

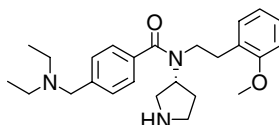
## Contents

### ARTICLES

#### Aminopyrrolidineamide inhibitors of site-1 protease

pp 4411–4414

Bruce A. Hay,\* Barbara Abrams, Alice Y. Zumbrunn, James J. Valentine, Laurie C. Warren, Stephen F. Petras, Lorraine D. Shelly, Angela Xia, Alison H. Varghese, Julie L. Hawkins, Jennifer A. Van Camp, Michael D. Robbins, Katherine Landschulz and H. James Harwood, Jr.

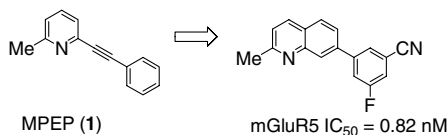


A series of aminopyrrolidineamide inhibitors of sterol regulatory element binding protein site-1 protease was identified.

#### Rational design of 7-arylquinolines as non-competitive metabotropic glutamate receptor subtype 5 antagonists

pp 4415–4418

Jared B. J. Milbank,\* Christopher S. Knauer, Corinne E. Augelli-Szafran, Annette T. Sakkab-Tan, Kristin K. Lin, Koji Yamagata, Jennifer K. Hoffman, Nian Zhuang, John Thomas, Paul Galatsis, John A. Wendt, John W. Mickelson, Roy D. Schwarz, Jack J. Kinsora, Susan M. Lotarski, Korana Stakich, Kristen K. Gillespie, Wing W. Lam and Abdul E. Mutlib

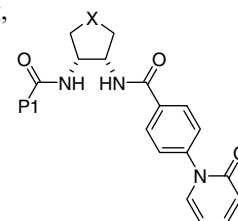


#### SAR and X-ray structures of enantiopure 1,2-*cis*-(1*R*,2*S*)-cyclopentyldiamine and cyclohexyldiamine derivatives as inhibitors of coagulation Factor Xa

pp 4419–4427

Jennifer X. Qiao,\* Chong-Hwan Chang, Daniel L. Cheney, Paul E. Morin, Gren Z. Wang, Sarah R. King, Tammy C. Wang, Alan R. Rendina, Joseph M. Luetzgen, Robert M. Knabb, Ruth R. Wexler and Patrick Y. S. Lam

In the search of Factor Xa (FXa) inhibitors structurally different from the pyrazole-based series, we identified a viable series of enantiopure *cis*-(1*R*,2*S*)-cycloalkyldiamine derivatives as potent and selective inhibitors of FXa. Among them, the cyclohexyldiamide **7** and cyclopentyldiamide **9** were the most potent neutral compounds, and had good anticoagulant activity comparable to the pyrazole-based analogs. Crystal structures of **7**-FXa and **9**-FXa illustrate binding similarities and differences between the five- and the six-membered core systems, and provide rationales for the observed SAR of P1 and linker moieties.

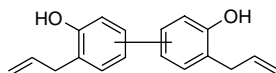


**7**. x = CH<sub>2</sub>CH<sub>2</sub>, P1 = 3-Cl-2-indolyl  
FXa K<sub>i</sub> = 0.67 nM, PT EC<sub>2x</sub> = 3.2 μM  
**9**. x = CH<sub>2</sub>, P1 = 5-Cl-2-thienyl  
FXa K<sub>i</sub> = 0.43 nM, PT EC<sub>2x</sub> = 1.7 μM

### Synthesis, cytotoxicity, and antiviral activities of new neolignans related to honokiol and magnolol

pp 4428–4431

Franck Amblard, Baskaran Govindarajan, Benjamin Lefkove, Kimberly L. Rapp, Mervi Detorio, Jack L. Arbiser and Raymond F. Schinazi\*



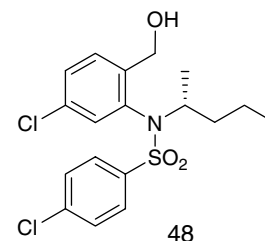
The synthesis of a series of new bisphenol derivatives bearing allylic moieties as potential analogs of honokiol and/or magnolol is reported. Certain compounds exhibited specific anti-proliferation activity and moderate anti-HIV-1 activity in vitro.

### *N*-(5-Chloro-2-(hydroxymethyl)-*N*-alkyl-arylsulfonamides as $\gamma$ -secretase inhibitors

pp 4432–4436

Michael F. Parker,\* Donna M. Barten, Carl P. Bergstrom, Joanne J. Bronson, Jason A. Corsa, Milind S. Deshpande, Kevin M. Felsenstein, Valerie L. Guss, Steven B. Hansel, Graham Johnson, Daniel J. Keavy, Wai Y. Lau, Jeremy Mock, C. V. C. Prasad, Craig T. Polson, Charles P. Sloan, David W. Smith, Owen B. Wallace, Henry H. Wang, Andrew Williams and Ming Zheng

A series of *N*-alkylbenzenesulfonamides were developed from a high throughput screening hit. Classic and parallel synthesis strategies were employed to produce compounds with good in vitro and in vivo  $\gamma$ -secretase activity.

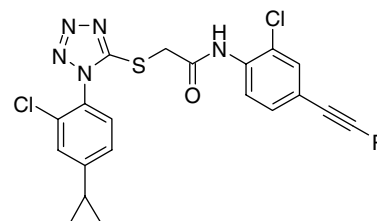


### Thiotetrazole alkynylacetanilides as potent and bioavailable non-nucleoside inhibitors of the HIV-1 wild type and K103N/Y181C double mutant reverse transcriptases

pp 4437–4441

Alexandre Gagnon,\* Ma'an H. Amad, Pierre R. Bonneau, René Coulombe, Patrick L. DeRoy, Louise Doyon, Jianmin Duan, Michel Garneau, Ingrid Guse, Araz Jakalian, Eric Jolicoeur, Serge Landry, Eric Malenfant, Bruno Simoneau and Christiane Yoakim

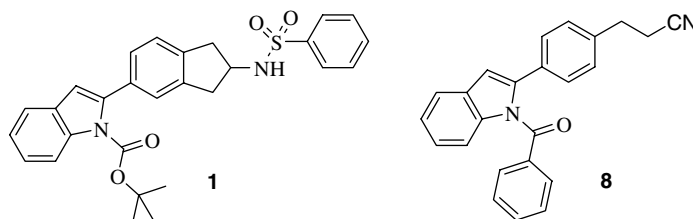
The SAR and PK studies of a series of thiotetrazolyl alkynylacetanilides as potent inhibitors of the HIV-1 RT is reported.



### 2-Aryl-*N*-acyl indole derivatives as liver X receptor (LXR) agonists

pp 4442–4446

Sunil Kher, Kirk Lake, Ila Sircar, Madhavi Pannala, Farid Bakir, James Zapf, Kui Xu, Shao-Hui Zhang, Juping Liu, Lisa Morera, Naoki Sakurai, Rick Jack and Jie-Fei Cheng\*

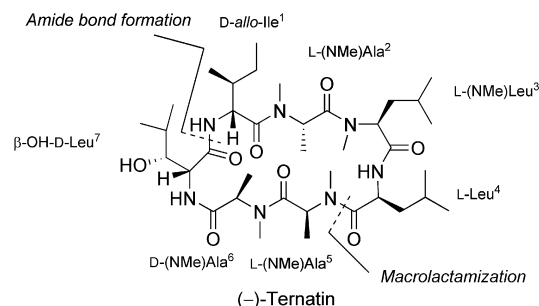


SAR studies on HTS hit compound **1** led to the identification of simpler 2-aryl-1-acyl compounds such as **8** which are potent LXR $\beta$  agonists.

**Convergent synthesis and in vivo inhibitory effect on fat accumulation of (–)-ternatin, a highly *N*-methylated cyclic peptide**

pp 4447–4449

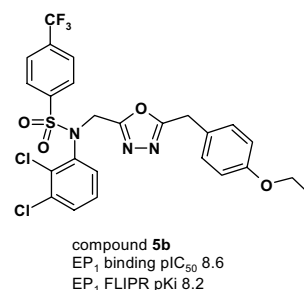
Kenichiro Shimokawa, Kaoru Yamada, Masaki Kita and Daisuke Uemura\*

**Identification and optimization of novel 1,3,4-oxadiazole EP<sub>1</sub> receptor antagonists**

pp 4450–4455

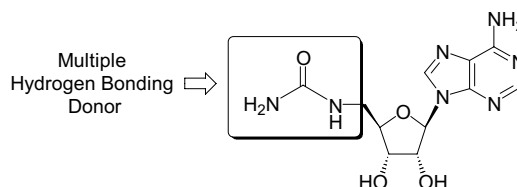
Adrian Hall,\* Susan H. Brown, Anita Chowdhury, Gerard M. P. Giblin, Mairi Gibson, Mark P. Healy, David G. Livermore, Richard J. McArthur Wilson, Alan Naylor, D. Anthony Rawlings, Shilina Roman, Emma Ward and Caroline Willay

The identification of a novel series of 1,3,4-oxadiazoles is described. The SAR of the series was explored and led to the identification of the most potent compound in the series, compound **5b** with a binding pIC<sub>50</sub> value of 8.6 (IC<sub>50</sub> 2.5 nM) and a FLIPR pK<sub>i</sub> value of 8.2 (K<sub>i</sub> 6.3 nM).

**Design, synthesis, and molecular modeling studies of 5'-deoxy-5'-ureidoadenosine: 5'-ureido group as multiple hydrogen bonding donor in the active site of *S*-adenosylhomocysteine hydrolase**

pp 4456–4459

Ting Wang, Hyun Joo Lee, Dilip K. Tosh, Hea Ok Kim, Shantanu Pal, Sun Choi, Yoonji Lee, Hyung Ryong Moon, Long Xuan Zhao, Kang Man Lee\* and Lak Shin Jeong\*



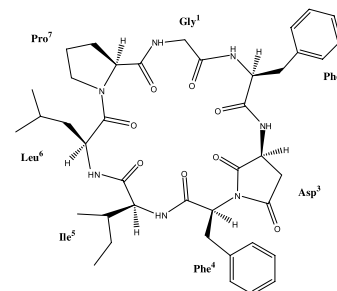
5'-Deoxy-5'-ureidoadenosine was designed and synthesized as a potent inhibitor of *S*-adenosylhomocysteine hydrolase (SAH), in which 5'-ureido group was essential for binding as multiple hydrogen bonding donor in the molecular modeling study.

**Gypsophin: A novel α-glucosidase inhibitory cyclic peptide from the roots of *Gypsophila oldhamiana***

pp 4460–4463

Jian-Guang Luo, Xiao-Bing Wang, Li Ma and Ling-Yi Kong\*

The elucidation and the α-glucosidase inhibitory activity of a new cyclic peptide are reported.

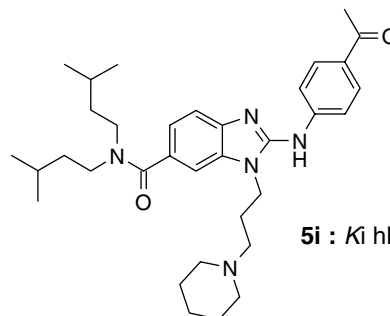


### Identification of a novel series of benzimidazoles as potent and selective antagonists of the human melanocortin-4 receptor

pp 4464–4470

Lydie Poitout,\* Valérie Brault, Carole Sackur, Sonia Bernetière, José Camara, Pascale Plas and Pierre Roubert

A novel series of benzimidazoles was identified and optimized, leading to the discovery of potent and selective antagonists of the human melanocortin-4 receptor. In addition, compound **5i** was shown to cross the blood–brain barrier after intravenous dosing in rats.



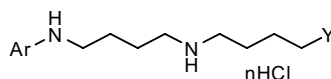
**5i** :  $K_i$  hMC4 = 2.0 nM



### Synthesis and bioevaluation of *N*-(arylalkyl)-homospermidine conjugates

pp 4471–4475

Songqiang Xie, Pengfei Cheng, Guangchao Liu, Yuangfang Ma, Jin Zhao, Mounir Chehtane, Annette R. Khaled, Otto Phanstiel, IV\* and Chaojie Wang\*



**1**: Y = NH<sub>2</sub>, n = 3

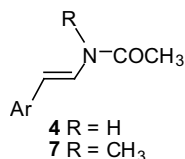
**2**: Y = N(CH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>NH, n = 4



### Synthesis and biological evaluation of *N*-acetyl- $\beta$ -aryl-1,2-didehydroethylamines as new HIV-1 RT inhibitors in vitro

pp 4476–4480

Pi Cheng, Zhi-Yong Jiang, Rui-Rui Wang, Xue-Mei Zhang, Qian Wang, Yong-Tang Zheng,\* Jun Zhou and Ji-Jun Chen\*

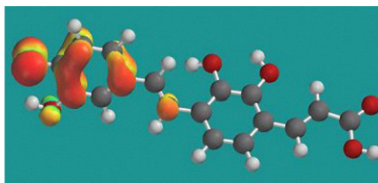
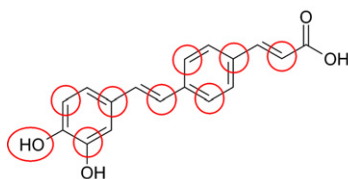


Compounds **4** and **7** were assayed as NNRTIs against HIV-1 for the first time. Compound **7a** (Ar = 2-Br-phenyl) exhibited a TI value of >13.2 ( $CC_{50}$  > 0.787 mM) in C8166 cells.

### Design, synthesis, and discovery of stilbene derivatives based on lithospermic acid B as potent protein tyrosine phosphatase 1B inhibitors

pp 4481–4486

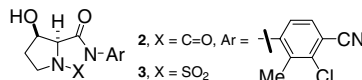
Mankil Jung,\* Yongnam Lee, Moonsoo Park, Hanjo Kim, Heekyeong Kim, Eunyoung Lim, Jungae Tak, Minjoo Sim, Dongeun Lee, Namsoo Park, Won Keun Oh, Kyu Yeon Hur, Eun Seok Kang and Hyun-Chul Lee



### Synthesis and SAR of tetrahydropyrrolo[1,2-*b*][1,2,5]thiadiazol-2(3*H*)-one 1,1-dioxide analogues as highly potent selective androgen receptor modulators

pp 4487–4490

Mark C. Manfredi,\* Yingzhi Bi, Alexandra A. Nirschl, James C. Sutton, Ramakrishna Seethala, Rajasree Golla, Blake C. Beehler, Paul G. Sleph, Gary J. Grover, Jacek Ostrowski and Lawrence G. Hamann

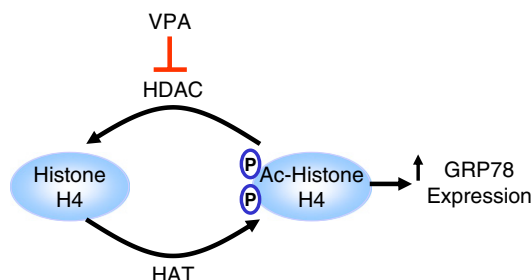


Herein, we report the effects of replacing the 3-oxo group of **2** with a sulfonyl group (e.g., **3**). These tetrahydropyrrolo[1,2-*b*][1,2,5]thiadiazol-2(3*H*)-one 1,1-dioxide analogues were found to be potent SARMs. Synthesis, binding and functional assay SAR, as well as in vivo characterization of a selected analogue in a standard rodent model are presented.

### Induction of GRP78 by valproic acid is dependent upon histone deacetylase inhibition

pp 4491–4494

Yuanyuan Shi, David Gerritsma, Anna J. Bowes, Alfredo Capretta and Geoff H. Werstuck\*

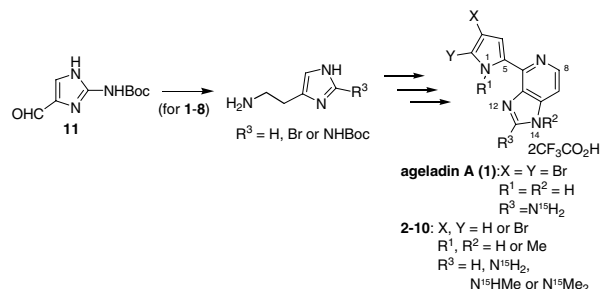


### Synthesis and matrix metalloproteinase (MMP)-12 inhibitory activity of ageladine A and its analogs

pp 4495–4499

Naoki Ando\* and Shiro Terashima

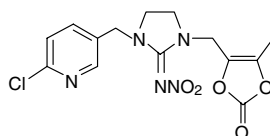
MMP-12 inhibitory activity assay clearly disclosed that the two bromine atoms and the three NH groups (1-NH, 14-NH and 15-NH<sub>2</sub>) were indispensable for **1** to exhibit excellent activity.



### Proinsecticide candidates *N*-(5-methyl-2-oxo-1,3-dioxol-4-yl)methyl derivatives of imidacloprid and 1-chlorothiazolylmethyl-2-nitroimino-imidazolidine

pp 4500–4503

Ikuya Ohno, Koichi Hirata, Chiharu Ishida, Makoto Ihara, Kazuhiko Matsuda and Shinzo Kagabu\*

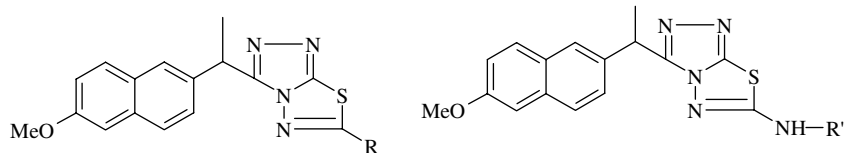


Preparation and biological behavior of prodrugs of imidacloprid is reported.

### Synthesis and pharmacological evaluation of condensed heterocyclic 6-substituted-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazole derivatives of naproxen

pp 4504–4508

Mohammad Amir,\* Harish Kumar and Sadique A. Javed



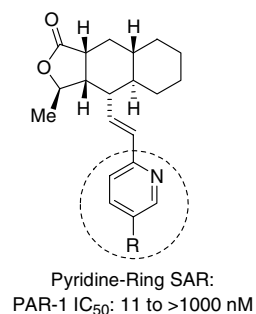
Some 6-substituted-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazole derivatives (**4a–f** and **5a–d**) have been synthesized by cyclisation of 4-amino-5-[1-(6-methoxy-2-naphthyl)ethyl]-3-mercapto-(4*H*)-1,2,4-triazole (**3**) with various substituted aromatic acids and aryl/alkyl isothiocyanates, through a single step reaction. The target compounds were pharmacologically evaluated for their anti-inflammatory and analgesic potentials by known experimental models.

### Himbacine derived thrombin receptor (PAR-1) antagonists: SAR of the pyridine ring

pp 4509–4513

Yan Xia,\* Samuel Chackalamannil, Martin Clasby, Darío Doller, Keith Eagen, William J. Greenlee, Hsingan Tsai, Jacqueline Agans-Fantuzzi, Ho-Sam Ahn, George C. Boykow, Yunsheng Hsieh, Charles A. Lunn and Madhu Chintala

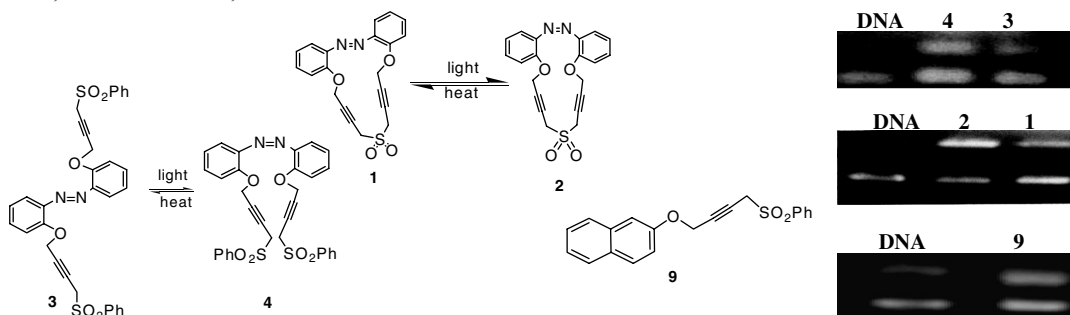
The SAR of the pyridine ring of himbacine derived thrombin receptor (PAR-1) antagonists is described.



### Synthesis and reactivity of azobenzene-based bispropargyl sulfones: Interesting comparison between cyclic and acyclic systems

pp 4514–4517

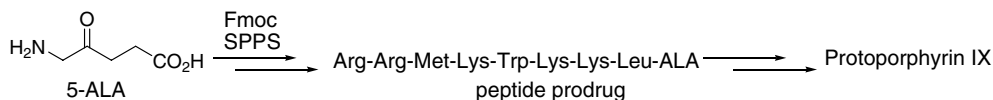
Debarati Mitra, Moumita Kar, Rhitankar Pal and Amit Basak\*



### Novel prodrug approach to photodynamic therapy: Fmoc solid-phase synthesis of a cell permeable peptide incorporating 5-aminolaevulinic acid

pp 4518–4522

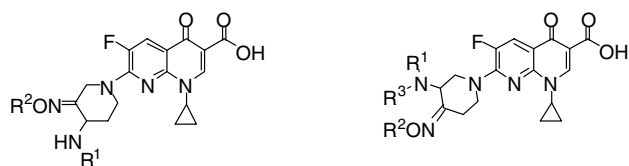
Mark J. Dixon, Ludovic Bourré, Alexander J. MacRobert and Ian M. Eggleston\*



**Synthesis and antibacterial activity of novel fluoroquinolones containing substituted piperidines**

pp 4523–4526

Zhao Dang, Yushe Yang,\* Ruyun Ji and Shuhua Zhang



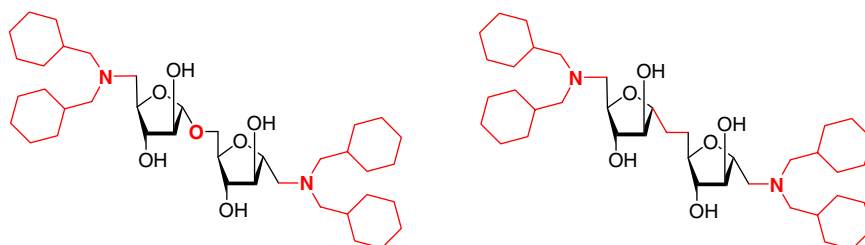
The design, synthesis, and antibacterial activity of new fluoroquinolones possessing substituted piperidine rings at the C-7 position are described.

**Synthesis of symmetrical C- and pseudo-symmetrical O-linked disaccharide analogs for arabinosyltransferase inhibitory activity in *Mycobacterium tuberculosis***

pp 4527–4530

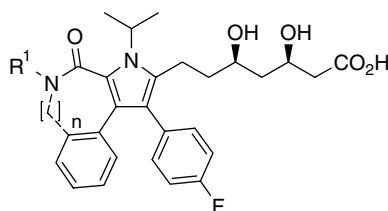
Ashish K. Pathak, Vibha Pathak, James R. Riordan, William J. Suling, Sudagar S. Gurchar, Gurdial S. Besra and Robert C. Reynolds\*

Syntheses of symmetrical C-linked and pseudo-symmetrical O-linked disaccharides structurally related to Araf motifs present in the cell wall of MTB and their arabinosyltransferase activity and in vitro inhibitory activity versus MTB H<sub>37</sub>Ra and *Mycobacterium avium* are reported.

**Design and synthesis of novel, conformationally restricted HMG-CoA reductase inhibitors**

pp 4531–4537

Jeffrey A. Pfefferkorn,\* Chulho Choi, Yuntao Song, Bharat K. Trivedi, Scott D. Larsen, Valerie Askew, Lisa Dillon, Jeffrey C. Hanselman, Zhiwu Lin, Gina Lu, Andrew Robertson, Catherine Sekerke, Bruce Auerbach, Alexander Pavlovsky, Melissa S. Harris, Graeme Bainbridge and Nicole Caspers



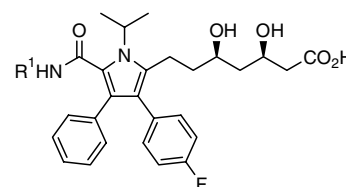
Using structure-based design, a novel series of conformationally restricted, pyrrole-based inhibitors of HMG-CoA reductase inhibitors were discovered.

**Design and synthesis of hepatoselective, pyrrole-based HMG-CoA reductase inhibitors**

pp 4538–4544

Jeffrey A. Pfefferkorn,\* Yuntao Song, Kuai-Lin Sun, Steven R. Miller, Bharat K. Trivedi, Chulho Choi, Roderick J. Sorenson, Larry D. Bratton, Paul C. Unangst, Scott D. Larsen, Toni-Jo Poel, Xue-Min Cheng, Chitase Lee, Noe Erasga, Bruce Auerbach, Valerie Askew, Lisa Dillon, Jeffrey C. Hanselman, Zhiwu Lin, Gina Lu, Andrew Robertson, Karl Olsen, Thomas Mertz, Catherine Sekerke, Alexander Pavlovsky, Melissa S. Harris, Graeme Bainbridge, Nicole Caspers, Huifen Chen and Matthias Eberstadt

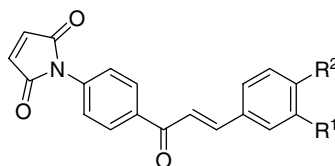
This manuscript describes the design and synthesis of a series of *N*-iso-propyl pyrrole-based inhibitors of HMG-CoA reductase for the treatment of hypercholesterolemia.



**Cytostatic activity of novel 4'-aminochalcone-based imides**

pp 4545–4550

Amitabh Jha,\* Chandrani Mukherjee, Alfred J. Rolle, Erik De Clercq, Jan Balzarini and James P. Stables

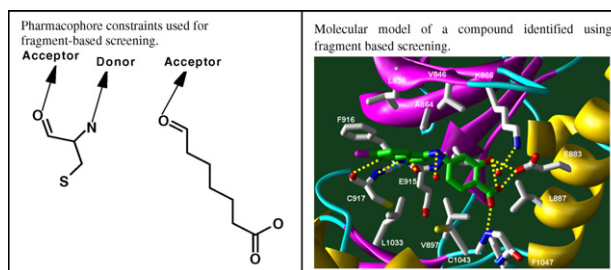


A series of 4'-aminochalcone-based maleimides were identified as novel cytostatic agents against three representative cancer cell lines. Representative compounds were well tolerated by mice in in vivo survival and toxicity studies.

**In-silico fragment-based identification of novel angiogenesis inhibitors**

pp 4551–4556

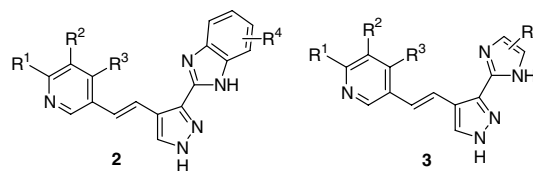
Sivanesan Dakshanamurthy,\* Min Kim, Milton L. Brown and Stephen W. Byers

**Design, synthesis, and evaluation of 3,4-disubstituted pyrazole analogues as anti-tumor CDK inhibitors**

pp 4557–4561

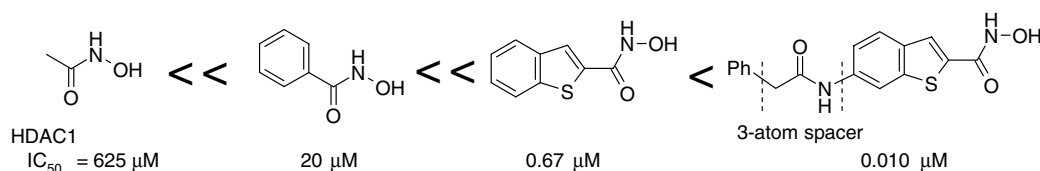
Ronghui Lin,\* George Chiu, Yang Yu, Peter J. Connolly,\* Shengjian Li, Yanhua Lu, Mary Adams, Angel R. Fuentes-Pesquera, Stuart L. Emanuel and Lee M. Greenberger

Two series of 3,4-disubstituted pyrazole analogues, 3-(imidazol-2-yl)-4-[2-(pyridin-3-yl)-vinyl]-pyrazoles (**2**) and 3-(benzimidazol-2-yl)-4-[2-(pyridin-3-yl)-vinyl]-pyrazoles (**3**), were synthesized as novel cyclin-dependent kinase (CDK) inhibitors. Representative compounds showed potent and selective CDK inhibitory activities and inhibited in vitro cellular proliferation in various human tumor cells. The design, synthesis, and preliminary biological evaluation of these pyrazole compounds are reported.

**Benzo[b]thiophene-based histone deacetylase inhibitors**

pp 4562–4567

David J. Witter,\* Sandro Belvedere, Liqiang Chen, J. Paul Secrist, Ralph T. Mosley and Thomas A. Miller



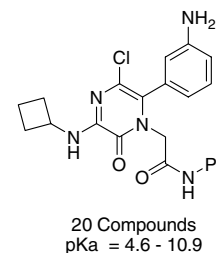
Benzo[b]thienyl hydroxamic acids were identified via a targeted screen of small molecule hydroxamic acids. Various substitutions were explored in the benzo[b]thiophene C5- and C6-positions which lead to a consistent finding that a three-atom spacer in the C6-position yielded optimal HDAC1 inhibition and anti-proliferative activity.

**Design, synthesis, and biological evaluation of pyrazinones containing novel P1 needles as inhibitors of TF/VIIa**

pp 4568–4574

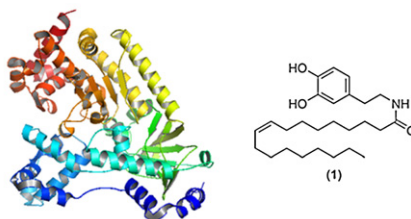
John I. Trujillo,\* Horng-Chih Huang, William L. Neumann, Matthew W. Mahoney, Scott Long, Wei Huang, Danny J. Garland, Carrie Kusturin, Zaheer Abbas, Michael S. South and David B. Reitz

The design, synthesis, and biological evaluation of 20 compounds with novel P1 needles is reported. The P1 needle replacements were selected based upon their reduced basicity compared to the parent phenyl amidine (pKa ~ 12), with the goal of the effort an orally bioavailable TF/VIIa inhibitor.

**Inhibitors of anthrax lethal factor**

pp 4575–4578

Brandon D. Gaddis, Larisa V. Avramova and Jean Chmielewski\*

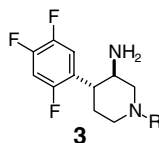


An inhibitor of anthrax lethal factor (**1**) was discovered. A subsequent SAR and mechanistic study was performed to identify uncompetitive inhibitors of anthrax lethal factor with good cell potency and low cytotoxicity.

**Discovery of 3-aminopiperidines as potent, selective, and orally bioavailable dipeptidyl peptidase IV inhibitors**

pp 4579–4583

Jason M. Cox,\* Bart Harper, Anthony Mastracchio, Barbara Leiting, Ranabir Sinha Roy, Reshma A. Patel, Joseph K. Wu, Kathryn A. Lyons, Huaibing He, Shiyao Xu, Bing Zhu, Nancy A. Thornberry, Ann E. Weber and Scott D. Edmondson

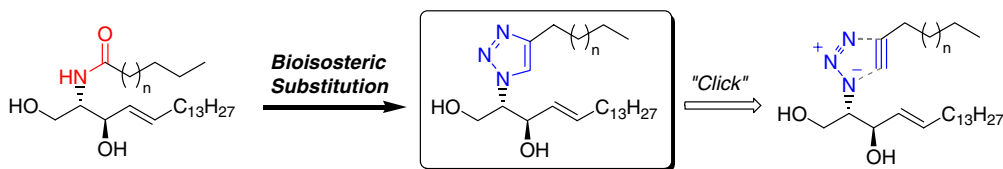


Substituted 3-aminopiperidines **3** were evaluated as DPP-4 inhibitors. The inhibitors showed good DPP-4 potency with superb selectivity over other peptidases (QPP, DPP8, and DPP9). Selected DPP-4 inhibitors were further evaluated for their hERG potassium channel, L-type calcium channel, Cyp2D6, and pharmacokinetic profiles.

**Design, synthesis, and preliminary biological evaluation of a novel triazole analogue of ceramide**

pp 4584–4587

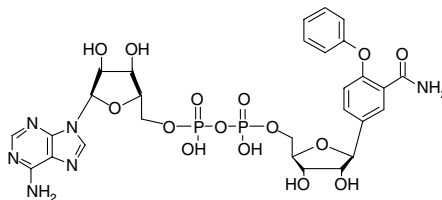
Sanghee Kim,\* Minjae Cho, Taeho Lee, Sukjin Lee, Hye-Young Min and Sang Kook Lee



### Synthesis of 4-phenoxybenzamide adenine dinucleotide as NAD analogue with inhibitory activity against enoyl-ACP reductase (InhA) of *Mycobacterium tuberculosis*

pp 4588–4591

Laurent Bonnac, Guang-Yao Gao, Liqiang Chen, Krzysztof Felczak, Eric M. Bennett, Hua Xu, TaeSoo Kim, Nina Liu, HyeWon Oh, Peter J. Tonge and Krzysztof W. Pankiewicz\*

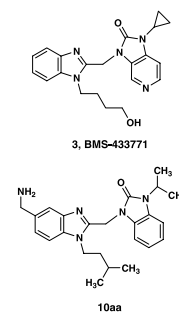


### Respiratory syncytial virus fusion inhibitors. Part 5: Optimization of benzimidazole substitution patterns towards derivatives with improved activity

pp 4592–4598

Xiangdong Alan Wang,\* Christopher W. Cianci, Kuo-Long Yu, Keith D. Combrink, Jan W. Thuring, Yi Zhang, Rita L. Civiello, Kathleen F. Kadow, Julia Roach, Zhufang Li, David R. Langley, Mark Krystal and Nicholas A. Meanwell

Extensive SAR studies and optimization of ADME properties of benzimidazol-2-one derivatives led to the identification of BMS-433771 (**3**) as an orally active RSV fusion inhibitor. In order to extend the structure–activity relationships for this compound series, substitution of the benzimidazole ring was examined with a view to establishing additional productive interactions between the inhibitor and functionality present in the proposed binding pocket. Amongst the compounds synthesized, the 5-aminomethyl analogue **10aa** demonstrated potent antiviral activity towards wild-type RSV and retained excellent inhibitory activity towards a virus that had been developed to express resistance to BMS-433771 (**3**), data consistent with an additional productive interaction between the inhibitor and the fusion protein target.

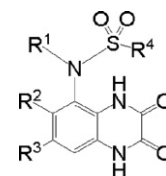


### *N*-(6,7-Dichloro-2,3-dioxo-1,2,3,4-tetrahydroquinoxalin-5-yl)-*N*-alkylsulfonamides as peripherally restricted *N*-methyl-D-aspartate receptor antagonists for the treatment of pain

pp 4599–4603

Christopher Deur,\* Arun K. Agrawal, Heidi Baum, John Booth, Susan Bove, Joan Brieland, Amy Bunker, Cleo Connolly, Joseph Cornicelli, JoAnn Dumin, Barry Finzel, Xinmin Gan, Sheila Guppy, Gregg Kamilar, Kenneth Kilgore, Pil Lee, Cho-Ming Loi, Zhen Lou, Mark Morris, Laurence Philippe, Sally Przybranowski, Frank Riley, Brian Samas, Brian Sanchez, Haile Tecle, Ziqiang Wang, Kathryn Welch, Michael Wilson and Karen Yates

A series of quinoxalinedione sulfonamides with potent NMDA receptor antagonist activity are discussed as potential pain therapeutics. The antagonists were optimized for oral bioavailability and decreased capacity to cross the blood–brain barrier.

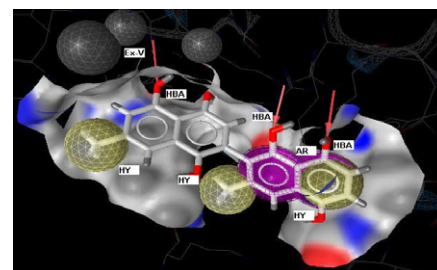


### A computational docking study for prediction of binding mode of diospyrin and derivatives: Inhibitors of human and leishmanial DNA topoisomerase-I

pp 4604–4612

Sandeep Chhabra, Pooja Sharma and Nanda Ghoshal\*

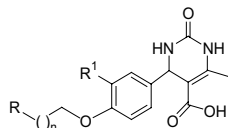
A computational approach was used to study the relative inhibitory mode of diospyrin with human and *Leishmania donovani* DNA–TopI. The interaction of amino derivatives of diospyrin with human TOP-I was studied extensively for antitumor activity. Further, a structure-based pharmacophore model was developed for *L. donovani* DNA–TopI inhibition that describes topological and spatial description of ligand–receptor interactions.



**Design and synthesis of 6-methyl-2-oxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid derivatives as PPAR $\gamma$  activators**

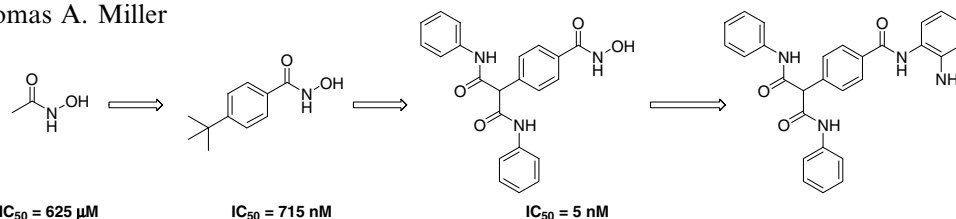
pp 4613–4618

Rakesh Kumar,\* Amit Mittal and Uma Ramachandran

**Design of novel histone deacetylase inhibitors**

pp 4619–4624

Phieng Siliphaivanh,\* Paul Harrington, David J. Witter, Karin Otte, Paul Tempest, Sam Kattar, Astrid M. Kral, Judith C. Fleming, Sujal V. Deshmukh, Andreas Harsch, Paul J. Secrist and Thomas A. Miller

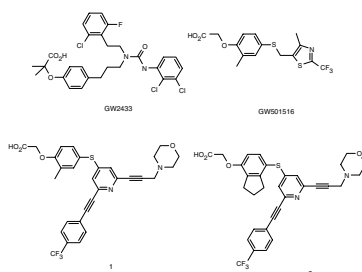


2-(4-((2-Aminophenyl)amino)carbonyl)phenyl)-*N,N'*-diphenylmalonamide containing excellent HDAC and cellular proliferation inhibitory activities was identified as a novel benzamide-derived HDAC inhibitor through iterative design starting from acetohydroxamic acid.

**Design of a partial PPAR $\delta$  agonist**

pp 4625–4629

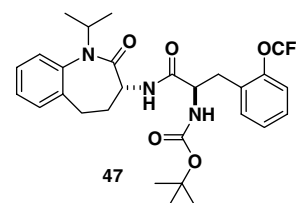
Ingrid Pettersson,\* Søren Ebdrup, Miroslav Havranek, Pavel Pihera, Marek Kořínek, John P. Mogensen, Claus B. Jeppesen, Eva Johansson and Per Sauerberg

**Discovery of a novel class of benzazepinone Na<sub>v</sub>1.7 blockers: Potential treatments for neuropathic pain**

pp 4630–4634

Scott B. Hoyt,\* Clare London, David Gorin, Matthew J. Wyvratt, Michael H. Fisher, Catherine Abbadie, John P. Felix, Maria L. Garcia, Xiaohua Li, Kathryn A. Lyons, Erin McGowan, D. Euan MacIntyre, William J. Martin, Birgit T. Priest, Amy Ritter, McHardy M. Smith, Vivien A. Warren, Brande S. Williams, Gregory J. Kaczorowski and William H. Parsons

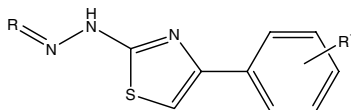
A series of benzodiazepines and benzazepinones were synthesized and evaluated as potential sodium channel blockers in a functional, membrane potential-based assay. One member of the benzazepinone series, compound **47**, displayed potent, state-dependent block of hNa<sub>v</sub>1.7, and was orally efficacious in a rat model of neuropathic pain.



### Synthesis and in vitro activity of 2-thiazolylhydrazone derivatives compared with the activity of clotrimazole against clinical isolates of *Candida* spp.

pp 4635–4640

Franco Chimenti, Bruna Bizzarri,\* Elias Maccioni, Daniela Secci, Adriana Bolasco, Rossella Fioravanti, Paola Chimenti, Arianna Granese, Simone Carradori, Daniela Rivanera, Daniela Lilli, Alessandra Zicari and Simona Distinto

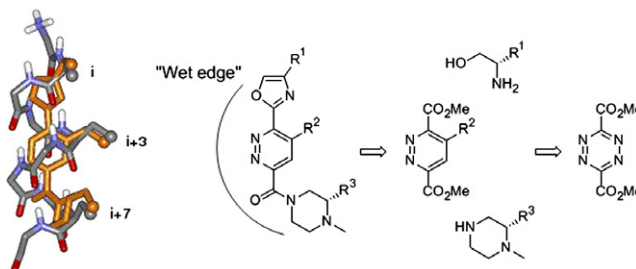


A novel series of 2-thiazolylhydrazone derivatives were prepared and evaluated for their in vitro activities against 22 clinical isolates of *Candida* spp., representing six different species, compared to clotrimazole as a reference compound.

### Heterocyclic $\alpha$ -helix mimetics for targeting protein–protein interactions

pp 4641–4645

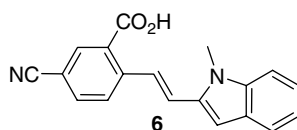
Shannon M. Biros, Lionel Moisan, Enrique Mann, Alexandre Carella, Dayong Zhai, John C. Reed and Julius Rebek, Jr.\*



### Human serum albumin binding assay based on displacement of a non selective fluorescent inhibitor

pp 4646–4649

Atli Thorarensen,\* Ronald W. Sarver,\* Fang Tian, Andrea Ho, Donna L. Romero and Keith R. Marotti

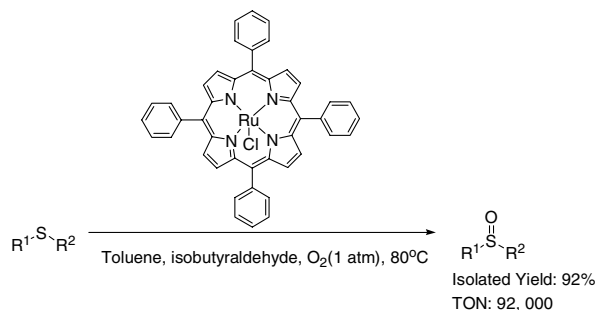


This paper describes the discovery of a novel fluorescent probe **6** and its utility in measuring compounds, affinity for human serum albumin (HSA).

### Selective oxidation of sulfides to sulfoxides catalyzed by ruthenium (III) meso-tetraphenylporphyrin chloride in the presence of molecular oxygen

pp 4650–4653

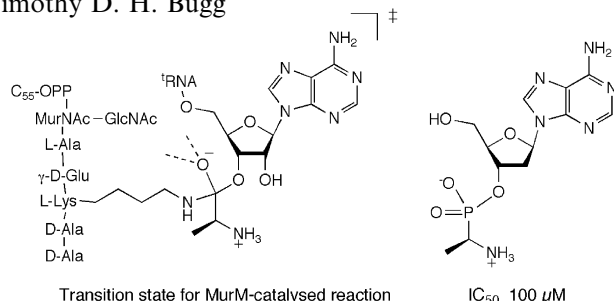
Xian-Tai Zhou, Hong-Bing Ji,\* Zhao Cheng, Jian-Chang Xu, Li-Xia Pei and Le-Fu Wang



**Adenosine phosphonate inhibitors of lipid II: Alanyl tRNA ligase MurM from *Streptococcus pneumoniae***

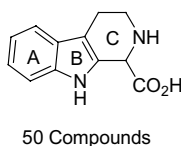
pp 4654–4656

Elena Cressina, Adrian J. Lloyd, Gianfranco De Pascale, David I. Roper, Christopher G. Dowson and Timothy D. H. Bugg\*

**Novel tetrahydro-β-carboline-1-carboxylic acids as inhibitors of mitogen activated protein kinase-activated protein kinase 2 (MK-2)**

pp 4657–4663

John I. Trujillo,\* Marvin J. Meyers,\* David R. Anderson, Shridhar Hegde, Matthew W. Mahoney, William F. Vernier, Ingrid P. Buchler, Kun K. Wu, Syaluan Yang, Susan J. Hartmann and David B. Reitz

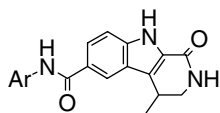


A structure–activity relationship study was conducted on a series of tetrahydro-β-carboline-1-carboxylic acid analogs against MK-2. The compounds were evaluated for their ability to inhibit TNFα production in vitro and in vivo.

**The discovery of carboline analogs as potent MAPKAP-K2 inhibitors**

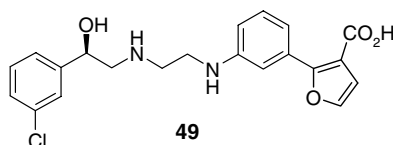
pp 4664–4669

Jiang-Ping Wu,\* Ji Wang, Asitha Abeywardane, Denise Andersen, Michel Emmanuel, Elda Gautschi, Daniel R. Goldberg, Mohammed A. Kashem, Susan Lukas, Wang Mao, Leslie Martin, Tina Morwick, Neil Moss, Christopher Pargellis, Usha R. Patel, Lori Patnaude, Gregory W. Peet, Donna Skow, Roger J. Snow, Yancey Ward, Brian Werneburg and Andre White

**Synthesis and evaluation of potent and selective β<sub>3</sub> adrenergic receptor agonists containing heterobiaryl carboxylic acids**

pp 4670–4677

Barry G. Shearer,\* Esther Y. Chao, David E. Uehling, David N. Deaton, Conrad Cowan, Bryan W. Sherman, Tula Milliken, Walter Faison, Kathleen Brown, Kimberly K. Adkison and Frank Lee

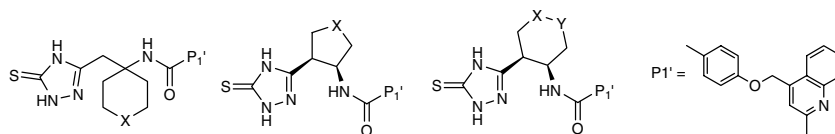


The design, synthesis, and SAR of a novel series of heterobiaryl phenethanolamine β<sub>3</sub> adrenergic receptor agonists are described. The furan analogue **49** was shown to elicit a significant dose-dependent lowering of plasma glucose in a rodent model of type 2 diabetes.

### Synthesis and structure–activity relationship of a novel, non-hydroxamate series of TNF- $\alpha$ converting enzyme inhibitors

pp 4678–4682

John L. Gilmore,\* Bryan W. King, Naoyuki Asakawa, Kimberly Harrison, Andrew Tebben, James E. Sheppeck, II, Rui-Qin Liu, Maryanne Covington and James J.-W. Duan

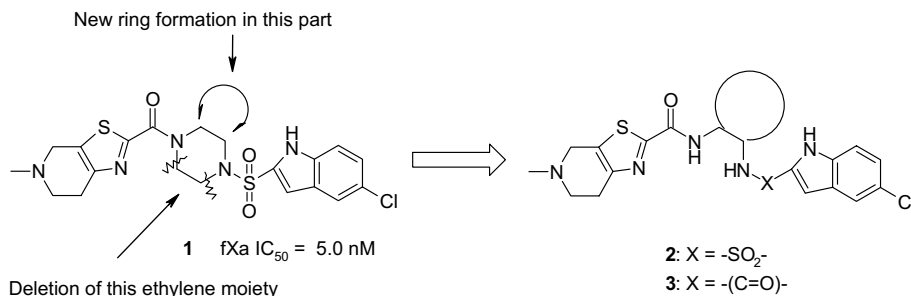


A novel series of TNF- $\alpha$  converting enzyme (TACE) inhibitors which are non-hydroxamate have been discovered. These compounds use a triazolethione moiety as the zinc binding ligand and exhibit  $IC_{50}$  values from 1.5 to 100 nM in a porcine TACE assay. They also have excellent selectivities over other MMPs.

### Cycloalkanediamine derivatives as novel blood coagulation factor Xa inhibitors

pp 4683–4688

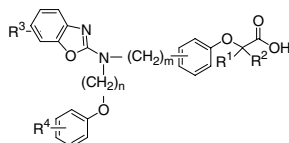
Tsutomu Nagata,\* Toshiharu Yoshino, Noriyasu Haginoya, Kenji Yoshikawa, Yumiko Isobe, Taketoshi Furugohri and Hideyuki Kanno



### Design and synthesis of highly potent and selective human peroxisome proliferator-activated receptor $\alpha$ agonists

pp 4689–4693

Yukiyoshi Yamazaki,\* Kazutoyo Abe, Tsutomu Toma, Masahiro Nishikawa, Hidefumi Ozawa, Ayumu Okuda, Takaaki Araki, Soichi Oda, Keisuke Inoue, Kimiyuki Shibuya, Bart Staels and Jean-Charles Fruchart



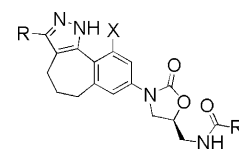
A combination of benzoxazole, phenoxyalkyl side chain and phenoxybutyric acids was identified as highly potent and selective h-PPAR $\alpha$  agonists. The synthesis, SAR studies and in vivo activities of the representative compounds are described.

### Synthesis and SAR of novel conformationally-restricted oxazolidinones possessing Gram-positive and fastidious Gram-negative antibacterial activity. Part 1: Substituted pyrazoles

pp 4694–4698

Frederick E. Boyer,\* J. V. N. Vara Prasad, Allison L. Choy, Louis Chupak, Michael R. Dermeyer, Qizhu Ding, Michael D. Huband, Wenhua Jiao, Takushi Kaneko, Vladimir Khlebnikov, Ji-Young Kim, Manjinder S. Lall, Samarendra N. Maiti, Karina Romero and Xiujuan Wu

A novel series of conformationally-restricted oxazolidinones were synthesized which possess a fused pyrazole ring substituted with various alkyl, aryl and heteroaryl substituents

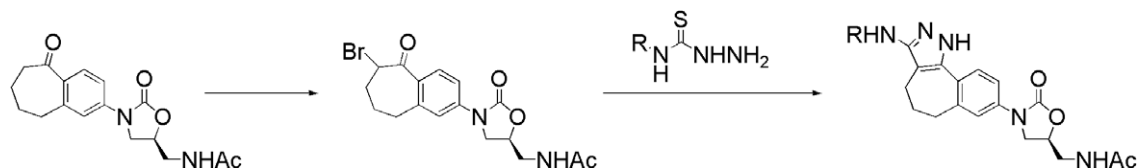


R = H, alkyl, aryl, or heteroaryl  
R' = alkyl, aryl, or heteroaryl  
X = H, F

**Synthesis and SAR of novel conformationally restricted oxazolidinones possessing Gram-positive and fastidious Gram-negative antibacterial activity. Part 2: Amino substitutions on heterocyclic D-ring system**

pp 4699–4702

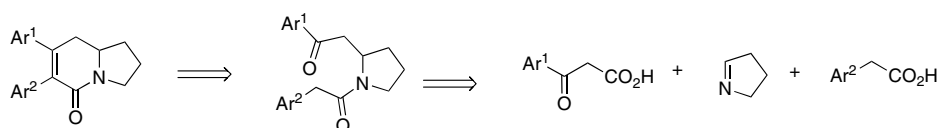
Allison L. Choy,\* J. V. N. Vara Prasad, Frederick E. Boyer, Michael D. Huband and Michael R. Dermeyer



**Synthesis, in vitro and in vivo cytotoxicity of 6,7-diaryl-2,3,8a-tetrahydroindolizin-5(1H)-ones**

pp 4703–4707

F. Scott Kimball, Ashok Rao Tunoori, Samuel F. Victory, Dinah Dutta, Jonathan M. White, Richard H. Himes and Gunda I. Georg\*

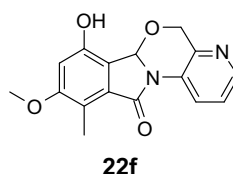


A 6,7-diaryl-2,3,8a-tetrahydroindolizin-5(1H)-one library was constructed and assayed for cytotoxicity toward the HCT-116 colon cancer cell line. Micromolar and sub-micromolar potencies were observed. One of the compounds displayed promising activity in the NCI's mouse hollow fiber assay.

**Design, synthesis, and structure–activity relationship studies of new phenolic DNA gyrase inhibitors**

pp 4708–4714

Thomas Lübbers,\* Peter Angehrn, Hans Gmünder and Silvia Herzig



Starting from 2-(anilinomethyl)-phenols **3** we report herein the design and synthesis of a series of novel 2,3-dihydroisoindol-1-ones structurally related to cyclothialidine **2** with DNA gyrase inhibitory activity. In this series, some compounds exhibited promising antibacterial activity.

**OTHER CONTENTS**

Summary of instructions to authors

p I

\*Corresponding author

Supplementary data available via ScienceDirect

**COVER**

Typical snapshot of **7b** bound to HIV-RT from an MC simulation. Carbon atoms of **7b** are gold; from the left, Tyr181, Tyr188, Phe227, Leu100, Lys101; Trp229 at the top, Val106 at the bottom. H-bond with Lys101 O on right. Some residues in front including Glu138 have been removed for clarity. The water on N5 is also H-bonded to a carboxylate O of Glu138. [Thakur, V. T.; Kim, J. T.; Hamilton, A. D.; Bailey, C. M.; Domaoal, R. A.; Wang, L.; Anderson, K. S.; Jorgensen, W. L. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5664.]

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