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# Bioorganic & Medicinal Chemistry Letters

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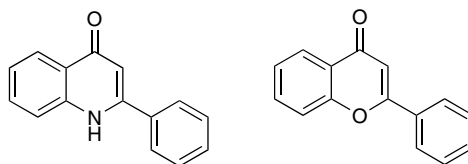


## Bioorganic & Medicinal Chemistry Letters Vol. 18, No. 21, 2008

### Contents

#### ARTICLES

- Azaflavones compared to flavones as ligands to the benzodiazepine binding site of brain GABA<sub>A</sub> receptors** pp 5713–5716  
 Jakob Nilsson, Elsebet Østergaard Nielsen, Tommy Liljefors, Mogens Nielsen, Olov Sterner\*

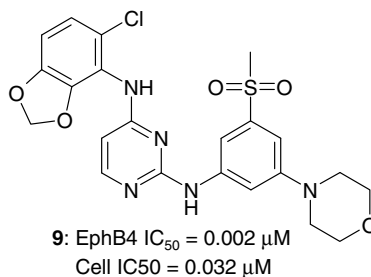


The affinity of azaflavone and flavone derivatives for the benzodiazepine binding site of the GABA<sub>A</sub> receptor was compared.

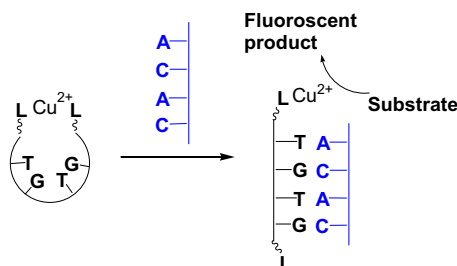


- Inhibitors of the tyrosine kinase EphB4. Part 2: Structure-based discovery and optimisation of 3,5-bis substituted anilinopyrimidines** pp 5717–5721

Catherine Bardelle, Tanya Coleman, Darren Cross, Sara Davenport, Jason G. Kettle\*, Eun Jung Ko, Andrew G. Leach, Andrew Mortlock, Jon Read, Nicola J. Roberts, Peter Robins, Emma J. Williams



- Nucleic acid controlled catalysts of carboxylic esters hydrolysis** pp 5722–5724  
 János Kovács, Andriy Mokhir\*

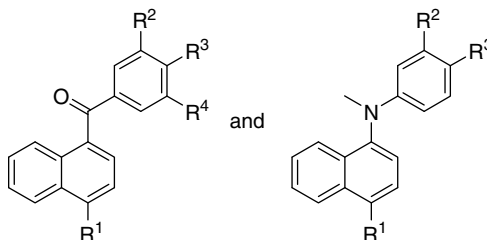


An optimized short DNA containing two ligands attached to its termini forms a catalytically inert complex with Cu<sup>2+</sup>. A complementary nucleic acid induces decomposition of this complex. The products formed may catalyze hydrolysis of carboxylic acid esters. We have demonstrated that this process can be applied for sequence specific detection of nucleic acids.

### Discovery of (naphthalen-4-yl)(phenyl)methanones and *N*-methyl-*N*-phenylnaphthalen-1-amines as new apoptosis inducers using a cell- and caspase-based HTS assay

pp 5725–5728

Songchun Jiang, Candace Crogan-Grundy, John Drewe, Ben Tseng, Sui Xiong Cai \*

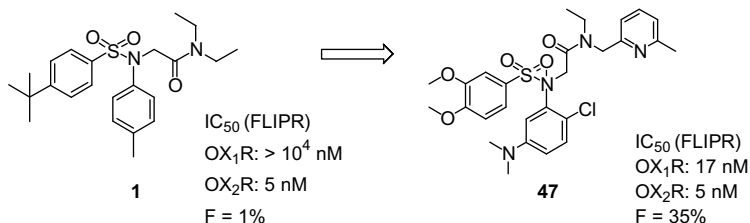


The discovery and SAR studies of (naphthalen-4-yl)(phenyl)methanones and *N*-methyl-*N*-phenylnaphthalen-1-amines as novel and potent apoptosis inducers is reported.

### *N*-Glycine-sulfonamides as potent dual orexin 1/orexin 2 receptor antagonists

pp 5729–5733

Hamed Aissaoui \*, Ralf Koberstein, Cornelia Zumbrunn, John Gatfield, Catherine Brisbane-Roch, Francois Jenck, Alexander Treiber, Christoph Boss

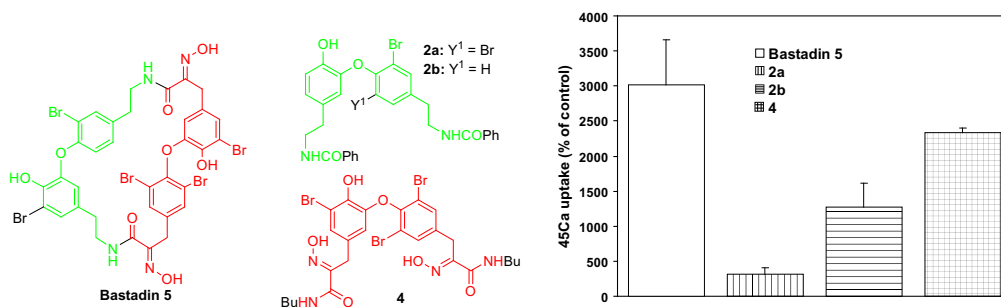


The structure–activity relationship and the synthesis of novel *N*-glycine-sulfonamides as  $OX_1R/OX_2R$  dual orexin antagonists are described. Compound **47** exhibited good oral bioavailability and has demonstrated in vivo activity in rats following oral administration.

### Open-chain half-bastadins mimic the effects of cyclic bastadins on calcium homeostasis in cultured neurons

pp 5734–5737

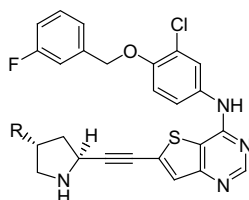
Elzbieta Zieminska, Jerzy W. Lazarewicz \*, Elias A. Couladouros, Vassilios I. Moutsos, Emmanuel N. Pitsinos \*



### Dual EGFR/ErbB-2 inhibitors from novel pyrrolidinyl-acetylenic thieno[3,2-*d*]pyrimidines

pp 5738–5740

Robert D. Hubbard, Scott H. Dickerson, Holly K. Emerson, Robert J. Griffin, Michael J. Reno, Keith R. Hornberger, David W. Rusnak, Edgar R. Wood, David E. Uehling, Alex G. Waterson \*

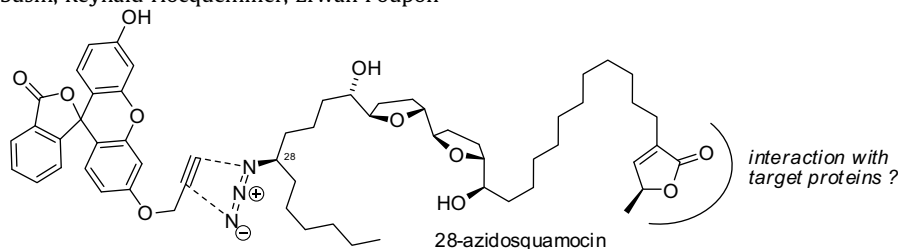


A novel class of substituted pyrrolidinyl-acetylenic thieno[3,2-*d*]pyrimidines has been identified that are potent and selective inhibitors of both EGFR/ErbB-2 receptor tyrosine kinases. The inhibitors are found to display a range of enzyme and cellular potency and also to display a varying level of covalent modification of the kinase targets. Selected molecules, including compound **15h**, were found to be potent in enzymatic and cellular assays while also demonstrating exposure in the mouse from an oral dose.

### Highly cytotoxic and neurotoxic acetogenins of the Annonaceae: New putative biological targets of squamocin detected by activity-based protein profiling

pp 5741–5744

S  verine Derbr  , Sophie Gil, Myriam Taverna, C  line Boursier, Val  rie Nicolas, Emmanuelle Demey-Thomas, Jo  lle Vinh, Santos A. Susin, Reynald Hocquemiller, Erwan Poupon\*



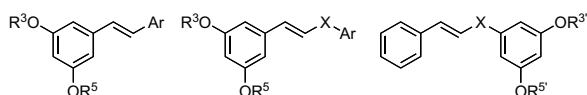
Combining hemisynthetic work, Cu-catalyzed Huisgen cycloaddition and proteomic techniques, we have identified new putative protein targets of squamocin ruling out the previously accepted 'complex I dogma' in the annonaceous acetogenin series.



### New classes of Gram-positive selective antibacterials: Inhibitors of MRSA and surrogates of the causative agents of anthrax and tuberculosis

pp 5745–5749

M. Shahjahan Kabir, Kathleen Engelbrecht, Rebecca Polanowski, Sarah M. Krueger, Rachel Ignasiak, Marc Rott, William R. Schwan, Mary E. Stemper, Kurt D. Reed, David Sherman, James M. Cook\*, Aaron Monte\*

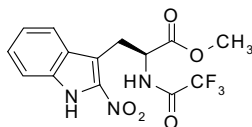


Substituted stilbene, phenoxy styrene, and phenothio styrene analogs of an antimicrobial natural product *E*-stilbene were synthesized and assayed for the ability to inhibit the growth of clinically significant bacteria.

### Regioselective nitration of *N*<sup>  </sup>,*N*<sup>1</sup>-bis(trifluoroacetyl)-*L*-tryptophan methyl ester: Efficient synthesis of 2-nitro and 6-nitro-*N*-trifluoroacetyl-*L*-tryptophan methyl ester

pp 5750–5752

Andrew S. Osborne, Phanneth Som, Jessica L. Metcalf, Robert S. Phillips\*



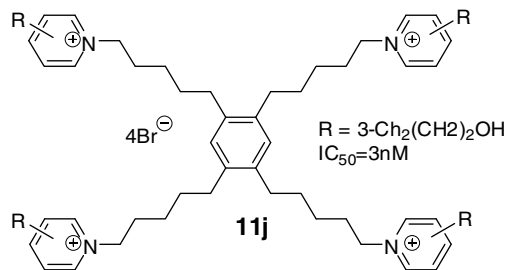
The nitration of *N*<sup>  </sup>,*N*<sup>1</sup>-bis(trifluoroacetyl)-*L*-tryptophan methyl ester is reported.



### Tetrakis-azaaromatic quaternary ammonium salts: Novel subtype-selective antagonists at neuronal nicotinic receptors that mediate nicotine-evoked dopamine release

pp 5753–5757

Zhenfa Zhang, Guangrong Zheng, Marharyta Pivavarchyk, A. Gabriela Deaciuc, Linda P. Dwoskin, Peter A. Crooks\*

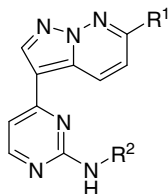


Tetrakis-azaaromatic quaternary ammonium salts were identified as antagonists with high affinity and selectivity at nAChR subtypes (nAChR) that mediate nicotine-evoked DA release. Analog **11j** (IC<sub>50</sub> = 3 nM), is a representative member of this novel structural class of selective nicotinic receptor antagonists.

**Synthesis and evaluation of pyrazolo[1,5-b]pyridazines as selective cyclin dependent kinase inhibitors**

pp 5758–5762

Kirk L. Stevens\*, Michael J. Reno, Jennifer B. Alberti, Daniel J. Price, Laurie S. Kane-Carson, Victoria B. Knick, Lisa M. Shewchuk, Anne M. Hassell, James M. Veal, Stephen T. Davis, Robert J. Griffin, Michael R. Peel

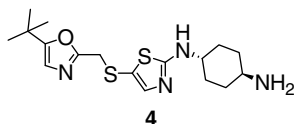


A novel series of pyrazolo[1,5-b]pyridazines have been synthesized and identified as cyclin dependant kinase inhibitors potentially useful for the treatment of solid tumors. Modification of the hinge-binding amine or the C(2)- and C(6)-substitutions on the pyrazolo[1,5-b]pyridazine core provided potent inhibitors of CDK4 and demonstrated enzyme selectivity against VEGFR-2 and GSK3 $\beta$ .

**A diaminocyclohexyl analog of SNS-032 with improved permeability and bioavailability properties**

pp 5763–5765

Ingrid C. Choong\*, Iana Serafimova, Junfa Fan, David Stockett, Erica Chan, Sravanthi Cheeti, Yafan Lu, Bruce Fahr, Phuongly Pham, Michelle R. Arkin, Duncan H. Walker, Ute Hoch\*

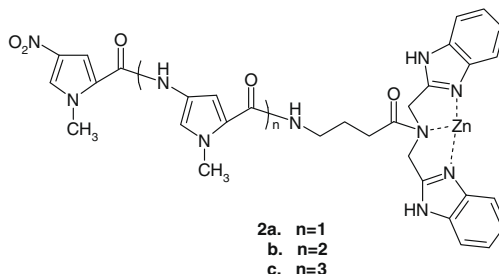


The identification of a selective CDK2, 7, 9 inhibitor **4** with improved permeability is described. The in vitro and PK properties of **4** are discussed.

**Synthesis and biological evaluation of the Zn (II)–IDB complexes appended with oligopolyamide as potent artificial nuclease**

pp 5766–5770

Chao Li, Ren-Zhong Qiao\*, Ya-Qin Wang, Yu-Fen Zhao\*, Rong Zeng



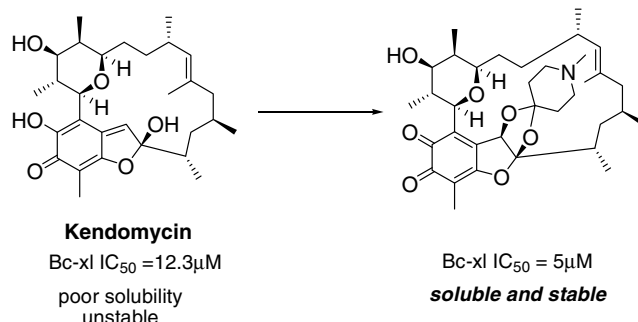
The synthesis and biological evaluation of Zn (II)–IDB complexes **2** as potent artificial nuclease are reported.

**Interaction of kendomycin and semi-synthetic analogues with the anti-apoptotic protein Bcl-xl**

pp 5771–5773

Christian O. Janssen, Stephanie Lim, Ee Peng Lo, Kah Fei Wan, Victor C. Yu, May Ann Lee, Siew Bee Ng, Martin J. Everett, Antony D. Buss, David P. Lane, Rustum S. Boyce\*

Discovery of a stable and soluble Bcl-xl inhibitor derived from kendomycin has been disclosed.

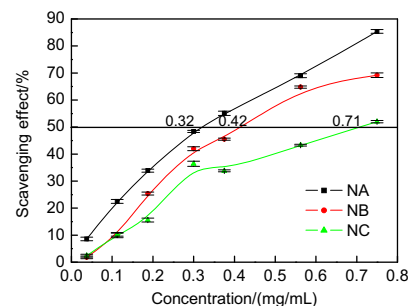


**Antioxidant activity of *N*-carboxymethyl chitosan oligosaccharides**

pp 5774–5776

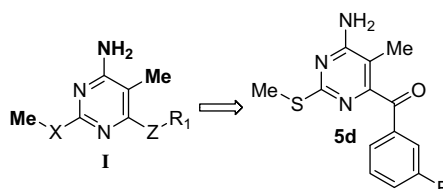
Tao Sun\*, Qian Yao, Dongxiang Zhou, Fang Mao

*N*-Carboxymethyl chitosan oligosaccharides with different degrees of substitution (NA: 0.28, NB: 0.41, and NC: 0.54, respectively) showed different DPPH and superoxide anion scavenging activity and reducing power. The difference may be related to the different radical scavenging mechanisms and donating effect of substituting carboxymethyl group.

**Towards novel *S*-DABOC inhibitors: Synthesis, biological investigation, and molecular modeling studies**

pp 5777–5780

Marco Radi, Lucilla Angeli, Luigi Franchi, Lorenzo Contemori, Giovanni Maga, Alberta Samuele, Samantha Zanolli, Mercedes Armand-Ugon, Emmanuel Gonzalez, Anuska Llano, Jose A. Esté, Maurizio Botta\*

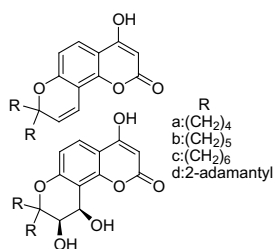


A small family of *S*-DABO cytosine analogs (*S*-DABOCs) has been synthesized and biologically evaluated as HIV-1 inhibitor both on wild type and drug-resistant mutants. An interesting compound (**5d**) has been identified which showed a predicted pharmacokinetic profile similar to that of anti-HIV drugs on the market. Molecular modeling studies have been finally performed in order to rationalize the results.

**Synthesis and free radical scavenging activity of some new spiropyranocoumarins**

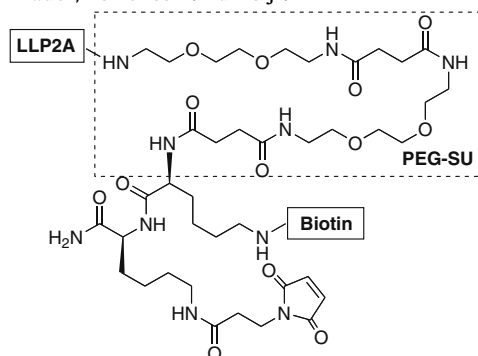
pp 5781–5784

Vassiliki Panteleon, Ioannis K. Kostakis, Panagiotis Marakos\*, Nicole Pouli, Ioanna Andreadou

**Application of a trifunctional reactive linker for the construction of antibody–drug hybrid conjugates**

pp 5785–5788

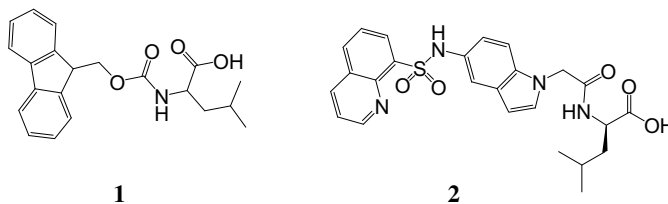
Joshua D. Thomas, Thomas Hofer, Christoph Rader, Terrence R. Burke Jr.\*



### The identification of neurotensin NTS1 receptor partial agonists through a ligand-based virtual screening approach

pp 5789–5791

Yi Fan\*, Margaret H. Lai, Kelly Sullivan, Michael Popiolek, Terrance H. Andree, Paul Dollings, Mark H. Pausch

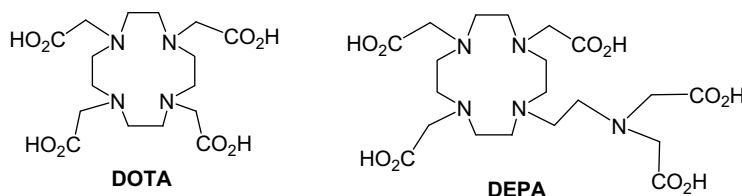


Two compounds were identified to produce partial agonist activity with potency in the moderate micromolar range as a result of ligand-based virtual screening.

### Synthesis and biological evaluation of a novel decadentate ligand DEPA

pp 5792–5795

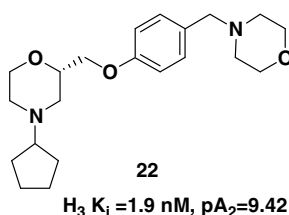
Hyun-Soon Chong\*, Sooyoun Lim, Kwamena E. Baidoo, Diane E. Milenic, Xiang Ma, Fang Jia, Hyun A. Song, Martin W. Brechbiel, Michael R. Lewis



### 2-Aryloxymethylmorpholine histamine H<sub>3</sub> antagonists

pp 5796–5799

Michael A. Letavic\*, John M. Keith, Kiev S. Ly, Pascal Bonaventure, Mark A. Feinstein, Brian Lord, Kirsten L. Miller, S. Timothy Motley, Diane Nepomuceno, Steven W. Sutton, Nicholas I. Carruthers

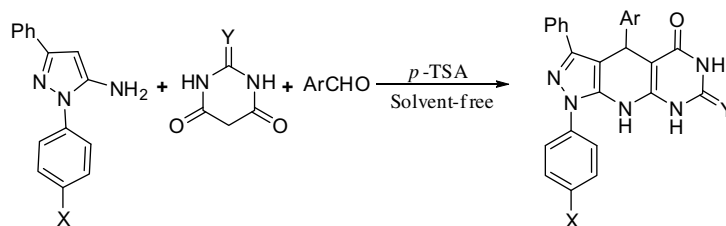


2-Aryloxymethylmorpholines are potent histamine H<sub>3</sub> antagonists.

### One-pot synthesis and antibacterial activities of pyrazolo[4,3':5,6]pyrido[2,3-d]pyrimidine-dione derivatives

pp 5800–5803

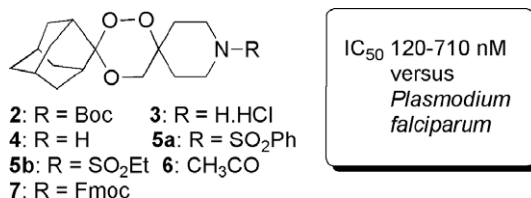
Ayoob Bazgir\*, Maryam Mohammadi Khanaposhtani, Ali Abolhasani Soorki



**Piperidine dispiro-1,2,4-trioxane analogues**

pp 5804–5808

Sunil Sabbani, Paul A. Stocks, Gemma L. Ellis, Jill Davies, Erik Hedenstrom, Stephen A. Ward, Paul M. O'Neill\*



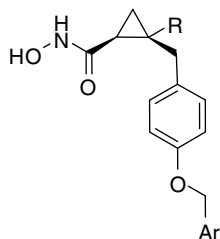
Dispiro *N*-Boc-protected 1,2,4-trioxanes were synthesised via Mo(acac)<sub>2</sub> catalysed perhydrolysis of *N*-Boc spirooxirane followed by condensation of the resulting  $\beta$ -hydroperoxy alcohol with 2-adamantanone. *N*-Boc 1,2,4-trioxane was converted to the 1,2,4-trioxane hydrochloride salt which was subsequently used to prepare piperidine dispiro-1,2,4-trioxane analogues which were assayed versus *Plasmodium falciparum* in vitro.

**Discovery of novel hydroxamates as highly potent tumor necrosis factor- $\alpha$  converting enzyme inhibitors.**

pp 5809–5814

**Part II: Optimization of the S3' pocket**

Robert D. Mazzola Jr.\*, Zhaoning Zhu, Lisa Sinning, Brian McKittrick, Brian Lavey, James Spitler, Joseph Kozlowski, Shih Neng-Yang, Guowei Zhou, Zhuyan Guo, Peter Orth, Vincent Madison, Jing Sun, Daniel Lundell, Xiaoda Niu

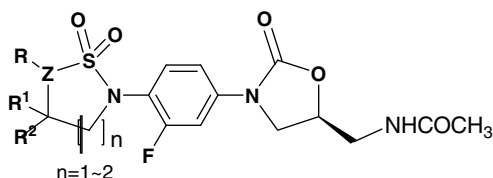


We herein disclose a novel series of cyclopropyl hydroxamates that are potent and selective TACE inhibitors with *K<sub>i</sub>* values in the picomolar range.

**Synthesis and antibacterial activities of novel oxazolidinones having cyclic sulfonamide moieties**

pp 5815–5818

Seoung Jong Kim, Myung-Ho Jung, Kyung Ho Yoo, Jung-Hyuck Cho, Chang-Hyun Oh\*

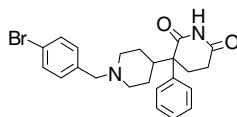


The synthesis of a new series of oxazolidinones having cyclic sulfonamide moieties is described. Their in vitro antibacterial activities against both Gram-positive and Gram-negative bacteria were tested and the effect of substituents on the oxazolidinone ring was investigated. A particular compound **15g** having [1,2,5]thiadiazolidin-1,1-dioxide moiety showed the most potent antibacterial activity.

**Synthesis and structure–activity relationship of benzetimide derivatives as human CXCR3 antagonists**

pp 5819–5823

Jean-Pierre Bongartz\*, Mieke Buntinx, Erwin Coesemans, Bart Hermans, Guy Van Lommen, Jean Van Wauwe




A novel class of CXCR3 antagonist is explored for its key contributing moieties toward its potency and selectivity regarding unwanted anti-cholinergic activity.

## OTHER CONTENTS

## Instructions to contributors

p I

\*Corresponding author

\* Supplementary data available via ScienceDirect

## COVER

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

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