HETEROCYCLES, Vol. 79, 2009, pp. 635 - 645. © The Japan Institute of Heterocyclic Chemistry
Received, 25th September, 2008, Accepted, 5th November, 2008, Published online, 10th November, 2008.
DOI: 10.3987/COM-08-S(D)29

# SYNTHESIS OF $N_b$-ACYLTRYPTAMINES AND THEIR 1-HYDROXY-TRYPTAMINE DERIVATIVES AS NEW $\alpha_2$-BLOCKERS[1,#]

**Koji Yamada,[a] Yoshio Tanaka,[b] and Masanori Somei[c,*,‡]**

[a]Faculty of Pharmaceutical Sciences, Health Sciences University of Hokkaido, Ishikari-Tobetsu, Hokkaido 061-0293, Japan. [b]Faculty of Pharmaceutical Sciences, Toho University, Funabashi, Chiba 274-8510, Japan. [c]Faculty of Pharmaceutical Sciences, Graduate School of Natural Science and Technology, Kanazawa University, Kakuma-machi, Kanazawa 920-1192, Japan
Corresponding author: e-mail address: syamoji_usa@r9.dion.ne.jp

**Abstract** – $N_b$-Acyl- and $N_b$-acyl-1-hydroxytryptamines are found to be novel and structurally simple $\alpha_2$-blocker for the treatment of erectile dysfunction.

Nowadays, a lot of people need a drug for the treatment of erectile dysfunction (ED). Sildenafil citrate (**1**, Figure 1) has been used as a promising drug, but it has some side-effects[2] to be improved. Although yohimbine[3] (**2**) is a folk medicine and widely used among people as a $\alpha_2$-blocker to treat ED, it is a powerful medicine and dangerous unless we are careful about quantity to take. Therefore, when the safer drug is found, it would not only bring happiness to a human being, but also be applied for raising the breeding rate of animals.[4,5] Cows and pigs could lay a lot of calves and child pigs, respectively and offer meat to us solving the significant problem of food shortage in the world.

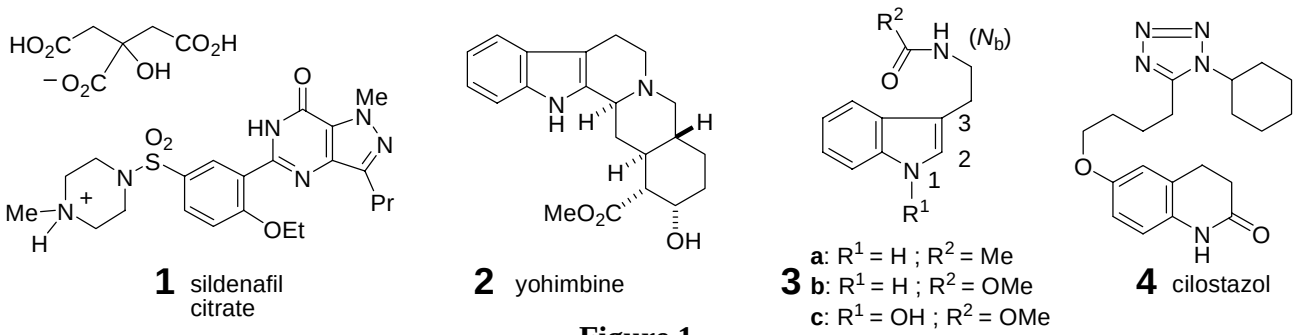



**Figure 1**

# Dedicated to the memory of Dr. John Daly

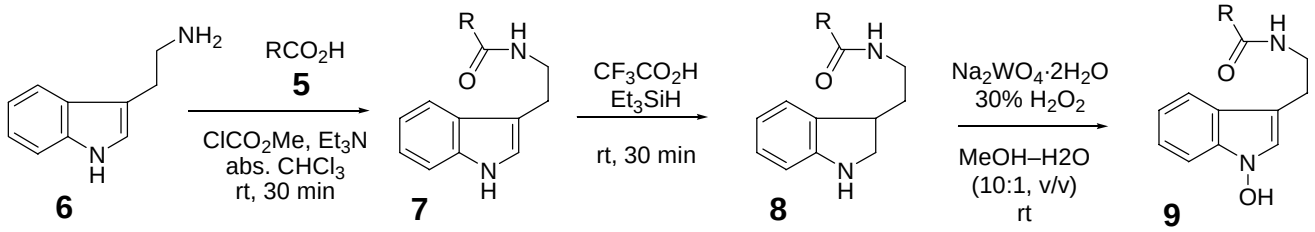
‡ Professor Emeritus of Kanazawa University. Present address: 2-40-3 Sodani, Hakusan-shi, Ishikawa, 920-2101, Japan.

In our project for developing a novel and potent $\alpha_2$-blocker, structurally simpler than **1** and **2**, we discovered that $N_b$-acetyl- (**3a**) and $N_b$-methoxycarbonyltryptamines (**3b**) have weak but reliable activity as a $\alpha_2$-blocker.[4] On the other hand, we succeeded in the establishment of 1-hydroxyindole chemistry.[5] As a result, we found that 1-hydroxy-$N_b$-methoxycarbonyltryptamine (**3c**: $IC_{50}$ 0.32 μM) is one of the best leads and ten times more potent than cilostazol (**4**: $IC_{50}$ 3.10 μM) in the inhibition test on arachidonic acid induced platelet aggregation in rabbit PRP.[6] It is expected to be a possible lead for cerebral and myocardial infarction.[7]

We attempted therefore to pursue the study of structure-activity relationship of $N_b$-acyltryptamines and their 1-hydroxytryptamine derivatives hoping to develop a potent lead for ED and cerebral infarction.

For the preparation of $N_b$-acyltryptamines, a conventional mixed anhydride method was applied. Appropriate carboxylic acids (**5**, Table 1) were treated with methyl chloroformate. The resultant anhydrides were then reacted with tryptamine (**6**) to afford the desired compounds (**7**) and the results are summarized in Table 1. Employing propanoic (**5a**), pentanoic (**5b**), heptanoic (**5c**), and nonanoic acids (**5d**), the corresponding $N_b$-propanoyl- (**7a**), $N_b$-pentanoyl- (**7b**), $N_b$-heptanoyl- (**7c**), and $N_b$-nonanoyltryptamines (**7d**) were produced in 94, 91, 95, and 93% yields, respectively. Cyclopropane- (**5e**), cyclohexane- (**5f**), and 2-furancarboxylic acids (**5g**) provided $N_b$-cyclopropanecarbonyl- (**7e**), $N_b$-cyclohexanecarbonyl- (**7f**), and $N_b$-2-furancarbonyltryptamine (**7g**) in the respective yields of 85, 61, and 62%.

**Table 1. Synthesis of $N_b$-Acyl-1-hydroxytryptamine Derivatives**




| Carboxylic Acid 5 | R | Compound 7 | Yield (%) | Compound 8 | Yield (%) | Compound 9 | Reaction Time (min) | Yield (%) |
|---|---|---|---|---|---|---|---|---|
| **5a** | —$CH_2Me$ | **7a** | 94 | **8a** | 98 | **9a** | 15 | 67 |
| **5b** | —$(CH_2)_3Me$ | **7b** | 91 | **8b** | 86 | **9b** | 15 | 61 |
| **5c** | —$(CH_2)_5Me$ | **7c** | 95 | **8c** | 87 | **9c** | 30 | 68 |
| **5d** | —$(CH_2)_7Me$ | **7d** | 93 | **8d** | 78 | **9d** | 30 | 61 |
| **5e** |  | **7e** | 85 | **8e** | 84 | **9e** | 30 | 69 |
| **5f** |  | **7f** | 61 | **8f** | 73 | **9f** | 30 | 62 |
| **5g** |  | **7g** | 62 | **8g** | 97*1 | **9g** | 30 | 64 |

*1: reacted at around 60 °C for 1 h.

According to the first step of our 1-hydroxyindole synthetic method,[5] $N_b$-acyltryptamines (**7**) were

converted to $N_b$-acyl-2,3-dihydrotryptamines (**8**) by the reduction with $Et_3SiH$ in trifluoroacetic acid at rt for 30 min. Thus, **7a**, **7b**, **7c**, and **7d** afforded 2,3-dihydro-$N_b$-propanoyl- (**8a**), -$N_b$-pentanoyl- (**8b**), -$N_b$-heptanoyl- (**8c**), and -$N_b$-nonanoyltryptamines (**8d**) in 98, 86, 87, and 78% yields, respectively. Similarly, **7e** and **7f** provided 2,3-dihydro-$N_b$-cyclopropanecarbonyl- (**8e**) and -$N_b$-cyclohexanecarbonyltryptamine (**8f**) in the respective yields of 84 and 73%. In the case of **7g**, the reduction was slow and heating at around 60 °C for 1 h was necessary to produce 2,3-dihydro-$N_b$-2-furancarbonyltryptamine (**8g**) in 97% yield.

In the second step, 2,3-dihydro-$N_b$-acyltryptamines **(8**) were led to the desired new $N_b$-acyl-1-hydroxytryptamines **(9**) by the oxidation with $Na_2WO_4{\cdot}2H_2O$ and 30% aqueous $H_2O_2$ in MeOH–$H_2O$. For example, **8a**, **8b**, **8c**, and **8d** produced 1-hydroxy-$N_b$-propanoyl- (**9a**), -$N_b$-pentanoyl- (**9b**), $N_b$-heptanoyl-1-hydroxy- (**9c**), and 1-hydroxy-$N_b$-nonanoyltryptamines (**9d**) in 67, 61, 68, and 61% yields, respectively. In the cases of **8e**, **8f**, and **8g**, $N_b$-cyclopropanecarbonyl- (**9e**), $N_b$-cyclohexanecarbonyl- (**9f**), and $N_b$-2-furancarbonyl-1-hydroxytryptamines **(9g)** were obtained in 69, 62, and 64% yields, respectively.

**Table 2. The Extent of Vascular Relaxation**

| Yohimbine: 100% | | | |
|---|---|---|---|
| **9b** | 25.6 ± 6.0% | **9d** | 79.0 ± 13% |
| **7b** | 26.9 ± 11.4% | **7d** | 80.7 ± 2.5% |
| **9c** | 66.2 ± 13.9% | **9e** | 15.7 ± 6.8% |
| **7c** | 70.0 ± 6.9% | **7e** | 21.4% |

With the desired compounds in hand, we next evaluated the relaxant potencies of **7b**-**e** and **9b**-**e** as a preliminary test. The extent of the vascular relaxation produced in the muscle contracted with clonidine is summarized in Figure 1, making the activity of yohimbine as a standard for 100. It is interesting to note that the activity increases depending on the length of $N_b$-acyl side chain.[5e,8] In addition, differences in activities are small between N(1)-H (**7b**-**e**) and N(1)-OH compounds (**9b**-**e**). These results strongly suggest that these simple tryptamine derivatives possess at least the antagonistic effect on vascular smooth muscle $\alpha_2$-AR.[8] The potencies of **7d** and **9d** reached to about 80% of that of yohimbine. Furthermore, $LD_{50}$ of **7d** was determined to be more than 80 mg/kg on ddy male mouse, showing its safety. The details will be reported elsewhere in due course.

In conclusion, we have succeeded in finding new leads for the treatment of ED. We named them SST-VED-I type compounds. In order to discover more potent $\alpha_2$-blocker, we are preparing tryptamines having various $N_b$-side chain. The biological evaluation concerning cerebral infarction is now in progress.

## EXPERIMENTAL

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded with a Shimadzu IR-420 and proton nuclear magnetic resonance

($^1$H-NMR) spectra with a JEOL GSX-500 or JEOL JMS-AX5 spectrometer with tetramethylsilane as an internal standard. Mass spectra (MS) were recorded on a JEOL JMS-SX102A instruments. Column chromatography was performed on silica gel ($SiO_2$, 100-200 mesh, from Kanto Chemical Co., Inc.) throughout the present study.

***N*$_b$-Propanoyltryptamine (7a) from Tryptamine (6) - General Procedure:** $Et_3N$ (1.89 mL, 13.6 mmol) and $ClCO_2Me$ (1.05 mL, 1.36 mmol) were added to a solution of propanoic acid (912.7 mg, 12.3 mmol) in anhydrous $CHCl_3$ (30 mL), and the mixture was stirred at 0 °C for 30 min. To the resulting mixture, **7** (2.17 g, 13.6 mmol) was added and the mixture was stirred at rt for 30 min. After addition of $H_2O$ the whole was 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 residue, which was column-chromatographed on $SiO_2$ with EtOAc–hexane (1:1, v/v) to give **7a** (2.51 g, 94%). **7a**: mp 88-89 °C (colorless fine needles, recrystallized from $Et_2O$). IR (KBr): 3377, 1635, 1563, 1453, 1368, 1250 cm$^{-1}$. $^1$H-NMR ($CDCl_3$) δ: 1.11 (3H, t, *J*=7.6 Hz), 2.14 (2H, q, *J*=7.6 Hz), 2.98 (2H, dt, *J*=6.6, 0.7 Hz), 3.61 (2H, q, *J*=6.6 Hz), 5.50 (1H, br s), 7.04 (1H, d, *J*=2.2Hz), 7.13 (1H, ddd, *J*=7.8, 7.1, 1.0 Hz), 7.21 (1H, ddd, *J*=7.8, 7.1, 1.2 Hz), 7.37 (1H, dt, *J*=7.8, 1.0Hz), 7.61 (1H, ddd, *J*=7.8, 1.2, 0.7 Hz), 8.09 (1H, br s). *Anal*. Calcd for $C_{13}H_{16}N_2O{\cdot}1/8H_2O$: C, 71.45; H, 7.50; N, 12.82. Found: C, 71.77; H, 7.34; N, 12.52.

***N*$_b$-Pentanoyltryptamine (7b) from 6** - In the general procedure for the synthesis of **7a**, $Et_3N$ (1.57 mL, 11.3 mmol), $ClCO_2Me$ (0.87 mL, 11.3 mmol), pentanoic acid (1.05 g, 10.3 mmol), anhydrous $CHCl_3$ (30 mL), and **6** (1.81 g, 11.3 mmol) were used. After the work-up and column-chromatography with EtOAc–hexane (2:3, v/v), **7b** (2.29 g, 91%) was obtained. **7b**: mp 93-94 °C (colorless powder, recrystallized from EtOAc–hexane). IR (KBr): 3377, 3237, 2927, 1630, 1561, 1450 cm$^{-1}$. $^1$H-NMR ($CDCl_3$) δ: 0.88 (3H, t, *J*=7.3 Hz), 1.26-1.34 (2H, m), 1.53-1.60 (2H, m), 2.11 (2H, t, *J*=7.5 Hz), 2.98 (2H, t, *J*=6.6 Hz), 3.61 (2H, q, *J*=6.6 Hz), 5.56 (1H, br s), 7.04 (1H, s), 7.13 (1H, ddd, *J*=7.9, 7.0, 0.9 Hz), 7.22 (1H, ddd, *J*=7.9, 7.0, 0.9 Hz), 7.38 (1H, dt, *J*=7.9, 0.9 Hz), 7.61 (1H, d, *J*=7.9 Hz), 8.09 (1H, br s). *Anal*. Calcd for $C_{15}H_{20}N_2O$: C, 73.73; H, 8.25; N, 11.47. Found: C, 73.48; H, 8.23; N, 11.42.

***N*$_b$-Heptanoyltryptamine (7c) from 6** - In the general procedure for the synthesis of **7a**, $Et_3N$ (1.19 mL, 8.58 mmol), $ClCO_2Me$ (0.66 mL, 8.58 mmol), heptanoic acid (1.01 g, 7.80 mmol), anhydrous $CHCl_3$ (30 mL), and **6** (1.37 g, 8.58 mmol) were used. After the work-up and column-chromatography with $CHCl_3$ **7c** (2.02 g, 95%) was obtained. **7c**: mp 97-98 °C (colorless powder, recrystallized from EtOAc–hexane). IR (KBr): 3410, 1632, 1565, 1457, 1425 cm$^{-1}$. $^1$H-NMR ($CDCl_3$) δ: 0.87 (3H, t, *J*=7.3 Hz), 1.21-1.31 (6H, m), 1.57 (2H, quint, *J*=7.5 Hz), 2.10 (2H, t, *J*=7.5 Hz), 2.98 (2H, t, *J*=6.6 Hz), 3.61 (2H, q, *J*=6.6 Hz), 5.52 (1H, br s), 7.04 (1H, d, *J*=2.2 Hz), 7.13 (1H, ddd, *J*=8.1, 7.0, 1.0 Hz), 7.22 (1H, ddd, *J*=8.1, 7.0, 1.0 Hz), 7.38 (1H, dt, *J*=8.1, 1.0 Hz), 7.61 (1H, d, *J*=8.1 Hz), 8.08 (1H, br s). *Anal*. Calcd for $C_{17}H_{24}N_2O$: C,

74.96; H, 8.88; N, 10.29. Found: C, 74.80; H, 8.92; N, 10.26.

***N*$_b$-Nonanoyltryptamine** (**7d**) **from 6** - In the general procedure for the synthesis of **7a**, $Et_3N$ (0.99 mL, 7.09 mmol), $ClCO_2Me$ (0.55 mL, 7.09 mmol), nonanoic acid (1.02 g, 6.45 mmol), anhydrous $CHCl_3$ (30 mL), and **6** (1.14 g, 7.09 mmol) were used. After the work-up and column-chromatography with EtOAc–hexane (1:2, v/v), **7d** (1.78 g, 93%) was obtained. **7d**: mp 101-102 °C (colorless fine needles, recrystallized from $CHCl_3$–hexane). IR ($CHCl_3$): 2950, 1652, 1506, 1165 cm$^{-1}$. $^1$H-NMR ($CDCl_3$) δ: 0.87 (3H, t, *J*=7.0 Hz), 1.22-1.31 (10H, m), 1.57 (2H, br quint, *J*=7.0 Hz), 2.10 (2H, t, *J*=7.6 Hz), 2.98 (2H, t, *J*=6.7 Hz), 3.61 (2H, q, *J*=6.7 Hz, collapsed to t, *J*=6.7 Hz, on addition of $D_2O$), 5.52 (1H, br s, disappeared on addition of $D_2O$), 7.04 (1H, s), 7.13 (1H, ddd, *J*=8.1, 7.1, 1.0 Hz), 7.21 (1H, ddd, *J*=8.1, 7.1, 1.0 Hz), 7.38 (1H, d, *J*=8.1 Hz), 7.61 (1H, d, *J*=8.1 Hz), 8.09 (1H, br s, disappeared on addition of $D_2O$). *Anal*. Calcd for $C_{19}H_{28}N_2O$: C, 75.96; H, 9.39; N, 9.33. Found: C, 75.66; H, 9.49; N, 9.24.

***N*$_b$-Cyclopropanecarbonyltryptamine** (**7e**) **from 6** - In the general procedure for the synthesis of **7a**, $Et_3N$ (1.81 mL, 13.0 mmol), $ClCO_2Me$ (1.00 mL, 13.0 mmol), cyclopropanecarboxylic acid (1.12 g, 13.0 mmol), anhydrous $CHCl_3$ (30 mL), and **6** (1.89 g, 11.8 mmol) were used. After the work-up and column-chromatography with EtOAc–hexane (1:2, v/v), **7e** (2.29 g, 85%) was obtained. **7e**: mp 105.5-107 °C (colorless prisms, recrystallized from $CHCl_3$). IR (KBr): 3280, 1611, 1566, 1251, 1235, 1197, 754 cm$^{-1}$. $^1$H-NMR ($CDCl_3$) δ: 0.69 (2H, td, *J*=7.9, 4.6 Hz), 0.97 (2H, dt, *J*=7.9, 4.6 Hz), 1.23 (1H, tt, *J*=7.9, 4.6 Hz), 2.99 (2H, t, *J*=6.8 Hz), 3.63 (2H, q, *J*=6.7 Hz, collapsed to t, *J*=6.7 Hz, on addition of $D_2O$), 5.69 (1H, br s, disappeared on addition of $D_2O$), 7.05 (1H, s), 7.13 (1H, ddd, *J*=8.1, 7.1, 1.1 Hz), 7.21 (1H, ddd, *J*=8.1, 7.1, 1.1 Hz), 7.38 (1H, dt, *J*=8.1, 1.1Hz), 7.61 (1H, br d, *J*=8.1 Hz), 8.12 (1H, br s, disappeared on addition of $D_2O$). *Anal*. Calcd for $C_{14}H_{16}N_2O$: C, 73.65; H, 7.06; N, 12.27. Found: C, 73.64; H, 7.09; N, 12.29.

***N*$_b$-Cyclohexanecarbonyltryptamine** (**7f**) **from 6** - In the general procedure for the synthesis of **7a**, $Et_3N$ (1.16 mL, 8.34 mmol), $ClCO_2Me$ (0.65 mL, 8.35 mmol), cyclohexanecarboxylic acid (1.07 g, 8.33 mmol), anhydrous $CHCl_3$ (25 mL), and **6** (1.21 g, 7.57 mmol) were used. After the work-up and column-chromatography with EtOAc–hexane (1:2, v/v), **7f** (1.25 g, 61%) was obtained. **7f**: mp 108.5-109 °C (colorless prisms, recrystallized from $CHCl_3$). IR (KBr): 3270, 2940, 1618, 1561, 1449, 1220, 748 cm$^{-1}$. $^1$H-NMR ($CDCl_3$) δ: 1.15-1.26 (3H, m), 1.34-1.41 (2H, m), 1.65-1.81 (5H, m), 1.99 (1H, tt, *J*=11.7, 3.5 Hz), 2.97 (2H, t, *J*=6.8 Hz), 3.60 (2H, q, *J*=6.8 Hz, collapsed to t, *J*=6.8 Hz, on addition of $D_2O$), 5.52 (1H, br s, disappeared on addition of $D_2O$), 7.03 (1H, s), 7.13 (1H, ddd, *J*=8.1, 7.1, 1.0 Hz), 7.21 (1H, ddd, *J*=8.1, 7.1, 1.0 Hz), 7.38 (1H, dt, *J*=8.1, 1.0Hz), 7.61 (1H, br d, *J*=8.1 Hz), 8.10 (1H, br s, disappeared on addition of $D_2O$). *Anal*. Calcd for $C_{17}H_{22}N_2O$: C, 75.52; H, 8.20; N, 10.36. Found: C, 75.33; H, 8.26; N, 10.29.

***N*$_b$-2-Furancarbonyltryptamine** (**7g**) **from 6** - In the general procedure for the synthesis of **7a**, $Et_3N$

(1.30 mL, 9.34 mmol), $ClCO_2Me$ (0.72 mL, 9.32 mmol), 2-furancarboxylic acid (1.04 g, 9.31 mmol), anhydrous $CHCl_3$ (30 mL), and **6** (1.21 g, 7.57 mmol) were used. After the work-up and column-chromatography with EtOAc–hexane (1:1, v/v), **7g** (1.33 g, 62%) was obtained. **7g**: mp 158-160 °C (colorless needles recrystallized from EtOAc). IR (KBr): 3255, 1613, 1592, 1533, 1315, 1303, 1192 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) δ: 3.28 (2H, t, *J*=6.8 Hz), 3.78 (2H, q, *J*=6.8 Hz, collapsed to t, *J*=6.8 Hz, on addition of $D_2O$), 6.47 (1H, br s, disappeared on addition of $D_2O$), 6.47 (1H, dd, *J*=3.5, 1.8 Hz), 7.08 (1H, s), 7.09 (1H, dd, *J*=3.5, 0.7 Hz), 7.13 (1H, ddd, *J*=8.1, 7.1, 1.0 Hz), 7.21 (1H, ddd, *J*=8.1, 7.1, 1.0 Hz), 7.36 (1H, dd, *J*=1.8, 0.7 Hz), 7.38 (1H, dt, *J*=8.1, 1.0Hz), 7.64 (1H, br d, *J*=8.1 Hz), 8.10 (1H, br s, disappeared on addition of $D_2O$). *Anal*. Calcd for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.94; H, 5.62; N, 11.01.

**2,3-Dihydro-*N*$_b$-propanoyltryptamine** (**8a**) **from 7a - General Procedure:** A mixture of **7a** (1.02 g, 4.74 mmol) and $Et_3SiH$ (1.89 mL, 11.9 mmol) in TFA (20 mL) was stirred at rt for 30 min. After evaporation of the solvent, the residue was made alkaline with 8% aqueous NaOH 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 an oil, which was column-chromatographed on $SiO_2$ with $CHCl_3$–MeOH–28% aqueous $NH_3$ (46:1:0.1, v/v) to give **8a** (1.01 g, 98%). **8a**: yellow viscous oil. IR (film): 3315, 2970, 1635, 1606, 1547, 1486, 1461 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) δ: 1.13 (3H, t, *J*=7.5 Hz), 1.78 (1H, dtd, *J*=13.6, 7.9, 6.0 Hz), 2.00 (1H, dddd, *J*=13.6, 7.9, 7.0, 5.0 Hz), 2.16 (2H, q, *J*=7.5 Hz), 2.82 (1H, br s, disappeared on addition of $D_2O$), 3.26-3.42 (4H, m), 3.72 (1H, t, *J*=8.8 Hz), 5.62 (1H, br s, disappeared on addition of $D_2O$), 6.67 (1H, d, *J*=7.3 Hz), 6.75 (1H, td, *J*=7.3, 0.9 Hz), 7.05 (1H, br t, *J*=7.3 Hz), 7.10 (1H, d, *J*=7.3 Hz). HR-MS *m/z:* Calcd for $C_{13}H_{18}N_2O$: 218.1419. Found: 218.1431.

**2,3-Dihydro-*N*$_b$-pentanoyltryptamine** (**8b**) **from 7b** - In the general procedure for the synthesis of **8a**, **7b** (102.1 mg, 0.42 mmol), $Et_3SiH$ (0.17 mL, 1.05 mmol), and TFA (3 mL) were used. After the work-up and column chromatography with the same eluent, **8b** (88.1 mg, 86%) was obtained. **8b**: yellow viscous oil. IR (film): 3290, 2930, 1640, 1605, 1552, 1484, 1461 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) δ: 0.91 (3H, t, *J*=7.5 Hz), 1.33 (2H, sex, *J*=7.5 Hz), 1.59 (2H, quint, *J*=7.5 Hz), 1.73 (1H, dtd, *J*=13.6, 8.0, 6.1 Hz), 1.99 (1H, dddd, *J*=13.6, 8.0, 7.0, 5.0 Hz), 2.13 (2H, t, *J*=7.5 Hz), 2.75 (1H, br s, disappeared on addition of $D_2O$), 3.27-3.42 (4H, m), 3.72 (1H, t, *J*=8.6 Hz), 5.60 (1H, br s, disappeared on addition of $D_2O$), 6.68 (1H, d, *J*=7.3 Hz), 6.75 (1H, td, *J*=7.3, 0.9 Hz), 7.05 (1H, br t, *J*=7.3 Hz), 7.11 (1H, d, *J*=7.3 Hz). HR-MS *m/z:* Calcd for $C_{15}H_{22}N_2O$: 246.1732. Found: 246.1743.

***N*$_b$-Heptanoyl-2,3-dihydrotryptamine** (**8c**) **from 7c**- In the general procedure for the synthesis of **8a**, **7c** (1.04 g, 3.82 mmol), $Et_3SiH$ (1.52 mL, 9.54 mmol), and TFA (20 mL) were used. After the work-up and column chromatography with EtOAc–hexane (2:1, v/v), **8c** (912.7 mg, 87%) was obtained. **8c**: pale brown viscous oil. IR (film): 3310, 2960, 1634, 1606, 1544, 1484, 1461 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) δ: 0.88

(3H, t, *J*=7.5 Hz), 1.25-1.34 (6H, m), 1.60 (2H, quint, *J*=7.5 Hz), 1.78 (1H, dtd, *J*=13.6, 7.9, 5.9 Hz), 1.99 (1H, dddd, *J*=13.6, 7.9, 7.1, 5.1 Hz), 2.12 (2H, t, *J*=7.7 Hz), 2.68 (1H, br s, disappeared on addition of $D_2O$), 3.27-3.42 (4H, m), 3.72 (1H, t, *J*=8.6 Hz), 5.60 (1H, br s, disappeared on addition of $D_2O$), 6.68 (1H, d, *J*=7.5 Hz), 6.75 (1H, td, *J*=7.5, 1.1 Hz), 7.05 (1H, br t, *J*=7.5 Hz), 7.10 (1H, d, *J*=7.5 Hz). HR-MS *m/z:* Calcd for $C_{17}H_{26}N_2O$: 274.2045. Found: 274.2057.

**2,3-Dihydro-*N*$_b$-nonanoyltryptamine** (**8d**) **from 7d** - In the general procedure for the synthesis of **8a**, **7d** (1.10 g, 3.65 mmol), $Et_3SiH$ (1.45 mL, 9.10 mmol), and TFA (20 mL) were used. After the work-up and column chromatography with EtOAc–hexane (1:1, v/v), **8d** (862.4 mg, 78%) was obtained. **8d**: mp 41-42.5 °C (colorless powder recrystallized from EtOAc–hexane). IR (KBr): 3300, 2935, 2870, 1638, 1546, 1486, 1465cm$^{-1}$. $^1$H-NMR (DMSO-$d_6$) δ: 0.84 (3H, t, *J*=7.0 Hz), 1.20-1.27 (10H, m), 1.45-1.57 (3H, m), 1.83 (1H, dtd, *J*=13.2, 7.6, 5.6 Hz), 2.04 (2H, t, *J*=7.5 Hz), 3.05 (1H, ddd, *J*=9.3, 8.1, 2.2 Hz), 3.09-3.16 (3H, m), 3.54 (1H, td, *J*=8.6, 1.7 Hz), 5.40 (1H, br s, disappeared on addition of $D_2O$), 6.47 (1H, d, *J*=7.5 Hz), 6.52 (1H, td, *J*=7.5, 0.7 Hz), 6.90 (1H, br t, *J*=7.5 Hz), 7.00 (1H, d, *J*=7.5 Hz), 7.80 (1H, br t, *J*=6.1 Hz, disappeared on addition of $D_2O$). *Anal*. Calcd for $C_{19}H_{30}N_2O$: C, 75.45; H, 10.00; N, 9.26. Found: C, 75.25; H, 10.16; N, 9.24.

***N*$_b$-Cyclopropanecarbonyl-2,3-dihydrotryptamine** (**8e**) **from 7e** - In the general procedure for the synthesis of **8a**, **7e** (137.3 mg, 0.60 mmol), $Et_3SiH$ (0.24 mL, 1.51 mmol), and TFA (3 mL) were used. After the work-up and column chromatography with EtOAc–hexane (2:1, v/v), **8e** (116.3 mg, 84%) was obtained. **8e**: mp 41-42.5 °C (colorless powder, recrystallized from EtOAc). IR (KBr): 3310, 1621, 1605, 1543, 1490, 1258, 1240 cm$^{-1}$. $^1$H-NMR (DMSO-$d_6$) δ: 0.60-0.67 (4H, m), 1.49-1.60 (2H, m), 1.86 (1H, dtd, *J*=13.4, 7.6, 5.4 Hz), 3.06 (1H, dd, *J*=8.8, 7.8 Hz), 3.12-3.17 (3H, m), 3.54 (1H, t, *J*=8.8 Hz), 5.41 (1H, br s, disappeared on addition of $D_2O$), 6.48 (1H, d, *J*=7.6 Hz), 6.53 (1H, td, *J*=7.6, 1.0 Hz), 6.90 (1H, br t, *J*=7.6 Hz), 7.01 (1H, d, *J*=7.6 Hz), 8.08 (1H, br t, *J*=6.0 Hz, disappeared on addition of $D_2O$). *Anal*. Calcd for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.17. Found: C, 72.81; H, 7.92; N, 11.88.

***N*$_b$-Cyclohexanecarbonyl-2,3-dihydrotryptamine** (**8f**) **from 7f** - In the general procedure for the synthesis of **8a**, **7f** (93.8 mg, 0.35 mmol), $Et_3SiH$ (0.14 mL, 0.88 mmol), and TFA (1.5 mL) were used. After the work-up and column chromatography with EtOAc–hexane (1:1, v/v), **8f** (68.7 mg, 73%) was obtained. **8f**: mp 109-111 °C (colorless plates, recrystallized from $CHCl_3$–hexane). IR (KBr): 3290, 2930, 1622, 1545, 1536, 1464, 1252 cm$^{-1}$. $^1$H-NMR ($CDCl_3$) δ: 1.16-1.29 (3H, m), 1.35-1.43 (2H, m), 1.65-1.68 (1H, m), 1.73-1.84 (4H, m), 1.95-2.05 (3H, m), 2.53 (1H, br s, disappeared on addition of $D_2O$), 3.26-3.41 (4H, m), 3.72 (1H, t, *J*=8.5 Hz), 5.60 (1H, br s, disappeared on addition of $D_2O$), 6.68 (1H, d, *J*=7.3 Hz), 6.75 (1H, td, *J*=7.3, 0.9 Hz), 7.05 (1H, br t, *J*=7.3 Hz), 7.11 (1H, d, *J*=7.3 Hz). *Anal*. Calcd for $C_{17}H_{24}N_2O$: C, 74.96; H, 8.88; N, 10.29. Found: C, 74.89; H, 8.96; N, 10.20.

***N*$_b$-2-Furanecarbonyl-2,3-dihydrotryptamine** (**8g**) **from 7g** - In the general procedure for the synthesis

of **8a**, **7g** (814.1 mg, 3.21 mmol), $Et_3SiH$ (1.28 mL, 8.03 mmol), and TFA (20 mL) were used. After the work-up and column chromatography with EtOAc–hexane (2:1, v/v), **8g** (794.3 mg, 97%) was obtained. **8g**: colorless viscous oil. IR ($CHCl_3$): 3275, 1651, 1592, 1515, 1475, 1285 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) δ: 1.87 (1H, dtd, *J*=13.7, 7.9, 6.0 Hz), 2.10 (1H, dtd, *J*=13.7, 7.9, 5.1 Hz), 3.33 (1H, dd, *J*=8.8, 6.3 Hz), 3.37-3.43 (1H, m), 3.47 (1H, dtd, *J*=13.7, 7.9, 6.3 Hz collapsed to dt, *J*=13.7, 7.9 Hz, on addition of $D_2O$), 3.57 (1H, ddt, *J*=13.7, 7.9, 6.3 Hz collapsed to ddd, *J*=13.7, 7.9, 6.3 Hz, on addition of $D_2O$), 3.75 (1H, t, *J*=8.8 Hz), 6.49 (1H, dd, *J*=3.5, 1.8 Hz), 6.54 (1H, br s, disappeared on addition of $D_2O$), 6.69 (1H, d, *J*=7.5 Hz), 6.76 (1H, td, *J*=7.5, 1.0 Hz), 7.05 (1H, br t, *J*=7.5 Hz), 7.09 (1H, dd, *J*=3.5, 0.8 Hz), 7.13 (1H, d, *J*=7.5 Hz), 7.42 (1H, dd, *J*=1.8, 0.8 Hz). HR-MS *m/z:* Calcd for $C_{15}H_{16}N_2O_2$: 256.1211. Found: 256.1214.

**1-Hydroxy-*N*$_b$-propanoyltryptamine** (**9a**) **from 8a - General Procedure**: A solution of 30% aqueous $H_2O_2$ (1.11 g, 9.80 mmol) in MeOH (3 mL) was added with stirring to a solution of **8a** (211.8 mg, 0.97 mmol) and $Na_2WO_4{\cdot}2H_2O$ (64.1 mg, 0.19 mmol) in MeOH (7 mL) and $H_2O$ (1 mL) under ice cooling. Stirring was continued at rt for 15 min. After addition of $H_2O$, the whole was 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 an oil, which was column-chromatographed on $SiO_2$ with $CHCl_3$–MeOH (99:1, v/v) to give **9a** (150.2 mg, 67%). **9a**: mp 132-133 °C (colorless fine prisms, recrystallized from $CHCl_3$). IR (KBr): 3290, 3100, 2935, 1598, 1566, 1352 $cm^{-1}$. $^1$H-NMR (DMSO-$d_6$) δ: 0.99 (3H, t, *J*=7.6 Hz), 2.06 (2H, q, *J*=7.6 Hz), 2.79 (2H, t, *J*=7.3 Hz), 3.30 (2H, td, *J*=7.3, 6.1 Hz, collapsed to t, *J*=7.3 Hz, on addition of $D_2O$), 6.98 (1H, dd, *J*=8.0, 7.3 Hz), 7.13 (1H, dd, *J*=8.0, 7.3 Hz), 7.24 (1H, s), 7.32 (1H, d, *J*=8.0 Hz), 7.53 (1H, d, *J*=8.0 Hz), 7.84 (1H, br t, *J*=6.1 Hz, disappeared on addition of $D_2O$), 11.01 (1H, s, disappeared on addition of $D_2O$). *Anal*. Calcd for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C,66.94; H, 6.95; N, 12.02.

**1-Hydroxy-*N*$_b$-pentanoyltryptamine** (**9b**) **from 8b** - In the general procedure for the synthesis of **9a**, 30% aqueous $H_2O_2$ (2.37 g, 20.9 mmol), MeOH (5 mL), **8b** (513.3 mg, 2.09 mmol), $Na_2WO_4{\cdot}2H_2O$ (138.0 mg, 0.42 mmol), MeOH (20 mL), and $H_2O$ (2.5 mL) were used. After the work-up and column chromatography with EtOAc–hexane (2:1, v/v), **9b** (331.2 mg, 61%) was obtained. **9b**: mp 114.5-115 °C (colorless powder, recrystallized from $CHCl_3$). IR ($CHCl_3$): 3125, 2922, 1649, 1513 $cm^{-1}$. $^1$H-NMR (DMSO-$d_6$) δ: 0.86 (3H, t, *J*=7.4 Hz), 1.25 (2H, sex, *J*=7.4 Hz), 1.47 (2H, quint, *J*=7.4 Hz), 2.05 (2H, t, *J*=7.4 Hz), 2.78 (2H, t, *J*=7.4 Hz), 3.30 (2H, td, *J*=7.4, 6.1 Hz, collapsed to t, *J*=7.4 Hz, on addition of $D_2O$), 6.98 (1H, ddd, *J*=8.1, 7.1, 1.0 Hz), 7.12 (1H, ddd, *J*=8.1, 7.1, 1.0 Hz), 7.23 (1H, s), 7.32 (1H, d, *J*=8.1 Hz), 7.53 (1H, d, *J*=8.1 Hz), 7.86 (1H, br t, *J*=6.1 Hz, disappeared on addition of $D_2O$), 11.00 (1H, s, disappeared on addition of $D_2O$). *Anal*. Calcd for $C_{15}H_{20}N_2O_2$: C, 69.20; H, 7.74; N, 10.76. Found: C, 69.17; H, 7.70; N, 10.68.

***N*$_b$-Heptanoyl-1-hydroxytryptamine** (**9c**) **from 8c** - In the general procedure for the synthesis of **9a**, 30% aqueous $H_2O_2$ (461.4 mg, 4.07 mmol), MeOH (1 mL), **8c** (111.3 mg, 0.41 mmol), $Na_2WO_4 \cdot 2H_2O$ (27.3 mg, 0.08 mmol), MeOH (4 mL), and $H_2O$ (0.5 mL) were used. After the work-up and column chromatography with EtOAc–hexane (2:1, v/v), **9c** (79.8 mg, 68%) was obtained. **9c**: mp 83-83.5 °C (colorless prisms, recrystallized from $CHCl_3$–hexane). IR (KBr): 3280, 2930, 1601, 1555, 1435, 1358, 1241 cm$^{-1}$. $^1$H-NMR (DMSO-$d_6$) δ: 0.86 (3H, t, *J*=7.5 Hz), 1.21-1.29 (6H, m), 1.47 (2H, quint, *J*=7.5 Hz), 2.04 (2H, t, *J*=7.5 Hz), 2.78 (2H, t, *J*=7.5 Hz), 3.29 (2H, td, *J*=7.5, 6.1 Hz, collapsed to t, *J*=7.5 Hz, on addition of $D_2O$), 6.98 (1H, ddd, *J*=8.1, 7.1, 1.0 Hz), 7.12 (1H, ddd, *J*=8.1, 7.1, 1.0 Hz), 7.24 (1H, s), 7.32 (1H, dt, *J*=8.1, 1.0 Hz), 7.52 (1H, dt, *J*=8.1, 1.0 Hz), 7.86 (1H, br t, *J*=6.1 Hz, disappeared on addition of $D_2O$), 11.00 (1H, s, disappeared on addition of $D_2O$). *Anal*. Calcd for $C_{17}H_{24}N_2O_2$: C, 70.80; H, 8.39; N, 9.71. Found: C, 70.73; H, 8.40; N, 9.64.

**1-Hydroxy-*N*$_b$-nonanoyltryptamine** (**9d**) **from 8d** - In the general procedure for the synthesis of **9a**, 30% aqueous $H_2O_2$ (451.3 mg, 3.98 mmol), MeOH (1 mL), **8d** (119.3 mg, 0.40 mmol), $Na_2WO_4 \cdot 2H_2O$ (26.7 mg, 0.08 mmol), MeOH (4 mL), and $H_2O$ (0.5 mL) were used. After the work-up and column chromatography with $CHCl_3$–MeOH (99:1, v/v), **9d** (75.8 mg, 61%) was obtained. **9d**: mp 82.5-83 °C (colorless powder, recrystallized from $CHCl_3$–hexane). IR ($CHCl_3$): 3155, 2915, 1648, 1510, 1457 cm$^{-1}$. $^1$H-NMR (DMSO-$d_6$) δ: 0.86 (3H, t, *J*=7.4 Hz), 1.15-1.30 (10H, m), 1.47 (2H, quint, *J*=7.4 Hz), 2.03 (2H, t, *J*=7.4 Hz), 2.78 (2H, t, *J*=7.4 Hz), 3.30 (2H, td, *J*=7.4, 6.1 Hz, collapsed to t, *J*=7.4 Hz, on addition of $D_2O$), 6.98 (1H, ddd, *J*=8.1, 7.1, 1.0 Hz), 7.12 (1H, ddd, *J*=8.1, 7.1, 1.0 Hz), 7.24 (1H, s), 7.32 (1H, d, *J*=8.1 Hz), 7.52 (1H, d, *J*=8.1 Hz), 7.86 (1H, br t, *J*=6.1 Hz, disappeared on addition of $D_2O$), 11.01 (1H, s, disappeared on addition of $D_2O$). *Anal*. Calcd for $C_{19}H_{28}N_2O_2$: C, 72.11; H, 8.92; N, 8.85. Found: C, 72.09; H, 8.96; N, 8.85.

***N*$_b$-Cyclopropanecarbonyl-1-hydroxytryptamine** (**9e**) **from 8e** - In the general procedure for the synthesis of **9a**, 30% aqueous $H_2O_2$ (498.0 mg, 4.39 mmol), MeOH (1 mL), **8e** (101.6 mg, 0.44 mmol), $Na_2WO_4 \cdot 2H_2O$ (29.2 mg, 0.09 mmol), MeOH (4 mL), and $H_2O$ (0.5 mL) were used. After the work-up and column chromatography with $CHCl_3$–MeOH (99:1, v/v), **9e** (74.6 mg, 69%) was obtained. **9e**: mp 155-158 °C (colorless prisms, recrystallized from EtOAc). IR (KBr): 3290, 3140, 2955, 1580, 1494, 1450, 1412, 1356, 1248, 1240, 1205 cm$^{-1}$. $^1$H-NMR (DMSO-$d_6$) δ: 0.60-0.69 (4H, m), 1.49-1.54 (1H, m), 2.80 (2H, t, *J*=7.4 Hz), 3.32 (2H, td, *J*=7.4, 6.1 Hz, collapsed to t, *J*=7.4 Hz, on addition of $D_2O$), 6.98 (1H, ddd, *J*=8.1, 7.1, 1.0 Hz), 7.13 (1H, ddd, *J*=8.1, 7.1, 1.0 Hz), 7.25 (1H, s), 7.32 (1H, dt, *J*=8.1, 1.0 Hz), 7.53 (1H, dt, *J*=8.1, 1.0 Hz), 8.15 (1H, br t, *J*=6.1 Hz, disappeared on addition of $D_2O$), 11.03 (1H, br s, disappeared on addition of $D_2O$). *Anal*. Calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.84; H, 6.57; N, 11.45.

***N*$_b$-Cyclohexanecarbonyl-1-hydroxytryptamine** (**9f**) **from 8f** - In the general procedure for the

synthesis of **9a**, 30% aqueous $H_2O_2$ (1.91 g, 16.8 mmol), MeOH (5 mL), **8f** (457.3 mg, 1.68 mmol), $Na_2WO_4 \cdot 2H_2O$ (112.7 mg, 0.34 mmol), MeOH (20 mL), and $H_2O$ (2.5 mL) were used. After the work-up and column chromatography with EtOAc–hexane (2:3, v/v), **9f** (297.9 mg, 62%) was obtained. **9f**: mp 138.5-140 °C (colorless fine needles, recrystallized from EtOAc–hexane). IR (KBr): 2940, 1628, 1535, 1448, 1368 $cm^{-1}$. $^1$H-NMR (DMSO-$d_6$) δ: 1.09-1.24 (3H, m), 1.28-1.36 (2H, m), 1.59-1.71 (5H, m), 2.06 (1H, tt, *J*=11.7, 3.4 Hz), 2.77 (2H, t, *J*=7.3 Hz), 3.28 (2H, br q, *J*=7.3 Hz, collapsed to t, *J*=7.3 Hz, on addition of $D_2O$), 6.98 (1H, t, *J*=8.0 Hz), 7.12 (1H, t, *J*=8.0 Hz), 7.22 (1H, s), 7.31 (1H, d, *J*=8.0 Hz), 7.53 (1H, d, *J*=8.0 Hz), 7.77 (1H, br t, *J*=6.1 Hz, disappeared on addition of $D_2O$), 11.01 (1H, s, disappeared on addition of $D_2O$). *Anal*. Calcd for $C_{17}H_{22}N_2O_2$: C, 71.30; H, 7.74; N, 9.78. Found: C, 71.33; H, 7.79; N, 9.75.

***N*$_b$-2-Furancarbonyl-1-hydroxytryptamine** (**9g**) **from 8g** - In the general procedure for the synthesis of **9a**, 30% aqueous $H_2O_2$ (2.94 g, 25.9 mmol), MeOH (5 mL), **8g** (696.9 mg, 2.58 mmol), $Na_2WO_4 \cdot 2H_2O$ (171.0 mg, 0.52 mmol), MeOH (25 mL), and $H_2O$ (3 mL) were used. After the work-up and column chromatography with EtOAc–hexane (1:1, v/v), **9g** (467.2 mg, 64%) was obtained. **9g**: mp 167-168 °C (decomp., colorless fine needles, recrystallized from $CHCl_3$–hexane). IR (KBr): 3680, 3120, 2950, 1628, 1598, 1531, 1317, 1187 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) δ: 2.90 (2H, t, *J*=7.5 Hz), 3.49 (2H, td, *J*=7.5, 6.1 Hz, collapsed to t, *J*=7.5 Hz, on addition of $D_2O$), 6.60 (1H, dd, *J*=3.4, 2.0 Hz), 6.98 (1H, ddd, *J*=8.0, 7.0, 1.0 Hz), 7.06 (1H, dd, *J*=3.4, 0.7 Hz), 7.13 (1H, ddd, *J*=8.0, 7.0, 1.0 Hz), 7.28 (1H, s), 7.32 (1H, d, *J*=8.0 Hz), 7.57 (1H, d, *J*=8.0 Hz), 7.80 (1H, dd, *J*=2.0, 0.7 Hz), 8.45 (1H, br t, *J*=6.1 Hz, disappeared on addition of $D_2O$), 11.02 (1H, s, disappeared on addition of $D_2O$). *Anal*. Calcd for $C_{15}H_{14}N_2O_3$: C, 66.65; H, 5.22; N, 10.37. Found: C, 66.63; H, 5.21; N, 10.36.

## REFERENCES AND NOTES


1. This report is part 135 of a series entitled “The Chemistry of Indoles.” Part 134: K. Yamada, F. Yamada, T. Shiraishi, S. Tomioka, and M. Somei, *Heterocycles*, 2009, **77**, 971.
2. J. Cartledge and I. Eardley, *Expert Opin. Pharmacother*., 1999, **1**, 137; K. Shigenobu, *Chemistry*, 2005, **60**, 14.
3. L. E. Saxton, The Alkaloids, Vol. 7, ed. by R. H. F. Manske, Academic Press, USA, 1960, pp. 1-199, 1960; E. Ernst and M. H. Pittler, *J. Urol.*, 1998, **159**, 433.
4. M. Somei, T. Iwaki, F. Yamada, Y. Tanaka, K. Shigenobu, K. Koike, N. Suzuki, and A. Hattori, *Heterocycles*, 2006, **68**, 1565.
5. a) M. Somei and T. Kawasaki, *Heterocycles*, 1989, **29**, 1251. b) M. Somei, *J. Synth. Org. Chem.*, 1991, **49**, 205. c) M. Somei, *Heterocycles*, 1999, **50**, 1157. d) M. Somei, Advances in Heterocyclic Chemistry, Vol. 82, ed. by A. R. Katritzky, Elsevier Science, USA, 2002, pp. 101-155. e) M. Somei,

Topics in Heterocyclic Chemistry, Vol. 6, ed. by S. Eguchi, Springer-Verlag, Berlin, 2006, pp. 77-111. f) M. Somei, *Yakugaku Zasshi*, 2008, **128**, 527.

6. M. Somei, K. Yamada, M. Hasegawa, M. Tabata, Y. Nagahama, H. Morikawa, and F. Yamada, *Heterocycles*, 1996, **43**, 1855.
7. M. Somei, JP Patent, 3795093 (2006).
8. M. Somei, K. Shigenobu, and Y. Tanaka, JP Patent, 3964417 (2007).