Journal of Medicinal Plants Studies
www.PlantsJournal.com

ISSN (E): 2320-3862
ISSN (P): 2394-0530
NAAS Rating: 3.53
www.plantsjournal.com
JMPS 2021; 9(1): 29-32

Received: 08-11-2020
Accepted: 17-12-2020

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A megastigmane glucoside from *Sambucus chinensis*

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Abstract
From the aerial part of *Sambucus chinensis*, a new megastigmane glucoside (1) was isolated, together with seven known compounds. The structure of compound 1 was elucidated by spectroscopic analysis together with the application of the modified Mosher's method to be (3*S*,5*R*,6*S*,9*R*)-megastigman-5,6-epoxy-3,9-diol 9-*O*-*β*-D-glucopyranoside. The structure of a closely related compound, sammangaoside B, has been reinvestigated, and it was assigned as (3*S*, 5*R*, 6*S*, 9S)-megastigman-5,6-epoxy-3,9-diol 9-*O*-*β*-D-glucopyranoside. Therefore, compound 1 is a new compound from nature.

Keywords: *Sambucus chinensis*, Adoxaceae, megastigmane, absolute structure

Introduction
Sambucus chinensis (Adoxaceae) is a perennial herb of 1 m to 2 m in height that grows in Japan, Taiwan, and China [1]. It is a component of a Chinese traditional formula that is expected to cure wounds and throbbing pain. However, its phytochemical investigation is quite limited. The aerial part of *S. chinensis* was collected on Okinawa Island, and the constituents in the 1-BuOH-soluble fraction were investigated. A new compound, megastigman-5,6-epoxy-3,9-diol 9-*O*-*β*-D-glucopyranoside (1), was isolated, along with seven known compounds (Fig. 1), and this paper deals with the structure elucidation of 1, including its absolute stereochemistry. Known compounds were spectroscopically identified as (6*R*,7*E*,9*R*)-megastigma-4,7-dien-9-ol *O*-*β*-D-glucopyranoside (2) [2], (6*R*,7*E*,9*R*)-megastigman-3-on-9-ol *O*-*α*-L-arabinopyranosyl (1"→6')-*β*-D-glucopyranoside (3) [3], citroside B (4) [4], actindioionoside (5) [5], prunasin (6) [6], lucumin (7) [7], and demethylalangiside (8) [8].

Results and Discussion
From the 1-BuOH-soluble fraction of the MeOH extract of the aerial part of *Sambucus chinensis*, a new megastigmane glucoside (1), together with seven known compounds (2–8), was isolated using various kinds of chromatographic techniques. This paper deals with the structural elucidation of compound 1.

Compound 1, $[\alpha]_D^{25}$ –37.6, was isolated as an amorphous powder, and its elemental composition was determined to $C_{19}H_{34}O_8$ by HR-ESI MS. A broad band at 3395 cm^{-1} shown in the IR spectrum indicated that 1 is a glycosidic compound. A set of six typical signals attributable to those of glucopyranose was observed in the ^{13}C-NMR spectrum, and the remaining 13 signals comprised four methyls, four methylenes, two methines bearing an oxygen atom, two oxygenated tertiary carbons and one quaternary carbon. The numbers of carbon atoms and these functionalities were suggestive that 1 was a megastigmane derivative. The three degrees of unsaturation demanded one more cyclic system besides a six-membered ring and a sugar moiety. The third cyclic system was assumed to be an epoxide ring from two oxygenated tertiary carbons that are frequently found in the megastigmane skeleton, and the ^{1}H-^{1}H COSY and HMBC correlations shown in Fig. 2 supported the assumption. Enzymatic hydrolysis of 1 gave a rearranged aglycone (1a) and D-glucose. The aglycone must have two ring systems from the results of HR-MS ($C_{13}H_{24}O_3$), and the ^{13}C-NMR chemical shifts of C-5 (δ_C 67.7) and C-6 (δ_C 71.3) were drastically shifted downfield at δ_C 78.9 and 90.9 (Table 1). A closely related megastigmane glucoside was isolated from *Scorodocarpus bornenensis* as scorospiroside [9].

^{13}C-NMR chemical shifts of scorospiroside at C-5 and C-6 were reported as δ_C 77.4 and 90.2, which are close to those of 1a, although NMR was run in a different solvent (pyridine-d_5). Two-dimensional NMR diagnosis in Fig. 3 (^{1}H-^{1}H COSY and HMBC) confirmed the structure, and the modified Mosher's method (Fig. 4) revealed 1a had the 3*S* configuration [10]. By the phase-sensitive NOESY correlation between H-9 and H_3-13, the configuration at the 9-position was determined to be *R* (Fig. 5). Therefore, the structure of 1 was elucidated to be as shown in Fig. 1. The same structure was proposed as sammangaoside B (9), isolated from *Clerodendrum inerme* [11]. The structure of sammangaoside B was determined by comparison of NMR with reported data [13, 14]. The same compound (9) was also isolated from *Tricalysia dubia* [12], and the configuration at the 9-postion was revised to be *S*, as shown 10 in Fig. 1. NMR data of 1 and 9 showed some discrepancy, especially at C-6 through C-10 and C-1' (Table 1). Compound 1 must have a different structure from sammangaoside B, as shown in Fig. 1.

Botanical safety handbook says that American and European elders, *S. canadensis* and *S. nigra*, respectively, contain cyanogenic glycosides, ingestion of which may cause vomiting or severe diarrhea [15]. Since more than 2 g of a cyanogenic glucoside, purnasin, was isolated from 5.45 kg of the title plant, the actual content of cyanogenic glycosides must be much higher than the amount isolated, and usage of this plant is recommended with care.

The monoterpene indole alkaloid glucoside δδalangiside is a characteristic compound of alangiaceous plants [16, 17]. Isolation of demethylalangiside (8) implies that Adoxaceae and Alangiaceae have some genetic relationship.

Table 1: NMR Spectroscopic Data for Compounds 1 and 1a, and Sammangaoside B (10) (C: 100 Hz; H: 400 MHz, CD_3OD).

	1		1a		10[a]
	C	H	C	H	
1	36.7	-	40.2	-	36.6
2	49.3	1.17 o	47.0	1.39 ddd 12, 4, 2	49.3
		1.47 ddd 13, 3, 2		1.55 dd 12, 12	
3	64.5	3.63 m	65.3	3.98 ddd12, 5, 3	64.4
4	42.6	1.60 dd 14, 9	46.9	1.71 dd 12, 11	42.6
		2.22 ddd 14, 5, 2		1.80 ddd 12, 5, 2	
5	67.7	-	78.9	-	67.4
6	71.3	-	90.9	-	70.8
7	27.8	1.75 m	28.1	1.91 dt 12, 2	27.9
		1.85 m		2.11 m	
8	35.2	1.72 2H m	36.4	1.47 dt 10, 2	34.4
				2.02 m	
9	76.5	3.83 m	78.0	4.10 dq 10, 6	77.8
10	20.0	1.20 3H d 6	21.2	1.19 3H d 6	21.8
11	29.6	1.17 3H s	26.3	1.19 3H s	29.5
12	25.9	1.04 3H s	29.1	0.98 3H s	25.9
13	21.3	1.37 3H s	27.9	1.17 3H s	21.3
1'	102.7	4.30 d 8			103.8
2'	75.3	3.12 dd 9, 8			75.3
3'	78.3	3.24 m			78.2
4'	72.0	3.24 m			71.7
5'	77.9	3.24 m			77.8
6'	63.0	3.64 dd 12, 6			62.8
		3.84 dd 12,.2			

o: overlapped signal.

[a]Data were taken from Ref. 11 and 12.

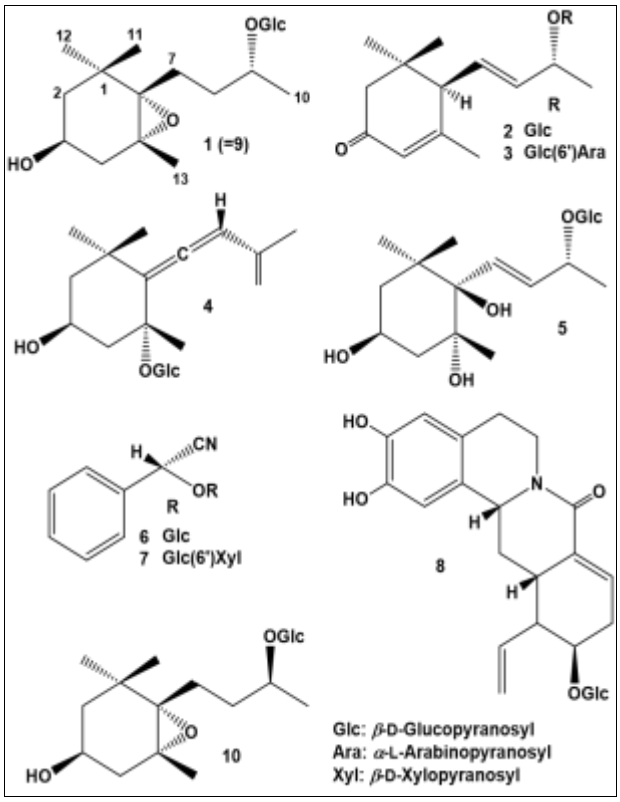

Fig 1: The structures of compounds isolated and sammangaoside b.

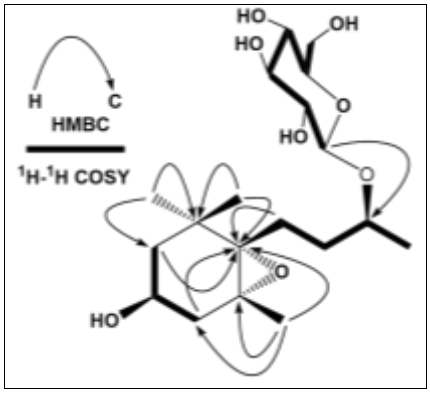

Fig 2: Diagnostic ^{1}H-^{1}H COSY and HMBC correlations of 1

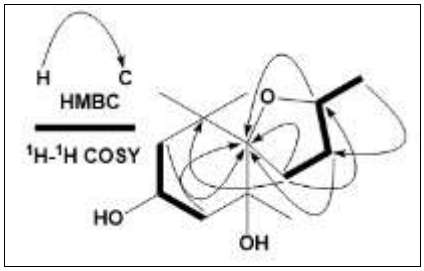

Fig 3: ^{1}H-^{1}H COSY and HMBC correlations of 1a

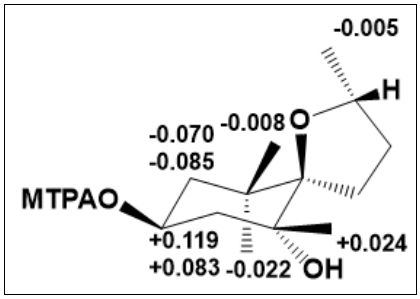

Fig 4: The results of the modified Mosher's method of la ($\Delta\delta s$- δ_R)

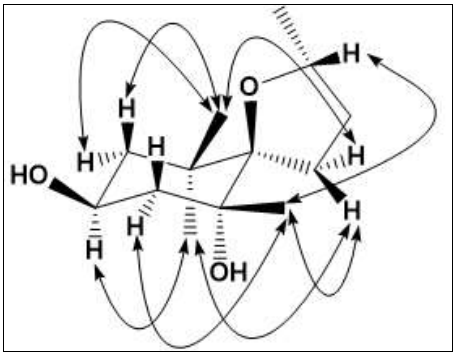

Fig 5: Phase-sensitive NOESY correlations of la

Experimental

General experimental procedure

Optical rotations were measured on a JASCO P-1030 digital polarimeter. IR spectrum was measured on Horiba FT-710. ^{1}H- and ^{13}C-NMR spectra were taken on a JEOL JNM α-400 spectrometer at 400 MHz and 100 MHz with tetramethylsilane as an internal standard. Positive-ion HR-ESI-MS was performed with an Applied Biosystems QSTAR XL NanoSpray TM System.

A highly-porous synthetic resin (Diaion HP-20) was purchased from Mitsubishi Chemical Corporation (Tokyo, Japan). Silica gel column chromatography (CC) was performed on silica gel 60 (E. Merck, Darmstadt, Germany), and ODS open CC on Cosmosil 75C_{18}-OPN (Nacalai Tesque, Kyoto) [Φ = 50 mm, L = 20 cm, linear gradient: MeOH-H_2O (1:9, 1 L) → (1:1, 500 mL) → (7:1, 500 mL), fractions of 10 g being collected]. The DCCC (Tokyo Rikakikai, Tokyo, Japan) was equipped with 500 glass columns (Φ = 2 mm, L = 40 cm), the lower and upper layers of a solvent mixture of $CHCl_3$-MeOH-H_2O-1-PrOH (9:12:8:2) being used as the stationary and mobile phases, respectively. Five-gram fractions were collected and numbered according to their order of elution with the mobile phase. HPLC was performed on an ODS column (Inertsil; GL Science, Tokyo, Japan; Φ = 6 mm, L = 25 cm, 1.6 mL/min), and the eluate was monitored with UV (254 nm) and refractive index monitors. *β-Glucosidase* from almond was purchased from Wako Pure Chemical Industries, Ltd (Osaka, Japan) and crude hesperidinase was a generous gift from Tanabe Pharmaceutical Co., Ltd. (Osaka, Japan).

Plant material

Aerial parts of *S. chinensis* were collected in Motobu-cho, Kunigami-gun Okinawa and a voucher specimen was deposited in the Herbarium of Faculty of Pharmaceutical Sciences, Graduate School of Biomedical and Health Sciences, Hiroshima University (03-SC-Okinawa-0701).

Extraction and isolation

Aerial parts of *S. chinensis* (5.45 kg) were extracted three times with MeOH (30 L × 3) at room temperature for one week and then concentrated to 3 L *in vacuo*. The concentrated extract was washed with *n*-hexane (3 L, 77.1 g), and then, the MeOH layer was concentrated to a gummy mass. The latter was suspended in H_2O (3 L) and extracted with EtOAc (3 L) to give 172 g of an EtOAc-soluble fraction. The aqueous layer was extracted with 1-BuOH (3 L) to give a 1-BuOH-soluble fraction (114 g), and the remaining H_2O-layer was concentrated to furnish 582 g of a H_2O -soluble fraction. The 1-BuOH-soluble fraction (119 g) was subjected to a Diaion HP-20 CC (Φ =60 mm, L = 55 cm), using H_2O-MeOH (4:1, 2 L), (3:2, 4 L), (2:3, 4 L), and (1:4, 4 L), and MeOH (4 L), with 1 L fractions being collected. The residue (26.0 g) in fractions 4–7 of the 20–40 % MeOH eluent was subjected to silica gel (Φ =60 mm, L = 46 cm) CC and elution with $CHCl_3$ (2 L), $CHCl_3$-MeOH [(99:1, 4 L), (97:3, 4 L), (19:1, 4 L), (37:3, 4 L), (9:1, 4 L), (7:1, 4 L), (4:1, 4 L), and (7:3, 3 L)], and MeOH (2 L), with 500 mL fractions being collected. The residue (2.04 g out of 4.07) in fractions 39–45 of the 10–12.5 % MeOH eluate was separated by ODS open CC. From fractions 68–95, 1.17 g of 6 was obtained. The residue (63.5 mg) in fractions 96–112 was purified by HPLC (MeOH-H_2O, 3:7) to give 3.5 mg of 1 from the peak at 20 min. The residue (2.51 g) in fractions 46–51, obtained on silica gel CC, was subjected ODS open CC and the residue (370 mg) in fractions 95–113 was purified by DCCC to give a residue (16.9 mg) in fractions 51–57, which was finally purified by HPLC (MeOH-H_2O, 3:7) to afford further amount of 1 (2.8 mg) from the peak at 20 min. The residue (2.49 g out of 4.12 g) in fractions 52–63, obtained on silica gel CC, was applied to ODS open CC to give a residue (107 mg) in fractions 148–159, which was then purified by DCCC to yield 52.0 mg of 8 and 24.7 mg of 3 in fractions 33–42 and 43–51, respectively. The residue (2.00 g) in fractions 64–76, obtained on silica gel CC was subjected ODS open CC. The residue (256 mg) in fractions 59–68 was applied to DCCC to give a residue (45.9 mg) in fractions 13–16 which was purified by HPLC (MeOH-H_2O, 3:7) to give 18.9 mg of 5 from the peak at 10 min. The residue (222 mg) fractions 69–78 was subjected to DCCC to give a residue (48.2 mg) in fractions 21–26 which was finally purified by HPLC (MeOH-H_2O, 3:7) to give 3.2 mg of 7 from the peak at 23 min.

The residue (21.0 g) in fractions 8–12 of the 40-60 % MeOH eluent, obtained on Diaion HP-20 CC was separated by silica gel CC (Φ =60 mm, L = 46 cm) CC and elution with $CHCl_3$ (2 L), $CHCl_3$-MeOH [(99:1, 4 L), (97:3, 4 L), (19:1, 4 L), (37:3, 4 L), (9:1, 4 L), (7:1, 4 L), (4:1, 4 L), and (7:3, 3 L)], and MeOH (2 L), with 500 mL fractions being collected. The residue (2.60 g) in fractions 38–45 was applied to ODS open CC and the residue (227 mg) thus obtained in fractions 141–151 was purified by DCCC to give 5.5 mg of 2 in fractions 94–96. The residue (2.62 g) in fractions 46–52 was similarly subjected to ODS open CC and the residue (311 mg) in fractions 127–139 was purified by DCCC to give 139 mg of 4 in fractions 30–40.

Compound 1 Amorphous powder, $[\alpha]_D^{25}$ –37.6 (*c* 0.17, MeOH); IR ν_{max} (film) cm^{-1}: 3395, 2929, 1455, 1385, 1078, 1036, 896; ^{1}H-NMR (400 MHz, CD_3OD): Table 1; ^{13}C-NMR (100 MHz, CD_3OD: Table 1; NMR: HR-ESI-MS (positive-ion mode) *m/z*: 413.2150 $[M+Na]^+$ (Calcd for $C_{19}H_{34}O_8Na$: 413.2145).

Enzymatic hydrolysis of 1

Compound 1 (5.3 mg) was hydrolyzed with 7.2 mg of *β-Glucosidase* in 2 mL of H_2O at 37 °C for 2 h and then 5 mg of crude hesperidinase was added. After 18 h, the reaction mixture was evaporated and subjected column CC (silica gel, 20 g) with CHI_3 (100 mL), $CHCl_3$-MeOH (19:1, 100 mL), $CHCl_3$-MeOH (9:1, 100 mL), $CHCl_3$-MeOH (17:3, 100 mL) and $CHCl_3$-MeOH (7:3, 100 mL), 12-mL fractions being corrected. Aglycone 1a (1.8 mg) and D-glucose (4.3 mg) were recovered in fractions 17-22 and 33-42, respectively.

Aglycone 1a: Amorphous powder, $[\alpha]_D^{28}$ –15.6 (*c* 0.12, MeOH); ^{1}H-NMR (400 MHz, CD_3OD): δ 0.89 (3H, s, H_3-12), 1.17 (3H, s, H_3-13), 1.187 (3H, d, J = 6 Hz, H_3-10), 1.191 (3H, s, H_3-11), 1.39 (1H, ddd, J = 2, 4, 12 Hz, H-2eq), 1.47 (1H, ddd, J = 2, 10, 10 Hz, H-8a), 1.55 (1H, dd, J = 12, 12 Hz, H-2ax), 1.71 (1H, dd, J = 11, 12 Hz, H-4ax), 1.80 (1H, ddd, J = 2, 5, 12 Hz, H-4eq), 1.91 (1H, ddd, J = 2, 12, 12 Hz, H-7a), 2.02 (1H, m, H-8b), 2.11 (1H, m, H-7b), 3.98 (1H,

ddd, *J* = 3, 5, 12 Hz, H-3), 4.10 (1H, qd, *J* = 6, 10 Hz, H-9); ^{13}C-NMR (100 MHz, CD_3OD): δ 21.2 (C-10), 26.3 C-11), 27.9 (C-13), 28.1 (C-7), 29.1 (C-12), 36.4 (C-8), 40.2 (C-1), 46.9 (C-4), 47.0 (C-2), 65.3 (C-3), 78.0 (C-9), 78.9 (C-5), 90.9 (C-6); HR-ESI-MS (positive-ion mode) *m*/*z*: 251.1627 $[M+Na]^+$ (Calcd for $C_{13}H_{24}O_3Na$: 251.1617).

D-glucose: $[\alpha]_D^{25}$ +35.7 (*c* 0.29, H_2O, after being dissolved in the solvent).

Preparation of (*R*)-and (*S*)-MTPA esters (1b and 1c) from 1a

A solution of 1a (0.8 mg) in 1 mL of dry CH_2Cl_2 were reacted with (*R*)-α-methoxy-α-trifluoromethylphenylacetic acid (MTPA) (27 mg) in the presence of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC) (18 mg) and *N*,*N*-dimethyl-4-aminopyridine (4-DMAP) (12 mg). The mixture was then occasionally stirred at room temperature for 45 min. After the addition of $CHCl_3$ (1.5 mL), the reaction mixture was successively washed with H_2O (1 mL), 4 M HCl (1 mL), $NaHCO_3$-saturated H_2O (1 mL), and brine (1 mL). The organic layer was dried with Na_2SO_4 and evaporated under reduced pressure. The residue was purified by preparative TLC [silica gel (0.25 mm thickness), being applied for 8 cm width, with development with $CHCl_3$-MeOH (9: 1) for 9 cm and then eluting with $CHCl_3$-MeOH (1: 1)] to furnish an ester 1b (0.5 mg) from the band at R_f = 0.67. Through the same procedure, 1c (0.1 mg, R_f = 0.59) were prepared from 1a (1.0 mg) using (*S*)-MTPA (42 mg), EDC (18 mg), and 4-DMAP (12 mg), respectively.

(*R*)-MTPA ester of 1a (1b): Amorphous powder, ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.92 (3H, s, H_3-12), 1.19 (3H, d, J = 6 Hz, H_3-10), 1.21 (3H, s, H_3-13), 1.27 (3H, s, H_3-11), 1.60 (1H, ddd, J = 2, 4, 12 Hz, H-2eq), 1.81 (1H, dd, J = 12, 12 Hz, H-2ax), 1.85 (1H, ddd, J = 2, 5, 12 Hz, H-4eq), 1.93 (1H, dd, J = 12, 12 Hz, H-4ax), 3.56 (3H, q, J = 1 Hz, -OCH_3), 4.09 (1H, m, H-9), 5.44 (1H, m, H-3), 7.39-7.41 (3H, m, aromatic protons), 7.51-7.55 (2H, m, aromatic protons); HR-ESI-MS (positive-ion mode) *m*/*z*: 467.2011 $[M+Na]^+$ (Calcd for $C_{23}H_{31}O_5F_3Na$: 467.2015).

(*S*)-MTPA ester of 1a (1c): Amorphous powder. ^{1}H-NMR (400 MHz, $CDCl_3$): *δ* 0.90 (3H, s, H_3-13), 1.20 (3H, d, *J* = 6 Hz, H_3-10), 1.23 (3H, s, H_3-13), 1.26 (3H, s, H_3-11), 1.53 (1H, ddd, *J* = 2, 4, 12 Hz, H-2eq), 1.73 (1H, dd, *J* = 12, 12 Hz, H-2ax), 1.93 (1H, ddd, *J* = 2, 5, 12 Hz, H-4eq), 2.05 (1H, dd, *J* = 12, 12 Hz, H-4ax), 3.55 (3H, q, *J* = 1 Hz, -OCH_3), 4.09 (1H, m, H-9), 5.43 (1H, m, H-3), 7.39-7.41 (3H, m, aromatic protons), 7.52-7.55 (2H, m, aromatic protons); HR-ESI-MS (positive-ion mode) *m*/*z*: 467.2023 $[M+Na]^+$(Calcd for $C_{23}H_{31}O_5F_3Na$: 467.2015).

Acknowledgements

The authors are grateful for access to the superconducting NMR instrument (JEOL JNM α-400) at the Analytical Center of Molecular Medicine of the Hiroshima University Faculty of Medicine, and an Applied Biosystem QSTAR XL system ESI (Nano Spray)-MS at the Analysis Center of Life Science of the Graduate School of Biomedical Sciences, Hiroshima University. This work was supported in part by Grants-in-Aid from the Ministry of Education, Science, Sports, Culture and Technology of Japan, the Japan Society for the Promotion of Science (Nos. 22590006, 23590130 and 25860078). Thanks are also due to the Research Foundation for Pharmaceutical Sciences and the Takeda Science Foundation for the financial support.

Conflict of interest

We declare that we have no conflict of interest.

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