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# Bioorganic & Medicinal Chemistry Letters

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## Bioorganic & Medicinal Chemistry Letters Volume 20, Issue 4, 2010

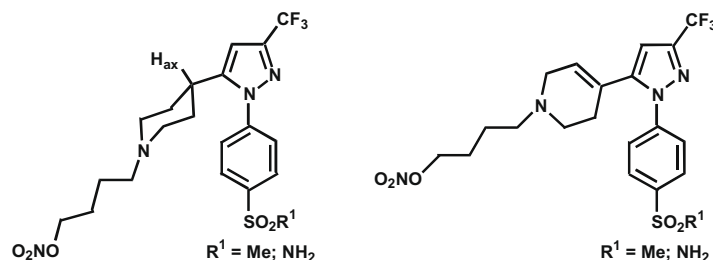
### Contents

#### ARTICLES

#### Celecoxib analogs possessing a *N*-(4-nitrooxybutyl)piperidin-4-yl or *N*-(4-nitrooxybutyl)-1,2,3,6-tetrahydropyridin-4-yl nitric oxide donor moiety: Synthesis, biological evaluation and nitric oxide release studies

pp 1324–1329

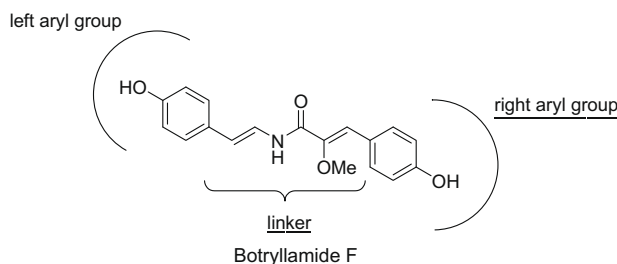
Morshed A. Chowdhury, Khaled R. A. Abdellatif, Ying Dong, Gang Yu, Zhangjian Huang, Moshfiquir Rahman, Dipankar Das, Carlos A. Velázquez, Mavanur R. Suresh, Edward E. Knaus\*



#### Synthesis and structure–activity relationship of botryllamides that block the ABCG2 multidrug transporter

pp 1330–1333

Kentaro Takada\*, Nobutaka Imamura, Kirk R. Gustafson, Curtis J. Henrich



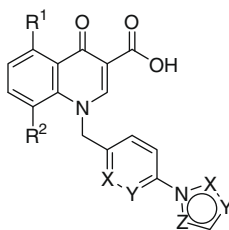
After the synthesis of botryllamide F and G, the requirement of the degree of double bond conjugation and the effect of variations in the substituents on the right aryl group were evaluated.



#### N-Heterocyclic derived *M*<sub>1</sub> positive allosteric modulators

pp 1334–1337

Scott D. Kuduk\*, Christina N. Di Marco, Victoria Cofre, Daniel R. Pitts, William J. Ray, Lei Ma, Marion Wittmann, Lone Veng, Matthew A. Seager, Kenneth Koeplinger, Charles D. Thompson, George D. Hartman, Mark T. Bilodeau



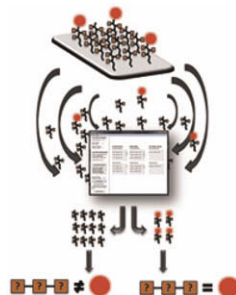
Replacement of a phenyl ring with *N*-linked heterocycles in a series of quinolone carboxylic acid *M*<sub>1</sub> positive allosteric modulators was investigated. In particular, a pyrazole derivative exhibited improvements in potency, free fraction, and CNS exposure.



### The Privileged Chemical Space Predictor (PCSP): A computer program that identifies privileged chemical space from screens of modularly assembled chemical libraries

pp 1338–1343

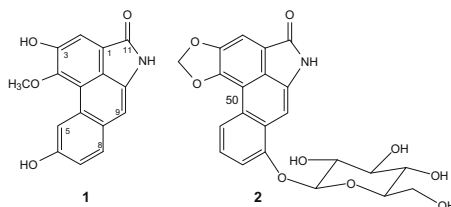
Steven J. Seedhouse, Lucas P. Labuda, Matthew D. Disney\*



### New potential antitumor compounds from the plant *Aristolochia manshuriensis* as inhibitors of the CDK2 enzyme

pp 1344–1346

Vinod R. Hegde\*, Scott Borges, Mahesh Patel, Pradip R. Das, Bonnie Wu, Vincent P. Gullo, Tze-Ming Chan

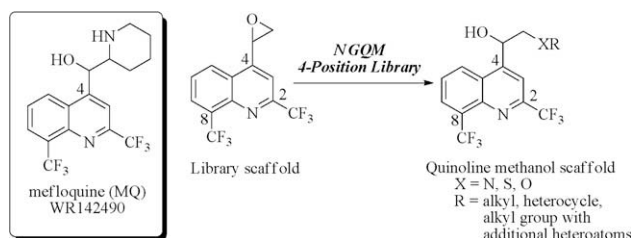


Two novel substituted phenanthrene compounds, SCH 546909 (**1**), and another glycoside (**2**) were isolated from the methanolic extract of the Chinese plant *Aristolochia manshuriensis*. The structures of **1** and **2** were established by NMR. They were identified as inhibitors of the CDK2 enzyme. Compound **1** was found to be a potent inhibitor of the CDK2 enzyme with an  $IC_{50}$  of 140 nM, whereas compound **2** was found to be less active with an  $IC_{50}$  of  $>10 \mu\text{M}$ .

### Structure–activity relationships amongst 4-position quinoline methanol antimalarials that inhibit the growth of drug sensitive and resistant strains of *Plasmodium falciparum*

pp 1347–1351

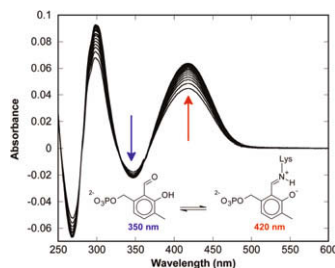
Erin Milner\*, William McCalmont, Jayendra Bhonsle, Diana Caridha, Dustin Carroll, Sean Gardner, Lucia Gerena, Montip Gettayacamin, Charlotte Lanteri, ThuLan Luong, Victor Melendez, Jay Moon, Norma Roncal, Jason Sousa, Anchalee Tungtaeng, Peter Wipf, Geoffrey Dow



### Chemoenzymatic synthesis of 1-deaza-pyridoxal 5'-phosphate

pp 1352–1354

Wait R. Griswold, Michael D. Toney\*



Formation of aspartate aminotransferase internal aldimine with 1-deaza-pyridoxal 5'-phosphate. The free cofactor analogue,  $\lambda_{\text{max}} \sim 350 \text{ nm}$ , displays a bathochromic shift upon formation of the internal aldimine,  $\lambda_{\text{max}} \sim 420 \text{ nm}$ . The internal aldimine with pyridoxal 5'-phosphate absorbs at  $\sim 430 \text{ nm}$ .



**pp 1355–1359**

The chemical structure shows a complex molecule with multiple sugar rings (glucose, mannose, galactose) linked by glycosidic bonds. It features several amino groups (NH<sub>2</sub>, NH), hydroxyl groups (OH), and a phosphate group (PO<sub>4</sub>). The molecule is highly branched and contains various functional groups, including carboxylic acids and amides.

pp 1360–1362

1 10 20 30 37

K C N T A T C A T Q R L A N F L V H S S N N F G A I L S S T N V G S N T Y

N T A T (m1)

N T A T (n1)

T Q R L A (m2)

T Q R L A (n2)

F L V H S S (m3)

F L V H S S (n3)

N F G A I L (m4)

N F G A I L (n4)

S T N V G S (m5)

S T N V G S (n5)



## pp 1363–1367

CN(C(=O)c1cc(Cl)ccc1-c1cc2nc(C3CC3)oc2o1)c4ccc(Cl)cc4

## pp 1368–1372

Chemical reaction scheme showing the synthesis of a fluorescent probe. The scheme starts with a general structure: LHS (light blue oval) - LINKER (yellow rectangle) - RHS (light green oval). The LHS contains an 'Aromatic group' and a 'HBA' (hydrogen bond acceptor) group. The LINKER contains a carbonyl group (C=O) and a nitrogen atom (N). The RHS contains a piperidine ring, a carbonyl group (C=O), and a pyridine ring. The reaction is catalyzed by 'Cat' and 'H<sub>2</sub>O' to produce a fluorescent probe. The probe has a 2,6-dichlorophenyl group attached to a pyridine ring, which is linked via a carbonyl group to a piperidine ring, which is further linked via a carbonyl group to a pyridine ring. The probe is labeled 'Fluorescent probe'.

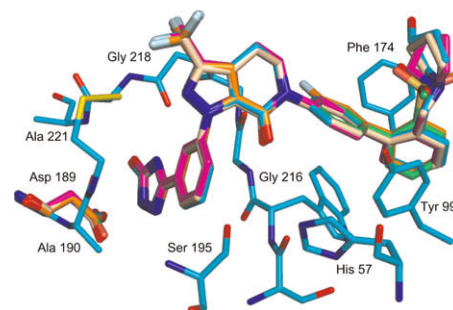
Using a pharmacophore model, based on known CGRP receptor antagonists, a novel series of oxadiazole CGRP receptor antagonists has been identified and the subsequent optimisation to enhance both potency and bioavailability is presented.

### Phenyltriazolinones as potent factor Xa inhibitors

pp 1373–1377

Mimi L. Quan\*, Donald J. P. Pinto, Karen A. Rossi, Steven Sheriff, Richard S. Alexander, Eugene Amparo, Kevin Kish, Robert M. Knabb, Joseph M. Luetgen, Paul Morin, Angela Smallwood, Francis J. Woerner, Ruth R. Wexler

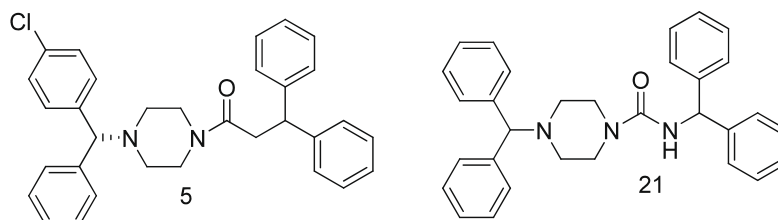
We have discovered that phenyltriazolinone is a novel and potent  $P_1$  moiety for coagulation factor Xa. X-ray structures of the inhibitors with a phenyltriazolinone in the  $P_1$  position revealed that the side chain of Asp189 has reoriented resulting in a novel  $S_1$  binding pocket which is larger in size to accommodate the phenyltriazolinone  $P_1$  substrate.



### Structure–activity relationships of diphenylpiperazine N-type calcium channel inhibitors

pp 1378–1383

Hassan Pajouhesh, Zhong-Ping Feng, Yanbing Ding, Lingyun Zhang, Hossein Pajouhesh, Jerrie-Lynn Morrison, Francesco Belardetti, Elizabeth Tringham, Eric Simonson, Todd W. Vanderah, Frank Porreca, Gerald W. Zamponi, Lester A. Mitscher, Terrance P. Snutch\*

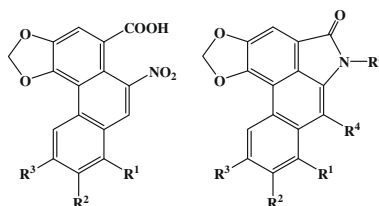


The synthesis and discovery of the potent N-type calcium channel blocker **5** ( $IC_{50}$  = 0.05  $\mu$ M) and **21** ( $IC_{50}$  = 0.15  $\mu$ M) is described. Following oral administration compounds **5** and **21** exhibit analgesic efficacy in the spinal nerve ligation model of neuropathic pain.

### Semi-synthetic aristolactams—inhibitors of CDK2 enzyme

pp 1384–1387

Vinod R. Hegde\*, Scott Borges, Haiyan Pu, Mahesh Patel, Vincent P. Gullo, Bonnie Wu, Paul Kirschmeier, Michael J. Williams, Vincent Madison, Thierry Fischmann, Tze-Ming Chan



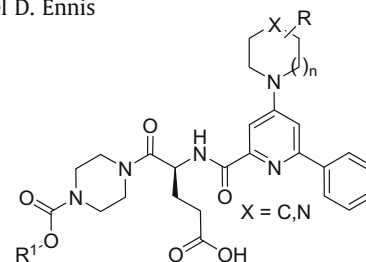
Several analogs of aristolochic acids were isolated and derivatized into their lactam derivatives to study inhibition in CDK2 assay. The study helped to derive some conclusions about the structure–activity relation around the phenanthrin moiety. Semi-synthetic aristolactam **21** showed good activity with inhibition  $IC_{50}$  of 35 nM in CDK2 assay. The activity of this compound was comparable to some of the most potent synthetic compounds reported in the literature.

### Part II: Piperazinyl-glutamate-pyridines as potent orally bioavailable P2Y<sub>12</sub> antagonists for inhibition of platelet aggregation

pp 1388–1394

John J. Parlow\*, Mary W. Burney, Brenda L. Case, Thomas J. Girard, Kerri A. Hall, Peter K. Harris, Ronald R. Hiebsch, Rita M. Huff, Rhonda M. Lachance, Deborah A. Mischke, Stephen R. Rapp, Rhonda S. Woerndle, Michael D. Ennis

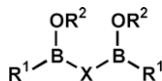
Efforts to refine the SAR of the piperazinyl-glutamate-pyridines for more potent analogs with improved pharmacokinetic profiles are described. Exploring substituted piperidines and other ring systems at the 4-pyridyl position led to compounds with improved potency and pharmacokinetic properties.



**Synthesis of bisboron compounds and their strong inhibitory activity on store-operated calcium entry**

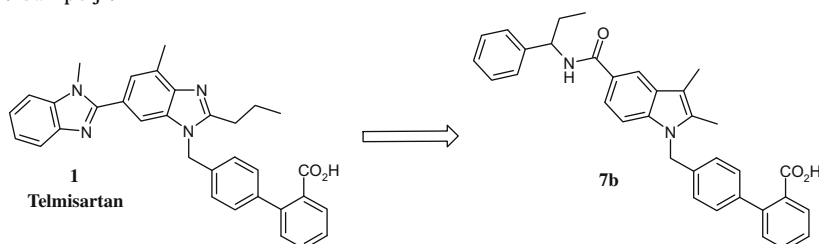
pp 1395–1398

Akinobu Z. Suzuki, Shoichiro Ozaki, Jun-Ichi Goto, Katsuhiko Mikoshiba\*

**Synthesis and biological activities of novel indole derivatives as potent and selective PPAR $\gamma$  modulators**

pp 1399–1404

Yann Lamotte\*, Paul Martres, Nicolas Faucher, Alain Laroze, Didier Grillot, Nicolas Ancellin, Yannick Saintillan, Véronique Beneton, Robert T. Gampe Jr.

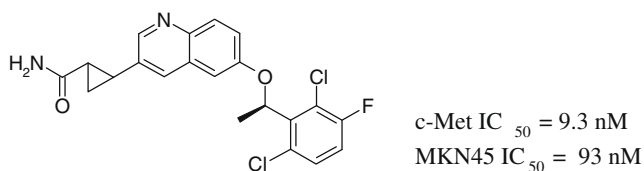


Starting from the structure of Telmisartan, a new series of potent and selective PPAR $\gamma$  modulators was identified. The synthesis, in vitro and in vivo evaluation of the most potent compounds are reported and the X-ray structure of compound **7b** bound to the PPAR $\gamma$  ligand binding domain is described.

**Discovery of 6-benzyloxyquinolines as c-Met selective kinase inhibitors**

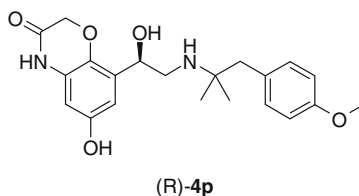
pp 1405–1409

Hiroki Nishii, Takashi Chiba, Kenji Morikami, Takaaki A. Fukami, Hiroshi Sakamoto, Kwangseok Ko, Hiroshi Koyano\*

**Discovery of olodaterol, a novel inhaled  $\beta_2$ -adrenoceptor agonist with a 24 h bronchodilatory efficacy**

pp 1410–1414

Thierry Bouyssou, Christoph Hoenke, Klaus Rudolf, Philipp Lustenberger, Sabine Pestel, Peter Sieger, Ralf Lotz, Claudia Heine, Frank H. Büttner, Andreas Schnapp, Ingo Konetzki\*



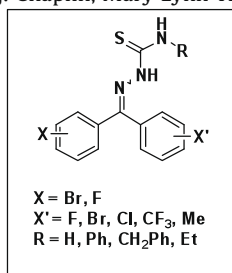
The discovery of the  $\beta_2$ -adrenoceptor agonist (R)-**4p** designated olodaterol is described. The preclinical profile of the compound suggests a bronchoprotective effect over 24 h in humans.



**Design, synthesis, and biological evaluation of potent thiosemicarbazone based cathepsin L inhibitors**

pp 1415–1419

G. D. Kishore Kumar, Gustavo E. Chavarria, Amanda K. Charlton-Sevcik, Wara M. Arispe, Matthew T. MacDonough, Tracy E. Strecker, Shen-En Chen, Bronwyn G. Siim, David J. Chaplin, Mary Lynn Trawick, Kevin G. Pinney\*

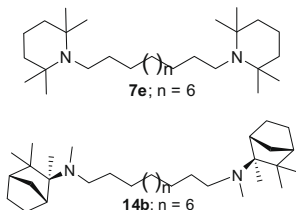


A variety of benzophenone thiosemicarbazone analogs have been designed and prepared by chemical synthesis. A sub-set of these compounds demonstrated potent inhibition of cathepsin L with minimal inhibition of cathepsin B.

**Novel bis-2,2,6,6-tetramethylpiperidine (bis-TMP) and bis-mecamylamine antagonists at neuronal nicotinic receptors mediating nicotine-evoked dopamine release**

pp 1420–1423

Zhenfa Zhang, Marharyta Pivavarchyk, Karunai Leela Subramanian, A. Gabriela Deaciu, Linda P. Dwoskin, Peter A. Crooks\*

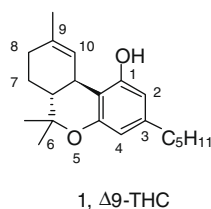


Compounds **7e** and **14b** demonstrated high potency in decreasing nicotine-evoked [ $^3\text{H}$ ]dopamine release from rat striatal slices ( $\text{IC}_{50} = 2.2$  and  $46$  nM, respectively). Such bis-tertiary amino analogs may provide a new strategy for the design of drugable ligands that have high inhibitory potency against nAChRs mediating nicotine-evoked dopamine release in striatum, which have been suggested to be target receptors of interest in the development of potential smoking cessation therapies.

**Synthesis and structure–activity relationship of substitutions at the C-1 position of  $\Delta^9$ -tetrahydrocannabinol**

pp 1424–1426

David Burdick, Russell DeOrazio\*, Peter Guzzo, Alicia Habershaw, Mark Helle, Bernard Paul, Mark Wolf

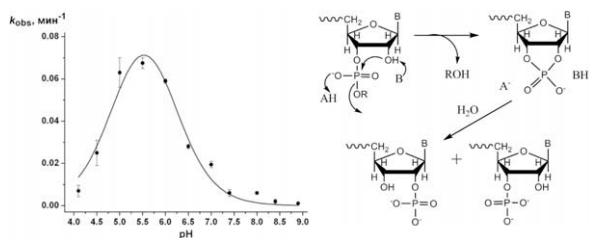


Modification of  $\Delta^9$ -THC (**1**) utilizing the C-1 triflate intermediates was investigated. The resulting compounds indicate that these modifications can lead to potent and selective  $\text{CB}_2$  ligands.

**RNA-hydrolyzing activity of human serum albumin and its recombinant analogue**

pp 1427–1431

Yulia V. Gerasimova, Tatyana V. Bobik, Natalya A. Ponomarenko, Makhmut M. Shakirov, Marina A. Zenkova, Nikolai V. Tamkovich, Tatyana V. Popova, Dmitry G. Knorre, Tatyana S. Godovikova\*



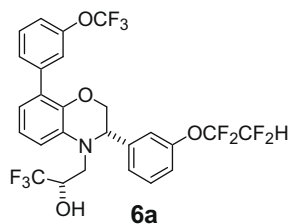
RNA hydrolysis in the presence of HSA and rHSA proceeds via 2',3'-cyclophosphate intermediates in accordance with a general acid–base mechanism of catalysis.



**Synthesis and discovery of 2,3-dihydro-3,8-diphenylbenzo[1,4]oxazines as a novel class of potent cholesteryl ester transfer protein inhibitors**

pp 1432–1435

Aihua Wang\*, Catherine P. Prouty, Patricia D. Pelton, Maria Yong, Keith T. Demarest, William V. Murray, Gee-Hong Kuo

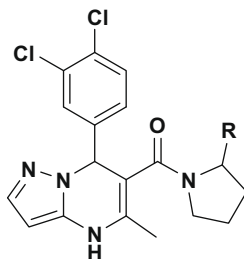


2,3-Dihydro-3,8-diphenylbenzo[1,4]oxazine **6a** is a potent inhibitor ( $IC_{50} = 26$  nM) of cholesteryl ester transfer protein (CETP). It possesses a favorable pharmacokinetic profile and long human liver microsome stability ( $t_{1/2} = 62$  min). It increases HDL-C in animal model studies. The SAR of this series is discussed herein.

**Pyrrolidine amides of pyrazolodihydropyrimidines as potent and selective  $K_v1.5$  blockers**

pp 1436–1439

John Lloyd\*, Heather J. Finlay, Wayne Vacarro, Tram Hyunh, Alexander Kover, Rao Bhandaru, Lin Yan, Karnail Atwal, Mary Lee Conder, Tonya Jenkins-West, Hong Shi, Christine Huang, Danshi Li, Huabin Sun, Paul Levesque



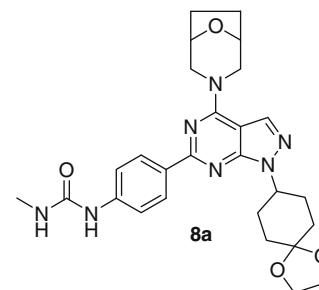
Design and synthesis of pyrazolodihydropyrimidines as  $K_v1.5$  blockers led to the discovery of **7d** as a potent and selective antagonist. This compound showed atrial selective prolongation of effective refractory period in rabbits and was selected for clinical development.

**Pyrazolopyrimidines as highly potent and selective, ATP-competitive inhibitors of the mammalian target of rapamycin (mTOR): Optimization of the 1-substituent**

pp 1440–1444

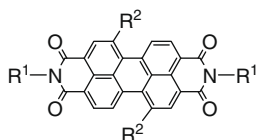
Kevin J. Curran\*, Jeroen C. Verheijen, Joshua Kaplan, David J. Richard, Lourdes Toral-Barza, Irwin Hollander, Judy Lucas, Semiramis Ayrat-Kaloustian, Ker Yu, Arie Zask

Combination of a 1-cyclohexyl ketal group with a 2,6-ethylene bridged morpholine in the 4-position and a ureidophenyl group in the 6-position of the pyrazolopyrimidine resulted in compound **8a**, that selectively suppressed key mTOR biomarkers in vivo for at least 8 h following oral administration and showed excellent activity in a tumor xenograft model.

**Interaction of heparin with cationic molecular probes: Probe charge is a major determinant of binding stoichiometry and affinity**

pp 1445–1447

Helga Szelke, Sarah Schübel, Job Harenberg, Roland Krämer\*



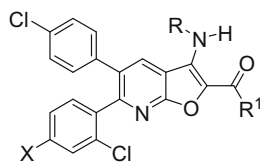
$R^1 = (CH_2)_6NH_3^+$  ; Spermine  
 $R^2 = O(CH_2)_3NH_3^+$  ; OMe ; Br

Fluorescent perylenediimide probes modified with 2, 4, 6, or 8 ammonium groups were synthesized and their binding to the antithrombotic drug heparin was studied by fluorescence spectroscopy in solution.

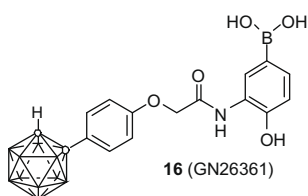


**Furo[2,3-*b*]pyridine-based cannabinoid-1 receptor inverse agonists: Synthesis and biological evaluation. Part 1****pp 1448–1452**

John S. Debenham\*, Christina B. Madsen-Duggan, Richard B. Toupence, Thomas F. Walsh, Junying Wang, Xinchun Tong, Sanjeev Kumar, Julie Lao, Tung M. Fong, Jing Chen Xiao, Cathy R.-R. C. Huang, Chun-Pyn Shen, Yue Feng, Donald J. Marsh, D. Sloan Stribling, Lauren P. Shearman, Alison M. Strack, Mark T. Goulet

**Boron-containing phenoxyacetanilide derivatives as hypoxia-inducible factor (HIF)-1 $\alpha$  inhibitors****pp 1453–1456**

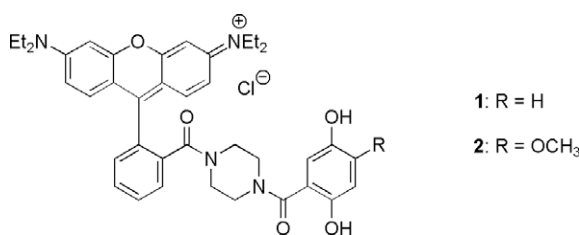
Kazuki Shimizu, Minako Maruyama, Yuka Yasui, Hidemitsu Minegishi, Hyun Seung Ban, Hiroyuki Nakamura\*




Compound **16** (GN25361) was found to be a potent inhibitor against HIF-1 $\alpha$  accumulation under hypoxic condition without affecting the mRNA expression level of HIF-1 $\alpha$ .

**A fluorescent redox sensor with tuneable oxidation potential****pp 1457–1459**

Radoslaw M. Kierat, Birgit M. B. Thaler, Roland Krämer\*

**OTHER CONTENTS****Corrigenda****pp 1460–1463**

\*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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