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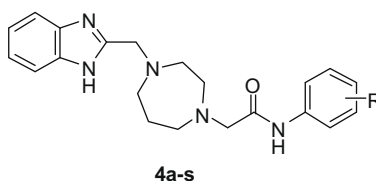
Contents

ARTICLES

Synthesis and biological evaluation of 1,4-diazepane derivatives as T-type calcium channel blockers

pp 2705–2708

Su Jin Gu, Jae Kyun Lee, Ae Nim Pae, Hye Jin Chung, Hyewon Rhim, So Yeob Han, Sun-Joon Min*, Yong Seo Cho*

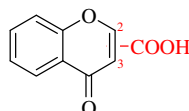


We have synthesized and biologically evaluated 1,4-diazepane derivatives as T-type calcium channel blockers. In this study, we discovered compound **4s**, a potential T-type calcium channel blocker with good selectivity over hERG and N-type calcium channels. In addition, it exhibited favorable pharmacokinetic characteristics for further investigation of T-type calcium channel related diseases.

Chromone-2- and -3-carboxylic acids inhibit differently monoamine oxidases A and B

pp 2709–2712

Stefano Alcaro*, Alexandra Gaspar, Francesco Ortuso, Nuno Milhazes, Francisco Oraldo, Eugenio Uriarte, Matilde Yáñez, Fernanda Borges*



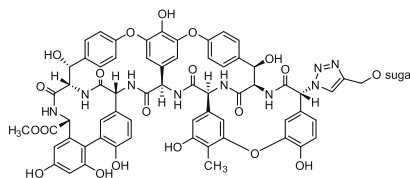
Docking experiments were carried out to explain the quite different inhibition activities of two carboxylic chromone isomers against A and B isoforms of monoamine oxidases.



Click reaction synthesis of carbohydrate derivatives from ristocetin aglycon with antibacterial and antiviral activity

pp 2713–2717

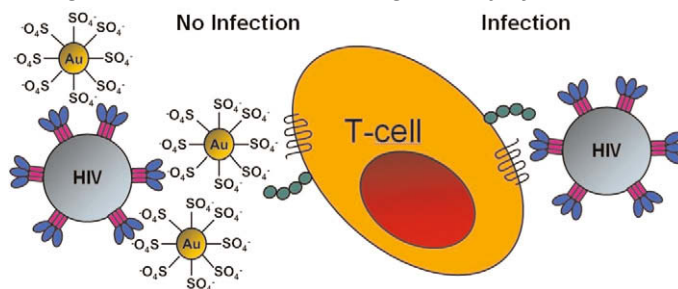
Gábor Pintér, Ilona Bereczki, Gyula Batta, Réka Ötvös, Ferenc Sztaricskai, Erzsébet Röth, Eszter Ostorházi, Ferenc Rozgonyi, Lieve Naesens, Mariann Szarvas, Zoltán Boda, Pál Herczegh*



Gold nanoparticles capped with sulfate-ended ligands as anti-HIV agents

pp 2718–2721

Paolo Di Gianvincenzo, Marco Marradi, Olga María Martínez-Ávila, Luis Miguel Bedoya, José Alcamí, Soledad Penadés*

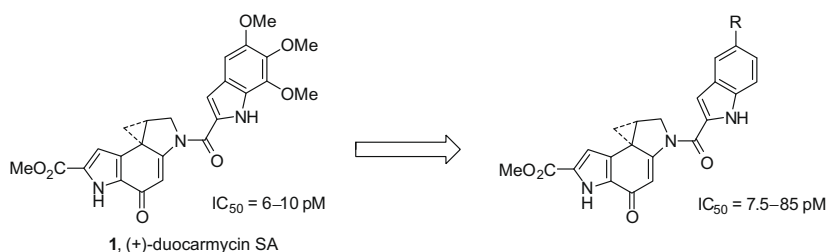


A golden opportunity against HIV. Gold nanoparticles coated with multiple copies of an amphiphilic sulphate-ended ligand inhibit in vitro the HIV infection of T-cells at nanomolar concentrations.

**Synthesis and evaluation of a series of C5'-substituted duocarmycin SA analogs**

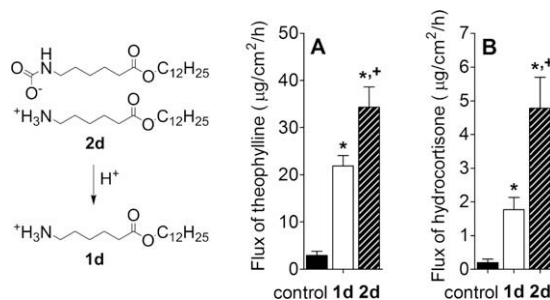
pp 2722–2725

William M. Robertson, David B. Kastinsky, Inkyu Hwang, Dale L. Boger*

**Transkarbams as transdermal permeation enhancers: Effects of ester position and ammonium carbamate formation**

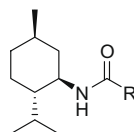
pp 2726–2728

Michal Novotný, Alexandr Hrabálek, Barbora Janušová, Jakub Novotný, Kateřina Vávrová*

**(–)-Menthylamine derivatives as potent and selective antagonists of transient receptor potential melastatin type-8 (TRPM8) channels**

pp 2729–2732

Giorgio Ortar*, Luciano De Petrocellis*, Ludovica Morera, Aniello Schiano Moriello, Pierangelo Orlando, Enrico Morera, Marianna Nalli, Vincenzo Di Marzo

R = Aryl, Alkyl, $(\text{CH}_2)_n\text{Ph}$, OAryl, NHAkyl

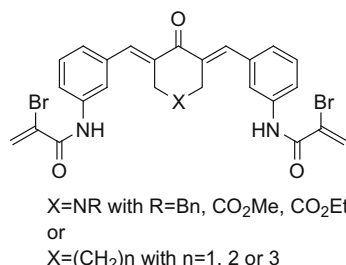
The evaluation of a series of (–)-menthylamine derivatives led to the identification of some potent TRPM8 antagonists with IC_{50} values versus icilin and (–)-menthol between 20 nM and 0.7 μM and between 4- and ~150-fold selective versus TRPV1 and TRPA1 activation.



Symmetrical α -bromoacryloylamido diaryldienone derivatives as a novel series of antiproliferative agents. Design, synthesis and biological evaluation

pp 2733–2739

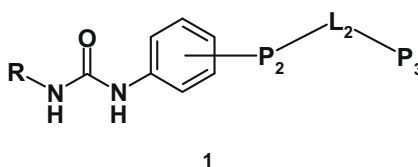
Romeo Romagnoli*, Pier Giovanni Baraldi*, Olga Cruz-Lopez, Carlota Lopez Cara, Maria Dora Carrion, Jan Balzarini, Ernest Hamel, Giuseppe Basso, Roberta Bortolozzi, Giampietro Viola



Exploration of secondary and tertiary pharmacophores in unsymmetrical *N,N'*-diaryl urea inhibitors of soluble epoxide hydrolase

pp 2740–2744

Sampath-Kumar Anandan*, Richard D. Gless

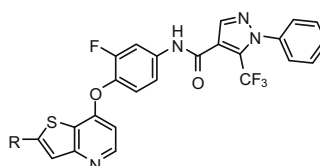


The impact of various secondary and tertiary pharmacophores on in vitro potency of soluble epoxide hydrolase (sEH) inhibitors based on the unsymmetrical urea scaffold **1** is discussed.

Identification of a novel series of potent RON receptor tyrosine kinase inhibitors

pp 2745–2749

Stéphane Raeppe*, Frédéric Gaudette, Michael Mannion, Stephen Claridge, Oscar Saavedra, Ljubomir Isakovic, Robert Déziel, Normand Beaulieu, Carole Beaulieu, Isabelle Dupont, Hannah Nguyen, James Wang, A. Robert Macleod, Christiane Maroun, Jeffrey M. Besterman, Arkadii Vaisburg

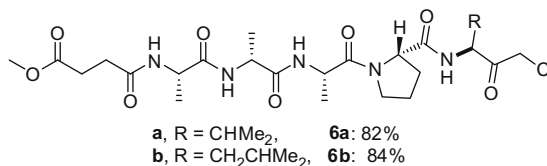


A novel series of *N*-(3-fluoro-4-(2-substituted-thieno[3,2-*b*]pyridin-7-yloxy)phenyl)-1-phenyl-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamides targeting RON receptor tyrosine kinase was designed and synthesized. SAR study of the series allowed us to identify compounds possessing either inhibitory activity of RON kinase enzyme in the low nanomolar range with low residual activity against the closely related c-Met or potent dual inhibitory activity against RON and c-Met, – with no significant activity against VEGFR2 in both cases.

Synthesis and biological evaluation of modified pentapeptides as potent proteinase K inhibitors

pp 2750–2754

Anilkumar R. Kore*, Muthian Shanmugasundaram, Irudaya Charles, Quoc Hoang



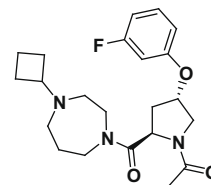
The synthesis and biological evaluation of modified pentapeptides **6a** and **6b** are described as potent proteinase K inhibitors.

Novel substituted pyrrolidines are high affinity histamine H₃ receptor antagonists

pp 2755–2760

Emily M. Stocking*, Leah Aluisio, John R. Attack, Pascal Bonaventure, Nicholas I. Carruthers, Christine Dugovic, Anita Everson, Ian Fraser, Xiaohui Jiang, Perry Leung, Brian Lord, Kiev S. Ly, Kirsten L. Morton, Diane Nepomuceno, Chandravan R. Shah, Jonathan Shelton, Akinola Soyode-Johnson, Michael A. Letavic*

Substituted pyrrolidines are potent histamine H₃ antagonists with favorable drug-like properties.

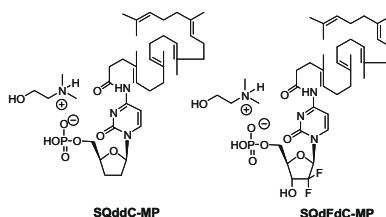


12k
hH₃ K_i=1.6 nM
hH₃ pA₂=9.50

Squalenoyl nucleoside monophosphate nanoassemblies: New prodrug strategy for the delivery of nucleotide analogues

pp 2761–2764

Joachim Caron, L. Harivardhan Reddy, Sinda Lepêtre-Mouelhi, Séverine Wack, Pascal Clayette, Christine Rogez-Kreuz, Rahima Yousfi, Patrick Couvreur, Didier Desmaële*



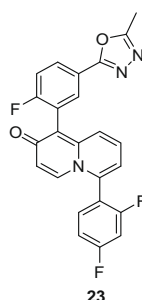
Nanoassemblies of squalenoyl prodrug of ddC-MP and dFdC-MP exhibit promising biological activities.



Synthesis and biological activity of 2H-quinolizin-2-one based p38α MAP kinase inhibitors

pp 2765–2769

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

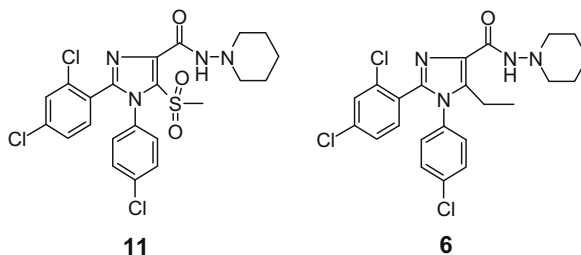


23

Probing the cannabinoid CB₁/CB₂ receptor subtype selectivity limits of 1,2-diarylimidazole-4-carboxamides by fine-tuning their 5-substitution pattern

pp 2770–2775

Jos H. M. Lange*, Martina A. W. van der Neut, Alice J. M. Borst, Mahmut Yildirim, Herman H. van Stuijvenberg, Bernard J. van Vliet, Chris G. Kruse



11

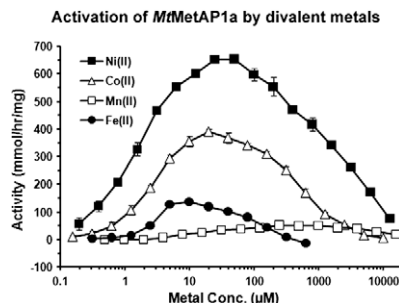
6

Compound 11 showed >~840-fold CB₁/CB₂ subtype selectivity whereas 6 was only 31-fold selective.

Expression and characterization of *Mycobacterium tuberculosis* methionine aminopeptidase type 1a

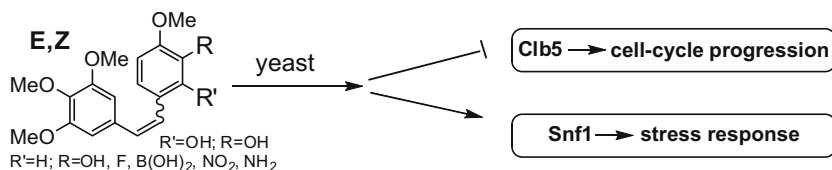
pp 2776–2779

Jing-Ping Lu, Qi-Zhuang Ye*

**Synthesis and biological evaluation of combretastatin analogs as cell cycle inhibitors of the G1 to S transition in *Saccharomyces cerevisiae***

pp 2780–2784

Paola Coccetti*, Giuseppe Montano, Alessandro Lombardo, Farida Tripodi, Fulvia Orsini, Roberto Pagliarin



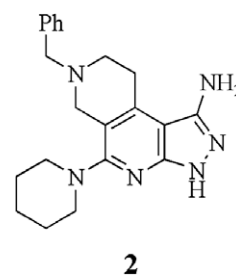
To enlighten new anti-tumor activities, a series of combretastatin A-4 derivatives and combretastatin A-1 were prepared and evaluated in arresting yeast growth. The G1 arrest induced by some of these compounds was characterized by the down-regulation of G1 cyclin Clb5 and activation of the stress activated kinase Snf1.

**Synthesis of 7-benzyl-5-(piperidin-1-yl)-6,7,8,9-tetrahydro-3H-pyrazolo[3,4-c][2,7]naphthyridin-1-ylamine and its analogs as bombesin receptor subtype-3 agonists**

pp 2785–2789

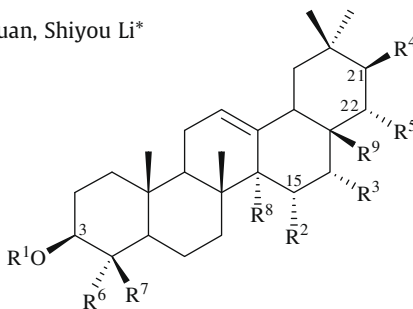
Cheng Guo*, Peter R. Guzzo, Mark Hadden, Bruce J. Sargent, Larry Yet, Yanqing Kan, Oksana Palyha, Theresa M. Kelly, Xiaoming Guan, Kim Rosko, Karen Gagen, Joseph M. Metzger, Jasminka Dragovic, Kathryn Lyons, Linus S. Lin, Ravi P. Nargund

The original structure assignment of **2**, a high-throughput screening hit obtained from an external vendor, was revised based on multiple NMR studies. A novel synthetic route was developed for **2** and multi-gram quantities were prepared for pharmacokinetic and efficacy studies. Its activity on the BRS-3 receptor was confirmed, and additional SAR was explored.

**Cytotoxicity and inhibition of DNA topoisomerase I of polyhydroxylated triterpenoids and triterpenoid glycosides**

pp 2790–2796

Ping Wang, Stacy Ownby, Zhizhen Zhang, Wei Yuan, Shiyu Li*



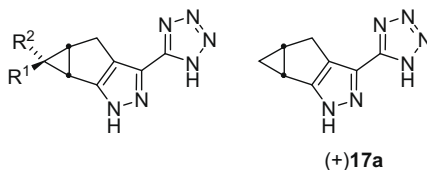
Some cytotoxic polyhydroxylated oleananes inhibited DNA topoisomerase I (TOP1) catalytic activity by interacting directly with the free enzyme and preventing the formation of the DNA–TOP1 complex.



Potent tricyclic pyrazole tetrazole agonists of the nicotinic acid receptor (GPR109a)

pp 2797–2800

P. Douglas Boatman*, Thomas O. Schrader, Michelle Kasem, Benjamin R. Johnson, Philip J. Skinner, Jae-Kyu Jung, Jerry Xu, Martin C. Cherrier, Peter J. Webb, Graeme Semple, Carleton R. Sage, Jens Knudsen, Ruoping Chen, Andrew K. Taggart, Ester Carballo-Jane, Jeremy G. Richman

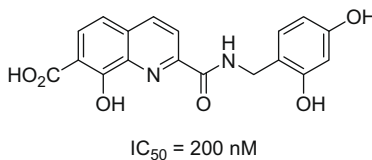


Tricyclic pyrazole tetrazoles which are potent partial agonists of the high affinity niacin receptor, GPR109a, have been discovered and optimized. One of these compounds has proven to be effective at lowering free fatty acids in vitro and in vivo.

Identification and structure–activity relationship of 8-hydroxy-quinoline-7-carboxylic acid derivatives as inhibitors of Pim-1 kinase

pp 2801–2805

Faten Sliman, Méline Blairvacq, Emilie Durieu, Laurent Meijer, Jordi Rodrigo, Didier Desmaële*

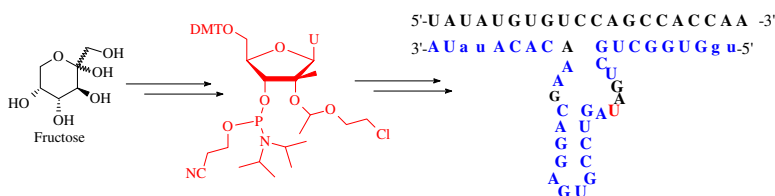


2-Substituted 8-hydroxy-quinoline-7-carboxylic acid compounds have been identified as small molecule inhibitors of the Pim-1 kinase and molecular docking studies have shown their potential binding mode.

**2-C-Methyluridine modified hammerhead ribozyme against the estrogen receptor**

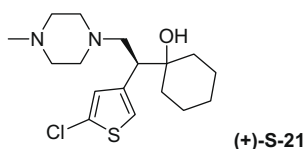
pp 2806–2808

Rodrigo Pontiggia, Osvaldo Pontiggia, Marina Simian, Javier M. Montserrat, Joachim W. Engels, Adolfo M. Iribarren*

**Heterocyclic cycloalkanol ethylamines as norepinephrine reuptake inhibitors**

pp 2809–2812

Joseph P. Sabatucci*, Paige E. Mahaney, Jennifer Leiter, Grace Johnston, Kevin Burroughs, Scott Cosmi, Yingru Zhang, Douglas Ho, Darlene C. Deecher, Eugene Trybulski

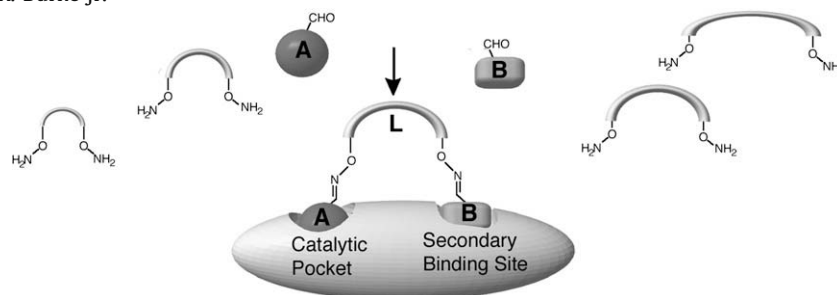


A series of heterocyclic cycloalkanol ethylamines have been prepared to expand our norepinephrine reuptake inhibitor (NRI) program. Synthesis of a variety of heterocycles identified (+)-**S-21**, a potent NRI efficacious in an animal model for thermoregulatory dysfunction.

A rapid oxime linker-based library approach to identification of bivalent inhibitors of the *Yersinia pestis* protein-tyrosine phosphatase, YopH

pp 2813–2816

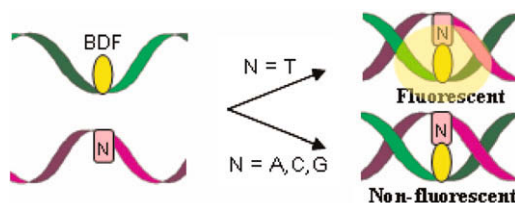
Fa Liu*, Ramin Mollaaghababa Hakami, Beverly Dyas, Medhanit Bahta, George T. Lountos, David S. Waugh, Robert G. Ulrich, Terrence R. Burke Jr.*



Design of environmentally sensitive fluorescent 2'-deoxyguanosine containing arylethynyl moieties: Distinction of thymine base by base-discriminating fluorescent (BDF) probe

pp 2817–2820

Yuta Shinohara, Katsuhiko Matsumoto, Kenji Kugenuma, Takashi Morii, Yoshio Saito*, Isao Saito*



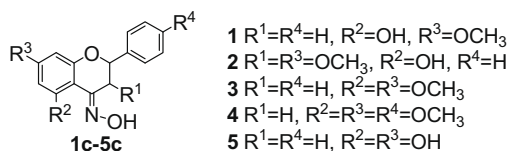
Distinction of thymine base by BDF probe



Cytotoxicity against KB and NCI-H187 cell lines of modified flavonoids from *Kaempferia parviflora*

pp 2821–2823

Chavi Yenjai*, Suchana Wanich



Structural modification of flavones isolated from *Kaempferia parviflora* afforded 16 flavonoid derivatives. Oxime **1c** exhibited dramatically strong cytotoxicity against KB and NCI-H187 cell lines with IC₅₀ values of 0.26 and 0.014 μM, respectively, while **2c** showed strong cytotoxicity against NCI-H187 cell line with an IC₅₀ value of 0.23 μM.

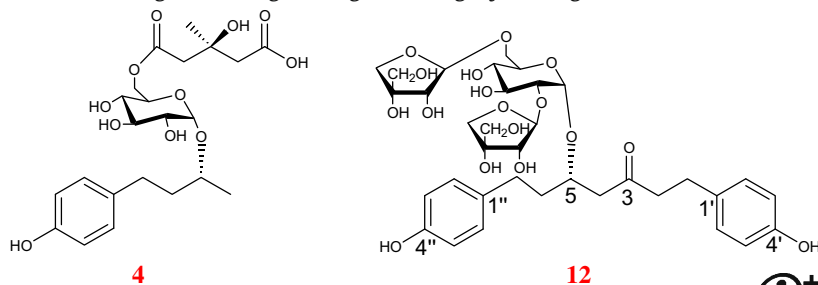


Inhibition of antigen-induced degranulation by aryl compounds isolated from the bark of *Betula platyphylla* in RBL-2H3 cells

pp 2824–2827

Seung Hyun Kim, Jung Hyun Park, Tae Bum Kim, Hyang Hwa Lee, Ki Yong Lee, Young Choong Kim, Sang Hyun Sung*

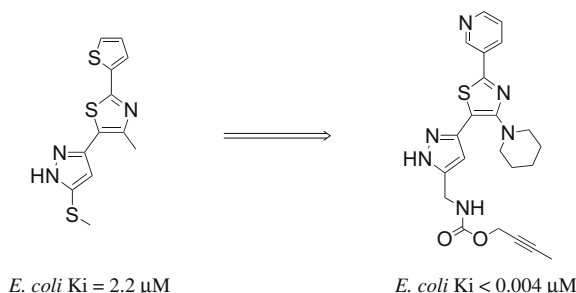
A series of arylbutanoids and diarylheptanoids was isolated from the bark of *Betula platyphylla*. These compounds showed significant inhibitory activity against antigen-induced degranulation of RBL-2H3 cells.



Discovery of pyrazolthiazoles as novel and potent inhibitors of bacterial gyrase

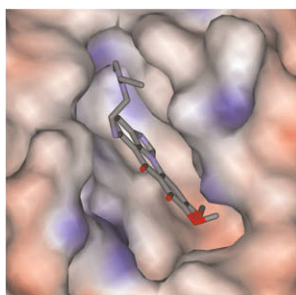
pp 2828–2831

Steven M. Ronkin*, Michael Badia, Steve Bellon, Anne-Laure Grillo, Christian H. Gross, Trudy H. Grossman, Nagraj Mani, Jonathan D. Parsons, Dean Stamos, Martin Trudeau, Yunyi Wei, Paul S. Charifson

**Imidazoacridin-6-ones as novel inhibitors of the quinone oxidoreductase NQO2**

pp 2832–2836

K. A. Nolan, M. P. Humphries, R. A. Bryce, I. J. Stratford*

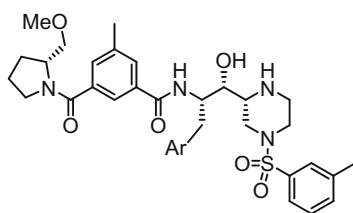


Electrostatic surface representation of NQO2 with **NSC660841** docked in the binding pocket. **NSC660841** is identified as the most potent inhibitor of NQO2 yet reported (IC_{50} = 6 nM).

Piperazine sulfonamide BACE1 inhibitors: Design, synthesis, and in vivo characterization

pp 2837–2842

Jared Cumming*, Suresh Babu*, Ying Huang, Carolyn Carrol, Xia Chen, Leonard Favreau, William Greenlee, Tao Guo, Matthew Kennedy, Reshma Kuvelkar, Thuy Le, Guoqing Li, Nansie McHugh, Peter Orth, Lynne Ozgur, Eric Parker, Kurt Saionz, Andrew Stamford, Corey Strickland, Dawit Tadesse, Johannes Voigt, Lili Zhang, Qi Zhang

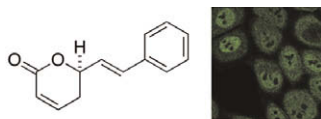


Design and optimization of a novel series of piperazine sulfonamide inhibitors of BACE1 are described, with an emphasis on SAR of the non-prime side and S2' binding motifs. The lead inhibitor demonstrated a prolonged inhibition of peripheral $A\beta_{40}$ in transgenic mice with a single acute dose.

The cytotoxic styryl lactone goniothalamin is an inhibitor of nucleocytoplasmic transport

pp 2843–2846

Jean-Yves Wach, Stephan Güttinger, Ulrike Kutay, Karl Gademann*

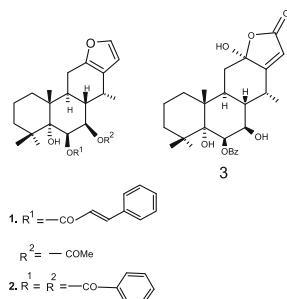


(*R*)-Goniothalamin
Inhibitor of Nuclear Export

New diterpenoids from *Caesalpinia* species and their cytotoxic activity

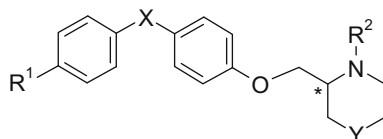
pp 2847–2850

Biswanath Das*, Yallamalla Srinivas, Chithaluri Sudhakar, Ibram Mahender, Keetha Laxminarayana, Parigi Raghavendar Reddy, Tuniki Venugopal Raju, Naga Mahesh Jakka, Janapala Venkateswara Rao

**Discovery of novel leukotriene A₄ hydrolase inhibitors based on piperidine and piperazine scaffolds**

pp 2851–2854

Vincent Sandanayaka, Bjorn Mamat, Nikhil Bhagat, Louis Bedell, Gudrun Halldorsdottir, Heida Sigthorsdottir, Þorkell Andrésson, Alex Kiselyov, Mark Gurney, Jasbir Singh*

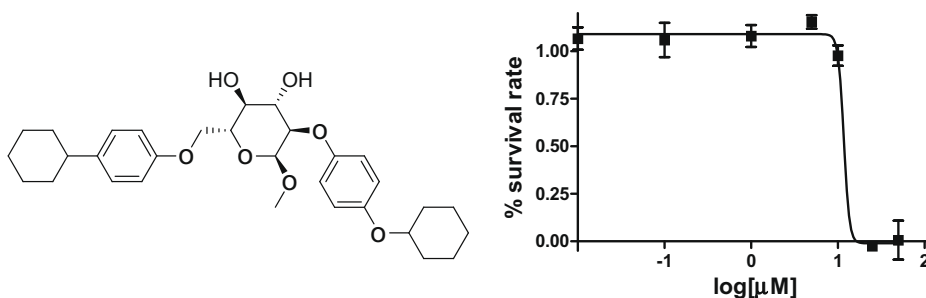


Novel piperidine and piperazine derivatives have been designed and tested as inhibitors of LTA₄ hydrolase (LTA₄H). Most potent compounds showed good potency in both enzymatic and functional human whole blood assay. Crystallography studies further confirmed observed structure–activity relationship and LTA₄H binding mode for analogs from the piperidine series.

Synthesis and anti-tumor activities of methyl 2-O-aryl-6-O-aryl'-D-glucopyranosides

pp 2855–2858

Hefang Shi, Bingcheng Zhou, Wenwen Li, Zhimin Shi, Biao Yu*, Renxiao Wang*

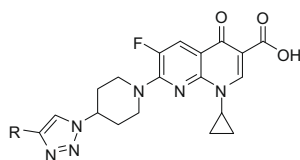


Structure of CAB-SHZH27 and its dose-dependent cytotoxicity on MDA-MB-231 cells.

**4-Substituted 4-(1H-1,2,3-triazol-1-yl)piperidine: Novel C7 moieties of fluoroquinolones as antibacterial agents**

pp 2859–2863

Xiaoguang Huang, Aiqin Zhang, Dongliang Chen, Zhenhua Jia, Xingshu Li*



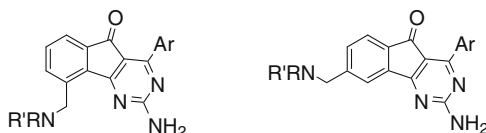
A series of novel quinolones based on 4-substituted 4-(1H-1,2,3-triazol-1-yl)piperidine as the C7 building blocks of quinolone core 7-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid was synthesized. The antibacterial activity of these new fluoroquinolones was evaluated by standard broth microdilution technique. Among them, the quinolone 1-cyclopropyl-6-fluoro-7-(4-(4-formyl-1H-1,2,3-triazol-1-yl)piperidin-1-yl)-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid exhibited comparable antibacterial activity against quinolone-susceptible and multidrug-resistant strains in comparison with ciprofloxacin and vancomycin, especially to *Staphylococcus aureus* and *Staphylococcus epidermidis*.



Methylene amine substituted arylindenopyrimidines as potent adenosine A_{2A}/A₁ antagonists

pp 2864–2867

Brian C. Shook*, Stefanie Rassnick, Daniel Hall, Kenneth C. Rupert, Geoffrey R. Heintzelman, Kristen Hansen, Devraj Chakravarty, James L. Bullington, Robert H. Scannevin, Brian Magliaro, Lori Westover, Karen Carroll, Lisa Lampron, Ronald Russell, Shawn Branum, Kenneth Wells, Sandra Damon, Scott Youells, Xun Li, Mel Osbourne, Keith Demarest, Yuting Tang, Kenneth Rhodes, Paul F. Jackson

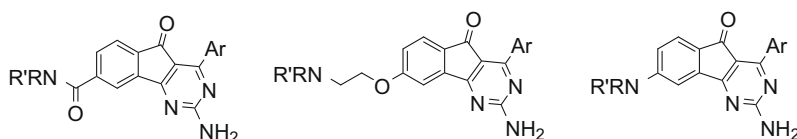


A novel series of arylindenopyrimidines were identified as A_{2A} and A₁ receptor antagonists. The series was optimized for in vitro activity by substituting the 8- and 9-positions with methylene amine substituents. The compounds show excellent activity in mouse models of Parkinson's disease when dosed orally.

Optimization of arylindenopyrimidines as potent adenosine A_{2A}/A₁ antagonists

pp 2868–2871

Brian C. Shook*, Stefanie Rassnick, Devraj Chakravarty, Nathaniel Wallace, Mark Ault, Jeffrey Crooke, J. Kent Barbay, Aihua Wang, Kristi Leonard, Mark T. Powell, Vernon Alford, Daniel Hall, Kenneth C. Rupert, Geoffrey R. Heintzelman, Kristen Hansen, James L. Bullington, Robert H. Scannevin, Karen Carroll, Lisa Lampron, Lori Westover, Ronald Russell, Shawn Branum, Kenneth Wells, Sandra Damon, Scott Youells, Derek Beauchamp, Xun Li, Kenneth Rhodes, Paul F. Jackson

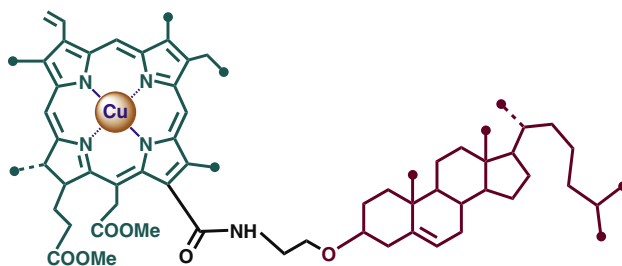


Two reactive metabolites were identified in vivo for the dual A_{2A}/A₁ receptor antagonist **1**. Two strategies were implemented to successfully mitigate the metabolic liabilities associated with **1**. Optimization of the arylindenopyrimidines led to a number of amide, ether, and amino analogs having comparable in vitro and in vivo activity.

Chlorin e6–cholesterol conjugate and its copper complex. Simple synthesis and entrapping in phospholipid vesicles

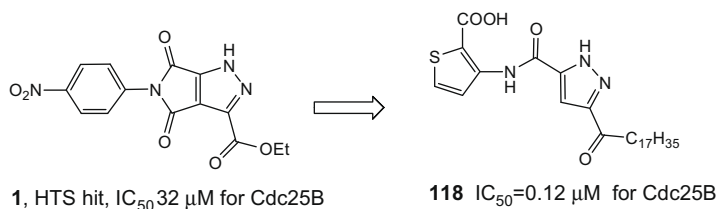
pp 2872–2875

Irina A. Nikolaeva, Alexander Yu. Misharin, Gelii V. Ponomarev, Vladimir P. Timofeev*, Yaroslav V. Tkachev

**Discovery and structural optimization of pyrazole derivatives as novel inhibitors of Cdc25B**

pp 2876–2879

Hai-Jun Chen, Yong Liu, Li-Na Wang, Qiang Shen, Jia Li*, Fa-Jun Nan*

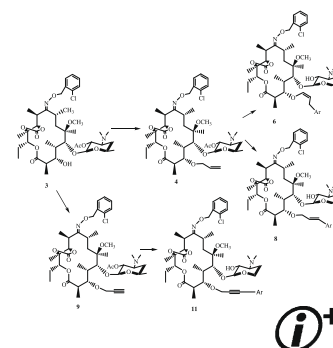


Synthesis and antibacterial activities of a novel alkylide: 3-O-(3-aryl-2-propargyl) and 3-O-(3-aryl-2-propenyl)clarithromycin derivatives

pp 2880–2883

Jian-Hua Liang*, Yue-Ying Wang, He Wang, Xiao-Li Li, Kun An, Ying-Chun Xu, Guo-Wei Yao

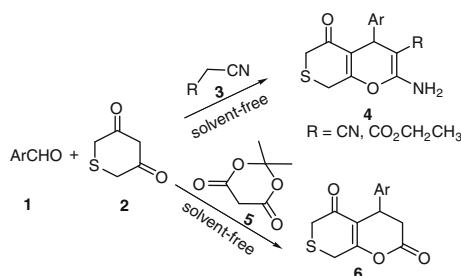
A series of novel alkylides, possessing three-atom length ether linkers instead of cladinose at 3-OH were designed, synthesized, and evaluated for their in vitro antibacterial activities.



Design and an efficient synthesis of new thiorotenone derivatives

pp 2884–2887

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



A series of novel 4-aryl-thiopyrano[3,4-*b*]pyran-5-one derivatives were synthesized through an efficient one-pot three-component reaction under solvent-free conditions. This work provides a new series of derivatives of thiorotenone with potential anticancer activity for biomedical screening.

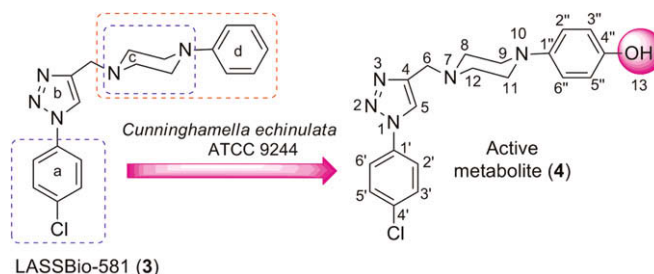


Design of new dopamine D2 receptor ligands: Biosynthesis and pharmacological evaluation of the hydroxylated metabolite of LASSBio-581

pp 2888–2891

Francine Pazini, Ricardo Menegatti, José R. Sabino, Carolina H. Andrade, Gilda Neves, Stela M. K. Rates, François Noël, Carlos A. M. Fraga, Eliezer J. Barreiro, Valéria de Oliveira*

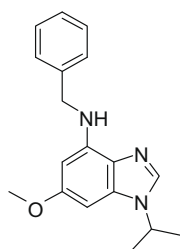
The biosynthesis of the *p*-hydroxylated metabolite of LASSBio-581 by *Cunninghamella echinulata* and its pharmacological evaluation is reported.



Identification of benzimidazole-based inhibitors of the mitogen activated kinase-5 signaling pathway

pp 2892–2896

Patrick T. Flaherty*, Ishveen Chopra, Prashi Jain, Shuyan Yi, Erika Allen, Jane Cavanaugh



Identification of novel benzimidazole inhibitors of MEK5 mediated phosphorylation of ERK5 is presented and early effects of structure on activity are presented.

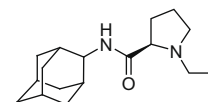


The development and SAR of pyrrolidine carboxamide 11 β -HSD1 inhibitors

pp 2897–2902

Hengmiao Cheng*, Jacqui Hoffman, Phuong Le, Sajiv K. Nair, Stephan Cripps, Jean Matthews, Christopher Smith, Michele Yang, Stan Kupchinsky, Klaus Dress, Martin Edwards, Bridget Cole, Evan Walters, Christine Loh, Jacques Ermoloeff, Andrea Fanjul, Ganesh B. Bhat, Jocelyn Herrera, Tom Pauly, Natilie Hosea, Genevieve Paderes, Paul Rejto

The design and development of a series of highly selective pyrrolidine carboxamide 11 β -HSD1 inhibitors are described. These compounds including PF-877423 demonstrated potent in vitro activity against both human and mouse 11 β -HSD1 enzymes. In an in vivo assay, PF-877423 inhibited the conversion of cortisone to cortisol. Structure guided optimization was carried out to improve metabolic stability for this pyrrolidine carboxamide series.



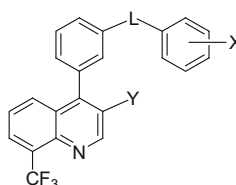
PF-877423

human enzyme Ki: 1.4 nM
mouse enzyme Ki: 0.63 nM
cell IC₅₀: 4.2 nM

Synthesis of 4-(3-biaryl)quinoline sulfones as potent liver X receptor agonists

pp 2903–2907

John W. Ullrich*, Robert Morris, Ronald C. Bernotas, Jeremy M. Travins, James Jetter, Rayomand Unwalla, Elaine Quinet, Ponnal Nambi, Irene Feingold, Christine Huselton, Christofer Enroth, Anna Wilhelmsson, Annika Goos-Nilsson, Jay Wrobel



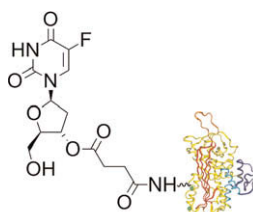
X = SO₂R¹, L = direct bond

A series of 4-(3-biaryl)quinoline sulfones was prepared. High affinity LXR β ligands with generally modest binding selectivity over LXR α and excellent agonist potency in LXR functional assays were identified.

Selective targeting of 2'-deoxy-5-fluorouridine to urokinase positive malignant cells in vitro

pp 2908–2911

Kara L. Vine*, Julie M. Locke, John B. Bremner, Stephen G. Pyne, Marie Ranson



5-FUdrsucc-PAI-2
conjugate

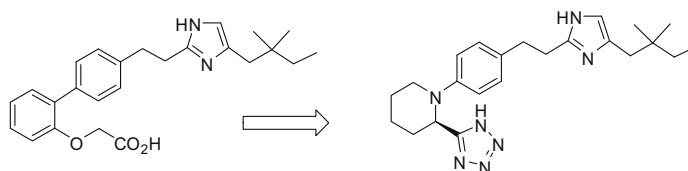
A urokinase targeting conjugate of 2'-deoxy-5-fluorouridine (5-FUdr) was synthesized and found to preferentially kill urokinase-over expressing cancer cells.



Synthesis and SAR of heterocyclic carboxylic acid isosteres based on 2-biarylethylimidazole as bombesin receptor subtype-3 (BRS-3) agonists for the treatment of obesity

pp 2912–2915

Mark Hadden*, Allan Goodman, Cheng Guo, Peter R. Guzzo, Alan J. Henderson, Kevin Pattamana, Megan Ruenz, Bruce J. Sargent, Brian Swenson, Larry Yet, Jian Liu, Shuwen He, Iyassu K. Sebbat, Linus S. Lin, Constantin Tamvakopoulos, Qianping Peng, Yanqing Kan, Oksana Palyha, Theresa M. Kelly, Xiao-Ming Guan, Joseph M. Metzger, Marc L. Reitman, Ravi P. Nargund



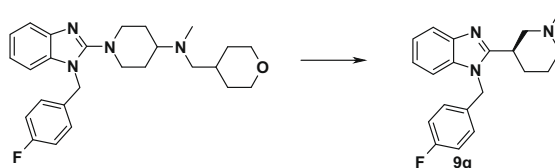
EC₅₀ = 54 nM (97%)

EC₅₀ = 15 nM (100%)

The discovery and structure–activity relationships of 2-(piperidin-3-yl)-1H-benzimidazoles as selective, CNS penetrating H₁-antihistamines for insomnia

pp 2916–2919

Karine Lavrador-Erb, Satheesh Babu Ravula*, Jinghua Yu, Said Zamani-Kord, Wilna J. Moree, Robert E. Petroski, Jianyun Wen, Siobhan Malany, Samuel R. J. Hoare, Ajay Madan, Paul D. Crowe, Graham Beaton*

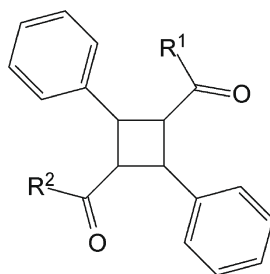


A series of 2-(piperidin-3-yl)-1H-benzimidazoles were identified as selective H₁-antihistamines for evaluation as potential sedative hypnotics. Representative compounds showed generally improved hERG selectivity over a previously identified 2-aminobenzimidazole series. While hERG activity could be modulated via manipulation of the benzimidazole N1 substituent, this approach led to a reduction in CNS exposure for the more selective compounds. One example, **9q**, retained a suitable selectivity profile with CNS exposure equivalent to known centrally active H₁-antihistamines.

Truxillic acid derivatives act as peroxisome proliferator-activated receptor γ activators

pp 2920–2923

Ramona Steri, Matthias Rupp, Ewgenij Proschak, Timon Schroeter, Heiko Zettl, Katja Hansen, Oliver Schwarz, Lutz Müller-Kuhrt, Klaus-Robert Müller, Gisbert Schneider, Manfred Schubert-Zsilavecz*

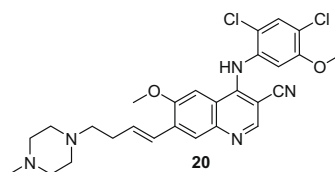


Structure-activity relationships of truxillic acid derivatives as subtype-selective PPAR γ activators are presented.

Optimization of 7-alkene-3-quinolinecarbonitriles as Src kinase inhibitors

pp 2924–2927

Diane H. Boschelli*, Daniel Wang, Yan Wang, Biqi Wu, Erick E. Honores, Ana Carolina Barrios Sosa, Inder Chaudhary, Jennifer Golas, Judy Lucas, Frank Boschelli

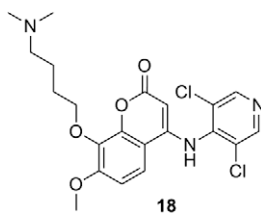


The 7-alkene-3-quinolinecarbonitrile **20**, a potent inhibitor of Src enzymatic and cellular activity with IC₅₀ values of 2.1 and 58 nM, respectively, had comparable efficacy to bosutinib in a colon tumor xenograft study.

Water-soluble PDE4 inhibitors for the treatment of dry eye

pp 2928–2932

Steven P. Govek*, Guy Oshiro, John V. Anzola, Clay Beauregard, Jasmine Chen, Avery R. Coyle, Daniel A. Gamache, Mark R. Hellberg, Jennifer N. Hsien, Julia M. Lerch, John C. Liao, James W. Malecha, Lena M. Staszewski, David J. Thomas, John M. Yanni, Stewart A. Noble, Andrew K. Shiau



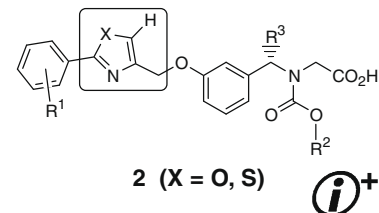
The development of a novel series of water-soluble PDE4 inhibitors led to the discovery of coumarin **18**, which is effective in a rabbit model of dry eye and a tear secretion test in rats.

Synthesis and structure–activity relationships of 2-aryl-4-oxazolymethoxy benzylglycines and 2-aryl-4-thiazolymethoxy benzylglycines as novel, potent PPAR α selective activators- PPAR α and PPAR γ selectivity modulation

pp 2933–2937

Xiang-Yang Ye*, Stephanie Chen, Hao Zhang, Kenneth T. Locke, Kevin O'Malley, Litao Zhang, Rajit Srivastava, Bowman Miao, Daniel Meyers, Hossain Monshizadegan, Debra Search, Denise Grimm, Rongan Zhang, Jonathan Lippy, Celeste Twamley, Jodi K. Muckelbauer, Chiehying Chang, Yongmi An, Vinayak Hosagrahara, Lisa Zhang, T.-J. Yang, Ranjan Mukherjee, Peter T. W. Cheng, Joseph A. Tino

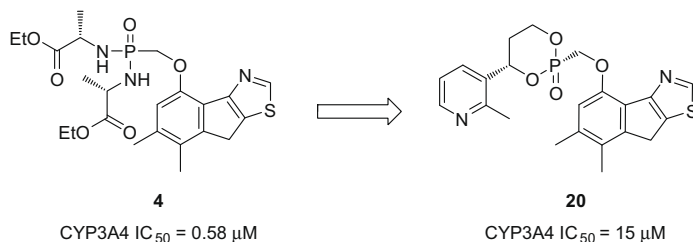
A series of potent, selective PPAR α modulators incorporating 2-aryl-4-oxazolymethoxy and 2-aryl-4-thiazolymethoxy into oxybenzylglycine framework were designed and synthesized (structure shown as **2**). The optimizations of R¹, R², and R³ in **2** have led to the identification of several potent, selective PPAR α modulators such as **2a**, **2l**, and **2s**. Their PK, in vivo pharmacology, and ADME profiles are discussed.



A prodrug approach towards the development of tricyclic-based FBPase inhibitors

pp 2938–2941

Tomoharu Tsukada, Kazuhiko Tamaki, Jun Tanaka, Toshiyuki Takagi, Taishi Yoshida, Akira Okuno, Takeshi Shiiki, Mizuki Takahashi, Takahide Nishi*

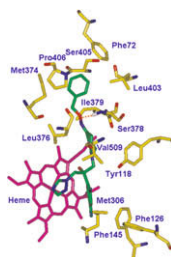


Introduction of pyridine-containing prodrug moieties into tricyclic-based FBPase inhibitors led to the discovery of prodrug **20**, which showed reduced CYP3A4 inhibitory potency compared to diamide prodrug **4**.

Structure-based rational design, synthesis and antifungal activity of oxime-containing azole derivatives

pp 2942–2945

Yulan Xu, Chunquan Sheng, Wenya Wang, Xiaoying Che, Yongbing Cao, Guoqiang Dong, Shengzheng Wang, Haitao Ji, Zhenyuan Miao, Jianzhong Yao, Wannian Zhang*



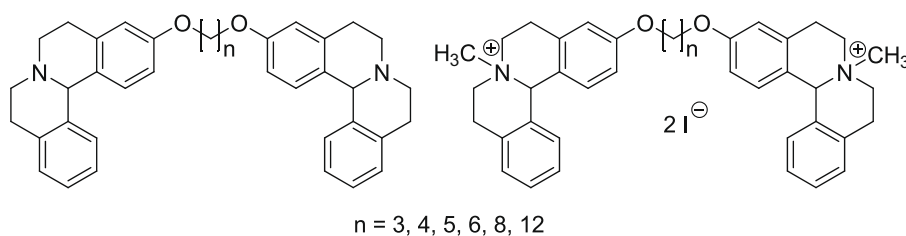
A series of oxime-containing new azoles with good in vitro antifungal activity were rational designed and synthesized.



Bivalent 5,8,9,13b-tetrahydro-6H-isoquino[1,2-a]isoquinolines and -isoquinolinium salts: Novel heterocyclic templates for butyrylcholinesterase inhibitors

pp 2946–2949

Maria Schulze, Oliver Siol, Michael Decker, Jochen Lehmann*



IC₅₀(AChE): 0.65 - 4.5 μ M
IC₅₀(BChE): 0.014 - 0.92 μ M

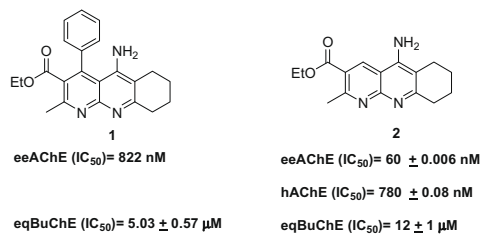
IC₅₀(AChE): 0.12 - 0.45 μ M
IC₅₀(BChE): 0.027 - 0.16 μ M



Molecular modelling, synthesis and acetylcholinesterase inhibition of ethyl 5-amino-2-methyl-6,7,8,9-tetrahydrobenzo[b][1,8]naphthyridine-3-carboxylate

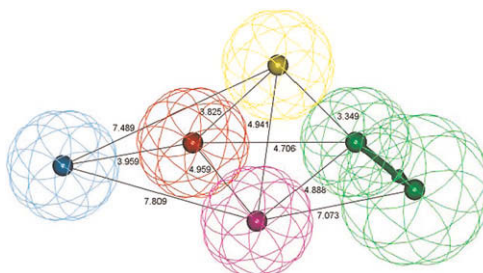
pp 2950–2953

Elena Soriano, Abdelouahid Samadi, Mourad Chioua, Cristóbal de los Ríos, José Marco-Contelles*

**A 3D-pharmacophore model for σ₂ receptors based on a series of substituted benzo[d]oxazol-2(3H)-one derivatives**

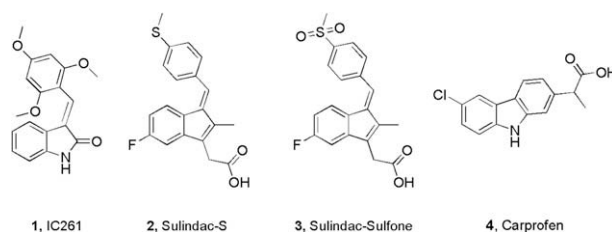
pp 2954–2957

Erik Laurini, Daniele Zampieri, Maria Grazia Mamolo, Luciano Vio, Caterina Zanette, Chiara Florio, Paola Posocco, Maurizio Fermeglia, Sabrina Pricl*

**Inhibition of γ-secretase by the CK1 inhibitor IC261 does not depend on CK1δ**

pp 2958–2963

Nicole Höttecke, Miriam Liebeck, Karlheinz Baumann, Robert Schubene, Edith Winkler, Harald Steiner, Boris Schmidt*

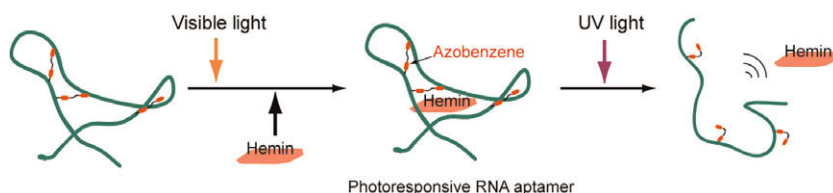


Structural similarity of IC261 and the GSM of the Sulindac-series (2, 4).

**In vitro selection of a photoresponsive RNA aptamer to hemin**

pp 2964–2967

Mingzhe Liu, Hiroshi Jinmei, Hiroshi Abe, Yoshihiro Ito*



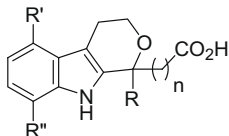
In vitro selection of photoresponsive RNA aptamer against hemin was reported.



The discovery and structure–activity relationships of pyrano[3,4-*b*]indole based inhibitors of hepatitis C virus NS5B polymerase

pp 2968–2973

Matthew G. LaPorte*, Tandy L. Draper, Lori E. Miller, Charles W. Blackledge, Lara K. Leister, Eugene Amparo, Alison R. Hussey, Dorothy C. Young, Srinivas K. Chunduru, Christopher A. Benetatos, Gerry Rhodes, Ariamala Gopalsamy, Torsten Herbertz, Christopher J. Burns, Stephen M. Condon*



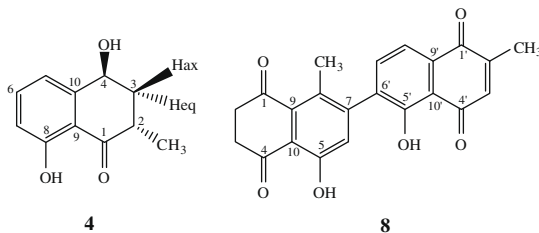
We describe the structure–activity relationship of the C1-group of pyrano[3,4-*b*]indole based inhibitors of HCV NS5B polymerase. Further exploration of the allosteric binding site led to the discovery of the significantly more potent compound **12**.



Bioactivity-guided isolation of mosquitocidal constituents from the rhizomes of *Plumbago capensis* Thunb

pp 2974–2977

T. Sreelatha, A. Hymavathi, J. Madhusudhana Murthy, P. U. Rani, J. Madhusudana Rao, K. Suresh Babu*

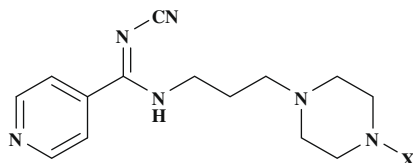


Bioassay guided isolation of mosquitocidal extract of *P. capensis* rhizomes yielded two new naphthaquinones, isoplumbagolone (**4**) and chitranane (**8**) along with six known compounds (**1–3**, **5–7**) as a mosquitocidal constituents, possessing varying degree of mosquitocidal potentials.

New 5-HT_{1A} receptor ligands containing a *N'*-cyanoisonicotinamidinium nucleus: Synthesis and in vitro pharmacological evaluation

pp 2978–2982

Ferdinando Fiorino, Beatrice Severino, Francesca De Angelis, Elisa Perissutti, Elisa Magli, Francesco Frecentese, Antonella Esposito, Paola Massarelli, Cristina Nencini, Vincenzo Santagada, Giuseppe Caliendo*



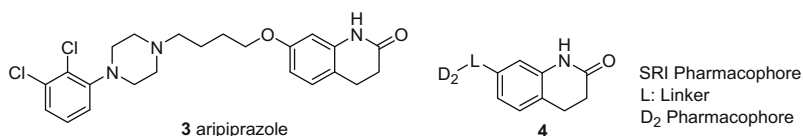
N'-Cyanoisonicotinamidinium derivatives, linked to an arylpiperazine moiety, were prepared to identify highly selective and potent 5-HT_{1A} ligands. *N'*-Cyano-*N*-(3-(4-(pyridin-2-yl)piperazin-1-yl)propyl)isonicotinamidinium (**4a**) with $K_i = 0.038$ nM, was the most active and selective derivative for the 5-HT_{1A} receptor.



Potent dihydroquinolinone dopamine D₂ partial agonist/serotonin reuptake inhibitors for the treatment of schizophrenia

pp 2983–2986

Yinfa Yan*, Ping Zhou, David P. Rotella*, Rolf Feenstra, Chris G. Kruse, Jan-Hendrik Reinders, Martina van der Neut, Margaret Lai, Jean Zhang, Dianne M. Kowal, Tikva Carrick, Karen L. Marquis, Mark H. Pausch, Albert J. Robichaud

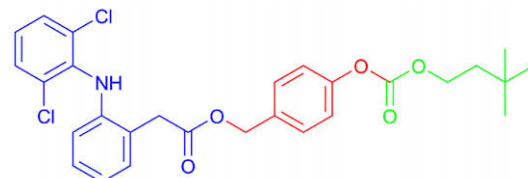


Peripheral site acetylcholinesterase inhibitors targeting both inflammation and cholinergic dysfunction

pp 2987–2990

Sherri Young, Karine Fabio, Christophe Guillon, Pramod Mohanta, Timothy A. Halton, Diane E. Heck, Robert A. Flowers II, Jeffrey D. Laskin, Ned D. Heindel*

The design and synthesis of dual-action anti-inflammatory and anticholinergic agents are reported. Several of the compounds studied noncompetitively inhibit acetylcholinesterase (AChE) in the submicromolar range and release a pharmacologically active NSAID upon hydrolysis.



7, IC₅₀ = 0.51 μM

NSAID (diclofenac)

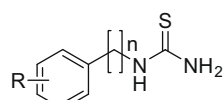
Alkyl-Aryl spacer

Choline bioisostere

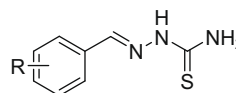
**Structural requirement(s) of N-phenylthioureas and benzaldehyde thiosemicarbazones as inhibitors of melanogenesis in melanoma B 16 cells**

pp 2991–2993

P. Thanigaimalai, Tuan Anh Le Hoang, Ki-Cheul Lee, Seong-Cheol Bang, Vinay K. Sharma, Cheong-Yong Yun, Eunmiri Roh, Bang-Yeon Hwang, Youngsoo Kim, Sang-Hun Jung*



1(a-q)



1(r-u)

n = 0, 1, 2, 3 or 4.

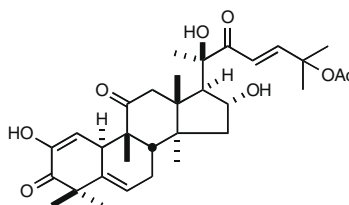
R = H, CH₃, CH₂CH₃, C(CH₃)₃, Cl, CH₂OH or OCH₃

To define the structural requirement of phenylthiourea, a series of thiourea and thiosemicarbazone analogs were prepared and evaluated as inhibitors of melanogenesis in melanoma B16 cells.

**Cucurbitacin E as a new inhibitor of cofilin phosphorylation in human leukemia U937 cells**

pp 2994–2997

Souichi Nakashima, Hisashi Matsuda, Ai Kurume, Yoshimi Oda, Seikou Nakamura, Masayuki Yamashita, Masayuki Yoshikawa*



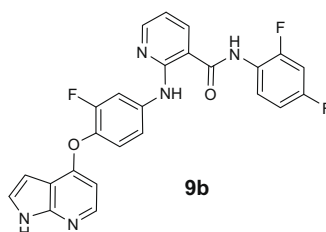
cucurbitacin E

We synthesized a biotin-linked cucurbitacin E to isolate target proteins based on affinity for the molecule. As a result, cofilin, which regulates the depolymerization of actin, was isolated and suggested to be a target. Cucurbitacins E and I inhibited the phosphorylation of cofilin in a concentration-dependent manner, and their effective concentrations having the same range as the concentrations at which they had cytotoxic effects in U937 cells. In addition, the fibrous-/globular-actin ratio was decreased after treatment with cucurbitacin E in HT1080 cells.

Design, synthesis and structure–activity relationships of novel biarylamine-based Met kinase inhibitors

pp 2998–3002

David K. Williams*, Xiao-Tao Chen, Christine Tarby, Robert Kaltenbach, Zhen-Wei Cai, John S. Tokarski, Yongmi An, John S. Sack, Barri Wautlet, Johnni Gullo-Brown, Benjamin J. Henley, Robert Jeyaseelan, Kristen Kellar, Veeraswamy Manne, George L. Trainor, Louis J. Lombardo, Joseph Fargnoli, Robert M. Borzilleri

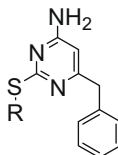


9b

Biarylamine-based inhibitors of Met kinase have been identified. Compound 9b demonstrated potent in vivo antitumor activity in the GTL-16 human tumor xenograft model.


Synthesis and biological evaluation of novel 2-arylalkylthio-4-amino-6-benzyl pyrimidines as potent HIV-1 non-nucleoside reverse transcriptase inhibitors**pp 3003–3005**

Hua Qin, Chang Liu, Jianfang Zhang, Ying Guo, Siwei Zhang, Zhili Zhang, Xiaowei Wang, Liangren Zhang, Junyi Liu*



A number of novel 2-arylalkylthio-4-amino-6-benzyl pyrimidines were designed and synthesized as potent NNRTIs. The results showed that the changes of $N_3H-C_4=O$ into $N_3=C_4-NH_2$ could increase the activity.

*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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