Selective Muscarinic Antagonists. I.[1] Synthesis and Antimuscarinic Properties of 4-Piperidyl Benzhydrylcarbamate Derivatives

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A series of 1-substituted-4-piperidyl benzhydrylcarbamate derivatives were synthesized and evaluated for binding affinity to M_1, M_2 and M_3 receptors, and for antimuscarinic activities. Receptor binding assays indicated that 1-benzyl-4-piperidyl benzhydrylcarbamate derivatives showed higher affinities for M_1 and M_3 receptors, and good selectivities for M_3 over M_2 receptor, than the corresponding ester analog. These results indicate that the urethane bond is a novel linker for muscarinic antagonists, and serves to lock the molecular conformation and allows the hydrophobic portion and cationic site of the molecule to bind to M_1 and M_3 muscarinic receptors. Among the prepared compounds, 1-(4-methylaminobenzyl)-4-piperidyl benzhydrylcarbamate monohydrochloride (18b, YM-58790) exhibited potent inhibitory activity on bladder pressure in reflexly-evoked rhythmic contraction, comparable to oxybutynin and was approximately ten times less inhibitory on oxotremorine-induced salivary secretion than oxybutynin in rats. Further evaluation of antimuscarinic effects on bradycardia and pressor in pithed rats, and on tremor in mice, demonstrated that YM-58790 can be useful for treatment of urinary urge incontinence as a bladder-selective M_3 antagonist with fewer side effects.

Key words YM-58790; 4-piperidyl benzhydrylcarbamate; muscarinic antagonist; urinary urge incontinence; urinary bladder contraction; salivary secretion

Urinary urge incontinence (UUI) is caused by hyperactivity of the detrusor muscle.[2] In man, bladder contraction is mediated mainly through muscarinic receptors, particularly M_3 subtype,[3] and muscarinic receptor antagonists are now widely used for the treatment of UUI, for example oxybutynin (**1**) and propantheline (**2**). However, treatment with these agents is associated with a variety of systemic side effects such as dry mouth, tachycardia and mydriasis.[2] These side effects result from their nonselective antimuscarinic effects. Tachycardia is caused by blockage of muscarinic M_2 receptor in the heart. Dry mouth and mydriasis are related to blockage of M_3 receptors in salivary glands and the pupil, respectively. Among these side effects, dry mouth most frequently limits the use of these agents. For example, the incidence with oxybutynin therapy ranges from 48% to 94%.[4,5] Consequently, muscarinic receptor antagonists with M_3 selectivity and bladder-selectivity would be potentially useful for the treatment of UUI.

Many studies on muscarinic receptor antagonists have revealed that several functional groups are required in a molecule to achieve potent antimuscarinic properties.[6] First, a protonated nitrogen atom near one end of the molecule acts as a cationic site to interact with the anionic site of the muscarinic receptor. Second, a relatively bulky and hydrophobic portion is located at the opposite end of the molecule from the protonated nitrogen atom. Lastly, an ester group is present between the protonated nitrogen atom and hydrophobic portion. Concerning the ester group, several hypotheses have been proposed:[6] for example, it may be required as an anionic site, or it may lock the molecular conformation to allow the cationic site and hydrophobic portion to interact with the muscarinic receptor. Many typical antimuscarinic agents possessing an ester bond have short duration, due partly to their instability toward hydrolysis.[7] If it acts only as a unit to lock the conformation, rather than as an anionic site, conversion into other appropriate linkages stable to hydrolysis should lead to the discovery of novel antagonists. Since the discovery of 1,1-dimethyl-4-(1,1-diphenylacetoxy)piperidinium bromide (4-DAMP, **3**) as a selective M_3 antagonist,[8] many attempts to discover novel antagonists have been made.[3] Moreover, a number of compounds with organ-selectivity between smooth muscle and secretory glands have been reported.[9–12]

In this study, in order to develop M_3 muscarinic antagonists with subtype-selectivity and bladder-selectivity for the treatment of UUI, a series of 1-substituted 4-piperidyl benzhydrylcarbamate derivatives related to 1-benzyl-4-piperidyl diphenylacetate (**4**),[13] a 4-DAMP derivative and putative M_3 selective antagonist, were synthesized. These new compounds were evaluated for their ability to bind to M_1, M_2 and M_3 receptors. Selected compounds with high affinity and selectivity for M_3 receptor were examined for their antimuscarinic activities

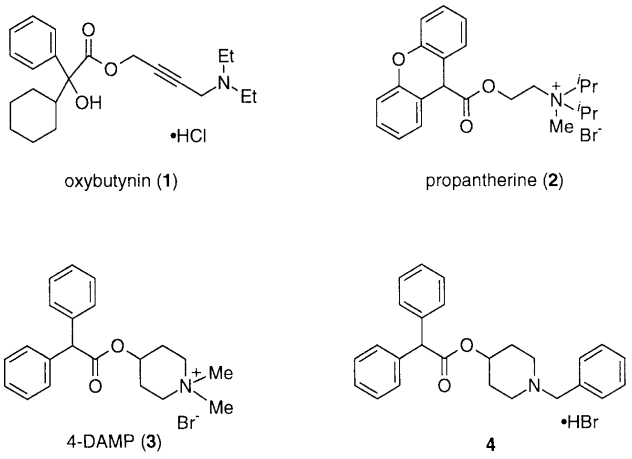

Fig. 1

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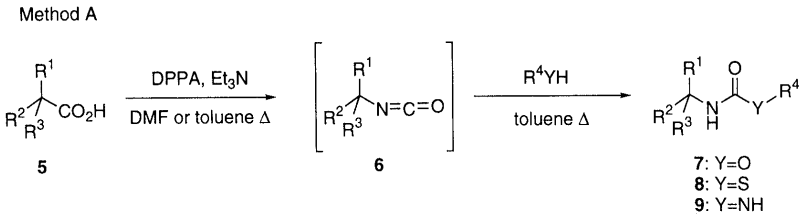


Chart 1

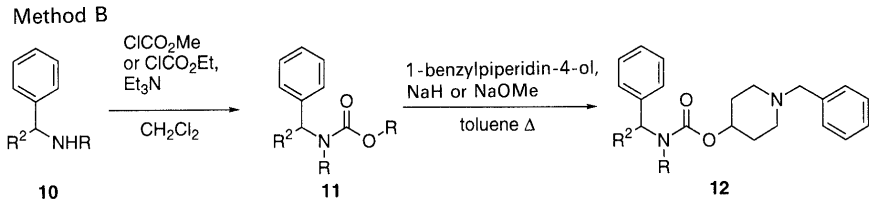


Chart 2

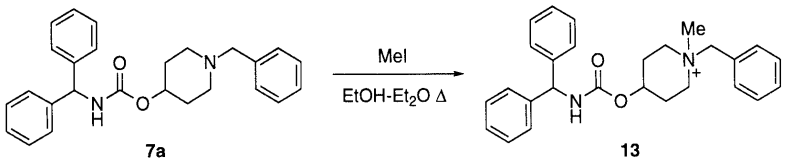


Chart 3

on bladder pressure in reflexly-evoked rhythmic contractions and oxotremorine-induced salivary secretion in rats. In addition, further investigations into their effects on bradycardia in pithed rats, as an indicator of M_2 antagonism, pressor in pithed rats, as a marker for M_1 antagonism, and tremor in mice, as indicative of effects on the central nervous system (CNS), were carried out. We now report the synthesis, structure–activity relationships, and pharmacological evaluation of this novel class of muscarinic antagonists.

Chemistry

Most of the 1-benzyl-4-piperidyl benzhydrylcarbamates and related compounds were prepared by two general methods. As shown in Chart 1 (Method A), the carbamates (**7**), thiocarbamate (**8**) and urea (**9**) were prepared from the corresponding carboxylic acids (**5**). Thus, Curtius rearrangement of **5** with diphenylphosphoryl azide (DPPA)[14] gave the appropriate isocyanates (**6**), which reacted with alcohols,[15,16] thiol and amine to give carbamates (**7**), thiocarbamate (**8**) and urea (**9**), respectively. In the alternative method (Method B), shown in Chart 2, conversion of benzylamine derivatives (**10**) to methyl or ethyl carbamates (**11**), followed by base-catalyzed transesterification in the presence of 1-benzyl-4-piperidinol gave the 1-benzyl-4-piperidyl carbamates (**12**). Quaternary ammonium salt (**13**) was obtained by reaction of 1-benzyl-4-piperidyl benzhydrylcarbamate (**7a**) with iodomethane (Chart 3). Substitution at the 1-position of the piperidine ring was performed as shown in Chart 4. Treatment of compound **7a** with 1-chloroethyl chloroformate[17] followed by methanolysis gave the hydrochloride salt of debenzylated piperidine (**14**). 1-Phenylpiperidine derivative (**15**) was prepared by phenylation of the free base of compound **14** with triphenylbithmuthine in the presence of copper acetate.[18] Alkylation with alkyl halides (Method C), or reductive alkylation with the corresponding aldehydes and sodium triacetoxyborohydride[19] (Method D) of compound **14** gave the 1-alkylpiperidine derivatives (**16a**—**16cc**). Hydrogenation of the nitro groups in **16g** and **16h** with Raney-Ni gave the aminobenzyl derivatives (**17a** and **17b**). The methylaminobenzyl derivatives (**18a** and **18b**) and aminomethylbenzyl derivative (**19**) were obtained by deprotection of the *tert*-butoxycarbonyl groups in **16aa** and **16bb** and trifluoroacetyl groups in **16cc**, respectively.

Results and Discussion

Affinities of the synthesized compounds for muscarinic receptor subtypes were measured based on inhibition of [^{3}H]-pirenzepine binding to rat cortex (M_1), [^{3}H]-quinuclidinyl benzilate (QNB) binding to rat heart (M_2) and [^{3}H]-*N*-methylscopolamine binding to rat salivary glands (M_3).[20] The results are presented in Tables 1—4. Initially, we focussed our efforts on investigating the effect of the urethane bond on affinity and selectivity for M_3 receptors, as shown in Table 1. 1-Benzyl-4-piperidyl *N*-benzhydrylcarbamate (**7a**) showed high affinities for M_1 and M_3 receptors with K_i values of 8.8 and 8.5 nM, respectively, and 21-fold selectivity for M_3 receptor over M_2 receptor, and was much more potent and selective than the diphenylacetate derivative (**4**). On the other hand, thiocarbamate (**8**) and urea (**9**) showed much lower affinities than **7a**. Introducing a methyl group at the nitrogen of the urethane moiety (**12a**) resulted in a remarkable reduction in binding affinities. These results suggest that a monosubstituted carbamate is preferable to bind to M_3 receptor. The urethane bond can thus be considered to be a novel linker in the muscarinic antagonist field to lock the conformation, and allows the hydrophobic portion and cationic site of the molecule to bind to M_1 and M_3 receptors.

Next, we investigated the effect of substituents on the nitrogen atom in the urethane bond of **7a**. Results are

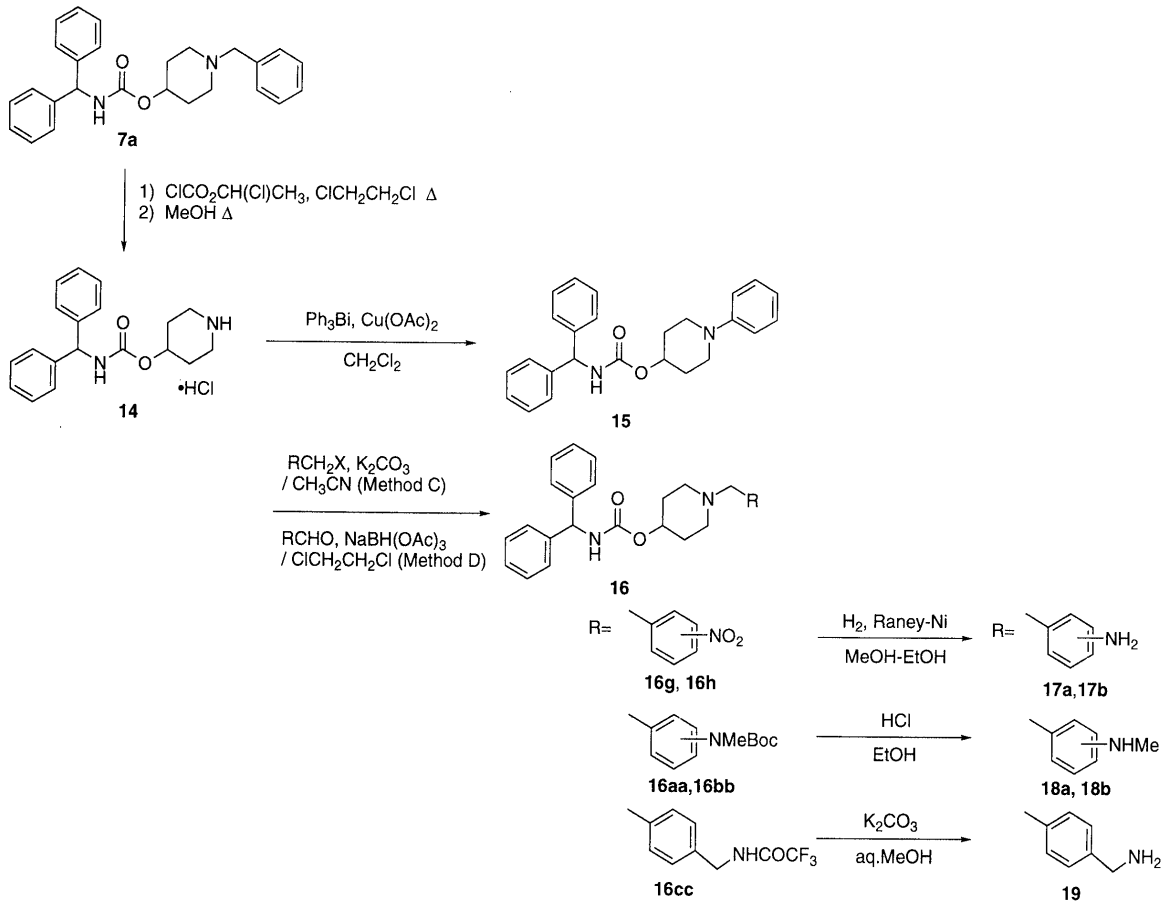
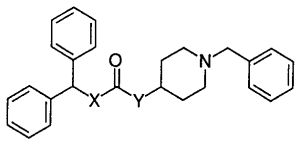


Chart 4

Table 1. Physical Data and Affinities for Muscarinic Receptors of Benzhydrylcarbamate Derivatives (**7a** and **12a**), Benzhydrylthiocarbamate (**8**) and Benzhydrylurea (**9**)



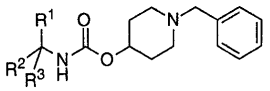
Compound	X	Y	Method[a]	Yield (%)	mp (°C)	Recrystn. solvent	K_i (nM)			Selectivity ratio
							M_1[b]	M_2[b]	M_3[b]	M_2/M_3
7a	NH	O	A	90	157—158	EtOH	8.8	180	8.5	21
8	NH	S	A	61	115—116	EtOH–Et_2O	490	>1000	420	>2.4
9	NH	NH	A	Quant.	186—188	CH_2Cl_2–(iso-Pr)$_2O$	270	11000	120	92
12a	NMe	O	B	84	162—164	MeOH–MeCN	690	5500	270	20
4	—	O	[c]	91	187—189	EtOH–Et_2O	150	400	95	4.2
1							6.6	18	6.5	2.8

a) See experimental section, chemistry. *b*) See experimental section, pharmacology. *c*) See reference 11.

listed in Table 2. Removal of one phenyl ring from the benzhydryl group of **7a**, *i.e.* compound **7b**, resulted in remarkably decreased affinity for all three subtypes. Among the 1-cycloalkyl-1-phenylmethyl derivatives (**12b**, **7d** and **7e**), the cyclobutyl and cyclopentyl derivatives (**12b** and **7d**) showed higher affinities for all subtypes than **7a**, but their selectivities for M_3 over M_2 receptor were much lower than for **7a**. Replacement of both phenyl rings of **7a** with cyclohexyl rings (**7f**) decreased affinities. In addition, introduction of a methyl group to the benzhydryl group (**7g**) led to a 10-fold reduction in affinity for M_3 receptor compared to **7a** due to steric bulkiness. These results suggest that the benzhydryl group is the best substituent for the nitrogen atom of the urethane bond for affinity and to ensure selectivity for M_3 receptor. One phenyl ring may be necessary to bind to the receptors and the other phenyl ring may fix the direction of the phenyl ring for interaction with the receptors.

Furthermore, we carried out modification of the piperidine moiety in **7a**. Results are shown in Table 3. A shift in the position of the urethane junction from the 4- to the 3-position of the piperidine ring (**7h**), and reduction

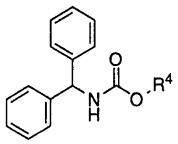
Table 2. Physical Data and Affinities for Muscarinic Receptors of 1-Benzyl-4-piperidyl Carbamate Derivatives (**7a—g** and **12b**)

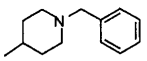
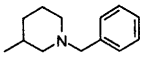
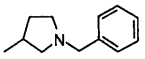
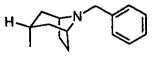
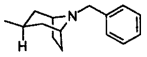
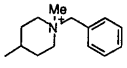


Compound	R^1	R^2	R^3	Method[a]	Yield (%)	mp (°C)	Recrystn. solvent	K_i (nM)			Selectivity ratio
								M_1[b]	M_2[b]	M_3[b]	M_2/M_3
7a	Ph	Ph	H	A	c)	c)	c)	8.8	180	8.5	21
7b	Ph	H	H	A	84	145—146	EtOH–Et_2O	3500	1100	2200	0.5
7c	Ph	Me	H	A	74	157—158	EtOH	160	510	88	6.3
12b	Ph	cyclo-Bu	H	B	10	150—152	MeOH–MeCN	2.7	16	2.7	5.9
7d	Ph	cyclo-Pen	H	A	49	160—162	EtOH–MeCN	4.1	18	4.6	3.9
7e	Ph	cyclo-Hex	H	A	68	161—162	EtOH	26	110	25	4.4
7f	cyclo-Hex	cyclo-Hex	H	A	17	160—161	MeOH–MeCN	420	>1000	250	>4.0
7g	Ph	Ph	Me	A	57	211—213	EtOH	120	1100	99	11

a) See experimental section, chemistry. *b*) See experimental section, pharmacology. *c*) See Table 1.

Table 3. Physical Data and Affinities for Muscarinic Receptors of Benzhydrylcarbamate Derivatives (**7a**, **h—m** and **13**)



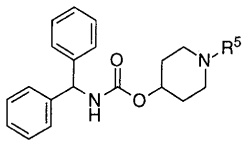
Compoud	R^4	Method[a]	Yield (%)	mp (°C)	Recrystn. solvent	K_i (nM)			Selectivity ratio
						M_1[b]	M_2[b]	M_3[b]	M_2/M_3
7a		A	c)	c)	c)	8.8	180	8.5	21
7h		A	61	153—155	Et_2O–hexane	>1000	>1000	>1000	—
7i		A	93	96—98	Et_2O–hexane	290	3100	240	7.4
7j		A	82	277—279 (dec.)	Aq. EtOH	340	380	420	0.90
7k		A	62	227—228	EtOH	4.4	89	2.8	32
7l		A	62	244—245	EtOH–Et_2O	1.5	4.5	2.0	2.3
7m		A	10	248—251	EtOH–Et_2O	NT[d]	>1000	170	>5.9
13		a)	99	117—127	EtOH–Et_2O	340	2500	250	10

a) See experimental section, chemistry. *b*) See experimental section, pharmacology. *c*) See Table 1. *d*) Not tested.

of the ring size to pyrrolidine (**7i**) remarkably decreased affinities for muscarinic receptors. In the benzylnortropane derivatives, the equatorial isomer (**7k**) was much more potent and selective than the axial one (**7j**), indicating that an equatorial urethane bond would be preferred for connection to the piperidine ring at the 4-position. This result was inconsistent with that of the tropane and pseudotropane esters of benzilic acid.[21] The quaternary salt of **7a** (**13**) showed lower affinity than the parent compound, despite the fact that it has been generally believed to be one of the approaches for increasing affinity for muscarinic receptor.[6] The quinuclidin-3-yl carbamate derivative (**7l**) was more potent than the 1-benzyl-4-piperidyl compound (**7a**), although it showed little selectivity for M_3 over M_2 receptor. On the other hand, the quinuclidin-4-yl derivative (**7m**) was much less potent than **7l**. These results suggest that the distance between the nitrogen atom in the piperidine ring and benzhydryl group, and the direction of the lone pair on the nitrogen atom significantly influence affinity for muscarinic receptors.

Finally, we investigated the effect of the substituent on

Table 4. Physical Data and Affinities for Muscarinic Receptors of 1-Substituted 4-Piperidyl Benzhydrylcarbamate Derivatives (**7a** and **14**—**19**)



Compoud	R^5	Method[a]	Yield (%)	mp (°C)	Recrystn. solvent	K_i (nM)			Selectivity ratio
						M_1[b]	M_2[b]	M_3[b]	M_2/M_3
7a	Bn	A	[c]	[c]	[c]	8.8	180	8.5	21
14	H	[a]	82	132—133	MeCN–Et_2O	250	2800	310	9.0
15	Ph	[a]	58	153	MeCN–Et_2O	>1000	>1000	>1000	—
16a	$(CH_2)_2Ph$	C	74	134	MeCN	>1000	5500	640	8.6
16b	Me	C	60	134—135	MeCN	370	2100	430	4.9
16c	CH_2-cyclo-Hex	C	53	120	MeCN	660	100	270	0.37
16d	CH_2Ph-2-Cl	C	57	118—119	MeCN	200	12000	120	100
16e	CH_2Ph-3-Cl	C	76	209—210	MeCN	63	3700	98	38
16f	CH_2Ph-4-Cl	C	60	139—140	MeCN	510	12000	280	43
16g	CH_2Ph-3-NO_2	C	81	150	MeCN–$(iso\text{-}Pr)_2O$	590	>1000	620	>1.6
16h	CH_2Ph-4-NO_2	C	59	96—98	MeCN	>1000	>1000	>1000	—
16i	CH_2Ph-2-Me	C	61	133—134	MeCN	180	>1000	150	>6.7
16j	CH_2Ph-3-Me	C	34	92—93	AcOEt–hexane	24	490	39	13
16k	CH_2Ph-4-Me	C	54	155—156	MeCN	60	470	29	16
16l	CH_2Ph-4-Et	D	60	116—117	MeCN	>1000	78	230	0.33
16m	CH_2Ph-4-OMe	C	46	145—146	MeCN	120	3400	43	79
16n	CH_2Ph-3-OH	D	68	151—152	EtOH–Et_2O	4.2	74	7.7	9.6
16o	CH_2Ph-4-OH	D	57	156—157	MeOH–MeCN	11	310	8.4	37
17a	CH_2Ph-3-NH_2	[a]	Quant.	215—222	MeCN–Et_2O	4.8	200	6.4	31
17b	CH_2Ph-4-NH_2	[a]	88	179—180	MeCN	9.9	160	7.6	21
18a	CH_2Ph-3-NHMe	[a]	73	139—140	EtOH–Et_2O	NT[d]	830	56	15
18b	CH_2Ph-4-NHMe	[a]	93	231—232 (dec.)	Aq. EtOH	28	260	15	11
16p	CH_2Ph-4-NMe_2	D	24	162—167	EtOH–Et_2O	130	530	28	19
19	CH_2Ph-4-CH_2NH_2	[a]	46	197—199	EtOH–Et_2O	27	44	4.3	10
16q	CH_2-1-naphthyl	C	52	149—150	MeCN	>1000	>1000	>1000	—
16r	CH_2-2-naphthyl	C	89	164—165	MeOH–MeCN	1000	>1000	470	>2.1
16s	CH_2-2-pyridyl	C	60	121—122	MeCN	39	440	21	21
16t	CH_2-3-pyridyl	C	80	140—141	MeCN	290	4900	44	110
16u	CH_2-4-pyridyl	C	75	162—163	MeCN	780	>1000	450	>2.2
16v	CH_2-2-thienyl	D	31	190—191	$CHCl_3$	51	650	20	33
16w	CH_2-3-thienyl	D	85	168—172	MeCN–Et_2O	10	350	6.0	58
16x	CH_2-2-furyl	D	88	195—196	MeCN–Et_2O	47	1000	27	37
16y	CH_2-3-furyl	D	90	185—186	MeOH–MeCN	89	1300	33	35
16z	CH_2-2-(1*H*-pyrrolyl)	D	50	181—182 (dec.)	EtOH	340	>1000	280	>3.5

a) See experimental section, chemistry. *b*) See experimental section, pharmacology. *c*) See Table 1. *d*) Not tested.

the nitrogen atom in the piperidine ring of compound **7a**, considered to be important for subtype-selectivity,[9,10] affinity for M_3 receptor, and selectivity for M_3 over M_2 receptor. Results are presented in Table 4. Shortening and elongating the linker between the nitrogen atom and benzene ring (**15** and **16a**) resulted in decreased affinities for muscarinic receptors. Removal of the benzyl group (**14**) and replacement of the benzyl group with methyl (**16b**) and cyclohexylmethyl groups (**16c**) also lowered the affinities. These results indicate that the benzyl group was crucial for binding to muscarinic receptors. With regard to the substituents on the benzene ring of the benzyl group, chloro (**16d**—**f**) and methyl groups (**16i**—**k**) were investigated. Among them, 3- and 4-methyl derivatives (**16j** and **16k**) were preferable for binding to M_3 receptor. Converting the methyl group (**16k**) to an ethyl group (**16l**) decreased affinities due to steric bulkiness. Among electron-donating groups, hydroxy (**16n** and **16o**) and amino groups (**17a** and **17b**) were good substituents, however, methylamino (**18b**) and dimethylamino (**16p**) had a lower affinity than **17b**. These results indicate that the hydrogen bond-donating property, not the electron-donation capability, of these substituents is most important for interaction with M_3 receptor. Furthermore, insertion of a methylene group between the benzene ring and the amino group of compound **17b** (**19**) led to almost the same result, except for slightly lower affinity for M_1 receptor.

As alternative substituents for the benzyl group, naphthylmethyl derivatives (**16q** and **16r**) and heteroarylmethyl derivatives (**16s**—**z**) were tested. The naphthylmethyl derivatives (**16q** and **16r**) showed much lower affinities for muscarinic receptors than **7a**. Most of the heteroarylmethyl derivatives showed higher selectivity for

M_3 receptor over M_2 receptor than the benzyl derivatives. The 2-pyridylmethyl derivative (**16s**), the most potent among the pyridylmethyl analogs (**16s—u**), was slightly less potent than **7a**. Among five-membered heterocycles, 3-thienylmethyl derivative (**16w**) showed the highest affinity for M_3 receptor, with a K_i value of 6.0 nM, and 60-fold selectivity for M_3 receptor over M_2 receptor. These results indicate that the 3-thienylmethyl group and the benzyl group are isosteric in this series.

Selected compounds with high affinity for M_3 receptor and good selectivity for M_3 receptor over M_2 receptor were examined for their antimuscarinic activities on bladder pressure in reflexly-evoked rhythmic contraction, oxotremorine-induced salivary secretion and oxotremorine-induced bradycardia. These results are listed in Table 5. Compounds **7a**, **16n**, **16o**, **16w**, **17a** and **18b** showed little effect on bradycardia, which is in contrast to oxybutynin. On the other hand, their inhibitory effects on urinary bladder contraction and salivary secretion were more potent than on bradycardia. These results correlated well with the results from *in vitro* binding assays. Amongst these compounds, **7a**, 3-amino derivative (**17a**) and 4-methylamino derivative (**18b**) were as potent as oxybutynin in rhythmic contraction. Surprisingly, the inhibitory effects of **17a** and **18b** on urinary bladder contraction were more potent than those on salivary secretion. Selectivity of activity on bladder pressure relative to that on salivary secretion was also observed in the 3-hydroxybenzyl derivative (**16n**). These results indicate that introduction of hydrogen bond-donating groups onto the benzene ring of the benzyl group may play an important role in differential antagonism between urinary bladder contraction and salivary secretion. Compared to oxybutynin, **18b** showed almost the same activity on bladder pressure and about ten times weaker inhibitory effect on salivary secretion.

Table 5. Effects of Selected Benzhydrylcarbamate Derivatives on Bradycardia, Urinary Bladder Contraction and Salivary Secretion in Rats

Compound	Bradycardia DR_{10} (mg/kg, i.v.)[a]	Rhythmic contraction ED_{30} (mg/kg, i.v.)[a]	Salivary secretion ID_{50} (mg/kg, i.v.)[a]	Selectivity ratio[b]
7a	NE (4.0)[c]	0.20	0.37	1.9
7k	NT[d]	0.41	0.36	0.87
16n	NE (1.4)[c]	0.46	16% (0.5)[e]	—
16o	NE (1.6)[c]	0.84	1.2	1.4
16w	NE (4.9)[c]	0.88	0.55	0.63
17a	NE (4.9)[c]	0.18	0.64	3.6
17b	NE (0.5)[c]	0.67	38% (0.5)[e]	—
18b	NE (6.0)[c]	0.36	2.4	6.7
19	NT[d]	4.4	32% (15.0)[e]	—
1	1.6	0.18	0.17	0.94

a) See experimental section, pharmacology. *b*) Selectivity ratios were calculated by dividing the IC_{50} values for salivary secretion by the ED_{30} values for rhythmic contraction. *c*) No effect at the dose in parentheses. *d*) Not tested. *e*) Inhibition % at the dose in parentheses.

Table 6. M_3 Antagonistic Activities *in Vitro*

Compound	Bladder contraction pA_2	Rb^+ efflux pIC_{50}	Selectivity ratio[a]
18b (YM-58790)	7.8	5.3	10
1	8.1	6.6	1.0

a) Selectivity ratios relative to oxybutynin were calculated from the antilogs of the differences between the pA_2 values for bladder contraction and the pIC_{50} values for Rb^+ efflux.

Further evaluation of **18b** (YM-58790) for selectivity between bladder and glands *in vitro* and effects on M_1 receptor and CNS *in vivo* were also carried out. As shown in Table 6, YM-58790 showed more selective antagonism between urinary bladder contraction and salivary secretion *in vitro* than oxybutynin. The effect of YM-58790 on McN-A343-induced pressor in pithed rats, as an indication of M_1 antagonism *in vivo*, was much less potent than bladder contraction. Furthermore, YM-58790 did not inhibit oxotremorine-induced tremor in mice at a dose of 3 mg/kg i.v., indicating that YM-58790 has low potential for penetration of the blood–brain barrier. These results suggested that YM-58790 could act as a peripherally-active selective M_3 antagonist *in vivo*.

In conclusion, the results of these studies indicate that 1-benzyl-4-piperidyl benzhydrylcarbamate derivatives have high affinities for M_1 and M_3 receptors and selectivities for M_3 over M_2 receptor, and that the urethane bond is a novel linker group in the field of muscarinic antagonists, that serves to lock the conformation and allow the hydrophobic portion and cationic site of the molecule to bind to M_1 and M_3 muscarinic receptors. Among the prepared compounds, 1-(4-methylaminobenzyl)-4-piperidyl benzhydrylcarbamate monohydrochloride (**18b**, YM-58790) exhibited potent inhibitory activity on bladder pressure in reflexly-evoked rhythmic contraction, similar to oxybutynin, and had approximately ten times less inhibitory effect on oxotremorine-induced salivary secretion than oxybutynin in rats. Further evaluation of antimuscarinic activities on bradycardia, pressor and tremor demonstrated that YM-58790 can be useful for treatment of urinary urge incontinence as a bladder-selective M_3 antagonist with fewer side effects.

Table 7. Comparison of Compound **18b** (YM-58790) and **1**

Compound	M_3 antagonism		M_1 antagonism	M_2 antagonism	CNS effect
	Rhythmic contraction ED_{30} (mg/kg, i.v.)	Salivary secretion ID_{50} (mg/kg, i.v.)	Pressor ID_{50} (mg/kg, i.v.)	Bradycardia DR_{10} (mg/kg, i.v.)	Tremor
18b (YM-58790)	0.36	2.4	NE (6.0)[a]	NE (6.0)[a]	0/5[b]
1	0.18	0.17	1.1	1.6	4/5[b]

a) No effect at the dose in parentheses. *b*) Inhibited/total tested at a dose of 3 mg/kg, i.v.

Table 8. Analytical and Spectral Data for Compounds **7a—m**

Compound	Formula	Analysis (%) Calcd (Found) C	H	N	Cl	^{1}H-NMR (DMSO-d_6) δ	FAB-MS m/z (MH^+)
7a	$C_{26}H_{28}N_2O_2$	77.97 (78.02	7.05 7.07	6.99 6.96)		1.50—1.80 (3H, m), 1.80—2.00 (2H, m), 2.21 (2H, t, J=8.8 Hz), 2.60—2.80 (1H, m), 3.48 (2H, s), 4.65—4.75 (1H, m), 5.30 (1H, br s), 5.95 (1H, br s), 7.20—7.35 (15H, m)	401
7b	$C_{20}H_{24}N_2O_2 \cdot HCl$	66.56 (66.51	6.98 6.98	7.76 7.76	9.82 9.87)	1.70—2.25 (4H, m), 2.90—3.20 (2H, m), 3.20—3.40 (2H, m), 4.05—4.35 (4H, m), 4.65—4.85 (1H, m), 7.20—7.40 (5H, m), 7.40—7.50 (3H, m), 7.60—7.85 (3H, m), 11.30 (1H, br s)	325
7c	$C_{21}H_{26}N_2O_2 \cdot C_4H_4O_4$[a] (65.79	66.06	6.65 6.57	6.16 6.17)		1.31 (3H, d, J=6.8 Hz), 1.50—1.65 (2H, m), 1.75—1.90 (2H, m), 2.10—2.30 (2H, m), 2.65—2.80 (2H, m), 3.53 (2H, s), 4.45—4.55 (1H, m), 4.45—4.70 (1H, m), 6.62 (2H, s), 7.20—7.40 (10H, m), 7.67 (1H, d, J=8.3 Hz)	339
7d	$C_{25}H_{32}N_2O_2 \cdot C_4H_4O_4$[a] (68.44	68.48	7.13 7.14	5.51 5.53)		0.95—1.10 (1H, m), 1.10—1.25 (1H, m), 1.25—1.70 (8H, m), 1.70—1.90 (2H, m), 2.05—2.30 (3H, m), 2.65—2.80 (2H, m), 3.54 (2H, s), 4.22 (1H, t, J=9.3 Hz), 4.40—4.60 (1H, m), 6.61 (2H, s), 7.15—7.45 (10H, m), 7.69 (1H, d, J=9.3 Hz)	393
7e	$C_{26}H_{34}N_2O_2$	76.81 (76.57	8.43 8.44	6.89 6.87)		0.75—0.85 (1H, m), 0.90—1.20 (5H, m), 1.40—1.60 (5H, m), 1.65—1.85 (4H, m), 2.00—2.20 (2H, m), 2.60—2.70 (2H, m), 3.43 (2H, s), 4.21 (1H, dd, J=8.8, 9.3 Hz), 4.40—4.50 (1H, m), 7.15—7.35 (10H, m), 7.61 (1H, d, J=9.3 Hz)	407
7f	$C_{26}H_{40}N_2O_4 \cdot C_4H_4O_4$[a] (68.24	68.16	8.39 8.34	5.30 5.19)		0.80—1.25 (10H, m), 1.35—1.45 (2H, m), 1.45—1.75 (12H, m), 1.75—1.90 (2H, m), 2.20—2.30 (2H, m), 2.55—2.80 (2H, m), 3.05—3.15 (1H, m), 3.56 (2H, s), 4.45—4.55 (1H, m), 6.61 (2H, s), 6.64 (1H, d, J=10.4 Hz), 7.25—7.40 (5H, m)	413
7g	$C_{27}H_{30}N_2O_2 \cdot HCl \cdot 0.1H_2O$ (71.44	71.62	6.95 6.98	6.19 6.09	7.83 8.08)	1.50—2.20 (4H, m), 1.95 (3H, s), 2.80—3.50 (4H, m), 4.00—4.40 (2H, m), 4.50—4.80 (1H, m), 7.20—7.60 (13H, m), 7.60—8.00 (3H, m), 11.20—11.50 (1H, m)	415
7h	$C_{26}H_{28}N_2O_2 \cdot C_2H_2O_2$[b] (73.40	73.34	6.59 6.65	6.11 6.08)		1.20—1.40 (1H, m), 1.40—1.55 (1H, m), 1.60—1.80 (1H, m), 1.80—1.90 (1H, m), 2.00—2.15 (2H, m), 2.55—2.65 (1H, m), 2.75—2.90 (1H, m), 3.49 (2H, s), 4.50—4.65 (1H, m), 5.84 (1H, d, J=9.3 Hz), 6.63 (1H, s), 7.15—7.40 (15H, m), 8.27 (1H, d, J=9.3 Hz)	401
7i	$C_{25}H_{26}N_2O_2$	77.69 (77.69	6.78 6.75	7.25 7.18)		1.80—1.95 (1H, m), 2.20—2.30 (1H, m), 2.30—2.45 (1H, m), 2.60—2.90 (3H, m), 3.57 (1H, d, J=12.7 Hz), 3.68 (1H, d, J=12.7 Hz), 5.16 (1H, m), 5.35 (1H, br s), 5.93 (1H, d, J=9.3 Hz), 7.20—7.40 (15H, m)[c]	387
7j	$C_{28}H_{32}N_2O_2 \cdot HCl$	72.63 (72.55	6.75 6.87	6.05 6.05	7.66 7.52)	1.80—2.00 (2H, m), 2.15—2.60 (6H, m), 3.60—3.80 (2H, m), 4.18 (2H, s), 4.75—4.80 (1H, m), 5.86 (1H, d, J=8.8 Hz), 7.20—7.40 (10H, m), 7.40—7.55 (3H, m), 7.60—7.80 (2H, m), 8.30 (1H, d, J=8.8 Hz), 10.31 (1H, br s)	427
7k	$C_{28}H_{32}N_2O_2 \cdot HCl$	72.63 (72.49	6.75 6.82	6.05 6.08	7.66 7.76)	1.90—2.05 (2H, m), 2.05—2.20 (2H, m), 2.20—2.40 (4H, m), 3.78 (2H, m), 4.14 (2H, d, J=7.9 Hz), 4.90—5.00 (1H, m), 5.83 (1H, d, J=9.2 Hz), 7.20—7.35 (10H, m), 7.40—7.50 (3H, m), 7.70—7.80 (2H, m), 8.39 (1H, d, J=9.2 Hz) 11.10 (1H, br s)	427
7l	$C_{21}H_{24}N_2O_2 \cdot HCl$	67.64 (67.59	6.76 6.69	7.51 7.54	9.51 9.54)	1.65—1.95 (3H, m), 1.95—2.15 (1H, m), 2.15—2.25 (1H, m), 2.90—3.30 (5H, m), 3.50—3.70 (1H, m), 4.80—4.90 (1H, m), 7.20—7.40 (10H, m), 8.47 (1H, d, J=8.3 Hz), 10.83 (1H, br s)	337
7m	$C_{21}H_{24}N_2O_2 \cdot HCl \cdot 0.25H_2O$ (66.98	66.83	6.81 6.71	7.42 7.49	9.39 9.43)	2.22 (6H, t, J=7.3 Hz), 3.37 (6H, t, J=7.3 Hz), 5.81 (1H, d, J=9.5 Hz), 7.20—7.35 (10H, m), 8.34 (1H, d, J=9.5 Hz), 10.29 (1H, br s)	337

a) Fumarate. *b*) Hemifumarate. *c*) Measured in $CDCl_3$.

Experimental

Melting points were determined on a Yanaco micro melting apparatus and are uncorrected. Proton magnetic resonance (^{1}H-NMR) spectra were obtained in $CDCl_3$ or dimethylsulfoxide-d_6 (DMSO-d_6) with a JEOL JNM-EX90, JNM-EX400, JNM-GX500 or JNM-A500 spectrometer. Chemical shifts are recorded in parts per million (δ), downfield relative to tetramethylsilane as the internal standard. Mass spectra (MS) were recorded on a JEOL JMS-DX300 or a Hitachi M-80 mass spectrometer. Elemental analyses were carried out on Yanaco MT-3 or MT-5 CHN analyzer and a Yokogawa IC 7000S Ion Chromatoanalyzer. Chromatographic separations were performed using a silica gel column (Wakogel C-200 or Merck Kieselgel 60 (30—400 mesh)). Analytical thin-layer chromatography (TLC) was carried out on precoated glass plates (Merck Kieselgel $60_{F_{254}}$).

Table 9. Analytical and Spectral Data for Compounds **8**, **9** and **12**—**15**

Compound	Formula	Analysis (%) Calcd (Found) C	H	N	Other	^{1}H-NMR (DMSO-d_6) δ	FAB-MS m/z (MH^+)
8	$C_{26}H_{28}N_2OS \cdot C_4H_4O_4$[a]	67.65 (67.70)	6.06 6.03	5.26 5.28	S, 6.02 S, 6.05)	1.50—1.60 (2H, m), 1.85—1.95 (2H, m), 2.10—2.25 (2H, m), 2.65—2.75 (2H, m), 3.25—3.40 (1H, m), 3.50 (2H, s), 6.13 (1H, d, J=8.8 Hz), 6.62 (2H, s), 7.20—7.40 (15H, m), 9.09 (1H, d, J=8.8 Hz)	417
9	$C_{26}H_{29}N_3O \cdot HCl$	71.63 (71.35	6.94 6.94	9.64 9.62	Cl, 8.13 Cl, 7.89)	1.65—1.85 (2H, m), 1.90—2.05 (2H, m), 1.90—3.05 (2H, m), 3.15—3.35 (2H, m), 3.55—3.65 and 3.80—3.85 (total 1H, m), 4.21 and 4.30 (total 2H, d, J=5.4 Hz), 5.80—5.95 (1H, m), 6.33 (1H, d, J=7.3 Hz), 6.98 (1H, d, J=9.2 Hz), 7.15—7.35 (10H, m), 7.40—7.50 (3H, m), 7.55—7.70 (2H, m), 10.61 and 10.77 (total 1H, br s)	400
12a	$C_{27}H_{30}N_2O_4 \cdot C_4H_4O_4$[a]	70.17 (69.93	6.46 6.50	5.28 5.24)		1.50—1.80 (2H, m), 1.70—1.90 (2H, m), 2.20—2.70 (4H, m), 2.65 (3H, s), 3.48 (2H, s), 4.60—4.75 (1H, m), 6.48 (1H, s), 6.61 (2H, s), 7.10—7.20 (4H, m), 7.20—7.45 (11H, m)	415
12b	$C_{24}H_{30}N_2O_4 \cdot C_4H_4O_4$[a]	68.00 (68.06	6.93 6.98	5.66 5.62)		1.45—1.90 (8H, m), 1.90—2.10 (1H, m), 2.10—2.25 (2H, m), 2.40—2.80 (4H, m), 3.49 (2H, s), 4.35—4.60 (2H, m), 6.62 (2H, s), 7.10—7.35 (10H, m), 7.56 (1H, d, J=8.8 Hz)	379
13	$C_{27}H_{31}IN_2O_2 \cdot 0.6H_2O$	58.61 (58.49	5.87 5.85	5.06 5.00	I, 22.94 I, 23.41)	1.70—2.30 (4H, m), 2.94 and 2.97 (3H, s), 3.30—3.60 (4H, m), 4.62 and 4.6 (2H, s), 4.70—4.85 (1H, m), 5.88 (1H, d, J=5.9 Hz), 7.20—7.45 (10H, m), 7.45—7.60 (5H, m), 8.23 and 8.31 (total 1H, d, J=8.8 Hz)	415
14	$C_{19}H_{22}N_2O_2 \cdot HCl \cdot 1.2H_2O$	61.93 (62.01	6.95 6.67	7.60 7.70	Cl, 9.62 Cl, 9.85)	1.75—1.90 (2H, m), 1.95—2.10 (2H, m), 2.95—3.10 (2H, m), 3.10—3.25 (2H, m), 4.75—4.80 (1H, m), 5.86 (1H, d, J=9.3 Hz), 7.20—7.40 (10H, m), 8.37 (1H, d, J=9.3 Hz), 9.14 (1H, br s), 9.34 (1H, br s)	311
15	$C_{25}H_{26}N_2O_4 \cdot C_2H_2O_4$[b]	68.05 (67.94	5.92 5.99	5.88 5.88)		1.50—1.75 (2H, m), 1.85—2.05 (2H, m), 2.97 (2H, t, J=9.8 Hz), 3.40—3.60 (2H, m), 4.65—4.80 (1H, m), 5.88 (1H, d, J=8.8 Hz), 6.76 (1H, t, J=7.3 Hz), 6.85—7.05 (2H, m), 7.15—7.45 (12H, m), 8.27 (1H, d, J=7.3 Hz)	387

a) Fumarate. *b*) Oxalate.

Authentic Materials Compound **4** was prepared as the monohydrogen bromide salt in our laboratory according to the reported method.[13b] Oxybutynin hydrochloride was purchased from Sigma Co.

Chemistry. General Methods Method A: 1-Benzyl-4-piperidyl Benzhydrylcarbamate (**7a**): DPPA (35.8 g, 0.13 mol) in *N*,*N*-dimethylformamide (DMF, 50 ml) was added to a solution of 1,1-diphenylacetic acid (25.0 g, 0.12 mol) and triethylamine (13.3 g, 0.13 mol) in DMF (200 ml) at 0 °C and stirred for 15 min. The solution was warmed to ambient temperature, stirred for 17 h, poured into ice-cold water and extracted with ethyl acetate–toluene (1 : 1). The organic layer was separated, washed with saturated sodium hydrogencarbonate ($NaHCO_3$) solution and dried over $MgSO_4$. The solvent was concentrated to 100 ml, diluted with toluene (500 ml) and concentrated to 200 ml. The resulting acyl azide solution was diluted with toluene (200 ml) and refluxed for 3 h. After cooling to 70 °C, 1-benzylpiperidin-4-ol (25.1 g, 0.13 mol) was added to the solution. The mixture was refluxed for 14 h and concentrated *in vacuo*. The residue was diluted with chloroform (500 ml), washed with water and dried over $MgSO_4$. After solvent was evaporated *in vacuo*, the residue was chromatographed on silica gel with $CHCl_3$–MeOH (97 : 3) as eluent to give **7a** (40.6 g, 86%) as a colorless solid. Recrystallization of **7a** (1.50 g) from ethanol gave 1.27 g of colorless crystals.

Method B: 1-Benzyl-4-piperidyl *N*-Benzhydryl-*N*-methylcarbamate Monofumarate (**12a**): Ethyl chloroformate (1.50 g, 14 mmol) was added dropwise to an ice-cooled solution of *N*-benzhydryl-*N*-methylamine (2.60 g, 13 mmol) and triethylamine (1.47 g, 14 mmol) in dichloromethane (50 ml). The mixture was stirred at room temperature for 4 d, washed with saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed on silica gel with $CHCl_3$–MeOH (50 : 1) as eluent to give ethyl *N*-benzhydryl-*N*-methylcarbamate (**11a**, 2.56 g, 72%) as a yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 1.26 (3H, t, J=7.2 Hz), 2.72 (3H, s), 4.20 (2H, q, J=7.2 Hz), 6.66 (1H, s), 7.10—7.50 (10H, m). FAB-MS m/z: 270 (MH^+). A solution of 1-benzylpiperidin-4-ol (3.98 g, 21 mmol) in methanol (50 ml) was treated with 4.8 N sodium methoxide solution in methanol (2.0 ml) and evaporated to dryness. To the residue, a solution of ethyl *N*-benzhydryl-*N*-methylcarbamate (2.55 g, 9.5 mmol) in toluene (70 ml) was added and the mixture heated under reflux for 1 d. After cooling, the mixture was poured into brine, extracted with ethyl acetate, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed on silica gel with $CHCl_3$–MeOH (50 : 1) as eluent to give 1-benzyl-4-piperidyl *N*-benzhydryl-*N*-methylcarbamate (3.30 g, 84%) as a yellow oil. This compound (1.50 g) was converted into the corresponding fumarate and recrystallized from methanol–acetonitrile to give 0.41 g of **12a** as colorless crystals.

Method C: 1-Phenethyl-4-piperidyl Benzhydrylcarbamate (**16a**): A mixture of **14** (0.80 g, 2.3 mmol), phenethyl bromide (0.33 ml, 2.4 mmol) and potassium carbonate (0.95 g, 6.9 mmol) in acetonitrile (10 ml) was heated at 80 °C overnight. The mixture was poured into saturated $NaHCO_3$ solution and extracted with ethyl acetate. The organic layer was separated, dried over $MgSO_4$ and concentrated *in vacuo*. The resulted crystalline product was recrystallized from acetonitrile to give **16a** (0.70 g, 74%) as colorless crystals.

Method D: 1-(4-Ethylbenzyl)-4-piperidyl Benzhydrylcarbamate Monofumarate (**16l**): A mixture of **14** (0.80 g, 2.3 mmol), 4-ethylbenzaldehyde (0.35 g, 2.3 mmol) and sodium triacetoxyborohydride (1.54 g, 7.3 mmol) in 1,2-dichloroethane (10 ml) was stirred at room temperature overnight. The mixture was poured into brine, alkalized with saturated $NaHCO_3$ solution and extracted with dichloromethane. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The resulting crystalline product was recrystallized from ethyl acetate–hexane to give 1-(4-ethylbenzyl)-4-piperidyl benzhydrylcarbamate (0.60 g, 60%) as colorless crystals. This compound (0.48 g)

Table 10. Analytical and Spectral Data for Compounds **16—19**

Compound	Formula	Analysis (%) Calcd (Found)				^{1}H-NMR (DMSO-d_6) δ	FAB-MS m/z (MH^+)
		C	H	N	Other		
16a	$C_{27}H_{30}N_2O_2$	78.23 (78.34	7.29 7.38	6.76 6.75)		1.50—1.80 (2H, m), 1.70—1.90 (2H, m), 2.25—2.45 (2H, m), 2.65 (3H, s), 3.48 (2H, s), 4.60—4.75 (1H, m), 6.48 (1H, s), 6.61 (2H, s), 7.10—7.20 (4H, m), 7.20—7.45 (11H, m)	415
16b	$C_{20}H_{24}N_2O_2$	74.05 (73.83	7.46 7.44	8.63 8.55)		1.40—1.60 (2H, m), 1.75—1.90 (2H, m), 2.00—2.20 (2H, m), 2.14 (3H, s), 2.50—2.70 (2H, m), 4.45—4.60 (2H, m), 5.86 (1H, d, J=9.5 Hz), 7.15—7.40 (10H, m), 8.24 (1H, d, J=9.5 Hz)	325
16c	$C_{26}H_{34}N_2O_2$	76.81 (76.88	8.43 8.45	6.89 6.85)		0.70—0.85 (2H, m), 1.05—1.25 (3H, m), 1.30—1.90 (8H, m), 1.90—2.15 (4H, m), 2.55—2.75 (2H, m), 3.32 (2H, d, J=9.8 Hz), 4.45—4.60 (1H, m), 5.86 (1H, d, J=9.3 Hz), 7.15—7.35 (10H, m), 8.25 (1H, d, J=9.3 Hz)	407
16d	$C_{26}H_{27}ClN_2O_2$	71.80 (71.70	6.26 6.29	6.44 6.52	Cl, 8.15 Cl, 8.15)	1.45—1.65 (2H, m), 1.75—1.90 (2H, m) 2.15—2.30 (2H, m), 2.60—2.80 (2H, m), 3.55 (2H, s), 4.45—4.65 (1H, m), 5.86 (1H, d, J=9.8 Hz), 7.20—7.50 (14H, m), 8.26 (1H, d, J=9.8 Hz)	435
16e	$C_{26}H_{27}ClN_2O_2 \cdot C_2H_2O_4$[a]	64.06 (63.80	5.57 5.52	5.34 5.34	Cl, 6.75 Cl, 6.86)	1.60—1.80 (2H, m), 1.90—2.05 (2H, m), 2.70—2.90 (2H, m), 2.95—3.10 (2H, m), 4.00 (2H, s), 4.65—4.75 (1H, m), 5.86 (1H, d, J=9.3 Hz), 7.15—7.55 (14H, m), 8.34 (1H, d, J=9.3 Hz)	435
16f	$C_{26}H_{27}ClN_2O_2$	71.80 (71.78	6.26 6.22	6.44 6.48	Cl, 8.15 Cl, 8.28)	1.45—1.60 (2H, m), 1.75—1.90 (2H, m), 2.05—2.25 (2H, m), 2.55—2.75 (2H, m), 3.43 (2H, s), 4.50—4.65 (1H, m), 5.86 (1H, d, J=9.3 Hz), 7.15—7.40 (14H, m), 8.26 (1H, d, J=9.3 Hz)	435
16g	$C_{26}H_{27}N_3O_4 \cdot HCl$	64.79 (64.78	5.86 5.89	8.72 8.75	Cl, 7.36 Cl, 7.25)	1.85—2.25 (4H, m), 3.00—3.20 (2H, m), 3.20—3.45 (2H, m), 4.40—4.55 (2H, m), 4.65—4.95 (1H, m), 5.80—5.95 (1H, m), 7.20—7.45 (11H, m), 7.70—7.85 (1H, m), 8.05—8.20 (1H, m), 8.25—8.45 (1H, m), 8.50—8.65 (1H, m), 11.10—11.50 (1H, m)	446
16h	$C_{26}H_{27}N_3O_4 \cdot C_4H_4O_4$[b] $\cdot 0.5H_2O$	63.15 (63.17	5.65 5.63	7.36 7.64)		1.50—1.65 (2H, m), 1.80—1.95 (2H, m), 2.20—2.30 (2H, m), 2.60—2.80 (2H, m), 3.62 (2H, s), 4.50—4.65 (1H, m), 5.86 (1H, d, J=9.3 Hz), 6.63 (2H, s), 7.20—7.40 (10H, m), 7.59 (2H, d, J=8.3 Hz), 8.19 (2H, d, J=8.3 Hz), 8.26 (1H, d, J=9.3 Hz)	446
16i	$C_{27}H_{30}N_2O_2$	78.23 (78.33	7.29 7.33	6.76 6.74)		1.40—1.60 (2H, m), 1.75—1.90 (2H, m), 2.10—2.25 (2H, m), 2.30 (3H, s), 2.60—2.75 (2H, m), 3.40 (2H, s), 4.50—4.60 (1H, m), 5.86 (1H, d, J=9.3 Hz), 7.10—7.15 (3H, m), 7.15—7.25 (3H, m), 7.25—7.40 (8H, m), 8.25 (1H, d, J=9.3 Hz)	415
16j	$C_{27}H_{30}N_2O_2$	78.23 (78.27	7.29 7.31	6.76 6.75)		1.45—1.60 (2H, m), 1.75—1.90 (2H, m), 2.05—2.20 (2H, m), 2.29 (3H, s), 2.60—2.75 (2H, m), 3.40 (2H, s), 4.50—4.60 (1H, m), 5.86 (1H, d, J=9.3 Hz), 7.10—7.15 (3H, m), 7.15—7.27 (3H, m), 7.27—7.35 (8H, m), 8.25 (1H, d, J=9.3 Hz)	415
16k	$C_{27}H_{30}N_2O_2$	78.23 (78.25	7.29 7.36	6.76 6.78)		1.40—1.60 (2H, m), 1.75—1.90 (2H, m), 2.05—2.15 (2H, m), 2.27 (3H, s), 2.60—2.70 (2H, m), 3.39 (2H, s), 4.50—4.60 (1H, m), 5.85 (1H, d, J=9.4 Hz), 7.10—7.20 (4H, m), 7.20—7.25 (2H, m), 7.25—7.40 (8H, m), 8.25 (1H, d J=9.4 Hz)	415
16l	$C_{28}H_{32}N_2O_2 \cdot C_2H_2O_4$[a] $\cdot 0.25H_2O$	68.88 (68.58	6.65 6.80	5.36 5.64)		1.18 (3H, t, J=7.3 Hz), 2.60—2.90 (2H, m), 1.95—2.10 (2H, m), 2.61 (2H, q, J=7.3 Hz), 2.85—3.00 (2H, m), 3.05—3.20 (2H, m), 4.08 (2H, s), 4.65—4.80 (1H, m), 5.86 (1H, d, J=9.3 Hz), 7.15—7.40 (14H, m), 8.35 (1H, d, J=9.3 Hz)	429
16m	$C_{27}H_{30}N_2O_3$	75.32 (75.30	7.02 7.04	6.51 6.56)		1.40—1.60 (2H, m), 1.75—1.90 (2H, m), 2.10—2.25 (2H, m), 2.60—2.70 (2H, m), 3.37 (2H, s), 3.73 (3H, s), 4.45—4.60 (1H, m), 5.86 (1H, d, J=9.3 Hz), 7.15—7.35 (14H, m), 8.26 (1H, d, J=9.3 Hz)	431
16n	$C_{26}H_{28}N_2O_3 \cdot C_2H_2O_2$[c] $\cdot 0.25H_2O$	70.20 (70.19	6.42 6.28	5.85 5.83)		1.45—1.60 (2H, m), 1.80—1.90 (2H, m), 2.10—2.30 (2H, m), 2.65—2.75 (2H, m), 3.41 (2H, s), 4.50—4.60 (1H, m), 5.86 (1H, d, J=9.3 Hz), 6.61 (1H, s), 6.64 (1H, dd, J=7.8, 1.9 Hz), 6.65—6.75 (2H, m), 7.09 (1H, t, J=7.8 Hz), 7.25—7.40 (10H, m), 8.25 (1H, d, J=9.3 Hz)	417

Table 10. (Continued)

Compound	Formula	Analysis (%) Calcd (Found) C	H	N	Other	^{1}H-NMR (DMSO-d_6) δ	FAB-MS m/z (MH^+)
16o	$C_{26}H_{28}N_2O_3 \cdot C_4H_4O_4$[b]	67.66 (67.38	6.06 6.06	5.26 5.25)		1.50—1.60 (2H, m), 1.80—1.90 (2H, m), 2.20—2.35 (2H, m), 2.80—2.90 (2H, m), 3.47 (2H, s), 4.50—4.60 (1H, m), 5.85 (1H, d, J=9.3 Hz), 6.60 (2H, s), 6.71 (2H, d, J=8.3 Hz), 7.10 (2H, d, J=8.3 Hz), 7.15—7.40 (10H, m), 8.25 (1H, d, J=9.3 Hz)	417
16p	$C_{28}H_{34}N_3O_2 \cdot 2HCl \cdot 0.75H_2O$	63.45 (63.43	6.94 6.82	7.93 7.99	Cl, 13.38 Cl, 13.19)	1.80—2.20 (4H, m), 2.70—3.40 (4H, m), 2.96 (6H, s), 4.05—4.15 (2H, m), 4.60—4.90 (1H, m), 5.85 (1H, d, J=9.4 Hz), 6.80—7.10 (2H, m), 7.20—7.50 (12H, m), 8.38 (1H, d, J=9.4 Hz), 10.60 (1H, br s)	444
16q	$C_{30}H_{30}N_2O_2$	79.97 (79.99	6.71 6.78	6.22 6.21)		1.60—2.00 (4H, m), 2.30 (2H, m), 2.60—2.85 (2H, m), 3.87 (2H, s), 4.70—4.80 (1H, m), 5.29 (1H, br s), 5.95 (1H, br s), 7.20—7.50 (14H, m), 7.70—7.80 (1H, m), 7.84 (1H, d, J=7.3 Hz), 8.28 (1H, d, J=7.3 Hz)	451
16r	$C_{30}H_{30}N_2O_2 \cdot C_4H_4O_4$[b]	72.07 (72.00	6.05 6.03	4.94 4.92)		1.50—1.70 (2H, m), 1.80—1.95 (2H, m), 2.25—2.40 (2H, m), 2.70—2.85 (2H, m), 3.70 (2H, s), 4.50—4.65 (1H, m), 5.86 (1H, d, J=8.3 Hz), 6.62 (2H, s), 7.20—7.40 (10H, m), 7.45—7.60 (3H, m), 7.80 (1H, s), 7.80—7.95 (3H, m), 8.26 (1H, d, J=8.3 Hz)	451
16s	$C_{25}H_{27}N_3O_2$	74.79 (74.97	6.78 6.80	10.47 10.45)		1.50—1.65 (2H, m), 1.80—1.90 (2H, m), 2.15—2.30 (2H, m), 2.60—2.75 (2H, m), 3.58 (2H, s), 4.50—4.60 (1H, m), 5.87 (1H, d, J=9.3 Hz), 7.20—7.35 (11H, m), 7.42 (1H, d, J=7.9 Hz), 7.70—7.80 (1H, m), 8.25 (1H, d, J=9.3 Hz), 8.48 (1H, d, J=4.9 Hz)	402
16t	$C_{25}H_{27}N_3O_2$	74.79 (74.90	6.78 6.82	10.47 10.45)		1.45—1.60 (2H, m), 1.80—1.90 (2H, m), 2.10—2.25 (2H, m), 2.60—2.75 (2H, m), 3.48 (2H, s), 4.50—4.60 (1H, m), 5.86 (1H, d, J=9.3 Hz), 7.20—7.40 (11H, m), 7.69 (1H, d, J=7.8 Hz), 8.27 (1H, d, J=9.3 Hz), 8.45—8.50 (2H, m)	402
16u	$C_{25}H_{27}N_3O_2$	74.79 (74.75	6.78 6.84	10.47 10.34)		1.50—1.65 (2H, m), 1.80—1.90 (2H, m), 2.10—2.25 (2H, m), 2.60—2.75 (2H, m), 3.49 (2H, s), 4.50—4.60 (1H, m), 5.80 (1H, d, J=9.8 Hz), 7.20—7.25 (2H, m), 7.25—7.40 (10H, m), 8.27 (1H, d, J=9.8 Hz), 8.50 (2H, dd, J=4.4, 1.5 Hz)	402
16v	$C_{24}H_{26}N_2O_2S \cdot C_4H_4O_4$[b] $\cdot 0.25H_2O$	63.80 (63.53	5.83 5.65	5.31 5.17	S, 6.08 S, 6.08)	1.50—1.65 (2H, m), 1.80—1.95 (2H, m), 2.20—2.40 (2H, m), 2.70—2.85 (2H, m), 3.74 (2H, s), 4.50—4.65 (1H, m), 5.86 (1H, d, J=9.8 Hz), 6.63 (2H, s), 6.95—7.00 (2H, m), 7.20—7.40 (10H, m), 7.40—7.45 (1H, m), 8.26 (1H, d, J=9.8 Hz)	407
16w	$C_{24}H_{26}N_2O_2S \cdot C_2H_2O_4$[a] $\cdot 0.25H_2O$	62.32 (62.35	5.73 5.62	5.59 5.55	S, 6.40 S, 6.57)	1.60—1.80 (2H, m), 1.95—2.10 (2H, m), 2.70—2.90 (2H, m), 3.00—3.15 (2H, m), 4.04 (2H, s), 4.65—4.75 (1H, m), 5.75—5.90 (1H, m), 7.17 (1H, d, J= 3.7 Hz), 7.20—7.40 (11H, m), 7.60 (1H, s), 8.28 (1H, d, J=9.3 Hz)	407
16x	$C_{24}H_{26}N_2O_3 \cdot C_4H_4O_4$[b]	66.39 (66.24	5.97 6.03	5.53 5.50)		1.45—1.60 (2H, m), 1.80—1.90 (2H, m), 2.15—2.30 (2H, m), 2.65—2.80 (2H, m), 3.52 (2H, s), 4.45—4.60 (1H, m), 5.85 (1H, d, J=9.3 Hz), 6.28 (1H, d, J=2.9 Hz), 6.40 (1H, dd, J=2.9, 2.0 Hz), 6.62 (2H, s), 7.20—7.25 (2H, m), 7.25—7.35 (8H, m), 7.58 (1H, t, J=2.0 Hz), 8.25 (1H, d, J=9.3 Hz)	391
16y	$C_{24}H_{26}N_2O_3 \cdot C_4H_4O_4$[b]	66.39 (66.41	5.97 5.97	5.53 5.63)		1.50—1.65 (2H, m), 1.80—1.90 (2H, m), 2.20—2.40 (2H, m), 2.70—2.85 (2H, m), 3.44 (2H, s), 4.50—4.65 (1H, m), 5.86 (1H, d, J=9.3 Hz), 6.45 (1H, s), 6.62 (2H, s), 7.20—7.35 (10H, m), 7.59 (1H, s), 7.62 (1H, s), 8.26 (1H, d, J=9.3 Hz)	391
16z	$C_{24}H_{27}N_3O_2 \cdot C_2H_2O_4$[a]	65.12 (64.82	6.10 6.00	8.76 8.82)		1.70—1.90 (2H, m), 1.95—2.10 (2H, m), 2.85—3.00 (2H, m), 3.00—3.20 (2H, m), 4.08 (2H, s), 4.65—4.75 (1H, m), 5.80—5.90 (1H, m), 6.05 (1H, s), 6.17 (1H, s), 6.84 (1H, s), 7.20—7.40 (10H, m), 8.33 (1H, d, J=9.3 Hz), 11.21 (1H, br s)	391
17a	$C_{26}H_{29}N_3O_2 \cdot 2HCl \cdot 0.2H_2O$	63.47 (63.35	6.43 6.42	8.54 8.51	Cl, 14.41 Cl, 14.64)	1.85—2.25 (4H, m), 3.00—3.35 (4H, m), 4.25—4.40 (2H, m), 4.65—4.85 (1H, m), 5.86 (1H, d, J=8.8 Hz), 7.20—7.70 (14H, m), 8.35—8.45 (1H, m), 11.30—11.50 (1H, m)	416

Table 10. (Continued)

Compound	Formula	Analysis (%) Calcd (Found) C	H	N	Other	^{1}H-NMR (DMSO-d_6) δ	FAB-MS m/z (MH^+)
17b	$C_{26}H_{29}N_3O_2 \cdot C_4H_4O_4$ [b]	67.78 (67.53	6.26 6.30	7.90 7.87)		1.50—1.70 (2H, m), 1.85—1.95 (2H, m), 2.30—2.50 (2H, m), 2.75—2.90 (2H, m), 3.52 (2H, s), 4.55—4.65 (1H, m), 5.85 (2H, d, J=9.3 Hz), 6.52 (2H, d, J=8.3 Hz), 6.58 (2H, s), 6.97 (2H, d, J=8.3 Hz), 7.20—7.40 (11H, m), 8.26 (1H, d, J=9.3 Hz)	416
18a	$C_{27}H_{31}N_3O_2 \cdot 2HCl \cdot 0.2H_2O$	62.31 (62.07	6.78 6.72	8.07 7.94	Cl, 13.62 Cl, 13.73)	1.85—2.25 (4H, m), 2.81 (3H, s), 2.95—3.20 (2H, m), 3.20—3.40 (2H, m), 4.15—4.35 (2H, m), 4.65—4.85 (1H, m), 5.35 (1H, br s), 5.85 (1H, d, J=8.6 Hz), 7.00—7.60 (14H, m), 8.25—8.45 (1H, m), 11.07 and 11.19 (total 1H, br s)	430
18b	$C_{27}H_{31}N_3O_2 \cdot HCl$	69.59 (69.52	6.92 7.07	9.02 8.97	Cl, 7.61 Cl, 7.79)	1.85—2.20 (4H, m), 2.68 (3H, s), 2.90—3.10 (2H, m), 3.20—3.40 (2H, m), 4.05—4.15 (2H, m), 4.60—4.85 (1H, m), 5.85 (1H, d, J=9.2 Hz), 5.97 (1H, br s), 6.54 (2H, d, J=7.9 Hz), 7.20—7.45 (12H, m), 8.20—8.40 (1H, m), 10.47 and 10.55 (total 1H, br s)	430
19	$C_{27}H_{31}N_3O_2 \cdot 2HCl \cdot 1.5H_2O$	61.25 (61.31	6.85 6.47	7.94 7.89	Cl, 13.39 Cl, 13.33)	1.80—2.25 (4H, m), 2.90—3.40 (4H, m), 4.04 (2H, s), 4.20—4.40 (2H, m), 4.60—4.90 (1H, m), 5.85 (1H, d, J=9.3 Hz), 7.20—7.45 (10H, m), 7.50—7.80 (4H, m), 8.25—8.50 (1H, m), 8.50 (1H, m), 8.52 (2H, br s), 11.20—11.55 (1H, m)	430

a) Oxalate. *b*) Fumarate. *c*) Hemifumarate.

was converted into the corresponding fumarate and recrystallized from methanol–acetonitrile to give **16l** (0.55 g) as colorless crystals.

Methyl Cyclobutylphenylmethylcarbamate (11b) Compound **11b** was prepared in a similar method to compound **11a**, using methyl chloroformate instead of ethyl chloroformate, in 66% yield. ^{1}H-NMR ($CDCl_3$) δ: 1.30—2.30 (6H, m), 2.40—2.90 (1H, m), 3.64 (3H, s), 4.60 (1H, t, J=9 Hz), 4.70—5.10 (1H, m), 7.10—7.50 (5H, m). FAB-MS m/z: 220 (MH^+).

4-Benzhydrylcarbamoyloxy-1-benzyl-1-methylpiperidinium Iodide (13) Iodomethane (3.0 ml, 48 mmol) was added to a solution of **7a** (0.83 g, 21 mmol) in ethanol (10 ml) and diethyl ether (10 ml) and the reaction mixture was stirred under reflux for 10 h. The solution was cooled to room temperature and concentrated *in vacuo*. The residue was crystallized from ethanol and diethyl ether to give **13** (1.11 g, 99%) as yellow crystals.

4-Piperidyl Benzhydrylcarbamate Monohydrochloride (14) 1-Chloroethyl chloroformate (1.00 ml, 9.3 mmol) was added to a solution of **7a** (2.0 g, 5.0 mmol) in 1,2-dichloroethane (20 ml) and the solution was refluxed for 3 h. After cooling to room temperature, the solvent was evaporated *in vacuo*, and the residue dissolved in methanol (20 ml) and refluxed for 4 h. After cooling to room temperature, the solution was treated with 4 N hydrogen chloride in ethyl acetate (3.0 ml) and the solvent was evaporated *in vacuo*. The resulting solid was recrystallized from acetonitrile–diethyl ether to give **14** (1.34 g, 77%) as colorless crystals.

1-Phenyl-4-piperidyl Benzhydrylcarbamate Monooxalate (15) Triphenylbismuthine (1.82 g, 4.1 mmol) and copper(II) acetate (0.31 g, 1.7 mmol) were added to a solution of 4-piperidyl benzhydrylcarbamate (1.07 g, 3.5 mmol) in dichloromethane (10 ml) and the reaction mixture was stirred at room temperature for 18 h. After insoluble material was removed by filtration, the filtrate was concentrated *in vacuo*, and the residue chromatographed on silica gel with hexane–ethyl acetate (3 : 2) as eluent to give 1-phenyl-4-piperidyl benzhydrylcarbamate (0.78 g, 58%) as a colorless solid. This compound was converted into the corresponding oxalate and recrystallized from acetonitrile–diethyl ether to give **15** (0.44 g) as colorless crystals.

1-(3-Aminobenzyl)-4-piperidyl Benzhydrylcarbamate Dihydrochloride (17a) A mixture of 1-(3-nitrobenzyl)-4-piperidyl benzhydrylcarbamate (2.50 g, 5.6 mmol) and Raney-Ni in methanol (100 ml) and ethanol (100 ml) was stirred under a hydrogen atmosphere at room temperature for 3 h. After the catalyst was filtered off, the filtrate was concentrated *in vacuo* to give 1-(3-aminobenzyl)-4-piperidyl benzhydrylcarbamate (2.40 g, quantitative). This compound (0.60 g) was converted into the corresponding hydrochloride and recrystallized from acetonitrile–diethyl ether to give **17a** (0.23 g) as pale yellow crystals.

1-[3-(Methylamino)benzyl]-4-piperidyl Benzhydrylcarbamate Dihydrochloride (18a) Di-*tert*-butyl dicarbonate (9.17 g, 42 mmol) was added to a solution of *N*-methyl-*m*-toluidine (4.65 g, 40 mmol) in dichloromethane (100 ml), stirred at room temperature for 1 d and poured into water. The organic layer was washed with 5% citric acid solution and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The resulting *tert*-butyl methyl-3-tolylcarbamate (9.60 g) was treated with *N*-bromosuccinimide (7.12 g, 40 mmol) and azobisisobutyronitrile (0.66 g, 4 mmol) in carbon tetrachloride (100 ml) for 1 h under reflux. After insoluble material was filtered off, the filtrate was concentrated *in vacuo*, and the residue chromatographed on silica gel with hexane–ethyl acetate (10 : 1) as eluent to give *tert*-butyl *N*-(3-bromomethylphenyl)-*N*-methylcarbamate (3.02 g, 25%) as a yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 1.46 (9H, s), 3.27 (3H, s), 4.47 (2H, s), 7.20—7.35 (4H, m). EI-MS m/z: 301 (M^+), 299 (M^+-2). 1-[3-(*N*-*tert*-Butoxycarbonyl-*N*-methylamino)benzyl]-4-piperidyl benzhydrylcarbamate (**16aa**) was obtained in 80% yield according to Method C from **14** and *tert*-butyl *N*-(3-bromomethylphenyl)-*N*-methylcarbamate. ^{1}H-NMR (DMSO-d_6) δ: 1.37 (9H, s), 1.45—1.60 (2H, m), 1.75—1.90 (2H, m), 2.05—2.25 (2H, m), 2.55—2.75 (2H, m), 3.16 (3H, s), 3.44 (2H, s), 4.45—4.65 (1H, m), 5.86 (1H, d, J=8.8 Hz), 7.05—7.35 (14H, m), 8.24 (1H, d, J=8.8 Hz). FAB-MS m/z: 530 (MH^+). A solution of **16aa** (3.90 g, 7.4 mmol) in ethanol (80 ml) was treated with 8 ml of 4 N hydrogen chloride in 1,4-dioxane and stirred at room temperature for 36 h. After the solution was concentrated *in vacuo*, the resulting residue was alkalized with saturated $NaHCO_3$ solution, extracted with ethyl acetate, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed on silica gel with $CHCl_3$–MeOH (30 : 1) as eluent to give 1-(3-methylaminobenzyl)-4-piperidyl benzhydrylcarbamate (2.32 g, 73%). This compound was converted into the corresponding hydrochloride and recrystallized from ethanol–diethyl ether to give 1.26 g of **18a** as colorless crystals.

1-(4-Aminomethylbenzyl)-4-piperidyl Benzhydrylcarbamate Dihydrochloride (19) Trifluoroacetic anhydride (5.8 ml, 42 mmol) was added to a mixture of 4-aminomethylbenzylalcohol (2.64 g, 19 mmol), pyridine (4.0 ml) and 1,2-dichloroethane (50 ml) with cooling in an ice-water bath. The mixture was stirred at ambient temperature overnight, then poured into water. The organic layer was separated, washed with 0.5 N hydrochloric acid, water and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The resulting residue was dissolved in acetone (100 ml) and treated with phosphate buffer (pH 6.9, 50 ml) at room temperature overnight. The solution was concentrated and extracted with chloroform. The organic layer was washed with water followed by brine, dried over $MgSO_4$ and concentrated *in vacuo* to give *N*-(4-hydroxymethylbenzyl)trifluoroacetamide (2.44 g, 26%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.69 (1H, br s), 4.52 (2H, d, J=5.8 Hz), 4.70 (2H, s), 6.55 (1H, br s), 7.20—7.60 (4H,

m). EI-MS *m/z*: 233 (M^+). *N*-(4-Methanesulfonyloxymethylbenzyl)-trifluoroacetamide, prepared from *N*-(4-hydroxymethylbenzyl)trifluoroacetamide with methanesulfonyl chloride in the presence of triethylamine in dichloromethane, was used in the next step without purification. 1-(4-Trifluoroacetamidomethylbenzyl)-4-piperidyl benzhydrylcarbamate (**16cc**) was quantitatively obtained as a colorless solid according to Method C from **14** and *N*-(4-methanesulfonyloxymethylbenzyl)trifluoroacetamide. ^{1}H-NMR ($CDCl_3$) δ: 1.60—2.00 (2H, m), 2.00—2.40 (2H, m), 2.40—2.80 (4H, m), 3.44 (2H, s), 4.45 (2H, d, J=5.8 Hz), 4.50—4.90 (1H, m), 5.27 (1H, d, J=8.3 Hz), 5.95 (1H, d, J=8.3 Hz), 6.80 (1H, br s), 7.20—7.60 (14H, m). FAB-MS *m/z*: 526 (MH^+). A mixture of **16cc** (1.31 g, 2.5 mmol) and potassium carbonate (0.20 g, 1.4 mmol) in methanol (20 ml) and water (4 ml) was stirred at room temperature for 6 h. After the solution was concentrated, the resulting residue was extracted with chloroform. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was converted into the corresponding hydrochloride and recrystallized from ethanol–diethyl ether to give **19** (0.61 g, 46%) as colorless crystals.

Pharmacology Muscarinic Receptor Binding Assays: Muscarinic receptor binding assays were performed using the reported method[20] with rat cortex, heart, and salivary glands using [^{3}H]-pirenzepine, [^{3}H]-quinuclidinyl benzilate and [^{3}H]-*N*-methylscopolamine as ligands for M_1, M_2 and M_3 receptors, respectively.

Rhythmic Contraction: Female Wistar rats were anesthetized with urethane (1.0 g/kg, s.c.). The bilateral ureters were ligated, then the urinary bladder was catheterized trans-urethrally and filled with saline to evoke reflex rhythmic contractions. After recording the peak intravesical pressure, compounds were cumulatively administered *via* the femoral vein. A pressure drop was measured in the period 5—10 min after each administration. A dose–response curve was obtained in each rat and the dose required to reduce the peak intravesical pressure by 30% (ED_{30}) was determined.

Salivary Secretion: Male Wistar rats were anesthetized with urethane (1.2 g/kg, i.p.). Compounds were intravenously administered 15 min prior to injection of oxotremorine (0.8 μmol/kg, i.v.). Saliva was collected by absorbent paper for 5 min after the injection of oxotremorine.

Pressor: The effect on pressor response caused by McN-A343 was determined in pithed rats.[20] Compounds were intravenously administered 15 min before the injection of McN-A343 (3 μmol/kg, i.v.).

Bradycardia: Bradycardia was evoked in pithed rats by intravenous injection of oxotremorine.[20] Compounds were administered 15 min prior to the challenge of oxotremorine. A dose shifting the dose–response curve of oxotremorine to the right by 10-fold (DR_{10}) was calculated.

Tremor: Test compounds were intravenously administered to male ICR mice 5 min prior to injection of oxotremorine (1 mg/kg, s.c.). Tremor was observed in the period 5—10 min after the injection of oxotremorine.

Rat Urinary Bladder Contraction: An excised rat bladder was suspended in an organ bath containing gassed Kreb's–Henseleit buffer at 37 °C and the isometric tension was measured. After construction of two dose–response curves to cumulatively added carbachol, compounds were added to the bath, and a dose–response curve to carbachol was established again.

Rb^+ Efflux from Rat Salivary Glands: The effect on Rb^+ efflux, a reflection of water outflow, from rat salivary glands was determined according to the reported method[22] with minor modifications. Chopped submandibular glands were loaded with ^{86}RbCl (100 mCi) in 5 ml of Kreb's–Henseleit buffer for 40 min at 37 °C. The glands were then placed in a flow cell perfused with the buffer solution (2 ml/min). After perfusion for 3 min, the perfusate was replaced by a buffer solution containing compounds and 10 μM of carbachol. The perfusate was collected and its radioactivity determined.

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