Regular Article

Development of κ Opioid Receptor Agonists by Focusing on Phenyl Substituents of 4-Dimethylamino-3-phenylpiperidine Derivatives: Structure–Activity Relationship Study of Matrine Type Alkaloids

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A series of new κ opioid receptor (KOR) agonists were developed from the lead compound 4-dimethylamino-1-pentanoylpiperidine (3), a matrine-type alkaloid. Derivatives of 3 were synthesized with a variety of phenyl substituents and evaluated for their antinociceptive effects. Additionally, their selectivity for an opioid receptor was investigated for *cis*-4c and d, and *trans*-4g, all of which had high activity exerted through the KOR.

Key words antinociceptive effect; kappa opioid receptor; piperidine; matrine; writhing test; mouse

We previously reported that (+)-matrine (**1**) and (+)-allomatrine (**2**), a typical matrine type lupine alkaloid isolated from some *Sophora* plants (Leguminosae), have antinociceptive properties identical to those of pentazocine[1] (Fig. 1). The effects of (+)-matrine are mediated mainly through activation of κ opioid receptors (KOR) and partially through μ receptors (MOR), while the effects of (+)-allomatrine are mediated only through activation of KOR.[2] Because the skeleton of the matrine type alkaloids differs from those of conventional KOR agonists, such as ethylketocyclazocine,[3] U-50488[4,5] and nalfurafine (TRK-820),[6] they have the potential to be derivatized into novel KOR agonists that may not induce side effects such as dysphoria and psychotomimetic actions[7,8] (Fig. 2). In fact, the structure–activity relationship (SAR) between the antinociceptive effects of these alkaloids and their structures is very interesting. During the development of new KOR agonists, compound **3** was identified as a lead compound by determining the essential structure required for the antinociceptive effects of (+)-matrine.[9–11] When compound **3** was derivatized and tested, the antinociceptive effects of 4-dimethylamino-1-pentanoyl-3-phenylpiperidine (**4a**) were more potent than those of the lead compound **3**. On the basis of the Topliss method,[12] we designed and synthesized phenyl derivatives of **4a** in an effort to further improve the activity. Herein, we report the synthesis of the derivatives of **4a** and their pharmacological effects.

Synthesis

The synthetic route to the intermediates, *cis*- and *trans*-**11a**–**e**, is shown in Chart 1. Hydrazones **7a**–**e** were prepared by condensation of commercially available 2,4,6-triisopropylbenzenesulfonyl hydrazide **5** and the respective acetophenones **6a**–**e**. Allylic alcohols **8a**–**e** were obtained through the Shapiro reaction with acrolein.[13] Oxidation of **8a**–**e** with MnO_2 yielded the respective dienones, followed by cyclization *via* a double aza-Michael reaction with benzylamine using microwave irradiation to give piperidones **9a**–**e**.[13] Piperidones **9a**–**e** were converted to oximes **10a**–**e** and subsequently reduced with metal sodium in EtOH to yield the separable diastereomers *cis*- and *trans*-**11a**–**d**, the 3,4-*cis* (matrine type) and 3,4-*trans* configuration compounds (allomatrine type). The relative configuration of these diastereomers were assigned by comparison to literature data and using the coupling constants from the ^{1}H-NMR spectra.[14] Amine **11e**, which has a chloro group on the *para* position of the benzene ring, was obtained by reduction with $LiAlH_4$ since dechlorination occurred during reduction with metal sodium.

An alternative synthetic route for **11f** and **g** was designed because only a trace of the expected allyl alcohol was obtained by the Shapiro reaction (Chart 2). Amidation of carboxylic acids **12f** and **g** and amine **13** in the presence of 1-ethy-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC) and 4-dimethylaminopyridine (DMAP) yielded amides **14f** and **g**, which was followed by Dieckmann condensation[15] with NaOEt to obtain β-keto lactam **15f** and **g**.

Separable amines *cis*- and *trans*-**11f** and **g** were obtained by reduction of oximes **16f** and **g**, which were oximated from the ketones **15f** and **g**. The relative configuration of *cis*- and *trans*-**11f** and **g** were also assigned from the coupling constant in the ^{1}H-NMR spectra.

As shown in Chart 3, the final synthetic steps involved treatment with HCHO and HCO_2H to afford the dimethylated amines *cis*- and *trans*-**17a**–**g**. After debenzylation, the target compounds *cis*- and *trans*-**4a**–**g** were obtained by *N*-acylation. To avoid dechlorination by reduction, debenzylation of the precursors *cis*- and *trans*-**4e**–**g** having the chloro group were carried out by using 1-chloroethyl chloroformate and MeOH.[16]

Biological Evaluation To evaluate the antinociceptive potencies of the compounds, the writhing test was performed *via* subcutaneous (s.c.) administration of *cis*- and *trans*-**4a**–**g** in mice. A single s.c. administration of all synthesized compounds produced a dose-dependent antinociceptive effect. The ED_{50} values of *cis*- and *trans*-**4a**–**g** are shown in Table 1. In the writhing test, the antinociceptive effects of *cis*-**4c**, **d** and *trans*-**4g** were strikingly different compared with those of pentazocine, which is a well-known selective KOR agonist. Common to matrine-type and allomatrine-type derivatives, generally the compounds with a substituent at the *ortho* or *meta* position on the benzene ring had higher antinociception, except for the compound having the fluoro substituent (**4d**). For example, *cis*-**4f** and **g** had higher activity than *cis*-**4e**, the activities of the *trans* compounds were also the same as

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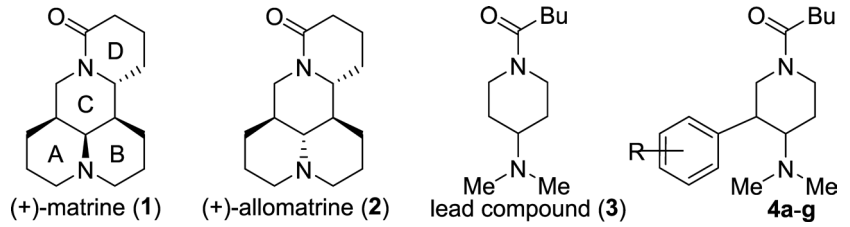


Fig. 1. Structure of (+)-Matrine Derivatives

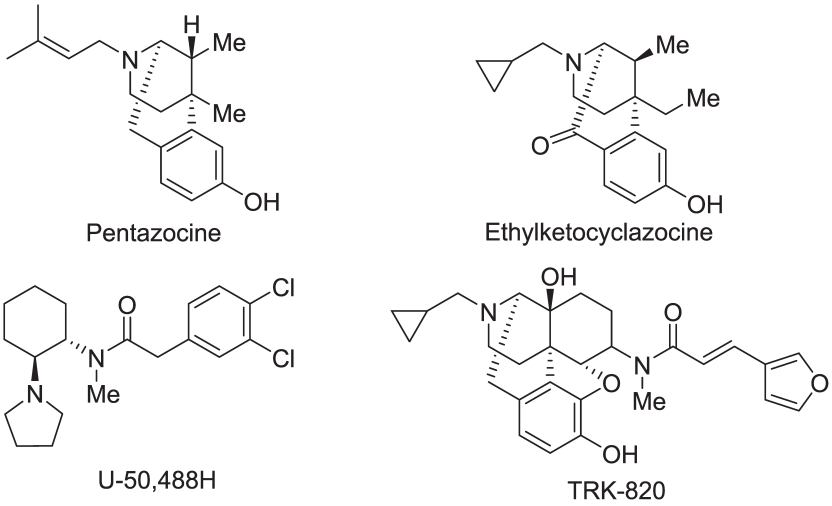
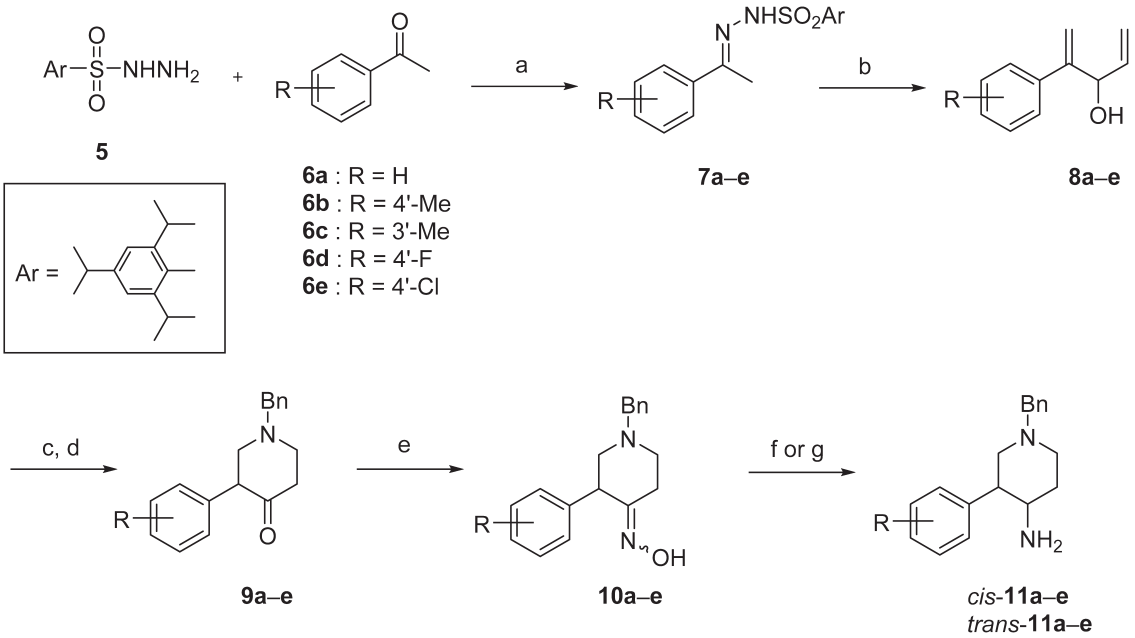


Fig. 2. Structure of Conventional κ-Opioid Receptor Agonists

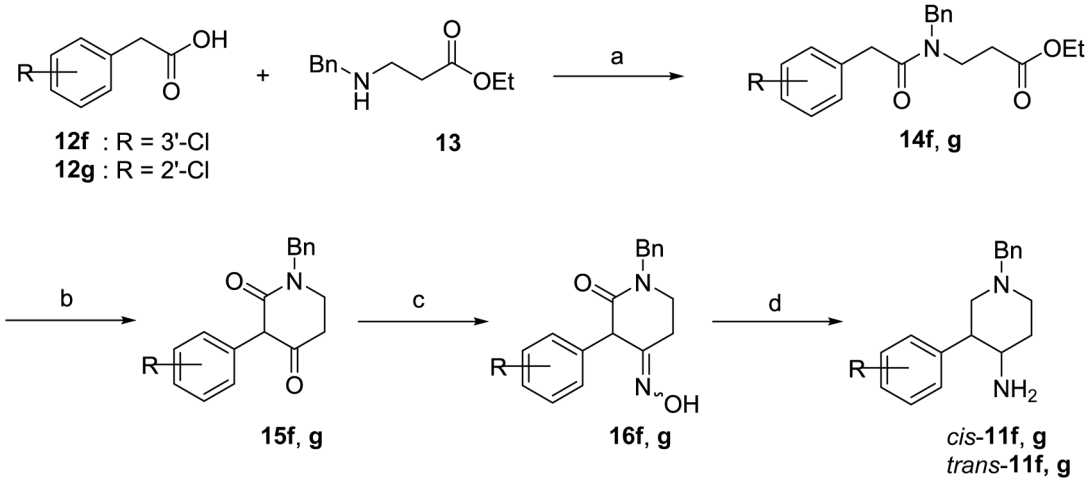


Reagents and reaction conditions: (a) THF, rt, 67–81%; (b) *n*-BuLi, acrolein, THF, −78°C, 82–97%; (c) activated MnO_2, CH_2Cl_2, rt; (d) $BnNH_2$, MeCN, 100°C, MW, two steps, 67–92%; (e) NH_2OH–HCl, AcONa, EtOH, H_2O, reflux, 95–99%; (f) Na, EtOH, reflux, 56–85%; (g) $LiAlH_4$, THF, reflux, 59–85%.

Chart 1

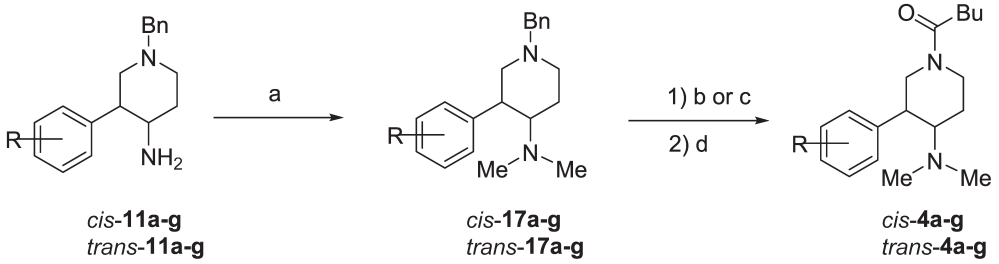
those of the *cis* compounds. From the results, we speculated that steric and electronic effects were more important than the type of substituent in determining the compound's potency. This observation may be explained by the restriction of free rotation of the benzene ring containing a substituent caused by steric hindrance between the benzene ring and dimethylamino moiety. Further studies are required to confirm this hypothesis.

Next, we investigated the opioid receptor selectivity of *cis*-**4c**, **d** and *trans*-**4g**, the three compounds with the highest antinociception, as shown in Fig. 3. The assessment of the selectivity was carried out using the writhing test with the MOR antagonist β-funaltrexamine (β-FNA), the δ-opioid receptor (DOR) antagonist naltrindole (NTI), or the KOR antagonist nor-BNI (norbinaltorphimine) as control compounds. In the presence of the synthesized compounds, there were scarcely any changes in the antinociceptive effects with β-FNA and



Reagents and reaction conditions: (a) EDC, DMAP, CH_2Cl_2, 0°C, 99%; (b) NaOEt, toluene, reflux; (c) NH_2OH–HCl, AcONa, EtOH, H_2O, reflux; (d) $LiAlH_4$, THF, reflux, three steps, 17–30%.

Chart 2



Reagents and reaction conditions: (a) 36% HCHO, HCO_2H, reflux, 41–99%; (b) 10% Pd–C, HCO_2NH_4, MeOH, reflux; (c) 1-chloroethyl chloroformate, CH_2Cl_2, rt, then MeOH, reflux; (d) BuCOCl, Et_3N, CH_2Cl_2, rt, two steps, 12–76%.

Chart 3

Table 1. ED_{50} Value in mg/kg of *cis*-**4a**–**g** and *trans*-**4a**–**g** for 30–40 Mice in Each Group

	R	ED_{50} in mg/kg
Pentazocine		3.80
1		4.70
cis-**4a**	H	5.47
cis-**4b**	4′-Me	8.07
cis-**4c**	3′-Me	0.91
cis-**4d**	4′-F	0.97
cis-**4e**	4′-Cl	6.44
cis-**4f**	3′-Cl	4.18
cis-**4g**	2′-Cl	2.21
2		5.89
trans-**4a**	H	4.80
trans-**4b**	4′-Me	8.33
trans-**4c**	3′-Me	5.78
trans-**4d**	4′-F	1.52
trans-**4e**	4′-Cl	4.92
trans-**4f**	3′-Cl	3.59
trans-**4g**	2′-Cl	0.60

NTI, but their effects were violently antagonized with nor-BNI. We assumed that the effects of *cis*-**4c** and **d**, matrine-type compounds, were only slightly antagonized by β-FNA because the antinociceptive effects of (+)-matrine (**1**) are partially mediated through MOR. The selectivity results were in agreement with what was expected from the known behavior of the control antagonists.

In summary, we succeeded in synthesizing the 4-dimethylamino-3-phenylpiperidine derivatives *cis*- and *trans*-**4a**–**g**. The phenyl derivatives *cis*-**4c**, **d** and *trans*-**4g** showed high antinociceptive effects mediated through the activation of KOR. The results are valuable in providing a starting point toward the development of a novel KOR selective agonist.

Experimental

Chemistry ^{1}H- (400 MHz) and ^{13}C-NMR (100 MHz) spectra were obtained on a Bruker AVIII-400 instrument, and chemical sifts are reported in ppm on the δ-scale from internal tetramethylsilane. Signal splitting patterns are described as singlet (s), doublet (d), triplet (t), quartet (q), septet (sept), multiplet (m) or broad (br), with coupling constants (J) in hertz (Hz). MS spectra were measured with a JEOL JMS D-600 and JMS T-100LP spectrometer by using the chemical ionization (CI) with isobutene, the electron impact (EI) methods, and electrospray ionization (ESI) methods. All melting points were measured with a Yanagimoto Micro melting point apparatus without collection. IR spectra were recorded on Perkin-Elmer Spectrum Two. Microwave irradiation were carried out on Biotage Initiator. Column chromatography was performed on Silica gel 60 (100–210 μm, Kanto Chemical Co., Inc.).

Acetophenone (2,4,6-Triisopropylbenzene)sulfonylhydrazone (7a) Acetophenone (2.00 g, 16.7 mmol) was added to a solution of 2,4,6-triisopropylbenzenesulfonyl hydrazide (5.00 g, 16.7 mmol) in tetrahydrofuran (THF). After being

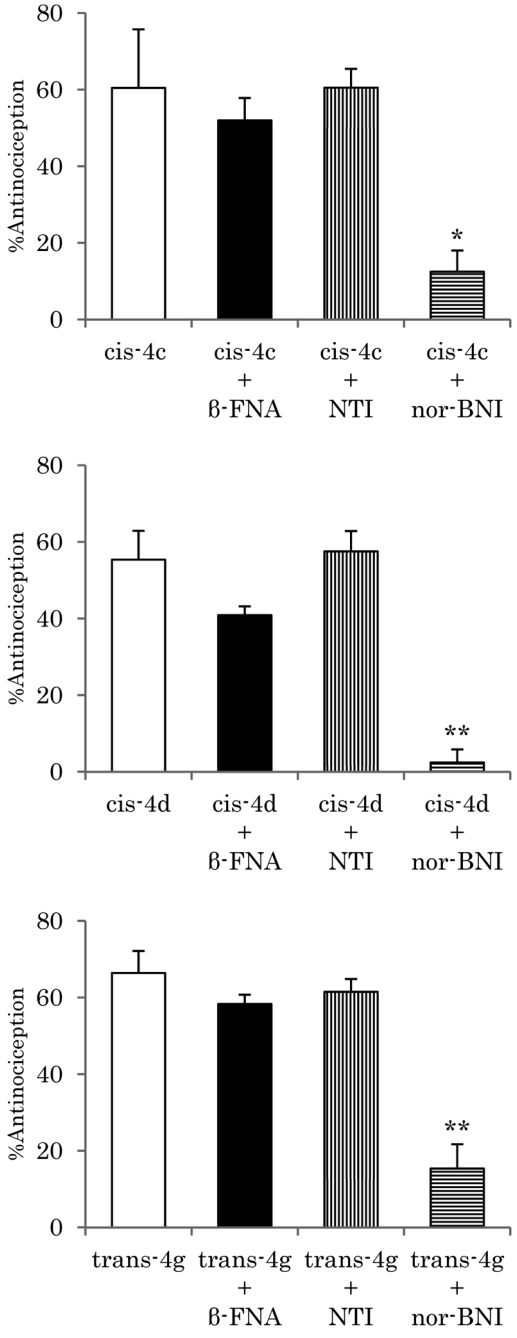


Fig. 3. The Blockage of Antinociceptive Effect of *cis*-**4c**, **d** and *trans*-**4g** (3 mg/kg, s.c.) after Pretreatment with MOR Antagonist *β*-FNA (40 mg/kg, s.c.), DOR Antagonist NTI (3.2 mg/kg, s.c.) or KOR Antagonist nor-BNI (3.2 mg/kg, s.c.) at 24 h, 15 min and 4 h before Administration of the Test Drug, Respectively, in the Acetic Acid-Induced Abdominal Constriction Assay in Mice[1,2]

Each column represents the mean shown with the S.E.M. for 10 mice in each group. *$p<0.05$ (*cis*-**4c**), **$p<0.01$ (*cis*-**4d** or *trans*-**4g**) *versus* the compound alone.

stirred at room temperature (rt) for 3 h, the solvent was evaporated. The resulting residue was purified by recrystallization with EtOH to yield **7a** (5.40 g, 13.5 mmol, 81%) as a colorless solid. All spectroscopic and analytical data were consistent with the literature.[17]

4′-Methylacetophenone (2,4,6-Triisopropylbenzene)sulfonylhydrazone (7b)

Prepared According to Procedure for the Preparation of **7a**

Yield: 67%, colorless solid, mp 145–147°C. ^{1}H-NMR ($CDCl_3$) δ: 1.24 (6H, d, J=6.9 Hz), 1.30 (12H, d, J=6.8 Hz), 2.15 (3H, s), 2.32 (3H, s), 2.88 (1H, sept, J=6.9 Hz), 4.33 (2H, sept, J=6.8 Hz), 7.10 (2H, d, J=8.1 Hz), 7.16 (2H, s), 7.52 (2H, d, J=8.1 Hz), 7.84 (1H, br). ^{13}C-NMR ($CDCl_3$) δ: 13.0, 21.2, 24.8, 24.8, 30.0, 34.2, 123.7, 126.2, 128.8, 131.4, 134.6, 139.5, 150.7, 151.3, 153.3. IR (KBr) cm^{-1}: 813, 1167, 1332, 1599, 2965, 3240. MS (ESI+) *m/z*: 415 ($M+H^+$, base peak). High resolution (HR)-MS (ESI+) *m/z*: Found 415.2432 (Calcd for $C_{24}H_{35}N_2O_2S$ ($M+H^+$) 415.2419).

3′-Methylacetophenone (2,4,6-Triisopropylbenzene)sulfonylhydrazone (7c)

Prepared According to Procedure for the Preparation of **7a**

Yield: 76%, colorless solid, mp 159–161°C. ^{1}H-NMR ($CDCl_3$) δ: 1.24 (6H, d, J=6.9 Hz), 1.30 (12H, d, J=6.8 Hz), 2.16 (3H, s), 2.31 (3H, s), 2.89 (1H, sept, J=6.9 Hz), 4.32 (2H, sept, J=6.8 Hz), 7.13–7.21 (4H, m), 7.39 (1H, d, J=7.7 Hz), 7.49 (1H, s), 7.71 (1H, br). ^{13}C-NMR ($CDCl_3$) δ: 13.1, 21.3, 23.5, 24.8, 29.9, 34.2, 123.4, 123.8, 126.8, 128.0, 130.1, 131.4, 137.2, 137.8, 150.7, 151.3, 153.3. IR (KBr) cm^{-1}: 907, 1166, 1331, 1600, 2964, 3244. MS (ESI+) *m/z*: 415 ($M+H^+$, base peak). HR-MS (ESI+) *m/z*: Found 415.2444 (Calcd for $C_{24}H_{35}N_2O_2S$ ($M+H^+$) 415.2419).

4′-Fluoroacetophenone (2,4,6-Triisopropylbenzene)sulfonylhydrazone (7d)

Prepared According to Procedure for the Preparation of **7a**

Yield: 70%, colorless solid, mp 177–179°C. ^{1}H-NMR ($CDCl_3$) δ: 1.24 (6H, d, J=6.9 Hz), 1,29 (12H, d, J=6.8 Hz), 2.15 (3H, s), 2.89 (1H, sept, J=6.9 Hz), 4.29 (2H, sept, J=6.8 Hz), 6.96–7.01 (2H, m), 7.10 (2H, s), 7.59–7.63 (2H, m). ^{13}C-NMR ($CDCl_3$) δ: 13.2, 23.5, 24.8, 29.9, 34.1, 115.0 (d, J=21.7 Hz), 123.8, 128.1 (d, J=8.4 Hz), 131.3, 133.6 (d, J=3.2 Hz), 149.6, 151.4, 153.4, 163.4 (d, J=249.5 Hz). IR (KBr) cm^{-1}: 836, 1169, 1511, 1600, 2959, 3241. MS (ESI+) *m/z*: 419 ($M+H^+$, base peak). HR-MS (ESI+) *m/z*: Found 419.2200 (Calcd for $C_{23}H_{32}FN_2O_2S$ ($M+H^+$) 419.2169).

4′-Chloroacetophenone (2,4,6-Triisopropylbenzene)sulfonylhydrazone (7e)

Prepared According to Procedure for the Preparation of **7a**

Yield: 71%, colorless solid. All spectroscopic and analytical data were consistent with the literature.[18]

2-Phenyl-1,4-pentadien-3-ol (8a) A solution of *n*-BuLi (3.44 mL, 5.50 mmol, 1.6 M, in *n*-hexane) was added dropwise to a solution of **7a** (1.00 g, 2.50 mmol) in THF (10 mL) at −78°C under the nitrogen atmosphere. The reaction mixture was stirred at −78°C for 30 min, then warmed to 0°C and further stirred for 15 min. Acrolein (578 mg, 9.30 mmol) was added to the reaction mixture at −78°C. After being stirred for 1 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with EtOAc. The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated. The resulting residue was purified by chromatography on SiO_2 (*n*-hexane–EtOAc=8 : 1) to yield the **8a** (345 mg, 2.16 mmol, 86%) as a colorless oil. All spectroscopic and analytical data were consistent with the literature.[19]

2-(4-Methylphenyl)-1,4-pentadien-3-ol (8b)

Prepared According to Procedure for the Preparation of **8a**

Yield: 82%, colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 2.35 (3H, s), 5.12 (1H, d, J=5.4 Hz), 5.18 (1H, dt, J=10.4, 1.4 Hz), 5.31–5.36 (2H, m), 5.37 (1H, br), 5.96 (1H, ddd, J=17.2, 10.4, 5.4 Hz), 7.15 (2H, d, J=8.1 Hz), 7.33 (2H, d, J=8.1 Hz). ^{13}C-NMR ($CDCl_3$) δ: 21.1, 74.5, 112.9, 115.9, 126.8, 129.0, 136.3, 137.5,

139.0, 149.7. IR (film) cm^{-1}: 920, 1513, 3025, 3389. MS (EI) *m/z*: 174 (M^+) 119 (base peak). HR-MS (EI) *m/z*: Found 174.1022 (Calcd for $C_{12}H_{14}O$ (M^+) 174.1045).

2-(3-Methylphenyl)-1,4-pentadien-3-ol (8c)

Prepared According to Procedure for the Preparation of **8a**

Yield: 86%, colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 2.36 (3H, s), 5.12 (1H, br), 5.19 (1H, dt, J=10.4, 1.4 Hz), 5.34 (1H, dt, J=17.2, 1.4 Hz), 5.37–5.38 (2H, m), 5.97 (1H, ddd, J=17.2, 10.4, 5.7 Hz), 7.10–7.13 (1H, m), 7.22–7.24 (3H, m). ^{13}C-NMR ($CDCl_3$) δ: 21.3, 74.2, 113.2, 115.6, 123.9, 127.5, 128.0, 128.3, 137.7, 138.9, 139.3, 149.9. IR (film) cm^{-1}: 1487, 1602, 3396. MS (CI) *m/z*: 175 ($M+H^+$), 157 (base peak). HR-MS (CI) *m/z*: Found 175.1137 (Calcd for $C_{12}H_{15}O$ ($M+H^+$) 175.1123).

2-(4-Fluorophenyl)-1,4-pentadien-3-ol (8d)

Prepared According to Procedure for the Preparation of **8a**

Yield: 82%, colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 5.06 (1H, d, J=5.0 Hz), 5.17 (1H, dt, J=10.4, 1.3 Hz), 5.31 (1H, dt, J=17.2, 1.4 Hz), 5.35 (1H, s), 5.38 (1H, s), 5.92 (1H, ddd, J=17.2, 10.4, 5.8 Hz), 6.98–7.03 (2H, m), 7.37–7.42 (2H, m). ^{13}C-NMR ($CDCl_3$) δ: 74.4, 113.5, 114.9 (d, J=21.3 Hz), 115.8, 128.5 (d, J=7.7 Hz), 135.3 (d, J=3.2 Hz), 138.7, 148.7, 162.2 (d, J=246.5 Hz). IR (film) cm^{-1}: 1509, 1599, 1686, 3440. MS (ESI−) *m/z*: 177 ($M-H^+$), 61 (base peak). HR-MS (ESI−) *m/z*: Found 177.0716 (Calcd for $C_{11}H_{10}FO$ ($M-H^+$) 177.0716).

2-(4-Chlorophenyl)-1,4-pentadien-3-ol (8e)

Prepared According to Procedure for the Preparation of **8a**

Yield: 97%, colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 5.08 (1H, d, J=5.7 Hz), 5.19 (1H, dt, J=10.4, 1.4 Hz), 5.32 (1H, dt, J=17.2, 1.4 Hz), 5.39 (1H, br), 5.43 (1H, t, J=1.1 Hz), 5.93 (1H, ddd, J=17.2, 10.4, 5.7 Hz), 7.30 (2H, d, J=8.7 Hz), 7.37 (2H, d, J=8.7 Hz). ^{13}C-NMR ($CDCl_3$) δ: 74.5, 114.2, 116.2, 128.3, 128.4, 133.5, 137.7, 138.6, 148.6. IR (film) cm^{-1}: 1012, 1091, 1491, 3376. MS (ESI−) *m/z*: 193 ($M-H^+$), 113 (base peak). HR-MS (ESI−) *m/z*: Found 193.0415 (Calcd for $C_{11}H_{10}ClO$ ($M-H^+$) 193.0420).

1-*N*-Benzyl-3-phenyl-4-piperidone (9a) Activated MnO_2 (4.00 g, 46.0 mmol) was added portionwise to a solution of **8a** (250 mg, 1.56 mmol) in CH_2Cl_2 (15 mL). After being stirred at rt for 4 h, the reaction mixture was filtered through Celite pad and evaporated. The resulting residue was used in the subsequent reaction without further purification. Benzylamine (212 mg, 1.99 mmol) was added to a solution of the residue in CH_3CN (10 mL). After being irradiated to microwave (100°C for 1 h), the reaction mixture was poured on H_2O and extracted with $CHCl_3$. The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated. The resulting residue was purified by chromatography on SiO_2 (*n*-hexane–EtOAc=2 : 1) to yield **9a** (310 mg, 1.17 mmol, 75% over two steps) as a light yellow oil. All spectroscopic and analytical data were consistent with the literature.[13]

1-*N*-Benzyl-3-(4-methylphenyl)-4-piperidone (9b)

Prepared According to Procedure for Preparation of **9a**

Yield: 70% over two steps, light yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 2.32 (3H, s), 2.46–2.56 (1H, m), 2.62–2.71 (2H, m), 2.76 (1H, dd, J=11.4, 10.0 Hz), 3.05–3.10 (1H, m), 3.17 (1H, ddd, J=11.4, 5.7, 2.4 Hz), 3.66 (2H, s), 3.78 (1H, dd, J=10.0, 5.7 Hz), 7.09–7.14 (4H, m), 7.26–7.29 (1H, m), 7.31–7.38 (4H, m). ^{13}C-NMR ($CDCl_3$) δ: 21.1, 40.7, 53.5, 56.0, 59.8, 61.9, 127.3, 128.4, 128.7, 128.9, 129.1, 133.6, 136.8, 137.9, 208.4. IR (film) cm^{-1}: 1351, 1453, 1718, 2802. MS (ESI+) *m/z*: 280 ($M+H^+$, base peak). HR-MS (ESI+) *m/z*: Found 280.1724 (Calcd for $C_{19}H_{22}NO$ ($M+H^+$) 280.1701).

1-*N*-Benzyl-3-(3-methylphenyl)-4-piperidone (9c)

Prepared According to Procedure for the Preparation of **9a**

Yield: 67% over two steps, light yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 2.32 (3H, s), 2.48–2.55 (1H, m), 2.61–2.71 (2H, m), 2.78 (1H, dd, J=11.4, 9.7 Hz), 3.02–3.09 (1H, m), 3.15 (1H, ddd, J=11.4, 5.7, 2.3 Hz), 3.65 (2H, s), 3.76 (1H, dd, J=9.7, 5.7 Hz), 7.01–7.07 (3H, m), 7.20 (1H, t, J=7.6 Hz), 7.22–7.28 (1H, m), 7.31–7.38 (4H, m). ^{13}C-NMR ($CDCl_3$) δ: 21.4, 40.7, 53.5, 56.3, 59.6, 61.9, 125.9, 127.3, 127.9, 128.2, 128.4, 128.9, 129.6, 136.6, 137.8, 137.9, 208.2. IR (film) cm^{-1}: 1454, 1715, 2915. MS (ESI+) *m/z*: 280 ($M+H^+$, base peak). HR-MS (ESI+) *m/z*: Found 280.1670 (Calcd for $C_{19}H_{22}NO$ ($M+H^+$) 280.1701).

1-*N*-Benzyl-3-(4-fluorophenyl)-4-piperidone (9d)

Prepared According to Procedure for the Preparation of **9a**

Yield: 92% over two steps, light yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 2.47–2.56 (1H, m), 2.63–2.76 (3H, m), 3.07–3.11 (1H, m), 3.17 (1H, ddd, J=11.4, 5.6, 2.4 Hz), 3.67 (2H, s), 3.80 (1H, dd, J=9.8, 5.6 Hz), 6.97–7.03 (2H, m), 7.17–7.20 (2H, m), 7.28–7.39 (5H, m). ^{13}C-NMR ($CDCl_3$) δ: 40.6, 53.3, 55.4, 59.7, 61.8, 115.2 (d, J=21.2 Hz), 127.4, 128.4, 129.0, 130.4 (d, J=7.9 Hz), 132.3, 137.4, 161.9 (d, J=245.5 Hz), 207.8. IR (film) cm^{-1}: 1511, 1602, 1717. MS (ESI+) *m/z*: 284 ($M+H^+$), 91 (base peak). HR-MS (ESI+) *m/z*: Found 284.1474 (Calcd for $C_{18}H_{19}FNO$ ($M+H^+$) 284.1451).

1-*N*-Benzyl-3-(4-chlorophenyl)-4-piperidone (9e)

Prepared According to Procedure for the Preparation of **9a**

Yield: 67% over two steps, light yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 2.46–2.55 (1H, m), 2.57–2.70 (2H, m), 2.74 (1H, dd, J=11.4, 9.8 Hz), 3.07–3.10 (1H, m), 3.16 (1H, ddd, J=11.4, 5.7, 2.4 Hz), 3.66 (2H, s), 3.79 (1H, dd, J=9.8, 5.7 Hz), 7.15 (2H, d, J=8.4 Hz), 7.26–7.30 (3H, m), 7.32–7.38 (4H, m). ^{13}C-NMR ($CDCl_3$) δ: 40.7, 53.4, 55.7, 59.6, 61.9, 127.5, 128.4, 128.5, 128.9, 130.3, 133.1, 135.1, 137.8, 207.7. IR (film) cm^{-1}: 1492, 1717, 2806. MS (ESI+) *m/z*: 300 ($M+H^+$, base peak). HR-MS (ESI+) *m/z*: Found 300.1171 (Calcd for $C_{18}H_{19}ClNO$ ($M+H^+$) 300.1155).

1-*N*-Benzyl-3-phenyl-4-hydroxyiminopiperidine (10a) NaOAc (1.94 g, 23.7 mmol) and NH_2OH–HCl (1.65 g, 23.7 mmol) were added to a solution of **9a** (630 mg, 2.37 mmol) in EtOH–H_2O 1 : 1 (20 mL). After being stirred at reflux for 3 h, the reaction mixture was alkalized with saturated aqueous Na_2CO_3 and extracted with $CHCl_3$. The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated to yield **10a** (650 mg, 2.32 mmol, 98%) as a brown oil and was used without further purification. ^{1}H-NMR shows double signal set (isomer A and B, ratio 2 : 1). All spectroscopic and analytical data were consistent with the literature.[13]

1-*N*-Benzyl-4-hydroxyimino-3-(4-methylphenyl)piperidine (10b)

Prepared According to Procedure for the Preparation of **10a**

Yield: 99%, brown oil. ^{1}H-NMR shows a doubled signal set (isomer A and B, ratio 2 : 1). ^{1}H-NMR ($CDCl_3$) δ: 2.15–2.23 (2H of isomer B, m), 2.31 (3H of isomer A, s), 2.32 (3H of isomer B, s), 2.40–2.54 (3H; 2H of isomer A, m, 1H of isomer B, m), 2.71–2.80 (3H; 2H of isomer A, m, 1H of isomer B, m), 2.84–2.96 (2H of isomer A, m), 3.04–3.08 (1H of isomer B, m), 3.32 (1H of isomer B, dt, J=12.0, 1.8 Hz), 3.54 (2H of isomer B, s), 3.56 (1H of isomer A, d, J=13.2 Hz), 3.60 (1H of isomer A, d, J=13.2 Hz), 3.64 (1H of isomer A, dd, J=8.4, 4.7 Hz), 4.64 (1H of isomer B, d, J=3.8 Hz), 7.10 (2H of isomer

B, d, J=8.0 Hz), 7.11 (2H of isomer A, d, J=8.0 Hz), 7.21 (2H of isomer A, d, J=8.0 Hz), 7.27–7.36 (10H, 5H of isomer A, m, 5H of isomer B, m), 7.45 (2H of isomer B, d, J=8.0 Hz). ^{13}C-NMR ($CDCl_3$), (isomer A) δ: 21.0, 23.5, 46.6, 52.5, 58.9, 62.6, 127.2, 128.3, 128.5, 128.9, 129.1, 136.0, 136.3, 137.9, 159.7; (isomer B) δ: 21.0, 29.2, 37.5, 53.7, 56.1, 62.8, 127.2, 128.2, 128.3, 128.9, 129.1, 135.8, 137.2, 138.2, 159.0. IR (film) cm^{-1}: 951, 1453, 1513, 3277. MS (ESI+) m/z: 295 (M+H$^+$, base peak). HR-MS (ESI+) m/z: Found 295.1827 (Calcd for $C_{19}H_{23}N_2O$ (M+H$^+$) 295.1810).

1-*N*-Benzyl-4-hydroxyimino-3-(3-methylphenyl)piperidine (10c)

Prepared According to Procedure for the Preparation of **10a**

Yield: 99%, brown oil. ^{1}H-NMR shows a doubled signal set (isomer A and B, ratio 2 : 1). ^{1}H-NMR ($CDCl_3$) δ: 2.20–2.25 (2H of isomer B, m), 2.32 (6H, 3H of isomer A, s, 3H of isomer B, s), 2.39 (1H of isomer A, dd, J=12.0, 4.4 Hz), 2.47–2.61 (3H, 2H of isomer A, m, 1H of isomer B, m), 2.70–2.74 (1H of isomer A, m), 2.83–2.89 (3H, 2H of isomer A, m, 1H of isomer B, m), 3.06–3.10 (1H of isomer B, m), 3.34 (1H of isomer B, dt, J=12.0, 1.9 Hz), 3.50 (1H of isomer B, d, J=13.0 Hz), 3.56 (1H of isomer A, d, J=13.3 Hz), 3.60 (1H of isomer A, d, J=13.3 Hz), 3.61–3.65 (2H, 1H of isomer A, m, 1H of isomer B, m), 4.64 (1H of isomer B, d, J=4.2 Hz), 7.01–7.05 (2H, 1H of isomer A, m, 1H of isomer B, m), 7.12–7.21 (5H, 2H of isomer A, m, 3H of isomer B, m), 7.24–7.37 (11H, 6H of isomer A, m, 5H of isomer B, m). ^{13}C-NMR ($CDCl_3$), (isomer A) δ: 21.4, 23.5, 46.9, 52.6, 58.7, 62.6, 125.7, 127.2, 127.5, 128.1, 128.3, 128.7, 129.2, 137.8, 137.9, 138.9, 159.6; (isomer B) δ: 21.5, 29.3, 37.8, 54.0, 55.8, 62.8, 125.4, 126.9, 127.1, 127.2, 128.2, 129.0, 129.4, 137.7, 138.3, 140.0, 159.0. IR (film) cm^{-1}: 1454, 1716, 2924. MS (ESI+) m/z: 295 (M+H$^+$, base peak). HR-MS (ESI+) m/z: Found 295.1784 (Calcd for $C_{19}H_{23}N_2O$ (M+H$^+$) 295.1810).

1-*N*-Benzyl-3-(4-fluorophenyl)-4-hydroxyiminopiperidine (10d)

Prepared According to Procedure for the Preparation of **10a**

Yield: 95%, brown oil. ^{1}H-NMR shows a doubled signal set (isomer A and B, ratio 2 : 1). ^{1}H-NMR ($CDCl_3$) δ: 2.15–2.23 (2H of isomer B, m), 2.39–2.56 (4H, 2H of isomer A, m, 2H of isomer B, m), 2.68–2.80 (2H of isomer A, m), 2.82–2.88 (2H of isomer A, m), 3.04–3.08 (1H of isomer B, m), 3.25–3.28 (1H of isomer B, m), 3.52 (1H of isomer B, d, J=13.0 Hz), 3.56 (1H of isomer B, d, J=13.0 Hz), 3.58 (2H of isomer A, s), 3.65 (1H of isomer A, dd, J=8.0, 4.6 Hz), 4.61 (1H of isomer B, d, J=3.9 Hz), 6.93–6.99 (4H, 2H of isomer A, m, 2H of isomer B, m), 7.24–7.34 (12H, 7H of isomer A, m, 5H of isomer B, m), 7.54 (2H of isomer B, dd, J=8.5, 5.6 Hz). ^{13}C-NMR ($CDCl_3$), (isomer A) δ: 23.4, 46.0, 52.3, 58.6, 62.5, 114.9 (d, J=21.0 Hz), 127.3, 128.3, 129.2, 130.1 (d, J=7.8 Hz), 134.7 (d, J=3.3 Hz), 137.3, 159.0, 161.6 (d, J=245.0 Hz); (isomer B) δ: 29.0, 37.1, 53.6, 56.0, 62.7, 114.8 (d, J=20.8 Hz), 127.2, 128.2, 129.0, 130.0 (d, J=7.8 Hz), 136.0 (d, J=3.0 Hz), 138.0, 158.3, 161.4 (d, J=244.4 Hz). IR (film) cm^{-1}: 1509, 1601, 3277. MS (ESI+) m/z: 299 (M+H$^+$, base peak). HR-MS (ESI+) m/z: Found 299.1581 (Calcd for $C_{18}H_{20}FN_2O$ (M+H$^+$) 299.1560).

1-*N*-Benzyl-3-(4-chlorophenyl)-4-hydroxyiminopiperidine (10e)

Prepared According to Procedure for the Preparation of **10a**

Yield: 99%, brown oil. ^{1}H-NMR shows a doubled signal set (isomer A and B, ratio 2 : 1). ^{1}H-NMR ($CDCl_3$) δ: 2.16–2.25 (2H of isomer B, m), 2.39–2.45 (1H of isomer B, m), 2.53–2.61 (2H of isomer A, m), 2.67–2.71(1H of isomer A, m), 2.76–2.86 (4H, 3H of isomer A, m, 1H of isomer B, m), 3.05–3.09 (1H of isomer B, m), 3.27 (1H of isomer B, dt, J=12.0, 1.7 Hz), 3.52 (1H of isomer B, d, J=12.9 Hz), 3.57 (1H of isomer B, d, J=12.9 Hz), 3.58 (2H of isomer A, s), 3.64 (1H of isomer A, dd, J=7.2, 5.0 Hz), 4.63 (1H of isomer B, d, J=3.8 Hz), 7.23–7.34 (16H, 9H of isomer A, m, 7H of isomer B, m), 7.51 (2H of isomer B, d, J=8.4 Hz). ^{13}C-NMR ($CDCl_3$), (isomer A) δ: 23.4, 46.3, 52.4, 58.5, 62.6, 127.3, 128.3, 128.3, 129.2, 130.0, 132.5, 137.4, 137.6, 159.4; (isomer B) δ: 29.1. 37.3, 53.7, 55.9, 62.8, 127.3, 128.2, 128.3, 129.1, 129.9, 132.1, 138.0, 138.8, 158.5. IR (film) cm^{-1}: 1091, 1493, 3270. MS (ESI+) m/z: 315 (M+H$^+$, base peak). HR-MS (ESI+) m/z: Found 315.1252 (Calcd for $C_{18}H_{20}ClN_2O$ (M+H$^+$) 315.1264).

***cis*- and *trans*-4-Amino-1-*N*-benzyl-3-phenylpiperidine (*cis*-, *trans*-11a)** Pieces of sodium metal (1.30 g, 56.5 mmol) was added portionwise to a solution of **10a** (200 mg, 0.71 mmol) in EtOH (10 mL). After being stirred at reflux for 20 h, the reaction mixture was cooled until rt and acidified with 10% aqueous HCl and evaporated. The resulting residue was alkalized with 1 M aqueous NaOH and extracted with $CHCl_3$. The organic layer was dried over anhydrous Na_2SO_4 and evaporated. The resulting residue was purified by chromatography on SiO_2 ($CHCl_3$–MeOH=10 : 1) to yield the primary amine (161 mg, 0.61 mmol, 85%, *cis*–*trans*=2 : 3) perspective as a yellow oil. All spectroscopic and analytical data of *cis*-**11a** were consistent with the literature.[13] *trans*-**11a**: ^{1}H-NMR ($CDCl_3$) δ: 1.43 (2H, br), 1.58 (1H, dq, J=12.8, 4.2 Hz), 1.95 (1H, ddd, J=12.8, 6.9, 2.6 Hz), 2.13 (1H, t, J=11.4 Hz), 2.16 (1H, dt, J=12.0, 2.6 Hz), 2.57 (1H, dt, J=10.8, 3.7 Hz), 2.86 (1H, dt, J=10.8, 4.2 Hz), 2.93 (1H, ddd, J=11.4, 3.7, 2.1 Hz), 2.96–3.02 (1H, m), 3.54 (2H, s), 7.21–7.25 (4H, m), 7.28–7.33 (6H, m). ^{13}C-NMR ($CDCl_3$) δ: 34.6, 52.8, 53.0, 53.6, 59.8, 62.8, 126.9, 127.0, 128.2, 128.2, 128.6, 129.1, 138.2, 141.6. IR (film) cm^{-1}: 1450, 1500, 2920. MS (CI) m/z: 267 (M+H$^+$, base peak). HR-MS (CI) m/z: Found 267.1884 (Calcd for $C_{18}H_{23}N_2$ (M+H$^+$) 267.1861).

***cis*- and *trans*-4-Amino-1-*N*-benzyl-3-(4-methylphenyl)-piperidine (*cis*-, *trans*-11b)**

Prepared According to Procedure for the Preparation of **11a**

Yield: 56% (*cis*–*trans*=2 : 3). *cis*-**11b**: yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 1.21 (2H, br), 1.66–1.73 (1H, m), 1.91–1.97 (1H, m), 2.31 (3H, s), 2.47–2.55 (2H, m), 2.68–2.77 (2H, m), 3.02–3.06 (1H, m), 3.18–3.21 (1H, m), 3.54 (1H, d, J=13.1 Hz), 3.60 (1H, d, J=13.1 Hz), 7.11 (2H, d, J=7.9 Hz), 7.19–7.24 (3H, m), 7.28–7.36 (4H, m). ^{13}C-NMR ($CDCl_3$) δ: 20.9, 32.7, 46.0, 48.7, 49.6, 52.5, 63.5, 126.9, 128.2, 128.3, 128.9, 129.1, 135.9, 138.5, 138.8. IR (film) cm^{-1}: 810, 1453, 1513, 2919. MS (ESI+) m/z: 281 (M+H$^+$, base peak). HR-MS (ESI+) m/z: Found 281.2036 (Calcd for $C_{19}H_{25}N_2$ (M+H$^+$) 281.2018). *trans*-**11b**: yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 1.37 (2H, br), 1.56 (1H, dq, J=12.7, 4.2 Hz), 1.93 (1H, ddd, J=12.7, 6.9, 2.6 Hz), 2.09 (1H, t, J=11.4 Hz), 2.14 (1H, dt, J=12.0, 2.6 Hz), 2.31 (3H, s), 2.52 (1H, dt, J=10.8, 3.8 Hz), 2.82 (1H, dt, J=10.8, 4.2 Hz), 2.90 (1H, ddd, J=11.4, 3.8, 2.1 Hz), 2.95–3.00 (1H, m), 3.53 (2H, s), 7.09–7.13 (4H, m), 7.20–7.31 (5H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 21.0, 34.6, 52.3, 53.0, 53.6, 60.0, 62.9, 126.9, 128.0, 128.2, 129.1, 129.3, 136.4, 138.2, 138.5. IR (film) cm^{-1}: 811, 1513, 2797, 2918. MS (ESI+) m/z: 281 (M+H$^+$), 264 (base peak). HR-MS (ESI+) m/z: Found 281.2024 (Calcd for

$C_{19}H_{25}N_2$ ($M+H^+$) 281.2018).

***cis*- and *trans*-4-Amino-1-*N*-benzyl-3-(3-methylphenyl)-piperidine (*cis*-, *trans*-11c)**

Prepared According to Procedure for the Preparation of **11a**

Yield: 72% (*cis*–*trans*=2 : 3). *cis*-**11c**: yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 1.31 (2H, br), 1.68–1.74 (1H, m), 1.93–1.99 (1H, m), 2.33 (3H, s), 2.50–2.58 (2H, m), 2.70–2.79 (2H, m), 3.03–3.07 (1H, m), 3.20–3.23 (1H, m), 3.56 (1H, d, J=13.1 Hz), 3.61 (1H, d, J=13.1 Hz), 7.03 (1H, d, J=7.4 Hz), 7.10–7.12 (2H, m), 7.17–7.25 (2H, m), 7.29–7.37 (4H, m). ^{13}C-NMR ($CDCl_3$) δ: 21.3, 32.5, 46.1, 48.4, 49.4, 52.3, 63.3, 125.2, 126.7, 126.9, 127.9, 128.0, 128.9, 129.0, 137.5, 138.4, 141.7. IR (film) cm^{-1}: 699, 1453, 1492, 2918. MS (ESI+) *m*/*z*: 281 ($M+H^+$, base peak). HR-MS (ESI+) *m*/*z*: Found 281.2000 (Calcd for $C_{19}H_{25}N_2$ ($M+H^+$) 281.2018). *trans*-**11c**: yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 1.57 (1H, dq, J=12.7, 4.1 Hz), 1.73 (2H, br), 1.93 (1H, ddd, J=12.7, 6.8, 2.6 Hz), 2.10 (1H, t, J=11.4 Hz), 2.14 (1H, dt, J=12.0, 2.6 Hz), 2.31 (3H, s), 2.53 (1H, dt, J=10.8, 3.7 Hz), 2.83 (1H, dt, J=10.8, 4.1 Hz), 2.90 (1H, ddd, J=11.4, 3.7, 2.1 Hz), 2.94–2.99 (1H, m), 3.52 (2H, s), 6.99–7.03 (3H, m), 7.18 (1H, t, J=7.8 Hz), 7.21–7.24 (1H, m), 7.26–7.31 (4H, m). ^{13}C-NMR ($CDCl_3$) δ: 21.4, 34.3, 52.4, 52.9, 53.5, 59.7, 62.8, 125.1, 126.9, 127.5, 128.1, 128.4, 128.9, 129.0, 138.1, 138.1, 141.3. IR (film) cm^{-1}: 704, 1454, 2918. MS (ESI+) *m*/*z*: 281 ($M+H^+$), 264 (base peak). HR-MS (ESI+) *m*/*z*: Found 281.1982 (Calcd for $C_{19}H_{25}N_2$ ($M+H^+$) 281.2018).

***cis*- and *trans*-4-Amino-1-*N*-benzyl-3-(4-fluorophenyl)-piperidine (*cis*-, *trans*-11d)**

Prepared According to Procedure for the Preparation of **11a**

Yield: 68% (*cis*–*trans*=1 : 1). *cis*-**11d**: yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 1.65–1.71 (1H, m), 1.87–1.95 (1H, m), 2.51–2.57 (2H, m), 2.66 (1H, dd, J=10.8, 3.0 Hz), 2.77 (1H, t, J=9.6 Hz), 3.02–3.06 (1H, m), 3.16–3.20 (1H, m), 3.55 (1H, d, J=13.1 Hz), 3.59 (1H, d, J=13.1 Hz), 6.97–7.01 (2H, m), 7.22–7.36 (7H, m). ^{13}C-NMR ($CDCl_3$) δ: 32.3, 45.5, 49.7, 53.5, 56.7, 63.4, 115.0 (d, J=11.1 Hz), 127.1, 128.3, 129.1, 130.1, 137.3, 138.3, 161.6 (d, J=244.8 Hz). IR (film) cm^{-1}: 1222, 1509, 2933. MS (ESI+) *m*/*z*: 285 ($M+H^+$), 267 (base peak). HR-MS (ESI+) *m*/*z*: Found 285.1770 (Calcd for $C_{18}H_{22}FN_2$ ($M+H^+$) 285.1767). *trans*-**11d**: yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 1.59 (1H, dq, J=12.5, 4.1 Hz), 1.92–1.96 (1H, m), 2.06–2.18 (2H, m), 2.57 (1H, dt, J=10.8, 3.7 Hz), 2.81 (1H, dt, J=10.8, 4.1 Hz), 2.90 (1H, ddd, J=11.4, 3.7, 2.1 Hz), 2.97–3.00 (1H, m), 3.54 (2H, s), 6.97–7.02 (2H, m), 7.16–7.22 (2H, m), 7.23–7.31 (5H, m). ^{13}C-NMR ($CDCl_3$) δ: 34.4, 51.6, 52.9, 53.8, 59.9, 62.9, 115.6 (d, J=21.1 Hz), 127.2, 128.4, 129.2, 129.6 (d, J=7.7 Hz), 137.2 (d, J=3.1 Hz), 138.1, 161.9 (d, J=244.9 Hz). IR (film) cm^{-1}: 1509, 1603, 2802, 2934. MS (ESI+) *m*/*z*: 285 ($M+H^+$), 250 (base peak). HR-MS (ESI+) *m*/*z*: Found 285.1775 (Calcd for $C_{18}H_{22}FN_2$ ($M+H^+$) 285.1767).

***cis*- and *trans*-4-Amino-1-*N*-benzyl-3-(4-chlorophenyl)-piperidine (*cis*-, *trans*-11e)** To a stirred suspension of $LiAlH_4$ (281 mg, 7.43 mmol) in THF (20 mL) was added dropwise a solution of **10e** (778 mg, 2.48 mmol) in THF (10 mL) at rt under nitrogen atmosphere. After being stirred at reflux for 1.5 h, the reaction mixture was quenched with H_2O and filtrated through Celite pad and extracted with $CHCl_3$. The residue was treated with THF and refluxed for 30 min. After filtration, the combined organic layers were dried over anhydrous Na_2SO_4 and evaporated. The resulting residue was purified by chromatography on SiO_2 ($CHCl_3$–MeOH=10 : 1) to yield the primary amine (581 mg, 1.94 mmol, 78%, *cis*–*trans*=4 : 1). *cis*-**11e**: yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 1.39 (2H, br), 1.64–1.71 (1H, m), 1.87–1.93 (1H, m), 2.50–2.56 (2H, m), 2.66 (1H, dd, J=10.8, 2.9 Hz), 2.78 (1H, t, J=9.8 Hz), 3.01–3.05 (1H, m), 3.17–3.20 (1H, m), 3.55 (1H, d, J=13.1 Hz), 3.59 (1H, d, J=13.1 Hz), 7.22–7.36 (9H, m). ^{13}C-NMR ($CDCl_3$) δ: 32.5, 45.7, 49.0, 49.5, 52.7, 63.3, 126.9, 128.1, 128.2, 128.9, 129.9, 132.0, 138.3, 140.1. IR (film) cm^{-1}: 1090, 1491, 2808, 2933. MS (ESI+) *m*/*z*: 301 ($M+H^+$, base peak). HR-MS (ESI+) *m*/*z*: Found 301.1472 (Calcd for $C_{18}H_{22}ClN_2$ ($M+H^+$) 301.1472). *trans*-**11e**: yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 1.46 (2H, br), 1.58 (1H, dq, J=12.7, 4.2 Hz), 1.93 (1H, ddd, J=12.7, 6.9, 2.6 Hz), 2.08 (1H, t, J=11.4 Hz), 2.15 (1H, dt, J=12.0, 2.6 Hz), 2.55 (1H, dt, J=10.8, 3.7 Hz), 2.82 (1H, dt, J=10.8, 4.2 Hz), 2.88 (1H, ddd, J=11.4, 3.7, 2.1 Hz), 2.96–3.00 (1H, m), 3.53 (2H, s), 7.16 (2H, d, J=8.4 Hz), 7.23–7.31 (7H, m). ^{13}C-NMR ($CDCl_3$) δ: 34.6, 52.0, 52.9, 53.6, 59.7, 62.8, 127.0, 128.2, 128.7, 129.0, 129.5, 132.5, 138.1, 140.1. IR (film) cm^{-1}: 1090, 1492, 2799, 2932. MS (ESI+) *m*/*z*: 301 ($M+H^+$, base peak). HR-MS (ESI+) *m*/*z*: Found 301.1447 (Calcd for $C_{18}H_{22}ClN_2$ ($M+H^+$) 301.1472).

3-{*N*-Benzyl-*N*-[2-(3-chlorophenyl)-acetyl]-amino}-propionic Acid Ethyl Ester (14f) 3-Chlorophenylacetic acid (2.47 g, 14.5 mmol) and ethyl 3-(*N*-benzylamino)propionate (3.00 g, 14.5 mmol) and DMAP (2.65 g, 21.8 mmol) were dissolved in CH_2Cl_2 (150 mL) at 0°C under nitrogen atmosphere. After being stirred for 1 h, EDC (3.31 g, 17.4 mmol) was added to the reaction mixture and stirred for 15 h. The reaction mixture was washed with saturated aqueous $KHSO_4$ and dried over anhydrous Na_2SO_4 and evaporated. The resulting residue was purified by chromatography on SiO_2 (*n*-hexane–EtOAc=2 : 1) to yield **14f** (5.18 g, 14.4 mmol, 99%) as a light yellow oil. The NMR spectra of **14f** showed a mixture of two rotamers. The ratio of two rotamers was 13 : 7. ^{1}H-NMR ($CDCl_3$) δ: 1.22 (3H of rotamer A, t, J=7.2 Hz), 1.25 (3H of rotamer B, t, J=7.1 Hz), 2.43 (2H of rotamer B, t, J=7.2 Hz), 2.64 (2H of rotamer A, t, J=6.9 Hz), 3.56 (2H of rotamer B, t, J=7.2 Hz), 3.64–3.68 (4H of rotamer A, m), 3.84 (2H of rotamer B, s), 4.06–4.15 (4H, 2H of rotamer A, m, 2H of rotamer B, m), 4.60 (2H of rotamer A, s), 4.62 (2H of rotamer B, s), 7.07–7.39 (18H, 9H of rotamer A, m, 9H of rotamer B, m). ^{13}C-NMR ($CDCl_3$) δ: 14.1, 32.6, 33.3, 40.2, 40.2, 42.8, 43.3, 48.1, 52.5, 60.5, 60.9, 126.1, 127.0, 127.0, 127.1, 127.4, 127.7, 127.9, 128.6, 128.9, 128.9, 129.0, 129.7, 129.8, 134.3, 134.4, 136.5, 136.7, 136.9, 137.1, 170.4, 170.9, 171.9. IR (film) cm^{-1}: 1190, 1450, 1650, 1730. MS (ESI+) *m*/*z*: 382 ($M+Na^+$, base peak). HR-MS (ESI+) *m*/*z*: Found 382.1234 (Calcd for $C_{20}H_{22}ClNNaO_3$ ($M+Na^+$) 382.1186).

3-{*N*-Benzyl-*N*-[2-(2-chlorophenyl)-acetyl]-amino}-propionic Acid Ethyl Ester (14g)

Prepared According to Procedure for the Preparation of **14f**

Yield: 99%. Light yellow oil. The NMR spectra of **14g** showed a mixture of two rotamers. The ratio of two rotamer was 13 : 7. ^{1}H-NMR ($CDCl_3$) δ: 1.23 (3H of rotamer A, t, J=7.1 Hz), 1.25 (3H of rotamer B, t, J=7.2 Hz), 2.53 (2H of rotamer B, t, J=7.4 Hz), 2.66 (2H of rotamer A, t, J=6.9 Hz), 3.63 (2H of rotamer B, t, J=7.4 Hz), 3.67 (2H of rotamer A, t, J=6.9 Hz), 3.80 (2H of rotamer A, s), 3.93 (2H of rotamer B, s), 4.07–4.16 (4H, 2H of rotamer A, m, 2H of rotamer B, m), 4.65 (2H of rotamer B, s), 4.66 (2H of rotamer A, s), 7.18–7.40 (18H, 9H of rotamer A, m, 9H of rotamer B, m). ^{13}C-NMR ($CDCl_3$) δ: 14.1, 32.6, 33.4, 38.0, 38.2, 42.8, 43.2, 48.4, 52.5, 60.5, 60.9, 126.3, 126.9, 126.9, 127.4, 127.6, 128.0, 128.3,

128.4, 128.5, 128.9, 129.3, 129.4, 130.9, 131.1, 133.3, 133.4, 134.0, 134.0, 136.6, 137.3, 170.1, 170.5, 170.9, 172.0. IR (film) cm^{-1}: 1375, 1445, 1651, 1731. MS (ESI+) *m/z*: 360 ($M+H^+$, base peak). HR-MS (ESI+) *m/z*: Found 360.1415 (Calcd for $C_{20}H_{23}ClNO_3$ ($M+H^+$) 360.1367).

1-*N*-Benzyl-3-(3-chlorophenyl)-2,4-piperidinedione (15f) To a stirred suspension of NaOEt (2.85 g, 41.8 mmol) in toluene (200 mL) was slowly added a solution of **14f** (5.00 g, 13.9 mmol) in toluene (40 mL) at rt under nitrogen atmosphere. After being stirred at reflux for 4 h, the reaction mixture was acidified with 1 M aqueous HCl and extracted with EtOAc. The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated to give **15f** and was used without further purification. For measurement of spectroscopic data, **15f** mixture was purified by chromatography on SiO_2 (*n*-hexane–EtOAc=2 : 3) to gain a colorless solid, mp 118–120°C. ^{1}H-NMR ($CDCl_3$) δ: 2.64–2.67 (2H, m), 3.45–3.56 (2H, m), 4.53 (1H, s), 4.72 (1H, d, *J*=14.5 Hz), 4.79 (1H, d, *J*=14.5 Hz), 7.07–7.09 (1H, m), 7.18–7.19 (1H, m), 7.28–7.40 (7H, m). ^{13}C-NMR ($CDCl_3$) δ: 37.7, 41.6, 50.7, 63.7, 127.1, 128.1, 128.2, 128.3, 128.6, 128.9, 130.0, 134.2, 134.7, 136.1, 167.0, 202.7. IR (KBr) cm^{-1}: 1381, 1479, 1603, 1661. MS (ESI+) *m/z*: 314 ($M+H^+$, base peak). HR-MS (ESI+) *m/z*: Found 314.0976 (Calcd for $C_{18}H_{17}ClNO_2$ ($M+H^+$) 314.0948).

1-*N*-Benzyl-3-(2-chlorophenyl)-2,4-piperidinedione (15g)

Prepared According to Procedure for the Preparation of **15f**

Colorless solid, mp 163–166°C. ^{1}H-NMR ($CDCl_3$) δ: 2.71–2.83 (2H, m), 3.48–3.55 (1H, m), 3.71 (1H, ddd, *J*=13.5, 8.6, 5.1 Hz), 4.61 (1H, d, *J*=14.6 Hz), 4.65 (1H, s), 4.90 (1H, d, *J*=14.6 Hz), 7.23–7.25 (1H, m), 7.29–7.39 (7H, m), 7.41–7.43 (1H, m). ^{13}C-NMR ($CDCl_3$) δ: 38.59, 41.71, 50.8, 62.9, 127.0, 127.9, 128.4, 128.9, 129.4, 129.7, 132.3, 133.2, 133.8, 136.3, 166.5, 201.8. IR (KBr) cm^{-1}: 1380, 1480, 1596, 1670. MS (ESI+) *m/z*: 314 ($M+H^+$, base peak). HR-MS (ESI+) *m/z*: Found 314.0981 (Calcd for $C_{18}H_{17}ClNO_2$ ($M+H^+$) 314.0948).

1-*N*-Benzyl-3-(3-chlorophenyl)-4-hydroxyimino-2-piperidone (16f)

Prepared According to Procedure for the Preparation of **10a**

Brown oil. ^{1}H-NMR shows a doubled signal set (isomer A and B, ratio 4 : 1). ^{1}H-NMR ($CDCl_3$) δ: 2.56 (1H of isomer B, dt, *J*=15.0, 5.0 Hz), 2.61–2.69 (2H, 1H of isomer A, dt, *J*=18.5, 4.5, 1H of isomer B, m), 2.81 (1H of isomer A, ddd, *J*=18.5, 9.5, 6.9 Hz), 3.11–3.24 (2H of isomer A, m), 3.31 (1H of isomer B, ddd, *J*=12.4, 9.4, 5.0 Hz), 3.41 (1H of isomer B, dt, *J*=12.4, 5.2 Hz), 4.55 (1H of isomer B, d, *J*=14.5 Hz), 4.62 (1H of isomer A, s), 4.68 (2H of isomer A, s), 4.83 (1H of isomer B, d, *J*=14.5 Hz), 5.33 (1H of isomer B, s), 7.16–7.19 (1H of isomer A, m), 7.23–7.37 (17H, 8H of isomer A, m, 9H of isomer B, m). ^{13}C-NMR ($CDCl_3$), (isomer A) δ: 23.9, 42.1, 50.4, 53.2, 125.5, 127.4, 127.8, 128.0, 128.2, 128.7, 130.0, 134.7, 136.2, 136.9, 154.5, 169.0; (isomer B) δ: 26.9, 44.4, 47.4, 50.7, 126.3, 127.5, 127.7, 128.1, 128.7, 128.7, 129.9, 134.4, 136.2, 138.0, 153.4, 167.9. IR (film) cm^{-1}: 972, 1485, 1635, 3215. MS (ESI+) *m/z*: 351 ($M+Na^+$, base peak). HR-MS (ESI+) *m/z*: Found 351.0900 (Calcd for $C_{18}H_{17}ClN_2NaO_2$ ($M+Na^+$) 351.0876).

1-*N*-Benzyl-3-(2-chlorophenyl)-4-hydroxyimino-2-piperidone (16g)

Prepared According to Procedure for the Preparation of **10a**

Brown oil. ^{1}H-NMR shows a single isomer. ^{1}H-NMR ($CDCl_3$) δ: 2.87 (2H, t, *J*=6.0 Hz), 3.39–3.54 (2H, m), 4.57 (1H, d, *J*=14.6 Hz), 4.74 (1H, s), 4.84 (1H, d, *J*=14.6 Hz), 7.20–7.42 (9H, m). ^{13}C-NMR ($CDCl_3$) δ: 24.2, 42.6, 50.7, 51.8, 126.7, 127.7, 128.3, 128.7, 128.9, 129.7, 132.6, 133.9, 134.0, 136.5, 155.3, 167.8. IR (film) cm^{-1}: 754, 1446, 1643, 3300. MS (ESI+) *m/z*: 329 ($M+H^+$, base peak). HR-MS (ESI+) *m/z*: Found 329.1102 (Calcd for $C_{18}H_{18}ClN_2O_2$ ($M+H^+$) 329.1057).

***cis*- and *trans*-4-Amino-1-*N*-benzyl-3-(3-chlorophenyl)-piperidine (*cis*-, *trans*-11f)**

Prepared According to Procedure for the Preparation of **11e**

Yield: 30% over three steps (*cis*–*trans*=3 : 1). ***cis*-11f**: yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 1.34 (2H, br), 1.65–1.72 (1H, m), 1.89–1.94 (1H, m), 2.54–2.67 (3H, m), 2.79 (1H, t, *J*=9.9 Hz), 3.02–3.06 (1H, m), 3.20–3.22 (1H, m), 3.57 (2H, s), 7.19–7.26 (4H, m), 7.30–7.37 (5H, m). ^{13}C-NMR ($CDCl_3$) δ: 18.4, 32.3, 46.0, 49.7, 57.6, 63.3, 126.6, 126.9, 127.0, 128.2, 128.9, 129.1, 129.3, 134.0, 138.3, 143.7. IR (film) cm^{-1}: 698, 1453, 1595, 2931. MS (ESI+) *m/z*: 301 ($M+H^+$, base peak). HR-MS (ESI+) *m/z*: Found 301.1506 (Calcd for $C_{18}H_{22}ClN_2$ ($M+H^+$) 301.1472). ***trans*-11f**: yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 1.54–1.63 (1H, m), 1.94 (1H, ddd, *J*=12.9, 6.9, 2.6 Hz), 2.10 (1H, t, *J*=11.4 Hz), 2.16 (1H, dt, *J*=12.0, 2.6 Hz), 2.56 (1H, dt, *J*=10.8, 3.8 Hz), 2.84 (1H, dt, *J*=10.8, 4.2 Hz), 2.90 (1H, ddd, *J*=11.4, 3.8, 2.1 Hz), 2.96–3.01 (1H, m), 3.54 (2H, s), 7.09–7.12 (1H, dt, *J*=6.9, 1.7 Hz), 7.20–7.26 (4H, m), 7.28–7.31 (4H, m). ^{13}C-NMR ($CDCl_3$) δ: 34.5, 52.3, 52.9, 53.5, 59.5, 62.8, 126.5, 127.0, 127.1, 128.1, 128.2, 129.1, 129.9, 134.4, 138.0, 143.7. IR (film) cm^{-1}: 698, 1453, 1595, 2932. MS (ESI+) *m/z*: 301 ($M+H^+$, base peak). HR-MS (ESI+) *m/z*: Found 301.1505 (Calcd for $C_{18}H_{22}ClN_2$ ($M+H^+$) 301.1472).

***cis*- and *trans*-4-Amino-1-*N*-benzyl-3-(2-chlorophenyl)-piperidine (*cis*-, *trans*-11g)**

Prepared According to Procedure for the Preparation of **11e**

Yield: 17% over three steps (*cis*–*trans*=3 : 2). ***cis*-11g**: yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 1.53 (2H, br), 1.59–1.69 (1H, m), 1.96–2.00 (2H, m), 2.18 (1H, dt, *J*=12.0, 2.5 Hz), 2.90–2.95 (2H, m), 2.97–3.02 (1H, m), 3.27–3.29 (1H, m), 3.56 (2H, s), 7.15 (1H, ddd, *J*=7.9, 6.9, 2.1 Hz), 7.22–7.33 (7H, m), 7.37 (1H, dd, *J*=7.9, 1.1 Hz). ^{13}C-NMR ($CDCl_3$) δ: 29.7, 32.3, 42.6, 48.6, 51.8, 63.5, 126.5, 127.0, 127.5, 128.2, 129.1, 129.2, 129.7, 134.3, 138.3, 139.2. IR (film) cm^{-1}: 749, 1473, 2925. MS (ESI+) *m/z*: 301 ($M+H^+$, base peak). HR-MS (ESI+) *m/z*: Found 301.1507 (Calcd for $C_{18}H_{22}ClN_2$ ($M+H^+$) 301.1472). ***trans*-11g**: yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 1.59 (1H, dq, *J*=12.8, 4.2 Hz), 1.95 (1H, ddd, *J*=12.8, 6.8, 2.7 Hz), 2.10–2.20 (2H, m), 2.57 (1H, dt, *J*=10.8, 3.7 Hz), 2.86 (1H, dt, *J*=10.8, 4.2 Hz), 2.93 (1H, ddd, *J*=11.4, 3.7, 2.1 Hz), 2.97–3.02 (1H, m), 3.54 (2H, s), 7.21–7.33 (9H, m). ^{13}C-NMR ($CDCl_3$) δ: 34.6, 47.6, 52.8, 53.2, 58.7, 62.5, 127.0, 127.1, 127.7, 128.2, 128.3, 129.0, 129.3, 129.9, 138.1, 138.8. IR (film) cm^{-1}: 753, 1474, 2927. MS (ESI+) *m/z*: 301 ($M+H^+$, base peak). HR-MS (ESI+) *m/z*: Found 301.1511 (Calcd for $C_{18}H_{22}ClN_2$ ($M+H^+$) 301.1472).

***cis*-1-*N*-Benzyl-4-*N*,*N*-dimethylamino-3-phenylpiperidine (*cis*-17a)** Thirty-seven percent HCHO (0.63 mL, 7.50 mmol, in aqueous solution) and HCO_2H (0.79 mL, 15.0 mmol) were added to ***cis*-11a** (200 mg, 0.75 mmol). After being stirred at reflux for 24 h, the reaction mixture was alkalized with 1 M aqueous NaOH and extracted with $CHCl_3$. The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated to yield ***cis*-17a** (205 mg, 0.70 mmol, 93%) as a brown oil and was used without further purification. ^{1}H-NMR ($CDCl_3$) δ: 1.68–1.72 (1H, m), 1.93–2.08 (2H, m), 2.11 (6H, s), 2.35–2.42 (2H, m), 2.98 (1H, dt, *J*=11.4, 2.3 Hz), 3.05–3.08 (1H, m),

3.15 (1H, d, J=2.7 Hz), 3.42 (1H, d, J=13.3 Hz), 3.47 (1H, d, J=13.3 Hz), 7.18–7.22 (2H, m), 7.23–7.24 (1H, m), 7.25–7.30 (5H, m), 7.77 (2H, d, J=7.2 Hz). ^{13}C-NMR ($CDCl_3$) δ: 25.0, 43.0, 43.7, 53.3, 59.1, 63.1, 66.6, 126.1, 126.8, 127.6, 128.1, 128.8, 130.6, 138.9, 143.0. IR (film) cm^{-1}: 1460, 1500, 2760, 2940. MS (EI) m/z: 294 ($M+H^+$), 91 (base peak). HR-MS (EI) m/z: Found 294.2072 (Calcd for $C_{20}H_{26}N_2$ ($M+H^+$) 294.2096).

***cis*-1-*N*-Benzyl-4-*N*,*N*-dimethylamino-3-(4-methylphenyl)piperidine (*cis*-17b)**

Prepared According to Procedure for the Preparation of *cis*-**17a**

Yield: 99%. Brown oil. ^{1}H-NMR ($CDCl_3$) δ: 1.66–1.70 (1H, m), 1.94–2.07 (2H, m), 2.12 (6H, s), 2.28–2.36 (1H, m), 2.32 (3H, s), 2.39 (1H, dd, J=11.4, 3.4 Hz), 2.97 (1H, d, J=11.4 Hz), 3.04 (1H, d, J=10.0 Hz), 3.11 (1H, br), 3.39 (1H, d, J=13.2 Hz), 3.48 (1H, d, J=13.2 Hz), 7.10 (2H, d, J=7.8 Hz), 7.18–7.28 (5H, m), 7.66 (2H, d, J=7.8 Hz). ^{13}C-NMR ($CDCl_3$) δ: 21.0, 25.1, 43.2, 43.3, 53.2, 59.3, 63.1, 66.7, 126.8, 128.1, 128.3, 128.8, 130.4, 135.4, 138.9, 140.0. IR (film) cm^{-1}: 1453, 1512, 2764, 2940. MS (ESI+) m/z: 309 ($M+H^+$), 264 (base peak). HR-MS (ESI+) m/z: Found 309.2351 (Calcd for $C_{21}H_{29}N_2$ ($M+H^+$) 309.2331).

***cis*-1-*N*-Benzyl-4-*N*,*N*-dimethylamino-3-(3-methylphenyl)piperidine (*cis*-17c)**

Prepared According to Procedure for the Preparation of *cis*-**17a**

Yield: 99%. Brown oil. ^{1}H-NMR ($CDCl_3$) δ: 1.68–1.72 (1H, m), 1.96–2.10 (2H, m), 2.12 (6H, s), 2.34–2.37 (1H, m), 2.36 (3H, s), 2.40 (1H, dd, J=11.4, 3.6 Hz), 2.97 (1H, dt, J=11.4, 2.3 Hz), 3.05–3.11 (2H, m), 3.41 (1H, d, J=13.2 Hz), 3.47 (1H, d, J=13.2 Hz), 7.03 (1H, d, J=7.5 Hz), 7.15–7.23 (2H, m), 7.25–7.33 (4H, m), 7.56 (1H, d, J=7.8 Hz), 7.63 (1H, s). ^{13}C-NMR ($CDCl_3$) δ: 21.5, 24.8, 43.0, 43.5, 53.1, 58.9, 62.9, 66.5, 126.6, 126.7, 127.2, 127.5, 127.9, 128.6, 131.2, 136.5, 138.8, 142.7. IR (film) cm^{-1}: 1453, 2765, 2940. MS (ESI+) m/z: 309 ($M+H^+$), 264 (base peak). HR-MS (ESI+) m/z: Found 309.2309 (Calcd for $C_{21}H_{29}N_2$ ($M+H^+$) 309.2331).

***cis*-1-*N*-Benzyl-4-*N*,*N*-dimethylamino-3-(4-fluorophenyl)piperidine (*cis*-17d)**

Prepared According to Procedure for the Preparation of *cis*-**17a**

Yield: 97%. Brown oil. ^{1}H-NMR ($CDCl_3$) δ: 1.69–1.73 (1H, m), 1.91 (1H, dq, J=12.4, 4.1 Hz), 2.07 (1H, dt, J=11.6, 2.9 Hz), 2.12 (6H, s), 2.29–2.34 (1H, m), 2.37 (1H, dd, J=11.5, 3.6 Hz), 2.94 (1H, dt, J=11.5, 2.3 Hz), 3.05–3.10 (1H, m), 3.13 (1H, br), 3.44 (2H, s), 6.95–6.99 (2H, m), 7.20–7.29 (5H, m), 7.73–7.77 (2H, m). ^{13}C-NMR ($CDCl_3$) δ: 24.7, 42.7, 43.0, 53.4, 58.9, 63.0, 66.5, 114.2 (d, J=20.5 Hz), 126.8, 128.1, 128.8, 131.9 (d, J=7.4 Hz), 138.5 (d, J=3.3 Hz), 138.7, 161.5 (d, J=244.0 Hz). IR (film) cm^{-1}: 1453, 1507, 2767, 2940. MS (ESI+) m/z: 313 ($M+H^+$), 250 (base peak). HR-MS (ESI+) m/z: Found 313.2112 (Calcd for $C_{20}H_{26}FN_2$ ($M+H^+$) 313.2080).

***cis*-1-*N*-Benzyl-3-(4-chlorophenyl)-4-*N*,*N*-dimethylamino-piperidine (*cis*-17e)**

Prepared According to Procedure for the Preparation of *cis*-**17a**

Yield: 99%. Brown oil. ^{1}H-NMR ($CDCl_3$) δ: 1.75–1.78 (1H, m), 2.02 (1H, dq, J=12.4, 4.0 Hz), 2.14 (1H, dt, J=11.6, 2.5 Hz), 2.23 (6H, s), 2.46 (1H, dd, J=11.6, 3.5 Hz), 2.93–2.98 (2H, m), 3.14–3.17 (1H, m), 3.36 (1H, br), 3.47 (2H, s), 7.23–7.31 (7H, m), 7.85 (2H, d, J=8.5 Hz). ^{13}C-NMR ($CDCl_3$) δ: 22.8, 41.2, 41.6, 52.7, 58.8, 62.8, 65.8, 127.1, 128.3, 128.3, 128.9, 132.0, 133.0, 138.1, 139.7. IR (film) cm^{-1}: 1490, 2767, 2941. MS (ESI+) m/z: 329 ($M+H^+$, base peak). HR-MS (ESI+) m/z: Found 329.1793 (Calcd for $C_{20}H_{26}ClN_2$ ($M+H^+$) 329.1785).

***cis*-1-*N*-Benzyl-3-(3-chlorophenyl)-4-*N*,*N*-dimethylamino-piperidine (*cis*-17f)**

Prepared According to Procedure for the Preparation of *cis*-**17a**

Yield: 97%. Brown oil. ^{1}H-NMR ($CDCl_3$) δ: 1.68–1.73 (1H, m), 1.91 (1H, dq, J=12.4, 4.1 Hz), 2.05–2.11 (1H, m), 2.13 (6H, s), 2.31–2.39 (2H, m), 2.93 (1H, dt, J=11.5, 2.3 Hz), 3.07–3.11 (2H, m), 3.42 (1H, d, J=13.2 Hz), 3.47 (1H, d, J=13.2 Hz), 7.19–7.33 (8H, m), 7.53–7.55 (1H, m). ^{13}C-NMR ($CDCl_3$) δ: 24.5, 42.9, 42.9, 53.1, 58.4, 62.8, 66.3, 126.1, 126.8, 128.0, 128.5, 128.7, 128.7, 130.6, 133.2, 138.5, 144.8. IR (film) cm^{-1}: 698, 1473, 1595, 2769, 2940. MS (ESI+) m/z: 329 ($M+H^+$, base peak). HR-MS (ESI+) m/z: Found 329.1816 (Calcd for $C_{20}H_{26}ClN_2$ ($M+H^+$) 329.1785).

***cis*-1-*N*-Benzyl-3-(2-chlorophenyl)-4-*N*,*N*-dimethylamino-piperidine (*cis*-17g)**

Prepared According to Procedure for the Preparation of *cis*-**17a**

Yield: 99%. Brown oil. ^{1}H-NMR ($CDCl_3$) δ: 1.84–1.88 (1H, m), 2.12 (6H, s), 2.13–2.19 (2H, m), 2.36–2.44 (2H, m), 2.86 (1H, dt, J=11.6, 2.6 Hz), 3.00–3.01 (1H, m), 3.41 (1H, d, J=13.6 Hz), 3.46 (1H, d, J=13.6 Hz), 3.71–3.74 (1H, m), 7.12–7.22 (7H, m), 7.25 (1H, dt, J=7.6, 1.5 Hz), 7.32 (1H, dd, J=7.9, 1.5 Hz). ^{13}C-NMR ($CDCl_3$) δ: 22.1, 30.0, 38.0, 53.4, 54.3, 58.5, 63.4, 126.3, 126.9, 127.2, 127.9, 128.2, 129.3, 129.5, 134.7, 138.1, 139.8. IR (film) cm^{-1}: 740, 1471, 2767, 2949. MS (ESI+) m/z: 329 ($M+H^+$, base peak). HR-MS (ESI+) m/z: Found 329.1833 (Calcd for $C_{20}H_{26}ClN_2$ ($M+H^+$) 329.1785).

***trans*-1-*N*-Benzyl-4-*N*,*N*-dimethylamino-3-phenylpiperidine (*trans*-17a)**

Prepared According to Procedure for the Preparation of *cis*-**17a**

Yield: 92%. Brown oil. ^{1}H-NMR ($CDCl_3$) δ: 1.68 (1H, dq, J=12.1, 3.7 Hz), 1.80–1.83 (1H, m), 1.96–2.12 (2H, m), 2.16 (6H, s), 2.75 (1H, dt, J=11.2, 2.8 Hz), 2.90–2.99 (2H, m), 3.02–3.05 (1H, m), 3.48 (1H, d, J=13.2 Hz), 3.52 (1H, d, J=13.2 Hz), 7.18–7.23 (4H, m), 7.25–7.29 (6H, m). ^{13}C-NMR ($CDCl_3$) δ: 22.9, 40.3, 46.6, 53.2, 62.1, 62.9, 64.9, 126.4, 127.0, 127.9, 128.2, 128.3, 129.1, 138.1, 142.8. IR (film) cm^{-1}: 1450, 2920. MS (CI) m/z: 295 ($M+H^+$), 116 (base peak). HR-MS (CI) m/z: Found 295.2163 (Calcd for $C_{20}H_{27}N_2$ ($M+H^+$) 295.2174).

***trans*-1-*N*-Benzyl-4-*N*,*N*-dimethylamino-3-(4-methylphenyl)piperidine (*trans*-17b)**

Prepared According to Procedure for the Preparation of *cis*-**17a**

Yield: 99%. Brown oil. ^{1}H-NMR ($CDCl_3$) δ: 1.66 (1H, dq, J=12.4, 3.8 Hz), 1.78–1.82 (1H, m), 2.00–2.06 (2H, m), 2.16 (6H, s), 2.29 (3H, s), 2.72 (1H, dt, J=11.1, 3.3 Hz), 2.88–2.95 (2H, m), 3.03 (1H, d, J=11.0 Hz), 3.47 (1H, d, J=13.3 Hz), 3.51 (1H, d, J=13.3 Hz), 7.06–7.11 (4H, m), 7.19–7.28 (5H, m). ^{13}C-NMR ($CDCl_3$) δ: 21.1, 22.7, 40.3, 46.2, 53.2, 62.2, 62.9, 64.9, 126.9, 127.6, 128.1, 129.0, 129.1, 135.7, 138.1, 139.8. IR (film) cm^{-1}: 1038, 1453, 1514, 2776, 2935. MS (ESI+) m/z: 309 ($M+H^+$), 264 (base peak). HR-MS (ESI+) m/z: Found 309.2343 (Calcd for $C_{21}H_{29}N_2$ ($M+H^+$) 309.2331).

***trans*-1-*N*-Benzyl-4-*N*,*N*-dimethylamino-3-(3-methylphenyl)piperidine (*trans*-17c)**

Prepared According to Procedure for the Preparation of *cis*-**17a**

Yield: 94%. Brown oil. ^{1}H-NMR ($CDCl_3$) δ: 1.68 (1H, dq, J=12.4, 3.9 Hz), 1.82 (1H, ddd, J=12.4, 6.3, 2.9 Hz), 2.01–2.08 (2H, m), 2.17 (6H, s), 2.32 (3H, s), 2.76 (1H, dt, J=11.1, 3.9 Hz), 2.88–2.95 (2H, m), 3.02–3.05 (1H, m), 3.48 (1H, d, J=13.2 Hz), 3.52 (1H, d, J=13.2 Hz), 6.99–7.01 (3H, m), 7.16 (1H, t, J=7.7 Hz), 7.21–7.26 (1H, m), 7.29–7.30 (4H, m). ^{13}C-NMR ($CDCl_3$) δ: 21.5, 22.8, 40.4, 46.6, 53.3, 62.1, 62.9, 64.9, 124.9, 127.0, 127.3, 128.2, 128.2, 128.6, 129.1, 137.7, 138.2, 142.8. IR (film) cm^{-1}: 1454, 2777, 2935. MS (ESI+) *m*/*z*: 309 (M+H$^+$), 264 (base peak). HR-MS (ESI+) *m*/*z*: Found 309.2313 (Calcd for $C_{21}H_{29}N_2$ (M+H$^+$) 309.2331).

***trans*-1-Benzyl-4-*N*,*N*-dimethylamino-3-(4-fluorophenyl)piperidine (*trans*-17d)**

Prepared According to Procedure for the Preparation of *cis*-**17a**

Yield: 74%. Brown oil. ^{1}H-NMR ($CDCl_3$) δ: 1.66 (1H, dq, J=12.4, 4.0 Hz), 1.82 (1H, ddd, J=12.4, 6.5, 3.0 Hz), 1.98–2.07 (2H, m), 2.16 (6H, s), 2.69 (1H, dt, J=11.2, 3.8 Hz), 2.87–2.97 (2H, m), 3.02–3.06 (1H, m), 3.48 (1H, d, J=13.1 Hz), 3.52 (1H, d, J=13.1 Hz), 6.94–6.98 (2H, m), 7.14–7.18 (2H, m), 7.23–7.33 (5H, m). ^{13}C-NMR ($CDCl_3$) δ: 22.6, 40.4, 46.1, 53.3, 62.3, 63.0, 65.2, 115.3 (d, J=21.1 Hz), 127.2, 128.3, 129.2, 129.3, 138.2, 138.5 (d, J=3.3 Hz), 161.5 (d, J=243.8 Hz). IR (film) cm^{-1}: 1453, 1509, 2779, 2935. MS (ESI+) *m*/*z*: 313 (M+H$^+$), 268 (base peak). HR-MS (ESI+) *m*/*z*: Found 313.2124 (Calcd for $C_{20}H_{26}FN_2$ (M+H$^+$) 313.2080).

***trans*-1-*N*-Benzyl-3-(4-chlorophenyl)-4-*N*,*N*-dimethylaminopiperidine (*trans*-17e)**

Prepared According to Procedure for the Preparation of *cis*-**17a**

Yield: 77%. Brown oil. ^{1}H-NMR ($CDCl_3$) δ: 1.66 (1H, dq, J=12.4, 3.9 Hz), 1.82 (1H, ddd, J=12.4, 6.4, 2.7 Hz), 2.00 (1H, t, J=11.0 Hz), 2.04 (1H, dt, J=11.8, 2.7 Hz), 2.16 (6H, s), 2.70 (1H, dt, J=11.0, 3.8 Hz), 2.86–2.96 (2H, m), 3.03–3.06 (1H, m), 3.48 (1H, d, J=13.4 Hz), 3.52 (1H, d, J=13.4 Hz), 7.13 (2H, d, J=8.4 Hz), 7.24 (2H, d, J=8.4 Hz), 7.24–7.32 (5H, m). ^{13}C-NMR ($CDCl_3$) δ: 22.3, 40.3, 46.2, 53.2, 61.9, 62.9, 65.0, 127.0, 128.2, 128.5, 129.1, 129.1, 131.9, 138.0, 141.3. IR (film) cm^{-1}: 1091, 1492, 2780, 2936. MS (ESI+) *m*/*z*: 329 (M+H$^+$, base peak). HR-MS (ESI+) *m*/*z*: Found 329.1818 (Calcd for $C_{20}H_{26}ClN_2$ (M+H$^+$) 329.1785).

***trans*-1-*N*-Benzyl-3-(3-chlorophenyl)-4-*N*,*N*-dimethylaminopiperidine (*trans*-17f)**

Prepared According to Procedure for the Preparation of *cis*-**17a**

Yield: 92%. Brown oil. ^{1}H-NMR ($CDCl_3$) δ: 1.66 (1H, dq, J=12.4, 3.8 Hz), 1.82 (1H, ddd, J=12.4, 6.0, 2.9 Hz), 1.99–2.08 (2H, m), 2.17 (6H, s), 2.71 (1H, dt, J=11.3, 3.8 Hz), 2.87–2.96 (2H, m), 3.04 (1H, ddd, J=11.0, 6.0, 3.8 Hz), 3.50 (2H, s), 7.08 (1H, dt, J=7.3, 1.5 Hz), 7.14–7.20 (4H, m), 7.22–7.31 (4H, m). ^{13}C-NMR ($CDCl_3$) δ: 22.4, 40.3, 46.5, 53.1, 61.7, 62.8, 64.9, 126.1, 126.6, 127.0, 127.9, 128.2, 129.1, 129.6, 134.0, 138.0, 144.9. IR (film) cm^{-1}: 698, 1453, 2781, 2935. MS (ESI+) *m*/*z*: 329 (M+H$^+$, base peak). HR-MS (ESI+) *m*/*z*: Found 329.1795 (Calcd for $C_{20}H_{26}ClN_2$ (M+H$^+$) 329.1785).

***trans*-1-Benzyl-3-(2-chlorophenyl)-4-*N*,*N*-dimethylaminopiperidine (*trans*-17g)**

Prepared According to Procedure for the Preparation of *cis*-**17a**

Yield: 41%. Brown oil. ^{1}H-NMR ($CDCl_3$) δ: 1.72 (1H, dq, J=12.1, 3.9 Hz), 1.82–1.92 (2H, m), 2.08 (1H, dt, J=11.4, 2.7 Hz), 2.18 (6H, s), 2.78–2.83 (1H, m), 2.94 (1H, ddd, J=11.3, 3.5, 2.1 Hz), 3.05 (1H, ddd, J=11.4, 5.9, 3.1 Hz), 3.51 (1H, d, J=13.3 Hz), 3.56 (1H, d, J=13.3 Hz), 3.56–3.59 (1H, m), 7.11 (1H, ddd, J=7.9, 7.2, 1.8 Hz), 7.19–7.33 (8H, m). ^{13}C-NMR ($CDCl_3$) δ: 22.0, 40.3, 41.9, 52.9, 60.5, 62.5, 64.0, 126.6, 126.9, 127.2, 128.1, 128.2, 128.9, 129.5, 134.1, 138.0, 139.5. IR (film) cm^{-1}: 750, 1036, 1453, 2780, 2936. MS (ESI+) *m*/*z*: 329 (M+H$^+$), 284 (base peak). HR-MS (ESI+) *m*/*z*: Found 329.1833 (Calcd for $C_{20}H_{26}ClN_2$ (M+H$^+$) 329.1785).

***cis*-4-*N*,*N*-Dimethylamino-1-*N*-pentanoyl-3-phenylpiperidine (*cis*-4a)** Pd–C (10 mg, 10% (w/w)) and HCO_2NH_4 (69 mg, 1.09 mmol) were added to a solution of *cis*-**17a** (50 mg, 0.17 mmol) in MeOH (3 mL). After being stirred at reflux for 4 h, the reaction mixture was filtrated through Celite pad and poured on H_2O and extracted with $CHCl_3$. The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated. The resulting residue was used in the subsequent reaction without further purification. Et_3N (53 μL, 0.60 mmol) and BuCOCl (36 μL, 0.30 mmol) were added to a solution of crude in CH_2Cl_2 (3 mL). After being stirred at rt for 18 h, the reaction mixture was alkalized with 1 M aqueous NaOH and extracted with $CHCl_3$. The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated. The resulting residue was purified by chromatography on SiO_2 ($CHCl_3$–MeOH=10 : 1) to yield *cis*-**4a** (20 mg, 0.07 mmol, 41% over two steps) as a light yellow oil. ^{1}H-NMR (C_6D_6, 80°C) δ: 0.81 (3H, t, J=6.9 Hz), 1.18–1.27 (3H, m), 1.44 (1H, dd, J=13.3, 3.3 Hz), 1.52–1.59 (3H, m), 1.75–1.90 (3H, m), 1.94 (6H, s), 2.24 (1H, dt, J=11.7, 4.5 Hz), 2.51–2.56 (1H, m), 2.88 (1H, m), 2.93 (1H, dd, J=13.4, 3.7 Hz), 7.04 (1H, tt, J=7.4, 1.5 Hz), 7.12 (2H, t, J=7.4 Hz), 7.31–7.32 (2H, m). ^{13}C-NMR (C_6D_6, 60°C) δ: 14.0, 22.7, 25.7, 27.5, 30.1, 32.6, 43.0, 59.8, 66.3, 78.1, 126.6, 128.2, 130.0, 141.9, 171.0. IR (film) cm^{-1}: 1050, 1450, 1640, 2960. MS (EI) *m*/*z*: 288 (M$^+$), 84 (base peak). HR-MS (EI) *m*/*z*: Found 288.2209 (Calcd for $C_{18}H_{28}N_2O$ (M$^+$) 288.2201).

***cis*-4-*N*,*N*-Dimethylamino-3-(4-methylphenyl)-1-*N*-pentanoylpiperidine (*cis*-4b)**

Prepared According to Procedure for the Preparation of *cis*-**4a**

Yield: 27% over two steps. Light yellow oil. ^{1}H-NMR (C_6D_6, 80°C) δ: 0.81 (3H, t, J=6.9 Hz), 1.22–1.36 (4H, m), 1.44–1.46 (1H, m), 1.57–1.58 (2H, m), 1.80–1.90 (3H, m), 1.96 (6H, s), 2.10 (3H, s), 2.25–2.27 (1H, m), 2.53 (1H, br), 2.90–2.96 (2H, m), 6.96 (2H, d, J=7.8 Hz), 7.24 (2H, d, J=7.8 Hz). ^{13}C-NMR (C_6D_6, 60°C) δ: 14.0, 20.9, 22.8, 25.5, 27.6, 30.2, 32.7, 42.9, 50.6, 66.4, 77.9, 129.1, 130.0, 136.0, 138.8, 171.1. IR (film) cm^{-1}: 1439, 1513, 1644, 2956. MS (ESI+) *m*/*z*: 303 (M+H$^+$, base peak). HR-MS (ESI+) *m*/*z*: Found 303.2467 (Calcd for $C_{19}H_{31}N_2O$ (M+H$^+$) 303.2436).

***cis*-4-*N*,*N*-Dimethylamino-3-(3-methylphenyl)-1-*N*-pentanoylpiperidine (*cis*-4c)**

Prepared According to Procedure for the Preparation of *cis*-**4a**

Yield: 26% over two steps. Light yellow oil. ^{1}H-NMR (C_6D_6, 80°C) δ: 0.81 (3H, t, J=7.3 Hz), 1.18–1.26 (3H, m),

1.44–1.60 (4H, m), 1.80–1.92 (3H, m), 1.97 (6H, s), 2.17 (3H, s), 2.24 (1H, dt, *J*=11.6, 4.5 Hz), 2.55–2.58 (1H, m), 2.87 (1H, m), 2.97 (1H, dd, *J*=13.5, 3.7 Hz), 6.89 (1H, d, *J*=7.6 Hz), 7.06 (1H, t, *J*=7.9 Hz), 7.16–7.21 (2H, m). ^{13}C-NMR (C_6D_6, 60°C) *δ*: 13.9, 21.5, 22.8, 25.7, 27.5, 30.1, 32.6, 43.0, 50.9, 66.4, 78.0, 127.1, 127.4, 128.2, 130.8, 137.5, 141.9, 171.0. IR (film) cm^{-1}: 1439, 1644, 2956. MS (ESI+) *m/z*: 303 (M+H$^+$, base peak). HR-MS (ESI+) *m/z*: Found 303.2423 (Calcd for $C_{19}H_{31}N_2O$ (M+H$^+$) 303.2436).

***cis*-4-*N*,*N*-Dimethylamino-3-(4-fluorophenyl)-1-*N*-pentanoylpiperidine (*cis*-4d)**

Prepared According to Procedure for the Preparation of *cis*-**4a**

Yield: 21% over two steps. Light yellow oil. ^{1}H-NMR (C_6D_6, 80°C) *δ*: 0.82 (3H, t, *J*=7.3 Hz), 1.19–1.28 (2H, m), 1.37–1.41 (3H, m), 1.51–1.71 (4H, m), 1.92 (6H, s), 1.95–1.97 (1H, m), 2.14 (1H, dt, *J*=11.7, 4.5 Hz), 2.46–2.52 (1H, m), 2.78 (1H, br), 2.84 (1H, dd, *J*=13.5, 3.4 Hz), 6.80 (2H, t, *J*=8.7 Hz), 7.19 (2H, br). ^{13}C-NMR (C_6D_6, 60°C) *δ*: 14.0, 22.8, 25.4, 27.6, 30.2, 32.7, 42.9, 50.7, 66.4, 77.8, 115.0 (d, *J*=20.6 Hz), 131.5 (d, *J*=7.4 Hz), 137.4, 162.2 (d, *J*=245.0 Hz), 171.1. IR (film) cm^{-1}: 1439, 1509, 1643, 2769, 2932. MS (ESI+) *m/z*: 307 (M+H$^+$, base peak). HR-MS (ESI+) *m/z*: Found 307.2219 (Calcd for $C_{18}H_{28}FN_2O$ (M+H$^+$) 307.2186).

***trans*-4-*N*,*N*-Dimethylamino-1-*N*-pentanoyl-3-phenylpiperidine (*trans*-4a)**

Prepared According to Procedure for the Preparation of *cis*-**4a**

Yield: 43% over two steps. Light yellow oil. ^{1}H-NMR (C_6D_6, 80°C) *δ*: 0.88 (3H, t, *J*=7.4 Hz), 1.21–1.39 (5H, m), 1.52 (1H, ddd, *J*=12.8, 6.1, 2.9 Hz), 1.67–1.75 (2H, m), 1.96 (6H, s), 2.12–2.17 (2H, m), 2.44 (1H, br), 2.59–2.67 (3H, m), 7.04–7.07 (3H, m), 7.14–7.18 (2H, m). ^{13}C-NMR (C_6D_6, 60°C) *δ*: 14.0, 22.9, 27.8, 30.1, 32.9, 40.1, 48.1, 53.1, 65.5, 77.7, 126.8, 128.1, 128.6, 142.1, 170.4. IR (film) cm^{-1}: 1060, 1440, 1640, 2930. MS (EI) *m/z*: 288 (M$^+$), 104 (base peak). HR-MS (EI) *m/z*: Found 288.2183 (Calcd for $C_{18}H_{28}N_2O$ (M$^+$) 288.2201).

***trans*-4-*N*,*N*-Dimethylamino-3-(4-methylphenyl)-1-*N*-pentanoylpiperidine (*trans*-4b)**

Prepared According to Procedure for the Preparation of *cis*-**4a**

Yield: 20% over two steps. Light yellow oil. ^{1}H-NMR (C_6D_6, 80°C) *δ*: 0.89 (3H, t, *J*=7.4 Hz), 1.23–1.39 (5H, m), 1.54–1.57 (1H, m), 1.68–1.75 (2H, m), 1.99 (6H, s), 2.14 (3H, s), 2.14–2.18 (2H, m), 2.46 (1H, br), 2.57–2.68 (3H, m), 6.99 (4H, br). ^{13}C-NMR (C_6D_6, 60°C) *δ*: 14.0, 20.9, 22.9, 27.9, 30.1, 33.0, 40.2, 47.5, 52.8, 65.6, 77.6, 127.9, 129.4, 136.1, 139.1, 170.4. IR (film) cm^{-1}: 1438, 1645, 2929. MS (ESI+) *m/z*: 303 (M+H$^+$, base peak). HR-MS (ESI+) *m/z*: Found 303.2451 (Calcd for $C_{19}H_{31}N_2O$ (M+H$^+$) 303.2436).

***trans*-4-*N*,*N*-Dimethylamino-3-(3-methylphenyl)-1-*N*-pentanoylpiperidine (*trans*-4c)**

Prepared According to Procedure for the Preparation of *cis*-**4a**

Yield: 63% over two steps. Light yellow oil. ^{1}H-NMR (C_6D_6, 80°C) *δ*: 0.88 (3H, t, *J*=7.3 Hz), 1.16–1.39 (5H, m), 1.54 (1H, ddd, *J*=12.9, 6.2, 3.1 Hz), 1.68–1.75 (2H, m), 1.99 (6H, s), 2.14–2.16 (2H, m), 2.17 (3H, s), 2.46 (1H, br), 2.57–2.70 (3H, m), 6.89–6.94 (3H, m), 7.11 (1H, t, *J*=7.5 Hz). ^{13}C-NMR (C_6D_6, 60°C) *δ*: 14.0, 21.5, 22.8, 27.9, 30.0, 33.0, 40.2, 45.1, 52.9, 65.5, 78.3, 125.2, 127.6, 128.5, 129.0, 137.9, 142.1, 170.5. IR (film) cm^{-1}: 1439, 1644, 2931. MS (ESI+) *m/z*: 303 (M+H$^+$, base peak). HR-MS (ESI+) *m/z*: Found 303.2413 (Calcd for $C_{19}H_{31}N_2O$ (M+H$^+$) 303.2436).

***trans*-4-*N*,*N*-Dimethylamino-3-(4-fluorophenyl)-1-*N*-pentanoylpiperidine (*trans*-4d)**

Prepared According to Procedure for the Preparation of *cis*-**4a**

Yield: 76% over two steps. Light yellow oil. ^{1}H-NMR (C_6D_6, 80°C) *δ*: 0.89 (3H, t, *J*=7.3 Hz), 1.14–1.23 (2H, m), 1.31–1.40 (2H, m), 1.44–1.51 (2H, m), 1.68–1.75 (2H, m), 1.93 (6H, s), 2.15 (2H, t, *J*=7.5 Hz), 2.49–2.51 (4H, m), 6.80–6.88 (4H, m). ^{13}C-NMR (C_6D_6, 60°C) *δ*: 14.1, 22.9, 27.9, 33.0, 40.2, 40.3, 48.9, 52.8, 65.5, 78.5, 115.4 (d, *J*=21.0 Hz), 129.7 (d, *J*=7.6 Hz), 137.9 (d, *J*=3.2 Hz), 162.1 (d, *J*=244.0 Hz), 170.7. IR (film) cm^{-1}: 1439, 1510, 1643, 2868, 2932. MS (ESI+) *m/z*: 307 (M+H$^+$), 160 (base peak). HR-MS (ESI+) *m/z*: Found 307.2218 (Calcd for $C_{18}H_{28}FN_2O$ (M+H$^+$) 307.2186).

***cis*-3-(4-Chlorophenyl)-4-*N*,*N*-dimethylamino-1-*N*-pentanoylpiperidine (*cis*-4e)** 1-Chloroethyl chloroformate (75 *μ*L, 0.69 mmol) was added to a solution of *cis*-**17e** in CH_2Cl_2 (4 mL). After being stirred at rt for 2 h, the reaction mixture was evaporated and alkalized with 1 M aqueous NaOH and extracted with $CHCl_3$. The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated. The resulting residue was briefly purified by chromatography on SiO_2 ($CHCl_3$–MeOH=40 : 1) to give brown oil. The oil was dissolved in methanol (15 mL) and stirred at reflux for 1 h. The reaction mixture was evaporated, the resulting residue was used in the subsequent reaction without further purification. Et_3N (0.18 mL, 1.26 mmol) and BuCOCl (76 *μ*L, 0.63 mmol) were added to a solution of the residue in CH_2Cl_2 (3 mL). After being stirred at rt for 24 h, the reaction mixture was alkalized with 1 M aqueous NaOH and extracted with $CHCl_3$. The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated. The resulting residue was purified by chromatography on SiO_2 ($CHCl_3$–MeOH=10 : 1) to yield *cis*-**4e** (30 mg, 0.09 mmol, 15% over three steps) as light yellow oil. ^{1}H-NMR (C_6D_6, 80°C) *δ*: 0.82 (3H, t, *J*=7.2 Hz), 1.20–1.35 (5H, m), 1.50–1.62 (4H, m), 1.89 (6H, s), 1.95–1.96 (1H, m), 2.20 (1H, br), 2.47 (1H, br), 2.81 (2H, br), 7.10 (2H, d, *J*=8.2 Hz), 7.14 (2H, br). ^{13}C-NMR (C_6D_6, 60°C) *δ*: 13.9, 22.7, 24.9, 27.5, 30.1, 32.7, 42.6, 50.6, 66.2, 77.7, 128.5, 131.4, 132.9, 139.9, 171.1. IR (film) cm^{-1}: 1093, 1445, 1643, 2957. MS (ESI+) *m/z*: 323 (M+H$^+$, base peak). HR-MS (ESI+) *m/z*: Found 323.1925 (Calcd for $C_{18}H_{28}ClN_2O$ (M+H$^+$) 323.1890).

***cis*-3-(3-Chlorophenyl)-4-*N*,*N*-dimethyl-1-*N*-pentanoylpiperidine (*cis*-4f)**

Prepared According to Procedure for the Preparation of *cis*-**4e**

Yield: 27% over three steps. Light yellow oil. ^{1}H-NMR (C_6D_6, 80°C) *δ*: 0.83 (3H, t, *J*=7.3 Hz), 1.15–1.48 (4H, m), 1.57–1.63 (3H, m), 1.89 (6H, s), 1.90–1.94 (3H, m), 2.11 (1H, dt, *J*=11.6, 4.5 Hz), 2.45–2.51 (1H, m), 2.74–2.81 (2H, m), 6.87 (1H, t, *J*=7.9 Hz), 7.02–7.05 (1H, m), 7.20–7.22 (1H, m), 7.45 (1H, s). ^{13}C-NMR (C_6D_6, 60°C) *δ*: 13.9, 22.8, 27.5, 30.1, 32.7, 33.8, 42.8, 53.5, 66.3, 77.6, 126.9, 129.2, 129.4, 130.3, 134.3, 143.8, 171.1. IR (film) cm^{-1}: 1435, 1643, 2956. MS (ESI+) *m/z*: 323 (M+H$^+$, base peak). HR-MS (ESI+) *m/z*: Found 323.1935 (Calcd for $C_{18}H_{28}ClN_2O$ (M+H$^+$) 323.1890).

***cis*-3-(2-Chlorophenyl)-4-*N*,*N*-dimethyl-1-*N*-pentanoylpiperidine (*cis*-4g)**

Prepared According to Procedure for the Preparation of *cis*-**4e**

Yield: 25% over three steps. Light yellow oil. ^{1}H-NMR (C_6D_6, 80°C) δ: 0.76 (3H, t, J=7.3 Hz), 1.13–1.18 (2H, m), 1.31–1.55 (5H, m), 1.82–1.91 (3H, m), 2.03 (6H, s), 2.28 (1H, br), 2.54 (1H, m), 3.02–3.05 (1H, m), 3.61 (1H, dd, J=8.6, 3.7 Hz), 6.78 (1H, dt, J=7.7, 1.5 Hz), 6.86 (1H, dt, J=7.8, 1.3 Hz), 7.21 (1H, dd, J=7.8, 1.5 Hz), 7.53 (1H, d, J=7.7 Hz). ^{13}C-NMR (C_6D_6, 60°C) δ: 13.9, 22.8, 27.2, 27.5, 30.2, 39.8, 43.2, 49.3, 65.2, 77.7, 126.4, 127.9, 129.9, 131.9, 134.6, 138.9, 170.8. IR (film) cm^{-1}: 1037, 1440, 1650, 2957. MS (ESI+) *m*/*z*: 323 (M+H$^+$, base peak). HR-MS (ESI+) *m*/*z*: Found 323.1936 (Calcd for $C_{18}H_{28}ClN_2O$ (M+H$^+$) 323.1890).

***trans*-3-(4-Chlorophenyl)-4-*N*,*N*-dimethylamino-1-*N*-pentanoylpiperidine (*trans*-4e)**

Prepared According to Procedure for the Preparation of *cis*-**4e**

Yield: 13% over three steps. Light yellow oil. ^{1}H-NMR (C_6D_6, 80°C) δ: 0.89 (3H, t, J=7.5 Hz), 1.31–1.40 (5H, m), 1.43–1.49 (1H, m), 1.68–1.75 (2H, m), 1.92 (6H, s), 2.15 (2H, t, J=7.5 Hz), 2.43–2.49 (4H, m), 6.80 (2H, d, J=8.5 Hz), 7.12 (2H, d, J=8.5 Hz). ^{13}C-NMR (C_6D_6, 60°C) δ: 14.0, 22.9, 27.8, 30.1, 32.9, 40.0, 46.6, 51.6, 65.5, 77.7, 128.8, 129.5, 132.6, 140.5, 170.4. IR (film) cm^{-1}: 1189, 1454, 1643, 2956. MS (ESI+) *m*/*z*: 323 (M+H$^+$, base peak). HR-MS (ESI+) *m*/*z*: Found 323.1937 (Calcd for $C_{18}H_{28}ClN_2O$ (M+H$^+$) 323.1890).

***trans*-3-(3-Chlorophenyl)-4-*N*,*N*-dimethyl-1-*N*-pentanoylpiperidine (*trans*-4f)**

Prepared According to Procedure for the Preparation of *cis*-**4e**

Yield: 18% over three steps. Light yellow oil. ^{1}H-NMR (C_6D_6, 80°C) δ: 0.89 (3H, t, J=7.4 Hz), 1.14–1.19 (1H, m), 1.30–1.47 (5H, m), 1.66–1.74 (2H, m), 1.90 (6H, s), 2.13 (2H, t, J=7.4 Hz), 2.40–2.51 (4H, m), 6.81 (1H, d, J=7.7 Hz), 6.89 (1H, t, J=7.7 Hz), 7.04 (1H, d, J=7.7 Hz), 7.16 (1H, s). ^{13}C-NMR (C_6D_6, 60°C) δ: 14.0, 22.9, 27.8, 30.1, 32.9, 40.0, 46.2, 50.9, 65.4, 77.7, 118.9, 126.4, 127.1, 129.9, 134.7, 144.3, 170.5. IR (film) cm^{-1}: 1454, 1643, 2957. MS (ESI+) *m*/*z*: 323 (M+H$^+$, base peak). HR-MS (ESI+) *m*/*z*: Found 323.1902 (Calcd for $C_{18}H_{28}ClN_2O$ (M+H$^+$) 323.1890).

***trans*-3-(2-Chlorophenyl)-4-*N*,*N*-dimethyl-1-*N*-pentanoylpiperidine (*trans*-4g)**

Prepared According to Procedure for the Preparation of *cis*-**4e**

Yield: 12% over three steps. Light yellow oil. ^{1}H-NMR (C_6D_6, 80°C) δ: 0.89 (3H, t, J=7.4 Hz), 1.24–1.40 (5H, m), 1.52 (1H, ddd, J=12.9, 6.4, 2.9 Hz), 1.70–1.78 (2H, m), 1.97 (6H, s), 2.14–2.22 (1H, m), 2.27–2.36 (2H, m), 2.49 (1H, m), 2.71 (1H, dt, J=11.1, 3.5 Hz), 3.32 (1H, dt, J=10.9, 4.2 Hz), 6.79 (1H, dt, J=7.6, 1.7 Hz), 6.96 (1H, dt, J=7.6, 1.2 Hz), 7.02 (1H, dd, J=7.9, 1.7 Hz), 7.20 (1H, dd, J=7.9, 1.2 Hz). ^{13}C-NMR (C_6D_6, 60°C) δ: 14.0, 22.9, 27.8, 30.1, 33.0, 40.1, 44.0, 51.6, 64.5, 77.7, 126.9, 127.9, 128.9, 130.0, 134.6, 138.9, 170.6. IR (film) cm^{-1}: 1035, 1438, 1644, 2931. MS (ESI+) *m*/*z*: 323 (M+H$^+$, base peak). HR-MS (ESI+) *m*/*z*: Found 323.1934 (Calcd for $C_{18}H_{28}ClN_2O$ (M+H$^+$) 323.1890).

Acetic Acid-Induced Abdominal Contraction Assay (Writhing Test)[1,2] Evaluation for antinociceptive effects were carried out by acetic acid writhing test using male ICR mice (Tokyo Laboratory Animals Science, Tokyo, Japan) weighing approximately 25–35 g (5–6 weeks old). Mice 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.). 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 drug dissolved in saline. After 10 min mice were observed for an additional 10 min during which abdominal contractions were counted. The % antinociception was calculated from the mean number of contractions in each test group and control group (% antinociception=[(mean control responses−test responses)/(mean control responses)]×100). ED_{50} values for each compound were determined by linear regression techniques. The statistical significance of differences between groups was assessed with analysis of variance followed by the Bonferroni–Dunnett test.

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Conflict of Interest The authors declare no conflict of interest.

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