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ONE-POT SYNTHESIS OF CARBAZOLES BY A DOMINO REACTION USING MICROWAVE HEATING AND ANTIPROLIFERATIVE ACTIVITIES OF CONSTITUENTS FROM *MURRAYA* PLANTS AGAINST CANCER STEM CELLS

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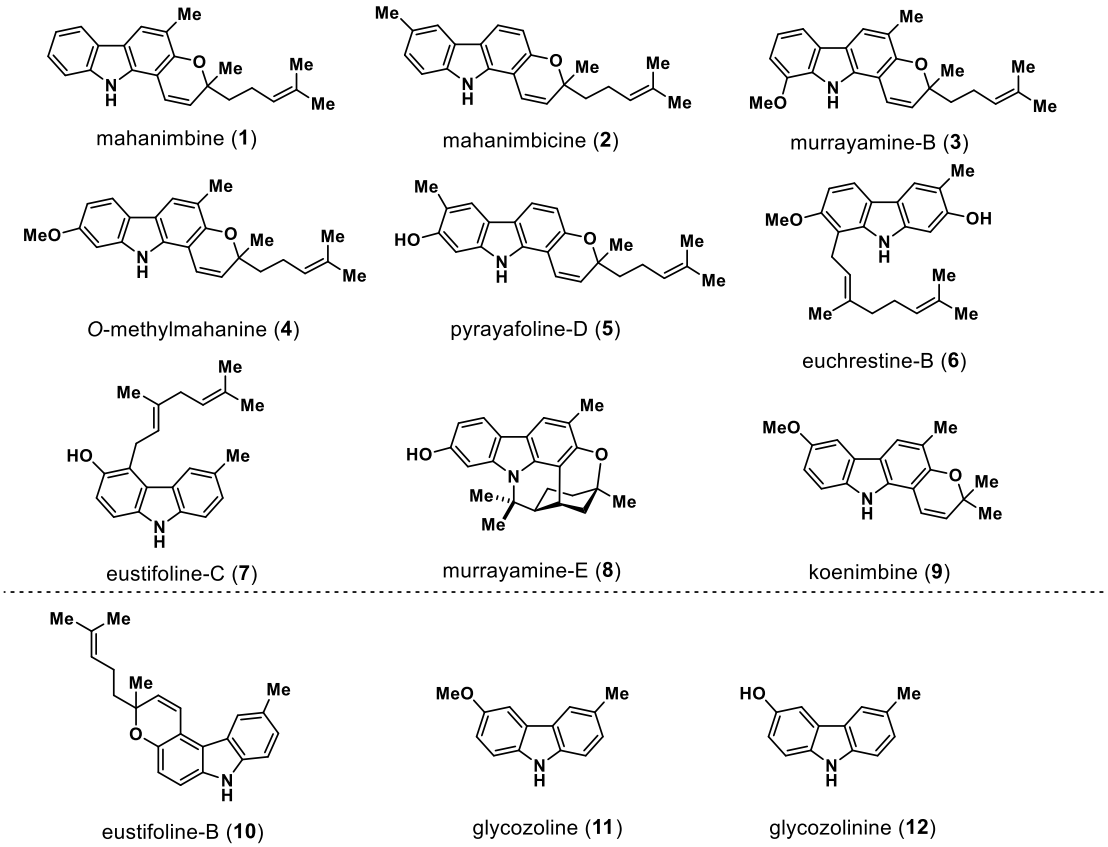
Abstract – Carbazoles could be easily and rapidly synthesized in a one-pot synthesis using 4-methyl-1-cyclohexanone and *p*-anisidine in a continuous microwave-heated reaction (1 h, 140 °C). Eustifoline-B, a trace constituent of the roots of *Murraya euchrestifolia*, was synthesized using the carbazole derivative glycozoline obtained by this method. Next, nine carbazoles isolated from the leaves of *M. koenigii* and three synthetic carbazoles were evaluated for their antiproliferative activities against human astrocytoma U-251 MG cells [that is, non-cancer stem cells (non-CSCs)] and cancer stem cells (CSCs) isolated by sphere formation. Carbazoles with geranyl or prenyl moieties showed antiproliferative activity against U-251 MG CSCs. In particular, the synthetic compound eustifoline-B showed significant antiproliferative activity against U-251 MG CSCs (IC_{50} = 2.9 μM). Interestingly, eustifoline-B showed an approximately 10-fold higher antiproliferative activity against U-251 MG CSCs than against U-251 MG non-CSCs (IC_{50} = 29.4 μM).

Murraya koenigii SPRENG (Family: Rutaceae) is a medicinal plant used in traditional medicine in South and Southeast Asia. The leaves of this plant are commonly known as "curry leaf" and are used as a spice and vegetable for flavoring soups and meat dishes. Various carbazoles have been isolated from *Murraya* plants. Previously, we reported the isolation and structural elucidation of two carbazole alkaloids, karapinchamines A and B, from the leaves of *M. koenigii* together with 12 known carbazole alkaloids.[1] Carbazole alkaloids derived from medicinal plants have recently attracted attention as anticancer drug seeds. For example, the principal constituent, mahanimbine (**1**), with a pyranocarbazole moiety from the

leaves of *M. koenigii* has been reported to show antiproliferative activities against various cancer cell lines. Compound **1** was suggested to exhibit antiproliferative activity by triggering cell cycle arrest, apoptosis, and modulating the AKT/mammalian target of rapamycin (mTOR) and signal transducer and activator of transcription 3 (STAT3) signaling pathways.[2]

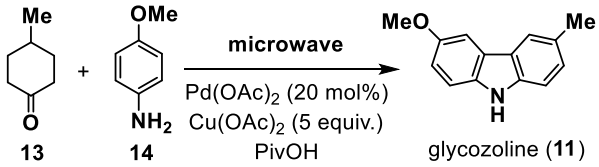


Scheme 1. Structures of compounds **1–12**

The presence of CSCs has recently been suggested to be a major cause of drug resistance in cancer cells. CSCs are present in small numbers in various types of cancer. CSCs have self-renewal and tumorigenic potential, resist current anticancer drugs and radiation, and play an important role in metastasis.[3] However, there are currently no anticancer drugs targeting CSCs in clinical use. Therefore, there is a pressing need to develop therapeutic agents that target CSCs. We have been searching for anticancer medicinal seeds, including compounds with antiproliferative activities against CSCs from traditional medicines and medicinal foodstuffs.[1,4] In the present study, a MeOH extract and its ethyl acetate (EtOAc)-soluble fraction from the leaves of *M. koenigii* showed antiproliferative activities against human astrocytoma U-251 MG cells [i.e., non-cancer stem cells (non-CSCs)] and their CSCs isolated by sphere formation. Therefore, we evaluated the antiproliferative activity of carbazole alkaloids isolated from *Murraya* plants.

Nine carbazole alkaloids, mahanimbine (**1**), mahanimbicine (**2**), murrayamine-B (**3**), *O*-methylmahanine (**4**), euchrestine B (**5**), eustifoline-C (**6**), murrayamine-E (**7**), koenimbine (**8**), and pyrayafoline-D (**9**), were obtained from the leaves of *M. koenigii* (Scheme 1).[1] Secondly, the domino reaction using microwave heating was investigated for the construction of the carbazole ring, and glycozoline (**11**) obtained by this method was used to synthesize eustifoline-B (**10**), a trace constituent in the roots of *M. euchrestifolia*, *via* **12**. The anticancer activities against U-251 MG CSCs and U-251 MG non-CSCs of the obtained compounds **1**-**12** were evaluated.

Eustifoline-B (**10**) with substituted pyran rings was isolated from the root bark of *M. euchrestifolia*.[5] However, the content of **10** in the plant was low (2 mg from the roots 900 g). Therefore, we planned to synthesize **10** for structure-activity relationship studies. Compound **10** was synthesized *via* the construction of carbazoles by Knölker et al.[6] Particularly, a carbazole framework was synthesized by Buchwald-Hartwig coupling of *p*-bromoanisole and *p*-toluidine in the presence of palladium(0) catalyst to form diarylamines, followed by oxidative cyclization under microwave irradiation in the presence of palladium(II) catalyst and copper(II) acetate.[6] In contrast, several carbazoles were synthesized by Diels–Alder cycloaddition with quinoneimine and diene followed by Plieninger indolization and oxidation by Kerr et al.[7] Furthermore, several carbazoles were synthesized from cyclohexanone and anilines under heating for 24 h by the palladium-catalyzed domino reaction via dehydrogenative aromatization and oxidative cyclization by Wang et al.[8] Regarding the above reports, we hypothesized that carbazole, glycozoline (**11**), could be synthesized from 4-methyl-1-cyclohexanone (**13**) and *p*-anisidine (**14**) in a one-pot synthesis by microwave heating without separating the intermediates (Scheme **2**).



Scheme 2. Synthesis of **11** from **13** and **14** under microwave heating

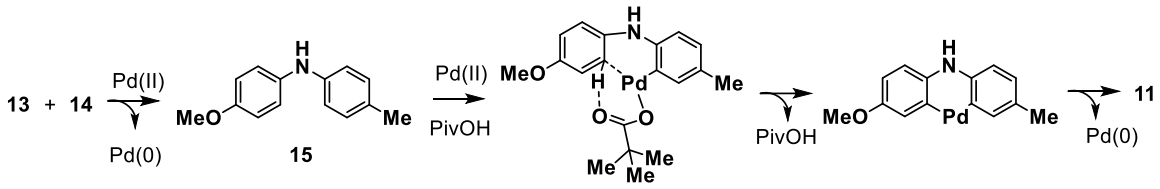
First, synthesis of **11** from **13** and **14** was performed for 6 h at 140 °C under microwave heating. As a result, compound **11** was obtained at a yield of 56% (Table 1, entry 1). Next, the reaction time was investigated, and the highest yield (77%) of **11** was obtained when the reaction time was 1 h (Table 1, entry 3). When the reaction time was longer than 1 h, thin-layer chromatography (TLC) analysis confirmed the formation of multiple unidentified compounds and reduced the yield of **11** (Table 1, entry 1, 2). When the reaction time was 0.5 h, the parts of **13** and **14** was recovered and the reaction did not proceed completely (Table 1, entry 4). In addition, when the reaction temperature was decreased below 140 °C, the yield of **11** decreased (Table 1, entry 5-8). When the reaction temperature was 80 °C, little reaction progressed (Table 1, entry 8). In the case of reactions of **13** and **14** with external heating instead of microwave heating, the yield of **11** was low (Table 1, entry 9-12). In particular, compound **11** could

not be obtained at a reaction temperature of 140 °C for 1 h and compounds **13** and **14** were recovered (Table 1, entry 12). These results suggest that microwave heating is helpful for the one-pot synthesis of carbazoles from cyclohexanone and aniline. Since diphenylamine **15** was obtained as a byproduct of this reaction, it was presumed that **15** was formed after the reaction of **13** and **14**. Similarly, **11** was obtained by oxidative cyclization reaction, as previously reported (Scheme 3).[8]

Table 1. Reaction conditions for glycozoline (**11**) synthesis from **13** and **14**

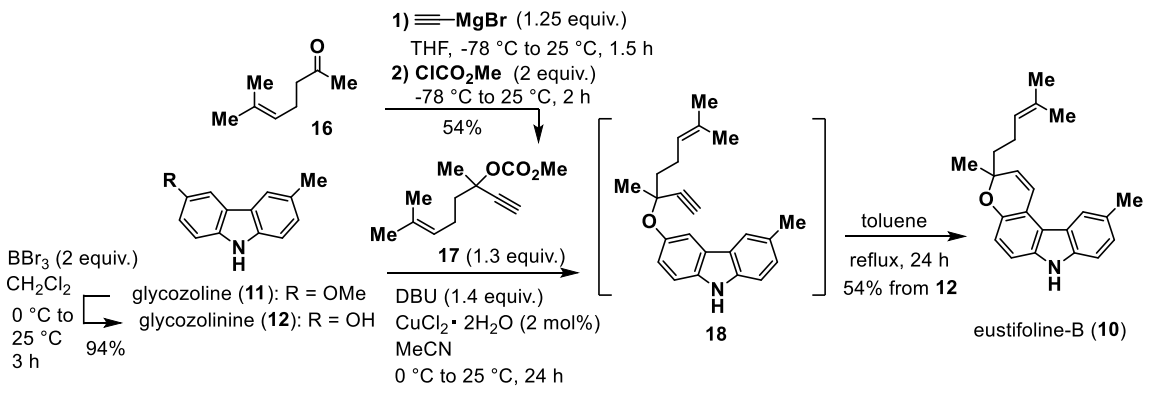
Entry	Temp. (°C)	Reaction time (h)	Yield (%)	Condition	Entry	Temp. (°C)	Reaction time (h)	Yield (%)	Condition
1	140	6	56	under microwave heating	9	140	24	45	under external heating
2	140	2	65		10	140	6	58	
3	140	1	77		11	140	2	23	
4	140	0.5	25		12	140	1	ND	
5	120	6	24						
6	120	2	14						
7	120	1	4.1						
8	80	6	1.9						

ND: not detected



Scheme 3. Presumed reaction mechanism of glycozoline (**11**)

The synthesis of eustifoline-B (**10**) from glycozoline (**11**) was performed under reaction conditions slightly modified from the method reported by Knölker et al.[6] Reaction of glycozolinine (**12**), obtained by demethylation of **11**, with carbonate **17**,[6] which was obtained from **16**, followed by rearrangement of the intermediate, aryl propargyl ether, gave **10** (Scheme **4**). Compound **10** was obtained from **11** at a total yield of 51%.



Scheme 4. Synthesis of eustifoline-B (**10**) from glycozoline (**11**)

Next, nine carbazoles **1–9** were isolated from the leaves of *M. koenigii* and three synthetic compounds **10–12** were evaluated for their antiproliferative activities against U-251 MG non-CSCs and their CSCs (Tables 2 and 3). CSCs were generated by the sphere formation assay, as described previously.[4a] Cell viability was determined using the CellTiter-Glo® 3D cell viability assay based on the quantification of cellular ATP levels. Adriamycin (ADR) was used as a positive control.

Table 2. Antiproliferative activities of isolated compounds **1–12** against U-251 MG CSCs

		Inhibition (%)					IC_{50}
Conc. (μM)	Control	1.875	3.75	7.5	15	30	(μM)
Mahanimbine (**1**)	0.0±6.8	-30.3±19.5	-22.5±11.2	85.3±5.5**	98.2±0.4**	73.4±45.3**	6.0
Murrayamine-B (**3**)	0.0±7.6	4.8±1.2	23.8±10.8**	89.4±1.7**	96.0±0.9**	98.0±0.9**	4.8
Euchrestine-B (**6**)	0.0±3.0	3.4±6.8	-21.5±4.6	62.0±3.5**	98.8±0.3**	99.5±0.4**	7.4
Eustifoline-C (**7**)	0.0±21.9	-42.9±33.1	-21.6±14.7	93.5±1.1**	99.4±0.3**	99.9±0.1**	6.1
Murrayamine-E (**8**)	0.0±11.7	4.8±12.0	8.5±8.3	58.5±6.8**	99.0±0.1**	99.4±0.3**	7.0
		Inhibition (%)					IC_{50}
Conc. (μM)	Control	3.125	6.25	12.5	25	50	(μM)
Mahanimbicine (**2**)	0.0±3.1	3.4±4.0	27.5±6.1**	75.7±4.6**	87.3±4.2**	93.8±0.6**	8.5
O-methylmahanine (**4**)	0.0±6.3	3.4±7.2	7.0±1.8	32.6±1.2**	44.3±4.3**	52.3±5.7**	23.9
Koenimbine (**9**)	0.0±2.2	24.7±2.2**	58.3±5.7**	86.4±0.7**	82.2±2.2**	87.5±1.7**	5.1
Eustifoline-B (**10**)	0.0±39.1	32.3±5.4	85.2±1.4**	99.2±0.2**	99.5±0.5**	100.0±0.1**	2.9
Glycozolinine (**12**)	0.0±0.9	-7.4±4.4	-7.0±3.3	4.7±1.5	11.8±4.4	47.5±14.2**	> 50

Each value represents the mean ± S.E.M *(N* = 3). The statistical significance of differences was analyzed using Dunnett's test ($^{*}P < 0.05$, $^{**}P < 0.01$, compared with the control group). Cells were incubated with test samples for 6 d.

Pyrayafoline-D (**5**) and glycozoline (**11**) showed no antiproliferative activity at 30 μM.

The IC_{50} value of adriamycin (positive control) was 0.051 μM.[4a]

Table 3. Antiproliferative activities of compounds **1–12** against U-251 MG non-CSCs

		Inhibition (%)					IC_{50}
Conc. (μM)	Control	1.875	3.75	7.5	15	30	(μM)
Mahanimbine (**1**)	0.0±1.1	-4.0±5.8	-0.3±5.5	9.7±2.9*	20.7±2.4**	57.8±4.7**	27.3
Mahanimbicine (**2**)	0.0±3.3	-2.1±7.0	-1.5±5.6	7.6±3.3	20.7±6.3**	54.6±1.7**	27.5
Murrayamine-B (**3**)	0.0±1.5	-3.2±4.0	4.9±3.2	2.6±1.0	6.2±4.0	25.9±2.7**	> 30
Euchrestine-B (**6**)	0.0±3.1	-6.3±5.2	-4.8±4.2	1.5±5.4	55.1±6.4**	99.6±0.1**	14.4
Eustifoline-C (**7**)	0.0±2.2	-6.5±6.6	-6.4±5.2	-2.1±5.3	44.0±16.6**	99.8±0.1**	16.4
Murrayamine-E (**8**)	0.0±4.2	-2.5±5.5	-1.8±6	14.1±5.1	26.9±2.4	99.3±0.2**	20.1
		Inhibition (%)					IC_{50}
Conc. (μM)	Control	3.125	6.25	12.5	25	50	(μM)
O-methylmahanine (**4**)	0.0±8.0	20±5.6*	20.9±2.8**	23.0±0.3**	21.9±2.6**	24.6±3.2**	> 50
Koenimbine (**9**)	0.0±1.9	20.1±1.6*	27.4±1.0**	34.6±6.8**	58.6±2.4**	70.7±5.8**	19.4
Eustifoline-B (**10**)	0.0±2.1	-8.8±4.8	-2.4±5.6	-8.5±8.9	13.1±12.6	99.9±0.0**	29.4
Glycozoline (**11**)	0.0±1.8	3.4±4.1	7.4±10.2	11.6±8.9	16.7±5.7	33.8±7.0**	> 50
Glycozolinine (**12**)	0.0±5.7	4.7±3.5	6.2±2.6	12.7±2.9	14.5±3.3	41.6±6.8**	> 50

Each value represents the mean ± S.E.M *(N* = 3). The statistical significance of differences was analyzed using Dunnett's test ($^{*}P < 0.05$, $^{**}P < 0.01$, compared with the control group). Cells were incubated with test samples for 72 h.

Pyrayafoline-D (**5**) did not show antiproliferative activities at 30 μM.

The IC_{50} value of adriamycin (positive control) was 0.041 μM.[4a]

All carbazoles with geranyl or prenyl moieties, except for pyrayafoline-D (**5**), showed significant antiproliferative activity against U-251 MG CSCs (IC_{50} = 4.8–23.9 μM). In particular, eustifoline B (**10**, IC_{50} = 2.9 μM) showed strong antiproliferative activity. A geranyl or prenyl group is essential for activity, as compounds **11** and **12** showed no activity. Interestingly, the activity of compounds **1–4**, **6–10** against U-251 MG CSCs was stronger than that against U-251 MG non-CSCs.

In conclusion, we synthesized eustifoline-B (**10**) *via* the construction of carbazole **11** using a microwave heating reaction. The desired carbazole **11** was synthesized in a shorter time using this microwave heating method, with a higher yield than when **11** was synthesized by the external heating method. In addition, **10** showed significant antiproliferative activity against U-251 MG CSCs (IC_{50} = 2.9 μM). Interestingly, **10** showed approximately 10-fold higher antiproliferative activity against U-251 MG CSCs than against U-251 MG non-CSCs (IC_{50} = 29.4 μM). There are few compounds with high selectivity for U-251 MG CSCs. We concluded that carbazoles with a geranyl moiety, such as **10**, could help treat cancers.

EXPERIMENTAL

ESIMS and high-resolution ESIMS, Agilent Technologies Quadrupole LC/MS 6130 (ESIMS), Shimadzu LCMS-IT-TOF (HRESIMS); ^{1}H-NMR spectra, Jeol JNM-ECS400 (400 MHz) spectrometers; ^{13}C-NMR spectra, Jeol JNM-ECS400 (101 MHz) were used for the experimental procedures. The following experimental materials were used for chromatography: normal-phase silica gel column chromatography, silica gel BW-200 (Fuji Silysia Chemical, Ltd., 150–350 mesh); reversed-phase silica gel column chromatography, Cosmosil140C_{18}-OPN (nacalaitesque); TLC, pre-coated TLC plates with silica gel 60F_{254} (Merck, 0.25 mm) (normal phase), and detection was achieved by spraying with 1% $Ce(SO_4)_2$–10% aqueous H_2SO_4 followed by heating.

Preparation of the MeOH extract, EtOAc fraction, and compounds 1–12

The MeOH extract and EtOAc fraction from the leaves of *M. koenigii* stored at Kyoto Pharmaceutical University were used as samples. As previously reported, compounds **1**–**12** were isolated from the EtOAc fraction.[1] Their preparation and separation methods were reported in the literature.[1] The isolated compounds were identified by comparison of their physical data (^{1}H-NMR, ^{13}C-NMR, and MS) with reported values.

Synthesis of 11 from 13 and 14

4-Methyl-1-cyclohexanone (**13**, 0.12 mL, 1.00 mmol), *p*-anisidine (**14**, 172 mg, 1.40 mmol), palladium(II) acetate (45 mg, 0.2 mmol), copper(II) acetate (908 mg, 5.00 mmol), and pivalic acid (4 mL) were added to a microwave vial (Biotage®) or flask. The solution in the microwave vial was stirred under microwave irradiation (Biotage® Initiator+) at 80–140 °C (150 W) for 1–6 h. In contrast, the solution in

the flask was heated at 140 °C for 1–24 h by external heating [thermostatic bath (aluminum block constant temperature bath), EYELA®]. After the reaction, the solution was diluted with Et_2O and a saturated K_2CO_3 water solution was added. The solution was extracted, and the organic layer was washed with brine. After drying, the organic layer was evaporated, and the residue was subjected to normal-phase column chromatography [EtOAc: *n*-hexane (1:20, v/v)] to give glycozoline (**11**). Compound **11** was identified by comparing its physical data (^{1}H-NMR, ^{13}C-NMR, and MS) with the reported values.

Synthesis of 12 from 11

Glycozoline (**11**, 153 mg, 0.72 mmol) was dissolved in CH_2Cl_2 (7 mL), and boron tribromide in CH_2Cl_2 (1.0 M, 1.5 mL, 1.50 mmol) was added at 0 °C. The reaction mixture was then stirred at 25 °C (room temperature) for 3 h. The solution was stirred again at 0 °C and water was added. The solution was extracted, and the organic layer was washed with brine and saturated $NaHCO_3$ water solution. After drying, the organic layer was evaporated, and the residue was subjected to normal-phase column chromatography [EtOAc: *n*-hexane (1:2, v/v)] to obtain glycozolinine (**12**, 134 mg, 94%). Compound **12** was identified by comparing its physical data (^{1}H-NMR, ^{13}C-NMR, and MS) with the reported values.

Synthesis of 10 from 12

Glycozolinine (**12**, 140 mg, 0.71 mmol) and copper(II) chloride dihydrate (2.0 mg, 0.012 mmol) were dissolved in MeCN (4.0 mL), and 3,7-dimethyloct-6-en-1-yn-3-yl methyl carbonate (**17**, 195 mg, 0.93 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.15 mL, 1.0 mmol) were added slowly at 0 °C. The reaction mixture was then stirred at 25 °C (room temperature) for 24 h. After the reaction, the solution was extracted from water using EtOAc, and the organic layer was washed with brine. After drying, the organic layer was evaporated, and compound **18** (239 mg, quant.) was obtained as a brown powder. The obtained compound was used in the subsequent reaction without purification.

A solution of **18** (150 mg, 0.45 mmol) in toluene (28 mL) was refluxed for 24 h by external heating [thermostatic bath (aluminum block constant temperature bath), EYELA®]. After the reaction, the organic layer was evaporated, and the residue was subjected to normal-phase column chromatography [EtOAc: *n*-hexane (1:20, v/v)] to give **10**. Compound **10** was identified by comparing its physical data (^{1}H-NMR, ^{13}C-NMR, and MS) with the reported values.

Eustifoline-B (**10**): 82 mg, 54% yield from **12** brown powders. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.45 (s, 3H), 1.58 (s, 3H), 1.65 (s, 3H), 1.73–1.83 (m, 2H), 2.15–2.21 (m, 2H), 2.52 (s, 3H), 5.11 (t-like, J = 7.2 Hz, 1H), 5.80 (d, J = 9.8 Hz, 1H), 6.91 (d, J = 8.6, 0.7 Hz, 1H), 7.13 (d, J = 8.6 Hz, 1H), 7.19 (dd, J = 8.2, 1.6 Hz, 1H), 7.27 (d, J = 8.2 Hz, 1H), 7.31 (d, J = 9.8 Hz, 1H), and 7.78 (br s like, 1H), 7.92 (s-like, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 17.7 (CH_3), 21.6 (CH_3), 22.8 (CH_2), 25.4 (CH_3), 25.7 (CH_3), 40.3 (CH_2), 77.2 (C), 110.3 (CH), 110.3 (CH), 115.3 (CH), 115.5 (C), 118.6 (C), 120.6 (CH), 122.3 (CH), 123.4 (C), 124.3 (CH), 126.8 (CH), 128.4 (C), 130.5 (CH), 131.7 (CH), 135.0 (C), 138.8 (C), and 146.6 (C); and

ESI-MS: *m/z* 330 $(M–H)^-$, 354 $(M+Na)^+$; HRMS (ESI) *m/z* 332.2027 (calcd for $C_{23}H_{26}NO$ $[M+H]^+$, 332.2014).

Cell culture

The glioblastoma cell line U-251 MG was purchased from American Type Culture Collection (Manassas, VA, USA). U-251 MG cells were cultured in Dulbecco's modified Eagle's medium (DMEM) with low glucose (Wako, Osaka, Japan). The medium contained 10% fetal bovine serum (FBS; Sigma-Aldrich, St. Louis, MO, USA) and 1% penicillin/streptomycin (PC/SM; Wako).

CellTiter–Glo 3D® cell viability assay for CSCs and non-CSCs

CSCs were seeded at a density of 3.0×10^3 cells per 90 μL per well in ultra-low attachment 96-well plates and treated with test compounds (10 μL per well) 24 h after seeding. After 6 d, the cell-containing medium was transferred to a 96-well white plate (96F NunclonTM Delta White Microwell SI; Thermo Fisher Scientific). CellTiter-Glo® 3D Reagent (Promega, Madison, WI, USA) was added at 100 μL per well, and the cell cultures were mixed by shaking for 5 min at 25 °C (room temperature) and then incubated for 25 min at 37 °C. The luminescence was measured using a luminometer (GloMax® Discover System; Promega). For non-CSCs, cells were seeded at a density of 3.0×10^3 cells per 90 μL per well in 96-well plates and treated with test compounds (10 μL per well) 24 h after seeding. After 3 d, cell viability was evaluated using the CellTiter-Glo ® 3D Reagent in a 96-well white plate.

Statistical analysis

Statistical analyses were performed using the GraphPad Prism 8.21 software. Statistical analysis was conducted using a one-way analysis of variance (ANOVA) followed by the Tukey–Kramer or Dunnett test to analyze differences between treatment groups. Differences were considered significant at $*P < 0.05$, $**P < 0.01$.

SUPPLEMENTARY MATERIALS

Supporting information can be downloaded from the ^{1}H-NMR and ^{13}C-NMR spectra of the synthetic compounds.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

ACKNOWLEDGMENTS

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REFERENCES

1. S. Nakamura, S. Nakashima, Y. Oda, N. Yokota, S. Maeda, S. Nishida, T. Matsumoto, T. Ohta, H. Matsuda, and M. Yoshikawa, *Bioorg. Med. Chem*., 2013, **21**, 1043.
2. C. Pei, Q. He, S. Liang, and X. Gong, *Med. Sci. Monit*., 2018, **24**, 6975.
3. (a) S. K. Singh, I. D. Clarke, M. Terasaki, V. E. Bonn, C. Hawkins, J. Squire, and P. B. Dirks, *Cancer Res.*, 2003, **15**, 5821; (b) H. D. Hemmati, I. Nakano, J. A. Lazareff, M. Masterman-Smith, D. H. Geschwind, M. Bronner-Fraser, and H. I. Kornblum, *Proc. Natl. Acad. Sci. U. S. A*., 2003, **100**, 15178; (c) S. Pasikanti, D. S. Reddy, J. Iqbal, P. K. Dubey, and P. Das, *Synthesis*, 2009, **22**, 3833; (d) T. Takada, K. Takata, and E. Ashihara, *J. Physiol. Sci*., 2016, **66**, 387.
4. (a) T. Yoneda, N. Kojima, T. Matsumoto, D. Imahori, T. Ohta, T. Yoshida, T. Watanabe, H. Matsuda, and S. Nakamura, *Org. Biomol. Chem.*, 2022, **20**, 196; (b) S. Nakamura, S. Nakashima, and H. Matsuda, *JAASP*, 2021, **10**, 1; (c) K. Ryu, S. Nakamura, S. Nakashima, and H. Matsuda, *J. Nat. Med.*, 2021, **75**, 308.
5. C. Ito and H. Fujiwara, *Chem. Pharm. Bull.*, 1990, **38**, 1548.
6. R. Hesse, A. W. Schmidt, and H.-J. Knölker, *Tetrahedron*, 2015, **71**, 3485.
7. T. P. Lebold and M. A. Kerr, *Org. Lett*., 2007, **9**, 1883.
8. L. Wen, L. Tang, Y. Yang, Z. Zha, and Z. Wang, *Org. Lett*., 2016, **18**, 1278.