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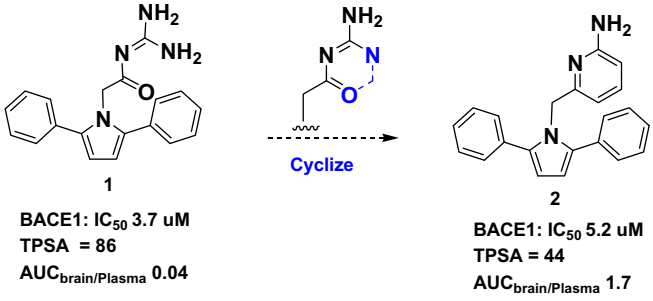
Contents

ARTICLES

Novel pyrrolyl 2-aminopyridines as potent and selective human β-secretase (BACE1) inhibitors pp 2068–2073

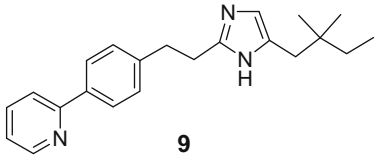
Michael S. Malamas*, Keith Barnes, Yu Hui, Matthew Johnson, Frank Lovering, Jeff Condon, William Fobare, William Solvibile, Jim Turner, Yun Hu, Eric S. Manas, Kristi Fan, Andrea Olland, Rajiv Chopra, Jonathan Bard, Menelas N. Pangalos, Peter Reinhart, Albert J. Robichaud

The 2-aminopyridine moiety is a bioisosteric replacement of the acylguanidine moiety with a lower Topological Polar Surface Area (TPSA) value and superior brain penetration.



Synthesis and SAR of derivatives based on 2-biarylethylimidazole as bombesin receptor subtype-3 (BRS-3) agonists for the treatment of obesity pp 2074–2077

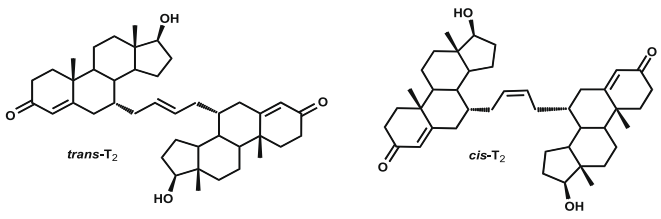
Jian Liu*, Shuwen He, Tianying Jian, Peter H. Dobbelaar, Iyassu K. Sebhat, Linus S. Lin, Allan Goodman, Cheng Guo, Peter R. Guzzo, Mark Hadden, Alan J. Henderson, Kevin Pattamana, Megan Ruenz, Bruce J Sargent, Brian Swenson, Larry Yet, Constantin Tamvakopoulos, Qianping Peng, Jie Pan, Yanqing Kan, Oksana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



A series of 2-biarylethylimidazole analogues were synthesized as BRS-3 selective agonists. Compound **9** was identified as a potent and selective BRS-3 agonist, which lowers food intake and body weight in rodents when administrated orally.

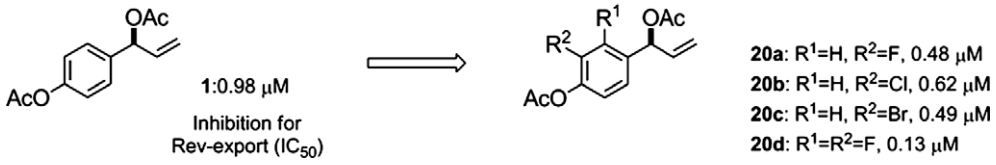
First synthesis of separable isomeric testosterone dimers showing differential activities on prostate cancer cells pp 2078–2081

Dominic Bastien, Valérie Leblanc, Éric Asselin, Gervais Bérubé*



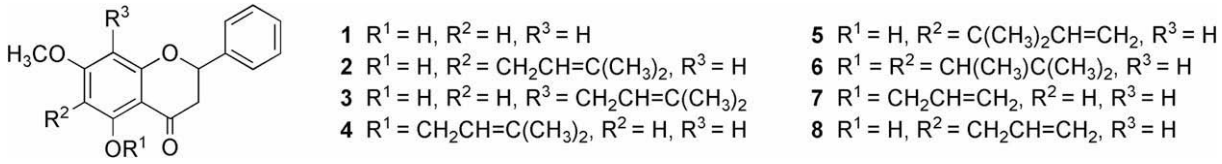
The synthesis of two testosterone dimers is reported. The synthesis led to two separable isomeric dimers (*trans* and *cis*, 2:1). X-ray diffraction crystallography confirmed the structure of the minor isomer. MTT assays showed that the *cis* dimer has the best activity against human prostate cancer cell lines.

Halogenated analogs of 1′-acetoxychavicol acetate, Rev-export inhibitor from *Alpinia galanga*, designed from mechanism of action **pp 2082–2085**
Satoru Tamura, Atsushi Shiomi, Tominori Kimura, Nobutoshi Murakami*



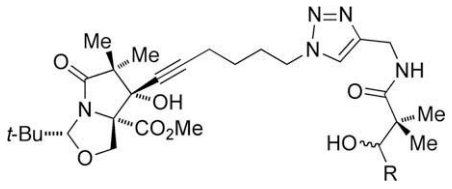
Rational design based on the mechanism of action disclosed the four halogenated analogs (**20a**–**20d**) as the more potent Rev-export inhibitors than 1′-acetoxychavicol acetate (**1**).

Efficient microwave-assisted prenylation of pinostrobin and biological evaluation of its derivatives as antitumor agents **pp 2086–2089**
Hadi Poerwono, Shigeru Sasaki, Yoshiyuki Hattori, Kimio Higashiyama*



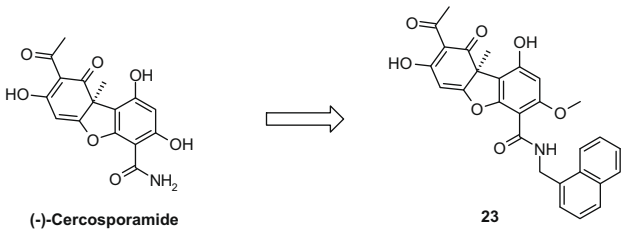
Pinostrobin (**1**) was converted to its prenylated or allylated derivatives (**2**–**8**) using a microwave reactor. All resulting compounds showed cytotoxic activity toward a panel of human tumor cell lines with significantly lower IC_{50} (μM) values than compound **1**.

Oxazolomycins: Natural product lead structures for novel antibacterials by click fragment conjugation **pp 2090–2094**
Claire L. Bagwell, Mark G. Moloney*, Muhammad Yaqoob

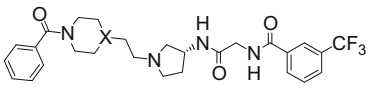


Conjugation of lactams and amides by Click homologation gives bioactive mimics of oxazolomycin.

Discovery of a novel selective PPARγ modulator from (−)-Cercosporamide derivatives **pp 2095–2098**
Akihiro Furukawa*, Tsuyoshi Arita, Susumu Satoh, Kenji Wakabayashi, Shinko Hayashi, Yumi Matsui, Kazushi Araki, Masanori Kuroha, Jun Ohsumi



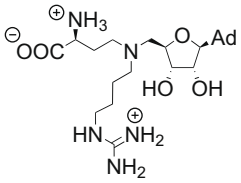
Synthesis and biological evaluation of 3-aminopyrrolidine derivatives as CC chemokine receptor 2 antagonists **pp 2099–2102**
Jee Woong Lim*, Youna Oh, Jong-Hoon Kim, Min-Ho Oak, Yongho Na, Jung-Ok Lee, Seung-Woo Lee, Heeyeong Cho, Woo-Kyu Park, Gildon Choi, Jongmin Kang*



X = C or N
R = H or halogen

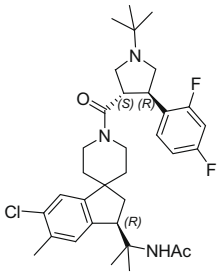
3-Aminopyrrolidine derivatives were synthesized and evaluated as potent chemokine receptor 2 (CCR2) antagonists.

Toward the development of potent and selective bisubstrate inhibitors of protein arginine methyltransferases **pp 2103–2105**
James Dowden*, Wei Hong, Richard V. Parry, Richard A. Pike, Stephen G. Ward



Non-reactive amine analogues of (*S*)-adenosyl methionine (AdoMet) bearing guanidine functionality were found to be potent inhibitors of PRMT1 (IC_{50} of ~3–6 μM) but weak inhibitors of the lysine methyltransferase SET7 (IC_{50} >100 μM).

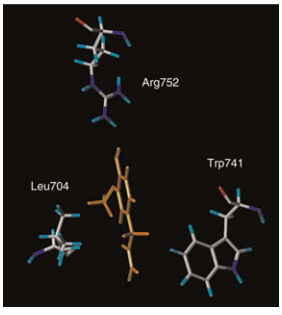
Discovery of a spiroindane based compound as a potent, selective, orally bioavailable melanocortin subtype-4 receptor agonist **pp 2106–2110**
Shuwen He*, Zhixiong Ye, Peter H. Dobbelaar, Iyassu K. Sebhat, Liangqin Guo, Jian Liu, Tianying Jian, Yingjie Lai, Christopher L. Franklin, Raman K. Bakshi, James P. Dellureficio, Qingmei Hong, Nancy N. Tsou, Richard G. Ball, Doreen E. Cashen, William J. Martin, David H. Weinberg, Tanya MacNeil, Rui Tang, Constantin Tamvakopoulos, Qianping Peng, Randy R. Miller, Ralph A. Stearns, Howard Y. Chen, Airu S. Chen, Alison M. Strack, Tung M. Fong, D. Euan MacIntyre, Matthew J. Wyvratt Jr., Ravi P. Nargund



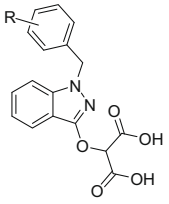
1

We report the design, synthesis and properties of spiroindane based compound **1**, a potent, selective, orally bioavailable, non-peptide melanocortin subtype-4 receptor agonist. Compound **1** shows excellent erectogenic activity in the rodent models.

Effect of essential oils, such as raspberry ketone and its derivatives, on antiandrogenic activity based on in vitro reporter gene assay **pp 2111–2114**
Yoshihisa Ogawa, Miki Akamatsu, Yudai Hotta, Akifumi Hosoda, Hiroto Tamura*



Synthesis and biological evaluations of novel bendazac lysine analogues as potent anticataract agents **pp 2115–2118**
Hong Shen, Shaohua Gou*, Jianping Shen, Yanqin Zhu, Yindi Zhang, Xuetai Chen*



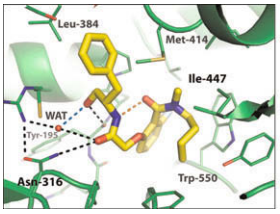
13-17

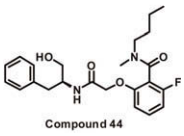
13: R=H
14: R=*p*-CH_3
15: R=*m*-F
16: R=*m*-Cl
17: R=*p*-Cl

Novel bendazac analogues and their salts have been designed, prepared and biological evaluated. Most of the resulting compounds showed good aqueous solubility and had potent protective activity against the oxidative damage to isolated lenses.

Inhibitors of hepatitis C virus polymerase: Synthesis and characterization of novel 2-oxy-6-fluoro-*N*-((*S*)-1-hydroxy-3-phenylpropan-2-yl)-benzamides **pp 2119–2124**
Cliff C. Cheng*, Gerald W. Shipps Jr., Zhiwei Yang, Noriyuki Kawahata, Charles A. Lesburg, José S. Duca, Jamie Bandouveres, Jack D. Bracken, Chuan-kui Jiang, Sony Agrawal, Eric Ferrari, H.-C. Huang

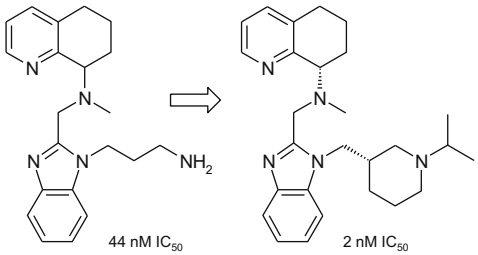
The crystal structure of NS5B (green) complexed with **44** (yellow). The intramolecular hydrogen bond is shown in orange. The intermolecular hydrogen bond from the inhibitor's hydroxyl group to the bound water molecule (labeled WAT) is shown in blue. The hydrogen bond network surrounding this water is shown in black. The coordinates have been deposited in the Protein Data Bank (Berman et. al., 2000) with accession code 3lkh. This figure was prepared using PyMOL (Delano, 2002). The mechanism of action of compound **44** has shown fully active (IC_{50} = 0.6 μM) against primer-initiated RNA synthesis involving multiple cycles of initiation and elongation catalyzed by NS5B, it was ineffective (IC_{50} >200 μM) in inhibiting the elongation of preformed NS5B enzyme–primer–template complexes.





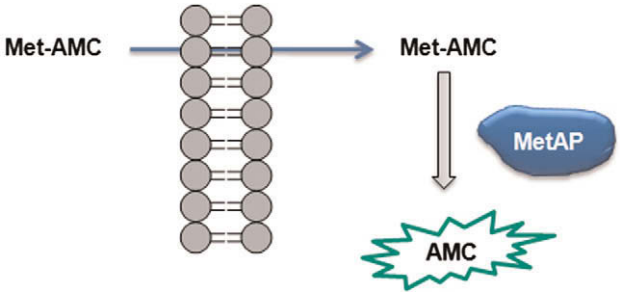
Compound 44

Novel N-substituted benzimidazole CXCR4 antagonists as potential anti-HIV agents **pp 2125–2128**
John F. Miller*, Elizabeth M. Turner, Kristjan S. Gudmundsson, Stephen Jenkinson, Andrew Spaltenstein, Michael Thomson, Pat Wheelan



The lead optimization of a series of N-substituted benzimidazole CXCR4 antagonists is described. Side chain modifications and stereochemical optimization led to substantial improvements in potency and protein shift to afford compounds with low nanomolar anti-HIV activity.

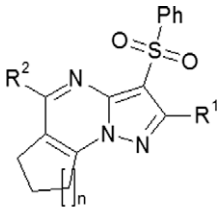
A cell-based assay that targets methionine aminopeptidase in a physiologically relevant environment **pp 2129–2132**
Sergio C. Chai, Qi-Zhuang Ye*



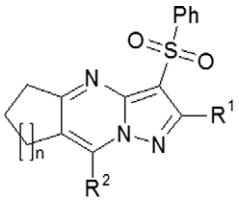
Synthesis of cycloalkane-annelated 3-phenylsulfonyl-pyrazolo[1,5-*a*]pyrimidines and their evaluation as 5-HT$_6$ receptor antagonists pp 2133–2136

Alexandre V. Ivachtchenko, Dmitri E. Dmitriev, Elena S. Golovina, Elena S. Dubrovskaya, Madina G. Kadieva, Angela G. Koryakova, Volodymyr M. Kysil, Oleg D. Mitkin, Sergey E. Tkachenko, Ilya M. Okun*, Anton A. Vorobiov

We synthesized and investigated the cycloalkane-annelated 3-phenyl-pyrazolo-[1,5-*a*]pyrimidine systems, **1** and **2**, as a novel scaffold for the development of highly selective and potent antagonists of the 5-HT$_6$ receptors.



1

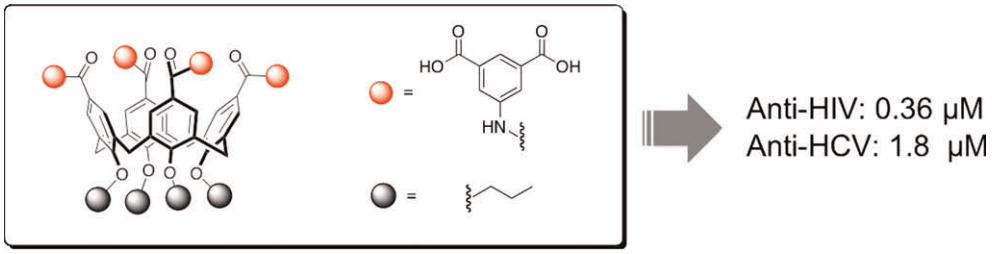


2

1, 2: R^1 = CH_3, SCH_3, OCH_2CH_2OH; R^2 = H, CH_3; n = 1, 2.

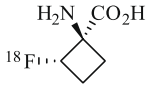
Discovery of a synthetic dual inhibitor of HIV and HCV infection based on a tetrabutoxy-calix[4]arene scaffold pp 2137–2139

Lun K. Tsou, Ginger E. Dutschman, Elizabeth A. Gullen, Maria Telpoukhovskaia, Yung-Chi Cheng*, Andrew D. Hamilton*



Synthesis and biological evaluation of *anti*-1-amino-2-[^{18}F]fluoro-cyclobutyl-1-carboxylic acid (*anti*-2-[^{18}F]FACBC) in rat 9L gliosarcoma pp 2140–2143

Weiping Yu, Larry Williams, Vernon M. Camp, Jeffrey J. Olson, Mark M. Goodman*

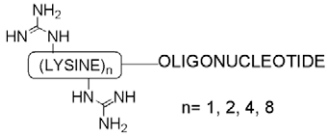


anti-2-[^{18}F]FACBC **9**

anti-2-FACBC **9**, the constitutional isomer of *anti*-FACBC, has been synthesized and [^{18}F] radiofluorinated in 30% decay-corrected yield. Biological evaluation using rat 9L gliosarcoma model showed that this tracer entered tumor cells via multiple amino acid transport systems including system L and system A in vitro with high tumor to brain ratio of 26:1 at 120 min post-injection in vivo.

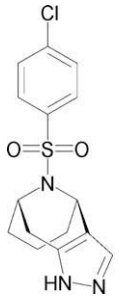
Stepwise synthesis of oligonucleotide–peptide conjugates containing guanidinium and lipophilic groups in their 3′-termini pp 2144–2147

Santiago Grijalvo, Montserrat Terrazas, Anna Aviñó, Ramón Eritja*



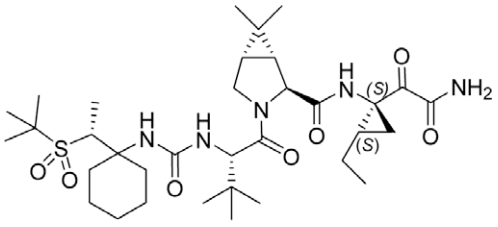
The synthesis of oligonucleotides having amino, guanidinium or lipophilic groups at the 3′-end is reported.

Discovery of sulfonamide–pyrazole γ-secretase inhibitors **pp 2148–2150**
Matthew N. Mattson, Martin L. Neitzel, David A. Quincy, Christopher M. Semko, Albert W. Garofalo, Pamela S. Keim, Andrei W. Konradi*, Michael A. Pleiss, Hing L. Sham, Elizabeth F. Brigham, Erich G. Goldbach, Hongbin Zhang, John-Michael Sauer, Guriqbal S. Basi



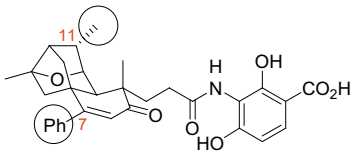
potent, CNS-penetrant
γ-Secretase inhibitor

Potent ketoamide inhibitors of HCV NS3 protease derived from quaternized P_1 groups **pp 2151–2155**
Srikanth Venkatraman*, Francisco Velazquez, Wanli Wu, Melissa Blackman, Vincent Madison, F. George Njoroge



K_i = 0.015 μM
EC_{90} = 0.40 μM

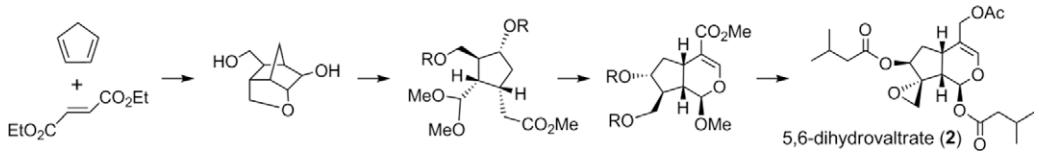
7-Phenylplatensimycin and 11-methyl-7-phenylplatensimycin: More potent analogs of platensimycin **pp 2156–2158**
Ki Po Jang, Chan Hyuk Kim, Seong Wook Na, Dong Seok Jang, Hiyoung Kim, Heonjoong Kang, Eun Lee*



7-Phenylplatensimycin
11-Methyl-7-phenylplatensimycin

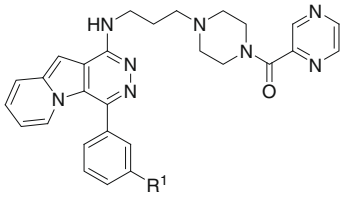
Carbonyl ylide cycloaddition strategy was employed in the synthesis of platensimycin analogs. 7-Phenylplatensimycin and 11-methyl-7-phenylplatensimycin are more potent analogs of platensimycin.

Bioisostere of valtrate, anti-HIV principle by inhibition for nuclear export of Rev **pp 2159–2162**
Satoru Tamura, Nobuhiro Shimizu, Katsuaki Fujiwara, Masafumi Kaneko, Tominori Kimura, Nobutoshi Murakami*



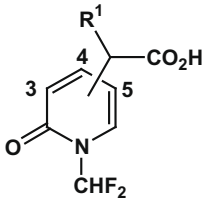
Based on the design from the MO calculation, 5,6-dihydrovaltrate (**2**) was synthesized and revealed to be the bioisostere of valtrate (**1**) showing anti-HIV activity by inhibition for nuclear export of Rev.

Identification of pyridazino[4,5-*b*]indolizines as selective PDE4B inhibitors **pp 2163–2167**
Andrew F. Donnell*, Paul J. Dollings*, John A. Butera, Arlene J. Dietrich, Kerri K. Lipinski, Afshin Ghavami, Warren D. Hirst



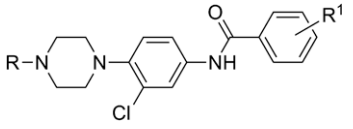
15, R = H, PDE4B K_i = 41 nM
16, R = NO_2 PDE4B K_i = 5.6 nM

Synthesis and biological evaluation of *N*-difluoromethyl-1,2-dihydropyrid-2-one acetic acid regioisomers: Dual Inhibitors of cyclooxygenases and 5-lipoxygenase **pp 2168–2173**
Gang Yu, P. N. Praveen Rao, Morshed A. Chowdhury, Khaled R. A. Abdellatif, Ying Dong, Dipankar Das, Carlos A. Velázquez, Mavanur R. Suresh, Edward E. Knaus*



3-, 4- and 5-regioisomers
R^1 = H, Me

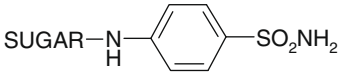
Synthesis and SAR of *N*-(4-(4-alklylpiperazin-1-yl)phenyl)benzamides as muscarinic acetylcholine receptor subtype 1 (M_1) anatgonists **pp 2174–2177**
Nicole R. Miller, R. Nathan Daniels, David Lee, P. Jeffrey Conn, Craig W. Lindsley*



M_1 IC_{50}s 350 nM to >1 μM
3- to 10-fold selective vs. M_2-M_5

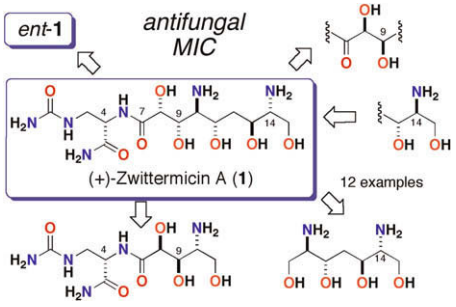
This Letter describes the synthesis and SAR, developed through an iterative analog library approach, of a novel series of selective M_1 mAChR antagonists, based on an *N*-(4-(4-alkylpiperazin-1-yl)phenyl)benzamide scaffold for the potential treatment of Parkinson's disease, dystonia and other movement disorders. Compounds in this series possess M_1 antagonist IC_{50}s in the 350 nM to >10 μM range with varying degrees of functional selectivity versus M_2–M_5.

Inhibition studies of a β-carbonic anhydrase from *Brucella suis* with a series of water soluble glycosyl sulfanilamides **pp 2178–2182**
Daniela Vullo, Isao Nishimori, Andrea Scozzafava, Stephan Köhler, Jean-Yves Winum*, Claudiu T. Supuran*

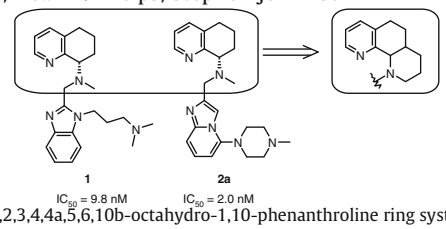


Ki (hCA I) = 510 – 1200 nM, Ki (hCA II) = 10-25 nM; Ki (bsCA 1) = 8.9 – 110 nM

Zwittermicin A: Synthesis of analogs and structure–activity studies **pp 2183–2185**
Evan W. Rogers, Doralyn S. Dalisay, Tadeusz F. Molinski*

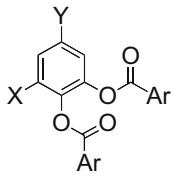


Synthesis of a novel tricyclic 1,2,3,4,4a,5,6,10b-octahydro-1,10-phenanthroline ring system and CXCR4 antagonists with potent activity against HIV-1 **pp 2186–2190**
John G. Catalano*, Kristjan S. Gudmundsson, Angilique Svolto, Sharon D. Boggs, John F. Miller, Andrew Spaltenstein, Michael Thomson, Pat Wheelan, Doug J. Minick, Dean P. Phelps, Stephen Jenkinson



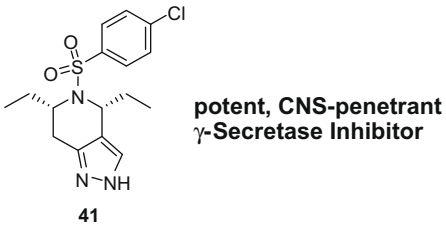
Stereorandom and diastereoselective syntheses of a novel 1,2,3,4,4a,5,6,10b-octahydro-1,10-phenanthroline ring system are described. Derivatives of all four diastereomers were prepared and isolated in >98% ee. The pure enantiomers were compared in order to determine the preferred absolute and relative configuration required for optimal anti-HIV activity. Anti-HIV potency and pharmacokinetic properties of the newly synthesized tricyclic octahydrophenanthroline inhibitors are presented and comparisons are made to previously reported bicyclic (8*S*)-*N*-methyl-5,6,7,8-tetrahydro-8-quinolinamine analogs.

Novel inhibitors of basal glucose transport as potential anticancer agents **pp 2191–2194**
Weihe Zhang, Yi Liu, Xiaozhuo Chen, Stephen C. Bergmeier*



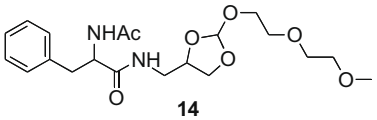
The synthesis and evaluation of a series of polyphenol as inhibitors of basal glucose transport and inducers of cancer cell death is reported.

Discovery of a novel sulfonamide-pyrazolopiperidine series as potent and Efficacious γ-Secretase Inhibitors **pp 2195–2199**
Xiaocong M. Ye*, Andrei W. Konradi, Jenifer Smith, Ying-Zi Xu, Darren Dressen, Albert W. Garofalo, Jennifer Marugg, Hing L. Sham, Anh P. Truong, Jacek Jagodzinski, Michael Pleiss, Hongbin Zhang, Erich Goldbach, John-Michael Sauer, Elizabeth Brigham, Michael Bova, Guriqbal S. Basi



Tuning the pH sensitivities of orthoester based compounds for drug delivery applications by simple chemical modification **pp 2200–2203**

Hélène Bruyère, Andrew D. Westwell, Arwyn T. Jones*



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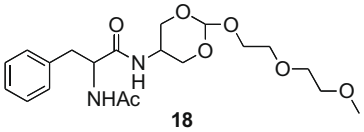


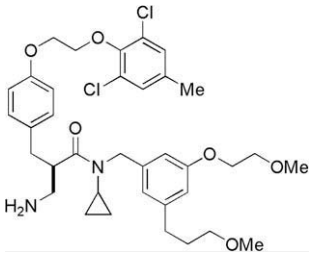
18

Small chemical modifications influence aqueous pH-sensitivity of orthoester conjugates.

Design and optimization of a substituted amino propanamide series of renin inhibitors for the treatment of hypertension **pp 2204–2209**

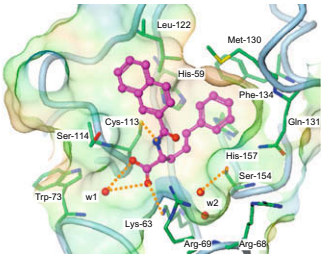
Austin Chen*, Christopher Bayly, Olivier Bezençon, Sylvia Richard-Bildstein, Daniel Dubé, Laurence Dubé, Sébastien Gagné, Michel Gallant, Mireille Gaudreault, Erich Grimm, Robert Houle, Patrick Lacombe, Sébastien Laliberté, Jean-François Lévesque, Suzanna Liu, Dwight MacDonald, Bruce Mackay, David Martin, Dan McKay, David Powell, L'uboš Remeň, Stephen Soisson, Sylvie Toulmond

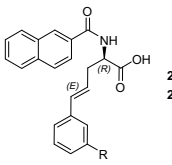
The design and synthesis of orally bioavailable, potent acyclic renin inhibitors are described therein.



Structure-based design of novel human Pin1 inhibitors (II) **pp 2210–2214**

Liming Dong, Joseph Marakovits, Xinjun Hou*, Chuangxing Guo*, Samantha Greasley, Eleanor Dagostino, RoseAnn Ferre, M. Catherine Johnson, Eugenia Kraynov, James Thomson, Ved Pathak, Brion W. Murray



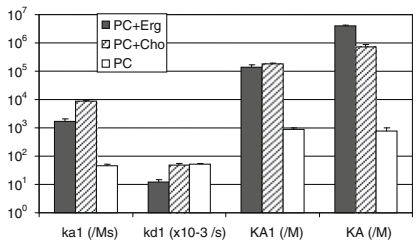


	R	K_i (nM)
23a	H	1800
23b	F	890

A series of non-phosphate small molecular Pin1 inhibitors was discovered utilizing SBDD approach. The structure–activity relationship of phosphate replacement groups was investigated.

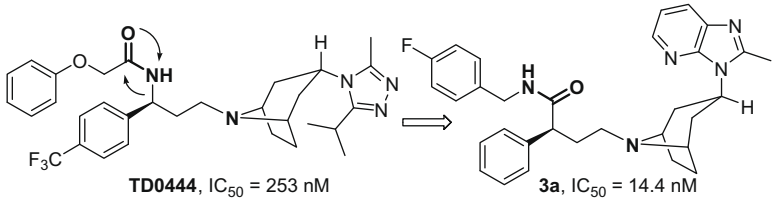
Sterol effect on interaction between amphidinol 3 and liposomal membrane as evidenced by surface plasmon resonance **pp 2215–2218**

Respati T. Swasono, Ryota Mouri, Nagy Morsy, Nobuaki Matsumori, Tohru Oishi, Michio Murata*



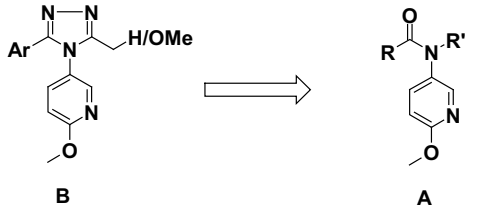
Amphidinol 3 was shown to possess 1000 and 5300 times higher affinity for both cholesterol- and ergosterol-containing liposomes, respectively than that without sterol by SPR.

Discovery of novel (*S*)-α-phenyl-γ-amino butanamide containing CCR5 antagonists via functionality inversion approach **pp 2219–2223**
Hu-Shan Zhang, Dong-Zhi Feng, Li Chen, Ya-Qiu Long*



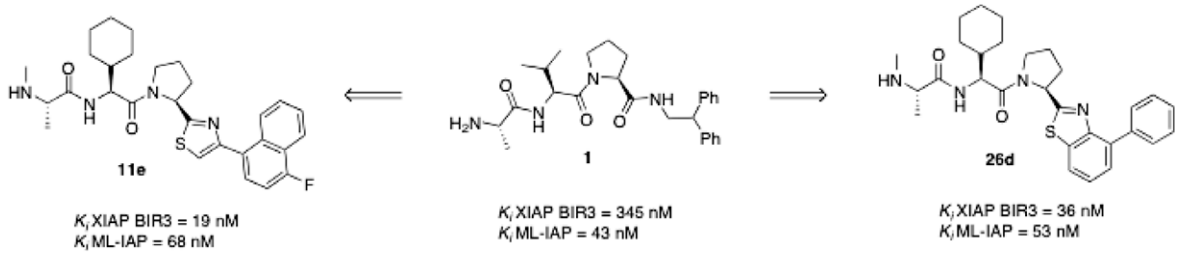
The (*S*)-α-phenyl-γ-amino butanamide derivatives display high potency to antagonize CCR5 with nanomolar IC_{50} values.

Identification of amide bioisosteres of triazole Oxytocin antagonists **pp 2224–2228**
Alan Brown*, Dave Ellis, Olga Wallace, Michael Ralph



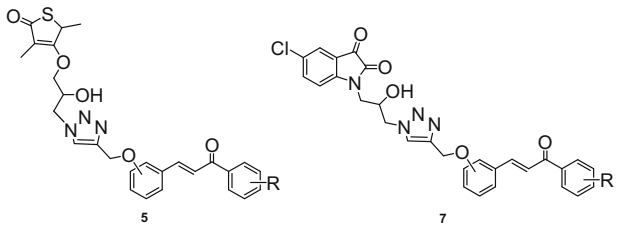
A series of amides, **A**, were prepared as potential bioisosteres of previously reported triazole Oxytocin antagonists **B**. A range of potent analogues were identified, although SAR for potency and selectivity over the related V_{1A} and V_2 receptors was found to be somewhat divergent from that observed for triazoles **B**. The high synthetic accessibility of targets **A** also facilitated the identification of a range of alternative left hand side (R) substituents with good levels of Oxytocin antagonism.

Antagonists of inhibitor of apoptosis proteins based on thiazole amide isosteres **pp 2229–2233**
Frederick Cohen*, Michael F. T. Koehler*, Philippe Bergeron, Linda O. Elliott, John A. Flygare, Matthew C. Franklin, Lewis Gazzard, Stephen F. Keteltas, Kevin Lau, Cuong Q. Ly, Vickie Tsui, Wayne J. Fairbrother



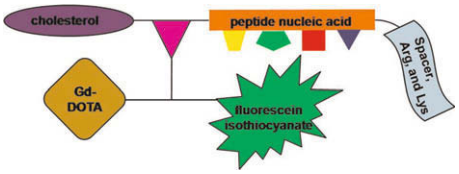
The co-crystal structure of peptide **1** with an ML-IAP BIR construct was used to guide amide bond replacement with either a thiazole or benzothiazole, leading to potent IAP antagonists such as **11e** and **26d**.

Comparison of the antiplasmodial and falcipain-2 inhibitory activity of β-amino alcohol thiolactone-chalcone and isatin-chalcone hybrids **pp 2234–2237**
Renate H. Hans, Jiri Gut, Philip J. Rosenthal, Kelly Chibale*



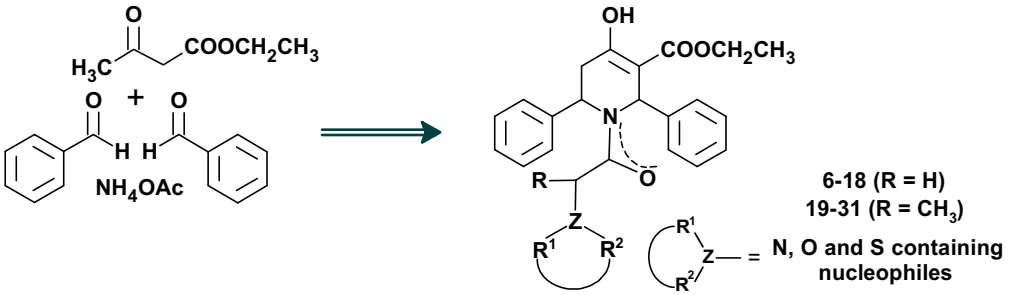
A novel 36-member β-amino alcohol triazole library was synthesized and evaluated for antimalarial and cysteine protease inhibitory activity.

MR contrast agent composed of cholesterol and peptide nucleic acids: Design, synthesis and cellular uptake **pp 2238–2241**
Rajendra Joshi, Ritu Mishra, Rolf Pohmann, Jörn Engelmann*



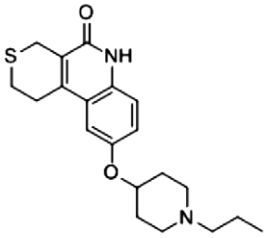
A new uptake-efficient targeted MR contrast agent based on cholesterol and peptide nucleic acids is reported.

Synthesis, crystal and antibacterial studies of diversely functionalized tetrahydropyridin-4-ol **pp 2242–2249**
Gopalakrishnan Aridoss, Shanmugasundaram Amirthaganesan, Yeon Tae Jeong*



Two series of diversely functionalized tetrahydropyridin-4-ol derivatives were synthesized and explored for their antibacterial activity against human pathogenic sensitive and resistant organisms.

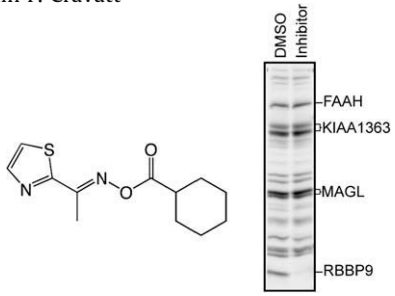
Synthesis and evaluation of tricyclic derivatives containing a non-aromatic amide as inhibitors of poly(ADP-ribose)polymerase-1 (PARP-1) **pp 2250–2253**
Chun-Ho Park, Kwangwoo Chun, Bo-Young Joe, Ji-Seon Park, Young-Chul Kim, Ji-Soo Choi, Dong-Kyu Ryu, Seong-Ho Koh, Goang Won Cho, Seung Hyun Kim, Myung-Hwa Kim*



Tricyclic PARP-1 inhibitor **12a** (IC_{50} = 42 nM) is reported.

12a IC_{50} = 42 nM

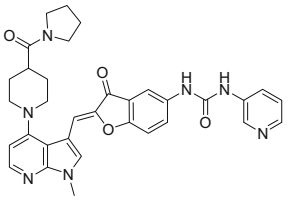
Oxime esters as selective, covalent inhibitors of the serine hydrolase retinoblastoma-binding protein 9 (RBBP9) **pp 2254–2258**
Daniel A. Bachovchin, Monique R. Wolfe, Kim Masuda, Steven J. Brown, Timothy P. Spicer, Virneliz Fernandez-Vega, Peter Chase, Peter S. Hodder, Hugh Rosen, Benjamin F. Cravatt*



High-throughput screening with activity-based probes identifies selective, covalent inhibitors of the uncharacterized serine hydrolase RBBP9.

4-Substituted-7-azaindoles bearing a ureidobenzofuranone moiety as potent and selective, ATP-competitive inhibitors of the mammalian target of rapamycin (mTOR) **pp 2259–2263**

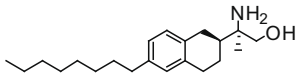
Hwei-Ru Tsou*, Gloria MacEwan, Gary Birnberg, Nan Zhang, Natasja Brooijmans, Lourdes Toral-Barza, Irwin Hollander, Semiramis Ayral-Kaloustian, Ker Yu



mTOR: IC_{50} = 8.2 nM
PI3Kα: IC_{50} = 909 nM
Selectivity: 111-fold
LNCap: IC_{50} = 12 nM

Stereochemistry–activity relationship of orally active tetralin S1P agonist prodrugs **pp 2264–2269**

Bin Ma*, Kevin M. Guckian, Edward Yin-Shiang Lin, Wen-Cherng Lee, Daniel Scott, Gnanasambandam Kumaravel, Timothy L. Macdonald, Kevin R. Lynch, Cheryl Black, Sowmya Chollate, Kyungmin Hahm, Gregg Hetu, Ping Jin, Yi Luo, Ellen Rohde, Anthony Rossomando, Robert Scannevin, Joy Wang, Chunhua Yang

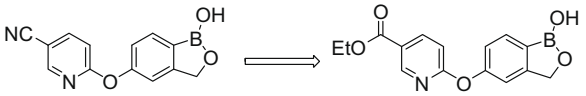


(2R,2'S)-**5** ED_{50} = 0.1 mg/kg
F = 55%

The synthesis, characterization and stereochemistry activity relationship of tetralin S1P agonist prodrugs is reported. (2*R*,2′*S*)-**5** (ED_{50} = 0.1 mg/kg) was identified as a good SphK2 substrate and potent S1P1 agonist with good oral bioavailability.

Design and synthesis of boron-containing PDE4 inhibitors using soft-drug strategy for potential dermatologic anti-inflammatory application **pp 2270–2274**

Yong-Kang Zhang*, Jacob J. Plattner, Tsutomu Akama, Stephen J. Baker, Vincent S. Hernandez, Virginia Sanders, Yvonne Freund, Richard Kimura, Wei Bu, Karin M. Hold, Xiao-Song Lu

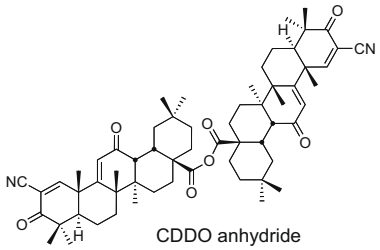


1 **2**

A carboxylic ester group is incorporated into boron-containing PDE4 inhibitors leading to the discovery of benzoxaborole carboxylic ester compounds with good potency against PDE4 and low emetic activity.

2-Cyano-3,10-dioxooleana-1,9(11)-dien-28-oic acid anhydride. A novel and highly potent anti-inflammatory and cytoprotective agent **pp 2275–2278**

Tadashi Honda*, Eric M. Padegimas, Emilie David, Chitra Sundararajan, Karen T. Liby, Charlotte Williams, Michael B. Sporn, Melean Visnick



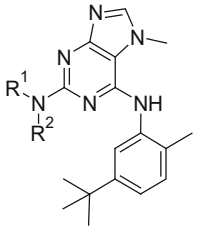
CDDO anhydride

CDDO anhydride, which is the first example of an oleanane triterpenoid anhydride, shows potency similar to or higher than the corresponding acid (CDDO) in various in vitro and in vivo assays related to inflammation and carcinogenesis.

Purine derivatives as potent γ-secretase modulators **pp 2279–2282**

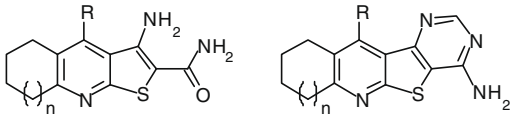
Alexey Rivkin*, Sean P. Ahearn, Stephanie M. Chichetti, Christopher L. Hamblett, Yudith Garcia, Michelle Martinez, Jed L. Hubbs, Michael H. Reutershan, Matthew H. Daniels, Phieng Siliphaivanh, Karin M. Otte, Chaomin Li, Andrew Rosenau, Laura M. Surdi, Joon Jung, Bethany L. Hughes, Jamie L. Crispino, George N. Nikov, Richard E. Middleton, Christopher M. Moxham, Alexander A. Szewczak, Sanjiv Shah, Lily Y. Moy, Candia M. Kenific, Flobert Tanga, Jonathan C. Cruz, Paula Andrade, Minilik H. Angagaw, Nirah H. Shomer, Thomas Miller, Benito Munoz, Mark S. Shearman

The development of a novel series of purines as γ-secretase modulators for potential use in the treatment of Alzheimer's disease is disclosed herein. Optimization of a previously disclosed pyrimidine series afforded a series of potent purine-based γ-secretase modulators with 300- to 2000-fold in vitro selectivity over inhibition of Notch cleavage and that selectively reduces Aβ42 in an APP-YAC transgenic mouse model.



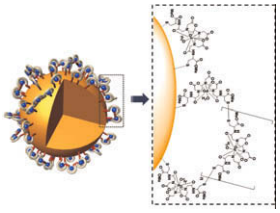
Inhibition of eEF2-K by thieno[2,3-*b*]pyridine analogues **pp 2283–2286**

Jeffrey W. Lockman*, Matthew D. Reeder, Kazuyuki Suzuki, Kirill Ostanin, Ryan Hoff, Leena Bhoite, Harry Austin, Vijay Baichwal, J. Adam Willardsen



Gold nanoparticles functionalized by gadolinium–DTPA conjugate of cysteine as a multimodal bioimaging agent **pp 2287–2291**

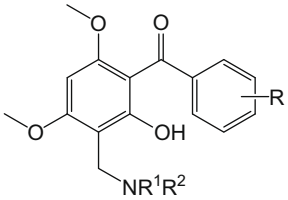
Ji-Ae Park, Hee-Kyung Kim, Joo-Hyun Kim, Sang-Won Jeong, Jae-Chang Jung, Gang-Ho Lee, Jongmin Lee, Yongmin Chang*, Tae-Jeong Kim*



The work describes the synthesis and in vivo application of Au@GdL (L = DTPA-bis(amide) conjugate of cysteine) as a highly efficient MRI/CT multimodal contrast agent.

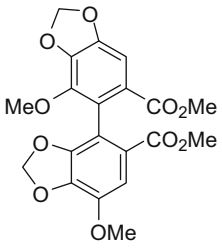
Synthesis and biological evaluation of nitrogen-containing benzophenone analogues as TNF-α and IL-6 inhibitors with antioxidant activity **pp 2292–2296**

Babasaheb P. Bandgar*, Sachin A. Patil, Jalinder V. Totre, Balaji L. Korbad, Rajesh N. Gacche, Baliram S. Hote, Shivkumar S. Jalde, Hemant V. Chavan



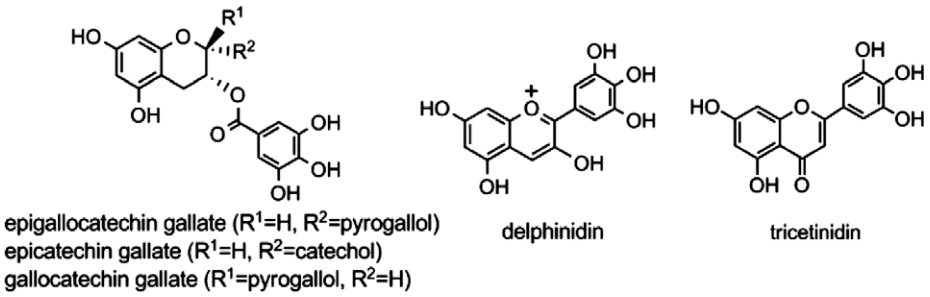
A novel series of nitrogen-containing benzophenone analogues were synthesized and screened against pro-inflammatory cytokines and antioxidant activity. All compounds were exhibited promising activity against IL-6. Except to this, compound **20e** were found to be effective inhibitor of TNF-α and IL-6. The compounds (**16a**, **17g**, **18f**, **18g**, **19g** and **20e**) were found promising antioxidant activity.

An improved method for the synthesis of γ-DDB **pp 2297–2298**
Chuanjun Song*, Peng Zhao, Zhiqiang Hu, Shuai Shi, Yanmei Cui, Junbiao Chang*



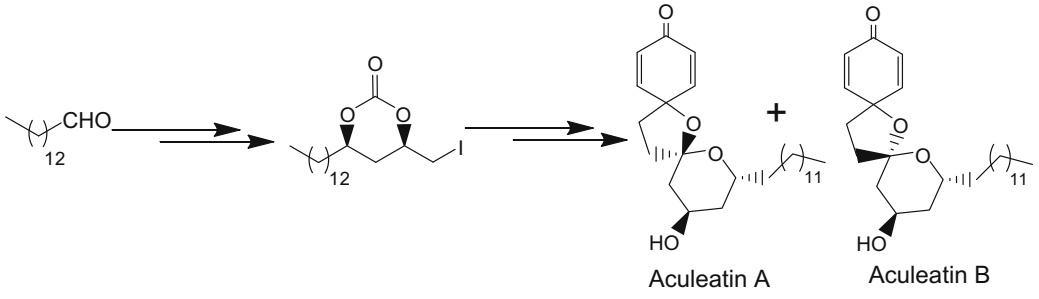
γ-DDB, an important member of the DDB family, was synthesized in good yield through anhydride-linker assisted intramolecular Ullmann reaction under mild reaction conditions.

New inhibitors for expression of IgE receptor on human mast cell **pp 2299–2302**
Satoru Tamura, Kunichika Yoshihira, Katsuaki Fujiwara, Nobutoshi Murakami*

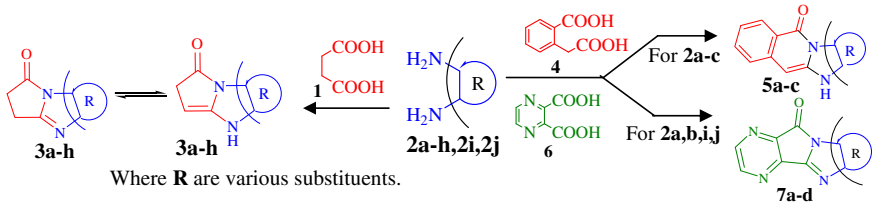


Three catechins, an anthocyanidin, and a flavone were disclosed as inhibitors for expression of IgE receptor, FcεRI, on human mast cell.

Stereoselective synthesis of bioactive natural spiroacetals aculeatins A and B **pp 2303–2305**
Biswanath Das*, Martha Krishnaiah, Chithaluri Sudhakar



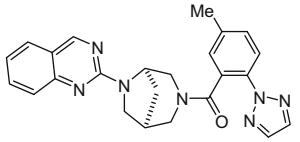
Solvent free synthesis, anti-inflammatory and anticancer activity evaluation of tricyclic and tetracyclic benzimidazole derivatives **pp 2306–2310**
Sham M. Sondhi*, Reshma Rani, Jaiveer Singh, Partha Roy, S. K. Agrawal, A. K. Saxena



Heterocyclic benzimidazole derivatives **3a–h, 5a-c** and **7a–d** have been synthesized by via microwave irradiation in good yields and their evaluation for anti-inflammatory and anticancer activity is reported.

Design and synthesis of conformationally constrained N,N-disubstituted 1,4-diazepanes as potent orexin receptor antagonists **pp 2311–2315**

Paul J. Coleman*, John D. Schreier, Georgia B. McGaughey, Michael J. Bogusky, Christopher D. Cox, George D. Hartman, Richard G. Ball, C. Meacham Harrell, Duane R. Reiss, Thomayant Prueksaritanont, Christopher J. Winrow, John J. Renger

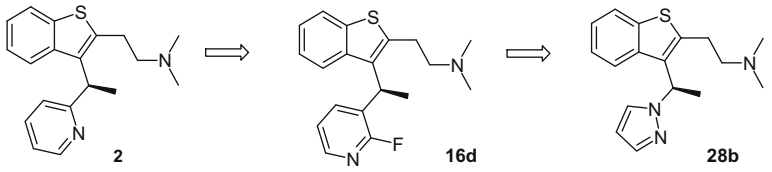


Compound **8c**
OX_1R Ki = 0.7 nM
OX_2R Ki = 0.9 nM

In this Letter we describe the design and synthesis of conformationally constrained N,N-disubstituted 1,4-diazepanes as orexin receptor antagonists such as **8c**. The design of these constrained analogs was guided by an understanding of the preferred solution and solid state conformation of the diazepane central ring.

Novel benzothiophene H_1-antihistamines for the treatment of insomnia **pp 2316–2320**

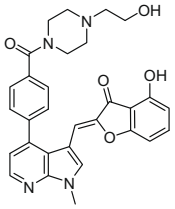
Wilna J. Moree*, Florence Jovic, Timothy Coon, Jinghua Yu, Bin-Feng Li, Fabio C. Tucci, Dragan Marinkovic, Raymond S. Gross, Siobhan Malany, Margaret J. Bradbury, Lisa M. Hernandez, Zhihong O'Brien, Jianyun Wen, Hua Wang, Samuel R. J. Hoare, Robert E. Petroski, Aida Sacaan, Ajay Madan, Paul D. Crowe, Graham Beaton*



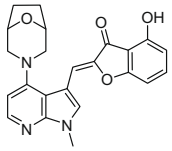
Structure–activity relationships around the lead H_1-antihistamine **2**, a potential agent for the treatment of insomnia, led to the identification of several potential backups with differences in projected pharmacokinetic profiles. While human PK of **16d** indicated a suitable half-life, the compound was not moved into development due to significant variability in pharmacokinetic profile. From preclinical studies, compound **28b** may represent a more suitable backup.

Discovery and optimization of 2-(4-substituted-pyrrolo[2,3-*b*]pyridin-3-yl)methylene-4-hydroxybenzofuran-3(2*H*)-ones as potent and selective ATP-competitive inhibitors of the mammalian target of rapamycin (mTOR) **pp 2321–2325**

Hwei-Ru Tsou*, Gloria MacEwan, Gary Birnberg, George Grosu, Matthew G. Bursavich, Joel Bard, Natasja Brooijmans, Lourdes Toral-Barza, Irwin Hollander, Tarek S. Mansour, Semiramis Ayral-Kaloustian, Ker Yu



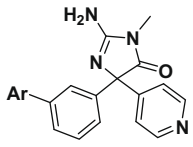
mTOR IC_{50} = 0.39 nM
PI3Kα IC_{50} = 100 nM
Selectivity: 256-fold
LNCap IC_{50} = 1 nM



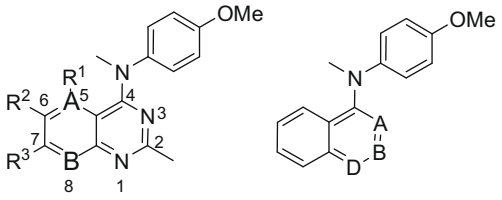
mTOR IC_{50} = 0.38 nM
PI3Kα IC_{50} = 104 nM
Selectivity: 274-fold
LNCap IC_{50} = 2 nM

Pyridinyl aminohydantoins as small molecule BACE1 inhibitors **pp 2326–2329**

Ping Zhou*, Yanfang Li, Yi Fan, Zheng Wang, Rajiv Chopra, Andrea Olland, Yun Hu, Ronald L. Magolda, Menelas Pangalos, Peter H. Reinhart, M. James Turner, Jonathan Bard, Michael S. Malamas, Albert J. Robichaud

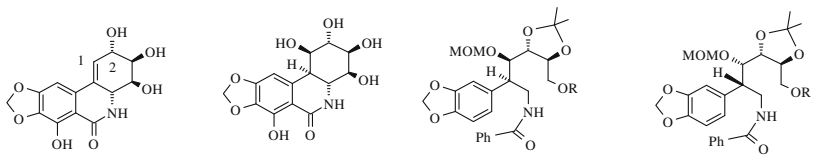


Discovery of *N*-methyl-4-(4-methoxyanilino)quinazolines as potent apoptosis inducers. Structure–activity relationship of the quinazoline ring **pp 2330–2334**
Nilantha Sirisoma, Azra Pervin, Hong Zhang, Songchun Jiang, J. Adam Willardsen, Mark B. Anderson, Gary Mather, Christopher M. Pleiman, Shailaja Kasibhatla, Ben Tseng, John Drewe, Sui Xiong Cai*



The synthesis and SAR studies of the quinazoline ring of *N*-methyl-4-(4-methoxyanilino)quinazolines as novel apoptosis inducers are reported.

Potent and selective inhibition of human cytochrome P450 3A4 by *seco*-pancratistatin structural analogs **pp 2335–2339**
James McNulty*, Jerald J. Nair, Mohini Singh, Denis J. Crankshaw, Alison C. Holloway

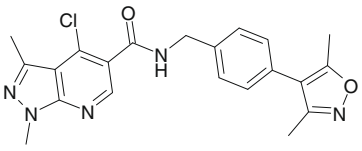


Narciclasine **7** *Ki* = 0.63 μM | Pancratistatin **6** *inactive* | R=TBS **18** or Tos **20** *Ki* = 0.07 and 0.03 μM | R=TBS **32** or Tos **36** *Ki* = 0.07 and 0.03 μM

seco-Derivatives of the anticancer agent pancratistatin bearing the 2*S*,3*S*,4*S*,5*S* configuration were accessed via a novel, highly diastereoselective *anti*-aldol reaction. Structure–activity relationships reveal important insights into the *seco*-pancratistatin pharmacophore as a potent and selective inhibitor of human cytochrome P450 3A4 (CYP3A4), and highlight features of concern in advancing a potent, selective anticancer agent in the pancratistatin series.

The identification a novel, selective, non-steroidal, functional glucocorticoid receptor antagonist **pp 2340–2343**
Joseph Rimland, Angela Dunne, Suchete S. Hunjan, Rosemary Sasse, Iain Uings, Dino Montanari, Matilde Caivano, Poonam Shah, David Standing, David Gray, David Brown, William Cairns, Ryan Trump, Paul W. Smith, Nicolas Bertheleme, Pier D'Alessandro, Sheraz Gul, Mythily Vimal, David N. Smith, Stephen P. Watson*

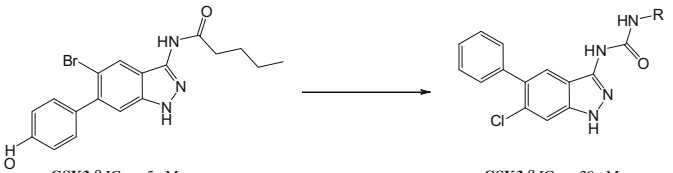
The identification of novel, potent, non-steroidal/small molecule functional GR antagonist GSK1564023A PR is described. Associated structure–activity relationships and the process of optimisation of an initial HTS hit are also described.



GSK1564023A

GR MMTV	pIC_{50}	7.0
GR NFkB	pIC_{50}	< 4.9
PR	pIC_{50}	5.5

Design of potent and selective GSK3β inhibitors with acceptable safety profile and pharmacokinetics **pp 2344–2349**
Dominique Lesuisse*, Gilles Tiraboschi, Alain Krick, Pierre-Yves Abecassis, Gilles Dutruc-Rosset, Didier Babin, Frank Halley, Fabienne Château, Sylvette Lachaud, Alain Chevalier, Dominique Quarteronet, Marie-Claude Burgevin, Céline Amara, Philippe Bertrand, Thomas Rooney

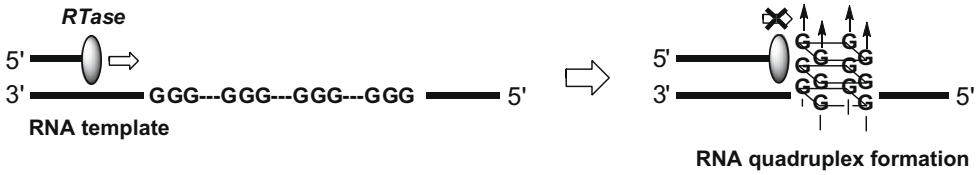


GSK3 β IC_{50} = 5 nM
CYP1A2 IC_{50} = 80 nM
F 1%

GSK3 β IC_{50} = 29 nM
CYP1A2 IC_{50} 2.2 μM
F 78%

From potent and selective inhibitors of GSK3β displaying CYP1A2 inhibition and poor PK properties mostly linked to metabolic instability and in vivo hydrolysis of the amide bond, we were able to obtain safe and orally available inhibitors with good half lives.

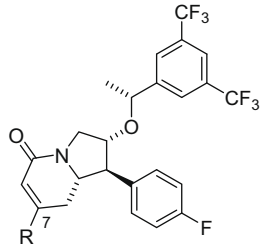
A reverse transcriptase stop assay revealed diverse quadruplex formations in UTRs in mRNA **pp 2350–2353**
Masaki Hagihara, Keisuke Yoneda, Hiroaki Yabuuchi, Yasushi Okuno, Kazuhiko Nakatani*



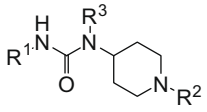
We developed an enzyme-based method to certify quadruplex formations in biologically important RNAs.

Tetrahydroindolizinone NK_1 antagonists **pp 2354–2358**
Jianming Bao*, Huagang Lu, Gregori J. Morriello, Emma J. Carlson, Alan Wheeldon, Gary G. Chicchi, Marc M. Kurtz, Kwei-Lan C. Tsao, Song Zheng, Xinchun Tong, Sander G. Mills, Robert J. DeVita

A new class of potent NK_1 receptor antagonists with a tetrahydroindolizinone core has been identified. This series of compounds demonstrated improved functional activities as compared to previously identified 5,5-fused pyrrolidine lead structures. SAR at the 7-position of the tetrahydroindolizinone core is discussed in detail. A number of compounds displayed high NK_1 receptor occupancy at both 1 h and 24 h in a gerbil foot tapping model. Compound **40** has high NK_1 binding affinity, good selectivity for other NK receptors and promising in vivo properties. It also has clean P_{450} inhibition and hPXR induction profiles.



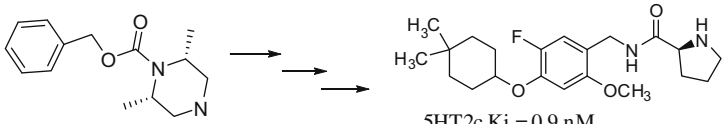
Reduction of hERG inhibitory activity in the 4-piperidinyl urea series of H3 antagonists **pp 2359–2364**
Michael Berlin*, Yoon Joo Lee, Christopher W. Boyce, Yi Wang, Robert Aslanian, Kevin D. McCormick, Steve Sorota, Shirley M. Williams, Robert E. West Jr., Walter Korfmacher



1

Structural features of the substituted 4-piperidinyl urea analogs **1**, responsible for the H3 antagonist activity, have been identified. Structure–activity relationship of the H3 receptor affinity, hERG ion channel inhibitory activity and their separation is described. Preliminary pharmacokinetic evaluation of the compounds of the series is addressed.

Orally active and brain permeable proline amides as highly selective 5HT2c agonists for the treatment of obesity **pp 2365–2369**
Kevin K.-C. Liu*, Bruce A. Lefker, Mark A. Dombroski, Phoebe Chiang, Peter Cornelius, Terrell A. Patterson, Yuan Zeng, Stephanie Santucci, Elizabeth Tomlinson, Colleen P. Gibbons, Ravi Marala, Janice A. Brown, Jimmy X. Kong, Eunsun Lee, Wendy Werner, Zane Wenzel, Craig Giragossian, Hou Chen, Steven B. Coffey

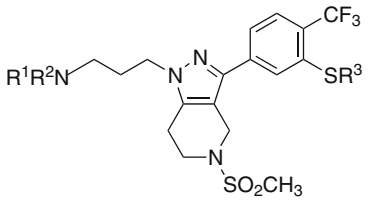


5HT2c Ki = 83 nM
poor brain penetration

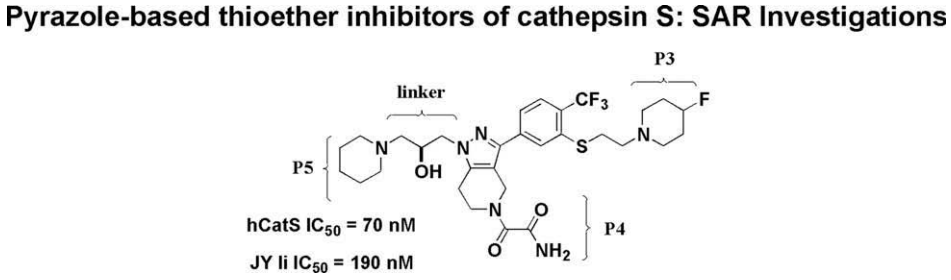
5HT2c Ki = 0.9 nM
good brain penetration

Brain-penetrable proline amides were developed as 5HT2c agonists with more than 1000-fold binding selectivity against 5HT2b receptor. After medicinal chemistry optimization and SAR studies, orally active proline amides with robust efficacy in a rodent food intake inhibition model were uncovered.

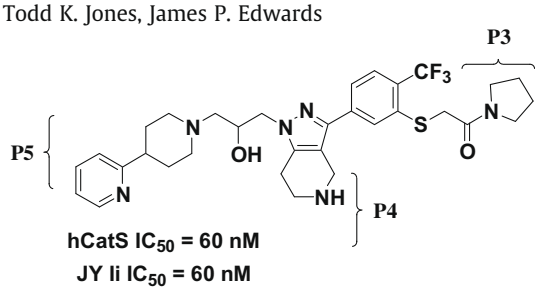
Discovery and SAR of novel pyrazole-based thioethers as cathepsin S inhibitors: Part 1 **pp 2370–2374**
Alice Lee-Dutra*, Danielle K. Wiener, Kristen L. Arienti, Jing Liu, Neelakandha Mani, Michael K. Ameriks, Frank U. Axe, Damara Gebauer, Pragnya J. Desai, Steven Nguyen, Mike Randal, Robin L. Thurmond, Siquan Sun, Lars Karlsson, James P. Edwards, Todd K. Jones, Cheryl A. Grice



Discovery and SAR of novel pyrazole-based thioethers as cathepsin S inhibitors. Part 2: Modification of P3, P4, and P5 regions **pp 2375–2378**
John J. M. Wiener*, Alvah T. Wickboldt Jr., Danielle K. Wiener, Alice Lee-Dutra, James P. Edwards, Lars Karlsson, Steven Nguyen, Siquan Sun, Todd K. Jones, Cheryl A. Grice



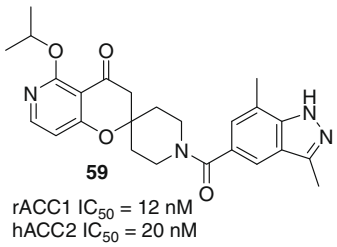
Thioether acetamides as P3 binding elements for tetrahydropyrido-pyrazole cathepsin S inhibitors **pp 2379–2382**
Danielle K. Wiener*, Alice Lee-Dutra, Scott Bembenek, Steven Nguyen, Robin L. Thurmond, Siquan Sun, Lars Karlsson, Cheryl A. Grice, Todd K. Jones, James P. Edwards



Pyrazole-based thioether amide inhibitors of cathepsin S: SAR investigations.

Discovery of small molecule isozyme non-specific inhibitors of mammalian acetyl-CoA carboxylase 1 and 2 **pp 2383–2388**
Jeffrey W. Corbett*, Kevin D. Freeman-Cook, Richard Elliott, Felix Vajdos, Francis Rajamohan, Darcy Kohls, Eric Marr, Hailong Zhang, Liang Tong, Meihua Tu, Sharad Murdande, Shawn D. Doran, Janet A. Houser, Wei Song, Christopher J. Jones, Steven B. Coffey, Leanne Buzon, Martha L. Minich, Kenneth J. Dirico, Susan Tapley, R. Kirk McPherson, Eliot Sugarman, H. James Harwood Jr., William Esler

The discovery and SAR of the isozyme non-selective acetyl-CoA carboxylase 1 and 2 inhibitor **59** is described.



OTHER CONTENTS

Corrigenda **pp 2389–2390**

*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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