ELSEVIER

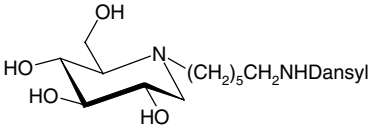
Bioorganic & Medicinal Chemistry Letters

Bioorganic & Medicinal Chemistry Letters Vol. 16, No. 8, 2006

# Contents

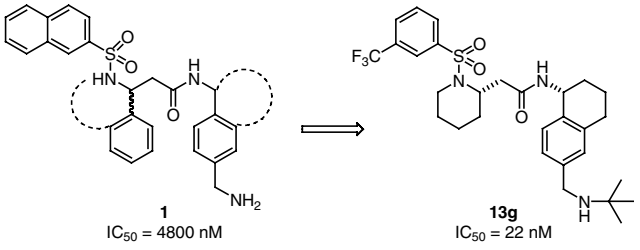
## ARTICLES

**Fluorescent glycosidase inhibiting 1,5-dideoxy-1,5-iminoalditols** pp 2067–2070
Peter Greimel, Herwig Häusler, Inge Lundt, Karen Rupitz, Arnold E. Stütz,* Chris A. Tarling, Stephen G. Withers and Tanja M. Wrodnigg



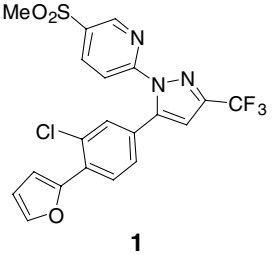

**A new class of bradykinin 1 receptor antagonists containing the piperidine acetic acid tetralin core** pp 2071–2075
Christopher Fotsch,* Gloria Biddlecome, Kaustav Biswas, Jian Jeff Chen, Derin C. D'Amico, Robert D. Groneberg, Nianhe Bruce Han, Feng-Yin Hsieh, Augustus Kamassah, Gondi Kumar, Dianna Lester-Zeiner, Qingyian Liu, David A. Mareska, Babak Bobby Riahi, Yueh-Ju Judy Wang, Kevin Yang, James Zhan, Joe Zhu, Eileen Johnson, Gordon Ng and Benny C. Askew

Compound **1** was an early lead in our bradykinin 1 receptor antagonist program. By adding two conformational constraints to this compound and by exploring the SAR of the aryl sulfonamide and terminal amine groups, we identified compound **13g**, which was 220-fold more potent than compound **1** and selective over the bradykinin 2 receptor.




**Synthesis and SAR of heteroaryl-phenyl-substituted pyrazole derivatives as highly selective and potent canine COX-2 inhibitors** pp 2076–2080
Hengmiao Cheng,* Kristin M. Lundy DeMello, Jin Li, Subas M. Sakya, Kazuo Ando, K. Kawamura, Tomoki Kato, Robert J. Rafka, Burton H. Jaynes, Carl B. Ziegler, Rod Stevens, Lisa A. Lund, Donald W. Mann, Carolyn Kilroy, Michelle L. Haven, Erik L. Nimz, Jason K. Dutra, Chao Li, Martha L. Minich, Nicole L. Kolosko, Carol Petras, Annette M. Silvia and Scott B. Seibel

The discovery of heteroaryl-phenyl-substituted pyrazole derivatives as canine selective COX-2 inhibitors is described. Structure–activity relationship (SAR) studies of this class of compounds led to the identification of compound **1** which demonstrated a canine whole blood COX-2 inhibitory $IC_{50}$ of 12 nM and selectivity ratio of COX-1/COX-2 greater than 4000-fold.

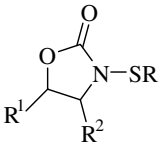



**1**

**N-thiolated 2-oxazolidinones: A new family of antibacterial agents for methicillin-resistant *Staphylococcus aureus* and *Bacillus anthracis*** **pp 2081–2083**

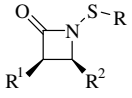
Rajesh Kumar Mishra, Kevin D. Revell, Cristina M. Coates, Edward Turos,* Sonja Dickey and Daniel V. Lim

A new family of N-thiolated 2-oxazolidinones having antibacterial activity against methicillin-resistant *Staphylococcus aureus* and *Bacillus anthracis* is reported. The effect of ring substituents and stereochemistry on antibacterial activity of these compounds was found to be similar to that of previously reported N-thiolated β-lactams.



**N-Thiolated β-lactams: A new family of anti-*Bacillus* agents** **pp 2084–2090**

Edward Turos,* Timothy E. Long, Bart Heldreth, J. Michelle Leslie, G. Suresh Kumar Reddy, Yang Wang, Cristina Coates, Monika Konaklieva, Sonja Dickey, Daniel V. Lim, Eduardo Alonso and Javier Gonzalez



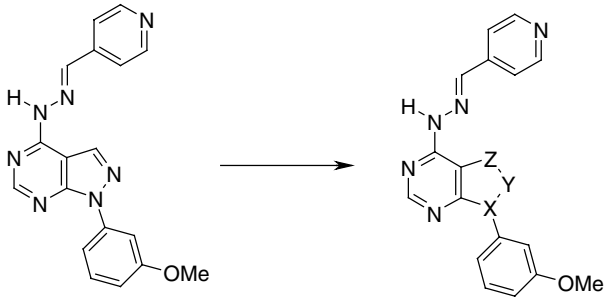
**1**

The evaluation of *N*-thiolated β-lactam antibiotics **1** as potential anti-*Bacillus* agents is reported.

**Synthesis and evaluation of novel heterocyclic inhibitors of GSK-3** **pp 2091–2094**

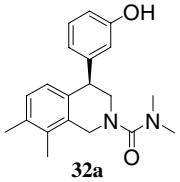
Terrence L. Smalley, Jr.,* Andrew J. Peat, Joyce A. Boucheron, Scott Dickerson, Dulce Garrido, Frank Preugschat, Stephanie L. Schweiker, Stephen A. Thomson and Tony Y. Wang

Novel heterocyclic GSK-3 inhibitors based on a previously described template have been synthesized as a potential treatment for diabetes. Several compounds exhibited excellent potency which could be rationalized using ab initio calculations.



**Inhibitors of human mitotic kinesin Eg5: Characterization of the 4-phenyl-tetrahydroisoquinoline lead series** **pp 2095–2100**

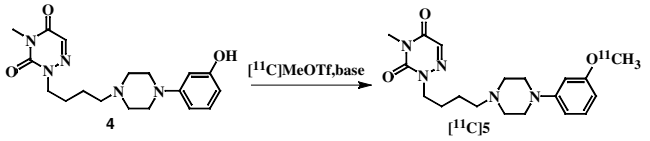
Christine M. Tarby,* Robert F. Kaltenbach, III, Tram Huynh, Andrew Pudzianowski, Henry Shen, Marie Ortega-Nanos, Steven Sheriff, John A. Newitt, Patricia A. McDonnell, Neil Burford, Craig R. Fairchild, Wayne Vaccaro, Zhong Chen, Robert M. Borzilleri, Joseph Naglich, Louis J. Lombardo, Marco Gottardis, George L. Trainor and Deborah L. Roussell



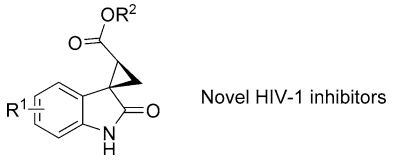
**32a**

ATPase $IC_{50}$ 104 nM

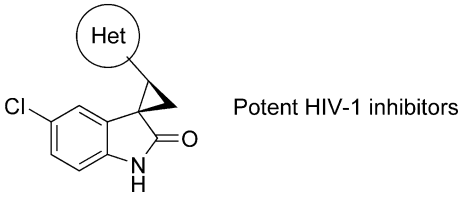
**Synthesis, in vitro and in vivo evaluation of [*O*-methyl-$^{11}$C] 2-{4-[4-(3-methoxyphenyl)piperazin-1-yl]-butyl}-4-methyl-2*H*-[1,2,4]-triazine-3,5-dione: A novel agonist 5-HT$_{1A}$ receptor PET ligand** **pp 2101–2104**
Jaya Prabhakaran, Ramin V. Parsey, Vattoly J. Majo, Shu-Chi Hsiung, Matthew S. Milak, Hadassah Tamir, Norman R. Simpson, Ronald L. Van Heertum, J. John Mann and J.S. Dileep Kumar*




**Design, synthesis and biological evaluations of novel oxindoles as HIV-1 non-nucleoside reverse transcriptase inhibitors. Part I** **pp 2105–2108**
Tao Jiang, Kelli L. Kuhen, Karen Wolff, Hong Yin, Kimberly Bieza, Jeremy Caldwell, Badry Bursulaya, Tom Yao-Hsing Wu and Yun He*

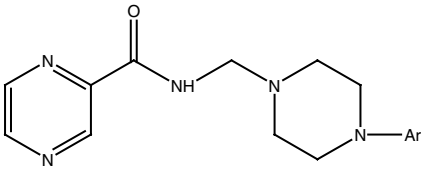



**Design, synthesis, and biological evaluations of novel oxindoles as HIV-1 non-nucleoside reverse transcriptase inhibitors. Part 2** **pp 2109–2112**
Tao Jiang, Kelli L. Kuhen, Karen Wolff, Hong Yin, Kimberly Bieza, Jeremy Caldwell, Badry Bursulaya, Tove Tuntland, Kanyin Zhang, Donald Karanewsky and Yun He*




**Synthesis of pyrazinamide Mannich bases and its antitubercular properties** **pp 2113–2116**
Dharmarajan Sriram,* Perumal Yogeeswari and Sushma Pobba Reddy

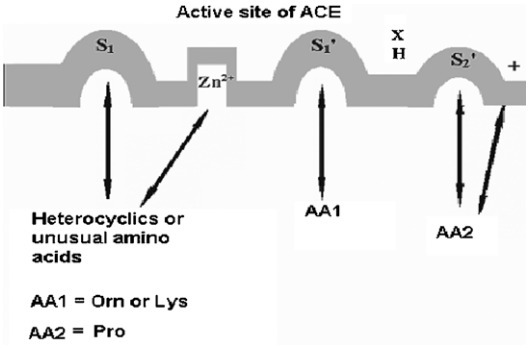
A series of pyrazinamide Mannich bases has been synthesized and evaluated for antimycobacterial activity in vitro and in vivo against *Mycobacterium tuberculosis* H37Rv. 1-Cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-4-((pyrazine-2-carboxamido)methyl)piperazin-1-yl)-4-oxoquinoline-3-carboxylic acid (**17**) was found to be the most active compound in vitro with MIC of 0.39 and 0.2 μg/mL against MTB and multidrug-resistant MTB, respectively. In the in vivo animal model, **17** decreased the bacterial load in lung and spleen tissues with 1.86 and 1.66-log10 protections, respectively.



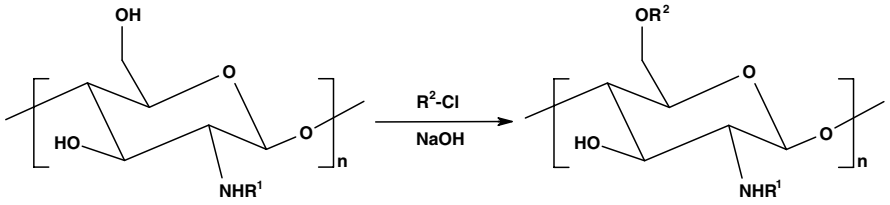

**1-17**

**Structure–activity relationship study between Ornithyl-Proline and Lysyl-Proline based tripeptidomimics as angiotensin-converting enzyme inhibitors** **pp 2117–2121**
Mahesh Chand Pavar, Kashif Hanif, Amir Azam, Sneh lata, M. A. Qadar Pasha and Santosh Pasha*

A designed library of tripeptidomimics of Ornithyl-Proline (Orn-Pro) and Lysyl-Proline (Lys-Pro), conjugated with various unnatural amino acids and carboxylic acid derived heterocyclics, was designed and synthesized as possible angiotensin-converting enzyme (ACE) inhibitors.




**Cytotoxic activities of water-soluble chitosan derivatives with different degree of deacetylation** **pp 2122–2126**
Jae-Young Je, Young-Sook Cho and Se-Kwon Kim*

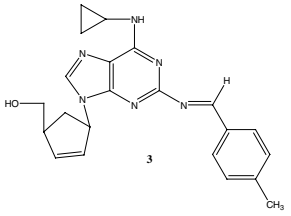



AE-chitosan :$R^1$ =H, $COCH_3$; $R^2$=$(CH_2)_2NH_2$

DMAE-chitosan :$R^1$=H, $COCH_3$; $R^2$=$(CH_2)_2N(CH_3)_2$

DEAE-chitosan :$R^1$=H, $COCH_3$; $R^2$=$(CH_2)_2N(CH_2CH_3)_2$

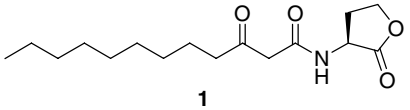
**Abacavir prodrugs: Microwave-assisted synthesis and their evaluation of anti-HIV activities** **pp 2127–2129**
Dharmarajan Sriram,* Perumal Yogeeswari, Naga Sirisha Myneedu and Vivek Saraswat




3

The synthesis of a new series of abacavir prodrugs involving $N^2$-substitution with various substituted benzaldehyde and ketone derivatives is described. The in vitro anti-HIV activities indicated that compound (3-(2-(4-methylaminobenzylideneamino)-6-(cyclopropylamino)-9*H*-purin-9-yl)cyclopentyl)methanol (**3**) was found to be most potent compound with $EC_{50}$ of 0.05 μM and $CC_{50}$ of >100 μM with selectivity index of >2000.

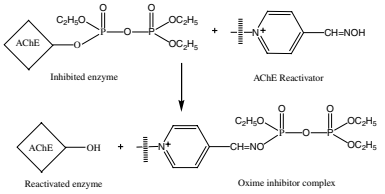
**Synthesis of *Pseudomonas* quorum-sensing autoinducer analogs and structural entities required for induction of apoptosis in macrophages** **pp 2130–2133**
Manabu Horikawa,* Kazuhiro Tateda, Etsu Tuzuki, Yoshikazu Ishii, Chihiro Ueda, Tohru Takabatake, Shinichi Miyairi, Keizou Yamaguchi and Masaji Ishiguro



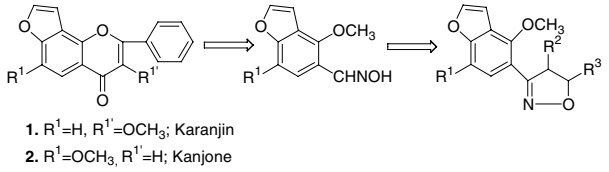

1

Synthesis of analogs of *Pseudomonas* quorum-sensing autoinducer, *N*-3-oxododecanoyl-L-homoserine lactone (**1**) and their structure–activity relationship for the apoptosis induction in macrophages are described.

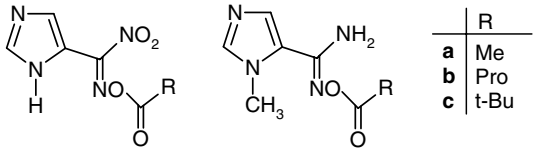
**Quaternary salts of 4,3′ and 4,4′ bis-pyridinium monooximes. Part 2: Synthesis and biological activity** **pp 2134–2138**
Chennamaneni Srinivas Rao, Vobalaboina Venkateswarlu* and Garlapati Achaiah



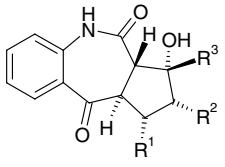

**Synthesis of novel benzofuran isoxazolines as protein tyrosine phosphatase 1B inhibitors** **pp 2139–2143**
Ghufran Ahmad, Pushpesh K. Mishra, Prasoon Gupta, Prem P. Yadav, Priti Tiwari, Akhilesh K. Tamrakar, Arvind K. Srivastava and Rakesh Maurya*



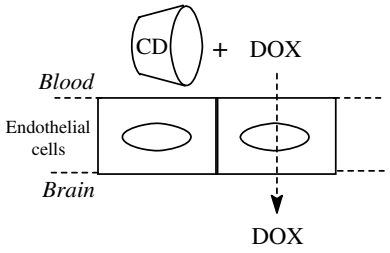

**Synthesis and ocular effects of imidazole nitrolic acid and amidoxime esters** **pp 2144–2147**
Larisa Oresmaa, Hanna Kotikoski, Matti Haukka, Olli Oksala, Esko Pohjala, Heikki Vapaatalo, Pirjo Vainiotalo and Paula Aulaskari*




**Matrix compare analysis discriminates subtle structural differences in a family of novel antiproliferative agents, diaryl-3-hydroxy-2,3,3a,10a-tetrahydrobenzo[*b*]cyclopenta[*e*]azepine-4,10(1*H*,5*H*)-diones** **pp 2148–2153**
Conrad Kunick,* Carola Bleeker, Christian Prühs, Frank Totzke, Christoph Schächtele, Michael H. G. Kubbutat and Andreas Link



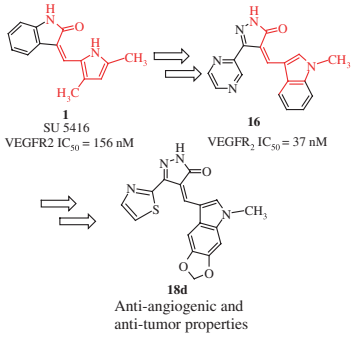
**Methylated β-cyclodextrin as P-gp modulators for deliverance of doxorubicin across an in vitro model of blood–brain barrier** pp 2154–2157
Sébastien Tilloy,* Véronique Monnaert, Laurence Fenart, Hervé Bricout, Roméo Cecchelli and Eric Monflier



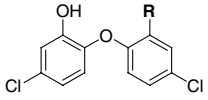

Methylated β-cyclodextrins (CDs) are used to increase the brain delivery of doxorubicin (DOX) by modifying the P-gp activity.

**Structure-guided identification of novel VEGFR-2 kinase inhibitors via solution phase parallel synthesis** pp 2158–2162
Rabindranath Tripathy,* Alyssa Reiboldt, Patricia A. Messina, Mohamed Iqbal, Jasbir Singh, Edward R. Bacon, Thelma S. Angeles, Shi X. Yang, Mark S. Albom, Candy Robinson, Hong Chang, Bruce A. Ruggeri and John P. Mallamo

Structural analysis of the essential binding elements of the oxindole-based kinase inhibitor (**1**) led to the identification of a novel class of heterocyclic-substituted pyrazolones. Knoevenagel condensation of a variety of activated methylene nucleophiles with indole or pyrrole carboxaldehydes provided a focused library of molecules, each containing elements of kinase pharmacophore probe. Initial screening for VEGFR-2 kinase inhibition eliminated several of the probes. Identification of an active pyrazolone motif and further optimization resulted in several highly potent VEGFR-2 inhibitors with cellular efficacy, anti-angiogenic activity ex vivo in rat aortic ring explant cultures, and oral anti-tumor efficacy in nude mice.

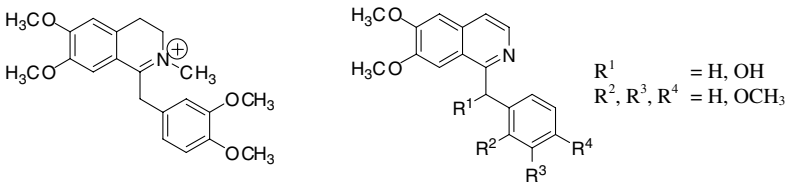



**Synthesis and biological activity of diaryl ether inhibitors of malarial enoyl acyl carrier protein reductase. Part 2: 2′-Substituted triclosan derivatives** pp 2163–2169
Joel S. Freundlich,* Min Yu, Edinson Lucumi, Mack Kuo, Han-Chun Tsai, Juan-Carlos Valderramos, Luchezar Karagyozov, William R. Jacobs, Jr., Guy A. Schiehser, David A. Fidock, David P. Jacobus and James C. Sacchettini



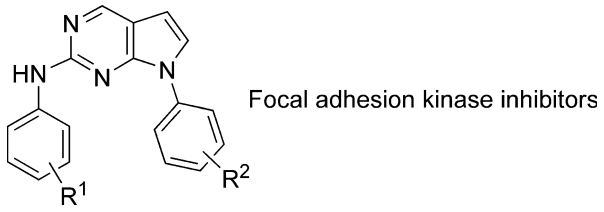

Inhibitors of *Plasmodium falciparum* enoyl acyl carrier protein reductase are presented that demonstrate nanomolar anti-parasitic efficacy.

**Isoquinoline derivatives as potential acetylcholinesterase inhibitors** pp 2170–2172
Sutthatip Markmee, Somsak Ruchirawat, Vilailak Prachyawarakorn, Kornkanok Ingkaninan and Nantaka Khorana*

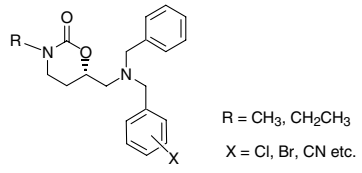



A series of seventeen 1-benzylisoquinoline derivatives were evaluated for acetylcholinesterase enzyme inhibition. Some of isoquinoline derivatives have shown 50% inhibition for acetylcholinesterase enzyme ($IC_{50}$) in micromolar range.

**Design and synthesis of 7*H*-pyrrolo[2,3-*d*]pyrimidines as focal adhesion kinase inhibitors. Part 1** **pp 2173–2176**
Ha-Soon Choi, Zhicheng Wang, Wendy Richmond, Xiaohui He, Kunyong Yang, Tao Jiang, Taebo Sim, Donald Karanewsky, Xiang-ju Gu, Vicki Zhou, Yi Liu, Osamu Ohmori, Jeremy Caldwell, Nathanael Gray and Yun He*

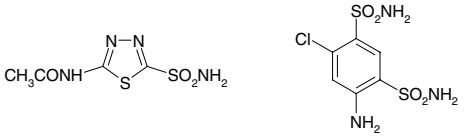



**Synthesis and antibacterial activities of chiral 1,3-oxazinan-2-one derivatives** **pp 2177–2181**
Guijun Wang,* Jean-Rene Ella-Menye and Vibha Sharma

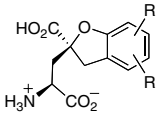



The compounds exhibit interesting antibacterial activities toward Gram-positive bacteria. The oxazinan-2-one is a new chiral heterocycle for potentially new class of antimicrobials.

**Carbonic anhydrase inhibitors: Cloning and sulfonamide inhibition studies of a carboxyterminal truncated α-carbonic anhydrase from *Helicobacter pylori*** **pp 2182–2188**
Isao Nishimori, Daniela Vullo, Tomoko Minakuchi, Kaori Morimoto, Saburo Onishi, Andrea Scozzafava and Claudiu T. Supuran*

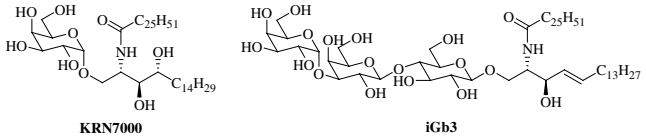


**Design, synthesis, and biological evaluation of a scaffold for iGluR ligands based on the structure of (−)-dysiherbaine** **pp 2189–2194**
Jamie L. Cohen, Agenor Limon, Ricardo Miledi and A. Richard Chamberlin*

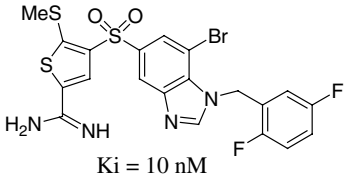


The design, synthesis, and iGluR activity of a series of 2,2-disubstituted dihydrobenzofurans that are structurally related to several glutamate containing natural products, including (−)-dysiherbaine, is described.

**Synthesis and biological evaluation of α-galactosylceramide (KRN7000) and isoglobotrihexosylceramide (iGb3)** pp 2195–2199
Chengfeng Xia, Qingjia Yao, Jens Schümann, Emmanuel Rossy, Wenlan Chen, Lizhi Zhu, Wenpeng Zhang, Gennaro De Libero and Peng George Wang*

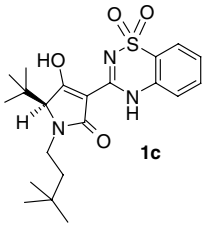



**A novel series of arylsulfonylthiophene-2-carboxamidine inhibitors of the complement component C1s** pp 2200–2204
Nalin L. Subasinghe,* Jeremy M. Travins, Farah Ali, Hui Huang, Shelley K. Ballentine, Juan José Marugán, Ehab Khalil, Heather R. Hufnagel, Roger F. Bone, Renee L. DesJarlais, Carl S. Crysler, Nisha Ninan, Maxwell D. Cummings, Christopher J. Molloy and Bruce E. Tomczuk

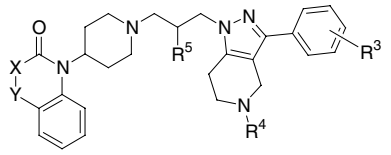



**An efficient, asymmetric solid-phase synthesis of benzothiadiazine-substituted tetramic acids: Potent inhibitors of the hepatitis C virus RNA-dependent RNA polymerase** pp 2205–2208
Karen A. Evans,* Deping Chai, Todd L. Graybill, George Burton, Robert T. Sarisky, Juili Lin-Goerke, Victor K. Johnston and Ralph A. Rivero

Solid-phase synthesis and SAR are described for a series of benzothiadiazine-substituted tetramic acid inhibitors of the hepatitis C virus RNA-dependent RNA polymerase, NS5B.

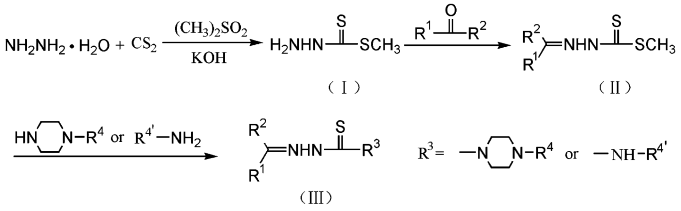



**The SAR of 4-substituted (6,6-bicyclic) piperidine cathepsin S inhibitors** pp 2209–2212
Cheryl A. Grice,* Kevin Tays, Haripada Khatuya, Darin J. Gustin, Christopher R. Butler, Jianmei Wei, Clark A. Sehon, Siquan Sun, Yin Gu, Wen Jiang, Robin L. Thurmond, Lars Karlsson and James P. Edwards



Noncovalent, potent, and selective inhibitors of the cysteine protease cathepsin S are reported.

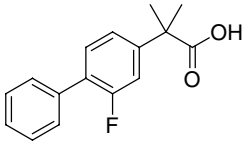
**Synthesis and anticancer activity of thiosemicarbazones** **pp 2213–2218**
Wei-xiao Hu,* Wei Zhou, Chun-nian Xia and Xi Wen



Twenty-six thiosemicarbazones (III-1–III-26) were synthesized via three steps starting from hydrazine hydrate and carbon disulfide. Their anticancer activities in vitro were evaluated. It shows that compounds III-15 and III-16 possess a higher inhibitory ability against P-388 and SGC-7901. Further testing shows that the value of $IC_{50}$ of compound III-16 against SGC-7901 reaches to 0.032 μM.

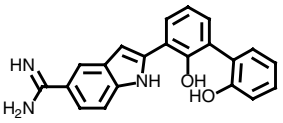
**The geminal dimethyl analogue of Flurbiprofen as a novel $A\beta_{42}$ inhibitor and potential Alzheimer's disease modifying agent** **pp 2219–2223**
Nicholas Stock,* Benito Munoz, Jonathan D. J. Wrigley, Mark S. Shearman, Dirk Beher, James Peachey, Toni L. Williamson, Gretchen Bain, Weichao Chen, Xiaohui Jiang, René St-Jacques and Peppi Prasit

The subtle modification of a selection of $A\beta_{42}$ inhibiting non-steroidal anti-inflammatory drugs (NSAIDs), through synthesis of the geminal dimethyl derivatives, was anticipated to ablate their cyclooxygenase activity whilst maintaining potency at $A\beta_{42}$ inhibition. One such compound, methylflurbiprofen, exhibited similar in vitro $A\beta_{42}$ inhibition to its parent NSAID Flurbiprofen and was further evaluated in the TG2576 mouse model of Alzheimer's disease and an animal model of gastro-intestinal (GI) impairment.



**Methylflurbiprofen**

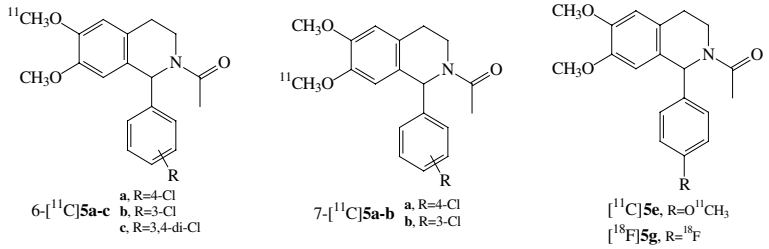
**Factor VIIa inhibitors: A prodrug strategy to improve oral bioavailability** **pp 2224–2228**
Jennifer R. Riggs,* Aleksandr Kolesnikov, John Hendrix, Wendy B. Young, William D. Shrader, Dange Vijaykumar, Robin Stephens, Liang Liu, Lin Pan, Joyce Mordenti, Michael J. Green and Juthamas Sukbuntherng



**3**

We have developed a series of potent and selective factor VIIa inhibitors based on the 2-[5-(5-carbamimidoyl-1H-benzoimidazol-2-yl)-6-hydroxy-biphenyl-3-yl]-succinic acid scaffold. These amidine-containing compounds have low oral bioavailability. Herein, we describe our efforts to improve the oral bioavailability of the parent amidine **3** via a prodrug strategy where the amidine basicity and polarity were reduced with either an alkoxy amidine or a carbamate prodrug.

**Synthesis of carbon-11 and fluorine-18 labeled *N*-acetyl-1-aryl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline derivatives as new potential PET AMPA receptor ligands** **pp 2229–2233**
Mingzhang Gao, Deyuan Kong, Abraham Clearfield and Qi-Huang Zheng*



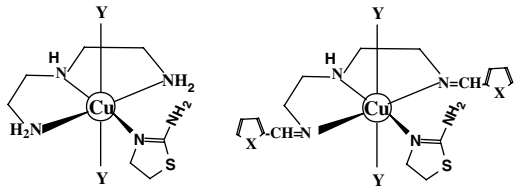
6-[$^{11}$C]**5a-c** **a**, R=4-Cl **b**, R=3-Cl **c**, R=3,4-di-Cl

7-[$^{11}$C]**5a-b** **a**, R=4-Cl **b**, R=3-Cl

[$^{11}$C]**5e**, R=O$^{11}$CH$_3$

[$^{18}$F]**5g**, R=$^{18}$F

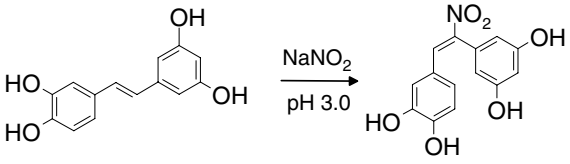
**Evaluation of anti-inflammatory and antioxidant activities of mixed-ligand Cu(II) complexes of dien and its Schiff dibases with heterocyclic aldehydes and 2-amino-2-thiazoline** pp 2234–2237
E. Pontiki, D. Hadjipavlou-Litina,* A. T. Chaviara and C. A. Bolos




Y = Cl, Br, $NO_3$ X = O, S, NH and Y = Cl, Br, $NO_3$

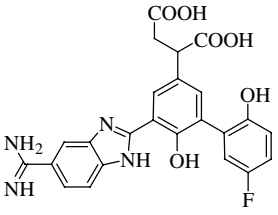
The anti-inflammatory and antioxidant activity of complexes of the type [Cu(dien)(2a-2tzn)$Y_2$] and [Cu(dienXX)(2a-2tzn)$Y_2$] is reported. Some of these compounds inhibit the carrageenin induced paw edema and present significant scavenging activity.

**The catecholic antioxidant piceatannol is an effective nitrosation inhibitor via an unusual double bond nitration** pp 2238–2242
Maria De Lucia, Lucia Panzella, Orlando Crescenzi, Alessandra Napolitano, Vincenzo Barone and Marco d'Ischia*

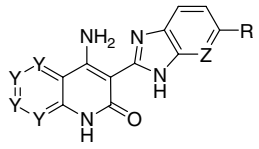



**Factor VIIa inhibitors: Improved pharmacokinetic parameters** pp 2243–2246
Aleksandr Kolesnikov,* Roopa Rai, Wendy B. Young, Joyce Mordenti, Liang Liu, Steven Torkelson, William D. Shrader, Ellen M. Leahy, Huiyong Hu, Erik Gjerstad, James Janc, Bradley A. Katz and Paul A. Sprengeler

Efforts to improve the potency and pharmacokinetic properties of small molecule factor VIIa inhibitors are described. Small structural modifications to existing leads allow the modulation of half-life and clearance, potentially making these compounds suitable candidates for drug development.

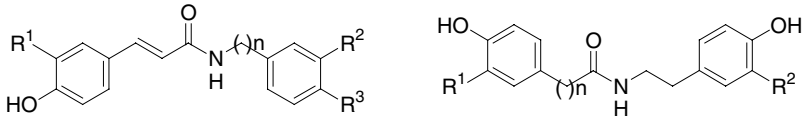



**Design and structure–activity relationship of heterocyclic analogs of 4-amino-3-benzimidazol-2-ylhydroquinolin-2-ones as inhibitors of receptor tyrosine kinases** pp 2247–2251
Kelly Frazier, Elisa Jazan, Christopher M. McBride, Sabina Pecchi, Paul A. Renhowe, Cynthia M. Shafer,* Clarke Taylor, Dirksen Bussiere, Molly Min He, Johanna M. Jansen, Gena Lapointe, Sylvia Ma, Jayesh Vora and Marion Wiesmann



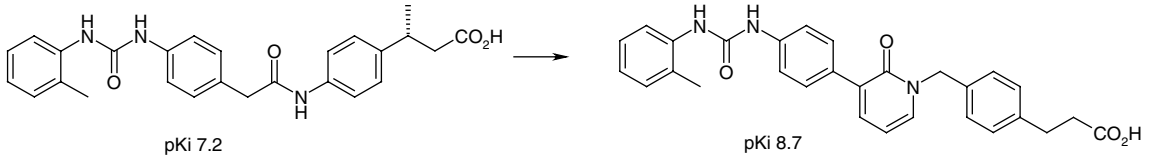

The synthesis and SAR of a series of novel heterocyclic analogs of the 4-amino-3-benzimidazol-2-ylhydroquinolin-2-one scaffold are reported.

**Analogues of *N*-hydroxycinnamoylphenalkylamides as inhibitors of human melanocyte-tyrosinase** **pp 2252–2255**
Sabrina Okombi, Delphine Rival, Sébastien Bonnet, Anne-Marie Mariotte, Eric Perrier and Ahcène Boumendjel*



Amides obtained by coupling caffeic acid, ferulic acid, *p*-hydroxycinnamic acid, and analogues with substituted phenylalkylamines were evaluated as inhibitors of the human melanocyte-tyrosinase. The most active compounds induce a complete enzyme-inactivation at 100 μM. At the latter concentration, kojic acid, used as a reference, was inactive.

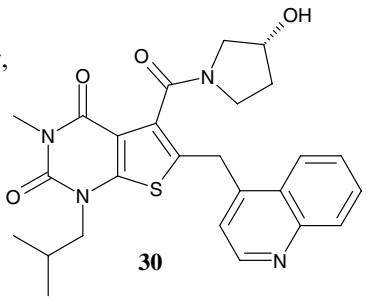
**Pyridone derivatives as potent and selective VLA-4 integrin antagonists** **pp 2256–2259**
Jason Witherington,* Vincent Bordas, Alessandra Gaiba, Phil M. Green, Antoinette Naylor, Nigel Parr, David G. Smith, Andrew K. Takle and Robert W. Ward



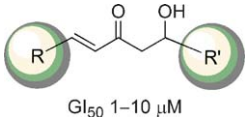

Employing molecular overlay studies of our initial leads with known VLA-4 antagonists has led to the hypothesis of a novel pharmacophore. Subsequent design and synthesis of analogues exploiting this hypothesis has afforded a novel series of potent and selective VLA-4 antagonists.

**Potent blockers of the monocarboxylate transporter MCT1: Novel immunomodulatory compounds** **pp 2260–2265**
S. D. Guile,* J. R. Bantick, D. R. Cheshire, M. E. Cooper, A. M. Davis, D. K. Donald, R. Evans, C. Eyssade, D. D. Ferguson, S. Hill, R. Hutchinson, A. H. Ingall, L. P. Kingston, I. Martin, B. P. Martin, R. T. Mohammed, C. Murray, M. W. D. Perry, R. H. Reynolds, P. V. Thorne, D. J. Wilkinson and J. Withnall

The synthesis and properties of a novel series of potent blockers of the monocarboxylate transporter, MCT1, are described. These compounds, exemplified by **30**, show potent immunomodulatory activity.

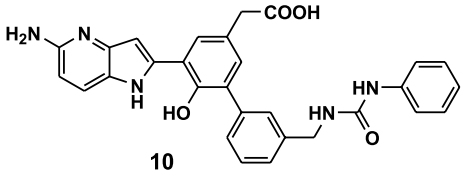



**β′-Hydroxy-α,β-unsaturated ketones: A new pharmacophore for the design of anticancer drugs** **pp 2266–2269**
José M. Padrón,* Pedro O. Miranda, Juan I. Padrón and Víctor S. Martín




The in vitro antitumor activity of diverse α,β-unsaturated ketones is reported.

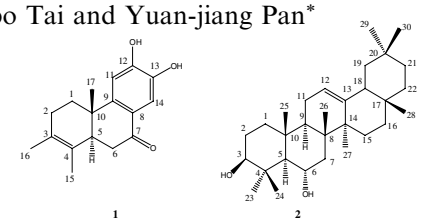
**Discovery of novel heterocyclic factor VIIa inhibitors** **pp 2270–2273**
Roopa Rai,* Aleksandr Kolesnikov, Paul A. Sprengeler, Steven Torkelson, Tony Ton, Bradley A. Katz, Christine Yu, John Hendrix, William D. Shrader, Robin Stephens, Ronnell Cabuslay, Ellen Sanford and Wendy B. Young



10

The structure activity relationships and binding mode of novel heterocyclic Factor VIIa inhibitors will be described. In these inhibitors, a highly basic 5-amidinoindole moiety has been successfully replaced with a less basic 5-aminopyrrolo[3,2-*b*]pyridine scaffold.

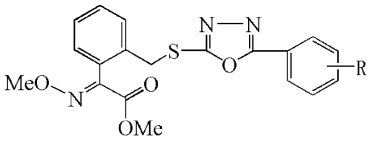
**Novel skeleton terpenes from *Celastrus hypoleucus* with anti-tumor activities** **pp 2274–2277**
Kui-wu Wang, Jian-shan Mao, Yuan-po Tai and Yuan-jiang Pan*


1 2

The structure of compound **1** and **2**

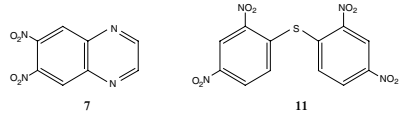
Celahypodiol **1**, an unusual 17-membered carbon diterpenoid with a novel skeleton, and a new triterpenoid 12-oleanene-3β,6α-diol **2**, together with four known compounds, were isolated from the stalks of *Celastrus hypoleucus* (Oliv.) Warb. Their structures were established by means of spectroscopic analysis, including 2D NMR. The new compounds exhibited anti-tumor activities against a panel of human tumor cell lines.

**Stereoselective synthesis and fungicidal activities of (*E*)-α-(methoxyimino)-benzeneacetate derivatives containing 1,3,4-oxadiazole ring** **pp 2278–2282**
Yan Li,* Jie Liu, Hongquan Zhang, Xiangping Yang and Zhaojie Liu




Fifteen novel (*E*)-α-(methoxyimino)-benzeneacetate derivatives containing 1,3,4-oxadiazole ring were stereoselectively synthesized. All of these derivatives exhibited potent fungicidal activity against *Rhizoctonia solani*, *Botrytis cinereapers*, *Gibberella zeae*, *Physalospora piricola* and *Bipolaris mayclis*.

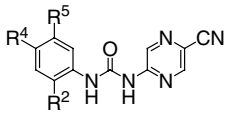
**Specific inhibitors of *Plasmodium falciparum* thioredoxin reductase as potential antimalarial agents** **pp 2283–2292**
A. D. Andricopulo, M. B. Akoachere, R. Krogh, C. Nickel, M. J. McLeish, G. L. Kenyon, L. D. Arscott, C. H. Williams, Jr., E. Davioud-Charvet* and K. Becker*



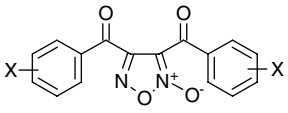
7 11

Uncompetitive inhibition of *Plasmodium falciparum* thioredoxin reductase by nitrophenyl derivatives.

**Synthesis and biological evaluation of 1-(2,4,5-trisubstituted phenyl)-3-(5-cyanopyrazin-2-yl)ureas as potent Chk1 kinase inhibitors** **pp 2293–2298**
Gaoquan Li,* Lisa A. Hasvold, Zhi-Fu Tao, Gary T. Wang, Stephen L. Gwaltney, II, Jyoti Patel, Peter Kovar, Robert B. Credo, Zehan Chen, Haiying Zhang, Chang Park, Hing L. Sham, Thomas Sowin, Saul H. Rosenberg and Nan-Horng Lin

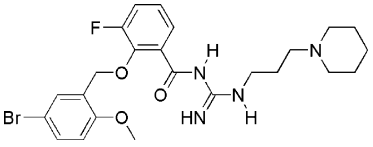



**Synthesis and evaluation of NO-release from symmetrically substituted furoxans** **pp 2299–2301**
William F. Nirode,* Jessica M. Luis, Jordan F. Wicker and Nanette M. Wachter



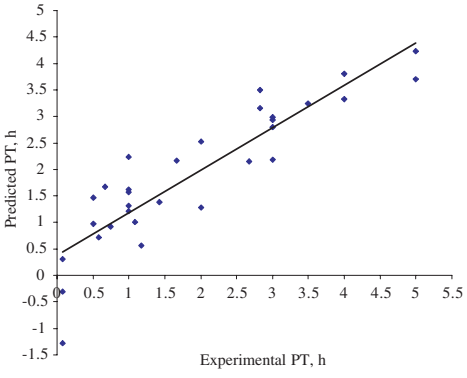

The effect of phenyl ring substituents on nitric oxide release from symmetrically substituted dibenzoylfuroxans (3,4-dibenzoyl-1,2,5-oxadiazole-2-oxides) was evaluated using the Griess reagent method.

**Identification and structure–activity relationships of a new series of Melanocortin-4 receptor antagonists** **pp 2302–2305**
Tricia J. Vos,* Suresh Balani, Christopher Blackburn, Ryan W. Chau, M. Diana Danca, Stacey V. Drabic, Cheryl A. Farrer, Michael A. Patane, Stephen G. Stroud, David L. Yowe and Christopher F. Claiborne




**QSAR study of mosquito repellents using Codessa Pro** **pp 2306–2311**
Alan R. Katritzky,* Dimitar A. Dobchev, Indrek Tulp, Mati Karelson and David A. Carlson

A QSAR treatment has been applied to a data set consists of 31 protection times for the repellents. A good 4-parameter model was found including the vapor pressure as external descriptor.



## OTHER CONTENTS

**Erratum** **p 2312**
**Summary of instructions to authors** **p I**

*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

## COVER

View of the crystal structure of the DB819-d(CGCGAATTCGCG)$_2$ complex, looking down the minor groove of the DNA (see Campbell, N.H.; Evans, D.A.; Lee, M.P.H.; Parkinson, G.N.; Neidle, S. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 15.). The DB819 molecule is shown in space-filling mode. Visualisation produced with the VMD program. [Humphrey, W.; Dalke, A.; Schulten, K. *J. Mol. Graphics* **1996**, *14*, 33.]



Indexed/Abstracted in: Beilstein, Biochemistry & Biophysics Citation Index, CANCERLIT, Chemical Abstracts, Chemistry Citation Index, Current Awareness in Biological Sciences/BIOBASE, Current Contents: Life Sciences, EMBASE/Excerpta Medica, MEDLINE, PASCAL, Research Alert, Science Citation Index, SciSearch, TOXFILE

ELSEVIER

ISSN 0960-894X