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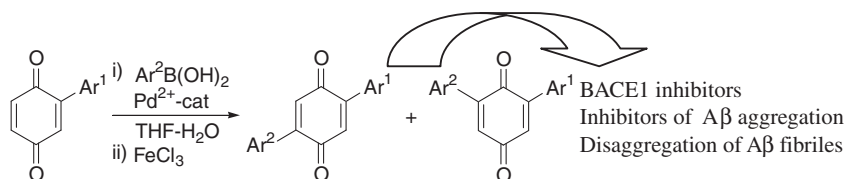
Contents

ARTICLES

Synthesis and evaluation of arylquinones as BACE1 inhibitors, β -amyloid peptide aggregation inhibitors, and destabilizers of preformed β -amyloid fibrils

pp 2183–2187

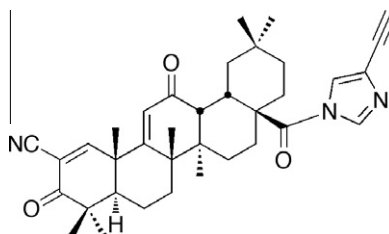
Andrea Ortega, Ángela Rincón, Karim L. Jiménez-Aliaga, Paloma Bermejo-Bescós*, Sagrario Martín-Aragón, María Teresa Molina, Aurelio G. Csáky*



Synthesis and biological evaluation of 1-[2-cyano-3,12-dioxooleana-1,9(11)-dien-28-oyl]-4-ethynylimidazole. A novel and highly potent anti-inflammatory and cytoprotective agent

pp 2188–2191

Tadashi Honda*, Alben T. Dinkova-Kostova, Emilie David, Eric M. Padegimas, Chitra Sundararajan, Melean Visnick, Ron Bumeister, W. Christian Wigley

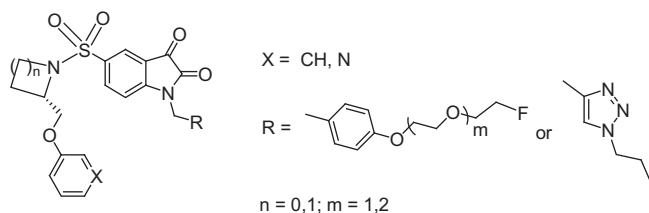


1-[2-Cyano-3,12-dioxooleana-1,9(11)-dien-28-oyl]-4-ethynylimidazole is a novel semisynthetic triterpenoid whose potency is much higher than the lead compound, 2-cyano-3,12-dioxooleana-1,9(11)-dien-28-oic acid for inhibition of NO production stimulated with IFN- γ and for induction of the cytoprotective enzymes, NQO1 and HO-1.

Synthesis and evaluation of isatin analogs as caspase-3 inhibitors: Introduction of a hydrophilic group increases potency in a whole cell assay

pp 2192–2197

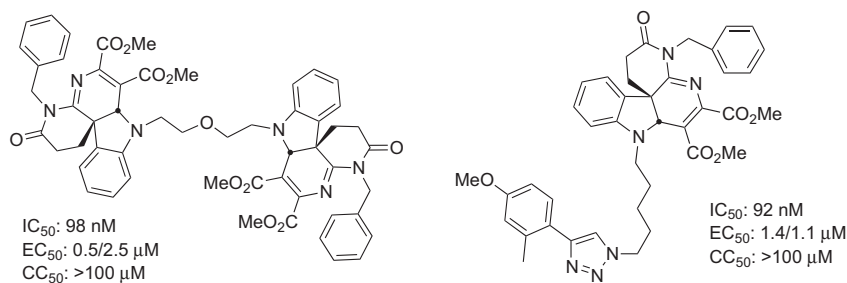
Wenhua Chu, Justin Rothfuss, Dong Zhou, Robert H. Mach*



Potent inhibitors of hepatitis C core dimerization as new leads for anti-hepatitis C agents

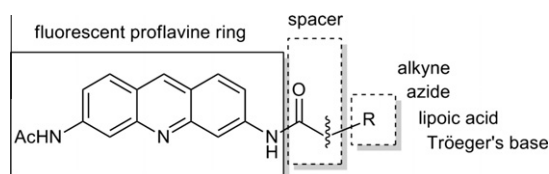
pp 2198–2202

Feng Ni, Smitha Kota, Virginia Takahashi, A. Donny Strosberg*, John K. Snyder*

**Proflavine derivatives as fluorescent imaging agents of amyloid deposits**

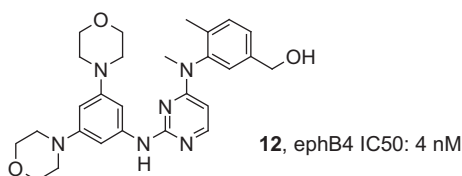
pp 2203–2206

Dominique Garin, Fatima Oukhatar, Andrew B. Mahon, Andrew C. Try, Michel Dubois-Dauphin, Frank M. Laferla, Martine Demeunynck, Marcelle Moulin Sallanon*, Sabine Chierici*

**Inhibitors of the tyrosine kinase EphB4. Part 4: Discovery and optimization of a benzylic alcohol series**

pp 2207–2211

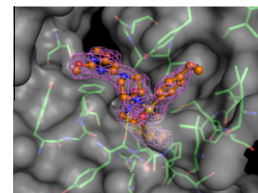
Bernard Barlaam, Richard Ducray*, Christine Lambert-van der Brempt, Patrick Plé, Catherine Bardelle, Nigel Brooks, Tanya Coleman, Darren Cross, Jason G. Kettle, Jon Read

**Investigation of the mode of binding of a novel series of *N*-benzyl-4-heteroaryl-1-(phenylsulfonyl)piperazine-2-carboxamides to the hepatitis C virus polymerase**

pp 2212–2215

Robert G. Gentles*, Steven Sheriff, Brett R. Beno, Changhong Wan, Kevin Kish, Min Ding, Xiaofan Zheng, Louis Chupak, Michael A. Poss, Mark R. Witmer, Paul Morin, Ying-Kai Wang, Karen Rigat, Julie Lemm, Stacey Voss, Mengping Liu, Lenore Pelosi, Susan B. Roberts, Min Gao, John F. Kadow

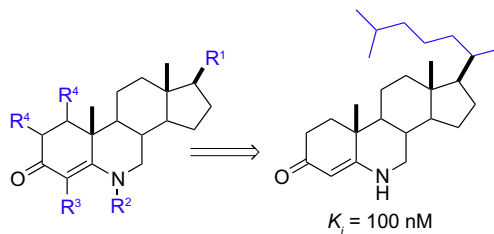
Structure based rationales for the activities of potent *N*-benzyl-4-heteroaryl-1-(phenylsulfonyl)-piperazine-2-carboxamide inhibitors of the hepatitis C viral polymerase are described. Comparison of co-crystal structures of a potent analog with both NS5B genotype 1a and genotype 1b provide possible explanations for the genotype-selectivity observed with this compound class and suggests opportunities for the further optimization of the series.



Inhibition of the *M. tuberculosis* 3 β -hydroxysteroid dehydrogenase by azasteroids

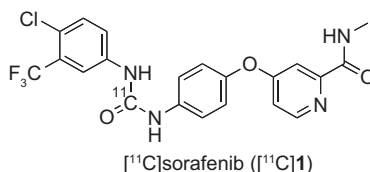
pp 2216–2219

Suzanne T. Thomas, Xinxin Yang, Nicole S. Sampson*

**[^{11}C]Sorafenib: Radiosynthesis and preliminary PET study of brain uptake in P-gp/Bcrp knockout mice**

pp 2220–2223

Chiharu Asakawa, Masanao Ogawa, Katsushi Kumata, Masayuki Fujinaga, Koichi Kato, Tomoteru Yamasaki, Joji Yui, Kazunori Kawamura, Akiko Hatori, Toshimitsu Fukumura, Ming-Rong Zhang*

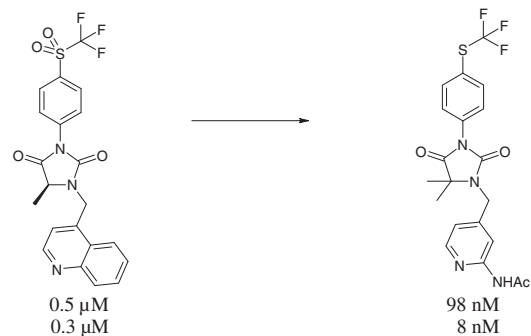
**Discovery of the first non-ATP competitive IGF-1R kinase inhibitors: Advantages in comparison with competitive inhibitors**

pp 2224–2228

Dominique Lesuisse*, Jacques Mauger, Conception Nemecek, Sébastien Maignan, Janine Boiziau, Greg Harlow, Augustin Hittinger, Swen Ruf, Hartmut Strobel, Anil Nair, Kurt Ritter, Jean-Luc Malleron, Anne Dagallier, Youssef El-Ahmad, Jean-Pierre Guilloteau, Houlfu Guizani, Hervé Bouchard, Corinne Venot

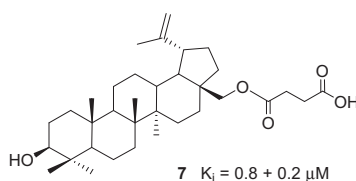
A new series of IGF-1R inhibitors related to hydantoins were identified from a lead originating from HTS. Their noncompetitive property as well as their slow binding characteristics provided a series of compounds with unique selectivity and excellent cellular activities.

IGF-1R (IC_{50})
IGF-1-induced proliferation (IC_{50})

**Synthesis and evaluation of library of betulin derivatives against the botulinum neurotoxin A protease**

pp 2229–2231

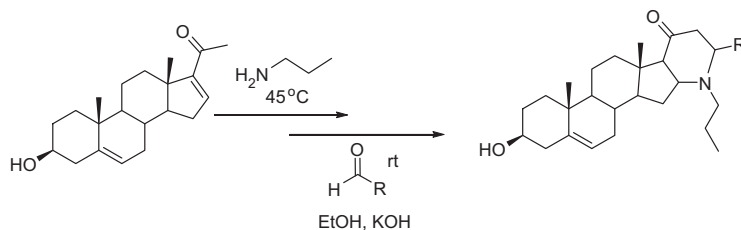
Peter Šilhár, Sami Alakurtti, Kateřina Čapková, Feng Xiaochuan, Charles B. Shoemaker, Jari Yli-Kauhahuoma*, Kim D. Janda*



Aza-annulation on the 16-dehydropregnenolone, via tandem intermolecular Aldol process and intramolecular Michael addition

pp 2232–2237

Manmeet Kumar, Preeti Rawat, Mohammad Faheem Khan, Arun Kumar Rawat, Arvind Kumar Srivastava, Rakesh Maurya*

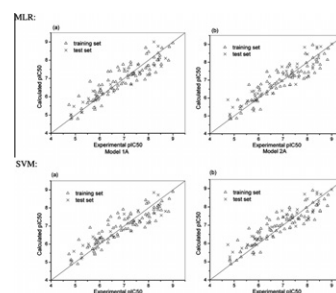


Prediction of biological activity of Aurora-A kinase inhibitors by multilinear regression analysis and support vector machine

pp 2238–2243

Aixia Yan*, Yang Chong, Liyu Wang, Xiaoying Hu, Kai Wang

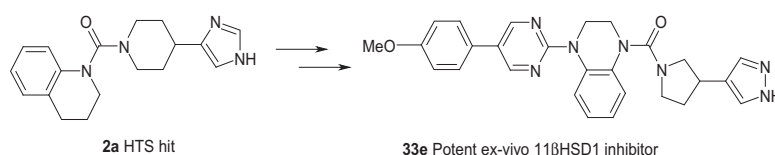
Four QSAR models were built by multilinear regression (MLR) analysis and support vector machine (SVM) method based on a series of 117 Aurora-A kinase inhibitors, which could be used for the predicting the activities of Aurora-A inhibitors.



Pyrrolidine-pyrazole ureas as potent and selective inhibitors of 11 β -hydroxysteroid-dehydrogenase type 1

pp 2244–2251

Olivier Venier*, Cécile Pascal, Alain Braun, Claudie Namane, Patrick Mougenot, Olivier Crespin, François Pacquet, Cécile Mougenot, Catherine Monseau, Bénédicte Onofri, Rommel Dadji-Faihun, Céline Leger, Majdi Ben-Hassine, Thao Van-Pham, Jean-Luc Ragot, Christophe Philippo, Stefan Güssregen, Christian Engel, Géraldine Farjot, Lionel Noah, Karima Maniani, Eric Nicolai*

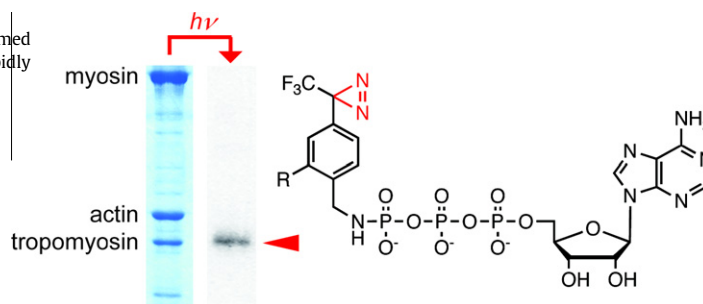


Rapidly photoactivatable ATP probes for specific labeling of tropomyosin within the actomyosin protein complex

pp 2252–2254

Souta Masuda, Takenori Tomohiro, Yasumaru Hatanaka*

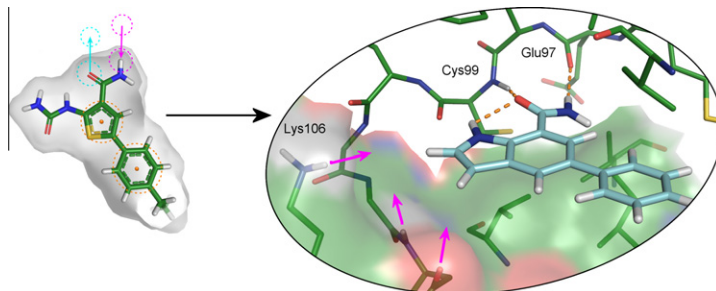
Tropomyosin-specific photoaffinity labeling from actomyosin motor was firstly performed using diazirine-based ATP analogs modified on the γ -phosphate group as a rapidly carbene-generating photophore.



3,5-Disubstituted-indole-7-carboxamides: The discovery of a novel series of potent, selective inhibitors of IKK- β

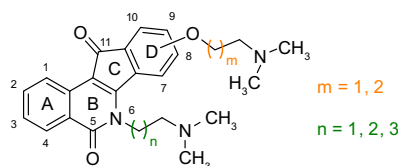
pp 2255–2258

David D. Miller, Paul Bamborough*, John A. Christopher, Ian R. Baldwin, Aurelie C. Champigny, Geoffrey J. Cutler, Jeffrey K. Kerns, Timothy Longstaff, Geoffrey W. Mellor, James V. Morey, Mary A. Morse, Hong Nie, William L. Rumsey, John J. Taggart

**Synthesis, cytotoxicity and topoisomerase inhibition properties of multifarious aminoalkylated indeno [1,2-c]isoquinolin-5,11-diones**

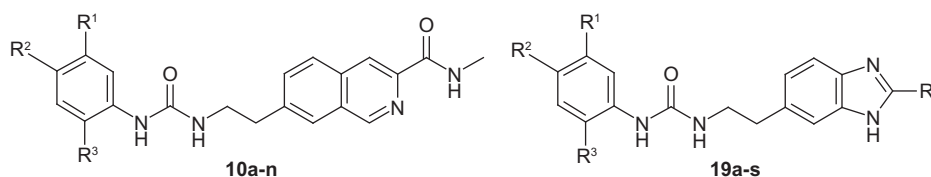
pp 2259–2263

Gang Ahn*, Nadège Schifano-Faux, Jean-François Goossens, Brigitte Baldeyrou, Axel Couture, Pierre Grandclaudon, Amélie Lansiaux, Adina Ryckebusch

**Design and synthesis of isoquinolines and benzimidazoles as RAF kinase inhibitors**

pp 2264–2269

Hans-Peter Buchstaller*, Lars Burgdorf, Dirk Finsinger, Frank Stieber, Christian Sirrenberg, Christiane Amendt, Matthias Grell, Frank Zenke, Mireille Krier

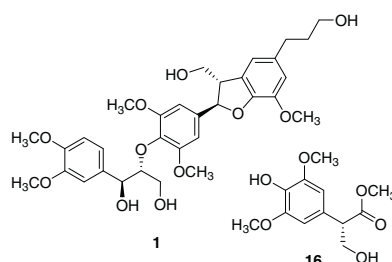


Potent c-RAF inhibitors bearing novel bicyclic heterocycles as key structural elements for the interaction with the hinge region are described.

Biological evaluation of phenolic constituents from the trunk of *Berberis koreana*

pp 2270–2273

Ki Hyun Kim, Eunjung Moon, Sang Un Choi, Sun Yeou Kim, Kang Ro Lee*



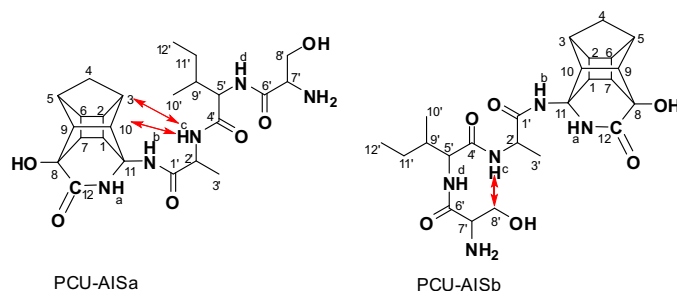
A bioassay-guided fractionation and chemical investigation of the trunk of *Berberis koreana* resulted in the isolation and identification of a new sesquilignan, named berbikonol (**1**), along with 14 known lignan derivatives (**2–15**) and a new phenolic compound, named berfussinol (**16**), together with five known ones (**17–21**).



Pentacycloundecane-based inhibitors of wild-type C-South African HIV-protease

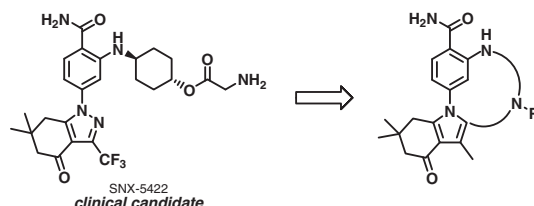
pp 2274–2277

Maya M. Makatini, Katja Petzold, Shimoga N. Sriharsha, Mahmoud E. S. Soliman, Bahareh Honarparvar, Per I. Arvidsson, Yasien Sayed, Patrick Govender, Glenn E. M. Maguire, Hendrik G. Kruger*, Thavendran Govender*

**Design and SAR of macrocyclic Hsp90 inhibitors with increased metabolic stability and potent cell-proliferation activity**

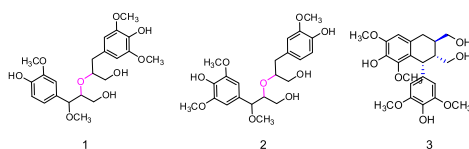
pp 2278–2282

Christoph W. Zapf*, Jonathan D. Bloom, Jamie L. McBean, Russell G. Dushin, Thomas Nittoli, Charles Ingalls, Alan G. Sutherland, John P. Sonye, Clark N. Eid, Jennifer Golas, Hao Liu, Frank Boschelli, Yongbo Hu, Erik Vogan, Jeremy I. Levin

**Inhibition of nitric oxide production in lipopolysaccharide-stimulated RAW264.7 macrophage cells by lignans isolated from *Euonymus alatus* leaves and twigs**

pp 2283–2286

Eun Ju Jeong, Jung Hee Cho, Sang Hyun Sung, Sun Yeou Kim, Young Choong Kim*

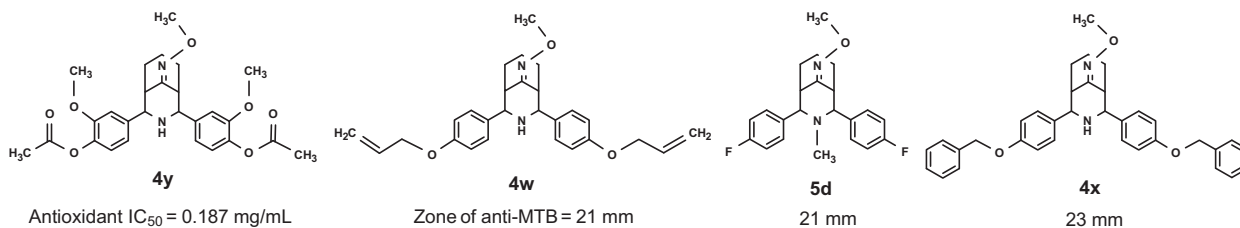


The 80% methanolic extract of *Euonymus alatus* leaves and twigs afforded three new lignans, (–)-*threo*-4,9,4',9'-tetrahydroxy-3,7,3',5'-tetramethoxy-8-O-8'-neolignan (**1**), (–)-*threo*-4,9,4',9'-tetrahydroxy-3,5,7,3'-tetramethoxy-8-O-8'-neolignan (**2**), (7*R*,8*R*,7'*R*)-(+)-lyoniresinol (**3**), together with seventeen known lignans (**4**–**20**). The structures of **1**–**20** were elucidated by extensive 1D and 2D spectroscopic methods including ¹H NMR, ¹³C NMR, ¹H–¹H COSY, HMQC, HMBC and NOESY. All the isolated compounds except for dilignans (**19**, **20**) significantly inhibited nitric oxide production in lipopolysaccharide-stimulated RAW264.7 cells.

**Facile synthesis and stereochemical investigation of Mannich base derivatives: Evaluation of antioxidant property and antituberculosic potency**

pp 2287–2296

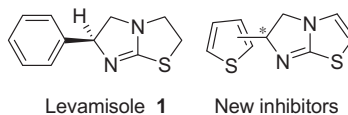
Paramasivam Parthiban, Viswalingam Subalakshmi, Krishnamurthy Balasubramanian, Md. Nurul Islam, Jae Sue Choi, Yeon Tae Jeong*



Synthesis and evaluation of thiophenyl derivatives as inhibitors of alkaline phosphatase

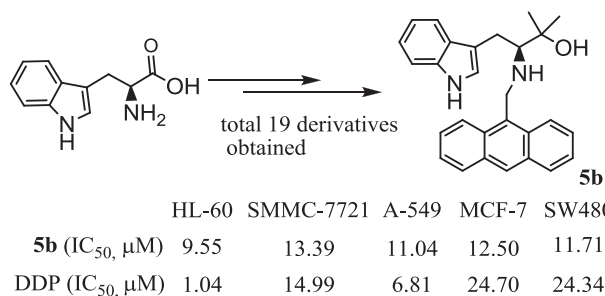
pp 2297–2301

Lei Chang, Do Le Duy, Saida Mébarek, Florence Popowycz, Stéphane Pellet-Rostaing*, Marc Lemaire*, René Buchet*

**Design, synthesis and cytotoxic activities of novel β -amino alcohol derivatives**

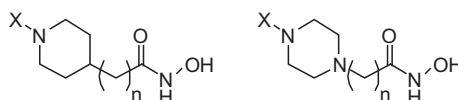
pp 2302–2304

Bing Bai, Xing-Yao Li, Yan Li*, Hua-Jie Zhu*

**Alkyl piperidine and piperazine hydroxamic acids as HDAC inhibitors**

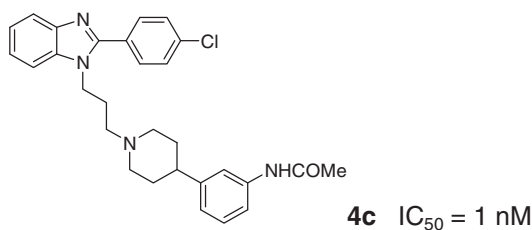
pp 2305–2308

Cristina Rossi, Marina Porcelloni, Piero D'Andrea, Christopher I. Fincham, Alessandro Ettore, Sandro Mauro, Antonella Squarcia, Mario Bigioni, Massimo Parlani, Federica Nardelli, Monica Binaschi, Carlo A. Maggi, Daniela Fattori*

**Synthesis and SAR investigations of novel 2-arylbenzimidazole derivatives as melanin-concentrating hormone receptor 1 (MCH-R1) antagonists**

pp 2309–2312

Chae Jo Lim, Nakjeong Kim, Eun Kyoung Lee, Byung Ho Lee, Kwang-Seok Oh, Sung-eun Yoo, Kyu Yang Yi*



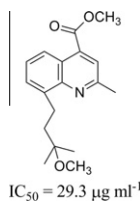
The synthesis and SAR of 2-arylbenzimidazoles as MCH-R1 antagonists are described.



A new quinoline derivative with cytotoxic activity from *Streptomyces* sp. neu50

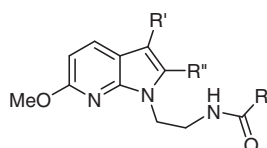
pp 2313–2315

Xiang-Jing Wang, Dian-Liang Gong, Ji-Dong Wang, Ji Zhang, Chong-Xi Liu, Wen-Sheng Xiang*

**Design and synthesis of 1-(2-alkanamidoethyl)-6-methoxy-7-azaindole derivatives as potent melatonin agonists**

pp 2316–2319

Matthieu Jeanty, Franck Suzenet*, Philippe Delagrangre, Olivier Nosjean, Jean A. Boutin, Daniel H. Caignard, Gérald Guillaumet



R = Me; R' = R'' = H,
 R = Et; R' = R'' = H,
 R = nPr; R' = R'' = H,
 R = Me; R', R'' = -(CH₂)₄-

Ki(MT₁) = 1.4 nM
 Ki(MT₁) = 3.3 nM
 Ki(MT₁) = 1.3 nM
 Ki(MT₁) = 9 nM

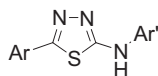
Ki(MT₂) = 0.6 nM
 Ki(MT₂) = 0.28 nM
 Ki(MT₂) = 0.3 nM
 Ki(MT₂) = 0.68 nM

New potent melatonin agonists based on a 7-azaindole scaffold are reported, along with some affinities-dependent pharmacomodulations.

**One-pot synthesis and anticancer studies of 2-arylamino-5-aryl-1,3,4-thiadiazoles**

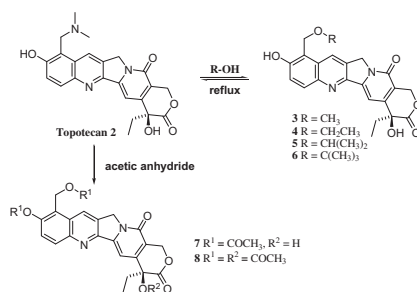
pp 2320–2323

Dalip Kumar*, Buchi Reddy Vaddula, Kuei-Hua Chang, Kavita Shah*

IC₅₀ : 4.3 μM - >1.0 mM**The solvolysis of topotecan in alcohols and acetic anhydride**

pp 2324–2326

Jiajun Li, Guolin Wang, Mengjie Dong*, Qian Zhang*



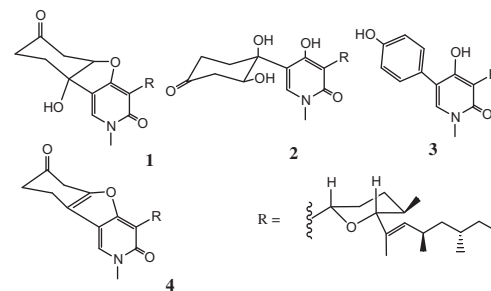
Six derivatives of 10-hydroxycamptothecin were prepared via solvolysis of topotecan in corresponding alcohols and acetic anhydride and evaluated in vitro as anti-tumor agents.

Biomimetic conversion of (–)-fusoxyppyridone and (–)-oxysporidinone to (–)-sambutoxin: Further evidence for the structure of the tricyclic pyridone alkaloid, (–)-fusoxyppyridone

pp 2327–2329

E. M. Kithsiri Wijeratne, A. A. Leslie Gunatilaka*

Biomimetic-type reactions of (–)-fusoxyppyridone (**1**) and (–)-oxysporidinone (**2**) afforded (–)-sambutoxin (**3**) and an analogue of **1**, identified as (–)-1'-(6')-dehydro-4,6'-anhydrooxysporidinone (**4**), thus confirming the structure previously proposed for **1** and suggesting that **1–3** bear the same relative stereochemistry. Oxidation of **4** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) yielded a hitherto unknown sambutoxin analogue, (–)-4,2'-anhydrosambutoxin (**5**).

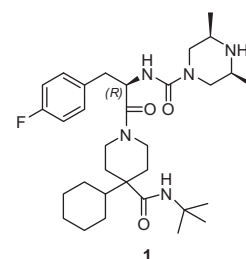


Discovery of a piperazine urea based compound as a potent, selective, orally bioavailable melanocortin subtype-4 receptor partial agonist

pp 2330–2334

Qingmei Hong*, Raman K. Bakshi, Brenda L. Palucki, Min K. Park, Zhixiong Ye, Shuwen He, Patrick G. Pollard, Iyassu K. Sebhat, Jian Liu, Liangqin Guo, Doreen E. Cashen, William J. Martin, David H. Weinberg, Tanya MacNeil, Rui Tang, Constantin Tamvakopoulos, Qianping Peng, Randy R. Miller, Ralph A. Stearns, Howard Y. Chen, Airu S. Chen, Alison M. Strack, Tung M. Fong, D. Euan MacIntyre, Matthew J. Wyvratt, Ravi P. Nargund

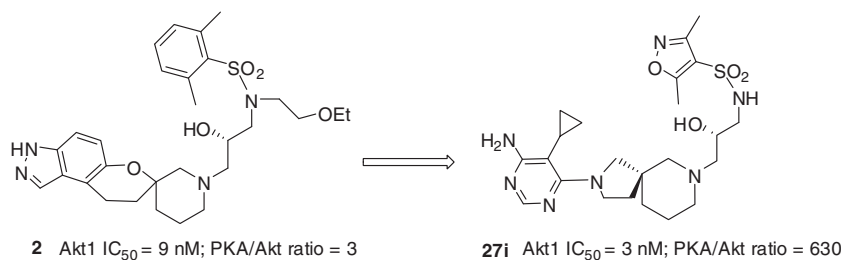
We report the discovery of piperazine urea based compound **1**, a potent, selective, orally bioavailable melanocortin subtype-4 receptor partial agonist. Compound **1** shows anti-obesity efficacy without potentiating erectile activity in the rodent models.



Discovery of spirocyclic sulfonamides as potent Akt inhibitors with exquisite selectivity against PKA

pp 2335–2340

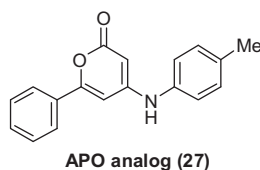
Rui Xu*, Anna Banka, James F. Blake, Ian S. Mitchell, Eli M. Wallace, Josef R. Bencsik, Nicholas C. Kallan, Keith L. Spencer, Susan L. Gloor, Matthew Martinson, Tyler Risom, Stefan D. Gross, Tony H. Morales, Wen-I Wu, Guy P. A. Vigers, Barbara J. Brandhuber, Nicholas J. Skelton



Antitumor agents 287. Substituted 4-amino-2H-pyran-2-one (APO) analogs reveal a new scaffold from neo-tanshinlactone with in vitro anticancer activity

pp 2341–2344

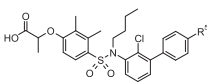
Yizhou Dong, Kyoko Nakagawa-Goto, Chin-Yu Lai, Susan L. Morris-Natschke, Kenneth F. Bastow, Kuo-Hsiung Lee*



Phenoxyacetic acids as PPAR δ partial agonists: Synthesis, optimization, and in vivo efficacy

pp 2345–2350

Karen A. Evans*, Barry G. Shearer, David D. Wisnoski, Dongchuan Shi, Steven M. Sparks, Daniel D. Sternbach, Deborah A. Winegar, Andrew N. Billin, Christy Britt, James M. Way, Andrea H. Epperly, Lisa M. Leesnitzer, Raymond V. Merrihew, Robert X. Xu, Millard H. Lambert, Jian Jin

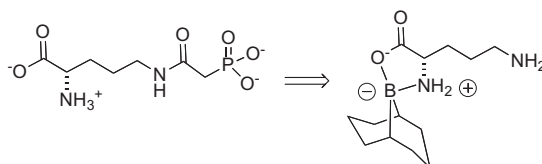


Compound	R ¹	hPPAR binding pIC ₅₀			hPPAR δ reporter	
		α	γ	δ	pEC ₅₀	EMax
46	OCF ₃	5.0	5.2	7.8	8.6	51
47	CF ₃	5.1	5.2	8.2	8.6	59

**N⁵-Phosphonoacetyl-L-ornithine (PALO): A convenient synthesis and investigation of influence on regulation of amino acid biosynthetic genes in *Saccharomyces cerevisiae***

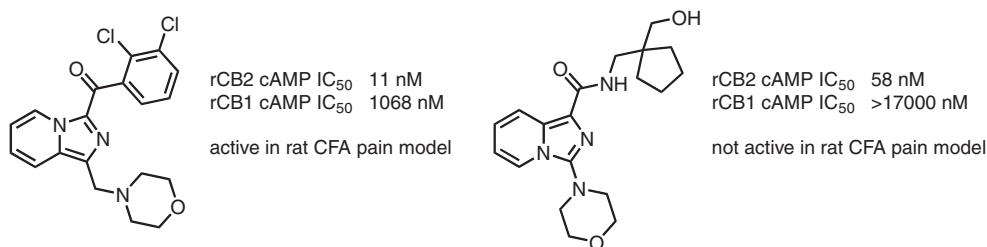
pp 2351–2353

Brad Johnson, Rachel Steadman, Krista D. Patefield, Jeffrey J. Bunker, Audrey L. Atkin*, Patrick Dussault*

**Imidazopyridine CB2 agonists: Optimization of CB2/CB1 selectivity and implications for in vivo analgesic efficacy**

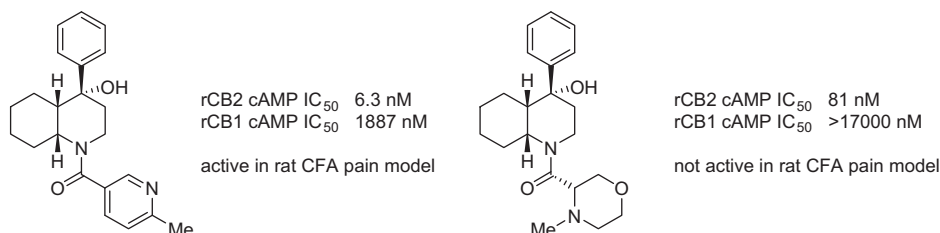
pp 2354–2358

B. Wesley Trotter*, Kausik K. Nanda, Christopher S. Burgey, Craig M. Potteiger, James Z. Deng, Ahren I. Green, John C. Hartnett, Nathan R. Kett, Zhicai Wu, Darrell A. Henze, Kimberly Della Penna, Reshma Desai, Michael D. Leidl, Wei Lemaire, Rebecca B. White, Suzie Yeh, Mark O. Urban, Stefanie A. Kane, George D. Hartman, Mark T. Bilodeau

**Decahydroquinoline amides as highly selective CB2 agonists: Role of selectivity on in vivo efficacy in a rodent model of analgesia**

pp 2359–2364

Peter J. Manley*, Amy Zartman, Daniel V. Paone, Christopher S. Burgey, Darrell A. Henze, Kimberly Della Penna, Reshma Desai, Michael D. Leidl, Wei Lemaire, Rebecca B. White, Suzie Yeh, Mark O. Urban, Stefanie A. Kane, George D. Hartman, Mark T. Bilodeau, B. Wesley Trotter

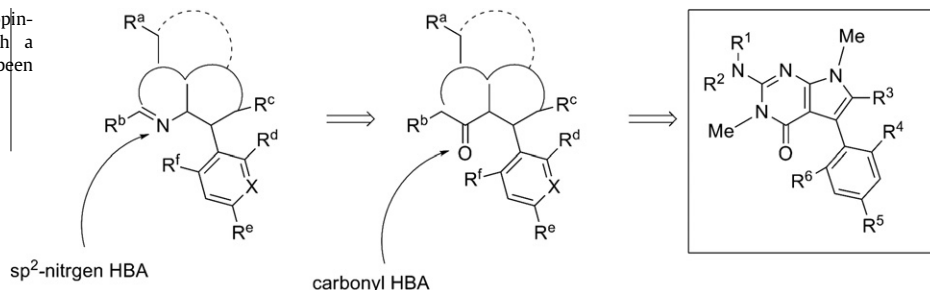


Discovery of pyrrolo[2,3-*d*]pyrimidin-4-ones as corticotropin-releasing factor 1 receptor antagonists with a carbonyl-based hydrogen bonding acceptor

pp 2365–2371

Kazuyoshi Aso*, Katsumi Kobayashi, Michiyo Mochizuki, Naoyuki Kanzaki, Yuu Sako, Takahiko Yano

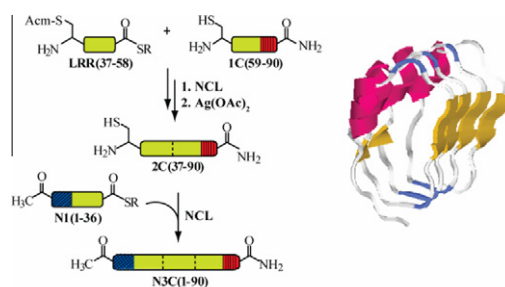
A new class of pyrrolo[2,3-*d*]pyrimidin-4-one corticotropin-releasing factor 1 (CRF₁) receptor antagonists with a carbonyl-based hydrogen bonding acceptor (HBA) has been designed and synthesized.



Artificial leucine rich repeats as new scaffolds for protein design

pp 2372–2375

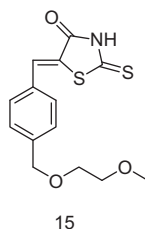
Hemda Baabur-Cohen, Subashini Dayalan, Inbal Shumacher, Rivka Cohen-Luria, Gonen Ashkenasy*



Evaluation of dihydropyrimidin-(2*H*)-one analogues and rhodanine derivatives as tyrosinase inhibitors

pp 2376–2379

Jinbing Liu*, Fengyan Wu, Lingjuan Chen, Jianming Hu, Liangzhong Zhao, Changhong Chen, Liwang Peng



15

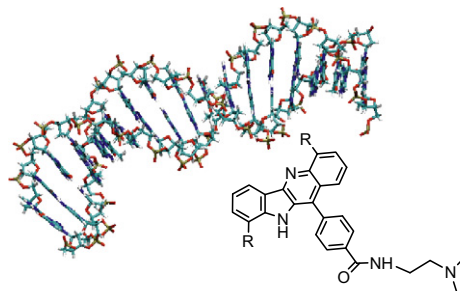
Compound **15** exhibited most potent tyrosinase inhibitory activity with IC₅₀ value of 0.56 mM. The inhibition mechanism analysis of compound **15** demonstrated that the inhibitory effect of the compound on the tyrosinase was irreversible.



In vitro anticancer activity and evaluation of DNA duplex binding affinity of phenyl-substituted indoloquinolines

pp 2380–2383

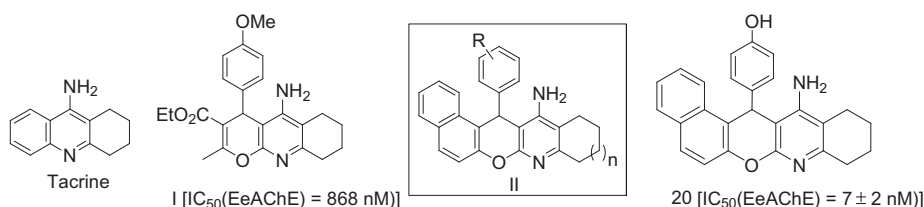
Fanny Riechert-Krause, Andrea Eick, Renate Grünert, Patrick J. Bednarski, Klaus Weisz*



Synthesis, biological assessment and molecular modeling of 14-aryl-10,11,12,14-tetrahydro-9H-benzo[5,6]chromeno[2,3-b]quinolin-13-amines

pp 2384–2388

Emna Maalej*, Fakher Chabchoub*, Abdelouahid Samadi, Cristóbal de los Ríos, Almudena Perona, Antonio Morreale, José Marco-Contelles*



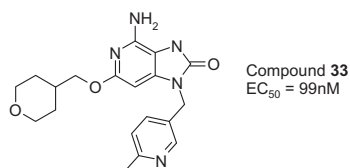
Structure of tacrine, the reference compound **I**, the target molecules {14-aryl-10,11,12,14-tetrahydro-9H-benzo[5,6]chromeno[2,3-b]quinolin-13-amines} (**II**) and the most potent AChEI (compound **20**) found in this work.



Design and optimisation of orally active TLR7 agonists for the treatment of hepatitis C virus infection

pp 2389–2393

Thien-Duc Tran*, David C. Pryde, Peter Jones, Fiona M. Adam, Neil Benson, Gerwyn Bish, Frederick Calo, Guiseppe Ciaramella, Rachel Dixon, Jonathan Duckworth, David N. A. Fox, Duncan A. Hay, James Hitchin, Nigel Horscroft, Martin Howard, Iain Gardner, Hannah M. Jones, Carl Laxton, Tanya Parkinson, Gemma Parsons, Katie Proctor, Mya C. Smith, Nicholas Smith, Amy Thomas



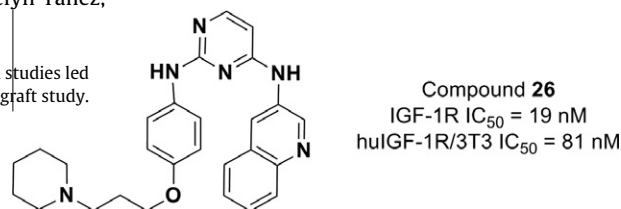
The synthesis and structure–activity relationships of a series of novel interferon inducers are described. Pharmacokinetic studies and efficacy assessment of a series of 8-oxo-3-deazapurine analogues led to the identification of compound **33**, a potent and selective agonist of the TLR7 receptor with an excellent in vivo efficacy profile in a mouse model.

Discovery of 2,4-bis-arylamino-1,3-pyrimidines as insulin-like growth factor-1 receptor (IGF-1R) inhibitors

pp 2394–2399

John L. Buchanan*, John R. Newcomb, David P. Carney, Stuart C. Chaffee, Lilly Chai, Rod Cupples, Linda F. Epstein, Paul Gallant, Yan Gu, Jean-Christophe Harmange, Kathy Hodge, Brett E. Houk, Xin Huang, Janan Jona, Smriti Joseph, H. Toni Jun, Rakesh Kumar, Chun Li, John Lu, Tom Menges, Michael J. Morrison, Perry M. Novak, Simon van der Plas, Robert Radinsky, Paul E. Rose, Satin Sawant, Ji-Rong Sun, Sekhar Surapaneni, Susan M. Turci, Keyang Xu, Evelyn Yanez, Huilin Zhao, Xiaotian Zhu

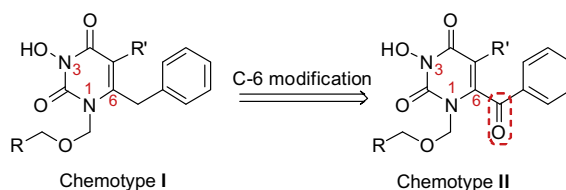
The discovery of 2,4-bis-arylamino-1,3-pyrimidines as IGF-1R inhibitors is described. Optimization studies led to the identification of **26**, which displayed tumor growth inhibition in a mouse Calu-6 tumor xenograft study.



6-Benzoyl-3-hydroxypyrimidine-2,4-diones as dual inhibitors of HIV reverse transcriptase and integrase

pp 2400–2402

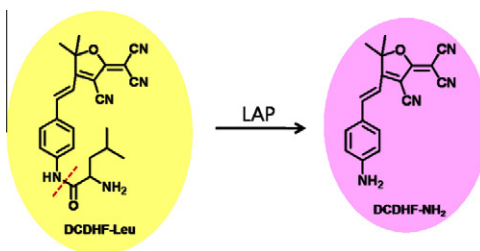
Jing Tang, Kasthuraiah Maddali, Christine D. Dreis, Yuk Y. Sham, Robert Vince, Yves Pommier, Zhengqiang Wang*



Small-molecule probe using dual signals to monitor leucine aminopeptidase activity

pp 2403–2405

Hey Young Yoon, So Hee Shim, Luck Ju Baek, Jong-In Hong*

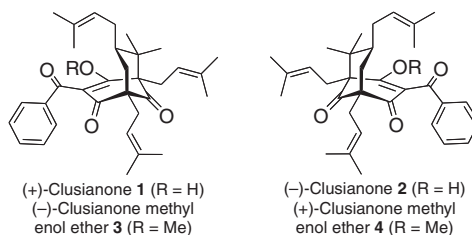


In this paper, we report a small-molecule probe which exhibits colorimetric and fluorogenic changes according to LAP activity.

**Asymmetric total synthesis of (+)- and (–)-clusianone and (+)- and (–)-clusianone methyl enol ether via ACC alkylation and evaluation of their anti-HIV activity**

pp 2406–2409

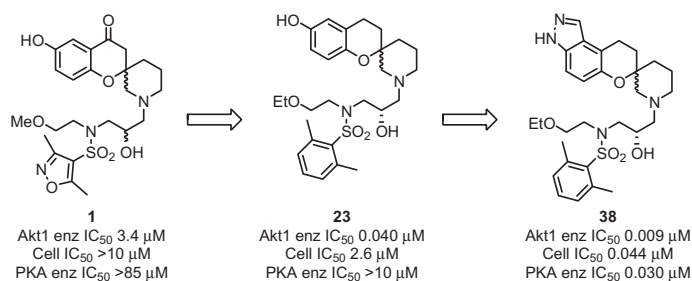
Michelle R. Garnsey, James A. Matous, Jesse J. Kwiek, Don M. Coltart*

**Discovery and SAR of spirochromane Akt inhibitors**

pp 2410–2414

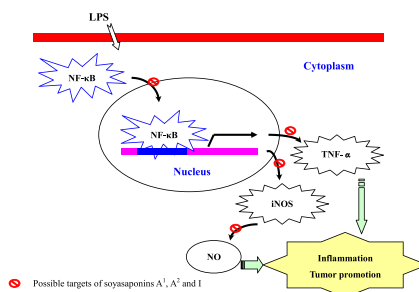
Nicholas C. Kallan*, Keith L. Spencer, James F. Blake, Rui Xu, Justin Heizer, Josef R. Bencsik, Ian S. Mitchell, Susan L. Gloor, Matthew Martinson, Tyler Risom, Stefan D. Gross, Tony H. Morales, Wen-I Wu, Guy P. A. Vigers, Barbara J. Brandhuber, Nicholas J. Skelton

A novel series of spirochromane pan-Akt inhibitors is reported. SAR optimization furnished compounds with improved enzyme potencies and excellent selectivity over the related AGC kinase PKA. Attempted replacement of the phenol hinge binder provided compounds with excellent Akt enzyme and cell activities but greatly diminished selectivity over PKA.

**Anti-inflammatory effect of soyasaponins through suppressing nitric oxide production in LPS-stimulated RAW 264.7 cells by attenuation of NF-κB-mediated nitric oxide synthase expression**

pp 2415–2418

Long-ying Zha*, Li-mei Mao, Xiao-cui Lu, Hong Deng, Ju-feng Ye, Xin-wei Chu, Su-xia Sun, Hai-ji Luo

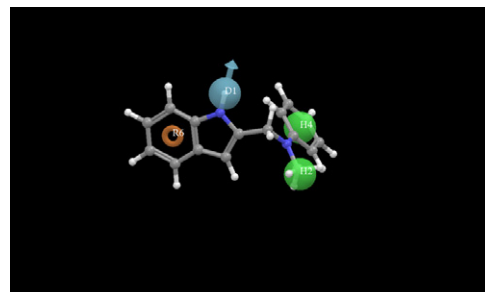


Exploration of new scaffolds as potential MAO-A inhibitors using pharmacophore and 3D-QSAR based in silico screening

pp 2419–2424

Suhas M. Shelke, Sharad H. Bhosale*, Radha Charan Dash, Mugdha R. Suryawanshi, Kakasaheb R. Mahadik

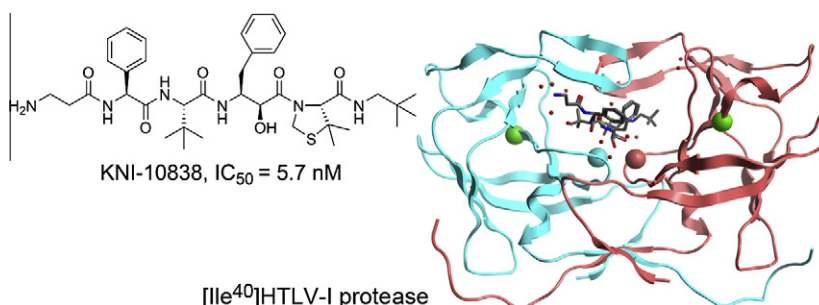
A pharmacophore model for MAO-A inhibition was generated and used for in silico screening to identify novel potential inhibitors.



Design and synthesis of several small-size HTLV-I protease inhibitors with different hydrophilicity profiles

pp 2425–2429

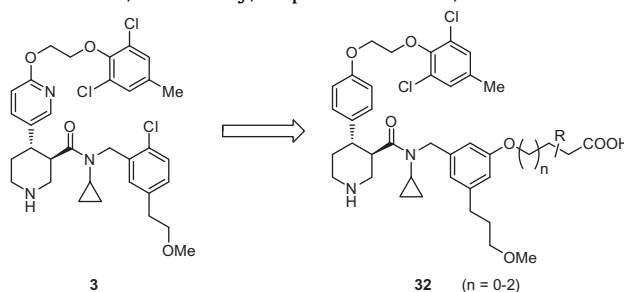
Jeffrey-Tri Nguyen, Keiko Kato, Koushi Hidaka, Henri-Obadja Kumada, Tooru Kimura, Yoshiaki Kiso*



The discovery and synthesis of potent zwitterionic inhibitors of renin

pp 2430–2436

Renee Aspiotis*, Austin Chen, Elizabeth Cauchon, Daniel Dubé, Jean-Pierre Falgout, Sébastien Gagné, Michel Gallant, Erich L. Grimm, Robert Houle, Hélène Juteau, Patrick Lacombe, Sébastien Laliberté, Jean-François Lévesque, Dwight MacDonald, Dan McKay, M. David Percival, Patrick Roy, Stephen M. Soisson, Tom Wu

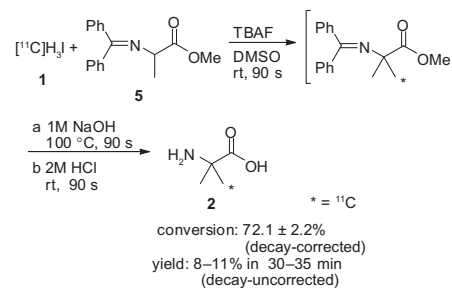


An efficient and expedient method for the synthesis of ¹¹C-labeled α-aminoisobutyric acid: A tumor imaging agent potentially useful for cancer diagnosis

pp 2437–2440

Koichi Kato*, Atsushi B. Tsuji, Tsuneo Saga, Ming-Rong Zhang

We describe the synthesis of ¹¹C-labeled α-aminoisobutyric acid **2** from iodo[¹¹C]methane and methyl *N*-(diphenylmethylene)-D,L-alaniate (**5**). The tetrabutylammonium fluoride (TBAF)-promoted α-[¹¹C]methylation of sterically hindered analog **5** was a key step in our synthesis process. Total radiochemical conversion of **2** was high and a remote-controlled synthesis was carried out. A comparative tumor positron emission tomography (PET) imaging study using the same model mouse showed higher uptake of **2** than with ¹¹C-labeled methionine and [¹⁸F] fluorodeoxyglucose (FDG).



pp 2441–2444

The diagram illustrates the three-step process of the AI-driven drug discovery pipeline:

- Construction of substrate library:** A collection of various chemical structures (represented by colored spheres and lines) is shown, representing the initial library of substrates.
- Selection of specific substrate:** A specific substrate (represented by a blue sphere and a green sphere) is selected from the library, indicated by a blue arrow pointing to a green C-shaped structure.
- Synthesis of specific inhibitor:** The selected substrate is used to synthesize a specific inhibitor (represented by a red sphere and a blue sphere), indicated by a blue arrow pointing to the final product.



pp 2445–2449

[illegible]

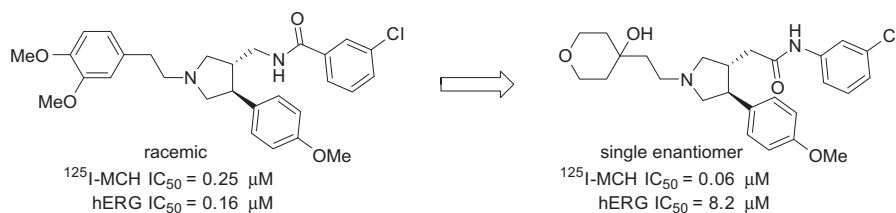
pp 2450–2455

pp 2456–2459

Novel pyrrolidine melanin-concentrating hormone receptor 1 antagonists with reduced hERG inhibition

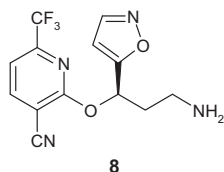
pp 2460–2467

Brian M. Fox, Reina Natero, Kevin Richard, Richard Connors, Philip M. Roveto, Holger Beckmann, Katrin Haller, Justin Golde, Shou-Hua Xiao, Frank Kayser*

**The discovery of novel, potent and highly selective inhibitors of inducible nitric oxide synthase (iNOS)**

pp 2468–2471

David R. Cheshire*, Anders Åberg, Gunilla M. K. Andersson, Glen Andrews, Haydn G. Beaton, Timothy N. Birkinshaw, Nigel Boughton-Smith, Stephen Connolly, Tony R. Cook, Anne Cooper, Sally L. Cooper, David Cox, John Dixon, Nigel Gensmantel, Peter J. Hamley, Richard Harrison, Paul Hartopp, Helena Käck, Paul D. Leeson, Timothy Luker, Antonio Mete, Ian Millichip, David J. Nicholls, Austen D. Pimm, Steve A. St-Gallay, Alan V. Wallace



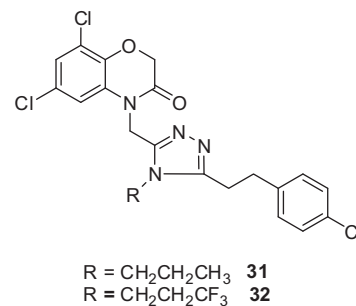
By careful analysis of experimental X-ray ligand crystallographic protein data across several inhibitor series we have discovered a novel, potent and selective series of iNOS inhibitors exemplified by compound **8**.

**Discovery of non-glucoside SGLT2 inhibitors**

pp 2472–2475

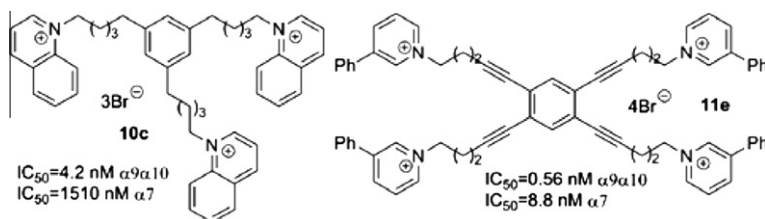
An-Rong Li*, Jian Zhang, Joanne Greenberg, TaeWeon Lee, Jiwen Liu

A series of benzothiazinone and benzoxazinone derivatives were discovered as SGLT2 inhibitors. The optimization led to the discovery of compounds **31** and **32**, which exhibited similar potency and better SGLT1 selectivity compared to dapagliflozin. These compounds may provide novel promising scaffolds, which are different from phlorizin-based SGLT2 inhibitors.

**Discovery of non-peptide, small molecule antagonists of $\alpha 9\alpha 10$ nicotinic acetylcholine receptors as novel analgesics for the treatment of neuropathic and tonic inflammatory pain**

pp 2476–2479

Guangrong Zheng, Zhenfa Zhang, Cheryl Dowell, Elzbieta Wala, Linda P. Dwoskin, Joseph R. Holtman, J. Michael McIntosh, Peter A. Crooks*

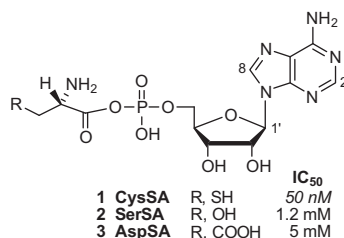


A series of azaaromatic quaternary ammonium analogs has been discovered as potent and selective $\alpha 9\alpha 10$ nicotinic acetylcholine receptor (nAChR) antagonists. The preliminary structure–activity relationships of these analogs suggest that increased rigidity in the linker units results in higher potency in inhibition of $\alpha 9\alpha 10$ nAChRs and greater selectivity over $\alpha 7$ nAChRs. These analogs represent a new class of analgesic for the treatment of neuropathic and tonic inflammatory pain.

Susceptibility and mode of binding of the *Mycobacterium tuberculosis* cysteinyl transferase mycothiol ligase to tRNA synthetase inhibitors

pp 2480–2483

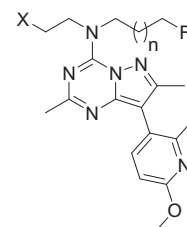
Maria-Teresa Gutierrez-Lugo, Carole A. Bewley*

**Potential CRF₁R PET imaging agents: *N*-Fluoroalkyl-8-(6-methoxy-2-methylpyridin-3-yl)-2,7-dimethyl-*N*-alkylpyrazolo[1,5-*a*][1,3,5]triazin-4-amines**

pp 2484–2488

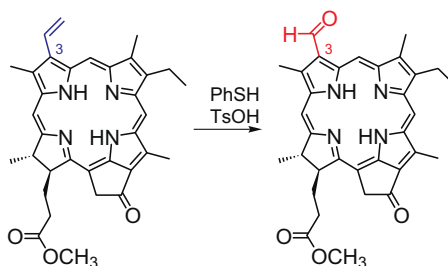
Dmitry Zuev*, Ronald J. Mattson*, Hong Huang, Gail K. Mattson, Larisa Zueva, Julia M. Nielsen, Edward S. Kozlowski, Xiaohua Stella Huang, Dedong Wu, Qi Gao, Nicholas J. Lodge, Joanne J. Bronson, John E. Macor

A series of *N*-(3-fluoroalkyl)-8-(6-methoxy-2-methylpyridin-3-yl)-2,7-dimethyl-*N*-alkylpyrazolo[1,5-*a*][1,3,5]triazin-4-amines were prepared and evaluated as potential CRF₁R PET imaging agents. Optimization of their CRF₁R binding potencies and octanol-phosphate buffer phase distribution coefficients resulted in discovery of analog **7e** (IC₅₀ = 6.5 nM, log *D* = 3.5).

**A mild conversion from 3-vinyl- to 3-formyl-chlorophyll derivatives**

pp 2489–2491

Toru Oba*, Yuki Uda, Kohei Matsuda, Takanori Fukusumi, Satoshi Ito, Kazuhisa Hiratani, Hitoshi Tamiaki*

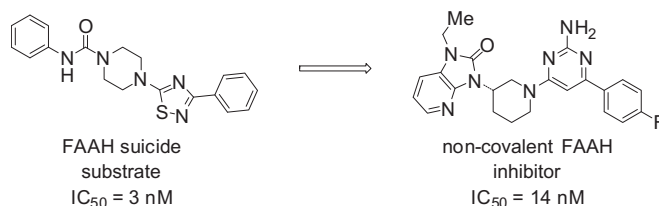


A chlorophyll-*a* derivative (3-vinyl-chlorin) was smoothly converted into the corresponding chlorophyll-*d* derivative (3-formyl-chlorin) under mild conditions: treatment with thiophenol in an acidic solution at room temperature.

Identification of potent, noncovalent fatty acid amide hydrolase (FAAH) inhibitors

pp 2492–2496

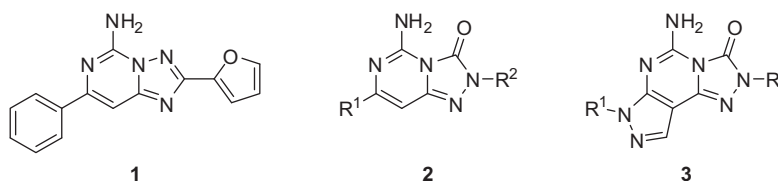
Darin J. Gustin*, Zhihua Ma, Xiaoshan Min, Yihong Li, Christine Hedberg, Cris Guimaraes, Amy C. Porter, Michelle Lindstrom, Dianna Lester-Zeiner, Guifen Xu, Timothy J. Carlson, Shouhua Xiao, Cesar Meleza, Richard Connors, Zhulun Wang, Frank Kayser



Potent and selective adenosine A_{2A} receptor antagonists: [1,2,4]-triazolo[4,3-c]pyrimidin-3-ones

pp 2497–2501

Joel M. Harris*, Bernard R. Neustadt, Hongtao Zhang, Jean Lachowicz, Mary Cohen-Williams, Geoff Varty, Jinsong Hao, Andrew W. Stamford

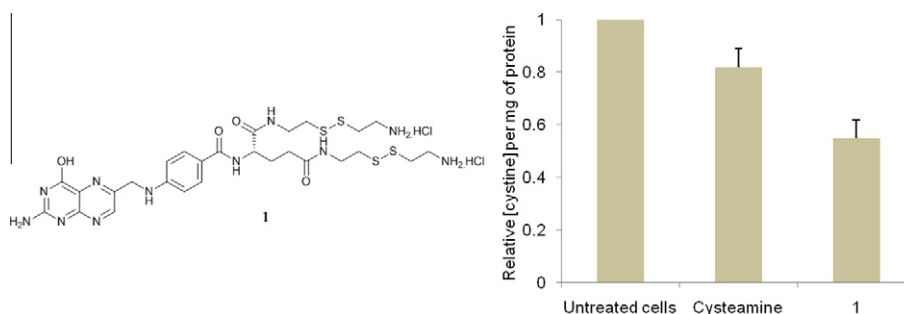


Antagonism of the adenosine A_{2A} receptor affords a possible treatment of Parkinson's disease. In the course of investigating pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine A_{2A} antagonists, we prepared [1,2,4]-triazolo[4,3-c]pyrimidin-3-ones with potent and selective (vs A₁) A_{2A} antagonist activity. Structure–activity relationships are described for this series.

Folate pro-drug of cystamine as an enhanced treatment for nephropathic cystinosis

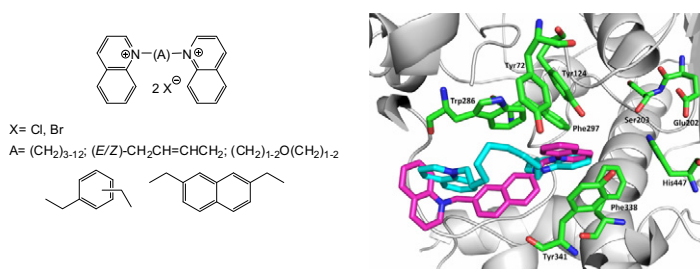
pp 2502–2504

Ziad Omran*, Graeme Kay, Emma E. Hector, Rachel M. Knott, Donald Cairns

**Preparation, in vitro screening and molecular modelling of symmetrical bis-quinolinium cholinesterase inhibitors—implications for early Myasthenia gravis treatment**

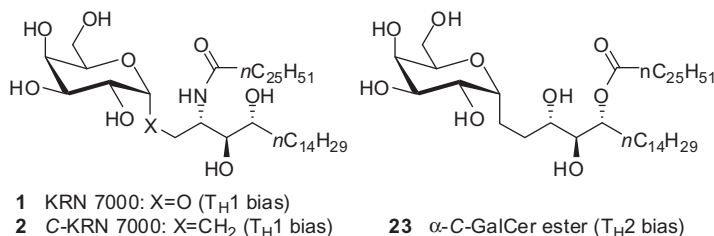
pp 2505–2509

Marketa Komloova, Kamil Musilek*, Anna Horova, Ondrej Holas, Vlastimil Dohnal, Frank Gunn-Moore, Kamil Kuca

**Use of the NEO strategy (Nucleophilic addition/Epoxy Opening) for the synthesis of a new C-galactoside ester analogue of KRN 7000**

pp 2510–2514

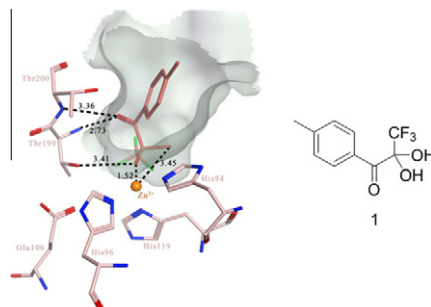
Aline Banchet-Cadeddu*, Agathe Martinez, Stéphane Guilleme, Véronique Parietti, Fanny Monneaux, Eric Hénon, Jean-Hugues Renault, Jean-Marc Nuzillard, Arnaud Haudrechy*



Virtual screening-driven identification of human carbonic anhydrase inhibitors incorporating an original, new pharmacophore

pp 2515–2520

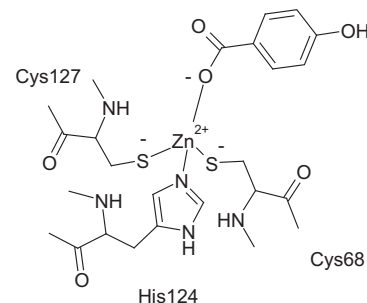
Nicolino Pala, Roberto Dallochio, Alessandro Dessì, Andrea Brancale, Fabrizio Carta, Simone Ihm, Alfonso Maresca, Mario Sechi*, Claudiu T. Supuran*



Carbonic anhydrase inhibitors. Inhibition of the β -class enzymes from the fungal pathogens *Candida albicans* and *Cryptococcus neoformans* with branched aliphatic/aromatic carboxylates and their derivatives

pp 2521–2526

Fabrizio Carta, Alessio Innocenti, Rebecca A. Hall, Fritz A. Mühlischlegel, Andrea Scozzafava, Claudiu T. Supuran*



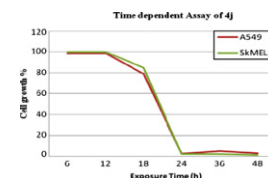
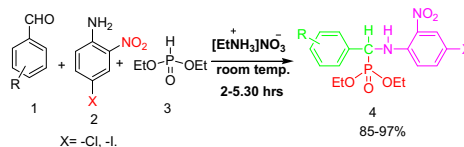
K_i = 7.61 μ M (hCA I); 7.28 μ M (hCA II); 9.5 nM (Can2); 110 nM (Nce103).

Ionic liquid promoted synthesis, antibacterial and in vitro antiproliferative activity of novel α -aminophosphonate derivatives

pp 2527–2532

Satish A. Dake, Dnyaneshwar S. Raut, Kiran R. Kharat, Rooth S. Mhaske, Satish U. Deshmukh, Rajendra P. Pawar*

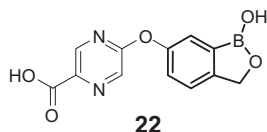
Ionic liquid ethyl ammonium nitrate is used as an excellent catalyst and solvent for three-component one-pot reaction of an aldehydes, amines and diethylphosphite to form novel α -aminophosphonates at room temperature. Among the various catalysts, the preparation of ethyl ammonium nitrate is an environmental friendly, cost effective and recyclable catalyst. Compounds **4b**, **4c**, **4d**, **4f** and **4j** were found more potent antibacterials against pathogenic microorganisms. Whereas, compounds **4a**, **4g**, **4h** and **4j** inhibits growth of active *Escherichia coli* NCIM 2645 and *Salmonella typhi* NCIM 2501. Compound **4j** was found a promising antiproliferative agent against A549 and SK-MEL2 human melanoma cell lines.



Synthesis and SAR of novel benzoxaboroles as a new class of β -lactamase inhibitors

pp 2533–2536

Yi Xia*, Kathy Cao, Yasheen Zhou, M. R. K. Alley, Fernando Rock, Manisha Mohan, Maliwan Meewan, Stephen J. Baker, Sarah Lux, Charles Z. Ding, Guofeng Jia, Maureen Kully, Jacob J. Plattner

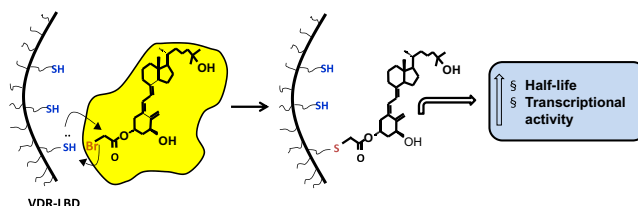


A new class of benzoxaborole β -lactamase inhibitors is described. 6-Aryloxy benzoxaborole, **22**, inhibited AmpC P99 and CMY-2 with K_i values in the low nanomolar range. Compound **22** restored antibacterial activity of ceftazidime against *Enterobacter cloacae* P99 expressing AmpC.

1 α ,25-Dihydroxyvitamin D₃-3 β -bromoacetate, a potential cancer therapeutic agent: Synthesis and molecular mechanism of action

pp 2537–2540

Rahul Ray*, James R. Lambert



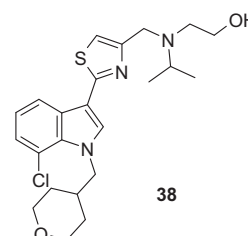
Synthesis of 1 α ,25-dihydroxyvitamin D₃-3 β -bromoacetate, a potential anti-cancer agent, and its probable mechanism of action, denoting its reduced catabolism is presented.

Design, synthesis and structure–activity relationships of (indo-3-yl) heterocyclic derivatives as agonists of the CB1 receptor. Discovery of a clinical candidate

pp 2541–2546

Paul Ratcliffe*, Julia M. Adam*, James Baker, Roberta Bursi, Robert Campbell, John K. Clark, Jean E. Cottney, Maureen Deehan, Anna-Marie Easson, Daniel Ecker, Darren Edwards, Ola Epemolu, Louise Evans, Ruth Fields, Stuart Francis, Paul Harradine, Fiona Jeremiah, Takao Kiyoi, Duncan McArthur, Angus Morrison, Paul Passier, Jack Pick, Peter G. Schnabel, Jurgen Schulz, Heinz Steinbrede, Glenn Walker, Paul Westwood, Grant Wishart, Joanna Udo de Haes

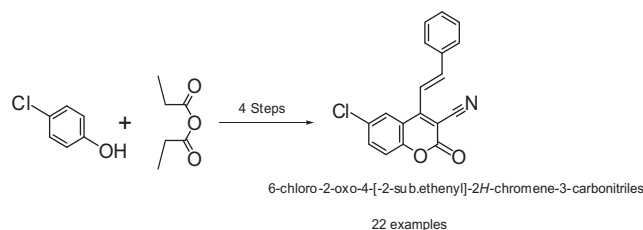
We report an expansion of the structure–activity relationship (SAR) of a novel series of indole-3- heterocyclic CB1 receptor agonists. Starting from the potent but poorly soluble lead, **1**, a rational approach was taken in order to balance solubility, hERG activity and potency while retaining the desired long duration of action within the mouse tail flick test. This led to the discovery of compound **38** which successfully progressed into clinical development.



Synthesis and biological evaluation of 4-styrylcoumarin derivatives as inhibitors of TNF- α and IL-6 with anti-tubercular activity

pp 2547–2549

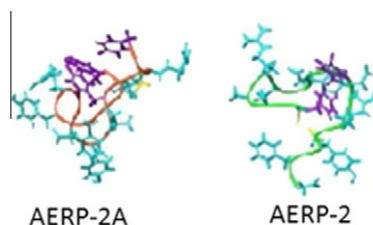
Kuldip Upadhyay, Abhay Bavishi, Shailesh Thakrar, Ashish Radadiya, Hardevsinh Vala, Shrey Parekh, Dhairya Bhavsar, Mahesh Savant, Manisha Parmar, Priti Adlakha, Anamik Shah*



Development of anti-EGF receptor peptidomimetics (AERP) as tumor imaging agent

pp 2550–2553

Datta E. Ponde*, ZiFen Su, Alan Berezov, Hongtao Zhang, Abbas Alavi, Mark I. Greene, Ramachandran Murali*

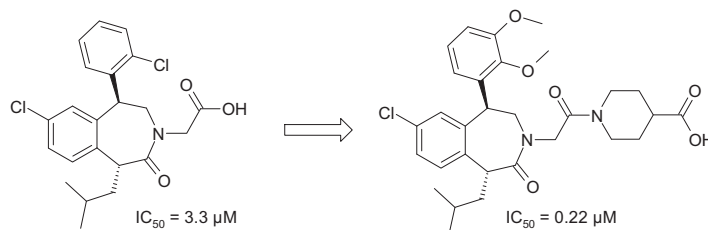


In certain human cancers, EGFR is over-expressed and is related to the metastatic potential of the tumor. We have developed two anti-EGFR receptor-binding peptidomimetics (AERP), as tumor-specific imaging agents. Our newly designed peptidomimetic, AERP, was conjugated to DTPA and labeled with ^{99m}Tc. The in vivo tumor accumulation of [^{99m}Tc] DTPA-AERP-2 was 1.6 \pm 0.1 %ID/g and tumor to muscle ratio was 5.5.

Identification and optimization of tetrahydro-2H-3-benzazepin-2-ones as squalene synthase inhibitors

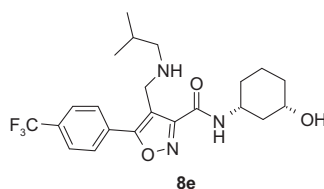
pp 2554–2558

Nils Griebenow*, Timo Flessner, Anja Buchmueller, Martin Raabe, Hilmar Bischoff, Peter Kolkhof

**Identification of potent, soluble, and orally active TRPV1 antagonists**

pp 2559–2563

Paul Ratcliffe*, John Maclean*, Lynn Abernethy, Tom Clarkson, Maureen Dempster, Anna-Marie Easson, Darren Edwards, Katy Everett, Helen Feilden, Peter Littlewood, Duncan McArthur, Deborah McGregor, Hazel McLuskey, Olaf Nimz, Lesley-Anne Nisbet, Ronnie Palin, Heather Tracey, Glenn Walker

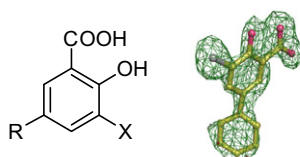


Optimization of a water soluble, moderately potent lead series of isoxazole-3-carboxamides was conducted, affording a compound with the requisite balance of potency, solubility and physicochemical properties for in vivo use. Compound **8e** was demonstrated to be efficacious in a rat model of inflammatory pain, following oral administration.

Probing the inhibitor selectivity pocket of human 20 α -hydroxysteroid dehydrogenase (AKR1C1) with X-ray crystallography and site-directed mutagenesis

pp 2564–2567

Ossama El-Kabbani*, Urmi Dhagat, Midori Soda, Satoshi Endo, Toshiyuki Matsunaga, Akira Hara

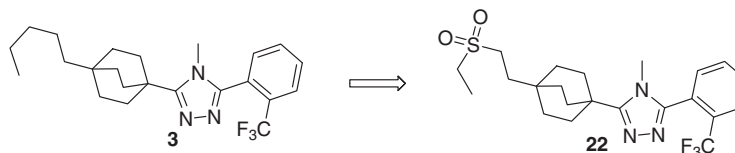


CPSA: X = Cl, R = Phenyl
DCSA: X = R = Cl

**Bicyclo[2.2.2]octyltriazole inhibitors of 11 β -hydroxysteroid dehydrogenase type 1. Pharmacological agents for the treatment of metabolic syndrome**


pp 2568–2572

Milana Maletic*, Aaron Leeman, Michael Szymonifka, Steven S. Mundt, Hratch J. Zokian, Kashmira Shah, Jasminka Dragovic, Kathy Lyons, Rolf Thieringer, Anne H. Vosatka, James Balkovec, Sherman T. Waddell



Following the discovery of a metabolic 'soft-spot' on a bicyclo[2.2.2]octyltriazole lead, an extensive effort was undertaken to block the oxidative metabolism and improve PK of this potent HSD1 lead. In this communication, SAR survey focusing on various alkyl chain replacements will be detailed. This effort culminated in the discovery of a potent ethyl sulfone inhibitor with an improved PK profile across species and improved physical properties.

*Corresponding author

 Supplementary data available via ScienceDirect

COVER

Botulinum neurotoxins are the most deadly toxins known to man, approximately 10 million times more deadly than cyanide. Botulinum neurotoxins are classified by the US Centers for Disease Control (CDC) as bioterrorism agents. The etiological agent responsible for botulinum intoxication is a metalloprotease; as such this is a key therapeutic target. Currently, there are no approved pharmacological treatments for botulinum intoxication. Discovering molecules that could be used as a path forward for therapeutic development as botulinum protease inhibitors is tantamount. A benzylidene cyclopentenedione-based inhibitor was found to be the first affinity reagent to covalently modify the active site of botulinum neurotoxin A light chain metalloprotease. Its kinetic parameters are reported and such an approach for inhibition of this deadly neurotoxin. [Capková, K.; Hixon, M. S.; Pellett, S.; Barbieri, J. T.; Johnson, E. A.; Janda, K. D. *Bioorg. Med. Chem. Lett.* **2010**, 20, 206.]

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