



# Bioorganic & Medicinal Chemistry

The International Journal for Research at the Interface  
of Chemistry and Biology



Volume 15  
Number 1  
January 2007

Available online at  
**ScienceDirect**

# BIOORGANIC & MEDICINAL CHEMISTRY

*Editor-in-Chief: Professor Chi-Huey Wong*

Department of Chemistry, BCC 338, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, USA  
Facsimile: (1) 858 784 2409

*American Regional Editor: Professor K. D. Janda, The Scripps Research Institute, Department of Chemistry, The Skaggs Institute for Chemical Biology, The Worm Institute of Research & Medicine, 10550 North Torrey Pines Road, La Jolla, CA 92037, USA  
Facsimile: (1) 858 784 2595*

*Japanese Regional Editor: Professor Y. Hashimoto, Institute of Molecular & Cellular Biosciences, The University of Tokyo, 1-1-1 Yayoi, Bunkyo-ku, Tokyo 113-0032, Japan  
Facsimile: (81) 3 5841 8495*

*European Regional Editor: Professor H. Waldmann, Department of Chemical Biology, Max-planck-Institut für Molekulare Physiologie, Otto-Hahn-Strasse 11, 44227 Dortmund, Germany  
Facsimile: (49) 231 133 2499*

## EXECUTIVE BOARD OF EDITORS FOR TETRAHEDRON PUBLICATIONS

*Chairman: Professor H. Waldmann*

*Editor Emeritus: Professor H. H. Wasserman*

**Professor D. L. Boger**, Department of Chemistry, The Scripps Research Institute, La Jolla, CA 92037, USA

**Professor S. G. Davies**, Chemistry Research Laboratory, Department of Chemistry, University of Oxford, Mansfield Road, Oxford, OX1 3TA, UK

**Professor B. Ganem**, Department of Chemistry and Chemical Biology, Baker Laboratory, Cornell University, Ithaca, NY 14853-1301, USA

**Professor L. Ghosez**, l'Institut Européen de Chimie et de Biologie (IECB) 33607 Pessac Cedex, France

**Professor Lin Guo-Qiang**, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, China

**Professor Y. Hashimoto**, Institute of Molecular & Cellular Biosciences, The University of Tokyo, III-Yayoi, Bunkyo-ku, Tokyo 113-0032, Japan

**Professor T. Hayashi**, Department of Chemistry, Faculty of Science, Kyoto University, Kyoto 606, Japan

**Professor K. D. Janda**, Department of Chemistry, The Scripps Research Institute, La Jolla, CA 92037, USA

**Professor S. F. Martin**, Department of Chemistry and Biochemistry, University of Texas, Austin, TX 78712, USA

**Professor W. B. Motherwell**, Department of Chemistry, University College, 20 Gordon Street, London WC1H 0AJ, UK

**Professor S. Neidle**, The School of Pharmacy, Department of Pharmaceutical & Biological Chemistry, University of London, London WC1N 1AX, UK

**Professor M. Shibasaki**, Graduate School of Pharmaceutical Sciences, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

**Professor R. J. K. Taylor**, Department of Chemistry, University of York, Heslington, York YO10 5DD, UK  
(Associate Editors, Dr. P. A. O'Brien and Dr. D. K. Smith)

**Professor E. J. Thomas**, Department of Chemistry, University of Manchester, Brunswick Street, Manchester M13 9PL, UK  
(Associate Editor, Professor J. A. Joule)

**Professor K. Tomioka**, Graduate School of Pharmaceutical Sciences, Department of Synthetic Medicinal Chemistry, Kyoto University, Kyoto 606-8501, Japan

**Professor H. Waldmann**, Max-Planck-Institut für Molekulare Physiologie, Department of Chemical Biology, Otto-Hahn-Strasse 11, 44227 Dortmund, Germany

**Professor H. H. Wasserman**, Department of Chemistry, Yale University, PO Box 208107, New Haven, CT 06520 8107, USA

**Professor R. M. Williams**, Department of Chemistry, Colorado State University, Fort Collins, CO 80523

**Professor C.-H. Wong**, Department of Chemistry, The Scripps Research Institute, La Jolla, CA 92037, USA

**Professor J. Wood**, Department of Chemistry, Colorado State University, Fort Collins, CO 80523-1872

**Professor Y. Yamamoto**, Department of Chemistry, Faculty of Science, Tohoku University, Sendai 980-8578, Japan  
(Associate Editor, Professor M. Hirama)

**Professor S. Z. Zard**, Laboratoire de Synthèse Organique, Ecole Polytechnique, F-91128, Cedex, France  
(Associate Editor, Dr. B. Sire)

### BOARD OF CONSULTING EDITORS

**P. S. Anderson**, Wilmington, DE  
**K-H. Altmann**, Zürich  
**P. G. Baraldi**, Ferrara  
**C. F. Barbas, III**, La Jolla, CA  
**J. K. Barton**, Pasadena, CA  
**C. Bertozzi**, Berkeley, CA  
**R. C. Breslow**, New York, NY  
**T. C. Bruice**, Santa Barbara, CA  
**A. R. Chamberlin**, Irvine, CA  
**E. J. Corey**, Cambridge, MA  
**B. Cravatt**, La Jolla, CA  
**S. J. Danishefsky**, New York, NY  
**P. B. Dervan**, Pasadena, CA  
**A. Eschenmoser**, Zürich  
**J.-M. Fang**, Taipei

**A. R. Fersht**, Cambridge  
**D. M. Floyd**, Princeton, NJ  
**G. I. Georg**, Minneapolis, MN  
**A. Giannis**, Leipzig  
**B. Giese**, Basel  
**P. Gmeiner**, Erlangen  
**H. B. Gray**, Pasadena, CA  
**G. L. Grunewald**, Lawrence, KS  
**P. Herrling**, Basel  
**D. Hilvert**, Zürich  
**L. C. Hsieh-Wilson**, Pasadena, CA  
**W. L. Jorgensen**, New Haven, CT  
**A. R. Katritzky**, Gainesville, FL  
**J. A. Katzenellenbogen**, Urbana, IL  
**J. Kelly**, La Jolla, CA

**P. Krosgaard-Larsen**, Copenhagen  
**R. A. Lerner**, La Jolla, CA  
**H. Liu**, Austin, TX  
**A. McKillop**, Northumberland  
**R. Metternich**, Berlin  
**S. Mignani**, Vitry-sur-Seine  
**L. A. Mitscher**, Lawrence, KS  
**K. C. Nicolaou**, La Jolla, CA  
**H. L. Pearce**, Indianapolis, IN  
**C. D. Poulter**, Salt Lake City, UT  
**J. Rebek, Jr.**, La Jolla, CA  
**B. Samuelsson**, Stockholm  
**J. Saunders**, San Diego, CA  
**S. L. Schreiber**, Cambridge, MA  
**P. G. Schultz**, La Jolla, CA

**P. Seeburger**, Zürich  
**O. Seitz**, Berlin  
**K. Shokat**, San Francisco, CA  
**R. Silverman**, Evanston, IL  
**J. Stubbe**, Cambridge, MA  
**C. T. Supuran**, Firenze  
**G. L. Verdine**, Cambridge, MA  
**S. Walker**, Cambridge, MA  
**C. T. Walsh**, Boston, MA  
**P. A. Wender**, Stanford, CA  
**G. Whitesides**, Cambridge, MA  
**R. V. Wolfenden**, Chapel Hill, NC



Contents lists available at ScienceDirect

# Bioorganic & Medicinal Chemistry

journal homepage: [www.elsevier.com/locate/bmc](http://www.elsevier.com/locate/bmc)

## Bioorganic & Medicinal Chemistry Volume 18, Issue 6, 2010

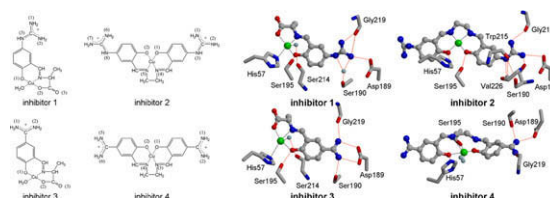
### Contents

#### 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\*

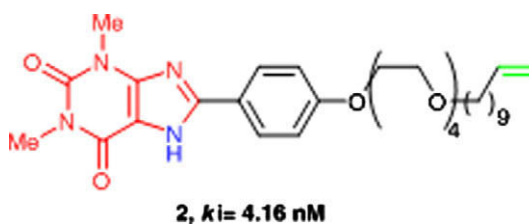


The crystal structures of the complexes of  $\beta$ -trypsin with *m*-guanidinosalicylidene-*L*-alaninato(aqua)copper(II) hydrochloride, [*N,N*-bis(*m*-guanidinosalicylidene)ethylenediaminato]copper(II), and [*N,N'*-bis(*m*-amidinosalicylidene)ethylenediaminato]copper(II) have been determined. The structural 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

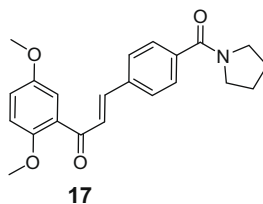


Synthesis of oligo(ethylene glycol)-alkene substituted theophyllines (positions 7 and/or 8) is described. Compound **2** showed high affinity and selectivity for  $A_{2B}$  receptor ( $K_i = 4.16$  nM,  $K_{iA_{2A}}/K_{iA_{2B}} = 24.1$ ). The alkenyl or azido substituents in some of the derivative allows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

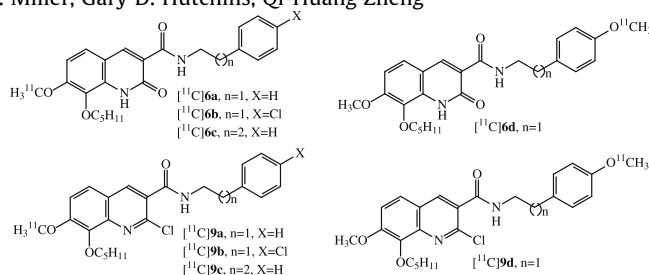


A series of novel 2',5'-dimethoxychalcone derivatives including 18 new compounds were synthesized and evaluated for cytotoxicities against two human cancer cell lines, NTUB1 (human bladder cancer cell line) and PC3 (human prostate cancer cell line) cell lines.

### 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\*

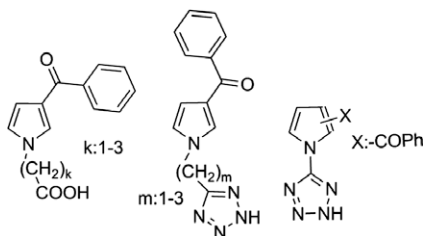


This paper reports the synthesis and in vitro biological evaluation of carbon-11-labeled quinoline derivatives as new candidate radioligands for PET imaging of cannabinoid CB2 receptor in cancer.

### 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

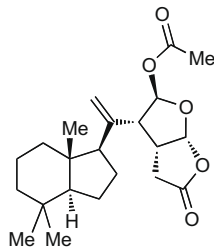


Potential inhibitors of aldose reductase enzyme, related to long-term complications of diabetes, were synthesized and tested. Pyrrolyl-tetrazole derivatives without an alkyl chain between the two aromatic rings have been shown significant inhibitory activity and selectivity.

### Chemical biology studies on norrisolide

pp 2115–2122

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



7: norrisolide

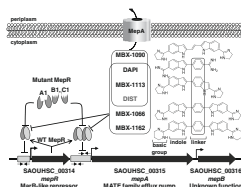
Our studies on the chemical biology of norrisolide are presented. This natural product was found to induce irreversible vesiculation of Golgi membranes and specifically block protein transport at the level of the Golgi apparatus. Through the use of fluorescent derivatives of norrisolide, we demonstrated 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



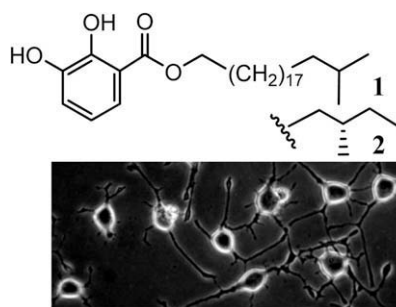
An analysis of efflux-mediated resistance to a panel of chemically related bis-indole antibiotics revealed interesting trends in the substrate specificities of the MepA efflux pump and the substrate-responsive repressor MepR in *Staphylococcus aureus*.



**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\*

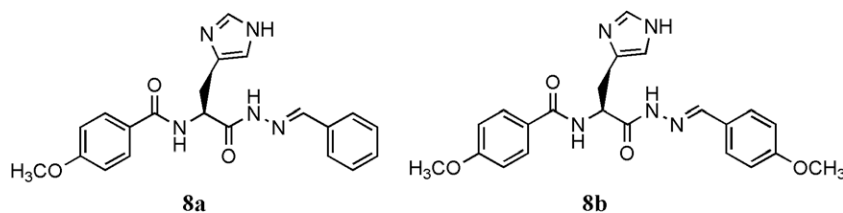


Two new alkyl 2,3-dihydroxybenzoates, gentisides A and B, were isolated from the traditional Chinese medicine *Gentiana rigescens* Franch. They showed a significant neuritogenic activity at 30  $\mu$ M against PC12 cells that was comparable to that seen for the best nerve growth factor concentration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

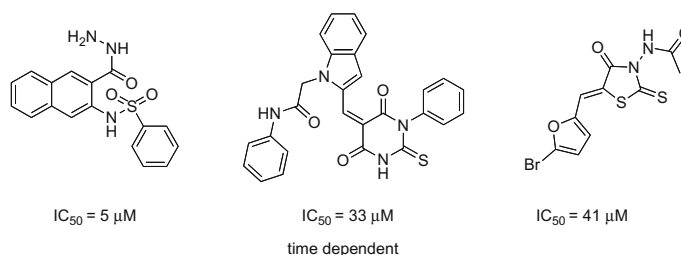


We studied SAR and molecular mechanism of novel acylhydrazone compounds targeting HIV-1 CA. Among synthesized compounds, **8a** and **8b** possessed the most promising antiviral activities.

**Exploration of inhibitors for diaminopimelate aminotransferase**

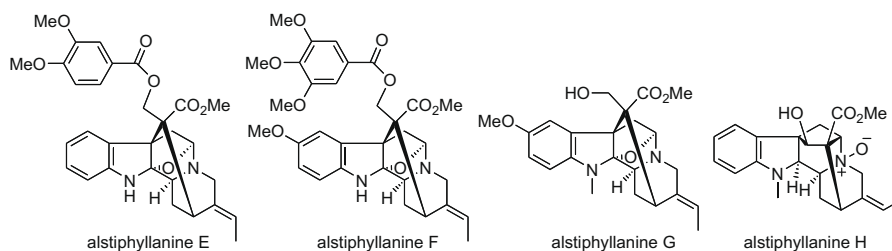
pp 2141–2151

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

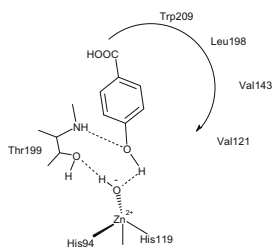
Hiroko Arai, Yusuke Hirasawa, Abdul Rahman, Idha Kusumawati, Noor Cholies Zaini, Seizo Sato, Chihiro Aoyama, Jiro Takeo, Hiroshi Morita\*



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

pp 2159–2164

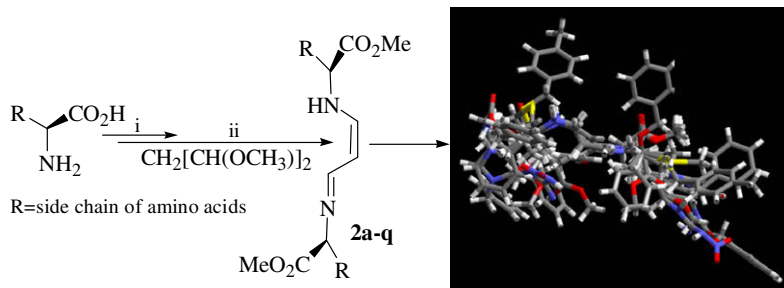
Alessio Innocenti, S. Beyza Öztürk Sarıkaya, İlhami Gülçin\*, Claudiu T. Supuran\*


 $K_i = 0.92 \mu\text{M}$  (hCA I);  $K_i = 0.87 \mu\text{M}$  (hCA II);  $K_i = 3.73 \mu\text{M}$  (hCA IX)

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

pp 2165–2172

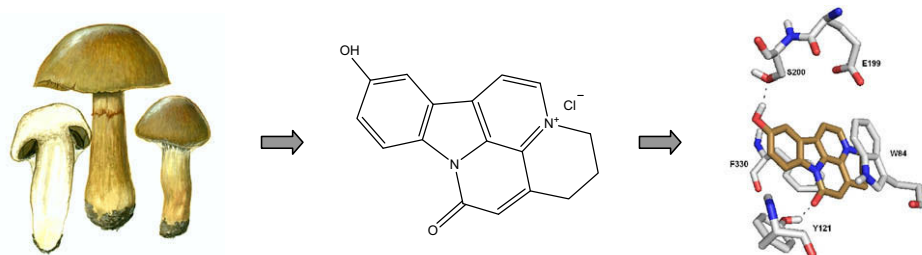
Yinjian Zhou, Ming Zhao\*, Yingting Wu, Chunyu Li, Jianhui Wu, Meiqing Zheng, Li Peng, Shiqi Peng\*



### Acetylcholinesterase inhibitors from the toadstool *Cortinarius infractus*

pp 2173–2177

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



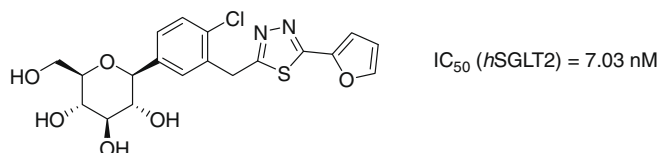
The isolation of acetylcholinesterase inhibitors ( $IC_{50} = 9.7 \mu\text{M}$ ) from fungal source is reported. The selective binding mode is resolved by docking studies. The pharmacological potential is further supported by  $A\beta$ -aggregation and cytotoxicity studies.



### Novel C-aryl glucoside SGLT2 inhibitors as potential antidiabetic agents: 1,3,4-Thiadiazolymethylphenyl 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\*

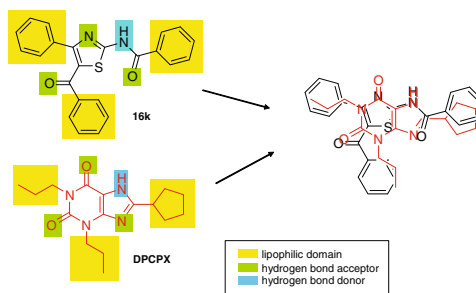


Novel C-aryl glucoside SGLT2 inhibitors containing 1,3,4-thiadiazole at the distal ring position were identified as potential antidiabetic agents. A selected compound demonstrated reasonable urinary glucose excretion and glucosuria in normal SD rats along with favorable blood glucose-lowering effects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

**2-Amino-5-benzoyl-4-phenylthiazoles: Development of potent and selective adenosine A<sub>1</sub> receptor antagonists**

pp 2195–2203

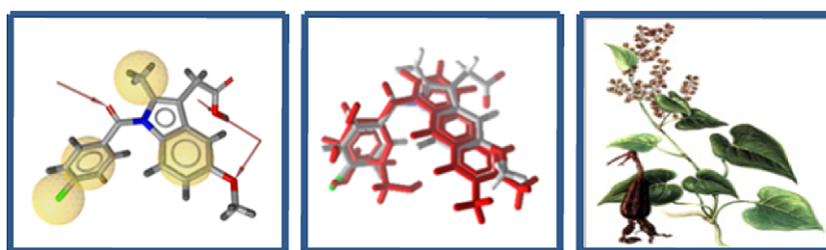
Anja B. Scheiff, Swapnil G. Yerande, Ali El-Tayeb, Wenjin Li, Gajanan S. Inamdard, Kamala K. Vasu, Vasudevan Sudarsanam, Christa E. Müller\*



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

pp 2204–2218

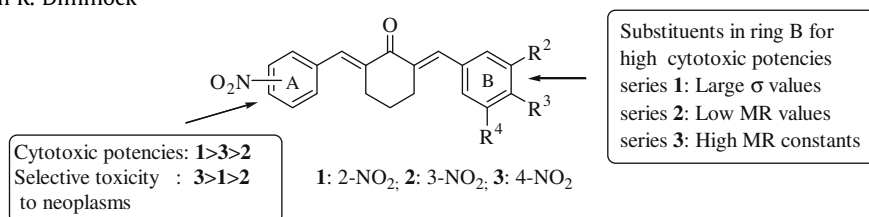
Thomas M. Ehrman, David J. Barlow\*, Peter J. Hylands



**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\*

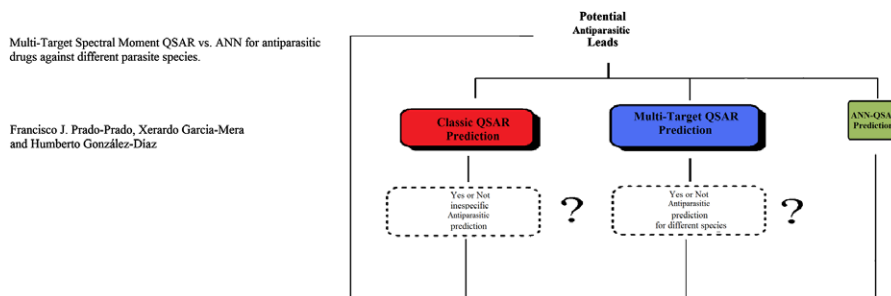


A number of 2-benzylidene-6-(nitrobenzylidene)cyclohexanones emerged as lead compounds which possess noteworthy cytotoxicity, selective toxicity towards neoplasms than non-malignant cells and well tolerated in mice in short-term toxicity studies.

**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\*

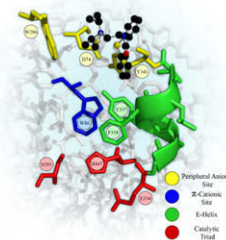


### Differential binding of phenothiazine urea derivatives to wild-type human cholinesterases and butyrylcholinesterase mutants

pp 2232–2244

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

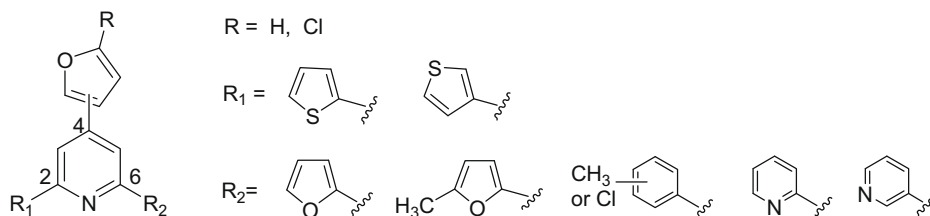
Most phenothiazine urea derivatives are specific butyrylcholinesterase inhibitors. Aminourea derivatives inhibit both acetylcholinesterase and butyrylcholinesterase and the use of butyrylcholinesterase mutants and elevated substrate reveals involvement of a salt linkage in that inhibitory process.



### 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\*

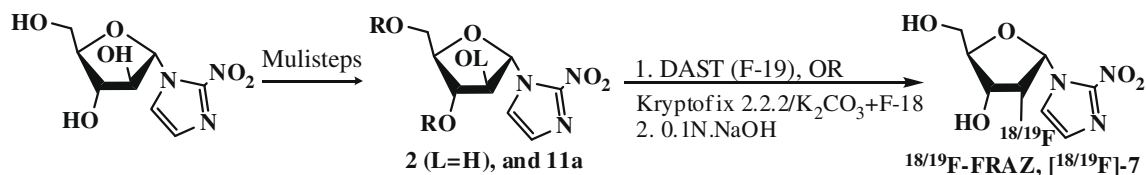


Designed and synthesized 48 2-thienyl-4-furyl-6-aryl pyridine derivatives were evaluated for their topoisomerase I and II inhibitory activity and cytotoxicity against several human cancer cell lines.

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

pp 2255–2264

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

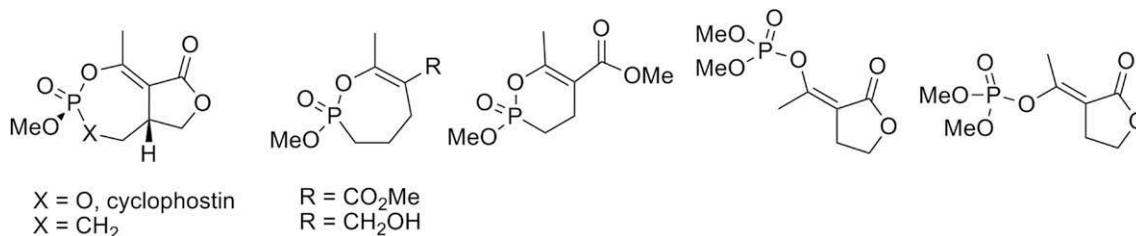


The synthesis and F-18 radiolabeling of FRAZ, an azomycin nucleoside-based novel compound, are shown. FRAZ has radiosensitization properties similar to FAZA, a clinical PET radiodiagnostic for hypoxic tumors.

### 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\*

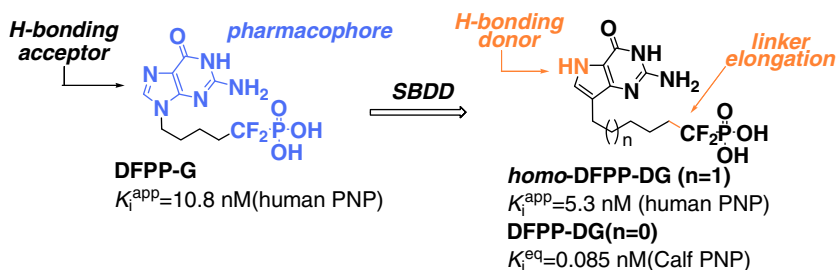




**Structural-based design and synthesis of novel 9-deazaguanine derivatives having a phosphate mimic as multi-substrate analogue inhibitors for mammalian PNPs**

pp 2275–2284

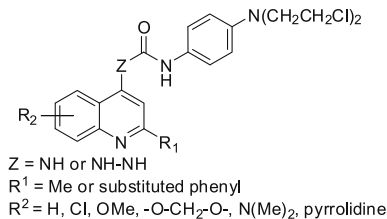
Sadao Hikishima, Mariko Hashimoto, Lucyna Magnowska, Agnieszka Bzowska, Tsutomu Yokomatsu\*



**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\*

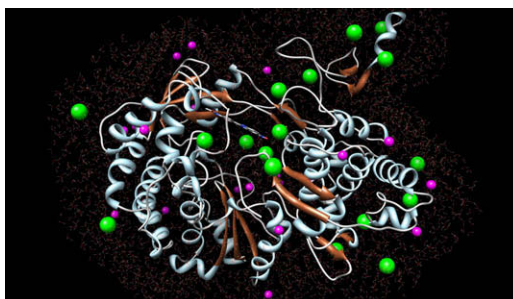


*Stylophora pycnosticta* (coral) CA is activated by amines and amino acids.

**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

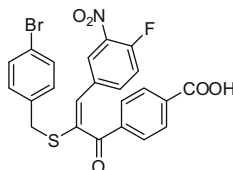
Michele Tonelli, Vito Boido, Paolo La Colla, Roberta Loddo, Paola Posocco, Maria Silvia Paneni, Maurizio Fermeglia, Sabrina Pricl\*



**Design, synthesis and evaluation of (*E*)- $\alpha$ -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\*

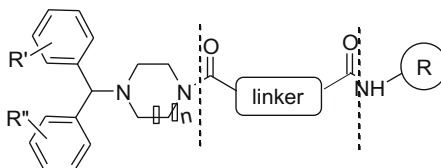


The design, synthesis and biological evaluation of novel (*E*)- $\alpha$ -benzylthio chalcones as BCR-ABL kinase inhibitors are described. The structure–activity relationship, in vitro cytotoxicity in K562, a human leukemic cell line and inhibition of BCR-ABL phosphorylation by these compounds is discussed.

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

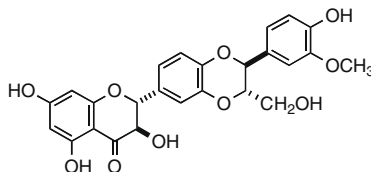
pp 2327–2336

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  $\mu$ 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  $\mu$ 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].

---

Available online at [www.sciencedirect.com](http://www.sciencedirect.com)



---

Indexed/Abstracted in: Beilstein, Biochemistry & Biophysics Citation Index, CANCERLIT, Chemical Abstracts, Chemistry Citation Index, Current Awareness in Biological Sciences/BIOBASE, Current Contents: Life Sciences, EMBASE/Excerpta Medica, MEDLINE, PASCAL, Research Alert, Science Citation Index, SciSearch, TOXFILE. Also covered in the abstract and citation database SCOPUS®. Full text available on ScienceDirect®

---



ELSEVIER

ISSN 0968-0896



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

Hiroko Arai<sup>a</sup>, Yusuke Hirasawa<sup>a</sup>, Abdul Rahman<sup>b</sup>, Idha Kusumawati<sup>b</sup>, Noor Cholies Zaini<sup>b</sup>, Seizo Sato<sup>c</sup>, Chihiro Aoyama<sup>c</sup>, Jiro Takeo<sup>c</sup>, Hiroshi Morita<sup>a,\*</sup>

<sup>a</sup> Faculty of Pharmaceutical Sciences, Hoshi University, Shinagawa, Tokyo 142-8501, Japan

<sup>b</sup> Faculty of Pharmacy, Airlangga University, Jalan Dharmawangsa Dalam, Surabaya 60286, Indonesia

<sup>c</sup> Central Research Laboratory, Nippon Suisan Kaisha, Ltd, 559-6 Kitano-machi, Hachioji, Tokyo 192-0906, Japan

### ARTICLE INFO

#### Article history:

Received 10 December 2009

Revised 29 January 2010

Accepted 30 January 2010

Available online 6 February 2010

#### Keywords:

Indole alkaloids

*Alstonia macrophylla*

Alstiphyllanines E–H

SGLT

### ABSTRACT

Three new picraline-type alkaloids, alstiphyllanines E–G (**1–3**) and a new ajmaline-type alkaloid, alstiphyllanine H (**4**) were isolated from the leaves of *Alstonia macrophylla* together with 16 related alkaloids (**5–20**). Structures and stereochemistry of **1–4** were fully elucidated and characterized by 2D NMR analysis. Alstiphyllanines E and F (**1** and **2**) showed moderate Na<sup>+</sup>-glucose cotransporter (SGLT1 and SGLT2) inhibitory activity. A series of a hydroxy substituted derivatives **21–28** at C-17 of the picraline-type alkaloids have been derived as having potent SGLT inhibitory activity. 10-Methoxy-*N*(1)-methylburnamine-17-*O*-veratrate (**6**) exhibited potent inhibitory activity, suggesting that the presence of an ester side chain at C-17 may be important to show SGLT inhibitory activity. Structure activity relationship of alstiphyllanines on inhibitory activity of SGLT was discussed.

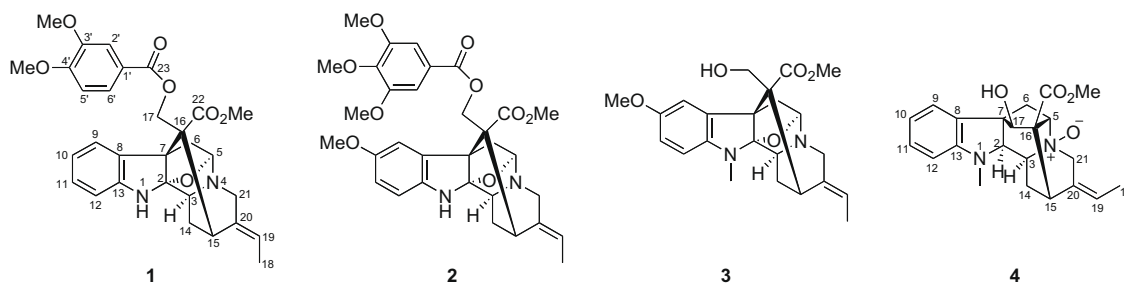
© 2010 Elsevier Ltd. All rights reserved.

### 1. Introduction

Na<sup>+</sup>-glucose cotransporter (SGLT) is a membrane protein that plays an important role in the re-absorption of glucose in the kidneys. SGLT is known to have three isoforms (SGLT1, SGLT2, and SGLT3).<sup>1–3</sup> SGLT1 is expressed primarily in the brush border membrane of mature enterocytes in the small intestine, where it absorbs dietary glucose and galactose from the gut lumen.<sup>4</sup> SGLT2 is only expressed in the renal cortex, where it is assumed to be present in the brush border membrane of the S1 and S2 segments of the proximal tubule, and to be responsible for the re-absorption of glucose from the glomerular filtrate.<sup>4</sup> It is expected that the inhi-

bition of SGLT could decrease glucose re-absorption and that this could thus result in an increase in urinary sugar excretion, and a decrease in blood glucose level. Thus, SGLT inhibitors have therapeutic potential for type 2 diabetes.<sup>5</sup>

Our screening study on SGLT inhibitors in traditional medicine<sup>6</sup> discovered that the methanol extract of *Alstonia macrophylla* shows moderate SGLT inhibitory activity. The genus *Alstonia*, which is widely distributed in tropical regions of Africa and Asia, are well-known rich sources of unique monoterpene indole alkaloids with various biological activities such as anticancer, antibacterial, anti-inflammatory, antitussive, and antimalarial properties.<sup>7</sup> Recently, several new indole alkaloids were isolated from extracts of *Alstonia*



\* Corresponding author. Tel./fax: +81 3 5498 5778.

E-mail address: moritah@hoshi.ac.jp (H. Morita).

species collected in Indonesia and Malaysia.<sup>8,9</sup> With an aim to isolate additional alkaloids against SGLT inhibitory activity, purification of extracts of *A. macrophylla* Wall.ex G. Don (Apocynaceae) collected in Indonesia led to four new alkaloids alstiphyllanines E–H (1–4) together with 16 known alkaloids (5–20). Herein we report the isolation and structure elucidation of four new indole alkaloids, alstiphyllanines E–H (1–4) from *A. macrophylla* as well as SGLT inhibitory activity and structure activity relationship (SAR) study of some picraline-type indole alkaloids.

## 2. Results and discussion

### 2.1. Structures of alstiphyllanines E–H (1–4)

Leaves of *A. macrophylla* were extracted with MeOH, and the extract was partitioned between EtOAc and 3% aqueous tartaric acid. Water-soluble materials, adjusted to pH 9 with satd aq Na<sub>2</sub>CO<sub>3</sub>, were extracted with CHCl<sub>3</sub>. The CHCl<sub>3</sub>-soluble materials were subjected to an LH-20 column (CHCl<sub>3</sub>/MeOH, 1:1) followed by a silica gel column (CHCl<sub>3</sub>/MeOH, 1:0–0:1). The eluted fractions were further separated by ODS HPLC (MeOH/H<sub>2</sub>O/TFA) to afford **1** (1.8 mg, 0.00050% dry weight), **2** (1.3 mg, 0.00036%), **3** (10.4 mg, 0.0029%), and **4** (3.6 mg, 0.0013%), together with 16 known alkaloids, burnamine-17-*O*-3',4',5'-trimethoxybenzoate<sup>10</sup> (**5**), 10-methoxy-*N*(1)-methylburnamine-17-*O*-veratrate<sup>10</sup> (**6**), alstiphyllanine D<sup>9</sup> (**7**), alstiphyllanine B<sup>9</sup> (**8**), alstiphyllanine C<sup>9</sup> (**9**), picralinal<sup>11</sup> (**10**), picrinine<sup>11</sup> (**11**), quaternine<sup>12</sup> (**12**), *O*-deacetylpicraline<sup>13</sup> (**13**), vincamedine<sup>14</sup> (**14**), vincamajine<sup>15</sup> (**15**), alstiphyllanine A<sup>9</sup> (**16**), vincamajine-17-*O*-veratrate<sup>16</sup> (**17**), vincamajine-17-*O*-3',4',5'-trimethoxybenzoate<sup>16</sup> (**18**), alstonal<sup>17</sup> (**19**), and alstonerine<sup>14</sup> (**20**).

Alstiphyllanine E (**1**, [ $\alpha$ ]<sub>D</sub><sup>26</sup> –93 (c 1.0, MeOH)) was revealed to have the molecular formula C<sub>30</sub>H<sub>32</sub>N<sub>2</sub>O<sub>7</sub>, by HRESITOFMS [*m/z* 533.2272 (M+H)<sup>+</sup>,  $\Delta$  –1.6 mmu]. The <sup>1</sup>H NMR data (Table 1) showed the presence of seven aromatic protons, an ethylidene side chain, a methyl ester function, and two methoxy groups. The HMBC cross-peak of H<sub>2</sub>-21 to C-19 indicated the ethylidene side chain at C-20. The position of each methoxy group was confirmed

by HMBC correlations of *O*-Me to C-3' and C-4'. HMBC correlations for H-5 to C-2, H<sub>2</sub>-17 to C-7, and H<sub>2</sub>-6 to C-16 indicated alstiphyllanine E possessed picraline-type skeleton. The molecular formulae of alstiphyllanine E was smaller than that of burnamin-17-*O*-3',4',5'-trimethoxybenzoate<sup>9</sup> by CH<sub>2</sub>O unit. Compared with <sup>1</sup>H NMR data of burnamin-17-*O*-3',4',5'-trimethoxybenzoate,<sup>9</sup> alstiphyllanine E was suggested a picraline-type backbone without *O*-Me at C-5'. The relative stereochemistry of **1** was elucidated by NOESY correlations as shown in computer-generated 3D drawing (Fig. 1). The NOESY correlation of H<sub>3</sub>-18 to H-15 indicated that the geometry of ethylidene side chain was *E*. The  $\beta$ -orientation of C-17 was elucidated by the NOESY correlation of H-14b/H-17a.

Alstiphyllanine F (**2**, [ $\alpha$ ]<sub>D</sub><sup>26</sup> –32 (c 1.0, MeOH)) was revealed to have the molecular formula C<sub>32</sub>H<sub>36</sub>N<sub>2</sub>O<sub>8</sub>, by HRESITOFMS [*m/z* 593.2511 (M+H)<sup>+</sup>,  $\Delta$  –1.2 mmu], which was larger than that of burnamin-17-*O*-3',4',5'-trimethoxybenzoate by CH<sub>2</sub>O unit. Compared with <sup>1</sup>H NMR data of burnamin-17-*O*-3',4',5'-trimethoxybenzoate, alstiphyllanine F was suggested a picraline-type backbone with *O*-Me. The HMBC cross-peak of H<sub>3</sub>-*O*-Me ( $\delta$ <sub>H</sub> 3.27) to C-10 ( $\delta$ <sub>C</sub> 156.5) revealed the presence of an indole moiety with a methoxy group at C-10. HRESITOFMS data [*m/z* 413.2080 (M+H)<sup>+</sup>,  $\Delta$  –0.4 mmu] of alstiphyllanine G (**3**, [ $\alpha$ ]<sub>D</sub><sup>26</sup> –42 (c 1.0, MeOH)) established the molecular formula, C<sub>23</sub>H<sub>28</sub>N<sub>2</sub>O<sub>5</sub>, which was larger than that of *O*-deacetylpicraline<sup>13</sup> by C<sub>2</sub>H<sub>4</sub>O unit. The NMR data of **3** were analogous to those of *O*-deacetylpicraline<sup>13</sup> except for the following observation: a methoxy signal ( $\delta$ <sub>H</sub> 3.70) and an *N*-methyl signal ( $\delta$ <sub>H</sub> 2.89) lacking in *O*-deacetylpicraline appeared for **3**. The presence of both methyl groups was verified by the HMBC correlations of the methoxy protons to C-10 and the *N*-methyl protons to C-2 and C-13.

Alstiphyllanine H (**4**, [ $\alpha$ ]<sub>D</sub><sup>26</sup> –21 (c 1.0, MeOH)) was obtained as a brown amorphous solid and was revealed to have the molecular formula C<sub>22</sub>H<sub>26</sub>N<sub>2</sub>O<sub>4</sub>, by HRESITOFMS [*m/z* 383.1971 (M+H)<sup>+</sup>,  $\Delta$  –2.7 mmu], which was larger than that of vincamajine<sup>15</sup> by an oxygen unit. The <sup>1</sup>H NMR data (Table 1) showed the presence of four aromatic protons, an ethylidene side chain, a methyl ester function, and an *N*-methyl group. Partial structures C-9–C-12,

**Table 1**  
<sup>1</sup>H NMR data [ $\delta$ <sub>H</sub> (J, Hz)] of alstiphyllanines E–H (1–4)

	<b>1</b> <sup>a</sup>	<b>2</b> <sup>a</sup>	<b>3</b> <sup>b</sup>	<b>4</b> <sup>a</sup>
2				3.55 (d, 4.8)
3	4.07 (s)	4.00 (s)	3.73 (d, 3.6)	4.39 (m)
5	5.56 (s)	5.56 (s)	4.72 (d, 2.6)	4.42 (m)
6a	2.67 (d, 15.4)	2.66 (15.1)	2.33 (dd, 13.9, 2.6)	2.53 (d, 14.4)
6b	3.17 (d, 15.4)	3.25 (m)	3.30 (d, 13.9)	2.73 (d, 14.4)
9	7.56 (d, 7.4)	7.03 (s)	6.93 (d, 2.6)	7.20 (d, 7.2)
10	6.54 (dd, 7.4, 7.2)			6.83 (dd, 7.2, 7.2)
11	6.87 (dd, 7.5, 7.2)	6.60 (d, 8.4)	6.73 (dd, 8.5, 2.6)	7.19 (dd, 7.6, 7.2)
12	6.73 (d, 7.5)	6.33 (d, 8.4)	6.59 (d, 8.5)	6.77 (d, 7.6)
14a	2.23 (d, 14.8)	2.29 (d, 15.1)	1.97 (m)	2.10 (m)
14b	2.41 (d, 14.8)	2.37 (d, 15.1)		2.74 (m)
15	3.40 (s)	3.35 (s)	3.48 (s)	3.36 (s)
17a	4.08 (d, 11.4)	4.09 (d, 10.9)	3.47 (d, 12.3)	4.16 (s)
17b	4.57 (d, 11.4)	4.94 (d, 10.9)	3.73 (d, 12.3)	
18	1.70 (d, 6.8)	1.76 (d, 7.2)	1.56 (dd, 7.1, 2.0)	1.61 (d, 6.5)
19	5.74 (q, 6.8)	5.76 (q, 7.2)	5.35 (q, 7.1)	5.55 (q, 6.5)
21a	4.25 (d, 17.1)	4.02 (m)	3.11 (d, 15.9)	4.46 (d, 15.1)
21b	4.00 (d, 17.1)	4.16 (d, 16.1)	3.66 (d, 15.9)	4.55 (d, 15.1)
CO <sub>2</sub> Me	3.75 (s)	3.80 (s)	3.72 (s)	3.73 (s)
10- <i>O</i> -Me		3.27 (s)	3.70 (s)	
3'- <i>O</i> -Me	3.86 (s)	3.89 (s)		
4'- <i>O</i> -Me	3.88 (s)	3.81 (s)		
5'- <i>O</i> -Me		3.89 (s)		
<i>N</i> (1)-Me			2.89 (s)	2.66 (s)
2'	7.15 (s)	6.91 (s)		
5'	6.94 (d, 8.4)			
6'	7.28 (d, 8.4)	6.91 (s)		

<sup>a</sup> TFA salt in CD<sub>3</sub>OD.

<sup>b</sup> Free base in CDCl<sub>3</sub>.

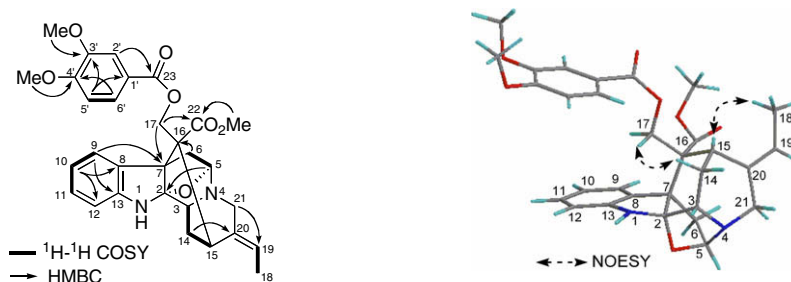


Figure 1. Selected 2D NMR correlations for alstiphyllanine E (1).

C-5–C-6, C-2–C-15, and C-18–C-19 were deduced from a detailed analysis of  $^1\text{H}$ - $^1\text{H}$  COSY spectrum of **4**. The HMBC cross-peaks of H<sub>3</sub>-18 to C-20 and H-19 to C-15 indicated the presence of an ethylidene side chain at C-20 (Fig. 2). And the presence of an indoline ring was elucidated by HMBC correlations for H-9 to C-7 and *N*-Me to C-2 and C-13. HMBC correlations for H-2, H-5, and H-6a to C-17 and H-6a and H-14a to C-16 indicated alstiphyllanine H possessed ajmaline-type skeleton. Comparison of  $^{13}\text{C}$  chemical shifts of C-3, C-5, and C-21 ( $\delta_{\text{C}}$  70.5, 77.4, and 67.3, respectively) in **4** with those ( $\delta_{\text{C}}$  53.2, 61.7, and 55.6, respectively) of vincamedine<sup>14</sup> indicated the presence of an *N*-oxide functionality at *N*-4. The relative stereochemistry of **4** was elucidated by NOESY correlations as shown in computer-generated 3D drawing (Fig. 2). NOESY correlations of H<sub>3</sub>-18 to H-21 indicated that the geometry of the ethylidene side chain was *Z*. The NOESY correlations of H-3/H-2 and H-14a and H-14b/H-17 indicated that H-2 was  $\alpha$ -orientated and H-17 was  $\beta$ -orientated. Oxidation of vincamajine with *m*-chloroperoxybenzoic acid (*m*-CPBA) afforded the *N*-oxide derivative, whose spectral data and the  $[\alpha]_{\text{D}}$  value were identical with those of natural alstiphyllanine H. Thus, the structure of alstiphyllanine H was elucidated as shown in Figure 2.

## 2.2. SGLT inhibitory activity

The *in vitro* SGLT inhibitory potential of alkaloids **1**–**20** was assessed by monitoring inhibition of uptake of methyl- $\alpha$ -D-glucopyranoside in cultured cells expressing SGLT1 or SGLT2 at 50  $\mu\text{M}$  (Table 3). As shown in Table 3, picaline-type alkaloids with vertrate or trimethoxybenzoate at C-17 such as compounds **1**, **2**, and **5**–**7**, showed inhibitory activity against SGLT1 and SGLT2. However, compounds **8** and **9** which have an *N*(4)-Me group were found to have no SGLT inhibitory activity. Any ajmaline and macroline type alkaloids (**4** and **14**–**20**) did not show inhibition on SGLT1 and SGLT2.

To discuss SAR of picaline-type alkaloids showing SGLT inhibitory activity, we prepared eight picaline-type derivatives **21**–**28** from **6** and **7** by use of acyl anhydride, *m*-CPBA, and boron tribromide, respectively (Table 4). As shown in Table 4, the presence of

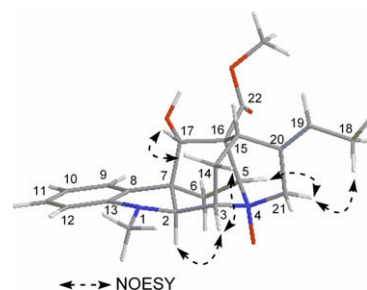
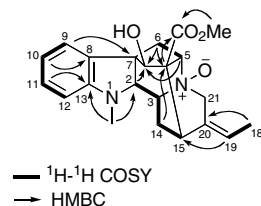


Figure 2. Selected 2D NMR correlations for alstiphyllanine H (4).

Table 2  
 $^{13}\text{C}$  NMR data ( $\delta_{\text{C}}$ ) of alstiphyllanines E–H (1–4)

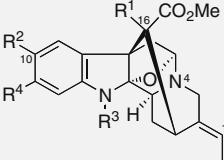
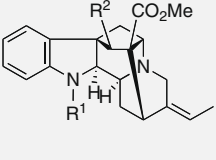
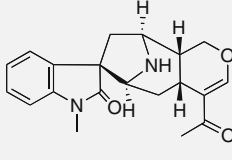
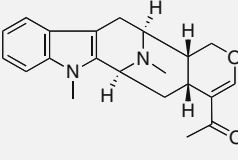
	1 <sup>a</sup>	2 <sup>a</sup>	3 <sup>b</sup>	4 <sup>a</sup>
2	109.5	106.6	109.6	70.9
3	54.8	53.3	49.4	70.5
5	90.5	89.9	86.9	77.4
6	41.6	44.6	44.8	32.1
7	53.1	53.1	52.7	57.3
8	132.9	136.0	134.2	130.1
9	128.4	117.4	113.3	126.4
10	122.4	156.5	154.5	120.9
11	129.6	112.9	112.9	129.7
12	112.1	112.8	109.5	110.7
13	149.4	143.8	145.4	155.2
14	20.4	22.5	21.6	22.9
15	39.9	37.0	33.0	36.3
16	59.0	58.5	57.5	63.3
17	67.3	69.6	64.1	74.6
18	13.1	14.7	13.1	12.8
19	128.2	126.0	119.9	122.1
20	132.9	132.5	137.8	129.5
21	42.2	47.2	46.7	67.3
22	172.8	174.8	174.6	171.3
23	166.3	166.5		
CO <sub>2</sub> Me	52.4	53.1	55.8	52.9
10-O-Me		56.2	51.8	
3'-O-Me	56.4	57.3		
4'-O-Me	56.4	61.8		
5'-O-Me		57.3		
<i>N</i> (1)-Me			30.1	35.0
1'	122.5	125.8		
2'	129.6	108.7		
3'	149.8	154.9		
4'	153.1	143.9		
5'	111.6	154.9		
6'	125.0	108.7		

<sup>a</sup> TFA salt in CD<sub>3</sub>OD.

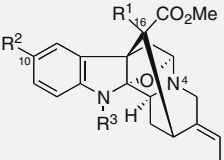
<sup>b</sup> Free base in CDCl<sub>3</sub>.

an *N*(1)-Me group promoted SGLT1 inhibitory activity when compared to those of **1**, **2** and **5**. Compound **22** which was converted a methoxy group at C-10 of **7** into a hydroxyl showed less activity against SGLT1, whereas *N*(4)-oxide derivatives **23** and **24** with a

**Table 3**  
Structures and SGLT inhibitory activity of alkaloids **1–20**

	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	Inhibition % <sup>a</sup>	
					SGLT1	SGLT2
<i>Picaline-type alkaloids</i>						
<b>1</b>	CH <sub>2</sub> O-Bz(OMe) <sub>2</sub>	H	H	H	60.3	85.9
<b>2</b>	CH <sub>2</sub> O-Bz(OMe) <sub>3</sub>	OMe	H	H	65.2	103.8
<b>3</b>	CH <sub>2</sub> OH	OMe	Me	H	14.0	31.6
<b>5</b>	CH <sub>2</sub> O-Bz(OMe) <sub>3</sub>	H	H	H	19Z	53.0
<b>6</b>	CH <sub>2</sub> O-Bz(OMe) <sub>2</sub>	OMe	Me	H	95.8	102.6
<b>7</b>	CH <sub>2</sub> O-Bz(OMe) <sub>3</sub>	OMe	Me	H	89.9	101.4
<b>8</b>	CH <sub>2</sub> O-Bz(OMe) <sub>2</sub>	OMe	Me	H	N(4)-Me	-10.3
<b>9</b>	CH <sub>2</sub> O-Bz(OMe) <sub>3</sub>	OMe	Me	H	N(4)-Me	-8.2
<b>10</b>	CHO	H	H	H		16.5
<b>11</b>	H	H	H	H		9.6
<b>12</b>	H	OMe	H	OMe		11.7
<b>13</b>	CH <sub>2</sub> OH	H	H	H		10.1
<i>Ajmaline-type alkaloids</i>						
<b>4</b>	Me	OH			N(4)-oxide	4.3
<b>14</b>	Me	OAc				22.0
<b>15</b>	Me	OH				11.5
<b>16</b>	Me	OAc			N(4)-oxide	5.3
<b>17</b>	Me	OBz(OMe) <sub>2</sub>				26.0
<b>18</b>	Me	OBz(OMe) <sub>3</sub>				7.2
<i>Macroline-type alkaloids</i>						
<b>19</b>						15.8
<b>20</b>						20.7
						
	picaline type ( <b>1–3</b> and <b>5–13</b> )	ajmaline type ( <b>4</b> and <b>14–18</b> )	macroline type <b>19</b>	macroline type <b>20</b>		

<sup>a</sup> Inhibition (%) at 50 μM.**Table 4**  
Structures and SGLT inhibitory activity of picaline-type derivatives **1, 2, 5–7, and 21–28**

	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Inhibition % <sup>a</sup> (IC <sub>50</sub> μM)	
				SGLT1	SGLT2
<b>1</b>	CH <sub>2</sub> O-Bz(OMe) <sub>2</sub>	H	H	60.3 (44)	85.9 (40)
<b>2</b>	CH <sub>2</sub> O-Bz(OMe) <sub>3</sub>	OMe	H	65.2 (39)	103.8 (40)
<b>5</b>	CH <sub>2</sub> O-Bz(OMe) <sub>3</sub>	H	H	19Z	53.0 (50)
<b>6</b>	CH <sub>2</sub> O-Bz(OMe) <sub>2</sub>	OMe	Me	95.8 (4)	102.6 (0.5)
<b>7</b>	CH <sub>2</sub> O-Bz(OMe) <sub>3</sub>	OMe	Me	89.9 (5)	101.4 (2)
<b>21</b>	CH <sub>2</sub> O-Bz	OMe	Me	85.2 (17)	100.1 (1)
<b>22</b>	CH <sub>2</sub> O-Bz(OH) <sub>3</sub>	OH	Me	46.9 (50)	95.6 (7)
<b>23</b>	CH <sub>2</sub> O-Bz(OMe) <sub>2</sub>	OMe	Me	N(4)-oxide	94.6 (5)
<b>24</b>	CH <sub>2</sub> O-Bz(OMe) <sub>3</sub>	OMe	Me	N(4)-oxide	93.8 (4)
<b>25</b>	CH <sub>2</sub> O-cinnamoyl	OMe	Me	96.3 (5)	102.8 (1)
<b>26</b>	CH <sub>2</sub> O-Ac	OMe	Me	5.4 (>100)	39.9 (78)
<b>27</b>	CH <sub>2</sub> OCOCH <sub>2</sub> CH <sub>3</sub>	OMe	Me	27.1 (97)	86.9 (12)
<b>28</b>	CH <sub>2</sub> O-Bn	OMe	Me	7.6 (>100)	25.7 (>100)
					
	picaline type ( <b>1, 2, 5–7, and 21–28</b> )				

<sup>a</sup> Inhibition (%) at 50 μM.

methoxy group at C-10 showed less activity against SGLT2. Aliphatic esters at C-17 such as **26** and **27** showed less activity against both SGLT1 and SGLT2, and the presence of an aromatic long side chain at C-17 such as cinnamoyl derivative **25** potentiated the inhibitory activity against SGLT1 and SGLT2. On the other hand,

the benzyl ether derivative **28** at C-17 did not show inhibitory activity.

In this work, three new picaline-type alkaloids, alstiphyllanines E–G (**1–3**) and a new ajmaline-type alkaloid, alstiphyllanine H (**4**) were isolated from the leaves of *A. macrophylla*, and their

structures were fully elucidated by 2D NMR analysis. SAR study of these alkaloids and synthetic analogue against STLT1 and SGLT2 suggested that the presence of picraline-type alkaloid with an ester side chain at C-17 may be important to show inhibitory activity.

### 3. Experimental section

#### 3.1. General methods

$^1\text{H}$  and 2D NMR spectra were recorded on a Bruker AV 400 spectrometer and chemical shifts were reported using residual  $\text{CD}_3\text{OD}$  ( $\delta_{\text{H}}$  3.31 and  $\delta_{\text{C}}$  49.0) as internal standards. Standard pulse sequences were employed for the 2D NMR experiments.  $^1\text{H}$ – $^1\text{H}$  COSY, HOHAHA, and NOESY spectra were measured with spectral widths of both dimensions of 4800 Hz, and 32 scans with two dummy scans were accumulated into 1 K data points for each of 256  $t_1$  increments. NOESY spectra in the phase sensitive mode were measured with a mixing time of 800 ms. For HMQC spectra in the phase sensitive mode and HMBC spectra, a total of 256 increments of 1 K data points were collected. For HMBC spectra with Z-axis PFG, a 50 ms delay time was used for long-range C–H coupling. Zero-filling to 1 K for  $F_1$  and multiplication with squared cosine-bell windows shifted in both dimensions were performed prior to 2D Fourier transformation.

#### 3.2. Material

The leaves of *A. macrophylla* were collected at Purwodadi Botanical Garden, Indonesia in 2006. The botanical identification was made by Ms. Sri Wuryanti, Purwodadi Botanical Garden, Indonesia. A voucher specimen has been deposited in the herbarium at Purwodadi Botanical Garden, Pasuruan, Indonesia.

#### 3.3. Extraction and isolation

The leaves of *A. macrophylla* (363.5 g) were extracted with MeOH. The MeOH extract (43.8 g) was treated with 3% tartaric acid (pH 2) and then partitioned with EtOAc. The aqueous layer was treated with satd aq  $\text{Na}_2\text{CO}_3$  aq to pH 9 and extracted with  $\text{CHCl}_3$  to give alkaloidal fraction (2.06 g). The alkaloidal fraction was purified by LH-20 column ( $\text{CHCl}_3/\text{MeOH}$ , 1:0) and  $\text{SiO}_2$  column ( $\text{CHCl}_3/\text{MeOH}$ , 1:0→0:1) and the fraction eluted by MeOH was purified by ODS HPLC ( $\text{CH}_3\text{CN}/\text{H}_2\text{O}/\text{CF}_3\text{CO}_2\text{H}$ , 45:55:0.1; flow rate, 2 mL/min; UV detection at 254 nm) to afford alstiphyllanines E (**1**, 1.8 mg, 0.00050% yield), F (**2**, 1.3 mg, 0.00036%), G (**3**, 10.4 mg, 0.0029%), and H (**4**, 3.6 mg, 0.0013%), together with known alkaloids, burnamine-17-*O*-3',4',5'-trimethoxybenzoate<sup>10</sup> (**5**), 10-methoxy-*N*(1)-methylburnamine-17-*O*-veratrate<sup>10</sup> (**6**), alstiphyllanine D<sup>9</sup> (**7**), alstiphyllanine B<sup>9</sup> (**8**), alstiphyllanine C<sup>9</sup> (**9**), picralina<sup>11</sup> (**10**), picrinine<sup>11</sup> (**11**), quaternine<sup>12</sup> (**12**), *O*-deacetylpicraline<sup>13</sup> (**13**), vincamedine<sup>14</sup> (**14**), vincamajine<sup>15</sup> (**15**), alstiphyllanine A<sup>9</sup> (**16**), vincamajine-17-*O*-veratrate<sup>16</sup> (**17**), vincamajine-17-*O*-3',4',5'-trimethoxybenzoate<sup>16</sup> (**18**), alstonal<sup>17</sup> (**19**), alstonerine<sup>14</sup> (**20**).

##### 3.3.1. Alstiphyllanine E (1)

Brown amorphous solid;  $[\alpha]_{\text{D}}^{26}$  –93 (c 1.0, MeOH); IR (film)  $\nu_{\text{max}}$  3390, 1740, and 1680  $\text{cm}^{-1}$ ; UV (MeOH)  $\lambda_{\text{max}}$  291 ( $\epsilon$  4700), 264 (6200), and 204 (27,000) nm;  $^1\text{H}$  and  $^{13}\text{C}$  NMR data (Tables 1 and 2); ESIMS  $m/z$  533 (M+H)<sup>+</sup>; HRESITOFMS  $m/z$  533.2272 [(M+H)<sup>+</sup>,  $\Delta$  –1.6 mmu, calcd for  $\text{C}_{30}\text{H}_{33}\text{N}_2\text{O}_7$ , 533.2288].

##### 3.3.2. Alstiphyllanine F (2)

Brown amorphous solid;  $[\alpha]_{\text{D}}^{26}$  –32 (c 1.0, MeOH); IR (film)  $\nu_{\text{max}}$  3420, 1740, and 1680  $\text{cm}^{-1}$ ; UV (MeOH)  $\lambda_{\text{max}}$  245 ( $\epsilon$  6800) and 204 (28,000) nm;  $^1\text{H}$  and  $^{13}\text{C}$  NMR data (Tables 1 and 2); ESIMS  $m/z$  593

(M+H)<sup>+</sup>; HRESITOFMS  $m/z$  593.2511 [(M+H)<sup>+</sup>,  $\Delta$  +1.2 mmu, calcd for  $\text{C}_{32}\text{H}_{37}\text{N}_2\text{O}_9$ , 593.2499].

##### 3.3.3. Alstiphyllanine G (3)

Brown amorphous solid;  $[\alpha]_{\text{D}}^{26}$  –42 (c 1.0, MeOH); IR (film)  $\nu_{\text{max}}$  3420 and 1720  $\text{cm}^{-1}$ ; UV (MeOH)  $\lambda_{\text{max}}$  306 ( $\epsilon$  1500), 240 (3500), and 204 (12,000) nm;  $^1\text{H}$  and  $^{13}\text{C}$  NMR data (Tables 1 and 2); ESIMS  $m/z$  413 (M+H)<sup>+</sup>; HRESITOFMS  $m/z$  413.2080 [(M+H)<sup>+</sup>,  $\Delta$  +0.4 mmu, calcd for  $\text{C}_{23}\text{H}_{28}\text{N}_2\text{O}_5$ , 413.2076].

##### 3.3.4. Alstiphyllanine H (4)

Brown amorphous solid;  $[\alpha]_{\text{D}}^{26}$  –21 (c 1.0, MeOH); IR (film)  $\nu_{\text{max}}$  3420 and 1740  $\text{cm}^{-1}$ ; UV (MeOH)  $\lambda_{\text{max}}$  291 ( $\epsilon$  1400) and 204 (10,000) nm;  $^1\text{H}$  and  $^{13}\text{C}$  NMR data (Tables 1 and 2); ESIMS  $m/z$  383 (M+H)<sup>+</sup>; HRESITOFMS  $m/z$  383.1944 [(M+H)<sup>+</sup>,  $\Delta$  –2.7 mmu, calcd for  $\text{C}_{22}\text{H}_{26}\text{N}_2\text{O}_4$ , 383.1971].

##### 3.3.5. Conversion of vincamajine (15) to alstiphyllanine H (4)

*m*-Chloroperoxybenzoic acid (0.9 mg) was added to a stirred solution of vincamajine (**15**, 0.9 mg) in  $\text{CH}_2\text{Cl}_2$  (0.2 mL) at room temperature. The mixture was stirred at 0 °C for 10 min, and washed with 20%  $\text{Na}_2\text{SO}_2$  (5 mL) and  $\text{H}_2\text{O}$  (5 mL), and concentrated to give a pale yellow solid. The residue was subjected to a silica gel column ( $\text{CHCl}_3/\text{MeOH}$ , 10:1) to give the N-oxide derivative (1.5 mg), whose spectral data and  $[\alpha]_{\text{D}}$  value were identical with those of alstiphyllanine H (**4**).

##### 3.3.6. Conversion of 6 to 3

A mixture of 39.6 mg of alkaloid **6** and 20 mL of 5% NaOMe were heated for 30 min under stirring. The solution was diluted with water and extracted with  $\text{CHCl}_3$ . The extract was treated with 3% tartaric acid (pH 2) and then partitioned with EtOAc. The aqueous layer was treated with saturated  $\text{Na}_2\text{CO}_3$  aq to pH 9 and extracted with  $\text{CHCl}_3$  to give **3** (27.1 mg, 95.8%).

##### 3.3.7. Conversion of 3 to its benzoate derivative (21)

To a solution of **3** (3.2 mg) in  $\text{CH}_2\text{Cl}_2$  (0.1 mL) was added benzoic anhydride (4.5 mg) and DMAP (3.2 mg), and the solution was stirred at room temperature. The mixture was diluted with  $\text{CHCl}_3$  and washed with water, satd aq  $\text{NaHCO}_3$ , and water. The organic phase was dried over  $\text{MgSO}_4$  and concentrated in vacuo, and then purified by an ODS HPLC ( $\text{MeOH}/\text{H}_2\text{O}/\text{formic acid}$ ; flow rate, 2 mL/min; UV detection at 254 nm) to obtain **21** (2.4 mg, 60.0%):  $[\alpha]_{\text{D}}^{27}$  –38 (c 0.1, MeOH); IR (film) 1740 and 1710  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  7.61 (dd, 7.6, 7.6, H-2', 6'), 7.55 (dd, 7.6, 7.6, H-4'), 7.39 (d, 7.6, H-3', 5'), 7.05 (d, 2.5, H-9), 6.57 (d, 8.6, H-12), 6.42 (dd, 2.5, 8.6, H-11), 5.66 (q, 6.9, H-19), 5.49 (br s, H-5), 4.78 (d, 10.9, H-17), 4.24 (d, 10.9, H-17) 4.12 (m, H-21), 3.70 (s, –OMe), 3.64 (br s, H-3, 15), 3.41 (s, –OMe), 3.35 (d, 15.0, H-6), 2.94 (s, –NMe), 2.53 (d, 15.0, H-6), 2.29 (d, 15.1, H-14), 2.19 (d, 15.1, H-14), 1.70 (d, 6.92, H-18); HRESIMS  $m/z$  517.2323 [calcd for  $\text{C}_{30}\text{H}_{33}\text{N}_2\text{O}_6$  (M+H)<sup>+</sup>, 517.2339].

##### 3.3.8. Conversion of 7 to its hydroxy derivative (22)

A solution of boron tribromide in  $\text{CH}_2\text{Cl}_2$  (1.0 M, 8.1  $\mu\text{L}$ ) was added dropwise to stirred solution of **7** (1.1 mg) in  $\text{CH}_2\text{Cl}_2$  (50  $\mu\text{L}$ ), stirring being continued for 15 min at 0 °C. The reaction mixture was quenched with water and diluted with EtOAc. The organic layer was successively washed with water and brine, dried with  $\text{MgSO}_4$ , and concentrated in vacuo. The residue was chromatographed on an ODS HPLC ( $\text{MeOH}/\text{H}_2\text{O}/\text{formic acid}$ , 55:45:0.1; flow rate, 2 mL/min; UV detection at 254 nm) to give compound **22** (0.3 mg, 30.3 %):  $[\alpha]_{\text{D}}^{27}$  –78 (c 0.1, MeOH); IR (film) 3420, 1740, and 1710  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  7.00 (d, 8.4, H-9), 6.87 (s, H-2', 6'), 6.58 (d, 2.5, H-12), 6.51 (dd, 8.4, 2.5, H-11), 5.74 (q, 7.7, H-19), 5.41 (br s, H-5), 4.53 (d, 11.4, H-17), 4.25 (d,



11.4, H-17), 4.19 (br s, H-3), 3.72 (br s, H-15), 3.99 (m, H-21), 3.70 (s, -OMe), 3.30 (m, H-6), 2.95 (s, -NMe), 2.60 (d, 15.9, H-6), 2.34 (d, 16.1, H-14), 2.28 (d, 16.1, H-14), 1.72 (d, 7.7, H-18); HRESIMS  $m/z$  551.2052 [calcd for  $C_{29}H_{31}N_2O_9(M+H)^+$ , 551.2030].

### 3.3.9. Conversion of 6 to its *N*(4)-oxide derivative (23)

To a solution of **6** (2.8 mg) in  $CHCl_3$  (0.3 mL) was added *m*-CPBA (1.0 mg) in  $CHCl_3$  (300  $\mu$ L) and the mixture was kept at 4 °C for 10 min. After evaporation, the residue was applied to a silica gel column ( $CHCl_3$ /MeOH, 9:1) to give **23** (1.0 mg, 34.8 %):  $[\alpha]_D^{27}$  -14 (c 0.5, MeOH); IR (film) 1740 and 1710  $cm^{-1}$ ;  $^1H$  NMR ( $CD_3OD$ )  $\delta$  7.24 (dd, 8.5, 2.0, H-5'), 7.11 (d, 2.0, H-2'), 7.03 (d, 2.6, H-9), 6.93 (d, 8.5, H-5'), 6.56 (d, 8.6, H-12), 6.40 (dd, 8.6, 2.6, H-11), 5.69 (q, 6.7, H-19), 5.05 (br s, H-5), 4.81 (d, 11.1, H-17), 4.34 (d, 16.4, H-21) 4.16 (d, 16.4, H-21), 4.03 (d, 3.2, H-3), 3.89 (s, -OMe), 3.88 (s, -OMe), 3.74 (s, -OMe), 3.60 (br s, H-15), 3.34 (s, -OMe), 3.30 (m, H-6), 2.95 (s, -NMe), 2.50 (m, H-6), 2.47 (m, H-14), 2.25 (d, 15.8, H-14), 1.72 (dd, 6.7, 2.3, H-18); HRESIMS  $m/z$  593.2522 [calcd for  $C_{32}H_{37}N_2O_9(M+H)^+$ , 593.2499].

### 3.3.10. Conversion of 7 to its *N*(4)-oxide derivative (24)

To a solution of **7** (1.0 mg) in  $CHCl_3$  was added *m*-CPBA (1.6 mg) in  $CHCl_3$  (300  $\mu$ L) and the mixture was kept at 4 °C for 10 min. After evaporation, the residue was applied to a silica gel column ( $CHCl_3$ /MeOH, 9:1) to give **24** (1.0 mg, 34.8 %):  $[\alpha]_D^{27}$  -24 (c 0.5, MeOH); IR (film) 1730 and 1720  $cm^{-1}$ ;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  7.08 (d, 2.6, H-12), 6.89 (s, H-2', 5'), 6.52 (d, 8.6, H-9), 6.52 (d, 8.6, H-9), 6.52 (d, 8.6, H-12), 6.36 (dd, 8.6, 2.6, H-11), 5.64 (q, 7.12, H-19), 5.21 (br s, 3.54, H-5), 4.80 (d, 10.9, H-17), 4.44 (d, 16.7, H-21) 4.32 (d, 16.7, H-21), 4.19 (d, 2.4, H-3), 4.06 (d, 10.9, H-17), 3.91 (s, -OMe), 3.88 (s, -OMe), 3.72 (s, -OMe), 3.45 (br s, H-15), 3.34 (s, -OMe), 3.30 (m, H-6), 3.00 (s, -NMe), 2.58 (dd, 15.6, 3.5, H-6), 2.54 (d, 15.7, H-14), 2.20 (d, 15.7, H-14), 1.69 (dd, 7.0, 2.0, H-18); HRESIMS  $m/z$  623.2624 [calcd for  $C_{33}H_{39}N_2O_{10}(M+H)^+$ , 623.2605].

### 3.3.11. Conversion of 3 to its cinnamoyl derivative (25)

Compound **3** (13.9 mg), hydrocinnamic acid (5.8 mg), and DMAP (5.7 mg), were combined with  $CH_2Cl_2$  (100  $\mu$ L). 1,3-Dicyclohexylcarbodiimide (DCC) (23.5 mg) in  $CH_2Cl_2$  (50  $\mu$ L) was added dropwise over 10 min at 0 °C. The solution was warmed to room temperature and stirred overnight. The reaction mixture was partitioned with  $CHCl_3$  and 1 N aq HCl, 10 % aq  $NaHCO_3$ , and water. The combined organic extract was dried ( $Na_2SO_4$ ) and concentrated in vacuo and then purified by an ODS HPLC (MeOH/ $H_2O$ /formic acid, 60:40:0.1; flow rate, 2 mL/min; UV detection at 254 nm) to obtain compound **25** (0.7 mg, 3.8%):  $[\alpha]_D^{27}$  -49 (c 0.5, MeOH); IR (film) 1740 and 1710  $cm^{-1}$ ;  $^1H$  NMR ( $CD_3OD$ )  $\delta$  7.52 (m, H-4', 8'), 7.41 (m, H-5', 6', 7'), 7.24 (d, 16.1, H-2'), 7.08 (s, H-9), 6.58 (s, H-11, 12), 5.97 (d, 16.1, H-1'), 5.52 (q, 7.4, H-19), 4.98 (m, H-5), 4.65 (d, 10.9, H-17), 4.08 (d, 10.9, H-17), 3.83 (m, H-21), 3.79 (m, H-3), 3.71 (s, -OMe), 3.68 (m, H-21), 3.48 (s, -OMe), 3.48 (m, H-15), 3.30 (m, H-6), 2.90 (s, -NMe), 2.39 (d, 14.6, H-6), 2.12 (d, 14.3, H-14), 2.04 (d, 14.3, H-14), 1.65 (d, 7.4, H-18); HRESIMS  $m/z$  543.2490 [calcd for  $C_{32}H_{35}N_2O_6(M+H)^+$ , 543.2495].

### 3.3.12. Conversion of 3 to its acetylate derivative (26)

Compound **3** (1.0 mg), acetic anhydride (7.5  $\mu$ L), triethylamine (2.5  $\mu$ L), and DMAP (0.5 mg) in  $CH_2Cl_2$  (50  $\mu$ L) was stirred at room temperature for 1.5 h. The reaction mixture was partitioned with  $CHCl_3$  and 10 % aq  $NaHCO_3$ . The combined organic extract was concentrated in vacuo and then purified by a silica gel column ( $CHCl_3$ /MeOH, 1:0-0:1) to obtain compound **26** (0.8 mg, 73.4%).  $[\alpha]_D^{27}$  -32 (c 0.5, MeOH); IR (film) 1740  $cm^{-1}$ ;  $^1H$  NMR ( $CD_3OD$ )  $\delta$  7.02 (d, 2.6, H-12), 6.73 (dd, 8.6, 2.6, H-11), 6.61 (d, 8.6, H-9), 5.51 (q, 7.3, H-19), 4.94 (m, H-5) 4.53 (d, 11.0, H-17), 3.86, (d, 11.0, H-17), 3.78 (d,

14.6, H-21), 3.72 (s, -OMe), 3.70 (s, -OMe), 3.44 (br s, H-3), 3.36 (m, H-21), 3.35 (m, H-15), 3.30 (m, H-6), 2.89 (s, -NMe), 2.36 (dd, 14.4, 2.8, H-6), 2.09 (d, 15.4, H-14), 2.00 (d, 15.4, H-14), 1.64 (d, 7.3, H-18), 1.54 (s, -COCH<sub>3</sub>); HRESIMS  $m/z$  455.2161 [calcd for  $C_{25}H_{31}N_2O_6(M+H)^+$ , 455.2182].

### 3.3.13. Conversion of 3 to its propionate derivative (27)

To a solution of **3** (1.6 mg) in  $CH_2Cl_2$  (0.05 mL) was added propionic anhydride (3  $\mu$ L), and DMAP (1.2 mg) in  $CH_2Cl_2$  (50  $\mu$ L) and the solution was stirred at room temperature. The mixture was diluted with  $CHCl_3$  and washed with water, satd aq  $NaHCO_3$ , and water. The organic phase was dried over  $MgSO_4$  and concentrated in vacuo and then purified by an ODS HPLC (MeOH/ $H_2O$ /formic acid; flow rate, 2 mL/min; UV detection at 254 nm) to obtain **27** (0.2 mg, 60.0%).  $[\alpha]_D^{27}$  -143 (c 0.1, MeOH); IR (film) 1740  $cm^{-1}$ ;  $^1H$  NMR ( $CD_3OD$ )  $\delta$  7.02 (d, 2.6, H-2), 6.80 (dd, 8.6, 2.6, H-11), 6.70 (d, 8.6, H-12), 5.74 (q, 6.5, H-19), 5.55 (br s, H-5) 4.52 (d, 11.2, H-17), 4.21 (m, H-21), 3.98 (m, H-21), 3.93, (d, 11.2, H-17), 3.75 (m, H-3), 3.74 (s, -OMe), 3.73 (s, -OMe), 3.64 (br s, H-15), 3.23 (d, 15.5, H-6), 2.95 (s, -NMe), 2.61 (d, 15.5, H-6), 2.32 (d, 14.6, H-14), 2.21 (d, 14.6, H-14), 1.84 (m, H-1'), 1.72 (d, 6.5, H-18), 0.85 (t, 7.5, H-2'); HRESIMS  $m/z$  469.2352 [calcd for  $C_{26}H_{33}N_2O_6(M+H)^+$ , 469.2339].

### 3.3.14. Conversion of 3 to its benzyl ether derivative (28)

To a solution of **3** (2.7 mg) in dry  $CH_2Cl_2$  (53  $\mu$ L) were added triethylamine (1.27  $\mu$ L), benzyl bromide (0.93  $\mu$ L), and DMAP (0.4 mg). The reaction mixture was heated for 3 h, then cooled to room temperature and diluted with  $CHCl_3$ . The organic phase was washed twice with an aqueous solution of  $NaHCO_3$  and once with water. The organic phase was dried  $Na_2SO_4$  and concentrated in vacuo. The residue was chromatographed on an ODS HPLC (MeOH/ $H_2O$ /formic acid, 61:39:0.1; flow rate, 2 mL/min; UV detection at 254 nm) to give **28** (0.6 mg, 18.2%):  $[\alpha]_D^{27}$  -4.6 (c 0.5, MeOH); IR (film) 1730  $cm^{-1}$ ;  $^1H$  NMR ( $CD_3OD$ )  $\delta$  7.64 (d, 7.8, H-3', 7'), 7.57 (m, H-4', 5', 6'), 6.85 (m, H-9, 12), 6.78 (d, 9.5, H-11), 5.65 (m, H-5), 5.62 (m, H-19), 4.61 (s, H-1'), 4.45 (d, 16.1, H-21), 4.41 (s, H-3), 3.97 (d, 16.1, H-21), 3.77, (m, H-15), 3.74 (s, -OMe), 3.72 (s, -OMe), 3.66 (d, 17.5, H-17), 3.61 (d, 17.5, H-17), 3.30 (m, H-6), 3.03 (s, -NMe), 2.54 (dd, 16.6, 3.7, H-6), 2.38 (m, H-14), 1.65 (d, 5.5, H-18); HRESIMS 503.2535 [calcd for  $C_{30}H_{35}N_2O_5(M+H)^+$ , 503.2546].

### 3.3.15. Uptake of Methyl- $\alpha$ -D-glucopyranoside in cultured cells expressing SGLT1 or SGLT2<sup>18</sup>

COS-1 cells were cultured at 37 °C in Dulbecco's modified Eagle's/Ham's F-12 medium (1:1) supplemented with 10% fetal calf serum. For the uptake assay, the cells were plated at  $1 \times 10^5$  cells/24-well plate (Asahi Techno Glass, Tokyo, Japan), and 1  $\mu$ g of each transporter plasmid was transfected into subconfluent cultures of COS-1 cells using Lipofectamine 2000 (Invitrogen). The cells were used 2–3 days after transfection. They were incubated in a pretreatment buffer [140 mM NaCl, 2 mM KCl, 1 mM  $CaCl_2$ , 1 mM  $MgCl_2$ , and 10 mM Hepes/Tris (pH 7.5)] with a test sample at 37 °C for 30 min. An uptake solution containing 80 mM methyl- $\alpha$ -D-glucopyranoside and 4  $\mu$ Ci/mL methyl  $\alpha$ -D-[U-<sup>14</sup>C]glucopyranoside was then added into each well and the mixture was incubated at 37 °C for 30 min. Following incubation, the plates were washed three times with cold stop buffer [140 mM choline chloride, 2 mM KCl, 1 mM  $CaCl_2$ , 1 mM  $MgCl_2$ , and 10 mM Hepes/Tris (pH 7.5)] containing 300  $\mu$ M phlorizin. The cells were then solubilized with 0.1 M NaOH, and their radioactivity was measured with a liquid scintillation counter (3100TR, Perkin-Elmer). Phlorizine was used as a standard drug for this bioassay and its  $IC_{50}$  values were 0.2 and 0.1 mM against SGLT1 and SGLT2, respectively.

## Acknowledgements

This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology of Japan and a grant from The Open Research Center Project in Hoshi University.

## References and notes

1. Lee, W.-S.; Kanai, Y.; Wells, R. G.; Hediger, M. A. *J. Biol. Chem.* **1994**, *269*, 12032–12039.
2. You, G.; Lee, W.-S.; Barros, E. J. G.; Kanai, Y.; Huo, T.-L.; Khawaja, S.; Wells, R. G.; Nigam, S. K.; Heidiger, M. A. *J. Biol. Chem.* **1995**, *270*, 29365–29371.
3. Mackenzie, B.; Panayotova-Heiermann, M.; Loo, D. D. F.; Lever, J. E.; Wright, E. M. *J. Biol. Chem.* **1994**, *269*, 22488–22491.
4. Wright, E. M.; Turk, E. *Pfugers Arch.* **2004**, *447*, 510–518.
5. Katsuno, K.; Fujimori, Y.; Takemura, Y.; Hitatochi, M.; Itho, F.; Komatsu, Y.; Fujikura, H.; Isaji, M. *J. Pharm. Exp. Ther.* **2007**, *320*, 323–330.
6. Morita, H.; Deguchi, J.; Motegi, Y.; Sato, S.; Aoyama, C.; Takeo, J.; Shiro, M.; Hirasawa, Y. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1070–1074.
7. (a) Kamarajan, P.; Sekar, N.; Mathuram, V.; Govindasamy, S. *Biochem. Int.* **1991**, *25*, 491–498; (b) Saraswathi, V.; Subramanian, S.; Ramamoorth, N.; Mathuram, V.; Govindasamy, S. *Med. Sci. Res.* **1997**, *25*, 167–170; (c) Keawpradub, N.; Kirby, G. C.; Steele, J. C. P.; Houghton, P. J. *Planta Med.* **1999**, *65*, 690–694; (d) Husain, K.; Jantan, I.; Kamaruddin, N.; Said, I. M.; Aimi, N.; Takayama, H. *Phytochemistry* **2001**, *57*, 603–606; (e) Husain, K.; Jantan, I.; Said, I. M.; Aimi, N.; Takayama, H. *J. Asian Nat. Prod. Res.* **2003**, *5*, 63–67; (f) Jagetia, G. C.; Baliga, M. S. *Phytother. Res.* **2006**, *20*, 103–109; (g) Khan, M. R.; Omoloso, A. D.; Kihara, M. *Fitoterapia* **2003**, *74*, 736–740; (h) Gupta, R. S.; Bhatnager, A. K.; Joshi, Y. C.; Sharma, M. C.; Khushalani, V.; Kachhawa, J. B. *Pharmacology* **2005**, *75*, 57–62.
8. Koyama, K.; Hirasawa, Y.; Zaima, K.; Hoe, T. C.; Chan, K.-L.; Morita, H. *Bioorg. Med. Chem.* **2008**, *16*, 6483–6488.
9. Hirasawa, Y.; Arai, H.; Zaima, K.; Oktarina, R.; Rahman, A.; Ekasari, W.; Indrayanto, G.; Zaini, N.; Morita, H. *J. Nat. Prod.* **2009**, *72*, 304–307.
10. Abe, F.; Yamauchi, T.; Shibuya, H.; Kitagawa, I.; Yamashita, M. *Chem. Pharm. Bull.* **1998**, *46*, 1235–1238.
11. Abe, F.; Chen, R.; Yamauchi, T.; Marubayashi, N.; Ueda, I. *Chem. Pharm. Bull.* **1989**, *37*, 887–890.
12. Mamatas-Kalamaras, S.; Sevenet, T.; Thal, C.; Potier, P. *Phytochemistry* **1968**, *7*, 2045–2051.
13. Burmel, R.; Medina, J. *Phytochemistry* **1968**, *7*, 2045–2051.
14. Caron, C.; Yachaoui, Y.; Massiot, G.; Men-Olivier, L.; Pusset, J.; Sevenet, T. *Phytochemistry* **1984**, *23*, 2355–2357.
15. Ratnayake, C.; Arambewela, L.; Silva, K.; Rahman, A.; Alvi, K. *Phytochemistry* **1975**, *14*, 1849–1854.
16. Abe, F.; Yamauchi, T.; Santisuk, T. *Phytochemistry* **1994**, *37*, 249–252.
17. Kam, T.; Choo, Y. J. *J. Nat. Prod.* **2004**, *67*, 547–552.
18. Sato, S.; Aoyama, C.; Takeo, J. *Bioorg. Med. Chem.* **2007**, *15*, 3445–3449.

## Source details

Feedback > Compare sources >

### Bioorganic and Medicinal Chemistry

Scopus coverage years: from 1993 to Present

Publisher: Elsevier

ISSN: 0968-0896 E-ISSN: 1464-3391

Subject area: [Pharmacology, Toxicology and Pharmaceutics: Pharmaceutical Science](#) [Chemistry: Organic Chemistry](#)  
[Biochemistry, Genetics and Molecular Biology: Clinical Biochemistry](#) [Pharmacology, Toxicology and Pharmaceutics: Drug Discovery](#) [View all](#)

Source type: Journal

[View all documents >](#)

[Set document alert](#)

[Save to source list](#)

[Source Homepage](#)

CiteScore 2019

5.5

SJR 2019

0.739

SNIP 2019

0.940

## Bioorganic and Medicinal Chemistry

#### COUNTRY

United Kingdom

Universities and research institutions in United Kingdom

#### SUBJECT AREA AND CATEGORY

Biochemistry, Genetics and Molecular Biology

- Biochemistry
- Clinical Biochemistry
- Molecular Biology
- Molecular Medicine

Chemistry

- Organic Chemistry

Pharmacology, Toxicology and Pharmaceutics

- Drug Discovery
- Pharmaceutical Science

#### PUBLISHER

Elsevier Ltd.

#### H-INDEX

154

#### PUBLICATION TYPE

Journals

#### ISSN

14643391, 09680896

#### COVERAGE

1993-2020

#### INFORMATION

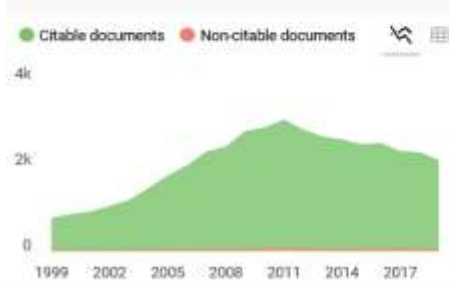
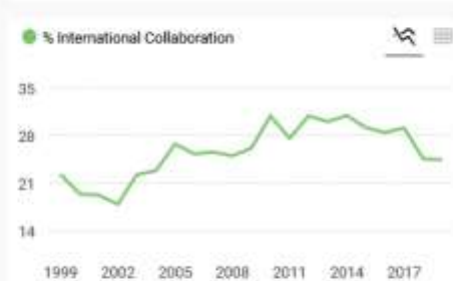
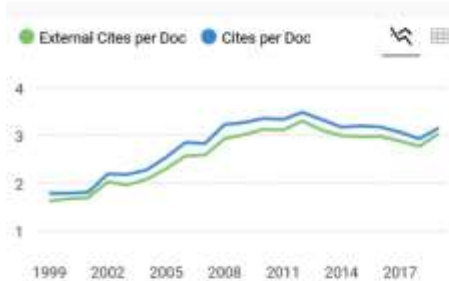
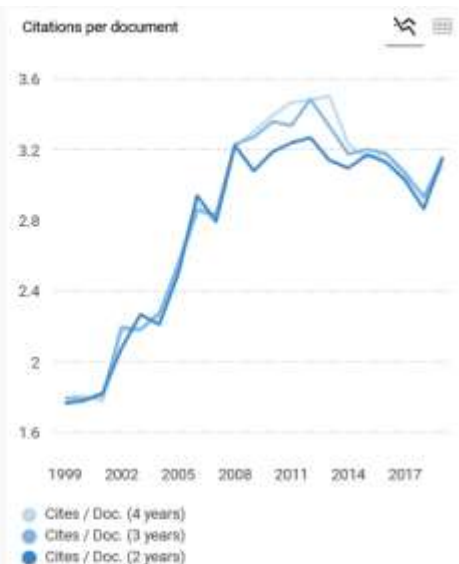
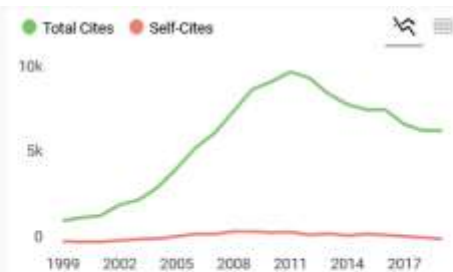
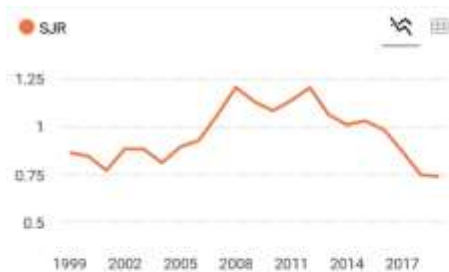
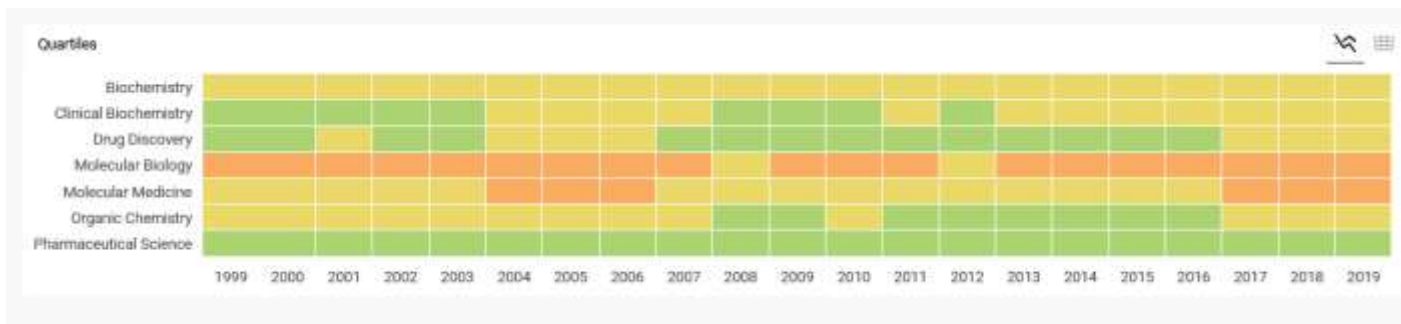
[Homepage](#)

[How to publish in this journal](#)

[Contact](#)

#### SCOPE

Bioorganic & Medicinal Chemistry publishes complete accounts of research of outstanding significance and timeliness on all aspects of molecular interactions at the interface of chemistry and biology, together with critical review articles. The journal publishes reports of experimental results in medicinal chemistry, chemical biology and drug discovery and design, emphasizing new and emerging advances and concepts in these fields. The aim of the journal is to promote a better understanding at the molecular level of life processes, and living organisms, as well as the interaction of these with chemical agents. The Journal welcomes papers on: the medicinal chemistry and associated biology (including target identification and validation) of established or new disease targets- the reporting of the discovery, design or optimization of potent new compounds or biological agents- the analysis and discussion of structure-activity relationships and pharmacological issues relevant to drug design and action using in vitro and in vivo models, including the use of computational techniques when closely linked to experimental data- the reporting of "first-in-class" new therapeutic compounds- the chemical biology or bioorganic/bioinorganic chemistry that significantly advances knowledge of a biological mechanism- methodological advances that are chemistry-based and which significantly impact on medicine or biology- the preparation and examination of biotherapeutics for the treatment of pathophysiological disease states- the development of materials for specific therapeutic targeting



**Bioorganic and Medicinal Chemistry**

Pharmaceutical Science

Q1

SJR 2019: 0.74

powered by scimagojr.com

Show this widget in your own website

Just copy the code below and paste within your html code:

```
<a href="https://www.scimagojr.com">
```