

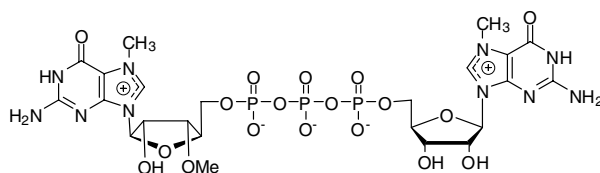
Contents

ARTICLES

Synthesis and biological evaluation of trimethyl-substituted cap analogs

pp 880–884

Anilkumar R. Kore* and Muthian Shanmugasundaram

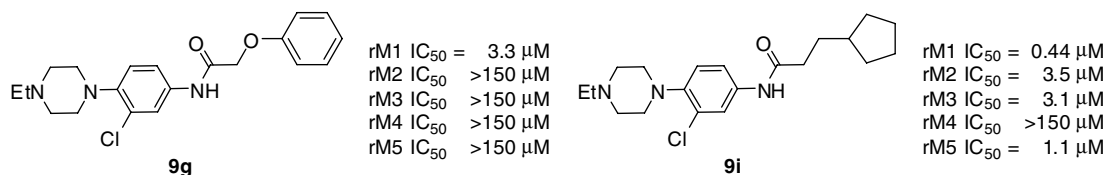


Design, synthesis, and biological evaluation of trimethyl-substituted cap analog $m_2^{7,3'O}G[5']ppp[5']m7G$ was reported.

Synthesis and SAR of selective muscarinic acetylcholine receptor subtype 1 (M1 mAChR) antagonists

pp 885–890

L. Michelle Lewis, Douglas Sheffler, Richard Williams, Thomas M. Bridges, J. Phillip Kennedy, J. T. Brogan, Matthew J. Mulder, Lyndsey Williams, Natalia T. Nalywajko, Colleen M. Niswender, Charles D. Weaver, P. Jeffrey Conn and Craig W. Lindsley*



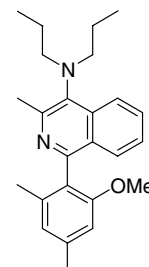
The synthesis and SAR of selective rM1 antagonists, such as **9g** (>45-fold selective versus rM2–rM5) and **9i** (>340-fold selective versus rM4), are described as part of a chemical probe development program for the Molecular Library Screening Network.

The design, synthesis and structure–activity relationships of 1-aryl-4-aminoalkylisoquinolines:

pp 891–896

A novel series of CRF-1 receptor antagonists

Taeyoung Yoon, Stéphane De Lombaert, Robbin Brodbeck, Michael Gulianello, Jayaraman Chandrasekhar, Raymond F. Horvath, Ping Ge, Mark T. Kershaw, James E. Krause, John Kehne, Diane Hoffman, Dario Doller and Kevin J. Hodgetts*

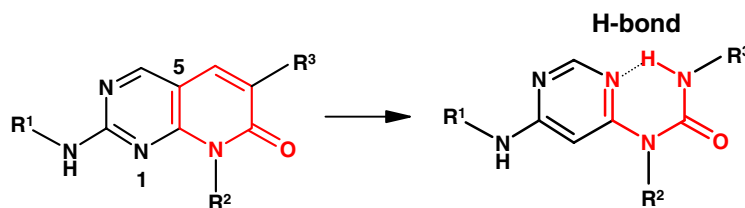


26j, CRF-1 K_i = 6 nM

Entry into a new class of protein kinase inhibitors by pseudo ring design

pp 897–900

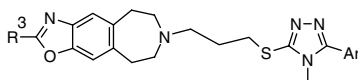
Pascal Furet,* Giorgio Caravatti, Vito Guagnano, Marc Lang, Thomas Meyer and Joseph Schoepfer

**New fused benzazepine as selective D₃ receptor antagonists. Synthesis and biological evaluation.**

pp 901–907

Part one: [h]-fused tricyclic systems

Fabrizio Micheli,* Giorgio Bonanomi, Simone Braggio, Anna Maria Capelli, Paolo Celestini, Federica Damiani, Romano Di Fabio, Daniele Donati, Stefania Gagliardi, Gabriella Gentile, Dieter Hamprecht, Marcella Petrone, Stefano Radaelli, Giovanna Tedesco, Silvia Terreni, Angela Worby and Christian Heidbreder



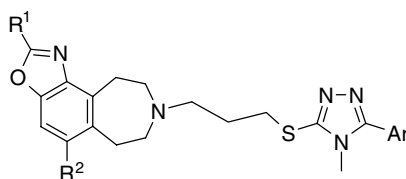
The synthesis of a new class of potent and selective D₃ antagonists is reported.

**New fused benzazepine as selective D₃ receptor antagonists. Synthesis and biological evaluation.**

pp 908–912

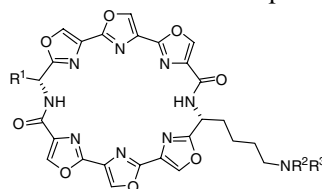
Part 2: [g]-Fused and hetero-fused systems

Fabrizio Micheli,* Giorgio Bonanomi, Simone Braggio, Anna Maria Capelli, Federica Damiani, Romano Di Fabio, Daniele Donati, Gabriella Gentile, Dieter Hamprecht, Ornella Perini, Marcella Petrone, Giovanna Tedesco, Silvia Terreni, Angela Worby and Christian Heidbreder

**Lysinyl macrocyclic hexaoxazoles: Synthesis and selective G-quadruplex stabilizing properties**

pp 913–917

Suzanne G. Rzuczek, Daniel S. Pilch, Edmond J. LaVoie and Joseph E. Rice*



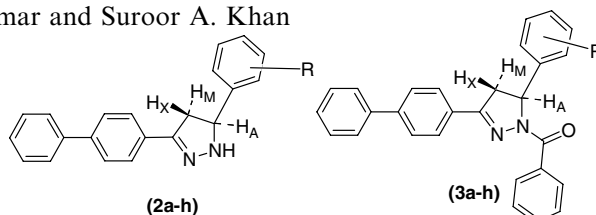
- 1a** R¹ = i-Pr, R², R³ = H
1b R¹ = i-Pr, R² = H, R³ = Ac
1c R¹ = i-Pr, R², R³ = Me
2 R¹ = (CH₂)₄NH₂, R², R³ = H

The synthesis of 24-membered macrocyclic hexaoxazoles incorporating one or two lysine residues is reported. Each compound was evaluated for selective stabilization of G-quadruplex DNA.

Synthesis and pharmacological evaluation of pyrazoline derivatives as new anti-inflammatory and analgesic agents

pp 918–922

Mohammad Amir,* Harish Kumar and Suroor A. Khan

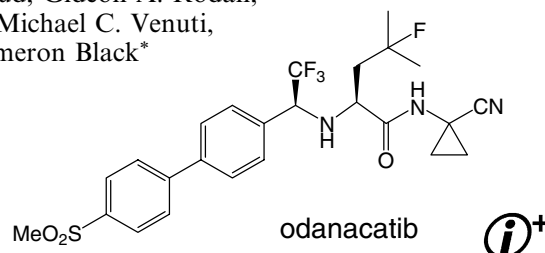


A series of 3-(4-biphenyl)-5-substituted phenyl-2-pyrazolines (**2a–h**) and 1-benzoyl-3-(4-biphenyl)-5-substituted phenyl-2-pyrazolines (**3a–h**) were synthesized by condensation of chalcones with hydrazine hydrate in solvent system ethanol and DMF. The newly synthesized compounds were screened for their anti-inflammatory and analgesic activity, and were compared with standard drug flurbiprofen.

The discovery of odanacatib (MK-0822), a selective inhibitor of cathepsin K

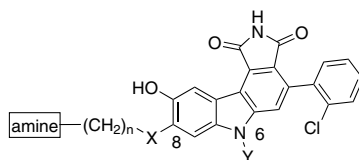
pp 923–928

Jacques Yves Gauthier, Nathalie Chauret, Wanda Cromlish, Sylvie Desmarais, Le T. Duong, Jean-Pierre Falgueyret, Donald B. Kimmel, Sonia Lamontagne, Serge Léger, Tammy LeRiche, Chun Sing Li, Frédéric Massé, Daniel J. McKay, Deborah A. Nicoll-Griffith, Renata M. Oballa, James T. Palmer, M. David Percival, Denis Riendeau, Joel Robichaud, Gideon A. Rodan, Sevgi B. Rodan, Carmai Seto, Michel Thérien, Vouy-Linh Truong, Michael C. Venuti, Gregg Wesolowski, Robert N. Young, Robert Zamboni and W. Cameron Black*

**Synthesis and structure–activity relationships of soluble 8-substituted 4-(2-chlorophenyl)-9-hydroxypyrrolo[3,4-*c*]carbazole-1,3(2*H*,6*H*)-diones as inhibitors of the Wee1 and Chk1 checkpoint kinases**

pp 929–933

Jeff B. Smaill, Ho H. Lee, Brian D. Palmer, Andrew M. Thompson, Christopher J. Squire, Edward N. Baker, R. John Booth, Alan Kraker, Ken Hook and William A. Denny*



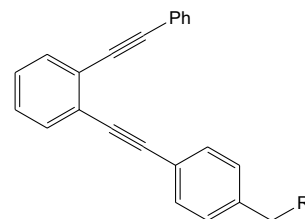
8-Substituted 4-(2-chlorophenyl)-9-hydroxypyrrolo[3,4-*c*]carbazole-1,3(2*H*,6*H*)-diones are potent, soluble inhibitors of Wee1 and Chk1 kinases. They inhibited the alkylator-induced phosphorylation of Cdc2 Tyr15 and abrogated the G2/M checkpoint in HT-29 cells, thus substantially enhancing the cytotoxicity of the DNA-damaging agent cisplatin.

Photoactivated enediynes as targeted antitumoral agents: Efficient routes to antibody and gold nanoparticle conjugates

pp 934–937

Danielle Falcone, Jane Li, Amit Kale and Graham B. Jones*

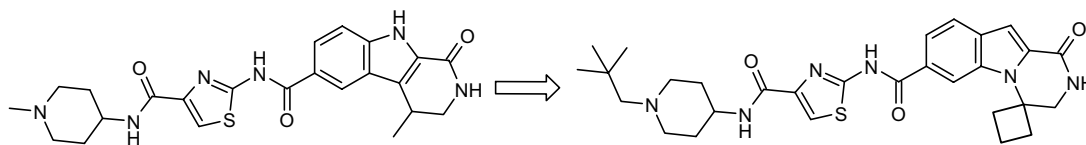
A readily accessible enediyne building block was transformed into a number of conjugates, and photoactivation of the core via the photo-Bergman cyclization effected. Application in the form of immunoconjugates and nanoparticles is demonstrated.



Pyrazinoindolone inhibitors of MAPKAP-K2

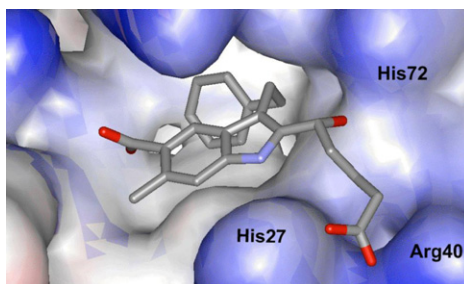
pp 938–941

D. R. Goldberg,* Y. Choi, D. Cogan, M. Corson, R. DeLeon, A. Gao, L. Gruenbaum, M. H. Hao, D. Joseph, M. A. Kashem, C. Miller, N. Moss, M. R. Netherton, C. P. Pargellis, J. Pelletier, R. Sellati, D. Skow, C. Torcellini, Y.-C. Tseng, J. Wang, R. Wasti, B. Werneburg, J. P. Wu and Z. Xiong

MAPKAP-k2 IC₅₀: 5 nMTHP-1 IC₅₀: >5,000 nMMAPKAP-k2 IC₅₀: 2 nMTHP-1 IC₅₀: 300 nM**Rational design of the first small-molecule antagonists of NHERF1/EBP50 PDZ domains**

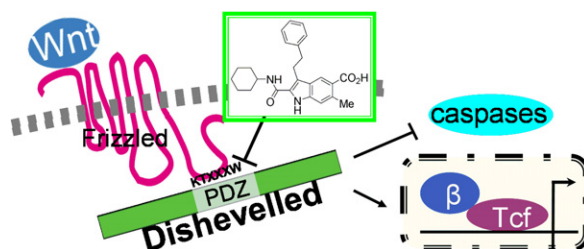
pp 942–945

Anand Mayasundari, Antonio M. Ferreira, Liwen He, Neeraj Mahindroo, Don Bashford and Naoaki Fujii*

i⁺**Indole-2-amide based biochemical antagonist of Dishevelled PDZ domain interaction down-regulates Dishevelled-driven Tcf transcriptional activity**

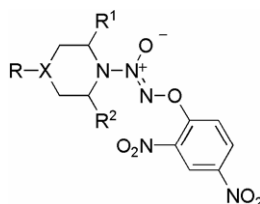
pp 946–949

Neeraj Mahindroo, Chandanamali Punchihewa, Allison M. Bail and Naoaki Fujii*

i⁺**Synthesis and in vitro anti-leukemic activity of structural analogues of JS-K, an anti-cancer lead compound**

pp 950–953

Harinath Chakrapani,* Michael M. Goodblatt, Vidya Udupi, Swati Malaviya, Paul J. Shami, Larry K. Keefer and Joseph E. Saavedra*



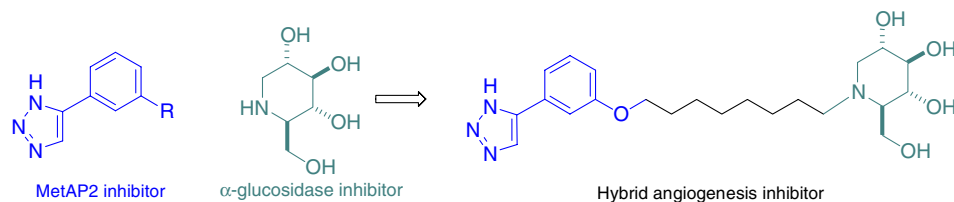
Synthesis and anti-leukemic activity of structural analogues of JS-K, an anti-cancer lead compound, are reported.

i⁺

Hybrid angiogenesis inhibitors: Synthesis and biological evaluation of bifunctional compounds based on 1-deoxynojirimycin and aryl-1,2,3-triazoles

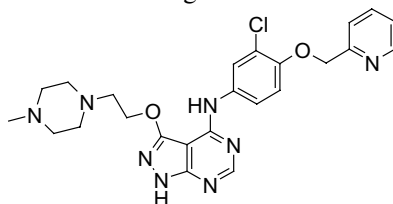
pp 954–958

Ying Zhou, Yunxue Zhao, Kathy M. O'Boyle and Paul V. Murphy*

**Novel 3-alkoxy-1H-pyrazolo[3,4-d]pyrimidines as EGFR and erbB2 receptor tyrosine kinase inhibitors**

pp 959–962

Richard Ducray,* Peter Ballard, Bernard C. Barlaam, Mark D. Dickinson, Jason G. Kettle, Donald J. Ogilvie and Catherine B. Trigwell



Novel 4-anilino-1H-pyrazolo[3,4-d]pyrimidines have been synthesized and evaluated in vitro for erbB2 and EGFR kinase inhibition. A representative compound displaying oral bioavailability in rat and dog illustrates the potential of this series to provide orally active erbB2 inhibitors.

Bioisosteric replacement of dihydropyrazole of 4S-(–)-3-(4-chlorophenyl)-N-methyl-N'-[(4-chlorophenyl)sulfonyl]-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamide (SLV-319) a potent CB1 receptor antagonist by imidazole and oxazole

pp 963–968

Brijesh Kumar Srivastava,* Rina Soni, Amit Joharapurkar, Kalapatapu V. V. M. Sairam, Jayendra Z. Patel, Amitgiri Goswami, Sandeep A. Shedage, Sidhartha S. Kar, Rahul P. Salunke, Shivaji B. Gugale, Amol Dhawas, Pravin Kadam, Bhupendra Mishra, Nisha Sadhwani, Vishal B. Unadkat, Prasenjit Mitra, Mukul R. Jain and Pankaj R. Patel

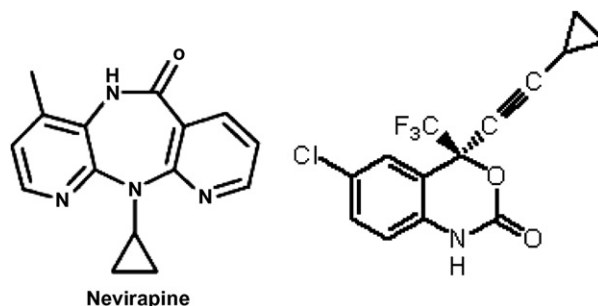
Design, synthesis and conformational analysis of few imidazole and oxazole as bioisosters of 4S-(–)-3-(4-chlorophenyl)-N-methyl-N'-[(4-chlorophenyl)sulfonyl]-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamide (SLV-319) **2** is reported. Computer assisted conformational analysis gave a direct clue for the loss of CB1 antagonistic activity without a fine docking simulation for the homology model.

Energetic effects for observed and unobserved HIV-1 reverse transcriptase mutations of residues L100, V106, and Y181 in the presence of nevirapine and efavirenz

pp 969–972

Marilyn B. Kroeger Smith,* Lenea H. Rader, Amanda M. Franklin, Emily V. Taylor, Katie D. Smith, Richard H. Smith, Jr., Julian Tirado-Rives and William L. Jorgensen

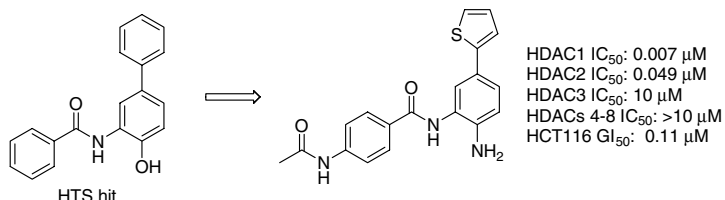
Computer modeling of nevirapine and efavirenz with HIV-1 reverse transcriptase variants.



Exploration of the internal cavity of histone deacetylase (HDAC) with selective HDAC1/HDAC2 inhibitors (SHI-1:2)

pp 973–978

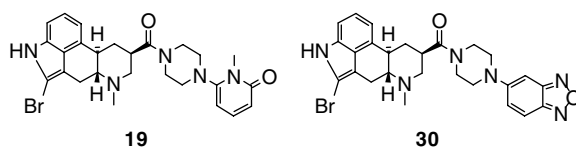
Joey L. Methot,* Prasun K. Chakravarty, Melissa Chenard, Joshua Close, Jonathan C. Cruz, William K. Dahlberg, Judith Fleming, Christopher L. Hamblett, Julie E. Hamill, Paul Harrington, Andreas Harsch, Richard Heidebrecht, Bethany Hughes, Joon Jung, Candia M. Kenific, Astrid M. Kral, Peter T. Meinke, Richard E. Middleton, Nicole Ozerova, David L. Sloman, Matthew G. Stanton, Alexander A. Szewczak, Sriram Tyagarajan, David J. Witter, J. Paul Secrist and Thomas A. Miller



Ergoline derivatives as highly potent and selective antagonists at the somatostatin sst₁ receptor

pp 979–982

Thomas Troxler,* Albert Enz, Daniel Hoyer, Daniel Langenegger, Peter Neumann, Paul Pfäffli, Philippe Schoeffter and Konstanze Hurth*

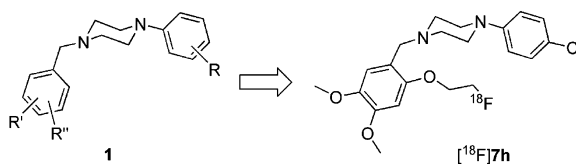


The optimization of ergoline derivatives into highly potent and selective non-peptidic somatostatin sst₁ receptor ligands is described. Derivatives **19** and **30** show sub-nanomolar affinity to the sst₁ receptor and >1000-fold selectivity over other somatostatin receptor subtypes. They behave as full antagonists in functional assays and show promising PK properties in rodents.

Discovery of a dopamine D₄ selective PET ligand candidate taking advantage of a click chemistry based REM linker

pp 983–988

Rainer Tietze, Stefan Löber, Harald Hübner, Peter Gmeiner, Torsten Kuwert and Olaf Prante*

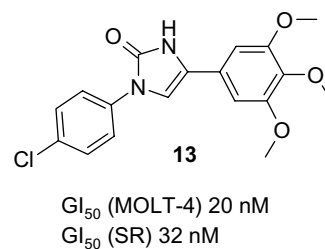


Design, synthesis, and in vitro antitumor activity of new 1,4-diarylimidazole-2-ones and their 2-thione analogues

pp 989–993

Cenzo Congiu,* Maria Teresa Cocco and Valentina Onnis

The synthesis and in vitro antitumor activity against the NCI 60 cell line panel of new 1,4-diarylimidazol-2(3H)-one derivatives and their 2-thione analogues is reported.

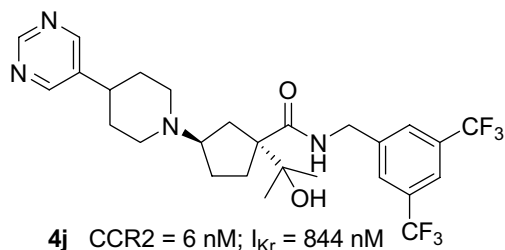


Potent heteroaryl piperidine and carboxyphenyl piperidine 1-alkyl-cyclopentane carboxamide CCR2 antagonists

pp 994–998

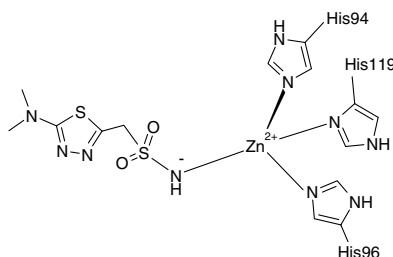
Alexander Pasternak,* Stephen D. Goble, Pasquale P. Vicario, Jerry Di Salvo, Julia M. Ayala, Mary Struthers, Julie A. DeMartino, Sander G. Mills and Lihu Yang

This report describes incorporation of 4-heteroaryl piperidine and 4-(carboxyphenyl)-piperidine subunits into our CCR2 antagonists, leading to new analogs retaining CCR2 potency, but with improved selectivity over I_{K_r} channel binding.

**Carbonic anhydrase inhibitors. Interaction of 2-*N,N*-dimethylamino-1,3,4-thiadiazole-5-methanesulfonamide with 12 mammalian isoforms: Kinetic and X-ray crystallographic studies**

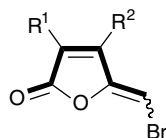
pp 999–1005

Claudia Temperini, Alessandro Cecchi, Nicholas A. Boyle, Andrea Scozzafava, Jaime Escribano Cabeza, Paul Wentworth, Jr., G. Michael Blackburn and Claudiu T. Supuran*

**Identifying the important structural elements of brominated furanones for inhibiting biofilm formation by *Escherichia coli***

pp 1006–1010

Yongbin Han, Shuyu Hou, Karen A. Simon, Dacheng Ren* and Yan-Yeung Luk*



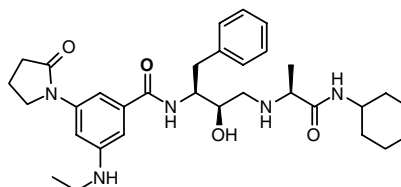
The most important and essential structural element of brominated furanones for inhibiting the formation of biofilm by *Escherichia coli* is identified.

**BACE-1 inhibitors Part 1: Identification of novel hydroxy ethylamines (HEAs)**

pp 1011–1016

Brian Clarke, Emmanuel Demont,* Colin Dingwall, Rachel Dunsdon, Andrew Faller, Julie Hawkins, Ishrut Hussain, David MacPherson, Graham Maile, Rosalie Matico, Peter Milner, Julie Mosley, Alan Naylor, Alistair O'Brien, Sally Redshaw, David Riddell, Paul Rowland, Virginie Soleil, Kathrine J. Smith, Steven Stanway, Geoffrey Stemp, Sharon Sweitzer, Pam Theobald, David Vesey, Daryl S. Walter, John Ward and Gareth Wayne

The discovery of novel BACE-1 inhibitors based on a hydroxy ethylamine (HEA) transition-state mimetic is described: X-ray crystallography facilitated the rapid optimisation of a micromolar hit and led to inhibitors capable of lowering amyloid production in a cell-based assay.



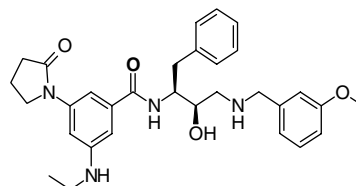
Compound 22
BACE-1: IC₅₀ = 13 nM
Aβ40: IC₅₀ = 310 nM

BACE-1 inhibitors part 2: Identification of hydroxy ethylamines (HEAs) with reduced peptidic character

pp 1017–1021

Brian Clarke, Emmanuel Demont,* Colin Dingwall, Rachel Dunsdon, Andrew Faller, Julie Hawkins, Ishrut Hussain, David MacPherson, Graham Maile, Rosalie Matico, Peter Milner, Julie Mosley, Alan Naylor, Alistair O'Brien, Sally Redshaw, David Riddell, Paul Rowland, Virginie Soleil, Kathrine J. Smith, Steven Stanway, Geoffrey Stemp, Sharon Sweitzer, Pam Theobald, David Vesey, Daryl S. Walter, John Ward and Gareth Wayne

Modification of the prime side of a lead di-amide series of BACE-1 inhibitors was investigated. Inhibitors with reduced peptidic character are presented and two different enzyme-binding modes are described. The compounds described lower amyloid production in a cell-based assay at sub-micromolar concentrations.



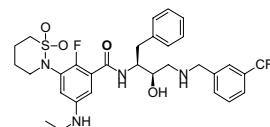
Compound 16
BACE-1: IC₅₀ = 40 nM
Aβ₄₀: IC₅₀ = 180 nM

BACE-1 inhibitors part 3: Identification of hydroxy ethylamines (HEAs) with nanomolar potency in cells

pp 1022–1026

Paul Beswick, Nicolas Charrier, Brian Clarke, Emmanuel Demont,* Colin Dingwall, Rachel Dunsdon, Andrew Faller, Robert Gleave, Julie Hawkins, Ishrut Hussain, Christopher N. Johnson, David MacPherson, Graham Maile, Rosalie Matico, Peter Milner, Julie Mosley, Alan Naylor, Alistair O'Brien, Sally Redshaw, David Riddell, Paul Rowland, John Skidmore, Virginie Soleil, Kathrine J. Smith, Steven Stanway, Geoffrey Stemp, Alistair Stuart, Sharon Sweitzer, Pam Theobald, David Vesey, Daryl S. Walter, John Ward and Gareth Wayne

Modifications to the non-prime side of a series of BACE-1 inhibitors are presented. This final round of optimisation led to inhibitors with nanomolar potency in a cell-based assay which were capable of lowering amyloid production in an animal model following oral administration.

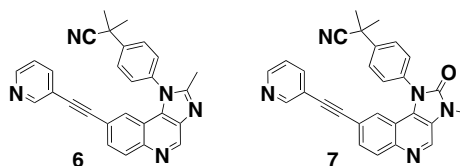


Compound 23
BACE-1: IC₅₀ = 4 nM
WT Aβ₄₀: IC₅₀ = 5 nM
SWE Aβ₄₀: IC₅₀ = 40 nM

Imidazo[4,5-c]quinolines as inhibitors of the PI3K/PKB-pathway

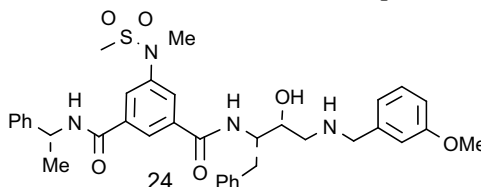
pp 1027–1030

Frédéric Stauffer,* Sauveur-Michel Maira, Pascal Furet and Carlos García-Echeverría

**Potent memapsin 2 (β-secretase) inhibitors: Design, synthesis, protein-ligand X-ray structure, and in vivo evaluation**

pp 1031–1036

Arun K. Ghosh,* Nagaswamy Kumaragurubaran, Lin Hong, Sarang Kulkarni, Xiaoming Xu, Heather B. Miller, Dandepally Srinivasa Reddy, Vajira Weerasena, Robert Turner, Wanpin Chang, Gerald Koelsch and Jordan Tang

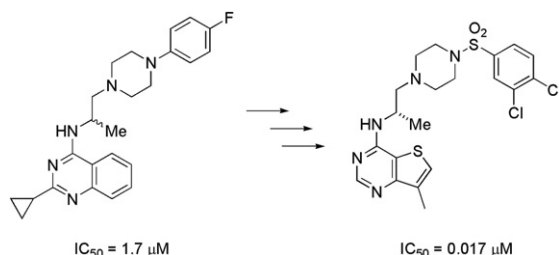


Structure-based design, synthesis, and biological evaluation of a series of potent memapsin 2 (β-secretase) inhibitors are described. Inhibitor **24** exhibited very impressive in vivo results with transgenic mice. The protein-ligand X-ray crystal structure provided molecular insight into the ligand-binding site interactions.

Discovery of potent LPA₂ (EDG4) antagonists as potential anticancer agents

pp 1037–1041

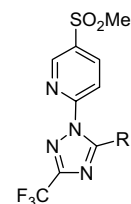
Hilary P. Beck,* Todd Kohn, Steven Rubenstein, Christine Hedberg, Ralf Schwandner, Kerstin Hasslinger, Kang Dai, Cong Li, Lingming Liang, Holger Wesche, Brendon Frank, Songhzu An, Dineli Wickramasinghe, Juan Jaen, Julio Medina, Randall Hungate and Wang Shen

**Comparative structure–activity relationship studies of 1-(5-methylsulfonylpyrid-2-yl)-5-alkyl and (hetero)aryl triazoles and pyrazoles in canine COX inhibition**

pp 1042–1045

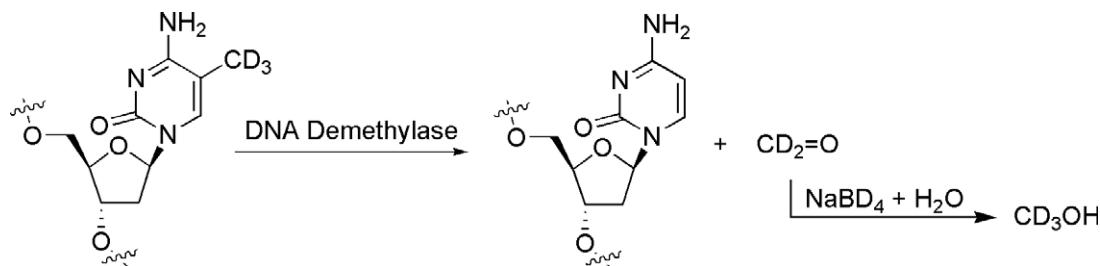
Subas M. Sakya,* Andrei Shavnya, Hengmiao Cheng, Chao Li, Bryson Rast, Jin Li, David A. Koss, Burton H. Jaynes, Donald W. Mann, Carol F. Petras, Scott B. Seibel, Michelle L. Haven and Michael P. Lynch

Structure–activity relationship (SAR) studies of novel 5-alkyl and 5-aryl/heteroaryl substituted 1,2,4-triazoles are described. The in vitro activity is compared to that of the pyrazole class of compounds with analogous side chains to delineate the contribution of the triazole ring nitrogen in binding to the active site. Both series are quite potent and selective in the canine whole blood (CWB) COX-2 assay, suggesting the increased binding contribution of the hydrophobic side chains.

**On the mechanism of demethylation of 5-methylcytosine in DNA**

pp 1046–1049

Stefan Hamm, George Just, Nathalie Lacoste, Nicolas Moitessier, Moshe Szyf and Orval Mamer*

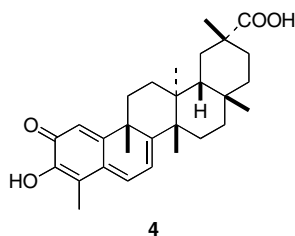


The $^2\text{H}_3$ -methyl group in DNA 5-[Me- $^2\text{H}_3$] is removed by MBD2 as dideuteroformaldehyde.

Antimitotic quinoid triterpenes from *Maytenus chuchuhuasca*

pp 1050–1052

Hiroshi Morita,* Yusuke Hirasawa, Akihiro Muto, Tadashi Yoshida, Setsuko Sekita and Osamu Shiota

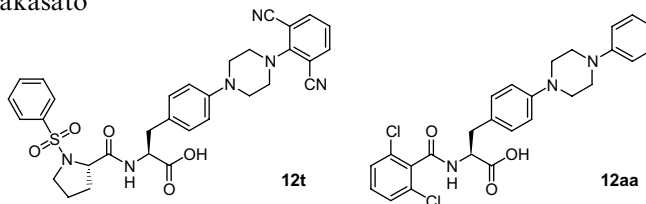


Four cytotoxic quinoid triterpenes, tingenone (1), 22 β -hydroxytingenone (2), pristimerin (3), and celastrol (4), isolated from *Maytenus chuchuhuasca*, potently inhibit the polymerization of tubulin.

Synthetic study of VLA-4/VCAM-1 inhibitors: Synthesis and structure–activity relationship of piperazinylphenylalanine derivatives

pp 1053–1057

Osamu Saku, Kiminori Ohta, Eri Arai, Yuji Nomoto, Hiroko Miura, Hiroaki Nakamura, Eiichi Fuse and Yoshisuke Nakasato*

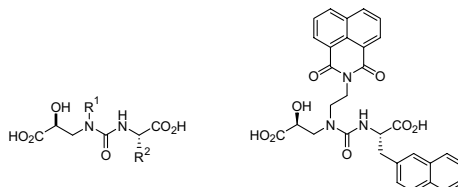


To improve poor pharmacokinetic characters of the preceding VLA-4 inhibitors, novel piperazinylphenylalanine derivatives were designed and optimized for oral bioavailability.

Targeting ACE and ECE with dual acting inhibitors

pp 1058–1062

Stephen Hanessian,* Sébastien Guesné, Ludivine Riber, Julien Marin, Alain Benoist, Philippe Menneccier, Alain Rupin, Tony J. Verbeuren and Guillaume De Nanteuil



A series of urea analogues related to SA6817 and a GSK phosphonic acid with reported ACE inhibitory activity were prepared and tested for dual ACE and ECE activities. Although excellent ACE and NEP inhibition was achieved, only modest ECE inhibition was observed with one analogue.

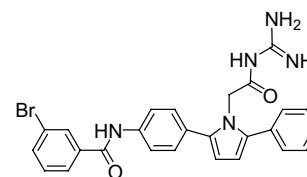


Acylguanidine inhibitors of β -secretase: Optimization of the pyrrole ring substituents extending into the S_1 and S_3 substrate binding pockets

pp 1063–1066

Derek C. Cole,* Joseph R. Stock, Rajiv Chopra, Rebecca Cowling, John W. Ellingboe, Kristi Y. Fan, Boyd L. Harrison, Yun Hu, Steve Jacobsen, Lee D. Jennings, Guixian Jin, Peter A. Lohse, Michael S. Malamas, Eric S. Manas, William J. Moore, Mary-Margaret O'Donnell, Andrea M. Olland, Albert J. Robichaud, Kristine Svenson, JunJun Wu, Eric Wagner and Jonathan Bard

Hit-to-lead optimization of a series of acyl guanidines by optimization of the interactions with the S_1 – S_3 and S_2' enzyme binding pockets led to submicromolar BACE-1 inhibitors.

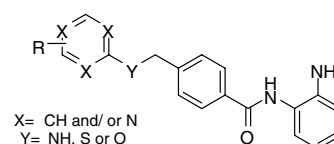


Design and synthesis of 4-[(s-triazin-2-ylamino)methyl]-N-(2-aminophenyl)-benzamides and their analogues as a novel class of histone deacetylase inhibitors

pp 1067–1071

Isabelle Paquin, Stéphane Raeppe,* Silvana Leit, Frédéric Gaudette, Nancy Zhou, Oscar Moradei, Oscar Saavedra, Naomy Bernstein, Franck Raeppe, Giliane Bouchain, Sylvie Fréchette, Soon H. Woo, Arkadii Vaisburg, Marielle Fournel, Ann Kalita, Marie-France Robert, Aihua Lu, Marie-Claude Trachy-Bourget, Pu Theresa Yan, Jianhong Liu, Jubrail Rahil, A. Robert MacLeod, Jeffrey M. Besterman, Zuomei Li and Daniel Delorme

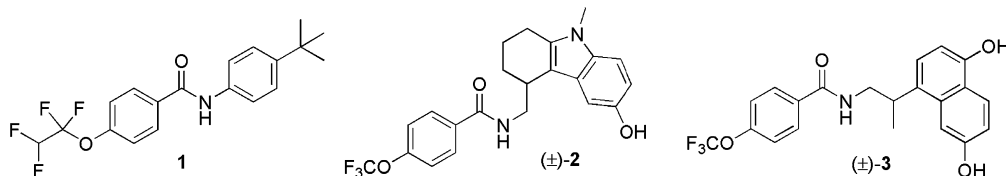
The synthesis and biological evaluation as histone deacetylase (HDACs) inhibitors of a variety of 4-(heteroarylaminomethyl)-N-(2-aminophenyl)-benzamides of the general structure shown is presented herein.



Synthesis of benzamide derivatives as TRPV1 antagonists

pp 1072–1078

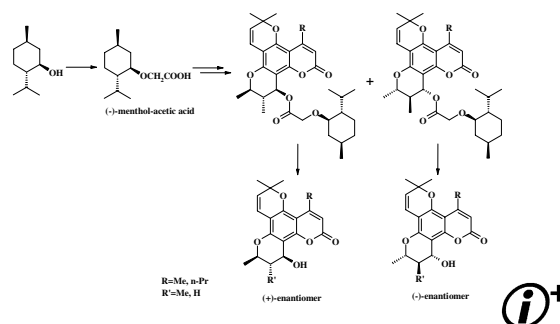
Yuji Shishido,* Madoka Jinno, Takafumi Ikeda, Fumitaka Ito, Masaki Sudo, Naoya Makita, Atsuko Ohta, Ayako Iki-Taki, Takashi Ohmi, Yoshihito Kanai, Tetsuya Tamura and Masato Shimojo

**Chemical resolution of (±)-calanolide A, (±)-cordatolide A and their 11-demethyl analogues**

pp 1079–1083

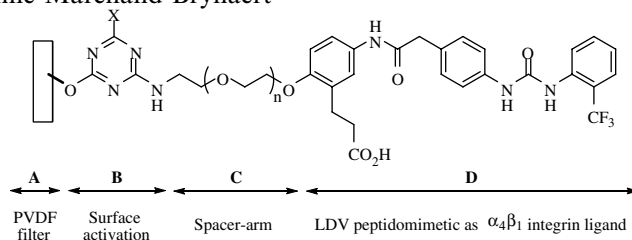
Tao Ma, Qi Gao, Zhiwei Chen, Lin Wang and Gang Liu*

The chemical resolution of (±)-calanolide A and (±)-cordatolide A into their corresponding optically active enantiomers is described in this paper. Their inhibitory activities against HIV-1 are also tested in vitro.

**A graftable LDV peptidomimetic: Design, synthesis and application to a blood filtration membrane**

pp 1084–1090

Maryam Momtaz, Vincent Rerat, Sonia Gharbi, Estelle Gérard, Vincent Pourcelle and Jacqueline Marchand-Brynaert*



A PVDF hydrophilic membrane was surface modified with a non-peptide mimic of the fibronectin LDV sequence designed as VLA-4 integrin ligand. Leukocyte depletion with such a filter was significantly improved.

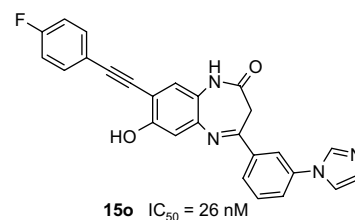
Synthesis and characterization of 8-ethynyl-1,3-dihydro-benzo[*b*][1,4]diazepin-2-one derivatives:

pp 1091–1095

Part 2. New potent non-competitive metabotropic glutamate receptor 2/3 antagonists

Thomas J. Woltering,* Geo Adam, Jürgen Wichmann, Erwin Goetschi, James N. C. Kew, Frédéric Knoflach, Vincent Mutel and Silvia Gatti

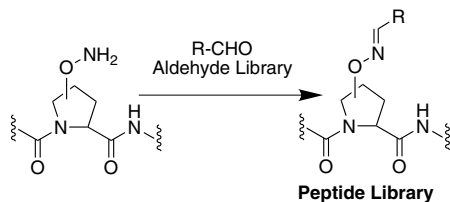
In a series of 1,3-dihydro-benzo[*b*][1,4]diazepin-2-ones the replacement of a nitrile by a five-membered heterocycle produced highly potent non-competitive group II mGluR antagonists. Further modification led to compounds with the ability to reverse LY354740-mediated inhibition of field excitatory postsynaptic potentials in the rat dentate gyrus.



Protected aminooxyprolines for expedited library synthesis: Application to Tsg101-directed proline–oxime containing peptides

pp 1096–1101

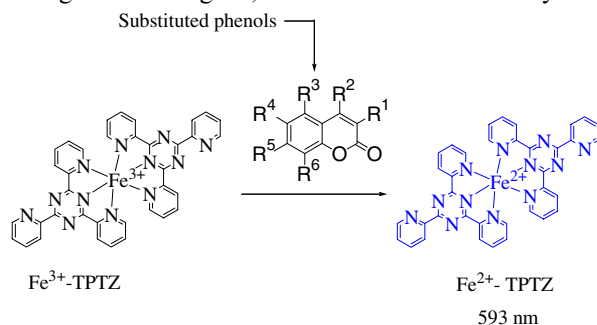
Fa Liu, Andrew G. Stephen, Robert J. Fisher and Terrence R. Burke, Jr.,*



Synthesis and protective effects of coumarin derivatives against oxidative stress induced by doxorubicin

pp 1102–1105

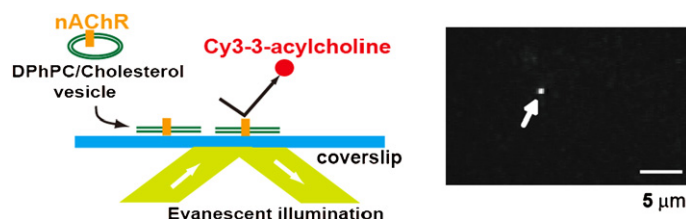
Adeline Beillerot, Juan-Carlos Rodríguez Domínguez, Gilbert Kirsch and Denyse Bagrel*



Cy3-3-acetylcholine: A fluorescent analogue of acetylcholine for single molecule detection

pp 1106–1109

Kenzo Fujimoto, Yoshinaga Yoshimura, Makoto Ihara, Kazuhiko Matsuda, Yuko Takeuchi,* Takaaki Aoki and Toru Ide



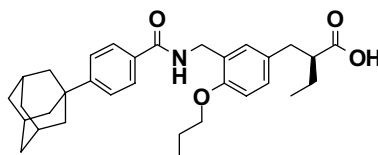
A novel fluorescent analogue of acetylcholine, Cy3-3-acetylcholine, was synthesized. Discrete intensity changes of fluorescent spots due to a single ligand binding/unbinding to nicotinic acetylcholine receptors were visualized under microscopy.



SAR-oriented discovery of peroxisome proliferator-activated receptor pan agonist with a 4-adamantylphenyl group as a hydrophobic tail

pp 1110–1115

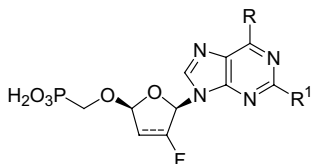
Jun-ichi Kasuga, Daisuke Yamasaki, Kiyoshi Ogura, Motomu Shimizu, Mayumi Sato, Makoto Makishima, Takefumi Doi, Yuichi Hashimoto and Hiroyuki Miyachi*



3-(4-Alkoxyphenyl)propanoic acid derivatives were prepared as candidate peroxisome proliferator-activated receptor (PPAR) $\alpha/\delta/\gamma$ pan agonists, based on our previous SAR studies directed toward the development of subtype-selective PPAR agonists.

Synthesis and anti-HIV activity of 2'-fluorine modified nucleoside phosphonates: Analogs of GS-9148 pp 1116–1119

Richard L. Mackman,* Kuei-Ying Lin, Constantine G. Booramra, Hon Hui, Janet Douglas, Deborah Grant, Oleg Petrakovsky, Vidya Prasad, Adrian S. Ray and Tomas Cihlar

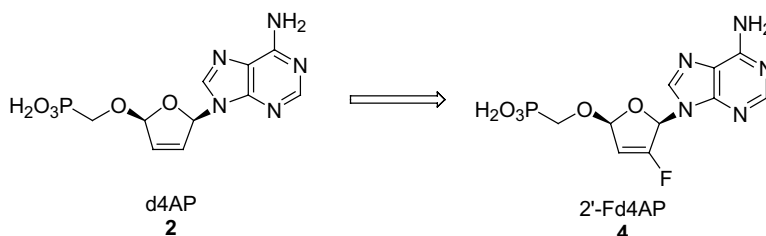


Modified purine analogs of nucleoside phosphonate GS-9148 (2'-F-d4AP) were synthesized and their anti-HIV activity evaluated.

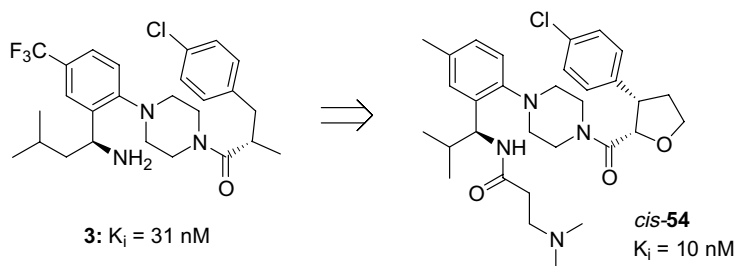
Synthesis and anti-HIV activity of GS-9148 (2'-Fd4AP), a novel nucleoside phosphonate HIV reverse transcriptase inhibitor pp 1120–1123

Constantine G. Booramra,* Richard L. Mackman, David Y. Markevitch, Vidya Prasad, Adrian S. Ray, Janet Douglas, Deborah Grant, Choung U. Kim and Tomas Cihlar

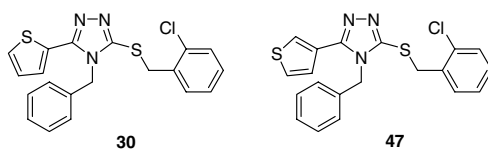
Compound **4** (2'-Fd4AP) was synthesized and maintained the favorable anti-HIV properties of **2** while demonstrating a marked reduction in mitochondrial toxicity to HepG2 cells.

**Syntheses of tetrahydrothiophenes and tetrahydrofurans and studies of their derivatives as melanocortin-4 receptor ligands** pp 1124–1130

Joe A. Tran, Caroline W. Chen, Fabio C. Tucci, Wanlong Jiang, Beth A. Fleck and Chen Chen*

**Triazole derivatives as non-nucleoside inhibitors of HIV-1 reverse transcriptase—Structure–activity relationships and crystallographic analysis** pp 1131–1134

Thorsten A. Kirschberg,* Mini Balakrishnan, Wei Huang, Rebecca Hluhanich, Nilima Kutty, Albert C. Licican, Damian J. McColl, Neil H. Squires and Eric B. Lansdon



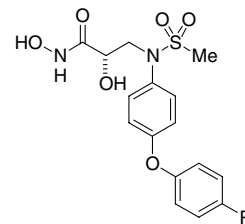
β -N-Biaryl ether sulfonamide hydroxamates as potent gelatinase inhibitors:

pp 1135–1139

Part 1. Design, synthesis, and lead identification

Shyh-Ming Yang,* Robert H. Scannevin, Bingbing Wang, Sharon L. Burke, Lawrence J. Wilson, Prabha Karnachi, Kenneth J. Rhodes, Bharat Lagu and William V. Murray

A new series of β -N-biaryl ether sulfonamide hydroxamates as novel gelatinase inhibitors is described.



R= Me, MMP-2: 61 nM, MMP-9: 7.8 nM
R= Cl, MMP-2: 35 nM, MMP-9: 4.7 nM

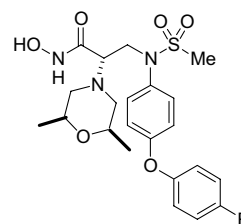
 β -N-Biaryl ether sulfonamide hydroxamates as potent gelatinase inhibitors:

pp 1140–1145

Part 2. Optimization of α -amino substituents

Shyh-Ming Yang,* Robert H. Scannevin, Bingbing Wang, Sharon L. Burke, Zhihong Huang, Prabha Karnachi, Lawrence J. Wilson, Kenneth J. Rhodes, Bharat Lagu and William V. Murray

A new series of α -amino- β -N-biaryl ether sulfonamide hydroxamates as potent gelatinase inhibitors is described.

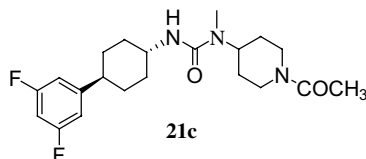


R= Me, MMP-2: 2.8 nM, MMP-9: 0.68 nM
R= Cl, MMP-2: 2.5 nM, MMP-9: 0.46 nM

Discovery of novel orally active ureido NPY Y5 receptor antagonists

pp 1146–1150

Guoqing Li,* Andrew W. Stamford,* Ying Huang, Kuo-Chi Cheng, John Cook, Constance Farley, Jun Gao, Lorraine Ghibaudo, William J. Greenlee, Mario Guzzi, Margaret van Heek, Joyce J. Hwa, Joe Kelly, Deborra Mullins, Eric M. Parker, Sam Wainhaus and Xiaoping Zhang

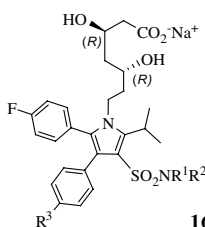


Structure–activity relationship studies leading to the potent, selective NPY Y5 receptor antagonist **21c** are described. Compound **21c** demonstrated dose-dependent anti-obesity effects in diet-induced obese rats after chronic oral administration.

Hepatoselectivity of statins: Design and synthesis of 4-sulfamoyl pyrroles as HMG-CoA reductase inhibitors

pp 1151–1156

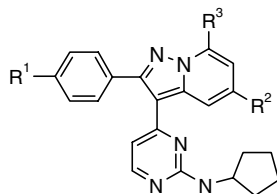
William K. C. Park,* Robert M. Kennedy, Scott D. Larsen, Steve Miller, Bruce D. Roth, Yuntao Song, Bruce A. Steinbaugh, Kevin Sun, Bradley D. Tait, Mark C. Kowala, Bharat K. Trivedi, Bruce Auerbach, Valerie Askew, Lisa Dillon, Jeffrey C. Hanselman, Zhiwu Lin, Gina H. Lu, Andrew Robertson and Catherine Sekerke



Pyrazolopyridines with potent activity against herpesviruses: Effects of C5 substituents on antiviral activity

pp 1157–1161

Kristjan S. Gudmundsson,* Brian A. Johns and Scott H. Allen

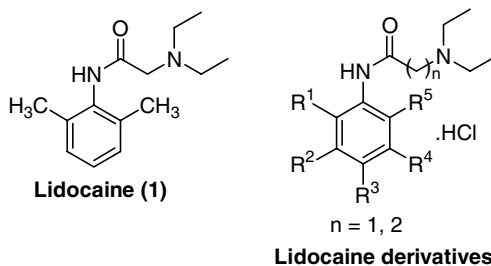


Synthesis of a series of 5-substituted as well as 5,7-disubstituted 3-[2-(cyclopentylamino)-4-pyrimidinyl]-2-phenylpyrazolo[1,5-*a*]pyridin-7-amines with potent activity against herpes simplex viruses is described. Synthetic approaches allowing for variation of the substitution pattern are outlined and resulting changes in antiviral activity are highlighted.

Synthesis and antispasmodic activity of lidocaine derivatives endowed with reduced local anesthetic action

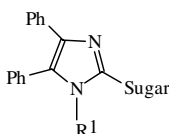
pp 1162–1166

Jorge C. S. Costa, Josiane S. Neves, Marcus V. N. de Souza, Rodrigo A. Siqueira, Nelilma C. Romeiro, Nubia Boechat, Patrícia M. R. e Silva and Marco A. Martins*

**Synthesis and antimicrobial activity of novel C-linked imidazole glycoconjugates**

pp 1167–1171

Lingaiiah Nagarapu,* A. Satyender, B. Rajashaker, K. Srinivas, P. Rupa rani, K. Radhika and G. Subhashini

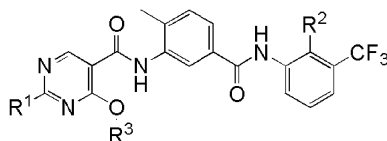


Nine novel C-2 chiral tetra substituted imidazoles were synthesized and screened for antibacterial and antifungal activities.

N-(3-(Phenylcarbamoyl)arylpyrimidine)-5-carboxamides as potent and selective inhibitors of Lck: Structure, synthesis and SAR

pp 1172–1176

Holly L. Deak,* John R. Newcomb, Joseph J. Nunes, Christina Boucher, Alan C. Cheng, Erin F. DiMauro, Linda F. Epstein, Paul Gallant, Brian L. Hodous, Xin Huang, Josie H. Lee, Vinod F. Patel, Stephen Schneider, Susan M. Turci and Xiaotian Zhu

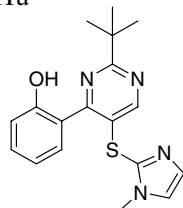


A novel class of selective Lck inhibitors is reported. X-ray co-crystal structural data, structure–activity relationships, and the synthesis of these inhibitors are described.

Three-component, one-pot synthesis of novel 2,4-substituted 5-azolythiopyrimidine library for screening against anti-influenza virus A

pp 1177–1180

Gang Cheng, Shukun Li, Jingya Li and Youhong Hu*

 $IC_{50} = 21.56 \text{ mg/mL}$

A novel three-component, one-pot reaction synthesizes 2,4-substituted 5-azolythiopyrimidines and Compound **A₁B₆C₁** exhibits a potent anti-influenza virus A activity ($IC_{50} = 21.56 \text{ mg/mL}$).

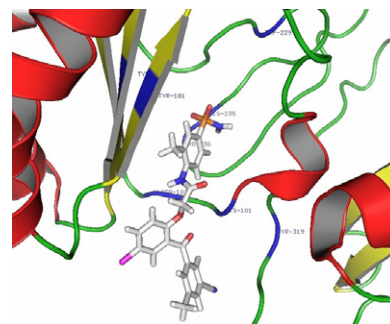


3D-QSAR models on clinically relevant K103N mutant HIV-1 reverse transcriptase obtained from two strategic considerations

pp 1181–1194

Amor A. San Juan*

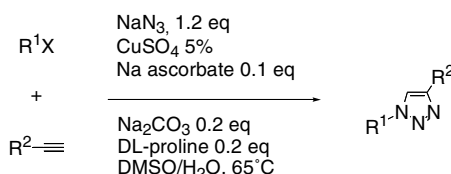
In this study, new alternative strategic routes are presented to generate 3D-QSAR model inhibitors for the clinically relevant Lys103Asn (K103N) mutant HIV-1 reverse transcriptase. The results demonstrated the feasibility of the two strategies to the present case and hold a promise for its general applicability to future QSAR studies. Further, the present study introduced the concept 'clamp-flex' for the rational design of targeted-inhibitor to overcome the K103N pan-class resistance mutation. The predictive models offer new insights into binding modes involving the hydrophobicity and flexibility of the active site.



Synthesis and antibiotic activity of a small molecules library of 1,2,3-triazole derivatives

pp 1195–1198

Marie Aufort, Jean Herscovici, Pascale Bouhours, Nicole Moreau and Christian Girard*

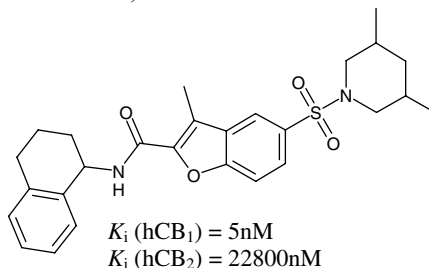


A small library of simple 1,4-disubstituted 1,2,3-triazoles was prepared using a known one-pot procedure starting from organic halides and terminal alkynes. The compounds were then tested for their antibacterial activity against normal and resistant species of *Staphylococcus aureus*.

Discovery of a novel class of selective human CB₁ inverse agonists

pp 1199–1206

Nicolas Foloppe,* Nicola H. Allen, Carol H. Bentley, Teresa D. Brooks, Guy Kennett, Antony R. Knight, Stefania Leonardi, Anil Misra, Nathaniel J. T. Monck and Daniel M. Sellwood

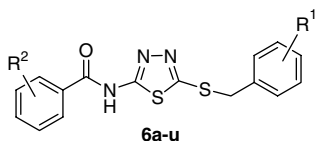


hCB₁ antagonist pharmacophore → virtual screening → binding assay → functional assay → new class of potent hCB₁ inverse agonists.

Discovery and SAR of 1,3,4-thiadiazole derivatives as potent Abl tyrosine kinase inhibitors and cytodifferentiating agents

pp 1207–1211

Marco Radi, Emmanuele Crespan, Giorgia Botta, Federico Falchi, Giovanni Maga, Fabrizio Manetti, Valentina Corradi, Manuela Mancini, Maria Alessandra Santucci, Silvia Schenone and Maurizio Botta*



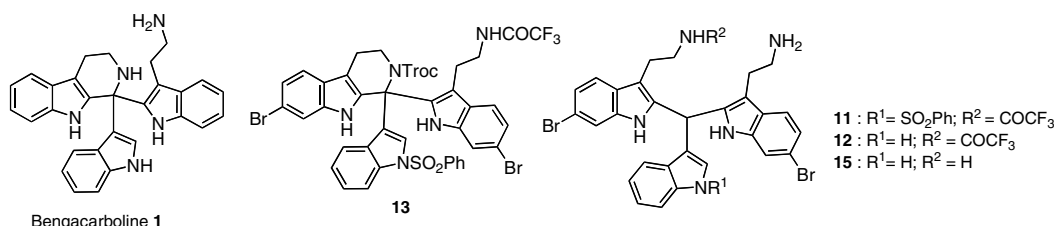
A series of substituted benzoylamino-2-[(4-benzyl)thio]-1,3,4-thiadiazoles (**6a–u**) has been discovered as potent Abl tyrosine kinase inhibitors showing an interesting inhibitory activity on murine myeloid 3B clone and drug resistant subclones.



Synthesis and biological evaluation of bengacarboline derivatives

pp 1212–1216

Annie Pouilhès, Cyrille Kouklovsky, Yves Langlois,* Jean-Pierre Baltaze, Stéphane Vispé, Jean-Philippe Annereau, Jean-Marc Barret, Anna Kruczynski and Christian Bailly

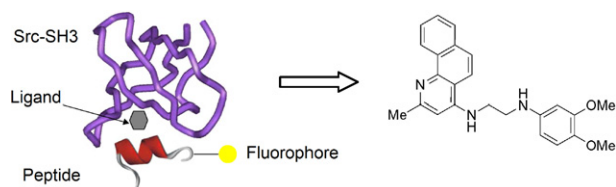


Bengacarboline derivatives (**11–13** and **15**) were synthesized. Seco derivatives **11** and **12** display a cytotoxic activity by inducing an accumulation of cells in the S phase of DNA synthesis.

In silico screening and biological evaluation of inhibitors of Src-SH3 domain interaction with a proline-rich ligand

pp 1217–1222

Noor Atatreh, Cvetan Stojkoski, Phillippa Smith, Grant W. Booker, Caroline Dive, A. David Frenkel, Sally Freeman* and Richard A. Bryce*

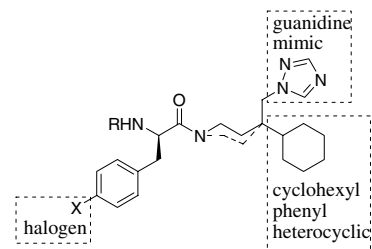


Synthesis and biological activity of novel peptide mimetics as melanocortin receptor agonists

pp 1223–1228

Xue-Wei Liu,* Jimei Ma, Anny-Odile Colson, Doreen Cross Doersen and Frank H. Ebetino

The design, synthesis, and biological activity of a series of peptidomimetic melanocortin receptor agonists is reported. Some binding affinity at the melanocortin receptors MC₃ and MC₄ was noted. In silico docking indicated that the relative positions of the hydrogen-bonding sites and hydrophobic regions of the compounds are reasonably well matched to the receptor-binding site. This may present a lead entry into a selective series of MC₄R agonists.

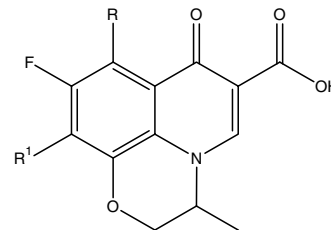


Novel ofloxacin derivatives: Synthesis, antimycobacterial and toxicological evaluation

pp 1229–1236

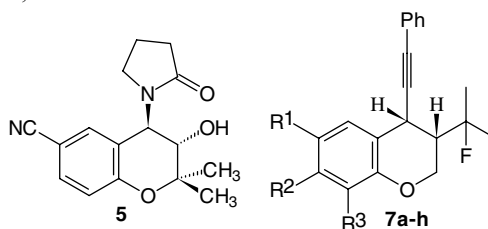
Murugesan Dinakaran, Palaniappan Senthilkumar, Perumal Yogeeswari, Arnab China, Valakunja Nagaraja and Dharmarajan Sriram*

Thirty novel 9-fluoro-2,3-dihydro-8,10-(mono/di-sub)-3-methyl-8-nitro-7-oxo-7*H*-[1,4]oxazino[2,3,4-*ij*]quinoline-6-carboxylic acids were synthesized and evaluated for in vitro and in vivo antimycobacterial activities. One compound was found to be the most active compound in vitro with MIC₉₉ of 0.19 μ M and 0.09 μ M against MTB and MTR-TB, respectively.

**The synthesis and biological evaluation of a range of novel functionalised benzopyrans as potential potassium channel activators**

pp 1237–1240

Elizabeth Tyrrell,* Kibur Hunie Tesfa, Iain Greenwood and Alistair Mann

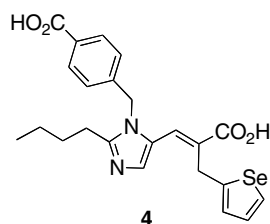


A range of novel benzopyrans **7a–h** have been synthesised and screened for K_{ATP} channel activity. In this study, the activities were compared to the benchmark K_{ATP} channel opener cromakalim **1**.

Selenosartans: Novel selenophene analogues of milfasartan and eprosartan

pp 1241–1244

Rebecca L. Grange, James Ziogas, Andrea J. North, James A. Angus and Carl H. Schiesser*



The synthesis and preliminary evaluation of selenophene-containing sartans (e.g. **4**; $pK_B = 8.3$) is reported.

OTHER CONTENTS**Summary of instructions to authors**

p I

*Corresponding author

* Supplementary data available via ScienceDirect

COVER

Overlay of high resolution co-crystal structures of *R*-**22**-ADP (cyan) and **1**-ADP (green) bound in an allosteric binding site of the mitotic kinesin KSP. [Roecker, A. J.; Coleman, P. J.; Mercer, S. P.; Schreier, J. D.; Buser, C. A.; Walsh, E. S.; Hamilton, K.; Lobell, R. B.; Tao, W.; Diehl, R. E.; South, V. J.; Davide, J. P.; Kohl, N. E.; Yan, Y.; Kuo, L. C.; Li, C.; Fernandez-Metzler, C.; Mahan, E. A.; Prueksaritanont, T.; Hartman, G. D. *Bioorg. Med. Chem. Lett.* **2007**, 17, 5677.]

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ISSN 0960-894X