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# Bioorganic & Medicinal Chemistry Letters

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## Bioorganic & Medicinal Chemistry Letters Vol. 18, No. 17, 2008

### Contents

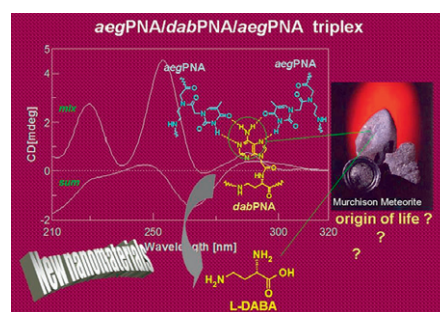
#### ARTICLES

##### Evidences for complex formation between *L*-dabPNA and *aeg*PNA

pp 4757–4760

Giovanni N. Roviello, Domenica Musumeci\*, Enrico M. Bucci, Mariangela Castiglione, Annalisa Cesarani, Carlo Pedone, Gennaro Piccialli

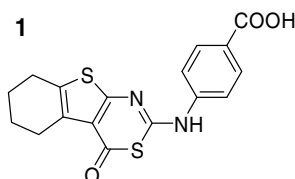
First evidence of *dab*PNA/*aeg*PNA complexes: (a) proposal for innovative self-assembling nanomaterials; (b) further contributes on the prebiotic role of *dab*PNAs and *aeg*PNAs.



##### A 4-aminobenzoic acid derivative as novel lead for selective inhibitors of multidrug resistance-associated proteins

pp 4761–4763

Stefan Leyers, Hans-Georg Häcker, Jeanette Wiendlocha, Michael Gütschow, Michael Wiese\*



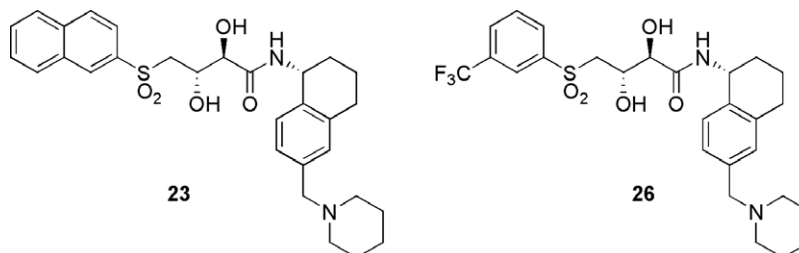
Structure of compound **1** a novel lead for selective inhibitors of multidrug resistance-associated proteins (MRPs).



##### Aryl sulfones as novel Bradykinin B1 receptor antagonists for treatment of chronic pain

pp 4764–4769

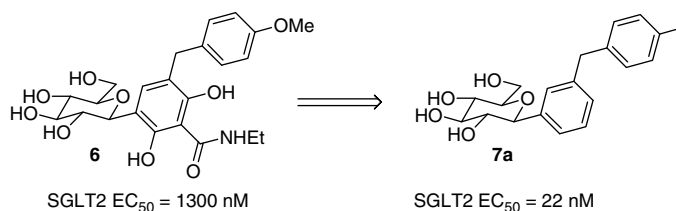
Kaustav Biswas\*, Toshihiro Aya, Wenyuan Qian, Tanya A. N. Peterkin, Jian Jeffrey Chen, Jason Human, Randall W. Hungate, Gondi Kumar, Leyla Arik, Dianna Lester-Zeiner, Gloria Biddlecome, Barton H. Manning, Hong Sun, Hong Dong, Ming Huang, Richard Loeloff, Eileen J. Johnson, Benny C. Askew



**Aglycone exploration of C-arylglucoside inhibitors of renal sodium-dependent glucose transporter SGLT2**

pp 4770–4773

Bruce A. Ellsworth\*, Wei Meng, Manorama Patel, Ravindar N. Girotra, Gang Wu, Philip M. Sher, Deborah L. Hagan, Mary T. Obermeier, William G. Humphreys, James G. Robertson, Aiying Wang, Songping Han, Thomas L. Waldron, Nathan N. Morgan, Jean M. Whaley, William N. Washburn\*

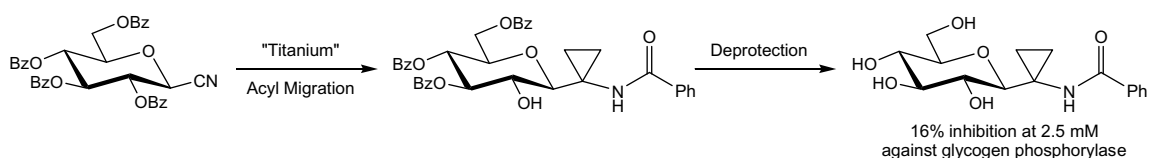


The evolution of potent and selective C-arylglucoside SGLT2 inhibitors from lead **6** to **7a** is described.

**Synthesis of a C-glucosylated cyclopropylamide and evaluation as a glycogen phosphorylase inhibitor**

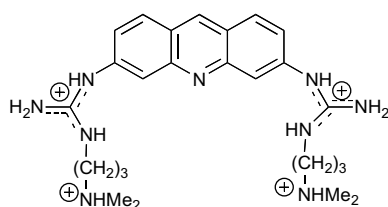
pp 4774–4778

Philippe Bertus, Jan Szymoniak, Erwann Jeanneau, Tibor Docsa, Pál Gergely, Jean-Pierre Praly, Sébastien Vidal\*

**Synthesis of *N*-acridinyl-*N'*-alkylguanidines: Dramatic influence of amine to guanidine replacement on the physicochemical properties**

pp 4779–4782

Walid Zeghida, Julien Debray, Carine Michel, Anne Milet, Pascal Dumy, Martine Demeunynck\*

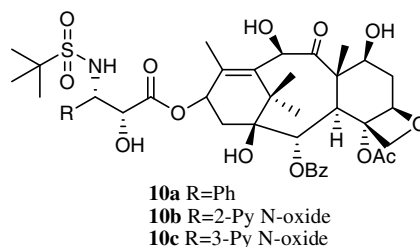


The synthesis and spectroscopic analysis of guanidinoacridines are reported.

**Synthesis and biological evaluation of novel 3'-*N*-*tert*-butylsulfonyl analogues of docetaxel**

pp 4783–4785

Bowen Ke, Yong Qin\*, Fengyan Zhao, Yi Qu\*

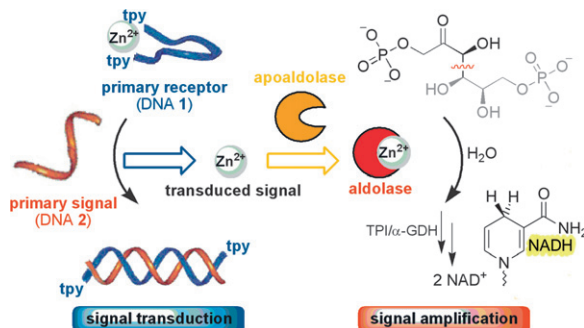


The synthesis of three novel 3'-*N*-*tert*-butylsulfonyl analogues of docetaxel **10a–c** with potent cytotoxicity against several human tumor cell lines is reported.

**Using enzymatic amplification by aldolase for the optical detection of DNA by an artificial signal cascade**

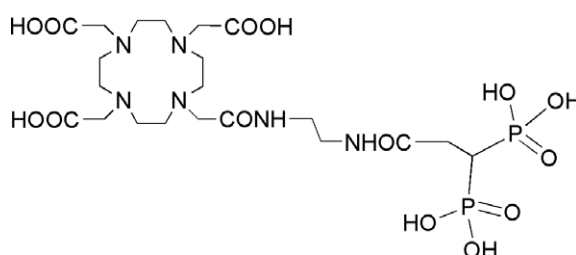
pp 4786–4788

Nora Graf, Susanne Kassube, Roland Krämer \*

**An osteoclast-targeting agent for imaging and therapy of bone metastasis**

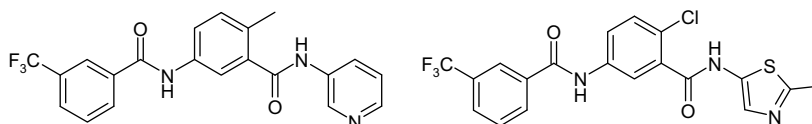
pp 4789–4793

Wei Liu, Asghar Hajibeigi, Mai Lin, Cynthia L. Rostollan, Zoltan Kovacs, Orhan K. Öz, Xiankai Sun \*

**Pyridyl and thiazolyl bisamide CSF-1R inhibitors for the treatment of cancer**

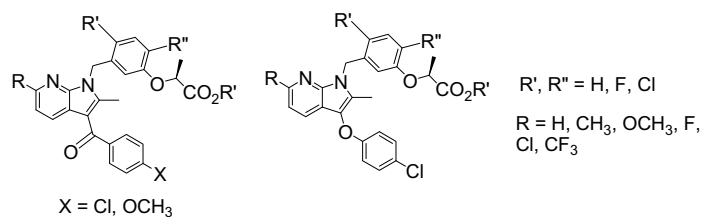
pp 4794–4797

David A. Scott \*, Brian M. Aquila, Geraldine A. Bebernitz, Donald J. Cook, Les A. Dakin, Tracy L. Deegan, Maureen M. Hattersley, Stephanos Ioannidis, Paul D. Lyne, Charles A. Omer, Minwei Ye, XiaoLan Zheng

**Highly functionalized 7-azaindoles as selective PPARγ modulators**

pp 4798–4801

Sheryl D. Debenham \*, Audrey Chan, Fiona WaiYu Lau, Weiguo Liu, Harold B. Wood, Karen Lemme, Lawrence Colwell, Bahanu Habulihaz, Taro E. Akiyama, Monica Einstein, Thomas W. Doebber, Neelam Sharma, Chaunlin F. Wang, Margaret Wu, Joel P. Berger, Peter T. Meinke



A series of highly functionalized 3-aryl and 3-phenoxy-2-methyl-7-azaindoles have been identified, which are potent selective PPARγ modulators (SPPARγMs). The SAR around substitution at the 6-position of the azaindole as well as substitution of the *N*-benzyl moiety is reported. 7-Azaindoles have significantly improved off-target profiles compared to the parent indole series.

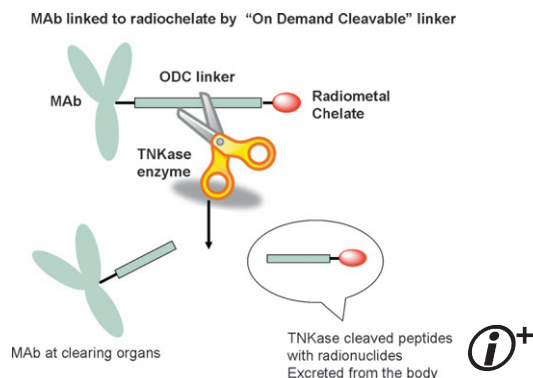


### Development of TNKase-specific cleavable peptide-linked radioimmunoconjugates for radioimmunotherapy

pp 4802–4805

Arutselvan Natarajan\*, Pappanaicken R. Kumaresan,  
Sally J. DeNardo, Gerald L. DeNardo, Gary Mirick, Kit S. Lam

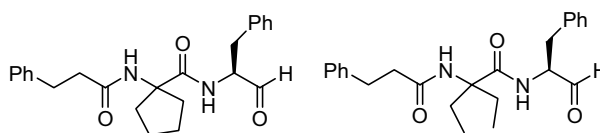
TNKase-specific peptide designed and linked to radiometal chelate and ChL6-MAb to prepare radioimmunoconjugate (RIC) for RIT. The radiochelate was cleaved 85% from RIC after 72 h in plasma by TNKase enzyme.



### Synthesis and calpain inhibitory activity of peptidomimetic compounds with constrained amino acids at the P<sub>2</sub> position

pp 4806–4808

Isaac O. Donkor\*, Rajani Korukonda

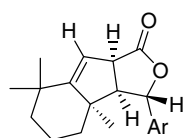


Peptidomimetic with P<sub>2</sub>  $\alpha$ -aminocyclopentane carboxylic acid.  $\mu$ -Calpain inhibition,  $K_i$  = 1.94  $\mu$ M, cathepsin B inhibition,  $K_i$  = 0.88  $\mu$ M. Peptidomimetic with P<sub>2</sub>  $\alpha,\alpha'$ -diethylglycine.  $\mu$ -Calpain inhibition,  $K_i$  = 0.08  $\mu$ M, cathepsin B inhibition,  $K_i$  = 2.91  $\mu$ M.

### Synthesis and cytotoxic activity of some novel polycyclic $\gamma$ -butyrolactones

pp 4809–4812

M. P. S. Ishar\*, Tilak Raj, Satyam Kumar Agrawal, A. K. Saxena, Lakhwinder Singh, Rajinder Singh, Surinderjit Singh Bhella



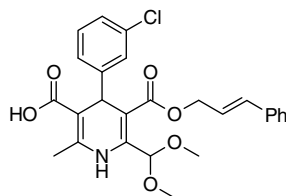
Ar = Ph-, *p*-me-Ph-, *p*-F-Ph-, *p*-Cl-Ph-, *p*-Br-Ph-,  
*p*-CN-Ph-, *p*-meo-Ph-, furan-2-yl

Some of the lactones display valuable cytotoxic activity against cancer cells.

### The structure–activity relationship study on 2-, 5-, and 6-position of the water soluble 1,4-dihydropyridine derivatives blocking N-type calcium channels

pp 4813–4816

Takashi Yamamoto\*, Seiji Niwa, Seiji Ohno, Munetaka Tokumasu, Yoko Masuzawa, Chika Nakanishi, Akira Nakajo, Tomoyuki Onishi, Hajime Koganei, Shin-ichi Fujita, Tomoko Takeda, Morikazu Kito, Yukitsugu Ono, Yuki Saitou, Akira Takahara, Seinosuke Iwata, Masataka Shoji

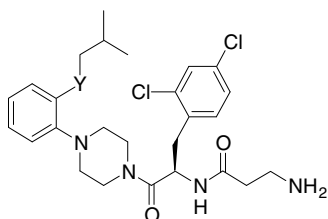


The structure–activity relationship of the 2-, 5-, and 6-position of 1,4-dihydropyridine-3-carboxylic acid-derived N-type calcium channel blockers is reported.

**Structure–activity relationship studies on a series of piperazinebenzylalcohols and their ketone and amine analogs as melanocortin-4 receptor ligands**

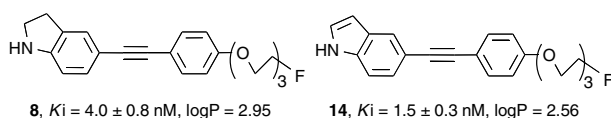
pp 4817–4822

Dragan Marinkovic, Fabio C. Tucci, Joe A. Tran, Beth A. Fleck, Jenny Wen, Chen Chen \*

**11a:** Y = CO,  $K_i$  = 24 nM**14a:** Y = CHO,  $K_i$  = 8.1 nM**15a:** Y = CHNH<sub>2</sub>,  $K_i$  = 3.2 nM**Synthesis and evaluation of indoliny- and indolylphenylacetylenes as PET imaging agents for  $\beta$ -amyloid plaques**

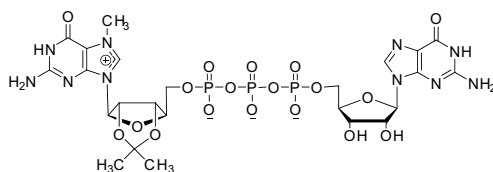
pp 4823–4827

Wenchao Qu, Seok-Rye Choi, Catherine Hou, Zhiping Zhuang, Shunichi Oya, Wei Zhang, Mei-Ping Kung, Rajesh Manchandra, Daniel M. Skovronsky, Hank F. Kung \*

**Synthesis and application of a new 2',3'-isopropylidene guanosine substituted cap analog**

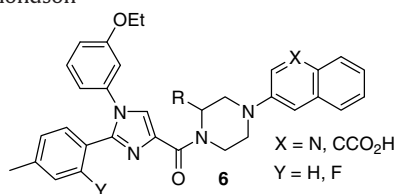
pp 4828–4832

Anilkumar R. Kore \*, Muthian Shanmugasundaram, Alexander V. Vlassov

The synthesis and biological evaluation of C2' and C3' disubstituted at m<sup>7</sup>Guo cap analog, that is, m<sup>7</sup>,2',3'-isopropylideneG[5']ppp[5']G is reported.**2-Substituted piperazine-derived imidazole carboxamides as potent and selective CCK1R agonists for the treatment of obesity**

pp 4833–4837

Richard Berger \*, Cheng Zhu, Alexa R. Hansen, Bart Harper, Zhesheng Chen, Tom G. Holt, James Hubert, Susan J. Lee, Jie Pan, Su Qian, Marc L. Reitman, Alison M. Strack, Drew T. Weingarth, Michael Wolff, Douglas J. MacNeil, Ann E. Weber, Scott D. Edmondson



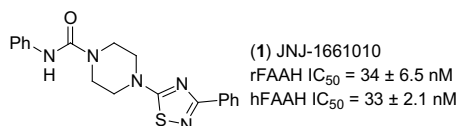
The synthesis and biological profile of imidazole carboxamides of general structure 6 as potent and selective cholecystokinin 1 receptor (CCK1R) agonists are described.



**Thiadiazolopiperazinyl ureas as inhibitors of fatty acid amide hydrolase**

pp 4838–4843

John M. Keith\*, Richard Apodaca, Wei Xiao, Mark Seierstad, Kanaka Pattabiraman, Jiejun Wu, Michael Webb, Mark J. Karbarz, Sean Brown, Sandy Wilson, Brian Scott, Chui-Se Tham, Lin Luo, James Palmer, Michelle Wennerholm, Sandra Chaplan, J. Guy Breitenbucher

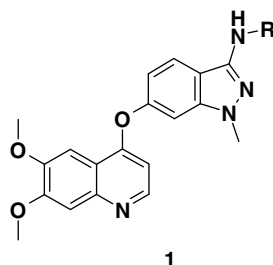


A series of thiadiazolopiperazinyl aryl urea fatty acid amide hydrolase (FAAH) inhibitors is described. The molecules were found to inhibit the enzyme by acting as mechanism-based substrates, forming a covalent bond with Ser241. SAR and PK properties are presented.

**Evaluation of indazole-based compounds as a new class of potent KDR/VEGFR-2 inhibitors**

pp 4844–4848

David Bauer\*, Douglas A. Whittington, Angela Coxon, James Bready, Shawn P. Harriman, Vinod F. Patel, Anthony Polverino, Jean-Christophe Harmange

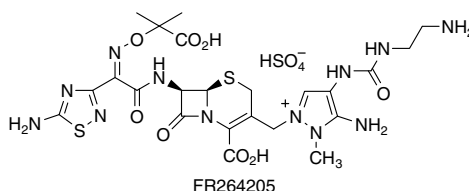


A novel class of potent and selective inhibitors of KDR incorporating an indazole moiety **1** is reported. The discovery, synthesis, and structure–activity relationships of this series of inhibitors have been investigated. The most promising compounds were also profiled to determine their pharmacokinetic properties and evaluated in a VEGF-induced vascular permeability assay.

**Synthesis and SAR of novel parenteral anti-pseudomonal cephalosporins: Discovery of FR264205**

pp 4849–4852

Ayako Toda\*, Hidenori Ohki, Toshio Yamanaka, Kenji Murano, Shinya Okuda, Kohji Kawabata, Kazuo Hatano, Keiji Matsuda, Keiji Misumi, Kenji Itoh, Kenji Satoh, Satoshi Inoue

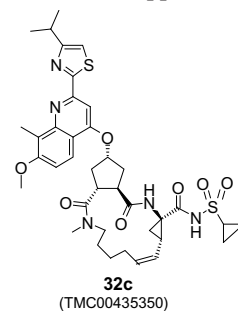


Synthesis and biological evaluation of novel cephalosporins with excellent anti-pseudomonal activity are reported.

**Structure–activity relationship study on a novel series of cyclopentane-containing macrocyclic inhibitors of the hepatitis C virus NS3/4A protease leading to the discovery of TMC435350**

pp 4853–4858

Pierre Raboisson\*, Herman de Kock, Åsa Rosenquist, Magnus Nilsson, Lourdes Salvador-Oden, Tse-I Lin, Natalie Roue, Vladimir Ivanov, Horst Wähling, Kristina Wickström, Elizabeth Hamelink, Michael Edlund, Lotta Vrang, Sandrine Vendeville, Wim Van de Vreken, David McGowan, Abdellah Tahri, Lili Hu, Carlo Boutton, Oliver Lenz, Frederic Delouvroy, Geert Pille, Dominique Surleraux, Piet Wigerinck, Bertil Samuelsson, Kenneth Simmen\*

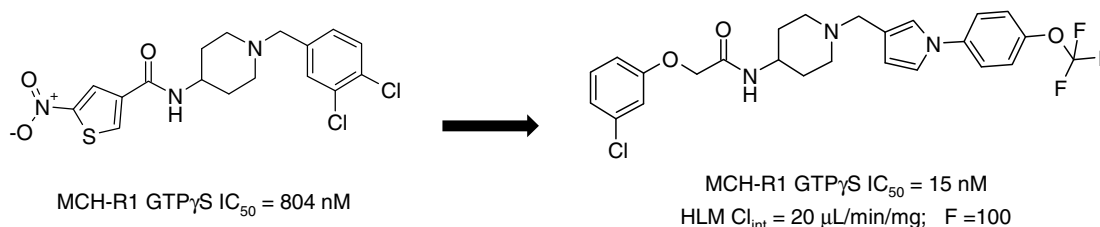


Lead optimization performed on cyclopentane-containing macrocyclic hepatitis C virus NS3/4A protease inhibitors led to the identification of TMC435350, **32c**, as a clinical candidate.

**Discovery of 1,3-disubstituted-1H-pyrrole derivatives as potent Melanin-Concentrating Hormone Receptor 1 (MCH-R1) antagonists**

pp 4859–4863

Susanne Berglund, Bryan J. Egner, Henrik Gradén, Joakim Gradén, David G. A. Morgan, Tord Inghardt\*, Fabrizio Giordanetto\*

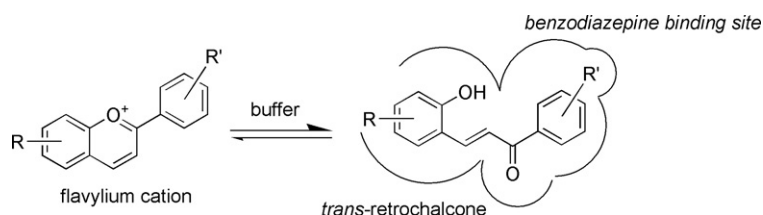


The optimization of an HTS-derived hit compound into a potent and metabolically stable MCH-R1 antagonist is described.

**Flavylium salts as in vitro precursors of potent ligands to brain GABA-A receptors**

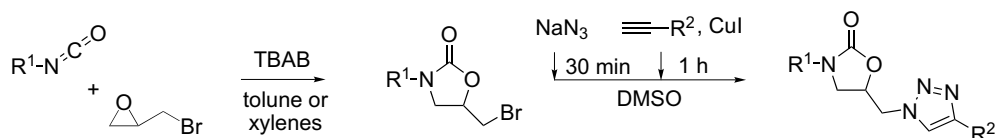
pp 4864–4867

Marie Kueny-Stotz, Stefan Chassaing, Raymond Brouillard, Mogens Nielsen\*, Maurice Goeldner\*

The synthesis of a series of derivatized flavylium cations was undertaken and the affinity to the benzodiazepine binding site on the GABA-A receptor evaluated. The observed high affinity for some derivatives (sub- $\mu$ M range) was explained by an in vitro transformation of the flavylium cation into the corresponding *trans*-retrochalcone, component which is proposed to be the active species in this series.**Synthesis of triazole-oxazolidinones via a one-pot reaction and evaluation of their antimicrobial activity**

pp 4868–4871

Jeffrey A. Demaray, Jason E. Thuener, Matthew N. Dawson, Steven J. Sucheck\*



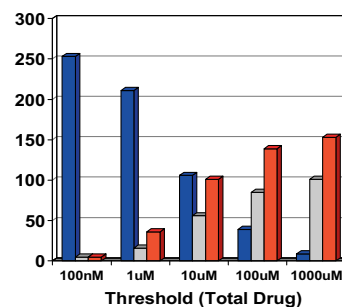
Triazole-oxazolidinones were synthesized using a three-component reaction and screened for antimicrobial activity.

**Physicochemical drug properties associated with in vivo toxicological outcomes**

pp 4872–4875

Jason D. Hughes\*, Julian Blagg\*, David A. Price\*, Simon Bailey, Gary A. DeCrescenzo, Rajesh V. Devraj, Edmund Ellsworth, Yvette M. Fobian, Michael E. Gibbs, Richard W. Gilles, Nigel Greene, Enoch Huang, Teresa Krieger-Burke, Jens Loesel, Travis Wager, Larry Whiteley, Yao Zhang

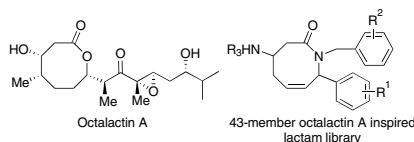
Relationships between physicochemical drug properties and toxicity were inferred from a data set consisting of animal in vivo toleration (IVT) studies on 245 preclinical Pfizer compounds; an increased likelihood of toxic events was found for less polar, more lipophilic compounds. This trend held across a wide range of types of toxicity and across a broad swath of chemical space.



**Synthesis of a natural product-inspired eight-membered ring lactam library via ring-closing metathesis**

pp 4876–4879

Neil Brown, Baohan Xie, Nataliya Markina, David VanderVelde, Jean-Pierre H. Perchellet, Elisabeth M. Perchellet, Kyle R. Crow, Keith R. Buszek\*

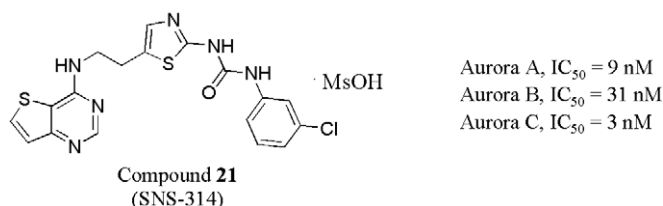


We have prepared a novel speculative eight-membered lactam demonstration library inspired by the antitumor natural product octalactin A. The basic scaffold was readily constructed in a convergent fashion via RCM from the corresponding diene amides. A cursory examination of the biological properties of the library validates the relevance and significance of these structures.

**Discovery of a potent and selective Aurora kinase inhibitor**

pp 4880–4884

Johan D. Oslob\*, Michael J. Romanowski, Darin A. Allen, Subramanian Baskaran, Minna Bui, Robert A. Elling, William M. Flanagan, Amy D. Fung, Emily J. Hanan, Shannon Harris, Stacey A. Heumann, Ute Hoch, Jeffrey W. Jacobs, Joni Lam, Chris E. Lawrence, Robert S. McDowell, Michelle A. Nannini, Wang Shen, Jeffrey A. Silverman, Michelle M. Sopko, Bradley T. Tangonan, Juli Teague, Josh C. Yoburn, Chul H. Yu, Min Zhong, Kristin M. Zimmerman, Tom O'Brien, Willard Lew

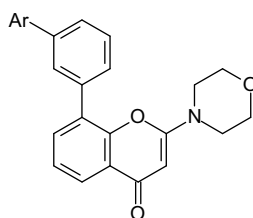


The discovery of a novel series of Aurora kinase inhibitors is disclosed.

**8-Biarylchromen-4-one inhibitors of the DNA-dependent protein kinase (DNA-PK)**

pp 4885–4890

Marine Desage-El Murr, Celine Cano, Bernard T. Golding, Ian R. Hardcastle, Marc Hummersome, Mark Frigerio, Nicola J. Curtin, Keith Menear, Caroline Richardson, Graeme C. M. Smith, Roger J. Griffin\*

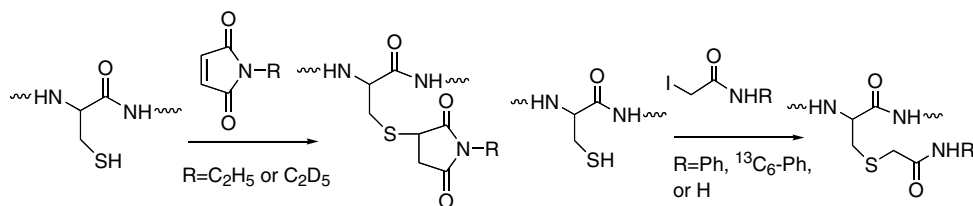


The synthesis and biological evaluation of libraries of 8-biarylchromen-4-ones enabled the elucidation of structure–activity relationships for inhibition of the DNA-dependent protein kinase (DNA-PK), with 8-(3-(thiophen-2-yl)phenyl)chromen-4-one and 8-(3-(thiophen-3-yl)phenyl)chromen-4-one being especially potent inhibitors.

**Electrospray ionization mass spectroscopic analysis of peptides modified with N-ethylmaleimide or iodoacetanilide**

pp 4891–4895

Masoud Zabet-Moghaddam, Tomoko Kawamura, Emi Yatagai, Satomi Niwayama\*

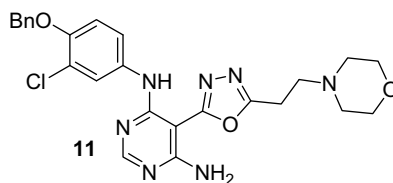




### A novel 5-[1,3,4-oxadiazol-2-yl]-N-aryl-4,6-pyrimidine diamine having dual EGFR/HER2 kinase activity: Design, synthesis, and biological activity

pp 4896–4899

Terry V. Hughes\*, Guozhang Xu, Steven K. Wetter, Peter J. Connolly, Stuart L. Emanuel, Prabha Karnachi, Scott R. Pollack, Niranjan Pandey, Mary Adams, Sandra Moreno-Mazza, Steven A. Middleton, Lee M. Greenberger

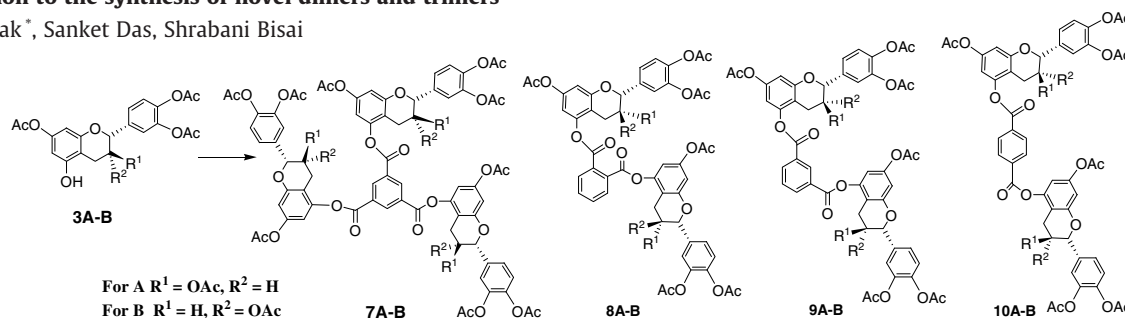


A novel 5-[1,3,4-oxadiazol-2-yl]-N-aryl-4,6-pyrimidine diamine **11** was synthesized and found to have potent dual EGFR/HER2 kinase inhibitory activity. The design, synthesis, and proposed binding conformation of **11** in EGFR kinase is described.

### Studies on the porcine liver esterase-catalyzed hydrolysis of pentaacetyl catechin and epicatechin: Application to the synthesis of novel dimers and trimers

pp 4900–4903

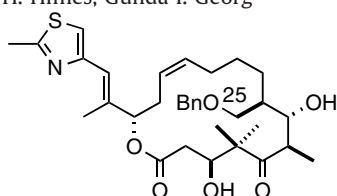
Amit Basak\*, Sanket Das, Shrabani Bisai



### Total synthesis and evaluation of C25-benzyloxyepothilone C for tubulin assembly and cytotoxicity against MCF-7 breast cancer cells

pp 4904–4906

Oliver E. Hutt, Bollu S. Reddy, Sajiv K. Nair, Emily A. Reiff, John T. Henri, Jack F. Greiner, Ting-Lan Chiu, David G. VanderVelde, Elizabeth A. Amin, Richard H. Himes, Gunda I. Georg\*



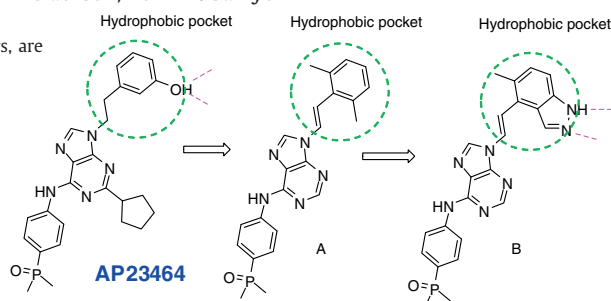
The total synthesis of C25-benzyloxy epothilone C is described. A sequential Suzuki–Aldol–Yamaguchi macrolactonization strategy was utilized employing a novel derivatized C8–C12 fragment. The C25-benzyloxy analog exhibited significantly reduced biological activity in microtubule assembly and cytotoxicity assays. Molecular modeling simulations indicated that excessive steric demand in the C25 position may reduce activity by disrupting key hydrogen bonds that are crucial for epothilone binding to  $\beta$ -tubulin.

### Novel N<sup>9</sup>-arenethenyl purines as potent dual Src/Abl tyrosine kinase inhibitors

pp 4907–4912

Yihan Wang\*, William C. Shakespeare, Wei-Sheng Huang, Raji Sundaramoorthi, Scott Lentini, Sasmita Das, Shuangying Liu, Geeta Banda, David Wen, Xiaotian Zhu, Qihong Xu, Jeffrey Keats, Frank Wang, Scott Wardwell, Yaoyu Ning, Joseph T. Snodgrass, Mark I. Broudy, Karin Russian, David Dalgarno, Tim Clackson, Tomi K. Sawyer


Novel N<sup>9</sup>-arenethenyl purines, optimized potent dual Src/Abl tyrosine kinase inhibitors, are described.



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\*Corresponding author

\* Supplementary data available via ScienceDirect

## COVER

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

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