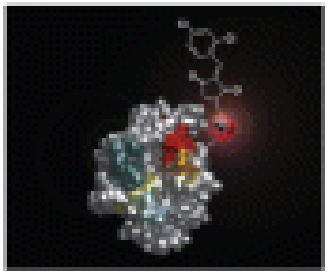
Volume 21 • Issue 21 • 1 November 2011 • ISSN 0960-894X

Bioorganic & Medicinal Chemistry Letters

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



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Bioorganic & Medicinal Chemistry Letters 21 (2011) 3181–3197

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Bioorganic & Medicinal Chemistry Letters Volume 21, Issue 11, 2011

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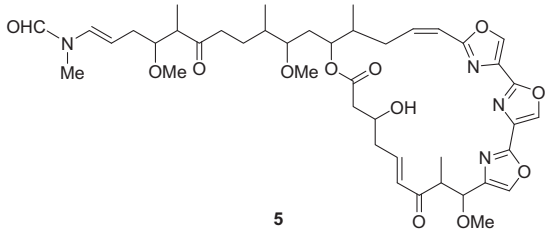

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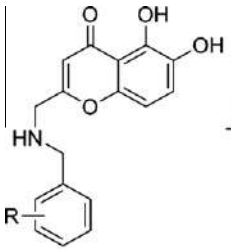
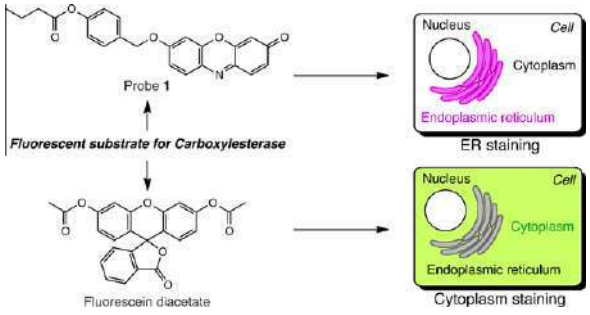
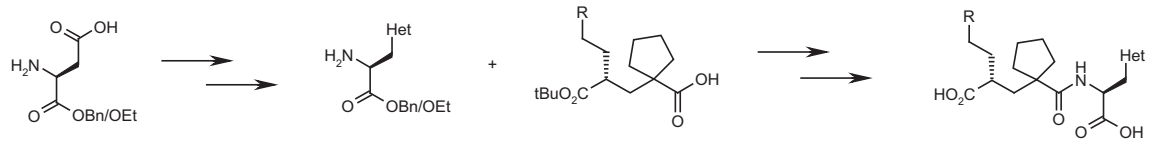
(19*Z*)-Halichondramide (**5**) with enhanced actin depolymerizing activity and potent antifungal activity.

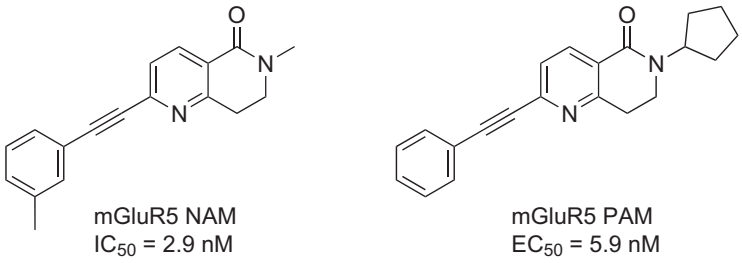


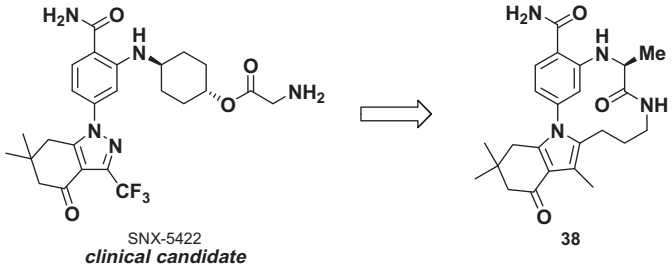
Compd	R	EC_{50} (μM)	CC_{50} (μM)
3i	3-Cl	14.0	>100
3j	3-Br	3.6	>100
3k	3-I	7.3	>100
3n	3-Me	2.0	>100



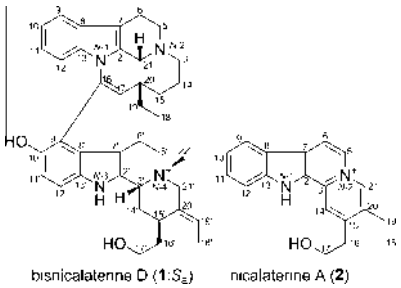


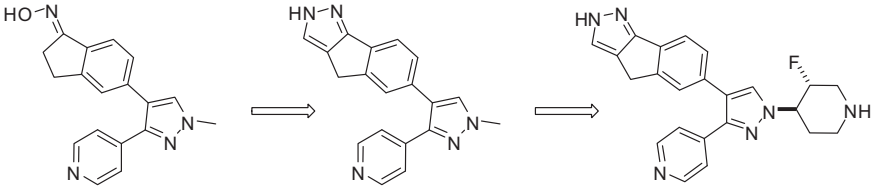
Novel heteroarylalanines derived from L-aspartic acid were designed and synthesised as potential inhibitors of Neutral Endopeptidase (NEP).





Two new indole alkaloids, bisnicalaterine D (**1**), consisting of an eburnane and a corynanthe type of skeletons, and nicalaterine A (**2**) were isolated from the bark of *Hunteria zeylanica*. Their structures were elucidated by various spectroscopic data such as NMR and CD spectra. A series of bisnicalaterines and nicalaterine A showed potent antiplasmodial activity against *Plasmodium falciparum* 3D7.





Compound 1a
BRaf IC_{50} = 0.02 nM

Compound 2a
BRaf IC_{50} = 2.2 nM

Compound 38
BRaf IC_{50} = 1.4 nM

*Corresponding author
Supplementary data available via ScienceDirect

COVER

Botulinum neurotoxins are the most deadly toxins known to man, approximately 10 million times more deadly than cyanide. Botulinum neurotoxins are classified by the US Centers for Disease Control (CDC) as bioterrorism agents. The etiological agent responsible for botulinum intoxication is a metalloprotease; as such this is a key therapeutic target. Currently, there are no approved pharmacological treatments for botulinum intoxication. Discovering molecules that could be used as a path forward for therapeutic development as botulinum protease inhibitors is tantamount. A benzylidene cyclopentenedione-based inhibitor was found to be the first affinity reagent to covalently modify the active site of botulinum neurotoxin A light chain metalloprotease. Its kinetic parameters are reported and such an approach for inhibition of this deadly neurotoxin. [Capková, K.; Hixon, M. S.; Pellett, S.; Barbieri, J. T.; Johnson, E. A.; Janda, K. D. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 206.]

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®

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ISSN 0960-894X

Bioorganic & Medicinal Chemistry Letters 21 (2011) 3417–3419

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Bioorganic & Medicinal Chemistry Letters

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New antiplasmodial indole alkaloids from *Hunteria zeylanica*

Alfarius E. Nugroho [a], Masatomo Sugai [a], Yusuke Hirasawa [a], Takahiro Hosoya [a], Khalijah Awang [b], A. Hamid A. Hadi [b], Wiwied Ekasari [c], Aty Widyawaruyanti [c], Hiroshi Morita [a,*]

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ARTICLE INFO

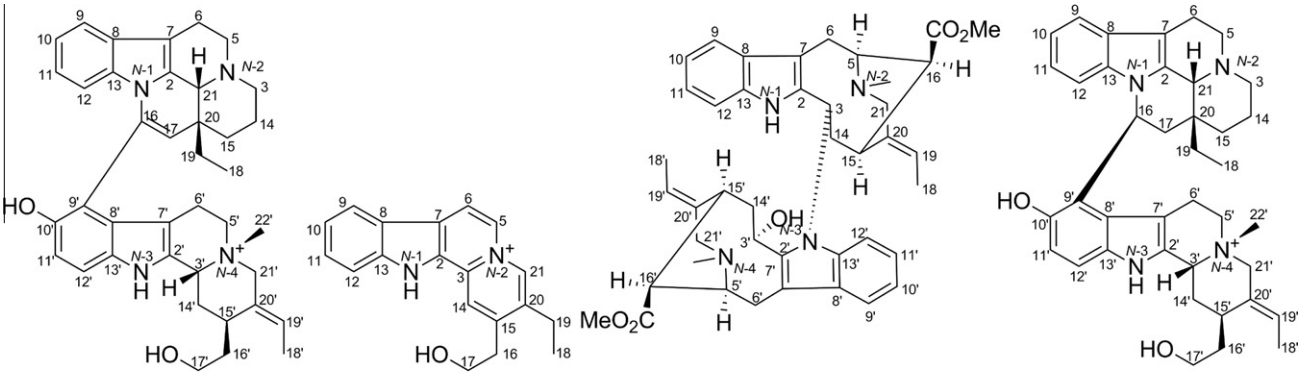
Article history:
Received 2 March 2011
Revised 24 March 2011
Accepted 29 March 2011
Available online 5 April 2011

Keywords:
Indole alkaloid
Bisnicalaterine D
Nicalaterine A
Hunteria zeylanica
Antiplasmodial activity

ABSTRACT

Two new indole alkaloids, bisnicalaterine D (**1**), consisting of an eburnane and a corynanthe type of skeletons, and nicalaterine A (**2**) were isolated from the bark of *Hunteria zeylanica*. Their structures were elucidated by various spectroscopic data such as NMR and CD spectra. A series of bisnicalaterines and nicalaterine A showed potent antiplasmodial activity against *Plasmodium falciparum* 3D7.

In our search for new bioactive alkaloids from tropical plants in Malaysia and Indonesia, we have previously reported a series of cassiarins with potent antiplasmodial activity.[1,2] *Hunteria zeylanica* (Retz.) Gardner ex Thwaites is a member of the Apocynaceae family in Malaysia, found mostly in Pahang and Selangor,[3] and the bark and leaves have been known to produce various skeletal alkaloids depending on the area where the plants were distributed.[4–9] In our previous paper,[10,11] we have reported the isolation of new bisindole alkaloids, bisnicalaterines A–C (**3**–**5**) from *H. zeylanica*. In this Letter, we report the isolation and structure elucidation of bisnicalaterine D (**1**), a new bisindole alkaloid consisting of an eburnane and a corynanthe type of skeletons, and nicalaterine A (**2**) as well as the antimalarial activity of **1**–**5** against *Plasmodium falciparum* 3D7.



bisnicalaterine D (**1**:S_a) nicalaterine A (**2**) bisnicalaterine A (**3**:R_a) bisnicalaterine B (**4**:S_a) bisnicalaterine C (**5**:R_a)

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doi:10.1016/j.bmcl.2011.03.104

The bark of *H. zeylanica*[12] was extracted with MeOH, and part (33 g) of the extract was treated with 3% tartaric acid (pH 2) and then partitioned with EtOAc. The aqueous layer was treated with saturated Na_2CO_3 (aq) to pH 10 and extracted with $CHCl_3$ and *n*-BuOH subsequently. The *n*-BuOH fraction was subjected to an HP-20 column (H_2O/MeOH 0:1 to 1:0), and the 80% MeOH fraction (3.5 g) was further separated by using a Sephadex LH-20 column. Fractions containing **1** was then separated by a silica gel column ($CHCl_3$/MeOH, 9:1 to 0:1), followed by an ODS Sep-Pak (MeOH/H_2O 1:9 to 1:0) to give bisnicalaterine D (**1**, 8.1 mg, 0.003%), while purification of fractions containing **2** by an amino silica gel column ($CHCl_3$/MeOH, 9:1 to 0:1) and a silica gel column ($CHCl_3$/MeOH, 8:2) yielded nicalaterine A (**2**, 2.0 mg, 0.0008%).

Bisnicalaterine D (**1**),[13] a yellowish amorphous solid, $[\alpha]_D^{20}$ −72 (*c* 1.0, MeOH), showed a molecular formula, $C_{39}H_{47}N_4O_2$, which was determined by HRESIMS [*m*/*z* 603.3689 $(M)^+$, Δ −0.5 mmu]. IR absorption band (3430 cm^{-1}) was characteristic of amino or hydroxyl group. ^1H and ^{13}C NMR data (Table 1) suggested the presence of one sp^3 quaternary carbon, 12 sp^3 methylenes, three sp^3 methines, three methyls, eight sp^2 methines, and 12 sp^2 quaternary carbons. The ^{13}C NMR spectrum of **1** is very similar to those of bisnicalaterines B (**4**).[11] Compared to spectroscopic data of **4**, **1** has two less sp^3 carbons, two additional sp^2 carbons (δ_c 131.9 and δ_c 117.7) and also 2 amu smaller which suggests the existence of an additional double bond in **1**. The existence of a double bond between C-16 and C-17 was confirmed by the HMBC correlations of H-17 to C-16, C-19, C-20, C-21 and C-9′, H_3-18 to C-20, and H-21 to C-15. Further analysis of the two-dimensional NMR data (^1H–^1H COSY, HMQC, and HMBC spectra) revealed the gross structure of **1** as shown in Figure 1.

Table 1
^1H and ^{13}C NMR data of bisnicalaterine D (**1**) and nicalaterine A (**2**) in CD_3OD at 300 K[a]

Position	1		2	
	[δ_H (*J*, Hz)]	[δ_c]	[δ_H (*J*, Hz)]	[δ_c]
2		125.3		131.5
3a	3.37 (1H, m)	46.7		132.4
3b	3.37 (1H, m)			
5a	3.87 (1H, m)	53.1	8.69 (1H, br s)	127.3
5b	3.97 (1H, m)			
6a	3.13 (1H, m)	16.9	8.44 (1H, br s)	117.0
6b	3.30 (1H, m)			
7		108.2		123.0
8		128.7		122.3
9	7.48 (1H, d, 7.6)	119.7	8.21 (1H, d, 7.6)	122.6
10	6.97 (1H, m)	121.7	7.39 (1H, t, 7.6)	124.0
11	6.69 (1H, t, 8.3)	124.2	7.64 (1H, t, 7.6)	130.4
12	5.83 (1H, d, 8.3)	113.4	7.70 (1H, br s)	113.7
13		136.2		143.0
14a	1.83 (1H, m)	19.4	8.58 (1H, s)	121.2
14b	1.98 (1H, m)			
15a	1.68 (1H, m)	29.1		151.1
15b	1.86 (1H, m)			
16		131.9	3.22 (2H, br s)	36.2
17	5.26 (1H, s)	117.7	4.09 (2H, br s)	61.4
18	1.11 (3H, t, 7.6)	8.8	1.45 (3H, t, 7.2)	13.7
19a	1.85 (1H, m)	27.9	2.98 (2H, q, 7.2)	24.8
19b	2.00 (1H, m)			
20		39.2		139.5
21	5.22 (1H, s)	59.1	8.94 (1H, s)	135.1
2′		131.3		
3′	4.68 (1H, dd, 11.0, 3.5)	62.8		
5a′	2.93 (1H, m)	52.2		
5b′	3.76 (1H, m)			
6a′	1.53 (1H, m)	18.7		
6b′	2.93 (1H, m)			
7′		102.6		
8′		126.8		
9′		112.1		
10′		150.9		
11′	6.96 (1H, m)	114.3		
12′	7.39 (1H, d, 8.2)	114.8		
13′		133.0		
14a′	2.16 (1H, m)	36.1		
14b′	2.25 (1H, m)			
15′	3.16 (1H, m)	30.4		
16a′	1.86 (1H, m)	34.5		
16b′	1.96 (1H, m)			
17a′	3.51 (1H, m)	60.1		
17b′	3.62 (1H, m)			
18′	1.73 (3H, d, 6.9)	13.3		
19′	5.79 (1H, q, 6.9)	132.1		
20′		129.2		
21a′	3.66 (1H, m)	68.1		
21b′	4.18 (1H, br d, 13.8)			
22′	2.50 (3H, s)	48.6		

[a] δ In ppm.

The stereochemistry of each monoterpeneindole unit in **1** was assigned by NOESY correlations as shown in computer-generated 3D drawing (Fig. 2). In unit A, the NOESY correlations of H_2-19/H-21 suggested that H-21 and an ethyl group (C-18–C-19) were β-oriented. While in unit B, the NOESY correlations of H-3′/H_3-22′, H-21′b, and H_2-16′, H_3-22′/H-21′b and H-21′b/H-16′b suggested that H-3′, C-16′ and C-22′ were β-oriented, while the correlations of H-19′/H-21′a and H-15′/H_3-18′ established the *E*-configuration of the ethylidene side chain. Thus the relative stereochemistry of units A and B was assigned as shown in Figure 2.

In the case of bisnicalaterines B (**4**) and C (**5**), there were two possible conformations around C-16–C-9′ bond, the twisted and extended conformations.[11] In bisnicalaterine D (**1**), the NOESY correlation of H-6′b/H-21 and the highly shifted chemical shift (δ_H 1.53 and 2.50, respectively) of H-6′a and H_3-22′ at ammonium nitrogen atom suggested that **1** possessed the twisted conformation observed in bisnicalaterine B (**4**).[11]

The absolute structure of **1** was deduced by comparing its CD spectrum to that of bisnicalaterine B (**4**). The CD spectrum[13] of **1** showed a similar CD pattern to that of **4**,[11] thus the absolute structure of **1** was determined to be of 20*R*, 21*R*, 4′*R*, 3′*R*, 15′*R*.

Nicalaterine A (**2**),[14] a yellowish amorphous solid, showed a molecular formula, $C_{19}H_{19}N_2O$, which was determined by HRESIMS [*m*/*z* 291.1496 $(M)^+$, Δ −0.1 mmu]. IR absorption band (3430 cm^{-1}) was characteristic of amino or hydroxyl group. The UV spectrum suggested the presence of a highly conjugated ring system [λ_{max} 386 (ε 8000), 346 (8300), 291 (6900), 240 (16,100), and 235 (sh, 15,000)] as in flavopereirine.[15] ^1H and ^{13}C NMR data (Table 1) suggested the presence of three sp^3 methylenes, one methyl, eight sp^2

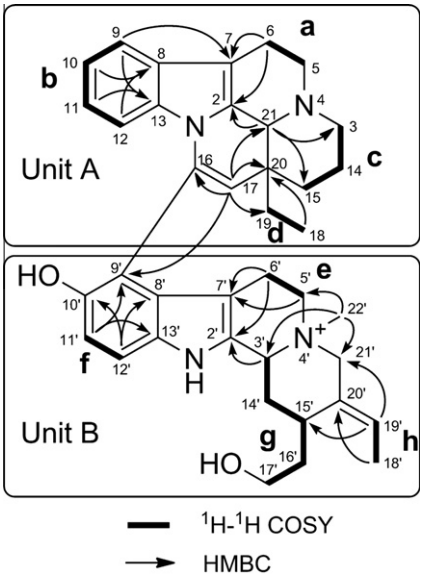

Figure 1. Selected 2D NMR correlations for bisnicalaterine D (**1**).

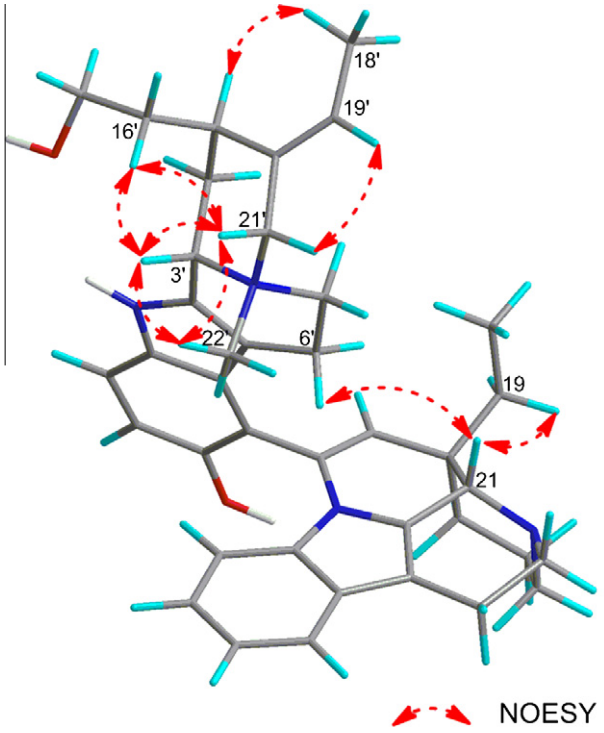

Figure 2. Selected NOESY correlations for bisnicalaterine D (**1**).

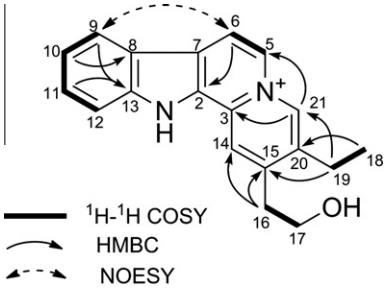

Figure 3. Selected 2D NMR correlations for nicalaterine A (**2**).

Table 2
Antiplasmodial activity of **1**–**5** against *P. falciparum* 3D7

Antiplasmodial activity (IC_{50}, μM)	Cytotoxic activity[a] (IC_{50}, μM)	SI
1 >50	>50	–
2 0.11	>50	>450
3 4.36	16.2	3.7
4 1.13	>50	>44
5 0.05	>50	>1000

[a] Against HL-60.

methines, and seven sp^2 quaternary carbons. The HMBC correlations of H_2-19 to C-15 and C-21, H_3-18 to C-20, and H_2-16 to C-15 and C-14 allowed the attachment of the ethyl side chain (C-18 and C-19) to C-20 and the 2-hydroxyethyl side chain to C-15. Further analysis of the two-dimensional NMR data (^{1}H–^{1}H COSY, HSQC, and HMBC spectra in CD_3OD) revealed the gross structure of **2** as shown in Figure 3.

Antimalarial activity[16–18] for **1**–**5** against *P. falciparum* 3D7 was evaluated (Table 2). Nicalaterine A (**2**) and bisnicalaterine C (**5**) showed potent antimalarial activity (IC_{50} 0.11 and 0.05 μM, respectively) with a good selectivity (SI >450 and >1000, respectively). Bisnicalaterine C (**5**) with an extended conformation showed 20 times more effective than that of bisnicalaterine B (**4**) with a twisted conformation. On the other hand, bisnicalaterine D (**1**), which also possessed a twisted conformation, showed practically no antimalarial activity. It is interesting to note that the conformation around the C-16 - C-9′ bond may play important roles to show antimalarial activity.

Acknowledgments

This work was partly 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, and Takeda Science Foundation.

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12. Bark of *H. zeylanica* were collected in Kampung Padang, Malaysia, in 1994. The botanical identification was made by Mr. Teo Leong Eng, Faculty of Science, University of Malaya. A voucher specimen (Herbarium No. KL 4345) is deposited at the Herbarium of the Department of Chemistry, University of Malaya, Kuala Lumpur, Malaysia.
13. Bisnicalaterine D, yellowish amorphous solid, $[\alpha]_D^{20}$ −72 (*c* 1.0, MeOH), UV (MeOH) λ_{max} 217 (ε 16800), 249 (6100), 277.5 (5300), 302 (4100); CD (MeOH) λ_{max} 205 (Δε 5.95), 218 (−6.09), 243 (6.54), 280 (−4.22), 365 (3.07); IR (KBr) ν_{max} 3430 cm^{-1}; ^{1}H and ^{13}C NMR data see Table 1; EI-MS *m*/*z* 603 M^+; HRESIMS [*m*/*z* 603.3689 $(M)^+$, calcd for $C_{39}H_{47}N_4O_2$, 603.3694].
14. Nicalaterine A (**2**), a yellowish amorphous solid, UV (MeOH) λ_{max}, 235 (sh, 15,000), 240 (16,100), 291 (6900), 346 (8300), and 386 (ε 8000); IR (KBr) ν_{max} 3430 cm^{-1}, ^{1}H and ^{13}C NMR data see Table 1; EI-MS *m*/*z* 291 M^+; HRESIMS [*m*/*z* 291.1496 $(M)^+$, calcd for $C_{19}H_{19}N_2O$, 291.1497].
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16. Human malaria parasites were cultured according to the method of Trager and Jensen.[17] The antimalarial activity of the isolated compounds was determined by the procedure described by Budimulja et al.[18] In brief, stock solutions of the samples were prepared in DMSO (final DMSO concentrations of <0.5%) and were diluted to the required concentration with complete medium (RPMI 1640 supplemented with 10% human plasma, 25 mM HEPES and 25 mM $NaHCO_3$) until the final concentrations of samples in culture plate wells were 10; 1; 0,1; 0,01; 0,001 μ/mL. The malarial parasite *P. falciparum* 3D7 clone was propagated in a 24-well culture plates. Growth of the parasite was monitored by making a blood smear fixed with MeOH and stained with Geimsa stain. The antimalarial activity of each compound was expressed as an IC_{50} value, defined as the concentration of the compound causing 50% inhibition of parasite growth relative to an untreated control. The percentage of growth inhibition was expressed according to following equation : Growth inhibition % = 100−[(test parasitaemia/control parasitemia) × 100]. Chloroqine: IC_{50} 0.011 μM.
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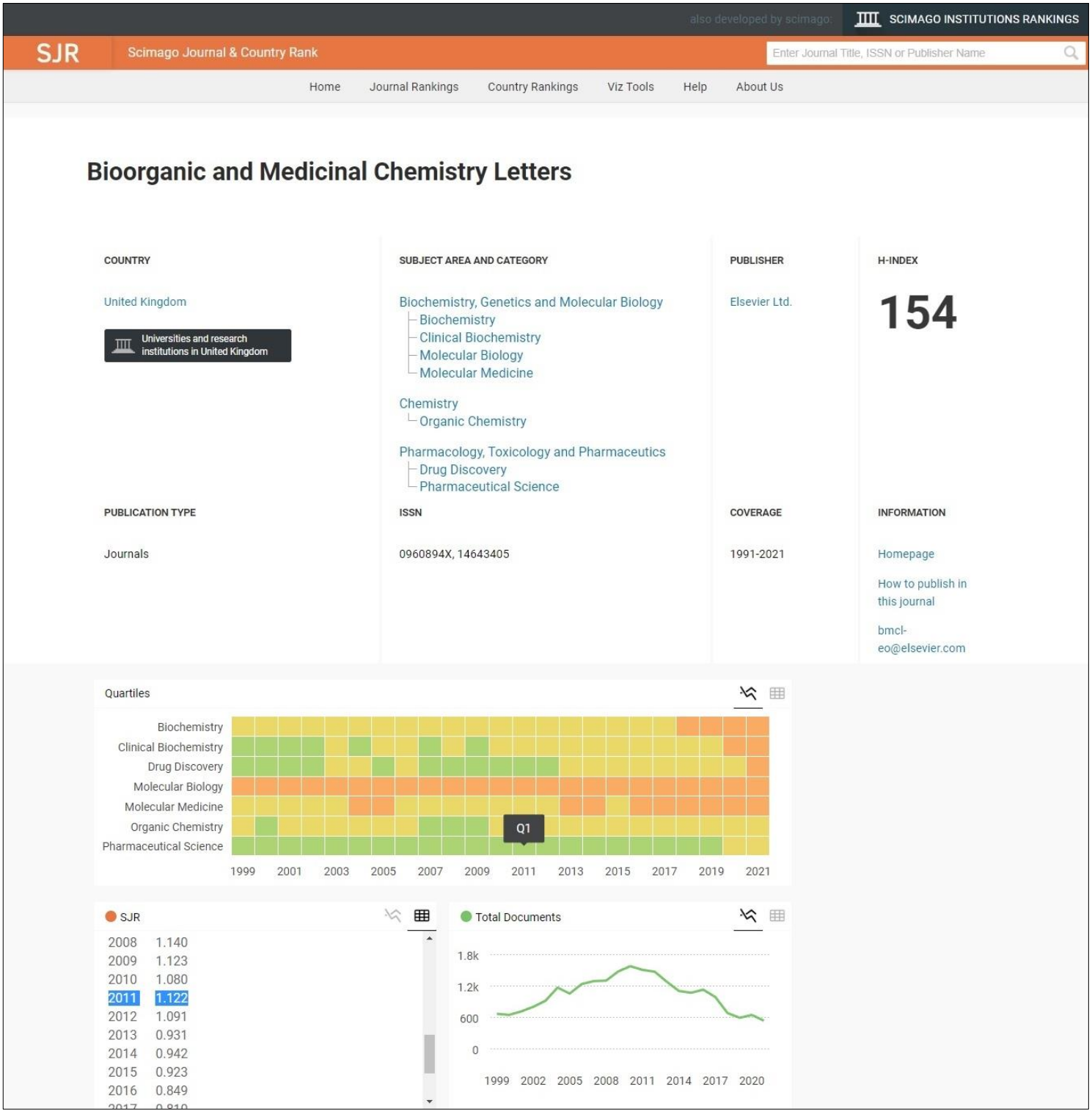

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Publisher: Elsevier

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

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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