

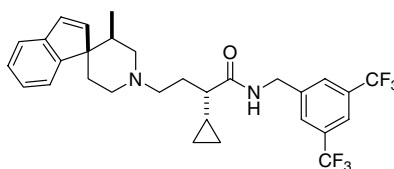
Contents

ARTICLES

4-Amino-2-alkyl-butyramides as small molecule CCR2 antagonists with favorable pharmacokinetic properties

pp 4715–4722

Gabor Butora,* Gregori J. Morriello, Shankaran Kothandaraman, Deodialsingh Guiadeen, Alexander Pasternak, William H. Parsons, Malcolm MacCoss, Pasquale P. Vicario, Margaret A. Cascieri and Lihu Yang

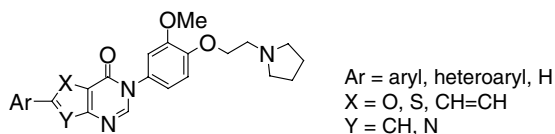


A novel class of CCR2 antagonists with high binding affinity ($IC_{50} = 4$ nM, human monocyte) and favorable pharmacokinetic profile is described.

The discovery and optimization of pyrimidinone-containing MCH R1 antagonists

pp 4723–4727

Donald L. Hertzog,* Kamal A. Al-Barazanji, Eric C. Bigham, Michael J. Bishop, Christy S. Britt, David L. Carlton, Joel P. Cooper, Alex J. Daniels, Dulce M. Garrido, Aaron S. Goetz, Mary K. Grizzle, Yu C. Guo, Anthony L. Handlon, Diane M. Ignar, Ronda O. Morgan, Andrew J. Peat, Francis X. Tavares and Huiqiang Zhou

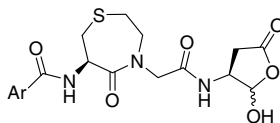


Optimization of a series of constrained melanin-concentrating hormone receptor 1 (MCH R1) antagonists has provided potent and selective compounds that are orally active in an animal model of obesity.

Synthesis and evaluation of thiazepines as interleukin-1 β converting enzyme (ICE) inhibitors

pp 4728–4732

Christopher D. Ellis,* Kofi A. Oppong, Michael C. Laufersweiler, Steven V. O'Neil, David L. Soper, Yili Wang, John A. Wos, Amy N. Fancher, Wei Lu, Maureen K. Suchanek, Richard L. Wang, Biswanath De and Thomas P. Demuth, Jr.

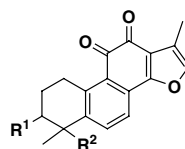


The synthesis of a series of monocyclic ICE inhibitors is reported.

Synthesis of novel chemical probes for the study of tanshinone binding proteins

pp 4733–4737

Jin-Soo Lee, Sun-Young Han, Myong Sang Kim, Chan-Mo Yu,
Myung Hee Kim, Seong Hwan Kim, Yong Ki Min* and Bum Tae Kim



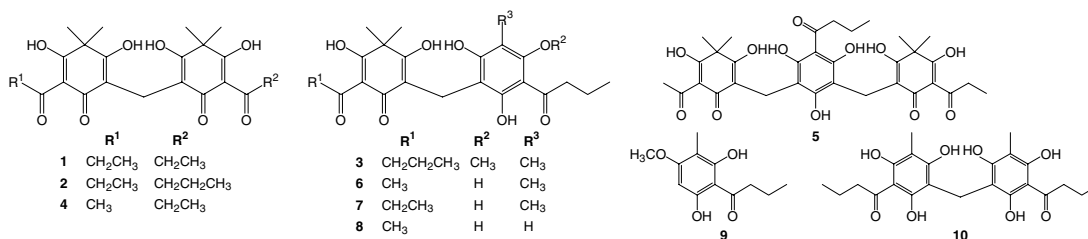
3-Hydroxytanshinone ($R^1=OH$, $R^2=CH_3$)
Tanshinone IIB ($R^1=H$, $R^2=CH_2OH$)

Novel diazirine or biotin-labeled tanshinone probes were synthesized and evaluated for TRAP inhibitory activity against RANKL-induced osteoclastogenesis in RAW264.7 cells.

Fatty acid synthase inhibitory activity of acylphloroglucinols isolated from *Dryopteris crassirhizoma*

pp 4738–4742

MinKyun Na, JunPil Jang, Byung Sun Min, Sang Jun Lee, Myung Sun Lee,
Bo Yeon Kim, Won Keun Oh* and Jong Seog Ahn

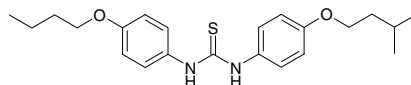


Bioassay-guided fractionation of a MeOH extract of the rhizomes of *Dryopteris crassirhizoma* led to the isolation of a series of acylphloroglucinols, as the active principles.

Symmetrical and unsymmetrical analogues of isoxyl; active agents against *Mycobacterium tuberculosis*

pp 4743–4747

Veemal Bhowruth, Alistair K. Brown, Robert C. Reynolds,
Geoffrey D. Coxon, Simon P. Mackay, David E. Minnikin and Gurdial S. Besra*

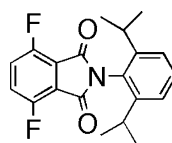


Analogues of isoxyl with symmetrical and unsymmetrical modifications have significantly enhanced activity against both *Mycobacterium tuberculosis* and *Mycobacterium bovis* BCG.

Tubulin polymerization inhibitors with a fluorinated phthalimide skeleton derived from thalidomide

pp 4748–4751

Tomonori Yanagawa, Tomomi Noguchi, Hiroyuki Miyachi, Hisayoshi Kobayashi*
and Yuichi Hashimoto*



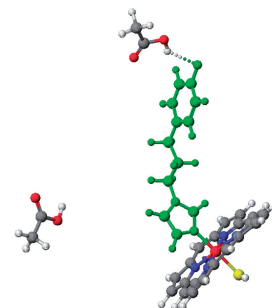
4,7FPP-33

4,7FPP-33 has been shown to possess potent tubulin polymerization inhibiting activity.

Synthesis, biochemical evaluation and rationalisation of the inhibitory activity of a range of 4-substituted phenyl alkyl imidazole-based inhibitors of the enzyme complex 17 α -hydroxylase/17,20-lyase (P450_{17 α})

Chirag H. Patel, Sachin Dhanani, Caroline P. Owen and Sabbir Ahmed*

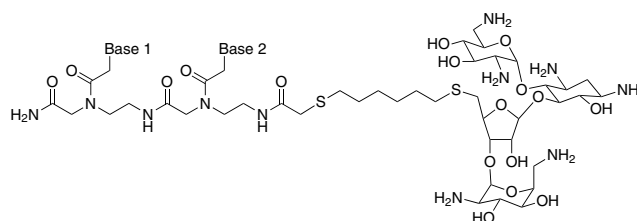
We report the synthesis and biochemical evaluation of a range of 4-substituted phenyl alkyl imidazole-based compounds which have been targeted against the two components of 17 α -hydroxylase/17,20-lyase (P450_{17 α}).



pp 4752–4756

A strategy for the design of selective RNA binding agents. Preparation and RRE RNA binding affinities of a neomycin-peptide nucleic acid heteroconjugate library

Soonsil Hyun, Kyung Hyun Lee and Jaehoon Yu*

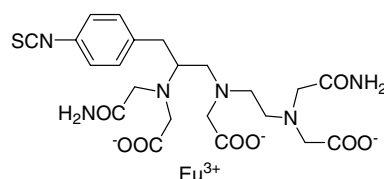


The screening of neomycin-peptide nucleic acid heteroconjugates against RRE RNA is reported. Selected compounds showed low nanomolar affinity (**4-AA**, $K_d = 58$ nM; **4-GG**, $K_d = 30$ nM) and specificity against the target.



Synthesis and properties of a neutral derivative of diethylenetriaminepentaacetic acid (DTPA)

Jari Peuralahti, Liisa Meriö, Veli-Matti Mikkala, Kaj Blomberg and Jari Hovinen*



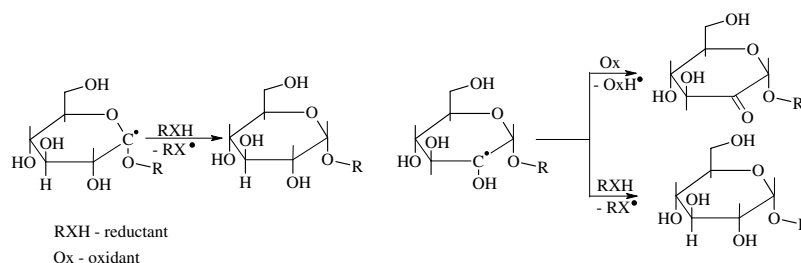
A neutral bifunctional derivative of DTPA europium(III) was synthesized and its suitability to dissociation-enhanced lanthanide fluorescence immunoassay was investigated.

pp 4760–4762

Effects of vitamins, coenzymes and amino acids on reactions of homolytic cleavage of the O-glycoside bond in carbohydrates

O. I. Shadyro,* R. M. Kisel, V. V. Vysotskii and I. P. Edimecheva

It has been established that vitamins B₁, K₃ and C, coenzyme Q₀ and amino acids cysteine and histidine effectively inhibit reactions of homolytic cleavage of the O-glycoside bond. This effect was shown to originate from either oxidation or reduction of the radicals of carbohydrates undergoing destruction:



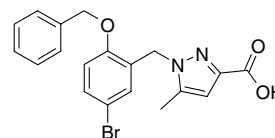
pp 4763–4766

Identification of novel pyrazole acid antagonists for the EP₁ receptor

pp 4767–4771

Stephen C. McKeown,* Adrian Hall, Gerard M.P. Giblin, Olivier Lorthioir, Richard Blunt, Xiao Q. Lewell, Richard J. Wilson, Susan H. Brown, Anita Chowdhury, Tanya Coleman, Stephen P. Watson, Iain P. Chessell, Adrian Pipe, Nick Clayton and Paul Goldsmith

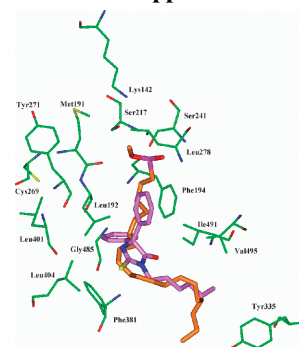
The discovery, synthesis, pharmacokinetic profile and structure–activity relationships of a novel series of EP₁ receptor antagonists is described.

EP₁ pKi = 7.8EP₃ pKi = <5.7**Binding mode of new (thio)hydantoin inhibitors of fatty acid amide hydrolase: Comparison with two original compounds, OL-92 and JP104**

pp 4772–4776

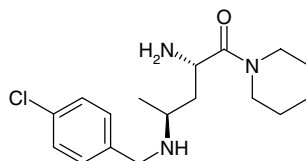
Catherine Michaux,* Giulio G. Muccioli, Didier M. Lambert and Johan Wouters

The binding mode of new (thio)hydantoin FAAH inhibitors is reported and compared with the one of known reference compounds. This study gives ideas to design more active compounds.

**Synthesis and dipeptidyl peptidase inhibition of *N*-(4-substituted-2,4-diaminobutanoyl)piperidines**

pp 4777–4779

Anna Soroka, Pieter Van der Veken, Ingrid De Meester, Anne-Marie Lambeir, Marie-Berthe Maes, Simon Scharpé, Achiel Haemers* and Koen Augustyns

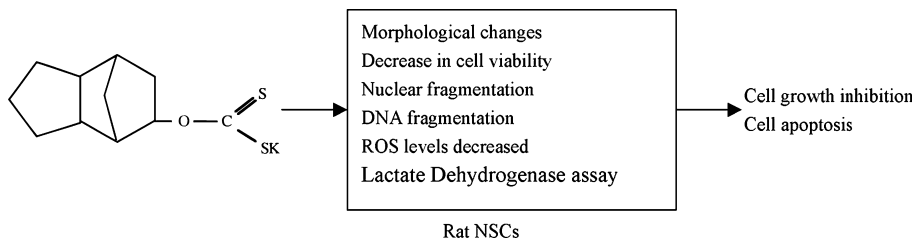


A method to prepare diastereomerically pure *N*-(4-substituted-2,4-diaminobutanoyl)piperidines as inhibitors of dipeptidyl peptidases is described. The (2*S*,4*S*)-4-methyl compound selectively inhibits dipeptidyl peptidase II with subnanomolar activity. A (4*R*)-methyl group or larger substituents decrease the activity.

D609 blocks cell survival and induces apoptosis in neural stem cells

pp 4780–4783

Nan Wang, Xin Lv, Le Su, BaoXiang Zhao,* ShangLi Zhang and JunYing Miao*



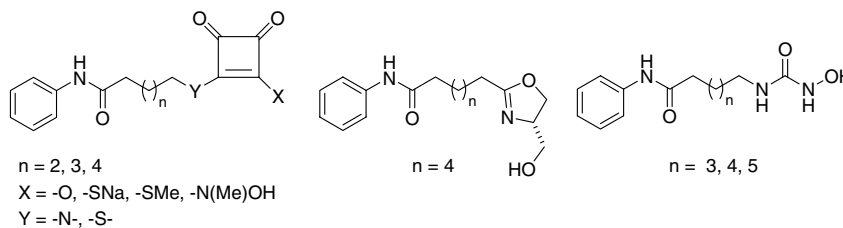
D609 could suppress cell survival and induce apoptosis in rat neural stem cells. Moreover, the changes of intracellular ROS level induced by D609 indicated that a modest level of ROS might be indispensable to NSC survival.



Exploring alternative Zn-binding groups in the design of HDAC inhibitors: Squaric acid, N-hydroxyurea, and oxazoline analogues of SAHA

pp 4784–4787

Stephen Hanessian,* Valerio Vinci, Luciana Auzzas, Mauro Marzi and Giuseppe Giannini

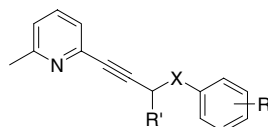


Analogues of suberoyl anilide hydroxamic acid (SAHA) were prepared by replacing the Zn-binding group with squaric acid, N-hydroxyurea, and 4-hydroxymethyl oxazoline, also varying the length of the aliphatic chain.

Structure–activity relationships for the linker in a series of pyridinyl-alkynes that are antagonists of the metabotropic glutamate receptor 5 (mGluR5)

pp 4788–4791

Peter Bach,* Karolina Nilsson, Tor Svensson, Udo Bauer, Lance G. Hammerland, Alecia Peterson, Andreas Wällberg, Krister Österlund, David Karis, Maria Boije and David Wensbo

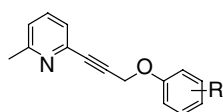


Studies of structure–activity relationships for the linker in a new series of metabotropic glutamate receptor 5 antagonists are presented together with in vitro and in vivo pharmacokinetic data.

A new series of pyridinyl-alkynes as antagonists of the metabotropic glutamate receptor 5 (mGluR5)

pp 4792–4795

Peter Bach,* Karolina Nilsson, Andreas Wällberg, Udo Bauer, Lance G. Hammerland, Alecia Peterson, Tor Svensson, Krister Österlund, David Karis, Maria Boije and David Wensbo



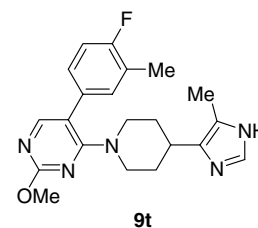
Synthesis and some structure–activity relationships for a new series of propargyl ethers as mGluR5 antagonists are reported.

Synthesis and biological activity of 5-aryl-4-(4-(5-methyl-1H-imidazol-4-yl)piperidin-1-yl)pyrimidine analogs as potent, highly selective, and orally bioavailable NHE-1 inhibitors

pp 4796–4799

Karnail S. Atwal,* Steven V. O'Neil, Saleem Ahmad,* Lidia Doweiko, Mark Kirby, Charles R. Dorso, Gamini Chandrasena, Bang-Chi Chen, Rulin Zhao and Robert Zahler

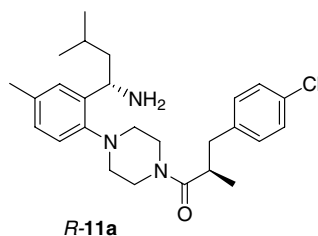
A series of potent inhibitors of the sodium hydrogen exchanger-1 (NHE-1) is described. Structure–activity relationships identified the 3-methyl-4-fluoro analog **9t** as a highly potent ($IC_{50} = 0.0065 \mu M$) and selective (NHE-2/NHE-1 = 1400) non-acylguanidine NHE-1 inhibitor. Pharmacokinetic studies showed that compound **9t** has an oral bioavailability of 52% and a plasma half life of 1.5 h in rats.



Propionylpiperazines as human melanocortin-4 receptor ligands

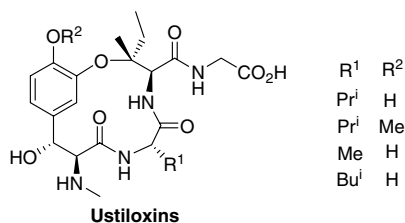
pp 4800–4803

Caroline W. Chen, Joe A. Tran, Wanlong Jiang, Fabio C. Tucci, Melissa Arellano, Jenny Wen, Beth A. Fleck, Dragan Marinkovic, Nicole S. White, Joseph Pontillo, John Saunders, Ajay Madan, Alan C. Foster and Chen Chen*

**Total synthesis and biological evaluation of ustiloxin natural products and two analogs**

pp 4804–4807

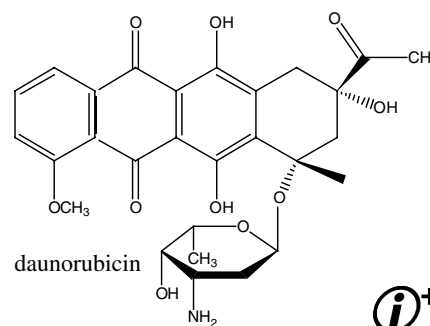
Pixu Li, Cory D. Evans, Erin M. Forbeck, Haengsoon Park, Ruoli Bai, Ernest Hamel* and M. M. Joullié*

**In vitro study of drug accumulation in cancer cells via specific association with CdS nanoparticles**

pp 4808–4812

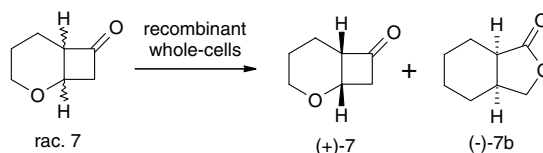
Jingyuan Li, Chunhui Wu, Feng Gao, Renyun Zhang, Gang Lv, Degang Fu, Baoan Chen and Xuemei Wang*

A novel approach is reported to enhance the efficient accumulation of daunorubicin on cancer cells through the combination with CdS nanoparticles.

**Resolution of fused bicyclic ketones by a recombinant biocatalyst expressing the Baeyer–Villiger monooxygenase gene Rv3049c from *Mycobacterium tuberculosis* H37Rv**

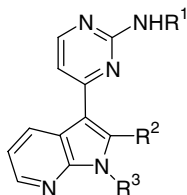
pp 4813–4817

Radka Snajdrova, Gideon Grogan and Marko D. Mihovilovic*



In contrast to previously reported Baeyer–Villiger monooxygenases, kinetic resolution processes of fused cyclobutanones are performed by engineered *Escherichia coli* expressing an enzyme from *Mycobacterium tuberculosis*.

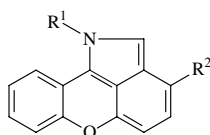
Synthesis of 2-amino-4-(7-azaindol-3-yl)pyrimidines as cyclin dependent kinase 1 (CDK1) inhibitors pp 4818–4821
 Shenlin Huang,* Ronghua Li, Peter J. Connolly, Stuart Emanuel and Steven A. Middleton



A novel series of 2-amino-4-(7-azaindol-3-yl)pyrimidines was discovered as cyclin dependent kinase 1 (CDK1) inhibitors. The core structure was synthesized via Pd(II) catalyzed coupling reaction. A number of analogues showed good potency for CDK1 and exhibited cellular antiproliferation activity. The structure–activity relationship is described.

Synthesis and antiproliferative activity of substituted benzopyranoisoindoles: A new class of cytotoxic compounds pp 4822–4825

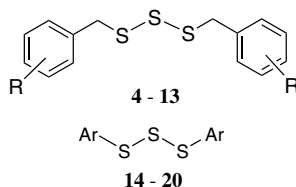
Christiana Hadjipavlou, Ioannis K. Kostakis, Nicole Pouli, Panagiotis Marakos,* Harris Pratsinis and Dimitris Kletsas



R¹ = CH₃CH₂, RRNCH₂CH₂
 R² = NO₂, RRNCH₂CH₂NH
 NRR = N(CH₃)₂, N(CH₂CH₃)₂, N(CH₂)₄



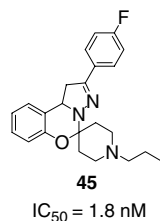
Synthesis and anti-tumor evaluation of new trisulfide derivatives pp 4826–4829
 Haoyun An,* Jenny Zhu, Xiaobo Wang and Xiao Xu



New bis-aromatic and heterocyclic trisulfide derivatives **5**, **7–10** were synthesized by optimizing lead dibenzyl trisulfide natural product (**4**) to evaluate their anti-tumor activities. Five compounds **5–7**, **9**, and **10** exhibited potent anti-tumor activities against eight different tumor cell lines with low cytotoxicity against HepG2. Initial SAR was discussed, and MOA of these anti-microtubule agents was suggested based on cell kinetic response patterns observed on RT-CES system.

New spiro-piperidines as 5-HT_{2B} receptor antagonists pp 4830–4833

Hugues Bienaymé, Laurent Chêne, Serge Grisoni,* Antonio Grondin, El-Bachir Kaloun, Stéphane Poigny, Houcine Rahali and Eric Tam



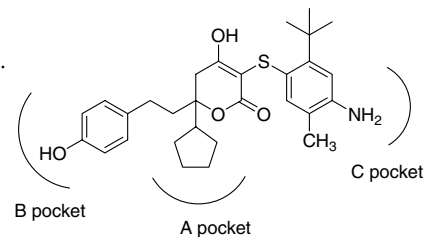
The synthesis of the compound **45** (IC₅₀ = 1.8 nM) and its analogs is reported.

Identification and structure-based optimization of novel dihydropyrones as potent HCV RNA polymerase inhibitors

pp 4834–4838

Hui Li,* John Tatlock, Angelica Linton, Javier Gonzalez, Allen Borchardt, Peter Dragovich, Tanya Jewell, Tom Prins, Ru Zhou, Julie Blazel, Hans Parge, Robert Love, Michael Hickey, Chau Doan, Stephanie Shi, Rohit Duggal, Cristina Lewis and Shella Fuhrman

The discovery and SAR of a novel series of HCV polymerase inhibitors are described.

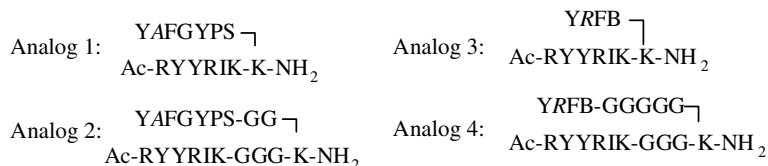


Compound 6: IC₅₀ = 0.93 μM (genotype 1b)

Synthesis and receptor binding properties of chimeric peptides containing a μ-opioid receptor ligand and nociceptin/orphanin FQ receptor ligand Ac-RYYRIK-amide

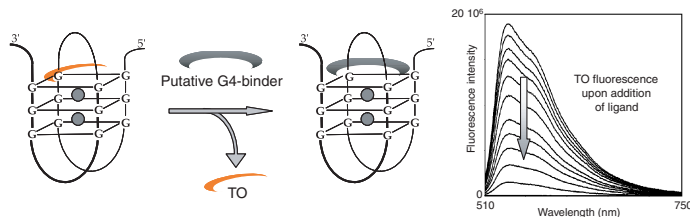
pp 4839–4841

Susumu Kawano, Akihiro Ambo and Yusuke Sasaki*


Development of a fluorescent intercalator displacement assay (G4-FID) for establishing quadruplex-DNA affinity and selectivity of putative ligands

pp 4842–4845

David Monchaud, Clémence Allain and Marie-Paule Teulade-Fichou*

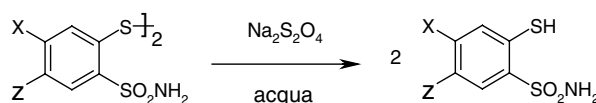


A fluorescent intercalator displacement assay (G4-FID) has been designed based on thiazole orange displacement from a quadruplex-forming oligonucleotide by putative quadruplex-ligands. It allows selection of high-affinity ligands, affinity ranking and viable determination of quadruplex- over duplex-selectivity.

Carbonic anhydrase inhibitors. Inhibition of the cytosolic human isozymes I and II, and the transmembrane, tumor-associated isozymes IX and XII with substituted aromatic sulfonamides activatable in hypoxic tumors

pp 4846–4851

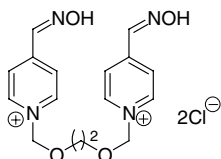
Franciszek Sączewski, Jarosław Sławiński, Anita Kornicka, Zdzisław Brzozowski, Elżbieta Pomarnacka, Alessio Innocenti, Andrea Scozzafava and Claudiu T. Supuran*



Bis-pyridiniumaldoxime reactivators connected with $\text{CH}_2\text{O}(\text{CH}_2)_n\text{OCH}_2$ linkers between pyridinium rings and their reactivity against VX

pp 4852–4855

Kyung-Ae Oh, Garp Yeol Yang, Daniel Jun, Kamil Kuca and Young-Sik Jung*



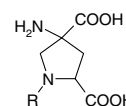
New bis-pyridinium oxime reactivators connected with $\text{CH}_2\text{O}(\text{CH}_2)_n\text{OCH}_2$ linkers between two pyridinium rings were designed and synthesized, and their reactivation potency was evaluated for AChE inhibited by organophosphorus VX agent.

Design and synthesis of APTCs (aminopyrrolidinetri-carboxylic acids): Identification of a new group III metabotropic glutamate receptor selective agonist

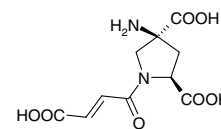
pp 4856–4860

Stephan Schann,* Christel Menet, Paul Arvault, Géraldine Mercier, Mélanie Frauli, Stanislas Mayer, Nadia Hubert, Nicolas Triballeau, Hugues-Olivier Bertrand, Francine Acher and Pascal Neuville

A new family of mGlu receptor orthosteric ligands called APTCs was designed and synthesized using parallel chemistry. Amongst them, **8a06** (FP0429) has been shown to be a full mGlu4 agonist and a partial mGlu8 agonist.



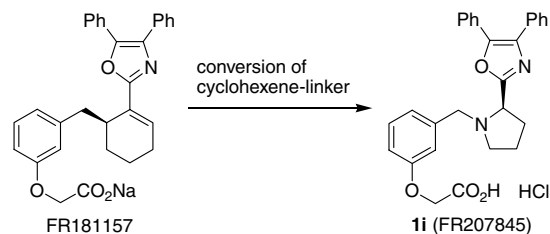
APTCs

**8a06** (FP0429)**Replacing the cyclohexene-linker of FR181157 leading to novel IP receptor agonists: Orally active prostacyclin mimetics. Part 6**

pp 4861–4864

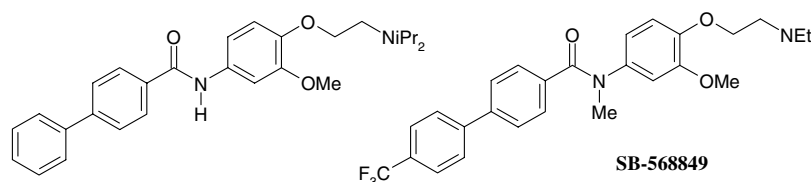
Akira Tanaka,* Kouji Hattori, Kiyoshi Taniguchi, Osamu Okitsu, Seiichiro Tabuchi, Mie Nishio, Yasunori Nagakura, Noriaki Maeda, Hidetsugu Murai and Jiro Seki

The synthesis and biological activity of novel derivatives of our previously reported IP receptor agonist FR181157, replacing the cyclohexene-linker, is described. Compound **1i** (FR207845) was identified as a potent non-prostanoid PGI_2 mimetic with a good oral bioavailability.

**SAR of biphenyl carboxamide ligands of the human melanin-concentrating hormone receptor 1 (MCH R1): Discovery of antagonist SB-568849**

pp 4865–4871

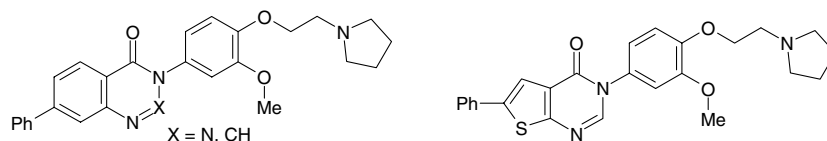
David R. Witty,* John H. Bateson, Guillaume J. Hervieu, Phillip Jeffrey, Christopher N. Johnson, Alison I. Muir, Peter J. O'Hanlon, Geoffrey Stemp, Alex J. Stevens, Kevin M. Thewlis, Shelagh Wilson and Kim Y. Winborn



Discovery of potent and stable conformationally constrained analogues of the MCH R1 antagonist SB-568849

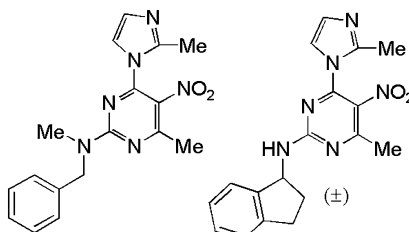
pp 4872–4878

David R. Witty,* John Bateson, Guillaume J. Hervieu, Kamal Al-Barazanji, Phillip Jeffrey, Dieter Hamprecht, Andrea Haynes, Christopher N. Johnson, Alison I. Muir, Peter J. O'Hanlon, Geoffrey Stemp, Alex J. Stevens, Kevin Thewlis and Kim Y. Winborn

**Discovery of a novel series of inhibitors of human cytomegalovirus primase**

pp 4879–4883

T. D. Cushing,* J. Adrian, X. Chen, H. DiMaio, B. Doughan, J. Flygare, L. Liang, V. Mayorga, S. Miao, H. Mellon, M.G. Peterson, J. P. Powers, F. Spector, C. Stein, M. Wright, D. Xu, Q. Ye and J. Jaen



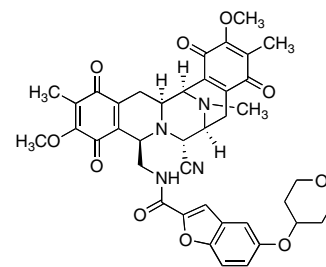
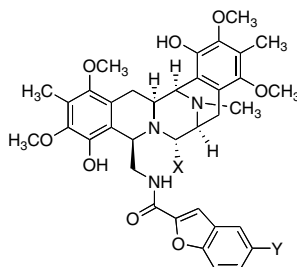
We have identified a new series of non-nucleoside inhibitors that are more potent than ganciclovir and cidofovir with a similar toxicity profile. SAR studies suggest that these inhibitors are specific for hCMV primase.

Evaluation of antitumor properties of novel saframycin analogs in vitro and in vivo

pp 4884–4888

Jeffrey R. Spencer,* Martin Sendzik, Jason Oeh, Peter Sabbatini, Stacie A. Dalrymple, Catherine Magill, Hyunjin M. Kim, Penglie Zhang, Neil Squires, Katherine G. Moss, Juthamas Sukbuntherng, Doris Graupe, John Eksterowicz, Peter R. Young, Andrew G. Myers and Michael J. Green

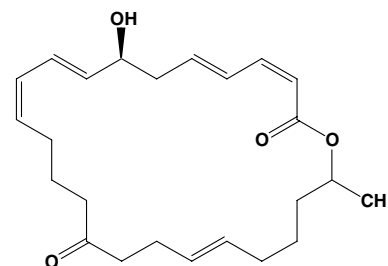
Novel analogs of (–)-saframycin A are described. Analogs are shown to be potent inhibitors of the in vitro growth of several tumor cells and active antitumor agents in a solid tumor model (HCT-116).

**Macrolactin N, a new peptide deformylase inhibitor produced by *Bacillus subtilis***

pp 4889–4892

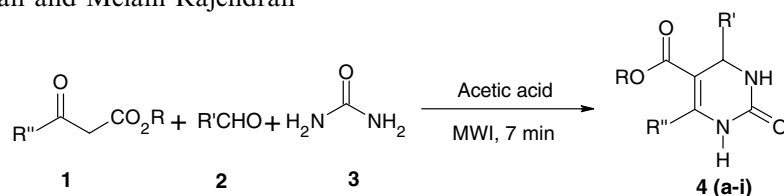
Jung-Sung Yoo, Chang-Ji Zheng, Sangku Lee, Jin-Hwan Kwak and Won-Gon Kim*

A new 24-membered ring lactone, macrolactin N, was isolated from a culture broth of *Bacillus subtilis* and its structure was established by various spectral analysis. Macrolactin N inhibited *Staphylococcus aureus* peptide deformylase with an IC₅₀ value of 7.5 μM.



Synthesis and cardiac effects of 3,4-dihydropyrimidin-2(1H)-one-5 carboxylates

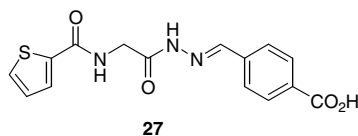
pp 4893–4897

Kuppusamy Sujatha, Pachaiyappan Shanmugam, Paramasivam T. Perumal,*
Doraisamy Muralidharan and Melani Rajendran

A series of 4-(substituted)-3,4-dihydropyrimidinone derivatives have been synthesized and evaluated for cardiovascular effects at different dose levels. The interaction with β -blocker and calcium channel blocker was also investigated. Entry **4d** emerged as the most interesting compound in this series.

Pharmacophore-based virtual screening: The discovery of novel methionyl-tRNA synthetase inhibitors pp 4898–4907

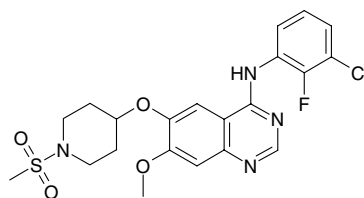
Su Yeon Kim, Yeon-Sook Lee, Taehee Kang, Sunghoon Kim and Jeewoo Lee*



Virtual screening of a chemical database of 508,143 commercially available chemicals was performed to search for new methionyl-tRNA synthetase (MetRS) inhibitors.

Inhibitors of epidermal growth factor receptor tyrosine kinase:

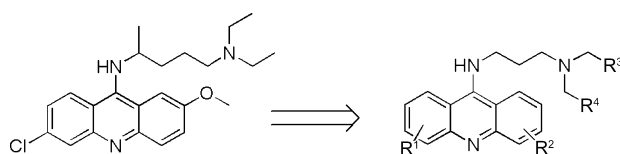
pp 4908–4912

Optimisation of potency and in vivo pharmacokineticsPeter Ballard, Robert H. Bradbury, Craig S. Harris, Laurent F. A. Hennequin, Mark Hickinson,
Jason G. Kettle,* Jane Kendrew, Teresa Klinowska, Donald J. Ogilvie, Stuart E. Pearson,
Emma J. Williams and Ingrid Wilson

20: EGFR $\text{IC}_{50} = 2 \text{ nM}$
KB Cell $\text{IC}_{50} = 7 \text{ nM}$

Structure–activity relationship study of 9-aminoacridine compounds in scrapie-infected neuroblastoma cells

pp 4913–4916

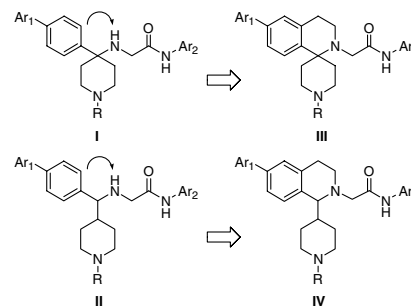
Barnaby C. H. May,* Juanita Witkop, John Sherrill, Marc O. Anderson, Peter B. Madrid,
Julie A. Zorn, Stanley B. Prusiner, Fred E. Cohen and R. Kiplin Guy

Tetrahydroisoquinolines as MCH-R1 antagonists

pp 4917–4921

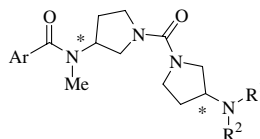
T. K. Sasikumar,* L. Qiang, W.-L. Wu, D. A. Burnett, W. J. Greenlee, K. O'Neill, B. E. Hawes, M. van Heek and M. Graziano

A series of potent and selective MCH-R1 antagonists have been discovered based on a piperidine glycineamide series.

**Synthesis and structure–activity relationships of retro bis-aminopyrrolidine urea (rAPU) derived small-molecule antagonists of the melanin-concentrating hormone receptor-1 (MCH-R1). Part 2**

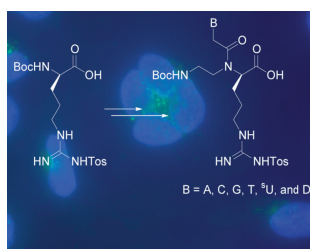
pp 4922–4930

Sarah Hudson,* Mehrak Kiankarimi, Martin W. Rowbottom, Troy D. Vickers, Dongpei Wu, Joseph Pontillo, Brett Ching, Wesley Dwight, Val S. Goodfellow, David Schwarz, Christopher E. Heise, Ajay Madan, Jenny Wen, William Ban, Hua Wang and Warren S. Wade*

The design, synthesis, and SAR of a series of retro bis-aminopyrrolidine ureas are described. Compounds from this series exhibited considerable binding affinity ($K_i = 1$ nM) and functional activity at MCH-R1, acceptable *CYP2D6* inhibition, and good rat brain exposure.**Synthesis of cell-permeable peptide nucleic acids and characterization of their hybridization and uptake properties**

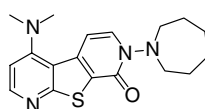
pp 4931–4935

Peng Zhou, Anca Dragulescu-Andrasi, Birendra Bhattacharya, Heather O'Keefe, Paolo Vatta, Jens J. Hyldig-Nielsen and Danith H. Ly*

**Correlation between brain/plasma ratios and efficacy in neuropathic pain models of selective metabotropic glutamate receptor 1 antagonists**

pp 4936–4940

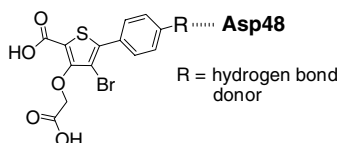
Guo Zhu Zheng,* Pramila Bhatia, Teodozjy Kolasa, Meena Patel, Odile F. El Kouhen, Renjie Chang, Marie E. Uchic, Loan Miller, Scott Baker, Sonya G. Lehto, Prisca Honore, Jill M. Wetter, Kennan C. Marsh, Robert B. Moreland, Jorge D. Brioni and Andrew O. Stewart



mGluR1 $IC_{50} = 1$ nM
 Chung $ED_{50} = 22$ μ mol/kg (i.p.)

Monocyclic thiophenes as protein tyrosine phosphatase 1B inhibitors: Capturing interactions with Asp48

pp 4941–4945

Zhao-Kui Wan,* Jinbo Lee, Weixin Xu, David V. Erbe,
Diane Joseph-McCarthy, Bruce C. Follows and Yan-Ling Zhang

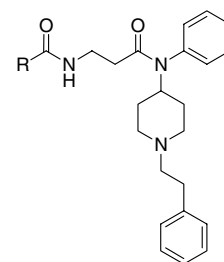
A series of monocyclic thiophenes was designed and synthesized as PTP1B inhibitors. Guided by X-ray co-crystal structural information and computational modeling, rational design led to key interactions with Asp48 and improved inhibitory potency against PTP1B.

Synthesis and evaluation of 3-aminopropionyl substituted fentanyl analogues for opioid activity

pp 4946–4950

Ravil R. Petrov, Ruben S. Vardanyan, Yeon S. Lee, Shou-wu Ma, Peg Davis,
Lucinda J. Begay, Josephine Y. Lai, Frank Porreca and Victor J. Hruby*

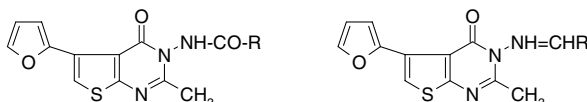
The synthesis and results of binding affinity and in vitro bioassays of novel fentanyl analogues are reported.



R: CH₃, C₂H₅, CF₃, C₂H₅NH,
CH₃CO-Phe, Tyr-D-Ala-Gly-Phe

Correlation of antibacterial activity of some *N*-[5-(2-furanyl)-2-methyl-4-oxo-4*H*-thieno[2,3-*d*]pyrimidin-3-yl]-carboxamide and 3-substituted-5-(2-furanyl)-2-methyl-3*H*-thieno[2,3-*d*]pyrimidin-4-ones with topological indices using Hansch analysis

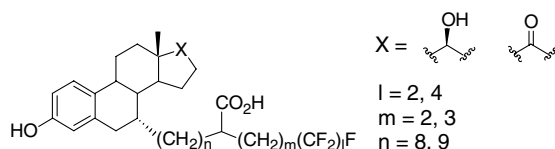
pp 4951–4958

Balasubramanian Narasimhan,* Meena Kumari, Nitin Jain,
Avinash Dhake and Chandrasekaran Sundaravelan

Correlation of antibacterial activity of some *N*-[5-(2-furanyl)-2-methyl-4-oxo-4*H*-thieno[2,3-*d*]pyrimidin-3-yl]-carboxamide and 3-substituted-5-(2-furanyl)-2-methyl-3*H*-thieno[2,3-*d*]pyrimidin-4-ones with topological indices using Hansch analysis indicated the importance of topological parameter $^3\chi$ in contribution to antibacterial activity.

Newly discovered orally active pure antiestrogens

pp 4959–4964

Yoshitake Kanbe,* Myung-Hwa Kim, Masahiro Nishimoto, Yoshihito Ohtake, Takaaki Yoneya,
Iwao Ohizumi, Toshiaki Tsunenari, Kenji Taniguchi, Shin-ichi Kaiho, Yoshiaki Nabuchi, Hiroshi Araya,
Setsu Kawata, Kazumi Morikawa, Jae-Chon Jo, Hee-An Kwon, Hyun-Suk Lim and Hak-Yeop Kim

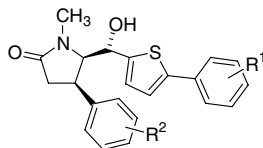
Steroid derivatives bearing the carboxy moiety in the long side chain at the 7- α position exhibited remarkable antiestrogen activities when administered orally.

4,5-Disubstituted *cis*-pyrrolidinones as inhibitors of type II 17 β -hydroxysteroid dehydrogenase.

pp 4965–4968

Part 3. Identification of lead candidate

Jill Wood, Cedo M. Bagi, Christiana Akuche, Antonietta Bacchiocchi, Jeremy Baryza, Marie-Luise Blue, Catherine Brennan, Ann-Marie Campbell, Soongyu Choi, James H. Cook, Patricia Conrad, Brian R. Dixon, Paul P. Ehrlich, Todd Gane, David Gunn,* Ted Joe, Jeffrey S. Johnson, Jerold Jordan, Richard Kramss, Peiyong Liu, Joan Levy, Derek B. Lowe, Ian McAlexander, Reina Natero, Anikó M. Redman, William J. Scott, Christopher Town, Ming Wang, Yamin Wang and Zhonghua Zhang

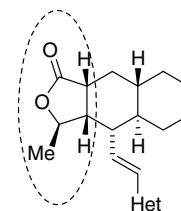
**Himbacine derived thrombin receptor (PAR-1) antagonists:**

pp 4969–4972

Structure–activity relationship of the lactone ring

Yan Xia,* Samuel Chackalamannil, Tze-Ming Chan, Michael Czarniecki, Darío Doller, Keith Eagen, William J. Greenlee, Hsingan Tsai, Yuguang Wang, Ho-Sam Ahn, George C. Boykow and Andrew T. McPhail

The structure–activity relationship (SAR) of the lactone ring of himbacine derived thrombin receptor (PAR-1) antagonists is described.



Lactone-Ring SAR:
PAR-1 IC₅₀ = 18-7000 nM

OTHER CONTENTS

Summary of instructions to authors

p I

*Corresponding author

Supplementary data available via ScienceDirect

COVER

View of the crystal structure of the DB819-d(CGCGAATTCGCG)₂ complex, looking down the minor groove of the DNA (see Campbell, N.H.; Evans, D.A.; Lee, M.P.H.; Parkinson, G.N.; Neidle, S. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 15). The DB819 molecule is shown in space-filling mode. Visualisation produced with the VMD program. [Humphrey, W.; Dalke, A.; Schulten, K. *J. Mol. Graphics* **1996**, *14*, 33.]

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