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SIMPLE SYNTHESSES OF ANALOGS OF A WASABI PHYTOALEXIN¹

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Abstract — Preparations of 5-nitroindol-1-yl (**5a**), 6-nitroindol-1-yl (**5b**), and 1,2,3-benzotriazol-1-yl 1-methoxyindole-3-carboxylates (**9**) are reported. These are active esters and proved to be useful intermediates for the preparations of ester and amide analogs of methyl 1-methoxyindole-3-carboxylate, a wasabi phytoalexin.

Pedras and co-workers² isolated methyl 1-methoxyindole-3-carboxylate^{2,3} (**1**) from Wasabi (*Wasabia japonica*, syn. *Eutrema wasabi*) as a phytoalexin (Scheme 1). In our project to determine the effect of 1-hydroxy and 1-methoxy moieties on the chemical reactivities^{4,5} and biological activities of indole compounds,⁶ we have much interested in the syntheses of various analogs of **1**. In this paper, we wish to describe a widely applicable and simple method for producing many kinds of ester and amide analogs of **1**.

We have already established a five-step synthetic method for **1** from indoline (**2**) in 51% overall yield.⁵ Among synthetic intermediates involved in the route, we selected 1-methoxyindole-3-carboxylic acid (**3**) as a starting material to meet our end. When we examined the reaction of **3** with 1-hydroxy-5-nitroindole (**4a**) and 1-hydroxy-6-nitroindole (**4b**) in the presence of DCC, 5-nitroindol-1-yl (**5a**) and 6-nitroindol-1-yl 1-methoxyindole-3-carboxylates (**5b**) were found to be isolated as crystallines in 84 and 76% yields, respectively. Similar reaction of indole-3-carboxylic acid (**6**) with **4a** provided **7** in 31% yield. By the reaction with 1-hydroxy-1,2,3-benzotriazole (**8**), **3** afforded 1,2,3-benzotriazol-1-yl 1-methoxyindole-3-carboxylate (**9**) in 89% yield.

Compounds (**5a**), (**5b**), and (**9**) are stable compounds and easy to handle. They can be stored at room temperature for months without decomposition in the absence of nucleophiles. In spite of these facts, they have intrinsic reactive nature as active esters, being suggested by the absorption band at 1760, 1751, and 1764 cm⁻¹, respectively, in their IR spectra. On the other hand, **7** has an absorption band at 1727 with a shoulder at 1756 cm⁻¹.

In accord with the expectations, alcohols reacted with **5a**, **5b**, and **9** in the presence of an appropriate base to give ester analogs of **1** in excellent yields. For example, 2-hydroxyethyl (**10a**) and 2-(*N,N*-dimethylamino)ethyl 1-methoxyindole-3-carboxylate (**10b**) were prepared by the reaction of **5a** either with ethylene glycol in the presence of NaH or with 2-(*N,N*-dimethylamino)ethanol in the presence of LiOH in 99 and 98% yields, respectively. The reaction of **5b** with 2-(*N,N*-dimethylamino)ethanol in the presence of LiOH also provided **10b** in 98% yield. Although the reaction of **3** with cholesterol in the presence of DCC did not afford cholest-5-en-3 β -yl 1-methoxyindole-3-carboxylate (**10c**) at all, **5a** reacted with cholesterol using NaH as a base to produce **10c**, but in only 38% yield

Scheme 1

The reaction of **9** with 2-(*N,N*-dimethylamino)ethanol in the presence of LiOH provided **10b** in 95% yield, while the same reaction of **7** afforded **11** in only 43% yield. Comparison of these results with those of **5a** and **5b** shows that the presence of 1-methoxy group plays an important role on enhancing the reactivities of **5a**, **5b**, and **9**. Among these three compounds, **5a** and **5b** seem to be superior to **9** from the point of recycling of the activators (**4a**, **4b**, and **8**). In fact, recovery of orange-colored and acidic **4a** and **4b** can be more easily carried out from the reaction mixture compared with that of **8**.

On the other hand, an acetylcholine analog, [2-(1-methoxyindol-3-yl)ethyl]trimethylammonium iodide (**10d**), could be produced by the treatment of **10b** with excess MeI in a quantitative yield. Acetylation of **10a** with Ac_2O -pyridine afforded **10e** in 94% yield, while **10a** was reproduced by alkaline hydrolysis of **10e** in 94% yield. Thus, preparations of various ester analogs of **1** would be possible from **5a**, **5b**, and **9**.

Amide analogs of **1** can also be obtained utilizing **5a**, **5b**, and **9** as starting materials. Reactions of **5a** in MeOH with dimethylamine, propylamine, *p*-methoxyphenethylamine, 2-aminoethanol, and hydrazine produced **12a**, **12b**, **12c**, **12d**, and **12e** in 82, 74, 84, 91, and 92% yields, respectively. The reaction of **5b** and **9** with 2-aminoethanol provided **12d** in 91 and 98% yields, respectively, while the same reaction of **7** afforded **13** in 37% yield. These results again prove the enhancing effect of a 1-methoxy group on the nucleophilic substitution reaction. A function of 1-hydroxyindoles as an activator of carboxylic acids is also demonstrated.

In conclusion, we have succeeded in isolating active esters (**5a**, **5b**, and **9**). They can be stored and used,

if need be, as useful reagents for preparing both ester and amide analogs of **1**. Biological evaluations of new compounds are now under investigation.

EXPERIMENTAL

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were determined with a Horiba FT-720 spectrophotometer, and ^1H -NMR spectra with a JEOL GSX-500 spectrometer with tetramethylsilane as an internal standard. MS spectra were recorded on a JEOL SX-102A spectrometer. Column chromatography was performed on silica gel (SiO_2 , 100–200 mesh, from Kanto Chemical Co., Inc.) throughout the present study.

5-Nitroindol-1-yl 1-Methoxyindole-3-carboxylate (5a) from 1-Methoxyindole-3-carboxylic acid (3) — A solution of 1-hydroxy-5-nitroindole (**4a**, 135.6 mg, 0.76 mmol) in anhydrous THF (2.0 mL) was added to a solution of **3** (96.7 mg, 0.51 mmol) and DCC (128.4 mg, 0.62 mmol) in anhydrous THF (3.0 mL), and the mixture was stirred at 62 °C for 5.5 h. After addition of H_2O and CHCl_3 –MeOH (95:5, v/v) to the reaction mixture, the whole was made basic (pH 11) by adding aqueous 2N NaOH under ice cooling, and extracted with CHCl_3 –MeOH (95:5, v/v). Urea was filtered off and washed with AcOEt. The combined extract and washings were washed with brine, dried over Na_2SO_4 , and evaporated under reduced pressure to leave a solid, which was column-chromatographed on SiO_2 with CHCl_3 –hexane (1:1, v/v) to give **5a** (149.4 mg, 84%). The H_2O layer was made acidic (pH 2) with aqueous 2N HCl, and extracted with CHCl_3 –MeOH (95:5, v/v). The extract was washed with brine, dried over Na_2SO_4 , and evaporated under reduced pressure to leave a solid, which was column-chromatographed on SiO_2 with CHCl_3 to give **4a** (34.1 mg, 25%) and **3** (1.3 mg, 1.3%) in the order of elution. **5a**: mp 186–188 °C (yellow powder, recrystallized from CHCl_3 –hexane). IR (KBr): 1760, 1515, 1344, 1191, 1062, 923, 740 cm^{-1} . ^1H -NMR (CDCl_3) δ : 4.25 (3H, s), 6.73 (1H, d, $J=3.4$ Hz), 7.33 (1H, d, $J=8$ Hz), 7.37 (1H, t, $J=7.5$ Hz), 7.42 (1H, d, $J=3.4$ Hz), 7.43 (1H, t, $J=7.5$ Hz), 7.58 (1H, d, $J=7.5$ Hz), 8.13 (1H, dd, $J=8$, 2.5 Hz), 8.17 (1H, d, $J=8$ Hz), 8.25 (1H, s), 8.63 (1H, d, $J=2.5$ Hz). MS (FAB $^+$) m/z : 352 (M^++1). Anal. Calcd for $\text{C}_{18}\text{H}_{13}\text{N}_3\text{O}_5 \cdot 1/4\text{H}_2\text{O}$: C, 60.76; H, 3.82; N, 11.81. Found: C, 60.69; H, 3.63; N, 11.82.

6-Nitroindol-1-yl 1-Methoxyindole-3-carboxylate (5b) from 3 — A solution of 1-hydroxy-6-nitroindole (**4b**, 276.8 mg, 1.55 mmol) in anhydrous THF (4.0 mL) was added to a solution of **3** (198.5 mg, 1.04 mmol) and DCC (258.4 mg, 1.25 mmol) in anhydrous THF (6.0 mL), and the mixture was stirred at 65 °C for 4.5 h. After the same work-up as described in the case of **5a** from **3** using CHCl_3 for extraction, **5b** (278.9 mg, 76%) was obtained. The same work-up of the H_2O layer as described above afforded **4b** (64.7 mg, 24%). **5b**: mp 166–169 °C (black prisms, recrystallized from AcOEt–hexane). IR (KBr): 1751, 1513, 1338, 1186, 1105 cm^{-1} . ^1H -NMR (CDCl_3) δ : 4.27 (3H, s), 6.66 (1H, dd, $J=3.5$, 1.1 Hz), 7.37 (1H, ddd, $J=7.9$, 7.5, 1.1 Hz), 7.43 (1H, ddd, $J=7.9$, 7.5, 1.1 Hz), 7.55 (1H, d, $J=3.5$ Hz), 7.58 (1H, dt, $J=7.9$, 1.1 Hz), 7.71 (1H, d, $J=8.8$ Hz), 8.05 (1H, dd, $J=8.8$, 1.9 Hz), 8.16 (1H, dt, $J=7.9$, 1.1 Hz), 8.26 (1H, br d, $J=1.9$ Hz), 8.28 (1H, s). Anal. Calcd for $\text{C}_{18}\text{H}_{13}\text{N}_3\text{O}_5$: C, 61.54; H, 3.73; N, 11.96. Found: C, 61.52; H, 3.71; N, 11.72.

5-Nitroindol-1-yl Indole-3-carboxylate (7) from Indole-3-carboxylic Acid (6) — A solution of **4a** (166.8 mg, 0.93 mmol) in anhydrous THF (2.0 mL) was added to a solution of **6** (101.0 mg,

0.63 mmol) and DCC (155.4 mg, 0.75 mmol) in anhydrous THF (3.0 mL), and the mixture was stirred at 60 °C for 24 h. The same work-up as described in the case of **5a** from **3**, using CHCl₃ for extraction and CHCl₃–hexane (2:1, v/v) as an eluent, afforded 5-nitroindole (21.5 mg, 14%) and **7** (62.4 mg, 31%) in the order of elution. After the same work-up of the H₂O layer as described above, **4a** (48.4 mg, 29%) and **6** (25.8 mg, 26%) were obtained in the order of elution. **7**: mp 209–212 °C (brown prisms, recrystallized from AcOEt–hexane). IR (KBr): 1756 (sh), 1727, 1521, 1438, 1330 cm⁻¹. ¹H-NMR (DMSO-*d*₆) δ: 6.87 (1H, dd, *J*=4.1, 1.3 Hz), 7.28 (1H, t, *J*=8 Hz), 7.31 (1H, t, *J*=8 Hz), 7.54 (1H, d, *J*=9 Hz), 7.61 (1H, d, *J*=8 Hz), 7.97–8.00 (2H, m), 8.09 (1H, dd, *J*=9, 2.2 Hz), 8.60 (1H, dd, *J*=4.1, 1.3 Hz), 8.69 (1H, d, *J*=2.2 Hz). 12.40 (1H, br s). *Anal.* Calcd for C₁₇H₁₁N₃O₄: C, 63.55; H, 3.45; N, 13.08. Found: C, 63.42; H, 3.66; N, 12.73.

1,2,3-Benzotriazol-1-yl 1-Methoxyindole-3-carboxylate (9) from 1-Methoxyindole-3-carboxylic acid (3) — A solution of 1-hydroxy-1,2,3-benzotriazole (**8**, 105.5 mg, 0.78 mmol) in anhydrous THF (2.0 mL) was added to a solution of **3** (99.2 mg, 0.52 mmol) and DCC (130.0 mg, 0.62 mmol) in anhydrous THF (4.0 mL), and the mixture was stirred at rt for 28.5 h, and then at 60 °C for 4 h. After the same work-up as described in the case of **5a** from **3**, using benzene–CHCl₃ (2:1, v/v) as an eluent, **9** (143.5 mg, 89%) was obtained. The same work-up of the H₂O layer as described above, using CHCl₃ for extraction, afforded **3** (7.1 mg, 7%). **9**: mp 132–134 °C (colorless prisms, recrystallized from CHCl₃–hexane). IR (KBr): 1764, 1627, 1575, 904 cm⁻¹. ¹H-NMR (CDCl₃) δ: 4.25 (3H, s), 7.37 (1H, t, *J*=7.5 Hz), 7.41–7.45 (2H, m), 7.49–7.56 (2H, m), 7.58 (1H, d, *J*=8 Hz), 8.09 (1H, d, *J*=8 Hz), 8.17 (1H, d, *J*=7.5 Hz), 8.33 (1H, s). MS (FAB⁺) *m/z*: 309 (M⁺+1). *Anal.* Calcd for C₁₆H₁₂N₄O₃·1/4H₂O: C, 61.43; H, 4.03; N, 17.91. Found: C, 61.66; H, 3.87; N, 17.91.

2-Hydroxyethyl 1-Methoxyindole-3-carboxylate (10a) i) from 5a — A solution of ethylene glycol (0.07 mL, 1.3 mmol) in DMF (2.0 mL) was added to 60% NaH (287.0 mg, 7.10 mmol) at 0 °C, and the mixture was stirred at rt for 15 min. To the mixture, a solution of **5a** (50.0 mg, 0.14 mmol) in DMF (3.0 mL) was added, and the mixture was stirred at rt for 30 min. After addition of H₂O, the whole was extracted with CHCl₃–MeOH (95:5, v/v). The extract was washed with brine, dried over Na₂SO₄, and evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO₂ with CHCl₃–MeOH (99:1, v/v) to give **10a** (33.2 mg, 99%). The H₂O layer was made acidic by adding aqueous 2N HCl and extracted with CHCl₃–MeOH (95:5, v/v). The extract was washed with brine, dried over Na₂SO₄, and evaporated under reduced pressure to give **4a** (23.1 mg, 91%). **10a**: colorless viscous oil. IR (film): 3400 (br), 1698, 1523, 1209, 744 cm⁻¹. ¹H-NMR (CDCl₃) δ: 1.51 (1H, br s), 3.96–3.99 (2H, m), 4.15 (3H, s), 4.47–4.50 (2H, m), 7.29 (1H, ddd, *J*=8.1, 7, 1 Hz), 7.33 (1H, ddd, *J*=8.1, 7, 1 Hz), 7.48 (1H, dd, *J*=8.1, 1 Hz), 7.99 (1H, s), 8.16 (1H, dd, *J*=8.1, 1 Hz). High-resolution MS *m/z*: Calcd for C₁₂H₁₃NO₄: 235.0845. Found: 235.0850.

ii) from 10e — 40% Aqueous Na₂CO₃ (1.5 mL) was added to a solution of **10e** (13.7 mg, 0.05 mmol) in MeOH (1.5 mL) and the mixture was stirred at rt for 30 min. After addition of ice and H₂O, the whole was extracted with CHCl₃–MeOH (95:5, v/v). The extract was washed with brine, dried over Na₂SO₄, and evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO₂ with CHCl₃ to give **10a** (10.9 mg, 94%).

***N,N*-Dimethylaminoethyl 1-Methoxyindole-3-carboxylate (10b) i) from 5a** — Lithium

hydroxide (35.2 mg, 1.47 mmol) was added to dimethylaminoethanol (2.0 mL, 20 mmol), and the mixture was stirred at 60 °C for 10 min. To the mixture, a solution of **5a** (51.5 mg, 0.15 mmol) in DMF (3.0 mL) was added and the whole was stirred at rt for 1.5 h. After the same work-up as described in the case of **10a** from **5a**, using CHCl₃–MeOH (97:3, v/v) as an eluent, **10b** (36.8 mg, 96%) was obtained. The same work-up of the H₂O layer as described above, using CHCl₃ for extraction, afforded **4a** (25.1 mg, 97%). **10b**: colorless oil. IR (KBr): 1698, 1207, 744 cm⁻¹. ¹H-NMR (CDCl₃) δ: 2.37 (6H, s), 2.76 (2H, t, *J*=6 Hz), 4.14 (3H, s), 4.44 (2H, t, *J*=6 Hz), 7.28 (1H, ddd, *J*=8, 7.7, 1.2 Hz), 7.31 (1H, ddd, *J*=8, 7.7, 1.2 Hz), 7.46 (1H, dt, *J*=8, 1.2 Hz), 7.99 (1H, s), 8.19 (1H, br d, *J*=8 Hz). High-resolution MS *m/z*: Calcd for C₁₄H₁₈N₂O₃: 262.1317. Found: 262.1316.

ii) from 5b — Lithium hydroxide (35.1 mg, 1.47 mmol) was added to dimethylaminoethanol (2.0 mL, 20 mmol) and the mixture was stirred at 60 °C for 10 min and at rt for additional 10 min. To the mixture, a solution of **5b** (51.3 mg, 0.15 mmol) in DMF (3.0 mL) was added, and the mixture was stirred at rt for 30 min. After the same work-up as described above, **10b** (37.4 mg, 98%) was obtained. The same work-up of H₂O layer as described above gave **4b** (24.9 mg, 95%).

iii) from 9 — Lithium hydroxide (37.2 mg, 1.55 mmol) was added to dimethylaminoethanol (2.0 mL, 20 mmol), and the mixture was stirred at 63 °C for 10 min. To the mixture, a solution of **9** (46.5 mg, 0.15 mmol) in DMF (3.0 mL) was added and the whole was stirred at rt for 1 h. After the same work-up as described above, **10b** (37.0 mg, 95%) was obtained. The same work-up of H₂O layer as described above, using CHCl₃–MeOH (95:5, v/v) for extraction, afforded **8** (7.9 mg, 40%).

Cholest-5-en-3β-yl 1-Methoxyindole-3-carboxylate (10c) from 5a — A solution of cholesterol (558.1 mg, 1.44 mmol) in DMF (8.0 mL) was added to 60% NaH (64.6 mg, 1.6 mmol), and the mixture was stirred at rt for 15 min. To the mixture, a solution of **5a** (101.5 mg, 0.29 mmol) in DMF (2.5 mL) was added, and the whole was stirred at rt for 3.5 h. After the same work-up as described in the case of **10a** from **5a** using CHCl₃–hexane (1:2, v/v) as an eluent, **10c** (59.7 mg, 38%) and cholesterol (459.1 mg) were obtained in the order of elution. The same work-up of H₂O layer as described above, using CHCl₃ for extraction and as an eluent, afforded an additional cholesterol (21.9 mg), **4a** (45.3 mg, 87%), and **3** (5.2 mg, 9%) in the order of elution. **10c**: viscous hard oil. IR (KBr): 2944, 1691, 1523, 1207, 744 cm⁻¹. ¹H-NMR (CDCl₃) δ: 0.69 (3H, s), 0.87 (3H, d, *J*=6.6 Hz), 0.86 (3H, d, *J*=6.6 Hz), 0.92 (3H, d, *J*=6.6 Hz), 1.08 (3H, s), 0.97–2.06 (26H, m), 2.45–2.54 (2H, m), 4.14 (3H, s), 4.84–4.91 (1H, m), 5.43 (1H, br d, *J*=4.9 Hz), 7.26 (1H, ddd, *J*=8, 7.6, 1 Hz), 7.31 (1H, ddd, *J*=8, 7.6, 1 Hz), 7.45 (1H, d, *J*=7.6 Hz), 7.95 (1H, s), 8.17 (1H, d, *J*=7.6 Hz). High-resolution MS (FAB⁺) *m/z*: Calcd for C₃₇H₅₃NO₃Na: 582.3923. Found: 582.3922 (M+Na)⁺.

[2-(1-Methoxyindol-3-carboxy)ethyl]trimethylammonium Iodide (10d) from 10b — Methyl iodide (1.0 mL, 16 mmol) was added to a solution of **10b** (36.8 mg, 0.14 mmol) in MeOH (2.0 mL) and the mixture was stirred at rt for 30 min. Solvent was evaporated under reduced pressure to leave a solid (**10d**, 50.3 mg, 99.7%). **10d**: mp 181–183 °C (colorless powder, recrystallized from CHCl₃–MeOH). IR (KBr): 1683, 1201, 746 cm⁻¹. ¹H-NMR (DMSO-*d*₆) δ: 3.20 (9H, s), 3.78–3.82 (2H, m), 4.17 (3H, s), 4.69 (2H, br s), 7.29 (1H, br t, *J*=7.8 Hz), 7.36 (1H, br t, *J*=7.8 Hz), 7.60 (1H, br d, *J*=7.8 Hz), 8.08 (1H, br d, *J*=7.8 Hz), 8.53 (1H, s). High-resolution MS (FAB⁺) *m/z*: 277 (M⁺–I). *Anal.* Calcd for C₁₅H₂₁N₂O₃I·1/4H₂O: C, 44.07; H, 5.30; N, 6.85. Found: C, 44.19; H, 5.11; N,

6.64.

2-Acetoxyethyl 1-Methoxyindole-3-carboxylate (10e) from 10a — Ac₂O (1.75 mL, 18.5 mmol) was added to a solution of **10a** (35.2 mg, 0.15 mmol) in anhydrous pyridine (3.5 mL) and the mixture was stirred at rt for 1.5 h. Solvent was evaporated under reduced pressure to leave a solid, which was column-chromatographed on SiO₂ with CHCl₃ to give **10e** (39.4 mg, 94%). **10e**: colorless oil. IR (film): 1739, 1704 cm⁻¹. ¹H-NMR (CDCl₃) δ: 2.10 (3H, s), 4.15 (3H, s), 4.42—4.45 (2H, m), 4.51—4.54 (2H, m), 7.28 (1H, br t, *J*=7.9 Hz), 7.32 (1H, br t, *J*=7.9 Hz), 7.47 (1H, d, *J*=7.9 Hz), 7.97 (1H, s), 8.16 (1H, d, *J*=7.9 Hz). High-resolution MS *m/z*: Calcd for C₁₄H₁₅NO₅: 277.0956. Found: 277.0950.

***N,N*-Dimethylaminoethyl Indole-3-carboxylate (11) from 7** — Lithium hydroxide (39.3 mg, 1.64 mmol) was added to dimethylaminoethanol (2.0 mL, 20 mmol), and the mixture was stirred at 60 °C for 10 min. To the mixture, a solution of **7** (53.4 mg, 0.17 mmol) in DMF (3.0 mL) was added, and the mixture was stirred at rt for 4.5 h. After the same work-up as described in the case of **10a** from **5a**, using CHCl₃ for extraction and CHCl₃–MeOH (97:3, v/v) as an eluent, 5-nitroindole (1.8 mg, 7%), **4a** (2.1 mg), **7** (10.1 mg, 19%), and **11** (16.4 mg, 43%) were obtained in the order of elution. The same work-up of H₂O layer as described above, using CHCl₃ for extraction, afforded additional **4a** (25.2 mg, total 27.3 mg, 92%). **11**: 129—131 °C (colorless needles, recrystallized from CHCl₃–hexane). IR (KBr): 1695, 1182 cm⁻¹. ¹H-NMR (CDCl₃) δ: 2.38 (6H, s), 2.78 (2H, t, *J*=5.9 Hz), 4.46 (2H, t, *J*=5.9 Hz), 7.23—7.27 (2H, m), 7.37—7.41 (1H, m), 7.89 (1H, d, *J*=3.1 Hz), 8.15—8.19 (1H, m), 8.89 (1H, br s). *Anal.* Calcd for C₁₃H₁₆N₂O₂: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.01; H, 6.95; N, 11.96.

General Procedure for Amide Analogs of Methyl 1-Methoxyindole-3-carboxylate: Amine was added to a solution of an active ester (**5a**, **5b**, **7**, or **9**) in an appropriate solvent and the mixture was stirred. After addition of H₂O to the reaction mixture, the whole was extracted with an organic solvent. The extract was washed with brine, dried over Na₂SO₄, and evaporated under reduced pressure to leave a crude product, which was column-chromatographed on SiO₂ with an eluent to give an amide product (**12**). The H₂O layer was made acidic by adding aqueous 2N HCl and extracted with CHCl₃. The extract was dried over Na₂SO₄, and evaporated under reduced pressure to give **4a**, **4b**, or **8**.

***N,N*-Dimethyl 1-Methoxyindole-3-carboxamide (12a) i) from 5a** — In the general procedure, 50% aqueous Me₂NH (1.0 mL, 9.6 mmol) and **5a** (35.1 mg, 0.1 mmol) in MeOH (3.0 mL) were used. The mixture was stirred at rt for 2 h and CHCl₃ was used for extraction. Using CHCl₃ as an eluent, **12a** (17.8 mg, 82%) was obtained. After the same work-up of H₂O layer as described in the general procedure, **4a** (16.9 mg, 95%) was obtained. **12a**: pale yellow oil. IR (film): 1612, 1533, 1452, 1394, 744 cm⁻¹. ¹H-NMR (CDCl₃) δ: 3.16 (6H, s), 4.12 (3H, s), 7.21 (1H, ddd, *J*=7.8, 7.4, 1 Hz), 7.29 (1H, ddd, *J*=7.8, 7.4, 1 Hz), 7.45 (1H, dt, *J*=7.8, 1 Hz), 7.57 (1H, s), 7.78 (1H, dt, *J*=7.4, 1 Hz). High-resolution MS *m/z*: Calcd for C₁₂H₁₄N₂O₂: 218. 1055. Found: 218. 1061.

ii) from 9 — In the general procedure, 50% aqueous Me₂NH (1.0 mL, 9.6 mmol) and **9** (23.6 mg, 0.073 mmol) in MeOH (3.0 mL) were used. The mixture was stirred at rt for 2 h and CHCl₃ was used for extraction. Using CHCl₃ as an eluent, **12a** (13.1 mg, 82%) was obtained.

***N*-Propyl 1-Methoxyindole-3-carboxamide (12b) from 5a** — In the general procedure,

n-propylamine (1.0 mL, 12.2 mmol) and **5a** (50.4 mg, 0.13 mmol) in CHCl₃ (3.0 mL) were used. The mixture was stirred at rt for 3.5 h and CHCl₃ was used for extraction. Using CHCl₃ as an eluent, **12b** (27.5 mg, 74%) was obtained. After the same work-up of H₂O layer as described in the general procedure, **4a** (20.2 mg, 86%) was obtained. **12b**: mp 82–85 °C (colorless needles, recrystallized from CHCl₃-hexane). IR (KBr): 1612, 1548 cm⁻¹. ¹H-NMR (CDCl₃) δ: 1.02 (3H, t, *J*=7.2 Hz), 1.67 (2H, sext, *J*=7.2 Hz), 3.46 (2H, br q, *J*=7.2 Hz), 4.12 (3H, s), 5.91 (1H, br t, *J*=7.2 Hz, disappeared on addition of D₂O), 7.26 (1H, ddd, *J*=8.1, 7.8, 1 Hz), 7.31 (1H, ddd, *J*=8.1, 7.8, 1 Hz), 7.48 (1H, dt, *J*=8.1, 1 Hz), 7.83 (1H, s), 7.92 (1H, dt, *J*=8.1, 1 Hz). MS *m/z*: 232 (M⁺). Anal. Calcd for C₁₃H₁₆N₂O₂: C, 67.22 ; H, 6.94 ; N, 12.06 . Found: C, 67.00 ; H, 7.01; N, 11.97.

***N*-*p*-Methoxyphenethyl 1-Methoxyindole-3-carboxamide (12c) from 5a** — In the general procedure, *p*-methoxyphenethylamine (1.0 mL, 6.8 mmol) and **5a** (50.4 mg, 0.14 mmol) in CHCl₃ (4.0 mL) were used. The mixture was stirred at rt for 3 h and CHCl₃ was used for extraction. Using CHCl₃ and CHCl₃-MeOH (99:1, v/v) successively as eluents, **4a** (2.0 mg) and **12c** (39.0 mg, 84%) were obtained in the order of elution. After the same work-up of H₂O layer as described in the general procedure, **4a** (6.0 mg, total 8.0 mg, 40%) was obtained. **12c**: colorless oil. IR (film): 1621, 1544, 1511, 1245, 1228 cm⁻¹. ¹H-NMR (CDCl₃) δ: 2.90 (2H, t, *J*=6.7 Hz), 3.73 (2H, q, *J*=6.7 Hz), 3.80 (3H, s), 4.10 (3H, s), 6.86–6.89 (2H, m), 7.16–7.20 (3H, m), 7.29 (2H, ddd, *J*=8, 7.5, 1 Hz), 7.45 (1H, dt, *J*=8, 1 Hz), 7.68 (1H, dt, *J*=8, 1 Hz), 7.78 (1H, s). High-resolution MS *m/z*: Calcd for C₁₉H₂₀N₂O₃: 324.1514. Found: 324.1491.

***N*-(2-Hydroxy)ethyl 1-Methoxyindole-3-carboxamide (12d) i) from 5a** — In the general procedure, ethanolamine (0.5 mL, 8.3 mmol) and **5a** (51.5 mg, 0.15 mmol) in DMF (3.0 mL) were used. The mixture was stirred at rt for 1.5 h and CHCl₃-MeOH (95:5, v/v) was used for extraction. Using CHCl₃-MeOH (99:1, v/v) as an eluent, **4a** (23.0 mg) and **12d** (31.7 mg, 92%) were obtained in the order of elution. After the same work-up of H₂O layer as described in the general procedure, **4a** (1.8 mg, total 24.8 mg, 95%) was obtained. **12d**: oil. IR (film): 1623, 1544, 1228 cm⁻¹. ¹H-NMR (CDCl₃) δ: 3.20 (1H, br s, disappeared on addition of D₂O), 3.64 (2H, q, *J*=5.2 Hz), 3.83 (2H, t, *J*=5.2 Hz), 4.09 (3H, s), 6.52 (1H, br t, *J*=5.2 Hz), 7.22–7.26 (1H, m), 7.30 (1H, ddd, *J*=7.9, 7.5, 1 Hz), 7.46 (1H, dt, *J*=7.9, 1 Hz), 7.85 (1H, s), 7.97 (1H, dt, *J*=7.9, 1 Hz). High-resolution MS *m/z*: Calcd for C₁₂H₁₄N₂O₃: 234.1004. Found: 234.1003.

ii) from 5b — In the general procedure, ethanolamine (0.5 mL, 8.3 mmol) and **5b** (50.1 mg, 0.14 mmol) in DMF (3.0 mL) were used. The mixture was stirred at rt for 30 min and CHCl₃-MeOH (95:5, v/v) was used for extraction. Using CHCl₃-MeOH (95:5, v/v) as an eluent, **4b** (24.8 mg, 98%) and **12d** (28.8 mg, 91%) were obtained in the order of elution.

iii) from 9 — In the general procedure, ethanolamine (0.5 mL, 8.3 mmol) and **9** (46.3 mg, 0.15 mmol) in DMF (3.0 mL) were used. The mixture was stirred at rt for 1.5 h and CHCl₃-MeOH (95:5, v/v) was used for extraction. Using CHCl₃-MeOH (95:5, v/v) as an eluent, **12d** (34.4 mg, 98%) was obtained. After the same work-up of the H₂O layer as described in the general procedure, using CHCl₃-MeOH (95:5, v/v) for extraction, **8** (10.8 mg, 53%) was obtained.

1-Methoxyindole-3-carbohydrazide (12e) from 5a — In the general procedure, 100% hydrazine hydrate (0.5 mL, 16 mmol) and **5a** (45.7 mg, 0.10 mmol) in DMF (3.0 mL) were used. The

mixture was stirred at rt for 30 min and CHCl_3 –MeOH (95:5, v/v) was used for extraction. Using CHCl_3 –MeOH (99:1, v/v) as an eluent, **4a** (10.1 mg) and **12e** (24.5 mg, 92%) were obtained in the order of elution. After the same work-up of the H_2O layer as described in the general procedure, **4a** (12.8 mg, total 22.9 mg, 99%) was obtained. **12e**: mp 157 – 159 °C (colorless powder, recrystallized from CHCl_3 –hexane). IR (KBr): 3324, 1616, 1536, 736 cm^{-1} . ^1H -NMR (CDCl_3) δ : 1.51 (2H, br s, disappeared on addition of D_2O), 4.13 (3H, s), 7.12 (1H, br s, disappeared on addition of D_2O), 7.27 (1H, br t, $J=8.2$ Hz), 7.32 (1H, br t, $J=8.2$ Hz), 7.48 (1H, dd, $J=8.2, 0.7$ Hz), 7.86 (1H, s), 7.93 (1H, d, $J=8.2$ Hz). MS m/z : 205 (M^+). Anal. Calcd for $\text{C}_{10}\text{H}_{11}\text{N}_3\text{O}_2 \cdot 1/4 \text{H}_2\text{O}$: C, 57.27; H, 5.28; N, 20.03. Found: C, 57.50; H, 5.25; N, 19.99.

N-(2-Hydroxy)ethyl Indole-3-carboxamide (13) from 7 — In the general procedure, ethanolamine (0.5 mL, 8.3 mmol) and **7** (47.3 mg, 0.15 mmol) in DMF (3.0 mL) were used. The mixture was stirred at rt for 30 min. Using CHCl_3 –MeOH (99:3, v/v) and CHCl_3 –MeOH (99:5, v/v) successively as eluents, **4a** (25.3 mg, 97%) and **13** (11.2 mg, 37%) were obtained in the order of elution. **13**: 189–191 °C (brown powder, recrystallized from CHCl_3 –MeOH–hexane). IR (KBr): 1590, 1573, 1552, 1211 cm^{-1} . ^1H -NMR ($\text{DMSO}-d_6$) δ : 3.32 (2H, q, $J=5.9$ Hz), 3.51 (2H, q, $J=5.9$ Hz, collapsed to t on addition of D_2O), 4.69 (1H, t, $J=5.9$ Hz, disappeared on addition of D_2O), 7.08 (1H, ddd, $J=7.9, 7.5, 1.1$ Hz), 7.13 (1H, ddd, $J=7.9, 7.5, 1.1$ Hz), 7.40 (1H, d, $J=7.9$ Hz), 7.80 (1H, t, $J=5.9$ Hz), 7.99 (1H, d, $J=2.9$ Hz, collapsed to s on addition of D_2O), 8.11 (1H, d, $J=7.9$ Hz), 11.50 (1H, s). MS m/z : 204 (M^+). Anal. Calcd for $\text{C}_{11}\text{H}_{12}\text{N}_2\text{O}_2 \cdot 1/6\text{H}_2\text{O}$: C, 63.76; H, 5.95; N, 13.52. Found: C, 63.66; H, 5.77; N, 13.53.

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