

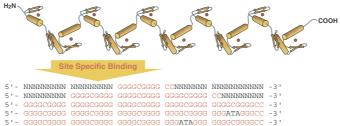
Bioorganic & Medicinal Chemistry Letters Vol. 15, No. 9, 2005

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^2 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, Niranjan Pandey, Sandra Moreno-Mazza, Steven A. Middleton and Linda K. Jolliffe

$$H_2N$$
 H_2N
 H_2N

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 IC₅₀ values of 0.28, 0.21, and 0.22 μ M, respectively, and were more potent than the clinically used ZD1694, **2** and LY231514, **3** against human TS.

X = F, Cl, Br, CN, NO₂, CF₃, OCF₃



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 [³H]MK801 binding, their NMDA-NR2B subtype selectivity and their affinity to HERG K+ channels.

MeO
$$NR^1$$
MeO NR^1
 $R^1 = H, Me$
 $R^2 = CI, OMe$

4

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

$$H_{2}N$$

$$H_{2}N$$

$$NH$$

$$N$$

$$R^{1}$$

$$Z = R, NHR$$

Reductive amination followed by acylation of polymer-linked formyl aryl amidines generate combinatorial libraries of aryl amidines. Potent small molecule naphthylamidine inhibitors ($K_i < 100 \text{ nM}$) 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 β -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 β -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: pp 2265–2269 Discovery of 1-(1*H*-benzimidazol-5-yl)-3-*tert*-butylurea derivatives

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

NO₂ IC₅₀= 0.120
$$\mu$$
M (rat-LHRH, Ca²⁺) 0.018 μ M (human-LHRH, Ca²⁺)

Reduction of a 4-pyrrole phenylacyl-containing peptide with trifluoroacetic acid-triisopropylsilane-phenol- H_2O during solid-phase peptide synthesis and its protein kinase C α inhibitory activity Jung Hwan Lee

pp 2271-2274

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. Laufersweiler, 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-e]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

Furanyl-1,3-thiazol-2-yl and benzoxazol-5-yl acetic acid derivatives: novel classes of heparanase inhibitor

pp 2295-2299

Stephen M. Courtney, Philip A. Hay, Richard T. Buck, Claire S. Colville, David J. Phillips, David I. C. Scopes, Faye C. Pollard, Martin J. Page, James M. Bennett, Margaret L. Hircock, Edward A. McKenzie, Maina Bhaman, Robert Felix, Colin R. Stubberfield* and Paul R. Turner

Using a furanylthiazole acetic acid as a starting point, a novel series of benzoxazol-5-yl acetic acid derivatives have been identified as heparanase inhibitors. Several compounds possess an IC_{50} of ~200 nM against heparanase.

Synthesis and antimycobacterial activity of ferrocenyl ethambutol analogues and ferrocenyl diamines

Dorothée Razafimahefa, Dimby Andrianina Ralambomanana, Lies Hammouche, Lydie Pélinski,* Sylvia Lauvagie, Christiane Bebear, Jacques Brocard and Jeanne Maugein

pp 2301–2303

$$R$$
 $R = H, CH2OH $R$$

The synthesis and initial in vitro evaluation of ferrocenyl diamino alcohols and diamines as a new class of antimycobacterial ethambutol analogues are reported.

Discovery and optimisation of potent, selective, ethanolamine inhibitors of bacterial phenylalanyl tRNA synthetase

pp 2305–2309

Richard L. Jarvest,* Symon G. Erskine, Andrew K. Forrest, Andrew P. Fosberry, Martin J. Hibbs, Joanna J. Jones, Peter J. O'Hanlon, Robert J. Sheppard and Angela Worby

High throughput screening of *Staphylococcus aureus* phenylalanyl tRNA synthetase (FRS) identified an ethanolamine as a submicromolar hit. Optimisation studies led to the enantiospecific lead **64**, a single-figure nanomolar inhibitor. The inhibitor series shows selectivity with respect to the mammalian enzyme and the potential for broad spectrum bacterial FRS inhibition.

A new development of matrix metalloproteinase inhibitors: twin hydroxamic acids as potent inhibitors pp 2311–2314 of MMPs

Armando Rossello,* Elisa Nuti, Maria Pia Catalani, Paolo Carelli, Elisabetta Orlandini, Simona Rapposelli, Tiziano Tuccinardi, Susan J. Atkinson, Gillian Murphy and Aldo Balsamo

Starting from the potent MMP-2/MMP-14 inhibitor (R)-1 we describe new dimeric compounds of type 2, which are able to give an inhibitor—enzyme interaction more complex than that allowed for monomeric compounds of type 1 potentially, thus influencing positively the potency and/or selectivity of the new compounds, if compared with those of (R)-1.

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

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

pp 2331-2334

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

N-DEVD-N'-morpholinecarbonyl-rhodamine 110: novel caspase-3 fluorogenic substrates for cell-based pp 2335–2338 apoptosis assay

Zhi-Qiang Wang,* Jinfang Liao and Zhenjun Diwu

The title compound is a single step cleavage fluorogenic substrate and has significantly higher enzyme turnover rate and sensitivity than existing fluorogenic substrates for detecting caspase-3 activity both in solution and living cells.

Stereospecific deuteration of 2-deoxyerythrose 4-phosphate using 3-deoxy-D-*arabino*-heptulosonate 7-phosphate synthase

pp 2339-2342

Rachel M. Williamson, Amy L. Pietersma, Geoffrey B. Jameson and Emily J. Parker*

The synthesis of racemic 2-deoxyerythrose 4-phosphate and the selection of one enantiomer of this compound as a substrate for 3-deoxy-D-*arabino*-heptulosonate 7-phosphate synthase are reported. When the enzyme reaction was carried out in deuterium oxide stereospecific deuteration of the product was observed.

Synthesis of O-galactosyl aldoximes as potent LacNAc-mimetic galectin-3 inhibitors

pp 2343-2345

Johan Tejler, Hakon Leffler and Ulf J. Nilsson*

Carbonic anhydrase inhibitors. Inhibition of the cytosolic and tumor-associated carbonic anhydrase isozymes I, II, and IX with a series of 1,3,4-thiadiazole- and 1,2,4-triazole-thiols

pp 2347–2352

Gabriela Laura Almajan, Alessio Innocenti, Luca Puccetti, Gheorghe Manole, Stefania Barbuceanu, Ioana Saramet, Andrea Scozzafava and Claudiu T. Supuran*

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 pp 2365-2369 treatment of male ED

Craig D. Boyle,* Ruo Xu,* Theodros Asberom, Samuel Chackalamannil, John W. Clader, William J. Greenlee, Henry Guzik, Yuequing 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.

O N N N N N Br

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

pp 2371-2374

OH

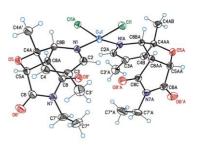
Noel A. Powell,* Emma H. Clay, Daniel D. Holsworth, John W. Bryant, Michael J. Ryan, Mehran Jalaie, Erli Zhang and Jeremy J. Edmunds

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

Synthesis and anthelmintic activity of 7-substituted 3,4a-dimethyl-4a,5a,8a,8b-tetrahydro-6*H*-pyrrolo-pp 2375–2379 [3',4':4,5]furo[3,2-*b*]pyridine-6,8(7*H*)-diones

Peter Jeschke,* Achim Harder, Winfried Etzel, Wolfgang Gau, Axel Göhrt, Jordi Benet-Buchholz and Gerhard Thielking

The synthesis of racemic 7-substituted 3,4a-dimethyl-4a,5a,8a,8b-tetrahydro-6*H*-pyrrolo[3',4':4,5]furo[3,2-*b*]pyridine-6,8(7*H*)-diones **1–6** having strong in vivo efficacy against the parasitic nematode *Haemonchus contortus* Rudolphi in sheep is described. After separation of the racemic compound **2** by HPLC the absolute configuration of the most anthelmintically active (4a*S*,5a*S*,8a*S*,8b*R*)-enantiomer **2a** was determined by single crystal X-ray analysis using its (4a*S*,5a*S*,8a*S*,8b*R*)-**2a**-CuCl₂ (2:1)-complex.



(4aS,5aS,8aS,8bR)-2a-CuCl2 (2:1)-complex

New pyrazolo[1',5':1,6]pyrimido[4,5-d]pyridazin-4(3H)-ones as potent and selective PDE5 inhibitors

pp 2381-2384

Joan Feixas, Maria Paola Giovannoni, Claudia Vergelli, Amadeu Gavaldà, Nicoletta Cesari, Alessia Graziano and Vittorio Dal Piaz*

A series of potent PDE5 inhibitors with high selectivity versus PDE6 was identified.

2,3-Diaminopyridine as a platform for designing structurally unique nonpeptide bradykinin B_1 receptor pp 2385–2388 antagonists

Dong-Mei Feng,* Jenny M. Wai, Scott D. Kuduk, Christina Ng, Kathy L. Murphy, Richard W. Ransom, Duane Reiss, Raymond S. L. Chang, Charles M. Harrell, Tanya MacNeil, Cuyue Tang, Thomayant Prueksaritanont, Roger M. Freidinger, Douglas J. Pettibone and Mark G. Bock

A novel class of 2,3-diaminopyridine bradykinin B_1 receptor antagonists and related SAR studies are disclosed.

1,
$$hBK_1 K_i = 200 nM$$
 $CH_3 H CF_3$
 $N H C CF_3$

3-(2-Ethoxy-4-{4-[3-hydroxy-2-methyl-4-(3-methylbutanoyl)phenoxy|butoxy}phenyl)propanoic acid: a brain penetrant allosteric potentiator at the metabotropic glutamate receptor 2 (mGluR2)

pp 2389-2393

Rowena V. Cube,* Jean-Michel Vernier, John H. Hutchinson, Michael F. Gardner, Joyce K. James, Blake A. Rowe, Herve Schaffhauser, Lorrie Daggett and Anthony B. Pinkerton

We have identified and synthesized a brain penetrant propanoic acid as an allosteric potentiator of the metabotropic glutamate receptor 2. Structure–activity relationship studies directed toward improving the potency, level of potentiation and brain penetration led to the discovery of **8** (EC₅₀ = $1200 \,\text{nM}$, 77% potentiation, 119% brain/plasma in rat, 20 mpk ip, brain level of $5700 \,\text{nM}$).

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-α) 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

QSAR for phospholipase A₂ inhibitions by 1-acyloxy-3-*N-n*-octylcarbamyl-benzenes Gialih Lin* and Gia-Yun Yu

pp 2405-2408

1-9 For the steady state inhibitions of PLA2 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 PLA2 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- α 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

 $P_{116}\hbox{: Pro-Gln-Glu-Glu-Lys-Ile-Thr-Lys-Glu-Ile-Leu-Asn-Gly-Lys}$

 P_{26} : Ala-Ala-Gly-Val-Asp-Tyr-Glu-Asp-Glu-Arg-Ile-Ser-Phe-Gln-Asp-Trp-Pro-Lys

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Corrigendum
Contributors to this issue
Instructions to contributors

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*Corresponding author

** Supplementary data available via ScienceDirect

COVER

Trisubstituted pyridazines derivatives (gold and blue) modeled in the active site of p38α MAP kinase crystal structure. A structure-based design approach was used to guide the evolution of the original class resulting in a novel p38α 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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