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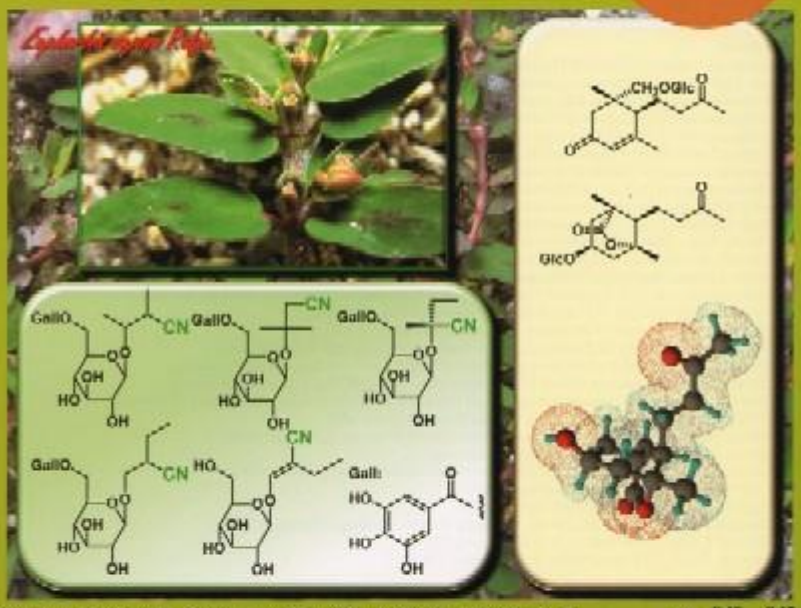

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Type: Review
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DOI https://doi.org/10.1248/cpb.57.765

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Diketopiperazine Alkaloids from a Deep Ocean Sediment Derived Fungus *Penicillium* sp.

Delaumonones A and B, New Antiplasmodial Quassinoids from *Laumoniera bruceadelpha*

Shiori Oshimi,[a] Aki Takasaki,[a] Yusuke Hirasawa,[a] Takahiro Hosoya,[a] Khalijah Awang,[b] A. Hamid A. Hadi,[b] Wiwied Ekasari,[c] Aty Widyawaruyanti,[c] and Hiroshi Morita*,[a]

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New quassinoids, delaumonones A (1) and B (2) have been isolated from the bark of *Laumoniera bruceadelpha* Nooteboom (Simaroubaceae) and the structures were elucidated by 2D NMR analysis and a chemical correlation. Delaumonones showed an antimalarial activity against *Plasmodium falciparum*.

Key words quassinoid; delaumonone; antimalarial activity; *Laumoniera bruceadelpha*

Malaria is one of the crucial infectious disease in the world and continues to cause morbidity and mortality on a large scale in tropical countries.[1)] The antimalarial potential of compounds derived from plants is proven by examples such as quinine from *Cinchona* species and artemisinin from *Artemisia annua*.[2)] The plants belonging to Simaroubaceae are known to contain various quassinoids with biological activities, such as antimalarial, antifeedant, anti-inflammatory, antiulcer, antipyretic, and cytotoxic activities.[3—6)] Recent studies of numerous Simaroubaceae plants have highlighted good antimalarial activity of certain quassinoids against chloroquine-resistant strains of *Plasmodium falciparum*.[7)] These results have prompted us to search for new quassinoids for possible antimalarial action.

With an aim to isolate additional antimalarial natural products,[8—13)] purification of the extracts from the bark of *Laumoniera bruceadelpha* Nooteboom (Simaroubaceae) collected in Malaysia led to isolate two new quassinoids, delaumonones A (**1**) and B (**2**). This paper describes the isolation and structural elucidation of **1** and **2** with an antimalarial activity against *P. falciparum*.

The bark of *L. bruceadelpha* (1.4 kg), which was collected in Malaysia, was extracted with MeOH, and the extract was partitioned between $CHCl_3$, *n*-BuOH, and H_2O. $CHCl_3$-soluble materials were subjected to a silica gel column ($CHCl_3$/MeOH), and then an ODS column followed by ODS HPLC to afford delaumonones A (**1**, 11.9 mg) and B (**2**, 5.6 mg) together with isobrucein A (**3**, 307.0 mg)[14)] and isobrucein B (**4**, 5.8 mg).[15)] *n*-BuOH-soluble materials were subjected to an HP-20 column, and then a silica gel column ($CHCl_3$/MeOH), followed by ODS HPLC to afford delaumonone A (**1**, 15.0 mg) together with brucein D (**5**, 1.2 mg)[16)] and yadanziolide A (**6**, 3.7 mg).[17)]

Delaumonone A (**1**), colorless solid, $[\alpha]_D^{20}$ +20 (c=1.0, MeOH), showed molecular formula, $C_{25}H_{32}O_{11}$, which was determined by HR-ESI-MS [*m/z* 531.1827 $(M+Na)^+$, Δ −1.5 mmu]. IR absorptions implied the presence of hydroxyl (3439 cm^{-1}) and carbonyl (1735, 1665 cm^{-1}) functionalities. ^{1}H- and ^{13}C-NMR data are presented in Table 1. The ^{13}C-NMR spectrum revealed 25 carbon signals due to five sp^2 quaternary carbons, three sp^3 quaternary carbons, one sp^2 methine, nine sp^3 methines, three methylenes, and four methyls. Among eight quaternary carbons (δ_C 45.7, 49.0, 81.0, 164.0, 168.2, 172.1, 173.8, 198.4), five quaternary carbons (δ_C 81.0, 168.2, 172.1, 173.8, 198.4) were ascribed to those bearing an oxygen atom.

The molecular structure of **1** was deduced from extensive analyses of the two-dimensional NMR data, including the ^{1}H–^{1}H COSY, HMQC, and HMBC spectra in CD_3OD (Fig. 1). The ^{1}H–^{1}H COSY and HOHAHA spectra revealed connectivities of five partial structures **a** (C-3—C-4 and C-18), **b** (C-5—C-7), **c** (C-9 and C-11—C-12), **d** (C-14—C-15), and **e** (C-2′—C-5′) as shown in Fig. 1. Connectivity of C-4 to C-5 was implied by an HMBC correlation for H_3-18 to C-5 (δ_C 42.4). HMBC correlations were observed for H_3-19 to C-1 (δ_C 81.5), C-5, C-9 (δ_C 41.6), and C-10 (δ_C 49.0), H-1 to C-2 (δ_C 198.4), H-3 to C-1, suggesting that C-19 was connected through C-10 in a decalin ring system. HMBC cross peaks for H_2-20 to C-8 (δ_C 45.7), C-12 (δ_C 75.0), and C-13 (δ_C 81.0) indicated that the presence of an ether bridge between C-13 and C-20. In addition, connection of unit **c** and a carboxylic acid through C-13 was also indicated by the HMBC correlations for H-12 to C-13 and C-21 (δ_C 172.1). The presence of an isopentanoate at C-15 was implied by the HMBC correlations for H-15 and H-3′ to C-1′ (δ_C 173.8). The presence of a δ-lactone ring characteristic of C_{20} quassinoid skeleton was indicated by an HMBC correlation for H-14 to C-16 (δ_C 168.2). Thus, the molecular structure of de-

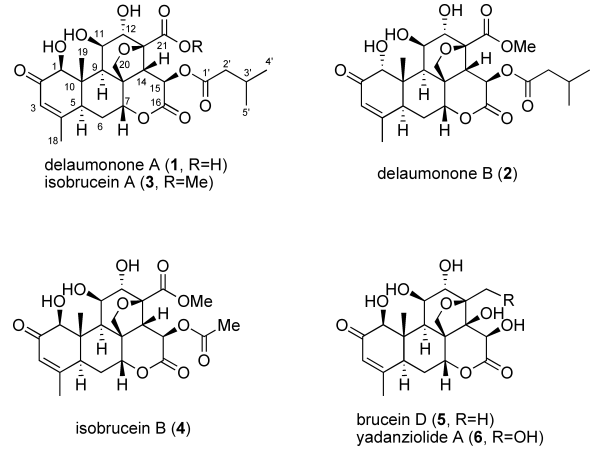


Chart 1

* To whom correspondence should be addressed. e-mail: moritah@hoshi.ac.jp

laumonone A was elucidated to be **1**.

The relative configuration of **1** was elucidated by NOESY correlations as depicted in the computer-generated three-dimensional drawing (Fig. 2). The NOESY correlations of H-1/H-5 and H-9, and H-9/H-5 and H-15 indicated that these protons at C-1, C-5, C-9, and C-15 were α-orientated. The β-orientation of H_3-19, H-7, and H-14, and α-orientation of H-11 were indicated by NOESY correlations of H-20/H-7 and H-14, and $^3J_{H-H}$ coupling constant (3.2 Hz) of H-9/H-11.

Table 1. ^{1}H- and ^{13}C-NMR Data for Delaumonones A and B (**1**, **2**) in CD_3OD at 300 K[a)]

Position	δ_H (int.; mult.; J (Hz))		δ_C	
	1	**2**	**1**	**2**
1	4.29 (1H, s)	3.89 (1H, s)	81.5	76.3
2			198.4	199.8
3	6.04 (1H, br s)	5.87 (1H, br s)	123.9	125.1
4			164.0	164.6
5	3.00 (1H, br d, 12.4)	3.06 (1H, br d, 12.7)	42.4	39.3
6a	1.96 (1H, m)	1.90 (1H, m)	27.8	28.9
6b	2.34 (1H, ddd, 14.8, 2.8, 2.8)	2.33 (1H, br d, 15.4)		
7	4.90 (1H, m)	4.90 (1H, m)	83.3	83.2
8			45.7	46.9
9	2.45 (1H, br d, 3.2)	2.70 (1H, br s)	41.6	35.3
10			49.0	44.7
11	4.72 (1H, br d, 5.2)	4.26 (1H, br d, 4.7)	73.8	72.5
12	4.20 (1H, br s)	4.20 (1H, br s)	75.0	76.4
13			81.0	84.0
14	3.26 (1H, m)	3.35 (1H, m)	51.2	51.2
15	6.25 (1H, m)	6.22 (1H, m)	68.7	66.0
16			168.2	169.6
18	1.97 (3H, s)	1.95 (3H, s)	21.2	22.5
19	1.19 (3H, s)	1.26 (3H, s)	10.1	14.8
20a	3.71 (1H, d, 7.6)	3.73 (1H, d, 7.6)	72.9	74.7
20b	4.68 (1H, d, 7.6)	4.71 (1H, d, 7.6)		
21			172.1	172.4
1′			173.8	173.1
2′	2.21 (2H, d, 6.8)	2.20 (2H, d, 6.8)	41.9	44.8
3′	2.07 (1H, m)	2.06 (1H, m)	25.2	26.7
4′	0.96 (3H, d, 6.8)	0.97 (3H, d, 6.6)	21.4	22.7
5′	0.97 (3H, d, 6.8)	0.98 (3H, d, 6.6)	21.4	22.7
OMe		3.79 (3H, s)		53.1

a) δ in ppm.

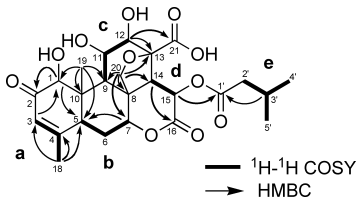


Fig. 1. Selected 2D NMR Correlations for Delaumonone A (**1**)

Treatment of **1** with TMS-diazomethane afforded a methyl ester derivative, whose spectroscopic data and specific rotation were identical with those of isobrucein A (**3**).[14)] Thus, the absolute configuration of delaumonone A was assigned as **1**.

Delaumonone B (**2**), colorless solid, $[\alpha]_D^{20}$ +18 (c=1.0, MeOH), showed molecular formula, $C_{26}H_{34}O_{11}$, which was determined by HR-ESI-MS [m/z 523.2180, $(M+H)^+$, Δ −0.1 mmu]. IR absorptions implied the presence of hydroxyl (3477 cm^{-1}) and carbonyl (1743, 1668 cm^{-1}) functionalities. ^{1}H- and ^{13}C-NMR data are presented in Table 1. The ^{13}C-NMR spectrum revealed 26 carbon signals due to five sp^2 quaternary carbons, three sp^3 quaternary carbons, one sp^2 methine, nine sp^3 methines, three methylenes, and five methyls. Among eight quaternary carbons (δ_C 44.7, 46.9, 84.0, 164.6, 169.6, 172.4, 173.1, 199.8), five quaternary carbons (δ_C 84.0, 169.6, 172.4, 173.1, 199.8) were ascribed to those bearing an oxygen atom.

^{1}H–^{1}H COSY, HMQC, and HMBC spectra in Fig. 3 suggested that **2** had the same pentacyclic backbone framework as that of isobrucein A (**3**),[14)] although the ^{1}H-NMR chemical shifts of H-1 (δ_H 3.89), H-9 (δ_H 2.70), and H-11 (δ_H 4.26) in **2** were remarkably not identical to those [H-1 (δ_H 4.17), H-9 (δ_H 2.33), and H-11 (δ_H 4.73)] in **3**, indicating that it was a stereoisomer of isobrucein A (**3**). The relative configuration of **2** was elucidated by NOESY correlations (Fig. 3). H-1 was assigned to be equatorial. NOESY cross peaks for H-1 to H_3-19 and H-11 were observed in the case of **2**, but not for **1** and **3**. This suggested that delaumonone B (**2**) was 1-*epi* form of isobrucein A (**3**). Thus, the relative configuration of delaumonone B (**2**) was assigned as shown.

Delaumonones A (**1**) and B (**2**) showed a potent *in vitro* antiplasmodial activity against *P. falciparum* 3D7 (IC_{50} **1**: 0.31 μg/ml; **2**: 0.60 μg/ml) and cytotoxicity against HL-60 cells (IC_{50} **1**: 1.6 μg/ml; **2**: 2.4 μg/ml). Among isolated quassinoids, isobrucein A[14)] (IC_{50} **3**: 0.024 μg/ml) were more active than delaumonones A and B, but also showed a potent cytotoxicity against HL-60 cells (IC_{50} **3**: 0.0068 μg/ml).

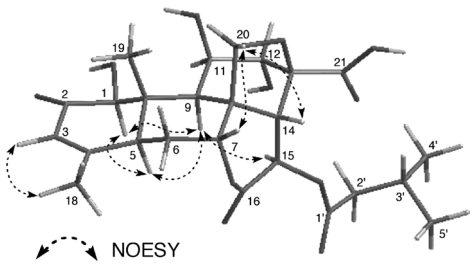
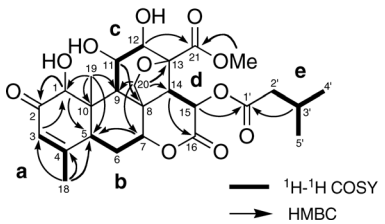


Fig. 2. Selected NOESY Correlations and Relative Configuration for Delaumonone A (**1**)



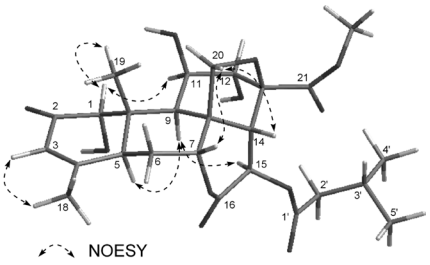


Fig. 3. Selected 2D NMR Correlations and Relative Configuration of Delaumonone B (**2**)

Delaumonones A and B had good selectivity index more than isobrucein A, suggesting that the presence of β-orientation of the hydroxyl group at C-1 and the methoxy carbonyl group at C-21 contributed to a cytotoxicity more than an antiplasmodial activity.

In this study, we have isolated two new quassinoids, delaumonones A and B (**1**, **2**) from the bark of *Laumoniera bruceadelpha*. Delaumonones showed an antimalarial activity against *P. falciparum*. Cytotoxic activity against cancer cells was influenced by the nature of the C-21 side chain and of configuration at C-1, which was not much affected by an antimalarial activity against *P. falciparum*.

Experimental

General Experimental Procedures Optical rotations were measured on a JASCO P-1030 polarimeter. UV spectra were recorded on a Shimadzu UV-250 spcetrophotometer and IR spectra on a JASCO FTIR-230 spectrometer. Mass spectra were obtained with a Micromass LCT spectrometer. ^{1}H and 2D NMR spectra were recorded on a 600 MHz spectrometer at 300 K, while ^{13}C-NMR spectra were measured on a 150 MHz spectrometer. Each NMR sample of delaumonones was prepared by dissolving in 30 μl of CD_3OD in 2.5 mm micro cells (Shigemi Co., Ltd.) and chemical shifts were reported using residual CD_3OD (δ_H 3.31 and δ_C 49.0) as internal standard. Standard pulse sequences were employed for the 2D NMR experiments. 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 and HOHAHA spectra in the phase sensitive mode were measured with a mixing time of 800 and 30 ms, respectively. 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.

Plant Material The bark of *Laumoniera bruceadelpha* was collected at Mersing, Malaysia in 2001. The botanical identification was made by Mr. Teo Leong Eng, Faculty of Science, University of Malaya. Voucher specimens (KL4099) are deposited in the Herbarium of Chemistry Department, University of Malaya.

Extraction and Isolation The bark of *L. bruceadelpha* (1.4 kg), which was collected at Malaysia, was extracted with MeOH, and a part (40 g) of the extract (126 g) was partitioned between $CHCl_3$, *n*-BuOH and H_2O. $CHCl_3$-soluble materials were subjected to a silica gel column ($CHCl_3$/MeOH, 1 : 0→0 : 1), in which a fraction eluted by $CHCl_3$/MeOH (40 : 1) was further purified on an ODS column with MeOH/H_2O (0 : 1→1 : 0) followed by ODS HPLC (55% MeOH) to afford delaumonone B (**2**, 5.6 mg) together with isobrucein A (**3**, 307.0 mg)[14] and isobrucein B (**4**, 5.8 mg).[15] A fraction eluted by $CHCl_3$/MeOH (0 : 1) was further purified on ODS HPLC with 55% MeOH containing 0.1% TFA to afford delaumonone A (**1**, 11.9 mg). *n*-BuOH-soluble materials were subjected to an HP-20 column (H_2O/MeOH, 1 : 0→0 : 1), in which a fraction eluted 80% MeOH was further purified on a silica gel column ($CHCl_3$/MeOH, 1 : 0→0 : 1) and ODS HPLC (55% MeOH containing 0.1% TFA) to afford delaumonone A (**1**, 15.0 mg) together with brucein D (**5**, 1.2 mg)[16] and yadanziolide A (**6**, 3.7 mg).[17] These compounds could also be isolated from EtOH extract of the same plant.

Delaumonone A (**1**): Colorless amorphous solid, $[\alpha]_D$ +20 (c=1.0, MeOH); IR (KBr) ν_{max} 3439, 1735, and 1665 cm^{-1}; ^{1}H- and ^{13}C-NMR (Table 1); ESI-MS (neg.) *m/z*: 507 $(M-H)^-$; HR-ESI-TOF-MS (pos.) *m/z*: 531.1827 $(M+Na)^+$, Calcd for $C_{25}H_{32}O_{11}Na$.

Delaumonone B (**2**): Colorless amorphous solid, $[\alpha]_D$ +18 (c=1.0, MeOH); IR (KBr) ν_{max} 3477, 1743, and 1668 cm^{-1}; ^{1}H- and ^{13}C-NMR (Table 1); ESI-MS (pos.) *m/z*: 545 $(M+Na)^+$; HR-ESI-TOF-MS (pos.) *m/z*: 523.2180 $(M+H)^+$, Calcd for $C_{26}H_{35}O_{11}$.

Conversion of Delaumonone A (1) to Isobrucein A (3) To a solution of delaumonone A (2.0 mg) in MeOH (0.2 ml) was added TMS-diazomethane (20 μl), and the mixture was kept at r.t. for 3 h. After evaporation, a compound (1.9 mg), whose spectroscopic data and $[\alpha]_D$ value were identical with those of natural isobrucein A (**3**), was obtained.

Antiplasmodial Activity Human malaria parasites were cultured according to the method of Trager and Jensen.[18] The antimalarial activity of the isolated compounds was determined by the procedure described by Budimulja *et al.*[19] 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 μg/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} 0.0061 μg/ml.

Cytotoxic Activity HL-60 (human blood premyelocytic leukemia) cell line was seeded onto 96-well microtiter plates at 1×10^4 cells per well. Cells were preincubated for 24 h at 37 °C in humidified atmosphere of 5% CO_2. Different concentrations of each compound (10 μl) were added to the cultures, and then the cells were incubated at 37 °C for 48 h. On the third day, 15 μl MTT solution (5 mg/ml) was added into each well of the cultured medium. After further 2 h of incubation, 100 μl of 10% SDS–0.01 N HCl solution was added to each well and the formazan crystals in each well were dissolved by stirring with a pipette. The optical density measurements were made using a micropipette reader (Benchmark Plus microplate spectrometer, BIO-RAD) equipped with a two wavelengths system (550, 700 nm). In each experiment, three replicate of wells were prepared for each sample. The ratio of the living cells was determined based on the difference of the absorbance between those of samples and controls. These differences are expressed in percentage and cytotoxic activity was indicated as an IC_{50} value.

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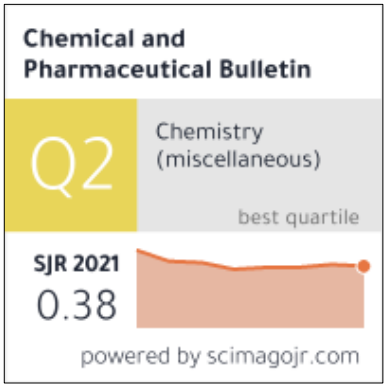

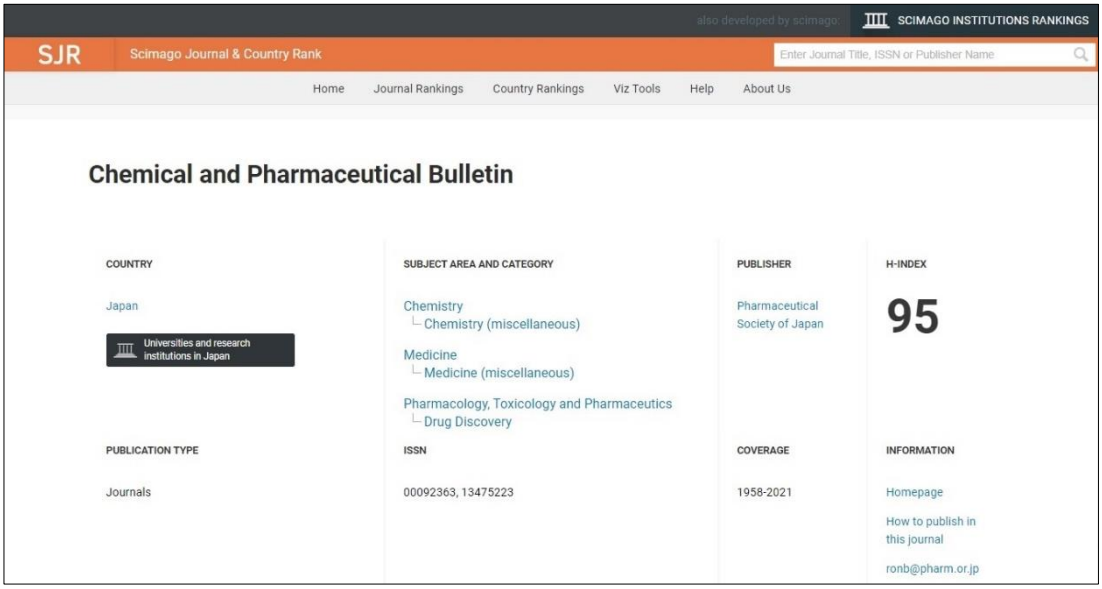

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