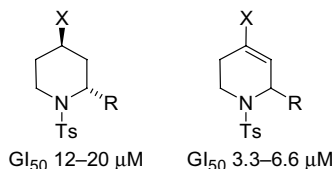


## Contents

### ARTICLES

**Antiproliferative activity of 2-alkyl-4-halopiperidines and 2-alkyl-4-halo-1,2,5,6-tetrahydropyridines in solid tumor cell lines** pp 2681–2684

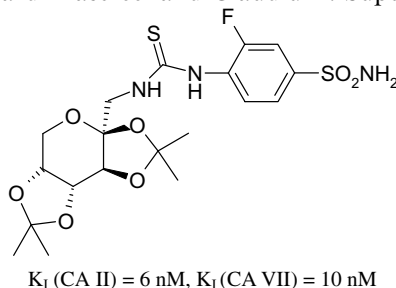
Leticia G. León, Rubén M. Carballo, María C. Vega-Hernández, Víctor S. Martín, Juan I. Padrón and José M. Padrón\*



The in vitro antitumor activity of *trans*-2-alkyl-4-halopiperidines and 2-alkyl-4-halo-1,2,5,6-tetrahydropyridines against human solid tumor cells is reported.

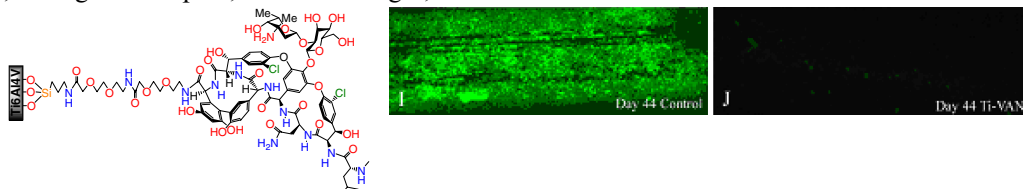
**Carbonic anhydrase inhibitors. Inhibition of isoforms I, II, IV, VA, VII, IX, and XIV with sulfonamides incorporating fructopyranose–thioureido tails** pp 2685–2691

Jean-Yves Winum,\* Anne Thiry, Khaled El Cheikh, Jean-Michel Dogné, Jean-Louis Montero, Daniela Vullo, Andrea Scozzafava, Bernard Masereel and Claudiu T. Supuran\*



**Covalent bonding of vancomycin to Ti6Al4V alloy pins provides long-term inhibition of *Staphylococcus aureus* colonization** pp 2692–2696

Om P. Edupuganti, Valentin Antoci, Jr., Samuel B. King, Binoy Jose, Christopher S. Adams, Javad Parvizi, Irving M. Shapiro, Allen R. Zeiger, Noreen J. Hickok and Eric Wickstrom\*

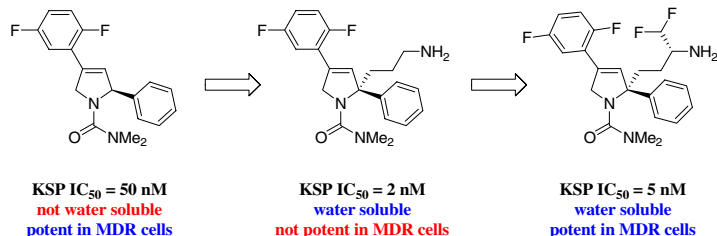


Vancomycin–oligoethyleneglycol–aminopropylsilyl–Ti6Al4V alloy pins were constructed by solid phase coupling. After 44 days storage in physiological buffer, control Ti6Al4V pins (left) were thoroughly colonized by *Staphylococcus aureus* (green), but not the vancomycin-protected Ti6Al4V pins (right).

### Kinesin spindle protein (KSP) inhibitors. Part V: Discovery of 2-propylamino-2,4-diaryl-2,5-dihydropyrroles as potent, water-soluble KSP inhibitors, and modulation of their basicity by $\beta$ -fluorination to overcome cellular efflux by P-glycoprotein

pp 2697–2702

Christopher D. Cox,\* Michael J. Breslin, David B. Whitman, Paul J. Coleman, Robert M. Garbaccio, Mark E. Fraley, Matthew M. Zrada, Carolyn A. Buser, Eileen S. Walsh, Kelly Hamilton, Robert B. Lobell, Weikang Tao, Marc T. Abrams, Vicki J. South, Hans E. Huber, Nancy E. Kohl and George D. Hartman

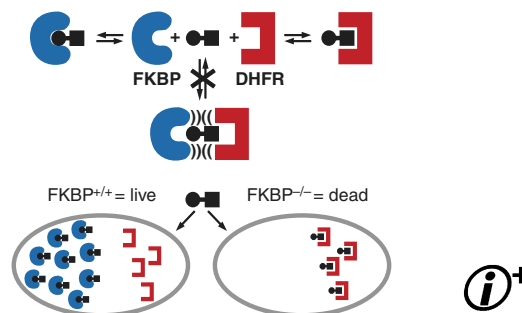


### Engineering small molecule specificity in nearly identical cellular environments

pp 2703–2705

Mark A. Sellmyer, Kryn Stankunas, Roger Briesewitz, Gerald R. Crabtree and Thomas J. Wandless\*

Differential expression of FKBP12 in mouse embryonic fibroblasts demonstrates selective detoxification of MTXSLF, a small molecule that binds either FKBP12 or DHFR but not both enzymes simultaneously.

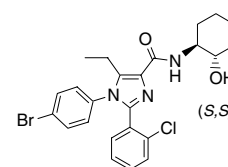


### Optimization of imidazole amide derivatives as cannabinoid-1 receptor antagonists for the treatment of obesity

pp 2706–2711

Roger A. Smith,\* Zahra Fathi, Furahi Achebe, Christiana Akuche, Su-Ellen Brown, Soongyu Choi, Jianmei Fan, Susan Jenkins, Harold C. E. Kluender, Anish Konkar, Rico Lavoie, Ronald Mays, Jennifer Natoli, Stephen J. O'Connor, Astrid A. Ortiz, Ning Su, Christy Taing, Susan Tomlinson, Theresa Tritto, Gan Wang, Stephan-Nicholas Wirtz, Wai Wong, Xiao-Fan Yang, Shihong Ying and Zhonghua Zhang

Imidazole-based cyclohexyl amides were identified as potent CB-1 antagonists. Incorporation of a hydroxyl moiety on the cyclohexyl ring provided a dramatic improvement in oral exposure in rodents, and further optimization provided **45**, which caused significant appetite suppression and robust, dose-dependent reduction of body weight gain in industry-standard rat models.

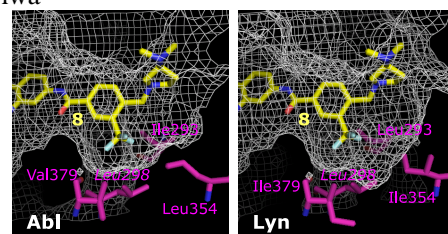


### Structural factors contributing to the Abl/Lyn dual inhibitory activity of 3-substituted benzamide derivatives

pp 2712–2717

Tatsuya Horio, Tomohiro Hamasaki, Toshihiko Inoue, Tatsushi Wakayama, Shinsaku Itou, Haruna Naito, Tetsuo Asaki, Hiroki Hayase and Tomoko Niwa\*

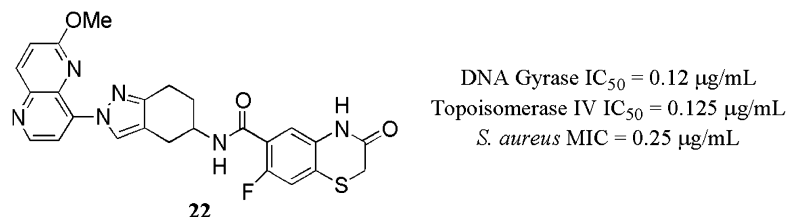
Inhibition and structural studies show that dual inhibition of Abl and Lyn kinases by 3-substituted benzamides can be explained by a high similarity in their modes of interaction with both kinases.



**Tetrahydroindazole inhibitors of bacterial type II topoisomerases. Part 2: SAR development and potency against multidrug-resistant strains**

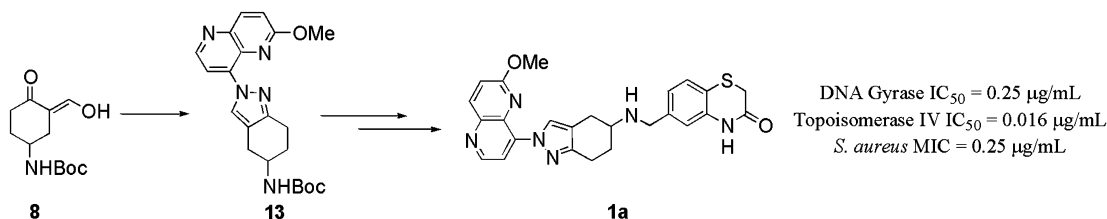
pp 2718–2722

John J. M. Wiener,\* Laurent Gomez, Hariharan Venkatesan, Alejandro Santillán, Jr., Brett D. Allison, Kimberly L. Schwarz, Shirin Shinde, Liu Tang, Michael D. Hack, Brian J. Morrow, S. Timothy Motley, Raul M. Goldschmidt, Karen Joy Shaw, Todd K. Jones and Cheryl A. Grice

**Novel pyrazole derivatives as potent inhibitors of type II topoisomerases. Part 1: Synthesis and preliminary SAR analysis**

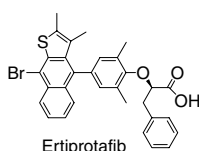
pp 2723–2727

Laurent Gomez,\* Michael D. Hack, Jiejun Wu, John J. M. Wiener, Hari Venkatesan, Alejandro Santillán, Jr., Daniel J. Pippel, Neelakandha Mani, Brian J. Morrow, S. Timothy Motley, Karen Joy Shaw, Ronald Wolin, Cheryl A. Grice and Todd K. Jones

**PTP1B inhibitor Ertiprotafib is also a potent inhibitor of I $\kappa$ B kinase  $\beta$  (IKK- $\beta$ )**

pp 2728–2730

Suja Shrestha, Bharat Raj Bhattarai, Heeyeong Cho, Joong-Kwon Choi and Hyeongjin Cho\*

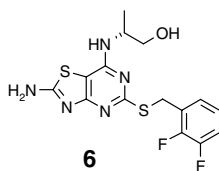


Ertiprotafib was developed as an inhibitor of PTP1B for the treatment of type 2 diabetes, and progressed to a phase II clinical trial. In this study, Ertiprotafib was shown to be a potent inhibitor of IKK- $\beta$  with an  $IC_{50}$  of 400 nM.

**SAR studies on thiazolo[4,5-*d*]pyrimidine based CXCR2 antagonists involving a novel tandem displacement reaction**

pp 2731–2734

Fraser Hunt,\* Caroline Austin, Rupert Austin, Roger Bonnert, Peter Cage, Jadeen Christie, Mark Christie, Clare Dixon, Steven Hill, Robert Jewell, Ian Martin, David Robinson and Paul Willis

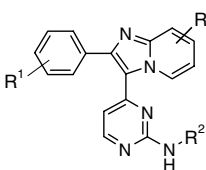


The optimisation of antagonists of the CXCR2 receptor is described involving a novel tandem displacement reaction culminating in the synthesis of **6**, a novel, potent and metabolically stable lead compound.

**Imidazo[1,2-*a*]pyridines with potent activity against herpesviruses**

pp 2735–2739

Kristjan S. Gudmundsson\* and Brian A. Johns



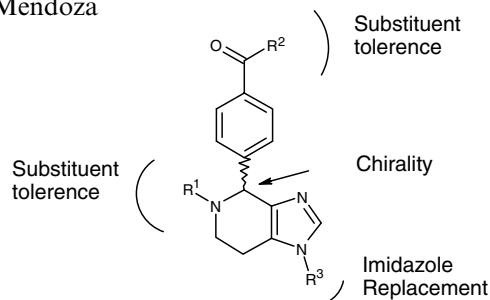
Synthesis of a series of 2-aryl-3-pyrimidyl-imidazo[1,2-*a*]pyridines with potent activity against herpes simplex viruses is described. Synthetic approaches allowing for variation of the 2-aryl, 3-heteroaryl as well as other imidazopyridine substituents are outlined and resulting effects on antiviral activity are highlighted. Several compounds with in vitro antiviral activity similar or better than acyclovir are described.

**Evaluation of *N*-(phenylmethyl)-4-[5-(phenylmethyl)-4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridin-4-yl]benzamide inhibitors of *Mycobacterium tuberculosis* growth**

pp 2740–2744

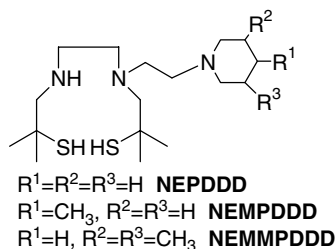
Michael D. Wall,\* Michael Oshin, Gavin A. C. Chung, Tony Parkhouse, Andrea Gore, Esperanza Herreros, Brian Cox, Ken Duncan, Brian Evans, Martin Everett and Alfonso Mendoza

The biological evaluation of non-covalent FAS II inhibitors containing the imidazopiperidine scaffold against *Mycobacterium tuberculosis* has been carried out with a view to assessment as a potential lead series of compounds. A summary of the chemistry carried out and the evaluation of results is described herein.

**DNA cleavage promoted by 2,9-dimethyl-4,7-diazadecane-2,9-dithiol (DDD) derivatives**

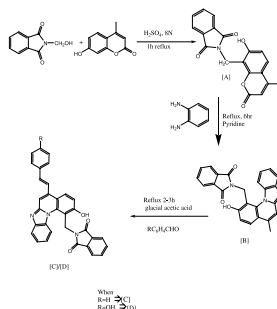
pp 2745–2748

Yuan-Cong Zhao, Ji Zhang, Yu Huang, Guan-Quan Wang and Xiao-Qi Yu\*

**Synthesis and evaluation of Novel Benzimidazole derivative [Bz-Im] and its radio/biological studies**

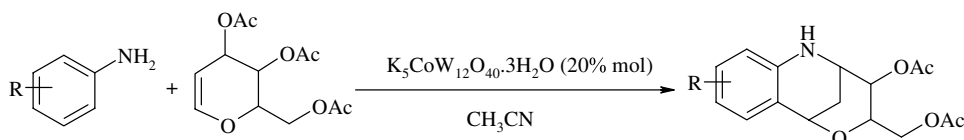
pp 2749–2755

Anjani K. Tiwari, Anil K. Mishra, Aruna Bajpai, Pushpa Mishra, Sweta Singh, Deepa Sinha and V. K. Singh\*



**Cobaltpolyoxometalate-catalyzed cyclization of glucal with aryl amines: Synthesis of 2,4-disubstituted tetrahydroquinolines** pp 2756–2759

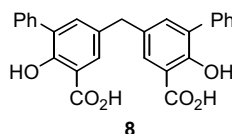
Ezzat Rafiee\* and A. Azad



Treatment of 3,4,6-tri-*O*-acetyl-D-glucal with various aryl amines under mild and neutral conditions gave sugar derived tetrahydroquinoline derivatives in short reaction times in the presence of  $K_5CoW_{12}O_{40} \cdot H_2O$  as an environmentally friendly, inexpensive, and reusable catalyst.

**Methylenedisalicylic acid derivatives: New PTP1B inhibitors that confer resistance to diet-induced obesity** pp 2760–2764

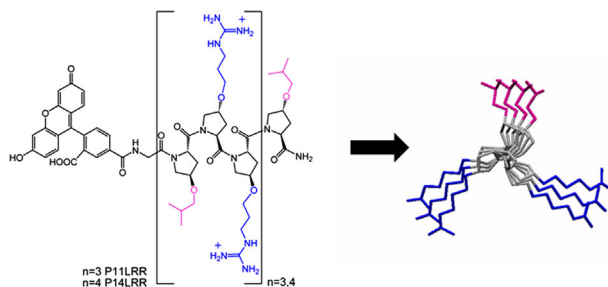
Suja Shrestha, Bharat Raj Bhattarai, Kyung Ja Chang, Keun-Hyeung Lee and Hyeongjin Cho\*



Compound **8** inhibited PTP1B in vitro and suppressed diet-induced weight gain in mice.

**Probing length effects and mechanism of cell penetrating agents mounted on a polyproline helix scaffold** pp 2765–2768

Iris Geisler and Jean Chmielewski\*

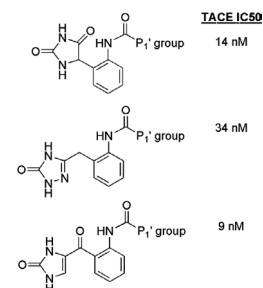


Investigations of length effects and mechanism of cell penetrating peptides displaying a rigid polyproline helix backbone are reported.

**Hydantoins, triazolones, and imidazolones as selective non-hydroxamate inhibitors of tumor necrosis factor- $\alpha$  converting enzyme (TACE)** pp 2769–2774

James E. Sheppeck, II,\* John L. Gilmore, Andrew Tebben, Chu-Biao Xue, Rui-Qin Liu, Carl P. Decicco and James J.-W. Duan

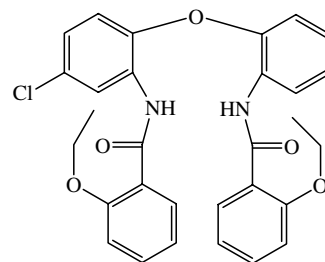
We have discovered novel hydantoins, triazolones, and imidazolones that are druglike, non-hydroxamate inhibitors of the Zn-metalloprotease TACE with nM potency. Synthesis, SAR, and MMP selectivity of these inhibitors is described and how they conform to a pharmacophore model of heterocyclic non-hydroxamate TACE inhibitors compared with the IK682-TACE X-ray crystal structure.



## 2-(2-(2-Ethoxybenzoylamino)-4-chlorophenoxy)-N-(2-ethoxybenzoyl)benzamine inhibits EAT cell induced angiogenesis by down regulation of VEGF secretion pp 2775–2780

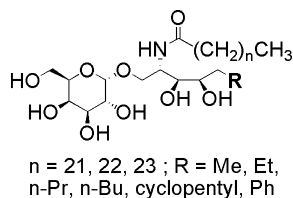
B. S. Priya, C. Anil Kumar, S. Nanjunda Swamy, Basappa, S. Naveen, J. Shashidhara Prasad and K. S. Rangappa\*

Compounds containing amide bond play a pivotal role in various pharmaceutical applications. 2-(2-(2-Ethoxybenzoylamino)-4-chlorophenoxy)-N-(2-ethoxybenzoyl)benzamine **4** is shown to be a potent antiangiogenic agent. In this study, we report the microwave-assisted synthesis, single crystal X-ray structure, and antiangiogenic effect of compound **4** in EAT cell induced angiogenesis. Treatment with compound **4** in vivo demonstrated down regulation of the secretion of VEGF in EAT cells and inhibition of blood vessels formation indicating the potential angioinhibitory effect of compound in EAT cells.



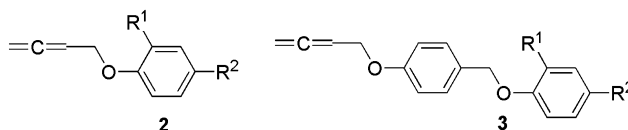
## Minimum structure requirement of immunomodulatory glycolipids for predominant Th2 cytokine induction and the discovery of non-linear phytosphingosine analogs pp 2781–2784

Tetsuya Toba, Kenji Murata, Kyoko Nakanishi, Bitoku Takahashi, Naohiro Takemoto, Minako Akabane, Takashi Nakatsuka, Seiichi Imajo, Takashi Yamamura, Sachiko Miyake and Hirokazu Annoura\*



## Synthesis and biological evaluation of 12 allenic aromatic ethers pp 2785–2788

San-yong Wang, Wei-wei Mao, Zhi-gang She,\* Chun-rong Li, Ding-qiao Yang, Yong-cheng Lin\* and Li-wu Fu



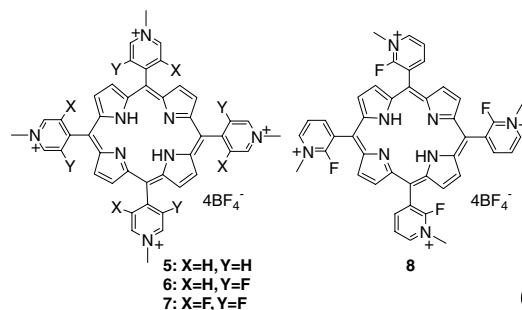
Twelve allenic aromatic ethers (**2** and **3**), some of them are natural products isolated from the mangrove fungus *Xylaria* sp. 2508 in the South China Sea, were synthesized. Their antitumor activities against KB and KBv200 cells were determined. All these compounds demonstrated cytotoxic potential, ranging from weak to strong activity. The structure–activity relationships suggested that the introduction of allenic moiety to the phenol hydroxyl group could generate or enhance cytotoxicity of these phenol compounds.



## Synthesis and in vitro photodynamic activities of water-soluble fluorinated tetrapyrrolylporphyrins as tumor photosensitizers pp 2789–2794

Yoon-Joo Ko, Kyung-Jin Yun, Min-Seok Kang, Jongmin Park, Kyung-Tae Lee,\* Seung Bum Park\* and Jung-Hyu Shin\*

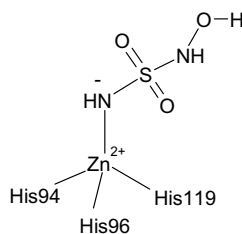
A series of water-soluble fluoro-substituted porphyrins were synthesized, and photocytotoxicity studies of these compounds evaluated by MTT assay on HeLa cells in vitro.



**Carbonic anhydrase inhibitors: The X-ray crystal structure of the adduct of *N*-hydroxysulfamide with isozyne II explains why this new zinc binding function is effective in the design of potent inhibitors**

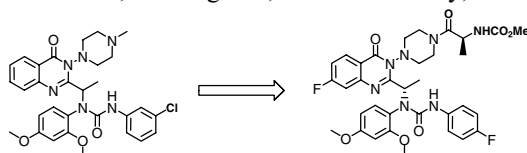
pp 2795–2801

Claudia Temperini, Jean-Yves Winum, Jean-Louis Montero, Andrea Scozzafava and Claudiu T. Supuran\*


**Quinazolinone fungal efflux pump inhibitors. Part 3: (*N*-methyl)piperazine variants and pharmacokinetic optimization**

pp 2802–2806

William J. Watkins,\* Lee Chong, Aesop Cho, Ramona Hilgenkamp, Maria Ludwikow, Negar Garizi, Nadeem Iqbal, John Barnard, Rajeshwar Singh, Deidre Madsen, Karen Lolans, Olga Lomovskaya, Uma Oza, Padmapriya Kumaraswamy, Andrea Blecken, Shuang Bai, David J. Loury, David C. Griffith and Michael N. Dudley

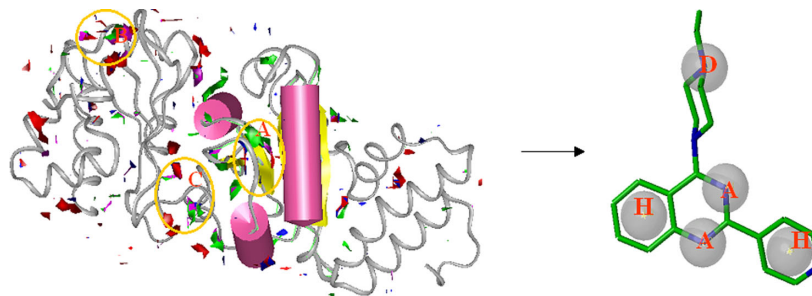


Further structure–activity relationships of a novel series of fungal efflux pump inhibitors with respect to potentiation of the activity of fluconazole against strains of *Candida albicans* and *Candida glabrata* over-expressing ABC-type efflux pumps are systematically explored. Rat protein binding, hepatocyte stability, and pharmacokinetics of selected analogues are reported.

**Small molecule inhibitors of *E. coli* primase, a novel bacterial target**

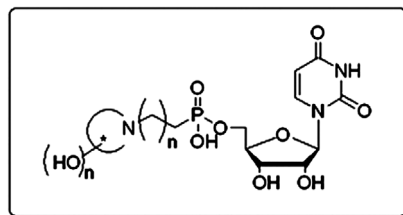
pp 2807–2810

Atul Agarwal,\* Shirley Louise-May, Jane A. Thanassi, Steven D. Podos, Jijun Cheng, Christy Thoma, Cuixian Liu, Jason A. Wiles, David M. Nelson, Avinash S. Phadke, Barton J. Bradbury, Milind S. Deshpande and Michael J. Pucci\*


**Phosphonoxins: Rational design and discovery of a potent nucleotide anti-*Giardia* agent**

pp 2811–2816

Dae-Hwan Suk, Dominik Rejman, Christine C. Dykstra, Radek Pohl, Krzysztof W. Pankiewicz and Steven E. Patterson\*



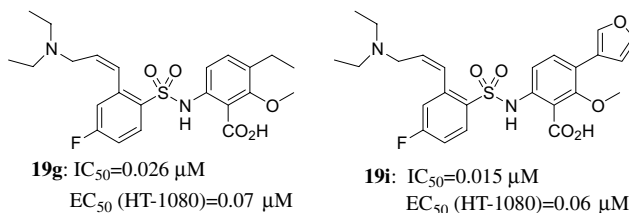
Phosphonoxins, a new class of synthetic, rationally designed anti-microbial agents, are described. From this class a sub-micromolar inhibitor of *Giardia* trophozoite growth has been identified.



**Lead optimization of methionine aminopeptidase-2 (MetAP2) inhibitors containing sulfonamides of 5,6-disubstituted anthranilic acids**

pp 2817–2822

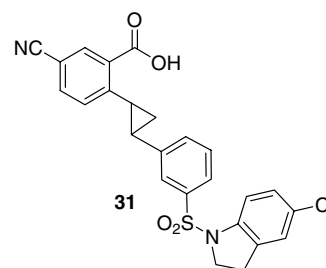
Gary T. Wang,\* Robert A. Mantei, Megumi Kawai, Jason S. Tedrow, David M. Barnes, Jieyi Wang, Qian Zhang, Pingping Lou, Lora A. Garcia, Jennifer Bouska, Melinda Yates, Chang Park, Russell A. Judge, Richard Lesniewski, George S. Sheppard and Randy L. Bell

**Preparation of novel anthranilic acids as antibacterial agents. Extensive evaluation of alternative amide bioisosteres connecting the A- and the B-rings**

pp 2823–2827

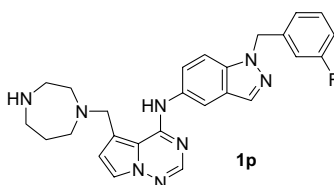
Atli Thorarensen,\* Brian D. Wakefield, Donna L. Romero, Keith R. Marotti, Michael T. Sweeney, Gary E. Zurenko, Douglas C. Rohrer, Fusen Han and Garold L. Bryant, Jr.

This paper describes the discovery of amide bioisosteres, an *E*-alkene and a *trans* cyclopropane, as potent antibacterial agents against Gram-positive organisms.

**Novel C-5 aminomethyl pyrrolotriazine dual inhibitors of EGFR and HER2 protein tyrosine kinases**

pp 2828–2833

Harold Mastalerz,\* Ming Chang, Ashvinikumar Gavai, Walter Johnson, David Langley, Francis Y. Lee, Punit Marathe, Arvind Mathur, Simone Oppenheimer, James Tarrant, John S. Tokarski, Gregory D. Vite, Dolatrai M. Vyas, Henry Wong, Tai W. Wong, Hongjian Zhang and Guifen Zhang

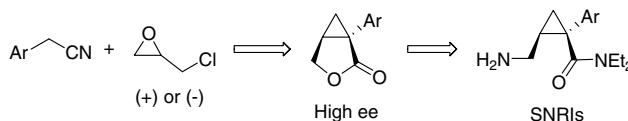


Novel C-5 aminomethyl pyrrolotriazines were optimized for dual EGFR and HER2 protein tyrosine kinase inhibition. The lead compound exhibited promising oral efficacy in both EGFR and HER2 driven human tumor xenograft models. It is hypothesized that its C-5 homopiperazine side chain binds in the ribose phosphate portion of the ATP binding pocket.

**Synthesis of enantiomerically pure milnacipran analogs and inhibition of dopamine, serotonin, and norepinephrine transporters**

pp 2834–2837

Heidi Roggen, Jan Kehler, Tine Bryan Stensbøl and Tore Hansen\*



Two enantiomeric series of milnacipran analogs have been synthesized and their effects on 5-HT, NE, and DA uptake inhibition have been measured.

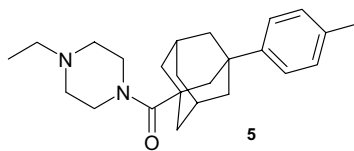




**Discovery and biological evaluation of adamantyl amide 11 $\beta$ -HSD1 inhibitors**

pp 2838–2843

Scott P. Webster,\* Peter Ward, Margaret Binnie, Eilidh Craigie, Kirsty M. M. McConnell, Karen Sooy, Andy Vinter, Jonathan R. Seckl and Brian R. Walker



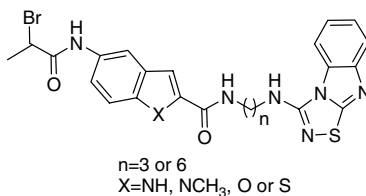
hHSD1  $IC_{50}$  = 82nM

The synthesis and biological activity of a series of adamantyl amide 11 $\beta$ -HSD1 inhibitors represented by **5** is reported.

**Hybrid molecules containing benzo[4,5]imidazo[1,2-d][1,2,4]thiadiazole and  $\alpha$ -bromoacryloyl moieties as potent apoptosis inducers on human myeloid leukaemia cells**

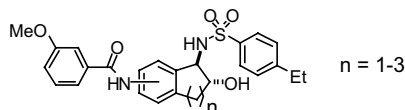
pp 2844–2848

Romeo Romagnoli,\* Pier Giovanni Baraldi,\* Maria Dora Carrion, Olga Cruz-Lopez, Delia Preti, Mojgan Aghazadeh Tabrizi, Francesca Fruttarolo, Jörg Heilmann, Jaime Bermejo and Francisco Estévez

**Aryl sulfonamido indane inhibitors of the Kv1.5 ion channel**

pp 2849–2853

Michael F. Gross, Serge Beaudoin,\* Grant McNaughton-Smith, George S. Amato, Neil A. Castle, Christine Huang, Anruo Zou and Weifeng Yu

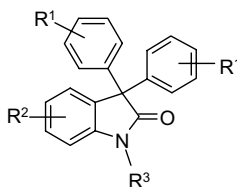


Structure–activity relationship of a new class of Kv1.5 inhibitors based on the indane scaffold was investigated.

**Syntheses and antiproliferative evaluation of oxyphenisatin derivatives**

pp 2854–2857

Muhammed K. Uddin, Serge G. Reignier, Tom Coulter, Christian Montalbetti,\* Charlotta Grånäs, Steven Butcher, Christian Krog-Jensen and Jakob Felding\*

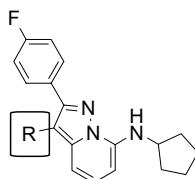


The syntheses and structure–antiproliferative relationship for oxyphenisatin analogues are reported.

**Pyrazolo[1,5-*a*]pyridine antiherpetics: Effects of the C3 substituent on antiviral activity**

pp 2858–2862

Brian A. Johns,\* Kristjan S. Gudmundsson and Scott H. Allen



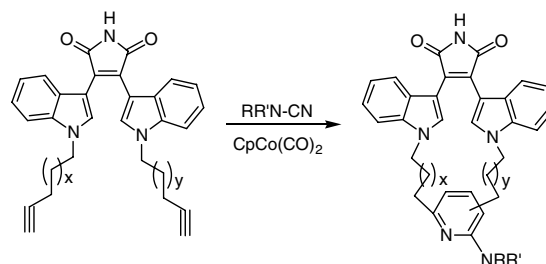
SAR explorations to understand the effects of the C3 substituent on antiviral activity for herpes simplex virus for a series of pyrazolo[1,5-*a*]pyridine derivatives is reported. Resulting data emphasizes the importance of the orientation and basicity of heteroatoms contained in the C3 substituent. During the course of this study, several novel synthetic approaches were developed further elaborating the available synthetic methodology for this important heterocycle.

**Novel bis(indolyl)maleimide pyridinophanes that are potent, selective inhibitors of glycogen synthase kinase-3**

pp 2863–2868

Han-Cheng Zhang,\* Llorente V. R. Boñaga, Hong Ye, Claudia K. Derian, Bruce P. Damiano and Bruce E. Maryanoff\*

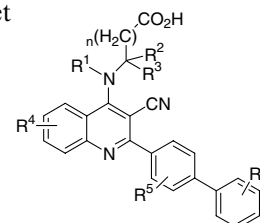
Bis(indolyl)maleimide pyridinophanes ('multiheterophanes'), from cobalt-mediated [2+2+2] cycloaddition, were found to be potent, selective inhibitors of GSK-3 $\beta$ . An X-ray structure of a co-crystal with GSK-3 $\beta$  is reported.

**PDE-10A inhibitors as insulin secretagogues**

pp 2869–2873

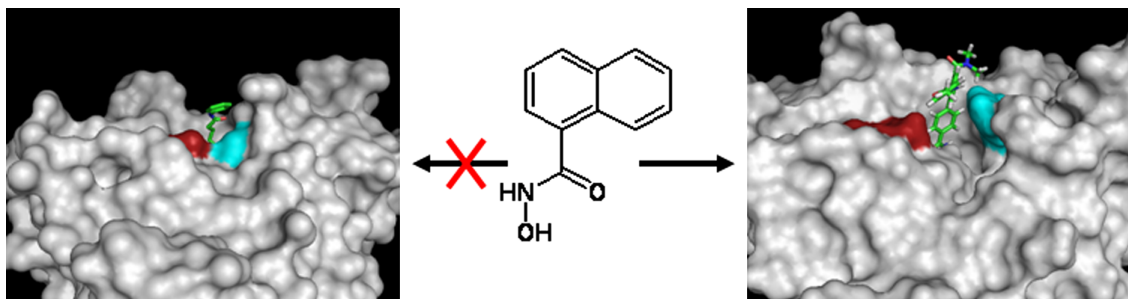
Louis-David Cantin,\* Steven Magnuson, David Gunn, Nicole Barucci, Marina Breuhaus, William H. Bullock, Jennifer Burke, Thomas H. Claus, Michelle Daly, Lynn DeCarr, Ann Gore-Willse, Helana Hoover-Litty, Ellalahewage S. Kumarasinghe, Yaxin Li, Sidney X. Liang, James N. Livingston, Timothy Lowinger, Margit MacDougall, Herbert O. Ogutu, Alan Olague, Ronda Ott-Morgan, Robert W. Schoenleber, Adrian Tersteegen, Philip Wickens, Zhonghua Zhang, Jian Zhu, Lei Zhu and Laurel J. Sweet

A series of quinoline-based PDE-10A inhibitors was determined to cause insulin secretion in vitro. Optimized compounds were evaluated in vivo where improvements in glucose tolerance and increases in insulin secretion were measured.

**Design and evaluation of 'Linkerless' hydroxamic acids as selective HDAC8 inhibitors**

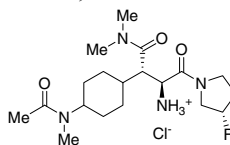
pp 2874–2878

Keris KrennHrubec, Brett L. Marshall, Mark Hedglin, Eric Verdin and Scott M. Ulrich\*



#### 4-Aminophenylalanine and 4-aminocyclohexylalanine derivatives as potent, selective, and orally bioavailable inhibitors of dipeptidyl peptidase IV pp 2879–2885

Joseph L. Duffy,\* Brian A. Kirk, Liping Wang, George J. Eiermann, Huaibing He, Barbara Leiting, Kathryn A. Lyons, Reshma A. Patel, Sangita B. Patel, Aleksandr Petrov, Giovanna Scapin, Joseph K. Wu, Nancy A. Thornberry and Ann E. Weber

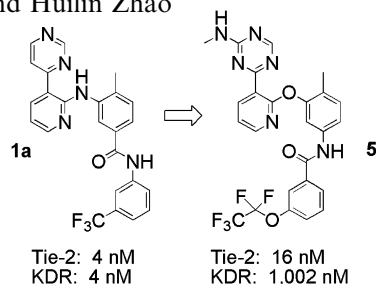


25 DPP-4 IC<sub>50</sub> = 16 nM

A novel series of 4-aminophenylalanine and 4-aminocyclohexylalanine derivatives were designed and evaluated as inhibitors of dipeptidyl peptidase IV (DPP-4). The cyclohexylalanine derivatives such as **25** afforded PK exposure in rat and dog, and efficacy in a murine OGTT experiment.

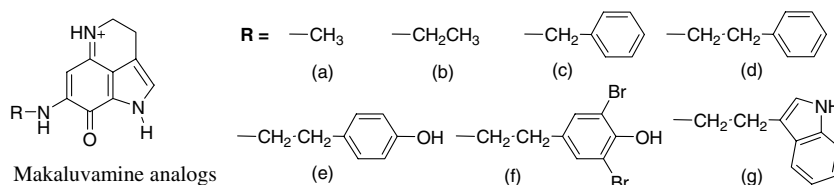
#### Synthesis, structural analysis, and SAR studies of triazine derivatives as potent, selective Tie-2 inhibitors pp 2886–2889

Brian L. Hodous,\* Stephanie D. Geuns-Meyer, Paul E. Hughes, Brian K. Albrecht, Steve Bellon, Sean Caenepeel, Victor J. Cee, Stuart C. Chaffee, Maurice Emery, Jenne Fretland, Paul Gallant, Yan Gu, Rebecca E. Johnson, Joseph L. Kim, Alexander M. Long, Michael Morrison, Philip R. Olivieri, Vinod F. Patel, Anthony Polverino, Paul Rose, Ling Wang and Huilin Zhao



#### Analogues of the marine alkaloid makaluvamines: Synthesis, topoisomerase II inhibition, and anticancer activity pp 2890–2893

Bidhan A. Shinkre, Kevin P. Raisch, Liming Fan and Sadanandan E. Velu\*

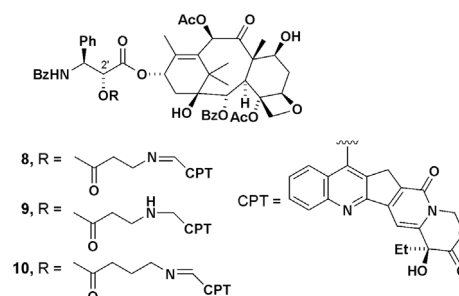


Synthesis, topoisomerase II inhibition, and anticancer activities of makaluvamine analogs are presented.



#### Antitumor agents. 256. Conjugation of paclitaxel with other antitumor agents: Evaluation of novel conjugates as cytotoxic agents pp 2894–2898

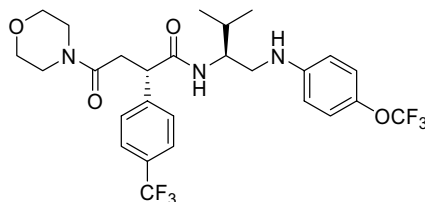
Kyoko Nakagawa-Goto, Seikou Nakamura, Kenneth F. Bastow, Alexander Nyarko, Chieh-Yu Peng, Fang-Yu Lee, Fang-Chen Lee and Kuo-Hsiung Lee\*



**Synthesis and SAR of succinamide peptidomimetic inhibitors of cathepsin S**

pp 2899–2903

Arnab K. Chatterjee,\* Hong Liu, David C. Tully, Jianhua Guo, Robert Epple, Ross Russo, Jennifer Williams, Michael Roberts, Tove Tuntland, Jonathan Chang, Perry Gordon, Thomas Hollenbeck, Christine Tumanut, Jun Li and Jennifer L. Harris

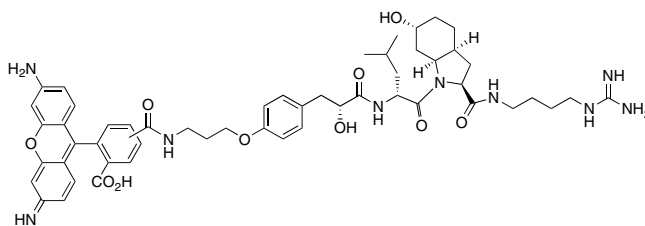


Peptidic, non-covalent inhibitors of lysosomal cysteine protease cathepsin S were investigated due to low oral bioavailability of initial leads, leading to an improved series of peptidomimetic inhibitors utilizing phenyl succinamides as the P2 residue.

**Synthesis of fluorescent-labeled aeruginosin derivatives for high-throughput fluorescence correlation spectroscopy assays**

pp 2904–2907

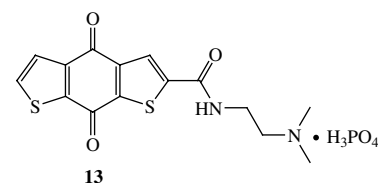
Yoichiro Hoshina, Yoshifumi Yamada, Hiroshi Tanaka, Takayuki Doi and Takashi Takahashi\*

**Cell differentiation enhancement by hydrophilic derivatives of 4,8-Dihydrobenzo[1,2-*b*:5,4-*b'*]dithiophene-4,8-diones in HL-60 leukemia cells**

pp 2908–2912

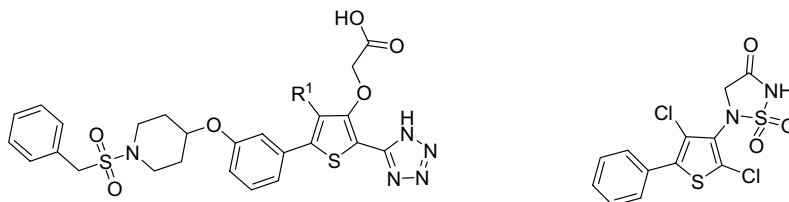
Yen-Fang Wen, Kuo-Hsiung Lee, Pi-Tsan Huang, Mei-Hwai Chen, Wu-Chian Shin, Li-Jiau Huang, Mei-Hua Hsu, Chun-Jen Chen and Sheng-Chu Kuo\*

*N*-(2-dimethylaminoethyl)-4,8-dihydrobenzo[1,2-*b*:5,4-*b'*]dithiophene-4,8-dione-2-carboxamide (**13**) and 2-(1-hydroxyethyl)-4,8-dihydrobenzo[1,2-*b*:5,4-*b'*]dithiophene-4,8-dione (**18**) were found to exhibit excellent differentiation effects on HL-60 cells. To improve the water solubility of compound **18**, its ester-type hydrophilic prodrugs (**23–26**) was synthesized.

**Probing acid replacements of thiophene PTP1B inhibitors**

pp 2913–2920

Zhao-Kui Wan, Bruce Follows,\* Steve Kirincich, Douglas Wilson, Eva Binnun, Weixin Xu, Diane Joseph-McCarthy, Junjun Wu, Michael Smith, Yan-Ling Zhang, May Tam, David Erbe, Steve Tam, Eddine Saiah and Jinbo Lee



A series of acid replacement groups were prepared and evaluated as PTP1B inhibitors. 2-Tetrazole and 3-thiourea were identified as potential acid replacement groups that display improved permeability versus our diacid thiophene lead compound.

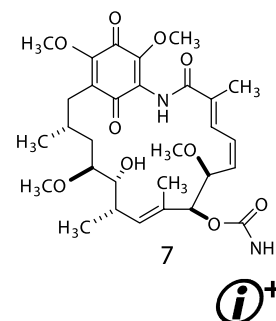


**Geldanamycin derivatives and neuroprotective effect on cultured P19-derived neurons**

pp 2939–2943

Sarin Tadtong, Duangdeun Meksuriyen, Somboon Tanasupawat, Minoru Isobe and Khanit Suwanborirux\*

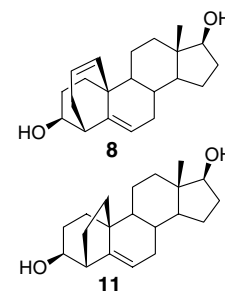
A series of *O*-alkyl and *N*-alkyl derivatives of geldanamycin were prepared and evaluated for in vitro activities against P19-derived neurons. 19-*O*-methylgeldanamycin (**7**), possessing wide therapeutic index between neuroprotective and neurotoxic activities, is the most promising derivative in neurodegenerative therapy against neurotoxic anticancer drugs.

**Bridged androstenediol analogs as ER- $\beta$  selective SERMs**

pp 2944–2948

Timothy A. Blizzard,\* Candido Gude, Wanda Chan, Elizabeth T. Birzin, Marina Mojena, Consuelo Tudela, Fang Chen, Kristin Knecht, Qin Su, Bryan Kraker, Mark A. Holmes, Susan P. Rohrer and Milton L. Hammond

A series of bridged androstenediol derivatives (e.g., **8** and **11**) was prepared. The bridged compounds exhibited reduced ER- $\beta$  selectivity relative to uncyclized analogs.


**OTHER CONTENTS****Corrigendum**

p 2949

**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.]

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