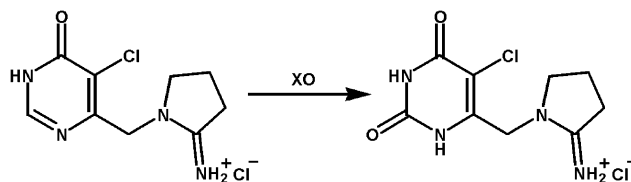


## Contents

### COMMUNICATIONS

**Synthesis and enzymatic evaluation of xanthine oxidase-activated prodrugs based on inhibitors of thymidine phosphorylase** pp 5247–5250

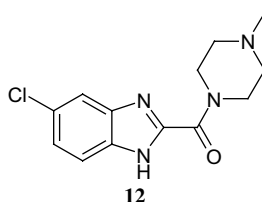
Philip Reigan, Abdul Gbaj, Edwin Chinje, Ian J. Stratford, Kenneth T. Douglas and Sally Freeman\*



A series of xanthine oxidase-activated prodrugs of known inhibitors of thymidine phosphorylase is described. These prodrugs were oxidised by xanthine oxidase at C-2 and/or C-4 of the uracil ring to generate the desired TP inhibitor. The scheme shows the prodrug of TPI.

**Synthesis and structure–activity relationships of indole and benzimidazole piperazines as histamine H<sub>4</sub> receptor antagonists** pp 5251–5256

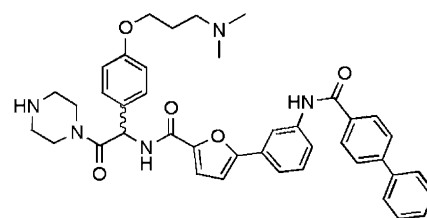
Nalan Terzioglu, Richard M. van Rijn, Remko A. Bakker, Iwan J. P. De Esch and Rob Leurs\*



**Optimizing the antibacterial activity of a lead structure discovered by ‘SAR by MS’ technology** pp 5257–5261

Elizabeth A. Jefferson,\* Punit P. Seth, Dale E. Robinson, Dana K. Winter, Alycia Miyaji, Lisa M. Risen, Stephen A. Osgood, Myra Bertrand and Eric E. Swayze

We report on lead optimization of a compound that was originally discovered to bind bacterial 23S rRNA near the L11 binding site and inhibit translation in vitro, but lacked detectable antibacterial activity. In this study, we were able to generate compounds with antibacterial activity against Gram-negative and Gram-positive pathogens, including a methicillin-resistant *S. aureus* strain.

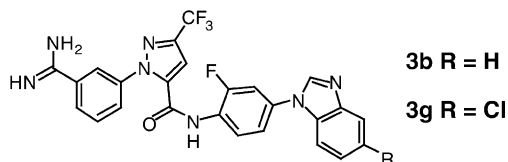


IC<sub>50</sub> = 9 μM (bacterial protein synthesis)  
MIC = 6–13 μM (*E. coli*) and 3–6 μM (*S. aureus*)

**SAR and factor IXa crystal structure of a dual inhibitor of factors IXa and Xa**

pp 5263–5267

Joanne M. Smallheer,\* Richard S. Alexander, Jianmin Wang, Shuaige Wang, Suanne Nakajima, Karen A. Rossi, Angela Smallwood, Frank Barbera, Debra Burdick, Joseph M. Luetttgen, Robert M. Knabb, Ruth R. Wexler and Prabhakar K. Jadhav

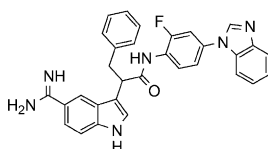


An X-ray crystal structure of compound **3b** complexed to fIXa shows a similar binding mode to that previously observed with pyrazole inhibitors in the fIXa active site. The best combination of fIXa potency and selectivity in this series was obtained with 5-chlorobenzimidazole analog **3g**.

**5-Amidinoindoles as dual inhibitors of coagulation factors IXa and Xa**

pp 5269–5273

Douglas G. Batt,\* Jennifer X. Qiao, Dilip P. Modi, Gregory C. Houghton, Deborah A. Pierson, Karen A. Rossi, Joseph M. Luetttgen, Robert M. Knabb, P. K. Jadhav and Ruth R. Wexler

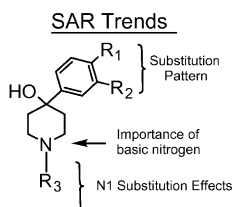


Structural features of a 5-amidinoindole inhibitor of factor Xa, which displayed modest inhibition of factor IXa were varied to increase potency and improve selectivity for factor IXa.

**Design and synthesis of 4-phenyl piperidine compounds targeting the mu receptor**

pp 5275–5279

Zhengming Chen,\* Ellen Davies, Wendy S. Miller, Shen Shan, Kenneth J. Valenzano and Donald J. Kyle

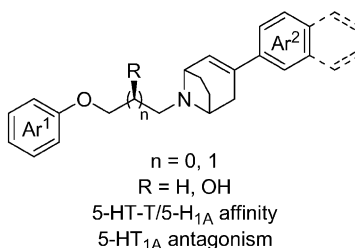


Small molecule mu agonists based on the 4-phenyl piperidine scaffold were designed and synthesized to further investigate the therapeutic potential of loperamide analogs. The resulting compounds show excellent agonistic activity towards the human mu receptor with interesting SAR trends within the series.

**Novel aryloxy-8-azabicyclo[3.2.1]oct-3-enes with 5-HT transporter and 5-HT<sub>1A</sub> affinity**

pp 5281–5284

Adam M. Gilbert,\* Thomas Coleman, Jason Kodah, Richard E. Mewshaw, Rosemary Scerni, Lee E. Schechter, Deborah L. Smith and Terrance H. Andree

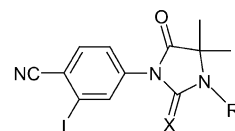


**Synthesis and structure–activity investigation of iodinated arylhydantoins and arylthiohydantoins for development as androgen receptor radioligands**

pp 5285–5288

Marcian E. Van Dort\* and Yong-Woon Jung

A series of side-chain derivatives of the arylhydantoin RU 58841 and the arylthiohydantoin RU 59063, wherein the aromatic trifluoromethyl was replaced with iodine, was synthesized for development as radioiodinated androgen receptor (AR) ligands. Compounds having *N*-(methyl) and *N*-(hydroxybutyl) side-chains displayed high AR binding affinity ( $0.71 \text{ nM} < K_i < 11 \text{ nM}$ ). The synthesis and SAR of these ligands are discussed.



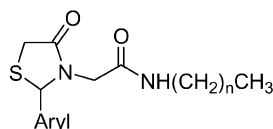
X = O; S

R = alkyl, phenalkyl, hydroxybutyl, cyanomethyl, etc.

**Synthesis and antiproliferative activity of 2-aryl-4-oxo-thiazolidin-3-yl-amides for prostate cancer**

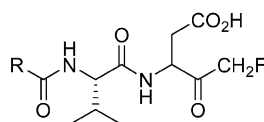
pp 5289–5293

Veeresa Gududuru, Eunju Hurh, James T. Dalton and Duane D. Miller\*

**Dipeptidyl aspartyl fluoromethylketones as potent caspase inhibitors: SAR of the *N*-protecting group**

pp 5295–5300

Sui Xiong Cai,\* Lufeng Guan, Shaojuan Jia, Yan Wang, Wu Yang, Ben Tseng and John Drewe

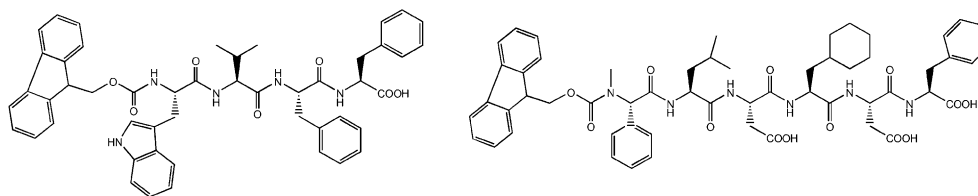


The synthesis and biological evaluation of a group of *N*-protected Val-Asp-fmk as caspase inhibitors is reported.

**More potent linear peptide inhibitors of mammalian ribonucleotide reductase**

pp 5301–5304

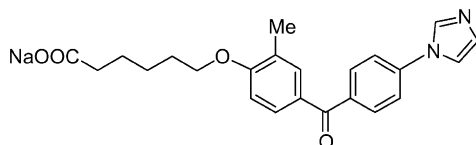
Chiheng Tan, Ying Gao, Jaskiran Kaur and Barry S. Cooperman\*



**Design and synthesis of 1-(4-benzoylphenyl)imidazole derivatives as new potent 20-HETE synthase inhibitors**

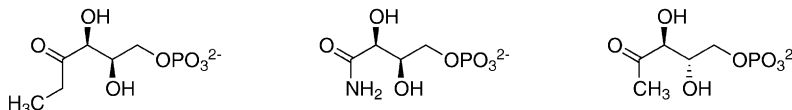
pp 5305–5308

Toshio Nakamura,\* Takaaki Ishii, Noriyuki Miyata, Kazuo Taniguchi, Yasumitsu Tomishima, Tomokazu Ueki and Masakazu Sato\*

7c : IC<sub>50</sub> 7.9nM
**Substrate analogs for the investigation of deoxyxylulose 5-phosphate reductoisomerase inhibition: synthesis and evaluation**

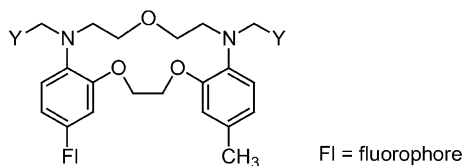
pp 5309–5312

Chanokporn Phaosiri and Philip J. Proteau\*


**Fluorescent sodium ion indicators based on the 1,7-diaza-15-crown-5 system**

pp 5313–5316

Vladimir V. Martin, Anca Rothe, Zhenjun Diwu and Kyle R. Gee\*

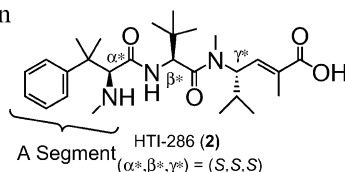


FI = fluorophore

**Synthesis and activity of novel analogs of hemiasterlin as inhibitors of tubulin polymerization: modification of the A segment**

pp 5317–5322

Ayako Yamashita,\* Emily B. Norton, Joshua A. Kaplan, Chuan Niu, Frank Loganzo, Richard Hernandez, Carl F. Beyer, Tami Annable, Sylvia Musto, Carolyn Discafani, Arie Zask and Semiramis Ayral-Kaloustian

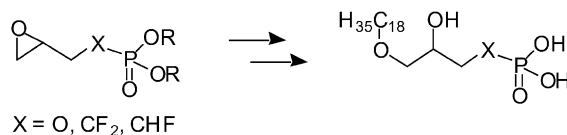


Analogues of HTI-286 (1), containing various aromatic rings in the A segment, were synthesized as potential inhibitors of tubulin polymerization, and the structure–activity relationships related to stereo- and regio-chemical effects of substituents on the aromatic ring in the A segment were studied.

**Alkyl lysophosphatidic acid and fluoromethylene phosphonate analogs as metabolically-stabilized agonists for LPA receptors**

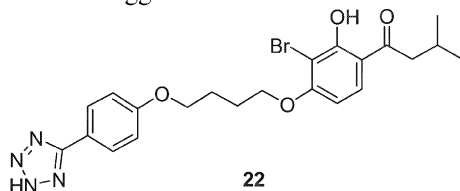
pp 5323–5328

Yong Xu, Masayuki Tanaka, Hiroyuki Arai, Junken Aoki and Glenn D. Prestwich\*

**Allosteric potentiators of the metabotropic glutamate receptor 2 (mGlu2). Part 1: Identification and synthesis of phenyl-tetrazolyl acetophenones**

pp 5329–5332

Anthony B. Pinkerton,\* Rowena V. Cube, John H. Hutchinson, Blake A. Rowe, Hervé Schaffhauser, Xiumin Zhao, Lorrie P. Daggett and Jean-Michel Vernier

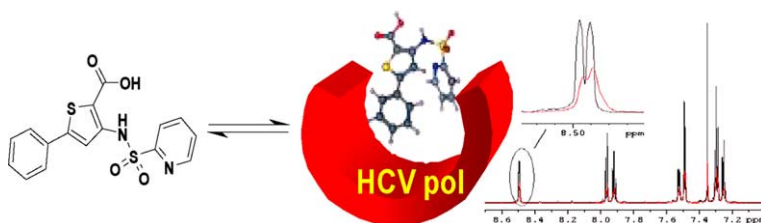


We have identified and synthesized a series of aryl-tetrazolyl acetophenones as positive allosteric potentiators of the metabotropic glutamate receptor 2. Structure activity relationship studies directed toward improving the potency and level of potentiation led to the discovery of **22** ( $EC_{50} = 93$  nM, 128% potentiation).

**HCV NS5B polymerase-bound conformation of a soluble sulfonamide inhibitor by 2D transferred NOESY**

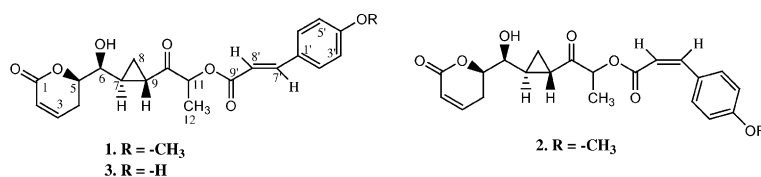
pp 5333–5337

Constantin G. Yannopoulos,\* Ping Xu, Feng Ni, Laval Chan, Oswy Z. Pereira, T. Jagadeeswar Reddy, Sanjoy K. Das, Carl Poisson, Nghe Nguyen-Ba, Nathalie Turcotte, Melanie Proulx, Lilianne Halab, Wuyi Wang, Jean Bédard, Nicolas Morin, Martine Hamel, Olivier Nicolas, Darius Bilimoria, Lucille L'Heureux, Richard Bethell and Gervais Dionne

**Three new compounds from the plant *Lippia alva* as inhibitors of chemokine receptor 5 (CCR5)**

pp 5339–5342

Vinod R. Hegde,\* Haiyan Pu, Mahesh Patel, Pradip R. Das, Julie Strizki, Vincent P. Gullo, Chuan-Chu Chou, Alexei V. Buevich and Tze-Ming Chan

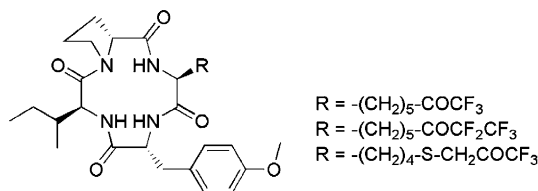


The 70% aqueous methanol extract of the Peruvian plant *Lippia alva* (Verbenaceae) was found to contain three novel compounds, **1**, **2**, and **3**, which were identified as inhibitors of the chemokine receptor CCR5. The structures of **1–3** were established based on extensive NMR studies. Compounds **1–3** inhibited CCR5 receptor signaling as measured by a calcium mobilization assay with  $IC_{50}$  values of 5.5, 6.0, and 7.2  $\mu$ g/mL, respectively.

**Novel histone deacetylase inhibitors: cyclic tetrapeptide with trifluoromethyl and pentafluoroethyl ketones**

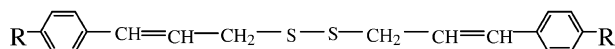
pp 5343–5346

Binoy Jose, Yusuke Oniki, Tamaki Kato, Norikazu Nishino,\* Yuko Sumida and Minoru Yoshida


**Bis[3-(4'-substituted phenyl)prop-2-ene]disulfides as a new class of antihyperlipidemic compounds**

pp 5347–5350

Meenakshi Sharma, Manisha Tiwari and Ramesh Chandra\*

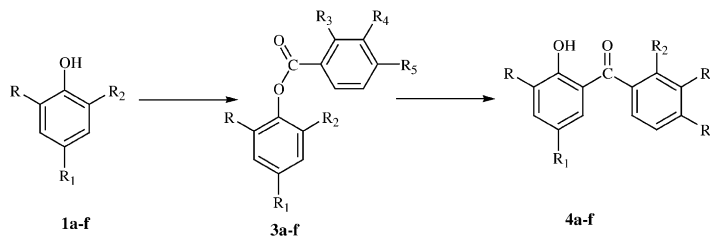


Novel derivatives of diallylsulfide, an active principle found in garlic, have been synthesized. The synthetic scheme, involving the Wittig reaction has been outlined. Among these derivatives, bis[3-(4'-nitrophenyl)prop-2-ene]disulfide has been found to be effective in lowering lipid levels and in inhibiting the activity of the enzyme HMG-CoA reductase, in Wistar rats.

**Synthesis of some newer analogues of substituted dibenzoyl phenol as potent anti-inflammatory agents**

pp 5351–5355

Shaukath Ara. Khanum, Venu T. D, Sheena Shashikanth\* and Aiysha Firdouse

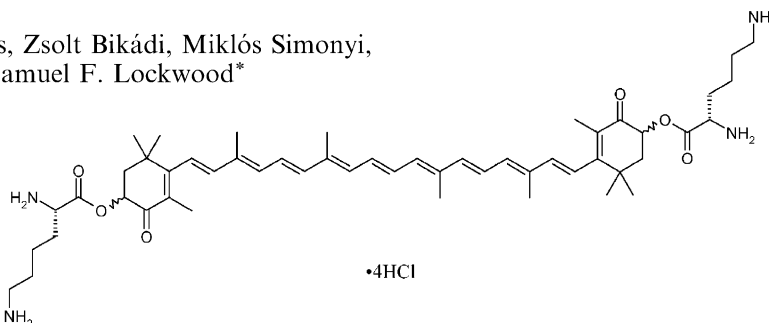


The newly synthesized compounds dibenzoyl phenols **4a–f** using microwave irradiation were screened for their anti-inflammatory activity and compared with standard drugs.

**In vitro plasma protein binding and aqueous aggregation behavior of astaxanthin dilysinate tetrahydrochloride**

pp 5357–5366

Ferenc Zsila, Ilona Fitos, Zsolt Bikádi, Miklós Simonyi, Henry L. Jackson and Samuel F. Lockwood\*

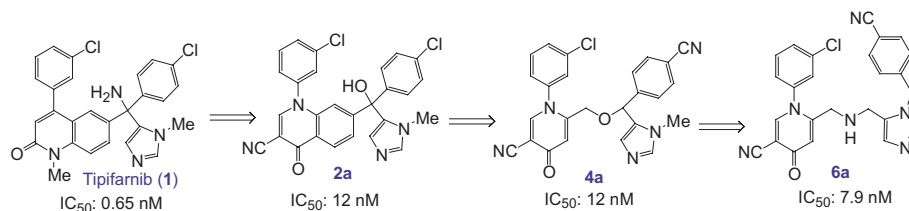


Distinct monomeric and chirally-complexed binding of astaxanthin dilysinate tetrahydrochloride to human serum albumin.

**Design, synthesis, and activity of 4-quinolone and pyridone compounds as nonthiol-containing farnesyltransferase inhibitors**

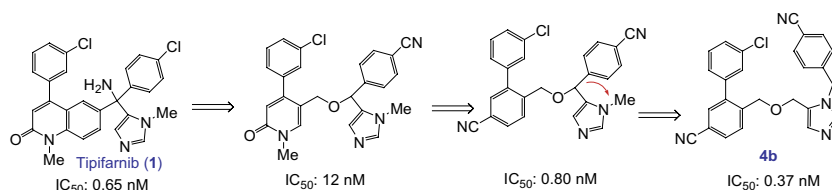
pp 5367–5370

Qun Li,\* Akiyo Claiborne, Tongmei Li, Lisa Hasvold, Vincent S. Stoll, Steven Muchmore, Clarissa G. Jakob, Wendy Gu, Jerry Cohen, Charles Hutchins, David Frost, Saul H. Rosenberg and Hing L. Sham

**Synthesis and activity of 1-aryl-1'-imidazolyl methyl ethers as non-thiol farnesyltransferase inhibitors**

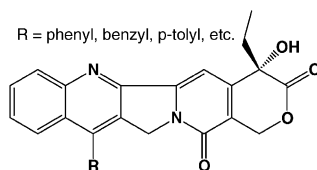
pp 5371–5376

Qun Li,\* Gary T. Wang, Tongmei Li, Stephen L. Gwaltney, II, Keith W. Woods, Akiyo Claiborne, Xilu Wang, Wendy Gu, Jerry Cohen, Vincent S. Stoll, Charles Hutchins, David Frost, Saul H. Rosenberg and Hing L. Sham

**Camptothecin analogs with bulky, hydrophobic substituents at the 7-position via a Grignard reaction**

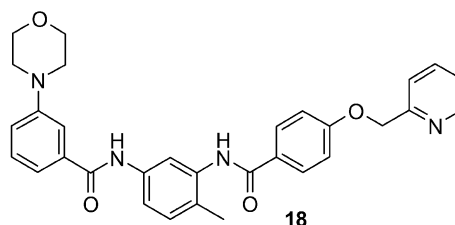
pp 5377–5381

Govindarajan Manikumar, Randy M. Wadkins, David Bearss, Daniel D. Von Hoff, Mansukhlal C. Wani\* and Monroe E. Wall

**A novel series of p38 MAP kinase inhibitors for the potential treatment of rheumatoid arthritis**

pp 5383–5387

Dearg S. Brown,\* Andrew J. Belfield, George R. Brown, Douglas Campbell, Alan Foubister, David J. Masters, Kurt G. Pike, Wendy L. Snelson and Stuart L. Wells

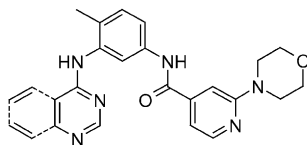


The discovery, rational analogue design, synthesis and SAR of a novel bisamide class of p38 MAP kinase inhibitor are reported. The activity in vitro is described for the series. The activity in vivo and pharmacokinetic properties are exemplified for the more potent analogues, such as **18**.

**Novel, potent and selective anilinoquinazoline and anilinyrimidine inhibitors of p38 MAP kinase**

pp 5389–5394

John G. Cumming,\* Caroline L. McKenzie, Stuart G. Bowden, Douglas Campbell, David J. Masters, Jason Breed and Philip J. Jewsbury

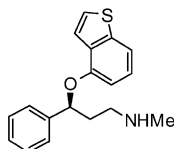


SAR studies led to the identification of 4-(3-benzoylamino-6-methyl-anilino)quinazolines as potent and selective inhibitors of p38 MAP kinase. Further optimisation led to the identification of a series of 4-(3-benzoylamino-6-methyl-anilino)pyrimidines as potent inhibitors of the p38 MAP kinase signalling pathway in vitro and in vivo.

**Benzothienyloxy phenylpropanamines, novel dual inhibitors of serotonin and norepinephrine reuptake**

pp 5395–5399

J. R. Boot, G. Brace, C. L. Delatour, N. Dezutter, J. Fairhurst, J. Findlay, P. T. Gallagher,\* I. Hoes, S. Mahadevan, S. N. Mitchell, R. E. Rathmell, S. J. Richards, R. G. Simmonds, L. Wallace and M. A. Whatton

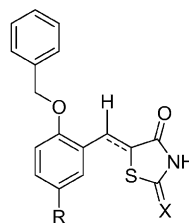


A series of benzothienyloxy phenylpropylamines have been prepared and are demonstrated to be inhibitors of both serotonin and norepinephrine reuptake.

**Synthesis and biological evaluation of thiazolidine-2,4-dione and 2,4-thione derivatives as inhibitors of translation initiation**

pp 5401–5405

Han Chen, Yun-Hua Fan, Amarnath Natarajan, Yuhong Guo, Julia Iyasere, Fred Harbinski, Lia Luus, William Christ, Huseyin Aktas and Jose A. Halperin\*

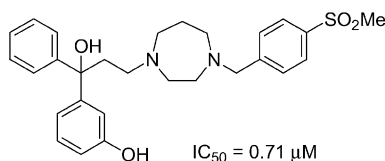


A series of 2'-benzyloxy-5'-substituted-5-benzylidene-thiazolidine-2,4-thione and -dione derivatives was synthesized and evaluated as inhibitors of translation initiation.

**Small molecule inhibitors of the CCR2b receptor. Part 1: Discovery and optimization of homopiperazine derivatives**

pp 5407–5411

Minoru Imai,\* Tatsuki Shiota, Ken-ichiro Kataoka, Christine M. Tarby, Wilna J. Moree, Takaharu Tsutsumi, Masaki Sudo, Michele M. Ramirez-Weinhouse, Daniel Comer, Chung-Ming Sun, Shinsuke Yamagami, Hiroko Tanaka, Takuya Morita, Takahiko Hada, Jonathan Greene, Doug Barnum, John Saunders, Peter L. Myers, Yoshinori Kato and Noriaki Endo



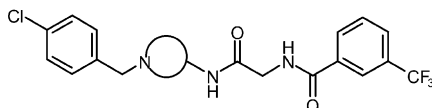
The discovery, the lead optimization, and the structure-activity relationship of *N,N'*-disubstituted homopiperazines are reported.



**Small molecule antagonists of the CCR2b receptor. Part 2: Discovery process and initial structure–activity relationships of diamine derivatives**

pp 5413–5416

Wilna J. Moree,\* Ken-ichiro Kataoka, Michele M. Ramirez-Weinhouse, Tatsuki Shiota, Minoru Imai, Masaki Sudo, Takaharu Tsutsumi, Noriaki Endo, Yumiko Muroga, Takahiko Hada, Hiroko Tanaka, Takuya Morita, Jonathan Greene, Doug Barnum, John Saunders, Yoshinori Kato, Peter L. Myers and Christine M. Tarby

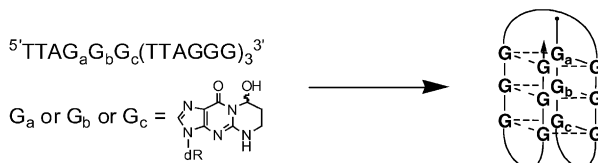


A lead evolution process is described that utilized the SAR of a homopiperazine series for the discovery of alternative cyclic diamine derivatives as nanomolar inhibitors of the interaction between MCP-1 and the CCR2b receptor.

**Effect of  $\gamma$ -hydroxypropano deoxyguanosine, the major acrolein-derived adduct, on monomolecular quadruplex structure of telomeric repeat d(TTAGGG)<sub>4</sub>**

pp 5417–5421

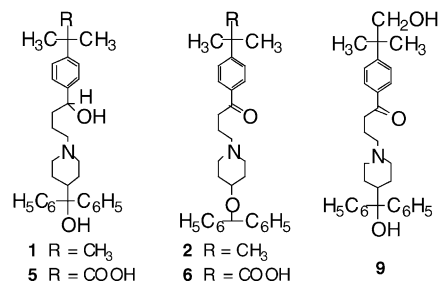
Giuliana D'Isa, Aldo Galeone, Giorgia Oliviero, Gennaro Piccialli, Michela Varra\* and Luciano Mayol

**Microbial oxidation of terfenadine and ebastine into fexofenadine and carebastine**

pp 5423–5426

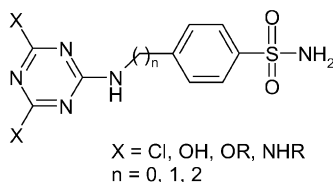
Claire Mazier, Maryse Jaouen, Marie-Agnès Sari and Didier Buisson\*

Fexofenadine **5** and carebastine **6** were obtained in good yield by optimization of culture conditions of microorganisms. Oxidation of **1** into **9** was observed as described in mammalian metabolism.

**Carbonic anhydrase inhibitors: synthesis and inhibition of cytosolic/tumor-associated carbonic anhydrase isozymes I, II, and IX with sulfonamides incorporating 1,2,4-triazine moieties**

pp 5427–5433

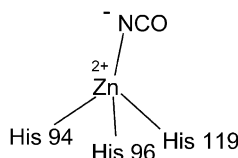
Vladimir Garaj, Luca Puccetti, Giuseppe Fasolis, Jean-Yves Winum, Jean-Louis Montero, Andrea Scozzafava, Daniela Vullo, Alessio Innocenti and Claudiu T. Supuran\*



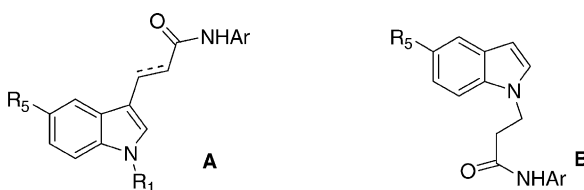
**Carbonic anhydrase inhibitors. Inhibition of the newly isolated murine isozyme XIII with anions**

pp 5435–5439

Alessio Innocenti, Jonna M. Lehtonen, Seppo Parkkila, Andrea Scozzafava and Claudiu T. Supuran\*

**New *N*-pyridinyl(methyl)-indolalkanamides acting as topical inflammation inhibitors**

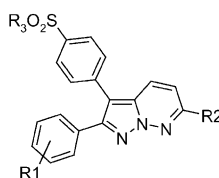
pp 5441–5444

Alexandra Dassonville, Anne Bret  ch  , Johan Evano, Muriel Duflos,\*  
Guillaume le Baut, Nicole Grimaud and Jean-Yves Petit

$R_1 = \text{H, Bn, 4Cl-Bn, morpholinoethyl}; R_5 = \text{H, Cl}$   
 $\text{Ar} = 4\text{-aminopyridine, 3-picolylamine or 2-amino-4,6-dimethylpyridine}$

**Identification of 2,3-diaryl-pyrazolo[1,5-*b*]pyridazines as potent and selective cyclooxygenase-2 inhibitors** pp 5445–5448

Paul Beswick, Sharon Bingham, Chas Bountra, Terry Brown, Kerry Browning, Ian Campbell, Iain Chessell, Nick Clayton, Sue Collins, John Corfield, Stephen Guntrip, Claudine Haslam, Paul Lambeth, Fiona Lucas, Neil Mathews, Graham Murkit, Alan Naylor,\* Neil Pegg, Elizabeth Pickup, Hazel Player, Helen Price, Alexander Stevens, Sharon Stratton and Joanne Wiseman



**OTHER CONTENTS**

Corrigendum  
Contributors to this issue  
Instructions to contributors

p 5449  
pp I–II  
pp III–VI

\*Corresponding author

**COVER**

Carbonic anhydrase (CA) isozyme XIII (CA XIII), a cytosolic isoform recently described, is able to catalyze carbon dioxide hydration to bicarbonate in the presence of high concentrations of bicarbonate/chloride, unlike CA I or CA II (other cytosolic isoforms) from which it mainly differs by the amino acid in position 200 (His in CA I, Thr in CA II and Val in CA XIII). The CA XIII resistance to inhibition by these physiological anions (bicarbonate and chloride) suggests an evolutionary adaptation of this isozyme to the presence of high concentrations of such anions, for example in the reproductive tract of both female and male, and its participation in metabolons with proteins involved in the anion exchange and transport, such as the anion exchangers (AE1-3) or the sodium bicarbonate cotransporter (NBC1 and NBC3) proteins [Innocenti, A.; Lehtonen, J. M.; Parkkila, S.; Scozzafava, A.; Supuran, C. T. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5435–5439].

Part of this cover graphic has been taken from the following paper: Lehtonen, J.; Shen, B.; Vihinen, M.; Casini, A.; Scozzafava, A.; Supuran, C. T.; Parkkila, A.-K.; Saarnio, J.; Kivelä, A. J.; Waheed, A.; Sly, W. S.; Parkkila, S. *J. Biol. Chem.* **2004**, *279*, 2719–2727.  
© 2004 by the American Society for Biochemistry and Molecular Biology.



Full text of this journal is available, on-line from **ScienceDirect**. Visit [www.sciencedirect.com](http://www.sciencedirect.com) for more information.

**CONTENTS**  
**Direct**

This journal is part of **ContentsDirect**, the *free* alerting service which sends tables of contents by e-mail for Elsevier books and journals. You can register for **ContentsDirect** online at: <http://contentsdirect.elsevier.com>

Indexed/Abstracted in: Adis LMS Drug Alerts, Beilstein, Biochemistry & Biophysics Citation Index, BIOSIS previews, CAB Abstracts, CAB Health, CANCERLIT, Chemical Abstracts, Chemistry Citation Index, Current Awareness in Biological Sciences/Elsevier BIOBASE, Current Contents: Life Sciences, EMBASE/Excerpta Medica, MEDLINE, PASCAL, Research Alert, Science Citation Index, SciSearch, TOXFILE



ISSN 0960-894X