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Bioorganic & Medicinal Chemistry Letters Vol. 18, No. 14, 2008

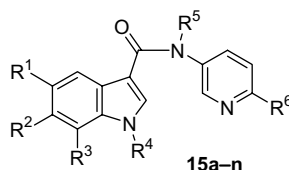
Contents

ARTICLES

Synthesis and structure–activity relationship of 1*H*-indole-3-carboxylic acid pyridine-3-ylamides: A novel series of 5-HT_{2C} receptor antagonists

pp 3844–3847

Chul Min Park, So Young Kim, Woo Kyu Park, No Sang Park, Churl Min Seong*



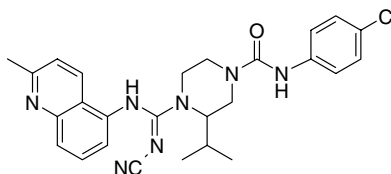
The synthesis and biological evaluation of a series of 1*H*-indole-3-carboxylic acid pyridine-3-ylamides 5-HT_{2C} receptor antagonists are described.



Synthesis and activity of *N*-cyanoguanidine-piperazine P2X₇ antagonists

pp 3848–3851

Patrick Betschmann, Brian Bettencourt, Diana Donnelly-Roberts, Michael Friedman*, Jonathan George, Gavin Hirst, Nathan Josephsohn, Donald Konopacki, Biqin Li, John Maull, Michael J. Morytko, Nigel StJohn Moore, Marian Namovic, Paul Rafferty, Jose-Andres Salmeron-Garcia, Edit Tarcsa, Lu Wang, Kevin Woller

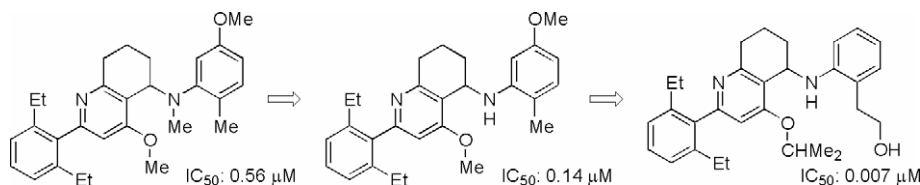


A novel series of cyanoguanidine-piperazine P2X₇ antagonists were identified and structure–activity relationship (SAR) studies described. Compounds were assayed for activity at human and rat P2X₇ receptors in addition to their ability to inhibit IL-1β release from stimulated human whole blood cultures. Compound **27** possesses potent activity (0.12 μM) in this latter assay and demonstrates moderate clearance in-vivo.

Design and optimization of aniline-substituted tetrahydroquinoline C5a receptor antagonists

pp 3852–3855

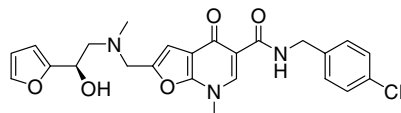
Yong Gong*, J. Kent Barbay, Mieke Buntinx, Jian Li, Jean Van Wauwe, Concha Claes, Guy Van Lommen, Pamela J. Hornby, Wei He



A series of aniline-substituted tetrahydroquinoline C5aR antagonists with distinct structure–activity relationships are presented.

Synthesis of 4-oxo-4,7-dihydrofuro[2,3-*b*]pyridine-5-carboxamides with broad-spectrum human herpesvirus polymerase inhibition pp 3856–3859

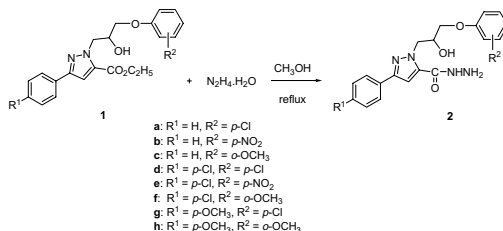
Mark E. Schnute^{*}, Roger J. Brideau, Sarah A. Collier, Michele M. Cudahy, Todd A. Hopkins, Mary L. Knechtel, Nancee L. Oien, Robert S. Sackett, Allen Scott, Mari L. Stephan, Michael W. Wathen, Janet L. Wieber



A new series of broad-spectrum herpesvirus polymerase inhibitors has been identified with antiviral activity against HCMV, HSV-1, EBV, and VZV. A practical synthesis of furo[2,3-*b*]pyridin-4-one-5-carboxylate esters is described.

Synthesis and discovery of autophagy inducers for A549 and H460 lung cancer cells, novel 1-(2'-hydroxy-3'-aroxypropyl)-3-aryl-1*H*-pyrazole-5-carbohydrazide derivatives pp 3860–3864

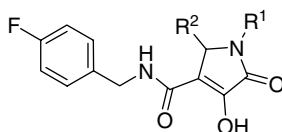
Chuan-Dong Fan, Bao-Xiang Zhao^{*}, Fang Wei, Gai-Hua Zhang, Wen-Liang Dong, Jun-Ying Miao^{*}



A series of novel 1-(2'-hydroxy-3'-aroxypropyl)-3-aryl-1*H*-pyrazole-5-carbohydrazide derivatives were synthesized. All of the 1-(2'-hydroxy-3'-aroxypropyl)-3-aryl-1*H*-pyrazole-5-carbohydrazide derivatives **2** could inhibit the growth of A549 cells in dosage- and time-dependent manners. Typically, compounds **2a** and **2d** induced A549 and H460 cells to autophagy, but did not inhibit the growth of HUVEC cells.

4-Hydroxy-5-pyrrolinone-3-carboxamide HIV-1 integrase inhibitors pp 3865–3869

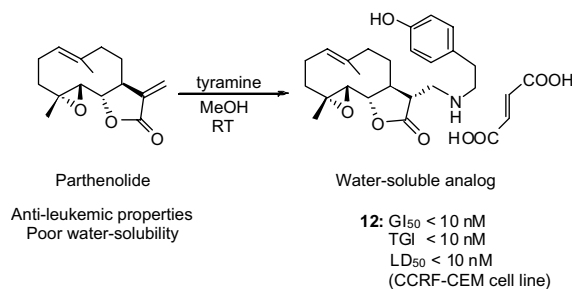
Paola Pace^{*}, Stéphane A. H. Spieser, Vincenzo Summa



A series of novel 4-hydroxy-5-pyrrolinone-3-carboxamide HIV-1 integrase inhibitors was identified. SAR around the pyrrolinone core resulted in the discovery of compounds with inhibitory activity in the low nanomolar range.

Antileukemic activity of aminoparthenolide analogs pp 3870–3873

Shama Nasim, Peter A. Crooks^{*}

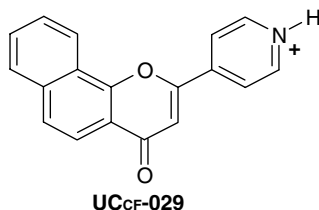


A series of aminoparthenolide analogs have been synthesized. Compound **12**, derived from tyramine, was found to be cytotoxic to acute lymphoblastic leukemia (ALL, CCRF-CEM) cells in culture at concentrations below 10 nM.

Activation of CFTR by UC_{CF}-029 and genistein

pp 3874–3877

Layla Al-Nakkash*, Mark F. Springsteel, Mark J. Kurth, Michael H. Nantz



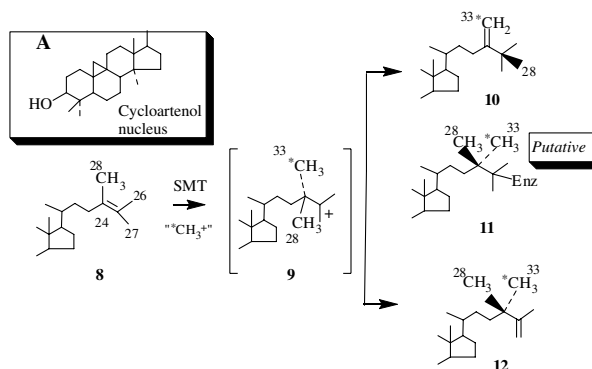
The effects of UCCF-029 on CFTR are compared with genistein.

Cyclobranol: A substrate for C25-methyl sterol side chains and potent mechanism-based inactivator of plant sterol methyltransferase

pp 3878–3881

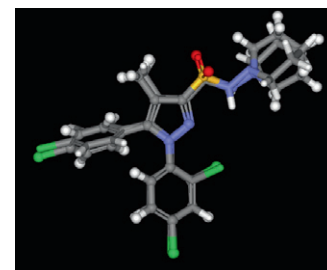
Junqing Wang, W. David Nes*

Cyclobranol **8A**, an analog of the cycloartenol substrate **1A** for the plant sterol C24-methyltransferase (SMT), was shown to be an acceptor of the soybean SMT1 as well as an inhibitor of enzyme action. The K_m and k_{cat} for **8A** was 37 μM and 0.006 min^{-1} , respectively. The enzyme-generated product was identified by MS and ^1H NMR to be a C24, C25-doubly alkylated $\Delta^{24(28)}$ -olefin **10A**. Inhibitor treatment was concentration and time-dependent affording an apparent K_i of 25 μM , a maximum rate of inactivation of 0.15 min^{-1} and a partition ratio (k_{cat}/k_{inact}) calculated to be 0.04.

**Facile synthesis, ex-vivo and in vitro screening of 3-sulfonamide derivative of 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxylic acid piperidin-1-ylamide (SR141716) a potent CB1 receptor antagonist**

pp 3882–3886

Brijesh Kumar Srivastava*, Rina Soni, Jayendra Z. Patel, Satadru Jha, Sandeep A. Shedage, Neha Gandhi, Kalapatapu V. V. M. Sairam, Vishwanath Pawar, Nisha Sadhwani, Prasenjit Mitra, Mukul R. Jain, Pankaj R. Patel

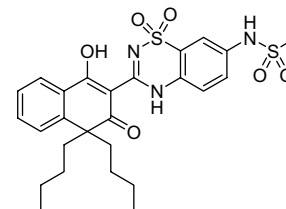


Facile synthesis of biaryl pyrazole sulfonamide derivative of 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxylic acid piperidin-1-ylamide (SR141716, **1**) and an investigation of the effect of replacement of the $-\text{CO}$ group in the compound **1** by the $-\text{SO}_2$ group in the aminopiperidine region is reported. Primary ex-vivo pharmacological testing of sulfonamide derivative **2** showed the loss of CB1 receptor antagonism.

Hepatitis C NS5B polymerase inhibitors: 4,4-Dialkyl-1-hydroxy-3-oxo-3,4-dihydronaphthalene-3-yl benzothiadiazine derivatives

pp 3887–3890

Douglas K. Hutchinson*, Teresa Rosenberg, Larry L. Klein, Todd D. Bosse, Daniel P. Larson, Wenping He, Wen W. Jiang, Warren M. Kati, William E. Kohlbrenner, Yaya Liu, Sherie V. Masse, Tim Middleton, Akhteruzzaman Molla, Debra A. Montgomery, David W. A. Beno, Kent D. Stewart, Vincent S. Stoll, Dale J. Kempf

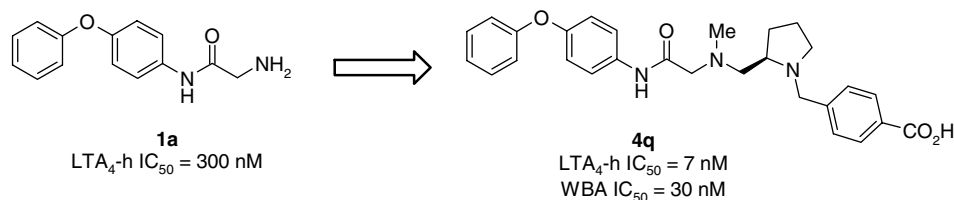


4,4-Dialkyl-1-hydroxy-3-oxo-3,4-dihydronaphthalene-3-yl benzothiadiazine derivatives were synthesized and evaluated as inhibitors of genotypes 1a and 1b HCV NS5B polymerase. A number of these compounds exhibited potent activity against genotypes 1a and 1b HCV polymerase in both enzymatic and cell culture activities. The representative compound above also showed favorable pharmacokinetics in the rat.

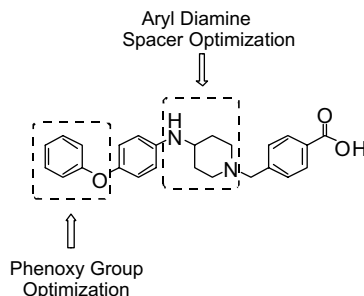


Synthesis of *N*-alkyl glycine amides as potent inhibitors of leukotriene A₄ hydrolase**pp 3891–3894**

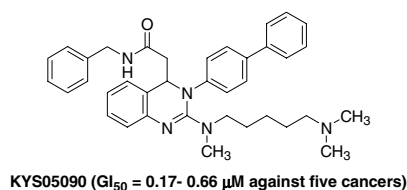
Bin Ye, John Bauman, Ming Chen, David Davey, Seock-Kyu Khim, Beverly King, Thomas Kirkland, Monica Kochanny, Amy Liang, Dao Lentz, Karen May, Lisa Mendoza, Gary Phillips, Victor Selchau, Sabine Schlyer, Jih-Lie Tseng, Robert G. Wei, Hong Ye, John Parkinson, William J. Guilford *

**Discovery of novel and potent aryl diamines as leukotriene A₄ hydrolase inhibitors****pp 3895–3898**

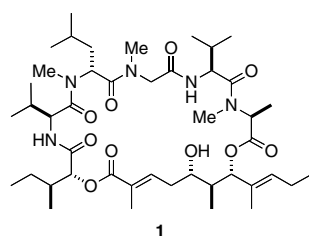
Seock-Kyu Khim, John Bauman, Jarred Evans, Beverly Freeman, Beverly King, Thomas Kirkland, Monica Kochanny, Dao Lentz, Amy Liang, Lisa Mendoza, Gary Phillips, Jih-Lie Tseng, Robert G. Wei, Hong Ye, Limei Yu, John Parkinson, William J. Guilford *

**T-type Ca²⁺ channel blockers suppress the growth of human cancer cells****pp 3899–3901**

Jae Ho Heo, Han Na Seo, Yun Jeong Choe, Sujin Kim, Chun Rim Oh, Young Deuk Kim, Hyewhon Rhim, Dong Joon Choo, Jungahn Kim, Jae Yeol Lee *

**Synthesis and cytotoxicity of aurilide analogs****pp 3902–3905**

Kiyotake Suenaga, Shuri Kajiware, Satomi Kuribayashi, Tomohisa Handa, Hideo Kigoshi *

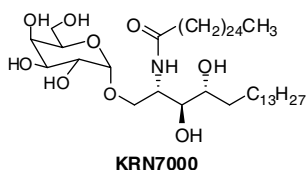


The artificial analogs of aurilide (**1**), a potent cytotoxic cyclodepsipeptide of marine origin, were synthesized, and the structure–activity relationships were investigated.

Synthesis of all stereoisomers of KRN7000, the CD1d-binding NKT cell ligand

pp 3906–3909

Jeong-Ju Park, Ji Hyung Lee, Subhash C. Ghosh, Gabriel Bricard, Manjunatha M. Venkataswamy, Steven A. Porcelli, Sung-Kee Chung*

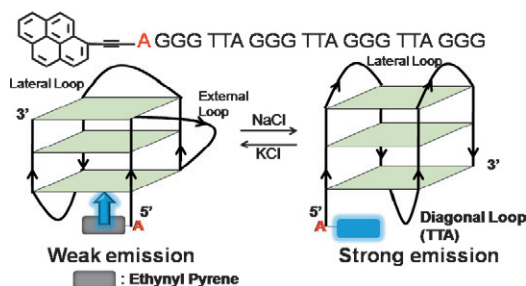


In an effort to understand the structure–activity relationships, we have carried out the synthesis of all eight KRN7000 stereoisomers, and their biological activities examined.

Detection of structure-switching in G-quadruplexes using end-stacking ability

pp 3910–3913

Young Jun Seo, Il Joon Lee, Byeang Hyeon Kim*

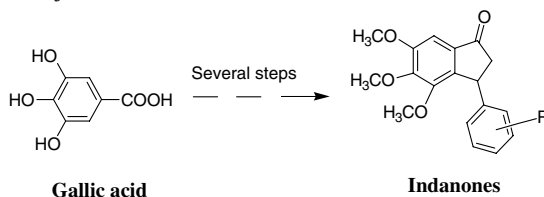


Structure-switching probe of the human G-quadruplex using a pyrene attached deoxyadenosine.

**Gallic acid-based indanone derivatives as anticancer agents**

pp 3914–3918

Hari Om Saxena, Uzma Faridi, Suchita Srivastava, J. K. Kumar, M. P. Darokar, Suaib Luqman, C. S. Chanotiya, Vinay Krishna, Arvind S. Negi*, S. P. S. Khanuja

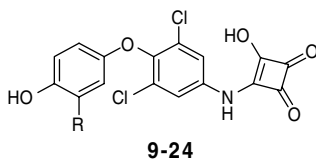


Gallic acid-based indanone derivatives have been synthesised. Indanones **10**, **11**, **12** and **14** showed potent anticancer activity (IC_{50} = 0.022–2.2 μ M) against human cancer cell lines. The most active indanone against MCF-7, i.e., hormone-dependent breast cancer cell line (**10**, IC_{50} = 2.2 μ M) showed no toxicity to human erythrocytes even at higher concentrations (100 μ g/ml, 258 μ M). While, some of the indanones exhibited toxicity to erythrocytes at higher concentrations. Gallic acid-based indanones may further be optimised as better anticancer agents with low toxicity.

**Design and synthesis of novel 3-hydroxy-cyclobut-3-ene-1,2-dione derivatives as thyroid hormone receptor β (TR- β) selective ligands**

pp 3919–3924

Saurin Raval*, Preeti Raval, Debduitta Bandyopadhyay, Krupal Soni, Digambar Yevale, Digvijay Jogiya, Honey Modi, Amit Joharapurkar, Neha Gandhi, Mukul R. Jain, Pankaj R. Patel

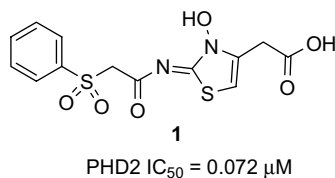


Design and synthesis of a novel 3-hydroxy-cyclobut-3-ene-1,2-dione derivatives are reported and their thyroid hormone receptor selectivity has been evaluated. 3-[3,5-Dichloro-4-(4-hydroxy-3-isopropylphenoxy)-phenylamino]-4-hydroxy-cyclobut-3-ene-1,2-dione **21** has shown selectivity towards thyroid hormone receptor β .

Discovery of novel hydroxy-thiazoles as HIF- α prolyl hydroxylase inhibitors: SAR, synthesis, and modeling evaluation

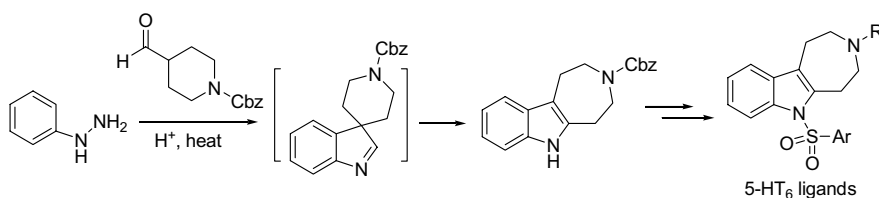
pp 3925–3928

Christopher M. Tegley*, Vellarkad N. Viswanadhan, Kaustav Biswas, Michael J. Frohn, Tanya A. N. Peterkin, Catherine Chang, Roland W. Bürli, Jennifer H. Dao, Henrike Veith, Norma Rogers, Sean C. Yoder, Gloria Biddlecome, Philip Tagari, Jennifer R. Allen, Randall W. Hungate


A regiospecific synthesis of a series of 1-sulfonyl azepinoindoles as potent 5-HT₆ ligands

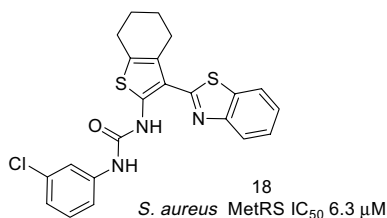
pp 3929–3931

Kevin G. Liu*, Jennifer R. Lo, Thomas A. Comery, Guo Ming Zhang, Jean Y. Zhang, Dianne M. Kowal, Deborah L. Smith, Li Di, Edward H. Kerns, Lee E. Schechter, Albert J. Robichaud


Identification of novel inhibitors of methionyl-tRNA synthetase (MetRS) by virtual screening

pp 3932–3937

John Finn*, Mark Stidham, Mark Hilgers, Kedar G. C.

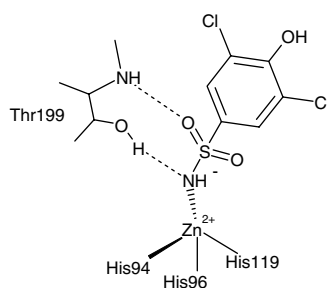


Multiple inhibitors of the antibacterial target, *Staphylococcus aureus* MetRS, were identified by virtual screening. The process consisted of building a Catalyst® pharmacophore from a ligand-*S. aureus* MetRS structure and using this pharmacophore to screen a commercial database. The top hits from this search were then docked into the *S. aureus* MetRS structure and this information was used to select compounds for testing. This resulted in a high hit rate of compounds that are in distinct structural classes from the known MetRS inhibitors.

Carbonic anhydrase inhibitors: Thioxolone versus sulfonamides for obtaining isozyme-selective inhibitors?

pp 3938–3941

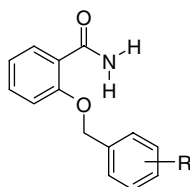
Alessio Innocenti, Alfonso Maresca, Andrea Scozzafava, Claudiu T. Supuran*



Novel alkoxybenzamide inhibitors of poly(ADP-ribose) polymerase

pp 3942–3945

Keith A. Menear*, Claire Adcock, Francisco Cuenca Alonso, Kristel Blackburn, Louise Copsey, Jan Drzewiecki, Alexandra Fundo, Armelle Le Gall, Sylvie Gomez, Hashim Javaid, Carlos Fenandez Lence, Niall M. B. Martin, Chris Mydlowski, Graeme C. M. Smith

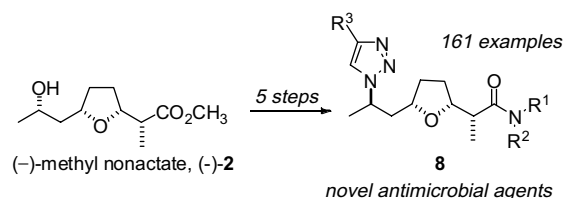


A novel series of alkoxybenzamides have been developed with restricted conformation through intramolecular hydrogen bond formation. The compounds exhibit low nM enzyme and cellular activity as poly(ADP-ribose) polymerase-1 (PARP-1) inhibitors.

Natural products in parallel synthesis: Triazole libraries of nonactic acid

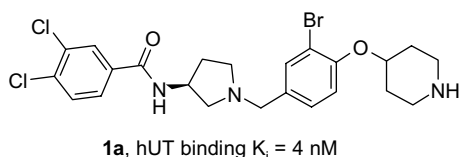
pp 3946–3949

Sarah B. Luesse, Gregg Wells, Abhijit Nayek, Adrienne E. Smith, Brian R. Kusche, Stephen C. Bergmeier*, Mark C. McMills, Nigel D. Priestley, Dennis L. Wright

**Urotensin-II receptor antagonists: Synthesis and SAR of N-cyclic azaalkyl benzamides**

pp 3950–3954

Jian Jin*, Ming An, Anthony Sapienza, Nambi Aiyar, Diane Naselsky, Henry M. Sarau, James J. Foley, Kevin L. Salyers, Steven D. Knight, Richard M. Keenan, Ralph A. Rivero, Dashyant Dhanak, Stephen A. Douglas



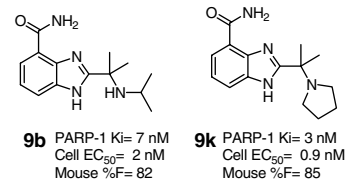
SAR exploration of the central diamine, benzyl, and terminal aminoalkoxy regions of the N-cyclic azaalkyl benzamide series led to the identification of very potent human urotensin-II receptor antagonists such as 1a with a K_i of 4 nM. The synthesis and structure–activity relationships (SAR) of N-cyclic azaalkyl benzamides are described.

Synthesis and SAR of novel, potent and orally bioavailable benzimidazole inhibitors of poly(ADP-ribose) polymerase (PARP) with a quaternary methylene-amino substituent

pp 3955–3958

Gui-Dong Zhu*, Viraj B. Gandhi, Jianchun Gong, Sheela Thomas, Yan Luo, Xuesong Liu, Yan Shi, Vered Klinghofer, Eric F. Johnson, David Frost, Cherrie Donawho, Ken Jarvis, Jennifer Bouska, Kennan C. Marsh, Saul H. Rosenberg, Vincent L. Giranda, Thomas D. Penning

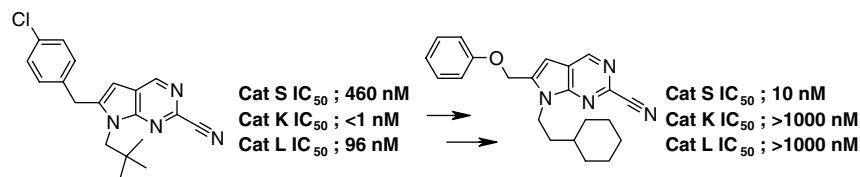
We discovered a novel series of potent and orally bioavailable PARP inhibitors containing a quaternary methylene-amino substituent at the C-2 position of the benzimidazole scaffold. Two optimized analogs, **9b** and **9k**, displayed excellent intrinsic and cellular potency, adequate pharmaceutical properties, and potentiated the efficacy of cytotoxic agent temozolomide (TMZ) in a B16F10 flank melanoma model.



Discovery of selective and nonpeptidic cathepsin S inhibitors

pp 3959–3962

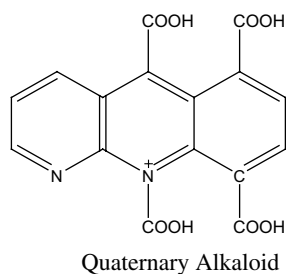
Osamu Irie*, Takeru Ehara, Atsuko Iwasaki, Fumiaki Yokokawa, Junichi Sakaki, Hajime Hirao, Takanori Kanazawa, Naoki Teno, Miyuki Horiuchi, Ichiro Umemura, Hiroki Gunji, Keiichi Masuya, Yuko Hitomi, Genji Iwasaki, Kazuhiko Nonomura, Keiko Tanabe, Hiroaki Fukaya, Takatoshi Kosaka, Christopher R. Snell, Allan Hallett



A serine protease inhibitor from hemolymph of green mussel, *Perna viridis*

pp 3963–3967

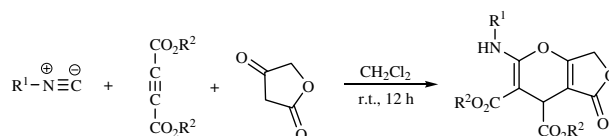
M. S. Khan, U. Goswami, S. R. Rojatkhar, M. I. Khan*



A simple and efficient approach to the synthesis of 4H-furo[3,4-b]pyrans via a three-component reaction of isocyanides

pp 3968–3970

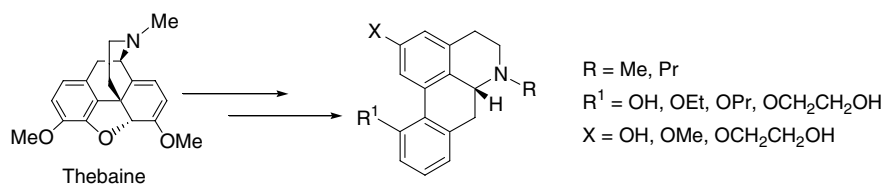
Ahmad Shaabani*, Ebrahim Soleimani, Afshin Sarvary, Ali Hossein Rezayan



Synthesis and binding studies of 2-O- and 11-O-substituted *N*-alkylnoraporphines

pp 3971–3973

Yu-Gui Si, Matthew P. Gardner, Frank I. Tarazi, Ross J. Baldessarini, John L. Neumeyer*

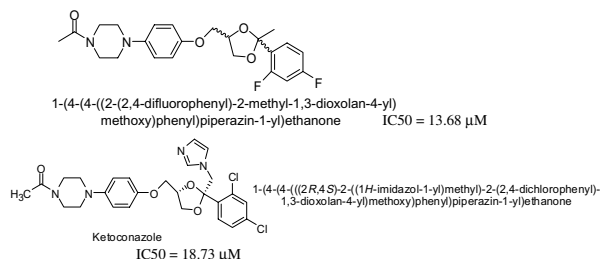


We synthesized several novel 2-O- or 11-O-substituted *N*-alkylnoraporphines and assessed their binding affinities at D₁, D₂ and 5-HT_{1A} receptors in rat forebrain tissue. The most D₂-potent (K_i = 97 nM) and selective novel agent (>100-fold vs. D₁ and 5-HT_{1A} sites) was *R*(-)-2-(2-hydroxyethoxy)-11-hydroxy-*N*-*n*-propylnoraporphine (compound 11).

Synthesis of novel ketoconazole derivatives as inhibitors of the human Pregnane X Receptor (PXR; NR1I2; also termed SXR, PAR)

pp 3974–3977

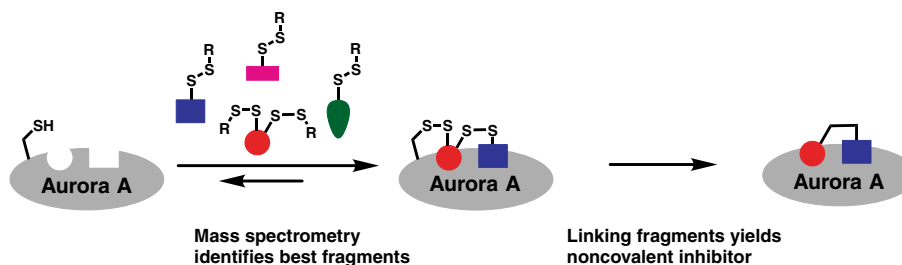
Bhaskar C. Das*, Ankanahlli V. Madhukumar, Jaime Anguiano, Sean Kim, Michael Sinz, Tatyana A. Zvyaga, Eoin C. Power, C. Robin Ganellin, Sridhar Mani*



Discovery of an Aurora kinase inhibitor through site-specific dynamic combinatorial chemistry

pp 3978–3981

Mark T. Cancilla, Molly M. He, Nina Viswanathan, Robert L. Simmons, Meggin Taylor, Amy D. Fung, Kathy Cao, Daniel A. Erlanson*

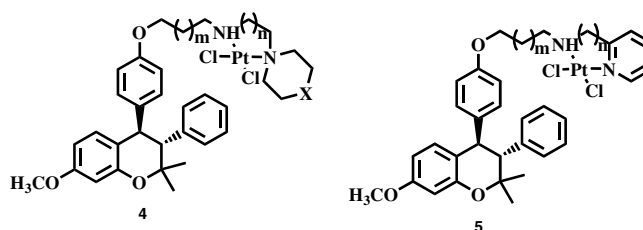


We demonstrate a fragment-based lead discovery method that combines site-directed ligand discovery with dynamic combinatorial chemistry to identify inhibitors of Aurora kinase A.

Synthesis and cytotoxic activity of benzopyran-based platinum(II) complexes

pp 3982–3987

Atul Gupta, Sanat K. Mandal, Valérie Leblanc, Caroline Descôteaux, Éric Asselin, Gervais Bérubé*



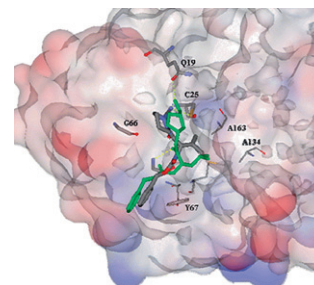
A series of benzopyran-based platinum complexes was synthesized as potential anticancer agents. The compounds were evaluated for their biological activity and showed significant in vitro cytotoxic activity in different breast cancer cell lines (MCF-7, MDA-MB-231, MDA-MB-436 and MDA-MB-468). Molecular modeling studies were performed to rationalize the results.

Effect of novel N-cyano-tetrahydro-pyridazine compounds, a class of cathepsin K inhibitors, on the bone resorptive activity of mature osteoclasts

pp 3988–3991

Seong Hwan Kim, Dong Joo Jhon, Jong Hwan Song, Jae Sung No, Nam Sook Kang*

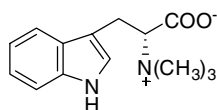
A novel cathepsin K inhibitor, [1-(2-cyano-tetrahydro-pyridazine-1-carbonyl)-2-methyl-propyl]-carbamic acid benzyl ester (**8**, IC₅₀ = 1 nM), inhibited the bone resorptive activity of mature osteoclasts.



Hypaphorine, an indole alkaloid from *Erythrina velutina*, induced sleep on normal mice

pp 3992–3994

Masaaki Ozawa, Kazuki Honda, Izumi Nakai, Akio Kishida, Ayumi Ohsaki*



hypaphorine (1)

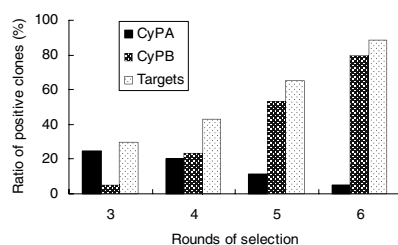
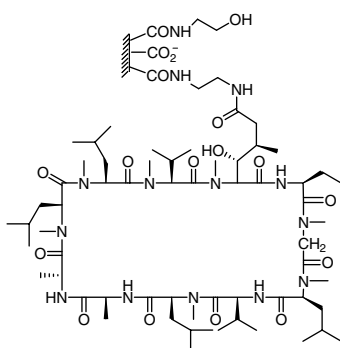
An indole alkaloid, hypaphorine (1) was isolated as a sleep inducing compound from the Brazilian medicinal plant, *Erythrina velutina* (Leguminosae). This compound was investigated for sleep promoting effects in mice, and significantly increased non-rapid eye movement (NREM) sleep time in mice during the first hour after its administration.

Simultaneous identification of multiple receptors of natural product using an optimized cDNA phage display cloning

pp 3995–3998

Qing-Li He, Hui Jiang, Feng Zhang, Hai-Bao Chen, Gong-Li Tang*

An optimized cDNA phage display cloning procedure is reported to simultaneously isolate two protein targets of cyclosporine A dependent on the binding affinity rather than the relative abundance in cells.

**Translocation of an Aib-containing peptide through cell membranes**

pp 3999–4001

Shun-ichi Wada*, Yasunari Hitora, Reiko Tanaka, Hidehito Urata

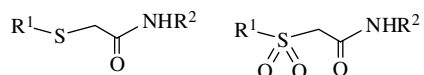
Peptide 1: Ac-U-N-I-I-U-P-L-L-U-P-I-C* (Ac:acetyl; U: α -aminoisobutyric acid)
 Peptide 2: Ac-A-N-I-I-A-P-L-L-A-P-I-C*

Aib (α -aminoisobutyric acid)-containing peptide 1 can translocate into cells and the replacement of Aib with Ala (2) inhibits the cellular uptake. The translocation of the Aib-containing peptide seems to involve an energy-independent process.

**Synthesis and evaluation of antitubercular activity of glycosyl thio- and sulfonyl acetamide derivatives**

pp 4002–4005

Samir Ghosh, Pallavi Tiwari, Shashi Pandey, Anup Kumar Misra*, Vinita Chaturvedi, Anil Gaikwad, Shalini Bhatnagar, Sudhir Sinha

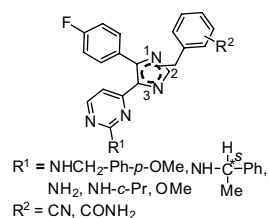


R^1 = mono-, disaccharides; R^2 = H, C_8H_{17} , $C_{12}H_{25}$

Synthesis and biological evaluation of trisubstituted imidazole derivatives as inhibitors of p38 α mitogen-activated protein kinase

pp 4006–4010

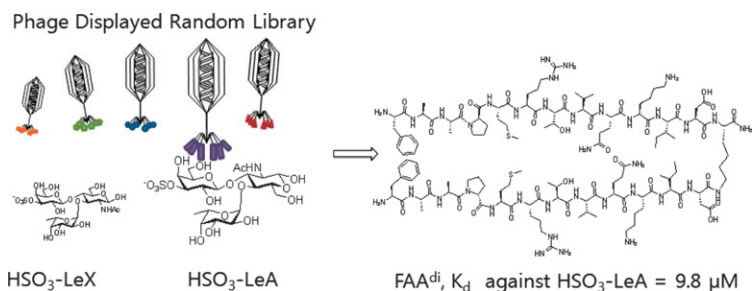
Dae-Kee Kim*, Jin-Hwi Lim, Jung A. Lee, Purushottam M. Dewang



Tentacle type peptides as artificial lectins against sulfated Lewis X and A

pp 4011–4014

Soonsil Hyun, Eun Hye Lee, Jihye Park, Jaehoon Yu*

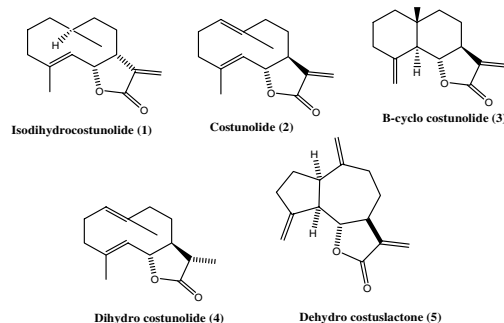


A new sesquiterpene lactone from the roots of *Saussurea lappa*: Structure–anticancer activity study

pp 4015–4017

A. Robinson, T. Vijay Kumar, E. Sreedhar, V. G. M. Naidu, Sistla Rama Krishna, K. Suresh Babu, P. V. Srinivas, J. Madhusudana Rao*

Phytochemical investigation of the roots of the *Saussurea lappa* yielded the new compound (**1**) along with known compounds (**2–5**). Anticancer active isolates and its derivatives were studied.

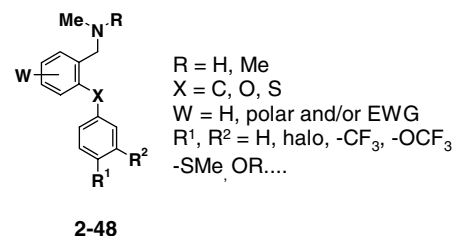


Designing rapid onset selective serotonin re-uptake inhibitors. 2: Structure–activity relationships of substituted (aryl)benzylamines

pp 4018–4021

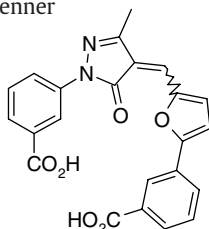
Donald S. Middleton*, Mark Andrews, Paul Glossop, Geoffrey Gymer, David Hepworth, Alan Jessiman, Patrick S. Johnson, Malcolm MacKenny, Michael J. Pitcher, Tony Rooker, Alan Stobie, Kim Tang, Paul Morgan

A series of substituted benzylamines **2–48** were prepared as part of a strategy to identify structurally differentiated and synthetically more accessible selective serotonin reuptake inhibitors, relative to clinical candidate **1**. In particular, **44** and **48**; demonstrated low nanomolar potency and good selectivity, in a structurally simplified template and, in vivo, very low V_{du}, significantly lower than **1**, and a more rapid T_{max}, consistent with our clinical objectives.



Discovery of new Gram-negative antivirulence drugs: Structure and properties of novel *E. coli* WaaC inhibitors pp 4022–4026

F. Moreau, N. Desroy, J. M. Genevard, V. Vongsouthi, V. Gerusz, G. Le Frallie, C. Oliveira, S. Floquet, A. Denis*, S. Escaich, K. Wolf, M. Busemann, A. Aschenbrenner

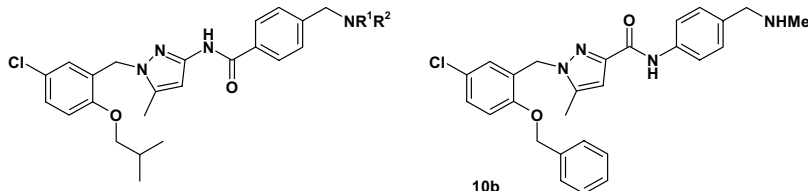


1a

WaaC is a new Gram-negative antivirulence target. The identification by virtual screening of the first micromolar inhibitor **1a** of this enzyme and the preliminary SAR generated from this family of aryl-pyrazolones is described.

Discovery of brain penetrant, soluble, pyrazole amide EP₁ receptor antagonists pp 4027–4032

Adrian Hall*, Andy Billinton, Alan K. Bristow, Susan H. Brown, Anita Chowdhury, Leanne Cutler, Gerard M. P. Giblin, Paul Goldsmith, Thomas G. Hayhow, Ian R. Kilford, Alan Naylor, Barry Passingham, D. Anthony Rawlings



4h: NR¹R² = NHEt

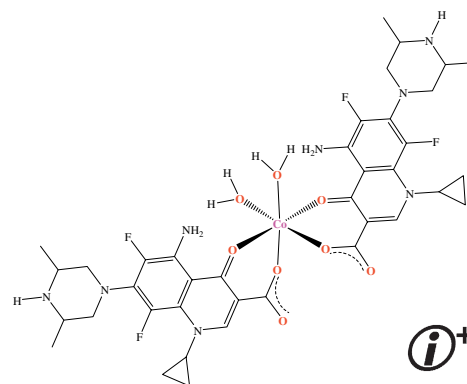
4j: NR¹R² = pyrrolidine

This letter details the discovery and characterisation of a series of amides and reversed amides as EP₁ antagonists. Compounds such as **4h**, **4j** and **10b** displayed good solubility, CNS penetration and in vivo pharmacokinetic parameters but failed to show satisfactory oral exposure.

Structure, antimicrobial activity and DNA-binding properties of the cobalt(II)–sparfloxacin complex pp 4033–4037

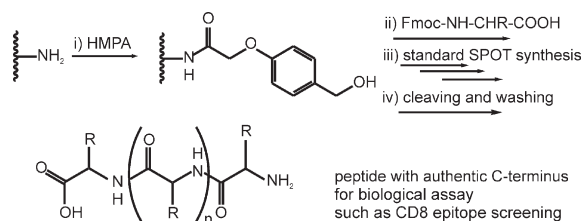
Eleni K. Efthimiadou, Alexandra Karaliota, George Psomas*

The synthesis, characterization, antimicrobial activity and DNA-binding properties of the mononuclear cobalt(II) complex with the third-generation quinolone sparfloxacin are reported.



Using hydroxymethylphenoxy derivatives with the SPOT technology to generate peptides with authentic C-termini pp 4038–4043

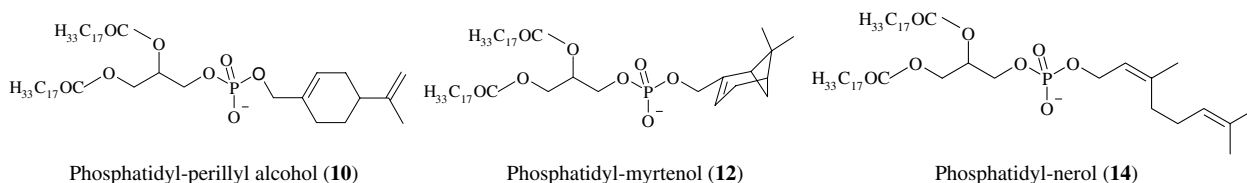
Bernhard Ay, Katja Landgraf, Mathias Streitz, Stephan Fuhrmann, Rudolf Volkmer, Prisca Boisguerlin*



The synthesis of the peptides cleavable peptides with authentic C-termini is reported and validated through T-cell stimulation by a synthesized CMV CD8 T-cell epitope.

Synthesis of phosphatidylated-monoterpene alcohols catalyzed by phospholipase D and their antiproliferative effects on human cancer cells pp 4044–4046

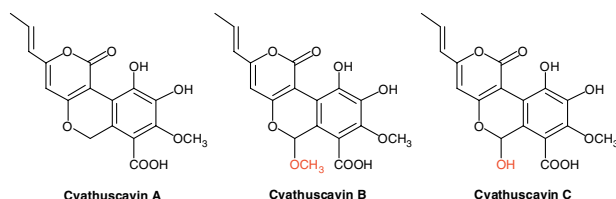
Yukihiro Yamamoto, Masashi Hosokawa*, Hideyuki Kurihara, Takashi Maoka, Kazuo Miyashita



Antiproliferative phosphatidylated-monoterpene alcohols were synthesized by phospholipase D catalyzed transphosphatidylation and their effects on human cancer cells were examined.

Cyathuscavins A, B, and C, new free radical scavengers with DNA protection activity from the Basidiomycete *Cyathus stercoreus* pp 4047–4050

Hahk-Soo Kang, Kyoung-Rok Kim, Eun-Mi Jun, Soon-Hye Park, Tae-Soo Lee, Joo-Won Suh, Jong-Pyung Kim*

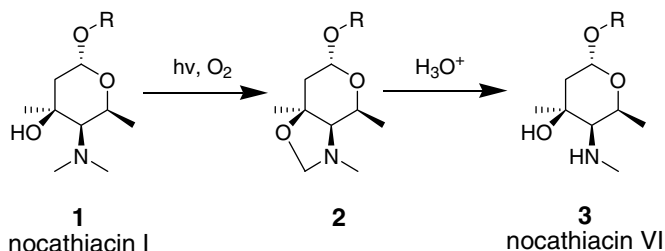


Cyathuscavins A–C (1–3) showing free radical scavenging activity and DNA protection activity were reported.

N-Demethylation of nocathiacin I via photo-oxidation

pp 4051–4053

Wenying Li*, Stella Huang, Xiaohong Liu, John E. Leet, Joseph L. Cantone, Kin S. Lam

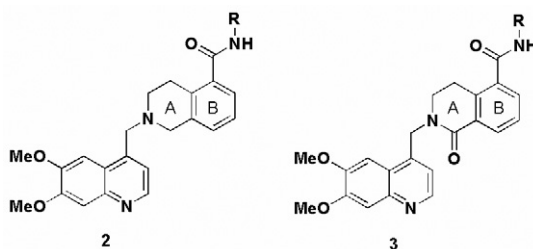


Irradiation of nocathiacin I (1) with UV light of 380 nm led to a cyclic product 2, which was hydrolyzed to yield the desired N-demethylation product, nocathiacin VI (3).

Discovery of novel 1,2,3,4-tetrahydroisoquinolines and 3,4-dihydroisoquinoline-1(2H)-ones as potent and selective inhibitors of KDR: Synthesis, SAR, and pharmacokinetic properties

pp 4054–4058

Deborah Choquette*, Yohannes Teffera, Anthony Polverino, Jean-Christophe Harmange



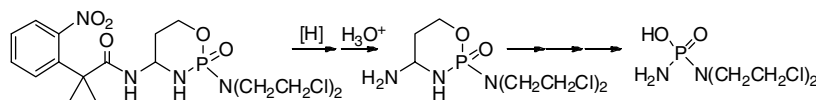
The synthesis, structure–activity relationships and pharmacokinetic properties of 1,2,3,4-tetrahydroisoquinolines (2) and 3,4-dihydroisoquinoline-1(2H)-ones (3), two novel classes of potent KDR inhibitors.



***N*-(2,2-Dimethyl-2-(2-nitrophenyl)acetyl)-4-aminocyclophosphamide as a potential bioreductively activated prodrug of phosphoramidate mustard**

pp 4059–4063

Yongying Jiang, Longqin Hu *

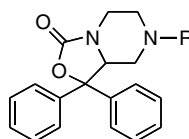


N-(2,2-Dimethyl-2-(2-nitrophenyl)acetyl)-4-aminocyclophosphamide isomers were synthesized as potential bioreductively activated prodrugs of phosphoramidate mustard and their mechanism of reductive activation was investigated.

Identifying structural features on 1,1-diphenyl-hexahydro-oxazolo[3,4-*a*]pyrazin-3-ones critical for Neuropeptide S antagonist activity

pp 4064–4067

Yanan Zhang, Brian P. Gilmour, Hernán A. Navarro, Scott P. Runyon *

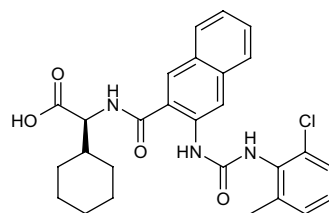


Description: Structural features important for Neuropeptide S antagonist activity have been identified through the synthesis and testing of a series of 7-substituted 1,1-diphenyl-hexahydro-oxazolo[3,4-*a*]pyrazin-3-ones.

Amino acid anthranilamide derivatives as a new class of glycogen phosphorylase inhibitors

pp 4068–4071

Karen A. Evans *, Yue H. Li, Frank T. Coppo, Todd L. Graybill, Maria Cichy-Knight, Mehul Patel, Jennifer Gale, Hu Li, Sara H. Thrall, David Tew, Francis Tavares, Stephen A. Thomson, James E. Weiel, Joyce A. Boucheron, Daphne C. Clancy, Andrea H. Epperly, Pamela L. Golden

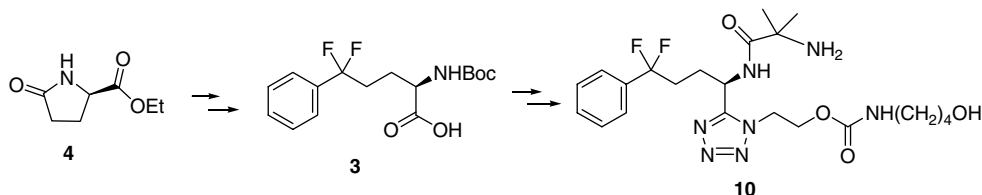


1c-(S): IC₅₀ (hLGPα) = 80 nM

(*D*)-2-*tert*-Butoxycarbonylamino-5,5-difluoro-5-phenyl-pentanoic acid: Synthesis and incorporation into the growth hormone secretagogues

pp 4072–4074

Jun Li *, Stephanie Y. Chen, Brian J. Murphy, Neil Flynn, Ramakrishna Seethala, Dorothy Slusarchyk, Mujing Yan, Paul Sleph, Hongjian Zhang, William G. Humphreys, William R. Ewing, Jeffrey A. Robl, David Gordon, Joseph A. Tino

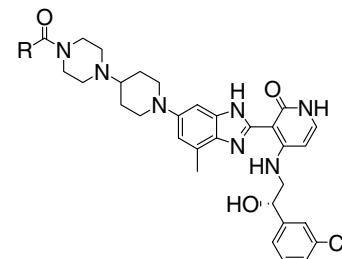


Balancing oral exposure with Cyp3A4 inhibition in benzimidazole-based IGF-IR inhibitors

pp 4075–4080

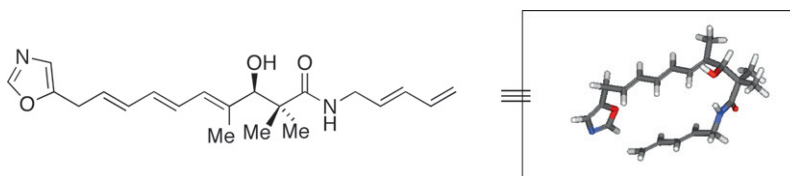
Kurt Zimmermann*, Mark D. Wittman, Mark G. Saulnier, Upender Velaparthi, David R. Langley, Xiaopeng Sang, David Frennesson, Joan Carboni, Aixin Li, Ann Greer, Marco Gottardis, Ricardo M. Attar, Zheng Yang, Praveen Balimane, Lorell N. Discenza, Dolatrai Vyas

3-(Benzimidazol-2-yl)-pyridine-2-one-based ATP competitive inhibitors of Insulin-like Growth Factor 1 Kinase (IGF-IR) were optimized for reduced Cyp3A4 inhibition and improved oral exposure. The use of malonate as methyl anion synthon via S_NAr reaction and double decarboxylation under mild conditions is demonstrated.

**On the antibiotic activity of oxazolomycin**

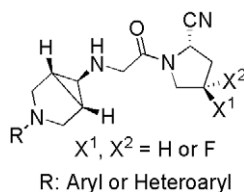
pp 4081–4086

Claire L. Bagwell, Mark G. Moloney*, Amber L. Thompson

**Discovery of conformationally rigid 3-azabicyclo[3.1.0]hexane-derived dipeptidyl peptidase-IV inhibitors**

pp 4087–4091

Jitendra A. Sattigeri*, Murugaiah M. S. Andappan, Kaushal Kishore, Srinivasan Thangathirupathy, Sinduja Sundaram, Shuchita Singh, Suchitra Sharma, Joseph A. Davis, Anita Chugh, Vinay S. Bansal

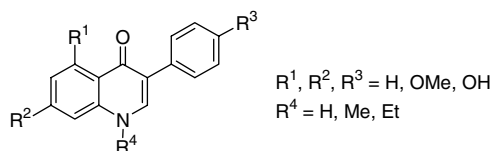


Novel and conformationally-rigid 3-azabicyclo[3.1.0]hexan-6-amine derivatives were investigated as P_2 amino partners in the cyanopyrrolidine class for DPP-IV inhibition.

Synthesis of azaisoflavones and their inhibitory activities of NO production in activated microglia

pp 4092–4094

Guo Hua Jin, Sang Keun Ha, Hye Min Park, Bomi Kang, Sun Yeou Kim, Hee-Do Kim, Jae-Ha Ryu, Raok Jeon*



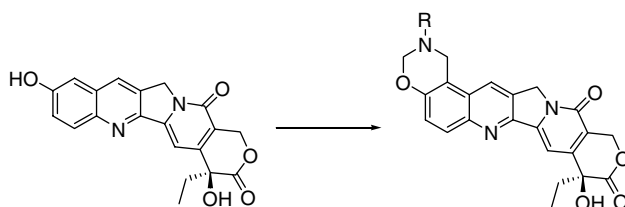
Synthesis of series of azaisoflavones and their inhibitory activities on the NO production in lipopolysaccharide activated microglia are reported.



Novel hexacyclic camptothecin derivatives. Part 1: Synthesis and cytotoxicity of camptothecins with an A-ring fused 1,3-oxazine ring

pp 4095–4097

Sheng Wang, Yuyan Li, Yonghui Liu, Aijun Lu*, Qidong You*



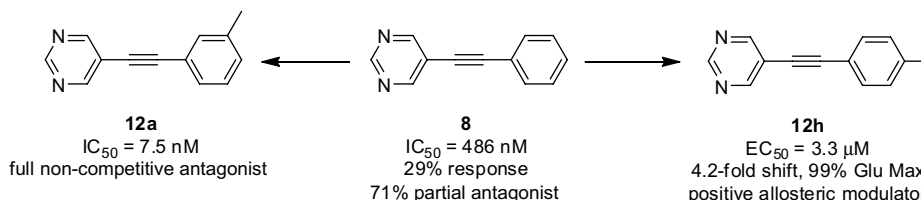
A novel series of A-ring modified hexacyclic camptothecin derivatives containing a 1,3-oxazine ring have been synthesized and evaluated for in vitro cytotoxicity.



Synthesis and SAR of a mGluR5 allosteric partial antagonist lead: Unexpected modulation of pharmacology with slight structural modifications to a 5-(phenylethynyl)pyrimidine scaffold

pp 4098–4101

Sameer Sharma, Alice L. Rodriguez, P. Jeffrey Conn, Craig W. Lindsley*

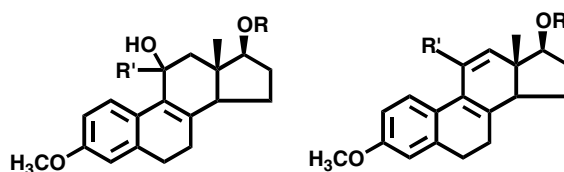


The synthesis and SAR of a mGluR5 allosteric partial antagonist lead **8** is described. We have identified 'molecular switches' on the distal phenyl ring that modulate modes of efficacy from mGluR5 partial antagonism in **8**, to full non-competitive antagonism **12a** to positive allosteric modulation **12h** by the addition of a 3- or 4-methyl group, respectively.

Synthesis and in vivo evaluation of 11-substituted estradiol derivatives as anti-implantation agents

pp 4102–4105

Indra Dwivedy, Atul Gupta*, Arvinder Grover, Vandana Srivastava, Man Mohan Singh, Suprabhat Ray

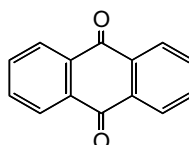


Synthesis of 11-substituted estradiol derivatives (**12–17**) has been carried out by the Grignard reaction with alkyl, allyl and benzyl halides on 17β-hydroxy-3-methoxy-11-oxo-estra-1,3,5(10),8(9)-tetraene (**10**). The novel compounds (**10** and **12–17**) were evaluated for their preliminary post-coital contraceptive (anti-implantation) activity in Sprague–Dawley rats.

Correlation between reduction potentials and inhibitions of Epstein–Barr virus activation by anthraquinone derivatives

pp 4106–4109

Junko Koyama*, Yu Nisino, Izumi Morita, Norihiro Kobayashi, Toshiyuki Osakai, Harukuni Tokuda

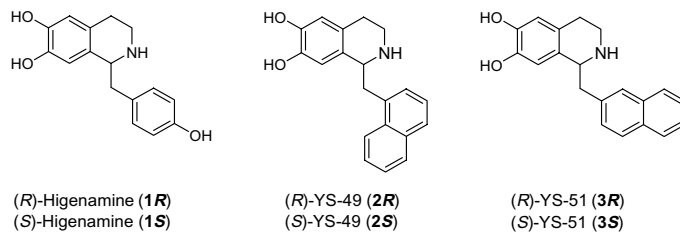


The structure–activity relationships between the inhibitory effects (logIC₅₀) and the first reduction potentials of anthraquinone derivatives are described.

Enantioselective synthesis of (*R*)-(+)- and (*S*)-(–)-higenamine and their analogues with effects on platelet aggregation and experimental animal model of disseminated intravascular coagulation

pp 4110–4114

Mi Kyung Pyo, Duck-Hyung Lee*, Doo-Hyun Kim, Ji-Hye Lee, Jong-Cheon Moon, Ki Churl Chang, Hye Sook Yun-Choi*

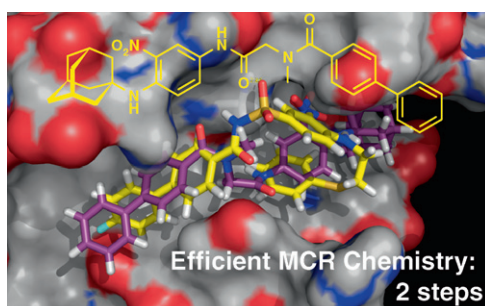


Six optically active tetrahydroisoquinoline alkaloids were synthesized and their effects on platelet anti-aggregation and experimental animal model of the disseminated intravascular coagulation (DIC) and multiple organ failure (MOF) were evaluated.

Isosteric exchange of the acylsulfonamide moiety in Abbott's Bcl-X_L protein interaction antagonist

pp 4115–4117

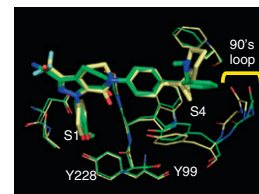
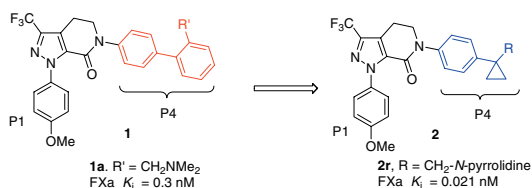
Alexander Dömling*, Walfrido Antuch, Barbara Beck, Vesna Schauer-Vukašinić



Achieving structural diversity using the perpendicular conformation of *alpha*-substituted phenylcyclopropanes to mimic the bioactive conformation of *ortho*-substituted biphenyl P4 moieties: Discovery of novel, highly potent inhibitors of Factor Xa

pp 4118–4123

Jennifer X. Qiao*, Daniel L. Cheney, Richard S. Alexander, Angela M. Smallwood, Sarah R. King, Kan He, Alan R. Rendina, Joseph M. Luetttgen, Robert M. Knabb, Ruth R. Wexler, Patrick Y. S. Lam

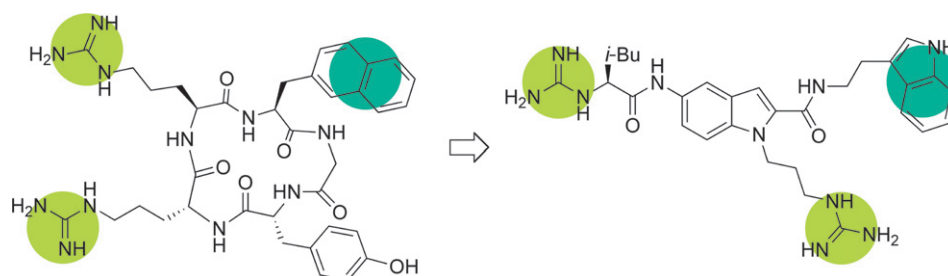


Ortho-substituted biphenyl moieties are widely used in drug design. We herein report a successful use of the perpendicular conformation of the *alpha*-substituted phenylcyclopropyl groups to mimic the aplanar, biologically active conformation of the *ortho*-substituted biphenyl moieties to achieve structural diversity. This is exemplified by the design and synthesis of a series of highly potent pyrazole-based Factor Xa (FXa) inhibitors bearing *alpha*-substituted phenylcyclopropyl P4 moieties. The designed perpendicular conformation was confirmed by the X-ray structure of FXa-bound compound **2r**. The potential structural basis for the high FXa potency in the phenylcyclopropyl P4 analogs and their improved FXa inhibitory activities compared with the biphenyl P4 counterparts are discussed.

Identification of novel non-peptide CXCR4 antagonists by ligand-based design approach

pp 4124–4129

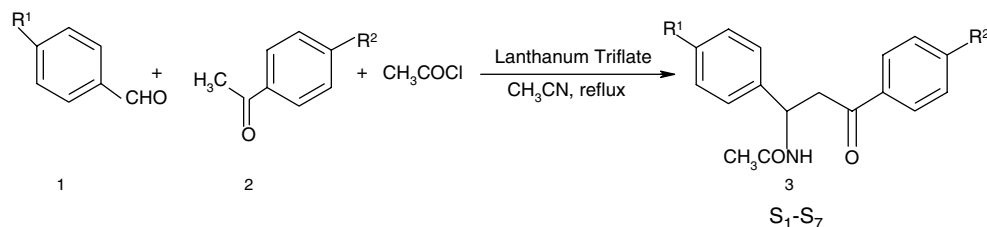
Satoshi Ueda, Manabu Kato, Shinsuke Inuki, Hiroaki Ohno, Barry Evans, Zi-xuan Wang, Stephen C. Peiper, Kazuki Izumi, Eiichi Kodama, Masao Matsuoka, Hideko Nagasawa, Shinya Oishi*, Nobutaka Fujii*



Reduction in post-prandial hyperglycemic excursion through α -glucosidase inhibition by β -acetamido carbonyl compounds

pp 4130–4132

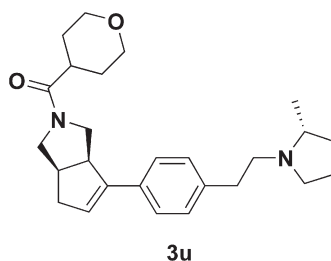
Ashok K. Tiwari*, Ravindra M. Kumbhare, Sachin B. Agawane, Amtul Z. Ali, K. Vijay Kumar



Novel H₃ receptor antagonists with improved pharmacokinetic profiles

pp 4133–4136

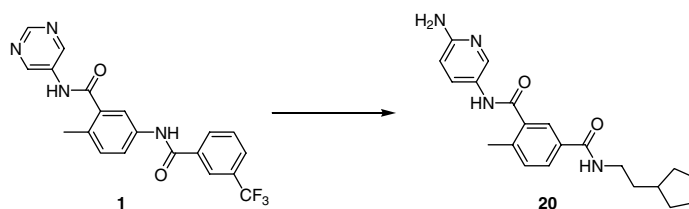
Vincent J. Santora*, Jonathan A. Covell, Rena Hayashi, Brian J. Hofilena, Jason B. Ibarra, Michelle D. Pulley, Michael I. Weinhouse, Graeme Semple, Albert Ren, Guilherme Pereira, Jeffrey E. Edwards, Marissa Suarez, John Frazer, William Thomsen, Erin Hauser, Jodie Lorea, Andrew J. Grottick



Discovery of a potent and selective c-Kit inhibitor for the treatment of inflammatory diseases

pp 4137–4141

Ning Chen*, Roland W. Bürl, Susana Neira, Randall Hungate, Dawei Zhang, Violeta Yu, Yen Nguyen, Yanyan Tudor, Matthew Plant, Shaun Flynn, Kristin L. Meagher, Matthew R. Lee, Xuxia Zhang, Andrea Itano, Michael Schrag, Yang Xu, Gordon Y. Ng, Essa Hu



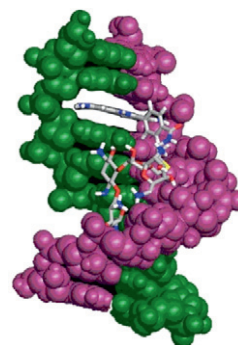
From the screening of our kinase-preferred library, we have identified **1** as a potent small-molecule c-Kit inhibitor. Extensive structure–activity relationship study, incorporated with modification on PKDM properties have led to a selective c-Kit inhibitor **20**. In an in vivo murine model of mast cell activation, **20** blocked the SCF-induced histamine release with an EC₅₀ of 26 nM.

Molecular recognition of a DNA:RNA hybrid: Sub-nanomolar binding by a neomycin–methidium conjugate

pp 4142–4145

Nicholas N. Shaw, Hongjuan Xi, Dev P. Arya*

The synthesis and binding studies of a neomycin conjugate capable of binding DNA:RNA hybrids in the sub-nanomolar range is presented.



pp 4146–4149


O=C(O)[C@H](Nc1c2c(c3ccccc13)nc4ccccc24)c5c(Br)c(=O)c6ccccc56

15c

pp 4150–4153



pp 4154–4158


 Xaa= Ile, *allo*-Ile
 Lys, Lys(Z)



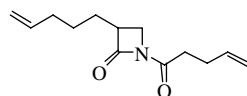
pp 4159–4162

Rc1ccc2c(c1)c(c3ccccc23)N(Xaa)

3-Alkenyl-2-azetidinones as fatty acid amide hydrolase inhibitors

pp 4163–4167

Allan Urbach, Giulio G. Muccioli, Eric Stern, Didier M. Lambert, Jacqueline Marchand-Brynaert*

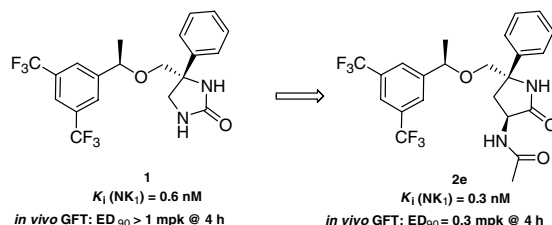
 $IC_{50} = 4.5 \mu M$ (FAAH) $IC_{50} = 657 \mu M$ (MGL)

The evaluation of lipophilic 2-azetidinone derivatives as FAAH/MGL potential inhibitors is reported for the first time. One compound (**9c**) is a good and selective inhibitor of FAAH.

**Discovery of a novel, potent and orally active series of γ -lactams as selective NK₁ antagonists**

pp 4168–4171

Sunil Paliwal*, Gregory A. Reichard, Sapna Shah, Michelle Laci Wroblewski, Cheng Wang, Carmine Stengone, Hon-Chung Tsui, Dong Xiao, Ruth A. Duffy, Jean E. Lachowicz, Amin A. Nomeir, Geoffrey B. Varty, Neng-Yang Shih



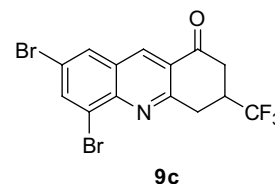
Replacement of nitrogen of the cyclic urea lead **1** with a carbon led to identification of a more potent and orally efficacious γ -lactam series of selective NK₁ antagonists. Optimization of the γ -lactam series provided several compounds (e.g., **2e**) with high affinity and excellent oral CNS activity.

Novel fluorinated acridone derivatives. Part 1: Synthesis and evaluation as potential anticancer agents

pp 4172–4176

Olugbeminiyi O. Fadeyi, Saudat T. Adamson, E. Lewis Myles, Cosmas O. Okoro*

We report on the synthesis of a novel series of fluorinated acridones from 5-trifluoromethyl-1,3-cyclohexanedione. The cytotoxic activities of the compounds were studied in several cancer cells. Compounds **9a**, **9c**, **9e**, **9f**, and **9h** exhibited significant anticancer activities in selected cell lines. Compound **9c** is the most active showing GI₅₀ that ranged in values from 0.13 to 26 μM , covering a wide range of cancer cell lines.

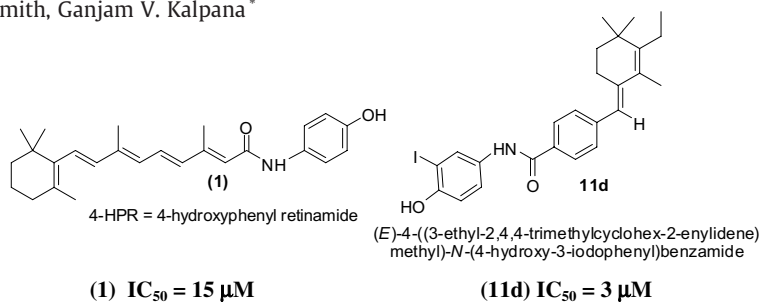


Cancer cell line

MCF7: GI₅₀ = 130 nMIGROV1: GI₅₀ = 1.29 μM **Design, synthesis of novel peptidomimetic derivatives of 4-HPR for rhabdoid tumors**

pp 4177–4180

Bhaskar C. Das*, Melissa E. Smith, Ganjam V. Kalpana*



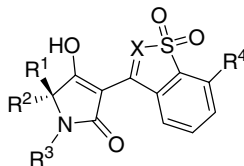
Novel peptidomimetic derivatives of 4-HPR with substitution of the alkene backbone with a rigid ring structure retains activity against rhabdoid tumor cells.



Structure-based design, synthesis, and biological evaluation of 1,1-dioxoisothiazole and benzo[*b*]thiophene-1,1-dioxide derivatives as novel inhibitors of hepatitis C virus NS5B polymerase

pp 4181–4185

Sun Hee Kim^{*}, Martin T. Tran, Frank Ruebsam, Alan X. Xiang, Benjamin Ayida, Helen McGuire, David Ellis, Julie Blazel, Chinh V. Tran, Douglas E. Murphy, Stephen E. Webber, Yuefen Zhou, Amit M. Shah, Mei Tsan, Richard E. Showalter, Rupal Patel, Alberto Gobbi, Laurie A. LeBrun, Darian M. Bartkowski, Thomas G. Nolan, Daniel A. Norris, Maria V. Sergeeva, Leo Kirkovsky, Qiang Zhao, Qing Han, Charles R. Kissinger



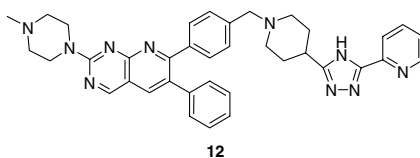
1,1-Dioxoisothiazole and benzo[*b*]thiophene-1,1-dioxide analogs were synthesized and tested as HCV NS5B polymerase inhibitors. Their PK properties were also evaluated.



Discovery of potent and cell-active allosteric dual Akt 1 and 2 inhibitors

pp 4186–4190

Tony Siu^{*}, Jun Liang, Jeannie Arruda, Yiwei Li, Raymond E. Jones, Deborah Defeo-Jones, Stanley F. Barnett, Ronald G. Robinson



12

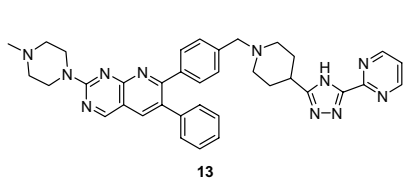
Akt 1/2 IC₅₀ (nM) = 9/27

Cell Akt 1/2 IC₅₀ (nM) = 36/52

The design and synthesis of potent and cell-active allosteric dual Akt 1 and 2 inhibitors devoid of hERG activity

pp 4191–4194

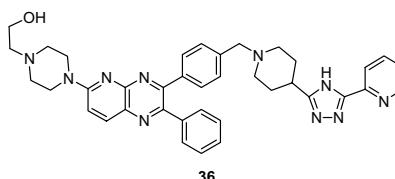
Tony Siu^{*}, Yiwei Li, Johnny Nagasawa, Jun Liang, Lida Tehrani, Peter Chua, Raymond E. Jones, Deborah Defeo-Jones, Stanley F. Barnett, Ronald G. Robinson



13

Cell Akt 1/2 IC₅₀ (nM) = 36/52

hERG IC₅₀ (nM) = > 10000



36

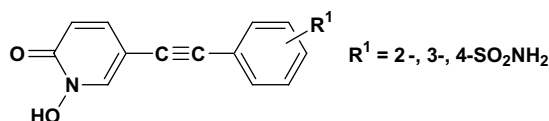
Cell Akt 1/2 IC₅₀ (nM) = 12/48

hERG IC₅₀ (nM) = > 10000

Synthesis and biological evaluation of 1-(benzenesulfonamido)-2-[5-(*N*-hydroxypyridin-2(1*H*)-one)]acetylene regioisomers: A novel class of 5-lipoxygenase inhibitors

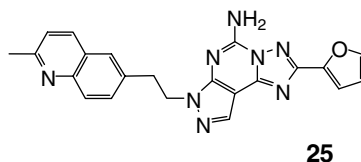
pp 4195–4198

Morshed Alam Chowdhury, Hua Chen, Khaled R. A. Abdellatif, Ying Dong, Kenneth C. Petruk, Edward E. Knaus^{*}



Biaryl and heteroaryl derivatives of SCH 58261 as potent and selective adenosine A_{2A} receptor antagonists pp 4199–4203

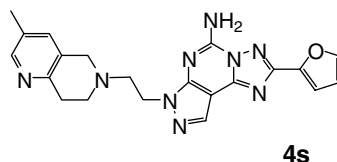
Unmesh Shah, Craig D. Boyle *, Samuel Chackalamannil, Bernard R. Neustadt, Neil Lindo, William J. Greenlee, Carolyn Foster, Leyla Arik, Ying Zhai, Kwokei Ng, Shiyong Wang, Angela Monopoli, Jean E. Lachowicz



The design and synthesis of biaryl and heteroaryl analogs of the adenosine A_{2A} receptor antagonist SCH 58261 are reported. Derivatives such as the quinoline **25** improve upon the pharmacological and pharmacokinetic properties of the parent phenethyl compound SCH 58261.

Design, synthesis, and evaluation of fused heterocyclic analogs of SCH 58261 as adenosine A_{2A} receptor antagonists pp 4204–4209

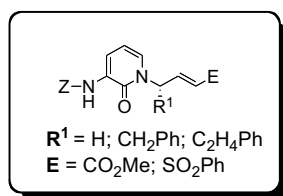
Unmesh Shah, Claire M. Lankin, Craig D. Boyle *, Samuel Chackalamannil, William J. Greenlee, Bernard R. Neustadt, Mary E. Cohen-Williams, Guy A. Higgins, Kwokei Ng, Geoffrey B. Varty, Hongtao Zhang, Jean E. Lachowicz



The design and synthesis of fused heterocyclic analogs of the adenosine A_{2A} receptor antagonist SCH 58261 are reported. Derivatives such as the tetrahydronaphthyridine **4s** not only improve upon the pharmacological and pharmacokinetic properties of SCH 58261, but also have high aqueous solubility.

Design and synthesis of novel 2-pyridone peptidomimetic falcipain 2/3 inhibitors pp 4210–4214

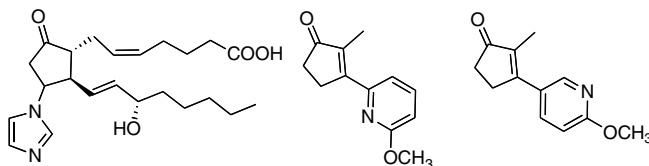
Edite Verissimo, Neil Berry, Peter Gibbons, M. Lurdes S. Cristiano, Philip J. Rosenthal, Jiri Gut, Stephen A. Ward, Paul M. O'Neill *



Here we present the design and synthesis of novel peptidomimetic falcipain inhibitors that should react as classical 'Michael acceptors' and in which the incorporation of a rigid scaffold moiety to define a conformation is evaluated for antimalarial activity.

Synthesis and screening of small molecule inhibitors of anthrax edema factor pp 4215–4218

Maria Estrella Jimenez, Kathryn Bush, Jennifer Pawlik, Laurie Sower, Johnny W. Peterson, Scott R. Gilbertson *



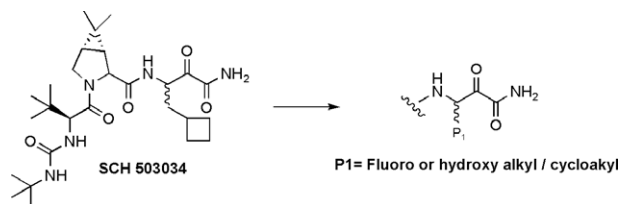
The development of series of small molecule inhibitors of anthrax edema factor is reported.



Hepatitis C virus NS3-4A serine protease inhibitors: SAR of new P1 derivatives of SCH 503034

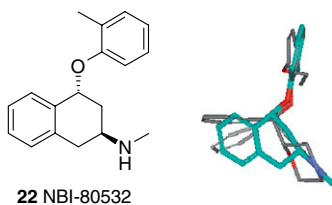
pp 4219–4223

S. Bogen*, A. Arasappan*, W. Pan, S. Ruan, A. Padilla, A. K. Saksena, V. Girijavallabhan, F. G. Njoroge

**Discovery of a potent, selective, and less flexible selective norepinephrine reuptake inhibitor (sNRI)**

pp 4224–4227

Dongpei Wu, Joseph Pontillo, Brett Ching, Sarah Hudson*, Yinghong Gao, Beth A. Fleck, Kathleen Gogas, Warren S. Wade*

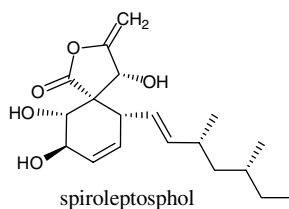


A rigid ring-constrained norepinephrine reuptake inhibitor with potent functional activity at the transporter ($IC_{50} = 8$ nM) was used to develop a model for the distance and orientation of key features necessary for interaction with NET.

**Spiroleptoshol isolated from *Leptosphaeria doliolum***

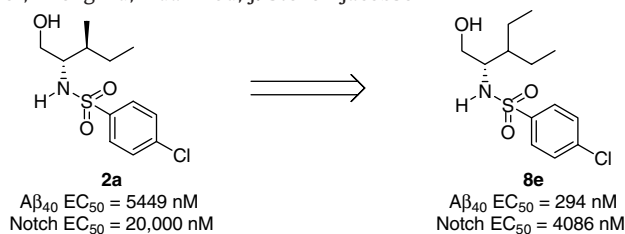
pp 4228–4231

Masaru Hashimoto*, Taro Tsushima, Takanori Murakami, Masahiro Nomiya, Noboru Takada, Kazuaki Tanaka

**Discovery of a novel series of Notch-sparing γ -secretase inhibitors**

pp 4232–4236

Anthony Kreft*, Boyd Harrison, Suzan Aschmies, Kevin Atchison, David Casebier, Derek C. Cole, George Diamantidis, John Ellingboe, Diane Hauze, Yun Hu, Donna Huryn, Mei Jin, Dennis Kubrak, Peimin Lu, Joseph Lundquist, Charles Mann, Robert Martone, William Moore, Aram Oganesian, Alex Porte, Dave R. Riddell, June Sonnenberg-Reines, Joseph R. Stock, Shaiu-Ching Sun, Erik Wagner, Kevin Woller, Zheng Xu, Hua Zhou, J. Steven Jacobsen

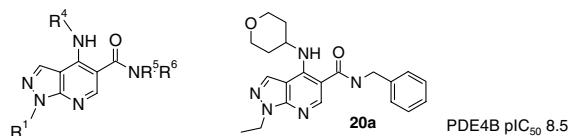


Lead optimization studies of Notch-sparing GSI **2a** led to the discovery of analog **8e** with improved γ -secretase inhibitory potency and Notch-sparing selectivity.

Pyrazolopyridines as a novel structural class of potent and selective PDE4 inhibitors

pp 4237–4241

J. Nicole Hamblin^{*}, Tony D. R. Angell, Stuart P. Ballantine, Caroline M. Cook, Anthony W. J. Cooper, John Dawson, Christopher J. Delves, Paul S. Jones, Mika Lindvall, Fiona S. Lucas, Charlotte J. Mitchell, Margarete Y. Neu, Lisa E. Ranshaw, Yemisi E. Solanke, Don O. Somers, Joanne O. Wiseman



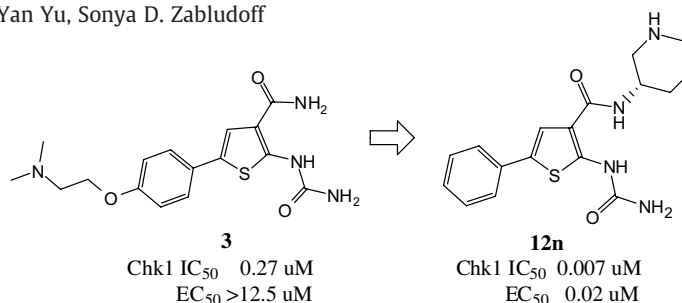
A series of pyrazolo[3,4-*b*]pyridine-5-carboxamides has been identified as potent inhibitors of PDE4. The SAR has been explored and these studies have highlighted compound **20a** which shows good potency, selectivity and rat PK suitable for oral dosing. The crystal structure of **20a** bound to PDE4B is also described.

Discovery of a novel class of 2-ureido thiophene carboxamide checkpoint kinase inhibitors

pp 4242–4248

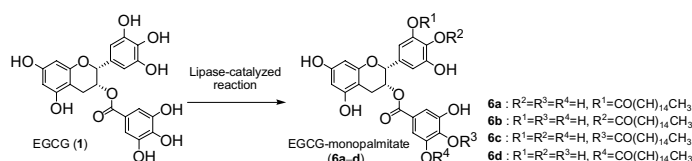
James W. Janetka^{*}, Lynsie Almeida, Susan Ashwell, Patrick J. Brassil, Kevin Daly, Chun Deng, Thomas Gero, Roberta E. Glynn, Candice L. Horn, Stephanos Ioannidis, Paul Lyne, Nicholas J. Newcombe, Vibha B. Oza, Martin Pass, Stephanie K. Springer, Mei Su, Dorin Toader, Melissa M. Vasbinder, Dingwei Yu, Yan Yu, Sonya D. Zabludoff

A series of thiophene carboxamide checkpoint kinase inhibitors (**3**) were discovered through HTS and optimized for cellular potency (**12n**).

**Enhanced anti-influenza A virus activity of (–)-epigallocatechin-3-O-gallate fatty acid monoester derivatives: Effect of alkyl chain length**

pp 4249–4252

Shuichi Mori, Shinya Miyake, Takayoshi Kobe, Takaaki Nakaya, Stephen D. Fuller, Nobuo Kato, Kunihiro Kaihatsu^{*}



A series of fatty acid monoester derivatives of (–)-epigallocatechin-3-O-gallate (EGCG) were prepared by one-pot lipase-catalyzed transesterification. The introduction of long alkyl chains enhanced anti-influenza A/PR8/34 (H1N1) virus activity up to 24-fold relative to native EGCG.

OTHER CONTENTS**Corrigenda**

pp 4253–4254

Summary of instructions to authors

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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