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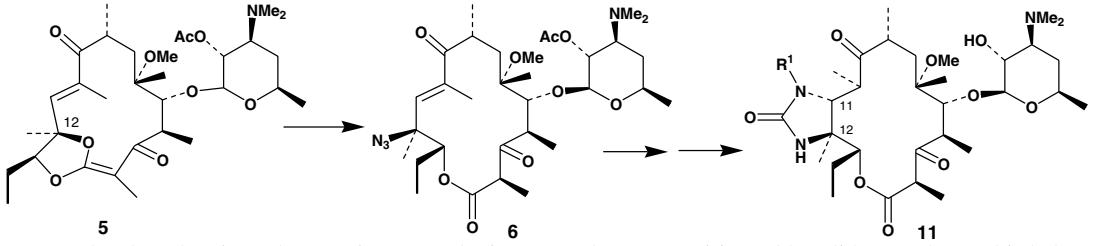
Bioorganic & Medicinal Chemistry Letters Vol. 17, No. 18, 2007

Contents

ARTICLES

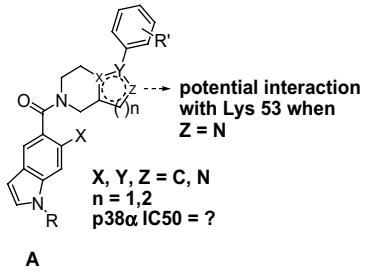
Synthesis and antibacterial activity of C11, C12-cyclic urea analogues of ketolides **pp 5013–5018**
Takushi Kaneko,* William McMillen and Meghan Keaney Lynch



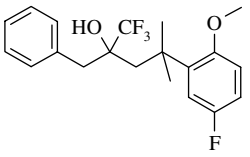
New chemistry was developed to introduce a nitrogen substituent at the C12 position of ketolide template. This led to syntheses of novel C11, C12-cyclic urea analogues of ketolides that exhibited potent in vitro antibacterial activity.

Synthesis and SAR of p38α MAP kinase inhibitors based on heterobicyclic scaffolds **pp 5019–5024**
T. G. Murali Dhar,* Stephen T. Wrobleski, Shuqun Lin, Joseph A. Furch, David S. Nirschl, Yi Fan, Gordon Todderud, Sidney Pitt, Arthur M. Doweyko, John S. Sack, Arvind Mathur, Murray McKinnon, Joel C. Barrish, John H. Dodd, Gary L. Schieven and Katerina Leftheris

The synthesis and structure–activity relationships (SAR) of p38α MAP kinase inhibitors based on heterobicyclic scaffolds are described. This effort led to the identification of compound (**21**) as a potent inhibitor of p38α MAP kinase. X-ray co-crystallography of an oxalamide analog (**24**) bound to unphosphorylated p38α is also disclosed.



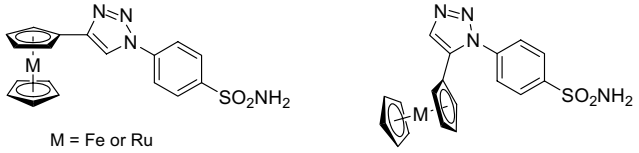
Identification of dissociated non-steroidal glucocorticoid receptor agonists **pp 5025–5031**
Daniel Kuzmich,* Tom Kirrane, John Proudfoot, Younes Bekkali, Renee Zindell, Laura Beck, Richard Nelson, Cheng-Kon Shih, Alison J. Kukulka, Zofia Paw, Patty Reilly, Rodney Deleon, Mario Cardozo, Gerald Nabozny and David Thomson



3

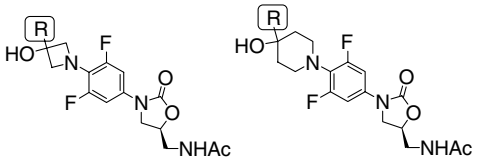
A new series of ligands for the glucocorticoid receptor (GR) is described. SAR development was guided by docking **3** into the GR active site and optimizing an unsubstituted phenyl ring for key interactions found in the steroid A-ring binding pocket.

Inhibition of carbonic anhydrase isozymes I, II and IX with benzenesulfonamides containing an organometallic moiety pp 5032–5035
Adam J. Salmon, Michael L. Williams, Alessio Innocenti, Daniela Vullo, Claudiu T. Supuran* and Sally-Ann Poulsen*



This manuscript describes the regioselective 1,3-DCR synthesis for both 1,4- and 1,5-disubstituted-1,2,3-triazole benzenesulfonamides from ethynylmetallocene substrates.

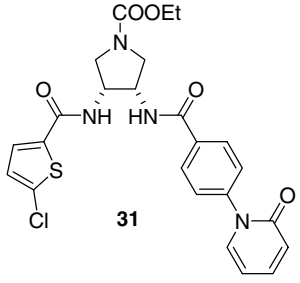
A distal methyl substituent attenuates mitochondrial protein synthesis inhibition in oxazolidinone antibacterials pp 5036–5040
Adam R. Renslo,* Andy Atuegbu, Prudencio Herradura, Priyadarshini Jaishankar, Mingzhe Ji, Karen L. Leach, Michael D. Huband, Michael R. Dermyer, Luping Wu, J. V. N. Vara Prasad and Mikhail F. Gordeev



Oxazolidinone analogs bearing substituted piperidine or azetidine C-rings are described. Analogs with a methyl group at the 3-position of the azetidine ring or the 4-position of the piperidine ring exhibited reduced mitochondrial protein synthesis inhibition while retaining good antibacterial potency.

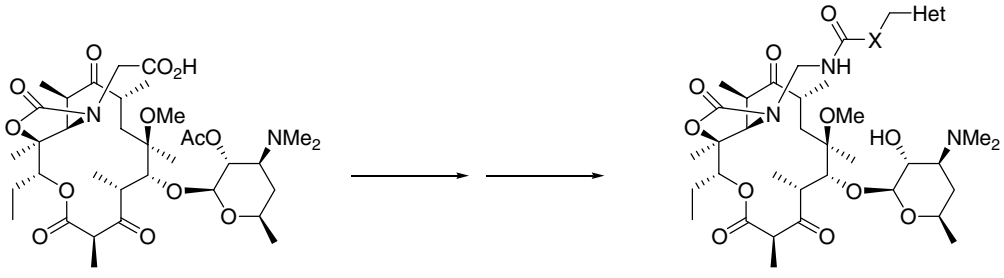
Enantiopure five-membered cyclicdiamine derivatives as potent and selective inhibitors of factor Xa. Improving in vitro metabolic stability via core modifications pp 5041–5048
Jennifer X. Qiao,* Tammy C. Wang, Gren Z. Wang, Daniel L. Cheney, Kan He, Alan R. Rendina, Baomin Xin, Joseph M. Luettgen, Robert M. Knabb, Ruth R. Wexler and Patrick Y. S. Lam

We previously reported a series of enantiopure *cis*-(1*R*,2*S*)-cyclopentyldiamine derivatives as potent and selective inhibitors of Factor Xa (FXa). Herein, we describe our approach to improve the metabolic stability of this series via core modifications. Multiple resulting series of compounds demonstrated similarly high FXa potency and improved metabolic stability in human liver microsomes compared with the cyclopentyldiamide **1**. (3*R*,4*S*)-Pyrrolidinyldiamide **31** was the best overall compound with a human FXa K_i of 0.50 nM, a PT EC_{2x} of 2.1 μM in human plasma, a bioavailability of 25%, and a $t_{1/2}$ of 2.7 h in dogs. Further biochemical characterization of compound **31** is also presented.

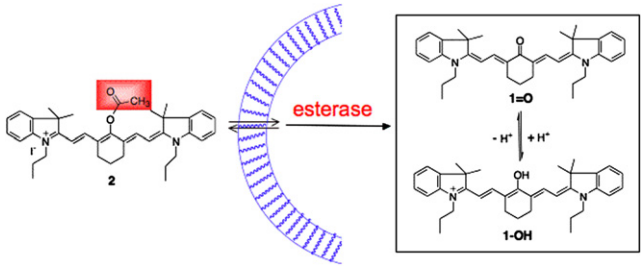


Novel tethers in ketolide antibiotics pp 5049–5053
Takushi Kaneko,* Karina Romero, Bryan Li and Richard Buzon

Novel tethers for ketolide analogues were developed using the Curtius rearrangement. The resulting compounds show potent in vitro and in vivo activity.

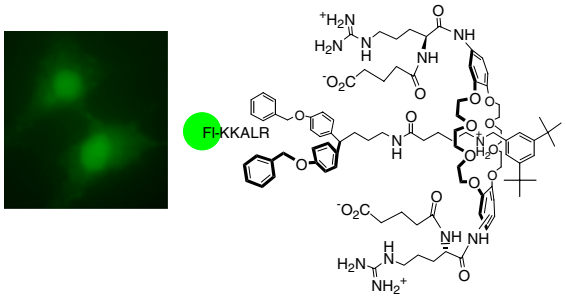


Membrane permeable esterase-activated fluorescent imaging probe **pp 5054–5057**
Youngmi Kim, Yongdoo Choi, Ralph Weissleder and Ching-Hsuan Tung*

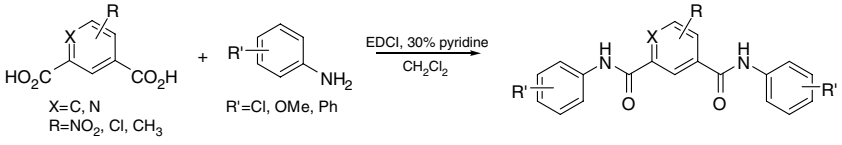


An esterase-triggered probe **2** derived from a cyanine-based pH sensitive dye was developed for cell labeling.

A host-rotaxane derivatized with carboxylic acids efficiently delivers a highly cationic fluoresceinated peptide **pp 5058–5062**
Jing Zhu, Brian E. House, Erin Fleck, Idit Isaacsohn, Angela F. Drew and David B. Smithrud*

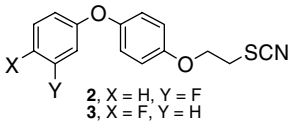


Cytotoxic small molecule dimers and their inhibitory activity against human breast cancer cells **pp 5063–5067**
M. Kyle Hadden and Brian S. J. Blagg*



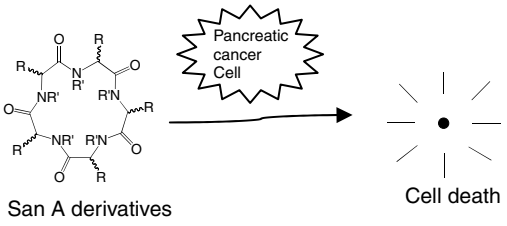
Small molecules based upon natural product dimers that exhibit cytotoxic activity were synthesized and evaluated for their anti-proliferative activity in human breast cancer cell lines.

Fluorine-containing aryloxyethyl thiocyanate derivatives are potent inhibitors of *Trypanosoma cruzi* and *Toxoplasma gondii* proliferation **pp 5068–5071**
Guadalupe García Liñares, Santiago Gismondi, Nicolás Osa Codesido, Silvia N. J. Moreno, Roberto Docampo and Juan B. Rodriguez*



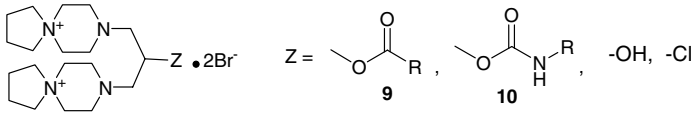
Fluorine-containing thiocyanate derivatives proved to be potent growth inhibitors of *Trypanosoma cruzi* and *Toxoplasma gondii*.

Identification of Sansalvamide a analog potent against pancreatic cancer cell lines **pp 5072–5077**
Po-Shen Pan, Kathleen L. McGuire and Shelli R. McAlpine*



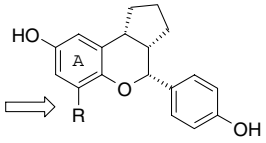
The potency of 31 Sansalvamide A derivatives in two pancreatic cancer cell lines is reported.

Unique spirocyclopiperazinium salt. Part 4: Modification of dispirocyclopiperazinium (DSPZ) salts as analgesics **pp 5078–5081**
Ang Li, Xin Wang, Cai-Qin Yue, Jia Ye, Chang-Ling Li and Run-Tao Li*



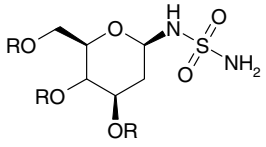
Compound **9**: R = Ph, inhibition of 117.0% in hot plate, dose 0.04 mmol/kg; **Z** = **OH**, inhibition of 88.9% in writhing test, inhibition of 91.8% in hot plate, dose 0.04 mmol/kg; **Z** = **Cl**, inhibition of 98.4%, dose 0.02 mmol/kg.

Benzopyrans as selective estrogen receptor β agonists (SERBAs). Part 4: Functionalization of the benzopyran A-ring **pp 5082–5085**
Bryan H. Norman,* Timothy I. Richardson, Jeffrey A. Dodge, Lance A. Pfeifer, Gregory L. Durst, Yong Wang, Jim D. Durbin, Venkatesh Krishnan, Sean R. Dinn, Shengquan Liu, John E. Reilly and Kendal T. Ryter



Structure activity relationship studies of the A-ring on the benzopyran scaffold.

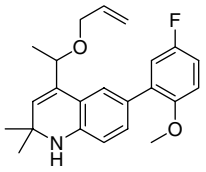
Carbonic anhydrase inhibitors. Inhibition of cytosolic isoforms I and II, and extracellular isoforms IV, IX, and XII with sulfamides incorporating sugar moieties **pp 5086–5090**
Pedro A. Colinas, Rodolfo D. Bravo, Daniela Vullo, Andrea Scozzafava and Claudiu T. Supuran*



R = Ac, Bn

Ki(CA II) = 6 -58 nM
Ki(CA IX) = 9 - 45 nM
Ki(CA XII) =5 - 32 nM

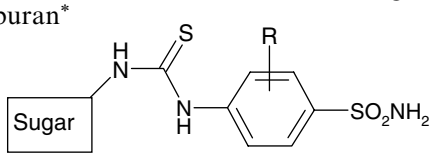
Discovery and SAR study of novel dihydroquinoline-containing glucocorticoid receptor agonists **pp 5091–5095**
Hidenori Takahashi,* Younes Bekkali, Alison J. Capolino, Thomas Gilmore, Susan E. Goldrick, Paul V. Kaplita, Lisa Liu, Richard M. Nelson, Donna Terenzio, Ji Wang, Ljiljana Zuvela-Jelaska, John Proudfoot, Gerald Nabozny and David Thomson



42 (+)- isomer: GR IC_{50} = 40 nM

The SAR study of novel class of glucocorticoid receptor agonist is reported.

Carbonic anhydrase inhibitors: Selective inhibition of the extracellular, tumor-associated isoforms IX and XII over isozymes I and II with glycosyl-thioureido-sulfonamides **pp 5096–5100**
Fatma-Zohra Smaine, Jean-Yves Winum,* Jean-Louis Montero, Zine Regainia, Daniela Vullo, Andrea Scozzafava and Claudiu T. Supuran*

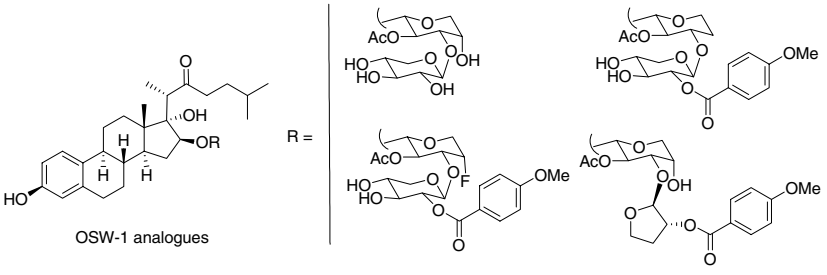


Sugar = glucose, galactose, mannose
R = H, F, Cl

Ki(CA II) = 0.8 -15 microM
Ki(CA IX) = 8 - 140 nM

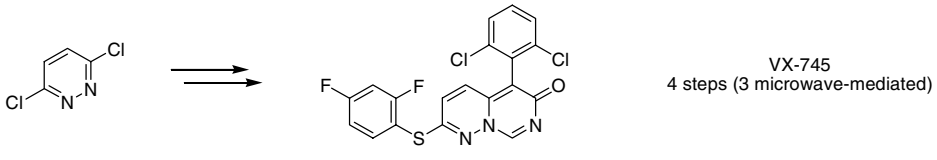
OSW-1 analogues: Modification of the carbohydrate moiety **pp 5101–5106**
Theophile Tschamber, Solange Adam, Yuji Matsuya, Seiji Masuda, Noriko Ohsawa, Sakiko Maruyama, Keiichi Kamoshita, Hideo Nemoto and Jacques Eustache*

Four new OSW-1 analogues with modified disaccharide moieties were synthesized and their cytotoxic activity against a range of cell lines was evaluated.



OSW-1 analogues

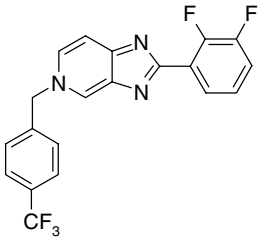
Rapid synthesis of VX-745: p38 MAP kinase inhibition in Werner syndrome cells **pp 5107–5110**
Mark C. Bagley,* Terence Davis,* Matthew C. Dix, Michal J. Rokicki and David Kipling*



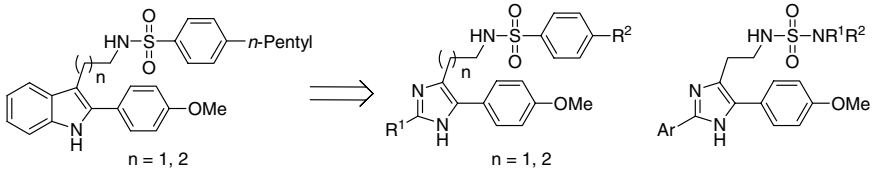
VX-745
4 steps (3 microwave-mediated)

A novel and efficient synthesis of VX-745 using primarily microwave dielectric heating is reported. Inhibition of p38α MAP kinase by VX-745 in Werner syndrome cells shows very high selectivity over the related JNK kinase.

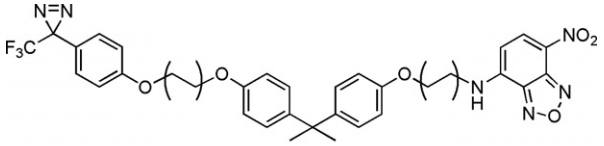
Antiviral 2,5-disubstituted imidazo[4,5-*c*]pyridines: Further optimization of anti-hepatitis C virus activity **pp 5111–5114**
Gerhard Puerstinger,* Jan Paeshuyse, Susanne Heinrich, Joachim Mohr, Nicole Schraffl, Erik De Clercq and Johan Neyts



Discovery of selective imidazole-based inhibitors of mammalian 15-lipoxygenase: Highly potent against human enzyme within a cellular environment **pp 5115–5120**
David S. Weinstein,* Wen Liu, Khehyong Ngu, Charles Langevine, Donald W. Combs, Shaobin Zhuang, Cindy Chen, Cort S. Madsen, Timothy W. Harper and Jeffrey A. Robl



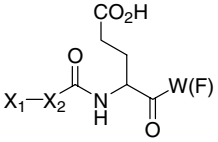
Synthesis of fluorescent and photoaffinity-labeled derivatives of bisphenol A and their inhibitory activity toward hypoxic expression of erythropoietin **pp 5121–5124**
Nobuhiro Maezawa, Hiroshi Tsuchikawa, Shigeo Katsumura,* Tomoko Kubo and Susumu Imaoka*



4

The synthesis of bisphenol A derivatives which have a fluorescent dye and a photo-reactive group and their biological evaluation are reported.

Tetrapeptide inhibitors of the glutamate vesicular transporter (VGLUT) **pp 5125–5128**
Sarjubhai A. Patel, Jon O. Nagy, Erin D. Bolstad, John M. Gerdes and Charles M. Thompson*

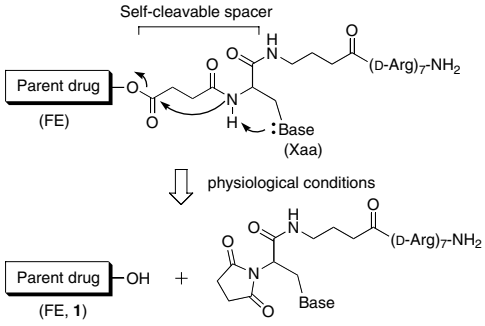


Tetrapeptides
$X_1X_2EW(F)$

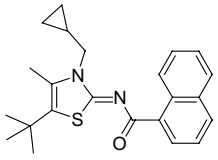
Inhibition of VGLUT by Tetrapeptides				
X_1	X_2	X_3	X_4	^{3}H-LGlu uptake (% of control)
D-Q	D-I	L -E	D-W	35 ± 3%
L-Q	D-I	L-E	D-W	28 ± 3%
D-W	L-N	D-E	D-F	41 ± 1%

Development of oligoarginine–drug conjugates linked to new peptidic self-cleavable spacers toward effective intestinal absorption pp 5129–5132
Yoshio Hayashi,* Kentaro Takayama, Yuka Suehisa, Takuya Fujita, Jeffrey-Tri Nguyen, Shiroh Futaki, Akira Yamamoto and Yoshiaki Kiso

New chemically triggered peptidic self-cleavable spacers were developed for drug-linked oligoarginine peptides.



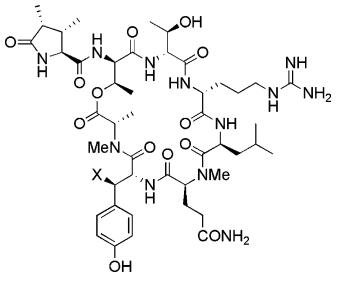
Sulfonamide derivatives as new potent and selective CB_2 cannabinoid receptor agonists pp 5133–5135
Hiroshi Ohta,* Tomoko Ishizaka, Mitsukane Yoshinaga, Aki Morita, Yasumitsu Tomishima, Yoshihisa Toda and Shuji Saito



CB_2 IC_{50} = 16 nM

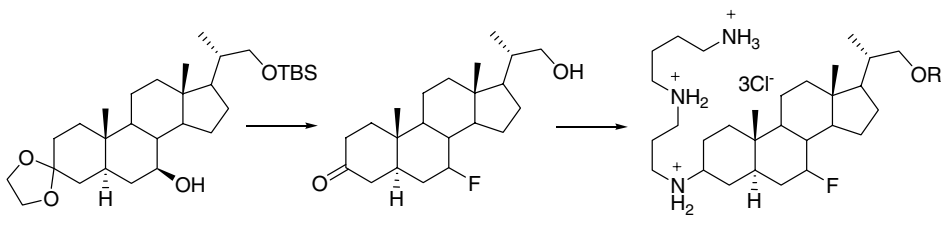
Compound **3f** exhibited high affinity for the human CB_2 receptor (CB_2 IC_{50} = 16 nM) and high selectivity for CB_2 over CB_1 (CB_1 IC_{50}/CB_2 IC_{50} = 106), and behaved as a full CB_2 receptor agonist in the [^{35}S]GTPγS binding assay (CB_2 EC_{50} = 7.2 nM, E_{max} = 100%).

Synthesis and cytotoxicity of desmethoxycallipeltin B: Lack of a quinone methide for the cytotoxicity of callipeltin B pp 5136–5138
Ravi Krishnamoorthy, Brooke L. Richardson and Mark A. Lipton*



1a, X=OCH_3 IC_{50}= 98±5 μM
1b, X=H IC_{50}= 128±10 μM

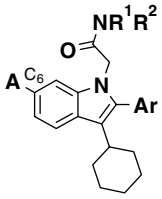
Synthesis and antimicrobial activity of 7-fluoro-3-aminosteroids pp 5139–5142
Sharaf Nawaz Khan, Bong Jin Kim and Hong-Seok Kim*



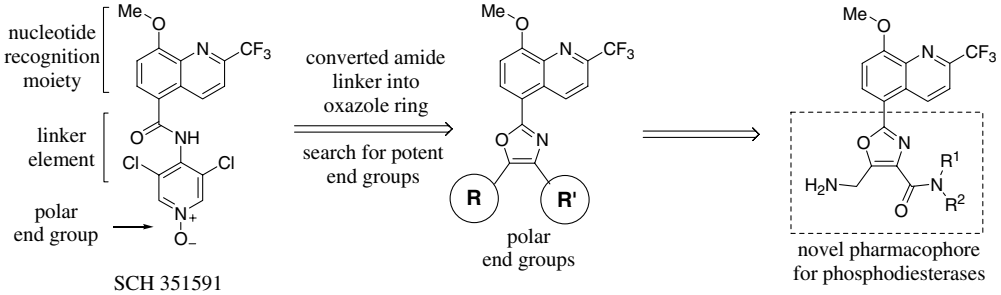
7 **14**: 7α-F; **15**: 7β-F **24 - 31**

Development of carboxylic acid replacements in indole-*N*-acetamide inhibitors of hepatitis C virus NS5B polymerase pp 5143–5149
Ian Stansfield,* Marco Pompei, Immacolata Conte, Caterina Ercolani, Giovanni Migliaccio, Mark Jairaj, Claudio Giuliano, Michael Rowley and Frank Narjes

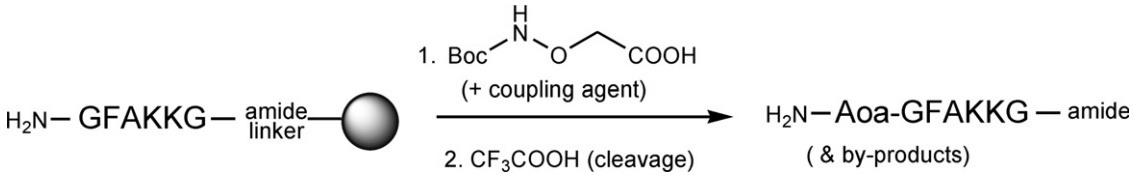
Allosteric inhibition of the hepatitis C virus (HCV) NS5B RNA-dependent RNA polymerase enzyme has recently emerged as a viable strategy toward blocking replication of viral RNA in cell-based systems. Here is described the optimization of potent indole-*N*-acetamides, bearing physicochemically diverse replacements for the C6 carboxylic acid, with reduced potential for formation of glucuronide conjugates.



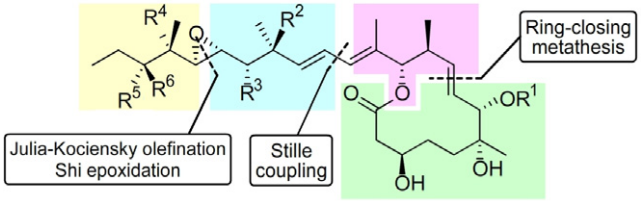
Discovery of a highly potent series of oxazole-based phosphodiesterase 4 inhibitors pp 5150–5154
Rongze Kuang,* Ho-Jane Shue, David J. Blythin, Neng-Yang Shih, Danlin Gu, Xiao Chen, John Schwerdt, Ling Lin, Pauline C. Ting, Xiaohong Zhu, Robert Aslanian, John J. Piwinski, Li Xiao, Daniel Prelusky, Ping Wu, Ji Zhang, Xiang Zhang, Chander S. Celly, Michael Minnicozzi, Motasim Billah and Peng Wang



Optimized synthesis of aminooxy-peptides as glycoprobe precursors for surface-based sugar–protein interaction studies pp 5155–5158
Carmen Jiménez-Castells, Beatriz G. de la Torre, Ricardo Gutiérrez Gallego and David Andreu*

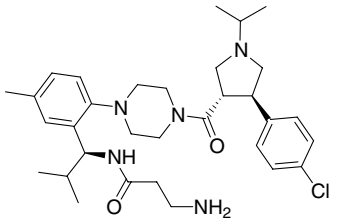


A synthetic entry to pladienolide B and FD-895 pp 5159–5164
Alexander L. Mandel, Brian D. Jones, James J. La Clair and Michael D. Burkart*



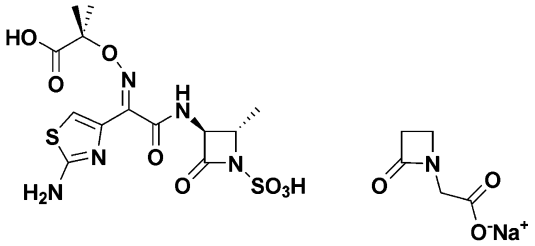
The synthesis of pladienolide B and FD-895 side-chains and undecenolide analogs are reported.

Pyrrolidines as potent functional agonists of the human melanocortin-4 receptor **pp 5165–5170**
Joe A. Tran, Caroline W. Chen, Wanlong Jiang, Fabio C. Tucci, Beth A. Fleck, Dragan Marinkovic, Melissa Arellano and Chen Chen*



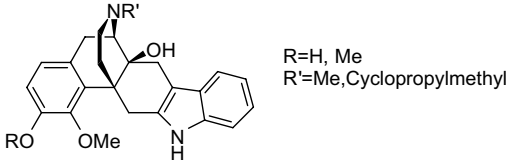
28c: K_i = 13 nM, EC_{50} = 6.9 nM, IA = 100%

A minimalistic approach to identify substrate binding features in B1 Metallo-β-lactamases **pp 5171–5174**
Andrés A. Poeylaut-Palena, Pablo E. Tomatis, Andreas I. Karsisiotis, Christian Damblon, Ernesto G. Mata* and Alejandro J. Vila*



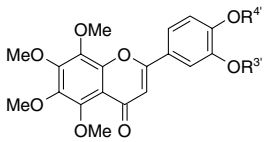
The 2-oxoazetidinylacetate sodium salt was synthesized as a model of a minimal β-lactam drug. This compound and the monobactam aztreonam were assayed as Metallo-β-lactamase substrate.

3-Hydroxy-4-methoxyindolomorphinans as delta opioid selective ligands **pp 5175–5176**
Trudy A. Smith, Linn N. Thatcher and Andrew Coop*



R=H, Me
R'=Me,Cyclopropylmethyl

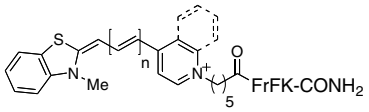
Anti-inflammatory property of the urinary metabolites of nobiletin in mouse **pp 5177–5181**
Shiming Li,* Shengmin Sang, Min-Hsiung Pan, Ching-Shu Lai, Chih-Yu Lo, Chung S. Yang and Chi-Tang Ho



$R^{3'}$ = H, Me; $R^{4'}$ = H, Me

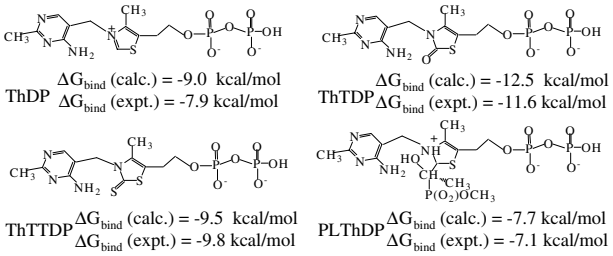
The identification and anti-inflammatory activity of nobiletin metabolites in mouse urine is reported.

Cyanine dye conjugates as probes for live cell imaging **pp 5182–5185**
Jay R. Carreon, Kelly M. Stewart, Kerry P. Mahon Jr., Stephanie Shin and Shana O. Kelley*



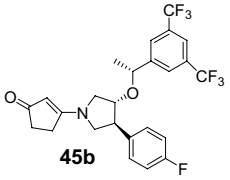
Theoretical calculation of the binding free energies for pyruvate dehydrogenase E1 binding with ligands **pp 5186–5190**
Ying Xiong, Yongjian Li, Hongwu He and Chang-Guo Zhan*

A promising computational protocol has been proposed to predict the binding free energies for the pyruvate dehydrogenase multienzyme complex (PDHc) E1 binding with its ligands.



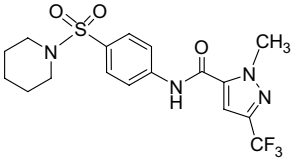
The discovery of potent, selective, and orally bioavailable hNK_1 antagonists derived from pyrrolidine **pp 5191–5198**
Peter Lin,* Lehua Chang, Robert J. DeVita, Jonathan R. Young, Ronsar Eid, Xinchun Tong, Song Zheng, Richard G. Ball, Nancy N. Tsou, Gary G. Chicchi, Marc M. Kurtz, Kwei-Lan C. Tsao, Alan Wheeldon, Emma J. Carlson, WaiSi Eng, H. Donald Burns, Richard J. Hargreaves and Sander G. Mills

SAR studies on amides, ureas, and vinylogous amides derived from pyrrolidine led to the discovery of several potent hNK_1 antagonists. One vinylogous amide (**45b**) had excellent potency, selectivity, pharmacokinetic profile, and functional activity in vivo. An in vivo rhesus macaque brain receptor occupancy PET study for compound **45b** revealed an estimated $Occ_{90} \sim 300$ ng/ml.



hNK1 IC_{50} = 0.11 nM

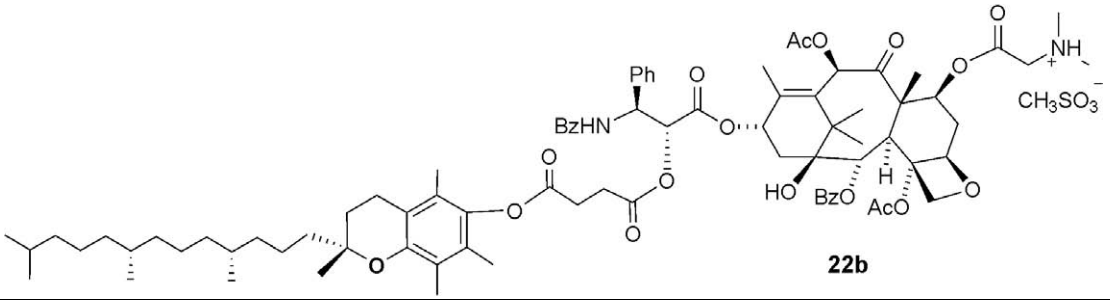
Non-nucleoside inhibitors of the measles virus RNA-dependent RNA polymerase complex activity: Synthesis and in vitro evaluation **pp 5199–5203**
Aiming Sun,* Nizal Chandrakumar, Jeong-Joong Yoon, Richard K. Plemper and James P. Snyder



Compound **14d**, IC_{50}= 12nM

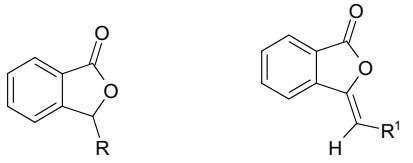
High-throughput screening has identified a nanomolar inhibitor of measles virus. A series of analogs have been synthesized and the most active compound, **14d** displayed low-nanomolar inhibition against the MV.

Antitumor agents. 258. Syntheses and evaluation of dietary antioxidant—taxoid conjugates as novel cytotoxic agents **pp 5204–5209**
Kyoko Nakagawa-Goto, Koji Yamada, Seikou Nakamura, Tzu-Hsuan Chen, Po-Cheng Chiang, Kenneth F. Bastow, Shao-Chun Wang, Bill Spohn, Mien-Chie Hung, Fang-Yu Lee, Fang-Chen Lee and Kuo-Hsiung Lee*



22b

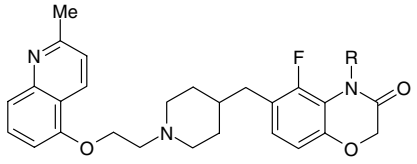
Synthesis, resolution, and antiplatelet activity of 3-substituted 1(3H)-isobenzofuranone **pp 5210–5213**
Hua Yang, Gao-Yun Hu,* Jun Chen, Yi Wang and Zhong-Hua Wang



6a-g **7a-g**

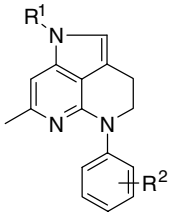
A series of 3-substituted-1(3H)-isobenzofuranone **6a**–**g** and **7a**–**g** were synthesized from phthalic anhydride. 3-alkyl-1(3H)-isobenzofuranone were resoluted. The antiplatelet activities of compounds were evaluated.

Studies on a series of potent, orally bioavailable, 5-HT_1 receptor ligands **pp 5214–5217**
Simon E. Ward,* Christopher N. Johnson, Peter J. Lovell, Claire M. Scott, Paul W. Smith, Geoffrey Stemp, Kevin M. Thewlis, Antonio K. Vong and Jeannette M. Watson



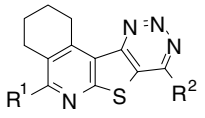
A series of selective 5-HT_{1ABD} ligands are described.

Novel substituted tetrahydrotriazaacenaphthylene derivatives as potent CRF_1 receptor antagonists **pp 5218–5221**
Gabriella Gentile,* Romano Di Fabio,* Francesca Pavone, Fabio Maria Sabbatini, Yves St-Denis, Maria Grazia Zampori, Giovanni Vitulli and Angela Worby



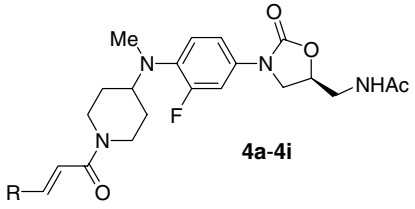
Novel unsaturated tetrahydrotriazaacenaphthylenes have been identified as potent and selective CRF_1 receptor antagonists showing good oral pharmacokinetic profile in rats.

Synthesis and SAR studies of novel antifungal 1,2,3-triazines **pp 5222–5226**
James C. A. Hunt, Emma Briggs, Eric D. Clarke and William G. Whittingham*



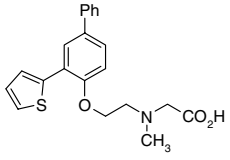
A range of pyridothieno-1,2,3-triazines with potent antifungal activity were prepared. By careful choice of substituents R^1 and R^2 activity was maintained and aqueous solubility significantly increased.

Synthesis and in vitro antibacterial activity of novel methylamino piperidinyl oxazolidinones **pp 5227–5232**
Brijesh Kumar Srivastava,* Rina Soni, Jayendra Z. Patel, Manish Solanki, Darshan Valani, Sunil Gupta, Bhupendra Mishra, Vijay Takale, Purvi Pandya, Mukul R. Jain and Pankaj R. Patel



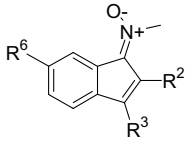
Design and synthesis of a few novel methylamino piperidinyl substituted oxazolidinones are reported and their antibacterial activities have been evaluated in MIC assay against broader panel of both susceptible and resistant Gram-positive strains.

Discovery and SAR studies of novel GlyT1 inhibitors **pp 5233–5238**
Magnus W. Walter,* Beth J. Hoffman, Kimberly Gordon, Kirk Johnson, Patrick Love, Matthew Jones, Teresa Man, Lee Phebus, Jon K. Reel, Helene C. Rudyk, Harlan Shannon, Kjell Svensson, Hong Yu, Matthew J. Valli and Warren J. Porter

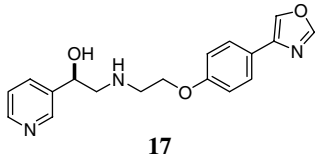


A novel series of GlyT1 inhibitors and their structure–activity Relationships (SAR) are described. Members of this series are highly potent and selective transport inhibitors which are shown to elevate glycine levels in cerebrospinal fluid.

Synthesis and structure–activity relationship of novel indene *N*-oxide derivatives as potent peroxisome proliferator activated receptor γ (PPARγ) agonists **pp 5239–5244**
Jin Hee Ahn,* Mi Sik Shin, Sun Ho Jung, Jin Ah Kim, Hye Min Kim, Se Hoan Kim, Seung Kyu Kang, Kwang Rok Kim, Sang Dal Rhee, Sung Dae Park, Jae Mok Lee, Jeong Hyung Lee, Hyae Gyeong Cheon* and Sung Soo Kim*



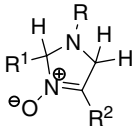
Discovery of potent and orally bioavailable heterocycle-based β_3-adrenergic receptor agonists, potential therapeutics for the treatment of obesity **pp 5245–5250**
Jennifer A. Lafontaine,* Robert F. Day, Joe Dibrino, John R. Hadcock, Diane M. Hargrove, Michael Linhares, Kelly A. Martin, Tristan S. Maurer, Nancy A. Nardone, David A. Tess and Paul DaSilva-Jardine



17

A novel series of heterocycle-based analogs were prepared and evaluated for their in vitro and in vivo biological activity as human β_3-adrenergic receptor (AR) agonists. Compound **17** showed excellent agonist potency at the β_3-AR, and a favorable pharmacokinetic profile in vivo. This compound increased rat oxygen consumption after oral administration, with an $ED_{20\%}$ of 2 mg/kg.

PASS-predicted design, synthesis and biological evaluation of cyclic nitrones as nootropics **pp 5251–5255**
Alka Marwaha, R. K. Goel* and Mohinder P. Mahajan*

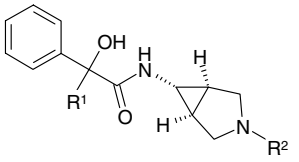


3

R = C_6H_4-OCH_3(*p*), Ph, cyclohexyl, benzyl, furyl
R^1 = Ph, C_6H_4-NMe_2(*p*)
R^2 = C_6H_4-NO_2(*p*)

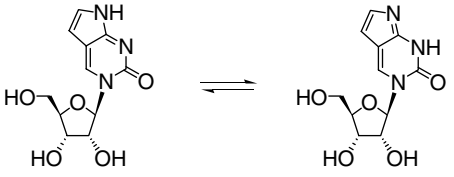
Some *N*-alkyl and *N*-aryl-substituted cyclic nitrones typified as **3** were designed with the help of PASS prediction, synthesized and evaluated pharmacologically as excellent nootropics/cognition enhancers.

Synthesis and optimization of novel and selective muscarinic M_3 receptor antagonists **pp 5256–5260**
Naresh Kumar,* Kirandeep Kaur, Shelly Aeron, Sankaranarayanan Dharmarajan, Arun D. V. Silamkoti, Anita Mehta, Suman Gupta, Anita Chugh, Jang B. Gupta, Mohammad Salman, Venkata P. Palle and Ian A. Cliffe



A series of constrained piperidine derivatives were synthesized as muscarinic M_3 receptor antagonists. In vitro evaluation of these compounds reveals high affinity for the M_3 receptor and high selectivity over the M_2 receptor.

Design and evaluation of a potential mutagen for Hepatitis C virus **pp 5261–5264**
Yung-Hyo Koh,* Jae Hoon Shim, Jean-Luc Girardet and Zhi Hong

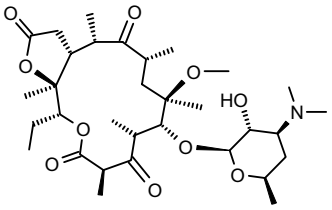


1 **1a**

Potential mutagen for HCV that could serve as a cytidine or a uridine.

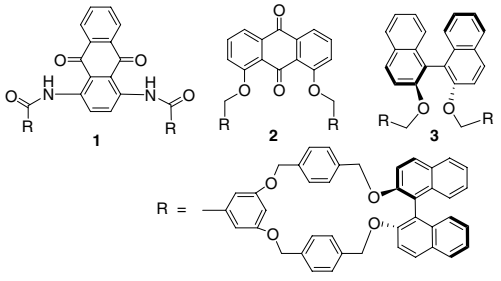
A novel ketolide class: Synthesis and antibacterial activity of a lead compound **pp 5265–5269**
Daniele Andreotti,* Ilaria Bientinesi, Stefano Biondi, Daniele Donati, Isabelle Erbetti, Sergio Lociuro, Carla Marchioro, Alfonso Pozzan, Emiliangelo Ratti and Silvia Terreni

1 (GW680788X)

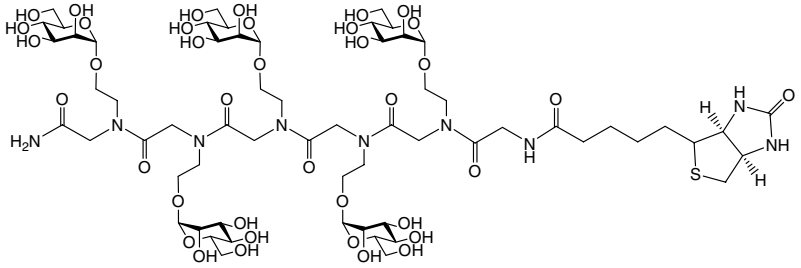


The synthesis of a novel ketolide class is reported together with the activity of its prototype GW680788X.

Synthesis and antibacterial activity of some novel chiral fluorophoric biscyclic macrocycles **pp 5270–5273**
Perumal Rajakumar,* Subramaniyan Selvam, Vellaisamy Shanmugaiah and Narayanasamy Mathivanan



Pentamer is the minimum structure for oligomannosylpeptoids to bind to concanavalin A **pp 5274–5278**
Hideya Yuasa,* Hiroyuki Honma, Hironobu Hashimoto, Miyuki Tsunooka and Kyoko Kojima-Aikawa



ELLA disclosed the smallest oligomannosylpeptoid recognized by ConA.

OTHER CONTENTS

Summary of instructions to authors **p I**
Errata **pp 5279–5280**
Retraction notice **p 5281**

*Corresponding author
Supplementary data available via ScienceDirect

COVER

Typical snapshot of **7b** bound to HIV-RT from an MC simulation. Carbon atoms of **7b** are gold; from the left, Tyr181, Tyr188, Phe227, Leu100, Lys101; Trp229 at the top, Val106 at the bottom. H-bond with Lys101 O on right. Some residues in front including Glu138 have been removed for clarity. The water on N5 is also H-bonded to a carboxylate O of Glu138. [Thakur, V. T.; Kim, J. T.; Hamilton, A. D.; Bailey, C. M.; Domaoal, R. A.; Wang, L.; Anderson, K. S.; Jorgensen, W. L. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5664.]

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