Bioorganic & Medicinal Chemistry Letters 19 (2009) 2607–2623

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

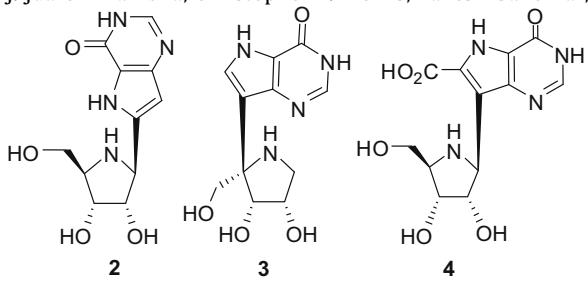
Bioorganic & Medicinal Chemistry Letters Vol. 19, No. 10, 2009

Contents

ARTICLES

Synthesis of analogs of forodesine HCl, a human purine nucleoside phosphorylase inhibitor—Part I pp 2624–2626

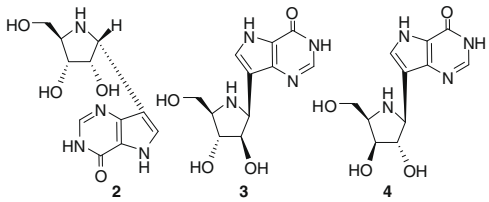
Vivekanand P. Kamath *, Jie Xue, Jesus J. Juarez-Brambila, Christopher B. Morris, Rakesh Ganorkar, Philip E. Morris Jr.



Forodesine HCl is being investigated as a potential therapeutic target for the control of T-cell proliferation. During our ongoing process development work on Forodesine HCl several novel compounds were identified as possible impurities in the process. Herein we present the synthesis of three novel compounds (**2**–**4**).

Synthesis of analogs of forodesine HCl, a human purine nucleoside phosphorylase inhibitor—Part II pp 2627–2629

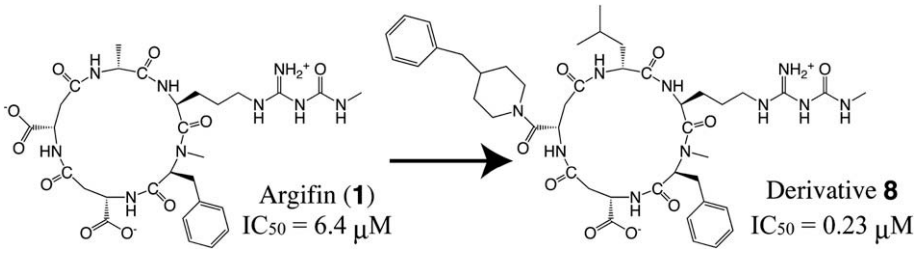
Vivekanand P. Kamath *, Jie Xue, Jesus J. Juarez-Brambila



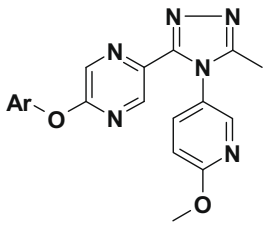
Forodesine HCl is being investigated as a potential therapeutic target for the control of T-cell proliferation. During the filing process for a New Drug Application (NDA) it became evident that there was a need to synthesize some stereo-isomers of forodesine HCl. Herein we present the synthesis of these three novel compounds (**2**–**4**).

Computer-aided rational molecular design of argifin-derivatives with increased inhibitory activity against chitinase B from *Serratia marcescens* pp 2630–2633

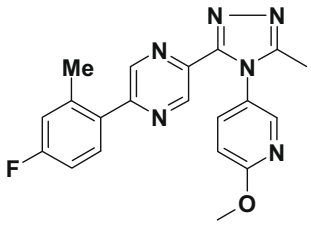
Hiroaki Gouda, Toshiaki Sunazuka, Kanami Iguchi, Akihiro Sugawara, Tomoyasu Hirose, Yoshihiko Noguchi, Yoshifumi Saito, Yuichi Yanai, Tsuyoshi Yamamoto, Takeshi Watanabe, Kazuro Shiomi, Satoshi Ōmura *, Shuichi Hirono *



Aryloxypyrazines as highly selective antagonists of Oxytocin **pp 2634–2636**
Alan Brown *, Dave Ellis, David Pearce, Michael Ralph, Nunzio Sciammetta



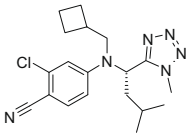
2



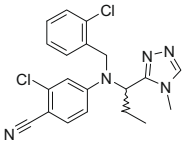
1

A range of aryloxypyrazines **2** were designed as potential mimics of the potent OT antagonist **1**. Compounds **2** were also potent OT antagonists. In addition, selectivity over the related V_{1A} receptor was significantly improved in several analogues of this type.

Synthesis and SAR of amino acid-derived heterocyclic progesterone receptor full and partial agonists **pp 2637–2641**
Marlys Hammond *, Jaclyn R. Patterson, Sharada Manns, Tram H. Hoang, David G. Washburn, Walter Trizna, Lindsay Glace, Eugene T. Grygielko, Rakesh Nagilla, Melanie Nord, Harvey E. Fries, Douglas J. Minick, Nicholas J. Laping, Jeffrey D. Bray, Scott K. Thompson



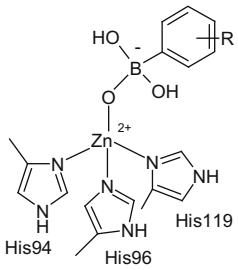
21
PR IC_{50} = 16 nM
PR T47D EC_{50} = 6.8 nM (38%)

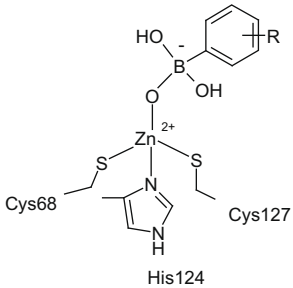


26
PR IC_{50}
PR T47D EC_{50} = 0.02 nM (97%)

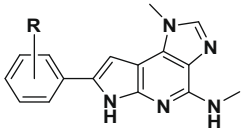
Two series of amino acid-derived heterocyclic progesterone receptor (PR) ligands are reported. Tetrazole-containing ligands behaved as potent PR partial agonists, while 1,2,4-triazole-containing ligands tended to act as PR full agonists in vitro.

Carbonic anhydrase inhibitors. Inhibition of the fungal β-carbonic anhydrases from *Candida albicans* and *Cryptococcus neoformans* with boronic acids **pp 2642–2645**
Alessio Innocenti, Jean-Yves Winum, Rebecca A. Hall, Fritz A. Mühlschlegel, Andrea Scozzafava, Claudiu T. Supuran *





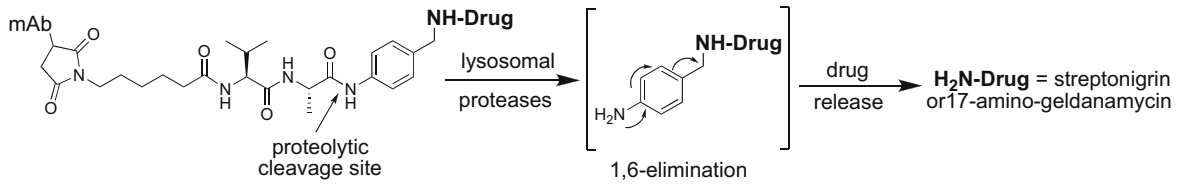
Synthesis, initial SAR and biological evaluation of 1,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-4-amine derived inhibitors of IκB kinase **pp 2646–2649**
James Kempson *, Junqing Guo, Jagabandhu Das, Robert V. Moquin, Steven H. Spergel, Scott H. Watterson, Charles M. Langevine, Alaric J. Dyckman, Mark Pattoli, James R. Burke, XiaoXia Yang, Kathleen M. Gillooly, Kim W. McIntyre, Laishun Chen, John H. Dodd, Murray McKinnon, Joel C. Barrish, William J. Pitts



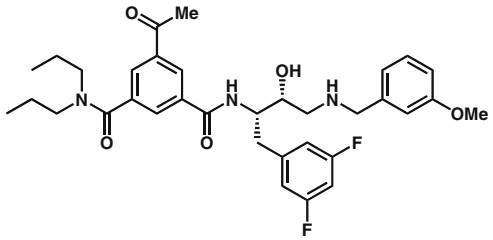
4

A new series of tricyclic-based inhibitors of IKK have been derived from an earlier lead compound. The synthesis and structure–activity relationships (SAR) are described. Compound **4k** inhibited TNF production in rats stimulated with LPS.

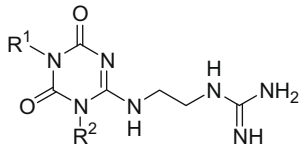
Novel immunoconjugates comprised of streptonigrin and 17-amino-geldanamycin attached via a dipeptide-*p*-aminobenzyl-amine linker system **pp 2650–2653**
Patrick J. Burke *, Brian E. Toki, David W. Meyer, Jamie B. Miyamoto, Kim M. Kissler, Martha Anderson, Peter D. Senter, Scott C. Jeffrey



Synthesis and SAR of hydroxyethylamine based phenylcarboxyamides as inhibitors of BACE **pp 2654–2660**
Yong-Jin Wu *, Yunhui Zhang, Andrew C. Good, Catherine R. Burton, Jeremy H. Toyn, Charles F. Albright, John E. Macor, Lorin A. Thompson



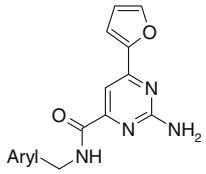
Triazinediones as prokineticin 1 receptor antagonists. Part 1: SAR, synthesis and biological evaluation **pp 2661–2663**
Janet L. Ralbovsky *, Joseph G. Lisko, Jeffrey M. Palmer, John Mabus, Kristen M. Chevalier, Mark J. Schulz, Alexey B. Dyatkin, Tamara A. Miskowski, Steven J. Coats, Pamela Hornby, Wei He



2

A series of guanidine triazinediones (**2**) were identified as potent PK1 receptor antagonists. A compound in this series inhibited the PK1 invoked prosecretory response in rat ileum tissue.

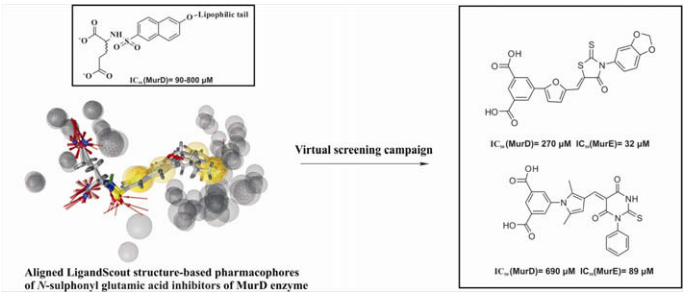
Antagonists of the human A_{2A} receptor. Part 5: Highly bio-available pyrimidine-4-carboxamides **pp 2664–2667**
Roger J. Gillespie, Samantha J. Bamford, Suneel Gaur, Allan M. Jordan *, Joanne Lerpiniere, Howard L. Mansell, Gemma C. Stratton



A novel series of antagonists of the human A_{2A} receptor demonstrate potency and selectivity over other receptor sub-types. Displaying in vivo potency in commonly used disease models and high oral bio-availability, this class of compounds may serve as clinically useful treatments for the relief of the symptoms associated with Parkinson's disease.

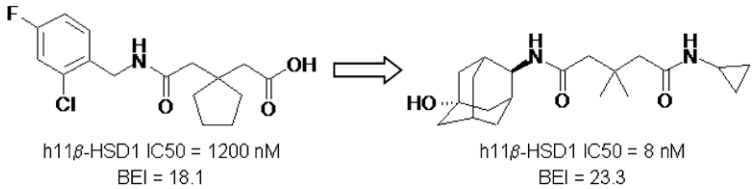
Discovery of novel benzene 1,3-dicarboxylic acid inhibitors of bacterial MurD and MurE ligases by structure-based virtual screening approach pp 2668–2673

Andrej Perdih, Andreja Kovač, Gerhard Wolber, Didier Blanot, Stanislav Gobec, Tom Solmajer *



Discovery and structure–activity relationships of pentanedioic acid diamides as potent inhibitors of 11β-hydroxysteroid dehydrogenase type I pp 2674–2678

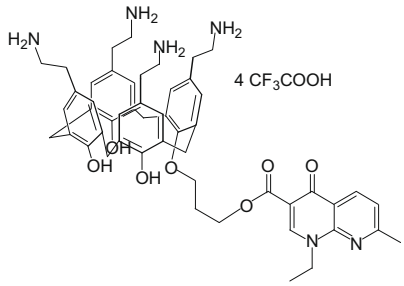
Didier Roche, Denis Carniato, Caroline Leriche, Franck Lepifre, Serge Christmann-Franck *, Ulrich Graedler, Christine Charon, Sophie Bozec, Liliane Doare, Fabien Schmidlin, Marc Lecomte, Eric Valeur



A hit identified from high throughput screening led after Hit-to-Lead-optimisation to a single digit nanomolar inhibitor of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) suitable for in vivo administration.

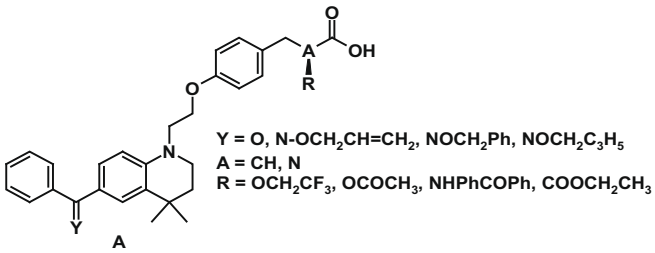
Towards calixarene-based prodrugs: Drug release and antibacterial behaviour of a water-soluble nalidixic acid/calix[4]arene ester adduct pp 2679–2682

Hugues Massimba Dibama, Igor Clarot, Stéphane Fontanay, Adel Ben Salem, Maxime Mourer, Chantal Finance, Raphaël E. Duval, Jean-Bernard Regnouf-de-Vains *



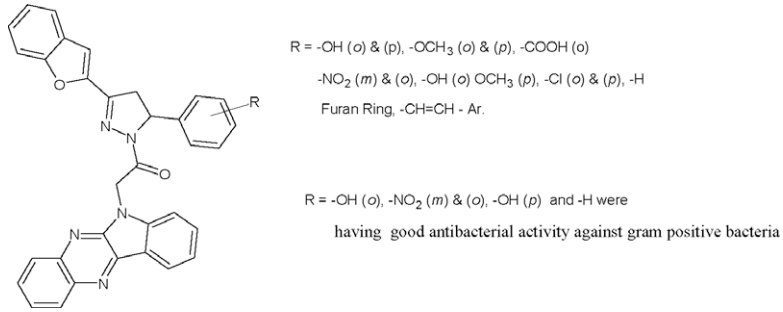
4,4-Dimethyl-1,2,3,4-tetrahydroquinoline-based PPARα/γ agonists. Part. II: Synthesis and pharmacological evaluation of oxime and acidic head group structural variations pp 2683–2687

Cécile Parmenon, Jérôme Guillard, Daniel-Henri Caignard, Nathalie Hennuyer, Bart Staels, Valérie Audinot-Bouchez, Jean-Albert Boutin, Catherine Dacquet, Alain Ktorza, Marie-Claude Viaud-Massuard *



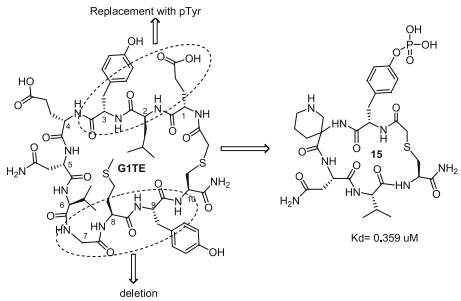
Microwave assisted synthesis of new indophenazine 1,3,5-trisubstruted pyrazoline derivatives of benzofuran and their antimicrobial activity pp 2688–2692

Kuntal Manna *, Yadvendra K. Agrawal



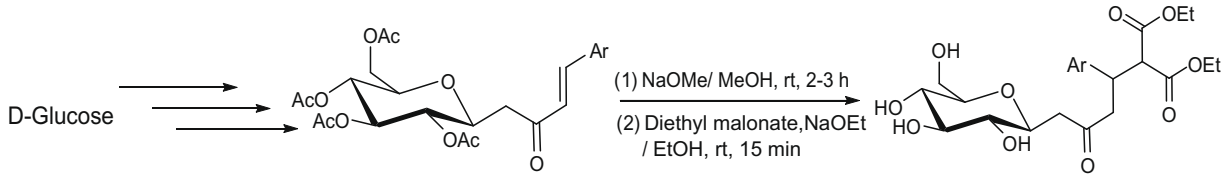
Discovery of thioether-bridged cyclic pentapeptides binding to Grb2-SH2 domain with high affinity pp 2693–2698

Sheng Jiang *, Chenzhong Liao, Lakshman Bindu, Biaolin Yin, Karen W. Worthy, Robert J. Fisher, Terrence R. Burke Jr., Marc C. Nicklaus, Peter P. Roller



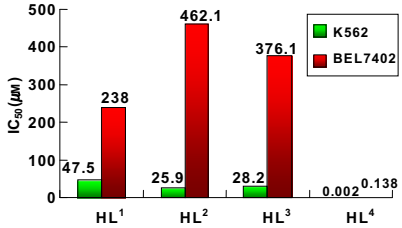
Synthetic studies in butenonyl C-glycosides: Preparation of polyfunctional alkanonyl glycosides and their enzyme inhibitory activity pp 2699–2703

Surendra Singh Bisht, Seerat Fatima, Akhilesh K. Tamrakar, Neha Rahuja, Natasha Jaiswal, Arvind K. Srivastava, Rama P. Tripathi *



Cytotoxicity and structure–activity relationships of four α-N-heterocyclic thiosemicarbazone derivatives crystal structure of 2-acetylpyrazine thiosemicarbazone pp 2704–2706

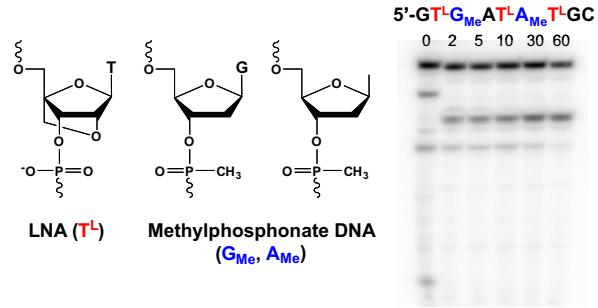
Ming-Xue Li *, Chun-Ling Chen, Chun-Sheng Ling, Jing Zhou, Bian-Sheng Ji *, Yan-Juan Wu, Jing-Yang Niu



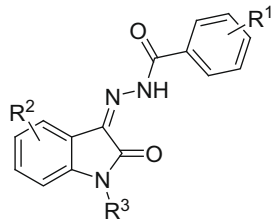
Four α-N-heterocyclic thiosemicarbazone derivatives were synthesized and tested for in vitro cytotoxicity against K562 leucocythemia cell line and BEL7402 liver cancer cell line, respectively. Different substituents on the thiosemicarbazone ligands show different levels of antitumor activity.

Nuclease resistant methylphosphonate-DNA/LNA chimeric oligonucleotides pp 2707–2709
Koji Nagahama, Rakesh N. Veedu, Jesper Wengel *

Synthesis, hybridization properties and 3′-exonucleolytic stability of novel chimeric 9-mer oligonucleotides containing methylphosphonate-DNA, DNA and LNA monomers are described.

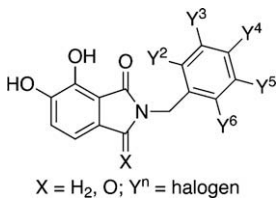


Discovery of substituted *N′*-(2-oxoindolin-3-ylidene)benzohydrazides as new apoptosis inducers using a cell- and caspase-based HTS assay pp 2710–2713
Nilantha Sirisoma, Azra Pervin, John Drewe, Ben Tseng, Sui Xiong Cai *

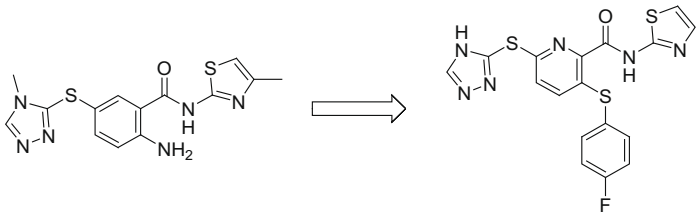


The discovery and SAR studies of substituted *N′*-(2-oxoindolin-3-ylidene)benzohydrazides as novel and potent apoptosis inducers are reported.

Examination of halogen substituent effects on HIV-1 integrase inhibitors derived from 2,3-dihydro-6,7-dihydroxy-1*H*-isoindol-1-ones and 4,5-dihydroxy-1*H*-isoindole-1,3(2*H*)-diones pp 2714–2717
Xue Zhi Zhao, Kasthuraiah Maddali, B. Christie Vu, Christophe Marchand, Stephen H. Hughes, Yves Pommier, Terrence R. Burke Jr. *

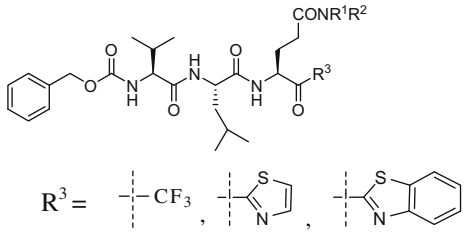


Discovery of novel 3,6-disubstituted 2-pyridinecarboxamide derivatives as GK activators pp 2718–2721
Morihiro Mitsuya *, Kenji Kamata, Makoto Bamba, Hitomi Watanabe, Yasuhiro Sasaki, Kaori Sasaki, Sumika Ohyama, Hideka Hosaka, Yasufumi Nagata, Jun-ichi Eiki, Teruyuki Nishimura



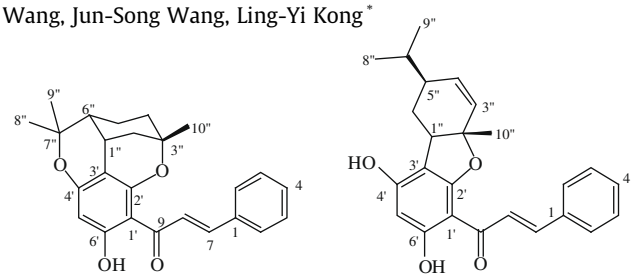
A novel class of 3,6-disubstituted 2-pyridinecarboxamide derivatives was designed based on X-ray analysis of the 2-aminobenzamide lead class.

New developments for the design, synthesis and biological evaluation of potent SARS-CoV 3CL^{pro} inhibitors **pp 2722–2727**
Thomas Regnier, Diganta Sarma, Koushi Hidaka, Usman Bacha, Ernesto Freire, Yoshio Hayashi *, Yoshiaki Kiso *



A series of trifluoromethyl, benzothiazolyl and thiazolyl ketone-containing peptidic compounds were synthesized and evaluated in vitro against SARS-CoV 3CL^{pro}.

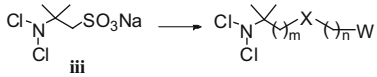
Two novel monoterpene–chalcone conjugates isolated from the seeds of *Alpinia katsumadai* **pp 2728–2730**
Shu-Zhen Hua, Jian-Guang Luo, Xiao-Bing Wang, Jun-Song Wang, Ling-Yi Kong *



2 **3**

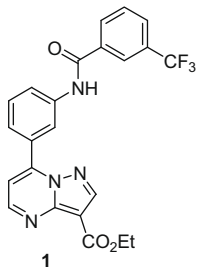
Two novel monoterpene–chalcone conjugates isorubraine (**2**) and sumadain C (**3**) were isolated from the seeds of *Alpinia katsumadai*. Their structures were elucidated and cytotoxic activities were evaluated. Compound **3** exhibited potent cytotoxic activity.

Quaternary ammonium *N,N*-dichloroamines as topical, antimicrobial agents **pp 2731–2734**
Charles Francavilla, Eddy Low, Satheesh Nair, Bum Kim, Timothy P. Shiau, Dmitri Debabov, Chris Celeri, Nichole Alvarez, Ashley Houchin, Ping Xu, Ron Najafi, Rakesh Jain *



A series of backbone modified and sulfonic acid replacement analogs of our topical, clinical candidate (**iii**) were synthesized.

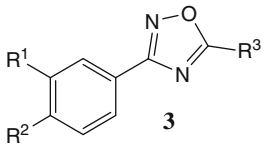
Identification of pyrazolo[1,5-*a*]pyrimidine-3-carboxylates as B-Raf kinase inhibitors **pp 2735–2738**
Ariamala Gopalsamy *, Greg Ciszewski, Yongbo Hu, Frederick Lee, Larry Feldberg, Eileen Frommer, Steven Kim, Karen Collins, Donald Wojciechowicz, Robert Mallon



1

Identification of pyrazolo[1,5-*a*]pyrimidine-3-carboxylates as B-Raf kinase Inhibitor and the SAR requirements are reported.

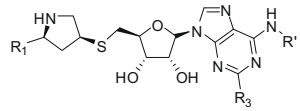
Synthesis and anticancer activities of novel 3,5-disubstituted-1,2,4-oxadiazoles **pp 2739–2741**
Dalip Kumar *, Gautam Patel, Emmanuel O. Johnson, Kavita Shah *



A library of 3,5-disubstituted-1,2,4-oxadiazoles were synthesized and evaluated for their in vitro anti-proliferative activities against various cancer cell lines. The series resulted in the identification of the most selective compound **3n** (>450-fold for LnCaP) and the most potent compound **3p** (9 nM, for LnCaP) along with several new cytotoxic agents.

Constrained (L-)-*S*-adenosyl-L-homocysteine (SAH) analogues as DNA methyltransferase inhibitors **pp 2742–2746**
Ljubomir Isakovic, Oscar M. Saavedra, David B. Llewellyn, Stephen Claridge, Lijie Zhan, Naomy Bernstein, Arkadii Vaisburg, Nadine Elowe, Andrea J. Petschner, Jubrail Rahil, Norman Beaulieu, France Gauthier, A.Robert MacLeod, Daniel Delorme, Jeffrey M. Besterman, Amal Wahhab *

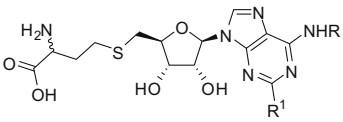
Potent SAH analogues with constrained homocysteine units have been designed and synthesized as inhibitors of human DNMT enzymes. The five membered (2*S*,4*S*)-4-mercaptopyrrolidine-2-carboxylic acid, in **1a**, was a good replacement for homocysteine. Optimization of **1a** changed the selectivity profile of these inhibitors. Chloro substitution at the 2-position, compound **1b**, retained potency against DNMT1 while N^6 alkylation, compound **7a**, conserved DNMT3b2 activity.

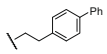
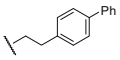


Cpd	R'	R^1	R^3	DNMT1 IC_{50}, μM	DNMT3b2 IC_{50}, μM
1a	H	CO_2H	H	1.1	0.27
1b	H	CO_2H	Cl	0.82	1.9
7a		CO_2H	H	3.7	0.26

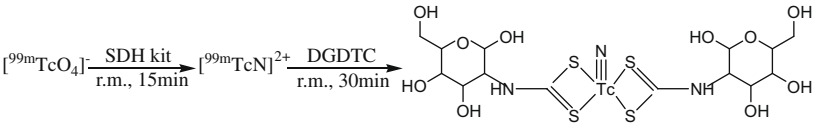
SAR around (L)-*S*-adenosyl-L-homocysteine, an inhibitor of human DNA methyltransferase (DNMT) enzymes **pp 2747–2751**
Oscar M. Saavedra, Ljubomir Isakovic, David B. Llewellyn, Lijie Zhan, Naomy Bernstein, Stephen Claridge, Franck Raeppel, Arkadii Vaisburg, Nadine Elowe, Andrea J. Petschner, Jubrail Rahil, Norman Beaulieu, A. Robert MacLeod, Daniel Delorme, Jeffrey M. Besterman, Amal Wahhab *

The inhibitory activity of base-modified SAH analogues and the specificity for binding to human DNMT1 and DNMT3b2 enzymes was explored. The 6-amino group was essential while the 7-N of the adenine ring of SAH could be replaced by CH– without loss of activity against both enzymes. The introduction of small groups at the 2-position of the adenine moiety favors DNMT1 over DNMT3b2 inhibition whereas alkylation of the N^6-amino moiety favors the inhibition of DNMT3b2 enzyme.



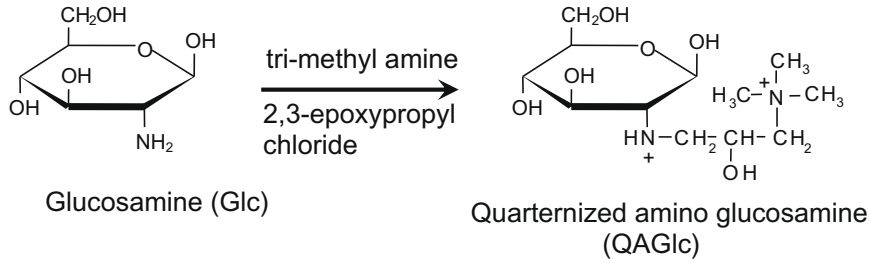
cpd	R	R^1	DNMT1 IC_{50} (μM)	DNMT3b2 IC_{50} (μM)
32		H	5.4	0.6
36		Cl	6.7	29

Synthesis and biological evaluation of a novel ^{99m}Tc nitrido radiopharmaceutical with deoxyglucose dithiocarbamate, showing tumor uptake **pp 2752–2754**
Junbo Zhang *, Jialei Ren, Xiao Lin, Xuebin Wang



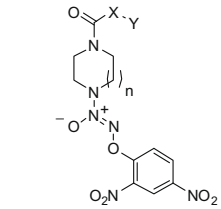
The deoxyglucose dithiocarbamate (DGDTC) was synthesized and radiolabelled with $[^{99m}TcN]^{2+}$ intermediate to form the ^{99m}TcN–DGDTC complex in high yield (>90%). The biodistribution results suggested ^{99m}TcN–DGDTC would be a promising candidate for tumor imaging.

The inhibitory mechanism of a novel cationic glucosamine derivative against MMP-2 and MMP-9 expressions **pp 2755–2759**
Eresha Mendis, Moon-Moo Kim, Niranjan Rajapakse, Se-Kwon Kim *



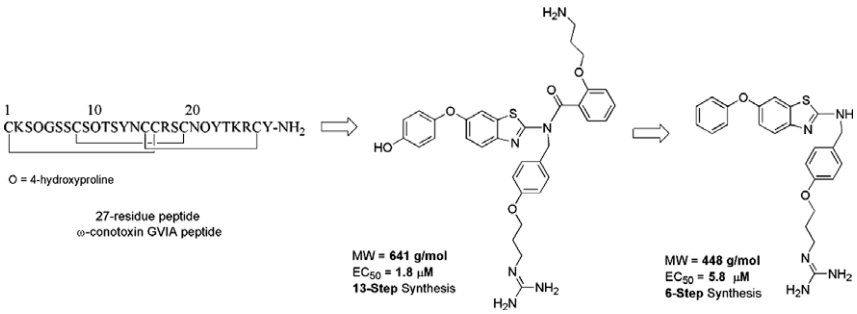
Novel Glc derivative suppresses MMP-9 and MMP-2 in HT1080 cells by decreasing transcriptional activation of MMP-9 and MMP-2 via transcription factors NF-κB and AP-1. PMA-stimulated expressions of ERK, JNK and p38 were altered in the presence of QAGlc confirming its mechanism of inhibition.

Synthesis and evaluation of piperazine and homopiperazine analogues of JS-K, an anti-cancer lead compound **pp 2760–2762**
Rahul S. Nandurdikar, Anna E. Maciag, Michael L. Citro, Paul J. Shami, Larry K. Keefer, Joseph E. Saavedra *, Harinath Chakrapani *

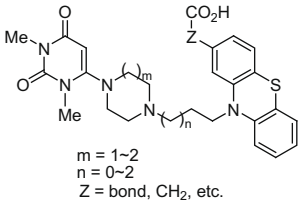


A number of structural analogues of JS-K, an anti-cancer lead compound, with nearly identical anti-proliferative activities are reported.

Low molecular weight non-peptide mimics of ω-conotoxin GVIA **pp 2763–2765**
Peter J. Duggan, Richard J. Lewis, Y. Phei Lok *, Natalie G. Lumsden, Kellie L. Tuck, Aijun Yang

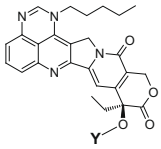


Synthesis and structure–activity relationships of phenothiazine carboxylic acids having pyrimidine-dione as novel histamine H_1 antagonists **pp 2766–2771**
Katsumi Kubota, Hirotaka Kurebayashi, Hirotaka Miyachi, Masanori Tobe, Masako Onishi, Yoshiaki Isobe *



Synthesis and biological activities of a pH-dependently activated water-soluble prodrug of a novel hexacyclic camptothecin analog pp 2772–2776

Jun Ohwada, Sawako Ozawa, Masami Kohchi, Hiroshi Fukuda, Chikako Murasaki, Hitomi Suda, Takeshi Murata, Satoshi Niizuma, Masao Tsukazaki, Kazutomo Ori, Kiyoshi Yoshinari, Yoshiko Itezono, Mika Endo, Masako Ura, Hiromi Tanimura, Yoko Miyazaki, Akira Kawashima, Shunsuke Nagao, Eitarou Namba, Koutarou Ogawa, Kazuko Kobayashi, Hisafumi Okabe, Isao Umeda, Nobuo Shimma *

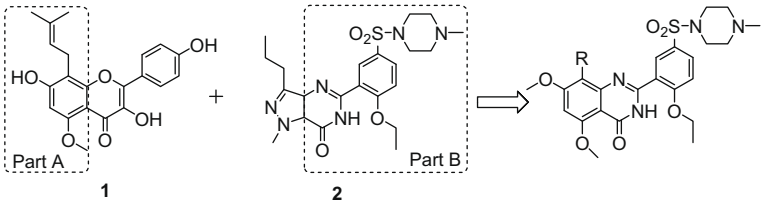


Y= H: CH0793076 (**1**)
Y= gly-sar (HCl salt): TP300

A pH-dependently activated water-soluble antitumor prodrug, CH4556300 (TP300, a hydrochloride), was designed and synthesized from a novel hexacyclic camptothecin analog, CH0793076 (**1**).

2-Phenylquinazolin-4(3*H*)-one, a class of potent PDE5 inhibitors with high selectivity versus PDE6 pp 2777–2779

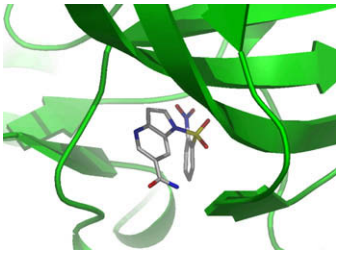
Hongliang Duan, Jin Zheng, Qinglin Lai, Zheng Liu, Guanghui Tian, Zhen Wang, Jianfeng Li, Jingshan Shen *



A novel class of 2-phenylquinazolin-4(3*H*)-one derivatives were designed and prepared as potent PDE5 inhibitors with high selectivity against PDE 6.

Discovery of 4-azaindoles as novel inhibitors of c-Met kinase pp 2780–2784

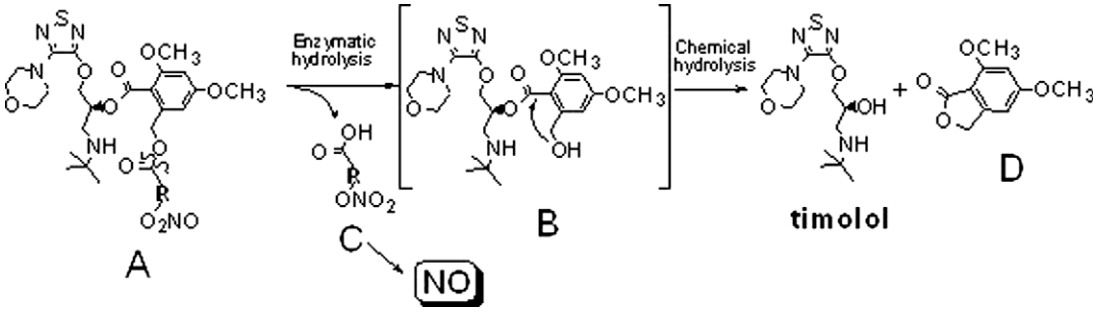
John Porter *, Simon Lumb, Richard J. Franklin, Jose M. Gascon-Simorte, Mark Calmiano, Kelly Le Riche, Bénédicte Lallemand, Jean Keyaerts, Helen Edwards, Alison Maloney, Jean Delgado, Lloyd King, Anne Foley, Fabien Lecomte, James Reuberson, Christoph Meier, Mark Batchelor



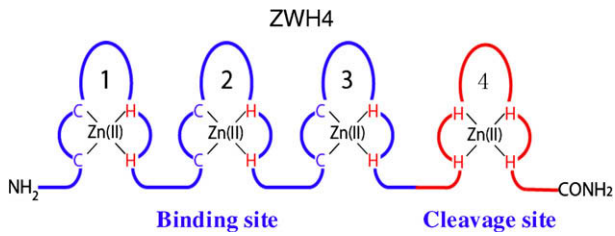
The SAR and X-ray crystal structure of a series of 4-azaindole inhibitors of c-Met kinase is reported.

Synthesis of novel nitric oxide (NO)-releasing esters of timolol pp 2785–2788

Valerio Chiroli *, Minerva R. Batugo, Stefano Biondi, Annalisa Bonfanti, Stefania Brambilla, David C. Gale, Lin Li, Daniela Miglietta, Fabio Nicoli, Ganesh A. Prasanna, Daniela Ronchetti, William F. Vernier, Wesley K. M. Chong

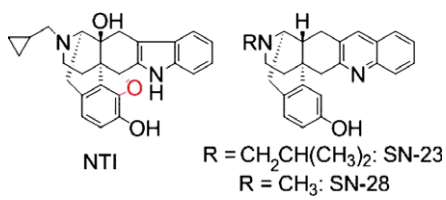


Novel zinc finger nuclease created by combining the Cys_2His_2- and His_4-type zinc finger domains **pp 2789–2791**
Shigeru Negi, Yoshiyuki Umeda, Saeko Masuyama, Koji Kano, Yukio Sugiura *



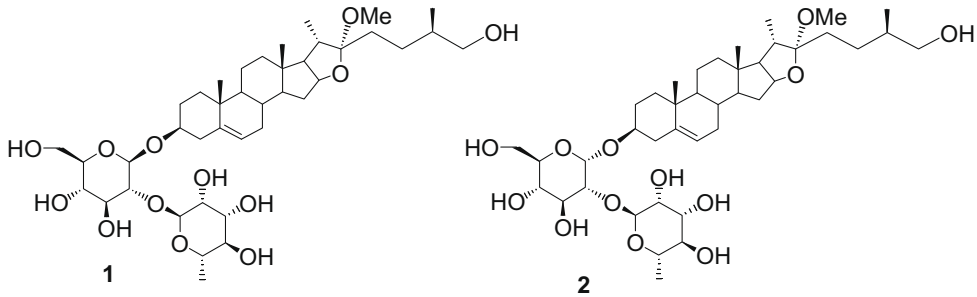
The new type of zinc finger nuclease (ZWH4) created by fusing Cys_2His_2- and His_4-type zinc finger domain. ZWH4 showed high DNA cleavage activity with sequence specificity for target plasmid DNA.

Design and synthesis of novel delta opioid receptor agonists and their pharmacologies **pp 2792–2795**
Hiroshi Nagase *, Yumiko Osa, Toru Nemoto, Hideaki Fujii, Masayuki Imai, Takashi Nakamura, Toshiyuki Kanemasa, Akira Kato, Hiroaki Gouda, Shuichi Hirono



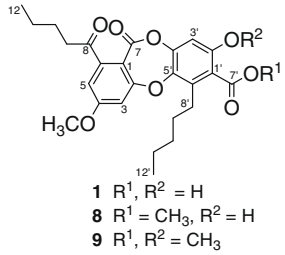
An accessory site of NTI would be only 4,5-epoxy ring. SN-23 and 28 with 10-methylene bridge showed satisfactory δ selectivities and potent agonist activities.

Synthesis and cytotoxicities of icogenin analogues with disaccharide residues **pp 2796–2800**
Haixing Wang, Fuqin Su, Liang Zhou, Xiaoguang Chen, Pingsheng Lei *



Two analogues of icogenin with simple disaccharide residues were synthesized in a facile and efficient way. Their cytotoxic activities were studied also.

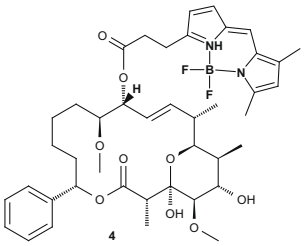
Protein tyrosine phosphatase 1B inhibitory effects of depsidone and pseudodepsidone metabolites from the Antarctic lichen *Stereocaulon alpinum* **pp 2801–2803**
Changon Seo, Jae Hak Sohn, Jong Seog Ahn, Joung Han Yim, Hong Kum Lee, Hyuncheol Oh *



Seven phenolic compounds (**1**–**7**) were isolated from *Stereocaulon alpinum* and evaluated for their PTP1B inhibitory activities.

Synthesis and characterization of a BODIPY-labeled derivative of Soraphen A that binds to acetyl-CoA carboxylase pp 2804–2807

Brian Raymer *, Michael Kavana, Allen Price, Bing Wang, Lisa Corcoran, Raviraj Kulathila, James Groarke, Theirry Mann

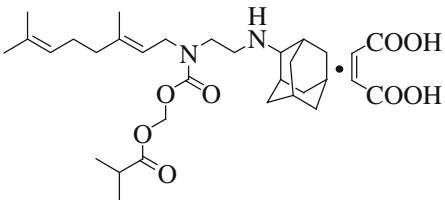


BODIPY-labeled Soraphen A analog **4** can identify compounds that bind to the Soraphen binding site of the acetyl-CoA carboxylase biotin carboxylase domain.

Synthesis and evaluation of carbamate prodrugs of SQ109 as antituberculosis agents pp 2808–2810

Qingyi Meng, Huibing Luo, Yibin Liu, Wei Li, Wen Zhang, Qizheng Yao *

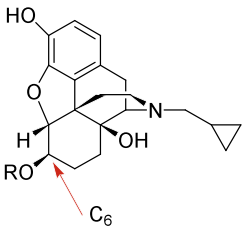
A new series of carbamate prodrugs of **SQ109** is disclosed. Bioavailability of **SQ109** after administration of prodrug **7a** was 91.4% compared with 21.4% after oral administration of **SQ109**. After oral administration of compound **7a**, the parent drug **SQ109** exhibited preferential tissue distribution into lung and spleen, the target organs of tubercular infection and replication.



7a

Design, synthesis, and characterization of 6β-naltrexol analogs, and their selectivity for in vitro opioid receptor subtypes pp 2811–2814

Andrea L. Pelotte, Ryan M. Smith, Mario Ayestas, Christina M. Dersch, Edward J. Bilsky, Richard B. Rothman, Amy M. Deveau *

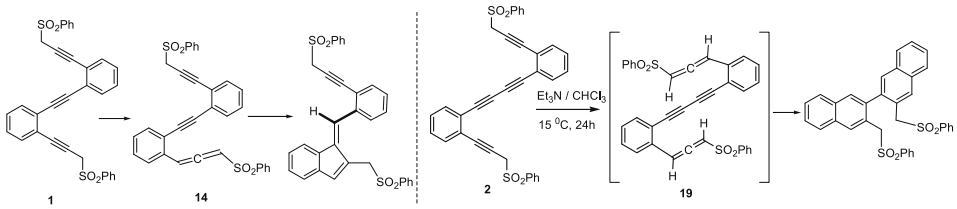


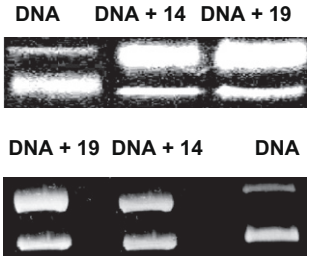
6β-naltrexol derivatives

Carbamate and sulfonate ester derivatives of 6β-naltrexol were synthesized, characterized, and screened for in vitro binding to μ, κ, and δ opioid receptor subtypes.

Design and synthesis of bisenediyne bissulfones and their reactivity under basic condition pp 2815–2818

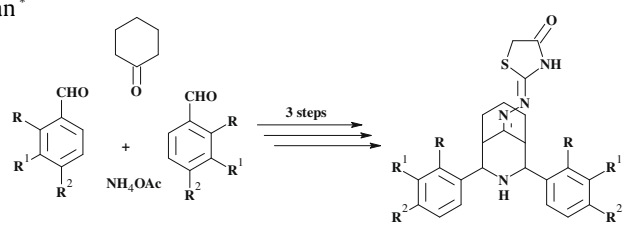
Sanket Das, Amit Basak *





Design, synthesis and biological evaluation of novel 2-[(2,4-diaryl-3-azabicyclo[3.3.1]nonan-9-ylidene)hydrazono]-1,3-thiazolidin-4-ones as a new class of antimicrobial agents **pp 2819–2823**

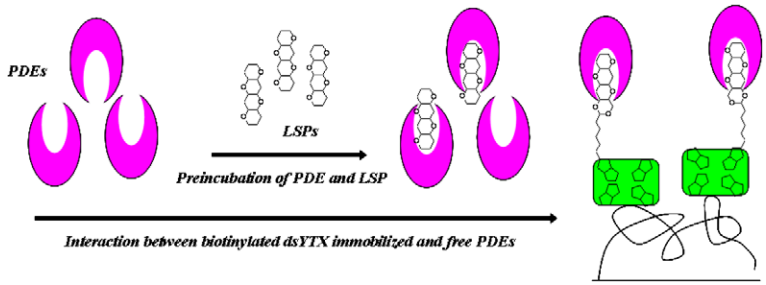
R. Ramachandran, M. Rani, S. Kabilan *



A series of 2,4-diaryl-3-azabicyclo[3.3.1]nonane-9-one thiosemicarbazones (**9**–**16**) obtained from the corresponding 2,4-diaryl-3-azabicyclo[3.3.1]nonane-9-ones (ABN) (**1**–**8**) upon cyclization with ethylbromoacetate in the presence of sodium acetate–acetic acid buffer afforded 2-[(2,4-diaryl-3-azabicyclo[3.3.1]nonan-9-ylidene)hydrazono]-1,3-thiazolidin-4-ones (**17**–**24**). The reported compounds were explored for their antibacterial and antifungal activities against sensitive and resistant organisms.

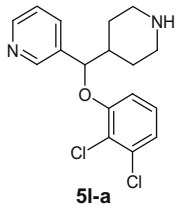
Surface plasmon resonance-based detection of ladder-shaped polyethers by inhibition detection method **pp 2824–2828**

Ryota Mouri, Tohru Oishi *, Kohei Torikai, Satoru Ujihara, Nobuaki Matsumori, Michio Murata *, Yasukatsu Oshima



4-Piperidines and 3-pyrrolidines as dual serotonin and noradrenaline reuptake inhibitors: Design, synthesis and structure–activity relationships **pp 2829–2834**

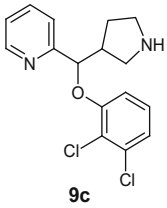
Paul V. Fish *, Mark D. Andrews, M. Jonathan Fray, Alan Stobie, Florian Wakenhut, Gavin A. Whitlock



5l-a

SRI, IC_{50} = 7 nM
NRI, IC_{50} = 6 nM
DRI, IC_{50} = 71 nM

HLM, $T_{1/2}$ > 120 min
CYP2D6-i, IC_{50} = 20,000 nM
K^+ hERG, IC_{50} = 5180 nM
(single enantiomer)



9c

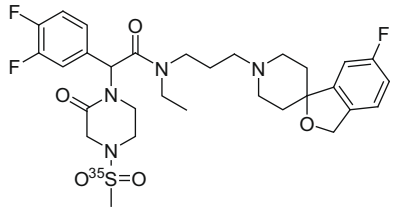
SRI, IC_{50} = 36 nM
NRI, IC_{50} = 14 nM
DRI, IC_{50} = 1060 nM

HLM, $T_{1/2}$ > 120 min
CYP2D6-i, IC_{50} = 5300 nM
K^+ hERG, IC_{50} = 10,000 nM
(single enantiomer)

[(Aryloxy)(pyridinyl)methyl]piperidine and pyrrolidine derivatives **5**–**9** are inhibitors of monoamine reuptake. Structure–activity relationships established that monoamine reuptake inhibition are functions of amine, pyridine isomer, aryloxy ring substitution and stereochemistry. Consequently, selective NRIs, selective SRIs, dual SNRIs and triple SNDRIs were all identified. Dual SNRIs **5l–a** and **9c** were evaluated in additional pharmacology and pharmacokinetic studies as representative examples from this series.

Identification and characterization of a selective radioligand for melanin-concentrating hormone 1-receptor (MCH1R) **pp 2835–2839**

Masahiko Ito *, Toshihiro Sakamoto, Takao Suzuki, Shinichiro Egashira, Minoru Moriya, Akane Ishihara, Hisashi Iwaasa, Hiroko Matsushita, Kazuho Nakase, Michael A. Wallace, Dennis Dean, Nagaaki Sato, Shigeru Tokita, Akio Kanatani

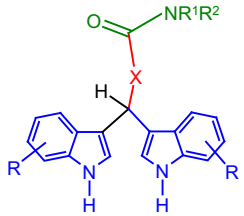


[^{35}S]**4a**

[^{35}S]**4a** was developed and characterized as a potent and selective radioligand for melanin-concentrating hormone 1-receptor (MCH1R).

Exploring bis-(indolyl)methane moiety as an alternative and innovative CAP group in the design of histone deacetylase (HDAC) inhibitors **pp 2840–2843**

Giuseppe Giannini *, Mauro Marzi, Maria Di Marzo, Gianfranco Battistuzzi, Riccardo Pezzi, Tiziana Brunetti, Walter Cabri, Loredana Vesci, Claudio Pisano



R^1=H, R^2=OH, X=$(CH_2)_5$

4d (ST2741) R = H HDAC1 = 730 nM HDAC3 = 350 nM HDAC6 = 6 nM

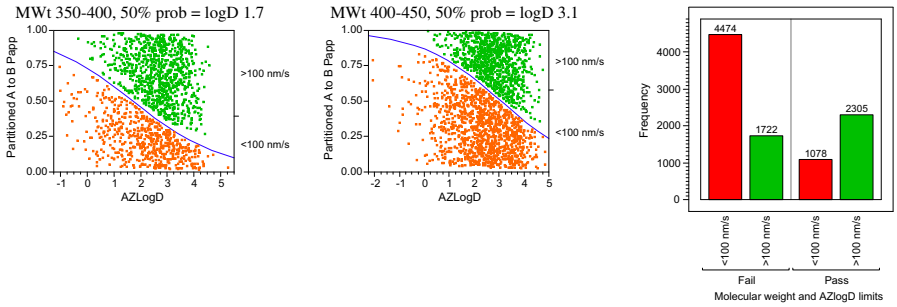
4h (ST3043) R= 7-MeO HDAC1 = 83 nM HDAC3 = 23 nM HDAC6 = 2.6 nM

4n (ST5732) R= 5-NO_2 HDAC1 = 140 nM HDAC3 = 18 nM HDAC6 = 20 nM

Starting from a common pharmacophore that characterizes this class of molecules, we designed and synthesized a series of hydroxamic acids containing a bis-(indolyl)methane moiety. HDAC inhibition profile and antiproliferative activity were evaluated. Three derivatives showed an interesting HDACi profile ranging from low to high nM.

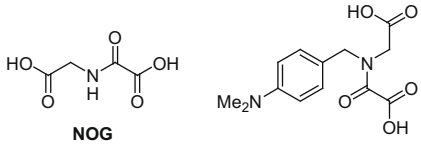
Defining optimum lipophilicity and molecular weight ranges for drug candidates—Molecular weight dependent lower log*D* limits based on permeability **pp 2844–2851**

Michael J. Waring *



Synthesis and activity of *N*-oxalylglycine and its derivatives as Jumonji C-domain-containing histone lysine demethylase inhibitors **pp 2852–2855**

Shohei Hamada, Tae-Dong Kim, Takayoshi Suzuki *, Yukihiro Itoh, Hiroki Tsumoto, Hidehiko Nakagawa, Ralf Janknecht *, Naoki Miyata *

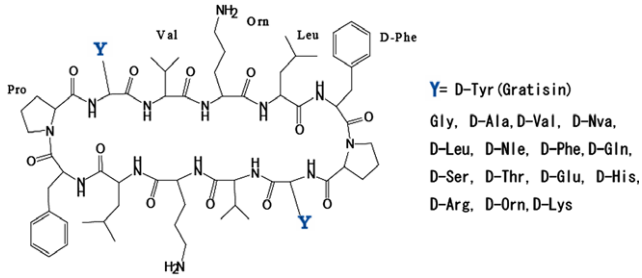


NOG **1**

N-Oxalylglycine (NOG) derivatives were synthesized and their inhibitory effect on histone lysine demethylase activity was evaluated. This study showed that NOG and compound **1** inhibit histone lysine demethylases both in enzyme assays and cellular assays.

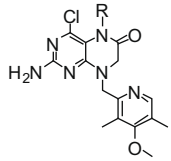
Syntheses of low-hemolytic antimicrobial gratisin peptides **pp 2856–2859**

Makoto Tamaki *, Manabu Kokuno, Ichiro Sasaki, Yumiko Suzuki, Michiko Iwama, Kenichi Saegusa, Yusuke kikuchi, Mitsuno Shindo, Masahiro Kimura, Yoshiki Uchida *



Discovery of 5-substituted 2-amino-4-chloro-8-((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)-7,8-dihydropteridin-6(5*H*)-ones as potent and selective Hsp90 inhibitors **pp 2860–2864**

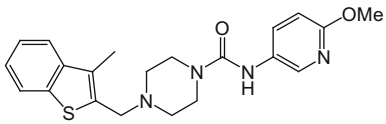
Xiaoyuan Li, Ellyn Shocron, Aimin Song, Neela Patel, Connie L. Sun *



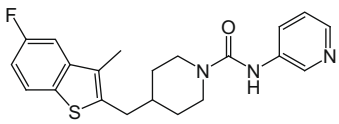
The discovery of a series of potent Hsp90 inhibitors is reported.

Benzothiophene piperazine and piperidine urea inhibitors of fatty acid amide hydrolase (FAAH) **pp 2865–2869**

Douglas S. Johnson *, Kay Ahn, Suzanne Kesten, Scott E. Lazerwith, Yuntao Song, Mark Morris, Lorraine Fay, Tracy Gregory, Cory Stiff, James B. Dunbar Jr., Marya Liimatta, David Beidler, Sarah Smith, Tyzoon K. Nomanbhoy, Benjamin F. Cravatt



PF-465 (**6g**)

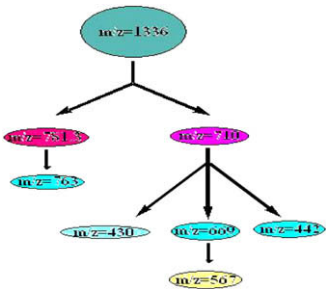


PF-946 (**13**)

The synthesis and SAR of a series of benzothiophene piperazine and piperidine urea FAAH inhibitors is described.

DNA-interaction and in vitro antimicrobial studies of some mixed-ligand complexes of cobalt(II) with fluoroquinolone antibacterial agent ciprofloxacin and some neutral bidentate ligands **pp 2870–2873**

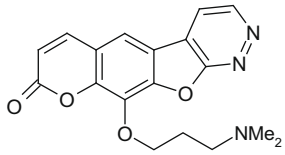
M. N. Patel *, M. R. Chhasatia, D. S. Gandhi



Synthesized complexes were proved to be more potent bactericides than the ligands. Electrophoresis studies reveal that binding to DNA through classical intercalation mode prevent the organisms from reproducing.

A new psoralen derivative with enlarged antiproliferative properties **pp 2874–2876**

Lisa Dalla Via, Jose Carlos González-Gómez, Lázaro Guillermo Pérez-Montoto, Lourdes Santana, Eugenio Uriarte, Sebastiano Marciani Magno, Ornella Gia *

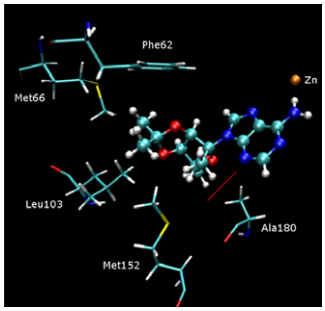


The synthesis of a new pyridazino[4,3-*h*]psoralen and the biological evaluation are reported.

Enhanced activity or resistance of adenosine derivatives towards adenosine deaminase-catalyzed deamination: Influence of ribose modifications pp 2877–2879

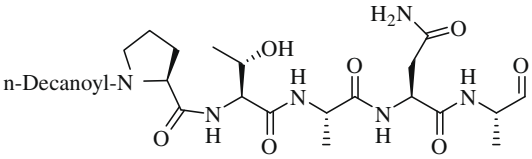
Giulio Vistoli, Alessandro Pedretti, Laura Alessandrini, Silvana Casati, Pierangela Ciuffreda, Giuseppe Meroni, Enzo Santaniello *

The paper describes modelling studies aimed to explain how the activity of adenosine deaminase on adenosine analogues and derivatives is affected by the introduction of protecting groups of the 2′,3′-hydroxyls and by the presence of a 1′-C-methyl in the nucleoside structure.



Substrate based peptide aldehyde inhibits bacterial type I signal peptidase pp 2880–2883

Peter Buzder-Lantos, Katrijn Bockstael, Jozef Anné, Piet Herdewijn *

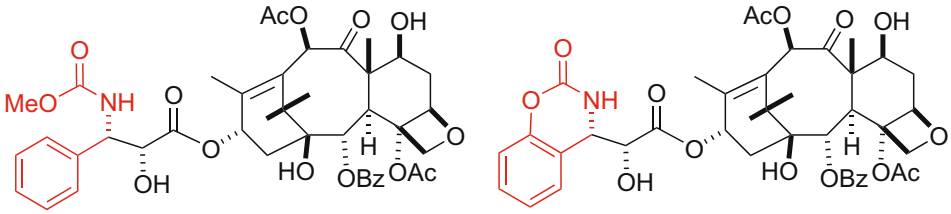


11, $IC_{50} = 0.09$ μM

The first example for a substrate-based peptide aldehyde as an inhibitor of bacterial type I signal peptidase ($IC_{50} = 0.09$ μM) is reported.

Synthesis and bioactivity of a side chain bridged paclitaxel: A test of the T-Taxol conformation pp 2884–2887

Mathis Hodge, Qiao-Hong Chen, Susan Bane, Shubhada Sharma, Maura Loew, Abhijit Banerjee, Ana A. Alcaraz, James P. Snyder, David G. I. Kingston *

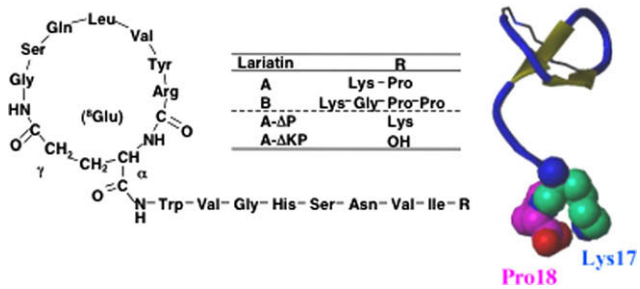


Highly active antiproliferative and tubulin polymerization agent

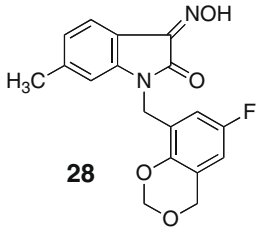
Inactive antiproliferative and tubulin polymerization agent

Lys17 in the 'lasso' peptide lariatin A is responsible for anti-mycobacterial activity pp 2888–2890

Masato Iwatsuki, Yukio Koizumi, Hiroaki Gouda, Shuichi Hirono, Hiroshi Tomoda *, Satoshi Ōmura

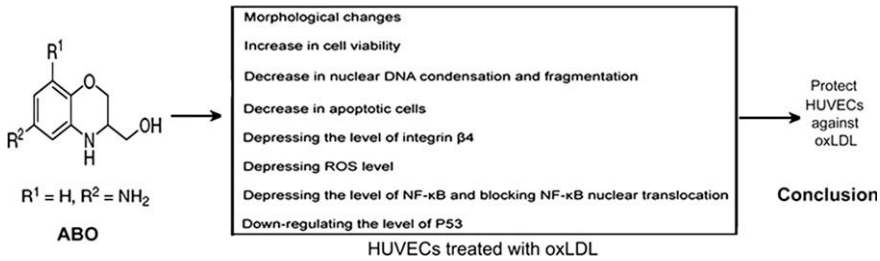


Structure-based design and parallel synthesis of *N*-benzyl isatin oximes as JNK3 MAP kinase inhibitors **pp 2891–2895**
Jingrong Cao, Huai Gao, Guy Bemis, Francesco Salituro, Mark Ledeboer, Edmund Harrington, Susanne Wilke, Paul Taslimi, S. Pazhanisamy, Xiaoling Xie, Marc Jacobs, Jeremy Green *



JNK3 K_i = 90 nM

Protective effects of a benzoxazine derivative against oxidized LDL-induced apoptosis and the increases of integrin β4, ROS, NF-κB and P53 in human umbilical vein endothelial cells **pp 2896–2900**
Xia Liu, Jing Zhao, JiPing Xu, BaoXiang Zhao *, Yun Zhang, ShangLi Zhang, JunYing Miao *



6-Amino-2,3-dihydro-3hydroxymethyl-1,4-benzoxazine (ABO) inhibited oxLDL-induced HUVEC apoptosis and depressed not only the levels of integrin β4, ROS, NF-κB and P53, but also NF-κB nuclear translocation.

OTHER CONTENTS

Instructions to contributors **p I**

*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.]

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