Synthesis of *N*-[2-(1-Piperidinyl)ethyl]benzamides

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Novel benzamide derivatives, *N*-[1-(aminocarbonyl)-2-(1-piperidinyl)ethyl]benzamides (4 and 5), were prepared from the reaction of β-piperidinoalanine (6) as the starting material.

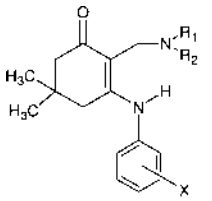
Key words β-piperidinoalanine; benzamide derivative; Mannich base; mixed anhydride; pivaloyl chloride; Schotten–Baumann reaction

In the course of our studies on the chemistry of enaminoketones,[1] we synthesized some enamino-ketone Mannich base derivatives depicted by the general formula **1** (Chart 1), and found that most had strong opioid analgesic activity.[2] Among the derivatives synthesized, compound **1a** or **1b** showed higher analgesic acitivity than that of morphine, and both compounds had various pharmacological activities such as sedative, antitussive, or anticonvulsant activities. These results suggested that **1a** or **1b** can interact with a variety of receptors in the central nervous system. On the basis of those studies, we attempted the chemical modification of the prototype compound **1** as shown in Chart 2. Thus the alicyclic moiety (part A enclosed in the dotted lines in **1**) was removed and the vinylogous amide moiety was divided into two amide moieties (parts B and C in structure **2**), leading to the malonodiamide Mannich base **2**. However, the synthesized compounds **2** were unstable. Therefore we planned to synthesize the Mannich base **3** in which the anilide moiety (part C in **2**) was replaced with a benzamide group. This molecule **3** bears a marked structural resemblance to some dopamine antagonists. In this paper, we report the synthesis of novel benzamide derivatives (**4** and **5** in Chart 3) with the general structure **3**.

Results and Discussion

For the preparation of the target compounds **4** and **5** starting from β-piperidinoalanine **6**, two rational synthetic pathways *via* amidation of this amino acid are possible. The efficient synthesis of starting material **6** and related compounds has already been reported.[3] To begin, we attempted the procedure *via* amidation of the carboxylic acid functionality. Thus treatment of **6** with methanolic hydrogen chloride gave the corresponding amino acid methyl ester **7** in excellent yield. The ester dihydrochloride **7** was reacted with methylamine and pyrrolidine to give corresponding amides **8** and **9** (87 and 72% yield, respectively), which were used in next step without further purification. Treatment of compound **8** with carboxylic acids in the presence of dicyclohexylcarbodiimide (DCC) gave the desired benzamide derivative **4**. In a similar manner, the reaction of **9** with carboxylic acids afforded corresponding benzamide derivatives **5a**—**d**. Since no reaction of **7** with piperidine occurred,[4] alternative amidation of the target compound **5e** was investigated and we found that a method *via* mixed anhydride was efficient. Thus the reaction of **6** with benzoyl chloride under Schotten–Baumann reaction conditions gave *N*-[(1-carboxy)-2-(1-piperidinyl)-ethyl]benzamide **10** in good yield. The reactant of **10** with pivaloyl chloride, giving a corresponding mixed anhydride, was allowed to react with piperidine to provide the desired **5e** in 50% yield. Using this procedure, compound **5a** was also obtained from **10** and pyrrolidine in 63% yield (see Chart 3). This method *via* mixed anhydride was also applicable for the preparation of **4** and **5b**—**d** and provides a new synthetic procedure for this class of compounds. The results are summarized in Table 1.[5]

The molecules of **4** and **5** synthesized above have frameworks similar to those of tiapride[6] and metoclopramide[7]

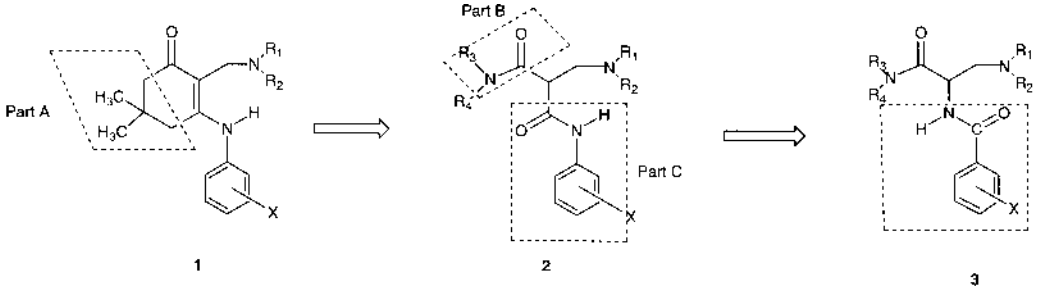


1

1a : R_1 (R_2) = $-(CH_2)_5-$, X = 2-Cl

1b : $R_1 = CH_3$, $R_2 = CH_2CH_2Ph$, X = 3-OCH_3

Chart 1



1 **2** **3**

Chart 2

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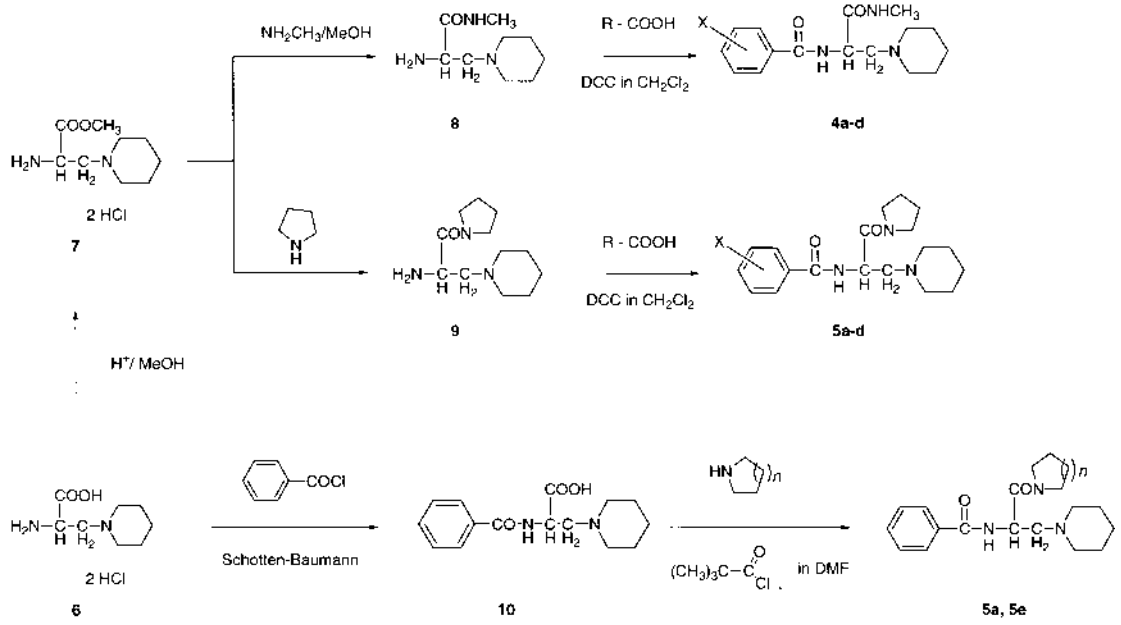
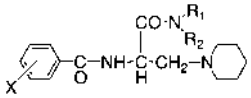


Chart 3

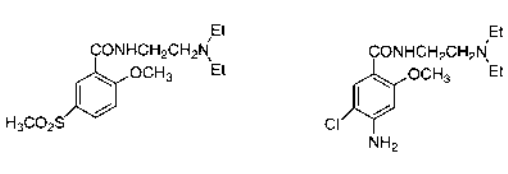
Table 1. Preparation of *N*-[(1-Aminocarbonyl)-2-(1-piperidinyl)ethyl]benzamides **4** and **5**



Compd. no.	X	–N(R1)C	mp (°C) (Solvent)	Formula	FAB-MS (MH^+)	Analysis (%) Calcd (Found)		
						C	H	N
4a	H	–$NHCH_3$	139—142 (AcOEt)	$C_{16}H_{23}N_3O_2$	290	66.41 (66.51	8.01 8.03	14.52 14.54)
4b	2-OCH_3, 4-NH_2, 5-Cl	–$NHCH_3$·	183 (dec.) (H_2O)	$C_{17}H_{25}ClN_4O_3$ ·HCl·H_2O	369	48.23 (48.10	6.67 6.61	13.23 13.20)
4c	3,4-OCH_3	–$NHCH_3$	154—155 (CH_3CN)	$C_{18}H_{27}N_3O_4$	350	61.87 (61.95	7.79 7.71	12.03 12.04)
4d	3,4,5-OCH_3	–$NHCH_3$	138—141 (AcOEt)	$C_{19}H_{29}N_3O_5$	380	60.14 (59.96	7.7 7.90	11.07 11.04)
5a	H		216—218 (dec.) (CH_3CN)	$C_{19}H_{27}N_3O_2$ ·HCl	330	62.37 (62.14	7.71 7.76	11.48 11.63)
5b	2-OCH_3, 4-NH_2, 5-Cl		175—177 (Acetone)	$C_{20}H_{29}ClN_4O_3$	409	58.74 (58.76	7.15 7.18	13.7 13.63)
5c	3,4-OCH_3		106—112 (AcOEt)	$C_{21}H_{31}N_3O_4$	390	64.76 (64.46	8.02 8.03	10.79 10.52)
5d	3,4,5-OCH_3		159—162 (CH_3CN)	$C_{22}H_{33}N_3O_5$	420	62.99 (62.90	7.93 7.84	10.02 10.15)
5e[a]	H		161–162 (CH_3CN)	$C_{20}H_{29}N_3O_2$	344	69.94 (69.86	8.51 8.50	12.23 12.21)

a) This compound was obtained by the method *via* mixed anhydride, other compounds were obtained by the method *via* ester **7**.

(Chart 4), which are clinically useful dopamine receptor antagonists. Molecular model examination of these compounds[8] suggested the possibility that compounds **4** and **5** may interact with the dopamine receptor. Further synthetic applications and pharmacological evaluations of the compounds synthesized are under investigation to find a new candidate with potent dopamine antagonist activity.



Tiapride Metoclopramide

Chart 4

Experimental

Melting points were uncorrected. Infrared (IR) spectra were measured with a Shimadzu FTIR-8100 spectrometer. ^{1}H- (500 MHz) and ^{13}C- (125 MHz) NMR spectra were obtained with a JEOL JNM A-500. Chemical shifts were expressed as δ ppm downfield from an internal tetramethylsilane (TMS) signal (0 ppm) or sodium 3-(trimethylsilyl)propionic 2,2,3,3-d_4 acid (TSP) signal (0 ppm) (in D_2O) for ^{1}H-NMR, and the carbon signal of the

corresponding solvent [$CDCl_3$ (77.0 ppm), DMSO-d_6 (39.5 ppm)], and TSP (0 ppm) (in D_2O) for ^{13}C-NMR, respectively. The signal assignments were confirmed with ^1H–^1H correlation spectroscopy (COSY), ^1H–^{13}C heteronuclear multiple quantum coherence (HMQC), and ^1H–^{13}C heteronuclear multiple bond connectivity (HMBC) spectra. FAB-MS were obtained with a JEOL JMS-HX110 mass spectrometer. Yield and physical data (MS, analysis) for compounds **4** and **5** are summarized in Table 1. Other spectroscopic data are recorded below.

Methyl α-Amino-1-piperidinepropanoate Dihydrochloride (7) Methanolic HCl (10%) was added to a solution of **6** in anhydrous methanol and the mixture was kept at room temperature for 24 h, then evaporated to dryness *in vacuo*. After a few such treatments with methanolic HCl, the residue finally crystallized completely. The yield was quantitative. Recrystallization from methanol gave an analytical sample of **7**. This compound was colorless prisms and quite hygroscopic, mp 178 °C (dec.). IR (KBr): 1759 cm^{-1}. Negative FAB-MS *m/z*: 257 $(M+2HCl-H)^-$. ^1H-NMR (DMSO-d_6) δ: 1.55 (2H, br s, 4-CH_2 of piperidine ring), 1.81—1.86 (4H, m, 3,5-CH_2 of piperidine ring), 3.17—3.51 [3H, m, 2-CH_2 of piperidine ring and $NH_2CH(CON=)C\underline{H}HN=$], 3.64—3.70 [3H, m, 6-$CH_2$ of piperidine ring and $NH_2CH(CON=)CH\underline{H}N=$], 3.79 (3H, s, CH_3), 4.90 [1H, q, *J*=4 Hz, $NH_2C\underline{H}(CON=)CH_2N=$], 9.64 (2H, br, NH_2). ^{13}C-NMR (DMSO-d_6) δ: 20.9 (C4 of piperidine ring), 22.3 (C3, C5 of piperidine ring), 47.8 [$NH_2\underline{C}H(CON=)CH_2$–], 53.2 (C2 of piperidine ring), 53.4 (CH_3), 55.6 ($NH_2CH(CON=)\underline{C}H_2$–), 56.0 (C6 of piperidine ring), 166.6 (CO). *Anal*. Calcd for $C_9H_{18}N_2O_2\cdot 2HCl\cdot 0.1H_2O$: C, 41.42; H, 7.80; N, 10.73. Found: C, 41.20; H, 7.66; N, 10.77.

α-Amino-*N*-methyl-1-piperidinepropionamide (8) Methyl α-amino-1-piperidinepropanoate dihydrochloride **7** (2 g, 7.7 mmol) was added to a 40% solution of methylamine in methanol (6 ml) and the reaction mixture was allowed to stand at room temperature for 3 h, then the solvent was evaporated to dryness. After addition of Et_2O to the residue, the separated precipitate was isolated by filtration. The filtrate was concentrated to dryness to give **8** (1.06 g, 74%). The precipitate was made basic with small amount of aqueous NaOH (*ca.* 2%), extracted with AcOEt, and the extract was concentrated to dryness to give **8** (0.18 g, 13%). The total yield was 87%. An analytical sample was obtained by recrystallization from diisopropylether, prisms, mp 99—100 °C. IR (KBr): 3376, 3325, 1651 cm^{-1}. FAB-MS *m/z*: 186 $(M+H)^+$. ^1H-NMR ($CDCl_3$) δ: 1.46 (2H, q, *J*=6 Hz, 4-CH_2 of piperidine ring), 1.58 (4H, q, *J*=6 Hz, 3,5-CH_2 of piperidine ring), 1.95 (2H, br s, NH_2), 2.36—2.42 (2H, m, 2-CH_2 of piperidine ring), 2.39 [1H, dd, *J*=13, 8 Hz, $NH_2CH(CON=)C\underline{H}HN=$], 248—2.49 (2H, m, 6-$CH_2$ of piperidine ring), 2.60 [1H, dd, *J*=13, 6 Hz, $NH_2CH(CON=)CH\underline{H}N=$], 2.80 (3H, d, *J*=5 Hz, CH_3), 3.50 [1H, dd, *J*=8, 6 Hz, $NH_2C\underline{H}(CON=)CH_2N=$], 7.88 (1H, br s, CONH). ^{13}C-NMR ($CDCl_3$) δ: 24.2 (C4 of piperidine ring), 25.7 (NCH_3), 26.1 (C3, C5 of piperidine ring), 51.6 [$NH_2\underline{C}H(CON=)CH_2$–], 54.4 (C2, C6 of piperidine ring), 62.2 [$NH_2CH(CON=)\underline{C}H_2$–], 175.1 (CO). *Anal*. Calcd for $C_9H_{19}N_3O$: C, 58.35; H, 10.34; N, 22.68. Found: C, 58.32; H, 10.32; N, 22.46.

2-Amino-3-(1-piperidinyl)-1-(1-pyrrolidinyl)-1-propanone (9) Methyl α-amino-1-piperidinepropanoate dihydrochloride **7** (2 g, 7.7 mmol) was added to pyrrolidine (5.5 ml) and stirred for 4 h. Et_2O was added to the reaction mixture and the precipitate was filtered off. The ethereal solution was concentrated, and the excess pyrrolidine was removed under reduced pressure to give **9** (1.31 g, 75%). An analytical sample was obtained by recrystallization from acetone/Et_2O. mp 42—46 °C. IR (KBr): 1638 cm^{-1}. FAB-MS *m/z*: 226 $(M+H)^+$. ^1H-NMR ($CDCl_3$) δ: 1.44 (2H, quintet, *J*=6 Hz, 4-CH_2 of piperidine ring), 1.51—1.62 (4H, m, 3,5-CH_2 of piperidine ring), 1.86 (2H, quintet, *J*=7 Hz, 3-CH_2 of pyrrolidine ring), 1.92—1.99 (2H, m, 4-CH_2 of pyrrolidine ring), 2.39 [1H, dd, *J*=13, 9 Hz, $NH_2CH(CON=)C\underline{H}HN=$], 2.43 (2H, m, 2-$CH_2$ of piperidine ring), 2.47 (1H, dd, *J*=13, 5 Hz, $NH_2CH(CON=)CH\underline{H}N=$), 2.52—2.57 (2H, m, 6-$CH_2$ of piperidine ring), 2.87 (2H, br s, NH_2), 3.41—3.46 (2H, m, 2-CH_2 of pyrrolidine ring), 3.50—3.58 (2H, m, 5-CH_2 of pyrrolidine ring), 3.77 (1H, dd, *J*=9, 5 Hz, $NH_2C\underline{H}(CON=)CH_2N=$). ^{13}C-NMR ($CDCl_3$) δ: 24.1 (C4 of piperidine ring, C3 of pyrrolidine ring), 25.9 (C3, C5 of piperidine ring), 26.0 (C4 of pyrrolidine ring), 45.9 (C2 of pyrrolidine ring), 46.2 (C5 of pyrrolidine ring), 51.0 [$NH_2\underline{C}H(CON=)CH_2$–], 55.1 (C2, C6 of piperidine ring), 63.7 [$NH_2CH(CON=)\underline{C}H_2$–], 172.3 (CO). *Anal*. Calcd for $C_{12}H_{23}N_3O\cdot 0.5H_2O$: C, 61.51; H, 10.32; N, 17.93. Found: C, 61.42; H, 10.14; N, 17.72.

***N*-[1-(Methylaminocarbonyl)-2-(1-piperidinyl)ethyl]benzamide (4a)** A solution of DCC (1.34 g, 6.5 mmol) in CH_2Cl_2 was added to a stirred solution of **8** (1.0 g, 5.4 mmol) and benzoic acid (0.79 g, 6.5 mmol) in CH_2Cl_2 and the mixture was stirred at room temperature for 1 d. The dicyclohexylurea (DCU) was removed by filtration and washed with a small amount of CH_2Cl_2. The filtrate was extracted three times with 1 N HCl and the extract was washed with CH_2Cl_2. The aqueous solution was made basic with anhydrous K_2CO_3 and the resulting precipitate was extracted with CH_2Cl_2. The extract was washed with brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to give **4a** (0.76 g, 49%) which was recrystallized from AcOEt to afford colorless prisms. IR (KBr): 3315, 3265, 1674, 1630 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.47—1.50 (2H, m, 4-CH_2 of piperidine ring), 1.57—1.62 (4H, m, 3,5-CH_2 of piperidine ring), 2.42—2.57 (2H, m, 2-CH_2 of piperidine ring), 2.47 [1H, dd, *J*=13,10 Hz, –NHCH(CON=)C$\underline{H}$HN=], 2.75 (2H, br, 6-CH_2 of piperidine ring), 2.84 (3H, d, *J*=5 Hz, NCH_3), 2.89 [1H, dd, *J*=13, 5 Hz, –NHCH(CON=)CH$\underline{H}$N=], 4.51 [1H, dt, *J*=10, 5 Hz, m, –NHC$\underline{H}$(CON=)CH_2N=], 7.40—7.44 (2H, m, 3,5H-aromatic), 7.47—7.50 (2H, m, 4H-aromatic, Ar-CON$\underline{H}$), 7.82— 7.84 (2H, m, 2,6H-aromatic), 8.25 (1H, br d, *J*=5 Hz, N$\underline{H}$$COCH_3$). ^{13}C-NMR ($CDCl_3$) δ: 23.9 (C4 of piperidine ring), 25.9 (NCH_3), 26.2 (C3, C5 of piperidine ring), 49.5 [–NH$\underline{C}$H(CON=)CH_2–], 54.3 (C2, C6 of piperidine ring), 59.6 [–NHCH(CON=)$\underline{C}$$H_2$–], 127.0 (C2, C6-aromatic), 128.4 (C3, C5-aromatic), 131.5 (C4-aromatic), 139.9 (C1-aromatic), 167.1 (Ar-$\underline{C}$O), 171.9 ($\underline{C}$ON-HCH_3).

Compounds **4b**—**d** and **5a**—**d** were also obtained according to the above procedure.

4-Amino-3-chloro-6-methoxy-*N*-[1-(methylaminocarbonyl)-2-(1-piperidinyl)ethyl]benzamide (**4b**): The yield was 35%. Treatment of **4b** with 20% HCl/EtOH gave the hydrochloride of **4b**. IR (KBr): 3465, 1684, 1622, 1606 cm^{-1}. ^1H-NMR (D_2O) δ: 1.67 (2H, br s, 4-CH_2 of piperidine ring), 1.87—1.88 (4H, m, 3,5-CH_2 of piperidine ring), 2.82 (3H, s, NCH_3), 3.30—3.38 (4H, m, 2,6-CH_2 of piperidine ring), 3.45 [1H, dd, *J*=14, 9 Hz, –NHCH(CON=)C$\underline{H}$HN=], 3.68 [1H, dd, *J*=14, 5 Hz, –NHCH(CON=)CH$\underline{H}$N=], 3.95 (3H, s, OCH_3), 5.07 [1H, dd, *J*=9, 5 Hz, –NHC$\underline{H}$(CON=)CH_2N=], 6.57 (1H, s, 3H-aromatic), 7.76 (1H, s, 6H-aromatic). ^{13}C-NMR (D_2O) δ: 23.8 (C4 of piperidine ring), 25.6 (C3, C5 of piperidine ring), 29.0 (NCH_3), 52.0 [–NH$\underline{C}$H(CON=)CH_2–], 57.0 (C2, C6 of piperidine ring), 59.1 (OCH_3), 60.7 [–NHCH(CON=)$\underline{C}$$H_2$–], 101.5 (C3-aromatic), 112.4 (C1-aromatic), 114.0 (C5-aromatic), 134.6 (C6-aromatic), 151.9 (C4-aromatic), 161.2 (C2-aromatic), 170.1 ($\underline{C}$O$NHCH_3$), 173.2 (Ar-$\underline{C}$O).

3,4-Dimethoxy-*N*-[1-(methylaminocarbonyl)-2-(1-piperidinyl)ethyl]-benzamide (**4c**): The yield was 26%. IR (KBr): 3260, 1620 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.48—1.52 (2H, m, 4-CH_2 of piperidine ring), 1.59—1.64 (4H, m, 3,5-CH_2 of piperidine ring), 2.44—2.48 [3H, m, 2-CH_2 of piperidine ring, –NHCH(CON=)C$\underline{H}$HN=], 2.77 (2H, br, 6-CH_2 of piperidine ring), 2.86 (3H, d, *J*=5 Hz, NCH_3), 2.91 [1H, dd, *J*=13, 4 Hz, –NHCH(CON=)CH$\underline{H}$N=], 3.921, 3.922 (each 3H, s, OCH_3), 4.46—4.49 [1H, m, –NHC$\underline{H}$(CON=)CH_2N=], 6.88 (1H, d, *J*=8 Hz, 5H-aromatic), 7.35—7.45 (1H, br, Ar-CON$\underline{H}$), 7.39 (1H, dd, *J*=8, 2 Hz, 6H-aromatic), 7.45 (1H, d, *J*=2 Hz, 2H-aromatic), 8.26 (1H, br s, CON$\underline{H}$$CH_3$). ^{13}C-NMR ($CDCl_3$) δ: 24.0 (C4 of piperidine ring), 26.0 (NCH_3), 26.3 (C3, C5 of piperidine ring), 49.6 [–NH$\underline{C}$H(CON=)CH_2–], 54.4 (C2, C6 of piperidine ring), 56.0 ($OCH_3\times 2$), 59.7 [–NHCH(CON=)$\underline{C}$$H_2$–], 110.4 (C2 or C5-aromatic), 110.5 (C5 or C2-aromatic), 119.8 (C6-aromatic), 126.6 (C1-aromatic), 149.0 (C3-aromatic), 152.0 (C4-aromatic), 166.8 (Ar-$\underline{C}$O), 172.2 ($\underline{C}$O$NHCH_3$).

3,4,5-Trimethoxy-*N*-[1-(methylaminocarbonyl)-2-(1-piperidinyl)ethyl]-benzamide (**4d**): The yield was 33%. IR (KBr): 3281, 1662, 1622 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.49—1.50 (2H, m, 4-CH_2 of piperidine ring), 1.51—1.52 (4H, m, 3,5-CH_2 of piperidine ring), 2.45—2.49 [3H, m, 2-CH_2 of piperidine ring, –NHCH(CON=)C$\underline{H}$HN=], 2.79 (2H, m, 6-CH_2 of piperidine ring), 2.86 (3H, d, *J*=4.5 Hz, NCH_3), 2.91—2.93 [1H, m, –NHCH(CON=)CH$\underline{H}$N=], 3.88 (3H, s, 4′-OCH_3), 3.90 (6H, s, 3′,5′-OCH_3), 4.46—4.49 [1H, m, –NHC$\underline{H}$(CON=)CH_2N=], 7.09 (2H, s, 2,6H-aromatic), 7.27 (1H, br, Ar-CON$\underline{H}$), 8.30 (1H, br , CON$\underline{H}$$CH_3$). ^{13}C-NMR ($CDCl_3$) δ: 24.0 (C4 of piperidine ring), 26.0 (NCH_3), 26.3 (C3, C5 of piperidine ring), 50.0 [–NH$\underline{C}$H(CON=)CH_2–], 54.4 (C2, C6 of piperidine ring), 56.3 (3′,5′-OCH_3), 59.6 [–NHCH(CON=)$\underline{C}$$H_2$–], 60.9 (4′-$OCH_3$), 104.5, (C2, C6-aromatic), 129.2 (C1-aromatic), 141.3 (C4-aromatic), 153.2 (C3, C5-aromatic), 166.8 (Ar-$\underline{C}$O), 172.1 ($\underline{C}$O$NHCH_3$).

N-[2-(1-Piperidinyl)-1-(1-pyrrolidinylcarbonyl)ethyl]benzamide (**5a**): The yield was 74%. Treatment of **5a** with 20% HCl/EtOH gave the hydrochloride of **5a**, which was recrystallized from CH_3CN to afford colorless needles. IR (KBr): 3218, 1666, 1645 cm^{-1}. ^1H-NMR (D_2O) δ: 1.68 (2H, br s, 4-CH_2 of piperidine ring), 1.85—1.91 (4H, m, 3,5-CH_2 of piperidine ring), 1.93—2.01 (4H, m, 3,4-CH_2 of pyrrolidine ring), 3.33—3.61 (4H, m, 2,6-CH_2 of piperidine ring), 3.48—3.67 [6H, m, 2,5-CH_2 of pyrrolidine ring, –NHCH(CON=)C$\underline{H_2}$N=], 5.30—5.33 [1H, m,

–NHCH(CON=)CH_2N=], 7.56—7.60 (2H, m, 3,5H-aromatic), 7.67—7.71 (1H, m, 4H-aromatic), 7.85—7.88 (2H, m, 2,6H-aromatic). ^{13}C-NMR (D_2O) δ: 23.8 (C4 of piperidine ring), 25.4 (C3, C5 of piperidine ring), 26.4 (C3 of pyrrolidine ring), 28.3 (C4 of pyrrolidine ring), 49.7 (C2 of pyrrolidine ring), 50.0 (C5 of pyrrolidine ring), 50.6 [–NHCH(CON=)CH_2–], 57.1 (C2, C6 of piperidine ring), 59.6 [–NHCH(CON=)CH_2–], 130.2 (C2, C6-aromatic), 131.8 (C3, C5-aromatic), 134.8 (C1-aromatic), 135.8 (C4-aromatic), 169.9 (=CHCON=), 173.3 (Ar-CO). This compound **5a** could also be prepared in a similar manner described for the preparation of **5e** in 63% yield.

4-Amino-3-chloro-6-methoxy-*N*-[2-(1-piperidinyl)-1-(1-pyrrolidinylcarbonyl)ethyl]benzamide (**5b**): The yield was 35%. IR (KBr): 3368, 1638 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.40—1.42 (2H, m, 4-CH_2 of piperidine ring), 1.50—1.55 (4H, m, 3,5-CH_2 of piperidine ring), 1.86—1.90 (2H, m, 3-CH_2 of pyrrolidine ring), 1.95—2.00 (2H, m, 4-CH_2 of pyrrolidine ring), 2.47 (4H, d, J=5 Hz, 2,6-CH_2 of piperidine ring), 2.62 [1H, dd, J=13, 7 Hz, –NHCH(CON=)CHHN=], 2.70 [1H, dd, J=13,7 Hz, –NHCH(CON=)CHHN=], 3.43—3.47 (1H, m, 2-CH_A of pyrrolidine ring), 3.54—3.57 (1H, m, 2-CH_B of pyrrolidine ring), 3.72—3.76 (2H, m, 5-CH_2 of pyrrolidine ring), 3.84 (3H, s, OCH_3), 4.57 (2H, s, Ar-NH_2), 4.93—4.94 [1H, q, J=7 Hz, –NHCH(CON=)CH_2N=], 6.23 (1H, s, 3H-aromatic), 8.03 (1H, s, 6H-aromatic), 8.48 (1H, br d, J=7 Hz, CONH). ^{13}C-NMR ($CDCl_3$) δ: 24.2 (C4 of piperidine ring), 26.0 (C3, C4 of pyrrolidine ring), 26.2 (C3, C5 of piperidine ring), 46.0 (C2 of pyrrolidine ring), 46.7 (C5 of pyrrolidine ring), 49.9 [–NHCH(CON=)CH_2–], 55.0 (C2, C6 of piperidine ring), 56.0 (OCH_3), 61.0 [–NHCH(CON=)CH_2–], 97.8 (C3-aromatic), 111.3 (C1-aromatic), 112.1 (C5-aromatic), 132.8 (C6-aromatic), 147.0 (C4-aromatic), 157.8 (C2-aromatic), 164.0 (Ar-CO), 170.6 (=CHCON=).

3,4-Dimethoxy-*N*-[2-(1-piperidinyl)-1-(1-pyrrolidinylcarbonyl)ethyl]-benzamide (**5c**): The yield was 45%. IR (KBr): 3245, 1628 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.40—1.43 (2H, m, 4-CH_2 of piperidine ring), 1.51—1.55 (4H, m, 3,5-CH_2 of piperidine ring), 1.88—1.92 (2H, m, 3-CH_2 of pyrrolidine ring), 1.96—2.04 (2H, m, 4-CH_2 of pyrrolidine ring), 2.46—2.51 (4H, m, 2,6-CH_2 of piperidine ring), 2.66 [1H, dd, J=13, 7 Hz, –NHCH(CON=)CHHN=], 2.73 [1H, dd, J=13, 7 Hz, –NHCH(CON=)CHHN=], 3.45—3.49 (1H, m, 2-CH_A of pyrrolidine ring), 3.53—3.58 (1H, m, 2-CH_B of pyrrolidine ring), 3.75—3.78 (2H, m, 5-CH_2 of pyrrolidine ring), 3.91, 3.92 (each 3H, s, OCH_3), 4.97 [1H, q, J=7 Hz, –NHCH(CON=)CH_2N=], 6.86 (1H, d, J=8 Hz, 5H-aromatic), 7.08 (1H, br d, J=7 Hz, CONH), 7.36 (1H, dd, J=8, 2 Hz, 6H-aromatic), 7.43 (1H, d, J=2 Hz, 2H-aromatic). ^{13}C-NMR ($CDCl_3$) δ: 24.2 (C4 of piperidine ring), 26.0 (C3, C4 of pyrrolidine ring), 26.2 (C3, C5 of piperidine ring), 46.0 (C2 of pyrrolidine ring), 46.7 (C5 of pyrrolidine ring), 49.6 [–NHCH(CON=)CH_2–], 55.0 (C2, C6 of piperidine ring), 56.0 (OCH_3×2), 61.0 [–NHCH(CON=)CH_2–], 110.3 (C2 or C5-aromatic), 110.6 (C5 or C2-aromatic), 120.0 (C6-aromatic) , 126.7 (C1-aromatic), 148.9 (C3-aromatic), 151.8 (C4-aromatic), 166.3 (Ar-CO), 170.3 (=CHCON=).

3,4,5-Trimethoxy-*N*-[2-(1-piperidinyl)-1-(1-pyrrolidinylcarbonyl)ethyl]-benzamide (**5d**): The yield was 50%. IR (KBr): 3318, 1664, 1633 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.40—1.44 (2H, m, 4-CH_2 of piperidine ring), 1.51—1.55 (4H, m, 3,5-CH_2 of piperidine ring), 1.88—1.92 (2H, m, 3-CH_2 of pyrrolidine ring), 1.98—2.02 (2H, m, 4-CH_2 of pyrrolidine ring), 2.46—2.52 (4H, m, 2,6-CH_2 of piperidine ring), 2.66 [1H, dd, J=13, 7 Hz, –NHCH(CON=)CHHN=], 2.74 [1H, dd, J=13, 7 Hz, –NHCH(CON=)CHHN=], 3.45—3.49 (1H, m, 2-CH_A of pyrrolidine ring), 3.53—3.56 (1H, m, 2-CH_B of pyrrolidine ring), 3.76 (2H, t, J=7 Hz, 5-CH_2 of pyrrolidine ring), 3.87 (3H, s, 4′-OCH_3), 3.89 (6H, s, 3′,5′-OCH_3), 4.96 [1H, q, J=7 Hz, –NHCH(CON=)CH_2N=], 7.06 (2H, s, 2,6H-aromatic), 7.15 (1H, d, J=7 Hz, CONH). ^{13}C-NMR ($CDCl_3$) δ: 24.2 (C4 of piperidine ring), 26.0 (C3, C4 of pyrrolidine ring), 26.2 (C3, C5 of piperidine ring), 46.0 (C2 of pyrrolidine ring), 46.7 (C5 of pyrrolidine ring), 49.7 [–NHCH(CON=)CH_2–], 54.9 (C2, C6 of piperidine ring), 56.3 (3′,5′-OCH_3), 60.8 [–NHCH(CON=)CH_2–, 4′-OCH_3], 104.6 (C2, C6-aromatic), 129.4 (C1-aromatic), 141.1 (C4-aromatic), 153.1 (C3, C5-aromatic),166.3 (Ar-CO), 170.2 (=CHCON=).

α-(Benzoylamino)-1-piperidinepropanoic Acid (10) Using a three-neck round-bottomed flask, benzoyl chloride (8.03 g, 57 mmol) was added dropwise to a vigorously stirred solution of **6** (7 g, 28.6 mmol) in 1 N NaOH (86 ml) and 2 N NaOH (43 ml) was added at the same time. In this experiment, it is advantageous to terminate the addition of both reagents together. The reaction mixture was stirred for 2 h at room temperature and then acidified with 20% HCl. The resulting mixture was washed with diethyl ether (Et_2O) and the resulting aqueous layer was evaporated to give residual oil. After the addition of ethanol to this residue, the precipitated insoluble solid was removed by filtration. The mother liquor was concentrated to dryness. The residue was passed through a column packed with ion-exchange resin (AG 11A8®, Bio-Rad Laboratories) to give crude product, which was recrystallized from H_2O to afford **10** (5.3 g, 67%), mp 139—141 °C (dec.). IR (KBr): 1647, 1605 cm^{-1}. FAB-MS m/z: 277 $(M+H)^+$. ^{1}H-NMR (D_2O) δ: 1.55—2.10 (6H, br, 3,4,5-CH_2 of piperidine ring), 2.90—3.82 (4H, br, 2,6-CH_2 of piperidine ring), 3.47 [1H, dd, J=13, 8 Hz, –NHCH(CON=)CHHN=], 3.61 [1H, dd, J=13, 6 Hz, –NHCH(CON=)CHHN=], 4.84 [1H, dd, J=8, 6 Hz, –NHCH(CON=)CH_2N=], 7.57 (2H, t, J=8 Hz, 3,5H-aromatic), 7.67 (1H, t, J=8 Hz, 4H-aromatic), 7.86 (2H, d-like, J=8 Hz, 2,6H-aromatic). ^{13}C-NMR (D_2O) δ: 23.9 (C4 of piperidine ring), 25.6 (C3, C5 of piperidine ring), 52.8 [–NHCH(CON=)CH_2–], 56.6 (C2, C6 of piperidine ring), 60.9 [–NHCH(CON=)CH_2–], 130.2 (C2, C6-aromatic), 131.7 (C3, C5-aromatic), 135.5 (C1 or C4-aromatic), 135.6 (C4 or C1-aromatic), 173.4 (CONH), 176.8 (COOH). *Anal*. Calcd for $C_{15}H_{20}N_2O_3\cdot H_2O$: C, 61.21; H, 7.53; N, 9.52. Found: C, 61.08; H, 7.53; N, 9.51.

***N*-[2-(1-Piperidinyl)-1-(1-piperidinylcarbonyl)ethyl]benzamide (5e) (Method *via* Mixed Anhydride)** To a solution of compound **10** (1 g, 3.6 mmol) and *N*-methylmorpholine (0.56 g, 5.5 mmol) in anhydrous dimethylformamide (DMF) (50 ml), pivaloyl chloride (0.67 g, 5.5 mmol)was added at −15 °C with stirring. After 5 min, piperidine (0.47 g, 5.5 mmol) was added and the reaction mixture was allowed to stand at 0 °C for 30 min and then overnight at room temperature with stirring. The reaction mixture was concentrated *in vacuo*, the residue was extracted with 1 N HCl, and the aqueous solution was washed with Et_2O and basified with K_2CO_3. The resulting precipitate was collected by filtration, washed with water, and dried to give **5e** (0.62 g, 50%), which was recrystallized from CH_3CN to afford colorless needles. IR (KBr): 3300, 1653, 1619 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.39—1.43 (2H, m, 4-CH_2 of piperidine ring), 1.51—1.59 (6H, m, 3,5-CH_2 of piperidine ring, 4-CH_2 of 1-acylpiperidine ring), 1.67 (4H, br s, 3,5-CH_2 of 1-acylpiperidine ring), 2.44—2.56 (4H, m, 2,6-CH_2 of piperidine ring), 2.64—2.69 [2H, m, –NHCH(CON=)CH_2N=], 3.53—3.58 (2H, m, 2,6-CH_A of 1-acylpiperidine ring), 3.62—3.67 (2H, m, 2,6-CH_B of 1-acylpiperidine ring), 5.21 [1H, q, J=7 Hz, –NHCH(CON=)CH_2N=], 7.20 (1H, br d, J=7 Hz, NH), 7.40—7.43 (2H, m, 3,5H-aromatic), 7.46—7.49 (1H, m, 4H-aromatic), 7.80—7.82 (2H, m, 2,6H-aromatic). ^{13}C-NMR ($CDCl_3$) δ: 24.2 (C4 of piperidine ring), 24.5 (C3 of 1-acylpiperidine ring), 25.6 (C4 of 1-acylpiperidine ring), 26.1 (C3, C5 of piperidine ring), 26.6 (C5 of 1-acylpiperidine ring), 43.4 (C2 of 1-acylpiperidine ring), 47.0 (C6 of 1-acylpiperidine ring), 47.6 [–NHCH(CON=)CH_2–], 55.1 (C2, C6 of piperidine ring), 61.8 [–NHCH(CON=)CH_2–], 127.1 (C2, C6-aromatic), 128.4 (C3, C5-aromatic), 131.4 (C4-aromatic), 134.3 (C1-aromatic), 166.5 (Ar-CO), 170.1 (=CHCON=).

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References and Notes

1) For example, see Miyano S., Abe N., Takeda K., Fujisaki F., Sumoto K., *Synthesis*, **1982**, 852 and references cited therein.
2) Prepn.: Miyano S., Abe N., Ger. Offen. 2323301 [*Chem. Abstr*., **80**, 70539*h* (1974)]; Pharmacology: Kase Y., Saita M., Takahama K., Masaki K., Miyata T., *Jpn. J. Pharmacol*., **24**, 85—86 (1974).
3) Abe N., Fujisaki F., Sumoto K., *Chem. Pharm. Bull*., **46**, 142—144 (1998).
4) Compound **7** is sparingly soluble in piperidine, and the reaction did not give the desired product under the same reaction conditions. Use of additional solvent resulted in the formation of unknown polymeric products.
5) Introductions of other amino functionalities instead of a piperidine ring substituent were also successful by the procedure *via* a mixed anhydride. These results together with pharmacological evaluation will be described elsewhere.
6) *a*) Bishoff S., Bittiger H., Delini-Stula A., Ortmann R., *Eur. J. Pharmacol*., **79**, 225—232 (1982); *b*) Chivers J. K., Gommeron W., Leysen J. E., Jenner P., Marsden C. D., *J. Pharm. Pharmacol*., **40**, 415—421 (1988); *c*) Jenner P., Elliott P. N. C., Clow A., Reavill C., Marsden C. D., *ibid*., **30**, 46—48 (1978).
7) Dumuis A., Sebben M., Bockaert J., *Naunyn-Schmideberg's Arch. Pharmacol.*, **340**, 403—410 (1989).
8) The computational molecular model examinations were carried out by "overlay" operation combined with MM2 calculation. Some of the compounds in this series showed significant dopamine antagonist activities. These results will be described elsewhere.