



**Bioorganic & Medicinal Chemistry Letters Vol. 15, No. 9, 2005**

# Contents

## Publisher's note

**p 2195**

## COMMUNICATIONS

**Effects of linking 15-zinc finger domains on DNA binding specificity and multiple DNA binding modes** pp 2197–2201  
Tsuyoshi Hirata, Wataru Nomura, Miki Imanishi and Yukio Sugiura\*



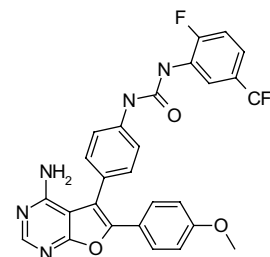
Multi-zinc finger protein, Sp1ZF15, shows site-specific binding and different DNA binding modes corresponding to the target sequences.

## Novel 4-amino-furo[2,3-*d*]pyrimidines as Tie-2 and VEGFR2 dual inhibitors

pp 2203–2207

Yasushi Miyazaki,\* Shinichiro Matsunaga, Jun Tang, Yutaka Maeda, Masato Nakano,  
Rocher J. Philippe, Megumi Shibahara, Wei Liu, Hideyuki Sato, Liping Wang and Robert T. Nolte

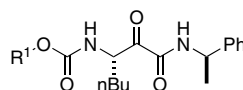
A novel class of furo[2,3-*d*]pyrimidines has been discovered as potent dual inhibitors of Tie-2 and VEGFR2 receptor tyrosine kinases (TK) and a diarylurea moiety at 5-position shows remarkably enhanced activity against both enzymes. One of the most active compounds, 4-amino-3-(4-((2-fluoro-5-(trifluoromethyl)phenyl)amino-carbonylamino)phenyl)-2-(4-methoxyphenyl)furo[2,3-*d*]pyrimidine (**7k**) is <3 nM on both TK receptors and the activity is rationalized based on the X-ray crystal structure.



# A structural screening approach to ketoamide-based inhibitors of cathepsin K

pp 2209–2213

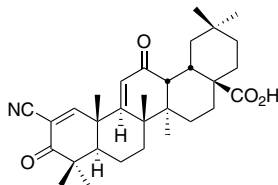
David G. Barrett, John G. Catalano, David N. Deaton,\* Stacey T. Long, Robert B. McFadyen, Aaron B. Miller, Larry R. Miller, Kevin J. Wells-Knecht and Lois L. Wright



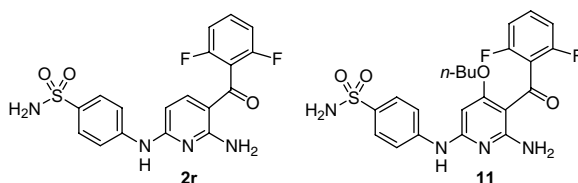
Several novel ketoamide-based inhibitors of cathepsin K have been identified. Starting from a modestly potent inhibitor, structural screening of P<sup>2</sup> elements led to 100-fold enhancements in inhibitory activity. Modifications to one of these leads resulted in an orally bioavailable cathepsin K inhibitor.

**Studies on the reactivity of CDDO, a promising new chemopreventive and chemotherapeutic agent: implications for a molecular mechanism of action**

pp 2215–2219

 Robin D. Couch, R. Greg Browning, Tadashi Honda, Gordon W. Gribble,  
 Dennis L. Wright, Michael B. Sporn and Amy C. Anderson\*

**3-Acyl-2,6-diaminopyridines as cyclin-dependent kinase inhibitors: synthesis and biological evaluation**

pp 2221–2224

 Ronghui Lin,\* Yanhua Lu, Steven K. Wetter, Peter J. Connolly, Ignatius J. Turchi,  
 William V. Murray, Stuart L. Emanuel, Robert H. Gruninger, Angel R. Fuentes-Pesquera,  
 Mary Adams, Niranjana Pandey, Sandra Moreno-Mazza, Steven A. Middleton and Linda K. Jolliffe


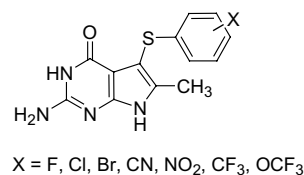
A novel series of 2,6-diamino-3-acylpyridines were designed and synthesized as cyclin-dependent kinase (CDK) inhibitors. The representative compounds **2r** and **11** showed potent CDK1 and CDK2 inhibitory activities and inhibited cellular proliferation in HeLa, HCT116, and A375 tumor cells.

**Novel 2-amino-4-oxo-5-arylthio-substituted-pyrrolo[2,3-*d*]pyrimidines as nonclassical antifolate inhibitors of thymidylate synthase**

pp 2225–2230

Aleem Gangjee,\* Hiteshkumar D. Jain and Roy L. Kisliuk

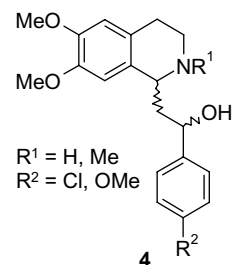
A series of 17 novel 2-amino-4-oxo-5-[(substituted phenyl)thio]pyrrolo[2,3-*d*]pyrimidines were synthesized as potential inhibitors of thymidylate synthase (TS) and as antitumor agents. The analogues contain a variety of electron withdrawing substituents on the phenyl ring of the side chain and were evaluated as inhibitors of human TS (hTS) and *Escherichia coli* TS and of human and *E. coli* dihydrofolate reductase (DHFR). The analogues **14**, **17**, and **18** were potent inhibitors of hTS with IC<sub>50</sub> values of 0.28, 0.21, and 0.22 μM, respectively, and were more potent than the clinically used ZD1694, **2** and LY231514, **3** against human TS.


**NMDA-NR2B subtype selectivity of stereoisomeric 2-(1,2,3,4-tetrahydro-1-isoquinolyl)ethanol derivatives**

pp 2231–2234

Georg Höfner, Cornelia E. Hoesl, Chris Parsons, Günther Quack and Klaus T. Wanner\*

The enantiopure 2-(1,2,3,4-tetrahydro-1-isoquinolyl)ethanol derivatives **4** were evaluated for their affinity to the ifenprodil binding site of the NMDA receptor, their potency to inhibit [<sup>3</sup>H]MK801 binding, their NMDA-NR2B subtype selectivity and their affinity to HERG K<sup>+</sup> channels.

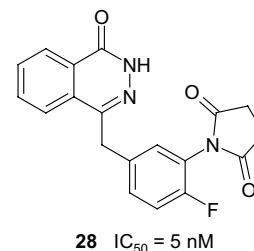


**Phthalazinones. Part 1: The design and synthesis of a novel series of potent inhibitors of poly(ADP-ribose)polymerase**

pp 2235–2238

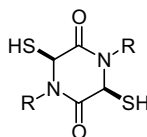
Vincent M. Loh, Jr.,\* Xiao-ling Cockcroft, Krystyna J. Dillon, Lesley Dixon, Jan Drzewiecki, Penny J. Eversley, Sylvie Gomez, Janet Hoare, Frank Kerrigan, Ian T. W. Matthews, Keith A. Menear, Niall M. B. Martin, Roger F. Newton, Jane Paul, Graeme C. M. Smith, Julia Vile and Alan J. Whittle

Screening of the Maybridge compound collection identified 4-arylphthalazinones as micromolar inhibitors of PARP-1 catalytic activity. Subsequent optimisation of both inhibitory activity and metabolic stability led to a novel series of *meta*-substituted 4-benzyl-2*H*-phthalazin-1-ones with low nanomolar, cellular activity as PARP-1 inhibitors and promising metabolic stability in vitro.

**Observations on the reactivity of thiyl radicals derived from 3,6-epidithiodiketopiperazine-2,5-diones and related congeners**

pp 2239–2242

S. T. Hilton, W. B. Motherwell,\* P. Potier, C. Pradet and D. L. Selwood

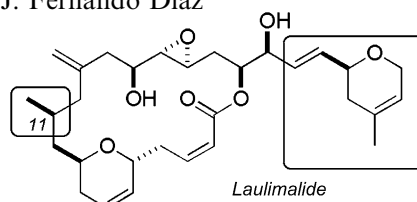


A range of thiyl radicals derived from the reduced form of epidithiodiketopiperazines (ETPs) act as polarity reversal catalysts for the hydrosilylation of an enol lactone but not for H-atom abstraction from a model ribose ester.

**Design, synthesis and biological evaluation of novel, simplified analogues of laulimalide: modification of the side chain**

pp 2243–2247

Ian Paterson,\* Dirk Menche, Anders E. Håkansson, Adrian Longstaff, David Wong, Isabel Barasoain, Rubén M. Buey and J. Fernando Díaz

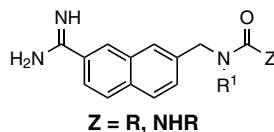


Novel, simplified analogues of the microtubule-stabilizing anticancer agent laulimalide, including the first derivatives with unnatural side chains, were designed by molecular modelling, synthesized by a late-stage diversification strategy, and evaluated in vitro for growth inhibition of human ovarian carcinoma cell lines.

**Solid-phase synthesis of naphthylamidines as factor VIIa/tissue factor inhibitors**

pp 2249–2252

Brad O. Buckman,\* Yuo-Ling Chou, Meg McCarrick, Amy Liang, Dao Lentz, Raju Mohan, Michael M. Morrissey, Kenneth J. Shaw, Lan Trinh and David R. Light

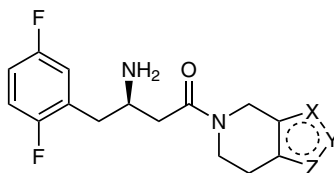


Reductive amination followed by acylation of polymer-linked formyl aryl amidines generate combinatorial libraries of aryl amidines. Potent small molecule naphthylamidine inhibitors ( $K_i < 100$  nM) of FVIIa/TF have been discovered and their activity against other serine proteases in the coagulation cascade are reported.

**Dipeptidyl peptidase IV inhibitors derived from  $\beta$ -aminoacylpiperidines bearing a fused thiazole, oxazole, isoxazole, or pyrazole**

pp 2253–2258

Wallace T. Ashton,\* Rosemary M. Sisco, Hong Dong, Kathryn A. Lyons, Huaibing He, George A. Doss, Barbara Leiting, Reshma A. Patel, Joseph K. Wu, Frank Marsilio, Nancy A. Thornberry and Ann E. Weber

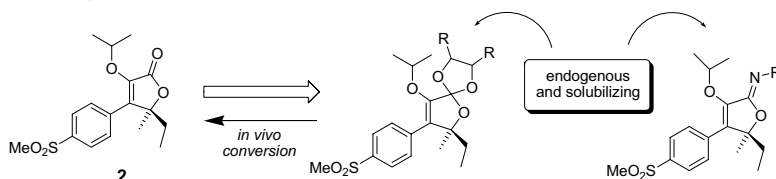


A series of  $\beta$ -aminoacylpiperidines bearing various fused five-membered heterocyclic rings was synthesized as dipeptidyl peptidase IV inhibitors. Potent and relatively selective inhibition could be obtained, depending on the choice of heterocycle, regioisomerism, and substitution.

**Novel approach to pro-drugs of lactones: water soluble imidate and *ortho*-ester derivatives of a furanone-based COX-2 selective inhibitor**

pp 2259–2263

Steve F. Poon,\* Nicholas Stock,\* Joseph E. Payne, Angela R. McGuire, Brian Stearns, Xiaoqing Yang, Weichao Chen, Benito Munoz and Nicholas D. Smith

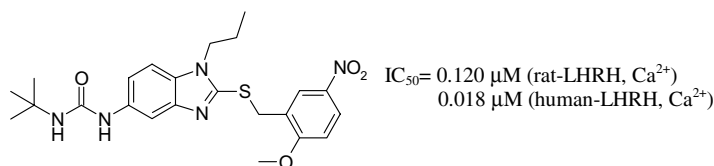


Interest in water soluble COX-2 inhibitors that can be administered intravenously led to the development of novel pro-drugs of a furanone based COX-2 inhibitor **2**. Transforming the lactone moiety of the furanone to an imidate or an *ortho*-ester with a hydrophilic, endogenous appendage resulted in water soluble pro-drugs that converted to the parent drug in vivo.

**Benzimidazoles as non-peptide luteinizing hormone-releasing hormone (LHRH) antagonists. Part 3: Discovery of 1-(1*H*-benzimidazol-5-yl)-3-*tert*-butylurea derivatives**

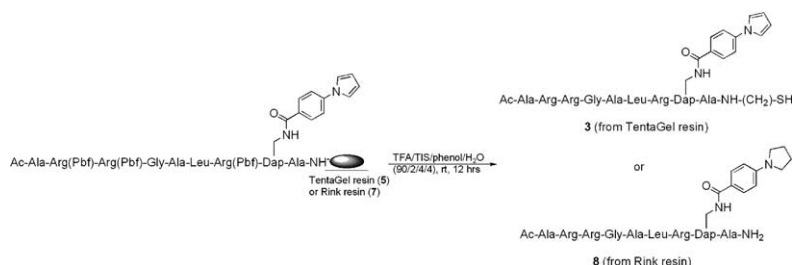
pp 2265–2269

Miyuki Tatsuta,\* Mikayo Kataoka, Kayo Yasoshima, Sachiko Sakakibara, Yuka Shogase, Makoto Shimazaki, Takeshi Yura, Yingfu Li, Noriyuki Yamamoto, Jang Gupta and Klaus Urbahns

**Reduction of a 4-pyrrole phenylacyl-containing peptide with trifluoroacetic acid–triisopropylsilane–phenol–H<sub>2</sub>O during solid-phase peptide synthesis and its protein kinase C  $\alpha$  inhibitory activity**

pp 2271–2274

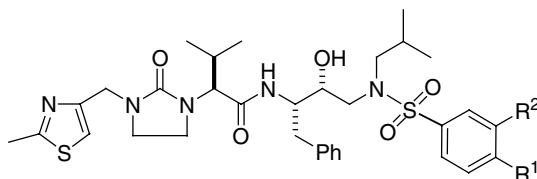
Jung Hwan Lee



**Oximinoarylsulfonamides as potent HIV protease inhibitors**

pp 2275–2278

Clinton M. Yeung,\* Larry L. Klein, Charles A. Flentge, John T. Randolph, Chen Zhao, MingHua Sun, Tatyana Dekhtyar, Vincent S. Stoll and Dale J. Kempf



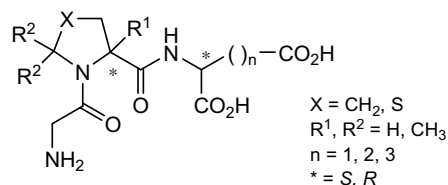
A novel series of arylsulfonamides with various  $R^1$  and  $R^2$  groups were prepared and evaluated as HIV protease inhibitors against both the wild type and A17 resistant viruses. The X-ray crystal structure of the most active oxime analog bound in the enzyme active site is presented.

**Analogues of the neuroprotective tripeptide Gly-Pro-Glu (GPE): synthesis and structure–activity relationships**

pp 2279–2283

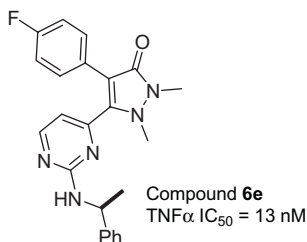
Sergio A. Alonso De Diego, Pilar Muñoz, Rosario González-Muñiz, Rosario Herranz, Mercedes Martín-Martínez, Edurne Cenarruzabeitia, Diana Frechilla, Joaquín Del Río, M. Luisa Jimeno\* and M. Teresa García-López\*

A series of Pro and/or Glu modified GPE analogues is described. Compounds incorporating  $P^{Me}$  and dmP showed higher affinity for glutamate receptors than GPE and neuroprotective effects similar to those of this endogenous tripeptide in culture hippocampal neurons exposed to NMDA.

**The development of monocyclic pyrazolone based cytokine synthesis inhibitors**

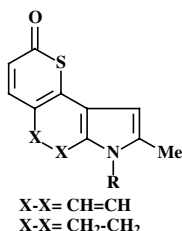
pp 2285–2289

Adam Golebiowski,\* Jennifer A. Townes, Matthew J. Lauferweiler, Todd A. Brugel, Michael P. Clark, Cynthia M. Clark, Jane F. Djung, Steven K. Laughlin, Mark P. Sabat, Roger G. Bookland, John C. VanRens, Biswanath De, Lily C. Hsieh, Michael J. Janusz, Richard L. Walter, Mark E. Webster and Marlene J. Mekel

**Synthesis and photochemotherapeutic activity of thiopyrano[2,3-*c*]indol-2-ones**

pp 2291–2294

Paola Barraja, Laura Sciabica, Patrizia Diana, Antonino Lauria, Alessandra Montalbano, Anna Maria Almerico, Gaetano Dattolo, Girolamo Cirrincione,\* Silvia Disarò, Giuseppe Basso, Giampietro Viola and Francesco Dall'Acqua

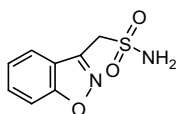




**Carbonic anhydrase inhibitors. Zonisamide is an effective inhibitor of the cytosolic isozyme II and mitochondrial isozyme V: solution and X-ray crystallographic studies**

pp 2315–2320

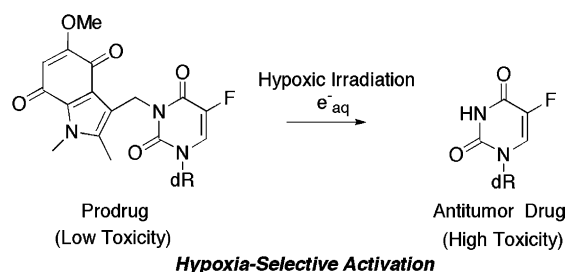
Giuseppina De Simone,\* Anna Di Fiore, Valeria Menchise, Carlo Pedone, Jochen Antel, Angela Casini, Andrea Scozzafava, Michael Wurl and Claudiu T. Supuran\*

**Hypoxia-selective activation of 5-fluorodeoxyuridine prodrug possessing indolequinone structure: radiolytic reduction and cytotoxicity characteristics**

pp 2321–2324

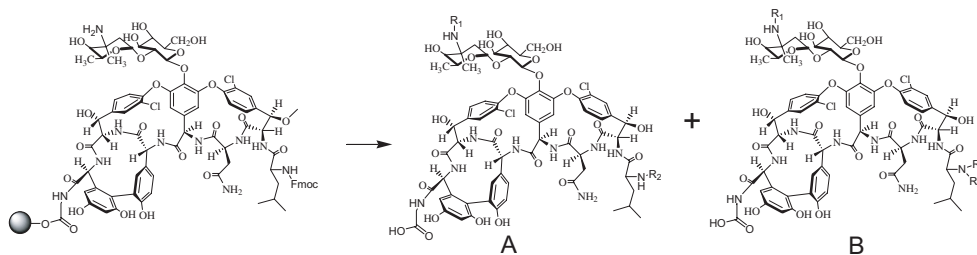
Kazuhito Tanabe,\* Yuji Makimura, Yukihiro Tachi, Akemi Imagawa-Sato and Sei-ichi Nishimoto\*

We designed and synthesized a 5-fluorodeoxyuridine (**5-FdUrd**) prodrug possessing an indolequinone structure that releases antitumor agent **5-FdUrd** via hypoxia-selective activation by ionizing radiation.

**Solid-phase synthesis and antibacterial evaluations of *N*-demethylvancomycin derivatives**

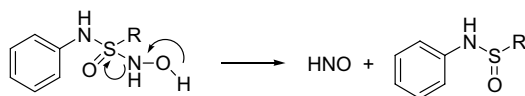
pp 2325–2329

Nian-Huan Yao, Gang Liu,\* Wen-Yi He, Changqun Niu, James R. Carlson and Kit S. Lam

***N*-Hydroxy sulfonimidamides as new nitroxyl (HNO) donors**

pp 2331–2334

Richard L. Pennington, Xin Sha and S. Bruce King\*



Chlorination and condensation of simple sulfonamides with *O*-benzyl and *O*-*tert*-butyl dimethyl siloxy hydroxylamine gives *O*-protected *N*-hydroxy sulfonimidamides. Deprotection of these compounds produces the corresponding sulfonamide and nitrous oxide, which provides evidence for the intermediacy of nitroxyl (HNO) and identifies these compounds as new potential HNO donors.

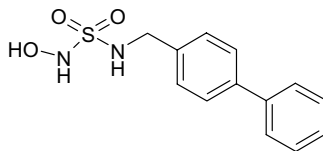




**Carbonic anhydrase inhibitors: synthesis and inhibition of cytosolic/tumor-associated carbonic anhydrase isozymes I, II, IX, and XII with *N*-hydroxysulfamides—a new zinc-binding function in the design of inhibitors**

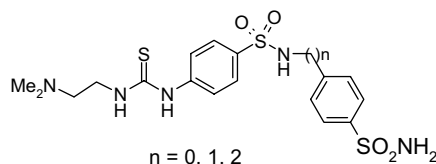
pp 2353–2358

Jean-Yves Winum, Alessio Innocenti, Jihane Nasr, Jean-Louis Montero, Andrea Scozzafava, Daniela Vullo and Claudiu T. Supuran\*

**Carbonic anhydrase inhibitors: synthesis and inhibition of cytosolic/tumor-associated carbonic anhydrase isozymes I, II, and IX with sulfonamides incorporating thioureido-sulfanilyl scaffolds**

pp 2359–2364

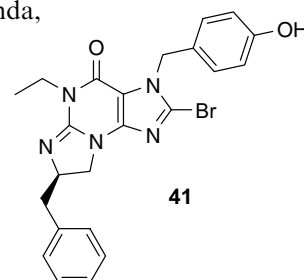
Luca Puccetti, Giuseppe Fasolis, Alessandro Cecchi, Jean-Yves Winum, Alessandro Gamberi, Jean-Louis Montero, Andrea Scozzafava and Claudiu T. Supuran\*

**Optimization of purine based PDE1/PDE5 inhibitors to a potent and selective PDE5 inhibitor for the treatment of male ED**

pp 2365–2369

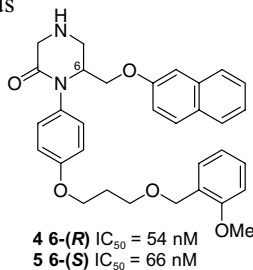
Craig D. Boyle,\* Ruo Xu,\* Theodros Asberom, Samuel Chackalamannil, John W. Clader, William J. Greenlee, Henry Guzik, Yueqing Hu, Zhiyong Hu, Claire M. Lankin, Dmitri A. Pissarnitski, Andrew W. Stamford, Yuguang Wang, Jeffrey Skell, Stanley Kurowski, Subbarao Vemulapalli, Jairam Palamanda, Madhu Chintala, Ping Wu, Joyce Myers and Peng Wang

In search of a PDE5 inhibitor for erectile dysfunction, an SAR was developed from a PDE1/PDE5 purine series of leads, which had modest PDE5 potency and poor isozyme selectivity. A compound (**41**) with PDE5 inhibition and in vivo activity similar to sildenafil was discovered from this effort. In addition, purine **41** demonstrated superior overall PDE isozyme selectivity when compared to the approved PDE5 inhibitors sildenafil, vardenafil, and tadalafil, which may result in a more favorable side-effect profile.

**Equipotent activity in both enantiomers of a series of ketopiperazine-based renin inhibitors**

pp 2371–2374

Noel A. Powell,\* Emma H. Clay, Daniel D. Holsworth, John W. Bryant, Michael J. Ryan, Mehran Jalaie, Erli Zhang and Jeremy J. Edmunds



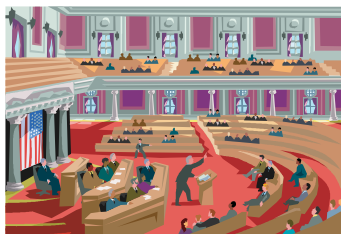
Both enantiomeric configurations of the 6-alkoxymethyl-1-aryl-2-piperazinone scaffold display equipotent renin inhibition activity and similar SAR patterns.



**Quorum sensing in *Vibrio harveyi*: probing the specificity of the LuxP binding site**

pp 2395–2398

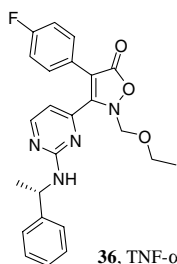
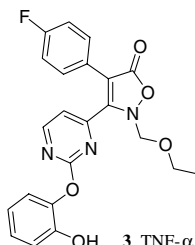
Colin A. Lowery, Kathleen M. McKenzie, Longwu Qi, Michael M. Meijler and Kim D. Janda\*



Session adjourned! DPD analogs fail to produce quorum.

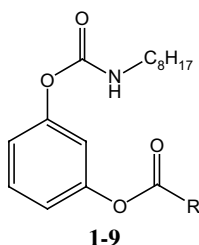
**The development of new isoxazolone based inhibitors of tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) production** pp 2399–2403

Steven K. Laughlin, Michael P. Clark,\* Jane F. Djung, Adam Golebiowski, Todd A. Brugel, Mark Sabat, Roger G. Bookland, Matthew J. Laufersweiler, John C. VanRens, Jennifer A. Townes, Biswanath De, Lily C. Hsieh, Susan C. Xu, Richard L. Walter, Marlene J. Mekel and Michael J. Janusz

**36**, TNF- $\alpha$  IC<sub>50</sub> = 200 nM**3**, TNF- $\alpha$  IC<sub>50</sub> = 140 nM**QSAR for phospholipase A<sub>2</sub> inhibitions by 1-acyloxy-3-*N*-*n*-octylcarbamyl-benzenes**

pp 2405–2408

Gialih Lin\* and Gia-Yun Yu

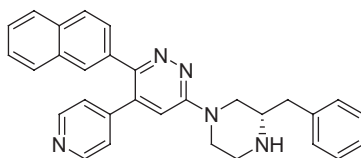
**1-9**

For the steady state inhibitions of PLA<sub>2</sub> by **1-9**,  $pK_i = 3.88 \pm 0.06 - (0.08 \pm 0.03)\sigma^* + (0.15 \pm 0.02)\pi$ . For the pre-steady state inhibitions of PLA<sub>2</sub> by **1-9**,  $\log(k_1/k_{-1}) = 5.21 \pm 0.01 - (0.09 \pm 0.01)\sigma^*$  and  $\log(k_2/k_{-2}) = -1.29 \pm 0.07 - (0.13 \pm 0.02)\pi$ .

**Design and synthesis of potent pyridazine inhibitors of p38 MAP kinase**

pp 2409–2413

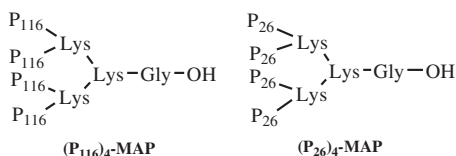
Nuria Tamayo,\* Lillian Liao, Martin Goldberg, David Powers, Yan-Yan Tudor, Violeta Yu, Lu Min Wong, Bradley Henkle, Scot Middleton, Rashid Syed, Timothy Harvey, Graham Jang, Randall Hungate and Celia Dominguez\*



Novel potent trisubstituted pyridazine inhibitors of p38 MAP (mitogen activated protein) kinase are described that have activity in both cell-based assays of cytokine release and animal models of rheumatoid arthritis. They demonstrated potent inhibition of LPS-induced TNF- $\alpha$  production in mice and exhibited good efficacy in the rat collagen induced arthritis model.

**Synthesis and bioactivities of two multiple antigen peptides as potential vaccine against schistosoma** pp 2415–2419

He-Qing Huang, Shu-Chun Li, Zhi-Hui Qin, Sheng-Li Cao, Yun Yao, Yu-Shi Liu,  
Huai-Yu Li, Meng-Shen Cai, Zhong-Jun Li\* and You-En Shi



**P<sub>116</sub>**: Pro-Gln-Glu-Glu-Lys-Ile-Thr-Lys-Glu-Ile-Leu-Asn-Gly-Lys

**P<sub>26</sub>**: Ala-Ala-Gly-Val-Asp-Tyr-Glu-Asp-Glu-Arg-Ile-Ser-Phe-Gln-Asp-Trp-Pro-Lys

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Corrigendum

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Contributors to this issue

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Instructions to contributors

pp III–VI

\*Corresponding author

Supplementary data available via ScienceDirect

**COVER**

Trisubstituted pyridazines derivatives (gold and blue) modeled in the active site of p38 $\alpha$  MAP kinase crystal structure. A structure-based design approach was used to guide the evolution of the original class resulting in a novel p38 $\alpha$  inhibitor series. [Tamayo, N.; Liao, L.; Goldberg, M.; Powers, D.; Tudor, Y.-Y.; Yu, V.; Wong, L. M.; Henkle, B.; Middleton, S.; Syed, R.; Harvey, T.; Jang, G.; Hungate, R.; Dominguez, C. *Bioorg. Med. Chem. Lett.* **2005**, 15, 2409.]



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ISSN 0960-894X