Synthesis of (1-Azabicyclo[3.3.0]octanyl)methyl-Substituted Aromatic Heterocycles and Their Muscarinic Activity[1)]

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In our development of drugs effective against Alzheimer's disease, we have researched a series of aromatic compounds having a characteristic cyclic amine, 1-azabicyclo[3.3.0]octane ring.

In this report, we describe synthesis of a series of aromatic heterocycles with the 1-azabicyclo[3.3.0]octane ring and their pharmacological evaluation. 3-Amino-5-(1-azabicyclo[3.3.0]octan-5-yl)methyl-1,2,4-oxadiazole (2b) showed the highest M_1 selectivity.

Key words Alzheimer's disease; 1-azabicyclo[3.3.0]octane; SK-946; heterocycle; muscarinic cholinergic receptor binding affinity

Certain biochemical deficiencies and pathological changes have been well documented in brains of Alzheimer's disease (AD) patients. Most consistent among them is the selective loss of certain neuronal populations. In particular, the cholinergic neurons that project from the basal forebrain to the cerebral cortex and hippocampus are at risk in AD.[2)] This selective cholinergic neurodegeneration is the basis of a cholinergic hypothesis, which triggered research efforts aimed at restoring the defective cholinergic transmission.

We have been studying the cognition activators in order to develop a new medicine for AD, and recently found a new compound, *N*-[2-(1-azabicyclo[3.3.0]octan-5-yl)ethyl]-2-nitroaniline fumarate (SK-946), which is highly efficacious and functionally selective for muscarinic M_1 affinity.[1)]

In a recent pharmacokinetic study of SK-946 on rats and dogs, it was found that 4-position of the aniline ring is hydroxylated easily.[3)] In addition, SK-946 displayed comparable affinities for cortical muscarinic M_1 receptors using either *N*-methylscopolamine (NMS) or oxotremorine-M (OXO-M) as radioligands.[4)] Therefore, the goal of this study was to prepare compounds that have greater metabolic stability and agonistic property for muscarinic M1 receptor than SK-946.

Naturally occurring muscarinic M_1 agonist arecoline has high activity *in vitro*. There are, however, major drawbacks associated with this compound including low clinical efficacy and poor metabolic stability.[5)] Many structural modifications have been made of arecoline to improve its pharmacological and pharmacokinetic properties towards a clinically more useful profile. One strategy most pursued for improving the pharmacological profile has been the replacement of the ester group with bioisosteric five-membered heterocyclic rings.[6)] Some of the achievements were the 1,2,4-oxadiazoles as L-658903,[7)] the 1,2,5-thiadiazoles as xanomeline[8)] and tetrazole rings.[9)] These modifications give high efficacy to the agonistic property at M_1 receptor and provide more stability than arecoline (Chart 1).

We have been studying the muscarinic activity of heterocycle derivatives based on the above. In this paper, we describe the synthesis and biological evaluation of heterocycles, as 1,2,4-oxadiazole, 1,2,5-thiadiazole and tetrazole derivatives, with the (1-azabicyclo[3.3.0]octan-5-yl)methyl moiety. The abilities of these compounds to improve cognitive function were assessed by radioligand binding assay using rats and passive avoidance tests in scopolamine-treated mice.

Chemistry

The five-membered azaheterocycles with the 1-azabicyclo[3.3.0]octanyl methyl group for biological tests were prepared as shown in Chart 2. The 1,2,4-oxadiazole ring was constructed from an ester and an oxime according to the method of Saunders *et al*.[7a)] Compounds **2a** and **2b** were prepared by condensation of methyl (1-azabicyclo[3.3.0]octan-5-yl)acetate (**1**)[10)] with $MeC(=NOH)NH_2$ and $H_2NC(=NOH)$-NH_2, respectively.

Reaction of 5-chloromethyl-1-azabicyclo[3.3.0]octane hydrochloride (**3**)[10)] with 5-methyltetrazole gave the tetrazole derivatives as a mixture of positional isomers **4a** and **4b**. Each isomer was obtained by chromatographic separation and its regiochemistry was spectroscopically assigned by the long-range H–C correlation spectroscopy (COSY) technique of NMR experiments.

(1-Azabicyclo[3.3.0]octan-5-yl)acetaldehyde (**5**) was prepared from corresponding cyano compound[10)] by reduction with $LiAl(OEt)_2H_2$. Reaction of the aldehyde **5** with acetone cyanohydrine and NH_3 in MeOH gave aminonitrile **6**, which was cyclized with sulfur monochloride to afford 3-chloro-4-(1-azabicyclo[3.3.0]octan-5-yl)methyl-1,2,5-thiadiazole (**7**) according to the method of Sauerberg *et al*.[8a)] Chloride **7** was treated with an appropriate sodium alkoxide to give the alkoxy compounds **8a** and **8b**.

Pharmacological Results and Discussion

The affinities of the present compounds for the M_1 and M_2 receptors were evaluated in terms of the abilities to displace [^{3}H]pirenzepine, an M_1-selective ligand, from rat cerebral cortex membrane and [^{3}H]quinuclidinyl benzilate (QNB) from rat cerebellum membrane, respectively, and were evaluated *in vivo* for behavioral efficacy to scopolamine-treated dementia models.

Initially, the affinity for muscarinic M_1 and M_2 receptors of 1,2,4-oxadiazole derivatives was examined (Table 1). 1,2,4-Oxadiazole derivatives showed strong affinity for muscarinic M_1 receptor. The 3-amino derivative **2b** had slightly stronger affinity for M_1 receptor (by displacement of [^{3}H]pirenzepine) than the 3-methyl congener **2a**.

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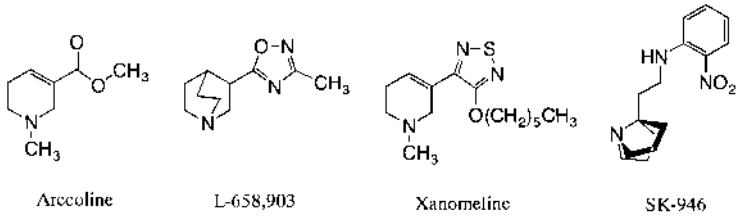

Chart 1

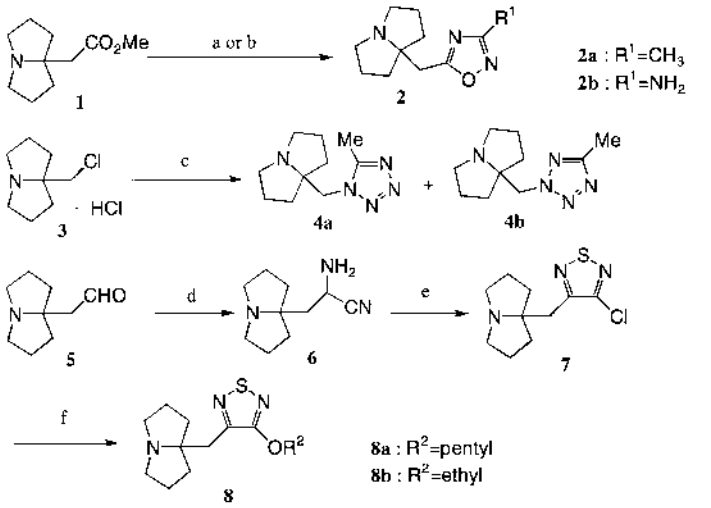

Chart 2

Table 1. Affinities for M_1 and M_2 Receptors of Heterocyclic Compounds with 1-Azabicyclo[3.3.0]octane Ring

Compound	Formula	Receptor affinities K_i (μM)[a]		Ratio of [^{3}H]QNB/[^{3}H]pirenzepine
		[^{3}H]Pirenzepine (M_1)	[^{3}H]QNB[b] (M_2)	
2a	$C_{11}H_{17}N_3O$	5.0	>50	>10.0
2b	$C_{10}H_{16}N_4O$	4.1	>50	>12.2
4a	$C_{10}H_{17}N_5$	4.3	>50	>11.6
4b	$C_{10}H_{17}N_5$	4.0	26.6	6.7
8a	$C_{15}H_{25}N_3OS$	0.23	0.84	3.7
8b	$C_{12}H_{19}N_3OS$	0.076	0.57	7.5
SK-946	—	0.12	1.4	11.7
(−)YM-796	—	1.8	7.7	4.3

a) K_i value (μM) calculated from the respective IC_{50} using the Cheng-Prusoff equation, $K_i = IC_{50}/1 + [L]/K_d$, where [L] and K_d are respectively ligand concentration and dissociation constant. K_d values: [^{3}H]pirenzepine, cortex, 7.1 nM; [^{3}H]QNB, cerebellum, 0.041 nM. *b*) [^{3}H]quinuclidinyl benzilate.

Studies by Showell and coworkers indicated that the potency of affinities for muscarinic M_1 receptor (by displacement of [^{3}H]*N*-methylscopolamine) of 3-amino and 3-methyl-1,2,4-oxadiazole derivatives having tetrahydropyridine were almost equal.[7]

Wadsworth and coworkers reported that the affinities of tetrazole derivatives with quinuclidine for muscarinic M_1 receptor were strong, but not as active as 1,2,4-oxadiazole derivatives (by displacement of [^{3}H]oxotremorine-M).[9] In our study, the affinity for muscarinic M_1 receptor of tetrazole derivatives **4a** and **4b** was as active as 1,2,4-oxadiazole derivatives **2a** and **2b** (Table 1).

The affinity for muscarinic M_1 receptor of 1,2,5-thiadiazole derivatives **8a** and **8b** with 1-azabicyclo[3.3.0]octane moiety was examined (Table 1). Studies by Sauerberg and coworkers showed that the affinities for muscarinic M_1 receptor of 3-*n*-pentyloxy-1,2,5-thiadiazole derivative having tetrahydropyridine were about ten times as active as the 3-ethoxy derivative (by displacement of [^{3}H]pirenzepine).[8] In 1-azabicyclo[3.3.0]octane derivatives, compound **8b** (3-ethoxy derivative) had stronger affinity for M_1 receptor than **8a** (3-*n*-pentyloxy).

1,2,4-Oxadiazole derivative **2b** exhibited the highest M_1 selectivity in our compounds. Thus, **2b** was chosen as the most desirable sample for the *in vivo* test, and ameliorated scopolamine induced impairment in passive avoidance tasks

Table 2. Effect of Compounds on Scopolamine Induced Failure of Step-through Passive Avoidance Response in ddY Mice

Compound	Dose (μg/kg)	n	R.T.[a] (s)	Criteria[b] (%)
Normal		20	295.5±4.48***	90^{+++}
Scopolamine control		20	98.2±22.75	10
2b	0.1 (*p.o.*)	20	114.4±26.46	20
	1.0 (*p.o.*)	20	212.3±23.08**	60^{++}
	10 (*p.o.*)	20	208.1±24.28**	55^{++}
SK-946	0.1 (*p.o.*)	20	158.1±29.03	35^{+}
	1.0 (*p.o.*)	20	196.5±25.90*	30^{+}
	10 (*p.o.*)	20	225.7±24.95**	45^{++}
(±)YM-796	1.0 (*p.o.*)	20	101.0±21.16	5
	10 (*p.o.*)	20	113.9±29.81	10
	100 (*p.o.*)	20	185.7±25.48*	35^{+}

a) R.T.: Latency in retention trial. *b*) Criteria (%)=(number of mice showing avoidance for more than 300 sec/total number of mice)×100. * $p<0.05$, ** $p<0.01$, *** $p<0.001$ *vs*. control (Student's *t*-test), $^{+}$ $p<0.05$, $^{++}$ $p<0.01$, $^{+++}$ $p<0.001$ *vs*. control (Fisher's exact probability test).

at 1.0 μg/kg (*p.o.*) (Table 2).

In conclusion, our aromatic heterocycles having the characteristic cyclic amine, 1-azabicyclo[3.3.0]octane ring, had strong activity to muscarinic M_1 receptor. Although this affinity to the receptor of **2b** was weaker than that of SK-946 *in vitro*, **2b** was about 10 times as active as SK-946 in passive avoidance tasks *in vivo*. This was thought to result from the fact shown below. 1,2,4-Oxadiazole ring of **2b** is more metabolically stable than aniline ring of SK-946, and, muscarinic M_1 agonistic property of **2b** ($QNB(IC_{50})/OXO\text{-}M(IC_{50})$ ratio equal to 15) is higher than that of SK-946.[11] Previous reports by our group have found that SK-946 has other activity in addition to muscarinic M_1 agonistic property: it increases acetylcholine release in relatively low concentrations.[4] It is possible that compound **2b** and other heterocyclic derivatives also have acetylcholine releasing activity.

Experimental

All melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. ^{1}H-NMR spectra were taken at 60 MHz with a JEOL JNM-60 spectrometer, or at 270 MHz with a JEOL JNM-GSX270 spectrometer. Chemical shifts are expressed in δ (ppm) values with tetramethylsilane as an internal standard and the following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad, dd=double doublet and dt=double triplet. Mass spectra (MS) were recorded on a JEOL JMS-DX300, or on a JEOL JMS-SX102. Infrared (IR) spectra were taken with JASCO IR-810, or Perkin-Elmer 1600. Elemental analyses were performed by Yanagimoto MT-5.

5-(1-Azabicyclo[3.3.0]octan-5-yl)methyl-3-methyl-1,2,4-oxadiazole (2a) Acetamide oxime (2.42 g, 32.7 mmol) suspended in tetrahydrofuran (THF) (75.0 ml) was heated to 60 °C with NaH (980 mg of a 60% dispersion in oil, 32.7 mmol) for 1 h in the presence of 4A molecular sieves (5.00 g). Compound **1** (5.00 g, 27.3 mmol) in THF (25.0 ml) was added and the reaction mixture was heated under reflux for 2 h. After cooling, the reaction mixture was filtered and the solvent was removed *in vacuo*. Brine (20 ml) was added to the residue, which was extracted with $CHCl_3$ (10 ml×3). The extracts were dried and evaporated *in vacuo*. The residue was distilled under reduced pressure (120 °C/7 mmHg) to give 3.69 g (65.3%) of **2a** as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.55—2.04 (8H, m, 3,4-CH_2-pyrrolidine), 2.39 (3H, s, CH_3), 2.60 (2H, dt, J=11, 6 Hz, 2-CH_2-pyrrolidine), 2.96 (2H, s, CH_2), 3.05 (2H, dt, J=11, 6 Hz, 2-CH_2-pyrrolidine). IR (neat) cm^{-1}: 2958, 2868, 1579, 1393. CIMS *m/z*: 208 $(M+1)^+$, 110 (base peak). *Anal*. Calcd for $C_{11}H_{17}N_3O$: C, 63.74; H, 8.27; N, 20.27. Found: C, 63.58; H, 8.16; N, 20.37.

3-Amino-5-(1-azabicyclo[3.3.0]octan-5-yl)methyl-1,2,4-oxadiazole (2b) Sodium metal (1.26 g, 54.8 mmol) was added to absolute EtOH (50 ml) stirred in the presence of 4A molecular sieves (12.0 g). After 15 min at room temperature, hydroxyguanidine hemisulfate hemihydrate (4.36 g, 32.8 mmol) was added and the stirring was continued for another hour. Compound **1** (1.00 g, 5.46 mmol) was added to the mixture, which was then heated under reflux for 2 h. After cooling, the reaction mixture was filtered and the solvent was removed *in vacuo*. Water (40 ml) was added to the residue, which had been extracted with CH_2Cl_2 (50 ml×4). The extracts were dried and evaporated *in vacuo*. White solid residue was recrystallized from *iso*-PrOH-petroleum ether to give 480 mg (42.2%) of **2b** as colorless prisms. ^{1}H-NMR ($CDCl_3$) δ: 1.55—2.03 (8H, m, 3,4-CH_2-pyrrolidine), 2.59 (2H, dt, J=11, 5 Hz, 2-CH_2-pyrrolidine), 2.85 (2H, s, CH_2) 3.06 (2H, dt, J=11, 5 Hz, 2-CH_2-pyrrolidine), 4.37 (2H, br s, NH_2). IR (KBr) cm^{-1}: 3348, 3207, 2966, 1661, 1591. MS *m/z*: 209 $(M+1)^+$, 110 (base peak). *Anal*. Calcd for $C_{10}H_{16}N_4O$: C, 57.67; H, 7.74; N, 26.90. Found: C, 57.43; H, 7.46; N, 26.98.

1-(1-Azabicyclo[3.3.0]octan-5-yl)methyl-5-methyltetrazole (4a) and 2-(1-Azabicyclo[3.3.0]octan-5-yl)methyl-5-methyltetrazole (4b) A solution of 5-chloromethyl-1-azabicyclo[3.3.0]octane hydrochloride (**3**) (588 mg, 3.00 mmol), 5-methyltetrazole (300 mg, 3.57 mmol), and triethylamine (1.50 g) in dimethyl formamide (DMF) was stirred at room temperature for 2 d. The reaction mixture was filtered and the solvent was removed *in vacuo*. The residue was chromatographed on silica gel eluting with Et_2O-triethylamine to give 226 mg (36.3%) of **4a** as a colorless oil and 70.0 mg (11.3%) of **4b** as colorless oil. **4a**: ^{1}H-NMR ($CDCl_3$) δ: 1.42—2.12 (8H, m, 3,4-CH_2-pyrrolidine), 2.54 (3H, s, CH_3), 2.61 (2H, dt, J=10, 7 Hz, 2-CH_2-pyrrolidine), 3.05 (2H, dt, J=10, 7 Hz, 2-CH_2-pyrrolidine), 4.43 (2H, s, CH_2). IR (neat) cm^{-1}: 2960, 2868, 1500, 1459. MS *m/z*: 207 (M^+), 110 (base peak). *Anal*. Calcd for $C_{10}H_{17}N_5$: C, 57.95; H, 8.27; N, 33.79. Found: C, 57.63; H, 8.41; N, 33.54.

4b: ^{1}H-NMR ($CDCl_3$) δ: 1.33—2.05 (8H, m, 3,4-CH_2-pyrrolidine), 2.53 (2H, dt, J=11, 7 Hz, 2-CH_2-pyrrolidine), 2.64 (3H, s, CH_3), 2.79 (2H, dt, J=11, 7 Hz, 2-CH_2-pyrrolidine), 4.13 (2H, s, CH_2). IR (neat) cm^{-1}: 2956, 2868, 1503, 1454. MS *m/z*: 207 (M^+), 110 (base peak). *Anal*. Calcd for $C_{10}H_{17}N_5$: C, 57.95; H, 8.27; N, 33.79. Found: C, 57.81; H, 8.39; N, 33.51.

3-Chloro-4-(1-azabicyclo[3.3.0]octan-5-yl)methyl-1,2,5-thiadiazole (7) To an ice cooed solution of (1-azabicyclo[3.3.0]octan-5-yl)acetaldehyde (**5**) (1.50 g, 4.52 mmol, 54% purity) in MeOH (5.0 ml) were added dropwise 10.3% NH_3-MeOH (10.0 ml) and acetone cyanohydrine (1.38 g, 16.2 mmol). The reaction mixture was stirred under NH_3 gas atmosphere at room temperature for 2 d, and evaporated *in vacuo* to give 2.03 g (76.9%, 31% purity by intensity of methylene proton of ^{1}H-NMR) of crude cyanohydrine derivative **6** as a yellow oil.

To a solution of sulfur monochloride (2.71 g, 18.1 mmol) in DMF (8.0 ml) was added over 15 min a solution of the crude **6** (2.03 g, 4.52 mmol) in DMF (3.0 ml) at 2—4 °C. The reaction mixture was stirred for an additional 2 h at 2—4 °C, and poured into ice water (50 ml). After filtration, the filtrate was alkalized with $NaHCO_3$ and extracted with CH_2Cl_2. The extracts were dried and concentrated *in vacuo* to give 2.60 g (30.8%, purity 26%) of **7**. The intermediate **7** was used without further purification. ^{1}H-NMR ($CDCl_3$) δ: 1.48—2.17 (8H, m, 3,4-CH_2-pyrrolidine), 2.61 (2H, dt, J=10, 6 Hz, 2-CH_2-pyrrolidine), 2.96 (2H, s, CH_2), 3.13 (2H, dt, J=10, 6 Hz, 2-CH_2-pyrrolidine). CIMS *m/z*: 244 $(M+1)^+$, 110 (base peak).

3-(1-Azabicyclo[3.3.0]octan-5-yl)methyl-4-pentoxy-1,2,5-thiadiazole (8a) A solution of compound **7** (1.30 g, 2.30 mmol) in pentanol (2.0 ml) was added to a solution of sodium pentoxide in pentanol prepared from sodium (350 mg, 15.2 mmol) and pentanol (12.0 ml). The reaction mixture was stirred at 50 °C for 2 h, then poured into ice-water (40 ml), and extracted with AcOEt (70 ml). The extracts were dried and evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with Et_2O-triethylamine, to give 134 mg (27.6%) of **8a** as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, t, J=7 Hz, CH_3), 1.37—2.06 (14H, m, 3,4-CH_2-pyrrolidine and O-CH_2-CH_2-CH_2-CH_2-CH_3), 2.56 (2H, dt, J=11, 5 Hz, 2-CH_2-pyrrolidine), 2.86 (2H, s, C-CH_2-C), 3.07 (2H, dt, J=11, 5 Hz, 2-CH_2-pyrrolidine), 4.37 (2H, t, J=7 Hz, O-CH_2). IR (neat) cm^{-1}: 2956, 1518, 1450. CIMS *m/z*: 296 ($(M+1)^+$, base peak). *Anal*. Calcd for $C_{15}H_{25}N_3OS$: C, 60.98; H, 8.53; N, 14.22. Found: C, 60.74; H, 8.34; N, 13.95.

3-(1-Azabicyclo[3.3.0]octan-5-yl)methyl-4-ethoxy-1,2,5-thiadiazole (8b) Similarly, reaction of compound **7** (1.30 g, 2.30 mmol) with sodium ethoxide in ethanol gave 51 mg (12.4%) of **8b** as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.43 (3H, t, J=7 Hz, CH_3), 1.44—2.05 (8H, m, 3,4-CH_2-pyrrolidine), 2.57 (2H, dt, J=11, 5 Hz, 2-CH_2-pyrrolidine), 2.86 (2H, s, C-CH_2-C), 3.07 (2H, dt, J=11, 5 Hz, 2-CH_2-pyrrolidine), 4.44 (2H, q, J=7 Hz, O-CH_2). IR (neat) cm^{-1}: 2956, 2866, 1518, 1450. CIMS *m/z*: 254 ($(M+1)^+$, base peak). *Anal*. Calcd for $C_{12}H_{19}N_3OS$: C, 56.89; H, 7.56; N, 16.58. Found: C, 56.93; H, 7.62; N, 16.37.

Biological Method

Preparation of Rat Brain Homogenate The rat brain homogenate was prepared as to previously reported.[1b)]

[^{3}H]Pirenzepine Binding Inhibition Assay for M_1 receptor was carried out as reported.[1b)]

[^{3}H]Quinuclidinyl Benzilate (QNB) Binding Inhibition Assay for M_2 receptors was carried out as reported method.[1b)]

Reference Compounds (±)-YM-796 was synthesized at our laboratory as fumarate salt.[12)]

Passive Avoidance Performance in Scopolamine-Treated Mice A passive avoidance learning test using mice was carried out according to the previously reported method.[1b)]

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