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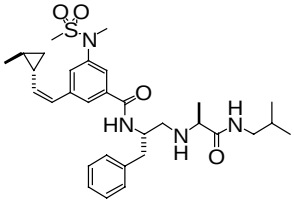
Contents

ARTICLES

BACE-1 inhibition by a series of ψ[CH_2NH] reduced amide isosteres **pp 3635–3638**

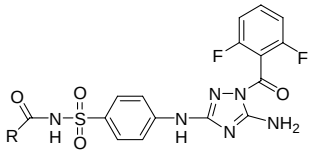
Craig A. Coburn,* Shawn J. Stachel, Kristen G. Jones, Thomas G. Steele, Diane M. Rush, Jillian DiMuzio, Beth L. Pietrak, Ming-Tain Lai, Qian Huang, Janet Lineberger, Lixia Jin, Sanjeev Munshi, M. Katharine Holloway, Amy Espeseth, Adam Simon, Daria Hazuda, Samuel L. Graham and Joseph P. Vacca

A new class of β-secretase inhibitors that incorporate a reduced amide transition state isostere as the key binding element is described. The incorporation of a 5-substituted isophthalamide scaffold at the N-terminal site of this isostere resulted in potent compounds that display impressive cellular IC_{50} values. The syntheses and BACE-1 activities of these inhibitors are reported.



Synthesis and evaluation of *N*-acyl sulfonamides as potential prodrugs of cyclin-dependent kinase inhibitor JNJ-7706621 **pp 3639–3641**

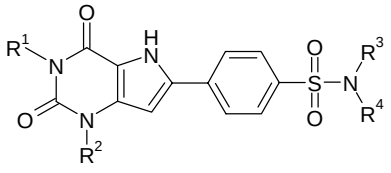
Shenlin Huang,* Peter J. Connolly, Ronghui Lin, Stuart Emanuel and Steve A. Middleton



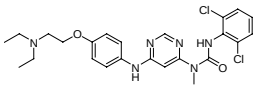
A novel prodrug strategy for cyclin-dependent kinase inhibitor JNJ-7706621 has been explored. Through N-acylation of a sulfonamide substituent, tails containing different solubilizing groups (amino, carboxyl, alkoxyl, and hydroxyl) were attached to JNJ-7706621. Most of the prodrugs exhibited good aqueous solubility and the *N*-acyl groups on the sulfonamide were metabolically cleaved to generate active drug in rat PK study.

New pyrrolopyrimidin-6-yl benzenesulfonamides: Potent A_{2B} adenosine receptor antagonists **pp 3642–3645**

Cristina Esteve, Arsenio Nueda, José Luis Díaz, Jorge Beleta, Alvaro Cárdenas, Estrella Lozoya, Maria Isabel Cadavid, Maria Isabel Loza, Hamish Ryder and Bernat Vidal*



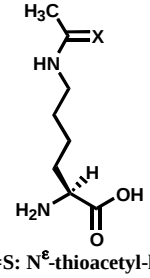
Development of *N*-4,6-pyrimidine-*N*-alkyl-*N*′-phenyl ureas as orally active inhibitors of lymphocyte specific tyrosine kinase **pp 3646–3650**
Jennifer A. Maier, Todd A. Brugel,* Mark Sabat, Adam Golebiowski, Matthew J. Laufersweiler, John C. VanRens, Corey R. Hopkins, Biswanath De, Lily C. Hsieh, Kimberly K. Brown, Vijayasurian Easwaran and Michael J. Janusz



A new class of lymphocyte specific tyrosine kinase (lck) inhibitors based on an *N*-4,6-pyrimidine-*N*-alkyl-*N*′-phenyl urea scaffold is described.

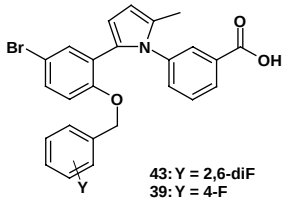
***N*$^{\varepsilon}$-Thioacetyl-lysine: A multi-facet functional probe for enzymatic protein lysine *N*$^{\varepsilon}$-deacetylation** **pp 3651–3656**
David G. Fatkins, Andrew D. Monnot and Weiping Zheng*

Peptides containing *N*$^{\varepsilon}$-thioacetyl-lysine and *N*$^{\varepsilon}$-acetyl-lysine were evaluated for their de(thio)acetylation catalyzed by human HDAC8 and SIRT1, two distinct protein deacetylases. *N*$^{\varepsilon}$-Thioacetyl-lysine was found to be a mimic of *N*$^{\varepsilon}$-acetyl-lysine for HDAC8-catalyzed reaction, but to confer inhibition against SIRT1.



X=S: N$^{\varepsilon}$-thioacetyl-lysine
X=O: N$^{\varepsilon}$-acetyl-lysine

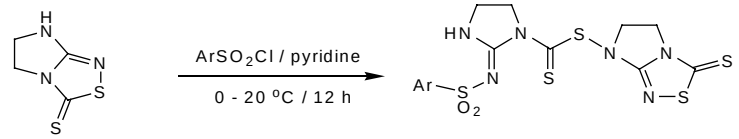
Structure–activity relationships of 1,5-biaryl pyrroles as EP_1 receptor antagonists **pp 3657–3662**
Adrian Hall,* Stephen Atkinson, Susan H. Brown, Iain P. Chessell, Anita Chowdhury, Nicholas M. Clayton, Tanya Coleman, Gerard M.P. Giblin, Robert J. Gleave, Beverley Hammond, Mark P. Healy, Matthew R. Johnson, Anton D. Michel, Alan Naylor, Riccardo Novelli, David J. Spalding and Sac P. Tang



43: Y = 2,6-diF
39: Y = 4-F

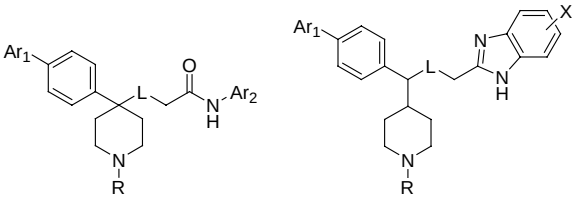
The SAR of novel 1,5-biaryl pyrrole derivatives is described. Compound **43** displayed the highest affinity in an in vitro [^{3}H]PGE_2 binding assay, whilst **39** displayed activity in the established FCA model of inflammatory pain (ED_{50} = 9.2 mg/kg).

Synthesis and in vitro anti-tumor activity of *N*-{1-[(3-thioxo-5,6-dihydroimidazo[2,1-*c*][1,2,4]thiadiazol-7-ylthio)thiocarbonyl]-2-imidazolidene}arylsulfonamides **pp 3663–3667**
Jarosław Sączewski, Zdziaław Brzozowski, Franciszek Sączewski,* Patrick J. Bednarski, Manuel Liebeke and Maria Gdaniec

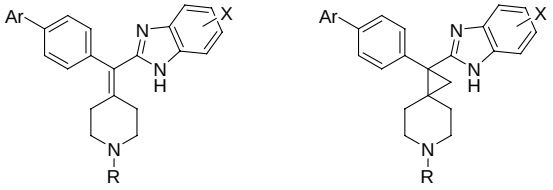


1 **2a-z**

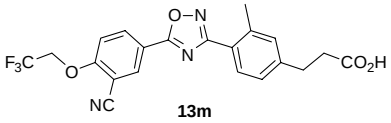
Synthesis and structure–activity relationships of piperidine-based melanin-concentrating hormone receptor 1 antagonists **pp 3668–3673**
Wen-Lian Wu,* Duane A. Burnett, Richard Spring, Li Qiang, Thavalakulamgara K. Sasikumar, Martin S. Domalski, William J. Greenlee, Kim O'Neill and Brian E. Hawes



Design and synthesis of orally efficacious benzimidazoles as melanin-concentrating hormone receptor 1 antagonists **pp 3674–3678**
Wen-Lian Wu,* Duane A. Burnett, Mary Ann Caplen, Martin S. Domalski, Chad Bennett, William J. Greenlee, Brian E. Hawes, Kim O'Neill, Blair Weig, Daniel Weston, Brian Spar and Timothy Kowalski



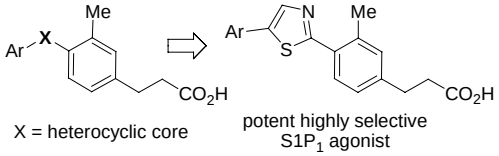
Discovery of 3-arylpropionic acids as potent agonists of sphingosine-1-phosphate receptor-1 ($S1P_1$) with high selectivity against all other known S1P receptor subtypes **pp 3679–3683**
Lin Yan,* Pei Huo, George Doherty, Lesile Toth, Jeffrey J. Hale, Sander G. Mills, Richard Hajdu, Carol A. Keohane, Mark J. Rosenbach, James A. Milligan, Gan-Ju Shei, Gary Chrebet, James Bergstrom, Deborah Card, Elizabeth Quackenbush, Alexandra Wickham and Suzanne M. Mandala



13m

A series of 3-arylpropionic acids were synthesized as potent and orally bioavailable $S1P_1$ receptor agonists that were highly selective against other S1P receptor subtypes. These highly selective $S1P_1$ agonists were able to lower peripheral blood lymphocytes in mice; one of them (i.e., **13m**) was found to be efficacious in a rat skin transplantation model.

Highly selective and potent agonists of sphingosine-1-phosphate 1 ($S1P_1$) receptor **pp 3684–3687**
Petr Vachal,* Leslie M. Toth, Jeffrey J. Hale, Lin Yan, Sander G. Mills, Gary L. Chrebet, Carol A. Koehane, Richard Hajdu, James A. Milligan, Mark J. Rosenbach and Suzanne Mandala

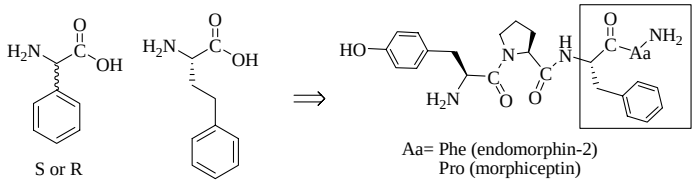


X = heterocyclic core

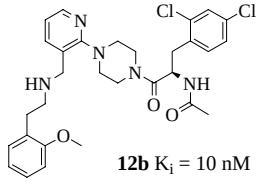
potent highly selective $S1P_1$ agonist

Novel series of sphingosine-1-phosphate (S1P) receptor agonists were developed through a systematic SAR aimed to achieve high selectivity for a single member of the S1P family of receptors, $S1P_1$. The optimized structure represents a highly $S1P_1$-selective and efficacious agonist: $S1P_1/S1P_2$, $S1P_1/S1P_3$, $S1P_1/S1P_4 > 10{,}000$-fold, $S1P_1/S1P_5 > 600$-fold, while EC_{50} ($S1P_1$) <0.2 nM. In vivo experiments are consistent with $S1P_1$ receptor agonism alone being sufficient for achieving desired lymphocyte-lowering effect.

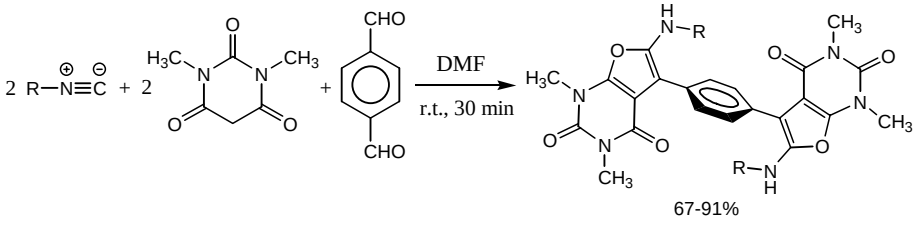
Opioid receptor binding and antinociceptive activity of the analogues of endomorphin-2 and morphiceptin with phenylalanine mimics in the position 3 or 4 pp 3688–3692
Yanfeng Gao, Xin Liu, Weixia Liu, Yuanming Qi, Xuefeng Liu, Yifeng Zhou and Rui Wang*



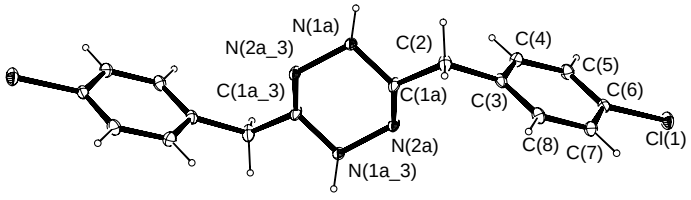
Design, synthesis, and SAR studies on a series of 2-pyridinylpiperazines as potent antagonists of the melanocortin-4 receptor pp 3693–3696
Joe A. Tran, Joseph Pontillo, Beth A. Fleck, Dragan Marinkovic, Melissa Arellano, Fabio C. Tucci, Marion Lanier, John Saunders, Wanlong Jiang, Caroline W. Chen, Alan C. Foster and Chen Chen*



Shaken not stirred: A facile synthesis of 1,4-bis(furo[2,3-*d*]-pyrimidine-2,4(1*H*,3*H*)-dione-5-yl)benzenes by one-pot reaction of isocyanides, *N*,*N*′-dimethylbarbituric acid, and terephthaldialdehyde pp 3697–3701
Mohammad Bagher Teimouri* and Reihaneh Bazhrang



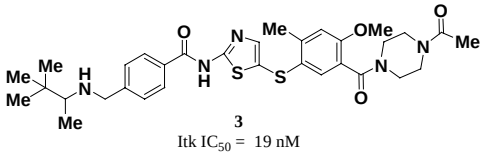
Synthesis, structure analysis, and antitumor activity of 3,6-disubstituted-1,4-dihydro-1,2,4,5-tetrazine derivatives pp 3702–3705
Guo-Wu Rao and Wei-Xiao Hu*



Fourteen compounds were prepared and their structures were determined by X-ray analysis and the semi-empirical calculation of PM3 method. Their antitumor activities in vitro were evaluated. The results show 3,6-disubstitute-1,4-dihydro-1,2,4,5-tetrazine is a kind of compound which possesses potential antitumor activities and that warrants further investigation.

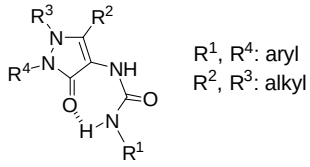
Discovery and SAR of 2-amino-5-(thioaryl)thiazoles as potent and selective Itk inhibitors **pp 3706–3712**
Jagabandhu Das,* Joseph A. Furch, Chunjian Liu, Robert V. Moquin, James Lin, Steven H. Spergel, Kim W. McIntyre, David J. Shuster, Kathleen D. O'Day, Becky Penhallow, Chen-Yi Hung, Arthur M. Doweyko, Amrita Kamath, Hongjian Zhang, Punit Marathe, Steven B. Kanner, Tai-An Lin, John H. Dodd, Joel C. Barrish and John Wityak

A series of structurally novel aminothiazole based small molecule inhibitors of Itk were prepared to elucidate their structure–activity relationships (SARs), selectivity, and cell activity in inhibiting IL-2 secretion in a Jurkat T-cell assay. Compound **3** is identified as a potent and selective Itk inhibitor which inhibits anti-TCR antibody induced IL-2 production in mice in vivo and was previously reported to reduce lung inflammation in a mouse model of ovalbumin induced allergy/asthma.



3
Itk IC_{50} = 19 nM
Jurkat IL-2 I_{50} = 250 nM

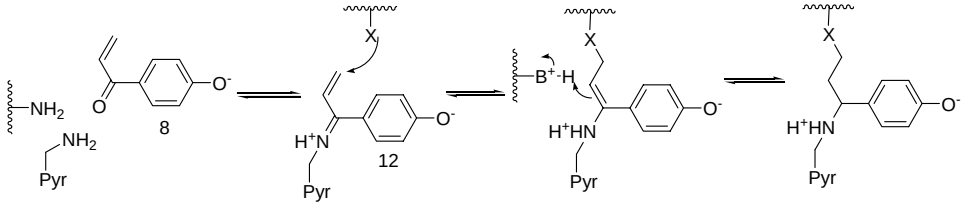
Potent hFPRL1 (ALXR) agonists as potential anti-inflammatory agents **pp 3713–3718**
Roland W. Bürli,* Han Xu, Xiaoming Zou, Kristine Muller, Jennifer Golden, Mike Frohn, Matthew Adlam, Matthew H. Plant, Min Wong, Michele McElvain, Kelly Regal, Vellarkad N. Viswanadhan, Philip Tagari and Randall Hungate



R^1, R^4: aryl
R^2, R^3: alkyl

The discovery of potent agonists for the human formyl-peptide-like 1 receptor (hFPRL1) is reported. Recent studies have indicated that agonizing this receptor may promote resolution of inflammation. Following oral administration, a representative compound showed efficacy in a mouse ear inflammation model.

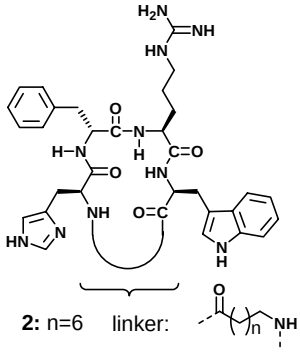
Inactivation of GABA transaminase by 4-acryloylphenol **pp 3719–3722**
Yun-Hai Tao, Hui-Bi Xu and Xiang-Liang Yang*



Possible mechanism of inactivation of GABA-T by 4-acryloylphenol.

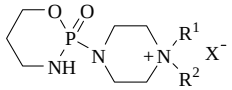
Design of cyclic peptides with agonist activity at melanocortin receptor-4 **pp 3723–3726**
Takenao Odagami, Yuko Tsuda,* Yuji Kogami, Hiroyuki Kouji and Yoshio Okada

The synthesis of the potent hMC-4R agonist **2** (ED_{50} = 15.4 nM) is reported.



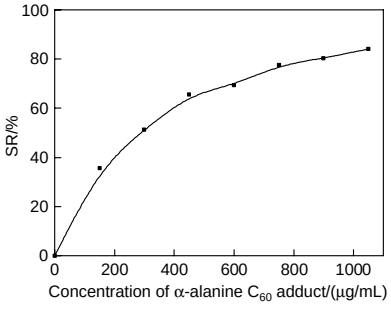
2: n=6 linker:

Novel class of cyclophosphamide prodrug: Cyclophosphamide spiropiperaziniums (CPSP) **pp 3727–3730**
Qi Sun, Run-Tao Li, Wei Guo, Jing-Rong Cui,* Tie-Ming Cheng and Ze-Mei Ge*

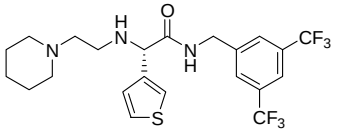


Radical scavenging activities of α-alanine C_{60} adduct **pp 3731–3734**
Tao Sun* and Zhude Xu

Water-soluble α-alanine C_{60} adduct showed an excellent efficiency in eliminating superoxide anion and hydroxyl radical. The 50% inhibiting concentration (IC_{50}) for superoxide anion was 184 μg/mL by spectrophotometry and 292 μg/mL by chemiluminescence. The IC_{50} for hydroxyl radical was 42 μg/mL. In different test systems, the results showed that α-alanine C_{60} adduct had comparable radical scavenging abilities as thiourea and ascorbic acid.



Discovery of 3,5-bis(trifluoromethyl)benzyl L-arylglycinamide based potent CCR2 antagonists **pp 3735–3739**
Lihu Yang,* Changyou Zhou, Liangqin Guo, Gregori Morriello, Gabor Butora, Alexander Pasternak, William H. Parsons, Sander G. Mills, Malcolm MacCoss, Pasquale P. Vicario, Hans Zweerink, Julia M. Ayala, Shefali Goyal, William A. Hanlon, Margaret A. Cascieri and Marty S. Springer

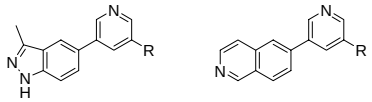


CCR2 antagonist: IC_{50}
30 nM (h monocyte binding)
50 nM (Ca flux)
9.6 nM (chemotaxis)

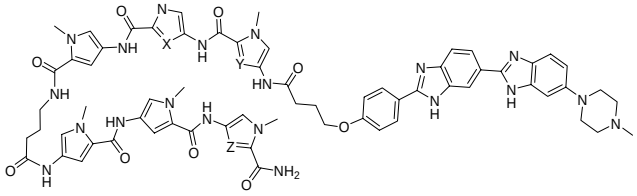
Extensive SAR of a screening hit resulted in a new series of potent and selective CCR2 receptor antagonists.

Identification of a novel 3,5-disubstituted pyridine as a potent, selective, and orally active inhibitor of Akt1 kinase **pp 3740–3744**
Sheela A. Thomas,* Tongmei Li, Keith W. Woods, Xiaohong Song, Garrick Packard, John P. Fischer, Robert B. Diebold, Xuesong Liu, Yan Shi, Vered Klinghofer, Eric F. Johnson, Jennifer J. Bouska, Amanda Olson, Ran Guan, Shayna R. Magnone, Kennan Marsh, Yan Luo, Saul H. Rosenberg, Vincent L. Giranda and Qun Li

Based on lead compounds **2** and **3** a series of 3,5-disubstituted pyridines have been designed and evaluated for inhibition of AKT/PKB. Modifications at the 3 position of the pyridine ring led to a number of potent compounds with improved physical properties, resulting in the identification of **11g** as a promising, orally active AKT inhibitor. The synthesis, structure–activity relationship studies, and pharmacokinetic data are presented in this paper.

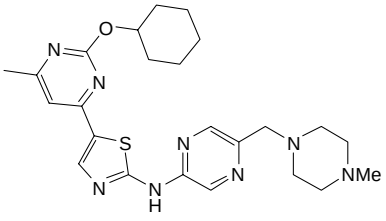


DNA sequence recognition by Hoechst 33258 conjugates of hairpin pyrrole/imidazole polyamides **pp 3745–3750**
Bryan J. Correa, Daniele Canzio, Alexandra L. Kahane, Putta Mallikarjuna Reddy and Thomas C. Bruice*



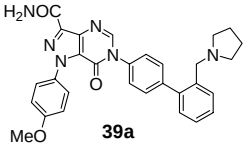
Identification of potent 5-pyrimidinyl-2-aminothiazole CDK4, 6 inhibitors with significant selectivity over CDK1, 2, 5, 7, and 9 **pp 3751–3754**
Tadashi Shimamura, Jun Shibata, Hideki Kurihara, Takashi Mita, Sachie Otsuki, Takeshi Sagara, Hiroshi Hirai and Yoshikazu Iwasawa*

A novel series of CDK4, 6 selective inhibitors with a 5-pyrimidinyl-2-aminothiazole scaffold was identified. Especially, compound **4** exhibited significant selectivity for CDK4, 6 over CDK1, 2, 5, 7, and 9. Compound **4** also inhibited pRb phosphorylation and BrdU incorporation in tumor models.



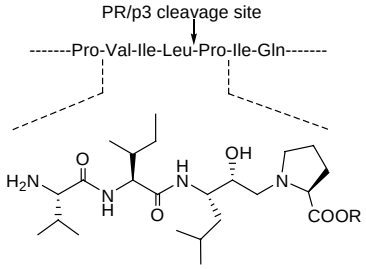
Compound **4**

Preparation of 1-(4-methoxyphenyl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-7(6*H*)-ones as potent, selective and bioavailable inhibitors of coagulation factor Xa **pp 3755–3760**
John M. Fevig,* Joseph Cacciola, Joseph Buriak Jr., Karen A. Rossi, Robert M. Knabb, Joseph M. Luettgen, Pancras C. Wong, Stephen A. Bai, Ruth R. Wexler and Patrick Y.S. Lam



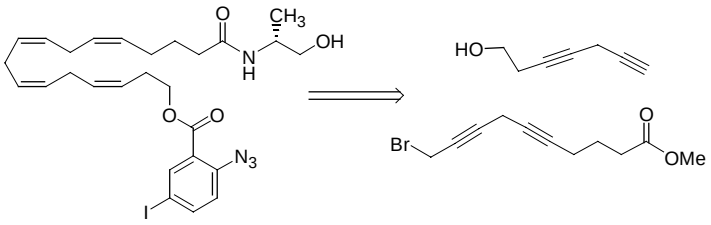
Previously, potent factor Xa inhibitors were described based on a pyrazole core. This manuscript will describe the synthesis and biological activity of factor Xa inhibitors containing the 1*H*-pyrazolo[4,3-*d*]pyrimidin-7(6*H*)-one and related bicyclic cores. Many of these compounds are potent, selective and orally bioavailable inhibitors of coagulation factor Xa.

Evaluations of substrate specificity and inhibition at PR/p3 cleavage site of HTLV-1 protease **pp 3761–3764**
Hiromi Naka, Kenta Teruya, Jeong Kyu Bang, Saburo Aimoto, Tadashi Tatsumi, Hiroyuki Konno, Kazuto Nosaka and Kenichi Akaji*



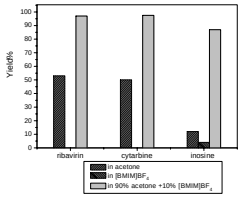
Core sequences necessary for substrate recognition and its inhibition at the PR/p3 site of HTLV-1 protease were clarified.

Synthesis of a potential photoactivatable anandamide analog **pp 3765–3768**
Laurence Balas,* Maria Grazia Cascio, Vincenzo Di Marzo and Thierry Durand



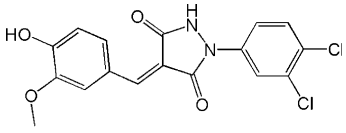
A potential photoreactive analog of anandamide was synthesized via selective hydrogenation of a skipped tetrayne intermediate. This compound might be a useful tool to search for new cannabinoid receptors.

Markedly enhancing lipase-catalyzed synthesis of nucleoside drugs' ester by using a mixture system containing organic solvents and ionic liquid **pp 3769–3771**
Bo Kai Liu, Na Wang, Zhi Chun Chen, Qi Wu and Xian Fu Lin*



Eightfold higher yields and three times faster reaction rates in lipase-catalyzed nucleoside drugs' ester synthesis were achieved by means of using a mixture solvent system composed of 90% acetone and 10% $[BMIM]BF_4$.

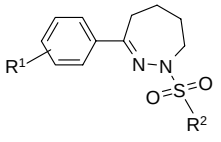
Putative therapeutic agents for the learning and memory deficits of people with Down syndrome **pp 3772–3776**
Nam Doo Kim, Jeonghyeok Yoon, Jung Ho Kim, Jung Tae Lee, Yong Sog Chon, Mi-Kyung Hwang, Ilho Ha* and Woo-Joo Song*



IC_{50} = 2.5 μM

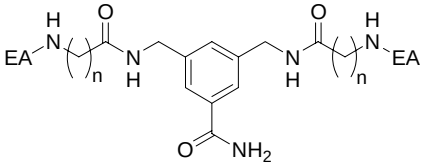
A novel series of DYRK1A inhibitors were identified by combination of in silico screening, in vitro assay, and cell-based screenings.

Array synthesis of progesterone receptor antagonists: 3-Aryl-1,2-diazepines **pp 3777–3779**
Robert W. Wiethe, Eugene L. Stewart, David H. Drewry, David W. Gray, Abdul Mehbob and William J. Hoekstra*



3

Bivalent inhibitors of glutathione *S*-transferase: The effect of spacer length on isozyme selectivity **pp 3780–3783**
Dean Y. Maeda,* Sumit S. Mahajan, William M. Atkins and John A. Zebala

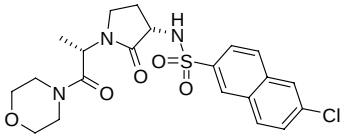


n = 1, 2, 3, 5, 7

Bivalent inhibitors based on ethacrynic acid (EA) were synthesized and evaluated for inhibition of glutathione *S*-transferase (GST) A1-1 and GST P1-1.

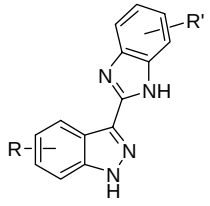
Design and synthesis of orally active pyrrolidin-2-one-based factor Xa inhibitors **pp 3784–3788**
Nigel S. Watson,* David Brown, Matthew Campbell, Chuen Chan, Laiq Chaudry, Máire A. Convery, Rebecca Fenwick, J. Nicole Hamblin, Claudine Haslam, Henry A. Kelly, N. Paul King, Cynthia L. Kurtis, Andrew R. Leach, Gary R. Manchee, Andrew M. Mason, Charlotte Mitchell, Champa Patel, Vipulkumar K. Patel, Stefan Senger, Gita P. Shah, Helen E. Weston, Caroline Whitworth and Robert J. Young

The synthesis is reported of the potent, selective fXa inhibitor **24** which shows highly encouraging rat and dog pharmacokinetic profiles and excellent oral bioavailability.



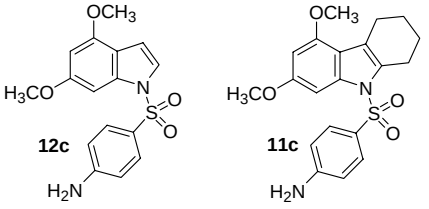
24 fXa Ki 6nM

3-Benzimidazol-2-yl-1*H*-indazoles as potent c-ABL inhibitors **pp 3789–3792**
Christopher M. McBride, Paul A. Renhowe, Thomas G. Gesner, Johanna M. Jansen, Julie Lin, Sylvia Ma, Yasheen Zhou and Cynthia M. Shafer*



The 3-benzimidazol-2-yl-1*H*-indazole scaffold was developed for our receptor tyrosine kinase (RTK) inhibitor program. In exploring the SAR of this series, a subset of these compounds were found to potently inhibit the enzyme c-ABL. The SAR of these compounds is described.

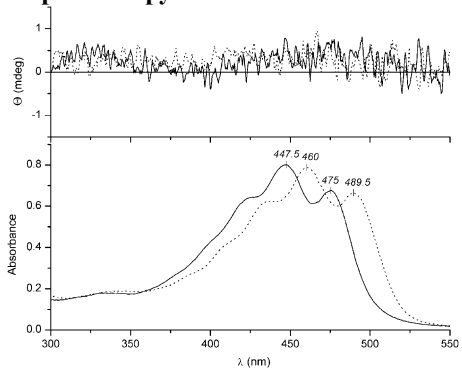
Binding of methoxy-substituted N_1-benzenesulfonylindole analogs at human 5-HT$_6$ serotonin receptors **pp 3793–3796**
Uma Siripurapu, Renata Kolanos, Małgorzata Dukat, Bryan L. Roth and Richard A. Glennon*



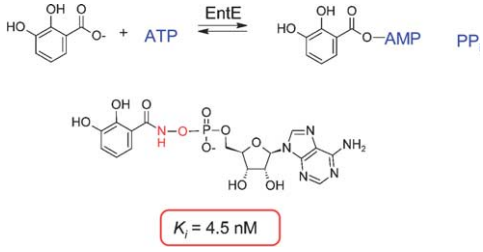
Indole analog **12c** (K_i = 0.8 nM) binds with high affinity at 5-HT$_6$ serotonin receptors; the presence of the methoxy groups results in enhanced affinity and might make an electronic contribution to binding. In contrast, 1,2,3,4-tetrahydrocarbazoles failed to behave in a similar manner and introduction of the methoxy groups resulted in decreased affinity (**11c**; K_i = 210 nM).

Association studies of aggregated aqueous lutein diphosphate with human serum albumin and α_1-acid glycoprotein in vitro: Evidence from circular dichroism and electronic absorption spectroscopy pp 3797–3801
Ferenc Zsila, Geoff Nadolski and Samuel F. Lockwood*

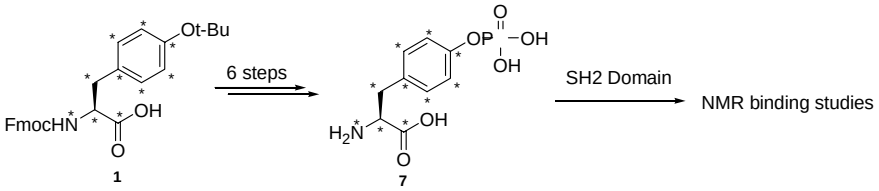
Lutein diphosphate salt (LdP) retains the spectroscopic characteristics of natural source lutein in organic solvent, and forms H- and J-type aggregates in aqueous solution—without evidence of stoichiometric binding to human serum albumin (HSA) in vitro.



Nanomolar inhibition of the enterobactin biosynthesis enzyme, EntE: Synthesis, substituent effects, and additivity pp 3802–3805
Brian P. Callahan,* Joseph V. Lomino and Richard Wolfenden

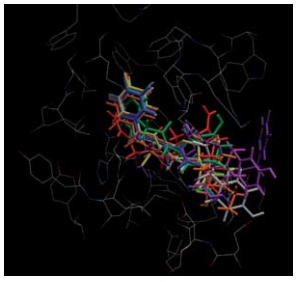


Facile synthesis and application of uniformly ^{13}C, ^{15}N-labeled phosphotyrosine for ligand binding studies pp 3806–3808
Adriaan W. Tuin, Gregg Siegal, Gijsbert A. van der Marel, Herman S. Overkleeft and Dmitri V. Filippov*

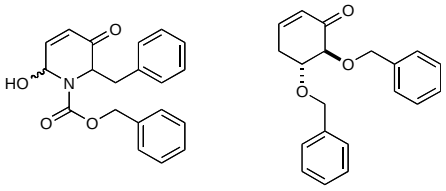


Design, synthesis and evaluation of novel uracil amino acid conjugates for the inhibition of *Trypanosoma cruzi* dUTPase pp 3809–3812
Orla K. Mc Carthy, Alessandro Schipani, Alex Musso Buendía, Luis M. Ruiz-Perez, Marcel Kaiser, Reto Brun, Dolores González Pacanowska and Ian H. Gilbert*

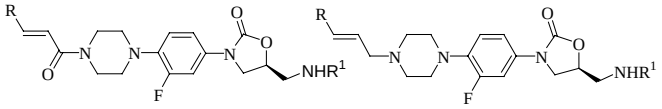
We report the in silico design and subsequent synthesis and biological evaluation of a novel class of uracil acetamide derivatives as potential anti-parasitic compounds.



Novel γ-secretase inhibitors discovered by library screening of in-house synthetic natural product intermediates **pp 3813–3816**
Yasuko Takahashi, Haruhiko Fuwa, Akane Kaneko, Makoto Sasaki, Satoshi Yokoshima, Hifumi Koizumi, Tohru Takebe, Toshiyuki Kan, Takeshi Iwatsubo,* Taisuke Tomita, Hideaki Natsugari* and Tohru Fukuyama*



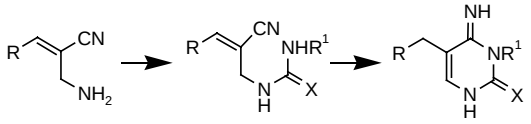
3D QSAR studies of *N*-4-arylacryloylpiperazin-1-yl-phenyl-oxazolidinones: A novel class of antibacterial agents **pp 3817–3823**
B.B. Lohray,* Neha Gandhi, Brijesh Kumar Srivastava and Vidya Bhushan Lohray



3-5 **6 & 7**

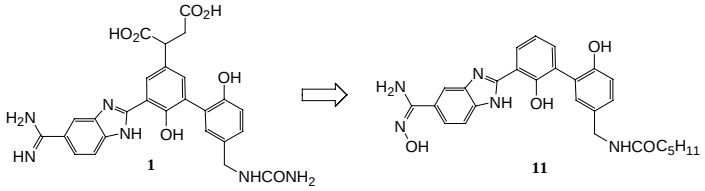
Three-dimensional QSAR studies for *N*-4-arylacryloylpiperazin-1-yl-phenyl-oxazolidinones were conducted using TSAR 3.3. The in vitro activities (MICs) of the compounds against *Staphylococcus aureus* ATCC 25923 exhibited a strong correlation with the prediction made by the model developed in the present study.

Synthesis and antibacterial evaluation of ureides of Baylis–Hillman derivatives **pp 3824–3828**
Somnath Nag, Richa Pathak, Manish Kumar, P.K. Shukla and Sanjay Batra*



The antibacterial activity of the (thio)ureas and 4-imino-3,4-dihydro-1*H*-pyrimidin-2-ones obtained from acetyl derivatives of Baylis–Hillman adducts is reported.

Efforts toward oral bioavailability in factor VIIa inhibitors **pp 3829–3832**
Dange Vijaykumar,* Roopa Rai, Michael Shaghafi, Tony Ton, Steve Torkelson, Ellen M. Leahy, Jennifer R. Riggs, Huiyong Hu, Paul A. Sprengeler, William D. Shrader, Colin O'Bryan, Ronnell Cabuslay, Ellen Sanford, Erik Gjerstadt, Liang Liu, Juthamas Sukbuntherng and Wendy B. Young

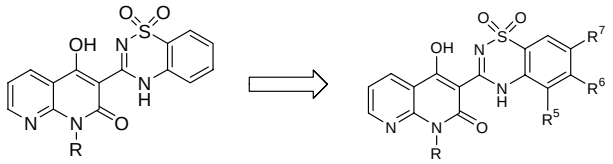


1 **11**

Efforts toward developing orally bioavailable factor VIIa inhibitors starting from parenteral lead compound **1** are described. SAR resulted in compound **11** with improved physicochemical properties, leading to enhanced oral absorption in rat.

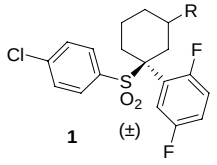
Inhibitors of HCV NS5B polymerase: Synthesis and structure–activity relationships of *N*-1-benzyl and *N*-1-[3-methylbutyl]-4-hydroxy-1,8-naphthyridon-3-yl benzothiadiazine analogs containing substituents on the aromatic ring pp 3833–3838

Todd W. Rockway,* Rong Zhang, Dachun Liu, David A. Betebenner, Keith F. McDaniel, John K. Pratt, David Beno, Debra Montgomery, Wen W. Jiang, Sherie Masse, Warren M. Kati, Tim Middleton, Akhteruzzaman Molla, Clarence J. Maring and Dale J. Kempf



3-Substituted *gem*-cyclohexane sulfone based γ-secretase inhibitors for Alzheimer's disease: Conformational analysis and biological activity pp 3839–3842

Richard A. Jelley,* Jason Elliott, Karl R. Gibson, Timothy Harrison, Dirk Beher, Earl E. Clarke, Huw D. Lewis, Mark Shearman and Jonathan D.J. Wrigley

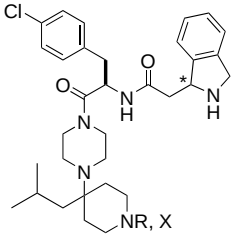


1

The synthesis, biological activity and conformational analysis of 3-substituted *gem*-cyclohexanes based on **1** have provided compounds with high γ-secretase activity.

Privileged structure based ligands for melanocortin receptors—4,4-Disubstituted piperidine derivatives pp 3843–3846

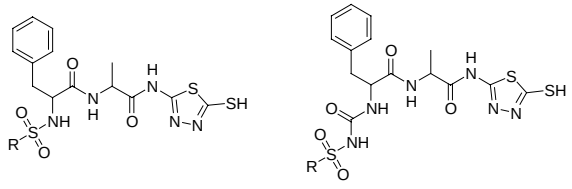
Steven L. Kuklish,* Ryan T. Backer, Karin Briner, Christopher W. Doecke, Saba Husain, Jeffrey T. Mullaney, Paul L. Ornstein, John M. Zgombick, Thomas P. O'Brien and Matthew J. Fisher



R = Me, Ac, Cap...
X = CH_2, O, S or SO_2

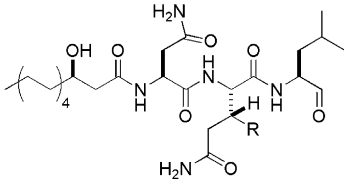
QSAR analysis of some 5-amino-2-mercapto-1,3,4-thiadiazole based inhibitors of matrix metalloproteinases and bacterial collagenase pp 3847–3854

Ashutosh Jamloki, C. Karthikeyan, N.S. Hari Narayana Moorthy and P. Trivedi*



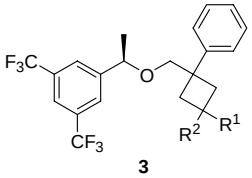
A quantitative structure–activity relationship (QSAR) study on 5-amino-2-mercapto-1,3,4-thiadiazole derivatives was performed to gain structural insight into the binding mode of the molecules to matrix metalloproteinases and bacterial collagenase.

Neurotrophic peptide aldehydes: Solid phase synthesis of fellutamide B and a simplified analog **pp 3855–3858**
John S. Schneekloth Jr., John L. Sanders, John Hines and Craig M. Crews*



A total synthesis of the naturally occurring lipopeptide aldehyde fellutamide B and a simplified analog is reported. Both the natural product and the analog showed potent cytotoxicity and activity in an NGF induction assay.

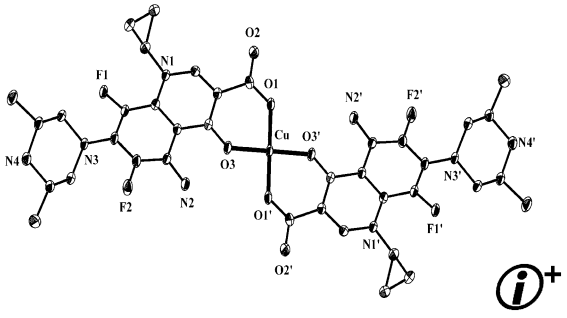
Cyclobutane derivatives as potent NK_1 selective antagonists **pp 3859–3863**
Michelle Laci Wrobleski, Gregory A. Reichard, Sunil Paliwal, Sapna Shah, Hon-Chung Tsui, Ruth A. Duffy, Jean E. Lachowicz, Cynthia A. Morgan, Geoffrey B. Varty and Neng-Yang Shih*



The discovery of a novel series of cyclobutane derivatives **3** as potent and orally active NK_1 selective antagonists is reported.

Crystal structure, spectroscopic, and biological study of the copper(II) complex with third-generation quinolone antibiotic *sparfloxacin* **pp 3864–3867**
Eleni K. Efthimiadou, Yiannis Sanakis, Catherine P. Raptopoulou, Alexandra Karaliota, Nikos Katsaros and George Psomas*

The synthesis, spectroscopic study, crystal structure, and biological activity of the mononuclear Cu(II) complex with the third-generation quinolone *sparfloxacin* are reported.



OTHER CONTENTS

Corrigenda **pp 3868–3869**
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*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

COVER

View of the crystal structure of the DB819-d(CGCGAATTCGCG)$_2$ complex, looking down the minor groove of the DNA (see Campbell, N.H.; Evans, D.A.; Lee, M.P.H.; Parkinson, G.N.; Neidle, S. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 15.). The DB819 molecule is shown in space-filling mode. Visualisation produced with the VMD program. [Humphrey, W.; Dalke, A.; Schulten, K. *J. Mol. Graphics* **1996**, *14*, 33.]

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