



Bioorganic & Medicinal Chemistry Letters Volume 21, Issue 5, 2011

Contents

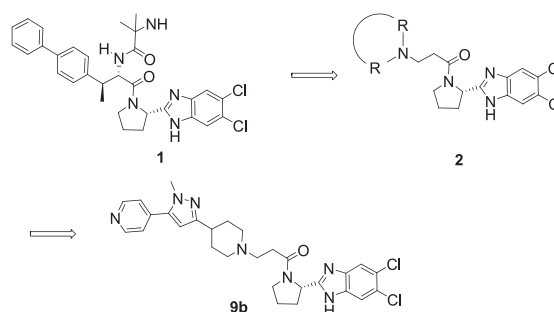
ARTICLES

Discovery of benzimidazole pyrrolidinyl amides as prolylcarboxypeptidase inhibitors

pp 1299–1305

Hong C. Shen*, Fa-Xiang Ding, Changyou Zhou, Yusheng Xiong, Andreas Verras, Renee M. Chabin, Suoyu Xu, Xinchun Tong, Dan Xie, Michael E. Lassman, Urmi R. Bhatt, Margarita M. Garcia-Calvo, Wayne Geissler, Zhu Shen, Dunlu Chen, Ranabir SinhaRoy, Jeffery J. Hale, James R. Tata, Shirly Pinto, Dong-Ming Shen, Steven L. Colletti

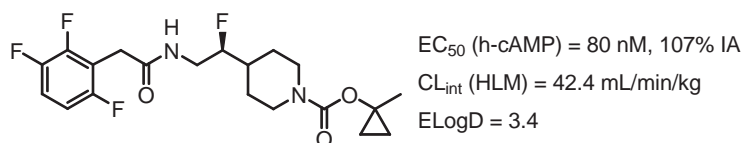
A series of benzimidazole pyrrolidinyl amides containing a piperidinyl group were discovered as novel prolylcarboxypeptidase (PrCP) inhibitors. Low-nanomolar IC_{50} 's were achieved for several analogs, of which compound **9b** displayed modest ex vivo target engagement in eDIO mouse plasma. Compound **9b** was also studied in vivo for its effect on weight loss and food intake in an eDIO mouse model and the results will be discussed.



Design and evaluation of a 2-(2,3,6-trifluorophenyl)acetamide derivative as an agonist of the GPR119 receptor

pp 1306–1309

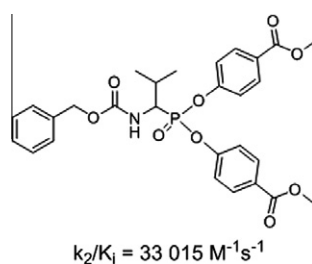
Vincent Mascitti*, Benjamin D. Stevens, Chulho Choi, Kim F. McClure, Cristiano R. W. Guimarães, Kathleen A. Farley, Michael J. Munchhof, Ralph P. Robinson, Kentaro Futatsugi, Sophie Y. Lavergne, Bruce A. Lefker, Peter Cornelius, Paul D. Bonin, Amit S. Kalgutkar, Raman Sharma, Yue Chen



Simple phosphonic inhibitors of human neutrophil elastase

pp 1310–1314

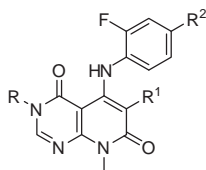
Marcin Sieńczyk, Łukasz Winiarski, Paulina Kasperkiewicz, Mateusz Psurski, Joanna Wietrzyk, Józef Oleksyszyn*



Discovery of TAK-733, a potent and selective MEK allosteric site inhibitor for the treatment of cancer

pp 1315–1319

Qing Dong, Douglas R. Dougan, Xianchang Gong, Petro Halkowycz, Bohan Jin, Toufike Kanouni, Shawn M. O'Connell, Nicholas Scorah*, Lihong Shi, Michael B. Wallace, Feng Zhou

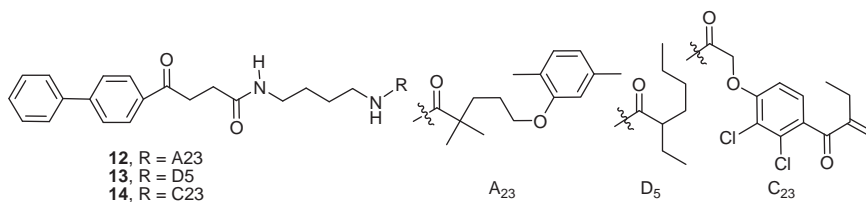


A series of potent 8-methylpyrido[2,3-d]pyrimidine-4,7(3H,8H)-dione inhibitors of MEK kinase was designed and synthesized. Structural properties and biological activities are described.

Solution-phase parallel synthesis and screening of anti-tumor activities from fenbufen and ethacrynic acid libraries

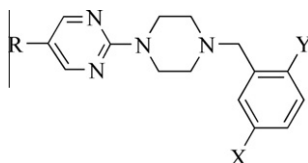
pp 1320–1324

Yuan-Hsiao Su, Li-Wu Chiang, Kee-Ching Jeng, Ho-Lien Huang, Jenn-Tzong Chen, Wuu-Jyh Lin, Chia-Wen Huang, Chung-Shan Yu*

**Anti-tumor pyrimidinylpiperazines bind to the prosurvival Bcl-2 protein family member Bcl-XL**

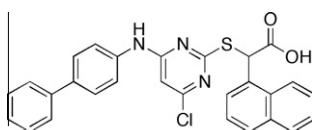
pp 1325–1328

Hassan M. Shallal, Jesika S. Faridi, Wade A. Russu*

**A novel class of dual mPGES-1/5-LO inhibitors based on the α -naphthyl pirinixic acid scaffold**

pp 1329–1333

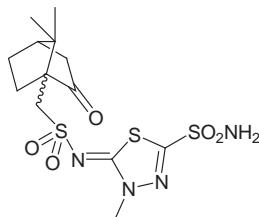
Martina Hieke, Christine Greiner, Theresa M. Thieme, Manfred Schubert-Zsilavecz, Oliver Werz, Heiko Zettl*

**Compound 16**IC₅₀ mPGES-1 = 0.94 μ MIC₅₀ 5-LO = 0.1 μ M (in PMNL)

(R)-/(S)-10-Camphorsulfonyl-substituted aromatic/heterocyclic sulfonamides selectively inhibit mitochondrial over cytosolic carbonic anhydrases

pp 1334–1337

Alfonso Maresca, Claudiu T. Supuran*

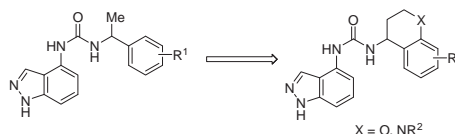


16 (1'R): Ki(CA I)= 5246 nM, Ki(CA II) = 1773 nM; Ki(CA VA)= 5.9 nM, Ki(CA VB)= 7.8 nM

Chroman and tetrahydroquinoline ureas as potent TRPV1 antagonists

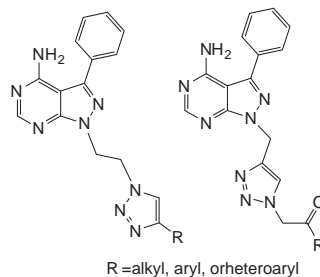
pp 1338–1341

Robert G. Schmidt, Erol K. Bayburt, Steven P. Latshaw, John R. Koenig, Jerome F. Daanen, Heath A. McDonald, Bruce R. Bianchi, Chengmin Zhong, Shailen Joshi, Prisca Honore, Kennan C. Marsh, Chih-Hung Lee, Connie R. Faltynek, Arthur Gomtsyan*

**Synthesis of 3-phenylpyrazolopyrimidine-1,2,3-triazole conjugates and evaluation of their Src kinase inhibitory and anticancer activities**

pp 1342–1346

Anil Kumar*, Israr Ahmad, Bhupender S. Chhikara, Rakesh Tiwari, Deendayal Mandal, Keykavous Parang*



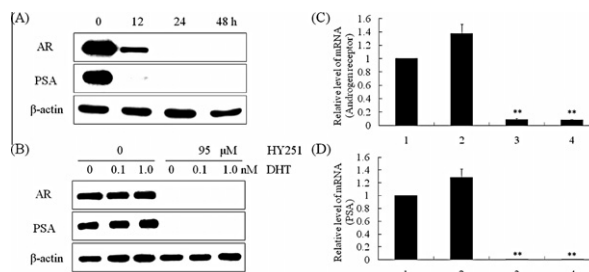
R =alkyl, aryl, orheteroaryl

The synthesis, Src kinase inhibitory potencies, and anticancer activities of two classes of 3-phenylpyrazolopyrimidine-1,2,3-triazole conjugates are reported.

**HY251, a novel decahydrocyclopenta[a]indene analog, from *Aralia continentalis* induces apoptosis via down-regulation of AR expression in human prostate cancer LNCaP cells**

pp 1347–1349

Ha Lim Oh, Chul-Hoon Lee*

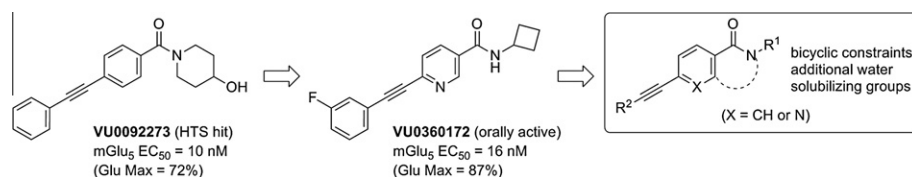


Effect of HY251, a novel decahydrocyclopenta[a]indene tetraol, on down-regulation of AR and PSA gene.

Synthesis and SAR of centrally active mGlu₅ positive allosteric modulators based on an aryl acetylenic bicyclic lactam scaffold

pp 1350–1353

Richard Williams, Jason T. Manka, Alice L. Rodriguez, Paige N. Vinson, Colleen M. Niswender, C. David Weaver, Carrie K. Jones, P. Jeffrey Conn, Craig W. Lindsley, Shaun R. Stauffer*

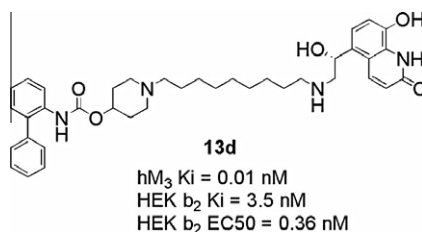


This Letter describes the hit-to-lead progression and SAR of a series of biphenyl acetylene compounds derived from an HTS screening campaign targeting the mGlu₅ receptor. 'Molecular switches' were identified that modulated modes of pharmacology, and several compounds within this series were shown to be efficacious in reversal of amphetamine induced hyperlocomotion in rats after ip dosing, a preclinical model that shows similar positive effects with known antipsychotic agents.

Discovery of muscarinic acetylcholine receptor antagonist and beta 2 adrenoceptor agonist (MABA) dual pharmacology molecules

pp 1354–1358

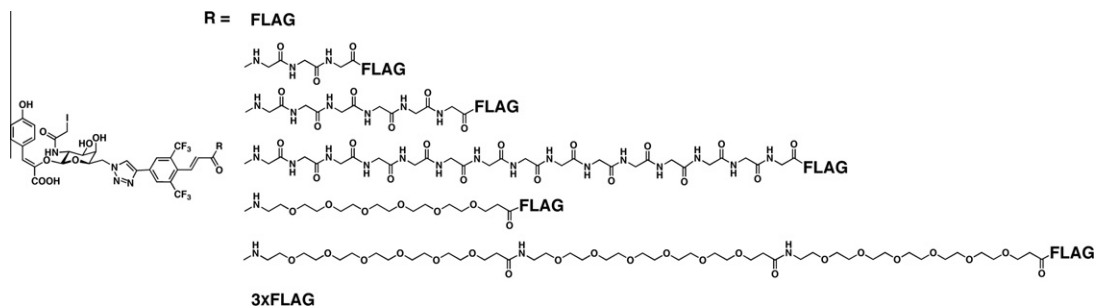
Adam D. Hughes*, Kay H. Chin, Sarah L. Dunham, Jeffrey R. Jasper, Kristin E. King, Tae Weon Lee, Mathai Mammen, Jerri Martin, Tod Steinfeld



The high performance of 3XFLAG for target purification of a bioactive metabolite: A tag combined with a highly effective linker structure

pp 1359–1362

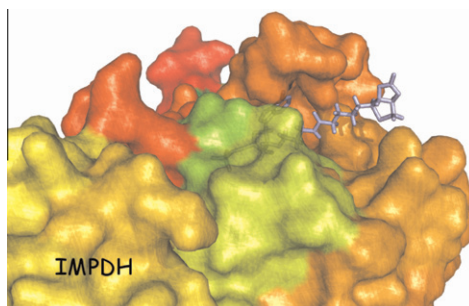
Minoru Ueda*, Yoshiyuki Manabe, Makoto Mukai



Specific biotinylation of IMP dehydrogenase

pp 1363–1365

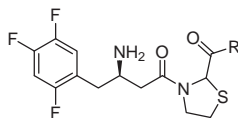
B. Christopher Hoefler, Deviprasad R. Gollapalli, Lizbeth Hedstrom*



Discovery of β -aminoacyl containing thiazolidine derivatives as potent and selective dipeptidyl peptidase IV inhibitors

pp 1366–1370

Woul Seong Park, Seung Kyu Kang, Mi Ae Jun, Mi Sik Shin, Ki Young Kim, Sang Dal Rhee, Myung Ae Bae, Min Sun Kim, Kwang Rok Kim, Nam Sook Kang, Sung-eun Yoo, Jie Oh Lee, Dong Hyun Song, Peter Silinski, Stephen Edward Schneider, Jin Hee Ahn*, Sung Soo Kim*

**Investigation of a novel molecular descriptor for the lead optimization of 4-aminoquinazolines as vascular endothelial growth factor receptor-2 inhibitors: Application for quantitative structure–activity relationship analysis in lead optimization**

pp 1371–1375

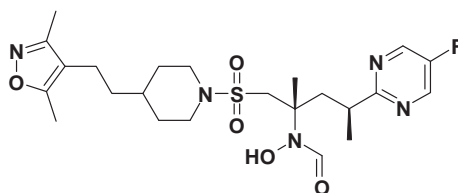
Joel K. Kawakami*, Yannica Martinez, Brandi Sasaki, Melissa Harris, Wendy E. Kurata, Alan F. Lau

Compounds within the 4-aminoquinazoline chemical series were docked to the KDR receptor followed by structure to activity relationship (QSAR) analysis. A novel molecular descriptor utilizing infrared vibrational frequency of the ligands is illustrated for rapid QSAR study.

**The design and synthesis of novel *N*-hydroxyformamide inhibitors of ADAM-TS4 for the treatment of osteoarthritis**

pp 1376–1381

Chris De Savi*, Andrew Pape, John G. Cumming, Attila Ting, Peter D. Smith, Jeremy N. Burrows, Mark Mills, Chris Davies, Scott Lamont, David Milne, Calum Cook, Peter Moore, Yvonne Sawyer, Stefan Gerhardt

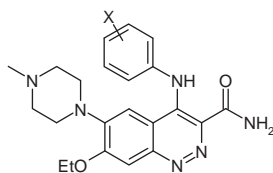


ADAM-TS4 IC_{50} = 0.69 nM
MMP-13 IC_{50} = >8100 nM

3-Amido-4-anilincinnolines as a novel class of CSF-1R inhibitor

pp 1382–1384

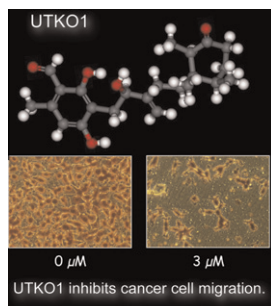
David A. Scott*, Les A. Dakin, David J. Del Valle, R. Bruce Diebold, Lisa Drew, Thomas W. Gero, Claude A. Ogoe, Charles A. Omer, Galina Repik, Kumar Thakur, Qing Ye, Xiaolan Zheng



Synthesis and anti-migrative evaluation of moverastin derivatives

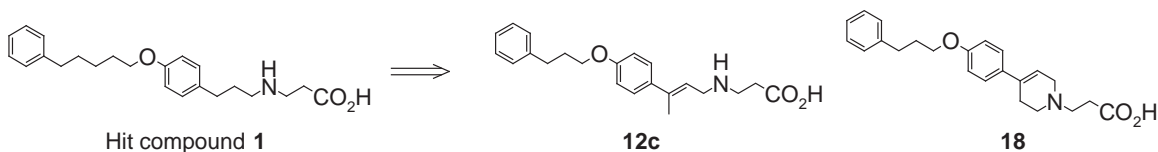
pp 1385–1389

Masato Sawada, Shin-ichiro Kubo, Koji Matsumura, Yasushi Takemoto, Hiroki Kobayashi, Etsu Tashiro, Takeshi Kitahara, Hidenori Watanabe*, Masaya Imoto*

**Structure–activity relationship studies of sphingosine-1-phosphate receptor agonists with *N*-cinnamyl- β -alanine moiety**

pp 1390–1393

Haruto Kurata*, Kazuhiro Otsuki, Kensuke Kusumi, Masakuni Kurono, Masahiko Terakado, Takuya Seko, Hirotaka Mizuno, Takeji Ono, Hiroshi Hagiya, Masashi Minami, Shinji Nakade, Hiromu Habashita*

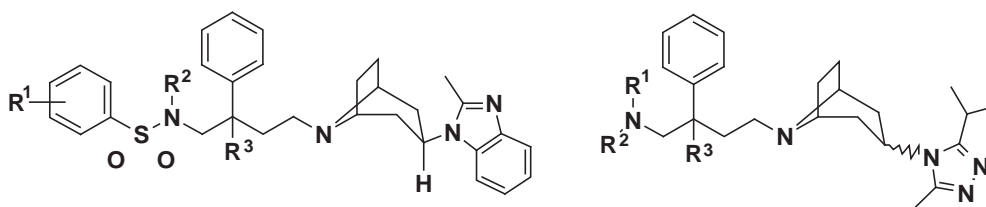


Structure–activity relationship of sphingosine-1-phosphate receptor agonist was examined. Novel S1P agonists with cinnamyl scaffold or 1,2,5,6-tetrahydropyridine scaffold were identified.

Synthesis and evaluation of 2-phenyl-1,4-butanediamine-based CCR5 antagonists for the treatment of HIV-1

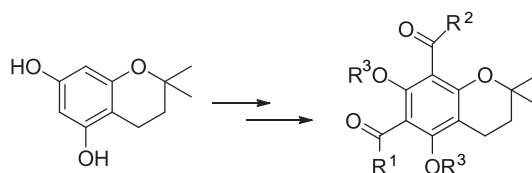
pp 1394–1398

Matthew D. Tallant*, Maosheng Duan, George A. Freeman, Robert G. Ferris, Mark P. Edelstein, Wieslaw M. Kazmierski, Pat J. Wheelan

**Synthesis of chroman aldehydes that inhibit HIV**

pp 1399–1401

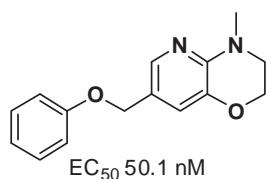
George A. Kraus*, John Mengwasser, Wendy Maury, ChoonSeok Oh



Discovery of novel positive allosteric modulators of the metabotropic glutamate receptor 5 (mGlu₅)

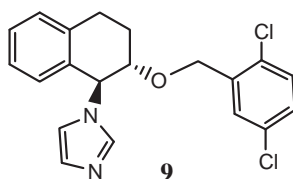
pp 1402–1406

Jeffrey G. Varnes*, Andrew P. Marcus, Russell C. Mauger, Scott R. Throner, Valerie Hoesch, Megan M. King, Xia Wang, Linda A. Sygowski, Nathan Spear, Reto Gadiant, Dean G. Brown, James B. Campbell

Positive allosteric modulators of mGlu₅ are described.**Design and synthesis of novel tetrahydronaphthyl azoles and related cyclohexyl azoles as antileishmanial agents**

pp 1407–1410

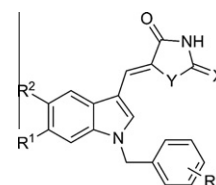
Vijay K. Marrapu, Nagarapu Srinivas, Monika Mittal, Nishi Shakya, Suman Gupta, Kalpana Bhandari*

A novel series of aryloxy tetrahydronaphthyl and cyclohexyl azoles were synthesized as antileishmanials. Among all, compound **9** was identified as the most potent analogue with both in vitro and in vivo activity against *Leishmania donovani*.**Synthesis and in vitro screening of novel N-benzyl aplysinopsin analogs as potential anticancer agents**

pp 1411–1413

Narsimha Reddy Penthala, Thirupathi Reddy Yerramreddy, Peter A. Crooks*

A series of novel substituted (Z)-5-((1-benzyl-1H-indol-3-yl)methylene)imidazolidin-2,4-diones (**3a–f**) and (Z)-5-((1-benzyl-1H-indol-3-yl)methylene)-2-iminothiazolidin-4-ones (**3g–o**) have been synthesized and evaluated for in vitro cytotoxicity against a panel of 60 human tumor cell lines. Compound **3i** exhibits potent growth inhibition against melanoma UACC-257 (GI₅₀ = 13.3 nM) and ovarian OVCAR-8 (GI₅₀ = 19.5 nM) cancer cells and significant cytotoxicity (LC₅₀ = 308 and 851 nM, respectively) against the same cell lines within this series of compounds. A second analog, **3a**, had GI₅₀ values of 307 and 557 nM against SK-MEL-2 melanoma and A498 renal cancer cell lines, and exhibited GI₅₀ values ranging from 0.30 to 6 μM against 98% of the cancer cell lines in the 60-cell panel.

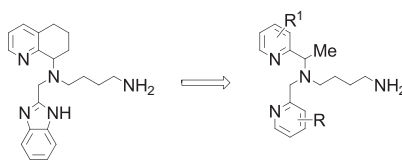


3a: X = O, Y = NH, R¹ = -COOCH₃, R² = H, R³ = *p*-CN
3i: X = NH, Y = S, R¹ = H, R² = Cl, R³ = *p*-F

Design of novel CXCR4 antagonists that are potent inhibitors of T-tropic (X4) HIV-1 replication

pp 1414–1418

Renato Skerlj*, Gary Bridger, Ernest McEachern, Curtis Harwig, Chris Smith, Alan Kaller, Duane Veale, Helen Yee, Krystyna Skupinska, Rossana Wauthy, Letian Wang, Ian Baird, Yongbao Zhu, Kate Burrage, Wen Yang, Michael Sartori, Dana Huskens, Erik De Clercq, Dominique Schols



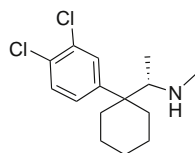
A novel series of CXCR4 antagonists were identified based on the substantial redesign of AMD070. These compounds possessed potent anti-HIV-1 activity and showed excellent pharmacokinetics in rat and dog.



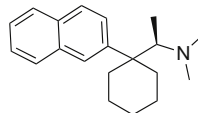
Discovery of *N*-methyl-1-(1-phenylcyclohexyl)ethanamine, a novel triple serotonin, norepinephrine and dopamine reuptake inhibitor

pp 1434–1437

Liming Shao*, Michael C. Hewitt, Fengjiang Wang, Scott C. Malcolm, Jianguo Ma, John E. Campbell, Una C. Campbell, Sharon R. Engel, Nancy A. Spicer, Larry W. Hardy, Rudy Schreiber, Kerry L. Spear, Mark A. Varney



24

81 57 30 (SERT, NET, DAT IC₅₀ nM)
53, 52 (HLM, MLM t_{1/2} min)

31

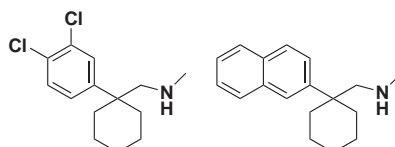
<1 21 28 (SERT, NET, DAT IC₅₀ nM)
32, 19 (HLM, MLM t_{1/2} min)

Active in mouse tail suspension test at 10 and 30 mpk PO.

Discovery of *N*-methyl-1-(1-phenylcyclohexyl)methanamine, a novel triple serotonin, norepinephrine, and dopamine reuptake inhibitor

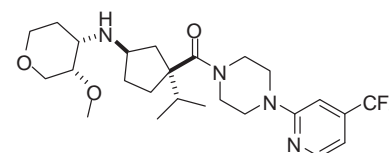
pp 1438–1441

Liming Shao*, Michael C. Hewitt, Fengjiang Wang, Scott C. Malcolm, Jianguo Ma, John E. Campbell, Una C. Campbell, Sharon R. Engel, Nancy A. Spicer, Larry W. Hardy, Rudy Schreiber, Kerry L. Spear, Mark A. Varney

*Triple SERT, NET, DAT reuptake Inhibitors*
*Oral activity in mouse Tail Suspension Test***Discovery of INCB10820/PF-4178903, a potent, selective, and orally bioavailable dual CCR2 and CCR5 antagonist**

pp 1442–1446

Changsheng Zheng, Ganfeng Cao, Michael Xia, Hao Feng, Joseph Glenn, Rajan Anand, Ke Zhang, Taisheng Huang, Anlai Wang, Ling Kong, Mei Li, Laurine Galya, Robert O. Hughes, Rajesh Devraj, Phillip A. Morton, D. Joseph Rogier, Maryanne Covington, Fred Baribaud, Niu Shin, Peggy Scherle, Sharon Diamond, Swamy Yeleswaram, Kris Vaddi, Robert Newton, Greg Hollis, Steven Friedman, Brian Metcalf, Chu-Biao Xue*

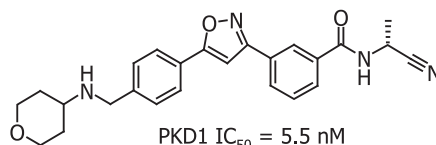
We report the discovery of a potent, selective, and orally bioavailable dual CCR2 and CCR5 antagonist (3*S*,4*S*)-*N*-[(1*R*,3*S*)-3-isopropyl-3-({4-[4-(trifluoromethyl)pyridin-2-yl]piperazin-1-yl}carbonyl)cyclopentyl]-3-methoxytetrahydro-2*H*-pyran-4-amine (INCB10820/PF-4178903). After evaluation in 28-day toxicology studies, INCB10820/PF-4178903 was selected as a clinical candidate.

INCB10820/PF-4178903

3,5-Diarylazoles as novel and selective inhibitors of protein kinase D

pp 1447–1451

Gabriel G. Gamber*, Erik Meredith, Qingming Zhu, Wanlin Yan, Chang Rao, Michael Capparelli, Robin Burgis, Istvan Enyedy, Ji-Hu Zhang, Nicolas Soldermann, Kimberley Beattie, Olga Rozhitskaya, Keith A. Koch, Nikos Pagratis, Vinayak Hosagrahara, Richard B. Vega, Timothy A. McKinsey, Lauren Monovich

PKD1 IC₅₀ = 5.5 nM

The preparation and SAR studies of a novel class of potent selective, and orally bioavailable PKD inhibitors are reported.

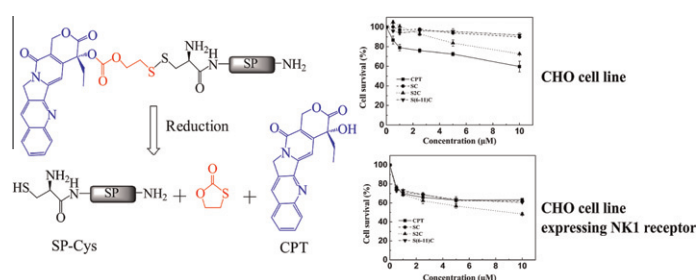


Improving anticancer activity and selectivity of camptothecin through conjugation with releasable substance P

pp 1452–1455

Wei Zhang, Jingjing Song, Lingyun Mu, Bangzhi Zhang, Liwei Liu, Yanhong Xing, Kairong Wang, Zhenya Li, Rui Wang*

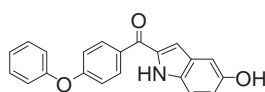
The substance P targeted CPT conjugates with a disulfide carbonate releasable linker exhibited significant cytotoxicity and selectivity to tumor cells that highly over-express neurokinin-1 receptor (NK1R).



Structure and activity relationship of 2-(substituted benzoyl)-hydroxyindoles as novel CaMKII inhibitors

pp 1456–1458

Masafumi Komiya*, Shigehiro Asano, Nobuyuki Koike, Erina Koga, Junetsu Igarashi, Shogo Nakatani, Yoshiaki Isobe



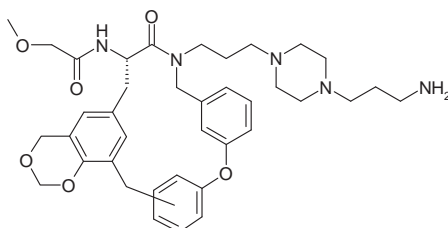
14

CaMKII Inhibition ; $IC_{50} = 0.61 \mu M$

Serendipitous discovery of a new class of agonists for the melanocortin 1 and 4 receptors and a new class of cyclophanes

pp 1459–1463

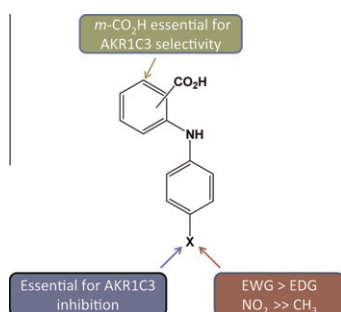
Kilian Conde-Frieboes*, Michael Ankersen, Jens Breinholt, Birgit Sehested Hansen, Kirsten Raun, Henning Thøgersen, Birgitte S. Wulff



Discovery of substituted 3-(phenylamino)benzoic acids as potent and selective inhibitors of type 5 17β-hydroxysteroid dehydrogenase (AKR1C3)

pp 1464–1468

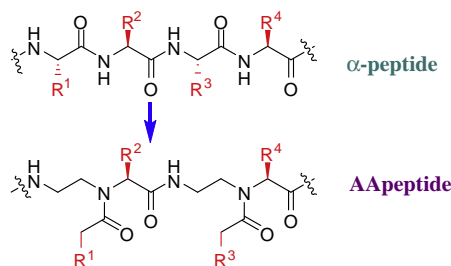
Adegoke O. Adeniji, Barry M. Twenter, Michael C. Byrns, Yi Jin, Jeffrey D. Winkler*, Trevor M. Penning*



Design and synthesis of AApeptides: A new class of peptide mimics

pp 1469–1471

Yaogang Hu, Xiaolong Li, Said M. Sebti, Jiandong Chen, Jianfeng Cai*

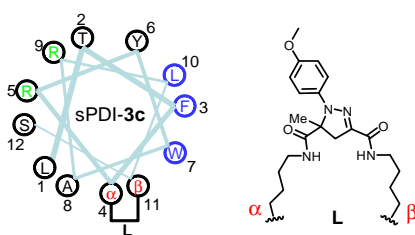


A new class of oligomeric peptidomimics were described and synthesized.

**Synthesis of cell-permeable stapled peptide dual inhibitors of the p53-Mdm2/Mdmx interactions via photoinduced cycloaddition**

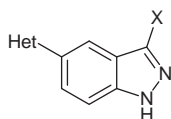
pp 1472–1475

Michael M. Madden, Avinash Muppidi, Zhenyu Li, Xiaolong Li, Jiandong Chen*, Qing Lin*

**Scaffold oriented synthesis. Part 3: Design, synthesis and biological evaluation of novel 5-substituted indazoles as potent and selective kinase inhibitors employing [2+3] cycloadditions**

pp 1476–1479

Irimi Akritopoulou-Zanze*, Brian D. Wakefield, Alan Gasielcki, Douglas Calvin, Eric F. Johnson, Peter Kovar, Stevan W. Djuric

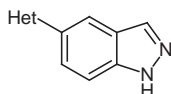


We report the synthesis and biological evaluation of 5-substituted indazoles and amino indazoles as kinase inhibitors. The compounds were synthesized in a parallel synthesis fashion from readily available starting materials employing [2+3] cycloaddition reactions and were evaluated against a panel of kinase assays. Potent inhibitors were identified for numerous kinases such as Rock2, Gsk3 β , Aurora2 and Jak2.

Scaffold oriented synthesis. Part 4: Design, synthesis and biological evaluation of novel 5-substituted indazoles as potent and selective kinase inhibitors employing heterocycle forming and multicomponent reactions

pp 1480–1483

Irimi Akritopoulou-Zanze*, Brian D. Wakefield, Alan Gasielcki, Douglas Calvin, Eric F. Johnson, Peter Kovar, Stevan W. Djuric

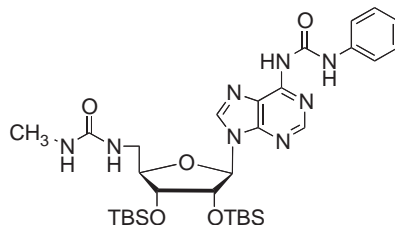


We report the synthesis and biological evaluation of 5-substituted indazoles as kinase inhibitors. The compounds were synthesized in a parallel synthesis fashion from readily available starting materials employing heterocycle forming and multicomponent reactions and were evaluated against a panel of kinase assays. Potent inhibitors were identified for Gsk3 β , Rock2, and Egfr.

A broad spectrum anticancer nucleoside with selective toxicity against human colon cells in vitro

pp 1484–1487

Jadd R. Shelton, Scott R. Burt, Matt A. Peterson*

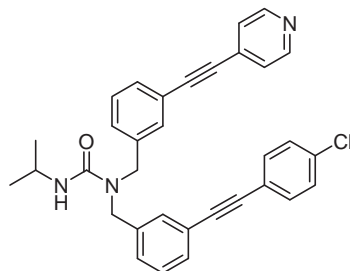


A majority of cell lines in the NCI-60 are inhibited with an average $GI_{50} = 3.13 \mu\text{M}$. Selective toxicity against human colon cancer cell lines (COLO 205, HCC-2998, HCT-116, HT29, KM12) was also exhibited (LC_{50} 's = 6–10 μM).

**Trisubstituted ureas as potent and selective mPGES-1 inhibitors**

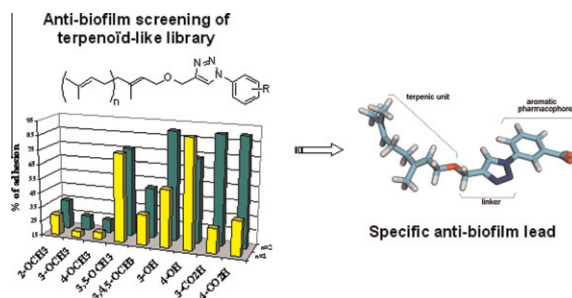
pp 1488–1492

Jean-François Chiasson*, Louise Boulet, Christine Brideau, Anh Chau, David Claveau, Bernard Côté, Diane Ethier, André Giroux, Jocelyne Guay, Sébastien Guiral, Joseph Mancini, Frédéric Massé, Nathalie Méthot, Denis Riendeau, Patrick Roy, Joel Rubin, Daigen Xu, Hongping Yu, Yves Ducharme, Richard W. Friesen

**Targeting bacterial biofilms: Design of a terpenoid-like library as non-toxic anti-biofilm compounds**

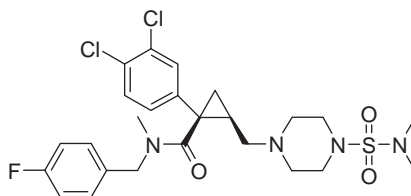
pp 1493–1497

Cheikh Sall, Linda Dombrowsky, Olivier Bottzeck, Annie Praud-Tabariès, Yves Blache*

**Identification of a new series of non-peptidic NK_3 receptor antagonists**

pp 1498–1501

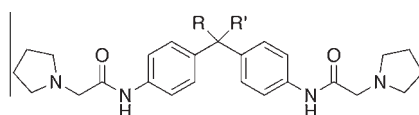
Karsten Juhl*, Tore Hansen, Jan Kehler, Nikolay A. Khanzhin, Morten B. Nørgaard, Thomas Ruhland, Dorrit B. Larsen, Klaus G. Jensen, Björn Steiniger-Brach, Søren M. Nielsen, Klaus B. Simonsen



Synthesis of GN8 derivatives and evaluation of their antiprion activity in TSE-infected cells

pp 1502–1507

Tsutomu Kimura, Junji Hosokawa-Muto, Yuji O. Kamatari, Kazuo Kuwata*



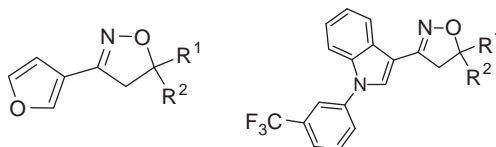
Antiprion Compounds
 $IC_{50} = 0.51\text{--}0.83 \mu\text{M}$ (GT+FK cells)

A series of GN8 derivatives were synthesized, and their antiprion activity was tested in TSE-infected mouse neuronal cells. GN8 derivatives bearing substituents at the benzylic position exhibited an improved antiprion activity with the IC_{50} values of 0.51–0.83 μM .

**Synthesis and biological activity of novel MIF antagonists**

pp 1508–1511

Sarala Balachandran*, Pradip K. Gadekar, Santosh Parkale, Vitthal N. Yadav, Divya Kamath, Sneha Ramaswamy, Somesh Sharma, Ram A. Vishwakarma, Nilesh M. Dagia

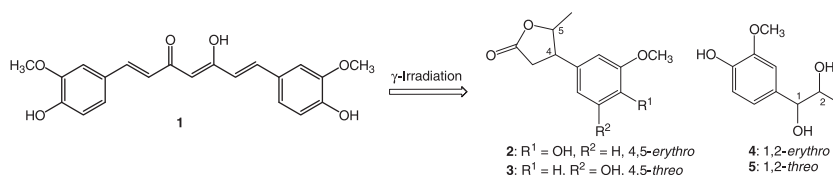


Two series of novel furan and indole compounds were synthesized and probed for inhibition of macrophage migration inhibitory factor (MIF) activity. Several compounds from both series inhibited the activity of MIF at levels equal to or significantly better than ISO-1 (an early MIF inhibitor). The majority of the compounds that robustly inhibited the spontaneous secretion/release/recognition of MIF from freshly isolated human peripheral blood mononuclear cells were from the furan series (compounds **5**, **9**, **13**, **15**, and **16**). In contrast, compounds that markedly inhibited the MIF-induced production of pro-inflammatory cytokines were predominantly from the indole series (compounds **26**, **29**, and **32**).

**Enhancement of pancreatic lipase inhibitory activity of curcumin by radiolytic transformation**

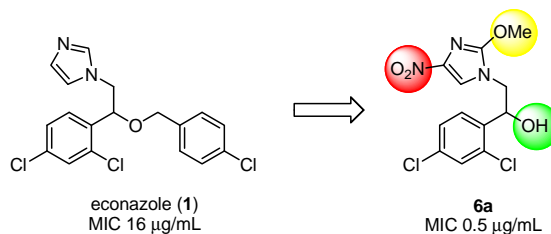
pp 1512–1514

Tae Hoon Kim*, Jae Kyung Kim, Hideyuki Ito, Cheorun Jo*

**Synthesis and antitubercular activity of monocyclic nitroimidazoles: Insights from econazole**

pp 1515–1518

Sang-Ho Lee, Suhyun Kim, Min-Han Yun, Yong Sup Lee, Sang-Nae Cho, Taegwon Oh, Pilho Kim*



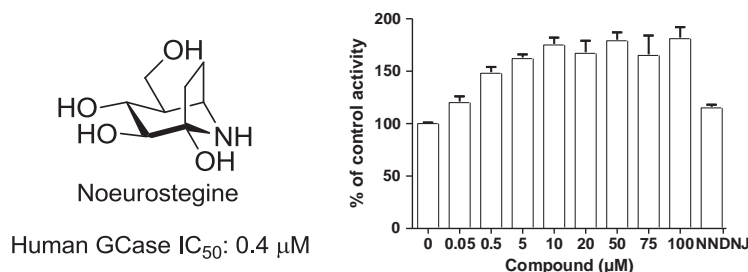
Econazole-derived nitroimidazoles were designed and synthesized as antitubercular agents.



Synthesis of N-alkylated neurostegines and evaluation of their potential as treatment for Gaucher's disease

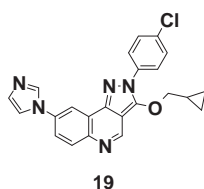
pp 1519–1522

Tina S. Rasmussen, Sarah Allman, Gabriele Twigg, Terry D. Butters*, Henrik H. Jensen*

**Exploring subtype selectivity and metabolic stability of a novel series of ligands for the benzodiazepine binding site of the GABA_A receptor**

pp 1523–1526

Samuel Hintermann*, Konstanze Hurth, Joachim Nozulak, Marina Tintelnot-Blomley, Reiner Aichholz, Joachim Blanz, Klemens Kaupmann, Johannes Mosbacher

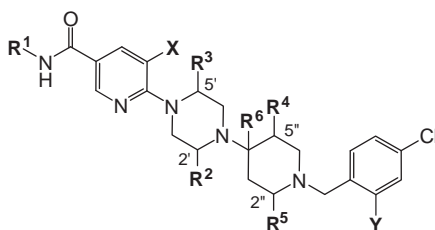


A novel series of agonists at the benzodiazepine binding site of the GABA_A receptor based on CGS-9896 was identified. SAR work and efforts to increase metabolic stabilities are described which led to the identification of potent agonists such as **19** with selectivities either for α2- or α1-containing GABA_A receptors.

II. SAR studies of pyridyl-piperazinyl-piperidine derivatives as CXCR3 chemokine antagonists

pp 1527–1531

Yuefei Shao*, Gopinadhan N. Anilkumar*, Carolyn DiIanni Carroll, Guizhen Dong, James W. Hall III, Doug W. Hobbs, Yueheng Jiang, Chung-Her Jenh, Seong Heon Kim, Joseph A. Kozlowski, Brian F. McGuinness, Stuart B. Rosenblum, Inna Schulman, Neng-Yang Shih, Youheng Shu, Michael K. C. Wong, Wensheng Yu, Lisa Guise Zawacki, Qingbei Zeng



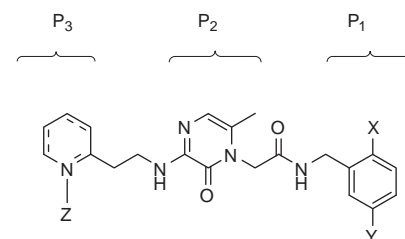
The structure–human CXCR3 binding affinity relationship of a series of pyridyl-piperazinyl-piperidine derivatives was explored.

P3 optimization of functional potency, in vivo efficacy and oral bioavailability in 3-aminopyrazinone thrombin inhibitors bearing non-charged groups at the P1 position

pp 1532–1535

Richard C. A. Isaacs*, Christina L. Newton, Kellie J. Cutrona, Swati P. Mercer, Bruce D. Dorsey, Colleen M. McDonough, Jacquelynn J. Cook, Julie A. Krueger, S. Dale Lewis, Bobby J. Lucas, Elizabeth A. Lyle, Joseph J. Lynch, Cynthia Miller-Stein, Maria T. Michener, Audrey A. Wallace, Rebecca B. White, Bradley K. Wong

A series of 3-aminopyrazinone P2 thrombin inhibitors bearing non-charged groups (X, Y) at the P1 benzylamino position was optimized with respect to functional potency, in vivo efficacy and oral bioavailability by manipulation of polarity at the P3 pyridine position (Z = H, piperidine; Z = O, pyridine-N-oxide).

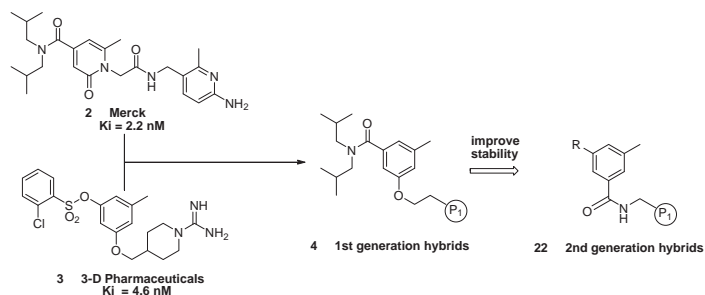


Design, synthesis and SAR of a series of 1,3,5-trisubstituted benzenes as thrombin inhibitors

pp 1536–1540

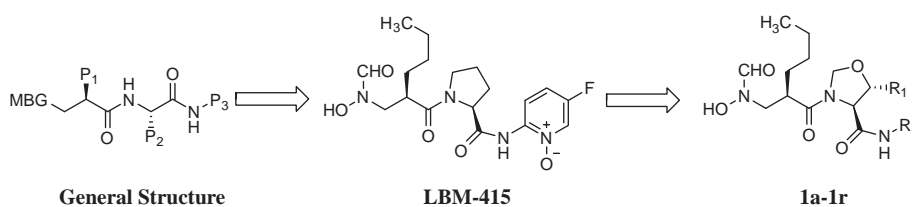
Richard C. A. Isaacs*, Christina L. Newton, Kellie J. Cutrona, Swati P. Mercer, Linda S. Payne, Kenneth J. Stauffer, Peter D. Williams, Jacquelynn J. Cook, Julie A. Krueger, S. Dale Lewis, Bobby J. Lucas, Elizabeth A. Lyle, Joseph J. Lynch, Daniel R. McMasters, Adel M. Naylor-Olsen, Maria T. Michener, Audrey A. Wallace

Structure based design techniques were used to exploit the putative similarity in binding mode of an aminopyridinone thrombin inhibitor **2** and a trisubstituted benzene inhibitor **3** to generate a new lead inhibitor **4**. Further optimization led to the identification of a novel series of potent thrombin inhibitor **22** with improved physical, chemical stability and in vitro functional potency.

**Synthesis and in vitro antibacterial activity of oxazolidinone LBM-415 analogs as peptide deformylase inhibitors**

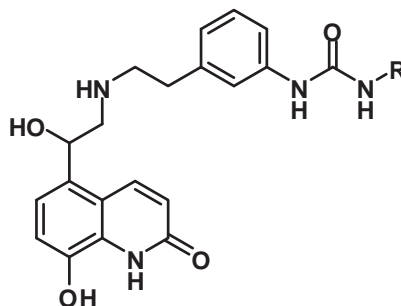
pp 1541–1544

Linliang Yu*, Weicheng Zhou, Zhenyu Wang

**Discovery of substituted phenyl urea derivatives as novel long-acting β_2 -adrenoreceptor agonists**

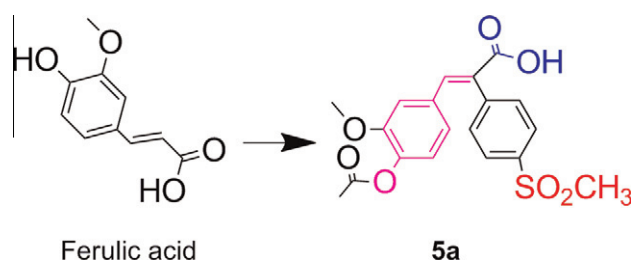
pp 1545–1548

Daniel Pérez*, Maribel Crespo, Laia Solé, Maria Prat, Carla Carcasona, Elena Calama, Raquel Otal, Amadeu Gavaldá, Mireia Gómez-Angelats, Montserrat Miralpeix, Carles Puig

**Design, synthesis and biological evaluation of novel 4-hydroxybenzene acrylic acid derivatives**

pp 1549–1553

Jin-Long Mao, Xiang-Kai Ran*, Jing-Zhen Tian, Bo Jiao, Hong-Lei Zhou, Li Chen, Zhen-Guo Wang

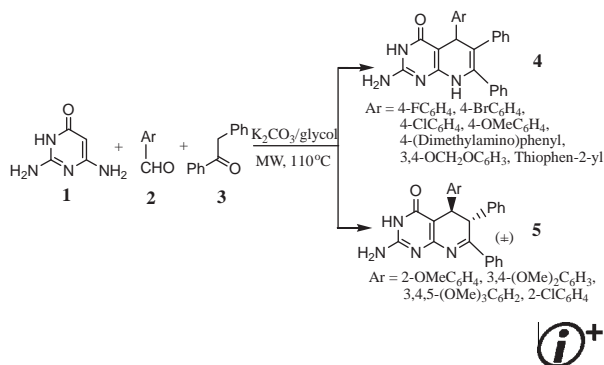


Substrate-controlled chemoselective synthesis and potent cytotoxic activity of novel 5,6,7-triarylpyrido[2,3-d]pyrimidin-4-one derivatives

pp 1554–1558

Feng Shi, Jie Ding, Shu Zhang, Wen-Juan Hao, Chuang Cheng, Shujiang Tu*

The substrate-controlled chemoselective synthesis of novel 5,6,7-triarylpyrido[2,3-d]pyrimidin-4-one derivatives has been achieved via microwave-assisted three-component reactions. Their cytotoxic activities to carcinoma SW1116 and SGC7901 cells were assayed. Compound **4b** exhibited more potent and efficacious cytotoxicity to SGC7901 cells than doxorubicin hydrochloride as positive control.



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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