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# Bioorganic & Medicinal Chemistry Letters

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

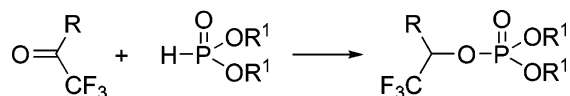
### Contents

#### ARTICLES

##### Synthesis of organophosphates with fluorine-containing leaving groups as serine esterase inhibitors with potential for Alzheimer disease therapeutics

pp 5528–5530

Galina F. Makhaeva, Alexey Y. Aksinenko, Vladimir B. Sokolov, Olga G. Serebryakova, Rudy J. Richardson \*



R = Ph, CF<sub>3</sub>, C(O)OEt  
R<sup>1</sup> = Me, Et, Bu

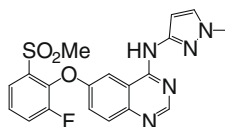
The synthesis of phosphates with fluorine-containing leaving groups and their antiesterase activity are reported.



##### Discovery and structure–activity relationships of a novel class of quinazoline glucokinase activators

pp 5531–5538

Tomoharu Iino \*, Yasuhiro Sasaki, Makoto Bamba, Morihiro Mitsuya, Akio Ohno, Kenji Kamata, Hideka Hosaka, Hiroko Maruki, Mayumi Futamura, Riki Yoshimoto, Sumika Ohyama, Kaori Sasaki, Masato Chiba, Norikazu Ohtake, Yasufumi Nagata, Jun-ichi Eiki, Teruyuki Nishimura

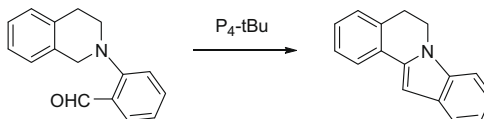


The discovery of a new lead structure of quinazoline class and the structure–activity relationships of quinazoline glucokinase activators are described.

##### A direct synthesis of 5,6-dihydroindolo[2,1-a]isoquinolines that exhibit immunosuppressive activity

pp 5539–5542

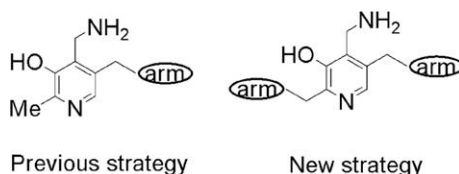
George A. Kraus \*, Vinayak Gupta, Marian Kohut, Navrozdeep Singh

Dihydroindolo[2,1-a]isoquinolines were synthesized from tetrahydroisoquinolines and  $\alpha$ -fluoroaldehydes by a novel two-step procedure. These compounds exhibited significant immunosuppressive activity against IL-2, IL-10 and IFN- $\gamma$ .

## Dendrimers in solution can have their remote catalytic groups folded back into the core: Enantioselective transaminations by dendritic enzyme mimics-II

pp 5543–5546

Sujun Wei, Jianing Wang, Scott Venhuizen, Rachid Skouta, Ronald Breslow \*

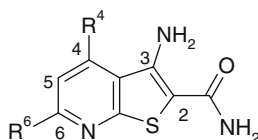


PAMAM dendrimers, which have double thioether arms, have been synthesized with a pyridoxamine core and chirally terminal amino groups. Transamination to afford natural isomers of phenylalanine and alanine induced enantioselectivity by the peripheral chiral caps, supporting a computer model that indicates folding of dendrimer chains back into the core.

## The discovery of thienopyridine analogues as potent IκB kinase β inhibitors. Part II

pp 5547–5551

Jiang-Ping Wu \*, Roman Fleck, Janice Brickwood, Alison Capolino, Katrina Catron, Zhidong Chen, Charles Cywin, Jonathan Emeigh, Melissa Foerst, John Ginn, Matt Hrapchak, Eugene Hickey, Ming-Hong Hao, Mohammed Kashem, Jun Li, Weimin Liu, Tina Morwick, Richard Nelson, Daniel Marshall, Leslie Martin, Peter Nemoto, Ian Potocki, Michel Liuzzi, Gregory W. Peet, Erika Scouten, David Stefany, Michael Turner, Steve Weldon, Clare Zimmitti, Denise Spero, Terence A. Kelly

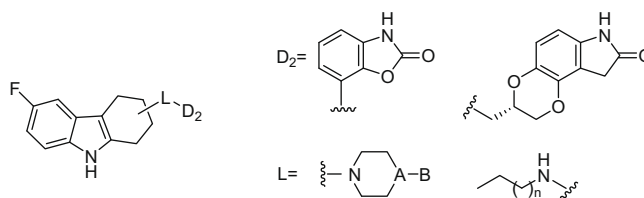


An SAR study that identified a series of thienopyridine-based potent IκB Kinase β (IKKβ) inhibitors is described.

## Tetrahydrocarbazole-based serotonin reuptake inhibitor/dopamine D<sub>2</sub> partial agonists for the potential treatment of schizophrenia

pp 5552–5555

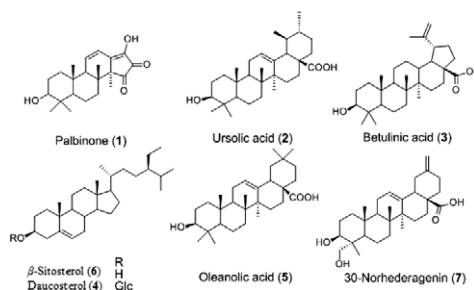
David P. Rotella \*, Geraldine R. McFarlane, Alexander Greenfield, Cristina Grosanu, Albert J. Robichaud, Rajiah Aldrin Denny, Rolf W. Feenstra, Sara Núñez-García, Jan-Hendrik Reinders, Martina van der Neut, Andrew McCreary, Chris G. Kruse, Kelly Sullivan, Farhana Pruthi, Margaret Lai, Jean Zhang, Dianne M. Kowal, Tikva Carrick, Steven M. Grauer, Rachel L. Navarra, Radka Graf, Julie Brennan, Karen L. Marquis, Mark H. Pausch



## Palbinone and triterpenes from Moutan Cortex (*Paeonia suffruticosa*, *Paeoniaceae*) stimulate glucose uptake and glycogen synthesis via activation of AMPK in insulin-resistant human HepG2 Cells

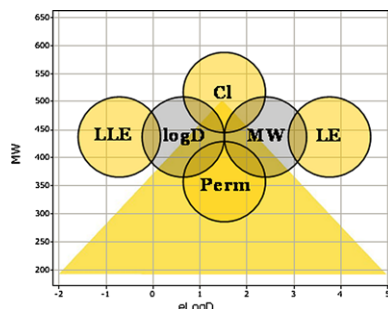
pp 5556–5559

Do Thi Ha, Dao Trong Tuan, Nguyen Bich Thu, Nguyen Xuan Nhiem, Tran Minh Ngoc, NamHui Yim, KiHwan Bae \*



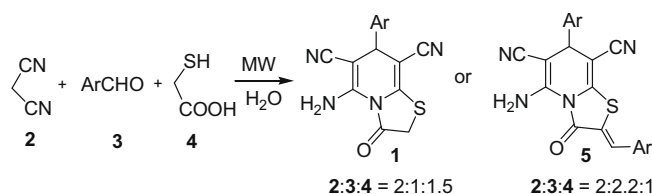
## Using the Golden Triangle to optimize clearance and oral absorption

pp 5560–5564

Ted W. Johnson<sup>\*</sup>, Klaus R. Dress, Martin Edwards

## Green chemoselective synthesis of thiazolo[3,2-a]pyridine derivatives and evaluation of their antioxidant and cytotoxic activities

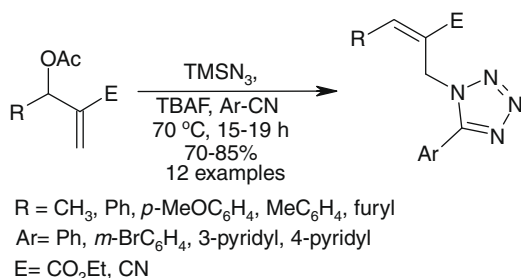
pp 5565–5568

Feng Shi, Chunmei Li, Ming Xia, Kangjie Miao, Yanxia Zhao, Shujiang Tu<sup>\*</sup>, Weifa Zheng<sup>\*</sup>, Ge Zhang, Ning Ma

The green chemoselective synthesis of thiazolo[3,2-a]pyridines was achieved in water via microwave-assisted three-component reactions with different molar ratios of the reactants. Their antioxidant activity and cytotoxicity to carcinoma HCT-116 cells and mice lymphocytes were bioassayed. Compound **5d** suggested selective cytotoxicity to tumor cell line HCT-116 cells.

Solvent free synthesis of 1,5-disubstituted tetrazoles derived from Baylis Hillman acetates as potential TNF- $\alpha$  inhibitors

pp 5569–5572

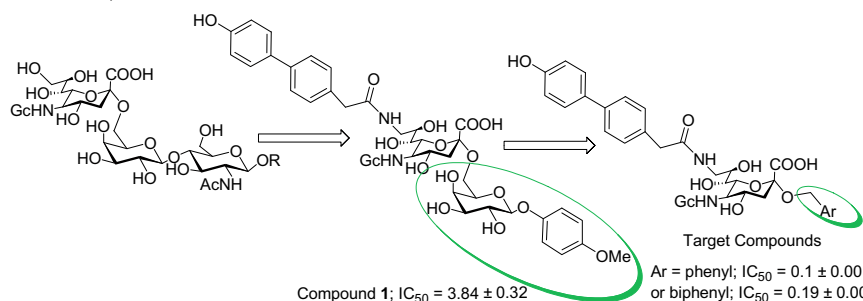
P. Srihari<sup>\*</sup>, Palash Dutta, R. Srinivasa Rao, J. S. Yadav, S. Chandrasekhar, P. Thombare, J. Mohapatra, A. Chatterjee, Mukul R. Jain<sup>\*</sup>

## Potent small molecule mouse CD22-inhibitors: Exploring the interaction of the residue at C-2 of sialic acid scaffold

pp 5573–5575

Hajjaj H. M. Abdu-Allah<sup>\*</sup>, Kozo Watanabe, Koji Hayashizaki, Chiaki Takaku, Taichi Tamanaka, Hiromu Takematsu, Yasunori Kozutsumi, Takeshi Tsubata, Hideharu Ishida, Makoto Kiso<sup>\*</sup>

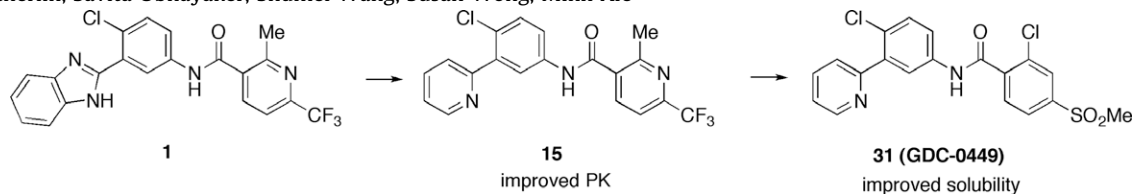
Replacing the galactose residue of CD22 ligand with benzyl or biphenylmethyl resulted in compounds with simplified structure and improved potency.



**GDC-0449—A potent inhibitor of the hedgehog pathway**

pp 5576–5581

Kirk D. Robarge<sup>\*</sup>, Shirley A. Brunton, Georgette M. Castanedo, Yong Cui, Michael S. Dina, Richard Goldsmith, Stephen E. Gould, Oivin Guichert, Janet L. Gunzner, Jason Halladay, Wei Jia, Cyrus Khojasteh, Michael F. T. Koehler, Karen Kotkow, Hank La, Rebecca L. LaLonde, Kevin Lau, Leslie Lee, Derek Marshall, James C. Marsters Jr., Lesley J. Murray, Changgeng Qian, Lee L. Rubin, Laurent Salphati, Mark S. Stanley, John H. A. Stibbard, Daniel P. Sutherlin, Savita Ubhayaker, Shumei Wang, Susan Wong, Minli Xie

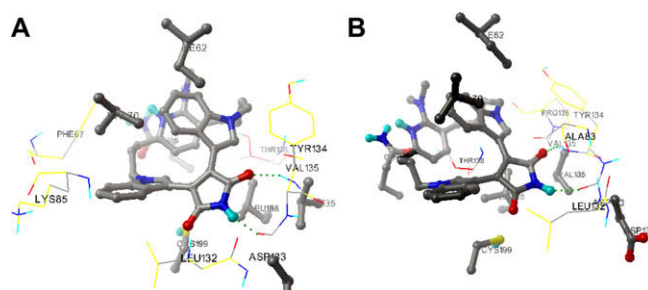


Starting from lead compound **1**, rescaffolding gave **15**. Further optimization resulted in the discovery of 2-pyridyl Hh antagonist **31** (GDC-0449), which is currently in human clinical trials.

**Structure based virtual screening of GSK-3 $\beta$ : Importance of protein flexibility and induced fit**

pp 5582–5585

Nibha Mishra, Arijit Basu<sup>\*</sup>, Venkatesan Jayaprakash, Ashoke Sharon, Mahua Basu, Kiran K. Patnaik

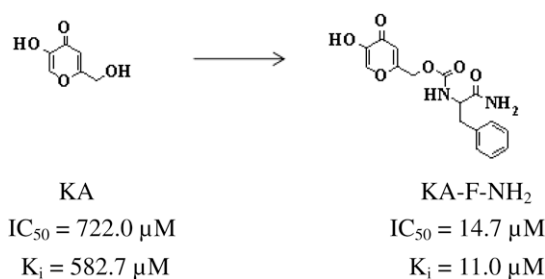


Interaction of Bis-(indole)maleimide pyridinophane (BIM) with (A) 1UV5 active site, (B) 2OW3 active site.

**Kojic acid–amino acid conjugates as tyrosinase inhibitors**

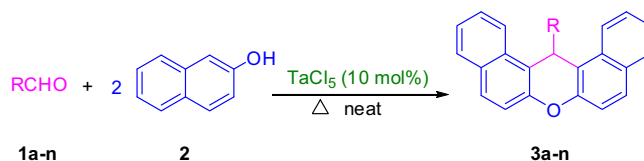
pp 5586–5589

Jin-Mi Noh, Seon-Yeong Kwak, Hyo-Suk Seo, Joo-Hyun Seo, Byung-Gee Kim, Yoon-Sik Lee<sup>\*</sup>

**Synthesis and in vitro study of 14-aryl-14H-dibenzo[*a,j*]xanthenes as cytotoxic agents**

pp 5590–5593

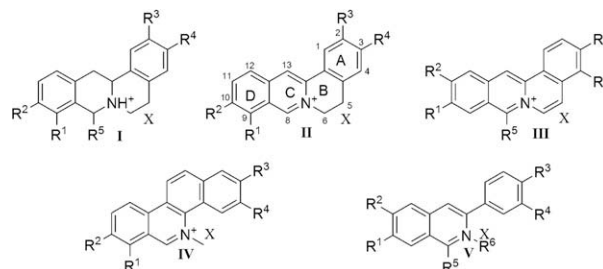
Asish K. Bhattacharya<sup>\*</sup>, Kalpeshkumar C. Rana, Mohammad Mujahid, Irum Sehar, Ajit K. Saxena



**Structure–activity relationship of isoform selective inhibitors of Rac1/1b GTPase nucleotide binding**

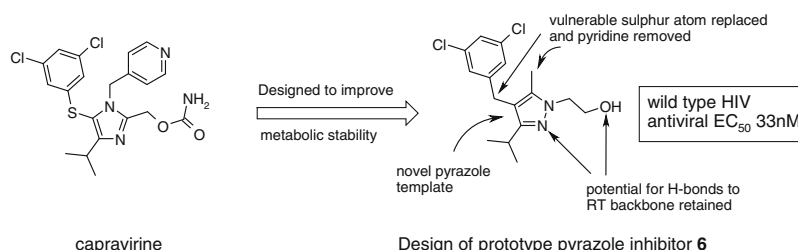
pp 5594–5598

Eric Beausoleil <sup>\*</sup>, Cédric Chauvignac, Thierry Taverne, Sandrine Lacombe, Laure Pognante, Bertrand Leblond, Diego Pallares, Catherine De Oliveira, Florence Bachelot, Rachel Carton, Hélène Peillon, Séverine Coutadeur, Virginie Picard, Nathalie Lambeng, Laurent Désiré, Fabien Schweighoffer

**Pyrazole NNRTIs 1: Design and initial optimisation of a novel template**

pp 5599–5602

Charles E. Mowbray <sup>\*</sup>, Catherine Burt, Romuald Corbau, Manos Perros, Isabelle Tran, Paul A. Stupple, Rob Webster, Anthony Wood

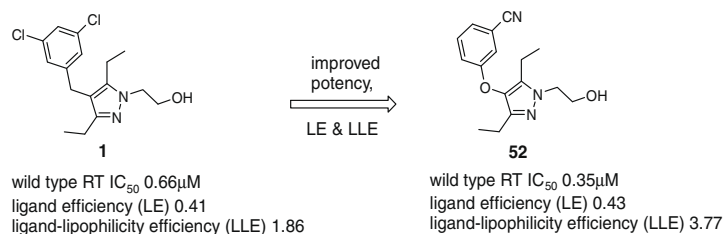


The design and synthesis of a novel series of non-nucleoside HIV reverse transcriptase inhibitors (NNRTIs) based on a pyrazole template is described. These compounds are active against wild type reverse transcriptase (RT) and retain activity against clinically important mutants.

**Pyrazole NNRTIs 3: Optimisation of physicochemical properties**

pp 5603–5606

Charles E. Mowbray <sup>\*</sup>, Romuald Corbau, Michael Hawes, Lyn H. Jones, James E. Mills, Manos Perros, Matthew D. Selby, Paul A. Stupple, Rob Webster, Anthony Wood

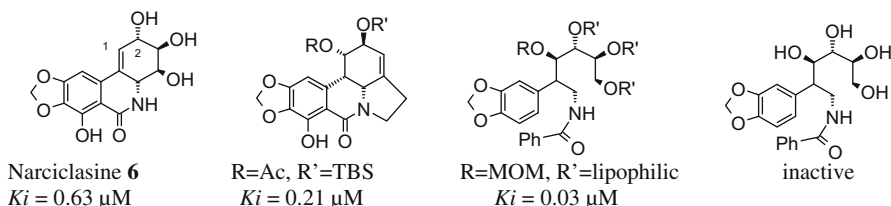


Our efforts to reduce overall lipophilicity and increase ligand-lipophilicity efficiency (LLE) by modification of the 3- or 5-substituents of pyrazole 1, a novel non-nucleoside HIV reverse transcriptase inhibitor (NNRTI) prototype were unsuccessful. In contrast replacement of the substituted benzyl group with corresponding phenylthio or phenoxy groups resulted in marked improvements in potency, ligand efficiency (LE) and LLE.

**Structure–activity studies on seco-pancratistatin analogs: Potent inhibitors of human cytochrome P450 3A4**

pp 5607–5612

James McNulty <sup>\*</sup>, Jerald J. Nair, Mohini Singh, Denis J. Crankshaw, Alison C. Holloway



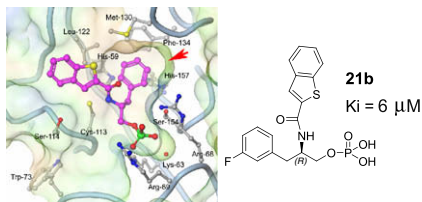
The cytochrome P450 3A4 inhibitory activity of two fully synthetic series of seco-analogs of the lycorane-type anticancer amaryllidaceae alkaloids is presented. Potent inhibitors are identified and a comprehensive and consistent view of the P450 pharmacophore is revealed in this important series involving a double bond or small H-bond acceptor at the C1 position in conjunction with lipophilic substitution at C2, C3 and/or C4.



## Structure-based design of novel human Pin1 inhibitors (I)

**pp 5613–5616**

Chuangxing Guo \*, Xinjun Hou \*, Liming Dong, Eleanor Dagostino, Samantha Greasley, RoseAnn Ferre, Joseph Marakovits, M. Catherine Johnson, David Matthews, Barbara Mroczkowski, Hans Parge, Todd VanArsdale, Ian Popoff, Joseph Piraino, Stephen Margosiak, James Thomson, Gerrit Los, Brion W. Murray



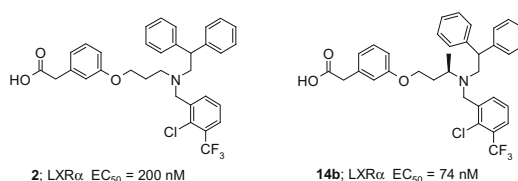
A series of novel non-peptide small molecular PIN1 inhibitors was discovered utilizing SBDD and combinatorial approach. The simplified pharmacophore opens the door for other drug-like Pin-1 inhibitor design.



## The discovery of *tertiary*-amine LXR agonists with potent cholesterol efflux activity in macrophages

**pp 5617–5621**

Joseph P. Marino Jr. \*, Lara S. Kallander, Chun Ma, Hye-Ja Oh, Dennis Lee, Dimitri E. Gaitanopoulos, John A. Krawiec, Derek J. Parks, Christine L. Webb, Kelly Ziegler, Michael Jaye, Scott K. Thompson



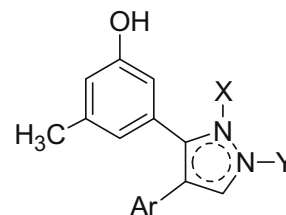
SAR studies around tertiary-amine lead molecule **2**, an LXR full agonist, revealed that steric and conformational changes to the acetic acid and propanolamine groups produce dramatic effects on agonist efficacy and potency. The new analogs possess good functional activity, demonstrating the ability to upregulate LXR target genes, as well as promote cholesterol efflux in macrophages.

## Design, synthesis, screening, and molecular modeling study of a new series of ROS1 receptor tyrosine kinase inhibitors

pp 5622–5626

Ibrahim M. El-Deeb, Byung Sun Park, Su Jin Jung, Kyung Ho Yoo, Chang-Hyun Oh, Seung Joo Cho, Dong Keun Han, Jae Yeol Lee, So Ha Lee

A series of rationally designed ROS1 tyrosine kinase inhibitors was synthesized and screened. Compound **12b** has showed good potency with IC<sub>50</sub> value of 209 nM, which is comparable with that of the reference lead compound **1**. Molecular modeling studies have been performed, that is, a homology model for ROS1 was built, and the screened inhibitors were docked into its major identified binding site. The docked poses along with the activity data have revealed a group of the essential features for activity. Overall, simplification of the lead compound **1** into compound **12b** kept the activity, while facilitated the synthetic advantages.

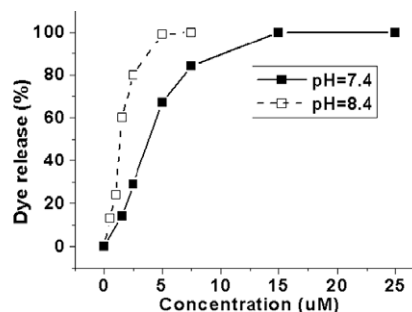
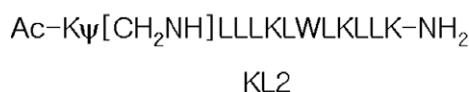


X = H, CH<sub>2</sub>CN, Y = H, CH<sub>2</sub>CN,  
Ar = aryl, heteroaryl

## Synthesis of antibacterial pseudopeptides with less hemolytic activity from a cytotoxic peptide and their pH-dependent activity

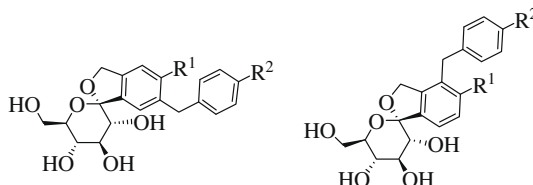
pp 5627–5631

Sung-Min Kim, Joung-Min Kim, Hyeongjin Cho, Keun-Hyeung Lee \*

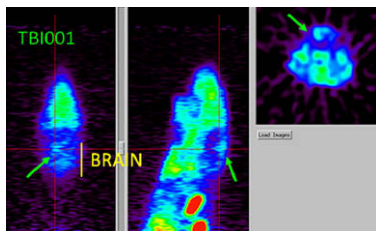


**O-Spiro C-aryl glucosides as novel sodium-dependent glucose co-transporter 2 (SGLT2) inhibitors**

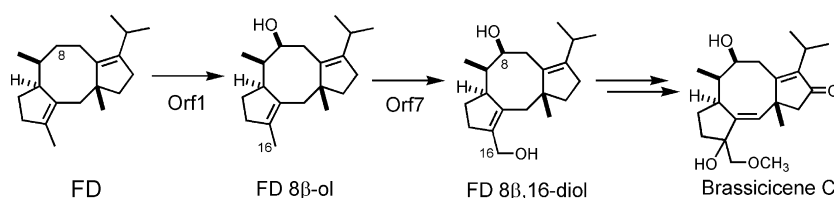
pp 5632–5635

Baihua Xu <sup>\*</sup>, Binhua Lv, Yan Feng, Ge Xu, Jiyan Du, Ajith Welihinda, Zelin Sheng, Brian Seed, Yuanwei Chen <sup>\*</sup>Two series of *O*-spiro *C*-aryl glucosides have been synthesized and evaluated for inhibition of hSGLT1 and hSGLT2.**Fully automated synthesis and initial PET evaluation of [<sup>11</sup>C]PBR28**

pp 5636–5639

Min Wang, Karmen K. Yoder, Mingzhang Gao, Bruce H. Mock, Xiao-Ming Xu, Andrew J. Saykin, Gary D. Hutchins, Qi-Huang Zheng <sup>\*</sup>Fully automated synthesis and initial PET evaluation of a TSPO radioligand [<sup>11</sup>C]PBR28 are reported.**Functional analyses of cytochrome P450 genes responsible for the early steps of brassicene C biosynthesis**

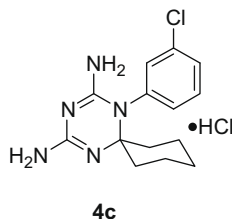
pp 5640–5643

Makoto Hashimoto <sup>\*</sup>, Yusuke Higuchi, Shunji Takahashi, Hiroyuki Osada, Toshiyuki Sakaki, Tomonobu Toyomasu, Takeshi Sassa, Nobuo Kato, Tohru Daiiri <sup>\*</sup>

We revealed that the Orf1 was an 8β-hydroxylation enzyme to yield FD 8β-ol, followed by successive 16-hydroxylation by the Orf7 to produce FD 8β16-diol in the brassicene C biosynthesis.

**Synthesis and in vitro evaluation of 2,4-diamino-1,3,5-triazine derivatives as neuronal voltage-gated sodium channel blockers**

pp 5644–5647

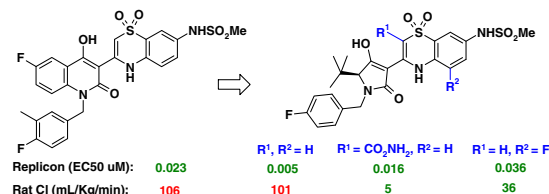
Xiang Ma <sup>\*</sup>, Thong-Yuen Poon, Peter Tsun Hon Wong, Wai-Keung Chui <sup>\*</sup>**4c**[<sup>3</sup>H]BTX, IC<sub>50</sub>: 4.0 (0.5) μMA series of 2,4-diamino-1,3,5-triazine derivatives was synthesized and examined as neuronal voltage-gated sodium channel blockers. Compound **4c** has shown significant in vitro neuronal sodium channel binding activity with no antifolate effect.

### Non-nucleoside inhibitors of HCV polymerase NS5B. Part 3: Synthesis and optimization studies of benzothiazine-substituted tetramic acids

pp 5648–5651

Javier de Vicente <sup>\*</sup>, Robert T. Hendricks, David B. Smith, Jay B. Fell, John Fischer, Stacey R. Spencer, Peter J. Stengel, Peter Mohr, John E. Robinson, James F. Blake, Ramona K. Hilgkamp, Calvin Yee, Junping Zhao, Todd R. Elworthy, Jahari Tracy, Elbert Chin, Jim Li, Al Lui, Beihan Wang, Connie Oshiro, Seth F. Harris, Manjiri Gbate, Vincent J. P. Leveque, Isabel Najera, Sophie Le Pogam, Sonal Rajyaguru, Gloria Ao-leong, Ludmila Alexandrova, Bill Fitch, Michael Brandl, Mohammad Masjedizadeh, Shao-yong Wu, Steve de Keczzer, Tatyana Voronin

Benzothiazine-substituted tetramic acids were discovered as highly potent non-nucleoside inhibitors of HCV NS5B polymerase. X-ray crystallography studies confirmed the binding mode of these inhibitors with HCV NS5B polymerase. Rational optimization of time dependent inactivation of CYP 3A4 and clearance was accomplished by incorporation of electron-withdrawing groups to the benzothiazine core.

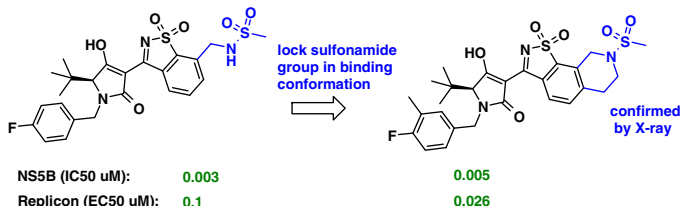


### Non-nucleoside inhibitors of HCV polymerase NS5B. Part 4: Structure-based design, synthesis, and biological evaluation of benzo[d]isothiazole-1,1-dioxides

pp 5652–5656

Javier de Vicente <sup>\*</sup>, Robert T. Hendricks, David B. Smith, Jay B. Fell, John Fischer, Stacey R. Spencer, Peter J. Stengel, Peter Mohr, John E. Robinson, James F. Blake, Ramona K. Hilgkamp, Calvin Yee, George Adjabeng, Todd R. Elworthy, Jim Li, Beihan Wang, Joe T. Bamberg, Seth F. Harris, April Wong, Vincent J. P. Leveque, Isabel Najera, Sophie Le Pogam, Sonal Rajyaguru, Gloria Ao-leong, Ludmila Alexandrova, Susan Larrabee, Michael Brandl, Andrew Briggs, Sunil Sukhtankar, Robert Farrell

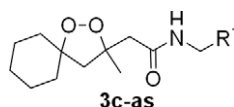
A structure-based approach led to the discovery of the benzoisothiazole-1,1-dioxide series as potent inhibitors of HCV polymerase NS5B. Molecular modeling also guided the optimization of the sulfonamide group.



### Synthesis and in vitro DMPK profiling of a 1,2-dioxolane-based library with activity against *Plasmodium falciparum*

pp 5657–5660

Derek C. Martyn, Galina Beletsky, Joseph F. Cortese, Erin Tyndall, Hanlan Liu, Maria M. Fitzgerald, Thomas J. O'Shea, Beirong Liang, Jon Clardy <sup>\*</sup>



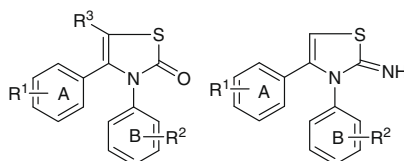
The synthesis, antiparasmodial activity and DMPK properties of a 43-member 1,2-dioxolane library is reported.



### Synthesis and anticancer activity of novel 3,4-diarylthiazol-2(3H)-ones (imines)

pp 5661–5664

Zong-Ying Liu, Yue-Ming Wang, Zhuo-Rong Li, Jian-Dong Jiang <sup>\*</sup>, David W. Boykin <sup>\*</sup>



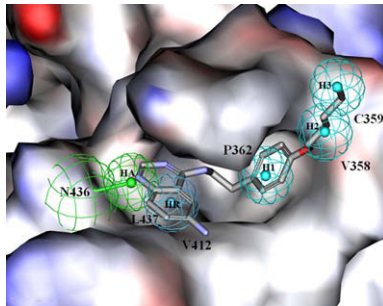
A series of 3,4-diarylthiazol-2(3H)-ones and three 3,4-diarylthiazol-2(3H)-imines were synthesized and evaluated for their cytotoxicity in a panel of human cancer cell lines.



**The first pharmacophore model for potent NF- $\kappa$ B inhibitors**

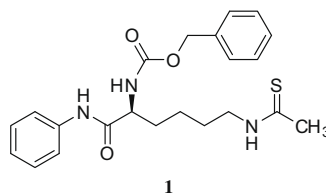
pp 5665–5669

Keng-Chang Tsai, Li-Wei Teng, Yi-Ming Shao, Yu-Chen Chen, Yu-Ching Lee, Minyong Li, Nai-Wan Hsiao \*

Pharmacophore features and a docking conformation are correctly matched onto NF- $\kappa$ B surface.**Identification of a cell-active non-peptide sirtuin inhibitor containing N-thioacetyl lysine**

pp 5670–5672

Takayoshi Suzuki \*, Tomomi Asaba, Erika Imai, Hiroki Tsumoto, Hidehiko Nakagawa, Naoki Miyata \*

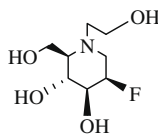


To identify cell-active sirtuin inhibitors containing N-thioacetyl lysine, we synthesized compound **1**, which was designed based on the structure of the reported N-ethoxycarbonylacetyl lysine-based sirtuin inhibitor NCS-12k. Compound **1** selectively inhibited SIRT1 in enzyme assays. Compound **1** also caused a dose-dependent increase in p53 acetylation in human colon cancer HCT116 cells, indicating the inhibition of SIRT1 in these cells.

**Amplification of the inhibitory activity of miglitol by monofluorination**

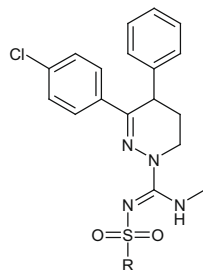
pp 5673–5674

Erik Prell, René Csuk \*

The synthesis of a monofluorinated  $\alpha$ -glycosidase inhibitor from miglitol is reported.**Synthesis and SAR of 1,4,5,6-tetrahydropyridazines as potent cannabinoid CB<sub>1</sub> receptor antagonists**

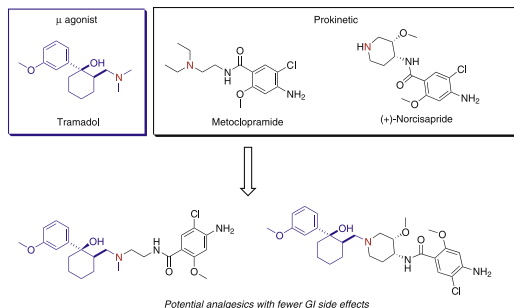
pp 5675–5678

Jos H. M. Lange \*, Arnold P. den Hartog, Martina A. W. van der Neut, Bernard J. van Vliet, Chris G. Kruse

Tetrahydropyridazines represent a novel class of potent CB<sub>1</sub> receptor antagonists.

## $\mu$ -Opioid/5-HT<sub>4</sub> dual pharmacologically active agents—Efforts towards an effective opioid analgesic with less GI and respiratory side effects (Part I)

pp 5679–5683

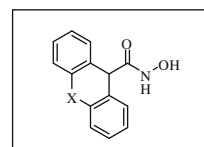
Liming Shao<sup>\*</sup>, Fengjiang Wang, Michael C. Hewitt, Timothy J. Barberich

## Diphenylmethylene hydroxamic acids as selective class IIa histone deacetylase inhibitors

pp 5684–5688

Pierre Tessier, David V. Smil, Amal Wahhab<sup>\*</sup>, Silvana Leit, Jubrail Rahil, Zuomei Li, Robert Déziel, Jeffrey M. Besterman

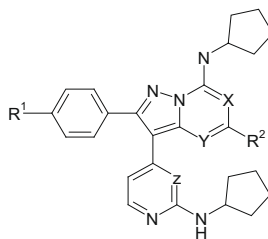
We have identified a series of diphenylmethylene hydroxamic acids as novel and selective HDAC class IIa inhibitors. *N*-Hydroxy-2,2-diphenylacetamide (**6**), has class IIa HDAC inhibitory activity in the sub-micromolar range, while the rigidified *N*-hydroxy-9*H*-xanthene-9-carboxamide (**13**), is slightly more selective for HDAC7. Substitution of **6** allows for the modulation of selectivity and potency amongst the class IIa HDAC isotypes.



cpd	X	HDAC class IIa isoforms IC <sub>50</sub> (μM)		
		4	5	7
<b>6</b>	H	0.75	0.14	0.39
<b>13</b>	O	0.25	0.11	0.05

## Pyrazolopyrimidines and pyrazolotriazines with potent activity against herpesviruses

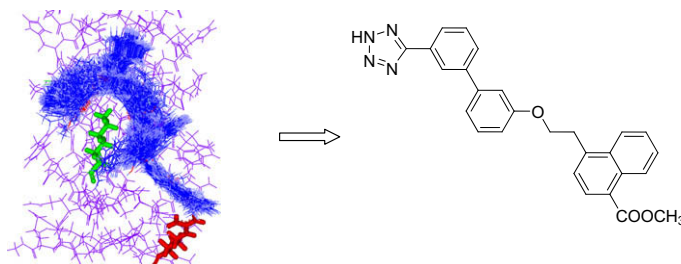
pp 5689–5692

Kristjan S. Gudmundsson<sup>\*</sup>, Brian A. Johns, Jason Weatherhead

Synthesis of several pyrazolo[1,5-*c*]pyrimidines, pyrazolo[1,5-*a*]pyrimidines and pyrazolo[1,5-*a*][1,3,5]triazines with potent activity against herpes simplex viruses is described.

## Structure-based design of substituted biphenyl ethylene ethers as ligands binding in the hydrophobic pocket of gp41 and blocking the helical bundle formation

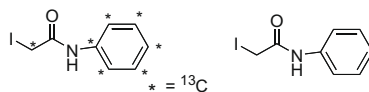
pp 5693–5697

Bin Liu<sup>\*</sup>, Rhoda W. Joseph, Bruce D. Dorsey, Robert A. Schiksnis, Katrina Northrop, Marina Bukhtiyarova, Eric B. Springman

Structure-based design of small molecule ligands binding in the hydrophobic pocket of gp41 and blocking the helical bundle formation is described.

### Synthesis of $^{13}\text{C}_7$ -labeled iodoacetanilide and application to quantitative analysis of peptides and a protein by isotope differential mass spectrometry

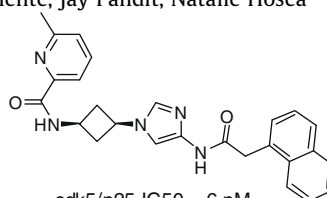
pp 5698–5702

Satomi Niwayama <sup>\*</sup>, Masoud Zabet-Moghaddam, Sadamu Kurono, Hanjoung Cho

$^{13}\text{C}_7$ -Labeled and unlabeled iodoacetanilide that covalently react with cysteine residues have been synthesized and applied to quantitative analysis of peptides and a protein.

### Potent and cellularly active 4-aminoimidazole inhibitors of cyclin-dependent kinase 5/p25 for the treatment of Alzheimer's disease

pp 5703–5707

Christopher J. Helal <sup>\*</sup>, Zhijun Kang, John C. Lucas, Thomas Gant, Michael K. Ahljanian, Joel B. Schachter, Karl E. G. Richter, James M. Cook, Frank S. Menniti, Kristin Kelly, Scot Mente, Jay Pandit, Natalie Hosea

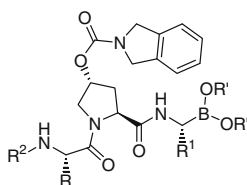
cdk5/p25  $\text{IC}_{50}$  = 6 nM  
 cdk5/p25 whole cell  $\text{IC}_{50}$  = 230 nM  
 18-fold cdk2/cyclin E selectivity

Using structure-based drug design, 4-aminoimidazoles were prepared with potent inhibition of cdk5/p25 in enzyme and whole cell assays and selectivity over cdk2.



### Synthesis and antiviral activity of HCV NS3/4A peptidomimetic boronic acid inhibitors

pp 5708–5711

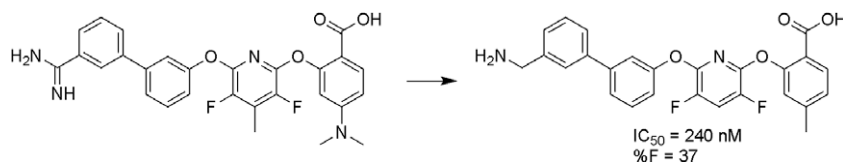
Amogh Bloor, Denise Hanway, Maria Joshi, David T. Winn, Gabriel Mendez, Marlana Walls, Ping Wei, Fuxin Qian, Xiaoli Zhang, Yuliang Zhang, Michael E. Hepperle, Xinqiang Li, David A. Campbell, Juan M. Betancort <sup>\*</sup>

The synthesis and evaluation of a series of peptidomimetic boronic acid inhibitors of the HCV NS3/4A protease is described. Data on their biochemical and cellular activities, mutant protease activity, and genotype coverage is reported.



### Identification of orally bioavailable, non-amidine inhibitors of Urokinase Plasminogen Activator (uPA)

pp 5712–5715

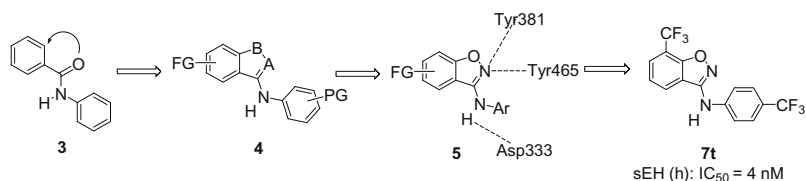
Christopher W. West <sup>\*</sup>, Marc Adler, Danny Arnaiz, Deborah Chen, Kieu Chu, Giovanna Gualtieri, Elena Ho, Christoph Huwe, David Light, Gary Phillips, Rebecca Pulk, Drew Sukovich, Marc Whitlow, Shendong Yuan, Judi Bryant

The discovery, synthesis, and early SAR work on a benzyl amine containing series of uPA inhibitors is reported.

### A strategy of employing aminoheterocycles as amide mimics to identify novel, potent and bioavailable soluble epoxide hydrolase inhibitors

pp 5716–5721

Hong C. Shen<sup>\*</sup>, Fa-Xiang Ding, Qiaolin Deng, Suoyu Xu, Xinchun Tong, Xiaoping Zhang, Yuli Chen, Gaochao Zhou, Lee-Yuh Pai, Magdalena Alonso-Galicia, Sophie Roy, Bei Zhang, James R. Tata, Joel P. Berger, Steven L. Colletti

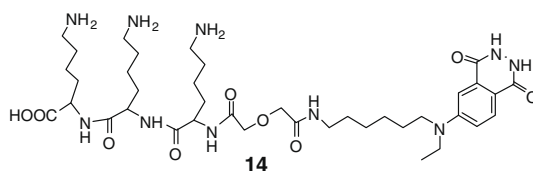


Distinct from previously reported urea and amide inhibitors of soluble epoxide hydrolase (sEH), a novel class of inhibitors were rationally designed based on the X-ray structure of this enzyme and known amide inhibitors. The structure–activity relationship (SAR) study was focused on improving the sEH inhibitory activity. Aminobenzisoxazoles emerged to be the optimal series, of which a potent human sEH inhibitor **7t** was identified with a good pharmacokinetics (PK) profile. The strategy of employing aminoheterocycles as amide replacements may represent a general approach to develop mimics of known hydrolase or protease inhibitors containing an amide moiety.

### Synthesis of novel isoluminol probes and their use in rapid bacterial assays

pp 5722–5726

Sundar Neelakantan, Iwan Surjawan, Huseyin Karacelik, Clair L. Hicks, Peter A. Crooks<sup>\*</sup>

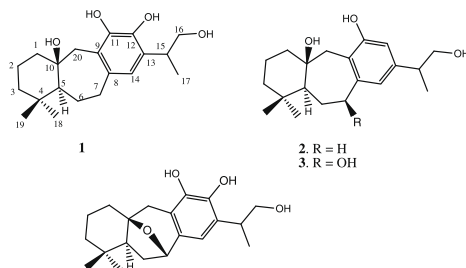


Rapid assays for bacteria have been developed utilizing novel LysLysLys-isoluminol (**14**) and GluGlu-isoluminol (**16**) probes. Compared to two conventional methods that are widely used, namely nucleic acid probes and polymerase chain reaction (PCR) assays, these current probe assays may have certain advantages, such as high sensitivity, and short preparation and assay time.

### Bioactivity-guided isolation of cytotoxic constituents from stem–bark of *Premna tomentosa*

pp 5727–5731

A. Hymavathi, K. Suresh Babu, V. G. M. Naidu, S. Rama Krishna, Prakash V. Diwan, J. Madhusudana Rao<sup>\*</sup>

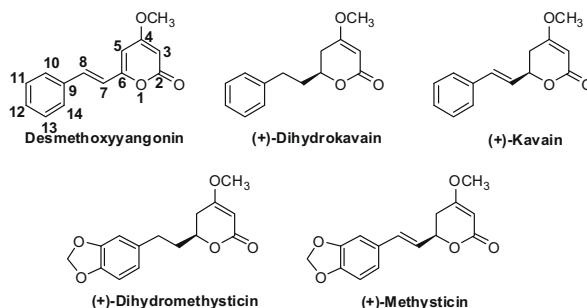


Bioactivity-guided column chromatographic separation of hexane extract led to the isolation of four new cytotoxic icetexane diterpenes (**1–4**), along with five known compounds (**5–9**). Compounds **1–3** were tested against the cancer cell lines for their cytotoxicity.

### Identification of methysticin as a potent and non-toxic NF-κB inhibitor from kava, potentially responsible for kava's chemopreventive activity

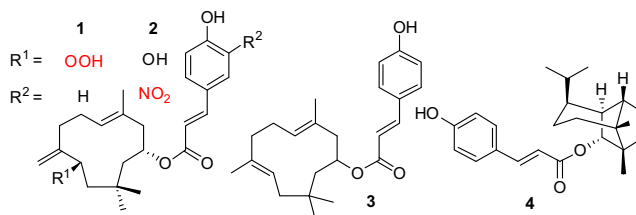
pp 5732–5736

Ahmad Ali Shaik, David Lee Hermanson, Chengguo Xing<sup>\*</sup>



**Sesquiterpenoids from *Pilea cavaleriei* subsp. *crenata***

pp 5737–5740

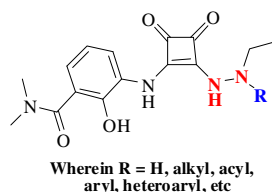
Gui-Hua Tang, Chang-Song Sun, Chun-Lin Long <sup>\*</sup>, Ma-Lin Li <sup>\*</sup>, Yue-Hu Wang, Min Luo, Hong-Sheng Wang, Ya-Na Shi

Three new humulane-type sesquiterpenes **1–3**, and a copaborneol derivative **4** were isolated from the methanol extract of *Pilea cavaleriei* subsp. *crenata*. Their structures were elucidated and cytotoxic activities were evaluated.

**Design, synthesis, and evaluation of novel 3-amino-4-hydrazine-cyclobut-3-ene-1,2-diones as potent and selective CXCR2 chemokine receptor antagonists**

pp 5741–5745

Shilan Liu, Yinhui Liu, Hongmei Wang, YiLi Ding, Hao Wu <sup>\*</sup>, Jingchao Dong, Angela Wong, Shu-Hui Chen <sup>\*</sup>, Ge Li, Manuel Chan, Nicole Sawyer, Francois G. Gervais, Martin Henault, Stacia Kargman, Leanne L. Bedard, Yongxin Han, Rick Friesen, Robert B. Lobell, David M. Stout



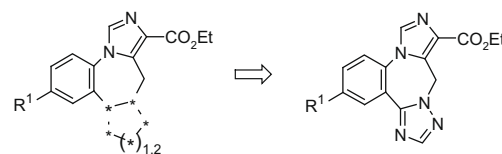
A novel series of 3-amino-4-hydrazine-cyclobut-3-ene-1,2-diones as potent and selective CXCR2 chemokine receptor antagonists were identified.

**Discovery of the imidazo[1,5-a][1,2,4]-triazolo[1,5-d][1,4]benzodiazepine scaffold as a novel, potent and selective GABA<sub>A</sub>  $\alpha 5$  inverse agonist series**

pp 5746–5752

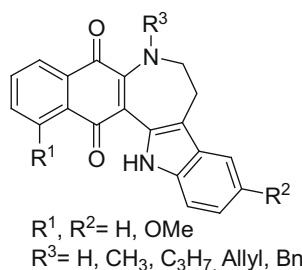
Guido Achermann, Theresa M. Ballard, Francesca Blasco, Pierre-Emmanuel Broutin, Bernd Büttelmann, Holger Fischer, Martin Graf, Maria-Clemencia Hernandez, Peter Hilty, Frédéric Knoflach, Andreas Koblet, Henner Knust, Anke Kurt, James R. Martin, Raffaello Masciadri, Richard H. P. Porter, Heinz Stadler, Andrew W. Thomas <sup>\*</sup>, Gerhard Trube, Jürgen Wichmann

Through iterative design cycles we have discovered a number of novel new classes where the imidazo[1,5-a][1,2,4]-triazolo[1,5-d][1,4]benzodiazepine was deemed the most promising GABA<sub>A</sub>  $\alpha 5$  inverse agonist class with potential for cognitive enhancement. This class combines a modest subtype binding selectivity with inverse agonism and has the most favourable molecular properties for further lead optimisation towards a central nervous system (CNS) acting medicine.

**Synthesis of 1,6,7,8-tetrahydro-naphtho[2,3-d]-azepino[4,5-b]indole-9,14-diones and their inhibitory effects on pro-inflammatory cytokines**

pp 5753–5756

Waya S. Phutdhawong <sup>\*</sup>, Wanwikar Ruensamran, Weerachai Phutdhawong, Thongchai Taechowisan



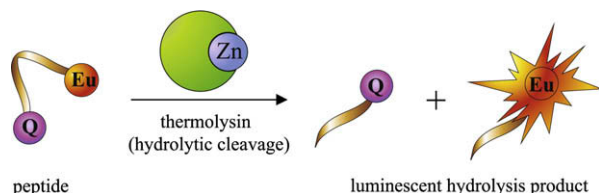
The synthesis and inhibitory effects on pro-inflammatory cytokines of 1,5,6,7,8,14b-hexahydro-naphtho[2,3-d]-azepino[4,5-b]indole-9,14-diones are reported.



### Lanthanide-based fluorogenic peptide substrate for the highly sensitive detection of thermolysin

pp 5757–5759

Ann-Kathrin Marguerre, Roland Krämer \*



A new fluorogenic, lanthanide-based oligopeptide substrate for the detection of the zinc-dependent endoprotease thermolysin is described. Using time-resolved fluorescence measurement, a highly sensitive assay for thermolysin was developed with a 50 pM detection limit (3.5 fmol).

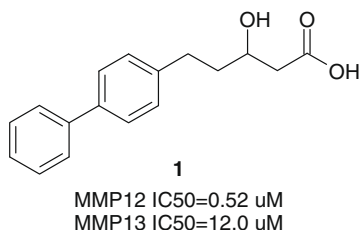


### The identification of $\beta$ -hydroxy carboxylic acids as selective MMP-12 inhibitors

pp 5760–5763

Ian P. Holmes, Simon Gaines, Steve P. Watson, Olivier Lorthioir, Adam Walker, Suzanne J. Baddeley, Shane Herbert, Danielle Egan, Máire A. Convery, Onkar M. P. Singh, Jeffrey W. Gross, John M. Strelow, Robert H. Smith, Augustin J. Amour, David Brown, Stephen L. Martin \*

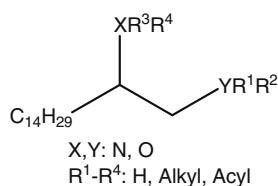
Identification of novel, selective MMP12 inhibitors



### Simple dihydrosphingosine analogues with potent activity against MDR-*Mycobacterium tuberculosis*

pp 5764–5768

Esther del Olmo \*, Gloria María Molina-Salinas, Ricardo Escarcena, Mario Alves, José L. López-Pérez, Rogelio Hernandez-Pando, Salvador Said-Fernández \*, Arturo San Feliciano

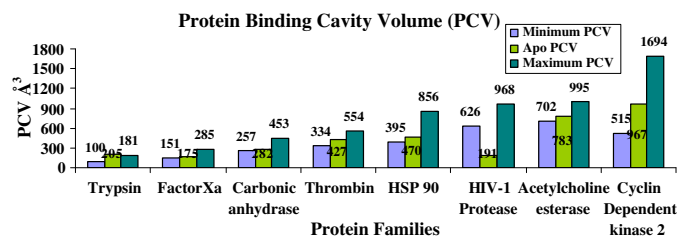


A number of dihydrosphingosine analogues were tested in vitro against several strains of *Mycobacterium tuberculosis* (MTB). Three (**3**, **4b** and **8b**) out of the fifteen evaluated compounds, displayed MIC values of 1.25  $\mu$ g/mL on virulent H37Rv and several MDR strains and, more interestingly, on one clinical isolate resistant to all the first-line anti-TB drugs.

### Variation of protein binding cavity volume and ligand volume in protein–ligand complexes

pp 5769–5772

N. Saranya, S. Selvaraj \*



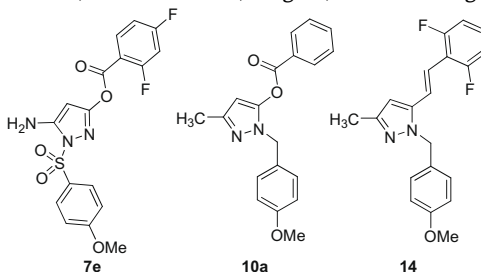
Variation in protein binding cavity volume (PCV) for different ligands illustrated in the graph for eight different protein families encompassing 200 protein–ligand complexes.



### Structure–activity relationship and improved hydrolytic stability of pyrazole derivatives that are allosteric inhibitors of West Nile Virus NS2B-NS3 proteinase

pp 5773–5777

Shyama Sidique, Sergey A. Shiryayev, Boris I. Ratnikov, Ananda Herath, Ying Su, Alex Y. Strongin, Nicholas D. P. Cosford \*

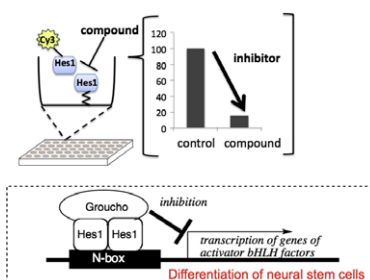


West Nile Virus (WNV) is a potentially deadly mosquito-borne flavivirus which has spread throughout the world. Herein we report the design, synthesis and in vitro evaluation of pyrazole derivatives that are inhibitors of WNV NS2B-NS3 proteinase with greatly improved stability in the assay medium.

### The first Hes1 dimer inhibitors from natural products

pp 5778–5781

Midori A. Arai \*, Ayako Masada, Toshiyuki Ohtsuka, Ryoichiro Kageyama, Masami Ishibashi



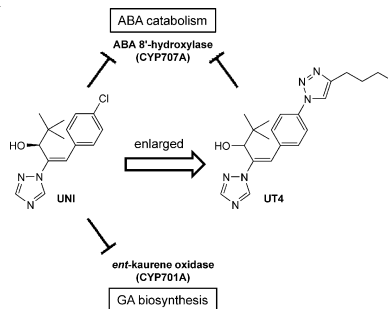
A high-throughput screening system for small molecule-inhibitors of the basic helix-loop-helix (bHLH) transcriptional repressor factor Hes1 was constructed. The first Hes1 dimer inhibitors were described.



### Enlarged analogues of uniconazole, new azole containing inhibitors of ABA 8'-hydroxylase CYP707A

pp 5782–5786

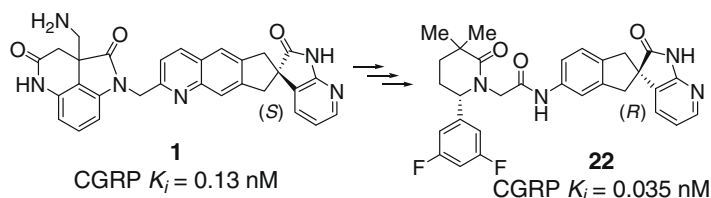
Yasushi Todoroki \*, Hikaru Aoyama, Saori Hiramatsu, Minaho Shirakura, Hataitip Nimitkeatkai, Satoru Kondo, Kotomi Ueno, Masaharu Mizutani, Nobuhiro Hirai



### Novel CGRP receptor antagonists through a design strategy of target simplification with addition of molecular flexibility

pp 5787–5790

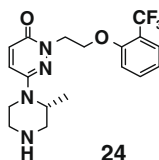
Michael R. Wood, Kathy M. Schirripa, June J. Kim, Amy G. Quigley, Craig A. Stump, Ian M. Bell, Rodney A. Bednar, John F. Fay, Joseph G. Bruno, Eric L. Moore, Scott D. Mosser, Shane Roller, Christopher A. Salvatore, Stefanie A. Kane, Joseph P. Vacca, Harold G. Selnick \*



**Design and synthesis of pyridazinone-based 5-HT<sub>2C</sub> agonists**

pp 5791–5795

Charlotte M. N. Allerton <sup>\*</sup>, Mark D. Andrews, Julian Blagg, David Ellis, Edel Evrard, Martin P. Green, Kevin K.-C. Liu, Gordon McMurray, Michael Ralph, Vivienne Sanderson, Robin Ward, Lesa Watson

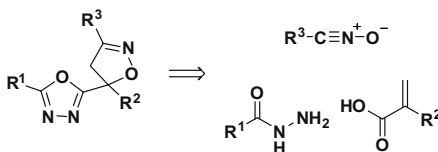


The design, synthesis and biological activity of pyridazinone derived, selective 5-HT<sub>2C</sub> agonists is described. Compound **24** showed efficacy in a pre-clinical model of urethral function which highlights potential efficacy in stress urinary incontinence.

**Synthesis and biological activity of 2-(4,5-dihydroisoxazol-5-yl)-1,3,4-oxadiazoles**

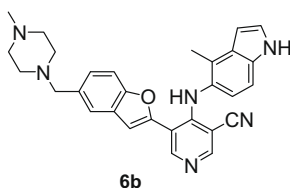
pp 5796–5798

Kristin A. Milinkevich, Choong L. Yoo, Thomas C. Sparks, Beth A. Lorschbach, Mark J. Kurth <sup>\*</sup>

**C-5 substituted heteroaryl-3-pyridinecarbonitriles as PKCθ inhibitors: Part II**

pp 5799–5802

Amar S. Prashad <sup>\*</sup>, Daniel Wang, Joan Subrath, Biqi Wu, Melissa Lin, Mei-Yi Zhang, Natasha Kagan, Julie Lee, Xiaoke Yang, Agnes Brennan, Divya Chaudhary, Xin Xu, Louis Leung, Jack Wang, Diane H. Boschelli

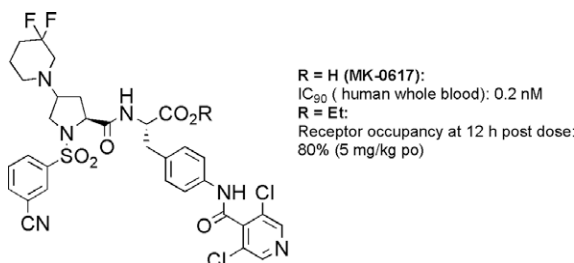


Analog **6b** with a 4-methylindol-5-ylamino group at C-4 and a 5-[(4-methylpiperazin-1-yl)methyl]-1-benzofuran-2-yl group at C-5 had an IC<sub>50</sub> value of 0.28 nM for the inhibition of PKCθ.

**Discovery of N-{N-[(3-cyanobenzene) sulfonyl]-4(R)-(3,3-difluoropiperidin-1-yl)-(L)-prolyl}-4-[(3',5'-dichloro-isonicotinoyl) amino]-(L)-phenylalanine (MK-0617), a highly potent and orally active VLA-4 antagonist**

pp 5803–5806

Shankar Venkatraman <sup>\*</sup>, Alec D. Lebsack, Kenneth Alves, Michael F. Gardner, Joyce James, Russell B. Lingham, Salony Maniar, Richard A. Mumford, Qian Si, Nicholas Stock, Kelly M. Treonze, Bowei Wang, Jasmine Zunic, Benito Munoz

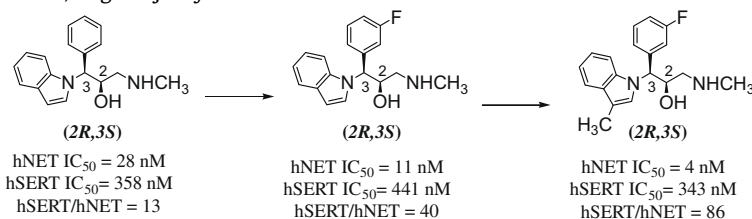




### Structure–activity relationships of the 1-amino-3-(1*H*-indol-1-yl)-3-phenylpropan-2-ol series of monoamine reuptake inhibitors

pp 5807–5810

Paige E. Mahaney<sup>\*</sup>, Callain Y. Kim, Richard D. Coghlan, Stephen T. Cohn, Gavin D. Heffernan, Christine A. Huselton, Eugene A. Terefenko, An T. Vu, Puwen Zhang, Kevin D. Burroughs, Scott A. Cosmi, Jenifer A. Bray, Grace H. Johnston, Darlene C. Deecher, Eugene J. Trybulski

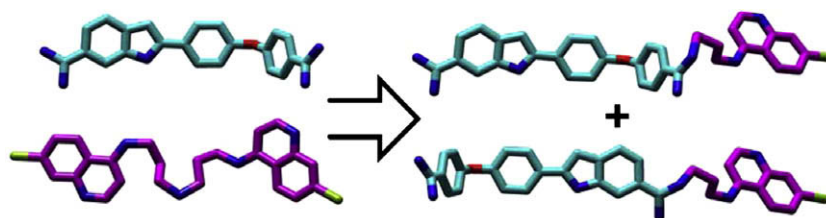


The SAR of a series of 1-amino-3-(1*H*-indol-1-yl)-3-phenylpropan-2-ols as monoamine reuptake inhibitors, with a goal to improve both potency toward inhibiting the norepinephrine transporter and selectivity over the serotonin transporter, is reported.

### Pharmacophore-guided lead optimization: The rational design of a non-zinc coordinating, sub-micromolar inhibitor of the botulinum neurotoxin serotype A metalloprotease

pp 5811–5813

J. C. Burnett<sup>\*</sup>, C. Wang, J. E. Nuss, T. L. Nguyen, A. R. Hermone, J. J. Schmidt, R. Gussio, P. Wipf<sup>\*</sup>, S. Bavari<sup>\*</sup>



The 3-zone pharmacophore for botulinum neurotoxin serotype A metalloprotease inhibition guided the design of a potent regioisomeric pair possessing a  $K_i = 600 (\pm 100)$  nM.



#### OTHER CONTENTS

##### Corrigendum

p 5814

##### Instructions to contributors

p I

<sup>\*</sup>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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