Synthesis and Anti-influenza Virus Activity of Tricyclic Compounds with a Unique Amine Moiety

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Several novel tricyclic compounds with a unique amine moiety (1, 2a—i) were designed and prepared based on the structure of triperiden for the development of anti-influenza virus agents. An *in vitro* antiviral assay showed that 1-(1-azabicyclo[3.3.0]octan-5-yl)-1-(4-fluorophenyl)-1-(2-tricyclo[3.3.1.1^{3,7}]decyl)methan-1-ol hydrochloride (2f) has a potent anti-influenza A virus activity. Furthermore, since 2f was well tolerated in mice, 2f is promising as a novel anti-influenza virus agent for humans.

Key words anti-influenza virus agent; 1-azabicyclo[3.3.0]octane; triperiden; adamantane

An epidemic of influenza, which is one of the infections of most concern for humans, occurs almost every year and occasionally on a global scale. Infections of the elderly, infants and chronic invalids with the virus can cause severe diseases such as pneumonia and encephalitis, and in some cases, can bring about the death of the patient.

Amantadine,[1] a well-known chemotherapeutic agent for infection, inhibits viral replications by acting on the membrane protein M2, which is located on the surface of the influenza A virus particle. This agent is not effective against the influenza B virus which does not have the M2 protein, and it has an adverse effect on the central nervous system. Ribavirin,[2] which is also a well-known antiviral agent, inhibits RNA synthesis in cells. Rationally designed neuraminidase (NA) inhibitors, zanamivir[3] and oseltamivir,[4] inhibit the release of the virus from cells by acting on NA, which is a membrane protein on the viral envelope. Meanwhile Presber *et al*.[5] reported that triperiden, one of the anti-parkinsonism agents, inhibits the replication of the influenza A virus. Ghendon *et al*.[6] suggested that it acts directly on hemagglutinin (HA), which is another membrane protein of the viral particle. On the other hand, Ott and Wunderli-Allenspach[7] proposed that the antiviral effect is caused by increase in the prelysosomal pH.

We noticed that the action of triperiden is different from the actions of amantadine, ribavirin and neuraminidase inhibitors, since it is expected that derivatives of triperiden having a different action mechanism would be effective against a virus acquiring drug tolerance. Combination therapy with already-known drugs would also be useful in chemotherapy. Thus, we designed novel derivatives based on triperiden to decrease the neurotoxicity of this agent and to increase its antiviral potency. First, we replaced the piperidinoethyl group of triperiden with a 1-azabicyclo[3.3.0]octyl group, which is an effective amine moiety for various biologically active substances.[8] Secondly, we introduced a 2-tricyclo[3.3.1.1^{3,7}]decyl group instead of the tricyclo[2.2.1.0^{2,6}]-heptyl group as a bulky and hydrophobic moiety. Thirdly, various functional groups were introduced into the benzene ring (Chart 1).

In this paper, we describe the syntheses and *in vitro* anti-influenza A virus activities of these compounds. We also mention the cytotoxicity tests of the most active compound **2f**.

Chemistry Diastereomixture **1** was prepared from 5-cyano-1-azabicyclo[3.3.0]octane (**3**)[9] *via* two addition reactions involving an initial addition of phenyllithium followed by treatment with Grignard reagent from 3-chlorotricyclo[2.2.1.0^{2,6}]heptane,[10] as shown in Chart 2. Each diastereomer was separated by silicagel column chromatography, and their chemical shifts were assigned by H/C shift correlated spectroscopy. The stereochemistry of each diastereomer was estimated by observations of the nuclear Overhauser effect (NOE) and shielding effect. The NOE difference spectrum showed that irradiation of the hydrogen atom of the hydroxy group in a major product led to an increase in the signal of

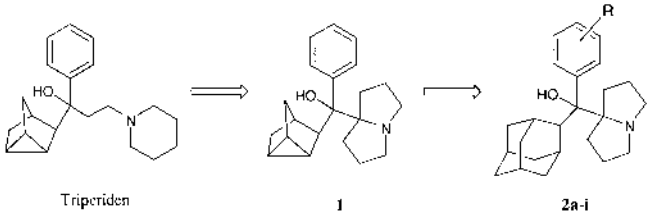
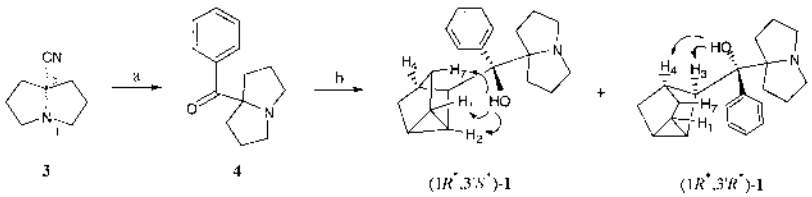


Chart 1



(a) PhLi, Et_2O; (b) 3-tricyclo[2.2.1.0^{2,6}]heptylmagnesium chloride, Et_2O

Chart 2

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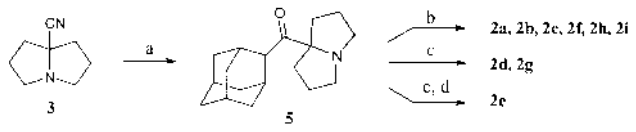
hydrogen atoms at the 1-, 2- and 7-positions of the tricycloheptane ring. Further, the upfield shift of the hydrogen atom at the 4-position of the ring was observed, and this shift can be caused by the shielding effect of the phenyl group. The chemical shifts of the hydrogen atom at the 4-position of the major product were 1.20—1.34 ppm, and that of the minor product was 2.35 ppm. In the minor product, however, NOE interactions of the hydrogen atom of the hydroxy group with the hydrogen atoms at the 3- and 4-positions of the tricycloheptane ring were observed in the NOE difference spectrum. Further, the upfield shifts of the hydrogen atoms at the 1- and 7-positions of the ring were observed. These shifts can also be caused by the shielding effect of the phenyl group. The chemical shift on the hydrogen atom at the 1-position of the major product was 1.50—1.58 ppm, and that of the minor product was 0.81—0.84 ppm. The chemical shifts at the 7-position of the major product were 0.84 and 1.62 ppm, while those of the minor product were 0.46 and 0.70 ppm. These data showed that the relative configuration of the major product was (1*R**,3′*S**) and that of the minor product was (1*R**,3′*R**), as shown in Chart 2.

Compounds **2a**—**i** (except **2e**) were prepared from **3** *via* two addition reactions. The first was an addition of 2-tricyclo[3.3.1.1^{3,7}]decyllithium[11] to **3** to yield 1-(1-azabicyclo[3.3.0]octan-5-yl)-1-(2-tricyclo[3.3.1.1^{3,7}]decyl)methan-1-one (**5**); the second was an addition of the appropriate aryl Grignard or aryllithium reagent[12] derived from aryl bromide to **5**, respectively (Chart 3). Compound **2e** was prepared by the deprotection of the oxathiolane group[13] to the carbonyl group after the addition of 4-(2-methyl-1,3-oxathiolane-2-yl)phenyllithium[12] to **5**.



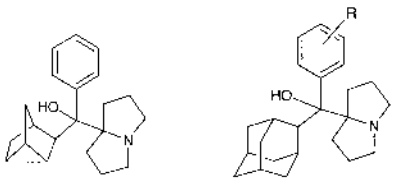
(a) 2-tricyclo[3.3.1.1^{3,7}]decyllithium, Et_2O; (b) appropriate arylmagnesium bromide, THF; (c) appropriate aryllithium, Et_2O; (d) $HgCl_2$, NaOH, THF-H_2O

Chart 3

Pharmacological Results and Discussion

The anti-influenza virus activities of **1**, **2a**—**i**, ribavirin and triperiden were evaluated *in vitro* at doses of 5 μg and 10 μg/ml. The tissue culture infectious doses ($TCID_{50}$) of influenza A virus in the presence or absence of test compounds were calculated by microscopic observations of the cytopathic effect (CPE) induced by the virus on Madin–Darby canine kidney (MDCK) cells. The activity values, $\Delta TCID_{50}$ ($\log_{10}$), shown in Table 1 indicate the differences between the $TCID_{50}$ ($\log_{10}$) of the test compound-treated group and that of the untreated group. Compound (1*R**,3′*S**)-**1** showed a higher activity than triperiden; the replacement of piperidine with 1-azabicyclo[3.3.0]octane enhanced the activity. The following hydrophobic group modification, namely, the substitution of tricyclo[3.3.1.1^{3,7}]decane for tricyclo[2.2.1.0^{2,6}]-heptane, led to a higher activity at a dose of 10 μg/ml; $\Delta TCID_{50}$ ($\log_{10}$) values showed that the activity of **2a** increased approximately five-fold over that of triperiden. In the modification of the phenyl group of **2a**, the introduction of a fluoro group to the *para* position produced the remarkably potent compound **2f**. Compound **2f** was approximately thirty times as active as triperiden at a dose of 10 μg/ml. The activity of ribavirin in this assay was slightly lower than that of

Table 1. Anti-influenza A Virus Activities *in Vitro* of Tricyclic Compounds



Compd.	R	mp (°C)	Formula[a]	$\Delta TCID_{50}$ ($\log_{10}$)[b]		CC_{50} (μg/ml)[c]
				5 μg/ml	10 μg/ml	
Ribavirin				0.33	1.83	>100
Triperiden[d]				0.00	0.50	
(1*R**,3′*S**)-**1**		203—206	$C_{21}H_{27}NO \cdot HCl$	0.17	0.83	
(1*R**,3′*R**)-**1**		192—195	$C_{21}H_{27}NO \cdot HCl$		0.00	
2a	H	238—242	$C_{24}H_{33}NO \cdot HCl$	0.00	1.17	32.5
2b	*p*-CH_3	220—225	$C_{25}H_{35}NO \cdot HCl$	0.17	1.34	36.9
2c	*p*-CF_3	235—238	$C_{25}H_{32}F_3NO \cdot HCl$	0.33	0.33	
2d	*p*-C_6H_5	187—190	$C_{30}H_{37}NO \cdot HCl$	2.17	−[e] (+)[f]	
2e	*p*-$COCH_3$	218—220	$C_{26}H_{35}NO_2 \cdot HCl$	0.50	1.00	
2f	*p*-F	232—235	$C_{24}H_{32}FNO \cdot HCl$	1.00	2.00	53.9
2g	*p*-$N(CH_3)_2$	146—148	$C_{26}H_{38}N_2O \cdot 2HCl$		0.17 (+)[f]	
2h	*m*-CF_3	210—213	$C_{25}H_{32}F_3NO \cdot HCl$	0.00	0.33	
2i	*o*-CH_3	195—200	$C_{25}H_{35}NO \cdot HCl$		−[e] (+)[f]	

a) All compounds had elemental analyses (C, H, N) within ±0.3% of the theoretical values. *b*) The difference between the log reduction of $TCID_{50}$ of test compound-treated group and that of untreated group. *c*) 50% cytotoxic concentration. *d*) A diastereomeric mixture. *e*) Not determined. *f*) Cytotoxicity.

2f; the $\Delta TCID_{50}$ (log_{10}) of ribavirin was 1.83 at a dose of 10 μg/ml. The 50% cytotoxic concentration (CC_{50}) of **2f** was 53.9 μg/ml in MDCK cells, and that of ribavirin was >100 μg/ml (Table 1).

We were anxious about a cholinolytic action of **2f**, because triperiden is an anti-parkinsonism drug. Thus, *in vivo* toxicity tests for triperiden and **2f** were performed using BALB/c mice. The administration of triperiden (i.p. 80 mg/kg) caused a transient convulsion and a lateral turning in one of two mice after eight minutes thirty seconds; these were probably from side-effects relating to the nervous system. In addition, a deficiency phenomenon was observed after thirteen minutes and ten seconds. The administration of **2f** in the same manner, however, did not induce any abnormalities for up to seventy minutes in two cases. No abnormal anatomical findings were observed with either of the administrations.

In conclusion, through the structure modification of triperiden we developed a novel and potent anti-influenza virus agent, **2f**, which had no adverse effects. Interactions of the agent with a biopolymer might be improved favorably by the modification. In the toxicity test of triperiden, however, we observed adverse effects, *i.e.*, transient convulsion, lateral turning and deficiency phenomenon, which might have been induced by a cholinolytic action caused by the anti-parkinsonism drug, while no side-effect was observed in the test of **2f** (i.p. 80 mg/kg). In addition, since the action mechanism of **2f** may be the same as that of triperiden, and may differ from those of amantadine and neuraminidase inhibitors, this agent is expected to be effective on variants of the influenza virus which are resistant toward these drugs.

Experimental

Melting points were measured on a Yanagimoto micromelting point apparatus and were uncorrected. Infrared (IR) spectra were obtained on a JASCO FT/IR-8000; ^{1}H-NMR spectra were obtained on a JEOL JNM-GSX 270 spectrometer (270 MHz for ^{1}H and 68 MHz for ^{13}C) using tetramethylsilane as an internal standard; mass spectra were obtained on a JEOL JMS-DX 300 spectrometer; and elemental analyses for C, H, and N were obtained on a Yanaco CHN Analyzer MT-5.

5-Benzoyl-1-azabicyclo[3.3.0]octane (4) To a solution of **3** (4.09 g, 30.0 mmol) in ether (30 ml), 1.8 M phenyllithium ether solution (20.0 ml, 36.0 mmol) was added dropwise over a period of 45 min at −50 to −60 °C. The mixture was stirred at 0 °C for 30 min, and water (20 ml) was added followed by the addition of 10% sulfuric acid (50 ml). After stirring at 0—5 °C for 2 h, the mixture was neutralized with $NaHCO_3$ and made basic with 20% NaOH. The aqueous layer was extracted with CH_2Cl_2 (3×100 ml). The combined organic layer was dried over Na_2SO_4, concentrated *in vacuo*, and distilled to afford 5.17 g (80.2%) of **4** as a colorless oil. bp: 126—129 °C (1.4 mmHg). ^{1}H-NMR ($CDCl_3$) δ: 1.64—1.98 (6H, m, 3,7-H, two protons of 4,6-H), 2.31—2.41 (2H, m, 4,6-H), 2.70—2.79 (2H, m, 2,8-H), 3.11—3.20 (2H, m, 2,8-H), 7.37—7.51 (3H, m, aromatic H), 8.01—8.04 (2H, m, aromatic H). IR (neat) cm^{-1}: 2963 (C–H), 1672 (C−O). MS (CI) *m/z*: 216 $(M+H)^+$.

(1*R)-1-(1-Azabicyclo[3.3.0]octan-5-yl)-1-phenyl-1-((3*S**)-3-tricyclo-[2.2.1.0^{2,6}]heptyl)methan-1-ol Hydrochloride ((1*R**,3′*S**)-1) and (1*R**)-1-(1-Azabicyclo[3.3.0]octan-5-yl)-1-phenyl-1-((3*R**)-3-tricyclo[2.2.1.0^{2,6}]-heptyl)methan-1-ol Hydrochloride ((1*R**,3′*R**)-1)** To a solution of **4** (8.00 g, 37.2 mmol) in ether (60 ml), a solution of 3-tricyclo[2.2.1.0^{2,6}]-heptylmagnesium chloride (81.8 mmol) in ether (80 ml) was added dropwise over a period of 30 min at −5 to 0 °C. The mixture was stirred at 20 °C for 2 h and poured into a saturated ammonium chloride solution (100 ml) in an ice bath. The ether layer was separated, and the aqueous layer was extracted with ether (3×150 ml). The organic layers were combined, dried over $MgSO_4$, concentrated *in vacuo*, and separated into each diastereomer by silicagel column chromatography (toluene/tetrahydrofuran (THF)). Each diastereomer was converted to hydrochloride with hydrogen chloride in ether and recrystallized from isopropanol to afford 3.51 g (27.2%) of (1*R**,3′*S**)-**1** and 1.84 g (14.3%) of (1*R**,3′*R**)-**1** as colorless prisms. (1*R**,3′*S**)-**1**: ^{1}H-NMR ($CDCl_3$) δ: 0.84 (1H, d, J=10.7 Hz, 7-tricycloheptane H), 1.08 (1H, d, J=10.3 Hz, 5-tricycloheptane H), 1.20—1.34 (4H, m, 4,5,6-tricycloheptane H, 4,6-azabicylooctane H), 1.50—1.58 (2H, m, 1,2-tricycloheptane H), 1.62 (1H, d, J=10.7 Hz, 7-tricycloheptane H), 1.72—1.92 (3H, m, one proton of 4,6-azabicylooctane H, two protons of 3,7-azabicylooctane H), 2.10—2.25 (3H, m, one proton of 4,6-azabicylooctane H, two protons of 3,7-azabicylooctane H), 2.30 (1H, s, 3-tricycloheptane H), 2.93—3.00 (2H, m, one proton of 4,6-azabicylooctane H, one proton of 2,8-azabicylooctane H), 3.23-3.28 (1H, m, 2,8-azabicylooctane H), 3.70—3.79 (1H, m, 2,8-azabicyclooctane H), 4.14—4.20 (1H, m, 2,8-azabicylooctane H), 4.47 (1H, br s, OH), 7.28—7.40 (4H, m aromatic H), 7.83-7.94 (1H, m, aromatic H), 10.9 (1H, br s, N^+H). ^{13}C-NMR ($CDCl_3$) δ: 12.46 (1-tricycloheptane C), 13.18 (6-tricycloheptane C), 13.24 (2-tricycloheptane C), 22.19, 25.37 (3,7-azabicyclooctane C), 29.79 (7-tricycloheptane C), 34.43 (5-tricycloheptane C), 34.54 (4-tricycloheptane C), 35.91, 37.64 (4,6-azabicyclooctane C), 50.23 (3-tricycloheptane C), 55.85, 58.80 (2,8-azabicyclooctane C), 79.02 (1-C), 89.80 (5-azabicyclooctane C), 127.07, 125.00, 128.50, 142.61 (aromatic C). IR (KBr) cm^{-1}: 3209 (O–H), 2990 (C–H). MS (CI) *m/z*: 310 $(M+H)^+$. (1*R**,3′*R**)-**1**: ^{1}H-NMR ($CDCl_3$) δ: 0.46 (1H, d, J=10.7 Hz, 7-tricycloheptane H), 0.70 (1H, d, J=10.7 Hz, 7-tricycloheptane H), 0.81—0.84 (1H, m, 1-tricycloheptane H), 1.14—1.26 (4H, m, 2,6-tricycloheptane H, 5-tricycloheptane H, 4,6-azabicyclooctane), 1.47 (1H, d, J=10.3 Hz, 5-tricycloheptane H), 1.83—2.38 (6H, m, 3,7-azabicyclooctane H, two protons of 4,6-azabicyclooctane H), 2.35 (1H, s, 4-tricycloheptane H), 2.51 (1H, s, 3-tricycloheptane H), 2.97—3.22 (3H, m, one proton of 4,6-azabicyclooctane H, two protons of 2,8-azabicyclooctane H), 3.66—3.75 (1H, m, 2,8-azabicyclooctane H), 3.95—4.01 (1H, m, 2,8-azabicyclooctane H), 4.99 (1H, s, OH), 7.22—7.53 (4H, m, aromatic H), 7.90—7.93 (1H, m, aromatic H), 11.6 (1H, br s, N^+H). ^{13}C-NMR ($CDCl_3$) δ: 12.18 (1-tricycloheptane C), 12.97 (6-tricycloheptane C), 14.82 (2-tricycloheptane C), 23.53, 25.61 (3,7-azabicyclooctane C), 29.58 (7-tricycloheptane C), 33.21 (4-tricycloheptane C), 34.28 (5-tricycloheptane C), 35.78, 37.03 (4,6-azabicyclooctane C), 52.56 (3-tricycloheptane C), 55.84, 57.77 (2,8-azabicyclooctane C), 79.42 (1-C), 91.47 (5-azabicyclooctane C), 125.87, 126.62, 127.15, 128.01, 128.29, 141.05 (aromatic C). IR (KBr) cm^{-1}: 3320 (O–H), 2878 (C–H). MS (CI) *m/z*: 310 $(M+H)^+$.

1-(1-Azabicyclo[3.3.0]octan-5-yl)-1-(2-tricyclo[3.3.1.13,7]decyl)methan-1-one (5) To a solution of **3** (5.45 g, 40.0 mmol) in ether (200 ml), a solution of 2-tricyclo[3.3.1.1^{3,7}]decyllithium (64.8 mmol) in ether (600 ml) was added dropwise over a period of 2 h at −50 °C. The mixture was stirred at −50 °C for 1 h, followed by stirring at room temperature for 18 h, and was then poured into ice water (500 ml). The solution was adjusted to pH 3 with 3 N HCl, stirred at 5 °C for 1.5 h, and extracted with ether (3×500 ml). The aqueous layer was adjusted to pH 9 with $NaHCO_3$ and extracted with ether (4×500 ml). The organic layers were combined, dried over Na_2SO_4, and concentrated to afford 9.02 g (82.5%) of **5** as colorless prisms. mp: 75 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.45—1.92 (16H, m, 4,6,8,9,10-tricyclodecane H, 3,7-azabicyclooctane H, two protons of 4,6-azabicycloocatane H), 2.03—2.13 (4H, m, 5,7-tricyclodecane H, two protons of 4,6-azabicycloocatane H), 2.22 and 2.27 (2H, s, 1,3-tricyclodecane H), 2.59—2.69 (2H, m, 2,8-azabicyclooctane H), 3.07—3.15 (2H, m, 2,8-azabicyclooctane H), 3.23 (1H, s, 2-tricyclodecane H). IR (KBr) cm^{-1}: 2903 (C–H), 1696 (C=O). MS (CI) *m/z*: 274 $(M+H)^+$.

1-(1-Azabicyclo[3.3.0]octan-5-yl)-1-phenyl-1-(2-tricyclo[3.3.1.13,7]-decyl)methan-1-ol Hydrochloride (2a) To a solution of **5** (1.50 g, 5.49 mmol) in THF (15 ml), a solution of phenylmagnesium bromide (16.5 mmol) prepared from bromobenzene and magnesium turnings in THF (15 ml) was added dropwise at −30 to −40 °C. The mixture was stirred at 20 °C for 18 h and poured into a saturated ammonium chloride solution in an ice bath. The solution was adjusted to pH 10 with 10% NaOH and extracted with ether (2×300 ml). The organic layers were combined, dried over Na_2SO_4, concentrated *in vacuo*, and recrystallized from CH_2Cl_2/MeOH. The resulting prisms were converted to hydrochloride with hydrochloric acid and lyophilized to afford 1.50 g (70.5%) of **2a** as a colorless powder. ^{1}H-NMR ($CDCl_3$) δ: 1.60—2.49 (22H, m, tricyclodecane H, 3,7-azabicyclooctane H, three protons of 4,6-azabicyclooctane H), 3.01—3.35 (4H, m, three protons of 2,8-azabicyclooctane H, one proton of 4,6-azabicyclooctane H), 4.18—4.29 (1H, m, 2,8-azabicyclooctane H), 5.18 (1H, br s, OH), 7.23—7.50 (4H, m, aromatic H), 7.97—8.00 (1H, m, aromatic H), 9.76 (1H, br s, N^+H). IR (KBr) cm^{-1}: 3376 (O–H), 2907 (C–H). MS (CI) *m/z*: 352 $(M+H)^+$.

1-(1-Azabicyclo[3.3.0]octan-5-yl)-1-(4-methylphenyl)-1-(2-tricyclo-[3.3.1.13,7]decyl)methan-1-ol Hydrochloride (**2b**): By a procedure similar to that described for **2a**, compound **2b** was prepared as colorless powders from **5** and 4-methylphenylmagnesium bromide in an 81.8% yield. ^{1}H-NMR

($CDCl_3$) δ: 1.17—1.22 (1H, m, 6-tricyclodecane H), 1.57—2.50 (21H, m, tricyclodecane H, 3,7-azabicyclooctane H, three protons of 4,6-azabicyclooctane), 2.33 (3H, s, CH_3), 2.83—3.15 (4H, m, three protons of 2,8-azabicyclooctane, one proton of 4,6-azabicyclooctane), 4.10—4.18 (1H, m, 2,8-azabicyclooctane H), 4.95 (1H, br s, OH), 7.06 (1H, dd, J=8.3, 2.0 Hz, 3-aromatic H), 7.16 (1H, dd, J=8.3, 2.0 Hz, 3-aromatic H), 7.30 (1H, dd, J=8.3, 2.0 Hz, 2-aromatic H), 8.11 (1H, dd, J=8.3, 2.0 Hz, 2-aromatic H), 10.1 (1H, br s, N^+H). IR (KBr) cm^{-1}: 3386 (O–H), 2903 (C–H). MS (CI) m/z: 366 $(M+H)^+$.

1-(1-Azabicyclo[3.3.0]octan-5-yl)-1-(2-tricyclo[3.3.1.13,7]decyl)-1-(4-trifluoromethylphenyl)methan-1-ol Hydrochloride (**2c**): By a procedure similar to that described for **2a**, compound **2c** was prepared as colorless powders from **5** and 4-trifluoromethylphenylmagnesium bromide in a 37.8% yield. ^{1}H-NMR ($CDCl_3$) δ: 1.13—1.18 (1H, m, 6-tricyclodecane H), 1.53—2.47 (21H, m, tricyclodecane H, 3,7-azabicyclooctane H, three protons of 4,6-azabicyclooctane), 2.90—3.48 (4H, m, three protons of 2,8-azabicyclooctane, one proton of 4,6-azabicyclooctane), 4.20—4.26 (1H, m, 2,8-azabicyclooctane H), 5.60 (1H, br s, OH), 7.40 (1H, d, J=8.3 Hz, 3-aromatic H), 7.52 (1H, d, J=8.3 Hz, 3-aromatic H), 7.73 (1H, d, J=8.3 Hz, 2-aromatic H), 8.34 (1H, d, J=8.3 Hz, 2-aromatic H), 10.7 (1H, br, N^+H). IR (KBr) cm^{-1}: 3393 (O–H), 2916 (C–H). MS (CI) m/z: 420 $(M+H)^+$.

1-(1-Azabicyclo[3.3.0]octan-5-yl)-1-(4-biphenyl)-1-(2-tricyclo[3.3.1.13,7]decyl)methan-1-ol Hydrochloride (**2d**): By a procedure similar to that described for **2a**, compound **2d** was prepared as colorless powders from **5** and biphenyllithium in a 76.1% yield. ^{1}H-NMR ($CDCl_3$) δ: 1.14—1.22 (1H, m, 6-tricyclodecane H), 1.55—2.47 (21H, m, tricyclodecane H, 3,7-azabicyclooctane H, three protons of 4,6-azabicyclooctane), 2.82—3.18 (4H, m, three protons of 2,8-azabicyclooctane, one proton of 4,6-azabicyclooctane), 4.01—4.13 (1H, m, 2,8-azabicyclooctane H), 5.04 (1H, m, OH), 7.32—7.76 (8H, m, aromatic H), 8.29 (1H, d, J=7.3 Hz, aromatic H), 10.5 (1H, br s, N^+H). IR (KBr) cm^{-1}: 3422 (O–H). 749, 699 (Ar–H). MS (CI) m/z: 428 $(M+H)^+$.

1-(4-Acetylphenyl)-1-azabicyclo[3.3.0]octan-5-yl)-1-(2-tricyclo[3.3.1.13,7]decyl)methan-1-ol Hydrochloride (**2e**): By a procedure similar to that described for **2a**, 1-(1-azabicyclo[3.3.0]octan-5-yl)-1-(4-(2-methyl-1,3-oxathiolane-2-yl)phenyl)-1-(2-tricyclo[3.3.1.1^{3,7}]decyl)methan-1-ol was prepared from **5** and 4-(2-methyl-1,3-oxathiolane-2-yl)phenyllithium in a 47.3% yield. The mixture of oxathiolane (1.00 g, 2.20 mmol) and $HgCl_2$ (598 mg, 2.20 mmol) in THF (50 ml) was stirred at room temperature for 5 min. After the addition of 0.1 N NaOH (2.20 ml), the mixture was stirred for 10 min and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, concentrated *in vacuo*, and purified by silicagel column chromatography. The resulting prisms were recrystallized from CH_2Cl_2/MeOH, converted to hydrochloride with hydrochloric acid, and lyophilized to afford 401 mg (46.2%) of **2e** as a colorless powder. ^{1}H-NMR ($CDCl_3$) δ: 1.14—1.18 (1H, m, 6-tricyclodecane H), 1.58—2.48 (21H, m, tricyclodecane H, 3,7-azabicyclooctane H, three protons of 4,6-azabicyclooctane), 2.62 (3H, s, $COCH_3$), 2.85—3.13 (4H, m, three protons of 2,8-azabicyclooctane, one proton of 4,6-azabicyclooctane), 4.09—4.17 (1H, m, 2,8-azabicyclooctane H), 5.42 (1H, br s, OH), 7.40 (1H, dd, J=8.3, 2.0 Hz, aromatic H), 7.89 (1H, dd, J=8.3, 2.0 Hz, aromatic H), 8.04 (1H, dd, J=8.3, 2.0 Hz, aromatic H), 8.34 (1H, dd, J=8.3, 2.0 Hz, aromatic H), 10.7 (N^+H). IR (KBr) cm^{-1}: 3424 (O–H). 1680 (C=O). MS (CI) m/z: 394 $(M+H)^+$.

1-(1-Azabicyclo[3.3.0]octan-5-yl)-1-(4-fluorophenyl)-1-(2-tricyclo[3.3.1.13,7]decyl)methan-1-ol Hydrochloride (**2f**): By a procedure similar to that described for **2a**, compound **2f** was prepared as colorless powders from **5** and 4-fluorophenylmagnesium bromide in a 65.9% yield. ^{1}H-NMR ($CDCl_3$) δ: 1.12—1.21 (1H, m, 6-tricyclodecane H), 1.52—2.44 (21H, m, tricyclodecane H, 3,7-azabicyclooctane H, three protons of 4,6-azabicyclooctane), 2.87—3.27 (4H, m, three protons of 2,8-azabicyclooctane, one proton of 4,6-azabicyclooctane), 4.10—4.21 (1H, m, 2,8-azabicyclooctane H), 5.33 (1H, br s, OH), 6.92—7.28 (3H, m, aromatic H), 8.16—8.23 (1H, m, aromatic H), 10.4 (1H, br s, N^+H). IR (KBr) cm^{-1}: 3420 (OH), 2911 (C–H). MS (CI) m/z: 370 $(M+H)^+$.

1-(1-Azabicyclo[3.3.0]octan-5-yl)-1-(4-(dimethylamino)phenyl)-1-(2-tricyclo[3.3.1.13,7]decyl)methan-1-ol Dihydrochloride (**2g**): By a procedure similar to that described for **2a**, compound **2g** was prepared as colorless powders from **5** and 4-(dimethylamino)phenyllithium in a 75.5% yield. ^{1}H-NMR ($CDCl_3$) δ: 1.17—1.23 (1H, m, 6-tricyclodecane H), 1.41—2.43 (21H, m, tricyclodecane H, 3,7-azabicyclooctane H, three protons of 4,6-azabicyclooctane), 2.86—3.20 (4H, m, three protons of 2,8-azabicyclooctane, one proton of 4,6-azabicyclooctane), 3.19 (6H, s, $N(CH_3)_2$), 4.11—4.20 (1H, m, 2,8-azabicyclooctane H), 5.42 (1H, br s, OH), 7.36—65 (2H, m, aromatic H), 7.92—7.98 (1H, m, aromatic H), 8.43—8.49 (1H, m, aromatic H), 10.3 (2H, br s, N^+H). IR (KBr) cm^{-1}: 3421 (OH). MS (CI) m/z: 395 $(M+H)^+$.

1-(1-Azabicyclo[3.3.0]octan-5-yl)-1-(2-tricyclo[3.3.1.13,7]decyl)-1-(3-trifluoromethylphenyl)methan-1-ol Hydrochloride (**2h**): By a procedure similar to that described for **2a**, compound **2h** was prepared as colorless powders from **5** and 3-trifluoromethylphenylmagnesium bromide in an 80.2% yield. ^{1}H-NMR ($CDCl_3$) δ: 1.05—1.19 (1H, m, 6-tricyclodecane H), 1.39—2.64 (21H, m, tricyclodecane H, 3,7-azabicyclooctane H, three protons of 4,6-azabicyclooctane), 2.87—3.30 (4H, m, three protons of 2,8-azabicyclooctane, one proton of 4,6-azabicyclooctane), 4.02—4.19 (1H, m, 2,8-azabicyclooctane H), 5.56 (1H, br s, OH), 7.28—7.64 (3H, m, aromatic H), 8.35—8.43 (1H, m, aromatic H), 10.8 (1H, br s, N^+H). IR (KBr) cm^{-1}: 3370 (O–H), 2901 (C–H). MS (CI) m/z: 420 $(M+H)^+$.

1-(1-Azabicyclo[3.3.0]octan-5-yl)-1-(2-methylphenyl)-1-(2-tricyclo-[3.3.1.13,7]decyl)methan-1-ol Hydrochloride (**2i**): By a procedure similar to that described for **2a**, compound **2i** was prepared as colorless powders from **5** and 2-methylphenylmagnesium bromide in a 55.1% yield. ^{1}H-NMR ($CDCl_3$) δ: 1.18—3.16 (26H, m, tricyclodecane H, azabicyclooctane H), 2.39 (3H, s, CH_3), 3.74—4.22 (1H, m, 2,8-azabicyclooctane H), 4.51 (1H, br s, OH), 7.08—7.31 (3H, m, aromatic H), 8.09—8.13 (1H, m, aromatic H), 10.3 (N^+H). IR (KBr) cm^{-1}: 3384 (OH), 2903 (C–H). MS (CI) m/z: 366 $(M+H)^+$.

Reference Compounds Triperiden was synthesized at our laboratory by a known procedure,[14] and ribavirin was purchased from Sigma-Aldrich.

Tests for the Anti-influenza Virus Activities Confluent monolayers of MDCK cells in 96-well plates were infected with the influenza virus (A/PR/8 strain) in the presence or absence of the test compounds. After incubation at 37 °C for 2 d, the CPE of the virus-infected culture were microscopically observed. The virus titer, $TCID_{50}$, was determined by microscopic observations of CPE at concentrations of 5 μg and 10 μg/ml of the test compounds. The $\Delta TCID_{50}$ (log_{10}) values were calculated as described in Table 1.

Cytotoxicitity Tests *in Vitro* A confluent monolayer of MDCK cells in a 96-well plate was incubated with the test compounds (ribavirin, **2a**, **2b**, **2f**) at 37 °C for 2 d. After the incubation, the cells were stained with a 0.1% neutral red solution and the dye incorporated into live cells was extracted with a mixture of 0.1 M NaH_2PO_4 and ethanol. The absorbance at 546 nm was determined. The cytotoxicity was calculated from the absorbance and expressed as CC_{50}.

Toxicity Tests *in Vivo* The toxicity tests were performed using two mice per group; male BALB/c mice weighing 30—35 g were used for the test. Triperiden and **2f** suspended in 5% gum arabic saline were injected intraperitoneally into mice at a dosage of 80 mg/kg (0.1 ml/10 g). The behaviors of mice were observed, and finally autopsies were performed.

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