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# Bioorganic & Medicinal Chemistry Letters

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## Bioorganic & Medicinal Chemistry Letters Vol. 18, No. 19, 2008

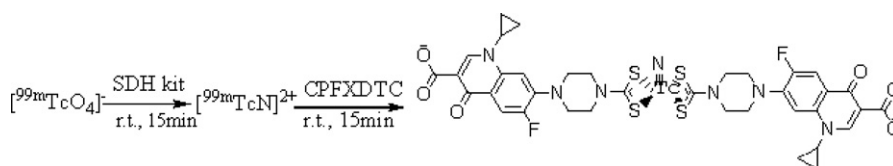
### Contents

#### ARTICLES

#### Synthesis and biodistribution of a novel $^{99m}\text{TcN}$ complex of ciprofloxacin dithiocarbamate as a potential agent for infection imaging

pp 5168–5170

Junbo Zhang\*, Haixun Guo, Shijian Zhang, Yan Lin, Xuebin Wang

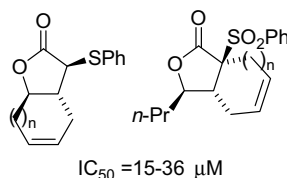


The ciprofloxacin dithiocarbamate (CPFXDTC) was synthesized and radiolabeled with  $[\text{}^{99m}\text{TcN}]^{2+}$  to form  $^{99m}\text{TcN-CPFXDTC}$  in high yield. The biodistribution results suggested  $^{99m}\text{TcN-CPFXDTC}$  would be a novel potential infection imaging agent.

#### $\gamma$ -Lactones $\alpha,\beta$ - and $\beta,\gamma$ -fused to carbocycles as novel antiproliferative drugs

pp 5171–5173

Leticia G. León, Rubén P. Machín, Carmen M. Rodríguez, José L. Ravelo, Víctor S. Martín, José M. Padrón\*

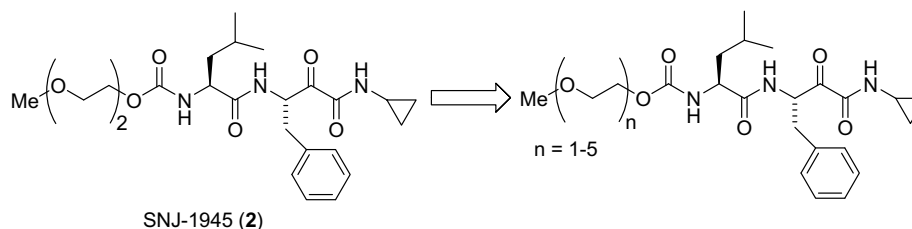


The synthesis and antiproliferative activity of  $\gamma$ -lactones  $\alpha,\beta$ -fused and  $\beta,\gamma$ -fused to carbocycles are reported.

#### Molecular design to enhance the penetration into the retina via ocular instillation

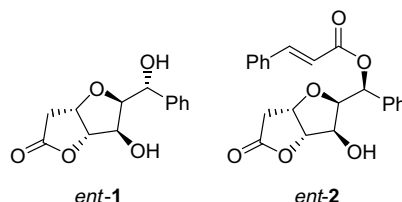
pp 5174–5177

Yoshihisa Shirasaki\*, Hiroaki Takahashi, Masazumi Yamaguchi, Jun Inoue



### Synthesis and antiproliferative activity of unnatural enantiomers of 7-*epi*-goniofufurone and crassalactone C pp 5178–5181

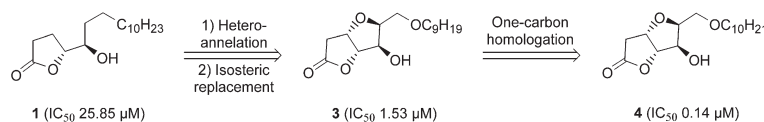
Velimir Popsavin\*, Goran Benedeković, Bojana Srećo, Mirjana Popsavin, Jovana Francuz, Vesna Kojić, Gordana Bogdanović



The unnatural styryl lactones (–)-7-*epi*-goniofufurone (*ent*-1) and (–)-crassalactone C (*ent*-2) have been synthesized and evaluated for their in vitro antitumour activities against a number of human neoplastic cell lines.

### Design, synthesis and antiproliferative activity of two new heteroannulated (–)-muricatacin mimics pp 5182–5185

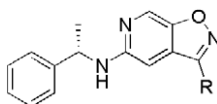
Velimir Popsavin\*, Bojana Srećo, Goran Benedeković, Mirjana Popsavin, Jovana Francuz, Vesna Kojić, Gordana Bogdanović



(–)-Muricatacin (**1**) and the related mimics **3** and **4** have been synthesized and evaluated for their in vitro antitumour activity.

### Design and synthesis of 2-amino-isoxazopyridines as Polo-like kinase inhibitors pp 5186–5189

Emily J. Hanan\*, Raymond V. Fucini, Michael J. Romanowski, Robert A. Elling, Willard Lew, Hans E. Purkey, Erica C. VanderPorten, Wenjin Yang

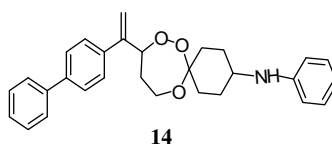


A series of 2-amino-isoxazopyridine analogs was identified as inhibitors of Polo-like kinase (Plk). Co-crystal structures of inhibitors with Plk demonstrate key binding motifs. Differential selectivity among the three Plk isoforms is observed.



### New functionalized 1,2,4-trioxepanes: Synthesis and antimalarial activity against multi-drug resistant *P. yoelii* in mice pp 5190–5193

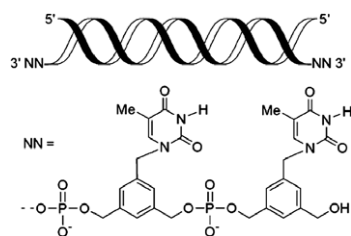
Chandan Singh\*, Shilpi Pandey, Ambuj K. Kushwaha, Sunil K. Puri



A series of new amino functionalized 1,2,4-trioxepanes **8–16** and ester functionalized 1,2,4-trioxepanes **17–19** have been synthesized and evaluated against multi-drug resistant *Plasmodium yoelii* in Swiss mice. Amino functionalized trioxepanes **14**, the most active compound of the series, showed 100% clearance of parasitaemia by oral route on day 4 and 75% protection to the treated mice beyond day 28.

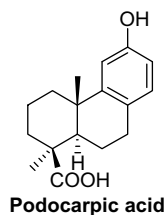
**Synthesis of nuclease-resistant siRNAs possessing benzene-phosphate backbones in their 3'-overhang regions** pp 5194–5196

Yoshihito Ueno\*, Takumi Inoue, Mahito Yoshida, Kayo Yoshikawa, Aya Shibata, Yoshiaki Kitamura, Yukio Kitade\*

**Design, synthesis and characterization of podocarpate derivatives as openers of BK channels**

pp 5197–5200

Yong-Mei Cui, Eriko Yasutomi, Yuko Otani, Takashi Yoshinaga, Katsutoshi Ido, Kohei Sawada, Tomohiko Ohwada\*

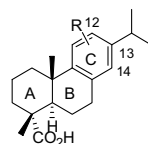


We found that the podocarpic acid structure provides a new scaffold for chemical modulators of large-conductance calcium-activated  $K^+$  channels (BK channels).

**Novel BK channel openers containing dehydroabietic acid skeleton: Structure–activity relationship for peripheral substituents on ring C**

pp 5201–5205

Yong-Mei Cui, Eriko Yasutomi, Yuko Otani, Takashi Yoshinaga, Katsutoshi Ido, Kohei Sawada, Tomohiko Ohwada\*

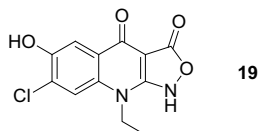


A series of dehydroabietic acid derivatives was synthesized and evaluated as BK channel openers in an assay system of CHO-K1 cells expressing hBK $\alpha$  channels.

**Isoxazolo[3,4-*b*]quinoline-3,4(1H,9H)-diones as unique, potent and selective inhibitors for Pim-1 and Pim-2 kinases: Chemistry, biological activities, and molecular modeling**

pp 5206–5208

Yunsong Tong\*, Kent D. Stewart, Sheela Thomas, Magdalena Przytulinska, Eric F. Johnson, Vered Klinghofer, Joel Levenson, Owen McCall, Niru B. Soni, Yan Luo, Nan-horng Lin, Thomas J. Sowin, Vincent L. Giranda, Thomas D. Penning

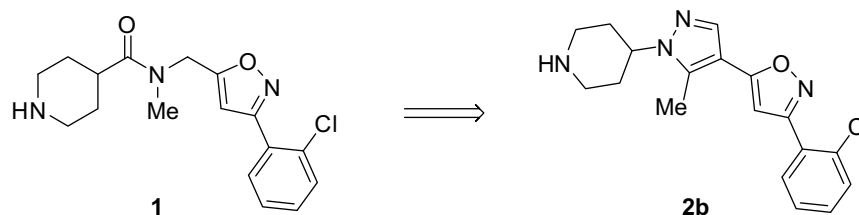


SAR studies guided by molecular modeling led to a potent inhibitor, **19**, against Pim-1 ( $K_i$  = 2.5 nM) and Pim-2 ( $K_i$  = 43.5 nM). The hydroxyl group is crucial for an H-bond interaction to the hinge region of the kinase active domain.

**Discovery and optimization of substituted piperidines as potent, selective, CNS-penetrant  $\alpha 4\beta 2$  nicotinic acetylcholine receptor potentiators**

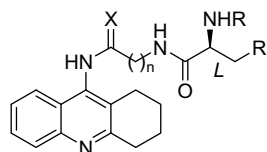
pp 5209–5212

Brian K. Albrecht\*, Virginia Berry, Alessandro A. Boezio, Lei Cao, Kristie Clarkin, Wenhong Guo, Jean-Christophe Harmange, Markus Hierl, Liyue Huang, Brett Janosky, Johannes Knop, Annika Malmberg, Jeff S. McDermott, Hung Q. Nguyen, Stephanie K. Springer, Daniel Waldon, Katrina Woodin, Stefan I. McDonough


**Tacrine based human cholinesterase inhibitors: Synthesis of peptidic-tethered derivatives and their effect on potency and selectivity**

pp 5213–5216

Stefania Butini, Egeria Guarino, Giuseppe Campiani\*, Margherita Brindisi, Salvatore Sanna Coccone, Isabella Fiorini, Ettore Novellino, Tatyana Belinskaya, Ashima Saxena, Sandra Gemma

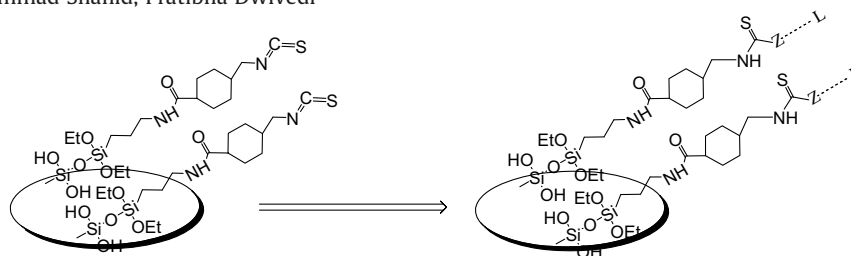


Synthesis and biological evaluation of tacrine based hChEIs containing specific peptidic tethers is described.

**N-(3-Triethoxysilylpropyl)-4-(isothiocyanatomethyl)-cyclohexane-1-carboxamide (TPICC): A heterobifunctional reagent for immobilization of biomolecules on glass surface**

pp 5217–5221

Arvind Misra\*, Mohammad Shahid, Pratibha Dwivedi



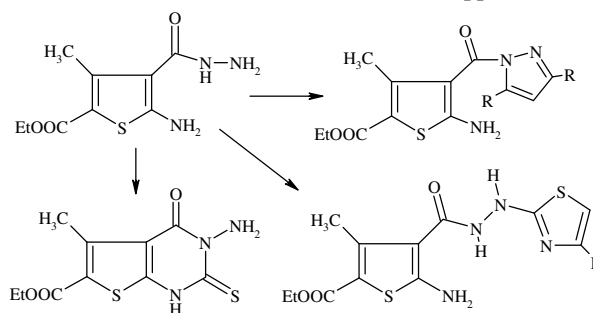
L = Ligands, peptides, oligonucleotides; Z = S, N.

**Design and synthesis of 3-pyrazolyl-thiophene, thieno[2,3-d]pyrimidines as new bioactive and pharmacological activities**

pp 5222–5227

H. N. Hafez\*, A. B. A. El-Gazzar

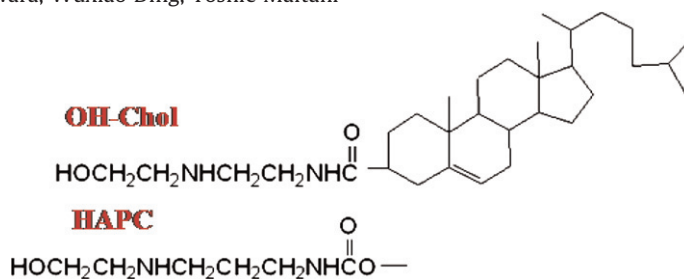
Two series of 5-ethyl-2-amino-3-pyrazolyl-4-methylthiophenecarboxylate and 2-thioxo-*N*<sup>3</sup>-aminothiopheno[2,3-*d*]pyrimidines were prepared from 3,5-diethyl-2-amino-4-methylthiophenecarboxylate and evaluated as anti-inflammatory, analgesic and ulcerogenic activities. Among the compounds studied, compounds which containing the substituted hydrazide at C-3 position **7**, **16**, and **17a** showed more potent anti-inflammatory and analgesic activities than the standard drug (Indomethacin and Aspirin), along without ulcerogenicity. While compounds **2**, **5**, **9**, **10**, and **11c** showed moderate activities. Some of the newly synthesized compounds have good to excellent antimicrobial activity.



**NaCl improves siRNA delivery mediated by nanoparticles of hydroxyethylated cationic cholesterol with amido-linker**

pp 5228–5232

Yoshiyuki Hattori\*, Ayako Hagiwara, Wuxiao Ding, Yoshie Maitani

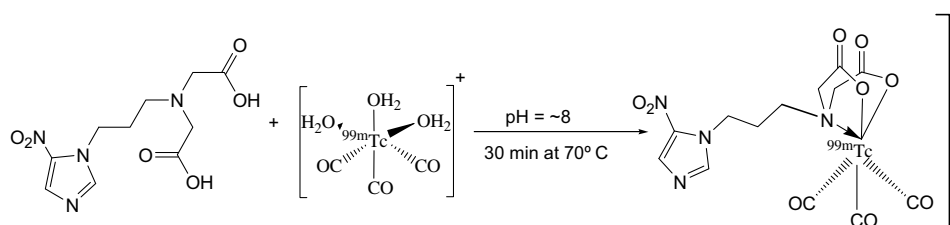


The structure of cationic derivatives of cholesterol.

**On the isolation and evaluation of a novel unsubstituted 5-nitroimidazole derivative as an agent to target tumor hypoxia**

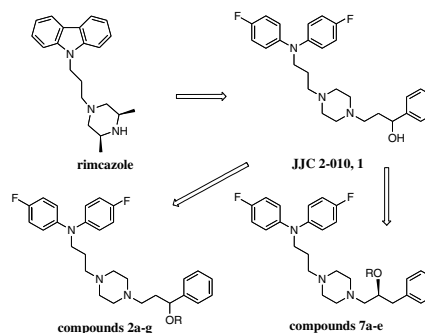
pp 5233–5237

Madhava B. Mallia, Suresh Subramanian, Anupam Mathur, H. D. Sarma, Meera Venkatesh, Sharmila Banerjee\*

**Dual DAT/σ1 receptor ligands based on 3-(4-(3-(bis(4-fluorophenyl)amino)propyl)piperazin-1-yl)-1-phenylpropan-1-ol**

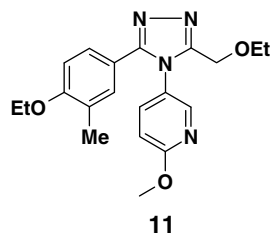
pp 5238–5241

Jianjing Cao, Theresa Kopajtic, Jonathan L. Katz, Amy Hauck Newman\*

**Triazole oxytocin antagonists: Identification of aryl ether replacements for a biaryl substituent**

pp 5242–5244

Alan Brown\*, Lindsay Brown, T. Bruce Brown, Andrew Calabrese, Dave Ellis, Nicholas Puhalo, Chris R. Smith, Olga Wallace, Lesa Watson

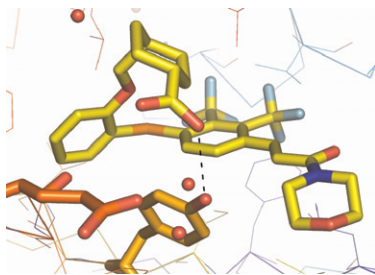


Several potent aryl ether/triazole oxytocin antagonists are described. The lead compound in this series, **11**, had significantly improved aqueous solubility over related systems containing a biaryl substituent.

**Structure–activity relationship of *ortho*- and *meta*-phenol based LFA-1 ICAM inhibitors**

pp 5245–5248

Edward Yin-Shiang Lin<sup>\*</sup>, Kevin M. Guckian, Laura Silvian, Donovan Chin, P. Ann Boriack-Sjodin, Herman van Vlijmen, Jessica E. Friedman, Daniel M. Scott



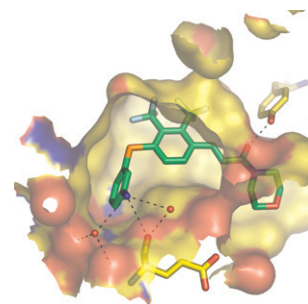
X-ray co-crystal data assisted the design of LFA-1 ICAM inhibitors based on *ortho*- and *meta*-phenol templates, leading to a compound which exploited a new hydrogen bond to the I-domain and which exhibited subnanomolar potency in the LFA-1/ICAM1-Ig assay.

**Design and synthesis of a series of *meta* aniline-based LFA-1 ICAM inhibitors**

pp 5249–5251

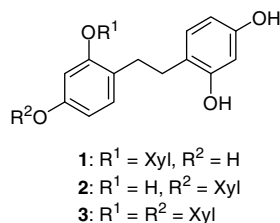
Kevin M. Guckian<sup>\*</sup>, Edward Yin-Shiang Lin, Laura Silvian, Jessica E. Friedman, Donovan Chin, Daniel M. Scott

A series of *meta*-substituted anilines were designed and synthesized to inhibit the interaction of LFA-1 with ICAM for the treatment of autoimmune disease. Design of these molecules was performed by utilizing a co-crystal structure for structure-based drug design. The resulting molecules were found to be potent and to possess favorable pharmaceutical properties.

**Molecular design of potent tyrosinase inhibitors having the bibenzyl skeleton**

pp 5252–5254

Hiromi Oozeki, Reiko Tajima, Ken-ichi Nihei<sup>\*</sup>

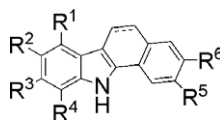


In order to develop water soluble tyrosinase inhibitors, bibenzyl xyloside **1** isolated from *Chlorophytum arundinaceum* (liliaceae), and its derivatives **2** and **3** were synthesized by using Wittig reaction and trichloroimidate glycosylation procedure as key steps. Xylosides **1–3** showed potent tyrosinase inhibitory activity with IC<sub>50</sub>s of 1.6, 0.43, and 0.73 μM, respectively, although each NMR data of synthetic bibenzyls was not identical to that of naturally occurring xyloside **1**.

**Discovery and biological evaluation of benzo[*a*]carbazole-based small molecule agonists of the thrombopoietin (Tpo) receptor**

pp 5255–5258

Phil B. Alper, Thomas H. Marsilje<sup>\*</sup>, Daniel Mutnick, Wenshuo Lu, Arnab Chatterjee, Michael J. Roberts, Yun He, Donald S. Karanewsky, Donald Chow, Jianmin Lao, Andrea Gerken, Tove Tuntland, Bo Liu, Jonathan Chang, Perry Gordon, H. Martin Seidel, Shin-Shay Tian

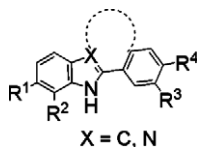


A novel series of benzo[*a*]carbazole-based small molecule agonists of the thrombopoietin (Tpo) receptor is reported. Members of this series have been identified which are full agonists with functional potency <50 nM and oral bioavailability in mice.

**Optimization of small molecule agonists of the thrombopoietin (Tpo) receptor derived from a benzo[a]carbazole hit scaffold**

pp 5259–5262

Thomas H. Marsilje\*, Phil B. Alper, Wenshuo Lu, Daniel Mutnick, Pierre-Yves Michellys, Yun He, Donald S. Karanewsky, Donald Chow, Andrea Gerken, Jianmin Lao, Min-Ju Kim, H. Martin Seidel, Shin-Shay Tian

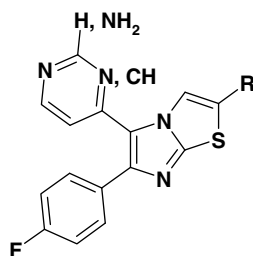


The lead optimization of a novel series of benzo[a]carbazole-based small molecule agonists of the thrombopoietin (Tpo) receptor is reported. Analog **21** demonstrates equivalent efficacy in the human megakaryocyte differentiation (CFU-mega) assay compared to Eltrombopag<sup>TM</sup>.

**Synthesis and biological activity of anticoccidial agents: 5,6-Diarylimidazo[2,1-b][1,3]thiazoles**

pp 5263–5267

Andrew Scribner\*, Susan Meitz, Michael Fisher, Matthew Wyvratt, Penny Leavitt, Paul Liberator, Anne Gurnett, Chris Brown, John Mathew, Donald Thompson, Dennis Schmatz, Tesfaye Biftu

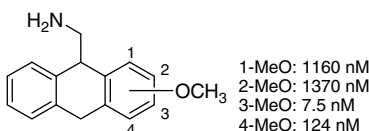


In this study, we present the synthesis and biological activity of 5,6-diarylimidazo[2,1-b][1,3]thiazoles, whose antiparasitic activity against *Eimeria* is due to inhibition of a parasite-specific cGMP-dependent protein kinase (PKG). From this series, several compounds showed subnanomolar in vitro activity and commercial levels of in vivo activity.

**Methoxy-substituted 9-aminomethyl-9,10-dihydroanthracene (AMDA) derivatives exhibit differential binding affinities at the 5-HT<sub>2A</sub> receptor**

pp 5268–5271

Gajanan K. Dewkar, Srinivas Peddi, Philip D. Mosier, Bryan L. Roth, Richard B. Westkaemper\*

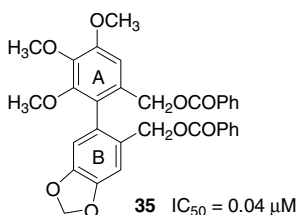


The synthesis and 5-HT<sub>2A</sub> receptor affinities of a series of methoxy-substituted 9-aminomethyl-9,10-dihydroanthracene (AMDA) derivatives are reported. Molecular modeling techniques are used to elucidate probable binding modes for the compounds.

**Synthesis of unsymmetrical biphenyls as potent cytotoxic agents**

pp 5272–5276

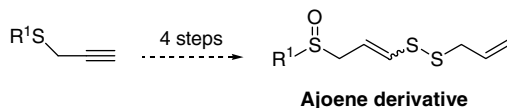
Gang Wu, Huan-Fang Guo, Kun Gao, Yi-Nan Liu, Kenneth F. Bastow, Susan L. Morris-Natschke, Kuo-Hsiung Lee, Lan Xie\*



**Substituted ajoenes as novel anti-cancer agents**

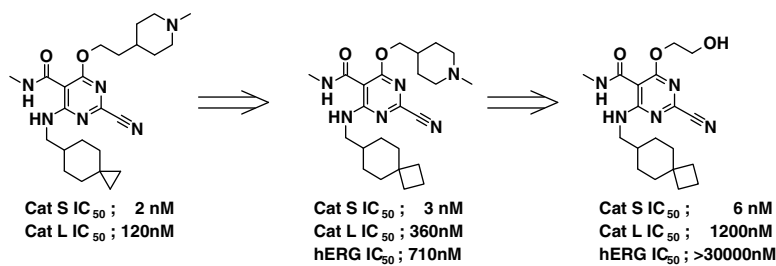
pp 5277–5279

Roger Hunter\*, Catherine H. Kaschula\*, Iqbal M. Parker, Mino R. Caira, Philip Richards, Susan Travis, Francois Taute, Thozama Qwebani

**Overcoming hERG issues for brain-penetrating cathepsin S inhibitors: 2-Cyanopyrimidines. Part 2**

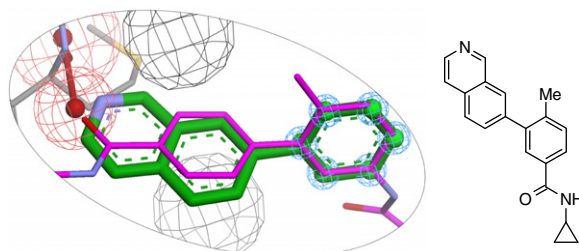
pp 5280–5284

Osamu Irie\*, Takatoshi Kosaka, Masashi Kishida, Junichi Sakaki, Keiichi Masuya, Kazuhide Konishi, Fumiaki Yokokawa, Takeru Ehara, Atsuko Iwasaki, Yuki Iwaki, Yuko Hitomi, Atsushi Toyao, Hiroki Gunji, Naoki Teno, Genji Iwasaki, Hajime Hirao, Takanori Kanazawa, Keiko Tanabe, Peter C. Hiestand, Marzia Malcangio, Alyson J. Fox, Stuart J. Bevan, Mohammed Yaqoob, Andrew J. Culshaw, Terance W. Hart, Allan Hallett

**Kinase array design, back to front: Biaryl amides**

pp 5285–5289

Ian Baldwin, Paul Bamborough\*, Claudine G. Haslam, Suchete S. Hunjan, Tim Longstaff, Christopher J. Mooney, Shila Patel, Jo Quinn, Don O. Somers



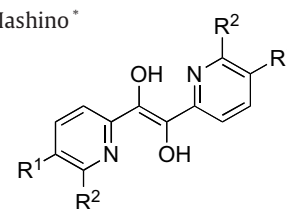
Most kinase-directed array strategies aim to add functionality to a fragment that binds in the purine subpocket of the ATP-site. Here, an alternative pharmacophore-guided array approach is described which set out to discover novel purine subpocket-binding groups. Results are shown for p38 $\alpha$  and cFMS kinase, for which multiple different series with nanomolar potency were discovered.

**2,2'-Pyridoin derivatives protect HL-60 cells against oxidative stress**

pp 5290–5293

Masashi Hatanaka, Chiho Nishizawa, Tomohiro Kakinoki, Kyoko Takahashi, Shigeo Nakamura, Tadahiko Mashino\*

The protective effects of 2,2'-pyridoin derivatives against oxidative stress in the HL-60 cell were evaluated. The derivatives **1–3** and **5–6** inhibited H<sub>2</sub>O<sub>2</sub>-induced cell death and intracellular oxidative stress more than ascorbic acid.

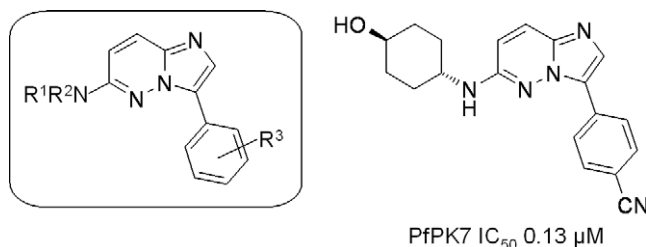


- 1: R<sup>1</sup> = H, R<sup>2</sup> = H
- 2: R<sup>1</sup> = H, R<sup>2</sup> = CH<sub>3</sub>
- 3: R<sup>1</sup> = H, R<sup>2</sup> = OCH<sub>3</sub>
- 5: R<sup>1</sup> = CH<sub>3</sub>, R<sup>2</sup> = H
- 6: R<sup>1</sup> = OCH<sub>3</sub>, R<sup>2</sup> = H

**Synthesis and in vitro evaluation of imidazopyridazines as novel inhibitors of the malarial kinase PfPK7**

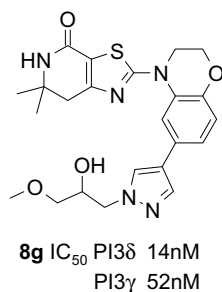
pp 5294–5298

Nathalie Boulouc, Jonathan M. Large, Ela Smiljanic, David Whalley, Keith H. Ansell, Christopher D. Edlin, Justin S. Bryans\*

**Optimization of a series of multi-isoform PI3 kinase inhibitors**

pp 5299–5302

Benjamin Perry\*, Rebekah Beevers, Gavin Bennett, George Buckley, Tom Crabbe, Lewis Gowers, Lynwen James, Kerry Jenkins, Chris Lock, Verity Sabin, Sara Wright

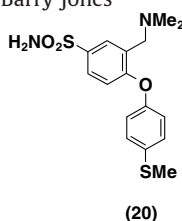


Optimization of the cellular and pharmacological activity of a novel series of PI3 kinase inhibitors targeting multiple isoforms is described.

**Designing rapid onset selective serotonin re-uptake inhibitors. Part 3: Site-directed metabolism as a strategy to avoid active circulating metabolites: Structure–activity relationships of (thioalkyl)phenoxy benzylamines**

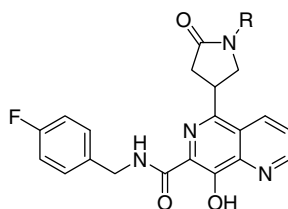
pp 5303–5306

Donald S. Middleton\*, Mark Andrews, Paul Glossop, Geoffrey Gymer, David Hepworth, Alan Jessiman, Patrick S. Johnson, Malcolm MacKenny, Alan Stobie, Kim Tang, Paul Morgan, Barry Jones

A series of thio-alkyl containing diphenylethers were designed and evaluated, as a strategy to competitively direct metabolism away from unwanted amine N-demethylation and deliver a pharmacologically inactive S-oxide metabolite. Overall, sulphonamide **20** was found to possess the best balance of target pharmacology, pharmacokinetics and metabolism profile.**Synthesis of 5-(1-H or 1-alkyl-5-oxopyrrolidin-3-yl)-8-hydroxy-[1,6]-naphthyridine-7-carboxamide inhibitors of HIV-1 integrase**

pp 5307–5310

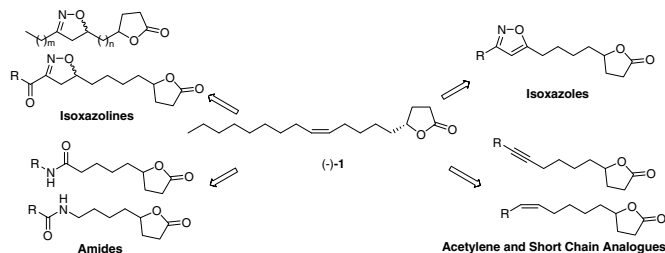
Jeffrey Y. Melamed\*, Melissa S. Egbertson, Sandor Varga, Joseph P. Vacca, Greg Moyer, Lori Gabryelski, Peter J. Felock, Kara A. Stillmock, Marc V. Witmer, William Schleif, Daria J. Hazuda, Yvonne Leonard, Lixia Jin, Joan D. Ellis, Steven D. Young

Antiviral Activity, IC<sub>95</sub> (50% NHS) = 63–125 nM

### Modification of the side chain of micromolide, an anti-tuberculosis natural product

pp 5311–5315

Hai Yuan, Rong He, Baojie Wan, Yuehong Wang, Guido F. Pauli, Scott G. Franzblau, Alan P. Kozikowski \*



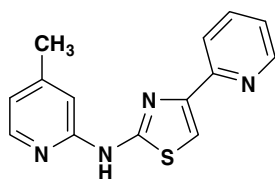
This paper describes a series of modifications of the side chain of micromolide, an anti-tuberculosis natural product. Most of the synthesized compounds showed significantly decreased activities, which suggests that the long aliphatic side chain of micromolide and its double bond are essential to its activity.



### Initial SAR studies on apamin-displacing 2-aminothiazole blockers of calcium-activated small conductance potassium channels

pp 5316–5319

Robert G. Gentles \*, Katherine Grant-Young, Shuanghua Hu, Yazhong Huang, Michael A. Poss, Charles Andres, Tracey Fiedler, Ronald Knox, Nicholas Lodge, C. David Weaver, David G. Harden



(13)

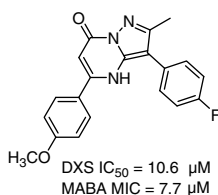
Comps	K <sub>Ca2.2</sub>	K <sub>Ca2.3</sub>
	Thallium Flux	[ <sup>125</sup> I]-Apamin
	IC <sub>50</sub> (μM)	Displacement
		IC <sub>50</sub> (μM)
13	0.059 (± 0.017)	0.004 (± 0.002)

An initial SAR study on a series of apamin-displacing 2-aminothiazole K<sub>Ca2</sub> channel blockers is described. Potent inhibitors such as *N*-(4-methylpyridin-2-yl)-4-(pyridin-2-yl)thiazol-2-amine (13) are disclosed.

### Structure–activity relationships of compounds targeting mycobacterium tuberculosis 1-deoxy-D-xylulose 5-phosphate synthase

pp 5320–5323

Jialin Mao, Hyungjin Eoh, Rong He, Yuehong Wang, Baojie Wan, Scott G. Franzblau \*, Dean C. Crick \*, Alan P. Kozikowski \*



2-Methyl-3-(4-fluorophenyl)-5-(4-methoxy-phenyl)-4H-pyrazolo[1,5-a]pyrimidin-7-one is identified to inhibit *Mycobacterium tuberculosis* DXS with an IC<sub>50</sub> of 10.6 μM.



#### OTHER CONTENTS

#### Summary of instructions to authors

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\*Corresponding author

Supplementary data available via ScienceDirect

**COVER**

Overlay of high resolution co-crystal structures of *R*-**22**-ADP (cyan) and **1**-ADP (green) bound in an allosteric binding site of the mitotic kinesin KSP. [Roecker, A. J.; Coleman, P. J.; Mercer, S. P.; Schreier, J. D.; Buser, C. A.; Walsh, E. S.; Hamilton, K.; Lobell, R. B.; Tao, W.; Diehl, R. E.; South, V. J.; Davide, J. P.; Kohl, N. E.; Yan, Y.; Kuo, L. C.; Li, C.; Fernandez-Metzler, C.; Mahan, E. A.; Prueksaritanont, T.; Hartman, G. D. *Bioorg. Med. Chem. Lett.* **2007**, 17, 5677.]

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