Synthesis and Pharmacological Evaluation of New 1-Hydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepines as Norepinephrine Potentiators

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4-Hydroxy-2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline (PI-OH) (1a) and its derivatives form a new class of compounds which possess norepinephrine (NE) potentiating activity. As a new series of compounds, 1-hydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepines (2a—f) were synthesized by the intramolecular Barbier reaction of *N*-[2-(2-iodophenyl)ethyl]phenacylamines (6a—f) with *n*-BuLi as a key reaction step. The potentiating activities of the benzazepines 2a—f on the contraction of rat anococcygeus muscle induced by NE were tested. Among the compounds tested in this study, compound 2a showed moderate potentiating activity (the activity ratio was 7.3-fold at 3×10^{-5} M).

Key words norepinephrine potentiator; norepinephrine reuptake inhibitor; 3-benzazepine; Barbier reaction; *N*-(phenylethyl)phenacylamine

Amine reuptake inhibitors have been developed as antidepressants. Tricyclic antidepressants such as desipramine prevent the neuronal reuptake of either norepinephrine (NE) or serotonin (5-HT).[1] In the past decade a number of nontricyclic antidepressants, including selective serotonin reuptake inhibitors (SSRI) as well as 5-HT and NE reuptake inhibitors (SNRI) such as fluvoxamine and milnacipran, which have diminished cardiovascular and anticholinergic liability, have been developed.[2] Atomoxetine, a selective inhibitor of NE reuptake, has recently attracted much interest in the treatment of attention deficit hyperactivity disorder (ADHD)[3] (Fig. 1).

We have reported on the synthesis of 4-hydroxy-2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline (PI-OH) (**1a**)[4,5] and the strong NE potentiating activity of PI-OH (**1a**) was found to be due to inhibition of NE reuptake. The potency of PI-OH (**1a**) was greater than that of the tricyclic antidepressant desipramine.[6] We have also studied the structure–activity relationships of the PI-OH (**1a**) analogues and have identified the importance of the 2-phenylethanolamine moiety of PI-OH for NE potentiation.[7,8] In addition, we have evaluated the substitution effects on the 4-phenyl group of PI-OH (**1a**) and have found that the activity of **1b** bearing a chlorine atom at the *para* position of the 4-phenyl group was greater than that of PI-OH (**1a**), however, the activity of the *meta* chloro analogue **1c** was less potent than that of PI-OH (**1a**).[7]

From these findings, 1-hydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (**2a**) and the derivatives **2b**—**f** which have a halogen atom on the 1-phenyl group of **2a** are interesting as new NE potentiators. This paper describes the synthesis and NE potentiating activity of the 3-benzazepines **2a**—**f**.

In previous papers, we reported on the convenient synthesis of PI-OH (**1a**) and its related compounds,[9] 3-hydroxy-3-phenylindoles,[10] and 1,2-diphenyl-1-hydroxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (**3**)[11] by the intramolecular Barbier reaction of the corresponding *N*-benzyl- and *N*-phenylphenacylamines, and *N*-[2-(2-iodophenyl)ethyl]-α-phenylphenacylamines with *n*-butyllithium (*n*-C_4H_9Li), both in good yields.

Thus, we synthesized 1-hydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepines (**2a**—**f**) by the intramolecular Barbier reaction of *N*-[2-(2-iodophenyl)ethyl]-*N*-methylphenacylamines (**6a**—**f**) as a key reaction step as shown in Chart 1. The condensation of *N*-methyl-2-(2-iodophenyl)ethylamine (**4**) with phenacyl bromides (**5a**—**f**)[7] gave the phenacylamines **6a**—**f**. Intramolecular cyclization of **6a**—**f** with *n*-BuLi afforded the 3-benzazepines **2a**—**f** in a yield of 14.7—38.7% along with the reduced compounds **7a**—**f** of the starting materials **6a**—**f** in a yield of 18.4—49.3%, respectively. Although compound **2a** was obtained in a moderate yield (38.7%) with the reduced compound **7a** in a yield of 18.4%, the halogenated compounds **2b**—**f** were produced in low yields (14.7—23.6%) with the reduced compounds **7b**—**f** in

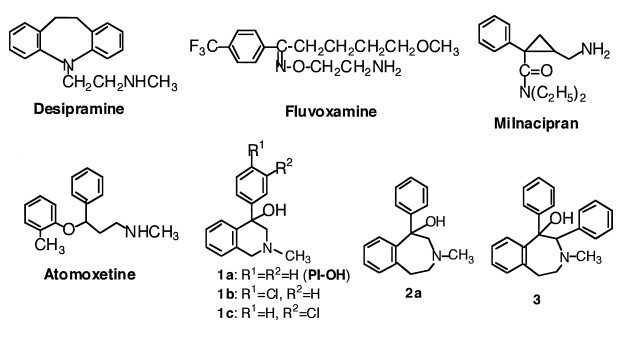

Fig. 1

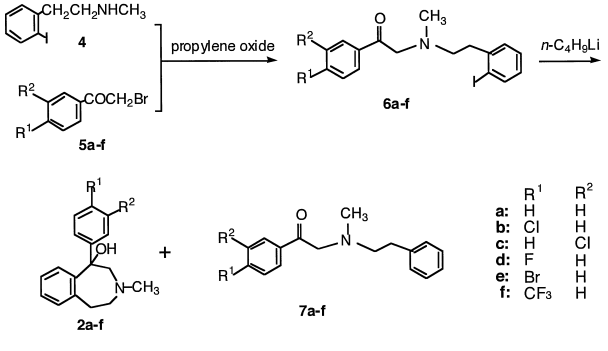

Chart 1

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Table 1. Potentiating Activities of 1-Hydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepines (**2a**—**f**) on the Response of Rat Anococcygeus Muscle to Norepinephrine

Compound	$n^{b)}$	pD_2 value (activity ratio)$^{a)}$					
		Concentration (M) of test compound					
		0	3×10^{-7}	10^{-6}	3×10^{-6}	10^{-5}	3×10^{-5}
PI-OH (**1a**)	8	5.97±0.05 (1.0)	6.47±0.12 (3.5)	6.84±0.09 (7.7)	7.13±0.09 (14.6)	7.28±0.08 (20.5)	7.34±0.10 (19.7)
2a	8	6.37±0.04 (1.0)		6.54±0.06 (1.5)	6.68±0.07 (2.2)	7.02±0.08 (4.8)	7.18±0.10 (7.3)
2b	8	6.09±0.06 (1.0)	(1.1)	6.11±0.10 (1.8)	6.31±0.12 (2.0)	6.35±0.11 (1.9)	6.31±0.10
2c	7	6.07±0.03 (1.0)	6.23±0.05 (1.5)	6.35±0.07 (2.0)	6.64±0.09 (3.9)	6.66±0.08 (4.0)	
2d	5	6.16±0.05 (1.0)		6.17±0.08 (1.0)	6.30±0.09 (1.4)	6.40±0.08 (1.7)	6.44±0.07 (1.9)
2e	8	6.18±0.06 (1.0)		6.37±0.11 (1.6)	6.65±0.11 (2.9)	6.64±0.07 (3.0)	6.54±0.08 (2.4)
2f	6	6.19±0.06 (1.0)		6.18±0.08 (1.0)	6.05±0.18 (0.9)	6.25±0.06 (1.2)	6.32±0.08 (1.4)

a) Activity ratio was calculated as the antilogarithm of the difference between the pD_2 values for NE obtained in the presence and absence of the test compounds. *b*) *n* is the number of experiments.

higher yields (35.1—49.3%).

The potentiating effects of the 3-benzazepines **2a**—**f** as well as PI-OH (**1a**) on the contraction of rat anococcygeus muscle induced by NE were determined by the methods reported in our previous papers.[6—8] The results of these experiments are shown in Table 1. Of the compounds prepared in this study, compound **2a** had no substituent on the 4-phenyl group and had moderate potentiating activity (activity ratio was 7.3-fold at 3×10^{-5} M).

4-(4-Chlorophenyl)isoquinoline **1b** showed greater potentiating activity[7] than PI-OH (**1a**), whereas 1-(4-chlorophenyl)-3-benzazepine **2b** in addition to **2d**—**f** showed no activity, even though 1-(3-chlorophenyl) derivative **2c** revealed almost the same activity as **2a**. These results indicated that 4-hydroxy-4-phenylisoqinoline with an ethanolamine moiety and a six-membered ring such as PI-OH (**1a**) was the preferred structure for the inhibition of NE reuptake rather than the 1-hydroxy-1-phenyl-3-benzazepines **2a**—**f** constructed with a seven-membered ring expanded from the isoquinoline structure of PI-OH (**1a**).

Experimental

General All melting points are given as uncorrected values. IR spectra were obtained with a Perkin-Elmer 1720 infrared fourier transform spectrometer. High-resolution mass (HR-MS) spectra were recorded on a JEOL JMS-D 300 spectrometer. ^{1}H-NMR spectra were recorded on a JEOL JNM-FX 200 spectrometer with tetramethylsilane as a standard.

***N*-[2-(2-Iodophenyl)ethyl]-*N*-methylphenacylamine (6a)** A solution of *N*-methyl-2-(2-iodophenyl)ethylamine (**4**) (1.228 g, 4.70 mmol), phenacyl bromide (**5a**) (0.468 g, 2.35 mmol) in dioxane (10 ml) was stirred at room temperature for 5 h. The mixture was filtered and the filtrate was evaporated to give an oil (1.124 g). This was subjected to column chromatography on SiO_2 with CH_2Cl_2–*n*-hexane–AcOEt (3 : 3 : 1) to afford **6a** as a pale brown oil (0.622 g, 69.5%). ^{1}H-NMR ($CDCl_3$) δ: 8.01 (2H, d, J=8.1 Hz), 7.79 (1H, d, J=8.6 Hz), 6.87 (1H, m), 3.92 (2H, s), 2.94 (2H, m), 2.80 (2H, m), 2.50 (3H, s). IR (KBr) cm^{-1}: 1741. HR-MS *m*/*z*: Calcd for $C_{17}H_{18}INO$: 378.0355 (M^+). Found: 378.0301.

Compounds **6b**—**f** were prepared in the same way as **6a**.

4-Chloro-*N*-[2-(2-iodophenyl)ethyl]-*N*-methylphenacylamine (6b) Compound **4** (1.028 g, 3.93 mmol) was treated with **5b** (0.417 g, 1.78 mmol) in dioxane (10 ml) to give a crude oil (0.793 g). This was subjected to column chromatography on SiO_2 with CH_2Cl_2–AcOEt (50 : 1) to afford **6b** as a pale brown oil (0.301 g, 40.8%). ^{1}H-NMR ($CDCl_3$) δ: 7.93 (2H, d, J=8.3 Hz), 7.77 (1H, d, J=7.6 Hz), 7.37 (2H, d, J=8.3 Hz), 6.87 (1H, m), 3.83 (2H, s), 2.91 (2H, m), 2.78 (2H, m), 2.46 (3H, s). HR-MS *m*/*z*: Calcd for $C_{17}H_{17}ClINO$: 413.0043 (M^+). Found: 413010.

3-Chloro-*N*-[2-(2-iodophenyl)ethyl]-*N*-methylphenacylamine (6c) Compound **4** (1.985 g, 7.60 mmol) was reacted with **5c** (0.801 g, 3.43 mmol) in dioxane (20 ml) under reflux for 2 h to give a crude oil (1.777 g). This was subjected to column chromatography on SiO_2 with CH_2Cl_2–AcOEt (10 : 1) to afford **6c** as a pale brown oil (1.108 g, 78.1%). ^{1}H-NMR ($CDCl_3$) δ: 7.98 (1H, dd, J=1.7, 1.7 Hz), 7.87 (1H, d-like, J=8.1 Hz), 7.78 (1H, d, J=7.6 Hz), 7.52 (1H, d-like, J=8.1 Hz), 7.38 (1H, d, J=8.1 Hz), 6.87 (1H, m), 3.86 (2H, s), 2.97 (2H, m), 2.74 (2H, m), 2.48 (3H, s). HR-MS *m*/*z*: Calcd for $C_{17}H_{17}ClINO$: 413.0043 (M^+). Found: 413.0018.

4-Fluoro-*N*-[2-(2-iodophenyl)ethyl]-*N*-methylphenacylamine (6d) Compound **4** (5.741 g, 22.0 mmol) was reacted with **5d** (2.377 g, 11.0 mmol) in dioxane (50 ml) under reflux for 2 h to give a crude oil (5.268 g). This was subjected to column chromatography on SiO_2 with CH_2Cl_2–AcOEt (7 : 1) to afford **6d** as a pale yellow oil (2.462 g, 28.2%). ^{1}H-NMR ($CDCl_3$) δ: 8.02 (2H, dd, J=8.8, 5.4 Hz), 7.78 (1H, d, J=8.1 Hz), 7.21 (2H, m), 6.87 (1H, m), 3.85 (2H, s), 2.96 (2H, m), 2.74 (2H, m), 2.47 (3H, s). HR-MS *m*/*z*: Calcd for $C_{17}H_{17}FINO$: 397.0339 (M^+). Found: 397.0335.

4-Bromo-*N*-[2-(2-iodophenyl)ethyl]-*N*-methylphenacylamine (6e) Compound **4** (5.335 g, 20.4 mmol) was reacted with **5e** (2.860 g, 10.3 mmol) in dioxane (60 ml) under reflux for 2 h to give a crude oil (7.519 g). This was subjected to column chromatography on SiO_2 with CH_2Cl_2–AcOEt (10 : 1) to afford **6e** as a yellow oil (1.981 g, 21.2%). ^{1}H-NMR ($CDCl_3$) δ: 7.84 (2H, d, J=8.6 Hz), 7.77 (1H, d, J=7.8 Hz), 7.54 (2H, d, J=8.6 Hz), 7.24 (2H, m), 6.88 (1H, m), 3.84 (2H, s), 2.94 (2H, m), 2.76 (2H, m), 2.47 (3H, s). HR-MS *m*/*z*: Calcd for $C_{17}H_{17}BrINO$: 457.9617 (M^+). Found: 457.9658.

***N*-[2-(2-Iodophenyl)ethyl]-*N*-methyl-4-trifluoromethylphenacylamine (6f)** Compound **4** (4.418 g, 16.9 mmol) was reacted with **5f** (2.224 g, 8.33 mmol) in dioxane (50 ml) under reflux for 2 h to give a crude oil (3.656 g). This was subjected to column chromatography on SiO_2 with CH_2Cl_2–AcOEt (15 : 1) to afford **6f** as a yellow oil (2.522 g, 67.7%). ^{1}H-NMR ($CDCl_3$) δ: 8.08 (2H, d, J=7.8 Hz), 7.77 (1H, d, J=8.1 Hz), 7.66 (2H, d, J=8.1 Hz), 7.21 (2H, m), 6.87 (1H, m), 3.89 (2H, s), 2.94 (2H, m), 2.77 (2H, m), 2.48 (3H, s). HR-MS *m*/*z*: Calcd for $C_{18}H_{17}F_3INO$: 447.0315 (M^+). Found: 447.0314.

1-Hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (2a) *n*-BuLi (0.42 ml of 1.6 M solution in *n*-hexane, 0.67 mmol) was added to a solution of **6a** (0.195 g, 0.51 mmol) in dry tetrahydrofuran (THF) (5 ml) under N_2 at −78 °C. The mixture was stirred for 10 min at −78 °C and then at room temperature for 10 min. H_2O (20 ml) was added and the mixture was extracted with ether (20 ml×4). The extract was dried over $MgSO_4$ and evaporated to give a brown oil (0.142 g). This was subjected to column chromatography on SiO_2 with CH_2Cl_2–AcOEt (1 : 1). The first fraction gave **7a** as a pale brown oil (0.0235 g, 18.4%). ^{1}H-NMR ($CDCl_3$) δ: 7.96 (2H, dd, J=8.0, 1.5 Hz), 7.64—7.10 (8H, m), 3.88 (2H, s), 2.84 (2H, s), 2.45 (3H, s).

HR-MS *m/z*: Calcd for $C_{17}H_{19}NO$: 252.1387 (M−1). Found: 252.1362. The second fraction gave **2a** as a pale yellow oil (0.0504 g, 38.7%). ^{1}H-NMR ($CDCl_3$) δ: 7.36 (5H, m), 7.10 (3H, m), 6.79 (1H, d, J=7.2 Hz), 3.30 (1H, ddd, J=12.5, 9.5, 2.5 Hz), 3.25 (1H, d, J=12.7 Hz), 2.96 (2H, m), 2.94 (1H, d, J=12.7 Hz), 2.60 (1H, ddd, J=11.5, 9.5, 2.5 Hz), 2.49 (3H, s). HR-MS *m/z*: Calcd for $C_{17}H_{19}NO$: 253.1463 (M^+). Found: 253.1464.

The oily product **2a** was converted to the hydrochloride as colorless needles (mp 215—218 °C (decomp.) from MeOH–acetone). IR (KBr) cm^{-1}: 3385, 2943. *Anal.* Calcd for $C_{17}H_{19}NO \cdot HCl \cdot 1/5\,H_2O$: C, 69.59; H, 7.01; N, 4.77. Found: C, 69.97; H, 6.89; N, 4.74.

The 3-benzazepines **2b**—**f** were prepared in the same way as **2a**.

1-(4-Chlorophenyl)-1-hydroxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (2b) Compound **6b** (1.027 g, 2.48 mmol) was treated with *n*-BuLi (2.5 ml of 1.6 M solution in *n*-hexane, 4.0 mmol) in dry THF (10 ml). The crude oily product (0.786 g) was subjected to column chromatography on SiO_2 with CH_2Cl_2–AcOEt (7 : 1). The first fraction gave **7b** as a pale yellow oil (0.257 g, 36.1%). ^{1}H-NMR ($CDCl_3$) δ: 7.89 (2H, d, J=8.3 Hz), 7.40—7.12 (5H, m), 7.35 (2H, d, J=8.3 Hz), 3.76 (2H, s), 2.81 (4H, m), 2.40 (3H, s). HR-MS *m/z*: Calcd for $C_{17}H_{18}ClNO$: 287.1078 (M^+). Found: 287.1080. The second fraction gave **2b** as a yellow oil (0.155 g, 21.7%). ^{1}H-NMR ($CDCl_3$) δ: 7.38 (2H, d, J=8.5 Hz), 7.32 (2H, d, J=8.5 Hz), 7.09 (3H, m), 6.77 (1H, d, J=8.3 Hz), 3.28 (1H, ddd, J=12.5, 9.5, 2.5 Hz), 3.20 (1H, d, J=12.7 Hz), 3.12—2.80 (2H, m), 2.86 (1H, d, J=12.7 Hz), 2.58 (1H, ddd, J=11.7, 9.5, 2.5 Hz), 2.49 (3H, s). HR-MS *m/z*: Calcd for $C_{17}H_{18}ClNO$: 287.1080 (M^+). Found: 287.1077.

The oily product **2b** was converted to the hydrochloride as colorless cubes (mp 217—219 °C from MeOH–acetone). IR (KBr) cm^{-1}: 3230, 2717. *Anal.* Calcd for $C_{17}H_{18}ClNO \cdot HCl \cdot 1/5\,H_2O$: C, 62.28; H, 5.96; N, 4.24. Found: C, 62.47; H, 5.99; N, 4.14.

1-(3-Chlorophenyl)-1-hydroxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (2c) Compound **6c** (1.077 g, 2.60 mmol) was treated with *n*-BuLi (2.0 ml of 1.6 M solution in *n*-hexane, 3.2 mmol) in dry THF (6 ml). The crude oily product (0.892 g) was subjected to column chromatography on SiO_2 with CH_2Cl_2–AcOEt (3 : 2). The first fraction gave **7c** as a pale yellow oil (0.263 g, 35.1%). ^{1}H-NMR ($CDCl_3$) δ: 7.94 (1H, dd, J=1.7, 1.7 Hz), 7.81 (1H, d, J=7.8 Hz), 7.48 (1H, d, J=8.1 Hz), 7.28 (1H, d, J=8.8 Hz), 7.24 (5H, m), 3.78 (2H, s), 2.79 (4H, m), 2.40 (3H, s). HR-MS *m/z*: Calcd for $C_{17}H_{18}ClNO$: 286.0997 (M−1). Found: 286.0973. The second fraction gave **2c** as a yellow oil (0.177 g, 23.6%). ^{1}H-NMR ($CDCl_3$) δ: 7.49 (1H, t-like, J=2.0 Hz), 7.28 (3H, m), 7.12—6.99 (3H, m), 6.76 (1H, d, J=8.1 Hz), 3.30 (1H, ddd, J=12.5, 9.5, 2.5 Hz), 3.19 (1H, d, J=12.7 Hz), 3.12—2.80 (2H, m), 2.86 (1H, d, J=12.7 Hz), 2.56 (1H, ddd, J=12.0, 9.5, 2.5 Hz), 2.47 (3H, s). HR-MS *m/z*: Calcd for $C_{17}H_{18}ClNO$: 287.1078 (M^+). Found: 287.1053.

The oily product **2c** was converted to the hydrochloride as colorless cubes (mp 220—222.5 °C from MeOH–acetone). IR (KBr) cm^{-1}: 3247, 2580. *Anal.* Calcd for $C_{17}H_{18}ClNO \cdot HCl$: C, 62.97; H, 5.91; N, 4.32. Found: C, 62.55; H, 5.78; N, 4.23.

1-(4-Fluorophenyl)-1-hydroxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (2d) Compound **6d** (2.422 g, 6.10 mmol) was treated with *n*-BuLi (8.0 ml of 1.6 M solution in *n*-hexane, 12.8 mmol) in dry THF (20 ml). The crude oily product (1.709 g) was subjected to column chromatography on SiO_2 with CH_2Cl_2–acetone (2 : 1). The first fraction gave **7d** as a pale yellow oil (0.617 g, 37.5%). ^{1}H-NMR ($CDCl_3$) δ: 7.98 (2H, dd, J=9.0, 5.4 Hz), 7.32—7.12 (5H, m), 7.04 (2H, t-like, J=8.8 Hz), 3.76 (2H, s), 2.81 (4H, m), 2.39 (3H, s). FAB-MS *m/z*: Calcd for $C_{17}H_{18}FNO$: 272.1451 (M+H). Found: 272.1461. The second fraction gave **2d** as a yellow oil (0.306 g, 18.5%). ^{1}H-NMR ($CDCl_3$) δ: 7.39 (2H, dd, J=9.0, 5.6 Hz), 7.16—6.98 (5H, m), 6.79 (1H, d, J=7.6 Hz), 3.23 (1H, ddd, J=12.5, 9.5, 2.5 Hz), 3.20 (1H, d, J=12.7 Hz), 3.06—2.80 (2H, m), 2.86 (1H, d, J=12.7 Hz), 2.57 (1H, m), 2.47 (3H, s). HR-MS *m/z*: Calcd for $C_{17}H_{18}FNO$: 271.1373 (M^+). Found: 271.1366.

The oily product **2d** was converted to the hydrochloride as colorless cubes (mp 203.5—204 °C from MeOH–acetone). IR (KBr) cm^{-1}: 3215, 2716. *Anal.* Calcd for $C_{17}H_{18}FNO \cdot HCl$: C, 66.34; H, 6.22; N, 4.55. Found: C, 66.33; H, 6.22; N, 4.53.

1-(4-Bromophenyl)-1-hydroxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (2e) Compound **6e** (1.978 g, 4.32 mmol) was treated with *n*-BuLi (3.5 ml of 1.6 M solution in *n*-hexane, 5.6 mmol) in dry THF (30 ml). The crude oily product (1.512 g) was subjected to column chromatography on SiO_2 with CH_2Cl_2–acetone (5 : 1). The first fraction gave **7e** as a pale brown oil (0.670 g, 46.5%). ^{1}H-NMR ($CDCl_3$) δ: 7.80 (2H, d, J=8.3 Hz), 7.53 (2H, d, J=8.3 Hz), 7.40—7.12 (5H, m), 3.81 (2H, s), 2.83 (4H, s), 2.43 (3H, s). FAB-MS *m/z*: Calcd for $C_{17}H_{18}BrNO$: 332.0650 (M+H). Found: 332.0669. The second fraction gave **2e** as a yellow oil (0.266 g, 18.5%). ^{1}H-NMR ($CDCl_3$) δ: 7.49 (2H, d, J=8.6 Hz), 7.32 (2H, d, J=8.6 Hz), 7.11 (3H, m), 6.76 (1H, d, J=7.8 Hz), 3.23 (1H, ddd, J=12.0, 9.0, 2.5 Hz), 3.20 (1H, d, J=12.7 Hz), 3.11—2.84 (2H, m), 2.90 (1H, d, J=12.7 Hz), 2.58 (1H, ddd, J=11.8, 9.3, 2.5 Hz), 2.50 (3H, s). HR-MS *m/z*: Calcd for $C_{17}H_{18}BrNO$: 331.0610 (M^+). Found: 331.0572.

The oily product **2e** was converted to the hydrochloride as colorless cubes (mp 223—224 °C from MeOH–acetone). IR (KBr) cm^{-1}: 3219, 2712. *Anal.* Calcd for $C_{17}H_{18}BrNO \cdot HCl \cdot 1/3\,H_2O$: C, 54.49; H, 5.20; N, 3.74. Found: C, 54.62; H, 5.15; N, 3.50.

1-Hydroxy-3-methyl-1-(4-trifluoromethylphenyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (2f) Compound **6f** (2.482 g, 5.55 mmol) was treated with *n*-BuLi (4.0 ml of 1.6 M solution in *n*-hexane, 6.72 mmol) in dry THF (10 ml). The crude oily product (1.994 g) was subjected to column chromatography on SiO_2 with CH_2Cl_2–AcOEt (1 : 1). The first fraction gave **7f** as a pale brown oil (0.879 g, 49.3%). ^{1}H-NMR ($CDCl_3$) δ: 8.00 (2H, d, J=8.1 Hz), 7.61 (2H, d, J=8.3 Hz), 7.20 (5H, m), 3.79 (2H, s), 2.80 (4H, s), 2.39 (3H, s). HR-MS *m/z*: Calcd for $C_{17}H_{18}F_3NO$: 321.1314 (M^+). Found: 321.1317. The second fraction gave **2f** as a yellow oil (0.262 g, 14.7%). ^{1}H-NMR ($CDCl_3$) δ: 7.64 (2H, d, J=8.8 Hz), 7.58 (2H, d, J=8.8 Hz), 7.20—6.91 (3H, m), 6.69 (1H, d, J=8.1 Hz), 3.29 (1H, ddd, J=12.5, 9.5, 2.5 Hz), 3.24 (1H, d, J=12.7 Hz), 3.16—2.80 (2H, m), 2.88 (1H, d, J=12.7 Hz), 2.59 (1H, ddd, J=12.0, 9.5, 2.5 Hz), 2.50 (3H, s). HR-MS *m/z*: Calcd for $C_{17}H_{18}F_3NO$: 321.1315 (M^+). Found: 321.1318.

The oily product **2f** was converted to the hydrochloride as colorless cubes (mp 224 °C from MeOH–acetone). IR (KBr) cm^{-1}: 3236, 2582. *Anal.* Calcd for $C_{17}H_{18}BrNO \cdot HCl$: C, 60.42; H, 5.35; N, 3.91. Found: C, 60.18; H, 5.19; N, 3.92.

Pharmacology Detailed methods used for the evaluation of compounds **2a**—**f** were reported in previous papers[7,8] from our laboratory. Isolated rat anococcygeus muscles were used for the potentiating activity assays of **2a**—**f** in response to NE, which were evaluated from a shift in the concentration–response curves of NE. The ability of a compound to potentiate the action of NE was expressed as the activity ratio, which was determined from the antilogarithm of the difference between the pD_2 values for NE (negative logarithm of the molar concentration of the agonist producing 50% of the maximum response) in the presence and absence of the test compounds.

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