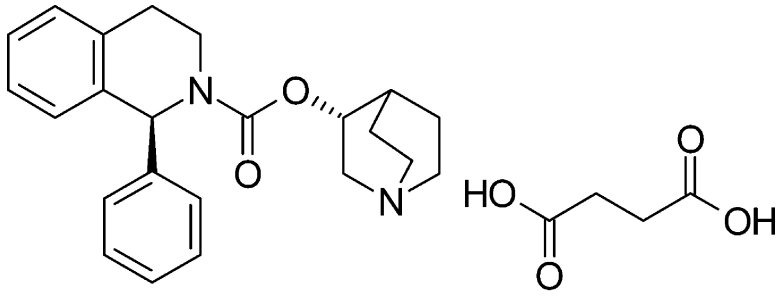
Journal of Medicinal Chemistry

Article

Synthesis and Antimuscarinic Properties of Quinuclidin-3-yl 1,2,3,4-Tetrahydroisoquinoline-2-carboxylate Derivatives as Novel Muscarinic Receptor Antagonists

Ryo Naito, Yasuhiro Yonetoku, Yoshinori Okamoto, Akira Toyoshima, Ken Ikeda, and Makoto Takeuchi

J. Med. Chem., **2005**, 48 (21), 6597-6606• DOI: 10.1021/jm050099q • Publication Date (Web): 28 September 2005



solifenacin succinate

More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 1 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

Journal of Medicinal Chemistry is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Synthesis and Antimuscarinic Properties of Quinuclidin-3-yl 1,2,3,4-Tetrahydroisoquinoline-2-carboxylate Derivatives as Novel Muscarinic Receptor Antagonists[1]

Ryo Naito,* Yasuhiro Yonetoku, Yoshinori Okamoto, Akira Toyoshima,† Ken Ikeda, and Makoto Takeuchi

Drug Discovery Research, Astellas Pharma Inc., 21 Miyukigaoka, Tsukuba, Ibaraki 305-8585, Japan

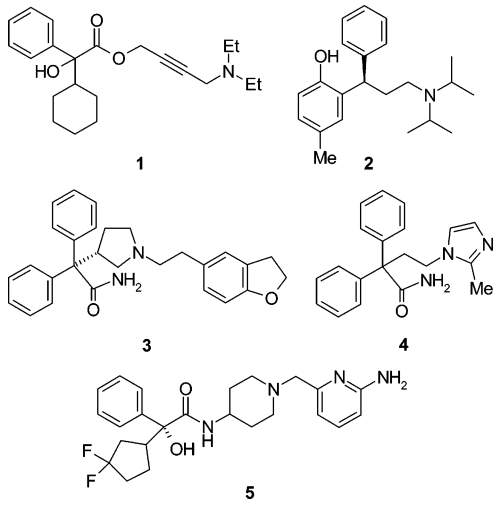
Received February 2, 2005

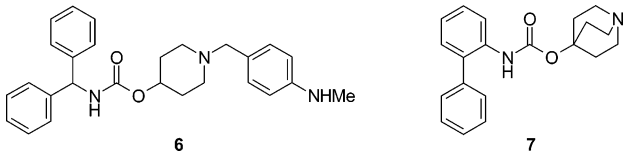
In the course of continuing efforts to develop potent and bladder-selective muscarinic M_3 receptor antagonists, quinuclidin-3-yl 1-aryl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate derivatives and related compounds were designed as conformationally restricted analogues of quinuclidin-3-yl benzhydrylcarbamate (**8**). Binding assays with rat muscarinic receptor subtypes revealed that the quinuclidin-3-yl 1-aryl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate derivatives showed high affinities for the M_3 receptor, and selectivity for the M_3 receptor over the M_2 receptor. Of these derivatives, (+)-(1*S*,3'*R*)-quinuclidin-3'-yl 1-phenyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate monohydrochloride (**9b**) exhibited almost the same inhibitory activity against bladder contraction to that of oxybutynin (**1**), and more than 10-fold selectivity for bladder contraction versus salivary secretion, demonstrating that **9b** may be useful for the treatment of symptoms associated with overactive bladder without having side effects such as dry mouth.

Introduction

Muscarinic receptor antagonists including oxybutynin (**1**)[2] are mainly used in the treatment of urinary frequency, urinary incontinence, or urgency associated with overactive bladder (OAB). However, treatment with muscarinic antagonists is well-known to be associated with a variety of systemic side effects, such as dry mouth, constipation, mydriasis, and tachycardia,[3] resulting from their nonselective antimuscarinic effects. Tachycardia is caused by blockage of muscarinic M_2 receptors in the heart, and dry mouth, constipation, and mydriasis occur due to the blockage of M_3 receptors in the salivary glands, the colon and the pupil, respectively. Among these side effects, dry mouth most frequently limits the use of these agents. Consequently, muscarinic receptor antagonists with subtype selectivity for the M_3 receptor over the M_2 receptor and bladder selectivity would be useful for treatment of OAB. Hence, many studies aimed at discovery of subtype-selective or tissue-selective muscarinic receptor antagonists have been reported, including those on tolterodine (**2**),[4] darifenacin (**3**),[5] KRP-197 (**4**),[6] and **5**.[7]

In two previous reports, we have described two series of carbamate derivatives, benzhydrylcarbamates[8] and biphenyl-2-ylcarbamates,[9] as novel bladder selective muscarinic M_3 receptor antagonists. Among these molecules, YM-58790 (**6**) and YM-46303 (**7**) showed good selectivity for bladder contraction versus salivary secretion in rats, in comparison with oxybutynin (**1**). Compounds **6** and **7** have common structural features: a hydrophobic region including two benzene rings, a basic nitrogen-containing ring, and a carbamate junction. The distances between the benzene rings and the nitrogen atom in the basic ring in compounds **6** and **7** were estimated to be in the range of 6−8 Å from X-ray crystallographic and modeling studies, similar to the distances reported for atropine and other muscarinic antagonists.[10−12] Our previous SAR studies suggested that introduction of the carbamate group at the junction resulted in creation of novel and selective M_3 receptor antagonists, and that both the hydrophobic region and the basic ring influence selectivity for the M_3 receptor. In contrast to **6**, which has high affinity and selectivity for the M_3 receptor, quinuclidin-3-yl benzhydrylcarbam-





* To whom correspondence should be addressed. Phone: +81-29-863-6730. Fax: +81-29-852-2971. E-mail: ryo.naito@jp.astellas.com.
† Present address: Development Division, Astellas Pharma Inc., 3-17-1 Hasune, Itabashi, Tokyo 174-8612, Japan.

10.1021/jm050099q CCC: $30.25
Published on Web 09/28/2005

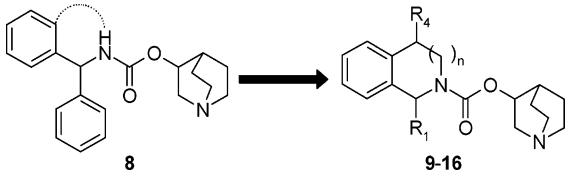
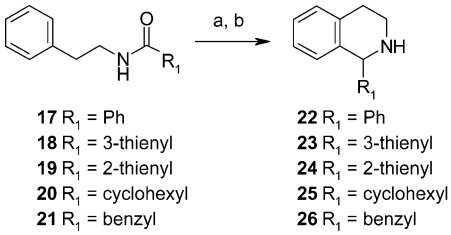


Figure 1. Design of quinuclidin-3-yl 1,2,3,4-tetrahydroisoquinoline-2-carboxylate derivatives (**9**−**16**).

Scheme 1[a]



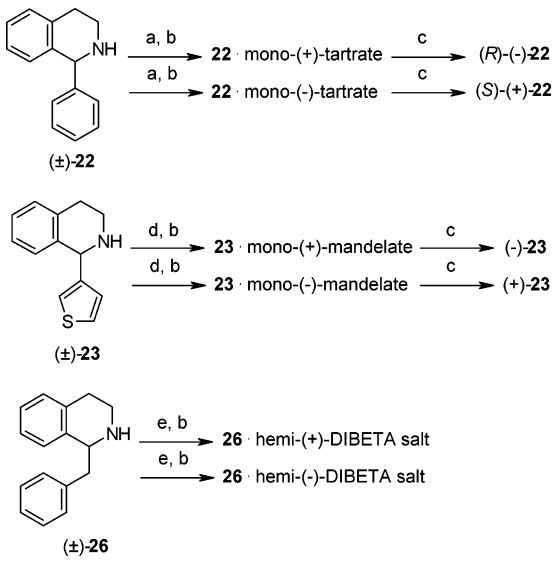
[a] Reagents and conditions: (a) $POCl_3$, P_2O_5, xylene, reflux; (b) $NaBH_4$, EtOH, rt.

ate (**8**) showed poor selectivity among the muscarinic receptor subtypes.[8] On the other hand, quinuclidin-3-yl and -4-yl 2-biphenylylcarbamate derivatives, including **7**, showed high affinities and selectivities for the M_3 receptor,[9] suggesting that proper arrangement of the two aromatic rings in the hydrophobic part of the molecule can improve subtype selectivity. We therefore hypothesized that restricting the conformation of the benzhydrylcarbamate moiety in **8** could lead to an increase in selectivity for the M_3 receptor over the M_2 receptor. Hence, in the course of continuing research to develop potent and more bladder-selective muscarinic M_3 receptor antagonists, quinuclidin-3-yl 1-aryl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate derivatives and related compounds were designed based on this hypothesis. These compounds were synthesized and evaluated for their affinities toward rat muscarinic receptors, and the effects of the stereochemistry of the substituent at the 1-position of the tetrahydroisoquinoline ring on affinity and subtype selectivity were investigated. We were also particularly interested in the influence of this modification on the selectivity for bladder contraction versus salivary secretion. Herein, we report the synthesis, structure−activity relationships, and pharmacological evaluation of this series of muscarinic M_3 receptor antagonists.

Chemistry

The intermediates, 1-substituted 1,2,3,4-tetrahydroisoquinolines (**22**−**26**), were synthesized using a Bischler−Nepieralski isoquinoline synthesis from the corresponding *N*-(2-phenylethyl)carboxamides (**17**−**21**), as shown in Scheme 1.[13] Optical resolution of 1-phenyl-1,2,3,4-tetrahydroisoquinoline (**22**) was carried out according to the reported method,[14] and **23** and **26** were resolved by using mandelic acid and dibenzoyltartaric acid (DIBETA), respectively (Scheme 2). From the report of Ludwig et al.[15] and our X-ray crystallographic analysis of the hydrochloride salt of (+)-**22** using Bijvoet's anomalous dispersion method,[16] the absolute configuration of (+)-**22** is *S*, although it had previously been reported that the configuration of (−)-**22** is *S*.[17,18] The syntheses of other intermediates, 1-phenylisoindoline (**27**),[19] 4-phenyl-1,2,3,4-tetrahydroisoquinoline (**28**),[13]

Scheme 2[a]



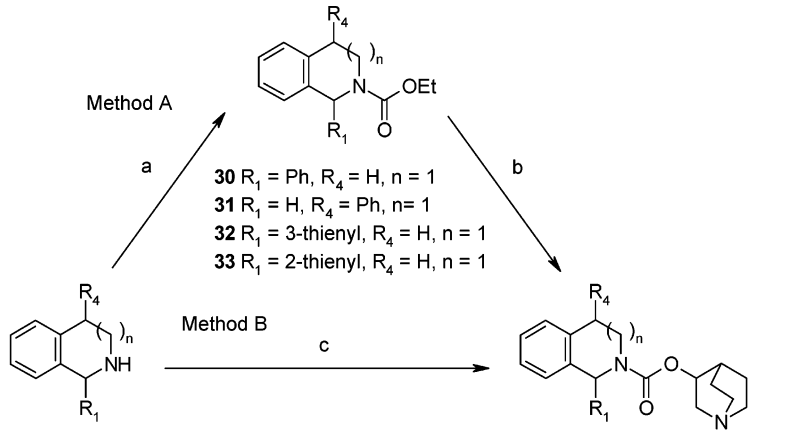
[a] Reagents: (a) (+)- or (−)-tartaric acid; (b) recrystallization; (c) aq NaOH; (d) (+)- or (−)-mandelic acid; (e) (+)- or (−)-DIBETA.

and 4-hydroxy-1-phenyl-1,2,3,4-tetrahydroisoquinolines (*cis*-**29** and *trans*-**29**),[20] were carried out according to the reported methods.

The (*R*)- and (*S*)-quinuclidin-3-yl carboxylate derivatives (**9**−**16**) were prepared from the 1,2,3,4-tetrahydroisoquinolines (**22**−**26**, **28**, and **29**) and isoindoline (**27**) via ethyl carboxylate derivatives (Method A) or directly (Method B), as shown in Scheme 3. The 1,2,3,4-tetrahydroisoquinolines [**22**, (+)-**23**, **24** and **28**] were treated with ethyl chloroformate in the presence of potassium carbonate in dichloromethane. The resulting ethyl 1,2,3,4-tetrahydroisoquinoline-2-carboxylates (**30**−**33**) were reacted with (*R*)-quinuclidin-3-ol [(*R*)-**34**][21] in the presence of sodium hydride in toluene, with continuous removal of the ethanol formed, to give (3*R*)-quinuclidin-3-yl carboxylates (**9**, **9a**, **9b**, **11**, **12b**, and **13**) (Method A). Using (*S*)-quinuclidin-3-ol [(*S*)-**34**] instead of (*R*)-**34**, (3*S*)-quinuclidin-3-yl ester derivatives (**9c** and **9d**) was also prepared. As an alternative method, (*R*)-quinuclidin-3-yl carboxylates (**10**, **12a**, **14**−**16**) were prepared from 1,2,3,4-tetrahydroisoquinolines [(−)-**23**, **25**, **26**, and **29**] and isoindoline (**27**) with (*R*)-quinuclidin-3-yl chloroformate monohydrochloride (**35**)[22] in pyridine (Method B). Some of the diastereomeric (3*R*)-quinuclidin-3-yl 1,2,3,4-tetrahydroisoquinoline-2-carboxylate derivatives (**13**, **14**, and **16**) were separated using preparative HPLC to give the desired single diastereomers.

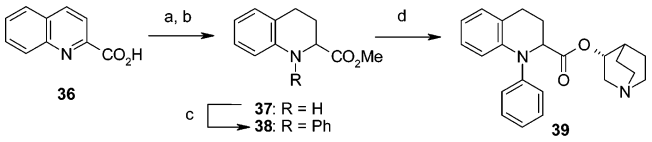
The quinoline-2-carboxylate derivative (**39**) was prepared as shown in Scheme 4. Hydrogenation of quinaldic acid (**36**) in the presence of Raney Ni followed by esterification gave methyl 1,2,3,4-tetrahydroquinoline-2-carboxylate (**37**). Phenylation at the 1-position of **37** was carried out using triphenylbismuthine and copper(II) acetate.[23] The resulting methyl 1-phenyl-1,2,3,4-tetrahydroquinoline-2-carboxylate (**38**) was converted to the corresponding quinuclidin-3-yl ester (**39**) according to Method A. The absolute configurations of **9b**, **12a**, and **16d** were determined by X-ray crystallography using Bijvoet's method. The configuration of **16c** was also determined relative to the known absolute configuration of (*R*)-quinuclidin-3-ol.

Scheme 3[a]



[a] Reagents and conditions: (a) $ClCO_2Et$, K_2CO_3, CH_2Cl_2, rt; (b) (*R*)- or (*S*)-quinuclidin-3-ol (**34**), NaH, toluene, reflux; (c) (*R*)-quinuclidin-3-yl chloroformate hydrochloride (**35**), pyridine, <−20 °C−rt.

Scheme 4[a]



[a] Reagents and conditions: (a) 1 atm of H_2, Raney Ni, 1 M aq NaOH, rt; (b) MeOH, $SOCl_2$, rt; (c) Ph_3Bi, $Cu(OAc)_2$, $ClCH_2CH_2Cl$, 80 °C; (d) (*R*)-**34**, NaH, toluene, reflux.

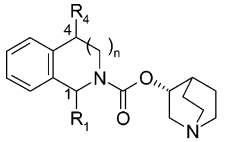
Results and Discussion

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 binding to rat heart (M_2), and [^{3}H]-*N*-methylscopolamine binding to rat salivary glands (M_3).[24] These results are presented in Tables 1 and 2. Initially, we focused our efforts on investigating the conversion of the benzhydryl moiety in **8** to other ring systems, including 1,2,3,4-tetrahydroisoquinoline (Table 1). Quinuclidin-3-yl 1-phenyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (**9**), a mixture of the diastereomers **9a** and **9b**, showed high affinities for M_1 and M_3 receptors, and also showed a higher M_3 selectivity over the M_2 receptor, compared with **8**. On the other hand, 1-phenylisoindoline-2-carboxylate (**10**) and 1-phenyl-1,2,3,4-tetrahydroquinoline-2-carboxylate (**39**) showed poor affinities for the M_3 receptor, compared to **9**, although **10** exhibited high selectivity for the M_3 receptor over the M_2 receptor. The shift of the phenyl ring from the 1- to the 4-position of the tetrahydroisoquinoline ring (**11**) resulted in loss of affinity for the M_3 receptor. These results indicate that the 1-phenyl-1,2,3,4-tetrahydroisoquinoline ring is appropriate for obtaining high affinity and selectivity for M_3 receptors, and **9a** was therefore selected as a lead compound.

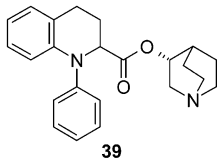
With respect to the 1-aryl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate derivatives (**9a**−**9d**, **12a**−**16d**), the effects of substituents at the 1- and 4-position of the tetrahydroisoquinoline ring and the influence of their stereochemistry on affinity and selectivity for the M_3 receptor were investigated. The results are shown in Table 2. Four diastereomers of quinuclidin-3-yl 1-phenyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (**9a**−**d**) were initially prepared and evaluated. The (3*R*)-quinuclidin-3-yl isomers (**9a** and **9b**) showed much higher affinity for the M_3 receptor than the 3*S* isomers (**9c** and **9d**). Of the two 3*R* isomers (**9a** and **9b**), the (1*R*)-1-phenyl-1,2,3,4-tetrahydroisoquinoline derivative (**9a**) showed over 10-fold higher affinity for the M_3 receptor than the 1*S* isomer (**9b**), although their selectivity ratios for the M_3 receptor over the M_2 receptor were almost the same. Both compounds **9a** and **9b** showed almost as high affinities for the M_1 receptor as for the M_3 receptor. These results indicate that modification of the benzhydryl moiety in **8** to form a 1-phenyl-1,2,3,4-tetrahydroisoquinoline ring can lead to improvement of selectivity for M_1 and M_3 receptors over the M_2 receptor by decreasing affinity for the M_2 receptor. The stereochemistry at both the 3-position of the quinuclidine ring and the 1-position of the tetrahydroisoquinoline ring are of importance in obtaining high affinity for the M_3 receptor.

Next, the effect of substituents at the 1-position of the tetrahydroisoquinoline ring on affinity and selectivity for the M_3 receptor was investigated. The 3- and 2-thienyl derivatives (**12** and **13**) showed similar affinities and selectivities for the M_3 receptor, compared to **9a** and **9b**. Among the 3-thienyl derivatives, **12a** showed higher affinity for the M_3 receptor and almost the same selectivity ratio between the M_2 and M_3 receptors, in comparison with **12b**, indicating that the relationship between stereochemistry at the 1-position of the 3-thienyl derivatives (**12a** and **12b**) and affinity for the M_3 receptor is similar to that for phenyl derivatives (**9a** and **9b**). All of the thienyl derivatives showed slightly

Table 1. Affinities of (*R*)-Quinuclidin-3-yl Carboxylate Derivatives (**9**−**11** and **39**) for Muscarinic Receptors



9-11

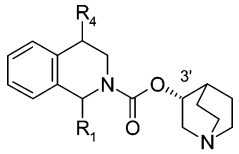


39

				K_i (nM)[a]			
compd	R_1	R_4	*n*	M_1	M_2	M_3	selectivity: M_2/M_3
9[b]	Ph	H	1	1.4 (0.94−2.6)	28 (23−35)	5.4 (4.7−6.3)	5.2
10[c]	Ph	H	0	8.4 (7.7−9.0)	440 (160−1300)	28 (26−30)	16
11[c]	H	Ph	1	52 (41−64)	>1000	>1000	—
39[c]				9.4 (8.7−10)	140 (99−190)	26 (24−27)	5.4
8				1.5 (1.4−1.5)	6.8 (6.3−7.4)	2.0 (1.7−2.3)	3.4
1				5.9 (5.6−6.1)	14 (12−16)	5.3 (5.2−5.4)	2.6

[a] Values were estimated from 8 to 12 data points and the numbers in parentheses are 95% confidence limits. [b] A mixture of the diastereomers **9a** and **9b**. [c] Compounds are mixtures of stereoisomers at the 1-position (**10**), the 4-position (**11**) and the 2-position (**39**).

Table 2. Affinities of Quinuclidin-3-yl 1-Substituted 1,2,3,4-Tetrahydroisoquinoline-2-carboxylate Derivatives (**9a**−**d** and **12a**−**16d**) for Muscarinic Receptors



9a-9d, 12a-16d

				K_i (nM)[a]			
compd	R_1	R_4	config	M_1	M_2	M_3	selectivity: M_2/M_3
9a	Ph	H	1*R*,3′*R*	0.32 (0.27−0.36)	8.7 (7.6−9.8)	0.82 (0.77−0.87)	11
9b	Ph	H	1*S*,3′*R*	10 (6.0−18)	120 (100−130)	10 (9.1−11)	12
9c	Ph	H	1*R*,3′*S*	440 (400−480)	1600 (1400−1900)	490 (430−540)	3.3
9d	Ph	H	1*S*,3′*S*	230 (160−350)	3500 (2900−4100)	1300 (1100−1600)	2.7
12a	3-thienyl	H	1*S*,3′*R*	0.95 (0.70−1.3)	15 (13−17)	3.5 (3.3−3.7)	4.3
12b	3-thienyl	H	1*R*,3′*R*	8.3 (5.7−12)	110 (93−130)	21 (20−23)	5.2
13a[b]	2-thienyl	H	3′*R*[c]	1.8 (1.3−2.7)	13 (12−15)	3.6 (2.3−5.5)	3.6
13b[b]	2-thienyl	H	3′*R*[c]	2.4 (0.51−12)	93 (82−110)	18 (17−19)	5.2
14a[b]	cHex	H	3′*R*[c]	6.6 (5.4−8.1)	22 (18−27)	6.7 (6.1−7.3)	3.3
14b[b]	cHex	H	3′*R*[c]	12 (5.8−24)	39 (32−48)	63 (55−72)	0.6
15a[d]	benzyl	H	3′*R*[c]	3.9 (1.3−12)	76 (58−100)	25 (22−28)	3.0
15b[d]	benzyl	H	3′*R*[c]	15 (8.4−27)	>1000	160 (89−280)	>6.3
16a[b,e]	Ph	OH	3′*R*[c]	36 (27−45)	1800 (1600−2100)	440 (370−510)	4.1
16b[b,e]	Ph	OH	3′*R*[c]	3.1 (2.4−3.8)	480 (350−600)	21 (18−24)	23
16c[b,f]	Ph	OH	1*R*,4*R*,3′*R*	11 (6.5−16)	1700 (1400−2100)	150 (140−160)	11
16d[b,f]	Ph	OH	1*S*,4*S*,3′*R*	41 (17−65)	850 (690−1000)	35 (30−41)	24

[a] Values were estimated from 8 to 12 data points and the numbers in parentheses are 95% confidence limits. [b] Separated by preparative HPLC (diastereomers eluted earlier: **13a**, **14a**, **16a** and **16c**, and later: **13b**, **14b**, **16b** and **16d**). [c] The configurations at 1- and 4-position were not determined. [d] Compounds **15a** and **15b** were prepared from the **26**·hemi-(+)-DIBETA salt and **26**·hemi-(−)-DIBETA salt, respectively. [e] Prepared from *cis*-1-phenyl-1,2,3,4-tetrahydroisoquinolin-4-ol (*cis*-**29**). [f] Prepared from *trans*-1-phenyl-1,2,3,4-tetrahydroisoquinolin-4-ol (*trans*-**29**).

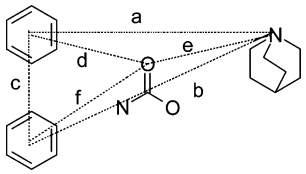
higher affinities for the M_1 receptor than those for the M_3 receptor. On the other hand, the low affinity and selectivity for the M_3 receptor of the 1-cyclohexyl derivatives (**14a** and **14b**) revealed that an aromatic substituent at the 1-position of the tetrahydroisoquinoline ring is preferable. Moreover, the benzyl derivatives (**15a** and **15b**) showed lower affinities for the M_3 receptor than **9a** and **9b**, since the benzene ring of the benzyl group is located too far from the basic nitrogen atom and can rotate more freely than the benzene rings of **9a** and **9b**. Furthermore, **14b**, **15a**, and **15b** showed higher affinities for the M_1 receptor than for the M_3 receptor, suggesting differences of the environment around the 1-position of the 1,2,3,4-tetrahydroisoquinoline ring between the M_1 and M_3 receptor. These results indicate that benzene and thiophene rings adjacent to the 1-position of the 1,2,3,4-tetrahydroisoquinoline ring adopt a conformation that is most appropriate for high affinity and selectivity for the M_3 receptor.

Last, a series of 4-hydroxyisoquinoline derivatives (**16a**−**d**) were evaluated. Although **16b** and **16d** showed moderate affinities for the M_3 receptor, all 4-hydroxyisoquinoline derivatives had decreased affinities for the M_3 receptor, compared to **9a** and **9b**, indicating that hydrophilic or hydrogen bond-donating character at the 4-position of the tetrahydroisoquinoline ring is unfavorable.

To understand the molecular features of the 1-phenyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate derivatives that lead to high affinity binding to the M_3 receptor, a molecular superimposition study was carried out. The GASP program (Genetic Algorithm Similarity Pro-

Figure 2. Superimposition of **7** (green), **8** (yellow) and **9a** (gray). All hydrogen atoms are hidden to improve visualization.

Table 3. Distances between the Centroids of the Benzene Rings, the Nitrogen Atoms of the Quinuclidine Rings and the Carbonyl Oxygen Atoms of the Carbamate Groups, and the Calculated Energy in the Superimposition Study of **7**, **8** and **9a**



	7	**8**	**9a**
a (centroid 1 − basic nitrogen)	6.2	6.3	6.6
b (centroid 2 − basic nitrogen)	8.4	8.9	8.9
c (centroid 1 − centroid 2)	4.3	4.7	4.7
d (centroid 1 − carbonyl oxygen)	3.2	3.3	3.5
e (basic nitrogen − carbonyl oxygen)	4.8	4.4	4.4
f (centroid 2 − carbonyl oxygen)	3.7	5.6	5.7
energy (kcal/mol)	17.98	14.52	15.69
minimum energy (kcal/mol)	17.97	14.52	15.65

gram)[25] was used to superimpose the most potent diastereomer among the quinuclidin-3-yl 1-phenyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylates, **9a**, and compounds **7** and **8** (the *R* isomer was used in this study). GASP does not require prior knowledge concerning either the receptor or the pharmacophore pattern, and it performs automatic molecular alignment with full conformational flexibility of the ligands. The results are shown in Figure 2 and Table 3. In this model, the basic nitrogen atoms and the centroids of the benzene rings in **7**, **8**, and **9a** overlapped well. Taking into consideration that even the less potent diastereomer (**9b**) showed relatively high affinity for the M_3 receptor, with a K_i value of 10 nM, the benzene ring of the tetrahydroisoquinoline moiety (benzene ring 1) may be more important for binding to the M_3 receptor than the benzene ring at the 1-position of the tetrahydroisoquinoline ring (benzene ring 2) and the benzene ring at the 1-position may modulate the interaction with the receptor. Furthermore, the remarkably decreased affinity for M_3 receptor of benzyl derivatives (**15a** and **15b**) suggests that the benzene ring 2 in **9a** may be fixed for preferred interaction with the M_3 receptor. On the other hand, significant overlap of the carbonyl oxygen atoms of the three compounds was not observed in the selected model or in other models. This suggests that the carbamate junction is necessary for locking the molecular conformation between the hydrophobic region and the amine ring, to generate a conformation that is suitable for interaction with the M_3 receptor. Consequently, proper arrangement of the two benzene rings and the nitrogen atom in the basic ring, achieved by conformational restriction of the benzhydrylcarbamate moiety in **8** through formation of a 1-phenyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate, may increase selectivity for the M_3 receptor over the M_2 receptor.

Table 4. M_3 Antagonistic Activities in Vivo

compd	rhythmic contraction, ED_{30} (mg/kg iv)[a]	salivary secretion, ID_{50} (mg/kg iv)[b]	selectivity index[c]
9a	0.036 ± 0.013	0.12 (0.089−0.14)	3.3
9b	0.18 ± 0.043	2.1 (1.9−2.3)	12
12a	0.016 ± 0.0016	0.11 (0.093−0.13)	6.9
12b	0.24 ± 0.12	1.3 (1.0−1.9)	5.4
1	0.20 ± 0.094	0.17 (0.13−0.21)	0.85
2	0.060 ± 0.025	0.26 (0.23−1.8)	4.3
3	0.058 ± 0.038	0.11 (0.092−0.013)	1.9

[a] Values are means ± SEM. [b] Values are means (95% confidence limits). [c] Selectivity indices were calculated by dividing the IC_{50} values for salivary secretion by the ED_{30} values for bladder contraction.

Table 5. Comparison of Compounds **1** and **9b**

	M_3 antagonism		M_1 antagonism: pressor	M_2 antagonism: bradycardia
compd	rhythmic contraction ED_{30} (mg/kg iv)[a]	salivary secretion ID_{50} (mg/kg iv)[b]	ID_{50} (mg/kg iv)[b]	DR_{10} (mg/kg iv)[b]
9b	0.18 ± 0.043	2.1 (1.9−2.3)	2.8 (2.6−3.0)	4.2 (3.0−7.5)
1	0.20 ± 0.094	0.17 (0.13−0.21)	1.1 (0.61−1.8)	1.6 (1.1−2.0)

[a] Values are means ± SEM. [b] Values are means (95% confidence limits).

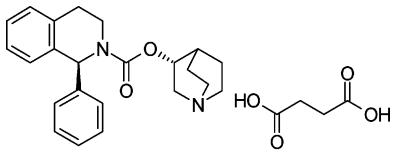
Among the compounds exhibiting high affinity and selectivity for the M_3 receptor, **9a**, **9b**, **12a**, and **12b** were selected for evaluation in vivo, in tests examining reflexly evoked rhythmic contraction and oxotremorine-induced salivary secretion in rats. Three reference compounds, nonselective oxybutynin (**1**) and bladder-selective tolterodine (**2**) and darifenacin (**3**), were also evaluated. As shown in Table 4, all compounds showed potent inhibitory activities on bladder pressure in a reflexly evoked rhythmic contraction test, with **9a** and **12a** showing particularly higher inhibitory activities with some bladder selectivity, compared to **1**. On the other hand, **9b** and **12b** showed almost the same inhibitory activities on bladder pressure, compared to **1**, and less potent inhibitory activities on salivary secretion. Among these compounds, **9b** showed more than 10-fold selective inhibitory activity on bladder pressure versus salivary secretion. The order of bladder selectivity in rats was **9b** > **2**, **12a**, **12b** > **3**, **9a** > **1**. Bladder selectivity of **9b** was also observed in vitro.[26]

Compound **9b** was selected for further pharmacological evaluation, since it showed the highest selectivity for bladder contraction versus salivary secretion. The results are shown in Table 5. In comparison with **1**, **9b** showed less potent activity against agonist-induced pressor and bradycardia in pithed rat, suggesting that **9b** is a weaker M_1 and M_2 receptor antagonist, respectively. On the basis of these results, **9b** could potentially be a bladder-selective M_3 antagonist with few side effects.

Conclusion

In the course of our continuing efforts to develop potent and bladder-selective M_3 antagonists, we designed and synthesized a series of quinuclidin-3-yl 1-aryl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate de-

rivatives and related compounds, as conformationally restricted analogues of quinuclidin-3-yl benzhydrylcarbamate (**8**). Binding assays showed that the quinuclidin-3-yl 1-aryl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate derivatives had higher selectivities for the M_3 receptor over the M_2 receptor, compared to **8**, and had high affinities for the M_3 receptor. Among these derivatives, (+)-(1*S*,3'*R*)-quinuclidin-3'-yl 1-phenyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate monohydrochloride (**9b**) exhibited almost the same inhibitory effect on bladder contraction and about a 10 times less potent inhibitory effect on salivary secretion in rats, in comparison with **1**, indicating that conformational restriction of the benzhydrylcarbamate moiety in **8** by formation of a 1-phenyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate can lead to an increase in subtype selectivity and bladder selectivity. Compound **9b** was selected as a clinical candidate in the form of its monosuccinate salt, solifenacin succinate (YM905),[26−28] and it has recently been



solifenacin succinate

approved by the United States Food and Drug Administration for the treatment of overactive bladder with symptoms of urgency, frequency, and urge incontinence.

Experimental Section

General. Melting points were determined using a Yanaco micro melting apparatus and are uncorrected. Proton nuclear magnetic resonance (^{1}H NMR) spectra were obtained in $CDCl_3$ or dimethyl sulfoxide-d_6 (DMSO-d_6) with a JNM-EX400, JNM-GX500 or JNM-A500 spectrometer. Chemical shifts are recorded in parts per million (δ), downfield relative to tetramethylsilane as an internal standard with coupling constants (J) reported in hertz (Hz). The peak shapes are denoted as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Mass spectra (MS) were recorded on a JEOL JMS-DX300 or a Hitachi M-80 mass spectrometer. Elementary analyses were carried out on a Yanaco MT-3 or a Yanaco MT-5 CHN analyzer and a Yokogawa IC 7000S Ion Chromatoanalyzer. Optical rotations were measured on a Horiba SEPA-200 polarimeter. X-ray diffraction measurements were made with a Rigaku AFC5R diffractometer using Cu Kα radiation. Chromatographic separations were performed on a silica gel column using Wakogel C-200 or Merck Silica gel 60 (0.040−0.063 mm). Analytical thin-layer chromatography (TLC) was carried out on glass plates precoated with Merck silica gel 60 F_{254}.

Authentic Material. Oxybutynin hydrochloride (**1**) was purchased from Sigma Co. Tolterodine tartrate (**2**) and darifenacin (**3**) were prepared at Yamanouchi Pharmaceutical Co., Ltd.

General Method for the Synthesis of 1-Substituted 1,2,3,4-Tetrahydoroisoquinolines. 1-(3-Thienyl)-1,2,3,4-tetrahydroisoquinoline (23). *N*-(2-Phenylethyl)thiophene-3-carboxamide[29] (**18**, 49.9 g, 234 mmol) was dissolved in xylene (500 mL) at 70 °C. To the solution were added phosphorus pentoxide (61.2 g, 431 mmol) and phosphoryl chloride (174 mL, 1.87 mol) and refluxed for 2.5 h. After the mixture was cooled to 30 °C, the solution was removed by decantation and washed with toluene. The residue was quenched with water and 20% aqueous NaOH solution and then extracted with ethyl acetate. The organic layer was washed with water, dried over $MgSO_4$, and evaporated in vacuo to give 1-(3-thienyl)-3,4-dihydroisoquinoline (41.7 g) as a dark brown oil, which was used for the next step without further purification. To the ice-cooled solution of 1-(3-thienyl)-3,4-dihydroisoquinoline (41.7 g) in ethanol (400 mL) was portionwisely added sodium borohydride (14.8 g, 412 mmol). The mixture was stirred at room temperature for 2.5 days and then poured into ice−water. The resulting solid was collected, washed with water, and dried at 30 °C in vacuo to give 1-(3-thienyl)-1,2,3,4-tetrahydroisoquinoline (**23**) (34.4 g, 82%) as a pale brown solid: ^{1}H NMR ($CDCl_3$) δ 1.87 (1H, br s), 2.75−2.90 (1H, m), 2.90−3.00 (1H, m), 3.00−3.15 (1H, m), 3.15−3.25 (1H, m), 5.22 (1H, s), 6.88 (1H, d, J = 8.0 Hz), 7.00 (1H, dd, J = 4.8, 1.6 Hz), 7.00−7.30 (5H, m); EI-MS m/z 215 (M^+).

Resolution of 1-Substituted 1,2,3,4-Tetrahydroisoquinoline Derivatives. (+)-(*S*)-1-Phenyl-1,2,3,4-tetrahydroisoquinoline [(+)-22]. Resolution of 1-phenyl-1,2,3,4-tetrahydroisoquinoline (**22**) was carried out as the reported method[14] with minor modification. Racemic **22** (1.88 kg, 8.97 mol) was converted to the corresponding (−)-tartrate in ethanol (16 L) followed by recrystallization from water (6 L) to give the (−)-tartrate (1.35 kg, 42%) as colorless crystals: mp 187−189 °C; ^{1}H NMR (DMSO-d_6) δ: 2.90−3.00 (1H, m), 3.10−3.20 (1H, m), 3.20−3.25 (1H, m), 3.30−3.35 (1H, m), 4.03 (2H, s), 5.49 (1H, s), 6.69 (1H, d, J = 7.9 Hz), 7.11 (1H, t, J = 6.1 Hz), 7.20−7.25 (2H, m), 7.30−7.45 (5H, m). FAB-MS m/z 210 (MH^+). The (−)-tartrate (1.35 kg) was neutralized with aqueous NaOH solution, then extracted with ethyl acetate. The organic layer was washed with water, then brine, and concentrated in vacuo. The resulting crystals were recrystallized from hexane to give (+)-**22** (627 g, 80%) as colorless crystals: mp 80−82 °C; ^{1}H NMR ($CDCl_3$) δ 1.77 (1H, br s), 2.80−2.90 (1H, m), 3.00−3.15 (2H, m), 3.20−3.30 (1H, m), 5.10 (1H, s), 6.75 (1H, d, J = 7.3 Hz), 7.03 (1H, m), 7.14 (2H, d, J = 3.7 Hz), 7.25−7.35 (5H, m); EI-MS m/z 209 (M^+); $[\alpha]^{25}_D$ = +47.6° (c = 2.83, CCl_4).

(−)-(*R*)-1-Phenyl-1,2,3,4-tetrahydroisoquinoline [(−)-22]: mp 80−82 °C; $[\alpha]^{25}_D$ = −47.8° (c = 2.88, CCl_4) [lit.[14] $[\alpha]^{25}_D$ = −47.6° (c = 6.46, CCl_4)]. ^{1}H NMR and MS spectra are similar to those of (+)-(*S*)-**22**.

(+)-1-(3-Thienyl)-1,2,3,4-tetrahydroisoquinoline [(+)−(23)]. Racemic **23** (31.69 g, 0.15 mol) was converted to the corresponding (−)-mandelate in ethanol−water (20:1) followed by recrystallization from ethanol−water (20:1) twice to give the (−)-mandelate (14.62 g, 25%) as colorless crystals: mp 132−133 °C; ^{1}H NMR (DMSO-d_6) δ 2.75−3.20 (4H, m), 4.80 (1H, s), 5.37 (1H, s), 6.80 (1H, d, J = 7.6 Hz), 7.02 (1H, dd, J = 5.2, 1.2 Hz), 7.15−7.40 (10H, m), 7.50 (1H, dd, J = 4.8, 2.8 Hz); FAB-MS m/z 216 (MH^+). The (−)-mandelate (14.42 g, 39 mmol) was neutralized with aqueous NaOH solution, then extracted with ethyl acetate. The organic layer was washed with water and then brine and concentrated in vacuo. The resulting crystals (8.37 g) were recrystallized from hexane (160 mL) to give (+)-**23** (6.83 g, 81%) as colorless crystals: mp 100−101 °C; ^{1}H NMR ($CDCl_3$) δ 1.76 (1H, br s), 2.83 (1H, dt, J = 16, 5.6 Hz), 2.90−3.00 (1H, m), 3.08 (1H, ddd, J = 12, 7.2, 5.6 Hz), 3.22 (1H, dt, J = 12, 6.0 Hz), 5.23 (1H, s), 6.88 (1H, d, J = 7.6 Hz), 7.00 (1H, dd, J = 4.8, 0.8 Hz), 7.05−7.15 (4H, m), 7.27 (1H, dd, J = 4.8, 2.8 Hz); EI-MS m/z 215 (M^+); $[\alpha]^{25}_D$ = +10.7° (c = 2.00, CCl_4).

(−)-1-(3-Thienyl)-1,2,3,4-tetrahydroisoquinoline [(−)-23]: mp 100−101 °C; $[\alpha]^{25}_D$ = −9.95° (c = 2.00, CCl_4). ^{1}H NMR and MS spectra are similar to those of (+)-**23**.

1-Benzyl-1,2,3,4-tetrahydroisoquinoline Hemi-(+)-DIBETA Salt [26 Hemi-(+)-DIBETA Salt]. Racemic **26**[13] (27.6 g, 123 mmol) was converted to the corresponding hemi-(+)-DIBETA salt in ethanol followed by recrystallization from ethanol−water (20:1) three times to give the hemi-(+)-DIBETA salt (7.03 g, 10%) as colorless crystals: ^{1}H NMR (DMSO-d_6) δ 2.72−2.93 (2H, m), 2.94−3.70 (2H, m), 3.17−3.30 (2H, m), 4.43 (1H, dd, J = 8.4, 5.3 Hz), 5.63 (1H, s), 7.10−7.35 (9H, m), 7.47 (2H, t, J = 7.5 Hz), 7.61 (1H, t, J = 7.5 Hz), 7.88−7.95 (2H, m); FAB-MS m/z 224 (MH^+). The optical purity was determined after neutralization as >99% by chiral HPLC [Chiralpak AD (4.6 × 250 mm; Daicel Chem. Co.), eluent: hexane−2-propanol−diethylamine (80:20:0.1)].

1-Benzyl-1,2,3,4-tetrahydroisoquinoline Hemi-(−)-DIBETA Salt [26 Hemi-(−)-DIBETA Salt]: obtained in 10% yield as colorless crystals from the mother liquor of **26** hemi-(+)-DIBETA salt. The optical purity was determined after neutralization as >99% by chiral HPLC.

(+)-(1*S*,3′*R*)-Quinuclidin-3′-yl 1-Phenyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate Monohydrochloride (9b). Method A. To a suspension of (+)-**22** (5.34 g, 26 mmol) and potassium carbonate (5.28 g, 38 mmol) in dichloromethane (100 mL) cooled in an ice bath was added ethyl chloroformate (2.91 mL, 27 mmol) in dichloromethane (10 mL), and the mixture was stirred at room temperature overnight. To the mixture was added water, and the mixture was stirred at room temperature for 30 min. The organic layer was separated, washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel using hexanes−ethyl acetate (10:1) as an eluent to give (+)-**30** (7.20 g, 100%) as a colorless oil: $[\alpha]^{25}_D$ = +199° (*c* = 1.03, EtOH); ^{1}H NMR (DMSO-d_6) δ 1.20−1.50 (3H, m), 2.70−2.80 (1H, m), 2.90−3.10 (1H, m), 3.20−3.30 (1H, m), 3.90−4.35 (3H, m), 6.20−6.55 (1H, m), 6.95−7.20 (9H, m); FAB-MS *m/z* 282 (MH^+). To a solution of (+)-**30** (12.0 g, 43 mmol) and (+)-(*R*)-quinuclidin-3-ol [(*R*)-**34**, 16.3 g, 128 mmol] in toluene (120 mL) was added sodium hydride (1.69 g, 42 mmol), and the mixture was heated at 140 °C (oil bath temperature) for 3 h with removal of resulting ethanol. The mixture was cooled to room temperature, poured into brine, then extracted with ethyl acetate. The organic layer was washed with water and then extracted with 20% hydrochloric acid. The aqueous layer was alkalized with 1 M aqueous NaOH solution to pH 9−10 and extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give (1*S*,3′*R*)-quinuclidin-3′-yl 1-phenyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (13.9 g, 89%) as a colorless oil. The free base was converted to the corresponding hydrochloride salt and recrystallized from acetonitrile−diethyl ether to give (+)-(1*S*,3′*R*)-quinuclidin-3′-yl 1-phenyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate monohydrochloride (**9b**, 10.1 g, 66%) as colorless crystals: mp 212−214 °C; $[\alpha]^{25}_D$ = +102° (*c* = 1.00, EtOH); ^{1}H NMR (DMSO-d_6) δ 1.70−2.10 (4H, m), 2.20−2.35 (1H, m), 2.75−3.65 (9H, m), 3.80−3.95 (1H, m), 4.85−5.00 (1H, m), 6.28 (1H, s), 7.10−7.40 (9H, m), 10.83 (1H, br s); FAB-MS *m/z* 363 (MH^+); Anal. ($C_{23}H_{26}N_2O_2$·HCl) C, H, N, Cl.

(1*RS*,3′*R*)-Quinuclidin-3′-yl 1-Phenyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (9): obtained from racemic 1-phenyl-1,2,3,4-tetrahydroisoquinoline (**22**) and (*R*)-**34** as a yellow oil in 33% yield; ^{1}H NMR (DMSO-d_6) δ 1.10−2.00 (5H, m), 2.20−2.95 (7H, m), 2.95−3.15 (1H, m), 3.20−3.55 (1H, m), 3.80−3.95 (1H, m), 4.55−4.70 (1H, m), 6.24 (1H, s), 7.00−7.40 (9H, m); FAB-MS *m/z* 363 (MH^+); Anal. ($C_{23}H_{26}N_2O_2$) C, H, N.

(1*R*,3′*R*)-Quinuclidin-3′-yl 1-Phenyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate Monohydrochloride (9a): obtained in 32% yield from (−)-**22** and (*R*)-**34** as colorless crystals, mp 197−199 °C (acetonitrile-diethyl ether); $[\alpha]^{25}_D$ = −151° (*c* = 0.500, EtOH); ^{1}H NMR (DMSO-d_6) δ 1.55−2.10 (4H, m), 2.10−2.40 (1H, m), 2.70−2.95 (2H, m), 3.00−3.70 (7H, m), 3.85−4.00 (1H, m), 4.85−5.00 (1H, m), 6.27 (1H, s), 7.10−7.40 (9H, m), 10.80 (1H, br s); FAB-MS *m/z* 363 (MH^+); Anal. ($C_{23}H_{26}N_2O_2$·HCl) C, H, N, Cl.

(1*R*,3′*S*)-Quinuclidin-3′-yl 1-Phenyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate Monohydrochloride (9c): obtained in 40% yield from (−)-**22** and (*S*)-**34** as colorless crystals, mp 212−214 °C (acetonitrile-diethyl ether); $[\alpha]^{25}_D$ = −97.4° (*c* = 0.500, EtOH); ^{1}H NMR (DMSO-d_6) δ 1.70−2.10 (4H, m), 2.20−2.35 (1H, m), 2.75−3.70 (9H, m), 3.80−3.95 (1H, m), 4.85−5.00 (1H, m), 6.28 (1H, s), 7.10−7.40 (9H, m), 11.01 (1H, br s); FAB-MS *m/z* 363 (MH^+); Anal. ($C_{23}H_{26}N_2O_2$·HCl) C, H, N, Cl.

(1*S*,3′*S*)-Quinuclidin-3′-yl 1-Phenyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate Monohydrochloride (9d): obtained in 74% yield from (+)-**22** and (*S*)-**34** as colorless crystals, mp 194−195 °C (acetonitrile-diethyl ether); $[\alpha]^{25}_D$ = +163° (*c* = 0.500, EtOH); ^{1}H NMR (DMSO-d_6) δ 1.50−2.05 (4H, m), 2.10−2.40 (1H, m), 2.70−3.00 (2H, m), 3.00−3.30 (5H, m), 3.30−3.70 (2H, m), 3.85−4.00 (1H, m), 4.85−5.05 (1H, m), 6.28 (1H, s), 7.10−7.45 (9H, m), 10.87 (1H, br s); FAB-MS *m*/z 363 (MH^+); Anal. ($C_{23}H_{26}N_2O_2$·HCl) C, H, N, Cl.

(3′*R*,4*RS*)-Quinuclidin-3′-yl 4-Phenyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (11): obtained in 25% yield from 4-phenyl-1,2,3,4-tetrahydroisoquinoline (**28**)[13] and (*R*)-**34** as a yellow oil in 25% yield; ^{1}H NMR (DMSO-d_6) δ 1.10−1.35 (1H, m), 1.35−1.75 (3H, m). 1.80−2.10 (2H, m), 2.60−3.00 (5H, m), 3.10−3.30 (1H, m), 3.60−3.85 (1H, m), 3.90−4.10 (1H, m), 4.15−4.25 (1H, m), 4.45−4.80 (2H, m), 6.90−7.35 (9H, m); FAB-MS *m/z* 363 (MH^+); Anal. ($C_{23}H_{26}N_2O_2$·0.3H_2O) C, H, N.

(+)-(1*R*,3′*R*)-Quinuclidin-3′-yl 1-(3-Thienyl)-1,2,3,4-tetrahydroisoquinoline-2-carboxylate Monooxalate (12b): obtained in 33% yield from (+)-**23** and (*R*)-**34** as colorless crystals, mp 166−167 °C (aq. ethanol); $[\alpha]^{25}_D$ = +57.6° (*c* = 1.00, H_2O); ^{1}H NMR (DMSO-d_6) δ 1.60−2.10 (4H, m), 2.20−2.35 (1H, m), 2.75−3.45 (8H, m), 3.50−3.70 (1H, m), 3.80−3.95 (1H, m), 4.85−5.00 (1H, m), 6.27 (1H, s), 6.90−7.10 (1H, m), 7.15−7.30 (5H, m), 7.49 (1H, dd, *J* = 4.4, 3.2 Hz).; FAB-MS *m/z* 369 (MH^+). Anal. ($C_{21}H_{24}N_2O_2S$·$C_2H_2O_4$) C, H, N, S.

(−)-(1*S*,3′*R*)-Quinuclidin-3′-yl 1-(3-Thienyl)-1,2,3,4-tetrahydroisoquinoline-2-carboxylate Mono-(−)-tartrate (12a). Method B. To a solution of (−)-1-(3-thienyl)-1,2,3,4-tetrahydroisoquinoline [(−)-**23**, 3.23 g, 15 mmol] in pyridine (45 mL) at −20 °C was added (*R*)-quinuclidin-3-yl chloroformate monohydrochloride (**35**,[21] 3.39 g, 15 mmol), and the mixture was stirred at room temperature for 1.5 h. After **35** (0.34 g, 1.5 mmol) was added, the mixture was stirred at room temperature for additional 30 min. The resulting mixture was diluted with ethyl acetate and extracted with water and then 1% hydrochloric acid. The combined aqueous layer was washed with ethyl acetate, alkalized with 1 M aqueous NaOH solution to pH 10, and extracted with ethyl acetate. The organic layer was washed with water, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel with chloroform−methanol-28% ammonium hydroxide solution (50:1:0.1) as an eluent to give (−)-(1*S*,3′*R*)-quinuclidin-3′-yl 1-(3-thienyl)-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (3.66 g, 66%) as a yellow oil. The free base (0.57 g, 1.5 mmol) was converted to the corresponding mono-(−)-tartrate and recrystallized from ethanol−water to give **12a** (0.43 g, 61%) as colorless crystals: mp 176−178 °C; $[\alpha]^{25}_D$ = −104° (*c* = 1.01, H_2O); ^{1}H NMR (DMSO-d_6) δ 1.80−2.00 (4H, m), 2.70−3.15 (7H, m), 3.30−3.50 (2H, m), 3.80−4.00 (1H, m), 4.02 (2H, s), 4.80−4.90 (1H, m), 6.28 (1H, s), 6.90−7.30 (6H, m), 7.49 (1H, dd, *J* = 5.4, 2.9 Hz); FAB-MS *m/z* 369 (MH^+); Anal. ($C_{21}H_{24}N_2O_2S$·$C_4H_4O_4$) C, H, N, S.

(1*RS*,3′*R*)-Quinuclidin-3′-yl 1-Phenylisoindoline-2-carboxylate (10): prepared from 1-phenylisoindoline (**27**)[19] and **35** as pale yellow amorphous in 60% yield; ^{1}H NMR (DMSO-d_6) δ 1.80−2.10 (4H, m), 2.30−2.40 (1H, m), 2.75−3.60 (6H, m), 3.90−4.05 (1H, m), 6.05−6.20 and 6.30−6.50 (total 1H, m), 7.05−7.35 (9H, m); FAB-MS *m/z* 349 (MH^+); Anal. ($C_{22}H_{24}N_2O_2$·0.3H_2O) C, H, N.

(−)-(3′*R*)-Quinuclidin-3′-yl 1-Benzyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate Monohydrochloride (15a): prepared from 1-benzyl-1,2,3,4-tetrahydroisoquinoline hemi-(+)-DIBETA salt [**26**·hemi-(+)-DIBETA salt] and **35** as colorless crystals in 44% yield, mp 248−250 °C (ethanol−acetonitrile−diethyl ether); $[\alpha]^{25}_D$ = −79.0° (*c* = 0.500, EtOH); ^{1}H NMR (DMSO-d_6) δ 1.40−2.05 (5H, m), 2.65−2.90 (2H, m), 2.95−3.20 (7H, m), 3.35−3.55 (2H, m), 3.85−4.10 (1H, m), 4.35−4.45, 4.70−4.80 (total 1H, m), 5.28 (1H, t, *J* = 7.2 Hz), 7.10−7.40 (9H, m), 10.40 (1H, br s); FAB-MS *m/z* 377 (MH^+); Anal. ($C_{24}H_{28}N_2O_2$·HCl) C, H, N, Cl.

(+)−(3′*R*)-Quinuclidin-3′-yl 1-Benzyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate Monohydrochloride (15b): prepared in 57% yield from **26** hemi-(−)-DIBETA salt and **35** as colorless crystals, mp 132−134 °C (ethanol-diethyl ether); $[\alpha]^{25}_D$ = +54.0° (*c* = 0.507, EtOH); ^{1}H NMR (DMSO-d_6) δ 1.50−2.10 (5H, m), 2.75−3.25 (7H, m), 3.30−3.55 (2H, m), 3.70−4.00 (1H, m), 4.05−4.15 (1H, m), 4.55−4.75 (1H, m), 5.15−

5.35 (1H, m), 7.10−7.40 (9H, m), 10.44 (1H, br s); FAB-MS *m/z* 377 (MH^+); Anal. ($C_{24}H_{28}N_2O_2$·HCl·0.75H_2O) C, H, N, Cl.

Separation of Diastereomers. Compounds **13a**, **13b**, **14a**, **14b**, **16a**−**d** were obtained as yellow oils by preparative HPLC separation (Chiralpak AD, 20 × 250 mm; Daicel Chem. Co.) with hexane−2-propanol−diethylamine (80:20:0.1 or 60:40:0.1) as eluents (the former eluted diastereomers: **13a**, **14a**, **16a**, **16c**, and the latters: **13b**, **14b**, **16b**, and **16d**).

(3′*R*)-Quinuclidin-3′-yl 1-(2-Thienyl)-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (13a and 13b). A mixture of **13a** and **13b** was prepared from 1-(2-thienyl)-1,2,3,4-tetrahydroisoquinoline (**24**)[13] in 64% yield by Method A.

13a: a yellow oil; $[\alpha]^{25}_D = -135°$ ($c = 1.00$, EtOH); ^{1}H NMR (DMSO-d_6) δ 1.35−2.25 (6H, m), 2.70−3.10 (6H, m), 3.20−3.45 (2H, m), 3.90−4.30 (1H, m), 4.80−4.90 (1H, m), 6.40−6.65 (1H, m), 6.65−6.80 (1H, m), 6.88 (1H, dd, $J = 4.8$, 3.2 Hz), 7.15−7.30 (5H, m); FAB-MS *m/z* 369 (MH^+); Anal. ($C_{21}H_{24}N_2O_2S$·0.2H_2O) C, H, N, S.

13b: a yellow oil; $[\alpha]^{25}_D = +118°$ ($c = 1.00$, EtOH); ^{1}H NMR (DMSO-d_6) δ 1.35−2.10 (6H, m), 2.65−3.10 (6H, m), 3.20−3.45 (2H, m), 3.90−4.50 (1H, m), 4.75−4.85 (1H, m), 6.40−6.80 (2H, m), 6.88 (1H, dd, $J = 4.8$, 3.2 Hz), 7.15−7.30 (7H, m); FAB-MS *m/z* 369 (MH^+); Anal. ($C_{21}H_{24}N_2O_2S$·0.2H_2O) C, H, N, S.

(3′*R*)-Quinuclidin-3′-yl 1-Cyclohexyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (14a and 14b). A mixture of **14a** and **14b** was prepared from 1-cyclohexyl-1,2,3,4-tetrahydroisoquinoline (**25**)[13] in 99% yield by Method B.

14a: a yellow oil; $[\alpha]^{25}_D = -10.0°$ ($c = 1.00$, EtOH); ^{1}H NMR ($CDCl_3$) δ 1.00−1.30 (5H, m), 1.30−2.15 (12H, m), 2.60−3.05 (6H, m), 3.15−4.09 (3H, m), 4.70−4.90 (2H, m), 7.06−7.25 (4H, m); EI-MS *m/z* 368 (M^+); Anal. ($C_{23}H_{32}N_2O_2$·0.25H_2O) C, H, N.

14b: a yellow oil; $[\alpha]^{25}_D = +7.29°$ ($c = 1.00$, EtOH); ^{1}H NMR ($CDCl_3$) δ 1.00−1.30 (5H, m), 1.35−2.10 (12H, m), 2.65−3.05 (6H, m), 3.15−4.07 (3H, m), 4.67−4.88 (2H, m), 7.05−7.22 (4H, m); EI-MS *m/z* 368 (M^+); Anal. ($C_{23}H_{32}N_2O_2$·0.25H_2O) C, H, N.

***cis*-(3′*R*)-Quinuclidin-3′-yl 4-Hydroxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (16a and 16b).** A mixture of **16a** and **16b** was prepared from *cis*-1-phenyl-1,2,3,4-tetrahydroisoquinoline-4-ol (cis-**29**)[20] in 72% yield by Method B.

16a: a colorless amorphous; $[\alpha]^{25}_D = -196°$ ($c = 0.500$, EtOH); ^{1}H NMR (DMSO-d_6, 90 °C) δ 1.20−1.70 (4H, m), 1.90−2.00 (1H, m), 2.50−2.80 (4H, m), 2.85−3.15 (3H, m), 4.16 (1H, dd, $J = 13$, 6.1 Hz), 4.55−4.70 (2H, m), 5.49 (1H, d, $J = 6.1$ Hz), 6.21 (1H, s), 6.97 (1H, $J = 7.3$ Hz), 7.00−7.40 (7H, m), 7.62 (1H, $J = 7.3$ Hz); FAB-MS *m/z* 379 (MH^+); Anal. ($C_{23}H_{26}N_2O_3$·0.5H_2O) C, H, N.

16b: a colorless amorphous; $[\alpha]^{25}_D = +197°$ ($c = 0.500$, EtOH); ^{1}H NMR (DMSO-d_6, 90 °C) δ 1.25−1.80 (4H, m), 1.90−2.00 (1H, m), 2.50−2.80 (5H, m), 2.90−3.15 (2H, m), 4.18 (1H, dd, $J = 13$, 5.5 Hz), 4.55−4.70 (2H, m), 5.49 (1H, d, $J = 5.5$ Hz), 6.22 (1H, s), 6.96 (1H, $J = 7.9$ Hz), 7.00−7.40 (7H, m), 7.62 (1H, $J = 7.9$ Hz); FAB-MS *m/z* 379 (MH^+); Anal. ($C_{23}H_{26}N_2O_3$··0.6H_2O) C, H, N.

***trans*-(3′*R*)-Quinuclidin-3′-yl 4-Hydroxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (16c and 16d).** A mixture of **16c** and **16d** was prepared from *trans*-1-phenyl-1,2,3,4-tetrahydroisoquinoline-4-ol (trans-**29**)[20] by Method B quantitatively.

16c: a colorless amorphous; $[\alpha]^{25}_D = -165°$ ($c = 0.503$, EtOH); ^{1}H NMR (DMSO-d_6) δ 1.20−1.80 (4H, m), 1.85−1.95 (1H, m), 2.55−2.80 (5H, m), 3.05−3.15 (1H, m), 3.50 (1H, dd, $J = 13$, 3.7 Hz), 3.88 (1H, dd, $J = 13$, 4.6 Hz), 4.60−4.70 (2H, m), 5.16 (1H, d, $J = 6.1$ Hz), 6.25 (1H, s), 7.10−7.35 (8H, m), 7.44 (1H, d, $J = 7.3$ Hz); FAB-MS *m/z* 379 (MH^+); Anal. ($C_{23}H_{26}N_2O_3$) C, H, N.

16d: a colorless amorphous; $[\alpha]^{25}_D = +175°$ ($c = 0.500$, EtOH); ^{1}H NMR (DMSO-d_6) δ 1.25−2.00 (5H, m), 2.40−2.75 (5H, m), 2.90−3.05 (1H, m), 3.49 (1H, dd, $J = 13$, 3.7 Hz), 3.87 (1H, dd, $J = 13$, 4.9 Hz), 4.55−4.70 (2H, m), 5.18 (1H, d, $J = 6.1$ Hz), 6.25 (1H, s), 7.10−7.35 (8H, m), 7.44 (1H, d, $J = 7.3$ Hz); FAB-MS *m/z* 379 (MH^+); Anal. ($C_{23}H_{26}N_2O_3$·0.2H_2O) C, H, N.

Methyl 1,2,3,4-Tetrahydroquinoline-2-carboxylate (37). Quinaldic acid (**36**, 5.07 g, 29 mmol) was hydrogenated at room temperature overnight in the presence of Raney Ni in 1 M aqueous NaOH solution (100 mL). After the catalyst was removed by filtration, the filtrate was neutralized with concentrated HCl (8.5 mL) and concentrated in vacuo. The resulting residue was dissolved in methanol (75 mL), and the solution was cooled in an ice bath. To the solution was cautiously added thionyl chloride (8.5 mL), and the mixture was stirred at room temperature overnight. After the mixture was concentrated in vacuo, the residue was diluted with water, alkalized with potassium carbonate, and then extracted with ethyl acetate. The organic layer was washed with water, dried over $MgSO_4$, and then evaporated in vacuo. The residue was chromatographed on silica gel with hexanes−ethyl acetate (5:1) as an eluent to give **37** (4.12 g, 74%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.95−2.05 (1H, m), 2.20−2.35 (1H, m), 2.70−2.90 (2H, m), 3.77 (3H, s), 4.03 (1H, dd, $J = 8.8$, 3.9 Hz), 4.35 (1H, br s), 6.58 (1H, d, $J = 7.3$ Hz), 6.64 (1H, dd, $J = 8.8$, 7.3 Hz), 6.90−7.05 (2H, m); EI-MS *m/z* 191 (M^+).

Methyl 1-Phenyl-1,2,3,4-tetrahydroquinoline-2-carboxylate (38). A mixture of **37** (2.00 g, 10 mmol), triphenylbismuthine (5.53 g, 12 mmol), and copper(II) acetate (1.90 g, 10 mmol) in 1,2-dichloroethane (35 mL) was stirred at 80 °C for 5 days. After the insoluble material was filtered off, the filtrate was concentrated in vacuo. The residue was chromatographed on silica gel with hexanes−ethyl acetate (10:1) as an eluent to give **38** (0.23 g, 9%) as a brown oil: ^{1}H NMR ($CDCl_3$) δ 2.00−2.40 (2H, m), 2.65−2.90 (2H, m), 3.65 (3H, s), 4.48 (1H, t, $J = 4.4$ Hz), 6.50−6.80 (2H, m), 6.80−7.50 (10H, m); FAB-MS *m/z* 267 (M^+).

(2*RS*,3′*R*)-Quinuclidin-3′-yl 1-Phenyl-1,2,3,4-tetrahydroquinoline-2-carboxylate (39): prepared from methyl 1-phenyl-1,2,3,4-tetrahydroquinoline-2-carboxylate (**38**) in 43% yield in the same manner to Method A as a yellow amorphous: ^{1}H NMR ($CDCl_3$) δ 1.20−1.35 (1H, m), 1.40−1.70 (3H, m), 1.85−2.00 (1H, m), 2.20−2.90 (9H, m), 3.10−3.15 (1H, m), 4.52 (1H, ddd, $J = 9.2$, 5.6, 3.6 Hz), 4.80−4.85 (1H, m), 6.60−6.80 (2H, m), 6.90−7.40 (7H, m); EIMS *m/z* 362 (M^+); Anal. ($C_{23}H_{26}N_2O_2$·0.25H_2O) C, H, N.

X-ray Crystallographic Analysis. The configurations of compounds **9b**, **12b**, **16c**, and **16d** were determined by X-ray crystallographic analysis.

Compound **9b** was converted to the hydrogen bromide salt (**9e**) and crystallized from ethanol−diethyl ether for X-ray crystallographic analysis. The absolute configuration is 1*S*,3′*R* by the comparison of intensities of Bijvoet's pairs. Formula, $C_{23}H_{27}N_2O_2Br$; crystal system, monoclinic; space group, $P2_1$; lattice parameters, $a = 7.550$ (3) Å, $b = 33.392$ (3) Å, $c = 9.425$ (2) Å, $\beta = 91.28$ (2) °, $V = 2375.6$ (10) Å^3; D_{calc}, 1.34 g/cm^3; Z value, 4.0; F_{000}, 1004; final R value, $R = 0.061$, $R_W = 0.103$; goodness of fit indicator, 1.30; Flack parameter = −0.03 (2).

Compound **12b** was converted to the phosphate salt (**12c**) and recrystallized from ethanol−diethyl ether for X-ray crystallographic analysis. The absolute configuration of **12b** is *R* by the comparison of intensities of Bijvoet's pairs. Formula, $C_{21}H_{27}N_2O_6PS$; crystal system, monoclinic; space group, $P2_1$; lattice parameters, $a = 21.570$ (1) Å, $b = 6.6041$ (7) Å, $c = 7.971$ (1) Å, $\beta = 94.771$ (9) °, $V = 1131.6$ (2) Å^3; D_{calc}, 1.37 g/cm^3; Z value, 2.0; F_{000}, 2522; final R value, $R = 0.047$, $R_W = 0.070$; goodness of fit indicator, 1.26; Flack parameter = −0.004(30).

16c: Formula, $C_{23}H_{26}N_2O_3$; crystal system, orthorhombic; space group, $P2_12_12_1$; lattice parameters, $a = 9.945$ (2) Å, $b = 31.993$ (1) Å, $c = 6.274$ (1) Å, $V = 1996.3$ (6) Å^3; D_{calc}, 1.26 g/cm^3; Z value, 4.0; F_{000}, 808; final R value, $R = 0.044$, $R_W = 0.062$; goodness of fit indicator, 1.09.

Compound **16d** was converted to the hydrobromide salt (**16e**) and recrystallized from ethanol-diethyl ether for X-ray crystallographic analysis. The absolute configuration is 1*S*,3′*R*,4*S* by the comparison of intensities of Bijvoet's pairs. Formula, $C_{23}H_{27}N_2O_3Br$; crystal system, orthorhombic; space

group, $P2_12_12_1$; lattice parameters, $a = 13.350$ (2) Å, $b = 17.437$ (1) Å, $c = 9.1331$ (7) Å, $V = 2126.1$ (3) Å^3; D_{calc}, 1.44 g/cm^3; Z value, 4; F_{000}, 952; final R value, $R = 0.036$, $R_W = 0.053$; goodness of fit indicator, 1.20; Flack parameter = −0.02 (2).

Molecular Modeling. The GASP module of SYBYL[30] was used to superpose the 1-phenyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate derivatives. GASP parameters were set to the following values: population size: 100, selection pressure: 1.1, maximum number of operations: 60,000, operations increment: 6500, fitness increment: 0.01, point cross-weight: 95.0, allele mutate weight: 96.0, full mutation weight: 0.0, full cross-weight: 0.0.

Muscarinic Receptor Binding Assays. Muscarinic receptor binding assays were performed in the reported method[24] 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 sc). The bilateral ureters were ligated, then the urinary bladder was catheterized transurethrally and filled with saline to evoke reflex rhythmic contractions. After recording the peak intravesical pressure, compounds were administered via the femoral vein cumulatively. Fall in the pressure was measured in the period of 5−10 min after each administration. A dose−response curve was obtained in each rat and the dose required to reduce 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 administered intravenously 15 min prior to injection of oxotremorine (0.8 μmol/kg iv). Saliva was collected by absorbent paper for 5 min after the injection of oxotremorine.

Pressor. Effect on the pressor response caused by McN-A343 was determined in pithed rats.[24] Compounds were administered intravenously 15 min before the injection of McN-A343 (3 μmol/kg iv).

Bradycardia. Bradycardia was evoked in pithed rats by intravenous injection of oxotremorine.[24] Compounds were administered 15 min prior to the challenge of oxotremorine. A dose shifting the dose−response curve of oxotremorine rightward by 10-fold (DR_{10}) was calculated.

Acknowledgment. We thank Dr. Yasuo Isomura, presently at Mochida Pharmaceutical Co., Ltd., for his efforts at Yamanouchi. We are grateful to Drs. Toshiyasu Mase and Hiromu Hara for useful discussions. We also thank Mr. Seiji Kobayashi, Dr. Minetake Kitagawa, and Mrs. Masako Tateishi-Hirano for the biological experiments, Mr. Hideaki Nakahara for X-ray crystallographic analysis, Mrs. Yoko Yamagiwa-Yokota for the superimposition study, and the members of the Structure Analysis Research division, Yamanouchi Pharmaceutical Co., Ltd., for NMR and mass spectral data and elemental analysis.

Supporting Information Available: Elemental analysis data of **9**−**16d** and **39**, and ORTEPII Drawings of **9e**, **12c**, **16c**, and **16e**. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) This work was presented in part at the 213th National Meeting of the American Chemical Society, San Francisco, CA, April 1997; Abstract MEDI-046.
(2) Majewski, R. F.; Camphell, K. N.; Dykstra, S.; Covington, R.; Simms, J. C. Anticholinergic agents. Esters of 4-alkyl- (or 4-polymethylene-)amino-2-butynols. *J. Med. Chem.* **1965**, *8*, 719−720.
(3) Andersson, K.-E. Current concepts in the treatment of disorders of micturition. *Drugs* **1988**, *35*, 477−494.
(4) Nilvebrant, L.; Hallen, B.; Larsson, G. Tolterodine—a new bladder selective muscarinic receptor antagonist: Preclinical pharmacological and clinical data. *Life Sci.* **1997**, *60*, 1129−1136.
(5) Wallis, R. M.; Napier, C. M. Muscarinic antagonists in development for disorders of smooth muscle function. *Life Sci.* **1999**, *64*, 395−401.
(6) Miyachi, H.; Kiyota, H.; Segawa, M. Novel imidazole derivatives with subtype-selective antimuscarinic activity (1). *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1807−1812.
(7) Mitsuya, M.; Kobayashi, K.; Kawakami, K.; Satoh, A.; Ogino, Y.; Kakikawa, T.; Ohtake, N.; Kimura, T.; Hitose, H.; Sato, A.; Numazawa, T.; Hasegawa, T.; Noguchi, K.; Mase, T. A potent, long-acting, orally active (2*R*)-2-[(1*R*)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenyl-acetamide: A novel muscarinic M_3 receptor antagonist with high selectivity for M_3 over M_2 receptors. *J. Med. Chem.* **2000**, *43*, 5017−5029.
(8) Naito, R.; Takeuchi, M.; Morihira, K.; Hayakawa, M.; Ikeda, K.; Shibanuma, T.; Isomura, Y. Selective muscarinic antagonists. I. Synthesis and antimuscarinic properties of 4-piperidyl benzhydrylcarbamate derivatives. *Chem. Pharm. Bull.* **1998**, *46*, 1274−1285.
(9) Naito, R.; Takeuchi, M.; Morihira, K.; Hayakawa, M.; Ikeda, K.; Shibanuma, T.; Isomura, Y. Selective muscarinic antagonists. II. Synthesis and antimuscarinic properties of biphenylylcarbamate Derivatives. *Chem. Pharm. Bull.* **1998**, *46*, 1286−1294.
(10) Rama Sastry, B. V. Anticholinergic drugs. In *Burger's Medicinal Chemistry and Drug Discovery*, John Wiley & Sons: 1996; Vol. 2, pp 59−117.
(11) Wess, J.; Buhl, T.; Lambrecht, G.; Mutschler, E. Cholinergic receptors. In *Comprehensive Medicinal* Chemistry; C. Hansch, Ed.; Pergamon Press: 1990; Vol. 3; pp 423−492.
(12) Turbanti, L.; Cerbai, G.; Garzelli, G.; Renzetti, A. R.; Criscuoli, M.; Subissi, A.; Bramanti, G.; Martinelli, A. *N*-Alkyl-nor-tropine ester of 2-phenyl-cyclohexenic Acids as New bronchodilator agents. Effects of structural and conformational modifications on affinity for muscarinic receptors. *Eur. J. Med. Chem.* **1992**, *27*, 449−462.
(13) Gray, N. M.; Cheng, B. K.; Mick, S. J.; Lair, C. M.; Contreras, P. C. Phencyclidine-like effects of tetrahydroisoquinolines and related compounds. *J. Med. Chem.* **1989**, *32*, 1242−1248.
(14) Leithe, W. Über die natürliche Drehung des polarisierten Lichites durch optisch aktive Basen IV. Die Drehung einiger synthetischer Isochinolin derivate. *Monasch. Chem.* **1929**, *53*−*54*, 956−962.
(15) Ludwig, M.; Beer, H.; Lotter, H.; Wanner, K. T. The absolute configuration of (1*S*)-(+)- and (1*R*)-(−)-1-phenyl-1,2,3,4-tetrahydroisoquinoline. A revision of the literature assignment. *Tetrahedron: Asymmetry* **1997**, *8*, 2693−2695.
(16) Nakahara, H.; Takeuchi, M.; Naito, R.; Kurihara, H.; Nagano, N.; Isomura, Y.; Mase, T. Absolute configuration of (+)-1-phenyl-1,2,3,4-tetrahydroisoquinoline hydrochloride. *Acta Crystallogr.* **1998**, *C54*, 651−653.
(17) Yamato, M.; Hashigaki, K.; Qais, N.; Ishikawa, S. Asymmetric synthesis of 1-alkyltetrahydroisoquinolines using chiral oxazolo-[2,3-*a*]tetrahydroisoquinolines. *Tetrahedron* **1990**, *46*, 5909−5920.
(18) McNab, H.; Monahan, L. C., 3-Hydroxypyrrole and 1*H*-pyrrol-3(2*H*)-ones. Part 3. Pyrrolones from pyrolyses of aminomethylene Meldrum's acid derivatives: Loss of chirality at the side of hydrogen transfer. *J. Chem. Soc., Perkin Trans. 1* **1988**, 869−873.
(19) Veber, D. N.; Lwowski, W. 1-Arylisoindoles. *J. Am. Chem. Soc.* **1964**, *86*, 4152−4158.
(20) Tikk, I.; Deák, G.; Tóth, G.; Tamás, J. Hydroxyiminoisoquinolin-3(2*H*)-ones. Part 4. Synthesis and reactions of isoquinoline-3,4-diones. *J. Chem. Soc., Perkin Trans. 1* **1984**, 619−623.
(21) Ringdahl, B.; Resul, B.; Dahlbom, R. Facile preparation of the enantiomers of 3-acetoxyquinuclidine and 3-quinuclidinol. *Acta Pharm. Suec.* **1979**, *16*, 281−283.
(22) Turconi, M.; Nicola, M.; Quintero, M. G.; Maiocchi, L.; Micheletti, R.; Giraldo, E.; Donetti, A. Synthesis of a new class of 2,3-dihydro-2-oxo-1*H*-benzimidazole-1-carboxylic acid derivatives as highly potent 5-HT_3 receptor antagonists. *J. Med. Chem.* **1990**, *33*, 2101−2108.
(23) Finet, J.-P. Arylation reaction with organobithmuth reagents. *Chem. Rev.* **1989**, *89*, 1487−1501.
(24) Doods, H. N.; Mathy, M.-J.; Davidesko, D.; van Charldorp, K. J.; de Jonge, A.; van Zwieten, P. A. Selectivity of muscarinic antagonists in radioligand and in vivo experiments for the putative M_1, M_2 and M_3 receptors. *J. Pharmacol. Exp. Ther.* **1987**, *242*, 257−262.
(25) Jones, G.; Willett, P.; Glen, R. C. A genetic algorithm for flexible molecular overlay and pharmacophore elucidation. *J. Comput.-Aided Mol. Des.* **1995**, *9*, 532−549.
(26) Ohtake, A.; Ukai, M.; Hatanaka, T.; Kobayashi, S.; Ikeda, K.; Sato, S.; Miyata, K.; Sasamata, M. In vitro and in vivo tissue selectivity profile of solifenacin succinate (YM905) for urinary bladder over salivary gland in rats. *Eur. J. Pharmacol.* **2004**, *492*, 243−250.

(27) Ikeda, K.; Kobayashi, S.; Suzuki, M.; Kitagawa, M.; Takeuchi, M.; Yamada, T.; Honda, K. M_3 receptor antagonism by the novel antimuscarinic agent solifenacin in the urinary bladder and salivary gland. *Arch. Pharmacol.* **2002**, *366*, 97−103.
(28) Kobayashi, S.; Ikeda, K.; Miyata, K. Comparison of in vitro selectivity profiles of solifenacin succinate (YM905) and current antimuscarinic drugs in bladder and salivary glands: a Ca^{2+} mobilization study in monkey cells. *Life Sci.* **2004**, *74*, 843−853.
(29) Ohkubo, M.; Kuno, A.; Katsuta, K.; Ueda, Y.; Shirakawa, K.; Nakanishi, H.; Kinoshita, T.; Takasugi, H. Studies on cerebral protective agents. X. Synthesis and evaluation of anticonvulsant activities for novel 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridines and related compounds. *Chem. Pharm. Bull.* **1996**, *44*, 778−784.
(30) GASP 1.0a, and SYBYL 6.4, Tripos, Inc., St. Louis, MO.

JM050099Q