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Bioorganic & Medicinal Chemistry Letters Volume 21, Issue 4, 2011

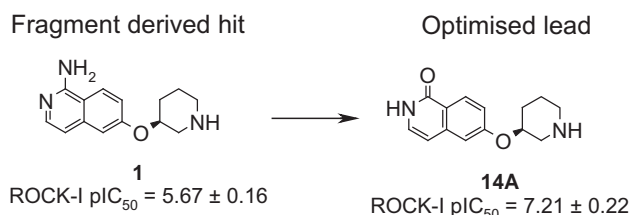
Contents

BMCL DIGEST

Optimisation of 6-substituted isoquinolin-1-amine based ROCK-I inhibitors

pp 1084–1088

Peter Ray*, Jane Wright, Julia Adam, Sylviane Boucharens, Darcey Black, Angus R. Brown, Ola Epemolu, Dan Fletcher, Margaret Huggett, Phil Jones, Steven Laats, Amanda Lyons, Jos de Man, Richard Morphy, Brad Sherborne, Lorcan Sherry, Nicole van Straten, Paul Westwood, Mark York

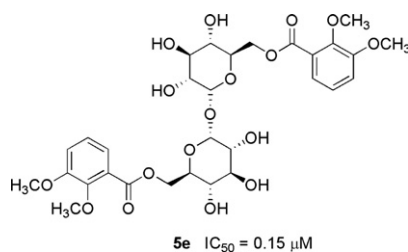


REGULAR ARTICLES

Synthesis and evaluation of trehalose-based compounds as anti-invasive agents

pp 1089–1091

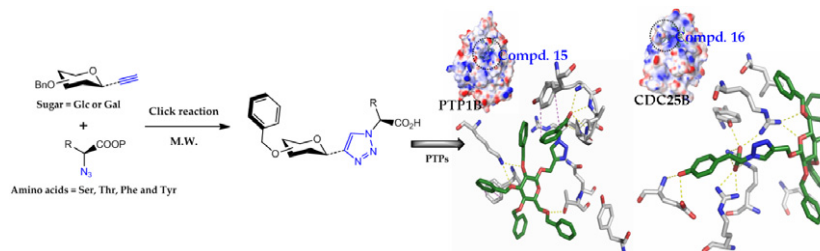
Yong-Li Jiang, Long-Qian Tang, Satoshi Miyana, Yasuhiro Igarashi, Ikko Saiki, Zhao-Peng Liu*



A unique and rapid approach toward the efficient development of novel protein tyrosine phosphatase (PTP) inhibitors based on 'clicked' pseudo-glycopeptides

pp 1092–1096

Jin-Wei Yang, Xiao-Peng He*, Cui Li, Li-Xin Gao, Li Sheng, Juan Xie, Xiao-Xin Shi, Yun Tang, Jia Li*, Guo-Rong Chen*



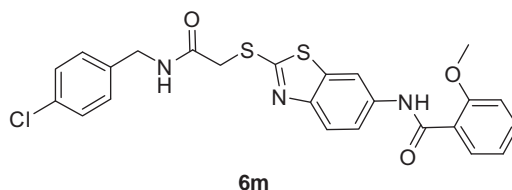
We report the 'click' fabrication of triazolyl glycopeptidomimetics as novel PTP1B and CDC25B inhibitors and their plausible binding modes with the targeted PTP via docking simulation.



Synthesis, structure–activity relationships and preliminary antitumor evaluation of benzothiazole-2-thiol derivatives as novel apoptosis inducers

pp 1097–1101

Zhao Wang, Xuan-Hong Shi, Jia Wang, Tian Zhou, You-Zhi Xu, Ting-Ting Huang, Yan-Fang Li, Ying-Lan Zhao, Li Yang, Sheng-Yong Yang, Luo-Ting Yu*, Yu-Quan Wei



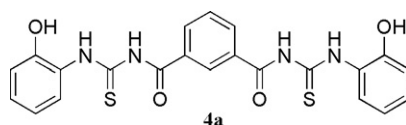
A series of novel benzothiazole-2-thiol derivatives were synthesized and evaluated for antitumor. The most potent compound **6m** exhibited good inhibitory activities against a panel of different types of human cancer cell lines with IC₅₀ values in the low micromolar range and induced apoptosis in HepG2 cancer cells.



Efficient synthesis and biological evaluation of 1,3-benzenedicarbonyl dithiureas

pp 1102–1104

Hao Peng, Yongju Liang, Le Chen, Liwu Fu*, Haiqin Wang, Hongwu He*

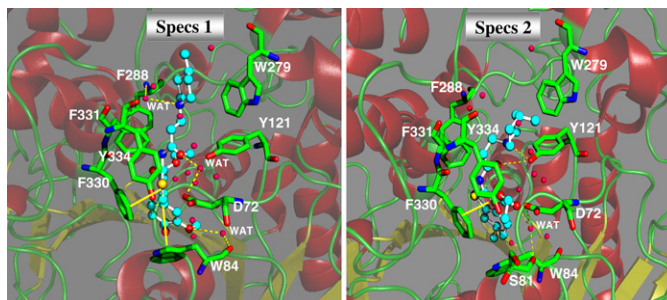


Discovery of dual binding site acetylcholinesterase inhibitors identified by pharmacophore modeling and sequential virtual screening techniques

pp 1105–1112

Shikhar Gupta, Adyary Fallarero, Päivi Järvinen, Daniela Karlsson, Mark S. Johnson, Pia M. Vuorela, C. Gopi Mohan*

Dual binding site acetylcholinesterase (AChE) inhibitors are promising for the treatment of Alzheimer's disease (AD). Inhibitors showing both the anti-aggregating Aβ and anti-cholinesterase effect bind to these sub-sites, the so called dual binding site in AChE enzyme. We adopted a strategy, by systematically integrating the in vitro and in silico techniques throughout the present work, to discover new cholinesterase inhibitors **Specs1** and **Specs2**, having good ADMET properties for the treatment of AD.

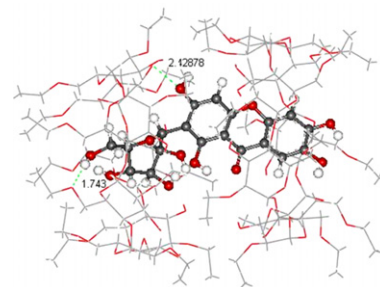


Investigation on a host–guest inclusion system by β-cyclodextrin derivative and its analytical application

pp 1113–1117

Lizhen Huang, Jiang He*, Ruihua Lu, Xia Ge, Jingjing Guo

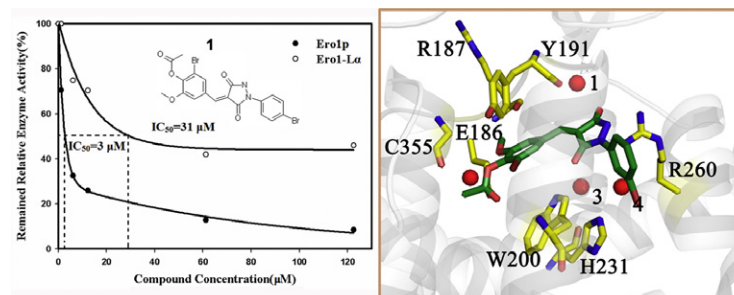
To elucidate a plausible complex structure for the supramolecular complex, we performed the molecular modelling study. The inclusion complex was emulated by entering the guest molecule from the large face of the CD cavity of the DE-β-CD molecule by steps. Subsequently, the energy minimization was carried out for each step without any constraint. Full-geometry optimization was performed, using the molecular mechanics MM+ method followed by the semiempirical AM1 method to obtain the minimum structure.



Identification of small molecular inhibitors for Ero1p by structure-based virtual screening

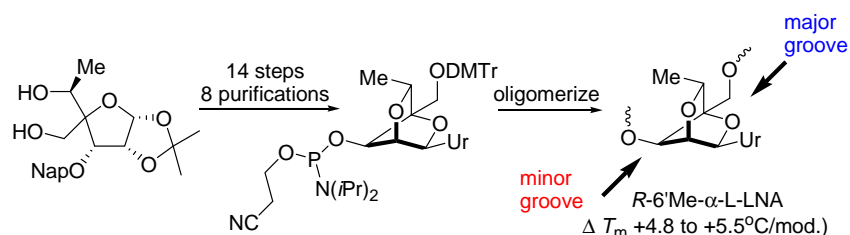
pp 1118–1121

Yanyan Chu, Xianjun Chen, Yi Yang*, Yun Tang*

**Synthesis and biophysical characterization of R-6'-Me- α -L-LNA modified oligonucleotides**

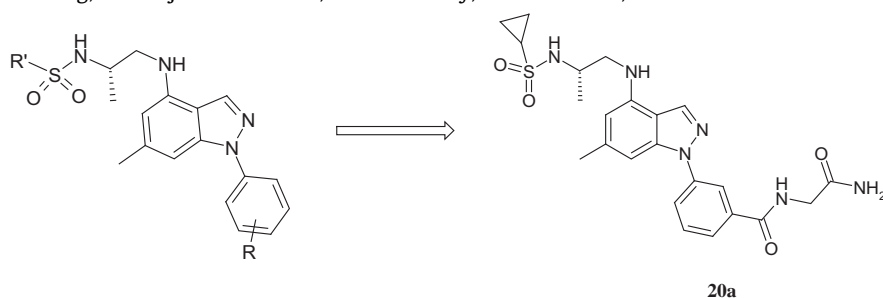
pp 1122–1125

Punit P. Seth*, Jinghua Yu, Charles R. Allerson, Andres Berdeja, Eric E. Swayze

**Discovery of a potent series of non-steroidal non α -trifluoromethyl carbinol glucocorticoid receptor agonists with reduced lipophilicity**

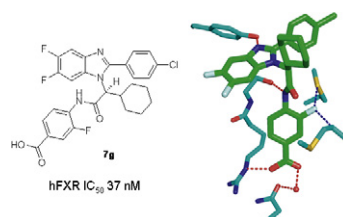
pp 1126–1133

Hawa Diallo*, Davina C. Angell, Heather A. Barnett, Keith Biggadike, Diane M. Coe, Tony W. J. Cooper, Andy Craven, James R. Gray, David House, Torquil I. Jack, Steve P. Keeling, Simon J. F. Macdonald, Iain M. McLay, Samuel Oliver, Simon J. Taylor, Iain J. Uings, Natalie Wellaway

**Optimization of a novel class of benzimidazole-based farnesoid X receptor (FXR) agonists to improve physicochemical and ADME properties**

pp 1134–1140

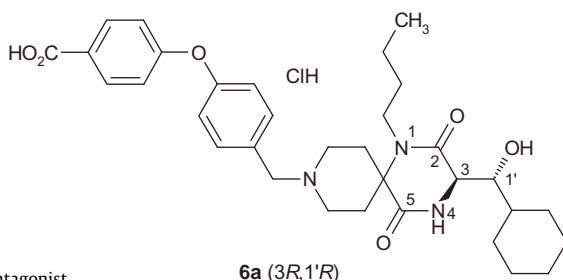
Hans G. F. Richter*, G. M. Benson, K. H. Bleicher, D. Blum, E. Chaput, N. Clemann, S. Feng, C. Gardes, U. Grether, P. Hartman, B. Kuhn, R. E. Martin, J.-M. Plancher, M. G. Rudolph, F. Schuler, S. Taylor



Spirodiketopiperazine-based CCR5 antagonist: Discovery of an antiretroviral drug candidate

pp 1141–1145

Rena Nishizawa*, Toshihiko Nishiyama, Katsuya Hisaichi, Chiaki Minamoto, Naoki Matsunaga, Yoshikazu Takaoka, Hisao Nakai, Stephen Jenkinson, Wieslaw M. Kazmierski, Hideaki Tada, Kenji Sagawa, Shiro Shibayama, Daikichi Fukushima, Kenji Maeda, Hiroaki Mitsuya

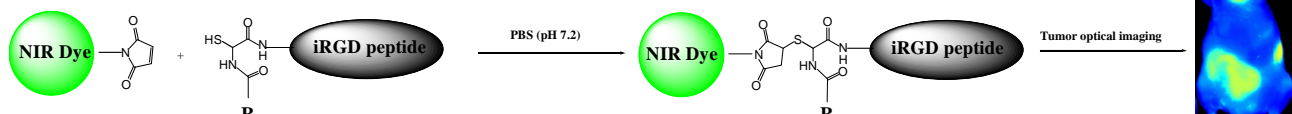


Molecular design of a new orally-available CCR5 antagonist.

Synthesis and evaluation of new iRGD peptide analogs for tumor optical imaging

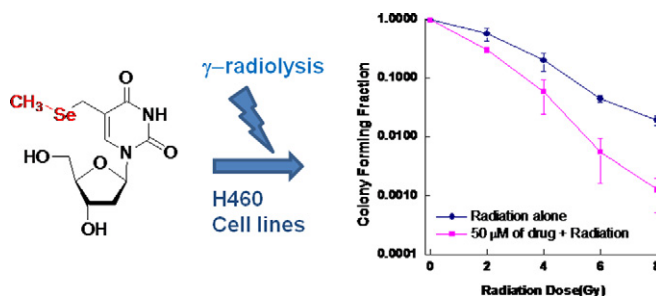
pp 1146–1150

Yunpeng Ye, Lei Zhu, Ying Ma, Gang Niu, Xiaoyuan Chen*

**Potent radiosensitizing agents: 5-Methylselenenyl- and 5-phenylselenenyl-methyl-2'-deoxyuridine**

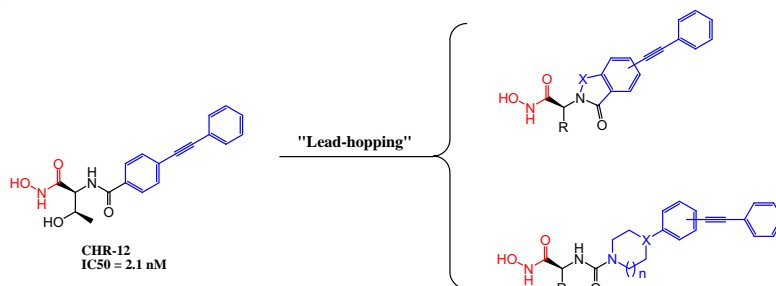
pp 1151–1154

Ambadas B. Rode, Byeong Mo Kim, Seon Hwa Park, In Seok Hong*, Sung Hee Hong*

**Design and synthesis of potent Gram-negative specific LpxC inhibitors**

pp 1155–1161

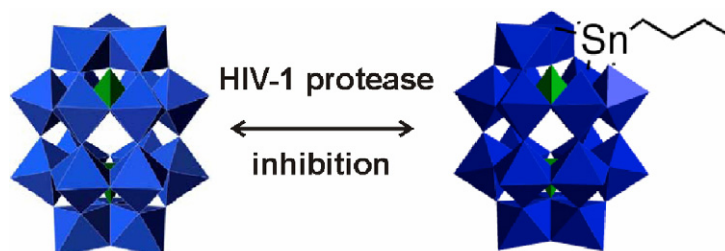
U. Faruk Mansoor*, Dilrukshi Vitharana, Panduranga Adulla Reddy, Dayna L. Daubaras, Paul McNicholas, Peter Orth, Todd Black, M. Arshad Siddiqui



HIV-1 protease inhibition potential of functionalized polyoxometalates

pp 1162–1166

Andreas Flütsch, Thilo Schroeder, Markus G. Grütter, Greta R. Patzke*

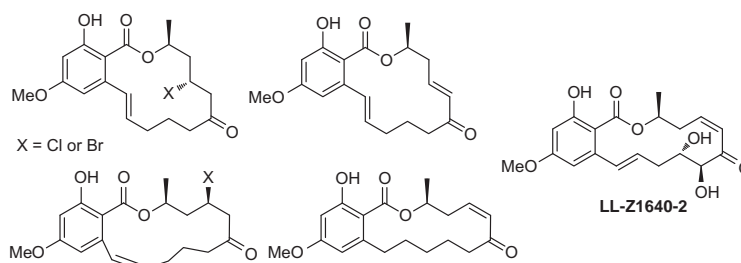


The inhibitory effect of functionalized polyoxotungstates with organic side chains on HIV-1 protease is investigated.

**Isosteric replacement of the Z-enone with haloethyl ketone and E-enone in a resorcylic acid lactone series and biological evaluation**

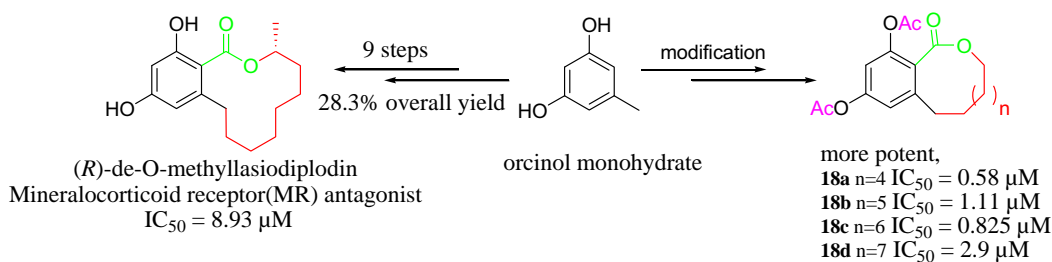
pp 1167–1170

Carmela Napolitano, Alessandro Natoni, Corrado Santocanale, Lasse Evensen, James B. Lorens, Paul V. Murphy*

**Synthesis, modification, and evaluation of (R)-de-O-methylasiodiplodin and analogs as nonsteroidal antagonists of mineralocorticoid receptor**

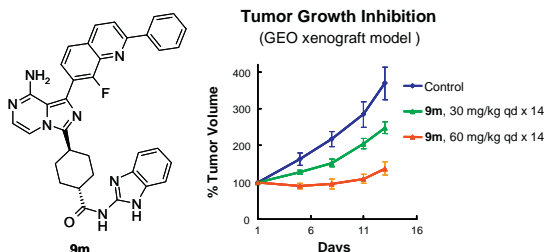
pp 1171–1175

Cheng-Shi Jiang, Rong Zhou, Jing-Xu Gong*, Li-Li Chen*, Tibor Kurtán, Xu Shen, Yue-Wei Guo*

**Potent and selective cyclohexyl-derived imidazopyrazine insulin-like growth factor 1 receptor inhibitors with in vivo efficacy**

pp 1176–1180

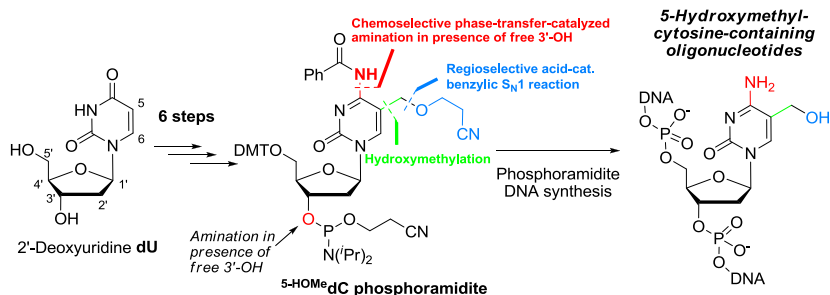
Meizhong Jin*, Andrew Kleinberg, Andy Cooke, Prafulla C. Gokhale, Kenneth Foreman, Hanqing Dong, Kam W. Siu, Mark A. Bittner, Kristen M. Mulvihill, Yan Yao, Darla Landfair, Matthew O'Connor, Gilda Mak, Jonathan A. Pachter, Robert Wild, Maryland Rosenfeld-Franklin, Qunsheng Ji, Mark J. Mulvihill*



Improved synthesis of 5-hydroxymethyl-2'-deoxycytidine phosphoramidite using a 2'-deoxyuridine to 2'-deoxycytidine conversion without temporary protecting groups

pp 1181–1184

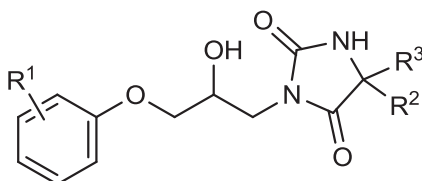
Anders S. Hansen, Armin Thalhammer, Afaf H. El-Sagheer, Tom Brown, Christopher J. Schofield*



Analysis of β -amino alcohols as inhibitors of the potential anti-tubercular target *N*-acetyltransferase

pp 1185–1190

Elizabeth Fullam, Areej Abuhammad, David L. Wilson, Matthew C. Anderton, Steve G. Davies, Angela J. Russell, Edith Sim*



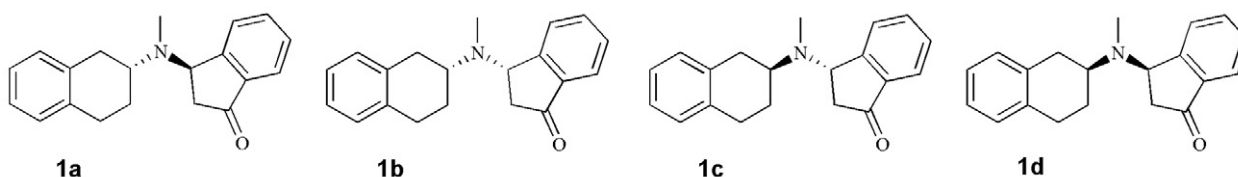
The synthesis and in vitro characterisation of a novel series of β -amino alcohol compounds based upon the hit compound identified from a screening program 3-[3'-(4''-cyclopent-2''-en-1''-yl)phenoxy]-2'-hydroxypropyl]-5,5-dimethylimidazolidine-2,4-dione against prokaryotic arylamine *N*-acetyltransferase enzymes are reported.



Synthesis and pharmacological evaluation of the individual stereoisomers of 3-[methyl(1,2,3,4-tetrahydro-2-naphthalenyl)amino]-1-indanone, a potent mast cell stabilising agent

pp 1191–1194

Adam J. Byrne, James W. Barlow, John J. Walsh*



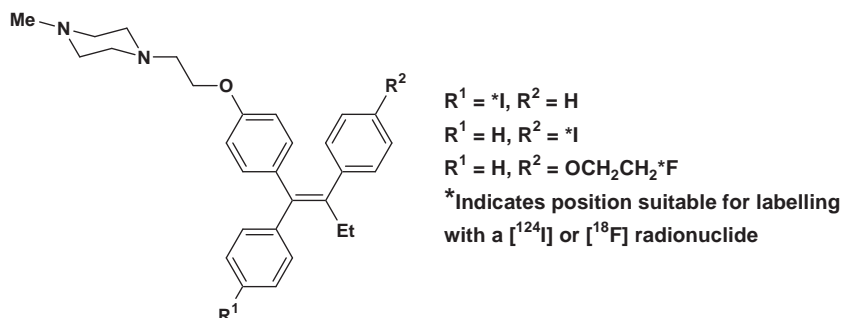
IC_{50} 1.51 μ M vs. 48/80 in RPMC
53% inhibition of anti IgE in PLMC
Most active isomer *in vivo*
vs. PCA reaction



Triaryl (Z)-olefins suitable for radiolabeling with iodine-124 or fluorine-18 radionuclides for positron emission tomography imaging of estrogen positive breast tumors

pp 1195–1198

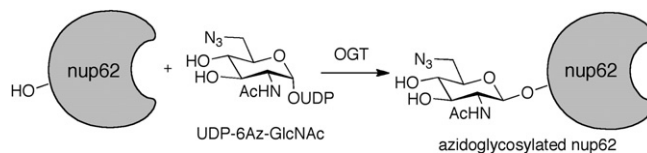
Khaled R. A. Abdellatif, Carlos A. Velázquez, Zhangjian Huang, Morshed A. Chowdhury, Edward E. Knaus*



6''-Azido-6''-deoxy-UDP-N-acetylglucosamine as a glycosyltransferase substrate

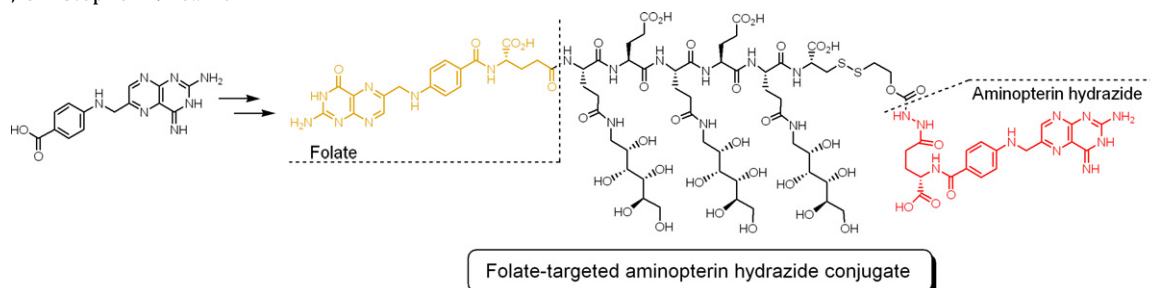
pp 1199–1201

Alain Mayer, Tracey M. Gloster, Wayne K. Chou, David J. Vocadlo, Martin E. Tanner*

**Design and regioselective synthesis of a new generation of targeted therapeutics. Part 3: Folate conjugates of aminopterin hydrazide for the treatment of inflammation**

pp 1202–1205

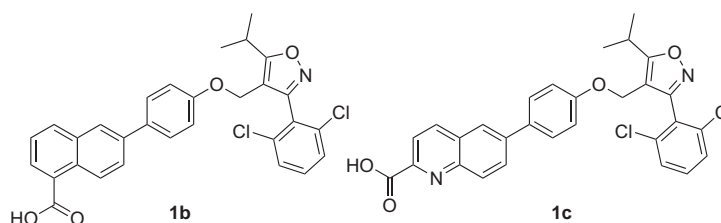
Iontcho R. Vlahov*, Fei You, Hari Krishna R. Santhapuram, Yu Wang, Jeremy F. Vaughn, Spencer J. Hahn, Paul J. Kleindl, Mingjin Fan, Christopher P. Leamon

**Conformationally constrained farnesoid X receptor (FXR) agonists: Heteroaryl replacements of the naphthalene**

pp 1206–1213

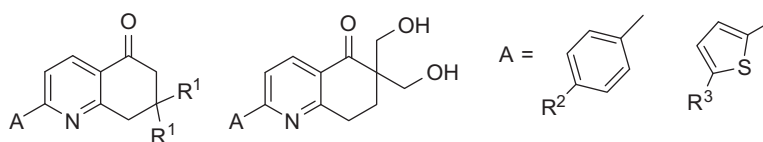
Jonathan Y. Bass, Justin A. Caravella, Lihong Chen, Katrina L. Creech, David N. Deaton*, Kevin P. Madauss, Harry B. Marr, Robert B. McFadyen, Aaron B. Miller, Wendy Y. Mills, Frank Navas III, Derek J. Parks, Terrence L. Smalley Jr., Paul K. Spearing, Dan Todd, Shawn P. Williams, G. Bruce Wisely

To improve on the drug properties of GSK8062 **1b**, a series of heteroaryl bicyclic naphthalene replacements were prepared. The quinoline **1c** was an equipotent FXR agonist with improved drug developability parameters relative to **1b**. In addition, GSK2324 **1c** lowered body weight gain and serum glucose in a DIO mouse model of diabetes.

**Synthesis and antitubercular evaluation of novel substituted aryl and thiophenyl tethered dihydro-6H-quinolin-5-ones**

pp 1214–1217

Srinivas Kantevari*, Santhosh Reddy Patpi, Balasubramanian Sridhar, Perumal Yogeeswari, Dharmarajan Sriram



R¹ = H, CH₃ R² = H, CH₃, OCH₃ R³ = H, Cl, Br

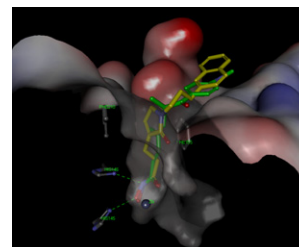
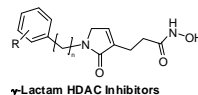
18 examples; **4e**: R¹ = CH₃, R³ = Cl and **4f**: R¹ = CH₃, R³ = Br (MIC = 3.13 µg/mL)

Structure and property based design, synthesis and biological evaluation of γ -lactam based HDAC inhibitors

pp 1218–1221

Eunhyun Choi, Chulho Lee, Jung Eun Park, Jeong Jea Seo, Misun Cho, Jong Soon Kang, Hwan Mook Kim, Song-Kyu Park, Kiho Lee, Gyoonee Han*

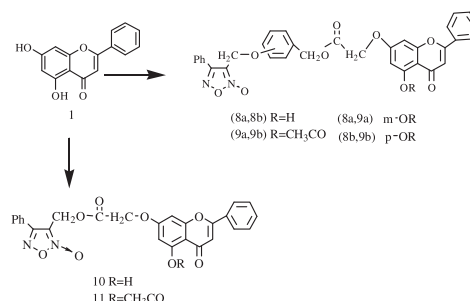
Based on QSAR study of the δ -lactam core HDAC inhibitors, the smaller γ -lactam core HDAC inhibitors were designed for biological and property optimization. The new 11 compounds were synthesized and evaluated in vitro assays. Phenyl, naphthyl and thiophenyl groups were introduced as the cap groups.

**Furoxan nitric oxide donor coupled chrysin derivatives: Synthesis and vasculoprotection**

pp 1222–1226

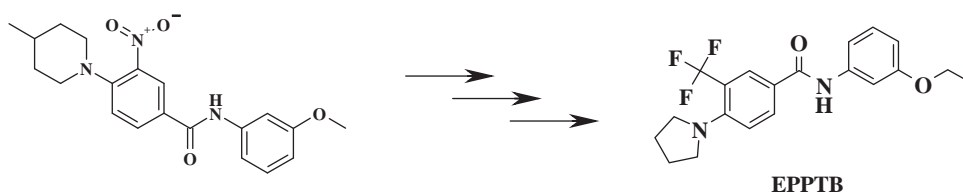
Xiao-Qing Zou, Sheng-Ming Peng, Chang-Ping Hu*, Li-Feng Tan, Han-Wu Deng, Yuan-Jian Li

A group of hybrid furoxan based nitric oxide-releasing chrysin derivatives was synthesized. All these chrysin derivatives released NO upon incubation with PBS at pH 7.4, exhibited inhibitory activities against aldose reductase and advanced glycation end-products formation in vitro. And some of them were even found to increase the glucose consumption of HepG2 cells.

**Selective antagonists of mouse trace amine-associated receptor 1 (mTAAR1): Discovery of EPPTB (R05212773)**

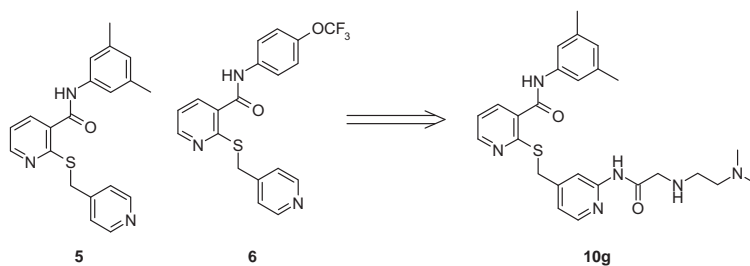
pp 1227–1231

Henri Stalder*, Marius C. Hoener, Roger D. Norcross

**Pyridylmethylthio derivatives as VEGF inhibitors: Part 2**

pp 1232–1235

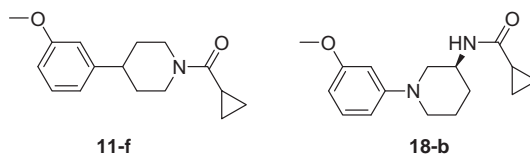
Hisashi Tajima*, Takahiro Honda, Kenji Kawashima, Yoshimasa Sasabuchi, Minoru Yamamoto, Masakazu Ban, Kazuyoshi Okamoto, Kenji Inoue, Takaaki Inaba, Yuriko Takeno, Takashi Tsuboi, Asaka Tonouchi, Hiroyuki Aono



Design and synthesis of 4-arylpiperidinyl amide and N-arylpiperidin-3-yl-cyclopropane carboxamide derivatives as novel melatonin receptor ligands

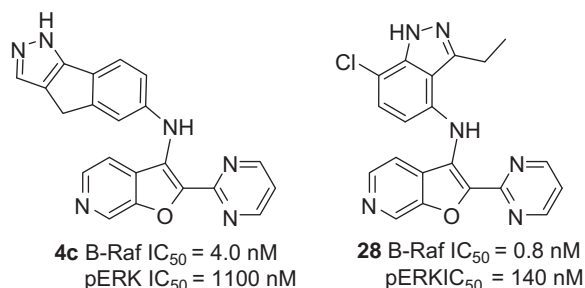
pp 1236–1242

Guiying Li*, Hao Zhou, Yu Jiang, Holger Keim, Sidney W. Topiol, Suresh B. Poda, Yong Ren, Gamini Chandrasena, Darío Doller

**Non-oxime inhibitors of B-Raf^{V600E} kinase**

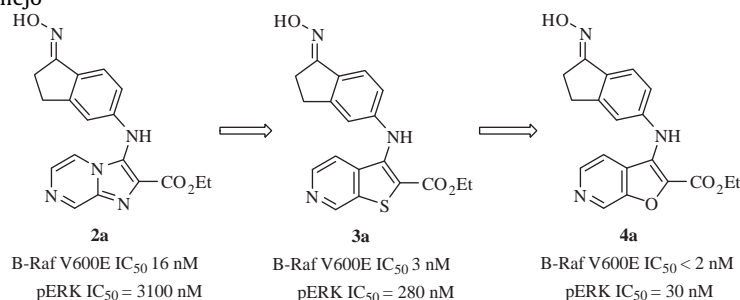
pp 1243–1247

Li Ren, Steve Wenglowsky*, Greg Miknis, Bryson Rast, Alex J. Buckmelter, Robert J. Ely, Stephen Schlachter, Ellen R. Laird, Nikole Randolph, Michele Callejo, Matthew Martinson, Sarah Galbraith, Barbara J. Brandhuber, Guy Vigers, Tony Morales, Walter C. Voegtli, Joseph Lyssikatos

Inhibitors of B-Raf^{V600E} kinase are reported for which indanone oximes are replaced with tricyclic pyrazoles and indazoles.**The Discovery of furo[2,3-c]pyridine-based indanone oximes as potent and selective B-Raf inhibitors**

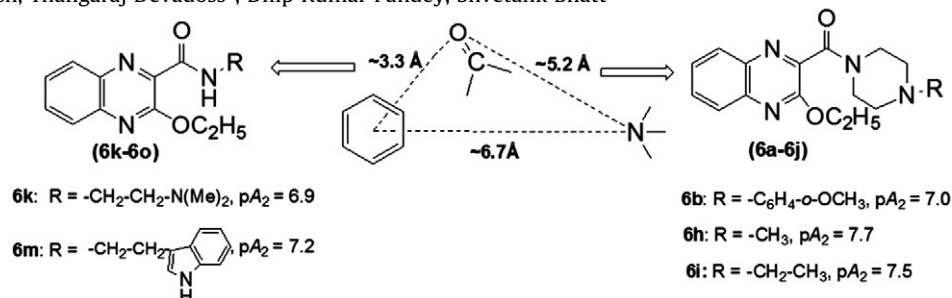
pp 1248–1252

Alex J. Buckmelter, Li Ren*, Ellen R. Laird*, Bryson Rast, Greg Miknis, Steve Wenglowsky, Stephen Schlachter, Mike Welch, Eugene Tarlton, Jonas Grina, Joseph Lyssikatos, Barbara J. Brandhuber, Tony Morales, Nikole Randolph, Guy Vigers, Matthew Martinson, Michele Callejo

**Discovery of new anti-depressants from structurally novel 5-HT₃ receptor antagonists: Design, synthesis and pharmacological evaluation of 3-ethoxyquinoxalin-2-carboxamides**

pp 1253–1256

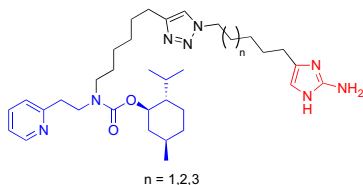
Radhakrishnan Mahesh, Thangaraj Devadoss*, Dilip Kumar Pandey, Shvetank Bhatt

Discovery of new anti-depressants from structurally novel 5-HT₃ receptor antagonists are described.

Synthesis and biological evaluation of 2-aminoimidazole/carbamate hybrid anti-biofilm and anti-microbial agents

pp 1257–1260

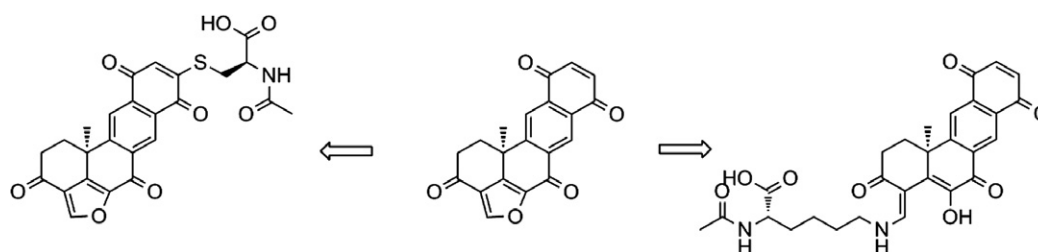
Steven A. Rogers, Erick A. Lindsey, Daniel C. Whitehead, Trey Mullikin, Christian Melander*



Chemical and biological explorations of the electrophilic reactivity of the bioactive marine natural product halenaquinone with biomimetic nucleophiles

pp 1261–1264

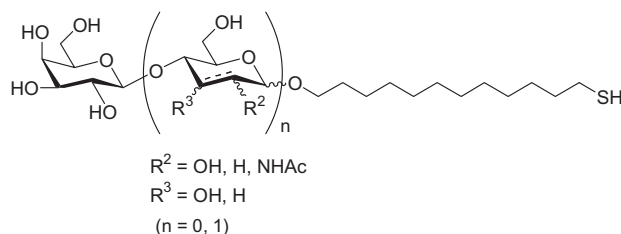
Jiayi Wang, Marie-Lise Bourguet-Kondracki, Arlette Longeon, Joëlle Dubois, Alexis Valentin, Brent R. Copp*



Synthesis and galectin-binding activities of mercaptododecyl glycosides containing a terminal β -galactosyl group

pp 1265–1269

Teiichi Murakami*, Kyoko Yoshioka, Yukari Sato, Mutsuo Tanaka, Osamu Niwa, Soichi Yabuki



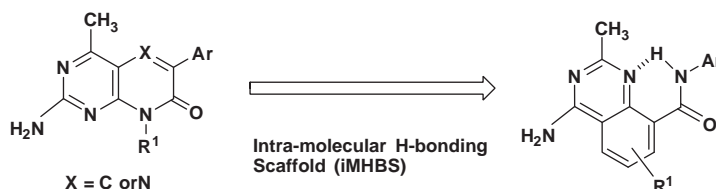
Synthesis of 12-mercaptododecyl β -galactoside-terminated glycosides and their galectin-binding activities evaluated by SPR measurements are described.



Quinazolines with intra-molecular hydrogen bonding scaffold (iMHBS) as PI3K/mTOR dual inhibitors

pp 1270–1274

Kevin K. C. Liu*, Xiaojun Huang, Shubha Bagrodia, Jeffrey H. Chen, Samantha Greasley, Hengmiao Cheng, Shaoxian Sun, Dan Knighton, Caroline Rodgers, Kristina Rafidi, Aihua Zou, Jiezhao Xiao, Shengyong Yan

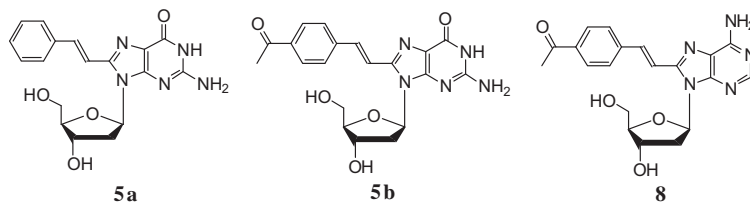


Intra-molecular hydrogen bonding was introduced to the quinazoline motif to form a pseudo ring (intra-molecular H-bond scaffold, iMHBS) to mimic our previous published core structures, pyrido[2,3-*D*]pyrimidin-7-one and pteridinone, as PI3K/mTOR dual inhibitors. This design results in potent PI3K/mTOR dual inhibitors and the purposed intra-molecular hydrogen bonding structure is well supported by co-crystal structure in PI3K γ enzyme. In addition, a novel synthetic route was developed for these analogs.

Design and synthesis of highly solvatochromic fluorescent 2'-deoxyguanosine and 2'-deoxyadenosine analogs

pp 1275–1278

Katsuhiko Matsumoto, Naoya Takahashi, Azusa Suzuki, Takashi Morii, Yoshio Saito*, Isao Saito*



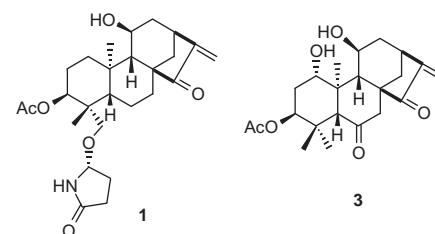
Chemical structures of aromatic fluorophore substituted purine nucleosides.

Pyrrolidinone diterpenoid from *Isodon excisus* and inhibition of nitric oxide production in lipopolysaccharide-induced macrophage RAW264.7 cells

pp 1279–1281

Seong Su Hong, Seon A Lee, Nahyun Kim, Ji Sang Hwang, Xiang Hua Han, Mi Kyeong Lee, Jae Kyung Jung, Jin Tae Hong, Youngsoo Kim, Dongho Lee, Bang Yeon Hwang*

A new pyrrolidinone diterpenoid, excisusin F (**1**), was isolated from the aerial parts of *Isodon excisus* (Lamiaceae), together with four known compounds, and their structures were determined mainly by NMR (1D and 2D) and mass spectrometry. Excisusin F (**1**) and inflexarabdonin E (**3**) showed potent inhibitory effects of LPS-induced nitric oxide production in RAW264.7 cells with the IC₅₀ value of 10.4 and 3.8 μ M, respectively.

**OTHER CONTENT****Corrigendum**

p 1282

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i+ Supplementary data available via ScienceDirect

COVER

Botulinum neurotoxins are the most deadly toxins known to man, approximately 10 million times more deadly than cyanide. Botulinum neurotoxins are classified by the US Centers for Disease Control (CDC) as bioterrorism agents. The etiological agent responsible for botulinum intoxication is a metalloprotease; as such this is a key therapeutic target. Currently, there are no approved pharmacological treatments for botulinum intoxication. Discovering molecules that could be used as a path forward for therapeutic development as botulinum protease inhibitors is tantamount. A benzylidene cyclopentenedione-based inhibitor was found to be the first affinity reagent to covalently modify the active site of botulinum neurotoxin A light chain metalloprotease. Its kinetic parameters are reported and such an approach for inhibition of this deadly neurotoxin. [Capková, K.; Hixon, M. S.; Pellett, S.; Barbieri, J. T.; Johnson, E. A.; Janda, K. D. *Bioorg. Med. Chem. Lett.* **2010**, 20, 206.]

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