SYNTHESIS OF 2-TRIFLUOROMETHYL-2,3,4,5-TETRAHYDRO-1*H*-3-BENZAZEPINE DERIVATIVES

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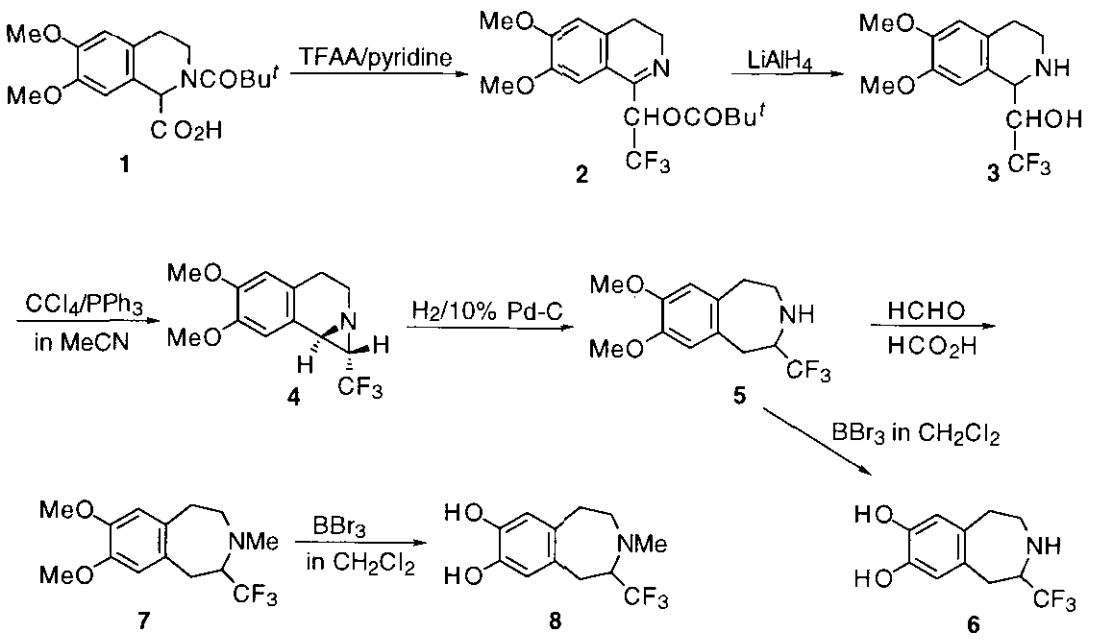
Abstract --- 2-Trifluoromethyl-3-benzazepines (**6** and **8**) were efficiently prepared from 1,2,3,4-tetrahydro-1-hydroxymethylisoquinoline (**3**) *via* ring expansion, utilizing a ring closure/ring opening strategy. *Introduction of the trifluoromethyl group at 2-position in* 7,8-dihydroxy-3-benzazepine (**9**) resulted in showing no affinity to dopamine D_1 and D_2 receptors.

During the last three decades, there has been a wealth of interest in the synthesis of functionalized 2,3,4,5-tetrahydro-1*H*-3-benzazepines[1] due largely to the potent affinity of these compounds for the dopamine receptor and their associated pharmacological properties.[2] In our previous study, the construction of the 3-benzazepine ring system has been efficiently achieved by the Friedel-Crafts type acylation of *N*-triflyl-*N*-(β-phenethyl)amino acids.[3] From a biological point of view, trifluoromethyl substitution often confers unique properties to a molecule in terms of increased lipophilicity, which in turn changes *in vivo* absorption and transport rates.[4] Especially, the introduction of a trifluoromethyl group into the α-position of the nitrogen in biological systems is of current interest.[5] Recently, we reported the synthesis of 1-(1-acyloxy-2,2,2-trifluoroethyl)-3,4-dihydroisoquinolines from *N*-acyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acids by the anomalous Dakin-West reaction employing trifluoroacetic anhydride.[6] The present paper deals with the synthesis of 2-trifluoromethyl-2,3,4,5-tetrahydro-1*H*-3-benzazepines by the use of this reaction and their affinity of dopamine D_1 and D_2 receptors. The synthetic strategy is shown in Scheme 1.

The starting material (**2**) was prepared in 92% yield by the reaction of **1** with trifluoroacetic anhydride (5 mol equiv.) in the presence of pyridine (10 mol equiv.) in CH_2Cl_2 at room temperature for 12 h.[6] Reduction of **2** with $LiAlH_4$ directly produced 1,2,3,4-tetrahydro-



Scheme 1

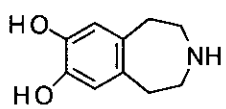
1-(1-hydroxy-2,2,2-trifluoroethyl)isoquinoline (**3**) in 88% yield, as a result of imine reduction and deacylation. The following ring closure and reductive ring opening sequence was used in the ring expansion of tetrahydroisoquinolines to 3-benzazepines.[1, 7] Thus, the resulting amino alcohol (**3**) was then cyclized to the aziridine (**4**) under Mitsunobu reaction conditions. It was found that Mitsunobu reaction of **3** to **4** was carried out in 88% yield using CCl_4 and PPh_3 in MeCN containing Et_3N. When DEAD was used instead of CCl_4, the reaction resulted in a compex mixture and the pure **4** was not isolated. The ^1H NMR spectra of compound (**4**) showed the signals for the aziridine protons H-1 at δ 2.67-2.69 (multiplet) and H-8b at δ 3.20 (doublet, *J*=2.0 Hz). As the coupling constants for *trans*- and *cis*-2-methoxycarbonyl-3-phenylaziridines are reported to be 2.3 and 6.5 Hz, respectively,[8] the aziridine (**4**) was determined to have the *trans* geometry. Hydrogenation of **4** in neutral media using Pd/C as catalyst gave the 3-benzazepine (**5**) (65%) and the starting material was recovered in 30% yield, in spite of long reaction time (24 h). If the reaction was carried out at room temperature for 6 h in acidic media (50% AcOH in MeOH), the 3-benzazepine (**5**) was isolated in 98% yield. *N*-Methylation of **5** with formalin and formic acid yielded *N*-methyl derivative (**7**) in good yield. *O*-Demethylation of **5** and **7** gave the corresponding catechol (**6**) and (**8**) in high yields, respectively. The target compounds as well as the synthetic intermediates were characterized by obtaining satisfactory spectral (^1H and ^{13}C NMR, IR, MS) data and elemental analyses.

Next, we investigated the affinities of **6** and **8** to the dopamine receptors using ^3H-SCH-23390 for the D_1 type and ^3H-YM-09515-2 for the D_2 type.[9] Dopamine and 2,3,4,5-tetrahydro-7,8-dihydroxy-1*H*-3-benzazepine (**9**) have shown almost equipotential affinities to both dopamine D_1 and D_2 receptors.[2] Unfortunately, the affinities of **6** and **8** to the dopamine D_1 and D_2

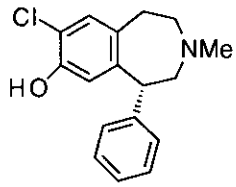
Table 1. Dopaminergic receptor affinities of 3-benzazepines in rat striatal membranes.

Compound	IC_{50} (μM)[a] [Inhibition (%)]		D_1/D_2 ratio
	D_1 (^{3}H-SCH-23390)	D_2 (^{3}H-YM-09151-2)	
dopamine	37.9	18.2	2.1
9	31.1	14.5	2.1
6	100 (0)	100 (0)	-
8	100 (0)	100 (0)	-
SCH-23390	0.0012	1 (35)	<0.001
YM-09151-2	1 (27)	0.0021	>476

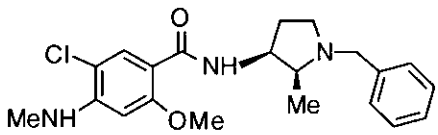
[a] IC_{50} was determined by linear regression analysis, which concentration was necessary to block ^{3}H-SCH-23390 or ^{3}H-YM-09151-2.



9



SCH-23390



YM-09151-2
(Nemonapride)

receptors were completely disappeared by the introduction of the trifluoromethyl group in the 2 position of **9** (Table 1). This might be due to a streric and/or electronic effects of the trifluoromethyl group.[5] It is considered that the basicity of azepine nitrogen was reduced by the neighboring trifluoromethyl group and these compounds (**6** and **8**) can not bind to the receptor.

EXPERIMENTAL

Mps were determined on a Yanagimoto hot-stage apparatus and are uncorrected. ^{1}H (270 MHz) and ^{13}C (68 MHz) NMR spectra were measured with tetramethylsilane (Me_4Si) as an internal reference and $CDCl_3$ as the solvent, unless otherwise noted. *J*-Values are given in Hz. IR spectra were recorded on a JASCO IR810 spectrophotometer. Only pertinent IR peaks are given. MS spectra (electron impact: 70 eV) were measured with a JEOL JMS-DS300 spectrometer. For column chromatography, SiO_2 (Merck, Art 9385) was used. Male Wistar rats, weighing 120-200 g, were obtained from Kitayama Laboratories (Kyoto, Japan). The following chemicals were generously donated by the companies listed: SCH-23390 and ^{3}H-SCH-23390 (2974.8 GBq/ mmol; New England Nuclear, USA); YM-09151-2 (Yamanouchi Pharm., Tokyo, Japan) and ^{3}H-YM-09151-2 (3011.8 GBq/mmol; New England Nuclear, USA). Dopamine hydrochloride was purchased from Sigma, USA. 7,8-Dihydroxy-2,3,4,5-tetrahydro-

1*H*-3-benzazepine (**9**) was prepared by the literature method.[10] mp 241-243 °C (decomp) (HBr salt) (lit.,[10] mp 233-237 °C).

1,2,3,4-Tetrahydro-1-(1-hydroxy-2,2,2-trifluoroethyl)-6,7-dimethoxyisoquinoline (3): A solution of **2** (3 g, 8 mmol) in dry THF (20 mL) was added gradually to a stirred suspension of $LiAlH_4$ (0.92 g, 24 mmol) in dry THF (10 mL) at 0 °C under an Ar atmosphere. The mixture was stirred for 0.5 h at 25 °C and then excess $LiAlH_4$ was decomposed at 0 °C by the addition of $Na_2SO_4 \cdot 10H_2O$ (1 g). The mixture was filtered through a celite pad and the filter pad was washed with AcOEt (3 x 30 mL). After the evaporation of the combined filtrate, the residue was dissolved in acetone (10 mL) and a solution of oxalic acid (0.73 mg, 8 mmol) in EtOH (5 mL) was added to the solution. The precipitate was collected by filtration and dried. The oxalate was partitioned into a mixture of 3% Na_2CO_3 (60 mL) and AcOEt (100 mL). The AcOEt solution was washed with brine (40 mL) and dried over Na_2SO_4. Evaporation of the solvent *in vacuo* gave **3** (2.06 g, 88%): mp 134-135 °C (CH_2Cl_2-hexane), Anal. Calcd for $C_{13}H_{16}NO_3F_3$: C, 53.61; H, 5.54; N, 4.81. Found: C, 53.49; H, 5.57; N, 4.68. MS m/z 291 (M^+, 0.4), 192 (100); IR υ_{max}/nujol (cm^{-1}) 3150 (br); ^1H NMR δ 2.63-2.70 (m, 2H), 2.97-3.04 (m, 2H), 3.00-3.20 (br, 2H), 3.81 (s, 3H), 3.83 (s, 3H), 4.09-4.13 (m, 2H), 6.57 (s, 1H), 6.68 (s, 1H); ^{13}C NMR δ 28.7 (CH_2), 39.6 (CH_2), 55.1 (CH), 55.8 (CH_3), 56.0 (CH_3), 71.6 (CH, $^2J_{CF}$=27.4), 111.0 (CH), 112.0 (CH), 124.5 (C), 125.2 (CF_3, $^1J_{CF}$=284.0), 128.0 (C), 147.1 (C), 148.4 (C).

1-Trifluoromethyl-1,3,4,8b-tetrahydro-6,7-dimethoxyazirino[2,1-*a*]isoquinoline (4): A solution of **3** (910 mg, 3.1 mmol), triphenylphosphine (935 mg, 3.6 mmol), CCl_4 (0.31 mL, 3.1 mmol), and Et_3N (0.44 mL, 3.1 mmol) in dry MeCN (10 mL) was stirred at rt for 30 h. The mixture was then evaporated and the residue was diluted with CH_2Cl_2 (80 mL) and 3% Na_2CO_3 (40 mL). The organic layer was washed with brine (30 mL), dried over Na_2SO_4, and evaporated *in vacuo*. The residue was chromatographed with AcOEt-hexane (1:1) as the eluent to give **4** (751 mg, 88%): mp 101-102 °C (CH_2Cl_2-hexane), Anal. Calcd for $C_{13}H_{14}NO_2F_3$: C, 57.14; H, 5.16; N, 5.13. Found: C, 56.91; H, 5.21; N, 4.98. MS m/z 273 (M^+, 100); ^1H NMR δ 2.50-2.56 (m, 2H), 2.67-2.69 (m, 1H), 2.85-2.96 (m, 1H), 3.20 (d, 1H, J=2.0), 3.44-3.52 (m, 1H), 3.86 (s, 3H), 3.91 (s, 3H), 6.59 (s, 1H), 6.87 (s, 1H); ^{13}C NMR δ 23.0 (CH_2), 36.7 (CH, $^3J_{CF}$=2.5), 36.8 (CH, $^2J_{CF}$=36.8), 42.1 (CH_2), 56.1 (CH_3), 56.1 (CH_3), 111.5 (CH), 111.9 (CH), 122.2 (C), 123.9 (C), 124.2 (CF_3, $^1J_{CF}$=272.8), 148.1 (C), 148.4 (C).

2-Trifluoromethyl-2,3,4,5-tetrahydro-7,8-dimethoxy-1*H*-3-benzazepine (5): A mixture of **4** (748 mg, 2.7 mmol) and 10% Pd-C (130 mg) in a mixture of AcOH (3 mL) and MeOH (3 mL) was stirred under a hydrogen atmosphere at rt for 6 h. The mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was diluted with CH_2Cl_2 (80 mL), washed with 5% Na_2CO_3 (30 mL) and brine (30 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was chromatographed with EtOAc-hexane (1:1) as the eluent to give **5** (736 mg, 98%) as a colorless oil. Analytical sample was prepared as oxalate: mp 177-179 °C

(acetone), Anal. Calcd for $C_{13}H_{16}NO_2F_3 \cdot 1/2\ (CO_2H)_2$: C, 52.50; H, 5.35; N, 4.37. Found: C, 52.49; H, 5.34; N, 4.46. MS m/z 275 (M^+, 34), 165 (100); IR υ_{max}/nujol (cm^{-1}) 3320 (br s); ^1H NMR δ 2.31 (s, 1H, D_2O changeable), 2.71-2.79 (m, 2H), 2.92-3.08 (m, 3H), 3.16-3.22 (m, 1H), 3.31-3.39 (m, 1H), 3.86 (s, 3H), 3.87 (s, 3H), 6.64 (s, 1H), 6.68 (s, 1H); ^{13}C NMR δ 37.6 (CH_2), 38.5 (CH_2), 47.1 (CH_2), 56.0 (CH_3), 56.1 (CH_3), 59.6 (CH, $^2J_{CF}$=27.1), 113.3 (CH), 113.7 (CH), 125.8 (CF_3, $^1J_{CF}$=281.0), 129.7 (C), 133.8 (C), 147.1 (C), 147.4 (C).

2-Trifluoromethyl-2,3,4,5-tetrahydro-7,8-dihydroxy-1*H*-3-benzazepine (6): A solution of BBr_3 (1.03 mL, 10.9 mmol) in CH_2Cl_2 (3 mL) was added dropwise to a stirred solution of **5** (600 mg, 2.2 mmol) in CH_2Cl_2 (6 mL) at -78 °C under an Ar atmosphere. The reaction mixture was stirred at -78 °C for 2 h and then at rt for 15 h. MeOH (10 mL) was added dropwise with ice-cooling and the mixture was stirred vigorously. The solvent was evaporated and the residue was crystallized from EtOH-Et_2O to give the HBr salt of **6** (658 mg, 92%): mp 223 °C (decomp)(EtOH-Et_2O), Anal. Calcd for $C_{11}H_{12}NO_2F_3 \cdot HBr$: C, 39.19; H, 4.18; N, 4.15. Found: C, 39.49; H, 4.01; N, 3.82. FABMS m/z 248 (M^++H, 100); ^1H NMR (D_2O) δ 3.00-3.05 (m, 1H), 3.19-3.41 (m, 4H), 3.77-3.83 (m, 1H), 4.15-4.26 (m, 1H), 6.87 (s, 1H), 6.93 (s, 1H).

2-Trifluoromethyl-2,3,4,5-tetrahydro-7,8-dimethoxy-3-methyl-1*H*-3-benzazepine (7): A solution of **5** (736 mg, 2.7 mmol), paraformaldehyde (95 mg, 2.8 mmol) in HCO_2H (6 mL) was stirred at 90 °C for 6 h. The solvent was evaporated and the residue was diluted with CH_2Cl_2 (80 mL) and 3% Na_2CO_3 (30 mL). The organic layer was washed with brine (30 mL), dried over Na_2SO_4, and evaporated *in vacuo*. The residue was chromatographed with EtOAc-hexane (1:1) as the eluent to give **7** (551 mg, 71%) as a colorless oil: HRMS Calcd for $C_{14}H_{18}NO_2F_3$: 289.1290, Found 289.1267. MS m/z 289 (M^+, 55), 220 (100); ^1H NMR δ 2.60+2.61 (s, 3H), 2.85-2.98 (m, 4H), 3.18-3.32 (m, 2H), 3.36-3.40 (m, 1H), 3.85 (s, 3H), 3.86 (s, 3H), 6.62 (s, 1H), 6.63 (s, 1H); ^{13}C NMR δ 31.9 (CH_2), 32.4 (CH_2), 41.5 (CH_3), 51.7 (CH_2), 56.0 (CH_3), 56.0 (CH_3), 63.3 (CH, $^2J_{CF}$=26.1), 113.0 (CH), 113.6 (CH), 126.5 (CF_3, $^1J_{CF}$=286.5), 129.0 (C), 132.7 (C), 146.9 (C), 147.5 (C).

2-Trifluoromethyl-2,3,4,5-tetrahydro-7,8-dihydroxy-3-methyl-1*H*-3-benzazepine (8): Compound (**8**) was obtained in 98% yield from **7** by the same procedure as described for **6**: mp 215 °C (decomp)(HCl salt)(EtOH-Et_2O), Anal. Calcd for $C_{12}H_{14}NO_2F_3 \cdot HCl$: C, 48.41; H, 5.08; N, 4.70. Found: C, 48.63; H, 5.20; N, 4.85. MS m/z 261 (M^+, 64), 192 (100); IR υ_{max}/nujol (cm^{-1}) 3380 (br); ^1H NMR (D_2O) δ 3.10-3.35 (m, 4H), 3.28 (s, 3H), 3.46-3.65 (m, 3H), 6.90 (s, 1H), 6.95 (s, 1H).

^{3}H-SCH-23390 and ^{3}H-YM-09151-2 Bindings: A receptor binding assay was carried out according to the method of Niwa *et al.*[9] with minor changes. Striata dissected from male Wistar rats were homogenized in 100 volumes of cold Tris buffer (0.05 mol/L, pH 7.4) with Biotron (set 7, 30 s, Kimura, Osaka, Japan). The homogenate was centrifuged twice (50,000

g) for 10 min at 4 °C, with resuspension of the pellet in fresh buffer. The final pellet was resuspended in Tris buffer containing 0.1 % (w/v) ascorbic acid, 120 mmol/L NaCl, 5 mmol/L KCl, 2 mmol/L $CaCl_2$ and 1 mmol/L $MgCl_2$ (pH 7.4), to give a final tissue concentration of 1-2 mg wet weight/mL. The membrane suspension containing radioligand and test compounds was incubated at 20 °C for 2 h. Then, Bound/Free-separation was carried out by rapid filtration using Cell Harvester over G-10 glass filters (Inotech, Switzerland). The filters were washed with ice cold Tris buffer, and were dried and counted in 4 mL scintillation cocktail using scintillation counter (Beckmann-LS6500, USA). Nonspecific binding of ^{3}H-YM-09151-2 and ^{3}H-SCH-23390 was determined in the presence of 10 μmol/L YM09151-2 and 10 μmol/L SCH-23390, respectively.

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Received, 15th December, 1997