Antinociceptive Effects of 1-Acyl-4-dialkylaminopiperidine and 1-Alkyl-4-dialkylaminopiperidine in Mice: Structure–Activity Relation Study of Matrine-Type Alkaloids

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We previously reported that (+)-matrine and (+)-allomatrine have antinociceptive properties mediated mainly through the activation of κ-opioid receptors. 1-Acyl-4-dialkylaminopiperidines were synthesized as the simplest derivatives of matrine, and the structure–activity relations were examined by the acetic acid-induced abdominal contraction test. The antinociceptive potencies of 1-alkyl-4-dialkylaminopiperidines were significantly lower than those of the corresponding 1-acyl-4-dialkylaminopiperidines. These findings suggest that the amide group of (+)-matrine is an essential functional group that influences antinociceptive potency.

Key words structure activity relationship; antinociception; matrine

We previously reported that a typical matrine-type lupine alkaloid, (+)-matrine (**1**), produced by some *Sophora* plants (Leguminosae) has antinociceptive properties that are identical to those of pentazocine, which are mediated mainly through activation of κ-opioid receptors and partially through μ-opioid receptors.[1] (+)-allomatrine (**2**), which is the C-6 epimer of (**1**), also has antinociceptive properties, although they are one-third the potency of those of (**1**). The effects of (+)-allomatrine are mediated only through activation of κ-opioid receptors.[2] The structure–activity relation of this antinociceptive effect was of interest, because the structure of the matrine-type alkaloids differs from those of conventional κ-opioid receptor agonists, such as ethylketocyclazocine, U-50488[3,4] and TRK-820[5] (Chart 1). The matrine-type alkaloids may serve as new κ-opioid receptor agonists that are more selective and without undesirable morphine-like side effects.

The 1-acyl-4-dialkylaminopiperidine compounds **3a**—**c** and **4a**—**c** were synthesized as the simplest derivatives of the matrine-type alkaloids, including the amide and tertiary amine groups that were thought to the pharmacophore for the antinociceptive effect. Furthermore, 1-alkyl-4-dialkylamionopiperidine compounds **5a**—**c** and **6a**—**c** were prepared easily from **3a**—**c** and **4a**—**c**, respectively (Chart 2). The antinociceptive effects of these compounds were examined with the acetic acid-induced abdominal contraction test (writhing test) to determine the structure–activity relations.

Synthesis Synthesis of the 1-acyl-4-dialkylaminopiperidines **3a**—**c** and **4a**—**c** was accomplished in short steps. They were prepared easily from **3a**—**c** and **4a**—**c**, respectively. Protected piperidine **7** was acylated with acetic anhydride (**8a**: R=Me, 99%), pentanoyl chloride (**8b**: R=Bu, 93%), and benzoyl chloride (**8c**: R=Ph, 99%) in the presence of triethylamine and 4-dimethylaminopyridine. Acidic deprotection of amides in compounds **8a**—**c** with 5% HCl in MeOH yielded ketones **9a**—**c** (70 to 99% yield). The reductive amination[6] of ketones **9a**—**c** with dimethylamine hydrochloride in the presence of $NaBH_3CN$ (pH 6) yielded 1-acyl-4-dimethylaminopiperidines **3a**—**c** (45 to 56% yield) (Chart 3). Ketones **9a**—**c** were aminated with dibutylamine in benzene followed by reduction with $NaBH_4$ in EtOH to yield 1-acyl-4-dibutylaminopiperidines **4a**—**c** with 58% to 85% yield. Amides **3a**—**c** and **4a**—**c** were reduced by $LiAlH_4$ in tetrahydrofuran (THF) to yield 1-alkyl-4-dibutylaminopiperidines **5a**—**c** and **6a**—**c** with 71% to 90% yield (Chart 4).

Animals and Drugs Male ICR mice (Tokyo Laboratory Animals Science, Tokyo, Japan), weighing approximately 30—35 g (6 weeks old) were used. Animals were housed in groups of 10 and had free access to food and water in an animal room that was maintained at 24±1 °C with a 12 h light–dark cycle (lights on 8 : 00 a.m.).

Acetic acid was purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan). All test compounds were dis-

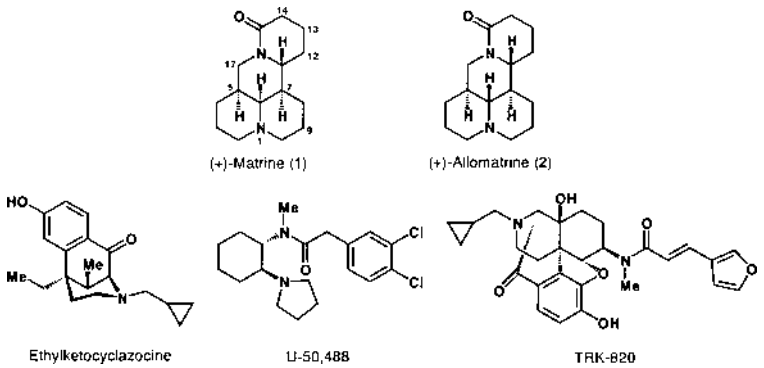

Chart 1

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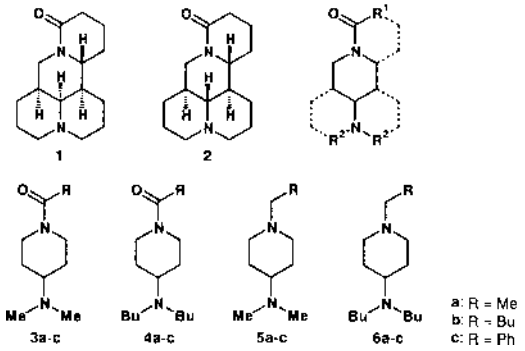
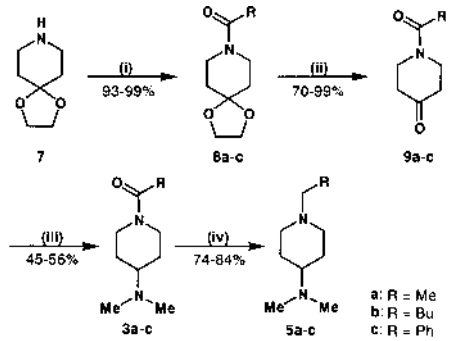
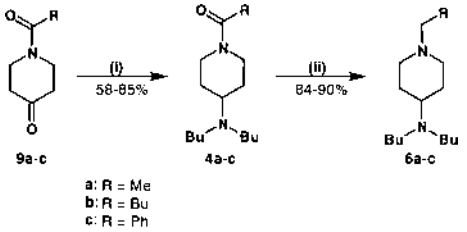


Chart 2



Reagents and reaction conditions; (i) $(RCO)_2O$ (R=Me) or RCOCl (R=Bu, Ph), Et_3N, DMAP, CH_2Cl_2, 0°, 1 h; (ii) HCl/MeOH (1 : 1, v/v), rt, 19—53 h; (iii) $Me_2NH \cdot HCl$, $NaBH_3CN$, EtOH, molecular sieves 3 Å, rt, 96 h; (iv) $LiAlH_4$, THF, reflux, 2 h.

Chart 3



Reagents and reaction conditions; (i) Bu_2NH, benzene, TsOH, reflux, 24 h; NaBH4, EtOH, rt, 1 h; (ii) $LiAlH_4$, THF, reflux, 2 h.

Chart 4

solved in saline or suspended in 0.5% carboxymethyl cellulose sodium salt (CMC). In the control group each mouse was injected with saline or 0.5% CMC in a volume of 10 ml/kg.

Acetic Acid-Induced Abdominal Contraction Assay (Writhing Test) Each mouse was injected i.p. with 0.7% acetic acid in a volume of 10 ml/kg 30 min after administration of the test drugs (10—100 mg/kg). After 10 min the animals were observed for an additional 10 min during which abdominal contractions were counted. The number of contractions in each test period was normalized to the mean number from the control group. The percent antinociception was expressed as: 100×(mean control responses−test responses)/(mean control responses).

Data Analysis All data are expressed as means±S.E. The statistical significance of differences between groups was assessed with analysis of variance followed by the Bonferroni–Dunn test. The ED_{50} values and 95% confidence intervals for the antinociceptive effects of compounds **3a**—**c** and **4a**—**c** were determined by linear regression techniques.

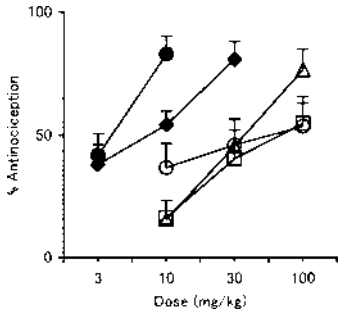


Fig. 1. Dose–Response Lines for the Antinociceptive Effect of s.c. Administration of (+)-Matrine **1** (●), (+)-Allomatrine **2** (◆), **3a** (○), **3b** (△), **3c** (□) in the Acid-Induced Abdominal Contraction Assay in Mice

Each point represents the mean±S.E. of 10 mice.

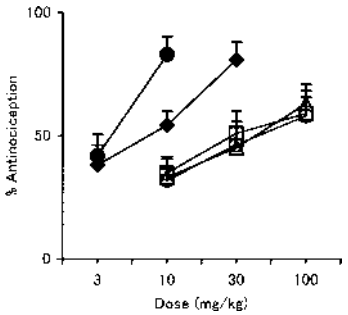


Fig. 2. Dose–Response Lines for the Antinociceptive Effect of s.c. Administration of (+)-Matrine **1** (●), (+)-Allomatrine **2** (◆), **4a** (○), **4b** (△), **4c** (□) in the Acid-Induced Abdominal Contraction Assay in Mice

Each point represents the mean±S.E. of 10 mice.

RESULTS

As shown in Fig. 1, compounds **3a**, **3b**, and **3c** (doses of 10—100 mg/kg, s.c.) produced dose-dependent inhibition of the writhing response in mice. The ED_{50} values (mg with 95% confidence intervals) were 69.7 mg (−148.7 to 288.1 mg) for **3a**, 52.6 mg (−93.7 to 198.9 mg) for **3b**, and 74.5 mg (−201.0 to 349.9 mg) for **3c**, respectively. As shown in Fig. 2, compounds **4a**, **4b**, and **4c** (doses of 10—100 mg/kg, s.c.) produced dose-dependent inhibition of the writhing response in mice. The ED_{50} values were 62.1 mg (−129.9 to 254.1 mg) for **4a**, 55.5 mg (−42.7 to 153.6 mg) for **4b**, and 52.5 mg (−184.9 to 290.0 mg) for **4c**, respectively. As above, all drugs with the amide group produced dose-dependent inhibition of the writhing response in mice.

In contrast, as shown in Figs. 3A and B, the antinociceptive potencies of **5a**—**c** and **6a**—**c** (100 mg/kg) were significantly lower than those of the corresponding amides **3a**—**c** and **4a**—**c**, respectively.

DISCUSSION

These experiments showed that 1-acyl-4-dialkylaminopiperidines **3a**—**c** and **4a**—**c**, which include the amide groups, produce dose-dependent antinociception in mice. The antinociceptive effects of **3a**—**c** and **4a**—**c** were approximately 2.5 times greater than those of **5a**—**c** and **6a**—**c**, respective-

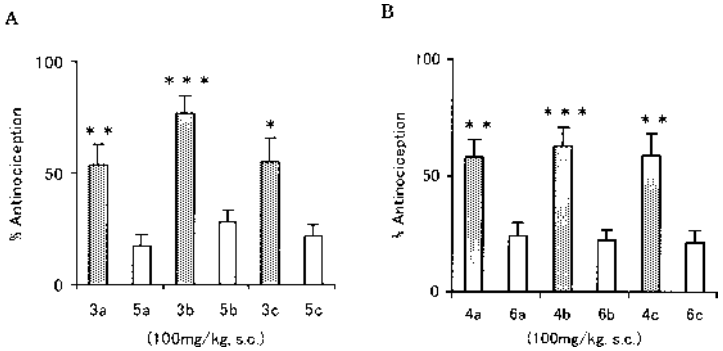


Fig. 3. (A) The Antinociceptive Effect of s.c. Administration of Amide Compounds **3a**—**c** in the Acid-Induced Abdominal Contraction Assay in Mice

*** $p<0.001$, ** $p<0.01$, * $p<0.05$ *versus* the corresponding amine compounds **5a**—**c**, respectively. Each column represents the mean±S.E. of 10 mice in each group.

(B) The Antinociceptive Effect of s.c. Administration of Amine Compounds **4a**—**c** in the Acid-Induced Abdominal Contraction Assay in Mice

*** $p<0.001$, ** $p<0.01$ *versus* the corresponding amine compounds **6a**—**c**, respectively. Each column represents the mean±S.E. of 10 mice in each group.

ly. These findings indicate that the amide group of (+)-matrine (**1**) is essential for antinociceptive potency. Development of matrine derivatives with greater potencies may be possible by further improvement of the lipophilicity through an acyl group and a less hindered tertiary amino group, because the antinociceptive potency of compound **3b**, which contains pentanoyl and dimethylamino groups, was greater than that of the other synthesized compounds. We obtained information in this study on structure–activity relations, but we failed to identify any compound with an antinociceptive potency greater than (**1**).

MATERIALS AND METHODS

General High resolution MS (HR-MS) were measured at 70 eV using a direct inlet system on a JEOL D300 spectrometer. ^{1}H- (270 MHz) and ^{13}C-NMR (67.8 MHz) spectra were recorded using tetramethylsilane (TMS) as an internal standard with a JEOL JNM-LA270 spectrometer. Column chromatography was carried out on Silica gel 60 (100—210 μm, Kanto Chemical Co., Inc.), Wako gel C-300 (45—75 μm, Wako Pure Chemical Industries, Ltd.), and Lichrospher Si 60 (40—63 μm, Merck).

1-(1,4-Dioxa-8-azaspiro[4.5]dec-8-yl)ethanone, 8a To a solution of the amine **7** (3.00 g, 20.95 mmol), triethylamine (9.40 ml, 62.83 mmol) and dimethylaminopyridine (DMAP) (0.26 g, 2.13 mmol) in CH_2Cl_2 (20 ml), cooled to 0 °C under nitrogen ,was added the acetic anhydride (3.00 ml, 31.74 mmol). The reaction mixture was stirred at 0 °C for 1 h. Then 10% NaOH was added, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The organic layer was washed with 10% HCl, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (ethyl acetate) and gave **8a** as colorless oil (3.85 g, 99%). ^{1}H-NMR ($CDCl_3$) δ: 1.65—1.73 (4H, m), 2.11 (3H, s), 3.53 (2H, ddm, J=5.8, 5.8 Hz), 3.69 (2H, ddm, J=5.8, 5.8 Hz), 3.98 (4H, s). ^{13}C-NMR ($CDCl_3$) δ: 21.3, 34.5, 35.4, 39.4, 44.3, 64.4, 106.7, 168.7. HR-MS *m/z*: 185.1061 (Calcd for $C_9H_{15}NO_3$ 185.1052).

1-(1,4-Dioxa-8-azaspiro[4.5]dec-8-yl)pentan-1-one, 8b As described for the preparation of **8a**, the amine **7** (3.06 g, 21.37 mmol) was acylated with pentanoyl chloride (3.80 ml, 32.01 mmol), DMAP (0.26 g, 2.13 mmol), and triethylamine (8.9 ml, 64.30 mmol) in CH_2C1_2 (20 ml), and purified by silica gel column chromatography (ethyl acetate/*n*-hexane 1 : 1): colorless oil, yield 4.51 g (93%); ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, t, J=7.3 Hz), 1.30—1.43 (2H, m), 1.55—1.72 (8H, m), 2.34 (2H, dd, J=7.7, 7.7 Hz), 3.53 (2H, ddm, J=5.8, 5.8 Hz), 3.69 (2H, ddm, J=5.8, 5.8 Hz), 3.98 (4H, s). ^{13}C-NMR ($CDCl_3$) δ: 22.4, 27.3, 32.9, 34.6, 35.5, 39.5, 43.4, 64.3, 106.8, 171.3. HR-MS *m/z*: 227.1516 (Calcd for $C_{12}H_{21}NO_3$ 227.1521).

(1,4-Dioxa-8-azaspiro[4.5]dec-8-yl)phenylmethanone, 8c As described for the preparation of **8a**, the amine **7** (1.30 g, 9.08 mmol) was acylated with benzoyl chloride (1.58 ml, 13.59 mmol), DMAP (0.11 g, 0.90 mmol), and triethylamine (3.80 ml, 27.37 mmol) in CH_2C1_2 (10 ml), and purified by silica gel column chromatography (ethyl acetate): colorless oil, yield 2.23 g (99%); ^{1}H-NMR (DMSO-d_6, 80 °C) δ: 1.55 (2H, dd, J=5.8, 5.8 Hz), 3.42 (2H, dd, J=5.8, 5.8 Hz), 3.81 (4H, s), 7.26—7.37 (5H, aromatic). ^{13}C-NMR ($CDCl_3$) δ: 34.8, 35.6, 40.2, 45.7, 64.4, 106.9, 126.7, 128.4, 129.5, 135.9, 170.3. HR-MS *m/z*: 247.1233 (Calcd for $C_{14}H_{17}NO_3$ 247.1208).

1-Acetylpiperidin-4-one, 9a To a solution of the amide **8a** (3.83 g, 20.68 mmol), 5% HCl (10 ml) in MeOH (10 ml) was added and the mixture was stirred at room temperature for 19 h. The reaction mixture was evaporated, and the aqueous layer was extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (ethyl acetate), to give **9a** as colorless oil (2.04 g, 70%). ^{1}H-NMR ($CDCl_3$) δ: 2.20 (3H, s), 2.48 (2H, dd, J=7.0, 7.0 Hz), 2.50 (2H, dd, J=7.0, 7.0 Hz), 3.78 (2H, dd, J=6.2, 6.2 Hz), 3.89 (2H, dd, J=6.2, 6.2 Hz). ^{13}C-NMR ($CDCl_3$) δ: 21.3, 40.6, 40.8, 41.2, 44.9, 169.2, 206.6. HR-MS *m/z*: 141.0800 (Calcd for $C_7H_{11}NO_2$ 141.0790).

1-Pentanoylpiperidin-4-one, 9b As described for the preparation of **9a**, the amide **8b** (4.51 g, 19.84 mmol) was deprotected with 5% HCl (10 ml) in MeOH (10 ml) for 53 h, and purified by silica gel column chromatography (ethyl acetate): colorless oil, yield 3.20 g (88%); ^{1}H-NMR ($CDCl_3$) δ: 0.95 (3H, t, J=7.3 Hz), 1.33—1.47 (2H, m), 1.60—1.71 (2H, m), 2.40—2.52 (6H, m), 3.78 (2H, dd, J=6.2, 6.2 Hz), 3.89 (2H, dd, J=6.2, 6.2 Hz). ^{13}C-NMR ($CDCl_3$) δ: 13.7, 22.4, 27.2, 32.8, 40.6, 40.7, 41.1, 44.0, 64.3, 171.9, 206.8. HR-MS

m/z: 183.1281 (Calcd for $C_{10}H_{17}NO_2$ 183.1259).

1-Benzoylpiperidin-4-one, 9c As described for the preparation of **9a**, the amide **8c** (2.23 g, 9.02 mmol) was deprotected with 5% HCl (5 ml) in MeOH (5 ml) for 50 h, and purified by silica gel column chromatography (ethyl acetate): pale yellow oil, yield 1.83 g (99%); ^{1}H-NMR (DMSO-d_6, 80 °C) δ: 2.34 (2H, dd, J=6.2, 6.2 Hz), 3.65 (2H, dd, J=6.2, 6.2 Hz), 7.26—7.37 (5H, aromatic). ^{13}C-NMR ($CDCl_3$) δ: 41.1, 64.4, 106.8, 126.8, 128.6, 130.1, 135.0, 170.8, 206.6. HR-MS *m/z*: 203.0916 (Calcd for $C_{12}H_{13}NO_2$ 203.0946).

1-(4-Dimethylaminopiperidin-1-yl)ethanone, 3a To a solution of the ketone **9a** (1.08 g, 7.65 mmol) in EtOH (13 ml) was successively added dimethylamine hydrochloride (1.35 g, 16.55 mmol), 3 Å molecular sieves, and $NaBH_3CN$ (0.80 g, 12.73 mmol). To the reaction mixture HCl/EtOH was added until pH 6 and stirred for 96 h at room temperature. Then it was evaporated, water (5 ml) and CH_2Cl_2 (10 ml) were added, the suspension was filtered, and the filtrate was washed with a saturated solution of NaOH and NaCl, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH/NH_4OHaq 70 : 9 : 1), to give **3a** as colorless oil (0.69 g, 53%). ^{1}H-NMR ($CDCl_3$) δ: 1.34 (2H, dddd, J=12.0, 12.0, 11.2, 4.3 Hz), 1.76—1.85 (2H, m), 2.04 (3H, s), 2.23 (6H, s), 2.29 (1H, dddd, J=11.2, 11.2, 3.7, 3.7 Hz), 2.53 (1H, ddd, J=12.0, 12.0, 2.3 Hz), 3.00 (1H, ddd, J=12.0, 12.0, 2.2 Hz), 3.79 (1H, ddm, J=13.5, 2.6 Hz), 4.57 (1H, ddm, J=13.3, 1.4 Hz). ^{13}C-NMR ($CDCl_3$) δ: 21.3, 27.7, 29.0, 40.7, 41.5, 45.5, 61.9, 168.6. HR-MS *m/z*: 170.1374 (Calcd for $C_9H_{18}N_2O$ 170.1419).

1-(4-Dimethylaminopiperidin-1-yl)pentan-1-one, 3b As described for the preparation of **3a**, the ketone **9b** (0.66 g, 3.60 mmol) was reductively aminated with dimethylamine hydrochloride (0.73 g, 9.00 mmol), $NaBH_3CN$ (0.23 g, 3.66 mmol), and purified by silica gel column chromatography (CH_2Cl_2/MeOH/NH_4OHaq 90 : 9 : 1): colorless oil, yield 425 mg (56%); ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, t, J=7.4 Hz), 1.30—1.43 (4H, m), 1.55—1.66 (2H, m), 1.74—1.90 (4H, m), 2.28 (6H, s), 2.30—2.40 (3H, m), 2.56 (1H, ddd, J=12.8, 12.8, 2.6 Hz), 3.01 (1H, ddd, J=12.9, 12.9, 2.6 Hz), 3.90 (1H, dm, J=13.5 Hz), 4.64 (1H, dm, J=13.9 Hz). ^{13}C-NMR ($CDCl_3$) δ: 13.7, 22.4, 27.4, 27.9, 29.1, 33.0, 40.7, 41.5, 44.8, 62.0, 171.3. HR-MS *m/z*: 212.1915 (Calcd for $C_{12}H_{24}N_2O$ 212.1889).

(4-Dimethylaminopiperidin-1-yl)phenylmethanone, 3c As described for the preparation of **3a**, the ketone **9c** (1.96 g, 9.64 mmol) was reductively aminated with dimethylamine hydrochloride (1.96 g, 24.00 mmol), $NaBH_3CN$ (0.61 g, 9.71 mmol), and purified by silica gel column chromatography (CH_2Cl_2/MeOH/NH_4OHaq 90 : 9 : 1): colorless oil, yield 1.00 g (45%); ^{1}H-NMR (DMSO-d_6, 80 °C) δ: 1.17—1.32 (2H, m), 1.65 (2H, dm, 14.3 Hz), 2.09 (3H, m), 2.24 (1H, dddd, J=10.7, 10.7, 3.8, 3.8 Hz), 2.82 (1H, ddd, J=11.1, 11.1, 2.8 Hz), 3.89 (1H, Br), 7.22—7.37 (5H, aromatic). ^{13}C-NMR ($CDCl_3$) δ: 41.6, 61.9, 126.6, 128.3, 129.4, 136.0, 170.0. HR-MS *m/z*: 232.1605 (Calcd for $C_{14}H_{20}N_2O$ 232.1575).

1-(4-Dibutylaminopiperidin-1-yl)ethanone, 4a To a solution of the ketone **9a** (0.90 g, 6.34 mmol), dibutylamine (0.98 g, 7.58 mmol) and *p*-toluenesulfonic acid monohydrate ($TsOH\cdot H_2O$) (0.12 g, 0.63 mmol) in benzene (10 ml) was added and the mixture was then refluxed with Dean–Stark for 24 h. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in EtOH (6 ml), $NaBH_4$ (0.24 g, 6.34 mmol) was slowly added and stirred at room temperature for 1 h. Then it was evaporated, water (5 ml) and CH_2Cl_2 (20 ml) were added, the suspension was filtered, and the filtrate was washed with a saturated solution of NaOH and NaCl, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH/NH_4OHaq 90 : 9 : 1), to give **4a** as colorless oil (1.37 g, 85%). ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, t, J=7.3 Hz), 1.22—1.48 (10H, m), 1.71—1.80 (2H, m), 2.09 (3H, m), 2.41 (4H, dd, J=7.3, 7.3 Hz), 2.48 (1H, ddd, J=12.9, 12.9, 2.6 Hz), 2.68 (1H, dddd, J=11.5, 11.5, 3.6, 3.6 Hz), 3.00 (1H, ddd, J=13.0, 13.0, 2.6 Hz), 3.85 (1H, dm, J=13.3 Hz), 4.67 (1H, dm, J=13.2 Hz). ^{13}C-NMR ($CDCl_3$) δ: 13.9, 20.4, 21.3, 27.7, 28.9, 31.1, 41.4, 46.2, 50.1, 58.2, 168.5. HR-MS *m/z*: 254.2380 (Calcd for $C_{15}H_{30}N_2O$ 254.2358).

1-(4-Dibutylaminopiperidin-1-yl)pentan-1-one, 4b As described for the preparation of **4a**, the ketone **9b** (0.80 g, 4.37 mmol) was reductively aminated with dibutylamine (0.69 g, 5.34 mmol), $NaBH_4$ (0.17 g, 4.49 mmol), and purified by silica gel column chromatography (CH_2Cl_2/MeOH/NH_4OHaq 140 : 9 : 1): colorless oil, yield 1.01 g (78%); ^{1}H-NMR ($CDCl_3$) δ: 0.92 (9H, dt, J=6.9, 7.0 Hz), 1.22—1.46 (12H, m), 1.55—1.67 (2H, m), 1.70—1.81 (2H, m), 2.33 (2H, dd, J=7.7, 7.7 Hz), 2.41 (4H, dd, J=7.3, 7.3 Hz), 2.47 (1H, ddd, J=12.8, 12.8, 2.6 Hz), 2.68 (1H, dddd, J=11.5, 11.5, 3.6, 3.6 Hz), 2.97 (1H, ddd, J=13.0, 13.0, 2.2 Hz), 3.89 (1H, dm, J=11.2 Hz), 4.67 (1H, dm, J=11.2 Hz). ^{13}C-NMR ($CDCl_3$) δ: 13.6, 13.7, 13.8, 20.2, 20.3, 22.2, 22.3, 27.2, 27.3, 27.7, 28.9, 30.9, 32.8, 41.3, 45.3, 29.9, 58.1, 171.0. HR-MS *m/z*: 296.2827 (Calcd for $C_{18}H_{36}N_2O$ 296.2828).

(4-Dibutylaminopiperidin-1-yl)phenylmethanone, 4c As described for the preparation of **4a**, the ketone **9c** (0.87 g, 4.28 mmol) was reductively aminated with dibutylamine (0.67 g, 5.18 mmol), $NaBH_4$ (0.17 g, 4.49 mmol), and purified by silica gel column chromatography (CH_2Cl_2/MeOH/NH_4OHaq 140 : 9 : 1): colorless oil, yield 0.79 g (58%); ^{1}H-NMR (DMSO-d_6, 80 °C) δ: 0.78 (6H, t, J=7.1 Hz), 1.12—1.34 (10H, m), 1.57 (2H, dm, J=12.5 Hz), 2.33 (4H, t, J=6.9 Hz), 2.61 (1H, dddd, J=11.3, 11.3, 3.6, 3.6 Hz), 2.76 (1H, dd, J=12.0, 12.0 Hz), 3.95 (2H, Br), 7.23—7.36 (5H, aromatic). ^{13}C-NMR ($CDCl_3$) δ: 13.9, 14.0, 20.4, 20.4, 28.0, 28.9, 30.9, 50.1, 50.2, 58.2, 58.3, 126.7, 128.2, 129.3, 136.1, 170.0. HR-MS *m/z*: 316.2532 (Calcd for $C_{20}H_{32}N_2O$ 316.2515).

(4-Dimethylaminopiperidin-1-yl)ethane, 5a To a solution of lithium aluminum hydride ($LiAlH_4$) (0.23 g, 6.06 mmol) in THF (3 ml) was added the solution of **3a** (676 mg, 3.97 mmol) in THF (2 ml), and then refluxed under nitrogen atmosphere for 2 h. The reaction mixture was quenched with water, and the solvent was evaporated. The residue was dissolved in CH_2Cl_2, washed with saturated K_2CO_3 and brine, dried over Na_2SO_4, and the solvent was evaporated. The residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH/NH_4OHaq 50 : 9 : 1) to give **5a** as colorless oil (456 mg, 74%). ^{1}H-NMR ($CDCl_3$) δ: 1.08 (3H, t, J=7.2 Hz), 1.52 (1H, ddd, J=11.9, 11.3, 3.6 Hz), 1.57 (1H, ddd, J=11.9, 11.3, 2.4 Hz), 1.77—1.93 (4H, m), 2.15 (1H,

dddd, J=11.3, 11.3, 3.8, 3.8 Hz), 2.28 (6H, s), 2.38 (2H, q, J=7.2 Hz), 3.01 (2H, dm, J=11.9 Hz). ^{13}C-NMR ($CDCl_3$) δ: 12.2, 28.0, 41.5, 52.2, 52.7, 62.3. HR-MS *m/z*: 157.1609 (Calcd for $C_9H_{21}N_2$ 157.1705).

(4-Dimethylaminopiperidin-1-yl)pentane, 5b As described for the preparation of **5a**, the amide **3b** (0.20 g, 0.94 mmol) was reduced with $LiAlH_4$ (0.04 g, 1.05 mmol), and purified by silica gel column chromatography (CH_2Cl_2/MeOH/NH_4OHaq 90 : 9 : 1): colorless oil, yield 0.16 g (81%); ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, t, J=6.9 Hz), 1.21—1.40 (4H, m), 1.44—1.65 (4H, m), 1.79 (2H, dm, J=10.7 Hz), 1.90 (2H, ddm, J=11.7, 11.7 Hz), 2.14 (1H, dddd, J=11.3, 11.3, 3.7, 3.7 Hz), 2.27 (6H, s), 2.29—2.33 (2H, m), 2.98 (2H, dm, J=10.9 Hz). ^{13}C-NMR ($CDCl_3$) δ: 13.8, 22.4, 26.7, 28.0, 29.7, 41.4, 53.0, 58.6, 62.1. HR-MS *m/z*: 198.2097 (Calcd for $C_{12}H_{26}N_2$ 198.2096).

(1-Benzylpiperidin-4-yl)dimethylamine, 5c As described for the preparation of **5a**, the amide **3c** (0.49 g, 2.12 mmol) was reduced with $LiAlH_4$ (97 mg, 2.56 mmol), and purified by silica gel column chromatography (CH_2Cl_2/MeOH/NH_4OHaq 90 : 9 : 1): colorless oil, yield 0.41 g (84%); ^{1}H-NMR ($CDCl_3$) δ: 1.48 (2H, m), 1.71 (2H, dm, J=12.4 Hz), 1.90 (2H, ddm, J=11.7, 11.7 Hz), 2.07 (1H, dddd, J=11.3, 11.3, 3.4, 3.4 Hz), 2.21 (6H, s), 2.87 (2H, dm, J=11.7 Hz), 3.43 (2H, s), 7.15—7.26 (5H, aromatic). ^{13}C-NMR ($CDCl_3$) δ: 28.2, 41.6, 52.9, 62.2, 63.0, 126.8, 128.0, 128.9, 138.4. HR-MS *m/z*: 218.1793 (Calcd for $C_{14}H_{22}N_2$ 218.1783).

(1-Ethylpiperidin-4-yl)dibutylamine, 6a As described for the preparation of **5a**, the amide **4a** (0.77 g, 3.03 mmol) was reduced with $LiAlH_4$ (0.18 g, 4.74 mmol), and purified by silica gel column chromatography (CH_2Cl_2/MeOH/NH_4OHaq 90 : 9 : 1): colorless oil, yield 0.69 g (90%); ^{1}H-NMR ($CDCl_3$) δ: 0.90 (6H, t, J=7.1 Hz), 1.07 (3H, t, J=7.2 Hz), 1.21—1.44 (8H, m), 1.58 (2H, dddd, J=12.0, 12.0, 10.4, 3.5 Hz), 1.70 (2H, dm, J=10.4 Hz), 1.86 (2H, ddd, J=11.7, 11.7, 2.1 Hz), 2.33—2.53 (7H, m), 3.00 (2H, dm, J=11.7 Hz). ^{13}C-NMR ($CDCl_3$) δ: 12.13, 13.94, 20.52, 27.95, 31.29, 50.36, 52.2, 53.3, 58.6. HR-MS *m/z*: 240.2572 (Calcd for $C_{15}H_{32}N_2$ 240.2565).

(4-Dibutylaminopiperidin-1-yl)pentane, 6b As described for the preparation of **5a**, the amide **4b** (0.25 g, 0.857 mmol) was reduced with $LiAlH_4$ (42 mg, 1.11 mmol), and purified by silica gel column chromatography (CH_2Cl_2/MeOH/NH_4OHaq 90 : 9 : 1): colorless oil, yield 0.23 g (89%); ^{1}H-NMR ($CDCl_3$) δ: 0.90 (9H, t, J=7.2 Hz), 1.19—1.63 (16H, m), 1.69 (2H, dm, J=10.9 Hz), 1.86 (2H, ddd, J=11.7, 11.7, 2.4 Hz), 2.28 (2H, dd, J=7.9, 7.9 Hz), 2.40—2.52 (5H, m), 3.00 (2H, dm, J=11.7 Hz). ^{13}C-NMR ($CDCl_3$) δ: 13.9, 14.0, 20.6, 22.5, 26.8, 28.0, 29.8, 31.3, 50.4, 53.8, 58.6, 58.9. HR-MS *m/z*: 282.3052 (Calcd for $C_{18}H_{38}N_2$ 282.3035).

(1-Benzylpiperidin-4-yl)dimethylamine, 6c As described for the preparation of **5a**, the amide **4c** (0.49 g, 2.12 mmol) was reduced with $LiAlH_4$ (97 mg, 2.56 mmol), and purified by silica gel column chromatography (CH_2Cl_2/MeOH/NH_4OHaq 90 : 9 : 1): colorless oil, yield 0.41 g (84%); ^{1}H-NMR ($CDCl_3$) δ: 1.48 (2H, m), 1.71 (2H, dm, J=12.4 Hz), 1.90 (2H, ddm, J=11.7, 11.7 Hz), 2.07 (1H, dddd, J=11.3, 11.3, 3.4, 3.4 Hz), 2.21 (6H, s), 2.87 (2H, dm, J=11.7 Hz), 3.43 (2H, s), 7.15—7.26 (5H, aromatic). ^{13}C-NMR ($CDCl_3$) δ: 28.2, 41.6, 52.9, 62.2, 63.0, 126.8, 128.0, 128.9, 138.4. HR-MS *m/z*: 218.1793 (Calcd for $C_{14}H_{22}N_2$ 218.1783).

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REFERENCES

1) Kamei J., Xiao P., Ohsawa M., Kubo H., Higashiyama K., Takahashi H., Li J.-S., Nagase H., Ohmiya S., *Eur. J. Pharmacol.*, **337**, 223—226 (1997).
2) Xiao P., Kubo H., Ohsawa M., Higashiyama K., Nagase H., Yan Y.-N., Li J.-S., Kamei J., Ohmiya S., *Planta Med.*, **65**, 230—233 (1999).
3) Halfpenny P. R., Horwell D. C., Hughes J., Hunter J. C., Ress D. C., *J. Med. Chem.*, **33**, 286—291 (1990).
4) Zimmerman D. M., Leander J. D., *J. Med. Chem.*, **33**, 895—902 (1990).
5) Nagase H., Hayakawa J., Kawamura K., Kawai K., Takezawa Y., Matsuura H., Tajima C., Endo T., *Chem. Pharm. Bull.*, **46**, 366—369 (1998).
6) Borch R. F., Bernstein M. D., Durst H. D., *J. Am. Chem. Soc.*, **93**, 2897—2904 (1971).