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# Bioorganic & Medicinal Chemistry

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## Bioorganic & Medicinal Chemistry Volume 19, Issue 13, 2011

### Contents

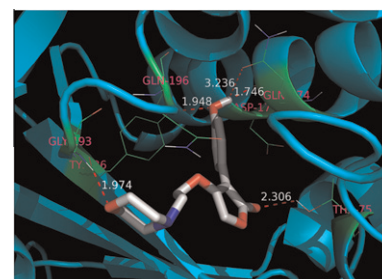
#### REGULAR ARTICLES

#### 4-Alkoxy-3-arylfuran-2(5H)-ones as inhibitors of tyrosyl-tRNA synthetase: Synthesis, molecular docking and antibacterial evaluation

pp 3884–3891

Zhu-Ping Xiao\*, Hui Ouyang, Xu-Dong Wang, Peng-Cheng Lv, Ze-Jun Huang, She-Rong Yu, Tian-Fang Yi, Ye-Ling Yang, Hai-Liang Zhu\*

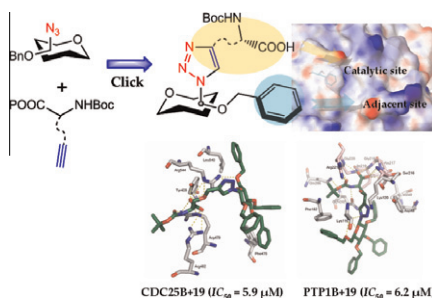
A series of novel 4-alkoxy-3-arylfuran-2(5H)-ones were synthesized and evaluated for their inhibitory activity against tyrosyl-tRNA synthetase from *Staphylococcus aureus*. 3-(4-Hydroxyphenyl)-4-(2-morpholinoethoxy)furan-2(5H)-one (**27**) is the most active with  $IC_{50} = 0.10 \pm 0.03 \mu M$  and is the most potent antibacterial agent against *S. aureus* ATCC 25923 with  $MIC_{50}$  value of  $0.23 \mu g/mL$ .



#### Facile fabrication of promising protein tyrosine phosphatase (PTP) inhibitor entities based on ‘clicked’ serine/threonine–monosaccharide hybrids

pp 3892–3900

Xiao-Peng He, Qiong Deng, Li-Xin Gao, Cui Li, Wei Zhang, Yu-Bo Zhou, Yun Tang, Xiao-Xin Shi, Juan Xie\*, Jia Li\*, Guo-Rong Chen\*, Kaixian Chen



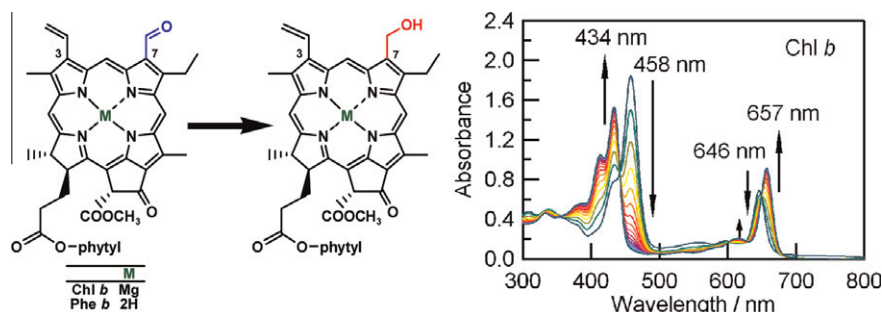
CDC25B+19 ( $IC_{50} = 5.9 \mu M$ ) PTP1B+19 ( $IC_{50} = 6.2 \mu M$ )



#### Effects of molecular structures on reduction properties of formyl groups in chlorophylls and pheophytins prepared from oxygenic photosynthetic organisms

pp 3901–3905

Kana Sadaoka, Shigenori Kashimura, Yoshitaka Saga\*

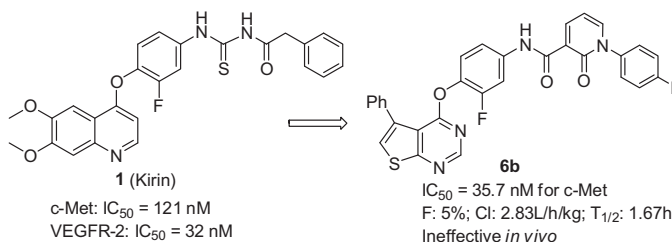


**Discovery of novel c-Met kinase inhibitors bearing a thieno[2,3-d]pyrimidine or furo[2,3-d]pyrimidine scaffold**

pp 3906–3918

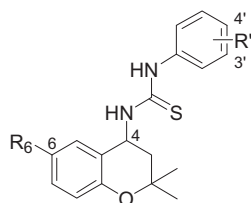
Ailing Zhao, Xin Gao, Yuanxiang Wang, Jing Ai, Ying Wang, Yi Chen, Meiyu Geng\*, Ao Zhang\*

A series of thieno[2,3-d]pyrimidines and furo[2,3-d]pyrimidines were synthesized and evaluated for the c-Met inhibition. Thieno[2,3-d]pyrimidine **6b** stood out as the most potent showing an  $IC_{50}$  of 35.7 nM. This compound displayed high inhibitory effect on cell proliferation in BaF3-TPR-Met cells and showed high selectivity for c-Met family against other 14 tested kinases. However, compound **6b** was found ineffective in the c-Met-dependent U-87MG human glioblastoma xenograft model that may be relevant to its poor PK profile.

**Modulation of the 6-position of benzopyran derivatives and inhibitory effects on the insulin releasing process**

pp 3919–3928

Xavier Florence\*, Sébastien Dilly, Pascal de Tullio, Bernard Pirotte, Philippe Lebrun

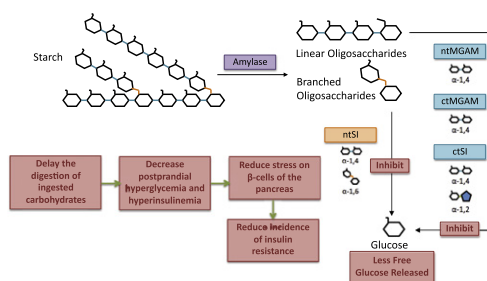


- $R_6$  = - $NH_2$ ; - $NHCHO$ ; - $NHCOCH_3$ ; - $NHCOOC(CH_3)_3$   
- $R'$  = 3' or 4'-Cl or -CN

**Mapping the intestinal alpha-glucogenic enzyme specificities of starch digesting maltase-glucoamylase and sucrase-isomaltase**

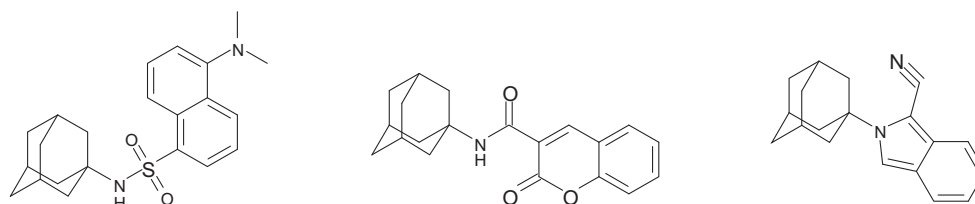
pp 3929–3934

Kyra Jones, Lyann Sim, Sankar Mohan, Jayakanthan Kumarasamy, Hui Liu, Stephen Avery, Hassan Y. Naim, Roberto Quezada-Calvillo, Buford L. Nichols, B. Mario Pinto, David R. Rose\*

**Synthesis and evaluation of fluorescent heterocyclic aminoadamantanes as multifunctional neuroprotective agents**

pp 3935–3944

Jacques Joubert, Sandra van Dyk, Ivan R. Green, Sarel F. Malan\*

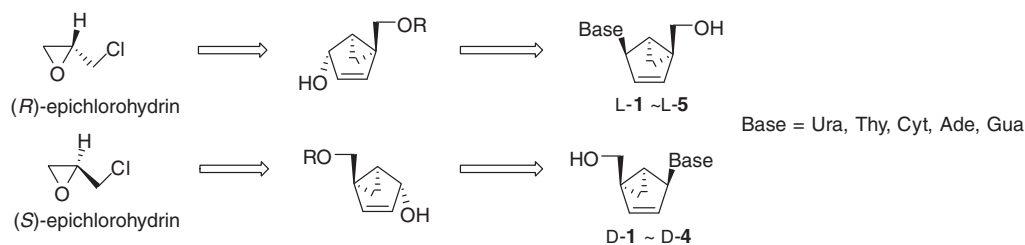


A series of fluorescent heterocyclic adamantane derivatives were found to possess a high degree of multifunctional neuroprotective activity.

**Synthesis of enantiomerically pure D- and L-bicyclo[3.1.0]hexenyl carbanucleosides and their antiviral evaluation**

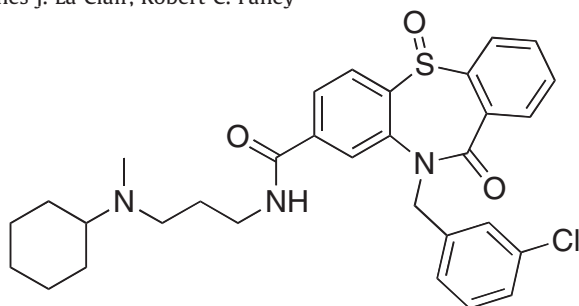
pp 3945–3955

Ah-Young Park, Won Hee Kim, Jin-Ah Kang, Hye Jin Lee, Chong-Kyo Lee, Hyung Ryong Moon\*

**Evaluation of NTF1836 as an inhibitor of the mycothiol biosynthetic enzyme MshC in growing and non-replicating *Mycobacterium tuberculosis***

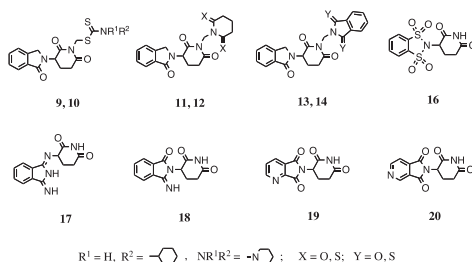
pp 3956–3964

Gerald L. Newton, Nancy Buchmeier, James J. La Clair, Robert C. Fahey\*

**Design, synthesis and biological assessment of novel N-substituted 3-(phthalimidin-2-yl)-2,6-dioxopiperidines and 3-substituted 2,6-dioxopiperidines for TNF- $\alpha$  inhibitory activity**

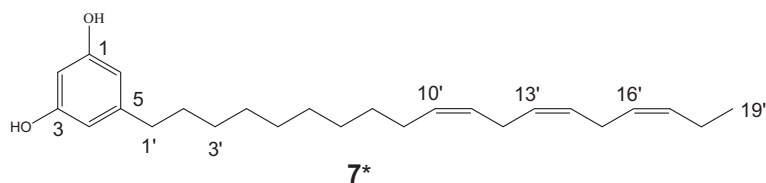
pp 3965–3972

Weiming Luo, Qian-sheng Yu, Isidro Salcedo, Harold W. Holloway, Debomoy K. Lahiri, Arnold Brossi, David Tweedie, Nigel H. Greig\*

Eleven N-substituted 3-(phthalimidin-2-yl)-2,6-dioxopiperidines and 3-substituted 2,6-dioxopiperidines were designed, synthesized and assessed for TNF- $\alpha$  lowering activity.**5-Alk(en)ylresorcinols as the major active components in wheat bran inhibit human colon cancer cell growth**

pp 3973–3982

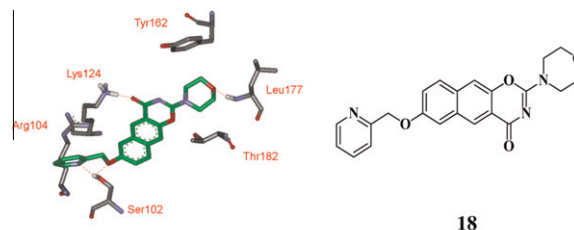
Yingdong Zhu, Dawn R. Conklin, Huadong Chen, Liyan Wang, Shengmin Sang\*



### Synthesis, structural elucidation, DNA-PK inhibition, homology modelling and anti-platelet activity of morpholino-substituted-1,3-naphth-oxazines

pp 3983–3994

Saleh Ihmaid, Jasim Al-Rawi\*, Christopher Bradley, Michael J. Angove, Murray N. Robertson, Rachel L. Clark

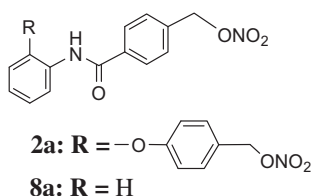
DNA-PK IC<sub>50</sub> = 0.096 μM

Twelve new *O*-substituted-morpholino-naphtho-oxazines were synthesised, characterised and used for DNA-PK IC<sub>50</sub> evaluation. The compound **18** is the most potent inhibitor. Docking of compound **18** within the binding pocket and SAR analyses of the poses support the observed activity.

### New microtubule polymerization inhibitors comprising a nitrooxymethylphenyl group

pp 3995–4003

Yasuyuki Kawaratani, Tomohiko Harada, Yoshiyuki Hirata, Yasuo Nagaoka, Susumu Tanimura, Makio Shibano, Masahiko Taniguchi, Masahide Yasuda, Kimiye Baba, Shinichi Uesato\*

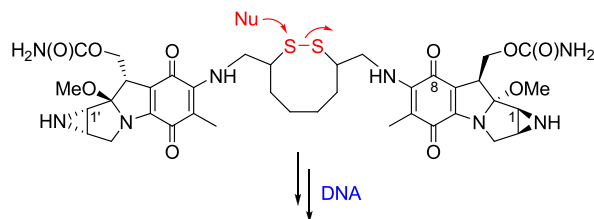


New compounds possessing a nitrooxymethylphenyl group were designed. Compounds **2a** and **8a** disrupted the formation of microtubules as did vincristine. The intraperitoneal administration (at 80 mg/kg) of **8a** reduced the growth of HCT116 xenografts in nude mice to T/C 55%.

### Synthesis and mechanistic studies of a mitomycin dimer containing an eight-membered cyclic disulfide

pp 4004–4013

Hyun Jung Park, Jae Jin Kim, Hyoung Rae Kim, Eun Kyung Lee, Eun Sook Kim, Choon Sik Jeong, Aree Moon, Sang Hyup Lee\*



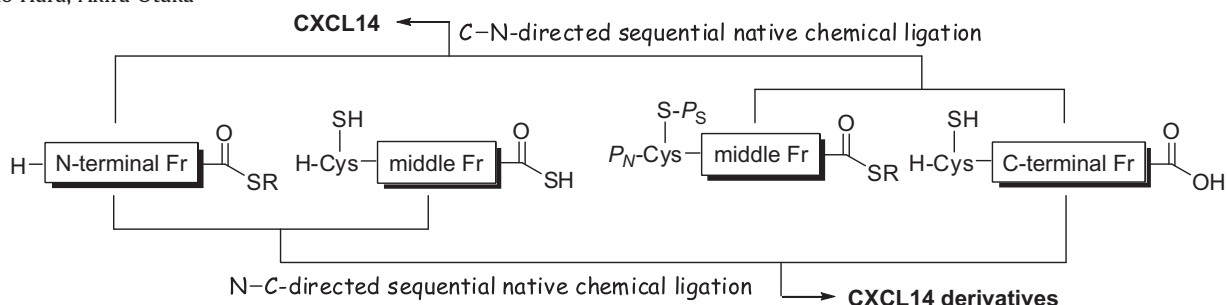
DNA ISC adducts

A mitomycin dimer containing an eight-membered cyclic disulfide underwent fast activation and was found to be highly efficient in generating DNA interstrand cross-link (ISC) adducts under nucleophilic activation conditions.

### Application of N-C- or C-N-directed sequential native chemical ligation to the preparation of CXCL14 analogs and their biological evaluation

pp 4014–4020

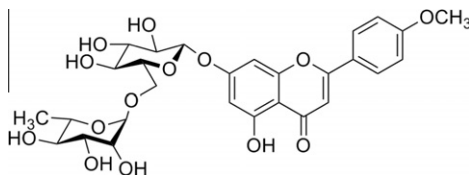
Kohei Tsuji, Akira Shigenaga, Yoshitake Sumikawa, Kosuke Tanegashima, Kohei Sato, Keisuke Aihara, Takahiko Hara, Akira Otaka\*



**Neuroprotective effects of linarin through activation of the PI3K/Akt pathway in amyloid- $\beta$ -induced neuronal cell death**

pp 4021–4027

Haiyan Lou, Peihong Fan, Ruth G. Perez, Hongxiang Lou\*

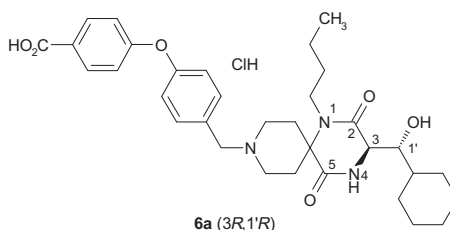


Linarin is a natural acetylcholinesterase inhibitor and the present study explored the neuroprotective effects against  $A\beta_{25-35}$ -induced neurotoxicity in cultured rat pheochromocytoma cells and the possible mechanisms involved.

**Discovery of 4-[4-((3*R*)-1-butyl-3-[(*R*)-cyclohexyl(hydroxy)methyl]-2,5-dioxo-1,4,9-triazaspiro[5.5]undec-9-yl)methylphenoxy]benzoic acid hydrochloride: A highly potent orally available CCR5 selective antagonist**

pp 4028–4042

Rena Nishizawa\*, Toshihiko Nishiyama, Katsuya Hisaichi, Chiaki Minamoto, Masayuki Murota, Yoshikazu Takaoka, Hisao Nakai, Hideaki Tada, Kenji Sagawa, Shiro Shibayama, Daikichi Fukushima, Kenji Maeda, Hiroaki Mitsuya

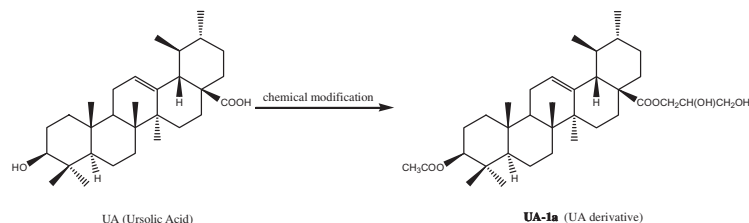


Discovery of a new orally available CCR5 antagonist.

**Synthesis of [3 $\beta$ -acetoxy-urs-12-en-28-oil]-1-monoglyceride and investigation on its anti tumor effects against BGC-823**

pp 4043–4050

Kai-Kai Bai, Fen-Ling Chen, Zhou Yu, Yun-Quan Zheng, Yong-Ning Li, Yang-Hao Guo\*

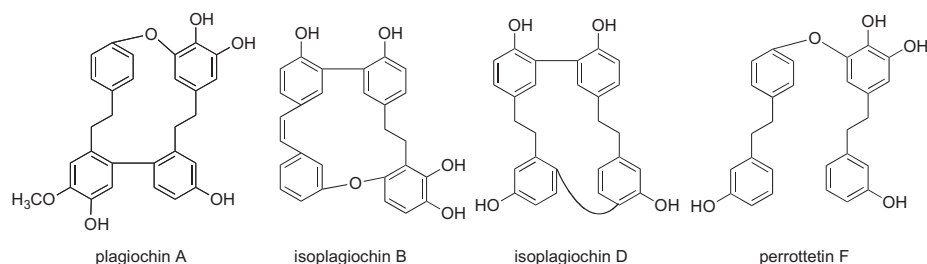


A series of ursolic acid derivatives (three novel compounds **UA-1a**, **UA-1b** and **UA-2**) by modification at the C-3 or/and C-28 positions were synthesized and their cytotoxicities against human cancer cell lines HepG2, HT-29, and BGC-823 were evaluated by MTT assay. Among the prepared derivatives, [3 $\beta$ -acetoxy-urs-12-en-28-oil]-1-monoglyceride (**UA-1a**) exhibited the highest antiproliferation activity. Its anti tumor activity against human gastric carcinoma BGC-823 was reported both in vitro and in vivo. The results indicated that **UA-1a** triggered the death of BGC-823 cells by inducing apoptosis via the mitochondria pathway.

**Vasorelaxant effects of macrocyclic bis(bibenzylyls) from liverworts**

pp 4051–4056

Hiroshi Morita\*, Kazumasa Zaima, Ikumi Koga, Aiko Saito, Haruka Tamamoto, Hiroki Okazaki, Toshio Kaneda, Toshihiro Hashimoto, Yoshinori Asakawa\*

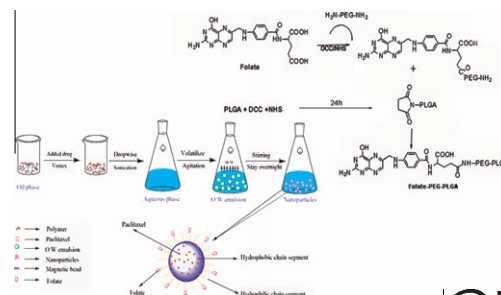


### Improved therapeutic effect of folate-decorated PLGA-PEG nanoparticles for endometrial carcinoma

pp 4057–4066

Changyan Liang, Yuebo Yang, You Ling, Yueshan Huang, Tian Li, Xiaomao Li\*

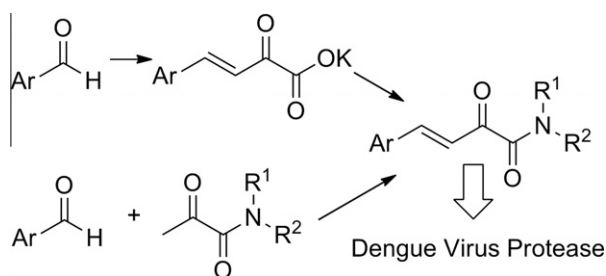
Folate (FOL) mediated poly-lactide-co-glycolide–polyethylene glycol nanoparticles (FOL-PEG-PLGA NPs) bearing paclitaxel (PTX) were prepared for the effective delivery of drug to endometrial carcinoma. The FOL-targeted PTX NPs showed a greater cytotoxicity against HEC-1A cancer cells in vitro and in vivo. These results suggest that the novel FOL-PEG-PLGA NPs could be a potential delivery system with excellent therapeutic efficacy for targeting the drugs to cancer cells.



### Synthesis and biological evaluation of $\alpha$ -ketoamides as inhibitors of the Dengue virus protease with antiviral activity in cell-culture

pp 4067–4074

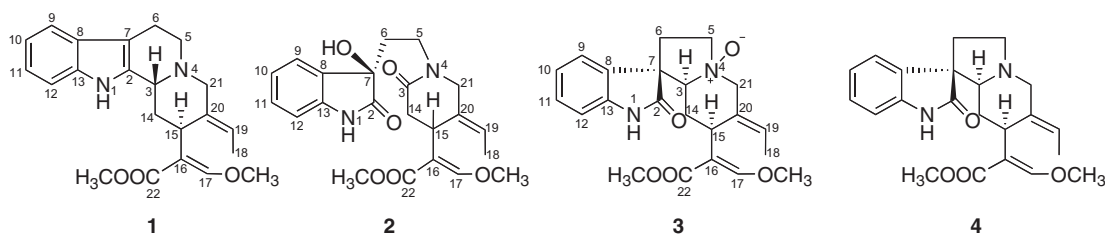
Christian Steuer, Christian Gege, Wolfgang Fischl, Karl H. Heinonen, Ralf Bartenschlager, Christian D. Klein\*



### New vasorelaxant indole alkaloids, villocarines A–D from *Uncaria villosa*

pp 4075–4079

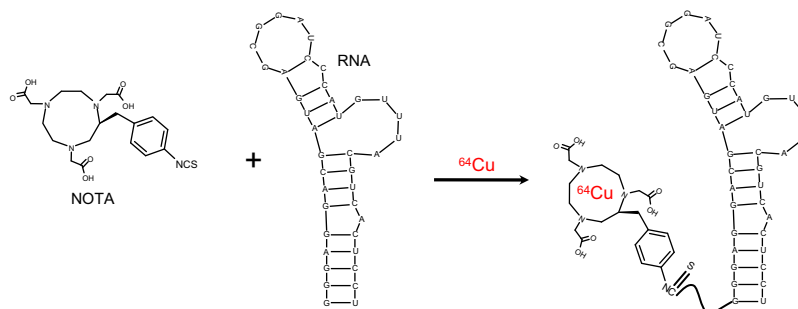
Hirota Matsuo, Ryuichi Okamoto, Kazumasa Zaima, Yusuke Hirasawa, Intan Safinar Ismail, Nordin Hj Lajis, Hiroshi Morita\*



### Synthesis and radiolabeling of chelator–RNA aptamer bioconjugates with copper-64 for targeted molecular imaging

pp 4080–4090

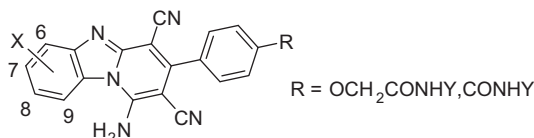
William M. Rockey, Ling Huang, Kyle C. Kloepping, Nicholas J. Baumhover, Paloma H. Giangrande\*, Michael K. Schultz\*



**Inhibition of the cellular function of perforin by 1-amino-2,4-dicyanopyrido[1,2-*a*]benzimidazoles**

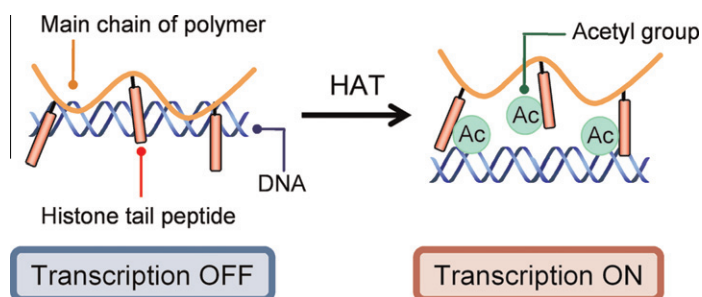
pp 4091–4100

Dani M. Lyons, Kristiina M. Huttunen, Kylie A. Browne, Annette Ciccone, Joseph A. Trapani, William A. Denny\*, Julie A. Spicer

**A hydrophilic polymer grafted with a histone tail peptide as an artificial gene regulator**

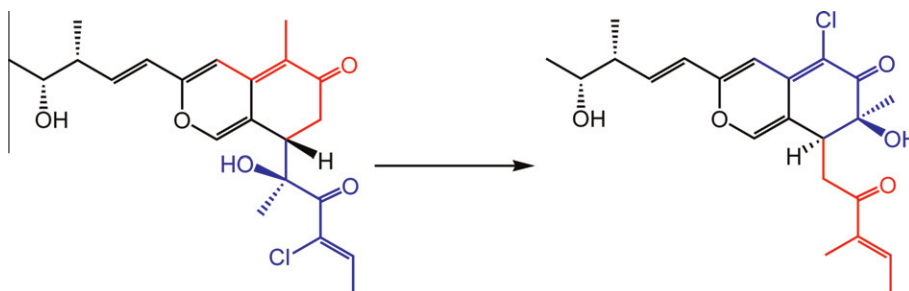
pp 4101–4105

Shujiro Shiosaki, Masanori Kuramoto, Riki Toita, Takeshi Mori, Takuro Niidome, Yoshiki Katayama\*

**New class azaphilone produced by a marine fish-derived *Chaetomium globosum*. The stereochemistry and biological activities**

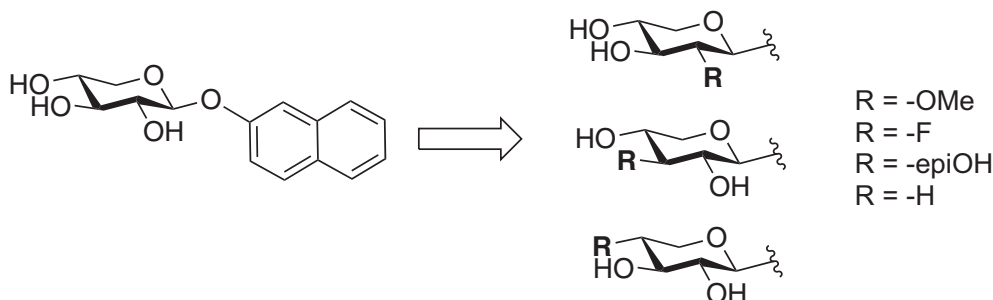
pp 4106–4113

Takeshi Yamada\*, Yasuhide Muroga, Masaaki Jinno, Tetsuya Kajimoto, Yoshihide Usami, Atsushi Numata, Reiko Tanaka

**Synthesis, conformation and biology of naphthoxylosides**

pp 4114–4126

Anna Siegbahn, Ulrika Aili, Agata Ochocinska, Martin Olofsson, Jerk Rönnols, Katrin Mani, Göran Widmalm, Ulf Ellervik\*

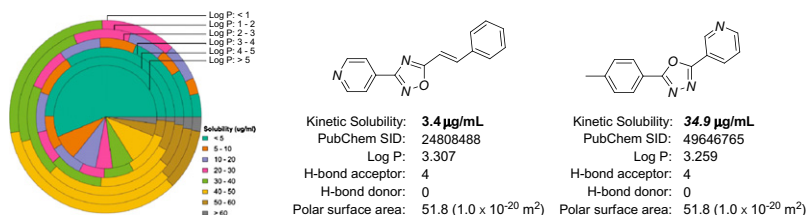




### Exploratory analysis of kinetic solubility measurements of a small molecule library

pp 4127–4134

Rajarshi Guha, Thomas S. Dexheimer, Aimee N. Kestranek, Ajit Jadhav, Andrew M. Chervenak, Michael G. Ford, Anton Simeonov, Gregory P. Roth\*, Craig J. Thomas\*



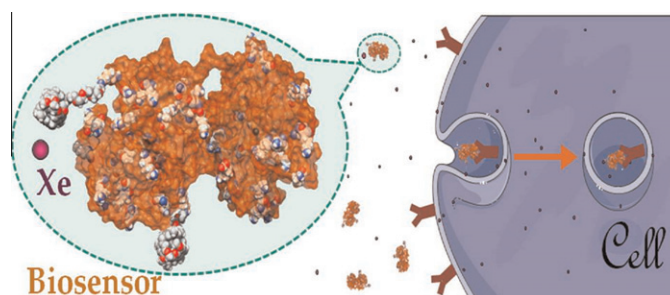
Kinetic solubility measurements are presented for a ~58,000 member library of small molecules and the data is examined in the context of physicochemical properties, assay outcomes and optimization strategies.



### Cell uptake of a biosensor detected by hyperpolarized $^{129}\text{Xe}$ NMR: The transferrin case

pp 4135–4143

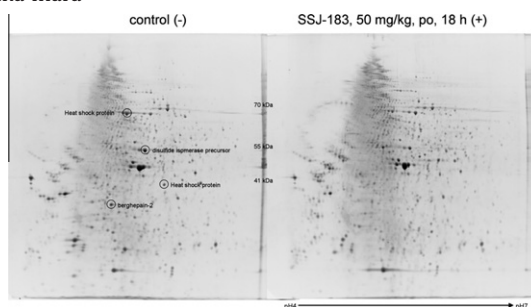
Céline Boutin, Antoine Stopin, Fatimazahra Lenda, Thierry Brotin, Jean-Pierre Dutasta, Nadège Jamin, Alain Sanson, Yves Boulard, François Leteurtre, Gaspard Huber, Aurore Bogaert-Buchmann, Nawal Tassali, Hervé Desvaux, Marie Carrière, Patrick Berthault\*



### *Plasmodium berghei* proteome changes in response to SSJ-183 treatment

pp 4144–4147

Jun Lu\*, Chika Arai, Abu Bakar Md, Masataka Ihara\*

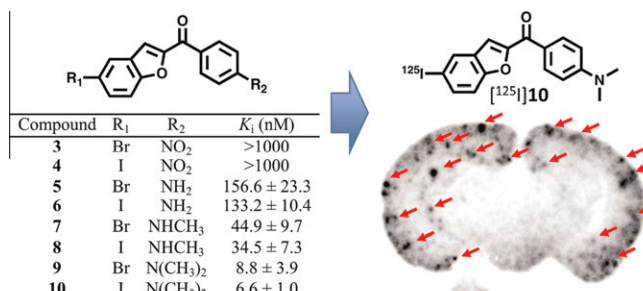


*Plasmodium berghei* proteome changes in response to SSJ-183 treatment.

### Synthesis and evaluation of benzofuran-2-yl(phenyl)methanone derivatives as ligands for $\beta$ -amyloid plaques

pp 4148–4153

Mengchao Cui, Masahiro Ono\*, Hiroyuki Kimura, Boli Liu, Hideo Saji\*





## OTHER CONTENTS

## Corrigendum

p 4154

\*Corresponding author

 Supplementary data available via ScienceDirect

## COVER

$^{129}\text{Xe}$  NMR-based biosensors are built via grafting of cryptophane precursors on transferrin. Internalization of these biosensors in eukaryotic cells is revealed through a specific signal on the  $^{129}\text{Xe}$  NMR spectrum, in agreement with fluorescence microscopy. These biosensors allow the first in-cell probing of biological events using hyperpolarized xenon. The cover illustration displays the partners of this approach: a K562 cell observed by fluorescence microscopy, the biosensor and xenon atoms; superimposed in yellow, the resulting  $^{129}\text{Xe}$  NMR spectrum. [Boutin, C.; Stopin, A.; Lenda, F.; Brodin, T.; Dutasta, J.-P.; Jamin, N.; Sanson, A.; Bouldard, Y.; Leteurtre, F.; Huber, G.; Bogaert-Buchmann, A.; Tassali, N.; Desvaux, H.; Carrière, M.; Berthault, P. *Bioorg. Med. Chem.* **2011**, 19, 4135.]

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