

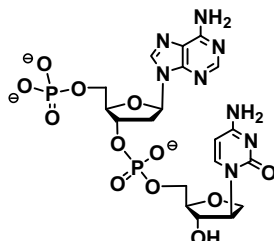
Contents

COMMUNICATIONS

Inhibition of the strand transfer step of HIV-1 integrase by non-natural dinucleotides

pp 4815–4817

Guochen Chi, Nouri Neamati and Vasu Nair*

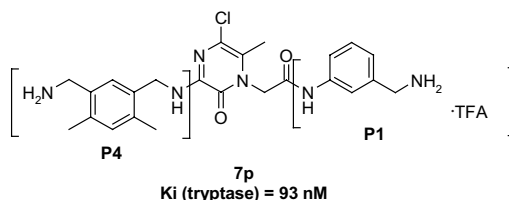


Remarkable selectivity for inhibition of the strand transfer step of HIV-1 integrase by novel dinucleotides.

Novel pyrazinone inhibitors of mast cell tryptase: synthesis and SAR evaluation

pp 4819–4823

Corey R. Hopkins,* Kent Neuenschwander, Anthony Scotese, Sharon Jackson, Thaddeus Nieduzak, Henry Pauls, Guyan Liang, Keith Sides, Dona Cramer, Jennifer Cairns, Sebastien Maignan and Magali Mathieu

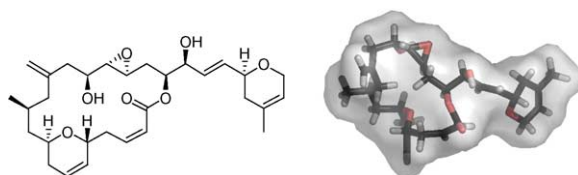


Computational comparison of microtubule-stabilising agents laulimalide and peloruside with taxol and colchicine

pp 4825–4829

Oriol Pineda, Jaume Farràs, Laura Maccari, Fabrizio Manetti, Maurizio Botta and Jaume Vilarrasa*

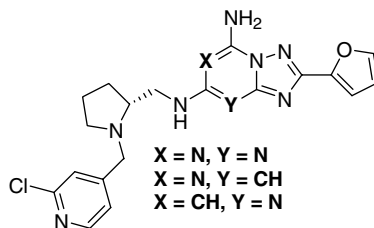
Microtubule-stabilising agents laulimalide and peloruside have been compared with tubulin-interacting drugs paclitaxel and colchicine by different computational approaches. Docking and QSAR-based programs point to a favourable interaction with the β tubulin paclitaxel binding site, although an additional, preferred binding site has been found at the α subunit of tubulin. All together provides a plausible rationalisation of the singular binding features of these microtubule stabilisers and paves the way for future structural studies.



Studies on adenosine A_{2a} receptor antagonists: comparison of three core heterocycles

pp 4831–4834

Chi B. Vu,* Deborah Pan, Bo Peng, Li Sha, Gnanasambandam Kumaravel, Xiaowei Jin, Deepali Phadke, Thomas Engber, Carol Huang, Jennifer Reilly, Stacy Tam and Russell C. Petter

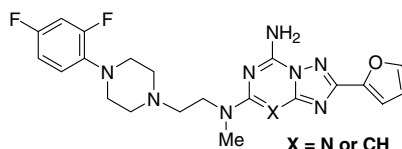


A comparison of the adenosine A_{2a} receptor antagonist activity of three heterocyclic series showed that the core deriving from [1,2,4]triazolo[1,5-*a*]triazine (X = N and Y = CH) afforded compounds with oral activity in the mouse catalepsy model.

Triamino derivatives of triazolotriazine and triazolopyrimidine as adenosine A_{2a} receptor antagonists

pp 4835–4838

Chi B. Vu,* Pamela Shields, Bo Peng, Gnanasambandam Kumaravel, Xiaowei Jin, Deepali Phadke, Joy Wang, Thomas Engber, Eman Ayyub and Russell C. Petter



Derivatives of triazolotriazine and triazolopyrimidine have been found to be potent and selective adenosine A_{2a} receptor antagonists with oral activity in the mouse catalepsy model.

End-capping of the modified melanocortin tetrapeptide (*p*-Cl)Phe-D-Phe-Arg-Trp-NH₂ as a route to hMC4R agonists

pp 4839–4842

L. N. Koikov,* F. H. Ebetino, J. C. Hayes, D. Cross-Doersen and J. J. Knittel*

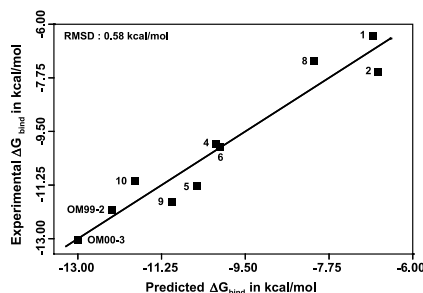


Of the 42 R'-X-(*p*-Cl)Phe-D-Phe-Arg-Trp-NH₂ (X = CO, SO₂, PO, PS) tested on the human (h)MC1, hMC3, and hMC4 receptors (R), the most potent MC4R agonists (EC₅₀ of 8–20 nM) were obtained by end-capping with R' = CH₂=CHCH₂ (9), NCCH₂ (16), NH₂COCH₂ (17), HCONHCH₂ (18), CH₃NH (19), CH₂=CHCH₂NH (21), 2-Th (23), PhCH₂ (30) and X = CO. These compounds possess 35–60-fold hMC4 versus hMC1Rs selectivity with urea LK-71 (19) being the most potent and selective at hMC4R (EC₅₀ = 8.5 nM, MC4/1R = 100). LK-75 (16) combines high potency at hMC4R and MC4/3R selectivity (EC₅₀ = 10.5 nM, MC4/3R = 290). SAR is discussed.

Modeling the binding affinities of β-secretase inhibitors: application to subsite specificity

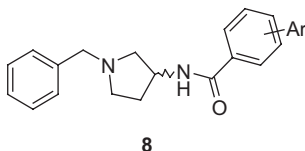
pp 4843–4846

Ramkumar Rajamani and Charles H. Reynolds*



***N*-(1-Benzylpyrrolidin-3-yl)arylbenzamides as potent and selective human dopamine D₄ antagonists** pp 4847–4850

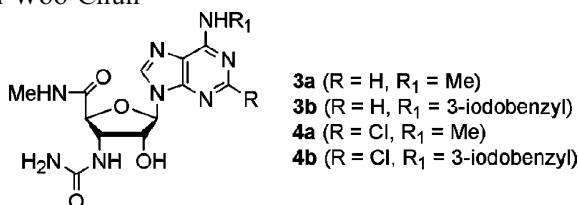
Ian Egle,* Nancy Barriault, Michel Bordeleau, Jillian Drage, Laurence Dube, Jack Peragine, Lucy Mazzocco, Jalaj Arora, Keith Jarvie and Ashok Tehim



A series of *N*-(1-benzylpyrrolidin-3-yl)arylbenzamides **8** has been prepared, and their structure–activity relationships studied. Potent ligands selective for human D₄ (hD₄) over hD₂ and α_1 have been identified. One example was determined to be an antagonist in a cAMP assay, with an IC₅₀ of 1500 nM.

Design and synthesis of 3'-ureidoadenosine-5'-uronamides: effects of the 3'-ureido group on binding to the A₃ adenosine receptor pp 4851–4854

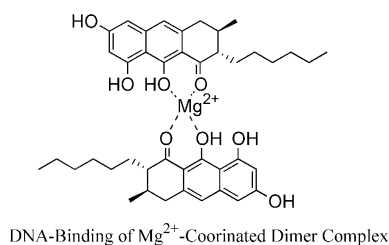
Lak Shin Jeong,* Myong Jung Kim, Hea Ok Kim, Zhan-Guo Gao, Soo-Kyung Kim, Kenneth A. Jacobson and Moon Woo Chun



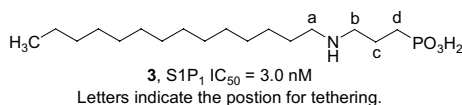
Novel 3'-ureidoadenosine analogues, **3** and **4** were synthesized from 1,2:5,6-di-*O*-isopropylidene- β -D-glucose in order to cause stronger hydrogen bonding than the corresponding 3'-aminoadenosine derivatives at the A₃ adenosine receptor.

New DNA binding ligands as a model of chromomycin A₃ pp 4855–4859

Shuhei Imoto, Yoshinari Haruta, Kyouichi Watanabe and Shigeki Sasaki*

**Design and synthesis of conformationally constrained 3-(*N*-alkylamino)propylphosphonic acids as potent agonists of sphingosine-1-phosphate (S1P) receptors** pp 4861–4866

Lin Yan,* Jeffrey J. Hale, Christopher L. Lynch, Richard Budhu, Amy Gentry, Sander G. Mills, Richard Hajdu, Carol Ann Keohane, Mark J. Rosenbach, James A. Milligan, Gan-Ju Shei, Gary Chrebet, James Bergstrom, Deborah Card, Hugh Rosen and Suzanne M. Mandala

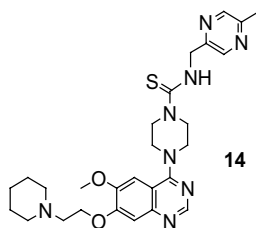


A series of conformationally constrained analogs of **3** were synthesized and evaluated as S1P receptor agonists. Several novel scaffolds were identified as suitable for further investigation.

Identification of 4-piperazin-1-yl-quinazoline template based aryl and benzyl thioureas as potent, selective, and orally bioavailable inhibitors of platelet-derived growth factor (PDGF) receptor

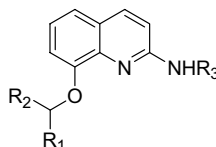
pp 4867–4872

Julie A. Heath,* Mukund M. Mehrotra,* Shannon Chi, Jin-Chen Yu, Athiwat Hutchaleelaha, Stanley J. Hollenbach, Neill A. Giese, Robert M. Scarborough and Anjali Pandey

 IC_{50} (β PDGFR) = 61 nM; kinase specificity: β PDGFR/Flt-3 > 100; (dog) $F\%$ = 38.8; $T_{1/2}$ = 10.8 h.**Synthesis and evaluation of 2-amino-8-alkoxy quinolines as MCHr1 antagonists. Part 1**

pp 4873–4877

Andrew J. Souers,* Dariusz Wodka, Ju Gao, Jared C. Lewis, Anil Vasudevan, Robert Gentles, Sevan Brodjian, Brian Dayton, Christopher A. Ogiela, Dennis Fry, Lisa E. Hernandez, Kennan C. Marsh, Christine A. Collins and Philip R. Kym

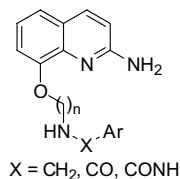


Hit-to-lead investigation of a 2-amino-8-alkoxy quinoline containing high throughput screening hit is described.

Synthesis and evaluation of 2-amino-8-alkoxy quinolines as MCHr1 antagonists. Part 2

pp 4879–4882

Anil Vasudevan,* Dariusz Wodka, Mary K. Verzal, Andrew J. Souers, Ju Gao, Sevan Brodjian, Dennis Fry, Brian Dayton, Kennan C. Marsh, Lisa E. Hernandez, Christopher A. Ogiela, Christine A. Collins and Philip R. Kym

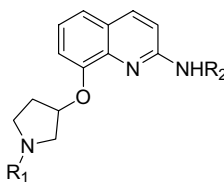


Melanin concentrating hormone (MCHr1) antagonists containing heteroatoms in the substituent at the 8-position, which demonstrate picomolar binding affinities and nanomolar functional antagonism of MCH, are described.

Synthesis and evaluation of 2-amino-8-alkoxy quinolines as MCHr1 antagonists. Part 3

pp 4883–4886

Andrew J. Souers,* Dariusz Wodka, Ju Gao, Jared C. Lewis, Anil Vasudevan, Sevan Brodjian, Brian Dayton, Christopher A. Ogiela, Dennis Fry, Lisa E. Hernandez, Kennan C. Marsh, Christine A. Collins and Philip R. Kym

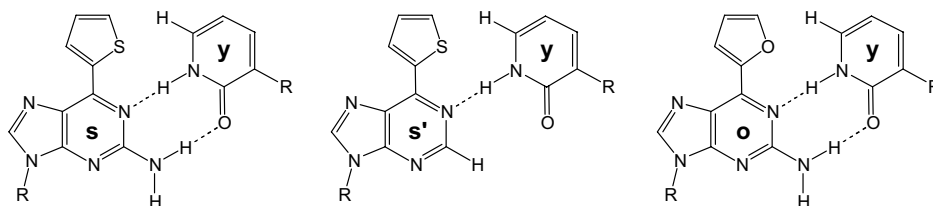


A series of potent and highly CNS penetrable melanin-concentrating hormone inhibitors is described.

Unnatural base pairs between 2- and 6-substituted purines and 2-oxo(1H)pyridine for expansion of the genetic alphabet

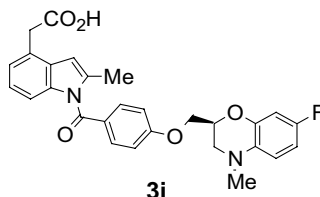
pp 4887–4890

Ichiro Hirao,* Tsuyoshi Fujiwara, Michiko Kimoto and Shigeyuki Yokoyama*

**Discovery of orally active prostaglandin D₂ receptor antagonists**

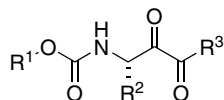
pp 4891–4895

Kazuhiko Torisu,* Kaoru Kobayashi, Maki Iwahashi, Yoshihiko Nakai, Takahiro Onoda, Toshihiko Nagase, Isamu Sugimoto, Yutaka Okada, Ryoji Matsumoto, Fumio Nanbu, Shuichi Ohuchida, Hisao Nakai and Masaaki Toda

Discovery process of a new PGD₂ receptor antagonists **3i** is reported.**Potent and selective P₂–P₃ ketoamide inhibitors of cathepsin K with good pharmacokinetic properties via favorable P^{1'}, P¹, and/or P³ substitutions**

pp 4897–4902

David G. Barrett, John G. Catalano,* David N. Deaton, Anne M. Hassell, Stacey T. Long, Aaron B. Miller, Larry R. Miller, Lisa M. Shewchuk, Kevin J. Wells-Knecht, Derril H. Willard, Jr. and Lois L. Wright

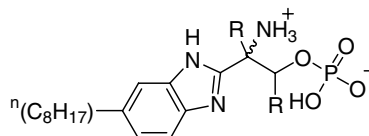


A series of ketoamides were synthesized and evaluated for inhibitory activity against cathepsin K. Exploration of the interactions between achiral P² substituents and the cysteine protease based on molecular modeling suggestions resulted in potent cathepsin K inhibitors that demonstrated high selectivity versus cathepsins B, H, and L. Subsequent modifications of the P³, P¹, and P^{1'} moieties afforded orally bioavailable inhibitors.

Synthesis of benzimidazole based analogues of sphingosine-1-phosphate: discovery of potent, subtype-selective S1P₄ receptor agonists

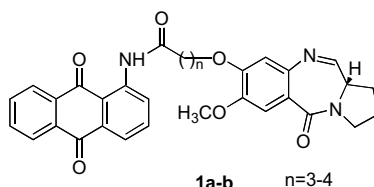
pp 4903–4906

Jeremy J. Clemens,* Michael D. Davis, Kevin R. Lynch and Timothy L. Macdonald

We report the synthesis and potencies of several selective S1P₄ receptor agonists.

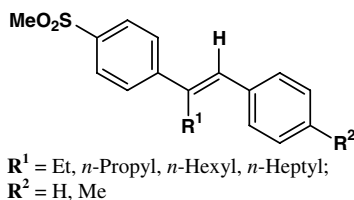
Pyrrolo[2,1-c][1,4]benzodiazepine–anthraquinone conjugates. Synthesis, DNA binding and cytotoxicity pp 4907–4909

Ahmed Kamal,* R. Ramu, G. B. Ramesh Khanna, Ajit Kumar Saxena,
M. Shanmugavel and Renu Moti Pandita

**A new class of acyclic 2-alkyl-1,2-diaryl (*E*)-olefins as selective cyclooxygenase-2 (COX-2) inhibitors**

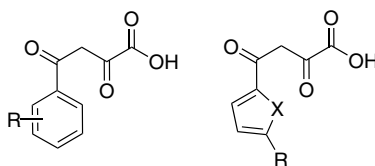
pp 4911–4914

Md. Jashim Uddin, P. N. Praveen Rao, Md. Abdur Rahim, Robert McDonald and
Edward E. Knaus*

**The identification and optimization of 2,4-diketobutyric acids as flap endonuclease 1 inhibitors**

pp 4915–4918

L. Nathan Tumey,* Bayard Huck, Elizabeth Gleason, Jianmin Wang, Daniel Silver,
Kurt Brunden, Sherry Boozer, Stephen Rundlett, Bruce Sherf, Steven Murphy,
Andrew Bailey, Tom Dent, Christina Leventhal, John Harrington and Youssef L. Bennani

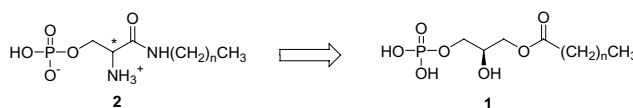


Flap endonuclease 1 (FEN1) is a key enzyme involved in base excision repair (BER), a primary pathway utilized by mammalian cells to repair DNA damage. In this report, we describe the identification and SAR of a series of 2,4-diketobutyric acid FEN1 inhibitors that may be useful as chemopotentiators.

Synthesis and biological evaluation of novel cytotoxic phospholipids for prostate cancer

pp 4919–4923

Veeresa Gududuru, Eunju Hurh, Gangadhar G. Durgam, Seoung Soo Hong, Vineet M. Sardar,
Huiping Xu, James T. Dalton and Duane D. Miller*

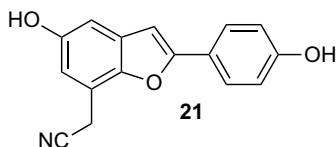


A series of serine amide phosphates (SAPs) and serine amide alcohols (SAAs) were prepared and evaluated for their in vitro cytotoxicity against five human prostate cancer cell lines. The SAR and biological activity of the synthesized compounds is reported.

7-Substituted 2-phenyl-benzofurans as ER β selective ligands

pp 4925–4929

Michael D. Collini,* David H. Kaufman, Eric S. Manas, Heather A. Harris, Ruth A. Henderson, Zhang B. Xu, Rayomand J. Unwalla and Chris P. Miller

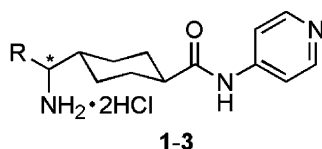


Substituted benzofuran **21** is a potent and selective ER ligand.

Synthesis and evaluation of 4-(1-aminoalkyl)-N-(4-pyridyl)cyclohexanecarboxamides as Rho kinase inhibitors and neurite outgrowth promoters

pp 4931–4934

Karine Gingras, Hovsep Avedissian, Eryk Thouin, Véronique Boulanger, Charles Essagian, Lisa McKerracher and William D. Lubell*

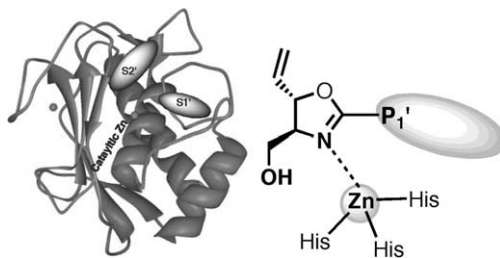


The influence of stereochemistry and alkyl side chain length on the bioactivity of the Rho kinase inhibitor Y-27632 [(+)-**1**, R = Me] was examined by the synthesis of (+)- and (–)-**1**, and two alkyl chain analogs (+)- and (–)-**2** (R = *n*-propyl) and (–)-**3** (R = *n*-octyl) as well as their evaluation in enzymatic and neurite outgrowth assays.

Synthesis and evaluation of novel oxazoline MMP inhibitors

pp 4935–4939

Gregory R. Cook,* Ethirajan Manivannan, Thane Underdahl, Viera Lukacova, Yufen Zhang and Stefan Balaz

**Effective inhibition of HIV-1 replication in cultured cells by external guide sequences and ribonuclease P**

pp 4941–4944

Jacob S. Barnor, Yumihiko Endo, Yuichiro Habu, Naoko Miyano-Kurosaki, Michiko Kitano, Hirokazu Yamamoto and Hiroshi Takaku*

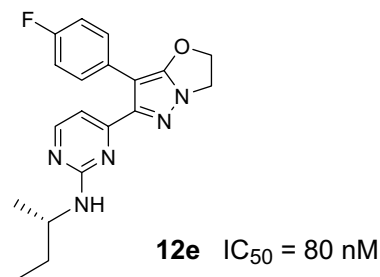
We examined the suppression effect of cleavage of the HIV-1 RNA gene on HIV-1 expression, using the catalytic RNA subunit RNase P and the 3'-half tRNA^{Try} [external guide sequence (EGS)] in vivo. HIV-1 expression was inhibited by the tRNA^{met}-EGS-U5 and U6-EGS-U5 from the tRNA^{met} and U6 promoters, respectively. There was no difference in the inhibitory effects on HIV-1 expression between the tRNA^{met} and U6 promoters.

The development of new bicyclic pyrazole-based cytokine synthesis inhibitors

pp 4945–4948

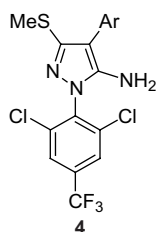
Jennifer A. Townes,* Adam Golebiowski, Michael P. Clark, Matthew J. Lauferweiler, Todd A. Brugel, Mark Sabat, Roger G. Bookland, Steve K. Laughlin, John C. VanRens, Biswanath De, Lily C. Hsieh, Susan C. Xu, Michael J. Janusz and Richard L. Walter

4-Aryl-5-pyrimidyl-based cytokine synthesis inhibitors of TNF- α production, which contain a novel bicyclic pyrazole heterocyclic core, are described. Many of these inhibitors showed low nanomolar activity against LPS-induced TNF- α production in a THP-1 cell-based assay and against human p38 α MAP kinase in an isolated enzyme assay. The X-ray crystal structure of a bicyclic pyrazole inhibitor co-crystallized with mutated p38 (mp38) is presented.

**Synthesis and GABA receptor potency of 3-thiomethyl-4-(hetero)aryl-5-amino-1-phenylpyrazoles**

pp 4949–4953

Sanath K. Meegalla,* Dario Doller, DeYou Sha, Rich Soll, Nancy Wisniewski, Gary M. Silver and Dale Dhanoa



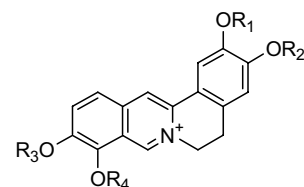
GABA receptor potency of 3-thiomethyl-4-(hetero)aryl-5-amino-1-phenylpyrazoles **4** and their synthesis is described.

Study on noncovalent complexes of cytotoxic protoberberine alkaloids with double-stranded DNA by using electrospray ionization mass spectrometry

pp 4955–4959

Wen-Hua Chen, Chi-Leung Chan, Zongwei Cai, Guo-An Luo and Zhi-Hong Jiang*

The first ESI-MS spectrometric investigation of the noncovalent complexes of four protoberberine alkaloids **1–4** with three double-stranded DNA sequences was described.



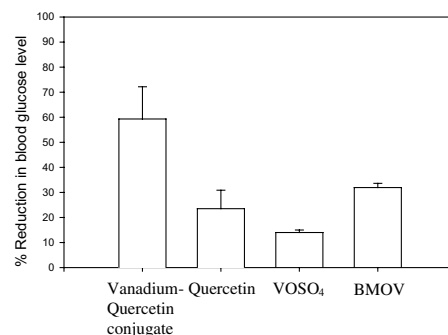
- 1: R₁-R₂ = -CH₂-, R₃ = R₄ = Me
- 2: R₁ = R₂ = R₃ = R₄ = Me
- 3: R₁ = R₃ = R₄ = Me, R₂ = H
- 4: R₁-R₂ = -CH₂-, R₃-R₄ = -CH₂-

Synthesis, structural properties and insulin-enhancing potential of bis(quercetinato)oxovanadium(IV) conjugate

pp 4961–4965

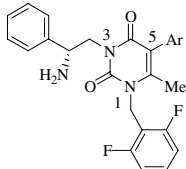
Ruchi Shukla, Vivek Barve, Subhash Padhye and Ramesh Bhonde*

Vanadium complex of naturally occurring flavonoid, quercetin, is structurally characterized and evaluated for its insulin-enhancing potential, which indicates it to be a potent oral insulin-enhancing agent of therapeutic value having hypoglycemic and mitogenic activity in both type 1 and type 2 diabetes.



Synthesis and structure–activity relationships of uracil derived human GnRH receptor antagonists: (R)-3-[2-(2-amino)phenethyl]-1-(2,6-difluorobenzyl)-6-methyluracils containing a substituted thiophene or thiazole at C-5 pp 4967–4973

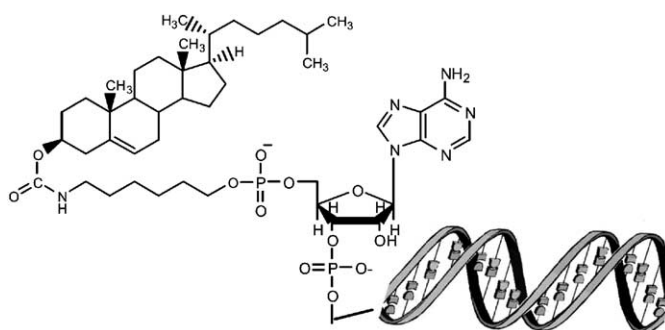
Martin W. Rowbottom,* Fabio C. Tucci, Patrick J. Connors, Jr., Timothy D. Gross, Yun-Fei Zhu, Zhiqiang Guo, Manisha Moorjani, Oscar Acevedo, Lee Carter, Susan K. Sullivan, Qiu Xie, Andrew Fisher, R. Scott Struthers, John Saunders and Chen Chen*



The design and synthesis of a number of 5-thiazolyl and 5-thienyl substituted uracils is described and results from SAR studies are summarized. The best compound showed $K_i = 2$ nM.

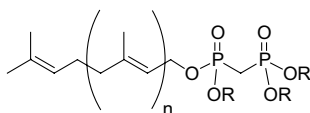
Steroid and lipid conjugates of siRNAs to enhance cellular uptake and gene silencing in liver cells pp 4975–4977

Christina Lorenz, Philipp Hadwiger,* Matthias John, Hans-Peter Vornlocher and Carlo Unverzagt



Synthesis of acyloxymethyl ester prodrugs of the transferable protein farnesyl transferase substrate farnesyl methylenediphosphonate pp 4979–4982

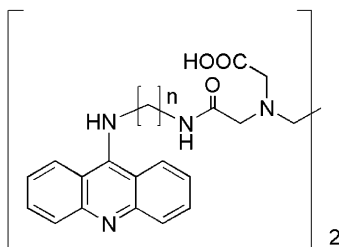
Jerry M. Troutman, Kareem A. H. Chehade, Katarzyna Kiegiel, Douglas A. Andres and H. Peter Spielmann*



R = -CH₂OCOt-Bu
n = 1–3

Synthesis of dimeric acridine derived antivirals pp 4983–4985

René Csuk,* Alexander Barthel, Torsten Brezesinski and Christian Raschke

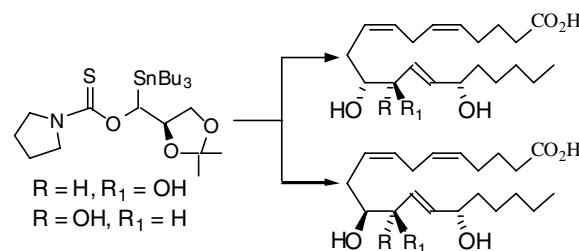


The synthesis of highly active, acridine derived antivirals is reported.

Asymmetric synthesis of the stereoisomers of 11,12,15(*S*)-trihydroxyeicosa-5(*Z*),8(*Z*),13(*E*)-trienoic acid, a potent endothelium-derived vasodilator pp 4987–4990

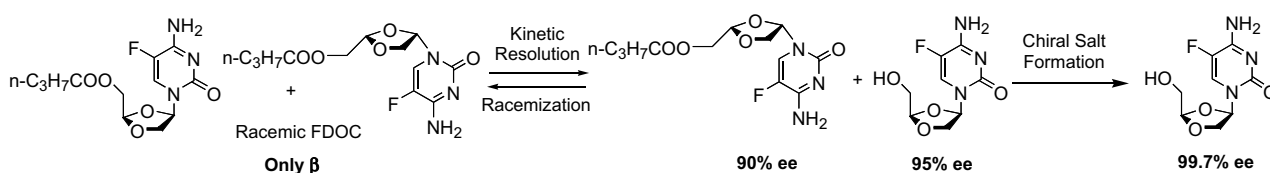
J. R. Falck,* Deb K. Barma, Suchismita Mohapatra, A. Bandyopadhyay, Komandla Malla Reddy, Jianjun Qi and William B. Campbell

The four stereoisomers 11,12,15(*S*)-THETA were prepared by a triply convergent, asymmetric route that exploited the stereospecific, copper mediated cross-coupling of α,β -dialkoxystannanes and the utility of dialkylthionocarbamates as orthogonal alcohol protective groups. Only 11(*R*),12(*S*),15(*S*)-THETA was comparable to natural material by HPLC, GC/MS, and in vitro bioassay.



Synthesis of enantiomerically pure D-FDOC, an anti-HIV agent pp 4991–4994

Shuli Mao, Martin Bouygues, Christopher Welch, Mirlinda Biba, Jen Chilenski, Raymond F. Schinazi and Dennis C. Liotta*

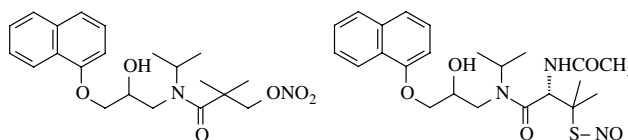


The D-enantiomer of FDOC was obtained in optically pure form via a tandem kinetic resolution/chiral salt crystallization protocol. In addition, conditions were developed that allowed the unwanted L-enantiomer to be racemized and recycled.



Synthesis and vasorelaxant properties of hybrid molecules out of NO-donors and the β -receptor blocking drug propranolol pp 4995–4997

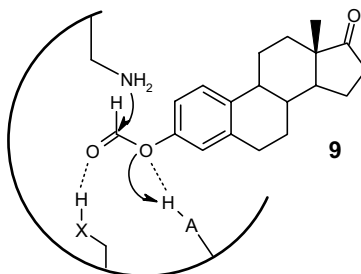
Michael Decker,* Andreas König, Erika Glusa and Jochen Lehmann



Hybrid molecules, which combine in the form of prodrugs the β -receptor blocker propranolol as well as different NO-donating moieties, were synthesized and vasodilatation was measured.

Estrone formate: a novel type of irreversible inhibitor of human steroid sulfatase pp 4999–5002

Erwin P. Schreiner* and Andreas Billich

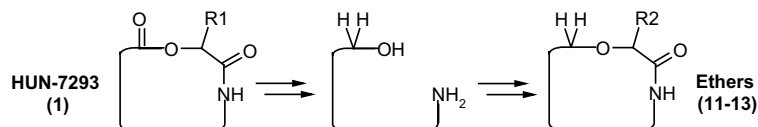


Estrone formate **9** is a novel type of irreversible inhibitor of human steroid sulfatase. We suggest transfer of the formyl residue to a nucleophilic functionality in the active site of the enzyme as previously proposed for the sulfamoyl moiety of EMATE.

Synthesis of ether analogues derived from HUN-7293 and evaluation as inhibitors of VCAM-1 expression

pp 5003–5006

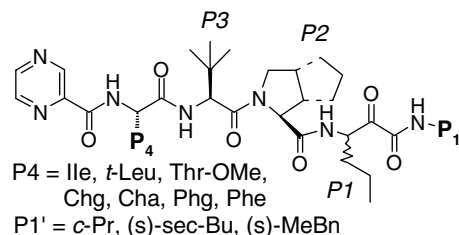
Erwin P. Schreiner,* Michael Kern, Andrea Steck and Carolyn A. Foster

**P4 and P1' optimization of bicycloproline P2 bearing tetrapeptidyl α -ketoamides as HCV protease inhibitors**

pp 5007–5011

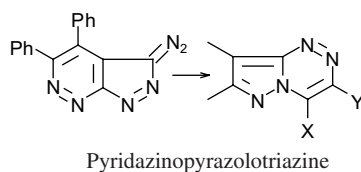
Yvonne Yip, Frantz Victor, Jason Lamar, Robert Johnson, Q. May Wang, John I. Glass, Nathan Yumibe, Mark Wakulchik, John Munroe and Shu-Hui Chen*

We describe herein the design, synthesis, and antiviral activity of a series of P4 modified tetrapeptidyl α -ketoamides as HCV protease inhibitors. The most promising analog identified through this SAR, **5a**, **5c**, and **5e** demonstrated excellent enzyme inhibitory potency, enzyme selectivity, cellular activity, and acceptable therapeutic indexes.

**Pyridazine derivatives and related compounds. Part 13: Synthesis and antimicrobial activity of some pyridazino[3',4':3,4]pyrazolo[5,1-*c*]-1,2,4-triazines**

pp 5013–5017

Ali Deeb,* Fatma El-Mariah and Mona Hosny




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*Corresponding author

+ Supplementary data available via ScienceDirect

COVER

Cover figure provided by **Indraneel Ghosh**, Department of Chemistry, University of Arizona. The cover depicts the **Dual Surface Selection** methodology developed by the author: the blue helix of htBl (center) allows structural selection with the Fc portion of Immunoglobulin (left), while the residues randomized on the red sheet of htBl (center) allows for functional selection against thrombin (right) [Rajagopal, S.; Meza-Romero, R.; Ghosh, I. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1389].



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