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Bioorganic & Medicinal Chemistry Volume 18, Issue 6, 2010

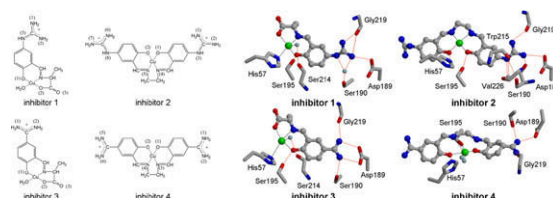
Contents

ARTICLES

Structural basis for the design of novel Schiff base metal chelate inhibitors of trypsin

pp 2076–2080

Daisuke Iyaguchi, Susumu Kawano, Kazuki Takada, Eiko Toyota*

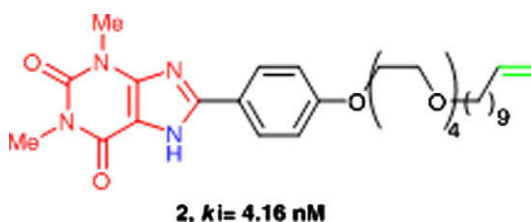


The crystal structures of the complexes of β -trypsin with *m*-guanidinosalicylidene-L-alaninato(aqua)copper(II) hydrochloride, [*N,N'*-bis(*m*-guanidinosalicylidene)ethylenediaminato]copper(II), and [*N,N'*-bis(*m*-amidinosalicylidene)ethylenediaminato]copper(II) have been determined. The structural and inhibitory activity data provide new avenues for designing novel inhibitors against physiologically important trypsin-like serine proteases.

Synthesis of theophylline derivatives and study of their activity as antagonists at adenosine receptors

pp 2081–2088

Jesús Hierrezuelo, J. Manuel López-Romero*, Rodrigo Rico, José Brea, M. Isabel Loza, Chengzhi Cai, Manuel Algarra

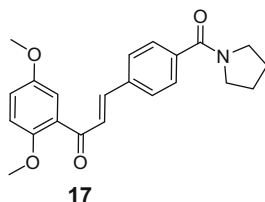


Synthesis of oligo(ethylene glycol)-alkene substituted theophyllines (positions 7 and/or 8) is described. Compound **2** showed high affinity and selectivity for A_{2B} receptor ($K_i = 4.16$ nM, $K_{iA_{2A}}/K_{iA_{2B}} = 24.1$). The alkenyl or azido substituents in some of the derivative allows for covalent attachment of them onto H-terminated silicon surfaces.

Synthesis and biological evaluation of 2',5'-dimethoxychalcone derivatives as microtubule-targeted anticancer agents

pp 2089–2098

Huang-Yao Tu, A-Mei Huang, Tzyh-Chyuan Hour, Shyh-Chyun Yang*, Yeong-Shiau Pu, Chun-Nan Lin*

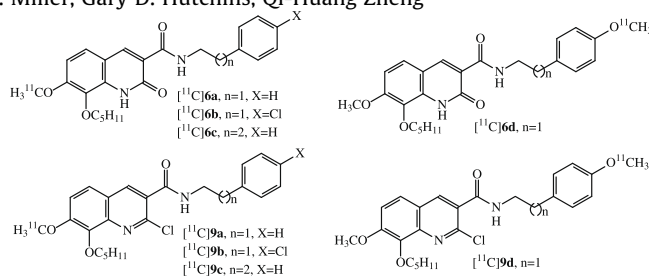


A series of novel 2',5'-dimethoxychalcone derivatives including 18 new compounds were synthesized and evaluated for cytotoxicities against two human cancer cell lines, NTUB1 (human bladder cancer cell line) and PC3 (human prostate cancer cell line) cell lines.

Synthesis and in vitro biological evaluation of carbon-11-labeled quinoline derivatives as new candidate PET radioligands for cannabinoid CB2 receptor imaging

pp 2099–2106

Mingzhang Gao, Min Wang, Kathy D. Miller, Gary D. Hutchins, Qi-Huang Zheng*

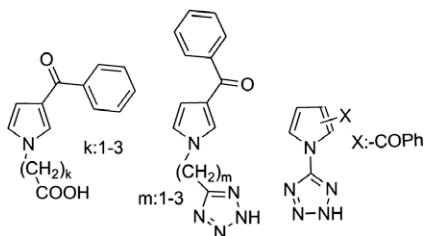


This paper reports the synthesis and in vitro biological evaluation of carbon-11-labeled quinoline derivatives as new candidate radioligands for PET imaging of cannabinoid CB2 receptor in cancer.

Design and synthesis of novel series of pyrrole based chemotypes and their evaluation as selective aldose reductase inhibitors. A case of bioisosterism between a carboxylic acid moiety and that of a tetrazole

pp 2107–2114

Kyriaki Pegklidou, Catherine Koukoulitsa, Ioannis Nicolaou*, Vassilis J. Demopoulos

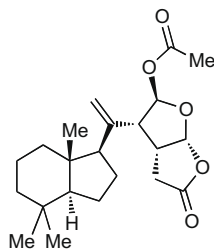


Potential inhibitors of aldose reductase enzyme, related to long-term complications of diabetes, were synthesized and tested. Pyrrolyl-tetrazole derivatives without an alkyl chain between the two aromatic rings have been shown significant inhibitory activity and selectivity.

Chemical biology studies on norrisolide

pp 2115–2122

Gianni Guizzunti*, Thomas P. Brady, Derek Fischer, Vivek Malhotra, Emmanuel A. Theodorakis*



7: norrisolide

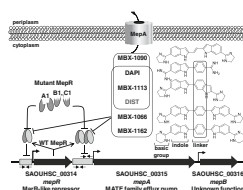
Our studies on the chemical biology of norrisolide are presented. This natural product was found to induce irreversible vesiculation of Golgi membranes and specifically block protein transport at the level of the Golgi apparatus. Through the use of fluorescent derivatives of norrisolide, we demonstrated that this compound binds directly to Golgi membranes, and that its perhydroindane core is necessary and sufficient for this binding.



Efflux-mediated bis-indole resistance in *Staphylococcus aureus* reveals differential substrate specificities for MepA and MepR

pp 2123–2130

Timothy J. Opperman*, John D. Williams, Chad Houseweart, Rekha G. Panchal, Sina Bavari, Norton P. Peet, Donald T. Moir, Terry L. Bowlin



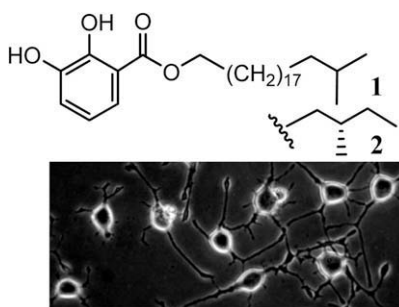
An analysis of efflux-mediated resistance to a panel of chemically related bis-indole antibiotics revealed interesting trends in the substrate specificities of the MepA efflux pump and the substrate-responsive repressor MepR in *Staphylococcus aureus*.



Gentisides A and B, two new neuritogenic compounds from the traditional Chinese medicine *Gentiana rigescens* Franch

pp 2131–2134

Lijuan Gao, Jinyou Li, Jianhua Qi*

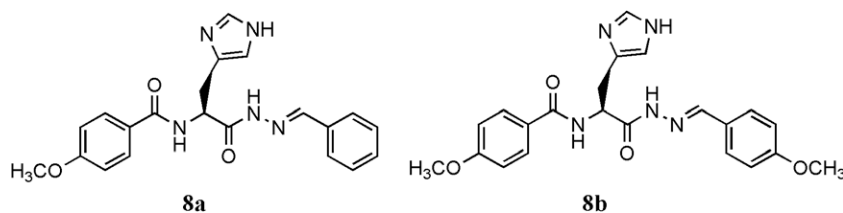


Two new alkyl 2,3-dihydroxybenzoates, gentisides A and B, were isolated from the traditional Chinese medicine *Gentiana rigescens* Franch. They showed a significant neuritogenic activity at 30 μ M against PC12 cells that was comparable to that seen for the best nerve growth factor concentration of 40 ng/mL.

SAR and molecular mechanism study of novel acylhydrazone compounds targeting HIV-1 CA

pp 2135–2140

Yinxue Jin, Zhiwu Tan, Meizi He, Baohe Tian, Shixing Tang, Indira Hewlett, Ming Yang*

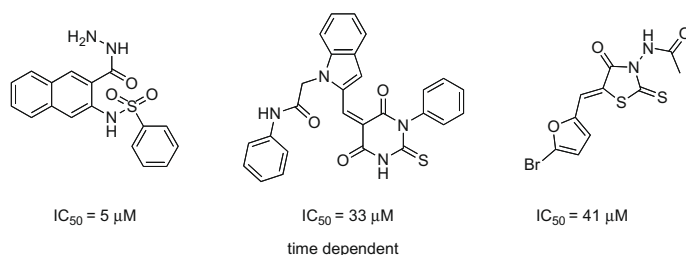


We studied SAR and molecular mechanism of novel acylhydrazone compounds targeting HIV-1 CA. Among synthesized compounds, **8a** and **8b** possessed the most promising antiviral activities.

Exploration of inhibitors for diaminopimelate aminotransferase

pp 2141–2151

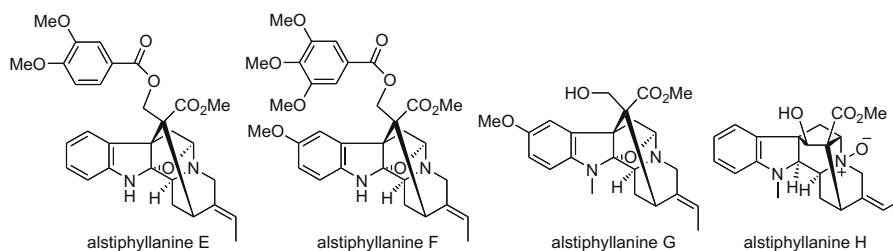
Chenguang Fan, Matthew D. Clay, Michael K. Deyholos, John C. Vederas*



Alstiphyllanines E–H, picraline and ajmaline-type alkaloids from *Alstonia macrophylla* inhibiting sodium glucose cotransporter

pp 2152–2158

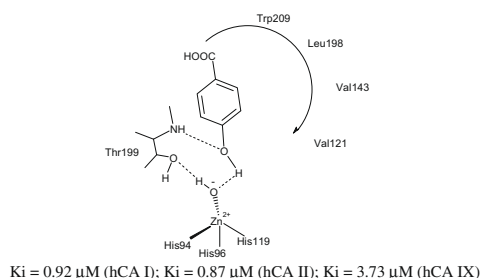
Hiroko Arai, Yusuke Hirasawa, Abdul Rahman, Idha Kusumawati, Noor Cholies Zaini, Seizo Sato, Chihiro Aoyama, Jiro Takeo, Hiroshi Morita*



Carbonic anhydrase inhibitors. Inhibition of mammalian isoforms I–XIV with a series of natural product polyphenols and phenolic acids

pp 2159–2164

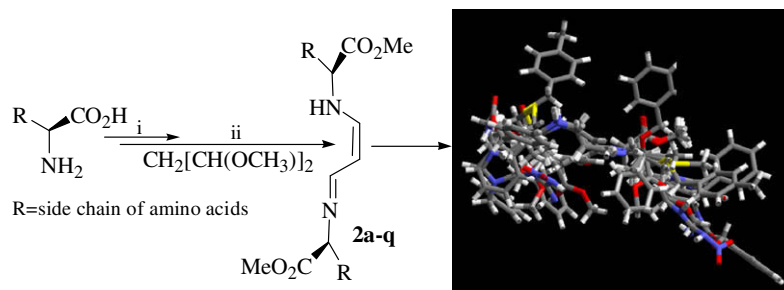
Alessio Innocenti, S. Beyza Öztürk Sarıkaya, İlhami Gülçin*, Claudiu T. Supuran*



A class of novel Schiff's bases: Synthesis, therapeutic action for chronic pain, anti-inflammation and 3D QSAR analysis

pp 2165–2172

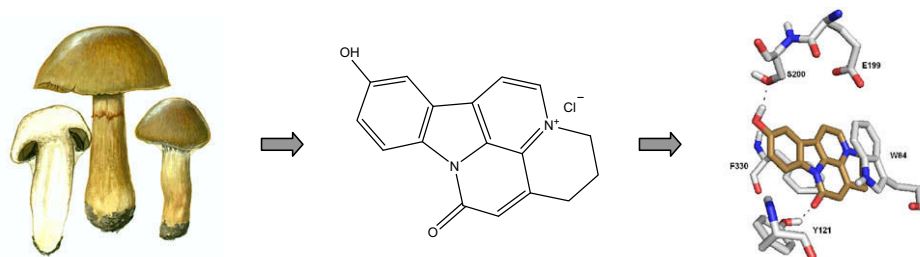
Yinjian Zhou, Ming Zhao*, Yingting Wu, Chunyu Li, Jianhui Wu, Meiqing Zheng, Li Peng, Shiqi Peng*



Acetylcholinesterase inhibitors from the toadstool *Cortinarius infractus*

pp 2173–2177

Torsten Geissler, Wolfgang Brandt, Andrea Porzel, Dagmar Schlenzig, Astrid Kehlen, Ludger Wessjohann, Norbert Arnold*



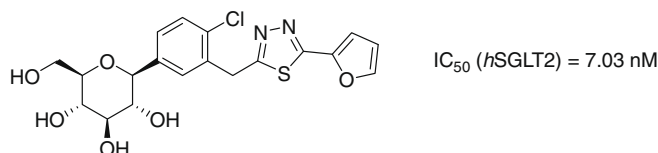
The isolation of acetylcholinesterase inhibitors ($\text{IC}_{50} = 9.7 \mu\text{M}$) from fungal source is reported. The selective binding mode is resolved by docking studies. The pharmacological potential is further supported by A β -aggregation and cytotoxicity studies.



Novel C-aryl glucoside SGLT2 inhibitors as potential antidiabetic agents: 1,3,4-Thiadiazolylmethylphenyl glucoside congeners

pp 2178–2194

Junwon Lee, Sung-Han Lee, Hee Jeong Seo, Eun-Jung Son, Suk Ho Lee, Myung Eun Jung, MinWoo Lee, Ho-Kyun Han, Jeongmin Kim, Jahyo Kang*, Jinhwa Lee*

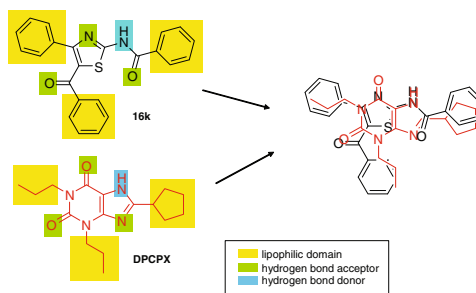


Novel C-aryl glucoside SGLT2 inhibitors containing 1,3,4-thiadiazole at the distal ring position were identified as potential antidiabetic agents. A selected compound demonstrated reasonable urinary glucose excretion and glucosuria in normal SD rats along with favorable blood glucose-lowering effects in db/db mice.

2-Amino-5-benzoyl-4-phenylthiazoles: Development of potent and selective adenosine A₁ receptor antagonists

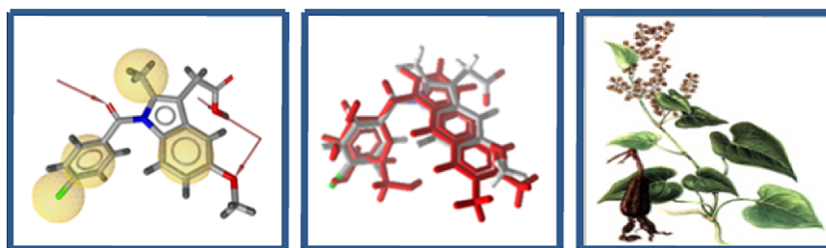
pp 2195–2203

Anja B. Scheiff, Swapnil G. Yerande, Ali El-Tayeb, Wenjin Li, Gajanan S. Inamdhar, Kamala K. Vasu, Vasudevan Sudarsanam, Christa E. Müller*

**In silico search for multi-target anti-inflammatories in Chinese herbs and formulas**

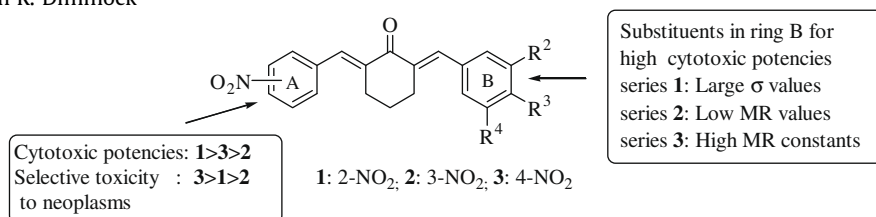
pp 2204–2218

Thomas M. Ehrman, David J. Barlow*, Peter J. Hylands

**Cytotoxic 2-benzylidene-6-(nitrobenzylidene)cyclohexanones which display substantially greater toxicity for neoplasms than non-malignant cells**

pp 2219–2224

Umashankar Das, Alireza Doroudi, H. Inci Gul, Hari N. Pati, Masami Kawase, Hiroshi Sakagami, Qing Chu, James P. Stables, Jonathan R. Dimmock*

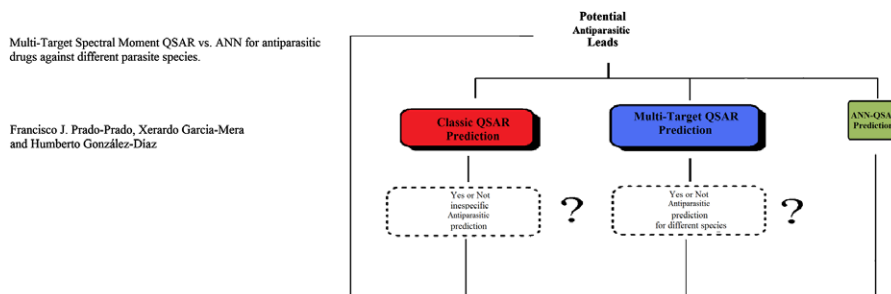


A number of 2-benzylidene-6-(nitrobenzylidene)cyclohexanones emerged as lead compounds which possess noteworthy cytotoxicity, selective toxicity towards neoplasms than non-malignant cells and well tolerated in mice in short-term toxicity studies.

Multi-target spectral moment QSAR versus ANN for antiparasitic drugs against different parasite species

pp 2225–2231

Francisco J. Prado-Prado*, Xerardo García-Mera, Humberto González-Díaz*

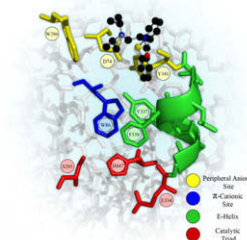


Differential binding of phenothiazine urea derivatives to wild-type human cholinesterases and butyrylcholinesterase mutants

pp 2232–2244

Sultan Darvesh*, Ian R. Pottie, Katherine V. Darvesh, Robert S. McDonald, Ryan Walsh, Sarah Conrad, Andrea Penwell, Diane Mataija, Earl Martin

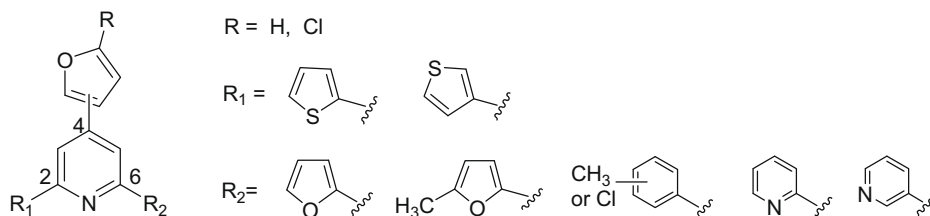
Most phenothiazine urea derivatives are specific butyrylcholinesterase inhibitors. Aminourea derivatives inhibit both acetylcholinesterase and butyrylcholinesterase and the use of butyrylcholinesterase mutants and elevated substrate reveals involvement of a salt linkage in that inhibitory process.



Synthesis of 2-(thienyl-2-yl or -3-yl)-4-furyl-6-aryl pyridine derivatives and evaluation of their topoisomerase I and II inhibitory activity, cytotoxicity, and structure–activity relationship

pp 2245–2254

Pritam Thapa, Radha Karki, Hoyoung Choi, Jae Hun Choi, Minho Yun, Byeong-Seon Jeong, Mi-Ja Jung, Jung Min Nam, Younghwa Na, Won-Jea Cho, Youngjoo Kwon*, Eung-Seok Lee*

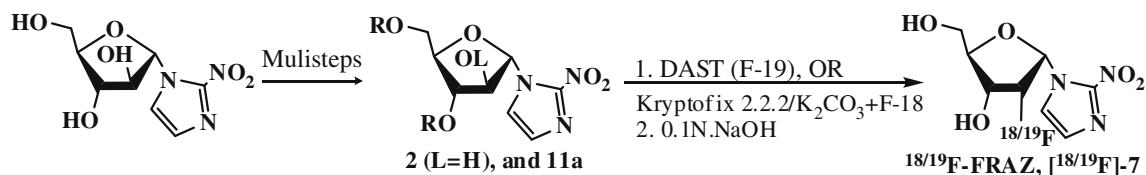


Designed and synthesized 48 2-thienyl-4-furyl-6-aryl pyridine derivatives were evaluated for their topoisomerase I and II inhibitory activity and cytotoxicity against several human cancer cell lines.

Synthesis, radiofluorination, and hypoxia-selective studies of FRAZ: A configurational and positional analogue of the clinical hypoxia marker, [¹⁸F]-FAZA

pp 2255–2264

Piyush Kumar*, Ebrahim Naimi, Alexander J. McEwan, Leonard I. Wiebe

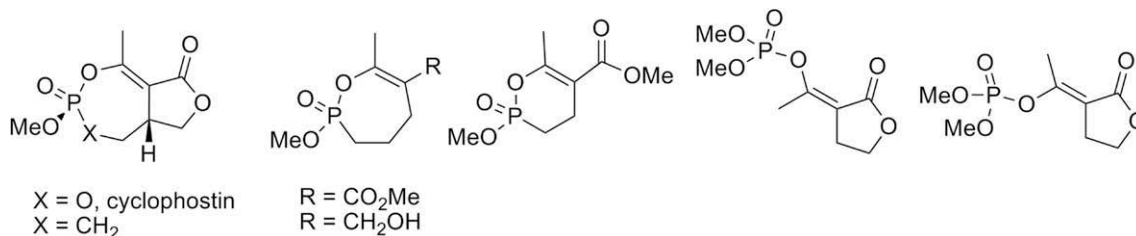


The synthesis and F-18 radiolabeling of FRAZ, an azomycin nucleoside-based novel compound, are shown. FRAZ has radiosensitization properties similar to FAZA, a clinical PET radiodiagnostic for hypoxic tumors.

Synthesis and kinetic analysis of some phosphonate analogs of cyclophostin as inhibitors of human acetylcholinesterase

pp 2265–2274

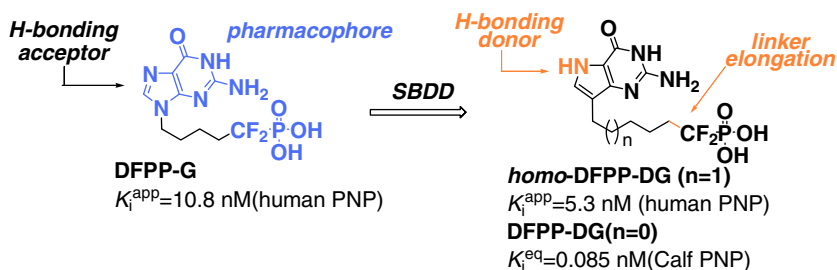
Supratik Dutta, Raj K. Malla, Saibal Bandyopadhyay, Christopher D. Spilling, Cynthia M. Dupureur*



Structural-based design and synthesis of novel 9-deazaguanine derivatives having a phosphate mimic as multi-substrate analogue inhibitors for mammalian PNPs

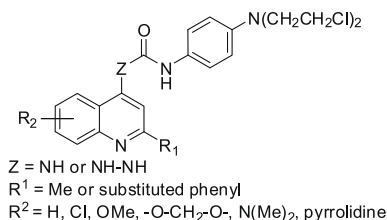
pp 2275–2284

Sadao Hikishima, Mariko Hashimoto, Lucyna Magnowska, Agnieszka Bzowska, Tsutomu Yokomatsu*


Potent DNA-directed alkylating agents: Synthesis and biological activity of phenyl N-mustard–quinoline conjugates having a urea or hydrazinecarboxamide linker

pp 2285–2299

Rajesh Kakadiya, Huajin Dong, Amit Kumar, Dodia Narsinh, Xiuguo Zhang, Ting-Chao Chou, Te-Chang Lee, Anamik Shah, Tsann-Long Su*


Carbonic anhydrase activators. The first activation study of a coral secretory isoform with amino acids and amines

pp 2300–2303

Anthony Bertucci, Didier Zoccola, Sylvie Tambutté, Daniela Vullo, Claudiu T. Supuran*

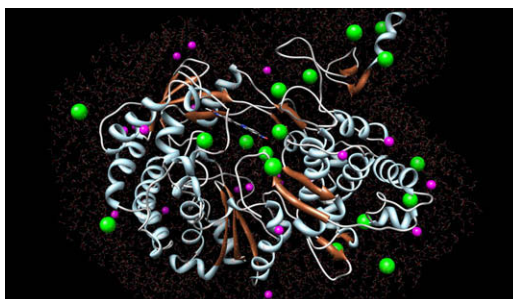


Stylophora pystillata (coral) CA is activated by amines and amino acids.

Pharmacophore modeling, resistant mutant isolation, docking, and MM-PBSA analysis: Combined experimental/computer-assisted approaches to identify new inhibitors of the bovine viral diarrhea virus (BVDV)

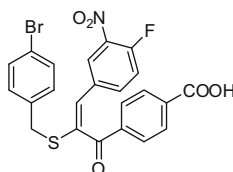
pp 2304–2316

Michele Tonelli, Vito Boido, Paolo La Colla, Roberta Loddo, Paola Posocco, Maria Silvia Paneni, Maurizio Fermeglia, Sabrina Pricl*



Design, synthesis and evaluation of (*E*)- α -benzylthio chalcones as novel inhibitors of BCR-ABL kinase**pp 2317–2326**

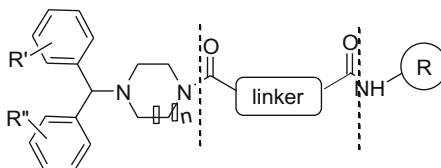
M. V. Ramana Reddy*, Venkat R. Pallela, Stephen C. Cosenza, Muralidhar R. Mallireddigari, Revathi Patti, Marie Bonagura, May Truongcao, Balaiah Akula, Shashidhar S. Jatiani, E. Premkumar Reddy*



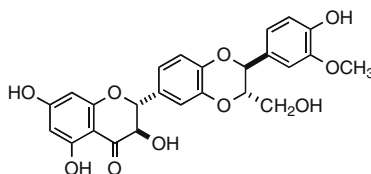
The design, synthesis and biological evaluation of novel (*E*)- α -benzylthio chalcones as BCR-ABL kinase inhibitors are described. The structure–activity relationship, in vitro cytotoxicity in K562, a human leukemic cell line and inhibition of BCR-ABL phosphorylation by these compounds is discussed.

**Synthesis and bradykinin inhibitory activity of novel non-peptide compounds, and evaluation of in vivo analgesic activity****pp 2327–2336**

Yoo Lim Kam, Hee-Kyung Rhee, Hwa-Jung Kim, Seung Keun Back, Heung Sik Na*, Hea-Young Park Choo*

**Melanogenesis inhibitors from the desert plant *Anastatica hierochuntica* in B16 melanoma cells****pp 2337–2345**

Souichi Nakashima, Hisashi Matsuda, Yoshimi Oda, Seikou Nakamura, Fengming Xu, Masayuki Yoshikawa*



The methanolic extract from the whole plants of *Anastatica hierochuntica* was found to inhibit melanogenesis in theophylline-stimulated murine B16 melanoma 4A5 cells. Among the constituents isolated, anastatin A, silybin A, isosilybins A and B, several flavonoids, etc. inhibited the melanogenesis with IC_{50} values of 6.1–32 μ M. With regard to the mechanism of action of silybins and isosilybins, the inhibition of tyrosinase activity suggested to be important. In addition, isosilybins A and B inhibited the mRNA expression of TRP-2, but silybins A and B oppositely enhanced the mRNA expression of tyrosinase, TRP-1 and -2 at 10 and/or 30 μ M, and the inhibition of phosphorylation of extracellular signal-regulated kinases (ERK1/2) is involved in the enhanced expression of mRNA, at least in part.

OTHER CONTENTS**Publisher's Note****p 2346****Erratum****pp 2347–2355**

*Corresponding author

Supplementary data available via ScienceDirect

COVER

An insight into biologically relevant chemical space showing the scaffolds of potential natural-product based inhibitors orbiting their target, the protein structure of protein 11-beta steroid dehydrogenase (PDB code 1xu7). Graphic produced using Pymol (<http://www.pymol.org>). [M. A. Koch, A. Schuffenhauer, M. Scheck, S. Wetzel, M. Casaulta, A. Odermatt, P. Ertl, H. Waldmann, Charting biologically relevant chemical space: A structural classification of natural products (SCONP), *PNAS* **2005**, 102, 17272–17277 and S. Wetzel, H. Waldmann, Cheminformatic analysis of natural products and their chemical space, *Chimia* **2007**, 61(6), 355–360].

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