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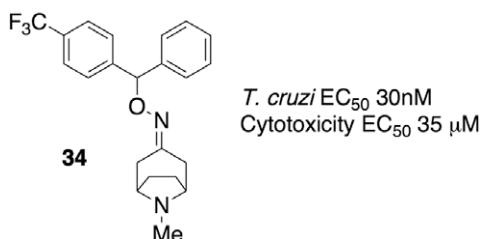


Bioorganic & Medicinal Chemistry Letters Volume 20, Issue 6, 2010

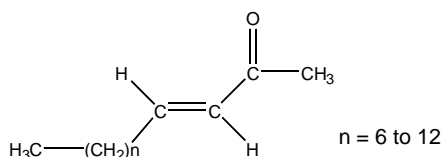
Contents

ARTICLES

- Discovery of novel and potent benzhydryl-tropane trypanocides highly selective for *Trypanosoma cruzi*** pp 1816–1818
G. A. Holloway, J. P. Parisot, P. M. Novello, K. G. Watson, T. Armstrong, R. C. A. Thompson, I. P. Street, J. B. Baell*

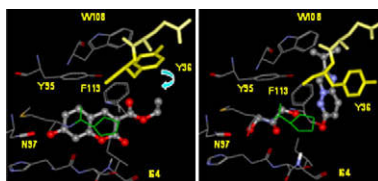


- Antimicrobial activity of long-chain (*E*)-3-alken-2-ones** pp 1819–1820
William F. Wood*, Aya Kubo, Tony B. Shaffer



A number of long-chain (*E*)-3-alken-2-one homologues of the naturally occurring antimicrobial compound (*E*)-3-tridecen-2-one were prepared and their antimicrobial activity reported.

- Fragment screening of inhibitors for MIF tautomerase reveals a cryptic surface binding site** pp 1821–1824
Larry R. McLean*, Ying Zhang, Hua Li, Yong-Mi Choi, Zuoning Han, Roy J. Vaz, Yi Li*

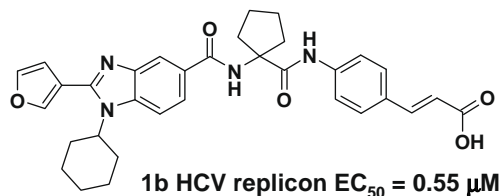


Fragment screening by in silico docking followed by X-ray crystallography demonstrates the formation of a previously unreported surface binding site in MIF that is hydrophobic and surrounded by aromatic side-chain residues.

Benzimidazole Thumb Pocket I finger-loop inhibitors of HCV NS5B polymerase: Improved drug-like properties through C-2 SAR in three sub-series

pp 1825–1829

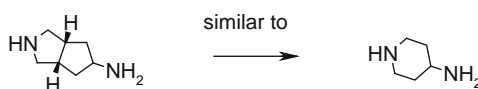
Pierre L. Beaulieu*, Nathalie Dansereau, Jianmin Duan, Michel Garneau, James Gillard, Ginette McKercher, Steven LaPlante, Lisette Lagacée, Louise Thauvette, George Kukolj



Evaluation of a 4-aminopiperidine replacement in several series of CCR5 antagonists

pp 1830–1833

Rémy C. Lemoine*, Ann C. Petersen, Lina Setti, Lijing Chen, Jutta Wanner, Andreas Jekle, Gabrielle Heilek, André deRosier, Changhua Ji, David M. Rotstein

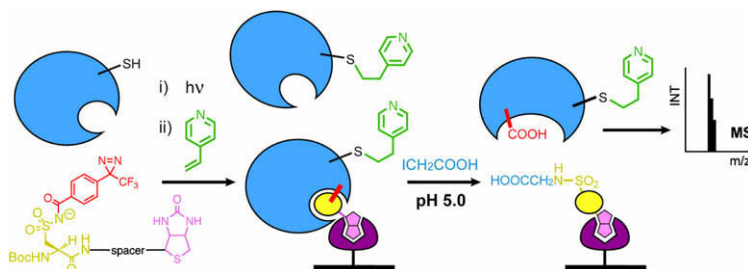


The bicyclic 5-amino-3-azabicyclo[3.3.0]octanes were shown to be effective replacements for the 4-aminopiperidine ring system found in several series of chemokine receptor CCR5 antagonists.

Efficient approach for profiling photoaffinity labeled peptides with a cleavable biotinyl photoprobe

pp 1834–1836

Nlandu B. Bongo, Takenori Tomohiro, Yasumaru Hatanaka*

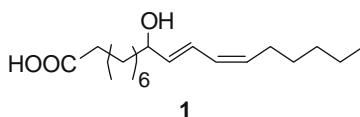


Highly efficient profiling of labeled peptide was achieved with cleavable biotinylated probe by utilizing selective S- and N-alkylation.

Unprecedented NES non-antagonistic inhibitor for nuclear export of Rev from *Sida cordifolia*

pp 1837–1839

Satoru Tamura, Masafumi Kaneko, Atsushi Shiomi, Guang-Ming Yang, Toshiaki Yamaura, Nobutoshi Murakami*

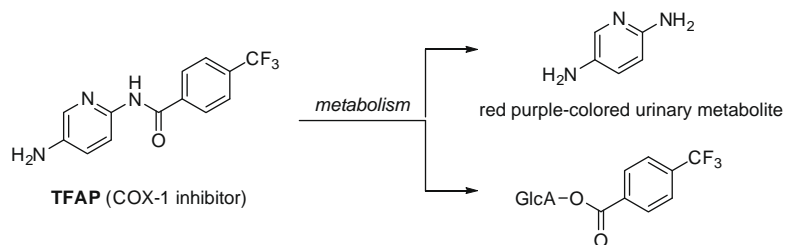


As an unprecedented NES non-antagonistic inhibitor for nuclear export of Rev, (10E,12Z)-9-hydroxyoctadeca-10,12-dienoic acid (**1**) was disclosed. Additionally, structure–activity relationship analysis clarified cooperation of several functionalities in potency of **1**.

Identification of urine metabolites of TFAP, a cyclooxygenase-1 inhibitor

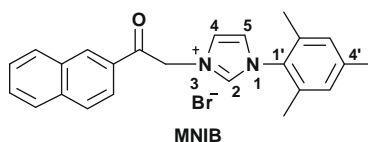
pp 1840–1843

Hiroki Kakuta*, Ryosuke Fukai, Zheng Xiaoxia, Fuminori Ohsawa, Takeshi Bamba, Kazumasa Hirata, Akihiro Tai

**Synthesis and antitumor activity of 1-mesityl-3-(2-naphthoylemethano)-1H-imidazolium bromide**

pp 1844–1847

Xianghui Zeng, Xiaodong Yang, Yanli Zhang, Chen Qing*, Hongbin Zhang*

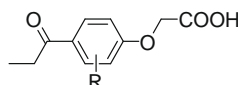


An imidazolium salt, 1-mesityl-3-(2-naphthoylemethano)-1H-imidazolium bromide (MNIB), has been investigated for its antitumor properties. In vitro studies demonstrate that MNIB is active against K562, SMMC-7721, EJ, AGZY, HEP-2, A549, HepG2, and Raji tumor cells, and can induce the G1 phase cell cycle arrest and apoptosis in K562 cells. Moreover, administration of MNIB significantly inhibited tumor growth in human non-small lung tumor (A549) xenografts.

Ethacrynic acid analogues lacking the α,β -unsaturated carbonyl unit—Potential anti-metastatic drugs

pp 1848–1850

Romy F. J. Janser, Ranjith K. Meka, Zack E. Bryant, Enoch A. Adogla, Elizabeth K. Vogel, Jaimie L. Wharton, Cynthia M. Tilley, Catherine N. Kaminski, Seth L. Ferrey, Severine Van slambrouck, Wim F. A. Steelant, Ingo Janser*

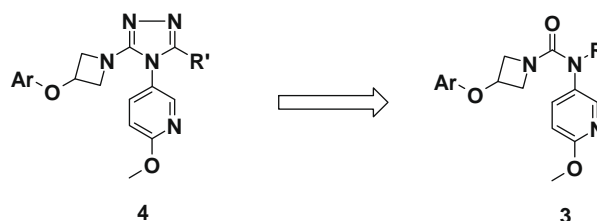


Analogues of ethacrynic acid, lacking the α,β -unsaturated carbonyl unit, were designed, synthesized, and subsequently evaluated for their cytotoxicity and anti-migratory effects against human MCF-7/AZ breast cancer cells.

Identification of a urea bioisostere of a triazole oxytocin antagonist

pp 1851–1853

Alan Brown*, Dave Ellis, Olga Wallace, Michael Ralph

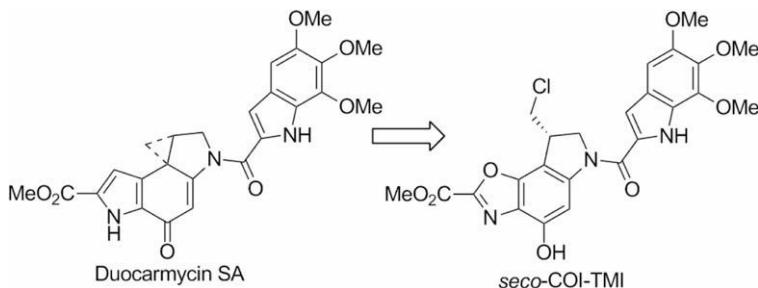


A series of azetidine ureas, **3**, were prepared as potential bioisosteres of previously reported azetidinyltriazole oxytocin antagonists, **4**. Several potent analogues were prepared and one, compound, **9**, demonstrated significant levels of selectivity over the closely related vasopressin V_{1A} receptor.

Synthesis and evaluation of duocarmycin SA analogs incorporating the methyl 1,2,8,8a-tetrahydrocyclopropa[c]oxazolo[2,3-e]indol-4-one-6-carboxylate (COI) alkylation subunit

pp 1854–1857

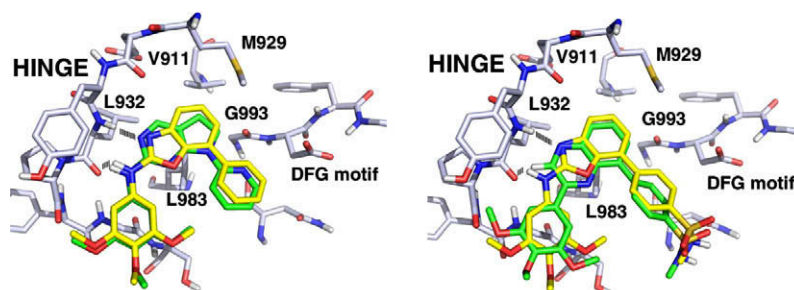
Kristopher E. Boyle, Karen S. MacMillan, David A. Ellis, James P. Lajiness, William M. Robertson, Dale L. Boger*



Design of two new chemotypes for inhibiting the Janus kinase 2 by scaffold morphing

pp 1858–1860

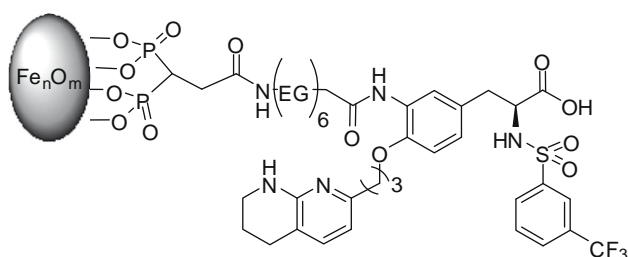
Pascal Furet*, Marc Gerspacher, Carole Pissot-Soldermann



Ultrasmall particle of iron oxide–RGD peptidomimetic conjugate: synthesis and characterisation

pp 1861–1865

Vincent Rerat, Sophie Laurent, Carmen Burtéa, Benoît Driesschaert, Vincent Pourcelle, Luce Vander Elst, Robert N. Muller, Jacqueline Marchand-Brynaert*



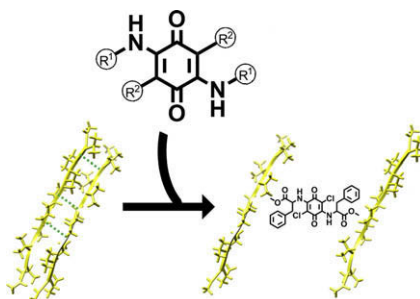
USPIO–peptidomimetic conjugate targeting Jurkat cells.



Synthesis and evaluation of a library of 2,5-bisdiamino-benzoquinone derivatives as probes to modulate protein–protein interactions in prions

pp 1866–1868

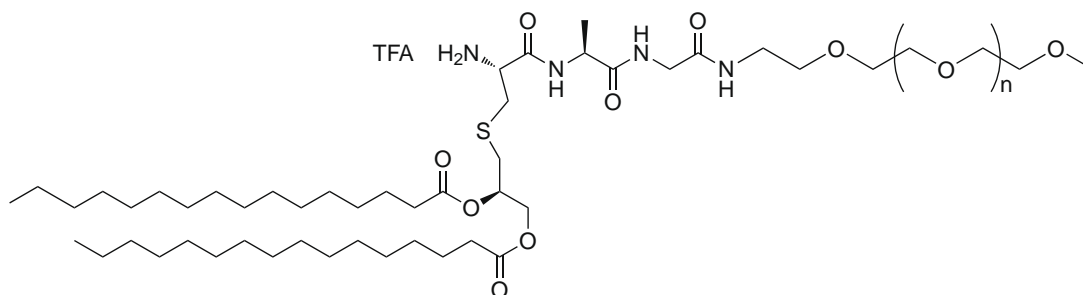
Hoang Ngoc Ai Tran, Salvatore Bongarzone, Paolo Carloni, Giuseppe Legname, Maria Laura Bolognesi*



Novel powerful water-soluble lipid immunoadjuvants inducing mouse dendritic cell maturation and B cell proliferation using TLR2 pathway

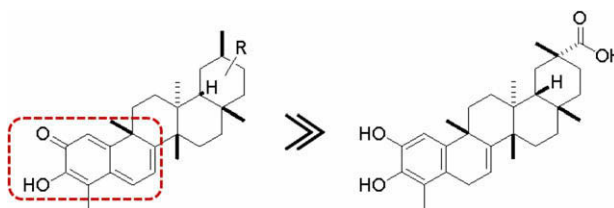
pp 1869–1872

Maria Vittoria Spanedda, Béatrice Heurtault, Steffen Weidner, Corinne Baehr, Emmanuelle Boeglin, Julien Beyrath, Sara Milosevic, Line Bourel-Bonnet, Sylvie Fournel*, Benoît Frisch*

**SARS-CoV 3CL^{pro} inhibitory effects of quinone-methide triterpenes from *Tripterygium regelii***

pp 1873–1876

Young Bae Ryu, Su-Jin Park, Young Min Kim, Ju-Yeon Lee, Woo Duck Seo, Jong Sun Chang, Ki Hun Park, Mun-Chual Rho*, Woo Song Lee*



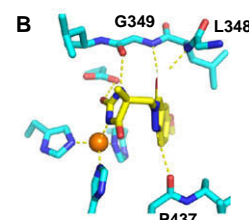
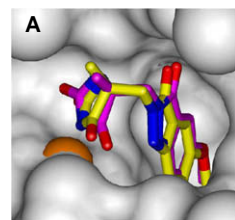
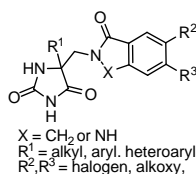
The presence of a quinone-methide moiety appears to play a relatively significant role in 3CL^{pro} inhibition.

**Discovery and SAR of hydantoin TACE inhibitors**

pp 1877–1880

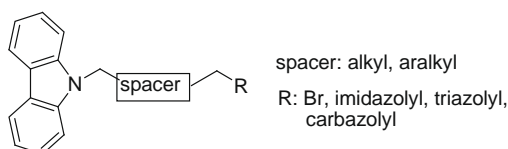
Wensheng Yu*, Zhuyan Guo*, Peter Orth, Vincent Madison, Lei Chen, Chaoyang Dai, Robert J. Feltz, Vinay M. Girijavallabhan, Seong Heon Kim, Joseph A. Kozlowski, Brian J. Lavey, Dansu Li, Daniel Lundell, Xiaoda Niu, John J. Piwinski, Janeta Popovici-Muller, Razia Rizvi, Kristin E. Rosner, Bandarpalle B. Shankar, Neng-Yang Shih, M. Arshad Siddiqui, Jing Sun, Ling Tong, Shelby Umland, Michael K. C. Wong, De-yi Yang, Guowei Zhou

A novel series of hydantoin TACE inhibitors is disclosed. The initial design and SAR optimization of the series, as well as accompanying X-ray structural and modeling considerations, are described.

**Synthesis, antibacterial and antifungal activities of some carbazole derivatives**

pp 1881–1884

Fei-Fei Zhang, Lin-Ling Gan, Cheng-He Zhou*

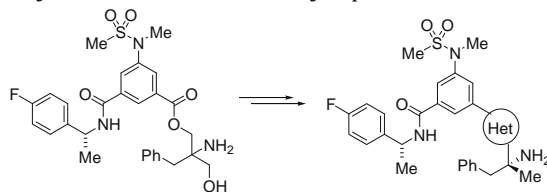


A series of carbazole derivatives were synthesized and evaluated for antibacterial and antifungal activities.

SAR of tertiary carbinamine derived BACE1 inhibitors: Role of aspartate ligand amine pK_a in enzyme inhibition

pp 1885–1889

Hemaka A. Rajapakse*, Philippe G. Nantermet, Harold G. Selnick, James C. Barrow, Georgia B. McGaughey, Sanjeev Munshi, Stacey R. Lindsley, Mary Beth Young, Phung L. Ngo, M. Katherine Holloway, Ming-Tain Lai, Amy S. Espeseth, Xiao-Ping Shi, Dennis Colussi, Beth Pietrak, Ming-Chih Crouthamel, Katherine Tugusheva, Qian Huang, Min Xu, Adam J. Simon, Lawrence Kuo, Daria J. Hazuda, Samuel Graham, Joseph P. Vacca

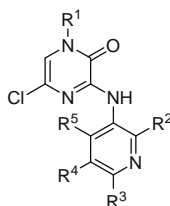


This Letter describes SAR of the tertiary carbinamine derived inhibitors of BACE1 revealed during the optimization of the unstable lead toward potent and stable heterocycle linked compounds. The incorporation of a flap interaction with the target enzyme was not critical for potency. A trend observed during this optimization was that the pK_a of the amine derived aspartate ligand needed to be at least close to that of the assay medium for BACE1 inhibition.

Synthesis and structure–activity relationships of N^3 -pyridylpyrazinones as corticotropin-releasing factor-1 (CRF₁) receptor antagonists

pp 1890–1894

Richard A. Hartz*, Vijay T. Ahuja, William D. Schmitz, Thaddeus F. Molski, Gail K. Mattson, Nicholas J. Lodge, Joanne J. Bronson, John E. Macor

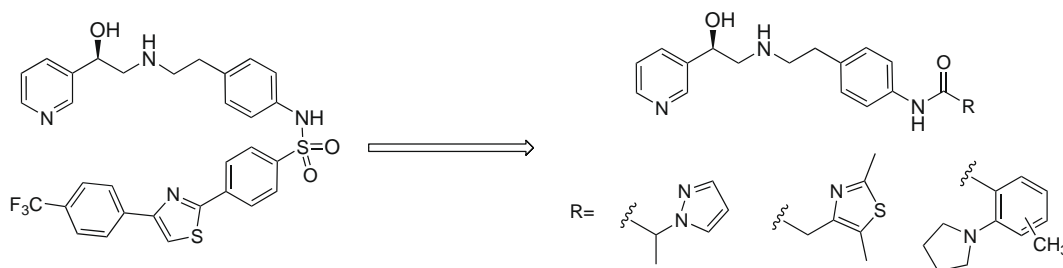


The structure–activity relationships of a series of N^3 -pyridylpyrazinones as corticotropin-releasing factor-1 receptor antagonists was investigated.

Heterocyclic acetamide and benzamide derivatives as potent and selective β_3 -adrenergic receptor agonists with improved rodent pharmacokinetic profiles

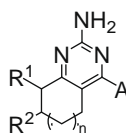
pp 1895–1899

Stephen D. Goble*, Liping Wang, K. Lulu Howell, Alka Bansal, Richard Berger, Linda Brockunier, Jerry DiSalvo, Scott Feighner, Bart Harper, Jiafang He, Amanda Hurley, Donna Hreniuk, Emma Parmee, Michael Robbins, Gino Salituro, Anthony Sanfiz, Eric Streckfuss, Eloisa Watkins, Ann E. Weber, Mary Struthers, Scott D. Edmondson

**Rigidified 2-aminopyrimidines as histamine H_4 receptor antagonists: Effects of substitution about the rigidifying ring**

pp 1900–1904

John R. Koenig*, Huaqing Liu, Irene Drizin, David G. Witte, Tracy L. Carr, Arlene M. Manelli, Ivan Milicic, Marina I. Strakhova, Thomas R. Miller, Timothy A. Esbenshade, Jorge D. Brioni, Marlon Cowart



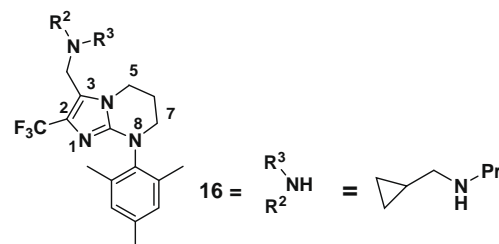
Three novel series of histamine H_4 receptor (H_4R) antagonists containing the 2-aminopyrimidine motif are reported.

Design, synthesis and evaluation of constrained tetrahydroimidazopyrimidine derivatives as antagonists of corticotropin-releasing factor type 1 receptor (CRF₁R)

pp 1905–1909

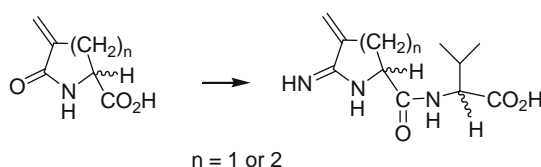
Vivekananda M. Vrudhula*, Bireshwar Dasgupta, Sokhom S. Pin, Kevin D. Burris, Lynn A. Balanda, Lawrence K. Fung, Tracey Fiedler, Kaitlin E. Browman, Matthew T. Taber, Jie Zhang, John E. Macor, Gene M. Dubowchik

Several tetrahydroimidazopyrimidines were prepared using silver assisted cyclization as the key step. The binding affinities of compounds thus prepared were evaluated in vitro toward hCRF₁R. Initial lead compound **16** ($K_i = 32$ nM) demonstrated modest putative anxiolytic effects in the mouse canopy test. Further optimization using parallel synthesis provided compounds with K_i 's <50 nM.

**Synthesis of amino acid conjugates to 2-imino-3-methylene-5-carboxypyrrolidine and 2-imino-3-methylene-6-carboxypiperidine**

pp 1910–1912

Robin E. Mitchell

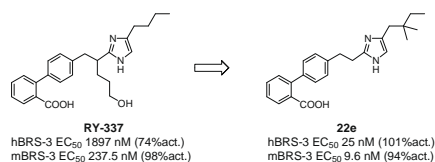


Synthesis and antibacterial activity of amino acid conjugates to 2-imino-3-methylene substituted 5-carboxypyrrolidine and 6-carboxypiperidine is described ($n = 1$, or 2).

**Discovery of substituted biphenyl imidazoles as potent, bioavailable bombesin receptor subtype-3 agonists**

pp 1913–1917

Shuwen He*, Peter H. Dobbelaar, Jian Liu, Tianying Jian, Iyassu K. Sebbat, Linus S. Lin, Allan Goodman, Cheng Guo, Peter R. Guzzo, Mark Hadden, Alan J. Henderson, Megan Ruenz, Bruce J. Sargent, Larry Yet, Theresa M. Kelly, Oksana Palyha, Yanqing Kan, Jie Pan, Howard Chen, Donald J. Marsh, Lauren P. Shearman, Alison M. Strack, Joseph M. Metzger, Scott D. Feighner, Carina Tan, Andrew D. Howard, Constantin Tamvakopoulos, Qianping Peng, Xiao-Ming Guan, Marc L. Reitman, Arthur A. Patchett, Matthew J. Wyvratt Jr., Ravi P. Nargund

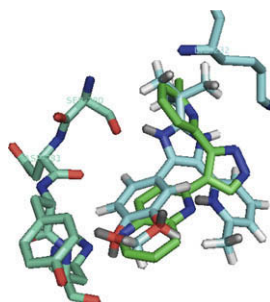


Extensive SAR studies of a series derived from **RY-337**, a novel non-peptidic bombesin receptor subtype-3 (BRS-3) agonist lead, led to the discovery of compound **22e** with significantly improved potency at both rodent and human BRS-3. Analogs in this series demonstrated good rat pharmacokinetics.

3D-QSAR and docking studies on transforming growth factor (TGF)- β receptor 1 antagonists

pp 1918–1923

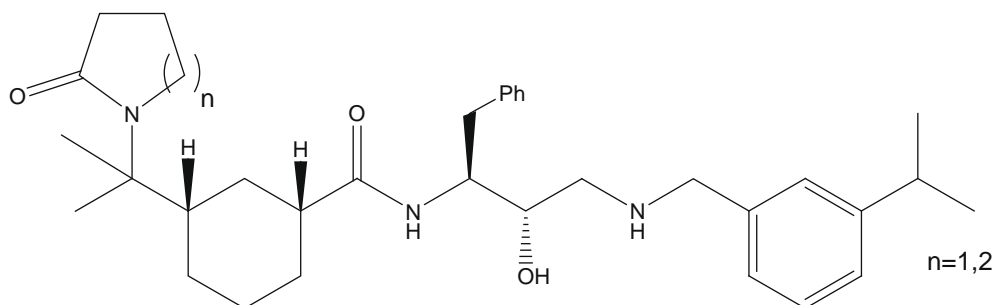
Werner J. Geldenhuys*, Hiroshi Nakamura



Structure-based design and synthesis of novel P2/P3 modified, non-peptidic β -secretase (BACE-1) inhibitors

pp 1924–1927

Stephen Hanessian*, Zhihui Shao, Claudia Betschart, Jean-Michel Rondeau, Ulf Neumann, Marina Tintelnot-Blomley

**New adjuvants to enhance anticoagulant activity of Warfarin**

pp 1928–1932

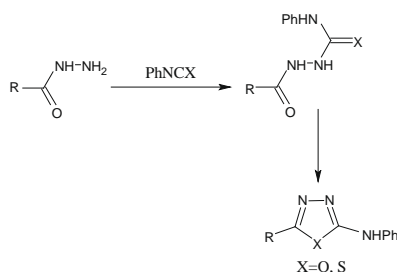
Jeremiah J. Stromich, Ashley K. Weber, Yousef R. Mirzaei, Michael D. Caldwell*, David E. Lewis*

Compounds	Dosage (mg/kg)	PT (4 d)	PT (10 d)	VII% (4 d)	VII% (10 d)	X% (4 d)	X% (10 d)
Control	0	12.8	12.9	400.0	321.3	60.6	58.1
warfarin (1)	0.25	37.0	24.4	29.5	56.2	10.0	14.9
1 +	0.25 + 2.5	40.5	35.4	20.3	35.0	4.8	7.7
1 +	0.25 + 2.5	12.0	108.4	264.0	18.4	58.8	3.6

**Synthesis, characterization, and in vitro antimicrobial activities of 5-alkenyl/hydroxyalkenyl-2-phenylamine-1,3,4-oxadiazoles and thiadiazoles**

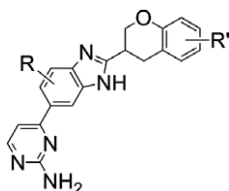
pp 1933–1938

Nida N. Farshori, Mudasir R. Banday, Anis Ahmad, Asad U. Khan, Abdul Rauf*

**The development of benzimidazoles as selective rho kinase inhibitors**

pp 1939–1943

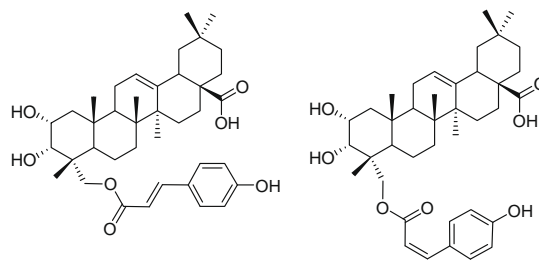
E. Hampton Sessions, Michael Smolinski, Bo Wang, Bozena Frackowiak, Sarwat Chowdhury, Yan Yin, Yen Ting Chen, Claudia Ruiz, Li Lin, Jennifer Pocas, Thomas Schröter, Michael D. Cameron, Philip LoGrasso, Yangbo Feng, Thomas D. Bannister*



Bioactivity-guided isolation of cytotoxic triterpenoids from the trunk of *Berberis koreana*

pp 1944–1947

Ki Hyun Kim, Sang Un Choi, Kang Ro Lee*

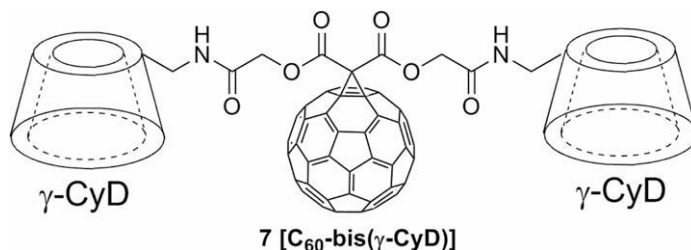


A bioassay-guided fractionation and chemical investigation of the trunk of *Berberis koreana* resulted in the isolation and characterization of two new triterpenoids (**1–2**), along with seven known triterpenoids (**3–9**).

**Syntheses of water-soluble [60]fullerene derivatives and their enhancing effect on neurite outgrowth in NGF-treated PC12 cells**

pp 1948–1952

Hiroki Tsumoto, Syo Kawahara, Yuki Fujisawa, Takayoshi Suzuki, Hidehiko Nakagawa, Kohfuku Kohda*, Naoki Miyata*

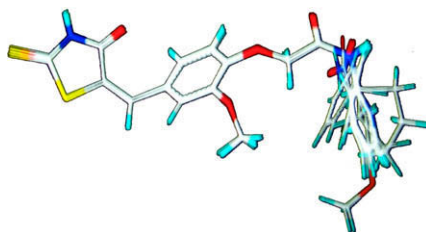


Syntheses of water-soluble C_{60} derivatives and the examination of their enhancing effect on neurite outgrowth of NGF-treated PC12 cells are reported.

**Novel glitazones: Design, synthesis, glucose uptake and structure–activity relationships**

pp 1953–1956

B. R. Prashantha Kumar, M. J. Nanjan*

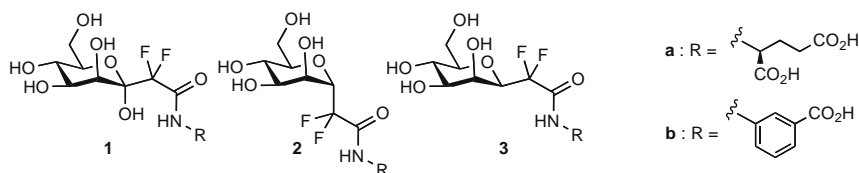


Designed, synthesized, and evaluated some novel glitazones for their antidiabetic activity.

Synthesis of fluorinated C-mannopectides as sialyl Lewis^x mimics for E- and P-selectin inhibition

pp 1957–1960

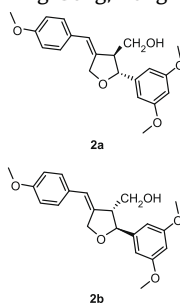
Vanessa Gouge-Ibert, Camille Pierry, Florent Poulain, Anne-Lise Serre, Céline Largeau, Virginie Escriou*, Daniel Scherman, Philippe Jubault, Jean-Charles Quirion, Eric Leclerc*



Synthesis, chiral resolution, and determination of novel furan lignan derivatives with potent anti-tumor activity

pp 1961–1964

Hai Ling Sun, Tian Tian Wang, Zhi Liang Lv, Ji Lu Feng, Dong Ping Geng, Yong Mei Li*, Ke Li*

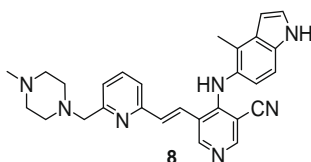


Two chiral furan lignan was synthesized, chiral separated and their absolute configuration was determined by circular dichroism spectra. Compound **2c** (IC_{50} = 12 μ M on QGY-7701), the racemate of **2a** and **2b**, is reported.

Optimization of 5-vinylaryl-3-pyridinecarbonitriles as PKC θ inhibitors

pp 1965–1968

Diane H. Boschelli*, Joan Subrath, Chuansheng Niu, Biqi Wu, Yan Wang, Julie Lee, Agnes Brennan, Melisa Ho, Bijia Deng, Xiaoke Yang, Xin Xu, Louis Leung, Jianyao Wang, James Atherton, Divya Chaudhary

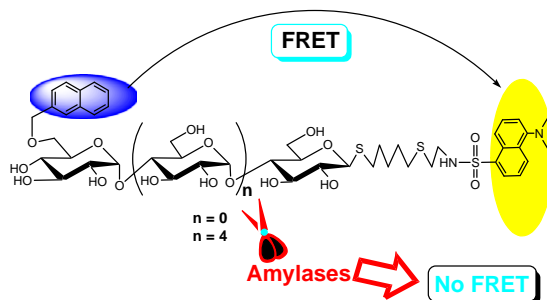


The 3-pyridinecarbonitrile **8** has an IC_{50} value of 1.1 nM for the inhibition of PKC θ and blocks the production of IL-2 in both stimulated murine T cells (IC_{50} = 34 nM) and human whole blood (IC_{50} = 500 nM).

Simple and conveniently accessible bi-fluorescence-labeled substrates for amylases

pp 1969–1971

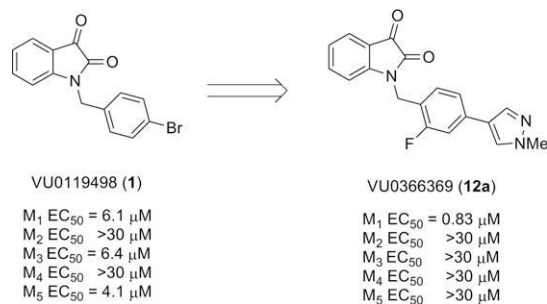
Hiroyuki Oka, Tetsuo Koyama, Ken Hatano, Daiyo Terunuma, Koji Matsuoka*

**Chemical lead optimization of a pan G α_q mAChR M $_1$, M $_3$, M $_5$ positive allosteric modulator (PAM) lead. Part II: Development of a potent and highly selective M $_1$ PAM**

pp 1972–1975

Thomas M. Bridges, J. Phillip Kennedy, Meredith J. Noetzel, Micah L. Breiningner, Patrick R. Gentry, P. Jeffrey Conn, Craig W. Lindsley*

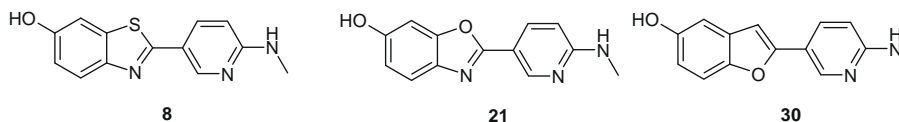
This Letter describes a chemical lead optimization campaign directed around VU0119498, a pan G α_q mAChR M $_1$, M $_3$, M $_5$ PAM, which previously afforded the first selective M $_5$ PAM. An iterative library synthesis approach delivered a novel chemotype with selective M $_1$ PAM activity (no activity at M $_2$ –M $_5$ @ 30 μ M), and comparable M $_1$ potency (EC_{50} = 830 nM) to the prototypical M $_1$ PAM, BQCA.



Synthesis and evaluation of 2-pyridylbenzothiazole, 2-pyridylbenzoxazole and 2-pyridylbenzofuran derivatives as ^{11}C -PET imaging agents for β -amyloid plaques

pp 1976–1980

Britt-Marie Swahn*, David Wensbo, Johan Sandell, Daniel Sohn, Can Slivo, David Pyring, Jonas Malmström, Erwan Arzel, Michaela Vallin, Margareta Bergh, Fredrik Jeppsson, Allan E. Johnson, Anders Juréus, Jan Neelissen, Samuel Svensson

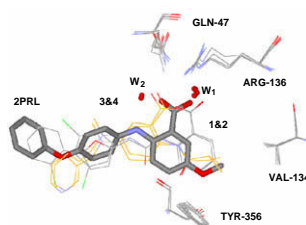


The syntheses and SAR of new series of β -amyloid binding agents are reported. The effort to optimize signal-to-background ratios for these ligands are described. Compounds **8**, **21** and **30** displayed desirable lipophilicity and pharmacokinetic properties. Compounds **8** and **21** were evaluated with in vitro autoradiographic studies and in vivo in APP/PS1 transgenic mice. It is shown that it was possible to increase the signal-to-background ratios compared to PIB **1**, as demonstrated by compounds **8** and **21**.

Discovery of novel inhibitors for DHODH via virtual screening and X-ray crystallographic structures

pp 1981–1984

Larry R. McLean*, Ying Zhang, William Degnen, Jane Peppard, Dasha Cabel, Chao Zou, Joseph T. Tsay, Arun Subramaniam, Roy J. Vaz, Yi Li*

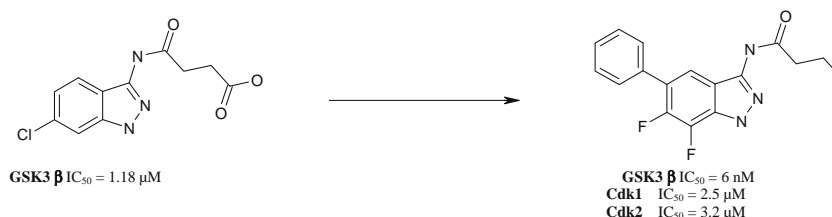


Several amino-benzoic acid derivatives were found to be DHODH inhibitors through virtual screening, biochemical, and X-ray crystallographic studies.

Rational design of potent GSK3 β inhibitors with selectivity for Cdk1 and Cdk2

pp 1985–1989

Dominique Lesuisse*, Gilles Dutruc-Rosset, Gilles Tiraboschi, Matthias K. Dreyer, Sébastien Maignan, Alain Chevalier, Frank Halley, Philippe Bertrand, Marie-Claude Burgevin, Dominique Quarteronet, Thomas Rooney



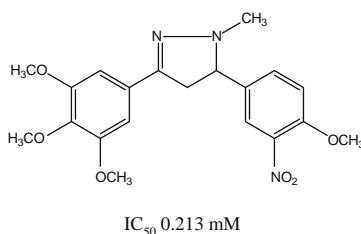
From an HTS hit, a series of potent and selective inhibitors of GSK3 β have been designed based on a Cdk2-homology model and with the help of several crystal structures of the compounds within Cdk2.



The synthesis and Angiotensin Converting Enzyme (ACE) inhibitory activity of chalcones and their pyrazole derivatives

pp 1990–1993

Marco Bonesi*, Monica R. Loizzo, Giancarlo A. Statti, Sylvie Michel, François Tillequin, Francesco Menichini



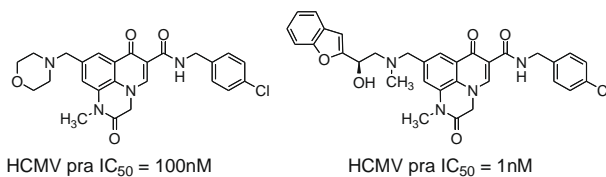
The synthesis and the ACE inhibitory activity of chalcones (**1–9**) and pyrazoles (**10–18**) are reported.



The design and development of 2-aryl-2-hydroxy ethylamine substituted 1*H*,7*H*-pyrido[1,2,3-*de*]quinoxaline-6-carboxamides as inhibitors of human cytomegalovirus polymerase

pp 1994–2000

Steven P. Tanis*, Joseph W. Strohbach*, Timothy T. Parker, Malcom W. Moon, Suvit Thaisrivongs, William R. Perrault, Todd A. Hopkins, Mary L. Knechtel, Nancee L. Oien, Janet L. Wieber, Kevin J. Stephanski, Michael W. Wathen

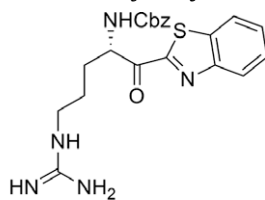


The design, synthesis, and SAR of a series of pyrido[1,2,3-*de*]quinoxaline-6-carboxamides is described. These activities led to entities with HCMV antiviral activity as low as 1 nM.

Design and evaluation of *Trypanosoma brucei* metacaspase inhibitors

pp 2001–2006

Maya Berg, Pieter Van der Veken, Jurgen Joossens, Venkatraj Muthusamy, Matthias Breugelmans, Catherine X. Moss, Jana Rudolf, Paul Cos, Graham H. Coombs, Louis Maes, Achiel Haemers, Jeremy C. Mottram, Koen Augustyns*



IC_{50} TbMCA2 = 0.6 μ M

We present the first inhibitors of metacaspase 2 of *Trypanosoma brucei* with low micromolar enzymatic activity. These compounds possess modest antiparasitic activity and have excellent selectivity when compared to mammalian caspases.

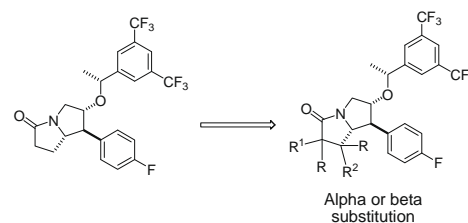


Substituted fused bicyclic pyrrolizinones as potent, orally bioavailable hNK₁ antagonists

pp 2007–2012

Gregori J. Morriello*, Sander G. Mills, Tricia Johnson, Mikhail Reibarkh, Gary Chicchi, Julie DeMartino, Marc Kurtz, P. Davies, K. L. C. Tsao, Song Zheng, Xinchun Tong, Emma Carlson, Karen Townson, F. D. Tattersall, Alan Wheeldon, Susan Boyce, Neil Collinson, Nadia Rupniak, Stephen Moore, Robert J. DeVita

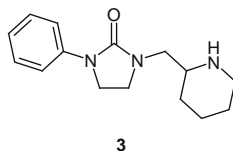
Previous work on human NK₁ (hNK₁) antagonists in which the core of the structure is a 5,5-fused pyrrolizinone has been disclosed. The structural-activity-relationship studies on simple α - and β -substituted compounds of this series provided several potent and bioavailable hNK₁ antagonists that displayed excellent brain penetration as observed by their good efficacy in the gerbil foot-tapping (GFT) model assay. Several of these compounds exhibited 100% inhibition of the foot-tapping response at 0.1 and 24 h with ID₅₀'s of less than 1 mpk. One particular α -substituted compound (**2b**) had an excellent pharmacokinetic profile across preclinical species with reasonable in vivo functional activity and minimal ancillary activity.



The identification of a selective dopamine D₂ partial agonist, D₃ antagonist displaying high levels of brain exposure

pp 2013–2016

Ian P. Holmes, Richard J. Blunt, Olivier E. Lorthioir, Stephen M. Blowers, Andy Gribble, Andrew H. Payne, Ian G. Stansfield, Martyn Wood, Patrick M. Woollard, Charlie Reavill, Claire M. Howes, Fabrizio Micheli, Romano Di Fabio, Daniele Donati, Silvia Terreni, Dieter Hamprecht, Luca Arista, Angela Worby, Steve P. Watson*

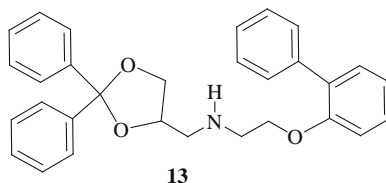


The identification of a hitherto unprecedented pharmacology in a compound (**3**) displaying highly selective DA D₂ partial agonism and DA D₃ antagonism, but devoid of activity at other aminergic receptors is described.

Discovery of a new series of 5-HT_{1A} receptor agonists

pp 2017–2020

Silvia Franchini, Adolfo Prandi, Claudia Sorbi, Annalisa Tait, Annamaria Baraldi, Piero Angeli, Michela Buccioni, Antonio Cilia, Elena Poggesi, Paola Fossa, Livio Brasili*



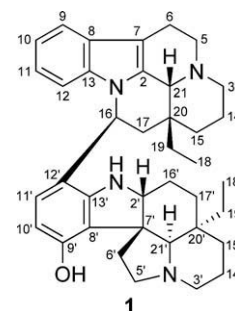
A new series of 5-HT_{1A} receptor agonists has been discovered. Compound **13**, which combines high selectivity (5-HT_{1A}/α₁ = 151) and good agonist potency (pD₂ = 7.82; E_{max} = 76), was found to be the most interesting of the series.

Bisleuconothine A, an eburnane–aspidosperma bisindole alkaloid from *Leuconotis griffithii*

pp 2021–2024

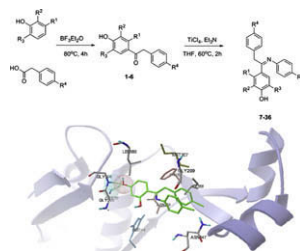
Yusuke Hirasawa, Tomokazu Shoji, Takashi Arai, Alfarius E. Nugroho, Jun Deguchi, Takahiro Hosoya, Nahoko Uchiyama, Yukihiro Goda, Khalijah Awang, A. Hamid A. Hadi, Motoo Shiro, Hiroshi Morita*

A new bisindole alkaloid, bisleuconothine A (**1**) consisting of an eburnane–aspidosperma type skeleton, was isolated from the bark of *Leuconotis griffithii*. The structure including absolute stereochemistry was elucidated on the basis of 2D NMR data and X-ray analysis. Bisleuconothine A (**1**) showed cell growth inhibitory activity against various human cancer cell lines.

**Design and synthesis of novel deoxybenzoin derivatives as FabH inhibitors and anti-inflammatory agents**

pp 2025–2028

Huan-Qiu Li, Yin Luo, Peng-Cheng Lv, Lei Shi, Chang-Hong Liu*, Hai-Liang Zhu*

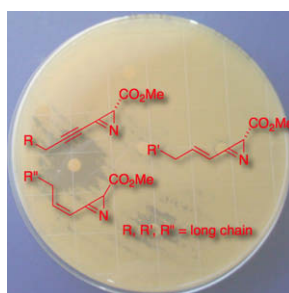


A novel series of deoxybenzoin derivatives were designed and synthesized. Based on the biological data obtained in this study, it can be concluded that compound **19** would be a potential *Escherichia coli* FabH inhibitor and promising anti-inflammatory agent. The binding model of compound **19** and *E. coli* FabH was also been researched.

**Synthesis and chain-dependent antifungal activity of long-chain 2H-azirine-carboxylate esters related to dysidazirine**

pp 2029–2032

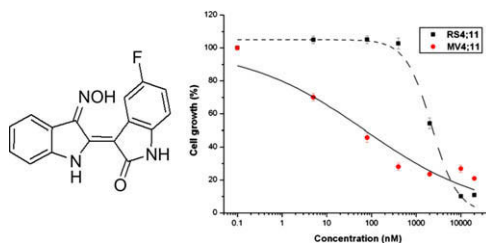
Colin K. Skepper, Doralyn S. Dalisay, Tadeusz F. Molinski*



Indirubin derivatives as potent FLT3 inhibitors with anti-proliferative activity of acute myeloid leukemic cells

pp 2033–2037

Soo Jeong Choi, Myoung Ju Moon, So Deok Lee, Sang-Un Choi, Sun-Young Han*, Yong-Chul Kim*

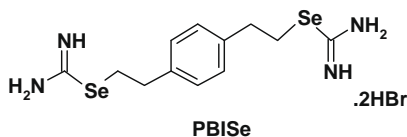


5-Fluoro-indirubin-3'-oxime, **13** exhibited potent inhibitory activity at FLT3 (IC_{50} = 15 nM) with more than 100-fold selectivity versus 6 other kinases and potent anti-proliferative effect for MV4;11 cells (IC_{50} = 72 nM) with 30-fold selectivity versus RS4;11 cells.

Synthesis and characterization of a novel iNOS/Akt inhibitor *Se,Se'*-1,4-phenylenebis(1,2-ethanediy)bisoselenourea (PBISe)—against colon cancer

pp 2038–2043

Dhimant Desai*, SubbaRao V. Madhunapantula, Krishnegowda Gowdahalli, Arati Sharma, Raghavendragowda Chandagaludoreswamy, Karam El-Bayoumy, Gavin P. Robertson, Shantu Amin

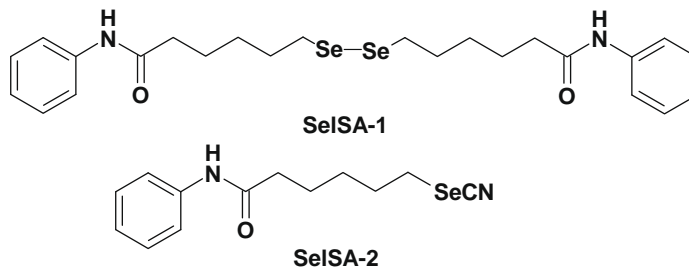


Our studies demonstrate that substitution of sulfur with selenium in known iNOS inhibitor increases the compound's potency by several folds in variety of different cancers cell lines tested. Hence, this approach may be used as a strategy to increase the efficacy of the anticancer agents.

SelSA, selenium analogs of SAHA as potent histone deacetylase inhibitors

pp 2044–2047

Dhimant Desai*, Ugur Salli, Kent E. Vrana, Shantu Amin



In order to develop novel HDAC inhibitors, two selenium analogs modeled after SAHA were synthesized and found to be highly potent HDAC inhibitors having IC_{50} values in low nanomolar range.

*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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