

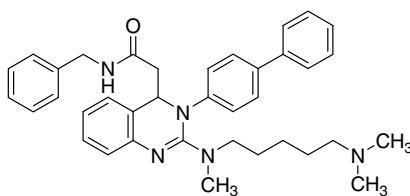
Contents

ARTICLES

Discovery of potent T-type calcium channel blocker

pp 5740–5743

Han Na Seo, Ja Youn Choi, Yun Jeong Choe, Yoonjee Kim, Hyewhon Rhim,
So Ha Lee, Jungahn Kim, Dong Jun Joo and Jae Yeol Lee*



KYS05090 ($IC_{50} = 41 \pm 1$ nM, $SI = 119.5$ for T/N-channel)

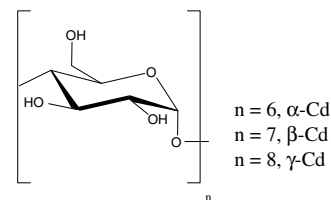
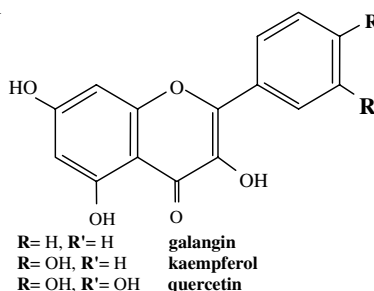


Studies on the interactions between some flavonols and cyclodextrins

pp 5744–5748

Maria Camilla Bergonzi,* Anna Rita Bilia, Lorenzo Di Bari,
Giovanni Mazzi and Franco Francesco Vincieri

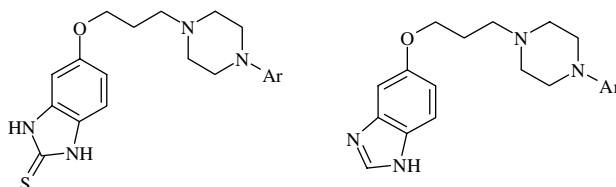
The interactions of some natural flavonols with α , β - and γ -Cds have been investigated. The complexes were characterized using different physico-chemical methods based on differential scanning calorimetry (DSC), infrared spectroscopy (IR) and NMR spectroscopy. Moreover, the water-solubility of the flavonols in the presence of Cds was also evaluated.



Two new phenylpiperazines with atypical antipsychotic potential

pp 5749–5753

Mirko Tomić,* Djurdjica Ignjatović, Gordana Tovilović, Deana Andrić,
Goran Roglić and Sladjana Kostić-Rajačić

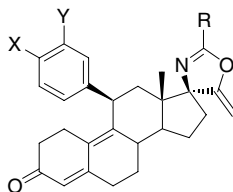


Eight new arylpiperazines were synthesized and evaluated in vitro, and the two most active phenylpiperazines were tested in vivo for atypical antipsychotic potential.

Synthesis and identification of novel 11 β -aryl-4',5'-dihydrospiro[estra-4,9-diene-17 β ,4'-oxazole] analogs with dissociated antiprogesterone activities

pp 5754–5757

Chunyang Jin,* G. Manikumar, John A. Kepler,* C. Edgar Cook, George F. Allan, Margaret Kiddoe, Sheela Bhattacharjee, Olivia Linton, Scott G. Lundeen and Zhihua Sui



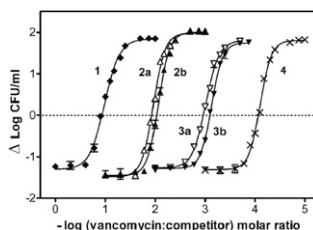
A series of novel 11 β -aryl-4',5'-dihydrospiro[estra-4,9-diene-17 β ,4'-oxazole] analogs have been synthesized and evaluated for their antiprogesterone and antigluocorticoid activities.

Design and evaluation of analogues of the bacterial cell-wall peptidoglycan motif L-Lys-D-Ala-D-Ala for use in a vancomycin biosensor

pp 5758–5762

Olivier Hernout, Karine Berthoin, Isabelle Delattre, Paul M. Tulkens, Stéphane Carryn and Jacqueline Marchand-Brynaert*

Use of an original microbiological approach to assess competition of synthetic compounds with the natural target of vancomycin in bacteria.



1: *N*- α -Ac-L-Lys-D-Ala-D-Ala tripeptide

2a: *N*-Boc-6-aminocaproyl-D-Ala-D-Ala

2b: *N*-Acetyl-6-aminocaproyl-D-Ala-D-Ala

3a: *N*-Boc-6-aminocaproyl-D-Ala-D-Ser

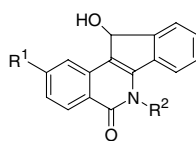
3b: *N*-Acetyl-6-aminocaproyl-D-Ala-D-Ser

4: D-Ala-D-Ala


Convenient synthesis of indeno[1,2-*c*]isoquinolines as constrained forms of 3-arylisquinolines and docking study of a topoisomerase I inhibitor into DNA–topoisomerase I complex

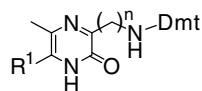
pp 5763–5767

Hue Thi My Van, Quynh Manh Le, Kwang Youl Lee, Eung-Seok Lee, Youngjoo Kwon, Tae Sung Kim, Thanh Nguyen Le, Suh-Hee Lee and Won-Jea Cho*


Design and synthesis of opioidmimetics containing 2',6'-dimethyl-L-tyrosine and a pyrazinone-ring platform

pp 5768–5771

Kimitaka Shiotani, Tingyou Li, Anna Miyazaki, Yuko Tsuda, Toshio Yokoi, Akihiro Ambo, Yusuke Sasaki, Sharon D. Bryant, Lawrence H. Lazarus and Yoshio Okada*



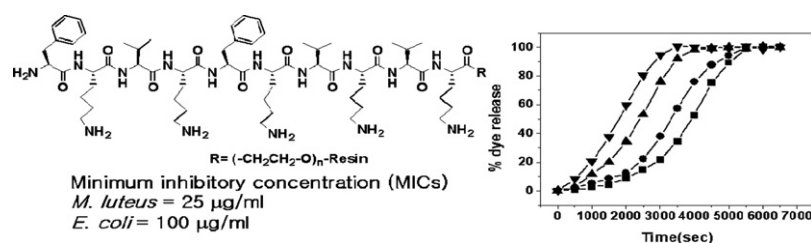
11 $n = 4$, $R^1 = \beta$ -phenethyl

3-[4'-*H*-Dmt-NH-(CH₂)₄]-6- β -phenethyl-5-methyl-2(1*H*)-pyrazinone **11** bound to μ -opioid receptors, $K_i\mu = 0.13$ nM and $K_i\delta/K_i\mu = 447$, and exhibited μ -agonism (GPI IC₅₀ = 15.9 nM) and δ -antagonism (MVD, $pA_2 = 6.35$).

Design and synthesis of novel antibacterial peptide-resin conjugates

pp 5772–5776

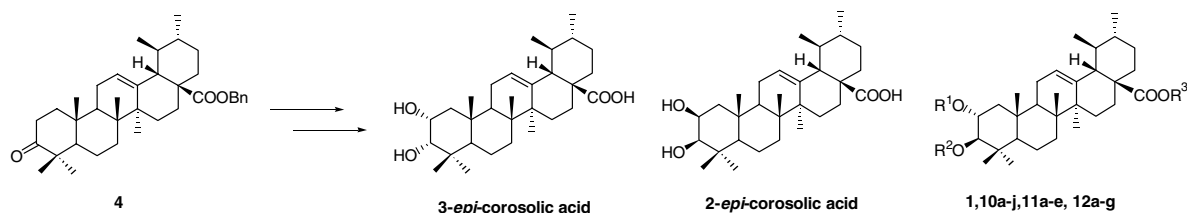
Won-Mi Cho, Bishnu Prasad Joshi, Hyeongjin Cho and Keun-Hyeung Lee*



Pentacyclic triterpenes. Part 5: Synthesis and SAR study of corosolic acid derivatives as inhibitors of glycogen phosphorylases

pp 5777–5782

Xiaolan Wen, Jun Xia, Keguang Cheng, Liying Zhang, Pu Zhang, Jun Liu,
Luyong Zhang, Peizhou Ni and Hongbin Sun*

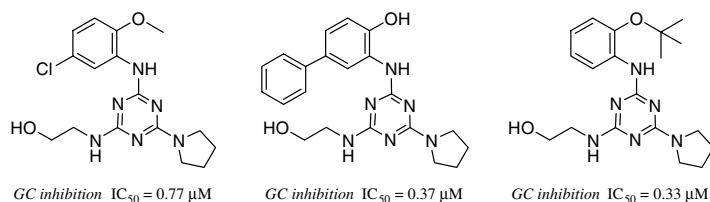


The synthesis and biological evaluation of corosolic acid derivatives as inhibitors of glycogen phosphorylases is described.

***N*⁴-Phenyl modifications of *N*²-(2-hydroxy)ethyl-6-(pyrrolidin-1-yl)-1,3,5-triazine-2,4-diamines enhance glucocerebrosidase inhibition by small molecules with potential as chemical chaperones for Gaucher disease**

pp 5783–5789

Wenwei Huang, Wei Zheng, Daniel J. Urban, James Inglese, Ellen Sidransky,*
Christopher P. Austin and Craig J. Thomas*

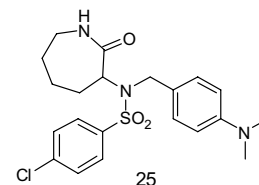


Amino-caprolactam derivatives as γ -secretase inhibitors

pp 5790–5795

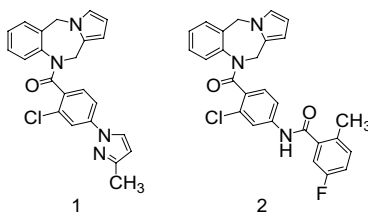
Michael F. Parker,* Joanne J. Bronson, Donna M. Barten, Jason A. Corsa, Wengsheng Du, Kevin M. Felsenstein, Valerie L. Guss, Darcy Izzarelli, Alice Loo, Kate E. McElhone, Larry R. Marcin, Ramesh Padmanabha, Roger Pak, Craig T. Polson, Jeremy H. Toyn, Sam Varma, Jian Wang, Victoria Wong, Ming Zheng and Susan B. Roberts

A series of amino-caprolactam sulfonamides were developed from a screening hit. Compounds with good in vitro and in vivo γ -secretase activity are reported.



Identification and synthesis of major metabolites of Vasopressin V₂-receptor agonist WAY-151932, and antagonist, Lixivaptan® pp 5796–5800

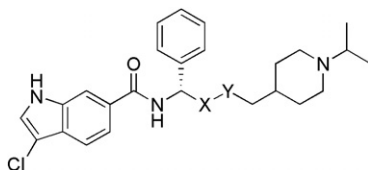
Albert J. Molinari,* Eugene J. Trybulski, Jehan Bagli, Susan Croce, John Considine, Jian Qi, Kadum Ali, William DeMaio, Lynne Lihotz and David Cochran



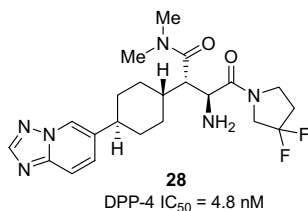
The synthesis and biological results for metabolites of the above vasopressin agonist **1** and antagonist **2** are presented.

D-Phenylglycinol-derived non-covalent factor Xa inhibitors: Effect of non-peptidic S4 linkage elements on affinity and anticoagulant activity pp 5801–5805

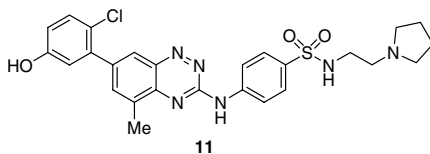
Valentine J. Klimkowski, Brian M. Watson, Michael R. Wiley, John Liebeschuetz, Jeffry B. Franciskovich, Jothirajah Marimuthu, Jolie A. Bastian, Daniel J. Sall, Jeffrey K. Smallwood, Nikolay Y. Chirgadze, Gerald F. Smith, Ronald S. Foster, Trelia Craft, Philip Sipes, Marcia Chastain and Scott M. Sheehan*

**4-Arylcyclohexylalanine analogs as potent, selective, and orally active inhibitors of dipeptidyl peptidase IV** pp 5806–5811

David E. Kaelin,* Abigail L. Smenton, George J. Eiermann, Huaibing He, Barbara Leiting, Kathryn A. Lyons, Reshma A. Patel, Sangita B. Patel, Alexandr Petrov, Giovanna Scapin, Joseph K. Wu, Nancy A. Thornberry, Ann E. Weber and Joseph L. Duffy

**The design and preliminary structure–activity relationship studies of benzotriazines as potent inhibitors of Abl and Abl-T315I enzymes** pp 5812–5818

Jianguo Cao, Richard Fine, Colleen Gritzen, John Hood, Xinshan Kang, Boris Klebansky, Dan Lohse, Chi Ching Mak, Andrew McPherson, Glenn Noronha,* Moorthy S. S. Palanki, Ved P. Pathak, Joel Renick, Richard Soll, Binqi Zeng and Hong Zhu

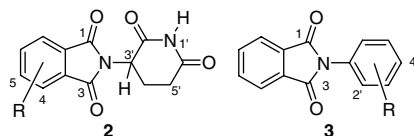


We describe the design, synthesis and structure–activity relationship studies in optimizing a series of benzotriazine compounds as potent inhibitors of both Abl and Abl-T315I enzymes.

Synthesis and TNF expression inhibitory properties of new thalidomide analogues derived via Heck cross coupling

pp 5819–5824

Scott G. Stewart,* Daniel Spagnolo, Marta E. Polomska, Melvin Sin, Mahdad Karimi and Lawrence J. Abraham

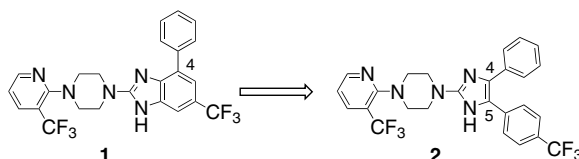


A series of novel thalidomide and *N*-phenylphthalimides were synthesised from their halide precursors using a Heck cross coupling reaction. This library of compounds was assessed for their ability to alter TNF production through measuring inhibition of TNF transcriptional activity.

Structure–activity relationship (SAR) investigations of substituted imidazole analogs as TRPV1 antagonists

pp 5825–5830

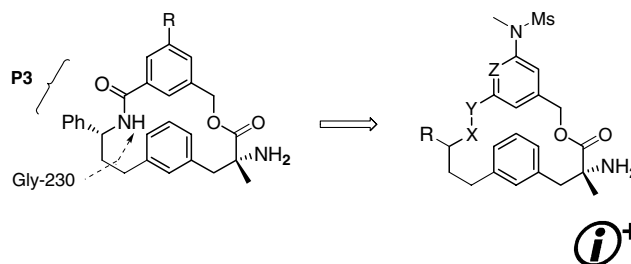
Vijay K. Gore,* Vu V. Ma, Rami Tamir, Narendra R. Gavva, James J. S. Treanor and Mark H. Norman

**Strategies toward improving the brain penetration of macrocyclic tertiary carbinamine BACE-1 inhibitors**

pp 5831–5835

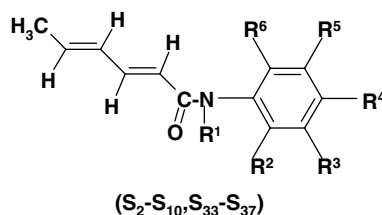
Keith P. Moore,* Hong Zhu, Hemaka A. Rajapakse, Georgia B. McGaughey, Dennis Colussi, Eric A. Price, Sethu Sankaranarayanan, Adam J. Simon, Nicole T. Pudvah, Jerome H. Hochman, Timothy Allison, Sanjeev K. Munshi, Samuel L. Graham, Joseph P. Vacca and Philippe G. Nantermet

This letter describes replacements for the P3 amide moiety present in previously reported tertiary carbinamine macrolactones. Although P-gp efflux issues associated with these amide-macrolactones were solved and brain penetration was measured in one case, potency was compromised in the process.

**Quantitative structure–activity relationship studies for prediction of antimicrobial activity of synthesized 2,4-hexadienoic acid derivatives**

pp 5836–5845

Balasubramanian Narasimhan,* Vikramjeet Judge, Rakesh Narang, Ruchita Ohlan and Sucheta Ohlan



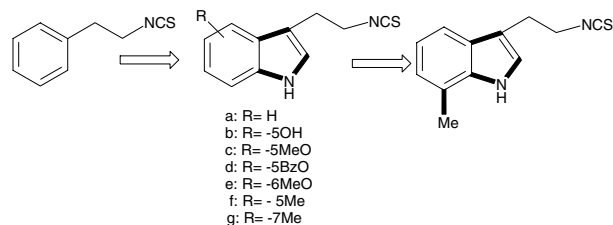
QSAR study of synthesized 2,4-hexadienoic acid derivatives as antimicrobial agents indicated the importance of the topological parameters especially the molecular connectivity indices ($^0\chi^v$, $^2\chi^v$, $^2\chi$) in contribution to antimicrobial activity.

Effect of indole ethyl isothiocyanates on proliferation, apoptosis, and MAPK signaling in neuroblastoma cell lines

pp 5846–5852

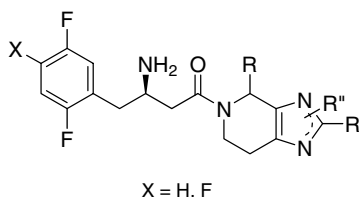
Rakesh K. Singh, Thilo S. Lange, Kyukwang Kim, Yongping Zou, Casey Lieb, Giselle L. Sholler and Laurent Brard*

Several indole ethyl isothiocyanate (**IEITC**) analogs were designed, synthesized, and screened in viability assays against neuroblastoma (**NB**) cells in vitro. The cytotoxicity of **IEITC** with non-polar groups such as –Me and –Benzoyloxy (BzO) was significantly higher than that of synthesized **IEITC** with polar groups such as –OH and –OMe. Substitution at the 5- and 7-position (**2d** and **2g**) resulted in an additional improvement. **7Me-IEITC (2g)** inhibited **NB** viability and proliferation along with caspase activation, inactivation of survival marker Akt, and activation of pro-apoptotic MAPKs.


Imidazopiperidine amides as dipeptidyl peptidase IV inhibitors for the treatment of diabetes

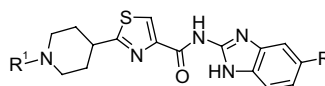
pp 5853–5857

Ping Chen,* Charles G. Caldwell, Robert J. Mathvink, Barbara Leiting, Frank Marsilio, Reshma A. Patel, Joseph K. Wu, Huaibing He, Kathryn A. Lyons, Nancy A. Thornberry and Ann E. Weber


A novel class of potent NF-κB signaling inhibitors

pp 5858–5862

Johann Leban,* Marcel Baierl, Jan Mies, Viola Trentinaglia, Sandra Rath, Kerstin Kronthaler, Kristina Wolf, Astrid Gotschlich and Markus H. J. Seifert

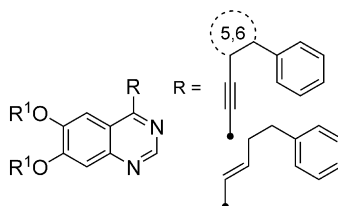


A novel class of NF-κB pathway signaling inhibitors was discovered by virtual screening, medicinal chemistry, and QSAR analysis. An initial set of compounds inhibited NF-κB signaling in a whole cell reporter gene assay in the micro-molar range. Activity was improved step by step by medicinal chemistry to yield nano-molar signaling inhibitors.

Synthesis and inhibitory activity of 4-alkynyl and 4-alkenylquinazolines: Identification of new scaffolds for potent EGFR tyrosine kinase inhibitors

pp 5863–5867

Yasunori Kitano,* Tsuyoshi Suzuki, Eiji Kawahara and Takahisa Yamazaki

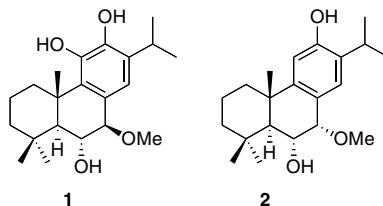


Novel chemotypes for EGFR TK inhibitors with IC₅₀ values in the nM range were reported.

Taxodistines A and B, abietane-type diterpenes from *Taxodium distichum*

pp 5868–5871

Yusuke Hirasawa, Emi Izawa, Yosuke Matsuno, Nobuo Kawahara, Yukihiro Goda and Hiroshi Morita*

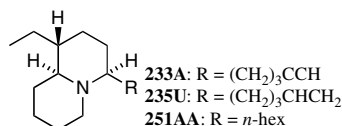


Two new abietane-type diterpenes, taxodistines A (**1**) and B (**2**), have been isolated by the guidance of inhibitory effect of tubulin polymerization from the fruits of *Taxodium distichum* and the structures were elucidated by using 2D NMR data. Taxodistine B (**2**) showed inhibition of tubulin polymerization.

Synthesis of poison-frog alkaloids 233A, 235U, and 251AA and their inhibitory effects on neuronal nicotinic acetylcholine receptors

pp 5872–5875

Naoki Toyooka,* Soushi Kobayashi, Dejun Zhou, Hiroshi Tsuneki, Tsutomu Wada, Hideki Sakai, Hideo Nemoto, Toshiyasu Sasaoka, H. Martin Garraffo, Thomas F. Spande and John W. Daly

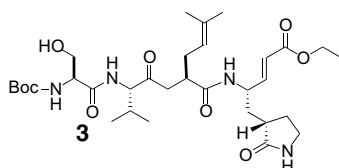


The synthesis and inhibitory effects on neuronal nicotinic acetylcholine receptors of the poison-frog alkaloids **233A**, **235U**, and **251AA** are described.

Structure-based design, synthesis, and biological evaluation of peptidomimetic SARS-CoV 3CLpro inhibitors

pp 5876–5880

Arun K. Ghosh,* Kai Xi, Valerie Grum-Tokars, Xiaoming Xu, Kiira Ratia, Wentao Fu, Katherine V. Houser, Susan C. Baker, Michael E. Johnson and Andrew D. Mesecar

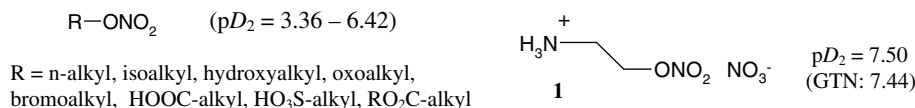


Structure-based design, synthesis, and biological evaluation of a series of peptidomimetic SARS-CoV 3CLpro inhibitors are described. Inhibitor **3**-bound SAR-3CLpro X-ray crystal structure provided molecular insight into the ligand-binding site interactions.

NO donors. Part 16: Investigations on structure–activity relationships of organic mononitrates reveal 2-nitrooxyethylammoniumnitrate as a high potent vasodilator

pp 5881–5885

Andreas Koenig, Carolin Roegler, Kathrin Lange, Andreas Daiber, Erika Glusa and Jochen Lehmann*

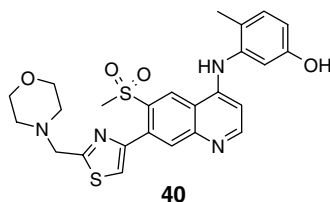


The vasoactive properties of 14 organic mononitrates were investigated in vitro using $PGF_{2\alpha}$ -precontracted porcine pulmonary arteries. Activities showed to be highly sensitive to the structure and substituents. Compound **1** was found to be slightly superior to the high potency trinitrate GTN.

The discovery of substituted 4-(3-hydroxyanilino)-quinolines as potent RET kinase inhibitors

pp 5886–5893

R. Graham Robinett, Alex J. Freemerman, Michael A. Skinner, Lisa Shewchuk and Karen Lackey*

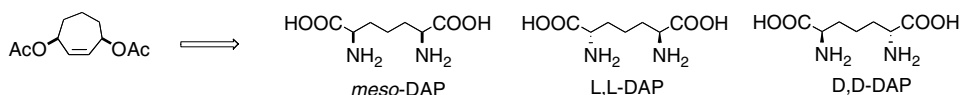


Substituted 4-(3-hydroxyanilino)-quinoline compounds, initially identified as small-molecule inhibitors of src family kinases, have been evaluated as potential inhibitors of RET kinase. Three compounds, **38**, **31**, and **40**, had K_i values of 3, 25, and 50 nM in an in vitro kinase assay; while a cell based kinase assay showed K_i values of 300, 100, and 45 nM, respectively. These compounds represent potential new leads for the treatment of medullary and papillary thyroid cancer.

**A straightforward stereoselective synthesis of *meso*-, (*S,S*)- and (*R,R*)-2,6-diaminopimelic acids from *cis*-1,4-diacetoxycyclohept-2-ene**

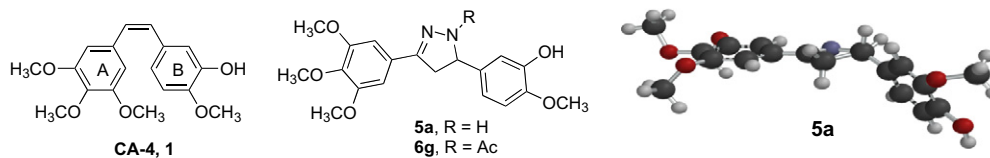
pp 5894–5896

Yukako Saito, Takumi Shinkai, Yuichi Yoshimura and Hiroki Takahata*

**Design, synthesis, and biological testing of pyrazoline derivatives of combretastatin-A4**

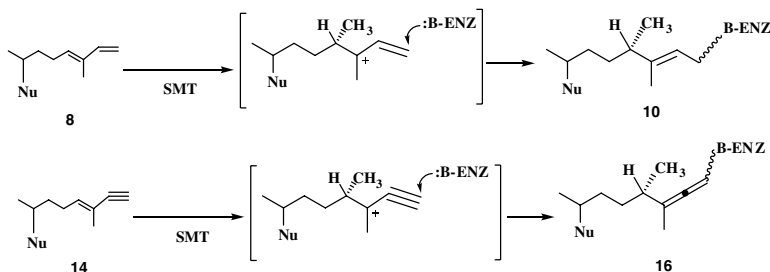
pp 5897–5901

Marlie Johnson, Brent Younglove, Lauren Lee, Regan LeBlanc, Herman Holt, Jr., Patrice Hills, Hilary Mackay, Toni Brown, Susan L. Mooberry and Moses Lee*

**Inactivation of soybean sterol 24-C-methyltransferase by elongated sterol side chains at C26**

pp 5902–5906

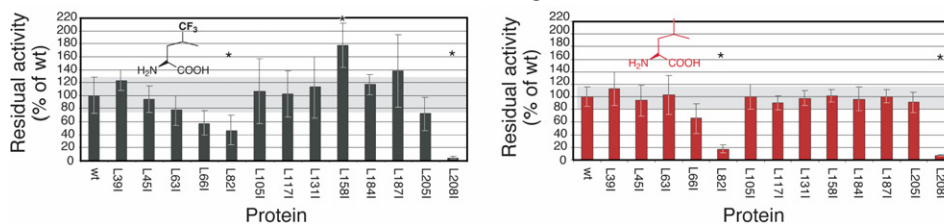
Zhihong Song and W. David Nes*



Fluorinated chloramphenicol acetyltransferase thermostability and activity profile: Improved thermostability by a single-isoleucine mutant

pp 5907–5911

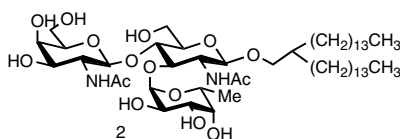
Natalya Voloshchuk, Man Xia Lee, Wan Wen Zhu, Ismet Caglar Tanrikulu and Jin Kim Montclare*



A lysate-based thermostability and activity profile is described for chloramphenicol acetyltransferase (CAT) expressed in trifluoroleucine, T (CAT T). CAT and 13 single-isoleucine CAT mutants were expressed in medium supplemented with T and assayed for thermostability.

**Synthesis and biological activities of glycosphingolipid analogues from marine sponge *Aplysinella rhax*** pp 5912–5915

Noriyasu Hada,* Taishi Nakashima, Suraj Prakash Shrestha, Ryo Masui, Yuji Narukawa, Kayoko Tani and Tadahiro Takeda

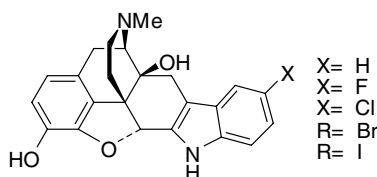


A novel glycosphingolipid analogue β -D-GalNAc(1-4)[α -D-Fucp(1-3)]- β -D-GlcNAc(1-R) (**2**) and some non-natural type trisaccharide analogues were synthesized, and their ability to inhibit the nitric oxide release was also examined.

5'-Halogenated analogs of oxymorphindole

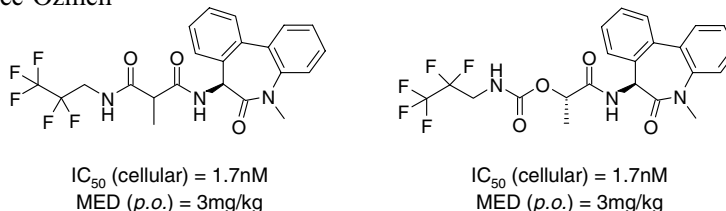
pp 5916–5917

Matthew D. Metcalf and Andrew Coop*

**Novel orally active, dibenzazepinone-based γ -secretase inhibitors**

pp 5918–5923

Jens-Uwe Peters,* Guido Galley,* Helmut Jacobsen, Christian Czech, Pascale David-Pierson, Eric A. Kitas and Laurence Ozmen

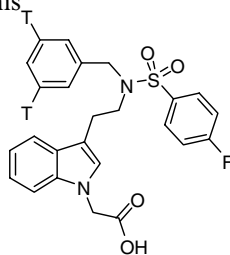


Malonamide analogues of LY411575 were found to be potent inhibitors of γ -secretase in vitro. The introduction of a pentafluoropropyl side chain improved the metabolic stability, and led to malonamide and carbamate analogues with in-vivo activity in models of Alzheimer's disease.

Synthesis and in vitro evaluation of a selective antagonist and the corresponding radioligand for the prostaglandin D₂ receptor CRTH2

pp 5924–5927

Trond Ulven,* Michael J. Gallen, Mads C. Nielsen, Nicole Merten, Carola Schmidt, Klaus Mohr, Christian Tränkle and Evi Kostenis



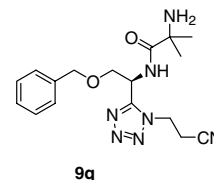
The first selective CRTH2 antagonist radioligand exhibits a pK_d of 9.0 and a specific radioactivity of 52 Ci/mmol.

Discovery, synthesis, and structure–activity studies of tetrazole based growth hormone secretagogues

pp 5928–5933

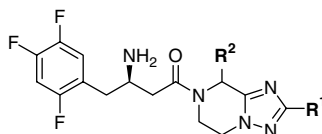
Andrés S. Hernández,* Peter T. W. Cheng, Christa M. Musial, Stephen G. Swartz, Rocco J. George, Gary Grover, Dorothy Slusarchyk, R. Krishna Seethala, Mark Smith, Kenneth Dickinson, Leah Giupponi, Daniel A. Longhi, Neil Flynn, Brian J. Murphy, David A. Gordon, Scott A. Biller, Jeffrey A. Robl and Joseph A. Tino*

A novel class of Growth Hormone Secretagogues (GHS), based on a tetrazole template, has been discovered. In vitro SAR and in vivo potency within this new class of GHS are described. The tetrazole **9q** exhibits good oral bioavailability in rats and dogs as well as efficacy following an oral 10 mg/kg dose in dogs. Solution and solid phase protocols for the synthesis of tetrazole based GHS have been developed.


Design, synthesis, and biological evaluation of triazolopiperazine-based β -amino amides as potent, orally active dipeptidyl peptidase IV (DPP-4) inhibitors

pp 5934–5939

Jennifer E. Kowalchick,* Barbara Leiting, KellyAnn D. Pryor, Frank Marsilio, Joseph K. Wu, Huaibing He, Kathryn A. Lyons, George J. Eiermann, Aleksandr Petrov, Giovanna Scapin, Reshma A. Patel, Nancy A. Thornberry, Ann E. Weber and Dooeop Kim

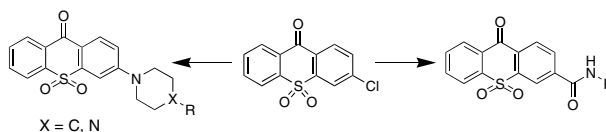


Various β -amino amides containing triazolopiperazine heterocycles have been prepared and evaluated as dipeptidyl peptidase IV (DPP-4) inhibitors. The in vitro profile of these compounds is described, and in vivo efficacy and pharmacokinetics are also presented.

Synthesis and screening of 3-substituted thioxanthen-9-one-10,10-dioxides

pp 5940–5943

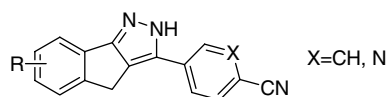
Pedro M. J. Lory, Maria E. Estrella-Jimenez, Matthew J. Shashack, Ganesh L. Lokesh, Amarnath Natarajan and Scott R. Gilbertson*



Discovery of 4'-(1,4-dihydro-indeno[1,2-c]pyrazol-3-yl)-benzonitriles and 4'-(1,4-dihydro-indeno[1,2-c]pyrazol-3-yl)-pyridine-2'-carbonitriles as potent checkpoint kinase 1 (Chk1) inhibitors

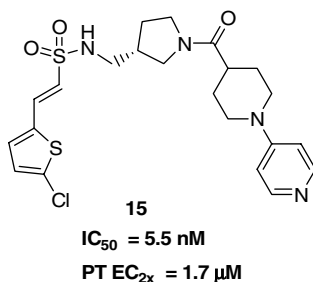
pp 5944–5951

Zhi-Fu Tao,* Gaoquan Li, Yunsong Tong, Kent D. Stewart, Zehan Chen, Mai-Ha Bui, Philip Merta, Chang Park, Peter Kovar, Haiying Zhang, Hing L. Sham, Saul H. Rosenberg, Thomas J. Sowin and Nan-Horng Lin

**Amino(methyl) pyrrolidines as novel scaffolds for factor Xa inhibitors**

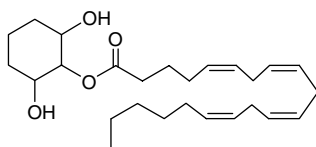
pp 5952–5958

Yan Shi,* Doree Sitkoff, Jing Zhang, Wei Han, Zilun Hu, Philip D. Stein, Ying Wang, Lawrence J. Kennedy, Stephen P. O'Connor, Saleem Ahmad, Eddie C.-K. Liu, Steve M. Seiler, Patrick Y. S. Lam, Jeffrey A. Robl, John E. Macor, Karnail S. Atwal and Robert Zahler

**Conformationally constrained analogues of 2-arachidonoylglycerol**

pp 5959–5963

Subramanian K. Vadivel, Sundararaman Vardarajan, Richard I. Duclos, Jr., JodiAnne T. Wood, Jianxin Guo and Alexandros Makriyannis*

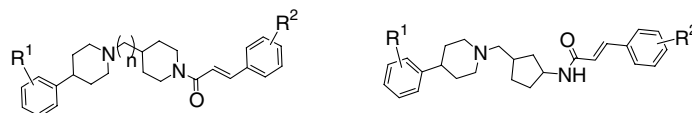


All isomeric 2-arachidonoyl esters of cyclohexane-1,2,3-triol were synthesized, tested as ligands for CB1 and CB2 receptors, and evaluated as substrates for both monoacylglycerol lipase (MGL) and fatty acid amide hydrolase (FAAH).

Synthesis and biological evaluation of phenyl piperidine derivatives as CCR2 antagonists

pp 5964–5968

Mingde Xia,* Cuifen Hou, Scott Pollack, James Brackley, Duane DeMong, Meng Pan, Monica Singer, Michele Matheis, Gil Olini, Druie Cavender and Michael Wachter



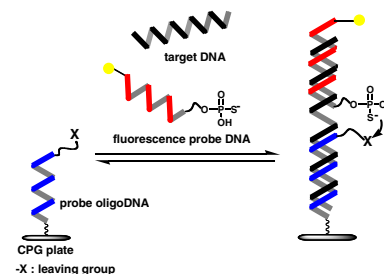
A series of phenyl piperidine derivatives have been synthesized and evaluated as CCR2 antagonists.

An effective method for the in situ synthesis of DNA–CPG conjugates using chemical ligation technology as tools for SNP analysis

pp 5969–5973

Akihiro Ohkubo, Kunihiro Tanaka, Haruhiko Taguchi, Kohji Seio, Hiroshi Nagasawa, Toshifumi Tsukahara and Mitsuo Sekine*

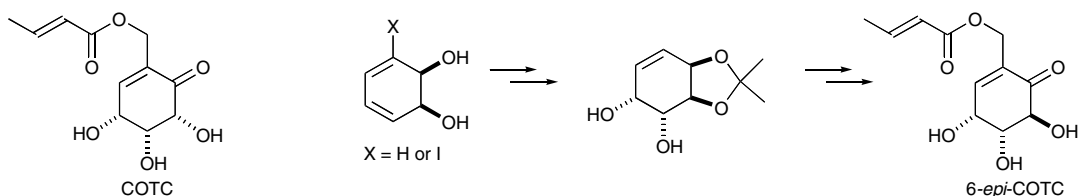
A new method for the SNP analysis by using a chemical ligation (CL) technique on CPG plates with high coupling efficiency is reported.



Arene *cis*-dihydrodiols: Useful precursors for the preparation of analogues of the anti-tumour agent, 2-crotonyloxymethyl-(4*R*,5*R*,6*R*)-4,5,6-trihydroxycyclohex-2-enone (COTC)

pp 5974–5977

Claire L. Arthurs, James Raftery, Helen L. Whitby, Roger C. Whitehead,*
Natasha S. Wind and Ian J. Stratford

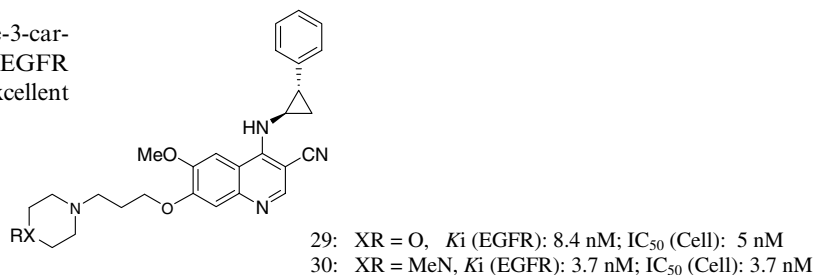


Synthesis and structure–activity relationship of 4-(2-aryl-cyclopropylamino)-quinoline-3-carbonitriles as EGFR tyrosine kinase inhibitors

pp 5978–5982

Madhavi Pannala, Sunil Kher, Norma Wilson, John Gaudette, Ila Sircar, Shao-Hui Zhang, Alexei Bakhirev, Guang Yang, Phoebe Yuen, Frank Gorcsan, Naoki Sakurai, Miguel Barbosa and Jie-Fei Cheng*

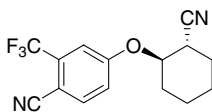
A series of 4-(2-aryl-cyclopropylamino)-quinoline-3-carbonitriles have been synthesized and tested for EGFR inhibition. Compounds **29** and **30** showed excellent enzymatic and cellular activities against EGFR.



(1*R*,2*S*)-4-(2-Cyano-cyclohexyl-oxy)-2-trifluoromethyl-benzonitrile, a potent androgen receptor antagonist for stimulating hair growth and reducing sebum production

pp 5983–5988

Lain-Yen Hu,* Daniel Du, Jennifer Hoffman, Yvonne Smith, Victor Fedij, Catherine Kostlan, Theodore R. Johnson, Yun Huang, Steve Kesten, William Harter, Wen Song Yue, Jie Jack Li, Nicole Barvian, Lorna Mitchell, Huangshu John Lei, Bruce Lefker, Mathew Carroll, Danielle Dettling, Teresa Krieger-Burke, Brian Samas, Radhika Yalamanchili, Kimberly Lapham, David Pocalyko, Drago Sliskovic, Susan Ciotti, Brenda Stoller, Mostofa A. Hena, Qizhu Ding, Samarendra N. Maiti, Michael Stier and Howard Welgus



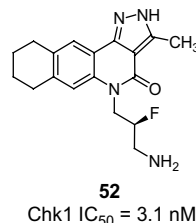
The synthesis, pharmacology, and pharmacokinetic profiles of (1*R*,2*S*)-4-(2-cyano-cyclohexyl-oxy)-2-trifluoromethyl-benzonitrile are reported. This agent demonstrated remarkable potency for stimulating hair growth in a male C3H mouse model as well as reducing sebum production in the male Syrian hamster ear model.

Optimization of a pyrazoloquinolinone class of Chk1 kinase inhibitors

pp 5989–5994

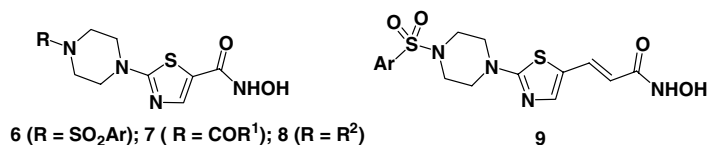
Edward J. Brnardic,* Robert M. Garbaccio, Mark E. Fraley, Edward S. Tasber, Justin T. Steen, Kenneth L. Arrington, Vadim Y. Dudkin, George D. Hartman, Steven M. Stirdivant, Bob A. Drakas, Keith Rickert, Eileen S. Walsh, Kelly Hamilton, Carolyn A. Buser, James Hardwick, Weikang Tao, Stephen C. Beck, Xianzhi Mao, Robert B. Lobell, Laura Sepp-Lorenzino, Youwei Yan, Mari Ikuta, Sanjeev K. Munshi, Lawrence C. Kuo and Constantine Kreatsoulas

The optimization of potency for a pyrazoloquinolinone class of Chk1 kinase inhibitors is described.

**Design and synthesis of thiazole-5-hydroxamic acids as novel histone deacetylase inhibitors**

pp 5995–5999

Sampath-Kumar Anandan,* John S. Ward, Richard D. Brokx, Trisha Denny, Mark R. Bray, Dinesh V. Patel and Xiao-Yi Xiao

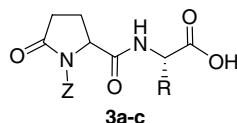


The synthesis, histone deacetylase (HDAC) inhibitory activity and the antiproliferative activity of thiazole-5-hydroxamic acids **6–9** are described.

Expedient synthesis of *N*-Z-pyroglutamyl-amino acid derivatives

pp 6000–6002

Alan R. Katritzky,* Parul Angrish, Ekaterina Todadze and Ion Ghiviriga



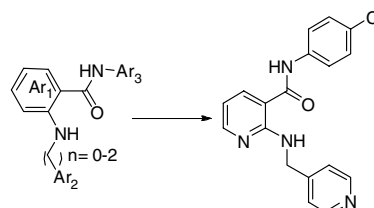
N-Z-Pyroglutamyl pseudopeptides **3** are advantageously derived by cyclization of an *N*-terminal glutamic acid residue.

**Discovery of *N*-phenyl nicotinamides as potent inhibitors of Kdr**

pp 6003–6008

Celia Dominguez,* Leon Smith, Qi Huang, Chester Yuan, Xiaohu Ouyang, Lynn Cai, Paul Chen, Joseph Kim, Timothy Harvey, Rashid Syed, Tae-Seong Kim, Andrew Tasker,* Ling Wang, Michael Zhang, Angela Coxon, James Bready, Charles Starnes, Danlin Chen, Yongmei Gan, Sessa Neervannan, Gondi Kumar, Anthony Polverino and Richard Kendall

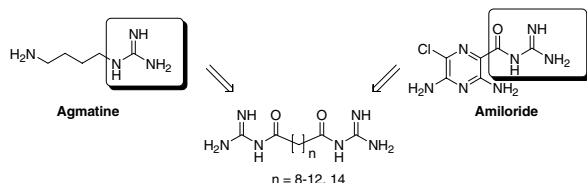
Inhibition of tumor-induced angiogenesis is a promising strategy in anticancer research. Neovascularization is a process required for both tumor growth and metastasis. Enhanced understanding of the underlying molecular mechanisms has led to the discovery of a variety of pharmaceutically attractive targets. Decades of investigation suggest that vascular endothelial growth factor (VEGF) and its receptors, in particular VEGFR2 or kinase insert-domain-containing receptor (Kdr), play a critical role in the growth and survival of endothelial cells in newly forming vasculature. The clinical utility of inhibitors of this receptor tyrosine kinase is currently under intense investigation. Herein, we report our efforts in this arena.



On the search of new I₂-IBS aliphatic ligands: Bis-guanidino carbonyl derivatives

pp 6009–6012

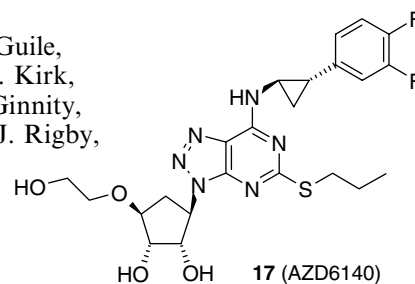
Jonathan Corcoran, Fernando Rodriguez, Isabel Rozas,* J. Javier Meana and Luis F. Callado

**From ATP to AZD6140: The discovery of an orally active reversible P2Y₁₂ receptor antagonist for the prevention of thrombosis**

pp 6013–6018

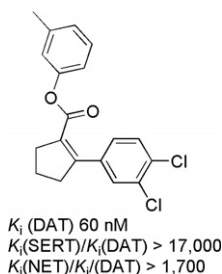
Brian Springthorpe,* Andrew Bailey, Patrick Barton, Timothy N. Birkinshaw, Roger V. Bonnert, Roger C. Brown, David Chapman, John Dixon, Simon D. Guile, Robert G. Humphries, Simon F. Hunt, Francis Ince, Anthony H. Ingall, Ian P. Kirk, Paul D. Leeson, Paul Leff, Richard J. Lewis, Barrie P. Martin, Dermot F. McGinnity, Michael P. Mortimore, Stuart W. Paine, Garry Pairaudeau, Anil Patel, Aaron J. Rigby, Robert J. Riley, Barry J. Teobald, Wendy Tomlinson, Peter J. H. Webbhorn and Paul A. Willis

Starting with ATP, the identification of novel P2Y₁₂ receptor antagonists are described. The leading compound, **17** (AZD6140), is currently in a phase III clinical trial for the treatment of acute coronary syndromes.

**High dopamine transporter selectivity can be displayed by remarkably simple non-nitrogen containing inhibitors**

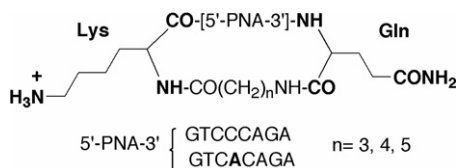
pp 6019–6025

Søren V. Boye, Fernando Ortega-Caballero, Steffen Sinning, Ove Wiborg, Henrik H. Jensen* and Mikael Bols*

**Solid-phase synthesis and thermal denaturation study of cyclic PNAs targeting the HIV-1 TAR RNA loop**

pp 6026–6030

Gregory Upert, Mohamed Mehiri, Audrey Di Giorgio, Roger Condom and Nadia Patino*

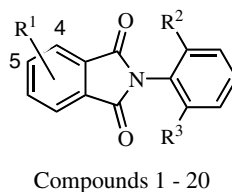
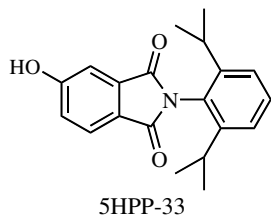


The solid-phase synthesis of cyclic PNA-based compounds and their binding to the HIV-1 TAR RNA fragment is reported.



Inhibitors of NF- κ B derived from thalidomide**pp 6031–6035**

Esperanza J. Carcache de-Blanco, Bulbul Pandit, Zhigen Hu, Jiandong Shi, Andrew Lewis and Pui-Kai Li*



$R^1 = 4 \text{ or } 5 \text{ CH}_3, \text{Cl}, \text{CO}_2\text{H}, \text{CO}_2\text{CH}_3, \text{NH}_2, \text{NO}_2, \text{NHCOCH}_3, \text{OH}, \text{OSO}_2\text{NH}_2$
 $R^2, R^3 = \text{H}, \text{Me}, \text{Et}, \text{Pr}, \text{iPr}, \text{iBu}, \text{F}, \text{Cl}, \text{Br}$

OTHER CONTENTS**Summary of instructions to authors****p I**

*Corresponding author

📄⁺ Supplementary data available via ScienceDirect**COVER**

The binding of compound **11** at the ATP pocket of Abl-T315I mutant. The hydroxyl group of phenyl interacts with Glu286 from the α C-helix. The gatekeeper residue Ile-315 forms hydrophobic interactions with the aromatic ring of the benzotriazine. [Cao, J.; Fine, R.; Gritzen, C.; Hood, J.; Kang, X.; Klebansky, B.; Lohse, D.; Mak, C. C.; McPherson, A.; Noronha, G.; Palanki, M. S. S.; Pathak, V. P.; Renick, J.; Soll, R.; Zeng, B.; Zhu, H. *Bioorg. Med. Chem. Lett.* **2007**, 17, 5812.]

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