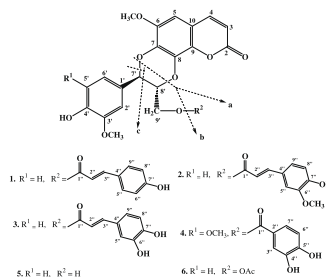
Bong Soo Nam, Hwan Kim, Chang-Hyun Oh, So Ha Lee, Seung Joo Cho, Tae Bo Sim, Jung-Mi Hah, Dong Jin Kim, Jung Hoon Choi, Kyung Ho Yoo *



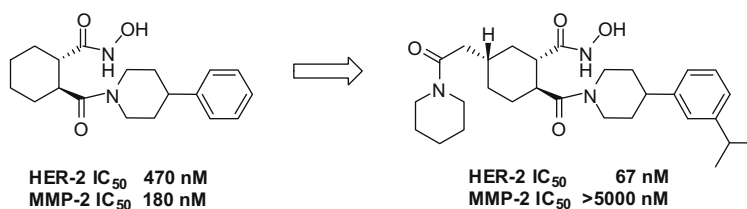
The synthesis of a novel series of aminoquinoline derivatives **1a-p** and their antiproliferative activities against A375 human melanoma cell line were described. Most compounds showed superior antiproliferative activities to Sorafenib as a reference compound. Among them, quinolinylloxymethylphenyl compounds **1k** and **1l** exhibited potent activities (IC₅₀ = 0.77 and 0.79 μM, respectively) and excellent selectivity against melanoma and fibroblast cell lines.

Repenins A–D, four new antioxidative coumarinolignoids from *Duranta repens* Linn.

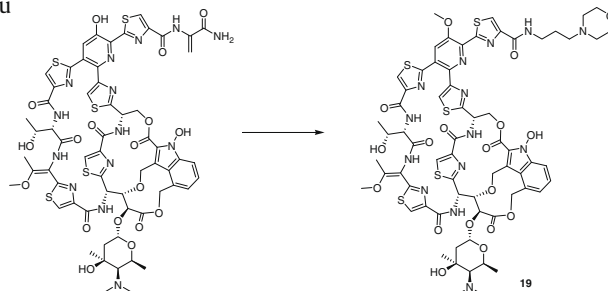
pp 3521–3524

Nisar Ahmad, Fozia Zeb, Ijaz Ahmad^{*}, Fanghai WangStructures and important mass fragmentation pattern of coumarinolignoids (**1–6**).**Compelling P1 substituent affect on metalloprotease binding profile enables the design of a novel cyclohexyl core scaffold with excellent MMP selectivity and HER-2 sheddase inhibition**

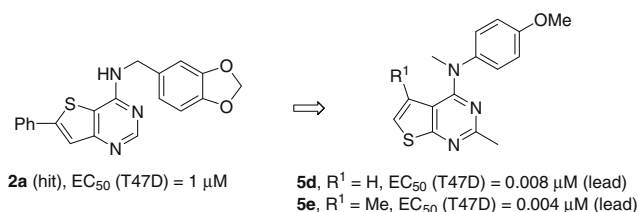
pp 3525–3530

David M. Burns^{*}, Yun-Long Li^{*}, Eric Shi, Chunhong He, Meizhong Xu, Jincong Zhuo, Colin Zhang, Ding-Quan Qian, Yanlong Li, Richard Wynn, Maryanne B. Covington, Kamna Katiyar, Cindy A. Marando, Jordan S. Fridman, Peggy Scherle, Steve Friedman, Brian Metcalf, Wenqing Yao**Nocathiacin analogs: Synthesis and antibacterial activity of novel water-soluble amides**

pp 3531–3535

Libo Xu^{*}, Amy K. Farthing, James F. Dropinski, Peter T. Meinke, Christine McCallum, Penny S. Leavitt, Emily J. Hickey, Lawrence Colwell, John Barrett, Kun LiuSynthesis and SAR of novel water-soluble amide analogs of nocathiacin **1** are reported. Compound **19** was selected for further evaluation.**Discovery of 4-anilino-*N*-methylthieno[3,2-*d*]pyrimidines and 4-anilino-*N*-methylthieno[2,3-*d*]pyrimidines as potent apoptosis inducers**

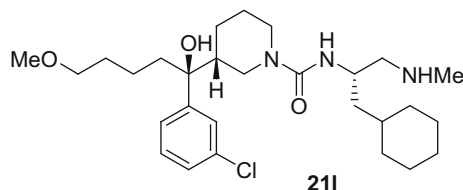
pp 3536–3540

William Kemnitzer, Nilantha Sirisoma, Chris May, Ben Tseng, John Drewe, Sui Xiong Cai^{*}The discovery and SAR studies of 4-anilino-*N*-methylthieno[3,2-*d*]pyrimidines and 4-anilino-*N*-methylthieno[2,3-*d*]pyrimidines as potent apoptosis inducers are reported.

Design and optimization of renin inhibitors: Orally bioavailable alkyl amines

pp 3541–3545

Colin M. Tice^{*}, Zhenrong Xu, Jing Yuan, Robert D. Simpson, Salvacion T. Cacatian, Patrick T. Flaherty, Wei Zhao, Joan Guo, Alexey Ishchenko, Suresh B. Singh, Zhongren Wu, Boyd B. Scott, Yuri Bukhtiyarov, Jennifer Berbaum, Jennifer Mason, Reshma Panemangalore, Maria Grazia Cappiello, Dominik Müller, Richard K. Harrison, Gerard M. McGeehan, Lawrence W. Dillard, John J. Baldwin, David A. Claremon

Human renin IC₅₀ = 0.47 nMPlasma renin IC₅₀ = 13 nM

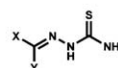
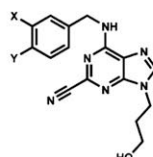
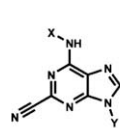
%F (dog) = 38

MW = 508

Antimalarial activity of thiosemicarbazones and purine derived nitriles

pp 3546–3549

Jeremy P. Mallari, Wendyam A. Guiguemde, R. Kiplin Guy^{*}



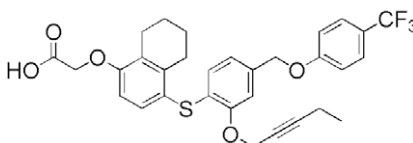
Inhibitor 2w

X = acetylamino, Y = H

EC₅₀ vs. 3D7, 0 mM pepstatin A = 15 ± 3 μMEC₅₀ vs. 3D7, 10 mM pepstatin A = 6 ± 3 μMEC₅₀ vs. K1, 0 mM pepstatin A = 15 ± 3 μMEC₅₀ vs. K1, 10 mM pepstatin A = 11 ± 5 μM**Identification of a PPARδ agonist with partial agonistic activity on PPARγ**

pp 3550–3554

Richard V. Connors^{*}, Zhulun Wang, Martin Harrison, Alex Zhang, Malgorzata Wanska, Steve Hiscock, Brian Fox, Michael Dore, Marc Labelle, Athena Sudom, Sheree Johnstone, Jinsong Liu, Nigel P. C. Walker, Anne Chai, Karen Siegler, Yang Li, Peter Coward^{*}

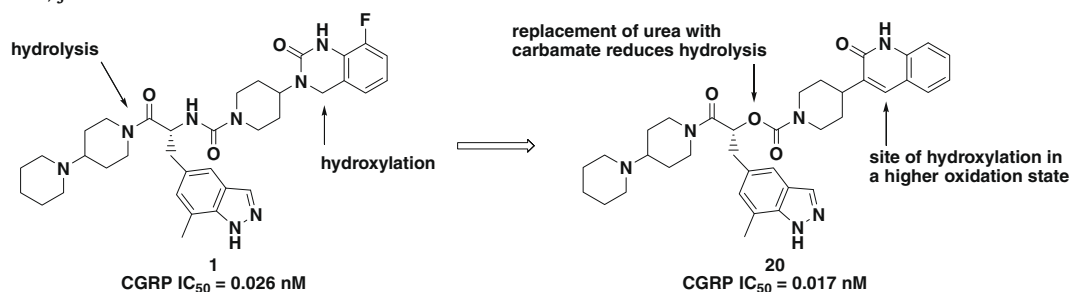


The discovery and optimization of a series of potent PPARδ full agonists with partial agonistic activity against PPARγ is described.

Carbamates as potent calcitonin gene-related peptide antagonists with improved solution stability

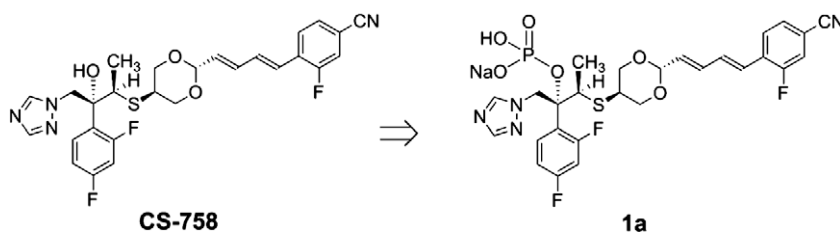
pp 3555–3558

Andrew P. Degnan^{*}, Charles M. Conway, Richard A. Dalterio, Robert Macci, Stephen E. Mercer, Richard Schartman, Cen Xu, Gene M. Dubowchik, John E. Macor



Synthesis, cleavage, and antifungal activity of a number of novel, water-soluble ester prodrugs of antifungal triazole CS-758 pp 3559–3563

Yoshiko Kagoshima, Makoto Mori, Eiko Suzuki, Takahiro Shibayama, Tamako Iida, Yasuki Kamai, Toshiyuki Konosu *

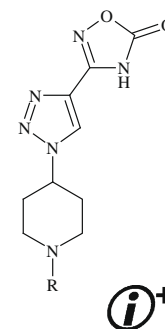


Synthesis and evaluation of some esters of CS-758, as injectable prodrugs, are described. The phosphoryl ester **1a** was converted to CS-758 in vivo.

Synthesis of novel 3-(1-(1-substituted piperidin-4-yl)-1H-1,2,3-triazol-4-yl)-1,2,4-oxadiazol-5(4H)-one as antifungal agents pp 3564–3567

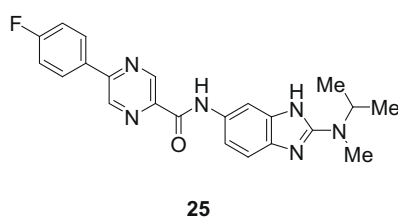
Jaiprakash N. Sangshetti, Rahul R. Nagawade, Devanand B. Shinde *

A novel series of 1,2,3 triazole compounds possessing 1,2,4 oxadiazole ring were efficiently synthesized. Synthesized compounds were evaluated for their in vitro antifungal activities using standard cup plate method. SAR for the series has been developed by comparing their MIC values with miconazole and fluconazole. Some of the synthesized compounds like **11a** and **11h** were found to be equal/more active than miconazole where as comparable to that of fluconazole.



Identification of 2-aminobenzimidazoles as potent melanin-concentrating hormone 1-receptor (MCH1R) antagonists pp 3568–3572

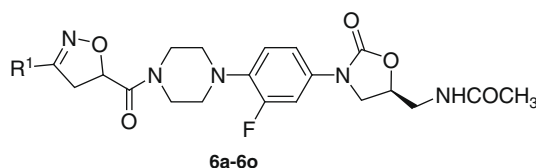
Minoru Moriya *, Hiroyuki Kishino, Shunji Sakuraba, Toshihiro Sakamoto, Takuya Suga, Hidekazu Takahashi, Takao Suzuki, Masahiko Ito, Junko Ito, Ryuichi Moriya, Norihiro Takenaga, Hisashi Iwaasa, Akane Ishihara, Akio Kanatani, Takehiro Fukami



We report the identification of potent and brain-penetrable 2-aminobenzimidazole based MCH1R antagonist **25**.

Synthesis and antibacterial evaluation of isoxazolinyl oxazolidinones: Search for potent antibacterial pp 3573–3576

Vandana Varshney, Nripendra N. Mishra, Praveen K. Shukla, Devi P. Sahu *



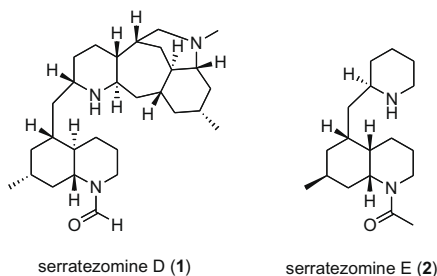
The synthesis and antibacterial activity of novel oxazolidinone analogues (**6a–o**) has been reported with **6i** being the most potent compound of the series showing MIC at 0.0866–0.7039 μ M.



Serratezomines D and E, new *Lycopodium* alkaloids from *Lycopodium serratum* var. *serratum*

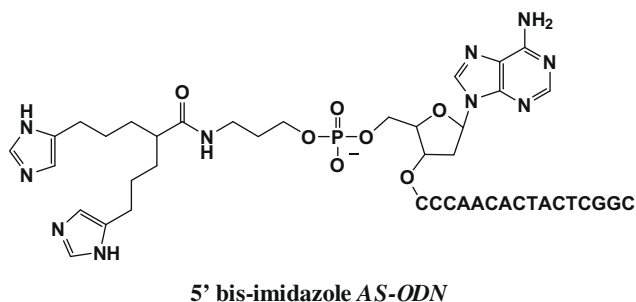
pp 3577–3580

Takaaki Kubota, Hiroko Yahata, Sunao Yamamoto, Shigeki Hayashi, Toshiro Shibata, Jun'ichi Kobayashi *

**Antiviral effect of ribonuclease conjugated oligodeoxynucleotides targeting the IRES RNA of the hepatitis C virus**

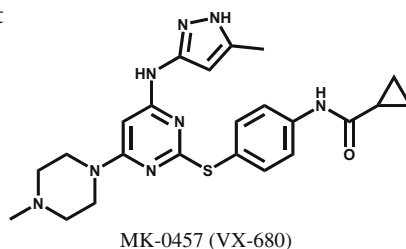
pp 3581–3585

Carly Gamble, Maud Trotard, Jacques Le Seyec, Valérie Abreu-Guerniou, Nicolas Gernigon, Fabienne Berrée, Bertrand Carboni, Brice Felden, Reynald Gillet *

**The discovery of the potent aurora inhibitor MK-0457 (VX-680)**

pp 3586–3592

David Bebbington, Hayley Binch, Jean-Damien Charrier, Simon Everitt, Damien Fraysse, Julian Golec, David Kay, Ronald Knegtel, Chau Mak, Francesca Mazzei, Andrew Miller, Michael Mortimore *, Michael O'Donnell, Sanjay Patel, Françoise Pierard, Joanne Pinder, John Pollard, Sharn Ramaya, Daniel Robinson, Alistair Rutherford, John Studley, James Westcott

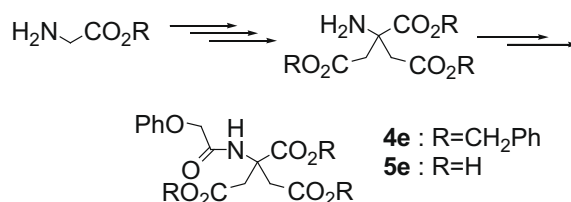


The identification of a novel series of Aurora kinase inhibitors and exploitation of their SAR, which led to the discovery of MK-0457 (VX-680), is described.

Discovery of novel lipophilic inhibitors of OXA-10 enzyme (class D β -lactamase) by screening amino analogs and homologs of citrate and isocitrate

pp 3593–3597

Joséphine Beck, Lionel Vercheval, Carine Bebrone, Adriana Herteg-Fernea, Patricia Lassaux, Jacqueline Marchand-Brynaert *



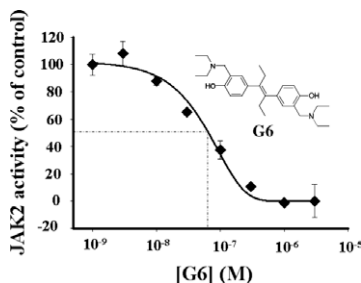
The title compounds have been synthesized by alkylation of glycinate imines with bromoacetates, acrylate or fumarate. Their biochemical activity was evaluated against representative β -lactamases of all classes. Out of these molecules, tested as free acids or esters, **5e** and **4e** emerged as modest inhibitor of BS3 and good inhibitor of OXA-10 enzymes respectively. This discovery is consistent with the active site hydrophobic character of class D comparatively to class A β -lactamases.



Identification of a novel inhibitor of JAK2 tyrosine kinase by structure-based virtual screening

pp 3598–3601

Róbert Kiss, Tímea Polgár, Annet Kirabo, Jacqueline Sayyah, Nicholas C. Figueroa, Alan F. List, Lubomir Sokol, Kenneth S. Zuckerman, Meghanath Gali, Kirpal S. Bisht, Peter P. Sayeski, György M. Keserű *



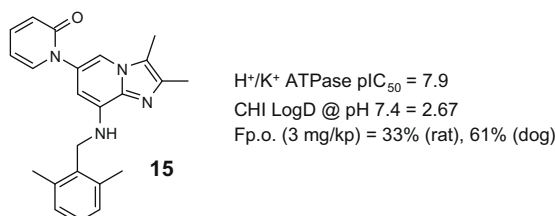
A specific and potent JAK2 inhibitor G6 was identified by structure-based virtual screening.



Orally active C-6 heteroaryl- and heterocyclyl-substituted imidazo[1,2-a]pyridine acid pump antagonists (APAs)

pp 3602–3606

Nick Bailey, Mark J. Bamford, Delphine Brissy, Joanna Brookfield, Emmanuel Demont *, Richard Elliott, Neil Garton, Irene Farre-Gutierrez, Thomas Hayhow, Gail Hutley, Antoinette Naylor, Terry A. Panchal, Hui-Xian Seow, David Spalding, Andrew K. Takle

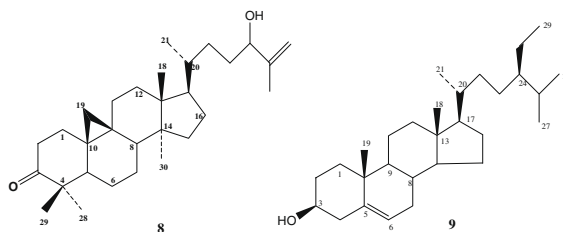


A series of novel imidazo[1,2-a]pyridine acid pump antagonists is described. Heteroaryl and heterocyclic substituents at the C-6 position were used for the optimization of developability characteristics through modulation of global physico-chemical properties.

The regulation of inflammatory cytokine secretion in macrophage cell line by the chemical constituents of *Rhus sylvestris*

pp 3607–3610

Yan Ding, Huu Tung Nguyen, Sung In Kim, Ha Won Kim, Young Ho Kim *

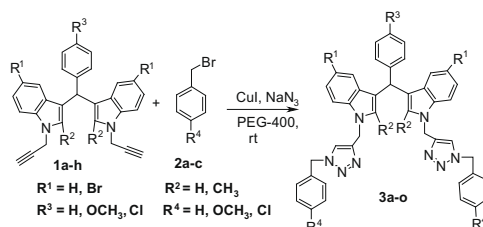


Bioassay-guided fractionation of the CH₂Cl₂-soluble extract led to the isolation of 10 compounds. Compounds **8** and **9** reduced the LPS-induced secretion of IL-6 and TNF-α in a RAW264.7 cell line.

Regioselective synthesis and biological evaluation of bis(indolyl)methane derivatized 1,4-disubstituted 1,2,3-bistriazoles as anti-infective agents

pp 3611–3614

M. Damodiran, D. Muralidharan, Paramasivan T. Perumal *



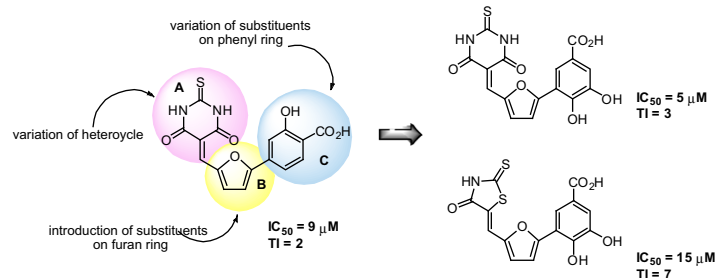
The regioselective synthesis of 1,4-disubstituted 1,2,3-bistriazoles from a variety of *N*-propargyl bis(indolyl)methanes with sodium azide using CuI as the catalyst in polyethyleneglycol-400 is reported. This process is of considerable synthetic advantages in terms of high atom economy, low environmental impact, mild reaction condition and good yields. The synthesized compounds have also been screened for their biological activity.



Exploration of novel thiobarbituric acid-, rhodanine- and thiohydantoin-based HIV-1 integrase inhibitors

pp 3615–3618

Suvi Rajamaki, Anna Innitzer, Chiara Falciani, Cristina Tintori, Frauke Christ, Myriam Witvrouw, Zeger Debyser, Silvio Massa, Maurizio Botta *

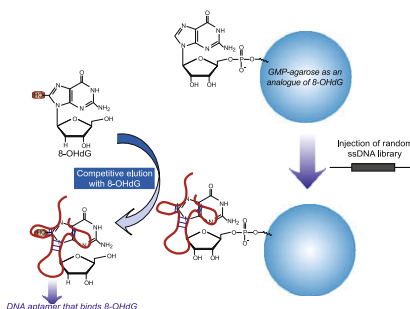


A novel compound inhibiting HIV-1 integrase has been identified by means of virtual screening techniques. A small family of structurally related molecules has been synthesized and biologically evaluated with some of the compounds possessing micromolar activity both in enzymatic and cellular assays.

Selection of a DNA aptamer that binds 8-OHdG using GMP-agarose

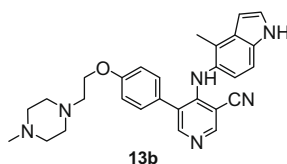
pp 3619–3622

Yusuke Miyachi *, Nobuaki Shimizu, Chiaki Ogino *, Hideki Fukuda, Akihiko Kondo

**Optimization of 5-phenyl-3-pyridinecarbonitriles as PKC θ inhibitors**

pp 3623–3626

Diane H. Boschelli *, Daniel Wang, Amar S. Prashad, Joan Subrath, Biqi Wu, Chuan Niu, Julie Lee, Xiaoke Yang, Agnes Brennan, Divya Chaudhary

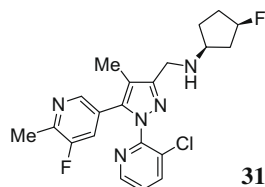


Analog **13b** with a 4-methylindol-5-ylamino group at C-4 and a 4-(2-(4-methylpiperazin-1-yl)ethoxy)phenyl group at C-5 had an IC_{50} value of 7.4 nM for the inhibition of PKC θ .

Discovery of novel arylpyrazole series as potent and selective opioid receptor-like 1 (ORL1) antagonists

pp 3627–3631

Kensuke Kobayashi, Minaho Uchiyama, Hirokatsu Ito, Hirobumi Takahashi, Takashi Yoshizumi, Hiroki Sakoh, Yasushi Nagatomi, Masanori Asai, Hiroshi Miyazoe, Tomohiro Tsujita, Mioko Hirayama, Satoshi Ozaki, Takeshi Tani, Yasuyuki Ishii, Hisashi Ohta, Osamu Okamoto *

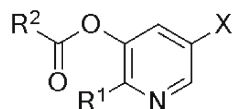


The synthesis and SAR of new ORL1 antagonists is described. Compound **31** displayed high intrinsic potency and selectivity against μ - and κ -opioid receptors, and hERG K⁺ channel.

Structure–activity relationships of heteroaromatic esters as human rhinovirus 3C protease inhibitors

pp 3632–3636

Isak Im, Eui Seung Lee, Soo Jeong Choi, Ju-Yeon Lee, Yong-Chul Kim *

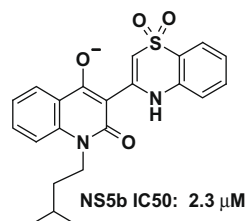
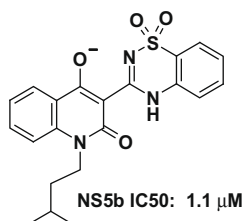


The non-peptidic inhibitors against HRV 3C protease, a series of novel heteroaromatic esters were synthesized and evaluated their activity.

Non-nucleoside inhibitors of HCV NS5B polymerase. Part 1: Synthetic and computational exploration of the binding modes of benzothiadiazine and 1,4-benzothiazine HCV NS5b polymerase inhibitors

pp 3637–3641

Robert T. Hendricks *, Jay B. Fell, James F. Blake, John P. Fischer, John E. Robinson, Stacey R. Spencer, Peter J. Stengel, April L. Bernacki, Vincent J. P. Leveque, Sophie Le Pogam, Sonal Rajyaguru, Isabel Najera, John A. Josey, Jason R. Harris, Steven Swallow

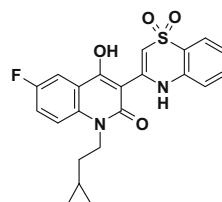


The importance of internal hydrogen bonding in a series of benzothiadiazine and 1,4-benzothiazine NS5b inhibitors has been explored. Computational analysis suggests HCV NS5b polymerase activity is best explained using the anionic forms.

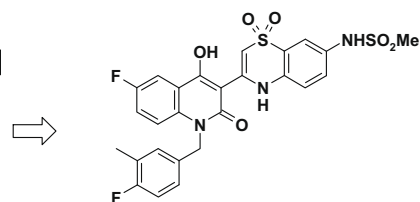
Non-nucleoside inhibitors of HCV polymerase NS5B. Part 2: Synthesis and structure–activity relationships of benzothiazine-substituted quinolinediones

pp 3642–3646

Javier de Vicente *, Robert T. Hendricks, David B. Smith, Jay B. Fell, John Fischer, Stacey R. Spencer, Peter J. Stengel, Peter Mohr, John E. Robinson, James F. Blake, Ramona K. Hilgenkamp, Calvin Yee, George Adjabeng, Todd R. Elworthy, Jahari Tracy, Elbert Chin, Jim Li, Beihan Wang, Joe T. Bamberg, Rebecca Stephenson, Connie Oshiro, Seth F. Harris, Manjiri Ghate, Vincent Leveque, Isabel Najera, Sophie Le Pogam, Sonal Rajyaguru, Gloria Ao-leong, Ludmila Alexandrova, Susan Larrabee, Michael Brandl, Andrew Briggs, Sunil Sukhtankar, Robert Farrell, Brian Xu



Replicon (EC₅₀ μM): 1.2

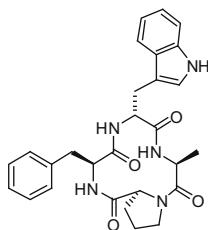


0.023

Nascent structure–activity relationship study of a diastereomeric series of kappa opioid receptor antagonists derived from CJ-15,208

pp 3647–3650

Roland E. Dolle *, Mathieu Michaut, Blanca Martinez-Teipel, Pamela R. Seida, Christopher W. Ajello, Alison L. Muller, Robert N. DeHaven, Patrick J. Carroll

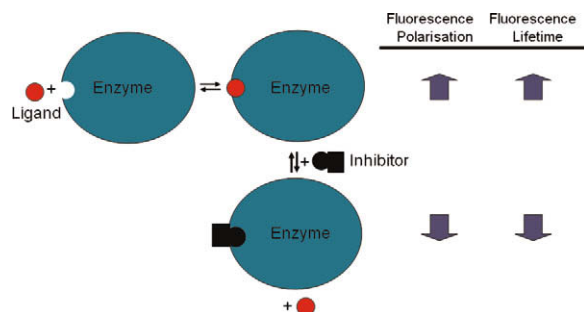


K_i = 5 nM (κ), 22 nM (μ),
>10,000 nM (δ)

Non-isotopic dual parameter competition assay suitable for high-throughput screening of histone deacetylases

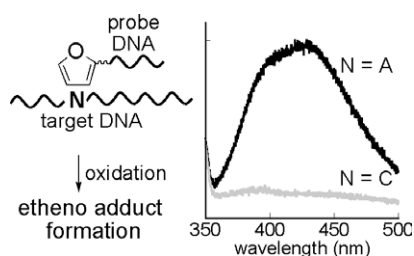
pp 3651–3656

Daniel Riester, Christian Hildmann, Patricia Haus, Antonia Galetovic, Andreas Schober, Andreas Schwienhorst, Franz-Josef Meyer-Almes *

**Sequence selective formation of 1,*N*⁶-ethenoadenine in DNA by furan-conjugated probe**

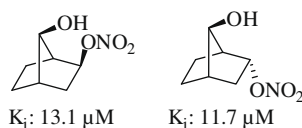
pp 3657–3660

Akio Kobori *, Jumpei Morita, Masato Ikeda, Asako Yamayoshi, Akira Murakami

We developed a 1,*N*⁶-ethenoadenosine-forming reaction at a target adenine in DNA duplex and applied it to a mutation diagnosis.**In vitro inhibition of human erythrocyte glutathione reductase by some new organic nitrates**

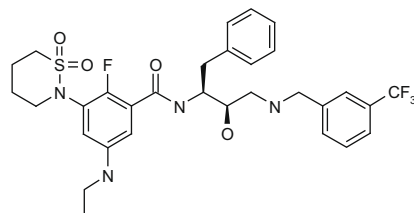
pp 3661–3663

Murat Şentürk *, Oktay Talaz, Deniz Ekinci, Hüseyin Çavdar *, Ömer İrfan Küfrevioğlu

**Second generation of BACE-1 inhibitors. Part 1: The need for improved pharmacokinetics**

pp 3664–3668

Nicolas Charrier, Brian Clarke, Leanne Cutler, Emmanuel Demont *, Colin Dingwall, Rachel Dunsdon, Julie Hawkins, Colin Howes, Julia Hubbard, Ishrut Hussain, Graham Maile, Rosalie Matico, Julie Mosley, Alan Naylor, Alistair O'Brien, Sally Redshaw, Paul Rowland, Virginie Soleil, Kathrine J. Smith, Sharon Sweitzer, Pam Theobald, David Vesey, Daryl S. Walter, Gareth Wayne



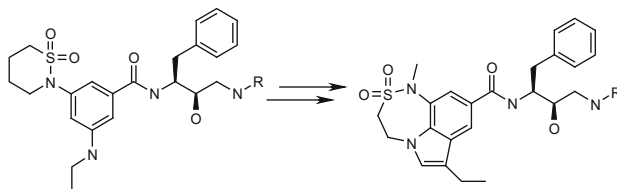
GSK188909
 BACE-1 IC_{50} = 2 nM
 $A\beta_{40}$ (WT, Swe) = 5, 30 nM
 Rat $F_{p.o.}$ (10 mg/kg) = 7%

This Letter demonstrates that our first generation of hydroxyethylamine BACE-1 inhibitors was unlikely to deliver a molecule suitable for progression in clinical trials; hence the necessity to discover a second generation of inhibitors with improved pharmacokinetics.

Second generation of BACE-1 inhibitors part 2: Optimisation of the non-prime side substituent

pp 3669–3673

Nicolas Charrier, Brian Clarke, Emmanuel Demont ^{*}, Colin Dingwall, Rachel Dunsdon, Julie Hawkins, Julia Hubbard, Ishrut Hussain, Graham Maile, Rosalie Matico, Julie Mosley, Alan Naylor, Alistair O'Brien, Sally Redshaw, Paul Rowland, Virginie Soleil, Kathrine J. Smith, Sharon Sweitzer, Pam Theobald, David Vesey, Daryl S. Walter, Gareth Wayne

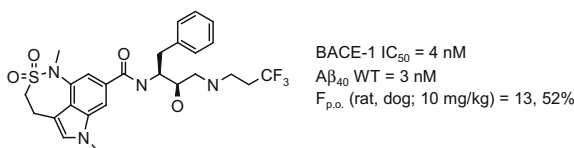


This article discloses the strategy that led to the discovery of a second series of hydroxyethylamine BACE-1 inhibitors with non-prime side substituents of higher binding efficiency.

Second generation of BACE-1 inhibitors part 3: Towards non hydroxyethylamine transition state mimetics

pp 3674–3678

Nicolas Charrier, Brian Clarke, Leanne Cutler, Emmanuel Demont ^{*}, Colin Dingwall, Rachel Dunsdon, Julie Hawkins, Colin Howes, Julia Hubbard, Ishrut Hussain, Graham Maile, Rosalie Matico, Julie Mosley, Alan Naylor, Alistair O'Brien, Sally Redshaw, Paul Rowland, Virginie Soleil, Kathrine J. Smith, Sharon Sweitzer, Pam Theobald, David Vesey, Daryl S. Walter, Gareth Wayne

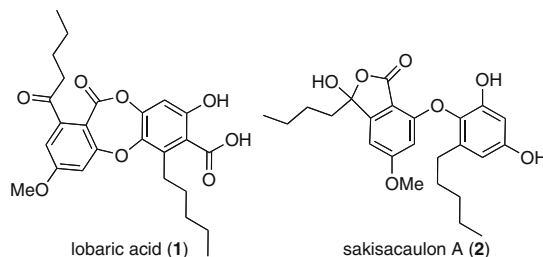


This article discloses the strategy that led to stable hydroxyethylamine BACE-1 inhibitors with nanomolar cell potency and good oral bioavailability and give insights into the design of compounds with the potential of increased brain penetration.

Antimitotic activity of lobaric acid and a new benzofuran, sakisacaulon A from *Stereocaulon sasakii*

pp 3679–3681

Hiroshi Morita ^{*}, Tomoe Tsuchiya, Koji Kishibe, Sayaka Noya, Motoo Shiro, Yusuke Hirasawa

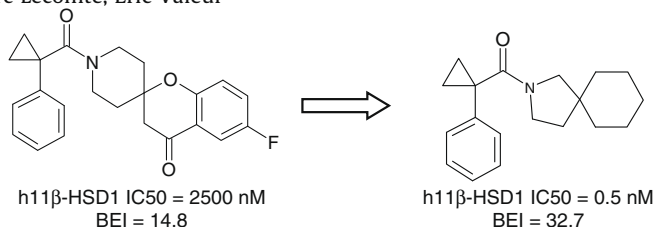


Lobaric acid (1) has been isolated from lichen, *Stereocaulon sasakii* together with a new benzofuran, sakisacaulon A (2). Lobaric acid (1) inhibited the polymerization of tubulin. Structure–activity relationship of lobaric acid and its derivatives on inhibitory activity of tubulin polymerization was discussed.

Discovery and structure-guided drug design of inhibitors of 11β-hydroxysteroid-dehydrogenase type I based on a spiro-carboxamide scaffold

pp 3682–3685

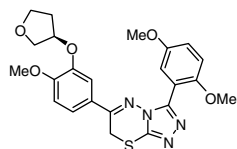
Franck Lepifre, Serge Christmann-Franck ^{*}, Didier Roche, Caroline Leriche, Denis Carniato, Christine Charon, Sophie Bozec, Liliane Doare, Fabien Schmidlin, Marc Lecomte, Eric Valeur



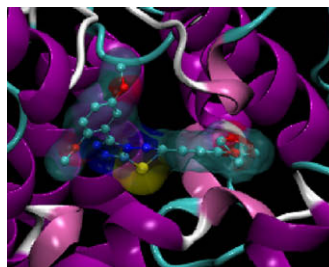
Structure-based drug design was used to optimise the initial hit yielding a sub-nanomolar IC₅₀ inhibitor (0.5 nM) on human 11β-HSD1 with a high binding efficiency index (BEI of 32.7) which was selective against human 11β-HSD2 (selectivity ratio > 200000).

Exploration and optimization of substituted triazolothiadiazines and triazolopyridazines as PDE4 inhibitors**pp 3686–3692**

Amanda P. Skoumbourdis, Christopher A. LeClair, Eduard Stefan, Adrian G. Turjanski, William Maguire, Steven A. Titus, Ruili Huang, Douglas S. Auld, James Inglese, Christopher P. Austin, Stephen W. Michnick, Menghang Xia, Craig J. Thomas *



PDE isoform	IC ₅₀ (nM)
PDE4A1A	0.26
PDE4B	2.3
PDE4B	1.6
PDE4D	1.9

**OTHER CONTENTS****Corrigenda****pp 3693–3694****Erratum****p 3695****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.]

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