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Synthesis of All Stereoisomers of 1-(4-Methoxyphenyl)-2,3,4,9-tetrahydro-*N*-methyl-1*H*-pyrido[3,4-*b*]indole-3-carboxamide

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Abstract: In this study, all four stereoisomers of tryptoline or tetrahydro-β-carboline were synthesized in high yields by the catalyst-free amidation of methyl ester using methylamine under mild conditions. All isomers of the obtained amide and the precursor methyl ester were subjected to cell viability measurements on HeLa cells. The results indicated that the stereochemistry of the derivatives is clearly related to cell viability.

Keywords: tryptoline; β-carboline; amidation; cytotoxicity

1. Introduction

A 2,3,4,9-tetrahydro-9*H*-pyrido[3,4-*b*]indole skeleton—known as tryptoline or tetrahydro-β-carboline—represents a large group of natural and synthetic alkaloids. Recently, tryptoline derivatives have attracted attention because of their anti-HIV, anti-inflammatory, anti-leishmanial, anti-trypanosomal, and anti-tumor activities [1–4]. Among these derivatives, 1,3-disubstituted tryptoline derivatives have attracted attention because of the relation between their stereochemistry and biological activities based on their asymmetric carbons. The known examples of such 1,3-disubstituted derivatives of tryptoline shown in Figure 1 are an antagonist of somatostatin receptor type 3 (**1**) [5], an antiviral agent for tobacco mosaic virus (**2**) [6], and an antioxidant as a radical scavenger (**3**) [7].

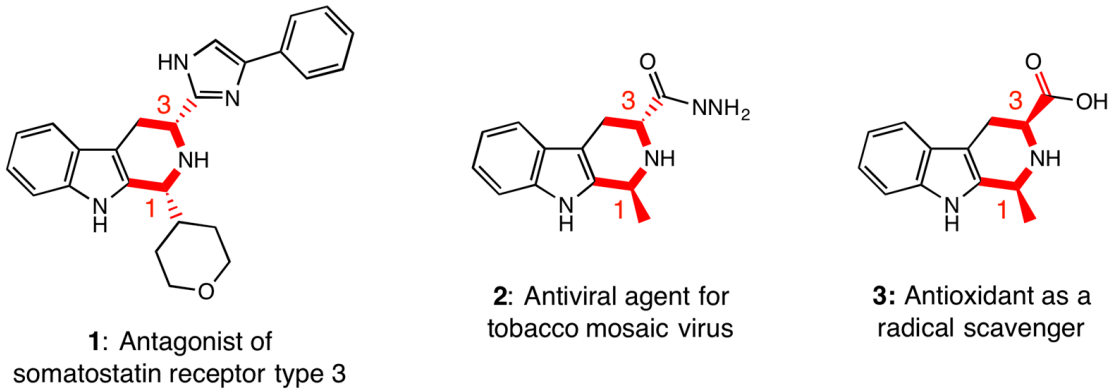

Figure 1. Representative bioactive compounds with 1,3-disubstituted tryptoline derivatives.

As stated above, 1,3-disubstituted derivatives of tryptoline serve as important bioactive motifs. Therefore, structural modification is performed at positions 1 and 3 to improve the bioactivities of tryptoline derivatives. The structural modification is mainly carried out at these positions during the formation of the piperidine ring using the Pictet–Spengler reaction. However, modification at positions 1 and 3 of the tryptoline derivative rings under severe conditions affects the stereochemistry of the asymmetric carbon, which is not preferred. To solve this issue, a catalyst-free and one-pot procedure for the direct synthesis of tryptoline methyl amides **8**–**11** from tryptoline methyl esters **4**–**7** and methylamine under mild conditions has been developed as an example. These amide derivatives **8**–**11** were synthesized to clarify the relation between the configuration of the derivatives and cell viability. These ester derivatives **4**–**7** which were easily converted to carboxylic acid derivatives by cytosolic esterases in cultured cells were unsuitable to investigate the relation. On the other hand, these amide derivatives **8**–**11** which were stable to enzymatic hydrolysis in cultured cells were suitable for our purpose.

2. Results

2.1. Chemistry

Amide bond formation by nucleophilic acyl substitution is one of the most well-known reactions in synthetic organic chemistry. Generally, a methyl ester is converted to either an acid halide or an activated ester from carboxylic acid, followed by the reaction of the activated compound with a primary amine to form an amide bond. Esters are well known to not react with a primary amine under mild conditions in the absence of a catalyst. As esters are stable compounds, reaction conditions such as high temperature and pressure and a strong base are required for conversion from the ester to an amide. Hence, in recent years, mild amidation using a metal or an organic base as a catalyst has been reported [8–10]. In this study, we reported that the direct amidation reaction of tryptoline methyl ester derivatives **4**–**7** under catalyst-free mild conditions gave corresponding amides **8**–**11** in high yield. In addition, the reaction associated with the functional group transformation does not affect the stereochemistry of the tryptoline ring.

Tryptoline methyl ester derivatives **4**–**7** as the starting materials were synthesized according to a previously reported method [11,12]. The synthesized derivatives **4**–**7** were dissolved in methanol, followed by the addition of an ethanolic solution of methylamine. Next, the reaction mixture was stirred in an autoclave reactor at 50 °C for 48 h. During this reaction, no pressure increase was observed. The reaction mixture was concentrated in vacuo, followed by the purification of the obtained residue by silica-gel column chromatography and recrystallization from hot ethanol to afford amide compounds **8**–**11** in high yields of 93–98% (Figure 2). The absolute and relative configuration of obtained amide derivatives **8**–**11** has been defined on the basis of ^{1}H coupling constants ($J_{H3\text{-}H4a}$ and $J_{H3\text{-}H4b}$) of NMR and correlation with ester derivatives **4**–**7** as starting material. The coupling constants ($J_{H3\text{-}H4a}$ = 5.0 Hz and $J_{H3\text{-}H4b}$ = 10.0 Hz) of the amide derivatives **8** and **10** agreed with that ($J_{H3\text{-}H4a}$ = 4.1 Hz and $J_{H3\text{-}H4b}$ = 11.1 Hz) of the ester derivatives **4** and **6** with the *cis* relative configuration [11,12]. These results indicate that the derivatives **8** and **10** have a *cis* relative configuration. The coupling constants ($J_{H3\text{-}H4a}$ = $J_{H3\text{-}H4b}$ = 4.5 Hz) of the amide derivatives **9** and **11** agreed with that ($J_{H3\text{-}H4a}$ = 4.5 Hz and $J_{H3\text{-}H4b}$ = 6.0 Hz) of the ester derivatives **5** and **7** with the *trans* relative configuration [11,12]. These results indicate that the derivatives **9** and **11** have a *trans* relative configuration. Given these results, the direct amidation reaction of tryptoline methyl ester derivatives does not affect the stereochemistry.

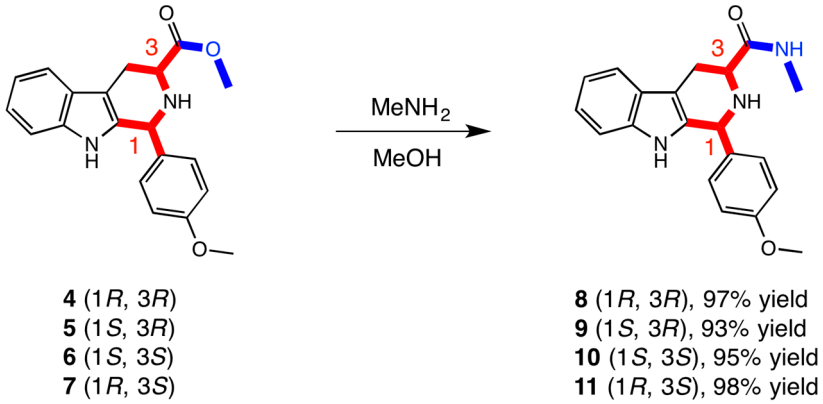

Figure 2. Catalyst-free amidation of tryptoline methyl ester derivatives **4**–**7** with methylamine under mild conditions.

2.2. Assessment of Cell Viability Using the WST-8 Method

Methyl ester derivatives **4**–**7** and methyl amide derivatives **8**–**11** were assayed for cell viability at a concentration of 165 μM for 24 h against HeLa cells by the WST-8 method using a cell counting kit. In this study, cell viability is defined as the ratio of the absorbance for the compound-treated cell sample to that for the no-compound-treated cell sample; this cell viability served as the negative control in the WST-8 assay. Table 1 summarizes these results.

Table 1. Percent (%) Cell viability of **4**–**11** at 165 μM using the WST-8 method.

	Methyl Ester Derivatives				**Methyl Amide Derivatives**			
	4 (1*R*,3*R*)	**5** (1*S*,3*R*)	**6** (1*S*,3*S*)	**7** (1*R*,3*S*)	**8** (1*R*,3*R*)	**9** (1*S*,3*R*)	**10** (1*S*,3*S*)	**11** (1*R*,3*S*)
% cell viability	67.8	89.9	55.8	98.2	52.8	83.8	40.7	66.9

The results revealed the higher cell viabilities for methyl amide derivative **9** (83.8%) and methyl ester derivatives **5** (89.9%) and **7** (98.2%). Other derivatives, methyl amide derivatives **8**, **10**, and **11**, and methyl ester derivatives **4** and **6** showed a weak cytotoxicity. The cell viability ranged from 40.7% to 67.8%. In the methyl amide derivatives **8**–**11** suitable for investigating the relationship between the stereoconfiguration and cell viability, the derivative **9** (1*S*,3*R*) indicated a particularly high cell viability. Given these results, the tryptoline derivatives with 1*S*,3*R* configurations are suitable to design a low-toxicity 1,3-disubstituted tryptoline derivative.

3. Materials and Methods

3.1. Chemistry

New compounds were characterized using ^{1}H-NMR, ^{13}C-NMR, ^{1}H–^{1}H COSY, and HMQC spectrometry, and mass spectrometry. NMR spectra were recorded on a ECA-500 spectrometer (500 MHz for ^{1}H and 125 MHz for ^{13}C, JEOL, Tokyo, Japan). Chemical shifts were reported as downfield shifts from Me_4Si in ppm. Low-resolution mass spectra were recorded on an LCMS-2020 instrument (Shimadzu, Kyoto, Japan), which was coupled to an LC-2030C 3D (Shimadzu, Japan) system under positive- and negative-ion dual-ion electrospray ionization condition (DUIS); electrospray ionization; and atmospheric pressure chemical ionization. Melting points recorded on a Yamato model MP-21 capillary apparatus were uncorrected. Optical rotation was recorded on a JASCO P-1020 digital polarimeter at 23.3 °C. Column chromatography was conducted using silica gel 60N (Kanto Chemical Co., Inc., Tokyo, Japan; spherical, neutral, particle size: 100–210 μm). The reaction progress was

monitored via thin-layer chromatography on silica gel 60 F_{254} (0.25 mm, Merck KGaA, Darmstadt, Germany). The NMR and MS spectra are provided in Supplementary Materials.

Typical procedure: First, methyl (1*R*,3*R*)-1-(4-methoxyphenyl)-2,3,4,9-tetrahydro-1*H*-pyrido-[3,4-*b*] indole-3-carboxylate (**4**, 1.0 g, 2.98 mmol) was dissolved in 50 mL of MeOH, followed by the addition of 1.4 mL of a 33% methylamine solution in absolute ethanol (Sigma-Aldrich, St. Louis, MI, USA; 534102). Second, the reaction mixture was stirred in an autoclave reactor at 50 °C. After stirring for 48 h, the reaction mixture was concentrated in vacuo. The obtained residue was purified using silica-gel column chromatography (10:1, CH_2Cl_2: acetone), affording 0.97 g of (1*R*,3*R*)-1-(4-methoxyphenyl)-2,3,4,9-tetrahydro-*N*-methyl-1*H*-pyrido[3,4-*b*]indole-3-carboxamide (**8**, 97% yield). The obtained product **8** was recrystallized from hot EtOH (740 mg, white crystal).

(1R,3R)-1-(4-Methoxyphenyl)-2,3,4,9-tetrahydro-N-methyl-1H-pyrido[3,4-b]indole-3-carboxamide **8**: Melting point: 223–225 °C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 2.81 (d, 3H, *J* = 5.0 Hz, –NHC<u>H</u>$_3$), 2.91 (ddd, 1H, *J* = 9.5 Hz and *J* = 16.0 Hz, H4a), 3.35 (dd, 1H, *J* = 5.0 Hz and *J* = 16.0 Hz, H4b), 3.64 (dd, 1H, *J* = 5.5 Hz and *J* = 10.0 Hz, H3), 3.80 (s, 3H, –OC<u>H</u>$_3$), 5.24 (s, 1H, H1), 6.84 (d, 2H, *J* = 9.0 Hz, 4-methoxyphenyl), 6.96 (bd, 1H, *J* = 4.5 Hz, –N<u>H</u>CH$_3$), 7.14 (d, 2H, *J* = 8.0 Hz, 4-methoxyphenyl), 7.16–7.21 (m, 2H, H5 and H6 in indole), 7.28 (dd, 1H, *J* = 7.0 Hz, H7 in indole), 7.60 (d, 1H, *J* = 7.5 Hz, H4 in indole), 7.70 (bs, 1H, NH in indole). ^{13}C-NMR (125 MHz, $CDCl_3$): δ 24.65 (C4), 25.94 (–NH<u>C</u>H$_3$), 52.23 (C3), 54.88 (C1), 55.33 (–O<u>C</u>H$_3$), 110.43, 110.84 (C7 in indole), 113.90 (4-methoxyphenyl), 118.52 (C4 in indole), 119.68 (C5 in indole), 122.21 (C6 in indole), 127.10, 129.81 (4-methoxyphenyl), 133.29, 133.37, 136.16, 159.36, 173.53 (–C=O). DUIS-MS (positive mode): *m/z* = 336 $[M + H]^+$, (negative mode): *m/z* = 334 $[M - H]^-$. Specific rotation: $[\alpha]_D$ + 59.0° (*c* = 1.0, MeOH).

(1S,3R)-1-(4-Methoxyphenyl)-2,3,4,9-tetrahydro-N-methyl-1H-pyrido[3,4-b]indole-3-carboxamide **9**: Compound **9** was prepared from compound **5** (200 mg, 0.60 mmol) according to typical procedure to yield 185 mg of **9** (93% yield). The obtained product **9** was recrystallized from hot EtOH (79 mg, white crystal). Melting point: 207–210 °C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 2.82–2.86 (m, 1H, H4a), 2.84 (d, 3H, *J* = 5.0 Hz, –NHC<u>H</u>$_3$), 3.42 (ddd, 1H, *J* = 1.5 Hz, *J* = 4.5 Hz and *J* = 15.5 Hz, H4b), 3.77 (dd, 1H, *J* = 5.0 Hz and *J* = 12.0 Hz, H3), 3.83 (s, 3H, –OC<u>H</u>$_3$), 5.16 (s, 1H, H1), 6.92 (d, 2H, *J* = 8.5 Hz, 4-methoxyphenyl), 7.02 (bd, 1H, *J* = 4.5 Hz, –N<u>H</u>–CH$_3$), 7.11–7.18 (m, 2H, H5 and H6 in indole), 7.23 (d, 1H, *J* = 8.0 Hz, H7 in indole), 7.26 (d, 2H, *J* = 9.0 Hz, 4-methoxyphenyl), 7.46 (s, 1H, N<u>H</u> in indole), 7.57 (d, 1H, *J* = 7.5 Hz, H4 in indole). ^{13}C-NMR (125 MHz, $CDCl_3$): δ 25.52 (C4), 25.84 (–NH–<u>C</u>H$_3$), 55.39 (–O<u>C</u>H$_3$), 58.17 (C3), 58.43 (C1), 110.32, 110.86 (C7 in indole), 114.42 (4-methoxyphenyl), 118.46 (C4 in indole), 119.71 (C5 in indole), 122.10 (C6 in indole), 127.23, 129.61 (4-methoxyphenyl), 132.67, 134.73, 136.09, 159.86, 173.23 (–C=O). DUIS-MS (positive mode): *m/z* = 336 $[M + H]^+$, (negative mode): *m/z* = 334 $[M - H]^-$. Specific rotation: $[\alpha]_D$ + 56.8° (*c* = 1.0, MeOH).

(1S,3S)-1-(4-Methoxyphenyl)-2,3,4,9-tetrahydro-N-methyl-1H-pyrido[3,4-b]indole-3-carboxamide **10**: Compound **10** was prepared from compound **6** (712 mg, 2.12 mmol) according to typical procedure to yield 674 mg of **10** (95% yield). The obtained product **10** was recrystallized from hot EtOH (359 mg, white crystal). Melting point: 224–225 °C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 2.81 (d, 3H, *J* = 5.0 Hz, –NH–C<u>H</u>$_3$), 2.91 (ddd, 1H, *J* = 1.3 Hz, *J* = 9.8 Hz and *J* = 16.0 Hz, H4a) 3.34 (dd, 1H, *J* = 5.5 Hz and *J* = 16.0 Hz, H4b), 3.63 (dd, 1H, *J* = 5.0 Hz and *J* = 9.5 Hz, H3), 3.79 (s, 3H, –OC<u>H</u>$_3$), 5.27 (s, 1H, H1), 6.84 (dd, 2H, *J* = 2.8 Hz and *J* = 6.8 Hz, 4-methoxyphenyl), 6.95 (bd, 1H, *J* = 4.5 Hz, –N<u>H</u>–CH$_3$), 7.14 (d, 2H, *J* = 85 Hz, 4-methoxyphenyl), 7.16–7.21 (m, 2H, H5 and H6 in indole), 7.29 (d, 1H, *J* = 8.0 Hz, H7 in indole), 7.60 (d, 1H, *J* = 8.0 Hz, H4 in indole), 7.70 (s, 1H, NH in indole). ^{13}C-NMR (125 MHz, $CDCl_3$): δ 24.67 (C4), 25.94 (–NH–<u>C</u>H$_3$), 52.24 (C3), 54.88 (C1), 55.33 (–O–<u>C</u>H$_3$), 110.44, 110.85 (C7 in indole), 113.91 (4-methoxyphenyl), 118.52 (C4 in indole), 119.69 (C5 in indole), 122.21 (C6 in indole), 127.12, 129.81 (C3 and C5 in 4-methoxyphenyl), 133.34, 133.40, 136.18, 159.37, 173.56 (–C=O). DUIS-MS (positive mode): *m/z* = 336 $[M + H]^+$, (negative mode): *m/z* = 334 $[M - H]^-$. Specific rotation: $[\alpha]_D$ − 63.0° (*c* = 0.1, MeOH).

(1R,3S)-1-(4-Methoxyphenyl)-2,3,4,9-tetrahydro-N-methyl-1H-pyrido[3,4-b]indole-3-carboxamide **11**: Compound **11** was prepared from compound **7** (500 mg, 1.49 mmol) according to typical procedure to yield 488 mg of **11** (98% yield). The obtained product **11** was recrystallized from hot EtOH (174 mg). Melting point: 207–209 °C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 2.81–2.29 (m, 1H, H4a), 2.84 (d, 3H, *J* = 4.5 Hz, –NH–C<u>H</u>$_3$), 3.42 (ddd, 1H, *J* = 1.5 Hz and *J* = 4.0 Hz and *J* = 8.0 Hz, H4b), 3.77 (dd, 1H, *J* = 4.5 Hz, H3), 3.83 (s, 3H, –OC<u>H</u>$_3$), 5.17 (s, 1H, H1), 6.92 (d, 2H, *J* = 8.0 Hz, 4-methoxyphenyl), 7.02 (bd, 1H, *J* = 3.5 Hz, –N<u>H</u>–CH$_3$), 7.11–7.17 (m, 2H, H5 and H6 in indole), 7.23 (d, 1H, *J* = 8.5 Hz, H7 in indole), 7.25 (d, 2H, *J* = 9.0 Hz, 4-methoxyphenyl), 7.46 (bs, 1H, NH in indole), 7.57 (d, 1H, *J* = 7.0 Hz, H4 in indole). ^{13}C-NMR (125 MHz, $CDCl_3$): δ 25.53 (C4), 25.85 (–NH–<u>C</u>H$_3$), 55.34 (–O<u>C</u>H$_3$), 58.18 (C3), 58.44 (C1), 110.34, 110.87 (C7 in indole), 114.44 (4-methoxyphenyl), 118.47 (C4 in indole), 119.72 (C5 in indole), 122.11 (C6 in indole), 127.24, 129.62 (4-methoxyphenyl), 132.68, 134.74, 136.10, 159.87, 173.24 (–C=O). DUIS-MS (positive mode): *m/z* = 336 $[M + H]^+$, (negative mode): *m/z* = 334 $[M - H]^-$. Specific rotation: $[\alpha]_D$ − 54.5° (*c* = 0.1, MeOH).

3.2. Assessment of Cell Viability Using the WST-8 Method

HeLa cells were seeded in a 96-well plate at 3000 cells/well. After the incubation of the cells at 37 °C for 24 h in 5% CO_2, the medium was replaced with each of a mixture of 100 μL of fresh medium and a 5-μL DMSO solution of 33 mM compounds **4**–**11** (final concentration: 165 μM), and the cells were incubated at 37 °C for 24 h in 5% CO_2. After incubation, 10 μL of the cell counting kit solution (cell counting kit for the WST-8 method, CK04, Dojindo Molecular Technologies Inc., Kumamoto, Japan) was added to each well, followed by the incubation of the cells at 37 °C for 2 h in 5% CO_2. All operations were performed according to the manual. The 450 nm absorbance of each well was measured using an iMark microplate absorbance reader (Bio-Rad Laboratories, Inc., Hercules, CA, USA). Each well was evaluated to calculate an average result using five biological replicates.

Supplementary Materials: The following are available online www.mdpi.com/1422-8599/2018/1/M973, Figure S1: ^{1}H-NMR spectrum of **8**, Figure S2: ^{13}C-NMR spectrum of **8**, Figure S3: H–H COSY spectrum of **8**, Figure S4: HMQC spectrum of **8**, Figure S5: DUIS mass spectrum of **8**, Figure S6: ^{1}H-NMR spectrum of **9**, Figure S7: ^{13}C-NMR spectrum of **9**, Figure S8: H–H COSY spectrum of **9**, Figure S9: HMQC spectrum of **9**, Figure S10: DUIS mass spectrum of **9**, Figure S11: ^{1}H-NMR spectrum of **10**, Figure S12: ^{13}C-NMR spectrum of **10**, Figure S13: H–H COSY spectrum of **10**, Figure S14: HMQC spectrum of **10**, Figure S15: DUIS mass spectrum of **10**, Figure S16: ^{1}H-NMR spectrum of **11**, Figure S17: ^{13}C-NMR spectrum of **11**, Figure S18: H–H COSY spectrum of **11**, Figure S19: HMQC spectrum of **11**, Figure S20: DUIS mass spectrum of **11**.

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Author Contributions: M.O., A.H., T.H. and W.H. performed and evaluated the experiments. M.O., W.H., and T.N. designed the research concept, confirmed the data analysis, and wrote the paper. All of the authors read and approved the final manuscript.

Conflicts of Interest: The authors declare no conflict of interest.

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