

Bioorganic & Medicinal Chemistry Letters Vol. 18, No. 8, 2008

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Design and campaign synthesis of pyridine-based histone deacetylase inhibitors

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David M. Andrews,* Keith M. Gibson, Mark A. Graham, Zbigniew S. Matusiak, Craig A. Roberts, Elaine S. E. Stokes, Madeleine C. Brady and Christine M. Chresta

The synthesis of the HDAC inhibitor 13b is reported. (HDAC1 enzyme pIC₅₀ 8.01.)

Novel uracil-based 2-aminoanilide and 2-aminoanilide-like derivatives: Histone deacetylase inhibition and in-cell activities

pp 2530-2535

Antonello Mai,* Andrea Perrone, Angela Nebbioso, Dante Rotili, Sergio Valente, Maria Tardugno, Silvio Massa, Floriana De Bellis and Lucia Altucci*

(j)+

Tetrazole based amides as growth hormone secretagogues

pp 2536–2539

James J. Li,* Haixia Wang, Jun Li, Fucheng Qu, Stephen G. Swartz, Andrés S. Hernández, Scott A. Biller, Jeffrey A. Robl, Joseph A. Tino,* Dorothy Slusarchyk, Ramakrishna Seethala, Paul Sleph, Mujing Yan, Gary Grover, Neil Flynn, Brian J. Murphy and David Gordon

Compound **31** (EC₅₀ = 0.2 nM)

A novel series of N1 substituted tetrazole amides were prepared and showed to be potent growth hormone (GH) secretagogues. Among them, hydroxyl containing analog 31 displayed excellent in vivo activity by increasing plasma GH 10-fold in an anesthetized IV rat model.

Use of γ -aminopropyl-coated glass surface for the patterning of oligonucleotides through oxime bond formation

pp 2540-2543

Nabil Dendane, Antoine Hoang, Eric Defrancq,* Françoise Vinet and Pascal Dumy



The patterning of oligonucleotides on glass slides and into the inner wall of capillary tubes have been achieved by using oxime bond formation.

Synthesis and characterization of 5,6,7,8-tetrahydroquinoline C5a receptor antagonists

pp 2544-2548

J. Kent Barbay,* Yong Gong, Mieke Buntinx, Jian Li, Concha Claes, Pamela J. Hornby, Guy Van Lommen, Jean Van Wauwe and Wei He

Synthesis and structure-activity relationships of a series of substituted 5,6,7,8-tetrahydroquinoline C5a receptor antagonists are reported.

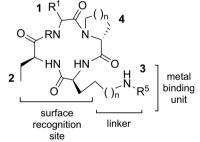
Synthesis and biological evaluation of histone deacetylase inhibitors that are based on FR235222:

pp 2549-2554

A cyclic tetrapeptide scaffold

Erinprit K. Singh, Suchitra Ravula, Chung-Mao Pan, Po-Shen Pan, Robert C. Vasko, Stephanie A. Lapera,

Sujith V. W. Weerasinghe, Mary Kay H. Pflum and Shelli R. McAlpine*



Cyclized FR235222 Derivative

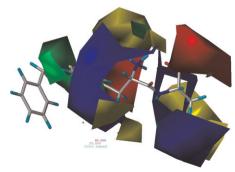


Design of high-affinity peptide conjugates with optimized fluorescence quantum yield as markers for small peptide transporter PEPT1 (SLC15A1)

Praveen M. Bahadduri, Abhijit Ray, Akash Khandelwal and Peter W. Swaan*

Based on our results of computational analysis, we have designed, synthesized, and performed in vitro activity assessment of novel Alexa Fluor-350-labeled dipeptides directed to identify novel substrates and inhibitors for human small peptide transporter PEPT1 in a high-throughput assay setting.

pp 2555–2557



Synthesis and antimicrobial activity of 7α -amino-23,24-bisnor-5 α -cholan-22-ol derivatives

pp 2558-2561

Sharaf Nawaz Khan, Young Mee Jung, Bong Jin Kim, Heeyeong Cho, Jinho Lee and Hong-Seok Kim*

A series of 7α -aminobisnorsteroids were synthesized and antimicrobial activity was assessed against Gram-positive and Gram-negative bacteria. 3α , 7α -Diaminobisnorsterol dihydrochloride 15 showed the highest antimicrobial activity against *Streptococcus pyogenes* 308A with a MIC value of 1.6 µg/mL. Among the tested compounds 13–20, compound 13 showed MHC at 100 µg/mL.



Design and synthesis of morpholine derivatives. SAR for dual serotonin & noradrenaline reuptake inhibition

pp 2562-2566

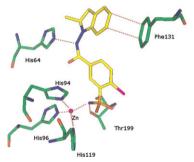
Paul V. Fish,* Christopher Deur, Xinmin Gan, Keri Greene, David Hoople, Malcolm Mackenny, Kimberly S. Para, Keith Reeves, Thomas Ryckmans, Cory Stiff, Alan Stobie, Florian Wakenhut and Gavin A. Whitlock

Morpholine derivatives 5, 8–23 are inhibitors of monoamine reuptake. Target compounds were prepared using a highly specific enzyme-catalysed resolution of racemic morpholine ester 26 as the key step. Structure–activity relationships established that serotonin and noradrenaline reuptake inhibition are functions of stereochemistry and aryl/aryloxy ring substitution.

Carbonic anhydrase inhibitors. Interaction of indapamide and related diuretics with 12 mammalian isozymes and X-ray crystallographic studies for the indapamide–isozyme II adduct

pp 2567-2573

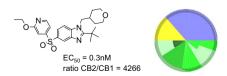
Claudia Temperini, Alessandro Cecchi, Andrea Scozzafava and Claudiu T. Supuran*



5-Sulfonyl-benzimidazoles as selective CB2 agonists

pp 2574–2579

Bie M. P. Verbist, Michel A. J. De Cleyn, Michel Surkyn, Erwin Fraiponts, Jeroen Aerssens, Marjoleen J. M. A. Nijsen and Harrie J. M. Gijsen*



Synthesis and exploration of the structure-activity relationship of a novel benzimidazole series as highly selective CB2 agonists are reported.



Design and campaign synthesis of piperidine- and thiazole-based histone deacetylase inhibitors

pp 2580-2584

David M. Andrews,* Elaine S. E. Stokes,* Greg R. Carr, Zbigniew S. Matusiak, Craig A. Roberts, Michael J. Waring, Madeleine C. Brady, Christine M. Chresta and Simon J. East

The synthesis of the HDAC inhibitor 16d is reported. (HDAC1 enzyme pIC₅₀ 7.46. A549a xenograft efficacy at 12.5 mg/kg.)

Synthesis and antimicrobial properties of Monensin A esters

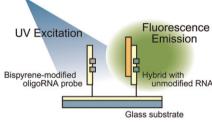
pp 2585-2589

Adam Huczyński, Joanna Stefańska, Piotr Przybylski, Bogumil Brzezinski* and Franz Bartl

Microarray-based label-free detection of RNA using bispyrene-modified 2'-O-methyl oligoribonucleotide as capture and detection probe

pp 2590-2593

Takashi Sakamoto, Akio Kobori and Akira Murakami*



We developed a novel oligonucleotide microarray for the detection of RNA without fluorescent labeling of target RNA. The technology may contribute to on-site gene diagnostics of various diseases.

Synthesis of new benzimidazole linked pyrrolo[2,1-c][1,4]benzodiazepine conjugates with efficient DNA-binding affinity and potent cytotoxicity

pp 2594-2598

Ahmed Kamal,* P. Praveen Kumar, K. Sreekanth, B. N. Seshadri and P. Ramulu

Benzimidazole linked pyrrolo[2,1-c][1,4]benzodiazepine conjugates were synthesized and displayed potential in vitro cytotoxicity against human cancer cell lines.

New chemotypes for cathepsin K inhibitors

pp 2599-2603

Naoki Teno,* Osamu Irie, Takahiro Miyake, Keigo Gohda, Miyuki Horiuchi, Sachiyo Tada, Kazuhiko Nonomura, Motohiko Kometani, Genji Iwasaki and Claudia Betschart

Cyano pyrimidine acetylene and cyano pyrimidine *t*-amine, which belong to a new chemical class, were prepared and tested for inhibitory activities against cathepsin K and the highly homologous cathepsins L and S. The use of novel chemotypes in the development of cathepsin K inhibitors has been demonstrated by derivatives of compounds 1 and 8.

Exploring predictive QSAR models for hepatocyte toxicity of phenols using QTMS descriptors Kunal Roy* and Paul L. A. Popelier*

pp 2604-2609



We construct predictive QSAR models for hepatocyte toxicity data of phenols using Quantum Topological Molecular Similarity (QTMS) descriptors along with hydrophobicity (log P) as predictor variables.



$\label{eq:def-def-def} \mbox{4'-Methyl-4,5'-bithiazole-based correctors of defective $\Delta F508$-CFTR cellular processing}$

pp 2610-2614

Choong Leol Yoo, Gui Jun Yu, Baoxue Yang, Lori I. Robins, A. S. Verkman and Mark J. Kurth*

Synthesis of 4'-modified noraristeromycins to clarify the effect of the 4'-hydroxyl groups for inhibitory activity against S-adenosyl-L-homocysteine hydrolase

pp 2615-2618

Takayuki Ando, Kenji Kojima, Praveen Chahota, Atsushi Kozaki, Nikalje D. Milind and Yukio Kitade*

$$\label{eq:R} \begin{split} \mathsf{R} &= \mathsf{OSO_3Na}, \, \mathsf{OSO_2NH_2}, \\ \mathsf{N_3}, \, \mathsf{NH_2}, \, \mathsf{OH} \end{split}$$

Hypoxia-inducible factor-1 and nuclear factor-kB inhibitory meroterpene analogues of bakuchiol, a constituent of the seeds of *Psoralea corylifolia*

pp 2619-2623

Cheng-Zhu Wu, Seong Su Hong, Xing Fu Cai, Nguyen Tien Dat, Ji-Xing Nan, Bang Yeon Hwang, Jung Joon Lee and Dongho Lee*

(i)+

Selective vasodilatation effect of sargahydroquinoic acid, an active constituent of *Sargassum micracanthum*, on the basilar arteries of rabbits

pp 2624-2627

Byong-Gon Park, Woon-Seob Shin, Yumi Um, Sungsik Cho, Gab-Man Park, Dong-Soo Yeon, Seong-Chun Kwon, Jungyeob Ham, Byoung Wook Choi and Seokjoon Lee*

 EC_{50} 11.8 μm on basilar artery: 140 μM on Cartoid Artery Selective Index (SI, EC_{50} for basilar): 11.9.

Synthesis of small molecule inhibitors of the orphan nuclear receptor steroidogenic factor-1 (NR5A1) based on isoquinolinone scaffolds

pp 2628–2632

Joshua Roth, Franck Madoux, Peter Hodder and William R. Roush*

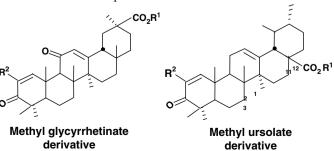
(i)+

Structure-dependent inhibition of bladder and pancreatic cancer cell growth by 2-substituted glycyrrhetinic and ursolic acid derivatives

pp 2633-2639

Gayathri Chadalapaka, Indira Jutooru, Alan McAlees, Tom Stefanac and Stephen Safe*

The 2-cyano and 2-trifluoromethyl substituted 1-en-3-one derivatives of methyl glycyrrhetinate and methyl ursolate are potent inhibitors of bladder and pancreatic cancer cell growth.



2-Arylbenzoxazoles as novel cholesteryl ester transfer protein inhibitors: **Optimization via array synthesis**

pp 2640-2644

Lalgudi S. Harikrishnan,* Muthoni G. Kamau, Timothy F. Herpin, George C. Morton, Yalei Liu, Christopher B. Cooper, Mark E. Salvati, Jennifer X. Qiao, Tammy C. Wang, Leonard P. Adam, David S. Taylor, Alice Ye A. Chen, Xiaohong Yin, Ramakrishna Seethala, Tara L. Peterson, David S. Nirschl, Arthur V. Miller, Carolyn A. Weigelt, Kingsley K. Appiah, Jonathan C. O'Connell and R. Michael Lawrence

NC NH Me Me

100

CETP SPA IC
$$_{50} = 0.010 \, \mu M$$

CETP WPA IC $_{50} = 0.91 \, \mu M$



Novel antibacterial azetidine lincosamides

pp 2645-2648

Hardwin O'Dowd,* Jason G. Lewis, Joaquim Trias, Rumi Asano, Johanne Blais, Sara L. Lopez, Craig K. Park, Charlotte Wu, Wen Wang and Mikhail F. Gordeev



The synthesis and evaluation of antibacterial azetidine lincosamides 1 are described.



N-D-Aldopentofuranosyl-N-[p-(isoamyloxy)phenyl]-thiourea derivatives: Potential anti-TB therapeutic agents

pp 2649-2651

Avraham Liav,* Shiva K. Angala, Patrick J. Brennan and Mary Jackson

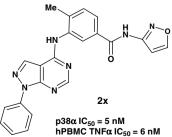
All four N-D-aldopentofuranosyl-N'-[p-(isoamyloxy)phenyl]-thiourea derivatives were synthesized and their MIC values against M.tb were determined.

Pyrazolo-pyrimidines: A novel heterocyclic scaffold for potent and selective p38α inhibitors

pp 2652-2657

Jagabandhu Das,* Robert V. Moquin, Sidney Pitt, Rosemary Zhang, Ding Ren Shen, Kim W. McIntyre, Kathleen Gillooly, Arthur M. Doweyko, John S. Sack, Hongjian Zhang, Susan E. Kiefer, Kevin Kish, Murray McKinnon, Joel C. Barrish, John H. Dodd, Gary L. Schieven and Katerina Leftheris

The synthesis and structure-activity relationships (SAR) of p38α MAP kinase inhibitors based on a pyrazolo-pyrimidine scaffold are described. These studies led to the identification of compound 2x as a potent and selective inhibitor of p38\alpha MAP kinase with excellent cellular potency toward the inhibition of TNFα production. Compound 2x was highly efficacious in vivo in inhibiting TNFα production in an acute murine model of TNF production. X-ray cocrystallography of a pyrazolo-pyrimidine analog 2b bound to unphosphorylated p38α is also disclosed.



Novel bisbenzimidazoles with antileishmanial effectiveness

pp 2658-2661

Annie Mayence, Aurélie Pietka, Margaret S. Collins, Melanie T. Cushion, Babu L. Tekwani, Tien L. Huang and Jean Jacques Vanden Eynde*

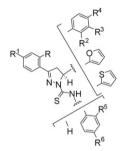
The synthesis and pharmacological profile of novel bisbenzimidazoles is reported.

Small molecules with structural similarities to siderophores as novel antimicrobials against *Mycobacterium tuberculosis* and *Yersinia pestis*

pp 2662–2668

Karen L. Stirrett, Julian A. Ferreras, Venkatesan Jayaprakash,* Barij N. Sinha, Tao Ren and Luis E. N. Quadri*

Synthesis and evaluation of compounds with structural similarities to *Mycobaterium* tuberculosis and *Yersinia pestis* siderophores as novel antimicrobials targeting the physiology of iron-scarcity adapted bacteria.





Carbonic anhydrase inhibitors: The X-ray crystal structure of ethoxzolamide complexed to human isoform II reveals the importance of thr200 and gln92 for obtaining tight-binding inhibitors

pp 2669-2674

Anna Di Fiore, Carlo Pedone, Jochen Antel, Harald Waldeck, Andreas Witte, Michael Wurl, Andrea Scozzafava, Claudiu T. Supuran* and Giuseppina De Simone*

An X-ray crystallographic study for the binding of ethoxzolamide to human carbonic anhydrase (CA) II provides useful insights for the design of novel CA inhibitors targeting different isozymes.



Alkyne-quinuclidine derivatives as potent and selective muscarinic antagonists for the treatment of COPD

pp 2675–2678

Jean-Philippe Starck, Laurent Provins,* Bernard Christophe, Michel Gillard, Sophie Jadot, Patrick Lo Brutto, Luc Quéré, Patrice Talaga and Michel Guyaux

$$R^3$$
 R^1
 R^2
 R^2

SAR around alkyne-quinuclidine derivatives allowed the discovery of highly potent muscarinic antagonists displaying interesting preferential slow off-rates from the M3 receptor.

$A \ novel \ bifunctional \ male imido \ CHX-A'' \ chelator \ for \ conjugation \ to \ thiol-containing \ biomolecules$

pp 2679-2683

Heng Xu, Kwamena E. Baidoo, Karen J. Wong and Martin W. Brechbiel*

Discovery of a novel indole series of EP₁ receptor antagonists by scaffold hopping

pp 2684-2690

Adrian Hall,* Andy Billinton, Susan H. Brown, Anita Chowdhury, Gerard M. P. Giblin, Paul Goldsmith, David N. Hurst, Alan Naylor, Sadhana Patel, Tiziana Scoccitti and Pamela J. Theobald

The discovery, synthesis, and biological activity of a novel series of indole EP1 receptor antagonists is described, such as compounds 10a and 12g. Compound 12g demonstrated in vivo efficacy in a preclinical model of inflammatory pain.

Scaffold oriented synthesis. Part 2: Design, synthesis and biological evaluation of pyrimido-diazepines as receptor tyrosine kinase inhibitors

pp 2691-2695

Vijaya Gracias, Zhiqin Ji, Irini Akritopoulou-Zanze,* Cele Abad-Zapatero, Jeffrey R. Huth, Danying Song, Philip J. Hajduk, Eric F. Johnson, Keith B. Glaser, Patrick A. Marcotte, Lori Pease, Nirupama B. Soni, Kent D. Stewart, Steven K. Davidsen, Michael R. Michaelides and Stevan W. Djuric

We report the discovery of the pyrimido-diazepine scaffolds as novel adenine mimics. Structure-based design led to the discovery of analogs with potent inhibitory activity against receptor tyrosine kinases, such as KDR, Flt3, and c-Kit. Compound 14 exhibited low nanomolar KDR enzymatic and cellular potencies ($IC_{50} = 9$ and 52 nM, respectively).

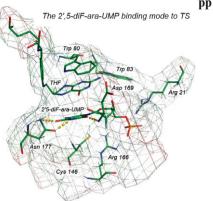
Identification of prostaglandin D₂ receptor antagonists based on a tetrahydropyridoindole scaffold

pp 2696-2700

Christian Beaulieu,* Daniel Guay, Zhaoyin Wang, Yves Leblanc, Patrick Roy, Claude Dufresne, Robert Zamboni, Carl Berthelette, Stephen Day, Nancy Tsou, Danielle Denis, Gillian Greig, Marie-Claude Mathieu and Gary O'Neill

A molecular modeling study of the interaction of 2'-fluoro-substituted analogues of dUMP/FdUMP with thymidylate synthase

Adam Jarmuła,* Anna Dowierciał and Wojciech Rode



pp 2701-2708

pp 2709-2713

Development of 2-tbutyl-N-methyl pyrimidones as potent inhibitors of HIV integrase

M. Emilia Di Francesco,* Paola Pace, Fabrizio Fiore, Francesca Naimo, Fabio Bonelli, Michael Rowley and Vincenzo Summa

HIV Spread CIC₉₅ (50% HHS) = 10 nM

Pyrano-[2,3b]-pyridines as potassium channel antagonists

Heather J. Finlay,* John Lloyd, Michael Nyman, Mary Lee Conder, Tonya West, Paul Levesque and Karnail Atwal

O HN OH 28

The design and synthesis of a series of highly functionalized pyrano-[2,3b]-pyridines is described. These compounds were assayed for their ability to block the I_{Kur} channel encoded by the gene hKV1.5 in patch-clamped L-929 cells. Six of the compounds in this series showed sub-micromolar activity, the most potent being 28 with an IC_{50} of 378 nM.

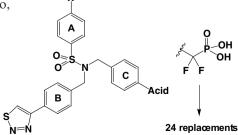
PTP1B inhibitors: Synthesis and evaluation of difluoro-methylenephosphonate bioisosteres on a sulfonamide scaffold

Christopher P. Holmes,* Xianfeng Li, Yijun Pan, Caiding Xu, Ashok Bhandari, Claire M. Moody, Joy A. Miguel, Steven W. Ferla, M. Nuria De Francisco, Brian T. Frederick, Sigun Zhou, Natalie Macher, Larry Jang,

Jennifer D. Irvine and J. Russell Grove

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pp 2714-2718



Synthesis and characterization of 1,3-dihydro-benzo|b||1,4|diazepin-2-one derivatives: Part 3. New potent non-competitive metabotropic glutamate receptor 2/3 antagonists

pp 2725-2729

Thomas J. Woltering,* Jürgen Wichmann, Erwin Goetschi, Geo Adam, James N. C. Kew, Frédéric Knoflach, Theresa M. Ballard, Jörg Huwyler, Vincent Mutel and Silvia Gatti

In a series of 1,3-dihydro-benzo[b][1,4]diazepin-2-ones the replacement of a (2-aryl)ethynyl-moiety by smaller substitutents produced highly potent non-competitive group II mGluR antagonists. After oral administration of, for example, 7p in vivo activity by reversal of the LY354740-induced hypolocomotion in mice could be demonstrated.

7p
$$IC_{50} = 16 \text{ nM}$$
 $ED_{50} = 3.3 \text{ mg/kg p.o.}$

N-Pyridin-3-yl- and N-quinolin-3-yl-benzamides: Modulators of Human Vanilloid Receptor 1 (TRPV1)

pp 2730-2734

Michele C. Jetter,* James J. McNally, Mark A. Youngman, Mark E. McDonnell, Adrienne E. Dubin, Nadia Nasser, Sui-Po Zhang, Ellen E. Codd, Ray W. Colburn, Dennis R. Stone, Michael R. Brandt, Christopher M. Flores and Scott L. Dax

$$\begin{array}{c} H \\ N \\ O \end{array}$$

The synthesis and biological activity of a series of 3-quinolinyl p-aminobenzamide TRPV1 antagonists are reported.

Des-A-ring benzothiadiazines: Inhibitors of HCV genotype 1 NS5B RNA-dependent RNA polymerase

pp 2735-2738

Pamela L. Donner,* Qinghua Xie, John K. Pratt, Clarence J. Maring, Warren Kati, Wen Jiang, Yaya Liu, Gennadiy Koev, Sherie Masse, Debra Montgomery, Akhter Molla and Dale J. Kempf

Described herein is a set of non-nucleoside, small molecule inhibitors of genotype 1 HCV polymerase based on a benzothiadiazine screening hit. After demonstrating that a methylsulfonylamino D-ring substituent increased the enzyme potency into the low nanomolar range, a minimum core required for activity was explored. We observed that small aromatic rings and alkenyl groups appended to the 5-position of the B-ring were optimal, resulting in inhibitors with low nanomolar potencies.

Synthesis and SAR of new pyrrolo[2,1-f][1,2,4]triazines as potent p38α MAP kinase inhibitors

pp 2739-2744

Stephen T. Wrobleski,* Shugun Lin, John Hynes, Jr., Hong Wu, Sidney Pitt, Ding Ren Shen, Rosemary Zhang, Kathleen M. Gillooly, David J. Shuster, Kim W. McIntyre, Arthur M. Doweyko, Kevin F. Kish, Jeffrey A. Tredup, Gerald J. Duke, John S. Sack, Murray McKinnon, John Dodd, Joel C. Barrish, Gary L. Schieven and Katerina Leftheris

Synthesis of a novel series of substituted pyrrolo[2,1-f][1,2,4]triazines have resulted in the identification of subnanomolar inhibitors of the p38a MAP kinase. Subsequent X-ray cocrystallographic studies with compound 30 have revealed the binding mode of this class of inhibitors within the $p38\alpha$ active site.

Synthesis, antiviral activity, and conformational studies of a P3 aza-peptide analog of a potent macrocyclic tripeptide HCV protease inhibitor

pp 2745-2750

John T. Randolph,* Xiaolin Zhang, Peggy P. Huang, Larry L. Klein, Kevin A. Kurtz, Alex K. Konstantinidis, Wenping He, Warren M. Kati and Dale J. Kempf

P3 Aza analog of a potent macrocyclic tripeptide inhibitor of HCV protease was over 2 orders of magnitude less active in both enzyme (NS3-4A) inhibition and sub-genomic replicon assays.

OTHER CONTENTS

Summary of instructions to authors

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*Corresponding author

(1) 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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ISSN 0960-894X