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# Bioorganic & Medicinal Chemistry Letters

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## Bioorganic & Medicinal Chemistry Letters Vol. 18, No. 24, 2008

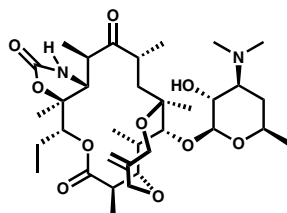
### Contents

#### ARTICLES

##### Synthesis of 3,6-bicyclolides: A novel class of macrolide antibiotics

pp 6315–6318

Yonghua Gai, Datong Tang\*, Guoyou Xu, Zhigang Chen, Alexander Polemeropoulos, Zhe Wang, Yat Sun Or



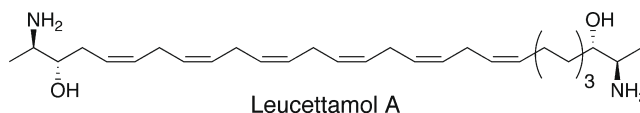
The synthesis of 3,6-bicyclolides from erythromycin A oxime is described. This novel class of bridged bicyclic macrolides demonstrates potent in vitro and in vivo activities against a broad spectrum of bacteria including resistant respiratory tract pathogens.



##### Leucettamol A: A new inhibitor of Ubc13-Uev1A interaction isolated from a marine sponge, *Leucetta aff. microrhaphis*

pp 6319–6320

Sachiko Tsukamoto\*, Tomoharu Takeuchi, Henki Rotinsulu, Remy E. P. Mangindaan, Rob W. M. van Soest, Kazuyo Ukai, Hisayoshi Kobayashi, Michio Namikoshi, Tomihisa Ohta, Hideyoshi Yokosawa

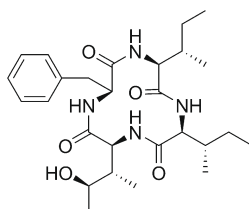


Leucettamol A is the first inhibitor of Ubc13-Uev1A interaction. Such inhibitors are presumed to be leads for anti-cancer agents that upregulate activity of the tumor suppressor p53 protein.

##### New cyclic tetrapeptides from *Nonomuraea* sp. TA-0426 that inhibit glycine transporter type 1 (GlyT1)

pp 6321–6323

Yuichi Terui\*, Yi-wen Chu, Jun-ying Li, Tsutomu Ando, Takuya Fukunaga, Takeshi Aoki, Yoshihisa Toda



WSS2219

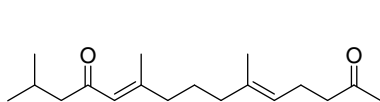
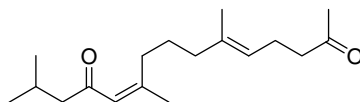
a selective inhibitor of GlyT1

IC<sub>50</sub> = 3.0 nM

**Vasodilatation effect of farnesylacetones, active constituents of *Sargassum siliquastrum*, on the basilar and carotid arteries of rabbits**

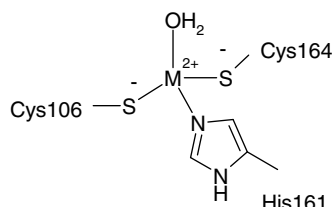
pp 6324–6326

Byong-Gon Park, Seong-Chun Kwon, Gab-Man Park, Jungyeob Ham, Woon-Seob Shin\*, Seokjoon Lee\*

(5E,10E)-6,10,14-trimethylpentadeca-5,10-diene-2,12-dione(**311**)(5E,10Z)-6,10,14-trimethylpentadeca-5,10-diene-2,12-dione(**312**)
**Carbonic anhydrase inhibitors. Inhibition of the  $\beta$ -class enzyme from the yeast *Saccharomyces cerevisiae* with anions**

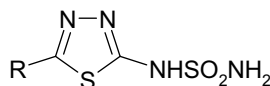
pp 6327–6331

Semra Isik, Feray Kockar\*, Oktay Arslan, Ozen Ozensoy Guler, Alessio Innocenti, Claudiu T. Supuran\*

 $K_I$  (iodide) = 10.3  $\mu$ M,  $K_I$  (sulfamide) = 8.7  $\mu$ M
**Carbonic anhydrase inhibitors: 2-Substituted-1,3,4-thiadiazole-5-sulfamides act as powerful and selective inhibitors of the mitochondrial isozymes VA and VB over the cytosolic and membrane-associated carbonic anhydrases I, II and IV**

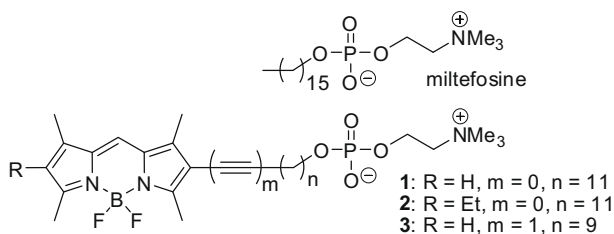
pp 6332–6335

Fatma-Zohra Smaine, Fabio Pacchiano, Marouan Rami, Véronique Barragan-Montero, Daniela Vullo, Andrea Scozzafava, Jean-Yves Winum\*, Claudiu T. Supuran\*

 $K_I$  = 4.2 – 32 nM (hCA VA) $K_I$  = 1.3 – 74 nM (hCA VB)
**Synthesis of BODIPY-labeled alkylphosphocholines with leishmanicidal activity, as fluorescent analogues of miltefosine**

pp 6336–6339

Valentín Hornillos, Eugenia Carrillo, Luis Rivas, Francisco Amat-Guerri\*, A. Ulises Acuña\*



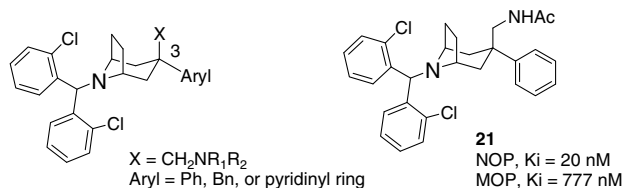
Highly fluorescent and photostable analogues of the leishmanicidal drug miltefosine have been prepared, in which the antiparasite activity has been preserved.



**Structure–activity relationships of 3-substituted *N*-benzhydryl-nortropane analogs as nociceptin receptor ligands for the treatment of cough**

pp 6340–6343

Shu-Wei Yang\*, Ginny Ho, Deen Tulshian, William J. Greenlee, Xiomara Fernandez, Robbie L. McLeod, Stephen Eckel, John Anthes

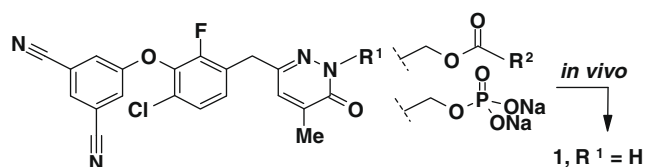


A series of 3-disubstituted-nortropane analogs have been identified to bind to the nociceptin receptor with high affinity. The syntheses and structure–activity relationships of these analogs are described.

**Orally bioavailable prodrugs of a BCS class 2 molecule, an inhibitor of HIV-1 reverse transcriptase**

pp 6344–6347

Todd R. Elworthy\*, James P. Dunn, J. Heather Hogg, Grace Lam, Y. David Saito, Tania M. P. C. Silva, Dimitrios Stefanidis, Witold Woroniecki, Eugenia Zhornisky, Amy S. Zhou, Klaus Klumpp

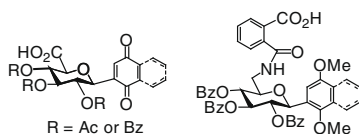


Pyridazinone **1** was derivatized into a series of hydroxymethyl esters, carbonates and one phosphate. These prodrugs were orally dosed to rats and afforded increases of 4.3- to 8.6-fold in 24-hour exposure of **1** (over that of parent) and not detected in blood plasma.

**β-C-Glycosiduronic acids and β-C-glycosyl compounds: New PTP1B inhibitors**

pp 6348–6351

Li Lin, Qiang Shen, Guo-Rong Chen\*, Juan Xie\*

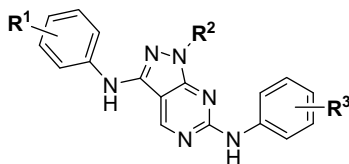


Benzoyl protected β-C-glycosyl compounds inhibit PTP1B with IC<sub>50</sub> in micromolar range.

**Identification and optimization of *N*<sup>3</sup>,*N*<sup>6</sup>-diaryl-1*H*-pyrazolo[3,4-*d*]pyrimidine-3,6-diamines as a novel class of ACK1 inhibitors**

pp 6352–6356

David J. Kopecky\*, Xiaolin Hao, Yi Chen, Jiasheng Fu, XianYun Jiao, Juan C. Jaen, Mario G. Cardozo, Jinsong Liu, Zhulun Wang, Nigel P. C. Walker, Holger Wesche, Shyun Li, Ellyn Farrelly, Shou-Hua Xiao, Frank Kayser\*

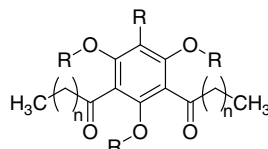


A new series of pyrazolo[3,4-*d*]pyrimidine-3,6-diamines was designed and synthesized as potent and selective inhibitors of the nonreceptor tyrosine kinase, ACK1. These compounds arose from efforts to rigidify an earlier series of *N*-aryl pyrimidine-5-carboxamides. The synthesis and structure–activity relationships of this new series of inhibitors are reported. The most promising compounds were also profiled for their pharmacokinetic properties.

**Discovery of diacylphloroglucinols as a new class of GPR40 (FFAR1) agonists**

pp 6357–6361

Sandip B. Bharate, Atish Rodge, Rajendra K. Joshi, Jaspreet Kaur, Shaila Srinivasan, S. Senthil Kumar, Asha Kulkarni-Almeida, Sarala Balachandran, Arun Balakrishnan, Ram A. Vishwakarma\*



$n = 0-15$ ;  $R = H$ , Alkyl

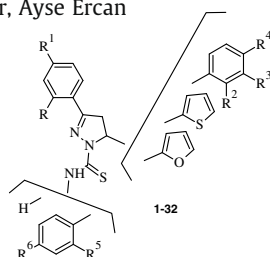
**19**:  $n = 9$ ,  $R = H$ ;  $EC_{50}$  0.07  $\mu M$ ,  $pEC_{50}$  7.12

Discovery of diacylphloroglucinols as a new class of GPR40 agonists is reported.

**Pyrazoline-based mycobactin analogues as MAO-inhibitors**

pp 6362–6368

Venkatesan Jayaprakash\*, Barij N. Sinha, Gulberk Ucar, Ayse Ercan

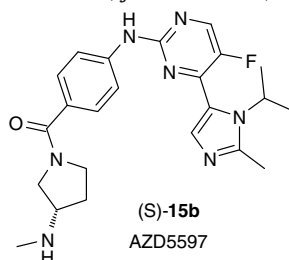


Thirty-two member pilot library of pyrazolines, synthesized as mycobactin analogues, were tested for MAO-inhibitory activity. Compound **7** ( $IC_{50}$ :  $2.84 \pm 0.19 \mu M$ ) and **11** ( $IC_{50}$ :  $19.45 \pm 1.02 \mu M$ ) were found to be potent and selective inhibitors of rat liver MAO-A and MAO-B, respectively. Docking studies revealed compound **11** as nonselective inhibitor of human MAO-A and MAO-B and others as selective towards human MAO-A.

**The discovery of AZD5597, a potent imidazole pyrimidine amide CDK inhibitor suitable for intravenous dosing**

pp 6369–6373

Clifford D. Jones\*, David M. Andrews, Andrew J. Barker, Kevin Blades, Paula Daunt, Simon East, Catherine Geh, Mark A. Graham, Keith M. Johnson, Sarah A. Loddick, Heather M. McFarland, Alexandra McGregor, Louise Moss, David A. Rudge, Peter B. Simpson, Michael L. Swain, Kin Y. Tam, Julie A. Tucker, Mike Walker

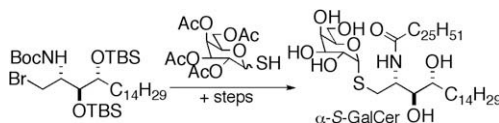


Describes the optimisation of an imidazole amide series, leading to the identification of (S)-**15b** (AZD5597) as a candidate for further development.

 **$\alpha$ -S-GalCer: Synthesis and evaluation for iNKT cell stimulation**

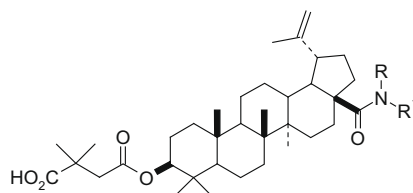
pp 6374–6376

Marisa L. Blauvelt, Maryam Khalili, Weonjoo Jaung, Janet Paulsen, Amy C. Anderson, S. Brian Wilson, Amy R. Howell\*



**Triterpene based compounds with potent anti-maturation activity against HIV-1****pp 6377–6380**

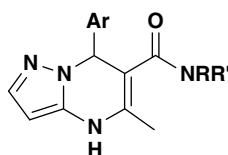
David Gerrish, In Chul Kim, Dange V. Kumar, Harry Austin, Jennifer E. Garrus, Vijay Baichwal, Michael Saunders, Rena S. McKinnon, Mark B. Anderson, Robert Carlson, Esther Arranz-Plaza, Kraig M. Yager \*



Efforts towards developing orally bioavailable HIV-1 maturation inhibitors starting from betulinic acid **1** are described. SAR resulted in improved potency, physicochemical properties, and enhanced oral absorption in rats.

**Dihydropyrazolopyrimidine Inhibitors of  $K_v1.5$  ( $I_{Kur}$ )****pp 6381–6385**

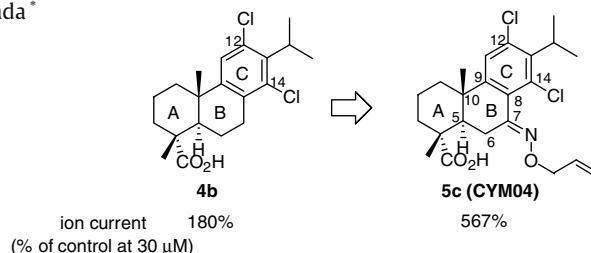
Wayne Vaccaro \*, Tram Huynh, John Lloyd, Karnail Atwal, Heather J. Finlay, Paul Levesque, Mary Lee Conder, Tonya Jenkins-West, Hong Shi, Lucy Sun



A series of dihydropyrazolopyrimidine inhibitors of  $K_v1.5$  ( $I_{Kur}$ ) have been identified. The synthesis, structure–activity relationships and selectivity against several other ion channels are described.

**Novel oxime and oxime ether derivatives of 12,14-dichlorodehydroabietic acid: Design, synthesis, and BK channel-opening activity****pp 6386–6389**

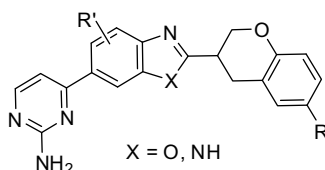
Yong-Mei Cui, Eriko Yasutomi, Yuko Otani, Takashi Yoshinaga, Katsutoshi Ido, Kohei Sawada, Masatoshi Kawahata, Kentaro Yamaguchi, Tomohiko Ohwada \*



The oxime ether structure, particularly when bearing O-short carbon chains, significantly increased the BK channel-opening activity of 12,14-dichlorodehydroabietic acid (**4b**).

**Benzimidazole- and benzoxazole-based inhibitors of Rho kinase****pp 6390–6393**

E. Hampton Sessions, Yan Yin, Thomas D. Bannister, Amiee Weiser, Evelyn Griffin, Jennifer Pocas, Michael D. Cameron, Claudia Ruiz, Li Lin, Stephan C. Schürer, Thomas Schröter, Philip LoGrasso, Yangbo Feng \*

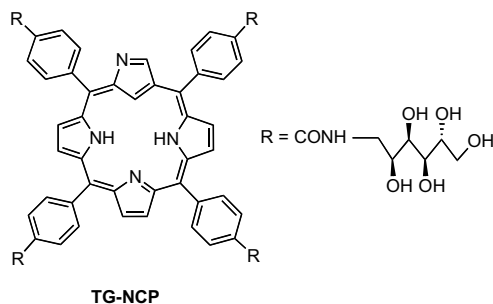


Rock inhibitors have been developed based on two distinct scaffolds, benzimidazoles and benzoxazoles. SAR studies and lead optimizations are described, which resulted in novel inhibitors of ROCK-II with excellent potency and selectivity.

### N-confused porphyrin possessing glucamine-appendants: Aggregation and acid/base properties in aqueous media

pp 6394–6397

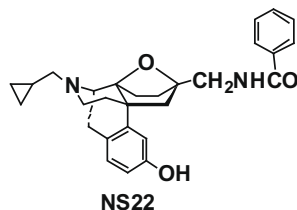
Yoshiya Ikawa, Hiroaki Ogawa, Hiroyuki Harada, Hiroyuki Furuta \*



### Synthesis of a novel 6,14-epoxymorphinan derivative and its pharmacology

pp 6398–6401

Toru Nemoto, Hideaki Fujii, Minoru Narita, Kan Miyoshi, Atsushi Nakamura, Tsutomu Suzuki, Hiroshi Nagase \*

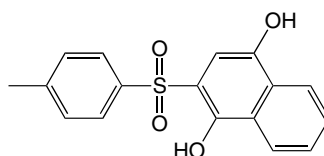


The antinociceptive effect of NS22 was evaluated in the tail-flick and the hot-plate test. NS22 showed a potent antinociceptive activity in mice (sc), which was attenuated with nor-BNI.

### Synthesis and biological evaluation of novel sulfonyl-naphthalene-1,4-diols as FabH inhibitors

pp 6402–6405

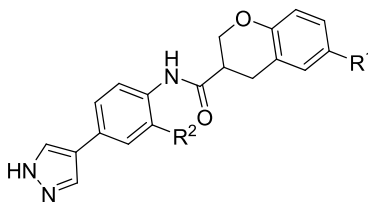
Mamoun M. Alhamadsheh, Norman C. Waters, Sarbjot Sachdeva, Patricia Lee, Kevin A. Reynolds \*



### Chroman-3-amides as potent Rho kinase inhibitors

pp 6406–6409

Yen Ting Chen, Thomas D. Bannister, Amiee Weiser, Evelyn Griffin, Li Lin, Claudia Ruiz, Michael D. Cameron, Stephan Schürer, Derek Duckett, Thomas Schröter, Philip LoGrasso, Yangbo Feng \*

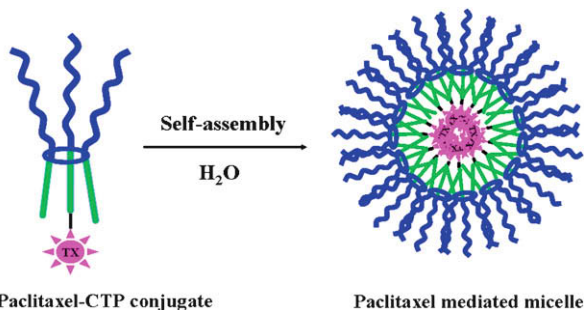


Here we report chroman-3-amides as potent ROCK inhibitors with sufficient kinase selectivity, cell permeability, stability, and desirable pharmacokinetic properties for study as potential therapeutic agents.

**A micellar prodrug of paclitaxel conjugated to cyclotriphosphazene**

pp 6410–6413

Yong Joo Jun, Jee Hyon Min, Da Eun Ji, Jin Hee Yoo, Ji Hyeon Kim, Hwa Jeong Lee, Byeongmoon Jeong, Youn Soo Sohn \*

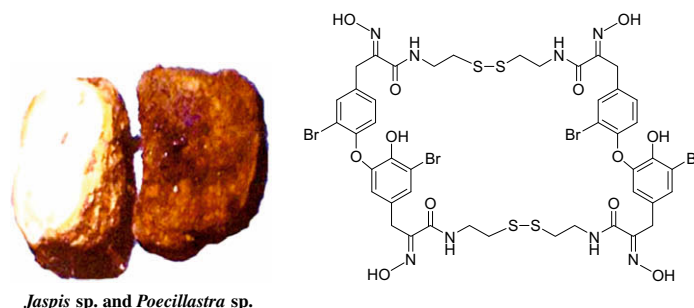


A novel biodegradable micelle-forming cyclotriphosphazene–paclitaxel conjugate was synthesized.

**Cytotoxic bromotyrosine derivatives from a two-sponge association of *Jaspis* sp. and *Poecillastra* sp.**

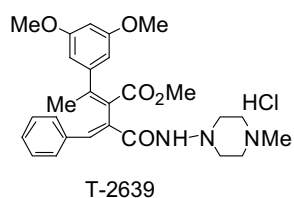
pp 6414–6418

Pramod B. Shinde, Yoon Mi Lee, Hung The Dang, Jongki Hong, Chong-O. Lee, Jee H. Jung \*

**Design, synthesis, and evaluation of orally active inhibitors of plasminogen activator inhibitor-1 (PAI-1) production**

pp 6419–6422

Hiroshi Miyazaki, Tsuyoshi Ogiku \*, Hiroshi Sai, Hiroshi Ohmizu, Jun Murakami, Akio Ohtani



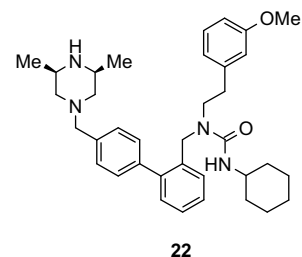
The design, synthesis, and evaluation of T-2639, orally active inhibitor of PAI-1 production, is reported.

**Identification of small molecule agonists of the motilin receptor**

pp 6423–6428

Tom D. Heightman \*, Elizabeth Conway, David F. Corbett, Gregor J. Macdonald, Geoffrey Stemp, Susan M. Westaway, Paolo Celestini, Stefania Gagliardi, Mauro Riccaboni, Silvano Ronzoni, Kalindi Vaidya, Sharon Butler, Fiona McKay, Alison Muir, Ben Powney, Kim Winborn, Alan Wise, Emma M. Jarvie, Gareth J. Sanger

High-throughput screening resulted in the identification of a series of novel motilin receptor agonists with relatively low molecular weights. The series originated from an array of biphenyl derivatives designed to target 7-transmembrane (7-TM) receptors. Further investigation of the structure–activity relationship within the series resulted in the identification of compound (22) as a potent and selective agonist at the motilin receptor.

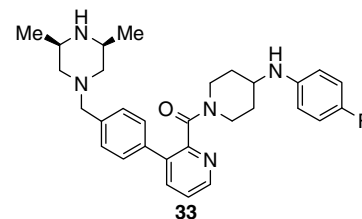


**The discovery of biaryl carboxamides as novel small molecule agonists of the motilin receptor**

pp 6429–6436

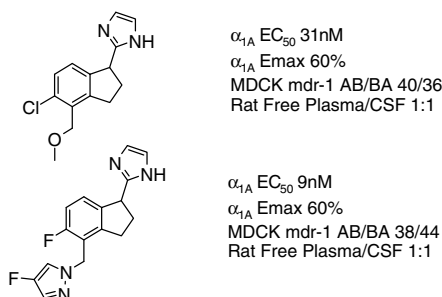
Susan M. Westaway\*, Samantha L. Brown, Elizabeth Conway, Tom D. Heightman, Christopher N. Johnson, Kate Lapsley, Gregor J. Macdonald, David T. MacPherson, Darren J. Mitchell, James W. Myatt, Jon T. Seal, Steven J. Stanway, Geoffrey Stemp, Mervyn Thompson, Paolo Celestini, Andrea Colombo, Alessandra Consonni, Stefania Gagliardi, Mauro Riccaboni, Silvano Ronzoni, Michael A. Briggs, Kim L. Matthews, Alexander J. Stevens, Victoria J. Bolton, Izzy Boyfield, Emma M. Jarvie, Sharon C. Stratton, Gareth J. Sanger

Optimisation of urea (**5**), identified from high throughput screening and subsequent array chemistry, has resulted in the identification of pyridine carboxamide (**33**) which is a potent motilin receptor agonist possessing favourable physicochemical and ADME profiles. Compound (**33**) has demonstrated prokinetic-like activity both in vitro and in vivo in the rabbit and therefore represents a promising novel small molecule motilin receptor agonist for further evaluation as a gastroprokinetic agent.

**Novel 2-imidazoles as potent, selective and CNS penetrant  $\alpha_{1A}$  adrenoceptor partial agonists**

pp 6437–6440

Lee R. Roberts\*, Justin Bryans, Kelly Conlon, Gordon McMurray, Alan Stobie, Gavin A. Whitlock

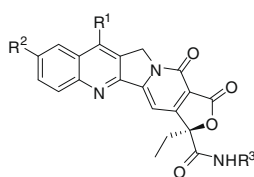


A series of novel 2-imidazoles is described, which combine potent and selective  $\alpha_{1A}$  partial agonist pharmacology with good CNS penetration.

**Semi-synthesis and biological activity of  $\gamma$ -lactones analogs of camptothecin**

pp 6441–6443

Mingzong Li, Weidong Tang, Fuxing Zeng, Liguang Lou\*, Tianpa You\*



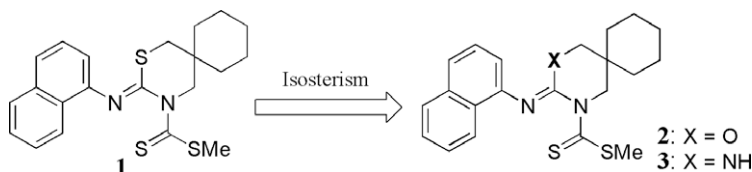
$\gamma$ -lactone of Camptothecin analogs

The semi-synthesis and antitumor activity of a series of  $\gamma$ -lactone of camptothecin analogs is reported.

**2-Arylimino-5,6-dihydro-4H-1,3-thiazines as a new class of cannabinoid receptor agonists. Part 3: Synthesis and activity of isosteric analogs**

pp 6444–6447

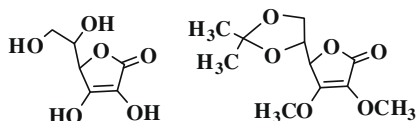
Hiroyuki Kai\*, Yasuhide Morioka, Yuji Koriyama, Kazuya Okamoto, Yasushi Hasegawa, Maki Hattori, Katsumi Koike, Hiroki Chiba, Shunji Shinohara, Yuka Iwamoto, Kohji Takahashi, Norihiko Tanimoto





**The effects of ascorbic acid on homolytic processes involving  $\alpha$ -hydroxyl-containing carbon-centered radicals** pp 6448–6450

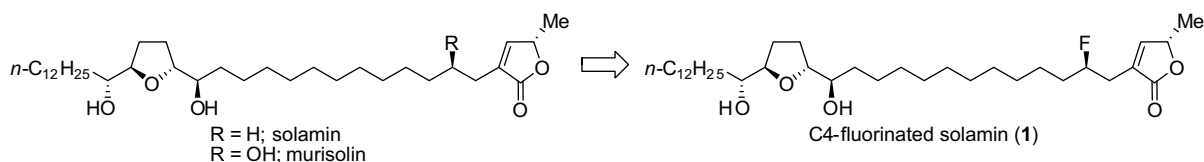
S. D. Brinkevich, O. I. Shadyro \*



Effects of ascorbic acid and 5,6-O-isopropylidene-2,3-O-dimethylascorbic acid on final product formation in radiolysis of ethanol, aqueous solutions of ethanol, ethylene glycol,  $\alpha$ -methylglycoside, maltose,  $\alpha$ -glycerophosphate, and  $\alpha$ -glucose phosphate were studied.

**Synthesis of C4-fluorinated solamins and their growth inhibitory activity against human cancer cell lines** pp 6451–6453

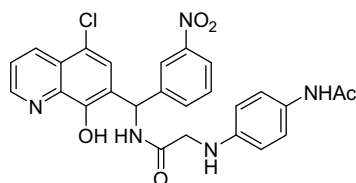
Naoto Kojima, Hiromi Hayashi, Satoshi Suzuki, Hiroaki Tominaga, Naoyoshi Maezaki, Tetsuaki Tanaka \*, Takao Yamori



C4-Fluorinated analogues of solamin, an antitumor acetogenin, were synthesized and investigated for their growth inhibitory activity against 39 tumor cell lines.

**N-((8-Hydroxy-5-substituted-quinolin-7-yl)(phenyl)methyl)-2-phenyloxy/amino-acetamide inhibitors of ADAMTS-5 (Aggrecanase-2)** pp 6454–6457

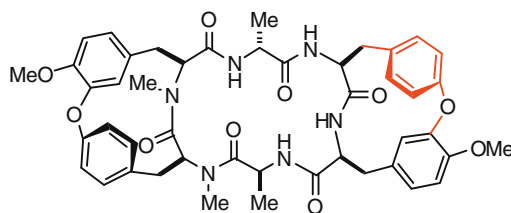
Adam M. Gilbert \*, Matthew G. Bursavich, Sabrina Lombardi, Katy E. Georgiadis, Erica Reifenberg, Carl R. Flannery, Elisabeth A. Morris



ADAMTS-5 IC<sub>50</sub>: 0.56  $\mu$ M  
ADAMTS-4 IC<sub>50</sub>: >22  $\mu$ M  
MMP-13 IC<sub>50</sub>: >100  $\mu$ M  
MMP-12 IC<sub>50</sub>: 25  $\mu$ M

**Design and synthesis of a bis(cycloisodityrosine) analogue of RA-VII, an antitumor bicyclic hexapeptide** pp 6458–6461

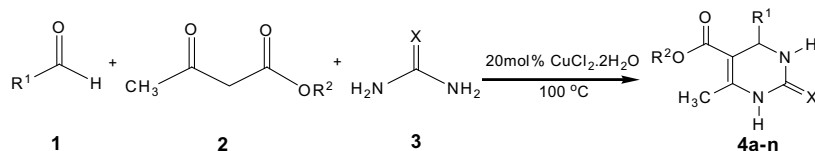
Ji-Ean Lee, Yukio Hitotsuyanagi, Yoshie Nakagawa, Saori Kato, Haruhiko Fukaya, Koichi Takeya \*



**Synthesis and in vitro evaluation of the antifungal activities of dihydropyrimidinones**

pp 6462–6467

Okram Mukherjee Singh\*, Sarangthem Joychandra Singh, Mutum Babita Devi, Laitonjam Nalini Devi, Nameirakpam Irabanta Singh, Sang-Gyeong Lee\*

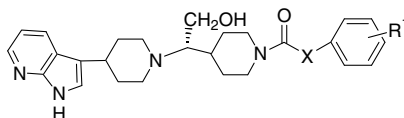


The synthesis of dihydropyrimidines under solvent-free conditions catalyzed by cupric chloride and their antifungal activities are reported.

**Synthesis and structure–activity relationship of 7-azaindole piperidine derivatives as CCR2 antagonists**

pp 6468–6470

Mingde Xia\*, Cuifen Hou, Duane DeMong, Scott Pollack, Meng Pan, Monica Singer, Michele Matheis, William Murray, Druie Cavender, Michael Wachter

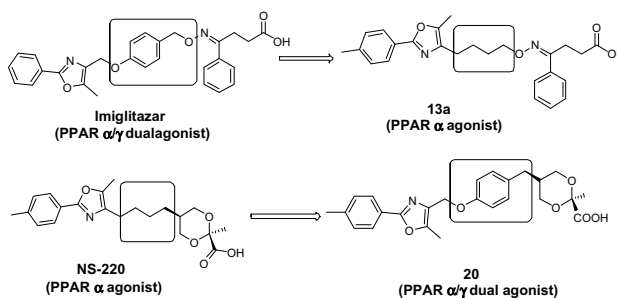


SAR studies led to the discovery of 7-azaindole piperidine derivatives as potent CCR2 antagonists displaying IC<sub>50</sub> values in the nanomolar range.

**Modulation of PPAR receptor subtype selectivity of the ligands: Aliphatic chain vs aromatic ring as a spacer between pharmacophore and the lipophilic moiety**

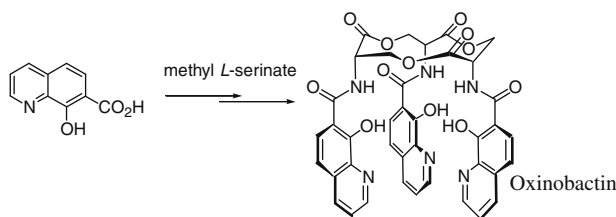
pp 6471–6475

Harikishore Pingali\*, Mukul Jain, Shailesh Shah, Pravin Patil, Pankaj Makadia, Pandurang Zaware, Kalapatapu V. V. M. Sairam, Jeevankumar Jamili, Ashish Goel, Megha Patel, Pankaj Patel

**Oxinobactin, a siderophore analogue to enterobactin involving 8-hydroxyquinoline subunits: Synthesis and iron binding ability**

pp 6476–6478

Amaury du Moulinet d'Hardemare\*, Nivine Alnaga, Guy Serratrice, Jean-Louis Pierre

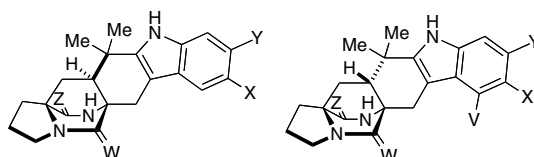


Synthesis of oxinobactin from 8-hydroxyquinoline and methyl-L-serinate. A new chiral siderophore analogue to enterobactin is reported and its iron complexing ability is evaluated by UV–vis spectrophotometric competitive studies.

**Calmodulin inhibitory activity of the malbrancheamides and various analogs**

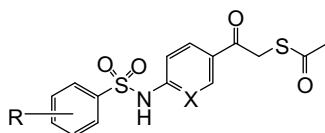
pp 6479–6481

Kenneth A. Miller, Mario Figueroa, Meriah W. N. Valente, Thomas J. Greshock, Rachel Mata, Robert M. Williams \*

 **$\alpha$ -Mercaptoketone based histone deacetylase inhibitors**

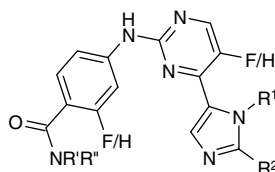
pp 6482–6485

Paul L. Wash, Timothy Z. Hoffman, Brandon M. Wiley, Céline Bonnefous, Nicholas D. Smith, Michael S. Sertic, Charles M. Lawrence, Kent T. Symons, Phan-Manh Nguyen, Kevin D. Lustig, Xin Guo, Tami Annable, Stewart A. Noble, Jeffrey H. Hager, Christian A. Hassig, James W. Malecha \*

The identification and lead optimization of a novel series of  $\alpha$ -mercaptoketone HDAC inhibitors is described.**Imidazole pyrimidine amides as potent, orally bioavailable cyclin-dependent kinase inhibitors**

pp 6486–6489

Clifford D. Jones \*, David M. Andrews, Andrew J. Barker, Kevin Blades, Kate F. Byth, M. Raymond V. Finlay, Catherine Geh, Clive P. Green, Marie Johannsen, Mike Walker, Hazel M. Weir

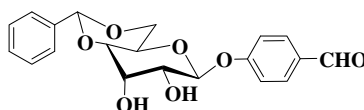


The SAR and optimisation of a novel series of imidazole pyrimidine amides is reported.

**Synthesis and biological evaluation of helcid analogues as mushroom tyrosinase inhibitors**

pp 6490–6493

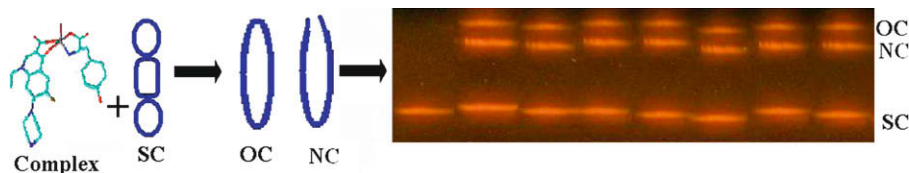
Wei Yi, Rihui Cao \*, Huan Wen, Qin Yan, Binhua Zhou, Yiqian Wan, Lin Ma, Huacan Song \*

**1c**A series of helcid analogues were synthesized and their inhibitory activities on the diphenolase activity of mushroom tyrosinase were investigated. Compound **1c** was found to be the most potent compound with IC<sub>50</sub> value of 0.052 mM.

### Five-coordinated oxovanadium(IV) complexes derived from amino acids and ciprofloxacin: Synthesis, spectral, antimicrobial, and DNA interaction approach

pp 6494–6500

M. N. Patel\*, S. H. Patel, M. R. Chhasatia, P. A. Parmar

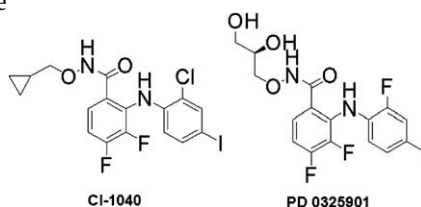


Synthesis of oxovanadium (IV), ciprofloxacin, and aminoacids. All the compounds were screened for antimicrobial activity in vitro and nuclease activity. Complexes exhibit comparable MIC values than standard drugs.

### The discovery of the benzhydroxamate MEK inhibitors CI-1040 and PD 0325901

pp 6501–6504

Stephen D. Barrett, Alexander J. Bridges, David T. Dudley, Alan R. Saltiel, James H. Fergus, Cathlin M. Flamme, Amy M. Delaney, Michael Kaufman, Sophie LePage, Wilbur R. Leopold, Sally A. Przybranowski, Judith Sebolt-Leopold, Keri Van Becelaere, Annette M. Doherty, Robert M. Kennedy, Dan Marston, W. Allen Howard Jr., Yvonne Smith, Joseph S. Warmus\*, Haile Tecle



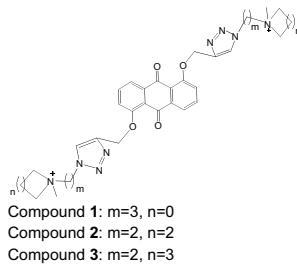
A novel series of benzhydroxamic esters were identified as potent MEK inhibitors. Optimization of these esters produced the two clinical candidates CI-1040 and PD 0325901.



### Novel anthraquinone derivatives: Synthesis via click chemistry approach and their induction of apoptosis in BGC gastric cancer cells via reactive oxygen species(ROS)-dependent mitochondrial pathway

pp 6505–6508

Shaoru Wang, Qilong Wang, Yan Wang, Lin Liu, Xiaocheng Weng, Guorui Li, Xiaolian Zhang, Xiang Zhou\*

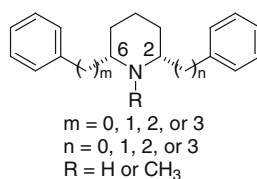


Three water soluble anthraquinone derivatives were synthesized via employing click chemistry and the mechanistic study of the apoptotic induction was conducted in this paper.

### Synthesis and evaluation of a series of homologues of lobelane at the vesicular monoamine transporter-2

pp 6509–6512

Guangrong Zheng, Linda P. Dwoskin, Agripina G. Deaciuc, Peter A. Crooks\*

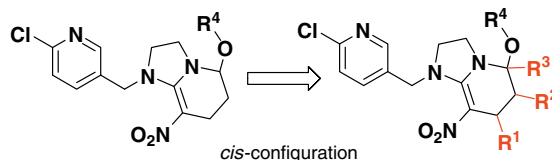


A series of lobelane homologues has been synthesized and evaluated for their [<sup>3</sup>H]DTBZ binding affinity at the vesicular monoamine transporter-2 (VMAT2). The structure-activity relationships (SAR) indicate that for retention of binding affinity at VMAT2, the lengths of the methylene linkers should be no shorter than one methylene unit at C-6 of the piperidine ring, and no shorter than two methylene units at C-2 of the piperidine ring. These results indicate that the intramolecular distances between the piperidine ring and two phenyl rings in lobelane analogues are an important criterion for retention of high affinity at VMAT2.

**cis-Nitromethylene neonicotinoids as new nicotinic family: Synthesis, structural diversity, and insecticidal evaluation of hexahydroimidazo[1,2- $\alpha$ ]pyridine**

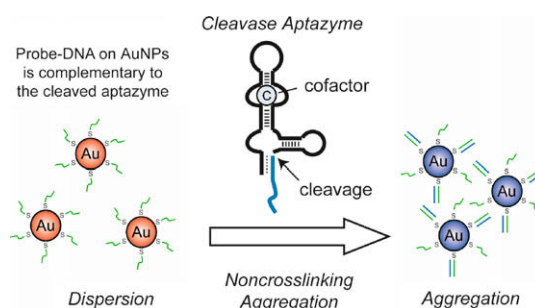
pp 6513–6516

Xusheng Shao, Wenwen Zhang, Yanqing Peng, Zhong Li\*, Zhongzhen Tian, Xuhong Qian\*

**Simple and rapid colorimetric detection of cofactors of aptazymes using noncrosslinking gold nanoparticle aggregation**

pp 6517–6520

Atsushi Ogawa\*, Mizuo Maeda\*

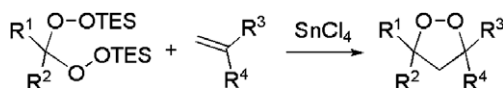


We easily detected cofactors of aptazymes using noncrosslinking gold nanoparticle aggregation.

**Synthesis of spiro-1,2-dioxolanes and their activity against *Plasmodium falciparum***

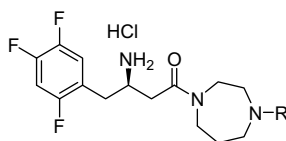
pp 6521–6524

Derek C. Martyn, Armando P. Ramirez, Meaghan J. Beattie, Joseph F. Cortese, Vishal Patel, Margaret A. Rush, K. A. Woerpel, Jon Clardy\*

A  $\text{SnCl}_4$ -mediated annulation was utilized to form a series of 1,2-dioxolanes, which were tested for activity against multiple strains of *Plasmodium falciparum*.**Synthesis and biological evaluation of homopiperazine derivatives with  $\beta$ -aminoacyl group as dipeptidyl peptidase IV inhibitors**

pp 6525–6529

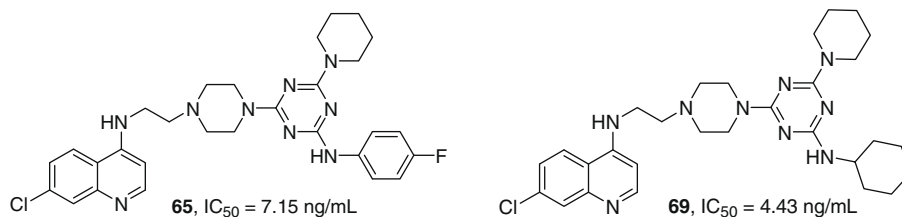
Jin Hee Ahn\*, Woul Seong Park, Mi Ae Jun, Mi Sik Shin, Seung Kyu Kang, Ki Young Kim, Sang Dal Rhee, Myung Ae Bae, Kwang Rok Kim, Sung Gyu Kim, Sun Young Kim, Sang Kwon Sohn, Nam Sook Kang, Jie Oh Lee, Duck Hyung Lee, Hyae Gyeong Cheon, Sung Soo Kim\*



**Synthesis and bioevaluation of hybrid 4-aminoquinoline triazines as a new class of antimalarial agents**

pp 6530–6533

Ashok Kumar, Kumkum Srivastava, S. Raja Kumar, S. K. Puri, Prem M. S. Chauhan\*

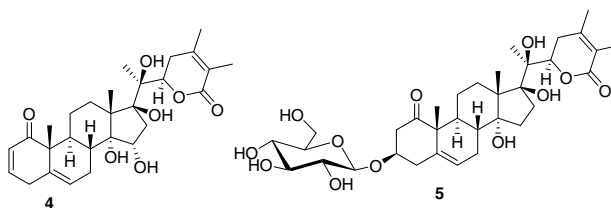


A series of new class of hybrid 4-aminoquinoline triazines were synthesized and screened against CQ sensitive strain 3D7 of *P. falciparum* in an in vitro model and CQ resistant strain N-67 of *P. yoelii* in an in vivo assay. The compounds **65** and **69** exhibited more than 99% suppression on day 4.

**Coagulanolide, a withanolide from *Withania coagulans* fruits and antihyperglycemic activity**

pp 6534–6537

Rakesh Maurya\*, Akanksha, Jayendra, Amar B. Singh, Arvind K. Srivastava

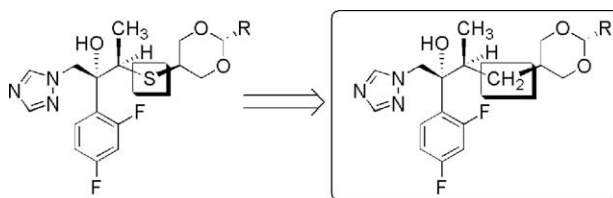


Isolation, structure elucidation of new compound **4** and antihyperglycemic activity of compounds **1–5** are reported.

**Carbon analogs of antifungal dioxane-triazole derivatives: Synthesis and in vitro activities**

pp 6538–6541

Takuya Uchida, Atsushi Somada, Yoshiko Kagoshima, Toshiyuki Konosu\*, Sadao Oida

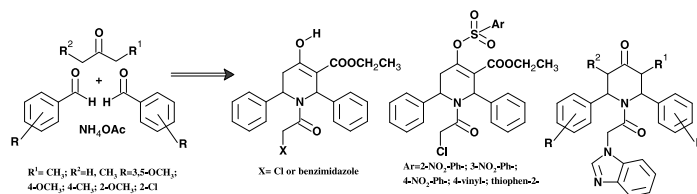


Stereoselective synthesis and in vitro antifungal activities of a novel series of triazole antifungal agents wherein the sulfur atom was replaced by a carbon atom are described.

**A facile synthesis, antibacterial, and antitubercular studies of some piperidin-4-one and tetrahydropyridine derivatives**

pp 6542–6548

Gopalakrishnan Aridoss, Shanmugasundaram Amirthaganesan, Nanjundan Ashok Kumar, Jong Tae Kim, Kwon Taek Lim, Senthamarakannan Kabilan, Yeon Tae Jeong\*



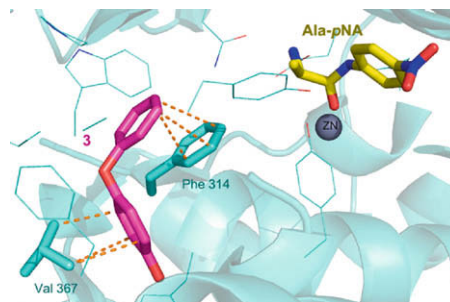
A series of substituted piperidones and tetrahydropyridine sulfonates were synthesized and explored for their antibacterial activities against sensitive and resistant organisms besides their antitubercular activity.



**Activation and inhibition of leukotriene A<sub>4</sub> hydrolase aminopeptidase activity by diphenyl ether and derivatives** pp 6549–6552

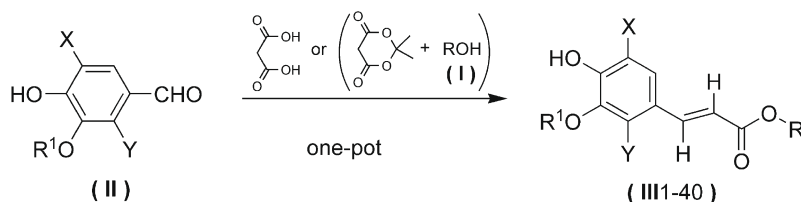
Xiaolu Jiang, Lu Zhou, Dengguo Wei, Hu Meng, Ying Liu\*, Luhua Lai\*

Diphenyl ether and derivatives can either activate or inhibit the aminopeptidase activity of leukotriene A<sub>4</sub> hydrolase, by binding at the hydrophobic pocket of LTA4H.

**Synthesis of *trans*-caffeate analogues and their bioactivities against HIV-1 integrase and cancer cell lines**

pp 6553–6557

Chun-nian Xia, Hai-bo Li, Feng liu, Wei-xiao Hu\*

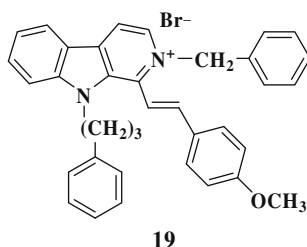


Forty caffeate analogues synthesized by one-pot methods were evaluated for their bioactivities. Four caffeate analogues possessed good HIV-IN inhibitory activities and several compounds showed good antitumor activities.

**Synthesis and cytotoxic activities of 1-benzylidene substituted  $\beta$ -carboline derivatives**

pp 6558–6561

Rihui Cao\*, Wei Yi, Qifeng Wu, Xiangdong Guan, Manxiu Feng, Chunming Ma, Zhiyong Chen, Huacan Song, Wenlie Peng\*

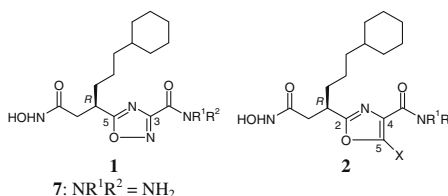
**19**

A series of new  $\beta$ -carboline derivatives, bearing a benzylidene substituent at position-1, has been prepared and evaluated in vitro against a panel of human cell lines. The *N*<sup>2</sup>-benzylated  $\beta$ -carbolinium bromates represented the most interesting cytotoxic activities. Compounds **19** were found to be the most potent compounds with IC<sub>50</sub> values lower than 5  $\mu$ M against 10 strains human tumor cell lines.

**Succinyl hydroxamates as potent and selective non-peptidic inhibitors of procollagen C-proteinase: Design, synthesis, and evaluation as topically applied, dermal anti-scarring agents**

pp 6562–6567

Simon Bailey\*, Paul V. Fish\*, Stephane Billotte, Jon Bordner, Doris Greiling, Kim James, Andrew McElroy, James E. Mills, Charlotte Reed, Robert Webster

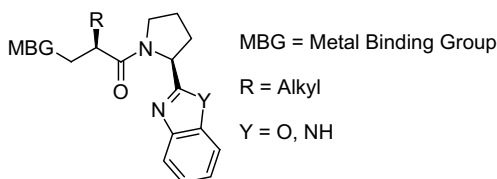
**7**: NR<sup>1</sup>R<sup>2</sup> = NH<sub>2</sub>

Succinyl hydroxamates **1** and **2** are disclosed as novel series of potent and selective inhibitors of procollagen C-proteinase which may have potential as anti-fibrotic agents. Carboxamide **7** was effective in a cell-based model of collagen deposition (fibroplasia model) and was very effective at penetrating human skin in vitro. Based on this profile, compound **7** (UK-383,367) was selected as a candidate for evaluation in clinical studies as a *topically* applied, dermal anti-scarring agent.

### Peptide deformylase inhibitors of *Mycobacterium tuberculosis*: Synthesis, structural investigations, and biological results

pp 6568–6572

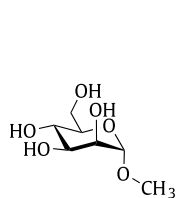
Arkadius Pichota\*, Jeyaraj Duraiswamy, Zheng Yin, Thomas H. Keller, Jenefer Alam, Sarah Liung, Gladys Lee, Mei Ding, Gang Wang, Wai Ling Chan, Mark Schreiber, Ida Ma, David Beer, Xinyi Ngew, Kakoli Mukherjee, Mahesh Nanjundappa, Jeanette W. P. Teo, Pamela Thayalan, Amelia Yap, Thomas Dick, Wuyi Meng, Mei Xu, James Koehn, Shi-Hao Pan, Kirk Clark, Xiaoling Xie, Carolyn Shoen, Michael Cynamon



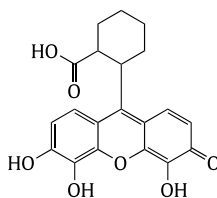
### Rational design of novel glycomimetics: Inhibitors of concanavalin A

pp 6573–6575

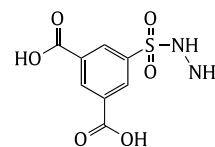
Karen T. Welch\*, Trent A. Turner, Callie E. Preast



Methyl  $\alpha$ -D-mannopyranoside  
 $IC_{50} = 350 \mu M$



NSC 119910  
 $IC_{50} = 29 \mu M$



NSC 120634  
 $IC_{50} = 19 \mu M$



## OTHER CONTENTS

### Instructions to contributors

p I

\*Corresponding author

Supplementary data available via ScienceDirect

## COVER

Overlay of high resolution co-crystal structures of **R-22**-ADP (cyan) and **1**-ADP (green) bound in an allosteric binding site of the mitotic kinesin KSP. [Roecker, A. J.; Coleman, P. J.; Mercer, S. P.; Schreier, J. D.; Buser, C. A.; Walsh, E. S.; Hamilton, K.; Lobell, R. B.; Tao, W.; Diehl, R. E.; South, V. J.; Davide, J. P.; Kohl, N. E.; Yan, Y.; Kuo, L. C.; Li, C.; Fernandez-Metzler, C.; Mahan, E. A.; Prueksaritanont, T.; Hartman, G. D. *Bioorg. Med. Chem. Lett.* **2007**, 17, 5677.]

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