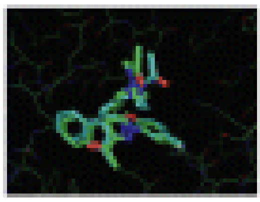
Bioorganic & Medicinal Chemistry Letters

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



Editor-in-Chief

DALE L. BOGER

ScienceDirect

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

PUBLISHED TWICE MONTHLY

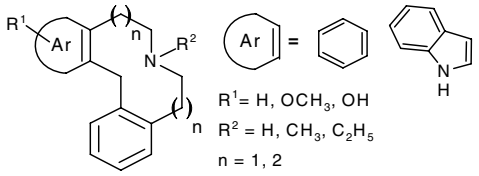
Orders, claims, and journal enquiries: Please contact the Regional Sales Office nearest you:
Orlando: Elsevier, Customer Service Department, 6277 Sea Harbor Drive, Orlando, FL 32887-4800, USA; phone: (877) 839 7126 [toll free within the USA]; (+1) (407) 563 6022 [outside the USA]; fax: (+1) (407) 363 1354; e-mail: JournalCustomerService-usa@elsevier.com
Amsterdam: Elsevier, Customer Service Department, PO Box 211, 1000 AE Amsterdam, The Netherlands; phone: (+31) (20) 4853757; fax: (+31) (20) 4853432; e-mail: JournalsCustomerServiceEMEA@elsevier.com
Tokyo: Elsevier, Customer Service Department, 4F Higashi-Azabu, 1-Chome Bldg., 1-9-15 Higashi-Azabu, Minato-ku, Tokyo 106-0044, Japan; phone: (+81) (3) 5561 5037; fax: (+81) (3) 5561 5047; e-mail: JournalsCustomerServiceJapan@elsevier.com
Singapore: Elsevier, Customer Service Department, 3 Killiney Road, #08-01 Winsland House I, Singapore 239519; phone: (+65) 63490222; fax: (+65) 67331510; e-mail: JournalsCustomerServiceAPAC@elsevier.com

Bioorganic & Medicinal Chemistry Letters

Bioorganic & Medicinal Chemistry Letters Vol. 18, No. 13, 2008

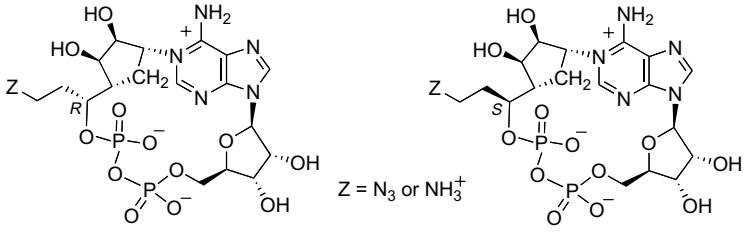
Contents

ARTICLES



pK_i for D_1: 6.79 to 9.45; for D_2: 6.41 to 8.45; pA_2 for 5-HT_{2A} : 7.21 to 9.97

A cross-target SAR was conducted with 13 azecine-styled compounds on D_1, D_2 and 5-HT_{2A} receptors. Surprisingly, molecular modifications aect the affinity for the D_1 receptor in the same manner as the 5-HT_{2A} receptor. The protein–ligand interactions were discussed with respect to the dierent binding pockets.



OTHER CONTENTS

*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

COVER

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

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

ELSEVIER

ISSN 0960-894X

Bioorganic & Medicinal Chemistry Letters 18 (2008) 3774–3777

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Sucutiniranes A and B, new cassane-type diterpenes from *Bowdichia nitida*

Yosuke Matsuno [a], Jun Deguchi [a], Yusuke Hirasawa [a], Kunio Ohyama [b], Hiroo Toyoda [b], Chieko Hirobe [c], Wiwied Ekasari [d], Aty Widyawaruyanti [d], Noor Cholies Zaini [d], Hiroshi Morita [a,*]

[a] *Faculty of Pharmaceutical Sciences, Hoshi University, Ebara 2-4-41, Shinagawa-ku, Tokyo 142-8501, Japan*
[b] *School of Pharmacy, Tokyo University of Pharmacy & Life Science, 1432-1 Horinouchi, Hachioji, Tokyo 192-0392, Japan*
[c] *Seisen University, Higashi Gotanda 3-16-21, Shinagawa-ku, Tokyo 141, Japan*
[d] *Airlangga University, Jalan Dharmawangsa Dalam, Surabaaya 60286, Indonesia*

ARTICLE INFO

Article history:
Received 21 March 2008
Revised 19 April 2008
Accepted 9 May 2008
Available online 16 May 2008

Keywords:
Diterpene
Sucutinirane A
Sucutinirane B
Bowdichia nitida
Cytotoxicity
Antiplasmodial activity

ABSTRACT

Two new cassane-type diterpenes, sucutiniranes A (**1**) and B (**2**), have been isolated from the seeds of *Bowdichia nitida* together with 6α-acetoxyvouacapane (**3**) and 6α,7β-diacetoxyvouacapane (**4**), and the structures of **1** and **2** were elucidated by using 2D NMR data and chemical correlations. Sucutinirane A (**1**) and **3** showed a moderate cytotoxicity against human colon carcinoma COLO201 cells, and 6α,7β-diacetoxyvouacapane (**4**) showed in vitro antiplasmodial activity against parasite *Plasmodium falciparum* 3D7.

Bowdichia nitida Spruce ex Benth., common name 'sucupira', is distributed in the Brazilian Amazon, and the seeds of this plant are used for rheumatic, antipyretic, and gouty agents.[1] So far, alkaloids, triterpenes, isoflavonoids, benzofuranes, and benzopyranes have been isolated from the genus *Bowdichia*.[2–4]

Our efforts on identifying new natural products from the seeds of *B. nitida* resulted in the isolation of two new cassane-type diterpenes, sucutiniranes A (**1**) and B (**2**). This Letter describes the structure elucidation of **1** and **2** on the basis of spectroscopic data and chemical correlations as well as cytotoxicity against human colon carcinoma COLO201 cells and antiplasmodial activity.

*Structures of sucutiniranes A (**1**) and B (**2**).* The seeds of *Bowdichia nitida* were extracted with MeOH, and the extract was partitioned between EtOAc and 3% tartaric acid. EtOAc-soluble materials were subjected to a silica gel column (hexane/EtOAc and $CHCl_3$/MeOH) and an ODS column (MeOH/H_2O) followed by HPLC (MeOH/H_2O) to afford sucutiniranes A (**1**, 0.0002% yield) and B (**2**, 0.00006%) together with 6α-acetoxyvouacapane (**3**, 0.02%)[5] and 6α,7β-diacetoxyvouacapane (**4**, 0.0008%).[6]

Sucutinirane A {**1**, $[\alpha]_D^{22}$ −24 (*c*, 1.0, $CHCl_3$)} was revealed to have the molecular formula $C_{22}H_{32}O_5$, by HRESITOFMS [*m*/*z* 399.2142 $(M+Na)^+$, Δ −0.5 mmu]. IR absorptions implied the presence of hydroxyl (3480 cm^{-1}) and carbonyl (1740 cm^{-1}) groups. The ^1H and ^{13}C NMR data (Table 1) suggested the presence of two carbonyl carbons, one sp^2 methine, one sp^2 quaternary carbon, five sp^3 methylenes, five sp^3 methines, three sp^3 quaternary carbons, and five methyl groups. The presence of the α, β-unsaturated γ-lactone moiety was substantiated by the signals of one sp^2 methine (δ_C 114.2), one sp^2 quaternary carbon (δ_C 175.0), one sp^3 quaternary carbon with two oxygen atoms (δ_C 107.6), and one carbonyl carbon (δ_C 173.4).

Partial structures **a** (C-1 to C-3) and **b** (C-5 to C-9, C-11, C-14, and C-17) were deduced from a detailed analysis of 2D NMR data of **1** (Fig. 1). The HMBC cross-peaks of H_3-19 to C-3, C-4, C-5, and C-18 indicated the connection among C-3, C-5, C-18, and C-19 through C-4. HMBC correlations for H_3-20 to C-1, C-5, C-9, and C-10 indicated connection among C-1, C-5, C-9, and C-20 through C-10. On the other hand, HMBC correlations for H-14 to C-12 and C-15, H_3-17 to C-13, and H-15 to C-12 and C-16 supported the location of the methyl group at C-14, and the α, β-unsaturated γ-lactone moiety at C-12 and C-13. Furthermore, the presence of an acetoxy group at C-6 was elucidated by the HMBC correlation for H-6 and H_3-22 to C-21. Thus, the gross structure of sucutinirane A was assigned to be **1** with a cassane-type skeleton[7] with the methyl group at C-14 and the α, β-unsaturated γ-lactone moiety at C-12 and C-13. The existence of cassane butenolides is rare as compared to that of cassane furanoditerpenes.

To assign the relative stereochemistry at the hemiketal C-12 position, **1** was acetylated with acetic anhydride in pyridine at

* Corresponding author. Tel./fax: +81 354985778.
E-mail address: moritah@hoshi.ac.jp (H. Morita).

0960-894X/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2008.05.035

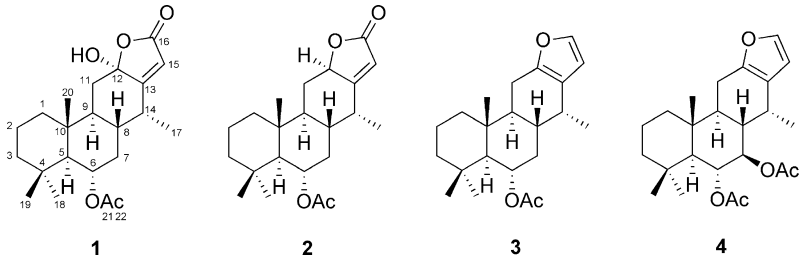


Table 1
^{1}H [δ_H (J, Hz)] and ^{13}C [δ_C] NMR Data of sucutiniranes A (**1**) and B (**2**)

	1[a]		**2**[b]	
	^{1}H	^{13}C	^{1}H	^{13}C
1a	1.10 (1H, m)	40.7	1.02 (1H, m)	39.7
1b	1.74 (1H, m)		1.71 (1H, m)	
2a	1.48 (1H, m)	19.5	1.47 (1H, m)	18.4
2b	1.59 (1H, m)		1.52 (1H, m)	
3a	1.29 (1H, m)	44.6	1.24 (1H, m)	43.4
3b	1.38 (1H, m)		1.39 (1H, m)	
4		34.1		33.1
5	1.31 (1H, d, 11.0)	58.4	1.22 (1H, m)	57.2
6	5.12 (1H, ddd, 11.0, 11.0, 4.1)	73.5	5.07 (1H, ddd, 11.1, 11.1, 4.3)	72.0
7a	1.49 (1H, m)	38.0	1.41 (1H, m)	36.7
7b	1.84 (1H, m)		1.88 (1H, m)	
8	1.84 (1H, m)	40.9	1.82 (1H, m)	38.7
9	1.54 (1H, m)	45.6	1.25 (1H, m)	44.4
10		39.5		38.7
11a	1.25 (1H, m)	38.9	0.99 (1H, m)	33.7
11b	2.38 (1H, dd, 12.9, 3.3)		2.50 (1H, ddd, 11.8, 6.4, 3.0)	
12		107.6	4.84 (1H, dd, 11.4, 6.4)	79.1
13		175.0		176.1
14	2.96 (1H, m)	37.3	2.95 (1H, m)	35.7
15	5.74 (1H, s)	114.2	5.68 (1H, s)	110.9
16		173.4		173.4
17	1.17 (3H, d, 7.3)	12.9	1.08 (3H, d, 7.3)	13.9
18	1.10 (3H, s)	37.2	1.06 (3H, s)	36.5
19	0.91 (3H, s)	23.0	0.89 (3H, s)	22.5
20	0.91 (3H, s)	15.8	0.88 (3H, s)	15.3
21		172.2		170.3
22	2.04 (3H, s)	21.9	2.06 (3H, s)	21.9

[a] In CD_3OD.
[b] In $CDCl_3$.

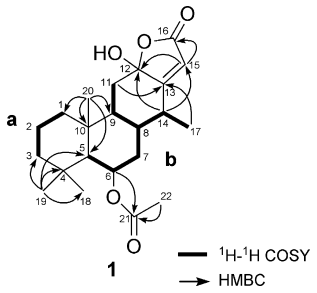


Figure 1. Selected 2D NMR correlations for sucutinirane A (**1**).

room temperature to afford the monoacetylated product **1a**. The relative stereostructure of **1a** as shown in computer-generated 3D drawing (Fig. 2) was deduced from cross-peaks observed in the NOESY spectrum and ^{3}J coupling constants. The NOESY correlation of H_3-17/H_3-24 indicated to be α-orientation for CH_3-17 and CH_3-24. Antiperiplanar conformation between H-5 and H-6 was preferred because of the coupling constant, $^{3}J_{H5/H6}$ = 11.0 Hz. The β-configuration of H-6, CH_3-19, and CH_3-20 was supported by the NOESY cross-peaks among H-6, H_3-19, and H_3-20, while the α-configuration of both H-5 and H-9 was supported by the NOESY cross-peak between H-5 and H-9. Furthermore, oxidation of the furan ring of 6α-acetoxyvouacapane (**3**) with *m*CPBA gave sucutinirane A (**1**) as shown in Scheme 1. Thus, the structure of sucutinirane A including relative stereochemistry was assigned as shown in Figure 2.

Sucutinirane B {**2**, $[\alpha]_D^{22}$ −33 (*c*, 0.2, $CHCl_3$)} was revealed to have the molecular formula $C_{22}H_{32}O_4$, by HRESITOFMS [*m/z* 361.2389 $(M+H)^+$, Δ +2.1 mmu]. IR absorptions implied the presence of carbonyl (1735 cm^{-1}) group. The ^{1}H and ^{13}C NMR data (Table 1), and 2D NMR correlations (Fig. 3) suggested that **2** had the same cassane-type skeleton as that of **1**, except for the presence of an oxymethine at C-12 (δ_H 4.84, δ_C 79.1). The relative stereochemistry of sucutinirane B (**2**) was deduced by NOESY spectrum (Fig. 4) and ^{3}J coupling constants. The configuration of β-oriented H-6, H-8, CH_3-19, and CH_3-20 was supported by the NOESY correlations of H-6/H-8, H-6/H_3-19, and H-8/H_3-20. The coupling constant, $^{3}J_{H5/H6}$ = 11.1 Hz indicated antiperiplanar conformation between H-5 and H-6. The α-configuration of H-5, H-9, H-12, and CH_3-17 was supported by the NOESY cross-peaks of H-5/H-9 and H-12/H-9 and H_3-17. Thus, the structure of **2** was assigned as 12-deoxy-sucutinirane A.

The absolute stereochemistry of sucutiniranes A (**1**) and B (**2**) was deduced by applying CD curves for γ-lactone chromophore.[8] The sign of the CD curve in MeOH [**1**: λ_{max} 222 nm (Δε −0.8) and 244 nm (Δε −0.6), **2**: λ_{max} 218 nm (Δε −1.1)] was negative, indicating that the chirality at C-12 of **1** and **2** was as shown in Figures 3 and 4.

To confirm the proposed structure for **2**, treatment of 6α-acetoxyvouacapane (**3**) with *m*CPBA in the presence of 1 drop 12 N HCl in $CHCl_3$ afforded sucutinirane B (**2**) together with two byproducts, compounds **5** and **6**, which was elucidated by 2D NMR correlations as shown in Figure 5. Stereochemistry of

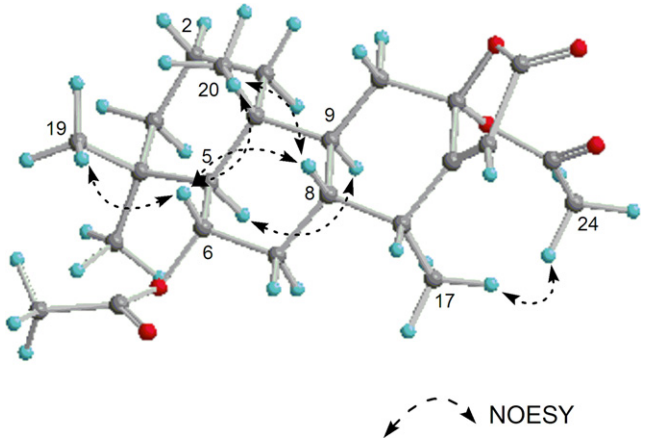
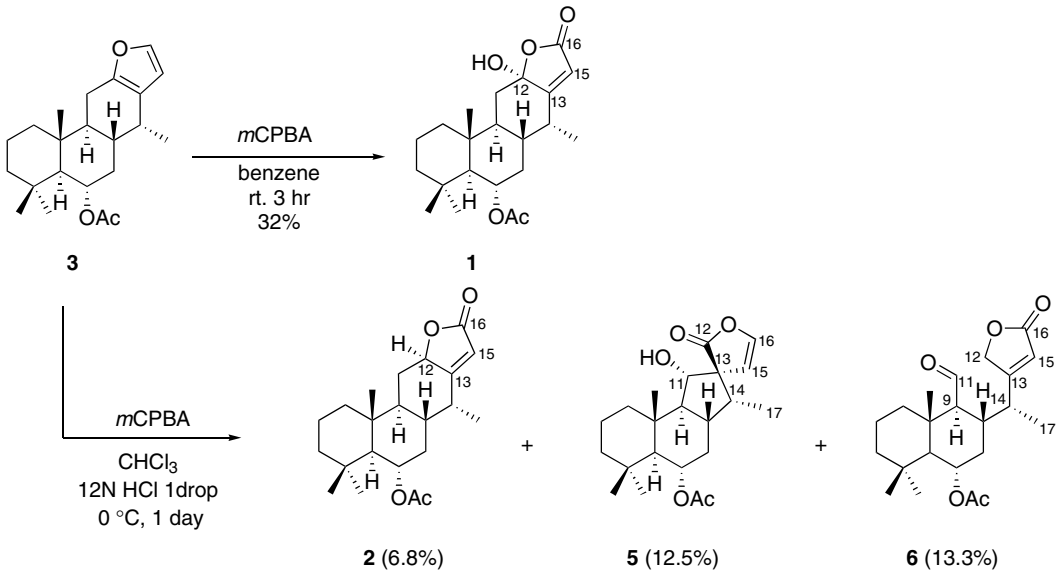


Figure 2. Selected NOESY correlations and relative stereochemistry of compound **1a**.



Scheme 1. Oxidation of 6α-acetoxyvouacapane (**3**) by *mCPBA*.

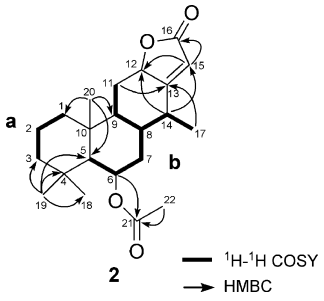


Figure 3. Selected 2D NMR correlations for sucutinirane B (**2**).

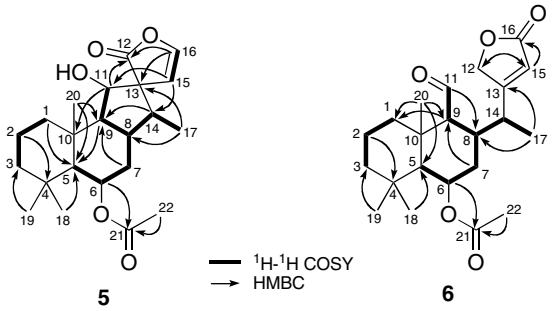


Figure 5. Selected 2D NMR correlations for **5** and **6**.

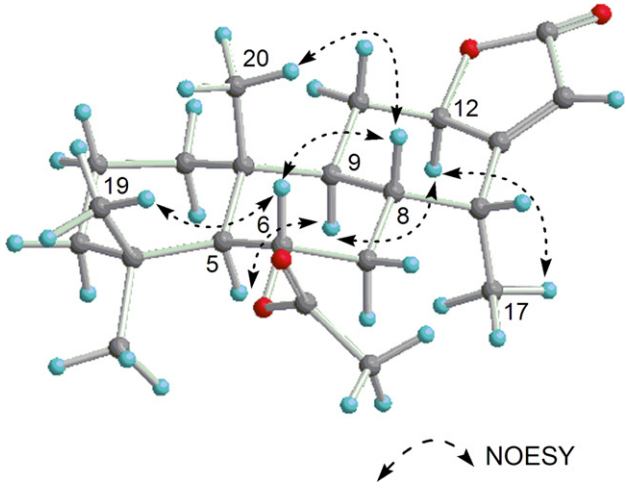


Figure 4. Selected NOESY correlations and relative stereochemistry of sucutinirane B (**2**).

a hydroxyl at C-11 and spiro carbon at C-13 for **5** was assigned by NOESY data of H-8/H-11 and H-15/H_3-17. Compound **5**, which was derived from oxidative intermediate at C-11 followed by epoxidation at Δ^{12} and Pinacol-type rearrangement, possesses a spirojoined β, γ-unsaturated γ-lactone, and cyclopentane bicycles with a hydroxyl group at C-11. On the other hand, compound **6**, which was produced from oxidative intermediate at C-11 followed by epoxidation at Δ^{15} and cleavage between C-11 and C-12 bond accompanied with cleavage of the epoxide, contains an aldehyde moiety at C-11 and an α, β-unsaturated γ-lactone moiety at C-14 (Scheme 1). These structures of **5** and **6** were also supported by HMBC (Fig. 5) and NOESY correlations.

Sucutinirane A (**1**) and 6α-acetoxyvouacapane (**3**) showed a moderate cytotoxicity against human colon carcinoma COLO201 cells with IC_{50} 37.3 and 86.6 μg/mL, respectively, while sucutinirane B (**2**), 6α,7β-diacetoxyvouacapane (**4**), and compounds **5** and **6** were inactive (IC_{50} > 100 μg/mL).

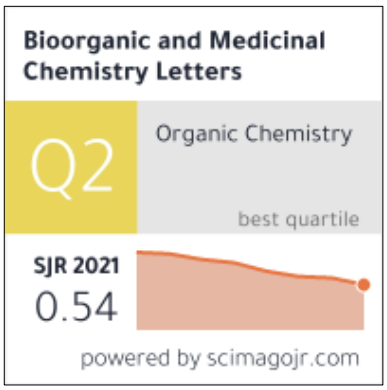
Each compound was also tested for its ability to inhibit *Plasmodium falciparum* growth.[9] 6α,7β-diacetoxyvouacapane (**4**) showed promising in vitro antiplasmodial activity against parasite *P. falciparum* 3D7 (IC_{50} 0.39 μg/mL) and a good selectivity index with regard to the cytotoxicity on COLO201 cells (IC_{50} > 100 μg/mL), whereas other compounds were inactive at a concentration of 1 μg/mL (Chloroqine: IC_{50} 0.006 μg/mL).

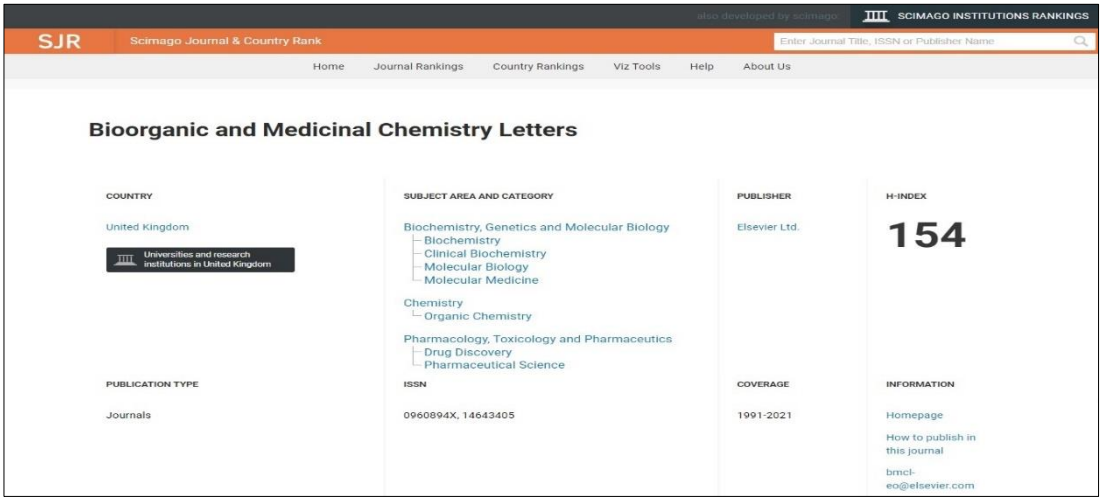
Acknowledgments

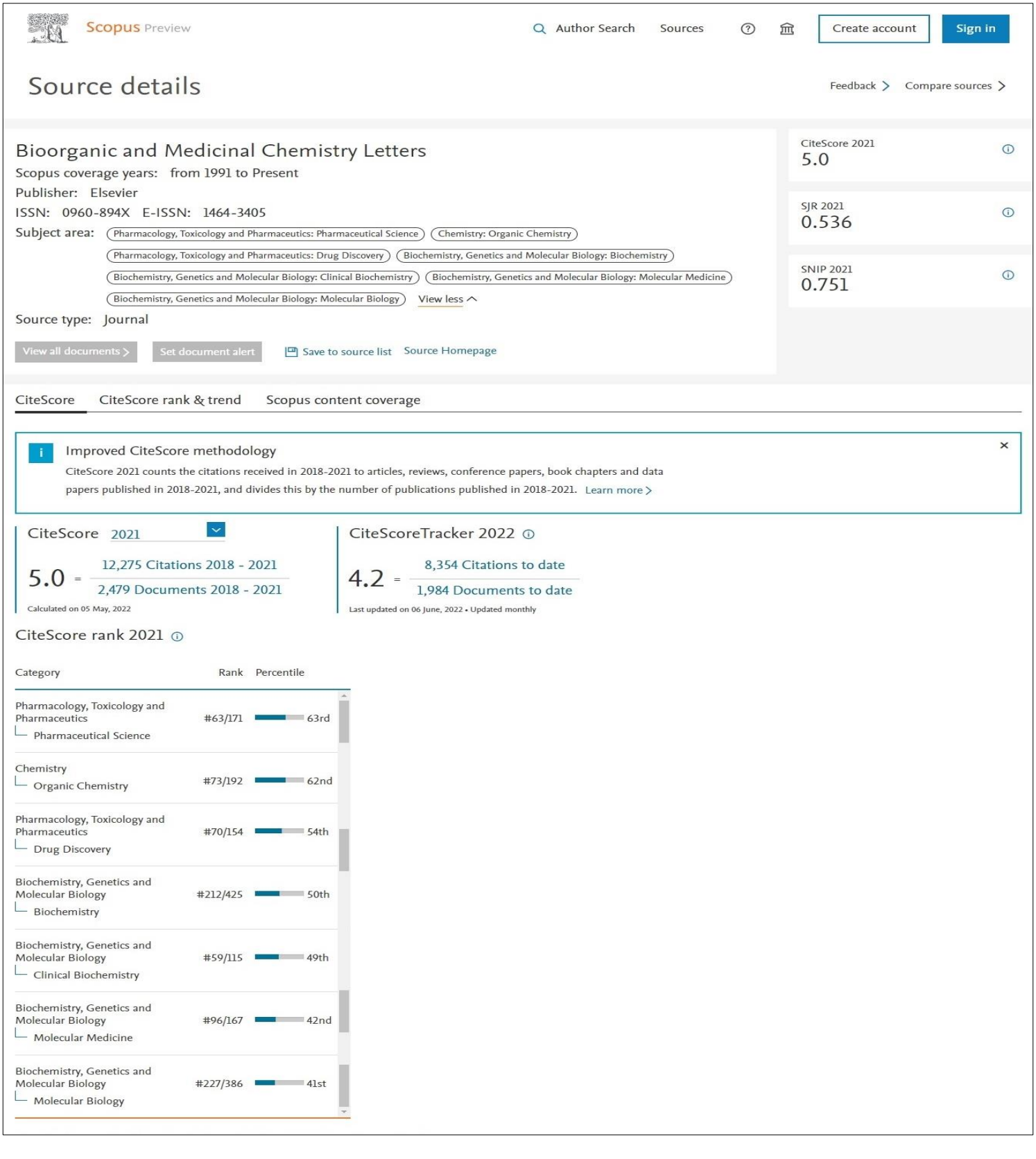
This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology of Japan, and grants from the Research Foundation for Pharmaceutical Sciences and The Open Research Center Project. We also acknowledge the financial support provided by Faculty of Pharmacy, Airlangga University, Indonesia.

References and notes

1. Hashimoto, G. *Illustrated Cyclopedia of Brazilian Medicinal Plants* **1996**, 642.
2. (a) Torrenegra, G. R.; Escarria, R. S.; Bauereiss, P.; Achenbach, H. *Planta Medica* **1985**, *3*, 276; (b) Barbosa-Filho, J. M.; Guedes, A. J. R.; Carlos, C. V.; Leitao, E. V.; Sobral, M.; Braz-Filho, R. *Journal of Asian Natural Products Research* **2004**, *1*, 11.
3. Melo, F. N.; Navarro, V. R.; Marcelo, S.; Emidio, V. L.; Barbosa-Filho, J. M.; Braz-Filho, R. *Natural Products Letters* **2001**, *4*, 261.
4. Brown, M. P.; Thomson, R. H.; Hausen, B. M.; Simatupang, M. H. *Justus Liebigs Annalen der Chemie* **1974**, *8*, 1295.
5. Mendes, F. N. P.; Silveira, E. R. *Phytochemistry* **1993**, *35*, 1499.
6. Mahajan, J. R.; Monterio, M. B. *J. Chem. Soc.* **1973**, *5*, 520.
7. Pudhom, K.; Sommit, D.; Suwankitti, N.; Petsom, A. *J. Nat. Prod.* **2007**, *70*, 1542.
8. Stöcklin, W.; Waddell, T. G.; Geissman, T. A. *Tetrahedron* **1970**, *26*, 2397.
9. Trager, W.; Jensen, J. B. *Science* **1976**, *193*, 673.


Bioorganic and Medicinal Chemistry Letters
Q2
Organic Chemistry
best quartile
SJR 2021
0.54
powered by scimagojr.com


SJR
Scimago Journal & Country Rank
SCIMAGO INSTITUTIONS RANKINGS
Home
Journal Rankings
Country Rankings
Viz Tools
Help
About Us
Bioorganic and Medicinal Chemistry Letters
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
0960894X, 14643405
COVERAGE
1991-2021
INFORMATION
Homepage
How to publish in this journal
bmcl-eo@elsevier.com


Scopus Preview
Author Search
Sources
Create account
Sign in
Source details
Feedback
Compare sources
Bioorganic and Medicinal Chemistry Letters
Scopus coverage years: from 1991 to Present
Publisher: Elsevier
ISSN: 0960-894X E-ISSN: 1464-3405
Subject area: Pharmacology, Toxicology and Pharmaceutics: Pharmaceutical Science
Chemistry: Organic Chemistry
Pharmacology, Toxicology and Pharmaceutics: Drug Discovery
Biochemistry, Genetics and Molecular Biology: Biochemistry
Biochemistry, Genetics and Molecular Biology: Clinical Biochemistry
Biochemistry, Genetics and Molecular Biology: Molecular Medicine
Biochemistry, Genetics and Molecular Biology: Molecular Biology
View less
Source type: Journal
View all documents
Set document alert
Save to source list
Source Homepage
CiteScore 2021
5.0
SJR 2021
0.536
SNIP 2021
0.751
CiteScore
CiteScore rank & trend
Scopus content coverage
Improved CiteScore methodology
CiteScore 2021 counts the citations received in 2018-2021 to articles, reviews, conference papers, book chapters and data papers published in 2018-2021, and divides this by the number of publications published in 2018-2021. Learn more
CiteScore 2021
5.0 = 12,275 Citations 2018 - 2021 / 2,479 Documents 2018 - 2021
Calculated on 05 May, 2022
CiteScoreTracker 2022
4.2 = 8,354 Citations to date / 1,984 Documents to date
Last updated on 06 June, 2022 • Updated monthly
CiteScore rank 2021
Category
Rank
Percentile
Pharmacology, Toxicology and Pharmaceutics
Pharmaceutical Science
#63/171
63rd
Chemistry
Organic Chemistry
#73/192
62nd
Pharmacology, Toxicology and Pharmaceutics
Drug Discovery
#70/154
54th
Biochemistry, Genetics and Molecular Biology
Biochemistry
#212/425
50th
Biochemistry, Genetics and Molecular Biology
Clinical Biochemistry
#59/115
49th
Biochemistry, Genetics and Molecular Biology
Molecular Medicine
#96/167
42nd
Biochemistry, Genetics and Molecular Biology
Molecular Biology
#227/386
41st