Bioorganic & Medicinal Chemistry 19 (2011) 4405–4412

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

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Bioorganic & Medicinal Chemistry Volume 19, Issue 15, 2011

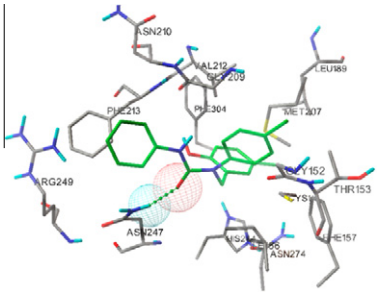
Contents

ARTICLES

Design, synthesis and biological evaluation of urea derivatives from *o*-hydroxybenzylamines and phenylisocyanate as potential FabH inhibitors **pp 4413–4420**

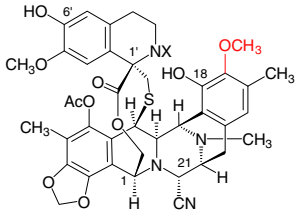
Zi-Lin Li, Qing-Shan Li, Hong-Jia Zhang, Yang Hu, Di-Di Zhu, Hai-Liang Zhu*

FabH, β-ketoacyl-acyl carrier protein (ACP) synthase III, is a particularly attractive target, since it is central to the initiation of fatty acid biosynthesis and is highly conserved among Gram-positive and Gram-negative bacteria. A series of *o*-hydroxybenzylamines **1**–**16** and its corresponding new urea derivatives **17**–**32** were synthesized and fully characterized by spectroscopic methods and elemental analysis. This new urea derivatives class demonstrates strong antibacterial activity. *Escherichia coli* FabH inhibitory assay and docking simulation indicated that the compounds 1-(5-bromo-2-hydroxybenzyl)-1-(4-fluorophenyl)-3-phenylurea (**18**) and 1-(5-bromo-2-hydroxybenzyl)-1-(4-chlorophenyl)-3-phenylurea (**20**) were potent inhibitors of *E. coli* FabH.



Chemistry of ecteinascidins. Part 3: Preparation of 2′-*N*-acyl derivatives of ecteinascidin 770 and evaluation of cytotoxicity **pp 4421–4436**

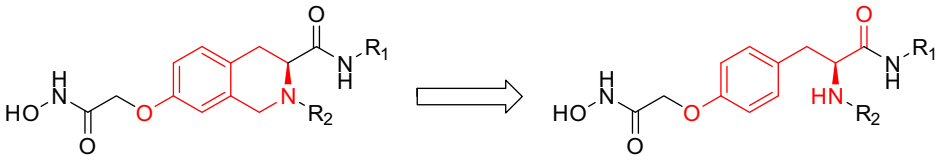
Panithi Saktrakulkla, Satoru Toriumi, Mitsuhiro Tsujimoto, Chamnan Patarapanich, Khanit Suwanborirux*, Naoki Saito*



Synthesis of 2′-*N*-amide analogues of ecteinascidin 770 (Et 770) via a three-step transformation employing an 18,6′-*O*-bisallyl protected derivative of Et 770 is presented along with in vitro cytotoxicity of the resulting amides.

Design, synthesis and biological evaluation of tyrosine-based hydroxamic acid analogs as novel histone deacetylases (HDACs) inhibitors **pp 4437–4444**

Yingjie Zhang, Jinhong Feng, Chunxi Liu, Hao Fang, Wenfang Xu*

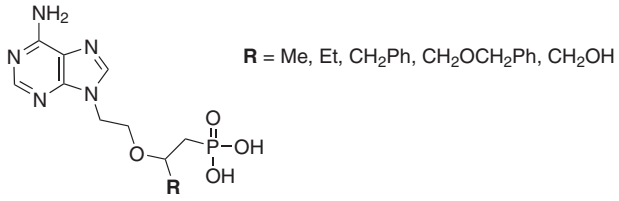


a.Tetrahydroisoquinoline-based hydroxamic acid

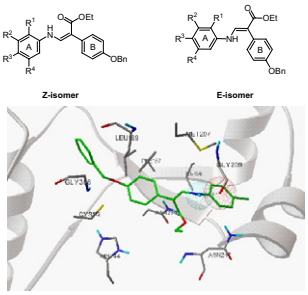
b.Tyrosine-basedhydroxamicacid

Based on the structure of our previously reported tetrahydroisoquinoline-based hydroxamic acids, a novel series of tyrosine-based hydroxamic acid derivatives was designed and synthesized as HDACs inhibitors.

Acyclic nucleoside phosphonates with a branched 2-(2-phosphonoethoxy)ethyl chain: Efficient synthesis and antiviral activity **pp 4445–4453**
Dana Hocková*, Antonín Holý, Graciela Andrei, Robert Snoeck, Jan Balzarini

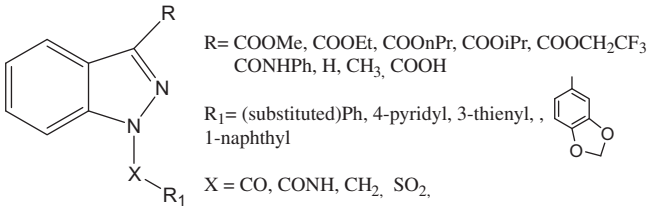


Discovery of vinylogous carbamates as a novel class of β-ketoacyl-acyl carrier protein synthase III (FabH) inhibitors **pp 4454–4459**
Huan-Qiu Li*, Yin Luo, Hai-Liang Zhu

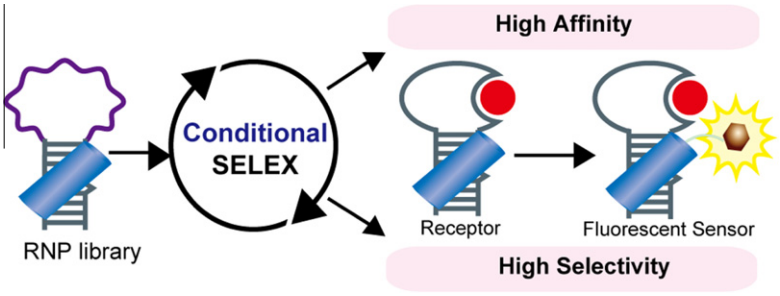


We first used a structure-based approach to develop 24 new vinylogous carbamates (**4a**–**15a**, **4b**–**15b**) that target FabH for the development of new antibiotics in this paper. Compound **6a** showed the most potent FabH inhibitory activity with IC_{50} of 2.6 μM, respectively. Docking simulation was performed to position compound **6a** into the *Escherichia coli* FabH active site to determine the probable binding conformation.

Design, synthesis and evaluation of *N*-benzoylindazole derivatives and analogues as inhibitors of human neutrophil elastase **pp 4460–4472**
Letizia Crocetti, Maria Paola Giovannoni*, Igor A. Schepetkin, Mark T. Quinn, Andrei I. Khlebnikov, Agostino Cilibrizzi, Vittorio Dal Piaz, Alessia Graziano, Claudia Vergelli

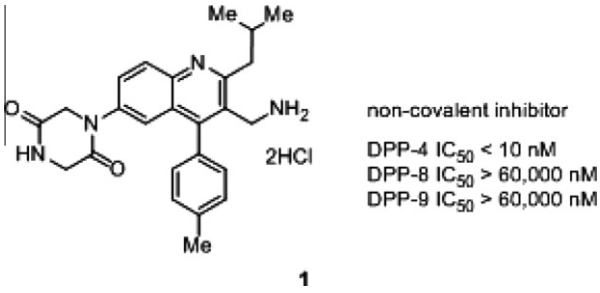


Construction of dopamine sensors by using fluorescent ribonucleopeptide complexes **pp 4473–4481**
Fong Fong Liew, Tetsuya Hasegawa, Masatora Fukuda, Eiji Nakata, Takashi Morii*



Discovery of potent, selective, and orally bioavailable quinoline-based dipeptidyl peptidase IV inhibitors targeting Lys554 **pp 4482–4498**

Hironobu Maezaki*, Yoshihiro Banno, Yasufumi Miyamoto, Yuusuke Moritou, Tomoko Asakawa, Osamu Kataoka, Koji Takeuchi, Nobuhiro Suzuki, Koji Ikedo, Takuo Kosaka, Masako Sasaki, Shigetoshi Tsubotani, Akiyoshi Tani, Miyuki Funami, Yoshio Yamamoto, Michiko Tawada, Kathleen Aertgeerts, Jason Yano, Satoru Oi

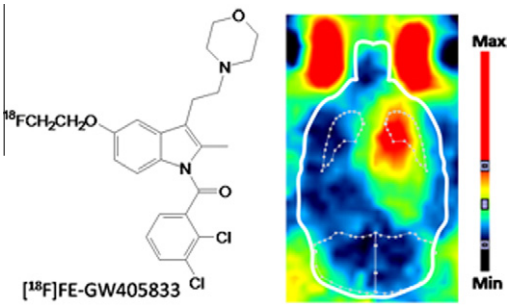


1

A novel series of quinoline-based dipeptidyl peptidase IV inhibitors were designed based on the co-crystallography and synthesized to target the side chain of Lys554 on the enzyme.

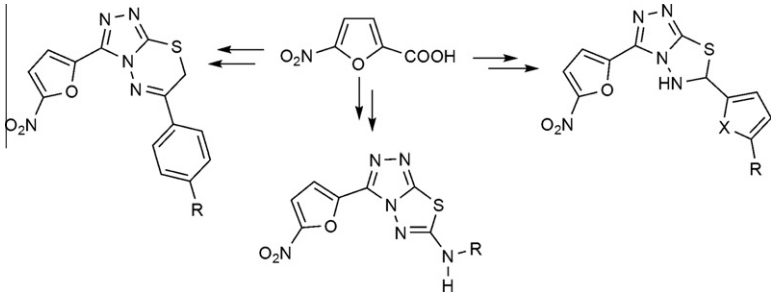
Synthesis, in vitro and in vivo evaluation of fluorine-18 labelled FE-GW405833 as a PET tracer for type 2 cannabinoid receptor imaging **pp 4499–4505**

Nele Evens, Caroline Vandeputte, Giulio G. Muccioli, Didier M. Lambert, Veerle Baekelandt, Alfons M. Verbruggen, Zeger Debyser, Koen Van Laere, Guy M. Bormans*



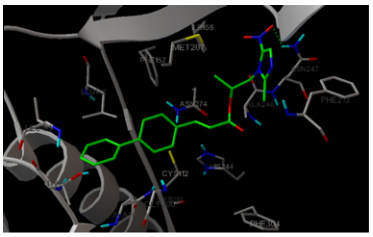
Synthesis of some new [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazines and [1,2,4]triazolo[3,4-*b*][1,3,4] thiadiazoles starting from 5-nitro-2-furoic acid and evaluation of their antimicrobial activity **pp 4506–4512**

Sahar M. I. Badr*, Rasha M. Barwa



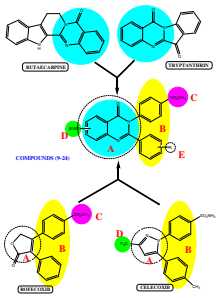
Synthesis, molecular modeling and biological evaluation of β-ketoacyl-acyl carrier protein synthase III (FabH) as novel antibacterial agents **pp 4513–4519**

Hong-Jia Zhang, Di-Di Zhu, Zi-Lin Li, Juan Sun, Hai-Liang Zhu*

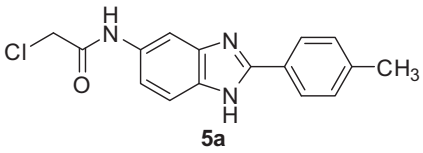


A series of novel cinnamic acid secnidazole ester derivatives have been designed and synthesized, and their biological activities were also evaluated as potential inhibitors of FabH. These compounds were assayed for antibacterial activity against *Escherichia coli*, *Pseudomonas aeruginosa*, *Bacillus subtilis* and *Staphylococcus aureus*. Compounds with potent antibacterial activities were tested for their *E. coli* FabH inhibitory activity. Compound **3n** showed the most potent antibacterial activity with MIC of 1.56–6.25 μg/mL against the tested bacterial strains and exhibited the most potent *E. coli* FabH inhibitory activity with IC_{50} of 2.5 μM. Docking simulation was performed to position compound **3n** into the *E. coli* FabH active site to determine the probable binding conformation.

Analogue-based design, synthesis and molecular docking analysis of 2,3-diaryl quinazolinones as non-ulcerogenic anti-inflammatory agents **pp 4520–4528**
E. Manivannan*, S. C. Chaturvedi

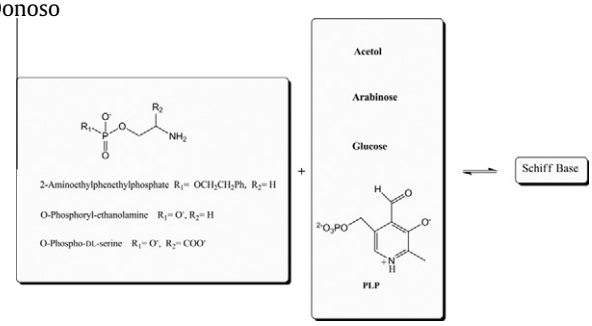


Discovery of benzimidazole derivatives as novel multi-target EGFR, VEGFR-2 and PDGFR kinase inhibitors **pp 4529–4535**
Yunqi Li, Chunyan Tan, Chunmei Gao, Cunlong Zhang, Xudong Luan, Xiaowu Chen, Hongxia Liu, Yuzong Chen, Yuyang Jiang*

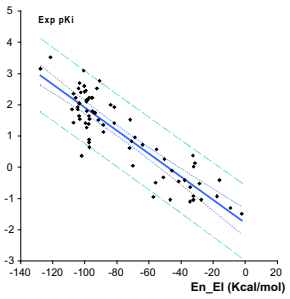


A series of benzimidazole derivatives have been discovered and synthesized as potent multi-target EGFR, VEGFR-2 and PDGFR inhibitors.

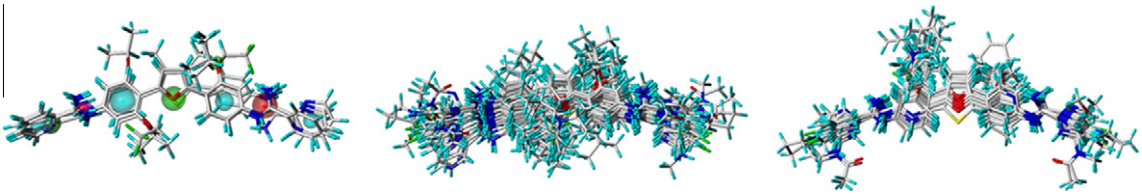
Understanding non-enzymatic aminophospholipid glycation and its inhibition. Polar head features affect the kinetics of Schiff base formation **pp 4536–4543**
Catalina Caldés, Bartolomé Vilanova*, Miquel Adrover, Francisco Muñoz, Josefa Donoso



Fragmental modeling of hPepT2 and analysis of its binding features by docking studies and pharmacophore mapping **pp 4544–4551**
Alessandro Pedretti, Laura De Luca, Cristina Marconi, Luca Regazzoni, Giancarlo Aldini, Giulio Vistoli*

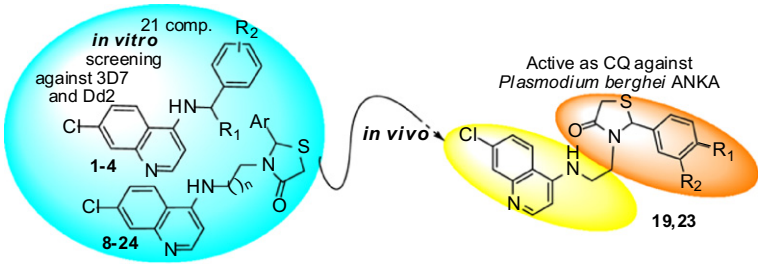


Molecular factors governing inhibition of arylimidamides against *Leishmania*: Conservative computational modeling to improve chemotherapies **pp 4552–4561**
Catharine J. Collar, Xiaohua Zhu, Karl Werbovetz, David W. Boykin, W. David Wilson*

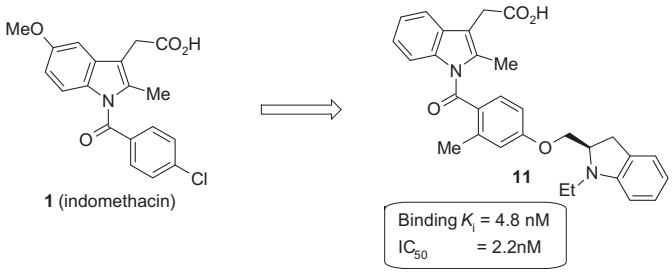


Synthesis and antimalarial activity of new heterocyclic hybrids based on chloroquine and thiazolidinone scaffolds **pp 4562–4573**
Fernando A. Rojas Ruiz, Rory N. García-Sánchez, Santiago Villabona Estupiñan, Alicia Gómez-Barrio, Diego F. Torres Amado, Berta Martín Pérez-Solórzano, Juan J. Nogal-Ruiz, Antonio R. Martínez-Fernández, Vladimir V. Kouznetsov*

A series of new 21 chloroquine molecules **1–4**, **8–24** were synthesized and screened for their antimalarial activity against chloroquine (CQ)-sensitive 3D7 and multidrug-resistance Dd2 strains of *Plasmodium falciparum*. Six compounds, four of them with benzylamino fragment, showed an excellent activity against Dd2 strain, up to 3-fold more active than CQ. In vivo preliminary results have shown that two compounds **19** and **23** are as active as CQ against *Plasmodium berghei* ANKA.

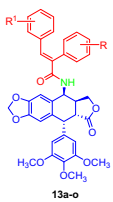


Discovery of selective indole-based prostaglandin D_2 receptor antagonist **pp 4574–4588**
Maki Iwahashi*, Atsushi Shimabukuro, Takahiro Onoda, Yoko Matsunaga, Yutaka Okada, Ryoji Matsumoto, Fumio Nambu, Hisao Nakai, Masaaki Toda



Discovery process of a new PGD2 receptor antagonist **11** is reported.

Synthesis and biological evaluation of 4β-acrylamidopodophyllotoxin congeners as DNA damaging agents **pp 4589–4600**
Ahmed Kamal*, Paidakula Suresh, M. Janaki Ramaiah, Adla Mallareddy, Banala Ashwini Kumar, Paidakula Raju, J. Vinay Gopal, S.N. C. V. L. Pushpavalli, A. Lavanya, Pranjal Sarma, Manika Pal-Bhadra*

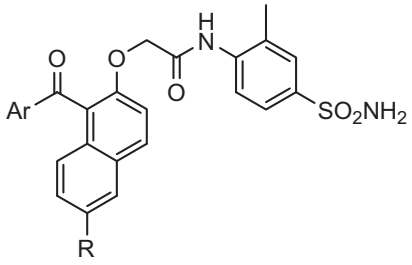


13a-o

13a: R = 3,4,5-trimethoxy, R^1 = 4-fluoro-3-methoxy
13b: R = 3,4,5-trimethoxy, R^1 = 3-fluoro-4-methoxy
13c: R = 3,4,5-trimethoxy, R^1 = 2-fluoro-5-methoxy
13d: R = 3,4,5-trimethoxy, R^1 = 2-fluoro-4-methoxy
13e: R = 3,4,5-trimethoxy, R^1 = 3-nitro-4-methoxy
13f: R = 3,4,5-trimethoxy, R^1 = 4-hydroxy-3-nitro
13g: R = 3,4,5-trimethoxy, R^1 = 4-nitro
13h: R = 3,4,5-trimethoxy, R^1 = 3-nitro
13i: R = 3,4,5-trimethoxy, R^1 = 4-methoxy
13j: R = 3,4,5-trimethoxy, R^1 = 3-methoxy
13k: R = 2-methoxy, R^1 = 4-nitro
13l: R = 2-methoxy, R^1 = 2-nitro
13m: R = 3,4,5-trimethoxy, R^1 = 4-hydroxy-3-methoxy
13n: R = 3,4,5-trimethoxy, R^1 = 3-hydroxy-4-methoxy
13o: R = 3,4,5-trimethoxy, R^1 = 4-hydroxy

Synthesis and biological activity of naphthyl-substituted (B-ring) benzophenone derivatives as novel non-nucleoside HIV-1 reverse transcriptase inhibitors **pp 4601–4607**

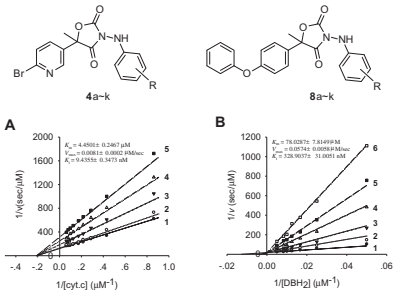
Xiao-Dong Ma, Xuan Zhang, Hui-Fang Dai, Shi-Qiong Yang, Liu-Meng Yang, Shuang-Xi Gu, Yong-Tang Zheng, Qiu-Qin He, Fen-Er Chen*



R = H, Br, CN

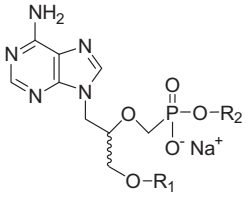
Design, syntheses, and kinetic evaluation of 3-(phenylamino)oxazolidine-2,4-diones as potent cytochrome bc_1 complex inhibitors **pp 4608–4615**

Fu Wang, Hui Li, Le Wang, Wen-Chao Yang, Jia-Wei Wu*, Guang-Fu Yang*



Synthesis and antiviral evaluation of 9-(*S*)-[3-alkoxy-2-(phosphonomethoxy)propyl]nucleoside alkoxyalkyl esters: Inhibitors of hepatitis C virus and HIV-1 replication **pp 4616–4625**

Nadejda Valiaeva, David L. Wyles, Robert T. Schooley, Julia B. Hwu, James R. Beadle, Mark N. Prichard, Karl Y. Hostetler*

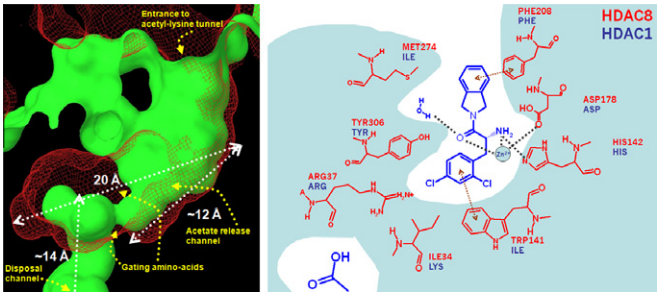


cmpd	R_1	R_2	stereochem	HCV[a] (μM)	HIV[b] (μM)
1	hydrogen	ODE	(*S*)	1.55	0.0001
15	methyl	ODE	(*S*)	1.43	0.03
16	methyl	ODE	(*R*)	4.65	4.8
18	ethyl	HDP	(*R*,*S*)	7.59	>10
19	isopropyl	HDP	(*R*,*S*)	31.7	>10

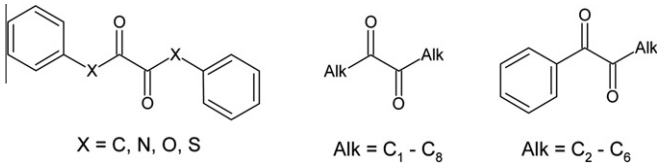
[a]BM4-5(1b) replicons; [b]LAI; ODE = octadecyloxyethyl, HDP = hexadecyloxypropyl

Human HDAC isoform selectivity achieved via exploitation of the acetate release channel with structurally unique small molecule inhibitors **pp 4626–4634**

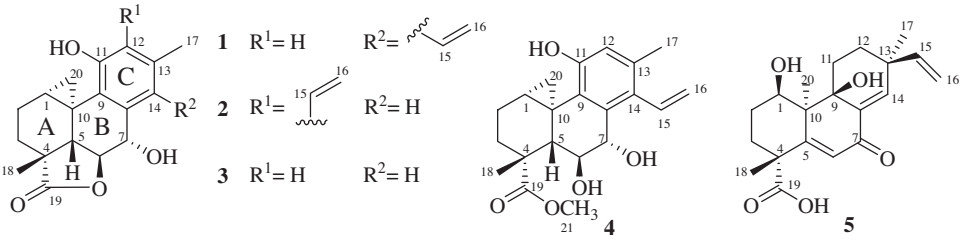
Lewis Whitehead*, Markus R. Dobler, Branko Radetich, Yanyi Zhu, Peter W. Atadja, Tavina Claiborne, Jonathan E. Grob, Andrew McRiner, Margaret R. Pancost, Anup Patnaik, Wenlin Shao, Michael Shultz, Ritesh Tichkule, Ruben A. Tommasi, Brian Vash, Ping Wang, Travis Stams



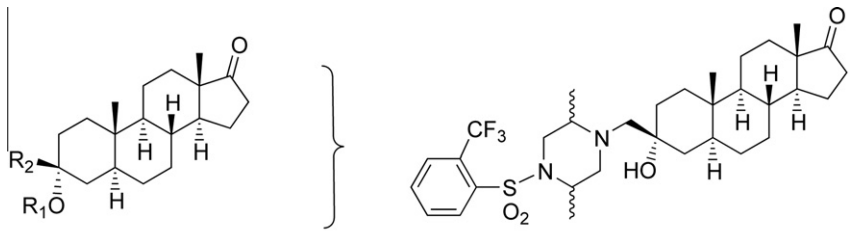
Requirements for mammalian carboxylesterase inhibition by substituted ethane-1,2-diones **pp 4635–4643**
Elizabeth I. Parkinson, M. Jason Hatfield, Lyudmila Tsurkan, Janice L. Hyatt, Carol C. Edwards, Latorya D. Hicks, Bing Yan, Philip M. Potter*



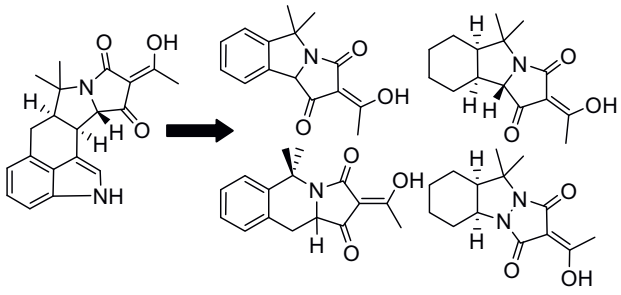
Arthrinins A–D: Novel diterpenoids and further constituents from the sponge derived fungus *Arthrinium* sp. **pp 4644–4651**
Sherif S. Ebada, Barbara Schulz, Victor Wray, Frank Totzke, Michael H. G. Kubbutat, Werner E. G. Müller, Alexandra Hamacher, Matthias U. Kassack, Wenhan Lin, Peter Proksch*



Development of 3-substituted-androsterone derivatives as potent inhibitors of 17β-hydroxysteroid dehydrogenase type 3 **pp 4652–4668**
René Maltais, Michelle-Audrey Fournier, Donald Poirier*



Synthesis and SERCA activities of structurally simplified cyclopiazonic acid analogues **pp 4669–4678**
Sheng Yao, Daniel Gallenkamp, Katharina Wölfel, Bettina Lüke, Michael Schindler, Jürgen Scherkenbeck*



*Corresponding author
Supplementary data available via ScienceDirect

COVER

The known veterinary anthelmintic and proton ionophore, closantel, was recently discovered to also exhibit potent chitinase inhibition activity and inhibit molting in the parasitic nematode, *Onchocerca volvulus*, the causative agent of the neglected tropical disease onchocerciasis. [C. Gloeckner, A. L. Garner, F. Mersha, Y. Oksov, N. Tricoche, L. M. Eubanks, S. Lustigman, G. F. Kaufmann, K. D. Janda, Repositioning of an existing drug for the neglected tropical disease Onchocerciasis, *Proc. Natl. Acad. Sci., U.S.A.* **2010**, *107*, 3424.]

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